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Eco-efficient downstream processing of fermentation products by intensified distillation processes

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Eco-efficient downstream processing of fermentation products by intensified distillation processes



Tamara Jankovic

Eco-efficient downstream processing of fermentation products by intensified distillation processes

Dissertation

for the purpose of obtaining the degree of doctor
at Delft University of Technology
by the authority of the Rector Magnificus,
Prof.dr.ir. T.H.J.J. van der Hagen;

Chair of the Board for Doctorates
to be defended publicly on
Friday 24th October 2025 at
10:00 o'clock

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Summary

The rapid rise in global energy demands has accelerated the depletion of fossil fuel reserves, raising significant concerns about long-term energy security. Beyond resource exhaustion, this growing dependency on fossil fuels has contributed to severe environmental pollution and climate change, leading to strict environmental regulations. Consequently, extensive research efforts have been devoted to developing methods for producing a wide range of platform chemicals from renewable sources. In that respect, industrial biotechnology holds significant potential to replace fossil fuel-dependent production of various chemicals. Nonetheless, improvements in the fermentation and downstream processing are often necessary to enhance the competitiveness of large-scale bioprocesses. Significant research efforts have been put into genetic engineering to improve microorganisms' performance and optimization of the fermentation process. However, downstream processing after fermentation has not been nearly as promptly addressed. A common limitation of the fermentation processes is the inhibition of microbial production by the products themselves which limits achievable product concentrations in the broth (often <10 wt%). Additionally, the formation of by-products and the presence of microorganisms complicate recovery process after fermentation. Consequently, downstream processing costs may significantly contribute to the total production costs (20-40% for the bulk biochemicals).

Process systems engineering is essential in developing competitive (bio)chemical processes, as it integrates process design and simulation in biotechnology. Hence, this thesis aims to advance industrial biotechnology by developing advanced, large-scale downstream processes for the recovery of fermentation products such as alcohols, diols, esters, carboxylic acids, and aromatic compounds. A systematic approach to downstream process development was undertaken through multiple case studies that were organized into chapters based on the characteristics of the primary product being recovered. Aspen Plus software was used as a computer-aided process engineering tool for process design. Various process intensification techniques (e.g. dividing-wall column and reactive distillation), heat integration and heat pumping were studied to reduce energy requirements and decrease total process costs. The performance of the developed processes was assessed through economic analysis and the evaluation of key sustainability metrics, including energy requirements, greenhouse gas emissions, water consumption, water losses, and toxic materials and pollutants intensity.

Chapter 2 focuses on designing downstream processing strategies tailored for low-boiling alcohols produced through fermentation, including ethanol, isopropanol, isobutanol, and hexanol. Since these products are sufficiently volatile, the end-product inhibition can be mitigated by continuously removing the product from the broth using a distillation-based loop around the bioreactor.

Heat pump-assisted vacuum distillation was demonstrated as an effective method for initial product recovery from the broth. Additionally, a novel pass-through distillation process was designed specifically for ethanol recovery. This innovative technique separates the evaporation and condensation parts of distillation by introducing an absorption-desorption loop between them. As a result, these operations can be conducted at different pressures, allowing the use of inexpensive cooling utilities while maintaining mild evaporation temperatures. Furthermore, a hybrid approach combining gas stripping with heat pump-assisted vacuum evaporation was developed for the recovery of isobutanol from fermentation broth. In all cases, the initial separation of the product from most of the broth under reduced pressure lowers the operational temperature, making it possible to reuse the remaining broth along with the microorganisms. This may improve fermentation performance by avoiding biomass loss, increasing substrate-to-product yield and reducing water requirements. Following this initial step, a preconcentration step using heat pump-assisted atmospheric distillation was carried out to remove most of the remaining water. The final purification method depended on the properties of the target product. Ethanol and isopropanol, which form homogeneous azeotropes with water, were purified using extractive distillation with ethylene glycol. In contrast, isobutanol and hexanol, which form heterogeneous azeotropes, were purified through a combination of simple distillation and liquid-liquid phase separation. Furthermore, a general methodology for recovering volatile alcohols from fermentation broths was developed and the performance of downstream processing was compared for the recovery of ethanol, isopropanol, isobutanol, and hexanol. Due to the higher hydrophobicity of longer-chain alcohols, their concentrations in the fermentation broth tend to be lower (e.g. 6.14 wt% for ethanol, 5.00 wt% for isopropanol, 1.61 wt% for isobutanol, and 0.24 wt% for hexanol). More dilute fermentation broths result in higher processing costs (0.08, 0.11, 0.16, and 0.53 $/kg, respectively) and increased energy requirements (0.96, 1.35, 2.02 and 3.07 $kW_{th}h/kg$, respectively) of the downstream processing. Finally, it was concluded that the primary factor influencing downstream processing efficiency is the achievable product concentration in the fermentation broth, rather than the alcohol chain length.

Chapter 3 focuses on developing recovery processes for aliphatic diols that can be produced through fermentation, including 1,3-propanediol, 2,3-butanediol, 1,4-butanediol, and 1,3-butanediol. Due to their high boiling points, simple distillation is unsuitable for separating these compounds from the fermentation broth. Instead, initial separation steps are required to remove biomass, as well as large organic and inorganic molecules. These initial steps result in a clarified, desalted solution, which then undergoes further treatment through preconcentration and final purification. Since these final two steps contribute significantly to overall purification costs due to their high energy requirements, this research focuses on enhancing them to improve the efficiency of downstream processing for aliphatic diols. The preconcentration step was designed to remove

most of water along with some light impurities using a heat pump-assisted vacuum distillation. The final purification step, which separates high-purity diol from residual light and heavy impurities, was effectively carried out in a dividing-wall column. Furthermore, a general methodology for recovering high-boiling components from dilute aqueous solutions was developed. Recovery processes for 1,3-propanediol, 2,3-butanediol, 1,4-butanediol, and 1,3-butanediol, designed according to this methodology, were compared. The performance of downstream processing was primarily determined by the product concentration in the fermentation broth, though the presence of impurities also played a significant role. Nonetheless, in all cases, the proposed methodology enabled the cost-effective (total recovery costs of 0.29-0.70 $/kg) and energy-efficient (primary energy requirements of 1.35-2.01 $kW_{th}h/kg$) recovery of valuable propanediol and butanediol from dilute aqueous solutions (7.0-10.0 wt%). Lastly, adaptable process design offers the possibility of using a single process configuration to produce various aliphatic diols depending on the market demand.

Chapter 4 discusses the development of recovery processes for various organic chemicals produced through different biotechnology-based processes, such as ethyl acetate, propionic acid, 2-phenylethanol, acetic acid, furfural, etc. While these processes differ due to the unique properties of each compound, they all rely on distillation as a primary recovery method. It was employed as the main separation technique to efficiently recover propionic, acetic, and succinic acids from dilute aqueous solutions. An adaptable dividing-wall column design was demonstrated to effectively recover propionic and acetic acids or perform esterification with methanol to recover methyl-propionate and methyl-acetate (total recovery costs of 0.40-0.47 $/kg). Distillation was also utilized as the primary technique in the recovery of ethyl acetate. Due to its high volatility, most of the ethyl acetate is separated in the fermenter off-gas. Consequently, product recovery was carried out from both the vapor and liquid phases, with an azeotropic dividing-wall column used effectively for final purification (total recovery costs of 0.61-1.09 $/kg). Furthermore, distillation-based downstream processing was effectively used for the solvent recovery and final purification of 2-phenylethanol after *in-situ* product recovery by liquid-liquid extraction. An adaptable azeotropic dividing-wall column was designed to recover high-purity 2-phenylethanol or perform esterification and recover 2-phenylethyl acetate (total recovery costs of 0.64-0.73 $/kg). Lastly, a sequence of distillation steps was developed to recover by-products (acetic acid, formic acid, furfural, 5-hydroxymethyl furfural) from the lignocellulosic biomass pretreatment process using liquid hot water (total recovery costs of 0.78 $/kg). This process could enhance the competitiveness of lignocellulosic biorefineries by enabling the valorization of additional products.

Furthermore, this thesis emphasizes the importance of advancing both upstream and downstream processes simultaneously to ensure the competitiveness and viability of entire bioprocesses. While the primary focus of this research is on recovery process development, it serves as an initial step toward achieving that broader goal. Chapter 5 highlights the significance of integrating upstream and downstream processes in bioprocess development. Isopropanol, along with acetone, and 2-phenylethanol, were selected as representative examples of low-boiling and high-boiling biochemicals. Large-scale bioprocesses for their production were designed to showcase the practical application of integrated process design. Isopropanol and acetone were produced through gas fermentation, with different combinations of products (isopropanol and acetone together or separately) considered. Previously developed advanced recovery processes, including heat pump-assisted vacuum distillation, followed by heat pump-assisted atmospheric distillation and extractive distillation, were employed. Detailed techno-economic analysis and life cycle assessments demonstrated competitive economic performance (total production costs of 0.57-0.74 $/kg) and reduced environmental impacts compared to fossil fuel-based production (reduced global warming potential by 138-160%). 2-phenylethanol was produced *de-novo* through fermentation from glucose. Two different *in-situ* product recovery processes were compared: liquid-liquid extraction using oleyl alcohol and product adsorption. In both cases, distillation-based separations were used to effectively recover the solvent and obtain high-purity 2-phenylethanol. Additionally, a sensitivity analysis was conducted to examine the influence of 2-phenylethanol concentration on total production costs. This analysis revealed that minimal costs were achieved at a concentration of 1.5 g/L, with concentrations above 1 g/L not resulting in a significant reduction in costs due to increased fermentation costs. Regardless of the used *in-situ* recovery technique, the developed processes for producing 2-phenylethanol were found to be highly cost-effective (total production costs of 9.03-9.40 $/kg).

Summarizing, this thesis illustrates the significant impact that advancements in downstream processing can have on overall process performance. Specifically, it supports the development of novel advanced separation processes, based on process intensification principles, which have received relatively limited attention in industrial biotechnology. These innovations can play a decisive role in determining the feasibility of bioprocesses for industrial-scale applications. Furthermore, the importance of incorporating downstream processing at the early stages of developing biotechnology-based processes is highlighted. The findings presented in this thesis have the potential to drive progress in industrial biotechnology and contribute to the successful commercialization of biotechnology-based products.

Samenvatting

De toename van de wereldwijde energievraag versnelt het opraken van fossiele brandstofreserves versneld, wat de lange termijn energiezekerheid bedreigt. Naast de uitputting van de fossiele brandstofreserves heeft deze groeiende afhankelijkheid van fossiele brandstoffen bijgedragen aan ernstige milieuproblemen, waaronder klimaatverandering. Dit heeft geleid tot strikte milieuregels. Daarom wordt er uitgebreid onderzoek gedaan naar processen om platformchemicaliën uit duurzame bronnen te produceren. In dit opzicht is industriële biotechnologie veelbelovend om de productie van diverse chemicaliën die van fossiele brandstoffen afhankelijk zijn te vervangen. Desalniettemin zijn verbeteringen in de fermentatietechnologie en opzuivering vaak noodzakelijk om de concurrentiepositie van grootschalige bioprocessen te versterken. Veel onderzoek is gericht op de genetische modificatie van micro-organismen om de prestaties te verbeteren en het optimaliseren van de fermentatieprocessen. Echter, de product opzuivering na de fermentatie krijgt niet altijd dezelfde prioriteit. Een veelvoorkomende beperking van fermentatieprocessen is de groei- en/of productie remmende werking van de producten zelf, wat de maximale productconcentratie (titer) in de fermentatie vloeistof beperkt (vaak <10 wt%). Bovendien maken bijproducten en de aanwezigheid van micro-organismen het opzuiveringsproces na de fermentatie complexer maken. Hierdoor kunnen de kosten van het opzuiveringsproces aanzienlijk bijdragen aan de totale productiekosten (20-40% voor bulk biochemicaliën).

Een proces-systeemtechnische benadering is essentieel voor de ontwikkeling van concurrerende (bio)chemische processen, omdat het procesontwerp en -simulatie van biotechnologische processen combineert. Dit proefschrift draagt bij aan de vooruitgang van industriële biotechnologie door het ontwikkelen van geavanceerde, grootschalige downstreamprocessen voor de terugwinning van fermentatieproducten zoals alcoholen, diolen, esters, carbonzuren en aromatische verbindingen. Een systematische aanpak voor de verbetering van opzuiveringsprocessen werd toegepast door middel van verschillende casussen, georganiseerd in hoofdstukken op basis van de eigenschappen van het hoofdproduct. Aspen Plus software werd gebruikt om computer-ondersteund biochemische processen te ontwerpen. Diverse procesintensificatie technieken (zoals tussenwandkolommen (dividing-wall columns) en reactieve destillatie), warmteterugwinning en warmtepompsystemen werden onderzocht om het energieverbruik en de totale proceskosten te verlagen. De prestaties van de ontwikkelde processen werden beoordeeld door middel van economische analyses en de evaluatie van duurzaamheidsindicatoren, zoals de energiebehoefte, broeikasgasemissies, waterverbruik, waterverliezen en de impact van giftige en verontreinigende stoffen.

Hoofdstuk 2 richt zich op de ontwikkeling van opzuiveringsstrategieën voor laagkokende alcoholen geproduceerd via fermentatie, waaronder ethanol, isopropanol, isobutanol en hexanol. Aangezien deze producten voldoende vluchtig zijn, kan productremming worden verminderd door met destillatie continu het product uit de fermentatie vloeistof te verwijderen en daarna te recyclen naar de bioreactor. Warmtepomp-ondersteunde vacuüm-destillatie bleek een effectieve methode te zijn voor de eerste productterugwinning. Bovendien werd een innovatief "pass-through" destillatieproces ontworpen, specifiek voor de terugwinning van ethanol. Dit proces scheidt de verdampings- en condensatiefasen van destillatie door een absorptie-desorptie cyclus toe te voegen, waardoor goedkope koelmiddelen kunnen worden gebruikt en milde verdamping temperaturen kunnen worden gehandhaafd. Verder werd een hybride aanpak ontwikkeld, waarbij gasverdrijving werd gecombineerd met warmtepomp-ondersteunde vacuümverdamping voor de terugwinning van isobutanol. In alle gevallen verlaagde de eerste stap de scheidingstemperatuur, waardoor de resterende fermentatie vloeistof en micro-organismen konden worden hergebruikt. Dit kan de fermentatieprestaties verbeteren door biomassaverlies te voorkomen, de substraat-naar-productopbrengst te verhogen en de waterbehoefte te verminderen. Na de biomassa scheiding werd een preconcentratiestap uitgevoerd met warmtepomp-ondersteunde atmosferische destillatie om het resterende water grotendeels te verwijderen. De uiteindelijke zuiveringsmethode was afhankelijk van de eigenschappen van het hoofdproduct. Ethanol en isopropanol, die homogene azeotropen met water vormen, werden gezuiverd door middel van extractieve destillatie met ethyleenglycol. Daarentegen werden isobutanol en hexanol, die heterogene azeotropen vormen, gezuiverd door een combinatie van eenvoudige destillatie en vloeistof-vloeistof fasescheiding. Verder werd een algemene methodologie ontwikkeld voor de terugwinning van vluchtige alcoholen uit fermentatievloeistoffen. De prestaties van de ontworpen opzuiveringsprocessen werden vergeleken voor ethanol, isopropanol, isobutanol en hexanol, waarbij bleek dat langere-keten alcoholen een lagere product concentratie (titer) hebben na fermentatie, wat resulteert in hogere opzuiveringskosten en energiebehoefte. De hogere hydrofobiciteit van alcoholen met langere koolstofketensleidt doorgaans tot lagere product concentraties (titers) na fermentatie (bijvoorbeeld 6,14 wt% voor ethanol, 5,0 wt% voor isopropanol, 1,61 wt% voor isobutanol en 0,24 wt% voor hexanol). Lagere product concentraties resulteren in hogere verwerkingskosten (respectievelijk 0,08, 0,11, 0,16 en 0,53 $/kg) en een toename van de energiebehoefte (respectievelijk 0,96, 1,35, 2,02 en 3,07 $kW_{th}h/kg$) voor de opzuivering. Uiteindelijk werd geconcludeerd dat de voornaamste factor die de efficiëntie van de product opzuivering beïnvloedt, de haalbare productconcentratie (titer) in de fermentatie vloeistof is, en niet de lengte van de alcoholketen.

Hoofdstuk 3 richt zich op de ontwikkeling van efficiënte opzuiveringsprocessen voor alifatische diolen die via fermentatie geproduceerd kunnen worden, zoals 1,3-propaandiol, 2,3-butaandiol, 1,4-butaandiol en 1,3-butaandiol. Vanwege hun hoge kookpunten is eenvoudige destillatie ongeschikt om deze verbindingen direct uit het fermentatie vloeistof te scheiden. Daarom zijn eerst scheidingsstappen nodig om biomassa en grote organische en anorganische moleculen te verwijderen. Dit resulteert in een gezuiverde, ontzoute oplossing, die vervolgens verder wordt geconcentreerd en uiteindelijk opgezuiverd. Deze laatste twee stappen verbruiken veel energie, waardoor ze een groot deel van de zuiveringskosten bepalen. Daarom richt dit onderzoek zich op het optimaliseren van het concentreren en opzuiveren om de efficiëntie van het totale proces te verbeteren. In de preconcentratiestap wordt het grootste deel van het water samen met lichte onzuiverheden verwijderd via warmtepomp ondersteunde vacuümdestillatie. De uiteindelijke opzuivering, waarbij diol tot hoge zuiverheid wordt gescheiden van resterende lichte en zware onzuiverheden, vindt plaats in een tussenwandkolom. Daarnaast is een algemene methode ontwikkeld voor het terugwinnen van hoogkokende componenten uit verdunde waterige oplossingen. Op basis van deze methode zijn de terugwinningsprocessen voor 1,3-propaandiol, 2,3-butaandiol, 1,4-butaandiol en 1,3-butaandiol met elkaar vergeleken. De efficiëntie van de verwerking hangt voornamelijk af van de fermentatie productconcentratie (titer), al spelen ook aanwezige onzuiverheden en bijproducten een belangrijke rol. Toch maakte de voorgestelde methode in alle gevallen een kosteneffectieve (totale kosten van 0,29-0,70 $/kg) en energie-efficiënte (primair energieverbruik van 1,35-2,01 $kW_{th}h/kg$) terugwinning van het waardevolle propaandiol en butaandiol uit verdunde waterige oplossingen (7,0-10,0 wt%) mogelijk. Tot slot biedt een flexibel procesontwerp de mogelijkheid om met één configuratie verschillende alifatische diolen te produceren, afhankelijk van de marktvraag.

Hoofdstuk 4 behandelt de ontwikkeling van terugwinning processen voor diverse organische chemicaliën die via biotechnologische processen worden geproduceerd, zoals ethylacetaat, propionzuur, 2-fenylethanol, azijnzuur en furfural. Hoewel deze processen variëren door de specifieke eigenschappen van elke stof, speelt destillatie in alle gevallen een centrale rol als scheidingsmethode. Zo werd destillatie gebruikt als de belangrijkste scheidingsmethode voor de efficiënte terugwinning van propionzuur, azijnzuur en barnsteenzuur uit verdunde waterige oplossingen. Een flexibel ontwerp voor een tussenwandkolom bleek effectief om propionzuur en azijnzuur te scheiden of om via verestering met methanol methylpropionaat en methylacetaat te produceren (totale terugwinningskosten: 0,40-0,47 $/kg). Ook bij de terugwinning van ethylacetaat speelde destillatie de hoofdrol. Door de hoge vluchtigheid van ethylacetaat wordt

een groot deel ervan al in de fermentor afgevangen via het afvoergas. Daarom vond de productterugwinning plaats vanuit zowel de gas- als vloeistoffase, met een azeotrope tussenwandkolom voor de uiteindelijke zuivering (totale opzuiveringskosten: 0,61-1,09 $/kg). Daarnaast werd destillatie effectief ingezet voor de opzuivering van 2-fenylethanol na een *in-situ* productextractie via vloeistof-vloeistofextractie. Een flexibele azeotrope dividing-wall kolom werd ontworpen om ofwel hoogzuiver 2-fenylethanol terug te winnen, ofwel via verestering 2-fenylethylacetaat te produceren (totale opzuiveringskosten: 0,64-0,73 $/kg). Tot slot werd een reeks destillatiestappen ontwikkeld voor de opzuivering van bijproducten (azijnzuur, mierenzuur, furfural en 5-hydroxymethylfurfural) uit het voorbehandelen van lignocellulose biomassa met heet water (totale opzuiveringskosten: 0,78 $/kg). Dit proces kan de concurrentiekracht van lignocellulose bioraffinaderijen versterken door de valorisatie van extra producten mogelijk te maken.

Daarnaast benadrukt deze thesis het belang van een gelijktijdige ontwikkeling van zowel upstream- als downstreamprocessen om de concurrentiekracht en haalbaarheid van volledige bioprocessen te waarborgen. Hoewel dit onderzoek zich primair richt op de ontwikkeling van opzuiveringsprocessen, vormt het een eerste stap richting dat bredere doel. Hoofdstuk 5 benadrukt het belang van integratie tussen voorbereidende (“upstream”) en opzuiveringsprocessen (“downstream”) bij de ontwikkeling van bioprocessen. Isopropanol en aceton, en 2-fenylethanol, werden geselecteerd als representatieve voorbeelden van respectievelijk laagkokende en hoogkokende biochemische stoffen. Waarvoor, grootschalige bioprocessen werden ontworpen om de praktische toepassing van geïntegreerd procesontwerp te demonstreren. Isopropanol en aceton werden geproduceerd via gasfermentatie, waarbij verschillende productcombinaties (gezamenlijke of afzonderlijke productie) werden geëvalueerd. Voor de opzuivering werden eerder ontwikkelde geavanceerde scheidingsprocessen toegepast, waaronder warmtepomp ondersteunde vacuümdestillatie, gevolgd door warmtepomp ondersteunde atmosferische destillatie en extractieve destillatie. Uitgebreide techno-economische analyses (TEA) en levenscyclusanalyses (LCA) toonden aan dat deze processen economisch concurrerend waren (totale productiekosten van 0,57-0,74 $/kg) en bovendien een aanzienlijke verlaging van de milieu-impact opleverden ten opzichte van fossiele productie (verminderde aardopwarmingsvermogen (“Global Warming Potential”) met 138-160%). 2-fenylethanol werd via fermentatie uit glucose geproduceerd. Twee verschillende *in-situ* productopzuiveringsmethoden werden vergeleken: vloeistof-vloeistofextractie met oleylalcohol en productadsorptie. In beide gevallen werd destillatie gebruikt voor de uiteindelijke terugwinning van oplosmiddelen en de productie van hoogzuiver 2-fenylethanol. Daarnaast werd

een gevoeligheidsanalyse uitgevoerd om de invloed van de productconcentratie op de totale productiekosten te onderzoeken. Hieruit bleek dat de minimale kosten werden bereikt bij een concentratie van 1,5 g/L, terwijl concentraties boven 1 g/L nauwelijks verdere kostenreductie opleverden vanwege hogere fermentatiekosten. Ongeacht de gebruikte *in-situ* opzuiveringsmethode bleken de ontwikkelde processen voor 2-fenylethanol zeer kosteneffectief te zijn (totale productiekosten van 9,03-9,40 $/kg).

Samenvattend laat deze thesis zien hoe belangrijke verbeteringen in downstream processing de algehele procesprestaties kunnen beïnvloeden. Specifiek ondersteunt het de ontwikkeling van nieuwe geavanceerde scheidingsprocessen, gebaseerd op principes van procesintensificatie, die tot nu toe relatief weinig aandacht hebben gekregen binnen de industriële biotechnologie. Deze innovaties spelen een cruciale rol bij de economische haalbaarheid van duurzame bioprocessen op industriële schaal. Daarnaast wordt onderstreept hoe essentieel het is om product opzuivering al in de vroege ontwikkelingsfase van biotechnologische processen te integreren. De bevindingen in deze thesis kunnen bijdragen aan de vooruitgang van de industriële biotechnologie en de succesvolle commercialisatie van biotechnologische producten ondersteunen.

Сажетак

Пораст глобалне потражње за енергијом убрзава исцрпљивање резерви фосилних горива, што изазива озбиљну забринутост у погледу дугорочне енергетске сигурности. Поред исцрпљивања ресурса, растућа зависност од фосилних горива доприноси загађењу животне средине и климатским променама, због чега се уводе строге еколошке регулативе. У таквим околностима, велики број истраживања усмерен је на развој метода за добијање различитих хемикалија из обновљивих извора. Индустријска биотехнологија се у том контексту намеће као значајна алтернатива производњи хемикалија зависној од фосилних горива. Ипак, како би биопроцеси били конкурентни на индустријском нивоу, потребна су даља унапређења, пре свега у области ферментације и пречишћавања производа. До сада су највећи напори били усмерени на генетичко инжењерство микроорганизама и оптимизацију услова ферментације. Међутим, процеси пречишћавања након ферментације нису добили једнаку пажњу. Једно од кључних ограничења у процесима ферментације јесте инхибиторни ефекат самог производа на микроорганизме, што често доводи до ниских коначних концентрација производа у смеши (обично испод 10 wt%). Поред тога, формирање нуспроизвода и присуство микроорганизама додатно компликују процес пречишћавања. Као резултат свега тога, трошкови процеса пречишћавања могу чинити значајан део укупних производних трошкова (20-40% у случају масовне производње биохемикалија).

Инжењерство процесних система има кључну улогу у развоју конкурентних (био)хемијских процеса, јер омогућава примену пројектовања и симулације процеса у биотехнологији. Полазећи од тога, циљ ове тезе је унапређење индустријске биотехнологије кроз развој напредних метода за пречишћавање различитих биохемикалија, као што су алкохоли, диоли, естери, карбоксилне киселине и ароматична једињења, у условима индустријске производње. Развој процеса пречишћавања заснован је на систематичном приступу, кроз више студија случаја које су организоване у поглавља на основу карактеристика примарног производа. Aspen Plus софтвер је коришћен као један од водећих алата за рачунарски подржано процесно инжењерство. Различите технике интензификације процеса (нпр. дестилациона колона са преградним зидом и реактивна дестилација), интеграција топлоте и примена топлотних пумпи проучаване су како би се смањили енергетски захтеви и укупни трошкови процеса. Ефикасност развијених процеса оцењена је путем економске анализе и евалуације кључних показатеља одрживости, који обухватају енергетске захтеве, емисије гасова са ефектом стаклене баште, потрошњу воде, губитке воде, као и формирање токсичних материјала и отпада.

Поглавље 2 посвећено је развијању процеса пречишћавања прилагођених ферментационој производњи алколола са ниским температурама кључања, као што су етанол, изопропанол, изобутанол и хексанол. Будући да су ови алкохоли довољно испарљиви, инхибиторни ефекат крајњег производа на микроорганизме може се ублажити континуираним уклањањем производа из ферментационе смеше коришћењем дестилацијског система интегрисаним са биореактором. Вакуум дестилација потпомогнута топлотном пумпом је предложена као ефикасна метода за почетно издвајање производа. Поред тога, развијена је нова метода дестилације, „pass-through distillation“, и примењена за издвајање етанола након ферментације. Ова иновативна техника раздваја процесе испаравања и кондензације увођењем апсорпционо-десорпционог система између њих. На тај начин се ове операције могу обављати под различитим притисцима, што омогућава коришћење јефтинијих система за хлађење, уз одржавање умерених температура испаравања. Поред тога, развијен је хибридни процес који комбинује абсорпције гасом и испаравања под вакуумом уз подршку топлотне пумпе. Овај процес је примењен за почетно издвајање изобутанола. У свим случајевима, почетно уздвајање производа из ферментационе смеше под смањеним притиском снижава оперативну температуру, што омогућава поновну употребу преостале ферментационе смеше заједно са микроорганизмима. Овај приступ може побољшати ефикасност ферментационог процеса избегавањем губитка биомасе, повећањем приноса и смањењем потрошње воде. Након овог корака, спроведена је преконцентрација уз помоћ вакуум дестилације потпомогнуте топлотном пумпом како би се уклонила већина преостале воде. Примењена метода завршног пречишћавања зависила је од својстава циљног производа. Етанол и изопропанол, који формирају хомогене азеотропе са водом, пречишћавани су екстрактивном дестилацијом са етилен-гликолом. Насупрот томе, изобутанол и хексанол, који формирају хетерогена азеотропе са водом, су пречишћавани комбиновањем једноставне дестилације и фазне сепарације течност-течност. Поред конкретних процеса, развијена је општа методологија за пречишћавање испарљивих алкохола из ферментационих смеша. Ефикасности процеса пречишћавања су упоређиване за етанол, изопропанол, изобутанол и хексанол. Како се алкохоли са дужим низом угљеника одликују већом хидрофобношћу, њихове концентрације у ферментационој смеши су обично ниже (нпр. 6,14 wt% за етанол, 5,0 wt% за изопропанол, 1,61 wt% за изобутанол и 0,24 wt% за хексанол). Мања концентрација производа у ферментационој смеши доводи до већих трошкова пречишћавања (0,08, 0,11, 0,16 и 0,53 $/kg, редом) и повећаних енергетских захтевима (0,96, 1,35, 2,02 и 3,07 $kW_{th}h/kg$, редом) процеса пречишћавања. На основу ових процеса је закључено да је концентрација

производа у ферментационој смеши примарни фактор који утиче на ефикасност процеса пречишћавања, а не дужина угљеничког ланца у молекулу алкохола.

Поглавље 3 је посвећено развоју процеса пречишћавања алифатичних диола који се могу производити ферментацијом, укључујући 1,3-пропанедиол, 2,3-бутанедиол, 1,4-бутанедиол и 1,3-бутанедиол. Због високих тачака кључања ових супстанци, једноставна дестилација није погодна за издвајање ових компоненти из ферментационе смеше. Стога је неопходно најпре уклонити биомасу, као и велике органске и неорганске молекуле из ферментационе смеше. Након ових почетних корака, потребно је извршити преконцентрацију и финално пречишћавање како би се добио крајњи производ из разређеног раствора. С обзиром на то да последњи кораци значајно доприносе укупним трошковима због високих енергетских захтева, овај рад је усмерен на њихово унапређење ради побољшања ефикасности процеса пречишћавања алифатичних диола. Поступак преконцентрације је осмишљен тако да уклони већину воде заједно са неким лаким нечистоћама користећи вакуум дестилацију потпомогнуту топлотном пумпом. Завршни корак пречишћавања, који раздваја диол високе чистоће од осталих лакших и тежих нечистоћа, може ефикасно бити спроведен у дестилационој колони са преградним зидом. Такође, развијена је општа методологија за пречишћавање компонената са високим тачкама кључања из разређених водених раствора. Процеси пречишћавања за 1,3-пропанедиол, 2,3-бутанедиол, 1,4-бутанедиол и 1,3-бутанедиол, који су развијени према овој методологији, упоређени су у овом раду. Перформансе процеса пречишћавања у великој мери зависе од концентрације производа у ферментационој смеши, иако је присуство нечистоћа такође има значајан утицај. У свим случајевима, предложена методологија омогућила је економично (укупни годишњи трошкови од 0,29-0,70 $/kg) и енергетски ефикасано (потреба за примарном енергијом од 1,35-2,01 $kW_{th}h/kg$) пречишћавање вредних пропанедиола и бутанедиола из разређених водених раствора (7,0-10,0 wt%). На крају, прилагодљиви дизајн процеса омогућава употребу исте процесне конфигурације за производњу различитих алифатичних диола, у зависности од захтева тржишта.

У поглављу 4 су развијани процеси пречишћавања различитих органских хемикалија произведених биотехнолошким процесима, као што су етил ацетат, пропионска киселина, 2-фенилетанол, сирћетна киселина, фурфурал и други. Иако се ови процеси разликују због јединствених својстава сваке компоненте, сви они користе дестилацију као главну методу за пречишћавање. Дестилација је примењена као главна техника за ефикасно пречишћавања пропионске, сирћетне и сукцинске киселине из разређених

водених раствора. Развијен је дизајн дестилационе колоне са преградним зидом који је ефикасано примењен за раздвајање пропионске и сирћетне киселине или за извођење естерификације са метанолом ради добијања метил-пропионата и метил-ацетата (укупни трошкови пречишћавања од 0,40-0,47 $/kg). Такође, дестилација је коришћена као основна техника за пречишћавање етил ацетата. Због високе испарљивости, већина етил ацетата се одваја у гасовитој фази из ферментатора, док мање количине остају у течној фази. Стога је пречишћавање производа извршено из обе фазе уз ефективну употребу азеотропске дестилационе колоне са преградним зидом за финално пречишћавање (укупни трошкови пречишћавања од 0,61-1,09 $/kg). Процес пречишћавања заснован на дестилацији успешно је коришћен и за регенерисање растварача и финално пречишћавање 2-фенилетанола након *in-situ* издвајања производа коришћењем екстракција течно-течно. Дизајнирана је азеотропска дестилациона колона са преградним зидом за пречишћавање 2-фенилетанола или за извођење естерификације и издвајање 2-фенилетил ацетата (укупни трошкови пречишћавања од 0,64-0,73 $/kg). На крају, развијен је низ дестилационих корака за пречишћавање споредних производа (сирћетна киселина, мравља киселина, фурфурал, 5-хидроксиметилфурфурал) из процеса третмана лигноцелулозне биомасе топлом водом (укупни трошкови пречишћавања 0,78 $/kg). Овај процес може значајно повећати конкурентност лигноцелулозних биорафинерија омогућавањем повећања производних капацитета.

Осим тога, ова дисертација истиче важност истовременог унапређења како процеса ферментације, тако и процеса пречишћавања, како би се осигурала конкурентност и одрживост целокупних биопроцеса. Ово истраживање, чији је примарни фокус на развоју процеса пречишћавања производа, представља тек почетни корак ка остварењу ширег циља. Поглавље 5 истиче важност интеграције процеса ферменације и пречишћавања током развоја биопроцеса. Изопропанол и 2-фенилетанол су одабрани као представници биохемикалија са ниским, односно високим тачкама кључања. Биопроцеси за њихову индустријски производњу су дизајнирани како би се показали практична примена интегрисаног приступа процесном инжењерству. Изопропанол и ацетон су произведени гасном ферментацијом, при чему су разматране различите комбинације производа (заједничка или одвојена производња изопропанола и ацетона). Примењен је раније развијен процесс пречишћавања, који укључује вакуум дестилацију потпомогнуту топлотном пумпом, атмосферску дестилацију такође потпомогнуту топлотном пумпом, и екстрактивну дестилацију. Детаљне техно-економске анализе и процене животног циклуса потврдиле су економску конкурентност (укупни

трошкови производње износили су 0,57-0,74 $/kg) и значајно смањење утицаја на животну средину у поређењу са производњом заснованом на фосилним горивима (смањен потенцијал глобалног загревања за 138-160%). С друге стране, 2-фенилетанол је добијен *de-novo* ферментацијом из глукозе. Разматране су две различите стратегије *in-situ* издвајања производа из ферментационе смеше: екстракција течно-течно уз употребу олеил алкохола и адсорпција производа. У оба случаја, након обих почетних корака, примењени су дестилациони процеси који су омогућили ефикасану сепарацију растварача и издвајање 2-фенилетанола високе чистоће. Поред тога, спроведена је анализа како би се испитало како концентрација 2-фенилетанола у ферментационој смеши утиче на укупне трошкове производње. Резлтати су показали да се минимални трошкови постижу при концентрацији од 1,5 g/L, док повећање концентрације изнад 1 g/L не доноси значајно смањење трошкова због скупљег процеса ферментације. Без обзира на примењену *in-situ* технику издвајања производа, развијени процеси за производњу 2-фенилетанола показали су се као веома економски исплативи, са укупним трошковима производње између 9,03-9,40 $/kg.

У закључку, ова докторска дисертација илуструје значајан утицај који напредак у процесима пречишћавања може имати на укупну ефикасност биопроцеса. Конкретно, ова теза подржава развој напредних процеса сепарације, заснованих на принципима интензификације процеса, који су добили релативно ограничену пажњу у индустријској биотехнологији. Иновације у процесима пречишћавања могу играти кључну улогу у одлучивању ефикасности биопроцеса на индустријском нивоу. Поред тога, наглашена је важност интеграције процеса пречишћавања већ у раним фазама развоја биотехнолошких процеса, чиме се омогућава постизање веће ефикасности и економске одрживости. Резултати представљени у овој дисертацији могу значајно допринети унапређењу индустријске биотехнологије и бити подстицај за успешну комерцијализацију биотехнолошких производа.



1 | Introduction

1. Introduction

Наука је као апстракција, једна врста поезије. (Михајло Пупин, физичар и инжењер електротехнике, познат по проналасцима из области телекомуникација)

Science is like abstraction, a kind of poetry. (Mihajlo Pupin, physicist and electrical engineer, famous for innovations in the sphere of telecommunications)

The recovery and purification of fermentation products are essential for the successful commercialization of many bioprocesses [1]. While fermentation enables biological production of valuable compounds, downstream processing transforms these raw microbial products into final products that meet market standards. Accordingly, downstream processing performance is crucial for the overall bioprocess performance, underscoring the need for efficient and cost-effective strategies. Nonetheless, compared to the extensive research and innovation in strain development and fermentation technologies, the development of downstream processing has received significantly less attention. Hence, this thesis seeks to address this research gap by developing cost-effective and energy-efficient recovery processes for industrial-scale fermentative production. Implementation of advanced process intensification principles minimizes the need for an external energy supply by maximizing energy recovery within the system. Reduced energy requirements can potentially result in more stable operations in times of uncertain energy supply. Moreover, the implementation of process intensification methods may significantly decrease greenhouse gas emissions, leading to more sustainable bioprocesses. For those who remain sceptical about the transformative effects advancements in downstream processing may have on the overall performance of the bioprocess, this thesis aims to provide clear and compelling evidence. However, before delving into innovations in downstream processing, it is important to explore the broader context of fundamental drivers behind the development of industrial fermentation.

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1.1. Industrial biotechnology as the main pillar for sustainable development

Extensive consumption of fossil carbon sources has resulted in significant environmental pollution and climate change. Furthermore, concerns over energy security are increasing due to the rapidly diminishing availability of fossil fuels [2]. As an attempt to address these growing issues, international efforts have been made to effectively respond to climate change by reducing greenhouse gas emissions and limiting global warming [3]. Moreover, increasingly stringent environmental regulations are imposing additional constraints on process development. Economic growth has been closely tied to negative environmental impact since Industrial Revolution. To sustain and advance economic growth, it is essential to break this link and pursue more sustainable pathways [4]. The overall goal requires finding an alternative for most of the oil, coal and gas used for energy supply, and the production of different materials and chemicals [5]. In that respect, industrial biotechnology presents a key technology for future economic development [6–8]. It challenges the traditional industrial processes by breaking the cycle of fossil carbon consumption [4]. Industrial biotechnology uses outstanding capabilities of microorganisms and/or enzymes to convert renewable feedstocks, or intermediates derived from these feedstocks, into higher-value-added products in various sectors (e.g. chemicals, food and feed, pharmaceuticals, fuels, etc.) [9]. Production of various biochemicals, especially platform chemicals and biofuels (e.g. ethanol, isopropanol, butanol, isobutanol, acetone, acetic acid, etc.), has a significant potential to enhance energy security, reduce greenhouse gas emissions [10], enable new economic opportunities for the development of rural areas and decentralize the production of biofuels. Hence, industrial biotechnology may significantly contribute to all three main pillars of sustainability: environmental, economic and social.

Several key technologies are already available for the production of various biochemicals from renewable sources [11]. Technologies for producing first-generation biofuels are already mature and well-established. However, the dominant feedstock is biomass that can be used for dietary purposes, such as corn or sugarcane. For this reason, the major drawback of first-generation biofuels is that their production directly threatens food availability [12]. Alternatively, lignocellulosic biomass, which is a significant non-fossil-derived energy resource [13], can be used to produce second-generation biofuels [14]. Lignocellulosic fermentation is a way to turn energy-dense lignocellulosic materials, which would otherwise be wasted, into different platform chemicals and biofuels. The second-generation biofuel production method by lignocellulosic fermentation can strengthen energy security without competing with food production [15,16]. Besides ethanol, higher alcohols (e.g. isobutanol, butanol, hexanol) can also be obtained by the fermentation from carbohydrate-based substrates [17].

As an alternative to lignocellulosic fermentation, gas fermentation can be implemented to convert syngas into different valuable chemicals such as ethanol, isopropanol, acetone, etc. Since microorganisms tolerate various impurities and variations in gas composition, gas from biomass gasification or even waste gases from different industries (e.g. steel industry) can be used as a syngas source for fermentation [18]. In the case of (fossil-based) syngas derived from the steel industry, employing it as a substrate for producing biochemicals offers considerable environmental benefits. Even though microorganisms are tolerant to a wide range of impurities and do not require strict standard syngas purity, high concentrations of some impurities (especially tars, nitric oxide, ammonia and hydrogen sulfide) might negatively affect microbial growth and product formation. To avoid such effects, a gas clean-up step (e.g. tar cracking, wet cleaning, usage of active carbon, etc.) is commonly implemented before the fermentation. Thus, removing potentially present impurities from the syngas would prevent any possible complications in the fermentation and recovery processes [19].

Compared to petrochemical production pathways, fermentation processes offer several advantages, including relatively mild fermentation conditions, the ability to utilize a diverse array of substrates (lignocellulosic biomass, municipal waste, organic waste biomass, and industrial off-gases), and a reduced environmental impact compared to traditional fossil fuel-based processes [20]. Despite fast development, significant improvements are still needed to make technologies for the production of biofuels and biochemicals from renewable sources competitive with fossil carbon-based processes [21]. Process systems engineering (PSE) is essential to translate biotechnology innovations into cost-effective and energy-efficient industrial-scale processes. In this context, the focus of PSE is on the multi-scale integration of processing methods for optimal functional performance of (bio)chemical manufacturing processes in a (sustainable) supply chain setting, while absorbing suitable process intensification methods within that setting [22]. Thus, PSE supports optimal usage of renewable resources in several ways: integration of various components of sustainable energy systems (e.g. energy from biomass, wind, solar, etc.), optimization of individual process operations, design and optimization of large-scale processes, incorporation of data-driven models for decision making, implementation of optimal scheduling and process control strategies, selection of the feedstock, optimization of supply chains, life cycle assessment and risk analysis, techno-economic evaluation of renewable energy projects, and so on.

1.2. Importance of downstream processing for competitive industrial-scale bioprocesses

The conventional bioprocess design approach implies starting from lab-scale experiments and scaling up the production process through a set of trial-and-error incremental steps. However, this approach may not be efficient enough to satisfy increasing market demand. To enable more efficient bioprocess development, it was suggested to "start with the end in mind" [9]. An industrial-scale bioprocess, including the downstream process, market size of product and feedstock availability, should be considered before defining the upstream process. Thus, both genetic engineering to enhance strain performance and resistance, and process development are necessary to ensure successful commercialization [23,24].

To date, significant effort has been put into the genetic engineering of microorganisms and optimization of the fermentation part in biochemical production processes [25]. However, downstream processing (DSP) of biochemicals on a large scale has not been studied that well. The main goal of DSP is to effectively recover the target product at the desired specifications from the bioreactor effluent [26]. Besides fermentation yield, productivity and product titer, downstream processing efficiency is the main indicator of bioprocess performance on an industrial scale [9]. The efficiency of DSP is strongly influenced by the upstream fermentation process. Small changes in the fermentation process may either significantly simplify or complicate the design of the recovery process [1].

The major limitation for widespread industrial production of various biochemicals by fermentation is the relatively low concentrations of products that can be achieved due to the toxic effect these chemicals often have on the microorganisms (so-called end-product inhibition phenomenon) [27]. When highly dilute aqueous streams are obtained, purification in a cost- and energy-efficient way is challenging. Due to low product concentrations, large equipment sizes are needed to achieve production scales that would be comparable to those of conventional petrochemical processes [28]. Large equipment is closely associated with high capital and operating costs, both for upstream and downstream processes. The end-product inhibition phenomenon remains a persistent problem for industrial-scale fermentation processes. For instance, one way to mitigate this drawback in the fermentative production of alcohols is to continuously remove inhibiting products from the broth by applying concurrent alcohol recovery and fermentation (CARAF) [27].

Another challenge in choosing the proper operating conditions for recovering valuable biochemicals from dilute fermentation broths is the presence of living microorganisms. Besides water and fermentation products, fermentation broth contains some biomass, gases and low concentrations of different non-volatile components [29]. Depending on the specific fermentation requirements, it may be possible to avoid significant loss of microbial biomass by allowing broth recycling to the fermentation after product separation. This approach may enhance the upstream fermentation process by increasing substrate-to-product yield and reducing fresh water requirements [19]. Therefore, operating conditions for the initial separation of valuable products from the broth should not harm microbial viability. Specifically, temperatures much higher than the optimal fermentation temperatures should be avoided for this initial separation. Furthermore, the usage of additional chemicals that might be toxic to the cells should be avoided. Depending on the product volatility, different recovery techniques can be implemented for this initial separation.

Thermodynamic constraints are frequently another challenge for the recovery of fermentation products from diluted broth. Many well-known bioproducts (ethanol, butanol, isopropanol, etc.) have boiling points close to that of water [30]. An additional complication is that azeotropes are commonly present (e.g. ethanol-water, isopropanol-water, butanol-water, isobutanol-water, 2-phenylethanol-water, etc.). An azeotrope is a mixture of two or more components that boils at a constant temperature and maintains a fixed composition in both the liquid and vapor phases. This unique characteristic means the components of an azeotropic mixture cannot be separated by simple distillation and more complex separation techniques are required. Lastly, some products have high boiling points (e.g. 1,3-propanediol, butanediols, 2-phenylethanol, etc.), which makes their separation from dilute aqueous solutions energy-intensive.

From a PSE viewpoint, there are also challenges related to e.g. bioprocess synthesis and design, process flowsheet optimization, economic viability and improvements of sustainability metrics.

As a result of all the mentioned limitations of fermentation processes, the cost of DSP can significantly impact the total production costs. Generally, the cost of DSP contributes 20-40% to the total production costs for bulk fermentation products [31]. Thus, efficient downstream processing is essential for cost-competitive bioprocesses. Besides reducing the total production costs, advanced downstream processing can reduce the overall energy requirements, greenhouse gas emissions and water requirements, leading to more sustainable bioprocesses that would facilitate an effective transition from fossil fuels to renewable alternatives.

1.3. Literature review on the main separation techniques in bio-based processes

There are numerous separation techniques available for recovering bio-based chemicals. Efficient recovery of bio-based chemicals from fermentation processes requires a well-structured approach often involving multiple stages of separation. The initial separation step focuses on recovering the product from the complex fermentation broth containing microbial cells, nutrients, and by-products. An important innovation in biobased process intensification is *in-situ* product recovery (ISPR), where the fermentation process is integrated with continuous product removal. This approach can significantly enhance fermentation yield and productivity by reducing inhibitory effects caused by product accumulation, while also minimizing downstream processing challenges and operational costs [32,33]. Nonetheless, after this initial separation step, additional purification is commonly needed to achieve the high-purity standards necessary to meet market requirements.

This section presents an overview of the primary separation techniques commonly employed for recovering bio-based chemicals, classified based on the dominant mechanism or driving force for the separation process [34,35]. More detailed literature reviews of the fermentation and recovery processes for producing specific chemicals are provided at the beginning of each section.

1.3.1. Phase-change separations

Distillation is a separation method that separates components of a mixture based on the volatility of these components. It is widely applied in the chemical and biochemical industries [35]. There are different types of distillation processes, such as ordinary distillation, azeotropic distillation and extractive distillation (see Figure 1-1). **Ordinary distillation** separates components based on their relative volatilities or the difference in their boiling points [36]. Nonetheless, this type of distillation cannot be employed to separate components that form azeotropes (e.g. ethanol and water). In the case of azeotrope formation, components cannot be separated by simple distillation and alternative techniques need to be employed (e.g. azeotropic or extractive distillation). **Azeotropic distillation** implies the addition of an entrainer that forms an azeotrope with one of the components from the mixture. Alternatively, **extractive distillation** implies the addition of an extractant that does not form an azeotrope with any of the components [36]. In both cases, the separation of components is achieved by altering their relative volatilities. Ordinary distillation can be employed to separate and preconcentrate bioalcohols from dilute aqueous broth, while azeotropic or extractive distillation methods can be implemented to dehydrate these alcohols and produce high-purity final products. Additionally, distillation can be used to purify biodiesel [35].

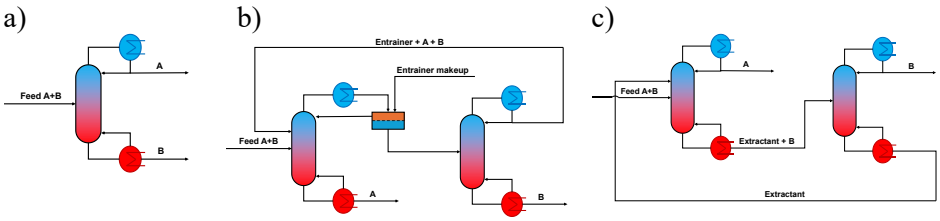


Figure 1-1. Schemes of a) ordinary distillation, b) azeotropic distillation and c) extractive distillation

Furthermore, **molecular distillation** is a specialized form of vacuum distillation that is designed to separate thermally sensitive components such as essential oils, pharmaceuticals, etc. It implies operation under very low pressure and minimized distance between evaporator and condenser to reduce the residence time. This method has been employed in the separation of bio-oils [37], purification of biodiesel [38], or isolating heat-sensitive components from biomass [36].

Hence, there are various applications of distillation in the recovery of bio-based chemicals. However, it is traditionally considered an unsuitable separation method for recovering fermentation products due to the presence of thermally sensitive components. Furthermore, distillation was assumed to be too energy-intensive for recovering fermentation products from the highly diluted broth [39].

Precipitation and **crystallization** are processes in which a substance is separated from a fluid by forming solid particles (see Figure 1-2). The precipitation process often implies the sudden aggregation of particles, whereby the formed structures are amorphous. Alternatively, in the crystallization process, the formed structures are highly organized, structured solid crystals. These processes can be induced by different factors such as changes in pH or temperature, addition of reagents, solvent evaporation, etc. Precipitation is often used for recovering carboxylic acids from fermentation broths (e.g. citric and succinic acid) [40]. Furthermore, these methods can be used for isolating proteins from aqueous solutions, recovering hemicelluloses from pretreated hydrolysates through ethanol precipitation [41], extracting lignin from kraft black liquor via acid precipitation, etc. [42,43].

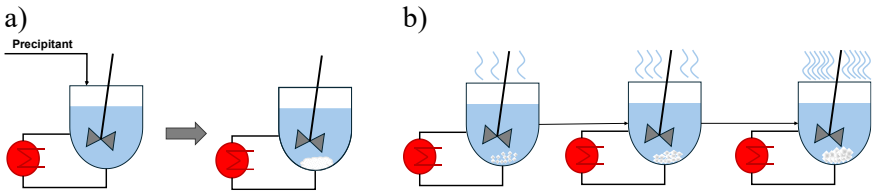


Figure 1-2. Schemes of a) precipitation and b) crystallization processes

1.3.2. Affinity-based separations

Liquid-liquid extraction involves separating components from a liquid mixture by introducing a second immiscible liquid, where the target component preferentially dissolves (see Figure 1-3). It is crucial for separating many biochemicals, whereby it is particularly effective for the recovery of high-boiling components or thermo-sensitive components present in very low concentrations in the fermentation broth. By implementing liquid-liquid extraction, the need to evaporate large amounts of water is mitigated. It has been frequently studied for recovering carboxylic acids from fermentation broths (e.g. citric, lactic, succinic acid, etc.). Thereby, different extractants have been proposed, such as amine-based (primary, secondary or tertiary amines), ionic (quaternary ammonium and imidazolium salts) or neutral extractants (hydrocarbons or oxygenated hydrocarbons without charged groups). In most cases, clarified broth containing valuable acid and impurities is sent to the extraction process. Carboxylic acid can be extracted from the broth while leaving impurities in the aqueous stream. In the next step, carboxylic acid can be transferred to an aqueous phase in the back-extraction step. Lastly, this aqueous phase can be purified to obtain the final acid product, while an additional regeneration step may be needed to allow the reuse of the solvent [40].

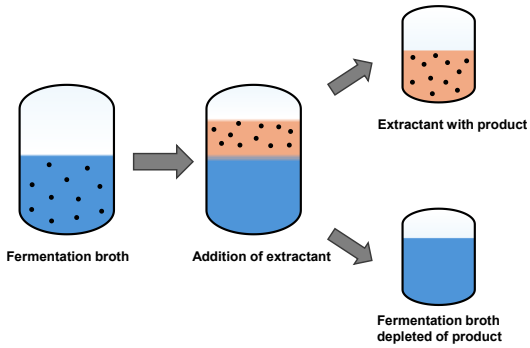


Figure 1-3. Scheme of liquid-liquid extraction

Besides recovering carboxylic acids, liquid-liquid extraction can be used for *in-situ* recovery of valuable fermentation products whose concentrations in the fermentation broth are very low. For example, different extractants have been studied for *in-situ* product recovery of 2-phenylethanol from fermentation broth, such as oleyl alcohol [44], oleic acid [45], polypropylene glycol [46] and ionic liquids [47].

Furthermore, **membrane extraction** is a special hybrid separation method in which a membrane acts as a selective barrier, allowing specific components of a liquid mixture to pass through while retaining others. It combines liquid-liquid extraction principles with membrane technology, providing controlled mass transfer without direct mixing of the phases. This technique can be used to remove

impurities (sulfuric acid, acetic acid, 5-hydroxymethyl furfural and furfural) from biomass hydrolysates in biofuel production. These impurities are formed during the biomass pretreatment step, which is needed to open the biomass structure and enable further enzymatic hydrolysis and fermentation steps. Nonetheless, these impurities are toxic to the microorganisms and their removal is crucial for the efficiency of the whole process. The major advantage of using membrane extraction for this process is preventing the formation of persistent emulsions and minimizing the phase toxicity effects [48,49].

Supercritical fluid extraction employs supercritical fluids to extract target compounds from a solid matrix or liquid mixture. The most widely used extractant in the food, pharmaceutical and chemical industries is supercritical CO_2 [34]. Supercritical fluid extraction is well-suited for extracting hydrophobic components such as pigments, phenolics, carotenoids, and lipids from biomass. However, the need for high-pressure conditions increases operational costs [35].

Solid-liquid extraction is a process used to separate soluble components from solid biomass using a liquid solvent. It can include traditional extraction methods as well as advanced techniques like ultrasound- and microwave-assisted extraction and pressurized subcritical liquid extraction [35]. This process may be employed to reduce biofuel production costs by extracting valuable components from biomass (e.g. phenolics, terpenes, sterols, enzymes, pigments, etc.) and facilitating their valorization [34].

Absorption is a separation process in which a gas or vapor is transferred into a liquid phase, either by physically dissolving (**physical absorption**) or reacting chemically (**chemical absorption**) with the liquid. In biorefineries, it is used to remove acid gases (H_2S and CO_2) from syngas before using it in a bioprocess (see Figure 1-4). Commonly, physical absorption processes use dimethyl esters or polyethylene glycol (Selexol process), cold methanol (Rectisol process), N-methyl-2-pyrollidone (Purisol process) and propylene carbonate (FLUOR process). Alternatively, the best-known chemical absorption process is based on aqueous methyldiethanolamine [34].

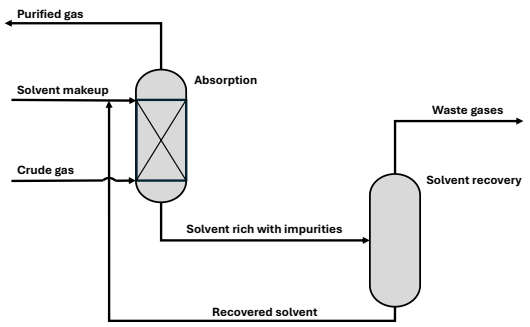


Figure 1-4. Scheme of absorption process

Adsorption implies the adhesion of molecules from a fluid onto the surface of a solid adsorbent. In biorefineries, it can be used for the *in-situ* recovery of fermentation products from a highly dilute broth (e.g. aromatic components, see Figure 1-5). Besides initial product recovery, adsorption can be used in the later separation and purification steps. For example, molecular sieves can be used to purify biofuels (e.g. ethanol-water system) [36]. Additionally, adsorption has been proven effective for removing inhibitors from biomass hydrolysates (furans, phenolics and acetic acid) [34] and impurities from raw biodiesel (glycerol, methanol, free fatty acids, and metals) [50].

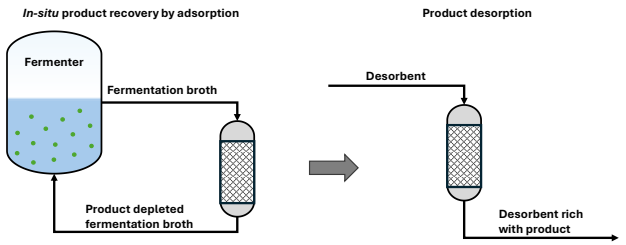


Figure 1-5. Scheme of the adsorption process

1.3.3. Size and/or charge-based separations

Membrane separation is a process in which a selective barrier (membrane) is used to separate components in a mixture based on differences in size, charge, or chemical affinity [51]. The mixture is passed through the membrane, allowing certain substances to pass through while retaining others. **Microfiltration** (0.050 to 10 µm), **ultrafiltration** (1 to 100 nm), and **nanofiltration** (<2 nm) are commonly applied based on the size of the molecules to be separated. These methods have been widely researched for application in various bioprocesses [52]. They play particularly significant roles in biorefineries, where solid biomass is a primary feedstock (see Figure 1-6). Furthermore, membrane separations can be used for purifying biodiesel [50], removing inhibitors, harvesting algal biomass, separating hemicelluloses from biomass hydrolyzates or pulp mill process water, recovering lignin from pulp mill waste or prehydrolysis liquor, etc [34]. Additionally, they can be employed for liquid mixture separations, as well as gas separations and purification [35].

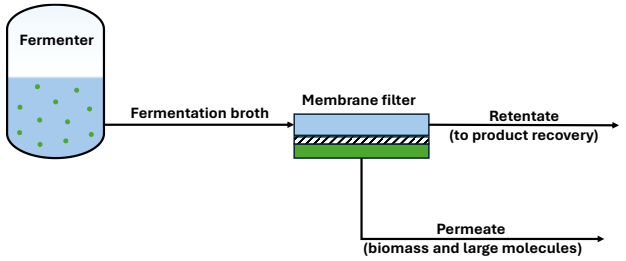


Figure 1-6. Removal of biomass and large molecules by membrane separation

Specialized membrane separation techniques are membrane pervaporation and pertraction. **Membrane pervaporation** is a separation process in which a liquid mixture is selectively permeated through a non-porous membrane, with one or more components vaporizing on the other side of the membrane and then being condensed. **Membrane pertraction** is a similar process where a liquid or gas mixture passes through a membrane, and the permeated components are absorbed by a receiving phase, often a liquid, on the other side of the membrane [53]. Both processes are highly selective and efficient and can be used for separating components and removing inhibitors in bio-based processes.

Centrifugation is widely used in bio-based processes to separate components based on their density by applying a rapid rotational force. This technique efficiently isolates particles, such as cells, cellular debris, proteins, or lipids, from liquid mixtures, making it essential in various biotechnological industries such as food production and pharmaceuticals (see Figure 1-8).

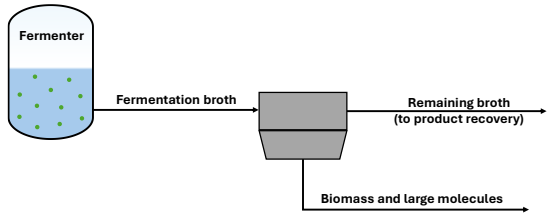


Figure 1-7. Removal of biomass by centrifugation

Ion exchange is a separation process in which ions in a liquid are exchanged with similarly charged ions from a solid resin or material. This process occurs when a solution containing unwanted ions passes through a medium that selectively attracts and replaces those ions with ions of the same charge. In bio-based processes, it can be used for the recovery of carboxylic acids (see Figure 1-8) [40]. In the recovery of 1,3-propanediol and butanediols after fermentation, ion exchange can be used to remove remaining inorganics from clarified broth. Additionally, this method can be used to remove inhibitors from biomass hydrolysates [54] and eliminate impurities from biodiesel [55].

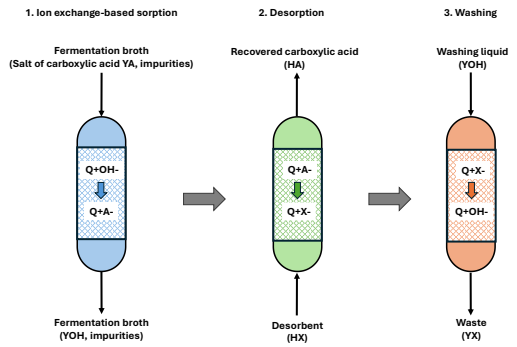


Figure 1-8. Ion exchange-based sorption process for recovery of carboxylic acids [40]

Electrodialysis is an electrochemical separation process that uses an electric field to drive the movement of ions through selective ion-exchange membranes. In bio-based processes, it is commonly mentioned for the separation of carboxylic acids from fermentation broths [40,52].

Chromatography is a separation method in which components of a mixture are separated based on their differential interactions with a stationary phase and a mobile phase. This method is highly versatile and widely used for the purification and recovery of high-value bio-based products, including amino acids, peptides, proteins, and bioactive compounds. Common types of chromatography used in bio-based processes include ion and cation exchange chromatography (recovery of carboxylic acids), gel filtration (protein purification), affinity chromatography and high-performance liquid chromatography [56].

1.3.4. Reactive separations

In addition to the previously described separation processes, process intensification principles can be applied by integrating separation and reaction into one equipment unit. Besides reduced equipment costs, combining chemical reaction with product separation can result in increased yield, selectivity and productivity while reducing energy requirements. Some examples of reactive separation are mentioned below.

Reactive distillation combines chemical reaction and distillation in a single unit (see Figure 1-9). In addition to lowering capital costs, it offers benefits such as energy savings, the ability to overcome equilibrium limitations, enhanced product selectivity, improved separation efficiency, and reduced reactant usage, which simplifies the recovery process [57]. It has been proven to be very efficient in biodiesel production [58]. Furthermore, reactive distillation has been successfully implemented to produce different fatty esters. This process resulted in a stoichiometric reactant feed rate and the elimination of the distillation column for separating alcohol-water mixtures [59]. Additional heat integration further reduced the energy requirements of the reactive distillation system by about 45% [60]. Furthermore, esterification of different carboxylic acids and simultaneous separation in a reactive distillation column have been studied for different carboxylic acids, such as succinic and acetic acid [61,62].

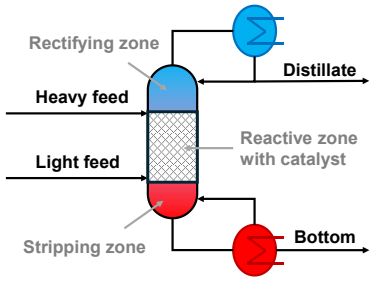


Figure 1-9. Scheme of reactive distillation

Reaction-membrane separations include membrane bioreactor and bioreactor-membrane pervaporation, bioreactor-membrane distillation, etc. Membrane bioreactors can be used for biodiesel production and refining. The benefits of these systems include high yield, as well as high purity and quality of the produced biodiesel. The potential drawbacks of these systems are fouling effects and membrane stability [63]. Furthermore, fermentation integrated with pervaporation has been studied for *in-situ* removal of butanol product [64]. Similarly, fermentation has been combined with bipolar membrane electrodialysis for succinic acid [65].

Reactive adsorption combines reaction and adsorption in one equipment unit. It has been previously applied in biodiesel production to simplify the process by eliminating conventional catalyst-related operations [66].

1.3.5. Research gaps

The diverse range of available separation techniques underscores the absence of a universal approach to designing separation processes. The selection of the most suitable recovery technique(s) should be based on factors such as the achievable product concentrations, thermodynamic properties, and the presence of other components such as by-products, microorganisms, or impurities. Hybrid processes integrating multiple techniques, including liquid-liquid extraction, adsorption, distillation and chemical reaction, may yield the most efficient and scalable results. Nonetheless, despite the critical importance of DSP in bio-based production, it remains a relatively underexplored area on an industrial scale. While advancements in fermentation technologies have led to increased production of biochemicals, the development of efficient and scalable DSP methods has not kept pace. This disparity poses significant challenges to the economic viability and large-scale bio-based processes.

One key issue is that fermentation processes are often developed with minimal consideration for the downstream separation and purification steps required to recover target products. As a result, DSP may become a bottleneck, leading to inefficiencies, increased operational costs, and difficulties in achieving high-purity products. Existing experimental studies on DSP primarily focus on small-scale systems, which may not directly translate to industrial-scale operations. These small-scale experiments often provide valuable insights but can sometimes lack the scalability needed to address challenges associated with large production volumes. More precisely, factors such as energy consumption, solvent usage, equipment design, and operational stability must be carefully evaluated and optimized for industrial applications. Furthermore, while numerous separation techniques have been explored, there is limited research on the integration and optimization of these methods for industrial-scale bio-based

processes. Process intensification strategies, such as reactive separations and hybrid separation techniques, hold significant promise but remain underutilized.

To bridge these research gaps, this thesis focuses on large-scale downstream processing, with a primary emphasis on fluid separation techniques. The research explores the application of various separation methods, particularly intensified distillation processes, for recovering a range of fermentation products, including alcohols, diols, esters, carboxylic acids, and aromatic compounds. While many bioproducts are outside the scope of this work, the study aims to tackle the challenges of industrial-scale processing and contribute to the development of more efficient, cost-effective, and sustainable methods for bio-based production processes.

1.4. Research questions

Process design and simulation play a vital role in the development of sustainable (bio)chemical processes, allowing the application of a process systems engineering approach in biotechnology [23,24]. In that respect, the main goal of this research is to improve the competitiveness of industrial biotechnology by developing advanced large-scale downstream processes, based on process intensification principles, for the recovery of various biochemicals after fermentation. Fermentation broth contains a mix of target product(s), by-products, various impurities and microorganisms, which makes the separation process especially challenging. Consequently, large-scale recovery processes after fermentation are often assumed to be quite costly and energy-intensive. This thesis aims to debunk this assumption by developing cost-effective and energy-efficient large-scale recovery processes for various fermentations. To achieve this goal, the following research questions have been addressed:

1. ***Which fluid separation techniques can be used to efficiently recover low-boiling fermentation products?***

Various volatile bioalcohols are valuable platform chemicals (e.g. ethanol, isopropanol, butanol, isobutanol, etc.). Hence, a lot of research effort has been put into developing fermentation processes for producing them. These processes have similar drawbacks, such as low product concentrations and the presence of microorganisms. Furthermore, volatile bioalcohols often have close-boiling points and form azeotropes with water. Due to similarities in the composition of fermentation broth and due to similar thermodynamic constraints, developing one methodology to streamline the design of downstream processing after fermentation would be highly beneficial. In addition to volatile bioalcohols, this methodology may be suitable for recovering other volatile components from highly diluted aqueous solutions (e.g. acetone, ethyl acetate, etc.).

2. ***Which fluid separation techniques can be used to efficiently recover high-boiling fermentation products?***

Besides producing volatile chemicals, fermentation can be used to generate valuable non-volatile compounds such as 1,3-propanediol, butanediols and 2-phenylethanol, among others. Similar to the recovery of volatile products, DSP in these cases must address challenges such as low product concentrations and the presence of microorganisms. However, the high boiling points of these compounds further complicate the recovery process. Depending on the boiling temperature and achievable broth concentration of the main product, different designs of the recovery process will be the most efficient.

3. ***How can process intensification principles be applied to fluid separation techniques to reduce energy requirements and costs of downstream processing (and the entire bioprocess)?***

Process intensification (PI) seeks to enhance process efficiency by offering novel solutions to reduce energy requirements, environmental footprint, total costs, safety risks and required processing volume. DSP is often one of the most energy-intensive steps, representing a significant portion of the overall process costs and environmental impact. Hence, developing advanced DSP based on PI techniques may significantly enhance the overall performance of the bioprocess. In that respect, this thesis explores ways innovative approaches of PI can be applied to different recovery processes, with particular attention to large-scale processes.

4. ***In what ways can process systems engineering (PSE) methods support the development of industrial biotechnology for the production of distillable biochemicals?***

Process systems engineering (PSE) focuses on making informed decisions across a range of scales, from molecular to enterprise levels, to improve efficiency, scalability, and sustainability. This research investigates how PSE methods can support the development of industrial biotechnology by developing processes that are energy-efficient, environmentally sustainable and cost-effective.

5. ***How does product concentration in the fermentation broth influence downstream processing performance for recovering distillable biochemicals?***

It is often emphasized that high product titer is a key factor in improving bioprocess competitiveness by facilitating DSP. Higher product concentrations in the fermentation broth undoubtedly result in less cost- and energy-intensive DSP. Nonetheless, high product concentrations may lead to a less efficient upstream fermentation process due to the end-product inhibition effect. Hence, analyzing the effects of initial product concentrations on the performance of DSP may be

crucial for developing an optimal bioprocess. Such a bioprocess integrates upstream and downstream parts, functioning most efficiently as a whole, while individual parts may be suboptimal. The results of this research, which focuses on DSP, should be coupled with relevant data from the upstream fermentation process to obtain a complete picture of the bioprocess performance.

1.5. Thesis outline

A systematic development of advanced downstream processes for the purification of commonly produced biochemicals has been performed through several case studies. Accordingly, this thesis has been organized in the following way:

1. **Chapter 1**: This chapter provides insights into the broad context of industrial biotechnology and highlights the importance of downstream processing. Furthermore, it outlines the research questions addressed in this thesis.
2. **Chapter 2**: This chapter focuses on designing downstream processing strategies specifically suited for low-boiling alcohols produced through fermentation, such as ethanol, isopropanol, isobutanol and hexanol. Furthermore, a general methodology for recovering volatile bioalcohols after fermentation has been established to enhance the scalability and industrial viability of fermentative production.
3. **Chapter 3**: In this chapter, effective preconcentration and final purification processes were developed for 1,3-propanediol, 2,3-, 1,4- and 1,3-butanediols. The outcome is an adaptable DSP strategy that can be adjusted and implemented across various fermentation processes. This work was extended to developing a methodology for recovering high-boiling components from dilute aqueous solutions.
4. **Chapter 4**: This chapter presents the development of recovery processes for various organic chemicals produced through different bio-based processes (ethyl acetate, propionic acid, 2-phenylethanol, etc). While these processes show limited similarities due to the distinct properties of each compound, they all rely on distillation as the primary recovery technique. The chapter highlights the versatility and applicability of distillation in downstream processing for diverse fermentation-derived chemicals.
5. **Chapter 5**: This chapter highlights the significance of integrating upstream and downstream processes in bioprocess development. Isopropanol, along with acetone, and 2-phenylethanol were selected as representative examples of volatile and non-volatile biochemicals. Large-scale bioprocesses for their production were designed to demonstrate the practical application of integrated process design.

6. **Chapter 6**: This is a conclusion chapter that summarizes findings from the research questions outlined in Chapter 1. Furthermore, it highlights the potential impact and contribution of this thesis to the field of industrial fermentation with an emphasis on product recovery.
7. **Chapter 7**: This is an outline chapter that opens venues for further research based on the findings of this thesis. It suggests areas where additional investigation could drive improvements and innovation in industrial biotechnology.

Furthermore, some additional information is included in the Appendices:

1. **Appendix A**: This Appendix contains more information about the main objective and constraints of process development. Furthermore, to maintain consistency and enable fair comparison, the same procedures were followed for the analysis of the economic and environmental impact in all case studies. More precisely, the methodology developed by the National Renewable Energy Laboratory (NREL) [67] was used to calculate total costs, while sustainability metrics [68] were determined to assess the sustainability of the developed processes. More details about these methods are given in Appendix A to avoid repetition in every section.
2. **Appendix B**: For simplicity, only conditions and compositions of the inlet and outlet process streams are included in the flowsheets of all developed processes, while other important process streams are numbered. The compositions and conditions of these streams for all processes are presented in Appendix B.
3. **Appendix C**: The most important design parameters of distillation columns (e.g. column size, top/bottom pressure and temperature, reflux ratio, distillate-to-feed ratio, bottom-to-feed ratio, reboiler and condenser duty, etc.) from all developed processes are provided in Appendix C.
4. **Appendix D**: More details about the recovery of hexanol after fermentation (related section 2.6) are presented in Appendix D.
5. **Appendix E**: This Appendix contains more details about the derived stoichiometric reactions used to model fermentation processes in sections 5.1 and 5.2.
6. **Appendix F**: Four scenarios were considered for the production of isopropanol and acetone by gas fermentation in section 5.1. For simplicity, only one flowsheet is presented in the main text, while flowsheets, conditions and compositions of the main process streams and design specifications of distillation columns for the remaining three scenarios are presented in Appendix F.



2 | Recovery of alcohols from fermentation broths

2. Recovery of alcohols from fermentation broths

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Lower alcohols are important platform chemicals. For some of them, in particular ethanol, 1-butanol, iso-butanol, and iso-propanol, fermentative production is feasible or already a reality at large scale as part of a circular bio-based economy, moving away from fossil carbon sources. Ethanol production through fermentation from biomass is a well-established process that has been used for many years [69]. Several plants have been built globally, with some still in operation, while others remain idle or have been shut down [70]. Furthermore, ethanol can also be obtained through gas fermentation. In 2018, LanzaTech opened the first commercial plant for ethanol production by syngas fermentation in China, subsequently expanding manufacturing to other plants [71]. The same company has recently tested isopropanol and acetone production by syngas fermentation on a pilot scale, but this technology has not reached an industrial scale yet [72,73]. Furthermore, ABE (acetone-butanol-ethanol) [74,75] and IBE (isopropanol-butanol-ethanol) [76] fermentations are promising alternatives to petrochemical production. Isobutanol was first commercially produced by the company Gevo, followed by a joint venture of BP and DuPont (Butamax) [77,78]. To the best of our knowledge, industrial production of longer-chain alcohols by biotechnology has not been established yet.

A major challenge for the commercialization of alcoholic fermentation is end-product toxicity, which limits achievable product concentrations in the broth [27]. Furthermore, a large processing throughput is required for an industrially relevant production capacity [27]. Accordingly, the costs related to the downstream processing can considerably contribute to the total production costs [31]. For example, the purification costs of ethanol and butanol were estimated to be about 21-29% [79–82] (recovery by azeotropic distillation [79], distillation coupled with molecular sieves [80,81], pressure-swing distillation [82]) and 40% [83] (recovery by distillation) of the total production costs. Therefore, improvements in downstream processing may significantly increase the competitiveness and viability of industrial fermentation technologies [21]. So far, substantial research effort has been put into genetic engineering to obtain more resistant microorganisms and increase fermentation titer [25]. Yet, the recovery of fermentation products has not attracted nearly as much attention. An efficient purification process may lead to a more sustainable bioprocess by reducing total production costs, energy requirements, CO_2 emissions and water requirements. Given the significant impact of the downstream process on the overall competitiveness of industrial fermentation, this chapter introduces advanced methods for recovering various bioalcohols following fermentation. The obtained results offer a valuable indication of the cost associated with the purification process that should not be overlooked when designing an industrial fermentation process [9].

2.1. Recovery of ethanol after syngas fermentation

Syngas fermentation is used industrially to produce diluted bioethanol (about 1-6 wt%). This research study proposes a novel downstream process that recovers bioethanol in an energy-efficient and cost-effective manner, improves fermentation yield by allowing recycling of all fermentation broth components (microbes, acetate and water), and is designed for full-scale industrial-level application. Thereby, vacuum distillation at fermentation temperature was conceptually studied as an initial ethanol recovery step, leading to a bottom stream that may be recycled. Advanced separation and purification techniques were designed to recover 99.5% of initially present ethanol as a high-purity product (99.8 wt%). Mechanical vapor recompression and heat integration methods were used to maximize the sustainability and eco-efficiency of the proposed recovery process. Implementation of these techniques on a process using 6 wt% ethanol feed stream decreased the total annual costs by 54.2% (from 0.175 to 0.080 $/kg$_{EtOH}$), reduced the primary energy requirement by 66.1% (from 2.820 to 0.956 kW$_{th}$h/kg$_{EtOH}$), lowered the CO_2 emission by up to 82.6% (from 0.414 to 0.072 kg$_{CO2}$/kg$_{EtOH}$), and reduced the fresh water usage by 62.6% (from 0.242 to 0.091 m^3_W/kg$_{EtOH}$). Sensitivity analysis of ethanol concentrations ranging from 6 to 1 wt% showed that the recovery costs and energy requirements increased to 0.336 $/kg$_{EtOH}$ and 1.78 kW$_{th}$h/kg$_{EtOH}$, respectively. Since ethanol recovery performs better but fermentation will perform worse at higher ethanol concentrations in the fermentation broth, there is a trade-off concentration for the overall process.

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2.1.1. Introduction

Syngas, a gas mixture rich in carbon monoxide (CO) and hydrogen (H_2), is an important base material in the chemical industry [5]. It can be used as a hydrogen source for the production of commercially valuable chemicals [84]. One commonly produced chemical from syngas is methanol. Bi-metallic catalysts, high temperatures (220-250 °C) and pressures (50-100 bar) are needed for the production process [85]. Another valuable chemical that can be obtained from syngas is ethanol. As a feedstock for biofuel production, syngas is traditionally further converted by the thermochemical Fischer-Tropsch process. However, this process requires high temperature (150-350 °C) and pressure (up to 30 bar) [86], as well as expensive catalysts. Furthermore, an additional water-gas shift reaction step is often required to obtain the exact H_2:CO ratio needed for certain catalysts [87].

An alternative to the Fischer-Tropsch process is syngas fermentation, in which different acetogenic organisms are used to ferment syngas into biofuels and biochemicals [88]. The schematic representation of the bioethanol production process from syngas is presented in Figure 2-1. The advantages of the gas fermentation process compared to the thermochemical process are moderate process conditions (temperatures below 40 °C and pressure below 10 bar [89]), adaptability of microorganisms to different H_2:CO ratios in syngas, and tolerance to many impurities which would lead to poisoning of chemical catalysts [19]. Due to the relatively high tolerance of microorganisms, a wide range of substrates can be used for the gas fermentation process. Instead of being used as a substrate for lignocellulosic fermentation, lignocellulosic biomass can be gasified to produce syngas, a substrate for syngas fermentation. This approach mitigates the main drawbacks of lignocellulosic fermentation. The lignin fraction of biomass (about 40%), which is not converted to biofuel in lignocellulosic fermentation, can be utilized [5]. Furthermore, the costly biomass pretreatment step needed before lignocellulosic fermentation (about 30-40% of the total production costs in lignocellulosic biorefineries) is not necessary [34]. In addition to lignocellulosic biomass, organic industrial waste and municipal waste can be used as feedstock for the gasification process, while industrial off-gases can be used as substrates for the gas fermentation process [5]. In the latter case, carbon dioxide emissions resulting from various industrial processes may be substantially reduced [28]. Furthermore, another renewable source of syngas is the electrochemical conversion of carbon dioxide (CO_2) and water (H_2O) [90].

However, there are several requirements for scaling up the syngas fermentation process to a commercial scale. When it comes to the syngas conversion part of the biofuel production process, it is necessary to provide a high gas-to-liquid mass transfer rate, effective regulation of this rate is needed and proper foam control [91]. Additionally, a considerable drawback of the syngas fermentation process is the relatively low product concentration [89]. Therefore, improved

separation and purification techniques are needed to recover fermentation products in a cost- and energy-efficient way.

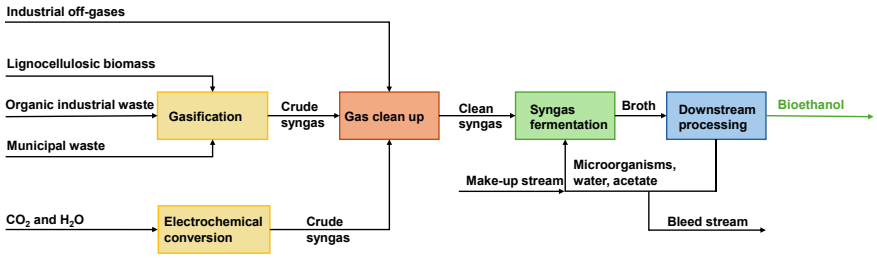


Figure 2-1. Process scheme of the bioethanol production by syngas fermentation

Nowadays, gas fermentation for producing bioethanol has been scaled up to industrial operation. The first commercial syngas fermentation plant, opened by LanzaTech in China in 2018 [71], uses steel mill off-gases as a carbon source while producing ethanol as the main product [92]. A similar process was applied at the Steelanol plant in Ghent, where LanzaTech's technology is used to convert furnace gases into ethanol on a larger scale, thereby preventing substantial CO_2 emissions from ArcelorMittal's facility. Exact data on the commercial process is not openly accessible, but the reactor for the syngas fermentation process is a gas-lift reactor with an external loop [91,93]. This reactor configuration may decrease mass transfer limitation that is a common restriction for scaling-up syngas fermentation processes [15,17]. The syngas fermentation broth is removed continuously from the bioreactor and sent to the ethanol purification section which is a distillation-based system. Other by-products are present only in traces and are not recovered. Formation of waste can be minimized by sending part of spent biomass to the anaerobic digestion or using it to make a fresh nutrient mixture that is continuously being fed to the bioreactor [94]. Many different methodologies and reactor types have been proposed for converting syngas to valuable biochemicals [95], but, to the best of our knowledge, the purification of syngas fermentation products is not that well studied. Due to the potentially significant cost contribution of downstream processing [31], optimization of this step can significantly improve the economic viability of the biofuel production process.

For this reason, this original research study focuses on enhancing the downstream processing of syngas fermentation products. The original contribution of this research is an eco-efficient process design for the effective bioethanol recovery from the syngas fermentation broth. The proposed novel downstream process recovers high-purity ethanol product while preventing loss of biomass and increasing the fermentation yield by enabling closed-loop process operation. Additionally, the influence of the bioethanol concentration in the fermentation broth on the key performance indicators of the proposed recovery process was analyzed.

2.1.2. Problem statement

The commercial syngas fermentation processes are continuous, whereby fermentation broth is constantly removed from the bioreactor. In addition to ethanol, which is the main product of the fermentation process, the removed broth also contains different coproducts of microorganisms' metabolism, as well as some living microorganisms [94]. For the current study, the composition of this fermentation broth stream, which is the feed stream for the bioethanol recovery process, is taken from the literature [29] and presented in Table 2-1. The stream's flowrate is calculated based on the assumption that the bioethanol production capacity of an industrial facility is about 150 ML/y (approximately 117 ktonne/y) [28].

Table 2-1. Condition and composition of the feed stream [29]

Parameter (unit)	Value
Temperature (°C)	37
Pressure (bar)	1
Mass flow (ktonne/y)	1905.3
Mass fractions	
Water	0.9215
Ethanol	0.0614
Acetic acid	0.0006
2,3-Butanediol	0.0085
Microorganisms	0.0081

The main requirements of the downstream process are high ethanol recovery in the form of high-purity product, mild operating conditions that enable the viability of present microorganisms and possibility to reduce upstream fermentation costs by recycling microorganisms, water and acetate. The major challenges in designing an optimal ethanol recovery process are the presence of living microorganisms in broth removed from the bioreactor, very low ethanol concentration, and constraints due to the ethanol-water azeotrope formation (see Table 2-2) [30].

2.1.3. Method of process design and simulation

To avoid loss of living biomass, separated microorganisms from the fermentation product stream may be recycled back into the bioreactor. This requires an initial separation step that does not use any additional chemicals that might harm living microorganisms, that is performed at temperatures that are not lethal for the microorganisms, and that has a residence time short enough for microorganisms to survive during the shortage of nutrients. Therefore, vacuum distillation was selected, in which the microorganisms directly flow to the aqueous bottom stream. For glucose to alcohol fermentation with yeast, it has been shown that stable pilot-scale operation is possible if fermentation broth is sent through a packed distillation column [96]. Additional distillation steps were designed to purify the top stream of the vacuum distillation column. Performing these distillations under

vacuum could offer a slight advantage, as the separation process becomes easier due to increased differences in relative volatility. However, implementing reduced pressure to all the following steps would require larger equipment and higher capital costs (CAPEX), resulting in no actual benefits compared to operating at ambient pressure. Therefore, the distillation steps following the first vacuum separation are performed under atmospheric pressure.

Table 2-2. Boiling points of all components and azeotropes (at 1 bar)

Pure components		Azeotropes		
Component	Tb (°C)	Component	Mass fraction	T (°C) / type
Ethanol	78.31	Ethanol	0.9557	78.15 /
Water	100.00	Water	0.0443	homogeneous
Acetic Acid	118.01			
2,3-butanediol	180.51			

Rigorous simulations for every part of the proposed ethanol recovery process were performed in Aspen Plus. Thermodynamic properties were determined using the Non-Random Two Liquid (NRTL) property method together with the Hayden O'Connell model for vapor phase association, due to the presence of acetic acid in the initial mixture [97]. The boiling points of the involved components and azeotropes are summarized in Table 2-2. Ethanol, which is the main product from syngas fermentation, has the lowest boiling point. Therefore, it could be separated as the top product in the distillation. However, due to the formation of the azeotrope, some water is separated together with ethanol. The other components have higher boiling points. Consequently, acetic acid and 2,3-butanediol, together with most of the water and present microorganisms are obtained at the bottom of a column. Note that acetic acid will only to a small extent be in the form of the volatile undissociated species at the fermentation pH and will largely be present as non-volatile sodium acetate salt. In the distillation calculations, both species were modelled as undissociated acetic acid, as a worst-case analysis. Since other products of microorganisms' metabolism are present in extremely low concentrations, commercial syngas fermentation processes focus solely on bioethanol recovery [94]. The aqueous solution containing small amounts of coproducts can be recycled to the bioreactor together with the microorganisms. This allows the bioethanol production process to be run in a closed loop and is expected to improve the overall efficiency [19]. Apart from avoiding the loss of biomass, returning this stream to the fermenter will result in higher ethanol yield. Namely, the recycling of acetic acid will increase the concentration of extracellular acetate in the fermentation broth to a level that enhances ethanol production [98,99].

The separated ethanol solution has to be further treated to obtain a final bioethanol purity that satisfies the required standards: 99.8 vol% in EU, 99.0 vol% in US and 99.6 vol% in Brazil [100]. Due to the azeotrope formation (Table 2-2), water-ethanol separation is complex and requires several steps. Firstly, the diluted mixture must be preconcentrated. Although many different separation techniques

have been proposed for this step [36,101], distillation remains the most commonly used for industrial applications [102]. The maximal ethanol purity that can be obtained in the distillate from the preconcentration step is nearly the azeotropic concentration. However, as ethanol concentration gets closer to the azeotropic one, the energy requirement for the preconcentration steps rises. Nevertheless, the energy requirement for further ethanol dehydration decreases as the feed stream to this part of the process becomes richer in ethanol. The optimal ethanol concentration after the preconcentration step, in terms of energy requirements and total purification costs, was reported to be 91 wt% [103]. Therefore, the preconcentration step in this work is designed to obtain a distillate with 91 wt% ethanol.

Secondly, to obtain a high-purity product, a dehydration step is needed. The most suitable techniques for large-scale ethanol dehydration are extractive distillation, azeotropic distillation and the usage of molecular sieves [102]. Since the flowrates considered for this process design are very large and the average experimental water adsorption capacity of zeolites is in the range 0.011-0.387 $g_{water}/g_{zeolite}$ [104], a rather large amount of zeolites is needed for ethanol dehydration (e.g. for a plant capacity of 150 ML/y ethanol, the 91wt% ethanol stream includes 1437.1 kg_{water}/h for which 1045.6-29.7 $tonne_{zeolite}$ is needed for 8 h operation). Azeotropic distillation is more energy-intensive than extractive distillation because the used light solvent must be completely evaporated. Moreover, solvent flowrate is also larger in azeotropic distillation [60]. Therefore, extractive distillation is commonly considered the best solution for industrial-scale bioethanol purification [100]. This separation technique implies the addition of a high-boiling solvent to the ethanol-water mixture. Ethylene glycol is a frequently used solvent for large-scale application [102]. In contrast to solvents used in azeotropic distillation, this solvent does not form an azeotrope with any present component. Instead, it changes the relative volatility of the present components [105]. The ternary system ethanol-water-ethylene glycol forms a single azeotrope without any liquid phase splitting areas [30]. In addition to lower energy requirement and smaller needed solvent flowrate, extractive distillation is more flexible regarding process sequence and requires a less complex control system compared to azeotropic distillation [106]. Furthermore, results of a comparative study of these three purification methods (molecular sieves, azeotropic distillation and extractive distillation) show that extractive distillation is the optimal method in terms of both investment and operating costs [107]. Therefore, extractive distillation with ethylene glycol is chosen as the optimal technique for the ethanol dehydration step.

2.1.4. Results and discussion

This section describes the results related to the process design for the preconcentration, dehydration, and the overall downstream processing section. Additionally, a techno-economic analysis was performed, and the key sustainability metrics were calculated.

Process design

Design of the preconcentration section

This part of the process focuses on obtaining a 91 wt% ethanol stream [103] from the syngas fermentation product stream. Different process configurations for this part of the downstream process are considered. The graphic representations of these configurations are given in Figure 2-2.

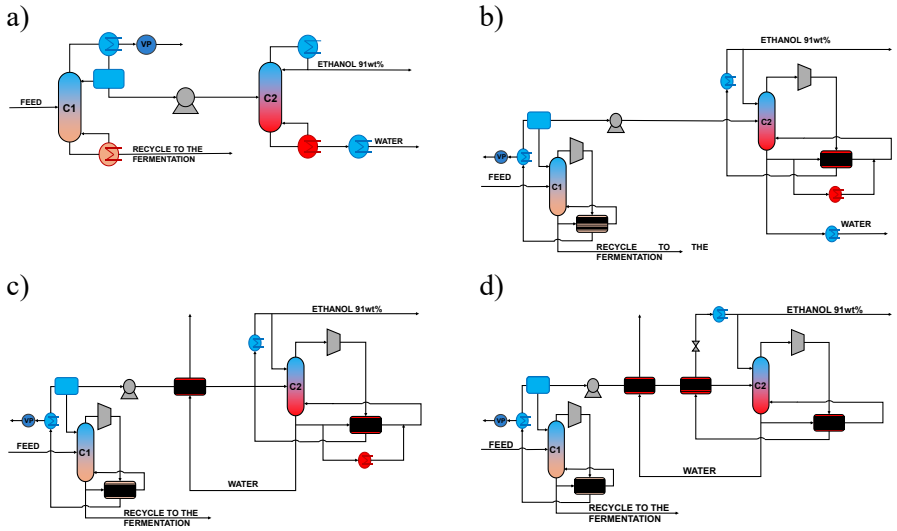


Figure 2-2. Process configurations for the bioethanol preconcentration part of the process: a) base case, b) scenario 1, c) scenario 2 and d) scenario 3

The base case scenario consists of a sequence of two distillation columns (C1 and C2). The first step in the recovery process is to separate ethanol from microorganisms, acetic acid and 2,3-butanediol. Since ethanol is the lightest of all present components, it will be separated in the distillate from C1 distillation column. To ensure sufficient liquid flow in the column (Table 2-2), some water will also be separated with ethanol, resulting in a stream that has about 58 wt% ethanol. An aqueous solution (>98 wt% water) containing small amounts of acetic acid, 2,3-butanediol and present microorganisms is obtained as the bottom product. To improve the efficiency of the overall bioethanol production process [19], this stream may be recycled to the bioreactor. The first distillation step is performed under reduced pressure to avoid operating at high temperatures that can harm the microorganisms. The conditions in column C1 can be designed

to ensure the viability of the present microorganisms [108]. The operating pressure, pressure drop and internals were designed in such a way that the temperature of the bottom product does not exceed the temperature in the bioreactor [109]. Since this column operates under reduced pressure, structured packing type Sulzer Mellapak 250 was assumed for its internals [110]. The condenser pressure was set to 0.055 bar which, with a pressure drop of 0.225 mbar per theoretical stage, results in 0.064 bar pressure at the bottom of the column. Relatable market data [111] were used when determining capital and energy costs for the vacuum pump that provides the required pressures in column C1. With defined operating conditions, the temperature in the column varies from around 37 °C at the bottom to about 21 °C at the top. Therefore, chilled water can be used as a cooling utility in the condenser of column C1. Since low-pressure distillate from column C1 is liquid, simple pumping is used to increase its pressure. This ethanol-water mixture is further preconcentrated by atmospheric distillation in column C2 to obtain 91 wt% ethanol in the distillate stream. Sieve tray internals were used for this column, with an assumed pressure drop of 8 mbar per tray [112]. The bottom product from this column is a pure water stream that can be sent back to the fermentation. Additional cooling of this stream is necessary to keep operating conditions in the bioreactor optimal for the present microorganisms.

Due to the large flowrate of the feed stream, heating duties for columns C1 and C2 are very high. Therefore, heat integration methods (e.g. Pinch Analysis) were considered to decrease energy requirements and several different scenarios were analyzed. Since temperatures in column C2 are much higher than in column C1, the first attempt at heat integration was to heat column C1 by using the product streams from column C2. Due to the significantly lower flowrates, the heat content of these streams is not nearly enough to replace the external heating needed for column C1. Nonetheless, these columns are separating relatively close-boiling components (ethanol and water). Since the temperature difference between the top and bottom products from these columns is not large, heat pumps can be used to decrease the total energy requirements. By implementing mechanical vapor recompression (MVR), the vapor coming from the top of the distillation column is compressed and used to evaporate the liquid coming from the bottom of the column [113]. When designing the MVR system, the reboiler duty for each distillation column was defined by specifying the outlet vapor fraction of the cold stream (liquid from the bottom of the column). The compressor pressure ratio was then adjusted to ensure that the compressed vapor could supply sufficient heat to the bottom liquid while maintaining a minimum log-mean temperature difference (LMTD) of 10 °C in the reboiler. The outlet temperature of the compressed vapor was also checked to avoid potential compressor damage due to high temperatures. Scenario 1 implies the implementation of MVR to both columns C1 and C2. However, using a single-stage compressor, the heat content of the top vapor from column C2 is not sufficient to completely replace the external heating required for this column. It

can provide about 89% heat needed to evaporate the bottom liquid. Therefore, two reboilers are needed for column C2. Compressed top vapor is used instead of a heating medium in the first reboiler, while external heating is used for the second reboiler. Even though there is still a need for external heating, implementing MVR to columns C1 and C2 drastically reduces the energy requirement for the preconcentration part of the process.

This process configuration (scenario 1) is further enhanced to obtain additional energy savings. Since the temperature of the distillate from column C1 is at 21 °C, the feed stream for column C2 is subcooled liquid. Therefore, preheating this stream will decrease heating duty for column C2, and consequently, the need for external heating. As the water stream from the bottom of column C2 needs to be cooled to be recycled to the fermenter, it can be used to preheat the feed stream for this column. Scenario 2 implies the implementation of MVR to both columns C1 and C2, with the described additional heat integration. Even though this heat exchange decreases reboiler duty for column C2, the compressed top vapor can provide about 95% of the required heat, and external heating is still needed. Since the bottom water stream from column C2 cannot provide sufficient heat to the feed stream, additional heat integration is considered.

The top compressed stream from column C2 must be additionally cooled after heat exchange in the MVR system. Consequently, the heat content of this stream can also be used to increase the temperature of the feed stream for column C2. Scenario 3 further improves scenario 2, by using both the bottom water product and the top stream from column C2 to heat the feed stream to this column to the boiling state. As a result of this heat integration, the reboiler duty for column C2 is decreased and the heat of compressed top vapor can completely replace external heating. Consequently, only one reboiler is needed for column C2. Even though the equipment installation cost for this scenario is almost doubled as compared to the process configuration without using MVR and heat integration (base case), utility cost and total energy requirements are reduced by 87.9% and 77.9%, respectively. Since the process configuration in scenario 3 provides the highest energy and utility savings, it is selected for the preconcentration part of the process. The comparison of energy requirements, equipment and utility costs for all scenarios is summarized in Table 2-3.

Table 2-3. Comparison of scenarios for the preconcentration process

	Primary energy requirements		Equipment cost		Utilities cost	
	Value* ($kW_{th}h/kg_{EtOH}$)	Diff. (%)	Value (k$)	Diff. (%)	Value (k$/y)	Diff. (%)
Base case	2.09		4,490		13,752	
Scenario 1	0.55	-73.5	9,438	110.2	2,151	-84.4
Scenario 2	0.50	-76.0	9,533	112.3	1,873	-86.4
Scenario 3	0.46	-77.9	9,569	113.1	1,667	-87.9

* The value is per kg of 91 wt% ethanol

Design of the ethanol dehydration section

The preconcentrated ethanol solution is further dehydrated by extractive distillation with ethylene glycol as solvent. For the dehydration part of the process, an extractive distillation column C3 and a solvent recovery column C4 are needed. These columns are designed with sieve tray internals, which have a pressure drop of 8 mbar per tray [112]. The solvent-to-feed mass ratio for column C3 was varied to find the value with the lowest energy requirement for this part of the process (columns C3 and C4). A solvent-to-feed ratio of 1.2 was determined (see Figure 2-3) and taken as the optimal value for process design. The top stream from column C3 is 99.8 wt% ethanol product. The bottom product, containing ethylene glycol and water, is sent to the solvent recovery column C4. Since water has a significantly lower boiling point than ethylene glycol, it is separated as a high-purity (>99.9 wt%) top product. To decrease the need for fresh water, this stream can also be cooled and recycled to the bioreactor. The bottom product from C4 is the recovered solvent (>99.9 wt%) that is reused in the extractive distillation column C3.

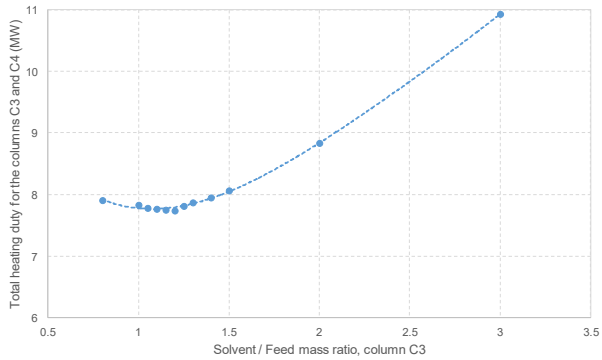


Figure 2-3. Influence of the solvent-to-feed ratio in column C3 on the total duty for columns C3 and C4, in the base case design of the bioethanol dehydration by extractive distillation

The reboiler temperature for column C3 is around 154 °C and medium-pressure steam can be used for heating. However, due to the high boiling point of ethylene glycol, the reboiler temperature for column C4 is approximately 199 °C. Therefore, more expensive high-pressure steam must be used to heat this column. Since the recovered solvent from column C4 has to be cooled before being recycled to column C3 [103], it can be used to evaporate part of the liquid from column C3. Although the heat content of the recovered solvent is not sufficient to completely replace the need for external heating for column C3, this integration results in about 20.2% energy savings for heating this column.

Dividing wall column (DWC) technology has been proposed as an alternative to the sequence of two distillation columns for the bioethanol purification

process [60,114,115]. Also, in the present study, a split shell column with a divided overhead section and a common bottom section was simulated for this part of the recovery process. This type of DWC has two condensers and only one reboiler. High-purity ethanol and water are recovered as top products, while ethylene glycol is obtained at the bottom. As DWC unit is not available in Aspen Plus, it was simulated as a thermodynamically equivalent sequence of two distillation columns. Thereby, the number of stages, location of feed stages, distillate-to-feed ratio, reflux ratio and vapor split were varied to minimize energy requirements of separation while ensuring high-purity of all product streams. Since DWC has only one reboiler, and the temperature in the reboiler is very high due to the presence of ethylene glycol, high-pressure steam must be used as a heating utility for this column. To decrease high-pressure steam usage, a side reboiler is added to the DWC configuration. Ethylene glycol product stream is used instead of heating utility for this reboiler. The comparison of energy requirements and utility cost for the sequence of two distillation columns with heat integration and DWC with side reboiler is given in Table 2-4.

Table 2-4. Comparison of energy requirements for the ethanol dehydration part of the process

		Two distillation columns with heat integration	**DWC with side reboiler**
Ethanol dehydration	Heating duty covered with heat integration/side reboiler (MW_{th})	1.18	1.24
	Need for medium-pressure steam (MW_{th})	4.68	n/a
	Need for high-pressure steam (MW_{th})	1.87	6.71
Full downstream process	Thermal energy requirements ($kW_{th}h/kg_{EtOH}$)	0.45	0.46
	Electrical energy requirements ($kW_{e}h/kg_{EtOH}$)	0.20	0.20
	Primary energy requirements ($kW_{th}h/kg_{EtOH}$)	0.96	0.97
	Total utility cost (k$/y)	4,054	4,441

The addition of a side reboiler to DWC decreases the need for high-pressure steam and lowers the total energy requirement below the amount needed for ethanol dehydration with a sequence of two distillation columns. However, the sequence of two distillation columns with previously described inter-column heat integration still results in the lowest utility cost for the whole ethanol recovery process. This is mainly due to the high cost of high-pressure steam needed to heat the DWC. Additionally, applying heat integration to the sequence of two distillation columns reduces the energy requirements below those needed for

DWC. The sequence of two distillation columns with heat integration provides the optimal process configuration in terms of total energy requirements and utility cost. Consequently, this process configuration was chosen for the design of the bioethanol recovery process.

Design of the full bioethanol recovery process

The proposed distillation sequence recovers a high-purity bioethanol product (99.8 wt%) from the syngas fermentation broth, with a recovery of 99.5%. The bottom product from the first distillation column, the aqueous solution with small amounts of acetic acid, 2,3-butanediol and microorganisms, can be recycled to the bioreactor. Additionally, two high-purity water streams can also be cooled and recycled to the fermentation step. Recycling these streams to the bioreactor prevents biomass loss, decreases the need for fresh water and may even improve ethanol yield in the bioreactor, resulting in a more efficient overall process. Lastly, after the extractive distillation step, the used solvent is recovered and recycled. Therefore, since non-product streams can be recycled and reused, the formation of waste streams is avoided.

The base case process configuration for the whole bioethanol recovery process extends the base case for the preconcentration part and consists of conventional distillation separations performed in columns C1, C2, C3 and C4. Therefore, the base process does not include any additional heat pumping or heat integration. The process flowsheet of this configuration is presented in Figure 2-4. The enhanced process design, presented in Figure 2-5, is obtained by applying several energy-saving techniques to the base process. Firstly, the closeness of temperatures at the top and the bottom of columns C1 and C2 offers the possibility of applying MVR to these columns. Thereby, compression ratios are 2.6 and 2.9, with outlet temperatures of compressed vapor of 103 and 143 ˚C, respectively. Secondly, additional heat integration is implemented to further decrease energy requirements. The top vapor stream and the bottom product from column C2 are used to heat the feed stream to this column to the boiling state. This heat integration significantly reduces the need for external heating for the whole process. The coefficient of performance (COP) for the MVR system is equal to the ratio between the heat that is transferred from the heat source (top compressed vapor) to the heat sink (reboiler) and the required compressor duty. In the proposed optimal process design, COP for MVR applied to columns C1 and C2 is equal to 12.2 and 9.0, respectively. Since the very conservative value of the electrical-to-thermal conversion factor of 2.5 [116,117] is still significantly lower than the COP values obtained for the designed MVR systems, it can be concluded that the proposed heat pumping and heat integration drastically improve the energy efficiency of the recovery process. Finally, the recovered solvent from the bottom of column C4 is used to partially heat column C3. This decreases the need for external heating for column C3 by about 20.2%. All implemented enhancements result in a significant reduction in total process costs and energy savings, which is analyzed in more detail in the following sections.

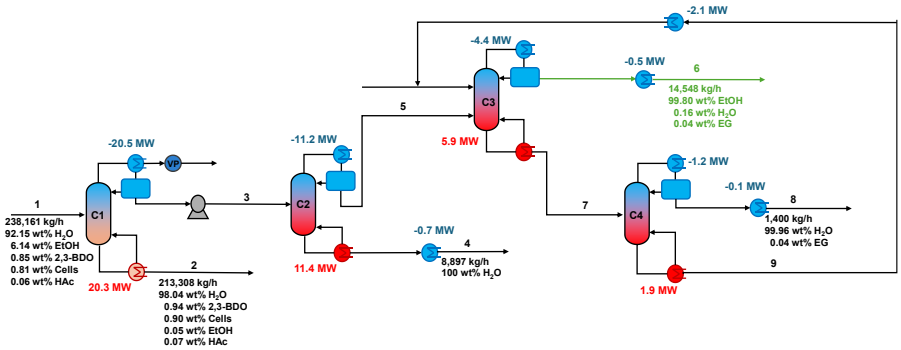


Figure 2-4. Base case bioethanol recovery process flowsheet (used abbreviations: H_2O - water, EtOH - ethanol, 2,3-BDO - 2,3-butanediol, HAc - acetic acid, EG - ethylene glycol, Cells - microorganisms)

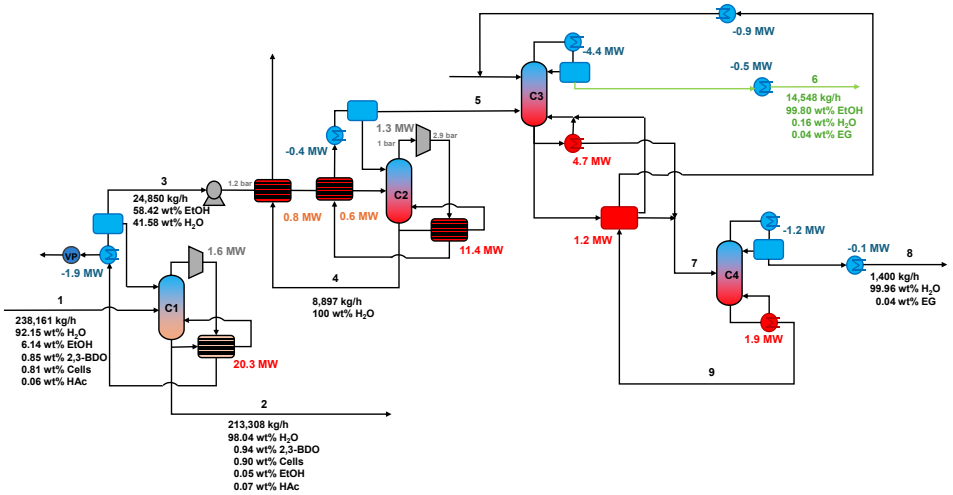


Figure 2-5. Enhanced bioethanol recovery process flowsheet (used abbreviations: H_2O - water, EtOH - ethanol, 2,3-BDO - 2,3-butanediol, HAc - acetic acid, EG - ethylene glycol, Cells - microorganisms)

The proposed downstream process is designed for the recovery of fuel-grade bioethanol from the syngas fermentation broth of specific composition (Table 2-1). However, due to the specificity of operating conditions in the fermenter and microorganisms used to convert sugars into bioethanol, the composition of the fermentation broth might vary. Apart from the considered trace components, other impurities can be detected (mainly aldehydes, esters, alcohols and carboxylic acids) [118]. This study focuses on the production of fuel-grade ethanol, for which there are no strict upper limits for present impurities as long as minimal ethanol purity is obtained and the total acidity is below a certain level [118]. However, the proposed recovery process can potentially be modified to produce food- or

solvent-grade ethanol for which purity specifications are more strict [119]. Therefore, the removal of present impurities might be required [118]. Additionally, acetaldehyde present in bioethanol can oxidize to acetic acid during the storage period, which increases the fuel acidity and reduces its quality [120]. As a result, several modifications have been considered to remove various impurities in bioethanol production. An additional degassing column can be added to remove all the light components present, including acetaldehyde and ethyl acetate [120,121]. Alternatively, extractive distillation can be used to remove acetaldehyde and ethyl acetate, while removing methanol separately in demethylizer unit [122]. Apart from adding additional separation units, C1 column can be converted into a hybrid column that obtains bioethanol solution as a side-product, while separating heavier components at the bottom and volatile components at the top [123]. Furthermore, process intensification techniques, such as cyclic distillation have been proven to be efficient in removing impurities in industrial-scale food-grade ethanol [124]. For smaller-scale bioethanol purification, the heat-integrated horizontal separation unit was developed to concentrate bioethanol solution, remove present volatile components and replace the first distillation column [125]. Besides light and heavy impurities, medium-volatile impurities (such as 1-butanol, 2-methyl-1-propanol, 2-methyl-1-butanol, 3-methyl-1-butanol and benzaldehyde) can accumulate in a nearly azeotropic water-ethanol mixture. These components can be removed as side streams from the rectification column [118]. Summing up, depending on the specific syngas fermentation broth composition and bioethanol purity requirements, the proposed recovery process is sufficiently flexible to be modified as needed to obtain a final product that satisfies the market demands.

Techno-economic analysis

Several economic aspects of the base case and the enhanced process design were calculated following NREL methodology (see more details in Appendix A) and are compared in Table 2-5.

Table 2-5. Key economic indicators of ethanol recovery after syngas fermentation

Economic indicators	**Base process**	**Enhanced process**	**Difference (%)**
CAPEX (k$)	10,067	19,619	94.9
OPEX (k$/y)	19,402	7,384	-61.9
OPEX ($/$kg_{EtOH}$)	0.167	0.063	
TAC (k$/y)*	20,409 / 21,416	9,345 / 11,307	-54.2 / -47.2
TAC ($/$kg_{EtOH}$)*	0.175 / 0.184	0.080 / 0.097	

*10-year payback period/5-year payback period

The total cost of process equipment installation for the base case is about 5,570 k$, whereby the largest part is the cost for the distillation columns (about 61.5%). After the implementation of MVR and additional heat integration, the total process equipment installation cost increases by 92.2% and equals 10,706 k$. This significant increase is mainly due to the usage of compressors in the MVR systems, but also due to additional heat exchangers for the heat integration sequences. The cost distribution to different types of equipment for the enhanced case is presented in Figure 2-6. The highest part of the equipment installation cost (about 44.3%) is the installation cost of compressors for the MVR systems. The costs of the distillation columns and heat exchangers are 32.0% and 21.8% of the total equipment installation cost, respectively.

The total CAPEX for the base case process are about 10,067 k$, while being 19,619 k$ for the enhanced process. This significant increase (about 94.9%) is mostly due to the more expensive process equipment, which stands for as much as 54.6% of the total CAPEX for the enhanced process. The cost distribution between the different parts of the CAPEX for the enhanced process design is presented in Figure 2-6.

The total OPEX for the base case process are about 19,402 k$/y, mostly due to the utilities cost (about 83.6% of the total OPEX) and labor cost (about 15.4% of the total OPEX). The highest contribution in utility cost is the cost for low-pressure steam (about 10,769 k$/y or 66.4% of total utility cost), chilled water needed in the condenser of column C1 (about 2,619 k$/y or 16.1% of total utility cost) and medium-pressure steam (about 2,007 k$/y or 12.4% of total utility cost). The total OPEX for the enhanced case process are about 7,384 k$/y. Therefore, the implementation of MVR and additional heat integration results in about 61.9% decrease in the OPEX (from 0.167 to 0.063 $/kg$_{EtOH}$). Even though the use of compressors in the MVR systems increases electricity cost to about 1,423 k$/y, the cost for chilled water and medium-pressure steam are decreased to 238 and 1,603 k$/y, respectively, while the usage of low-pressure steam is completely avoided. The contribution of different parts of OPEX for the enhanced process is presented in Figure 2-6. The reduced need for chilled water and medium-pressure steam, as well as the avoided need for low-pressure steam, decreases the total utility cost to about 54.9% of the total OPEX. Consequently, the contribution of the total labour cost is increased to about 40.4% of the total OPEX (in relative terms), without a significant change in its absolute value. The costs for maintenance, property insurance and ethylene glycol make-up are significantly lower, together about 4.7% of the total OPEX. Among utilities, the cost distribution is: 35.1% electricity cost, 39.5% medium-pressure steam cost, 19.0% high-pressure steam cost, 5.9% chilled water cost, and the remaining 0.5% is cooling water cost.

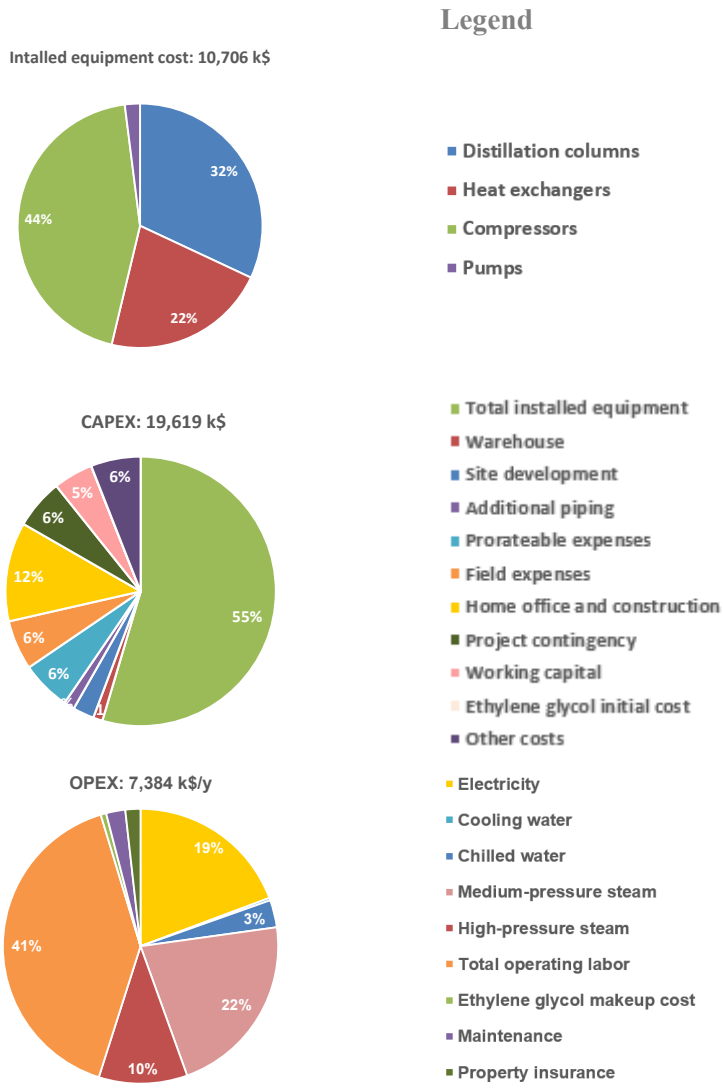


Figure 2-6. Total installed equipment cost, CAPEX and OPEX for the enhanced process

The enhanced process reduces TAC by about 54.2% (from 20,409 to 9,345 k$/y) with a typical payback period of 10 years, and by about 47.2%, (from 21,416 to 11,307 k$/y) when considering a shorter payback period of 5 years. Even though applying MVR and additional heat integration increases CAPEX, the significant reduction of the OPEX leads to a less expensive process overall. Expressed in relative terms (per kg of recovered bioethanol), the TAC for the base case and the enhanced process are 0.175 and 0.080 $/kg$_{EtOH}$, respectively (for a 10-year payback period), and 0.184 and 0.097 $/kg$_{EtOH}$ (for 5-year payback period).

Sustainability assessment

The environmental impact of the developed process was evaluated by determining the main sustainability metrics. The followed methodology is presented in Appendix A, while the values of the main sustainability metrics are summarized in Table 2-6.

Table 2-6. Key sustainability metrics of ethanol recovery after syngas fermentation

Sustainability metrics	**Base process**	**Enhanced process**	**Difference (%)**
Thermal energy requirements ($kW_{th}h/kg_{EtOH}$)	2.817	0.450	-84.0
Electrical energy requirements (kW_eh/kg_{EtOH})	0.001	0.202	n/a
Primary energy requirements ($kW_{th}h/kg_{EtOH}$)	2.820	0.956	-66.1
Fresh water requirements (m^3_W/kg_{EtOH})	0.242	0.091	-62.6
Fresh water loss (m^3_W/kg_{EtOH})	0.019	0.007	-64.7
CO_2 emissions (kg_{CO2}/kg_{EtOH})*	0.415 / 0.414	0.164 / 0.072	-60.4 / -82.6
Material intensity (kg_{waste}/kg_{EtOH})	0	0	0
Pollutant emissions ($kg_{pollutant}/kg_{EtOH}$)	0	0	0
Toxic emissions ($kg_{toxic\ material}/kg_{EtOH}$)	0	0	0

*Grey/green electricity

- ***Energy intensity:*** The thermal energy requirements in the base case process are 2.817 $kW_{th}h/kg_{EtOH}$. The implementation of MVR and heat integration significantly reduces the need for heating utilities and results in 84.0% reduction in the thermal energy requirements, with a final value of 0.450 $kW_{th}h/kg_{EtOH}$. Nonetheless, the electrical energy requirements in the base case process are negligible, while being equal to 0.202 kW_eh/kg_{EtOH} in the enhanced process. This is due to the use of compressors for the MVR systems. The total energy requirements for the base case and the enhanced case are 2.820 and 0.956 $kW_{th}h/kg_{EtOH,}$ respectively. Thus, the enhanced process design can provide 66.1% energy savings.
- ***Water consumption:*** The total need for cooling water is 0.240 m^3_W/kg_{EtOH} for the base case and 0.090 m^3_W/kg_{EtOH} for the enhanced process. The decrease of 62.4% in the required cooling water is mostly due to the implementation of MVR heat pump systems. Commonly, it is estimated that about 7% of cooling water is lost [68]. Therefore, the loss of cooling water expressed per unit of recovered bioethanol is 0.017 and 0.006 m^3_W/kg_{EtOH} for the base case and the enhanced process, respectively. Additionally, a steam condensate recovery of 70% is assumed to account for potential steam leaks, condensate losses, steam trap failures, and other possible inefficiencies in

the steam generation and usage process [126]. Taking this into account, the total water usage is reduced by 62.6%, from 0.242 m^3_W/kg_{EtOH} for the base case to 0.091 m^3_W/kg_{EtOH} for the enhanced process. The total specific loss of water is also decreased by about 64.7%, from 0.019 m^3_W/kg_{EtOH} for the base case to 0.007 m^3_W/kg_{EtOH} for the enhanced process.

- ***Material intensity:*** Besides a high-purity ethanol product, output streams from both the base and the enhanced process are the aqueous solution containing living microorganisms and products of their metabolism other than ethanol and the two high-purity water streams. To prevent biomass loss and decrease the need for fresh water in the fermenter, these streams may be recycled to the fermenter. Since all output streams are either product streams or can be reused/recycled, there is no formation of additional waste. Therefore, the material intensity is zero.
- ***Greenhouse gas emission:*** The total CO_2 emission for the base case process is 0.415 kg_{CO2}/kg_{EtOH} (for grey electricity usage) and 0.414 kg_{CO2}/kg_{EtOH} (for green electricity usage). This minor difference is due to the low influence of electricity in this process configuration. The enhanced process (with MVR and heat integration) reduces the total CO_2 emission by 60.4% and 82.6% if grey or green electricity is used, respectively. More precisely, the enhanced process emits 0.164 kg_{CO2}/kg_{EtOH} (grey electricity case) and 0.072 kg_{CO2}/kg_{EtOH} (green electricity case). Due to the implementation of the MVR systems, the electricity cost becomes significant (about 19.3% of OPEX). The source of electricity substantially influences the total greenhouse gas emissions of the proposed bioethanol recovery process design.
- ***Pollutants and toxic materials:*** Both the base case and the enhanced case processes do not emit pollutants (other than CO_2) and toxic materials. Consequently, the sustainability metrics characterizing these indicators are equal to zero.

Sensitivity analysis: Influence of the product concentration in the fermentation broth on the downstream processing performance

Even though the nominal design considered 6 wt% ethanol in the syngas fermentation broth, the ethanol concentration in industrial fermentation broth may differ for various plants. To determine the impact of the ethanol concentration in the feed stream (the broth stream continuously removed from the fermenter), this mass fraction was decreased while keeping the total feed flowrate constant. The concentrations of microbes and acetic acid were also kept constant. Modest changes might occur in the concentration of these non-volatile components, but such changes would have no significance on the performance of the proposed recovery process, as these components are recovered as the bottom stream of the first separations unit (vacuum distillation). Moreover, to determine if the proposed process can efficiently treat more diluted feed streams, size of the process equipment was not varied in this analysis.

The changes in key performance indicators for different ethanol fractions in the fermentation broth are listed in Table 2-7 and illustrated in Figure 2-7.

Table 2-7. Changes in key performance indicators for various feed compositions

Ethanol wt% in broth	**6**	**5**	**4**	**3**	**2**	**1**
Economic indicators						
OPEX ($/kg$_{EtOH}$)	0.063	0.071	0.083	0.100	0.134	0.233
TAC ($/kg$_{EtOH}$)	0.080	0.092	0.109	0.134	0.186	0.336
Sustainability metrics						
Thermal energy requirements ($kW_{th}h/kg_{EtOH}$)	0.45	0.45	0.45	0.45	0.45	0.45
Electrical energy requirements (kW_eh/kg_{EtOH})	0.20	0.22	0.26	0.30	0.37	0.53
Primary energy requirements ($kW_{th}h/kg_{EtOH}$)	0.96	1.01	1.11	1.19	1.37	1.78
Fresh water requirements (m^3_W/kg_{EtOH})	0.09	0.09	0.09	0.09	0.09	0.09
Fresh water loss (m^3_W/kg_{EtOH})	0.007	0.007	0.007	0.007	0.007	0.007
CO_2 emissions (kg_{CO2}/kg_{EtOH})*	0.164 /0.072	0.174 /0.072	0.192 /0.072	0.207 /0.072	0.241 /0.072	0.315 /0.072

* Grey/green electricity

Large differences were found if the ethanol concentration in the fermentation broth decreases from 6 to 1 wt%: The total annual cost per kg of recovered bioethanol exponentially increases from 0.080 to 0.336 $/kg$_{EtOH}$. Since the equipment installation cost (the highest part of CAPEX) does not change, the increase in TAC is mostly due to the increase in OPEX. Similarly, the total OPEX per kilogram of recovered bioethanol increase from 0.063 to 0.233 $/kg$_{EtOH}$ and the added price for bioethanol downstream processing follows the same increasing trend. This value rises from 0.086 to 0.371 $/kg$_{EtOH}$.

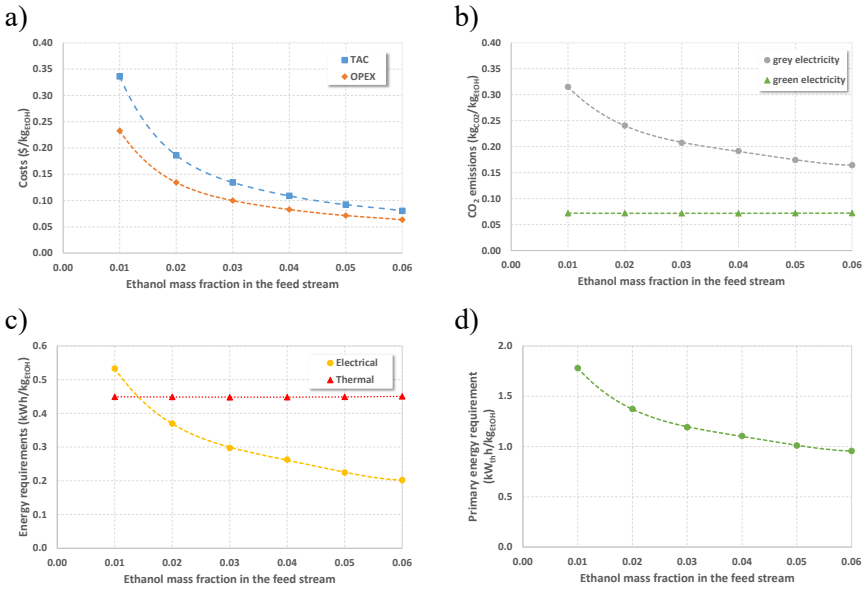


Figure 2-7. Influence of the ethanol concentration in the feed stream (fermentation broth) on various parameters of the enhanced process: a) TAC and OPEX, b) CO_2 emissions, c) thermal and electrical energy requirements, d) primary energy requirement. The benchmark value of the ethanol mass fraction in the feed stream was 0.06

In addition to the economic analysis, the calculation of the process sustainability metrics was also performed. If the ethanol concentration in fermentation broth decreases from 6 to 1 wt%, change in the thermal energy requirements per unit product are negligible. However, the electrical energy requirements significantly increase, from 0.20 to 0.53 kW$_e$h/kg$_{EtOH}$. This is due to a higher compression duty in the MVR systems. With decreasing initial ethanol concentration, a smaller fraction of the feed stream needs to be evaporated in columns C1 and C2. Thus, flowrate of the top steam used to evaporate the bottom liquid in the MVR heat pump system becomes smaller and a higher pressure ratio is needed to provide sufficient heat exchange. Consequently, the total primary energy requirement per unit of recovered bioethanol increases from 0.96 to 1.78 kW$_{th}$h/kg$_{EtOH}$. Still, this is much less than the value of 8.9 MJ/kg$_{EtOH}$ (2.5 kW$_{th}$h/kg$_{EtOH}$) that has been

reported by others for similar recovery of fuel-grade ethanol from a 1 wt% ethanol feed stream [127].

Lastly, the CO_2 emission is significantly affected by the initial concentration of ethanol if grey electricity is used for power supply. This is due to the high impact of electricity used to power compressors in the MVR systems. If the ethanol concentration in fermentation broth decreases from 6 to 1 wt%, the total CO_2 emission per kilogram of recovered bioethanol with the usage of grey electricity increases from 0.164 to 0.315 kg_{CO2}/kg_{EtOH}. On the contrary, the total CO_2 emission per kilogram of recovered bioethanol with the usage of green electricity hardly changes, since changes in the thermal energy requirement are negligible.

Summing up, higher ethanol concentration in the fermentation broth results in a more profitable and more sustainable downstream process. Considering the trends in Figure 2-7, increasing ethanol concentration beyond 6 wt% would marginally improve the overall performance of the downstream process. However, lower ethanol concentrations (about 2-3 wt%) during the fermentation do not lead to excessive downstream cost and should remain in scope due to the effect of ethanol concentration on the upstream process.

2.1.5. Conclusion

The result of this research study is a highly advanced downstream process design for the recovery of bioethanol in a large-scale syngas fermentation process (production capacity of about 117 ktonne/y bioethanol) while avoiding negative effects on the living biomass present. Improved purification techniques were implemented to efficiently recover 99.5% of the ethanol from the very dilute fermentation broth (>92 wt% water) as a high-purity product (99.8 wt% ethanol). Operating conditions for the first separation unit can be designed to allow recycling of the aqueous solution containing microorganisms and other products of their metabolism to the fermentation step. This may prevent biomass loss, allow the fermentation step to be performed in a closed loop, and improve ethanol productivity. Moreover, the need for fresh water in the bioreactor would be decreased by recycling two high-purity water streams.

By implementing MVR heat pumping systems and additional heat integration, the CAPEX increased by 94.9%, but OPEX decreased by 61.9% and TAC decreased by 54.2%, while the primary energy requirement reduced by 66.1%, CO_2 emission decreased by 60.4% or even 82.6% (for grey or green electricity), and fresh water requirement reduced by 62.6%. Thus, advanced energy-saving techniques can significantly improve the economic viability and sustainability of the proposed bioethanol recovery process.

Analysis of the influence of the ethanol concentration in the fermentation broth undoubtedly shows that higher ethanol concentration leads to a better performance of the downstream process. On the contrary, fermentation performance would decrease with increasing ethanol concentration due to the inhibitory effect on microorganisms. In that context, the proposed downstream process performance remains competitive even at lower feed concentrations of 2-3 wt% ethanol (which would allow better fermentation performance). While the exact trade-off concentration for the full process of bioethanol production by syngas fermentation is yet to be determined, the results of this research provide a valuable contribution to that goal and should be coupled with relevant data from the upstream fermentation process.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream processing of bioethanol from syngas fermentation, Separation and Purification Technology. 322 (2023) 124320. https://doi.org/10.1016/j.seppur.2023.124320. This file includes insight into an additional process configuration considered for the preconcentration section, the cost distribution for the base and enhanced process, an analysis of the bioethanol product purity influence on the energy requirement, and the influence of ethanol fraction in the fermentation broth on the key performance indicators.

2.2. Recovery of ethanol using pass-through distillation

Distillation is the most used separation technology at industrial scale, but using distillation in bio-based processes (e.g. fermentation processes to produce bioethanol) is quite challenging when mild temperatures are needed to keep the microbes alive. Vacuum distillation can be used to perform evaporation at low temperatures but setting a low distillation pressure fixes the condensation temperature to very low values that may require expensive refrigeration.

Pass-through distillation (PTD) is an emerging hybrid separation technology that effectively combines distillation with absorption in a sorption-assisted distillation process that decouples the evaporation and condensation steps. This is achieved by inserting between the evaporation and condensation steps an absorption-desorption loop that passes through the component to be separated and allows the use of different pressures and types of heating and cooling utilities.

This paper is the first to present the process design and rigorous simulation (implemented in Aspen Plus) of a new pass-through distillation process for bioethanol (~100 ktonne/y plant capacity), proving its effectiveness in concurrent alcohol recovery and fermentation (CARAF). Combining PTD with heat pumps leads to low recovery costs of 0.122 $/kg$_{EtOH}$ and energy requirements of only 1.723 kW$_{th}$h/kg$_{EtOH}$. Alternatively, combining PTD with multi-effect distillation resulted in 0.131 $/kg$_{EtOH}$ recovery costs and 1.834 kW$_{th}$h/kg$_{EtOH}$ energy intensity.

This section was published as:
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2.2.1. Introduction

A practical, low-cost, microbe-compatible separation process is needed to commercialize a concurrent alcohol recovery and fermentation (CARAF) process. Pass-through distillation is a newcomer to the field of industrial separation [128], which may fill this need by addressing some of the practical limitations of distillation in CARAF, and reducing the otherwise high operating temperatures and costs [27]. Thus, the main objective of this research is to expand implementations of novel pass-through distillation (PTD) technology. In this respect, spreading of PTD technology is advanced by presenting the first design of an industrial-scale bioethanol recovery process from dilute fermentation broth. To enhance the performance of PTD, it was coupled with advanced vapor recompression or multi-effect distillation systems. Besides the technical evaluation, an analysis of economic and environmental impact was performed to prove the high competitiveness and effectiveness of this new technology for concurrent alcohol recovery and fermentation. Furthermore, an additional novelty in this work is the development of a reliable property model for a complex system containing an electrolyte (lithium bromide) and two polar solvents (ethanol and water). In addition to continuously removing the inhibitory product from the fermentation broth, the proposed recovery processes enable recycling of biomass and most of the water to the fermentation. Consequently, the fermentation may be enhanced by increasing yield, avoiding biomass loss and reducing water requirements. Thus, the outcome of this work contributes to the advancement of the biotech industry by enabling widespread use of CARAF also to other bio-based processes.

2.2.2. Problem statement

In classic distillation, the evaporation and condensation steps are carried out at the same pressure, thus making it difficult to apply to bio-based systems due to the resulting operating temperatures. The selection of pressure in distillation is a key design step, as the pressure will set both the boiling and condensation temperatures, and consequently, the type of heating and cooling utilities needed. Usually, the evaporation temperature should be lower than that of a cheap heating utility (high-pressure steam), and the condensation temperature should be higher than that of a cheap cooling utility (cooling water). However, setting a single pressure to satisfy both temperature constraints is not always possible, e.g. in vacuum distillation (used to separate heat-sensitive materials). Vacuum distillation has potential application in the separation of fermentation products, whereby conditions should ensure the viability of microorganisms present in the aqueous surroundings. However, a potential challenge is that lowering the operating pressure (to allow evaporation at low temperature) also leads to low condensation temperature that requires expensive refrigeration utilities instead of cheaper cooling water. This issue can be solved conveniently by pass-through distillation, which inserts an absorption-desorption loop between the evaporation

and condensation steps such that it decouples them in terms of pressure [24]. The evaporator pressure can now be sufficiently low to allow boiling at temperatures that do not exceed the defined upper limit, while the condenser pressure is sufficiently high to allow condensation at temperatures suitable for using conventional utilities.

2.2.3. Pass-through distillation technology

Working principle

The working principle of pass-through distillation (a novel sorption-assisted fluid separation process) is illustrated in Figure 2-8. Evaporation and condensation steps can take place at different pressures by using an absorption-desorption loop that decouples them. Decoupling allows the evaporator to operate at very low pressure (and thus low temperature) while the condenser operates at higher pressure (low-cost cooling).

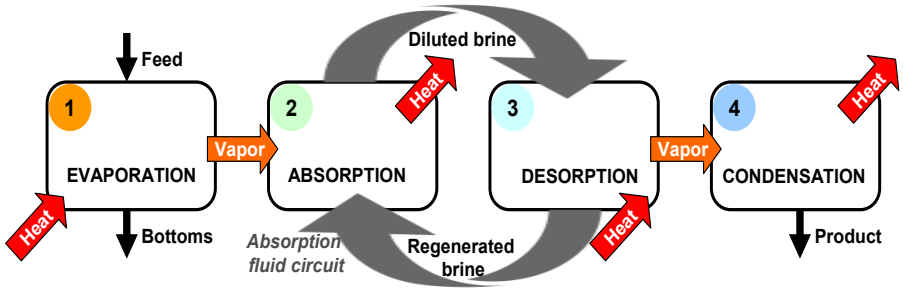


Figure 2-8. Working principle of pass-through distillation, based on an open loop absorption/desorption cycle inserted in-between evaporation and condensation

A PTD process involves three main pieces of equipment: an evaporator, a gas/vapor absorber, and a regenerator for the absorption fluid (shown schematically in Figure 2-9). A liquid feed stream is fed to an evaporator vessel, where a part of it is turned to vapor that leaves the evaporator through a port near its top, while the unevaporated portion leaves the vessel as a bottom stream. The vapor from the evaporator is then drawn through an absorber vessel where it contacts an absorbent fluid. The absorption fluid must have a very low vapor pressure and a high affinity for the main chemical constituents in the vapor generated by the evaporator. Solutions of highly hygroscopic and water-soluble salts are good non-volatile candidates for PTD in aqueous service, e.g. lithium bromide (LiBr), lithium chloride (LiCl), and calcium chloride ($CaCl_2$). LiBr brine is used in the absorption chiller industry and dehumidification equipment, being the least corrosive of the salts mentioned [129,130].

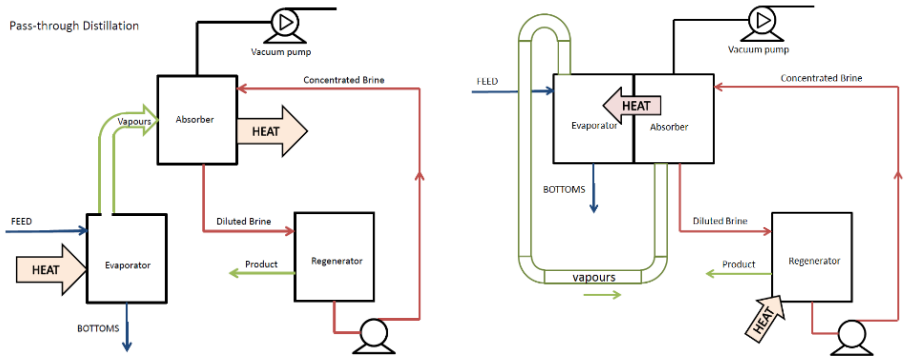


Figure 2-9. Schematics of a pass-through distillation process: without (left) and with (right) thermally integrated evaporation and gas absorption (TIEGA)

When water or polar compounds (e.g., alcohols) must be removed, a concentrated LiBr solution can be used as hygroscopic working/absorbent fluid. This brine absorbs the vapor coming from the evaporator (where the saturated feed is evaporated at low pressure) and leaves the vessel at the bottom, as part of a diluted brine solution. The diluted working fluid is pumped to the desorber/regenerator (a conventional still), where the passed-through components are evaporated at a higher pressure (using external heat) and then condensed using cooling water. Even though in the PTD process the same components are evaporated twice, there are possibilities for significant energy savings. Firstly, the heat released during absorption can be reused for the evaporation step. These operations can be fully integrated into a single unit (as shown in Figure 2-9), known as a stripping-absorption module (SAM) [131]. In this equipment unit, heat pipes are used to transfer *in-situ* the heat released by absorption to the evaporation section of the unit. In the SAM, the evaporator and absorber work essentially at the same absolute pressure. Notably, PTD does not necessarily require a SAM to work, but this is one of the best solutions for effective heat transfer from the absorption to the evaporation step. Secondly, there are different possibilities for enhancing the desorption part of the PTD. This original research analyses in more detail the energy savings that can be obtained by using advanced heat pumping systems (vapor recompression), or multi-effect distillation (MED) in this step.

The main advantages of PTD are the following: applicability to heat-sensitive materials, avoidance of expensive refrigeration utilities, smaller equipment size compared to vacuum distillation technologies and highly competitive energy requirements [128].

Pilot plant development

Drystill has invented and patented a stripping absorption module (SAM) as an innovative heat and mass exchange device that can enhance the overall pass-through distillation (PTD) process [131]. Furthermore, proprietary SAMs were built and tested at bench- and pilot-scale to prove the effectiveness of this new technology. Lithium bromide and lithium chloride solutions have both been successfully used as absorbent fluids [27]. The constructed pilot plant (Figure 2-10) features a SAM with 100 copper heat pipes (25 mm in diameter by 55 cm in length) that could boil water at a temperature as low as 20 °C and a rate of up to 50 kg/h. Additionally, a single-effect regenerator was included to provide the reuse of brine and maintain continuous operation practically indefinitely [27]. Both watery and high-solid aqueous slurries have been successfully tested in this pilot project.



Figure 2-10. Pass-through distillation pilot-scale unit in operation at Fielding Chemical Technologies with the stripping-absorption module built by Drystill [128]

2.2.4. Results and discussion

This section describes the main results related to the design and simulation of a PTD process used for concurrent alcohol recovery and fermentation in bioethanol production. Since this novel technology implies the usage of an electrolyte solution to absorb ethanol, with some water, from the fermentation broth, a reliable property model had to be developed first to accurately account for all interactions in this complex system. A bioethanol purification process using PTD was designed to obtain a high-purity final product (99.8 wt%), with a production capacity of 100 ktonne/y. Heat integration and heat pumping options were proposed. Finally, a complete analysis of process performance, both in terms of economic and sustainability indicators, was conducted to prove the competitiveness and effectiveness of the newly proposed design.

Property model

Modeling a PTD process is challenging in terms of physical properties due to the presence of the absorbent fluid (LiBr-water). There are a number of commercial platforms available that are able to model such systems, e.g. Engineering Equation Solver (EES), Absorption Simulator (ABSIM) or Aspen Plus [132]. While there is previous work on binary systems ethanol-water (including CO_2 and other organic impurities) [133,134], LiBr-water [135], and LiBr-ethanol [136], this work is the first to bring together all components in a unique process design. Modeling the ternary system LiBr-ethanol-water is complex since the interactions between the electrolyte and the two solvents need to be considered. Additionally, a proper thermodynamic model must account for the interactions between two polar solvents. Accurate modeling of relations between these components is a crucial aspect in the further development of reliable process simulations.

The electrolyte-NRTL model combined with the Redlich-Kwong equation of state, known as ElecNRTL-RK, was used in Aspen Plus as the most suitable option [137]. It describes the Gibbs excess energy using local compositions and is applied to a completely dissociated electrolyte. The model works well over extensive concentration and temperature ranges, making it extremely useful in process modeling. At infinite dilution of electrolyte systems, this model reduces to the Debye-Hückel model, while for non-electrolyte systems, it reduces to the Non-Random Two Liquid (NRTL) model [138]. The ElecNRTL-RK model characterizes the behavior of ternary systems by using binary interactions [139]. Therefore, regressions based on experimental data for binary systems [133,135,136] were used in Aspen Plus to determine the binary interaction parameters (BIPs) that properly describe the complex ternary system. However, deviation of the obtained property model from the available literature data for the system LiBr-ethanol was significant (over 40%).

To solve this problem, a published method for predicting salting effects in ternary salt-alcohol-water systems [140] was used to estimate the equilibrium data for the LiBr-ethanol-water mixture. This methodology implies using Tan's modification of the Wilson model to account for both solvent-solvent and solvent-electrolyte interactions in the complex ternary system. Solvent-solvent interaction parameters and vapor pressure data for electrolyte-solvent systems were used to predict equilibrium data for the ternary system [140]. The estimation of the data for the system LiBr-ethanol-water was performed in MATLAB. The data predicted using this method were included in the BIPs regression in Aspen Plus for the system LiBr-ethanol, with a lower weight factor compared to the experimental data. Consequently, the deviation between regressed data and literature data for system LiBr-ethanol decreased significantly (to about 3.8%).

Additionally, since experimental data for system LiBr-ethanol are available for up to 23 wt% LiBr, recommendations from the literature [141] were used to estimate the equilibrium data for higher LiBr concentrations. The proposed relation describes the dependency of the vapor pressure of an electrolyte-solvent system on the temperature, ionic strength, molecular weight, electrolyte and solvent parameters. As temperature, ionic strength and molecular weights are fixed for a certain system, the electrolyte and solvent parameters are variable. Initially, the vapor pressures calculated using literature parameters for the LiBr-ethanol mixture were compared with the available experimental data [136]. Since the total deviation was about 9.7%, data regression was performed in MATLAB to update the values of the electrolyte and solvent parameters. Literature data for these parameters were used as initial values, while the mean relative error was used as an objective function to be minimized. The electrolyte and solvent parameters determined in this way resulted in only about 0.8% deviation from the available literature data for the LiBr-ethanol system. The obtained parameters were used to estimate data for higher concentrations of LiBr in the LiBr-ethanol system. These data were included in BIPs regression in Aspen Plus, also with a lower weight factor compared to the experimental data [136]. The deviation of the regressed data from the literature data [136] for LiBr concentrations higher than 15 wt% was reduced from about 8.0% to 5.9%, whereby the total deviation (along the whole concentration range) was reduced to less than 3.2%.

The values of BIPs obtained by performing the parameter regression in Aspen Plus are summarized in Table 2-8.

Table 2-8. ElecNRTL-RK binary interaction parameters for water (i) – lithium bromide (j) and ethanol (i) – lithium bromide (j)

Parameter	Molecule or electrolyte		Molecule or electrolyte		Value
$c_{i,j}$	H_2O		Li^+	Br^-	49.1146
$c_{j,i}$	Li^+	Br^-	H_2O		-23.7669
$d_{i,j}$	H_2O		Li^+	Br^-	2201.39
$d_{j,i}$	Li^+	Br^-	H_2O		-915.851
$e_{i,j}$	H_2O		Li^+	Br^-	-70.3447
$e_{j,i}$	Li^+	Br^-	H_2O		31.2823
$\alpha_{i,j}$	H_2O		Li^+	Br^-	0.0335707
$c_{i,j}$	Ethanol		Li^+	Br^-	83.1575
$c_{j,i}$	Li^+	Br^-	Ethanol		-47.6692
$d_{i,j}$	Ethanol		Li^+	Br^-	-2447.64
$d_{j,i}$	Li^+	Br^-	Ethanol		2822.35
$e_{i,j}$	Ethanol		Li^+	Br^-	-905.818
$e_{j,i}$	Li^+	Br^-	Ethanol		486.525
$\alpha_{i,jj}$	Ethanol		Li^+	Br^-	0.0199508

The adequacy of the proposed property model was proven by comparing the predicted values with experimental data available for all binary systems [133,135,136]. This comparison is presented in Figure 2-11. The deviation of the T-xy diagram for the system ethanol-water generated with the developed property model vs experimental data [133] is only 0.5%. The predicted vapor pressure for the system LiBr-water differs from the literature data [135] by 6.5%. Lastly, the deviation of the predicted vapor pressures for the system LiBr-ethanol from the values reported in the literature [136] is less than 3.2%.

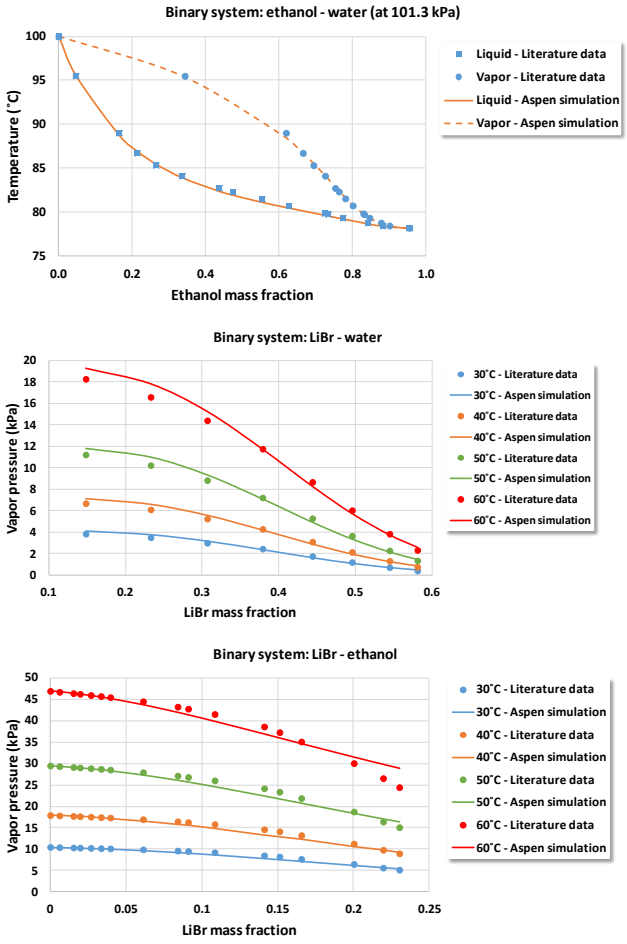


Figure 2-11. Comparison between the results predicted by the developed Aspen Plus property model (ElecNRTL-RK) and literature data [133,135,136]

Additional validation of the proposed property model was performed by comparing the predicted data for the ternary system LiBr-ethanol-water against experimental data for similar systems using $CaCl_2$ or $ZnCl_2$ as salts [142]. As $CaCl_2$, $ZnCl_2$ and LiBr are all highly hygroscopic and water-soluble salts [143], a similar behavior can be expected when dissolved in ethanol-water solvent mixtures. The results of the comparison for isobaric systems with different salt concentrations are presented in Figure 2-12. Very similar trends can be observed, which confirms that the property model for the system LiBr-ethanol-water is reliable.

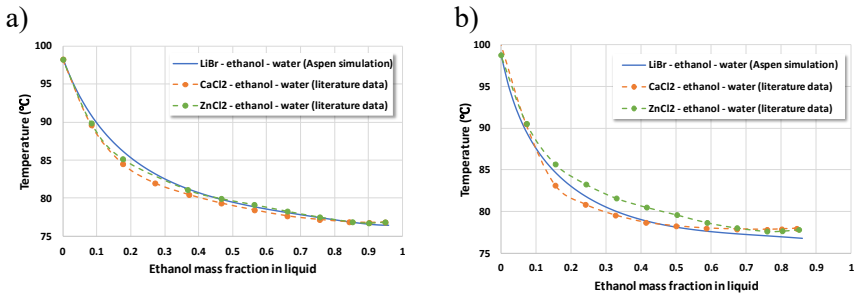


Figure 2-12. Comparison between the results predicted by the proposed Aspen Plus property model for system LiBr-ethanol-water with literature data [142] for systems $CaCl_2$-ethanol-water and $ZnCl_2$-ethanol-water at a pressure of 94.5 kPa: a) 5 wt% of salt in liquid, b) 15 wt% of salt in liquid

Lastly, since the ethanol recovery from the fermentation broth is the main goal of this study, the dependency of the ethanol mass fraction in the vapor phase on the ethanol mass fraction in the liquid phase in the ternary system LiBr-ethanol-water is presented in Figure 2-13.

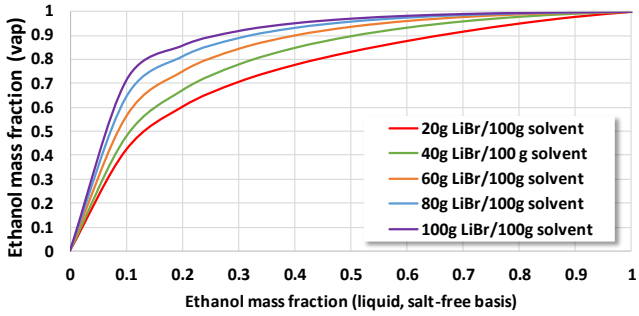


Figure 2-13. Predicted ternary data by the Aspen Plus property model (ElecNRTL-RK) for the ternary system LiBr-ethanol-water (at 50 ˚C)

Process design and simulation

Using the reliable property model developed, the recovery of bioethanol from a fermentation broth by PTD was designed. Rigorous process simulations for all unit operations were developed in Aspen Plus.

Setting of initial conditions

The feed to the PTD process is the fermentation broth containing ethanol, water, carbon dioxide (CO_2), as well as non-volatile microorganisms and inert components (which can be neglected in the simulation, as they are removed in the first step without evaporation). The feedstock for this process was considered to have an ethanol concentration of 5 wt%, which is on the lower side of typical broth concentrations after fermentation [36,144]. The feed flowrate was chosen such that ~100 ktonne/y of ethanol can be recovered. Furthermore, the broth was considered at 37 °C and 1 bar [145]. As CO_2 is a key metabolic product of microorganisms in the fermenter, it is present in the fermentation broth sent to downstream processing. The CO_2 concentration in this stream (0.1 wt%) is equal to its solubility in water at 37 °C and 1 bar [146].

Due to the presence of CO_2 in the feed stream, the first step in the ethanol recovery is the removal of some of the CO_2 using a degasser unit. The operating pressure for this step (0.065 bar) was chosen such that over 50% of the initially present CO_2 is removed. However, pressure reduction causes vaporization of some ethanol and water from the feed stream. As much as 4.3% of initially present ethanol is removed together with CO_2 and some water, as carbon dioxide also serves the purpose of removing ethanol from a liquid solution [147]. That ethanol is recovered later to minimize product loss.

Evaporation and absorption parts of PTD

The evaporation and absorption parts of PTD can be coupled and performed in one process unit. The stripping absorption module (SAM) is a specific piece of equipment developed by Drystill [131], which uses the heat of absorption to vaporize the feed. SAM is basically an evaporator and gas absorber combined in a single low-pressure vessel, with heat pipes passing through the bulkhead that separates them. Heat pipes conduct heat from the hot absorber to the relatively cooler evaporator. The evaporator generates vapors that are ducted into the gas absorber and absorbed into a stream of absorbent fluid. Under the right conditions, the heat demanded by the evaporator is exactly matched to the heat supply from the absorber, and the SAM will operate with no externally applied heating or cooling. So roughly the same quantity of heat is involved in each process: the latent heat of evaporation [27]. This piece of equipment is not available off-the-shelf in the process simulator (Aspen Plus) so it has to be described via an equivalent combination of unit operations, as shown in Figure 2-14. The SAM is operated under reduced pressure so that ethanol and water vapor can be produced from the fermentation broth without the temperature exceeding the optimum

fermentation temperature. A temperature in the region of 37 °C (as the upper limit) needs to be maintained for the optimum ethanol production rate [145]. Operating below this temperature also maintains a degree of safety, such that in the case of a deviation from normal operation, a temperature rise will not cause damage to the used microorganisms. When designing SAM unit in Aspen Plus, the operating temperature and pressure were first selected. Furthermore, the LiBr brine flow rate was determined to ensure sufficient heat supply for the evaporation process. Finally, the vapor fraction in the evaporation section of the SAM unit was defined to allow adequate recovery of ethanol from the fermentation broth, while maintaining a high ethanol concentration in the produced vapor to simplify subsequent recovery steps. More details about the design of this unit are presented below.

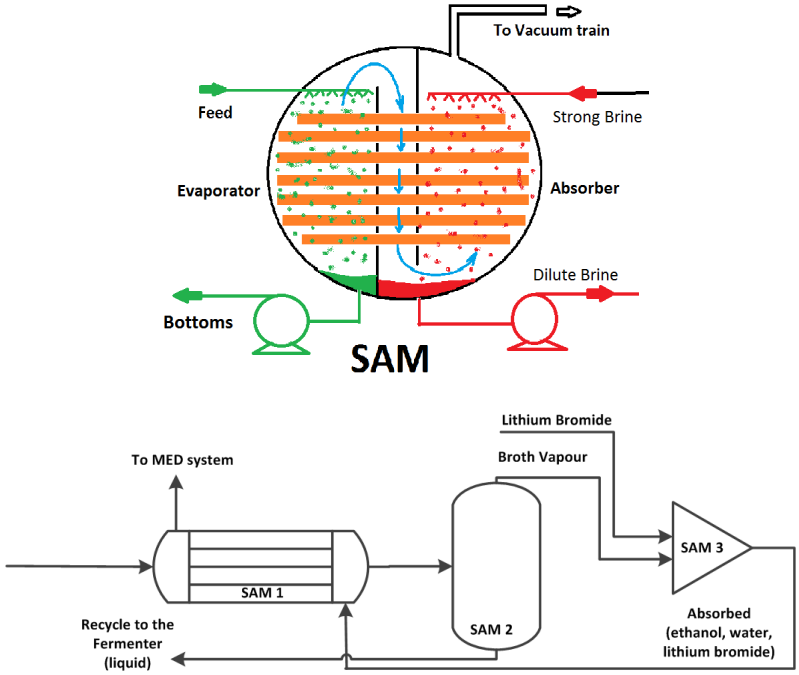


Figure 2-14. Stripping-absorption module (SAM) working principle and the corresponding equivalent of conventional units (usable in Aspen Plus simulations)

Vaporization taking place in the SAM aims to maximize ethanol concentration in the vapor phase product that is sent to the absorber unit. The remaining liquid from the evaporation step contains most of the water and microorganisms. This stream can be recycled to the fermenter to avoid biomass loss and allow fermentation to be performed in a closed loop [19]. This flash step is achieved by heat transfer from the hotter absorbed fluid. The operating pressure of the SAM was determined such that the addition of heat to the feed broth causes the evaporation of ethanol from the broth. Figure 2-15 can be used to select an

appropriate operating pressure in the SAM. As the broth temperature after the degassing step is reduced to about 34 °C, the SAM operating pressure was varied while keeping the temperature constant. As the total ethanol vaporization happens at 0.054 bar, this pressure value was chosen for operation. The optimal vapor fraction in the SAM was selected after further analysis.

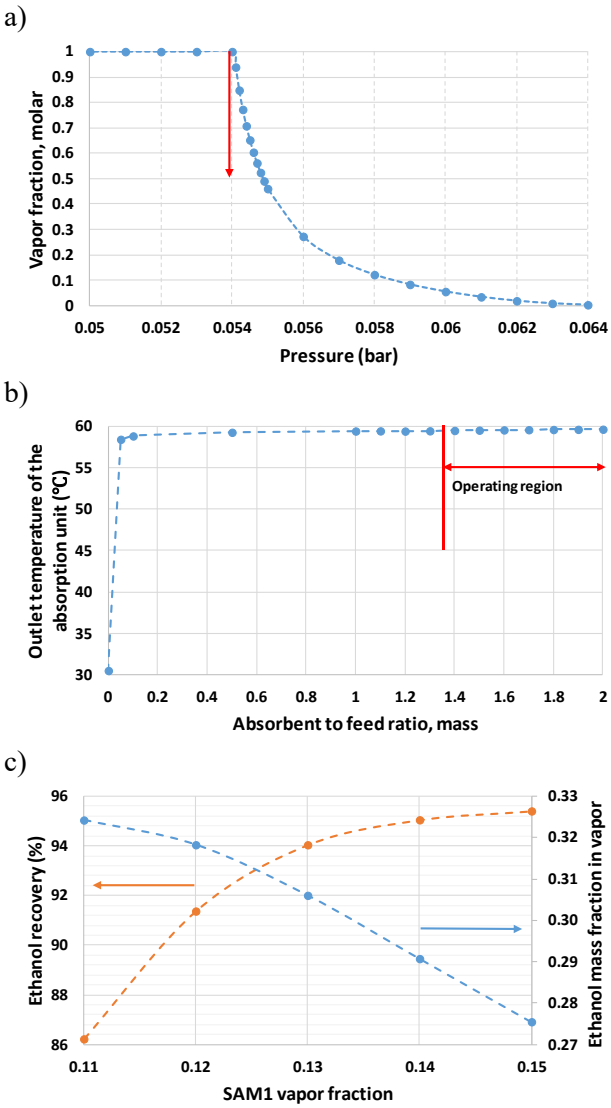


Figure 2-15. Design parameters of the SAM unit: a) vapor fraction of ethanol from the fermentation broth at varying pressures at 34 °C (chosen value is 0.054 bar), b) dependence of the outlet temperature of the SAM on the absorbent to feed ratio (chosen value is 1.4), c) dependence of the ethanol recovery and concentration in vapor phase on vapor fraction of the SAM evaporator part (chosen value is 0.125)

The flow rate of LiBr/water solution relative to the vapor feed is another operating parameter that has a key effect on the process design. A feed temperature of the lithium bromide solution of 50 °C, and a concentration of ~50 wt% were considered as suggested in the literature [148]. Absorption is exothermic and releases heat that is used to evaporate ethanol and water vapor from the fermentation broth. This heat, released during the absorption process, is transferred via heat pipes to the evaporation part of the SAM unit. Heat pipes are known for their ability to transfer substantial quantities of heat with a nominal temperature difference (5 K) driving force [149]. This virtue can be achieved by phase changes of separate working fluid in the heat pipes. Hence, the flowrate of LiBr brine was varied until the diluted brine stream (after the absorption step) was able to provide the heat required for the evaporation step. This leads to a minimum absorbent-to-feed ratio of 1.4 on a mass basis. Figure 2-15 shows that bringing concentrated LiBr brine into contact with ethanol and water vapors leads to a jump in temperature, which reflects the release of energy during the absorption process. However, the temperature at the outlet from the absorber increases gradually with increasing absorbent flow. It has been already proven that the inlet brine flowrate has a small effect on the temperature difference obtained during the absorption process [150]. The required flowrate of concentrated LiBr brine was determined by the minimum heat capacity of the diluted brine needed to provide heat for the evaporation step.

In the initial design of the SAM unit, to obtain ~19 wt% of ethanol in the vapor after the evaporator unit, as much as 35% of ethanol from the feed stream remains in the broth that is recycled to the fermenter. In addition to not fully recovering the main product, recycling this stream with ~2 wt% of ethanol to the fermenter is not favorable due to the inhibitory effects ethanol has on microorganisms [151]. Higher concentrations of ethanol in the separated vapor would lead to even less recovery, while lower concentrations are not convenient for further downstream processing. To increase ethanol concentration in the vapor sent to the absorber unit, and to minimize both the loss of ethanol and its concentration in the recycle stream, a stripping column was added before the SAM unit. Ethanol from the liquid product of the degasser unit is stripped with vapor formed in the evaporator unit of SAM. The liquid product from this stripping column is sent to the evaporation part of SAM, while the vapor product, rich in ethanol, is sent to the absorption part of SAM (Figure 2-16 and Figure 2-18). This additional column brings several benefits: the vapor sent to the absorption part of SAM contains ~32 wt% of ethanol, whereby only ~3% of the ethanol from the feed stream remains in the recycle stream that has less than 0.2 wt% ethanol. Therefore, ethanol loss is reduced by about 91%, while the stream being recycled to the fermenter contains amounts of ethanol that cause negligible inhibition of the microbes. The added stripping column also operates under reduced pressure. Hence, the structured packing type Sulzer Mellapak 250 was selected as internals, with a pressure drop of 0.225 mbar per theoretical stage [110].

The performance of the evaporator was optimized by varying vapor fraction (defined as the operating parameter for the heat exchanger in Aspen Plus representation of the SAM unit) and analyzing effects on the ethanol recovery and concentration in the vapor stream being sent to the absorber part of the SAM (see Figure 2-15). Higher ethanol concentrations in the vapor, which is more favorable for the further purification process, result in lower recovery since more ethanol remains in the stream being recycled to the fermenter. A vapor fraction of 0.125 was chosen for the evaporation part of the SAM, since at this value the ethanol concentration in the separated vapor is higher than 30 wt%, while the recovery is higher than 92% (value before recovering ethanol separated with CO_2).

Desorption and condensation parts of PTD

To recycle the absorbent fluid in a continuous circuit, the diluted brine (coming from the SAM) must be regenerated to its original concentrated state by desorption. This process involves evaporating all components that have been absorbed during the transit through the SAM absorber chamber. Separated ethanol and water vapor are further condensed and sent to additional purification. The desorber unit can operate at higher pressures and higher temperatures, since the brine contains no temperature-sensitive substances (those being removed already as bottoms of the SAM). Thus, following the desorption step, condensation is also performed at higher temperatures, which allows the use of cooling water rather than expensive refrigeration.

While the SAM ensures an effective heat recovery from the absorption to the evaporation step, the desorption step still requires external heating. Therefore, different process integration opportunities can be considered to obtain maximal energy savings. Two alternatives for enhancing the desorption and condensation parts of the PTD process were analyzed in this original study: the usage of heat pumping systems and the implementation of multi-effect distillation (MED). As the temperature difference between the vapor phase and the concentrated brine is negligible, heat pumping can be effectively used to reduce the energy requirements. In this system, the formed vapor can be compressed (leading to a temperature increase) and used to evaporate the diluted brine. Thus, the electrical energy needed for compression replaces the much higher thermal energy required initially. Alternatively, the high heating requirements of the desorption step can be significantly reduced by applying MED. This heat integration method implies splitting the diluted brine stream and reusing heat supplied to the high-pressure part of this brine to heat up other parts of the diluted brine [152].

Configuration 1: Heat pump-assisted desorption and condensation

The first configuration is based on heat pump (vapor recompression) assisted desorption of the PTD, noted here as PTD-VRC (see Figure 2-16).

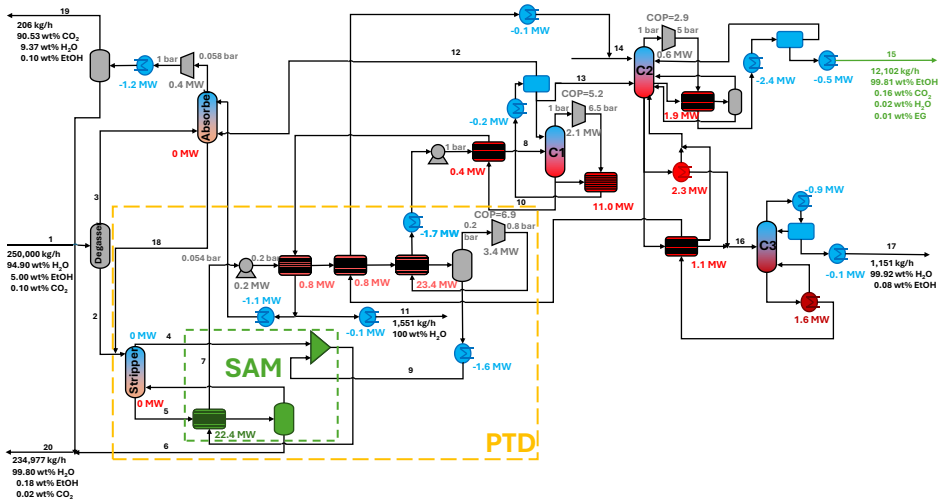


Figure 2-16. Flowsheet of the bioethanol recovery from the fermentation broth by process configuration 1 (PTD-VRC) – heating duties (red), cooling duties (blue), compressor/pump duties (grey), water (H_2O), ethanol (EtOH), ethylene glycol (EG)

The diluted brine from the SAM unit should be pumped to an appropriate pressure for the desorption and condensation steps that follow. As evaporating ethanol and water from the diluted brine is very energy-demanding (~25 MW of heating duty for this plant capacity), advanced energy-saving techniques should be implemented. The desorbed vapor can be compressed and used to evaporate part of the diluted brine in the desorber unit. This heat pumping design significantly reduces the external heating for the desorption step. The performance of the PTD process was optimized by determining the desorption operating pressure that minimizes the total energy requirements (considering both thermal and electrical energy) for this part of the bioethanol recovery process. Besides the minimum temperature difference to ensure efficient heat exchange, an additional limitation of this optimization process is that the resulting temperature for the condensation part should allow the use of cooling water as a cheap utility. As the specific energy requirements (per kg ethanol) for the PTD process are the lowest at 0.2 bar (Figure 2-17), this value was chosen as the optimal operating pressure for the desorption and condensation parts. Expensive refrigeration is avoided at this operating pressure since a condensation temperature of ~72 °C is suitable for using cooling water. After evaporating ethanol and some water, the regenerated LiBr brine can be recycled and reused in the SAM unit [128].

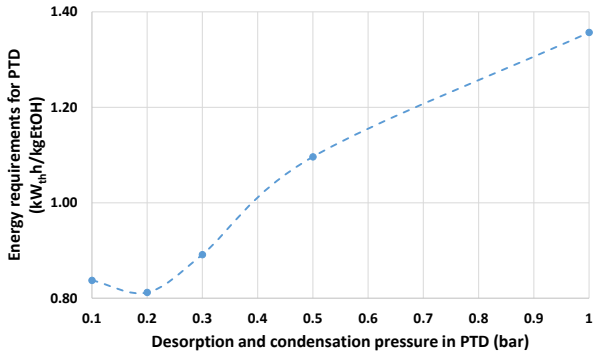


Figure 2-17. Influence of operating pressure for desorption and condensation parts of PTD process on energy requirements

A potential limitation for applying this heat pump-assisted design for the desorption part is the relatively high temperature of the compressed vapor (about 254 °C) that is needed to provide sufficient heat in the desorber unit. However, the temperature of the compressed vapor should not present a constraint as specific industrial compressors have been designed for much higher outlet temperatures, such as centrifugal compressors offered by MAN Energy Solutions [153]. Furthermore, the outlet temperature from the compressor is reduced after applying heat integration.

Configuration 2: Multi-effect distillation (MED)

An alternative option is replacing the desorber unit in PTD with multi-effect distillation (MED) to enhance the desorption part, a combination noted here as PTD-MED (see Figure 2-18). In this case, the brine may be regenerated using less than half the energy that is originally delivered by the heat pipes into the SAM evaporator.

In this work, three MED stages were chosen (as typical in industry to balance the equipment cost vs. energy savings) such that the feed stream (the diluted brine after the SAM unit) is split into high-pressure (HP), medium-pressure (MP) and low-pressure (LP) streams. Other configurations are also possible. However, adding more stages in the MED results in higher capital costs due to additional equipment units. Furthermore, with the increasing number of MED stages, the temperature within the first distillation stage rises, which might increase operating costs and cause thermally induced fouling of the MED installations [128].

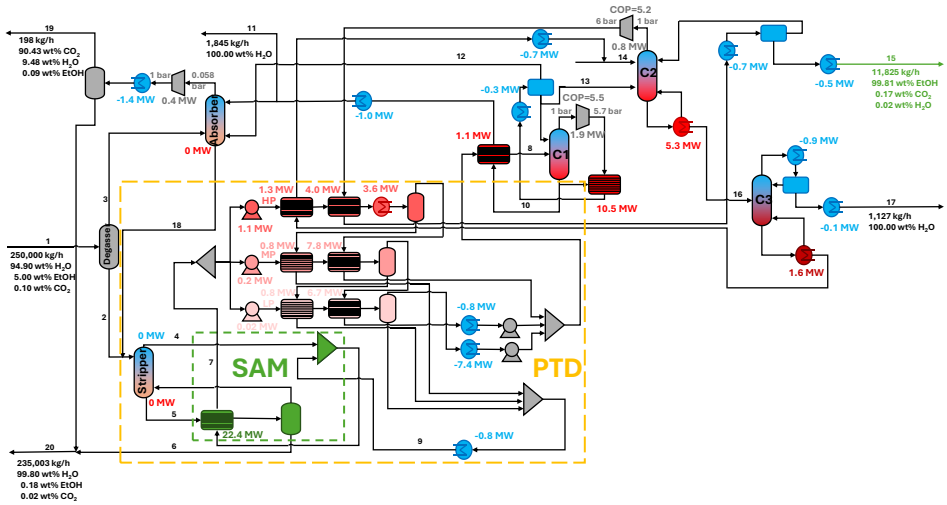


Figure 2-18. Flowsheet of the bioethanol recovery from the fermentation broth by process configuration 2 (PTD-MED) – heating duties (red and pink), cooling duties (blue), compressor/pump duties (grey), water (H_2O), ethanol (EtOH), ethylene glycol (EG)

One of the key advantages of PTD is the decoupling of the evaporation and condensation processes. The inserted absorption step allows the liquid stream to have its pressure altered more easily, thus allowing MED to be used to desorb ethanol and water resulting in energy savings. Multiple flash vessels are used at different pressure levels to provide heat recovery from the hotter, higher-pressure streams to the cooler, lower-pressure ones. For a given split ratio, there is a minimum pressure difference required between the MED pressure levels to give a temperature gradient sufficiently large such that efficient heat transfer is possible. For a sufficient temperature difference between the hot and cold streams to produce the specified vapor fraction, there is a minimum operation pressure for the MED stages. The higher-pressure levels can be operated at any pressure above this (not necessarily optimally) and deliver the required heating effect. This means that a direct link can be made between the split ratio of the streams that enter the MED process and the minimum operating pressures. The minimum operating pressure for each stage, which does not lead to a temperature crossover in heat exchangers, is the dependent variable.

The optimization of the PTD process with MED implied identifying the split ratio that results in minimal total energy requirements for this part of the bioethanol recovery process. Split ratios in the vicinity of a value of 1 were explored. It should be noted that a split ratio of 1.2, for example, means that the ratio between the flowrates of the HP and MP streams and the MP and LP streams is 1.2. The split ratio was changed in the Aspen Plus simulation and the minimum pressure was established by manually adjusting the pressure in the MP and HP streams until there was no temperature crossover detected. The pressure of the LP stream

(0.09 bar) was defined in a way that allows later condensation with cooling water (30 ˚C). The MP and HP streams need to take a pressure that gives the product streams of the flash unit temperatures that allow the necessary heat transfer to take place.

Figure 2-19 gives a visual representation of how the required pressure of each stream changes with differing split ratios. As the split ratio increases, such that more flow is sent to the higher-pressure streams, the pressure needed in the HP and MP levels is reduced, whereby these changes are more noticeable for the HP stream. A higher flow rate in the HP stream for example gives it a higher heat capacity flow rate, reducing the change in temperature required by that material to deliver a certain amount of heating. A lower inlet temperature of the hot stream in the heat exchanger is therefore required to meet the cold stream outlet specification and thus a lower pressure is needed. For split ratios above roughly 1.05 this pressure change is rather gradual. Below this, however, a vast increase in pressure is required as the hot vapor stream is cooled so much that it completely condenses and becomes a liquid. At this point, its temperature falls drastically until it is the same as for the cold stream, and a temperature cross is detected. Below a split ratio of 0.95 the pressure required rises so significantly that it would be completely impractical and hence is not included in this study.

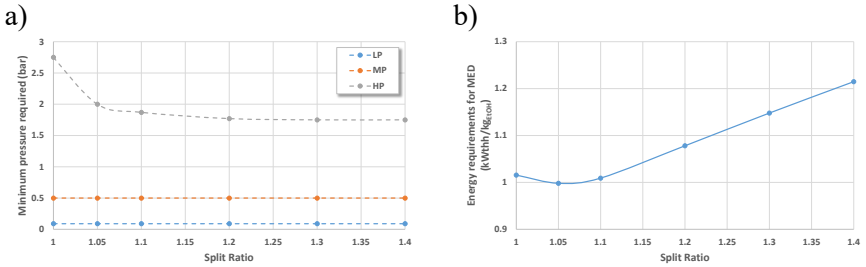


Figure 2-19. a) Minimum pressure required in each stream of the MED system, b) energy requirements for MED

Figure 2-19 suggests that a split ratio of above 1.05 is sensible due to the minimization of the operating pressure required. A split ratio above this value will result in a further reduction in operating pressure and in a decrease in temperature of hot utility required to achieve vaporization in the HP stream. Yet, this advantage comes at a decreasing rate (shown by the reducing gradient in Figure 2-19), at the expense of a higher flow rate to be heated by the utility, hence increasing process energy requirements. Therefore, analysis of energy requirements for the MED part of the process depending on defined split ratio was performed and results are also presented in Figure 2-19. Both thermal and electrical energy requirements were included in this analysis (as described in a later section). With a defined split ratio of 1.05 total energy requirements are the lowest, while the required pressure for the HP stream is reasonable (~2 bar). Therefore, this value was chosen as the optimal one for splitting the diluted brine from the SAM.

The actual operating pressures of the flash vessels in the MED system need to be established for the defined split ratio of 1.05. The pressure in the HP and MP stream were increased manually until no temperature crossover was detected. A minimum approach temperature of 10 ˚C was chosen for each of the heat exchangers. This temperature difference avoids unnecessarily large heat exchangers. The HP flash is operated at 2.0 bar, the MP flash at 0.5 bar and the LP at 0.09 bar. Without using MED, the heating requirements are ~25 MW, but splitting the stream into three stages and using heat integration opportunities results in a hot utility duty of only 8.9 MW (64% reduction). After separating ethanol and water from the diluted stream from the SAM, the regenerated brine can be recycled and reused in the SAM [128].

Ethanol preconcentration

After the condensation part of PTD, the ethanol concentration is increased from 5 wt% in the fermentation broth to ~32 wt%. However, to obtain bioethanol that satisfies the required standards (99.8 vol% in EU, 99.0 vol% in US and 99.6 vol% in Brazil [100]), additional purification is required. Due to the formation of azeotrope between ethanol and water (Table 2-9), several steps are needed in further processing. Firstly, the dilute ethanol-water mixture needs to be preconcentrated. At the industrial scale, this step is usually performed by using conventional distillation [102]. Being a lower boiling component, ethanol is separated as a top product, together with some water due to the azeotrope formation. The highest ethanol concentration that can be obtained in this step is nearly the azeotropic one. Yet, approaching the azeotropic concentration in the top stream increases the energy requirements for this separation, but further purification to anhydrous product becomes less energy demanding. The optimal ethanol concentration after the preconcentration has been determined to be 91 wt% ethanol [103]. This value was used subsequently.

Table 2-9. Boiling points of ethanol and water, and azeotrope formation (at 1 bar)

Pure components		Azeotrope		
Component	Tb (°C)	Mass fraction	T (°C)	type
Ethanol	78.31	0.9557	78.15	homogenous
Water	100.00	0.0443		

Ethanol preconcentration takes place in distillation column C1 (see Figure 2-16), operating at atmospheric pressure (1 bar). Sieve trays with a pressure drop of 8 mbar per tray were used as internals [112]. As the condensed ethanol-water mixture after the PTD is still at reduced pressure, simple pumps can be used to increase the pressure of this liquid stream to the atmospheric one. However, after increasing its pressure, the feed stream to column C1 is subcooled liquid resulting in larger heating duty requirements. The top product of this column is the preconcentrated ethanol stream, while the bottom product is pure water. This water stream can be cooled and recycled to the fermenter to decrease the need for fresh water for the upstream part of the bioethanol production process.

Consequently, this stream can be used to preheat the feed stream to column C1. Even though the described heat integration reduces the external heating requirements, still more than 10 MW (about 11.0 and 10.5 MW for PTD-VRC and PTD-MED, respectively) of heating duty is needed.

However, since this column separates relatively close-boiling components, additional energy savings can be obtained by implementing mechanical vapor recompression (MVR). In this heat pumping method, vapor coming from the top of the distillation column is compressed and used to evaporate liquid from the bottom of the distillation column [113]. This results in significant reduction in need for external heating and cooling. By applying MVR to column C1, the need for external heating is completely avoided, while the need for external cooling is reduced by over 97%. The coefficient of performance (COP), which is equal to the ratio of the upgraded heat (i.e. duty covered by the compressed vapor) and the required power (compression duty) [113], is around 5 (5.2 and 5.5 for PTD-VRC and PTD-MED, respectively), thus proving significant energy savings. The compression ratio that is needed for these MVR systems is about 6.4 for PTD-VRC and 5.6 for PTD-MED, meaning that multi-stage compressors should be used.

To obtain a high-purity final bioethanol product, a partial condenser was considered for column C1 to remove the remaining CO_2 in the ethanol-water mixture (streams 12 and 13 in Figure 2-16 and Figure 2-18 are vapor and liquid distillates, respectively). However, this would lead to more ethanol being lost with CO_2. Figure 2-20 shows that to obtain 99.8 wt% ethanol, a vapor fraction of 0.1 on a mass basis is needed in a C1 partial condenser, resulting in a recovery of only ~81% ethanol. However, this significant loss of product was not considered satisfactory and further modifications in process design were conducted.

To avoid losing a significant amount of ethanol, an additional absorption column has been included (Absorber column in Figure 2-16 and Figure 2-18). The bottom product (water) from column C1 is firstly used to preheat the feed stream to this column. Afterward, part of this water stream is used to absorb ethanol from CO_2-rich vapor streams from both the degasser unit (stream 3 in Figure 2-16 and Figure 2-18) and the C1 partial condenser (stream 12 in Figure 2-16 and Figure 2-18). The top product from this column is vapor stream containing mostly water and CO_2. Water from this stream is condensed, mixed with the stream containing microorganisms and recycled to the fermenter, while the remaining CO_2-rich vapor stream is released from the process. The bottom product from this stripping column is water and ethanol stream that is being sent to the stripping column before the SAM unit. Including this additional column in the process design significantly reduces the amount of lost ethanol in the CO_2-rich streams, from ~14% to less than 0.002% of the initially present ethanol. As the added absorption column does not require any external heating, the overall energy requirements are not increased. Due to the reduced operating pressure of this column, structured

packing (type Sulzer Mellapak 250) was chosen as internals, with a pressure drop of 0.225 mbar per theoretical stage [110].

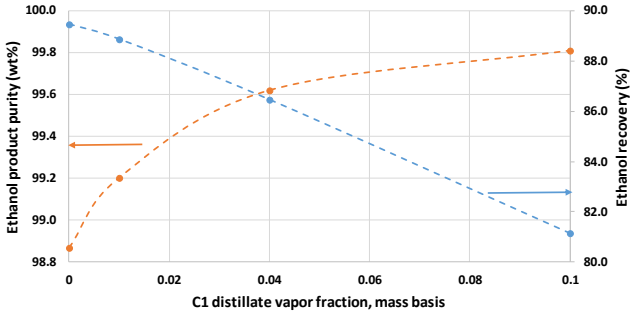


Figure 2-20. Dependency of ethanol product purity and recovery on the vapor fraction in C1 partial condenser

Ethanol dehydration

The distillate product from the C1 preconcentration column needs to be further dehydrated to obtain an on-spec product. On industrial scale, the most common dehydration techniques are extractive distillation, azeotropic distillation and adsorption on zeolite [102]. Adsorption is not a proper method in this case since a rather large amount of zeolite is needed due to the large flowrates in the considered process design. With an average adsorption capacity in the range of 0.011-0.387 $g_{water}/g_{zeolite}$ [104], about 24-848 $tonne_{zeolite}$ is needed for 8 h operation (for the considered capacity). Furthermore, azeotropic distillation has several disadvantages compared to extractive distillation for large-scale ethanol dehydration: larger solvent flowrates are needed, energy requirements are higher since all added solvent needs to be completely evaporated [60] and the required control system is more complicated [101]. Therefore, extractive distillation (ED) is often chosen as the best option for ethanol dehydration at an industrial level [100]. In this dehydration method, a high-boiling solvent is added to the ethanol-water mixture. This solvent changes the relative volatility of the components, without forming azeotropes with any of them [100]. Ethylene glycol is commonly used as solvent for large-scale ethanol dehydration by extractive distillation [102]. Overall, as ED with ethylene glycol had been proven to be the most effective method for ethanol dehydration, it was chosen for the final purification step.

This process is performed in extractive distillation column C2 and solvent recovery column C3 which operate at atmospheric pressure (1 bar). Sieve trays (with a pressure drop of 8 mbar per tray) were considered as internals [112]. A solvent-to-feed mass ratio of 1.2 was used since it has been determined to be the optimal one for the ethanol dehydration part of the process [154]. The top product from the ED column C2 is a high-purity (99.8 wt%) bioethanol product, while the bottom product containing solvent and water is sent to the solvent recovery column C3. Pure water, separated as the top product from column C3, can be cooled down and recycled to the fermenter to reduce fresh water requirements for this step. The bottom product is recovered solvent that is being recycled and reused in column C2.

Having designed the ethanol dehydration part of the process, additional energy savings can be obtained by using heat integration opportunities. The complete ethanol recovery process with applying heat pump-assisted desorption step (PTD-VRC) and MED (in PTD-MED) were designed, and their performance is compared in the following sections.

Process design of the full bioethanol recovery

Configuration 1 – PTD with heat pump-assisted desorption (PTD-VRC)

The flowsheet of the overall ethanol recovery process using PTD-VRC configuration is shown in Figure 2-16.

As the temperature at the top and bottom of extractive distillation column C2 are 76 °C and 155 °C, respectively, compressing the top vapor would not provide sufficient heat to the reboiler. Nonetheless, a side reboiler (1.9 MW) can be added wherein the compressed top vapor is used to evaporate part of the liquid side stream. Using this heat integration, the heating duty for column C2 is reduced by about 36% (from 5.3 MW to 3.4 MW). Additionally, the external cooling for this column is decreased by 37% (from -3.8 MW to -2.4 MW). The COP of this heat pump system is about 2.9. Since this value is higher than the ideal COP of an industrial heat pump (starting from 2.0 [155]) and also higher than the conservative value of the thermal-electrical conversion factor (about 2.5 [156]), the proposed heat pump system can reduce the total energy requirements for this column, leading to energy savings. As the required compression ratio is 5.0, a multi-stage compressor should be used.

Furthermore, since the recovered ethylene glycol from the bottom of column C3 must be cooled before being reused in extractive distillation column C2 [103], it can be utilized to evaporate part of the bottom liquid from column C2. Even though the recovered solvent cannot provide sufficient heat to eliminate the need for heating utilities for column C2, this heat integration results in an additional 21% reduction in external heating requirements. As a result of the described heat integrations, the total need for external heating for the extractive distillation column is reduced by about 57% (from 5.3 MW to 2.3 MW).

Moreover, additional heat integration can be applied to improve the performance of the desorption part of the PTD process. The bottom product (water) from the preconcentration column C1 can evaporate part of the ethanol and water from diluted brine before being used to absorb ethanol from CO_2-rich streams. By this heat integration, the required heating duty for the desorption step is reduced by ~0.8 MW. Additionally, the recovered solvent needs to be further cooled even after being used to evaporate part of the bottom liquid from the extractive distillation column C2 [103]. Consequently, it can also be used to evaporate part of the diluted brine and to reduce the total heating duty for the desorption step by an additional 0.8 MW. Therefore, using the heat content of hot process streams in the desorption step can reduce the total heating requirements by more than 6%. Although this reduction is not that large, the compressor duty decreases by about 7% (from 3.7 MW to 3.4 MW) and the outlet temperature of the compressed vapor decreases from 254 °C to 242 °C. The COP for the vapor recompression system is ~6.9, while the compression ratio is 4.0. Accordingly, the described heat integrations lead to a safer and less energy-intensive bioethanol recovery process.

Configuration 2 – PTD combined with multi-effect distillation (PTD-MED)

The flowsheet of the overall ethanol recovery process using PTD-MED is presented in Figure 2-18.

The largest heating duty in this process configuration is the one needed to evaporate part of the HP stream in the MED process (about 9.0 MW). Therefore, additional heat integration and heat pumping were applied to decrease energy requirements for this step. Firstly, the recovered ethylene glycol from the bottom of column C3 is used to heat part of the HP stream, which decreases external heating requirements by about 1.3 MW. Secondly, top vapor from extractive distillation column C2 is compressed and used to evaporate part of HP stream. This implementation of heat pumping reduced external heating requirements by additional 4.0 MW, having a COP of 5.2, which confirms the large energy savings. The compression ratio needed for this heat pump system is 6.0, which indicates that a multi-stage compressor should be used. Overall, the external heating for the MED part of the process is reduced by about 60% (from 8.9 MW to 3.6 MW).

Techno-economic analysis

More details about the methodology for performing the economic evaluation of the developed process are presented in Appendix A. The calculated economic indicators for both configurations of the bioethanol recovery process are summarized in Table 2-10.

Table 2-10. Key economic indicators of ethanol recovery using PTD

Economic indicators	**PTD-VRC**	**PTD-MED**
CAPEX (k$)	33,595	28,378
OPEX (k$/y)	8,481	9,512
OPEX ($/$kg_{EtOH}$)	0.088	0.101
TAC (k$/y)	11,840	12,349
TAC ($/$kg_{EtOH}$)	0.122	0.131

The total costs for installing all process equipment units are 18,213 k$ for PTD-VRC and 15,470 k$/y for PTD-MED. The cost distribution between different equipment types is presented in Figure 2-21. For PTD-VRC, the largest part of the equipment cost is the cost for compressors (~55%) and heat exchangers (~28%), whereby the costs for distillation columns, pumps and flash vessels are significantly lower (respectively 13%, 3% and 1%). In case of PTD-MED, by far the biggest part of equipment expenses is the cost for heat exchangers (~37%) and compressors (~34%), followed by the cost for the distillation columns (~16%) and pumps (~11%), while the cost for flash vessels is significantly lower (only ~2%). CAPEX are 33,595 k$ for PTD-VRC and 28,378 k$ for PTD-MED. The equipment costs are the largest contributor to the CAPEX in both process configurations (about 54-55%, shown in Figure 2-21).

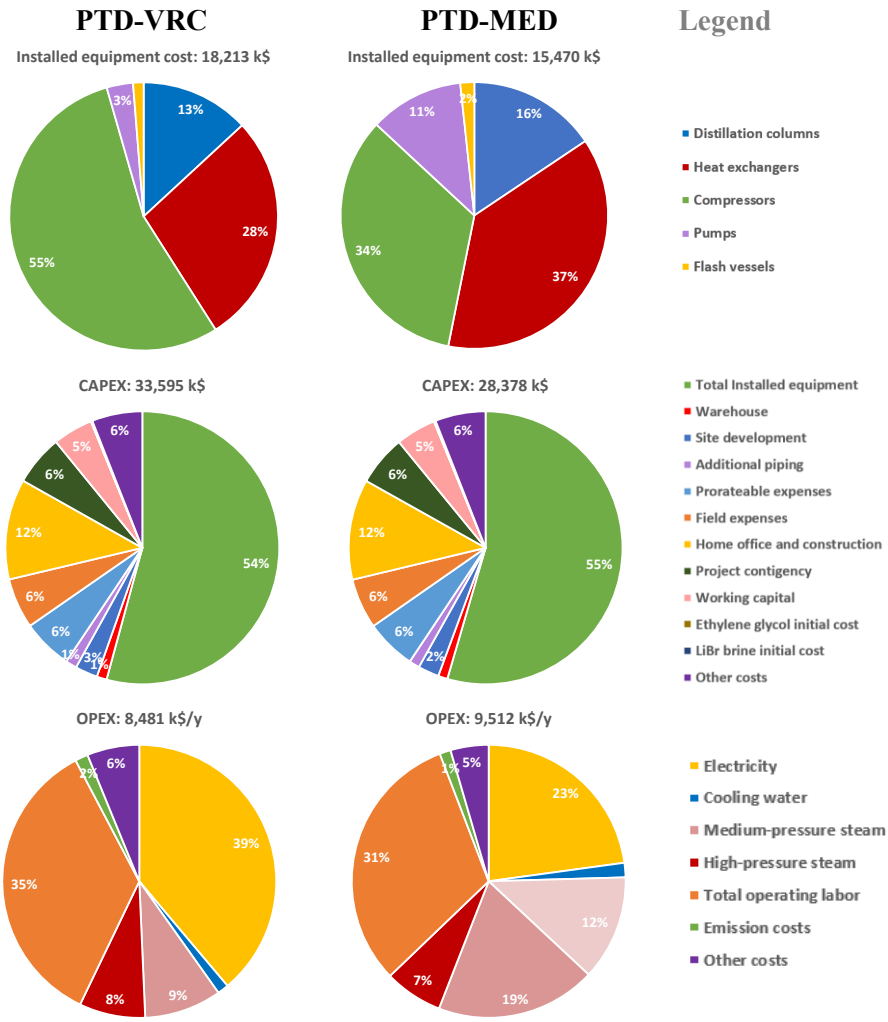


Figure 2-21. Total installed equipment cost, CAPEX and OPEX for bioethanol recovery processes

OPEX for both process configurations are also presented in Figure 2-21. OPEX for PTD-VRC is 8,481 k$/y, which is mostly due to the cost for utilities (~57%) and operating labor (~35%). The high electricity cost (~39% of the total OPEX) is mainly due to the usage of compressors (accounting together ~96% of the electricity cost), whereby the electricity cost for pumps is significantly lower (~4%). In the case of PTD-MED, OPEX is 9,512 k$/y. The largest part of the OPEX is the cost of utilities (over 62%) and operating labor (~31%). Among the cost for utilities, the largest distribution is due to the different types of heating utilities (together ~38% of the total OPEX). Expressed in relative terms, the OPEX for two process configurations are 0.088 and 0.101 $/kg$_{EtOH}$, respectively.

When both CAPEX and OPEX are taken into account, the TAC for the bioethanol recovery process is 11,840 k$/y for PTD-VRC and 12,349 k$/y for PTD-MED, which amounts to 0.122 and 0.131 $/kg$_{EtOH}$ respectively. The economic assessments of the developed process configurations prove the competitiveness of the proposed designs for the large-scale bioethanol recovery from the fermentation broth [60,103,154].

Summing up, the PTD-MED system requires less investment, but the PTD-VRC option is more favorable in terms of operating costs. The effect of the assumed payback period on the TAC for both process configurations is presented in Figure 2-22. For a payback period of less than 3.5 years, PTD-MED is more economically favorable, but if the payback period exceeds 3.5 years, using PTD-VRC leads to a much lower TAC.

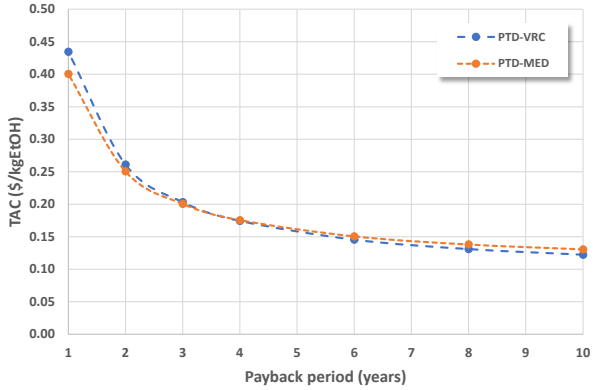


Figure 2-22. Effect of payback period on the specific total annual cost

However, due to the large contribution of utilities to the OPEX, the availability and cost of certain types of utilities must be determined per site prior to choosing the best option. If the price ratio for heating utilities (steam) to electricity is smaller than currently assumed (conversion factor 2.5), then PTD-MED is more likely to become the better solution for the PTD process. This is due to the fact that the expenses ratio for heating utilities to electricity is currently ~38/23 for this case, while for the PTD-VRC option, this ratio is ~17/39.

Sustainability assessment

In addition to the economic analysis, a significant focus was put on evaluating the performance of the designed recovery processes in terms of environmental impact. More details about the methodology for estimating the environmental impact of the developed process are presented in Appendix A. Table 2-11 summarizes the main sustainability metrics [68] for both process configurations of the bioethanol recovery from the fermentation broth.

Table 2-11. Key sustainability metrics of ethanol recovery using PTD

Sustainability metrics	**PTD-VRC**	**PTD-MED**
Thermal energy requirements ($kW_{th}h/kg_{EtOH}$)	0.320	0.889
Electrical energy requirements (kW_eh/kg_{EtOH})	0.561	0.378
Primary energy requirements ($kW_{th}h/kg_{EtOH}$)	1.723	1.834
Water consumption (m^3_w/kg_{EtOH})	0.158	0.234
Water loss (m^3_w/kg_{EtOH})	0.011	0.016
CO_2 emissions (kg_{CO2}/kg_{EtOH})*	0.292 / 0.035	0.309 / 0.136
Material intensity (kg_{waste}/kg_{EtOH})	0.000	0.000
Pollutant emissions ($kg_{pollutant}/kg_{EtOH}$)**	0.000	0.000
Toxic emissions ($kg_{toxic\ materal}/kg_{EtOH}$)**	0.000	0.000

*Grey / green electricity

**Excluding emitted CO_2

- ***Energy intensity:*** Regarding thermal energy requirements, 0.320 $kW_{th}h/kg_{EtOH}$ is needed in PTD-VRC process and 0.889 $kW_{th}h/kg_{EtOH}$ is needed in PTD-MED process. Higher usage of thermal energy for PTD-MED is mostly due to the need for external heating in the MED section. The electrical energy requirements are 0.561 kW_eh/kg_{EtOH} (PTD-VRC) and 0.378 kW_eh/kg_{EtOH} (PTD-MED). The larger electrical energy requirement for PTD-VRC is mainly due to the compressor used in the heat pump-assisted desorber unit. The overall primary energy requirements (considering both the thermal and electrical energy usage) are 1.723 and 1.834 $kW_{th}h/kg_{EtOH}$ for PTD-VRC and PTD-MED, respectively. The performed analysis of energy requirements has demonstrated that both designed bioethanol recovery processes are highly competitive for the large-scale operation (1.1-2.1 $kW_{th}h/kg_{EtOH}$) [60,103,154].
- ***Water consumption:*** The total need for cooling water is 0.147 m^3_w/kg_{EtOH} for PTD-VRC and 0.218 m^3_w/kg_{EtOH} for PTD-MED. Taking into account loss of both cooling water and steam condensate, the total need for water for two process configurations is 0.158 and 0.234 m^3_w/kg_{EtOH}, respectively. Furthermore, about 0.011 m^3_w/kg_{EtOH} of water is lost with the bioethanol recovery in PTD-VRC, whereby the total water losses in PTD-MED are 0.016 m^3_w/kg_{EtOH}.
- ***Material intensity:*** In addition to high-purity bioethanol product, the output streams from both process configurations are the stream containing living microorganisms and heavy inert components that might be recycled to the

fermenter, and water streams that are cooled and also may be recycled to the fermenter. Furthermore, the recovered LiBr brine and ethylene glycol are being reused in the process. Lastly, the CO_2-rich stream that is emitted was accounted for in the greenhouse gas emissions metrics and therefore it was not considered here. Since no stream is waste, the material intensity for both designed configurations equals zero.

- ***Greenhouse gas emission:*** If grey electricity is used, the total CO_2 emissions are 0.292 kg_{CO2}/kg_{EtOH} for PTD-VRC and 0.309 kg_{CO2}/kg_{EtOH} for PTD-MED. However, if green electricity is used, the total CO_2 emissions for PTD-VRC are reduced by ~88% to only 0.035 kg_{CO2}/kg_{EtOH}, whereas for PTD-MED this reduction is ~56% to 0.136 kg_{CO2}/kg_{EtOH}.
- ***Pollutant and toxic emissions:*** Besides the already mentioned CO_2, the bioethanol recovery from fermentation broth does not emit any other pollutants or toxic materials.

2.2.5. PTD technology perspectives

PTD is a new method that should certainly be added to the separation technologies toolbox, being useful in applications where classic distillation is not suitable and other methods are either too costly or too prone to fouling. It can be applied not only to the recovery of bioalcohols, but also to the processing of complex aqueous waste streams, which are too contaminated to be treated and are presently incinerated at great cost. Other applications may include: organic solvents recovery, water removal for drying of chemicals, aroma recovery in the food industry, concentrating orange juice, separation of heat-sensitive materials, purification of pharmaceutical products, etc.

As proven in this study, PTD can also be coupled with advanced heat pumping systems or MED to reduce total energy requirements, resulting in an overall highly competitive downstream process. Performing evaporation and condensation at different pressures offers several advantages as compared to conventional vacuum distillation:

- Applicability of this technology is expanded to highly heat-sensitive materials.
- Usage of expensive refrigeration is avoided, potentially resulting in significantly lower operating costs [128].
- Equipment size is reduced as compared to conventional distillation columns [128].
- The field of application can be extended to new processes, e.g. ethanol recovery from fermentation broth. Continuous separation of fermentation products will significantly reduce end-product inhibition and thus increase fermentation yield. Furthermore, keeping temperatures below 37°C allows the recycling of present microorganisms to the fermenter.

Significant biomass loss can be avoided in this way, while allowing fermentation to be performed in a closed loop [128].

Even though PTD technology has some limitations (e.g. difficulties in finding appropriate absorption fluids, or properly modeling the thermodynamic properties), and might not be suitable for every application, its effectiveness has been demonstrated in situations where water serves as the primary volatile component and lithium bromide solution functions as the absorbent fluid [128]. While it may not be the best technology for large-scale ethanol recovery, it has been proven to be highly competitive and effective [102]. As such, it should be added to the separation methods toolbox. Additionally, the usage of PTD may be even more beneficial in the case of more volatile products than ethanol, which would otherwise lead to lower condensation temperatures in the initial separation step. Further research is needed to determine other combinations of volatile components and absorbent fluids.

2.2.6. Conclusions

The main innovations in this original research are multifaceted. One novelty is related to the rigorous modelling of the complex ternary system LiBr-ethanol-water. A reliable property model was developed to account for interactions between the present electrolyte and two solvents, as well as relations among two polar solvents. Another novelty consists of the implementation of pass-through distillation (PTD) technology for industrial-scale bioethanol recovery from the dilute fermentation broth.

The proposed PTD process can effectively recover more than 94% of ethanol from the fermentation broth, while concentrating the water-ethanol mixture from 5 wt% to over 30 wt% and providing full recycle of biomass. The flexibility of PTD technology was expanded by developing and comparing two designs for the desorption and the condensation parts: heat pump (vapor recompression) assisted desorber (PTD-VRC) and multi-effect distillation (PTD-MED). Also, the preconcentration and dehydration sections were designed for both options to obtain high-purity (99.8 wt%) bioethanol.

The performed analysis of economic and environmental impacts proved that PTD is a competitive technology that can be used in large-scale concurrent alcohol recovery and fermentation (0.122 $\$/kg_{EtOH}$ and 1.723 $kW_{th}h/kg_{EtOH}$ for PTD enhanced with heat pumps, and 0.131 $\$/kg_{EtOH}$ and 1.834 $kW_{th}h/kg_{EtOH}$ for PTD coupled with multi-effect distillation). Apart from removing inhibitory product from the broth, recycling the separated microorganisms with most of the water may enhance the fermentation process by avoiding biomass loss and reducing water requirements. As both options proved to be cost-effective and energy-efficient, the choice of the best configuration depends on the exact site location and the availability of different utilities.

As PTD has already been proven to be efficient on bench- and pilot-scale levels by Drystill, this original research offers insights into the application of this novel technology on an industrial level. Further research that explores the application of the PTD process to other systems would be extremely beneficial. Species that require refrigeration for condensation, as well as thermally unstable components, are an important direction in which to focus future research.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, I.R. McGregor, A.A. Kiss, Bioethanol separation by a new pass-through distillation process, Separation and Purification Technology 336 (2023) 126292. https://doi.org/10.1016/j.seppur.2024.126292. This file provides additional details regarding the development of a reliable property model for the system LiBr-ethanol-water and the followed methodology for assessing the economic and environmental impact of the designed processes.

2.3. Recovery of isopropanol and acetone after syngas fermentation

Isopropanol and acetone production by syngas fermentation is a promising alternative to conventional fossil carbon-dependent production. However, this alternative technology has not yet been scaled up to an industrial level due to the relatively low product concentrations (about 5 wt% in total). This original research aims to develop cost-effective and energy-efficient processes for the recovery of isopropanol and acetone from highly dilute fermentation broth (>94 wt% water) for large-scale production (about 100 ktonne$_{IPA+AC}$/y).

Vacuum distillation and pass-through distillation enhanced with heat pumps or multi-effect distillation were efficiently coupled with regular atmospheric distillation and extractive distillation in several innovative intensified downstream processes. Over 99.2% of isopropanol and 100% of acetone were recovered as high-purity end-products (>99.8 wt%). Advanced heat pumping (mechanical vapor recompression) and heat integration techniques were implemented to decrease total annual costs (0.109-0.137 \$/kg$_{IPA+AC}$), reduce energy requirements (1.348-2.043 kW$_{th}$h/kg$_{IPA+AC}$) and lower CO_2 emissions (0.067-0.191 kg$_{CO2}$/kg$_{IPA+AC}$), resulting in highly competitive recovery processes.

The proposed three novel isopropanol and acetone recovery processes from dilute broth significantly contribute to the expansion of sustainable industrial fermentation. Furthermore, this original research is the first one to develop novel pass-through distillation technology for the complex isopropanol- acetone-water system. All the designed processes are highly economically competitive and environmentally viable. In addition to recovering efficiently both isopropanol and acetone, the designed downstream processes offer the possibility to enhance the fermentation process by recycling all the present microorganisms and reducing the fresh water requirements.

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2.3.1. Introduction

Isopropanol and acetone are examples of essential platform chemicals that are mainly produced from fossil carbon sources. The total global market of these chemicals is about 10 billion US$ [73] with an expanding trend [157]. Isopropanol is an important industrial solvent and precursor, pharmaceutical ingredient, disinfectant, and fuel additive. Similarly, acetone has applications as an industrial solvent and platform chemical, but can also be used for enhancing fuel performance [73,157,158]. In industry, isopropanol is primarily produced from propylene through direct or indirect hydration, while acetone is mainly produced as a by-product of phenol in the cumene process. Even though these processes usually result in high conversion rates and selectivity, increasing feedstock costs and stricter environmental regulations are becoming limiting factors [157]. However, the manufacturing of these chemicals through fermentation processes is a promising, sustainable alternative [72,159].

To date, numerous research studies have explored the pathways for synthesizing acetone and isopropanol [73,157,158,160–163]. The main obstacle to commercialization is the low yield on carbohydrates that has been achieved so far [73]. However, LanzaTech has recently engineered *Clostridium autoethanogenum* and *Clostridium auto* strains to produce isopropanol and acetone from syngas. Substrate gases for fermentation can be either waste gases from heavy industries or syngas formed by biomass gasification. These gases can be converted to mixtures of isopropanol and acetone by engineered bacteria [164]. The technology has already been tested on a pilot scale [73], but an industrial scale has not been reached yet [164]. Due to product inhibition, concentrations of isopropanol and acetone in fermentation broth will certainly be below 10 wt% [165]. These low titers lead to a challenge for designing downstream processes, which is expected to be a significant cost contributor in large-scale processes [24]. However, few studies have been published on the recovery of isopropanol and acetone from syngas fermentation broth [166–168], mainly focusing on recovering only one of these components, and usually not on an industrial scale. Therefore, this original study is the first one to conceptually design eco-efficient large-scale (production capacity 100 $ktonne_{IPA+AC}/y$) recovery methods for both isopropanol and acetone after syngas fermentation.

2.3.2. Problem statement

Recovery of isopropanol and acetone was designed for a large-scale industrial plant with a total isopropanol and acetone productivity of about 100 ktonne/y. The feed stream for this process is broth taken from the fermenter. It had already been proven that the microorganisms can tolerate about 50 g/L of isopropanol and acetone [169], while the mass ratio between produced isopropanol and acetone is 4:1 [73]. Hence, it was considered that isopropanol and acetone concentrations are 4 and 1 wt%, respectively. The concentration of acetate was determined relative to the concentration of isopropanol [163]. Additionally, some microorganisms and non-volatile inert components are present in the fermentation broth. These heavy components can be practically neglected in the simulations as they are removed in the first step, without evaporation. Nonetheless, the fermentation broth is very diluted, containing over 94 wt% water, which is the main challenge for product purification. This stream is at atmospheric pressure (1 bar) and fermentation temperature of 30 ˚C [161,162]. Besides the highly dilute stream and the presence of living microorganisms, purification of syngas fermentation products is challenging due to the closeness of boiling points and the water-isopropanol azeotrope (Table 2-12).

Table 2-12. Boiling points of pure components and azeotrope formation at 1 bar

Pure components		Azeotrope		
Component	Tb (°C)	Component	Mass fraction	T (°C) / type
Acetone	56.25	Isopropanol	0.8717	80.23 /
Isopropanol	82.25	Water	0.1283	homogenous
Water	100.00			
Acetic acid	117.95			

2.3.3. Method of process design and simulation

As suggested earlier [19,154], bacteria may be recycled to the fermentation if the initial recovery step ensures viability of the bacteria. Thus, the recovery process was designed in a way to initially separate isopropanol and acetone from the microorganisms and most of the water without harming microbial viability. Two different options were considered for this step: vacuum distillation and pass-through distillation. Accordingly, an additional novelty in this research is pass-through distillation design for a complex isopropanol-acetone-water system and the development of the required thermodynamic property model. Microorganisms with most of the water may be recycled to the fermentation to avoid loss of biomass, reduce the need for fresh water and allow the upstream fermentation to operate in a closed loop [19]. Traces of acetate and minerals will also be recycled, but can be used by the microorganisms [73]. Furthermore, several distillation steps are needed to obtain high-purity final isopropanol and acetone products from the separated aqueous solution. Advanced heat pumping

and heat integration techniques were considered to reduce energy requirements and greenhouse gas emissions. For evaluating the designed processes, the economic (capital, operating and total recovery costs) and environmental impact (energy intensity, water consumption, CO_2 emissions, etc.) were calculated to determine the overall cost and energy efficiency. Rigorous simulations for every step in the recovery process were developed in Aspen Plus.

2.3.4. Results and discussion

This section presents the results of the process design for the recovery of isopropanol and acetone from the fermentation broth. Additionally, outcomes of the techno-economic evaluation and calculation of sustainability metrics are provided and analyzed.

Process design

Process flowsheets of the three designed process configurations, VD, PTD-VRC and PTD-MED, are presented in Figure 2-25, Figure 2-26 and Figure 2-27, respectively.

Separating products from the fermentation broth

The first step in the recovery process is separation of isopropanol and acetone from the remaining fermentation broth, whereby temperature conditions are kept appropriate for microorganisms. Vacuum distillation and pass-through distillation were designed for this initial separation.

Vacuum distillation

To ensure that the operating temperature does not exceed the fermentation temperature (30 ˚C), isopropanol and acetone can be separated from most of the fermentation broth using vacuum distillation. This process configuration is referred to as VD (see Figure 2-25), which is further discussed afterward. Thermodynamic properties were specified with the NRTL property method coupled with the Hayden O'Connell model for vapor phase association [97] due to the presence of acetic acid. Vacuum distillation is performed in distillation column C1, which was designed assuming the structured packing type Sulzer Mellapak 250 for its internals [110]. A condenser pressure of 0.032 bar was selected, with a pressure drop of 0.225 mbar per theoretical stage [110]. At this operating pressure, the temperature in this column drops from about 30 ˚C at the bottom to only 10 ˚C at the top. Consequently, cooling water cannot be used for the cooling and more expensive chilled water is required. Additionally, the heating duty required for this column is very high (about 22 MW) due to the large feed flowrate. However, the relative closeness of top and bottom temperatures offers possibility to apply mechanical vapor recompression (MVR) to this column [170]. This heat pump design implies compressing vapor coming from the top of a

distillation column and using the compressed vapor to evaporate liquid from the bottom of the column [113]. The coefficient of performance (COP) of this system is the ratio of exchanged heating duty (between compressed top vapor and bottom liquid) and required compressor duty. The COP of MVR for column C1 (8.8) is significantly higher than the electrical-to-thermal energy conversion factor, for which 2.5 is a conservative value [156]. Therefore, MVR drastically reduces energy requirements for this separation.

Isopropanol and acetone are completely separated from the remaining fermentation broth in this first distillation step. The top stream contains about 28.8 wt% isopropanol and 7.2 wt% acetone and requires further processing. The bottom stream contains most of the water, all microorganisms and all other inert compounds. As mentioned, this stream may be recycled to fermentation to enhance the performance of the upstream process.

Pass-through distillation

The described vacuum distillation results in a very low condensation temperature (10 ˚C). Consequently, usage of chilled water is required. Pass-through distillation (PTD) is a new separation technique that can avoid such a low condensation temperature. This can be of even greater significance if the upper-temperature limit is lower than the assumed 30 ˚C since it would result in a higher vacuum and consequently, lower condensation temperature. The working principle of PTD is decoupling of evaporation and condensation by using an absorption-desorption loop with concentrated lithium-bromide (LiBr) solution as absorbent fluid [27]. The PTD consists of four steps: evaporation, absorption, desorption and condensation. Firstly, part of the liquid feed stream is evaporated, and the formed vapor is absorbed using the absorbent fluid. These evaporation and absorption steps can be integrated into one process unit, called the stripping-absorption module (SAM), which does not require external heating [131]. After leaving the SAM unit, the absorbed components are evaporated from the diluted absorbent fluid and then condensed. As a result, evaporation can be performed at lower pressure (and temperature) that does not harm heat-sensitive compounds, while condensation can operate at higher pressure (and temperature), which allows the usage of cheaper cooling utilities. Besides suitability to heat-sensitive materials and lower operating costs due to the elimination of expensive refrigeration utilities, the benefit of PTD is reduced equipment size compared to vacuum distillation technologies, resulting in lower investment costs. Furthermore, energy requirements are highly competitive as compared to distillation [27].

Designing a PTD recovery process is challenging due to the presence of absorbent fluid. A reliable thermodynamic property model is needed. Therefore, interactions between the electrolyte absorbent (LiBr) and four polar solvents (water,

isopropanol, acetone and acetic acid) were taken into account. The ElecNRTL-RK, electrolyte-NRTL model coupled with Redlich-Kwong equation of state, was chosen [137] since it describes complex systems using binary interactions. Experimental data [135,136,171,172] for binary systems were used to determine values of binary interaction parameters (BIPs).

As mentioned, the evaporation and absorption parts of PTD can be coupled in the SAM unit. To improve the performance of the PTD process by lowering potential product losses, and increasing isopropanol and acetone concentration in the vapor that is being sent to the absorption part, SAM was preceded by stripping column C1 (see Figure 2-26 and Figure 2-27, further discussed afterward). Isopropanol and acetone concentrations are maximized in the outlet vapor from this column before these compounds are absorbed using concentrated LiBr solution. The liquid phase remaining from the evaporation step contains most of the water, microorganisms and inert compounds, and may be recycled to the fermentation. The selected operating pressure for the SAM unit (0.0432 bar) ensures complete evaporation while maintaining 30˚C (Figure 2-23). The vapor fraction in SAM (0.11) was selected such that the isopropanol recovery in the formed vapor is more than 99% (Figure 2-23). Subsequent absorption of this vapor by LiBr solution releases heat that is transferred by heat pipes to the evaporation part of the SAM [131]. The flowrate of absorbent fluid relative to the flowrate of vapor feed (1.6 on a mass basis) was determined such that the diluted brine could provide heat for the evaporation step. Consequently, effective heat recovery from absorption to the evaporation part was achieved.

After the SAM, the diluted brine is regenerated and recycled in a continuous circuit [27]. Previously absorbed isopropanol and acetone, with some water, are desorbed from the diluted stream and then condensed. Two alternative approaches were considered for desorption and condensation: heat pump (vapor recompression) assisted desorption and multi-effect distillation. These process configurations are referred to as PTD-VRC and as PTD-MED, respectively (Figure 2-26 and Figure 2-27).

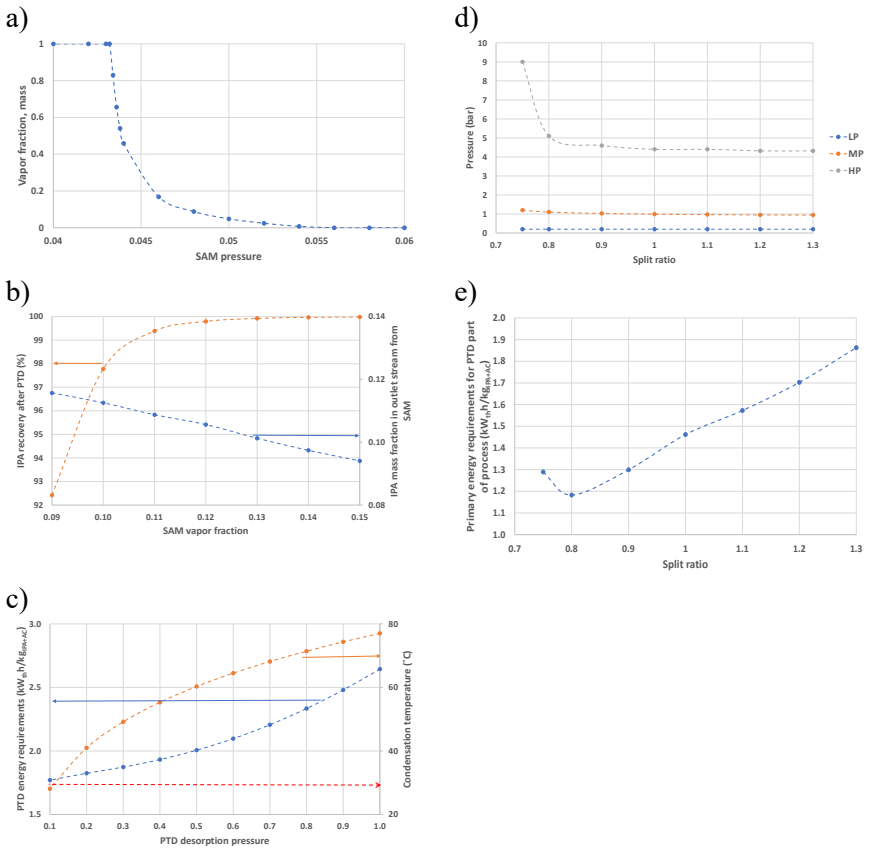


Figure 2-23. Operating parameters for PTD: a) pressure in SAM unit, b) defined vapor fraction in SAM unit, c) desorption pressure in PTD-VRC configuration, d) split ratio in PTD-MED configuration - high pressure (HP), medium pressure (MP) and low pressure (LP) pressure steam, e) split ratio in PTD-MED configuration - energy requirements

In the PTD-VRC, the desorbed vapor is compressed to provide heat for desorption. This heat pump design was applied since evaporating isopropanol and acetone from diluted brine is very energy intensive. The operating pressure for this part of the PTD (0.2 bar) was chosen to minimize energy requirements for PTD while keeping the condensation temperature (about 41 ˚C) appropriate for using cheaper cooling water (Figure 2-23). The coefficient of performance (COP) of this heat pump system is 6.75. Since this value is again much higher than the conservative value of the electrical to thermal energy conversion factor of 2.5 [156], enhancing the desorption step with vapor recompression significantly improves energy efficiency. After the desorption step, the recovered brine can be reused in the SAM unit [27]. The separated products mixture contains about

28.7 wt% isopropanol and 7.2 wt% acetone, whereby recovery from the fermentation broth is 99.4% and 100% for isopropanol and acetone, respectively.

In the alternative configuration (PTD-MED), concentrated brine is regenerated in three MED stages such that the feed stream is separated into high-pressure (HP), medium-pressure (MP) and low-pressure (LP) streams. The split ratio between these streams (the ratio between flowrates of HP and MP, as well as between MP and LP) determines the minimum pressure difference needed for heat exchange. The pressure of the LP stream (0.2 bar) was determined such that its condensation is possible using cooling water rather than chilled water. With increasing split ratio, flowrates of higher-pressure streams increase. Consequently, the required pressures of HP and MP decrease, but more external heating is needed to heat up the HP stream. To achieve the minimum energy requirements and reasonable pressures, a split ratio of 0.8 was chosen (Figure 2-23). The operating pressures of HP and MP are 5.1 bar and 1.1 bar, respectively. Enhancing desorption with MED results in about 64% reduction in external heating requirements relative to simple desorption from the unseparated diluted brine (from about 23 MW to about 8 MW). The recovered brine can be recycled to the SAM unit [27]. The stream with separated products contains about 28.7 wt% isopropanol (99.2% recovery) and 7.2 wt% acetone (100% recovery).

Acetone purification

The separated isopropanol and acetone mixture from the fermentation broth, either by vacuum distillation (VD) or by PTD coupled with vapor recompression (PTD-VRC) or multi-effect distillation (PTD-MED), needs to be pumped to atmospheric pressure for purification. In the next distillation column C2, acetone, being the most volatile component (Table 2-12), is recovered (100% recovery) in the distillate at high purity (about 99.8 wt%), while a mixture of isopropanol and water is obtained as the bottom product.

As the feed stream to this column is subcooled liquid, it is preheated by implementing heat integration that will be discussed in a later section. Even after heating the feed stream, the required reboiler duty for acetone separation is about 4.0 MW. However, since this column separates relatively close-boiling components, MVR can be applied to reduce energy requirements. COP for this MVR system is in the range of 5.2-6.5, depending on the design of the initial separation step (VD, PTD-VRC or PTD-MED). In all cases, applying heat pumping to this step results in significant energy savings.

Isopropanol purification

Separation of high-purity isopropanol from aqueous solution is challenging due to an azeotrope (Table 2-12). Following recommendations from the literature [173–178], extractive distillation with ethylene glycol was chosen for final isopropanol dehydration. Nonetheless, since the bottom product from column C2 contains only about 31.1 wt% of isopropanol, preconcentration is needed prior to dehydration by extractive distillation. This is done in distillation column C3, where a concentrated isopropanol solution is obtained as the top product while pure water is obtained at the bottom. As the azeotropic composition is approached in the distillate, energy requirements for the preconcentration step increase, but subsequent dehydration becomes less energy intensive. Therefore, energy requirements for the overall process (without implementing any heat integration and heat pumping) were analyzed as a function of the concentration of isopropanol after preconcentration (Figure 2-24). The total energy requirements decrease up to about 86 wt% of isopropanol in the C3 distillate, so this extent of preconcentration is selected. The bottom stream of this column is pure water that can be cooled and recycled to the fermentation to decrease the need for fresh water. Due to the closeness of boiling points of components that are being separated, the reboiler duty required for column C3 is relatively high (about 5.8 MW). Nevertheless, MVR can also be applied to this column, with a COP in the range of 5.2-5.4.

The preconcentrated isopropanol solution is further dehydrated using extractive distillation with ethylene glycol in column C4. The top stream from this column is high-purity (99.8 wt%) isopropanol. The bottom stream contains the ethylene glycol and remaining water, and is sent to solvent recovery column C5. The ethylene glycol is recovered as the bottom stream from column C5 for reuse in column C4. The remaining water is recovered at 100 wt% purity as the top product from column C5 and can be cooled and recycled to the upstream process. The ratio of ethylene glycol to feed flowrate (1.1 on a mass basis) was determined to minimize energy requirements for columns C4 and C5 (Figure 2-24). Due to big differences between top and bottom temperatures from columns C4 and C5, MVR is not suitable. However, since the recovered solvent from column C5 needs to be cooled before reuse in column C4 [174], this stream can be used to evaporate part of the bottom liquid from column C4. This heat integration reduces the need for external heating for column C4 by about 16-17%. Columns C2, C3, C4 and C5 operate at atmospheric pressure, with sieve trays and a pressure drop of 8 mbar per tray [112].

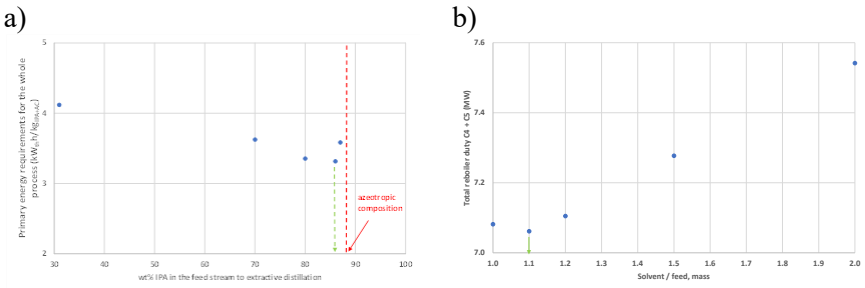


Figure 2-24. a) Isopropanol concentration after preconcentration (energy requirements on y-axis are prior to implementing heat pumping and heat integration), b) Solvent-to-feed ratio for extractive distillation

Full isopropanol and acetone recovery processes

Flowsheets of the developed recovery processes are presented in Figure 2-25, Figure 2-26 and Figure 2-27. All three process designs recover acetone and isopropanol each at 99.8 wt% purity with recoveries of 100% and more than 99.2%, respectively. At the same time, process conditions were designed such that viability of present microorganisms is not harmed. Even though additional experimental validation might be needed, it has been shown that microorganisms can survive exposing fermentation broth to vacuum [96,179,180]. If also applicable in the current case, the separated microorganisms in aqueous stream can be recycled to the upstream process. Additionally, if some CO_2 is present in the fermentation broth, the proposed processes can be expanded by adding initial degassing step under reduced pressure. In case some products are also removed, they should be captured with water in an additional stripping column and returned to the recovery process. Furthermore, the temperature of the fermentation broth higher than 30 ˚C will not affect much the design of the recovery process. For example, with the fermentation broth of 37 ˚C in VD process configuration, the required pressure in column C1 would increase to 0.052 bar, while total heating requirements for distillation columns would alter for less than 0.5%. Therefore, the proposed processes are suitable for the recovery of isopropanol and acetone from fermentation broths of different temperatures.

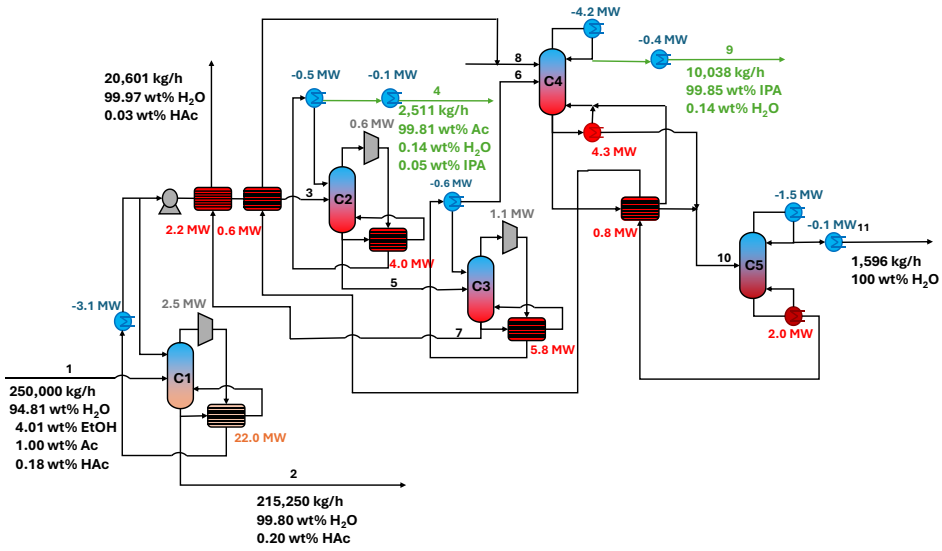


Figure 2-25. Flowsheet of isopropanol and acetone recovery process using VD process configuration (H_2O - water, IPA - isopropanol, Ac - acetone, HAc - acetic acid)

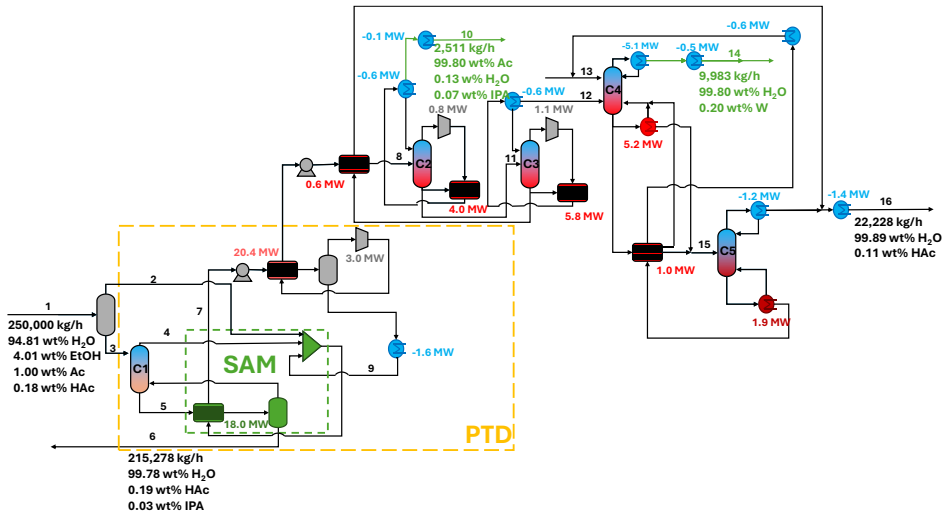


Figure 2-26. Flowsheet of isopropanol and acetone recovery process using PTD-VRC process configuration (H_2O - water, IPA - isopropanol, Ac - acetone, HAc - acetic acid)

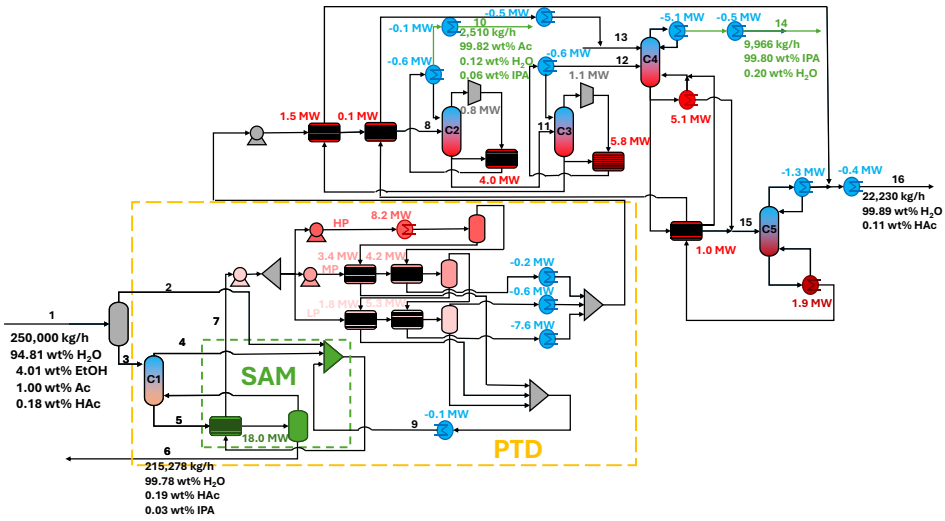


Figure 2-27. Flowsheet of isopropanol and acetone recovery process using PTD-MED process configuration (H_2O - water, IPA - isopropanol, Ac - acetone, HAc - acetic acid)

Besides MVR, additional heat integration is proposed to further reduce energy requirements. As previously mentioned, the water-isopropanol-acetone mixture separated from the rest of the fermentation broth, either by VD, PTD-VRC or PTD-MED, becomes subcooled liquid after pumping to atmospheric pressure. Therefore, preheating this stream to its boiling point can reduce the reboiler duty for column C2, and consequently, the compressor duty required in the MVR system applied to this column. In all process configurations, pure water from the bottom of the isopropanol preconcentration column C3 was used to preheat the feed stream to the acetone purification column C2. The heat capacity of this water stream in PTD-VRC is enough to preheat the water-isopropanol-acetone mixture. However, in VD and PTD-MED, additional heating is needed to preheat this stream to its boiling point. As ethylene glycol needs to be further cooled after evaporating part of the bottom liquid from column C4 [174], this stream can be used to preheat the feed stream to column C2. In this way, sufficient heat is provided in both VD and PTD-MED. These heat integrations reduced the reboiler duty for column C2 by about 41% (from 6.8 to 4.0 MW), about 12% (from 4.6 to 4.0 MW) and about 28% (from 5.6 to 4.0 MW) in VD, PTD-VRC and PTD-MED, respectively.

Techno-economic analysis

More details about the followed methodology for performing economic analysis of the developed process are presented in Appendix A. Economic comparison between all three designed process configurations is presented in Figure 2-28 and Table 2-13. Total installation costs are 15,488, 15,438 and 13,478 k$ for VD, PTD-VRC and PTD-MED, respectively. The largest contribution to equipment cost is due to compressors in case of VD (about 44%) and PTD-VRC (about 51%), due to heat pump systems, and heat exchangers used in multi-effect distillation for PTD-MED (about 42%).

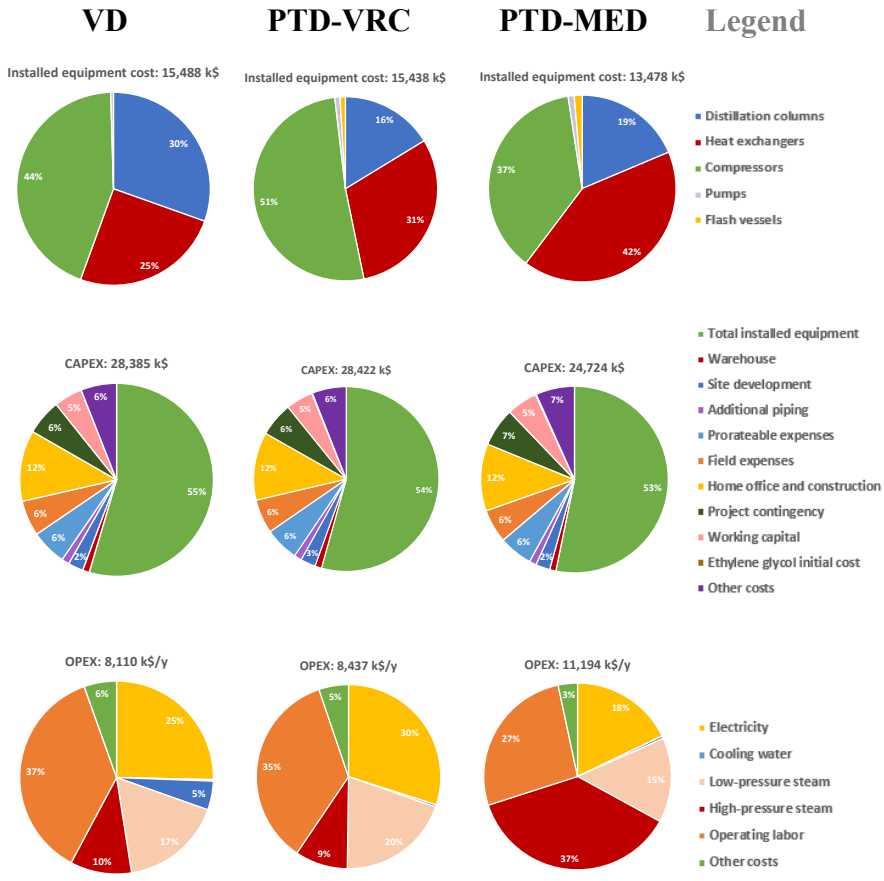


Figure 2-28. Comparison of economic indicators for all processes

Table 2-13. Key economic indicators of isopropanol and acetone recovery

Economic indicators	VD	PTD-VRC	PTD-MED
CAPEX (k$)	28,385	28,422	24,724
OPEX (k$/y)	8,110	8,441	11,199
OPEX ($/kg$_{IPA+AC}$)	0.081	0.084	0.112
TAC (k$/y)	10,949	11,284	13,671
TAC ($/kg$_{IPA+AC}$)	0.109	0.113	0.137

CAPEX are 28,385, 28,422 and 24,724 k$ for VD, PTD-VRC and PTD-MED, respectively. For all process configurations, the main contribution to CAPEX is due to the equipment installed (about 53-55%). Therefore, recovering isopropanol and acetone using pass-through distillation coupled with multi-effect distillation (PTD-MED) is the best option in terms of capital investment, due to the lower equipment cost.

OPEX for VD, PTD-VRC and PTD-MED is 8,110, 8,441 and 11,199 k$/y, respectively, with utilities as main cost contributor (about 57%, 60% and 70%, respectively). Among utilities, electricity costs dominate OPEX for VD and PTD-VRC (about 25% and 30%) due to implemented heat-pump systems. For PTD-MED, high-pressure steam costs dominate (about 37%) due to the evaporation of the HP stream and heating the solvent recovery column C5. Per kilogram of recovered isopropanol and acetone, the OPEX is 0.081, 0.084 and 0.112 $/kg$_{IPA+AC}$ for VD, PTD-VRC and PTD-MED, respectively. Therefore, VD and PTD-VRC designs are more appropriate than PTD-MED in terms of operating costs. However, cost for utilities highly depends on the site location, whereas the used costs are fixed according to literature recommendations [115]. If the unit cost ratio for heating to electricity is much lower than the value assumed, the PTD-MED becomes the optimal process configuration. Alternatively, if using electricity is more favorable, then the VD and PTD-VRC designs are better options.

The total annual cost (taking into account both CAPEX and OPEX) is 10,949, 11,284 and 13,671 k$/y, corresponding to 0.109, 0.113 and 0.137 $/kg$_{IPA+AC}$, for VD, PTD-VRC and PTD-MED, respectively. Since market prices for isopropanol and acetone are assumed to be 1.0-1.32 and 0.88-1.05 $/kg, respectively [167,181], all proposed process designs are highly economically competitive. Furthermore, to expand flexibility of the performed economic evaluation, the influence of the payback period on total costs is analyzed and presented in Figure 2-29. The designed recovery processes are competitive even with shorter payback periods (e.g. with a payback period of 3 years, recovery costs for all three process designs are lower than 0.2 $/kg$_{IPA+AC}$).

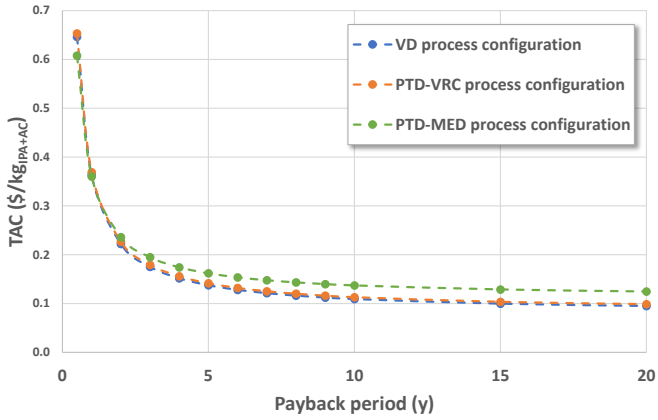


Figure 2-29. Influence of payback period on the total annual costs

Sustainability assessment

More details about the followed methodology for estimating the environmental impact of the developed process are presented in Appendix A. Table 2-14 gives an overview of the environmental impact of the proposed processes.

Table 2-14. Key sustainability metrics of isopropanol and acetone recovery

Sustainability metrics	**VD**	**PTD-VRC**	**PTD-MED**
Thermal energy requirements ($kW_{th}h/kg_{IPA+AC}$)	0.502	0.566	1.214
Electrical energy requirements (kW_eh/kg_{IPA+AC})	0.338	0.418	0.331
Primary energy requirements ($kW_{th}h/kg_{IPA+AC}$)	1.348	1.612	2.043
CO_2 emission* (kg_{CO2}/kg_{IPA+AC})	0.221/0.067	0.264/0.073	0.342/0.191
Water consumption (m_w^3/kg_{IPA+AC})	0.145	0.162	0.261
Water loss (m_w^3/kg_{IPA+AC})	0.011	0.012	0.019
Pollutant emission ($kg_{pollutant}/kg_{IPA+AC}$)	0	0	0
Toxic materials emission ($kg_{toxic\ materials}/kg_{IPA+AC}$)	0	0	0

*Grey/green electricity

- ***Energy intensity***: Due to the need for heating the HP stream in the multi-effect distillation, thermal energy requirements are the highest for PTD-MED (1.214 $kW_{th}h/kg_{IPA+AC}$). Contrary, electrical energy requirements are the highest for PTD-VRC (0.418 kW_eh/kg_{IPA+AC}), mainly due to the compressors used in heat pump assisted desorption in PTD and MVR systems. The primary energy requirements, which take into account both thermal and electrical energy, are 1.348, 1.612 and 2.043 $kW_{th}h/kg_{IPA+AC}$ for VD, PTD-VRC and PTD-MED, respectively. Notably, lower concentrations of isopropanol and acetone in the feed stream would lead to more energy-intensive recovery processes. Yet, the proposed recovery processes are still highly competitive even for treating more dilute fermentation broths (e.g. primary energy requirements for VD process configuration are lower than 2 or 3 $kW_{th}h/kg_{IPA+AC}$ for 2.5 or 1.2 wt% total isopropanol and acetone in the feed stream, respectively).
- ***Water consumption***: PTD-MED requires the most fresh water (0.261 m^3/kg_{IPA+AC}), while PTD-VRC and VD need less (0.162 and 0.145 m^3/kg_{IPA+AC}). This is mainly due to the condensation of HP, MP and LP streams and higher external heating requirements. Water losses are also the highest for this configuration (0.019 m^3/kg_{IPA+AC}).
- ***Material intensity***: Besides high-purity isopropanol and acetone, output streams from all proposed configurations are the remaining fermentation broth (containing most of the water, the microorganisms, the other nonvolatile components) and two high-purity water streams. These streams may be recycled to fermentation. Therefore, the value of the material intensity metric for all designed recovery processes is equal to zero. More detailed insight should be obtained with reliable data for the fermentation process [182,183].
- ***Greenhouse gas emissions***: The CO_2 emission is the highest for PTD-MED both in case of using green (0.191 kg_{CO2}/kg_{IPA+AC}) and grey (0.342 kg_{CO2}/kg_{IPA+AC}) electricity. This is due to the significantly higher heating requirements, originating from the multi-effect distillation in PTD-MED.
- ***Pollution and toxic materials***: Values of these sustainability metrics are zero since pollutants (besides the already described CO_2) and toxic materials are not emitted.

Sensitivity analysis: Influence of the product concentration in the fermentation broth on the downstream processing performance

The effect of the product concentration in the fermentation broth on the downstream processing performance was analyzed and presented in Figure 2-30.

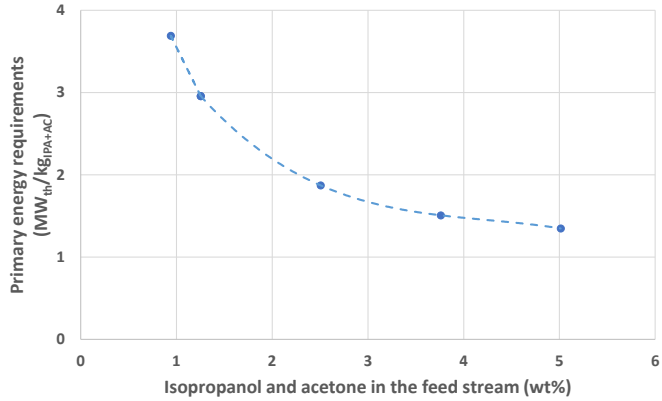


Figure 2-30. Influence of the isopropanol and ethanol concentration in the feed stream on the total energy requirements of the recovery process

As expected, the recovery process becomes less energy-intensive when the initial product concentrations are higher. Nonetheless, it may be seen that the energy requirements of the recovery process are not drastically high even with an initial product concentration of only 2 wt%. Given that the high product concentrations are inhibiting the fermentation process, it may not be optimal to push fermentation product concentrations to high values. The optimal product concentration in the broth should be determined by analyzing the total bioprocess consisting of upstream fermentation and downstream recovery process. This is beyond the scope of the present research. However, the results presented in this study offer valuable insight into the performance of the advanced downstream processes.

2.3.5. Conclusion

The results of this original research can substantially contribute to the scale-up of isopropanol and acetone production by syngas fermentation. Novel industrial-scale (production capacity 100 $ktonne_{IPA+AC}/y$) vacuum distillation and pass-through distillation processes, in combination with regular atmospheric distillation and extractive distillation, were successfully designed. High-purity isopropanol and acetone (each 99.8 wt%) products can be obtained with recoveries of more than 99.2%, while allowing full recycle of biomass and water to enhance the upstream fermentation process. The implemented advanced heat pumping and heat integration significantly reduced the energy requirements and CO_2 emissions. As all three processes are highly competitive (cost of 0.109-0.137 $\$/kg_{IPA+AC}$, and energy use of 1.348-2.043 $kW_{th}h/kg_{IPA+AC}$), the exact configuration should be chosen depending on the plant location. By proposing three cost-effective and energy-efficient downstream process designs, this unique research represents a major step towards the expansion of industrial fermentation technology as an alternative to conventional fossil fuel-based processes.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced purification of isopropanol and acetone from syngas fermentation, Journal of Chemical Technology and Biotechnology. 99 (2023) 714-726. https://doi.org/10.1002/jctb.7576. This file provides more details about novel pass-through distillation technology, insight into the development of the property model used for designing isopropanol and acetone recovery using pass-through distillation, design parameters of distillation columns for all three process configurations (VD, PTD-VRC and PTD-MED), pinch analysis before and after implementing heat pumping and heat integration, and influence of payback period on the total annual costs.

2.4. Recovery of isobutanol after fermentation from glucose

Isobutanol is a highly attractive renewable alternative to conventional fossil fuels, with superior fuel properties as compared to ethanol and 1-butanol. Even though the isobutanol production by fermentation has significant potential, complex downstream processing is limiting the widespread implementation of this technology. Accordingly, this original research significantly contributes to the advancement in industrial biofuel production by developing two eco-efficient downstream processes for the industrial-scale recovery of isobutanol (production capacity 50 ktonne$_{IBUT}$/y), from a highly dilute fermentation broth (>98 wt% water). Vacuum distillation and a novel hybrid combination of gas stripping and vacuum evaporation were coupled with atmospheric azeotropic distillation to recover over 99.9% of isobutanol as a high-purity product (100 wt%). Advanced heat pumping and heat integration techniques were further implemented to allow the complete electrification of these recovery processes. Furthermore, implementation of these techniques significantly decreased total annual costs (0.131-0.161 \$/kg$_{IBUT}$), reduced energy requirements (0.488-0.807 kW$_e$h/kg$_{IBUT}$) and lowered CO_2 emissions (0.303-0.449 kg$_{CO2}$/kg$_{IBUT}$), resulting in highly competitive purification processes. In addition to efficiently recovering isobutanol, the designed downstream processes provide the potential to enhance the fermentation process by recycling all present microorganisms and reducing water demand. Therefore, the results of this original research substantially contribute to the advancement in industrial biotechnology and the wide spreading of biofuel production.

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2.4.1. Introduction

The most mature fermentation technology is the production of bioethanol from either lignocellulosic biomass or syngas. Even though methods for using ethanol as a renewable fuel are well-established [184], higher alcohols are potentially better replacements for conventional fuels due to their higher energy density [185]. The main limitations of using ethanol as biofuel are significantly lower energy density compared to gasoline (about 19.6 and 32 MJ/kg for ethanol and gasoline, respectively), high hygroscopicity and higher vapor pressure that complicate ethanol storage and transport [20]. Alternatively, 1-butanol has been gaining significance as a superior sustainable fuel alternative [186]. Its large-scale production is commonly based on acetone-butanol-ethanol fermentation (ABE). The main advantage of 1-butanol compared to ethanol is higher energy content (27-29.2 MJ/kg), being close to the one of gasoline. Furthermore, there is practically no need to modify automobile engines due to a higher mixing ratio and better compatibility with gasoline. Additionally, 1-butanol is more suitable for transport and storage using existing systems due to its low corrosivity [20]. However, biofuels can be upgraded even further by using isobutanol. Compared to 1-butanol, isobutanol has a higher octane number [187] and can be more easily converted to biojet fuel [20]. Furthermore, isobutanol is less toxic to the microorganisms, potentially resulting in higher achievable concentrations and less complex downstream processing [188]. Therefore, isobutanol may be a very attractive renewable alternative to fossil carbon-based fuels [20] and has already been studied as a potential biofuel [189–191].

Isobutanol is an important platform chemical with an estimated industrial production of about 500 ktonne/y [17]. It is commonly produced in fossil fuel-based processes, whereby there are three main approaches. Firstly, isobutanol is traditionally synthesized by hydrogenation of isobutylaldehyde, which is obtained from propylene in a carbonylation reaction with syngas. The main drawbacks of this pathway are extreme process conditions (temperature of about 150-200 ˚C and pressure about 200-400 bar), low catalyst stability and relatively low yield [20]. Secondly, isobutanol can be produced from syngas in the presence of different catalysts [192]. However, intermediate steps in this pathway are the production of methanol, ethanol and propanol, whereby high productivity and selectivity of isobutanol are dependent on high temperature (up to 420 ˚C) and pressures (up to 250 bar) [20]. Lastly, Guerbet reaction was proposed for the synthesis of isobutanol from methanol and 1-propanol. This production pathway consists of several steps: oxidative dehydrogenation to produce aldehydes from alcohols, aldol condensation of formed aldehydes to produce alcohol-aldehydes, dehydration of alcohol-aldehydes to form olefine aldehydes and finally, hydrogenation of olefine aldehydes to produce isobutanol [193]. However, this

reaction still requires the usage of expensive catalysts and relatively severe process conditions (temperature of about 200 ˚C). All these processes are dependent on fossil fuels, require extreme process conditions and expensive catalysts, and are very energy-intensive [20]. Therefore, a more environmentally friendly alternative for the production of isobutanol is an important step towards sustainable development.

Isobutanol synthesis by fermentation presents an attractive renewable alternative to conventional fossil fuel-based production processes. The major advantages of this production pathway are mild process conditions, minimized environmental impact and usage of biomass that does not compete with food production (e.g. lignocellulosic or waste biomass). However, isobutanol is not naturally synthesized in significant amounts by any microorganisms [188]. Nevertheless, as natural production pathways exist, considerable focus of research has been put on engineering different microorganisms [17]. Genetic engineering on different types of bacteria is mainly focused on introducing isobutanol production pathways into bacterial cells [194,195]. A typically used metabolic pathway is a modification of the pathway to L-valine [17]. Unlike the synthesis of 1-butanol, the metabolic pathway of isobutanol synthesis is less complex and not dependent on acetyl-CoA, resulting in a lower possibility of side-product formation [187]. A combination of different gene manipulations resulted in an isobutanol titer of 22 g/L [196]. Alternatively, engineering strategies on yeasts imply overexpression of specific genes, blocking competitive pathways and localizing isobutanol production pathway in a certain part of the cell [197,198]. Thus, all of these genetic engineering approaches strive to overcome the major problem of product toxicity by developing tolerant strains. In that sense, adaptive evolution methods may lead to more efficient isobutanol production in the future [199]. Alternatively, continuous concurrent alcohol recovery and fermentation (CARAF) can overcome product toxicity limitations [27]. Recent advances in fermentation technology have significantly contributed to the industrial production of isobutanol. Company Gevo established the first bio-isobutanol production plant in 2010 with a production capacity of about 750,000-1,000,000 gallons/y [20,77] Furthermore, BP and DuPont combined expertise in 2016 to form Butamax, a joint venture for producing bio-isobutanol [78].

Even though isobutanol production by fermentation has significant potential, significant advancements in downstream processing are required to make this bioprocess competitive with petrochemical production. Thus, this original research significantly contributes to the advancement in industrial biofuel production by developing an efficient large-scale downstream process for recovering isobutanol from a highly dilute fermentation broth. The main novelty in the proposed process design is a hybrid combination of gas stripping and heat

pump-assisted vacuum evaporation that ensures complete recovery of isobutanol while maintaining operating conditions appropriate for the present microorganism. Additionally, apart from enhancing the process with heat pump systems, a dividing-wall column is proposed as an additional process intensification opportunity. Therefore, the highly competitive recovery process proposed here may substantially improve the attractiveness of the overall fermentative production of isobutanol.

2.4.2. Problem statement

Due to the inhibitory effects isobutanol has on microorganisms, its concentration in the fermentation broth is about 16 g/L [187]. As a product of microbial metabolism, some CO_2 is dissolved in this stream (about 0.13 wt%) [146]. Some microorganisms and inert components are also present but can be neglected in simulations as they are removed in the first steps without evaporation. Nonetheless, the fermentation broth contains more than 98 wt% water, while the concentration of the main product is less than 2 wt%. Consequently, purifying isobutanol from highly dilute fermentation broth up to a high-purity final product is complex and may be very cost- and energy-intensive [24]. Furthermore, due to the large water throughput that is needed, equipment costs can be significant [20].

Apart from the highly dilute feed stream, the closeness of boiling points and thermodynamic limitations due to azeotrope formation (Table 2-15) complicate the recovery process even more.

Table 2-15. Boiling points of pure components and azeotrope formation at 1 bar

Pure components		Azeotrope		
Component		Mass fraction	T (°C)	Type
Water	100.00	0.3473	90.28	heterogeneous
Isobutanol	107.68	0.6527		

Furthermore, the presence of living microorganisms is a limiting factor that determines operating conditions for the first separation step. This initial separation of isobutanol from most of the fermentation broth should be performed without toxic chemicals, at moderate temperatures and with short residence times so that microorganisms can survive the lack of nutrients.

2.4.3. Method of process design and simulation

Several different separation techniques have been studied for *in-situ* separation of isobutanol from dilute aqueous solution [20,200]. The first potential recovery option is adsorption with activated carbon and polystyrene-divinylbenzene [201]. However, these adsorbents have not been employed in the real fermentation broth so far and the desorption process has not been investigated [20]. Additionally, microorganisms can easily cause adsorbent fouling. Furthermore, simple pervaporation or hybrid hydrophobic-hydrophilic pervaporation processes [202] can also be used for *in-situ* recovery of isobutanol from dilute solutions. However, the selectivity of membrane materials needs to be improved to increase overall energy efficiency [200]. Moreover, finding membranes suitable for industrial-scale process is challenging [20]. Solvent extraction is another option for isobutanol separation from an aqueous solution. This method does not require high temperatures, resulting in low energy requirements [200]. However, common extractants are usually toxic to microorganisms. Additionally, further purification is needed as isobutanol still has to be removed from the extractant, while different impurities that are present in the fermentation broth can significantly complicate this process [20]. Another method for isobutanol purification is salting-out, during which isobutanol ends up in the organic phase, while all salt remains in the aqueous phase after liquid-liquid phase splitting [203]. Following the recovery of salt from dilute solution is the common drawback of this method due to energy intensity. Salting-out extraction is a novel type of purification method that improves the separation of valuable products. However, the efficiency of the separation process highly depends on the used combination and amounts of organic solvent and salting-out agent. In inappropriate combinations, some salt may end up in the organic phase, resulting in reduced separation efficiency [20]. Another option for *in-situ* recovery is gas stripping which implies removing isobutanol from dilute broth using different gases. Isobutanol is obtained in the gaseous stream that needs to be condensed for further treatment [185,204,205] This method can conveniently use gases already produced in the fermentation process, such as carbon dioxide. However, the amount of present gases might not be enough to completely separate products, and additional gas source may be needed [20]. The nature of used gases for isobutanol striping will determine the complexity of the following condensation step. Lastly, vacuum evaporation has been proposed and is already used method of isobutanol recovery from fermentation broth. Company GEVO is using GIFT (Gevo Integrated Fermentation Technology) system to separate isobutanol from the fermentation broth. In this system, a side stream is taken from the fermenter and partially evaporated under reduced pressure [206]. Formed vapor, containing significantly increased isobutanol content compared to the fermentation

broth [77], is condensed and further purified. However, the remaining liquid broth that is being recycled to the fermenter still contains a significant amount of isobutanol product [206]. Furthermore, even though vacuum evaporation can use a low-temperature heat source, this process can be very energy-demanding.

This study advances isobutanol fermentation by developing advanced recovery processes for a high-capacity industrial plant producing about 50 ktonne of isobutanol per year [207]. Two methods were proposed for the first separation step: vacuum distillation (VD process configuration, see Figure 2-31) and novel hybrid separation combining gas stripping and vacuum evaporation (GS-VE process configuration, see Figure 2-32). In both cases, the usage of additional chemicals that might harm present cells is avoided, and moderate temperatures are maintained by applying reduced pressure. Even though exposing fermentation broth to vacuum might require additional experimental validation, it has already been proven that reduced pressure does not jeopardize microbial viability [96,179,180]. Microorganisms, other non-volatile inert components and most of the present water will flow directly to the bottom stream in the initial separation step. After isobutanol is removed, this aqueous stream may be recycled to the fermentation to avoid biomass loss, enable a closed-loop upstream process and reduce fresh water requirements [19]. Additional testing of microorganisms that are recycled might be needed to avoid any infection possibilities. Furthermore, continuous removal of isobutanol from the fermenter decreases inhibitory effects and increases fermentation productivity. Following this initial separation step, performed either by vacuum distillation or a combination of vacuum flashing and gas stripping, the obtained isobutanol-water mixture is more concentrated as compared to the fermentation broth. However, further purification is needed to obtain a high-purity final product. Due to the azeotrope formation, the separated mixture needs to be concentrated close to the azeotropic composition using conventional atmospheric distillation. The nearly azeotropic mixture formed is heterogeneous, and simple phase separation can be used to obtain most of the isobutanol in the organic phase. Lastly, to recover a high-purity isobutanol product, an additional distillation step is necessary. Rigorous simulations for every step in the designed recovery process were developed in Aspen Plus. Operating conditions for the initial separation steps were chosen not to threaten microbial viability but to ensure complete isobutanol recovery from the fermentation broth. The presence of microorganisms in the feed stream can be neglected in the simulations as they are removed in these first separation steps without evaporation. The following distillation steps were designed to recover the high-purity isobutanol product while minimizing energy requirements.

2.4.4. Results and discussion

This section contains the main results related to the process design and simulation, techno-economic and sustainability analyses.

Process design

Recovering isobutanol from the rest of the fermentation broth

The first step in the recovery process is separating isobutanol, with some water, from most of the fermentation broth, while keeping operating conditions appropriate for present microorganisms. Two different methods were designed for this initial separation step: conventional vacuum distillation assisted with heat pump systems (VD) and novel combination of gas stripping and heat pump-assisted vacuum evaporation (GS-VE), as described in the following sections.

Vacuum distillation

The flowsheet of isobutanol recovery using VD process configuration is presented in Figure 2-31.

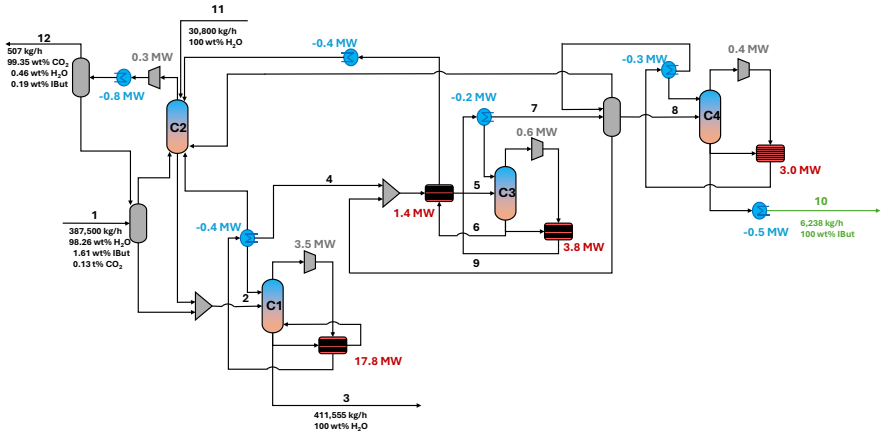


Figure 2-31. Isobutanol recovery by VD process configuration (H_2O – water, IBut – isobutanol, CO_2 – carbon dioxide)

Since some CO_2 is present in the stream taken from the fermenter, the first step in the purification process is its removal in a simple degasser vessel (F1 in Figure 2-31) under reduced pressure. The operating pressure for this step (0.05 bar) was chosen such that more than 70% of the initially present CO_2 is removed in a vapor phase. Some isobutanol is also evaporated in this step, but it is later captured with water in stripping column C2 and returned to the recovery process. Furthermore, to maintain moderate temperatures that will not harm microbial viability, vacuum distillation was applied to separate isobutanol with some water from most of the fermentation broth. The defined condenser pressure for vacuum distillation

column C1 is the same as for the degassing step (0.05 bar), with a pressure drop of 0.225 mbar per theoretical stage. Structured packing type Sulzer Mellapak 250 was chosen for its internals [110].

Additionally, as some CO_2 is still present, a partial condenser with both vapor and liquid distillate was defined for column C1. The vapor distillate stream is also sent to column C2 where separated isobutanol is recovered with water and returned to the recovery process. Under these operating conditions, the temperature in column C1 varies from about 36 ˚C at the bottom to about 22 ˚C at the top. Due to the low condensation temperature, chilled water needs to be used as a cooling utility instead of cheaper cooling water. Furthermore, as a result of large flowrates and closeness of boiling temperatures, the reboiler duty for this column is very high (about 17.7 MW). However, a relatively small difference in the top and bottom column temperatures can be exploited to apply mechanical vapor recompression (MVR). In this heat pump system, vapor coming from the top of the distillation column is compressed and used to evaporate liquid from the bottom of the distillation column. Consequently, the need for both external heating and external cooling can be significantly reduced [113]. The coefficient of performance (COP), a measure of the obtained energy savings, is equal to the ratio of the upgraded heat (exchanged between the compressed top vapor and bottom liquid) and required compressor duty. COP values higher than 2.5, which is a conservative value of the electrical-to-thermal conversion factor [156], prove the high energy efficiency of the MVR system. Since COP for the MVR system applied to column C1 (about 5.2) is significantly higher than the electrical-to-thermal conversion factor, energy requirements for this separation are drastically reduced. After this initial step, isobutanol is completely separated from most of the fermentation broth in a top stream from column C1 (stream 4). This stream contains ~24 wt% isobutanol and requires processing to obtain the high-purity final product. The bottom aqueous product from column C1 containing all present microorganisms and non-volatile inert components (stream 3) may be returned to the fermentation process.

Gas stripping and vacuum evaporation

Figure 2-32 illustrates the flowsheet of isobutanol recovery using GS-VE process configuration.

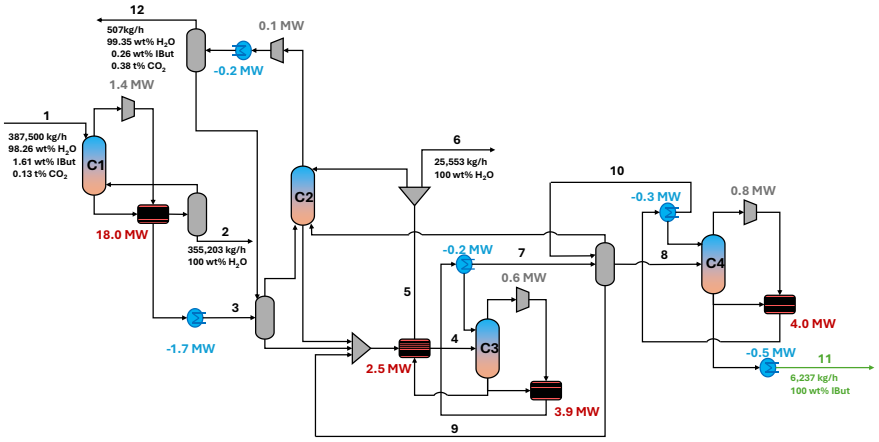


Figure 2-32. Isobutanol recovery by GS-VE process configuration (H_2O – water, IBut – isobutanol, CO_2 – carbon dioxide)

A novel hybrid separation method combining gas stripping and vacuum evaporation was developed to further reduce energy requirements for the initial separation step. In this process design, the broth taken from the fermenter is firstly sent to stripping column C1 in which gas is used to separate isobutanol from the aqueous feed stream. This column operates under reduced pressure (0.04 bar) to ensure that temperature does not harm microbial viability. A pressure drop of 0.225 mbar per theoretical stage and structured packing type Sulzer Mellapak 250 was realistically considered [110]. Furthermore, a part of the remaining broth, depleted of isobutanol, is evaporated under reduced pressure and then separated in the simple flash vessel. Residual liquid broth containing most of the water, all the present microorganisms and non-volatile inert components (stream 2), may be recycled to the fermentation. The generated steam is sent to striping column C1 where it is used to completely remove isobutanol from the feed stream. Since evaporating a part of the depleted broth is very energy intensive (about 18.1 MW), vapor recompression is applied to reduce the energy requirements. The top product from column C1, vapor rich in isobutanol, is compressed (COMP2 in Figure 2-32) and then used to evaporate part of the depleted broth. A COP value of 13.0 indicates a significant reduction in the energy requirements for this initial separation step. Isobutanol-water vapor mixture is then condensed (stream 3) and sent to the degassing unit to remove most of the CO_2. The isobutanol that is separated with CO_2 is captured with water in column C2 and returned to the recovery process. As a result of this initial separation step, the isobutanol concentration increased from 1.6 wt% to about 19 wt% in the obtained aqueous

solution. However, further purification is needed to obtain high-purity final product.

Further isobutanol purification

After the initial separation step, performed either by VD or GS-VE, additional processing is required to achieve isobutanol product of high purity. This is performed in several steps due to the azeotrope formation. Firstly, the isobutanol-water mixture is concentrated in the distillation column C3. The top product from this column is nearly azeotropic mixture (stream 7) while the bottom product is pure water (stream 6). Since the top azeotropic mixture is heterogenous, simple decanting (in a 3-phase flash unit F3 in Figure 2-31 and F4 in Figure 2-32) is used to separate two liquid phases. Water-rich phase (stream 9) still contains some isobutanol (about 9-11 wt%). To avoid loss of valuable product, this stream is recycled to column C3. Contrarily, isobutanol-rich phase (stream 8) is sent to distillation column C4 for final purification. Additionally, the gas stream containing mostly CO_2, with some water and isobutanol, is separated in this flash unit. This stream is sent to column C2 in which isobutanol is captured with water and returned to the recovery process. More than 99.9% of isobutanol from the fermentation broth is recovered as a high-purity product (100 wt%) from the bottom of column C4 (stream 10 in Figure 2-31 and stream 11 in Figure 2-32). The top product from this column is nearly azeotropic isobutanol-water mixture that is recycled to the flash unit. Both columns C3 and C4 are operating at atmospheric pressure with pressure drop of 8 mbar per stage and have sieve trays for internals [112].

Since the required heating duties for columns C3 and C4 are relatively high, additional energy-saving opportunities were considered. Firstly, since the feed stream to column C3 is subcooled liquid, bottom water product from this column is used to preheat it to the boiling state. This water stream (stream 6 in Figure 2-31 and stream 5 in Figure 2-32) is then used in column C2 to capture the isobutanol separated in the CO_2-rich streams. The amount of water in this stream is sufficient to capture all the isobutanol from gaseous streams in process configuration GS-VE. Contrarily, in the VD process design, an additional water stream is needed to minimize loss of isobutanol. Even after preheating the feed stream, the reboiler duty for column C3 is about 3.8-3.9 MW, depending on the process configuration. Nonetheless, the temperatures at the top (about 90 ˚C) and bottom (about 104 ˚C) of this column are relatively close and MVR can be implemented. COP for the implemented MVR systems are in range 6.2-6.3, which indicates significant energy savings that are obtained with heat pumping. Furthermore, since the temperature difference at the top and the bottom of column C4 is also rather small (about 90 ˚C at the top and 111 ˚C at the bottom), MVR can be applied to reduce heating requirements (about 3.0-4.0 MW). The COP for the applied MVR systems

are in the range of 5.1-7.3, indicating a noticeable reduction in the energy requirements for this column.

Lastly, dividing-wall column (DWC) technology was proposed as an alternative for sequences of two or more distillation columns [115]. A split shell column with a divided bottom section and a common overhead section system was simulated as a substitution for the distillation columns C3 and C4 (Figure 2-33).

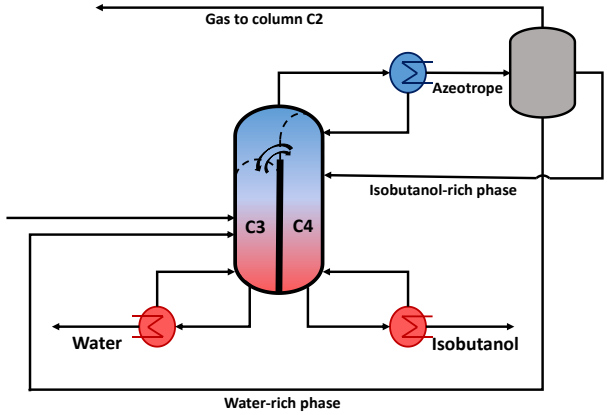


Figure 2-33. Azeotropic dividing-wall column design

In this design, the left side of DWC replaces column C3, while the right side replaces column C4. In total, the DWC system has two reboilers and only one condenser. The bottom products from this unit are pure water (from the left side of DWC) and isobutanol product (from the right side of DWC), while the top product is a nearly azeotropic isobutanol-water mixture that is sent to the flash unit for phase separation. Water-rich phase containing about 11 wt% of isobutanol is recycled as a feed stream to the left part of DWC. Isobutanol-rich phase is returned to the right part of DWC. Additionally, a gas stream containing most of the remaining CO_2 with some water and isobutanol is separated from the flash vessel. This stream is recycled to column C2 to recover the separated isobutanol. This highly integrated distillation system resulted in almost identical thermal energy requirements compared to the sequence of two distillation columns (6.95 and 6.81 MW_{th}, respectively). Similarly, after applying heat pumps to both DWC and the sequence of two separate distillation columns, electrical energy requirements were almost identical (1.05 and 1.02 MW_e, respectively). Comparing the complete isobutanol recovery process when the sequence of distillation columns C3 and C4, or single DWC is used, overall performance is very similar: TAC, energy requirements and CO_2 emissions are higher by only 0.6, 1.3 and 1.1%, respectively, in the case of DWC. Nonetheless, since the DWC system integrates two columns into one shell, it is a more compact design that reduces CAPEX, required footprint and minimizes operator workload compared

to the sequence of two distillation columns. Therefore, DWC remains an attractive novel opportunity for isobutanol recovery from an aqueous solution.

Techno-economic analysis

More details about the followed methodology for estimating the economic performance of the developed process are presented in Appendix A. Results of a detailed comparison of economic performance are presented in Table 2-16 and Figure 2-34.

Table 2-16. Key economic indicators in isobutanol recovery

Economic indicator	**VD**	**GS-VE**
CAPEX (k$)	22,123	17,797
OPEX (k$/y)	5,821	4,756
OPEX ($/kg$_{IBUT}$)	0.117	0.095
TAC (k$/y)	8,033	6,536
TAC ($/kg$_{IBUT}$)	0.161	0.131

The equipment installation costs are 12,028 and 9,685 k$ for process configurations VD and GS-VE, respectively. The largest contribution to equipment installation costs is cost for compressors used in applied heat pump systems (about 57% and 50% of the total installed equipment costs). Higher equipment expense for VD process is mainly due to the cost for installing vacuum distillation column C1 and belonging MVR system. The CAPEX for VD and GS-VE recovery process designs are 22,123 and 17,797 k$, respectively (where about 54% is the equipment cost).

The OPEX for VD and GS-VE are 5,821 and 4,756 k$/y, or expressed per kilogram of product, 0.117 and 0.095 $/kg$_{IBUT}$, respectively. The highest contributions to OPEX in both cases are the cost for operating labor (51-63% of the OPEX) and electricity (about 31-42% of the OPEX).

The total annual costs, accounting for both CAPEX and OPEX, with a payback period of 10 years, are 8,033 and 6,536 k$/y, corresponding to 0.161 and 0.131 $/kg$_{IBUT}$, for VD and GS-VE, respectively. Furthermore, the added minimum selling price for recovered isobutanol is 0.176 and 0.143 $/kg$_{IBUT}$, respectively. Since isobutanol market prices are assumed to be in the range 1.16-1.28 $/kg$_{IBUT}$ [181], both designed recovery processes are highly economically competitive. However, the novel recovery process combining gas striping and vacuum evaporation is a more suitable option in terms of both capital and operating costs.

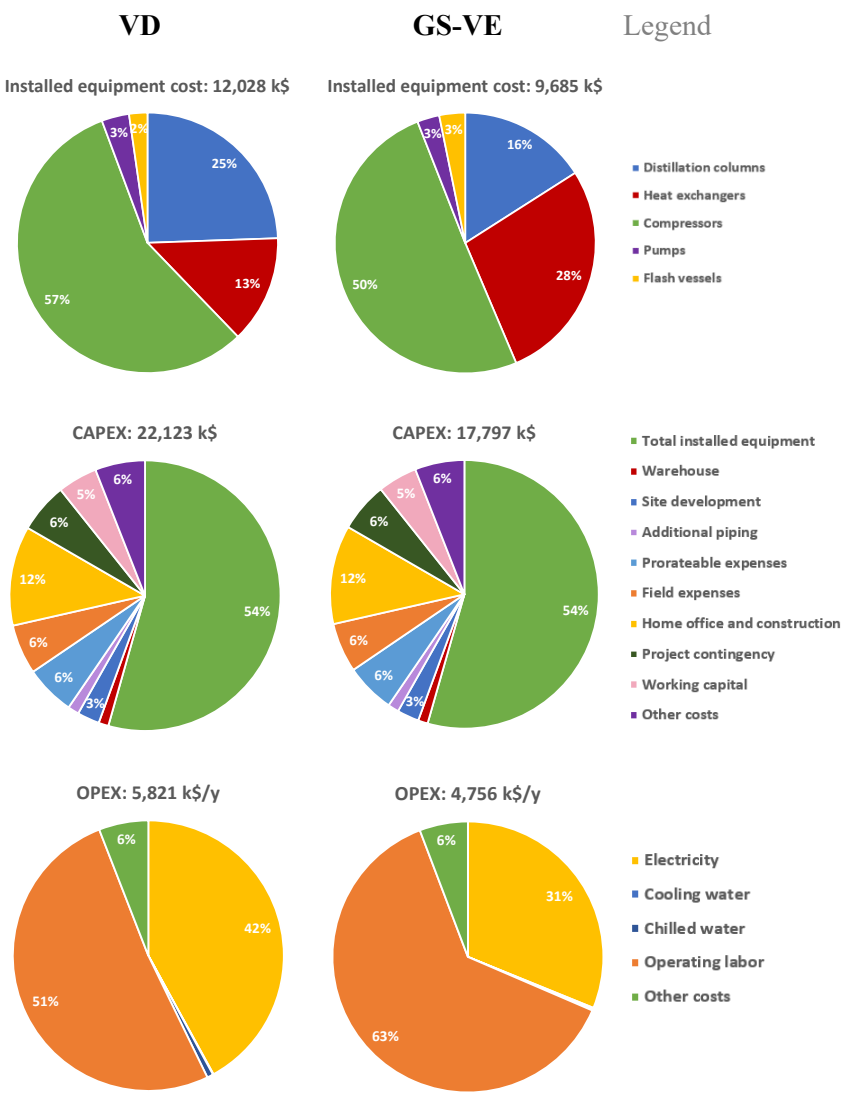


Figure 2-34. Comparison of economic indicators

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Flexibility of performed economic evaluation was expanded by analyzing the influence of the payback period on TAC (Figure 2-35).

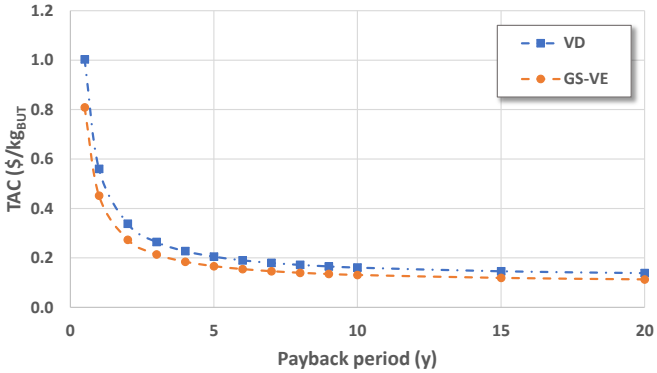


Figure 2-35. Effect of payback period on isobutanol recovery costs

Although TAC rises with a decreasing payback period, even with a payback period set to 5 years, TAC remains below 0.2 $/kg$_{IBUT}$ for both recovery processes. Additionally, with a payback period of 6 months, TAC is lower than 0.9 and 1.1 $/kg$_{IBUT}$ for VD and GS-VE, respectively. Therefore, both designed processes are highly competitive even with shorter payback periods.

Sustainability assessment

More details about the methodology for estimating the environmental impact of the developed process are presented in Appendix A. The calculated sustainability metrics, which determine the environmental impact of the designed processes are summarized in Table 2-17.

Table 2-17. Key sustainability metrics in isobutanol recovery

Sustainability metrics	**VD**	**GS-VE**
Thermal energy requirements ($kW_{th}h/kg_{IBUT}$)	0.000	0.000
Electrical energy requirements (kW_eh/kg_{IBUT})	0.807	0.488
CO_2 emission (kg_{CO2}/kg_{IBUT})*	0.449 / 0.081	0.303 / 0.081
Water consumption (m_w^3/kg_{IBUT})	0.064	0.082
Water loss (m_w^3/kg_{IBUT})	0.004	0.005
Pollutant emission ($kg_{pollutant}/kg_{IBUT}$)	0.000	0.000
Toxic materials emission ($kg_{toxice\ materials}/kg_{IBUT}$)	0.000	0.000

*Grey/green electricity

- ***Energy intensity***: As a result of implemented heat pumping and additional heat integration, both designed processes are independent of external heating and can be powered only by electricity. Consequently, thermal energy requirements are equal to zero, while electrical energy requirements for VD and GS-VE recovery processes are 0.807 and 0.488 kW_eh/kg_{IBUT}, respectively. Primary energy requirements, accounting for all used sources of energy, are equal to the electrical energy requirements, corresponding to 2.018 and 1.219 $kW_{th}h/kg_{IBUT}$, respectively. Higher energy requirement in the VD process is mainly due to the used compressor in the MVR system applied to column C1.

  Besides improving energy efficiency, the implementation of the proposed heat pump systems is a significant step toward the electrification of biofuel production processes. In these systems, electricity used to power compressors replaces a much higher amount of thermal energy, thus providing renewable heat by upgrading waste heat streams. Using renewable electricity instead of fossil fuels to power process can considerably improve the sustainability of biofuel production processes.
- ***Water consumption***: In the designed VD and GS-VE recovery processes, 0.064 and 0.082 m^3_w/kg_{IBUT}, respectively, are needed. Accordingly, water losses are 0.004 and 0.005 m^3_w/kg_{IBUT}, respectively. Higher requirements in GS-VE recovery process are mainly due to the water required to condense the isobutanol-water vapor used to evaporate part of the depleted broth in the vapor recompression system.
- ***Material intensity***: Besides the recovered isobutanol product, the output stream in both cases is depleted fermentation broth that may be recycled to the fermenter. Furthermore, in GS-VF process, there is an additional pure water outlet stream that can be recycled to the upstream process to further reduce the need for fresh water. Additionally, CO_2-rich outlet stream was taken into account in greenhouse gas emission sustainability metrics and was not considered as waste here. Therefore, the values of material intensity metrics for the designed isobutanol recovery processes are equal to zero. More detailed insight could be obtained with reliable data from the upstream fermentation process.
- ***Greenhouse gas emissions***: Due to higher electrical energy demand, the CO_2 emissions are higher for the VD recovery process (0.449 kg_{CO2}/kg_{IBUT}) than for the GS-VE recovery process (0.303 kg_{CO2}/kg_{IBUT}) if grey electricity has to be used. If processes can be powered with green electricity, CO_2 emissions are only a consequence of CO_2 present in the fermentation broth and are equal to 0.081 kg_{CO2}/kg_{IBUT} for both isobutanol recovery processes. Nonetheless, this outlet stream is already captured as high-purity CO_2 that

may be used as feedstock for other processes, in which case it would not be emitted at all.

- ***Pollution and toxic materials***: Values of these sustainability metrics are equal to zero because pollutants and toxic materials (other than CO_2 that is already taken into account) are not emitted.

Sensitivity analysis: Influence of the product concentration in the fermentation broth on the downstream processing performance

While the initial design assumed a concentration of 1.6 wt% isobutanol in the fermentation broth, the isobutanol concentration in industrial fermenters may slightly vary among different plants. To assess the effect of isobutanol concentration in the feed stream (the broth removed from the fermenter) on the designed recovery processes, a detailed sensitivity analysis was performed. Isobutanol concentration in the fermentation broth was varied, whereby the feed flowrate remained constant. The effect of the isobutanol concentration on the economic and environmental indicators is shown in Figure 2-36.

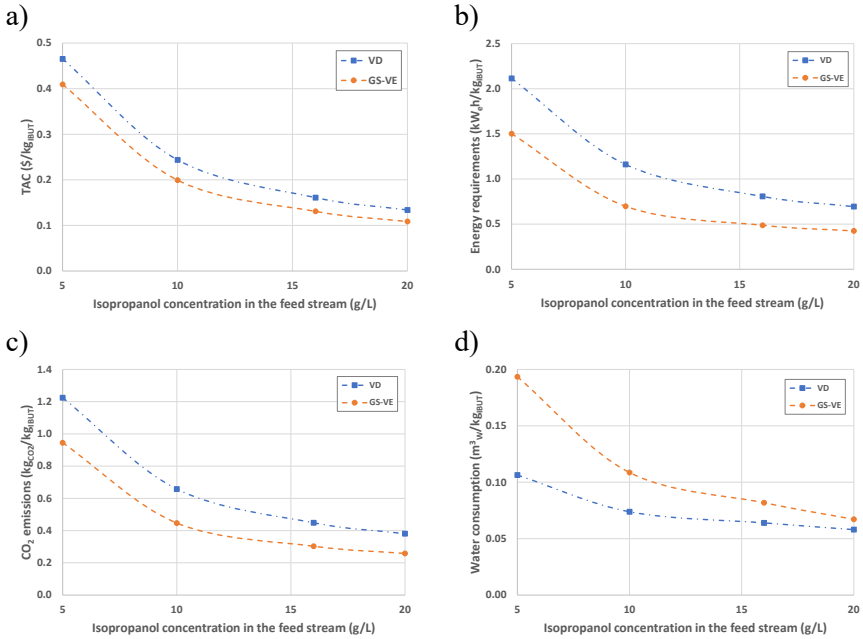


Figure 2-36. Sensitivity analysis – the effect of isobutanol concentration in the fermentation broth on: a) total annual costs (TAC), b) energy requirements, c) CO_2 emissions – grey electricity usage, d) water consumption

A more dilute feed stream leads to more cost- and energy-intensive recovery processes. A very similar trend can be noticed in the change of economic and environmental indicators with changing feed composition. However, even with 1 wt% of isobutanol in the fermentation broth, the total annual costs, energy requirements, CO_2 emissions and water consumption are lower than 0.25 $/kg$_{IBUT}$, 1.2 kW$_eh/kg_{IBUT}$, 0.66 kg$_{CO2}$/kg$_{IBUT}$ and 0.08 m^3_W/kg$_{IBUT}$ for the VD recovery process, while these metrics are lower than 0.20 $/kg$_{IBUT}$, 0.70 kW$_eh/kg_{IBUT}$, 0.45 kg$_{CO2}$/kg$_{IBUT}$ and 0.11 m^3_W/kg$_{IBUT}$ for the GS-VE recovery process. Therefore, the newly designed processes are capable of efficiently recovering the high-purity isobutanol product from even more diluted fermentation broth.

2.4.5. Conclusion

This original study concludes that the proposed two eco-efficient processes for the recovery of isobutanol from highly dilute fermentation broth (>98 wt% water) for industrial-scale production capacity (about 50 ktonne/y) are feasible and viable. Both vacuum distillation and a novel hybrid combination of gas stripping and vacuum evaporation, coupled with regular atmospheric distillation and azeotropic distillation, are able to recover over 99.9% of isobutanol as a high-purity product (100 wt%) while providing recycle of biomass and water to enhance the fermentation process. Moreover, the implementation of heat pumping and heat integration can maximize the economic and environmental performance of the designed processes by allowing complete (green) electrification. The performed sensitivity analysis showed that both developed recovery processes are capable of efficiently recovering isobutanol from even more dilute aqueous solutions

The results of this work indicate that the combination of gas stripping and vacuum evaporation for continuous recovery of isobutanol from the fermentation broth is clearly superior to vacuum distillation due to lower total recovery costs (0.131 compared to 0.161 $/kg$_{IBUT}$) and energy requirements (0.488 compared to 0.807 kW$_e$h/kg$_{IBUT}$). Moreover, using a dividing-wall column is recommended as an additional process intensification method.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Enhanced isobutanol recovery from fermentation broth for sustainable biofuels production, Energy Conversion and Management: X. 21 (2024) 100520. https://doi.org/10.1016/j.ecmx.2023.100520. This file provides additional information about the Pinch analysis of isobutanol recovery processes VD and GS-VE before and after enhancement with heat pumps. Additionally, design specifications of distillation columns are presented.

2.5. Recovery after IBE (isopropanol-butanol-ethanol) fermentation

Isopropanol-butanol-ethanol (IBE) fermentation is a superior biofuel production technology as compared to acetone-butanol-ethanol (ABE) fermentation due to the better fuel properties of the obtained products. However, low product concentrations, thermodynamic constraints and the presence of microorganisms lead to complex downstream processing that limits the competitiveness of this biofuel production method. Thus, this original research proposes a novel thermally self-sufficient and eco-efficient downstream process for industrial-scale recovery after IBE fermentation (74 ktonne/y capacity), from a highly dilute broth (>97 wt% water). Gas stripping and heat pump-assisted vacuum evaporation were implemented to separate valuable products from most of the broth. Furthermore, an advanced highly integrated heat pump-assisted azeotropic dividing-wall column was designed to recover high-purity (99 wt%) butanol biofuel and isopropanol-ethanol fuel supplement (89 wt%). The proposed purification process recovers over 99% of biofuel products in a cost-effective (0.130 $/kg$_{IBE}$) and energy-efficient way (0.673 kW$_e$h/kg$_{IBE}$) while allowing full recycle of biomass and most of the separated water. Besides improving yield by continuously recovering the inhibitory products, fermentation can be further enhanced by avoiding biomass loss and reducing water requirements. Lastly, the implemented energy-saving techniques ensure complete electrification of the proposed IBE recovery process. Therefore, the original results of this research study significantly contribute to the development of sustainable biofuel production processes.

This section was published as:
T. Janković, A.J.J. Straathof, A.A. Kiss, Thermally self-sufficient heat pump-assisted azeotropic dividing-wall column for biofuels recovery from isopropanol-butanol-ethanol fermentation. Chemical Engineering and Processing – Process Intensification. 197 (2024) 109689.

2.5.1. Introduction

While technologies for producing higher alcohols by fermentation may not be as mature and well-developed as those for bioethanol, their higher energy content potentially makes them superior renewable fuel alternatives. Compared to ethanol, 1-butanol (abbreviated to butanol) has a higher energy density (about 27-29.2 $MJ/kg_{butanol}$ vs 19.6 $MJ/kg_{ethanol}$), a higher compatibility and mixing ratio with gasoline that eliminates the need to modify automobile engines, and lower corrosivity that facilitates storage and transport using existing infrastructure [208]. The common biobutanol production by fermentation is performed via the acetone-butanol-ethanol (ABE) pathway. However, limited variety and incomplete utilization of substrates, high by-product formation, and low productivity are limiting the wide-spreading of industrial ABE fermentation [209]. Furthermore, the extensive formation of acetone, which is a non-fuel and corrosive chemical, might jeopardize the economic viability of the ABE fermentation processes [76]. Significant effort has been put into genetic engineering to develop acetone-free butanol production. Nonetheless, the risk of unexpected behavior of modified microorganisms in industrial-scale semi-sterile processes is not negligible [76]. Furthermore, inhibition of key genes for the synthesis of acetone resulted in higher acid concentrations but lower butanol production [210]. Therefore, converting acetone into another valuable chemical might be more beneficial than inhibiting its formation [209]. In that respect, isopropanol can be produced instead of acetone in isopropanol–butanol–ethanol (IBE) fermentation [211]. Isopropanol is an important commodity chemical that can also be used as a fuel supplement [167]. Furthermore, a mixture of solvents produced by IBE fermentation might be directly used as a renewable automotive fuel [76,209,211]. Nonetheless, microorganisms commonly employed in the IBE fermentation are more easily inhibited by-product formation, resulting in lower concentrations compared to the ABE fermentation [76]. Thus, advanced recovery processes are needed to support the development of industrial-scale biofuel production by IBE fermentation.

2.5.2. Problem statement

Being taken from the fermentation step, the feed stream for this process is at atmospheric pressure (1 bar) and fermentation temperature (30 ˚C) [208]. Due to the inhibitory effects, fermentation broth contains relatively low product concentrations (approximately 1.73, 0.69 and 0.02 wt% of butanol, isopropanol and ethanol, respectively) [209]. Consequently, recovering valuable biochemicals from the highly dilute fermentation broth (>97 wt% water) cost-effectively and energy-efficiently is challenging. Besides the low product concentrations, thermodynamic constraints significantly complicate the recovery process (Table 2-18). In addition to two azeotropes that are present in the ABE fermentation (butanol-water and ethanol-water), the IBE fermentation products also form a third azeotrope (isopropanol-water), making the purification process even more complex.

Additionally, some living microorganisms and non-volatile inert components are present in the feed stream. They can be realistically assumed to be nonvolatile. Therefore, they are completely removed in the first distillation step, and their separation does not need simulation. However, this is a limiting factor that determines operating conditions for the initial separation of valuable biochemicals from most of the fermentation broth.

Table 2-18. Boiling points of pure components and formation of azeotropes at 1 bar

Pure components		Azeotropes		
Component	Tb (˚C)	Component	Mass fraction	T (˚C) / type
Acetone	56.13	Ethanol	0.9562	78.15 / homogeneous
Ethanol	78.31	Water	0.0438	
Isopropanol	82.05	Isopropanol	0.8729	80.13 / homogeneous
Water	100.02	Water	0.1271	
Butanol	117.75	Butanol	0.5798	92.53 / heterogeneous
		Water	0.4202	

2.5.3. Method of process design and simulation

The recovery process was designed for a large-scale industrial IBE fermentation, with a total production capacity of about 74 ktonne/y IBE (50, 20 and 4 ktonne/y of butanol, isopropanol and ethanol, respectively).

To our knowledge, extensive work has been performed on product recovery from the ABE fermentation [36,212–220], but only a few studies have been published on downstream processing after the IBE fermentation. An efficient recovery process is needed to separate valuable products after the fermentation and purify them to meet market requirements. The feed stream for the recovery process is broth taken directly from the fermenter. Due to the end-product toxicity

phenomenon, this stream is commonly a very dilute aqueous solution containing valuable fermentation products (butanol, isopropanol and ethanol), microorganisms, non-volatile inert components and potentially some CO_2 as a product of microorganisms' metabolism. Thus, advanced separation techniques are needed to ensure adequate product recovery and purification from a complex dilute mixture. *In-situ* recovery by gas-stripping and adsorption was combined with a sequence of seven distillation columns to purify fermentation products. However, the designed downstream processes resulted in high energy consumption even after heat integration [221]. A combination of extractive and azeotropic distillation, whereby butanol is used as an entrainer, was implemented for the dehydration of IBE mixture starting from 4-6 wt% IBE in feed, with total energy requirements of about 6.5-8.2 MJ/kg_{IBE} [222]. Furthermore, a sequence of six distillation columns was designed to recover high-purity butanol and dehydrate isopropanol and ethanol mixture [223], using a feed stream (31,282 kg/h with 4.46 wt% butanol, 2.37 wt% isopropanol, 0.29 wt% ethanol and 92.88 wt% water) after the gas stripping *in-situ* product removal [221]. In this design, extractive distillation was used to remove water from the isopropanol and ethanol mixture [223], instead of previously proposed pressure swing distillation [221], resulting in lower energy consumption (about 1.2-2.2 $kW_{th}h/kg_{IBE}$). Moreover, liquid-liquid extraction in combination with extractive distillation was developed to dehydrate the IBE mixture from 22,592 kg/h feed containing 5.47 mol% butanol, 3.57 mol% isopropanol and 0.02 mol% ethanol [224]. This design was extended with an organic Rankine cycle to reduce the total purification costs [225]. Further developing downstream processing after gas stripping *in-situ* product removal [221], a sequence of distillation columns, including extractive distillation with dimethyl sulfoxide, was suggested to reduce energy requirements (to about 2.8 $kW_{th}h/kg_{IBE}$) [226]. Lastly, reactive distillation with ethylene oxide was proposed to recover butanol and dehydrate isopropanol-ethanol mixture [227] using the same feed [221]. Even though energy usage is reduced to about 1.7 $kW_{th}h/kg_{IBE}$, and ethylene glycol is produced as a side product, using ethylene oxide to remove excess water may bring additional risks due to the extremely hazardous nature of this substance [228].

However, none of the suggested downstream processing methods were developed for a large-scale industrial IBE fermentation, with the largest butanol production capacity reported being cca. 11 ktonne/y [221,223,226,227]). Furthermore, several downstream processing studies [223,226,227] used the stream after gas stripping and adsorption as a feed, but the costs associated with these operations were excluded in the final evaluation of the purification process. Alternatively, even higher fermentation product concentrations were assumed [224,225] in the feed stream. Thus, the primary objective of this original research is to develop an

enhanced recovery process for industrial-scale IBE fermentation (74 ktonne/y IBE = 50, 20 and 4 ktonne/y of butanol, isopropanol and ethanol, respectively), directly from the dilute stream after the fermentation. The major novelty in this study is the design of an advanced heat pump-assisted azeotropic dividing-wall column, resulting in less energy- and economically intensive purification process. Enhancing dividing-wall columns with advanced heat pumping systems has already been researched and proven highly efficient for different systems [229-232]. Still, it has never been considered for recovery of the IBE fermentation products. Thus, advanced heat pumping and heat integration methods were considered to reduce overall recovery costs, energy requirements and CO_2 emissions. Additionally, implementing a combination of gas stripping and heat pump-assisted vacuum evaporation removes products from a highly dilute fermentation broth (>97 wt% water) without harming microbial viability, thus allowing the recycling of microorganisms with most of the water. Continuously removing inhibitory products from broth can significantly improve the upstream process by increasing fermentation productivity, avoiding loss of biomass and reducing water requirements. Rigorous simulations for every part of the recovery process are developed using Aspen Plus as an industrial computer-aided process engineering (CAPE) tool.

2.5.4. Results and discussion

This section contains the main results related to the thermodynamic property model, process design of the IBE fermentation products recovery, economic and sustainability analyses.

Thermodynamic property model

Due to a strongly non-ideal system, NRTL-HOC property method was chosen to describe the complex thermodynamic interactions between different components in the feed stream. HOC extension (Hayden-O'Connell) was included to reliably describe interactions of polar components in the vapor phase [97].

To ensure the validity of the chosen property model, the predicted thermodynamic properties, presented in Table 2-18 were tested against relevant literature [30]. The binary interaction parameters of this system are summarized in Table 2-19, while the ternary diagram and residue curve map are presented in Figure 2-37.

Table 2-19. Values of the NRTL-HOC binary interaction parameters (values of d_{ij}, e_{ij}, e_{ji}, f_{ij} and f_{ji} are zero)

Components *i* - *j*	a_{ij}	a_{ji}	b_{ij}	b_{ji}	c_{ij}
Water – Acetone	8.5012	-3.5004	-2,280.09	1,347.96	0.3
Water – Ethanol	3.7555	-0.9852	-676.031	302.237	0.3
Water – Isopropanol	6.6784	-1.3477	-1,444.3	438.615	0.3
Water – Butanol	7.5558	-1.1934	-1,390.56	455.482	0.3
Acetone – Ethanol	-1.1757	-0.0764	462.206	174.538	0.3
Acetone – Isopropanol	-2.6868	2.8235	909.193	-694.328	0.3
Acetone – Butanol	-10.984	10.8195	4,065.8	-3,764.79	0.3
Ethanol – Isopropanol	0.1288	0.657	-215.981	-42.6169	0.3
Ethanol – Butanol	0	0	-127.819	199.039	0.3
Isopropanol – Butanol	0	0	203.73	-208.906	0.3

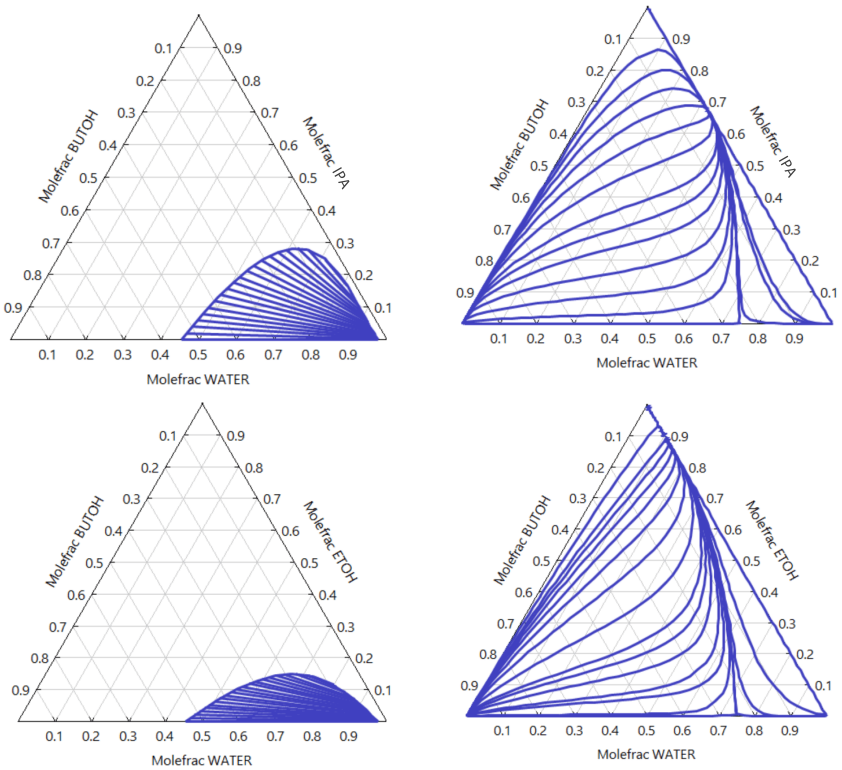


Figure 2-37. Ternary diagrams (left) and residue curve maps (right) for the water-alcohols systems. Notation: butanol – BUTOH, isopropanol – IPA, ethanol - ETOH

Process design

The flowsheet of the designed process is illustrated in Figure 2-38.

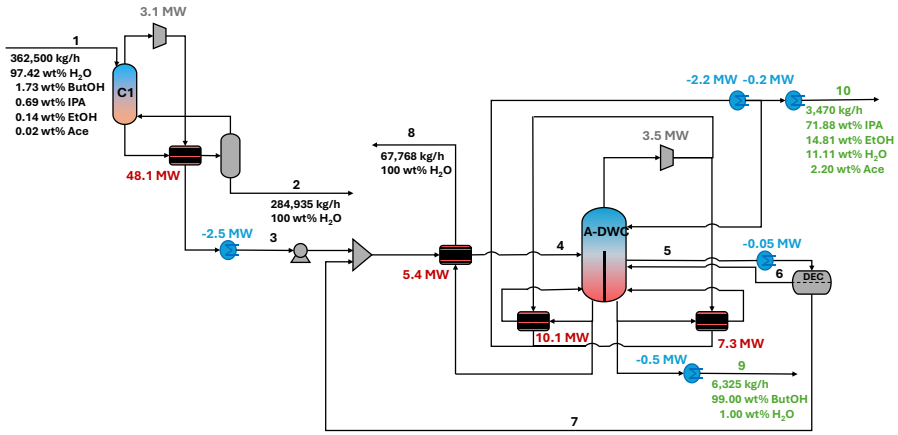


Figure 2-38. Flowsheet of the recovery process after IBE fermentation

Gas stripping and vacuum evaporation

Initially, butanol, isopropanol and ethanol, with some water, need to be separated from the rest of the fermentation broth. Due to the present living microorganisms, operating conditions must not harm microbial viability. A combination of gas stripping and heat pump-assisted vacuum evaporation was designed for this initial step to avoid the usage of additional chemicals that might harm microbial viability and maintain moderate temperatures. Exposing the microorganisms to a reduced pressure should be tested prior to implementation on a large scale, but it has already been shown that a vacuum does not compromise the survival of microorganisms [96,179,180]. Moreover, a degassing step under reduced pressure can be added to deal with any CO_2 present in the fermentation broth. Valuable products that are removed with CO_2 in the gas stream should be recaptured (absorbed) with water and returned to the (liquid) recovery process to minimize product losses. However, in the designed initial separation process, the feed stream (broth taken from the fermenter) is sent to the stripping column C1 in which gas (bottom vapor) is used to strip volatile organic products from most of the fermentation broth. The operating pressure for this column was chosen to be 0.038 bar to maintain moderate temperatures. Due to the reduced pressure, the structured packing type Sulzer Mellapak 250 (with a pressure drop of 0.225 mbar per theoretical stage) was chosen for the column's internals [110]. The bottom aqueous stream, depleted of valuable fermentation products, is further partially evaporated under reduced pressure (0.042 bar). The remaining liquid, containing most of the present water with microorganisms and non-volatile inert components, may be recycled to the fermentation. The formed vapor is used in

the stripping column C1 to remove butanol, isopropanol, and ethanol from the initial fermentation broth. However, since vacuum evaporation is very energy-intensive (about 48 MW), an advanced heat pumping system is applied to reduce the need for external heating. Vapor recompression is implemented by compressing the product-rich top vapor from column C1 and using it to evaporate part of the depleted aqueous stream. A measure of obtained energy savings can be expressed through the coefficient of performance (COP), which is equal to the ratio of exchanged heat (between the compressed vapor and the liquid stream) and required compressor duty [113]. COP values higher than 2.5, which is the conservative value of the electrical-to-thermal conversion factor [156], indicate the energy efficiency of the implemented heat pump systems. COP values for the described vapor recompression-assisted vacuum distillation is about 15.7, proving significant energy savings. Furthermore, complete electrification of this part of the process is achieved with the described vapor recompression design. Being separated in the vapor phase after gas stripping, valuable products need to be condensed for further treatment. After this initial separation, the obtained product mixture contains 8.1, 3.2, and 0.7 wt% of butanol, isopropanol, and ethanol, respectively. Despite the increased concentrations, further purification is needed to obtain high-purity biofuels.

Azeotropic dividing-wall column (A-DWC)

Due to the formation of three azeotropes, several steps are required to obtain high-purity biofuel products. Firstly, the liquid mixture of fermentation products, recovered by the first separation step, is pumped to the atmospheric pressure (1 bar) for further purification. Even though a very large amount of water is removed in the first step (about 284,935 kg/h), additional preconcentration is needed. Butanol, isopropanol, and ethanol form azeotropes with water that have lower boiling points compared to pure water (Table 2-18). Thus, most of the present water can be removed as a bottom product from a distillation column, while all valuable products are obtained as a top product. Furthermore, the mixture of valuable fermentation products, with some water, can be treated in another distillation column whereby isopropanol and ethanol are separated as a top product, while butanol is obtained as a bottom product. Since butanol-water azeotrope is heterogeneous (Table 2-18), an additional phase splitting in a decanter is needed to obtain a high-purity butanol product. Therefore, a sequence of at least two distillation columns with a decanter is needed to separate pure water, pure butanol and a mixture of isopropanol and ethanol. However, these columns can be merged into one azeotropic dividing-wall column (A-DWC) with a common overhead section and a divided bottom section (Figure 2-39) [115]. In this highly integrated system, only one column shell with two reboilers and one condenser is needed. Water and butanol are obtained as the bottom products, while

isopropanol-ethanol mixture is obtained as the top product. Additionally, a side stream to liquid-liquid phase splitting unit is needed due to the heterogeneity of the butanol-water azeotrope. Since this dividing-wall column unit is not available in Aspen Plus, an equivalent combination of three distillation columns is simulated (Figure 2-39). The left part of A-DWC is presented with A-DWC$_{LB}$, while the right part of A-DWC is separated into top rectifying (A-DWC$_{RT}$) and bottom stripping (A-DWC$_{RB}$) sections.

In total, A-DWC has 60 stages, whereby the rectifying and stripping sections have 30 stages both. A pressure drop of 8 mbar per stage was assumed [112]. The aqueous product mixture, obtained after the initial separation step, is fed to the 31st stage of A-DWC on the left side, which is the 1st stage of the left stripping section. Pure water (100 wt%) is obtained as the bottom product from the left side. A side stream is taken from the 6th stage of the right stripping section (36th stage of A-DWC) and sent to the decanter for liquid-liquid phase splitting. The butanol-rich phase is returned to the 7th stage of the right stripping section (37th stage of A-DWC), while the aqueous phase is recycled to the 1st stage of the left stripping section (31st stage of A-DWC). High-purity butanol product (99.0 wt%) is obtained as the bottom product from the right side. The mixture of isopropanol and ethanol, with some water, obtained as the distillate (about 71.9, 14.8, 2.2, and 11.1 wt% of isopropanol, ethanol, acetone, and water, respectively) can be used as fuel supplement [167,233–235]. Small amounts of acetone have been proven not to negatively affect fuel performance [236]. Liquid flowing down in the rectifying section of A-DWC is directed to the right stripping section, while the feed stream ensures sufficient liquid in the left stripping section.

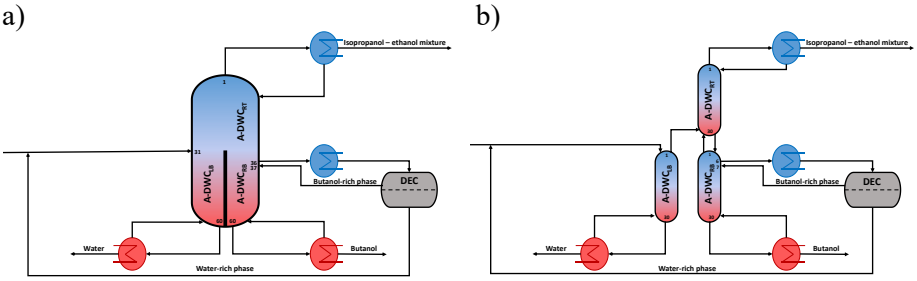


Figure 2-39. a) A-DWC and b) equivalent configuration of distillation units (simulated in Aspen Plus)

The described integrated A-DWC design is further enhanced with heat pumping and heat integration. Firstly, the aqueous mixture of valuable fermentation products obtained after the initial separation is subcooled liquid and can be heated to the boiling state to reduce overall reboiler duty for A-DWC. Since pure water product from A-DWC can be recycled to the fermentation with prior cooling, this stream can be used for heating the feed stream to A-DWC. With this heat

integration, the total reboiler duty for A-DWC is lowered by about 5.4 MW. Furthermore, as the top and bottom temperatures of the column are relatively close, mechanical vapor recompression (MVR) can be applied to reduce the need for both external heating and external cooling [113]. In this heat pumping system, vapor from the top of the column is compressed and used to evaporate the bottom liquids from the left and right sides. COP of the MVR system applied to A-DWC is about 4.9. Thus, significant energy savings are obtained and complete electrification of this part of the process is provided with the implementation of the advanced heat pumping systems. The implementation of the described heat integration and heat pumping results in a highly integrated system that might be challenging to control. Nevertheless, it has already been demonstrated that a comparable heat pump-assisted extractive distillation process can be properly controlled [231,237].

Techno-economic analysis

More details about the methodology followed for estimating the costs of the developed process are presented in Appendix A. The results of the performed economic evaluation are summarized in Table 2-20 and Figure 2-40.

Table 2-20. Key economic indicators in recovery after IBE fermentation

Economic indicators	Value
CAPEX (k$)	33,922
OPEX (k$/y)	6,761
OPEX ($/kg$_{IBE}$)	0.086
TAC (k$/y)	10,153
TAC ($/kg$_{IBE}$)	0.130

The total cost for installing all equipment units is 18,474 k$, whereby the largest contribution is the cost of compressors used in the applied heat pump systems (about 50% of the total equipment cost). The costs of the installed heat exchangers, distillation columns, pumps, and flash vessels make the remaining 50% of the total equipment costs (about 27, 21, 1, and 1%, respectively). The total CAPEX is equal to 33,922 k$, whereby the biggest part is the equipment installation cost (about 54% of CAPEX). The total OPEX is 6,761 k$/y or, expressed per kilogram of recovered biofuel, 0.086 $/kg$_{IBE}$. The largest contribution to OPEX is the cost of electricity (about 47% of OPEX), mainly due to the applied heat pump systems, and the cost of operating labor (about 44% of OPEX). The contribution of cost for cooling water and other operating costs is significantly lower (1 and about 8% of OPEX, respectively).

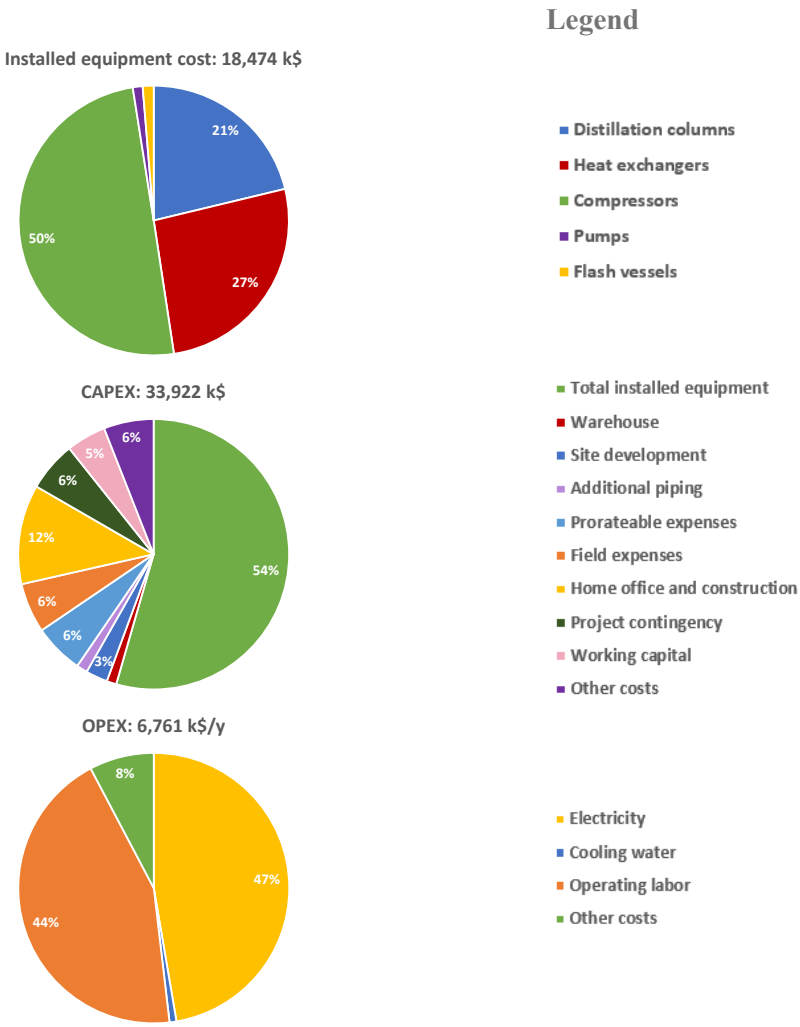


Figure 2-40. Cost contribution to the CAPEX and OPEX

The total annual cost (TAC), accounting for both CAPEX and OPEX with a payback period of 10 years, is 10,153 k$/y or, expressed per kilogram of recovered biofuels, 0.130 $/kg$_{IBE}$, which is in the same range as the cost of bioethanol. Additionally, the minimum added selling price for the biofuels recovery is 0.144 $/kg$_{IBE}$. As the estimated market prices for butanol, isopropanol and ethanol are about 1.20, 1.12 and 0.89 $/kg$_{IBE}$ [181], the newly designed IBE recovery process is highly competitive. Even though initial investment costs are higher due to additional equipment units that are needed for the designed heat integration and heat pumping modules, OPEX and consequently, TAC are drastically reduced (by 65.3 and 51.7%, respectively).

Furthermore, the flexibility of the performed economic evaluation is extended by analyzing the influence of the payback period on the TAC, which is presented in Figure 2-41. Shorter payback periods lead to an increase in TAC. However, even with a payback period of 4 years or only 1 year, the TAC for biofuels recovery is lower than 0.20 $/kg$_{IBE}$ or 0.52 $/kg$_{IBE}$, respectively, indicating the economic competitiveness of the designed recovery process.

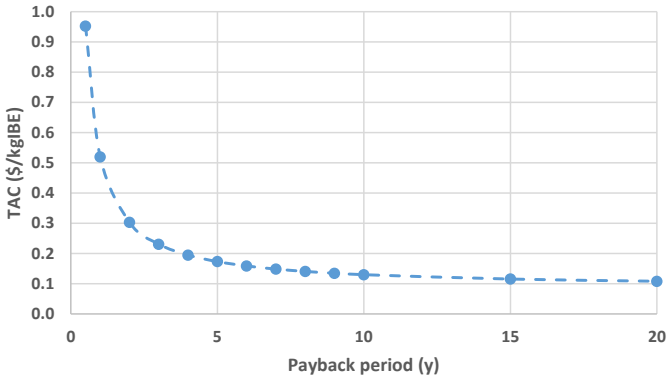


Figure 2-41. Effect of the payback period on the IBE recovery costs

Sustainability assessment

More details about the methodology for estimating the environmental impact of the developed process are presented in Appendix A. The calculated values of the main sustainability metrics are presented in Table 2-21.

Table 2-21. Key sustainability metrics in recovery after IBE fermentation

Sustainability metrics	Value
Thermal energy requirements ($kW_{th}h/kg_{IBE}$)	0.000
Electrical energy requirements (kW_eh/kg_{IBE})	0.673
Primary energy requirements (kW_eh/kg_{IBE}) / ($kW_{th}h/kg_{IBE}$)	0.673 / 1.683
CO_2 emissions (kg_{CO2}/kg_{IBE})*	0.307 / 0.000
Water consumption (m^3_W/kg_{IBE})	0.096
Water loss (m^3_W/kg_{IBE})	0.007
Pollutant emission ($kg_{pollutant}/kg_{IBE}$)	0.000
Toxic materials emission ($kg_{toxicmaterial}/kg_{IBE}$)	0.000

*Grey/green electricity

- ***Energy intensity***: Due to the implemented heat pump systems, both the initial separation step (gas stripping combined with vacuum evaporation) and the purification in A-DWC are independent of external heating (being thermally self-sufficient) and can be powered only by electricity. The electrical energy requirements for the designed recovery process are 0.673 $kW_e h/kg_{IBE}$, while the thermal energy requirements are equal to zero, making this process thermally self-sufficient. The primary energy requirements that account for all types of energy used are equivalent to 1.683 $kW_{th} h/kg_{IBE}$ in thermal energy units. Thus, besides improving energy efficiency, the implementation of heat pump systems is a significant step towards the electrification of biorefineries. Using renewable electricity instead of fossil-based thermal energy can drastically improve the sustainability and competitiveness of biofuel production processes.
- ***Water consumption***: The total water need for the designed recovery process is 0.096 m^3_W/kg_{IBE}, due to condensation of the vapor mixture of fermentation products and cooling condenser of A-DWC. Accordingly, the total loss of water is 0.007 m^3_W/kg_{IBE}.
- ***Material intensity***: Besides the recovered high-purity butanol and isopropanol-ethanol mixture, output streams from the designed purification process are the aqueous solution containing microorganisms and non-volatile inert components, and the high-purity water stream (bottom product from A-DWC). Since both streams may be recycled to the fermentation, the value of material intensity sustainability metrics is equal to zero.
- ***Greenhouse gas emissions***: The total CO_2 emissions in the case of using grey electricity are 0.307 kg_{CO2}/kg_{IBE}. Nevertheless, if the designed recovery process can be powered by renewable electricity, the total CO_2 emissions are reduced to zero due to the complete electrification of the recovery process.
- ***Pollution and toxic materials***: Values of these metrics are zero as the designed recovery process does not emit any pollutants and toxic materials, apart from CO_2 that was already included in the greenhouse gas emissions metrics.

The implementation of heat pump and heat integration systems increased electrical energy requirements due to the usage of compressors in heat pump systems. Nonetheless, the thermal energy requirements are significantly reduced. Consequently, the primary energy requirements and CO_2 emissions, which are related to energy usage, are drastically decreased (by about 76.9 and 62.0%, respectively).

2.5.5. Conclusion

The original downstream processing design proposed here allows the eco-efficient large-scale (production capacity of 74 ktonne/y IBE) recovery of high-purity (99 wt%) butanol biofuel and isopropanol-ethanol fuel supplement (~89 wt%) from a very dilute fermentation broth (>97 wt% water). A novel combination of gas stripping and heat pump-assisted vacuum evaporation can be implemented to efficiently recover valuable products from most of the fermentation broth while allowing full recycle of biomass and most of the water back to the fermentation. Furthermore, a highly integrated heat pump-assisted azeotropic dividing-wall column allows the separation of pure butanol biofuel and water from an isopropanol–ethanol mixture that may be used as a fuel supplement. Lastly, the implementation of advanced heat pump and heat integration systems avoids any dependence on fossil-based thermal energy, thus presenting an important step toward the green electrification of industrial biotechnology. Therefore, the major significance of this original research study is the design of a cost-effective (0.130 $\$/kg_{IBE}$) and energy-efficient (0.673 kW_eh/kg_{IBE}) IBE recovery process that may significantly contribute to the application of sustainable biofuel production technology. It is worth noting that good downstream processing cannot compensate for poor fermentation (and the other way around), so both process steps have to be very good.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Thermally self-sufficient heat pump-assisted azeotropic dividing-wall column for biofuels recovery from isopropanol-butanol-ethanol fermentation, Chemical Engineering and Processing – Process Intensification. 197 (2024) 109689. https://doi.org/10.1016/j.cep.2024.109689. This file provides additional details about the methodology for assessing the economic and environmental impact of the designed process. Furthermore, the effects of implemented heat pump and heat integration systems on the key performance indicators are analyzed. Lastly, the influence of the required butanol product purity is presented.

2.6. Recovery of low-boiling products from fermentation broth: Bioalcohols

This section emphasizes that advanced separation and purification based on process intensification principles are crucial for overall efficient production processes. The efficient downstream process offers the possibility of recovering high-purity products while enhancing the fermentation step by continuously removing inhibitory products, and recycling microorganisms with most of the present water. Besides higher productivity, the upstream process can be greatly improved by avoiding biomass loss, enabling closed-loop operation and decreasing the need for fresh water. Applying heat pumping, heat integration and other methods of process intensification (PI) can drastically reduce energy requirements and CO_2 emissions. Additionally, the opportunity to use renewable electricity instead of conventional fossil energy presents a significant step toward (green) electrification and decarbonization of the chemical industry.

Due to the stronger toxicity effects on microbes, the achievable concentrations of monohydric aliphatic alcohols in the fermentation broth decrease with the increasing chain length. Specifically, the concentrations used here are 6.14, 5.00, 1.61 and 0.24 wt% of ethanol, isopropanol, isobutanol and hexanol, respectively. More dilute fermentation broths lead to more complex recovery processes. The total purification costs increase from 0.080 $/kg for ethanol, 0.109 $/kg for isopropanol and 0.161 $/kg for isobutanol to 0.529 $/kg for hexanol. A similar trend is noticeable for the energy usage (0.960, 1.348, 2.018 and 3.069 $kW_{th}h/kg$, respectively) and the related CO_2 emissions (0.164, 0.221, 0.449 and 0.555 kg_{CO2}/kg, respectively).

The achievable product concentration in the fermentation broth - and not so much the alcohol chain length - has the biggest influence on the performance of downstream processing. Therefore, simultaneous development of both upstream and downstream processing is necessary to ensure the competitiveness and viability of industrial fermentation processes.

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T. Janković, A.J.J. Straathof, A.A. Kiss, A perspective on downstream processing performance for recovery of bioalcohols. Journal of Chemical Technology and Biotechnology. 99 (2024) 1933-1940.

2.6.1. Summary of the major challenges for recovery of bioalcohols from fermentation

A key problem in the field of industrial biotechnology is that bioalcohols are toxic to cells and thus contribute to fermentation stress and limit the operational range [238]. When the concentration of alcohol increases during fermentation, limits are reached in the productivity, broth titer, yield of alcohol on substrate, and substrate feed concentration [238]. The end-product toxicity phenomenon refers to the inhibitory effects bioalcohols have on microbial growth, substrate consumption or product formation [27]. The critical concentration of bioalcohols for product formation is strongly related to the hydrophilicity of the product. Typically, a larger amount of more hydrophobic products can accumulate in the cell membrane [160]. In general, this activity leads to disruption of membrane integrity and fluidity, which can result in inhibition of carbon-substrate uptake, nutrient transport, membrane potential dependent ATP production and energy generation, intracellular acidification, leakage from protoplasm, etc. Microbes are inherently much less tolerant to advanced solvents such as butanol and propanol. More hydrophobic alcohols (e.g. butanol, hexanol) can cause greater disruption of the lipid bilayers of cell membranes and more inhibition compared to less hydrophobic alcohols (e.g. ethanol) at the same concentrations [239]. Thus, longer-chain alcohols are more toxic to microorganisms compared to shorter-chain alcohols due to stronger inhibition effects [160]. Accordingly, concentrations of ethanol in the fermentation broth that microorganisms can tolerate (5-6 wt% [29] from syngas fermentation or 5-12 wt% from glucose fermentation) [144] are higher than non-harmful concentrations of isopropanol (4-5 wt% from syngas fermentation) [169], isobutanol (~1.6 wt% from glucose fermentation) [187] and 1-hexanol (~0.2 wt% from glucose fermentation) [240]. Besides the nature of the fermentation product, pH, substrate type, microbe type, temperature, aeration, nutrients and additives also influence the extent of inhibition [160]. Furthermore, the use of lignocellulosic feedstock introduces other complications, as fermentations must tolerate other additional inhibiting compounds (e.g. organic acids, phenolics, and furan derivatives). The need to co-ferment a mixture of C5 and C6 sugars presents a challenge in selecting a suitable microbe. Nonetheless, the end-product inhibition phenomenon remains a persistent, unsolved problem for industrial-scale alcoholic fermentations, despite decades of research and development. However, it can be mitigated by continuously removing the product from the broth while fermentation is ongoing. This product recovery strategy has been shown in many research studies to be beneficial, but it is not yet widespread in industrial practice [238,241].

Low achievable product concentrations in the fermentation broth ultimately lead to high water throughput (diluted aqueous streams), which is associated with large

capital expenditure and operating expenses both in upstream and downstream processing [36]. Water dominates the composition of the stream that is sent to downstream processing. Removing all the water in a cost-effective and energy-efficient way is very challenging [27].

Furthermore, the microorganisms in the fermentation broth should be removed from the product in an initial purification step. One approach in the recovery of bioalcohols is to separate biomass from the fermentation broth prior to product purification. The separated cells can be recycled back to the fermenter. However, regrowing the separated wet cells might be necessary, resulting in lower product yield relative to the substrate. Furthermore, some product might easily be separated with the cells which requires additional washing, resulting in dilution that complicates downstream processing. Another option to mitigate the mentioned complications is to use a separation technique that removes the product from the broth while keeping cells viable for recycling with most of the fermentation broth. Besides avoiding loss of biomass, this approach may increase product-to-substrate yield (as less substrate is spent on growth) and reduce water requirements [19]. A crucial requirement in this case is that the recovery process must be conducted at a temperature compatible with the microbes to avoid a negative impact on cell viability. For example, the optimum fermentation temperature for industrial yeast strains in bioethanol fuel production is ~37 °C. Any recovery process operating at a higher temperature will risk cell death, negating any potential benefits [145]. Additionally, chemicals that might be toxic to microbes must be avoided in the initial separation steps.

Moreover, the boiling points of alcohols commonly produced by fermentation (e.g. ethanol, isopropanol, isobutanol, butanol, etc.) and water are relatively close (see Table 2-22). All these alcohols form azeotropes with water (see Table 2-22), which complicates their purification. Thus, advanced fluid separation techniques are required to break the formed azeotropes and allow the recovery of high-purity products.

To date, much effort has been put into the genetic engineering of an industrially relevant microbial strain that can simultaneously ferment mixed sugars and tolerate inhibitors, while also delivering acceptable titer, productivity, and yield. Unfortunately, genetic engineering to enable the metabolism of multiple sugars worsens tolerance to solvents and other inhibitors. Considerably more attention has been paid to the genetic engineering of strains with special features and tolerances than to recovery technologies. Until an ideal industrial microbe is identified, a stronger focus on the downstream alcohol recovery and separation steps can yield significant commercial progress [35,138]. A practical, low-cost,

microbe-compatible separation process is needed to commercialize a concurrent alcohol recovery and fermentation (CARAF) process [27].

Table 2-22. Boiling points of pure components and azeotrope formation at 1 bar

Pure components		Azeotrope		
Component	Tb (°C)	Component	Mass fraction	T (°C) / type
Ethanol	78.3	Ethanol	0.9562	78.2 /
Isopropanol	82.1	Water	0.0438	homogeneous
Water	100.0	Isopropanol	0.8717	80.1 /
Isobutanol	107.7	Water	0.1283	homogeneous
1-Butanol	117.8	Isobutanol	0.6527	90.3 /
Hexanol	156.8	Water	0.3473	heterogeneous
		1-Butanol	0.5798	92.5 /
		Water	0.4202	heterogeneous
		Hexanol	0.3185	97.8 /
		Water	0.6815	heterogeneous

2.6.2. Methodology for designing the purification process

To efficiently mitigate all mentioned challenges and recover fermentation products in a cost-effective and energy-efficient way, we propose several steps to be followed when designing downstream processing sequences for the recovery of volatile chemicals after fermentation (Figure 2-42).

Different separation techniques (precipitation, extractive distillation, chromatography, membrane separations) have been studied for the purification of common volatile fermentation products from diluted solutions [36,238]. However, the reported yields of the recovered components are usually insufficiently high or the usage of additional chemicals that are toxic for microorganisms is required. Additionally, most of the documented data refer to lab-scale without considering scaling-up to an industrial-level plant, which might be impractical due to the high cost of equipment and/or additional chemicals [34,242]. On the contrary, distillation is the most commonly used separation technique for large-scale purification [102,115]. Besides being already mature on an industrial level, distillation does not require the usage of additional chemicals that might harm living cells and can be designed to obtain high-purity products with high recoveries. Therefore, this perspective further develops the usage of distillation as the main fluid separation method for purifying volatile biochemicals from fermentation broths.

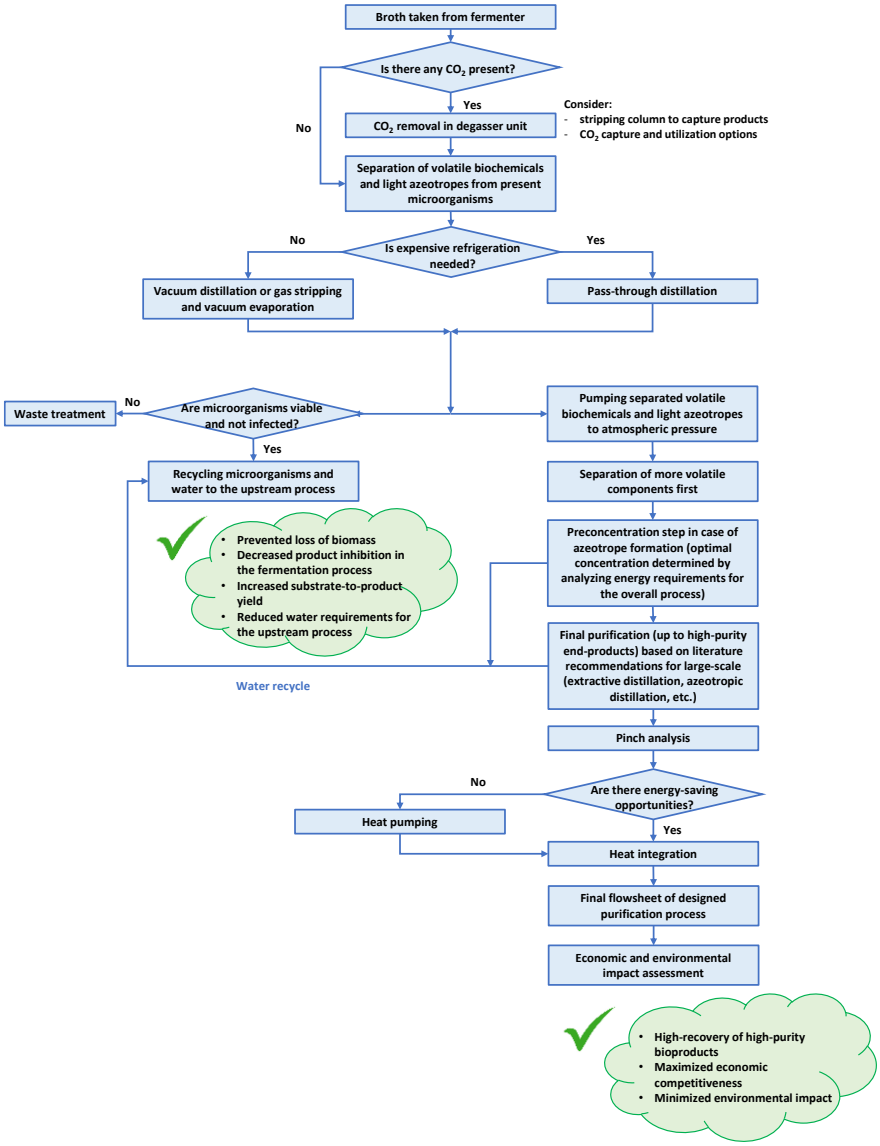


Figure 2-42. Proposed methodology for purification of volatile bioalcohols from fermentation broths

The first step in a recovery process should be the separation of target products from microorganisms, preferably in a way that does not threaten the viability of cells and avoids infection. This separation should be performed without additional chemicals, at moderate temperatures and with relatively short residence time so that cells can survive without additional nutrients. Commonly, microorganisms can be separated from the rest of the broth using a solid-liquid separation such as centrifugation, flocculation, or microfiltration. However, for the recovery of

volatile biochemicals, vacuum distillation is a potential option to skip the solid-liquid separation step [180,243]. During vacuum distillation of fermentation broth, microorganisms will flow directly to the aqueous bottom stream, resulting in a short residence time, which is important to keep cells alive without additional nutrients. Furthermore, exposing microorganisms to reduced pressure might require additional experimental validation, but it has already been proven on the pilot scale that fermentation broth can be exposed to vacuum [96] as cells remain in the liquid phase. The operating pressure for this step should be chosen such that the reboiler temperature does not exceed the temperature appropriate for the used microorganism. Volatile biochemicals can be obtained as an aqueous top stream from this distillation column. As an alternative to vacuum distillation, a novel hybrid combination of gas stripping and vacuum evaporation can be used to effectively separate volatile fermentation products from dilute broth. This process implies partially evaporating product-depleted broth and using the formed vapor to strip volatile products from the broth. The product-enriched vapor is then condensed and sent to further purification to obtain a high-purity final product. The operating pressure of this initial separation step depends on the allowed evaporation temperature. The selected operating pressure determines the condensation temperature. Consequently, depending on the evaporation reboiler temperature, the condensation temperature might be low such that expensive refrigeration is needed.

This potential constraint can be avoided by implementing pass-through distillation, which implies decoupling the evaporation and condensation steps by inserting an adsorption-desorption loop using an electrolyte absorption fluid. Part of the fermentation broth, containing valuable volatile products, is firstly evaporated from the rest of the feed stream, including the microorganisms. The vapor is absorbed by the LiBr absorption fluid in an exothermic reaction [128]. The heat released by the absorption can be used for the evaporation step in a unique process equipment unit called a stripping-absorption module [131]. The target products are later desorbed from the dilute LiBr brine and condensed. Therefore, the working principle of pass-through distillation allows evaporation to be performed at lower pressure and temperature, while condensation can be performed at higher pressure and temperature. Consequently, the temperature limit for heat-sensitive components will not be exceeded and cheaper cooling utilities can be used [27]. The operating conditions can be kept appropriate for the microorganisms since they are separated during the first evaporation step and never contact the absorption fluid.

Due to mild temperatures and moderate process conditions, in cases of conventional vacuum distillation, gas stripping coupled with vacuum evaporation or novel pass-through distillation, microorganisms with most of the water from the fermentation broth may be recycled to the fermentation. As a result, fermentation might operate in a closed loop without biomass loss and with decreased requirements for fresh water. Recycling microorganisms to fermentation might also increase substrate-to-product yield, as less substrate needs to be spent for microbial growth. Reusing the separated water in the fermentation step can significantly reduce the environmental impact of the overall bioprocess. Furthermore, continuously removing fermentation products from the broth may decrease inhibition effects and increase fermentation yield. From this initial separation step, the solution of volatile biochemicals that is obtained is more concentrated than the fermentation broth. Since this stream with products is under reduced pressure, simple pumping can be used to increase its pressure to atmospheric one for further treatment. Note that keeping a vacuum for the next purification steps would result in unnecessarily large equipment and high capital and operating costs.

Since CO_2 will be present in the fermentation broth as a metabolic co-product, its separation in a degasser unit might be added before the described steps [120,121]. This can be done in a simple flash vessel by reducing pressure. Operating conditions should be chosen such that most of the CO_2 is evaporated, while the remaining fermentation broth remains liquid. In case a product such as acetone or ethanol is partly removed with CO_2, it can be captured with water in a stripping column and returned to the recovery process.

Depending on the composition of volatile biochemicals in the separated aqueous stream, an additional preconcentration step might be needed before final purification. The optimal concentration after this preconcentration step should be determined considering the total energy requirements for the overall purification process. Water separated from this step can be cooled and recycled to reduce fresh water requirements upstream.

If, following the initial separation step, the resulting stream contains multiple volatile products, the composition of this stream determines the purification to end-products that satisfy market conditions, whereby more volatile components are typically separated first. Some biochemical products, such as acetone, do not form azeotropes with water and simple distillation can be used to obtain final products. However, azeotropes (Table 2-22) will often complicate separation and lead to multiple steps. Depending on the nature of the azeotrope, different purification techniques have been proven to be optimal in terms of investment and operating costs for the large-scale plant and should be followed. Bioethanol,

which is already widely used as a renewable fuel, forms a homogeneous azeotrope with water at around 95.6 wt%. Consequently, additional dehydration is needed to obtain a final product that satisfies the required standards [100]. Several studies have proven that for large-scale dehydration, extractive distillation with ethylene glycol is preferred to azeotropic distillation or the use of molecular sieves, due to lower operating costs, lower energy requirements, smaller solvent flowrates, a more flexible process sequence, and a less complicated control system [102,106,107]. Similarly, extractive distillation with ethylene glycol has also been recommended for large-scale isopropanol dehydration [176]. 1-Butanol, isobutanol and hexanol, which are more energy-dense and less hygroscopic than ethanol, form heterogeneous azeotropes with water, and simple liquid-liquid phase separation can be used. Conventional processes for the separation of biobutanol from acetone-butanol-ethanol fermentation (ABE fermentation) are based on different sequences of distillation columns. However, hybrid heat pump-assisted azeotropic dividing-wall column distillation has recently been proposed as a novel and less energy-intensive alternative [212,213]. Therefore, reliable literature recommendations for large-scale purification up to a high-purity end-product should be followed when choosing final purification methods.

Due to relatively low product concentrations and large flowrates and high water concentrations, some of the described steps might require high heating duties. Therefore, additional process intensification and integration opportunities should be considered to improve the competitiveness of the overall biochemical production process by reducing overall costs, energy requirements and CO_2 emissions. If there are no heat integration opportunities within the system, heat pumping can be considered as a means to upgrade low-grade heat sources and create additional possibilities for heat recovery. However, each heat pump implementation entails higher capital costs due to the need for compressors. Consequently, heat pumps are typically reserved for cases where simple heat integration alone cannot achieve the desired energy savings.

2.6.3. Process intensification opportunities

Process Intensification (PI) is defined as improvements of a process at unit operational, functional and/or phenomena levels that can be obtained by integration of unit operations, integration of functions and phenomena or targeted enhancement of the phenomena for a set of target operations. PI uses a set of innovative techniques in process engineering, integration and equipment design to offer breakthrough solutions for making chemical processes with smaller environmental footprint, cost-effective, energy-efficient, more controllable and safer, and smaller processing volume. In that respect, different PI techniques can be implemented to enhance the downstream processing of volatile biochemicals from the fermentation broth, and some of them are discussed in more detail.

As this perspective is considering the recovery of volatile fermentation products, most of the feed stream for the downstream process is composed of water and relatively close boiling components. Due to very similar temperatures of hot and cold process streams, the system's pinch temperature is around 100 ˚C and not much energy can be recovered within the process due to insufficient temperature difference [244]. Additionally, since process throughputs are large for an industrial-scale plant, significant amounts of water (>90 wt% of the feed stream) need to be evaporated in reboilers of distillation columns. Consequently, the heating requirements for these columns can easily be very high, on the order of tens of MW. However, since these distillation columns are separating relatively close boiling components, the temperature difference between the top and bottom of the column is not large (usually less than 30 ˚C). This feature can be used to apply heat pumps. More precisely, mechanical vapor recompression (MVR) can be implemented to enhance lower-grade energy in the condenser and use it to power the reboiler [115]. In MVR, vapor that is coming from the top of the distillation column is compressed and used to evaporate liquid from the bottom of the column. Consequently, the need for external heating can be completely avoided, while the need for external cooling is significantly reduced [113].

This phenomenon can be understood using Pinch analysis before and after intensifying a process with MVR. Presented on the temperature-enthalpy diagram, the hot and cold composite curves represent the cumulative heat availability (hot composite curve) and heat demand (cold composite curve) in a process at different temperature levels. Additionally, these two composite curves can be used to derive the grand composite curve which represents the net heat surplus or deficit in a process at each temperature level. As a typical example, composite curves for the isobutanol recovery process before and after applying heat pumping and heat integration are presented in Figure 2-43. Pinch analysis is a useful method to determine the maximum amount of energy that can be

recovered in a system (overlapping area between the hot and cold composite curves, or 'pocket' area in the grand composite curve). As temperatures of all process streams are very close before applying heat pumping, the overlapping area of the hot and cold composite curve is relatively small (usually less than 15%). Therefore, the amount of heat that can be recovered within the system is small, while the need for both external heating and external cooling is significant. Implementing MVR shifts composite curves and substantially increases the overlapping area. As a result, much more energy can be recovered by using hot process streams to heat up cold process streams. This significantly reduces the need for both external heating and cooling [113], resulting in decreased energy requirements (by about 60-80%) and total recovery costs (by about 40-80%). Furthermore, since CO_2 emissions are directly related to energy usage, implementation of advanced heat pump systems can significantly increase the sustainability of the overall biochemical production process by lowering these emissions (reduction in CO_2 emissions for the recovery process by about 60-75% in case electricity from fossil fuels has to be used, or even up to 100% if green electricity is available) [154,245].

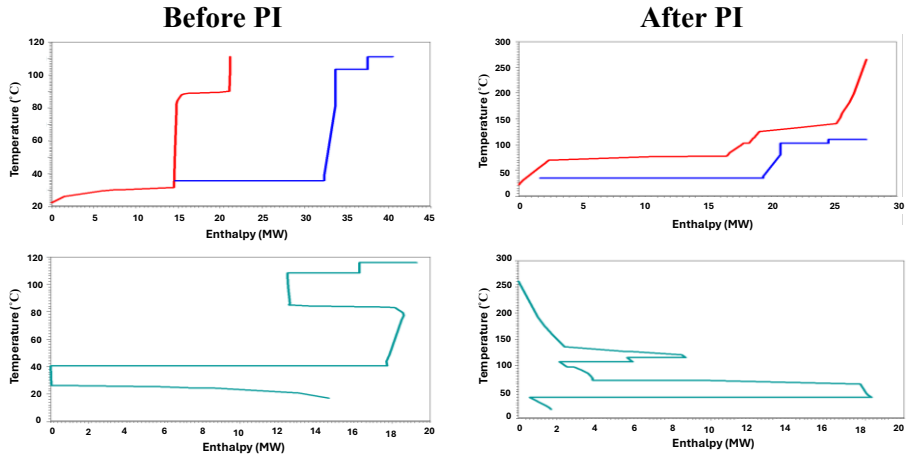


Figure 2-43. Composite curves (top row) and Grand composite curve (bottom row) before and after enhancing the isobutanol recovery process [246]

Besides improving the energy efficiency of the overall recovery process, the implementation of heat pumps is a significant step towards (green) electrification of the chemical industry and reduction of greenhouse gas emissions. Using heat pumps provides renewable heat by upgrading waste heat streams. In MVR, electrical energy needed to power the compressor replaces a significantly higher amount of thermal energy. This is especially important since the chemical industry is the third largest industrial source of greenhouse gas emissions, after the steel and cement industry [13]. Using renewable electricity to power compressors in

heat pump systems, instead of fossil fuels as the primary energy source would significantly reduce the overall carbon footprint of biochemical production processes. In that respect, process systems engineering can significantly contribute to leveraging the opportunity to use green electricity by ensuring the availability of environmentally friendly energy sources (e.g. wind, solar, hydro or geothermal energy), optimizing the energy supply, storage and management, integrating smart technologies, conducting life cycle assessment of the entire bioprocess, optimizing the entire supply chain, ensuring compliance with environmental regulations, providing relevant training for the employees and raising awareness of broader community. Besides substantial environmental benefits, the use of green electricity can lead to significant economic and social advantages.

After implementing heat pump systems, additional heat integration opportunities should be considered to maximize energy savings and improve overall process efficiency. Lastly, different process intensification opportunities can be used for the final dehydration of commonly produced bioproducts. For example, if separation of a multi-component mixture is needed (e.g. purification after ABE fermentation), a dividing-wall column (DWC) can be used. In this novel design, a sequence of two or more conventional distillation columns is integrated into one shell [115]. Depending on the components that need to be separated, the integrated design can result in significant energy savings compared to the sequence of conventional distillation columns. Furthermore, the more compact design can lead to lower capital costs [212]. However, the distillation column sequence and DWC should be compared per system, since DWC is not always the optimal solution [154].

Thus, the described PI methods lead to more efficient separation processes. By maximizing the amount of energy that can be recovered within the process (e.g. by applying heat pump or heat integration systems), the need for external energy supply is minimized. Reduced energy requirements can potentially result in more stable operation in times of uncertain energy supply. Moreover, given the correlation between CO_2 emissions and energy usage, implementation of PI methods will decrease these emissions, resulting in more sustainable bioprocesses.

The final flowsheet of the recovery process is developed after considering opportunities for heat pumping, heat integration and additional process intensification. Lastly, to evaluate the overall performance of the designed process, the economic and environmental impact should be analyzed. The complete assessment of economic factors, including both total capital (CAPEX) and total operating (OPEX) costs, can be conducted following the NREL

procedure [67], for example. Environmental performance can be assessed by calculating several sustainability metrics: energy intensity, water consumption, material intensity, greenhouse gas emissions, pollutants and toxic materials. The smaller values of these metrics indicate better process performance in terms of sustainability [68]. For more detail results, the complete life-cycle assessment should be performed. Following the proposed methodology for the design of advanced downstream processes may significantly contribute to a more sustainable development by minimizing the overall environmental impact of bioprocesses. Furthermore, the significant reduction in the total production costs will make the fermentative production of chemicals more economically attractive to stakeholders.

2.6.4. Effects of bioalcohol product on downstream processing performance

Following the previously explained methodology, a generic block flow diagram for the purification of alcohols from the dilute fermentation broth was derived (see Figure 2-44). Ethanol, isopropanol, isobutanol and 1-hexanol (further referred to as hexanol) were chosen as typical C2, C3, C4 and C6 alcohols that can be obtained by fermentation. Given that differences regarding toxicity to microorganisms, achievable fermentation titers, physical and thermodynamic properties, market price, etc., are much larger among alcohols with different number of carbon atoms than among different isomers of alcohols with the same number of carbon atoms, similar trends in downstream processing performance may be expected if different isomers were chosen. Furthermore, the fermentative production of methanol and C5 alcohols has not attracted that much attention and was therefore not analyzed in this study [17]. Similarly, there have been only a few studies on the production of C8 alcohols by microbial fermentation [247]. Due to the very low achievable titers (maximum about 0.1 g/L of 1-octanol) [248], additional research is needed to make the 1-octanol fermentation competitive to those of shorter-chain alcohols [249].

Even though all alcohols commonly produced by fermentation and considered here (e.g. ethanol, isopropanol, isobutanol, hexanol) behave somewhat similarly in aqueous systems (e.g., all form minimum boiling azeotropes with water), the performance of the overall bioalcohol production process strongly depends on the type of the alcohol that is produced. Lower concentrations are achievable in fermenters for longer alcohols, thus larger bioreactors are required to obtain a relevant production capacity. Consequently, the capital and operating costs of the upstream fermentation part will increase. However, market demands for these alcohols are different, which strongly affects the magnitude of the required production capacity. The global ethanol market was estimated to be about

102 million tonnes in 2022, with a growth rate of 4.80% until 2032 [250]. Being significantly smaller compared to ethanol, the global isopropanol market in 2022 was about 3.1 million tonnes with a growth rate of about 3.22% until 2035 [251]. Even smaller, the global isobutanol market was estimated to be 0.65 million tonnes in 2022, with an expected growth of 5.05% until 2032 [252].

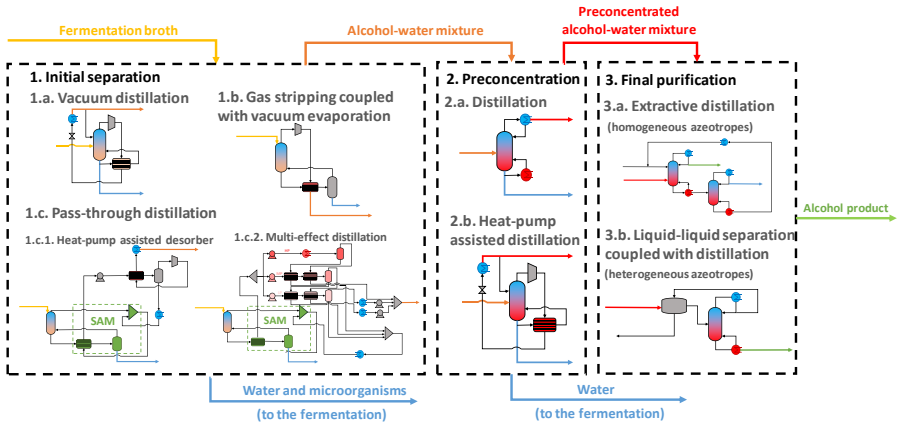


Figure 2-44. Generic flowsheets of downstream processing of alcohols from dilute fermentation broth. The final purification can be performed by extractive distillation (to deal with the formation of homogeneous alcohol-water azeotropes) or by liquid-liquid separation and distillation (to break the heterogeneous alcohol-water azeotropes)

In addition to influencing the upstream fermentation process, the type of bioalcohol produced significantly affects the performance of the downstream process. More precisely, the purification of fermentation products from more dilute broth in a cost-effective and energy-efficient way is more challenging. Thus, downstream processing costs can also be expected to be higher with the increase in the chain length of the bioalcohol product due to the more diluted fermentation broth. Figure 2-45 shows the main key performance indicators for the highly advanced downstream processes based on process intensification principles for the purification of different alcohols after fermentation. Note that this figure is a summary of the determined economic and sustainability metrics from the previous sections. Additionally, more details about the downstream processing design for the recovery of hexanol after fermentation are presented in Appendix D.

Realistically achievable concentrations of alcohols in the fermentation broth were assumed, as follows: 6.14 wt% ethanol [29], 5.01 wt% isopropanol including small amounts of acetone [169], 1.61 wt% isobutanol [187] and 0.24 wt% hexanol [240]. Nonetheless, it should be noted that the achievable concentrations of alcohols may vary depending on the type of fermentation process, which would significantly affect the performance of the downstream process. For example,

higher concentrations of ethanol (about 5-12 wt%) [144] are achievable in fermentation from glucose compared to fermentation from syngas (about 5-6 wt%) [29]. Thus, the downstream process would be less expensive after ethanol fermentation from glucose due to the higher product concentrations in the broth.

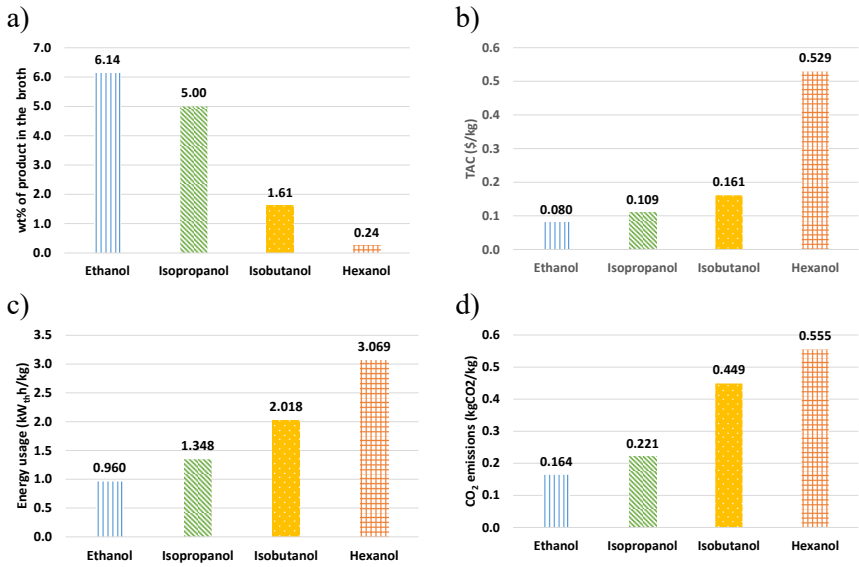


Figure 2-45. Comparison of downstream processing performance for different alcohols: a) product concentration in the broth, b) total annual costs (TAC), b) energy requirements and d) CO_2 emissions

Furthermore, due to the specific market demands for these alcohols, different plant production capacities were assumed for each of them: 100 [154], 100 [253], 50 [246] and 10 ktonne/y of ethanol, isopropanol and acetone, isobutanol and hexanol production, respectively. All of the downstream processes mentioned were obtained after maximal energy recovery within the system which resulted in a significant reduction of the total recovery costs. The total recovery costs increase with the chain length of alcohols, whereby the most significant increase happens from C4 to higher alcohols. Calculated following the NREL methodology [67] with 10 years payback period, the total recovery costs are 0.080 $/kg for ethanol [154], 0.109 $/kg for isopropanol and acetone [253], 0.161 $/kg for isobutanol [246] and 0.529 $/kg for hexanol. For comparison, the reported production cost of lignocellulosic bioethanol is about 0.83 $/kg [254], while the production costs of biobased and fossil fuel-based butanol were estimated to be 1.24 and 1.01 $/kg, respectively [255]. Thus, it can be concluded that the downstream processes analyzed in this study are highly competitive. However, it should be noted that there is a large increase in the downstream processing cost if

the obtained alcohol concentration in the fermentation broth is lower than 1 wt% (about 1 g/L). There are multiple reasons for this trend. Firstly, the total capital costs do not decrease directly proportionally with the production capacity if product concentration in the broth also decreases. More dilute feed streams still require relatively large equipment units for the initial separation and preconcentration steps (e.g. if vacuum distillation is used for the initial separation step, column diameter for the first column is in the range 4.0 – 4.3 m), whereby only the equipment units for the final purification are smaller due to the lower amounts of final products. Moreover, the total operating costs increase with the decrease of alcohol concentration in the feed stream: 0.063 $/kg for ethanol [154], 0.081 $/kg for isopropanol [253], 0.117 $/kg for isobutanol [246] and 0.529 $/kg for hexanol. This is mainly due to the higher energy needed per kilogram of recovered product. For example, MVR heat pump system may be implemented to the initial separation of bioalcohols from most of the fermentation broth to decrease the energy usage for this step [113]. In this system, vapor containing valuable fermentation products can be compressed and used to evaporate these products from a dilute aqueous solution. Hence, if the concentration of alcohol in the feed stream is lower, less vapor needs to be formed. However, a higher compression ratio is needed to ensure that the smaller amount of compressed vapor can provide sufficient heat to the dilute aqueous solution. If this initial separation is performed by vacuum distillation, a higher reflux ratio is needed to provide sufficient liquid flow down the column. Consequently, the required heating duty for this column would be larger and the necessary compressor duty in the MVR system would also increase (e.g. compressor duties in the MVR systems implemented to the initial vacuum distillation columns are about 1.6 [154], 2.5 [253] and 3.5 MW [246] for ethanol, isopropanol and isobutanol recovery). The electrical energy requirements in the recovery processes originate mainly from the compressors in the heat pump systems (as the energy required for the pumps represents only a minor part of the total electrical energy usage), so higher compressor duties (in case of more dilute feed streams) lead to an increase in the energy usage expressed per kilogram of recovered alcohol (e.g. 0.200 [154], 0.338 [253], 0.807 [246] and 1.169 kW_eh/kg for ethanol, isopropanol, isobutanol and for hexanol, respectively). Additionally, heat pump systems might not be able to completely replace the usage of steam for heating. For instance, ethanol and isopropanol form homogeneous azeotropes with water that needs to be treated to obtain high-purity bioalcohol final products. Extractive distillation with ethylene glycol has been proven as the best option for large-scale purification in terms of initial investment and operating costs [102,107]. However, ethylene glycol, which makes the most of the bottom product, has a much higher boiling point compared to ethanol or isopropanol (about 197.2 ˚C compared to 78.3 and 82.1 ˚C, respectively), which are obtained as top products. Due to the large temperature

difference between the top and bottom of the distillation column, heat pump systems cannot be implemented, and external heating is required. Somewhat more thermal energy is needed for isopropanol purification compared to ethanol purification (0.502 $kW_{th}h/kg$ [253] for isopropanol compared to 0.450 $kW_{th}h/kg$ [154] for ethanol). However, isobutanol and hexanol form heterogeneous azeotropes with water and simple liquid-liquid phase separation combined with conventional distillation is sufficient to provide high-purity products. In the case of isobutanol recovery, pure isobutanol is obtained as the bottom product from the distillation column, while nearly azeotropic isobutanol-water mixture is obtained as the top product. Since the temperature difference is not large (about 107.7 ˚C at the bottom and 90.3 ˚C at the top), MVR can be applied to decrease the total energy requirements for that separation part by about 40% [246]. Thus, the complete electrification of the isobutanol recovery after the fermentation is possible and there is no need for usage of external thermal energy [246]. On the contrary, even though hexanol forms a minimum boiling azeotrope with water (97.8 ˚C), it has a much higher boiling point (156.8 ˚C). Therefore, MVR cannot be applied to the final purification step and steam must be used for heating, resulting in higher thermal energy requirements as compared to isobutanol recovery (0.145 $kW_{th}h/kg$), but still lower than those for ethanol and isopropanol recovery due to the absence of a high-boiling solvent. Nonetheless, the total primary energy requirements, that take into account both electrical and thermal energy through the electrical-to-thermal conversion factor (conservative value of 2.5) [156], increase with the increase in the alcohol chain length: 0.960, 1.348, 2.018 and 3.069 $kW_{th}h/kg$ for ethanol, isopropanol, isobutanol and hexanol, respectively. Another important key performance indicator is the amount of carbon dioxide (CO_2) that is emitted per kilogram of recovered product. Since these emissions are related to the total energy requirements, an increase in alcohol chain length also results in higher CO_2 emissions in the downstream processing: 0.164 [154], 0.221 [253], 0.449 [246] and 0.555 kg_{CO2}/kg for ethanol, isopropanol, isobutanol and hexanol. In comparison, the carbon footprints of ethanol and petrochemically produced isopropanol were estimated to be 0.81 kg_{CO2}/kg [256] and 1.85 kg_{CO2}/kg [73].

It should be noted that more expensive downstream processing in the case of longer-chain alcohols is mostly due to lower product concentrations in the feed stream and not the nature of alcohol. The nature of alcohol (e.g. hydrophobicity) substantially affects the fermentation process and determines the product concentration in the feed stream to the downstream processing. Moreover, the recovery of isobutanol and hexanol from aqueous mixtures is somewhat easier compared to the purification of ethanol and isopropanol due to the heterogeneity of the formed azeotropes (see Table 2-22). In these cases, a simple liquid-liquid

phase separation followed by conventional distillation can be used to recover high-purity products. Contrarily, ethanol and isopropanol form homogeneous azeotropes and more complex extractive distillation (using a high-boiling solvent) is needed. The comparison of the total recovery costs of ethanol and higher alcohols starting from various concentrations in the fermentation broth is presented in Figure 2-46.

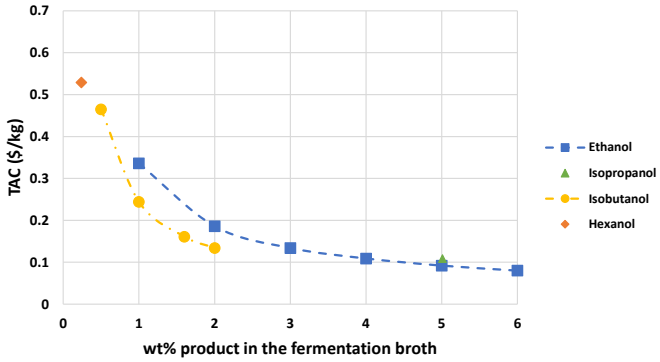


Figure 2-46. Influence of the product concentration in the fermentation broth to the total recovery costs

Due to similar physical properties, isopropanol and ethanol recovery costs are comparable. Furthermore, the low concentrations of longer-chain alcohols in the fermentation broth are the main reason for the more expensive downstream processing. For example, the total isobutanol recovery costs starting from 1.61 wt% in the feed stream are lower than the expected ethanol recovery costs starting from the same initial concentration. The reason for this is the already mentioned, namely the easier separation that results from the heterogeneity of the isobutanol-water azeotrope. Thus, the concentration of the alcohol product in the fermentation broth has the most significant influence on the downstream processing performance. Nonetheless, in the case of higher alcohols with lower achievable fermentation titers, the overall production process might still be viable because of less complex separations. Lastly, even though expressed per kilogram of recovered bioalcohols, the results presented in Figure 2-46 were obtained assuming different production capacities (100 ktonne/y of ethanol and isopropanol separately, 50 ktonne/y of isobutanol and 10 ktonne/y of hexanol). Thus, TAC for recovering hexanol and isobutanol might benefit from the economy of scale assuming that there is sufficient market demand to increase the production capacity. However, since OPEX is roughly proportional to the production capacity, it is only the contribution of CAPEX that may decrease. Yet, considering that CAPEX makes only a minor part of TAC, whereas the

contribution of OPEX is much larger [154,246,253], changes in the production capacity should not significantly affect the trend presented in Figure 2-46.

Thus, even though recovering higher alcohols after fermentation is more expensive due to the more dilute feed stream, the market prices of these alcohols are higher. According to the available data, the prices of these alcohols at the end of 2023 in North America were the following: 0.591 $/kg for ethanol [257], 1.310 $/kg for isopropanol [258], 2.043 $/kg for isobutanol [259] and 2.500 $/kg [260] for hexanol. Consequently, the total purification costs correspond to about 13.5, 8.3, 7.9 and 21.2% of the current market prices for ethanol, isopropanol, isobutanol and hexanol, respectively. Thus, producing longer-chain alcohols might be more profitable, despite the more costly downstream processing due to the higher market prices of these chemicals. Additionally, a margin between market price and total recovery costs is 0.511, 1.201, 1.882 and 1.971 $/kg for ethanol, isopropanol, isobutanol and hexanol, respectively. However, this margin does not include fermentation costs and would further reduce once these costs are also included. To the best of our knowledge, a complete comparison of the fermentation costs for different alcohols has not been reported, and literature data focused on the production of only one alcohol cannot be compared due to the differences in the applied methodologies for evaluating the process performance [167,261–263]. Even though the margin between market price and total production costs increases with the increasing chain length of alcohols, it can be expected that fermentation costs increase as well. This is mainly due to the lower achievable concentrations, which leads to the larger required bioreactors, and higher capital and operating costs. However, additional research and a fair comparison (on the same basis) of the fermentation processes for different alcohols are needed to obtain a full picture. Notably, the cost of both upstream fermentation and downstream processes should be taken into account to ensure a sustainable and competitive design of an industrial-scale plant. In that respect, this perspective paper expresses the importance of downstream processing in the overall bioalcohol production process. Furthermore, the overall comparison offers valuable insight into the performance of downstream processing that can be expected industrially. This information is of substantial significance for the development of large-scale fermentative production of bioalcohols.

2.6.5. Conclusion

This dissertation provides novel insights into the purification of volatile biochemicals from highly diluted fermentation broths and a generic framework for the design of downstream processes. Significant loss of biomass may be avoided by implementing vacuum distillation or pass-through distillation for initial separation of valuable products from most of the broth. Furthermore, literature recommendations for large-scale purification should be followed to maximize downstream process performance. Advanced process intensification techniques, heat pump systems and heat integration can be applied to significantly reduce downstream processing energy requirements and costs.

Additionally, this section provides a critical insight into the eco-efficiency and performance of downstream processing for the purification of different alcohols (ethanol, isopropanol, isobutanol, hexanol) from fermentation broth. Achievable concentrations of longer-chained alcohols are lower due to stronger toxic effects. Consequently, the purification of valuable fermentation products from more dilute streams is more economically and environmentally intensive. However, the more expensive downstream processing in the case of longer-chain alcohols is mainly due to the lower concentrations in the fermentation broth and not the nature of the alcohol product. Despite more expensive recovery processes, longer-chain alcohols are higher-value products with smaller markets. Thus, the choice of the most profitable alcohol to produce should be made after coupling and analyzing the performance of both upstream and downstream processes.

3 | Recovery of diols from fermentation broths



3. Recovery of diols from fermentation broths

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Propanediols (PDO) and butanediols (BDO) are platform chemicals that are commonly produced through fossil-carbon-dependent routes. However, these chemicals can be obtained more sustainably, through different fermentation processes. These alternative production pathways have been attracting the attention of various companies, such as DuPont, Genencor [264,265], LanzaTech, National Renewable Energy Laboratory (NREL), BioPrincipia [266–268], Genomatica and Novamont [269–271]. Nonetheless, there are some drawbacks of the fermentation process that limit the wide spreading of these technologies. One significant challenge for successful commercialization of fermentative production is a complex purification process. The complexity of the downstream processing is mainly attributed to the relatively low product concentrations in the broth (about 5-15 wt% depending on the fermentation method). Furthermore, the high boiling points of these diols, low volatility, and high hydrophilicity complicate recovery from a highly dilute fermentation broth. Lastly, the potential formation of by-products and the presence of residual substrates, biopolymers and inorganics introduce additional difficulties. Due to the complex fermentation broth, several steps are often required in the downstream processing (see Figure 3-1) [272,273]. Since fermentation broth is usually very dilute and PDO/BDO has a higher boiling point compared to water, the initial removal of biomass, biopolymers and inorganics from the medium is needed before the final purification. Conventionally, the initial step is the removal of cells from the fermentation broth by microfiltration. Nonetheless, some liquid containing valuable PDO/BDO product will also be removed with the cells and an additional cell washing by diafiltration is needed to maximize product recovery. After the microfiltration step, some biopolymers present in the microfiltered broth will be removed by an additional ultrafiltration step. Furthermore, inorganics remaining from the fermentation (e.g. salts) are commonly removed from the filtered broth by ion exchange steps, resulting in a dilute desalted aqueous solution. Lastly, a preconcentration step to remove most of the water and a final purification step to remove the remaining light and heavy by-products are needed to obtain a high-purity PDO/BDO product. Besides the previously mentioned common methods for the initial recovery steps, several other techniques have been investigated (e.g. chromatography [274,275], extraction [276], reactive extraction [277–280] salting-out extraction [281–284], sugaring-out extraction [285], slating-out [286,287], etc.). Nonetheless, these methods are usually studied on a small scale and are often not applicable for scale-up to an industrial capacity due to low achievable recoveries (extraction, reactive extraction), insufficient product purities (extraction, reactive extraction), high energy requirements (chromatography, salting-out extraction), large need for additional chemicals and problems related to their recovery and reuse (extraction, reactive extraction, salting-out extraction) [273,288].

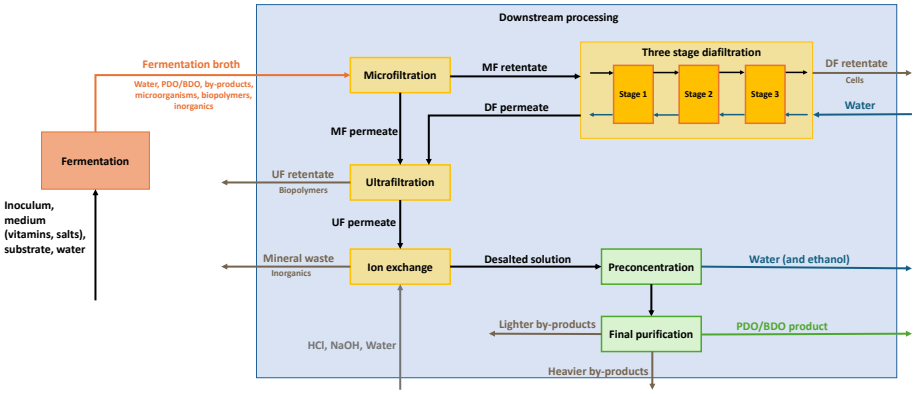


Figure 3-1. Block flow diagram of the complete bioprocess (upstream and downstream)

The last two steps in the downstream processing (preconcentration and final purification) may significantly contribute to the total recovery costs due to the high energy use. Thus, the goal of the original research presented in this chapter is to improve the competitiveness of the PDO and BDO fermentation processes by enhancing preconcentration and final purification parts of the recovery process. As initial steps in the recovery process are conventional methods already commonly used on an industrial scale, they were not the focus of this research.

3.1. Recovery of 1,3-propanediol

PDO (1,3-propanediol) is a platform chemical that is obtained by petrochemical routes and by fermentation. The latter needs relatively complex downstream processing after fermentation, due to the modest concentration of the high-boiling product, and the presence of microorganisms and many impurities in the fermentation medium. This novel research proposes an original large-scale (production capacity of 23-32 ktonne/y) process for the final purification of PDO and dominant by-products, from the fermentation of glucose or glycerol. Following the initial microfiltration, diafiltration, ultrafiltration and ion exchange steps, heat pump-assisted vacuum distillation was implemented to remove most of the water from the broth. Afterwards, an advanced highly integrated dividing-wall column was designed to allow the final purification of PDO (product purity >99.9 wt%) from light and heavy by-products. Fermentation by-products that are present in significant amounts can also be recovered and valorized. Overall, the developed final purification processes demonstrate cost-effectiveness (0.150-0.274 $/kg$_{product}$) and energy-efficiency (1.258-3.175 $kW_{th}h/kg_{product}$) which contributes to the competitiveness of the overall downstream processing (0.256-0.384 $/kg and 1.487-3.496 $kW_{th}h/kg_{product}$).

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3.1.1. Introduction

1,3-Propanediol (PDO) is an attractive platform chemical that can be used as a monomer for the production of different polymers (e.g. polyesters and polyurethanes) which have good resistance to stains and wash fastness properties [288]. Furthermore, PDO has potential applications as a solvent, antifreeze or protective agent and in the synthesis of pharmaceuticals, cosmetics, detergents, laminates, resins and adhesives [289]. The global demand for PDO increased significantly after the start of the commercial polytrimethylene terephthalate (PTT) production by Shell in 1995 [289]. Due to its unique zigzag structure, PTT has many advantages compared to similar polymers (e.g. polyethylene terephthalate (PET) and polybutylene terephthalate (PBT)). It has excellent tensile and stretch recovery because applied forces do not only cause stretching but also trigger bending and twisting of molecular bonds. Thus, a PTT fiber has superior stretch recovery abilities. Moreover, PTT-based fabrics are soft, easily dyeable with the possibility of multiple deep shades, resistant to many stains and exhibit superior wash fastness. Among others, PTT has great potential for applications in the carpet, textile, film and packaging industries [289]. According to openly available market data, the bulk price for high-purity PDO is about 3.8-4.2 $/kg. In 2021, the PDO market was estimated at 433.4 million $ with an expected growth rate of 11.5% [290], while the PTT market was valued at 896.8 million $ with an expected growth rate of 5.4% [291].

Traditionally, PDO has been produced by petrochemical synthesis whereby production processes from acrolein by DuPont and from ethylene oxide by Shell are the most dominant [292]. In the first route, acrolein is converted to 3-hydroxypropanol by catalytic solution phase hydration, followed by hydrogenation to obtain PDO. In the second route, hydroformylation of ethylene oxide is used to produce 3-hydroxypropanol that is later extracted and hydrogenated to PDO. The most significant drawbacks of these conventional processes are the requirements for high operating pressure and temperature, usage of expensive catalysts, presence of toxic intermediates, very low yields (about 40 and 80% for the acrolein and ethylene oxide-based routes, respectively) and environmental concerns [289]. To avoid these drawbacks, industrial production of PDO by microorganisms has been developed [293,294]. Currently, the microbial production of PDO is mainly based on two different fermentation technologies. The first fermentation route uses a recombinant *Escherichia coli* to obtain PDO from glucose. The commercialization of this production method has been undertaken by DuPont and Genencor [264,265]. The second way to microbially produce PDO is the fermentation of glycerol by different microorganisms (natural or genetically engineered strains) [295–299]. Being a major byproduct of the biodiesel production processes, glycerol is a useful

feedstock for PDO production [288]. The fermentation of glycerol to PDO has been commercialized in China and France [300]. Significant research effort has been put into developing genetically engineered microorganisms, enhancing metabolic efficiency and increasing fermentation titers [265,288,293]. Nonetheless, there are still some bottlenecks in the fermentative production of PDO (e.g. low titer due to product inhibition, low yield, high formation of by-products, etc. [293]). Many of the mentioned drawbacks of the fermentation process will reflect on the downstream processing performance. However, the recovery of PDO from complex fermentation broth has not received nearly as much attention [293]. Low product concentrations, large amounts of water that has a lower boiling point than PDO, presence of microorganisms, biopolymers and inorganics in the fermentation medium, etc., are challenges for an efficient recovery process on an industrial scale. Considering the importance of the separations for the commercial viability of the biotechnological process [34,35], the main goal of this original research is to enhance the fermentative PDO production by an intensified recovery process that can be applied to various fermentation pathways. In that respect, the focus of this work is on developing a highly advanced process for the final purification of PDO after the initial filtration and ion exchange steps, which will be shortly explained later.

In the heart of the developed process is an integrated dividing-wall column (DWC) that can efficiently recover high-purity PDO product while removing all the light and heavy by-products that may be present. The developed process was also extended to purifying and valorizing by-products that are present in significant amounts.

3.1.2. Problem statement

Since microbial production of PDO is mainly based on two routes (fermentation from glucose and fermentation from glycerol), two recovery processes were designed (further referred to as case 1 and case 2). The composition of the fermentation broth was taken from the published literature and presented in Table 3-1.

In the case of fermentation from glucose using *E.coli* strain (case 1), the composition of the broth is the following: 12.90 wt% PDO, 5.35 wt% dry cells, 1.48 wt% glycerol, 0.20 wt% inorganics, 0.10 wt% biopolymers, 0.10 wt% glucose and remaining 79.96 wt% water [265]. Alternatively, in the case of fermentation from glycerol using *Klebsiella pneumoniae* (case 2), the composition of the broth is the following: 10.21 wt% PDO, 5.35 wt% dry cells, 3.17 wt% 2,3-butanediol (BDO), 1.33 wt% succinic acid, 0.41 wt% ethanol, 0.25 wt% lactic acid, 0.25 wt% acetic acid, 0.20 wt% inorganics, 0.10 wt% biopolymers and 78.72 wt% water [298]. Inorganics include mainly salts

remaining from the fermentation medium, while biopolymers stand for the lysed microorganisms and other present organic molecules. Thus, the amount of formed byproducts is much higher in the case when glycerol is used as a substrate (case 2).

Table 3-1. Composition of the fermentation broth and the feed stream to the preconcentration with boiling points of main components at 1 bar

Component	Mass fraction in the fermentation broth	Mass fraction in the feed stream to preconcentration	Tb (˚C)
Case 1			
Water	0.7996	0.8893	100.00
1,3-Propanediol	0.1290	0.1002	214.22
Glycerol	0.0148	0.0105	287.85
Glucose	0.0001	0.0001	/
Dry cells	0.0535	0.0000	/
Inorganics	0.0020	0.0000	/
Biopolymers	0.0010	0.0000	/
Case 2			
Ethanol	0.0041	0.0029	78.29
Water	0.7872	0.8820	100.00
Acetic acid	0.0025	0.0018	117.90
2,3-Butanediol	0.0317	0.0225	180.70
1,3-Propanediol	0.1021	0.0795	214.22
Lactic acid	0.0025	0.0018	216.85
Succinic acid	0.0133	0.0094	317.85
Dry cells	0.0535	0.0000	/
Inorganics	0.0020	0.0000	/
Biopolymers	0.0010	0.0000	/

Summarizing, the main challenges in the downstream processing are highly diluted streams, high boiling points of PDO and presence of microorganisms and impurities in the fermentation broth. Consequently, an advanced purification process is necessary to make PDO production cost-effective an energy efficient.

3.1.3. Methods of process design and simulation

To the best of our knowledge, only a simple sequence of distillation columns has been proposed to remove present water and purify PDO from light and heavy impurities [272,301–304]. This original research substantially strengthens the development of sustainable microbial PDO production by designing the two final steps in the recovery process (preconcentration and final purification). Rigorous simulations for all operations in the developed process were designed in Aspen Plus. Due to the highly complex mixtures, the NRTL-HOC property method was used to describe the interactions between different components. To ensure a fair comparison between the two cases, the total production capacity of about

23 ktonne/y of PDO was assumed, and the flowrates of the feed streams to the recovery process were back-calculated accordingly: 23,800 kg/h in case 1 and 30,000 kg/h in case 2. The chosen plant capacity is similar to the starting industrial plants for PDO fermentation from glycerol in Jiangsu, China (capacity of about 20 ktonne/y) [288].

A detailed economic and environmental analysis was conducted to evaluate the performance of the designed recovery process. Approximate costs for the initial separation steps (microfiltration, cell washing, ultrafiltration and ion exchange) were also calculated and added to the costs for the designed preconcentration and final purification steps to obtain a complete picture of the downstream processing performance.

3.1.4. Results and discussion

This section contains key information on process design and simulation, techno-economic and sustainability analyses.

Process design

Flowsheets of the developed recovery processes are presented in Figure 3-2 and Figure 3-3.

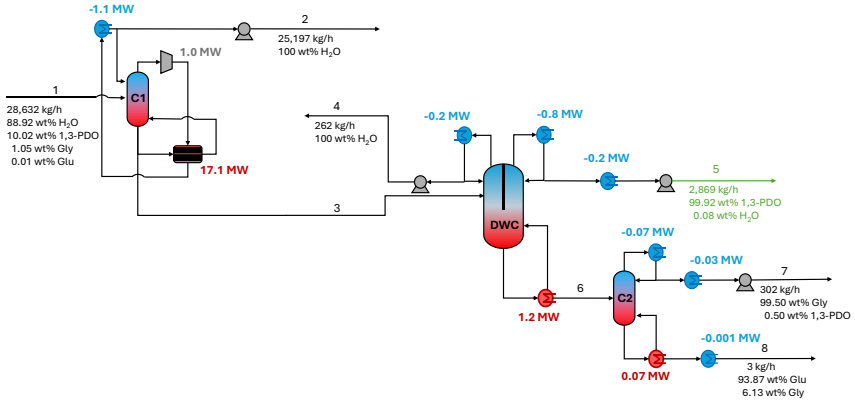


Figure 3-2. Downstream process for the recovery of PDO after fermentation - Case 1a (excluding column C2) and Case 1b (including column C2), (abbreviations: H_2O – water, 1,3-PDO – 1,3-propanediol, Gly – glycerol, Glu – glucose)

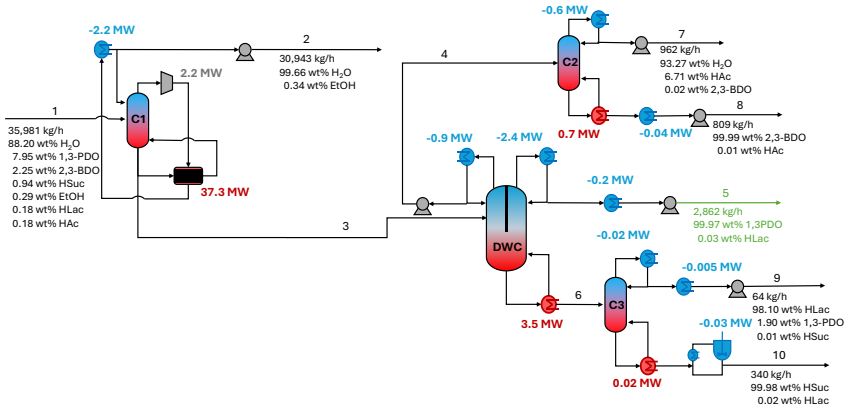


Figure 3-3. Downstream process for the recovery of PDO after fermentation – Case 2a (excluding columns C2 and C3) and Case 2b (including columns C2 and C3), (abbreviations: H_2O – water, 1,3-PDO – 1,3-propanediol, 2,3-BDO – 2,3-butanediol, HSuc – succinic acid, EtOH – ethanol, HLac- lactic acid, HAc – acetic acid)

Initial downstream processing

Considering the complexity of the fermentation broths, several steps are required in the downstream processing (see Figure 3-1) [272]. Thus, the composition of the feed stream to the preconcentration and final purification steps will differ from the composition of the broth from the fermenter. A reasonable composition of the feed stream for these steps was obtained by performing mass balance calculations for the prior downstream processing steps. These calculations were fully automated in Excel as described in more detail below.

The initial step in the recovery process is the removal of cells by microfiltration. It was assumed that all cells were removed from the broth in this step, whereby microfiltration can reach about 120 g of dry cells per kilogram (equivalent to about 480 g of wet cells mass per kilogram). Therefore, some liquid containing PDO will be separated with the cells in the microfiltration retentate. Since about 41.5% of the PDO from the fermentation broth will be separated in the microfiltration retentate, a cell washing step is needed to minimize the loss of PDO to about 4%. Washing of the microfiltration retentate can be performed in a three-stage counter-current diafiltration, whereby water is used as the washing liquid. Higher amounts of washing water will decrease the loss of PDO but will result in more dilute streams that complicate further downstream processing. Thus, 90% recovery of PDO from the microfiltration retentate was assumed and the flowrate of washing water was varied to close the mass balances for the diafiltration part of the recovery process. Furthermore, the filtered fermentation broth (microfiltration permeate) and washing water enriched with fermentation products (diafiltration permeate) were jointly sent to the ultrafiltration. This step

is necessary to remove biopolymers that were not removed in the previous microfiltration step. Ultrafiltration membranes can be used as a selective barrier for the separation of the remaining larger organic molecules [305]. It was assumed that about 50 g/L of biopolymers could be obtained in the ultrafiltration retentate while being completely removed from the permeate. However, the degree of biopolymer removal will strongly depend on the applied ultrafiltration technology. Additional washing may be applied to recover PDO from the ultrafiltration retentate. Nonetheless, only about 1.4% of PDO from the fermentation broth will be lost with the biopolymers in this stream. Such an additional washing step would result in even higher dilution of the stream that is sent to further downstream processing. This would lead to larger equipment units and higher energy requirements. Therefore, recovering the PDO from the ultrafiltration retentate was not considered in this study. Furthermore, the removal of inorganics from the ultrafiltration permeate is necessary after the ultrafiltration step. This can be achieved in a series of cation and anion exchange units. Cation exchange units contain resin in H^+ form that can be regenerated with an acid solution (e.g. HCl). Contrarily, anion exchange resin is in OH^- form and is recovered with a base solution (e.g. NaOH). To ensure a continuous operation, at least two cation exchange and two anion exchange trains need to operate alternately. The following approximations were assumed when calculating mass balances for the ion exchange step: 99% of inorganics were removed from the ultrafiltration retentate, 1% of PDO and 10% of other present organic compounds were lost in this step, which resulted in 2% dilution.

The obtained desalted solution is the feed stream for the following preconcentration and final purification steps which are the main focus of this study (see Table 2-9). In case 1, this stream has a flowrate of 28,633 kg/h and contains about 10.02 wt% PDO, 1.05 wt% glycerol, 0.01 wt% glucose and 88.93 wt% water. Due to the washing water in the diafiltration step and the dilution in the ion exchange, the feed stream to the preconcentration step is more dilute compared to the broth from the fermenter. Similarly, the desalted solution in case 2 has a flowrate of about 35,981 kg/h, with the following composition: 7.95 wt% PDO, 2.25 wt% BDO, 0.94 wt% succinic acid, 0.29 wt% ethanol, 0.18 wt% lactic acid, 0.18 wt% acetic acid and 88.20 wt% water.

Preconcentration

The previously described initial purification steps are needed to remove cells, organic and inorganic impurities from the fermentation broth. Nonetheless, the desalted solution that is obtained after the ion exchange is still very dilute and a preconcentration step is required to remove large amounts of water. Being the only lighter component than PDO in the desalted solution, pure water can be obtained as the top product in case 1, while the bottom product consists of PDO, glycerol, glucose and some water. Contrarily, in case 2, ethanol will be separated with water as the top product, while PDO, BDO, succinic acid, lactic acid, acetic acid and some water will be obtained at the bottom. Vacuum distillation in column C1 can be applied to facilitate the separation and reduce energy requirements for this step. The operating pressure of 0.060 bar (top pressure) was chosen to minimize reboiler duty while keeping the condensation temperature (about 36 ˚C) appropriate for the usage of inexpensive cooling utilities (e.g. cooling water). Due to the reduced pressure operation, structured packing type Mellapak 250 with a pressure drop of 0.225 mbar per theoretical stage was selected as internals [110]. Lower distillation temperatures also minimize the risk of degradation of trace impurities such as glucose, which leads to yellowing of the purified PDO.

The distillate-to-feed mass ratio for column C1 was varied to minimize the total energy requirements for column C1 and the following removal of the remaining light impurities and water (the next step in the recovery process). More water separated in the distillate of column C1 would result in a higher reboiler duty of column C1, but a less intensive next separation. Nonetheless, the temperature difference at the top and the bottom of column C1 increases as the distillate-to-feed ratio increases because the bottom product becomes more concentrated with higher boiling components. Consequently, the implementation of heat pump systems might not be so effective. In case the temperature difference at the top and the bottom of the distillation column is not large, a mechanical vapor recompression (MVR) system can be applied to decrease the total energy requirements. This heat pump system implies compressing vapor from the top of the column and using it to evaporate the bottom liquid [113]. As a result, the electrical energy required to power the compressor can replace much larger amounts of thermal energy, while allowing complete electrification of this step. If the temperature difference between the top and the bottom of the distillation column is too large, the top vapor cannot be compressed enough to provide sufficient heat to the bottom liquid. Thus, the influence of the distillate-to-feed ratio of column C1 was varied to minimize the total energy requirements for the preconcentration step (in column C1) and the following removal of light impurities. Alternatively, multi-effect distillation may be implemented to reduce the thermal energy requirements for the preconcentration step in the recovery

process. This energy-saving technique implies using multiple evaporators, each operating at successively lower pressure. The vapor from one evaporator is used as a heating medium in the next one, resulting in significant energy savings. Consequently, external heating is usually only needed to heat up the stream in the part of the process with the highest pressure. Even though the implementation of multi-effect evaporation can significantly reduce the overall energy requirements, an external thermal energy supply is still needed. Contrarily, the MVR system (which gives similar or better energy savings) can allow complete electrification of the preconcentration step which is an important step towards (green) electrification of industrial bioprocesses.

In case 1, water is the only component lighter than PDO in the feed stream to the preconcentration step (see Table 3-1). Theoretically, all water can be removed in column C1 and subsequent removal of light components is not needed. Nonetheless, this results in a very large temperature difference at the top and the bottom of this column (about 36 and 141 ˚C at the top and the bottom, respectively), which makes it impossible to apply the MVR system. Thus, the total energy requirements in case all water is removed in only one distillation column are much higher (more than 5.8 times higher) than if two columns were used, whereby the MVR system is applied to the first column. Finally, a distillate-to-feed ratio of 0.88 on a mass basis was defined as the operating specification for column C1 as this value leads to the minimal energy requirements. The top product from column C1 is pure water, while the bottom product contains PDO, some water and heavy impurities (83.49, 7.68, 8.75 and 0.08 wt% of PDO, water, glycerol and glucose, respectively).

In case 2, most of the water and ethanol can be obtained as the top product from column C1, while the remaining water with light impurities (acetic acid and BDO) can be removed at the top of the next distillation column (further discussed later). The minimal energy requirements for these steps were obtained using a distillate-to-feed ratio of 0.86 and using MVR for column C1. The top product from column C1 is 99.66 wt% water with 0.34 wt% ethanol, which may be recycled back upstream. The bottom product from C1 contains mainly PDO (about 56.81 wt%), with some water (17.82 wt%), light impurities (1.29 wt% acetic acid and 16.06 wt% BDO) and heavy impurities (6.75 wt% succinic and 1.29 wt% lactic acid). Additionally, depending on the fermentation strategy, some residual substrate (glycerol) might be present in this stream.

Thus, in both cases, the MVR system was applied to the preconcentration column C1, allowing a complete electrification of this step. However, due to the presence of more by-products and the lower temperature differences between PDO and the first lighter and heavier component, the separations are more complex in case 2.

Accordingly, a higher reflux ratio (0.80 compared to 0.01), reboiler duty (37.3 MW_{th} compared to 17.1 MW_{th}) and compressor duty (2.2 MW_e compared to 1.0 MW_e) are needed in case 2 than in case 1. The energy savings obtained with the implementation of this heat pump system can be expressed through the coefficient of performance (COP). This value is equal to the ratio of the exchanged heat (between the compressed vapor and bottom liquid) and the required compressor duty [113]. COP values greater than the electrical-to-thermal conversion factor (with a conservative value of 2.5 [306]) indicate that the heat pump system reduces the total energy requirements. COP values for the MVR systems applied to column C1 are 16.3 and 17.0 for cases 1 and 2, respectively. Thus, the implementation of these heat pumps reduced the total energy requirements for the preconcentration step by about 85%.

Final purification in an integrated dividing-wall column

Even though most of the water from the feed stream is removed in the preconcentration column C1, a much smaller amount of water (in case 1) and some light components (in case 2) need to be removed in the next distillation column. The top product from this column would be water and all components lighter than PDO (pure water in case 1, water with BDO and acetic acid in case 2), while the bottom product would be PDO with the remaining heavier components (glycerol and glucose in case 1, succinic and lactic acid in case 2). Lastly, to obtain pure PDO product, an additional distillation step is needed to remove heavy impurities. The top product from this column would be pure PDO, while the bottom product would consist of the remaining heavy components. Thus, a sequence of at least two conventional distillation columns would be needed to separate high-purity PDO product from all lighter and heavier components. Alternatively, a thermodynamically equivalent highly integrated dividing-wall column system (DWC) [307] can be used to replace this sequence of two distillation columns (see Figure 3-4).

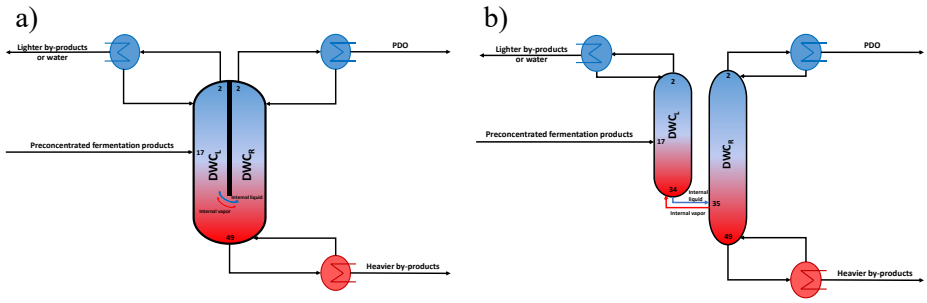


Figure 3-4. a) DWC design and b) the equivalent sequence of distillation columns – the numbers in the column indicate the column tray number

A dividing-wall column with a common bottom section and a divided overhead section is the proper column design. This design implies the initial removal of light components, followed by the subsequent purification of PDO from heavy components. Thus, the DWC has two top products (lighter components and PDO) and two condensers, while having only one bottom product (heavier components) and one reboiler. Due to the large temperature difference between the top products (about 24-26 ˚C and 116-123 ˚C), thermal insulation will be needed for the internal wall to ensure the energy efficiency of DWC. As another option, a dividing-wall column with a common overhead section and a dividing bottom section is a possible DWC column design. It implies the initial removal of heavier components, followed by purification of PDO from lighter components. Thus, PDO is obtained as one of the two bottom products (PDO and heavier components), while lighter components are the only top product. In this design, the temperature difference between two products at the dividing side of the column (PDO and heavier components) would be smaller (<50 ˚C). However, this DWC design would result in more than 54% higher energy requirements because the PDO product has to be evaporated twice. Thus, DWC with the common bottom and the divided overhead section is the best configuration in terms of total energy requirements.

As the DWC process unit is not available off-the-shelf in Aspen Plus, a thermodynamically equivalent sequence of two distillation columns was used in simulations, as presented in Figure 3-4. The left and right parts of DWC are presented with DWC_L and DWC_R, respectively, whereby DWC_L has only a condenser, while DWC_R has both a reboiler and a condenser. The number of stages, position of the feed stage, operating pressure, distillate rate, reflux ratio and vapor split were varied to ensure recovery of high-purity PDO product while minimizing total energy requirements. The condenser pressure of 0.030 bar with a pressure drop of 0.225 mbar per theoretical stage was defined for both DWC_L and DWC_R to minimize the required heating duty for DWC while maintaining DWC_L condenser temperature sufficiently high (about 26 ˚C) for the usage of

chilled water. Due to the operation under reduced pressure, the structured packing type Mellapak 250 was also selected for DWC internals [110]. DWC has 50 stages in total, whereby the convention in Aspen Plus implies that the first stage is a condenser, while the last one is a reboiler. The wall is placed at the top 34 stages (33 excluding condensers). The feed stream to DWC, the preconcentrated mixture from the bottom of column C1, is fed to the 17th stage of DWC_L (also the 17th stage of DWC). The top product from DWC_L contains water (in case 1) and all components lighter than PDO (BDO and acetic acid in case 2). As there is no reboiler, the bottom liquid from DWC_L goes to DWC_R, while a part of the vapor rising in DWC_R (29.7 and 32.8% in case 1 and case 2, respectively) is redirected to DWC_L to ensure sufficient vapor flow in the left side of DWC. The top product from DWC_R is a high-purity PDO product (>99.9 wt%), while the bottom product contains all heavier components (glycerol and glucose in case 1, succinic and lactic acid in case 2).

The described DWC was designed to minimize the energy requirements for the considered compositions of the fermentation broth. Nonetheless, different compositions of the feed stream to DWC might require additional tuning of operating parameters to obtain efficient separation. Thus, the proposed DWC design can be adapted to effectively separate high-purity PDO product from lighter and heavier by-products that may be formed in various fermentation processes.

Case study 1: PDO fermentation from glucose

In this case, the feed stream to DWC contains mainly PDO and water, with some glycerol and glucose. As water is the only component lighter than PDO, it will be obtained at the top of DWC_L with purity of 100 wt%. The top product from DWC_R is high-purity PDO (99.92 wt%), while the bottom product is mainly glycerol (98.57 wt%) with some glucose (0.94 wt%) and a small amount of remaining PDO (0.50 wt%). The top water stream is very pure (100 wt%) and may be used somewhere (e.g. in the fermentation).

Regarding the bottom product, two alternatives were considered: case 1a, in which the whole glycerol-glucose mixture was considered as a waste stream, would be the worst-case scenario, and case 1b, in which glycerol was recovered by an additional vacuum distillation step in column C2. Reduced pressure (condenser pressure of 0.030 bar) and pH control need to be applied to avoid polymerization of glycerol to polyglycerol, dehydration to acrolein or oxidation to glycerose [308]. The top product of column C2 is glycerol (99.50 wt%), which satisfies technical grade standards (min. 95.5 wt% [309]). The bottom product contains glucose (93.87 wt%) and some remaining glycerol (6.13 wt%). This stream was considered the waste stream in further analysis of case 1b.

Nonetheless, if there are potential uses of this stream, the performance of the overall process would be just slightly better as the flowrate of this stream is not significant.

Case study 2: PDO fermentation from glycerol

In this case, the desalted solution that is fed to column C1 contains by-products both lighter and heavier than PDO. Thus, the top product from DWC_L contains the remaining water, BDO and acetic acid (50.67, 45.68 and 3.65 wt%, respectively). As in case 1, the top product from DWC_R is a high-purity PDO product (99.98 wt%), while the bottom contains mainly succinic and lactic acids with a small amount of remaining PDO (84.08, 15.62 and 0.03 wt% of succinic acid, lactic acid and PDO, respectively).

As in case 1, two scenarios were analyzed: case 2a (the worst-case scenario) in which the bottom stream with heavier by-products (succinic and lactic acid) and the top stream with remaining water and lighter by-products (BDO and acetic acid) were considered as waste streams, and case 2b in which BDO and succinic acid were recovered as valuable by-products that are present in significant amounts (about 6 and 3 ktonne/y, respectively).

Due to the large boiling point difference between BDO and acetic acid, a simple vacuum distillation step is sufficient to obtain a high-purity BDO by-product (100 wt%) at the bottom of column C2. The top product from this column is a water-acetic acid mixture (about 93.27 wt% water and 6.71 wt% acetic acid) that needs to be sent to wastewater treatment. Due to a large temperature difference between the top and the bottom of this column (24 and 99 ˚C, respectively), MVR cannot be implemented to this column and low-pressure steam is needed for heating. Nonetheless, the required reboiler duty for this column is not large (less than 0.7 MW) due to the relatively easy separation. Furthermore, due to the large difference in boiling points (see Table 2-9), succinic acid may be separated from lactic acid in distillation column C3. Reduced pressure (condenser pressure of 0.020 bar) distillation is needed to maintain temperatures lower than the succinic acid decomposition temperature (about 235 ˚C [310]) and to minimize lactic acid oligomerization. Moreover, it should be noted that further testing is required to check the exact extent of the oligomerization reactions. Nonetheless, the bottom product from this column is succinic acid (99.98 wt%) that will crystallize after cooling. The top product is a very small process stream that mainly consists of lactic acid (98.10 wt%) and small amounts of PDO (1.90 wt%). This stream was considered a waste stream in further analysis due to lactic acid oligomerization. In case the remaining substrate is present in the bottom stream from column C1, an additional distillation step will be needed to separate succinic acid from the remaining glycerol. Lastly, it should be noted that the esterification reactions may

happen due to the presence of alcohol (PDO) and carboxylic acids (succinic and lactic acid). Nonetheless, the esterification reactions without an acid catalyst are very slow [311], while the structured packing in DWC offers the advantage of lower liquid holdup and shorter residence time compared to tray internals. Furthermore, PDO concentrations are very low at the bottom stages of DWC, where concentrations of acids are significant. Thus, the influence of the esterification reactions will likely be negligible, but additional testing might be needed prior to implementation on real-life industrial processes.

Techno-economic analysis

The determined economic indicators are summarized in Table 3-2 and Table 3-3, and presented in Figure 3-5 and Figure 3-6. The costs of the preconcentration and final purification steps are calculated following the NREL methodology (see more details in Appendix A). The approximate costs of the initial downstream processing steps (i.e. microfiltration, diafiltration, ultrafiltration and ion exchange) were estimated by adjusting the market prices from the available literature [302] to the assumed process capacity using the *six-tenths factor rule* [312] and installation factors [67]. The influence of payback period on the downstream processing costs is presented in Figure 3-7.

Table 3-2. Key economic indicators of the PDO recovery process in cases 1a and 1b: initial recovery steps (a), preconcentration and final purification steps (b) and total recovery process (c)

Economic indicators	**Case 1a**			**Case 1b**		
	(a)	(b)	(c)	(a)	(b)	(c)
CAPEX (k$)	2,908	11,006	13,914	2,908	11,592	14,500
OPEX (k$/y)	2,355	2,725	5,080	2,398	2,634	5,032
OPEX ($/kg$_{product}$)	0.103	0.119	0.221	0.095	0.104	0.198
TAC (k$/y)	2,646	3,826	6,472	2,689	3,793	6,482
TAC ($/kg$_{product}$)	0.115	0.167	0.282	0.106	0.150	0.256

Table 3-3. Key economic indicators of the PDO recovery process in cases 2a and 2b: initial recovery steps (a), preconcentration and final purification steps (b) and total recovery process (c)

Economic indicators	**Case 2a**			**Case 2b**		
	(a)	(b)	(c)	(a)	(b)	(c)
CAPEX (k$)	3,387	18,917	22,304	3,387	20,498	23,885
OPEX (k$/y)	2,181	4,386	6,567	2,106	4,743	6,848
OPEX ($/kg$_{product}$)	0.095	0.192	0.287	0.066	0.148	0.213
TAC (k$/y)	2,520	6,278	8,797	2,444	6,792	9,237
TAC ($/kg$_{product}$)	0.110	0.274	0.384	0.076	0.212	0.288

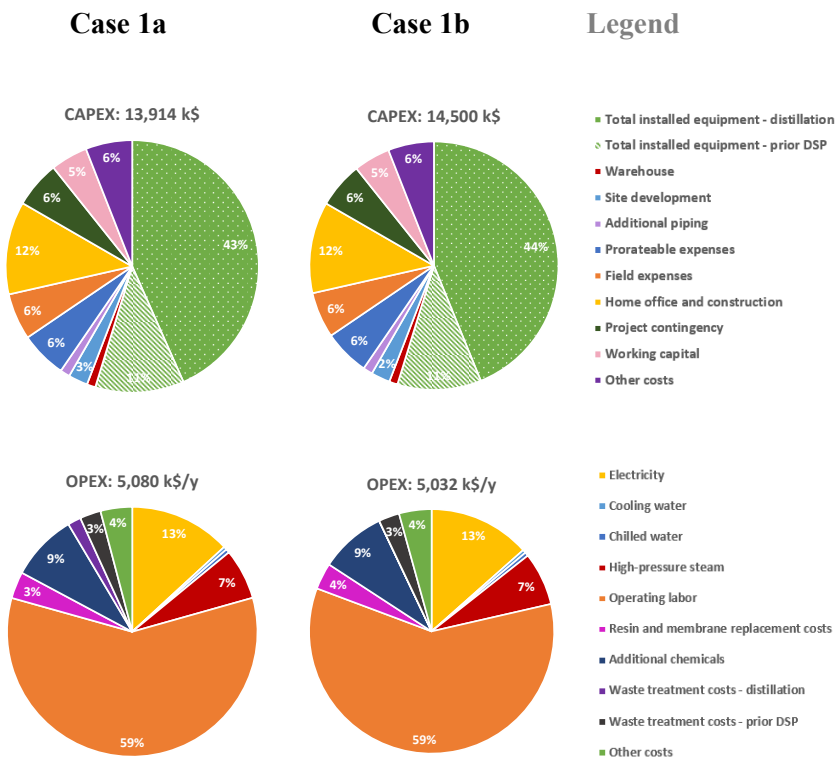


Figure 3-5. Comparison of economic indicators of the total recovery process in cases 1a and 1b

The total costs of installing all equipment units for the overall recovery process are 7,613, 7,938, 12,205 and 13,081 k$ in cases 1a, 1b, 2a and 2b. Thereby, the costs of equipment in the preconcentration and final purification parts of the recovery processes are the major contributors to the total equipment costs (about 79-86%). Among the equipment costs of the preconcentration and final purification, the biggest contribution is the cost of distillation columns (about 38-39%), compressors in heat pump systems (about 28-32%) and heat exchangers (about 26-27%), while costs for pumps and flash vessels are much smaller (about 3-6 and <1%). Among the equipment costs of the initial recovery steps, the biggest contribution is due to the cation and anion exchange modules (40-41 and 30%, respectively) and pumps (about 22-23%), while the costs of filtration modules are much lower (about 1, 3 and 3% for microfiltration, diafiltration and ultrafiltration modules). Overall, the reason for much lower equipment costs in case 1 is the lower feed flowrate due to the more concentrated feed stream. The calculated CAPEX for the total recovery process are 13,914 and 14,500 k$ for cases 1a and 1b, 22,304 and 23,885 k$ for cases 2a and 2b. Since the total equipment costs

make up the largest part of the total CAPEX (about 54-55% in all cases whereby equipment costs of the designed preconcentration and final purification steps, and the initial recovery steps are about 43-47% and 11-8% of CAPEX, respectively), the higher CAPEX in cases 2a and 2b are mainly due to the higher equipment cost.

The determined OPEX for the total recovery process are 5,080, 5,032, 6,567 and 6,848 k$/y in cases 1a, 1b, 2a and 2b, respectively. Expressed per kilogram of recovered product, the total OPEX are 0.221, 0.198, 0.287 and 0.213 $/kg$_{product}$ in cases 1a, 1b, 2a and 2b, respectively. Thereby, the contribution of the designed preconcentration and final purification parts is about 54, 52, 67 and 69% of the total OPEX. The largest contributor to OPEX in all cases is the cost of operating labor (59% of the total OPEX in cases 1a and 1b, 46 and 44% of the total OPEX in cases 2a and 2b). The higher contribution of labor costs in total OPEX in case 1 is mainly due to the lower value of OPEX, while the absolute value of labor costs is approximately the same in all cases. Similarly, the contribution of electricity and heating utilities costs in cases 1a and 1b (about 13 and 7% of the total OPEX, respectively) are lower compared to the contribution in cases 2a and 2b (about 19 and 12-14% of the total OPEX, respectively) due to the lower feed stream flowrate. Nonetheless, it should be noted that the costs of utilities are mainly due to the preconcentration and final purification steps. Furthermore, waste treatment costs (including wastewater treatment) are higher in cases 1a and 2a (about 5 and 4% of the total OPEX, respectively) than in cases 1b and 2b (about 3% of the total OPEX). The biggest contributor to the total waste treatment costs is the wastewater from diafiltration, ultrafiltration and ion exchange steps. Moreover, the waste treatment costs are lower in downstream processing after fermentation from glucose (cases 1a, 1b) due to fewer by-products in the fermentation broth. Significant contributors to the total OPEX are costs of the additional chemicals required to regenerate cation and anion exchange resins (about 8-9% of the total OPEX) and costs of membrane and resin replacements (about 3-4% of the total OPEX).

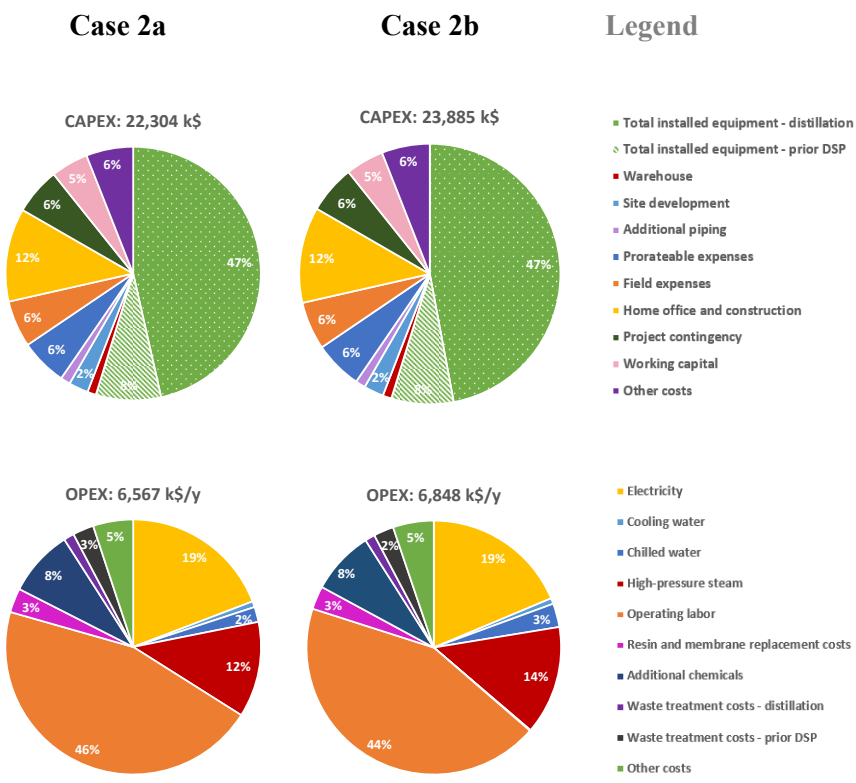


Figure 3-6. Comparison of economic indicators of the total recovery process in cases 2a and 2b

Thus, TAC that includes both CAPEX and OPEX with PBP of 10 years are 6,472, 6,482, 8,797 and 9,237 k$/y for the total recovery process in cases 1a, 1b, 2a and 2b, respectively. Expressed per kilogram of recovered product, TAC are 0.282 $/kg$_{product}$ for case 1a, 0.256 $/kg$_{product}$ for case 1b, 0.384 $/kg$_{product}$ for case 2a and 0.288 $/kg$_{product}$ for case 2b. Less expensive recovery in cases 1a and 1b as compared to cases 2a and 2b is due to the higher product concentration, smaller amounts of by-products in the feed stream and larger temperature differences between PDO and by-products. Furthermore, recovering the fermentation by-products from the broth (e.g. glycerol in case 1b, BDO and succinic acid in case 2b) can substantially reduce specific TAC (reduction of more than 9% in case 1b compared to case 1a, and reduction of about 25% in case 2b compared to case 2b) despite somewhat higher CAPEX due to the additional equipment units. This arises because more product is recovered, while less waste is produced. Consequently, TAC is lower due to the lower costs of waste management, while specific TAC is distributed to a higher amount of recovered products. Lastly, the contribution of the designed preconcentration and final purification steps to the total TAC are 59, 59, 71 and 74% in cases 1a, 1b, 2a and 2b. The largest contribution of these steps in cases 2a and 2b is due to more complex separations (more dilute fermentation broth, higher concentrations of by-products, lower temperature differences between PDO and by-products). Considering the significant contribution of the preconcentration and final purification costs to the total recovery costs, the proposed advanced process design might significantly improve the overall process viability. Furthermore, since the costs of biobased PDO production were estimated to 1.37-2.40 $/kg$_{PDO}$ for the fermentation of biomass [313] and 0.96-1.09 $/kg$_{PDO}$ for the fermentation of raw glycerol [314], with prevailing recovery costs, the results of this study present a major step forward in the development of competitive fermentative PDO production.

Moreover, the analysis of the PBP influence on TAC for the total PDO recovery process (see Figure 3-7) shows competitive process performance even for shorter PBP [313,315]. For example, for PBP of only one year, TAC are higher than 1.0 $/kg solely in case 2a. Thus, in the case of multiple fermentation by-products present in the broth, recovering those present in substantial quantities may enhance the economic performance of the overall process.

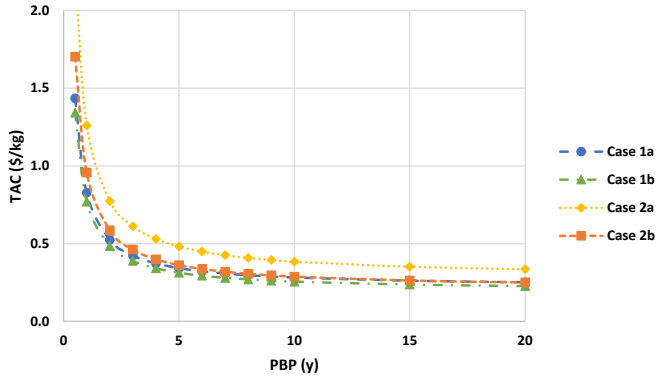


Figure 3-7. Influence of the payback period on TAC for the overall recovery process

Sustainability assessment

The calculated values of sustainability metrics are summarized in Table 3-4 and Table 3-5. The specific values of all sustainability metrics were obtained considering the total products flowrate (PDO and the recovered by-products).

Table 3-4. Key sustainability metrics of the PDO recovery process in cases 1a and 1b: initial recovery steps (a), preconcentration and final purification steps (b) and total recovery process (c)

Sustainability metrics	Case 1a			Case 1b		
	(a)	(b)	(c)	(a)	(b)	(c)
Thermal energy requirements ($kW_{th}h/kg_{product}$)	0.000	0.403	0.403	0.000	0.386	0.386
Electrical energy requirements ($kW_eh/kg_{product}$)	0.102	0.379	0.480	0.092	0.349	0.440
Primary energy requirements ($kW_{th}h/kg_{product}$)	0.254	1.350	1.604	0.230	1.258	1.487
Water consumption ($m^3_w/kg_{product}$)	0.000	0.138	0.138	0.000	0.129	0.129
Water loss ($m^3_w/kg_{product}$)	0.000	0.010	0.010	0.000	0.009	0.009
CO_2 emissions, grey electricity ($kg_{CO2}/kg_{product}$)	0.046	0.245	0.292	0.042	0.229	0.271
CO_2 emissions, green electricity ($kg_{CO2}/kg_{product}$)	0.000	0.073	0.073	0.000	0.070	0.070
Material intensity ($kg_{waste}/kg_{product}$)	0.640	0.106	0.746	0.579	0.001	0.580
Wastewater intensity ($kg_{waste}/kg_{product}$)	4.823	0.000	4.823	4.364	0.000	4.364
Pollutant emissions ($kg_{pollutant}/kg_{product}$)	0.000	0.000	0.000	0.000	0.000	0.000
Toxic emissions ($kg_{toxic\ material}/kg_{product}$)	0.000	0.000	0.000	0.000	0.000	0.000

Table 3-5. Key sustainability metrics of the PDO recovery process in cases 2a and 2b: initial recovery steps (a), preconcentration and final purification steps (b) and total recovery process (c)

Sustainability metrics	Case 2a			Case 2b		
	(a)	(b)	(c)	(a)	(b)	(c)
Thermal energy requirements ($kW_{th}h/kg_{product}$)	0.000	1.222	1.222	0.000	1.045	1.045
Electrical energy requirements ($kW_eh/kg_{product}$)	0.128	0.782	0.910	0.092	0.567	0.659
Primary energy requirements ($kW_{th}h/kg_{product}$)	0.321	3.175	3.496	0.229	2.462	2.691
Water consumption ($m^3_w/kg_{product}$)	0.000	0.348	0.348	0.000	0.278	0.278
Water loss ($m^3_w/kg_{product}$)	0.000	0.025	0.025	0.000	0.020	0.020
CO_2 emissions, grey electricity ($kg_{CO2}/kg_{product}$)	0.058	0.542	0.600	0.042	0.417	0.459
CO_2 emissions, green electricity ($kg_{CO2}/kg_{product}$)	0.000	0.185	0.185	0.000	0.159	0.159
Material intensity ($kg_{waste}/kg_{product}$)	0.852	0.446	1.299	0.608	0.032	0.640
Wastewater intensity ($kg_{waste}/kg_{product}$)	6.089	0.314	6.403	4.345	0.224	4.569
Pollutant emissions ($kg_{pollutant}/kg_{product}$)	0.000	0.000	0.000	0.000	0.000	0.000
Toxic emissions ($kg_{toxic\ material}/kg_{product}$)	0.000	0.000	0.000	0.000	0.000	0.000

- ***Energy intensity**:* Due to the required external heating in the distillation steps, the thermal energy requirements of the total recovery process are 0.403, 0.386, 1.222 and 1.045 $kW_{th}h/kg_{product}$ in cases 1a, 1b, 2a and 2b, respectively. Significantly more thermal energy is required in cases 2a and 2b due to the lower product concentration and more complex separation in DWC as compared to cases 1a and 1b. The electrical energy requirements for the total recovery process are 0.480, 0.440, 0.910 and 0.659 $kW_eh/kg_{product}$ in cases 1a, 1b 2a and 2b, respectively. Thereby, the contribution of the designed preconcentration and final purification steps to the total electrical energy requirements is 79-86%. Due to the more complex separation in the preconcentration column C1, a higher reflux ratio is needed in cases 2a and 2b. Consequently, a larger compressor duty in the MVR system applied to this column is required. As electricity to power this compressor is the biggest contributor to electrical energy usage, the electrical energy requirements are higher in cases 2a and 2b compared to cases 1a and 1b. Furthermore, the total primary energy requirements for the overall recovery process are 1.604, 1.487, 3.496 and 2.691 $kW_{th}h/kg_{product}$ in case 1a, case 1b, case 2a and case 2b, respectively, whereby the preconcentration and final purification

contribute to 84-91%. Thus, the more complex feed stream in cases 2a and 2b leads to more energy-intensive downstream processing. Nonetheless, the proposed recovery processes are highly energy-efficient compared to the reported literature data for biobased (non-renewable energy use of 10.3 kWh/kg_{PDO}) and petroleum-based PDO production (non-renewable energy use of 16.9 kWh/kg_{PDO}) [301].

- ***Water consumption**:* In the calculation of water consumption metrics, it was assumed that high-purity water streams separated in the preconcentration and final purification parts of the process may be reused in the initial recovery steps (e.g. water required for the diafiltration and ion exchange steps) to reduce the overall fresh water requirements. As a consequence of higher energy use in the distillation, more water is needed in cases 2a and 2b (0.348 and 0.278 $m^3_w/kg_{product}$, respectively) compared to cases 1a and 1b (0.138 and 0.129 $m^3_w/kg_{product}$). Accordingly, the amounts of lost water are 0.010, 0.009, 0.025 and 0.020 $m^3_w/kg_{product}$ for cases 1a, 1b, 2a and 2b, respectively.
- ***Greenhouse gas emissions**:* Due to higher energy requirements, CO_2 emissions are higher in cases 2a and 2b (0.600 and 0.459 $kg_{CO2}/kg_{product}$ if grey electricity is used, 0.185 and 0.159 $kg_{CO2}/kg_{product}$ if green electricity is used, respectively) compared to cases 1a and 1b (0.292 and 0.271 $kg_{CO2}/kg_{product}$ if grey electricity is used, 0.073 and 0.070 $kg_{CO2}/kg_{product}$ if green electricity is used). Given that CO_2 emissions of the total biobased and petroleum-based PDO production process were estimated to 2.5-5.9 kg_{CO2}/kg_{PDO} [313] and 7.0 kg_{CO2}/kg_{PDO} [301], the proposed recovery processes have much lower environmental impact.
- ***Material intensity**:* Considering only the designed preconcentration and final purification parts of the PDO recovery process, material intensity metric is the lowest in case 1b (0.001 $kg_{waste}/kg_{product}$) as the top product from DWC_L is high-purity water that is not a waste stream, while glycerol is recovered from the bottom of DWC_R. If the glycerol is not recovered, as in case 1a, the material intensity metric is significantly higher (0.106 $kg_{waste}/kg_{product}$). Contrarily, there is the largest amount of waste per kilogram product in case 2a (0.446 $kg_{waste}/kg_{product}$) as no fermentation by-products are recovered. If BDO and succinic acid are recovered as in case 2b, the material intensity metric is significantly lower (0.032 $kg_{waste}/kg_{product}$). However, the initial recovery steps (microfiltration, diafiltration, ultrafiltration and ion exchange) will result in much higher waste formation due to the removal of biomass, biopolymers, inorganics, etc. Thus, the estimated material intensity metrics for these steps are 0.640, 0.579, 0.852 and 0.608 $kg_{waste}/kg_{product}$in cases 1a, 1b, 2a and 2b. Considering the material intensity of the initial steps in the downstream process, recovery of by-products that are present in significant amounts can be suggested to minimize the impact of the overall process.

- ***Wastewater intensity**:* Due to the need to remove valuable products from the microfiltration retentate and regenerate anion and cation resins, significant amounts of wastewater are formed in the initial recovery steps. The values of wastewater intensity metrics in cases 1a/b, 2a/b are 4.823, 4.364, 6.403 and 4.569 $kg_{wastewater}/kg_{product}$.
- ***Pollutant and toxic materials**:* Since all waste streams are accounted for in the material and wastewater intensity metrics, while no pollutants and toxic materials are formed, the values of these metrics are zero in all cases.

3.1.5. Conclusion

The new downstream process proposed in this study was proven effective for 1,3-propanediol recovery after various fermentation processes: from glucose using *E. coli* (cases 1a and 1b) or from glycerol using *K. pneumoniae* (cases 2a and 2b). Following the initial separation of cells, biopolymers and inorganics by conventional filtration and ion-exchange steps, a vacuum distillation step can be implemented to remove most of the present water. This step may be enhanced with a mechanical vapor recompression heat pump system to significantly decrease the overall energy usage. The final product purification can be performed in an integrated dividing-wall column that can efficiently separate high-purity 1,3-propanediol (>99.9 wt%) from lighter and heavier by-products. Recovering and valorizing by-products that are present in significant amounts in the fermentation broth is suggested to substantially reduce the total recovery costs (from 0.282 to 0.256 $/kg$_{product}$ in cases 1a and 1b, or from 0.384 to 0.288 $/kg in cases 2a and 2b) and energy requirements (from 1.604 to 1.487 $kW_{th}h/kg_{product}$ in cases 1a and 1b, or from 3.496 to 2.691 $kW_{th}h/kg_{product}$ in cases 2a and 2b). Considering that water removal and final purification significantly contribute to the total downstream processing costs (59-74%), the results of this original research advance the large-scale 1,3-propanediol production (about 23 ktonne/y of 1,3-propanediol and 2-9 ktonne/y of by-products) by proposing a highly-integrated recovery process that can adapt to different compositions of fermentation broth. Depending on the specific concentrations of light and heavy impurities after the ion exchange step, the proposed process design can be easily adjusted to efficiently recover high-purity PDO product. Lastly, by comparing the recovery after two different fermentation processes this study emphasizes the importance of the broth composition on the downstream processing performance. Less diluted fermentation broth with fewer by-products in cases 1a and 1b results in more cost-effective and energy-efficient downstream processing. In that respect, the upstream fermentation and downstream recovery parts should be developed simultaneously to ensure the competitiveness and viability of the overall bioprocess.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Eco-efficient downstream processing of 1,3-propanediol applicable to various fermentation processes, Process Biochemistry. 143 (2024) 210-224. https://doi.org/10.1016/j.procbio.2024.04.040. This file contains details about the initial steps in the downstream processing of the fermentation broth: microfiltration, diafiltration, ultrafiltration and ion exchange. Furthermore, detailed results of economic analysis are presented. The last section contains details about the validation of the thermodynamic property method.

3.2. Recovery of 2,3-, 1,4- and 1,3-butanediols

The butanediols (BDOs), 2,3-, 1,4- and 1,3-butanediol, are platform chemicals that are mainly produced from fossil hydrocarbons but may be obtained through fermentation. However, low product concentration, by-product formation and high boiling temperatures of BDOs hinder downstream processing and increase overall fermentation costs. This study increases the competitiveness of industrial biotechnology by designing a large-scale process (broth processing capacity of 160 ktonne/y) for the final purification of BDOs after fermentation (recovery >99%). It includes an initial preconcentration step in a vacuum distillation column to remove most water and light impurities. The initial removal of most water and implementation of a heat pump system allowed significant energy reduction. At the heart of the process is an integrated dividing-wall column that can efficiently purify BDO from the remaining light and heavy impurities. Moreover, a single process design was proven effective in purifying different BDOs to >99.4 wt%. This was cost-effective (total purification costs of 0.208-0.243 $/kg$_{BDO}$) and energy-efficient (with primary energy requirements of 1.854-176 kW$_{th}$h/kg$_{BDO}$). The proposed purification sequence can be used for each BDO type, which offers flexibility in developing sustainable bioprocesses for BDO production.

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3.2.1. Introduction

Among the perspective bioproducts that may be obtained through the fermentation process, butanediols (BDOs) are important platform chemicals with a wide variety of applications [273].

2,3-Butanediol (2,3-BDO) can be used as an intermediate for producing fuels, jet, diesel, high-octane gasoline, synthetic rubbers [316], solvents (e.g. methylethylketone (MEK) [317,318]), drugs, cosmetics, lotions, softening agents, plasticizers, printing inks, fertilizers, etc. [319], with the global market estimated to be 270 million $ in 2022 and an expected growth rate of 3.5% until 2031 [320]. Fermentative production of 2,3-BDO has been recently gaining attention due to higher productivity and lower toxicity compared to commonly produced monohydric alcohols [321]. LanzaTech, National Renewable Energy Laboratory (NREL) and BioPrincipia are some of the leaders in developing the production of 2,3-BDO from renewable sources [266–268].

1,4-Butanediol (1,4-BDO) is an important platform chemical commonly used as a solvent and for producing polyesters, polyurethanes, plastic fibers and pharmaceuticals [322]. Its global market was estimated to be about 6.5 billion $ in 2022, with an expected growth rate of 9.4% until 2032 [323]. Conventionally, 1,4-BDO is produced through the Reppe process [324]. Additionally, several different routes for 1,4-BDO production were developed: from 1,3-butadiene (Mitsubishi chemicals and Toyo Soda), propylene oxide (Lyondell) and butane (Davy Process Technology and BP). However, the Reppe process is dominant due to high yields and few steps [322]. In addition to the fossil fuel-based processes, research attempts were made to produce 1,4-BDO by genetically engineered microorganisms [325]. Genomatica and Novamont are leading the commercialization of the sustainable 1,4-BDO production [269,270].

1,3-Butanediol (1,3-BDO) is also a commodity chemical commonly used as a solvent for food flavoring agents, as a hypoglycemic agent, in the production of polyester and polyurethane resins, biologically active compounds and liquid crystals, synthetic rubbers, resins and latex [271]. The global 1,3-BDO market was estimated to be 188.2 million $ in 2023, with a projected growth rate of 3.7% [326]. Traditionally, 1,3-BDO is produced from acetylene or ethylene. Alternatively, 1,3-BDO can be obtained by microorganisms as patented by Genomatica [271].

1,2-Butanediol (1,2-BDO) is used to synthesize polyester polyols, plasticizers, cosmetics and pharmaceuticals [327]. Currently, it is dominantly produced from fossil-based n-butene via epoxidation and hydration reactions [328]. Alternatively, biomass may be used as a renewable feedstock for producing 1,2-BDO. However, the reported yields of converting biomass-derived substrates to 1,2-BDO have been low, while reaction pathways and catalytic mechanisms remain unclear [328]. Furthermore, the development of bioprocesses for direct production of 1,2-BDO has become a recent topic of interest. However, the obtained product concentrations are still relatively low (e.g. 0.15 g/L was obtained using genetically engineered *Escherichia coli* [327]) and additional improvements are needed to allow scaling up of this technology.

A significant research effort has been put into developing genetically engineered microorganisms that can produce different BDOs from renewable sources. Thus, fermentation of renewable carbon sources has an important potential to become a sustainable alternative to fossil hydrocarbon-based processes for the production of BDOs [329]. Yet, recovery of different BDOs after the fermentation has not been as promptly addressed as the fermentation process. Therefore, the main goal of this study is to enhance the development of sustainable and competitive BDOs' fermentation processes by advancing downstream processing. In that respect, we propose a novel large-scale (broth processing capacity of about 160 ktonne/y) downstream processing design that may be easily adapted for the final purification of 2,3-, 1,4- or 1,3-BDO after fermentation. The recovery of 1,2-BDO has not been included in the analysis due to the very low fermentation titers achieved so far. Since initial downstream processing (filtration and ion exchange required to remove biomass, biopolymers and inorganics) steps are conventionally used in industrial fermentation, they were not the focus of this work. Instead, our work focuses on the preconcentration and final purification parts of the recovery process.

3.2.2. Problem statement

Three fermentation processes were considered: case 2-3 (purification of 2,3-BDO), case 1-4 (purification of 1,4-BDO) and case 1-3 (purification of 1,3-BDO). Accordingly, the compositions of the fermentations broths in these cases were taken from the published literature [321,322,330] and presented in Table 3-6.

Table 3-6. Composition of the feed stream to downstream processing after different fermentation processes

Case 2-3			**Case 1-4**		
Component	Mass fraction	Tb (˚C)	Component	Mass fraction	Tb (˚C)
Ethanol	0.0105	78.3	Ethanol	0.0021	78.3
Water	0.8750	100.0	Water	0.9279	100.0
Formic acid	0.0003	100.6	Gbl	4e-5	204.0
Acetic acid	0.0089	117.9	1,4-BDO	0.0697	228.0
3-HB	0.0093	143.0	HTHF	0.0002	246.8
2,3-BDO	0.0930	180.7	Pyr	3e-6	251.2
Lactic acid	0.0007	216.8	Glucose	2e-5	/*
Succinic acid	0.0020	317.8			

Case 1-3		
Component	Mass fraction	Tb (˚C)
Ethanol	0.0052	78.3
Water	0.9109	100.0
Acetic acid	0.0052	118.0
4-HB	0.0052	143.0
1,3-BDO	0.0725	207.5
Glucose	0.0010	/*

*does not exist as a stable liquid that boils

In all cases, the concentration of BDO is about 7- 9 wt% while water makes the most of broth (87-91 wt%). Additionally, both light (ethanol, formic acid, acetic acid, 3-hydroxy-2-butanone (3-HB), 4-hydroxy-2-butanone (4-HB) and gamma butyrolactone (Gbl)) and heavy by-products (lactic acid, succinic acid, 2-(4-hydroxybutoxy)-THF (HTHF), 2-pyrrolidone (Pyr) and glucose) are present in this stream. To allow a fair comparison with the published literature and between different cases in this study, a feed flowrate of 20,000 kg/h was assumed in all cases, and it is assumed that prior steps for removing cells, biopolymers, and salts do not change this composition. Due to the mentioned similarities in the composition of the broth after the fermentative production of 2,3, 1,4- and 1,3-BDO, and similar thermodynamic interactions, it may be expected that one adaptable process design will be able to purify all three BDOs. This approach would enhance flexibility of the bioproduction of BDOs.

Several challenges in the fermentation affect the downstream processing (e.g., low titers, presence of microorganisms, formation of by-products). Thus, the expenses of the separation process significantly contribute to the total production cost [331].

3.2.3. Method of process design and simulation

The existing studies on the recovery of BDOs after fermentation mainly focus on 2,3-BDO, while less work has been reported on the recovery of other BDOs. In that respect, various techniques have been proposed for separating high-boiling product from the fermentation broth. Solvent extraction has been limited to a small scale due to relatively low recovery and large required amounts of solvent. Similarly, salting-out extraction requires large amounts of salts and solvents, the recovery of which is energy-intensive. Salting-out (e.g. with K_2CO_3 [286,287]) requires complex pretreatment steps and significant amounts of salting-out agents [331]. Contrarily, sugaring-out extraction offers the possibility of reusing sugaring-out agents as substrates for microbes in the fermentation. However this method has resulted in lower product recoveries relative to salting-out extraction [284]. Additionally, the potential toxicity of the solvent may pose a constraint when using extraction, salting-out extraction or sugaring-out extraction for product recovery. Reactive extraction with aldehydes and acidic catalysts [280] has disadvantage of using mineral acids which generate a lot of waste, may cause corrosion issues and are expensive [284]. Acidic anion-exchange resins have been proposed as an alternative to soluble acidic catalysts but proteins and salts from the broth decrease catalytic activity. Pervaporation has scaling-up limitations due to membrane fouling, equipment costs and process duration. Yet, all of these techniques require additional steps to obtain high-purity BDO product. Alternatively, as none of the BDOs form azeotropes with water and differences in boiling points are significant, distillation may be used for both the preconcentration and final purification. Distillation is a mature separation technology that can be easily operated on a large scale. Nonetheless, distillation implies evaporating large amounts of water which may lead to an energy-intensive process. Several distillation-based process configurations have been proposed for the final purification of BDOs (mainly 2,3-BDO) [321,332,333]. The total energy requirements for recovering 90% of 2,3-BDO (product purity of 99.0 wt%) from fermentation broth (9.3 wt% 2,3-BDO) using these techniques are in the range of 3.2-8.6 $kW_{th}h/kg_{BDO}$. Extraction-assisted distillation processes using isobutanol, 1-butanol [334] and oleyl alcohol [335] have been also studied. When these purification processes are used, about 3.1 – 6.5 $kW_{th}h/kg_{BDO}$ is needed to recover 90% of 2,3-BDO from broth (9.3 wt% 2,3-BDO). Finally, a dividing-wall column (DWC) configuration was explored for recovering 2,3-BDO after fermentation. The proposed DWC design has its wall placed in the middle of the column and

recovers the BDO product as a side stream. The top and bottom products from the DWC contain water with all light impurities and heavy impurities, respectively. A vapor recompression system has been proposed in which the top vapor from the DWC is compressed and used for partial evaporation of the feed stream to reduce the duty of the DWC's reboiler [336]. In total, ~6.2 $kW_{th}h/kg_{BDO}$ is needed to recover 90% of 2,3-BDO (product purity of 99 wt%) from the feed stream (9.3 wt%).

The novelty of this original study is twofold. Firstly, research on the downstream processing after fermentation is expanded on the recovery of other BDOs besides 2,3-BDO. Additionally, the proposed advanced purification process improves the cost-effectiveness and energy efficiency of the BDOs' recovery. Process intensification principles were implemented as these were proven to significantly improve environmental impact [337]. Unlike the previously proposed recovery processes, we consider separating most water and light impurities before final purification, using a heat pump-assisted distillation column. After this step, DWC may be used to purify BDO from the remaining light and heavy impurities. This process configuration might significantly reduce the equipment size and the thermal energy requirements of DWC because most of the water is separated in the first step. However, the preconcentration step is very energy intensive, and the implementation of the heat pump system may be crucial for energy efficiency.

Rigorous simulations for all process operations were performed in Aspen Plus. The complex interactions between different components in the broth were described using the NRTL (case 1-4) or NRTL-HOC (cases 2-3 and 1-3) thermodynamic property model. This model (Non-Random Two Liquid) uses binary interaction parameters to describe vapor-liquid (VLE) and liquid-liquid equilibrium (LLE) of highly non-ideal mixtures. HOC extension (Hayden-O'Connell) was used in cases 2-3 and 1-3 to describe complex interactions of polar components (e.g. carboxylic acids) in the vapor phase [97].

3.2.4. Results and discussion

This section provides key information on process design and simulation, as well as techno-economic and sustainability analyses.

Process design

The flowsheets of these processes are presented in Figure 3-8, Figure 3-9 and Figure 3-10.

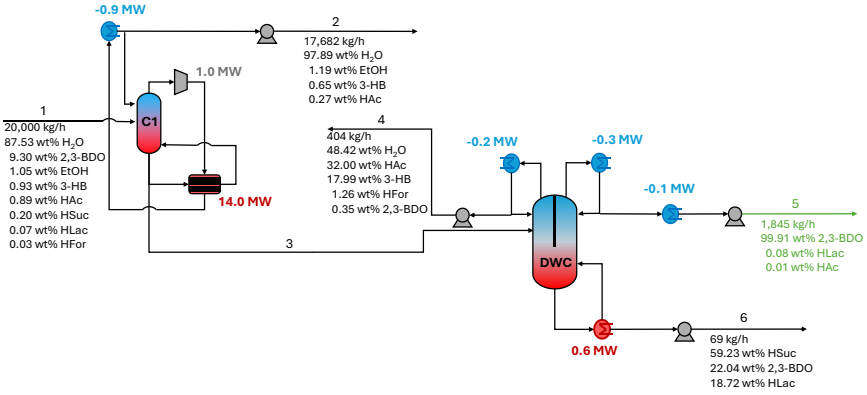


Figure 3-8. Downstream process for the final purification of 2,3-BDO after fermentation (case 2-3), abbreviations: H_2O – water, 2,3-BDO – 2,3-butanediol, EtOH – ethanol, HFor – formic acid, HAc – acetic acid, HLac – lactic acid, HSuc – succinic acid and 3-HB – 3-hydroxy-2-butanone

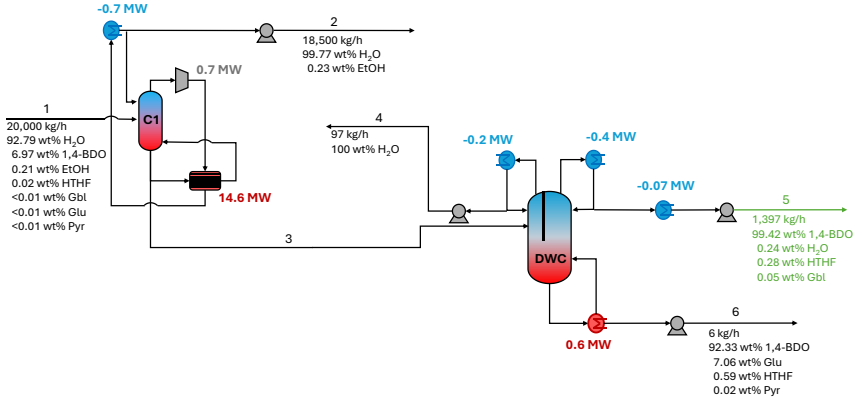


Figure 3-9. Downstream process for the final purification of 1,4-BDO after fermentation (case 1-4), abbreviations: H_2O – water, 1,4-BDO – 1,4-butanediol, EtOH – ethanol, Gbl – gamma butyrolactate, HTHF – 2-(4-hydroxybutoxy)-THF, Pyr – 2-pyrrolidone and Glu – glucose

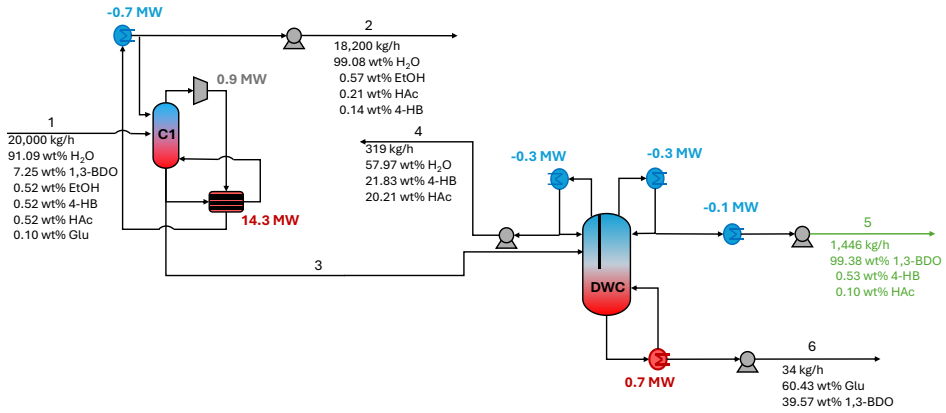


Figure 3-10. Downstream process for the final purification of 1,3-BDO after fermentation (case 1-3), abbreviations: H_2O – water, 1,3-BDO – 1,3-butanediol, EtOH – ethanol, HAc – acetic acid, 4-HB – 4-hydroxy-2-butanone and Glu – glucose

Initial water removal

Due to the high concentration of water, presence of many by-products and microorganisms, several steps are required in the downstream processing. After the initial filtration and ion exchange steps (not included in this study), the fermentation broth is still very dilute. Thus, a preconcentration step can be implemented to remove most of the water with some light by-products before the final purification. This step may be performed in distillation column C1 (see Figure 3-8, Figure 3-9 and Figure 3-10), whereby most of the water with light by-products is separated as the top product while BDO with heavy by-products and the remaining light components is obtained at the bottom. Reduced pressure operation in this column can facilitate separation, decrease energy requirements and avoid high temperatures that may lead to degradation of components. The operating pressure of 0.130 bar (top pressure) was chosen to minimize reboiler duty while allowing the usage of inexpensive cooling utilities (e.g. cooling water) in the condenser. The structured packing type Mellapak 250 with a pressure drop of 0.225 mbar per theoretical stage was defined for internals due to the reduced pressure operation [110].

Practically, all components lighter than BDO can be separated as the top product from column C1. However, temperature difference between the top and the bottom of the distillation column would be too high to use heat pumps because the bottom product would become concentrated with high boiling components. Due to the high-water content of the feed stream, the preconcentration step is very energy-intensive (reboiler duty of over 12 MW). Thus, energy-saving opportunities in this step are crucial for the energy efficiency of the complete purification process. In that respect, the proper choice of operating parameters

should allow implementation of the heat pump system that would significantly reduce energy requirements for the complete downstream processing. More precisely, not separating all light components in the distillate of column C1 decreases the temperature difference between the top and the bottom of this column allowing the implementation of mechanical vapor recompression (MVR). This heat pump system involves compressing the top vapor from the distillation column and using it instead of external heating utility in the reboiler. Consequently, electrical energy for powering the compressor replaces much higher thermal energy [113]. If the temperature difference between the top and bottom of the distillation column is too large, hot compressed vapor cannot provide sufficient heat to evaporate the bottom liquid. The measure of obtained energy savings with the heat pump systems may be expressed through coefficient of performance (COP). COP is equal to the ratio between exchanged thermal energy (between compressed top vapor and bottom liquid) and the required electrical energy to power the compressor [113]. COP values higher than 2.5, which is a conservative value of the electrical-to-thermal conversion factor [156], prove the energy efficiency of the installed heat pump system. COP values of the installed MVR systems are >14. Thus, the installed heat pump systems resulted in significant energy savings while allowing complete (green)electrification of the preconcentration step.

Finally, the top product from column C1 contains most of the water with some light impurities (case 2-3: 98.0 wt% water, 1.2 wt% ethanol, 0.6 wt% 3-HB and 0.3 wt% acetic acid; case 1-4: 99.8 wt% water and 0.2 wt% ethanol; case 1-3: 99.1 wt% water, 0.6 wt% ethanol, 0.2 wt% acetic acid and 0.2 wt% 3-HB). Due to their small amounts, valorization of by-products from this stream was not considered. Instead, this stream was sent to the wastewater treatment, the costs of which were included in further economic and sustainability analysis. If the small amounts of by-products do not interfere, this stream may be used upstream to reduce fresh water demand.

Final purification in a dividing-wall column

After the preconcentration step, a final purification is required to obtain a high-purity BDO product. Firstly, the remaining water and light impurities may be removed as the top product of the next distillation column. The bottom product from this column would contain BDO and heavy impurities. To obtain the final product, an additional distillation step is required. The top product from this column would be purified BDO, while all heavy impurities would be separated as the bottom product. Thus, a sequence of at least two distillation columns is required to separate BDO from light and heavy impurities. Alternatively, a dividing-wall column with a divided overhead section and common bottom section (DWC) may be used for the final purification (Figure 3-11). This is a

highly integrated system that merges two distillation columns into one shell and reduces number of heat exchangers that are required (one reboiler and two condensers). As the DWC unit is not available in Aspen Plus, it was simulated as a thermodynamically equivalent sequence of two distillation columns (Figure 3-11). Left and right parts of DWC are presented as DWC_L and DWC_R, respectively. The number of stages, location of the feed stage, reflux ratio, distillate-to-feed ratio and vapor split were varied to allow high recovery of high-purity BDO product while minimizing energy requirements. DWC has 20 stages in total, whereby the first and the last stages are the condenser and reboiler by the convention in Aspen Plus. The wall is placed in the top 14 stages (13 excluding the condenser). Due to the large temperature difference between the two top products (BDO and light impurities), thermal insulation will be needed to ensure energy efficiency of DWC. The bottom liquid from DWC_L is sent to DWC_R, while the part of the rising vapor from DWC_R is directed to DWC_L to ensure sufficient vapor flow. Due to the similarities in the fermentation broth composition, a similar vapor split is required for recovering high-purity BDO products in all cases (about 23-42% of the rising vapor from DWC_R is sent to DWC_L). Likewise, a similar ratio of DWC_L and DWC_R's cross-section areas (position of the wall) is needed (DWC_L and DWC_R's surface areas are 24-34 and 66-76% of the total DWC's surface area). Consequently, the operation of the same DWC unit may be easily adapted to purify different BDOs [338]. The DWC operates at reduced pressure (top pressure of 0.1 bar) to avoid high temperatures that may lead to decomposition while allowing usage of less expensive heating and cooling utilities (medium-pressure steam in reboiler and cooling water in condensers). Due to the required vacuum, structured packing type Mellapak 250 with a pressure drop of 0.225 mbar per theoretical stage was chosen for the DWC's internals [110].

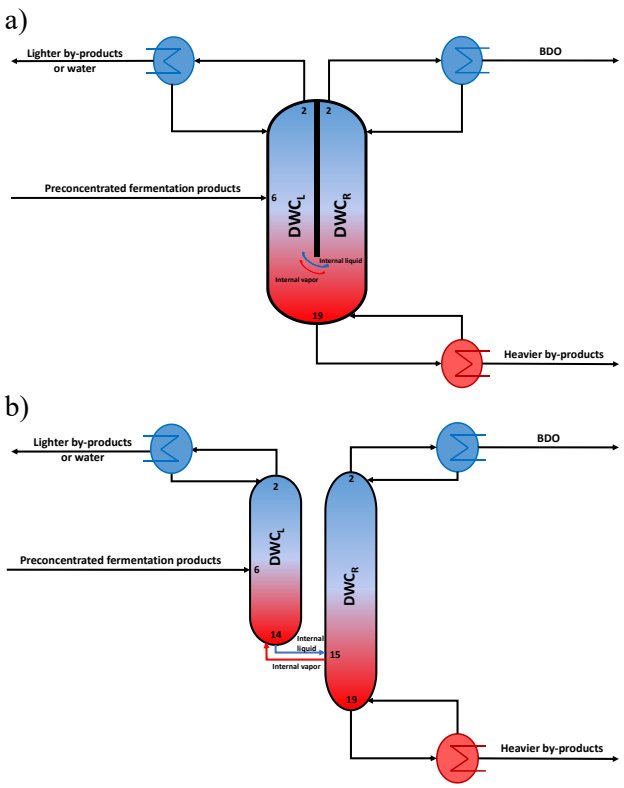


Figure 3-11. a) DWC design and b) the equivalent sequence of distillation columns – the numbers in the column indicate the column tray number

Finally, high-purity BDO product (>99.4 wt%) is obtained as the top product from DWC_R in all cases. Due to the relatively small amounts, none of the by-products was purified. The top product from DWC_L contains the remaining light impurities (water, acetic acid, formic acid, 4-HB, 3-HB and GBL). As for the top product of column C1, it was assumed that this stream would be sent to wastewater treatment. The bottom product from DWC_R contains fermentation by-products heavier than BDO (succinic acid, lactic acid, HTHF, 2-pyrrolidone and glucose). It was assumed that these streams could be burnt for energy and the appropriate gate fee was included in the economic analysis.

Techno-economic analysis

The results of the performed economic analysis are summarized in Table 3-7 and presented in Figure 3-12. The influence of the payback period on the downstream processing costs is presented in Figure 3-13.

Table 3-7. Key economic indicators of the final purification of BDOs

Economic indicators	**Case 2-3**	**Case 1-4**	**Case 1-3**
CAPEX (k$)	9,402	8,419	9,111
OPEX (k$/y)	2,340	1,471	1,903
OPEX ($/kg$_{BDO}$)	0.159	0.132	0.164
TAC (k$/y)	3,280	2,313	2,814
TAC ($/kg$_{BDO}$)	0.222	0.208	0.243

The installed equipment cost is 5,141, 4,612 and 4,984 k$ in cases 2-3, 1-4 and 1-3, respectively. In all cases, the largest contributor to the total equipment cost is the cost of heat exchangers (about 39-42%) and compressors (about 30-36%), followed by the cost of distillation columns (about 21-23%). In comparison, the cost of pumps is significantly lower (about 4-5% of the total equipment costs). Slightly lower equipment costs when recovering 1,4-BDO (case 1-4) are mainly due to the marginally lower cost of distillation columns and compressor in the MVR system. Since installed equipment cost makes up the largest part of CAPEX (about 55%), CAPEX are slightly lower in case 1-4 (8,419 k$) compared to cases 2-3 (9,402 k$) and 1-3 (9,111 k$).

Calculated OPEX for the final purification of BDO are 2,340, 1,471 and 1,903 k$/y in cases 2-3, 1-4 and 1-3, respectively. Expressed per kilogram of BDO product, the total OPEX are 0.159, 0.132 and 0.164 $/kg$_{BDO}$. The largest contributors to OPEX are the labor costs (30-48%), the cost of wastewater treatment and handling heavy impurities (5-33%) and electricity cost (20-23%). The costs of medium-pressure steam, cooling water and other operating costs are much lower (about 10-15%, <1% and 6-8%). Lower OPEX in case 1-4 is mainly because of lower wastewater treatment (due lower amounts of light impurities) and electricity expenses (due to lower required compressor power in the MVR system).

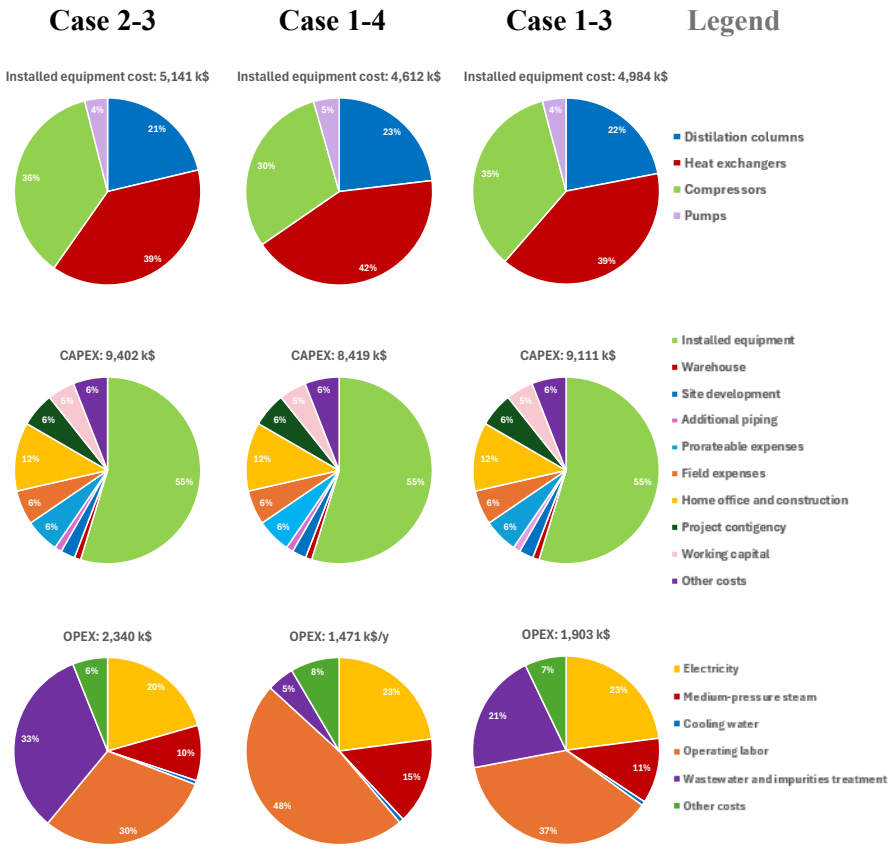


Figure 3-12. Comparison of economic indicators of the final BDO purification in cases 2-3, 1-4 and 1-3

Finally, TAC, which include both CAPEX and OPEX with a PBP of 10 years, are 3,280, 2,313 and 2,814 k$/y, or 0.222, 0.208 and 0.243 $/kg$_{BDO}$ in cases 2-3, 1-4 and 1-3, respectively. Since CAPEX and OPEX are the lowest when recovering 1,4-BDO (case 1-4), absolute TAC are also the lowest in this case. Nonetheless, TAC for the final purification of BDO in all cases is lower than 0.3 $/kg$_{BDO}$ with a PBP of 10 years. However, TAC do not increase drastically even with shorter PBP (see Figure 3-13). For example, with a PBP of three years or only one year, TAC are 0.371-0.430 and 0.796-0.958 $/kg$_{BDO}$. The net unit production cost of 2,3-BDO from sugarcane bagasse was determined to be 1.13-2.28 $/kg, with the minimum selling price of 1.86- 3.99 $/kg [339]. Moreover, the minimum selling price of 2,3-BDO produced from sucrose, molasses or glycerol was estimated to be about 4-5.2 and 3.7-5.7 $/kg$_{BDO}$ for production capacities of 10 and 20 ktonne/y, respectively [280]. Considering the significant contribution of downstream processing to total production costs [331], the proposed

cost-effective and adaptable process for the final purification may represent a major advancement toward competitive fermentative production of BDOs.

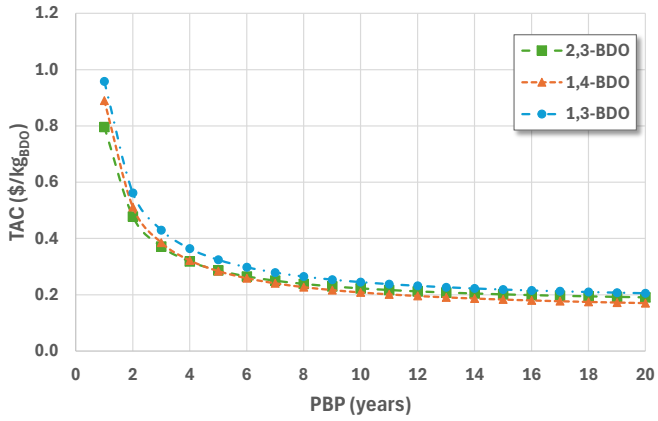


Figure 3-13. Influence of the payback period (PBP) on the specific total annual costs (TAC) for purification

Sustainability assessment

The determined key sustainability metrics are summarized in Table 3-8.

Table 3-8. Key sustainability metrics of the final purification of BDOs

Sustainability metrics	**Case 2-3**	**Case 1-4**	**Case 1-3**
Thermal energy requirements ($kW_{th}h/kg_{BDO}$)	0.506	0.662	0.615
Electrical energy requirements (kW_eh/kg_{BDO})	0.539	0.502	0.624
Primary energy requirements ($kW_{th}h/kg_{BDO}$)	1.854	1.917	2.176
Water consumption (m^3_w/kg_{BDO})	0.145	0.145	0.161
Water loss (m^3_w/kg_{BDO})	0.010	0.011	0.012
CO_2 emissions, grey electricity (kg_{CO2}/kg_{BDO})	0.319	0.324	0.373
CO_2 emissions, green electricity (kg_{CO2}/kg_{BDO})	0.073	0.096	0.089
Wastewater intensity ($m^3_{wastewater}/kg_{BDO}$)	0.010	0.014	0.013
Material intensity (kg_{waste}/kg_{BDO})	0.037	0.004	0.024
Pollutant emissions ($kg_{pollutant}/kg_{BDO}$)	0	0	0
Toxic emissions ($kg_{toxic\ materal}/kg_{BDO}$)	0	0	0

- ***Energy intensity***: The thermal energy requirements are 0.506, 0.662 and 0.615 $kW_{th}h/kg_{BDO}$ in cases 2-3, 1-4 and 1-3, respectively. As DWC's reboiler duty is similar in all cases (~0.9 MW_{th}), the lowest thermal energy requirements in case 2-3 are due to the largest product flowrate. The electrical energy requirements are 0.539, 0.502 and 0.624 kW_eh/kg_{BDO} in cases 2-3, 1-4 and 1-3. The largest electricity demand in case 1-3 is for powering the compressor in the MVR system applied to column C1. Thus, the total primary energy requirements for the final purification of BDO are 1.854 $kW_{th}h/kg_{BDO}$ in case 2-3, 1.917 $kW_{th}h/kg_{BDO}$ in case 1-4 and 2.176 $kW_{th}h/kg_{BDO}$ in case 1-3. To the best of our knowledge, the published processes for the recovery of BDO after fermentation have energy requirements ranging from approximately 3.1 to 8.6 $kW_{th}h/kg_{BDO}$ [321,332-335], with the process using DWC requiring approximately about 6.2 $kW_{th}h$ to recover 1 kg of BDO [336]. Thus, our process allows a more energy-efficient purification of BDO after fermentation.
- ***Greenhouse gas emissions***: Being related to energy usage, CO_2 emissions follow the same trend as energy requirements: 0.319, 0.324 and 0.373 kg_{CO2}/kg_{BDO} if grey electricity is used, or 0.073, 0.096 and 0.089 kg_{CO2}/kg_{BDO} if green electricity is used. Considering that the total climate effect of fossil-based and bio-based 2,3-BDO production was estimated to be 7.36 and 4.03 kg CO2 eq [340], the proposed purification process can reduce the total emissions.
- ***Water consumption***: By decreasing thermal energy requirements with installing the heat pump system, water consumption (0.145-0.161 m^3_{water}/kg_{BDO}) and water loss (0.010-0.012 m^3_{water}/kg_{BDO}) are significantly reduced.
- ***Material intensity****:* Since the top streams from column C1 and DWC_L were accounted for in the wastewater treatment metrics, only the bottom product of DWC was considered in the calculation of the material intensity. Thus, the obtained values are 0.037, 0.004 and 0.024 kg_{waste}/kg_{BDO}. Significantly lower values in case 1-4 compared to cases 2-3 and 1-3 are due to the less heavy by-products in the fermentation broth.
- ***Wastewater intensity***: The top products from column C1 and DWC_L would be sent to the wastewater treatment. Since the fermentation broth is very dilute, large water flowrates need to be treated. Thus, the values of wastewater intensity metrics are 0.010, 0.014 and 0.013 $m^3_{wastewater}/kg_{BDO}$ in cases 2-3, 1-4 and 1-3, respectively.
- ***Pollutant and toxic materials***: Since pollutants and toxic materials are not formed, values of these metrics are equal to zero in all cases.

3.2.5. Conclusion

The proposed downstream processing design enables eco-efficient large-scale (broth processing capacity of 160 ktonne/y) purification of BDOs from a dilute fermentation broth (initial BDO concentration ranging from 6.97 to 9.30 wt%). Due to similarities in thermodynamic properties and broth composition when producing 2,3-, 1,4-, and 1,3-BDO, a single process configuration was proven to effectively purify different BDOs after fermentation, offering additional flexibility in developing competitive bioprocesses for BDO production. To significantly reduce the overall energy requirements, a preconcentration step in a heat pump-assisted vacuum distillation column may be implemented before final purification. Removing most of the water and light impurities in this step significantly decreases reboiler duty and equipment size in the final purification. A proper choice of operating parameters allows implementation of a mechanical vapor recompression heat pump system to the preconcentration column, drastically reducing overall energy requirements and minimizing dependence on external steam for heating. The final purification of BDO product from the remaining light and heavy impurities may be effectively performed in an integrated dividing-wall column. Finally, this downstream processing configuration was proven to cost-effectively (total purification costs of 0.208-0.243 $\$/kg_{BDO}$) and energy-efficiently (total energy requirement of 1.854-2.176 $kw_{th}h/kg_{BDO}$) recover over 99% of BDO as a high-purity product (>99.4 wt%).

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Adaptable downstream processing design for recovery of butanediols after fermentation, Chemcial Engineering Research and Design. 213 (2025) 210-230. https://doi.org/10.1016/j.cherd.2024.12.011. This file contains information about the thermodynamic property model, design parameters of distillation columns, hydraulic profiles of distillation columns, temperature and liquid composition profiles of DWC and detailed calculations of equipment and labor costs.

3.3. Recovery of high-boiling products from fermentation broth: Aliphatic diols

Fermentation can be used to obtain a wide variety of valuable high-boiling components. Among these components, microorganisms can produce aliphatic diols (e.g. propanediols, butanediols, etc.) in significant concentrations (e.g. 5-15 wt%). Nonetheless, the high boiling points of these components, presence of microorganisms and the formation of by-products complicate recovery after fermentation. Hence, this perspective offers valuable insights in the downstream processing options. A novel methodology was developed for recovering high-boiling components from dilute aqueous solutions, whereby both light and heavy impurities are present. The basic steps in the proposed methodology are heat pump-assisted preconcentration and final purification in a dividing-wall column. These steps allow effective separation of high-purity product from water, light and heavy impurities.

Furthermore, processes for the recovery of 1,3-propanediol, 2,3-, 1,4- and 1,3-butanediol, designed according to the proposed methodology, were compared. The downstream processing performance is mainly determined by the product concentration in the fermentation broth but is also influenced by, the amount of impurities in the broth.

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T. Janković, S. Sharma, A.J.J. Straathof, A.A. Kiss, Eco-efficient recovery of non-volatile products from fermentation broth: Aliphatic diols, Journal of Chemical Technology and Biotechnology, in press.

3.3.1. Summary of the main challenges in the recovery of diols

Aliphatic diols are typical examples of valuable chemicals that can be produced in significant amounts by fermentation. Fermentative production of these chemicals has several drawbacks that complicate the downstream processing. The first challenge for downstream processing is product concentration in the fermentation broth. Even though these diols are less hydrophobic than mono-alcohols, hence less inhibiting, concentrations achieved in the fermentation broths are modest (<15 wt%). Therefore, the feed stream to the recovery process is highly diluted. Consequently, large equipment units are required to achieve sufficient production capacity for an industrially relevant scale.

These diols are high-boiling components (see Table 3-9), with a boiling point of way over 100 ˚C (the boiling point of water at atmospheric pressure) [30]. Thus, they cannot be simply removed from the broth by evaporation. On the contrary, evaporating large amounts of water can be very energy-intensive, if poorly designed, possibly resulting in high operating costs.

Table 3-9. Boiling points (at 1 bar) of the diols commonly produced by the fermentation

Component	Boiling point (˚C)
2,3-butanediol (2,3-BDO)	180.7
1,3-butanediol (1,3-BDO)	207.5
1,3-propanediol (1,3-PDO)	214.2
1,4-butanediol (1,4-BDO)	228.0

An additional challenge for the recovery process is the common presence of by-products (e.g. different carboxylic acids, ethanol, etc.) [265,298,321,322,330]. Depending on the concentrations of these by-products, it may be worth valorizing them. Valorizing by-products could improve downstream processing performance by reducing specific costs and energy requirements. However, recovering by-products that are present in very small amounts may significantly increase capital costs due to new equipment units, without bringing major benefits.

Lastly, microorganisms, residual substrate, biopolymers and inorganics are present in the fermentation broth that is sent to product recovery. To allow biomass recycling, these microorganisms should preferably be separated from the broth without harming their viability.

Considering the above-mentioned challenges, several steps are required to obtain a high-purity final product, to separate microorganisms, and to possibly recover some of the by-products. Consequently, the costs of downstream processing may be a significant contributor to the total production costs. Improving downstream operations is expected to enhance overall process performance by reducing these

costs, while the application of process intensification principles presents opportunities to improve energy efficiency. In this context, we propose a methodology for recovering high-boiling products from dilute aqueous solutions containing both light and heavy impurities. This perspective offers valuable insights into the recovery of aliphatic diols from the fermentation broth, with an emphasis on the purification of desalted and clarified aqueous solution.

3.3.2. Role of distillation in the recovery of diols

The performance of the downstream processing in the fermentative production of diols has been analyzed using 1,3-propanediol (PDO), 2,3-, 1,4- and 1,3-butanediols (BDOs) as representative examples. These chemicals were chosen as their production by fermentation has recently attracted much attention. Among others, companies such as DuPont [264,265], LanzaTech, BioPrincipia [266–268], Genomatica and Novamont [269–271] are actively developing fermentative production of these valuable chemicals. To the best of our knowledge, the fermentative production of various other diols (e.g., ethylene glycol, 1,2-propanediol, pentanediols) [17] has been a topic of research but remains in the early stages of development. Consequently, these were not included in the present study.

Due to the complexity of the fermentation broth, several steps are often needed in the recovery process [273]. Since both light and heavy impurities are present in the fermentation broth, PDO/BDO is the middle-boiling product in the fermentation broth. Hence, it would be very energy-intensive to use simple distillation as an *in-situ* product recovery technique. Furthermore, the high boiling point of PDO/BDO would require the usage of extreme vacuum conditions to ensure that temperatures would not harm microbial viability. For these reasons, initial separation steps, such as filtration and ion exchange, are typically employed to remove biomass and the majority of large organic and inorganic molecules. These operations are well-established in industrial fermentation processes and are therefore not the focus of this work. Instead, the emphasis is placed on advancing the subsequent stages of the recovery process, which are often the most energy-intensive (see Figure 3-1).

A result of these initial separation steps is a desalted and clarified aqueous stream containing PDO/BDO product and some by-products. Thus, additional preconcentration and final purification steps are required to separate water, light and heavy impurities and recover a high-purity final product. Distillation plays a major role as the main recovery technique in these steps. It is a mature separation technique, commonly used on an industrial scale. It does not require the usage of any additional chemicals that would complicate the downstream processing and influence the environmental impact of the process. Moreover, since none of the

considered diols forms an azeotrope with water, there is no need for more complex techniques such as extractive or azeotropic distillation. Nonetheless, the preconcentration step may be very energy-intensive due to the large amounts of water that need to be removed. The final purification step is complex due to the common presence of both lower and higher boiling impurities. Hence, advanced distillation techniques are needed to ensure the energy efficiency of the overall bioprocess. In that respect, we propose a methodology for recovering high-boiling products from dilute aqueous solutions containing both light and heavy impurities. This methodology may be applied to the preconcentration and final purification steps in PDO/BDO recovery after fermentation. Furthermore, it may facilitate the development of industrial-scale fermentative processes by indicating the costs of the recovery process. These data should be coupled with relevant data from the upstream process to obtain a full picture of the bioprocess performance.

However, it should be noted that in case a high-boiling product is present in very small concentrations in the fermentation broth (e.g. achievable concentration of 2-phenylethanol in the fermentation broth is <0.3 wt%), distillation would have to be coupled with some other technique for *in-situ* product recovery (e.g. liquid-liquid extraction, product adsorption, etc.). In this case, distillation would be used in the final purification, to separate valuable product from the used solvent. Thus, a slightly different approach would be needed. This is not covered by the presented methodology which focuses on recovery of the high-boiling products from a dilute aqueous solution.

3.3.3. Methodology of the recovery of high-boiling products from aqueous solution

The proposed methodology for the recovery of high-boiling products from a dilute aqueous solution is pictured in Figure 3-14.

Initially, most of the water, with some light impurities (e.g. ethanol if present), should be removed from the rest of the mixture containing valuable high-boiling products. Separating most of the water at this stage would significantly reduce equipment size and energy requirements in the final purification part of the process. We propose a multi-stage preconcentration step in the distillation column in which most light components are removed without losing the main product [341,342]. Even though possible, not all water and light impurities should be separated in this step. This would limit the implementation of heat pump systems as it would result in a large temperature difference between the top and the bottom of the preconcentration column. Alternatively, with the proper choice of operating parameters, it is possible to separate most of the water, with some light impurities, while keeping the top and bottom column temperature sufficiently close for implementing heat pumps. Mechanical vapor recompression

(MVR) is a state-of-the-art industrial heat pump system that can be applied when separating close-boiling components. It implies compressing vapor from the top of the column and using it instead of an external heating utility to evaporate the bottom liquid in a reboiler [113]. Hence, the electrical energy required to power the compressor can replace much higher thermal energy that would be needed to heat the reboiler. Furthermore, the implementation of the MVR system allows complete (green) electrification of the preconcentration step. If needed, a reduced pressure can be applied to this column to avoid the formation of high temperatures. An aqueous stream separated as the top product from the preconcentration column can be reused in the fermentation (if high purity) or sent to the wastewater treatment (if impurities are present). The bottom stream from this column contains PDO/BDO products with some water and remaining light and heavy impurities. This stream needs to be sent to the final purification to obtain a high-purity product.

The final purification part of the recovery process consists of two steps. Initially, the remaining water and light impurities should be separated as a top product from the distillation column. Secondly, the main product must be separated (as a top product) from the remaining heavy impurities (that are obtained as a bottom product). Thus, a sequence of two distillation columns is required for this separation. Alternatively, these two columns can be merged into one dividing-wall column (DWC). This equipment unit may reduce operating costs by improving the energy efficiency of the separation. Additionally, it also reduces capital costs by merging two column shells into one, decreasing the number of needed heat exchangers and reducing the required area [343]. Nonetheless, DWC may not always be the best option, and it should be compared to the sequence of distillation columns for the specific composition of the fermentation broth [154]. A reduced pressure operation is likely to be needed for the final purification part of the process due to the high boiling temperatures of these diols (see Table 3-9). Depending on the amounts of the present light or heavy impurities, it may be worth valorizing some of them. Otherwise, these streams should be sent to the waste treatment or burned for energy, and appropriate costs must be accounted for.

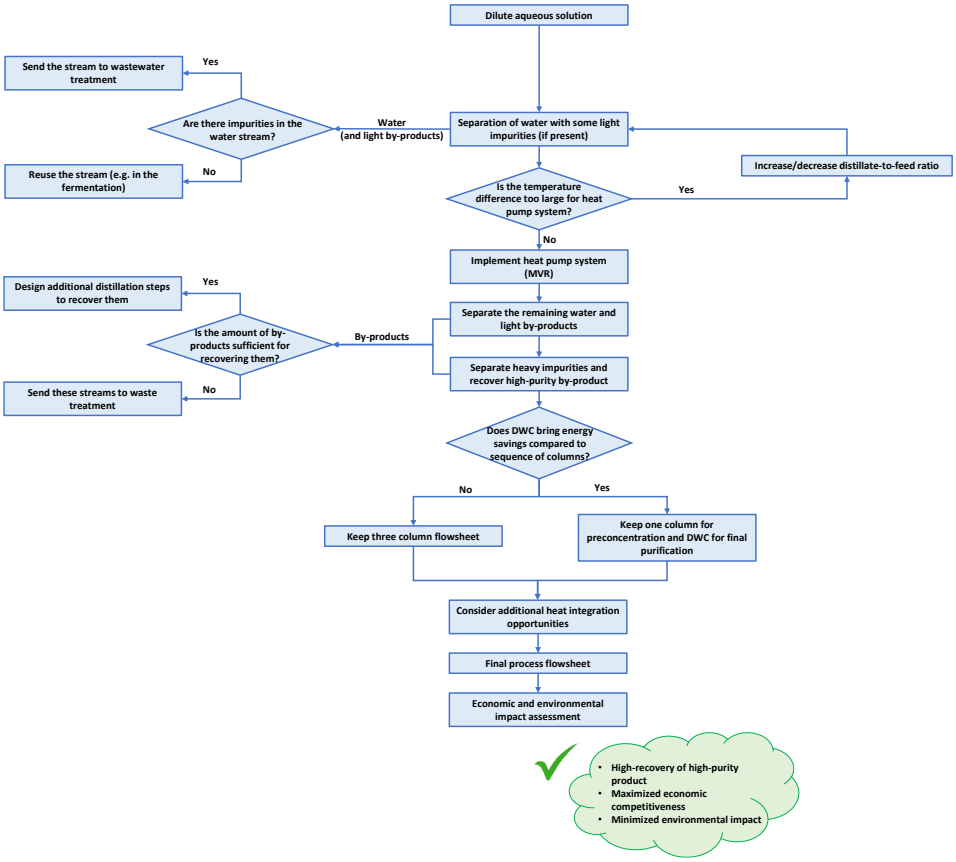


Figure 3-14. Proposed methodology for purification of high-boliling products from aqueous

After designing the preconcentration step, enhanced by the MVR system, and the final purification step, additional heat integration opportunities should be considered to further minimize energy requirements. Finally, once the final process flowsheet is developed, economic and sustainability analysis should be performed to evaluate the impact of the developed process.

To the best of our knowledge, the proposed methodology differs significantly from the published studies on the purification of diols after fermentation. So far, a simple sequence of distillation columns has been proposed to remove present water and purify PDO from light and heavy impurities [272,301–304]. On the contrary, more research has been done on the recovery of BDOs (mainly 2,3-BDO). However, a multistage preconcentration step in which most of the water and light components are removed without losing valuable product has not been proposed. Some studies considered an evaporation step in a flash unit before the final purification [321,336]. In this step, smaller amounts of impurities are

removed while most of the light components are sent to the final purification. As a result, the final step requires larger equipment units with higher thermal energy demands. Moreover, in the final purification step, BDO is recovered as a side stream, while water with light by-products is removed as the top product and heavy by-products are obtained at the bottom of the column. Consequently, the temperature difference between the top and the bottom of the column is too large, and the heat pump system can only be used to preheat the feed stream but not to evaporate the bottom liquid. Alternatively, removing all light components in a flash evaporator unit was suggested before the final distillation. The top vapor from the distillation column can be compressed and used to partially heat the evaporator unit [332]. However, one-stage separation caused BDO loss. Furthermore, the installed heat pump system could not supply sufficient heat in the flash unit. On the contrary, we propose a multi-stage preconcentration step in the heat pump-assisted distillation column C1 in which most light components are removed without losing BDO product. Thus, the reboiler duty and equipment size in the final purification step will be smaller due to the significantly reduced flowrate of the feed stream to this step. Additionally, the MVR system in column C1 can completely cover the thermal energy requirements of the preconcentration step. As this operation is very energy-intensive, the implemented heat pump system drastically reduces the energy requirements of the total downstream process [341,342].

3.3.4. Effects of diol product on downstream processing performance

A generic block flow diagram for the purification of high-boiling products from the dilute fermentation broth was derived (see Figure 3-15) following the previously explained methodology. A comparison between the downstream processing performance of different diols after fermentation is presented in Figure 3-16. Please note that the results for 1,3-propanediol recovery presented in this figure are the same as the results for case 1a in section 3.1.

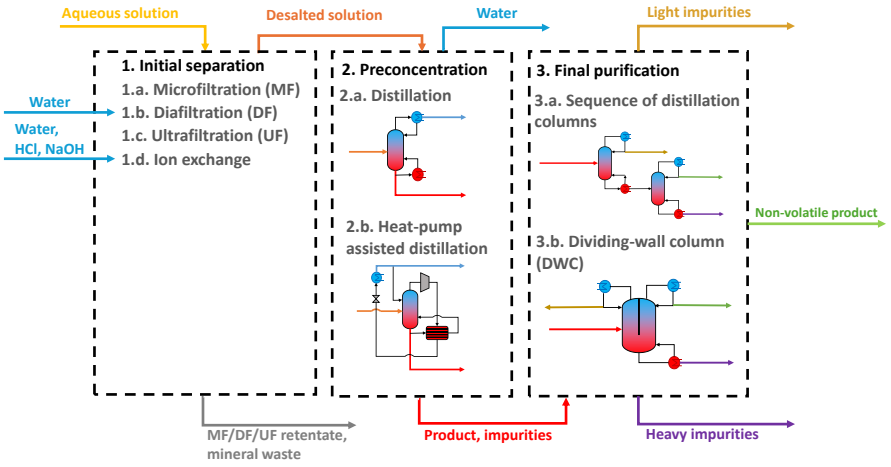


Figure 3-15. Generic block flow diagram for the purification of non-volatile products from the dilute aqueous stream

As can be observed, a smaller initial product concentration in the fermentation broth results in higher costs, energy requirements and CO_2 emissions in the downstream process. This is in line with common observations such as those previously derived for the purification of volatile bioalcohols after fermentation [344]. However, it is noteworthy that the performance of the 1,4-BDO recovery process shows a slight deviation from the trends observed in the recovery processes of 1,3-PDO, 2,3-BDO, and 1,3-BDO. Specifically, the costs, energy consumption, and CO_2 emissions for 1,4-BDO recovery are lower than those for 1,3-BDO recovery, despite the slightly lower product concentration in the broth. This is primarily attributed to the reduced presence of light and heavy impurities in the broth, which simplifies the separation process and lowers utility costs. Additionally, reduced wastewater treatment costs further contribute to the overall decrease in purification expenses. In conclusion, both the concentration of the main product and the level of impurities in the broth play crucial roles in determining the efficiency of downstream processing. Among these factors, the

initial concentration of the main product has the greatest impact on the recovery process.

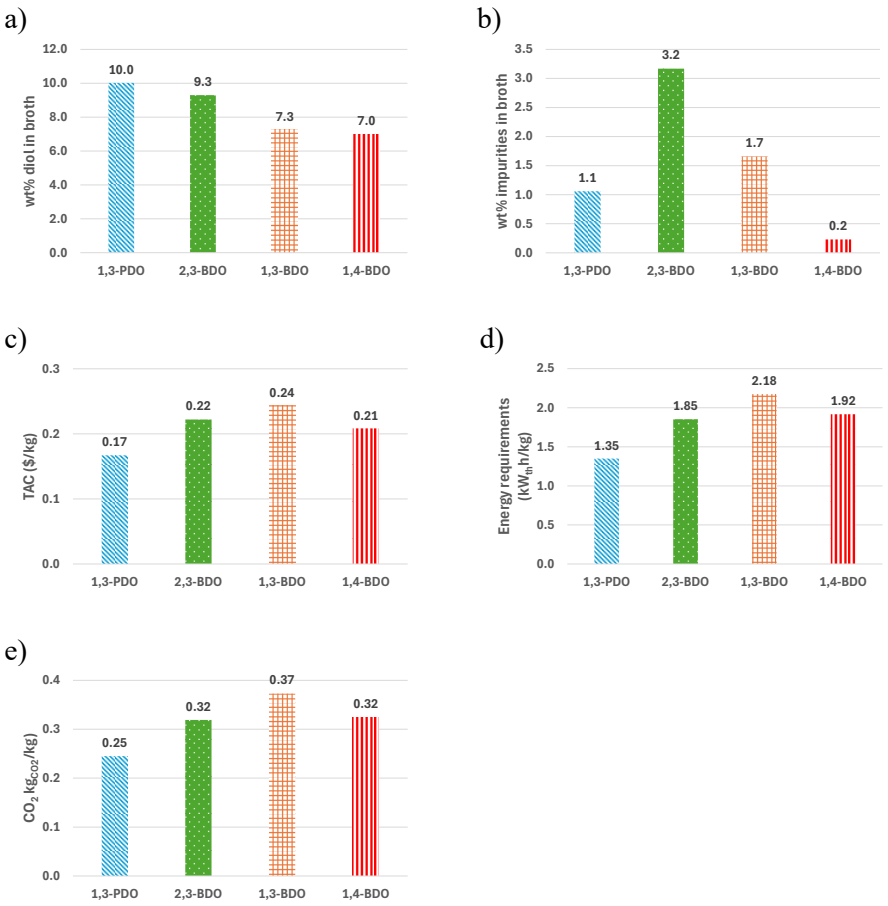


Figure 3-16. Assumed initial compositions and determined performance of the downstream processing for recovery of different diols after fermentation and initial separation: a) wt% of diol in the fermentation broth, b) wt% of impurities in the fermentation broth, c) total annual purification costs d) primary energy requirements and e) CO2 emissions (1,3-PDO – 1,3-propanediol, 2,3-BDO – 2,3-butanediol, 1,4-BDO – butanediol, 1,3-BDO – butanediol)

However, a significant impurity load can significantly increase recovery costs by making the separation process more complex and raising waste treatment expenses. Nevertheless, if the fermentation broth contains considerable amounts of by-products, valorising these by-products could enhance the overall cost-effectiveness of the process. For instance, valorising by-products in the recovery of 1,3-PDO after fermentation reduced the total recovery costs (per kilogram of all recovered products) by 9-25% [342].

Given that all considered diols have similar properties (e.g. composition in the fermentation broth, boiling points, etc.), it may be expected that one process design can be effectively used to purify all of them. This offers an interesting possibility of having one process capable of producing different diols depending on the current market demand.

3.3.5. Conclusion

This perspective offers an important overview of the downstream processing performance in the recovery of non-volatile products after fermentation. It proposes a novel methodology for recovering high-boiling products for dilute aqueous streams in case light and heavy impurities are present. To minimize energy requirements, two steps are necessary in the downstream processing. Initially, most of the water with light impurities can be separated in the preconcentration step. Afterward, a valuable fermentation product can be recovered from the remaining water, light and heavy impurities in the final purification. A proper choice of operating parameters in the preconcentration step should allow the implementation of the heat pump system. This would drastically reduce overall energy requirements, allow (green) electrification of the preconcentration step and reduce equipment size in the final purification.

The developed methodology is applicable to the preconcentration and final purification steps in the recovery of different diols after fermentation. The higher concentrations of the diols in the broth generally lead to more cost-effective and energy-efficient downstream processing. Nonetheless, impurities in the broth additionally influence the downstream processing performance. Higher amounts of impurities complicate the separation process and increase economic and environmental costs.

Finally, a similar downstream processing configuration that can effectively recover 1,3-PDO, 2,3-, 1,4- and 1,3-BDO offers an interesting opportunity to utilize a single process capable of producing different diols based on current market demand.



4 | Recovery of other organic components

4. Recovery of other organic components

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Besides alcohols, considered in chapter 2, and diols, considered in chapter 3, fermentation can be used to produce a wide variety of different distillable products (e.g. carboxylic acids, esters, aromatic components, etc.). Furthermore, various by-products worth recovering may be formed in different steps of an industrial bioprocess. For example, the biomass pretreatment step, which is necessary in the case of lignocellulosic fermentation, often results in the formation of acetic acid, formic acid, furfural, etc. Valorizing (some of) these by-products may increase the competitiveness of the whole bioprocess. The recovery of fermentation products and valorization of by-products have somewhat similar challenges as previously studied. Low product concentrations, thermodynamic constraints, presence of by-products and microorganisms commonly need to be addressed to ensure cost-effective and energy-efficient bioprocess. Furthermore, there are always some bioprocess specifics (e.g. charged form of carboxylic acids, aerobic nature of ethyl acetate fermentation, etc.) that must be accounted for when developing downstream process.

This chapter explores the recovery of different organic compounds. Even though not commonly considered in biotechnology, distillation was used as the main recovery technique in all considered processes. Thus, this chapter emphasizes the applicability of distillation in the downstream processing of different organic chemicals. For some of them (e.g. ethyl acetate), distillation was used for both *in-situ* product recovery and final purification. For the others (e.g. propionic acid, 2-phenylethanol), distillation is used for the final purification but must be coupled with another technique for the initial recovery steps. Advanced process intensification techniques were implemented to reduce energy requirements and costs of the downstream processing. Thus, this chapter proves that distillation can be used energy-efficiently as a separation technique in various aspects of industrial biotechnology.

4.1. Recovery of propionic acid

Propionic acid is a valuable platform chemical that is usually produced via fossil routes. As these are energy-intensive and eco-unfriendly processes, fermentative production of propionic acid is becoming more attractive. However, the complex downstream processing (due to low achievable product concentrations, high water content, presence of by-products and thermodynamic constraints), presents a potential barrier to scale-up this technology. This original research proposes a novel intensified large-scale (production capacity of ~20 ktonne/y) process for the final recovery of propionic acid after the initial biomass and counterion removal. Vacuum distillation steps ensure the recovery of a high-purity succinic acid product (>99.9 wt%) and a water stream that may be recycled to the fermentation to reduce the fresh water requirements. The main unit that follows is a highly integrated heat pump-assisted dividing-wall column (DWC), which allows the effective separation of propionic (>99.9 wt%) and acetic acid (99.4 wt%) products. Alternatively, it can serve as a reactive DWC that performs the esterification and separation of methyl propionate (99.8 wt%), methyl acetate (91.0 wt%) as higher added value products, and water by-product. If needed, extractive distillation can be implemented additionally to recover methyl acetate at higher purity (99.9 wt%). Overall, both options are proven to be economically interesting (recovery costs of 0.399-0.469 $/kg$_{product}$ considering the product price of 1.349-1.802 $/kg$_{product}$) and environmentally attractive (3.206-3.678 kW$_{th}$h/kg$_{product}$).

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4.1.1. Introduction

Propionic acid is an important platform chemical with an estimated global market of 450,000 tonnes, accompanied by a yearly growth rate of about 2.7% [345]. Due to its antimicrobial properties, the primary usage of propionic acid is as a preservative in feed, grain, bakery and dairy, as well as in herbicides. The usage of propionic acid as a preservative is generally based on the undissociated acid which can more easily penetrate through the cell wall. Alternatively, propionic acid salts can be used in the equivalent concentrations as the pure acid. However, their effect is slower and shorter because propionic acid must be released from the salt which is often a slow process. Moreover, propionic acid is typically preferred for preserving animal feed due to its more appealing taste for animals and possible increase in feed intake. Contrarily, propionic acid salts are usually more acceptable as preservatives for human consumption due to their neutral taste and smell [346]. Additionally, sodium propionate is widely used in the pharmaceutical industry for treating wound infections, conjunctivitis and dermatoses, while propionic esters can be used as artificial fruit flavors, plasticizers and volatile solvents [347]. Due to its sweetness, methyl propionate is commonly used as a flavoring agent and fragrance. Furthermore, it is a frequent solvent and platform chemical in the production of paints, varnishes [348] and other valuable chemicals such as polymethyl methacrylate [349]. Similarly, methyl acetate is widely used as a solvent for resins and oils, in paints, adhesives, nail varnish removers, etc [350]. Presently, propionic acid is mainly produced petrochemically via Reppe or Larson processes, whereby BASF, The Dow Chemical Company, Eastman Chemical and Perstorp dominate the global propionate market [345]. Due to the drawbacks associated with highly energy-intensive processes, nonrenewable feedstocks and environmental concerns, the production of propionic acid via fermentation is becoming more attractive. The most suitable producer for industrial-scale propionic acid fermentation is *Propionibacterium* [345]. So far, significant research effort has been invested into the fermentative production of propionic acid with the main focus on increasing fermentation titer [351–357], because the end-product toxicity remains the principal challenge for the feasibility of the large-scale process. The high permeability of cell membranes towards undissociated forms of carboxylic acids can cause acidification of cytoplasm, ATP exhaustion and dissipation of proton-motive force [40]. Even though fermentation at low pH has been attempted for some acids (acetic acid, citric acid, succinic acid, etc.), exposing *Propionibacterium* strains to low pH leads to inhibition and low product concentrations [358]. Contrarily, cell membranes are significantly less permeable to the anions of carboxylic acids. Thus, a commonly used approach is fermentation in a pH range higher than the pK_a of carboxylic acid (4.87 for

propionic acid) which leads to the transformation of the carboxylic group to the carboxylate group. This is usually performed by the addition of a base (e.g. NaOH, $Ca(OH)_2$, or others), which results in salt formation [40].

In the fermentative production of propionic acid, common by-products are acetic and succinic acids [353–356]. However, due to the necessary pH regulation in the fermenter, these acids are also present as salts in the fermentation broth. Therefore, several steps are required for the downstream processing to obtain carboxylic acids as final products: removal of cells and debris, counterion removal to obtain carboxylic acids from salts, water removal (preconcentration) and final purification to obtain high-purity end-products (Figure 4-1). The initial removal of cells and debris after the fermentation is done by well-known methods, such as filtration. Furthermore, several alternative methods have been studied for the removal of counterions. Precipitation using sulfuric acid, with co-production of gypsum ($CaSO_4 \cdot 2H_2O$) can be very convenient if $Ca(OH)_2$ is used for the pH control in the fermentation. This method has already been proven effective for citric acid and lactic acid fermentations [40]. However, using $Ca(OH)_2$ for pH control in propionic acid fermentation would lead to the precipitation of calcium succinate (solubility of 8.9-19.3 g/L [40]) and its removal with cells in the initial filtration step. Furthermore, the amount of gypsum that would be produced is slightly higher than the amount of carboxylic acids that can actually be recovered. Additionally, part of the monosaccharides would be lost due to adsorption on the gypsum surface. Besides sugars, formed gypsum would contain additional impurities such as ash and lignin, which would increase the disposal cost in industrial processing [359]. Alternatively, bipolar membrane electrodialysis (BME) can be used to obtain an aqueous carboxylic acid solution, which is sent to further purification, and an aqueous base solution, which can be reused in the fermentation for pH control. This process can efficiently combine cation and anion exchange membranes to replace cations in carboxylic acid salts with hydrogen ions [360,361]. The main cost contribution of BME is due to the membranes and energy requirements [360]. To the best of our knowledge, no detailed research on propionic acid recovery from fermentation using BME has been reported and precise costs cannot be determined. Yet, the reported BME energy requirements for the recovery of different carboxylic acids (0.60-0.95 kWh/kg for lactic acid, 1.5 kWh/kg for pyruvic acid, or 2.30-4.88 kWh/kg for succinic acid which is dicarboxylic [360]) indicate substantial minimum costs. Recovery of a solution of the three acids (propionic, acetic and succinic) from ultrafiltered fermentation broth might be possible, as indicated by exploring studies with some carboxylic acids [362,363]. Furthermore, additional options for counterion removal are the usage of ion exchange adsorbents or extractants (which usually lead to the co-production of

aqueous mineral salt solution) and thermal degradation of carboxylate salts (which may be very energy intensive) [40]. Nonetheless, whatever counterion removal method is used, further purification is required to obtain the pure carboxylic acid. Additionally, *in-situ* recovery of propionic acid by extractive fermentation, adsorption with anion-exchange resin and electrodialysis fermentation has been tested on a lab scale but has not been scaled up yet [347]. However, additional purification to obtain high-purity product will still be needed following these initial recovery steps.

Consequently, this research focuses on the preconcentration and purification steps in the recovery of carboxylic acids (Figure 4-1) in case these acids are obtained in an aqueous solution after the removal of cells, dissolved biopolymers, and mineral ions by membrane filtrations and BME, for example. The main goal of this work is to enhance the fermentation of carboxylic acids by developing a highly advanced downstream process that can simultaneously propionic and by-products (acetic and succinic acids) from an aqueous solution in a cost-effective and energy-efficient manner.

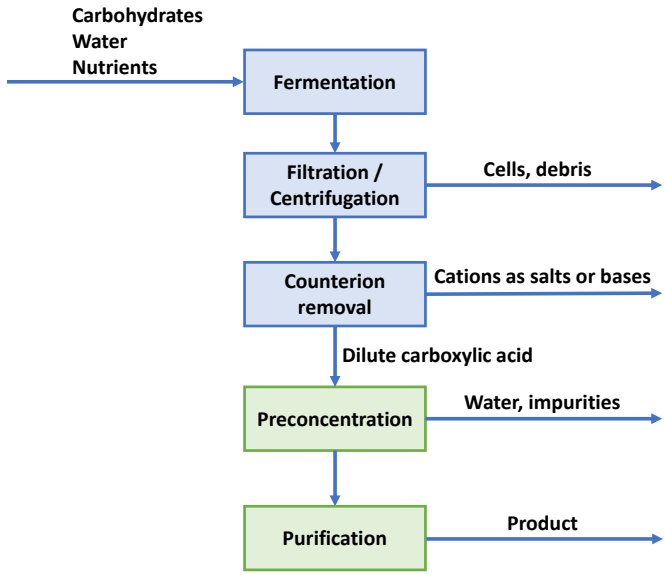


Figure 4-1. General downstream processing steps for the purification of carboxylic acids

4.1.2. Problem statement

The most common by-products reported in significant concentrations in the propionic acid fermentation are acetic and succinic acid [353,354,356,364,365]. Given the absence of available data on the concentrations of these acids in the aqueous mixture obtained after removing cells, dissolved biopolymers, and minerals, concentrations equal to those in the fermenter were assumed for the base case. Subsequently, a sensitivity analysis was performed to evaluate the effects of lower product concentrations in the aqueous solution. Thus, the feed stream to the recovery process is a dilute aqueous solution containing about 7.2 wt% propionic acid, 2.7 wt% succinic acid and 2.3 wt% acetic acid, while water makes the remaining >87.8 wt% [354]. Acetic acid and succinic acid are substantial by-products in propionic acid fermentation, so they may be worth recovering and valorizing, although their separation is also very challenging.

Depending on the used microorganism and its metabolic pathway for propionic acid synthesis, some lactic acid may be present besides already mentioned by-products. However, it has been shown that lactic acid concentrations in the fermentation broth can be minimized in several ways. Firstly, lactic acid can be catabolized by microorganisms to produce propionic acid. Accordingly, propionic acid titer and fermentation yield have been reported to increase even after substrate exhaustion until lactic acid was consumed [357]. Furthermore, a proper choice of operating conditions in the fermenter can lead to a complete absence of lactic acid in the final broth while concentrations of acetic and succinic acids are not nearly as much affected. For example, an increase in the fermenter's headspace pressure resulted in a significantly higher titer of propionic acids while lactic acid was completely depleted. Moreover, a lower agitation rate in the fermenter resulted in a lower concentration of lactic acid but this effect is less significant compared to the mentioned pressure increase [366]. As the presence of lactic acid in the final fermentation broth can be minimized or completely mitigated, it was not included in this study.

Besides the high content of water, which is lighter boiler compared to the carboxylic acids (Table 4-1), thermodynamic constraints (e.g. water-propionic acid azeotrope [30] and a tangent pinch between water and acetic acid, see Table 4-1) are additional complications for the recovery process. When the production of methyl acetate and methyl propionate is preferred over recovering carboxylic acids, four more azeotropes can potentially be formed: e.g. methanol-methyl acetate, water-methyl acetate, methanol-methyl propionate and water-methyl propionate (see Table 4-1) [30]. Therefore, a reliable property method is necessary to properly describe the interactions among various components and ensure the validity of the overall process design

Table 4-1. Boiling points of pure components and azeotrope formation (at 1 bar)

Pure components		Azeotrope		
Component	Tb (°C)	Component	Mass fraction	T (°C)
Methyl acetate	57.05	Methanol	0.1810	53.60
Methanol	64.53	Methyl acetate	0.8190	
Methyl propionate	79.46	Water	0.0123	56.96
Water	100.02	Methyl acetate	0.9877	
Acetic acid	118.01	Methanol	0.4697	61.91
Propionic acid	141.14	Methyl propionate	0.5303	
Dimethyl succinate	196.37	Water	0.0900	71.59
Monomethyl succinate	217.51	Methyl propionate	0.9100	
Succinic acid	317.60	Water	0.8120	99.52
		Dimethyl succinate	0.1880	
		Water	0.8769	100.01
		Propionic acid	0.1231	

4.1.3. Method of process design and simulation

Even though different methods have been proposed for the recovery of carboxylic acids from dilute streams (e.g. liquid-liquid extraction, membrane separations, etc.), the achieved recoveries and product purities are usually insufficiently high [367–370]. Extensive usage of additional chemicals may complicate further the processing, as the potential solubility of these components in water and toxicity to the microorganisms would make recycling of water to the fermentation difficult. Moreover, available data for the recovery of carboxylic acids were usually obtained from the lab scale without considering scale-up, which might result in high operating costs and additional challenges [371]. Thus, distillation was chosen as the final fluid separation technique due to its common usage on an industrial level, the possibility of achieving high recoveries and high purities of all three considered acids and the absence of chemicals that would complicate the recovery process. Besides recovering high-purity fermentation products, distillation can also recover pure water that may replace fresh water in the process (e.g. in the upstream fermentation). Furthermore, even though conventional distillation of highly dilute aqueous streams might be very energy intensive, advanced process intensification methods might substantially reduce overall energy requirements. In that context, this paper is the first one to propose an adaptable heat pump-assisted dividing-wall column that can be either used for the separation of propionic and acetic acid from an aqueous stream (case 1) or as a reactive DWC to produce and separate the methyl esters of these acids (cases 2a and 2b) as higher added value products. Given that concentrations of carboxylic acids after the counterion removal might differ from those in the fermenter, a sensitivity analysis was conducted to evaluate the performance of the developed processes if feed streams were more dilute. Rigorous simulations for every process operation were developed in Aspen Plus.

4.1.4. Results and discussion

This section contains key information about process design, techno-economic and sustainability assessments.

Thermodynamic modeling

UNIQUAC property method coupled with Hayden-O'Connell correction model for vapor phase association was chosen as the most suitable to describe the thermodynamic properties in a complex mixture of components [97]. Missing binary interaction parameters were estimated using UNIFAC method based on group contributions. To ensure the validity of the developed property model, this was tested against experimental data from the literature

Process design

Flowsheets of the developed processes are presented in Figure 4-2, Figure 4-3 and Figure 4-4.

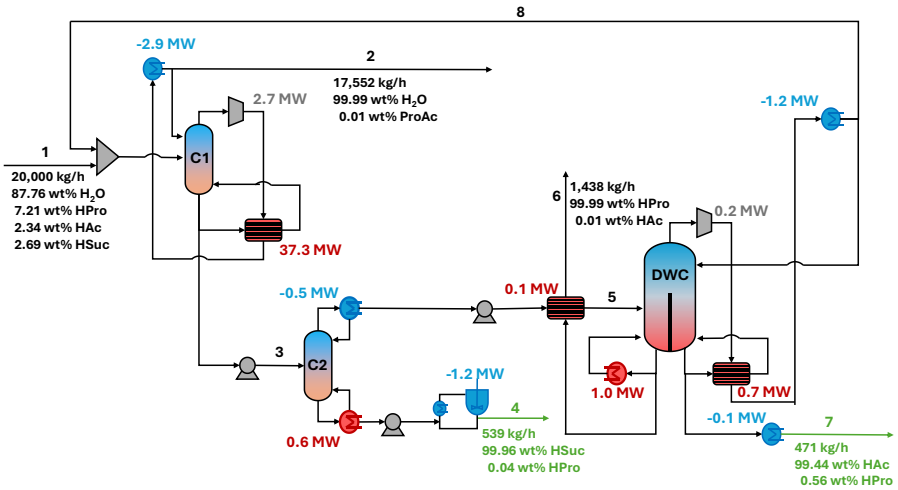


Figure 4-2. Downstream process for the recovery of propionic, acetic and succinic acid - Case 1 (abbreviations: H_2O – water, HPro – propionic acid, HAc – acetic acid, HSuc – succinic acid)

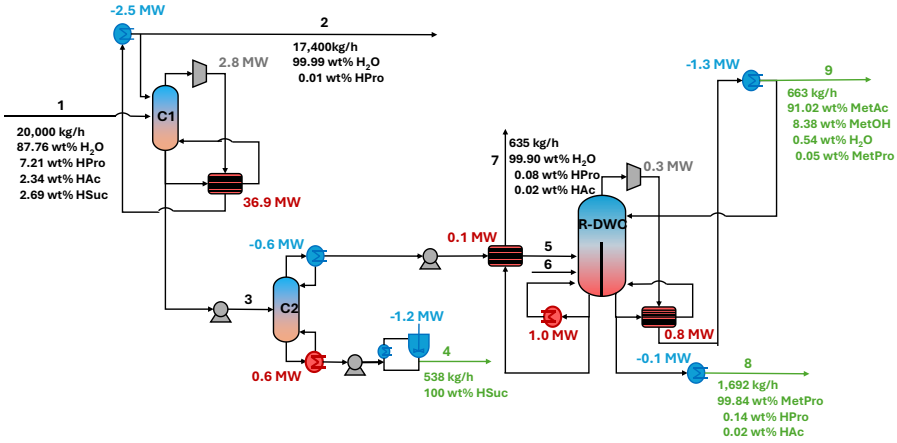


Figure 4-3. Downstream process for the recovery of propionic, acetic and succinic acid – Case 2a (abbreviations: H_2O – water, HPro – propionic acid, HAc – acetic acid, HSuc – succinic acid, MetPro – methyl propionate, MetAc – methyl acetate, MetOH – methanol)

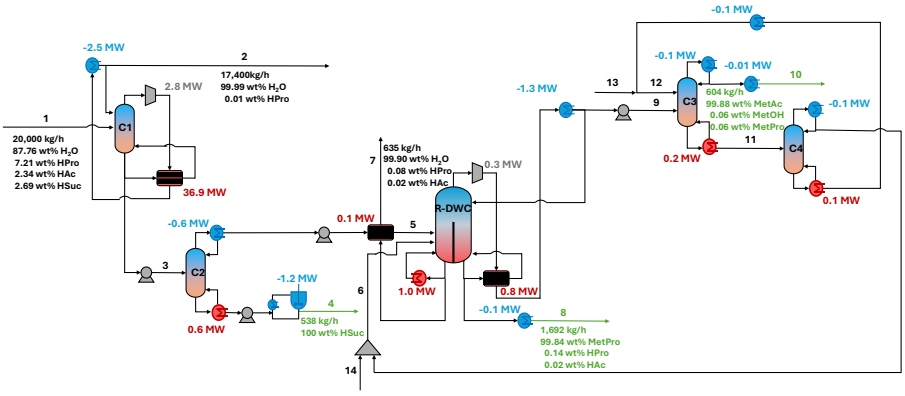


Figure 4-4. Downstream process for the recovery of propionic, acetic and succinic acid – Case 2b (abbreviations: H_2O – water, HPro – propionic acid, HAc – acetic acid, HSuc – succinic acid, MetPro – methyl propionate, MetAc – methyl acetate, MetOH – methanol)

Pre-concentration step

As the feed stream for the recovery process is very dilute (>87.8 wt% water), an initial step is to remove most of the water. This step is important to ensure efficient recovery of pure carboxylic acids and is critical in case of further esterification. Being the lightest component, water is obtained as the distillate, while a mixture of carboxylic acids with some water is obtained as the bottom product of column C1 (Figure 4-2, Figure 4-3 and Figure 4-4). Due to the mentioned difficulties in water–acetic acid and water-propionic acid separations, this initial distillation is performed under vacuum. The operating pressure (0.08 bar) was chosen to minimize the energy requirements for this step while keeping the condensation temperature appropriate for the usage of inexpensive cooling water. Considering low-pressure operation, structured packing type Mellapak 250 (with a pressure drop of 0.225 mbar per theoretical stage [110]) was selected for column C1. The distillate-to-feed ratio for this column (0.87 on a mass basis) was determined to ensure the removal of ~99% of the water from the feed while keeping the loss of acetic and propionic acid below 0.5% each. The bottom product from column C1 contains three carboxylic acids with some water and it requires further processing.

Despite being very energy intensive, this distillation separates relatively close boiling components, presenting an opportunity for the implementation of heat pumps. Mechanical vapor recompression (MVR), which implies using compressed top vapor from the distillation column to evaporate the bottom liquid, is an appropriate heat pump design for this column [113]. The effectiveness of the implemented heat pump system can be evaluated by calculating the coefficient of performance (COP), which is the ratio of upgraded heat (exchanged between the compressed vapor and bottom liquid) and required compressor duty. COP values greater than the electrical to thermal conversion factor (conservative value of 2.5 [156]) confirm the possible energy savings (n.b. the ideal COP for heat pumps is above 2.0 [155]). The COP of the MVR system applied to column C1 is 13.2-13.6, proving that very high energy savings are feasible. Besides the significant reduction in energy requirements, the implementation of MVR system is an important step toward electrification as it replaces large amounts of thermal energy with much less electrical energy.

Succinic acid separation

As succinic acid has a much higher boiling point than propionic acid, it can easily be separated from the rest of the mixture as a bottom product in distillation column C2 (Figure 4-2, Figure 4-3 and Figure 4-4). Due to the dicarboxylic nature of succinic acid, its esterification would lead to the formation of both mono- and dimethyl succinate [310]. Additionally, the formation of a water-dimethyl succinate azeotrope (see Table 4-1) might further complicate the recovery process. Therefore, the best option on a large-scale, is to remove succinic acid prior to further separation of acetic and propionic acid or their methyl esters. Thus, separation of succinic acid is performed in distillation column C2. Due to the large boiling point difference, this separation is relatively easy. However, reduced pressure is required (0.10 bar) to ensure that the reboiler temperature (~243 ˚C) is still suitable for the usage of high-pressure steam. As a result of the reduced operating pressure, Mellapak structured packing type 250 was also assumed for this column [110]. Despite the high reboiler temperature, there is no risk of succinic acid decomposition at the defined conditions [372]. The bottom product from column C2 is pure liquid succinic acid (100 wt%), while the top product is an acetic acid-propionic acid-water mixture that needs to be further treated. Liquid succinic acid product can be pumped to atmospheric pressure and cooled, which would result in crystallization. In case some non-volatile impurities were not removed in the previous processing steps (filtration, BME, etc.), they will end up in this stream and additional purification might be required.

Case 1: Recovering pure propionic and acetic acid

Due to the thermodynamic constraints, several steps are required to recover pure propionic acid and also pure acetic acid. Our initial reasoning was that propionic acid might be obtained as the bottom product of the first distillation column as it has the highest boiling point in the acetic acid–propionic acid-water mixture that is obtained as the top product from column C2. The top product from this column would be a water-acetic acid mixture with a small amount of propionic acid, that needs to be further treated in the next distillation column. Acetic acid would be obtained as the bottom product from this column, while the top product would be mainly water, with small amounts of propionic and acetic acid. To avoid any loss of valuable fermentation products, this stream can be recycled to column C1. Therefore, a sequence of two distillation columns would lead to high-purity propionic acid and acetic acid products. In an improved design, these two columns were merged into one dividing-wall column (DWC) with a common overhead section and divided bottom section (Figure 4-5). This highly integrated system consists of only one column shell, one condenser and two reboilers. Since the DWC unit is not readily available in Aspen Plus, it can be simulated as the thermodynamic equivalent combination of distillation columns (Figure 4-5).

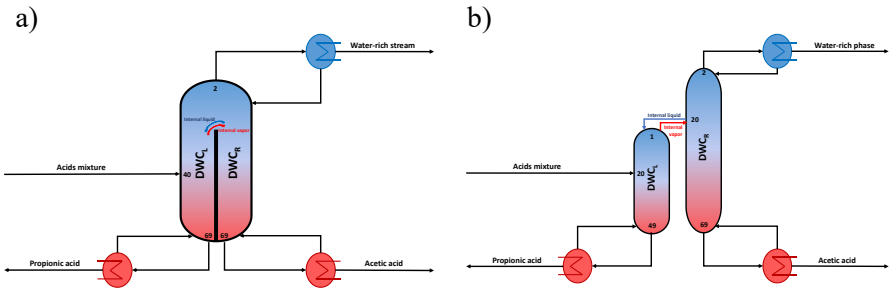


Figure 4-5. DWC designed for case 2a (a) and the equivalent sequence of distillation columns (b), numbers in the column indicate column trays

The left and right parts of DWC are presented as DWC_L and DWC_R, respectively. The number of stages, feed stage location, reflux ratio, bottom rate and liquid split were varied to minimize the energy requirements for DWC while ensuring sufficient purities of the recovered acids. Thus, propionic acid (>99.9 wt%) is recovered as the bottom product from DWC_L, while acetic acid (>99.9 wt%) is recovered as the bottom product from DWC_R. The DWC has 70 stages in total, whereby the convention in Aspen Plus implies that the first stage is the condenser and the last stage is the reboiler. The wall that separates DWC_L and DWC_R is placed along the bottom 49 stages. The feed stream containing a mixture of water, propionic and acetic acid, enters the DWC at the 40th stage (20th stage of DWC_L). Since DWC_L does not have a condenser, all its top vapor goes to DWC_R. About 52% of the top liquid flowing down in DWC_R is redirected to DWC_L, to ensure sufficient liquid flow at this side of the DWC. As the temperature difference on both sides of the wall in the DWC is not large, special thermal insulation is not required. Sieve trays with a pressure drop of 8 mbar per tray were assumed for DWC internals [112]. The required diameter of the DWC is 1.2 m, whereby the required tray areas for DWC_L and DWC_R are approximately equal.

There is no need to perform the described separations under reduced pressure since low-pressure steam can provide sufficient heat for both reboilers. Therefore, the water–acetic acid–propionic acid mixture obtained from the top of column C2 needs to be pumped to the atmospheric pressure. Afterward, it becomes a subcooled liquid that can be heated using the propionic acid bottom product to reduce total reboiler duty for the DWC. Furthermore, MVR can be applied using the top compressed vapor from the DWC to heat the bottom liquid from DWC_R. This reboiler is a better option for MVR than a DWC_L reboiler due to the lower temperature and lower compressor duty required. The COP of the applied heat pump system is around 3.1, hence higher than the 2.0 that is required to be effective [155], which proves the energy efficiency of this heat pump system.

Case 2: Recovering methyl esters of propionic and acetic acids

Instead of recovering pure propionic acid and acetic acid, an alternative is to obtain their methyl esters, which have higher market values. Thus, the flexibility of the recovery process was increased by transforming the previously designed DWC into a reactive dividing-wall column (R-DWC). Methanol was selected as the reactive agent because it forms lighter esters than higher alcohols do. Moreover, unlike higher alcohols, methanol does not form an azeotrope with water. Thus, the purification after esterification is more straightforward if methanol is used as a reactive agent. The simulations in Aspen Plus were performed using a combination of equilibrium models for vapor-liquid equilibrium and rate-based models for kinetics. The kinetic model includes two reversible reactions that are equilibrium-limited:

$$HPro + MetOH \leftrightarrow MetPRo + H_2O \quad (1)$$

$$HAc + MetOH \leftrightarrow MetAc + H_2O \quad (2)$$

As previously recommended for the reactive esterification of lactic acid [310], Amberlyst 36 catalyst (strong acid catalyst type, density of 800 g/L, minimum capacity of 5.40 eq/kg, with maximum operating temperature of 150 °C) was chosen [373]. Kinetic data for the esterification and hydrolysis reactions were gathered from the literature [374,375] and adjusted for the power law kinetics expression that is commonly used in Aspen Plus for defining the kinetics of rate-based reactions. The obtained pre-exponential factors were expressed per mass of catalyst, while catalyst density (800 g/L) allows conversion into catalyst volume-based units. Mole fractions of components were used as the basis for the rate expressions, whereby liquid was defined as the reactive phase. Table 4-2 provides the kinetic parameters.

Table 4-2. Kinetic parameters for the esterification and hydrolysis reactions

Equilibrium reaction	Reaction type	Pre-exponential factor ($kmol/kg_{cat}$ s)	Activation energy (kJ/kmol)
HPro + MetOH ↔ MetPro + H_2O	Esterification	$4.27 \cdot 10^3$	45,282
	Hydrolysis	$8.47 \cdot 10^{-1}$	26,650
HAc + MetOH ↔ MetAc + H_2O	Esterification	$8.20 \cdot 10^3$	45,600
	Hydrolysis	$4.87 \cdot 10^2$	41,924

A sequence of at least two distillation columns is required to perform esterification and separate the formed products (water, methyl acetate and methyl propionate). The esterification reactions are performed in the first reactive distillation column. Being the highest boiling product of the esterification reactions, water can be separated at the bottom of this column. Furthermore, methyl propionate and methyl acetate are separated as the bottom and top products from the second distillation column. As in case 1, these two columns can be integrated into one reactive dividing-wall column (R-DWC) with a common overhead section and divided bottom section (Figure 4-6). Generally, R-DWC has been previously proven to be highly competitive compared to the sequence of conventional distillation columns [115,376]. Chemical reactions and separation of more than two products can effectively be performed in only one equipment unit, as proven in real-life industrial examples [376–378]. This column was simulated as an equivalent sequence of two distillation columns (Figure 4-6) and designed according to the procedure recommended in the literature [379].

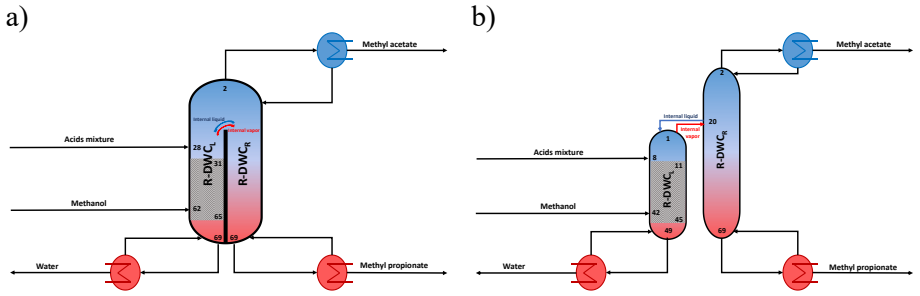


Figure 4-6. R-DWC designed for case 2b (a) and the equivalent sequence of distillation columns (b), numbers in the column indicate column trays, grey patterned part indicates reactive area

To extend the flexibility of the proposed recovery process design in case 1, the developed DWC design was adjusted for reactive distillation. The feed stages, catalyst holdup, reactive stages, liquid split ratio, reflux ratio and reboiler duties were varied until the desired product specifications were obtained. The top product from column C2, an aqueous mixture of propionic and acetic acid, and methanol are fed to the 28th and 62nd stages of DWC (8th and 42nd stage of DWC$_L$), respectively. The esterification reactions are performed in R-DWC$_L$, whereby the catalyst is placed from the 11th to 45th stage (from the 31st to 65th stage of R-DWC) with 11.7 kg of catalyst per stage. R-DWC$_R$ performs separation between the formed methyl propionate and methyl acetate. The top vapor from R-DWC$_L$ goes to R-DWC$_R$, while about 44% of the top liquid from column R-DWC$_R$ is redirected to R-DWC$_L$. The bottom product from R-DWC$_L$ is a pure water stream that is formed in the esterification reactions. This stream can be used to preheat the R-DWC$_L$'s feed stream with a mixture of acids and then recycled to the

fermentation to reduce water requirements. The bottom product from R-DWC$_R$ is high-purity methyl propionate (99.8 wt%), while the top product is 91.0 wt% methyl acetate. Due to the operation at atmospheric pressure, common trays hosting the catalyst in bags design [380] were assumed for the R-DWC internals. The total diameter of R-DWC is 1.3 m, whereby the required tray area for R-DWC$_R$ is about 2.5 larger compared to R-DWC$_L$. The top vapor stream that is being sent to R-DWC$_R$ contains 75.1 wt% methyl propionate, 18.8 wt% methyl acetate and only 5.0 wt% water.

The obtained methyl acetate with a purity over 90 wt% (which is of commercial quality) can be used in the production of artificial leather, as flavouring, paint remover and solvent for varnishes, resins, oils and nitrocellulose [381]. However, additional steps need to be taken if higher purity methyl acetate is required, due to the formation of a methanol-methyl acetate azeotrope. Extractive distillation with dimethyl sulfoxide (DMSO) is a common way for this separation [382,383]. The addition of DMSO to methanol-methyl acetate mixture changes the relative volatility of the two components and facilitates separation. As shown in Figure 4-4, the extractive distillation is performed in column C3, while the DMSO is recovered for reuse in column C4. The exact flowrate of DMSO (1.4 times higher on a mole basis, than the flowrate of the methanol-methyl acetate feed stream) was determined by minimizing the total energy requirements for the methyl acetate purification (columns C3 and C4). The top product from column C3 is a high-purity methyl acetate product (99.9 wt%), while the bottom product is a DMSO-methanol mixture that is sent to the solvent recovery column C4. The top product from this column is methanol that can be recycled to R-DWC, while the bottom product is recovered DMSO that can be reused in column C3. Columns C3 and C4 can potentially be merged into one dividing-wall column with a common bottom and a divided overhead section. This column would have only one reboiler and two condensers. However, this would lead to somewhat higher operating costs as high-pressure steam would have to be used for heating. Alternatively, using a sequence of two distillation columns allows the usage of low-pressure steam for the first column (reboiler temperature of about 157 ˚C) and high-pressure steam only for the second column (reboiler temperature of about 193 ˚C). In addition, an MVR heat pump system can be implemented to R-DWC by using the top compressed vapor to evaporate the bottom liquid from R-DWC$_R$. The COP of this heat pump system is about 2.8.

Techno-economic evaluation

The calculated economic indicators for both developed processes are presented in Table 4-3 and Figure 4-7.

Table 4-3. Key economic indicators of propionic acid recovery

Economic indicators	**Case 1**	**Case 2a**	**Case 2b**
CAPEX (k$)	25,334	26,284	30,221
OPEX (k$/y)	5,274	7,635	7,619
OPEX ($/$kg_{product}$)	0.269	0.330	0.336
TAC (k$/y)	7,807	10,264	10,641
TAC ($/$kg_{product}$)	0.399	0.444	0.469

The total costs for installing all process equipment units are 13,887 k$ for case 1, 14,407 k$ for case 2a and 16,592 k$ for case 2b. The largest part of the equipment costs is due to distillation columns (46-52%), followed by the cost for compressors (20-32%) and heat exchangers (22-28%). The CAPEX for the designed processes are 25,334, 26,284 and 30,221 k$ for cases 1, 2a and 2b, respectively. The costs for equipment make the largest part of CAPEX (~55%) for all processes. While the CAPEX for case 1 and case 2a are very similar, the CAPEX for case 2b is somewhat higher mainly due to the additional equipment (distillation columns, heat exchangers, pumps).

The OPEX for cases 1, 2a and 2b are 5,274, 7,635 and 7,619 k$/y, respectively. The contribution of different costs to the total OPEX for case 1 is the following: 57% for operating labor, 28% for electricity, 4% for low-pressure steam, 3% for high-pressure steam, 1% for cooling water and 7% for other costs. The reason for much higher OPEX for cases 2a and 2b is the cost for methanol (2,292 and 2,156 k$/y, with methanol price of 0.310 $/$kg_{product}$ as reported in the market data from 2023 [384]) which makes 30 and 28% of the total OPEX. The lower cost for methanol in case 2b is due to the fact that recovered methanol from column C4 can be reused in R-DWC. Apart from the methanol cost, costs for operating labor (39% of OPEX) and electricity (20% of OPEX) contribute significantly to OPEX for case 2a and case 2b, while costs for low-pressure steam (3% of OPEX), high-pressure steam (2-3% of OPEX), cooling water (<1% of OPEX) and other costs (5-6% of OPEX) are much lower. Per mass of recovered product, the OPEX for the designed recovery processes is 0.269, 0.330 and 0.336 $/$kg_{product}$ for cases 1, 2a and 2b, respectively.

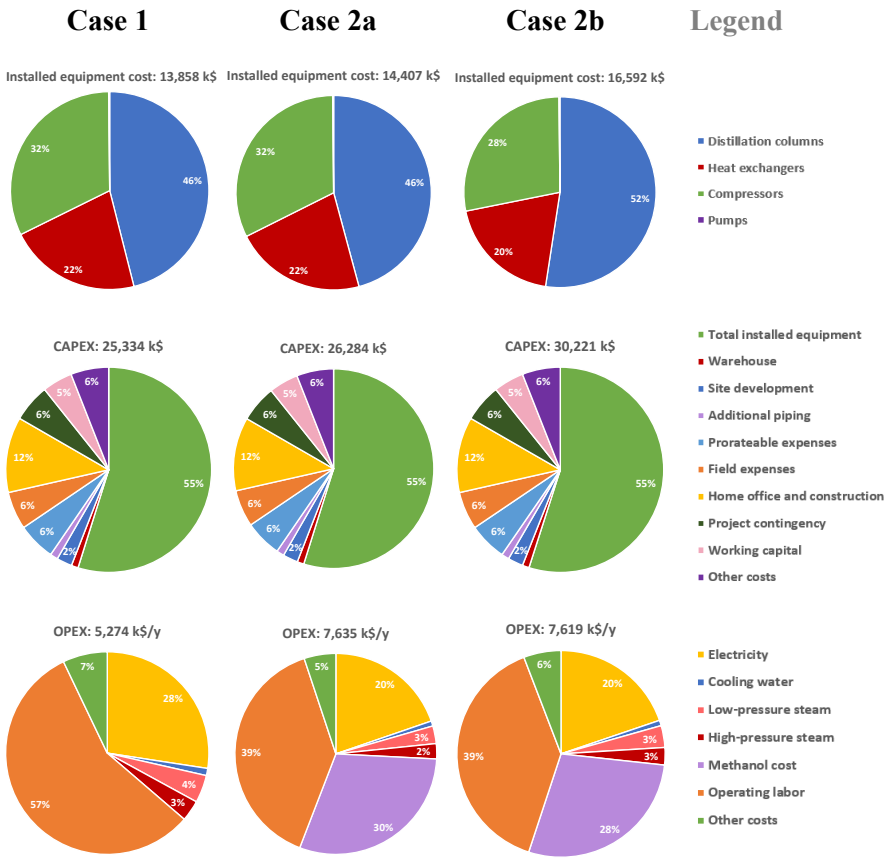


Figure 4-7. Comparison of economic indicators for the designed recovery processes

Finally, the calculated TAC are 7,807 k$/y (or 0.399 $/kg$_{product}$) for case 1, 10,264 k$/y (or 0.444 $/kg$_{product}$) for case 2a and 10,641 k$/y (or 0.469 $/kg$_{product}$) for case 2b. However, as propionic, acetic and succinic acids are the products in case 1, while methyl esters (methyl propionate, methyl acetate) and succinic acid are recovered in cases 2a and 2b, comparison of the TAC with mass-averaged market prices (AMP) of the product is needed. According to reliable market data [381,385,386], average market prices for the products are 1.349, 1.761 and 1.802 $/kg$_{product}$ for cases 1, 2a and 2b, respectively. Thus, the difference between average market price and TAC is much higher in cases 2a and 2b (1.318 and 1.332 $/kg$_{product}$) as compared to case 1 (0.950 $/kg$_{product}$). Despite more expensive recovery processes, the higher prices of methyl acetate and methyl propionate (as compared to acetic and propionic acid) lead to a higher margin between average market price and TAC. Additionally, the purification of methyl acetate from 91.0 to 99.9 wt% results in a slightly higher margin. To assess profitability, costs of

fermentation and prior downstream processing (biomass removal, counterion removal) also need to be considered.

Depending on the business strategy, different payback periods might be required by the investors. Thus, an analysis of the payback period (PBP) effect on the total recovery costs was performed and is presented in Figure 4-8. For case 1, TAC are lower than the average market price for PBP of 2 years, while shorter PBP leads to a more expensive recovery process compared to the market prices of products. Contrarily, TAC for cases 2a and 2b are lower than the average market price even with a PBP of 1 year. Thus, the margin between the average market price and TAC strongly depends on the specified PBP.

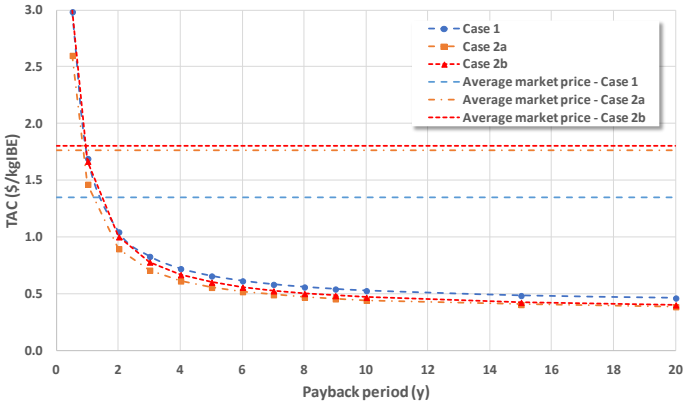


Figure 4-8. Influence of the payback period on TAC

Sustainability assessment

The calculated sustainability metrics are summarized in Table 4-4. All the specific values were obtained based on the total products' flowrate.

Table 4-4. Key sustainability metrics

	Case 1	Case 2a	Case 2b
Thermal energy requirements ($kW_{th}h/kg_{product}$)	0.644	0.535	0.635
Electrical energy requirements ($kW_eh/kg_{product}$)	1.214	1.068	1.091
Primary energy requirements ($kW_{th}h/kg_{product}$)	3.678	3.206	3.361
Water consumption ($m^3_w/kg_{product}$)	0.417	0.364	0.387
Water loss ($m^3_w/kg_{product}$)	0.029	0.025	0.027
CO_2 emissions ($kg_{CO2}/kg_{product}$)*	0.658 / 0.105	0.573 / 0.085	0.598 / 0.101
Material intensity ($kg_{waste}/kg_{product}$)	0.000	0.000	0.000
Pollutant emissions ($kg_{pollutant}/kg_{product}$)	0.000	0.000	0.000
Toxic emissions ($kg_{toxic\ materal}/kg_{product}$)	0.000	0.000	0.000

*Grey/green electricity

- ***Energy intensity:*** Thermal energy requirements are 0.644, 0.535 and 0.635 $kW_{th}h/kg_{product}$ for case 1, case 2a and case 2b, respectively. Additionally, electrical energy requirements for these processes are 1.214, 1.068 and 1.091 $kW_eh/kg_{product}$, respectively. The primary energy requirements are 3.678 $kW_{th}h/kg_{product}$ for case 1, 3.206 $kW_{th}h/kg_{product}$ for case 2a and 3.361 $kW_{th}h/kg_{product}$ for case 2b. Notably, recovering the methyl esters instead of pure acids is less energy-demanding, due to the lower boiling points and larger relative volatility of esters. Given that the total energy requirements for the propionic acid production from glycerol were assumed to be 120.4-138.9 MJ/kg_{HPro}, whereby the energy for the fermentation makes only a minor contribution [387], the process proposed in this study is a major step towards more competitive production of propionic acid by industrial fermentation. Additionally, since the designed preconcentration and final purification steps can be expected to be more energy-demanding compared to the prior operations (e.g. counterion removal by BME [360]), minimizing energy requirements for these steps is of crucial importance for the viability of the overall production process.
- ***Water consumption:*** Due to thermal energy requirements, the water consumption and loss are the highest for case 1 (0.417 and 0.029 $m^3_w/kg_{product}$, respectively). Water consumption and loss are somewhat

lower for case 2a (0.364 and 0.025 $m^3_w/kg_{product}$) and case 2b (0.387 and 0.027 $m^3_w/kg_{product}$).

- ***Greenhouse gas emissions:*** CO_2 emissions are the highest in case 1 due to the highest energy requirements (0.658 and 0.105 $kg_{CO2}/kg_{product}$ for grey and green electricity usage, respectively). Recovering methyl esters of propionic and acetic acids leads to lower CO_2 emissions both in case of grey (0.573 and 0.598 $kg_{CO2}/kg_{product}$ for cases 2a and 2b) and green electricity (0.085 and 0.101 $kg_{CO2}/kg_{product}$ for cases 2a and 2b) usage. Available data on the carbon footprint of propionic acid (4.40 $kg_{CO2}/_{HPro}$ [388]), acetic acid (1.67 kg_{CO2}/kg_{HAc} [389]) and ethyl acetate (1.67 kg_{CO2}/kg_{EtAc} [390]), may indicate the total greenhouse emissions for these products.
- ***Material intensity:*** In case 1, besides propionic, acetic and succinic acids products, the outlet stream is pure water from the top of column C1 which can be used elsewhere. Besides methyl propionate, methyl acetate and succinic acid products, the outlet streams in cases 2a and 2b are the top aqueous product of column C1 and the bottom water product from DWC_L. These streams are also pure enough for use elsewhere. Thus, as there are no waste outlet streams in any of the recovery processes, the material intensity metrics are equal to zero.
- ***Pollutant and toxic materials:*** There is no formation of pollutants or toxic materials in the developed processes. Also, the DMSO used for the extractive distillation in case 2b can be completely recovered in the solvent recovery column C4. Thus, the values of these metrics are equal to zero for all recovery processes.

The comparison of these metrics between cases should only serve as an indication due to the different natures of the recovered products. Nonetheless, since all of the sustainability metrics are reflected in the total recovery costs (e.g. costs of electrical energy, heating and cooling utilities, etc.), the most reliable comparison is the one between TAC and average market prices.

Sensitivity analysis: Influence of the product concentration in the fermentation broth on the downstream processing performance

Since concentrations of carboxylic acids in the feed to the designed process can vary depending on the prior processes, these concentrations were varied in a sensitivity analysis while the production capacity remained constant. Figure 4-9 presents the results of the sensitivity analysis. Lower concentrations of carboxylic acid in the feed stream lead to higher TAC, energy requirements, CO_2 emissions in the case of grey electricity usage, and water consumption. Especially concentrations lower than 10 wt% (>90 wt% water) result in poorer performance. To the best of our knowledge, the costs of the propionic acid recovery from a highly dilute aqueous stream have not been reported. Nonetheless, the reported energy requirements for the recovery of high-purity acetic and lactic acid from dilute streams by liquid-liquid extraction might give some indication (~1.7-6.9 kWh/$kg_{product}$ and ~11.1-55.6 kWh/kg_{HAc} or 10 and 1 wt% of acetic acid in the feed, or ~15.3 kWh/kg_{HLac} and ~138.9 kWh/kg_{HLac} for 10 and 1 wt% of lactic acid in the feed) [391]. Thus, the proposed processes for recovery of carboxylic acids from aqueous solution are competitive even with more dilute streams.

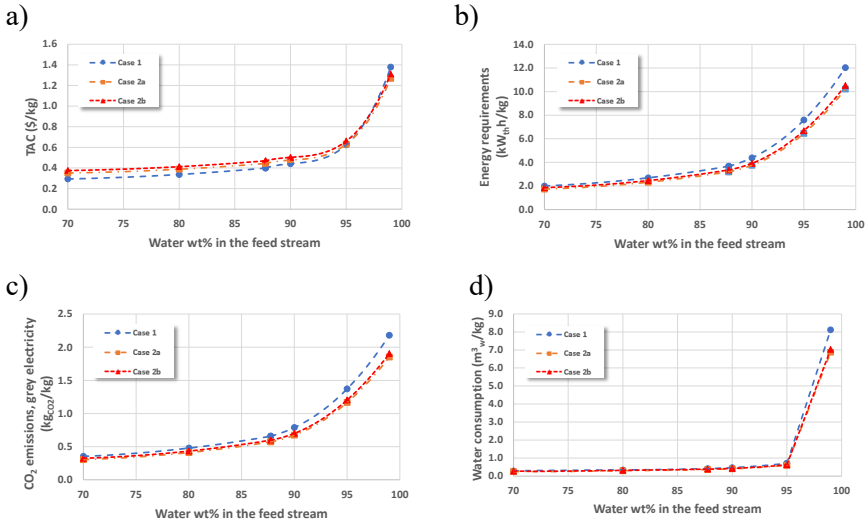


Figure 4-9. Sensitivity analysis results: influence of the water content in the feed stream on the main economic and sustainability indicators: total annual costs, b) energy requirements, c) CO_2 emissions when using grey electricity and d) water consumption

4.1.5. Conclusion

The proposed intensified downstream process was demonstrated to successfully recover high-purity propionic, acetic and succinic acid or methyl propionate, methyl acetate and succinic acid, while simultaneously allowing recycle of water to the fermentation. The initial distillation step to remove most of the water from the fermentation broth should be performed under reduced pressure to facilitate the separation, decrease product loss and increase efficiency. A mechanical vapor recompression heat pump system can be applied to reduce energy requirements by more than 13 times. Separating succinic acid as the next step in the process allows flexibility in further recovery of propionic and acetic acid or of their methyl esters. At the heart of the process is a highly integrated heat pump-assisted dividing-wall column which allows the separation of the high-purity propionic and acetic acid from aqueous solution, or it can serve as a reactive dividing-wall column (same design but adapted to host a solid catalyst on the reactive stages) that can efficiently perform the esterification with methanol and the separation of the methyl esters and water by-product. An additional extractive distillation step might be needed if methyl acetate purities higher than 91 wt% are required. Even though all developed process are promising options for large-scale recovery (capacity of ~20 ktonne/y), the esterification of propionic and acetic acid is a superior option due to the higher margin that could be obtained (1.318 and 1.332 $/kg$_{product}$ compared to 0.950 $/kg$_{product}$). However, it should be noted that the costs of fermentation, filtration/centrifugation and counterion removal will further decrease the above-mentioned margins. As these costs are the same for all cases discussed in this work, recovering the esters (methyl propionate and methyl acetate) will still be more cost-effective than recovering the acids (propionic and acetic acids). Overall, this original research contributes to advancements in the fermentative production of carboxylic acids by proposing an efficient process design that can be adapted for the recovery of propionic and acetic acids or esters (methyl propionate, methyl acetate) and succinic acid, depending on the market demand.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Adaptable heat pump-assisted dividing-wall column design for intensified downstream processing of bio-propionic acid, Separation and Purification Technology. 350 (2024) 127832. https://doi.org/10.1016/j.seppur.2024.127832. This file provides additional details about the developed property model and its validation with experimental data. Furthermore, details about the design of distillation columns are provided.

4.2. Recovery of ethyl acetate

Ethyl acetate is a platform chemical conventionally obtained through fossil fuel routes, but more recently its production by fermentation from carbohydrates has been scaled up to a pilot scale. Yet, the complexity of downstream processing (low product concentrations in liquid broth and in off-gas, azeotrope formation, the presence of microorganisms) may complicate industrial application. This original theoretical study is the first to develop advanced downstream processing, based on process intensification principles, for large-scale recovery (~10 ktonne/y) of ethyl acetate after fermentation. To minimize product losses, ethyl acetate is separated from both the liquid broth and off-gas. The final purification is performed in a highly integrated azeotropic dividing-wall column. The economic and sustainability analysis shows that using refrigeration for initial product separation from the gas phase is more cost-effective (~0.61 $/kg$_{EtAC}$) and less energy-intensive (2.20-2.40 kW$_{th}$h/kg$_{EtAC}$) than compression combined with high-pressure condensation using chilled water (1.09 $/kg$_{EtAC}$ and 9.98 kW$_{th}$h/kg$_{EtAC}$).

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4.2.1. Introduction

The production of esters from renewable sources has been a recent research focus of metabolic engineering [392]. These esters can be used as platform chemicals, or directly as fuel additives, flavoring and fragrance compounds [393]. In that context, ethyl acetate is one of the important short-chain esters that can be obtained in the fermentation process. It has various applications as a flavor compound, green solvent and platform chemical for the synthesis of biodiesel, paints, coating additives, adhesives, solvents, herbicides and resins [394–396]. The ethyl acetate market size has been projected to expand from 6.25 billion $ in 2024 to about 9.91 billion $ by 2031, with an annual growth rate of 6.8% during the forecast period [394]. Currently, ethyl acetate is primarily used for production of paints and coating additives (about 47%), adhesives, sealants, and pigments, and as a solvent [394]. The ethyl acetate market price in the USA at the end of 2023 was 1.74 $/kg [397]. Some key market players are Celanese, Eastman Chemicals, INEOS Group Holdings SA, and Solvents Limited [394].

Current industrial production of ethyl acetate uses different processes among which Fischer esterification is the most common one (contributing about 85% to the total global production) [398]. This process implies a reaction between ethanol and acetic acid in the presence of an acidic catalyst [399]. The relatively inexpensive raw materials and formation of water as a by-product are the benefits of using Fischer esterification for ethyl acetate synthesis. Alternative processes are acetaldehyde dimerization, a direct reaction between acetic acid and ethylene, and dimerization of ethanol [398]. All the mentioned reactions depend on fossil carbon-based hydrocarbons and require relatively expensive catalysts, high temperatures and pressures [399]. An alternative to petrochemical processes is the production of bio-based ethyl acetate from bioethanol. For example, in 2022, CropEnergies and Johnson Matthey built the first plant in Europe that uses renewable ethanol as a petrol substitute in the production of ethyl acetate [400]. Additionally, a new option is the microbial production of ethyl acetate by fermentation of renewable sources or waste materials [395]. This process might serve specific markets and may be more sustainable when sufficiently developed. Initially, the capability of different yeasts to produce ethyl acetate has been the focus of research for the synthesis of aroma compounds [401–403]. Furthermore, significant effort has been put into developing a microbial synthesis process for the production of ethyl acetate as a bulk product [399,404–409]. The yeast *Kluyveromyces marxianus* has been selected as the best candidate for the bulk production of ethyl acetate [399]. Under aerobic conditions, this yeast can directly convert sugars into ethyl acetate while minimizing the formation of by-products. Furthermore, this yeast is capable of metabolizing lactose which allows using whey as an inexpensive fermentation substrate [399]. Additional advantages of

K. marxianus are good thermal tolerance and relatively high tolerance to ethyl acetate although growth inhibition happens at about 17 g/L of ethyl acetate [408,409]. Unlike some yeast species (e.g. *Hansenula mrakii* and *Pichia anomala*) [399], microbial degradation of the formed ethyl acetate was not reported with *K. marxianus* [410] while the ester production can be controlled by the iron level [404,408]. Lastly, the production of ethyl acetate by this yeast has been scaled up to a pilot scale (70 L stirred reactor) [408]. Similar attempts have not been reported for any other fermentation process producing ethyl acetate.

To the best of our knowledge, the recovery of fermentative ethyl acetate on a large scale has not been thoroughly studied. Therefore, the main goal of this original research is to explore effective downstream processing options for large-scale recovery of ethyl acetate from fermentation. In that respect, this study is the first one to develop several recovery processes, based on process intensification principles, for the recovery of ethyl acetate (production capacity of about 10 ktonne/y). The results of this study will be crucial for obtaining a fully realistic picture of the industrial feasibility of ethyl acetate synthesis by fermentation.

4.2.2. Problem statement

Relatively low titer and yields are still significant drawbacks of ethyl acetate production by fermentation [395]. For example, despite the relatively high tolerance of *K. marxianus* [409], pilot scale experiments demonstrated that achievable concentrations of ethyl acetate in the liquid broth were less than 0.4 wt% (4 g/L) [408]. Moreover, due to the aerobic nature of the fermentation process and the high volatility of ethyl acetate, some of the product will be stripped by the air stream from the fermenter [409]. Even though higher than in the liquid phase, concentrations of ethyl acetate in the exhaust gas were still relatively low (less than 4 wt%) [408]. Thus, advanced processes for the recovery of ethyl acetate from very dilute streams are required to increase the competitiveness of the overall bioprocess. Furthermore, continuous product recovery may mitigate the end-product inhibition effects and possibly improve the fermentation yield.

4.2.3. Method of process design and simulation

To ensure maximal product recovery, this study aims to recover ethyl acetate from both the exhaust gas from the fermenter and the liquid broth. The composition of the exhaust gas differs from the composition of the dry air supplied to the fermenter due to oxygen consumption, carbon dioxide (CO_2) formation by the microorganisms, and stripping of some water and ethyl acetate from the broth. The concentrations of ethyl acetate and water in the off-gas from the fermenter have been reported for the pilot scale reactor. Thereby, the maximum achievable concentration of ethyl acetate in the off-gas was assumed [408]. Additionally, the oxygen consumption, carbon dioxide formation and off-gas flowrate were determined by solving a system of nonlinear equations (the nitrogen balance around the reactor [411], Henry's law for O_2 and the ratio of the formed CO_2 and consumed O_2) in MATLAB using *fsolve* function. Thereby, it was assumed that the flowrates of inert gases (N_2 and argon) were the same in the inlet gas and the off-gas (due to low solubility in water) [412,413], respiratory quotient was 1.15 [408] and dissolved O_2 concentration was about 30% of the equilibrium concentration. The ratio of flowrates of the off-gas and liquid broth flow rates were determined from pilot-scale data [408] (based on the known gas flowrate and an operation time of 13 h for which the ethyl acetate concentration is at maximum in both phases).

Ethanol and acetate are common by-products in the ethyl acetate production by *K. marxianus*. Being less volatile than ethyl acetate, these compounds were reported to accumulate in the liquid fermentation broth [408]. As shown in the experiments on a pilot scale, it may be possible to minimize the formation of one of these metabolites by controlling the fermentation conditions [408]. Due to the high volatility of ethyl acetate, its evaporation from the liquid broth may be performed under conditions that will not damage the microbial viability. For example, reduced pressure evaporation may be applied to avoid high temperatures that would harm microorganisms. Ideally, this approach would allow most of the fermentation broth, after ethyl acetate removal, to be recycled back to the fermenter, which might improve the fermentation process by avoiding loss of biomass, reducing water requirements and increasing substrate-to-product yield [19]. However, having acetate as a by-product in the broth would significantly complicate this recycling. Removal of acetate would be complex and expensive [40], while recycling it would lead to accumulation as the microorganisms are not able to consume it. It has been proven that *K. marxianus* can use ethanol after the depletion of sugars. However, acetate cannot be metabolized once ethanol is depleted [404]. Thus, recycling small amounts of ethanol should not negatively impact the fermentation and might even decrease the amount of substrate that is needed. In that respect, it may be more convenient

to minimize the production of acetate during the fermentation, while allowing some ethanol formation. Thus, the reported concentrations of biomass, sugars, ethyl acetate and ethanol in the liquid broth for pilot-scale experiments were used [408]. Additionally, it was assumed that concentration of dissolved O_2 was about 30% of the equilibrium concentration while concentration of dissolved CO_2 was equal to its solubility.

Having ethanol instead of acetate as by-product of the fermentation may allow most of the liquid broth, with microorganisms and some ethanol, to be recycled upstream after ethyl acetate separation. However, the recovery of ethyl acetate from an aqueous solution that contains ethanol is complex due to the possible formation of four azeotropes (see Table 4-5 and Figure 4-10). Therefore, an advanced downstream process is needed to effectively recover ethyl acetate after the fermentation. There are several requirements for this recovery process. Firstly, even though the amount of ethyl acetate stripped with the off-gas is much higher than the amount remaining in the liquid, efficient recovery from both phases is necessary to minimize product losses. Secondly, the initial separation of ethyl acetate from the liquid should be performed under conditions that will not harm microbial viability (moderate temperatures and absence of chemicals). Finally, a commercial-grade purity ethyl acetate product (>99.5%) [414,415] should be obtained from the water–ethyl acetate–ethanol mixture. The design of the ethyl-acetate recovery process was performed using Aspen Plus as computer-aided process engineering (CAPE) tool.

Table 4-5. Boiling points of pure components and formation of azeotropes at 1 bar

Pure components		Azeotropes		
Component	Tb (˚C)	Component	Mass fraction	T (˚C) / type
Ethyl acetate	77.20	Water	0.0874	70.33 / homogeneous
Ethanol	78.31	Ethyl acetate	0.7864	
Water	100.02	Ethanol	0.1262	
Acetic acid	118.01	Water	0.0903	71.39 / heterogeneous
		Ethyl acetate	0.9097	
		Ethanol	0.7024	71.78 / homogeneous
		Ethyl acetate	0.2976	
		Water	0.0438	78.15 / homogeneous
		Ethanol	0.9562	

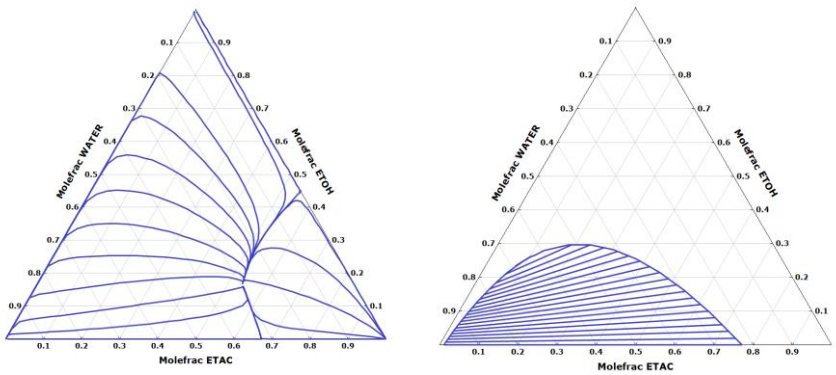


Figure 4-10. Residue curve map (left) and ternary diagram (right) of the ethyl acetate (ETAC) - ethanol (ETOH) - water system at 1 bar

4.2.4. Results and discussion

This section presents all details about the design of the downstream processing (DSP) of ethyl acetate after the fermentation – see process flowsheets in Figure 4-12 and Figure 4-14. In addition, results of the economic and environmental assessment are given for a fair comparison of the performance of the developed processes.

Thermodynamic property model

Due to the multiple components present in the fermentation broth and off-gas, the NRTL-HOC model (Non-Random Two Liquid model with Hayden-O'Connell extension) defined in Aspen Plus was chosen to properly account for the thermodynamic interactions. The NRTL (Non-Random Two Liquid) model describes vapor-liquid and liquid-liquid equilibria of strongly non-ideal mixtures using binary interaction parameters. The HOC (Hayden-O'Connell) extension was used to describe the dimerization of carboxylic acids in the vapor phase. Non-condensable gases (nitrogen, oxygen, carbon dioxide, etc.) were defined as Henry components.

However, the NRTL liquid activity property model is reliable for fluid separations up to moderate pressures. As one of the recovery processes (case 1) implies compression of the exhaust gas from the fermenter and high-pressure condensation with chilled water, the PSRK (Predictive Soave-Redlich-Kwong) property model from Aspen Plus was used to describe high-pressure operations. This model is based on the PSRK equation of state which can accurately predict thermodynamic interactions up to high temperatures and pressures using UNIFAC (UNIversal Functional Activity Coefficient) interaction parameters [97]. Furthermore, the REFPROP (REFerence fluid PROperties) model was used for the design of the refrigeration cycle (case 2). This model was developed by the

NIST (National Institute of Standards and Technology) to predict thermodynamic and transport properties of industrially important fluids such as different refrigerants and hydrocarbons [416].

Process design

Determining feed composition

The composition of the humid exhaust gas is the following: 71.99 wt% N_2, 20.74 wt% O_2, 2.91 wt% ethyl acetate, 2.20 wt% CO_2, 1.32 wt% argon and 0.84 wt% water. Furthermore, the composition of the liquid fermentation broth is the following: 94.50 wt% water, 4.55 wt% non-volatile components (biomass and sugars), 0.54 wt% ethanol, 0.28 wt% ethyl acetate, 0.13 wt% CO_2 and <0.01 wt% O_2 [408]. The determined ratio of flowrates of the off-gas and liquid broth flow rates is 1.2 on a mass basis. Flowrates of the gas and liquid feed to the downstream processing were back-calculated to obtain production capacity of about 10 ktonne/y as sufficient for continuous industrial operation (39,800 and 33,000 kg/h, respectively).

DSP design: Initial separation of ethyl acetate from the liquid fermentation broth

Besides ethyl acetate and ethanol, the aqueous broth from the fermenter contains some living microorganisms. Thus, the initial separation of fermentation products should be performed under moderate conditions that will not harm microbial viability. Consequently, most of the broth may be recycled to the fermenter to avoid biomass loss, reduce water requirements and increase fermentation yield [19]. A recently described hybrid combination of gas stripping and vacuum evaporation [246] was used to remove volatile fermentation products from the liquid broth. An alternative option would be to use liquid-liquid extraction [417]. Nonetheless, the drawbacks of this approach are the high volatility of ethyl acetate that may potentially lead to product and solvent losses, relatively large required volumes of solvent, possibly inefficient transfer of product into solvent phase due to the high dilution of the feed stream, difficulties related to the solvent recovery, etc. On the contrary, the gas stripping combined with vacuum evaporation effectively utilizes the high volatility of ethyl acetate for its separation from the higher boiling liquid broth. In this separation technique, the liquid broth from the fermenter is fed on top of the stripping column C1 in which gas is used to separate volatile products from most of the broth. This column operates at a reduced pressure (top pressure of 0.040 bar) to ensure moderate temperatures (28.6 ˚C at the top and 30.4 ˚C at the bottom of the column) that will not harm the microbial viability. Due to the reduced pressure operation, structured packing type Sulzer Mellapack 250 and pressure drop of 0.225 mbar per theoretical stage were considered for this column [110]. To provide gas for stripping in column C1, the

bottom product from this column, which is the liquid depleted of ethyl acetate and ethanol, is partially evaporated under reduced pressure. The remaining liquid contains mainly water with microorganisms and non-volatile inert components (stream 3). This stream may be recycled upstream. The formed vapor is sent to the bottom of column C1 and used to strip ethyl acetate and ethanol from the liquid fermentation broth. To reduce energy requirements of this initial separation step, a vapor recompression heat pump system is applied to the vacuum evaporation operation. The top stream from column C1, vapor rich in ethyl acetate and ethanol, is compressed (in COMP1) and used to evaporate part of the fermentation broth (in HEX1). A measure of the obtained energy savings can be evaluated by calculating the coefficient of performance (COP) of the implemented heat pump system. COP is equal to the ratio of the upgraded heat (exchanged between the liquid and the compressed vapor) and the compressor duty that is required to enable this evaporation.[113] COP values higher than 2.5, which is a conservative value of the electrical-to-thermal conversion factor [156], prove the energy efficiency of the applied heat pump systems. COP value of the described vapor recompression system is 20.5, which confirms significant energy savings. Furthermore, this system allows complete electrification of the vacuum evaporation.

After this initial step in the recovery process, about 87% of water from the fermentation broth is removed in flash vessel F1 (stream 3), while ethyl acetate and ethanol concentrations are increased by a factor of 7.5. However, this stream is still very dilute (>92 wt% water) and contains some dissolved gases that should be removed. Initially, simple phase separation in a flashing unit F2 was used to remove most of the present gases. As some volatile fermentation products are removed with these gases, additional steps were applied (multi-stage compression (COMP2) combined with condensation using cooling water (HEX2) and phase separation in a flashing unit (F3)) to minimize product losses. The remaining liquid streams with ethyl acetate and ethanol are sent to further purification in the azeotropic dividing-wall column (A-DWC).

Downstream processing design: Separation of ethyl acetate from the exhaust off-gas

Being a highly volatile product, ethyl acetate is mostly stripped with the off-gas. However, the concentration of the valuable fermentation product in the off-gas is still relatively small (~ 2 wt%). Thus, an advanced downstream process is required to separate the fermentation product from non-condensable gases. Two cases were considered for the recovery of ethyl acetate from exhaust gas. In the first case (case 1), atmospheric off-gas from the fermenter was compressed and ethyl acetate was condensed using chilled water. In the second case (case 2), refrigeration was used to cool atmospheric exhaust gas and condense ethyl acetate. Alternative options for the initial recovery of volatile chemicals, such as ethyl acetate, from a gas stream are membrane separations, adsorption and absorption. The performance of the membrane separation system strongly depends on the exact type of membrane used (cost, availability, susceptibility to fouling, replacement rate, etc.). As these quantitative data were not available [418], and relatively high costs may be expected due to the large gas flowrate, membrane separations were not considered in this study. Furthermore, adsorption was not considered due to drawbacks related to a desorption step (required regeneration of adsorbent which leads to a considerable energy cost), and large expected equipment and adsorbent costs due to the large gas flowrate [419]. Finally, when using absorption to recover low-concentrated volatile components from gas phase, large amounts of absorbing liquid are likely to be needed. Thus, large equipment units are needed for further processing, which may result in high capital and operating costs. Moreover, depending on the specific application of ethyl acetate and related standards regarding product purity, absorbent liquid may also need to satisfy safety standards (e.g. for applications in the food industry). Thus, absorption was also not examined for the initial separation of ethyl acetate from the gas phase [419,420]. As pilot scale experiments reported that ethanol accumulated in the liquid phase and was not present in the off-gas [408], it was not included in the gas feed stream to the downstream processing. However, if some ethanol is also present in the off-gas, it will be separated with ethyl acetate due to a higher boiling point (see Table 4-5).

Case 1 – Compression and high-pressure condensation using chilled water

Due to the high volatility of ethyl acetate and the presence of non-condensable gases (nitrogen, oxygen, carbon dioxide, argon), low-temperature cooling (using refrigeration) is required to completely separate ethyl acetate from the atmospheric exhaust gas. Alternatively, if off-gas from the fermenter is compressed, cooling at moderate temperatures (using chilled water) may be sufficient to condense ethyl acetate. In this case, off-gas from the fermenter is firstly compressed (in a multi-stage compressor COMP3) to the defined pressure. High-pressure gas is then cooled using chilled water (HEX3), while condensed ethyl acetate and water are separated from the remaining gases in a simple flash unit (F4). However, some ethyl acetate will likely remain in the gas phase and additional stripping with water will be needed to minimize product loss. This can be performed in a stripping column C2 where gas is fed at the bottom while water is fed at the top. The bottom product from this column is mainly water with stripped ethyl acetate, while the top product is a vapor stream with the remaining non-condensable gases (stream 6). As this column operates at increased pressure, simple sieve trays with a pressure drop of 8 mbar per stage were used for its internals [112].

With a defined cooling temperature of 10 ˚C (which may be achieved using chilled water at 5 ˚C), the relationship between the outlet pressure of the compressor COMP3 (and consequently compressor duty) and flowrate of the water needed for stripping (in column C2) was examined (see Figure 4-11), with the constraint of recovering over 99.9% of ethyl acetate from the off-gas. With the increase in gas pressure, the amount of ethyl acetate that remains in the gas phase after cooling decreases. Consequently, the amount of water needed to strip the remaining product from the gas also decreases. Since this aqueous stream with stripped ethyl acetate needs to be further processed, lower water flowrates will result in lower thermal energy requirements for the following distillation steps. On the contrary, gas compression to higher pressures will lead to larger compressor duties. Thus, there is a trade-off between the electrical energy needed to power the compressor and the thermal energy needed in the following distillation processes. Total primary energy requirements that account for both electrical and thermal energy were considered to determine the outlet pressure of the compressor and the water flowrate. The total energy requirements of the whole recovery process were compared for two compressor outlet pressures (10 and 40 bar). These pressures were chosen because the amount of water required to strip ethyl acetate from the remaining gas stream drastically increases for outlet compressor pressures lower than 10 bar, but does not decrease significantly for gas pressures higher than 40 bar. When the off-gas from the fermenter is compressed to 40 rather than 10 bar, the electrical energy requirements increase

by 64% while the thermal energy requirements decrease by 43%. Consequently, the total energy requirements are approximately 24% higher if the gas is compressed to 40 bar. This is mainly due to the higher electrical energy requirements in the multi-stage compressor. Due to the large flowrate of the exhaust gas from the fermenter, compression is very energy intensive. Thus, compressing off-gas to moderate pressures and using larger amounts of water leads to a less energy-intensive recovery process. Consequently, a compressor outlet pressure of 10 bar was chosen. Lower pressures would require a much larger water flowrate (e.g. almost two times larger water flowrate is needed if outlet pressure from the compressor is 5 bar) which would lead to higher CAPEX and were therefore not considered.

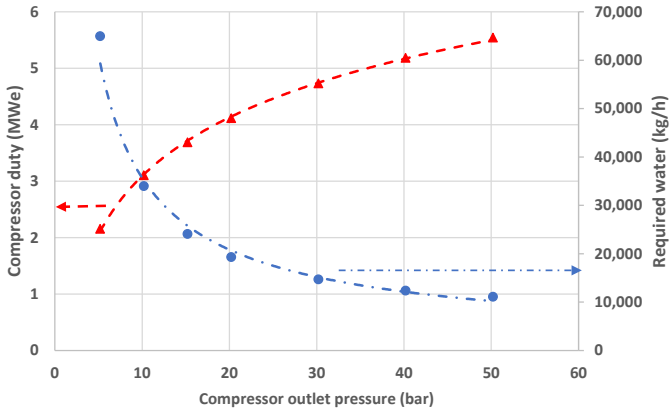


Figure 4-11. Determination of the compressor outlet pressure in case 1

Finally, over 99.9% of ethyl acetate is recovered from the exhaust gas. The aqueous streams containing ethyl acetate should be sent to the final purification in A-DWC. The remaining non-condensable gases were obtained in the top product stream (stream 6) from stripping column C2 (74.67 wt% nitrogen, 21.51 wt% oxygen, 2.26 wt% carbon dioxide, 1.36 wt% argon and 0.19 wt% water). However, even with moderate outlet compressor pressure, the total energy requirements of the initial separation of ethyl acetate from the off-gas are relatively high (about 3.1 MW_e is needed to recover 1,157 kg/h of ethyl acetate).

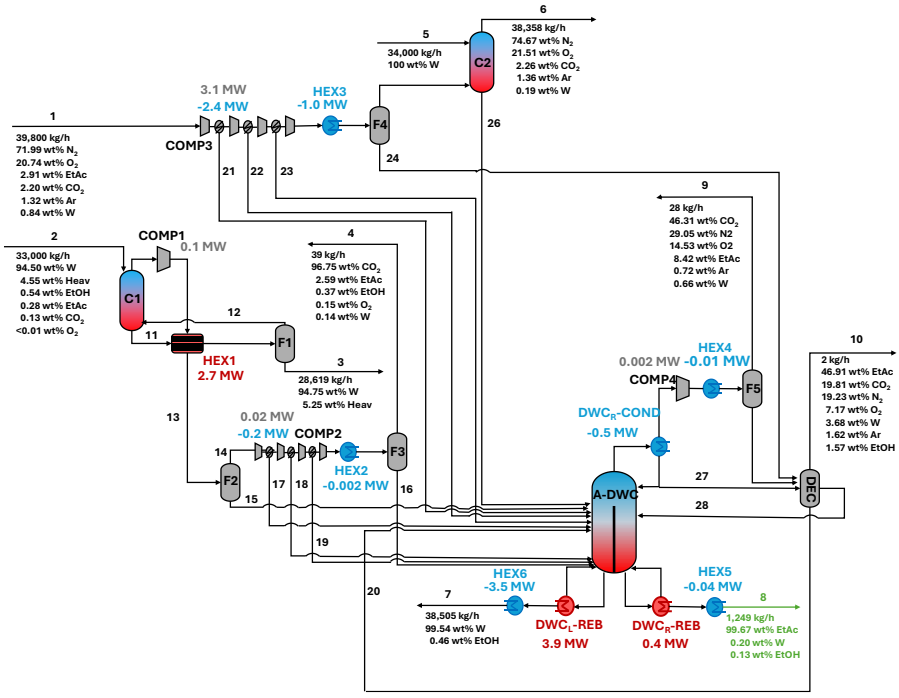


Figure 4-12. Flowsheet of the ethyl acetate recovery process - case 1

Case 2 – Low-temperature condensation using refrigerants

Since compression of large gas flows is energy-intensive, an alternative recovery process implying condensation of ethyl acetate directly from the atmospheric off-gas was designed. Due to the high volatility of ethyl acetate, very low temperatures are needed for sufficient product recovery. Thus, an auto-cascade refrigeration cycle may be used. In this system, a zeotropic mixture of two refrigerants with different boiling points (e.g. R-170 and R-290) is used to achieve low temperatures through multiple stages of evaporation and condensation within a single cycle (see Figure 4-13) [421].

The exhaust gas from the fermenter is cooled in two steps. In the first step, cold gas from the final cooling step is used instead of cooling utility in HEX3. Parts of the ethyl acetate and water have been removed from the gas phase after this step (in flashing unit F4). The remaining gas is sent to the final cooling step in which the refrigeration cycle is used to provide sufficiently low temperatures (in HEX4). The residual ethyl acetate and water may be separated from non-condensable gases in this step. The described two-step cooling drastically reduces refrigeration usage. Specifically, using the cooled gas from the second step in the first cooling step may decrease the total cooling duty by 58-65%.

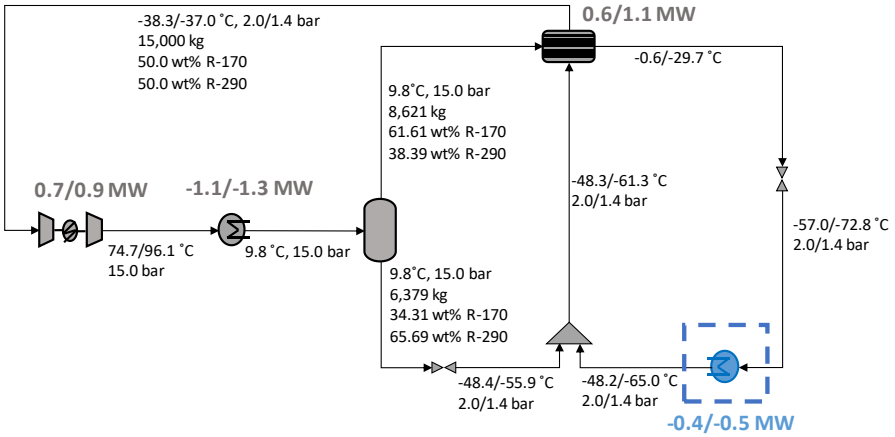


Figure 4-13. Flowsheet of the refrigeration cycle (ethyl acetate is condensed in the blue marked heat exchanger; if there are differences in stream parameters or energy requirements, the following order applies: case 2a/case 2b)

Initially, a moderate refrigeration at -50 ˚C was used for the final cooling step (case 2a). Yet, this temperature is not sufficiently low to completely recover ethyl acetate from the gas. About 8.3% of ethyl acetate from the fermenter off-gas is lost in the gas stream remaining from the final cooling. A possible option would be to absorb the remaining ethyl acetate from the gas using water. However, due to relatively low concentrations of ethyl acetate in the remaining gas (about 0.25 wt%) and the large gas flowrate, large amounts of water would be required to ensure sufficient product recovery. This would further increase capital costs and thermal energy needs in the final purification step. For example, to ensure that ethyl acetate losses in the remaining gas are not higher than 5%, about 80,000 kg/h of water would be needed in the stripping column. Additionally, the liquid product from this column is very dilute (about 0.1 wt% ethyl acetate). Thus, this option was not considered. Alternatively, even lower-temperature refrigeration at -70 ˚C may be used to recover over 99.0% of ethyl acetate from the exhaust gas (case 2b). Although the product recovery is higher in the case of lower-temperature condensation, the refrigeration cycle becomes more expensive. Thus, to compare the performance of these recovery processes, the final purification of ethyl acetate was designed for both refrigeration temperatures (case 2a and case 2b). In both cases, ethyl acetate-rich streams (>97 wt% ethyl acetate), recovered after refrigeration, are heated in HEX5 (using the aqueous bottom product of A-DWC) and sent to the final purification in A-DWC. After being used in the first cooling step (as a cooling utility in HEX5), the remaining gas that consists of nitrogen (74.61-74.78 wt%), oxygen (21.50-51.55 wt%), carbon dioxide (2.28 wt%) and ethyl acetate (0.03-0.25 wt%) is heated to ~10 ˚C. The total energy use for the initial separation of ethyl acetate from the fermenter

off-gas are 0.7 MW_e (case 2a) and 0.9 MW_e (case 2b), with recoveries of 92.7 and 99.0%.

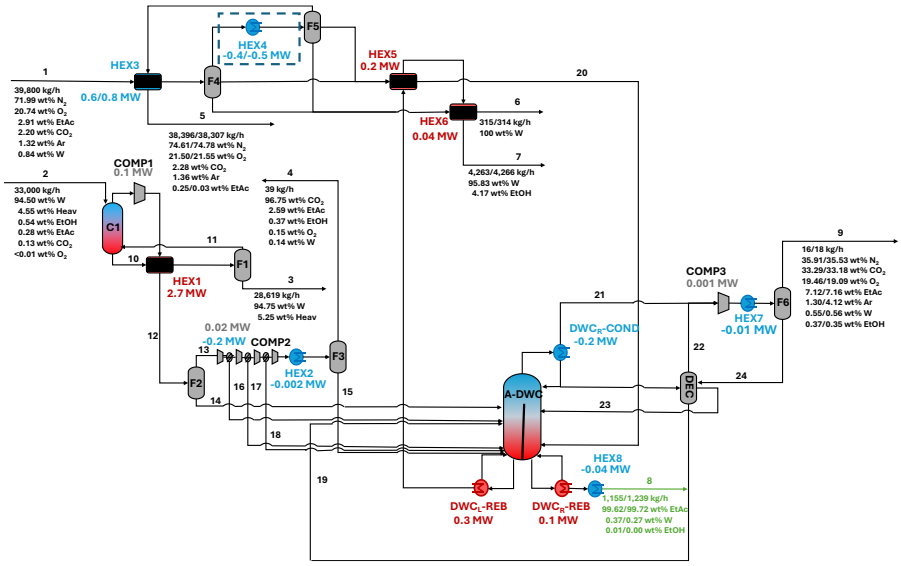


Figure 4-14. Flowsheet of the ethyl acetate recovery process - case 2 (marked heat exchanger requires refrigeration; if there are differences in stream parameters or energy requirements, the following order applies: case 2a/case 2b)

Downstream processing design: Final purification of ethyl acetate

After the initial recovery steps, ethyl acetate, ethanol and some water are separated from the liquid broth and the off-gas from the fermenter. This separation is challenging due to the potential formation of four azeotropes (see Table 4-5). Many separation techniques have been studied to work around thermodynamic limitations, whereby distillation-based operations are commonly proposed for large-scale processes. For example, pressure swing distillation uses pressure changes to influence vapor-liquid equilibrium of azeotropic mixture and move distillation boundaries [422]. Pervaporation-assisted distillation enhances conventional distillation by using selective membranes to effectively remove desired components [423]. Extractive distillation implies addition of an extractive reagent that changes relative volatility of the mixture. Thereby, the potential of ionic liquids to replace conventional solvents for ethanol-ethyl acetate separation is intensively investigated [424,425]. Furthermore, heterogeneous-azeotropic distillation has been proposed as a novel distillation technique that effectively couples distillation column with liquid-liquid separator [426]. Water (which is already present in the mixture) may be used as an extractive agent to facilitate the separation of ethyl acetate and ethanol. The benefits of this technique are absence of additional chemicals that may lead to complications related to recovery,

handling, toxicity or disposal; moderate capital investment for a large-scale process and reduction in energy requirements of separation due to effective usage of liquid-liquid-vapor separation [427]. Thus, it was used as the main recovery technique in the final purification after separating valuable products from the fermentation broth and off-gas.

Due to a highly complex mixture, several steps are required to obtain a high-purity ethyl acetate product. Initially, water may be used as an entrainer to break ethanol-ethyl acetate azeotrope [426,427] and remove most of the ethanol. Theoretically, in the first distillation column, most of the water with ethanol may be obtained as the bottom product, while ethyl acetate with some water may be obtained at the top. Furthermore, since ethyl acetate and water form a heterogeneous azeotrope, an additional treatment using distillation coupled with phase splitting in a decanter is needed. High-purity ethyl acetate product may be obtained at the bottom of the second distillation column, while a nearly azeotropic mixture may be obtained at the top. This stream is sent to the decanter from which ethyl acetate-rich phase is returned to the second distillation column, while aqueous phase may be recycled to the first distillation column. Hence, a sequence of two distillation columns with a decanter is needed to recover high-purity ethyl acetate. Alternatively, these columns may be integrated into one azeotropic dividing-wall column (A-DWC) with a common overhead and a divided bottom section (see Figure 4-15) [115,428]. As a dividing-wall column equipment unit is not available in Aspen Plus, it was simulated as a thermodynamically equivalent sequence of distillation columns (see Figure 4-15). The left and right sides of A-DWC are presented with A-DWC_L and A-DWC_R, respectively. Due to relatively small temperature differences between different sides of the inner wall, thermal insulation will not be required to allow thermal efficiency of A-DWC. Moreover, a suitable control strategy has been proven to effectively handle heat transfer across the wall of DWC [429]. In this system, most of the water with ethanol is obtained as the bottom product from A-DWC_L. If worth it, the ethanol from this stream may be recovered using a heat pump-assisted preconcentration step followed by final purification using extractive distillation with ethylene glycol, as previously suggested [154]. However, ethanol recovery is kept out-of-scope of the current paper since the costs and revenues of this process would obscure the costs and revenues of the ethyl acetate recovery. The top vapor from this column is sent to the A-DWC_R, while part of the liquid flowing down in A-DWC_R is directed to the first floor of A-DWC_L to ensure sufficient liquid flow in this part of A-DWC. High-purity ethyl acetate product is recovered at the bottom of A-DWC_R while a nearly azeotropic ethyl acetate-water mixture is obtained at the top of A-DWC_R and sent to the decanter. The ethyl acetate-rich phase from DEC is returned to A-DWC_R, while the water-rich phase is returned

to A-DWC$_L$. Thus, the dividing-wall column merges two conventional distillation columns into only one unit while reducing the number of heat exchangers (A-DWC has two reboilers (DWC$_L$-REB and DWC$_R$-REB) and only one condenser (DWC-COND)). Even though this is a highly integrated system, it has been proven that dividing-wall columns can be effectively controlled [430]. The number of stages, position of the feed stage, bottom product rate, reflux ratio and liquid split were varied to ensure high recovery of high-purity ethyl acetate product while minimizing the total energy requirements for the final purification. Due to the atmospheric operation, sieve trays with a pressure drop of 8 mbar were chosen for A-DWC's internals [112]. A-DWC has 30 stages in total, with the condenser as 1st stage and the reboiler as last stage according to the convention in Aspen Plus, while the wall is placed at the bottom 20 stages (19 excluding reboilers). After the initial separation of ethyl acetate, ethanol, and some water (either using high-pressure condensation with chilled water in case 1 or low-temperature atmospheric condensation with refrigerants in cases 2a and 2b), multiple streams need to be fed to A-DWC$_L$. The exact location of the feed stages depends on the technique applied for the initial recovery of ethyl acetate from the gas stream, due to differences in the compositions and flowrates of the feed streams. Generally, feed streams with high water concentration are fed on the top stages as water is used as an extractive agent. Contrarily, feed streams with lower water and higher ethyl acetate concentrations are fed on the bottom stages. Consequently, ethanol is removed with most of the water as the bottom stream from A-DWC while a nearly azeotropic mixture of ethyl acetate and water is obtained in the top vapor stream. This vapor stream is fed to the 10th stage of A-DWC$_R$ (also the 10th stage of A-DWC, see Figure 4-15), while part of the liquid from this stage is directed to A-DWC$_L$. The distillate from A-DWC$_R$ is sent to a decanter (DEC) for phase splitting. Organic and aqueous phases from the decanter are returned to the 12th stage of A-DWC$_R$ (also the 12th stage of A-DWC, see Figure 4-15) and the 6th stage of A-DWC$_L$ (the 16th stage of A-DWC, see Figure 4-15), respectively. The high-purity ethyl acetate product is recovered as the bottom stream from A-DWC$_R$. Lastly, ethyl acetate recovered from the fermenter off-gas in cases 2a and 2b is fed to the 25th stage of A-DWC$_R$. This stream may be preheated using the bottom product stream from A-DWC$_L$ to reduce thermal energy requirements in A-DWC$_R$ by over 60%.

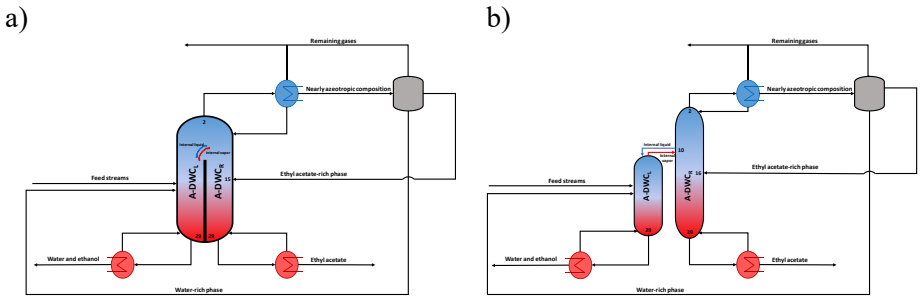


Figure 4-15. a) A-DWC design and b) the equivalent sequence of distillation columns – the numbers in the columns indicate stage numbers

Furthermore, due to the residual gases after the initial purification steps, a partial vapor-liquid condenser (DWC_R-COND) was defined for A-DWC_R and a possibility of vapor separation in DEC was considered. To minimize ethyl acetate losses, these vapor streams are compressed (in COMP3) and cooled to 25 ˚C using cooling water (in HEX7). As condensed ethyl acetate may be recycled back to DEC, product loss in the remaining vapor is less than 0.2%. Finally, the high-purity ethyl acetate product is recovered in all three cases (product purity ≥99.5 wt%). Product recoveries in case 1 and case 2b are high (100 and 99%, respectively). On the contrary, product recovery in case 2a is about 92% mainly due to the ethyl acetate that was not recovered from the off-gas after moderate refrigeration at -50 ˚C.

Techno-economic evaluation

The economic performance indicators of the developed downstream processes (case 1, cases 2a and 2b) are summarized in Table 4-6 and presented in Figure 4-16. The total equipment installation costs are the highest in case 1 when ethyl acetate is recovered from the gas phase by compression and high-pressure condensation using cooling water (8,190 k$). This is mainly due to the costs of the compressors (about 72% of the total installed equipment costs), whereby the cost of a multi-stage compressor for compressing the off-gas from the fermenter is the biggest contributor (about 92% of the total costs of compressors, or about 66% of the total installed equipment costs). On the contrary, the total equipment installation costs are lower when low-temperature condensation by refrigeration is used to recover ethyl acetate from the fermenter off-gas (4,797 k$ in case 2a and 5,316 k$ in case 2b). The cost of equipment in the refrigeration cycle makes approximately 50 and 54% of the total equipment cost in cases 2a and 2b, respectively. The higher cost of refrigeration equipment in case 2b is mainly due to the more expensive compressor required to ensure lower condensation temperature. Considering different equipment types, the biggest contributors are the costs of compressors (72, 53 and 56% of the total equipment costs in cases 1, 2a and 2b, respectively), heat exchangers (12, 26 and 26% of the total equipment

costs in cases 1, 2a and 2b, respectively) and distillation columns (12, 12 and 11% of the total equipment costs in cases 1, 2a and 2b, respectively), while costs of pumps (3, 6 and 5% of the total equipment costs in cases 1, 2a and 2b, respectively) and flash vessels are significantly lower (1, 2 and 2% of the total equipment costs in cases 1, 2a and 2b, respectively). Furthermore, the calculated CAPEX are much higher in case 1 (15,137 k$) compared to cases 2a (8,823 k$) and 2b (9,784 k$). This is mainly due to higher equipment costs, which make about 54% of CAPEX.

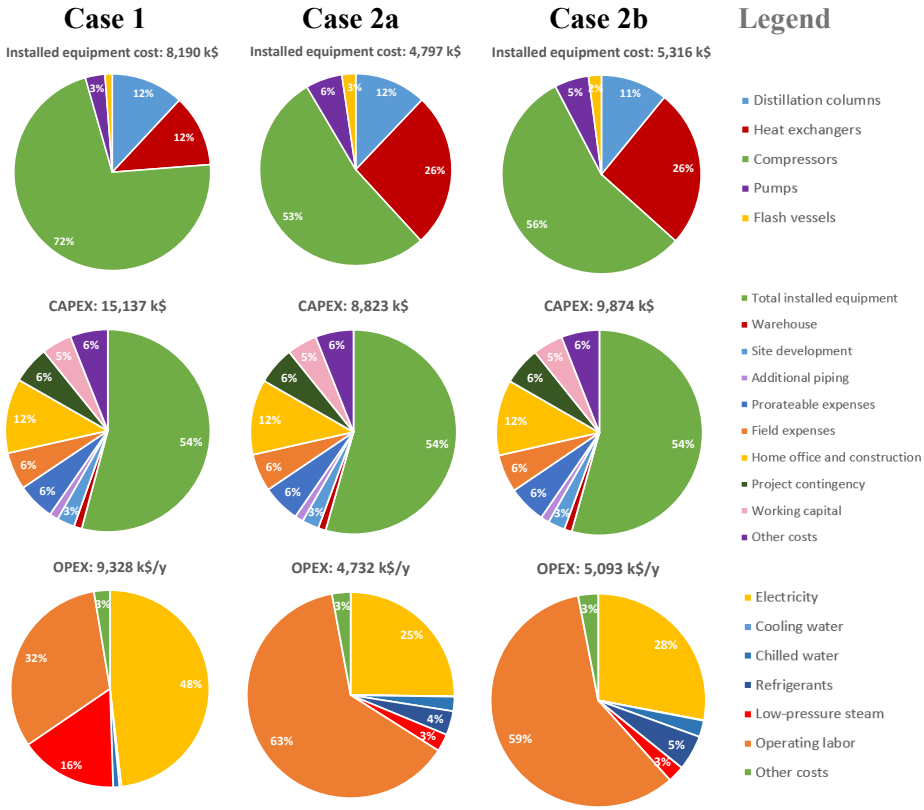


Figure 4-16. Comparison of economic indicators of ethyl acetate recovery

The determined OPEX are 9,328, 4,732 and 5,093 k$/y in cases 1, 2a and 2b. Expressed per kilogram of recovered ethyl acetate, these values are 0.934, 0.511 and 0.514 $/kg$_{EtAc}$, respectively. In case 1, the biggest contributor to OPEX is the cost of utilities (about 65% of OPEX) and labor (about 32% of OPEX). The largest part of utilities' costs is the cost of electricity (about 74%), whereby the cost of electricity to power the multi-stage compressor for the initial compression of the fermenter off-gas is the most dominant one (about 95% of the total electricity cost). On the contrary, utilities' costs are smaller when refrigeration is used in the

initial recovery of ethyl acetate from the gas phase (about 34 and 38% in cases 2a and 2b, respectively). Consequently, the contribution of labor costs in OPEX is higher (about 63 and 59% in cases 2a and 2b, respectively) even though the absolute costs are very similar. Among the costs of utilities, the biggest contributors are the costs of electricity (25- 28% of OPEX), refrigeration (4-5% of OPEX), low-pressure steam (3% of OPEX) and chilled water (2% of OPEX), while the cost of cooling water is much smaller (0.1% of OPEX). However, it should be noted that utilities' costs may vary significantly depending on the exact plant location.

Lastly, TAC that include CAPEX and OPEX with a PBP of 10 years are 10,842, 5,615 and 6,071 k$/y, or expressed per kilogram of ethyl acetate 1.085, 0.607 and 0.613 $/kg$_{EtAc}$ in cases 1, 2a and 2b. The more expensive recovery process in case 1 is primarily due to the more expensive recovery of ethyl acetate from the gas phase. More precisely, the higher CAPEX because of the costly multi-stage compressor for compressing the fermenter's off-gas and more expensive OPEX because of the electricity required to power this compressor. Case 2b is more attractive than case 2a because the extent of ethyl acetate recovery is larger by a factor 99/92 in case 2b. Therefore, the amount of the fermentation broth needed for a fixed annual ethyl acetate production is by a factor 99/92 smaller for case 2b, leading to savings on the fermentation costs that will be larger than the difference between the aforementioned 0.607 and 0.613 $/kg$_{EtAc}$. According to the available market data, ethyl acetate price in North America in 2023 was 1,739 $/kg$_{EtAc}$.[431] Thus, the margin between the market price and the costs of the recovery process for case 2b is 1.126 $/kg$_{EtAc}$. The cost of fermentation must be significantly smaller than this margin for the economic feasibility of the overall process. Design and economic evaluation of the fermentation are outside the scope of this paper, even though they are needed to get a full picture of the overall process.

Ethyl acetate is commonly produced by reactive distillation from ethanol and acetic acid. The operation and control of the reactive distillation process has been widely studied [432,433]. Since this is a reversible reaction, hydrolysis may be used to obtain bio-based ethanol and acetic acid from ethyl acetate. Yet, production of bio-based ethanol through fermentation (from lignocellulosic biomass or gas fermentation) have already been proven effective on an industrial scale [434]. Thus, it seems hardly profitable to produce ethanol by hydrolysing ethyl acetate made by fermentation.

Table 4-6. Key economic indicators of the designed ethyl acetate recovery processes (dry air supply to the fermenter)

	Case 1	Case 2a	Case 2b
Ethyl acetate recovery (%)	100.0	92.1	98.9
Economic indicators			
CAPEX (k$)	15,137	8,823	9,784
OPEX (k$/y)	9,328	4,732	5,093
OPEX ($/$kg_{EtAc}$)	0.934	0.511	0.514
TAC (k$/y)	10,842	5,615	6,071
TAC ($/$kg_{EtAc}$)	1.085	0.607	0.613

Sustainability assessment

The results of the environmental impact analysis are summarized in Table 4-7.

Table 4-7. Key sustainability metrics of the designed ethyl acetate recovery processes (dry air supply to the fermenter)

	Case 1	Case 2a	Case 2b
Ethyl acetate recovery (%)	100.0	92.1	98.9
Sustainability metrics			
Thermal energy requirements ($kW_{th}h/kg_{EtAc}$)	3.410	0.323	0.298
Electrical energy requirements (kW_eh/kg_{EtAc})	2.627	0.752	0.840
Primary energy requirements ($kW_{th}h/kg_{EtAc}$)	9.976	2.204	2.399
CO_2 emissions (kg_{CO2}/kg_{EtAc})*	0.494 / 1.692	0.284 / 0.627	0.070 / 0.453
Water consumption (m^3_w/kg_{EtAc})	0.570	0.123	0.056
Water loss (m^3_w/kg_{EtAc})	0.042	0.009	0.004
Material intensity (kg_{waste}/kg_{EtAc})	0	0	0
Pollutant emissions ($kg_{pollutant}/kg_{EtAc}$)	0	0	0
Toxic emissions ($kg_{toxic\ material}/kg_{EtAc}$)	0	0	0

*green/grey electricity usage

- ***Energy intensity***: Both thermal and electrical energy requirements are the highest in case 1 (3.410 $kW_{th}h/kg_{EtAc}$ and 2.627 kW_eh/kg_{EtAc}). The largest part of the thermal energy is used in the reboiler of A-DWC_L due to the water that is removed as the bottom product of A-DWC_L. This stream's flowrate is much larger in case 1 compared to cases 2a and 2b due to the water used to strip the remaining ethyl acetate from the gas phase in column C2. On the contrary, flowrates of all feeds to A-DWC are much smaller in cases 2a and 2b as additional water was not used. Consequently, the total thermal energy requirements are much smaller (0.323 and 0.298 $kW_{th}h/kg_{EtAc}$ in cases 2a and 2b, respectively). Furthermore, the largest part of the electrical energy requirements in case 1 is due to the electricity needed to power the multi-stage

compressor for compressing the fermenter off-gas. Contrarily, compressors in the refrigeration systems in cases 2a and 2b require less power which makes the total electrical energy requirements much smaller (0.752 and 0.840 kW_sh/kg_{EtAc} in cases 2a and 2b, respectively). Finally, the total primary energy requirements are significantly higher in case 1 (9.976 $kW_{th}h/kg_{EtAc}$), compared to cases 2a and 2b (2.204 and 2.399 $kW_{th}h/kg_{EtAc}$, respectively).

- ***Greenhouse gas emissions***: As CO_2 emissions are strongly related to energy usage, these emissions are the highest in case 1, in which 1.692 or 0.494 kg_{CO2}/kg_{EtAc} is emitted if grey or green electricity is used. On the contrary, CO_2 emissions are much lower in cases 2a and 2b. However, CO_2 emissions are higher in case 2a (0.627 or 0.284 kg_{CO2}/kg_{EtAc} if grey or green electricity is used) compared to case 2b (0.453 or 0.070 kg_{CO2}/kg_{EtAc} if grey or green electricity is used) due to the larger amounts of the remained ethyl acetate in the gas phase that is accounted for through CO_2 equivalents [390].
- ***Water consumption***: Due to the significantly higher thermal energy requirements, water requirements and water loss are the highest in case 1 (0.570 and 0.042 m^3_w/kg_{EtAc}, respectively). Contrarily, these values are much lower in cases 2a and 2b (approximately 0.056-0.123 and 0.004-0.009 m^3_w/kg_{EtAc}, respectively).
- ***Material intensity***: As waste is not formed in any of the developed recovery processes, values of material intensity metrics are equal to zero in all cases. Nonetheless, it should be noted that the bottom stream from DWC_L, if not further processed to recover ethanol or used upstream, should be sent to the wastewater treatment.
- ***Pollutant and toxic materials***: Since no pollutants or toxic materials are emitted, the values of these metrics are zero in all cases.

Sensitivity analysis: Influence of the product concentration in the fermentation broth on the downstream processing performance

The recovery of ethyl acetate after the fermentation using the developed case 2b has been proven to be the most cost-effective and energy-efficient due to the high product recovery and reasonable costs. A sensitivity analysis was performed on this case to examine the influence of the achievable ethyl acetate concentration in the broth on the performance of the downstream processing. The results of this analysis are presented in Figure 4-17.

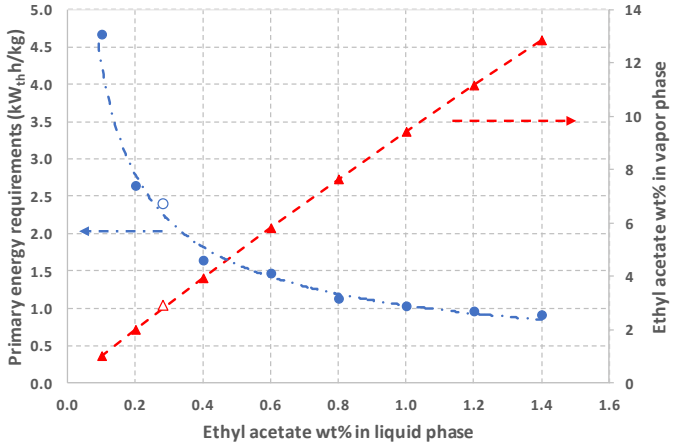


Figure 4-17. Sensitivity analysis: influence of the achievable product concentration in the fermentation on the downstream processing performance of case 2b. Markers are simulated cases, with the open marker being the base case.

Generally, the increase of ethyl acetate concentration in the liquid broth would lead to the linear increase of ethyl acetate concentration in the off-gas from the fermenter (defined by Henry's law). Due to the less diluted feed streams (both liquid and gas), the energy requirements of the downstream processing would decrease. This decrease is more drastic with extremely low product concentrations in the broth while it becomes milder for higher concentrations. For example, about 1.5 or 1.1 $kW_{th}h/kg_{EtAc}$ are required to recover high-purity ethyl acetate product when its concentration in the liquid broth is 0.6 or 1.0 wt% (about 5.8 and 9.4 wt% in the exhaust gas), respectively. Therefore, even a slight increase in ethyl acetate concentration from the ones assumed in this study would significantly decrease the downstream processing costs. Nonetheless, obtaining higher product concentrations in the fermentation is challenging due to the inhibitory effects and a lot of research effort has been put into developing more tolerant microorganisms. In that respect, it is worth noting that the energy requirements (and costs) of the downstream processing would not drastically decrease above a

certain concentration of the product in the broth (e.g. 1.0 wt%, see Figure 4-17). Thus, very high product concentrations in the fermentation broth may not be necessary to make the production process competitive. Hence, simultaneous development of the upstream fermentation and the downstream process is necessary for successful scale-up.

The results of this study offer a realistic picture of the downstream processing performance after the specific fermentation process. Nonetheless, it should be mentioned that novel approaches to obtain ethyl acetate by fermentation include anaerobic fermentation of glucose with hydrogen co-production [435] and of carbon monoxide [436] will lead to off-gas streams very different from those of the aerobic process considered in the current paper. However, the same approach might be used for developing the ethyl acetate recovery process.

Alternative option: Supplying pure oxygen to the fermenter

As microorganisms need only oxygen from the dry air supplied to the fermenter, an alternative approach would be to supply only pure oxygen such that the gas-to-liquid ratio in the fermentation would be much smaller. In the context of downstream processing (DSP), more ethyl acetate would be recovered from the liquid phase and less from the gas phase. However, an oxygen-rich gas stream would require additional safety measures. To compare the DSP performance when dry air or pure oxygen is supplied to the fermenter, the recovery processes were modified to recover ethyl acetate when pure oxygen is used upstream (cases 1, 2a and 2b were modified to cases 3, 4a and 4b, respectively) while keeping the same production capacity and O_2 supply per kg of liquid broth. As less exhaust gas is available when only oxygen is supplied upstream, the amount of ethyl acetate stripped by this gas is much smaller. Due to the much larger ethyl acetate concentration in the gas phase compared to the liquid phase, the needed gas flowrate is only slightly reduced (35,600 kg/h) while the required liquid flowrate is significantly increased (110,500 kg/h).

Key performance indicators for these processes are summarized in Table 4-8. The comparison with Table 4-6 suggests that supplying pure oxygen to the fermenter instead of dry air does not bring real benefits. In case 1, the initial separation of ethyl acetate from the gas feed is significantly more expensive than the initial separation from the liquid feed stream. In case 3, a large relative increase in the recovery costs from the liquid phase (due to the larger flowrates) is compensated by a small relative decrease in recovery costs from the gas phase. On the contrary, in cases 2a and 2b, the costs of the initial separation of ethyl acetate from the gas phase are not as dominant as in case 1. Thus, a slight relative decrease in these costs in cases 4a and 4b cannot compensate for a large relative increase in the costs of the initial separation of ethyl acetate from the liquid feed.

Table 4-8. Key performance indicators of the designed ethyl acetate recovery processes (oxygen supply to the fermenter)

	Case 3	**Case 4a**	**Case 4b**
Ethyl acetate recovery (%)	99.4	93.3	98.7
Economic indicators			
CAPEX (k$)	17,404	11,903	12,643
OPEX (k$/y)	9,098	5,381	5,668
OPEX ($/$kg_{EtAc}$)	0.914	0.574	0.573
TAC (k$/y)	10,839	6,571	6,932
TAC ($/$kg_{EtAc}$)	1.089	0.701	0.700
Sustainability metrics			
Thermal energy requirements ($kW_{th}h/kg_{EtAc}$)	3.491	1.128	1.069
Electrical energy requirements (kW_eh/kg_{EtAc})	2.464	0.943	1.003
Primary energy requirements ($kW_{th}h/kg_{EtAc}$)	9.652	3.485	3.576
CO_2 emissions (kg_{CO2}/kg_{EtAc})*	0.506 / 1.629	0.351 / 0.781	0.176 / 0.634
Water consumption (m^3_w/kg_{EtAc})	1.067	0.202	0.144
Water loss (m^3_w/kg_{EtAc})	0.077	0.015	0.011
Material intensity (kg_{waste}/kg_{EtAc})	0	0	0
Pollutant emissions ($kg_{pollutant}/kg_{EtAc}$)	0	0	0
Toxic emissions ($kg_{toxic\ material}/kg_{EtAc}$)	0	0	0

*green/grey electricity usage

4.2.5. Conclusion

The newly developed downstream processes were proven to efficiently recover ethyl acetate after the aerobic fermentation process. The initial separation of volatile products from the liquid broth may be performed using a hybrid combination of gas stripping and vacuum evaporation. This approach may allow recycling of the remaining liquid broth with the microorganisms upstream. The initial separation of ethyl acetate from the fermenter's off-gas may be performed using high-pressure cooling with less expensive chilled water or low-temperature atmospheric cooling with more expensive refrigeration. Following the initial recovery steps, an advanced azeotropic dividing-wall column was demonstrated to efficiently separate high-purity ethyl acetate product from water and ethanol. Finally, the total ethyl acetate purification process was proven to be more cost-effective (total recovery costs of 0.61 \$/kgEtAc compared to 1.09 \$/kg_{EtAc}) and less energy-intensive (total energy requirements of 2.20-2.40 $kW_{th}h/kg_{EtAc}$ compared to 9.98 $kW_{th}h/kg_{EtAc}$) when refrigeration is used for the initial separation from the gas feed stream. Thus, the results of this original study suggest that vapor ethyl acetate should be recovered directly from the atmospheric off-gas using low-temperature condensation. Moreover, even though more expensive, lower temperature condensation (refrigeration temperature of about -70 ˚C compared to -50 ˚C) is more favorable due to the higher ethyl acetate recovery (99% compared to 92%)

Moreover, downstream processing in case only pure oxygen is supplied to the fermenter instead of dry air is more expensive due to the slightly lower gas feed and much larger liquid feed. This increase is especially significant if refrigeration is used for the recovery of ethyl acetate from the gas phase due to the smaller contribution of these costs in the total recovery costs.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream processing for sustainable ethyl acetate production by fermentation, AIChE Journal. e18684 (2024) 1-18. https://doi.org/10.1002/aic.18684. This file contains numerical data from the key figures in the main manuscript text, additional details about the used property models, validation of the obtained results and the design of the recovery process when pure oxygen (instead of air) is supplied to the fermenter.

4.3. Recovery of 2-phenylethanol and 2-phenylethyl acetate

2-Phenylethanol (2PE) and 2-phenylethyl acetate (2PEAc) are valuable aroma compounds with growing market demands. As an alternative to conventional petrochemical production, more valuable natural forms of these chemicals can be obtained by biotransformation. Low product concentrations, resulting from significant product toxicity to microorganisms, and high boiling points of products complicate recovery process. In-situ product recovery by liquid-liquid extraction can be used to increase bioprocess yield and productivity. However, the subsequent purification of 2PE and 2PEAc is challenging due to the multiple phases, high-boiling temperatures of main products, occurrence of remaining substrate and by-products, and presence of microorganisms. The main goal of this original work is to improve the competitiveness of the biotechnological production of 2PE by using in-silico methods to develop an advanced industrial process for the final purification after centrifugation. An adaptable dividing-wall column was designed to remove 2PE with 2PEAc from organic phase or to esterify 2PE to pure 2PEAc. The production flexibility of the developed process allows adjustability to market demand. Additionally, recovery of co-produced ethanol from aqueous phase can increase the economic and environmental performance of the developed process. As confirmed by detailed techno-economic analysis, the proposed processes can cost-effectively (total recovery costs of 0.64-0.72 $/kg$_{2PE/2PEAc}$) and energy-efficiently (primary energy requirements of 1.83-2.05 $kW_{th}h/kg_{2PE/2PEAc}$) recovery of 2PE or 2PEAc after biotransformation. The developed process enhances economic and environmental viability of biotechnological 2PE production by reducing costs and energy requirements, while ensuring flexibility to adapt to market demands.

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4.3.1. Introduction

Nowadays, usage of fragrances has become widespread, with countless scents and aromas becoming an integral part of daily life. Among them, 2-phenylethanol (2PE) stands out as a valuable aromatic alcohol with a rose scent. It has a broad range of applications in various industries: food and beverage, cosmetics, perfumes, pharmaceuticals, etc. It is commonly added as an organoleptic enhancer in many food products (e.g. ice creams, puddings, chewing gums, cookies, candies, etc.), and often used in aroma therapy, production of antiseptics, preservatives, cleaning agents and personal care products [437]. Lastly, 2PE can be used to synthesize different valuable products (e.g. styrene, 2-phenylethyl acetate, phenylacetaldehyde, phenylacetic acid, diphenyl ether, etc.) [438]. Among these components, 2-phenylethyl acetate (2PEAc) is a valuable aroma component with a similar rose scent. Similarly to 2PE, 2PEAc is often used as a flavoring agent [439,440] in the production of perfumes, cosmetics, personal care products, fragrances, cleaning products, waxes, polishes, biocidal products [441].

Global production of 2PE has been continuously increasing (e.g. from 7,000 tonne in 1990 to 10,000 tonne in 2010) [442]. Its global market has been estimated to be more than 255 million $ in 2021, of which 130 M$ is the market for natural 2PE, with an expected annual growth of over 5.5% between 2022 and 2028 [443]. Currently, most of the 2PE is produced through three dominant petrochemical processes: Friedel-Craft reaction of ethylene oxide and benzene, catalytic reduction of styrene oxide, and oxidation of propylene with 2-phenylethyl hydroperoxide [442]. 2PEAc is usually produced from 2PE by esterification with acetic acid or by transesterification with acetate esters. Conventional processes for producing 2PE and 2PEAc depend on fossil hydrocarbon but lead to low prices, in the order of magnitude of 20-30 $/kg [442]. Alternatively, 2PE is currently extracted from the essential oils of different flowers (most often roses, but also jasmine, lilies, etc.). However, these processes are expensive (about 1,000 $/kg) and cannot satisfy market demand [444]. The high demand for 2PE in food, cosmetics and pharmaceuticals, leads to growing interest in natural production methods for these compounds. Depending on the specific regulatory definitions, the final products obtained through different biotechnological processes might be classified as of natural origin [437]. Consequently, production of 2PE by biotransformation has been a focus of research [437,442,444,445]. Many different pathways were studied, whereby yeast bioconversion of L-phenylalanine through the Ehrlich pathway is the dominant one [46,445,446]. Nonetheless, significant improvements are still needed to make bioprocesses economically attractive for large-scale production of this component.

Therefore, the main goal of this original research is to develop an advanced final purification process for the industrial-scale production of 2PE by biotransformation. As downstream processing costs often contribute substantially to the overall production costs and energy usage for specialty chemicals [31,447], the results of this study may significantly advance the development of viable industrial fermentative production of flavors and fragrances. Consequently, the proposed downstream process may reduce overall production costs for natural aroma compounds, making them more competitive with petrochemical alternatives.

4.3.2. Problem statement

A major drawback that hinders scale-up of 2PE bioconversion is product inhibition which results in low product concentrations (<1 wt%) [448]. Thus, an effective downstream process is crucial for the effectiveness of the whole bioprocess. *In-situ* product removal (ISPR) techniques have been actively studied to increase production yields. In that respect, *in-situ* liquid-liquid extraction has been especially effective [46]. This technique implies a multi-phase system in which the product is produced by microorganisms in an aqueous phase and simultaneously extracted into solvent. Consequently, the product concentration in the aqueous phase remains modest and inhibition effects may be mitigated [442]. Generally, this method has been widely used in flavor production due to its simplicity, scalability and reasonable costs [448]. However, this method has certain limitations, such as the need to select a solvent that is immiscible with water and non-toxic to microorganisms, as well as challenges in efficiently separating the desired product from the solvent. Alternative ISPR approaches include membrane-assisted solvent extraction, adsorption, solvent immobilization, and organophilic pervaporation [444]. Membrane-assisted solvent extraction can reduce the risk of emulsion formation, but membranes may be prone to fouling from broth components and are often custom-made, making them costly for large-scale applications [449,450]. Adsorption using hydrophobic resins ensures high product purity [451,452], but it may suffer from low adsorption capacity and potential interference from impurities in the fermentation broth. Solvent immobilization can mitigate solvent toxicity concerns but comes with increased costs and system complexity [444]. Organophilic pervaporation is another promising ISPR method but shares similar membrane-related challenges with membrane-assisted solvent extraction [448]. Considering its simplicity, scalability and potential for continuous operation, liquid-liquid extraction was chosen as the ISPR method in this work, with subsequent recovery steps designed accordingly. Solvents that have been investigated for the *in-situ* removal of 2PE by liquid-liquid extraction include oleic acid [45,453], oleyl alcohol, polypropylene glycol [46] and recently ionic liquids [47]. Due to its high

extraction power (partition coefficient >30 for 2PE), biocompatibility and safety, polypropylene glycol 1200 (PPG) has been suggested as a promising solvent to effectively remove 2PE and 2PEAc from the aqueous phase. A fed-batch process using PPG for *in-situ* product recovery resulted in 26.5 g/L 2PE and 6.1 g/L 2PEAc in the organic phase [46]. After ISPR by liquid-liquid extraction, additional downstream processing steps (solvent recovery and final product purification) are required to obtain high-purity 2PE product from the final bioreactor content [442]. To the best of our knowledge, this has not been addressed nearly as promptly as the metabolic engineering or design of the fermentation process with ISPR.

Therefore, the main goal of this original research is to develop an advanced final purification process for the industrial-scale production of 2-PE by biotransformation, using *in-silico* methods. As downstream processing costs often contribute substantially to the overall production costs and energy usage for specialty chemicals [31], the results of this study can significantly advance the development of viable industrial bioproduction of flavors and fragrances. Consequently, the proposed downstream process can reduce overall production costs for natural aroma compounds, making them more competitive with petrochemical alternatives.

4.3.3. Method of process design and simulation

Composition of feed streams for the final recovery process was determined based on reported experimental data [46] for a 30-hour fed-batch biotransformation process with ISPR using liquid-liquid extraction. *Kluyveromyces marxianus* CBS200 was employed to produce 2-PE and 2PEAc from L-phenylalanine (L-Phe) through biotransformation, while PPG was used as a solvent in the liquid-liquid extraction process [46]. The addition of the precursor (L-Phe) from the beginning and *in-situ* product removal resulted in high product-to-substrate molar yields of the biotransformation process: 0.82 mol_S/mol_{2PE} and $0.13 mol_S/mol_{2PEAc}$ [46]. Following the *in-situ* product recovery, centrifugation is needed to separate biomass, organic and aqueous phases before the final purification. The costs of this process were included in the techno-economic assessment of the solvent recovery and final purification processes. Furthermore, saturation of the organic phase with water and the aqueous phase with organic solvent was assumed. Thus, the composition of the organic phase is the following: 95.99 wt% PPG, 2.49 wt% 2PE, 0.94 wt% water and 0. 57 wt% 2PEAc. The composition of the aqueous feed stream is the following: 95.73 wt% water, 1.72 wt% ethanol, 0.96 wt% L-phenylalanine (L-Phe), 0.96 wt% PPG, 0.48 wt% glucose, 0.13 wt% carbon dioxide (CO_2) and 0.03 wt% 2PE. Even though ethanol and CO_2 were not reported in the organic phase, if present they will end up in the

top aqueous product from the distillation column and will not threaten product purity. Both liquid streams enter the final recovery section at 1 bar and 30 ˚C (fermentation conditions) and the mass ratio of aqueous phase to organic liquid is 1.62.

Distillation was chosen as the main recovery technique because it is already a mature separation technology that can be easily operated on an industrial scale. The primary focus was on 2PE recovery from the organic phase. However, the recovery of ethanol was also considered [154] due to its significant amount in the aqueous phase (about 18 g/L) [46]. Process intensification principles were implemented to improve the energy efficiency of the developed downstream process. Rigorous simulations for every process operation in the final purification process were developed in Aspen Plus. NRTL-HOC (Non-Random Two Liquid model with Hayden-O'Connell extension) was used to properly describe complex interactions between components [97]. Due to the substantial contribution of energy cost to the total recovery costs, the downstream process design was designed to minimize energy requirements (and consequently utility costs) in the total recovery process. The performance of the developed recovery process was evaluated by analyzing the economic and environmental impact following the published procedures [67,68]. Furthermore, to assess the performance of the total recovery process, centrifugation costs were roughly estimated from the market data [454] and published literature [67].

4.3.4. Results and discussion

This section contains details about process design, economic and sustainability assessments.

Process design

The part of the 2PE production process that was designed here is presented in Figure 4-18 by green dashed boxes. The flowsheets of 2PE and 2PEAc recovery from the organic phase are presented in Figure 4-19. The flowsheet of ethanol recovery from the aqueous phase is presented in Figure 4-22.

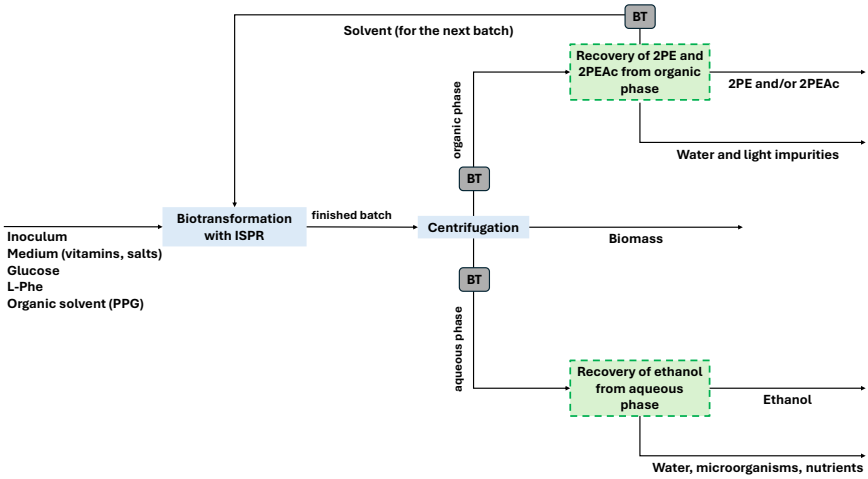


Figure 4-18. Block flow diagram of 2PE production process; the focus of this study is presented by green boxes with a dashed outline; ISPR stands for *in-situ* product recovery; BT stands for the buffer tanks

2-Phenylethanol recovery from the organic phase

The boiling points (at 1 bar) of components present in the organic phase after biotransformation are 100 ˚C for water, 219 ˚C for 2PE, 240 ˚C for 2PEAc [30] and >280 ˚C for PPG [455]. Thus, water, 2PE and 2PEAc can be evaporated from higher boiling PPG. However, both 2PE and 2PEAc form heterogeneous azeotropes with water (7.02 wt% 2PE and 92.98 wt% water, and 3.42 wt% 2PEAc and 96.58 wt% water) and liquid-liquid splitting should be coupled with distillation to obtain high-purity products. Due to the relatively high boiling temperatures, vacuum distillation was chosen to allow steam usage for heating reboilers and avoid any decomposition risks. Moreover, process intensification through a dividing-wall column (DWC) was implemented to decrease the energy requirements. Two alternatives were considered for recovering fermentation products from the organic phase. **Case 1** implies recovery of high-purity 2PE and 2PEAc as a byproduct. **Case 2** involves the esterification of 2PE with acetic acid to high-purity 2PEAc.

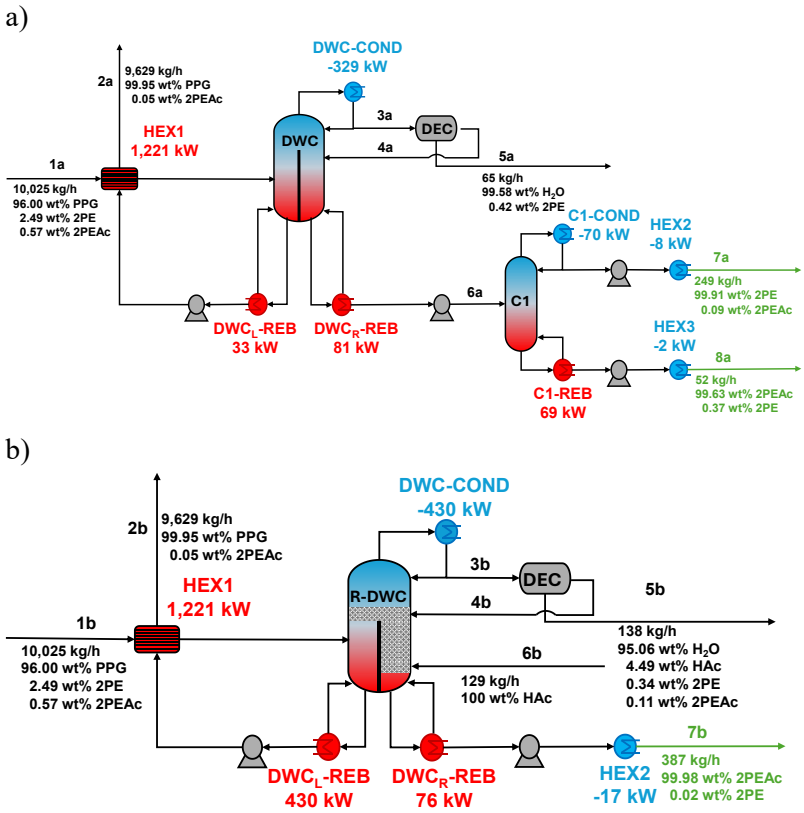


Figure 4-19. Process flowsheets of 2PE and 2PEAc recovery from the organic phase: a) case 1, b) case 2, abbreviations: 2PE – 2-phenylethanol, 2PEAc – 2-phenylethyl acetate, PPG – polypropylene glycol, H_2O – water

Both cases allow solvent recovery and reuse in the *in-situ* product recovery. The same DWC design may be used in both scenarios, with adjustments in case 2 (e.g. addition of catalyst and a feed stream for acetic acid). The process adaptability provides valuable flexibility and enables easy adjustments in response to market demand.

Case 1: Purification of 2-phenylethanol

To effectively separate 2PE and 2PEAc from PPG and water dissolved in PPG, a sequence of two distillation columns may be used. High-purity PPG can be obtained as a bottom product from the first column, while the second column may be used to separate the mixture of 2PE and 2PEAc (as the bottom product) from the remaining water (the top product). Additionally, liquid-liquid splitting of the top product in a decanter should be included to achieve concentrations of 2PE and 2PEAc beyond their azeotrope composition with water. Alternatively, these two columns may be merged into one thermodynamically equivalent dividing-wall column (DWC) with a common overhead and dividing bottom section (see Figure 4-20). This highly integrated configuration is built of one column shell, one condenser and two reboilers. Besides reducing equipment costs compared to the simple sequence of distillation columns, DWC can often improve the energy efficiency of the separation [115]. Since the DWC unit is not available off-the-shelf in Aspen Plus, it was simulated as a thermodynamically equivalent sequence of distillation columns (see Figure 4-20). DWC_L and DWC_R stand for the left and right sides of DWC. The top vapor from DWC_L goes to DWC_R, while part of the liquid flowing down in DWC_R is redirected to DWC_L to provide sufficient liquid flow in this side of DWC. DWC has 20 stages in total (in Aspen Plus, condenser and reboiler are the 1st and last stage, respectively), whereby the wall is placed at the bottom 15 stages (14 stages excluding reboiler). The operating pressure of 0.053 bar (in condenser) was selected to ensure that steam can be used in reboilers and cooling water in condenser. Structured packing type Mellapak 250X was chosen to minimize pressure drop (0.225 mbar per theoretical stage) in the column [110].

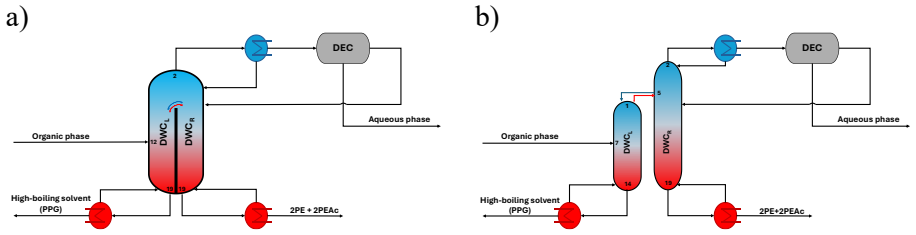


Figure 4-20. a) DWC and b) equivalent sequence of distillation columns

Finally, pure PPG (>99.9 wt%) is recovered as the bottom product from DWC_L and may be reused for in situ product recovery. The top product from DWC_R is sent to the decanter for phase splitting. The formed light phase, which may be used upstream, contains 99.6 wt% water and 0.4 wt% 2PE On the contrary, the heavy phase from the decanter is sent back to DWC_R. The bottom product of DWC_R is a mixture of 2PE and 2PEAc (82.7 and 17.3 wt%, respectively). An additional purification step in distillation column C1 (see Figure 4-19) is needed to recover high-purity 2PE (99.9 wt%) and 2PEAc (99.6 wt%) as top and bottom products. Additionally, as PPG needs to be cooled before being reused, it can preheat the feed stream to the DWC (HEX1 in Figure 4-19). This heat integration reduces the energy use for DWC by over 74%. Compared to the simple sequence of distillation columns, DWC implementation reduced energy requirements by about 28% (both options with heat integration). In total, about 1.388 $kW_{th}h/kg_{2PE/2PEAc}$ is needed to recover high-purity 2PE (99.9 wt%) and 2PEAc (99.6 wt%). Considering the biotransformation yields, and the product recoveries (99.9% for 2PE and 90.8% for 2PEAc), the total molar substrate-to-product yields would be 81.8% for 2PE and 13.6% for 2PEAc. Additionally, over 99.9% of PPG may be reused for *in-situ* product recovery.

Case 2: Esterification of 2-phenylethanol to 2-phenylethyl acetate

An alternative to recovering pure 2PE is to transform it into 2PEAc by esterification with acetic acid, according to reaction:

$$2PE + HAc \rightleftharpoons 2PEAc + H_2O.$$

Amberlyst 15 may effectively catalyze this reaction [456,457]. Kinetic data for the esterification and hydrolysis reactions were obtained from the literature [457] and adapted to the power law model used in Aspen Plus. The pre-exponential factors were expressed per kilogram of catalyst, while molarity was used as the basis for the rate expressions. The liquid phase was defined as the reactive phase. The kinetic parameters are provided in Table 4-9.

Table 4-9. Kinetic parameters of the esterification and hydrolysis reactions

Reaction type	Pre-exponential factor $((m^3)^2/(kmol\ kg_{cat}\ s))$	Activation energy (J/mol)
Esterification	0.147566	32,722.68
Hydrolysis	0.000331	49,292.68

The previously developed DWC was transformed into a reactive dividing-wall column (R-DWC) (see Figure 4-21). By integrating separation and reaction into a single equipment unit, reactive distillation offers major advantages over conventional technologies [458]. Similar to case 1, PPG is recovered as the bottom product from R-DWC$_L$. However, in this case, the esterification reaction is performed in R-DWC$_R$. The position of the acetic acid feed stage, reactive zone and catalyst amount were varied according to the literature recommendations [379] to ensure high purity 2PEAc product and minimize impurities in the water distillate stream. Finally, acetic acid is fed to the 17th stage of R-DWC$_R$, while the catalyst is placed from 3rd to 16th stage of R-DWC$_R$. As previously concluded, the reaction is kinetically controlled and large amounts of catalysts are needed to ensure sufficient conversion (>99%) [457]. Hence, 30 kg of catalyst is placed on stages 3rd – 5th and 20 kg on stages 6th – 16th, equal to 13% and 27% of the available volume per stage, respectively. Finally, high-purity 2PEAc (>99.9 wt%) is obtained as the bottom product from R-DWC$_R$. As in case 1, the top product from R-DWC$_R$ is sent to the decanter. The heavy phase is returned to R-DWC$_R$, while the light phase contains water (95.1 wt%) and acetic acid (4.5 wt%) with small amounts of remaining 2PE (0.3 wt%) and 2PEAc (0.1 wt%). As a worst-case scenario, it was assumed that this stream would be sent to the wastewater treatment and related costs are included. As in case 1, high-temperature PPG bottom product was used to preheat the feed stream to R-DWC (HEX1 in Figure 4-19) resulting in over 70% reduction in energy requirements. Thus, about 1.320 $kW_{th}h/kg_{2PEAc}$ is needed to esterify 2PE and recover high-purity 2PEAc (>99.9 wt%). Considering the previously mentioned biotransformation yields, and the total molar substrate-to-product (2PEAc) yield would be 96.7%. Furthermore, over 99.9% of PPG (99.9 wt%) may be reused in the biotransformation process. It should be noted that the origin of acetic acid and the type of catalyst used may determine if the obtained 2PEAc fulfills all the legalization norms to be labeled as 'natural'. Thus, additional expertise from the flavor legalization area would be needed to ensure that final products follow current legalization guidelines [459]. This is out of scope of our work which focuses on the technical development of the recovery process.

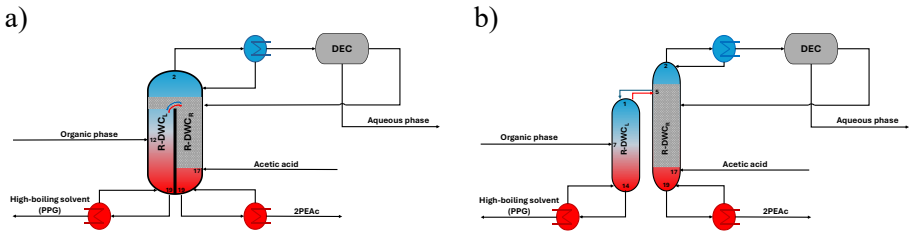


Figure 4-21. a) R-DWC and b) equivalent sequence of distillation columns

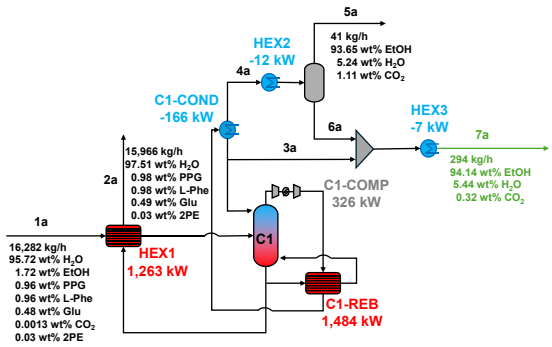
Ethanol recovery from the aqueous phase

In addition to 2PE recovery from the organic phase, we considered ethanol recovery from the aqueous phase. Ethanol is a bulk chemical with a market price significantly smaller than the ones of 2PE and 2PEAc (more than 100 times). Additionally, the production capacity of ethanol in this process is relatively small (about 2.3 ktonne/y). After centrifugation, the aqueous phase is commonly sent to wastewater treatment. Hence, if ethanol is not recovered, additional wastewater treatment costs would need to be paid for this stream. Furthermore, as this phase contains some valuable nutrients, ethanol separation may allow its reuse in the bioreactor. However, this requires additional testing before implementation. Thus, sending the aqueous phase after ethanol separation to wastewater treatment is considered as the worst-case scenario.

Ethanol forms a light homogeneous azeotrope with water (95.57 wt% ethanol and 4.43 wt% water, 78.15 ˚C at 1 bar). Hence, a simple distillation may separate the azeotropic mixture, while a more complex dehydration step is required to obtain a high-purity product. To compare these alternatives, two options were considered for the ethanol recovery: **Option A** – separation of hydrous (95 vol%) and **Option B** – separation of anhydrous ethanol (99.5 wt%).

In both cases, the initial separation of ethanol (with some water) from most of the aqueous phase is performed in distillation column C1 (Figure 4-22). The bottom product from this column contains most of the water (97.5 wt%), L-Phe (1.0 wt%), PPG (1.0 wt%) and glucose (0.5 wt%). This stream may heat the feed stream to column C1 (HEX1 in Figure 4-22) to reduce the reboiler duty by 44%. A partial vapor-liquid condenser was assumed for this column to remove the remaining CO_2. As some ethanol is separated with vapor distillate, cooling and simple phase splitting was designed to minimize ethanol loss. Condensed ethanol is mixed with liquid distillate from column C1 and makes the final hydrous ethanol product stream in option A (95.3 vol% ethanol, 4.4 vol% water and 0.3 vol% CO_2). On the contrary, the top product from column C1 in option B contains about 91 wt% ethanol as this concentration has been proven to minimize total energy requirements for the preconcentration and final purification steps in ethanol recovery [103]. Final purification was performed by extractive distillation with ethylene glycol (column C2 in Figure 4-22b) with a solvent-to-feed mass ratio of 1.2 [154]. High-purity ethanol product (99.5 wt%) is obtained as the distillate of column C2, while the ethylene glycol-water mixture is sent to the solvent recovery (column C4 in Figure 4-22b). Pure water (99.8 wt%) is separated as the top product of this column, while ethylene glycol (>99.9 wt%) is recovered as the bottom product and may be reused in the extractive distillation column C2.

a)



b)

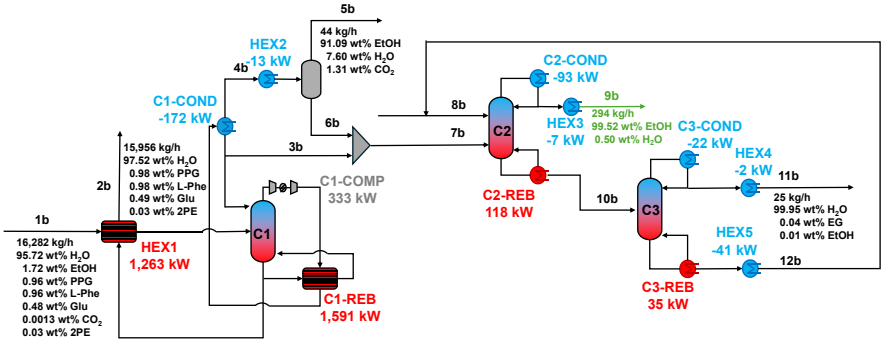


Figure 4-22. Process flowsheets of ethanol recovery from the aqueous phase: a) option A, b) option B, abbreviations: EtOH – ethanol, 2PE – 2-phenylethanol, 2PEAc – 2-phenylethyl acetate, PPG – polypropylene glycol, H_2O – water, EG – ethylene glycol, CO_2 – carbon dioxide, L-Phe – L-phenylalanine, Glu – glucose

Distillation columns C1, C2 and C3 operate at atmospheric pressure and sieve trays with a pressure drop of 8 mbar per tray were assumed [112]. Since the temperature difference between the top and the bottom of column C1 is not significant (about 20 ˚C), a mechanical vapor recompression (MVR) can be applied to reduce energy requirements. This heat pump system implies compressing the top vapor from the distillation column and using hot compressed vapor to evaporate the bottom liquid (instead of heating utility in the reboiler) [113]. Implementing the MVR system reduces the energy requirements of column C1 by over 78%. Another alternative is not to separate ethanol and to send the whole aqueous phase to the wastewater treatment. This option is referred to as **Option C** and is used in the economic analysis.

Techno-economic analysis

The total costs for separating ethanol from the aqueous phase are 0.604 $/kg$_{EtOH}$ when hydrous ethanol is recovered (Option A) or 0.851 $/kg$_{EtOH}$ when anhydrous ethanol is recovered (Option B). Comparing these costs with the market prices of hydrous and anhydrous ethanol (0.64 $/kg and 0.80 $/kg, respectively [460]), shows that only recovering hydrous ethanol from the aqueous stream (Option A) is marginally profitable. Further dehydration is more expensive due to the required capital and operating costs for two additional process steps (extractive distillation and solvent recovery) and the relatively small process scale for producing bulk chemicals such as ethanol. Since recovering hydrous ethanol may be only marginally profitable, further comparison of the total recovery costs in cases 1 and 2 is performed assuming that the whole aqueous stream is sent to the wastewater treatment (the worst-case scenario) and related costs are included. The results of the economic analysis are presented in Table 4-10 and Figure 4-23. For simplicity, the specific costs are expressed per kilogram of recovered 2PE and/or 2PEAc.

Thus, the total recovery costs when recovering 2PE as the main product and 2PEAc as a by-product (0.643 $/kg$_{2PE/2PEAc}$) are slightly lower compared to when esterification is performed and 2PEAc is recovered (0.728 $/kg$_{2PE/2PEAc}$). However, the total recovery costs make only a minor fraction of the market price of petrochemically produced 2PE and 2PEAc (about 22 and 28 $/kg, respectively [442]) in both cases. Hence, the choice of the main product should depend on the current market prices and demand for these chemicals.

Table 4-10. Key performance indicators in terms of economics and sustainability when recovering 2PE and 2PEAc (case 1) or 2PEAc (case 2) from the organic phase while sending the aqueous phase to the wastewater treatment*

	Case 1	**Case 2**
Products		
2PE (ktonne/y)	1.99	/
2PEAc (ktonne/y)	0.42	3.09
Economic indicators		
CAPEX (k$)	2,557	2,003
OPEX (k$/y)	1,295	2,049
TAC (k$/y)	1,551	2,250
TAC ($/kg$_{2PE/2PEAc}$)	0.643	0.728

*cost of centrifuge is included

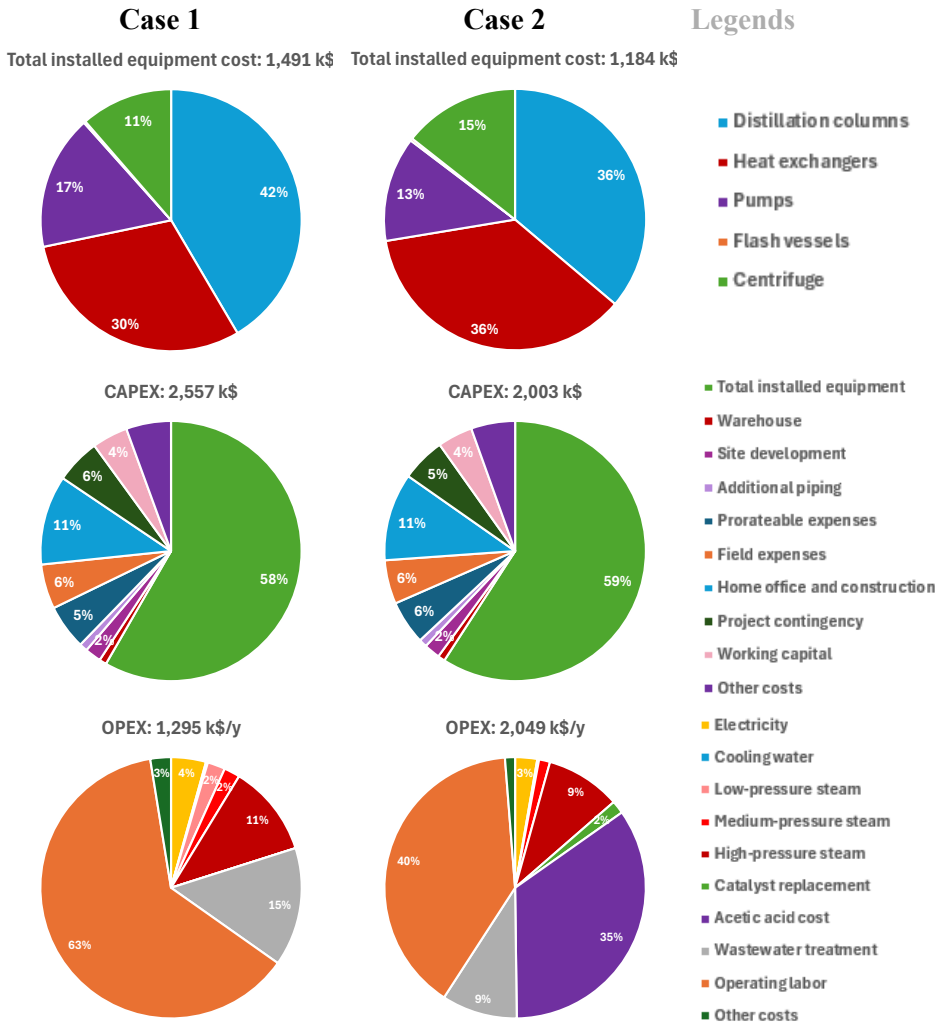


Figure 4-23. Economic indicators of the total downstream process when recovering 2PE and 2PEAc (case 1) or 2PEAc (case 2) from the organic phase while sending the aqueous phase to the wastewater treatment (centrifuge costs are included)

Sustainability assessment

The key sustainability metrics of the total recovery process in cases 1 and 2 when the whole aqueous stream is sent to the wastewater treatment are summarized in Table 4-11. Specific values presented in this section are expressed per kilogram of recovered 2PE and/or 2PEAc.

Table 4-11. Key performance indicators in terms of economics and sustainability when recovering 2PE and 2PEAc (case 1) or 2PEAc (case 2) from the organic phase while sending the aqueous phase to the wastewater treatment*

	Case 1	**Case 2**
Products		
2PE (ktonne/y)	1.99	/
2PEAc (ktonne/y)	0.42	3.09
Sustainability metrics		
Thermal energy requirements ($kW_{th}h/kg_{2PE/2PEAc}$)	1.374	1.310
Electrical energy requirements ($kW_eh/kg_{2PE/2PEAc}$)	0.271	0.211
Primary energy requirements ($kW_{th}h/kg_{2PE/2PEAc}$)	2.052	1.838
Water consumption ($m^3_w/kg_{2PE/2PEAc}$)	0.237	0.271
Water loss ($m^3_w/kg_{2PE/2PEAc}$)	0.018	0.020
CO_2 emissions, green electricity ($kg_{CO2}/kg_{2PE/2PEAc}$)	0.287	0.242
CO_2 emissions, grey electricity ($kg_{CO2}/kg_{2PE/2PEAc}$)	0.411	0.338
Material intensity ($kg_{waste}/kg_{2PE/2PEAc}$)	0	0
Wastewater intensity ($m^3_{ww}/kg_{2PE/2PEAc}$)	0.054	0.042
Pollutants and toxic materials ($kg_{pt}/kg_{2PE/2PEAc}$)	0	0

*cost of centrifuge is included

- ***Energy requirements***: The total energy requirements are slightly lower when 2PEAc is recovered (1.838 $kW_{th}h/kg_{2PE/2PEAc}$) compared to when 2PE and 2PEAc are recovered separately (2.052 $kW_{th}h/kg_{2PE/2PEAc}$). This is mainly due to the higher product flowrate. Thereby, thermal energy use contributes by 67-71% to the total energy requirements.
- ***Water consumption***: Water requirements and water loss are slightly lower if 2PE is valorized (0.237 and 0.018 $m^3_w/kg_{2PE/2PEAc}$, respectively) compared to when 2PEAc is recovered (0.271 and 0.020 $m^3_w/kg_{2PE/2PEAc}$).
- ***Greenhouse gas emissions***: CO_2 emissions are slightly higher when 2PE is recovered (0.411 $kg_{CO2}/kg_{2PE/2PEAc}$ if using grey electricity or 0.287 $kg_{CO2}/kg_{2PE/2PEAc}$ if using green electricity) compared to when 2PEAc is recovered (0.338 $kg_{CO2}/kg_{2PE/2PEAc}$ if using grey electricity or 0.242 $kg_{CO2}/kg_{2PE/2PEAc}$ if using green electricity).
- ***Material intensity***: Since waste is not formed in the developed processes, the values of these metrics are equal to zero. The wastewater streams are accounted for in the wastewater intensity metrics and are not included here.
- ***Wastewater intensity***: The wastewater intensity is mainly the result of treating the aqueous phase after centrifugation. This metric is slightly lower when

2PEAc is recovered due to a larger product flowrate (0.042 compared to 0.054 $m^3_{ww}/kg_{2PE/2PEAc}$).

- ***Pollutant and toxic materials***: Since pollutant and toxic materials are not formed in the developed recovery processes, the values of these metrics are zero.

Additional options

Note that this bioprocess [46] converts L-phenylalanine to 2PE while using glucose as a substrate for microbial growth. An alternative option would be *de-novo* fermentation from glucose which is less expensive than L-phenylalanine [461]. Furthermore, lignocellulosic biomass has been studied as a carbon source for 2PE fermentation [462]. Nonetheless, concentrations of the main products in the feed streams to downstream processing after *de-novo* fermentation with *in-situ* product removal are likely to be similar to the assumed ones. Therefore, the proposed process design may be easily adapted to different types of upstream production process. As ethanol recovery is hardly profitable, there is an incentive to minimize ethanol production during fermentation. That will not only save on glucose for fermentation but also 4 k$/y on aqueous waste treatment costs. Furthermore, even though PPG was used as the organic solvent, the developed processes may be altered if another high-boiling solvent is used (e.g. oleic acid). Higher concentrations of 2PE and 2PEAc in the organic phase would improve downstream processing performance (e.g. energy requirements would decrease by about 14% if product concentrations doubled). Nonetheless, this would complicate and increase the costs of the biotransformation process. Thus, an analysis covering both upstream and downstream processes is required to obtain the overall picture. The results of our work are a step forward and may give an indication of the cost-effectiveness and energy efficiency of the recovery process.

4.3.5. Conclusion

The novel adaptive downstream process proposed here can be successfully used for industrial recovery of 2-phenylethanol after biotransformation with *in-situ* product removal by liquid-liquid extraction and centrifugation. At the core of the downstream process is an integrated vacuum dividing-wall column that can effectively remove the high-boiling organic solvent (e.g. polypropylene glycol) and separate 2PE and 2PEAc product mixture from water, or perform an esterification reaction to obtain the pure 2PEAc. The developed final purification process can recover high-purity 2PE or 2PEAc products in a cost-effective way (total recovery costs of 0.643-0.728 $\$/kg_{2PE/2PEAc}$). Advanced process intensification, heat pump and heat integration systems resulted in energy-efficient recovery process (primary energy requirements of 1.838-2.052 $kW_{th}h/kg_{2PE/2PEAc}$). Furthermore, the adaptability of the developed process to recover either 2-phenylethanol or 2-phenylethyl acetate allows modifications in response to market demand. An additional profit may be obtained by recovering hydrous ethanol from the aqueous phase.

Additional information can be found in the *Supplementary Information* file accompanying the following publication: T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream processing for recovery of 2-phenylethanol and 2-phenylethyl acetate after biotransformation, Journal of Chemical Technology and Biotechnology, in press (2024). https://doi.org/10.1002/jctb.70027. This file contains details about determination of the feed compositions, design of distillation columns, and economic and sustainability analysis of the developed processes including separate analysis for recovery from the organic and aqueous phases.

4.4. Recovery of by-products after biomass pretreatment

This original research contributes to enhancing viability of biorefineries through recovering valuable by-products from the liquid remaining after the biomass pretreatment by hot liquid water. A novel downstream processing is developed for recovery of acetic acid, formic acid, furfural and 5-hydroxymethylfurfural (HMF) by enhanced distillation. The major challenge in this research is the processing of the highly diluted initial solution (>96wt% water) and thermodynamic limitations due to possible formations of several azeotropes. This new process recovers 78.7% of acetic acid (99.8 wt%), while the rest of it is recycled back to the biomass pretreatment step together with most of the separated water from the initial solution. Over 99.5% of formic acid, furfural and HMF are also recovered, at purities of 74.7 wt%, 98.0 wt% and 100 wt%, respectively. Vapor recompression and heat integration are implemented to decrease the energy use. The results demonstrate a 77.4% decrease in total annual costs (from 3.442 to 0.779 $/kg$_{product}$), 75.0% reduction in minimum average selling price (from 3.502 to 0.875 $/kg$_{product}$), 81.1% reduction in energy requirements (from 75.411 to 14.658 $kW_{th}h/kg_{product}$) and up to 99.7% decrease in CO_2 emissions (from 11.172 to 0.031 $kg_{CO2}/kg_{product}$).

This section was published as:
T. Janković, A.J.J. Straathof, A.A. Kiss, Turning waste into value: eco-efficient recovery of by-products from biomass pretreatment in lignocellulosic biorefineries, Biofuels, Bioproducts and Biorefining. 17 (2023) 1654-1667.

4.4.1. Introduction

First-generation biofuels are produced from biomass that can also be used in nutritional purposes. Therefore, even though technologies for their production are well-developed, their implementation directly competes with food production [12]. Conversely, feedstocks for the production of second-generation biofuels are cellulosic materials grown on non-agricultural land and different kinds of agricultural residues. Lignocellulosic biomass is a non-food crop that can be grown on land which is not suitable for food production [463]. Using it as a feedstock for the production of second-generation biofuels does not threaten the food supply chain. However, technologies for production of second-generation biofuels are still not well-established [21]. Significant improvements are needed to enhance economic viability of lignocellulosic biorefineries to make them competitive to fossil-based fuel production [113].

Lignocellulosic biomass is mainly composed of three polymers: 40-50% cellulose, 25-30% hemicellulose and 15-20% lignin [464], which are organized into a complex non-uniform matrix. Cellulose, the major constituent of lignocellulosic biomass, is a linear polymer of glucose [465]. Hemicellulose is composed of several different amorphous polysaccharides. It can easily be decomposed to different monosaccharides, such as xylose, arabinose, glucose, galactose and mannose. Unlike cellulose, hemicellulose chains are usually branches [464]. Lastly, lignin is a complex polymeric structure that provides sufficient strength and mechanical resistance to plant tissue [466]. It is mainly composed of three phenylpropane units: p-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol [467]. Due to the complex and diverse structure of lignocellulosic biomass, it is recalcitrant to enzymatic hydrolysis [468,469] and a pretreatment step is needed in order to enable conversion into fermentable sugars [470,471]. Since this step can significantly contribute to the total cost in biorefineries (up to 30-40%) [34], its enhancement has potential to drastically increase economic viability and competitiveness of biorefineries. One possible approach to this is to recover and valorize the by-products that are generated during the biomass pretreatment step (Figure 4-24). To the best of our knowledge, there are no designs proposed for the by-products recovery process in the literature. Thus, this study investigates in more detail the opportunity to enhance the lignocellulosic biorefineries by recovering valuable by-products after the biomass pretreatment.

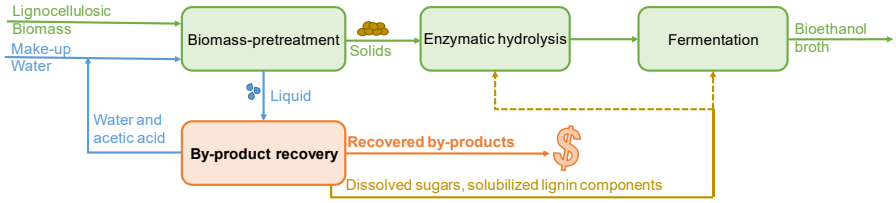


Figure 4-24. Simplified scheme of biomass pretreatment with by-product recovery (designing the by-product recovery process is the focus of this research study)

Numerous different methods have been proposed for treating lignocellulosic biomass before the enzymatic hydrolysis step [472]. These methods can be divided into physical pretreatments, chemical pretreatments, biological pretreatments, and their combinations. The limitation of physical pretreatment methods is high cost due to extensive energy usage. A common problem with chemical pretreatment methods is the usage of additional chemicals, which might facilitate the pretreatment step but can significantly complicate the downstream processing. Lastly, for biological pretreatment methods, which often result in low yield and long reaction time, more efficient processes need to be developed [473]. Due to the lack of additional chemicals, hot liquid water and steam explosion pretreatment methods are potentially eco-efficient solutions. The hot liquid water pretreatment method implies treating biomass with hot liquid water at temperatures between 160°C and 190°C in order to increase its digestibility [468]. During this process, water removes most of hemicellulose and part of the lignin, leaving cellulose more accessible for enzymatic hydrolysis. This biomass pretreatment process does not require additional catalysts, as hydronium ions, which are formed by auto-ionization of water, act as catalyst [472]. Pretreatment by steam explosion consists of short exposure biomass to high pressure and temperature, followed by rapid depressurization. The result is disruption of the biomass matrix that increases accessibility of cellulose for enzymatic hydrolysis [474,475]. Even though both described methods are proven to effectively pretreat lignocellulosic biomass, hot liquid water method offers several advantages compared to steam explosion: milder operating conditions, lower energy requirements since high-pressure steam does not have to be generated, reduced equipment complexity without need for high-pressure reactors, and absence of the risk of soluble lignin components precipitation [476-478]. Additionally, it offers possibility to recover and valorize generated by-products [479].

After pretreating biomass with hot liquid water method, the solid fraction is processed further in enzymatic hydrolysis and fermentation steps. The monosaccharides in the remaining liquid may also be fermentable, but due to the presence of by-product that act as fermentation inhibitors, the value of the

remaining liquid is relatively low. Therefore, the main focus of this research is downstream processing of this liquid, which might otherwise become a waste stream. The major challenge in the analyzed process is to recover the generated by-products from a very dilute solution remaining after the biomass pretreatment by hot liquid water [35]. Correspondingly, improved separation techniques need to be implemented in order to obtain by-product in forms that satisfy market purity requirements.

The original contribution of this research is novel process design for recovery of valuable by-products generated during industrial biomass pretreatment step. The proposed processing sequence, consisting of several distillation steps, is designed for large industrial operational scale. Advanced heat pumping and heat integration techniques are used to improve overall process performance. Acetic acid, formic acid, furfural and 5-hydroxymethylfurfural are recovered in forms that satisfy the market requirements. Implementing the results of this study at an industrial scale would not only eliminate expenses associated with disposing or treating the wastewater stream that remains after biomass pretreatment step, but also result in an additional profit since all the recovered by-products can be valorized on the market.

4.4.2. Problem statement

The main objective of this original research is to develop an optimal process design for recovery of generated by-products after hot liquid water pretreatment of poplar biomass. Poplar biomass has been widely studied for this pretreatment and can lead to a dilute solution (>96 wt% water) of different valuable by-products. Hydrolysis of acetyl groups in the hemicellulose chain results in the formation of acetic acid. Degradation of pentoses from hemicellulose, mainly xylose and arabinose, leads to the formation of furfural. On the other hand, 5-hydroxymethyl furfural (HMF) is a result of the degradation of hexoses, mainly glucose, galactose and mannose. Decomposition of furfural can result in the formation of formic acid, while decomposition of HMF can result in the formation of formic acid and levulinic acid. Besides being economically valuable, these components are known to inhibit fermentation reactions [480–482], as mentioned before. Accordingly, their removal offers a possibility to obtain higher bioethanol yields. In addition to mentioned components, the liquid remaining after the biomass pretreatment by hot liquid water might also contain dissolved sugars and different solubilized lignin components. The composition of this liquid, which is also the feed stream for the designed by-products recovery process, is taken from the experimental data reported by our research group [483] at TU Delft and presented in Table 4-12.

Table 4-12. Condition and composition of feed stream

Feed stream	
Temperature (°C)	99.7
Pressure (bar)	1.000
Mass flow (kg/h)	110,000
Mass fraction	
Water	0.9657
Acetic Acid	0.0175
Formic Acid	0.0043
Furfural	0.0030
HMF	0.0013
Levulinic acid	0.0001
High-boiling components	0.0083

There are several challenges for by-products recovery from the defined solution. Very dilute solution remaining after the biomass pretreatment step (>96 wt% water) complicates the recovery process. Additionally, the components present in the feed stream can potentially form three azeotropes: water-furfural, water-acetic acid-formic acid, and water- formic acid. Lastly, the separation of acetic acid from aqueous solution is complex due to the tangent pinch at high water concentrations [30]. Properties of the components present in the feed stream, as well as potential azeotropes are presented in Table 4-13.

Table 4-13. List of components and azeotropes (boiling points at 1 atm)

Pure components		Azeotropes		
Component	T_b (°C)	Component	Molar / mass fraction	T (°C) / type
Water	100.02	Water	0.9066 / 0.6454	97.79
Formic acid	100.55	Furfural	0.0934 / 0.3546	/heterogeneous
Acetic acid	118.01	Water	0.3607 / 0.1715	106.50
Furfural	161.70	Formic acid	0.4998 / 0.6073	/homogenous
Levulinic acid	256.98	Acetic acid	0.1395 / 0.2212	
HMF	281.85	Water	0.4566 / 0.2475	106.81
Glucose	343.85	Formic acid	0.5434 / 0.7525	/homogenous

4.4.3. Method of process design and simulation

Different methods have been studied in literature for recovery of the involved components from diluted solutions, such as precipitation, membrane separations, chromatography and liquid-liquid extraction. However, common drawbacks of these recovery methods are insufficiently high recovery yields and usage of additional chemicals, which complicates further processing. Additionally, scale-up is often not considered as research is only done at lab-scale [371]. Therefore, distillation is chosen as the main fluid separation technique for this process. Since it does not require additional chemicals, it can potentially present an eco-friendly solution with possibility to recover all generated by-products. To design recovery by distillation, rigorous simulations for every process operation are developed in Aspen Plus. Components present in the feed stream are specified according to the recommendations from the literature [484]. Since the initial solution contains different carboxylic acids, the thermodynamic properties are specified using NRTL property method coupled with Hayden-O'Connell correction model for vapor phase association [97].

Considering the thermodynamic properties of the components present in the feed stream, a specific order of separations is proposed. Due to the highly diluted initial solution used, it is necessary to concentrate it by separating as much water as possible. Since furfural forms a light heterogeneous azeotrope with water (Figure 4-25), furfural will be separated with water in the first separation step. The resulting water-furfural mixture is further treated by an additional distillation, while pure furfural can be recovered by simple liquid phase separation in a decanter due to the heterogeneity of the mixture. From the remaining components, the lowest boiling points are ones of formic acid and acetic acid. Recovery of these components from the aqueous mixture is complex due to the presence of four distillation regions (Figure 4-25) and the possible formation of two azeotropes (water-acetic acid-formic acid, and water-formic acid). Since the concentration of acetic acid in the feed stream is the highest of all by-products, its recovery is crucial. Therefore, in order to avoid the separation of formic acid, together with acetic acid and most of the remaining water, the next distillation step is performed at a temperature below the one required for the formation of the ternary azeotrope. Additional purification of the separated water-acetic acid mixture is required to obtain high-purity acetic acid, but this step is rather complex due to the tangent pinch at high water concentrations. The remaining stream after the separation of acetic acid and most of the water contains mainly formic acid and heavier components. Due to the large temperature difference, formic acid, with small amounts of remaining acetic acid and water, can easily be separated from HMF and other heavier components by distillation. If needed, this mixture can further be treated to obtain high-purity formic acid. In the final distillation

step, HMF is separated from the dissolved sugars and solubilized lignin components, which can be sent to enzymatic hydrolysis or fermentation depending on the state of hydrolysis of the present sugars.

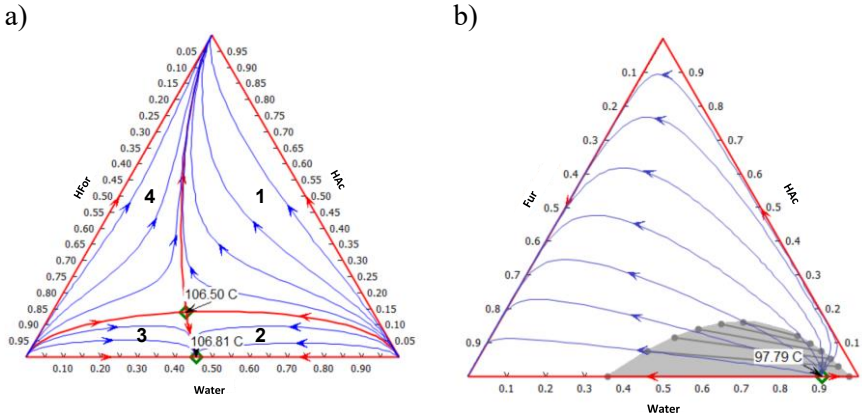


Figure 4-25. a) Residue curve map for system water – formic acid (HFor) – acetic acid (HAc) and b) Ternary diagram for system water – furfural (Fur) – acetic acid (HAc), mole basis

4.4.4. Results and discussion

This section provides key information on process design and simulation, as well as techno-economic and sustainability analyses.

Process design

This section focuses on the optimal design for recovery of valuable by-products generated by the pretreatment of poplar biomass by hot liquid water. The processing capacity is designed for an industrial level application, assuming 8,000 operating hours per year. Recovered by-products are acetic acid, formic acid, furfural and HMF, and all of them are obtained in forms that can be valorized in the market.

The proposed process (Figure 4-26) is composed of seven distillation columns and one decanter. The first step is to separate the water-furfural light heterogeneous azeotrope as a top product in column C1. High-purity furfural product is obtained by additional distillation in column C2 and phase separation in decanter DEC1. The proposed sequence results in 100% furfural recovery, while the purity of the obtained product is 98.0 wt%. The bottom product from column C2 is water, which is not a waste stream since it can be recycled to the biomass pretreatment step. Even after the separation of the water-furfural azeotrope, the remaining solution is still very dilute and the next step is to concentrate it in column C3. The top product of this column is mostly water, with

0.6wt% of acetic acid. About 15.9% of the initially present acetic acid is separated together with water. This stream can be recycled to the biomass pretreatment step, as diluted acetic acid can increase the digestibility of biomass by providing the mild-low pH required for the pretreatment step [483,485–487]. Furthermore, recycling acetic acid to the pretreatment step leads to the enhancement of this step without using any additional chemicals. The effects of recycling this stream with diluted acetic acid is out-of-scope of this research, but it is proposed based on published results proving that this procedure does improve the outcome of the pretreatment step [483]. However, the accumulation of acetic acid might also increase degradation in this step. Therefore, an additional experimental investigation would be needed before the implementation of the proposed recycling to a real industrial-scale biorefinery. The bottom product of column C3 is a less diluted solution of all components present in the feed stream, except furfural. This stream is further distilled in column C4. Acetic acid, together with most of the remaining water, is separated as top product. To obtain high-purity acetic acid, additional purification in column C5 is needed. In this way, 78.6% of initially present acetic acid is recovered as bottom product stream, at a purity of 99.8 wt%. Approximately 3.2% of acetic acid from the feed stream is separated with water as top product of this column. This stream contains less than 0.2 wt% acetic acid and can also be recycled to the biomass pretreatment step. Bottom product from column C4 is mainly composed of formic acid and heavier components. The next step is to separate formic acid, with small amounts of remaining acetic acid and water, as top product in column C6. In this way, about 99.5% of formic acid is recovered in a stream that contains 74.7 wt% formic acid. Such composition (distillation area 3 in Figure 4-25a) disables the high recovery of pure formic acid by simple distillation due to the formation of the water-formic acid azeotrope. Additional purification of this stream might not be necessary as there are already applications [488] and hence a market for 70 wt% formic acid solution. Alternatively, one potential solution is to apply reactive distillation with methanol, to overcome thermodynamic constrains of azeotrope formation and recover the formic acid as methyl formate [489]. The last separation is the recovery of HMF from other heavy components in column C7. With a recovery of about 99.9%, HMF is obtained as 100 wt% top product of this column. The bottom product is composed of the remaining heavy components, mainly dissolved sugars and solubilized lignin components. Depending on the degree of hydrolysis, this stream can be sent either to the enzymatic hydrolysis or to the fermentation step.

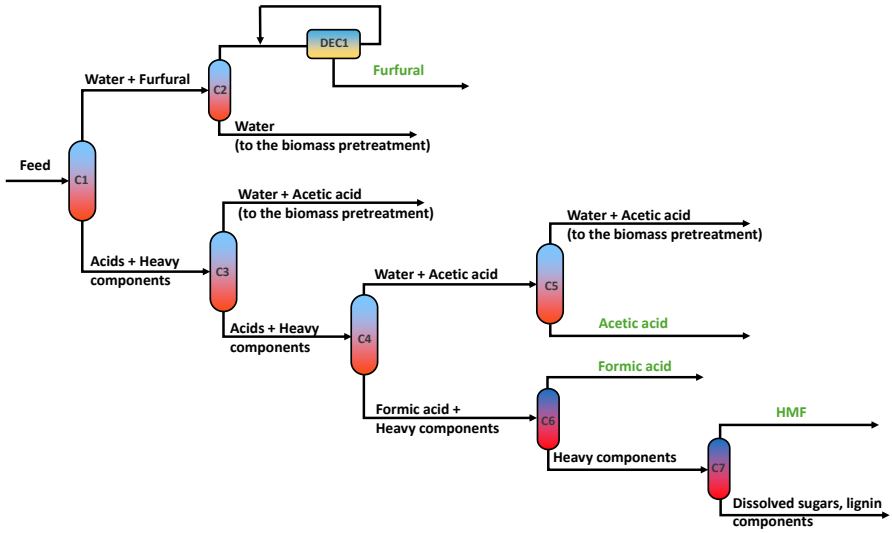


Figure 4-26. Conceptual design of the by-product recovery process

Summing up, this fluid separation process recovers acetic acid, formic acid, furfural and HMF in forms that satisfy market requirements in terms of purity. Notably, maximal amounts of all the generated by-products are achieved and nothing is wasted. The non-product streams containing mostly water, with small fraction of acetic acid, can be recycled to the biomass pretreatment step. Additionally, the stream with dissolved sugars and solubilized lignin components might still be useful within the bioethanol production process, although this needs testing. In a state-of-the art process, without by-products recovery, the fermentable components present in this stream might be wasted and not used for biofuel production. Therefore, this original recovery process adds value, without producing any additional waste stream.

Design of the distillation sequence

Seven distillation columns are needed for the described by-products recovery process. Due to the highly diluted feed stream, it is necessary to evaporate large amounts of water. Consequently, columns C1, C3, C4 and C5 have relatively large number of stages and high reboiler duties. On the other hand, these columns are separating close boiling components, which offers an excellent opportunity to use heat pumps [113]. More precisely, mechanical vapor recompression (MVR) can be implemented on these columns to decrease their primary energy use. This solution implies compressing the top vapor from the column and then using it to evaporate the bottom liquid.

However, in order to obtain an optimal heat exchange between the compressed top vapor and the bottom liquid, an appropriate pressure ratio for compressor discharge has to be chosen [490]. In order to achieve a larger pressure ratio, a higher compressor duty is needed. This results in increase in both equipment costs, due to need for larger compressors, and operating costs, due to higher electricity usage. Conversely, a larger pressure ratio means a higher log-mean temperature difference (LMTD) in the reboiler, thus a lower 1/LMTD. Therefore, since the driving force for the heat exchange is higher, a smaller heat exchange area of the reboiler is needed. Furthermore, some physical constraints have to be taken into account when defining a pressure ratio of a compressor. Firstly, the discharge temperature of compressed vapor must not exceed a certain limit due to safety reasons. Secondly, the LMTD for the reboiler has to be above a certain value in order to insure an efficient heat exchange. The schematic representation of the MVR system, as well as the dependence of compressor duty and (LMTD) of reboiler on the pressure ratio of a compressor are given in Figure 4-27.

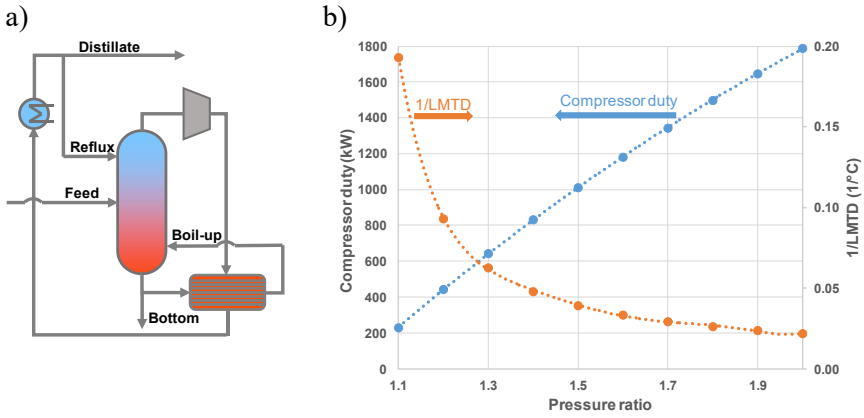


Figure 4-27. a) MVR heat pump design; b) Dependence of the compressor duty and LMTD on the pressure ratio

In the proposed optimal recovery process, MVR is applied to columns C1, C3, C4 and C5. Thus, the total need for utility usage is drastically decreased, which results in reduction of the operating cost, energy requirements and CO_2 emission, making the whole process more sustainable. MVR is not implemented on column C2, which has a relatively low reboiler duty. Additional cost for the compressor for this column would be greater than the savings due to the decreased usage of external heating and cooling. MVR is also not applied to columns C6 and C7, which, apart from having low reboiler duties, also separate far-boiling components.

Columns C1, C2, C3, C4 and C5 are operated at atmospheric pressure. Sieve trays are with a pressure drop of 8 mbar per stage are assumed for these distillation columns [112]. However, in order to avoid thermal degradation, it is preferable for columns C6 and C7 to be operated at lower pressures. The operating conditions are chosen in such a way that it is possible to use cooling water for the condensing top vapor and steam for the evaporating bottom liquid in these columns. In this way, the requirement for more expensive utilities is avoided. Structured packing type Sulzer Mellapak 250, with a pressure drop of 0.225 mbar per theoretical stage, is assumed for internals for these columns [110]. All the associated costs due to the usage of vacuum pumps are included in the economic assessment.

Apart from implementing MVR, it is possible to obtain additional energy savings by using heat integration, or other process intensification options for fluid separations [491], such as cyclic distillation [492]. In the proposed by-product recovery process, heat integration is implemented by using the heat content of the top product from column C4 to evaporate the bottom liquid from column C2. In this way, the need for external heating and cooling is decreased even more, resulting in lower total energy requirements, CO_2 emission and operating costs. The complete flowsheet with implemented MVR and heat integration is presented in Figure 4-28, along with key design and operation parameters.

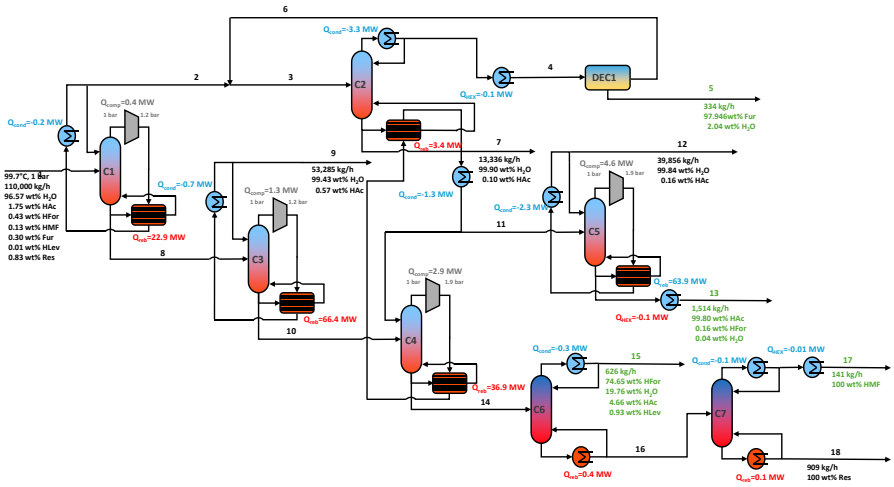


Figure 4-28. By-products recovery process flowsheet (H_2O – water, HAc – acetic acid, HFor – formic acid, Fur – furfural, HMF – 5-hydroxymethyl furfural, HLev – levulinic acid, Res – heavy components, mostly dissolved sugars and solubilized lignin)

Techno-economic analysis

A comparison of different project costs before and after the implementation of MVR and heat integration is presented in Table 4-14. The total cost for installing all equipment units for the base case process is 13,288 k$, whereby about 63% is the cost for the distillation columns (shells and internals), 36% is the cost for the heat exchangers and 1% is the cost for the decanter and pumps. However, the total equipment cost for the enhanced process is 33,274 k$. This increase in the total equipment cost after the implementation of MVR and heat integration is mainly due to the use of four compressors. As much as 60% of the total equipment cost for the enhanced process is the cost for compressors, while 25% is the cost for the distillation columns (shells and internals), 15% for heat exchangers and less than 1% for decanter and pumps. The distribution of the costs for specific types of equipment for the enhanced case process is presented in Figure 4-29.

Cost contributions are shown in Figure 4-29. The CAPEX calculated in this way equals 24,001 k$ for the base case process and 61,235 k$ for the enhanced process. The increase in the total equipment cost after implementing MVR and heat integration is the main reason for the increase in CAPEX by about 155.1%.

Total OPEX of the base case process are 69,616 k$/y, while being only 10,166 k$/y for the enhanced process. This drastic decrease of about 85.4% in the total OPEX is a result of implementing MVR and heat integration. More precisely, the maximized recovery of heat contained in the process results in the minimization of requirements for external heating or cooling. Therefore, the much lower utility requirements lead to a lower OPEX.

In the base case process, by far the largest part of the OPEX (about 94%) is the cost for low-pressure steam, which is used to evaporate bottom liquid from columns C1-C5. After the implementation of MVR, the need for external heating for columns C1, C3, C4 and C5 is avoided. By integrating the top stream from column C4 and bottom stream from column C2, there is also no need for external heating for column C2. Hence, after enhancing the base case process, the use of low-pressure steam is completely avoided. The requirements for external cooling for these columns are also minimized. The distribution of costs for specific parts of OPEX for the enhanced process is presented in Figure 4-29. Due to the use of four compressors, OPEX is mainly determined by the cost of electricity (72%). The total operating labor cost is also significant (16%), while the other parts of OPEX have a lower share.

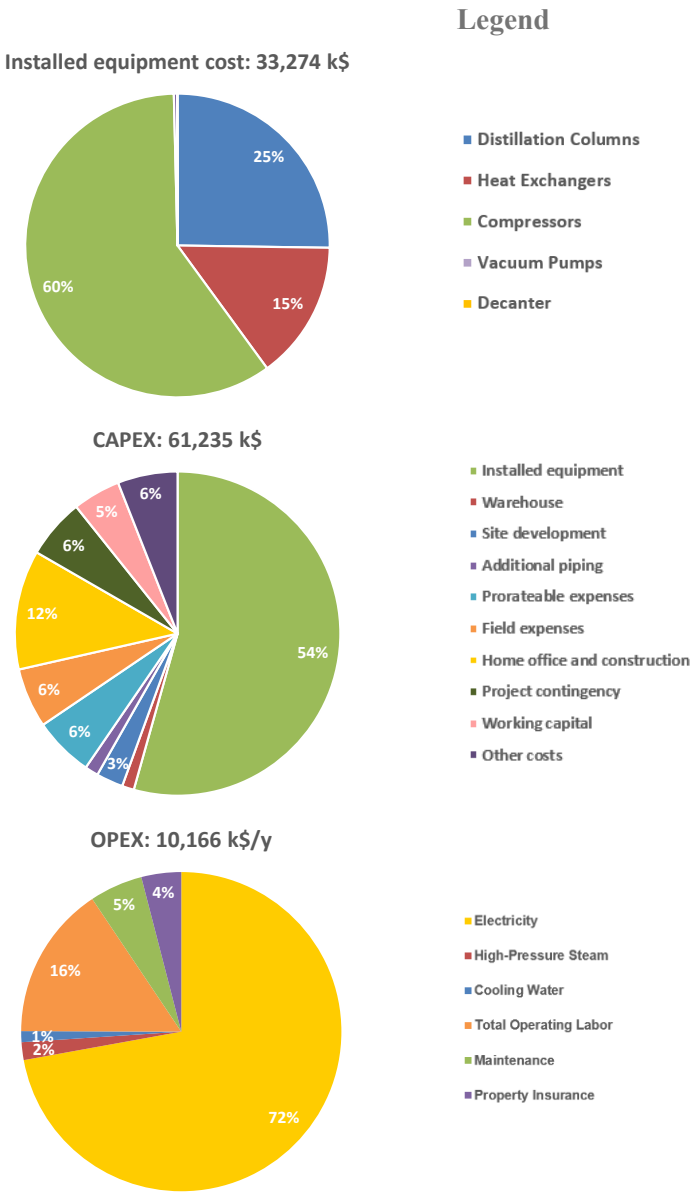


Figure 4-29. Cost contribution to the installed equipment cost, CAPEX, and OPEX.

Total annual costs (TAC) were calculated using 10 years of payback time. The value of TAC for the base case process is equal to 72,016 k$/y, while for the enhanced process this cost is reduced to 16,289 k$/y. Since OPEX is dominant over CAPEX in the calculation of TAC, even though CAPEX is increased after the implementation of MVR and heat integration, significant reduction in OPEX results in about 77.4% decrease in TAC.

The benefits of applying MVR and heat integration are even more obvious if the costs are expressed per kg product as a basis. The OPEX and TAC per kilogram of product are 3.33 and 3.44 $/kg$_{product,}$ respectively for the base case process and only 0.49 and 0.78 $/kg$_{product}$ for the enhanced process. Therefore, the implementation of MVR and heat integration significantly lowers the total costs, resulting in a better economic viability of the process.

Table 4-14. Key economic indicators of recovery of by-products from biomass pretreatment

Economic indicators	**Base Case Process**	**Enhanced Process**	**Reduction (%)**
CAPEX (k$)	24,001	61,235	n/a
OPEX (k$/y)	69,616	10,166	85.4
OPEX ($/kg$_{product}$)	3.33	0.49	
TAC (k$/y)	72,016	16,289	77.4
TAC ($/kg$_{product}$)	3.44	0.78	
MASP ($/kg$_{product}$)	3.50	0.87	75.0

In addition to the cost estimation, the minimum average selling price (MASP) of recovered products both for the base case process and for the enhanced process was determined. Obtained values are compared to the weighted average price that can be realized on the market (1.07 $/kg). The calculated MASP for the base case is 3.50 $/kg which is much higher than the average market selling price, leading to an unprofitable process. On the other hand, the implementation of MVR and heat integration decreased a MASP by about 75.0%, to a competitive value of 0.87 $/kg. In order to evaluate the obtained MASP, a comparison with previously reported values is performed. Literature MASP is calculated using minimum selling prices for specific products reported in the literature and production capacity analysed in this research study [493–495]. A MASP value of 1.06 $/kg$_{product}$ is obtained by this procedure. Therefore, the proposed novel recovery process is highly competitive and presents an economically viable and profitable process.

Sensitivity analysis: Influence of different cost contributors to the minimum average selling price

Since cost and MASP estimation are subject to uncertainty [67], sensitivity analysis is performed to further investigate the profitability of the proposed process design. The influence of changes in different cost contributors on the MASP is given in Figure 4-30.

The purchase cost of the equipment has the highest impact on the MASP, whereby with about 50% increase in the equipment cost the MASP becomes higher than the average market selling price (assuming that the average market selling price does not change). The second highest impact on the MASP is that of the electricity. The analyzed process would still be profitable up to an increase of almost 60% in the electricity cost. The impact of the total labor cost on the MASP is significantly lower and even with a 100% increase in labor costs the process is still profitable. Lastly, the costs of cooling water and high-pressure steam have extremely small impact on the MASP. This is due to the low cost of cooling water relative to the cost of other utilities and the low consumption of high-pressure steam.

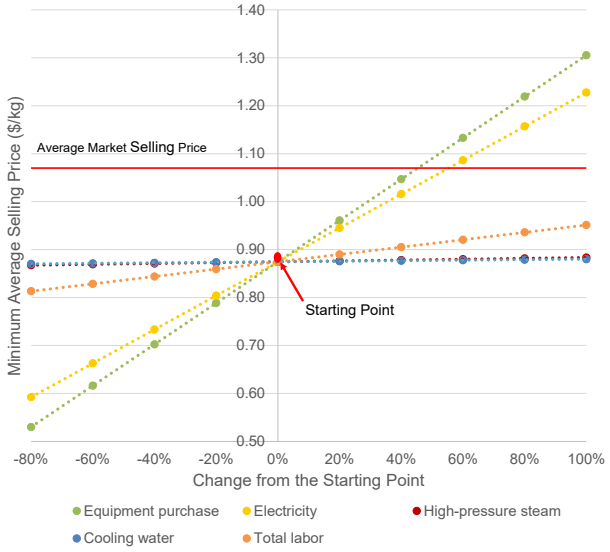


Figure 4-30. Sensitivity analysis of the minimum average selling price if costs of a particular item decrease or increase

Moreover, an additional analysis showed that the MASP is lower than the average market selling price even if concentration of acetic acid in the feed stream reduces from 1.75 to only 1wt%. However, an increase in acetic acid concentration in the feed stream would result in a more profitable process.

Sustainability metrics

The key sustainability metrics of the developed processes are summarized in Table 4-15.

Table 4-15. Key sustainability metrics of recovery of by-products from biomas pretreatment

Sustainability metrics	**Base Case Process**	**Enhanced Process**	**Reduction (%)**
Thermal energy requirements ($kW_{th}h/kg_{product}$)	77.411	0.170	99.8
Electrical energy requirements ($kW_eh/kg_{product}$)	n/a	5.795	n/a
Primary energy requirements ($kW_{th}h/kg_{product}$)	77.411	14.658	81.1
Material intensity ($kg_{waste}/kg_{product}$)	0	0	0
Fresh water requirements ($m_w^3/kg_{product}$)	13.440	0.728	94.6
Fresh water loss ($m_w^3/kg_{product}$)	0.994	0.051	94.9
CO_2 emissions ($kg_{CO2}/kg_{product}$)	11.172	3.062/ 0.031*	72.6/ 99.7*
Toxic emissions ($kg_{toxic\ material}/kg_{product}$)	0	0	0
Pollutant emissions ($kg_{pollutant}/kg_{product}$)	0	0	0

*electricity from non-renewable sources/green electricity

- ***Energy intensity:*** Thermal energy requirement for the base case is 77.41 $kW_{th}h/kg_{product}$, while for the enhanced process it is 0.17 $kW_{th}h/kg_{product}$. The drastic reduction of about 99.8% is due to decreased need for external heating after the implementation of MVR and heat integration. The electrical energy requirement for the base case process is negligible, but for the enhanced case it is 5.80 $kW_eh/kg_{product}$ (as a result of the compressors usage). For the calculation of the total energy requirements an electric to thermal conversion factor of 2.5 is used to take into account the inefficiencies in power generation [116,117]. As a result, the total energy requirement of 14.66 $kW_{th}h/kg_{product}$ for the enhanced case process is much lower than 77.41 $kW_{th}h/kg_{product}$ for the base case process. Hence, the implementation of MVR and heat integration results in about 81.1% total energy savings.
- ***Material intensity:*** Since both the base case and the enhanced case have same inputs and outputs, there is no difference in material intensity. The only input is the feed stream, with a flowrate of 110,000 kg/h. The outputs are: acetic acid (1,514.5 kg/h), furfural (333.8 kg/h), formic acid (626.0 kg/h), HMF (141.1 kg/h), three streams containing water and small amounts of acetic acid (106,475.5 kg/h in total) and a stream with dissolved sugars (909.1 kg/h); being in total 110,000 kg/h. Therefore, there is no waste produced and material intensity is equal to zero.

- ***Water consumption**:* Since the total (condenser) cooling duties for the base case and the enhanced process are -203.3 and -11.1 MW_{th} respectively, the required water flowrates are 35,000 and 1,904 m_w^3/h, respectively. Expressed per kilogram of product as basis, the amount of used cooling water is 13.3 $m_w^3/kg_{product}$ in the base case and 0.73 $m_w^3/kg_{product}$ in the enhanced process. Losses of cooling water caused by evaporation must be compensated by fresh water. According to the calculation methodology [68], about 7% of cooling water is lost. Thus, the amount of lost water is 2,450 m_w^3/h for the base case and only 133 m_w^3/h for the enhanced case. Additionally, about 70% of steam condensate recovery is assumed to include potential steam leaks, condensate losses, steam trap failures and other possible inefficiencies in the steam generation and usage [126]. Taking this into account, the total fresh water requirements are 13.44 and 0.73 $m_w^3/kg_{product}$ for the base case and the enhanced process respectively. Therefore, apart from drastically decreasing the energy requirements, the use of MVR and heat integration also results in 94.6% reduction in water consumption. Additionally, the total specific loss of fresh water is decreased by about 94.9%, from 0.99 to only 0.05 $m_w^3/kg_{product}$.
- ***Greenhouse gas emission***: Since the usage of electricity in the base case process is negligible compared to the thermal energy requirements, the CO_2 emission in this case is 11.17 $kg_{CO2}/kg_{product}$ regardless of the electricity source. After the implementation of MVR and heat integration, the usage of electricity becomes significant due to the compressors needed for the MVR heat pump systems. Therefore, the source of electricity notably affects the CO_2 emission. If grey electricity (sourced from fossil fuels) is used for supplying power to compressors, the CO_2 emission is reduced to 3.06 $kg_{CO2}/kg_{product}$ (72.6% savings relative to the base case). However, if green electricity is used, the total emission of CO_2 is only 0.03 $kg_{CO2}/kg_{product}$ (99.7% savings relative to the base case).
- ***Toxic materials and pollutants***: Since the designed process does not emit toxic materials or pollutants, the metrics describing these factors are equal to zero.

A comparison of analyzed sustainability metrics before and after implementing MVR and heat integration is given in Table 4-14. Material intensity, toxic emission and pollutant emission indicators are the same for both the base case process and the enhanced one since no waste, toxic materials or pollutants are produced. However, enhancing the base process leads to a drastic decrease in energy requirements, water consumption and CO_2 emissions. This is the result of changing the initial process flowsheet in a way that maximizes the usage of energy already contained in the process and that minimizes the usage of external energy sources. Consequently, the obtained result is more environmentally friendly process design.

4.4.5. Conclusion

The novelty of this original research has been proven by a feasible optimal process design for the recovery of valuable by-products from the liquid remaining after the hot liquid water pretreatment of lignocellulosic biomass. The newly designed process can recover acetic acid, formic acid, furfural and HMF in forms that can be valorized on the market. Improved separation methods have to be used in order to recover these components from a very dilute initial solution (>96 wt% water) and overcome thermodynamic limitations due to the possible formation of three azeotropes (water-furfural, water-acetic acid-formic acid and water-formic acid), as well as the tangent pinch in water-acetic acid mixtures. About 78.6% of acetic acid is recovered as the high-purity product stream (99.8 wt%), while the rest of it is in the forms of diluted aqueous solutions that can be recycled to the biomass pretreatment step to increase biomass digestibility. Recoveries of all the other components are higher than 99.5%, whereby the purities of the product streams are 74.7 wt% for formic acid, 98.0 wt% for furfural and 100 wt% for HMF. This process does not have any waste streams, as the separated water can be recycled back to the biomass pretreatment step, while the dissolved sugars and solubilized lignin components may be kept in the bioethanol production process.

In order to get a more environmentally friendly process by decreasing energy use, MVR and heat integration were successfully applied. The main results of this enhancement are: 155.1% increase in CAPEX (from 24,001 to 61,235 k$), 85.4% reduction in OPEX (from 3.33 to 0.49 $/kg$_{product}$), 77.4% reduction in TAC (from 3.44 to 0.78 $/kg$_{product}$), with a payback time of 10 years, about 75.0% reduction in MASP (from 3.50 to 0.87 $/kg$_{product}$), 81.1% reduction in the primary energy requirements (from 77.41 to 14.66 $kW_{th}h/kg_{product}$), 94.6% reduction in fresh water requirements (from 13.44 to 0.73 $m_w^3/kg_{product}$), 72.6% reduction in CO_2 emission if grey electricity is used (from 11.17 to 3.06 $kg_{CO2}/kg_{product}$) or 99.7% reduction in the CO_2 emission if green electricity is used (from 11.17 to 0.03 $kg_{CO2}/kg_{product}$). Hence, the implementation of MVR and heat integration drastically increases the economic viability and sustainability of the proposed process, despite an initially larger CAPEX requirement.

4.5. Versatility of distillation in downstream processing

Distillation is a physical process that relies on differences in boiling points or relative volatilities to separate and purify components in a liquid mixture. It is believed that distillation was initially used to produce alcoholic beverages and concentrate essential oils from natural products in China around 800 BC [496]. Over the centuries, distillation has developed into a widely utilized separation method and remains the most commonly applied technique at an industrial scale today [170]. Despite having a dominant role in the chemical industry, it has traditionally not been considered a crucial separation technique in biotechnology [497], largely due to key challenges associated with downstream processing after fermentation. These include:

- *Dilute streams*: Bio-based reactions typically occur at low product and substrate concentrations to minimize inhibitory effects. As a result, bioreactor effluent is usually highly diluted [497]. Achieving industrially relevant production capacities under these conditions requires significant water throughput, which leads to high capital costs (due to the need for large equipment) and elevated operating costs (due to the high energy demands) [27].
- *Low product concentrations*: End-product inhibition is a persistent challenge in many fermentation processes, leading to relatively low achievable product concentrations [27]. As a result, downstream processing can become energy-intensive.
- *Formation of by-products and presence of impurities*: As a result of microbial metabolism, the formation of by-products is common in many bioprocesses. Furthermore, renewable feedstocks are typically less pure than the starting materials used in chemical processes, unless expensive feedstock purification is undertaken [497]. While microorganisms often tolerate various impurities, the presence of by-products and impurities can substantially complicate downstream processing.
- *Sensitive components*: Most microorganisms or biocatalysts are sensitive to temperature and stress which limits the operating window for the initial separation steps [497].

It has traditionally been assumed that fermentation broths are too dilute for distillation to be an effective separation technique without using excessive energy. Additionally, distillation temperatures were thought to be too high for sensitive microorganisms, and fermentation products were considered not volatile enough for distillation to be feasible. However, each of these assumptions was challenged in this chapter. Distillation may not always be the best option for recovery after fermentation, but it holds significant underutilized potential. The versatility of

distillation in downstream processing after fermentation is evident in its application across various case studies, each highlighting its effectiveness in recovering valuable products and by-products. Distillation proves to be an indispensable tool in several stages of product purification, offering robust methods for separating, concentrating, and purifying fermentation-derived substances.

In the recovery of propionic acid, distillation plays a critical role after biomass and counterion removal. It can be used to selectively remove water, recovering the propionic acid and by-products (acetic and succinic acids). This process can also be extended to the esterification of the recovered acids, allowing the production of esters that have value in the flavouring and fragrance industries. The versatility here lies in its ability to not only recover the target product but also upgrade it into useful derivatives while maintaining the high purity of the final products.

Similarly, distillation serves a crucial function in the recovery of ethyl acetate, an organic solvent obtainable through fermentation. In this case, distillation is employed for both *in-situ* recovery from the liquid phase and the final product purification. Besides recovering the target compound, distillation may improve the overall yield by separating inhibiting compounds early in the process.

In the recovery of 2-phenylethanol and 2-phenylethyl acetate, distillation is crucial for solvent recovery and final product purification. However, due to the high boiling points and very low product concentrations in the fermentation broth, an additional method, such as liquid-liquid extraction, is needed for *in-situ* product recovery. Therefore, combining distillation with other recovery techniques may lead to the most efficient downstream process.

Finally, in addition to the purification of the final product, distillation proves its versatility in the recovery of by-products. Recovering and valorizing by-products after the biomass pretreatment in lignocellulosic biorefineries, such as acetic acid, formic acid, furfural and HMF, may improve the economic performance of the overall process by minimizing waste formation and increasing the product versatility.

Across these case studies, distillation demonstrates its adaptability and efficiency in handling different challenges in downstream processing after fermentation. Whether it is purifying a product, recovering by-products, or upgrading materials, distillation remains a core technique in making fermentation processes more sustainable and economically viable.



5 | Integrating upstream and downstream processes

5. Integrating upstream and downstream processes

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While this thesis primarily focuses on improving the recovery process, this chapter takes a step toward integrating upstream and downstream processes. For optimal operation, the entire bioprocess should be designed to minimize costs and environmental impact per kilogram of the final product. However, optimizing upstream and downstream processes separately does not necessarily lead to the best overall outcome, as their integration may result in suboptimal performance. To address the interdependencies between the bioreaction and downstream separation steps, a systems-based strategy is needed. This integration provides deeper insight into how conditions in one phase influence the other, helping to identify bottlenecks and areas for improvement. Successful process development relies on multidisciplinary collaboration to achieve the best results.

To demonstrate the practical application of integrated process design, this chapter presents two large-scale bioprocesses. Isopropanol with acetone and 2-phenylethanol were selected as representative examples of low-boiling and high-boiling biochemicals. The upstream fermentation, *in-situ* product recovery, and final purification steps were designed and integrated into a complete production process. Advanced process intensification, heat integration, and heat pumping techniques were implemented to maximize energy efficiency. Finally, this chapter highlights the importance of incorporating downstream processing early in process development.

5.1. Isopropanol and acetone production by gas fermentation

This study advances the development of syngas fermentation by designing the first industrial-scale process design for producing isopropanol (IPA) and acetone from steel off-gas, with a production capacity of 46-50 ktonne per year. The process was rigorously developed in Aspen Plus, with a comprehensive techno-economic assessment and life-cycle analysis performed to evaluate process performance. The developed process maximizes energy efficiency by utilizing the heat content of steel off-gas and implementing advanced heat pump systems. As a result, the process is thermally self-sufficient and can operate solely on renewable electricity. Efficient utilization of waste gases results in substantial reductions in global warming potential compared to fossil-based production (144-160% for IPA and 138-149% for acetone). The unit production cost of 0.57-0.74 $/kg$_{IPA/Ac}$ and potential profit margins of 49-65% testify to the cost-effectiveness of the developed process. Moreover, valorizing biomass as a by-product further lowers production costs by 6-11%. These findings demonstrate the environmental sustainability and cost-effectiveness of syngas fermentation from steel mill off-gas, establishing it as a potentially viable alternative to conventional petrochemical processes. This technology may hold great potential in reducing environmental impact and carbon emissions in industrial chemical production.

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G.J.A. Brouwer, T. Janković, J.A. Posada, A.J.J. Straathof, A.A. Kiss, Thermally self-sufficent process for sustainable production of isopropanol and acetone via syngas fermentation.

5.1.1. Introduction

Isopropanol (IPA) and acetone are essential platform chemicals predominantly derived from fossil carbon sources. The total global market in 2022 has been estimated at 3.1 and 8.1 million tonnes for IPA and acetone respectively, with a growth rate of 3.2-3.9% until 2035 [498,499]. Besides fossil fuel-based production, isopropanol and acetone can be produced through more sustainable pathways. For example, isopropanol can be obtained through fermentation [167] or biotransformation of ethanol [500], while acetone has been commercially produced using acetone-butanol-ethanol (ABE) fermentation [501,502]. Moreover, fermentation of steel mill off-gas presents a promising sustainable pathway for isopropanol and acetone production, replacing petrochemical-based production while reducing greenhouse gas emissions from the steel industry [72,166]. In addition to utilizing renewable feedstocks, the fermentation process operates under milder conditions than conventional petrochemical production processes

Application of process systems engineering approaches, through process design and simulation is crucial for successfully developing and commercializing sustainable (bio)chemical processes [23,24]. In that respect, this original research addresses the unexplored potential of industrial-scale production, by proposing a novel, advanced large-scale plant capable of producing ~46-50 ktonne/year of >99% pure IPA and/or acetone. Furthermore, the applicability of the proposed process design was extended by varying target product(s) (IPA and acetone produced together or separately) and achievable broth concentrations (2.3-4.4 wt%). Additionally, valorising biomass as a by-product was considered to increase the profitability of the developed processes, as demonstrated in the previous analysis of pilot-scale fermentative production [73]. Comprehensive techno-economic analysis and life-cycle assessments were conducted to evaluate and compare performances of all considered scenarios. Hence, this novel study offers a product-flexible, cost-effective and energy-efficient process design for IPA and acetone production via syngas fermentation.

5.1.2. Problem statement

It has already been proven on an industrial scale that *Clostridium autoethanogenum* can convert energy-rich steel mill off-gas into ethanol [71]. Furthermore, recent advancements demonstrated the feasibility of continuous isopropanol and acetone production via gas fermentation at a pilot scale (120 L reactor) while reporting a negative global warming potential (GWP) for these products [73,164]. However, an industrial-scale production process has not been reached yet. Similarly, a full-scale process design for isopropanol and acetone production via gas fermentation remains unreported. IPA and acetone production

by gas fermentation presents multiple challenges in both fermentation and downstream processing. These include challenges in strain development, mass transfer limitations (especially when scaling-up bioreactors), low product concentrations that complicate downstream processing, presence of the microorganisms in the broth that is sent to the downstream processing, thermodynamic constraints (e.g. formation of azeotrope between isopropanol and water), development of the proper control strategy, etc. While this research does not address all of these challenges, it represents a significant step in the development of this process by exploring the untapped potential of industrial-scale production and proposing the first large-scale process design. The obtained results may substantially accelerate the successful scale-up of this emerging technology.

5.1.3. Method of process design and simulation

The feed for the IPA and acetone production process is a synthetic gas blend (50% CO, 10% H_2, 20% CO_2, 20% N_2), which is in line with recent pilot-scale validation [73]. However, it should be noted that, depending on the gas source, additional purification steps may be needed before the fermentation process. This falls beyond the scope of this study, which primarily concentrates on rigorously modelling gas fermentation and downstream processing. Key process parameters such as dilution rate, mass transfer capacity, product selectivity, and gas conversion were taken into account in process design [503]. **Scenario 1** implies a CO volumetric mass transfer rate of 10 g/(L h). CO volumetric mass transfer rate of up to 8.5 g/(L h) was deemed feasible for ethanol [93] production in a 840 m^3 bioreactor (565 m^3 ungassed volume), at a lower overhead pressure (1.1 bar). Given the slightly higher assumed overhead pressure (1.4 bar) and potentially more enhancing mass transfer-enhancing effects of IPA compared to ethanol [504], the used CO volumetric mass transfer rate of 10 g/(L h) may be realistically achievable. Within Scenario 1, different product combinations were considered: **Scenario 1a** – IPA and acetone (both recovered as high-purity products), **Scenario 1b** – IPA and **Scenario 1c** – Acetone. Additionally, **Scenario 2** considers isopropanol and acetone production (both recovered as high-purity products) with a higher CO volumetric mass transfer rate of 14.9 g/(L h). 85% conversion of CO and 90% total product selectivity (80% IPA and 10% acetone if both products are produced), previously demonstrated as realistic in pilot-scale fermentation [73], were considered in all scenarios. The flowrate of the steel mill off-gas remained constant across all scenarios (~429 ktonne/y), while the production capacity varied slightly between scenarios due to previously mentioned differences in the fermentation process (46-50 ktonne/y). The gas fermentation to isopropanol and/or acetone was modeled as previously described for isopropanol production via gas fermentation

at 37 ºC, pH 6, and dilution rate of 0.1 h^{-1} [505], using the 120 L pilot data [73]. The key fermentation parameters for all scenarios are compared in Table 5-1.

Table 5-1. Comparison of the key fermentation parameters

Scenario	**1a**	**1b**	**1c**	**2**
CO volumetric mass transfer rate (g/(L h))	10	10	10	14.9
CO conversion (%)	85	85	85	85
IPA selectivity (%)	80	90	/	80
Acetone selectivity (%)	10	/	90	10
IPA concentration in liquid broth (wr%)	2.22	2.40	/	4.01
Acetone concentration in liquid broth (wt%)	0.27	/	2.28	0.44

The bioreactor was modelled as a stoichiometric reactor. Thereby, fermentation stoichiometry was treated as a black box and derived using thermodynamic principles [506] considering acetic acid and biomass as by-products. More details about the derivation of fermentation models are presented Appendix E. The overall black box stoichiometric reactions were obtained:

90% Isopropanol selectivity

$$8.26\ CO + 1.65\ H_2 + 2.56\ H_2O + 3.1 \cdot 10^{-2} NH_4^+ + 0.17\ OH^- \rightarrow 1.00\ \mathbf{C_3H_8O}\ (\text{IPA}) + 0.14\ CH3COO^- + 4.8 \cdot 10^{-3}\ CH_3COOH + 0.15\ CH_{1.8}O_{0.5}N_{0.2}\ (\text{Biomass}) + 4.81\ CO_2$$

90% Acetone selectivity

$$7.33\ CO + 1.47\ H_2 + 1.72\ H_2O + 2.7 \cdot 10^{-2} NH_4^+ + 0.15\ OH^- \rightarrow 1.00\ \mathbf{C_3H_6O}\ (\text{Acetone}) + 0.12\ CH3COO^- + 4.2 \cdot 10^{-3}\ CH_3COOH + 0.13\ CH_{1.8}O_{0.5}N_{0.2}\ (\text{Biomass}) + 3.94\ CO_2$$

80% Isopropanol and 10% acetone selectivity

$$9.18\ CO + 1.84\ H_2 + 2.80\ H_2O + 3.4 \cdot 10^{-2} NH_4^+ + 0.15\ OH^- \rightarrow 1.00\ \mathbf{C_3H_8O}\ (\text{IPA}) + 0.15\ \mathbf{C_3H_6O}\ (\text{Acetone}) + 0.12\ CH3COO^- + 4.0 \cdot 10^{-3}\ CH_3COOH + 0.17\ CH_{1.8}O_{0.5}N_{0.2}\ (\text{Biomass}) + 5.32\ CO_2$$

As previously used for gas fermentation in ethanol production, the external-loop airlift reactor was employed for the bioreactor configuration. This reactor configuration leads to higher liquid velocities and shorter mixing times compared to commonly used bubble columns, and offers a possibility of heat exchange and introduction of fresh feed through the external loop [93]. The recently developed advanced downstream process, consisting of vacuum distillation followed by heat pump-assisted distillation and extractive distillation, was applied to efficiently recover fermentation products while allowing the recycling of microbial biomass back to the fermenter [253]. Reusing fermentation broth after product recovery by vacuum distillation has already been proven effective for similar processes [529,530]. This approach allows reusing of biomass and most of the water, while allowing closed loop operation [19]. Traces of acetic acid that will also be recycled to the fermenter, can be metabolized by the microorganisms.

Advanced heat integration techniques were considered to utilize the heat content of the hot steel mill off-gas and maximize energy recovery within the process. Additionally, Combined Heat and Power (CHP) and wastewater treatment and recycling were included to minimize environmental burden [507].

Aspen Plus was used as a computer-aided process engineering tool to rigorously model the gas fermentation unit and the recovery steps of the IPA and acetone production process [508]. To properly describe complex interactions between different components, several thermodynamic property models were used. Due to the presence of electrolytes, ElecNRTL (extension of the Non-Random Two Liquid model for electrolytes) property method was used to model the fermentation process. Given the strong nonideality of the considered systems and the presence of carboxylic acids, NRTL-HOC (Non-Random Two Liquid model with Hayden-O'Connell extension for the vapor phase) property method was used to properly describe vapor-liquid equilibrium in the distillation operations [97]. Lastly, because of the low refrigeration temperatures and the requirement for refrigerants, REFPROP (REFerence fluid PROperties) model was used for the design of the refrigeration cycle [416].

5.1.4. Results and discussion

Process design

A block flow diagram of the whole process is presented in Figure 5-1, including the system boundaries and scopes of the cradle-to-gate LCA.[509]

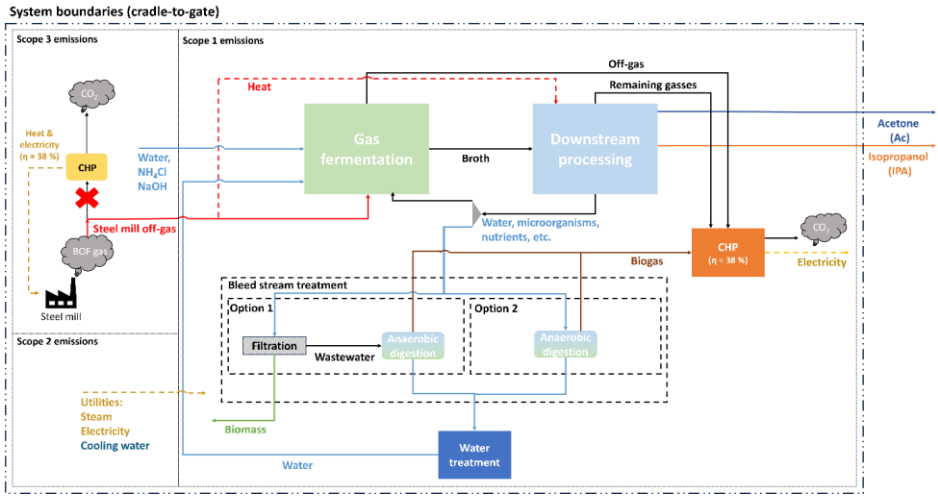


Figure 5-1. Block flow diagram of the main processing stages for the syngas fermentation process producing high-purity isopropanol and acetone, including the system boundaries (cradle-to-gate) and all three emission scopes

Gas fermentation and downstream processing were rigorously modelled in this study and a comprehensive flowsheet is presented in Figure 5-2. Scenario 1a was chosen as a representative case, while the flowsheets of other scenarios are provided in Appendix F. Depending on the primary products and the achievable concentrations in the fermentation broth, there are certain structural differences between the scenarios. If only IPA is produced (Scenario 1b), distillation column C2 is not needed. Similarly, if only acetone is produced (Scenario 1c), columns C3, C4 and C5 are not required. If the fermentation titer is higher (Scenario 2), the steel mill off-gas heat can completely cover thermal energy requirements, and only one reboiler is needed for column C1.

The developed processes produce 46-50 ktonne/y of IPA and/or acetone through the gas fermentation process. The CO volumetric mass transfer rate of 10 g/(L h) in scenarios 1a, 1b and 1c resulted in a fermentation titer of about 20 g/L. The higher CO volumetric mass transfer rate of 14.9 g/(L h) in scenario 2 resulted in a fermentation titer that is still below 50 g/L which is the upper product concentration tested for biomass growth [160] (see Table 5-1). Nonetheless, it should be noted that this scenario is a rather optimistic as the inhibitory effects of acetic acid may have additive effects to those of isopropanol and acetone. This has been studied for ethanol and organic acids growth inhibiting effects on yeast [510]. The growth inhibiting effects do not necessarily negatively affect anaerobic and catabolic product formation, since less biomass formation increases the product selectivity as long as the microorganisms grow just enough to maintain viability.

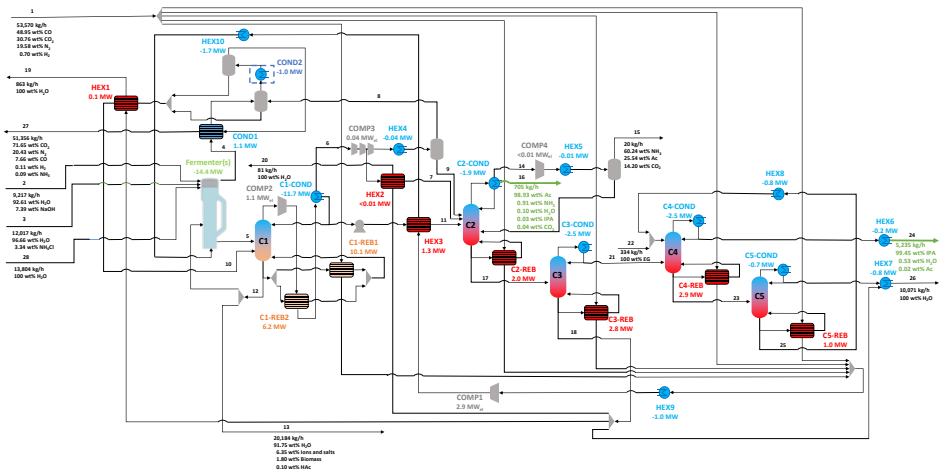


Figure 5-2. Flowsheet of the isopropanol and acetone production process in Scenario 1a (abbreviations: C – column, HEX – heat exchangers, REB – reboiler, COND – condenser, COMP – compressor)

After the fermentation, vacuum distillation (C1) was implemented to separate volatile products from the broth with microorganisms. It was assumed that 90% of the broth could be reused in the fermentation. The remaining 10% was assumed to be sent to the anaerobic digestion as a base case for all scenarios. Additionally, biomass valorization was considered as an additional opportunity for all scenarios. The next step in the recovery process is to recover high-purity acetone (~99 wt%) as the most volatile component (in C2). Furthermore, most of the remaining water was removed (in C3) to achieve IPA concentration of ~86 wt% before the extractive distillation. This IPA concentration before the extractive distillation has been previously proven to minimize energy requirements of the preconcentration and final purification steps in IPA recovery [253]. Finally, extractive distillation with ethylene glycol (in C4 and C5) was implemented to obtain high-purity IPA (>99 wt%). Heat integration was applied by utilizing a hot steel mill off-gas instead of external steam in the reboilers of distillation columns (C1-REB1, C2-REB, C3-REB, C4-REB and C5-REB). The heat content of steel mill off-gas was sufficient to completely cover thermal energy requirements in scenarios 1c and 2 (column C1 has only one reboiler: C1-REB1). However, additional heating is required in the reboiler of column C1 in scenarios 1a and 1b. To meet this energy demand while minimizing total energy requirements, a mechanical vapor recompression (MVR) heat pump system was installed. This heat pump system implies compressing top vapor from the distillation column and using it instead of a heating utility in the reboiler [113]. Hence, column C1 in these scenarios has two reboilers: the first one uses steel mill off-gas instead of heating utility (C1-REB1), while the second one relies on the MVR system (C1-REB2). Hence, the developed processes are completely thermally self-sufficient since all of the considered scenarios can be powered only by (green) electricity, excluding the need for external steam.

Techno-economic analysis

The results of the performed TEA are presented in Figure 5-3. In all scenarios, the total installed equipment costs are dominated by the bioreactor costs (56.1-68.5%, see Figure 5-3a). Compressors and CHP systems also play a significant role, contributing 15.0-19.5% and 8.3-13.0% respectively. Due to the advanced downstream processing strategy, the costs of distillation columns are minimized (3.8-5.7%). This is because valuable products are initially separated from most of the broth in the first step, drastically reducing processing throughput and column size for the subsequent recovery steps. Scenario 2 has the lowest total equipment costs (see Figure 5-3a), due to higher achievable product concentrations in the fermentation broth, reducing processing throughput requirements and leading to smaller equipment units. When comparing scenario 1b with scenario 1a, the larger bioreactor size (due to more IPA separated in the vapor phase) results in slightly

higher total equipment costs despite lower costs of the distillation columns and heat exchangers. Similarly, due to acetone's higher volatility, scenario 1c requires a larger bioreactor volume, leading to one additional. Consequently, equipment costs are the highest in scenario 1c despite reduced distillation column and heat exchanger expenses. Since CAPEX calculation is based on the total equipment costs, total CAPEX (see Figure 5-3b) are the lowest in scenario 2 (107,2 M$), the highest in scenario 1c (177.4 M$), while being relatively similar in scenarios 1a (154.2 M$) and 1b (155.8 M$).

The largest contributors to the total OPEX (see Figure 5-3c) are the costs of pH control (40.0-43.9%) and labour costs (30.6-35.4%). It is worth noting that pH control expenses could potentially be reduced by using alternative agents, such as NH_4OH instead of both NH_4Cl and NaOH. However, optimizing the pH control system was not the primary focus of this study. Furthermore, contrary to traditional fermentation processes which have OPEX dominated by feedstock expenses, the use of the steel-mill "waste" off-gas requires paying the price for the unused gas potential in flaring and heat integration, resulting in only 0.03-0.04% of the OPEX. Moreover, the advanced downstream process design avoids additional expenses by allowing efficient broth recycling. Although similar across all scenarios, only in scenario 2 the electricity produced within the system is sufficient to fully meet electrical requirements. As a result, the net electricity generation in scenario 2 significantly lowers expenses, bringing the total OPEX to 16.9 M$/y. In contrast, scenarios 1a, 1b, and 1c have higher electrical energy demands, primarily due to the additional compressor in the MVR system. Consequently, OPEX in these cases are higher, amounting to 18.3, 19.4, and 19.5 M$/y, respectively. Nonetheless, it is important to note that all developed processes are thermally self-sufficient and can be fully powered by (green) electricity (electricity form renewable sources). Scenarios 1b and 1c have slightly higher OPEX than 1a, mainly due to increased maintenance and property insurance costs, which are calculated based on equipment expenses. Additionally, NaOH costs are higher due to the slightly increased acetate production and larger bioreactor volumes.

Most importantly, the estimated unit production costs (see Figure 5-3d) in all scenarios (0.58-0.74 $/kg$_{product}$) are significantly lower than the isopropanol and acetone market prices (1.08 $/kg$_{IPA}$ and 0.88 $/kg$_{Ac}$). The higher achievable product concentrations in the broth assumed for scenario 2 can help to reduce both fermentation and recovery costs, resulting in the most cost-effective process. Possible margins between the market prices and production costs of 49-65% prove the cost-effectiveness of the developed processes.

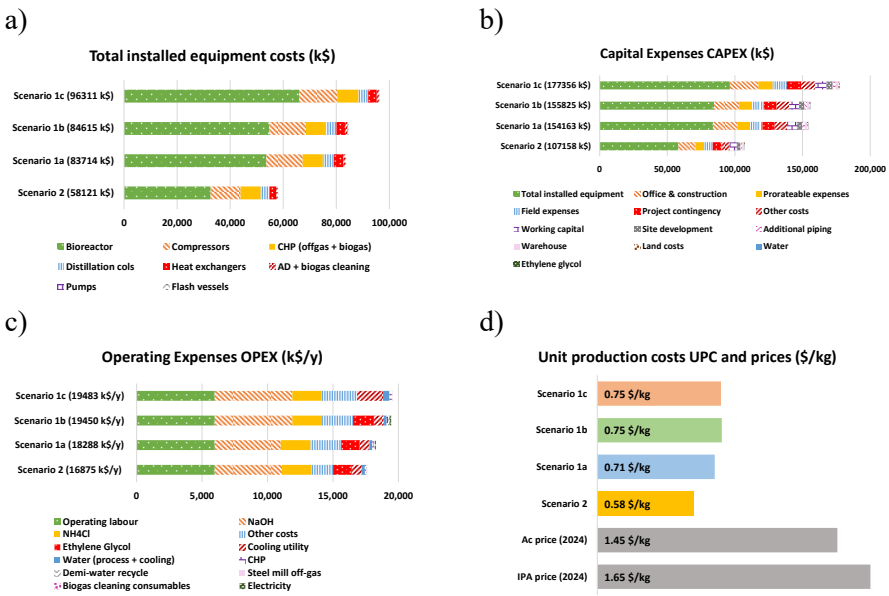


Figure 5-3. Comparison of techno-economic performance of the considered scenarios: a) total installed equipment costs, b) total capital expenses (CAPEX), c) total operating expenses (OPEX) and d) unit production costs

The unit production costs (UPC) were calculated based on a 10-year payback period (PBP). However, the impact of the PBP on UPC was analyzed, and the results are presented in Figure 5-4. In general, UPC increases as the PBP decreases, with a particularly significant rise when the PBP is shorter than three years. Conversely, extending the PBP beyond 10 years results in only a marginal reduction in UPC. Nevertheless, even with a PBP of just four years, the UPC remains lower than the market prices of IPA and acetone.

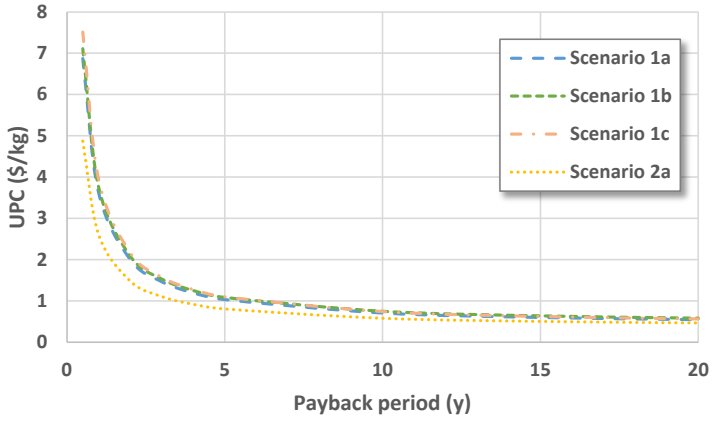


Figure 5-4. Influence of the payback period on the unit production costs

Life-cycle assessment

The cradle-to-gate life-cycle assessment results per product according to the performed economic allocation, presented in Figure 5-5 and Figure 5-6, highlight the significant environmental benefits of the developed process compared to fossil-based production. The economically allocated environmental impacts of the detailed and integrated plant design of this study show comparable GWP results to the pilot-scale study [73]. Remarkably, when comparing the GWP from the current study to those of fossil IPA and fossil acetone production [511], a GWP reduction of 144-160% for IPA and 138-149% for acetone is achievable (calculated as the relative error). This substantial improvement is largely attributed to the prevention of CO_2 emissions through gas fermentation, which converts waste gases into valuable chemicals instead of releasing them through flaring. Additionally, assuming that the thermal energy from hot syngas can be utilized within the gas fermentation plant, steam consumption is eliminated which further reduces CO_2 emissions (see system boundaries in Figure 5-1). Furthermore, integrating CHP and anaerobic digestion reduces overall electricity demand by 93-120%.

The developed syngas fermentation processes offer significant environmental advantages over conventional petrochemical production by reducing fine particulate matter formation, human carcinogenic toxicity, land use and freshwater eutrophication (see Figure 5-5 and Figure 5-6). While marine eutrophication, stratospheric ozone depletion, and water consumption are slightly higher than in conventional petrochemical production, water consumption is effectively reduced by allowing water reuse within the process. Therefore, efficient water management is considered important for the design of more sustainable chemical production using (syngas) fermentation.

Hence, by replacing fossil feedstocks with a sustainable gas fermentation approach, the developed processes not only mitigate greenhouse gas emissions but also transform waste gases into high-value products. By reducing harmful emissions and environmental degradation, syngas fermentation presents a more sustainable alternative to conventional petrochemical pathways with a strong potential to drive the transition toward greener chemical manufacturing. Still, steel mill off-gas is finite and will only be able to supply a fraction of the currently consumed IPA and acetone.

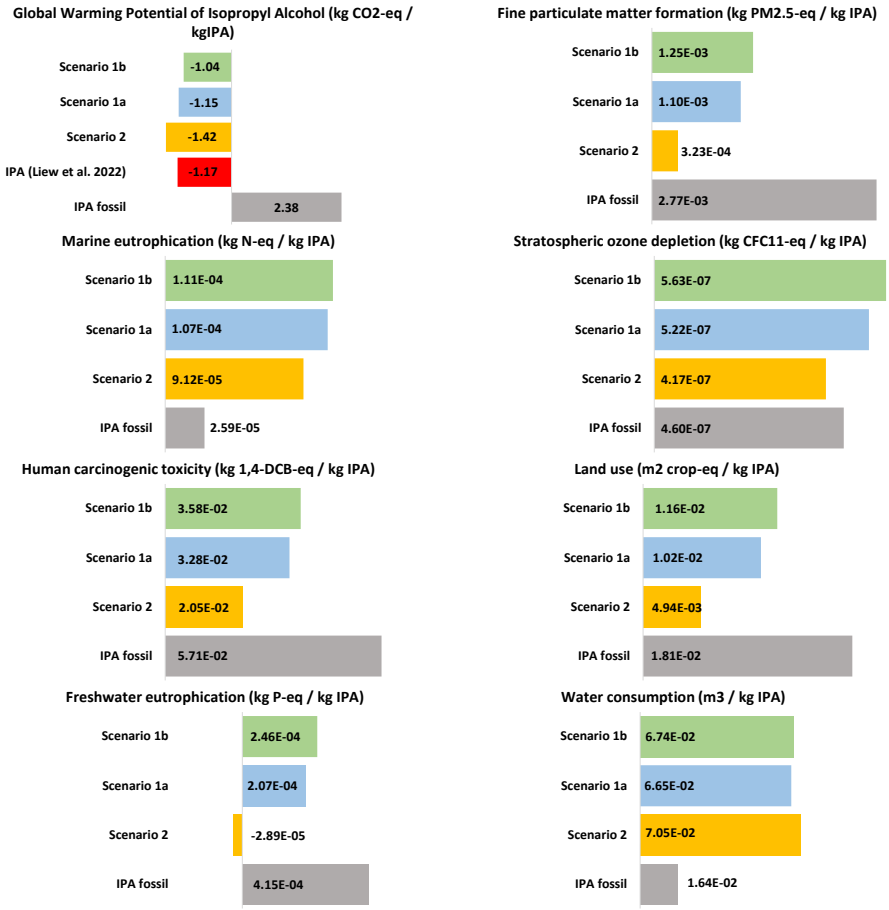


Figure 5-5. Comparison of life-cycle environmental impacts for isopropanol production after economic allocation

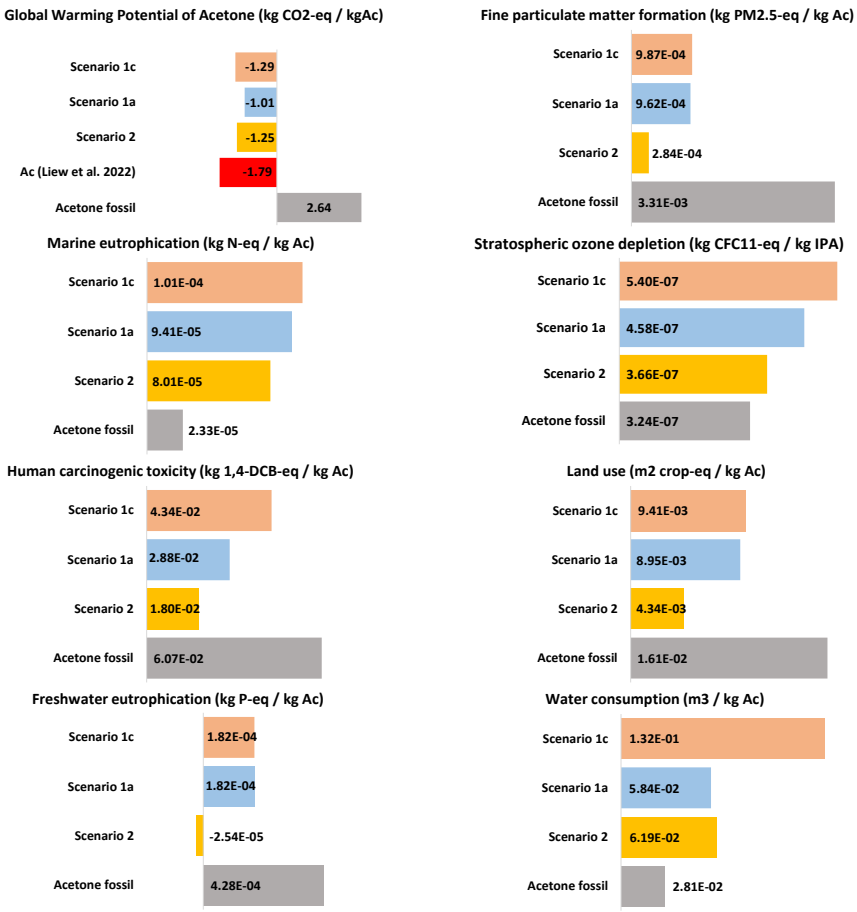


Figure 5-6. Comparison of life-cycle environmental impacts for acetone production after economic allocation

Impact of valorizing biomass as a by-product

The previous analysis assumed that the broth bleed stream would be sent to the anaerobic digestion. Alternatively, an additional microfiltration step could be included before the anaerobic digestion to separate biomass, which may be used as animal feed. This would allow valorization of the biomass as a by-product in the IPA and acetone production process.

Despite additional costs of the filtration units, CAPEX is slightly lower (<3%) for all scenarios when biomass is valorized, mainly due to the lower costs of anaerobic digestion and CHP. OPEX is slightly higher when biomass is valorized due to the additional costs of membrane consumables and higher electricity demand due to the microfiltration step. Furthermore, electricity requirements are higher (by 27-358%; primary energy requirements increase 0.12 $kW_{th}h/kg_{IPA/Ac}$ for scenario 1a, 1b and 2; and 0.32 $kW_{th}h/kg_{IPA/Ac}$ for scenario 1c) if biomass is separated before the anaerobic digestion due to higher electrical energy requirements and lower production of electricity. When calculating the UPC for IPA and acetone, biomass revenue is subtracted from the total costs. Thereby, a biomass selling price of 0.81 $\$/kg_{biomass}$ (soybean meal) was used [512–514]. Hence, even though the total costs are higher when biomass is valorized, the UPC for IPA and acetone are lower (6-11%) due to additional profit generated from biomass valorization (~0.05 $/kg).

When biomass is valorized as a substitute for soybean meal in animal feed, the global warming potential of the products is slightly lower. However, biomass is not used for energy generation causing more electricity to be required. Therefore, causing a net increase for the formation of fine particulate matter, human carcinogenic toxicity, land use impact, stratospheric ozone depletion, and freshwater eutrophication. Additionally, the marine eutrophication and water consumption are slightly higher.

5.1.5. Conclusion

This research presents a novel industrial-scale syngas fermentation process for producing isopropanol and acetone from steel mill off-gas, demonstrating environmental and economic benefits over conventional fossil-based methods. The effective utilization of steel mill off-gas gas heat content and implementation of advanced heat pump systems lead to thermally self-sufficient processes by allowing operation entirely on renewable electricity. Additionally, anaerobic digestion and CHP systems contribute to lower overall electricity demand.

By utilizing steel mill off-gas as a carbon and energy source, while accounting for credits from avoided flaring, the developed gas fermentation processes significantly reduce greenhouse gas emissions leading to a decrease in global warming potential by 144-160% for IPA and 138-149% for acetone compared to petrochemical-based production. The economic viability was proven by a competitive unit production cost of 0.58-0.74 $\$/kg_{IPA/Ac}$ and with profit margins of 49-65% compared to 2024 market prices. Furthermore, the valorization of biomass as a by-product further enhances cost efficiency, reducing production costs by 6-11%.

By offering a sustainable, energy-efficient, and economically feasible alternative to conventional petrochemical processes, syngas fermentation may represent an important step toward reducing industrial carbon footprints and fostering greener chemical manufacturing.

5.2. *De-novo* fermentation of 2-phenylethanol

2-Phenylethanol (2PE) is a valuable aroma component that can be obtained through de-novo fermentation from glucose. However, its toxicity at very low concentrations (<2.5 g/L) limits the fermentation titer, rate and yield. To address this challenge, in-situ product removal has been explored, leading to a recent scale-up to pilot scale. Nonetheless, industrial scale has yet to be achieved. This original research pioneers the conceptual development of two large-scale (2 ktonne2PE/y) production processes for 2PE via de-novo fermentation from glucose. Liquid-liquid extraction with oleyl alcohol and adsorption by hydrophobic resins followed by ethanol desorption, were alternatives considered for in-situ 2PE removal. For either design, solvent recovery and final purification were performed using advanced distillation techniques including heat pump-assisted distillation and a dividing-wall column. A fermentation titer of approximately 1.5 g_{2PE}/L_{broth} minimized production costs, by achieving a balance between upstream and downstream processing costs. This resulted in a cost-effective 2PE production for both designs of the recovery process (9.03-9.40 $/kg_{2PE}$). Sensitivity analysis revealed that glucose, oleyl alcohol, and ethanol costs strongly impact total production costs. This novel study provides a comprehensive and scalable process framework for the large-scale production of 2PE through de-novo *fermentation. By integrating in-situ product removal and energy-efficient purification strategies, it marks a significant step forward in industrial biotechnology.*

This chapter was submitted for publication as:
T. Janković, T. Fecker, JM Daran, A.J.J. Straathof, A.A. Kiss, Advanced process design for large-scale *de-novo* 2-phenylethanol production via fermentation

5.2.1. Introduction

Among the various chemicals produced via microbial transformation, 2-phenylethanol (2PE) has attracted significant attention due to its unique applications and relatively high market value. 2PE is a valuable aromatic alcohol with a rose-like scent, widely used in fragrances and perfume, cosmetics and personal care products, food and beverage, aroma therapy, pharmaceuticals, antiseptics, preservatives and cleaning agents [437]. The global market of 2PE was estimated at over 255 million $ in 2021 with an expected annual growth of over 5.5% between 2022 and 2028 [443]. Nowadays, most of 2PE is produced through petrochemical processes. In addition to reliance on fossil carbon and harsh operating conditions, these methods often result in undesirable by-products that limit the applicability of 2PE [445]. As a result, the biological production of 2PE has been gaining interest. Despite significant research efforts, naturally derived 2PE remains expensive (~1,000 $/kg for plant extraction and ~300 $/kg for microbial processes [445]) compared to petrochemical production (5-20 $/kg [442,444]). Hence, large improvements are necessary to make the biological production of 2PE competitive with fossil fuel-based processes. In this context, this novel research advances the field of sustainable industrial fermentation by developing two cost-effective large-scale 2-phenylethanol production processes through fermentation.

5.2.2. Problem statement

From the various biotechnological approaches explored to produce 2PE, whole-cell conversion of L-phenylalanine through the Erlich pathway has garnered significant attention [46,445,446]. However, this approach involves a multi-stage process and relies on costly L-phenylalanine as a precursor. Alternatively, 2PE can be produced *de-novo* from renewable glucose through fermentation [44,461]. Due to these advantages, this study focuses on *de-novo* 2PE production through fermentation from glucose.

A major constraint in scaling up both whole-cell biotransformation of L-phenylalanine and *de-novo* fermentation from glucose is the toxicity of 2PE to microbial growth. Consequently, achievable 2PE concentrations in fermentation broth remain low, often below 2.5 g_{2PE}/L_{broth} [44]. This low product yield leads to high water throughput, necessitating large processing equipment and increasing capital costs. Additionally, 2PE's high boiling point (217.6 ˚C) complicates its separation from the dilute aqueous phase, making downstream processing highly energy-intensive and costly. To mitigate end-product toxicity and enhance production efficiency, *in-situ* product removal (ISPR) techniques can be employed [27]. Among these, liquid-liquid extraction and adsorption by hydrophobic resins show strong potential for industrial-scale processes.

In liquid-liquid extraction, a water-immiscible extractant with a high affinity for 2PE is introduced in the fermentation broth, where it continuously removes 2PE from the aqueous phase. The effectiveness of this technique has been demonstrated in several studies, with commonly used extractants including oleic acid [45], oleyl alcohol [44], polypropylene glycol [46] and ionic liquids [47]. DAB.bio has developed a novel integrated bioreactor concept, known as Fermentation Accelerated by Separation Technology (FAST), that enables continuous liquid-liquid extractive fermentation [515]. Recent pilot fermentations at 500 L scale have confirmed the feasibility of this approach for 2PE production [44]. Instead, in the sorption process, 2PE is adsorbed by a solid resin and subsequently desorbed using an inexpensive solvent, such as ethanol. Various hydrophobic polymers with amorphous structures have demonstrated efficiency in ISPR for 2PE production [516–521]. Both liquid-liquid extraction and product adsorption/desorption significantly increase 2PE concentrations in the solvent phase, compared to the fermentation broth. As a result, ISPR not only enhances fermentation productivity and yield but also facilitates final product purification. Given the strong potential of these ISPR techniques, this study aims to evaluate their performance in large-scale fermentation processes. To fulfil this goal, design and simulation of both processes are required.

Along with the low 2PE concentration, thermodynamic constraints present additional challenges for downstream processing. The 2PE-rich streams will include some water, and later on in the process, formation of a heterogeneous azeotrope of 6.49 wt% 2PE and 93.51 wt% water [30], leads to additional liquid-liquid separation steps to obtain a high-purity final product.

5.2.3. Method of process design and simulation

Thermodynamic property models

Aspen Plus was used as a computer-aided process engineering (CAPE) tool to simulate each unit operation [508]. Due to the complexity of the process, several thermodynamic property models were used: i) ElecNRTL (extension of Non-Random Two Liquid model for application in systems with electrolytes) was used to model the fermentation process due to the presence of salts and electrolytes in the fermentation broth; ii) UNIF-LL (UNIFAC model based on liquid-liquid equilibrium data) was used to accurately account for phase split in liquid-liquid extraction; and iii) NRTL-HOC (Non-Random Two Liquid model with Hayden-O'Connell extension for vapor phase) was used to model adsorption and final purification using distillation [97].

Process design

The block flow diagram of the developed processes is presented in Figure 5-7. Generally, the 2PE production process consists of four steps: fermentation, *in-situ* product removal (by liquid-liquid extraction or product adsorption), solvent recovery and final purification to obtain high-purity product (removal of any remaining impurities). It is important to note that careful adjustment of operating conditions during ISPR is crucial to minimize stress on microorganisms and maintain their viability and productivity. After ISPR, most of the broth containing microorganisms is returned to the bioreactor to minimize biomass loss, reduce freshwater consumption and enable closed-loop operation. A 10% bleed was applied to all recycle streams entering the fermenter to prevent the accumulation of salts, biomass, or fermentation by-products.

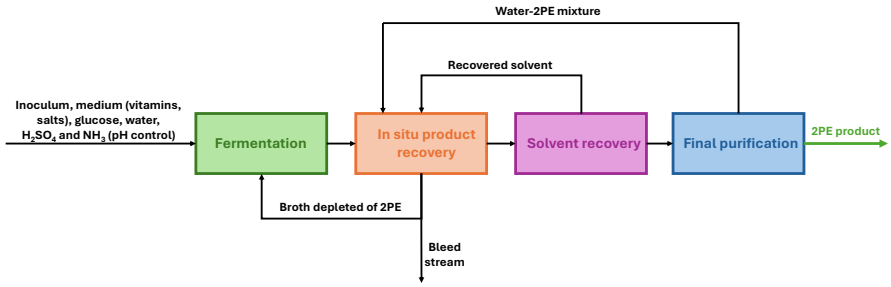


Figure 5-7. Block flow diagram of 2PE production process

For designing industrial 2PE processes incorporating ISPR, a reliable fermentation model is essential for determining realistic values for input and output stream values for the bioreactor. Fermentation was assumed to begin in a batch phase. When a particular 2PE concentration is reached, it will be switched to fully continuous operation including ISPR, and a steady state is maintained. ISPR is terminated at some point because of infection risk and accumulation of impurities. The 2PE remaining in the bioreactor may be recovered using end-of-pipe recovery [522]. If the steady-state can be maintained very long as compared to the start-up, shut-down and downtime phases, designing only the steady-state phase is reasonable. Hence, this work models the steady-state operation of the 2PE production process. More detials abot the used fermentation model are presented in Appendix E – Fermentation models. In short, it was assumed that 2PE inhibits product formation and growth similarly, according to the fixed ratio between the increase in biomass (X) and 2PE concentrations during batch fermentation [461]. Based on this assumption, the ratio between maximum specific production and growth rates was determined to be 0.12 mol_{2PE}/mol_X. Furthermore, the formation of by-products was considered negligible due to continued strain development and optimization of fermentation conditions. Hence, product-to-substrate yield (0.168 mol_{2PE}/mol_S) was calculated based on

early batch experimental data and the glucose amount that would otherwise be used for the formation of ethanol, which was a side product under suboptimal conditions. The following constant molar stoichiometry was obtained:

$$C_6H_{12}O_6 + 2.850\ O_2 + 0.280\ NH_3 \rightarrow 1.400\ X + 3.256\ CO_2 + 4.320\ H_2O + 0.168\ C_8H_{10}O$$

Thereby, X represents dry biomass with formula $CH_{1.8}O_{0.5}N_{0.2}$, as commonly used in bioprocess simulations [523].

The pH for continuous fermentation was set to ~5 [44] using control by 25 wt% NH_3 and 98 wt% H_2SO_4 solutions. NH_3 is added in the fermenter as it is one of the necessary reactants in the fermentation reaction, while H_2SO_4 is used to fine-tune pH in the fermenter. Additionally, Na_3PO_4 and $MgSO_4$ were included as medium components (0.34-0.35 and 0.02-0.03wt%, respectively), while vitamins and antifoam addition were not considered in Aspen Plus simulations. The temperature of the fermenter was specified at 30˚C as previously used in pilot experiments [44]. A glucose conversion of 99% was assumed, and the reaction heat was calculated based on the approximate combustion enthalpy for organic components of 460 kJ/mol_{O2} [523]. Fermentation settings were determined based on the 2PE concentration in the fermentation broth, which was kept below 2.5 g_{2PE}/L_{broth} to prevent product inhibition. Hence, 2PE concentration was varied between 0.1 and ~2 g_{2PE}/L_{broth}. Flowrates of all inlet streams were back-calculated to achieve a production capacity of about 2 $ktonne_{2PE}$/y, regardless of the 2PE concentration in the broth. The required broth volume was calculated from previously determined broth flowrate and growth rate. The required number of fermenters was determined assuming a maximum fermenter size of 500 m^3, with 90% working volume. To choose a fermenter configuration, aeration and mixing costs were compared for two reactor types: bubble column (BC) and stirred-tank reactor (STR) [25]. A sequence of two vessels, increasing in size by a factor of 10 [25], was assumed for the seed train.

As previously mentioned, two processes were considered for 2PE purification from fermentation broth: **Process A** involves using liquid-liquid extraction as an ISPR technique. Oleyl alcohol was selected as the extractant for ISPR, as it had been demonstrated effective for pilot-scale continuous extractive fermentation [44]. The extraction process was simulated as a three-stage counter-current extraction column. Even though integrating fermentation and extraction into one equipment unit is feasible [524], this novel unit is not available in Aspen Plus. An oleyl alcohol flowrate was determined to enable recovery of >95% of 2PE from the fermentation broth. **Process B** utilizes hydrophobic adsorption followed by desorption with ethanol as the ISPR technique. Prior to the adsorption step, fermentation broth was centrifuged to remove

microorganisms. As an alternative to centrifugation, filtration may be used to remove microorganisms from the fermentation broth. The biomass-rich stream was largely recycled to the fermenters to minimize biomass loss. The adsorbed 2PE was desorbed using hydrous ethanol as an inexpensive solvent. In both processes, the remaining aqueous phase depleted of 2PE was largely recycled to the bioreactor. The solvent (oleyl alcohol or ethanol) rich in 2PE, was sent to the solvent recovery and final 2PE purification sections. In both processes, distillation was used as the main separation technique in these steps. Recovered solvents (oleyl alcohol and ethanol) can be recycled for reuse in ISPR. Since the amount of impurities in the recovered solvents are below 1 wt%, a conservative bleed of 1% was assumed for these streams to avoid impurity buildup. As mentioned, the processes modeled in this work present steady-state operation.

5.2.4. Results and discussion

Process design

Flowsheets of the developed processes are presented in Figure 5-8 and Figure 5-9.

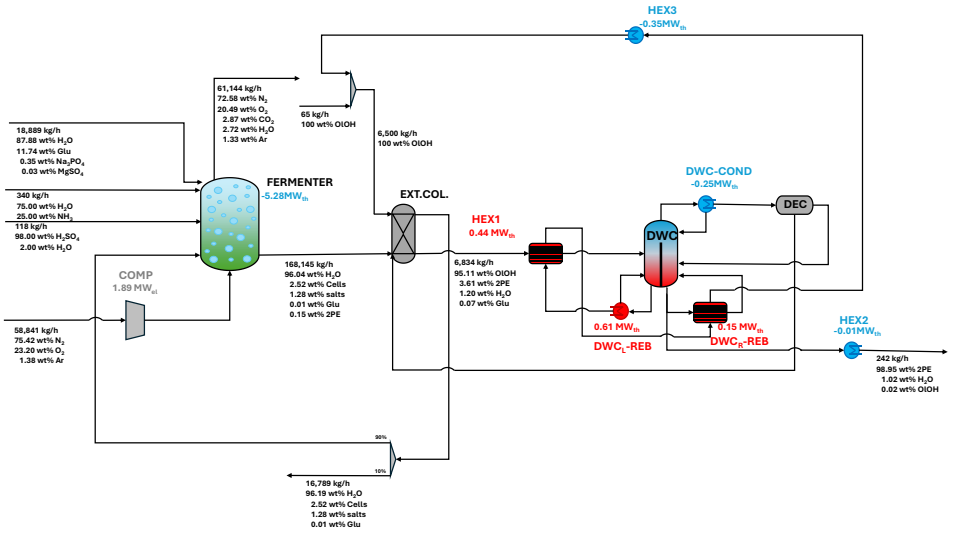


Figure 5-8. Process A - 2PE *de-novo* fermentation from glucose with liquid-liquid extraction as the ISPR technique and final purification by distillation

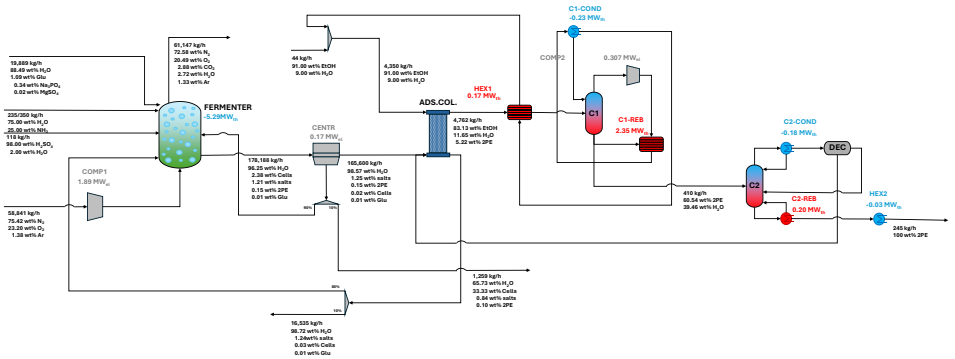


Figure 5-9. Process B - 2PE *de-novo* fermentation from glucose with product adsorption as the ISPR technique and final purification by distillation

Fermentation

To ensure sufficient mixing, a superficial gas velocity (corrected for pressure) of 0.2 m/s was assumed for a BC. This resulted in a gassed power input of 1.96 kW/m^3_{broth}, or an electrical energy requirement of 396 kW_e for gas compression (assumed isentropic operation) if the fermenter is a BC. In a STR, an impeller power input of 1.79 kW/m^3_{broth} is required to achieve the same total power input while maintaining sufficient reactor aeration, resulting in a specific power of approximately 0.17 kW/m^3_{broth}. In total, 836 kW_e are required if the fermenter is a STR. Since the capital costs of BC and STR are relatively similar [525] and a STR requires significantly more electrical energy input, the BC fermenter configuration was chosen and appropriate capital and operating costs were included in the economic analysis.

Downstream processing

Process A – ISPR using liquid-liquid extraction

When determining the oleyl alcohol flowrate, a trade-off must be considered: using more solvent increases 2PE recovery but results in a lower 2PE concentration in the solvent, complicating subsequent separation. Additionally, higher solvent flowrate leads to larger equipment sizes and increased capital costs, as well as higher operating costs in downstream steps due to greater reboiler energy requirements. An oleyl alcohol-to-broth flowrate ratio of 0.039 (mass basis) was selected to allow recovery of >95% of 2PE from the fermentation broth (Figure 5-10). As a result, after the extraction process, the aqueous phase was completely depleted of 2PE (<0.01 wt%), while the concentration of oleyl alcohol in the aqueous phase remained insignificant (<0.01 wt%). Conversely, the concentration of 2PE in the organic phase was more than 24 times higher than in the fermentation broth. This stream was sent to the solvent recovery and final 2PE purification sections.

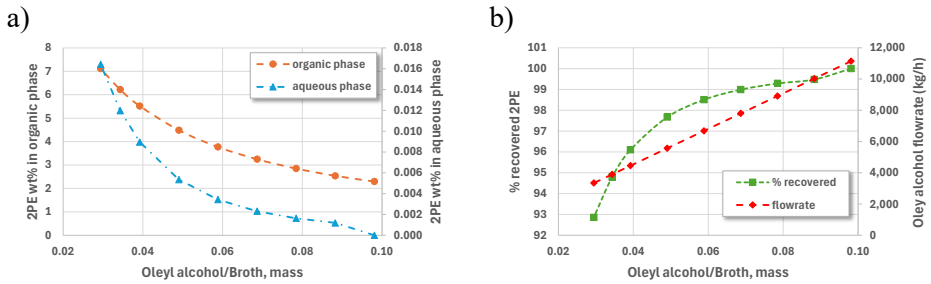


Figure 5-10. Dependence of a) 2PE concentration in the organic and aqueous phases, b) % recovered 2PE and oleyl alcohol flowrate on oleyl alcohol/broth mass ratio (chosen value: 0.039)

A two-step purification was required to obtain highly pure 2PE from its mixture with oleyl alcohol and water. Oleyl alcohol could be recovered at the bottom of a first distillation column, while a second distillation column could separate 2PE at the bottom from the water-2PE mixture at the top. Additionally, liquid-liquid separation in a decanter was needed due to the formation of a heterogeneous azeotrope between water and 2PE. The two columns were effectively integrated into one azeotropic dividing-wall column (A-DWC) with a common overhead section and a divided bottom section (Figure 5-11). This energy-efficient unit reduces capital costs as it minimizes the number of column shells, heat exchangers and the required plant area. As the A-DWC unit is not available in Aspen Plus, it was simulated as an equivalent sequence of thermally integrated distillation columns (Figure 5-11), where A-DWC$_L$ and A-DWC$_R$ represent the left and right parts of A-DWC. Oleyl alcohol (>99.8 wt%) was recovered at the bottom of A-DWC$_L$ and was reused in the extraction step. High-purity 2PE (~99.0 wt%) was recovered at the bottom of A-DWC$_R$, while a nearly azeotropic water-2PE mixture was obtained as the top product. This mixture was sent to the decanter for liquid-liquid phase splitting. To minimize 2PE loss, the 2PE-rich phase was returned to A-DWC, while the water-rich phase was recycled to the extraction column. Since oleyl alcohol needs to be cooled before being reused in the extraction column, it was used to preheat the feed stream to A-DWC, reducing the reboiler duty of A-DWC$_L$ by ~38%. Additionally, oleyl alcohol can also replace heating utility in A-DWC$_R$'s reboiler. Thus, the two mentioned heat integrations reduced the total heating duty of A-DWC by 45-49%.

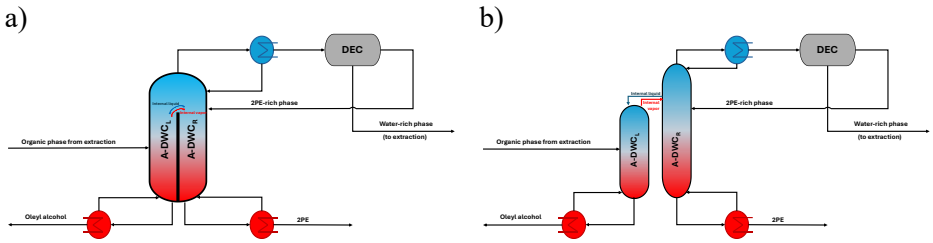


Figure 5-11. a) Azeotropic dividing-wall column, b) Equivalent sequence of distillation columns

Process 2 – ISPR using adsorption by hydrophobic resin

Macronet MN200 resin which efficiently adsorbs 2PE from a multicomponent mixture was assumed for process modeling (adsorption capacity of 210 g_{2PE}/kg_{resin}). However, alternative resins with similar properties have already been explored [516–521]. As previously mentioned, adsorbed 2PE was desorbed using hydrous ethanol as a cost-effective solvent. The obtained mixture of ethanol, 2PE and water was sent to the solvent recovery and final 2PE purification sections. Being the lightest boiling component, ethanol (with some water) was recovered as the top product from column C1 (Figure 5-9). The remaining 2PE and water, separated at the bottom of column C2, are sent to column C2. A high-purity 2PE (~100 wt%) was obtained as the bottom product from C2. The nearly azeotropic 2PE-water mixture obtained as the top product of column C2 was sent to a decanter for liquid-liquid phase splitting. To minimize product loss, the 2PE-rich phase was returned to column C2, while the aqueous phase was recycled to the adsorption step. The optimal ethanol concentration for desorption was determined to minimize the energy requirements of column C1 (Figure 5-12). As ethanol concentration approaches the azeotropic point, its separation on the top of column C1 becomes more energy-intensive, requiring a higher reboiler duty due to the higher required reflux ratio. Given the non-significant temperature difference at the top and the bottom of column C1, a mechanical vapor recompression (MVR) heat pump system could be implemented to decrease energy requirements. This heat pump system implies compressing vapor from the top of the column and using it as a heating source in the reboiler. Consequently, the electrical energy required to power the compressor can replace much higher thermal energy [113]. Additionally, as the top vapor from column C1 needs to be further cooled before being returned to the column, it may be used to preheat the feed stream to this column. This may reduce the reboiler duty of column C1 by about 7-8%. However, as ethanol concentration approaches the azeotropic point, a higher compressor power in the MVR system is required (Figure 5-12). Finally, an ethanol concentration of 91 wt% in the desorbent was chosen as higher concentrations significantly increase energy requirements. Simultaneously, lower concentrations only marginally reduce energy requirements while increasing the

required equipment size. The obtained energy savings with the implementation of the MVR system to column C1 can be measured through the coefficient of performance (COP). COP is equal to the ratio of the upgraded heat (exchanged between the compressed vapor and bottom liquid) and the required compressor power. Since the COP of the designed system is 5.0-9.7, which is significantly higher than the conservative value of the electrical-to-thermal conversion factor (about 2.5), it may be concluded that the implemented MVR system brings significant energy savings compared to simple distillation without a heat pump. Furthermore, this allows (green) electrification of the ethanol recovery step, while thermal energy is required only in the final 2PE purification.

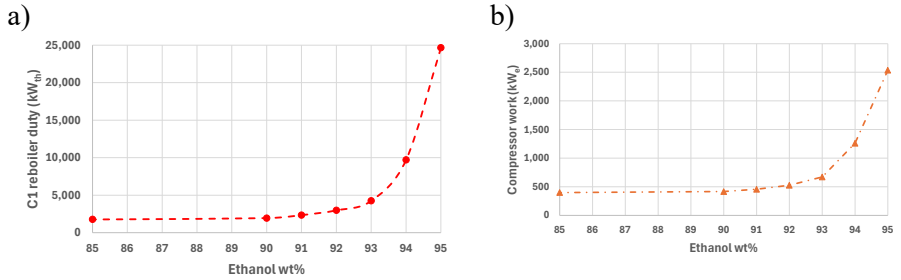


Figure 5-12. Dependance of a) reboiler duty of C1 column, b) compressor duty in the MVR system for column C1 on ethanol wt% in the desorbent

Optimal 2PE concentration in the fermentation broth

The impact of 2PE concentration in the fermentation broth on unit production costs (UPC) was analyzed and the results presented in Figure 5-13.

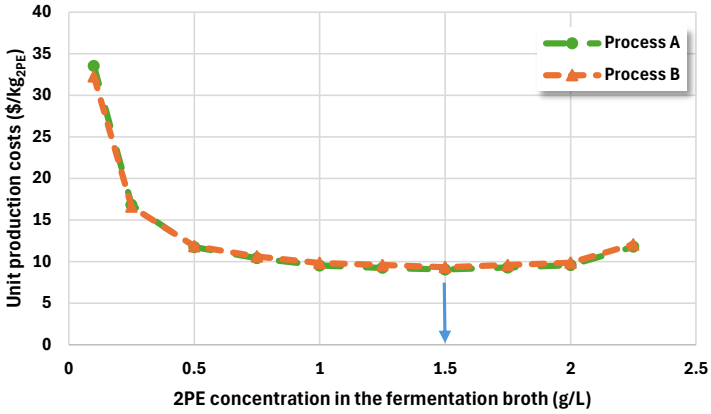


Figure 5-13. Effects of 2PE concentration in the fermentation broth on the total production costs (minimal value for 1.5 g_{2PE}/L_{broth})

The UPC increases significantly only when 2PE concentrations fall below 0.5 g_{2PE}/L_{broth}. Conversely, for concentrations above 1.0 g_{2PE}/L_{broth}, the changes in UPC are not that significant. A key finding is that 2PE concentration of approximately 1.5 g_{2PE}/L_{broth} in the fermentation broth results in the minimum unit production costs for both processes. Notably, this does not necessarily align with the highest product formation rate. Using the calculated maximum specific growth rate (μ^{max}) of 0.17 h^{-1}, the highest product formation rate is observed at a 2PE concentration of 1.0 g_{2PE}/L_{broth}, decreasing for both lower and higher concentrations. A 2PE concentration of 1.0 g_{2PE}/L_{broth} results in a slightly higher UPC than 1.5 g_{2PE}/L_{broth} because of the increased cost of downstream processing. Lower 2PE concentrations necessitate larger processing throughput to achieve the same production capacity, resulting in larger equipment units (higher CAPEX) and a more energy-intensive recovery process (higher OPEX). On the contrary, despite reducing the costs of the recovery process costs, 2PE concentration higher than 1.5 g_{2PE}/L_{broth} increases the fermentation costs leading to a rise in the total production costs. These insights are crucial for optimizing industrial-scale natural 2PE production. They demonstrate that it is not necessary to push 2PE concentration to extreme limits, as an optimal balance between upstream and downstream processing exists. Maintaining a 2PE concentration of around 1.5 g_{2PE}/L_{broth} offers a cost-effective solution by minimizing overall production expenses while ensuring competitive process efficiency. Detailed analysis of economic and environmental performance is provided for this concentration of 2PE in the fermentation broth of 1.5g_{2PE}/L_{broth}.

Techno-economic analysis

A comparison of the main economic indicators for 2PE production process with 1.5 g_{2PE}/L_{broth} is given in Table 5-2 and Figure 5-14.

Table 5-2. Key economic indicators of *de-novo* 2PE production with 1.5 g_{2PE}/L_{broth}

	Process A	**Process B**
2PE concentration in the broth (wt%)	0.15	0.15
Total process yield (mol_{2PE}/mol_{Glu})	0.160	0.165
Economic indicators		
CAPEX (k$)	27,251	31,207
OPEX (k$/y)	14,704	15,323
OPEX ($/$kg_{2PE}$)	7.62	7.81
TAC (k$/y)	17,429	18,444
TAC ($/$kg_{2PE}$)	9.03	9.40

In general, the largest contributors to equipment costs are fermenters and seed trains (46-53%), compressors (about 25-26%) and flash units (about 10-11%). The extraction or adsorption column also represent a significant portion of the total equipment costs in both processes (about 5-81%). Furthermore, the centrifuge cost is not negligible contributor when using adsorption for ISPR (about 4%). The costs of distillation columns are low (about 1-2%). Also, heat exchangers and pumps contribute relatively little (accounting for 2-4% and 1-2% of the total equipment costs, respectively). Overall, the total equipment costs are higher if adsorption is used for ISPR (process B), primarily due to the additional compressor and centrifuge. As a result, the total capital costs (CAPEX) for process B are 15% higher than those for process A. The total operating costs (OPEX) for process B are also slightly higher compared to process A (by 4%). This difference is mainly due to higher resin replacement costs (assuming an annual replacement) and increased electricity due to the additional compressor in the MVR system. In contrast, the costs of solvent make up and high-pressure steam are higher in process A. However, by far the largest contribution to OPEX in both cases is feedstock (glucose, NH_3, Na_2PO_4, $MgSO_4$, H_2SO_4, water) cost, which accounts for approximately 57-59% of the total operating expenses. This is because substantial amounts of glucose are required relative to the product yield. Other operating costs, such as energy requirements, are minimized, reflecting an energy-efficient process design.

When considering both CAPEX and OPEX with a payback period of 10 years, the total annual costs (TAC), are slightly lower (by 6%) when using liquid-liquid extraction (process A) than when using adsorption (process B). Nonetheless, the unit production costs in both processes (9.03-9.40 $/kg$_{2PE}$) are in the range of the price of petrochemically produced 2PE (5-20 $/kg [442,444]) and are significantly lower than the costs associated with naturally produced 2PE (~1,000 $/kg for plant extraction and ~300 $/kg for microbial processes [445]). This suggests that both designed processes represent a major step forward in advancing industrial biotechnology of 2PE production. The choice of optimal ISPR design depends strongly on plant location and available utilities. ISPR by liquid–liquid extraction with oleyl alcohol allows continuous operation, while adsorption-based ISPR followed by ethanol desorption requires cyclic processing. Oleyl alcohol is more expensive and its recovery demands higher thermal energy, whereas usage of ethanol involves lower solvent costs but higher electrical energy requirements for solvent recovery. Furthermore, considering that the market price of L-phenylalanine (~10-30 $/kg$_{L\text{-}Phe}$ [526]) is very similar to that of 2PE, and given the cost-effectiveness demonstrated in this study, large-scale fermentative production of 2PE from glucose is more attractive than bioconversion of L-phenylalanine to 2PE.

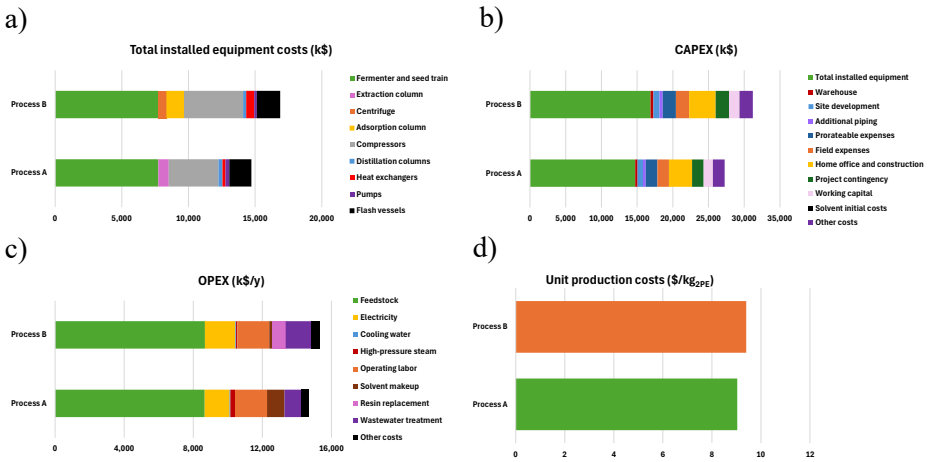


Figure 5-14. Comparison of the key economic indicators for the two designed 2PE production processes: a) total installed equipment costs, b) CAPEX, c) OPEX and d) unit production costs

Total annual costs (TAC) in the previous calculations were calculated assuming a payback period (PBP) of 10 years. An analysis was performed to examine the effects of payback period on total annual costs (see Figure 5-15). Even though TAC increase with shorter PBP, the developed processes are still cost-effective even for shorter PBP. TAC are lower than 16 or 24 $/kg_{2PE}$ with a payback period of two or only one year. On the contrary, the processes are less costly for longer PBP. Nonetheless, this decrease becomes insignificant for PBP longer than 10 years.

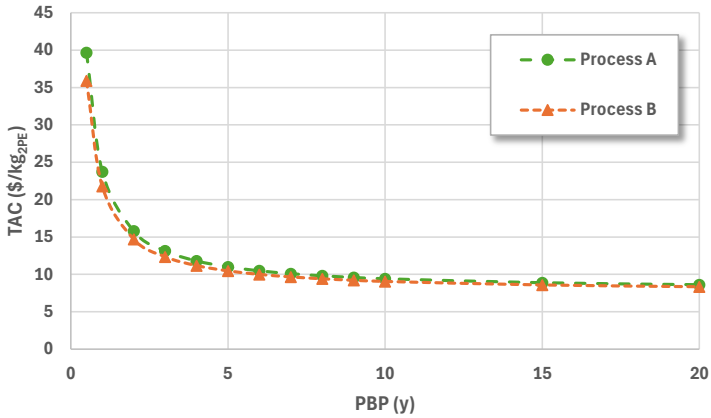


Figure 5-15. Effects of the pay-back period on total annual costs

Sustainability assessment

The main sustainability metrics for the developed processes are summarized in Table 5-3. A graphic representation of energy requirements and CO_2 emissions is presented in Figure 5-14.

Table 5-3. Key sustainability metrics of *de-novo* 2PE production with 1.5 g_{2PE}/L_{broth}

	Process A	**Process B**
2PE concentration in the broth (wt%)	0.15	0.15
Total process yield (mol_{2PE}/mol_{Glu})	0.160	0.165
Sustainability indicators		
Thermal energy requirements ($kW_{th}h/kg_{2PE}$)	2.508	0.652
Electrical energy requirements (kW_eh/kg_{2PE})	8.722	10.493
Primary energy requirements ($kW_{th}h/kg_{2PE}$)	24.312	26.884
CO_2 emissions, green electricity (kg_{CO2}/kg_{2PE})	0.462	4.912
CO_2 emissions, grey electricity (kg_{CO2}/kg_{2PE})	4.440	0.127
Utility water requirements (m^3_W/kg_{2PE})	4.664	4.064
Utility water losses (m^3_W/kg_{2PE})	0.329	0.285
Wastewater intensity (m^3_{WW}/kg_{2PE})	0.069	0.072

- ***Energy requirements***: Generally, thermal energy requirements are higher in process A due to the reboiler duty of A-DWC. In contrast, electrical energy requirements are higher in process B due to the compressor in the MVR system. As a result, the primary energy requirements are slightly higher in process B.
- ***Greenhouse gas emissions***: If electricity is sourced from fossil fuels (grey electricity), process B results in higher CO_2 emissions due to its greater primary energy requirements. However, if renewable electricity (green electricity) is used, process A produces more CO_2 emissions due to its higher reliance on thermal energy.
- ***Utility water requirements and loss***: Utility water requirements are related to the cooling of the fermenters and thermal energy requirements. Utility water requirements and water loss are higher in process A due to higher thermal energy requirements.
- ***Wastewater intensity***: Process B generates slightly more wastewater compared to process A. This difference is primarily due to water losses in the bleed stream after centrifugation.

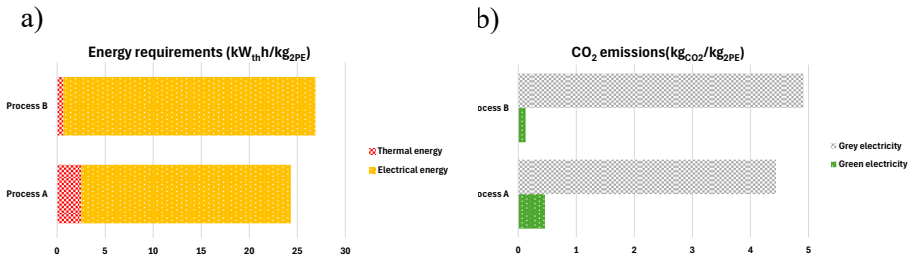


Figure 5-16. Comparison of the key sustainability metrics for the two designed 2PE production processes: a) energy requirements and b) CO_2 emissions

Effects of glucose price, solvent price and wastewater treatment costs

The effects of glucose price, wastewater treatment costs, solvent price and makeup fraction on the total 2PE production costs were analyzed using 1.5 g_{2PE}/L_{broth} as a representative concentration. The results are summarized in Figure 5-17.

- Glucose price: As major contributor to OPEX, the cost of glucose has the most significant contribution to the total 2PE production costs. Any increase or decrease in glucose price results in a proportional change in the production costs for both processes.
- Wastewater treatment costs: Compared to the glucose price, variations in wastewater treatment costs have a much lower effect on the total production costs. Nonetheless, this is slightly more pronounced in process B due to its higher wastewater amount.
- Solvent prices: The cost-effectiveness of the process is highly sensitive to fluctuations in oleyl alcohol and ethanol prices. An increase or a decrease in these prices directly affects 2PE production costs.
- Makeup fraction of solvent: A makeup of 1% was assumed for both oleyl alcohol or ethanol. However, variations in the makeup fraction may influence the process's economics by changing both solvent makeup costs and waste treatment expenses. The makeup fraction of oleyl alcohol has a greater influence on 2PE production costs than ethanol, due to its higher price.

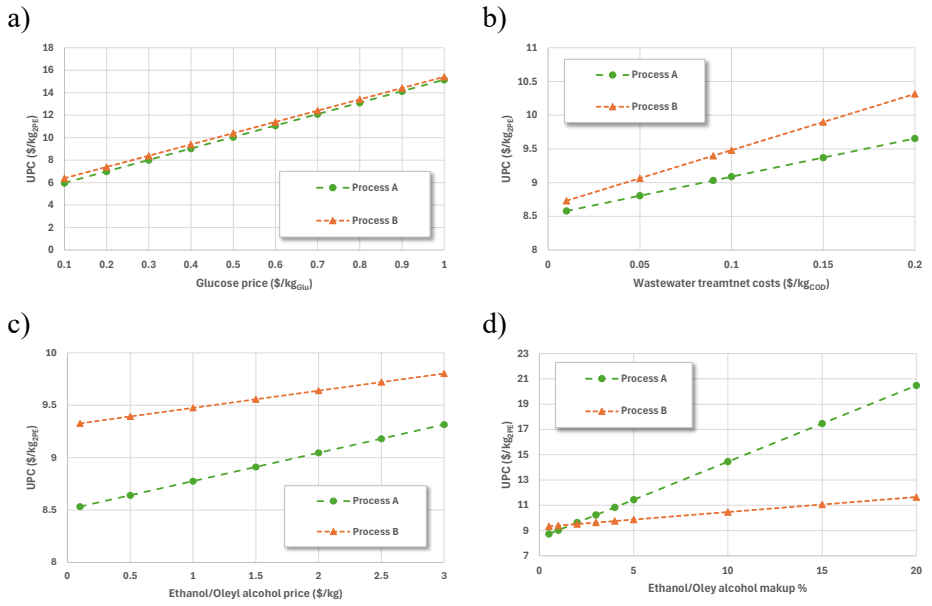


Figure 5-17. a) Effects of glucose price, b) wastewater treatment costs, c) ethanol or oleyl alcohol costs and d) makeup fraction

5.2.5. Conclusion

This original study is the first to develop two large-scale (~2 $ktonne_{2PE}/y$) processes for fermentative production of *de-novo* 2PE from glucose. This study compares *in-situ* product removal either by liquid-liquid extraction or adsorption by hydrophobic resins, followed by final purification using advanced distillation techniques. A key finding of this work is the identification of an optimal 2PE concentration of approximately 1.5 g_{2PE}/L_{broth}, where unit production costs are minimized due to the balance between upstream and downstream processing. This resulted in highly cost-competitive 2PE production (9.03-9.40 $\$/kg_{2PE}$), regardless of the method used for *in-situ* product recovery. Higher 2PE concentration leads to higher fermentation costs, while lower concentrations significantly increase both upstream and downstream expenses. Furthermore, sensitivity analysis revealed that glucose, oleyl alcohol and ethanol prices have a significant impact on the total production costs. These findings are crucial for developing a competitive industrial-scale process, demonstrating that maximizing 2PE concentration is not always necessary, but rather finding an optimal balance is key to reducing overall production costs.



6 | Conclusion(s)

6. Conclusion(s)

Живот јесте и заувек ће остати једначина која се не може решити, али садржи одређене познате факторе. (Никола Тесла, пионир инжењерства електротехнике, најпознатији по свом доприносу у пројектовању модерног система напајања)

Life is and will ever remain an equation incapable of solution, but it contains certain known factors. (Nikola Tesla, pioneer of electrical engineering, known for his contributions to the design of the modern alternating current electricity supply system)

The importance of separation processes in industrial biotechnology cannot be overstated. As biotechnology continues to revolutionize industries such as biofuels, specialty chemicals and pharmaceuticals, efficient recovery and purification remain critical to economic viability. Since downstream processing costs can significantly impact total production expenses, any improvements in the separation process play a crucial role in enhancing overall cost-effectiveness and determining the feasibility of commercial applications [35]. Nonetheless, the main focus of biotechnology is often on product development, genetic engineering of microorganisms and enhancing the bioreaction step. Until ideal conditions for the upstream process are met, enhancing the recovery process may significantly increase the competitiveness of the overall bioprocess [497]. In that respect, the research presented in this thesis contributes to the advancements in industrial technology by offering critical insights into the downstream processing performance for the recovery of many valuable platform and specialty chemicals.

6.1. Fluid separation techniques for efficient recovery of low-boiling fermentation product

Findings from research question 1: *Which fluid separation techniques can be used to efficiently recover low-boiling fermentation products?*

In this thesis, fermentation products with boiling points lower than water (approximately 100 °C) or those that form light-boiling azeotropes with water were classified as volatile. Many valuable chemicals produced through fermentation, such as ethanol, isopropanol, isobutanol, 1-butanol, 1-hexanol, acetone, and ethyl acetate, fall into this category. These products often inhibit growth and activity of the producing microorganisms at relatively low concentrations, typically below 10 wt%. This end-product inhibition can be alleviated through *in-situ* product recovery (ISPR), a technique that involves continuous removal of the desired product during fermentation.

For ISPR to be effective, it must preserve microbial viability by avoiding potentially toxic chemicals and extreme operating conditions. Thus, fermentation products should ideally be removed at temperatures close to the fermentation temperature. Distillation is traditionally viewed as unsuitable for ISPR due to the high operating temperatures, which could harm microorganisms. However, employing reduced-pressure evaporation, in a closed loop around a bioreactor, may offer a viable alternative by enabling efficient product separation at lower temperatures without adversely affecting microbial viability or causing product loss. This approach avoids using additional chemicals that may complicate later recovery and influence the overall environmental impact of the bioprocess. As proved in the previous chapters of this thesis, different distillation-based techniques (vacuum distillation, pass-through distillation, gas stripping combined with vacuum evaporation) can be used to separate volatile fermentation products from the fermentation broth at an industrial scale.

Besides efficiently removing volatile products, reduced-pressure distillation may allow biomass recycling to the fermenter. Cell recycling can increase biomass concentration and substrate-to-product yield, potentially reducing the required fermenter volume [25]. Furthermore, water usage can be minimized by recycling water after product separation, enhancing the overall sustainability of the process. Thus, besides simplifying downstream processing, ISPR by vacuum distillation may significantly improve the fermentation process. After ISPR, distillation can efficiently be used to separate the valuable product from the remaining water, light and heavy impurities. In cases of azeotrope formation, hybrid systems like extractive distillation or distillation coupled with liquid-liquid phase splitting may be needed to obtain a high-purity final product.

6.2. Fluid separation techniques for efficient recovery of high-boiling fermentation product

Findings from research question 2: *Which fluid separation techniques can be used to efficiently recover high-boiling fermentation products?*

In this thesis, non-volatile fermentation products were defined as those with boiling points higher than water and which do not form low-boiling azeotropes with water. These characteristics prevent their evaporation from the broth without the complete removal of water, which would be very energy-intensive. Furthermore, their high boiling points make distillation unsuitable as an ISPR technique without compromising microbial viability. Thus, an initial separation of biomass from the product using alternative methods is necessary. The choice of approach depends on the achievable concentration and the specific nature of the fermentation product.

For instance, achievable concentrations of aliphatic diols (1,3-propanediol, 2,3-, 1,4- and 1,3-butanediol) are not extremely low (5-15 wt%). Therefore, a common practice is to remove biomass, large organic molecules and inorganic impurities by using filtration and ion exchange. After these initial steps, it is necessary to recover valuable product from a dilute aqueous solution (possibly more dilute than broth). As previously proven in section 3, distillation can be efficiently used to separate water (preconcentration step) and recover a high-purity product from the remaining light and heavy impurities (final preconcentration step).

On the contrary, when achievable product concentrations are extremely low (e.g. the tolerable concentration of 2-phenylethanol in the broth is about 0.2 wt%), another ISPR technique, other than distillation, is required for the initial removal of the valuable product from the broth. Among others, techniques such as liquid-liquid extraction using biocompatible solvents, product adsorption or membrane separations have been extensively studied for this purpose. After this initial separation, further purification is needed to recover the product from solvents (extractant or desorber liquid). Distillation can effectively be employed to obtain a high-purity final product while enabling the reuse of the solvents.

Lastly, when the valuable fermentation product is present in an ionized form (e.g. carboxylic acids), several steps may be needed (removal of cells and debris, and counterion removal) before the final purification. Once the cells and debris have been filtered out, and the acid has been converted from an anion form to an acid form, distillation can be efficiently used to recover a high-purity product.

In summary, recovery of non-volatile products necessitates the use of multiple separation techniques. Initially, the separation of biomass and other large molecules, or *in-situ* product removal are required. Nonetheless, distillation remains a critical component of subsequent purification processes, efficiently recovering high-purity products and facilitating the recycling of water or solvents.

6.3. Process intensification principles in the recovery of biobased processes

Findings from research question 3: *How can process intensification principles be applied to fluid separation techniques to reduce energy requirements and costs of downstream processing (and the entire bioprocess)?*

Using conventional simple distillation for downstream processing after fermentation is feasible, but it can be highly energy-intensive and costly. Advanced distillation technologies, such as heat pump-assisted distillation, heat-integrated distillation, dividing-wall column, and reactive distillation, provide innovative solutions that may improve efficiency and decrease overall purification costs.

Heat pump-assisted distillation is one such innovation that may significantly reduce energy requirements of distillation process. By using a heat pump to recover and reuse waste heat, this technology minimizes need for external heating sources, reducing the overall energy demand. In addition to reducing the external heating requirements, heat pumps may allow partial or complete (green) electrification of the recovery process.

Heat-integrated distillation takes energy optimization a step further by linking multiple distillation columns together in a manner that allows the heat from one column to be used in another. This process of thermal integration reduces the need for external heating and cooling sources, ensuring that energy is used as efficiently as possible.

Dividing-wall column is a very promising technology in cases where multiple components need to be separated simultaneously. This technology uses a single column with an internal wall, enabling the separation of different products without the need for additional distillation units. As a result, dividing-wall columns may reduce both energy consumption and the capital cost associated with installing multiple columns.

Reactive distillation combines chemical reaction and separation processes in a single unit. Consequently, it may reduce the number of processing steps and lower energy consumption. In industrial biotechnology, reactive distillation can be used

to separate water or recover solvent while simultaneously producing desired bio-based chemicals.

Together, these advanced distillation technologies advance industrial biotechnology by reducing energy consumption, minimizing waste, and improving the efficiency of product recovery. As proven in this thesis, advanced distillation technologies may be implemented to drastically decrease energy requirements (60-80%) and costs (by about 40-80%) of the separation process.

6.4. Role of process systems engineering in the development of industrial biotechnology

Findings from research question 4: *In what ways can process systems engineering (PSE) methods support the development of industrial biotechnology for the production of distillable biochemicals?*

As proven in this thesis, the process systems engineering (PSE) approach should serve as a key pillar in the development of industrial biotechnology, providing tools and methodologies needed to design, optimize, and scale up biotechnological processes. Process design and simulation allow exploration of various phenomena and interactions between different process parts while minimizing need for experimental validation. As shown by many examples in this thesis, the role of PSE in scaling up bioprocesses from laboratory to industrial scale is crucial. It enables prediction and mitigation of potential bottlenecks before full-scale implementation, saving time and resources. Hence, PSE methods should be used as powerful instruments to accelerate development of efficient and sustainable bioprocesses.

6.5. Influence of product concentration on the performance of the recovery process

Findings from research question 5: *How does product concentration in the fermentation broth influence downstream processing performance for recovering distillable biochemicals?*

Product concentration in the fermentation broth plays a key role in determining energy requirements for downstream processing, directly influencing overall production cost. This concentration is limited by the inhibitory effects that high product concentration has on present microorganisms (reduced growth rate and substrate consumption rate) [151]. The maximum product concentration in the fermentation broth is highly dependent on the specific fermentation conditions and microorganisms used. Anyhow, it can be concluded that the cost of the upstream fermentation process will rise with increasing product concentration [154]. On the contrary, lower product concentration in the

fermentation broth will result in a less profitable and sustainable downstream process. However, it is important to note that recovery costs do not rise sharply unless product concentrations are extremely low (e.g., below 1 wt%). Therefore, if it significantly benefits the fermentation process, lower product concentrations should still be considered.

6.6. Significance and potential impact of this thesis

The development of industrial biotechnology has significantly advanced in recent years, offering the potential to produce a wide range of valuable platform and specialty chemicals through biological processes. By utilizing renewable resources such as biomass, waste materials or off-gases, industrial biotechnology provides a more sustainable and environmentally friendly alternative to traditional chemical production methods. The ability to produce high-value chemicals through various biotechnology-based processes is seen as a key path to achieving sustainability goals while maintaining economic competitiveness. Accordingly, this shift toward biobased production is gaining significant recognition, attracting not only extensive research attention but also growing interest from companies. However, despite significant industrial development, many biotechnology-based production plants have been shut down or remain inactive due to financial challenges [70]. Thus, significant improvements are still needed to make these processes competitive with traditional petrochemical production.

In that respect, the results of this original research may have a significant impact on advancing industrial biotechnology by enhancing the recovery process. Specifically, the development of advanced separation techniques for multiple platform and specialty chemicals demonstrates their suitability for large-scale industrial applications, addressing a critical gap in current bioprocessing technologies. Furthermore, a key contribution of this work is the application of process intensification principles, which have maximized energy efficiency and minimized costs of the recovery process. The comprehensive comparison of process performance indicators, presented in Table 6-1, further validates these advancements, providing a robust framework for evaluating and improving separation efficiency.

Table 6-1. Summary of the recovery costs for the analysed biochemcials

Product	Costs of recovery process ($/kg)	Market price ($/kg)
Ethanol[a]	0.080[a]	0.591 [257]
Isopropanol and acetone	0.109	1.310 [258]
Isobutanol	0.161	2.043 [259]
Hexanol	0.529	2.500 [260]
1,3-propanediol[b]	0.150-0.274[c]	3.800-4.200 [290]
2,3-butanediol[b]	0.222	/
1,4-butanediol[b]	0.208	1.774 [527]
1,3-butanediol[b]	0.243	/
Propionic acid[a]	0.399[c]	0.856 [528]
Ethyl acetate	0.607-1.085	1.740 [397]
2-phenylethanol / 2-phenylethyl acetate[a]	0.643-0.728	5-20

[a]from syngas fermentation
[b]initial recovery steps not included
[c]including recovery of by-products
.

In conclusion, this thesis provides compelling evidence of the transformative impact that advancements in downstream processing can have on overall process performance. The research emphasizes the importance of integrating downstream processing early in the development of bio-based production processes. The findings presented here have the potential to accelerate the progress of industrial biotechnology and support the successful commercialization of bio-based products.



7 | Outlook

7. Outlook

Као што муња у тамној ноћи обасја путнику цео хоризонт пред њим, тако се таквом муњом у мозгу генијалног човека отварају у науци нови видици и откривају нове области науке. (Милутин Миланковић, математичар, астроном, климатолог, геофизичар и грађевински инжењер, познат по теорији о дугорочним климатским променама Земље узрокованим астрономским променама у положају Земље у односу на Сунце (Миланковићеви циклуси) и по карактеризацији планета Сунчевог система у делу „Канон Земљине инсолације“)

Just as lightning on a dark night illuminates the entire horizon before a traveller, so with such lightning in the brain of a man of genius, new vistas in science open up and new areas of science are discovered. (Milutin Milanković, mathematician, astronomer, climatologist, geophysicist and civil engineer, known for his theory on Earth's long-term climate changes due to astronomical shifts (Milankovitch cycles) and his characterization of the Solar system's planets in the "Canon of the Earth’s Insolation.")

Looking forward, the insights gained from this research open several promising avenues for future work. While the current study has provided a comprehensive understanding of the downstream processing performance in the recovery of many valuable fermentation products, there remain numerous opportunities for further exploration. Some of these are discussed in more detail below.

Integration of the upstream and downstream processes

This thesis has primarily focused on enhancing the downstream processing part of bioprocesses. However, it is essential to consider the design of the entire bioprocess, including both the upstream and downstream parts. By integrating all stages of the bioprocess, a more comprehensive approach to process design can be achieved.

To obtain the most efficient operation, the entire bioprocess should be developed with the goal of minimizing costs and environmental burden per kilogram of final product [26]. It is important to recognize that optimizing the upstream and downstream processes individually does not necessarily result in an optimal overall process. In fact, optimizing each part independently could lead to suboptimal performance when both phases are considered in tandem. Instead, a systems-based approach is needed, one that accounts for the interdependencies between the upstream bioreaction and downstream separation and purification steps. By optimizing the bioprocess as a whole, these interdependencies can be identified and leveraged, leading to a more efficient and cost-effective operation.

An integrated approach may also enable a deeper analysis of the interactions between the two key parts of the bioprocess, upstream and downstream. Understanding how conditions in one part affect the performance of the other is essential for identifying bottlenecks and areas for improvement. For instance, downstream processing can offer important insights during the development of upstream processes, such as the early detection of impurities that could substantially raise overall costs. Furthermore, the end-goal commercial process should guide decision-making in developing both the upstream and downstream parts of the process [26].

Process systems engineering perspective in the development of industrial biotechnology

The research summarized in this thesis presents only a small part of the potential impact process systems engineering (PSE) may have on the development of industrial biotechnology. Besides enabling process development and optimization through efficient process design and simulation tools, PSE may contribute to the sustainability of industrial biotechnology through all three pillars of sustainability: environmental, economic and societal. Techniques such as Life Cycle Analysis (LCA) and Techno-Economic Analysis (TEA) allow early assessment of the environmental and economic impacts of bioprocesses. These evaluations inform decisions on resource utilization, waste management, and energy efficiency. Societally, PSE supports development of biotechnological solutions that address global challenges such as food security, public health, and

resource distribution. By advancing the development of industrial biotechnology, PSE may contribute to improving the quality of life and fostering economic opportunities in underdeveloped regions. It may empower local communities, reduce dependency on fossil fuels, and enhance resilience against supply chain disruptions. Furthermore, a key societal impact of PSE is its role in promoting education, training, and workforce development in sustainable industries. A multidisciplinary approach, combining expertise from various fields, is crucial for achieving the best results and ensuring the successful integration of PSE-driven innovations into industrial biotechnology. Thus, utilizing various PSE techniques may significantly accelerate commercialization of novel biotechnological solutions.

Experimental testing/validation

In designing a process using Aspen Plus, the need for experimental testing can often be minimized if rigorous models of equipment units and reliable kinetic and thermodynamic models are employed. Rigorous unit operation models in Aspen Plus are developed based on extensive experimental validation and proven to realistically replicate the behavior and performance of real-life units under a certain range of operating conditions. The use of reliable thermodynamic models ensures accurate prediction of phase equilibria, heat and mass transfer, and other critical process phenomena, aligning closely with experimental results. Furthermore, to accurately represent real-world systems, all approximations made during simulations (e.g. leaving out some components) should be realistic. However, certain advanced or complex processes may still benefit from experimental testing to validate specific aspects. For example, reactive distillation systems, where chemical reactions occur in the presence of catalysts, may require experimental validation to confirm reaction kinetics, catalyst performance, and compatibility under real-world conditions. Similarly, pass-through distillation processes that rely heavily on property models for highly specific systems may benefit from experimental testing to refine model parameters or validate assumptions under non-ideal conditions. By focusing experimental efforts on these critical areas while leveraging Aspen Plus for other standard operations, the overall process design can achieve a balance between reliability and efficiency.

Nonetheless, it is important to emphasize that further analysis is required to confirm microorganism viability following product separation when vacuum distillation is used for *in-situ* product recovery. Previous studies [529,530] have demonstrated that broth subjected to vacuum distillation can be reused in fermentation, a concept that has also been tested at the pilot scale [96]. Because cells are non-volatile, they migrate directly to the bottom of the distillation column, and the short retention time minimizes concerns about nutrient shortages.

Additionally, it has been shown that cells can survive reduced-pressure conditions [531]. However, the shear forces generated by rapid pressure changes require careful evaluation. For instance, microorganisms have been observed to withstand hydrostatic pressure changes of approximately 2 atm per minute when cycled through an industrial gas lift bioreactor [532]. To ensure microbial viability, measures may be necessary to control the rate of pressure change during the distillation process. If recycling the bottom stream from vacuum distillation to fermentation, the fraction to be purged and the growth rate required during fermentation will depend on the fraction of viable microorganisms after the separation process.

Analysis of process dynamics

The processes developed in this thesis represent steady-state operations. Nonetheless, as bioprocesses are very complex, the need for a deeper understanding of process dynamics becomes crucial. These processes can be influenced by a wide range of factors, including environmental conditions, substrate availability and properties, and the activity of microorganisms or enzymes. Furthermore, processes with intermittent input of energy (e.g. renewable electricity) or feedstock should be flexible enough to handle challenges in supply and ensure consistent performance. Analyzing the dynamic behavior of the system is important for identifying potential sources of instability, which can impact the efficiency, yield, and cost-effectiveness of the process. It is essential to develop robust control strategies that can manage these dynamic fluctuations. Analysis of process dynamics provides the foundation for designing such strategies, enabling real-time monitoring and adjustment of critical process parameters.

Additionally, analyzing process dynamics is particularly crucial in highly integrated processes, such as some of the advanced distillation processes used in this thesis. These integrated systems often operate with fewer degrees of freedom, meaning that the interactions between different process units are more tightly coupled. As a result, it becomes essential to ensure that the entire system is controllable and stable under varying conditions. A thorough understanding of dynamics allows identification of potential risks and the design of effective control strategies that prevent instability or inefficiencies in these complex systems.

Lastly, the analysis of process dynamics and the development of control strategies are also vital during startup and shutdown operations. These phases are inherently challenging due to the significant changes in process conditions that occur as the system transitions from one state to another. Hence, reliable insight into process

dynamics and control may enhance product consistency and quality, ensure safe operation, and minimize waste, energy consumption, and overall cost.

Development of thermodynamic property models

A reliable thermodynamic property model is essential in process development and simulation, as it ensures accurate predictions of real-life processes. Such models are crucial for optimizing process design, improving efficiency, and minimizing operational risks, particularly in complex systems involving multiple phases and components. Hence, the development of advanced thermodynamic tools is becoming increasingly important in the field of bioprocess engineering, particularly due to the complexity of biobased systems. Unlike traditional chemical processes, bioprocesses involve a wide range of different components, including microorganisms, organic and inorganic impurities, gases, ions, and biopolymers, which interact in intricate ways. These interactions may lead to non-ideal behaviors that complicate certain operations in the bioprocesses. Therefore, the ability to accurately model such systems using thermodynamic tools is essential to improving the efficiency and scalability of biotechnological processes.
Looking forward, continued progress in thermodynamic modeling tools will be essential for addressing the challenges associated with biobased systems. Researchers and engineers should focus on refining these models to account for the unique characteristics of biological components and their interactions.

Development of novel and enhancement of existing distillation technologies

This thesis emphasizes the potential of distillation in the downstream processing of different bio-based processes. In that respect, the development of novel and the enhancement of existing distillation technologies will be fundamental to advancements in biochemical engineering. However, to meet the increasingly stringent product specifications and sustainability goals, there is a pressing need to innovate and optimize distillation processes, focusing on both energy efficiency and environmental impact [170].

Advances in distillation technologies are crucial for improving process efficiency, lowering energy consumption, and reducing environmental footprints. Techniques like heat integration, divided-wall columns, and reactive distillation are already in the spotlight, offering solutions to reduce energy demand while enhancing separation performance. Furthermore, hybrid distillation systems like membrane distillation, cyclic distillation or HiGee distillation hold great promise for improving the cost-effectiveness and sustainability of industrial separation processes.

Additionally, there is considerable potential in further developing the pass-through distillation (PTD) technology. The research presented in this thesis demonstrates that PTD is a highly competitive technology for large-scale recovery of volatile alcohols after fermentation. However, this should be viewed as just the first step in advancing this innovative technology. PTD has significant potential for a wide range of applications, including the recovery of organic solvents, water removal for chemical drying, aroma recovery in the food industry, concentration of orange juice, separation of heat-sensitive materials, and purification processes, among others.

Thus, continued research and development in novel distillation technologies, along with the optimization of existing systems, will be crucial for improving efficiency, scalability, and sustainability of industrial separation processes, including downstream processing in biotechnology. Although mature and well-established technology, there is still significant potential for innovation and breakthroughs in distillation.

Nomenclature

Abbreviations – general

CAPE	Computer-aided process engineering
CAPEX	Capital expenditures
CARAF	Concurrent alcohol removal and fermentation
CHP	Combined Heat and Power
COD	Chemical oxygen demand
COP	Coefficient of performance
DSP	Downstream processing
DWC	Dividing-wall column
HOC	Hayden O'Connell thermodynamic property model
HP	High-pressure stream in sections 2.2 and 2.3
ISPR	*In-situ* product recovery
LCA	Life cycle assessment
LMTD	Logarithmic mean temperature difference
LP	Low-pressure stream in sections 2.2 and 2.3
MASP	Minimum average selling price
MED	Multi-effect distillation
MP	Medium-pressure stream in sections 2.2 and 2.3
MASP	Minimum average selling price
MINLP	Mixed-integer nonlinear programming
MVR	Mechanical vapor recompression
NREL	National Renewable Energy Laboratory
NRTL	Non-Random Two Liquid thermodynamic property model
OPEX	Operating expenditures
PBP	Payback period
PI	Process intensification
PSE	Process systems engineering
REFPROP	Reference fluid properties thermodynamic property model
TAC	Total annual costs
TEA	Techno-economic analysis
UNIFAC	Universal functional activity coefficient thermodynamic property model
UNIQUAC	Universal quasichemical thermodynamic property model
UPC	Unit production costs

Abbreviations – chemical species

1,3-BDO	1,3-butanediol
1,4-BDO	1,4-butanediol
2,3-BDO	2,3-butanediol
1,3-PDO	1,3-propanediol
2PE	2-phenylethanol
2PEAc	2-phenylethyl acetate
3-HB	3-hydroxy-2-butanone
4-HB	4-hydroxy-2-butanone
Ac	Acetone
CO2	Carbon dioxide
DMSO	Dimethyl sufoxide
EG	Ethylene glycol
EtAc	Ethyl acetate
EtOH	Ethanol
GBL	Gamma butyrolactone
Glu	Glucose
Gly	Glycerol
Fur	Furfural
H_2O	Water
HAc	Acetic acid
HFor	Formic acid
HLac	Lactic acid
HLEv	Levulinic acid
HMF	Hydroxymethylfurfural
HPro	Propionic acid
HSuc	Succinic acid
HTHF	2-(4-hydroxybutoxy)-tetrahydrofuran
IPA	Isopropanol
IBut	Isobutanol
MetAc	Methyl acetate
MetOH	Methanol
MetPro	Methyl propionate
PYR	2-pyrrolidone
THF	Tetrahydrofuran

References

[1] M.L. Shuler, F. Kargi, Bioprocess engineering: Basic concepts, Prentice Hall PTR, Upper Saddle River, 2002.

[2] M.A.H. Khan, S. Bonifacio, J. Clowes, A. Foulds, R. Holland, J.C. Matthews, C.J. Percival, D.E. Shallcross, Investigation of Biofuel as a Potential Renewable Energy Source, Atmosphere. 12 (2021) 1289. https://doi.org/10.3390/atmos12101289.

[3] United Nations, Adoption of the Paris Agreement, 2015.

[4] OECD, Industrial Biotechnology and Climate Change, 2011.

[5] F.M. Liew, M.E. Martin, R.C. Tappel, B.D. Heijstra, C. Mihalcea, M. Köpke, Gas Fermentation - A Flexible Platform for Commercial Scale Production of Low-Carbon-Fuels and Chemicals from Waste and Renewable Feedstocks, Frontiers in Microbiology. 7 (2016) 694. https://doi.org/10.3389/fmicb.2016.00694.

[6] OECD, Future prospects for industrial biotechnology, 2011.

[7] S. Mahapatra, D. Kumar, B. Singh, P.K. Sachan, Biofuels and their sources of production: A review on cleaner sustainable alternative against conventional fuel, in the framework of the food and energy nexus, Energy Nexus. 4 (2021) 100036. https://doi.org/10.1016/j.nexus.2021.100036.

[8] G. Berndes, M. Hoogwijk, R. Van Den Broek, The contribution of biomass in the future global energy supply: A review of 17 studies, Biomass and Bioenergy. 25 (2003) 1–28. https://doi.org/10.1016/S0961-9534(02)00185-X.

[9] H.J. Noorman, J.J. Heijnen, Biochemical engineering's grand adventure, Chemical Engineering Science. 170 (2017) 677–693. https://doi.org/10.1016/j.ces.2016.12.065.

[10] European Commission, Directive on the European Parliament and of the Council on substantiation and communication of explicit environmental claims (Green Claims Directive), European Commission, 2023.

[11] P. Karka, F. Johnsson, S. Papadokonstantakis, Perspectives for Greening European Fossil-Fuel Infrastructures Through Use of Biomass: The Case of Liquid Biofuels Based on Lignocellulosic Resources, Frontiers in Energy Research. 9 (2021) 636782. https://doi.org/10.3389/fenrg.2021.636782.

[12] S.N. Naik, V. V. Goud, P.K. Rout, A.K. Dalai, Production of first and

second generation biofuels: A comprehensive review, Renewable and Sustainable Energy Reviews. 14 (2010) 578–597. https://doi.org/10.1016/j.rser.2009.10.003.

[13] D.S. Mallapragada, Y. Dvorkin, M.A. Modestino, D. V. Esposito, W.A. Smith, B.M. Hodge, M.P. Harold, V.M. Donnelly, A. Nuz, C. Bloomquist, K. Baker, L.C. Grabow, Y. Yan, N.N. Rajput, R.L. Hartman, E.J. Biddinger, E.S. Aydil, A.D. Taylor, Decarbonization of the chemical industry through electrification: Barriers and opportunities, Joule. 7 (2023) 23–41. https://doi.org/10.1016/j.joule.2022.12.008.

[14] A. Adewuyi, Underutilized Lignocellulosic Waste as Sources of Feedstock for Biofuel Production in Developing Countries, Frontiers in Energy Research. 10 (2022) 1–21. https://doi.org/10.3389/fenrg.2022.741570.

[15] S. Nanda, R. Azargohar, A.K. Dalai, J.A. Kozinski, An assessment on the sustainability of lignocellulosic biomass for biorefining, Renewable and Sustainable Energy Reviews. 50 (2015) 925–941. https://doi.org/10.1016/j.rser.2015.05.058.

[16] L.T.M. Pham, H. Choudhary, R. Gauttam, S.W. Singer, J.M. Gladden, B.A. Simmons, S. Singh, K.L. Sale, Revisiting Theoretical Tools and Approaches for the Valorization of Recalcitrant Lignocellulosic Biomass to Value-Added Chemicals, Frontiers in Energy Research. 10 (2022) 1–18. https://doi.org/10.3389/fenrg.2022.863153.

[17] A.J.J. Straathof, Transformation of biomass into commodity chemicals using enzymes or cells, Chemical Reviews. 114 (2014) 1871–1908. https://doi.org/10.1021/cr400309c.

[18] L. Puiman, M.P. Elisiário, L.M.L. Crasborn, L.E.C.H. Wagenaar, A.J.J. Straathof, C. Haringa, Gas mass transfer in syngas fermentation broths is enhanced by ethanol, Biochemical Engineering Journal. 185 (2022) 1–7. https://doi.org/10.1016/j.bej.2022.108505.

[19] J. Daniell, M. Köpke, S.D. Simpson, Commercial Biomass Syngas Fermentation, Energies. 5 (2012) 5372–5417. https://doi.org/10.3390/en5125372.

[20] C. Fu, Z. Li, C. Jia, W. Zhang, Y. Zhang, C. Yi, S. Xie, Recent advances on bio-based isobutanol separation, Energy Conversion and Management: X. 10 (2021) 100059. https://doi.org/10.1016/j.ecmx.2020.100059.

[21] Z. Usmani, M. Sharma, A.K. Awasthi, T. Lukk, M.G. Tuohy, L. Gong, P. Nguyen-Tri, A.D. Goddard, R.M. Bill, S.C. Nayak, V.K. Gupta,

Lignocellulosic biorefineries: The current state of challenges and strategies for efficient commercialization, Renewable and Sustainable Energy Reviews. 148 (2021) 111258. https://doi.org/10.1016/j.rser.2021.111258.

[22] L.A.M. van der Wielen, S.I. Mussatto, J. van Breugel, Bioprocess intensification: Cases that (don't) work, New Biotechnology. 61 (2021) 108–115. https://doi.org/10.1016/j.nbt.2020.11.007.

[23] A.C. Dimian, C.S. Bildea, A.A. Kiss, Integrated Process and Product Design, Elsevier B.V., 2014. https://doi.org/10.1016/B978-0-444-62700-1.00001-2.

[24] A.A. Kiss, J. Grievink, M. Rito-Palomares, A systems engineering perspective on process integration in industrial biotechnology, Journal of Chemical Technology and Biotechnology. 90 (2015) 349–355. https://doi.org/10.1002/jctb.4584.

[25] H.J. Noorman, W. Van Winden, J.J. Heijnen, R.G.J.M. Van Der Lans, Intensified Fermentation Processes and Equipment, in: Intensification of Biobased Processes, The Royal Society of Chemistry, Croydon, 2018: pp. 1–41. https://doi.org/10.1039/9781788010320-00001.

[26] M.C. Cuellar, A.J. Straathof, Downstream of the bioreactor: advancements in recovering fuels and commodity chemicals, Current Opinion in Biotechnology. 62 (2020) 189–195. https://doi.org/10.1016/j.copbio.2019.11.012.

[27] I. McGregor, S. Furlong, Concurrent Alcohol Recovery and Fermentation Using Pass-Through Distillation, Industrial Biotechnology. 13 (2017) 107–112. https://doi.org/10.1089/ind.2017.29081.imc.

[28] M. Köpke, C. Mihalcea, J.C. Bromley, S.D. Simpson, Fermentative production of ethanol from carbon monoxide, Current Opinion in Biotechnology. 22 (2011) 320–325. https://doi.org/10.1016/j.copbio.2011.01.005.

[29] S.R. Trevethick, J.C. Bromley, G.W. Waters, M. Koepke, L.P. Tran, R. Jensen Overgaard, Multi-stage bioreactor processes, WO 2016/065217 A1, 2016.

[30] J. Gmehling, J. Menke, J. Krafczyk, K. Fischer, Azeotropic Data, Wiley-VCH, 2004.

[31] A.J.J. Straathof, The Proportion of Downstream Costs in Fermentative Production Processes, in: Comprehensive Biotechnology, Elsevier B.V., 2011: pp. 811–813. https://doi.org/10.1016/B978-0-08-088504-9.00492-X.

[32] A.G. Santos, T.L. de Albuquerque, B.D. Ribeiro, M.A.Z. Coelho, *In situ* product recovery techniques aiming to obtain biotechnological products: A glance to current knowledge, Biotechnology and Applied Biochemistry. 68 (2021) 1044–1057. https://doi.org/10.1002/bab.2024.

[33] U.A. Salas-Villalobos, R. V. Gómez-Acata, J. Castillo-Reyna, O. Aguilar, *In situ* product recovery as a strategy for bioprocess integration and depletion of inhibitory products, Journal of Chemical Technology and Biotechnology. 96 (2021) 2735–2743. https://doi.org/10.1002/jctb.6797.

[34] S. Ramaswamy, H.-J. Huang, B. V. Ramao, Separation and Purification Technologies in Biorefineries, Wiley, Chichester, 2013. https://doi.org/10.1002/9781118493441.

[35] A.A. Kiss, J.P. Lange, B. Schuur, D.W.F. Brilman, A.G.J. van der Ham, S.R.A. Kersten, Separation technology–Making a difference in biorefineries, Biomass and Bioenergy. 95 (2016) 296–309. https://doi.org/10.1016/j.biombioe.2016.05.021.

[36] H.-J. Huang, S. Ramaswamy, U.W. Tschirner, B. V. Ramarao, A review of separation technologies in current and future biorefineries, Separation and Purification Technology. 62 (2008) 1–21. https://doi.org/10.1016/j.seppur.2007.12.011.

[37] S. Wang, Y. Gu, Q. Liu, Y. Yao, Z. Guo, Z. Luo, K. Cen, Separation of bio-oil by molecular distillation, Fuel Processing Technology. 90 (2009) 738–745. https://doi.org/10.1016/j.fuproc.2009.02.005.

[38] Y. Wang, J. Nie, M. Zhao, S. Ma, L. Kuang, X. Han, S. Tang, Production of biodiesel from waste cooking oil via a two-step catalyzed process and molecular distillation, Energy and Fuels. 24 (2010) 2104–2108. https://doi.org/10.1021/ef901347b.

[39] A.J.J. Straathof, T. Janković, A.A. Kiss, Distillation for *in situ* recovery of volatile fermentation products, Trends in Biotechnology. (2025). https://doi.org/10.1016/j.tibtech.2024.12.009.

[40] C.S. López-Garzón, A.J.J. Straathof, Recovery of carboxylic acids produced by fermentation, Biotechnology Advances. 32 (2014) 873–904. https://doi.org/10.1016/j.biotechadv.2014.04.002.

[41] Z. Liu, P. Fatehi, M.S. Jahan, Y. Ni, Separation of lignocellulosic materials by combined processes of pre-hydrolysis and ethanol extraction, Bioresource Technology. 102 (2011) 1264–1269. https://doi.org/10.1016/j.biortech.2010.08.049.

[42] F. Öhman, H. Wallmo, H. Theliander, Precipitation and filtration of

lignin from black liquor of different origin, Nordic Pulp and Paper Research Journal. 22 (2007) 188–193. https://doi.org/10.3183/npprj-2007-22-02-p188-193.

[43] F. Öhman, H. Wallmo, H. Theliander, An improved method for washing lignin precipitated from kraft black liquor - The key to a new biofuel, Filtration. 7 (2007) 309–315.

[44] A. Brewster, A. Oudshoorn, M. Van Lotringen, P. Nelisse, E. Van Den Berg, M. Luttik, J-M Daran, Inhibition Control by Continuous Extractive Fermentation Enhances *De Novo* 2-Phenylethanol Production by Yeast, Biotechnology and Bioengineering. 122 (2024) 287–297. https://doi.org/10.1002/bit.28872.

[45] D. Stark, T. Münch, B. Sonnleitner, I.W. Marison, U. Von Stockar, Extractive bioconversion of 2-phenylethanol from L-phenylalanine by *Saccharomyces cerevisiae*, Biotechnology Progress. 18 (2002) 514–523. https://doi.org/10.1021/bp020006n.

[46] M.M.W. Etschmann, J. Schrader, An aqueous-organic two-phase bioprocess for efficient production of the natural aroma chemicals 2-phenylethanol and 2-phenylethylacetate with yeast, Applied Microbiology and Biotechnology. 71 (2006) 440–443. https://doi.org/10.1007/s00253-005-0281-6.

[47] U. Domanska, P. Okuniewska, K. Paduszynski, M. Krolikowska, M. Zawadzki, M. Więckowski, Extraction of 2-phenylethanol (PEA) from aqueous solution using ionic liquids: Synthesis, phase equilibrium investigation, selectivity in separation, and thermodynamic models, Journal of Physical Chemistry B. 121 (2017) 7689–7698. https://doi.org/10.1021/acs.jpcb.7b04294.

[48] D.L. Grzenia, X. Qian, S.S. da Silva, X. Wang, S.R. Wickramasinghe, Membrane Extraction for Biofuel Production, in: Membrane Science and Technology, Elsevier B.V., 2011: pp. 213–233. https://doi.org/10.1016/B978-0-444-53728-7.00010-0.

[49] D.L. Grzenia, D.J. Schell, S. Ranil Wickramasinghe, Membrane extraction for detoxification of biomass hydrolysates, Bioresource Technology. 111 (2012) 248–254. https://doi.org/10.1016/j.biortech.2012.01.169.

[50] W.N.A. Wan Osman, M.H. Rosli, W.N.A. Mazli, S. Samsuri, Comparative review of biodiesel production and purification, Carbon Capture Science and Technology. 13 (2024) 100264. https://doi.org/10.1016/j.ccst.2024.100264.

[51] C. Charcosset, Membrane processes in biotechnology: An overview, Biotechnology Advances. 24 (2006) 482–492. https://doi.org/10.1016/j.biotechadv.2006.03.002.

[52] Y. He, D.M. Bagley, K.T. Leung, S.N. Liss, B.Q. Liao, Recent advances in membrane technologies for biorefining and bioenergy production, Biotechnology Advances. 30 (2012) 817–858. https://doi.org/10.1016/j.biotechadv.2012.01.015.

[53] D. Cascaval, A.-I. Galaction, D. Boldureanu, Application of Pertraction in Biotechnology, in: Encyclopedia of Membrane Science and Technology, Wiley, 2013: pp. 1–53. https://doi.org/https://doi.org/10.1002/9781118522318.emst105.

[54] K. Chen, S. Hao, H. Lyu, G. Luo, S. Zhang, J. Chen, Ion exchange separation for recovery of monosaccharides, organic acids and phenolic compounds from hydrolysates of lignocellulosic biomass, Separation and Purification Technology. 172 (2017) 100–106. https://doi.org/10.1016/j.seppur.2016.08.004.

[55] R. Banavali, A.K. Schultz, K.-D. Topp, M.T. Vandersall, Ion Exchange Resins in Biodiesel Processing, in: The Biodiesel Handbook, AOCS Press, Urbaana, Illinois, 2010: pp. 85–97.

[56] J.A. Asenjo, B.A. Andrews, Protein purification using chromatography: Selection of type, modelling and optimization of operating conditions, Journal of Molecular Recognition. 22 (2009) 65–76. https://doi.org/10.1002/jmr.898.

[57] A.A. Kiss, M. Jobson, X. Gao, Reactive Distillation: Stepping Up to the Next Level of Process Intensification, Industrial and Engineering Chemistry Research. 58 (2019) 5909–5918. https://doi.org/10.1021/acs.iecr.8b05450.

[58] A.A. Kiss, Process Intensification Technologies for Biodiesel Production Reactive Separation Processes, Springer, Arnhem, 2014. http://www.springer.com/series/8884.

[59] A.C. Dimian, C.S. Bildea, F. Omota, A.A. Kiss, Innovative process for fatty acid esters by dual reactive distillation, Computers and Chemical Engineering. 33 (2009) 743–750. https://doi.org/10.1016/j.compchemeng.2008.09.020.

[60] A.A. Kiss, D.J.-P.C. Suszwalak, Enhanced bioethanol dehydration by extractive and azeotropic distillation in dividing-wall columns, Separation and Purification Technology. 86 (2012) 70–78. https://doi.org/10.1016/j.seppur.2011.10.022.

[61] A. Orjuela, A. Kolah, C.T. Lira, D.J. Miller, Mixed succinic acid/acetic acid esterification with ethanol by reactive distillation, Industrial and Engineering Chemistry Research. 50 (2011) 9209–9220. https://doi.org/10.1021/ie200133w.

[62] A. Orjuela, A. Kolah, X. Hong, C.T. Lira, D.J. Miller, Diethyl succinate synthesis by reactive distillation, Separation and Purification Technology. 88 (2012) 151–162. https://doi.org/10.1016/j.seppur.2011.11.033.

[63] I.M. Atadashi, M.K. Aroua, A.R. Abdul Aziz, N.M.N. Sulaiman, Membrane biodiesel production and refining technology: A critical review, Renewable and Sustainable Energy Reviews. 15 (2011) 5051–5062. https://doi.org/10.1016/j.rser.2011.07.051.

[64] W. Van Hecke, P. Vandezande, S. Claes, S. Vangeel, H. Beckers, L. Diels, H. De Wever, Integrated bioprocess for long-term continuous cultivation of *Clostridium acetobutylicum* coupled to pervaporation with PDMS composite membranes, Bioresource Technology. 111 (2012) 368–377. https://doi.org/10.1016/j.biortech.2012.02.043.

[65] L. Luo, E. van der Voet, G. Huppes, Biorefining of lignocellulosic feedstock - Technical, economic and environmental considerations, Bioresource Technology. 101 (2010) 5023–5032. https://doi.org/10.1016/j.biortech.2009.12.109.

[66] A.A. Kiss, Biodiesel by Reactive Absorption - Towards Green Technologies, Elsevier B.V., 2009. https://doi.org/10.1016/S1570-7946(09)70141-5.

[67] D. Humbird, R. Davis, L. Tao, C. Kinchin, D. Hsu, A. Aden, P. Schoen, J. Lukas, B. Olthof, M. Wordey, D. Sexton, D. Dudgeon, Process Design and Economics for Biochemical Conversion of Lignocellulosic Biomass to Ethanol, 2011.

[68] J. Schwarz, B. Beloff, E. Beaver, Use Sustainability Metrics to Guide Decision-Making, Chemical Engineering Progress. 98 (2002) 58–63.

[69] Y. Lin, S. Tanaka, Ethanol fermentation from biomass resources: Current state and prospects, Applied Microbiology and Biotechnology. 69 (2006) 627–642. https://doi.org/10.1007/s00253-005-0229-x.

[70] T. Raj, K. Chandrasekhar, A. Naresh Kumar, J. Rajesh Banu, J.J. Yoon, S. Kant Bhatia, Y.H. Yang, S. Varjani, S.H. Kim, Recent advances in commercial biorefineries for lignocellulosic ethanol production: Current status, challenges and future perspectives, Bioresource Technology. 344 (2022) 126292. https://doi.org/10.1016/j.biortech.2021.126292.

[71] N. Fackler, B.D. Heijstra, B.J. Rasor, H. Brown, J. Martin, Z. Ni, K.M. Shebek, R.R. Rosin, S.D. Simpson, K.E. Tyo, R.J. Giannone, R.L. Hettich, T.J. Tschaplinski, C. Leang, S.D. Brown, M.C. Jewett, M. Köpke, Stepping on the Gas to a Circular Economy: Accelerating Development of Carbon-Negative Chemical Production from Gas Fermentation, Annual Review of Chemical and Biomolecular Engineering. 12 (2021) 439–470. https://doi.org/10.1146/annurev-chembioeng-120120-021122.

[72] B. Molitor, H. Richter, M.E. Martin, R.O. Jensen, A. Juminaga, C. Mihalcea, L.T. Angenent, Carbon recovery by fermentation of CO-rich off gases - Turning steel mills into biorefineries, Bioresource Technology. 215 (2016) 386–396. https://doi.org/10.1016/j.biortech.2016.03.094.

[73] F.E. Liew, R. Nogle, T. Abdalla, B.J. Rasor, C. Canter, R.O. Jensen, L. Wang, J. Strutz, P. Chirania, S. De Tissera, A.P. Mueller, Z. Ruan, A. Gao, L. Tran, N.L. Engle, J.C. Bromley, J. Daniell, R. Conrado, T.J. Tschaplinski, R.J. Giannone, R.L. Hettich, A.S. Karim, S.D. Simpson, S.D. Brown, C. Leang, M.C. Jewett, M. Köpke, Carbon-negative production of acetone and isopropanol by gas fermentation at industrial pilot scale, Nature Biotechnology. 40 (2022) 335–344. https://doi.org/10.1038/s41587-021-01195-w.

[74] I. Veza, M.F. Muhamad Said, Z.A. Latiff, Recent advances in butanol production by acetone-butanol-ethanol (ABE) fermentation, Biomass and Bioenergy. 144 (2021) 105919. https://doi.org/10.1016/j.biombioe.2020.105919.

[75] Y. Ni, Z. Sun, Recent progress on industrial fermentative production of acetone-butanol-ethanol by Clostridium acetobutylicum in China, Applied Microbiology and Biotechnology. 83 (2009) 415–423. https://doi.org/10.1007/s00253-009-2003-y.

[76] C.F. dos Santos Vieira, F. Maugeri Filho, R. Maciel Filho, A. Pinto Mariano, Acetone-free biobutanol production: Past and recent advances in the Isopropanol-Butanol-Ethanol (IBE) fermentation, Bioresource Technology. 287 (2019) 121425. https://doi.org/10.1016/j.biortech.2019.121425.

[77] Ryan Chris, An Overview of Gevo's Biobased Isobutanol Production Process Isobutanol Production Process 1, (2023). www.gevo.com.

[78] BP, BP and DuPont joint venture, Butamax, (2017). https://www.bp.com/en/global/corporate/news-and-insights/press-releases/bp-and-dupont-joint-venture.html.

[79] R.K. Warren, D.G. Macdonald, G.A. Hill, The design and costing of a continuous ethanol process using wheat and cell recycle fermentation, Bioresource Technology. 47 (1994) 121–129. https://doi.org/10.1016/0960-8524(94)90109-0.

[80] M.S. Krishnan, F. Taylor, B.H. Davison, N.P. Nghiem, Economic analysis of fuel ethanol production from corn starch using fluidized-bed bioreactors, Bioresource Technology. 75 (2000) 99–105. https://doi.org/10.1016/S0960-8524(00)00047-X.

[81] J.R. Kwiatkowski, A.J. McAloon, F. Taylor, D.B. Johnston, Modeling the process and costs of fuel ethanol production by the corn dry-grind process, Industrial Crops and Products. 23 (2006) 288–296. https://doi.org/10.1016/j.indcrop.2005.08.004.

[82] N. Arifeen, R. Wang, I.K. Kookos, C. Webb, A.A. Koutinas, Process design and optimization of novel wheat-based continuous bioethanol production system, Biotechnology Progress. 23 (2007) 1394–1403. https://doi.org/10.1021/bp0701517.

[83] N. Qureshi, H.P. Blaschek, ABE production from corn: A recent economic evaluation, Journal of Industrial Microbiology and Biotechnology. 27 (2001) 292–297. https://doi.org/10.1038/sj.jim.7000123.

[84] J. Yu, J.A. Odriozola, T.R. Reina, Dry Reforming of Ethanol and Glycerol: Mini-review, Catalysts. 9 (2019) 1015. https://doi.org/10.3390/catal9121015.

[85] C. Acquarola, M. Ao, T. Bhatelia, B. Prakash, S. Faka, V. Pareek, M.T. Shah, Simulations and Optimization of a Reduced CO_2 Emission Process for Methanol Production Using Syngas from Bi-reforming, Energy & Fuels. 35 (2021) 8844–8856. https://doi.org/10.1021/acs.energyfuels.1c00227.

[86] L. V. Teixeira, L.F. Moutinho, A.S. Romão-Dumaresq, Gas fermentation of C1 feedstocks: commercialization status and future prospects, Biofuels, Bioproducts and Biorefining. 12 (2018) 1103–1117. https://doi.org/10.1002/bbb.1912.

[87] F.M. Liew, M. Köpke, S. Dennis Simpson, Gas Fermentation for Commercial Biofuels Production, in: Liquid, Gaseous and Solid Biofuels - Conversion Techniques, 2013: pp. 125–152. https://doi.org/10.5772/52164.

[88] J.R. Phillips, R.L. Huhnke, H.K. Atiyeh, Syngas Fermentation: A Microbial Conversion Process of Gaseous Substrates to Various

Products, Fermentation. 3 (2017) 28. https://doi.org/10.3390/fermentation3020028.

[89] M. Köpke, S.D. Simpson, Pollution to products: recycling of 'above ground' carbon by gas fermentation, Current Opinion in Biotechnology. 65 (2020) 180–189. https://doi.org/10.1016/j.copbio.2020.02.017.

[90] S. Lu, Y. Shi, N. Meng, S. Lu, Y. Yu, B. Zhang, Electrosynthesis of Syngas via the Co-Reduction of CO_2 and H_2O, Cell Reports Physical Science. 1 (2020) 100237. https://doi.org/10.1016/j.xcrp.2020.100237.

[91] X. Li, B.J. Cossey, S.R. Trevethick, Fermentation of gaseous substrates, US 9,617,509 B2, 2017.

[92] X. Ou, X. Zhang, Q. Zhang, X. Zhang, Life-cycle analysis of energy use and greenhouse gas emissions of gas-to-liquid fuel pathway from steel mill off-gas in China by the LanzaTech process, Frontiers in Energy. 7 (2013) 263–270. https://doi.org/10.1007/s11708-013-0263-9.

[93] L. Puiman, B. Abrahamson, R.G.J.M. van der Lans, C. Haringa, H.J. Noorman, C. Picioreanu, Alleviating mass transfer limitations in industrial external-loop syngas-to-ethanol fermentation, Chemical Engineering Science. 259 (2022) 117770. https://doi.org/10.1016/j.ces.2022.117770.

[94] R.M. Handler, D.R. Shonnard, E.M. Griffing, A. Lai, I. Palou-Rivera, Life Cycle Assessments of Ethanol Production via Gas Fermentation: Anticipated Greenhouse Gas Emissions for Cellulosic and Waste Gas Feedstocks, Industrial & Engineering Chemistry Research. 55 (2016) 3253–3261. https://doi.org/10.1021/acs.iecr.5b03215.

[95] K. Asimakopoulos, H.N. Gavala, I. V. Skiadas, Reactor systems for syngas fermentation processes : A review, Chemical Engineering Journal. 348 (2018) 732–744. https://doi.org/10.1016/j.cej.2018.05.003.

[96] F. Taylor, M.J. Kurantz, N. Goldberg, J.C. Craig Jr., Effects of ethanol concentration and stripping temperature on continuous fermentation rate, Applied Microbiology and Biotechnology. 48 (1997) 311–316. https://doi.org/10.1007/s002530051055.

[97] Aspen Physical Property System, Aspen Technology, Bedford, 2020.

[98] K. Valgepea, R. de S.P. Lemgruber, K. Meaghan, R.W. Palfreyman, T. Abdalla, B.D. Heijstra, J.B. Behrendorff, R. Tappel, M. Kopke, S.D. Simpson, L.K. Nielsen, E. Marcellin, Maintenance of ATP Homeostasis Triggers Metabolic Shifts in Gas-Fermenting Acetogens, Cell Systems. 4 (2017) 505–515. https://doi.org/10.1016/j.cels.2017.04.008.

[99] S. Schulz, B. Molitor, L.T. Angenent, Acetate augmentation boosts the ethanol production rate and specificity by *Clostridium ljungdahlii* during gas fermentation with pure carbon monoxide, Bioresource Technology. 369 (2023) 128387. https://doi.org/10.1016/j.biortech.2022.128387.

[100] A.A. Kiss, R.M. Ignat, C.S. Bildea, Optimal Extractive Distillation Process for Bioethanol Dehydration, Computer Aided Chemical Engineering. 33 (2014) 1333–1338. https://doi.org/10.1016/B978-0-444-63455-9.50057-X.

[101] A.K. Frolkova, V.M. Raeva, Bioethanol Dehydration: State of the Art, Theoretical Foundations of Chemical Engineering. 44 (2010) 469–482. https://doi.org/10.1134/S0040579510040342.

[102] A. Singh, G.P. Rangaiah, Review of Technological Advances in Bioethanol Recovery and Dehydration, Industrial and Engineering Chemistry Research. 56 (2017) 5147–5163. https://doi.org/10.1021/acs.iecr.7b00273.

[103] A.A. Kiss, R.M. Ignat, Optimal Economic Design of an Extractive Distillation Process for Bioethanol Dehydration, Energy Technology. 1 (2013) 166–170. https://doi.org/10.1002/ente.201200053.

[104] M. Tatlier, G. Munz, S.K. Henninger, Relation of water adsorption capacities of zeolites with their structural properties, Microporous and Mesoporous Materials. 264 (2018) 70–75. https://doi.org/10.1016/j.micromeso.2017.12.031.

[105] M. Errico, B.-G. Rong, Synthesis of new separation processes for bioethanol production by extractive distillation, Separation and Purification Technology. 96 (2012) 58–67. https://doi.org/10.1016/j.seppur.2012.05.022.

[106] A. Meirelles, S. Weiss, H. Herfurth, Ethanol Dehydration by Extractive Distillation, Journal of Chemical Technology & Biotechnology. 53 (1992) 181–188. https://doi.org/10.1002/jctb.280530213.

[107] P.A. Bastidas, I.D. Gil, G. Rodriguez, Comparison of the main ethanol dehydration technologies through process simulation, in: 20th European Symposium on Computer Aided Process Engineering – ESCAPE20, 2010.

[108] P.A. Sechrist, N. Bourdakos, R.J. Conrado, A.H. Gao, J.C. Bromley, C.D. Mihalcea, M.E. Martin, I. Palou-Rivera, J.H. Tizard, Process and system for product recovery and cell recycle, US 10,610,802 B2, 2020.

[109] X. Sun, H.K. Atiyeh, R.L. Huhnke, R.S. Tanner, Syngas fermentation process development for production of biofuels and chemicals: A review,

Bioresource Technology Reports. 7 (2019) 100279. https://doi.org/10.1016/j.biteb.2019.100279.

[110] Sulzer, Structured packings, (2023). https://www.sulzer.com/en/products/separation-technology/structured-packings.

[111] Marpa, Roots vacuum pumps, (2023). https://marpavacuum.com/en/roots-vacuum-pumps.

[112] E. Volker, How to design and optimise sieve trays, WelChem. (2020). https://welchem.com/fileadmin/pub/WelChem_SieveTray_2020-1.pdf.

[113] A.A. Kiss, C.A. Infante Ferreira, Mechanically Driven Heat Pumps, in: Heat Pumps in Chemical Process Industry, CRC Press, Boca Raton, 2016: pp. 189–251. https://doi.org/10.1201/9781315371030.

[114] A.A. Kiss, R.M. Ignat, Innovative single step bioethanol dehydration in an extractive dividing-wall column, Separation and Purification Technology. 98 (2012) 290–297. https://doi.org/10.1016/j.seppur.2012.06.029.

[115] A.A. Kiss, Design, Control and Economics of Distillation, in: Advanced Distillation Technologies: Design, Control and Applications, Wiley, Chichester, 2013: pp. 37–66. https://doi.org/10.1002/9781118543702.

[116] C.A. Balaras, E.G. Dascalaki, I. Psarra, T. Cholewa, Primary Energy Factors for Electricity Production in Europe, Energies. 16 (2023) 93. https://doi.org/10.3390/en16010093.

[117] Directive 2012/27/EU of the European Parliament and of the Council of 25 October 2012 on energy efficiency, amending Directives 2009/125/EC and 2010/30/EU and repealing Directives 2004/8/EC and 2006/32/EC, Official Journal of European Union. (2012).

[118] T. Bisgaard, M. Mauricio-Iglesias, J.K. Huusom, K. V. Gernaey, J. Dohrup, M.A. Petersen, J. Abildskov, Adding Value to Bioethanol through a Purification Process Revamp, Industrial and Engineering Chemistry Research. 56 (2017) 5692–5704. https://doi.org/10.1021/acs.iecr.7b00442.

[119] Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives, Official Journal of the European Union. (2008).

[120] F.R.M. Batista, A.J.A. Meirelles, A Strategy for Controlling Acetaldehyde Content in an Industrial Plant of Bioethanol, IFAC Proceedings Volumes. 7 (2009) 928–933.

https://doi.org/10.3182/20090712-4-tr-2008.00152.

[121] N. Marriaga, Performance indicators of bioethanol distillation, Dyna. 76 (2009) 85–92.

[122] M. Decloux, J. Coustel, Simulation of a neutral spirit production plant using beer distillation, International Sugar Journal. 107 (2005) 628–643.

[123] P.M. Hoch, J. Espinosa, Conceptual Design and Simulation Tools Applied to the Evolutionary Optimization of a Bioethanol Purification Plant, Industrial and Engineering Chemistry Research. 47 (2008) 7381–7389. https://doi.org/10.1021/ie800450a.

[124] O. Bedryk, A. Shevchenko, O.S. Mishchenko, V.N. Maleta, A.A. Kiss, Industrial experience in using cyclic distillation columns for food grade alcohol purification, Chemical Engineering Research and Design. 192 (2023) 102–109. https://doi.org/10.1016/j.cherd.2023.02.026.

[125] E. Papadakis, J.K. Huusom, J. Abildskov, Economic analysis of a horizontal diabatic separation system, Chemical Engineering Research and Design. 147 (2019) 709–720. https://doi.org/10.1016/j.cherd.2019.05.023.

[126] N.P. Lieberman, E.T. Lieberman, Steam Generation, in: A Working Guide to Process Equipmen, McGrawHill, 2022: pp. 261–276.

[127] L.M. Vane, F.R. Alvarez, Membrane-assisted vapor stripping: energy efficient hybrid distillation-vapor permeation process for alcohol - water separation, Journal of Chemical Technology & Biotechnology. 83 (2008) 1275–1287. https://doi.org/10.1002/jctb.

[128] A.A. Kiss, I.R. McGregor, S. Furlong, Pass-through distillation - A new player in separation technology, NPT Procestechnologie. 1404 (2014).

[129] J. Pátek, J. Klomfar, Solid-liquid phase equilibrium in the systems of LiBr-H_2O and LiCl-H_2O, Fluid Phase Equilibria. 250 (2006) 138–149. https://doi.org/10.1016/j.fluid.2006.09.005.

[130] M.R. Conde, Properties of aqueous solutions of lithium and calcium chlorides: Formulations for use in air conditioning equipment design, International Journal of Thermal Sciences. 43 (2004) 367–382. https://doi.org/10.1016/j.ijthermalsci.2003.09.003.

[131] I.R. McGregor, C.H. Belchers, Stripping absorption module, US 8,757,599 B2, 2014.

[132] C. Somers, A. Mortazavi, Y. Hwang, R. Radermacher, P. Rodgers, S. Al-Hashimi, Modeling water/lithium bromide absorption chillers in ASPEN Plus, Applied Energy. 88 (2011) 4197–4205.

https://doi.org/10.1016/j.apenergy.2011.05.018.

[133] R.H. Perry, D.W. Green, Distillation, in: Perry's Chemical Engineering Handbook, McGraw-Hill, 1997: pp. 13–10.

[134] N. Hu, D.W. Schaefer, Effect of impurity compounds on ethanol hydration, Journal of Molecular Liquids. 155 (2010) 29–36. https://doi.org/10.1016/j.molliq.2010.05.001.

[135] K.R. Patil, A.D. Trlpathi, G. Pathak, S.S. Katti, Thermodynamic Properties of Aqueous Electrolyte Solutions. 1. Vapor Pressure of Aqueous Solutions of LiCl, LiBr and LiI, Journal of Chemical and Engineering Data. 35 (1990) 166–168.

[136] K. Nasirzadeh, R. Neueder, W. Kunz, Vapor Pressures, Osmotic and Activity Coefficients of Electrolytes in Protic Solvents at Different Temperatures. 2. Lithium Bromide in Ethanol, Journal of Solution Chemistry. 33 (2004) 1429–1446. https://doi.org/10.1007/s10953-004-1057-9.

[137] Y. Lin, A. ten Kate, M. Moojier, J. Deldago, P.L. Fosbal, K. Thomsen, Comparison of Activity Coefficient Models for Electrolyte Systems, AIChE Journal. 56 (2009) 1334–1351. https://doi.org/10.1002/aic.12040.

[138] G.M. Bollas, C.C. Chen, P.I. Barton, Refined electrolyte-NRTL model: Activity Coefficient Expressions for Application to Multi-Electrolyte Systems, AIChE Journal. 54 (2008) 1608–1624. https://doi.org/10.1002/aic.11485.

[139] ENRTL-RK, (2023). https://knowledgecenter.aspentech.com.

[140] T. Chou, A. Tanioka, W. Model, Predicting the Effect of Dissolved Salt on the Vapor-Liquid Equilibria for Alcohol-Water-Salt Systems, 77 (1999) 329–334.

[141] L.A. Cisternas, E.J. Lam, An analytic correlation for the vapour pressure of aqueous and non-aqueous solutions of single and mixed electrolytes. Part II. Application and extension, Fluid Phase Equilibria. 62 (1991) 11–27. https://doi.org/10.1016/0378-3812(91)87002-Q.

[142] P.D. Ghuge, N.A. Mail, S.S. Joshi, Fluid Phase Equilibria Effect of $CaCl_2$ and $ZnCl_2$ salts on isobaric vapor-liquid equilibrium in separation of the azeotropic mixture of ethanol + water, Fluid Phase Equilibria. 537 (2021) 113000. https://doi.org/10.1016/j.fluid.2021.113000.

[143] Y. Yao, S. Liu, Basic Equations for Properties of Common Liquid Desiccants, in: Ultrasonic Technology for Desiccant Regeneration, Wiley, 2014: pp. 293–306. https://doi.org/10.1002/9781118921616.app1.

[144] D.-J. Seo, A. Takenaka, H. Fujita, K. Mochidzuki, A. Sakoda, Practical considerations for a simple ethanol concentration from a fermentation broth via a single adsorptive process using molecular-sieving carbon, Renewable Energy. 118 (2018) 257–264. https://doi.org/10.1016/j.renene.2017.11.019.

[145] R. Liu, F. Shen, Impacts of main factors on bioethanol fermentation from stalk juice of sweet sorghum by immobilized Saccharomyces cerevisiae (CICC 1308), Bioresource Technology. 99 (2008) 847–854. https://doi.org/10.1016/j.biortech.2007.01.009.

[146] W. Knoche, Chemical Reactions of CO2 in Water, in: Biophysics and Physiology of Carbon Dioxide, Proceedings in Life Sciences, 1980: pp. 3–11. https://doi.org/10.1007/978-3-642-67572-0_1.

[147] C.R. Silva, M.N. Esperança, A.J.G. Cruz, L.F. Moura, A.C. Badino, Stripping of ethanol with CO_2 in bubble columns: Effects of operating conditions and modeling, Chemical Engineering Research and Design. 102 (2015) 150–160. https://doi.org/10.1016/j.cherd.2015.06.022.

[148] F. Mandani, H. Ettouney, H. El-Dessouky, LiBr-H_2O absorption heat pump for single-effect evaporation desalination process, Desalination. 128 (2000) 161–176. https://doi.org/10.1016/S0011-9164(00)00031-X.

[149] H. Shabgard, M.J. Allen, N. Sharifi, S.P. Benn, A. Faghri, T.L. Bergman, Heat pipe heat exchangers and heat sinks: Opportunities, challenges, applications, analysis, and state of the art, International Journal of Heat and Mass Transfer. 89 (2015) 138–158. https://doi.org/10.1016/j.ijheatmasstransfer.2015.05.020.

[150] Y.M. Chen, C.Y. Sun, Experimental study on the heat and mass transfer of a combined absorber-evaporator exchanger, International Journal of Heat and Mass Transfer. 40 (1997) 961–971. https://doi.org/10.1016/0017-9310(96)00155-X.

[151] Á. Fernández-Naveira, H.N. Abubackar, M.C. Veiga, C. Kennes, Carbon monoxide bioconversion to butanol-ethanol by Clostridium carboxidivorans: kinetics and toxicity of alcohols, Applied Microbiology and Biotechnology. 100 (2016) 4231–4240. https://doi.org/10.1007/s00253-016-7389-8.

[152] R. Agrawal, Multieffect Distillation for Thermally Coupled Configurations, AIChE Journal. 46 (2000) 2211–2224. https://doi.org/10.1002/aic.690461113.

[153] Horizontal split centrifugal compressors, MAN Energy Solutions. (2023). https://www.man-es.com/oil-

gas/products/compressors/centrifugal.

[154] T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream processing of bioethanol from syngas fermentation, Separation and Purification Technology. 322 (2023) 124320. https://doi.org/10.1016/j.seppur.2023.124320.

[155] SPRSUN, What Is a Good COP for an Air to Water Heat Pump?, (2021). https://sprsunheatpump.com/what-is-a-good-cop-for-an-air-to-water-heat-pump.html.

[156] BP, Approximate Conversion Factors, Statistical Review of World Energy. (2021). https://www.bp.com/en/global/corporate/energy-economics/statistical-review-of-world-energy/using-the-review/definitions-and-explanatory-notes.html.

[157] H. Yang, C. Zhang, N. Lai, B. Huang, P. Fei, D. Ding, P. Hu, Y. Gu, H. Wu, Efficient isopropanol biosynthesis by engineered Escherichia coli using biologically produced acetate from syngas fermentation, Bioresource Technology. 296 (2020) 122337. https://doi.org/10.1016/j.biortech.2019.122337.

[158] Y.J. Ko, J. Cha, W.Y. Jeong, M.E. Lee, B.H. Cho, B. Nisha, H.J. Jeong, S.E. Park, S.O. Han, Bio-isopropanol production in *Corynebacterium glutamicum*: Metabolic redesign of synthetic bypasses and two-stage fermentation with gas stripping, Bioresource Technology. 354 (2022) 127171. https://doi.org/10.1016/j.biortech.2022.127171.

[159] L. Liu, J. Yang, Y. Yang, L. Luo, R. Wang, Y. Zhang, H. Yuan, Consolidated bioprocessing performance of bacterial consortium EMSD5 on hemicellulose for isopropanol production, Bioresource Technology. 292 (2019) 121965. https://doi.org/10.1016/j.biortech.2019.121965.

[160] S.D. Simpson, M. Koepke, F. Liew, W.Y. Chen, Recombinant microorganisms and uses thereof, WO 2012/115527 A2, 2012.

[161] K. Arslan, T. Schoch, F. Höfele, S. Herrschaft, C. Oberlies, F. Bengelsdorf, M.C. Veiga, P. Dürre, C. Kennes, Engineering Acetobacterium woodii for the production of isopropanol and acetone from carbon dioxide and hydrogen, Biotechnology Journal. 17 (2022) 1–12. https://doi.org/10.1002/biot.202100515.

[162] K.D. Ramachandriya, M.R. Wilkins, M.J.M. Delorme, X. Zhu, D.K. Kundiyana, H.K. Atiyeh, R.L. Huhnke, Reduction of acetone to isopropanol using producer gas fermenting microbes, Biotechnology and Bioengineering. 108 (2011) 2330–2338. https://doi.org/10.1002/bit.23203.

[163] T. Jojima, M. Inui, H. Yukawa, Production of isopropanol by metabolically engineered Escherichia coli, Applied Microbiology and Biotechnology. 77 (2008) 1219–1224. https://doi.org/10.1007/s00253-007-1246-8.

[164] LanzaTech, Closing the Carbon Cycle and Creating a Pathway to Net-Zero, (2022). https://lanzatech.com/closing-the-carbon-cycle-and-creating-a-pathway-to-net-zero/ (accessed July 10, 2023).

[165] A.J.J. Straathof, Modelling of end-product inhibition in fermentation, Biochemical Engineering Journal. 191 (2023) 108796. https://doi.org/10.1016/j.bej.2022.108796.

[166] S. Redl, S. Sukumara, T. Ploeger, L. Wu, T. Ølshøj Jensen, A.T. Nielsen, H. Noorman, Thermodynamics and economic feasibility of acetone production from syngas using the thermophilic production host *Moorella thermoacetica*, Biotechnology for Biofuels. 10 (2017) 1–17. https://doi.org/10.1186/s13068-017-0827-8.

[167] W. Panjapakkul, M.M. El-Halwagi, Technoeconomic Analysis of Alternative Pathways of Isopropanol Production, ACS Sustainable Chemistry and Engineering. 6 (2018) 10260–10272. https://doi.org/10.1021/acssuschemeng.8b01606.

[168] V. Van Hoof, L. Van den Abeele, A. Buekenhoudt, C. Dotremont, R. Leysen, Economic comparison between azeotropic distillation and different hybrid systems combining distillation with pervaporation for the dehydration of isopropanol, Separation and Purification Technology. 37 (2004) 33–49. https://doi.org/10.1016/j.seppur.2003.08.003.

[169] M. Koepke, S. Simpson, F. Liew, W. Chen, Fermentation process for producing isopropanol using a recombinant microorganisms, US9365868B2, 2016.

[170] A.A. Kiss, Distillation technology - still young and full of breakthrough opportunities, Journal of Chemical Technology and Biotechnology. 89 (2014) 479–498. https://doi.org/10.1002/jctb.4262.

[171] T.A. Al-sahhaf, N.J. Jabbar, Vapor-Liquid Equilibrium of the Acetone-Water-Salt System, Journal of Chemical and Engineering Data. (1993) 522–526.

[172] E.Z.O. Sada, T. Ohno, S. Kito, Salt effect on vapor-liquid equilibria for acetone-water system, Journal of Chemical Engineering of Japan. 5 (1972) 215–218.

[173] Y. Cui, Z. Zhang, X. Shi, C. Guang, J. Gao, Triple-column side-stream extractive distillation optimization via simulated annealing for the

benzene/isopropanol/water separation, Separation and Purification Technology. 236 (2020) 116303. https://doi.org/10.1016/j.seppur.2019.116303.

[174] Y. Li, Q. Ye, N. Wang, L. Chen, H. Zhang, Y. Xu, Energy-efficient extractive distillation combined with heat-integrated and intermediate reboilers for separating acetonitrile/isopropanol/water mixture, Separation and Purification Technology. 262 (2021) 118343. https://doi.org/10.1016/j.seppur.2021.118343.

[175] B. Shan, Q. Zheng, Z. Chen, Y. Shen, F. Zhang, Y. Wang, Z. Zhu, Dynamic control and performance comparison of conventional and dividing wall extractive distillation for benzene/isopropanol/water separation, Journal of the Taiwan Institute of Chemical Engineers. 128 (2021) 73–86. https://doi.org/10.1016/j.jtice.2021.08.005.

[176] X. Liu, J. Wu, Y. Lei, X. Wu, Y. Man, H. Luo, Q. Xiong, Data-driven surrogate optimized and intensified extractive distillation process for clean separation of isopropanol from water: A sustainable alternative, Journal of Cleaner Production. 383 (2023) 135475. https://doi.org/10.1016/j.jclepro.2022.135475.

[177] Z. Lei, J. Zhang, B. Chen, Separation of aqueous isopropanol by reactive extractive distillation, Journal of Chemical Technology and Biotechnology. 77 (2002) 1251–1254. https://doi.org/10.1002/jctb.700.

[178] B. Shan, C. Niu, D. Meng, Q. Zhao, B. Huo, Y. Ma, Y. Wang, F. Zhang, Z. Zhu, Dynamic control of heat pump assisted extractive distillation process for separation of ethyl acetate/isopropanol/water mixture, Journal of Chemical Technology and Biotechnology. 96 (2021) 2368–2381. https://doi.org/10.1002/jctb.6764.

[179] M.C. Cuellar, A.J.J. Straathof, Improving Fermentation by Product Removal, in: Intensification of Biobased Processes, Royal Society of Chemistry, Croydon, 2018: pp. 86–108. https://doi.org/10.1039/9781788010320-00086.

[180] J. Sundquist, H.W. Blanch, C.R. Wilke, Vacuum Fermentation, in: Extractive Bioconversions, CRC Press, Boca Raton, 1990: pp. 237–258.

[181] A.J.J. Straathof, A. Bampouli, Potential of commodity chemicals to become bio-based according to maximum yields and petrochemical prices, Biofuels, Bioproducts & Biorefining. 11 (2017) 798–810. https://doi.org/10.1002/bbb.1786.

[182] A.P. Dicks, A. Hent, Green Chemistry Metrics, A guide to Determining and Evaluating Process Greenness, Springer, Jiapur, 2015.

https://doi.org/10.1007/978-3-319-10500-0.

[183] R.A. Sheldon, Metrics of Green Chemistry and Sustainability: Past, Present, and Future, Sustainable Chemistry and Engineering. 6 (2018) 32–48. https://doi.org/10.1021/acssuschemeng.7b03505.

[184] A. Demirbas, Biofuels securing the planet's future energy needs, Energy Conversion and Management. 50 (2009) 2239–2249. https://doi.org/10.1016/j.enconman.2009.05.010.

[185] A. Baez, K.M. Cho, J.C. Liao, High-flux isobutanol production using engineered Escherichia coli: A bioreactor study with *in situ* product removal, Applied Microbiology and Biotechnology. 90 (2011) 1681–1690. https://doi.org/10.1007/s00253-011-3173-y.

[186] N. Qureshi, B.C. Saha, M.A. Cotta, V. Singh, An economic evaluation of biological conversion of wheat straw to butanol: A biofuel, Energy Conversion and Management. 65 (2013) 456–462. https://doi.org/10.1016/j.enconman.2012.09.015.

[187] K. Novak, J. Baar, P. Freitag, S. Pflügl, Metabolic engineering of *Escherichia coli* for isobutanol production on chemically defined medium and cheese whey as alternative raw material, Journal of Industrial Microbiology and Biotechnology. 47 (2020) 1117–1132. https://doi.org/10.1007/s10295-020-02319-y.

[188] E. Ofuonye, K. Kutin, D.T. Stuart, Engineering *Saccharomyces cerevisiae* fermentative pathways for the production of isobutanol, Biofuels. 4 (2013) 185–201. https://doi.org/10.4155/bfs.12.85.

[189] A.V. Kale, A. Krishnasamy, Effects of variations in fuel properties on a homogeneous charge compression ignited light-duty diesel engine operated with gasoline-isobutanol blends, Energy Conversion and Management. 258 (2022) 115373. https://doi.org/10.1016/j.enconman.2022.115373.

[190] K.R. Asfar, H. Hamed, Combustion of fuel blends, Energy Conversion and Management. 39 (1998) 1081–1093.

[191] M. Deniz Altinkurt, Y. Emre Ozturk, A. Turkcan, Effects of isobutanol fraction in diesel–biodiesel blends on combustion, injection, performance and emission parameters, Fuel. 330 (2022) 125554. https://doi.org/10.1016/j.fuel.2022.125554.

[192] X. Gao, T. Zhang, Y. Wu, G. Yang, M. Tan, X. Li, H. Xie, J. Pan, Y. Tan, Isobutanol synthesis from syngas on Zn-Cr based catalysts: New insights into the effect of morphology and facet of ZnO nanocrystal, Fuel. 217 (2018) 21–30. https://doi.org/10.1016/j.fuel.2017.12.065.

[193] S. Veibel, J.I. Nielsen, On the mechanism of the Guerbet reaction, Tetrahedron. 23 (1967) 1723–1733. https://doi.org/10.1016/S0040-4020(01)82571-0.

[194] S. Boecker, P. Schulze, S. Klamt, Growth-coupled anaerobic production of isobutanol from glucose in minimal medium with *Escherichia coli*, Biotechnology for Biofuels and Bioproducts. 16 (2023) 1–13. https://doi.org/10.1186/s13068-023-02395-z.

[195] P. Gu, F. Li, Z. Huang, Engineering *Escherichia coli* for Isobutanol Production from Xylose or Glucose–Xylose Mixture, Microorganisms. 11 (2023) 1–12. https://doi.org/10.3390/microorganisms11102573.

[196] S. Atsumi, T. Hanai, J.C. Liao, Non-fermentative pathways for synthesis of branched-chain higher alcohols as biofuels, Nature. 451 (2008) 86–89. https://doi.org/10.1038/nature06450.

[197] K. Morita, Y. Nomura, J. Ishii, F. Matsuda, A. Kondo, H. Shimizu, Heterologous expression of bacterial phosphoenol pyruvate carboxylase and Entner–Doudoroff pathway in *Saccharomyces cerevisiae* for improvement of isobutanol production, Journal of Bioscience and Bioengineering. 124 (2017) 263–270. https://doi.org/10.1016/j.jbiosc.2017.04.005.

[198] S. Lane, Y. Zhang, E.J. Yun, L. Ziolkowski, G. Zhang, Y.S. Jin, J.L. Avalos, Xylose assimilation enhances the production of isobutanol in engineered *Saccharomyces cerevisiae*, Biotechnology and Bioengineering. 117 (2020) 372–381. https://doi.org/10.1002/bit.27202.

[199] N.M. Lakshmi, P. Binod, R. Sindhu, M.K. Awasthi, A. Pandey, Microbial engineering for the production of isobutanol: current status and future directions, Bioengineered. 12 (2021) 12308–12321. https://doi.org/10.1080/21655979.2021.1978189.

[200] A. Oudshoorn, L.A.M. Van Der Wielen, A.J.J. Straathof, Assessment of options for selective 1-butanol recovery from aqueous solution, Industrial and Engineering Chemistry Research. 48 (2009) 7325–7336. https://doi.org/10.1021/ie900537w.

[201] B. Claessens, M. De Staercke, E. Verstraete, G. V. Baron, J. Cousin-Saint-Remi, J.F.M. Denayer, Identifying Selective Adsorbents for the Recovery of Renewable Isobutanol, ACS Sustainable Chemistry and Engineering. 8 (2020) 9115–9124. https://doi.org/10.1021/acssuschemeng.0c02316.

[202] M. Omidali, A. Raisi, A. Aroujalian, Separation and purification of isobutanol from dilute aqueous solutions by a hybrid

hydrophobic/hydrophilic pervaporation process, Chemical Engineering and Processing: Process Intensification. 77 (2014) 22–29. https://doi.org/10.1016/j.cep.2014.01.002.

[203] C. Fu, Z. Li, Z. Sun, S. Xie, A review of salting-out effect and sugaring-out effect: driving forces for novel liquid-liquid extraction of biofuels and biochemicals, Frontiers of Chemical Science and Engineering. 15 (2021) 854–871. https://doi.org/10.1007/s11705-020-1980-3.

[204] L. Tao, E.C.D. Tan, R. Mccormick, M. Zhang, A. Aden, X. He, B.T. Zigler, Techno-economic analysis and life-cycle assessment of cellulosic isobutanol and comparison with cellulosic ethanol and n-butanol, Biofuels, Bioproducts and Biorefining. 8 (2013) 30–48. https://doi.org/10.1002/bbb.1431.

[205] A. Roussos, N. Misailidis, A. Koulouris, F. Zimbardi, D. Petrides, A feasibility study of cellulosic isobutanol production-process simulation and economic analysis, Processes. 7 (2019). https://doi.org/10.3390/pr7100667.

[206] W.A. Evanko, A.M. Eyal, D.A. Glassner, F. Miao, A.A. Aristidou, K. Evans, P.R. Gruber, A.C. Hawkins, Recovery of higher alcohols from dilute aqueous solutions, US 8,101,808 B2, 2012.

[207] B. Lund, Renewable Chemicals and Advanced Biofuels Forward-Looking Statements, (2013) GEVO.

[208] F. Zhang, K. Zhang, X.Y. Xian, H.Q. Chen, X.W. Chen, Z. Zhang, Y.R. Wu, Elimination of carbon catabolite repression through gene-modifying a solventogenic *Clostridium sp*. strain WK to enhance butanol production from the galactose-rich red seaweed, Science of the Total Environment. 861 (2023) 160559. https://doi.org/10.1016/j.scitotenv.2022.160559.

[209] F. Zhang, K. Zhang, Z. Zhang, H.Q. Chen, X.W. Chen, X.Y. Xian, Y.R. Wu, Efficient isopropanol-butanol-ethanol (IBE) fermentation by a gene-modified solventogenic *Clostridium* species under the co-utilization of Fe(III) and butyrate, Bioresource Technology. 373 (2023) 128751. https://doi.org/10.1016/j.biortech.2023.128751.

[210] D. Lehmann, D. Hönicke, A. Ehrenreich, M. Schmidt, D. Weuster-Botz, H. Bahl, T. Lütke-Eversloh, Modifying the product pattern of *Clostridium acetobutylicum*: Physiological effects of disrupting the acetate and acetone formation pathways, Applied Microbiology and Biotechnology. 94 (2012) 743–754. https://doi.org/10.1007/s00253-011-3852-8.

[211] E. Rochón, G. Cortizo, M.I. Cabot, M.T. García Cubero, M. Coca, M.D.

Ferrari, C. Lareo, Bioprocess intensification for isopropanol, butanol and ethanol (IBE) production by fermentation from sugarcane and sweet sorghum juices through a gas stripping-pervaporation recovery process, Fuel. 281 (2020) 118593. https://doi.org/10.1016/j.fuel.2020.118593.

[212] I. Patrascu, C.S. Bîldea, A.A. Kiss, Enhanced biobutanol separation by a heat pump assisted azeotropic dividing-wall column, Chemical Engineering Transactions. 69 (2018) 205–210. https://doi.org/10.3303/CET1869035.

[213] I. Patraşcu, C.S. Bîldea, A.A. Kiss, Eco-efficient butanol separation in the ABE fermentation process, Separation and Purification Technology. 177 (2017) 49–61. https://doi.org/10.1016/j.seppur.2016.12.008.

[214] K. Kraemer, A. Harwardt, R. Bronneberg, W. Marquardt, Separation of butanol from acetone-butanol-ethanol fermentation by a hybrid extraction-distillation process, Computers and Chemical Engineering. 35 (2011) 949–963. https://doi.org/10.1016/j.compchemeng.2011.01.028.

[215] A.B. Van Der Merwe, H. Cheng, J.F. Görgens, J.H. Knoetze, Comparison of energy efficiency and economics of process designs for biobutanol production from sugarcane molasses, Fuel. 105 (2013) 451–458. https://doi.org/10.1016/j.fuel.2012.06.058.

[216] N. Abdehagh, F.H. Tezel, J. Thibault, Separation techniques in butanol production: Challenges and developments, Biomass and Bioenergy. 60 (2014) 222–246. https://doi.org/10.1016/j.biombioe.2013.10.003.

[217] A. Kujawska, J. Kujawski, M. Bryjak, W. Kujawski, ABE fermentation products recovery methods - A review, Renewable and Sustainable Energy Reviews. 48 (2015) 648–661. https://doi.org/10.1016/j.rser.2015.04.028.

[218] J. Kujawski, A. Rozicka, M. Bryjak, W. Kujawski, Pervaporative removal of acetone, butanol and ethanol from binary and multicomponent aqueous mixtures, Separation and Purification Technology. 132 (2014) 422–429. https://doi.org/10.1016/j.seppur.2014.05.047.

[219] K. Knozowska, A. Kujawska, G. Li, J. Kujawa, M. Bryjak, W. Kujawski, F. Lipnizki, L. Ahrné, I. Petrinić, J.K. Kujawski, Membrane assisted processing of acetone, butanol, and ethanol (ABE) aqueous streams, Chemical Engineering and Processing - Process Intensification. 166 (2021). https://doi.org/10.1016/j.cep.2021.108462.

[220] G. Liu, L. Gan, S. Liu, H. Zhou, W. Wei, W. Jin, PDMS/ceramic composite membrane for pervaporation separation of acetone-butanol-

ethanol (ABE) aqueous solutions and its application in intensification of ABE fermentation process, Chemical Engineering and Processing: Process Intensification. 86 (2014) 162–172. https://doi.org/10.1016/j.cep.2014.06.013.

[221] K.A. Pyrgakis, T. de Vrije, M.A.W. Budde, K. Kyriakou, A.M. López-Contreras, A.C. Kokossis, A process integration approach for the production of biological iso-propanol, butanol and ethanol using gas stripping and adsorption as recovery methods, Biochemical Engineering Journal. 116 (2016) 176–194. https://doi.org/10.1016/j.bej.2016.07.014.

[222] V.H. Grisales Díaz, G. Olivar Tost, Energy efficiency of a new distillation process for isopropanol, butanol, and ethanol (IBE) dehydration, Chemical Engineering and Processing - Process Intensification. 112 (2017) 56–61. https://doi.org/10.1016/j.cep.2017.01.005.

[223] H. Zhang, Q. Ye, L. Chen, N. Wang, Y. Xu, Y. Li, Purification of isopropanol-butanol-ethanol (IBE) from fermentation broth: process intensification and evaluation, Chemical Engineering and Processing - Process Intensification. 158 (2020) 108182. https://doi.org/10.1016/j.cep.2020.108182.

[224] Y. Xu, J. Li, Q. Ye, Y. Li, L. Chen, H. Zhang, N. Wang, A novel energy-efficient extraction-assisted distillation design for isopropanol–butanol–ethanol purification for use of gasoline additive, Journal of Chemical Technology and Biotechnology. 96 (2021) 1381–1398. https://doi.org/10.1002/jctb.6659.

[225] J. Kong, G. Wan, J. Yan, Q. Yi, X. Hao, X. Liu, L. Sun, Design and control of extraction combined with extractive distillation for separation isopropanol-butanol-ethanol-water with organic Rankine cycle, Separation and Purification Technology. 313 (2023) 123443. https://doi.org/10.1016/j.seppur.2023.123443.

[226] I.N. Oksal, D.B. Kaymak, Selection of eco-efficient downstream separation configuration for isopropanol–butanol–ethanol purification process, Chemical Engineering Communications. 210 (2023) 2101–2115. https://doi.org/10.1080/00986445.2023.2183125.

[227] I.N. Oksal, D.B. Kaymak, Design and control of an energy-efficient intensified process for biobutanol purification from isopropanol-butanol-ethanol (IBE) fermentation broth, Chemical Engineering and Processing - Process Intensification. 193 (2023) 109542. https://doi.org/10.1016/j.cep.2023.109542.

[228] J. Liu, F. Zhang, W. Xu, N. Shi, S. Mu, Thermal reactivity of ethylene

oxide in contact with contaminants: A review, Thermochimica Acta. 652 (2017) 85–96. https://doi.org/10.1016/j.tca.2017.03.008.

[229] A. Yang, Y. Su, W. Shen, I.L. Chien, J. Ren, Multi-objective optimization of organic Rankine cycle system for the waste heat recovery in the heat pump assisted reactive dividing wall column, Energy Conversion and Management. 199 (2019) 112041. https://doi.org/10.1016/j.enconman.2019.112041.

[230] A. Yang, S. Sun, A. Eslamimanesh, S. Wei, W. Shen, Energy-saving investigation for diethyl carbonate synthesis through the reactive dividing wall column combining the vapor recompression heat pump or different pressure thermally coupled technique, Energy. 172 (2019) 320–332. https://doi.org/10.1016/j.energy.2019.01.126.

[231] I. Patraşcu, C.S. Bildea, A.A. Kiss, Dynamics and control of a heat pump assisted extractive dividing-wall column for bioethanol dehydration, Chemical Engineering Research and Design. 119 (2017) 66–74. https://doi.org/10.1016/j.cherd.2016.12.021.

[232] I. Patraşcu, C.S. Bîldea, A.A. Kiss, Dynamics and control of a heat pump assisted azeotropic dividing-wall column for biobutanol purification, Chemical Engineering Research and Design. 146 (2019) 416–426. https://doi.org/10.1016/j.cherd.2019.04.029.

[233] Y. Li, Y. Chen, G. Wu, J. Liu, Experimental evaluation of water-containing isopropanol-n-butanol-ethanol and gasoline blend as a fuel candidate in spark-ignition engine, Applied Energy. 219 (2018) 42–52. https://doi.org/10.1016/j.apenergy.2018.03.051.

[234] E. Alptekin, Evaluation of ethanol and isopropanol as additives with diesel fuel in a CRDI diesel engine, Fuel. 205 (2017) 161–172. https://doi.org/10.1016/j.fuel.2017.05.076.

[235] D. Perlman, Isopropanol blended with aqueous ethanol for flame coloration without use of salts or hazardous solvents, US005858031A, 1999.

[236] A. Elfasakhany, Performance and emissions analysis on using acetone–gasoline fuel blends in spark-ignition engine, Engineering Science and Technology, an International Journal. 19 (2016) 1224–1232. https://doi.org/10.1016/j.jestch.2016.02.002.

[237] W.L. Luyben, Estimating refrigeration costs at cryogenic temperatures, Computers and Chemical Engineering. 103 (2017) 144–150. https://doi.org/10.1016/j.compchemeng.2017.03.013.

[238] L.M. Vane, Separation technologies for the recovery and dehydration of

alcholos from fermentation broths, Biofuels, Bioproducts and Biorefining. 2 (2008) 553–588. https://doi.org/10.1002/bbb.108.

[239] J.A. Cray, A. Stevenson, P. Ball, S.B. Bankar, E.C.A. Eleutherio, T.C. Ezeji, R.S. Singhal, J.M. Thevelein, D.J. Timson, J.E. Hallsworth, Chaotropicity: A key factor in product tolerance of biofuel-producing microorganisms, Current Opinion in Biotechnology. 33 (2015) 228–259. https://doi.org/10.1016/j.copbio.2015.02.010.

[240] H.J. Oh, J.K. Ko, G. Gong, S.M. Lee, Y. Um, Production of Hexanol as the Main Product Through Syngas Fermentation by *Clostridium carboxidivorans* P7, Frontiers in Bioengineering and Biotechnology. 10 (2022) 1–11. https://doi.org/10.3389/fbioe.2022.850370.

[241] C.A. Cardona, Ó.J. Sánchez, Fuel ethanol production: Process design trends and integration opportunities, Bioresource Technology. 98 (2007) 2415–2457. https://doi.org/10.1016/j.biortech.2007.01.002.

[242] S. Wang, R. Li, X. Yi, T. Fang, J. Yang, H. Bae, Isoprene Production on Enzymatic Hydrolysate of Peanut Hull Using Different Pretreatment Methods, BioMed Research Internationa; (2016) 4342892. https://doi.org/10.1155/2016/4342892.

[243] B.L. Maiorella, H.W. Blanch, C.R. Wilke, Biotechnology report, Economic Evaluation of Alternative Ethanol Fermentation Processes, Biotechnology and Bioengineering. 26 (1984) 1003–1025. https://doi.org/10.1038/283520b0.

[244] R. Smith, Chemical Process Design and Integration, John Wiley & Sons Ltd., Chichester, 2016.

[245] T. Janković, A.J.J. Straathof, A.A. Kiss, Turning waste into value: eco-efficient recovery of by-products from biomass pretreatment in lignocellulosic biorefineries, Biofuels, Bioproducts and Biorefining. 17 (2023) 1654–1667. https://doi.org/10.1002/bbb.2532.

[246] T. Janković, A.J.J. Straathof, A.A. Kiss, Enhanced isobutanol recovery from fermentation broth for sustainable biofuels production, Energy Conversion and Management: X. 21 (2024) 100520. https://doi.org/10.1016/j.ecmx.2023.100520.

[247] M.K. Akhtar, H. Dandapani, K. Thiel, P.R. Jones, Microbial production of 1-octanol: A naturally excreted biofuel with diesel-like properties, Metabolic Engineering Communications. 2 (2015) 1–5. https://doi.org/10.1016/j.meteno.2014.11.001.

[248] C. Dellomonaco, J.M. Clomburg, E.N. Miller, R. Gonzalez, Engineered reversal of the β-oxidation cycle for the synthesis of fuels and chemicals,

Nature. 476 (2011) 355–359. https://doi.org/10.1038/nature10333.

[249] F. Kremer, L.M. Blank, P.R. Jones, M.K. Akhtar, A comparison of the microbial production and combustion characteristics of three alcohol biofuels: Ethanol, 1-butanol, and 1-octanol, Frontiers in Bioengineering and Biotechnology. 3 (2015) 1–7. https://doi.org/10.3389/fbioe.2015.00112.

[250] Ethanol Market Analysis: Industry Market Size, Plant Capacity, Production, Operating Efficiency, Demand & Supply, End-User Industries, Sales Channel, Regional Demand, Company Share, Manufacturing Process, Policy and Regulatory Landscape, 2015-2032, Chem Analyst. (2023). https://www.chemanalyst.com/industry-report/ethanol-market-594.

[251] Isopropyl Alcohol (IPA) Market Analysis: Industry Market Size, Plant Capacity, Production, Operating Efficiency, Demand & Supply, End-User Industries, Sales Channel, Regional Demand, Company Share, Manufacturing Process, Policy and Regulatory Landscape, 2, Chem Analyst. (2023). https://www.chemanalyst.com/industry-report/isopropyl-alcohol-ipa-187.

[252] Iso Butanol Alcohol Market Analysis: Industry Market Size, Plant Capacity, Production, Operating Efficiency, Demand & Supply, End-User Industries, Sales Channel, Regional Demand, Company Share, Manufacturing Process, 2015-2032, Chem Analyst. (2023). https://www.chemanalyst.com/industry-report/iso-butanol-market-776.

[253] T. Janković, A.J.. Straathof, A.A. Kiss, Advanced purification of isopropanol and acetone from syngas fermentation, Journal of Chemical Technology & Biotechnology. 99 (2023) 714–726. https://doi.org/10.1002/jctb.7576.

[254] S. Chovau, D. Degrauwe, B. Van Der Bruggen, Critical analysis of techno-economic estimates for the production cost of lignocellulosic bio-ethanol, Renewable and Sustainable Energy Reviews. 26 (2013) 307–321. https://doi.org/10.1016/j.rser.2013.05.064.

[255] M. Uyttebroek, W. Van Hecke, K. Vanbroekhoven, Sustainability metrics of 1-butanol, Catalysis Today. 239 (2015) 7–10. https://doi.org/10.1016/j.cattod.2013.10.094.

[256] Ethanol, Carbon Cloud. (2023). https://apps.carboncloud.com/climatehub/product-reports/id/11607069111.

[257] Ethanol Price Trend and Forecast, Chem Analyst. (2023).

https://www.chemanalyst.com/Pricing-data/ethanol-13.

[258] Isopropyl Alcohol (IPA) Price Trend and Forecast, Chem Analyst. (2023). https://www.chemanalyst.com/Pricing-data/isopropyl-alcohol-31.

[259] Iso Butanol Price Trend and Forcast, Chem Analyst. (2023). https://www.chemanalyst.com/Pricing-data/iso-butanol-22.

[260] API Price Trend Dashboard - Hexanol, Pharma Compass. (2023). https://www.pharmacompass.com/price/hexanol-8103.

[261] D.J. O'Brien, L.H. Roth, A.J. McAloon, Ethanol production by continuous fermentation-pervaporation: A preliminary economic analysis, Journal of Membrane Science. 166 (2000) 105–111. https://doi.org/10.1016/S0376-7388(99)00255-0.

[262] A. Devi, A. Niazi, M. Ramteke, S. Upadhyayula, Techno-economic analysis of ethanol production from lignocellulosic biomass–a comparison of fermentation, thermo catalytic, and chemocatalytic technologies, Bioprocess and Biosystems Engineering. 44 (2021) 1093–1107. https://doi.org/10.1007/s00449-020-02504-4.

[263] F. Bauer, C. Hulteberg, Isobutanol from glycerine - A techno-economic evaluation of a new biofuel production process, Applied Energy. 122 (2014) 261–268. https://doi.org/10.1016/j.apenergy.2014.02.037.

[264] C.E. Nakamura, G.M. Whited, Metabolic engineering for the microbial production of 1,3-propanediol, Current Opinion in Biotechnology. 14 (2003) 454–459. https://doi.org/10.1016/j.copbio.2003.08.005.

[265] M. Emptage, S.L. Haynie, L.A. Laffend, Process for the biological production of 1,3-propanediol with high titer, US 2009/0253192 A1, 2009.

[266] M. Köpke, C. Mihalcea, F.M. Liew, J.H. Tizard, M.S. Ali, J.J. Conolly, B. Al-Sinawi, S.D. Simpson, 2,3-Butanediol production by acetogenic bacteria, an alternative route to chemical synthesis, using industrial waste gas, Applied and Environmental Microbiology. 77 (2011) 5467–5475. https://doi.org/10.1128/AEM.00355-11.

[267] S. Simpson, The LanzaTech process is driving innovation, Https://Www.Energy.Gov/Sites/Prod/Files/2017/07/F35/BETO_2017WTE-Workshop_SeanSimpson-LanzaTech.Pdf. (2017).

[268] NREL, Partnership Receives Funding To Commercialize NREL's 2,3-Butanediol Fermentation Process, (2022). https://www.nrel.gov/news/program/2022/partnership-receives-funding-to-commercialize-nrels-2-3-butanediol-fermentation-process.html.

[269] Genomatica, The Better BDO, GenoTM Bio-BDO, (2016). https://www.genomatica.com/bdo/.

[270] Genomatica, Novamont opens world ' s first commercial plant for bio-production of a major intermediate chemical, Globe News Wire. (2016).

[271] A.P. Burgard, M.J. Burk, R.E. Osterhout, P. Pharkya, Organisms for the production of 1,3-butanediol, US 9,017,093 B2, 2015.

[272] D.M. Adkesson, A.W. Alsor, L.A. Shu, J.M. Disney, B. c. Dravis, F. Patrick, J.M. Gaddy, G.F. Gallagher, W.F. Lehnhardt, J.C. Lievense, M.L. Luyben, M. Seapan, R.E. Trotter, G.M. Wenndt, E.K. Yu, Purification of biologically-produced 1,3-propanediol, WO 2004/101479 A2, 2004.

[273] Z.L. Xiu, A.P. Zeng, Present state and perspective of downstream processing of biologically produced 1,3-propanediol and 2,3-butanediol, Applied Microbiology and Biotechnology. 78 (2008) 917–926. https://doi.org/10.1007/s00253-008-1387-4.

[274] P. Anand, R.K. Saxena, R.G. Marwah, A novel downstream process for 1,3-propanediol from glycerol-based fermentation, Applied Microbiology and Biotechnology. 90 (2011) 1267–1276. https://doi.org/10.1007/s00253-011-3161-2.

[275] M.H. Cho, S.I. Joen, S.H. Pyo, S. Mun, J.H. Kim, A novel separation and purification process for 1,3-propanediol, Process Biochemistry. 41 (2006) 739–744. https://doi.org/10.1016/j.procbio.2005.11.013.

[276] J.J. Malinowski, Evaluation of liquid extraction potentials for downstream separation of 1,3-propanediol, Biotechnology Techniques. 13 (1999) 127–130. https://doi.org/10.1023/A:1008858903613.

[277] J.J. Malinowski, Reactive extraction for downstream separation of 1,3-propanediol, Biotechnology Progress. 16 (2000) 76–79. https://doi.org/10.1021/bp990140g.

[278] J. Hao, F. Xu, H. Liu, D. Liu, Downstream processing of 1,3-propanediol fermentation broth, Journal of Chemical Technology and Biotechnology. 81 (2006) 102–108. https://doi.org/10.1002/jctb.1369.

[279] J. Hao, H. Liu, D. Liu, Novel route of reactive extraction to recover 1,3-propanediol from a dilute aqueous solution, Industrial and Engineering Chemistry Research. 44 (2005) 4380–4385. https://doi.org/10.1021/ie049346z.

[280] A.A. Koutinas, B. Yepez, N. Kopsahelis, D.M.G. Freire, A.M. de Castro, S. Papanikolaou, I.K. Kookos, Techno-economic evaluation of a

complete bioprocess for 2,3-butanediol production from renewable resources, Bioresource Technology. 204 (2016) 55–64. https://doi.org/10.1016/j.biortech.2015.12.005.

[281] H. Fu, Y. Sun, Z. Xiu, Continuous countercurrent salting-out extraction of 1,3-propanediol from fermentation broth in a packed column, Process Biochemistry. 48 (2013) 1381–1386. https://doi.org/10.1016/j.procbio.2013.06.017.

[282] Z.G. Li, Y.Q. Sun, W.L. Zheng, H. Teng, Z.L. Xiu, A novel and environment-friendly bioprocess of 1,3-propanediol fermentation integrated with aqueous two-phase extraction by ethanol/sodium carbonate system, Biochemical Engineering Journal. 80 (2013) 68–75. https://doi.org/10.1016/j.bej.2013.09.014.

[283] J.Y. Dai, Y.Q. Sun, Z.L. Xiu, Separation of bio-based chemicals from fermentation broths by salting-out extraction, Engineering in Life Sciences. 14 (2014) 108–117. https://doi.org/10.1002/elsc.201200210.

[284] S. Xie, Z. Li, G. Zhu, W. Song, C. Yi, Cleaner production and downstream processing of bio-based 2,3-butanediol: A review, Journal of Cleaner Production. 343 (2022) 131033. https://doi.org/10.1016/j.jclepro.2022.131033.

[285] J.Y. Dai, C.J. Liu, Z.L. Xiu, Sugaring-out extraction of 2,3-butanediol from fermentation broths, Process Biochemistry. 50 (2015) 1951–1957. https://doi.org/10.1016/j.procbio.2015.08.004.

[286] A.S. Afschar, C.E. Vaz Rossell, R. Jonas, A. Quesada Chanto, K. Schaller, Microbial production and downstream processing of 2,3-butanediol, Journal of Biotechnology. 27 (1993) 317–329. https://doi.org/10.1016/0168-1656(93)90094-4.

[287] L. Caballero-Sanchez, A.A. Vargas-Tah, P.E. Lázaro-Mixteco, A.J. Castro-Montoya, Recovery of 1,4-butanediol from aqueous solutions through aqueous two-phase systems with K_2CO_3, Chemical Engineering Research and Design. 201 (2024) 150–156. https://doi.org/10.1016/j.cherd.2023.11.015.

[288] Y.Q. Sun, J.T. Shen, L. Yan, J.J. Zhou, L.L. Jiang, Y. Chen, J.L. Yuan, E.M. Feng, Z.L. Xiu, Advances in bioconversion of glycerol to 1,3-propanediol: Prospects and challenges, Process Biochemistry. 71 (2018) 134–146. https://doi.org/10.1016/j.procbio.2018.05.009.

[289] H. Liu, Y. Xu, Z. Zheng, D. Liu, 1,3-Propanediol and its copolymers: Research, development and industrialization, Biotechnology Journal. 5 (2010) 1137–1148. https://doi.org/10.1002/biot.201000140.

[290] 1,3 Propanediol Market Share, Size, Trends, Industry Analysis Report, By Application (Polytrimethylene Terephthalate, Polyurethane, Personal Care & Detergents, Pharmaceutical, Food & Beverages, Heat Transfer Fluid, Inks and Coatings, and Others), Polaris Market Research. (2022). https://www.polarismarketresearch.com/industry-analysis/1-3-propanediol-market.

[291] Polytrimethylene Terephthalate Market Size, Share & Trends Analysis Report By End-use (Automotive, Textiles), By Type (Petroleum, Bio-based), By Application (Film Materials, Fiber), By Region, And Segment Forecasts, 2022 - 2030, Grand View Research. (2022). https://www.grandviewresearch.com/industry-analysis/polytrimethylene-terephthalate-market.

[292] T. Haas, B. Jaeger, R. Weber, S.F. Mitchell, C.F. King, New diol processes: 1,3-propanediol and 1,4-butanediol, Applied Catalysis A: General. 280 (2005) 83–88. https://doi.org/10.1016/j.apcata.2004.08.027.

[293] G. Kaur, A.K. Srivastava, S. Chand, Advances in biotechnological production of 1,3-propanediol, Biochemical Engineering Journal. 64 (2012) 106–118. https://doi.org/10.1016/j.bej.2012.03.002.

[294] R.K. Saxena, P. Anand, S. Saran, J. Isar, Microbial production of 1,3-propanediol: Recent developments and emerging opportunities, Biotechnology Advances. 27 (2009) 895–913. https://doi.org/10.1016/j.biotechadv.2009.07.003.

[295] S.M. Lee, W.K. Hong, S.Y. Heo, J.M. Park, Y.R. Jung, B.R. Oh, M.H. Joe, J.W. Seo, C.H. Kim, Enhancement of 1,3-propanediol production by expression of pyruvate decarboxylase and aldehyde dehydrogenase from Zymomonas mobilis in the acetolactate-synthase-deficient mutant of *Klebsiella pneumoniae*, Journal of Industrial Microbiology and Biotechnology. 41 (2014) 1259–1266. https://doi.org/10.1007/s10295-014-1456-x.

[296] Z. Wu, Z. Wang, G. Wang, T. Tan, Improved 1,3-propanediol production by engineering the 2,3-butanediol and formic acid pathways in integrative recombinant *Klebsiella pneumoniae*, Journal of Biotechnology. 168 (2013) 194–200. https://doi.org/10.1016/j.jbiotec.2013.04.022.

[297] T. Homann, C. Tag, H. Biebl, W.D. Deckwer, B. Schink, Fermentation of glycerol to 1,3-propanediol by *Klebsiella* and *Citrobacter* strains, Applied Microbiology and Biotechnology. 33 (1990) 121–126. https://doi.org/10.1007/BF00176511.

[298] Y.Z. Xu, N.N. Guo, Z.M. Zheng, X.J. Ou, H.J. Liu, D.H. Liu,

Metabolism in 1,3-propanediol fed-batch fermentation by a D-lactate deficient mutant of *Klebsiella pneumoniae*, Biotechnology and Bioengineering. 104 (2009) 965–972. https://doi.org/10.1002/bit.22455.

[299] B. Tabah, A. Varvak, I.N. Pulidindi, E. Foran, E. Banin, A. Gedanken, Production of 1,3-propanediol from glycerol via fermentation by *Saccharomyces cerevisiae*, Green Chemistry. 18 (2016) 4657–4666. https://doi.org/10.1039/c6gc00125d.

[300] T.A. Ewing, N. Nouse, M. van Lint, J. van Haveren, J. Hugenholtz, D.S. van Es, Fermentation for the production of biobased chemicals in a circular economy: a perspective for the period 2022-2050, Green Chemistry. 24 (2022) 6373–6405. https://doi.org/10.1039/d1gc04758b.

[301] R.P. Anex, A.L. Ogletree, Life-Cycle Assessment of Energy-Based Imacts of a Biobased Process for Producing 1,3-Propanediol, in: Feedstocks for the Future, American Chemical Society, Washington, 2006: pp. 222–238. https://doi.org/10.1021/bk-2006-0921.ch017.

[302] E. Molel, H. Phillips, A. Smith, 1, 3-Propanediol from Crude Glycerol, University of Pennsylvania, 2015.

[303] R.A. Urban, B.R. Bakshi, 1,3-Propanediol from fossils versus biomass: A life cycle evaluation of emissions and ecological resources, Industrial and Engineering Chemistry Research. 48 (2009) 8068–8082. https://doi.org/10.1021/ie801612p.

[304] J.A. Posada, L.E. Rincón, C.A. Cardona, Design and analysis of biorefineries based on raw glycerol: Addressing the glycerol problem, Bioresource Technology. 111 (2012) 282–293. https://doi.org/10.1016/j.biortech.2012.01.151.

[305] Ultrafiltration (UF) details A closer look, DuPont. https://www.dupont.com/water/technologies/ultrafiltration-uf.html.

[306] T. Ito, F. Yoshida, Vapor-Liquid Equilibria of Water-Lower Fatty Acid Systems: Water-Formic Acid, Water Acetic Acid and Water-Propionic Acid, Journal of Chemical and Engineering Data. 8 (1963) 315–320. https://doi.org/10.1021/je60018a012.

[307] A.A. Kiss, Process Intensification: Industrial Applications, in: Process Intensification in Chemical Engineering: Design Optimization and Control, Springer, Cham, 2016: pp. 221–260. https://doi.org/10.1007/978-3-319-28392-0.

[308] T. Attarbachi, M.D. Kingsley, V. Spallina, New trends on crude glycerol purification: A review, Fuel. 340 (2023) 127485. https://doi.org/10.1016/j.fuel.2023.127485.

[309] M.S. Ardi, M.K. Aroua, N.A. Hashim, Progress, prospect and challenges in glycerol purification process: A review, Renewable and Sustainable Energy Reviews. 42 (2015) 1164–1173. https://doi.org/10.1016/j.rser.2014.10.091.

[310] I. Pazmiño-Mayorga, M. Jobson, A.A. Kiss, Conceptual design of a dual reactive dividing wall column for downstream processing of lactic acid, Chemical Engineering and Processing - Process Intensification. 164 (2021). https://doi.org/10.1016/j.cep.2021.108402.

[311] K.S. Bankole, G.A. Aurand, Kinetic and thermodynamic parameters for uncatalyzed esterification of carboxylic acid, Research Journal of Applied Sciences, Engineering and Technology. 7 (2014) 4671–4684. https://doi.org/10.19026/rjaset.7.850.

[312] M.S. Peters, K.D. Timmerhaus, R.E. West, Plant Design and Economics for Chemical Engineers, 5th ed., New York, 2003.

[313] J.G.G. Jonker, M. Junginger, J. Posada, C.S. Ioiart, A.P.C. Faaij, F. van der Hilst, Economic performance and GHG emission intensity of sugarcane- and eucalyptus-derived biofuels and biobased chemicals in Brazil, Biofuels, Bioproducts and Biorefining. 13 (2019) 950–977. https://doi.org/10.1002/bbb.1986.

[314] J.A. Posada, C.A. Cardona, J.C. Higuita, J.A. Tamayo, Y.A. Pisarenko, Design and economic analysis of the technological scheme for 1,3-propanediol production from raw glycerol, Theoretical Foundations of Chemical Engineering. 47 (2013) 239–253. https://doi.org/10.1134/S0040579513030093.

[315] B.S. Shrirame, A.R. Varma, S.S. Sahoo, K. Gayen, S.K. Maity, Techno-commercial viability of glycerol valorization to 1,2- and 1,3-propanediol using pinch technology, Biomass and Bioenergy. 177 (2023) 106943. https://doi.org/10.1016/j.biombioe.2023.106943.

[316] B.G. Harvey, W.W. Merriman, R.L. Quintana, Renewable Gasoline, Solvents, and Fuel Additives from 2,3-Butanediol, ChemSusChem. 9 (2016) 1814–1819. https://doi.org/10.1002/cssc.201600225.

[317] E.R. Sacia, M. Balakrishnan, M.H. Deaner, K.A. Goulas, F.D. Toste, A.T. Bell, Back Cover: Highly Selective Condensation of Biomass-Derived Methyl Ketones as a Source of Aviation Fuel (ChemSusChem 10/2015), ChemSusChem. 8 (2015) 1820–1820. https://doi.org/10.1002/cssc.201500556.

[318] D. Song, Y.G. Yoon, C.J. Lee, Conceptual design for the recovery of 1,3-Butadiene and methyl ethyl ketone via a 2,3-Butanediol-dehydration

process, Chemical Engineering Research and Design. 123 (2017) 268–276. https://doi.org/10.1016/j.cherd.2017.05.019.

[319] A.M. Białkowska, Strategies for efficient and economical 2,3-butanediol production: new trends in this field, World Journal of Microbiology and Biotechnology. 32 (2016) 1–14. https://doi.org/10.1007/s11274-016-2161-x.

[320] Transparency Market Research, 2,3-Butanediol Market, (2022). https://www.transparencymarketresearch.com/2-3-butanediol-market.html.

[321] J. Haider, M.A. Qyyum, A. Hussain, M. Yasin, M. Lee, Techno-economic analysis of various process schemes for the production of fuel grade 2,3-butanediol from fermentation broth, Biochemical Engineering Journal. 140 (2018) 93–107. https://doi.org/10.1016/j.bej.2018.09.002.

[322] C.C. Satam, M. Daub, M.J. Realff, Techno-economic analysis of 1,4-butanediol production by a single-step bioconversion process, Biofuels, Bioproducts and Biorefining. 13 (2019) 1261–1273. https://doi.org/10.1002/bbb.2016.

[323] Transparency Market Research, 1,4-Butanediol Market, (2022). https://www.gminsights.com/industry-analysis/1-4-butanediol-market.

[324] P. Luo, X. Li, Application and Market of 1,4-butanediol Production of Reppe Method in China, American Journal of Chemical Engineering. 9 (2021) 34. https://doi.org/10.11648/j.ajche.20210902.11.

[325] M.J. Burk, S.J. Van Dien, A.P. Burgard, W. Niu, Compositions and Methods for the Biosynthesis of 1,4-Butanediol and Its Precursors, US 2009/0075351 A1, 2009.

[326] Verified Market Reports, 1,3-Butanediol Market Insights, (2024). https://www.verifiedmarketreports.com/product/1-3-butanediol-market/.

[327] N. Qin, F. Zhu, Y. Liu, D. Liu, Z. Chen, Metabolic Engineering of Escherichia coli for De Novo Production of 1,2-Butanediol, ACS Synthetic Biology. 13 (2024) 351–357. https://doi.org/doi.org/10.1021/acssynbio.3c00606.

[328] L. Zhang, S. Huang, J. Qiu, B. Wang, B.B. Yan, J. Zhang, B. Zhou, J. Chen, X. Zeng, Selective transformation of biomass-derived substrates to 1,2-butanediol: A comprehensive review and new insights, Industrial Crops and Products. 202 (2023) 116984. https://doi.org/10.1016/j.indcrop.2023.116984.

[329] A. Forte, A. Zucaro, R. Basosi, A. Fierro, LCA of 1,4-butanediol

produced via direct fermentation of sugars from wheat straw feedstock within a territorial biorefinery, Materials. 9 (2016) 1–22. https://doi.org/10.3390/MA9070563.

[330] M. Baldassarre, A. Cesana, F. Bordes, Process for bio-1,3-butanediol purification from a fermentation broth, WO 2020/058381 A1, 2020. https://patentimages.storage.googleapis.com/4e/c7/d1/b2392bca55fe67/US10286504B2.pdf.

[331] P.M. Gawal, S. Subudhi, Advances and challenges in bio-based 2,3-BD downstream purification: A comprehensive review, Bioresource Technology Reports. 24 (2023) 101638. https://doi.org/10.1016/j.biteb.2023.101638.

[332] N. Van Duc Long, J. Hong, L.C. Nhien, M. Lee, Novel hybrid-blower-and-evaporator-assisted distillation for separation and purification in biorefineries, Chemical Engineering and Processing: Process Intensification. 123 (2018) 195–203. https://doi.org/10.1016/j.cep.2017.11.009.

[333] J. Hong, N. Van Duc Long, G.R. Harvianto, J. Haider, M. Lee, Design and optimization of multi-effect-evaporation-assisted distillation configuration for recovery of 2,3-butanediol from fermentation broth, Chemical Engineering and Processing - Process Intensification. 136 (2019) 107–115. https://doi.org/10.1016/j.cep.2019.01.002.

[334] J. Haider, G.R. Harvianto, M.A. Qyyum, M. Lee, Cost- and Energy-Efficient Butanol-Based Extraction-Assisted Distillation Designs for Purification of 2,3-Butanediol for Use as a Drop-in Fuel, ACS Sustainable Chemistry and Engineering. 6 (2018) 14901–14910. https://doi.org/10.1021/acssuschemeng.8b03414.

[335] G.R. Harvianto, J. Haider, J. Hong, N. Van Duc Long, J.J. Shim, M.H. Cho, W.K. Kim, M. Lee, Purification of 2,3-butanediol from fermentation broth: Process development and techno-economic analysis, Biotechnology for Biofuels. 11 (2018) 1–16. https://doi.org/10.1186/s13068-018-1013-3.

[336] J. Haider, M.A. Qyyum, L.Q. Minh, M. Lee, Purification step enhancement of the 2,3-butanediol production process through minimization of high pressure steam consumption, Chemical Engineering Research and Design. 153 (2020) 697–708. https://doi.org/10.1016/j.cherd.2019.11.005.

[337] D. Vallejo-Blancas, B. Huerta-Rosas, J.J. Quiroz-Ramírez, J.G. Segovia-Hernández, E. Sánchez-Ramírez, Control properties of sustainable alternatives to produce 2,3-butanediol, Chemical Engineering Research

and Design. 186 (2022) 473–484. https://doi.org/10.1016/j.cherd.2022.08.020.

[338] BenitM, Distillation Engineering, (2024). http://www.benitm.com/?pn=tech.distillation_02.

[339] S. Gadkari, V. Narisetty, S.K. Maity, H. Manyar, K. Mohanty, R.B. Jeyakumar, K.K. Pant, V. Kumar, Techno-Economic Analysis of 2,3-Butanediol Production from Sugarcane Bagasse, Industrial and Engineering Chemistry Research. 11 (2023) 8337–8349. https://doi.org/10.1021/acssuschemeng.3c01221.

[340] F. Ebrahimian, A. Mohammadi, Assessing the environmental footprints and material flow of 2,3-butanediol production in a wood-based biorefinery, Bioresource Technology. 387 (2023) 129642. https://doi.org/10.1016/j.biortech.2023.129642.

[341] T. Janković, S. Sharma, A.J.J. Straathof, A.A. Kiss, Adaptable downstream processing design for recovery of butanediols after fermentation, Chemical Engineering Research and Design. 213 (2025) 210–220. https://doi.org/10.1016/j.cherd.2024.12.011.

[342] T. Janković, A.J.J. Straathof, A.A. Kiss, Eco-efficient downstream processing of 1,3-propanediol applicable to various fermentation processes, Process Biochemistry. 143 (2024) 210–224. https://doi.org/10.1016/j.procbio.2024.04.040.

[343] A.A. Kiss, Dividing-Wall Column, in: Advanced Distillation Technologies, John Wiley and Sons Ltd, Chichester, 2013.

[344] T. Janković, A.J.J. Straathof, A.A. Kiss, A perspective on downstream processing performance for recovery of bioalcohols, Journal of Chemical Technology and Biotechnology. 99 (2024) 1933–1940. https://doi.org/10.1002/jctb.7690.

[345] R.A. Gonzalez-Garcia, T. McCubbin, L. Navone, C. Stowers, L.K. Nielsen, E. Marcellin, Microbial propionic acid production, Fermentation. 3 (2017) 1–20. https://doi.org/10.3390/fermentation3020021.

[346] U.-R. Samel, W. Kohler, A. Garner, Keuser, Propionic acid and derivatives, in: Ullmann's Encyclopedia of Industrial Chemistry, 2011: pp. 295–309. https://doi.org/10.1002/14356007.a22.

[347] Z. Wang, J. Sun, A. Zhang, S. Yang, Propionic Acid Fermentation, in: Bioprocessing Technologies in Biorefinery for Sustainable Production of Fuels, Chemicals, and Polymers, 2013: pp. 331–350. https://doi.org/10.1002/9781118642047.ch18.

[348] Methyl propionate, PubChem. (2023). https://pubchem.ncbi.nlm.nih.gov/compound/Methyl-propionate.

[349] J.P.C. Pereira, L.A.M. van der Wielen, A.J.J. Straathof, Perspectives for the microbial production of methyl propionate integrated with product recovery, Bioresource Technology. 256 (2018) 187–194. https://doi.org/10.1016/j.biortech.2018.01.118.

[350] Global Methyl Acetate Market Outlook, Expert Market Research. (2024). https://www.expertmarketresearch.com/reports/methyl-acetate-market.

[351] C.C. Stowers, B.A. Rodriguez, B.M. Cox, Fermentation based hydrolyzed corn and/or sugar can mash to produce propionic acid, US 2016/017384 A1, 2016.

[352] S.-T. Yang, E. Ammar, C.C. Stowers, B.A. Rodriguez, Process for producing n-propanol and propionic acid using metabolically engineered Propionibacteria, US 10,150,951 B2, 2018.

[353] X. Feng, F. Chen, H. Xu, B. Wu, H. Li, S. Li, P. Ouyang, Green and economical production of propionic acid by *Propionibacterium freudenreichii* CCTCC M207015 in plant fibrous-bed bioreactor, Bioresource Technology. 102 (2011) 6141–6146. https://doi.org/10.1016/j.biortech.2011.02.087.

[354] Z. Liu, C. Ma, C. Gao, P. Xu, Efficient utilization of hemicellulose hydrolysate for propionic acid production using *Propionibacterium acidipropionici*, Bioresource Technology. 114 (2012) 711–714. https://doi.org/10.1016/j.biortech.2012.02.118.

[355] S. Suwannakham, S.T. Yang, Enhanced propionic acid fermentation by Propionibacterium acidipropionici mutant obtained by adaptation in a fibrous-bed bioreactor, Biotechnology and Bioengineering. 91 (2005) 325–337. https://doi.org/10.1002/bit.20473.

[356] A. Zhang, S.T. Yang, Engineering Propionibacterium acidipropionici for enhanced propionic acid tolerance and fermentation, Biotechnology and Bioengineering. 104 (2009) 766–773. https://doi.org/10.1002/bit.22437.

[357] B.A. Rodriguez, C.C. Stowers, V. Pham, B.M. Cox, The production of propionic acid, propanol and propylene via sugar fermentation: An industrial perspective on the progress, technical challenges and future outlook, Green Chemistry. 16 (2014) 1066–1076. https://doi.org/10.1039/c3gc42000k.

[358] J.L. Rehbergert, B.A. Glatz, Response of Cultures of *Propionibacterium* to Acid and Low pH : Tolerance and Inhibition, Journal of Food

Protection. 61 (1998) 211–216. https://doi.org/10.4315/0362-028X-61.2.211.

[359] H.A. Seong, J.S. Lee, S.Y. Yoon, W.Y. Song, S.J. Shin, Fermentation characteristics of acid hydrolysates by different neutralizing agents, International Journal of Hydrogen Energy. 41 (2016) 16365–16372. https://doi.org/10.1016/j.ijhydene.2016.05.003.

[360] É. Hülber-Beyer, K. Bélafi-Bakó, N. Nemestóthy, Low-waste fermentation-derived organic acid production by bipolar membrane electrodialysis-an overview, Chemical Papers. 75 (2021) 5223–5234. https://doi.org/10.1007/s11696-021-01720-w.

[361] P. Boyaval, C. Corre, Production of propionic acid, Le Lait. 75 (1995) 453–461. https://doi.org/10.1016/0023-7302(96)80128-X.

[362] D. Arslan, Y. Zhang, K.J.J. Steinbusch, L. Diels, H.V.M. Hamelers, C.J.N. Buisman, H. De Wever, *In-situ* carboxylate recovery and simultaneous pH control with tailor-configured bipolar membrane electrodialysis during continuous mixed culture fermentation, Separation and Purification Technology. 175 (2017) 27–35. https://doi.org/10.1016/j.seppur.2016.11.032.

[363] M. Szczygiełda, J. Antczak, K. Prochaska, Separation and concentration of succinic acid from post-fermentation broth by bipolar membrane electrodialysis (EDBM), Separation and Purification Technology. 181 (2017) 53–59. https://doi.org/10.1016/j.seppur.2017.03.018.

[364] S.-T. Hsu, S.-T. Yang, Propionic Acid Fermentation of Lactose, Biotechnology and Bioengineering. 38 (1991) 571–578.

[365] Z. Wang, Y. Jin, S. Yang, High Cell Density Propionic Acid Fermentation with an Acid Tolerant Strain of *Propionibacterium acidipropionici*, 112 (2015) 502–511. https://doi.org/10.1002/bit.25466.

[366] C.C. Stowers, B.M. Cox, B.A. Rodriguez, Development of an industrializable fermentation process for propionic acid production, Journal of Industrial Microbiology and Biotechnology. 41 (2014) 837–852. https://doi.org/10.1007/s10295-014-1423-6.

[367] V. Inyang, D. Lokhat, Propionic acid recovery from dilute aqueous solution by emulsion liquid membrane (ELM) technique: optimization using response surface methodology (RSM) and artificial neural network (ANN) experimental design, Separation Science and Technology. 57 (2022) 284–300. https://doi.org/10.1080/01496395.2021.1890774.

[368] A. Kaur, D.K. Vohra, Study of bulk liquid membrane as a separation technique to recover acetic and propionic acids from dilute solutions,

Indian Journal of Chemical Technology. 17 (2010) 133–138.

[369] Y.S. Aşçi, I. Inci, Extraction equilibria of propionic acid from aqueous solutions by Amberlite LA-2 in diluent solvents, Chemical Engineering Journal. 155 (2009) 784–788. https://doi.org/10.1016/j.cej.2009.09.024.

[370] A. Keshav, S. Chand, K.L. Wasewar, Recovery of propionic acid from aqueous phase by reactive extraction using quarternary amine (Aliquat 336) in various diluents, Chemical Engineering Journal. 152 (2009) 95–102. https://doi.org/10.1016/j.cej.2009.03.037.

[371] Q.-Z. Li, X.-J. Feng, H.-B. Zhang, H.-Z. Liu, M. Xian, C. Sun, J.-M. Wang, X.-L. Jiang, Recovery Processes of Organic Acids from Fermentation Broths in the Biomass-Based Industry, Journal of Microbiology and Biotechnology. 26 (2016) 1–8. https://doi.org/10.4014/jmb.1505.05049.

[372] F.J. Caires, L.S. Lima, C.T. Carvalho, M. Ionashiro, Thermal behaviour of succinic acid, sodium succinate and its compounds with some bivalent transition metal ions, Thermochimica Acta. 500 (2010) 6–12. https://doi.org/10.1016/j.tca.2009.11.015.

[373] DuPont™ AmberLyst™ Polymeric Catalysts, (2021). https://www.dupont.com/brands/amber-series.html.

[374] Y.T. Tsai, H. mu Lin, M.J. Lee, Kinetics behavior of esterification of acetic acid with methanol over Amberlyst 36, Chemical Engineering Journal. 171 (2011) 1367–1372. https://doi.org/10.1016/j.cej.2011.05.049.

[375] Y.T. Tsai, H. mu Lin, M.J. Lee, Kinetics of Catalytic Esterification of Propionic Acid with Methanol over Amberlyst 36, Industrial & Engineering Chemictry Research. 50 (2011) 1171–1176. https://doi.org/10.1016/j.cej.2011.05.049.

[376] A.A. Kiss, J.J. Pragt, C.J.G. van Strien, Reactive dividing-wall columns-how to get more with less resources?, Chemical Engineering Communications. 196 (2009) 1366–1374. https://doi.org/10.1080/00986440902935507.

[377] A.A. Kiss, C.S. Bildea, A control perspective on process intensification in dividing-wall columns, Chemical Engineering and Processing: Process Intensification. 50 (2011) 281–292. https://doi.org/10.1016/j.cep.2011.01.011.

[378] Ö. Yildirim, A.A. Kiss, E.Y. Kenig, Dividing wall columns in chemical process industry: A review on current activities, Separation and Purification Technology. 80 (2011) 403–417.

https://doi.org/10.1016/j.seppur.2011.05.009.

[379] W.L. Luyben, C.C. Yu, Reactive Distillation Design and Control, John Wiley & Sons, Hoboken, 2008. https://doi.org/10.1002/9780470377741.

[380] Reactive Distillation Column, Maleta Cyclic Distillation. (2023). https://www.maletacd.com/index.php/distillation-column/reactive-distillation-column.

[381] Methyl acetate 90%, VICHEMIC INDUSTRIES. (2023). https://vichemic.pl/en/produkt/methyl-acetate-90-79-20-9/.

[382] E. Graczová, B. Šulgan, S. Barabas, P. Steltenpohl, Methyl acetate-methanol mixture separation by extractive distillation: Economic aspects, Frontiers of Chemical Science and Engineering. 12 (2018) 670–682. https://doi.org/10.1007/s11705-018-1769-9.

[383] L. Berg, A.I. Yeh, The separation of methyl acetate from methanol by extractive distillation, Chemical Engineering Communications. 30 (1984) 113–117. https://doi.org/10.1080/00986448408911119.

[384] Methanol Price Trend and Forecast, Chem Analyst. (2023). https://www.chemanalyst.com/Pricing-data/methanol-1.

[385] Pricing data, Chem Analyst. (2023). https://www.chemanalyst.com/Pricing/Pricingoverview.

[386] Methyl acetate 99.5%, VICHEMIC INDUSTRIES. (2023). https://vichemic.pl/en/produkt/methyl-acetate-99-5-ar-79-20-9/.

[387] J.A. Posada, C.A. Cardona, Propionic acid production from raw glycerol using commercial and engineered strains, Industrial and Engineering Chemistry Research. 51 (2012) 2354–2361. https://doi.org/10.1021/ie201300d.

[388] Propionic acid, fossil based, Carbon Cloud. (2023). https://apps.carboncloud.com/climatehub/product-reports/id/143249778560.

[389] Acetic acid, Carbon Cloud. (2023). https://apps.carboncloud.com/climatehub/product-reports/id/67148333700#:~:text=”Acetic acid.,match the latest climate science.

[390] Ethyl acetate, Carbon Cloud. (2023). https://apps.carboncloud.com/climatehub/product-reports/id/3223056066806.

[391] E. Reyhanitash, T. Brouwer, S.R.A. Kersten, A.G.J. van der Ham, B.

Schuur, Liquid–liquid extraction-based process concepts for recovery of carboxylic acids from aqueous streams evaluated for dilute streams, Chemical Engineering Research and Design. 137 (2018) 510–533. https://doi.org/10.1016/j.cherd.2018.07.038.

[392] A.J. Kruis, A.C. Bohnenkamp, C. Patinios, Y.M. van Nuland, M. Levisson, A.E. Mars, C. van den Berg, S.W.M. Kengen, R.A. Weusthuis, Microbial production of short and medium chain esters: Enzymes, pathways, and applications, Biotechnology Advances. 37 (2019) 107407. https://doi.org/10.1016/j.biotechadv.2019.06.006.

[393] P.O. Saboe, H.R. Monroe, W.E. Michener, L.P. Manker, S.J. Haugen, G.T. Beckham, E.M. Karp, In situ product recovery of bio-based ethyl esters via hybrid extraction-distillation, Green Chemistry. 21 (2019) 5306–5315. https://doi.org/10.1039/c9gc01844a.

[394] Ethyl Acetate Marker Analysis, Coherent Market Insights. (2024). https://www.coherentmarketinsights.com/market-insight/ethyl-acetate-market-2353.

[395] S. Zhang, F. Guo, W. Yan, W. Dong, J. Zhou, W. Zhang, F. Xin, M. Jiang, Perspectives for the microbial production of ethyl acetate, Applied Microbiology and Biotechnology. 104 (2020) 7239–7245. https://doi.org/10.1007/s00253-020-10756-z.

[396] A. Zirahi, H. Sadeghi Yamchi, A. Haddadnia, M. Zirrahi, H. Hassanzadeh, J. Abedi, Ethyl acetate as a bio-based solvent to reduce energy intensity and CO_2 emissions of in situ bitumen recovery, AIChE Journal. 66 (2020) e16828. https://doi.org/10.1002/aic.16828.

[397] B. Šulgan, J. Labovský, Z. Labovská, Multi-aspect comparison of ethyl acetate production pathways: Reactive distillation process integration and intensification via mechanical and chemical approach, Processes. 8 (2020) 1–32. https://doi.org/10.3390/pr8121618.

[398] Y.S. Mahajan, Ethyl acetate production by Fischer esterification : use of excess of acetic acid and complete separation sequence, International Journal of Chemical Reactor Engineering. 22 (2024) 1–14. https://doi.org/10.1515/ijcre-2024-0019.

[399] C. Löser, T. Urit, T. Bley, Perspectives for the biotechnological production of ethyl acetate by yeasts, Applied Microbiology and Biotechnology. 98 (2014) 5397–5415. https://doi.org/10.1007/s00253-014-5765-9.

[400] CropEnergies, Ground-breaking ceremony for first production plant for green ethyl acetate in Europe, (2022).

https://www.cropenergies.com/en/press/details/ground-breaking-ceremony-for-first-production-plant-for-green-ethyl-acetate-in-europe.

[401] D.M. Díaz-Montaño, M.L. Délia, M. Estarrón-Espinosa, P. Strehaiano, Fermentative capability and aroma compound production by yeast strains isolated from Agave tequilana Weber juice, Enzyme and Microbial Technology. 42 (2008) 608–616. https://doi.org/10.1016/j.enzmictec.2007.12.007.

[402] G. Dragone, S.I. Mussatto, J.M. Oliveira, J.A. Teixeira, Characterisation of volatile compounds in an alcoholic beverage produced by whey fermentation, Food Chemistry. 112 (2009) 929–935. https://doi.org/10.1016/j.foodchem.2008.07.005.

[403] A.M. Molina, J.H. Swiegers, C. Varela, I.S. Pretorius, E. Agosin, Influence of wine fermentation temperature on the synthesis of yeast-derived volatile aroma compounds, Applied Microbiology and Biotechnology. 77 (2007) 675–687. https://doi.org/10.1007/s00253-007-1194-3.

[404] T. Urit, A. Stukert, T. Bley, Formation of ethyl acetate by *Kluyveromyces marxianus* on whey during aerobic batch cultivation at specific trace element limitation, (2012) 1313–1323. https://doi.org/10.1007/s00253-012-4107-z.

[405] C. Löser, T. Urit, P. Keil, T. Bley, Studies on the mechanism of synthesis of ethyl acetate in *Kluyveromyces marxianus* DSM 5422, Applied Microbiology and Biotechnology. 99 (2015) 1131–1144. https://doi.org/10.1007/s00253-014-6098-4.

[406] C. Löser, T. Urit, F. Nehl, T. Bley, Screening of *Kluyveromyces* strains for the production of ethyl acetate: Design and evaluation of a cultivation system, Engineering in Life Sciences. 11 (2011) 369–381. https://doi.org/10.1002/elsc.201000178.

[407] T. Urit, C. Löser, M. Wunderlich, T. Bley, Formation of ethyl acetate by *Kluyveromyces marxianus* on whey: Studies of the ester stripping, Bioprocess and Biosystems Engineering. 34 (2011) 547–559. https://doi.org/10.1007/s00449-010-0504-9.

[408] C. Löser, T. Urit, A. Stukert, T. Bley, Formation of ethyl acetate from whey by *Kluyveromyces marxianus* on a pilot scale, Journal of Biotechnology. 163 (2013) 17–23. https://doi.org/10.1016/j.jbiotec.2012.10.009.

[409] T. Urit, R. Manthey, T. Bley, C. Löser, Formation of ethyl acetate by *Kluyveromyces marxianus* on whey: Influence of aeration and inhibition

of yeast growth by ethyl acetate, Engineering in Life Sciences. (2013) 247–260. https://doi.org/10.1002/elsc.201200077.

[410] C. Löser, T. Urit, S. Förster, A. Stukert, T. Bley, Formation of ethyl acetate by *Kluyveromyces marxianus* on whey during aerobic batch and chemostat cultivation at iron limitation, Applied Microbiology and Biotechnology. 96 (2012) 685–696. https://doi.org/10.1007/s00253-012-4205-y.

[411] P. Duboc, U. Von Stockar, Systematic Errors in Data Evaluation Due to Ethanol Stripping and Water Vaporization, Biotechnology and Bioengineering. 58 (1998) 428–439.

[412] Argon (Ar) and water, Lenntech. (2024). https://www.lenntech.com/periodic/water/argon/argon-and-water.htm.

[413] Nitrogen (N) and water, Lenntech. (2024). https://www.lenntech.com/periodic/water/nitrogen/nitrogen-and-water.htm.

[414] Ethyl Acetate, ReAgent. (2024). https://www.chemicals.co.uk/ethyl-acetate.

[415] Ethyl acetate, DutchChems. (2024). https://www.dutchchems.com/product/ethyl-acetate/.

[416] Reference Fluid Thermodynamic and Transport Properties Database (REFPROP), NIST. (2024). https://www.nist.gov/programs-projects/reference-fluid-thermodynamic-and-transport-properties-database-refprop.

[417] D.W. Armstrong, S.M. Martin, H. Yamazaki, Production of ethyl acetate from dilute ethanol solutions by Candida utilis, Biotechnology and Bioengineering. 26 (1984) 1038–1041. https://doi.org/10.1002/bit.260260905.

[418] F.I. Khan, A.K. Ghoshal, Removal of volatile organic compounds from polluted air, Journal of Loss Prevention in the Process Industries. 13 (2010) 527–545. https://doi.org/10.2495/WP100101.

[419] C. Wylock, P.P. Eloundou Mballa, C. Heilporn, F. Debaste, M.L. Fauconnier, Review on the potential technologies for aromas recovery from food industry flue gas, Trends in Food Science and Technology. 46 (2015) 68–74. https://doi.org/10.1016/j.tifs.2015.08.002.

[420] I. Lukin, L. Pietzka, K. Groß, A. Górak, G. Schembecker, Economic evaluation of rotating packed bed use for aroma absorption from bioreactor off-gas, Chemical Engineering and Processing - Process

Intensification. 154 (2020) 108011. https://doi.org/10.1016/j.cep.2020.108011.

[421] K. Du, S. Zhang, W. Xu, X. Niu, A study on the cycle characteristics of an auto-cascade refrigeration system, Experimental Thermal and Fluid Science. 33 (2009) 240–245. https://doi.org/10.1016/j.expthermflusci.2008.08.006.

[422] L. Gales, A. Mendes, C. Costa, Recovery of acetone, ethyl acetate and ethanol by thermal pressure swing adsorption, Chemical Engineering Science. 58 (2003) 5279–5289. https://doi.org/10.1016/j.ces.2003.09.006.

[423] K. Sato, K. Sugimoto, T. Nakane, Separation of ethanol/ethyl acetate mixture by pervaporation at 100-130 °C through NaY zeolite membrane for industrial purpose, Microporous and Mesoporous Materials. 115 (2008) 170–175. https://doi.org/10.1016/j.micromeso.2007.10.054.

[424] Z. Zhu, Y. Ri, H. Jia, X. Li, Y. Wang, Y. Wang, Process evaluation on the separation of ethyl acetate and ethanol using extractive distillation with ionic liquid, Separation and Purification Technology. 181 (2017) 44–52. https://doi.org/10.1016/j.seppur.2017.03.011.

[425] D.L. Zhang, Y.F. Deng, C.B. Li, J. Chen, Separation of ethyl acetate - Ethanol azeotropic mixture using hydrophilic ionic liquids, Industrial and Engineering Chemistry Research. 47 (2008) 1995–2001. https://doi.org/10.1021/ie070658m.

[426] A.J. Toth, A. Szanyi, K. Koczka, P. Mizsey, Enhanced separation of highly non-ideal mixtures with extractive heterogeneous-azeotropic distillation, Separation Science and Technology (Philadelphia). 51 (2016) 1238–1247. https://doi.org/10.1080/01496395.2015.1107099.

[427] A.J. Toth, Comprehensive evaluation and comparison of advanced separation methods on the separation of ethyl acetate-ethanol-water highly non-ideal mixture, Separation and Purification Technology. 224 (2019) 490–508. https://doi.org/10.1016/j.seppur.2019.05.051.

[428] J.A. Caballero, I.E. Grossmann, Synthesis of Complex Thermally Coupled Distillation Systems Including Divided Wall Columns, AIChE Journal. 59 (2013) 1139–1159. https://doi.org/10.1002/aic.13912.

[429] C. Ehlers, M. Schroder, G. Fieg, Influence of Heat Transfer Across the Wall of Dividing Wall Columns on Energy Demand, AIChE Journal. 61 (2015) 1648–1662. https://doi.org/10.1002/aic.14747.

[430] X. Qian, K.H. Lin, S. Jia, L.T. Biegler, K. Huang, Nonlinear model predictive control for dividing wall columns, AIChE Journal. 69 (2023)

1–22. https://doi.org/10.1002/aic.18062.

[431] Ethyl Acetate Price Trend and Forecast, Chem Analyst. (2023). https://www.chemanalyst.com/Pricing-data/ethyl-acetate.

[432] N. Vora, P. Daoutidis, Analysis and nonlinear control of an ethyl acetate reactive distillation column, Proceedings of the American Control Conference. 4 (1998) 2113–2117. https://doi.org/10.1109/ACC.1998.703000.

[433] H.Y. Lee, H.P. Huang, I.L. Chien, Control of reactive distillation process for production of ethyl acetate, Journal of Process Control. 17 (2007) 363–377. https://doi.org/10.1016/j.jprocont.2006.10.002.

[434] LanzaTech, World's leading steel company, ArcelorMittal and LanzaTech announce first ethanol samples from commercial flagship carbon capture and utilisation facility in Ghent, Belgium, (2023). https://lanzatech.com/worlds-leading-steel-company-arcelormittal-and-lanzatech-announce-first-ethanol-samples-from-commercial-flagship-carbon-capture-and-utilisation-facility-in-ghent-belgium/.

[435] A.C. Bohnenkamp, A.J. Kruis, A.E. Mars, R.H. Wijffels, J. Van Der Oost, S.W.M. Kengen, R.A. Weusthuis, Multilevel optimisation of anaerobic ethyl acetate production in engineered Escherichia coli, Biotechnology for Biofuels. 13 (2020) 1–14. https://doi.org/10.1186/s13068-020-01703-1.

[436] J.C. Dykstra, J. van Oort, A.T. Yazdi, E. Vossen, C. Patinios, J. van der Oost, D.Z. Sousa, S.W.M. Kengen, Metabolic engineering of *Clostridium autoethanogenum* for ethyl acetate production from CO, Microbial Cell Factories. 21 (2022) 1–11. https://doi.org/10.1186/s12934-022-01964-5.

[437] S. Mitri, M. Koubaa, R.G. Maroun, T. Rossignol, J.M. Nicaud, N. Louka, Bioproduction of 2-Phenylethanol through Yeast Fermentation on Synthetic Media and on Agro-Industrial Waste and By-Products: A Review, Foods. 11 (2022) 109. https://doi.org/https://doi.org/10.3390/foods11010109.

[438] C. Conde Mejía, L. Conde Báez, Biorefinery, an integrated concept: Analysis of bioethanol and aromas production from whey, in: Biofuels and Biorefining: Volume 1: Current Technologies for Biomass Conversion, Elsevier Inc., 2022: pp. 447–471. https://doi.org/10.1016/B978-0-12-824116-5.00007-6.

[439] S.M.G. Saerens, F.R. Delvaux, K.J. Verstrepen, J.M. Thevelein, Production and biological function of volatile esters in *Saccharomyces*

cerevisiae, Microbial Biotechnology. 3 (2010) 165–177. https://doi.org/10.1111/j.1751-7915.2009.00106.x.

[440] D. Pérez, M. Denat, L. Pérez-Través, J.M. Heras, J.M. Guillamón, V. Ferreira, A. Querol, Generation of intra- and interspecific *Saccharomyces* hybrids with improved oenological and aromatic properties, Microbial Biotechnology. 15 (2022) 2266–2280. https://doi.org/10.1111/1751-7915.14068.

[441] PubChem, Phenethyl acetate, (2024). https://pubchem.ncbi.nlm.nih.gov/compound/Phenethyl-acetate#section=Uses.

[442] O. Martínez-Avila, A. Sánchez, X. Font, R. Barrena, Bioprocesses for 2-phenylethanol and 2-phenylethyl acetate production: current state and perspectives, Applied Microbiology and Biotechnology. 102 (2018) 9991–10004. https://doi.org/10.1007/s00253-018-9384-8.

[443] Global Market Insights, 2-Phenylethanol Market Size, (2022). https://www.gminsights.com/industry-analysis/2-phenylethanol-market.

[444] D. Hua, P. Xu, Recent advances in biotechnological production of 2-phenylethanol, Biotechnology Advances. 29 (2011) 654–660. https://doi.org/10.1016/j.biotechadv.2011.05.001.

[445] Y. Wang, H. Zhang, X. Lu, H. Zong, B. Zhuge, Advances in 2-phenylethanol production from engineered microorganisms, Biotechnology Advances. 37 (2019) 403–409. https://doi.org/10.1016/j.biotechadv.2019.02.005.

[446] M. Larroude, J.M. Nicaud, T. Rossignol, *Yarrowia lipolytica* chassis strains engineered to produce aromatic amino acids via the shikimate pathway, Microbial Biotechnology. 14 (2021) 2420–2434. https://doi.org/10.1111/1751-7915.13745.

[447] G.Q. Chen, X. Liu, On the future fermentation, Microbial Biotechnology. 14 (2021) 18–21. https://doi.org/10.1111/1751-7915.13674.

[448] X. Qian, W. Yan, W. Zhang, W. Dong, J. Ma, K. Ochsenreither, M. Jiang, F. Xin, Current status and perspectives of 2-phenylethanol production through biological processes, Critical Reviews in Biotechnology. 39 (2019) 235–248. https://doi.org/10.1080/07388551.2018.1530634.

[449] P. Vargai, I. Červeňanský, M. Mihaľ, J. Markoš, Design of hybrid systems with *in-situ* product removal from fermentation broth: Case study for 2-phenylethanol production, Chemical Engineering and Processing - Process Intensification. 134 (2018) 58–71.

https://doi.org/10.1016/j.cep.2018.10.011.

[450] M. Mihal', R. Vereš, J. Markoš, Investigation of 2-phenylethanol production in fed-batch hybrid bioreactor: Membrane extraction and microfiltration, Separation and Purification Technology. 95 (2012) 126–135. https://doi.org/10.1016/j.seppur.2012.04.030.

[451] C.H. Shu, Y.J. Chen, W.O.C. Nirwana, C. Cahyani, Enhanced bioconversion of L-phenylalanine into 2-phenylethanol via an oxygen control strategy and in situ product recovery, Journal of Chemical Technology and Biotechnology. 93 (2018) 3035–3043. https://doi.org/10.1002/jctb.5662.

[452] C.H. Shu, S.S. Jhou, W.O.C. Nirwana, Temperature control and in situ product recovery strategies to enhance the bioconversion of L-phenylalanine into 2-phenylethanol, Journal of Chemical Technology and Biotechnology. 96 (2021) 899–908. https://doi.org/10.1002/jctb.6598.

[453] A. Chacón-Izquierdo, A.E. Magdaleno-Cruz, A. López-Molina, L. Conde-Baéz, E. Mas-Hernández, C. Conde-Mejía, Design of a separation process for natural 2-phenylethanol with solvent selection based on safety criteria, Journal of Chemical Technology and Biotechnology. 97 (2022) 2103–2108. https://doi.org/10.1002/jctb.7081.

[454] MadeInChina, Self-Cleaning Biological Ferment Disc Centrifuge Machine Disk Stack Centrifuge Food Industry, (2024). https://gaokangmedicallab.en.made-in-china.com/product/eQZrfKNunLpF/China-Self-Cleaning-Biological-Ferment-Disc-Centrifuge-Machine-Disk-Stack-Centrifuge-Food-Industry.html?pv_id=1i93gketn5cf&faw_id=1i93gq1qq330.

[455] CarlRoth, Polypropylene glycol 1200, (2024). https://www.carlroth.com/nl/nl/polypropyleenglycolen-ppg/polypropylene-glycol-1200/p/1aa2.1.

[456] K. Jayant, S.M. Mahajani, Feasibility of reactive chromatography for the production of 2-phenyl ethyl acetate, Canadian Journal of Chemical Engineering. 101 (2023) 5874–5885. https://doi.org/10.1002/cjce.24827.

[457] K. Jayant, C. Gupta, S. Seethamraju, S.M. Mahajani, Entrainer assisted production of high purity 2-phenyl ethyl acetate by reactive distillation, Separation and Purification Technology. 331 (2024) 125650. https://doi.org/10.1016/j.seppur.2023.125650.

[458] A.A. Kiss, R. Muthia, I. Pazmiño-Mayorga, J. Harmsen, M. Jobson, X. Gao, Conceptual methods for synthesis of reactive distillation processes:

recent developments and perspectives, Journal of Chemical Technology and Biotechnology. 99 (2024) 1263–1290. https://doi.org/10.1002/jctb.7633.

[459] EU Flavoring Legalisation, European Flavour Association. (2024). https://effa.eu/eu-legislation/flavouring-legislation.

[460] CEPEA, Average prices for anhydrous and hydrous ethanol are record high in the 21/22 season, (2022). https://www.cepea.esalq.usp.br/en/brazilian-agribusiness-news/average-prices-for-anhydrous-and-hydrous-ethanol-are-record-high-in-the-21-22-season.aspx?pagina=9%0A.

[461] E.J. Hassing, P.A. de Groot, V.R. Marquenie, J.T. Pronk, J.M.G. Daran, Connecting central carbon and aromatic amino acid metabolisms to improve de novo 2-phenylethanol production in Saccharomyces cerevisiae, Metabolic Engineering. 56 (2019) 165–180. https://doi.org/10.1016/j.ymben.2019.09.011.

[462] J. Mierzejewska, K. Dąbkowska, K. Chreptowicz, A. Sokołowska, Hydrolyzed corn stover as a promising feedstock for 2-phenylethanol production by nonconventional yeast, Journal of Chemical Technology and Biotechnology. 94 (2019) 777–784. https://doi.org/10.1002/jctb.5823.

[463] D. Chiaramonti, A. Giovannini, R. Janssen, R. Mergner, Lignocellulosic ethanol production plant by Biochemtex in Italy Lignocellulosic Ethanol Process and Demonstration A Handbook Part I, WIP Renewable Energies, Munich, 2013.

[464] M. Tayyab, A. Noman, W. Islam, S. Waheed, Y. Arafat, F. Ali, M. Zaynab, S. Lin, H. Zhang, W. Lin, Bioethanol production from lignocellulosic biomass by environment-friendly pretreatment methods : A review, Applied Ecology and Environmental Research. 16 (2017) 225–249. https://doi.org/10.15666/aeer/1601.

[465] A.M. Borrero-Lopez, C. Valencia, J.M. Franco, Lignocellulosic Materials for the Production of Biofuels, Biochemicals and Biomaterials and Applications of Lignocellulose-Based Polyurethanes: A Review, Polymers. 14 (2022) 881. https://doi.org/10.3390/polym14050881.

[466] X. Zhao, L. Zhang, D. Liu, Biomass recalcitrance. Part I: the chemical compositions and physical structures affecting the enzymatic hydrolysis of lignocellulose, Biofuels, Bioproducts and Biorefining. (2012). https://doi.org/10.1002/BBB.

[467] F.H. Isikgor, C.R. Becer, Lignocellulosic biomass: a sustainable platform

for the production of bio-based chemicals and polymers, Polymer Chemistry. 6 (2015) 4497–4559. https://doi.org/10.1039/c5py00263j.

[468] Y. Bin, C.E. Wyman, Biofuels Methods and Protocols, in: J.R. Mielenz (Ed.), Biofuels Methods and Protocols, Humana Press, 2013: pp. 103–115. https://doi.org/10.1007/978-1-60761-214-8.

[469] H. Jorgensen, J.B. Kristensen, C. Felby, Enzymatic conversion of lignocellulose into fermentable sugars: challenges and opportunities, Biofuels, Bioproducts and Biorefining. 1 (2007) 119–134. https://doi.org/10.1002/BBB.

[470] B. Yang, C.E. Wyman, Pretreatment: the key to unlocking low-cost cellulosic ethanol Bin, Biofuels, Bioproducts and Biorefining. 2 (2008) 26–40. https://doi.org/10.1002/BBB.

[471] X. Zhao, L. Zhang, D. Liu, Biomass recalcitrance. Part II: Fundamentals of different pre-treatments to increase the enzymatic digestibility of lignocellulose, Biofuels, Bioproducts and Biorefining. (2012). https://doi.org/10.1002/BBB.

[472] L.J. Jönsson, C. Martín, Pretreatment of lignocellulose: Formation of inhibitory by-products and strategies for minimizing their effects, Bioresource Technology. 199 (2016) 103–112. https://doi.org/10.1016/j.biortech.2015.10.009.

[473] M.F.S. Khan, M. Akbar, Z. Xu, H. Wang, A review on the role of pretreatment technologies in the hydrolysis of lignocellulosic biomass of corn stover, Biomass and Bioenergy. 155 (2021) 106276. https://doi.org/10.1016/j.biombioe.2021.106276.

[474] I. De Bari, A. Giuliano, M.T. Petrone, G. Stoppiello, V. Fatta, C. Giardi, F. Razza, A. Novelli, From Cardoon Lignocellulosic Biomass to Bio-1,4 Butanediol: An Integrated Bioerefinary Model, Processes. 8 (2020) 1585.

[475] G. Brodeur, E. Yau, K. Badal, J. Collier, K.B. Ramachandran, S. Ramakrishnan, Chemical and physicochemical pretreatment of lignocellulosic biomass: A review, Enzyme Research. (2011) 787532. https://doi.org/10.4061/2011/787532.

[476] A.W. Bhutto, K. Qureshi, K. Harijan, R. Abro, T. Abbas, A.A. Bazmi, S. Karim, G. Yu, Insight into progress in pre-treatment of lignocellulosic biomass, Energy. 122 (2017) 724–745. https://doi.org/https://doi.org/10.1016/j.energy.2017.01.005.

[477] H. Zabed, J.N. Sahu, A.N. Boyce, G. Faruq, Fuel ethanol production from lignocellulosic biomass: An overview on feedstocks and technological approaches, Renewable and Sustainable Energy Reviews.

66 (2016) 751–774. https://doi.org/10.1016/j.rser.2016.08.038.

[478] H.A. Ruiz, M. Conrad, S.N. Sun, A. Sanchez, G.J.M. Rocha, A. Romaní, E. Castro, A. Torres, R.M. Rodríguez-Jasso, L.P. Andrade, I. Smirnova, R.C. Sun, A.S. Meyer, Engineering aspects of hydrothermal pretreatment: From batch to continuous operation, scale-up and pilot reactor under biorefinery concept, Bioresource Technology. 299 (2020) 122685. https://doi.org/10.1016/j.biortech.2019.122685.

[479] W.H. Chen, S. Nižetić, R. Sirohi, Z. Huang, R. Luque, A.M. Papadopoulos, R. Sakthivel, X. Phuong Nguyen, A. Tuan Hoang, Liquid hot water as sustainable biomass pretreatment technique for bioenergy production: A review, Bioresource Technology. 344 (2022) 126207. https://doi.org/10.1016/j.biortech.2021.126207.

[480] J.K. Ko, Y. Um, Y.C. Park, J.H. Seo, K.H. Kim, Compounds inhibiting the bioconversion of hydrothermally pretreated lignocellulose, Applied Microbiology and Biotechnology. 99 (2015) 4201–4212. https://doi.org/10.1007/s00253-015-6595-0.

[481] P.T. Pienkos, M. Zhang, Role of pretreatment and conditioning processes on toxicity of lignocellulosic biomass hydrolysates, Cellulose. 16 (2009) 743–762. https://doi.org/10.1007/s10570-009-9309-x.

[482] L.J. Jönsson, B. Alriksson, N.-O. Nilvebrant, Bioconversion of lignocellulose: inhibitors and detoxification, Biotechnology for Biofuels. 6 (2013) 16. https://doi.org/10.1186/1754-6834-6-16.

[483] J.M. Jiminez-Gutierrez, Pretreatment of lignocellulosic biomass for acetic acid co-valorization, Delft University of Technology, 2023.

[484] Characterization of Lignocellulosic Biomass with Specification in Aspen Properties, Aspen Technology, 2021. https://knowledgecenter.aspentech.com.

[485] J. Peng, A.E.F. Abomohra, M. Elsayed, X. Zhang, Q. Fan, P. Ai, Compositional changes of rice straw fibers after pretreatment with diluted acetic acid: Towards enhanced biomethane production, Journal of Cleaner Production. 230 (2019) 775–782. https://doi.org/10.1016/j.jclepro.2019.05.155.

[486] H. Zhang, Y. Xu, S. Yu, Co-production of functional xylooligosaccharides and fermentable sugars from corncob with effective acetic acid prehydrolysis, Bioresource Technology. 234 (2017) 343–349. https://doi.org/10.1016/j.biortech.2017.02.094.

[487] K. Huang, J. Luo, R. Cao, Y. Su, Y. Xu, Enhanced Xylooligosaccharides Yields and Enzymatic Hydrolyzability of Cellulose using Acetic Acid

Catalysis of Poplar Sawdust, Journal of Wood Chemistry and Technology. 38 (2018) 371–384. https://doi.org/10.1080/02773813.2018.1500608.

[488] N. Singhal, M. Kumar, P.K. Kanaujia, J.S. Virdi, MALDI-TOF mass spectrometry: An emerging technology for microbial identification and diagnosis, Frontiers in Microbiology. 6 (2015) 791. https://doi.org/10.3389/fmicb.2015.00791.

[489] D. Painer, S. Lux, M. Siebenhofer, Recovery of Formic Acid and Acetic Acid from Waste Water Using Reactive Distillation, Separation Science and Technology. 50 (2015) 2930–2936. https://doi.org/10.1080/01496395.2015.1085407.

[490] H. Luo, C.S. Bildea, A.A. Kiss, Novel Heat-Pump-Assisted Extractive Distillation for Bioethanol Purification, Industrial and Engineering Chemistry Research. 54 (2015) 2208–2213. https://doi.org/10.1021/ie504459c.

[491] A.A. Kiss, R. Smith, Rethinking energy use in distillation processes for a more sustainable chemical industry, Energy. 203 (2020) 117788. https://doi.org/10.1016/j.energy.2020.117788.

[492] C. Pătruţ, C.S. Bîldea, I. Liţă, A.A. Kiss, Cyclic distillation - Design, control and applications, Separation and Purification Technology. 125 (2014) 326–336. https://doi.org/10.1016/j.seppur.2014.02.006.

[493] F. Kabir, A.D. Patel, J.C. Serrano-ruiz, J.A. Dumesic, R.P. Anex, Techno-economic analysis of dimethylfuran (DMF) and hydroxymethylfurfural (HMF) production from pure fructose in catalytic processes, Chemical Engineering Journal. 169 (2011) 329–338. https://doi.org/10.1016/j.cej.2011.03.018.

[494] R. Morales-Vera, J. Crawford, C. Dou, R. Bura, R. Gustafson, Techno-Economic Analysis of Producing Glacial Acetic Acid from Poplar Biomass via Bioconversion, (2020) 1–16.

[495] A.H. Motagamwala, C.T. Maravelias, J.A. Dumesic, Solvent System for Effective Near-term Production of Hydroxymethylfurfural (HMF) with Potential for Long-term Improvement, Energy & Environmental Science. 12 (2019) 2212–2222. https://doi.org/https://doi.org/10.1039/C9EE00447E.

[496] M.R. Resetarits, M.J. Lockett, Distillation, Encyclopedia of Physical Science and Technology. 3 (2003) 547–559. https://doi.org/10.1016/B0-12-227410-5/00182-4.

[497] P. Lutze, Distillation in Bioprocessing, in: Distillation: Operation and

Applications, Elsevier Inc., 2014: pp. 337–365. https://doi.org/10.1016/B978-0-12-386876-3.00008-9.

[498] Chem Analyst, Isopropyl Alcohol (IPA) Market Analysis, (2023). https://www.chemanalyst.com/industry-report/isopropyl-alcohol-ipa-187.

[499] Chem Analyst, Acetone Market Analysis, (2023). https://www.chemanalyst.com/industry-report/acetone-market-272.

[500] Y. Wang, J. Lu, M. Xu, C. Qian, F. Zhao, Y. Luo, H. Wu, Efficient Biosynthesis of Isopropanol from Ethanol by Metabolically Engineered *Escherichia coli*, ACS Sustainable Chemistry and Engineering. 10 (2022) 13857–13864. https://doi.org/10.1021/acssuschemeng.2c04663.

[501] Q. Jin, Z. An, A. Damle, N. Poe, J. Wu, H. Wang, Z. Wang, H. Huang, High Acetone-Butanol-Ethanol Production from Food Waste by Recombinant *Clostridium saccharoperbutylacetonicum* in Batch and Continuous Immobilized-Cell Fermentation, ACS Sustainable Chemistry and Engineering. 8 (2020) 9822–9832. https://doi.org/10.1021/acssuschemeng.0c02529.

[502] Y. Jiang, J. Liu, W. Jiang, Y. Yang, S. Yang, Current status and prospects of industrial bio-production of n-butanol in China, Biotechnology Advances. 33 (2015) 1493–1501. https://doi.org/10.1016/j.biotechadv.2014.10.007.

[503] G.J.A. Brouwer, T. Janković, A.J.J. Straathof, A.A. Kiss, J.A. Posada, Sustainable Industrial-Scale Plant Design for Syngas Fermentation to Isopropyl Alcohol and Acetone : Economic and Environmental Sustainability Assessment, Systems & Control Transactions. (2025).

[504] G. Keitel, U. Onken, The effect of solutes on bubble size in air-water dispersions, Chemical Engineering Communications. 17 (1982) 85–98. https://doi.org/10.1080/00986448208911616.

[505] G.J.A. Brouwer, H. Shijaz, J.A. Posada, Modelling and Parametric Analysis for Improving Technical Performance of Industrial-Scale Basic Oxygen Furnace Gas Fermentation to Isopropyl Alcohol, Computer Aided Chemical Engineering. 53 (2024) 403–408. https://doi.org/10.1016/B978-0-443-28824-1.50068-5.

[506] J.J. Heijnen, J.P. van Dijken, In search of a thermodynamic description of biomass yields for chemotrophic growth of microorganisms, Pure and Applied Chemistry. 39 (1992) 833–858. https://doi.org/10.1351/pac199365091887.

[507] P. Kehrein, M. Jafari, M. Slagt, E. Cornelissen, P. Osseweijer, J. Posada, M. van Loosdrecht, A techno-economic analysis of membrane-based

advanced treatment processes for the reuse of municipal wastewater, Water Reuse. 11 (2021) 705–725. https://doi.org/10.2166/wrd.2021.016.

[508] AspenTech, AspenPlus V12, (2020). https://www.aspentech.com/en/products/engineering/aspen-plus.

[509] A. Keys, M. Van Hout, B. Daniëls, Decarbonisation options for the Dutch Steel industry, 2019. https://www.pbl.nl/downloads/pbl-2019-decarbonisation-options-for-the-dutch-steel-industry-3723pdf.

[510] O.A. Antoce, V. Antoce, K. Takahashi, N. Pomohaci, I. Namolosanu, A calorimetric method applied to the study of yeast growth inhibition by alcohols and organic acids, American Journal of Enology and Viticulture. 48 (1997) 413–422. https://doi.org/10.5344/ajev.1997.48.4.413.

[511] ecoinvent v3.11, (2024). https://ecoinvent.org/ecoinvent-v3-11/.

[512] A.J.P. Nunes, L.L. Dalen, G. Leonardi, L. Burri, Developing sustainable, cost-effective and high-performance shrimp feed formulations containing low fish meal levels, Aquaculture Reports. 27 (2022) 101422. https://doi.org/10.1016/j.aqrep.2022.101422.

[513] Producer Price Index by Commodity: Processed Foods and Feeds: Other Soybean Products, Including Isolates and Concentrates, Federal Reserve Bank of St. Luis Economic Data. (2023). https://fred.stlouisfed.org/series/WPU029201122.

[514] Commodity Markets, World Bank Group. (2024). https://www.worldbank.org/en/research/commodity-markets.

[515] A. Oudshoorn, D.A. Schaefer, M. Van Lotringen, Multiphase biocatalytic reactor and separator system, EP 4 332 212 A1, 2022.

[516] H. Wang, Q. Dong, C. Meng, X. ai Shi, Y. Guo, A continuous and adsorptive bioprocess for efficient production of the natural aroma chemical 2-phenylethanol with yeast, Enzyme and Microbial Technology. 48 (2011) 404–407. https://doi.org/10.1016/j.enzmictec.2011.01.006.

[517] I. Červeňanský, M. Mihaľ, J. Markoš, Pertraction-adsorption *in situ* product removal system: design and mathematical modeling, Chemical Engineering and Processing - Process Intensification. 143 (2019) 107604. https://doi.org/10.1016/j.cep.2019.107604.

[518] J. Mei, H. Min, Z. Lü, Enhanced biotransformation of l-phenylalanine to 2-phenylethanol using an in situ product adsorption technique, Process Biochemistry. 44 (2009) 886–890.

https://doi.org/10.1016/j.procbio.2009.04.012.

[519] F. Gao, A.J. Daugulis, Bioproduction of the aroma compound 2-phenylethanol in a solid-liquid two-phase partitioning bioreactor system by *Kluyveromyces marxianus*, Biotechnology and Bioengineering. 104 (2009) 332–339. https://doi.org/10.1002/bit.22387.

[520] T. Chantasuban, F. Santomauro, D. Gore-Lloyd, S. Parsons, D. Henk, R.J. Scott, C. Chuck, Elevated production of the aromatic fragrance molecule, 2-phenylethanol, using *Metschnikowia pulcherrima* through both de novo and ex novo conversion in batch and continuous modes, Journal of Chemical Technology and Biotechnology. 93 (2018) 2118–2130. https://doi.org/10.1002/jctb.5597.

[521] I. Šimko, E. Roriz, M. Gramblička, V. Illeová, M. Polakovič, Adsorption separation of 2-phenylethanol and L-phenylalanine on polymeric resins: Adsorbent screening, single-component and binary equilibria, Food and Bioproducts Processing. 95 (2015) 254–263. https://doi.org/10.1016/j.fbp.2014.11.005.

[522] M.C. Cuellar, A.J.J. Straathof, Improving Fermentation by Prodcut Removal, in: Intensification of Biobased Processes, Royal Society of Chemistry, Croydon, 2018: pp. 86–108. https://doi.org/https://doi.org/10.1039/9781788010320-00086.

[523] J.J. Heijnen, M.C.M. van Loosdrecht, L. Tijhuis, A Black Box Mathematical Model to Calculate Auto- and Heterothrophic Biomass Yields Based on Gibbs Energy Dissipation, Biotechnology and Bioengineering. 40 (1992) 1139–1154.

[524] DAB.bio, DAB.bio's revolutionary FAST biomanufacturing platform, (2023). https://dab.bio/technology-downstream-processing.

[525] D. Humbird, R. Davis, J.D. McMillan, Aeration costs in stirred-tank and bubble column bioreactors, Biochemical Engineering Journal. 127 (2017) 161–166. https://doi.org/10.1016/j.bej.2017.08.006.

[526] Chemical BooK, L-Phenylalanine, (2025). https://www.chemicalbook.com/SupplierPriceList_EN.aspx?cbn=CB2488691&c=25KG#price.

[527] Chem Analyst, Butanediol Price Trend and Forecast, (2024). https://www.chemanalyst.com/Pricing-data/butanediol-54.

[528] Chem Analyst, Propionic Acid Price Trend and Forecast, (2024). https://www.chemanalyst.com/Pricing-data/propionic-acid-1184.

[529] N.P.T. Nguyen, C. Raynaud, I. Meynial-Salles, P. Soucaille, Reviving

the Weizmann process for commercial n-butanol production, Nature Communications. 9 (2018) 1–8. https://doi.org/10.1038/s41467-018-05661-z.

[530] J. Zhang, C. Lei, G. Liu, Y. Bao, V. Balan, J. Bao, *In-Situ* Vacuum Distillation of Ethanol Helps to Recycle Cellulase and Yeast during SSF of Delignified Corncob Residues, ACS Sustainable Chemistry and Engineering. 5 (2017) 11676–11685. https://doi.org/10.1021/acssuschemeng.7b03084.

[531] C. Verseux, Bacterial Growth at Low Pressure: A Short Review, Frontiers in Astronomy and Space Sciences. 7 (2020) 1–10. https://doi.org/10.3389/fspas.2020.00030.

[532] L. Puiman, E.A. Benalcázar, C. Picioreanu, H.J. Noorman, C. Haringa, Downscaling Industrial-Scale Syngas Fermentation to Simulate Frequent and Irregular Dissolved Gas Concentration Shocks, Bioengineering. 10 (2023) 518. https://doi.org/https://doi.org/10.3390/bioengineering10050518.

[533] P. Kehrein, M. Van Loosdrecht, P. Osseweijer, J. Posada, Exploring resource recovery potentials for the aerobic granular sludge process by mass and energy balances-energy, biopolymer and phosphorous recovery from municipal wastewater, Environmental Science: Water Research and Technology. 6 (2020) 2164–2179. https://doi.org/10.1039/d0ew00310g.

[534] A. Akbulut, Techno-economic analysis of electricity and heat generation from farm-scale biogas plant: Çiçekdaĝi case study, Energy. 44 (2012) 381–390. https://doi.org/10.1016/j.energy.2012.06.017.

[535] K. Starr, A. Ramirez, H. Meerman, G. Villalba, X. Gabarrell, Explorative economic analysis of a novel biogas upgrading technology using carbon mineralization. A case study for Spain, Energy. 79 (2015) 298–309. https://doi.org/10.1016/j.energy.2014.11.015.

[536] United Nations, UN Comtrade Database, (2024). https://comtradeplus.un.org/.

[537] I. Patraşcu, C.S. Bîldea, A.A. Kiss, Novel eco-efficient process for dimethyl carbonate production by indirect alcoholysis of urea, Chemical Engineering Research and Design. 160 (2020) 486–498. https://doi.org/10.1016/j.cherd.2020.06.020.

[538] A.A. Kiss, D.J.-P.C. Suszwalak, Innovative dimethyl ether synthesis in a reactive dividing-wall column, Computers and Chemical Engineering. 38 (2012) 74–81. https://doi.org/10.1016/j.compchemeng.2011.11.012.

[539] J. Mantingh, A.A. Kiss, Enhanced process for energy efficient extraction

of 1,3-butadiene from a crude C4 cut, Separation and Purification Technology. 267 (2021) 118656. https://doi.org/10.1016/j.seppur.2021.118656.

[540] M. Huijbregts, Z.J.N. Steinmann, P.M.F.M. Elshout, G. Stam, F. Verones, M.D.M. Vieira, M. Zijp, R. van Zelm, ReCiPe 2016 - A harmonized life cycle impact assessment method at midpoint and endpoint level, National Institute for Public Health and the Environment. (2016) 194. https://www.rivm.nl/bibliotheek/rapporten/2016-0104.pdf.

[541] NIST Standard Reference Database Number 69, NIST. (2023). https://doi.org/https://doi.org/10.18434/T4D303.

[542] J.J. Heijnen, A thermodynamic approach to predict Black Box model parameters for microbial growth, in: Biothermodynamics: The Role of Thermodynamics in Biochemical Engineering, EPFL Press, Lausanne, 2013: pp. 443–472.

[543] R. Kleerebezem, M.C.M. Van Loosdrecht, A generalized method for thermodynamic state analysis of environmental systems, Critical Reviews in Environmental Science and Technology. 40 (2010) 1–54. https://doi.org/10.1080/10643380802000974.

Appendix A – Method of process design, economic and environmental evaluation

This Appendix contains more details about process design and the followed methods for determining the economic and environmental impact of the developed processes.

Process design

The main focus during design of recovery processes was on minimizing total energy requirements. Even though there is no theoretical guarantee of a global optimum for non-convex mixed-integer nonlinear problems (MINLP), such as optimization of chemical processes, minimization of external energy requirements reduces total recovery costs. This is because OPEX dominates over CAPEX (except when considering extremely short payback periods), while a large part of OPEX is related to cost of energy supply (both thermal and electrical energy usage).

Distillation columns were designed using rigorous models. Thereby, equilibrium-based models were used for vapor-liquid phase behavior, while rate-based models were implemented to describe reaction kinetics. Besides total number of trays and feed tray location, parameters such as distillate-to-feed or bottoms-to-feed ratio and reflux or boilup ratio were often selected to ensure high recovery of high-purity products. Additionally, common decision variables included vapor or liquid fraction, solvent-to-feed ratio, and others. When designing MVR system, isentropic compressor type was chosen. Reboiler in the MVR system was defined by specifying vapor fraction of cold outlet stream. Finally, compressor ratio was varied to ensure sufficient heat for the reboiler while maintaining appropriate temperature difference in the heat exchanger (~10 ˚C). Furthermore, the process design was subject to constraints such as temperature limits in the initial separation step (in case microorganisms were present), high recovery and purity of valuable products, high purity of water streams intended for reuse in fermentation, temperature of the compressed vapor and complete recovery of solvents or electrolytes to enable reuse and minimize environmental impact.

Techno-economic evaluation

In order to properly evaluate eco-efficiency of the designed process, a complete techno-economic analysis, including both total capital (CAPEX) and operating (OPEX) expenditures, was performed following methodology of the National Renewable Energy Laboratory (NREL) [67]. Total CAPEX were calculated taking into account direct capital costs, related to equipment purchase and installation costs, as well as other indirect capital costs. Cost estimation correlations were used to calculate the installation cost for process equipment [115]. Marshall and Swift cost index value was used in the equipment cost calculation to account for the effect of time (1638.2 for the end of 2018 or 1773.4 for the end of 2021). In addition to the process equipment installation cost, in the calculation of CAPEX, the following factors were taken into account: home office and construction, field expenses, prorateable expenses, project contingency, working capital, site development, additional piping, warehouse and solvent initial cost [67]. Total OPEX were determined considering both variable and fixed operating costs. The variable operating costs include costs for utilities and make-up solvent, while fixed operating costs imply costs for labor, maintenance and property insurance [67]. The cost for all used utilities was calculated following recommendations from the published literature [115] and adjusted for the effect of time. Thereby, the following approximations of the utility costs were considered for 2013: 60.48 $/MWh for electricity, 28.01 $/ MWh for low-pressure steam, 29.59 $/MWh for medium-pressure steam, 35.59 $/MWh for high-pressure steam and 1.27 $/MWh for cooling water. The costs of vacuum system were included based on relevant market data for such equipment [111]. Furthermore, increased size of distillation columns operating under reduced pressures was accounted for in cost correlations, and impact of material of construction was also incorporated. This ensures that both technical and economic implications of low-pressure operation are reflected in the overall process evaluation. Furthermore, in section 5.1, anaerobic digestion performance and costs were estimated based on the chemical oxygen demand (COD) to electricity scenario [533], including a near-atmospheric digester [534], biogas cleaning unit [535] and biogas cleaning consumables [535]. The fixed and variable operating costs of CHP were assumed to be 2.1 $/MW of produced electricity (2024) [536]. The estimation of costs to upgrade wastewater from anaerobic digestion to demineralized water (total costs: 0.62 $/m^3 in 2024), was done as described by Kehrein *et al.* for the optimized process [507].

Total annual cost (TAC) were calculated from the following formula: $TAC=CAPEX/PBP + OPEX$, usually using a payback period (PBP) of 10 years. Specific TAC, or unit production costs (UPC), were calculated by dividing TAC ($/y) with total production capacity (kg/y), resulting in costs per kilogram of product. The influence of the payback period on the unit production costs were analysed. Nonetheless, it should be noted that the costs of different contributors to CAPEX and OPEX will strongly depend on the exact plant location. Therefore,

the economic analysis conducted in this work should be considered as a preliminary indication of economic performance. A more detailed and comprehensive economic evaluation should be carried out before implementing any of the developed processes in real-world applications.

Sustainability assessment

Growing concerns on environmental pollution undoubtedly emphasize need for more sustainable development. In most of the sections, environmental impact of the developed process was assessed by determining several key sustainability metrics: energy intensity, water consumption, material intensity, toxic emissions and pollutant emissions complemented with greenhouse gas emissions [68]. Better process performance, in terms of environmental impact, results in lower values of these sustainability metrics.

- ***Energy intensity*** is a measure of heat and electrical energy needed for the process. It is expressed per kilogram of product [68]. Primary energy requirements account for both thermal and electrical energy usage, whereby inefficiencies in power generation are considered through thermal-electrical conversion. The electrical-to-thermal conversion factor quantifies the amount of heat needed to produce a unit of electrical output and is typically expressed as ratio of heat input to electrical output. This factor accounts for the overall energy efficiency of electricity generation, including all losses in the conversion process and distribution systems. A conservative value of 2.5 was used to calculate the primary energy requirements [117]. Based on pertinent industry data from BP [156], estimated thermal equivalent efficiency factor for converting non-fossil electricity to primary energy is about 40%, with a positive trend of improvement. This factor is calculated based on the equivalent amount of fossil fuel input required to generate a certain amount of electricity in a standard thermal power plant. Thus, about 2.5 units of primary energy are required to produce 1 unit of electricity, so the used value for the electrical-to-thermal conversion is a realistic one.
- ***Water consumption*** is expressed as the amount of fresh water used per unit of output [537].
- ***Material intensity*** presents the amount of formed waste per kilogram of product [68] or non-product [182,183] per kilogram of product.
- ***Wastewater intensity*** present the amount of wastewater per kilogram of recovered product [183].
- ***Greenhouse gas emission*** is expressed as the amount of carbon dioxide (CO_2) emitted per kilogram of product [537]. This sustainability metric was calculated based on recommendations from the literature [538,539]. The source of the used electricity can potentially have a significant impact on greenhouse gas emissions. To accurately assess these emissions, a clear differentiation was made between electricity obtained from fossil fuels (grey electricity) and electricity obtained from renewable sources (green electricity).
- ***Pollutants and toxic materials*** present the amount of emitted pollutants and toxic materials per kilogram of product [68].

A collaborative work in section 5.1 led to a more comprehensive life-cycle assessment (LCA) for the isopropanol and acetone production by gas fermentation. The Life Cycle Assessment was performed cradle-to-gate using the ReCiPe 2016 Midpoint Hierarchical method (V1.04) [540] and the US life cycle impacts from the Ecoinvent database V3.11 [511]. Due to their relevance for the bioprocesses, the following midpoint indicator categories were assessed:

- ***Global warming potential*** (GWP in $kg_{CO2\text{-}eq}/kg_p$)
- ***Stratospheric ozone depletion*** (SOD in $kg_{CFC11\text{-}eq}/kg_p$
- ***Fine particulate matter formation*** (FPMF in $kg_{PM2,5\text{-}eq}/kg_p$)
- ***Freshwater eutrophication*** (FWE in $kg_{P\text{-}eq}/kg_p$)
- ***Marine eutrophication*** (ME in $kg_{N\text{-}eq}/kg_p$)
- ***Human Carcinogenic Toxicity*** (HCT in $kg_{1,4\text{-}DCB\text{-}eq}/kg_p$)
- ***Land use*** ($m^2_{crop\text{-}eq}/kg_p$)
- ***Freshwater use*** (m^3/kg_p)

The scope 1,2 and 3 emissions were accounted for in the analysis. Regarding scope 2 emissions, electricity grid mixture was used for the US, whereas steam was assumed to be generated from natural gas. The scope 3 emissions were accounted for assuming the steel mill off-gas used for the fermentation as already flared CO_2 emissions, thus allocating avoided CO_2 emissions to the system. However, the steel mill could generate heat and electricity from flaring the steel mill off-gas. This was compensated for by attributing the environmental impacts of industrial heat from natural gas combustion to the syngas fermentation process. The environmental impacts were economically allocated to IPA or acetone based on the market price. Additionally, production of other by-products (i.e., biomass as a replacement of soybean meal in animal feed or electricity generation) was accounted for using substitution.

Appendix B – Conditions and compositions of the main process streams

This Appendix contains more details about the conditions and compositions of the main process streams.

Table B-1. Conditions and compositions of the main output streams from Figure 2-4 and Figure 2-5 (ethanol recovery from syngas fermentation)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (°C)	37.0	37.2	21.2	37.0	77.98	30.0
Pressure (bar)	1.000	0.064	1.112	1.232	1.184	1.000
Mass flow (kg/h)	238,161	213,308	24,853	8,897	15,956	14,548
Mass fractions						
Water	0.9215	0.9804	0.4158	1.0000	0.0090	0.0016
Ethanol	0.0614	0.0005	0.5842	0.0000	0.9100	0.9980
Acetic acid	0.0006	0.0007	0.0000	0.0000	0.0000	0.0000
2,3-Butanediol	0.0085	0.0094	0.0000	0.0000	0.0000	0.0000
Microorganisms	0.0081	0.0090	0.0000	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0004

Stream	**7**	**8**	**9**
Temperature (°C)	152.2	37.0	199.5
Pressure (bar)	1.248	1.000	1.120
Mass flow (ktonne/y)	20.608	1,400	19,208
Mass fractions			
Water	0.0687	0.9996	0.0008
Ethanol	0.0000	0.0000	0.0000
Acetic acid	0.0000	0.0000	0.0000
2,3-Butanediol	0.0000	0.0000	0.0000
Microorganisms	0.0000	0.0000	0.0000
Ethylene glycol	0.9313	0.0004	0.9992

Table B-2. Conditions and compositions of the main streams from Figure 2-16 (ethanol recovery by pass-through distillation, configuration 1, PTD-VRC)

Stream	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Temperature (˚C)	37.0	33.9	33.9	30.7	33.9	34.1	40.8
Pressure (bar)	1.000	0.065	0.065	0.052	0.054	0.054	0.054
Flowrate (kg/h)	250,000	248,279	1,721	41,292	266,799	233,132	96,864
Mass fractions							
Water	0.9490	0.9513	0.6141	0.6738	0.9960	0.9982	0.5587
Ethanol	0.0500	0.0482	0.3144	0.3227	0.0040	0.0018	0.1415
LiBr	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2983
CO_2	0.0010	0.0005	0.0715	0.0035	0.0000	0.0000	0.0015
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Stream	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Temperature (˚C)	79.8	50.0	105.6	37.0	75.9	75.9	60.0
Pressure (bar)	1.112	0.054	1.232	1.232	1.000	1.000	1.120
Flowrate (kg/h)	41,292	55,572	26,551	1,551	1,474	13,267	15,288
Mass fractions							
Water	0.6738	0.4731	1.0000	1.0000	0.0722	0.0879	0.0010
Ethanol	0.3227	0.0069	0.0000	0.0000	0.8424	0.9106	0.0000
LiBr	0.0000	0.5199	0.0000	0.0000	0.0000	0.0000	0.0000
CO_2	0.0035	0.0000	0.0000	0.0000	0.0854	0.0015	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9990

Stream	**15**	**16**	**17**	**18**	**19**	**20**
Temperature (˚C)	30.0	154.5	37.0	32.6	60.7	33.8
Pressure (bar)	1.000	1.248	1.000	0.065	1.000	0.054
Flowrate (kg/h)	12,102	16,438	1,151	26,144	206	234,977
Mass fractions						
Water	0.0002	0.0708	0.9992	0.9312	0.0937	0.9980
Ethanol	0.9981	0.0000	0.0008	0.0681	0.0010	0.0018
LiBr	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CO_2	0.0016	0.0000	0.0000	0.0000	0.9053	0.0002
Ethylene glycol	0.0001	0.9291	0.0000	0.0007	0.0000	0.0000

Table B-3. Conditions and compositions of the main streams from Figure 2-18 (ethanol recovery by pass-through distillation, configuration 2, PTD-MED)

Stream	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Temperature (˚C)	37.0	33.9	33.9	30.7	33.9	34.1	40.8
Pressure (bar)	1.000	0.065	0.065	0.052	0.054	0.054	0.054
Flowrate (kg/h)	250,000	248,279	1,721	41,237	266,495	232,868	96,836
Mass fractions							
Water	0.9490	0.9513	0.6141	0.6741	0.9960	0.9982	0.5578
Ethanol	0.0500	0.0482	0.3144	0.3224	0.0040	0.0018	0.1423
LiBr	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2984
CO_2	0.0010	0.0005	0.0715	0.0035	0.0000	0.0000	0.0015
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Stream	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Temperature (˚C)	85.1	50.0	105.6	37.0	75.8	75.8	60.0
Pressure (bar)	1.370	0.054	1.232	1.232	1.000	1.000	1.120
Flowrate (kg/h)	41,236	55,598	26,845	1,845	1,439	12,952	14,740
Mass fractions							
Water	0.6809	0.4715	1.0000	1.0000	0.0717	0.0872	0.0001
Ethanol	0.3156	0.0088	0.0000	0.0000	0.8416	0.9112	0.0000
LiBr	0.0000	0.5197	0.0000	0.0000	0.0000	0.0000	0.0000
CO_2	0.0035	0.0000	0.0000	0.0000	0.0868	0.0015	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9999

Stream	**15**	**16**	**17**	**18**	**19**	**20**
Temperature (˚C)	30.0	154.5	37.0	32.6	60.5	33.8
Pressure (bar)	1.000	1.248	1.000	0.065	1.000	0.054
Flowrate (kg/h)	11,825	15,866	1,127	25,826	198	235,003
Mass fractions						
Water	0.0002	0.0711	1.0000	0.9315	0.0948	0.9980
Ethanol	0.9981	0.0000	0.0000	0.0678	0.0009	0.0018
LiBr	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CO_2	0.0017	0.0000	0.0000	0.0000	0.9043	0.0020
Ethylene glycol	0.0000	0.9289	0.0000	0.0007	0.0000	0.0000

Table B-4. Conditions and compositions of the main process streams from Figure 2-25 (isopropanol and acetone recovery after syngas fermentation, process configuration VD)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	30.0	82.7	30.0	88.7	79.8
Pressure (bar)	1.000	0.043	1.300	1.000	1.312	1.300
Flowrate (kg/h)	250,000	215,250	34,750	2,511	32,239	11,638
Mass fractions						
Water	0.9481	0.9980	0.6392	0.0014	0.6888	0.1386
Isopropanol	0.0401	0.0000	0.2885	0.0005	0.3109	0.8613
Acetone	0.0100	0.0000	0.0721	0.9981	0.0000	0.0000
Acetic acid	0.0018	0.0020	0.0002	0.0000	0.0002	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Stream	**7**	**8**	**9**	**10**	**11**
Temperature (˚C)	105.6	75.0	30.0	148.9	30.0
Pressure (bar)	1.232	1.200	1.000	1.504	1.000
Flowrate (kg/h)	20,601	12,802	10,038	14,402	1,596
Mass fractions					
Water	0.9997	0.0000	0.0014	0.1110	1.0000
Isopropanol	0.0000	0.0000	0.9985	0.0000	0.0000
Acetone	0.0000	0.0000	0.0000	0.0000	0.0000
Acetic acid	0.0003	0.0000	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	1.0000	0.0000	0.8890	0.0000

Table B-5. Conditions and compositions of the main process streams from Figure 2-26 (isopropanol and acetone recovery after syngas fermentation, process configuration PTD-VRC)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	26.3	26.3	27.0	30.2	30.2
Pressure (bar)	1.000	0.043	0.043	0.042	0.043	0.043
Flowrate (kg/h)	250,000	2,299	247,701	32,423	241,942	215,278
Mass fractions						
Water	0.9481	0.5260	0.9520	0.6482	0.9974	0.9978
Isopropanol	0.0401	0.2662	0.0380	0.2885	0.0007	0.0003
Acetone	0.0100	0.2072	0.0083	0.0626	0.0000	0.0000
Acetic acid	0.0018	0.0006	0.0018	0.0007	0.0019	0.0019
LiBr	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	33.3	81.8	55.0	30.0	88.9	79.9
Pressure (bar)	0.041	1.200	0.043	1.000	1.312	1.300
Flowrate (kg/h)	85,656	34,722	50,934	2,511	32,211	11,574
Mass fractions						
Water	0.5229	0.6401	0.4431	0.0013	0.6899	0.1391
Isopropanol	0.1232	0.2870	0.0115	0.0007	0.3093	0.8609
Acetone	0.0293	0.0722	0.0000	0.9980	0.0000	0.0000
Acetic acid	0.0003	0.0007	0.0000	0.0000	0.0008	0.0000
LiBr	0.3243	0.0000	0.5454	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Stream	**13**	**14**	**15**	**16**
Temperature (˚C)	75.0	30.0	149.8	30.0
Pressure (bar)	1.200	1.000	1.504	1.000
Flowrate (kg/h)	12,802	9,983	14,392	22,228
Mass fractions				
Water	0.0000	0.0020	0.1105	0.9989
Isopropanol	0.0000	0.9980	0.0000	0.0000
Acetone	0.0000	0.0000	0.0000	0.0000
Acetic acid	0.0000	0.0000	0.0000	0.0011
LiBr	0.0000	0.0000	0.0000	0.0000
Ethylene glycol	1.0000	0.0000	0.8895	0.0000

Table B-6. Conditions and compositions of the main process streams from Figure 2-27 (isopropanol and acetone recovery after syngas fermentation, process configuration PTD-MED)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	26.3	26.3	27.0	30.2	30.2
Pressure (bar)	1.000	0.043	0.043	0.042	0.043	0.043
Flowrate (kg/h)	250,000	2,299	247,701	32,423	241,942	215,278
Mass fractions						
Water	0.9481	0.5260	0.9520	0.6482	0.9974	0.9978
Isopropanol	0.0401	0.2662	0.0380	0.2885	0.0007	0.0003
Acetone	0.0100	0.2072	0.0083	0.0626	0.0000	0.0000
Acetic acid	0.0018	0.0006	0.0018	0.0007	0.0019	0.0019
LiBr	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	32.3	81.8	55.0	30.0	88.9	79.9
Pressure (bar)	0.041	1.200	0.043	1.000	1.312	1.300
Flowrate (kg/h)	90,417	34,710	55,695	2,510	32,320	11,569
Mass fractions						
Water	0.4729	0.6405	0.3686	0.0012	0.6903	0.1403
Isopropanol	0.1919	0.2866	0.1326	0.0006	0.3089	0.8596
Acetone	0.0277	0.0722	0.0000	0.9982	0.0000	0.0000
Acetic acid	0.0003	0.0007	0.0000	0.0000	0.0008	0.0000
LiBr	0.3072	0.0000	0.4987	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**13**	**14**	**15**	**16**		
Temperature (˚C)	75.0	30.0	149.7	30.0		
Pressure (bar)	1.200	1.000	1.504	1.000		
Flowrate (kg/h)	12,802	9,966	14,406	22,230		
Mass fractions						
Water	0.0000	0.0020	0.1113	0.9989		
Isopropanol	0.0000	0.9980	0.0000	0.0000		
Acetone	0.0000	0.0000	0.0000	0.0000		
Acetic acid	0.0000	0.0000	0.0000	0.0011		
LiBr	0.0000	0.0000	0.0000	0.0000		
Ethylene glycol	1.0000	0.0000	0.8887	0.0000		

Table B-7. Condition and composition of the main process streams from Figure 2-31 (isobutanol recovery, VD process configuration)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	28.2	35.7	21.9	81.0	103.6
Pressure (bar)	1.000	0.055	0.059	0.050	1.200	1.152
Flowrate (kg/h)	387,500	437,825	411,555	25,765	29,788	19,452
Mass fractions						
Water	0.9826	0.9848	1.0000	0.7546	0.7716	1.0000
Isobutanol	0.0161	0.0148	0.0000	0.2439	0.2260	0.0000
CO_2	0.0013	0.0004	0.0000	0.0015	0.0024	0.0000
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	84.7	83.0	82.9	30.0	25.0	11.7
Pressure (bar)	1.000	1.200	1.000	1.152	1.000	1.200
Flowrate (kg/h)	10,337	13,862	3,965	6,238	30,800	507
Mass fractions						
Water	0.3419	0.2004	0.8826	0.0000	1.0000	0.0046
Isobutanol	0.6513	0.7943	0.1092	1.0000	0.0000	0.0019
CO_2	0.0069	0.0053	0.0082	0.0000	0.0000	0.9935

Table B-8. Condition and composition of the main process streams from Figure 2-32 (isobutanol recovery, GS-VE process configuration)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	29.7	24.8	84.9	32.2	32.2
Pressure (bar)	1.000	0.042	0.095	1.200	1.152	1.152
Flowrate (kg/h)	387,500	355,203	32,297	41,065	30,553	25,553
Mass fractions						
Water	0.9826	1.0000	0.7912	0.8314	1.0000	1.0000
Isobutanol	0.0161	0.0000	0.1932	0.1616	0.0000	0.0000
CO_2	0.0013	0.0000	0.0156	0.0070	0.0000	0.0000
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	63.4	61.0	61.0	58.1	30.0	9.0
Pressure (bar)	1.000	1.200	1.000	1.000	1.152	1.200
Flowrate (kg/h)	10,513	17,088	4,058	10,851	6,237	507
Mass fractions						
Water	0.3413	0.2022	0.8795	0.3183	0.0000	0.0038
Isobutanol	0.6314	0.7784	0.0910	0.6511	1.0000	0.0026
CO_2	0.0273	0.0194	0.0295	0.0306	0.0000	0.9935

Table B-9. Condition and composition of the main process streams from Figure 2-38 (recovery after isopropanol-butanol-ethanol (IBE) fermentation)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	29.9	37.3	98.3	94.7	92.2
Pressure (bar)	1.000	0.042	0.080	1.450	1.280	1.280
Flowrate (kg/h)	362,500	284,935	77,561	90,214	32,300	19,646
Mass fractions						
Water	0.9742	1.0000	0.8795	0.8698	0.4509	0.2196
Butanol	0.0173	0. 0000	0.0807	0.0832	0.3853	0.5702
Isopropanol	0.0069	0. 0000	0.0322	0.0349	0.1091	0.1460
Ethanol	0.0014	0. 0000	0.0066	0.0113	0.0547	0.0643
Acetone	0.0002	0. 0000	0.0010	0.0008	0.0000	0.0000

Stream	**7**	**8**	**9**	**10**
Temperature (˚C)	92.2	111.0	30.0	30.0
Pressure (bar)	1.280	1.480	1.480	1.000
Flowrate (kg/h)	12,654	67,768	6,325	3,470
Mass fractions				
Water	0.8101	1.0000	0.0100	0.1111
Butanol	0.0981	0. 0000	0.9900	0.0000
Isopropanol	0.0519	0. 0000	0.0000	0.7188
Ethanol	0.0399	0. 0000	0.0000	0.1481
Acetone	0.0000	0. 0000	0.0000	0.0220

Table B-10. Conditions and compositions of the main streams from Figure 3-2 (1,3-propanediol recovery in cases 1a and 1b)

Stream	**1**	**2**	**3**	**4**	**5**
Temperature (˚C)	37.0	36.2	59.0	24.1	30.2
Pressure (bar)	1.000	1.000	0.069	1.000	1.000
Flowrate (kg/h)	28,632	25,197	3,436	262	2,869
Mass fractions					
Water	0.8892	1.0000	0.0768	1.0000	0.0008
1,3-Propanediol	0.1002	0.0000	0.8349	0.0000	0.9992
Glycerol	0.0105	0.0000	0.0875	0.0000	0.0000
Glucose	0.0001	0.0000	0.0008	0.0000	0.0000

Stream	**6**	**7**	**8**
Temperature (˚C)	190.0	30.0	30.0
Pressure (bar)	0.041	1.000	0.034
Flowrate (kg/h)	305	302	3
Mass fractions			
Water	0.0000	0.0000	0.0000
1,3-Propanediol	0.0050	0.0050	0.0000
Glycerol	0.9857	0.9950	0.0613
Glucose	0.0094	0.0000	0.9387

Table B-11. Conditions and compositions of the main streams from Figure 3-3 (1,3-propanediol recovery in cases 2a and 2b)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	37.0	35.9	46.8	25.7	30.0	171.1
Pressure (bar)	1.000	0.060	0.069	0.030	1.000	0.041
Flowrate (kg/h)	35,981	30,943	5,037	1,771	2,862	404
Mass fractions						
Water	0.8820	0.9966	0.1782	0.5067	0.0000	0.0000
1,3-Propanediol	0.0795	0.0000	0.5681	0.0000	0.9997	0.0030
2,3-Butanediol	0.0225	0.0000	0.1606	0.4568	0.0000	0.0000
Succinic acid	0.0094	0.0000	0.0675	0.0000	0.0000	0.8408
Ethanol	0.0029	0.0034	0.0000	0.0000	0.0000	0.0000
Lactic acid	0.0018	0.0000	0.0129	0.0000	0.0003	0.1562
Acetic acid	0.0018	0.0000	0.0129	0.0365	0.0000	0.0000

Stream	**7**	**8**	**9**	**10**
Temperature (˚C)	24.3	30.0	30.0	30.0
Pressure (bar)	1.000	1.000	0.020	1.000
Flowrate (kg/h)	962	809	64	340
Mass fractions				
Water	0.9327	0.0000	0.0000	0.0000
1,3-Propanediol	0.0000	0.0000	0.0190	0.0000
2,3-Butanediol	0.0002	0.9999	0.0000	0.0000
Succinic acid	0.0000	0.0000	0.0001	0.9998
Ethanol	0.0000	0.0000	0.0000	0.0000
Lactic acid	0.0000	0.0000	0.9810	0.0002
Acetic acid	0.0671	0.0001	0.0000	0.0000

Table B-12. Conditions and compositions of the main streams from Figure 3-8 (2,3-butanediol recovery, case 2-3)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	50.1	70.7	47.5	30.1	149.2
Pressure (bar)	1.000	1.000	0.134	1.000	1.000	1.000
Flowrate (kg/h)	20,000	17,682	2318	404	1845	68
Mass fractions						
Water	0.8753	0.9789	0.0844	0.4842	0.0000	0.0000
2,3-Butanediol	0.0930	0.0000	0.8025	0.0035	0.9991	0.2204
Ethanol	0.0105	0.0119	0.0000	0.0000	0.0000	0.0000
3-hydroxy-2-butanone	0.0093	0.0065	0.0314	0.1799	0.0000	0.0000
Acetic Acid	0.0089	0.0027	0.0559	0.3200	0.0001	0.0000
Succinic Acid	0.0020	0.0000	0.0175	0.0000	0.0000	0.5923
Lactic Acid	0.0007	0.0000	0.0061	0.0000	0.0008	0.1872
Formic Acid	0.0003	0.0000	0.0022	0.0126	0.0000	0.0000

Table B-13. Conditions and compositions of the main streams from Figure 3-9 (1,4-butanediol recovery, case 1-4)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	51.9	55.9	45.9	30.0	164.4
Pressure (bar)	1.000	1.000	0.134	1.000	1.000	1.000
Flowrate (kg/h)	20,000	18,500	1500	97	1397	6
Mass fractions						
Water	0.9279	0.9977	0.0672	1.0000	0.0024	0.0000
1,4-Butanediol	0.0697	0.0000	0.9293	0.0000	0.9942	0.9233
Ethanol	0.0021	0.0023	0.0000	0.0000	0.0000	0.0000
2-(4-hydroxybutoxy)-tetrahydrofuran	0.0002	0.0000	0.0027	0.0000	0.0028	0.0059
Gamma butyrolactone	<0.0001	0.0000	0.0005	0.0000	0.0005	0.0000
Glucose	<0.0001	0.0000	0.0003	0.0000	0.0000	0.0706
2-Pyrrolidone	<0.0001	0.0000	<0.0001	0.0000	0.0000	0.0002

Table B-14. Conditions and compositions of the main streams from Figure 3-10 (1,3-butanediol recovery, case 1-3)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	50.6	66.5	47.1	30.1	155.5
Pressure (bar)	1.000	1.000	0.134	1.000	1.000	1.000
Flowrate (kg/h)	20,000	18,200	1800	319	1446	34
Mass fractions						
Water	0.9109	0.9908	0.1029	0.5797	0.0000	0.0000
1,3-Butanediol	0.0725	0.0000	0.8060	0.0000	0.9938	0.3957
Ethanol	0.0052	0.0057	0.0000	0.0000	0.0000	0.0000
4-hydroxy-2-butanone	0.0052	0.0014	0.0430	0.2183	0.0053	0.0000
Acetic Acid	0.0052	0.0021	0.0366	0.2021	0.0010	0.0000
Glucose	0.0010	0.0000	0.0115	0.0000	0.0000	0.6043

Table B-15. Conditions and compositions of the main streams from Figure 4-2 (propionic acid recovery in case 1)

Stream	**1**	**2**	**3**	**4**	**5**
Temperature (˚C)	30.0	41.5	53.9	30.0	113.6
Pressure (bar)	1.000	0.080	0.150	1.000	1.300
Flowrate (kg/h)	20,000	17,552	2,623	539	2,084
Mass fractions					
Water	0.8776	0.9999	0.0668	0.0000	0.0841
Propionic acid	0.0721	0.0001	0.5494	0.0004	0.6912
Acetic acid	0.0234	0.0000	0.1785	0.0000	0.2247
Succinic acid	0.0269	0.0000	0.2053	0.9996	0.0000

Stream	**6**	**7**	**8**
Temperature (˚C)	155.2	30	99.7
Pressure (bar)	1.552	1.552	1.000
Flowrate (kg/h)	1,438	471	175
Mass fractions			
Water	0.0000	0.0000	0.9979
Propionic acid	0.9999	0.0056	0.0008
Acetic acid	0.0001	0.9944	0.0013
Succinic acid	0.0000	0.0000	0.0000

Table B-16. Conditions and compositions of the main streams from figures Figure 4-3 and Figure 4-4 (propionic acid recovery, cases 2a and 2b)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	30.0	41.05	54.9	30.0	86.8	56.0
Pressure (bar)	1.000	0.080	0.150	1.000	1.400	1.600
Flowrate (kg/h)	20,000	17,400	2,600	538	2,062	927
Mass fractions						
Water	0.8776	0.9999	0.0589	0.0000	0.0742	0.0000
Propionic acid	0.0721	0.0001	0.5541	0.0000	0.6987	0.0000
Acetic acid	0.0234	0.0000	0.1800	0.0000	0.2270	0.0000
Succinic acid	0.0269	0.0000	0.2071	1.0000	0.0000	0.0000
Methanol	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
Methyl propionate	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Methyl acetate	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
DMSO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	53.8	30.0	54.1	30.0	157.4	60.0
Pressure (bar)	1.552	1.552	1.000	1.000	1.232	1.200
Flowrate (kg/h)	635	1,692	663	604	1,162	1,103
Mass fractions						
Water	0.9990	0.0000	0.0054	0.0000	0.0031	0.0000
Propionic acid	0.0008	0.0014	0.0000	0.0000	0.0000	0.0000
Acetic acid	0.0000	0.0002	0.0000	0.0000	0.0000	0.0000
Succinic acid	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000
Methanol	0.0000	0.0000	0.0838	0.0006	0.0475	0.0000
Methyl propionate	0.0000	0.0000	0.9102	0.9988	0.0000	0.0000
Methyl acetate	0.0000	0.9984	0.0005	0.0006	0.0000	0.0000
DMSO	0.0000	0.0000	0.0000	0.0000	0.9494	1.0000

Stream	**13**	**14**
Temperature (˚C)	60	56.0
Pressure (bar)	1.200	1.600
Flowrate (kg/h)	< 1	872
Mass fractions		
Water	0.0000	0.0000
Propionic acid	0.0000	0.0000
Acetic acid	0.0000	0.0000
Succinic acid	0.0000	0.0000
Methanol	0.0000	1.0000
Methyl propionate	0.0000	0.0000
Methyl acetate	0.0000	0.0000
DMSO	1.0000	0.0000

Table B-17. Conditions and compositions of the main process streams from Figure 4-12 (ethyl acetate recovery, case 1)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	11.5	32.0	30.5	25.0	20.2	21.5
Pressure (bar)	1.000	1.000	0.043	6.000	10.000	10.000
Flowrate (kg/h)	39,800	33,000	28,619	39	34,000	38,358
Mass fraction						
Water	0.0084	0.9450	0.9475	0.0014	1.0000	0.0019
Ethyl acetate	0.0291	0.0028	0.0000	0.0259	0.0000	0.0000
Ethanol	0.0000	0.0054	0.0000	0.0037	0.0000	0.0000
Nitrogen	0.7199	0.0000	0.0000	0.0000	0.0000	0.7467
Oxygen	0.2074	0.0001	0.0000	0.0015	0.0000	0.2151
Carbon dioxide	0.0220	0.0013	0.0000	0.9675	0.0000	0.0226
Argon	0.0132	0.0000	0.0000	0.0000	0.0000	0.0136
Heavy components (biomass and sugars)	0.0000	0.0455	0.0525	0.0000	0.0000	0.0000

Stream	**7**	**8**	**9**	**10**
Temperature (˚C)	25.0	52.1	25.0	44.7
Pressure (bar)	1.232	1.232	2.500	1.000
Flowrate (kg/h)	38,505	1,249	28	2
Mass fraction				
Water	0.9954	0.0020	0.0066	0.0368
Ethyl acetate	0.0000	0.9967	0.0842	0.4691
Ethanol	0.0046	0.0013	0.0000	0.0157
Nitrogen	0.0000	0.0000	0.2905	0.1923
Oxygen	0.0000	0.0000	0.1453	0.0717
Carbon dioxide	0.0000	0.0000	0.4631	0.1981
Argon	0.0000	0.0000	0.0072	0.0162
Heavy components (biomass and sugars)	0.0000	0.0000	0.0000	0.0000

Table B-18. Conditions and compositions of the main process streams from Figure 4-14 (ethyl acetate recovery, case 2a)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	11.5	32.0	30.5	25.0	10.0	20.0
Pressure (bar)	1.000	1.000	0.043	6.000	1.000	1.000
Flowrate (kg/h)	39,800	33,000	28,619	39	38,396	315
Mass fraction						
Water	0.0084	0.9450	0.9475	0.0014	0.0000	1.0000
Ethyl acetate	0.0291	0.0028	0.0000	0.0259	0.0025	0.0000
Ethanol	0.0000	0.0054	0.0000	0.0037	0.0000	0.0000
Nitrogen	0.7199	0.0000	0.0000	0.0000	0.7461	0.0000
Oxygen	0.2074	0.0001	0.0000	0.0015	0.2150	0.0000
Carbon dioxide	0.0220	0.0013	0.0000	0.9675	0.0228	0.0000
Argon	0.0132	0.0000	0.0000	0.0000	0.0136	0.0000
Heavy components (biomass and sugars)	0.0000	0.0455	0.0525	0.0000	0.0000	0.0000

Stream	**7**	**8**	**9**
Temperature (˚C)	83.0	30.0	25.0
Pressure (bar)	1.232	1.232	3.000
Flowrate (kg/h)	4,263	1,155	16
Mass fraction			
Water	0.9583	0.0037	0.0055
Ethyl acetate	0.0000	0.9962	0.0712
Ethanol	0.0417	0.0001	0.0037
Nitrogen	0.0000	0.0000	0.3591
Oxygen	0.0000	0.0000	0.1946
Carbon dioxide	0.0000	0.0000	0.3329
Argon	0.0000	0.0000	0.0130
Heavy components (biomass and sugars)	0.0000	0.0000	0.0000

Table B-19. Conditions and compositions of the main process streams from Figure 4-14 (ethyl acetate recovery, case 2b)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	11.5	32.0	30.5	25.0	10.0	20.0
Pressure (bar)	1.000	1.000	0.043	6.000	1.000	1.000
Flowrate (kg/h)	39,800	33,000	28,619	39	38,307	314
Mass fraction						
Water	0.0084	0.9450	0.9475	0.0014	0.0000	1.0000
Ethyl acetate	0.0291	0.0028	0.0000	0.0259	0.0003	0.0000
Ethanol	0.0000	0.0054	0.0000	0.0037	0.0000	0.0000
Nitrogen	0.7199	0.0000	0.0000	0.0000	0.7478	0.0000
Oxygen	0.2074	0.0001	0.0000	0.0015	0.2155	0.0000
Carbon dioxide	0.0220	0.0013	0.0000	0.9675	0.0228	0.0000
Argon	0.0132	0.0000	0.0000	0.0000	0.0136	0.0000
Heavy components (biomass and sugars)	0.0000	0.0455	0.0525	0.0000	0.0000	0.0000

Stream	**7**	**8**	**9**
Temperature (˚C)	66.1	30.0	25.0
Pressure (bar)	1.232	1.232	3.000
Flowrate (kg/h)	4,266	1,239	18
Mass fraction			
Water	0.9583	0.0027	0.0056
Ethyl acetate	0.0000	0.9972	0.0716
Ethanol	0.0417	0.0000	0.0035
Nitrogen	0.0000	0.0000	0.3553
Oxygen	0.0000	0.0000	0.1909
Carbon dioxide	0.0000	0.0000	0.3318
Argon	0.0000	0.0000	0.0412
Heavy components (biomass and sugars)	0.0000	0.0000	0.0000

Table B-20. Condition and composition of the main streams from Figure 4-19 (2PE recovery from the organic phase after fermentation with ISPR by liquid-liquid extraction)

Stream	1a	2a	3a	4a	5a	6a
Temperature (˚C)	30.0	40.0	31.2	31.2	31.2	133.7
Pressure (bar)	1.000	1.000	0.053	0.053	0.053	0.100
Flowrate (kg/h)	10,025	9,629	160	95	65	301
Mass fractions						
PPG	0.9600	0.9995	0.0000	0.0000	0.0000	0.0000
2PE	0.0249	0.0000	0.3875	0.9426	0.0042	0.8271
2PEAc	0.0057	0.0005	0.0011	0.0028	0.0000	0.1729
Water	0.0009	0.0000	0.6113	0.0546	0.9958	0.0000

Stream	7a	8a	1b	2b	3b	4b
Temperature (˚C)	30.0	30.0	30.0	40.0	34.0	34.0
Pressure (bar)	1.000	1.000	1.000	1.000	0.053	0.053
Flowrate (kg/h)	249	52	10,025	9,629	138	1
Mass fractions						
PPG	0.0000	0.0000	0.9600	0.9995	0.0000	0.0000
2PE	0.9991	0.0037	0.0249	0.0000	0.3875	0.2699
2PEAc	0.0009	0.9963	0.0057	0.0005	0.0011	0.6105
Water	0.0000	0.0000	0.0009	0.0000	0.6113	0.0824

Stream	5b	6b	7b
Temperature (˚C)	34.0	30.0	30.0
Pressure (bar)	0.053	1.000	1.000
Flowrate (kg/h)	138	129	387
Mass fractions			
PPG	0.0000	0.0000	0.0000
2PE	0.0034	0.0000	0.0002
2PEAc	0.0011	0.0000	0.9998
Water	0.9506	0.0000	0.0000
Acetic acid	0.0449	1.0000	0.0000

Table B-21. Condition and composition of the main streams from Figure 4-22 (ethanol valorisation from the aqueous phase after fermentation with ISPR by liquid-liquid extraction)

Stream	**1c**	**2c**	**3c**	**4c**	**5c**	**6c**
Temperature (˚C)	30	38.2	68.2	68.2	25.0	25.0
Pressure (bar)	1.000	1.312	1.000	1.000	1.000	1.000
Flowrate (kg/h)	16,282	15,966	252	63	41	22
Mass fractions						
PPG	0.0096	0.0098	0.0000	0.0000	0.0000	0.0000
2-PE	0.0003	0.0003	0.0000	0.0000	0.0000	0.0000
Water	0.9572	0.9751	0.0548	0.0355	0.0524	0.0038
Ethanol	0.0172	0.0000	0.9434	0.6369	0.9365	0.0749
L-Phe	0.0096	0.0098	0.0000	0.0000	0.0000	0.0000
Glucose	0.0048	0.0049	0.0000	0.0000	0.0000	0.0000
CO_2	0.0013	0.0000	0.0019	0.3276	0.0111	0.9214
Ethylene glycol	0	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**7c**	**1d**	**2d**	**3d**	**4d**	**5d**
Temperature (˚C)	30.0	30	38.1	68.9	68.9	25.0
Pressure (bar)	1.000	1.000	1.312	1.000	1.000	1.000
Flowrate (kg/h)	294	16,282	15,956	261	65	44
Mass fractions						
PPG	0.0000	0.0096	0.0098	0.0000	0.0000	0.0000
2-PE	0.0000	0.0003	0.0003	0.0000	0.0000	0.0000
Water	0.0544	0.9572	0.9752	0.0851	0.0524	0.0760
Ethanol	0.9414	0.0172	0.0000	0.9129	0.6316	0.9109
L-Phe	0.0000	0.0096	0.0098	0.0000	0.0000	0.0000
Glucose	0.0000	0.0048	0.0049	0.0000	0.0000	0.0000
CO_2	0.0032	0.0013	0.0000	0.0020	0.3160	0.0131
Ethylene glycol	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**6d**	**7d**	**8d**	**9d**	**10d**	**11d**
Temperature (˚C)	25.0	62.9	60.0	43.4	156.4	30.0
Pressure (bar)	1.000	1.000	1.100	1.000	1.248	1.000
Flowrate (kg/h)	22	305	366	279	391	25
Mass fractions						
PPG	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2-PE	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Water	0.0051	0.0838	0.0000	0.0005	0.0649	0.9995
Ethanol	0.0713	0.9126	0.0000	0.9952	0.0000	0.0001
L-Phe	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Glucose	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CO_2	0.9237	0.0036	0.0000	0.0000	0.0000	0.0000
Ethylene glycol	0.0000	0.0000	1.0000	0.0000	0.9351	0.0004

Table B-22. Condition and composition of the main streams from Figure 4-28 (recovery of by-products after biomass pretreatment)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (°C)	99.7	99.0	93.5	26.0	27.1	27.4
Pressure (bar)	1.000	1.000	1.000	1.000	1.000	1.000
Mass flow (kg/h)	110,000	13,670	14,836	1,500	334	1,167
Mass fraction						
Water	0.9657	0.9751	0.9708	0.198	0.0204	0.9199
Acetic Acid	0.0175	0.0009	0.0009	0.0000	0.0000	0.0000
Formic Acid	0.0043	0.0000	0.0000	0.0000	0.0000	0.0000
Furfural	0.0030	0.0239	0.0283	0.2802	0.9796	0.0801
HMF	0.0013	0.0000	0.0000	0.0000	0.0000	0.0000
Levulinic acid	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000
High-boiling components	0.0083	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (°C)	105.6	109.7	99.7	111.2	99.8	99.7
Pressure (bar)	1.232	1.408	1.000	1.472	1.300	1.000
Mass flow (kg/h)	13,336	96,330	53,285	43,046	41,369	39,855
Mass fraction						
Water	0.9990	0.9643	0.9943	0.9273	0.9619	0.9984
Acetic Acid	0.0010	0.0198	0.0057	0.0372	0.0380	0.0016
Formic Acid	0.0000	0.0049	0.0000	0.0109	0.0000	0.0000
Furfural	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
HMF	0.0000	0.0015	0.0000	0.0033	0.0000	0.0000
Levulinic acid	0.0000	0.0001	0.0000	0.0001	0.0000	0.0000
High-boiling components	0.0000	0.0094	0.0000	0.0211	0.0000	0.0000
Stream	**13**	**14**	**15**	**16**	**17**	**18**
Temperature (°C)	26.00	129.1	34.8	234.9	26.0	26.5
Pressure (bar)	1.000	1.376	0.050	0.054	0.010	0.012
Mass flow (kg/h)	1,514	1,676	626	1,050	141	909
Mass fraction						
Water	0.0004	0.0738	0.1976	0.0000	0.0000	0.0000
Acetic Acid	0.9980	0.0174	0.0466	0.0000	0.0000	0.0000
Formic Acid	0.0016	0.2788	0.7465	0.0000	0.0000	0.0000
Furfural	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
HMF	0.0000	0.0843	0.0000	0.1344	1.0000	0.0000
Levulinic acid	0.0000	0.0035	0.0093	0.8656	0.0000	0.0000
High-boiling components	0.0000	0.5423	0.0000	0.0000	0.0000	1.0000

Table B-23. Condition and composition of the main streams from Figure 5-2 (isopropanol and acetone production by gas fermentation, scenario 1a)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	1,100	20.0	34.8	37.0	37.0	8.6
Pressure (bar)	1.013	1.103	1.400	1.400	1.400	0.048
Flowrate (kg/h)	53,570	9,217	12,017	52,784	217,472	517
Mass fractions						
Water	/	0.9261	0.9666	0.0217	0.8975	0.0947
Isopropanol	/	/	/	0.0072	0.0222	0.2632
Acetone	/	/	/	0.0028	0.0027	0.1849
CO	0.4895	/	/	0.0745	<0.0001	0.0009
CO_2	0.3076	/	/	0.6935	0.0009	0.4053
H_2	0.0070	/	/	0.0011	<0.0001	<0.0001
N_2	0.1958	/	/	0.1987	<0.0001	0.0026
NH_3	/	/	/	0.0005	0.0002	0.0481
NaOH	/	0.0739	/	/	/	/
NH_4Cl	/	/	0.0334	/	/	/
Ions and salts	/	/	/	/	0.0596	/
Biomass	/	/	/	/	0.0167	/
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	66.7	10.0	10.0	37.0	81.5	36.9
Pressure (bar)	1.200	1.300	1.300	1.300	1.200	0.059
Flowrate (kg/h)	128	258	131	1,608	16,719	201,844
Mass fractions						
Water	0.2792	0.0019	0.0969	0.6646	0.6578	0.9175
Isopropanol	0.5902	0.0139	0.4346	0.2358	0.3035	/
Acetone	0.1250	0.0877	0.4351	0.0873	0.0377	/
CO	<0.0001	0.0026	<0.0001	<0.0001	<0.0001	/
CO_2	<0.0001	0.8053	<0.0001	0.0109	<0.0001	/
H_2	<0.0001	<0.0001	<0.0001	<0.0001	/	/
N_2	<0.0001	0.0052	<0.0001	<0.0001	/	/
NH_3	0.0043	0.0834	0.0210	0.0011	0.0009	/
Acetic acid	/	/	/	0.0003	<0.0001	0.0010
Ions and salts	/	/	/	/	/	0.0635
Biomass	/	/	/	/	/	0.0180
Stream	**13**	**14**	**15**	**16**	**17**	**18**
Temperature (˚C)	36.2	37.0	25.0	37.0	88.8	105.6
Pressure (bar)	0.059	1.000	3.000	1.000	1.312	1.232
Flowrate (kg/h)	20,184	78	15	705	16,253	10,158
Mass fractions						
Water	0.9175	0.0004	/	0.0010	0.6796	1
Isopropanol	/	0.0001	/	0.0003	0.3203	/
Acetone	/	0.7550	0.2544	0.9893	<0.0001	/
CO	/	<0.0001	/	/	/	/
CO_2	/	0.0392	0.1421	0.0004	/	/
H_2	/	<0.0001	/	/	/	/
N_2	/	<0.0001	/	/	/	/
NH_3	/	0.2053	0.6024	0.0091	/	/

Stream	**13**	**14**	**15**	**16**	**17**	**18**
Acetic acid	0.0010	/	/	/	/	/
Ions and salts	0.0635	/	/	/	/	/
Biomass	0.0180	/	/	/	/	/
Stream	**19**	**20**	**21**	**22**	**23**	**24**
Temperature (˚C)	30.2	53.8	80.0	75.0	149.0	30.0
Pressure (bar)	1.232	1.232	1.000	1.200	1.504	1.000
Flowrate (kg/h)	863	81	6,095	334	7,550	5,235
Mass fractions						
Water	1	1	0.1457	/	0.1139	0.0053
Isopropanol	/	/	0.8541	/	<0.0001	0.9945
Acetone	/	/	<0.0001	/	/	0.0002
Ethylene glycol	/	/	/	1	0.8861	/

Stream	**25**	**26**	**27**	**28**
Temperature (˚C)	202.3	30.0	32.0	30.0
Pressure (bar)	1.232	1.000	1.300	1.400
Flowrate (kg/h)	6,693	10,071	51,367	13,804
Mass fractions				
Water	/	0.9999	/	1
CO	/	/	0.0766	/
CO_2	/	/	0.7165	/
H_2	/	/	0.0011	/
N_2	/	/	0.2043	/
NH_3	/	/	0.0011	/
Ethylene glycol	1	0.0001	/	/

Table B-24. Condition and composition of the main streams from Figure 5-8 (2PE *de-novo* production by fermentation from glucose by process A)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (°C)	99.7	99.0	93.5	26.0	27.1	27.4
Pressure (bar)	1.000	1.000	1.000	1.000	1.000	1.000
Mass flow (kg/h)	110,000	13,670	14,836	1,500	334	1,167
Mass fraction						
Water	0.9657	0.9751	0.9708	0.198	0.0204	0.9199
Acetic Acid	0.0175	0.0009	0.0009	0.0000	0.0000	0.0000
Formic Acid	0.0043	0.0000	0.0000	0.0000	0.0000	0.0000
Furfural	0.0030	0.0239	0.0283	0.2802	0.9796	0.0801
HMF	0.0013	0.0000	0.0000	0.0000	0.0000	0.0000
Levulinic acid	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000
High-boiling components	0.0083	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (°C)	105.6	109.7	99.7	111.2	99.8	99.7
Pressure (bar)	1.232	1.408	1.000	1.472	1.300	1.000
Mass flow (kg/h)	13,336	96,330	53,285	43,046	41,369	39,855
Mass fraction						
Water	0.9990	0.9643	0.9943	0.9273	0.9619	0.9984
Acetic Acid	0.0010	0.0198	0.0057	0.0372	0.0380	0.0016
Formic Acid	0.0000	0.0049	0.0000	0.0109	0.0000	0.0000
Furfural	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
HMF	0.0000	0.0015	0.0000	0.0033	0.0000	0.0000
Levulinic acid	0.0000	0.0001	0.0000	0.0001	0.0000	0.0000
High-boiling components	0.0000	0.0094	0.0000	0.0211	0.0000	0.0000

Table B-25. Condition and composition of the main streams from Figure 5-9 (2PE *de-novo* production by fermentation from glucose by process B)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (°C)	99.7	99.0	93.5	26.0	27.1	27.4
Pressure (bar)	1.000	1.000	1.000	1.000	1.000	1.000
Mass flow (kg/h)	110,000	13,670	14,836	1,500	334	1,167
Mass fraction						
Water	0.9657	0.9751	0.9708	0.198	0.0204	0.9199
Acetic Acid	0.0175	0.0009	0.0009	0.0000	0.0000	0.0000
Formic Acid	0.0043	0.0000	0.0000	0.0000	0.0000	0.0000
Furfural	0.0030	0.0239	0.0283	0.2802	0.9796	0.0801
HMF	0.0013	0.0000	0.0000	0.0000	0.0000	0.0000
Levulinic acid	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000
High-boiling components	0.0083	0.0000	0.0000	0.0000	0.0000	0.0000
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (°C)	105.6	109.7	99.7	111.2	99.8	99.7
Pressure (bar)	1.232	1.408	1.000	1.472	1.300	1.000
Mass flow (kg/h)	13,336	96,330	53,285	43,046	41,369	39,855
Mass fraction						
Water	0.9990	0.9643	0.9943	0.9273	0.9619	0.9984
Acetic Acid	0.0010	0.0198	0.0057	0.0372	0.0380	0.0016
Formic Acid	0.0000	0.0049	0.0000	0.0109	0.0000	0.0000
Furfural	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
HMF	0.0000	0.0015	0.0000	0.0033	0.0000	0.0000
Levulinic acid	0.0000	0.0001	0.0000	0.0001	0.0000	0.0000
High-boiling components	0.0000	0.0094	0.0000	0.0211	0.0000	0.0000

Appendix C – Design parameters of distillation columns

This Appendix contains more details about the design of distillation columns. It should be noted that the first stage is the condenser (if there is a condenser) and the last stage is the reboiler (if there is a reboiler) by convention in Aspen Plus.

Table C-1. Design parameters of the distillation columns from Figure 2-4 and Figure 2-5 (ethanol recovery from syngas fermentation)

Distillation column	**C1**	**C2**	**C3**	**C4**
Number of stages	40	30	32	16
Feed stage	20	15	4 (ethylene glycol) 24 (91 wt% ethanol)	8
Top pressure (bar)	0.055	1.000	1.000	1.000
Bottom pressure (bar)	0.064	1.232	1.248	1.120
Top temperature (°C)	21	78	78	100
Bottom temperature (°C)	37	106	154	199
Reboiler duty (MW)	20.3	11.4	5.9	1.9
Condenser duty (MW)	-20.5	-11.2	-4.4	-1.2
Reflux ratio (mass basis)	0.88	1.57	0.27	0.34
Distillate-to-feed ratio (mass basis)	0.105	0.642	0.912	0.068
Column diameter (m)	4.2	2.4	1.5	1.0

Table C-2. Design parameters of the distillation columns from Figure 2-16 and Figure 2-18 (ethanol recovery by pass-through distillation)

Distillation column	**Stripper**	**C1**	**C2**	**C3**	**Adsorber**
Process configuration 1 – PTD-VRC					
Number of stages	10	30	32	16	30
Feed stage	1 (broth) 10 (vapor)	15	4 (solvent) 24 (91% ethanol)	8	1 (broth) 30 (vapor)
Top pressure (bar)	0.052	1.000	1.000	1.000	0.058
Bottom pressure (bar)	0.054	1.232	1.248	1.120	0.065
Top temperature (°C)	30.7	75.9	75.6	99.5	34.6
Bottom temperature (°C)	33.9	105.6	154.5	199.0	32.6
Reboiler duty (MW)	0	11.0	5.3	1.	0
Condenser duty (MW)	0	-9.7	-3.8	-0.9	0
Reflux ratio (mass basis)	/	1.54	0.35	0.31	/
Distillate-to-feed ratio (mass basis)	/	0.357	0.912	0.070	/
Column diameter (m)	4.5	2.3	1.4	0.9	1.2
Process configuration 2 – PTD-MED					
Number of stages	10	30	32	16	30
Feed stage	1 (broth) 10 (vapor)	15	4 (solvent) 24 (91% ethanol)	8	1 (broth) 30 (vapor)
Top pressure (bar)	0.052	1.000	1.000	1.000	0.058
Bottom pressure (bar)	0.054	1.232	1.248	1.120	0.065
Top temperature (°C)	30.7	75.8	75.5	99.	34.8
Bottom temperature (°C)	33.9	105.6	154.5	200.0	32.6
Reboiler duty (MW)	0	10.5	5.3	1.6	0
Condenser duty (MW)	0	-9.5	-3.9	-0.9	0
Reflux ratio (mass basis)	/	1.53	0.40	0.32	/
Distillate-to-feed ratio (mass basis)	/	0.349	0.913	0.071	/
Column diameter (m)	4.5	2.2	1.4	0.9	1.2

Table C-3. Design parameters of distillation columns from Figure 2-25, Figure 2-26 and Figure 2-27 (isopropanol and acetone recovery after syngas fermentation)

Distillation column	C1	C2	C3	C4	C5
Process configuration VD					
Number of stages	48	40	30	64	30
Feed stage	32	20	20	8 (ethylene glycol) 40 (86% isopropanol)	10
Top pressure (bar)	0.032	1.000	1.000	1.000	1.00
Bottom pressure (bar)	0.043	1.312	1.232	1.504	1.232
Top temperature (°C)	10.2	55.9	79.8		99.6
Bottom temperature (°C)	30.0	88.7	105.6	148.9	203.6
Reboiler duty (MW)	22.	4.0	5.9	5.	2.0
Condenser duty (MW)	-22.6	-4.0	-5.3	-4.3	-1.5
Reflux ratio (mass basis)	0.22	10.00	0.84	1.29	0.50
Distillate-to-feed ratio (mass basis)	0.139	0.072	0.361	0.862	0.111
Column diameter (m)	4.4	1.8	1.7	1.6	1.0
Process configuration PTD-VRC					
Number of stages	10	40	30	64	30
Feed stage	1 (broth) 10 (vapor)	20	20	8 (ethylene glycol) 40 (86% isopropanol)	10
Top pressure (bar)	0.041	1.000	1.000	1.00	1.000
Bottom pressure (bar)	0.043	1.312	1.232	1.504	1.232
Top temperature (°C)	27.0	55.9	79.9	81.8	99.6
Bottom temperature (°C)	31.2	88.9	105.6	149.8	202.9
Reboiler duty (MW)	/	4.0	5.8	6.2	1.9
Condenser duty (MW)	/	-3.8	-5.3	-5.2	-1.2
Reflux ratio (mass basis)	/	10.00	0.84	1.80	0.25
Distillate-to-feed ratio (mass basis)	/	0.073	0.359	0.863	0.110
Column diameter (m)	4.1	1.8	1.7	1.8	1.0
Process configuration PTD-MED					
Number of stages	10	40	30	64	30
Feed stage	1 (broth) 10 (vapor)	20	20	8 (ethylene glycol) 40 (86% isopropanol)	10
Top pressure (bar)	0.041	1.000	1.000	1.000	1.00
Bottom pressure (bar)	0.043	1.312	1.232	1.504	1.232
Top temperature (°C)	27.0	55.9	79.9	81.8	99.6
Bottom temperature (°C)	31.2	88.9	105.6	149.7	202.6
Reboiler duty (MW)	/	4.0	5.8	6.1	1.9
Condenser duty (MW)	/	-3.8	-5.3	-5.1	-1.3
Reflux ratio ratio (mass basis)	/	10.00	0.84	1.77	0.25
Distillate-to-feed ratio (mass basis)	/	0.072	0.359	0.861	0.111
Column diameter (m)	4.1	1.8	1.7	1.8	1.0

Table C-4. Design parameters of distillation columns from Figure 2-31 and Figure 2-32 (isobutanol recovery, before applying heat pumping and heat integration)

Distillation column	**C1**	**C2**	**C3**	**C4**
Process configuration VD				
Number of stages	40	10	20	20
Feed stage	20	1 (liquid) 10 (vapor)	10	5
Top pressure (bar)	0.050	0.050	1.000	1.000
Bottom pressure (bar)	0.059	0.052	1.152	1.152
Top temperature (°C)	21.9	28.3	83.7	81.7
Bottom temperature (°C)	35.7	28.0	103.6	111.2
Reboiler duty (MW)	22.8	0.0	3.8	3.0
Condenser duty (MW)	-14.6	0.0	-3.4	-2.8
Reflux ratio (mass basis)	0.008	/	0.01	0.1
Distillate-to-feed ratio (mass basis)	0.060	/	0.347	0.550
Column diameter (m)	4.0	1.1	1.2	1.4
Process configuration GS-VE				
Number of stages	10	10	20	20
Feed stage	1 (liquid) 10 (vapor)	1 (liquid) 10 (vapor)	10	5
Bottom pressure (bar)	0.040	0.050	1.000	1.000
Top pressure (bar)	0.042	0.052	1.152	1.152
Top temperature (°C)	27.8	23.0	63.4	58.1
Bottom temperature (°C)	29.7	16.2	103.6	111.2
Reboiler duty (MW)	0.0	0.0	3.9	4.0
Condenser duty (MW)	0.0	0.0	-3.6	-3.7
Reflux ratio (mass basis)	/	/	0.01	0.11
Distillate-to-feed ratio (mass basis)	/	/	0.256	0.560
Column diameter (m)	4.2	1.7	1.2	1.7

Table C-5. Design parameters of distillation columns from Figure 2-38 (recovery after isopropanol-butanol-ethanol fermentation)

Distillation column	**C1**	**A-DWC**		
		A-DWC$_{LB}$	**A-DWC$_{RB}$**	**A-DWC$_{RT}$**
Number of stages	20	31	31	31
Feed stage	1 (liquid) 10 (vapor)	1	1 (inner liquid) 7 (organic phase)	31
Top pressure (bar)	0.038	1.240	1.240	1.000
Bottom pressure (bar)	0.042	1.480	1.480	1.240
Top temperature (°C)	27.5	98.7	91.7	78.3
Bottom temperature (°C)	29.9	111.0	123.8	91.5
Reboiler duty (MW)	0.0	10.1	7.3	0.0
Condenser duty (MW)	0.0	0.0	0.0	-16.1
Boilup ratio (mass basis)	/	0.24	4.00	/
Distillate-to-feed ratio (mass basis)	/	/	/	0.078
Column diameter (m)	6.4		3.0	

Table C-6. Design parameters of distillation columns from Figure 3-2 (1,3-propanediol recovery in cases 1a and 1b)

Distillation column	**C1**	**DWC**		**C2**
		DWC$_{L}$	**DWC$_{R}$**	
Number of stages	40	34	50	20
Feed stage	30	17 (liquid) 34 (vapor)	35	10
Top pressure (bar)	0.060	0.030	0.030	0.030
Bottom pressure (bar)	0.069	0.037	0.041	0.034
Top temperature (°C)	36.2	24.1	116.0	182.6
Bottom temperature (°C)	59.0	122.9	190.0	239.0
Reboiler duty (MW)	17.1	0.0	1.2	0.07
Condenser duty (MW)	-17.1	-0.2	-0.8	-0.07
Reflux ratio (mass basis)	0.01	0.10	0.20	0.01
Distillate-to-feed ratio (mass basis)	0.880	/	0.578	0.990
Column diameter (m)	3.0	1.5		0.3

Table C-7. Design parameters of distillation columns from Figure 3-3 (1,3-propanediol recovery in cases 2a and 1b)

Distillation column	**C1**	**DWC**		**C2**	**C3**
		DWC_L	**DWC_R**		
Number of stages	40	34	50	20	10
Feed stage	30	17 (liquid) 34 (vapor)	35	10	5
Top pressure (bar)	0.060	0.030	0.030	0.030	0.020
Bottom pressure (bar)	0.069	0.037	0.041	0.034	0.022
Top temperature (°C)	35.9	25.7	122.7	24.3	124.3
Bottom temperature (°C)	46.8	128.0	171.1	98.9	208.3
Reboiler duty (MW)	37.3	0.0	3.5	0.7	0.02
Condenser duty (MW)	-37.3	-1.0	-2.4	-0.6	-0.02
Reflux ratio (mass basis)	0.80	/	2.50	0.02	0.20
Distillate-to-feed ratio (mass basis)	0.860	0.178	0.350	/	/
Bottoms-to-feed ratio (mass basis)	/	/	/	0.46	0.84
Column diameter (m)	4.4	2.4		0.9	0.2

Table C-8. Design parameters of distillation columns from Figure 3-8 (2,3-butanediol recovery, case 2-3)

Distillation column	**C1**	**DWC**	
		DWC_L	**DWC_R**
Number of stages	20	14	20
Position of the feed stage	15	6 (bottom stream from C1) 14 (vapor from DWC_R)	15
Top pressure (bar)	0.130	0.100	0.100
Bottom pressure (bar)	0.134	0.103	0.104
Top temperature (˚C)	50.1	47.4	121.0
Bottom temperature (˚C)	70.7	121.9	149.2
Reboiler duty (MW)	14.0	0.0	0.6
Condenser duty (MW)	-14.0	-0.2	-0.3
Reflux ratio (mass basis)	0.18	/	0.88
Distillate-to-feed ratio (mass basis)	0.965	0.254	0.51
Column diameter (m)	2.2	1.1	

Table C-9. Design parameters of distillation columns from Figure 3-9 (1,4-butanediol recovery, case 1-4)

Distillation column	**C1**	**DWC**	
		DWC_L	**DWC_R**
Number of stages	20	14	20
Position of the feed stage	15	6 (bottom stream from C1) 14 (vapor from DWC_R)	15
Top pressure (bar)	0.130	0.100	0.100
Bottom pressure (bar)	0.134	0.103	0.104
Top temperature (˚C)	50.8	45.8	97.3
Bottom temperature (˚C)	55.6	98.4	164.3
Reboiler duty (MW)	14.6	0.0	0.6
Condenser duty (MW)	-14.6	-0.2	-0.4
Reflux ratio (mass basis)	0.16	/	0.87
Distillate-to-feed ratio (mass basis)	0.925	0.038	0.566
Column diameter (m)	2.2	1.1	

Table C-10. Design parameters of distillation columns from Figure 3-10 (1,3-butanediol recovery, case 1-3)

Distillation column	**C1**	**DWC**	
		DWC_L	**DWC_R**
Number of stages	20	14	20
Position of the feed stage	15	6 (bottom stream from C1) 14 (vapor from DWC_R)	15
Top pressure (bar)	0.130	0.100	0.100
Bottom pressure (bar)	0.134	0.103	0.104
Top temperature (˚C)	50.6	47.0	141.2
Bottom temperature (˚C)	66.5	142.0	155.5
Reboiler duty (MW)	14.3	0.0	0.7
Condenser duty (MW)	-14.3	-0.3	-0.3
Reflux ratio (mass basis)	0.16	/	0.87
Distillate-to-feed ratio (mass basis)	0.910	0.085	0.420
Column diameter (m)	2.2	1.0	

Table C-11. Design parameters of distillation columns from Figure 4-2 (propionic acid recovery in case 1)

Distillation column	**C1**	**C2**	**DWC**	
			DWC_L	**DWC_R**
Number of stages	60	20	50	70
Position of the feed stage	40	10	1 (inner liquid) 20 (acid mixture)	20
Top pressure (bar)	0.080	0.100	1.160	1.000
Bottom pressure (bar)	0.093	0.104	1.552	1.552
Top temperature (˚C)	41.5	51.9	107.7	99.7
Bottom temperature (˚C)	53.9	243.1	155.2	132.6
Reboiler duty (MW)	37.3	0.6	1.0	0.7
Condenser duty (MW)	-37.5	-0.5	0.0	-1.6
Reflux ratio (mass basis)	2.2	0.5	/	13.7
Distillate-to-feed ratio (mass basis)	0.87	0.79	/	/
Bottom rate (kg/h)	/	/	1,438	471
Column diameter (m)	5.7	0.8	1.2	

Table C-12. Design parameters of distillation columns from Figure 4-3 and Figure 4-4 (propionic acid recovery in cases 2a and 2b)

Distillation column	**C1**	**C2**	**R-DWC**	
			R-DWC$_L$	**R-DWC$_R$**
Number of stages	60	20	50	70
Position of the feed stage	40	10	1 (inner liquid) 20 (acid mixture)	20
Top pressure (bar)	0.080	0.100	1.160	1.000
Bottom pressure (bar)	0.093	0.104	1.552	1.552
Top temperature (˚C)	41.5	51.9	63.9	54.1
Bottom temperature (˚C)	53.9	243.1	112.4	93.3
Reboiler duty (MW)	36.9	0.6	1.0	0.8
Condenser duty (MW)		-0.6	0.0	-1.8
Reflux ratio (mass basis)	2.2	0.5	/	/
Reflux ratio (mole basis)	/	/	/	18.1
Distillate-to-feed ratio (mass basis)	0.87	0.79	/	/
Bottom rate (kmol/h)	/	/	35.2	19.2
Column diameter (m)	5.8	0.8	1.3	

Distillation column	**C3**	**C4**
Number of stages	30	20
Position of the feed stage	4 (DMSO) 20(methyl acetate)	10
Top pressure (bar)	1.000	1.000
Bottom pressure (bar)	1.232	1.152
Top temperature (˚C)	56.6	64.3
Bottom temperature (˚C)	157.4	192.9
Reboiler duty (MW)	0.2	0.1
Condenser duty (MW)	-0.1	-0.1
Reflux ratio (mole basis)	0.7	2.0
Distillate rate (kmol/h)	8.2	1.7
Column diameter (m)	0.3	0.2

Table C-13. Design parameters of distillation columns from Figure 4-12 (ethyl acetate recovery in case 1)

Distillation column	**C1**	**C2**
Number of stages	16	15
Position of the feed stage	1 (liquid) 16 (vapor)	1 (liquid) 15 (vapor)
Top pressure (bar)	0.040	10.00
Bottom pressure (bar)	0.043	10.11
Top temperature (˚C)	28.6	21.5
Bottom temperature (˚C)	30.4	19.3
Reboiler duty (MW)	/	/
Condenser duty (MW)	/	/
Reflux ratio (mass basis)	/	/
Bottom-to-feed ratio (mass basis)	/	/
Diameter (m)	1.6	1.4
Distillation column	**A-DWC**	
	A-DWC$_L$	**A-DWC$_R$**
Number of stages	20	30
Position of the feed stage	1 (liquid from A-DWCR) 2 (liquid from F2 and F5) 3 (liquid from 1st and 2nd stage of COMP2) 4 (liquid from 3rd stage of COMP2) 5 (liquid from 1st stage of COMP3) 6 (aqueous phase from DEC) 18 (liquid from F3, liquid from 2nd and 3rd stage of COMP3)	10 (vapor from A-DWCL) 12 (organic phase from DEC)
Top pressure (bar)	1.080	1.000
Bottom pressure (bar)	1.232	1.232
Top temperature (˚C)	73.6	54.6
Bottom temperature (˚C)	104.8	82.7
Reboiler duty (MW)	3.9	0.4
Condenser duty (MW)	0.0	-0.5
Reflux ratio (mass basis)	/	0.73
Bottom-to-feed ratio (mass basis)	0.979	0.415
Diameter (m)	1.4	

Table C-14. Design parameters of distillation columns from Figure 4-14 (ethyl acetate recovery in case 2a)

Distillation column	**C1**		
Number of stages	16		
Position of the feed stage	1 (liquid) 16 (vapor)		
Top pressure (bar)	0.040		
Bottom pressure (bar)	0.043		
Top temperature (˚C)	28.6		
Bottom temperature (˚C)	30.4		
Reboiler duty (MW)	/		
Condenser duty (MW)	/		
Reflux ratio (mass basis)	/		
Bottom-to-feed ratio (mass basis)	/		
Diameter (m)	1.6		
Distillation column		**A-DWC**	
	A-DWC$_L$		**A-DWC$_R$**
Number of stages	20		30
Position of the feed stage	1 (liquid from A-DWC$_R$) 2 (liquid from F2) 5 (liquid from 1st stage of COMP3) 6 (aqueous phase from DEC) 18 (liquid from F3, liquid from 2nd and 3rd stage of COMP3)		10 (vapor from A-DWC$_L$) 12 (organic phase from DEC) 25 (separated ethyl acetate from gas)
Top pressure (bar)	1.080		1.000
Bottom pressure (bar)	1.232		1.232
Top temperature (˚C)	72.5		54.3
Bottom temperature (˚C)	100.8		82.2
Reboiler duty (MW)	0.3		0.1
Condenser duty (MW)	0.0		-0.2
Reflux ratio (mass basis)	/		0.76
Bottom-to-feed ratio (mass basis)	0.970		0.660
Diameter (m)		0.6	

Table C-15. Design parameters of distillation columns from Figure 4-14 (ethyl acetate recovery in case 2b)

Distillation column	**C1**	
Number of stages	16	
Position of the feed stage	1 (liquid) 16 (vapor)	
Top pressure (bar)	0.040	
Bottom pressure (bar)	0.043	
Top temperature (˚C)	28.6	
Bottom temperature (˚C)	30.4	
Reboiler duty (MW)	/	
Condenser duty (MW)	/	
Reflux ratio (mass basis)	/	
Bottom-to-feed ratio (mass basis)	/	
Diameter (m)	1.6	
Distillation column	**A-DWC**	
	A-DWC$_L$	**A-DWC$_R$**
Number of stages	20	30
Position of the feed stage	1 (liquid from A-DWC$_R$) 2 (liquid from F2) 5 (liquid from 1st stage of COMP3) 6 (aqueous phase from DEC) 18 (liquid from F3, liquid from 2nd and 3rd stage of COMP3)	10 (vapor from A-DWC$_L$) 12 (organic phase from DEC) 25 (separated ethyl acetate from gas)
Top pressure (bar)	1.080	1.000
Bottom pressure (bar)	1.232	1.232
Top temperature (˚C)	72.6	54.7
Bottom temperature (˚C)	100.8	82.1
Reboiler duty (MW)	0.3	0.1
Condenser duty (MW)	0.0	-0.2
Reflux ratio (mass basis)	/	0.63
Bottom-to-feed ratio (mass basis)	0.970	0.650
Diameter (m)	0.6	

Table C-16. Design parameters of distillation columns from Figure 4-19 (2PE and 2PEAc recovery from organic phase)

Distillation column	**DWC**		**C1**
	DWC_L	**DWC_R**	
Number of stages	15	20	20
Position of the feed stage	1 (liquid from DWC_R) 7 (organic phase)	5 (vapor from DWC_L) 10 (stream from decanter)	15
Top pressure (bar)	0.054	0.053	0.050
Bottom pressure (bar)	0.057	0.057	0.054
Top temperature (˚C)	124.7	32.7	128.2
Bottom temperature (˚C)	210.7	133.7	154.5
Reboiler duty (MW)	0.3	0.1	0.1
Condenser duty (MW)	0.0	-0.3	-0.1
Reflux ratio (mass basis)	/	3.2	1.2
Bottom-to-feed ratio (mass basis)	0.961	/	0.910
Distillate -to-feed ratio (mass basis)	/	/	0.83
Distillate rate (kg/h)	/	160	
Column diameter (m)	1.1		0.4

Distillation column	**R-DWC**	
	$R\text{-}DWC_L$	**$R\text{-}DWC_R$**
Number of stages	15	20
Position of the feed stage	1 (liquid from DWC_R) 7 (organic phase)	5 (vapor from DWC_L) 6 (stream from decanter) 17 (acetic acid)
Top pressure (bar)	0.054	0.053
Bottom pressure (bar)	0.057	0.057
Top temperature (˚C)	122.8	34.0
Bottom temperature (˚C)	210.7	156.0
Reboiler duty (MW)	0.4	0.1
Condenser duty (MW)	0.0	-0.3
Reflux ratio (mass basis)	/	3.8
Bottoms-to-feed ratio	0.961 (mass basis)	1.1 (mole basis, acetic acid)
Column diameter (m)	1.1	

Table C-17. Design parameters of distillation columns from Figure 4-28 (recovery of by-products after biomass pretreatment)

Distillation column	**C1**	**C2**	**C3**	**C4**
Number of stages	52	30	60	48
Position of the feed stage	35	12	40	36
Top pressure (bar)	1.000	1.000	1.000	1.000
Bottom pressure (bar)	1.408	1.232	99.7	1.376
Top temperature (˚C)	99.0	96.7	1.472	99.8
Bottom temperature (˚C)	109.7	105.6	111.2	129.1
Reboiler duty (MW)	22.0	3.4	65.4	40.3
Condenser duty (MW)	-21.9	-3.2	-66.4	-40.8
Reflux ratio (mole basis)	1.6	3.4	1.0	0.6
Distillate-to-feed ratio (mole basis)	0.125	0.080	0.566	0.990
Column diameter (m)	2.9	1.1	4.8	4.3

Distillation column	**C5**	**C6**	**C7**
Number of stages	66	20	10
Position of the feed stage	33	10	7
Top pressure (bar)	1.000	0.050	0.010
Bottom pressure (bar)	1.520	0.054	0.012
Top temperature (˚C)	99.7	34.3	150.3
Bottom temperature (˚C)	131.6	234.9	246.5
Reboiler duty (MW)	70.5	0.4	0.09
Condenser duty (MW)	-70.4	-0.3	-0.09
Reflux ratio (mole basis)	1.8	0.6	3.0
Bottoms-to-feed ratio (mole basis)	0.011	/	/
Distillate-to-feed ratio (mole basis)	/	0.740	0.182
Column diameter (m)	7.2	0.7	0.5

Table C-18. Design parameters of distillation columns from Figure 5-2 (isopropanol and acetone recovery production by fermentation)

Distillation column	**C1**	**C2**	**C3**	**C4**	**C5**
Number of stages	48	40	30	64	30
Feed stage	32 (broth) 20 (condensed off-gas)	20 (from C1) 19 (from COMP2) 14 and 19 (from flash units)	20	8 (ethylene glycol) 40 (86% isopropanol)	10
Top pressure (bar)	0.048	1.000	1.000	1.000	1.00
Bottom pressure (bar)	0.059	1.312	1.232	1.504	1.232
Top temperature (°C)	8.6	55.9	79.9	81.7	99.6
Bottom temperature (°C)	36.3	88.7	105.6	149.0	202.3
Reboiler duty (MW)	16.3	4.0	2.8	3.1	1.0
Condenser duty (MW)	-16.7	-4.0	-2.5	-2.5	-0.7
Reflux ratio (mass basis)	0.82	15.1	0.66	1.6	0.32
Distillate-to-feed ratio (mass basis)	0.08	1.03 (acetone as feed basis)	0.38	0.86	0.11
Column diameter (m)	3.9	1.2	1.1	1.3	0.7

Table C-19. Design parameters of distillation columns from Figure 5-8 (2PE production by *de-novo* fermentation combined with ISPR by liquid-liquid extraction)

Distillation column	**A-DWC**	
	A-DWC$_L$	**A-DWC$_R$**
Number of stages	10	20
Position of the feed stage	1 (liquid from DWC$_R$) 5 (organic phase)	10 (vapor from DWC$_L$) 15 (stream from decanter)
Top pressure (bar)	0.069	0.067
Bottom pressure (bar)	0.071	0.071
Top temperature (˚C)	108.9	37.8
Bottom temperature (˚C)	240.2	58.2
Reboiler duty (MW)	0.6	0.1
Condenser duty (MW)	0.0	-0.3
Reflux ratio (mass basis)	/	0.1
Bottom-to-feed ratio (mass basis)	0.951	/
Bottoms rate (kg/h)	/	241
Column diameter (m)	0.8	

Table C-20. Design parameters of distillation columns from Figure 5-9 (2PE production by *de-novo* fermentation combined with ISPR by adsorption)

Distillation column	**C1**	**C2**
Number of stages	20	20
Position of the feed stage	10	10 (from C1) 15 (stream from decanter)
Top pressure (bar)	1.000	1.000
Bottom pressure (bar)	1.152	1.152
Top temperature (˚C)	78.0	99.1
Bottom temperature (˚C)	100.4	222.8
Reboiler duty (MW)	2.3	0.2
Condenser duty (MW)	-2.3	-0.2
Reflux ratio (mass basis)	0.95	0.7
Distillate-to-feed ratio (mass basis)	0.914	0.423
Column diameter (m)	1.1	0.4

Appendix D – Recovery of 1-hexanol after fermentation

This Appendix contains more details about recovery process of 1-hexanol after fermentation. The data presented in this appendix were used for comparison's sake in section 2.6.

Process design

Downstream process for hexanol purification was designed following the procedure described in section 2.6. Flowsheet of the developed recovery process is presented in Figure D-1, while condition and composition of the main process streams are given in Table D-1. The feed stream to this process contains only 0.24 wt% hexanol, while the rest is water. There will also be some microorganisms and non-volatile inert components present, but they can be neglected in the simulations because they are removed in the initial step without evaporation. The flowrate of the feed stream (550,00 kg/h) was calculated to ensure hexanol productivity of about 10 ktonne/y.

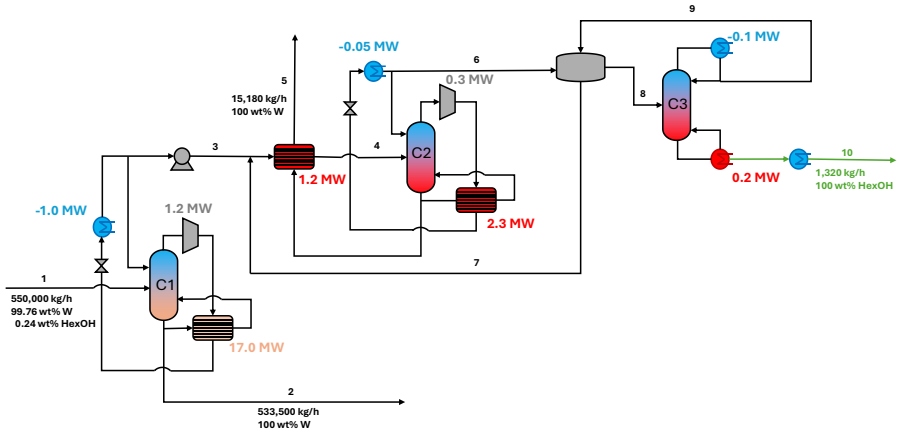


Figure D-1. Process flowsheet of hexanol recovery, condition and composition of the numbered process streams is presented in Table D-1

The first step in the recovery process is separation of hexanol product, with some water from most of the fermentation broth in vacuum distillation column C1. This column operates under reduced pressure (top pressure of 0.035 bar with a pressure drop of 0.225 mbar per theoretical stage) to ensure that the bottom temperature (~31 ˚C) does not harm microbial viability. Bottom product of this column is mainly water with some microorganisms and inert non-volatile components that

may be recycled to fermentation. Top product from this column is a hexanol-water mixture that is pumped to atmospheric pressure for further downstream processing. MVR system can be applied to this column to reduce energy requirements by 82.5% and allow a complete electrification of this step.

Table D-1. Condition and composition of the main process stream for hexanol recovery, stream numbers correspond to those in Figure D-1

Stream	**1**	**2**	**3**	**4**	**5**
Temperature (˚C)	30.0	30.5	24.8	89.1	38.2
Pressure (bar)	1.000	0.044	1.3	1.200	1.152
Flowrate (kg/h)	550,000	533,500	16,500	19,462	15.180
Mass fractions					
Water	0.9976	1.0000	0.9200	0.9306	1.0000
Hexanol	0.0024	0.0000	0.0800	0.0694	0.0000
Stream	**6**	**7**	**8**	**9**	**10**
Temperature (˚C)	94.9	97.0	97.0	95.1	30.0
Pressure (bar)	1.000	1.000	1.000	1.000	1.312
Flowrate (kg/h)	4,282	2,962	1,571	251	1,320
Mass fractions					
Water	0.6845	0.9895	0.0917	0.5734	0.0000
Hexanol	0.3155	0.0105	0.9083	0.4266	1.0000

Even though large amounts of water are removed in the initial step (~533,500 kg/h), the top product from column C1 is still very dilute (~ 8 wt% of hexanol). Thus, additional preconcentration is performed in distillation column C2. The top product from this column is a nearly azeotropic (~31.55 wt% hexanol and ~68.45 wt% water) mixture, while the bottom product is pure water. This water stream can be used to preheat the feed stream to column C2 (after pumping to atmospheric pressure, the top product from column C1 is subcooled liquid) and may be recycled to fermentation. Furthermore, since temperature difference at top and bottom of column C2 is not large (~95 and 104 ˚C, respectively), MVR system can also be applied to reduce energy requirements of this step by 64.2%.

Top product from column C2, a nearly azeotropic hexanol-water mixture, is sent to simple liquid-liquid phase separation in a two-phase flash unit. The formed water-rich phase can be recycled to column C2 to minimize product losses. The hexanol-rich phase is sent to the final purification in distillation column C3. Top product from this column is an azeotropic hexanol-water mixture that is recycled to the liquid-liquid separation unit, while bottom product is high-purity hexanol (100 wt%). Due to the large temperature difference (~98 ˚C at the top and ~165 ˚C at the bottom of column C3), heat pump systems cannot be applied, and heating by external steam is required for this column.

Analysis of key performance indicators

The main key performance indicators in terms of economics and sustainability are summarized in Table D-2.

A complete economic analysis of the developed process for the purification of hexanol from a highly dilute feed stream was performed following published NREL procedure [67]. Total capital costs (CAPEX), standing for equipment purchase and installation costs, home office and construction, field expenses, prorateable expenses, project contingency, working capital, site development, additional piping and warehouse, are equal to 14,534 k$. The largest contribution to CAPEX is the cost of equipment (calculated following the published cost correlations) [115] that is about 7,958 k$. The total operating costs (OPEX), including cost of utilities, operating labor, maintenance and property insurance, are 4,137 k$/y or 0.392 $/kg. The biggest contributor to OPEX is the cost of operating labor (about 2,984 k$/y) and cost of utilities (about 936 k$/y). The total annual costs (TAC), including both CAPEX and OPEX with a payback period of 10 years, are 5,590 k$/y or 0.529 $/kg.

Furthermore, the environmental performance of the hexanol recovery process was estimated by calculating several sustainability metrics: energy requirements, CO_2 emissions, water consumption, material intensity, pollutants and toxic emissions [68]. Thermal and electrical energy requirements stand for the required thermal and electrical energy per kilogram of recovered product, while primary energy requirements account for the overall energy usage through electrical-to-thermal conversion factor (a conservative value of 2.5 was used) [156]. Thermal energy requirements for the developed recovery process are 0.145 $kW_{th}h/kg$ due to the heating requirements for column C3. Additionally, electrical energy requirements are equal to 1.169 kW_eh/kg and mainly come from the usage of compressors in the MVR systems applied to columns C1 and C2. Thus, primary energy requirements for hexanol recovery are 3.069 $kW_{th}h/kg$. The CO_2 emissions are related to the energy usage and were calculated following the published correlations [538,539]. If green electricity (electricity from renewable sources) is available, these emissions are only 0.022 kg_{CO2}/kg due to the significant electrification of recovery process. Alternatively, these emissions are 0.555 kg_{CO2}/kg if grey electricity (electricity form fossil fuels) has to be used. The total water consumption was calculated assuming 7% loss of cooling water and 70% recovery of steam condensate [126]. Therefore, about 0.174 m^3_w/kg is required, while about 0.012 m^3_w/kg is lost. Material intensity, toxic materials and pollutants sustainability metrics stand for the amount of waste, toxic materials and pollutants that is formed per kilogram of recovered hexanol [68]. Since there are no waste streams (outlet streams from the recovery process are hexanol product,

most of the fermentation broth from the bottom of column C1 that may be returned to the fermentation, and pure water from the bottom of column C2 may also be recycled to the fermentation), material intensity metric is equal to zero. Similarly, toxic materials and pollutants are not formed, and values of these metrics are equal to zero.

Table D-2. Comparison of the main sustainability and economic indicators

Key performance indicator	Value
Product concentration in the fermentation broth (wt%)	0.24
Thermal energy requirements ($kW_{th}h/kg$)	0.145
Electrical energy requirements ($kW_{e}h/kg$)	1.169
Primary energy requirements ($kW_{th}h/kg$)	3.069
CO_2 emissions, grey electricity (kg_{CO2}/kg)	0.555
OPEX ($/kg)	0.392
Total annual costs ($/kg)	0.529
Market price ($/kg)	2.500
Margin between market price and TAC for purification ($/kg)	1.971

Appendix E – Fermentation models

As already mentioned, bioreactors in sections 5.1 and 5.2 were modeled as stoichiometric reactors. Therefore, this appendix provides further details on the derived fermentation stoichiometries.

Isopropanol and acetone gas fermentation

The fermentation stoichiometry was derived as a black box model using thermodynamic principles [506,541,542] considering acetic acid and biomass as by-products.

Catabolic and anabolic reactions

Overall catabolic reactions from CO and H_2 to isopropyl alcohol, acetone and acetic acid and anabolic reaction for biomass formation ($CH_{1.8}O_{0.5}N_{0.2}$) are summarized in Table E-1.

Table E-1. Overall catabolic and anabolic reactions

Product	Reaction
Isopropanol	$9CO(g) + 4H_2O(l) \rightarrow 1C_3H_8O(aq) + 6CO_2(g)$
	$9H_2(g) + 3CO_2(g) \rightarrow 1C_3H_8O(aq) + 5H_2O(l)$
Acetone	$8CO(g) + 3H_2O(l) \rightarrow 1C_3H_6O(aq) + 5CO_2(g)$
	$8H_2(g) + 3CO_2(g) \rightarrow 1C_3H_8O(aq) + 5H_2O(l)$
Acetic Acid	$4CO(g) + 2H_2O(l) \rightarrow 1CH_3COO^-(aq) + 1H^+(aq) + 2CO_2(g)$
	$4H_2(g) + 2CO_2(g) \rightarrow 1CH_3COO^-(aq) + 1H^+(aq) + 2H_2O(l)$
Biomass	$2.1CO(g) + 0.6H_2O(l) + 0.2NH_4^+(aq) \rightarrow 1CH_{1.8}O_{0.5}N_{0.2}(aq) + 0.2H^+(aq) + 1.1CO_2(g)$
	$2.1H_2(g) + 1CO_2(g) + 0.2NH_4^+(aq) \rightarrow 1CH_{1.8}O_{0.5}N_{0.2}(aq) + 0.2H^+(aq) + 1.5H_2O(l)$

Conditions for the steel mill off-gas fermentation

Pilot-scale results reported by LanzaTech [73] for the isopropanol (IPA) and acetone production via gas fermentation were used. These results include gas composition (50 vol% CO, 20 vol% CO_2, 20 vol% N_2, 10 vol% H_2), product compositions (more than 90% product selectivity) and additional piloting conditions (85% gas utilisation, 1.4 bar overhead pressure, volumetric IPA productivity of about 3 g/L/h). Additionally, the optimal growth conditions were earlier described by LanzaTech for the patented *Clostridium autoethanogenum* [160]. The main fermentation conditions are summarized in Table E-2.

Table E-2. The main gas fermentation conditions

Fermentation conditions	Units	Scenario 1a: 80% IPA & 10% Acetone	Scenario 1b: 90% IPA	Scenario 1c: 90% Acetone	Scenario 2: 80% IPA & 10% Acetone
CO volumetric mass transfer rate	g_{CO}/L/h	10	10	10	14.9
pH	-	6	6	6	6
T	°C	37	37	37	37
p_{Top}*	bar	1.40	1.40	1.40	1.40
p_{bottom}*	bar	3.84	3.84	3.84	3.84
$p_{Average}$*	bar	2.62	2.62	2.62	2.62
$H_{fermenter}$	m	25.0	25.0	25.0	25.0
pCO	bar	1.310	1.310	1.310	1.310
pH_2	bar	0.262	0.262	0.262	0.262
pCO_2	bar	0.524	0.524	0.524	0.524
C_{IPA}	g/L	20.0	21.5	-	32.6
$C_{Acetone}$	g/L	2.8	-	19.2	4.5
$C_{AceticAcid}$ (with recycle)	g/L	11.9	29.9	8.09	37.1

*Fermenter pressure

The IPA titer of the pilot process was not disclosed. Similarly, it was not reported whether the IPA titer was a performance-limiting factor [73].

Calculations of Gibbs energy (ΔG) for the process reactions

The catabolic and anabolic reactions ΔG values were corrected for the temperature (ΔG^{0T}) using the Helmholtz equation:

$$\frac{\Delta G^{0T}}{T} = \frac{\Delta G^{0}}{T_0} + \Delta G^{0}\left(\frac{1}{T} - \frac{1}{T_0}\right)$$

Furthermore, the Gibbs free energies of the reactions were corrected for the concentrations of the reaction components, including the pH [506].

For a reaction of $aA\ (g)\ +\ bB\ (aq)\ \rightarrow\ cC\ (aq) +\ dD\ (g)$ this gives:

$$\Delta G^{r} = \Delta G^{0T} + RTln\left(\frac{C_C^{c} \cdot P^{*d}_{D}}{P^{*a}_{A} \cdot C_B^{b}}\right)$$

Whereby, T is temperature (K), T_0 is standard temperature (298.15 K), R is ideal gas constant (8.314 J/mol/K), ΔG^0 is Gibbs free energy change at standard conditions (C = 1 M, T = 298.15 K), ΔG^r is Gibbs free energy at the biochemical reaction conditions.

The experimental values of Gibbs free energy of dissipation (ΔG_{Dis}) [506] were used for biomass. Moreover, since the Gibbs free energy of anabolic part of the reaction (ΔG_{An}) only depends on the nature of the electron donor and type of

conversion (anaerobic, aerobic, auto/heterotrophic, +/- reverse electron transfer) [506], no corrections were necessary to the experimental ΔG_{An} values in terms of T, pH and concentrations. Additionally, Gibbs free energy for maintenance (mG) only depends on the temperature and not on the type of electron donor or acceptor and was calculated from the following equation:

$$mG(T) = 4.5\ exp\left(\frac{-69000}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right)$$

The used values of Gibbs free energies of dissipation and maintenance are presented in Table E-3.

Table E-3. Values of Gibbs free energy of dissipation and maintenance

Quantitiy	**Units**	**Value**
ΔG_{Dis} (CO to Biomass)	kJ/mol_x	1105
ΔG_{Dis} (H_2 to Biomass)	kJ/mol_x	1061
mG (T = 310. 15 K)	$kJ/mol_x/h$	13.211

λ_{cat} and m_s present number of times catabolic reaction needs to run to create 1 mol_x [543] or provide energy required per mol_x per hour [542], respectively. Thereby, X is defined as the 1-C equivalent of dry biomass.

$$l_{Cat} = \frac{\Delta G_{An} + \Delta G_{Dis}}{-\Delta G_{Cat}}$$

$$m_s = \frac{mG}{-\Delta G_{Cat}}$$

The maximum biomass yield ($Y_{X/S}^{Met}$) was determined using the following equation [543]:

$$Y_{X/S}^{Met} = -\frac{1}{Y_S^{An} + l_{Cat} \cdot Y_S^{Cat}}$$

Theoretical Gibbs free energies and theoretical yields for CO and H_2 are presented in Table E-4 for IPA as the main product, in Table E-5 for acetone as the main product and in Table E-6 for a mixture of IPA and acetone as the main products. The energies are given in kJ/mol carbon source, whereby H_2 is electron donor and CO_2 is carbon source.

Table E-4. Thermodynamic variables and reaction yields per electron donor (CO or H_2) and the different products (isopropanol, acetic acid or biomass) for isopropanol as a main product ($Y_{IPA/CO}$ = 0.90 g_{IPA}/g_{CO}, with the rest going to biomass and acetic acid as by-products)

Electron donor		**CO**			**H_2**		
Product	Unit	IPA	Acetic Acid	Biomass	IPA	Acetic Acid	Biomass
ΔG^0	kJ/mol	-40.9	-43.7	-54.5	-20.9	-23.7	-12.5
ΔH^0	kJ/mol/K	-61.6	-64.8	-93.7	-64.4	-67.6	-99.5
ΔG^{0T}	kJ/mol	-40.1	-42.9	-52.9	-19.1	-22.0	-9.0
ΔG^r ($\Delta G_{cat}/\Delta G_{an}$)	kJ/mol	-42.1	-43.6	-63.4	-15.4	-16.9	-10.6
λ_{cat}	mol_s/mol_x	2.75	5.97	/	7.58	15.58	/
m_s	mol_s/mol_x	$3.48 \cdot 10^{-2}$	$7.58 \cdot 10^{-2}$	/	$9.54 \cdot 10^{-2}$	$1.96 \cdot 10^{-1}$	/
$Y_{x/s}^{Met}$	mol_x/mol_s	$3.73 \cdot 10^{-2}$	$3.58 \cdot 10^{-2}$	/	$1.42 \cdot 10^{-2}$	$1.55 \cdot 10^{-2}$	/

Table E-5. Thermodynamic variables and reaction yields per electron donor (CO or H_2) and the different products (isopropyl alcohol, acetic acid or biomass) for acetone as a main product ($Y_{Acetone/CO}$ = 0.90 g_{Ac}/g_{CO}, with the rest going to biomass and acetic acid as by-products)

Electron donor		**CO**			**H_2**		
Product	Unit	Acetone	Acetic Acid	Biomass	Acetone	Acetic Acid	Biomass
ΔG^0	kJ/mol	-40.3	-43.7	-54.5	-20.3	-23.7	-12.5
ΔH^0	kJ/mol/K	-56.0	-64.8	-93.7	-58.8	-67.6	-99.5
ΔG^{0T}	kJ/mol	-39.7	-42.9	-52.9	-18.8	-22.0	-9.0
ΔG^r (ΔG_{cat})	kJ/mol	-41.7	-43.6	-63.4	-15.0	-16.9	-10.6
λ_{cat}	mol_s/mol_x	3.12	5.97	/	8.77	15.58	/
m_s	mol_s/mol_x	$3.96 \cdot 10^{-2}$	$7.58 \cdot 10^{-2}$	/	$1.10 \cdot 10^{-1}$	$1.96 \cdot 10^{-1}$	/
$Y_{x/s}^{Met}$	mol_x/mol_s	$3.69 \cdot 10^{-2}$	$3.58 \cdot 10^{-2}$	/	$1.38 \cdot 10^{-2}$	$1.55 \cdot 10^{-2}$	/

Table E-6. Thermodynamic variables and reaction yields per electron donor (CO or H_2) and the different products (isopropanol, acetone, acetic acid or biomass) for isopropanol and acetone as a mixture of products ($Y_{IPA/CO}$ = 0.80 g_{IPA}/g_{CO}, $Y_{Acetone/CO}$ = 0.10 g_{Ac}/g_{CO}, with the rest going to biomass and acetic acid as by-products)

Electron donor		**CO**			
Product	Unit	IPA	Acetone	Acetic Acid	Biomass
ΔG^0	kJ/mol	-40.9	-40.3	-43.7	-54.5
ΔH^0	kJ/mol/K	-61.6	-56.0	-64.8	-93.7
ΔG^{0T}	kJ/mol	-40.1	-39.7	-42.9	-52.9
ΔG^r (ΔG_{cat})	kJ/mol	-42.1	-42.4	-43.6	-63.4
λ_{cat}	mol_s/mol_x	2.75	3.07	5.97	/
m_s	mol_s/mol_x	$3.48 \cdot 10^{-2}$	$3.89 \cdot 10^{-2}$	$7.58 \cdot 10^{-2}$	/
$Y_{x/s}^{Met}$	mol_x/mol_s	$3.73 \cdot 10^{-2}$	$3.75 \cdot 10^{-2}$	$3.58 \cdot 10^{-2}$	/
Electron donor		**H_2**			
Product	Unit	IPA	Acetone	Acetic Acid	Biomass
ΔG^0	kJ/mol	-20.9	-20.3	-23.7	-12.5
ΔH^0	kJ/mol/K	-64.4	-58.8	-67.6	-99.5
ΔG^{0T}	kJ/mol	-19.1	-18.8	-22.0	-9.0
ΔG^r (ΔG_{cat})	kJ/mol	-15.4	-15.7	-16.9	-10.6
λ_{cat}	mol_s/mol_x	7.58	8.37	15.58	/
m_s	mol_s/mol_x	$9.54 \cdot 10^{-2}$	$1.05 \cdot 10^{-1}$	$1.96 \cdot 10^{-1}$	/
$Y_{x/s}^{Met}$	mol_x/mol_s	$1.42 \cdot 10^{-2}$	$1.45 \cdot 10^{-2}$	$1.55 \cdot 10^{-2}$	/

Overall process reactions

Ratio of consumption between CO and H_2 in the gas fermentation was assumed to be linked to ratio of abundance in the gas lift reactor, thus CO:H_2 in a 5:1 ratio. Overall process reaction rates ($mol_i/mol_x/h$) were calculated for the 90% isopropanol selectivity, 90% acetone selectivity, and 80% isopropanol with 10% acetone selectivity. Formation of acetic acid and biomass as by-products was assumed and pH control was included (OH^-). The obtained reaction rates are summarized in Table E-7. Within the reported range of growth rates for the pilot scale process [164], the growth rate of 0.1 h^{-1} was selected. With 90% biomass retention/recycle, the effective biomass growth rate was 0.01 h^{-1}.

Table E-7. Overall process reactions ($mol_i/mol_x/h$)

Substance rate ($mol_i/mol_x/h$)	**Fermentation** 90% Isopropanol production	90% Acetone production	80% Isopropanol + 10% Acetone production
CO	-8.257	-7.331	-9.177
H_2	-1.651	-1.466	-1.835
Water	-2.561	-1.721	-2.796
Ammonium	$-3.056 \cdot 10^{-2}$	$-2.686 \cdot 10^{-2}$	$-3.398 \cdot 10^{-2}$
OH^-	-0.1725	-0.1530	-0.1515
Isopropanol	1.000	-	1.000
Acetone	-	1.000	0.1454
Acetic acid	$4.809 \cdot 10^{-3}$	$4.223 \cdot 10^{-3}$	$4.033 \cdot 10^{-3}$
$Acetate^-$	0.1419	0.1246	0.1190
Biomass	0.1528	0.1343	0.1699
CO_2	4.810	3.939	5.325

(+) is production, (-) is consumption

The following stoichiometric reactions were obtained:

90% Isopropanol selectivity

$$8.26\ CO + 1.65\ H_2 + 2.56\ H_2O + 3.1 \cdot 10^{-2} NH_4^+ + 0.17\ OH^- \rightarrow 1.00\ \mathbf{C_3H_8O}\ (IPA) + 0.14\ CH3COO^- + 4.8 \cdot 10^{-3}\ CH_3COOH + 0.15\ CH_{1.8}O_{0.5}N_{0.2}\ (Biomass) + 4.81\ CO_2$$

90% Acetone selectivity

$$7.33\ CO + 1.47\ H_2 + 1.72\ H_2O + 2.7 \cdot 10^{-2} NH_4^+ + 0.15\ OH^- \rightarrow 1.00\ \mathbf{C_3H_6O}\ (Acetone) + 0.12\ CH3COO^- + 4.2 \cdot 10^{-3}\ CH_3COOH + 0.13\ CH_{1.8}O_{0.5}N_{0.2}\ (Biomass) + 3.94\ CO_2$$

80% Isopropanol and 10% acetone selectivity

$$9.18\ CO + 1.84\ H_2 + 2.80\ H_2O + 3.4 \cdot 10^{-2} NH_4^+ + 0.15\ OH^- \rightarrow 1.00\ \mathbf{C_3H_8O}\ (IPA) + 0.15\ \mathbf{C_3H_6O}\ (Acetone) + 0.12\ CH3COO^- + 4.0 \cdot 10^{-3}\ CH_3COOH + 0.17\ CH_{1.8}O_{0.5}N_{0.2}\ (Biomass) + 5.32\ CO_2$$

2-Phenylethanol *de-novo* fermentation

Some kinetic data are available for strain IMX2179 [44,461], but only for batch and fed-batch operation. The initial oxygen uptake rate during batch fermentation [44] proceeded exponentially, and this was used to obtain an initial maximum specific growth rate $\mu_{0,max}$ = 0.17 h^{-1}. Later, the specific growth rate decreased. It was assumed that this was caused by inhibition due to increasing 2PE concentration c_p, and the following equation was used to describe this [165]:

$$\mu^{\max} = \mu_0^{\max}\left(1-\frac{c_p}{c_p^{crit,\mu}}\right)$$

For the critical 2PE concentration at which growth would stop, $c_p^{crit,\mu}$ = 2.5 g/L was used [44].

During batch production, biomass and 2PE seem to increase in a fixed ratio [461], from which the maximum specific production rate can be derived: q_p^{max}/μ^{max} = 0.12 mol_p/mol_x = 0.59 g_p/g_x, so $q_{p,0}^{max}$ = 0.020 $mol_p/(mol_x\ h)$. This implies that product formation was assumed to be inhibited similarly as growth.

Furthermore, the simulation of batch fermentation using the mass balances for biomass and 2PE only requires a value for the initial amount of inoculated biomass. Figure E-1 was obtained when using $c_{x,0}$ = 0.075 g_x/L, which shows a satisfactory correspondence with the literature data. Note that [461] calculated μ^{max} = 0.10 h^{-1} as an average value, whereas it ranges from 0.17 to 0.08 h^{-1} in Figure E-1.

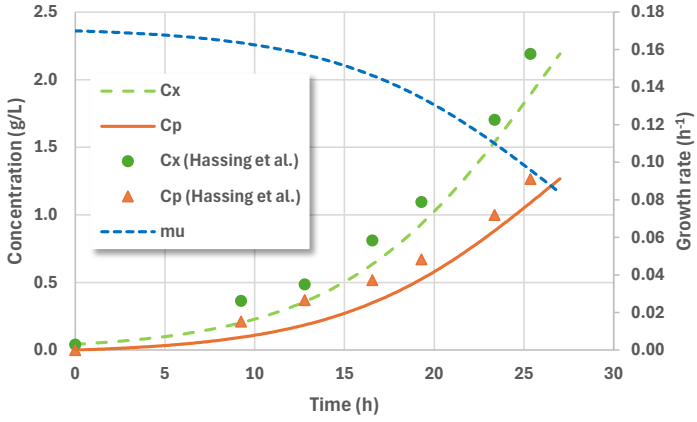


Figure E-1. Progress of batch fermentation according to model simulation as described in the text

For calculating the amount of glucose needed, the formation of side products was neglected, assuming these can be largely eliminated upon continued metabolic engineering and choosing optimized feeding conditions. Then, the specific substrate consumption rate $-q_s$ will depend on growth rate, product formation rate and maintenance rate m_s according to:

$$-q_s = \frac{\mu}{Y_{x/s}^{\max}} + \frac{q_p}{Y_{p/s}^{\max}} + m_s$$

Parameters $Y_{x/s}^{max}$ and $Y_{p/s}^{max}$ indicate how much substrate is used for biomass and for product, respectively.

During exponential growth in the batch before maintenance becomes significant, this equation is rewritten as:

$$-q_s^{\max} = \frac{\mu^{\max}}{Y_{x/s}^{\max}} + \frac{q_p^{\max}}{Y_{p/s}^{\max}} = \frac{\mu^{\max}}{Y_{x/s}^{\max}} + \frac{0.12\mu^{\max}}{Y_{p/s}^{\max}} = \left(\frac{1}{Y_{x/s}^{\max}} + \frac{0.12}{Y_{p/s}^{\max}}\right)\mu^{\max} = \frac{\mu^{\max}}{Y_{x/s}^{*}}$$

Here, $Y_{x/s}^{*}$ is a stochiometric parameter that may be constant under specific conditions. Literature data for the early batch glucose concentrations [461] was used and the amount used for ethanol production (half a mole of glucose per mole of ethanol) was added. Comparing with the 2PE concentrations led to $Y_{x/s}^{*}$ = 1.4 mol_x/mol_s, = 0.29 g_p/g_x. Then, a constant molar stoichiometry might be a reasonable approximation:

$$C_6H_{12}O_6 + 2.8500\ O_2 + 0.2800\ NH_3 \rightarrow 1.4000\ X + 3.2560\ CO_2 + 4.3200\ H_2O + 0.1680\ C_8H_{10}O$$

Thereby *X* stands for biomass, with the exact formula $CH_{1.8}O_{0.5}N_{0.2}$, as commonly used in bioprocess simulations [523]. Nonetheless, it should be noted that biomass needs to be defined as a *'non-conventional component*' in Aspen Plus. By default, it will have a molecular mass of 1 g/mol. To account for the real weight of biomass (~24.6 g/mol) and close mass balances, biomass is called X' in this convention and the previous stoichiometric reaction needs to be corrected as follows:

$$C_6H_{12}O_6 + 2.8500\ O_2 + 0.2800\ NH_3 \rightarrow \mathbf{34.4768}\ X' + 3.2560\ CO_2 + 4.3200\ H_2O + 0.1680\ C_8H_{10}O$$

If inhibition by 2PE is kept modest, the concentration of unconsumed glucose leaving the steady state during ISPR will probably be low [165]. This implies that the glucose feed concentration will be converted approximately to the biomass concentration according to the coefficients in the stoichiometric equation.

The volume-specific rate ($r_i = q_i \cdot c_x$ mol/(L h)) at which this reaction occurs depends on the concentration of 2PE (which can be controlled by ISPR) and on the concentration of biomass. The latter can be controlled by the substrate feed concentration as mentioned, but can become even larger if cell retention is used. Constraints are the feasible 2PE mass transfer rate, the feasible oxygen transfer rate, and the feasible biomass concentration.

Appendix F – Isopropanol and acetone production by gas fermentation

Section 5.1 presents a flowsheet of scenario 1a as a representative one for isopropanol and acetone production by gas fermentation. However, three additional scenarios were developed: **Scenario 1b** – production of isopropanol assuming CO mass transfer rate of 10 g/(L h), **Scenario 1c** – production of acetone assuming CO mass transfer rate of 10 g/(L h) and **Scenario 2** – production of isopropanol and acetone assuming CO mass transfer rate of 14.9 g/(L h). Hence, this Appendix contains flowsheets, along with mass and energy balances, of isopropanol and/or acetone production by gas fermentation via scenarios 1b, 1c and 2.

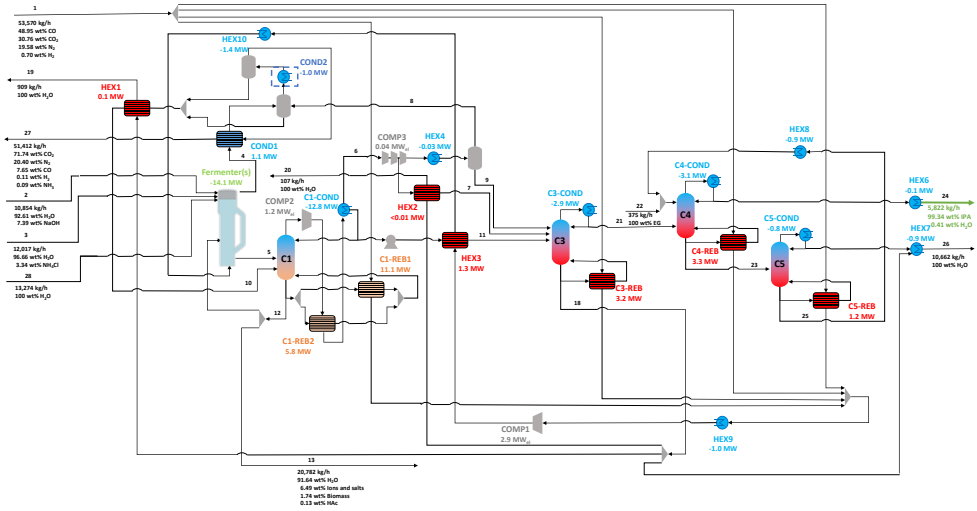


Figure F-1. Flowsheet of the developed process for isopropanol prodcution by gas fermentation in scenario 1b

Table F-1. Condition and composition of the main streams from Figure F-1 (isopropanol production by gas fermentation, scenario 1b)

Stream	1	2	3	4	5	6
Temperature (˚C)	1,100	20.0	34.8	37.0	37.0	13.5
Pressure (bar)	1.013	1.103	1.400	1.400	1.400	0.048
Flowrate (kg/h)	53,570	10,854	12,017	52,732	224,015	533
Mass fractions						
Water	/	0.9261	0.9666	0.0216	0.8881	0.1407
Isopropanol	/	/	/	0.0077	0.0240	0.4187
CO	0.4895	/	/	0.0746	<0.0001	0.0013
CO_2	0.3076	/	/	0.6957	0.0009	0.3920
H_2	0.0070	/	/	0.0011	<0.0001	<0.0001
N_2	0.1958	/	/	0.1989	<0.0001	0.0025
NH_3	/	/	/	0.0004	0.0002	0.0448

Stream	**1**	**2**	**3**	**4**	**5**	**6**
NaOH	/	0.0739	/	/	/	/
NH_4Cl	/	/	0.0334	/	/	/
Ions and salts	/	/	/	/	0.0704	/
Biomass	/	/	/	/	0.0162	/
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	71.2	10.0	10.0	37.0	85.3	36.9
Pressure (bar)	1.200	1.300	1.300	1.300	1.200	0.059
Flowrate (kg/h)	215	239	65	1,559	17,223	207,818
Mass fractions						
Water	0.2540	0.0031	0.1616	0.7308	0.6759	0.9064
Isopropanol	0.7422	0.0216	0.8266	0.2608	0.3234	/
CO	<0.0001	0.0028	<0.0001	<0.0001	<0.0001	/
CO_2	0.0014	0.8706	0.0071	0.0075	<0.0001	/
H_2	<0.0001	<0.0001	<0.0001	<0.0001	/	/
N_2	<0.0001	0.0057	<0.0001	<0.0001	/	/
NH_3	0.0024	0.0962	0.0047	0.0005	0.0007	/
Acetic acid	/	/	/	0.0004	<0.0001	0.0013
Ions and salts	/	/	/	/	/	0.0649
Biomass	/	/	/	/	/	0.0174
Stream	**13**	**18**	**19**	**20**	**21**	**22**
Temperature (˚C)	36.4	105.6	30.2	53.8	74.0	75.0
Pressure (bar)	0.059	1.232	1.232	1.232	1.000	1.200
Flowrate (kg/h)	20,782	10,694	909	107	6,809	375
Water	0.9064	1	1	1	0.1485	/
Isopropanol	/	/	/	/	0.8494	/
Acetic acid	0.0013	/	/	/	/	/
Ethylene glycol	/	/	/	/	/	1
Ions and salts	0.0649	/	/	/	/	/
Biomass	0.0174	/	/	/	/	/
Stream	**23**	**24**	**25**	**26**	**27**	**28**
Temperature (˚C)	148.5	30.0	202.3	30.0	32.0	30.0
Pressure (bar)	1.504	1.000	1.232	1.000	1.300	1.400
Flowrate (kg/h)	8,478	5,822	7,495	10,066	51,412	13,804
Mass fractions						
Water	0.1164	0.0041	/	0.9999	/	1
Isopropanol	<0.0001	0.9934	/	/	/	/
CO	/	/	/	/	0.0765	/
CO_2	/	/	/	/	0.7174	/
H_2	/	/	/	/	0.0011	/
N_2	/	/	/	/	0.2040	/
NH_3	/	/	/	/	0.0011	/
Ethylene glycol	0.8836	/	1	0.0001	/	/

Table F-2. Design parameters of distillation columns from Figure F-1 (isopropanol production by gas fermentation in scenario 1b)

Distillation column	C1	C3	C4	C5
Number of stages	48	30	64	30
Feed stage	32 (broth) 20 (condensed off-gas)	20 (from C1) 9 (from COMP2) 5 (from flash unit)	8 (ethylene glycol) 40 (86% isopropanol)	10
Top pressure (bar)	0.048	1.000	1.000	1.00
Bottom pressure (bar)	0.059	1.232	1.504	1.232
Top temperature (°C)	13.5	73.9	46.9	99.6
Bottom temperature (°C)	36.4	105.6	148.5	202.3
Reboiler duty (MW)	17.0	2.9	3.1	1.2
Condenser duty (MW)	-17.4	-2.9	-2.5	-0.8
Reflux ratio (mass basis)	0.82	0.67	1.45	0.32
Distillate-to-feed ratio (mass basis)	0.08	0.389	0.855	0.116
Column diameter (m)	4.0	1.2	1.3	0.7

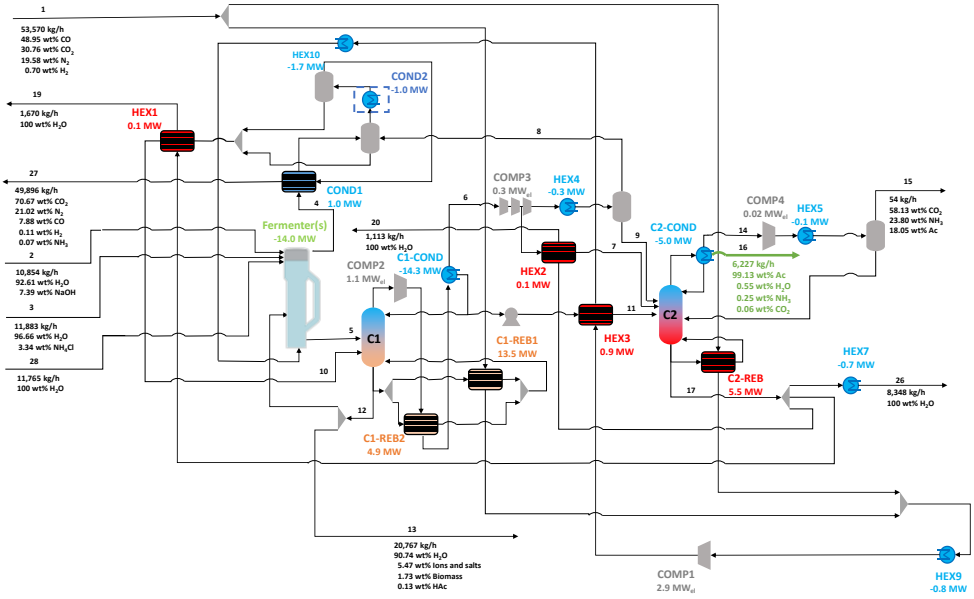


Figure F-2. Flowsheet of the developed process for acetone prodcution by gas fermentation in scenario 1c

Table F-3. Condition and composition of the main streams from Figure F-2 (isopropanol and acetone production by gas fermentation, scenario 1c)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	1,100	20.0	34.8	37.0	37.0	11.0
Pressure (bar)	1.013	1.103	1.400	1.400	1.400	0.048
Flowrate (kg/h)	53,570	10,854	11,883	51,947	223,031	4,969
Mass fractions						
Water	/	0.9261	0.9666	0.0216	0.8899	0.1027
Acetone	/	/	/	0.0234	0.0228	0.8284
CO	0.4895	/	/	0.0757	<0.0001	0.0002
CO_2	0.3076	/	/	0.6758	0.0009	0.0597
H_2	0.0070	/	/	0.0011	<0.0001	<0.0001
N_2	0.1958	/	/	0.2019	<0.0001	0.0003
NH_3	/	/	/	0.0005	0.0002	0.0088
NaOH	/	0.0739	/	/	/	/
NH_4Cl	/	/	0.0334	/	/	/
Ions and salts	/	/	/	/	0.0699	/
Biomass	/	/	/	/	0.0161	/
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	59.2	10.0	10.0	37.0	78.4	36.3
Pressure (bar)	1.200	1.300	1.300	1.300	1.200	0.059
Flowrate (kg/h)	3,087	336	1,547	2,386	12,778	207,671
Mass fractions						
Water	0.1503	0.0011	0.0298	0.4704	0.8338	0.9074
Acetone	0.8458	0.1560	0.9394	0.4816	0.1659	/
CO	<0.0001	0.0023	<0.0001	<0.0001	<0.0001	/
CO_2	0.0010	0.7803	0.0204	0.0436	<0.0001	/
H_2	<0.0001	<0.0001	<0.0001	<0.0001	/	/
N_2	<0.0001	0.0042	<0.0001	<0.0001	/	/
NH_3	0.0028	0.0560	0.0104	0.0041	0.0003	/
Acetic acid	/	/	/	0.0002	<0.0001	0.0013
Ions and salts	/	/	/	/	/	0.0740
Biomass	/	/	/	/	/	0.0173
Stream	**13**	**14**	**15**	**16**	**17**	**26**
Temperature (˚C)	36.3	48.6	25.0	48.6	107.4	30.0
Pressure (bar)	0.059	1.000	3.000	1.000	1.312	1.312
Flowrate (kg/h)	20,767	692	54	6,227	11,130	8,348
Mass fractions						
Water	0.9074	0.0033	0.0002	0.0055	1	1
Acetone	/	0.8814	0.1805	0.9914	/	/
CO	/	<0.0001	<0.0001	<0.0001	/	/
CO_2	/	0.0627	0.5813	0.0006	/	/
H_2	/	<0.0001	<0.0001	<0.0001	/	/
N_2	/	<0.0001	<0.0001	<0.0001	/	/
NH_3	/	0.0526	0.2380	0.0025	/	/
Acetic acid	0.0013	/	/	/	/	/
Ions and salts	0.0740	/	/	/	/	/
Biomass	0.0173	/	/	/	/	/

Stream	**27**
Temperature (˚C)	32.0
Pressure (bar)	1.300
Flowrate (kg/h)	49,896
Mass fractions	
Water	<0.0001
Acetone	0.0024
CO	0.0788
CO_2	0.7067
H_2	0.0011
N_2	0.2102
NH_3	0.0007

Table F-4. Design parameters of distillation columns from Figure F-2 (acetone production by gas fermentation in scenario 1c)

Distillation column	**C1**	**C2**
Number of stages	48	40
Feed stage	32 (broth) 20 (condensed off-gas)	20 (from C1) 10 (from COMP2) 9 and 10 (from flash units)
Top pressure (bar)	0.048	1.000
Bottom pressure (bar)	0.059	1.312
Top temperature (°C)	11.0	48.6
Bottom temperature (°C)	36.4	107.4
Reboiler duty (MW)	18.4	5.5
Condenser duty (MW)	-17.7	-5.0
Reflux ratio (mass basis)	0.9	4.0
Distillate-to-feed ratio (mass basis)	0.08	1.02 (acetone as feed basis)
Column diameter (m)	4.1	1.9

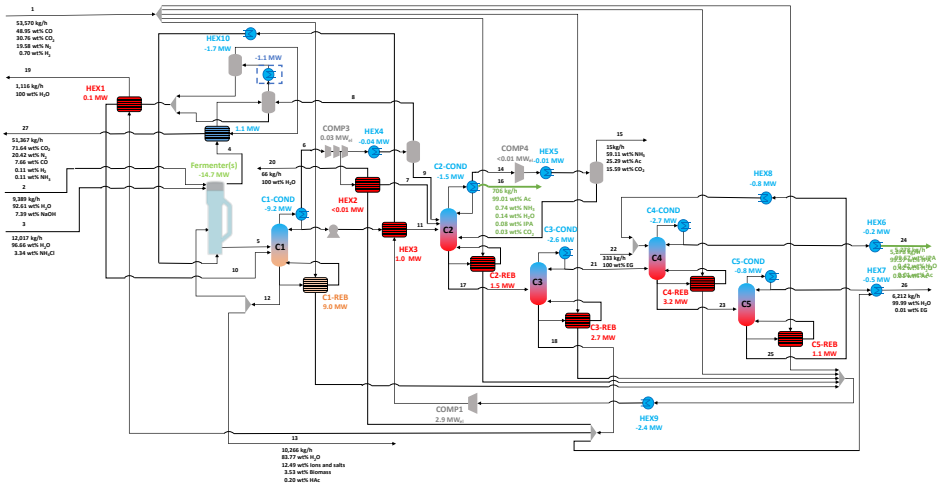


Figure F-3. Flowsheet of the developed process for isopropanol and acetone prodcution by gas fermentation in scenario 2

Table F-5. Condition and composition of the main streams from Figure F-3 (isopropanol and acetone production by gas fermentation, scenario 2)

Stream	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (˚C)	1,100	20.0	34.8	37.0	37.0	8.9
Pressure (bar)	1.013	1.103	1.400	1.400	1.400	0.048
Flowrate (kg/h)	53,570	9,389	12,017	53,185	114,179	405
Mass fractions						
Water	/	0.9261	0.9666	0.0208	0.8084	0.0911
Isopropanol	/	/	/	0.0118	0.0401	0.3060
Acetone	/	/	/	0.0044	0.0044	0.2355
CO	0.4895	/	/	0.0739	<0.0001	0.0009
CO_2	0.3076	/	/	0.6900	0.0009	0.3154
H_2	0.0070	/	/	0.0011	<0.0001	<0.0001
N_2	0.1958	/	/	0.1972	<0.0001	0.0019
NH_3	/	/	/	0.0008	0.0002	0.0491
NaOH	/	0.0739	/	/	/	/
NH_4Cl	/	/	0.0334	/	/	/
Ions and salts	/	/	/	/	0.1141	/
Biomass	/	/	/	/	0.0317	/
Stream	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (˚C)	65.6	10.0	10.0	37.0	81.8	36.9
Pressure (bar)	1.200	1.300	1.300	1.300	1.200	0.059
Flowrate (kg/h)	132	163	109	1,981	13,099	102,655
Mass fractions						
Water	0.2140	0.0017	0.0761	0.5585	0.5633	0.8377
Isopropanol	0.6141	0.0129	0.3709	0.3157	0.3881	/
Acetone	0.1662	0.1032	0.5164	0.1106	0.0477	/
CO	<0.0001	0.0022	<0.0001	<0.0001	<0.0001	/

Stream	**7**	**8**	**9**	**10**	**11**	**12**
CO_2	<0.0001	0.7730	<0.0001	0.0134	<0.0001	/
H_2	<0.0001	<0.0001	<0.0001	<0.0001	/	/
N_2	<0.0001	0.0047	<0.0001	<0.0001	/	/
NH_3	0.0044	0.1023	0.0238	0.0014	0.0008	/
Acetic acid	/	/	/	0.0004	<0.0001	0.0020
Ions and salts	/	/	/	/	/	0.1249
Biomass	/	/	/	/	/	0.0353
Stream	**13**	**14**	**15**	**16**	**17**	**18**
Temperature (˚C)	36.9	40.2	25.0	40.2	88.3	105.6
Pressure (bar)	0.059	1.000	3.000	1.000	1.312	1.232
Flowrate (kg/h)	10,266	78	15	706	12,620	6,563
Mass fractions						
Water	0.8377	0.0007	/	0.0014	0.5875	1
Isopropanol	/	0.0003	/	0.0008	0.4125	/
Acetone	/	0.7992	0.2529	0.9901	<0.0001	/
CO	/	<0.0001	/	/	/	/
CO_2	/	0.0328	0.1559	0.0003	/	/
H_2	/	<0.0001	/	/	/	/
N_2	/	<0.0001	/	/	/	/
NH_3	/	0.1669	0.5911	0.0074	/	/
Acetic acid	0.0020	/	/	/	/	/
Ions and salts	0.1249	/	/	/	/	/
Biomass	0.0353	/	/	/	/	/
Stream	**19**	**20**	**21**	**22**	**23**	**24**
Temperature (˚C)	24.4	42.8	79.9	75.0	149.8	30.0
Pressure (bar)	1.232	1.232	1.000	1.200	1.504	1.000
Flowrate (kg/h)	1,116	66	6,058	333	7,496	5,278
Mass fractions						
Water	1	1	0.1406	/	0.1107	0.0042
Isopropanol	/	/	0.8593	/	<0.0001	0.9957
Acetone	/	/	<0.0001	/	/	0.0001
Ethylene glycol	/	/	/	1	0.8893	/

Stream	**25**	**26**	**27**
Temperature (˚C)	202.9	30.0	32.0
Pressure (bar)	1.232	1.000	1.300
Flowrate (kg/h)	6,666	6,212	51,367
Mass fractions			
Water	/	0.9999	/
CO	/	/	0.0766
CO_2	/	/	0.7164
H_2	/	/	0.0011
N_2	/	/	0.2042
NH_3	/	/	0.0011
Ethylene glycol	1	0.0001	/

Table F-6. Design parameters of distillation columns from Figure F-3 (isopropanol and acetone production by gas fermentation in scenario 2)

Distillation column	**C1**	**C2**	**C3**	**C4**	**C5**
Number of stages	48	40	30	64	30
Feed stage	32 (broth) 20 (condensed off-gas)	20 (from C1) 19 (from COMP2) 14 and 19 (from flash units)	20	8 (ethylene glycol) 40 (86% isopropanol)	10
Top pressure (bar)	0.048	1.000	1.000	1.000	1.00
Bottom pressure (bar)	0.059	1.312	1.232	1.504	1.232
Top temperature (°C)	8.9	55.9	79.9	81.8	99.6
Bottom temperature (°C)	37.0	88.7	105.6	149.8	202.9
Reboiler duty (MW)	9.0	4.0	2.7	3.2	1.1
Condenser duty (MW)	-9.2	-4.0	-2.5	-2.7	-0.7
Reflux ratio (mass basis)	0.4	11.5	0.7	1.8	0.4
Distillate-to-feed ratio (mass basis)	0.12	1.213 (acetone as feed basis)	0.48	0.863	0.111
Column diameter (m)	3.0	1.0	1.1	1.3	0.7

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Ја осећам много више но и што могу да кажем. Стога Вас молим да јачину мојих осећања не мерите по слабости мојих речи. (Никола Тесла, пионир инжењерства електротехнике, најпознатији по свом доприносу у пројектовању модерног система напајања наизменичном струјом)

I feel much more than I can express. Therefore, I ask you not to measure the strength of my feelings by the weakness of my words. (Nikola Tesla, pioneer of electrical engineering, known for his contributions to the design of modern alternating current electricity supply system)

As my PhD journey draws to an end, I find myself facing the most challenging chapter to write. Not due to the lack of inspiration, but because finding the right words to express my gratitude was not a simple task. Like life itself, a PhD is not a solitary journey. Many people have contributed, directly or indirectly, to the completion of this thesis. My intention is to extend my heartfelt thanks to all of these incredible people who have supported me throughout this journey. If I happen to unintentionally overlook anyone, I offer my sincerest apologies.

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List of publications

Journal papers

1. T. Janković, T. Fecker, JM. Daran, A.J.J. Straathof, A.A. Kiss, Advanced process design for large-scale *de-novo* 2-phenylethanol production via fermentation, Journal of Chemical Technology and Biotechnology, in press.
2. T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream process design for recovery of 2-phenylethanol and 2-phenylethyl acetate after biotransformation, Journal of Chemical Technology and Biotechnology, in press. https://doi.org/10.1002/jctb.70027
3. T. Janković, A.J.J. Straathof, S. Sharma, A.A. Kiss, Eco-efficient recovery of non-volatile products from fermentation broth: Aliphatic diols, Journal of Chemical Technology and Biotechnology, in press.
4. A.J.J. Straathof, T. Janković, A.A. Kiss, Distillation for *in-situ* recovery of volatile fermentation products, Trends in Biotechnology. 43 (2025) 1540-1549. https://doi.org/10.1016/j.tibtech.2024.12.009
5. T. Janković, S. Sharma, A.J.J. Straathof, A.A. Kiss, Adaptable downstream processing design for recovery of butanediols after fermentation, Chemical Engineering Research and Design. 213 (2025) 210-220. https://doi.org/10.1016/j.cherd.2024.12.011
6. T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream processing for sustainable ethyl acetate production by fermentation, AIChE Journal. e18684 (2025) 1-18. https://doi.org/10.1002/aic.18684
7. T. Janković, A.J.J. Straathof, A.A. Kiss, Eco-efficient downstream processing of 1,3-propanediol applicable to various fermentation broths, Process Biochemistry. 143 (2024) 210-224. https://doi.org/10.1016/j.procbio.2024.04.040
8. T. Janković, A.J.J. Straathof, A.A. Kiss, Adaptable heat pump-assisted dividing-wall column design for intensified downstream processing of bio-propionic acid, Separation and Purification Technology. 350 (2024) 127832. https://doi.org/10.1016/j.seppur.2024.127832
9. T. Janković, A.J.J. Straathof, A.A. Kiss, Thermally self-sufficient heat pump-assisted azeotropic dividing-wall column for biofuels recovery from isopropanol-butanol-ethanol fermentation, Chemical Engineering and Processing – Process Intensification. 197 (2024) 109689. https://doi.org/10.1016/j.cep.2024.109689
10. T. Janković, A.J.J. Straathof, I.R. McGregor, A.A. Kiss, Bioethanol separation by a new pass-through distillation process, Separation and Purification Technology. 336 (2024) 126292. https://doi.org/10.1016/j.seppur.2024.126292

11. T. Janković, A.J.J. Straathof, A.A. Kiss, Enhanced isobutanol recovery from fermentation broth for sustainable biofuels production, Energy Conversion and Management X. 21 (2024) 100520. https://doi.org/10.1016/j.ecmx.2023.100520
12. T. Janković, A.J.J. Straathof, A.A. Kiss, A perspective on downstream processing performance for recovery of bioalcohols, Journal of Chemical Technology and Biotechnology. 99 (2023) 1933-1940. https://doi.org/10.1002/jctb.7690
13. T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced purification of isopropanol and acetone from syngas fermentation, Journal of Chemical Technology and Biotechnology. 99 (2023) 714-726. https://doi.org/10.1002/jctb.7576
14. T. Janković, A.J.J. Straathof, A.A. Kiss, Process systems engineering perspectives on eco-efficient downstream processing of volatile biochemicals from fermentation, Frontiers in Energy Research. 11 (2024) 1340612. https://doi.org/10.3389/fenrg.2023.1340612
15. T. Janković, A.J.J. Straathof, A.A. Kiss, Turning waste into value: eco-efficient recovery of by-products from biomass pretreatment in lignocellulosic biorefineries, Biofuels, Bioproducts and Biorefining. 17 (2023) 1654-1667. https://doi.org/10.1002/bbb.2532
16. T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced processing of bioethanol from syngas fermentation, Separation and Purification Technology. 322 (2023) 124320. https://doi.org/10.1016/j.seppur.2023.124320

Conference proceedings

1. Tamara Janković, Siddhant Sharma, Adrie J. J. Straathof, Anton A. Kiss, Adaptable dividing-wall column design for intensified purification of butanediols after fermentation. Systems & Control Transactions. 4 (2025) 2284-2290. https://doi.org/10.69997/sct.155564
2. Gijs A.A. Brouwer, Tamara Janković, Adrie J. J. Straathof, Anton A. Kiss, John A. Posada, Sustainable industrial-scale plant design for syngas fermentation of isopropyl alcohol to acetone: Economic and environmental sustainability assessment. Systems & Control Transactions. 4 (2025) 473-478 https://doi.org/10.69997/sct.167278
3. T. Janković, A.J.J. Straathof, I.R. McGregor, A.A. Kiss, Design of a novel pass-through distillation process for bioethanol recovery, Computer Aided Chemical Engineering. 53 (2024) 2443-2448. https://doi.org/10.1016/B978-0-443-28824-1.50408-7
4. T. Janković, A.J.J. Straathof, A.A. Kiss, Enhanced hot-liquid water pretreatment of biomass with recovery and valorization of side products.

Computer Aided Chemical Engineering. 52 (2023) 2111-2116. https://doi.org/10.1016/B978-0-443-15274-0.50336-X

Magazine articles

1. T. Janković, A.J.J. Straathof, I.R. McGregor, A.A. Kiss, Pass-through distillation for concurrent alcohol recovery and fermentation, NPT Procestechnologie. 2401 (2024) 21-27.

Submitted for publication

1. G.J.A. Brouwer, T. Janković, J.A. Posada, A.J.J. Straathof, A.A. Kiss, Thermally self-sufficient process for sustainable production of isopropanol and acetone via syngas fermentation

Conference participation

1. 15th European Congress of Chemical Engineering (ECCE) & 8th European Congress of Applied Biotechnology (ECAB), 8-10 September 2025, Lisbon, Portugal
   Tamara Janković, Adrie J. J. Straathof, Anton A. Kiss, Techno-economic and sustainability assessment of purification processes for recovery of fermentation products.
2. European Symposium on Computer Aided Process Engineering, ESCAPE35 Conference, 6-9 July 2025, Ghent, Belgium
   Tamara Janković, Siddhant Sharma, Adrie J. J. Straathof, Anton A. Kiss, Adaptable dividing-wall column design for intensified purification of butanediols after fermentation.
3. European Symposium on Computer Aided Process Engineering, ESCAPE35 Conference, 6-9 July 2025, Ghent, Belgium
   Gijs A.A. Brouwer, Tamara Janković, Adrie J. J. Straathof, Anton A. Kiss, John A. Posada, Sustainable industrial-scale plant design for syngas fermentation of isopropyl alcohol to acetone: Economic and environmental sustainability assessment.
4. Biobased Future Conference, 16-18 June 2025, Belgrade, Serbia
   Tamara Janković, Adrie J. J. Straathof, Anton A. Kiss, Advanced distillation-based purification processes for effective recovery of fermentation products

5. CLIB International Conference CIC2025, 18-19 February 2025, Düsseldorf, Germany
   T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced distillation-based purification processes for effective recovery of fermentation products.
6. Netherlands Process Technology Symposium, NPS19, 8-9 October 2024, Groningen, The Netherlands
   T. Janković, A.J.J. Straathof, A.A. Kiss, Advanced downstream processing for recovery of bioalcohols from fermentation broths.
7. European Congress of Biotechnology, ECB2024, 30 June – 3 July 2024, Rotterdam, The Netherlands
   T. Janković, A.J.J. Straathof, A.A. Kiss, Eco-efficient downstream processing of isopropanol and acetone from syngas fermentation.
8. European Symposium on Computer Aided Process Engineering & 15th International Symposium on Process Systems Engineering, ESCAPE34&PSE2024, 2-6 June, Florence, Italy.
   T. Janković, A.J.J. Straathof, I.R. McGregor, A.A. Kiss, Design of a novel pass-through distillation process for bioethanol recovery.
9. Himmelfahrtstagung on Bioprocess Engineering 2024 – Novel Strategies and Technologies for Sustainable Bioprocess and Bioproducts, BioPro-2024, 6-8 May 2024, Regensburg, Germany
   A.J.J. Straathof, T. Janković, A.A. Kiss, Energy-efficient volatile bioproduct purification with cell retention by involving vacuum distillation or stripping.
10. Carbon Recycling Network – 4th Annual Conference, CRN-2024, 25-27 March 2024, Macclesfield, UK
    A.J.J. Straathof, M.P. Elisiaro, W. van Hecke, H. de Wever, H. Noorman, T. Janković, A.A. Kiss, Integration of syngas fermentation and ethanol recovery
11. 14th European Congress of Chemical Engineering, ECCE14, 17-21 September 2023, Berlin, Germany
    T.Janković, A.J.J. Straathof, A.A. Kiss, Eco-efficient recovery of valuable by-products from hot-liquid water pretreatment of biomass.
12. Computer-Aided Process Engineering Forum. CAPE Forum 2023, 6-8 September 2023, Porto, Portugal
    T. Janković, A.J.J. Straathof, A.A. Kiss, Enhanced recovery of bioethanol from syngas fermentation.
13. Netherlands Process Technology Symposium, NPS18,6-7 July 2023, University of Twente, Enschede, The Netherlands
    T. Janković, A.J.J. Straathof, A.A. Kiss, Eco-friendly recovery of valuable by-products for enhancing hot-liquid water pretreatment of biomass.

14. AIChE – Process Development Symposium Europe, PDS-EU, 26-28 June 2023, Frankfurt am Main, Germany
    T. Janković, A.J.J. Straathof, A.A. Kiss, Novel process for valuable by-products recovery from hot-liquid water pretreatment of biomass,
15. European Symposium on Computer Aided Process Engineering, ESCAPE33, 18-21 June 2023, Athens, Greece
    T. Janković, A.J.J. Straathof, A.A. Kiss, Enhanced hot-liquid water pretreatment of biomass with recovery and valorization of side products.

Curriculum vitae



Tamara Janković was born on February 3, 1999, in Vancouver, Canada. During her early education, she excelled in numerous state-level competitions in subjects such as mathematics, chemistry, biology, and literature. Notable achievements include the 2013 October Award for outstanding cultural contributions (for a mosaic inspired by Borislav Pekić's novels), a state award in chemistry in 2016, and the prestigious Vuk's Award for exceptional academic achievements in 2017.

In 2017, she began her undergraduate studies in Chemical Process Engineering at the University of Belgrade. She completed her bachelor's degree in 2021 with a thesis titled *"Kinetic model and determination of rate constants for the enzymatically catalysed synthesis of fructo-oligosaccharides from sucrose,"* supervised by Professor Nikola Nikačević. She continued with a master's degree in the same field, further advancing her research through a thesis entitled *"Development of a Kinetic Model and Optimization of a Continuous Intensified Reactor for the Production of Prebiotics."* Throughout her studies, Tamara was awarded a state scholarship for gifted students and was recognized as the best student of her generation by the faculty. She also received the Gordana Jakčić Kašiković and Dragiša Kašiković award for the best female student from technical universities at the University of Belgrade.

In September 2022, she began her PhD research at Delft University of Technology under the supervision of Professors Anton Kiss and Adrie Straathof. Her research focused on developing advanced recovery processes for the *"Eco-efficient downstream processing of fermentation products by intensified distillation processes."*

In April 2025, Tamara joined Corbion as a Process Specialist in Downstream Processing.

