CASCADING REACTOR–SEPARATOR SETS REDUCES TOTAL PROCESSING TIME FOR LOW YIELD MICHAELIS–MENTEN REACTIONS: MODEL PREDICTIONS

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Integration of reaction with separation has often been claimed to provide enhanced processing due to alleviation of processing constraints which, like equilibrium limitation or product inhibition, are common in enzyme-catalyzed reactions. In this paper, a mathematical model is developed to assess the effect of cascading sets of enzyme reactors and physical separators (which, when the number of sets tends to infinity, is equivalent to full integration of reaction and separation), when compared with the classical unit operation approach, in terms of total time required to effect reaction and separation for a given overall conversion. The analysis is laid out using several relevant reactional parameters [final conversion of substrate (χ_f), equilibrium constant (K_{eq}) and dimensionless dissociation constants of substrate and product ($K^*_{m,S}$ and $K^*_{m,P}$)] and separational parameters [extent of separation in a single step (ζ) and ratio of time scales for molecular transport and chemical reaction (Ξ)]. Cascading provides a gain in processing time, up to an optimum at a finite degree of cascading, only for reaction-controlled processes (typified by low ζ, low Ξ, low K_{eq}, low $K^*_{m,P}$, high χ_f and high $K^*_{m,S}$); hence, full integration is not necessarily the best processing solution. Lengthening of the cascade leads to a decrease in the maximum substrate conversion while permitting higher degrees of product recovery.

Keywords: Enzymatic reaction; Physical separation; Integration; Cascading; Unit operations

INTRODUCTION

Downstream separation processes have been traditionally employed whenever the chemical reaction in a given reactor does not, due to thermodynamic or kinetic constraints, approach the extent required by the desired product specifications. In the design of a reaction/separation process, several factors have to be taken into account, viz. energy, number of equilibrium-limited (or mass transfer-limited) stages, hydrodynamic pattern and overall throughput rate, as well as time requirements (Proust *et al.*, 1980). Often a major portion of the cost of the final product arises from operational costs associated with separation which, when expressed per unit mass of desired product, tend to be inversely proportional to the initial concentration of said product (Belter *et al.*, 1986). Although methods of separation can be tailored to a given process/product, they may in general be classified into three major groups according to the driving force employed to provide the positive increment in Gibbs free energy required for spontaneous generation of two or more phases with different concentrations: (i) those which contribute energy to the system in the form of work (e.g. pressure-driven processes such as ultra-, nano- and hyperfiltration; force-driven processes such as ultracentrifugation; and electrically-driven processes such as electrodialysis and electrophoresis when the exclusion threshold of the porous membranes or the drag coefficient threshold is well between the molecular weight of the two components); (ii) those which contribute energy to the system in the form of heat from a higher temperature source (e.g. purification by vaporization when one of the components is much more volatile than the other as in evaporation and distillation) or remove energy from the system in the form of heat to a lower temperature sink (e.g. cold crystallization) in ways that resemble a thermal engine; and (iii) those which contribute energy to the system carried by matter added (e.g. purification by adsorption using zeolites when the molecular shape of one component is rather different from the shape of the other). Once the two or more phases with a different concentration of the desired product have been generated, separation between them may be achieved via bulk forces (e.g. gravitational forces as in settling, centrifugal forces as in centrifugation and pressure forces as in macro- and microfiltration).

Conceptualization of separation as a unit operation that comes after the other unit operation termed reaction has, however, been undergoing a shift towards a more global view in recent years. As a matter of fact, in order to avoid and/or alleviate problems which arise in several reactors where low

purities and yields are obtained, the idea of cascading and eventually integrating reaction and separation has arisen. Such processing decision may allow one not only to increase the efficiency of the reactor by shifting the reaction equilibrium favourably (which can in turn be achieved via cascaded or continuous removal of products from the reaction medium) but also to decrease the extent of purification via preventing the concentration of reactant drop to relatively low values.

In the biotechnological field, volumetric productivities are typically low when compared to traditional chemical process counterparts mainly due to the intrinsic low volumetric activity of the biocatalyst, inhibition by substrates and/or products, and degradation of products inside the reactor; these problems, usually coupled with the high degree of purification necessary to obtain several products, lead to multiple step processes with consequent low overall yields. Scientific and technological approaches aimed at reducing limiting factors on the molecular level which characterize biological reactions have encompassed (i) increase in biocatalyst concentration in the reaction medium (e.g. via immobilization), (ii) improvement of catalyst activity and stability (e.g. via protein and genetic engineering) and (iii) maintenance of optimal processing conditions for biocatalyst operation (e.g. via continuous removal of products formed) (Bailey and Ollis, 1986; Cabral, 1991). The latter approach, implemented via cascading and eventually integrating reaction and separation steps, has been consubstantiated in extractive fermentation and extractive biocatalysis, depending on whether metabolically viable cells or enzyme extracts thereof are used (Eggers *et al.*, 1989); processes that lie under such methodological umbrella comprise (but are not limited to) liquid–liquid systems (Lilly *et al.*, 1987; Cabral, 1991; Bart *et al.*, 1992; Roychoudhury *et al.*, 1995), vapor–liquid systems (Davies and Jeffrey, 1973; Hills *et al.*, 1990; Sundquist *et al.*, 1991; DeGarmo *et al.*, 1992; Paiva and Malcata, 1994; Xu and Chuang, 1996), supercritical fluid systems (Marty *et al.*, 1992; 1994), solid–liquid systems (Martinek *et al.*, 1989; Matsumura, 1991; Strathmann and Gudernatsch, 1991; van der Wielen *et al.*, 1993; 1996; van der Padt *et al.*, 1996; Jansen, 1996; Jansen *et al.*, 1996; Mazzotti *et al.*, 1996) and solid–gas systems (Takeuchi and Uraguchi, 1977; Parvaresh *et al.*, 1992; Groot *et al.*, 1992; Kemp and Macrae, 1992).

This paper attempts to quantitatively address the issue of kinetic enhancement brought about by cascading and eventually integrating reaction and separation phenomena with respect to the classical unit operation approach. The model system selected is an enzyme-catalyzed reaction following a Michaelis–Menten reversible mechanism with a 1 : 1

stoichiometry that evolves from a pure substrate to a thermodynamically ideal substrate/product homogeneous mixture; a monoglyceride (say, *sn*-1) with a given single type of long-chain saturated fatty acid residue that isomerizes to another positional form (say, *sn*-2) at room temperature in the presence of an insoluble, nonselective lipase (containing trace amounts of water bound to its proteinaceous backbone) is a good example of such ideal (liquid) system. Selection of a binary system rather than a ternary (possibly dilute) solution agrees with the current trend of process intensification brought about by increasing substrate concentration to the highest degree possible (which avoids use of solvents that add to downstream separation problems). In order to account for thermodynamic and kinetic inhibition (or constraints), the case of a reversible reaction coupled with inhibition of the catalyst by reactant and product was selected as a case study. The objective function to be considered in this analysis is the time required for performance of the set of reaction and separation operations for a predefined overall conversion of substrate; selection of time is justified by the fact that it plays the role of a currency in the kinetic domain, i.e. time is the price to be paid if one wants to bring about actual phenomena that proceed at finite rates.

MATHEMATICAL DEVELOPMENT

Unit Operation Approach

Consider one reaction unit in series with one separation unit (see Fig. 1(a)). The steady-state mass balance to substrate within a well-stirred batch reactor (or, equivalently, a continuous plug-flow reactor) under isothermal conditions reads

$$-\frac{dC_S}{dt} = r\{C_S, C_P\} \tag{1}$$

which, in its simplest form, is subject to the initial (or boundary) conditions

$$t = 0, \quad C_S = C_0, \quad C_P = 0. \tag{2}$$

Here C_S denotes the substrate concentration, C_P the product concentration, t the batch time (or the reactor space time), r the rate expression and subscript 0 the starting (or inlet) conditions.

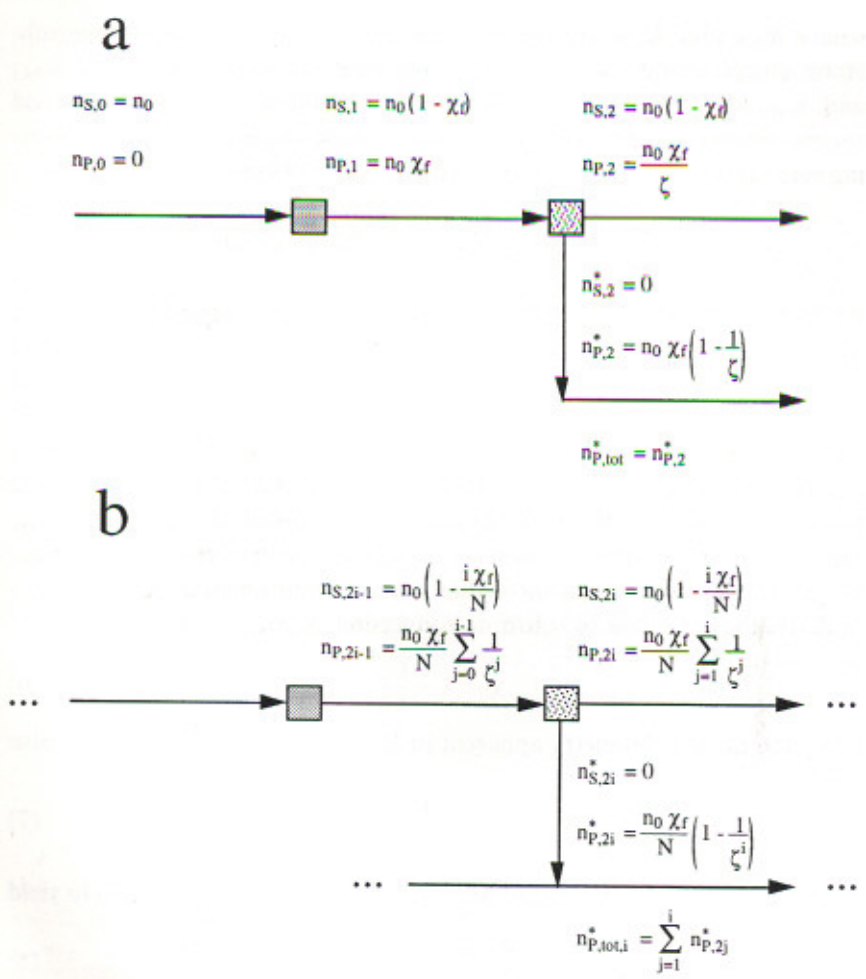

FIGURE 1 Sequence of (a) one reaction unit (▩) and one separation unit (▨) and (b) generic i-th set of one reaction unit (▩) and one separation unit (▨) in a cascade of N sets subject to the inlet conditions $n_{S,0} = n_0$ and $n_{P,0} = 0$.

Assume that chemical transformation of substrate (S) into product (P) occurs via a reaction catalyzed by an enzyme (E) according to the following Michaelis–Menten reversible mechanism assumed to satisfy quasi-equilibrium conditions at all times:

$$E + S \overset{K_{m,S}}{\rightleftharpoons} ES \underset{k_{cat,r}}{\overset{k_{cat,f}}{\rightleftharpoons}} EP \overset{K_{m,P}}{\rightleftharpoons} E + P \tag{3}$$

where $K_{m,S}$ and $K_{m,P}$ are the dissociation constants of the enzyme/substrate complex and the enzyme/product complex, respectively, and $k_{cat,f}$ and $k_{cat,r}$ are first order intrinsic kinetic constants for the forward and reverse reaction, respectively; under this postulated mechanism, the following rate expression can be derived (Proust *et al.*, 1980):

$$r = \frac{v_{max,f}(C_S/K_{m,S}) - v_{max,r}(C_P/K_{m,P})}{1 + (C_S/K_{m,S}) + (C_P/K_{m,P})} \tag{4}$$

where the rates under saturation conditions of enzyme are given by

$$\begin{aligned} v_{max,f} &= k_{cat,f}\, C_{E,tot} \\ v_{max,r} &= k_{cat,r}\, C_{E,tot} \end{aligned} \tag{5}$$

and $C_{E,tot}$ denotes the total concentration of (active) enzyme. It will be assumed hereafter that the enzyme, in insoluble form, is contained in a packed bed and does not undergo deactivation; therefore, $v_{max,f}$ and $v_{max,r}$ can be considered virtually constant irrespective of the variation of volume of the reaction system and throughout the reaction timeframe.

Recall the definition of substrate conversion, χ, viz.

$$\chi = 1 - \frac{C_S}{C_0}. \tag{6}$$

Coupling the stoichiometry apparent in Eq. (3) with Eq. (6), one may also write

$$\chi = \frac{C_P}{C_0}. \tag{7}$$

Equation (4) may be rearranged with the help of Eqs. (2), (6) and (7) to yield

$$r^*\{\chi\} = \frac{K^*_{m,P}[K_{eq} - (1 + K_{eq})\chi]}{K^*_{m,P}K_{eq}(1 + K^*_{m,S}) + K_{eq}(K^*_{m,S} - K^*_{m,P})\chi} \tag{8}$$

where the dimensionless variables are defined as

$$\begin{aligned} r^* &= \frac{r}{v_{max,f}} \\ K^*_{m,S} &= \frac{K_{m,S}}{C_0} \\ K^*_{m,P} &= \frac{K_{m,P}}{C_0} \\ K_{eq} &= \frac{v_{max,f}/K_{m,S}}{v_{max,r}/K_{m,P}} \end{aligned} \tag{9}$$

and K_{eq} denotes the equilibrium constant.

Integration of Eq. (1) up to a generic time $t_{1,uo}$ (and hence final conversion χ_f) with the help of Eq. (2) after having incorporated Eqs. (6)–(8) leads to

$$t^*_{1,uo} = -K_{eq}\left\{\frac{K^*_{m,S} - K^*_{m,P}}{K^*_{m,P}(1+K_{eq})}\chi_f + \frac{K_{eq}K^*_{m,S}(1+K^*_{m,P}) + K^*_{m,P}(1+K^*_{m,S})}{K^*_{m,P}(1+K_{eq})^2}\ln\left(1-\frac{1+K_{eq}}{K_{eq}}\chi_f\right)\right\} \tag{10}$$

which is valid from initial to equilibrium conversion, i.e. for the range

$$0 < \chi_f < \frac{K_{eq}}{1+K_{eq}}. \tag{11}$$

Here the dimensionless time, defined as

$$t^*_{1,uo} = \frac{t_{1,uo}}{C_0/v_{max,f}} \tag{12}$$

may be seen as the ratio between the actual batch (or space) time and the time it would take to fully deplete the substrate if the enzymatic reaction remained pseudo zero-order and only the forward reaction occurred.

Assume now that the physical separation process aimed at recovering pure product P may be described by the following mass balance to the desired product

$$-\frac{dn_P}{dt} = k_{mt}A\frac{n_P}{V} \tag{13}$$

where n_P denotes the number of moles of product P, k_{mt} the phenomenological coefficient (a conductance) describing mass transport, A the (constant) area available for that transport and V the (varying) volume of the mixture. Such a separation may to advantage be effected in a porous membrane, subject to an adequate driving pressure, with its bulk structure treated in such way that only the reaction product possesses the size and shape adequate for permeation, or with its inner surface chemically treated in such a way that only the reaction product possesses the outer chemical or polar characteristics adequate for permeation; in such type of separator the interfacial area remains essentially constant irrespective of the overall system volume. The driving force for mass transport, usually written as $(C_P - C_{P\infty})$, was tentatively simplified to C_P (or, equivalently, n_P/V) by

assuming that $C_{P\infty}$ was negligibly small. Equation (13) is subject to the initial (or boundary) condition

$$t = 0, \quad n_P = n_0\chi. \tag{14}$$

On the other hand, the whole volume of the (ideal) mixture can be calculated via

$$V = n_S v_S + n_P v_P \tag{15}$$

where v_S and v_P denote the (constant) molar volume of substrate and product, respectively, and n_S the number of moles of substrate (which is tentatively assumed to be a constant for integration purposes, thus paralleling a totally selective recovery procedure towards product P). Combination of Eqs. (6), (7) and (12)–(15) yields, after integration

$$t^*_{2,uo} = \Xi\left((1-\chi_f)\ln\{\zeta\} + \chi_f\left(1-\frac{1}{\zeta}\right)\right) \tag{16}$$

where the dimensionless parameters are defined as

$$\begin{aligned} \Xi &= \frac{n_0 v^2 v_{max,f}}{A k_{mt}} \\ \zeta &= \frac{n_{P,1}}{n_{P,2}} \end{aligned} \tag{17}$$

and where advantage was taken from the further simplifying assumption that $v_S = v_P = v$, on the one hand, and from Eqs. (11) and (15) and the fact that $C_0 = n_0/V_0$, on the other. Parameter Ξ may be viewed as the ratio of two time scales, namely $n_0 v/Ak_{mt}$ (i.e. the time scale associated with molecular transport of product P) and $1/vv_{max,f}$ (i.e. the time scale associated with chemical reaction, which was previously used in the definition of t^*); parameter ζ may be viewed as the degree of depletion of product P (hence $\zeta > 1$).

Cascade Approach

Assume now that the reaction/separation operations are cascaded in an alternated fashion as depicted in Fig. 1(b). In this situation, Eq. (8), as applied to the $(2i-1)$-th reactor unit in the series, should read

$$r^*_{2i-1}\{\chi\} = \frac{K^*_{m,P}\left[\left(K_{eq} - C^*_{P,2(i-1)} + \chi_{2(i-1)}\right) - (K_{eq}+1)\chi\right]}{K_{eq}\left[K^*_{m,P}\left(1+K^*_{m,S}\right) + K^*_{m,S}\left(C^*_{P,2(i-1)} - \chi_{2(i-1)}\right) + \left(K^*_{m,S} - K^*_{m,P}\right)\chi\right]} \tag{18}$$

where $i = 1, 2, \ldots, N$, $C^*_{S,2(i-1)}$ and $C^*_{P,2(i-1)}$ are the initial (or inlet) concentrations of substrate and product, respectively, in each of the reactors, defined as

$$C^*_{S,2(i-1)} = \frac{C_{S,2(i-1)}}{C_0}$$
$$C^*_{P,2(i-1)} = \frac{C_{P,2(i-1)}}{C_0} \tag{19}$$

and $r^*_{2i-1}\{\chi\}$ is the rate expression for the reaction that takes place in the $(2i-1)$-th reactor in the cascade, with i denoting a generic reactor/separator pair. Obviously $C^*_{S,2(i-1)}$ and $C^*_{P,2(i-1)}$ are below unity for every reactor unit but the first (for which $C^*_{S,2(i-1)} = 1$ and $C^*_{P,2(i-1)} = 0$).

Integration of Eq. (1) up to a generic time $t^*_{1,ca,2i-1}$ (and hence final conversion $i\chi_f/N$, where N is the total number of reactor/separator sets) after combination with Eq. (18) and with the cascade dimensionless counterpart of Eq. (2), viz.

$$t^* = 0, \quad \chi = (i-1)\frac{\chi_f}{N} \tag{20}$$

(where t^* is the dimensionless space time in the reactor and provided that conversion at the inlet of any reactor is always referred to C_0), leads to

$$t^*_{1,ca,2i-1} = \frac{K_{eq}(K^*_{m,P} - K^*_{m,S})}{K^*_{m,P}(1+K_{eq})}\frac{\chi_f}{N} + \frac{\left(\begin{array}{c} K_{eq}\Big((K^*_{m,P} + K^*_{m,S}K_{eq})\Big(2(1-i)(\chi_f/N) + C^*_{P,2(i-1)}\Big)\Big) \\ +K^*_{m,P}(1+K^*_{m,S}(1+K_{eq})) + K^*_{m,S}K_{eq}\Big) \end{array}\right)}{K^*_{m,P}(1+K_{eq})^2} \times \ln\left\{\frac{K_{eq} - C^*_{P,2(i-1)} + 2K_{eq}(1-i)(\chi_f/N)}{K_{eq} - C^*_{P,2(i-1)} - (1+K_{eq}(2i-1))(\chi_f/N)}\right\} \tag{21}$$

which is the generalization of Eq. (10) to N reactor/separator sets for a generic $C^*_{P,2(i-1)}$. Equation (21) is valid for the range

$$0 < \chi_f < \frac{K_{eq} - C^*_{P,2(i-1)}}{1 + K_{eq} - 2(i-1)/N}. \tag{22}$$

In this approach (and for the sake of simplicity) it was assumed that every reactor unit was able to produce the same conversion of substrate and that the whole cascade would lead to the same overall conversion of substrate (i.e. χ_f) as the unit operation apparatus described previously.

Recalling Fig. 1(b) and Eq. (15), Eq. (19) may be transformed into

$$C^*_{S,2(i-1)} = \frac{1 - i(\chi_f/N)}{1 - \left(i + \sum_{j=1}^{i}(1/\zeta^j)\right)(\chi_f/N)}$$
$$C^*_{P,2(i-1)} = \frac{\left(\sum_{j=0}^{i-1}(1/\zeta^j)\right)(\chi_f/N)}{1 - \left(i + \sum_{j=1}^{i}(1/\zeta^j)\right)(\chi_f/N)}. \tag{23}$$

The total time required by the whole set of chemical reactions to occur, $T^*_{1,ca}$, will then be written as

$$T^*_{1,ca} = \sum_{i=1}^{N} t^*_{1,ca,2i-1}. \tag{24}$$

An interesting asymptotic situation of Eq. (21) occurs when no thermodynamic or kinetic (product) inhibition is present, and is given by

$$\lim_{\substack{K_{eq}\to\infty \\ K^*_{m,P}\to\infty}} t^*_{1,ca,2i-1} = \frac{\chi_f}{N} + K^*_{m,S} \ln\left\{\frac{1 + 2(1-i)(\chi_f/N)}{1 - (2i-1)(\chi_f/N)}\right\} \tag{25}$$

where, as expected, the functionality was reduced to $K^*_{m,S}$ and χ_f/N only.

The counterpart of Eq. (16) may, recalling Fig. 1(b), be written as

$$t^*_{2,ca,2i} = \Xi\left(\left(1 - i\frac{\chi_f}{N}\right)\ln\{\zeta\} + \frac{\chi_f}{N}\left(1 - \frac{1}{\zeta^i}\right)\right) \tag{26}$$

or, equivalently,

$$T^*_{2,ca} = \sum_{i=1}^{N} t^*_{2,ca,2i} = \Xi\left(\left(N - \frac{\chi_f(N+1)}{2}\right)\ln\{\zeta\} + \chi_f\left(1 - \frac{1 - (1/\zeta^N)}{N(\zeta - 1)}\right)\right) \tag{27}$$

where $T^*_{2,ca}$ is the total time necessary for the separation steps. In this approach (and for the sake of simplicity) it was assumed that each separation unit was able to produce the same degree of depletion of product from the mixture (i.e. the same value for ζ).

RESULTS AND DISCUSSION

Parametric Nature of the Problem

In the theoretical development presented above, six parameters were invoked to predict the value of total processing time (T^*) for a given conversion of substrate (χ_f):

(i) one cascading parameter, which is the number (N) of reactor/separator sets ($N=1$ for the unit operation process; $N \geq 2$ for the multiple unit, cascaded process); as N tends to infinity, the cascaded process approaches a fully integrated reaction/separation process;
(ii) three reactional parameters, which describe the thermodynamic inhibition (equilibrium constant, K_{eq}) and the kinetic inhibition by either the reactant (Michaelis–Menten constant associated with the reactant, $K^*_{m,S}$) or the product (Michaelis–Menten constant associated with the product, $K^*_{m,P}$); and
(iii) two separational parameters, which describe the extent of separation (ζ) and the rate of separation (as the rate of chemical reaction divided by the rate of physical separation, Ξ).

Recall that the total processing time (T^*) is defined as the sum of the total time for the chemical reaction to occur to a preset degree of conversion (T^*_1) and the total time required for the physical separation to occur to a preset degree of recovery (T^*_2). Although T^*_1 is described as a function of five parameters (viz. $T^*_1 = T^*_1\{\chi_f, N, K_{eq}, K^*_{m,P}, K^*_{m,S}\}$ and T^*_2 is described as a function of four parameters (viz. $T^*_2 = T^*_2\{\chi_f, N, \zeta, \Xi\}$), the variation in T^* can at times be predicted in a more straightforward fashion from the variation of fewer parameters that either affect only the reactor (see (i) below) or only the separator (see (ii) below), or affect both reactor and separator but in opposite direction (see (iii) below), viz.:

(i) when $K^*_{m,P}$ is varied, only T^*_1 is affected since T^*_2 is not a function of $K^*_{m,P}$: with increasing $K^*_{m,P}$, i.e. lower product inhibition, T^*_1 decreases and so does the total processing time. A similar reasoning can be applied to parameters $K^*_{m,S}$ and K_{eq}. All these parameters (i.e. $K^*_{m,S}$, $K^*_{m,P}$ and K_{eq}) play a role upon Ξ and thus, indirectly, upon T^*_2 (although $C^*_{P,2(i-1)}$ also appears in the aforementioned equations, it should be borne in mind that it can be computed solely from the parameters that directly affect the performance of each reactor and separator);

(ii) when ζ is varied, only T_2^* is affected since T_1^* is not a function of ζ: with decreasing ζ, i.e. a lesser degree of separation, T_2^* decreases and so does the total processing time. Analogously, an increase in Ξ will always lead to an increase in T_2^* and thus in the total processing time (note that Ξ is itself a function of reaction parameters, the reason why a change in Ξ will also play a role upon T_1^*); and

(iii) when only χ_f is varied, both T_1^* and T_2^* are affected. Intuitively, it would be expected that larger conversions (i.e. higher χ_f) would be associated with longer processing times; however, although this presumption always holds for the total reaction time (i.e. T_1^*), it is not necessarily satisfied by the total separation time (i.e. T_2^*). Recall in this regard that Eq. (27) can asymptotically be written as

$$\lim_{\chi_f \to 0} T_{2,ca}^* = N\,\Xi \ln\{\zeta\} \tag{28}$$

and that its derivative with respect to χ_f reads

$$\frac{\partial T_{2,ca}^*}{\partial \chi_f} = \Xi\left(1 - \frac{1-(1/\zeta^N)}{N(\zeta-1)} - \frac{N+1}{2}\ln\{\zeta\}\right). \tag{29}$$

Hence, when separation time prevails over reaction time (i.e. when $T_2^* \gg T_1^*$ and so T^* is approximately equal to T_2^*), then nil conversions are associated with finite processing times that increase with N; furthermore, the aforementioned derivative can turn from positive to negative when N is increased thus eventually leading to a decrease in the overall processing time. From a physicochemical point of view, these mathematical properties are explained because it takes longer to recover a given fraction of product P from a mixture that is more dilute in P (as happens when χ_f is reduced) since the rate of mass transport is proportional to the concentration of P, as apparent in Eq. (13), and this trend is emphasized when the degree of cascading is increased. (It should be reminded that equilibrium constraints, set forth by Eqs. (11) and (22), limit conversion to a maximum threshold, χ_f, that is dependent upon N, K_{eq} and ζ.)

Comprehensive comparison of T^* vs. χ_f plots (not shown) upon variation of all six parameters by several reasonable orders of magnitude has revealed that the most critical processes are those defined as either reaction-controlled or separation-controlled (since the remaining plethora of cases behave as intermediate forms between those). This two-fold, asymptotic approach, which will be considered below in more detail, provides a key to elucidating which processes may present a processing time advantage brought about by cascading and eventual integration.

Numerical Example

A convenient case study where the equations derived above can be used for the unit operation approach (i.e. $N=1$) and a 2-set reactor–separator cascade (i.e. the simplest cascaded process that can be devised) is worked out in Fig. 2. It is remarkable that dividing up evenly the overall extent of conversion ($\chi_f=0.500$) between the two reactors not only leads to a lower overall processing time ($T^*=3.566$ vs. $T^*=4.278$) but also allows a higher amount of desired product to be obtained ($n^*_{P,tot}=0.473$ vs. $n^*_{P,tot}=0.450$).

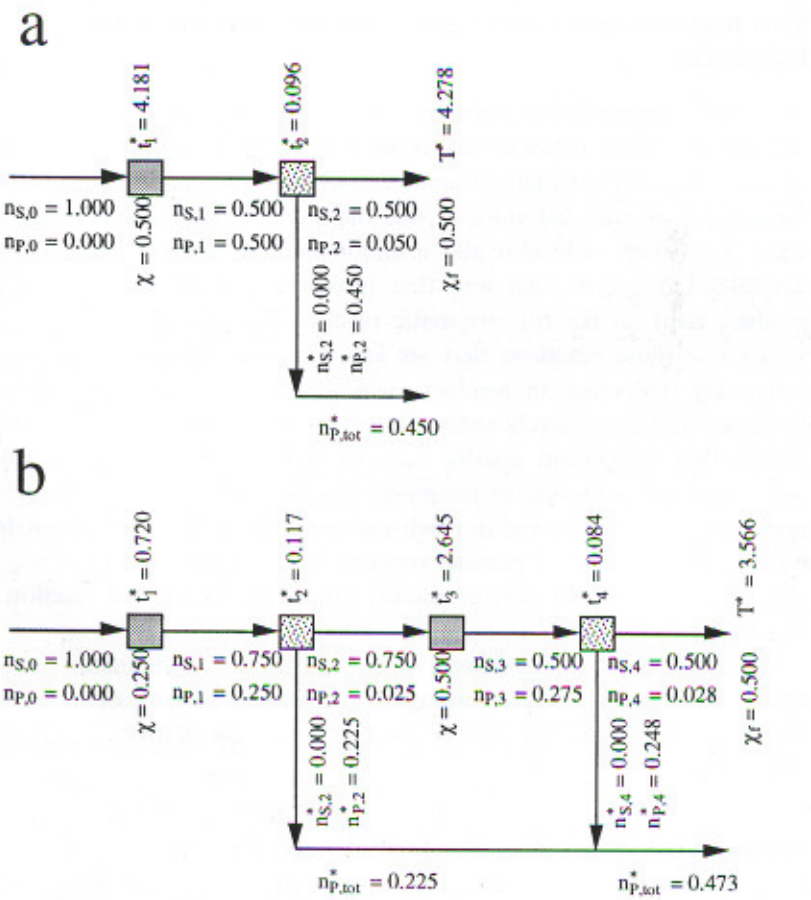

FIGURE 2 Numerical example for (a) the unit operation approach ($N=1$) and (b) a two-step cascade approach ($N=2$), where the reaction unit is denoted as ▨ and the separation unit as ▩. Parameters were arbitrarily set at $K_{eq}=1.5$, $K^*_{m,S}=10^{-3}$, $K^*_{m,P}=10^{-4}$, $\zeta=10$, $\Xi=0.06$ and $\chi_f=0.5$.

Improved Product Recovery upon Cascading

When the number of reactor/separator sets is increased, the amount of product recovered (i.e. $n^*_{P,tot}$) will always increase provided that χ_f is well below χ_{eq}, and this general realization unfolds an intrinsic advantage of cascading. When the number of cascaded sets becomes very large (i.e. when $N \to \infty$), the system approaches full integration; when such a limit is reached, $n^*_{P,tot} \to n_0 \chi_f$, so all product generated by chemical reaction is eventually recovered as pure P irrespective of the separation degree (ζ) in each stage.

Yield Reduction upon Cascading in the Vicinity of Thermodynamic Equilibrium

As already mentioned, equilibrium restrictions set forth as Eqs. (11) and (22) do not allow substrate conversion go beyond χ_{eq}. Those equations indicate that the maximum attainable conversion is (mainly) dependent on the number of cascaded units, N, and the thermodynamic equilibrium constant, K_{eq} (since ζ will also play a minor, indirect role via $C^*_{P,2(i-1)}$): these variables interact in such way that intensification of cascading reduces product yield further for enzymatic reactions associated with higher K_{eq} values (i.e. those reactions that are less thermodynamically constrained); conversely, reduction in product yield upon cascading is negligible for reactions that are severely constrained by a small value of K_{eq}. It is well known that integration usually leads to higher overall substrate conversions; however, it should be reminded that the overall conversion (χ_f) was preset (rather than allowed to reach a maximum) in the above rationale, as was preset the extent of product recovery in the separators (ζ); hence, not all molecules of P that were eventually produced by chemical reaction will be ever recovered unless $\zeta \to \infty$.

Since product yield is reduced when complete (thermodynamic) conversion is approached, then advantages of cascading reactor/separator units should instead be sought at the level of reduction of overall processing time.

Reaction Control and Separation Control

Since Ξ can be viewed as the ratio of the reaction rate to the separation rate, it is clear that low values for Ξ will be characteristic of reaction-controlled processes; such an asymptotic situation, which is approached faster when parameter ζ takes low values, leads to ascending curves for the χ_f vs.

T^* plots (for a typical example of such plots, see Fig. 3(a)). When T^* is plotted as a function of N (at a given χ_f), two situations can prevail when N increases: either (i) T^* monotonically increases with N or (ii) T^* decreases down to a minimum and then increases again (for a typical example of such plots, see Fig. 4(a)); the latter situation is obviously the only one where (limited) cascading provides a processing time advantage. In fact, inspection of Fig. 4(a) indicates that the situation associated with the uppermost curve will provide a processing time advantage up to ca. 8

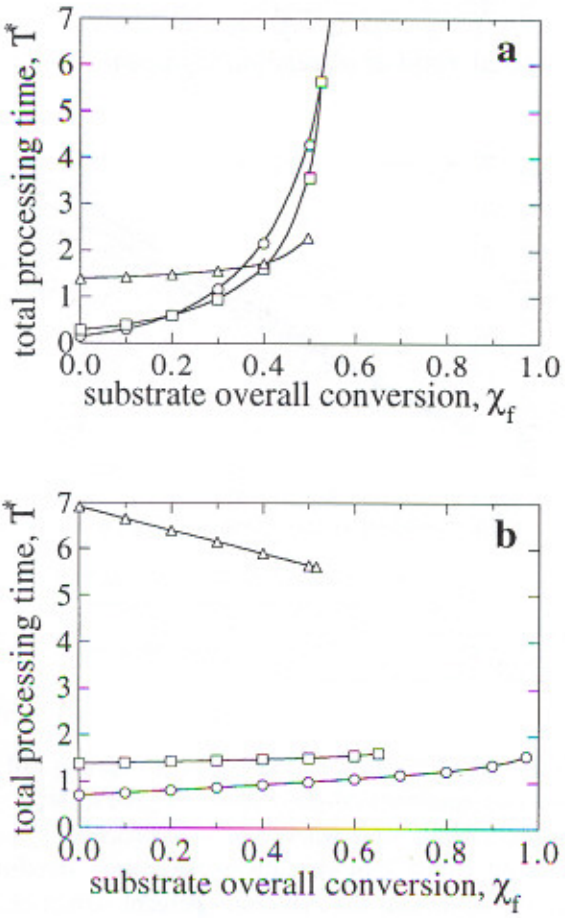

FIGURE 3 Total processing time (T^*) versus overall conversion (χ_f) for (a) a reaction-controlled process with parameters arbitrarily set at $K_{eq} = 1.5$, $K^*_{m,S} = 10^{-3}$, $K^*_{m,P} = 10^{-4}$, $\zeta = 10$ and $\Xi = 0.06$, and (b) a separation-controlled process with parameters arbitrarily set at $K_{eq} = 150$, $K^*_{m,S} = 10^{-3}$, $K^*_{m,P} = 10^{-2}$, $\zeta = 10$ and $\Xi = 0.30$, for three levels of N: $N = 1$ (○), $N = 2$ (□) and $N = 10$ (△).

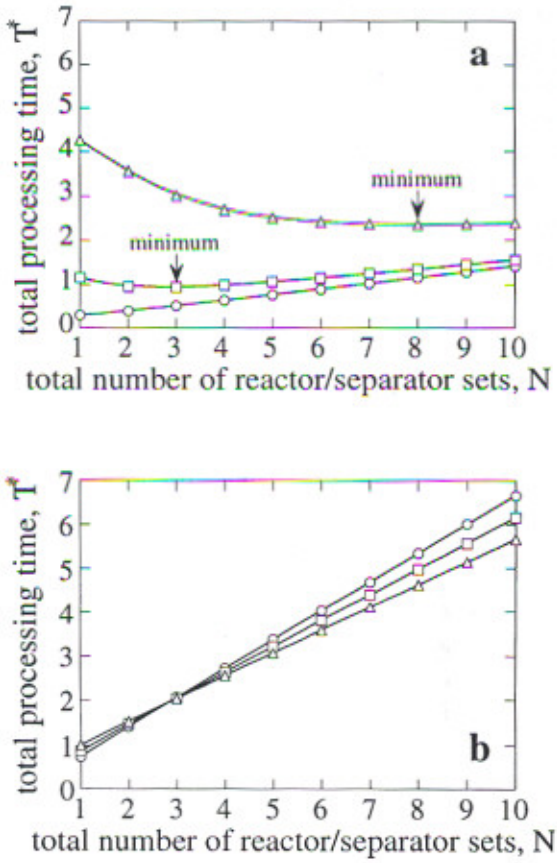

FIGURE 4 Total processing time (T^*) versus number of cascaded reactor/separator sets (N) for (a) a reaction-controlled process and (b) a separation-controlled process. The parameters were arbitrarily set at (a) $K_{eq}=1.5$, $K^*_{m,S}=10^{-3}$, $K^*_{m,P}=10^{-4}$, $\zeta=10$ and $\Xi=0.06$, and (b) $K_{eq}=150$, $K^*_{m,S}=10^{-3}$, $K^*_{m,P}=10^{-2}$, $\zeta=10$ and $\Xi=0.30$. Three levels of χ_f were considered: $\chi_f=0.1$ (○), $\chi_f=0.3$ (□) and $\chi_f=0.5$ (△).

reactor/separator sets, although essentially no processing difference will be expected when such number is slightly lower (say, 6) or larger (say, 10); the middle curve describes a case where the best processing time advantage will be experienced at $N=3$, or virtually in the range extending from $N=2$ to $N=4$. It is also clear that the maximum percent reduction in processing time, when taking the unit operation case as reference, increases as χ_f increases: in our case, the uppermost curve ($\chi_f=0.5$) is associated with a reduction of processing time up to 45% whereas the second curve ($\chi_f=0.3$) provides a reduction of up to 19%.

By the same token, high values of Ξ will lead to separation-controlled processes; such an asymptotic situation, which is approached faster when parameter ζ takes high values, leads to either ascending or descending curves for the χ_f vs. T^* plots (for a typical example of such plots, see Fig. 3(b)). In this type of processes, T^* always increases with N. This realization is shown in more detail in the typical example depicted as Fig. 4(b): inspection of this figure indicates that T^* increases linearly with N (and that remarkably all such curves intersect each other at $N=3$). Such linear behaviour can be derived from Eq. (27) because T^* is approximately equal to T_2^* for separation-controlled processes: Eq. (27) will approximately degenerate into $T_2^* = \Xi(\chi_f + N(1 - \chi_f/2)\ln\{\zeta\})$ when ζ is large. Cascading separation-limited processes is always unfavourable when compared with the classical unit operation approach.

CONCLUSIONS

Cascading can decrease total processing time for reaction-controlled processes only and full process integration may (but not necessarily will) prove advantageous for such processes. Reaction-controlled processes occur when the processing parameters show the following trend: Ξ is low (reaction proceeds slowly with regard to separation), ζ is low (extent of separation is small and so the separation step is expected to take place fast), K_{eq} is low (the reaction is thermodynamically constrained), $K_{m,S}^*$ is high (substrate inhibition is negligible), $K_{m,P}^*$ is low (product inhibition plays an important role) and χ_f is high (reaction is pushed towards equilibrium). In such cases, a T^* vs. N plot will be required and visual inspection necessary to determine whether (and up to which degree) cascading will be useful.

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NOTATION

A	Area available for mass transfer [m^2]
C	Molar concentration [$mol\,m^{-3}$]
k	First order intrinsic kinetic constant [s^{-1}]
K	Equilibrium constant
K_m	Michaelis–Menten parameter [$mol\,m^{-3}$]
k_{mt}	Mass transfer coefficient [$m\,s^{-1}$]
n	Number of moles [mol]
N	Total number of reactor/separator sets
r	Rate of reaction [$mol\,m^{-3}\,s^{-1}$]
t	Batch time or reactor space time [s]
T	Total processing time [s]
v	Molar volume [$m^3\,mol^{-1}$]
v_{max}	Maximum reaction rate [$mol\,m^{-3}\,s^{-1}$]
V	Volume of the mixture [m^3]

Greek letters

χ	Substrate conversion, C_P/C_0
ζ	Dimensionless extent of separation, $n_{P,2i-1}/n_{P,2i}$
Ξ	Dimensionless ratio of time scales for reaction and separation, $(n_0 v^2 v_{max,f})/(A k_{mt})$

Subscripts

ca	Cascade approach
cat	Catalyst
E	Enzyme
eq	Equilibrium
f	Forward reaction
f	Final
i	Generic reactor/separator set
P	Product
r	Reverse reaction
S	Substrate
tot	Total
uo	Unit operation approach
0	Starting or initial conditions
1	Reactor
2	Separator

$1, 3, \ldots, 2N-1$	Conditions at outlet of reactors
$2, 4, \ldots, 2N$	Conditions at outlet of separators

Superscript

$*$	Dimensionless parameter

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