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Techno-Economic Evaluation of an Ultrasound-Assisted Enzymatic Reactive Distillation Process

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Abstract

Enzymatic Reactive Distillation (ERD) is a bioreactive process, in which enzymes are immobilized on column internal surface, and helps to overcome chemical reaction and phase equilibrium limitations. The activation of enzymes by ultrasound (US) leads to ultrasound-assisted ERD (US-ERD) which might display more eco-efficiency than standard processing of valuable chemicals. Reaction rate improvements of more than 50% could be achieved by the assistance of US.

An US-ERD process for the synthesis of butyl butyrate (10 kilotons per year, 99 wt% purity) was designed. A techno-economic evaluation via process optimization was carried out to minimize the annual costs, by using an evolutionary algorithm. The techno-economic evaluation shows that the US-ERD process and the ERD share nearly equal costs. Installation costs of the US equipment are high but they are compensated by a 12% lower reactive section height and a 7% lower total height of the US-ERD column in comparison to ERD.

Keywords: Biocatalysis, Optimization, Process intensification, Sonochemistry

1. Introduction

Process intensification (PI) in distillation aims at further increasing the sustainability, eco-efficiency, production efficiency and yield of industrial processes (Lutze and Górak, 2013; Lutze *et al.*, 2012; Schmidt-Traub and Górak, 2006; Shah *et al.*, 2012). It comprises novel equipment, processing technologies, new catalysts and reaction routes and process development methods that offer significant improvements in (bio-) chemical processing among conventional processes (Lutze and Sudhoff, 2016; Schmidt-Traub and Górak, 2006). To combine chemical reaction and thermodynamic separation inside a single unit is one of the most known examples of PI (Górak and Stankiewicz, 2011; Schmidt-Traub and Górak, 2006). Conventional reaction-separation sequences can be outperformed by the integrated reactive separation processes which potentially lead to large savings of capital, energy, and materials by elimination of equipment for product recovery and recycling of unconverted reactants (Górak and Hoffmann, 2001; Górak and Stankiewicz, 2011; Schneider *et al.*, 2001). Within green PI the integration of separation and biochemical reaction under mild conditions is one of three major components (Liu *et al.*, 2010). One example of green PI is the combination of distillation technology with enzymatically catalyzed reactions which was successfully demonstrated, recently (Heils *et al.*, 2015; Heils *et al.*, 2014; Wierschem *et al.*, 2016a). The first experimental investigation of an Enzymatic Reactive Distillation (ERD) process was reported by Paiva *et al.* (2003) for the synthesis of butyl butyrate (BuBu) by the transesterification of ethyl butyrate (EtBu) with butanol (BuOH), using lipase as catalyst. On top of that Heils *et al.* investigated the usage of enzyme immobilized in a hydrophobic silica gel, which was applied as coating on structured packing (Heils *et al.*, 2014; Heils *et al.*, 2012). Furthermore the feasibility of the ERD was demonstrated with help of an ERD model-based analysis and with experiments in a batch ERD set-up (Heils *et al.*, 2014; Heils *et al.*, 2012). A continuous ERD process for the transesterification of EtBu was investigated by Wierschem *et al.* (2016b). Several experiments in a pilot-scale ERD column were conducted to show process feasibility and the outcome of this work is a validated ERD model that is able to precisely describe the ERD process (Wierschem *et al.*, 2016b) and used within this work. BuBu is a volatile ester with a pleasant aroma, used in the flavor industry to create sweet fruity flavors similar to that of pineapple. Other esters used in the cosmetic industry can also be produced using enzyme-catalyzed synthesis routes (Khan and Rathod, 2015). These enzymatic reactions are often limited in conversion and are rather slow but can be intensified by using ultrasound (US) which leads to increased reaction rates and by applying distillation, which increases the conversion by *in-situ* product removal (Alves *et al.*, 2014; Gharat and

Rathod, 2013; Lye and Woodley, 1999; Thompson and Doraiswamy, 1999; Wierschem *et al.*, 2017). The beneficial effects of US on the enzymatic reaction of the transesterification of EtBu rate have recently been reported (Wierschem *et al.*, 2017) indicating a 50% increase in the reaction rate compared to the unsonicated system at conditions of 338 K and an EtBu to BuOH molar ratio of 5 mol/mol. This work was the basis to validate the ERD model due to the investigation and determination of enzyme kinetics, which were subsequently implemented into the ERD model (Wierschem *et al.*, 2016b).

The synergies between US irradiation and ERD are now brought together in an integrated setup. Hence, this work is the first to propose an ultrasound-assisted Enzymatic Reactive Distillation (US-ERD) process. A techno-economic evaluation and optimization of the US-ERD process is performed, which is then compared against the optimized ERD process in which enzyme coated packing is solely used (no US). The comprehensive mathematical model of ERD which was previously developed to describe the mass transfer, packing properties and the catalyst kinetics (Wierschem *et al.*, 2016b) is used here for the US-ERD process design and optimization. Figure 1 illustrates the proposed configuration for the US-ERD process. The capacity considered in our case study is 10 kiloton per year (ktpy) product stream of BuBu (99 wt% purity), obtained by transesterification of EtBu with BuOH and yielding to ethanol (EtOH) as co-product (Eq. (1)).

The enzymatic catalyst, lipase B from the yeast *Candida antarctica* (CalB) (EC 3.1.1.3), is known as an efficient and robust enzyme catalyzing several organic reactions, including transesterification. Within ERD, the enzymes are immobilized in a thin film, coated on the surface of structured packing that is usually used for conventional distillation (e.g. Sulzer BX[®]) (Heils *et al.*, 2014). It is also possible to immobilize enzymes in form of enzyme-beads, but there was no effect of US on enzyme activity observed for this type of immobilization (Wierschem *et al.*, 2017).

2. Problem Statement

Combining enzymatic reaction and distillation in form of ERD facilitates an *in-situ* product removal, which circumvents the conversion limitation of the enzymatic reaction. While the implementation of the transesterification of EtBu in ERD has been reported, investigated and demonstrated on pilot-scale (Wierschem *et al.*, 2016b) the assessment of beneficial effects of

US application on the reaction rate of the transesterification has so far only been demonstrated in lab-scale reaction experiments (Wierschem *et al.*, 2017b). In order to analyze if the combination of both techniques in form of US-ERD bears the potential to further increase reaction rates and improve the ERD, the current study presents a model-based analysis of the performance of ERD without US and US-ERD. Therefore, we have defined a case study in which the minimum total annual costs (TAC) of the US-ERD column, for a production capacity of 10 kiloton of BuBu per year with a purity specification of 99 wt% have to be determined for an annual operation of 8000 hours. The basis of the techno-economic evaluation is a validated ERD model (Wierschem *et al.*, 2016b) extended by cost functions, where US-assisted enzymatic reaction kinetics are implemented (Wierschem *et al.*, 2017). An objective function is minimized to yield for the lowest TAC. Note that commercial US equipment applied to distillation is currently not available, therefore assumptions for equipment costs and design are provided by Smart Material Corp., a technology supplier of US equipment.

3. Cost Estimation

The cost calculations for the ERD process include the column shell, condenser, reboiler, packing and enzyme costs, US equipment costs, as well as utilities (e.g. steam, electricity). Investment costs are annualized based on assumed interest rate and operating time and cost estimates are updated on the basis of economic cost indices to the year 2014. Table 1 provides the basis of cost estimation for equipment and utilities. The key economic performance indicators used are the total investment costs (TIC), total operating costs (TOC), and TAC. The detailed calculation of the TIC and TOC for the equipment is presented in the Supplementary data, Section A.

As US equipment does not exist for reactive distillation columns, we assume that US transducer have a diameter of 2-3 cm, and three of them are connected to one power amplifier. It is further assumed that all the ingoing power into the amplifier equals the outgoing power into the liquid volume. Our assumption is also that one transducer is used to impinge a liquid volume of 0.5 L with 50 W as used in the reaction kinetics investigation (Wierschem *et al.*, 2017). Depending on the liquid hold-up in the reactive section of the column the numbers of transducer and power amplifiers are calculated.

The volume fraction of enzyme per cubic meter packing is scaled-up from the pilot-scale column and amounts to 31.82 kg/m³ of column volume. In our previous validation experiments there was no loss in activity observed for enzyme beads after 200 hours of

operation (Wierschem *et al.*, 2016b). With these results, a prediction of the enzyme stability over a period of one year is not legitimate. On top of that, other studies show long-term enzyme stability. Heils *et al.* (2012) showed a stable coated packing after an initial washing step over a long period. Hama *et al.* (2011) showed long-term stability of CalB for about ten months and Anderson *et al.* (1998) regarded enzymes as stable for several thousand hours, which underlines our assumption that the enzyme can be stable for one year. For the optimization an activity loss of the enzyme is neglected and it remains the same activity for the period of one year. The costs of enzyme entrapped in coated packing, which is not commercially available, are assumed to be as high as the costs for the enzyme beads IMMCALB-T2-1000XL from ChiralVision B.V., The Netherlands, at 20 kg and 100 kg scale (see Table 1). The same amount needed for coated packing is assumed to have the same price as for the enzyme beads. The price for 20 kg and 100 kg of enzyme beads are known and a linear cost function was used to calculate prices in between. For higher scales up to 300 kg the price per ton is proposed to be the similar as for 100 kg.

4. Results and Discussion

Aspen Custom Modeler[®] was used for the rate-based simulations of the ERD process, based on the recently developed and experimentally validated model (Wierschem *et al.*, 2016b). The modified UNIFAC (Dortmund) model (UNIF-DMD) was used as most suitable property model for modeling the activity coefficients of the chemical system of the transesterification of ethyl butyrate. More detailed information on the thermodynamic model is available in previous work (Heils *et al.*, 2014). The kinetics for the (US-assisted) enzymatic reaction is taken from our earlier work (Wierschem *et al.*, 2017). For the enzyme coated packing a reduced ordered bi bi kinetic approach was employed for both, the kinetics without US and the kinetics with US assistance – see Eq. (2). It accounts for substrate inhibition by BuOH according to Bisswanger (Bisswanger, 2008). The kinetic parameters for the kinetics without US are presented in Table 2 and the ones for the US-assisted kinetics in Table 3. For the US-assisted kinetics v_{max} is lower compared to the kinetics without US but the lower value of $K_{i,BuOH}$ compensates for the lower v_{max} , so that the reaction rates are higher for substrate ratios of EtBu over BuOH higher than 2.

$$v = \frac{v_{max} \cdot [BuOH][EtBu]}{K_{i,BuOH} \cdot [EtBu] + K_{m,EtBu} \cdot [BuOH] + K_{m,BuOH} \cdot [EtBu] + [BuOH][EtBu]} \quad (2)$$

The production capacity and the purity specifications are set as fixed variables. Instead of those two, the feed stream and the substrate ratio were set free. The according optimization problem is solved by means of an evolutionary algorithm described in the literature (Keller *et al.*, 2013). In order to account for various constraints that are not included in the simulation model, the objective function is represented by a sum of the TAC and additional penalty functions (see Eq. (3)). The penalty functions account for constraint violations according to process specifications or fluid dynamic considerations that need to be met. Penalty1 is given by Eq. (11) and addresses the maximum temperature limit of the enzyme (in K). Fluid dynamic operation limits are considered by Eq. (5) and (6), taking into account that the range for the *F-factor* lies between 0.2 $\sqrt{\text{Pa}}$ and 2.5 $\sqrt{\text{Pa}}$ and the maximum *F-factor* is set to 2 $\sqrt{\text{Pa}}$ and the liquid load $liq_load_{\min}$ should be higher than the value of 0.05 $\text{m}^3/\text{m}^2/\text{h}$ (Bravo *et al.*, 1985; Goedecke, 2006; Keller *et al.*, 2013; Sulzer Chemtech Ltd, 2003).

$$\min \text{ Objective function} = \min \left(\text{TAC} + \sum \text{penalty} \right) \quad (3)$$

$$\text{penalty1} = \begin{cases} 9999999, & \text{if } T_{\max, \text{enzyme}} > 343 \\ 0, & \text{if } T_{\max, \text{enzyme}} \leq 343 \end{cases} \quad (4)$$

$$\text{penalty2} = \begin{cases} \text{TAC} + \text{TAC} \cdot ((F\text{-factor}_{\min} - 0.2) / 0.2)^2, & \text{if } F\text{-factor}_{\min} < 0.2 \\ 0, & \text{if } F\text{-factor}_{\min} \geq 0.2 \end{cases} \quad (5)$$

$$\text{penalty3} = \begin{cases} \text{TAC} + \text{TAC} \cdot ((liq_load_{\min} - 0.05) / 0.05)^2, & \text{if } liq_load_{\min} < 0.05 \\ 0, & \text{if } liq_load_{\min} \geq 0.05 \end{cases} \quad (6)$$

The minimization of the objective function is a minimization of the TAC (description of its calculation is within the Supplementary data, Section A) and the above mentioned penalties. The equality constraints are provided by the rate-based model within the simulation software of Aspen Custom Modeler[®]. The design degrees of freedom, which are manipulated by the optimization algorithm, are the reflux ratio (*RR*), the distillate-to-feed-ratio (*D/F*), the column head pressure p_{Head} and the height of each section (h_{Section}) whereby Section1, Section2 and Section3 denote the rectifying section, the reactive section and the stripping section, respectively. Their boundaries are given in Table 4 and Table 5 and a graphical explanation of the free, fixed and manipulated variables of the optimization problem is provided by Figure 2. The number of individuals per generation, is 10 and the three individuals with the lowest objective function are used to determine the parameters of the next generation by mutation

1 and recombination. Table 6 provides the control parameters of the evolutionary algorithm
2 used for our optimization studies. The optimization is terminated if no improvement of the
3 objective function is achieved within 20 consecutive generations.

4 Note that, the complex process model, accounting for mass transfer, thermodynamic and
5 economic models, results in a highly non-linear optimization problem, which is not only hard
6 to solve, but is likely to have multiple locally optimal solutions. Especially the evaluation of
7 the single individuals requires advanced measures to improve convergence properties of the
8 single simulations. Thus, in order to increase the computational robustness the evaluation of a
9 single individual for a new vector of design variables is generated as follows. A converged
10 snapshot with an initial solution is saved and imported prior to each optimization run. From
11 there a homotopy approach is used to continually transpose the decision variables of the
12 present individual. In case the homotopy approach does not converge the snapshot is imported
13 again and the individual is discarded by setting a high value for the objective function. When
14 a run did converge the value of the objective function is sent back to the EA, which selects the
15 ‘fittest’ individuals to proceed with as described by Keller *et al.* (2013). Convergence of the
16 optimization by means of the evolutionary algorithm was achieved in reasonable time over a
17 reasonable number of a few hundred generations. In case of more complex optimization
18 problems with an increased number of decision variables a hybrid optimization method as e.g.
19 presented by Urselmann *et al.* (2015) and Skiborowski *et al.* (2015) should be considered to
20 improve the performance of the optimization.

21 22 **4.1. ERD optimization**

23 In this section the results of the optimization of the ERD process without US are discussed.
24 Table 4 lists the decision variables, the lower/upper bounds of each variable, as well as the
25 optimized values. Figure 3 shows the composition and temperature profiles along the ERD
26 column for the optimized design. In terms of performance, the ERD process without US is
27 characterized by 97.4% conversion of BuOH, 80.4% conversion of EtBu, 99.0 wt% purity of
28 BuBu in the bottom stream (1250.0 kg/h), and 61.4 wt% purity of EtOH in the top stream
29 (644.0 kg/h). The head pressure is at 15 kPa corresponding to the maximum temperature
30 allowed due to the thermal instability of the enzymatic catalyst. The pressure drop over the
31 column height is 1.3 kPa. The rectifying section is small (0.3 m) as the separation between
32 EtBu and EtOH is easy within the concentration range up to the distillate composition of
33 61.4 wt% of EtOH as the vapor-liquid-equilibrium verifies (Supplementary data, Section B).
34 The height of the reactive and stripping section is 4.1 m and 3.0 m respectively, resulting in a

total column height of 7.4 m, and a column diameter of 1.39 m. The substrate ratio is EtBu:BuOH = 1.21 and the total feed stream is 1894.0 kg/h. That leads to the following TIC_{Plant} and TOC_{Plant} that are summarized in Figure 4 with their partial cost contribution. The value of the objective function, which is the TAC, amounts to 18.41 M €/yr and all penalty functions are equal to zero. The TIC_{Plant} amount to 2.53 M € so that the annuity is 361 000 €/yr. The TOC_{Plant} amount to 18.05 M €/yr and are 50 times larger than the annuity. Figure 4 shows the shares of the considered items for the annuity and the TOC without raw material costs (RM). The main cost driver is the raw material costs, which exhibit a share of 98% of the TOC_{Plant} . Consequently, the investment costs are of minor importance compared to the operating costs. For convenience, Figure 5 shows the objective function values for each optimized generation and the 10 different individuals leading to the optimized solution.

4.2. US-ERD optimization

Table 5 lists the decision variables, the lower/upper bounds of the acceptable range, as well as the optimized values for the US-ERD process. Figure 6 shows the composition and temperature profiles over the column height of the US-ERD for the optimal run.

The conversion is practically the same as in the case of ERD without US and the values are 98.0% conversion of BuOH and 82.0% conversion of EtBu. The leaving streams exhibit a purity of BuBu of 99.0 wt% with 1250.0 kg/h in the bottom and a purity of EtOH of 64.2 wt% with 615.7 kg/h in the distillate, which is slightly purer as in the ERD without US. The pressure is at 15 kPa as in the ERD without US and the total column height is 6.9 m with a diameter of 1.34 m and therefore, the column is smaller than in the ERD case. Due to the higher reaction rate for the US-assisted ERD, as compared to ERD, a smaller reactive section height (3.6 m compared to 4.1 m) is needed. The rectifying section is 0.6 m high and the stripping section is smaller for US-ERD compared to ERD (2.7 m compared to 3.0 m), since the exiting stream from the reactive section is closer to the fixed bottom purity. The substrate ratio is EtBu:BuOH = 1.19 and the total feed stream is 1865.7 kg/h.

The cost contributions for the US-ERD are summarized in Figure 7. The objective function amounts to 18.45 M €/yr, while the penalties are zero. The TIC_{Plant} result in 3.17 M € and accordingly the annuity amounts to 451 000 €/yr. The TOC_{Plant} again have the highest cost share with 18.00 M €/yr with 17.62 M €/yr for the raw materials. For completeness, Figure 8 shows the resulting objective function for each optimized generation.

Notably, both processes, ERD and US-ERD, result in very similar costs. The objective function of the US-ERD is higher by 40 000 €/yr compared to the ERD. The difference of the

processes is that the US-ERD exhibits higher installation costs, this being mainly driven by higher US equipment costs, and lower operating costs due to a smaller reactive section.

A volume of approximately 387 L is impinged with US, which indicates that 773 transducer and hence 258 amplifiers are necessary. This results in an annuity of the US equipment of 131 000 €/yr, and a total of 38.7 kW power input. These assumptions are subject to high uncertainty and however, based on these assumptions the US-ERD is not advantageous compared to the ERD.

A uniform distribution of the US field is essential for an accurate operation. Fluctuations in the US field can lead to an uneven acceleration of the enzymes and therefore influence the reaction rates. An US field in the distillation column might not be uniformly applied without equipment testing. A proposal to avoid testing of new equipment could be the usage of commercially available devices as side reactors that guarantee a uniform distribution of the US field.

4.3. Economic Sensitivity

Literature references show that for various chemical systems further improvement in reaction rate acceleration by US application is possible.(Alves *et al.*, 2014; Gharat and Rathod, 2013; Khan and Rathod, 2015; Thompson and Doraiswamy, 1999) To find out how an increase in reaction rates influences the costs of the US-ERD we introduced a reaction enhancement factor to the US-assisted kinetics in order to further accelerate the reaction rates, and checked by sensitivity analysis the impact of faster reaction rates on the costs. A higher reaction rate accounts for a smaller reactive section, leading to less enzyme usage and less US equipment lowering the TIC and thereby also the TAC of the US-ERD. Conversion is kept constant compared to the US-ERD scenario previously described, while only the height of the reactive section is changing. Figure 9 shows that at higher reaction rates, the height of the reactive section and the TIC of the process are significantly reduced. However, the TOC are nearly unaffected, such that the reduction in TAC can nearly completely be attributed to the reduced annuity, although the TAC are only minimally affected. The costs of the US equipment as well as packing and enzyme costs are reduced due to the decreased height of the reactive section. Already at a reaction factor of 1.11 the TAC of the US-ERD supersedes the ERD as the cost beneficial process option. Further improvements, which have been reported for other reactions in the literature could lead to even higher cost advantages.(Alves *et al.*, 2014; Gharat and Rathod, 2013; Khan and Rathod, 2015)

The uncertainty in costing of the US equipment necessitates a sensitivity analysis, which represents an investigation of the impact of US equipment costs on the TAC. Therefore, the total investment costs for bare US equipment, TIC_US, are varied from 100 000 € to 1 Million € (Figure 10). The costs of bare US equipment for the optimized US-ERD scenario amount to approximately 220 000 €. As Figure 10 shows, the impact of the US equipment costs on the TAC is rather small. A more than fourfold increase in the TIC_US from 220 000 € to 1 Million € leads to a 2.5% increase in the TAC. The TIC for the process increase significantly, but they only have a small share to the TAC. Hence, only a minor impact of the US equipment costs on the TAC is observable.

5. Conclusion

The ultrasound-assisted Enzymatic Reactive Distillation (US-ERD) proposed here features faster reaction rates that lead to a 12% smaller reactive section of the distillation column compared to the ERD without US and a 7% smaller total column height. The techno-economic evaluation shows that the US-ERD process requires a 25% higher annuity, at slightly lower total operating costs. The total operating costs per year, of which 98% amount to the material costs, are 43 times higher than the annuity, translated ultimately into practically equal total annual costs (TAC), as in the case of the ERD alternative. Installation costs of the US equipment are compensated by lower reactive section height and therefore less costs for enzyme. Nonetheless, a higher increase in the reaction rate by improved ultrasound application would lead to significant cost advantages. Sensitivity analysis shows that if the reaction rates could be further increased by US investment costs can be lowered.

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Tables

Table 1. Cost basis for installation and operation

Variable	Costs	Unit	Reference
Ultrasound (US)			
Transducer	120	€/piece	Smart Material Corp., Germany
Power amplifier	500	€/piece	Smart Material Corp., Germany
Utilities			
Electricity	12.35	€/GJ	Luyben, 2011 (Luyben, 2011)
Steam (6 bar)	7.78	\$/GJ	Luyben, 2011 (Luyben, 2011)
Steam (42 bar)	9.88	\$/GJ	Luyben, 2011 (Luyben, 2011)
Cooling water	0.05	\$/t	Luyben, 2011 (Luyben, 2011)
Catalyst			
Enzyme (100 kg scale)	900	€/kg	ChiralVision B.V., The Netherlands
Enzyme (20 kg scale)	1400	€/kg	ChiralVision B.V., The Netherlands
Substrate			
BuOH	627.8	€/t	Niesbach <i>et al.</i> , 2013 (Niesbach <i>et al.</i> , 2013)
EtBu	2019	\$/t	Sunlong Industrial & Trading Ltd., China

Table 2. Kinetic parameters for coated packing kinetic model without US

Parameter	Value	Unit
$v_{\max}$	0.668	[mol/(s·kg _{cat})]
$K_{m,\text{BuOH}}$	0	[mol/l]
$K_{m,\text{EtBu}}$	25.252	[mol/l]
$K_{i,\text{BuOH}}$	0.054	[mol/l]

Table 3. Kinetic parameters for coated packing US-assisted kinetic model

Parameter	Value	Unit
$v_{\max}$	0.509	[mol/(s·kg _{cat})]
$K_{m,\text{BuOH}}$	0	[mol/l]
$K_{m,\text{EtBu}}$	25.256	[mol/l]
$K_{i,\text{BuOH}}$	0.007	mol/l

Table 4. Optimization variables for the ERD process without US

Decision variables	Lower Bound	Upper Bound	Optimal Value	Unit
Reflux ratio	2.0	8.0	5.6	[kg/kg]
Distillate-to-feed-ratio	0.30	0.70	0.34	[kg/kg]
h_{Section1}	0.1	0.5	0.3	[m]
h_{Section2}	2.0	8.0	4.1	[m]
h_{Section3}	0.1	4.0	3.0	[m]
p_{Head}	0.13	0.18	0.15	[kPa]

Table 5. Optimization variables for the US-ERD process

Decision variables	Lower Bound	Upper Bound	Optimal Value	Unit
Reflux ratio	2.0	8.0	5.3	[kg/kg]
Distillate-to-feed-ratio	0.30	0.70	0.33	[kg/kg]
h_{Section1}	0.1	0.8	0.6	[m]
h_{Section2}	2.0	8.0	3.6	[m]
h_{Section3}	0.1	4.0	2.7	[m]
p_{Head}	0.13	0.18	0.15	[kPa]

Table 6. Control parameters of the evolutionary algorithm

Control parameter	1 st phase	2 nd phase	3 rd phase	4 th phase
Generation to change phase	90	150	200	-
Intermediate recombination probability	0.2	0.5	0	0.5
Global mutation probability	0.7	0.3	0	0.1
Local mutation probability	0.7	0.3	0.9	0.1
Local mutation radius	1.00	0.50	0.10	0.01

Figures

Figure 1. Scheme of the US-ERD process with the enzyme coated packing placed in the US-assisted reactive section.

Figure 2. Manipulated variables of the optimization. The total feed stream ($\dot{m}_{\text{Feed,tot}}$) and the substrate ratio (χ_{Feed}) are set free and therefore the bottom stream ($\dot{m}_{\text{Bottom}}$) and the bottom mass fraction (w_{EtBu}) are fixed. The reboiler and condenser duties (Q_{Reb} and Q_{Cond}) are free variables, whereas the reflux ratio (RR) and the distillate-to-feed-ratio (D/F) are fixed and manipulated within the optimization.

Figure 3. Simulated profiles: liquid molar fractions (left) and liquid temperature (right) for the ERD column without US with enzyme coated packing.

Figure 4. Total investment cost (TIC) and total operating cost (TOC) without raw material costs (RM) of the optimized ERD process without US.

Figure 5. Objective function values dependency on the generations, during the optimization run of the ERD process without US.

Figure 6. Simulated profiles: liquid molar fractions (left) and liquid temperature (right) for the US-ERD column with enzyme coated packing.

Figure 7. Total investment cost (TIC) and total operating cost (TOC) without raw material costs (RM) of the optimized US-ERD process.

Figure 8. Objective function values dependency on the generations, during the optimization run of US-ERD process.

Figure 9. a) Sensitivity analysis for the total annualized costs (TIC) as function of changes in the reaction rate, expressed by a reaction enhancement factor. b) Sensitivity analysis for the total investment costs (TIC) as function of changes in the reaction rate, expressed by a reaction enhancement factor.

Figure 10: a) Sensitivity analysis for the total annualized costs (TAC) as function of changes in the investment costs for bare US equipment. b) Sensitivity analysis for the total investment costs (TIC) as function of changes in the investment costs for bare US equipment. The costs for the optimized point are highlighted.