Optimal Design of Interconnected Bioreactors: New Results

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The optimal design of two interconnected continuous stirred bioreactors in which a single reaction occurs is presented. The term "optimal" should be understood here as the minimum of the total volume of the reactors required to perform a given conversion rate, given a quantity of matter to be converted per time unit. In determining the optimal volume, it is assumed that the input flow may be distributed among the tanks and also that a recirculation loop can be used. The analysis of the optimal configurations is investigated, and the concept of "steady-state equivalent biological system" is highlighted. The class of growth functions for which the results of this study hold is quite wide and includes, in particular, Monod, Haldane, and Aiba kinetics.

Introduction

The question of optimally designing chemical or biochemical systems has been assessed by several authors these last 30 years. An important effort has been made by the chemical engineering community to develop general and systematic theories for optimizing process synthesis [see, for instance, the article by Feinberg (2002)]. This task turns out to be much more complex for the case of biological systems. One reason for that is the difficulty in finding a simple and yet accurate model to represent all the important dynamics of living organisms interacting in a biosystem. Furthermore, it should be noticed that most of the existing results are limited to the optimal design (in a sense to be cleared later on) of a series (cascade connection) of N continuous stirred-tank (bio)-reactors (CSTR).

Biological processes can usually be classified into two classes of systems: microbiological- and enzyme-based reactions. In simple terms, microbiological-based reactions define (bio)reactions where a substrate degradation is associated with the growth of certain organisms, while, the enzyme-based reaction can be viewed as a chemical reaction with specific growth-rate functions. Design techniques for enzyme-based reactions are more common in the literature due to the fact that related industries (typically pharmaceutical ones) usually deal with the production of high added-value molecules.

Given a model of a series of CSTR, representing enzyme or microbiological reactions, and a flow rate to be treated, Q, the problem of determining optimal conditions for a steady-state operation is of great interest. For instance, conditions have been proposed to minimize the total retention time (TRT) required to attain a given conversion rate, S_N/S_0 (here S_0 and S_N denote, respectively, the input and output substrate concentrations). Observe that this specific problem is equivalent to the minimization of the total required volume (TRV) when Q is constant (as is the case at steady state). The main motivation for using a series of CSTRs is that their industrial operating conditions and reliability are better if compared to a plug-flow reactor (PFR). Thus, the problem of finding conditions under which the performance of a series of CSTRs is comparable to that obtained with a PFR is of great practical interest.

The pioneering work by Grieves et al. (1964) experimentally compared the performances of a single biological CSTR to those of a PFR for a single Monod kinetic reaction. It was shown that, for identical residence times, the PFR gives better conversion rates than the CSTR. Thus, under appropriate conditions, the total volume of N reactors in series can be smaller than the volume that would be required if only one

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tank is used. Following this idea and using the mathematical optimization procedure proposed by Luyben and Tramper (1982), Hill and Robinson (1989) solved the theoretical optimization scheme for a single microbiological reaction and proved that a system composed of three reactors in series exhibit comparable—and, in some cases, depending upon the considered kinetic, even better—performances than a PFR [cf. Hill and Robinson (1989)]. In particular, it was established that the optimum residence time of bioreactors along the series always decreases. It was also verified that these results hold for biological reactions inhibited by the product [cf. Wall and Hill (1992)]. It should be noticed that the results of Hill and Robinson were in accordance with the "fourth polynomial equation" first proposed in 1966 by Bischoff to optimally compute the optimal concentrations of substrate in each tank of a series of two bioreactors [cf. Bischoff (1966)]. Let us emphasize that in the work by Hill and Robinson (1989), a recirculation loop was not generically included in the scheme, and the possibility of distributing the input flow among the different reactors of the series was not considered either.

In the context of biological reactions inhibited by the product (as is the case, for example, for ethanol production), the largest number of the design techniques for improving the performance of a series of CSTR found in the literature today are based on tanks having the same volumes. In this case, the degrees of freedom in the optimization problem are composed of the different flow rates and input substrate concentrations to be injected into each reactor in the series [cf. Dourado et al. (1987)]. A numerical procedure to cope with this optimization problem is proposed in this last reference, but the technique does not allow us to draw any additional qualitative information about the designed system.

More recently, the largest number of studies related to the optimal design of biological reactors either deal with membrane reactors [cf., for example, Prazeres (1994) or Muslu 2000)] or are devoted to specific applications such as the design of a wastewater treatment plant. In some cases, the design technique is based on the solution of a certain mixed integer–dynamic optimization or even a nonlinear programming problem. In this context we could mention, for instance, Rigopoulos and Linke (2002) and Vidal et al. (2002). Besides these articles, one can also find a number of studies that, however, remain essentially experimental [cf. Lee et al. (1996) or Villadsen (1998)].

The idea of the present article is to restrict our attention to a simple microbiological reactor configuration and to solve the steady-state design problem rigorously from a mathematical point of view. It should be noticed here that although motivated by a microbiological problem, the results are derived in a generic manner and hold for a wide class of kinetic functions (specified in the sequel). This study differs significantly from the existing results in the following way. We could divide the just-mentioned studies treating the optimal design problem of N bioreactors in the series into two distinct classes: those concerned with the computation of the volumes of the different reactors, given a single input flow rate feeding the first reactor [as in Hill and Robinson (1989)], and those concerned with the computation of the optimal distribution of the inputs (both the flow rates and the concentrations) in each unit of the series of tanks [all of them with the same volumes, as in Dourado et al. (1987)]. Surprisingly, the determination of the optimal volumes of the tanks (not necessarily equal) in the case where the input flow is distributed among the units of the series has never been investigated. In addition, just a few articles propose the use of a recirculation loop to eventually improve the results, but from the best of the authors' knowledge, none of them offer a theoretical proof.

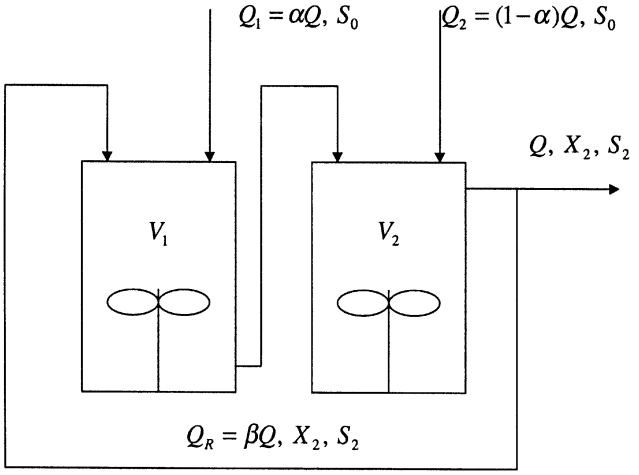

Figure 1. Two tank system.

The system to be considered in the present study is represented in Figure 1 where V_1 and V_2 are the volumes of the reactors, αQ is a part of the total flow rate, Q, feeding the first reactor [while the remaining part $(1-\alpha)Q$ feeds the second one], βQ is the recirculation flow rate, S_0 and S_2 are the input and output substrate concentrations, and X_2 is the biomass concentration in the second tank.

We emphasize that the only "distribution of the input" we allow in the present article is the separation of the flow entering the two reactors as αQ and $(1-\alpha)Q$. One can think about the possibility of considering distinct input substrate concentrations into each reactor (S_{in1} and S_{in2} instead of S_0 for both tanks). However, this situation seems to be of little interest, because more water per time unit than Q would be required for the dilution of a nominal substrate, S_0.

The aim of the present work is to investigate the possible benefits of using a distributed feeding system and a recirculation loop in a system composed of two reactors in series, as shown in Figure 1. The benefit will be measured in terms of the TRV to perform a given conversion rate. Observe in Figure 1 that if $\alpha = 1$ (single feeding system) and $\beta = 0$ (no recirculation), the actual system is exactly equivalent to the one studied by Hill and Robinson (1989) for $N = 2$ (two reactors in series). The problem considered in this article may then be stated as follows: Given positive numbers $\bar{S}_0$, $\bar{S}_2$ (with $\bar{S}_2 < \bar{S}_0$), $\bar{Q}$, and the model of the process, do values of α (with $0 \le \alpha \le 1$) and β ($\beta \ge 0$) exist such that the TRV $(V_1 + V_2)$ is smaller than the one obtained with the model of Hill and Robinson (1989)?

The general solution to this problem is rigorously solved mathematically and illustrated by simulations.

The article is organized as follows. In the "Modeling" section, the general mass-balance model of the series of bioreactors is introduced. In the "Design Problem" section, the gen-

eral optimization problem is formalized. In the "Optimal Solutions" section, the problem is solved for a general class of kinetic functions (including the Monod, Haldane, and Aiba laws). In particular, the concept of a steady-state equivalent biological system (SSEBS) is introduced. Then the "Design" section investigates the stability of the obtained optimal configuration. In the "Application" section, the results are illustrated and discussed for both Monod and Haldane kinetics. Finally, an example of the SSEBS principle is given before some concluding remarks are made and perspectives are drawn.

Modeling

Assuming a single biological reaction in the two reactors, the dynamical equations of the general system represented in Figure 1 are given by

$$\begin{cases} \dot{X}_1 = \beta\dfrac{Q}{V_1}X_2 - (\alpha+\beta)\dfrac{Q}{V_1}X_1 + \mu(S_1)X_1 \\ \dot{S}_1 = \alpha\dfrac{Q}{V_1}S_0 + \beta\dfrac{Q}{V_1}S_2 - (\alpha+\beta)\dfrac{Q}{V_1}S_1 - \dfrac{\mu(S_1)X_1}{Y} \\ \dot{X}_2 = (\alpha+\beta)\dfrac{Q}{V_2}X_1 - (1+\beta)\dfrac{Q}{V_2}X_2 + \mu(S_2)X_2 \\ \dot{S}_2 = (1-\alpha)\dfrac{Q}{V_2}S_0 + (\alpha+\beta)\dfrac{Q}{V_2}S_1 - (1+\beta)\dfrac{Q}{V_2}S_2 \\ \qquad\qquad - \dfrac{\mu(S_2)X_2}{Y} \end{cases} \quad (1)$$

where X_1, S_1, X_2, and S_2 are, respectively, the biomass and substrate concentrations in the first and the second reactor; αQ and $(1-\alpha)Q$ are the input flow rates in the first and in the second reactor, respectively; while βQ is the recirculation flow rate. In addition, μ is the kinetic function, and Y is the substrate consumption rate. Finally, V_1 and V_2 are the volumes of reactors 1 and 2, respectively.

Design Program

Introducing auxiliary variables $Z_1 = X_1 + YS_1$ and $Z_2 = X_2 + YS_2$, we have

$$\begin{cases} \dot{Z}_1 = \beta\dfrac{Q}{V_1}Z_2 - (\alpha+\beta)\dfrac{Q}{V_1}Z_1 + \alpha Y\dfrac{Q}{V_1}S_0 \\ \dot{Z}_2 = (\alpha+\beta)\dfrac{Q}{V_2}Z_1 - (1+\beta)\dfrac{Q}{V_2}Z_2 + (1-\alpha)Y\dfrac{Q}{V_2}S_0 \end{cases} \quad (2)$$

For steady-state operation of the system, the following are required $\dot{Z}_1 = 0$ and $\dot{Z}_2 = 0$. Together with a substrate balance at steady state in the two reactors ($\dot{S}_1 = 0$ and $\dot{S}_2 = 0$) leads to

$$\begin{cases} \beta\dfrac{Q}{V_1}S_2 - (\alpha+\beta)\dfrac{Q}{V_1}S_1 + \alpha\dfrac{Q}{V_1}S_0 = \dfrac{\mu(S_1)X_1}{Y} \\ (1-\alpha)\dfrac{Q}{V_2}S_0 + (\alpha+\beta)\dfrac{Q}{V_2}S_1 - (1+\beta)\dfrac{Q}{V_2}S_2 = \dfrac{\mu(S_2)X_2}{Y} \\ \dfrac{X_1}{Y} = S_0 - S_1 \\ \dfrac{X_2}{Y} = S_0 - S_2 \end{cases} \quad (3)$$

The system, depicted in Eq. 1, at steady state is then described by the system of equations (Eqs. 3). Moreover, physical considerations about the system lead to the following constraints

$$\alpha \in [0, 1] \text{ and } \beta \geq 0 \quad (4)$$

$$X_1 \geq 0 \Rightarrow \alpha S_0 - (\alpha+\beta)S_1 + \beta S_2 \geq 0 \quad (5)$$

$$X_2 \geq 0 \Rightarrow (1-\alpha)S_0 + (\alpha+\beta)S_1 - (1+\beta)S_2 \geq 0 \quad (6)$$

$$S_0 > S_1 \geq 0 \quad (7)$$

$$S_0 > S_2 \geq 0 \quad (8)$$

from which it is easy to establish that Eqs. 5–8 imply the following inequalities

$$0 \leq \alpha + \beta\frac{S_2 - S_1}{S_0 - S_1} \leq \frac{S_0 - S_2}{S_0 - S_1} \quad (9)$$

Given $Q = \bar{Q} > 0$, $S_2 = \bar{S}_2 > 0$, and $S_0 = \bar{S}_0 > \bar{S}_2$, it is straightforward to show from Eqs. 3 that the total volume, V, to be minimized can be expressed as a function of α, β, and S_1

$$\begin{aligned} V(\alpha, \beta, S_1) &= V_1 + V_2 \\ &= \bar{Q}\left(\frac{\alpha\bar{S}_0 - (\alpha+\beta)S_1 + \beta\bar{S}_2}{\mu(S_1)(\bar{S}_0 - S_1)} + \frac{(1-\alpha)\bar{S}_0 + (\alpha+\beta)S_1 - (1+\beta)\bar{S}_2}{\mu(\bar{S}_2)(S_0 - \bar{S}_2)}\right) \\ &= \bar{Q}\left[\left(\frac{1}{\mu(S_1)} - \frac{\bar{S}_0 - S_1}{\mu(\bar{S}_2)(\bar{S}_0 - \bar{S}_2)}\right)\left(\alpha + \beta\frac{\bar{S}_2 - S_1}{\bar{S}_0 - S_1}\right) + \frac{1}{\mu(\bar{S}_2)}\right] \end{aligned} \quad (10)$$

We are then concerned with the following optimization problem.

Optimization problem ($\mathcal{P}$). Given numbers $\overline{Q}$, $\overline{S}_0$, and $\overline{S}_2$ such that $\overline{Q} > 0$, $\overline{S}_0 > \overline{S}_2 > 0$, and a kinetic function $\mu(\cdot) \geq 0$, minimize the objective function

$$J(\alpha, \beta, S_1) = a(S_1)\left(\alpha + \beta\frac{\overline{S}_2 - S_1}{\overline{S}_0 - S_1}\right) \tag{11}$$

where

$$a(S_1) = \frac{1}{\mu(S_1)} - \frac{\overline{S}_0 - S_1}{\mu(\overline{S}_2)(\overline{S}_0 - \overline{S}_2)} \tag{12}$$

under the constraints expressed in Eqs. 4, 7, and 9.

Remark. If $\alpha = 1$ (no distribution of the input flow) and $\beta = 0$ (no recirculation loop), notice that the objective function just given is reduced to the one considered in Hill and Robinson (1989) for two tanks.

Optimal Solutions

We consider the following technical hypothesis, where μ' denotes $d\mu/dS$:

Hypothesis H1. The kinetic function $\mu()$ has the following properties:

(1) $\mu(0) = 0$

(2) $\mu(S) > 0$, $\forall S > 0$

(3) The function $\mu'(S)/\mu(S)^2$ is decreasing on $(0, \overline{S}_0]$.

Remark. This hypothesis is not only valid for specific kinetics but for a large class of kinetic functions. In particular, both Monod, Haldane, and Aiba kinetics satisfy this hypothesis (see the Application section).

We begin with the following lemma:

Lemma L1. Under Hypothesis H1, the function $S_1 \rightarrow a(S_1)$ has two roots on the interval $(0, \overline{S}_0]$, namely, S_1' and $\overline{S}_2$ (possibly identical), and the following holds

$$a(S_1) \leq 0 \quad \text{and} \quad S_1 \in (0, \overline{S}_0) \Leftrightarrow S_1 \in \left[\min(\overline{S}_2, S_1'), \max(\overline{S}_2, S_1')\right] \tag{13}$$

Proof. See the Appendix.

The preceding lemma establishes some basic properties of the function $a()$. Observe that the precise value of the root S_1' will depend on the specific kinetic considered and the data of the problem. Now we are able to characterize the optimal solutions $(\alpha^*, \beta^*, S_1^*)$ of the optimization problem ($\mathcal{P}$).

Proposition P1. Under Hypothesis H1, let S_1' and $\overline{S}_2$ be the two roots (possibly identical) of the function $a()$ on $(0, \overline{S}_0]$. One of the following cases occurs:

(1) If $S_1' > \overline{S}_2$, then the optimal solution of the optimization problem ($\mathcal{P}$) is given by $\alpha^* = 1$, $\beta^* = 0$, and S_1^* is the unique solution on $[0, \overline{S}_0]$ of

$$\mu(S_1^*)^2 = \mu'(S_1^*)\mu(\overline{S}_2)(\overline{S}_0 - \overline{S}_2) \tag{14}$$

(2) If $S_1' < \overline{S}_2$, then there exists an infinity of optima (α^*, β^*) that lie on the line

$$\alpha + \beta\frac{\overline{S}_2 - S_1^*}{\overline{S}_0 - S_1^*} - \frac{\overline{S}_0 - \overline{S}_2}{\overline{S}_0 - S_1^*} = 0, \qquad \alpha \in [0, 1] \qquad \beta \geq 0 \tag{15}$$

where $S_1^* \in (S_1', \overline{S}_2]$ is the solution of

$$\mu'(S_1)(\overline{S}_0 - S_1) - \mu(S_1) = 0 \tag{16}$$

(3) If $S_1' = \overline{S}_2$, then the optimal solution of the optimization problem ($\mathcal{P}$) is given by $\alpha^* = 1$, β^* is any arbitrary positive value and $S1^* = \overline{S}_2$.

Proof. See the Appendix.

Remark. Observe from Eqs. 14 and 16 in the situations 1 and 2 of the preceding proposition that the optimal concentration in the first reactor S_1^* is such that $\mu'(s_1^*) > 0$.

Design Analysis

Stability

The design of reactors in the series has been studied in the previous sections in order to take advantage of the properties of pistonlike systems, assuming that it is easier to operate N perfectly mixed reactors in series than a single-piston reactor. However, it is important to verify whether this cascade of perfectly mixed reactors is stable. Otherwise, the implementation of a control system would be mandatory to maintain the process around its optimal equilibrium, and the practical advantage of dealing with "simpler" plants than "pistonlike" systems would not be so obvious anymore. Furthermore, in the presence of a recirculation loop, the stability of the designed process has to be checked carefully.

Proposition P2. When α and β are not simultaneously null, the equilibrium point $(X_1^e, S_1^e, X_2^e, S_2^e) \in \mathbb{R}_+^4$ of the system depicted in Eq. 1 is locally asymptotically stable if the following conditions are satisfied:

$$\begin{cases} (\alpha + \beta)Y\dfrac{Q}{V_1} + (1 + \beta)Y\dfrac{Q}{V_2} + \mu'(S_1^e) + \mu'(S_2^e) > 0 \\ (\alpha + \beta)Y^2\dfrac{Q^2}{V_1V_2} + (\alpha + \beta)Y\dfrac{Q}{V_1}\mu'(S_2^e) \\ + (1 + \beta)Y\dfrac{Q}{V_2}\mu'(S_1^e) + \mu'(S_1^e)\mu'(S_2^e) > 0 \end{cases} \tag{17}$$

Proof. See the Appendix.

Remark. From the preceding proposition, it follows that if both conditions $\mu'(S_1^e) \geq 0$ and $\mu'(S_2^e) \geq 0$ are satisfied, then the local asymptotic stability of the designed system is guaranteed.

Discussion of the results

We have presented two propositions in the previous sections. The first one defines the optimal solutions to the problem of minimizing the TRV to perform a given conversion rate, and the second shows conditions under which the local stability of the designed system is guaranteed.

Several remarks are in order.

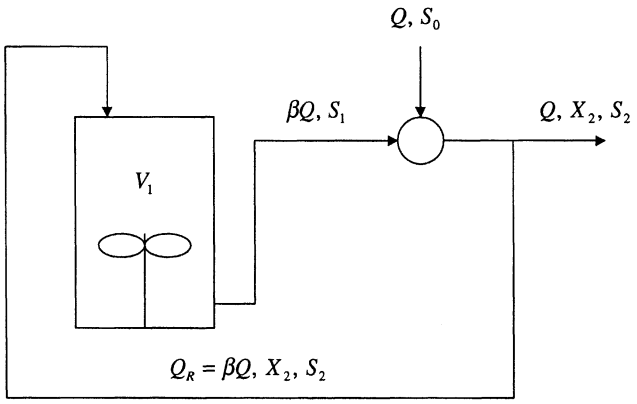

Figure 2. Limit case when $S_1' < S_2$ with $\alpha^* = 0$ and $\beta^* = (\bar{S}_0 - \bar{S}_2)/(S_2 - S_1^*)$.

As stated in the Proposition P1, we have three different strategies for minimizing the TRV depending on the relation between the roots S_1' and $\bar{S}_2$ of the function $a()$. The specific values of these roots depend on the kinetics and the data of each particular problem. Moreover, S_1' is exactly the limit value already proposed by Hill and Robinson (1989), and no improvement was suggested beyond this value. In fact, following Proposition P1, there is sometimes an infinity of configurations allowing a decrease of the TRV. The magnitude of the possible improvement, in the case $\bar{S}_2 > S_1'$, is investigated in the Application section. Again, notice that the results in this article are valid for both Monod and Haldane kinetics as well as for any kinetic function verifying Hypothesis H1.

When $\bar{S}_2 > S_1'$, the optimal design consists of a class of systems having exactly the same total volume, but differ significantly from the manner they are fed and in the way the recirculation loop is used. The extreme cases, namely, $\alpha = 0$ and $\beta = 0$, are of special interest. If $\alpha = 0$, only the second tank having null volume (see Figure 2) is fed, while a recirculation loop is needed to provide the first reactor with water. In fact, in this case $S_1^* < \bar{S}_2$ and the input flow rate is used to dilute the concentration arriving from the first tank. This is a very interesting case in which the decrease in the TRV can be very important (see the Application section).

Supposing $\bar{S}_2 > S_1'$, and motivated by the exact equivalence between the steady state of these configurations (same total volume, same input–output behaviors), we introduce here the concept of SSEBS. This concept is very promising, since it allows the user to optimize the configuration not only with respect to the optimization criterion used in this article, that is, the TRV, but with any other related one, for instance, a performance index associated with the transient behavior of a specific optimized configuration. Additional degrees of freedom can then be used (as controllability, observability) to choose the final required design. An example of the use of this concept is given in the next section.

Finally, to summarize this section, it is of particular interest to point out the following general results, which are valid whatever the kinetic functions may be, provided they satisfy Hypothesis H1:

- Given the data of a specific problem to be solved, if $S_1' > \bar{S}_2$, neither the implementation of a recirculation loop nor the "distribution" of the input flow rate between the two tanks allows any improvement with respect to the results that exist in the literature.
- If $S_1' < \bar{S}_2$, then there exists an infinity of optimal configurations having the same TRV, allowing us to propose the concept of SSEBS. Observe that the optimal value, S_1^*, of the substrate concentration in the first reactor, given by Eq. 14, is independent of α, β, and $\bar{S}_2$. In this case, additional considerations such as economical or structural (observability, controllability, and so on) can be used to globally optimize the desired process (see the next section). In this sense, these results can be viewed as a generalization (for the case of two tanks) of the original results proposed by Hill and Robinson (1989).
- Finally, we also propose sufficient conditions for the local stability of the designed system at a given equilibrium point, even when a recirculation loop is present.

Application

Monod kinetic

In this case, μ has the following expression

$$\mu(S) = \mu_{\max} \frac{S}{S + K_S} \tag{18}$$

where $\mu_{\max} > 0$ is the maximum growth rate and $K_S > 0$ the half saturation coefficient. We check that the hypothesis H1 is satisfied

$$S \to \mu'(S)/\mu(S)^2 = \frac{K_S}{\mu_0 S^2} \searrow$$

The root S_1' of the function $a()$ is in this case given by

$$S_1' = \frac{K_S(\bar{S}_0 - \bar{S}_2)}{\bar{S}_2 + K_S} \tag{19}$$

The following general optimization procedure can then be used: Given K_S, $\bar{S}_2$, and S_0, compute S_1' as expressed by Eq. 19 and directly apply Proposition P1, that is:

- If $S_1' > \bar{S}_2$, the optimal solution is given by $\alpha^* = 1$, $\beta^* = 0$, and S_1^*, solution of Eq. 14, computed as

$$S_1^* = \sqrt{\frac{K_S \bar{S}_2(\bar{S}_0 - \bar{S}_2)}{\bar{S}_2 + K_S}} \tag{20}$$

- If $S_1' < \bar{S}_2$, there exists an infinity of equivalent configurations (having the same TRV). Equation 16 yields

$$S_1^2 + 2S_1 K_S - \bar{S}_0 K_S = 0$$

which has only one nonnegative root

$$S_1^* = -K_S + \sqrt{K_S(K_S + \bar{S}_0)} \tag{21}$$

Notice that α and β cannot be simultaneously null, and their optimal values α^* and β^* are given by Eq. 15. Let us ana-

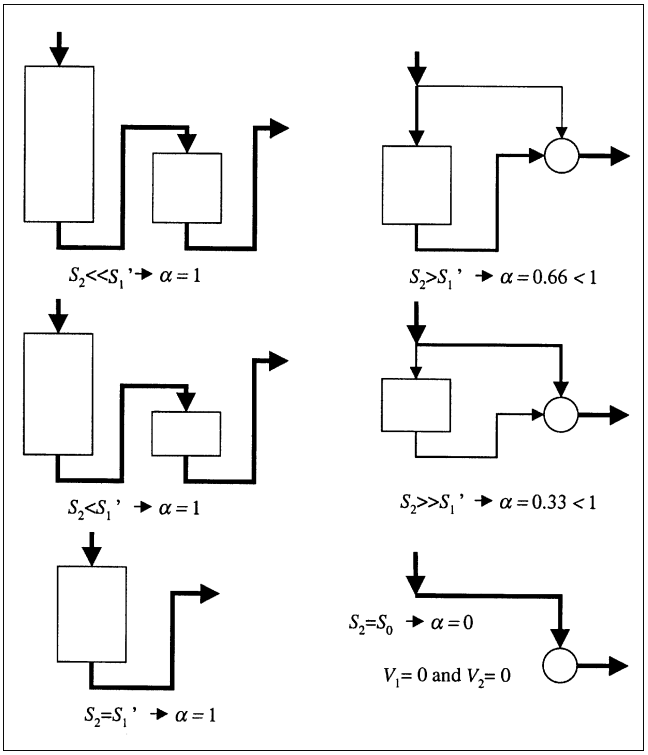

Figure 3. Optimal designs with $\beta = 0$ when S_2 varies from 0 to S_0.

lyze the case corresponding to the choice $\beta = 0$. In this situation, if the required conversion ratio $\bar{S}_2/\bar{S}_0$ increases, then the ratio between the input flow entering the first reactor, namely $\alpha\bar{Q}$, and the flow used for diluting the output of this reactor, $(1-\alpha)\bar{Q}$, decreases, as is shown in Figure 3. In fact, the value given by Eq. 21 is the limit value of S_2 (denoted by $\bar{S}_2^{\lim}$ in the sequel) for which the proposed method allows an improvement in the design when compared to the results proposed by Hill and Robinson (1989). Indeed, the value of S_1^* given by Eq. 21 is the limit value for which $S_1' = \bar{S}_2$. Notice that the condition $S_1' < \bar{S}_2$ is exactly equivalent to the condition given by Hill and Robinson under the form

$$\frac{S_2}{\bar{S}_0} > -\frac{K_S}{\bar{S}_0} + \sqrt{\left(\frac{K_S}{\bar{S}_0}\right)^2 + \frac{K_S}{\bar{S}_0}} \tag{22}$$

- Finally, if $S_1' = \bar{S}_2$, the optimal solution is given by $\alpha^* = 1$, β^* is an arbitrary positive value, and $S_1^* = \bar{S}_2$. In other words, only one reactor is needed and it is fed with the entire flow, $\bar{Q}$.

With the Monod law, μ' is always positive and Proposition P2 provides the asymptotic stability of the system in any case.

As an illustrative example, let us consider a fictitious model with the parameters given in Table 1.

Table 1. Parameter Values for the Example Using a Monod Kinetic

$\mu_{\max}$	K_S	$\bar{S}_0$	$\bar{Q}$
0.045 h^{-1}	0.1, 1, 5, 10, 20, or 30 mg.L^{-1}	100 mg.L^{-1}	1 h/L^{-1}

Let us investigate the optimal configurations when $\bar{S}_2$ varies from 1 mgl^{-1} to $\bar{S}_0$. Only one value for $\mu_{\max}$ is used, since it only affects the final computation of the volumes. Obviously, the greater the maximum growth rate, the smaller the volumes. This is not case for K_S, however, which directly affects the computation of S_1'. This is why several values of K_S are used in the following simulations. The growth rates with the different values of K_S are plotted in Figure 4.

Using the preceding results and given a value of K_S, computing the limit value of S_2 is straightforward, as previously

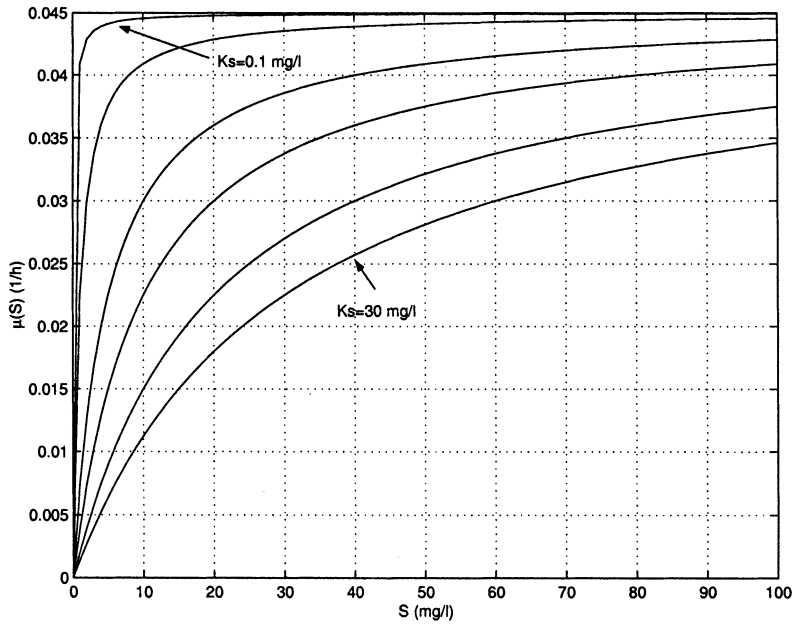

Figure 4. Function $\mu(S)$ with the different model parameters: Monod kinetics.

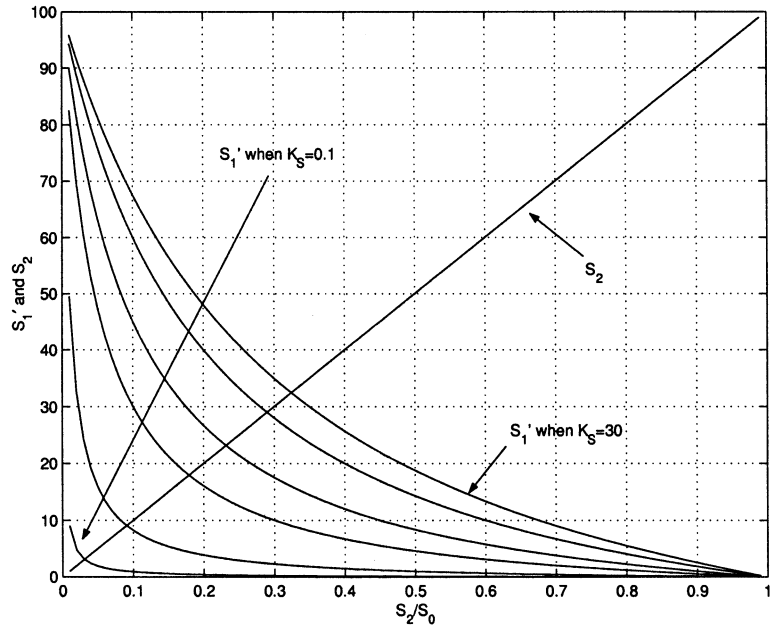

Figure 5. S_1' and $\bar{S}_2$: Monod kinetics.

mentioned. For instance, if $K_S = 10$ mg/L, this value is given by $\bar{S}_2^{\lim} = 23.17$ mg/L. In other words, as long as any required $\bar{S}_2$ is such that $\bar{S}_2 < \bar{S}_2^{\lim}$, the optimal design is exactly the one proposed by Hill and Robinson (1989). This is illustrated in the Figure 5, where both S_2' and $\bar{S}_2$ are presented as functions of S_2/S_0.

In order to simplify the interpretation of the results (and particularly those obtained when $\bar{S}_2 > \bar{S}_2^{\lim}$), we present the optimal results corresponding to the configuration obtained with $\beta^* = 0$. Figure 6 presents the optimal values for S_1 when $\bar{S}_2$ varies from 1 to $\bar{S}_0$ and K_S from 0.1 to 30 for the proposed design method and for the design proposed by Hill and Robinson. As expected (see previous comments), no change is observed as long as $\bar{S}_2 < S_2^{\lim}$ is satisfied. The optimal individual volumes are presented in Figure 7, and the ratio V_2/V_1 is plotted in Figure 8, when $\bar{S}_2$ varies from 1 to $\bar{S}_2^{\lim}$ and K_S from 0.1 to 30 mg/L. To compare the two available designs, the total required volumes using our approach and the ap-

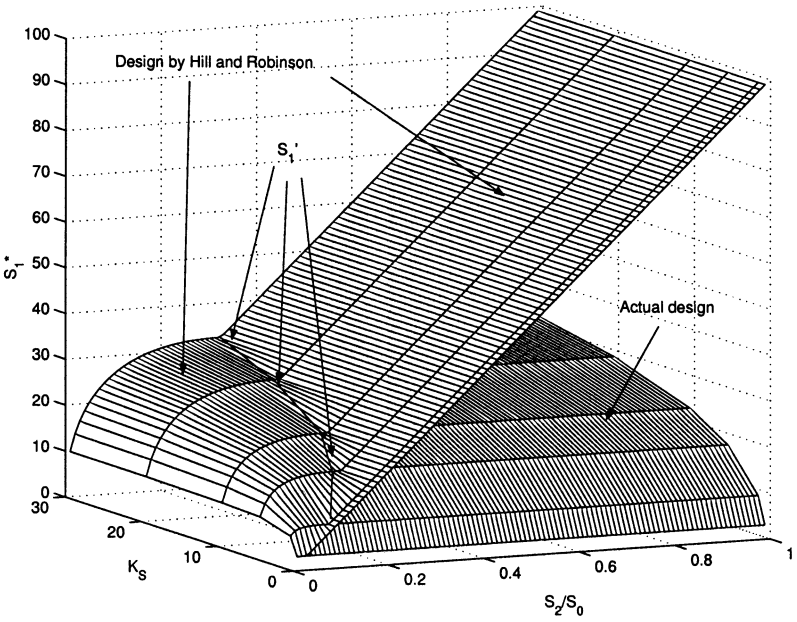

Figure 6. S_1^* with the proposed design and with the design of Hill and Robinson.

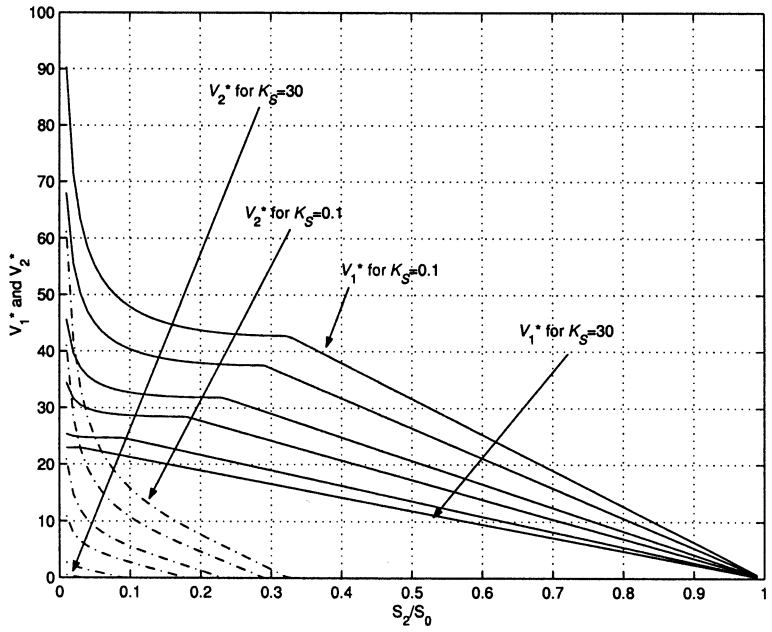

Figure 7. V_1^* (solid line) and V_2^* (dotted line).

proach by Hill and Robinson are plotted in Figure 9. In order to emphasize the gain that can be obtained using our design approach, the ratio between the total required volumes using our and the Hill–Robinson's approaches are represented in Figure 10, as is the total volume gain in the percentage (see Figure 11). Notice, as expected, that the design proposed in this article allows a continuous and significant decrease in the total required volume when $\bar{S}_2$ varies from 1 to $\bar{S}_0$, while it does not converge to zero when using the design by Hill and Robinson (1989). Finally, the corresponding optimal values of α are represented in the Figure 12.

Haldane kinetic

In this case, μ has the following expression

$$\mu(S) = \mu_o \frac{S}{S^2/K_I + S + K_S} \tag{23}$$

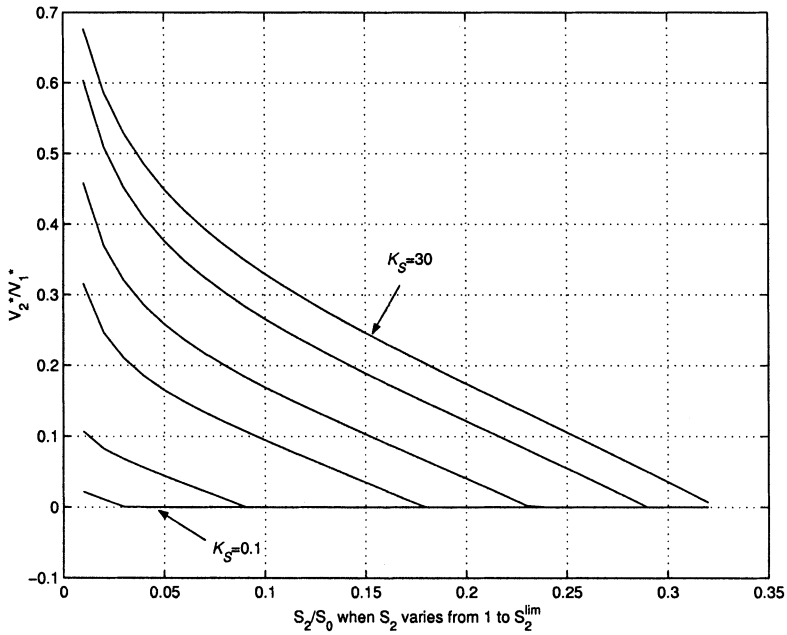

Figure 8. V_2^*/V_1^* when $\bar{S}_2$ varies from 1 to S_2^{lim}.

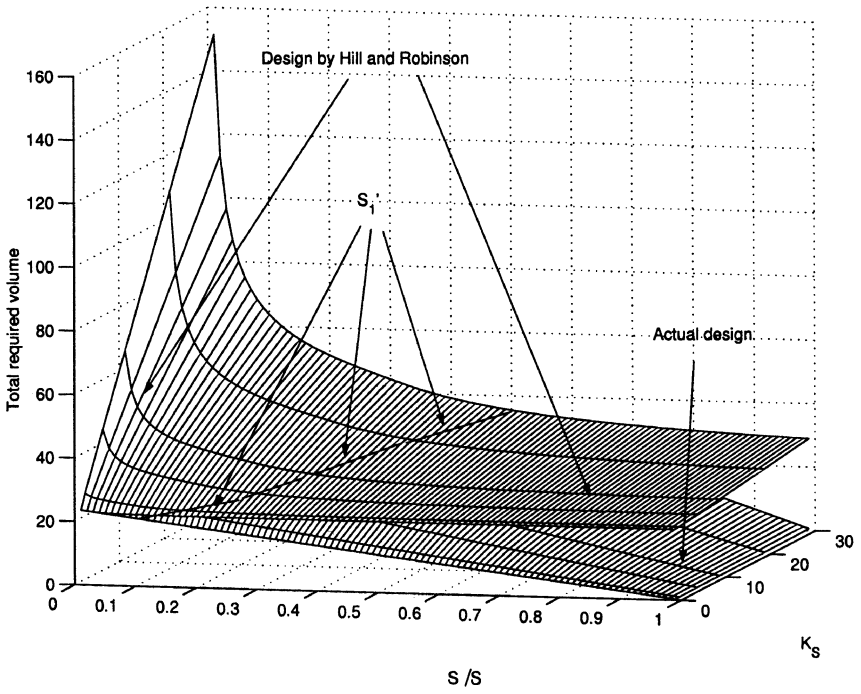

Figure 9. Total required volumes following the Hill and Robinson design and the proposed one.

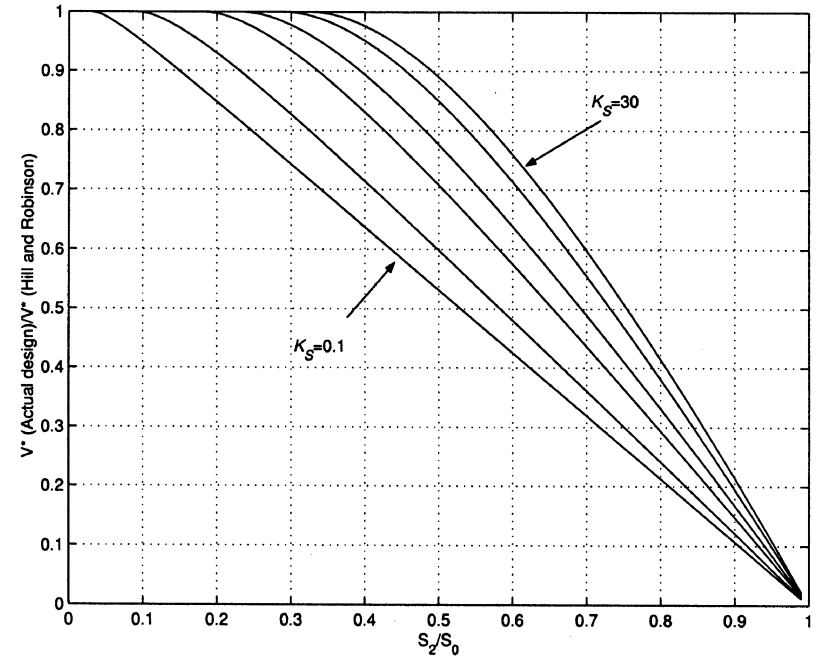

Figure 10. Ratio between the total required volume with the design of Hill and Robinson and with the proposed one.

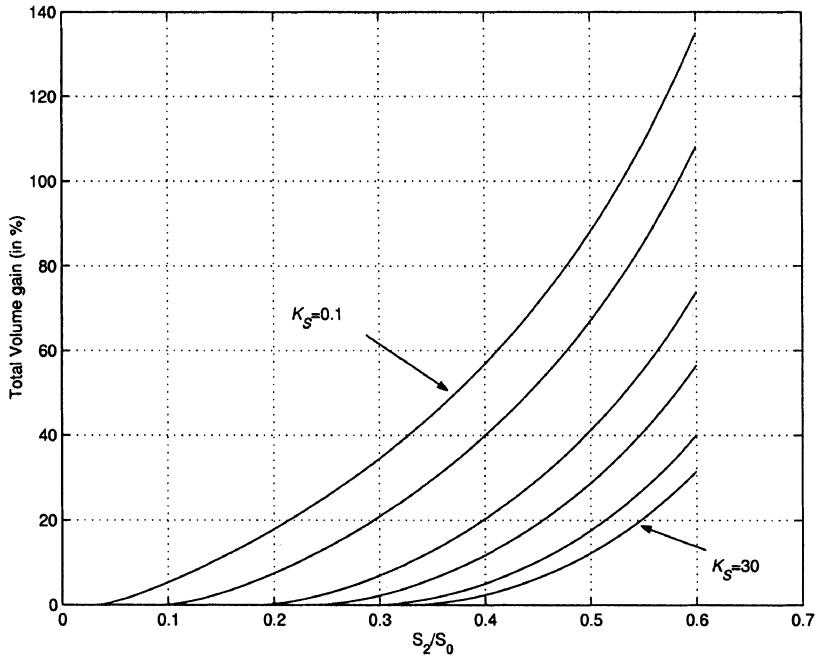

Figure 11. Total volume gain (in percentage).

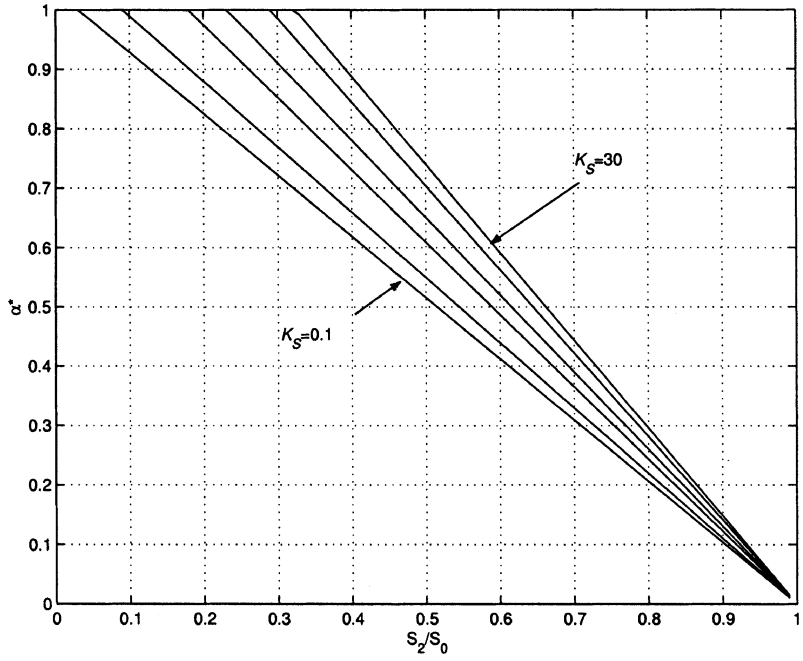

Figure 12. Optimal value of α.

Table 2. Parameter Values for the Example Using a Haldane Kinetic

μ_0	K_S	K_I	$\overline{S}_0$	$\overline{Q}$
0.045 h^{-1}	0.1, 1, 5, 10, 20 or 30 $mg.L^{-1}$	30 $mg.L^{-1}$	100 $mg.L^{-1}$	1 L/h^{-1}

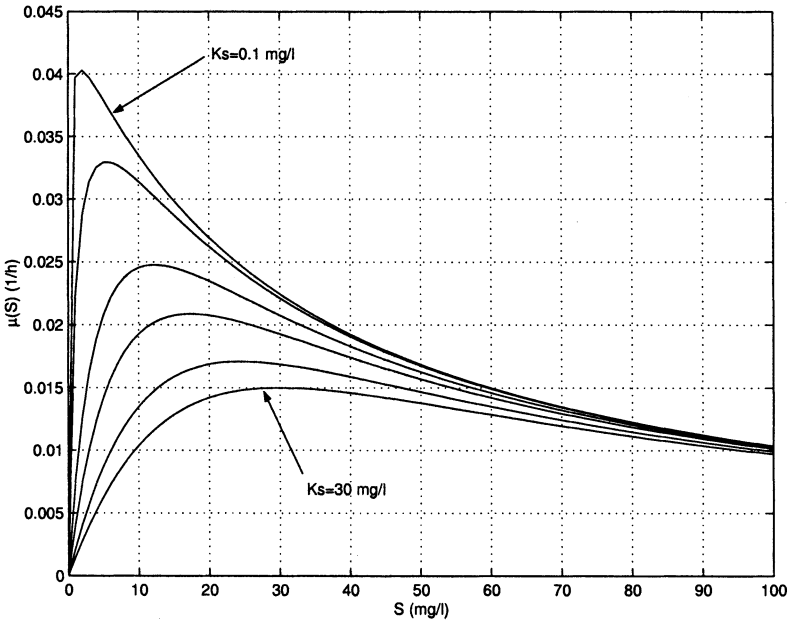

Figure 13. Function $\mu(S)$ with the different model parameters: Haldane kinetics.

where $K_I > 0$ is the inhibition constant. One can easily check that Hypothesis H1 is satisfied

$$S \to \frac{\mu'(S)}{\mu(S)^2} = \frac{1}{\mu_0}\left(\frac{K_S}{S^2} - \frac{1}{K_i}\right) \searrow$$

In this case, the root S_1' of $a()$ is given by

$$S_1' = \frac{K_s K_I\left(\bar{S}_0 - \bar{S}_2\right)}{\bar{S}_0\bar{S}_2 + \bar{S}_2 K_I + K_s K_I} \tag{24}$$

Supposing that $S_1' > \bar{S}_2$, and applying our proposed design procedure, we get S_1^*, the solution of Eq. 14, given by

$$S_1^* = \sqrt{\frac{K_S K_I \bar{S}_2\left(\bar{S}_0 - \bar{S}_2\right)}{\bar{S}_0\bar{S}_2 + \bar{S}_2 K_I + K_s K_I}} \tag{25}$$

If $S_1' < \bar{S}_2$, however, there exists an infinity of equivalent configurations, and the optimal value of S_1, the solution of Eq. 16, is now given by

$$S_1^* = -\frac{K_S K_I}{\bar{S}_0 + K_I} + \frac{\sqrt{K_S K_I\left[K_S K_I + \bar{S}_0\left(\bar{S}_0 + K_I\right)\right]}}{\bar{S}_0 + K_I} \tag{26}$$

Notice that with Haldane law, one has

$$\mu'(S) \geq 0 \Leftrightarrow S \leq \hat{S} = \sqrt{K_S K_I}$$

Then, we deduce the following properties:

- When $\bar{S}_2 \leq \hat{S}$, we have $\mu'(S_1^*) \geq 0$ in any case of Proposition P1. Then, the condition (Eq. 17) of Proposition P2 is always satisfied, and the optimal design is always stable.
- When $\bar{S}_2 \geq \hat{S}$, case 1 of Proposition P1 is never optimal (see Eq. 14), and the value of S_1^* in case 2 is independent of $\bar{S}_2$.

In order to illustrate the results, let us consider the model parameters in Table 2 and investigate what the optimal configurations are when $\bar{S}_2$ varies from 1 to $\bar{S}_0$ for each value of K_S indicated in the preceding display. The growth rates with the different values of K_S are plotted in Figure 13.

Results similar to those obtained for the Monod kinetic are reported in Figures 14 to 21 . In order to simplify the presentation, as in the Monod case, only the configuration corresponding to $\beta = 0$ has been chosen and only α is used to satisfy the conditions of Proposition P1 (see Figure 20). However, to better illustrate the SSEBS concept discussed in the sequel, we have also computed, for $K_S = 10$, different values for α and β as a function of S_2/S_0. In other words, for a given conversion rate S_2/S_0, we have computed the set of optimal pairs (α, β) that verify Eq. 15, and, therefore, define, for a given S_2/S_0, an SSEBS (cf. Figure 22).

Now, let us turn our attention to the analysis of the results obtained with the Haldane kinetic. For the different values of K_S that have been chosen, the corresponding limit values are given in Table 3. Furthermore, since $S_2 > S_1'$ these values are also the optimal ones, S_1^* (see Figures 14 and 21). It is particularly interesting to notice that, for any value of K_S, the values of $S_2^{\lim}$ are smaller than the argument of the maximum of the Haldane curve obtained for $\hat{S}_2 = \sqrt{K_S K_I}$ that are given in Table 4. It is interesting to point out that the value of S_1^*, which minimizes the TVR, does not coincide with the value that maximizes the growth rate. This fact is in total agreement with the results found in the literature, emphasizing this point.

As in the Monod case, the improvement in the TRV that can be obtained when compared to the procedure proposed by Hill and Robinson (1989), is significative in certain cases (see Figures 18 to 19). In the case of the Haldane kinetic, the

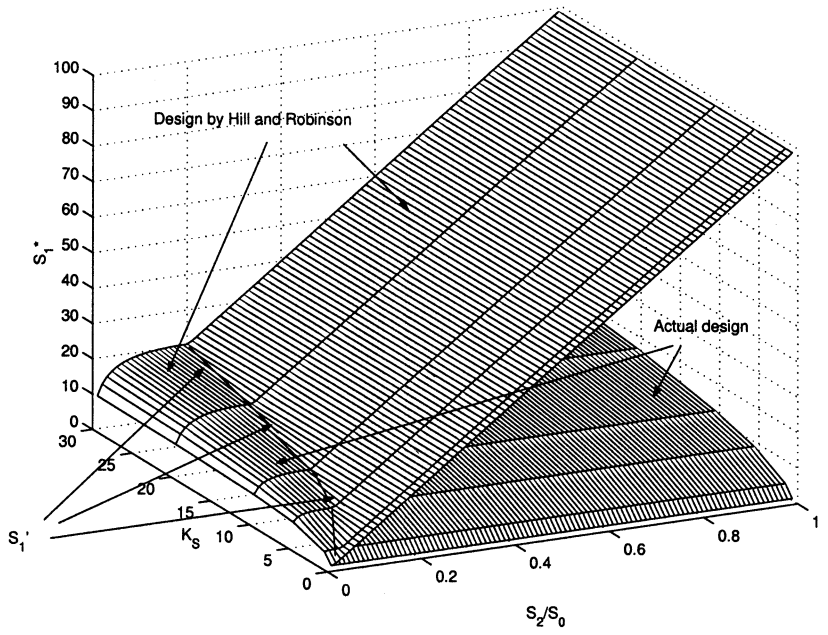

Figure 14. S_1^* with the proposed design and with the design of Hill and Robinson.

improvement in the TRV is much more relevant as S_2/S_0 increases (see Figure 17).

SSEBS concept

As pointed out in the previous sections, the optimal solution of the problem in terms of TRV may not be unique. In this case, an important question is how to choose one among the set of optimal solutions, that is, a set of SSEBS. The term "equivalent systems" must be interpreted here as systems having the same optimal TRV.

To illustrate the ideas, consider the following problem: Suppose we are given a biological process governed by a known Haldane kinetic, a flow rate to be treated, and some input and output substrate concentrations. Design a reactor configuration that allows the flow rate to be treated in a minimum TRV configuration.

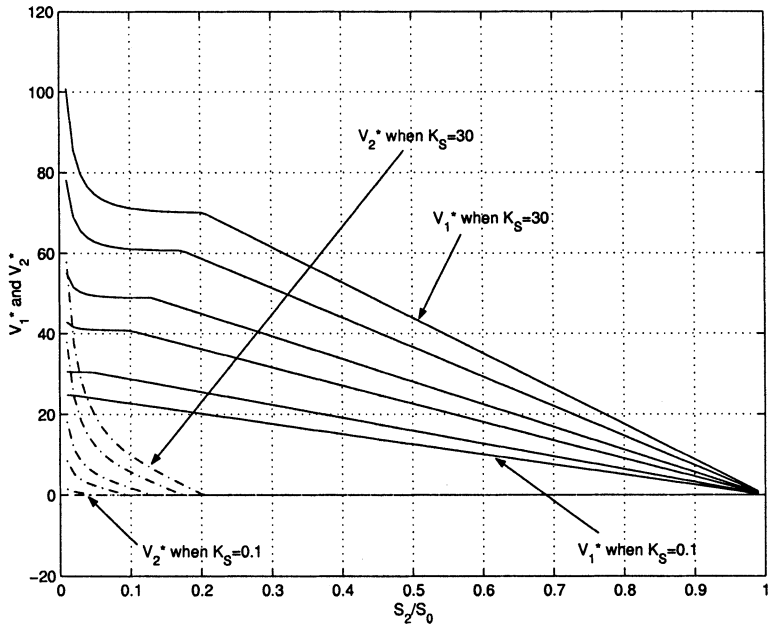

Figure 15. V_1^* (solid line) and V_2^* (dotted line).

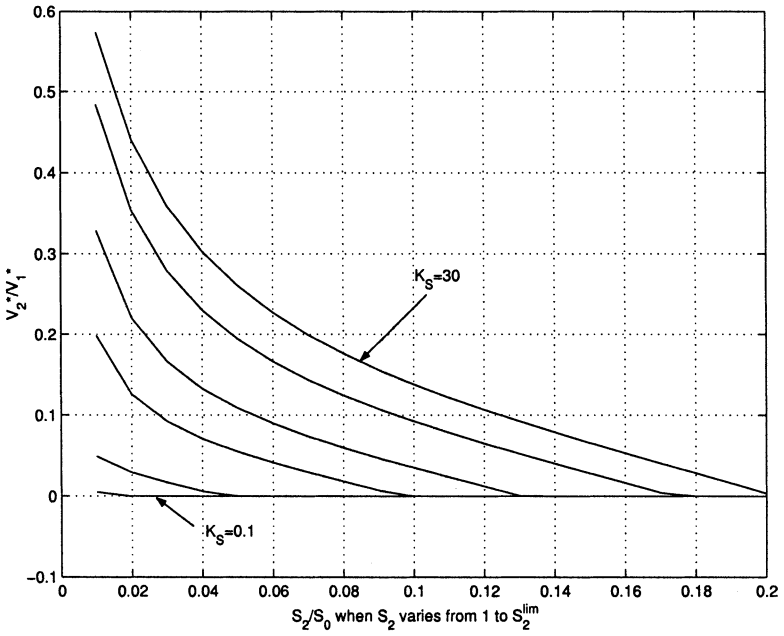

Figure 16. V_2^*/V_1^* when $\bar{S}_2$ varies from 1 to S_2^{lim}.

To simplify the presentation consider just an example with the parameters $\mu_0 = 0.045$ h^{-1}, $K_S = 10$ mg/L, $K_I = 30$ mg/L, $\bar{S}_0 = 100$ mg/L, $\bar{Q} = 1$ L/h, Y = 0.05 (yield coefficient), and $\bar{S}_2 = 20$. Following the results in the previous sections, it is straightforward to verify that the following two configurations are SSEBS:

- *Configuration A:* We find $\alpha = 0.92$, $\beta = 0$, $V_1 = 45$ L, and $V_2 = 0$. In this case, only a fraction of the input flow is fed into the first reactor, and no recirculation is needed;
- *Configuration B:* We find $\alpha = 0$, $\beta = 11.52$, $V_1 = 45$ L, and $V_2 = 0$. In such a configuration, the input flow is mixed with the reactor one's output flow, and is then recirculated through a recirculation loop.

In other words, at steady state, these two reactor configurations have exactly the same input–output behavior, and their TRVs are exactly the same. Notice that the TRV obtained with the approach by Hill and Robinson (1989) is 48.15 L, whereas the proposed approach leads to 45 L.

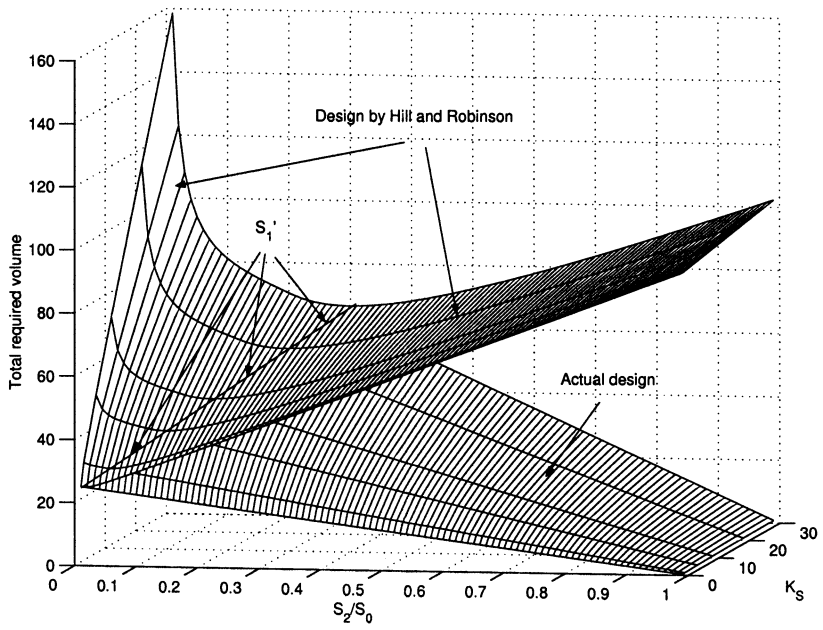

Figure 17. Total required volumes following the Hill and Robinson design and the proposed one.

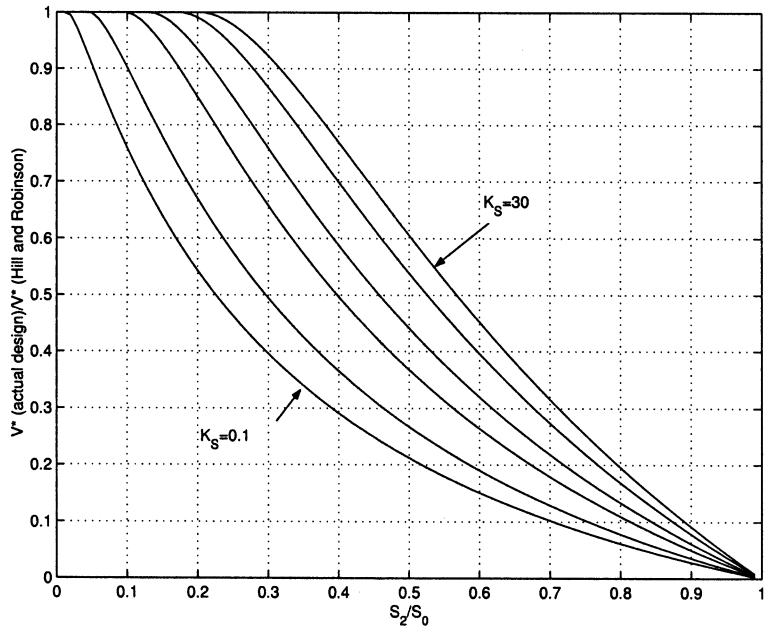

Figure 18. Ratio between the total required volume with the design of Hill and Robinson and with the proposed one.

Now, one might wonder which of the two configurations proposed in this example is the best one. Other performance criteria can be used to classify these TRV-optimal configurations. For instance, one possible criterion is to choose the configuration that has the best pole locations in the linearized open loop. The first configuration has eigenvalues closer to the imaginary axis than the second one (real parts equal to -0.02 for the first and -0.256 for the second). This suggests that the steady-state operation will be approached faster in the second configuration. This fact can be explained by the presence of the recirculation loop that acts as a feedback on the system. Furthermore, it is straightforward to establish that the two configurations are observable when either X_1 or S_1 is measured, but that only the first configura-

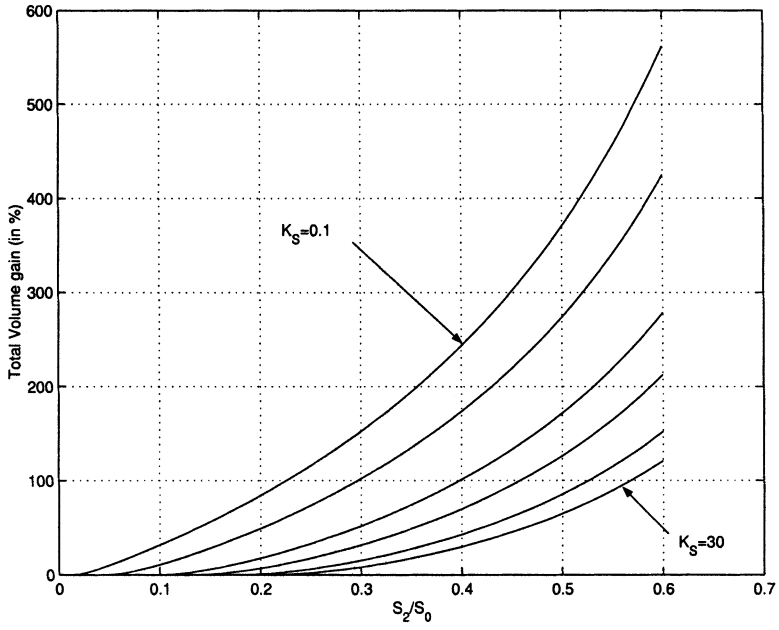

Figure 19. Total volume gain (in percentage).

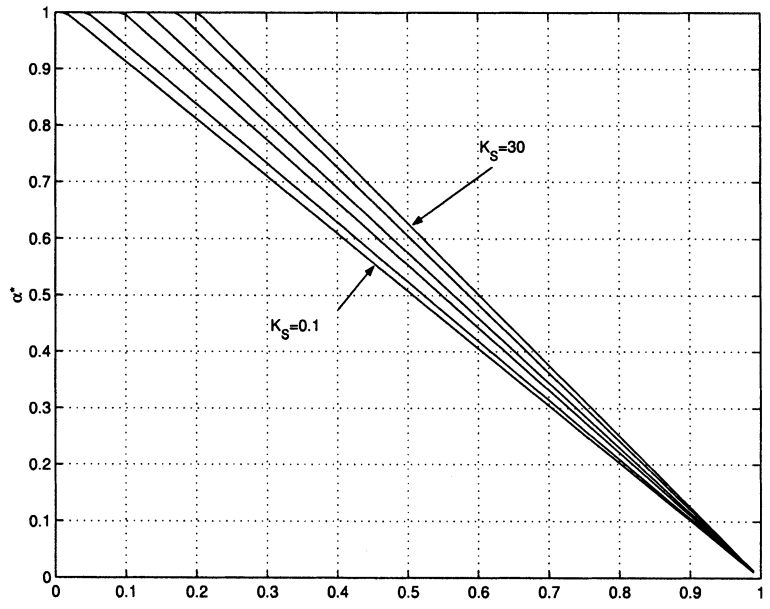

Figure 20. Optimal value of α.

tion is controllable when Q is used as the control input. The preceding arguments can be used to decide which configuration is preferable.

Conclusion

In this article, the optimal design [in the sense of the minimization of the total retention time, or equivalently, of the total required volume (TRV)] of two interconnected biological reactors has been revisited. It is postulated that a single biological reaction occurs and the kinetic functions satisfy some mild technical assumptions (hypothesis H1), which include in particular the class of Monod, Haldane, and Aiba functions. The problem was formulated as follows: Given the model of the biological process and a flow rate, $\overline{Q}$, to be treated per time unit at steady-state operation, determine the minimum TRV to attain a specified conversion rate $\overline{S}_2/\overline{S}_0$.

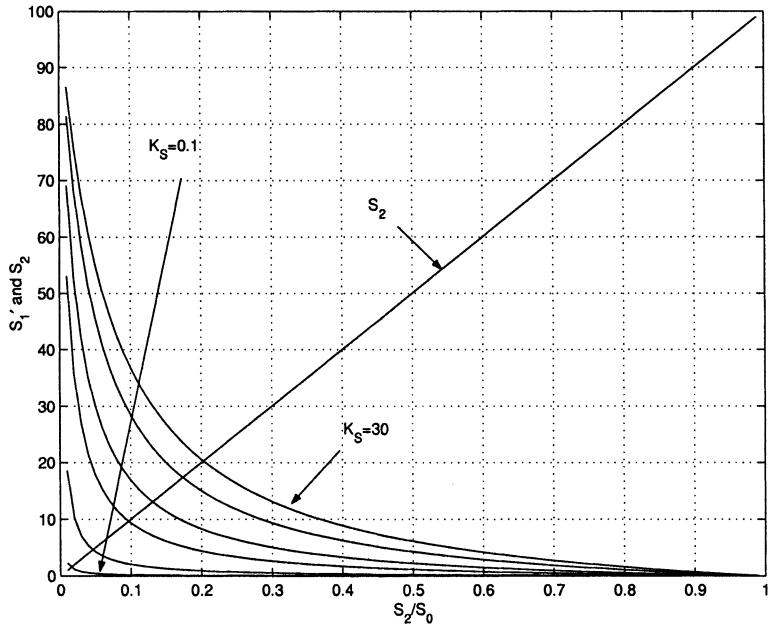

Figure 21. S_1' and $\overline{S}_2$: Haldane kinetics.

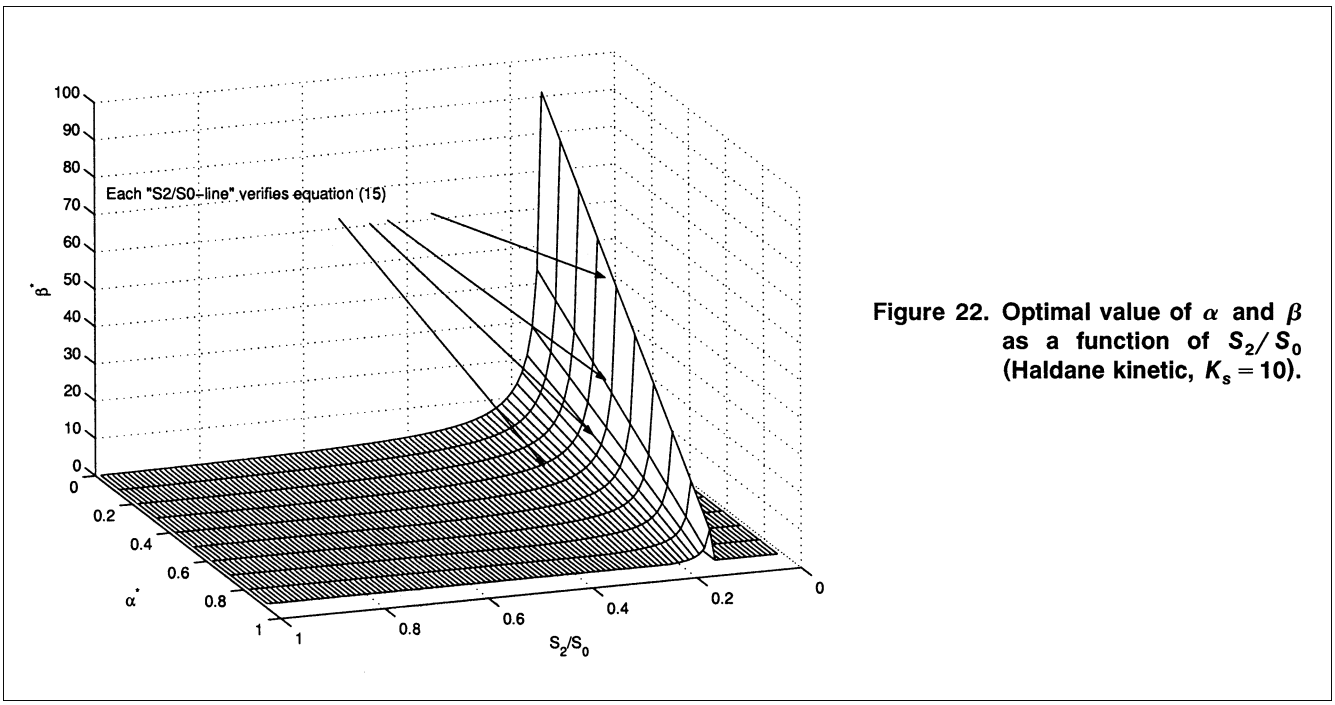

Figure 22. Optimal value of α and β as a function of S_2/S_0 (Haldane kinetic, $K_s = 10$).

Table 3. Limit Values of S2 in the Example Using a Haldane Kinetic

K_S (mg L^{-1})	0.1	1	5	10	20	30
S_2^{lim} (mg L^{-1})	1.4962	4.5786	9.6497	13.0577	17.3582	20.2842

In determining the optimal solution we have investigated the following situations:

(1) Different volumes for the tanks;
(2) Distribution of the input flow rate among the tanks;
(3) The presence of a recirculation loop.

It was shown that the optimal solution of the problem of minimizing the TRV depends on the ratio $S_1'/\bar{S}_2$, where S_1' is one of the two roots of a particular second-order equation whose coefficients are determined from the system data. More specifically, if $S_1' > \bar{S}_2$, the optimal design is obtained by considering only the input to the first reactor, while no recirculation is needed. At one extreme, one has $S_1' = \bar{S}_2$, which corresponds to the case where only one tank is needed. Notice that these last conclusions are in total agreement with the results found in the existing literature.

For the case in which $S_1' < \bar{S}_2$, we showed that the TRV can be significantly decreased by distributing the input flow rate and introducing a recirculation loop with a certain recirculation flow rate. In such a case, the optimal solution is not unique and the concept of steady-state equivalent biological systems is introduced to help the designer to choose one among all the possible TRV-optimal solutions. This new concept is interesting because it allows the designer to consider additional properties of each one of the TRV-optimal solutions, such as observability or controllability, and then to decide which one is the "best" with respect to these additional criteria. It is important to notice that the stability of the new proposed family of processes is also analyzed. Finally, we emphasize that our design approach is based on the steady-state solution of the system. Despite the progress that we have achieved, a number of research questions regarding the dynamic properties of the designed system deserve future investigation.

Table 4. Values of S for Which the Haldane Kinetic is Maximum

K_S (mg L^{-1})	0.1	1	5	10	20	30
$\hat{S}_2$(mg L^{-1})	1.7321	5.4772	12.2474	17.3205	24.4949	30.000

Another topic of future research concerns more complex biological processes, such as multicomponent reactions in which more than one species reacts. The extension of the results to the design of more than two reactors, with many biological reactions occurring in each one, is also under investigation. Another exciting research topic is the use of a larger class of kinetic functions and, in particular, those involving a product inhibition. On this subject, it should be noticed that a number of product-inhibiting functions, such as the Aiba kinetic that is well suited to describe ethanol inhibition, already satisfy Hypothesis H1 (cf. Aiba and Shoda, 1969), given that the product, at steady-state, is linearly related to the substrate concentration.

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Appendix

Proof of Lemma L1

Note that $a(\bar{S}_2) = 0$ and $\lim_{S_1 \to 0^+} a(S_1) = +\infty$. Using the Intermediate Value Theorem yields

$$\exists\ \tilde{S}_1 \in \left(0,\ \bar{S}_2\right) \text{ s.t. } a\left(\tilde{S}_1\right) = a\left(\bar{S}_0\right) = \frac{1}{\mu\left(\bar{S}_0\right)} > 0.$$

By the Rolle theorem, we have

$$\exists\ \hat{S}_1 \in \left(\tilde{S}_1,\ \bar{S}_0\right) \text{ s.t. } \frac{da}{dS_1}\left(\tilde{S}_1\right) = 0.$$

Furthermore, we have

$$\frac{da}{dS_1}(S_1) = -\frac{\mu'(S_1)}{\mu(S_1)^2} + \frac{1}{\mu\left(\bar{S}_2\right)\left(\bar{S}_0 - \bar{S}_2\right)},$$

and thus $S_1 \to (da/dS_1)(S_1)$ is increasing on $[0,\ \bar{S}_0]$. Then, the restriction of $a()$ on the interval $[0,\ \bar{S}_0]$ is strictly convex, and $\hat{S}_1$ is the unique minimum of $a()$ on the interval $[0,\ \bar{S}_0]$. Two cases can arise:

- If $\hat{S}_1 = S_2$, then $a(S_1) \geq 0$, whatever S_1 in $[0,\ \bar{S}_0]$, and we have $a(S_1) = 0 \Leftrightarrow S_1 = \bar{S}_2$;
- If $\hat{S}_1 \neq \bar{S}_2$, we use the fact that $a(\bar{S}_2) = 0$ to conclude that we have $a(\hat{S}_1) < 0$ and that the function $S_1 \to a(S_1)$ is increasing on the interval $[\hat{S}_1,\ \bar{S}_0]$. Thus, on this interval there exists exactly one value of S_1 (denoted S_{1d}) such that $a(S_{1d}) = 0$. Moreover, $S_1 \to a(S_1)$ is decreasing on the interval $[0,\ \hat{S}_1]$. Thus, on this interval, there exists exactly one value of S_1 (denoted S_{1g}) such that $a(S_{1g}) = 0$. Finally, since $a(\hat{S}_1) < 0$, we have the following equivalence

$$a(S_1) \leq 0,\ S_1 \in \left[0,\ \bar{S}_0\right] \Leftrightarrow S_1 \in \left[S_{1g},\ S_{1d}\right].$$

Furthermore, since $a(\bar{S}_2) = 0$, one has $S_{1g} = S_2$ or $S_{1d} = S_2$.

Proof of Proposition P1

(1) *Case 1:* $S_1' > \bar{S}_2$. In this case, using Lemma L1 it follows that $S_1^* \in [\bar{S}_2,\ S_1']$.

Since $(S_2 - S_1)/(S_0 - S_1) < 0$, whatever $S_1 \in [\bar{S}_2,\ S_1']$, the minimum of J is then obtained for $\alpha^* = 1$ and $\beta^* = 0$. Finally, since for any $S_1 \in [\bar{S}_2,\ S_1']$ one has $(\bar{S}_0 - \bar{S}_2)/(S_0 - S_1) > 1$, it is easy to verify that the constraints Eqs. 4, 7, 9 hold. The optimal value of S_1 is then obtained by solving $(da/dS_1)(S_1) = 0$. Observe that

$$\frac{da}{dS_1}(S_1) = -\frac{\mu'(S_1)}{\mu(S_1)^2} + \frac{1}{\mu\left(\bar{S}_2\right)\left(\bar{S}_0 - \bar{S}_2\right)}.$$

From Hypothesis H1, it follows that da/dS_1 has only one root $S_1^* \in [0,\ \bar{S}_0]$. Thus

$$\mu(S_1^*)^2 = \mu'(S_1^*)\,\mu\left(\bar{S}_2\right)\left(\bar{S}_0 - \bar{S}_2\right).$$

(2) *Case 2:* $S_1' < \bar{S}_2$. In this case, using Lemma L1 we get $S_1^* \in [S_1',\ \bar{S}_2]$. Whatever $S_1 \in [S_1',\ \bar{S}_2]$, the maximum of $(\alpha,\ \beta) \to \alpha + \beta(\bar{S}_2 - S_1)/(\bar{S}_0 - S_1)$ under Eqs. 4, 7, 9 is obtained on the line, $\sigma(S_1)$, defined as

$$\sigma(S_1) = \left\{ (\alpha,\ \beta) \middle| \alpha + \beta\frac{\bar{S}_2 - S_1}{\bar{S}_0 - S_1} = \frac{\bar{S}_0 - \bar{S}_2}{\bar{S}_0 - S_1},\ \alpha \in [0, 1]\ \ \beta \geq 0 \right\}.$$

In that case, one has $J(\alpha^*(S_1),\ \beta^*(S_1),\ S_1) = a(S_1)(\bar{S}_0 - \bar{S}_2)/(\bar{S}_0 - S_1)$. The value of S_1^* that minimizes J is then obtained by solving

$$\frac{\partial J}{\partial S_1}(S_1^*) = 0 \Leftrightarrow \frac{da}{dS_1}(S_1^*) = -\frac{a(S_1^*)}{\bar{S}_0 - S_1^*}.$$

Using Lemma L1, one has $(\partial J/\partial S_1)(S_1') < 0$ and $(\partial J/\partial S_1)(\bar{S}_2) \geq 0$. Thus, $S_1^* \in (S_1',\ \bar{S}_2]$. Furthermore, one has

$$\frac{da}{dS_1}(S_1) = -\frac{\mu'(S_1)}{\mu(S_1)^2} + \frac{1}{\mu\left(\bar{S}_2\right)\left(\bar{S}_0 - \bar{S}_2\right)}$$

and

$$\frac{a(S_1)}{\bar{S}_0 - S_1} = \frac{1}{\left(\bar{S}_0 - S_1\right)\mu(S_1)} - \frac{1}{\mu\left(\bar{S}_2\right)\left(\bar{S}_0 - \bar{S}_2\right)},$$

thus S_1^* satisfies

$$\mu'(S_1)\left(\bar{S}_0 - S_1\right) = \mu(S_1).$$

(3) *Case 3:* $S_1' = \bar{S}_2$. In cases 1 and 2, let $S_1' \to \bar{S}_2$, we obtain that the optimum is attained for $\alpha^* = 1$, for arbitrary $\beta^* \geq 0$, and $S_1^* = \bar{S}_2$. Thus, in this case, one has $V_2^* = 0$.

Proof of Proposition P2

For simplicity, denote $D_1 = Q/V_1$ and $D_2 = Q/V_2$. The dynamics of Eq. 1 in the $(Z_1,\ Z_2,\ X_1,\ X_2)$ coordinates takes the

following "cascade" form

$$\begin{cases} \dfrac{d}{dt}\begin{bmatrix} Z_1 \\ Z_2 \end{bmatrix} = M\begin{bmatrix} Z_1 \\ Z_2 \end{bmatrix} + Y\begin{bmatrix} \alpha D_1 \\ (1-\alpha)D_2 \end{bmatrix} S_0 \\ \dfrac{d}{dt}\begin{bmatrix} X_1 \\ X_2 \end{bmatrix} = M\begin{bmatrix} X_1 \\ X_2 \end{bmatrix} + \begin{bmatrix} \mu(Z_1/Y - X_1/Y) \\ \mu(Z_2/Y - X_2/Y) \end{bmatrix} \end{cases}$$

with $M = \begin{pmatrix} -(\alpha+\beta)D_1 & \beta D_1 \\ (\alpha+\beta)D_2 & -(1+\beta)D_2 \end{pmatrix}$.

According to the stability results of cascade systems [cf. Vidyasagar (1980)], the local asymptotic stability of an equilibrium point $(Z_1^e, Z_2^e, X_1^e, X_2^e)$ is guaranteed when:

- The (Z_1, Z_2) subsystem is locally asymptotically stable, that is, when M is Hurwitz;
- The (X_1, X_2) subsystem is locally asymptotically stable at the equilibrium $(Z_1, Z_2) = (Z_1^e, Z_2^e)$. A sufficient condition for that is to have the linearized dynamics Hurwitz.

The eigenvalues (λ_1, λ_2) of the matrix M are such that

$$\lambda_1 + \lambda_2 = \mathrm{tr}(M) = -(\alpha+\beta)D_1 - (1+\beta)D_2 < 0$$
$$\lambda_1\lambda_2 = \det(M) = (\alpha+\beta)D_1D_2 > 0,$$

M is Hurwitz and the subsystem (Z_1, Z_2) is always asymptotically stable.

The linearization of the system (X_1, X_2) at the equilibrium point (X_1^e, X_2^e) and $(Z_1, Z_2) = (Z_1^e, Z_2^e)$, is locally asymptotically stable if the matrix

$$N = M + \begin{pmatrix} -\mu'(S_1^e)/Y & 0 \\ 0 & -\mu'(S_2^e)/Y \end{pmatrix}$$

is Hurwitz. This is satisfied when the following holds

$$\mathrm{tr}(N) = -(\alpha+\beta)D_1 - (1+\beta)D_2 - \mu'(S_1^e)/Y - \mu'(S_2^e)/Y < 0$$

$$\det(N) = \left[(\alpha+\beta)D_1 + \mu'(S_1^e)/Y\right]\left[(1+\beta)D_2 + \mu'(S_2^e)/Y\right] - (\alpha+\beta)\beta D_1D_2 > 0,$$

which is exactly Eq. 17. In summary, the matrices M and N being Hurwitz, the local asymptotic stability of the whole system is guaranteed from standard results of cascade systems [cf. Vidyasagar (1980)].

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