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DOI
10.1016/j.tibtech.2024.12.009

Publication date
2025

Document Version
Final published version

Published in
Trends in Biotechnology

CellPress
OPEN ACCESS

Trends in
Biotechnology

Review

Distillation for *in situ* recovery of volatile fermentation products

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Many fermentation products inhibit their own microbial production, which complicates industrial-scale fermentation development for these products. When a product is volatile, this inhibition can be circumvented by removing product during fermentation through evaporation in a loop around the bioreactor. Microbes can survive this loop if its temperature is reduced using vacuum. Then, regrowing of microbes is not required. From a separation efficiency viewpoint, the evaporation loop should not use a single equilibrium stage, but a multistage vacuum distillation column. Such *in situ* product removal (ISPR) by vacuum distillation has hardly been recognized as an option, however. Costs for this product removal with subsequent purification are modest, even when product titers are low. A prerequisite is the use of advanced energy integration and heat pumping methods.

Highlights

In situ product removal (ISPR) is required for microbial production of hydrophobic chemicals.

Vacuum distillation coupled to a bioreactor is effective for ISPR of volatile products.

Process intensification allows low costs for ISPR and product purification.

Even products with a boiling point of 170°C can be vacuum distilled from aqueous broth (if they are sufficiently hydrophobic).

Why *in situ* removal of fermentation products?

Industrial biotechnology methods can convert renewable feedstocks into useful chemicals, which may contribute to sustainability [1,2]. Fermentations that are used, however, are typically inhibited by their product [3], which complicates the development of competitive industrial production processes. Figure 1 shows that hydrophobic products, in particular, completely stop cell growth at a low critical product concentration ($c_p^{crit,\mu}$). Products that are more hydrophobic, having a higher **log $P^{o/w}$** (see Glossary) value, will partition more strongly to cellular membranes and to hydrophobic regions of proteins and hence are more prone to causing cell malfunction. It seems that microbes can be found or engineered to tolerate product concentrations only up to a boundary that is indicated tentatively by a line in Figure 1. This figure only includes small, uncharged molecules, which will pass cell walls almost unrestricted. Carboxylic acids and amines are not discussed here because they are typically largely present in fermentations as charged species (carboxylate or ammonium), such that their inhibition also depends on pH and other factors.

The upper tolerance boundary implies that many hydrophobic fermentation products can reach less than 10 g/l in the aqueous broth. Thus, a fermentation with an industrially competitive production rate of 2 g/(l h) would be complete in 5 h, and the bioreactor would mostly be in downtime for emptying, cleaning, sterilizing, and filling. A typical downtime is 10–15 h, leading to very inefficient bioreactor use. Moreover, substrate is also used inefficiently, as a relatively large portion of the substrate must be invested to grow sufficient microbes to produce at a rate of 2 g/(l h). Overall, such a process is not likely to be economically feasible.

To continue production without reaching product concentrations that are too inhibiting, one must apply ISPR [4–6]. During fermentation, the broth is contacted with another phase (gaseous, liquid, or solid) to which the product partitions selectively. The other (auxiliary) phase can be brought in the bioreactor (internal ISPR) or fermentation broth can be contacted with the auxiliary phase in a loop around the bioreactor (external ISPR); the phases should separate easily. Fermentation

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 https://doi.org/10.1016/j.tibtech.2024.12.009

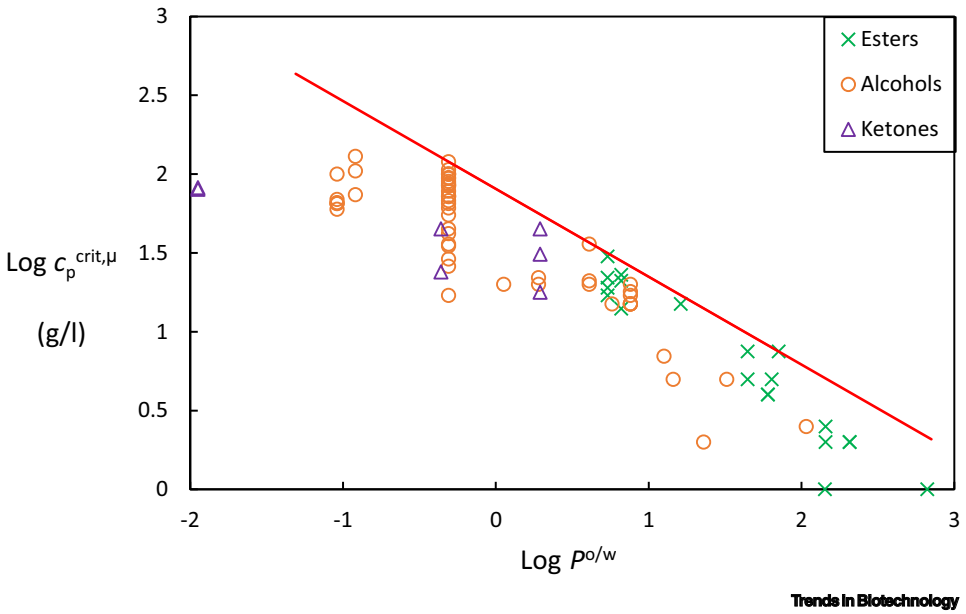

Figure 1. Published product concentrations that stop microbial growth [3], as a function of the product's hydrophobicity. The line is a provisional upper tolerance boundary.

with ISPR is also called extractive fermentation. Numerous publications discuss how to operate this [4–9]. For example, the type of liquid extractant or solid adsorbent can be varied widely.

For the use of a gaseous auxiliary phase (hence ISPR using the product's volatility), **gas-stripping fermentation**, **vacuum fermentation**, **vacuum flash fermentation**, and **pervaporation** have frequently been studied [10]. Traditionally, distillation has not been considered an option for ISPR [5,11]. However, distillation is the workhorse of the chemical industry for product recovery, separation, and purification. In industrial distillation, the feed is continuously introduced in a stage around the middle of the distillation column, with more volatile components gradually moving to the top exit (distillate) and less volatile components to the bottom. The countercurrent multistage operation of distillation is much more effective than evaporation or gas-stripping operations, which use a single equilibrium stage. Therefore, the first of the more widely accepted heuristics for the selection of separation processes is to favor distillation unless **relative volatilities** are less than 1.05 [12].

The traditional absence of distillation as an ISPR method might be based on implicit assumptions such as: (i) fermentation products are rarely volatile; (ii) distillation temperatures are too high for microbes; (iii) distillation uses too much energy; and (iv) fermentation products are too dilute for distillation. Here, we address each of these critical points and debunk them, guided by recent cases that found ways to apply distillation for ISPR. Our analysis demonstrates that the whole product range for which distillation is feasible as an ISPR method.

Which fermentation products are volatile?

There is a wide range of fermentation products that are volatile, as listed in Table 1. Many of them are important, as demonstrated by their industrial or pilot production. Moreover, typically they inhibit their production by fermentation.

Glossary

Activity coefficient: thermodynamic factor (γ) used to account for deviation of a compound's property in a mixture relative to its ideal behavior.
Bleed stream: a minor part of a liquid recycle stream sent to waste, to prevent the accumulation of impurities in the process. This is called purge in the case of gas streams.
Gas-stripping fermentation: product is removed by gas that is sent through the bioreactor.
Heat integration: a technique used to improve the energy efficiency of a process by recovering and reusing heat between different process streams or units.
Heat pump: a device that transfers heat from a lower-temperature source to a higher-temperature sink by upgrading low-level heat by use of external power (e.g., compression).
Log $P^{o/w}$: the logarithm of a compound's partition coefficient between water and 1-octanol; indicates the compound's hydrophobicity.
Pervaporation: liquid-phase contacts a membrane that has a gas phase or a vacuum at the other side, which drives the evaporation of the liquid-phase components (after their permeation through the membrane). The membrane may retard the evaporation of specific components and therefore increase the selectivity of evaporation.
Relative volatility: $\alpha^{\infty}_{p/w}$; the volatility of product relative to water, leading to selectivity of evaporation at equilibrium conditions.
Vacuum fermentation: product evaporates from the broth in the bioreactor due to decreased pressure.
Vacuum flash fermentation: fermentation broth is cycled through a vacuum vessel in which vapor–liquid equilibrium is approached.

Table 1. Examples of volatile fermentation products

Class	Product	log $P^{o/w}$	BP (°C)[a]	Status[b]
Mono-alcohols	Ethanol	–0.31	78	I
	1-Propanol	0.25	97	L
	Isopropanol	0.05	82	P
	1-Butanol	0.88	118	I
	Isobutanol	0.76	108	I
	1-Hexanol	2.03	158	L
	2-Phenylethanol	1.36	218	P
Polyols	Ethylene glycol	–1.69	197	L
	1,2-Propandiol	–0.92	188	L
	1,3-Propanediol	–1.04	211	I
	1,4-Butanediol	–0.83	235	I
	2,3-Butanediol	–0.92	183	P
	1,3-Butanediol	–0.74	207	I
	Glycerol	–1.76	290	P
Ketones	Acetone	–0.92	56	I
	Butanone	–0.24	80	L
	Nootkatone	0.29	Unknown	I
Aldehydes	Butyraldehyde	0.88	74.8	L
Esters	Ethyl acetate	3.84	77	P
	Isobutyl acetate	0.73	117	L
	Butyl butyrate	1.78	165	L
Alkenes	Isobutene	2.82	–7	P
	Isoprene	2.34	34	P
	Styrene	2.42	145	L
	Valancene	2.95	274	I

[a]BP, boiling point.
[b]I, proven at industrial scale; L, proven at laboratory scale; P, piloted.

Although lower carboxylic acids such as acetic acid are volatile, they are not included here because they occur largely as nonvolatile carboxylate species at typical fermentation pH.

In addition to the volatile fermentation products of Table 1, volatile impurities may enter the bioreactor with the substrate, such as furfural with lignocellulose hydrolysate. Also, these impurities can inhibit the fermentation and might be removed *in situ*.

Distilling at fermentation temperature

ISPR should avoid conditions that are detrimental to the microbes because the microbes should keep forming product. Therefore, volatile product must be removed at temperatures close to the fermentation temperature. The use of vacuum can bring evaporation to a sufficiently low temperature. A frequently used method, for example in [13,14], is vacuum fermentation (Figure 2). However, in the vacuum fermentation workflow the bioreactor serves as merely one equilibrium stage, which is not very effective from a separation technology point of view. Subsequent condensation of product from off-gas will typically be performed in a multistage operation, but not in a countercurrent mode that would make it very efficient. As some water will co-evaporate, subsequent separation of water and product will be required; for example, by conventional distillation. Many

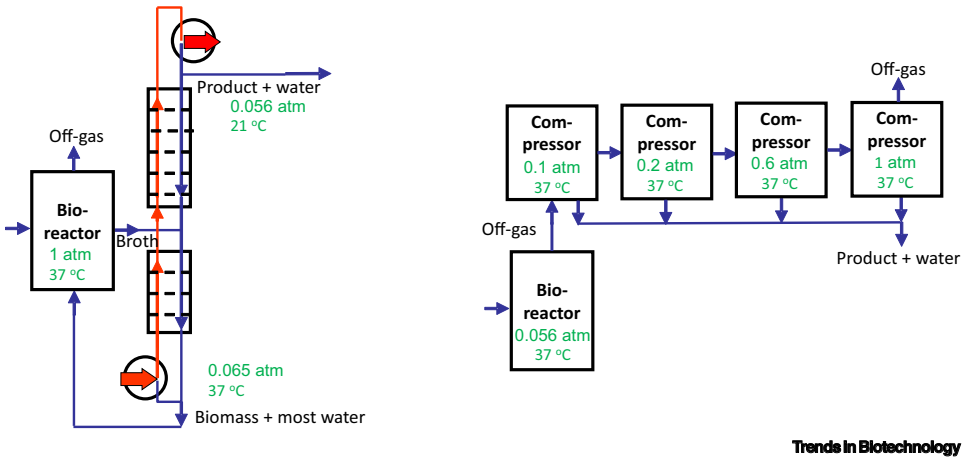

Figure 2. *In situ* product removal (ISPR) by vacuum distillation (left) and by vacuum fermentation (right), under typical operation conditions.

other papers discuss vacuum evaporation of product (flashing) during fermentation at atmospheric pressure (e.g., [15–17]), but this is still a single-stage operation with limitations similar to those of vacuum fermentation.

An alternative configuration uses vacuum distillation, as shown in Figure 2A. Here, the fermentation is performed at conventional pressure (e.g., atmospheric) and the fermentation broth is cycled over a vacuum distillation column. Some experimental studies have recently been published on this. Zhang and colleagues distilled ethanol from fermented lignocellulosic hydrolysate and successfully reused the remaining broth for fermentation [18]. Others distilled butanol from broth under vacuum and recycled the broth [19] or assumed that the broth could be recycled [20].

As the vacuum distillation operates in countercurrent mode, any volatile product, at any specific height in the column, will move up relative to water if the relative volatility $\alpha_{p/w}$ between product and water is greater than 1. If this is the case at the bottom of a distillation column with sufficient countercurrent equilibrium stages, the volatile product will not leave the column at the bottom such that almost all volatile product will leave over the top of the column. This allows complete removal of product from the broth.

If the ISPR loop through the distillation column is operated at a temperature that is acceptable to the microbes, they may still experience conditions that might be harsh. The vacuum pressure as such can be survived [21], but shear forces due to a too-quick change in pressure might be detrimental. However, bacteria survive hydrostatic pressure switches of ~2 atm when cycled each minute through an industrial gas lift bioreactor of 25 m height [22]. The pressure change between a bioreactor and a vacuum distillation column will be of the order of magnitude of 2 atm, and actions might be needed to prevent such a change being too abrupt. In addition to experiencing the vacuum, the microbes may also lack nutrients in the distillation column. Although laboratory-scale operation of ISPR by distillation did not lead to much loss in viability [18], industry uses different equipment dimensions and different flow rates, and microbial viability should also be tested under conditions that microbes experience during distillation at industrial scale. No such studies are available, although patent reports suggest industrial operation of vacuum distillation of syngas fermentation broth [23].

The desired microbes might foul distillation column packings, especially if conditions allow growth, but packings could be designed to minimize such risk, and steaming in place (SIP) should

be feasible. This is also relevant because the distillation column cycle around the fermentation should be sterilizable to prevent the introduction of undesired microbes.

Energy use and costs as a function of product concentration

Recent reports [24–26] show industrial-scale designs for the removal of alcohols from various fermentation broths using vacuum distillation or related vacuum stripping methods, with subsequent purification of the alcohols by additional distillations. To prevent excessive energy use, a range of advanced energy-saving techniques was implemented. Although conventional vacuum distillation may be energy intensive for the initial recovery of volatile products from dilute fermentation broths, relatively close temperatures at the top and bottom of the vacuum distillation column allow the application of **heat pump** systems. Furthermore, **heat integration** and heat pumping may be used to maximize energy recovery in the next downstream steps. Consequently, energy requirements of the recovery process can be reduced by about 60–80% while allowing (green) electrification (of the whole recovery process or certain parts). Furthermore, this minimized the alcohol recovery costs, although costs for energy still dominated other costs, such as equipment investment. A key parameter was the assumed alcohol concentration in the broth (Figure 3). At higher concentrations, less water needs to be removed per amount of product, which saves on costs.

The calculated alcohol recovery costs are in the range of recovery costs by other methods or lower [24–26]. Moreover, recycling the alcohol-depleted broth to the fermentation will significantly save on fermentation costs, but this still needs quantification. In any case, the virtually complete removal of product from the broth that is recycled prevents some product becoming lost in an unavoidable **bleed stream**.

Figure 3 shows that even 1-hexanol, with a concentration of merely 2 g/l and a boiling point of 158° C, leaves the vacuum distillation column at the top, together with only a minor fraction of the water. Thus, a low boiling point with a high concentration of product is not a requirement for technical feasibility of *in situ* vacuum distillation. The critical factors to consider are discussed later.

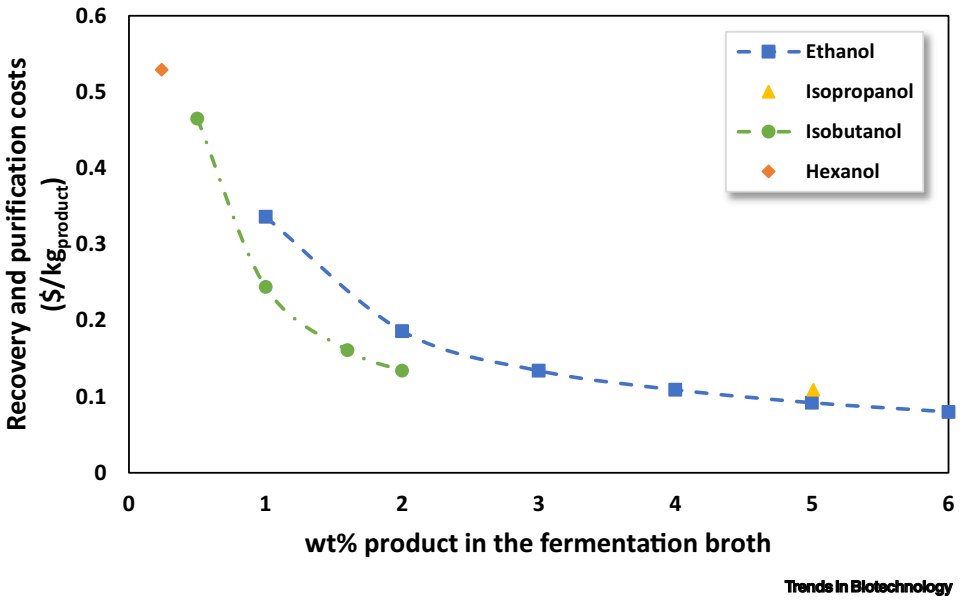

Figure 3. Costs of recovering fermentation products from broth using vacuum fermentation, including subsequent purification [26].

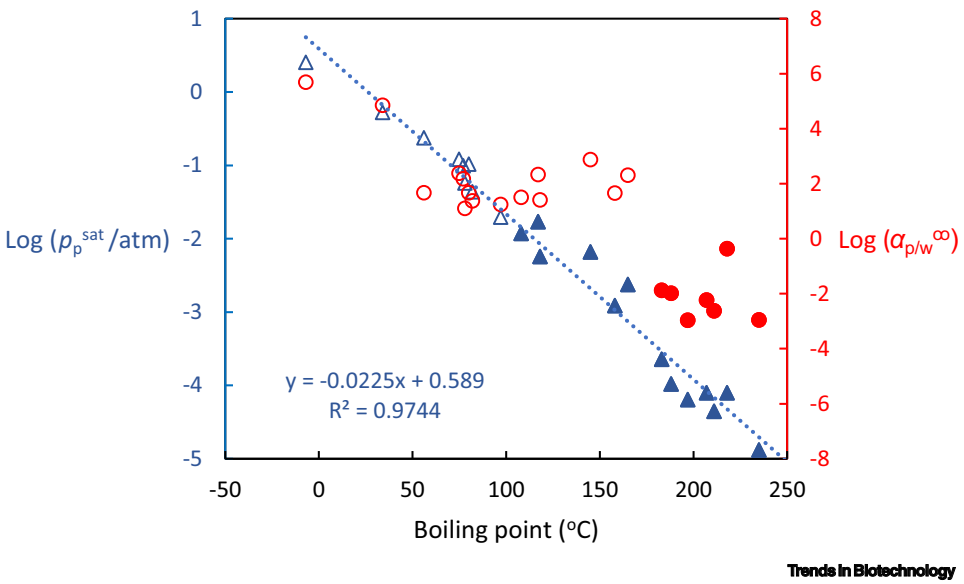

Figure 4. Saturated vapor pressures (blue, with a broken correlation line for which the equation is given) and relative volatilities (red) of the products listed in Table 1 in the main text. Open markers indicate products that boil lower than water (blue) and products that are more volatile than water when in infinitely dilute aqueous solution (red).

Which products are sufficiently volatile?

The volatility at 20°C is known for most of the volatile fermentation products that were mentioned in Table 1, in terms of their saturated vapor pressure p_p^{sat}. Figure 4 shows that its logarithm correlates with the atmospheric boiling point of these products. Only for a minority of the considered products is the boiling point lower than that of water and the volatility higher than that of water.

However, the saturated vapor pressures are volatilities of the pure products. In the bottom of the vacuum distillation column, in case only traces of product leave the column, the products are in

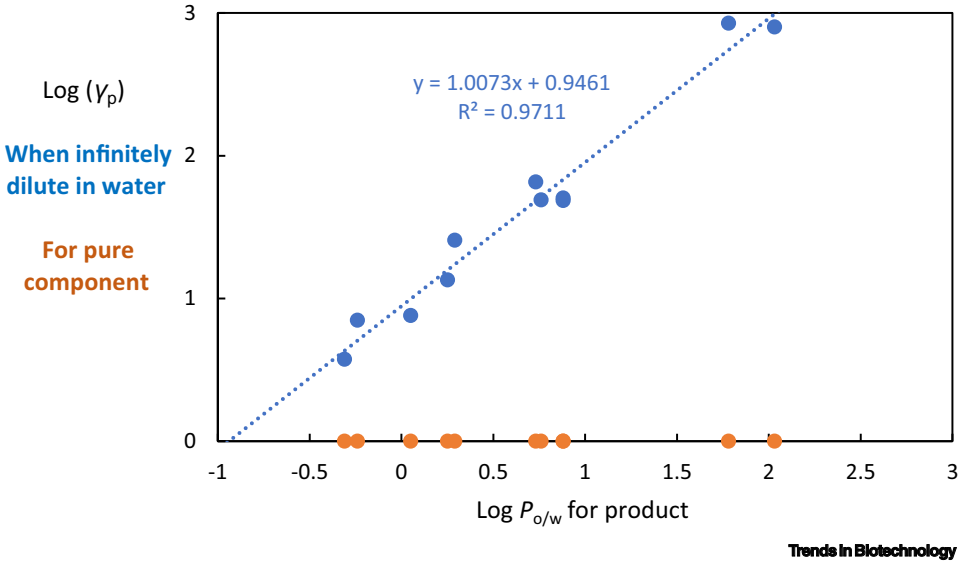

Figure 5. Activity coefficients of volatile products from Table 1 in the main text as a function of their hydrophobicity. Orange markers, for pure product. Blue markers and correlation line, for product infinitely dilute in water.

Box 1. Product properties required for ISPR by distillation

For product (subscript p) and water (subscript w), equilibrium composition y in vapor phase and x in infinitely dilute aqueous solution are related to overall pressure p, saturated vapor pressure p^{sat}, and infinite dilution activity coefficient of product γ_p^{∞}:

$$y_p p = \gamma_p^{\infty} x_p p_p^{sat} \quad [I]$$

$$y_w p = x_w p_w^{sat}. \quad [II]$$

Therefore, the definition of the relative volatility in very dilute water can be expressed in terms of p^{sat} and γ_p^{∞}, while using $x_w = 1$:

$$\alpha_{p/w}^{\infty} \equiv \lim_{x_p \to 0} \frac{y_p/x_p}{y_w/x_w} = \frac{\gamma_p^{\infty} p_p^{sat}}{p_w^{sat}}. \quad [III]$$

In logarithmic terms:

$$\log \alpha_{p/w}^{\infty} = \log \gamma_p^{\infty} + \log p_p^{sat} - \log p_w^{sat}. \quad [IV]$$

For each of the three right-hand terms, expressions were obtained:

$$\log \gamma_p^{\infty} = 1.0073 \log P^{o/w} + 0.9461 \quad [V]$$

$$\log p_p^{sat} = -0.0225BP + 0.589 \quad [VI]$$

$$-\log p_w^{sat} = -\log (0.0231 \text{ atm}). \quad [VII]$$

Now, substituting in the three right-hand term leads to:

$$\log \alpha_{p/w}^{\infty} = 1.0073 \log P^{o/w} + 0.9461 - 0.0225BP + 0.589 - \log (0.0231) \quad [VIII]$$

$$\log \alpha_{p/w}^{\infty} = 1.0073 \log P^{o/w} - 0.0225BP + 3.1715, \quad [IX]$$

where BP is boiling point. This equation was used to obtain values of $\alpha_{p/w}^{\infty}$ for Figure 4 in the main text.

Data for 20°C were used, but no large changes in $\alpha_{p/w}^{\infty}$ are expected when typical fermentation temperatures (30–37°C) apply.

Taking the condition that $\alpha_{p/w}^{\infty} > 1$ implies that $\log \alpha_{p/w}^{\infty} > 0$. So:

$$0 < 1.0073 \log P^{o/w} - 0.0225BP + 3.1715. \quad [X]$$

Therefore, a product can be distilled from water if its BP and $\log P^{o/w}$ have values that satisfy:

$$0.0223BP - 3.1485 < \log P^{o/w}. \quad [XI]$$

dilute aqueous solution. This can lead to very high **activity coefficients** of the products. For about half of the aforementioned products, infinite dilution activity coefficients in water were found [27], and their logarithm $\log \gamma_p^{\infty}$ correlated strongly with their log $P^{o/w}$ value, as shown in Figure 5.

The background of this correlation is that a single hydrophobic molecule in water prevents hydrogen bonding between water molecules, leading to a tendency of the water molecules to push the hydrophobic product out of the aqueous liquid. Thus, a hydrophobic product is much more volatile in dilute aqueous liquid than in pure product liquid; in the latter, hydrophobic interactions with neighboring molecules keep the product molecules together. For 1-hexanol, this translates into an enormous activity coefficient increase, from 1 to 800 when going from pure liquid to dilute aqueous solution, whereas for ethanol it leads to a modest increase from 1 to 3.7.

Recalling that product at the bottom of the distillation column will move up relative to water if the local volatility relative to water is greater than 1, one needs to know $\alpha_{p/w}^{\infty}$, with the infinity symbol indicating infinite dilution in water. As shown in Box 1, one can derive that $\alpha_{p/w}^{\infty}$ is negatively correlated to the product's atmospheric boiling point, as expected, and positively correlated to the product's log $P^{o/w}$ value, because hydrophobicity increases the product's volatility in water.

Taking the boiling points and hydrophobicities of the volatile products of Table 1, Figure 4 shows that most of these products are more volatile than water when infinitely dilute in water. Only the diols and 2-phenylethanol are not volatile enough to be distilled from water. Such compounds will still be purified by distillation [28], but cannot use vacuum distillation for ISPR.

As shown in Box 1, the condition that $\alpha_{p/w}^{\infty} > 1$ for distilling product from fermentation broth translates into:

$$0.0223BP - 3.15 < \log P^{o/w}. \quad [1]$$

Equation 1 indicates which combinations of low-enough boiling point and high-enough hydrophobicity make a product distillable from fermentation broth. Bearing in mind that hydrophobicity causes microbial toxicity (Figure 1), this condition of high hydrophobicity is favorable for *in situ* removal by vacuum distillation.

Also liquid–liquid extraction can *in situ* remove volatile fermentation products if they are sufficiently hydrophobic. Then, distillation will still be used for subsequent regeneration of extraction solvent. A suitable extraction solvent might not be found due to many requirements in addition to high extraction capacity and suitable volatility; for example, low microbial toxicity, low aqueous solubility, low viscosity, and fast phase separation. *In situ* distillation avoids adding a new compound and needs fewer process steps.

Azeotropes

Although products that fulfil the condition of Equation 1 can be completely distilled from fermentation broth, these products are likely to leave the top of the distillation column jointly with a substantial fraction of water. The reason for this is that the value of $\alpha_{p/w}$ decreases while the product-to-water ratio increases towards the top of the column. The more product molecules in water, the more the product's hydrophobic portions interact and the lower the product's volatility. This is reflected in γ_p becoming lower than γ_p^{∞}, while the activity coefficient of water increases. At a particular increased product-to-water ratio this results in a value of $\alpha_{p/w}$ that decreases to 1. This is the highest ratio that can leave the top of the column and corresponds to the azeotropic composition. Specific interactions between water and product molecules determine what this composition will be.

Nonetheless, water concentrations higher than azeotropic are sometimes separated in the initial removal of the product from the broth, ensuring that vapor flow through the distillation column is sufficient to allow the implementation of a heat pump system. Additional distillation-based operations may be used to concentrate the water–product mixture to a nearly azeotropic composition and obtain pure product from it. As shown in examples [24,25], there are several energy-efficient ways to obtain pure product from azeotropic mixtures with water, so these azeotropic mixtures are no obstacle to the implementation of *in situ* vacuum distillation. On the contrary, in some cases (e.g., 1-butanol, isobutanol, 1-hexanol) a low-boiling azeotrope allows initial separation of

fermentation product (with some water) as the top product of the vacuum distillation column. Hence, there is no need to evaporate all of the water from the broth, which would otherwise lead to a more energy-intensive process.

Stripping of volatile fermentation products by gas streams in bioreactors

Aerobic fermentations need aeration, and some other fermentations need continuous gassing as well; for example, syngas fermentations. Especially for aerobic fermentations, the off-gas flows are much larger than the CO_2 off-gas flow of anaerobic fermentations, because air is easily used in large excesses. This leads to some *in situ* removal of volatile products by stripping [29,30]. The rate of removal depends particularly on product volatility and on off-gas flow rate. A lot of research has focused on recovering the volatile components from the gas streams [31–33]. The main challenges for industrial-scale downstream processing are a large flow rate of fermentation off-gas and a low product concentration. Membrane separations, adsorption, and absorption can be costly for industrial-scale plants due to large equipment units, large amounts of adsorbent or absorbing liquid, and energy-intensive desorption or solvent recovery steps. Alternatively, the off-gas can be cooled to condense the fermentation product. This may be done at higher pressure using inexpensive cooling utilities (e.g., cooling or chilled water) or at atmospheric pressure using low-temperature condensation with refrigerants. Thereby, a lower boiling point of the main product would require more extreme refrigeration temperatures to achieve the same recovery. For example, to recover about 95% of ethyl acetate or isoprene from a gas stream with 2 wt% product, refrigeration requires about –50°C and –90°C, respectively. Although refrigerants are more expensive than water, compressing off-gas to high pressures is very energy intensive due to the large gas flow rates. Hence, the choice of recovery technique depends on the product to be recovered, its concentration in the exhaust gas, and the gas flow rate (process scale).

Concluding remarks

Recent reports show that vacuum distillation is technically feasible and economically attractive for *in situ* removal of volatile fermentation products. Bioproduct titers as low as 2 g/l may suffice if the product is sufficiently volatile and valuable.

The range of products that can be completely distilled from fermentation broth is not limited to products with a lower boiling point than water. Due to their non-ideal solubility behavior in water, products with a boiling point up to about 170°C can be removed from broth by vacuum distillation if they are hydrophobic. Fermentation products are typically more inhibiting when more hydrophobic and hence more urgently need removal during fermentation. Overall, this leads to a favorable situation for the use of vacuum distillation for ISPR during fermentation. This possibility has been overlooked for decades but is increasingly gaining interest leading to new research questions (see Outstanding questions).

Outstanding questions

For ISPR by distillation, several studies report the costs of recovering products from fermentation broth, but no quantification of the associated cost reduction of the fermentation has been determined yet. This cost reduction will be due to recycling of microbes, water, and unconsumed nutrients.

A related question is the determination of the trade-off value of the product concentration at which ISPR should be operated. Higher concentrations make fermentation slower and more expensive due to more inhibition, but lower concentrations make product removal more expensive because more broth needs to be processed per amount of purified product.

Microbial viability should be tested at conditions that microbes experience during vacuum distillation at industrial scale (due to pressure change or nutrient limitation).

Declaration of interests

We, the authors and our immediate family members, have no financial interests to declare.

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