

Bioprocess intensification

Cases that (don't) work

van der Wielen, Luuk A.M.; Mussatto, Solange I.; van Breugel, Jan

DOI

[10.1016/j.nbt.2020.11.007](https://doi.org/10.1016/j.nbt.2020.11.007)

Publication date

2021

Document Version

Final published version

Published in

New Biotechnology

Citation (APA)

van der Wielen, L. A. M., Mussatto, S. I., & van Breugel, J. (2021). Bioprocess intensification: Cases that (don't) work. *New Biotechnology*, 61, 108-115. <https://doi.org/10.1016/j.nbt.2020.11.007>

Important note

To cite this publication, please use the final published version (if applicable). Please check the document version above.

Copyright

Other than for strictly personal use, it is not permitted to download, forward or distribute the text or part of it, without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license such as Creative Commons.

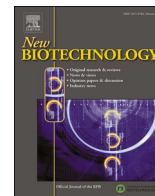
Takedown policy

Please contact us and provide details if you believe this document breaches copyrights. We will remove access to the work immediately and investigate your claim.



Contents lists available at ScienceDirect

New BIOTECHNOLOGY

journal homepage: www.elsevier.com/locate/nbt

Full length Article

Bioprocess intensification: Cases that (don't) work

Luuk A.M. van der Wielen^{a,b,*}, Solange I. Mussatto^c, Jan van Breugel^d^a Bernal Institute, University of Limerick, Ireland^b Department of Biotechnology, Delft University of Technology, the Netherlands^c Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Kemitorvet, Building 220, 2800, Kongens Lyngby, Denmark^d BioBased Innovation (BBI), previously CTO Corbion, the Netherlands

ARTICLE INFO

Keywords:

Techno-Economic assessment
Thermodynamic analysis
Integrated biobased manufacturing
Bioprocess intensification

ABSTRACT

Development of affordable and low carbon biobased manufacturing depends critically on strategies that reduce cost and emission profiles. This paper indicates that efforts around the reduction of capital costs by intensification of process equipment need to be carefully weighed against the inherently fast increasing financial and climate costs of driving forces used for the intensification. The fundamental relation between capital expenditures (CAPEX) and operational expenditures (OPEX) of intensified and non-intensified biobased processes and their financial and climatic impacts are emphasized and provisionally explored for a few industrial processes. General learnings flag the importance in particular of OPEX minimisation for sustainable bio-economic development.

1. Introduction

Biobased manufacturing is an indispensable pillar of sustainable 'green' economic development, in combination with wind and solar renewable energy and with increased circularity of carbon and other (nitrogen) streams. Significant challenges exist to enhance material utilisation from renewable feedstocks, often with high oxygen content (biomass, sugars, municipal solid waste, waste industry gases such as CO₂ and CO), in an industrial landscape that is designed to optimise hydrocarbon yields from fossil feedstocks of coal, crude oil and natural gas. Improving product(s) yield on feedstock is critical and directly correlated to optimising economic impacts and revenues and lowering operational expenditures (OPEX), as well as to reduction of emissions and waste streams. Profitability and environmental footprint are thereby strongly related, ideally synergistically.

A second group of challenges is related to the current situation in which feedstock and conversion technology are essentially developed around feedstocks with a high water content or dissolved in aqueous streams. Whether (clean) water is a main or byproduct, volumes are

large and the components to be converted are relatively dilute. There is a significant need to intensify and integrate the associated process equipment to control the capital expenditures (CAPEX).

Process Intensification [1] (PI) is "commonly seen as one of the most promising development paths for the chemical process industry and one of the most important progress areas for modern chemical engineering". In their publication in 2009, Gerven and Stankiewicz reviewed the PI field, and summarised this into a generic approach across principles of time and length scales, thermodynamic conditions and potential synergy (process integration aspects) as is shown in Fig. 1. These observations were further extended in [2]. In that case, integration of unit operations, such as *in situ* product recovery in bioreactors or cell retention systems, represents a specific class of process intensification, with complex design rules [3]. Those ideas were also elaborated in [4–6] for bioprocesses, and provided a range of useful insights into design rules for industrial scale bioprocesses. In all cases, the attention of PI efforts was significantly focused on maximising driving forces (Δ) to increase (intensify) conversion and transport rates (R) in order to reduce scales, volumes (V) and thus CAPEX of such processes. (Fig. 1, Fig. 2).

Abbreviations: a , specific mass transfer area per unit; A , membrane area; k , mass transfer coefficient; N , transmembrane flux; R , rate of flow; V , volume; W^* , (thermodynamic) work per unit of time; W_{lost}^* , lost work; W_{min}^* , minimum work requirement; Δ , driving force; Δc , difference in composition across the interface; ΔP , pressure difference across the membrane; $\Delta \pi$, difference in osmotic pressures across the membrane; φ_v , permeate volumetric flowrate; φ_m , mass flowrate; κ , proportionality constant; π , osmotic pressure of the retentate; ρ , fluid density; AUX, auxiliary materials or resources; CAPEX, capital expenditures; EBIDTA, Earnings Before Interest, Taxes, Depreciation, and Amortization; IRR, internal rate of return; NPV, nett present value; OPEX, operational expenditures; PBT, pay back time; PI, process intensification; RoI, return on investment.

* Corresponding author at: Department of Biotechnology, Delft University of Technology, Van der Maasweg 9, 2629 HZ Delft, the Netherlands.

E-mail address: L.A.M.vanderWielen@tudelft.nl (L.A.M. van der Wielen).

<https://doi.org/10.1016/j.nbt.2020.11.007>

Received 28 July 2020; Received in revised form 9 November 2020; Accepted 11 November 2020

Available online 19 November 2020

1871-6784/© 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

While CAPEX-related expenditures are critical components in process design choices, they are not the only ones. In our experience, an integral approach is necessary to optimise the full economic and climate potential of biobased manufacturing. (Bio) process integration is defined as the collection of measures maximising financial and climate impacts of manufacturing plants, balancing equipment related approaches such as in (bio)process intensification with those on yields and use of auxiliaries. Hence, in this article, we place (bio)PI in a broader context of (bio)process integration by exploring the following questions:

- 1 Is maximising rates and thus driving forces a generally beneficial concept or are there inherent and fundamental restrictions to this orientation of PI, especially for biobased manufacturing?
- 2 Yields of product from feedstocks are central in economic models as well as in environmental footprint. Is the general focus of (bio)PI on rate and driving force maximisation the right trend, (even) if the basic yields of product are equal in intensified and non-intensified situations?
- 3 True challenges in biobased manufacturing are especially with competitiveness of commodity products such as energy carriers (fuels) and base chemicals, their energy yields from feedstock in a system/environment, given the non-equal playing field with fossil alternatives. Can PI be expected to be a large/sole contributor to solving this issue or is integration with other/additional strategies desirable or even necessary?
- 4 Conventional biorefineries are generally developed around one or two central products (ethanol or sugar & ethanol, pulp & paper, starch, vegetable oils) with residues labelled as 'waste', often used to cover the plant's energy requirements. An integrated strategy to convert all feedstocks into marketable products [7] is likely to improve the economics and environmental footprint of the operation, but how does it relate to PI strategies with their enhanced energy requirements?

From our experiences with a range of projects at the interface of academic bioprocess engineering research and education, and industry implementation and commercialisation, we have started to explore these questions. The following is meant to start a broader effort supported by a number of ongoing projects.

2. Is maximising rates and driving forces good guidance?

Maximising rates in and between process equipment is generally seen as the core embodiment of PI, by lowering equipment volume and

Driving forces and Process Economics

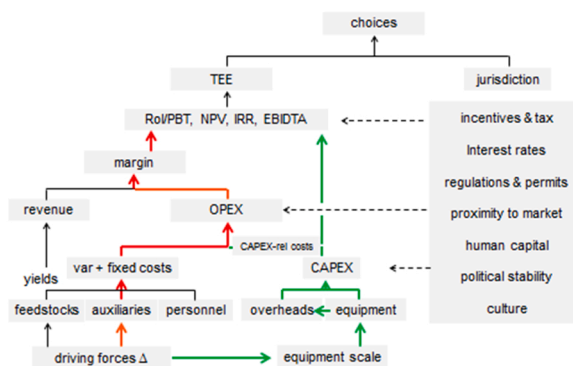


Fig. 2. Schematic overview of the relation between process economics and societal aspects in investment decision making in biobased manufacturing. Coloured lines indicate the impact of process intensification of CAPEX (green) and auxiliaries (red) on economics of intensified processes.

thus the associated capital costs. 'Rates' can be mass or molar (flow) rates, which can be translated using density into volumetric (flow) rates. In the following text, 'rates' (R) are used in a generic manner, specifying when necessary and using other variables and parameters in consistent units.

Depending on the type of process, the driving forces (Δ) can be related to gradients in concentration or composition, pressure, temperature, electrical potential for charged species, or other force fields represented by a certain potential gradient (gravity, centrifugal, magnetic, etc.) and a combination thereof. There are several excellent textbooks on the generalisation for multicomponent mass transfer under multiple driving forces such as [8,9]. The former still represents one of the most straightforward engineering approaches to transfer under multiple driving forces in multicomponent systems, relating driving force and sum of gradients in those potentials in terms of their equivalent Gibbs free energy contributions. The generalised Maxwell-Stefan model is effectively a force balance, equating sum of applicable driving forces and combined friction due to velocity differences between the diffusing species. This allows a straightforward approach to combining multiple driving forces due to gradients in composition (activity), electrical potential, pressure related energy and centrifugal force, among others. Similar approaches have been proposed for (bio)chemical conversion

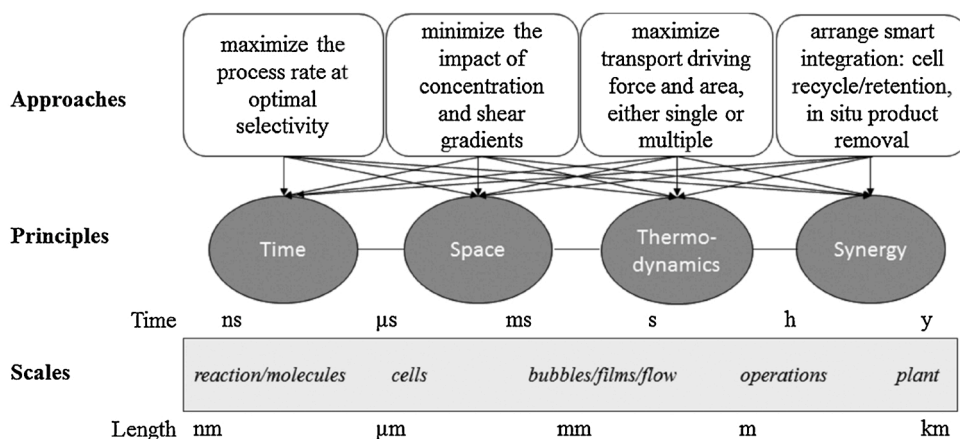


Fig. 1. The links of 4 main PI approaches and 4 main PI principles, in a multi-scale framework (from [5]).

and microbial growth such as [10–14]. The driving force is also in these cases related via irreversible thermodynamics to gradients in molar Gibbs energy or chemical potential.

Adopting the general essential structure of the relation between (mass transfer or reaction) rate and applicable driving force(s), we arrive at the following, oversimplified mathematical relation:

$$R = \kappa \Delta \quad (1)$$

with κ being a proportionality constant in consistent units, relating increase in driving force Δ to increase in rate R . As an example, for processing mass flow rate φ_m in a contactor with volume V , limited by mass transfer of a single species through a mass transfer interface under dilute conditions in a fluid described by linear driving force model, we obtain:

$$\varphi_m = a V k \Delta c \quad (2)$$

with a being the specific mass transfer area per unit volume and k being the mass transfer coefficient. For a biphasic system, k is the overall mass transfer coefficient, and Δc is the difference in composition across the interface, corrected for the distribution of the transferring species at equilibrium. In column type contactors, location dependency leads to (sets of coupled) differential equations, but the concept remains the same.

The above is an oversimplification that breaks down especially with non-linear and coupled systems and those with extremely high driving forces [8,12], but generally applies at low to medium driving forces and uncoupled systems. Volumes V of process equipment reduce when conversion and transport rates increase. So in the above example

$$V = \varphi_m / (a k \Delta c) \quad (3)$$

Intensification in these examples can be achieved by increased power input by mixing (stirred tanks) or flow rate (column contactors) enlarging the specific area for mass transfer and mass transfer coefficient, by increasing composition differences (concentrated feedstocks and *in situ* product removal), or by affecting thermodynamic and kinetic conditions by using new structured materials for conversion and separation. Specific area a and mass transfer k correlate to fluid flow characteristics (Sherwood relations), but variations for a specific technology are generally modest under practical conditions.

Values for k can be estimated using the applicable mass transfer correlations, which are functions of fluid (flow) conditions ($Sh \sim Re^p$ with power p being 0.3 laminar flow ... 0.6 for packed columns ... 0.8 for turbulent systems) and fluid properties (especially mixture viscosities). For LL and GL multiphase systems, increased fluid flow intensification also increases interfacial area for mass transfer, but in practice these are restricted by loading and flooding limits and practical phenomena such as emulsification and foaming. We realise this is a bold statement, requiring further evidence to verify potential for PI including those limits. They are practically constant in porous matrices (resins, adsorbents, membranes for separation and porous catalysts for conversion), unless these allow for convective flow such as monolithic and other structures [15].

CAPEX for an industrial plant is composed of fixed and working capital for the operation plus the (fraction of) R&D and start-up costs of the facility. Fixed capital is generally estimated on the basis of purchase costs (PC) of equipment and a number of overhead factors accounting for applicable piping, electrical, instrumentation, buildings and yard works, auxiliary facilities, engineering and construction [16]. The overhead factors are generally estimated as the cumulated fraction or Lang factor of PC. The Lang factor ranges from 4 to 5 for large scale commodity plants to approximately 8–9 for (bio) pharmaceutical or other specialty plants. Given the common use of the Lang factor and comparable methods, the simplification is adopted here that CAPEX is generally proportional to equipment sizes and thus reciprocally with driving forces Δ .

Scale factors often apply for volume-based equipment such as bioreactors, distillation, extraction and adsorption equipment. Scale effects are generally represented with a power law relationship:

$$\frac{CAPEX_1}{CAPEX_0} = \left(\frac{V_1}{V_0}\right)^n \quad (4)$$

with n ranging from 0.6 for volume based equipment. For rate based equipment such as membranes and chromatography, but also heat exchangers, n is closer to unity. The subscripts 0 refer respectively to the reference situation and 1 to the intensified, scaled-down version. Hence the capital expenditures of intensified processes, relative to a benchmark scale (0) relate as:

$$\frac{CAPEX_1}{CAPEX_0} = 1 / \left(\frac{\Delta_1}{\Delta_0}\right)^n \quad (5)$$

where Δ_0 relates to the driving force in the original, non-intensified benchmark situation, and Δ_1 to the scaled-down, intensified process. Note that in terms of driving force dependencies, Eq. (5) indicates that increased driving forces are generally less effective for systems with scale effects, than for systems without scale effects.

3. Bringing OPEX to the stage

An important assumption in PI is constant operational expenditures of intensified manufacturing processes that do not relate to CAPEX, when conversion and processing yields are approximately constant. In analysing this critical assumption, reference is made back to the conversion and transport rates R . Again, it is stated that those rates R are essentially proportional to the acting driving force(s) Δ , following Eq. 1.

A common and critical assumption is that the thermodynamic efficiency of the driving force remains comparable to the non-intensified reference or benchmark case. Below, it is shown that this assumption is fundamentally incorrect. This is in practical terms independent of its nature – whether related to composition, pressure, temperature, electrical or other nature. Common irreversible thermodynamics of open systems [17,18] relates the associated (thermodynamic) work per unit of time (\dot{W}) of the driving force acting on a flow with rate R multiplied with the size of the driving force Δ

$$W = R \Delta. \quad (6)$$

As an example, see the Bernoulli relation or mechanical energy balance where (mechanical) work per unit of time for pressure driven processes equals volumetric flowrate times pressure difference, in the absence of differences in potential and kinetic energy. Analogously, the electrical equivalent indicates that electrical power required for a current I through a resistance under an electrical potential difference is also the product of that current and the electrical potential difference.

There is a minimum amount of work per unit of time \dot{W}_{min} , which for separation processes is given by the differences in Gibbs energy of product flows and feedstocks as shown by [19]. For separation processes that require specific flow structures, such as countercurrent vapour and liquid flows in distillation, additional net work due to irreversibilities is required to create such a dissipative structure [19,21]. The work for systems with energy intensive phase changes is approximately one order of magnitude larger than \dot{W}_{min} [19] and is effectively lost (\dot{W}_{lost}).

Again, it is known that the (flow) rate R is proportional to the applicable driving force. Hence the power (work per unit of time) related to the process with driving force Δ , now reads as:

$$\dot{W} = \kappa \Delta^2 \quad (7)$$

This has an unfortunate and generic consequence, namely that the work per unit of time necessary for such (intensified) processes is proportional to the square of the driving force. Assuming that the useful part is proportional to the flow (rate), the excess part that is lost is a strongly

increasing function of the degree of process intensification. This is work that generally cannot be recovered in a useful form, as it is often converted into low temperature (low value) heat. It can also be represented as an undesirable dilution of products or indirectly by regeneration of auxiliary flows such as solvents, sorbents, resins and, in particular processes, water.

This notion has been developed in a generic way as exergy analysis, which refers to the remaining useful work that a flow can exert in a particular reference environment [20]. Exergy analysis was originally developed for thermal operations, but can straightforwardly be generalised to include non-thermal operations [21], broadening its relevance for biobased manufacturing in [22]. Exergy analysis as a fundamental thermodynamic efficiency method complements Life Cycle Assessment (LCA) methods, that focus on broader environmental and nowadays also societal impacts [23].

As a result, the variable fraction of OPEX that relates to production capacity is strongly impacted by this fundamental efficiency, even if production yields and capacity itself are approximately constant. The variable fraction of OPEX relates to the background of the specific driving force, which are auxiliary energy flows such as electrical power, heat, steam, etc., or to auxiliary material flows such as solvents, adsorbent or ion exchange materials, etc. with energy demanding regeneration cycles. This unfortunate, inherent situation has a dual negative effect, namely on strong increases of the associated operational costs, as well as on increased carbon and other emissions (which also further increase costs of waste handling).

The variable, auxiliaries fraction (AUX) of the OPEX of intensified processes has to cover both useful and lost parts of the work in terms of steam, electricity, auxiliary materials or other cost factors. AUX is proportional to \dot{W} and thus to the square of the driving force(s) on the process. Part is inevitable (\dot{W}_{min}) and part is the price to pay for the intensification (\dot{W}_{lost}). So comparing the variable, auxiliaries fraction of the intensified situation AUX_1 , to that of the non-intensified, benchmark situation AUX_0 , we obtain

$$\frac{AUX_1}{AUX_0} = \left(\frac{\Delta_1}{\Delta_0}\right)^2 \quad (8)$$

For investment decisions, both AUX and CAPEX related fractions of OPEX matter. They are essentially related to economic indicators such as Return on Investment (RoI), Payback Time (PBT), and to Nett Present Value (NPV). For keeping oversight, the present work is restricted to simple economic indicators such as RoI and PBT.

The fundamental challenge of PI – not often emphasized – can be illustrated by showing the interdependencies of the degree of intensification on all parameters and key performance indicators (KPIs) of intensified process, as in the scheme below (Fig. 2). Our observation based on a range of process design studies is that the overall effect of reduced CAPEX (shown as green lines) is seriously challenged by significant increases in the auxiliaries-related contribution to the OPEX (red lines). Moreover, the environmental footprint will also increase significantly due to direct use of auxiliaries or indirectly due to their recycling. Increased climate awareness, stricter environmental regulations, and investors' preference for 'green investments', will emphasize control of the AUX-component of OPEX – more and more in the future.

The generic principle is illustrated graphically by plotting the CAPEX ratio for the intensified and benchmark cases versus the ratio of applicable driving forces (Fig. 3). The resulting figure also indicates the ratio of the auxiliaries' contribution to the OPEX (AUX) for the process intensified and benchmark cases versus the ratio of respective driving forces. Note that the horizontal axis with ratio of driving forces is logarithmic. In the practice of industrial processes, these ratios of driving forces vary less: halving or doubling is a more common range. Fig. 3 is indicative: for actual processes, minimum work and restrictions to (minimum) driving force need to be taken into account, as well as the intensification strategy: lowering CAPEX for a fixed productivity or

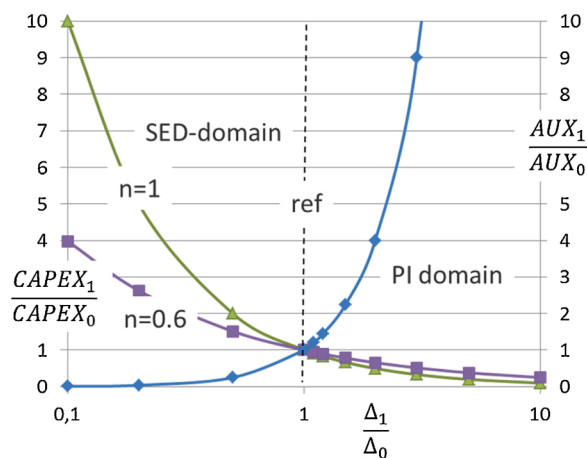


Fig. 3. Indicative impact of degree of process intensification on CAPEX and the auxiliaries' fraction in OPEX.

optimising productivity for fixed CAPEX.

The right-hand side of the dotted line in the plot is the PI domain. Here the linear reduction in CAPEX with increasing driving force can be challenged severely by fast rising costs of auxiliaries and the increased environmental footprint of the process. The left-hand side of this figure shows low driving force situations and thus operating closer to thermodynamic equilibrium with significantly reduced auxiliaries requirements and consequently lower OPEX and emission profiles. This strategy, which can be called sustainable (bio) economic development (SED), is obviously at the expense of (increased) CAPEX, and the net impact will be a compromise.

Some indications for the current balance of auxiliaries and CAPEX related contributions to OPEX are shown in Table 1, derived from Petrides [24] and Efe et al. [27]. Both contributions to OPEX are of a comparable size, and both reduce when the scale of manufacturing increases from specialties of a few metric tonnes per year to commodity products in the 10 s to 100 s kilotons per year. Here raw materials costs dominate and yields on feedstock are central cost drivers.

Use of auxiliaries in biobased manufacturing can contribute as much as 40 % of OPEX for biopharmaceutical and specialties manufacturing [24–26]. This is generally in the form of chemical consumables, resin replacements and other auxiliary material costs. In commodity products, auxiliaries amount to approximately 15–25 % in [24,27]. In the case of commodity products, such as ethanol, butanol and organic acids, costs of auxiliaries can be both in the form of *out-of-battery-limit* utility costs such as purchased electricity, steam and heat, or as CAPEX-related costs allocated to the energy systems of the plant such as cogeneration and boiler installations. The associated energy flows are used directly for the main products (by evaporation, distillation, compressing, mixing, etc) or indirectly for the recycling and regeneration of auxiliaries materials as adsorbents, ion exchange resins, solvents and process water.

4. Sustainable (bio) economic development (SED)

With the increased urgency for more SED by governments and society in general, and stimulated by the introduction of carbon taxes and legal emissions restrictions, the balance will shift to using less auxiliaries and consequently to lower driving forces. For existing technologies, this implies that higher CAPEX should be seen in this light and guide PI principles of increased driving forces. This clear societal trend will also favour new and emerging technologies with inherently lower auxiliary materials and energy use.

Additionally, the SED trend will also emphasize 'sustainable CAPEX'.

Table 1

Key numbers for selected biobased processes. Data from [24] unless indicated otherwise.

OPEX contribution kta – kton/yr	Mab		Insulin		Citric acid		Ethanol [27]	
	M\$/yr	%	M\$/yr	%	M\$/yr	%	M\$/yr	%
Raw materials		12.9		27.3		40.9		61.7
CAPEX related		46.7		24.1		28.7		144
Labor (other fixed)		14.6		7.3		8.3		10.6
Auxiliaries (AUX)		22.2		39.5		21.2		13.3
Total OPEX	130		110		22.2		102	
Revenue	179		180		25.6		145	
CAPEX (in M\$)	477		178		43.6		255	
Main product(s)	1544	kg/yr	1800	kg/yr	183	Kta	166 370	kta ETOH kta sugar

With that, it is implied that process equipment that is more durable can be modified and upgraded for new uses, and can be recycled in new and future plants. This will also lead to increased interest in ‘brown field’ developments, the partial or entire redevelopment of existing industrial sites for alternative uses. Clear examples are the various biorefinery initiatives with enhanced utilisation of residual streams, such as black liquor in pulp & paper, bagasse in the cane sugar and ethanol industry, and palm biomass in palm oil refineries. Here existing utilities can be used and expanded for processes that improve overall yield from feedstocks, reduced emissions and thus improved sustainability.

5. Contributions of CAPEX and AUX to OPEX in practise

As further evidence of our general observation to prioritise total OPEX reduction over PI’s central attention for CAPEX reduction, 2 concrete industrial cases of increasing complexity are presented. They relate to:

- concentrating aqueous product streams using membrane technology, such as ultrafiltration of proteins and nanofiltration/reversed osmosis of small molecules.
- production of cane ethanol and sugar in conventional Brazilian plants [27] and a hypothetical intensified ‘Biostil’ process in an identical environment and the same feedstock. In the ‘Biostil’ process, the inhibitory product ethanol is continuously and *in situ* removed, recycling the producing yeast to the fermenters operating at a close-to zero growth situation. The case includes a hypothetical 2nd generation extension of the existing (brown field) facility. This will improve the yield of products and feedstock utilisation, and reduce emissions.

5.1. Concentrating aqueous product streams using membrane technology

Membrane technology has widespread use in concentrating aqueous products in the manufacture of biotechnology products, food and potable water, as well as cell recycling. A majority of processes is pressure driven, with molecular thermodynamic properties of the components and membrane determining efficiency.

The CAPEX of the membrane process is to a large extent determined by the purchased membrane area A , including installed vessels, pipes and pump(s). Using a simple flux model for transmembrane flux N [8]:

$$N = k (\Delta P - \Delta\pi) \text{ and } \varphi_v = \frac{\varphi_m}{\rho} = A k (\Delta P - \Delta\pi) \quad (9)$$

with φ_v being permeate volumetric flowrate, φ_m the mass flowrate and ρ the fluid density. The pressure difference across the membrane (ΔP) is counteracted by the difference in osmotic pressures ($\Delta\pi$) across the membrane, effectively lowering the driving force. Assuming a nearly pure aqueous permeate, the nett driving force equals the actual pressure difference minus the osmotic pressure of the retentate (π). Thus the actual pressure difference must exceed the osmotic pressure of the

retentate to obtain any relevant flux. Membrane area is reduced with increasing driving force. With CAPEX being proportional to the installed membrane area A , we obtain:

$$\text{CAPEX} \sim A = \frac{\varphi_v}{N} = \frac{\varphi_m/\rho}{k (\Delta P - \pi)} \quad (10)$$

OPEX is determined by the pressure-related energy consumption, which equals the work exerted by pressure on the permeating liquid. The related work per unit of time can be calculated using the Bernoulli equation. A minimum amount of work has to be performed in relation to the osmotic pressure (compare to minimum reflux ratio in distillation), and the rest of the work is dissipated (‘lost’) to increase the rate of permeation. Therefore it is insightful to split the total pressure related shaft work of the pump into the minimum useful work for separating these flows (at zero flux) and the lost work to accelerate the process. Here we assume that total shaft work is available for the process. Using the Bernoulli equation for constant kinetic and potential energy:

$$\dot{W}_s = \varphi_m \int_1^2 \frac{dp}{\rho} = \varphi_m \left(\pi + (\Delta P - \pi) \right) = \dot{W}_{min} + \dot{W}_{lost} \quad (11)$$

The osmotic pressure of protein solutions can be as high as 2.5–5 bar, while for reversed osmosis of small molecules, osmotic pressures can be several tens of bars up to 100 bar in brines. Operating pressures need to exceed this value, so there is a minimum work requirement \dot{W}_{min} to create a system that is ‘ready to operate’ (comparable to complete reflux in distillation). The excess work beyond the minimum determines the rate of permeation or the level of process intensification, and is lost during permeation (*i.e.* converted in low temperature heat).

$$\dot{W}_{min} = A k (\Delta P - \pi)\pi \text{ and } \dot{W}_{lost} = A k (\Delta P - \pi)^2 \quad (12)$$

The lost work is the energetic price to pay for intensification. The lost work depends strongly on permeation rate and thus on the nett pressure difference. The higher the level of process intensification, the higher is the lost work. This becomes critical for modern reversed osmosis membranes that can operate at pressures as high as 250 bar, where electrical pumping energy costs can become excessive. Even though membrane separations can operate at lower energy costs per unit of product than concentrating techniques that rely on phase change (with inherently high heats of evaporation), large scale purification of potable water from sea of brackish water is still favoured by multi-effect evaporation.

The case is analyzed for enlarged productivity by intensified driving force $\Delta_1 = (\Delta p_1 - \pi)$ for a fixed membrane area. Fig. 4 shows the ratio of CAPEX per unit product (CAPEX/φ_v) for intensified (1) and benchmark (0) situations *versus* the ratio in nett driving forces Δ_1/Δ_2 , as well as the ratios of minimum and lost work *versus* the same. The ratio in driving forces for ultrafiltration of protein solutions is based on a representative osmotic pressure of 2.5 bar and a working range of actual pressures of up to 25 bar, and for reversed osmosis on an osmotic pressure of 25 bar (seawater) and a working pressure range up to 250 bar, which is the

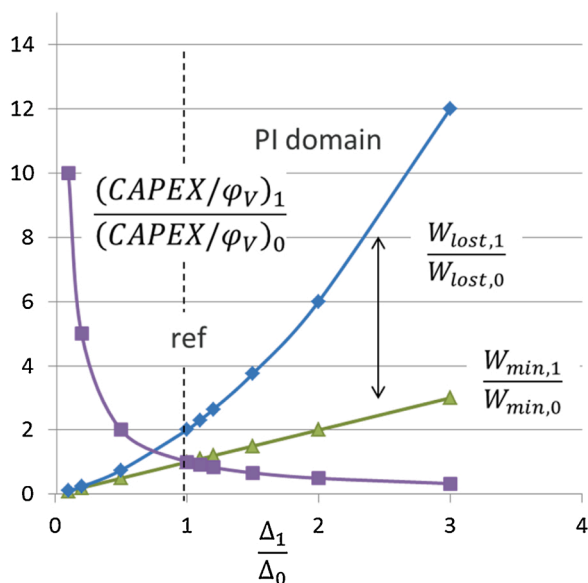


Fig. 4. Impact of degree of process intensification as ratio of driving forces on CAPEX, and minimum and lost work in OPEX for pressure driven membrane concentration processes.

practical maximum for modern industrial units. The reference or benchmark cases are at operating pressures of 10 and 100 bar respectively. This scales the ratio of nett driving forces from 0 to 3.

Again we see that the PI domain shows excessive lost work relative to the minimum useful work, and thus high OPEX. The ratio of CAPEX per unit product is reciprocal to the driving force ratio, offsetting reduction in capital expenditures against fast growing operational expenditures. The operational optimum obviously depends on exact cost numbers, but our observation is supported by the specific example of membrane based concentration processes.

5.2. Ethanol case: comparing conventional, intensified and lignocellulosic plants

The general principle as illustrated in Fig. 3 applies to many industrial scale processes. Here the specific case is illustrated of ethanol and sugar manufacturing from sugar cane as described by [27].

5.2.1. Conventional plant

The 2005 benchmark process of 5 million tonnes of sugar cane is a typical commercial scale ethanol and sugar plant. The process design and associated techno-economic evaluation is elaborated in significant detail. They were verified with the Brazilian sugar and ethanol industry players and follow common protocols accepted in the international chemical and fuels industries. The base case considers ethanol and sugar manufacturing while selling excess electrical power to the grid.

5.2.2. Lignocellulosics plant

The report also includes a process design following the same approach for a so-called ‘bolt-on’ lignocellulosic facility using sugar cane bagasse as a 2nd generation feedstock, projected 10 years into the then-future (2015). The design bears many similarities with the actually implemented [28] GranBio lignocellulosic ethanol plant in Lagoas, Brazil, as well as with the corn stover based facility of [29] DSM POET in Emmetsburg (USA), both launched around 2015. Published data and investments confirm those anticipated in the study of [27]. The 2015 facility follows, in the reasoning of this study, the path of process

integration utilising factory-based residuals of the original benchmark plant, with further steps in energy integration taken. Note that significantly less bagasse is combusted, and CAPEX of the cogeneration unit is halved.

5.2.3. ‘Biostil’ plant

In parallel, the economic and emission numbers are estimated of a hypothetical process intensified plant, that follows the so-called ‘Biostil’ [30,31] concept. Here ethanol as an inhibitory fermentation product is removed *in situ* by distillation from the fermentation broth, after the microbial biomass has been separated and recycled to the fermentors. The central fermentors effectively operate at a lower ethanol concentration, hence with less inhibitory effect, increasing ethanol production rate and thus lowering the fermentor volume and CAPEX.

There are more projected benefits of the Biostil concept, such as closed process water loop by feeding concentrated molasses or starch to the facility, operation at high substrate concentrations and therefore reduced (halved) stillage volume. The closed water cycle actually also leads to a build-up of contaminants in the feedstock, especially those that are not volatile such as salts and solids. This results in a high osmotic pressure that is partially inhibitory to the production organism (yeast) and potentially leads to undesired formation of glycerol as byproduct, but also effectively prevents bacterial contamination. In terms of overall performance, the intensified ‘Biostil’ version of the process can now be compared to the 2005 Conventional Plant and the 2015 Lignocellulosic base case. In reality, ‘Biostil’ has been explored for the Brazilian ethanol sector but does not seem to have led to successful implementations. We are not aware of actual commercial plants operating on a sugar cane feedstock.

For all relevant details, as well as ASPEN (Advanced System for Process Engineering) and SuperProDesign based calculations and underlying assumptions, reference should be made to the original report [27]. In Table 2, a summary of a number of key technical and economic numbers for the 3 plant designs is presented.

5.3. Comparing base case, intensified case and lignocellulosic plants

It is realised that only the benchmark (2005) plant is reasonably verified, and that the intensified and lignocellulosic versions are speculative. However, comparing those to literature reports of comparable (but not equal) commercial units, it is felt that the results in Table 2 give a reasonable first insight that supports our general view, developed on the basis of more simple cases.

The benchmark plant under 2005 conditions has a positive economic profile with a 17 % RoI. Actual CAPEX in Brazil are lower given the large scale at which ethanol plants have been constructed. The numbers in Table 2 are based on US and North European practices, and the translation (in 2005) has shown a location factor of approximately 40 %. However, since all CAPEX and OPEX models are based on US and EU references, they have been employed here. It shows the typical characteristics of commodity processes, such as a domination of the raw materials costs (60 %) of the OPEX. It should be recognised that the plant design includes inherently its own utilities, since power and steam production are based on the residues of the feedstock bagasse through the cogeneration unit.

The core processes are distinguished of the sugar cane conversion to main products sugar and ethanol and the utilities-related section of CAPEX which is close to half of the fixed capital cost. Hence, AUX includes the capital costs associated with the utilities (steam and power) while the rest of CAPEX is allocated to core process. Under this assumption, AUX is approximately 13 % of OPEX whereas the rest of CAPEX charges around 11 % of OPEX. Note that the CoGen (cogeneration) unit is significantly oversized due to the historic need to dispose of the enormous annual bagasse streams as residuals of the sugar extraction. It is now converted to sustainable electricity and sold to the grid, yielding a \$10 m revenue contribution.

Table 2

Scenario analysis of Cane Ethanol and Sugar co-production in Conventional Production (2005), Process Intensification through the Biostil concept, and full Lignocellulosic feedstock utilisation in a hypothetical 2015 Plant. From [28].

item	2005	"BioStil"	2015	unit
sugarcane	5000	5000	5000	kton/yr
EtOH	166	166	397	kton/yr
sugar	370	370	370	kton/yr
power to/from grid (MW)	346	173	−4,0	MW
power to/from grid (M\$/yr)	106	5,3	−1,2	M\$/yr
Revenue	1453	1400	2281	M\$/yr
OPEX	1016	1014	1425	M\$/yr
Margin	437	386	857	M\$/yr
RoI	171%	161%	258%	
Installed Equipment Costs in millions of dollars	IEC 2005 M\$	"BioStil" M \$	IEC 2015 M\$	
Cane Mills	9,5	9,5	9,5	
Clarification	6,6	6,6	7,4	
Evaporation	191	191	191	
Crystallisers	100	100	100	
Fermentors	106	7,0	246	
Distillation	9,9	6,5	160	
Pretreat/hydroly			272	
Cogen	490	490	209	
	1147	1077	1347	
Direct Fixed Capital	2215	2080	2883	
Work/start-up 15 %	332	312	432	
CAPEX	2547	2392	3315	
Operating Costs in millions of dollars /yr	IEC 2005 M \$/yr	"BioStil" M \$/yr	IEC 2015 M \$/yr	
Raw materials (sugar cane)	627	627	627	
Enzymes, other pretreatment			194	
Operating Materials	1,2	1,1	1,4	
Utilities (*)	0,6	1,2	2,3	
Waste handling (*)	0,8	1,6	3,6	
total variable costs	653	667	894	
FIXED (incl personnel)	7,2	7,2	148	
CAPEX Related (10 %)	255	239	332	
Gen Operating Costs	3,6	3,6	5,1	
OPEX	1016	1014	1425	
fraction AUX of OPEX	IEC 2005	"BioStil"	IEC 2015	
AUX (%)	133%	146%	8,7%	
AUX (M\$)	\$135	\$149	\$125	
VAR OpM+Util+Watse	\$2,6	\$4,0	\$7,3	
CAPEX-rel	\$109	\$109	\$5,1	

(*) estimated double for "biostil" given higher energy uses.

When translating the benchmark design to the intensified Biostil plant, the reported intensifications of reduced volumes of fermentation (due to lower ethanol inhibition) and stillage (use of concentrated feedstock and recycling of process water) were included. Halving of the volumes was assumed and translated with the appropriate scale factors to the reduced CAPEX. The price to pay is using part of the excess steam and electricity from the CoGen for the associated additional work: recycle flows as well as increased reboiler duties. This is at the expense of selling excess power to the electricity grid, so it is assumed that half of the additional energy demand was needed and consequently electricity revenue is halved. Also in the process intensified case, the lignocellulosic plant still has a power excess to be sold to the grid. Therefore in the final economic comparison, the altered revenue contributions are also taken into account. This results in a lower margin, even though CAPEX was also slightly reduced, resulting in a slight reduction of RoI for the intensified Biostil plant (16.1 %) relative to the benchmark plant (17 %). In conclusion, this form of PI does not work so well.

In the history of development of sugar cane ethanol (and sugar), inefficient combustion of bagasse was installed to dispose of the bagasse volumes. The CoGen unit helped to convert bagasse into a desired product, renewable electricity, that serves the growing Brazilian energy

demand. But through today's eyes, a conversion of the gate-delivered/preprocessed carbon source merits a better fate than conversion to renewable electricity, such as to renewable liquid fuels and chemical products [7,31]. The lignocellulosic plant (2015) is designed with the 2005 insights to convert part of the lignocellulosic feedstock into more valuable liquid biofuels such as ethanol and even purchase electricity from the grid confirms this viewpoint.

This implies additional investments in the associated pretreatment and hydrolysis infrastructure as well as scaling up ethanol production and purification. This also has an impact on the energy demand of the plant in terms of steam and power requirements. The 2015 design was made such that the steam requirements of the plant were covered, and the shortage of power was purchased from the grid. CAPEX related to Cogen unit was more than halved. At the price levels used (2005), this is shown to be economic. Obviously, CAPEX is significantly increased, but the design projects significantly improved margin and a 60 % higher RoI (25.8 %) relative to benchmark.

These results once more emphasize the need to focus on yield increase and reduction of auxiliaries in the OPEX, in addition to or even beyond process intensification options.

6. In conclusion

Process intensification offers opportunities to reduce capital costs in industrial plants. While this will provide interesting alternatives to today's practices, this trend underestimates the potential increases in operational costs. In a number of cases, it could be demonstrated that the increases in OPEX due to intensification outweigh the economic advantages of process intensification. A more fundamental analysis using irreversible thermodynamics indicates an inherent origin of the observation, and thus potentially a wider impact. If this is the case, a more OPEX-centric emphasis in support of a sustainable (bio)economic development is anticipated.

It is important to evidence these observations further, by means of additional and wider cases studies of industrial relevance, indicating in which cases the impacts of PI match the OPEX penalties. With a planet realising more and more the need to sustainable (bio) economic development, it is time for a holistic bioprocess integration methodology bundling together techno-economic and broader societal impacts, especially on environment.

Acknowledgements

The authors thank V.V. Ranade (Queens University Belfast, Northern Ireland), H. Noorman and W. van Winden (DSM), and J.J. Heijnen, M. Ottens and A.J.J. Straathof (Delft University of Technology, NL) for valuable discussions over the years that help shape the ideas presented in this paper.

This research did not receive any specific grant from funding agencies in the public, commercial and not-for-profit sectors.

References

- [1] van Gerven T, Stankiewicz A. Structure, Energy, Synergy, Time. The Fundamentals of Process Intensification. *Ind Eng Chem Res* 2009;48:2465–74. <https://doi.org/10.1021/ie801501y>.
- [2] Utkar RP, Ranade VV. Intensifying multiphase reactions and reactors: Strategies and examples. (2017). *ACS Sustain Chem Eng* 2017;5(5):3607–22. <https://doi.org/10.1021/acssuschemeng.7b01788>.
- [3] Oudshoorn A, van den Berg C, Roelands CPM, Straathof AJJ, van der Wielen LAM. Short-cut calculations for integrated product recovery options in fermentative production of bio-bulk chemicals. *Proc. Biochemistry* 2010;45:1605–15. <https://doi.org/10.1021/ie900537w>.
- [4] Cuellar MC, Heijnen J, van der Wielen LAM. Large-scale production of diesel-like biofuels – process design as an inherent part of microorganism development. *Biotech J* 2013;8(6):682–9. <https://doi.org/10.1002/biot.201200319>.
- [5] Noorman HJ, van Winden W, Heijnen JJ, van der Lans RGJM. Intensified fermentation processes and equipment. In: Gorak A, Stankiewicz A, editors. *Green chemistry series*; 2018. <https://doi.org/10.1039/9781010320-00001>. No 55.

- [6] Noorman HJ, Heijnen JJ. Biochemical engineering's grand adventure. *Chem Eng Sci* 2017;170:677–93. <https://doi.org/10.1016/j.ces.2016.12.065>.
- [7] Alves CM, Valk M, de Jong S, Bonomi A, van der Wielen LAM, Mussatto SI. Techno-economic assessment of biorefinery technologies for aviation biofuels supply chains in Brazil. *Biofuels Bioprod Biorefining* 2016. <https://doi.org/10.1002/bbb.1711>.
- [8] Wesselingh JA, Krishna R. Mass transfer in multicomponent mixtures. Delft University Press; 2000. Accessed 9-11-2020. <https://dare.uva.nl/search?identifier=72ac3734-b78a-41ca-941d-216e7706ffe2>.
- [9] Bird RB, Stewart WE, Lightfoot EN. Transport phenomena. 2 ed. Wiley; 2007. accessed 9-11-2020 https://www.academia.edu/37707900/Transport_Ph_enomena_Bird_Stewart_Lightfoot_Second_Edition_pdf.
- [10] Von Stockar U, Marison I, Janssen M, Patiño R. Calorimetry and thermodynamic aspects of heterotrophic, mixotrophic, and phototrophic growth. *J Therm Anal Calorim* 2011;104:45–52. <https://doi.org/10.1007/s10973-010-1278-7>.
- [11] Von Stockar U. Biothermodynamics of live cells: a tool for biotechnology and biochemical engineering. *J Non-equilibrium Thermodyn* 2010;35:4. <https://doi.org/10.1515/jnetdy.2010.024>.
- [12] Von Stockar U van der Wielen LAM. Thermodynamics in biochemical engineering. *J Biotechnol* 1997;59(1):25–37. [https://doi.org/10.1016/S0168-1656\(97\)00167-3](https://doi.org/10.1016/S0168-1656(97)00167-3).
- [13] Heijnen JJ, Van Dijken JP. In search of a thermodynamic description of biomass yields for the chemotrophic growth of microorganisms. *Biotechnol Bioengng* 1992; 39(8):833–58. <https://doi.org/10.1002/bit.260390806>.
- [14] Heijnen JJ. Impact of thermodynamic principles in systems biology. *Biosys Eng II* 2010;139–62. <https://doi.org/10.1007/978-3-642-13866-9>.
- [15] Coppens MO. Scaling-up and down in nature-inspired way. *Ind Eng Chem Res* 2005;44:5011–9. <https://doi.org/10.1021/ie0490482>.
- [16] Mussatto SI, Bikaki N. Techno-economic considerations for lignocellulosic biomass fractionation in a biorefinery context. In: Mussatto SI, editor. *Biomass fractionation technologies for a lignocellulosic feedstock based biorefinery*. Waltham, MA: Elsevier Inc.; 2016. p. 587–610. <https://doi.org/10.1016/B978-0-12-802323-5.00025-6>.
- [17] De Groot SR, Mazur P. Nonequilibrium thermodynamics. Amsterdam: North-Holland Publ. Co; 1962. <https://doi.org/10.1002/bbpc.19620661027>.
- [18] Glansdorf P, Prigogine I. Thermodynamic theory of structure, stability and fluctuations. London/New York/Sidney/Toronto: A division of John Wiley & Son; 1970. <https://doi.org/10.1126/science.176.4042.1410>.
- [19] King CJ. Separation processes. Chapter 13 energy requirements of separation processes. UC Berkeley Books. Org McGraw Hill Book Company, nowadays free access through Permalink; 1980. Accessed 15-7-2020, <https://escholarship.org/uc/item/1b96n0xv>.
- [20] Lazzaretto A, Tsatsaronis G. A general process-based methodology for exergy costing. In: Duncan AB, Fiszdon J, O'Neal D, Den Braven K, editors. *Proc. ASME advanced energy systems division*, 36. New York: ASME; 1996. p. 413–28.
- [21] Hinderink AP, FPJM Kerkhof, Lie ABK, de Swaan Arons J, van der Kooij HJ. Exergy analysis with a flowsheeting simulator I Theory; calculating exergies of materials streams. *Chem Eng Sci* 1996;51(20):4693–700. [https://doi.org/10.1016/0009-2509\(96\)00220-5](https://doi.org/10.1016/0009-2509(96)00220-5).
- [22] Maia MLO, Ottens M, van der Wielen LAM. Exergy analysis of chromatographic separations in a fixed bed column. *Ind Eng Chem Res* 2004;43:3183–93. <https://doi.org/10.1021/ie030603u>.
- [23] Posada JA, Ossweijer P. Socioeconomic and environmental considerations for sustainable supply and fractionation of lignocellulosic biomass in a biorefinery context. In: Mussatto SI, editor. *Biomass fractionation technologies for a lignocellulosic biorefinery*. Elsevier; 2016. <https://doi.org/10.1016/C2014-0-01890-4>. ISBN 978-0-12-802323-5.
- [24] Petrides D. Bioprocess design and economics. In: Harrison RG, Todd PW, Rudge SR, Petrides D, editors. *In bioseparations science and engineering*. 2nd edition. Oxford University Press; 2015. ISBN 978-0-19-539181-7. https://www.academia.edu/41126037/BIOSEPARATIONS_SCIENCE_AND_E_ENGINEERING Accessed 9-11-2020.
- [25] Nfor BK, Ahamed T, van Dedem GWK, van der Wielen LAM, Ottens M. Design strategies for integrated protein purification processes: challenges, progress and outlook. *J Chem Technol Biotechnol* 2008;83(2):124–32. <https://doi.org/10.1002/jctb.1815>.
- [26] Nfor BK, Verhaert PDEM, van der Wielen LAM, Hubbuch J, Ottens M. Rational and systematic protein purification process development: the next generation. *Trends Biotechnol* 2009;27(12):673–9. <https://doi.org/10.1016/j.tibtech.2009.09.002>.
- [27] Efe C, Straathof AJJ, van der Wielen LAM. Technical and economical feasibility of production of ethanol from sugar cane and sugar cane bagasse. 2005. ISBN 078-90-809691-809696-2 and Delft University Repository via <https://repository.tudelft.nl/islandora/object/uuid%3A5f3b7381-0da3-4d26-b334-9b4856ecacda>. Accessed 15-7-2020.
- [28] <http://www.granbio.com.br/en/site/granbio-begins-producing-second-generation-ethanol/> Accessed 15-7-2020.
- [29] <https://www.biofuelsdigest.com/bdigest/2017/04/12/poet-dsms-project-liberty-reaching-production-goals/>. Accessed 15-7-2020.
- [30] Gerlach I, Hass VC, Mandenius C-F. Conceptual design of an operator training simulator for a bioethanol plant. *Process* 2015;3:664–83. <https://doi.org/10.3390/pr3030664>.
- [31] Mussatto SI, Dragone GM. Biomass pretreatment, biorefineries and potential products for a bioeconomy development. In: Mussatto SI, editor. *Biomass fractionation technologies for a lignocellulosic feedstock based biorefinery*. Waltham, MA: Elsevier Inc.; 2016. p. 1–22. <https://doi.org/10.1016/B978-0-12-802323-5.00001-3>.