ChE class and home problems

The object of this column is to enhance our readers' collection of interesting and novel problems in chemical engineering. Problems of the type that can be used to motivate the student by presenting a particular principle in class, or in a new light, or that can be assigned as a novel home problem, are requested as well as those that are more traditional in nature, which elucidate difficult concepts. Please submit them to Professor H. Scott Fogler, ChE Department, University of Michigan, Ann Arbor, MI 48109.

CSTR's IN BIOCHEMICAL REACTIONS

An Optimization Problem

F. XAVIER MALCATA
Universidade Catolica Portuguesa
Escola Superior de Biotecnologia
4200 Porto, Portugal

F. Xavier Malcata is currently a PhD student at the University of Wisconsin, Madison. He earned a BSc in chemical engineering from the Portuguese State University (Oporto) in 1986. He is a member of the teaching staff of the College of Biotechnology of the Portuguese Catholic University. His research interests are mainly focused on the application of the principles of chemical engineering to the solution of problems in the food technology field.

ENZYMES ARE THE functional units of cell metabolism. They are specialized globular proteins with an extraordinary catalytic power and with orders of magnitude greater than most of the synthetic catalysts [1]. Enzymes are remarkable catalysts due not only to their powerful activity, but also to their high specificity and versatility. These characteristics have emphasized their industrial application for the catalysis of a great number of reactions within the food, medical, and cleaning fields [2].

Many enzymes are oligomers composed of distinct subunits or monomers. If the sites are identical and completely independent of each other, then a classical Michaelis-Menten kinetic equation results [3]. If the presence of substrate on one site influences the binding of the substrate to vacant sites, or the rate of product formation at other occupied sites, then a situation arises where the substrate itself acts as a modifier or effector yielding substrate activation or substrate inhibition [4]. Such enzymes are called allosteric enzymes, and their catalytic activity can be substantially increased or decreased in response to such substrate molecules acting as control signals. The behavior of these regulatory enzymes can be modeled by assuming a concerted transition of protein subunits: the first substrate molecule bound to the enzyme alters the enzyme's structure so that the remaining sites have a stronger, or weaker, affinity for the substrate [5].

This paper concerns a particular interest in positive cooperativity for the homotropic enzyme [1]. This phenomenon leads to a sigmoidal relationship between the kinetic rate and the substrate concentration [6]. The simple sequential interaction model [7, 8] has been throughly reported in literature as yielding good fits to experimental data. This model introduces a number of interaction parameters, or factors by which the intrinsic binding constants are increased as the substrate molecules bind to the active sites. Assume that the enzyme contains n equivalent binding sites, and that the cooperativity in substrate binding is very marked; in this situation the concentrations of all enzyme-substrate complexes containing less than n molecules of substrate are negligible at any appreciable substrate concentration compared to the intrinsic dissociation constant for the substrate/enzyme complex. The kinetic equation then reduces to the Hill equation [9]

The Hill kinetic equation can be used even if the cooperativity of the binding is not very high; however in this case parameter n loses its physical meaning and is commonly referred to as the apparent number of substrate binding sites [4]. Such adjustable parameters can be easily obtained from a graphical logarithmic construction based on Eq.(1), known as the Hill plot [4].

$$v = \frac{v_{max} C^n}{K' + C^n} \qquad (1)$$

For homogeneous enzymatic catalysis taking place in an aqueous solution of substrate, the continuous stirred tank reactor (CSTR) possesses a number of relevant features for industrial operation. Besides the lower construction costs when compared to classical tubular reactors, the efficient stirring of the reactor ensures uniform temperature (thus avoiding hot spots), coupled with ease of access to the interior surface for manutention and appreciable residence times [10]. Extensive literature is available on the optimization procedures leading to a minimum in the overall reactor volume of a series of CSTR's performing a chemical reaction described by a given kinetic equation [11-15]. The main goal of this paper is to apply the classical approach for optimization of reactor design to a slightly involved home problem in the biochemical field. Although the general solution can be graphically obtained, a number of analytical asymptotic solutions are developed. These solutions enable one to obtain a quick estimate of the size profile of the series of CSTR's.

PROBLEM STATEMENT

Consider a system of CSTR's in series which is currently being designed to perform a homogeneous, enzyme-catalyzed reaction in the liquid phase described by the Hill equation. Isothermal and steady state conditions of operation are assumed. The characteristic time scale associated with the enzyme deactivation is very large when compared to the time scale associated with the enzyme-catalyzed reaction.

1. Show that the minimum overall reactor volume is obtained when the following condition applies

$$\frac{\partial Da_i}{\partial C^*_i} + \frac{\partial Da_{i+1}}{\partial C^*_i} = 0 \tag{2}$$

2. Prove that the foregoing condition leads to

$$n\frac{C^*_{i-1,opt}}{C^*_{i,opt}} = n - 1 + \left(\frac{C^*_{i,opt}}{C^*_{i+1,opt}}\right)^n \tag{3}$$

for the case where Eq. (1) is used as the kinetic equation describing the behavior of the reactive system.

3. Show that Eq. (3) leads to

$$C^*_{i,opt} = C^{*\,i/N}_N \tag{4}$$

when n equals unity.

4. Show that the optimization condition for large N and C^*_N, and small n is met when the concentration of substrate at any intermediate stream is equal to the arithmetic mean of the upstream and downstream consecutive concentrations.

5. Derive the following equation

$$C^*_{1,opt} = \left[\frac{1}{n}\right]^{\frac{1}{n-1}} \left[n^N\ C^{*\,n-1}_N\right]^{\frac{1}{n\left[1-\left[\frac{1}{n}\right]^N\right]}} \tag{5}$$

from Eq. (1), on the assumption that N and C^*_N are small, and n is large.

6. Consider the conversion of fructose-1,6-diphosphate to fructose-6-phosphate catalyzed by the enzyme phosphofructokinase. Assume that the reaction is carried out under such conditions that it can be considered approximately irreversible. Compute the volume of each reactor in a series of CSTR's leading to a minimal overall volume where the foregoing reaction will take place. The following data are available:

$$N = 3, \quad n = 2, \quad C_o = 2.6\times 10^{-2}\ \text{mol}\cdot\text{m}^{-3},$$
$$C_N = 5.5\times 10^{-3}\ \text{mol}\cdot\text{m}^{-3};\ v_{max} = 1.3\times 10^{-4}\ \text{mol}\cdot\text{m}^{-3}\cdot\text{s}^{-1},$$
$$K' = 4.6\times 10^{-5}\ \text{mol}^2\cdot\text{m}^{-6},\ Q = 3.6\times 10^{-3}\ \text{m}^3\cdot\text{s}^{-1}$$

PROBLEM SOLUTION

1. A mass balance to the substrate for each CSTR takes the form

$$Da_i = \frac{\left(C^*_{i-1} - C^*_i\right)\left(K^* + C^{*\,n}_i\right)}{C^{*\,n}_i} \tag{6}$$

The minimum volume for the whole reactor system is obtained when the following condition applies

$$\frac{\partial}{\partial C^*_i}\sum_{i=1}^{N} Da_i = 0 \tag{7}$$

Since C^*_i appears only in the ith and $(i+1)$th terms of the foregoing summation, one finally obtains Eq. (2) from Eqs. (6) and (7).

2. Using Eq. (6) in Eq. (2), one obtains

$$\frac{K^*(n-1)C^{*\,n}_{i,opt} - C^{*\,2n}_{i,opt} - nK^*C^*_{i-1,opt}C^{*\,n-1}_{i,opt}}{C^{*\,2n}_{i,opt}} + \frac{K^* + C^{*\,n}_{i+1,opt}}{C^{*\,n}_{i+1,opt}} = 0 \tag{9}$$

Some algebraic manipulation can now be performed on Eq. (9), yielding Eq. (3) as the resulting equation. Eq. (3) is graphically plotted in Figure 1 for a number of values for parameter n.

3. Eq. (3) can be easily transformed to

$$C^*_{i+1,opt} = \frac{C^{*\,2}_{i,opt}}{C^*_{i-1,opt}} \tag{10}$$

when n = 1. Applying the foregoing recursive relation from i = 1 up to a generic i, one gets

$$C^*_i = C^{*\,i}_1 \tag{11}$$

In particular, Eq. (11) gives the following result

$$C^*_N = C^{*\,N}_1 \tag{12}$$

for the case where i = N. Combination of Eqs. (11) and (12) finally enables one to obtain Eq. (4).

4. Eq. (3) can be written in a slightly different form, namely

$$n\frac{C^*_{i-1,opt}}{C^*_{i,opt}} = n - 1 + \exp\left[n\ ln\left(\frac{C^*_{i,opt}}{C^*_{i+1,opt}}\right)\right] \tag{13}$$

Taking advantage from the fact that the fractional change in concentration between consecutive stages is small due to the large N and C^*_N, one can expand the exponential term in Eq. (13) as a MacLaurin series [16] and truncate it after the linear term in order to obtain

$$\frac{C^*_{i-1,opt}}{C^*_{i,opt}} = 1 + ln\left[\frac{C^*_{i,opt}}{C^*_{i+1,opt}}\right] \tag{14}$$

Rearranging Eq. (14), one obtains

$$C^*_{i+1,opt} = C^*_{i,opt}\ \exp\left[1 - \frac{C^*_{i-1,opt}}{C^*_{i,opt}}\right] \tag{15}$$

The exponential term in Eq. (15) can be similarly expanded as discussed previously in order to give

$$C^*_{i,opt} = \frac{C^*_{i-1,opt} + C^*_{i+1,opt}}{2}, \text{ q.e.d.} \tag{16}$$

5. If n-1 is small compared to $(C^*_{i,opt}/C^*_{i+1,opt})^n$,

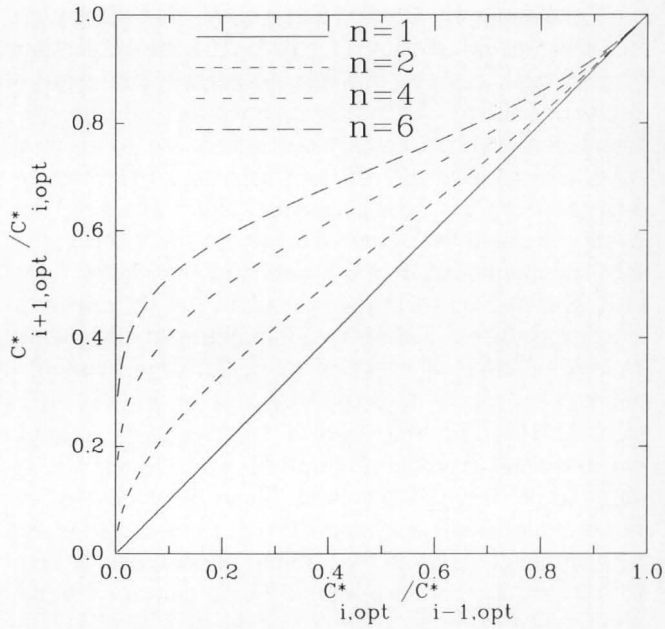

FIGURE 1. Relation between $C^*_{i+1,opt}/C^*_{i,opt}$ and $C^*_{i,opt}/C^*_{i-1,opt}$ yielding the minimum overall reactor volume, for a number of values for parameter n.

then Eq. (3) reduces to

$$C^*_{i+1,opt} = C^*_{i,opt}\left[\frac{C^*_{i,opt}}{n\ C^*_{i-1,opt}}\right]^{\frac{1}{n}} \tag{17}$$

Applying the foregoing recursive relation from i = 1 up to the current i, one obtains

$$C^*_{i,opt} = \left[\frac{1}{n}\right]^{\sum_{j=1}^{i-1}(i-j)\left[\frac{1}{n}\right]^j} \left[C^*_{1,opt}\right]^{\sum_{j=0}^{i-1}\left[\frac{1}{n}\right]^j} \tag{18}$$

The first exponential summation in Eq. (18) can be rearranged as follows

$$\sum_{j=1}^{i-1}(i-j)\left[\frac{1}{n}\right]^j = \frac{1}{n}\sum_{j=1}^{i-1}\sum_{m=0}^{j-1}\left[\frac{1}{n}\right]^m \tag{19}$$

Eq. (19) can be transformed into

$$\sum_{j=1}^{i-1}(i-j)\left[\frac{1}{n}\right]^j = \frac{1}{n}\sum_{j=1}^{i-1}\frac{1-\left[\frac{1}{n}\right]^j}{1-\frac{1}{n}} \tag{20}$$

with the aid of the summation property of the geometric series [17]. Eq. (20) can be again rearranged to give

$$\sum_{j=1}^{i-1} (i-j)\left[\frac{1}{n}\right]^j = \frac{1}{n-1}\left[i - \sum_{j=0}^{i-1}\left[\frac{1}{n}\right]^j\right] \quad (21)$$

which is equivalent to

$$\sum_{j=1}^{i-1} (i-j)\left[\frac{1}{n}\right]^j = \frac{i}{n-1} - \frac{n}{(n-1)^2}\left[1-\left[\frac{1}{n}\right]^i\right] \quad (22)$$

The second exponential summation in Eq. (18) can be written as

$$\sum_{j=0}^{i-1} \left[\frac{1}{n}\right]^j = \frac{n}{n-1}\left[1-\left[\frac{1}{n}\right]^i\right] \quad (23)$$

where a similar reasoning was followed. The combination of Eqs. (22) and (23) with Eq. (18), coupled to the condition i = N leads, after some manipulation, to Eq. (5).

6. Using the definition of normalized variables and dimensionless parameters as given in the nomenclature, one gets $C^*_N = 0.212$ and $K^* = 0.0680$. Use of Eq. (3) for i = 1 and i = 2 gives

$$C^*_{1,opt} = 0.50000\, C^*_{2,opt} + 11.130\, C^{*3}_{2,opt} \quad (24)$$

and

$$1376.9\, C^{*7}_{2,opt} + 185.65\, C^{*5}_{2,opt} + 19.473\, C^{*3}_{2,opt} + 0.62500\, C^*_{2,opt} - 2.0000 = 0 \quad (25)$$

A trial-and-error method applied to Eq. (25) gives $C^*_{2,opt} = 0.3224$ as the only solution with physical meaning. Application of this result in Eq. (24) yields $C^*_{1,opt} = 0.5342$. Eq. (6) can now be used with the foregoing results in order to obtain $Da_{1,min} = 0.5768$ and $Da_{2,min} = 0.3504$. These values correspond to the volumes of $V_{1,min} = 0.4150$ m³ and $V_{2,min} = 0.2521$ m³, respectively.

CONCLUSIONS

The optimal intermediate concentrations can in general be obtained from a numerical trial-and-error solving procedure based on Eq. (3), as outlined previously. The total number of solutions of the corresponding polynomial in $C^*_{N-1,opt}$ is, nevertheless, a strong increasing function of N. This fact may lead to numerical instability, coupled to extra numerical work when the iterative procedure converges to roots with no physical meaning. Therefore, a graphical iterative construction on Figure 1 similar to the stagewise calculation known as McCabe-Thiele method for binary systems undergoing distillation [18] proves safer and faster. The major steps of such graphical procedure are as follows: (i) arbitrate $C^*_{1,opt}$; (ii) draw a horizontal line from the point of coordinates ($C^*_{1,opt}$, $C^*_{2,opt}/C^*_{1,opt}$) until intersection with the main diagonal; (iii) draw a vertical line from the foregoing point until intersection with the line corresponding to the assumed n; (iv) iterate steps (ii) and (iii) until $C^*_{N,opt}$ is obtained; (v) if $C^*_{N,opt}$ is larger than expected, arbitrate a smaller $C^*_{1,opt}$; if $C^*_{N,opt}$* is smaller than expected, arbitrate a larger $C^*_{1,opt}$; in both cases, repeat from step (ii) until convergence is achieved according to a user-defined criterion.

The result denoted as Eq. (10) was initially reported by Luyben and Tramper [14] for the case of single-sited enzymes following simple Michaelis-Menten kinetics. It is interesting to note that the optimal intermediate concentrations of substrate as given by Eq. (3) do not depend on the kinetic constant K*. Therefore, for any two consecutive CSTR's with known inlet concentration to the first reactor and outlet concentration from the second one, the intermediate concentration leading to a minimal overall reactor volume is uniquely defined.

The minimization of the objective function chosen corresponds to the minimization of the total capital investment if a scale-up factor of unity is assumed for the equipment cost. Currently, however, such exponent factor tends to be lower, as in the general-purpose six-tenths-factor rule for geometrically and mechanically similar reactors [19]. Moreover, the total number of reactors remains arbitrary after the optimization procedure on the concentrations has been performed. As suggested elsewhere by Malcata [15] for a similar system, the best compromise is found when two objective functions are combined, a hierarchical order being defined on the basis of intrinsic costs. The minimization of the total holding time ensures that the thermal degradation of substrate is kept at a minimum for any given overall conversion (first priority, or higher intrinsic cost); the actual number of reactors required is then found by applying a suitable fractional-exponent law for equipment scale-up (second priority, or lower intrinsic cost).

The asymptotic expressions developed for the optimal intermediate concentrations, Eqs. (16) and (18), are useful for a direct calculation whenever the associated limiting conditions are satisfied. In practice,

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if the standard graphical construction based on Figure 1 starting with C^*_1 not less than 0.85 (say) leads to a final value for C^*_N lower than required, then Eq. (16) can be used as a good approximation of Eq. (3). This approximation gets better as N increases and/or C^*_N increases and/or n decreases. If, on the other hand, the reverse graphical construction based on Figure 1 starting with C^*_N/C^*_{N-1} not greater than $[20(n-1)]^{-1/n}$ (say) leads to a final value for C^*_o larger than unity, then Eq. (5) can be used as a good approximation for $C^*_{1,opt}$ as obtained from Eq. (3). This approximation gets better as N decreases and/or C^*_N decreases and/or n increases.

NOMENCLATURE

- C = concentration of substrate, $mol \cdot m^{-3}$
- C_o = concentration of substrate at the inlet stream of the first reactor, $mol \cdot m^{-3}$
- C_i = concentration of substrate at the outlet stream of the ith reactor, $mol \cdot m^{-3}$
- C^*_i = normalized concentration of substrate at the outlet stream of the ith reactor
- $C^*_{i,opt}$ = normalized concentration of substrate at the outlet stream of the ith reactor leading to the minimum overall reactor volume
- Da_i = Damköhler number for the ith reactor, $(v_{max} \cdot V_i/Q \cdot C_o)$
- $Da_{i,min}$ = Damköhler number for the ith reactor leading to the minimum overall reactor volume, $(v_{max} \cdot V_{i,min}/Q \cdot C_o)$
- j = dummy integer variable for the summations
- K' = kinetic constant, $mol^n \cdot m^{-3n}$
- K^* = dimensionless kinetic constant, (K'/C_o^n)
- m = dummy integer variable for the summations
- n = apparent number of substrate binding sites per enzyme molecule
- N = total number of reactors in the series
- Q = volumetric flow rate through the reactor system, $m^3 \cdot s^{-1}$
- V_i = volume of the ith reactor, m^3
- $V_{i,min}$ = volume of the ith reactor leading to minimum overall reactor volume, m^3
- v = kinetic rate, $mol \cdot m^{-3} \cdot s^{-1}$
- v_{max} = maximum kinetic rate of the enzyme under study, $mol \cdot m^{-3} \cdot s^{-1}$

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