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Bioreactive separation technology: A retrospective and perspective

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ABSTRACT

Biocatalysis, using enzymes or whole cells, offers high selectivity under mild conditions, but its broader application is often hindered by slow kinetics, equilibrium limitations, product inhibition and the processing of dilute streams in the presence of enzymes and cells. Bioreactive separation, defined as the simultaneous process of biocatalysis and separation, provides a powerful concept to overcome these barriers and therefore offers the potential of superiority over conventional processes. The current retro- and perspective paper, which is the result of an interdisciplinary workshop with academic and industry experts from the areas of biotechnology, fluid separations and process systems engineering, provides a focussed review, paired with a distinct novel definition

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of bioreactive separations that links to multifunctional reactors in chemical engineering and in situ product removal in biocatalysis. By establishing a common framework, this definition connects different research areas and enables systematic development. The current status of bioreactive separation processes is evaluated using SWOT analyses to identify key potentials and challenges. Based on this, a vision for 2040 is outlined, highlighting the need for advances in integration strategies, biocatalyst design, modelling and simulation, and applied research. Overall, a coordinated progress in these areas can significantly enhance the scalability and sustainability of bioprocessing.

1. Introduction

The chemical industry plays a vital role in shaping both our personal lives and the technical world around us. From everyday products such as plastics [1,2], pigments [3,4], and tires [5,6] to more specialized applications like batteries [7,8], pharmaceuticals [9–11], and dental materials [12], chemicals form the foundation of modern society. Chemicals are indispensable in agriculture for producing fertilizers [13,14], in healthcare for synthesizing essential drugs [10,11], and in energy systems for developing advanced materials for renewable energy technologies [8,15,16]. Without the chemical industry, many of the conveniences and innovations we rely on would not be possible. There is, however, an imminent need for a phase-out of traditional fossil-based production processes, due to the finite availability of fossil resources, the associated greenhouse gas emissions and energy requirements that result from harsh operating conditions for classical chemical processes, including high temperatures and pressures [14,17]. Furthermore, these processes frequently require the use of potentially hazardous solvents and other utilities, raising environmental and safety concerns [18]. For example, the production of plastics generates significant amounts of greenhouse gas emissions [19], while solvent-intensive processes contribute to water and soil pollution [20]. These drawbacks highlight the need for cleaner, more sustainable approaches to a green chemical manufacturing [21].

Biocatalysis offers an attractive alternative to traditional chemical processes, using biological catalysts, such as enzymes or whole cells, to facilitate chemical reactions under mild conditions [22–24]. Biocatalytic processes are known for their high (regio- and stereo)selectivity and the ability to produce complex molecules with minimal waste. In the pharmaceutical industry enzymes are already exploited to synthesize active ingredients for drugs with fewer by-products compared to conventional methods [25]. Despite these attractive advantages, biocatalysis is not free of challenges, as comparably slow reaction rates [22,26] and the need to purify dilute aqueous product streams [23], which often hinder their industrial scalability and economic viability. One of the central challenges in biotechnology is to make processes sufficiently efficient and economically competitive with existing chemical processes [23,27]. Process intensification, particularly in the form of process integration, offers various possibilities for overcoming the aforementioned limitations [28–30], specifically through the systematic application of model-based methods as an extension to empirical process development. This allows processes to be designed more efficiently as a whole, while the potential of alternative AI-supported protein engineering lies in transforming biology into a programmable catalyst platform for scalable chemical processes [31–33].

Process intensification and, especially, the integration of reaction and separation steps in form of reactive separation processes can also enhance the efficiency of biocatalytic processes [34]. This approach, which we further refer to as bioreactive separation processes with a definition derived in Section 2, addresses the previously stated common limitations of most biocatalytic processes. Notably for equilibrium-limited reactions, it is well known that simultaneous separation of the product can drive the reaction equilibrium, increase overall yield even up to full conversion and significantly improve process efficiency metrics, such as energy demand and production costs [35]. Reactive separation processes, which from the reaction perspective are also referred to as multi-functional multi-phase reactors [36], mostly exploit multiple phase systems for a simultaneous mass transfer and a (bio-)chemical reaction. From the perspective of fluid separations, this naturally results in the classification of various reactive separation processes, such as reactive absorption, adsorption, chromatography, distillation and extraction, as illustrated in Fig. 1, following the description of Górak and Stankiewicz [37]. Research on these reactive separation processes has seen a considerable interest in the early 2000s with various textbooks published in the last 20 years, covering primarily (petro-)chemical production processes [38–42]. While reactive distillation was recognized as the front-runner of industrial process intensification by Harmsen [43], Stankiewicz [44] summarizes several key barriers that need to be overcome for a wider industrial implementation, which largely summarize the outcome of the Vision 2020 from the 2000 separations roadmap of the American Institute of Chemical Engineers (AIChE), also described in the book of Stankiewicz and Moulijn [45]. The predicted surpassing of the respective technological gaps, especially in terms of tools for process simulation and design, technology transfer by means of multidisciplinary approaches, and general barriers towards the application of new technologies, has primarily been achieved for the highlighted technologies. Out of these, only membrane reactors have so far seemed to be considered for a wider application for bioreactions [46].

For bioprocessing, reactive separation processes have primarily been investigated in terms of in situ product removal, which has seen a considerable interest and has been an active research area for more than 30 years [47]. Nevertheless, beyond this the concept of reactive separations in the context of biotechnology applications has seen less focussed systematic multidisciplinary studies compared to chemical production processes. Following the classification from Górak and Stankiewicz [37], Fellechner et al. [48] provided an elaborate review on bioreactive separation processes for enzymatic reactions, covering the state-of-the-art, highlighting several technological challenges and concluding the big potential for further development. Yet, compared to the broad literature available for chemical reactive separations, only few

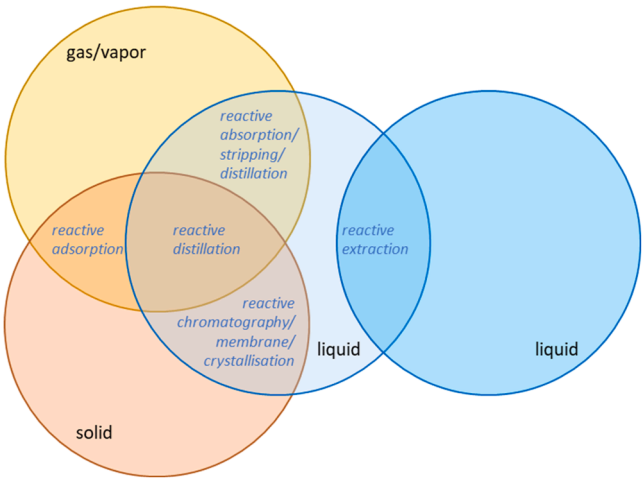


Fig. 1. Definition of reactive separation processes according to involved phases, adapted from [37].

books cover reactive separations for biotechnological processes [49,50].

Considering the industrial preference for simple and well-understandable robust processes, which is somewhat in conflict with the oftentimes highly-integrated concept of reactive separations, we believe that there is an even more pronounced need for measures and methods to overcome the technical gaps and technological barriers for fostering the development and industrial implementation of bioreactive separations. The current review and perspective article is supposed to build a foundation for this endeavour.

On this basis, we want to outline a vision for the future development of biocatalytic reactive separation processes in 2040, inspired by the Vision 2020, which was drafted 25 years ago in the 2000 Separations Roadmap of the AIChE. Improving the adaption of these process intensification concepts can directly contribute to the United Nations' Sustainable Development Goals (SDGs), particularly SDG 7 (Affordable and Clean Energy), SDG 9 (Industry, Innovation, and Infrastructure), and SDG 12 (Responsible Consumption and Production), by reducing energy consumption, minimizing waste, and promoting cleaner technologies. Thus, bioreactive separation processes can seemingly contribute to creating more sustainable (bio)chemical processes, not only supporting industrial innovation but also helping to address global challenges such as climate change, resource depletion, and environmental degradation.

The manuscript has been developed as a joint effort by the co-authors on the basis of a three-day workshop and subsequent exchange on the topic of Biocatalytic Reactive Separation Processes, which was organized as part of the Scoping initiative funded by the Volkswagen Stiftung. This workshop enabled us to engage in a multidisciplinary exchange involving 30 experts from the area of biocatalysis, fluid separations and process systems engineering, both from academia and industry. With this joint manuscript, we would like to make the experiences and results of the workshop available to the community. Prior to diving deeper into selected processes, the next section provides the first explicit definition and conceptual delineation of bioreactive separation processes based on a cross-disciplinary analysis spanning the fields of biotechnology, reaction engineering, fluid separations, and process systems engineering. Section 3 further provides a focused review of the relevant technology classes, summarizing the current status of biocatalytic reactive separations coupled with an evaluation of the Technology Readiness Level (TRL) [51] as a field-level classification tool. The overview considers specific case studies for each of the different reactive separations, in accordance to the multi-phase discrimination proposed by Górak and Stankiewicz [37]. The reported TRL assignments are based on the literature reviewed and the interpretation of the authors, drawing on both peer-reviewed publications and publicly available industrial reports, pilot-scale demonstrations, and technology disclosures. Given the limited availability of peer-reviewed documentation for industrial implementations, particularly at higher TRLs, the reported values should be regarded as indicative rather than definitive. Readers are therefore strongly encouraged to consider the underlying references in conjunction with the assigned TRLs when evaluating the maturity of individual technologies. For a more refined analysis of the development needs common key challenges are identified and a SWOT (Strenghts, Weaknesses, Opportunities, and Threats) analysis of each technology is presented in Section 4. Based on this analysis, a vision 2040 is described in Section 5, addressing academic and industrial needs, as well as educational needs and promising applications. Finally, a summary and a conclusion are presented in Section 6.

2. Definition of bioreactive separation technology

The discussions at the workshop made it clear that at current state there is no broadly accepted established general definition of bioreactive separation technology. The specific understanding of bioreactive separation technology and even process intensification in a more general way depends largely on the perspective of the specific community and the individual study program and research activities. Several excellent general textbooks on process intensification have been published [42,52,53], which provide different but closely related definitions of process intensification. Various definitions found in literature are summarized in the review article of Keil [28], also covering a range of reactive separation processes. Building on the analysis presented by Skiborowski and Sudhoff [54], we follow the practical definition that process intensification can be understood as a “tool for the targeted enhancement of the different phenomena at different scales to overcome bottlenecks and limitations in performance and to achieve a targeted benefit based on a set of performance criteria”. The different phenomena can be classified in accordance with Freund and Sundmacher [55] to four scales: (i) fundamental and molecular, (ii) phase and transport, (iii) equipment and operation, and (iv) process and plant level, as depicted in Fig. 2 for a membrane-assisted reactive distillation process. For the specific case of reactive distillation, it easily becomes apparent that all four scales are affected, considering the depicted process integration (process and plant), the use of reactive internals for heterogeneous catalysis (operation and equipment), as well as the specific mass and heat transfer (phase and transport) and the type of catalyst and possible solvents (fundamental and molecular).

Reactive separation technology in general can be considered as an established type of process intensification, which, depending on the perspective, is often described either as a multifunctional reactor, for which some kind of separation is integrated into the reactor, or as an intensified separation process, for which some limitation can be overcome by integrating a reaction, as e.g. in chemical absorption processes [44]. Stankiewicz [44] further refines that if “the reaction and separation are integrated in order to benefit from the interaction effect between those two, for instance a shift of the reaction product composition beyond the equilibrium by an in situ separation/removal, or an enhancement of the separation efficiency by a chemical reaction. One speaks in those cases about reactive separations or separative reactors.” Focussing primarily on continuously operated processes, the available definitions of reactive separations in chemical engineering context are however limited to equipment-integrated concepts, in which reaction and separation occur simultaneously, discriminating them from reaction-separation sequences, as illustrated in Fig. 3, which further extends to hybrid separation processes that combine different separation technologies [44,56,57]. To be specific, the top left “reaction-separation sequence with recycle” is not considered as a reactive separation process. The membrane-assisted reactive distillation process in Fig. 2 would accordingly be classified as a hybrid reactive separation process.

In biotechnology, in situ product removal/recovery (ISPR) is the dominant concept considered for the integration of reaction and separation, while the term bioreactive separation has rarely been used in the existing literature. Following the definition provided by Woodley et al. [47,58], ISPR, which is “often synonymously called ‘extractive’ fermentation or bioconversion (biotransformation or biocatalysis), involves actions taken for the immediate separation of a product from its producing cell” and can be achieved both in batch and continuous operation by either internal or external integration between reaction and separation, as shown in Fig. 4. Thus, for ISPR it is irrelevant whether the separation unit is located in the reactor itself (internal ISPR) or outside the reactor (external ISPR). Note, that the external product removal in a continuously operated process (bottom right in Fig. 4) is equivalent to the conventional reaction separation sequence in Fig. 3 and while considered as ISPR in the definition of Woodley et al [41,52] is not representing an integrated reaction separation process (reactive separation) in the previously discussed context of process intensification. In ISPR, the separation phase could be in direct contact with the biocatalyst or in indirect contact, where the catalyst is isolated from the separation phase [34]. While initially considered primarily for the intensification of batch fermentation processes [47], various types of reactive separations for ISPR of enzymatic reactions have been investigated in the recent decades [48].

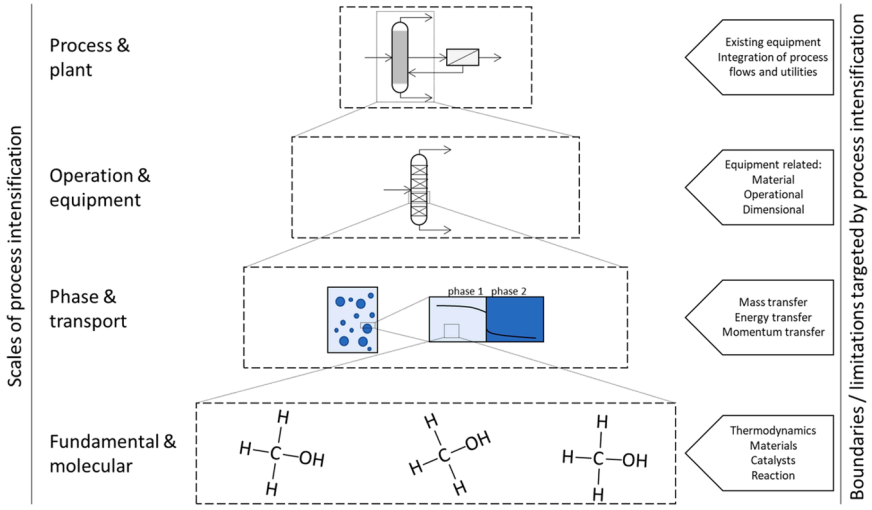


Fig. 2. Conceptual illustration of process intensification (PI) across the different scales, adapted from [54].

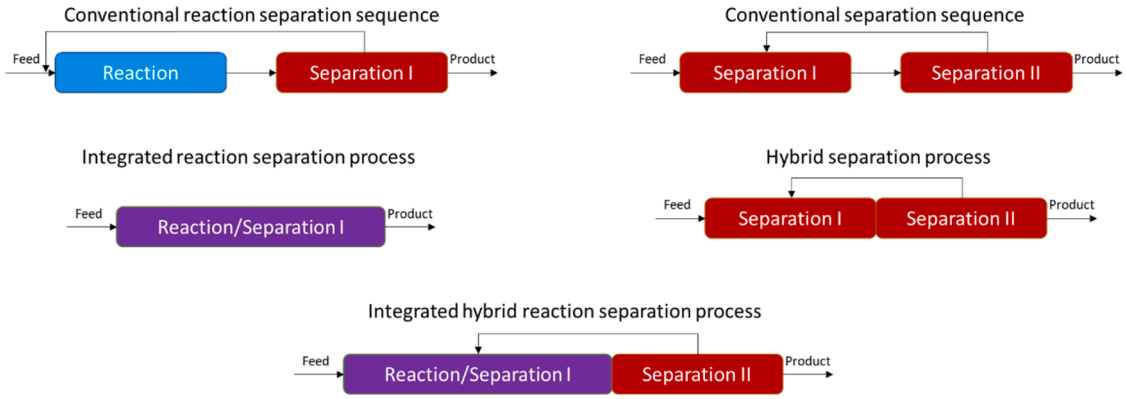


Fig. 3. Classification of different types of integration between continuously operated reaction and separation processes, adapted from [56].

In a continuously operated chemical process, a conventional reaction-separation sequence with a recycle stream (Fig. 3, *top left and* Fig. 4, *bottom right*) to the reactor does only affect the feed to the reactor, but does neither overcome a limitation in the reactor, nor in the subsequent separation. However, in a (semi-)batch operation, in which the reaction and separation progress simultaneously, the recycle and consequently the feed to the reactor is continuously shifting, allowing to overcome the individual limitations of the reactor and separation stages, as e.g. for the external product removal (*cf.* Fig. 4, *top right*), such as for a membrane-assisted esterification reaction [59].

In order to integrate the different definitions of reactive separations and ISPR, we propose the following definition of a bioreactive separation technology applicable to enzymatic and whole cell catalysis:

"A bioreactive separation technology is characterized by an **integration of a biocatalytic reaction and separation**, which independent of internal or external integration, **changes the conditions under which the reaction or separation takes place while simultaneously affecting each other**"

This definition covers those of ISPR and reactive separations and can best be illustrated by the phenomena that occur for a representative fluid element [55], as depicted in Fig. 5. While reactions do affect the state of the fluid element due to the reaction rates, a separation results in mass and energy transfer from or to the fluid element. Both reaction and separation need to occur simultaneously for a reactive separation, whereby a bioreactive separation requires a biocatalytic reaction. Following this definition, a continuously operated reaction-separation sequence, as depicted in Fig. 3 is still not considered as a reactive separation, as reaction and separation do not occur simultaneously. However, an external integration of reaction and separation in a batch operation, as e.g. achieved via an external pervaporation membrane connected with a batch reactor, is considered a reactive separation and a bioreactive separation if e.g. using an enzyme or whole cell as catalyst. A basic prerequisite for the simultaneous operation of reaction and separation is that the respective operating windows overlap, e.g. temperature, pressure, pH, solvent, etc..

According to the proposed definition, the separation or retention of catalysts, cells, or enzymes (e.g., via ultrafiltration) is explicitly not regarded as a bioreactive separation. Rather, such operations are considered solely as strategies for immobilization, not as bioreactive separation processes, as illustrated in the top part of Fig. 6. This also includes concepts in which cells or enzymes are enclosed in a semi-permeable membrane for a localized immobilization of the catalyst [60]. However, if membranes are used not only for immobilisation of the catalyst, but also such that their selective transport properties lead to component removal and, in turn, shift an equilibrium or minimise inhibition effects, such processes are also considered bioreactive separation processes. Some respective examples are described in the following references [61–64].

In order to clarify the distinction between (semi-)batch and continuously operated reactors with an external separation and recycling strategy three further examples are illustrated in Fig. 6, indicating the respective relationship. While the continuous flow reactor with embedded separation in the centre obviously implements the concurrent reaction and separation fluxes on the fluid element along the direction of

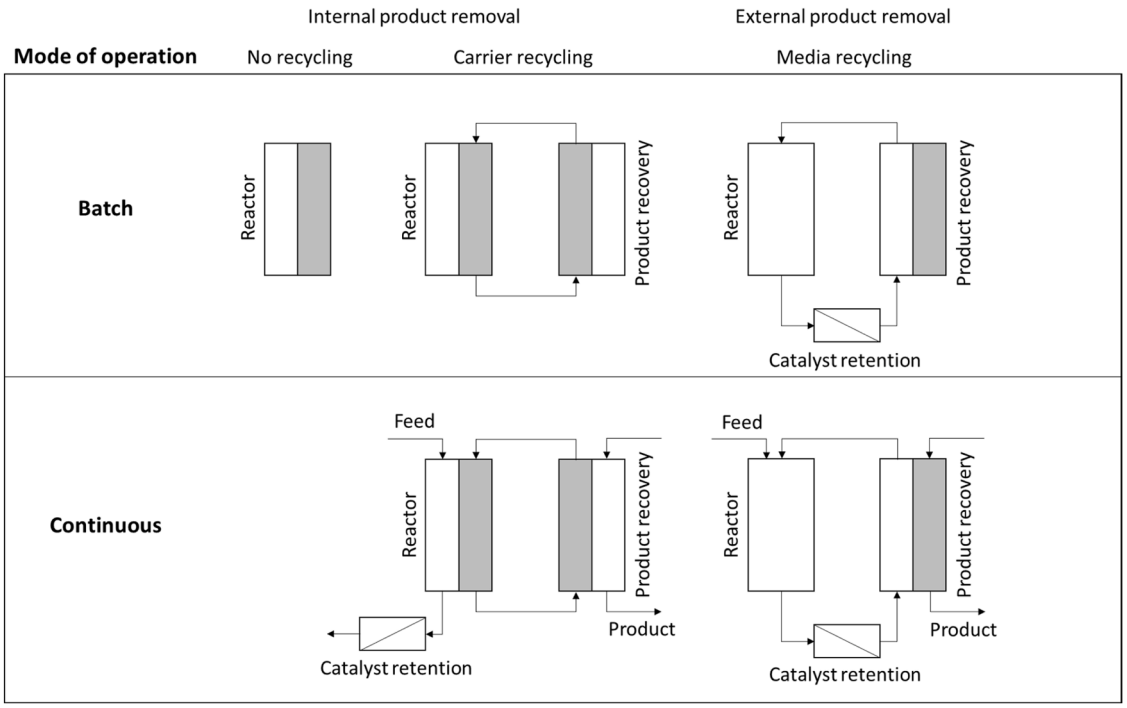


Fig. 4. Types of in situ product removal (ISPR), where white and grey in the boxes refers to different phases, adapted from [47].

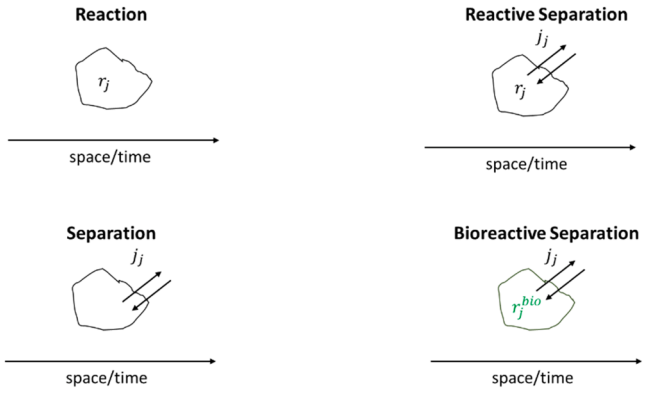


Fig. 5. Graphical representation of reaction, separation and (bio)reactive separation on the basis of the average experience of a fluid element in respect to change in state variables: x, p, T, etc. r represents a reaction, while j represents a mass transfer due to separation.

the flow, this performance can be approximated in the temporal direction for a (semi-)batch reactor with an externally coupled separation, assuming that the reactor volume is sufficiently well mixed, following the classical theory of ideal reactors [65]. This covers the integrated reaction separation process (Fig. 3) and the batch ISPR (Fig. 4). By contrast, the fluid element in a continuously operated sequence of a reactor and a separation unit with a recycle do experience locally and timewise separated either reaction or separation fluxes. Only when approaching the limiting case, by either an infinite recycle (total back mixing) the continuously operated external loop approaches the state of an internal integration, as discussed in detail in the paper of Baldea [66], or cascading of reaction and separation steps, such continuous external integration approaches the reactive separation.

3. Current status of bioreactive separations

Following the above set definition, we evaluate the current status of applications and research on bioreactive separation technologies in the literature. Although the term bioreactive separation has rarely been applied as such, various integrated reactive separation processes have already been successfully demonstrated and applied in the (bio-)chemical industry [29]. A biocatalytic reaction can theoretically be combined with any suitable separation technology. However, matching operating windows are a prerequisite for any type of reactive separation [35]. While the excellent performance of biocatalysts at around ambient conditions make them particularly attractive for sustainable production processes, the limited stability towards harsher conditions results in a more confined operating window for bioreactive separations [67,68]. Yet, genetic engineering and the discovery of hyperthermophilic enzymes that are stable above 100 °C can expand these windows drastically [68,69]. While stability issues are a major concern in many studies [70], even single-pass use of enzymes has seen commercial application in many cases [71]. In the sense of this manuscript, both fermentation and enzymatic reactions are considered as biocatalytic reactions and a survey of bioreactive separations is presented, categorized in accordance with the phase systems, as illustrated in Fig. 1. For this review, the Scopus database was used for combinations of ISPR or reactive processes with enzymatic reactions and separation technologies. Processes that we believe to be the most mature for presentation are presented. The result of this search is shown in Fig. 7, where also the search terms are listed. For vapor-liquid systems in total 250 references where found, for liquid-liquid systems 499 references were found, while for solid-liquid systems 175 references were found.

However, the term “extraction” is sometimes used synonymously for “separation”. Therefore, for the liquid-liquid systems it has to be mentioned, that additional search terms “solvent” or “liquid” or “solution” leads to 379 references. Furthermore, the search based on the term “ISPR” also covers continuously operated reaction-separation sequences with recycles (cf. Fig. 4, bottom right), which are not considered as bioreactive separation processes. Thus, the actual number of publications on bioreactive separation processes represents only a fraction of the publications listed in Fig. 7.

The following discussion has no claim for completeness, but illustrates that bioreactive separations, in agreement with the above

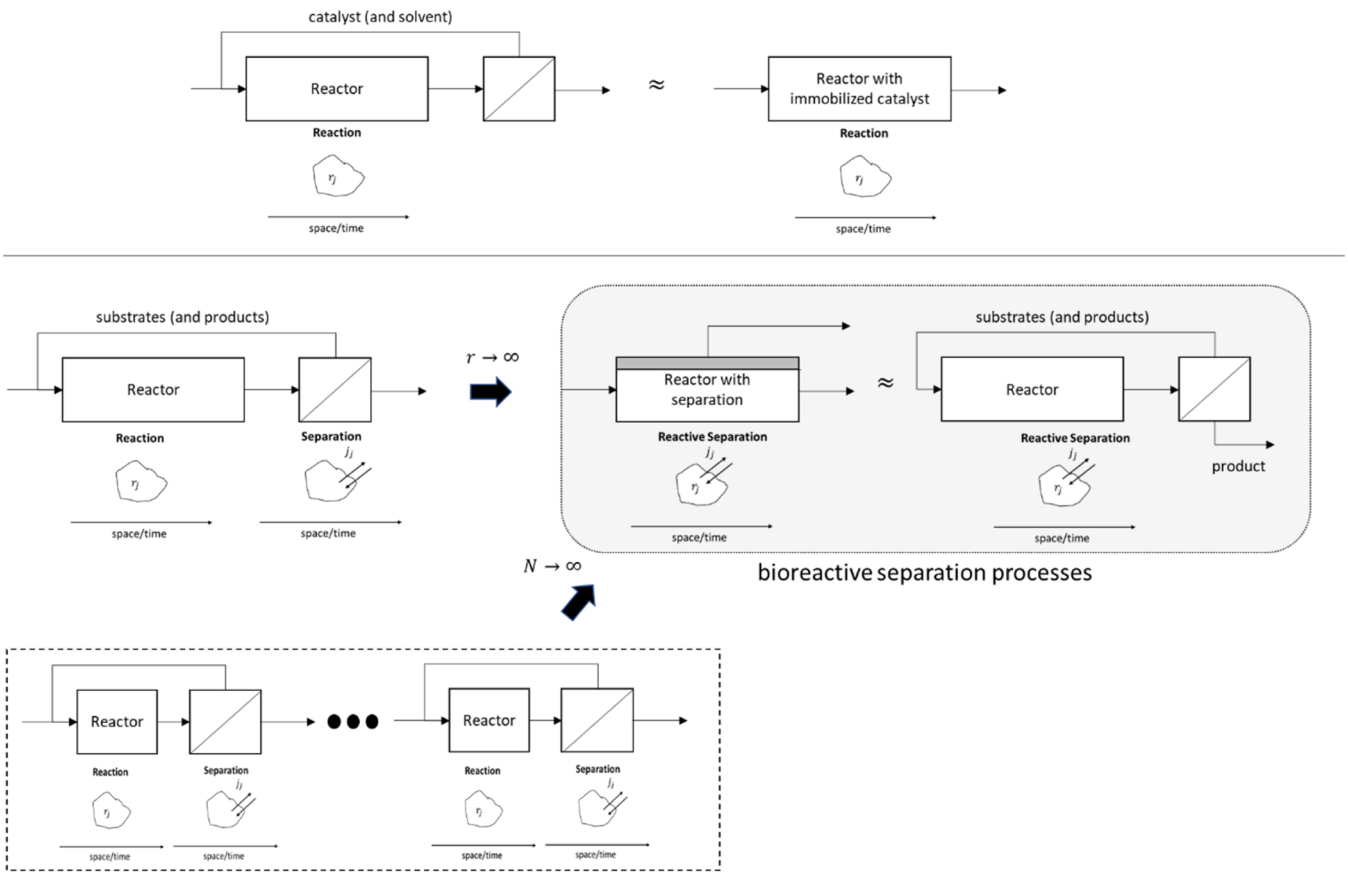


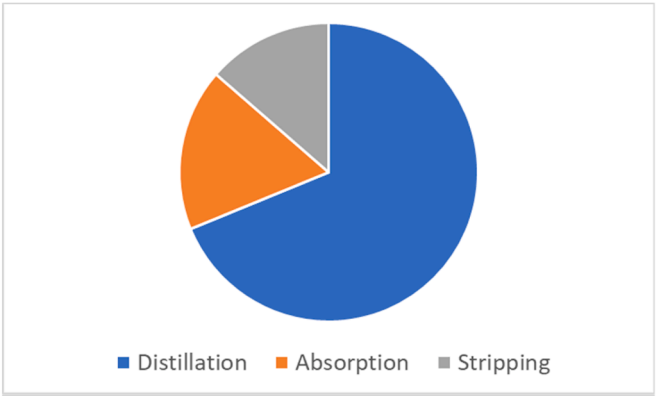
Fig. 6. Illustration of some configurations and the respective average experience of the fluid elements along the length-/timescale.

definition, have already seen a considerable interest in the past. Given the retrospective and perspective nature of this article, the purpose of the comparative analyses is to differentiate and analyze technology classes at the field level, rather than to guide a specific technology selection for specific applications. Based on the search terms, continuously operated reaction-separation processes with recycle streams as ISPR processes according to Fig. 4 bottom right are also included in the search. While these do not directly qualify as bioreactive separation process according to our definition we include them in the following discussion with an according notification. They generally provide a good basis for further integration into a bioreactive separation process.

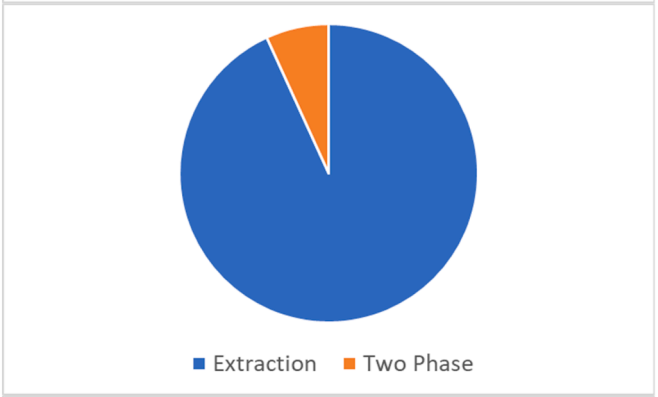
3.1. Selected vapor/gas-liquid systems

As illustrated in Fig. 1, vapor/gas-liquid systems cover bioreactive distillation, absorption and stripping processes. We further consider membrane reactors with membrane distillation and pervaporation as a representative bioreactive separation in this category. In the recent decades, especially enzymatic reactive distillation and absorption have seen a comparably large research interest. The chapter of Wierschem et al. [67] provides an overview on the research on both, enzymatic reactive absorption and distillation. More up-to date review articles are available for enzymatic reactive absorption by Molina-Fernandez and Luis [72] and by Chaussard et al. [73] for enzymatic reactive distillation in specific. In the context of reactive absorption, studies so far focussed primarily on carbon capture applications with carbonic anhydrase. This is particularly interesting as the focus is on improving the separation through the reaction, rather than improving the reaction through the separation. Carbonic anhydrase is an ancient metalloenzyme ubiquitous in nature [74]. In fact, it is one of the most active enzymes with a turnover number of up to 10^6 s^{-1} [75]. Unlike chemical activators like piperazine, which are commonly added solvents such as aqueous N-methyldiethanolamine (MDEA), carbonic anhydrase acts as a real catalyst, preserving the thermodynamically favourable properties of the solvent system, while accelerating the reaction rates and thereby intensifying the mass transfer [67]. Results of experimental and model-based studies indicate that enzyme-enhanced systems operate effectively at lower temperatures and with lower solvent concentrations, potentially outperforming classical activated amines as solvent systems in reactive absorption [76]. While various academic studies have investigated different solvent systems [77], immobilization techniques [67,78] and contacting equipment [79,80], also industrial research with large scale applications has been pursued [81]. While the high price of carbonic anhydrase and its limited stability in harsh conditions have been repeatedly highlighted as major limitations [75], the Canadian company CO2 Solutions Inc., which has recently been acquired by SAIPEM, reports on a TRL of 8-9, building on extensive testing and employment in a pulp mill application [82] and further studies [82,83]. The Amager Resource Center in Denmark also tested this concept on a large scale several years ago [84].

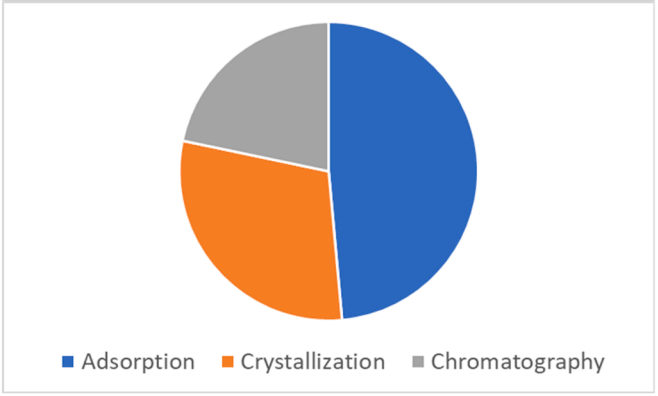
As summarized by Chaussard et al. [73], enzymatic reactive distillation has been investigated for two decades by now, with a still limited set of sixteen studies that however already bridged from laboratory to pilot-scale experiments and model-based techno-economical optimization. All studies so far focussed on transesterification reactions catalysed by immobilized lipase. The enzymatic reactive distillation columns basically fix the reactive zone in the middle part of the column, while an in situ removal of products via distillation shifts the reaction equilibrium towards full conversion and simultaneously reduces the effects of product inhibition by continuously removing the products from the reactive zone. The concept is illustrated for the transesterification of ethyl butyrate with butanol in Fig. 8, showing the equilibrium limited reaction (top left), the operating window (bottom left) and the structure of the reactive distillation column with the reaction zone (green) and



Vapor-Liquid: total 250
1. In-situ product removal OR In-situ product recovery OR ISPR AND Biocatal* OR enzym* OR fermentation AND
distillation OR absorption OR stripping
2. Reactive distillation OR reactive absorption* OR reactive stripping AND enzym* OR biocatal* OR fermentation



Liquid-Liquid: total 499
1. In-situ product removal OR In-situ product recovery OR ISPR AND Biocatal* OR enzym* OR fermentation AND
extraction OR two phase
2. Reactive extraction OR reactive two phase
AND
enzym* OR biocatal* OR fermentation



Solid-Liquid: total 175
1. In-situ product removal OR In-situ product recovery OR ISPR AND Biocatal* OR enzym* OR fermentation AND
adsorption OR crystalli* OR chromatrogr*
2. Reactive adsorption OR reactive crystalli* OR reactive chromatograph* AND
enzym* OR biocatal* OR fermentation

Fig. 7. Results of the literature survey with Scopus data base. Survey was done in February 2026. Left: Cake diagrams of the share of different systems. Right: total amount of references found as well as the search terms used.

possible catalytic packings (right). The experimental investigations have been conducted in batch and continuously operated columns of up to 12 m height [85–87]. While most studies focussed on transesterification reactions of ethyl or butyl acetate or butyrate, the studies also investigated the advanced potential of enantioselective synthesis in the kinetic resolution of chiral compounds such as *(R)*-phenylethyl acetate using immobilized lipase (CalB) [88]. Process models ranging from equilibrium-based to rate-based models have been developed and validated, taking into account mass transfer, thermodynamics, and enzyme kinetics [85,88–90]. These models enable predictive simulations and are essential for equipment design, scale-up, and process optimization. Even further intensified enzymatic reactive dividing wall columns have been investigated both experimentally and model-based, to enable a simultaneous separation of multiple product streams with enzymatic catalysis within a single column shell [89,90]. Considering that all research activities so far were entirely conducted at academic institutes a TRL of 5 can be assumed. Yet, it has to be recognized that continuously operated columns with up to 12 m height have been operated in the research studies, enabling successful model validation and process control [89, 90], including linear model predictive control, validated in the above mentioned 12 m dividing wall column [91].

While the previously discussed applications of bioreactive absorption and distillation focus entirely on enzymes, the application of reactive separations for fermentation processes has seen less academic research, but several industrial implementations. One such example is the Biostil process, which is a continuously operated fermentation integrated with distillation, and centrifugation for bioethanol production [92]. The development of this technology was driven by the necessity to enhance energy and process efficiency. As biofuel, bioethanol offers high octane and clean-burning characteristics that enable efficient combustion and lower tailpipe emissions. A defining feature of the Biostil process is the continuous removal of ethanol from the fermenter via a loop that includes solid-liquid separation (centrifugation) followed by vacuum distillation, which maintains the productivity in the fermenter. The centrifuge is utilised for the separation of biomass from the fermentation broth, while the recycling of yeast to the fermenter is a vital step in maintaining high yeast cell concentrations and productivity. Therefore, this in an ISPR process according to Fig. 4 bottom right and

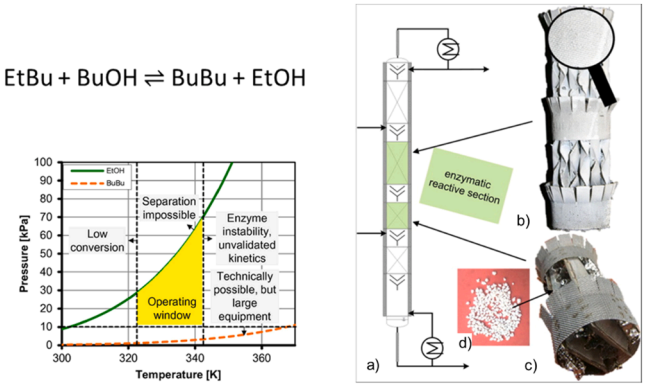


Fig. 8. Reaction scheme (top left), operating window (bottom left) demonstrating suitable operation conditions in respect to pressure and temperature, and process concept (right a) with catalytic packings (right b and c) for the immobilization of enzymes in the reactive zone for the transesterification of ethyl butyrate with butanol, where b has coated packings and c has bags for immobilised enzymes introduced in the packings. Reproduced from [85] with permission from Elsevier.

not in total line with the definition of bioreactive separation. Meanwhile, non-yeast solids, which include bacteria, are directed towards the distillation column in which the increased heat ensures the effective deactivation of microbial activity. The real-time separation of active and inactive biomass constitutes a bioreactive separation loop that preserves catalytic activity while concomitantly removing inhibitory or undesired components. By employing a multi effect distillation further energy integration is exploited as additional means for process intensification. Operated at a capacity of up to 150,000 L per day [93] the Biostil process offers an increase in yield from 87 % to 94.5 % when compared with a conventional fermentation. Furthermore, the stillage volume per litre of ethanol was reduced from 11 L to 0.8 L [92]. As the Biostil process is applied in industry since 1982 [92] and currently within the portfolio of Chematur Engineering (Sweden), a TRL of 9 can be considered. The basic concept of the Biostil Process is shown in Fig. 9.

An up-to-date review on the integration of distillation and fermentation for the in situ recovery of volatile fermentation products is provided by Straathof et al. [94]. Compared to vacuum columns, the integration of membrane distillation and bioreactors offers an alternative emerging bioreactive separation that integrates biological conversion with thermal membrane separation for high-quality wastewater reuse and resource recovery [95]. The membrane can either be submerged within or arranged in a side stream to the fermenter enabling simultaneous bioreaction and selective separation. For waste water treatment the bioreactions are predominantly performed by living microorganisms, including thermophilic strains for high-temperature operation. These can be metabolically active communities under

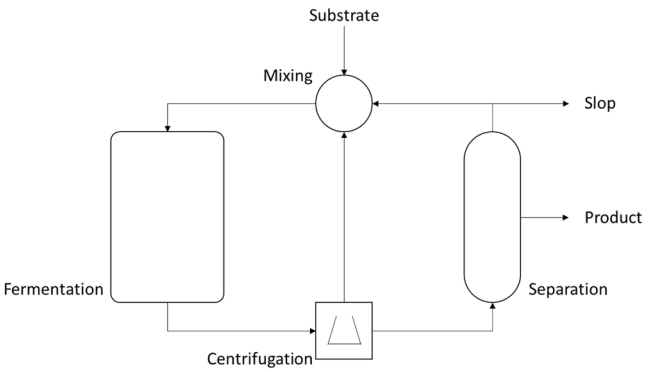


Fig. 9. Basic concept of the Biostil process, adapted from [92].

either aerobic, anaerobic, or anoxic conditions [96]. The membrane distillation unit enables vapor-phase transport, effectively rejecting salts, pathogens, and low molecular weight organics, while retaining reactive species in the bioreactor for further degradation. Most systems have been validated in laboratory setups, but a few aerobic and anaerobic membrane distillation bioreactors with real wastewater have approached TRL 6 [95]. However, long-term pilot-scale demonstrations in industrial settings are still scarce and continued scale-up and fouling control are critical to commercialization.

Nogueira et al. [97] provide a more elaborate review on the different kinds of gas-liquid-based bioreactive separations for ethanol production, covering fermentation under vacuum, with gas stripping and pervaporation. Bioreactive stripping is also studied as a more general method for simultaneous product removal in fermentation [98]. Applied to volatile compounds like ethanol, n-butanol, acetone, and benzaldehyde, bioreactive stripping enhances yields by continuously removing inhibitory products during cultivation. Microorganisms such as *Clostridium acetobutylicum* and *S. cerevisiae* are commonly used [98]. Compared to bioreactive distillation, gas stripping operates at lower temperatures (10 – 37 °C), preserving microbial viability and reducing energy input. However, separation efficiency and selectivity are generally lower, and additional condensation steps are required. Stripping gas choice (e.g., CO_2 or N_2) influences both product recovery and fermentation conditions. Systems using off-gas recycling or biogenic CO_2 offer partial process integration. However, most systems have been evaluated at the laboratory scale using synthetic media only, with limited exploration of real substrates [98]. Continuous operations remain rare [99] due to operational complexity and contamination risks. Consequently, bioreactive stripping systems for fermentation remain at TRL 5, while recent patents demonstrate the industrial attractiveness of this process [100–103].

Another type of membrane-based bioreactive separations are bioreactive pervaporation processes, which integrate fermentation or enzymatic reactions with a selective membrane separation via pervaporation, as e.g. considered for esterification reactions in which water is separated with a hydrophilic membrane [104]. While lipase catalysts and hydrophilic membranes are commercially available, the integrated membrane bioreactor concepts have been demonstrated primarily in laboratory and pilot-scale studies [104], reaching a TRL of 5. Pervaporation can also be coupled with the reaction in the biotechnological synthesis of high-quality fragrances and flavourings [105,106].

Stripping and pervaporation can more generally enable the continuous removal of volatile products like butanol directly from the fermentation broth [107] and can also be combined in a hybrid bioreactive separation, as outline in the review of Outram et al. [108] for ABE-fermentation (acetone, butanol, ethanol). The separation of the volatile products reduces product inhibition and allows higher substrate loadings and prolonged biocatalyst activity. The pervaporation process typically employs hydrophobic membranes, such as PDMS (Polydimethylsiloxane) [109–111]. While a phase change in the broth and cell removal are avoided, the permeating components evaporate when passing through the membrane. A scheme for a two-stage fermentation integrated with organophilic pervaporation for the production of ABE is shown in Fig. 10. Similar systems are still validated under laboratory conditions [112,113], limiting the TRL to 4.

3.2. Selected liquid-liquid systems

Liquid-liquid phase separation can be exploited in reactive extraction in which a microbial or enzymatic reaction is performed in a liquid phase while the second liquid phase can facilitate in situ product removal and/or substrate feeding. Extraction has frequently been considered in bioreactive processes, especially for in situ product removal [114]. This can be attributed to the fact that a separation can be implemented comparably easy internally in the reactor, provided that the extraction agent does not have a significant negative effect on the

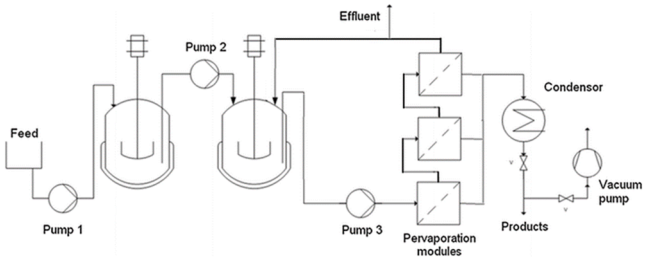


Fig. 10. Laboratory setup consisting of a two-stage fermentation integrated with organophilic pervaporation. Reproduced from [112], by permission from Oxford University Press.

biochemical reaction. The latter does however represent a quite sever limitation for the selection of possible solvents. The product range essentially comprises simple alcohols and organic acids, as well as flavourings in some cases [114]. In 1994, Cargill filed a patent on a lactic acid production and separation process [115] where the extraction takes place simultaneously to the fermentation in terms of an ISPR process with external loop according to Fig. 4 bottom right.

Beyond that, further specialized processes have been proposed, for example for L-phenylalanine production using genetically modified *E. coli*, where accumulation of the product inhibits key biosynthetic enzymes [116,117]. To counteract this, reactive extraction employs an organic two-phase system: an organic phase with a selective carrier (Di (2-ethylhexyl)phosphoric acid in kerosene) extracts the target product from the aqueous phase, followed by back-extraction into an acidic aqueous acceptor. Two implementation strategies are highlighted to improve mass transfer, using either hollow-fibre membranes or liquid–liquid centrifuges. The latter offers more robust operation under pressure fluctuations and higher mass transfer rates. The overall scheme is depicted in Fig. 11. Integration into fed-batch processes was achieved via ultrafiltration bypasses that provided cell-free permeate for extraction. A cost calculation carried out by the industrial partner of the research study showed that the use of integrated separation can reduce total costs by around 10% [93]. This is however one of few examples in which the economic evaluation for an integrated process has also been published. While pilot-scale operation and modelling confirm feasibility and clear metabolic benefits, challenges remain in interface stability, membrane area requirements, and carrier toxicity, limiting the TRL to 5. Nevertheless, this ISPR process with an external loop does not yet represent the specified simultaneous reaction and separation according to the definition of the bioreactive separation process.

Extraction is not only employed with fermentation. Fellechner et al. [48] provide an elaborate overview of enzymatic reactive extraction processes, which have been widely investigated, e.g. for condensation, hydrolysis and dehydrogenation reactions. For enzymatic transesterification of sunflower oil in a biphasic aqueous–organic system a cascade of a continuous stirred tank reactors was integrated with a continuous centrifugal contactor separator (CCCS) enabling enzyme recycling via aqueous phase retention [118]. The CCCS offers robust mixing and efficient phase disengagement, making it particularly suited for free enzymes in low interfacial tension systems. Several studies also considered reaction cascades performed in a bioreactive extraction [48]. However, almost all of these studies were performed in batch operation [48]. Johansen et al. [119] proposed a more sophisticated bioreactive extraction process with an enzymatic reaction cascade that combines enzymatic conversion in the aqueous phase by means of two cofactor-dependent dehydrogenases, liquid–liquid extraction of the intermediate and an esterification by an immobilized lipase in the organic phase. The two phases are linked through a continuous centrifugal contactor, providing efficient mixing and phase separation, and a detailed kinetic model validated using miniplant experiments. The lipase was further integrated into the extraction centrifuge in a subsequent study, resulting in a reactive extraction centrifuge [120]. These enzymatic processes can be considered as TRL 4.

An alternative to aqueous-organic or organic-organic extraction systems are aqueous two-phase systems (ATPS) in which additional surfactants and salts are used as additives to generate two aqueous phases to enable a gentle separation of biomolecules [121]. Consequently, ATPS have also been considered in the context of integrated fermentation processes in literature [122–124]. While several studies have demonstrated that organic media can have a negative influence on enzyme activity [125–128], it is assumed that this effect is less pronounced with ATPS [48,129]. ATPS have so far only been considered in laboratory experiments for integration with fermentation, limiting the TRL of ATPS-based bioreactive extraction to 4.

3.3. Selected solid-liquid systems

For solid-liquid systems again a number of separation processes can be considered for bioreactive separations, including crystallization, adsorption and chromatography. Crystallisation offers a very simple way of separating a product if this product precipitates under the reaction conditions. Once solid, the product can be filtered off or separated by centrifugation [130]. The product can either crystallise directly [131], as a salt [132] or by supplying additives [133]. The crystallisation itself can take place either spontaneously or induced. However, unlike the previous bioreactive separations the use of crystallization as reactive separation was first considered only quite recently with a first publication less than 10 years ago [134]. A schematic diagram of an

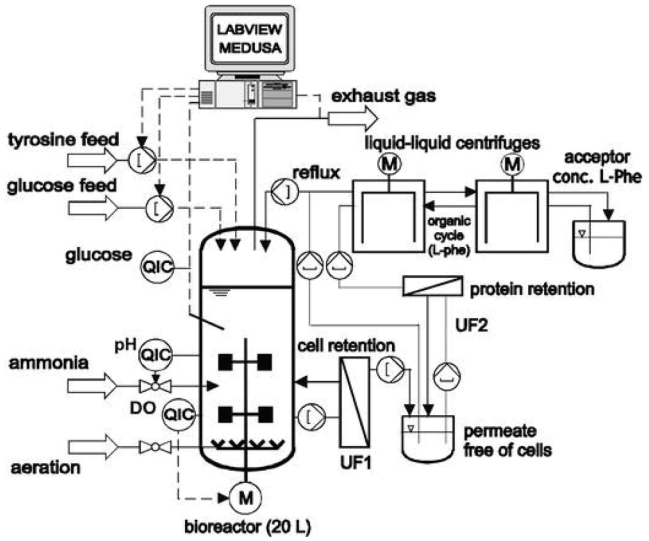


Fig. 11. Process scheme of a phenylalanine fermentation with integrated product separation. Reproduced from [117], with permission from SNCSC.

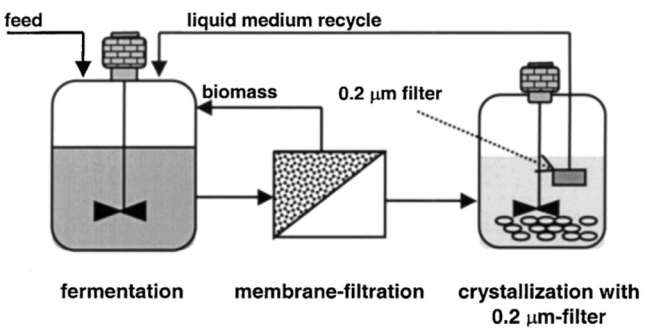


Fig. 12. Process scheme of a fermentation crystallization process. Reproduced from [135], with permission from Wiley.

integrated fermentation-crystallization process for 4-oxoisophorone reduction by *S. cerevisiae* is shown in Fig. 12. Here, the external loop according to Fig. 4 bottom right implies an ISPR process which serves as a first step towards a bioreactive separation process. A recent review on reaction integrated crystallisation in biocatalysis was given by Hülsewede et al. [134]. As most of the work is experimental the TRL is assumed to be 3.

Direct product precipitation enables the recovery of a purified product without the need for additional downstream separation steps. This also avoids contamination with organic solvents, which is often problematic in pharmaceutical and food applications. An example is the fermentation of lactic acid, which is removed in situ as calcium lactate by precipitation [114]. The potential of in situ precipitation has also been demonstrated for the solid–solid enzymatic conversion of calcium maleate to calcium D-malate [114].

Adsorption requires the identification of an appropriate adsorbent, but offers the advantage of high separation efficiency at low temperatures - as is usually the case in biotechnological processes. Adsorbents can in principle be tailored to the target component. Most studies on bioreactive adsorption focus on enzymatic reactive chromatography, covering hydrolysis, isomerization and transesterification reactions [48]. Beyond these, further model systems include the synthesis and separation of isomaltose [136,137] and the synthesis and separation of laminaribiose [138–140]. In these specific examples, zeolites were used to specifically isolate a product in an enzymatic reaction cascade before it reacts to form an undesirable by-product due to a subsequent reaction. The set-up of the multiphase fluidized bed adsorber for the enzymatic production of isomaltose is shown in Fig. 13. The biotransformation of other sugars in combination with simulated moving bed chromatography was also investigated and it was successfully demonstrated that such a combination is also possible [141,142]. Further studies investigated the combination of enantioselective chromatography with enzymatic racemisation, which significantly increased the yield [143,144]. Basically, however, the work was carried out on a laboratory scale. Initial models were developed, based on the enzyme kinetics and the separation, which can serve as a good starting point for scale-up. Therefore, the TRL is categorised at 3-4. Interestingly, Fellechner et al. [48] point out that there was basically no further research on enzymatic reactive chromatography in the last decade.

3.4. Cost analysis of bioreactive separation processes

By using bioreactive separation technologies, higher yields, conversion, and selectivity can be achieved. Ultimately, this can translate into added financial value. For the example of (non-bio) reactive distillation, Harmsen reviewed various industrial case studies [43] and reported savings potentials in operating costs, capital costs, or purely energy-related costs in the range of 15–80%. For the few industrial bioreactive separation processes, we are not aware of comparable studies on techno-economic assessments and comparative studies for different technologies. This may be due to grounded in the limited availability of suitable process models. Several academic studies have conducted cost evaluations for ISPR processes that represent reaction-separation sequences with recycles and reported possible energy and cost savings. Gonzáles-Peñas et al. [145] evaluated, in an academic study, an ABE fermentation intensified by in situ liquid–liquid extraction in a biphasic bioreactor for batch as well as a fed-batch process. Various scenarios and two extractants were considered. The cost evaluation was performed as a techno-economic assessment based on process simulation (Excel® + Aspen Plus®) and a discounted free cash flow analysis to determine the minimum butanol selling price. CAPEX/OPEX were estimated, among others, using the Aspen Process Economic Analyzer. The benefit of ISPR was demonstrated as cost and energy relief, with the minimum selling price reduced by 29% compared to the base scenario, accompanied by 34% savings in material costs and an 80% reduction in water consumption. A further ABE fermentation was investigated by Chen et al. [146] in an academic study, focusing on the downstream process after an in-situ gas stripping fermentation, where the resulting biphasic condensate stream was used as feed for optimized distillation sequences. The cost evaluation was carried out via process simulation (UniSim Design, NRTL/UNIQUAC) and techno-economic analysis using total annual cost and energy demand as key indicators, based on a plant capacity of 30 kt a^{-1} butanol. The benefit of ISPR/phase separation was quantified: compared to the conventional distillation concept, the energy demand decreased by 25.8% and TAC by 17.4%. Outram et al. [147] compared different ISPR techniques for ABE fermentation (including flash/vacuum, gas stripping, pervaporation, liquid–liquid extraction, perstraction, and adsorption) to consistently assess energy demand and economics. As the fermentation was simulated, a clear assignment according to Fig. 4 is not possible. The cost evaluation was based on UniSim process simulations (energy and mass balances) and an economic estimate using the Bridgewater method for CAPEX, with OPEX derived from mass balance and specific energy demand. The benefit of ISPR was quantified: perstraction was the only technique that reduced total energy demand relative to batch by ~5% and increased profit by 175%. The additional payback times ranged from approximately 2.2 to 4.5 years depending on the technology. Wierschem et al. performed a techno-economic evaluation of an ultrasound-assisted enzymatic reactive distillation for the synthesis of 10 kta butyl butyrate [148]. Although the ultrasound-assisted distillation has a higher investment due to the ultrasound device, the annuity increases by 25% because less catalyst is needed. Also, the highght of the ultrasound-assisted distillation was smaller. As mentioned earlier, a cost calculation was also performed for phenylalanine fermentation, indicating an added value of up to 10% for an ISPR process [93]. In that case, the cost evaluation was carried out by an industrial partner (DSM Biotech GmbH), which is why the costing methodology is, understandably, only described in broad terms.

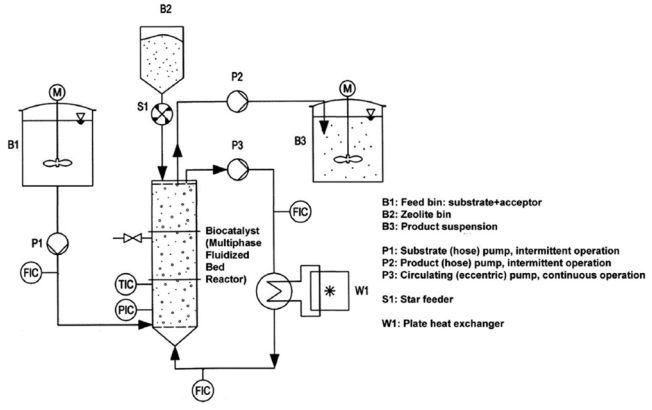


Fig. 13. Process scheme of a multiphase fluidized bed reactor with integrated adsorption. Reproduced from [137], with permission from Taylor & Francis.

3.5. Summary of the literature survey

When comparing the different systems, it becomes apparent that vapor/gas-liquid systems are by far the most advanced and industrial examples have been reported for both bioreactive distillation, with fermentation, and bioreactive absorption with enzymes. However, on closer inspection the number of systems which have been extensively investigated is rather small. Considering enzymatic reactive absorption and distillation it is quite striking that enzymatic reactive absorption was almost exclusively investigated for carbon capture with carbonic anhydrase and that enzymatic reactive distillation was almost exclusively investigated for transesterification reactions with lipase. In the case of extraction - representing liquid-liquid systems - there are also individual applications that are highly developed. In contrast, examples

in the field of solid-liquid systems have reached the lowest TRL, despite a wide range of investigated applications.

Membranes can be employed in almost all of the considered phase systems, with especially membrane contactors being applicable for membrane distillation in vapor/gas-liquid and membrane extractor in liquid-liquid systems. Pervaporation (vapor/liquid) has been widely investigated in the context of membrane bioreactors, whereas nanofiltration or reverse osmosis (liquid/liquid) have not yet received wide attention for bioreactive separations. While the use of micro- and ultrafiltration membranes is widely applied for whole cell or enzyme retention, it does not reflect a bioreactive separation in accordance with the provided definition as long as the retention of the catalyst is the sole function of the membrane. So far, the use of membranes for in situ product removal is largely limited to the use of hydrophilic membranes for water separation in esterification reactions. Other applications are in the focus of academic research and currently limited for industrial application.

Overall, it appears as if the combination of separation with fermentation is more technologically advanced than bioreactive separations with application of pure enzymes. This may be due to the fact that fermentation processes typically generate larger production volumes, and integrated processes offer the potential to increase yield, a key factor for bulk products, where raw material costs dominate production costs. In contrast, pure enzymes are mostly applied for specialty products, such as in the pharmaceutical industry, where profit margins are higher and the yield based on the educt is of lesser importance. In addition, the rate of reaction of fermentation processes are an order of magnitude slower than enzymatic processes, which means that the mass transport for separation does not represent a bottleneck in the process. However, contrary to the identified industrial applications, enzymatic reactive separations have seen more structured research efforts and the derivation of sophisticated models, some validated even with pilot-scale experiments, enabling a systematic model-based evaluation of the techno-economical potential and the bottlenecks that need to be overcome to yield the conditions for an economically viable application. This is of particular importance for these highly integrated processes, for which a variety of methods, such as genetic engineering, thermodynamic predictions as well as optimal control and design methods may help to enable improved processes.

4. Challenges and SWOT-analysis

As apparent from the previous discussion, bioreactive separation processes not only have a high potential to increase the efficiency of classical biocatalytic processes and provide more sustainable alternatives to classical chemical processes, but have also seen quite diverse research. However, several scientific and technical challenges need to be addressed to increase the rather limited number of successful industrial implementation. These challenges are diverse and span from fundamental scientific issues to practical limitations, penetrating, but also connecting research in the areas of biotechnology, fluid separations and process systems engineering, mandating a multidisciplinary approach. It has been widely recognized that sustainable processes are generally not the product of a single discipline, but usually result from an intersection of different perspectives [149,150]. To better understand the need for such a multidisciplinary approach and pinpoint specific research needs the following sections summarize the major challenges for bioreactive separations and present a SWOT analysis for the different bioreactive separation technologies.

4.1. Challenges in bioreactive separation

As highlighted for the various systems described in Section 3, a sufficient stability of the biocatalyst is an important requirement. Improved stability can however be accomplished by various means. Genetic engineering of the biocatalyst can enhance stability, flexibility, and simplify adaptation to different reactions [22,151,152]. However, also the environment and the conditions that the biocatalyst experiences can be modified via the selection of an ideal solvent and possible additives [77]. Another option that has received considerable attention, especially in combination with thermal separations, such as enzymatic reactive absorption and distillation, are the different means for biocatalyst immobilization. Yet, while immobilization can help to create a more ideal local environment in a narrow operating window that helps to improve stability and may even improve activity [67], it may limit the amount of accessible enzyme compared to a dissolved enzyme [153] and suffer from mass transfer limitations. Most importantly in the context of bioreactive separations, the integrated separation can, apart from improving the yield, also overcome product inhibition but limit the operating window [34].

In order to yield practically relevant and competitive solutions the overall process performance needs to be at least competitive with chemical processes. As such the overall process should be considered in an early phase of process development, too. As demonstrated for enzymatic reactive distillation, this can only be accomplished by sufficiently accurate process models, which enable a techno-economical evaluation, while accounting for the strongly nonlinear coupling between the different scales from the molecular to the process level. A key challenge is the lack of sufficiently accurate thermodynamic models, as well as reaction and mass transfer kinetics. The potential of thermodynamic predictions to describe solubility, yield, and kinetics is demonstrated in literature [154–156]. Biochemical processes are characterized by complex reaction cascades and multi-component mixtures in which minor components, such as additives, and impurities can have a tremendously influence on the overall process performance [22,34]. Many systems suffer from missing or incomplete experimental data, in order to predict process behaviour or optimize processes with the simulation and optimization toolbox from process systems engineering. While the reported studies for enzymatic reactive distillation primarily indicate the feasibility and power of an integrated experimental and model-based optimization [85], the complex multicomponent systems and intertwined kinetics of fermentation processes make them far less accessible for model-based design methods, limiting the development almost exclusively to tedious and expensive experimental development. The ability to generate reliable data for reaction as well as separation quickly with advanced analytical techniques and to pursue a systematic model development and experimental design is essential for overcoming this limitation. In addition, these data need to be findable, accessible, interoperable, and reusable [157].

While model systems help in understanding fundamental principles, real-world industrial applications often face strict time constraints, requiring fast adaptation and scalability. Identifying bottlenecks in bioreactive separation processes is crucial for optimization, whether they stem from mass transfer, reaction rates, or operational stability. Furthermore, ensuring the long-term operational stability of biocatalysts remains a major challenge. Factors such as fouling, deactivation, and loss of activity must be minimized to maintain efficiency over extended periods of operation. While peak performance is often the focus of research, industrial applications demand robust and stable processes capable of operating efficiently under varying conditions. Simplicity in process design is another important aspect to ensure acceptance by operators.

Despite all these challenges, the existing examples of bioreactive separation processes already indicate the huge potential. A full exploitation of this potential does however mandate a multidisciplinary approach, which considers the highly nonlinear interactions from the molecular to the process scale, in order to overcome limitations that cannot be resolved solely in the individual fields of research [22,158]. A collaborative approach between biotechnology, fluid separations and process systems engineering as well as other disciplines, such as reaction and genetic engineering is therefore indispensable for broadening the understanding of bioreactive processes and creating a basis for

bioreactive separations as innovative solutions in the field of biotechnological production processes [23,159]. In particular, an integrative approach that bridges from material and catalyst development to process design by process models already at an early stage of process development can enable significant time and cost savings and unlock previously unutilised potential [160–162]. Such a holistic approach can only be accomplished by means of an integrated experimental and model-based development. Molecular and process models can contribute to understanding molecular interactions, reaction mechanisms and separation dynamics, and can reduce the need for extensive experimental trials through targeted planning [163,164]. Improved knowledge of molecular interactions allows for the development of flexible and adaptable bioreactive processes capable of handling variable feedstocks and conditions. The integration of automation and digitalization further enhances process monitoring and efficiency, reducing manual intervention and improving reproducibility [22]. Evaluating the environmental and economic impact of these processes from a life cycle perspective can contribute to the development of truly sustainable solutions [17,152].

4.2. SWOT analysis

In order to provide a distinct analysis for the individual bioreactive separations, an analysis of the strengths, weaknesses, opportunities and threats (SWOT) is presented in the following. This analysis enables a well-founded assessment of the potential and competitive advantages as well as the hurdles that need to be overcome in order to successfully integrate bioreactive separation technology into industrial processes. To provide a more refined analysis, at first a SWOT analysis for general reactive separation technologies is conducted with results in Table 1. Subsequently, a SWOT analysis for all specific bioreactive separations is provided in Tables 2,3,4,5,6,7,8,9,10. For each of these tables, the specific points that relate only to the bioreactive and not the general reactive separation are highlighted in green italic text. A general weakness for all new technologies is that the first devices will certainly come from manufacturing rather than standard production, and will therefore be expensive. Please note that the following analysis is based on the review of the individual technologies reported in Section 3, as well as intense discussions between the authors, reflecting the cumulative experience and expectations.

The subsequent tables offer an insight into the individual SWOT for each reactive separation technology, with specific features for bioreactive separation highlighted in italic text.

As evident from the SWOT analysis, bioreactive separations provide several benefits that are common across the different technologies.

Table 1
SWOT analysis for general aspects on (bio)reactive separation, independent of individual separation technology.

Strengths	**Opportunities**
Product removal drives reaction beyond equilibrium	Higher selectivity and conversion with fewer side reactions
Coupled heat/mass transfer can lower energy use	Advanced materials and internals
Fewer, smaller units reduce capital cost	Hybrid separation concepts
Basic models exist	Advanced modelling allows consideration of strongly nonlinear interactions
High biocatalyst selectivity	*Tailoring biocatalyst performance and stability to specific application by genetic engineering*
Product removal relieves inhibition, boosts activity	
Weaknesses	**Risks/Threats**
Need for overlapping operating windows limits the flexibility regarding feedstock and product specifications *(specifically challenging for biocatalytic systems)*	Conventional processes and equipment may seem simpler and be favoured in industrial practise
Simultaneous reaction and separation make modeling, simulation and optimization more challenging and important	Strong coupling can cause instability or runaways
Complex systems (e.g. electrolytes) and biocatalyst (long-term) activity further increase modelling effort	Lack of standards and regulatory barriers
	Potential sensitivity of biocatalyst to inhibitors

Table 2
SWOT analysis for (bio)reactive distillation.

Strengths	**Opportunities**
Established, proven technology for continuous operation	Energy savings via heat integration (e.g. heat pumps)
Wide operating range, high product purity	Digital tools for design, control, and monitoring
Reaction heat can drive separation	*Pressure tuning or membrane distillation for milder conditions*
	Advances in enzyme engineering and immobilization strategies for high temperature tolerance or other limitations
Weaknesses	**Risks/Threats**
Not suitable for heat-sensitive components	Tighter CO_2 and energy regulations
Reactive azeotropes complicate design	*Increased risk of foaming due to complex media*
High heat demand and CO_2 emissions	*Fouling or loss of immobilized enzyme activity*
Temperature limitation due to potential denaturation of the biocatalysts (stability limited by temperature and residence time)	
Short residence times demand high reaction rates	

Table 3
SWOT analysis for (bio)reactive absorption.

Strengths	**Opportunities**
Enhanced mass transfer via reaction	Development of green solvents (ionic liquids, DES, etc.)
Tailored solvents for specific applications	Environmental applications (VOC capture, pollution control)
Flexible equipment options (columns, towers, contactors)	Energy-related uses (flue gas treatment, CO_2 capture)
Simultaneous capture and conversion of gaseous substrates	Innovation in equipment design
Low-temperature operation suitable for biocatalysts	*Biocatalyst engineering for solvent, pH, and temperature tolerance*
Weaknesses	**Risks/Threats**
Solvent regeneration is energy- and cost-intensive	Environmental regulations on solvents
Requires sufficient solubility in chosen solvent	Solvent toxicity or disposal challenges
Solvent degradation/contamination reduces efficiency	Highly specific, less transferable solutions
Solvent–biocatalyst compatibility critical	*Biocatalyst sensitivity to gas impurities (e.g. NOx)*
Immobilization needed if solvents require thermal regeneration	*Increased risk of foaming due to complex media*

Table 4
SWOT analysis for (bio)reactive stripping.

Strengths	**Opportunities**
Efficient removal of volatile products	Synergy with aeration in bioprocesses
Suitable for viscous systems	Use of intensified mass transfer equipment (e.g. membrane contactors, rotating beds)
Low-temperature operation possible (with inert gases) improves biocatalyst stability	*Potential application of biofilms and localized gas feeding*
Weaknesses	**Risks/Threats**
Limited to volatile products	Unintended co-removal of components
Foaming and condensation reduce efficiency	Additional energy demand for gas compression or heating
Solvent or water loss with stripping gas	Safety risks with flammable stripping gases
Low selectivity if multiple volatiles are present	*Oxygen limitations due to stripping gas mixing*
High hydrodynamic stress may damage biocatalysts	*Off-gas contamination with biocatalysts*
Large volumes of stripping gas required	

Table 5
SWOT analysis for (bio)reactive pervaporation.

Strengths	**Opportunities**
Highly hydrophilic and also some organophilic dense membranes available	Development of advanced membrane materials
Product separation and catalyst retention in single step	Use of fermentation heat to reduce energy demand
	Possibility of co-factor retention
Weaknesses	**Risks/Threats**
Limited range of commercial membranes	Complex development compared to established processes
Vacuum operation requires energy for evaporation/condensation	Membrane fouling, scaling, or degradation in long-term use
Experimental screening generally necessary	Clogging by proteins, cells, or biofilms reduces performance
High temperatures (for strong driving force) can inactivate biocatalysts	

Table 6
SWOT analysis for (bio)reactive extraction.

Strengths	**Opportunities**
Selective separation via tailored solvents	Use of aqueous two-phase systems (low/no toxicity)
Operates under mild conditions	Process intensification with centrifuges
Residence time adjustable	*Enzyme engineering for solvent tolerance*
Second phase can supply substrates continuously	*Tailored solvents for biocatalyst stability and selectivity*
Biocatalyst inhibition avoided by continuous substrate transfer and product removal	*Biocatalyst immobilization in Pickering emulsions*
Biocatalyst retention possible via polarity differences	
Weaknesses	**Risks/Threats**
Balancing hydrodynamics and mass transfer is critical	Stringent safety and toxicity regulations
Possible solvent leaching into raffinate	Emulsification challenges in phase separation
Further downstream solvent recovery required	*Solvent toxicity to biocatalysts requires careful selection*
Organic solvents often poorly biocompatible	

Table 7
SWOT analysis for (bio)reactive membrane nanofiltration/ultrafiltration.

Strengths	**Opportunities**
Separation by steric hindrance and polarity	Developing fouling-resistant membranes
Pressure-driven, no phase transition	Tailored membranes for selectivity and stability
Operates at low temperatures favorable for biocatalysts	Continuous operation via diafiltration (substrate feed + product removal)
Biocatalyst retention possible	*Co-factor retention possible*
Weaknesses	**Risks/Threats**
Limited long-term membrane stability	Limited industrial adoption due to stability issues
High investment and maintenance costs	*Long-term stability by fouling, scaling, or clogging by proteins, cells, or biofilms*
Limited selectivity and screening required	
Limited membrane and biocatalyst compatibility with organic solvents	
In general membranes are difficult to sterilized	

Continuous removal of products allows reactions to proceed beyond equilibrium limits, increasing conversion and yield. The integration of reaction and separation can reduce the number and size of equipment, lowering capital investment, while coupled heat and mass transfer may reduce overall energy consumption. Biocatalysts can particularly contribute with high selectivity, while in situ substrate feeding and product removal can mitigate inhibition effects, thereby increasing catalytic activity. Advances in new materials, hybrid separation concepts, and enzyme engineering further expand the potential applications of bioreactive separations. In particular AI-based enzyme engineering is a strong opportunity for all types of processes.

Several challenges are shared across technologies. Especially the need for overlapping operating windows of (bio-)reaction and separation limits flexibility with respect to feedstocks and product specifications, and requires a dedicated design of the bioreactive separation process, considering the interrelated decisions of the separation process, solvent and biocatalyst choices. The sensitivity of biocatalysts with respect to temperature, pH, solvents, and inhibitors represents a major aspect that makes the development of bioreactive separations more challenging than chemical reactive separations. Fouling, scaling, and contamination can impair membranes, adsorbents, or resins, while regeneration and solvent recovery add further operational burdens. In

Table 8
SWOT analysis for (bio)reactive adsorption.

Strengths	**Opportunities**
Adsorbents can be tailored to application	Novel adsorbents from renewable resources or molecular design
High product selectivity	Tailored adsorbents for simultaneous adsorption and immobilization
Mild operating conditions favourable for biocatalyst application	Higher local concentrations in adsorbent phase
Product removal relieves inhibition and boosts activity	Ion-exchange resins enable regeneration via pH shift
	Multipurpose adsorbents used for biocatalyst immobilization or for generation of favourable microenvironments
Weaknesses	**Risks/Threats**
Continuous operation complex	High investment for specialized adsorbents
Regeneration/desorption required	Adsorbent surface chemistry may be toxic to biocatalysts
Limited adsorbent capacity	*Unfavourable adsorption of enzymes or leaching during desorption*
Trade-offs between selectivity and regeneration	
Susceptible to fouling in complex media	

Table 9
SWOT analysis for (bio)reactive chromatography.

Strengths	**Opportunities**
Very high (stereo)selectivity possible	Reusable resins with tailored functionalities
Functionalized media available	High-purity production for APIs and fine chemicals
Mild operating conditions favourable for biocatalysts	Continuous chromatography concepts
Product removal enhances catalyst activity	*Multipurpose resins for biocatalyst immobilization or for generation of favourable microenvironments*
Weaknesses	**Risks/Threats**
Continuous operation difficult	Resource intensive
Limited throughput, high dilutions	Fouling, scaling, and leaching of the resin
Resin regeneration required	*Unfavourable adsorption of enzymes or leaching during desorption*
Integration into reaction–separation schemes is challenging	*Biofouling due to whole cells or proteins can block the resin*
Fouling or clogging by biomass possible	

Table 10
SWOT analysis for (bio)reactive crystallization.

Strengths	**Opportunities**
Direct product formation possible	In situ monitoring tools for process control
Mild conditions favourable for biocatalysts	Chiral resolution via selective crystallization
Product inhibition reduced by crystallization	Concentration-driven separation
	Enzyme engineering for higher tolerance to crystallization conditions
Weaknesses	**Risks/Threats**
Continuous operation complex	Impurities or structural changes in crystals
Limited to crystallizable products; nucleation/growth hard to control	Co-crystallization with substrates or impurities
Crystals may be contaminated with proteins or enzymes	*Crystallization conditions may restrict biocatalyst compatibility*

order to consider the diverse interrelated effects only a holistic approach that accounts for the nonlinear relationships by means of a multiscale model can yield a targeted development of the bioreactive separations. This can only be accomplished by means of an integrative approach that brings together biotechnology for robust and selective biocatalysts, fluid separation science for suitable unit operations, and process systems engineering for reliable process design, control, and scale-up.

5. Vision 2040

In order to enable the integration of reaction and separation and speed up the development of bioreactive separation processes we propose a vision for 2040, inspired by the Vision 2020 from the 2000 separations roadmap of the AIChE [45]. However, rather than proposing a technology-specific roadmap with quantified milestones and ownership, this section outlines key scientific, technological, and educational directions that are widely regarded as enabling for the field, while recognizing that concrete milestones, prioritization, and implementation pathways will depend on application context and stakeholder perspective. For that purpose, we define several objectives for fundamental and applied research as well as the education of future biochemical process engineers. Finally, some dedicated applications are proposed that show particularly high relevance and prospect.

5.1. Fundamental research

Bioreactive separation technology holds great potential for the future of bioprocessing. However, its successful implementation relies on addressing fundamental scientific questions. In particular, a comprehensive understanding of key interactions between bioractions and the operating conditions of separation processes will be essential for designing efficient, scalable, and sustainable bioreactive separation systems. To advance bioreactive separations, fundamental research must address the following three central pillars:

a) **Identifying the optimum level of integration**
   The efficiency of bioreactive separations depends on how tightly biocatalysis and separation are coupled. The interfaces in multicomponent multi-phase environments are critical, yet complex, requiring accurate multiscale models that link molecular interactions to process-scale performance. Special attention must be given to evolving and metastable systems, where modelling and experimental validation remain particularly challenging.
b) **Engineering robust biocatalysts**
   Enzymes and microorganisms must be tailored to the conditions of separation steps, especially in mixed media and at fluid interfaces. This can result in adverse targets for enzyme engineering, as temperature stability limits the application in reactive distillation or pervaporation, while both processes may help to avoid substrate and product inhibition, limiting the need for improved substrate/product tolerance. This calls for directed enzyme engineering, systematic screening, and optimization strategies to ensure activity and stability under process conditions. Identifying the decisive parameters across scales will guide the development of catalysts and processes with maximum efficiency.
c) **Developing advanced modeling and simulation**
   Modeling is essential to capture the coupled dynamics of reaction and separation. The key questions are the necessary degree of model accuracy and the most effective methods to represent system behavior, including hybrid (physics-informed) machine learning methods. To achieve this, measured data as well as relevant process metadata need to be accessible and interoperable. Model-based experimental design can reduce experimental effort and provide insights into the mutual influence of catalysis and separation on their microenvironments, while optimal control and design allow for the identification of bottlenecks and conditions for a techno-economically and environmentally attractive operation.

By advancing integration strategies, biocatalyst design, and multiscale modeling, bioreactive separation can be transformed into a core technology for future bioprocessing, enabling efficient, integrated, and sustainable production systems.

5.2. Applied research

To enable the industrial application of bioreactive separations, applied research must address four key areas:

a) **Managing impurities and novel feedstocks**
   Impurities strongly influence both biocatalyst activity and separation efficiency. Their effects must be systematically understood, and mitigation strategies developed. In parallel, the transition to sustainable processes requires incorporating renewable and unconventional feedstocks into bioreactive separation systems without compromising stability or performance. Process development needs to quickly account for the real multicomponent feedstocks.
b) **Ensuring robustness and usability**
   Industrial adoption demands predictable, user-friendly tools. Models must be both reliable and practical, offering clear decision criteria for selecting bioreactive separation technologies. Standardized protocols and experimentally validated key parameters are essential to ensure robustness and ease of implementation. At the same time, practitioners must accept that complex systems and questions cannot be tackled with simple heuristics and appreciate the integrative power of complex multiscale models that can account for the inherent nonlinearity.
c) **Adapting and innovating equipment design**
   Most conventional reactors are not designed for integrated biocatalysis and separation. Novel equipment concepts may be required, and strategies for retrofitting existing equipment developed. Operation and control of such systems require new approaches to ensure stability and efficiency. Advanced manufacturing techniques, such as 3D printing, open additional opportunities for shaping and stabilizing biocatalysts, enhancing efficiency and reusability [165].
d) **Establishing scale-up criteria**
   Clear guidelines for scaling bioreactive separation processes are largely missing. Identifying rules for scale-up and evaluating integration efficiency at different scales are crucial to bridge the gap between laboratory success and industrial implementation.

By addressing these applied research challenges, bioreactive separation can mature into a robust, scalable, and sustainable alternative to conventional separation technologies, accelerating its adoption in industrial bioprocessing.

To provide a brief example for the interdisciplinary fundamental and applied research on bioreactive separation processes, we refer to the INnovaTive Enzymes and polyionic-liquids based membRAnes as CO_2 Capture Technology (INTERACT) project [166] as an example. The project was executed as a cooperation project funded within the 7th Framework Program of the European Commission between 2013-2017. The consortium was composed of eleven partners from industry and academia, working on the development of enzymatically catalysed reactive absorption processes. While the enzyme carbonic anhydrase was produced by Novozymes (since 2024 Novonesis), academic partners from Technical University of Denmark, TU Dortmund University und KU Leuven, together with IK4Cidetec, Solvioinc and Sintef worked on the development and characterization of solvent systems [77,167,168] and contacting technologies for the implementation of gas-liquid contacting in reactive absorption. The implementations covered on the one hand classical packed columns with dissolved and immobilized enzymes [153, 169,170], as well as innovative biocatalyst delivery systems [78] and

rotating packed beds [79]. On the other hand specialized gas membranes and membrane contactors based on polymerized ionic liquids were fabricated and tested for CO_2 capture [171,172]. Technology development was complemented with process modelling [76,173] for economic and LCA assessment carried out by the partners SUPREN and Prodintec. One of the most interesting results enabled by the collaborative research that covered system development, experimental characterization and detailed process modelling was the identification of innovative operating conditions for cyclic absorption process, for which the enzyme enables low -temperature absorption that enables increased cyclic loadings and a reduced energy penalty for post-combustion carbon capture [174].

5.3. Education

Advancing bioreactive separation technology requires dedicated educational efforts that go beyond traditional curricula. Four key aspects should be emphasized:

a) **Creating awareness**
   Biochemical engineers must develop at least a basic understanding of process intensification and bioreactive separations. This awareness is the foundation for recognizing the relevance and potential of these technologies in future bioprocessing.
b) **Understanding benefits and challenges in multiscale systems**
   Students and professionals need to grasp both the opportunities and limitations of integrating reaction and separation. Process modelling and simulation are powerful tools to build this understanding, as they make trade-offs, synergies, and bottlenecks visible. Awareness and understanding of the multiscale nature of the systems can best be achieved through practical training and insights via computer simulations.
c) **Fostering collaboration skills**
   Bioreactive processes cannot be mastered by a single discipline. Success depends on teamwork between biotechnologists, chemists, biochemical engineers, separation specialists and process systems engineers. This requires openness to collaboration and strong communication skills to bridge disciplinary boundaries. including a common language and terminology as well as a common nomenclature (as much as this is possible).
d) **Ensuring knowledge transfer between academia and industry**
   New scientific developments must be carried into practice not only through graduates entering industry but also via targeted lifelong learning opportunities. Academia should take an active role in providing continuing education and professional training formats that enable practitioners to integrate the latest research insights into real-world applications. However, feedback from industry is also needed on its everyday needs, which rarely play a role in academia, e.g. regulatory and approval procedures.

By combining awareness, technical insight, interdisciplinary collaboration, and effective knowledge transfer, education can prepare the next generation of engineers and practitioners to drive innovation and implementation of bioreactive separation technologies [175,176].

5.4. Potential applications in future

Bioreactive separation technology holds vast potential to revolutionize industrial processes beyond its current applications. By integrating biocatalysis and separation in a single step, it enables more efficient, selective, and sustainable processing solutions, opening the door to transformative innovations across diverse fields. Key application areas include:

a) **Biochemical recycling**
   Enzymatic processes offer a highly selective degradation of plastic from fossil and renewable sources, overcoming the limitations of conventional recycling with mixed or contaminated plastics [177]. Bioreactive separation can continuously remove degradation products, drive reactions forward, and improve efficiency in polymer-to-monomer conversion.
b) **Biomining**
   Microorganisms can extract valuable metals from ores, industrial residues, or electronic scrap, avoiding the energy-intensive and pollutive nature of conventional mining [178]. Coupling biocatalysis with selective separation could enhance metal recovery while reducing environmental impact.
c) **Carbon capture, storage, and utilization (CCSU)**
   Beyond CO_2 capture, biocatalytic systems can transform CO_2 into valuable products such as organic acids, biofuels, or specialty chemicals [17]. Integrating separation into these processes improves yields, reduces energy demand, and strengthens the economic viability of CO_2 utilization.
d) **Battery recycling**
   Bioreactive separation can aid in recovering and purifying metals from spent batteries, offering a sustainable alternative to smelting and leaching [179]. Such processes support the circular economy and secure critical raw materials for energy storage technologies.
e) **Water management**
   Many industrial wastewater treatments depend on energy-intensive oxidation or chemical degradation. Enzyme-driven reactions provide selective and sustainable alternatives [180], simultaneously removing as well as revalorization of pollutants and enabling recovery of valuable compounds.
f) **Hydrogen production and utilization**
   In closed-loop biocatalytic cascades, bioreactive separation can stabilize hydrogen-consuming or -producing enzymes, improving efficiency and enabling practical hydrogen-based energy systems [181].
g) **Electrobiocatalytic processes**
   By integrating electrochemical and biocatalytic reactions, bioreactive separation can boost efficiency in sustainable chemical synthesis, energy storage, and environmental remediation [182].
h) **Biorefineries**
   The use of renewable raw materials is primarily made possible by research in the field of biorefineries. Inhibitions occur in the interactions between the various necessary enzymes and the complex substrates. Bioreactive processes can help to make biorefineries more efficient in this regard [183,184].

Of course, existing biotechnological production processes also have the potential to be intensified through targeted measures – in particular model-based methods – and thus continue to produce a high-quality and sustainable product in the future. In the coming decades, bioreactive separation can make a decisive contribution to the UN SDGs. By improving resource efficiency (SDG 12), enabling cleaner industrial processes (SDG 9), and reducing environmental impact (SDG 13), it supports a transition toward global sustainability. Applications in biochemical recycling, biomining, and battery recycling foster a circular economy (SDG 11), while CO_2 utilization and water management address climate resilience and access to clean water (SDG 6). Hydrogen production and electrobiocatalysis further strengthen clean energy systems (SDG 7). Leveraging nature's selectivity with smart separation strategies, bioreactive separation has the potential to transform industrial processes and drive innovation in line with global sustainability goals.

6. Conclusion

Bioreactive separation represents a promising strategy for overcoming the intrinsic limitations of biocatalysts and advancing sustainable process intensification. As highlighted in this review perspective

paper, integrating reaction and separation can drive conversions beyond equilibrium limits, increase selectivity, and reduce energy demand and equipment size. At the same time, the SWOT analysis clearly shows that these advantages are accompanied by substantial challenges, including the narrow overlap of operating windows, the sensitivity of biocatalysts to inhibitors and stress factors. The design and scale-up of these systems can substantially benefit from process modelling, simulation and optimization, which however also comes with considerable challenges due to the complex multicomponent systems and multiscale effects.

To address these issues, we identified three fundamental research pillars: **identifying the optimum level of integration** through multiscale models, **engineering robust biocatalysts** for mixed media and interfaces, and **advancing modelling and simulation tools** to guide experimental work. In parallel, applied research must focus on understanding impurity effects, developing user-friendly models and standardized protocols, adapting and retrofitting reactor concepts, and establishing clear scale-up criteria. Ultimately, dedicated sensing and control strategies need to be developed for the integrated processes. Education also plays a crucial role: biochemical engineers must be trained to recognize the opportunities and challenges of bioreactive separations, apply modelling and simulation tools, work effectively in interdisciplinary teams, and transfer new developments into industry through lifelong learning.

The potential impact of bioreactive separations extends far beyond academic interest. Applications in biochemical recycling, biomining, CO_2 utilization, battery recycling, water management, hydrogen systems, and electrobiocatalysis demonstrate their relevance for industrial innovation and global sustainability. By contributing to improved resource efficiency, cleaner production, and reduced environmental impact, these technologies directly support the United Nations Sustainable Development Goals.

In conclusion, the development and industrial implementation of bioreactive separation requires an integrative approach that unites biotechnology, fluid separation science, and systems engineering, as well as other disciplines, such as reaction and genetic engineering. Only through such interdisciplinary collaboration can the full potential of bioreactive separations be realized—transforming biocatalysis into a scalable, competitive, and sustainable foundation for the future of the chemical industry.

AI statement

During the preparation of this work the authors used ChatGPT in order to check the text for grammar and style. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Thomas Waluga: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Daniel Ohde:** Writing – review & editing, Project administration. **Marion Ansorge-Schumacher:** Writing – review & editing. **Regina Benfer:** Writing – review & editing. **Wilfried Bluemke:** Writing – review & editing. **Heiko Briesen:** Writing – review & editing. **Jakob Burger:** Writing – review & editing. **Anja Drews:** Writing – review & editing. **Johannes Gescher:** Writing – review & editing. **Christiane Glasmacher-Remberg:** Writing – review & editing. **Marcus Grünewald:** Writing – review & editing. **Niels Hansen:** Writing – review & editing. **Christoph Held:** Writing – review & editing. **Dirk Holtmann:** Writing – review & editing. **Selin Kara:** Writing – review & editing. **Jan von Langermann:** Writing – review & editing. **Andreas Liese:** Writing – review & editing, Project administration, Funding acquisition. **Jørgen Magnus:** Writing – review & editing. **Alexander Pelzer:** Writing – review & editing. **Jürgen Pleiss:** Writing – review & editing. **Tina Radespiel:** Writing – review & editing. **Jens-Uwe Repke:** Writing – review & editing. **Katrin Rosenthal:** Writing – review & editing. **Anett Schallmey:** Writing – review & editing. **Irina Smirnova:** Writing – review & editing, Project administration, Funding acquisition. **John M. Woodley:** Writing – review & editing. **Thomas Wucherpfennig:** Writing – review & editing. **Michael Zavrel:** Writing – review & editing. **Tim Zeiner:** Writing – review & editing. **Mirko Skiborowski:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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