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Purification performance index and separation cost indicator for experimentally based systematic downstream process development

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ABSTRACT

Cost-driven downstream process development and optimization is only possible when a complete process concept is either modeled or set up in laboratory scale, which requires comprehensive data or respective time and effort. Before that stage the decisions to apply or discard alternative purification steps are based on practical feasibility, experimental yield and purity improvement, without estimates for their cost-efficiency within the process.

This article introduces two new parameters to overcome that problem. The purification performance index (PPI) weights the improvement in product purity achieved by a single step and relates it to the boundaries of the process. In this way the purification performance is assessed as a percentage of the required total purification. The separation cost indicator (SCI) combines purification rating and yield losses with cost data. Thereby cost-efficiency of single purification steps or step combinations can be estimated without the need of a complete process concept.

1. Introduction

"Process development and especially conceptual design is regarded as the most important design stage since the major decisions affecting the whole lifecycle of the process are done in this phase. The performance of the process is relied on the decisions made during process development" [1]. Especially for pharmaceutical products the downstream process accounts for a major part of the production costs [2]. But even for production of bio-based bulk chemicals the cost of purification can mount up to over 50% [3]. On the other hand time and effort for developing efficient processes also cause significant costs [4]. Furthermore, especially for biotechnological products the need for shorter time-to-market and the difficulties to change an established process due to quality assurance and regulations like GMP lead to suboptimal processes [5]. These conflicts motivate continuous research in the field of systematic process design.

Harjo et al. comprehensively present a systematic procedure for manufacturing phytochemicals [6]. Design strategies for, e.g. protein purification processes are well reviewed by Nfor et al. [7] who distinguish between heuristic, algorithmic, high throughput experimental and hybrid methods. While heuristics can establish process alternative trees and eliminate some alternatives on a qualitative level with little information [8], further quantitative evaluation of the remaining alternatives is inevitable. These steps can differ either by unit operation, mass separating agent and/or operating conditions.

The choice between alternatives always requires rating, ultimately by costs [9]. For chemical processes Gadewar et al. state that a sound operating cost calculation is essential, but only available by comprehensive experimental and model-based investigation in the later phases of conceptual design [10]. Leser et al. introduced an expert system for protein purification based on economic separations coefficients (ESC) [11]. Although only four qualitative cost factors were employed, the employed algorithm allows a cost-based design of chromatographic sequences. However, Asenjo et al. later found that using the purity after each separation as selection criterion may lead to better processes [12,13].

Steffens et al. demonstrated cost-driven development of bioprocesses by shortcut modeled effluent concentrations and operating costs of different unit operations [14]. The estimated product value was balanced against expenses, where only yield losses accounted for costs. The MINLP approach of Simeonidis et al. for protein purification with peptide tags, in which the target function is to minimize the number of chromatographic steps [15], is extended by Lienqueo et al. by a cost function [16]. This profit function is the difference between revenue and costs of a series of chromatographic steps.

Abbreviations: ABx, mixed-mode ion exchange (resin); CF, clearance factor; CHOP, Chinese hamster ovary cell proteins; HIC, hydrophobic interaction (resin); IgG1, immunoglobulin G1; Log PI, logarithmic purification index; PI, purification index; PPI, purification performance index; ProA, Protein A (resin); Q, anion-exchange (resin); S, cation-exchange (resin); SCI, separation cost indicator.

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It arises from the need to balance yields, purities and costs, but Lienqueo finds that the chosen function results in maximum recovery. Groep et al. employed an arctangent correlation between final purity and revenue and estimated operating costs to be linearly proportional to the amount of material processed in each operation [17].

These approaches allow process synthesis and optimization in a system-wide, rather than unit-by-unit, sense. For a systematic downstream process development the evaluation of alternative process steps with regard to their performance within the total process is essential. The most advanced methods to quantify the influence of single step performance on the total process costs are proposed by Huenupi et al. and Shene et al. For investigation of operational conditions of aqueous two-phase extraction [18] and ion exchange chromatographic separation [19] a cost function is set up which estimates the influence of the single step yield, outlet purity and concentration on the operational costs of the total process relative to a base case. That allows, e.g. considering the impact of yield losses on production costs. However, the total process concept is known a priori and necessary to reason all terms in the process-specific function. Even the contribution of each term to the total costs must be estimated and framed in advance, which is questionable in view of the purpose of the method.

But the decisions having most significant consequences on total costs are made in earlier phases of process design [20]. Hence, it is desirable to base these decisions upon costs for the complete process, even before comprehensive process concepts are available. These costs are not directly deducible from investigation of single steps, especially not from few experiments, which focus on technical feasibility, achievable yields and purities. A quantitative relation between purification and cost-efficiency of a process step is not yet available.

For these reasons, new key performance indicators for rating purification and cost-efficiency on basis of single step purity improvement, yield and specific costs are introduced. In contrast to previous indicator-based methods for process design [21] the proposed indicators do not require complete mass and energy balances and can be applied from the beginning of experimental investigation.

2. Theory

2.1. Purification rating

Purity is the fraction of the target product in a mixture with contaminants, it is defined as:

$$\text{Purity}\times = \frac{\text{amount of product}}{\text{amount of product} + \text{amount of total impurities}}. \quad (1)$$

There are two common measures for purification achieved with a single step j:

$$\text{Purity difference}: \Delta x = x_{\text{out},j} - x_{\text{in},j} \quad (2)$$

and

$$\text{Purification factor}: \frac{x_{\text{out},j}}{x_{\text{in},j}}. \quad (3)$$

Another measure is the clearance factor as defined, e.g. by Asenjo et al. [22]:

$$\text{Clearance factor(CF)}: \frac{x_{\text{out},j}/x_{\text{in},j}}{(1-x_{\text{out},j})/(1-x_{\text{in},j})} \quad (4)$$

In order to assess the purification of one step as percentage of the total process to be developed, the purity of the initial mixture x_0 and the target purity x_f must be considered as given boundaries of the downstream process.

Two ways of normalizing purification measures are:

1. Purification index (PI_j):

$$\frac{x_{\text{out},j} - x_{\text{in},j}}{x_f - x_0} \quad (5)$$

2. Logarithmic purification index ($\log \text{PI}_j$):

$$\frac{\lg(x_{\text{out},j}) - \lg(x_{\text{in},j})}{\lg(x_f) - \lg(x_0)} \quad (6)$$

Log PI can be obtained as ratio of the logarithmized purification factors of the step and the total process.

Though both normalized purification measures range from 0% to 100%, the weighting of single steps within a process can differ considerably. That is illustrated in Fig. 1 showing a downstream process designated to purify a crude mixture ($x_0 = 0.1\%$) into a high-purity final product ($x_f = 99.9\%$). The different ways of rating purification are compared using three typical steps within this process.

The first step in the process (A) starts with very low initial purity and results in moderate purity according to a several-fold product concentration. An intermediate step (B) ranging from moderate to high purity represents another part of the process, but fails to achieve the target purity. Usually it takes much effort to reach very high purities [23], so the depicted final step (C), which already starts from high purity, must still be considered difficult. These steps are chosen arbitrarily, so equal rating is implausible. But according to the considerations above, a balanced weighting should yield that none of these efficient steps is rated much lower than the others.

The step ratings by the classical measures purity difference and purification factor as well as by clearance factor (CF) are illustrated on the left side of Fig. 1. PI and log PI rating on the right side are normalized, but very imbalanced over the process, causing the need for a new rating:

3. Purification performance index (PPI_j):

$$\frac{\tanh^{-1}(2x_{\text{out},j} - 1) - \tanh^{-1}(2x_{\text{in},j} - 1)}{\tanh^{-1}(2x_f - 1) - \tanh^{-1}(2x_0 - 1)} \quad (7)$$

The area hyperbolic tangent weighting of the new purification measure PPI appears to be less straightforward, but with Eq. (8) it turns out, that PPI can similarly be obtained as ratio of the logarithmized clearance factors of the step and the total process.

$$\tanh^{-1}(2x - 1) = \frac{1}{2}\ln\left(\frac{x}{1-x}\right) \quad (8)$$

As demonstrated in Fig. 1, the PPI appears to be most balanced over the whole purity range of a downstream process and can thus be used to link the purification performance with the expected effort.

2.2. Cost-estimation

The influence of single purification steps on the total process costs is easily assessable as soon as a complete downstream process concept is set up.

The specific process costs (κ_{tot}) of a general process with one conversion step (complete upstream) and n purification steps can be calculated from the specific costs for all steps ($\kappa_{\text{conversion}}$ and $\kappa_{\text{pur},1},\ldots,\kappa_{\text{pur},n}$) as:

$$\kappa_{\text{tot}} m_{\text{prod}} = \kappa_{\text{conversion}} \frac{m_{\text{prod}}}{Y_{\text{tot}}} + \kappa_{\text{pur},1} \frac{m_{\text{prod}}}{Y_{\text{tot}}} + \kappa_{\text{pur},2} \frac{m_{\text{prod}} Y_1}{Y_{\text{tot}}} + \ldots + \kappa_{\text{pur},n} \frac{m_{\text{prod}} Y_{n-1}}{Y_{\text{tot}}}, \quad (9)$$