Optimal Control Policy for Substrate Inhibited Kinetics with Enzyme Deactivation in an Isothermal CSTR

A slow enzyme deactivation process taking place in parallel with the main enzymatic reaction in a continuous stirred-tank reactor can cause a departure from the optimal operating conditions, or, even a reactor failure. One way of minimizing productivity losses and maintaining optimal reactor conditions is by properly manipulating the flow rate of the reactor. The optimal flow-control policy for typical enzyme kinetics with parallel enzyme deactivation is derived. Both the complete and an approximate analytical solution are presented. The approximate solution, which is actually a quasisteady-state solution, is a very good approximation when the deactivation process is slow compared to the main enzymatic reaction and can be easily implemented as a feedback control based on the current state of the reactor. If the deactivation kinetics is the same as that of the main reaction and the cost of the reactant is negligible compared to that of the product, the quasisteady-state solution is indeed the exact solution.

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SCOPE

One of the major problems in the operation of continuous stirred enzymatic reactors is the decay of the activity of the enzyme with time. This enzyme deactivation process causes the system to be continuously on a transient so that an optimal steady state operation cannot be maintained. From a practical standpoint there are four different control modes that can be applied to improve the operation of an enzymatic CSTR: A shut-off operation for enzyme replacement when the conversion reaches a predetermined low level; continuous addition of enzyme to make up for the loss of activity; optimal manipulation of the temperature or the pH of the system; and varying the flow rate of the continuous system in a manner resulting in optimal overall operation. Previous studies have examined the first three of the above possibilities, (Verhoff and Schlager, 1981; Haas et al., 1974; Sadana, 1979; Part et al., 1981), and produced control schemes which resulted in improved reactor operation. However, there are several problems associated with the application of these control modes such as the requirement of a detailed description of the kinetics of both the main reaction and the deactivation process, the very narrow temperature and pH range within which enzymes remain active, and the fact that a rather complicated scheme is needed for the implementation of the controls.

In this work, attention is focused on the possibility of manipulating the flow rate of the reactor in order to achieve optimal reactor performance. This mode of control is particularly attractive because it can be implemented with existing flow control instruments and, in addition, it requires only a minimal knowledge of the various kinetic expressions. The variation of the flow rate in two different reactor configurations was considered by Lambda and Dudukovic (1974), who also examined the effect on a profit indicator of various enzyme rate and enzyme deactivation functions. No optimization problem was solved, however, and the control of the flow rate aimed at maintaining a predetermined but nonoptimal constant exit conversion. Here, the optimal control problem is solved and the flow rate profile that minimizes a realistic performance index is derived. A more representative expression for the rate of the enzyme decay is used which assumes that deactivation is caused by the reactants or the products and therefore couples the deactivation process to the main enzymatic reaction. Methods employed in the analysis include the minimum principle in the derivation of the complete optimal control policy and perturbation methods in the derivation of an approximate but much simpler solution.

CONCLUSIONS AND SIGNIFICANCE

The optimal flow rate profile is derived for an immobilized enzyme CSTR with enzyme deactivation taking place in parallel with the main reaction. Although the various simulations were performed for the case of substrate inhibited kinetics, the obtained solutions are general enough to handle any other type of rate expression. For a reactor charged initially with reactant only, the structure of the solution of this singular problem consists of the flow rate set initially at the lower bound until the point of entrance to the singular arc. The variation of the flow rate along the singular arc is determined and this variation constitutes the optimal flow manipulation for as long as the operation is profitable (i.e., till the integrand of the performance index becomes zero). At that point the flow rate is increased to

the upper bound to purge any remaining product out of the reactor. The points of entrance and exit from the singular arc are determined and expressions for the path along the singular arc are given. The application of the optimal flow rate results in significant improvements of the performance index over the uncontrolled case, and, furthermore, the derived control is very easy to implement in existing reactors. Both the complete solution and an approximate analytical solution based on the quasisteady-state approximation are derived and the agreement between the two is shown to be excellent when the enzyme deactivation process is slow compared to the main reaction. The structure of the approximate solution indicates that optimal performance can be obtained by varying the flow rate so that the conversion remains constant at a predetermined level which minimizes the performance index. Expressions for the optimal

conversion levels are given. Such a policy is very easy to implement with a feedback control scheme that measures the current level of conversion and varies the flow rate appropriately to maintain the conversion at the predetermined level.

No detailed knowledge of the kinetics is thus necessary and the control requires only the measurement of the current concentration of the main reactant.

INTRODUCTION

Immobilized enzymes suspended in a stirred tank or in a tubular reactor as a packed, moving or fluidized bed are being increasingly used in a variety of applications because of their high activity and specificity in catalyzing useful reactions. An important consideration for the performance of immobilized enzyme reactor systems is the deactivation of the enzymes whereby they lose, with use, some of their potency as catalysts. This decay of catalytic activity has serious consequences on the process economics, first because of the high cost of enzyme replacement and, second, because of a departure of the state of the reactor from the point of optimal operation.

Several aspects of enzyme deactivation have been addressed by previous studies. Among them, the interaction of physical and chemical factors that influence deactivation is discussed in Laidler and Bunting (1973) and the sequence of enzyme transformations that lead to deactivation in Reiner (1969). Expressions for the kinetics of enzyme decay that correspond to various deactivation mechanisms can be found also in Laidler and Bunting (1973). Other related problems have been examined by various investigators, such as the effect of enzyme decay on the effectiveness factor of a single pellet of immobilized enzyme (Korus and O'Driscoll, 1975, 1976), and the effectiveness of several protective measures against the undesirable effects of enzyme decay in catalytic pellets (Lee and Reilly, 1978).

Further research into the mechanisms of enzyme action is expected to lead to a better understanding of the phenomenon of deactivation and more effective measures to prevent or slow down the rate at which it occurs. However, for as long as deactivation is taking place, it will be accompanied by an undesirable departure of the state of the reactor from the optimal point with the obvious consequences on the economics of the process. To better illustrate the point, consider the effect of enzyme deactivation on the performance of an isothermal CSTR with an enzyme immobilized in it that catalyzes the reaction $A \rightarrow B$. Assuming that external mass transfer resistance around the particles with immobilized enzymes is negligible and also neglecting intraparticle diffusion, the dynamics of this CSTR is described by

$$\dot{c}_A = \frac{F}{V}[c_{A0} - c_A] - a\frac{kc_A}{c_A^2 + K_s c_A + K} \qquad (1)$$

For illustrative purposes only, substrate inhibited kinetics was assumed to describe the rate of reactant depletion in Eq. 1. If the enzyme activity a is constant, a steady state for c_A is obtained at the intersection of the curve $kc_A/(c_A^2 + K_s c_A + K)$ with the straight line $(F/aV)(c_{A0} - c_A)$ representing, respectively, the rates of reactant consumption by reaction and the net rate of reactant addition by the feed (Figure 1). If enzyme deactivation is taking place, a varies with time, and Eq. 1 must be considered together with an equation that describes the change of the activity with time. No steady state exists in this case other than the trivial one obtained for $a = 0$ and $c_A = c_{A0}$.

However, as it is most often the case, the kinetics of the deactivation process is much slower than the kinetics of the main enzymatic reaction so that c_A can be considered to be at all times at a quasisteady state (QSS) obtained from Eq. 1 by setting $\dot{c}_A = 0$. This quasisteady state is obtained again as the intersection of the curve and the straight line described above, with the difference that the slope of the straight line is not constant but decreases as the activity decreases with time. Therefore, the state of the reactor, initially at point A corresponding to activity equal to unity, will move progressively through a sequence of quasisteady states, B, C, etc.,

corresponding to decreasing values of the activity, as the enzyme deactivation process is occurring alongside with the main reaction (Figure 1a). Clearly, the initial point of operation, A, chosen to optimize certain performance criteria, cannot be maintained and the reactor will precipitate through a series of suboptimal states to truly uneconomical operation. If the curve for the main reaction kinetics has the shape shown in Figure 1b, then multiple steady states are possible and in the succession of quasi-steady states a jump from a high conversion quasi-steady state (C) to a low conversion one (C') will take place. In this case, which is equivalent to reactor failure, the deactivation effects are more pronounced and a sudden drop in productivity will complicate the already undesirable departure from the optimal operating conditions.

There are various types of control that one can employ to counter the above effects of enzyme deactivation. Thus, it is possible to cease operation when the enzyme activity falls below a low level or to add fresh enzyme to make up for the activity loss (Verhoff and Schlager, 1981), or, one can manipulate the temperature or the pH of the reactor to achieve an overall optimal operation (Chou et al., 1967; Szepe and Levenspiel, 1968; Ogunge and Ray, 1971; Haas et al., 1974; Sadana, 1979; Park et al., 1981). Although they produced definite improvements over the uncontrolled case, the above control schemes have various disadvantages. The first possibility is clearly not optimal, the second is suboptimal with respect to a combined performance index involving the cost of both the enzyme and the overall reactor volume, and the third is not very practical because of the narrow ranges within which temperature and pH can be varied without causing denaturation of the enzyme. Furthermore, all alternatives require rather complicated schemes for their implementation and detailed knowledge of the kinetics of the main reaction and the deactivation process.

In this work another control possibility is examined, that of the flow rate manipulation. This type of control can be achieved with commercially available instruments and can be applied to existing reactors with minimal modification. The optimal control problem is formulated and solved using the Minimum Principle to give the variation of the flow rate with time that minimizes the performance index. Approximate solutions which utilize the concept of the quasisteady state are also obtained and compared to the complete solution. These approximate solutions point to an interesting possibility of implementing the optimal control policy with a feedback scheme that requires minimal knowledge of the kinetics of the two processes and, finally, examples demonstrate the adequacy of the approximate solution and the improvements that can be achieved over the uncontrolled operation of the enzymatic CSTR.
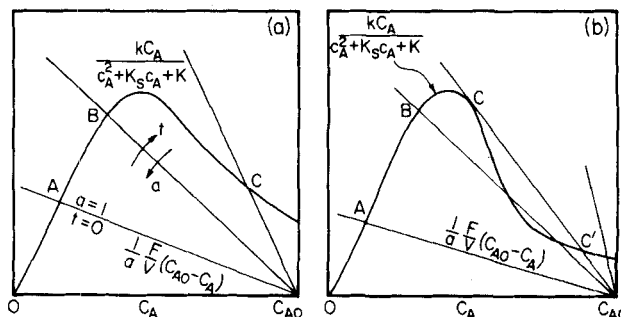

Figure 1. Movement of quasisteady state of an enzymatic CSTR caused by a decline in the activity of the enzyme: (a) single steady state, (b) multiple steady states.

FORMULATION OF THE PROBLEM

Consider the operation of a CSTR with an enzyme immobilized in it that catalyzes the reaction $A \rightarrow B$. The reactor is initially charged with fresh enzyme and reactant A at a concentration equal to the concentration of the stream that will be used subsequently to feed the reactor during continuous operation. As it was discussed in the introduction, the quasisteady state of operation changes continuously as a result of the continuous decline of the activity of the enzyme with time, thus making it impossible to maintain optimal operation. The objective of the present analysis is to derive a control policy for the flow rate of the reactor which counters the enzyme deactivation effects and yields an optimal operation according to a performance index to be presented in the sequel.

Assuming negligible external mass transfer resistance and intraparticle diffusion, the reactor dynamics for isothermal operation is described by the equation.

$$\dot{c}_A = \frac{F}{V} [c_{A0} - c_A] - ar(c_A, c_B, T); \quad c_A(0) = c_{A0}. \tag{2}$$

where r is the rate of depletion of reactant A or formation of product B per unit volume. Although a rate expression of the form

$$r = \frac{kc_A}{c_A^2 + K_s c_A + K} \tag{3}$$

corresponding to substrate inhibited kinetics was used in the numerical examples to be presented in later sections, the derived solution for the control is general and can be applied to any other type of functional relationship between the rate and the concentrations.

To complete the description one needs an expression for the time rate of change of the activity of the enzyme. Many previous works assumed an exponential decline of the activity taking place independently of the main reaction and various cases seem to be represented well in this way. However, if the deactivation is due to poisoning by the reactant or the product, different expressions for the change of the activity must be used. Such expressions have been developed by Do and Weiland (1980) who also point out that the deactivation rate expression can have only certain basic forms if it is to be consistent with the rate expression of the main reaction. In particular, it must have the same denominator with the main kinetics. For kinetics similar to that of Eq. 3 the deactivation rate can be one of the following types:

$$-\dot{a} = r_d = \begin{cases} k_d c_A^n a / (c_a^2 + K_s c_A + K) & (4a) \\ k_d c_A^{n-1} c_B a / (c_A^2 + K_s c_A + K) & (4b) \end{cases}$$

Equations 4a and 4b correspond to parallel and series poisoning mechanisms, respectively, and the exponent n may take on the values {1,2,3} depending on the exact steps of the poisoning mechanism. [See Do and Weiland (1980) for details.]

It should be noticed that when a general rate of the form indicated in Eq. 2 is used, or when a series poisoning mechanism is occurring, the rates r and r_d are functions of c_B as well as of c_A. An equation for the dynamics of c_B is obtained by making a balance on B over the reactor:

$$\dot{c}_B = -\frac{F}{V} c_B + ar; \quad c_B(0) = 0 \tag{5}$$

Equations 2 and 5 can be combined to give

$$\frac{d}{dt}(c_A + c_B) = -\frac{F}{V}(c_A + c_B - c_{A0}); \quad c_A(0) + c_B(0) = c_{A0}$$

the solution of which is $c_A + c_B = c_{A0}$ at all times. Therefore, a second equation for the dynamics of c_B is not needed but c_B can be substituted by

$$c_B = c_{A0} - c_A \tag{6}$$

in the differential equations for c_A and the activity.

The above conclusion is a consequence of the initial and the

operating conditions that were chosen for this case, namely, the reactor being charged initially with pure A and the feed being free of B and of concentration equal to the initial concentration of A in the reactor. If any of the above conditions is not satisfied Eq. 6 can still be used except for an initial period of time during which the existing variation between the initial condition for $(C_A + C_B)$ and its steady state is washed out and the steady-state plane (Eq. 6) is approached exponentially with a time constant F/V. Further details on the applicability of Eq. 6 can be found in Aris (1969) and Asbjørnsen and Fjeld (1970).

A parallel poisoning mechanism directly by the reactant, ($n = 1$), for the enzyme deactivation process, and substrate inhibited kinetics for the main reaction of the type of Eq. 3 is first considered in this section. The treatment of this simpler case will thus serve as a vehicle in presenting the structure of the solution of the optimal control problem. The solution for the case of general kinetics for the main reaction and deactivation process will be presented in the following section.

The reactor dynamics for this case is described by Eqs. 2 and 4a with Eq. 3 for the rate of the main reaction. Equations 2 and 4a can be rendered dimensionless by defining the following dimensionless variables.

$$\tau = \frac{kt}{c_{A0}^2}, \quad A = \frac{c_A}{c_{A0}}, \quad Q = \frac{Fc_{A0}^2}{kV}$$

$$\gamma = \frac{K_s}{c_{A0}}, \quad \beta = \frac{K}{c_{A0}^2}, \quad \epsilon = \frac{k_d}{k} c_{A0} \tag{7}$$

With these dimensionless variables the reactor dynamics is described by the differential equations

$$\dot{A} = Q(1 - A) - a \frac{A}{A^2 + \gamma A + \beta} \tag{8a}$$

$$\dot{a} = -a\epsilon \frac{A}{A^2 + \gamma A + \beta} \tag{8b}$$

and initial conditions

$$A(0) = 1 \text{ and } a(0) = 1 \tag{8c}$$

where the dot is now taken to indicate differentiation with respect to the dimensionless time τ.

To complete the formulation of the optimal control problem one needs a performance index for the operation of the enzymatic CSTR. If the overall profit of the process is considered, then such an index can have the form:

$$J' = \int_o^{t_f} \{c_3' F(c_{A0} - c_A) - c_1' - c_2' F c_{A0}\} dt \tag{9}$$

where the three terms of the integrand represent revenues per unit time from the product, fixed costs per unit time and raw material costs per unit time, in this order. In the index of Eq. 9 it is assumed that no credit for the unreacted A is available, that is, the reactant A cannot be recycled economically to the process after the product B has been separated from it. If this assumption is not made a credit for the unreacted A (equal to $c_2' F c_A$) must be added to the integrand of Eq. 9 which is then reduced to the usual criterion of productivity:

$$J' = \int_o^{t_f} \{F c_B(c_3' - c_2') - c_1'\} dt \tag{10}$$

Both cases will be examined in the optimization problem. Using Eq. 7 and the following dimensionless groups

$$J = \frac{J'}{c_3' V c_{A0}}, \quad c_1 = \frac{c_1' c_{A0}}{c_3' V K} \text{ and } c_2 = \frac{c_2'}{c_3'} \tag{11}$$

the performance index can be written in dimensionless form as

$$J = \int_o^{\tau_f} \{Q(1 - A) - c_1 - c_2 Q\} d\tau \tag{12}$$

and the optimal control problem then is to find the flow rate Q that minimizes $(-J)$ subject to the system dynamics as given by Eqs. 8.

It will be more convenient algebraically to define the fractional conversion of the reactant, ξ, as $\xi = 1 - A$ and use ξ instead of A. The problem, then, can be stated in terms of this variable as:

$$\min_{Q} (-J) = -\int_o^{\tau f} \{Q\xi - c_1 - c_2 Q\}d\tau \qquad (13)$$

subject to the following reactor dynamics:

$$\dot{\xi} = -Q\xi + a\frac{(1 - \xi)}{\xi^2 + \gamma'\xi + \beta'} \qquad (14a)$$

$$\dot{a} = -a\epsilon\frac{(1 - \xi)}{\xi^2 + \gamma'\xi + \beta'} \qquad (14b)$$

and the constraint for the control:

$$Q_* \leq Q \leq Q^* \qquad (15)$$

where Q^* and Q_* are the maximum and minimum, respectively, allowed space velocity. In this paper Q_* is taken to be zero.

THEORETICAL ANALYSIS

For the general optimal control problem:

$$\min_{u} J = \int_o^{\tau f} L(x,u)d\tau; \quad u_{\min} \leq u \leq u_{\max} \qquad (16)$$

subject to state dynamics

$$\dot{x} = h(x,u) \qquad (17)$$

the Hamiltonian is defined as

$$H = L(x,u) + \lambda^T h(x,u) + \nu_1(u - u_{\max}) + \nu_2(u - u_{\min}) \qquad (18a)$$

where the coefficient ν_1 is defined as $\nu_1 = 0$ if $u \neq u_{\max}$ and $\nu_1 \neq 0$ if $u = u_{\max}$. The coefficient ν_2 is defined in a similar manner. Equation 18a can be written in the form

$$H = H^* + \nu_1(u - u_{\max}) + \nu_2(u - u_{\min}) \qquad (18b)$$

with

$$H^* = L(x,u) + \lambda^T h(x,u) \qquad (18c)$$

and then the necessary condition for optimality is

$$\left(\frac{\partial H}{\partial u}\right)^T = \left(\frac{\partial h}{\partial u}\right)^T\lambda + \left(\frac{\partial L}{\partial u}\right)^T = 0 \qquad (19)$$

with the following equations for the state and adjoint variables:

$$\dot{x} = h(x,u) \qquad (20)$$

$$\dot{\lambda} = -\left(\frac{\partial H}{\partial x}\right)^T = -\left(\frac{\partial h}{\partial x}\right)^T\lambda - \left(\frac{\partial L}{\partial x}\right)^T \qquad (21)$$

For free time problems and autonomous systems, we have, in addition:

$$H = L + \lambda^T h = 0 \qquad (22)$$

A typical approach for the solution of this type of problem is to integrate Eqs. 20 and 21 with the proper boundary conditions (Koppel, 1968), evaluating the control at each time step as function of the state and adjoint variables from Eq. 19. For those systems, however, which are linear in the control, Eq. 19 cannot be used for the evaluation of the control, contributing thus to a special class of singular control problems. It can be shown (Bryson and Ho, 1969), that the solution in this case is that of a bang-bang control:

$$u^*(t) = \begin{cases} u_{\min} & \text{if } H_u^* > 0 \\ u_{\max} & \text{if } H_u^* < 0 \end{cases} \qquad (23)$$

Thus, for a linear singular problem the control variable will take the extreme values allowed as long as $H_u^* \neq 0$. If $H_u^* = 0$, the minimum principle cannot tell what the control should be. However, if H_u^* is zero over a finite interval of time, so must be its time derivatives and repeated differentiation of the relation $H_u^* = 0$ with

respect to time will eventually yield an explicit relationship between the optimal control u^* and the state vector. The path followed by u during the time period over which u is not on the boundaries is often called singular arc. It turns out that an even number of differentiations with respect to time is always required to yield the relationship that gives u along the singular path; if two differentiations are required then the trajectory of u over the time interval is said to be a first order singular arc, etc. For such a singular arc a more general necessary condition for convexity has been derived and may be stated as:

$$(-1)^k\frac{\partial}{\partial u}\left[\left(\frac{d}{dt}\right)^k H_u\right] \geq 0 \qquad (24)$$

where k is the order of the singular arc.

Applying the above results to the optimal control problem of Eqs. 13, 14 and 15 the following are obtained:
Hamiltonian:

$$0 = H = -(Q\xi - c_1 - c_2 Q) + \lambda_1(-Q\xi + af)$$
$$+ \lambda_2'(-a\epsilon f) + \nu_1(Q - Q^*) + \nu_2(Q - Q_*)$$

where $\nu_1 = 0$ if $Q \neq Q^*$ and $\nu_1 \neq 0$ if $Q = Q^*$, and ν_2 is similarly defined. Setting $\lambda_2 = \epsilon\lambda_2'$, the Hamiltonian can be written as:

$$0 = H = -(Q\xi - c_1 - c_2 Q) + \lambda_1(-Q\xi + af)$$
$$+ \lambda_2(-af) + \nu_1(Q - Q^*) + \nu_2(Q - Q_*) \qquad (25)$$

State Equations: Changing the independent variable from τ to $\theta = \epsilon\tau$ the equations for the state and adjoint variables become:

$$\epsilon\frac{d\xi}{d\theta} = -Q\xi + af(\xi), \quad \xi(0) = 0 \qquad (26a)$$

$$\frac{da}{d\theta} = -af(\xi), \quad a(0) = 1 \qquad (26b)$$

where $f(\xi) = (1 - \xi)/(\xi^2 + \gamma'\xi + \beta')$, and
Adjoint Equations:

$$\epsilon\frac{d\lambda_1}{d\theta} = (1 + \lambda_1)Q + (\epsilon\lambda_2' - \lambda_1)af_\xi, \quad (\lambda_1(\theta_f)) = 0$$

$$\epsilon\frac{d\lambda_2'}{d\theta} = (\epsilon\lambda_2' - \lambda_1)f, \quad \lambda_2'(\theta_f) = 0$$

or in terms of λ_2:

$$\epsilon\frac{d\lambda_1}{d\theta} = (1 + \lambda_1)Q + (\lambda_2 - \lambda_1)af_\xi, \quad \lambda_1(\theta_f) = 0 \qquad (27a)$$

$$\frac{d\lambda_2}{d\theta} = (\lambda_2 - \lambda_1)f, \quad \lambda_2(\theta_f) = 0 \qquad (27b)$$

In Eq. 27a, f_ξ means differentiation with respect to ξ.
Necessary Condition:

$$0 = \frac{\partial H^*}{\partial Q} = \frac{\partial H}{\partial Q} = -(1 + \lambda_1)\xi + c_2 \qquad (28)$$

for singular arc.

Since the Hamiltonian is linear in the control Q, the usual necessary condition $H_Q = 0$ does not contain the control variable and, therefore, cannot be used for the determination of the optimal control policy. Subsequent differentiation with respect to time, as discussed earlier in this section, yields:

$$0 = \frac{d}{d\theta}(H_Q) = -a[(1 + \lambda_1)f + (\lambda_2 - \lambda_1)\xi f_\xi] \qquad (29)$$

$$\frac{d^2}{d\theta^2}(H_Q) = 0 \rightarrow Q = \frac{2aff_\xi + a\xi ff_{\xi\xi} - 2a\xi f_\xi^2 + \epsilon\xi ff_\xi}{2\xi f_\xi + \xi^2 f_{\xi\xi} - 2\xi^2 f_\xi^2/f}$$

$$= \frac{af}{\xi} + \frac{\epsilon\xi ff_\xi}{2\xi f_\xi + \xi^2 f_{\xi\xi} - 2\xi^2 f_\xi^2/f} \qquad (30)$$

Then, combining the minimum principle and the result of Eq. 23, one obtains for the optimal control:

$$Q = \begin{cases} Q_* = 0 & \text{if} \quad -(1+\lambda_1)\xi + c_2 > 0 \\ Q^* & \text{if} \quad -(1+\lambda_1)\xi + c_2 < 0 \\ \dfrac{af}{\xi} + \dfrac{\epsilon \xi f f_\xi}{2\xi f_\xi + \xi^2 f_{\xi\xi} - 2\xi^2 f_\xi^2/f} & \text{if} \quad -(1+\lambda_1)\xi + c_2 = 0 \end{cases}$$

(31)

Since the initial value of ξ is equal to zero and $c_2 > 0$, it can be seen from the above equation that $-(1+\lambda_1)\xi + c_2 > 0$, so that the reactor is started with the minimal flow rate which is taken here to be zero. As the reaction progresses and the conversion increases, ξ also increases and at some point $-(1+\lambda_1)\xi + c_2$ becomes equal to zero. At this point the flow rate enters the singular arc: it is raised to a value and subsequently follows the path indicated by the third of the Eqs. 31.

It will be useful to be able to predict the point at which the control enters the singular arc. This can be done by noting that during the initial phase of operation for which $Q = 0$, the state equations (Eqs. 26) can be integrated to yield an explicit relationship for the activity as a function of ξ, as follows:

$$\epsilon \frac{d\xi}{d\theta} = af(\xi) \tag{32}$$

$$\frac{da}{d\theta} = -af(\xi) \tag{33}$$

and combining Eqs. 32 and 33:

$$\frac{da}{d\theta} = -\epsilon \frac{d\xi}{d\theta}$$

which, when integrated with initial conditions $a(0) = 1$ and $\xi(0) = 0$, yields:

$$a(\theta) = 1 - \epsilon \xi(\theta) \tag{34}$$

Equation 34 is valid during the startup period for which $Q = 0$. At the point of entrance in the singular arc, $H_Q = 0$ and also H and $dH_Q/d\theta$ are zero. Therefore, at that point, Eqs. 25, 28 and 29 are valid and can be used to eliminate λ_1 and λ_2 among them to obtain a relationship between the activity and ξ:

$$\frac{c_1}{c_2} = \frac{-af^2}{\xi^2 f_\xi} \tag{35}$$

or, after using Eq. 34 for a:

$$\frac{c_1}{c_2} = \frac{-(1 - \epsilon\xi)f^2(\xi)}{\xi^2 f_\xi} \tag{36}$$

Equation 36 involves ξ as the sole variable. If an expression for the kinetics, $f(\xi)$, is available, Eq. 36 can be used to determine the conversion point at which the flow rate enters the singular arc. By integrating Eq. 32 with 34 for $a(\theta)$, the time point of entrance can also be determined. After the control has entered the singular arc it stays there for as long as the integrand of the performance index, Eq. 12, remains positive, namely, for as long as the inequality $Q(\xi - c_2) > c_1$ is satisfied. This is so because, if the objective is to maximize J as defined in Eq. 12, the operation should cease when the net incremental return becomes nonpositive. The above requirement indicates that the operation cannot end on a singular arc because at the end point $\lambda_1(\theta_f) = 0$ and Eq. 28 gives $\xi(\theta_f) = c_2$ which is in violation of the above inequality, unless $c_1 = 0$. If $c_1 > 0$, the optimal control should stay on the singular arc till $Q(\xi - c_2) = c_1$ at which point it takes the maximum allowed value Q^* as dictated by Eq. 31 for $H_Q < 0$. The end of operation is determined again at the point at which $Q^*(\xi - c_2) = c_1$.

The above control policy was tested in a number of simulated operations presented in the following section. For a given initial condition of the state the above control policy was applied and the final state conditions determined. Using the so obtained final state, the known final conditions for the adjoint variables and the same control, the state and adjoint equations were integrated backwards and H_Q evaluated at each point. The very good agreement between these values and those obtained in the forward integration shows that the control policy described above is at least one optimal

solution.

In conclusion, the optimal control law is to use the lowest (initially) and highest (finally) flow rate allowed, except along the singular arc. Provided that a reliable under dynamic conditions $f(\xi)$ function is available, the points of entrance and exit from the singular arc can be found and the optimal manipulation of the flow rate along the singular arc be determined by integrating simultaneously the state and adjoint equations with the proper boundary conditions and evaluating the control at each time step from Eq. 31. For the case considered in this work the numerical scheme required is quite simpler than those encountered in most optimal control problems because by substituting the control law of Eq. 31 in the state Eq. 26a the two state equations become uncoupled:

$$\frac{d\xi}{d\theta} = \frac{-\xi^2 f f_\xi}{2\xi f_\xi + \xi^2 f_{\xi\xi} - 2\xi^2 f_\xi^2/f} \tag{37}$$

The above equation can be integrated with initial condition corresponding to the conversion at the entrance of the singular arc and the resulting $\xi(\theta)$ function be substituted into Eq. 26b the integration of which yields the variation of the activity along the singular path.

It is thus seen that the implementation of the control law (Eq. 31) is rather simple and also can be prescribed in advance for a particular operation. In some cases, however, much simpler solutions can be obtained and these possibilities are discussed below.

SPECIAL CASES

Case 1: $\epsilon \ll 1$

This case is equivalent to the deactivation process being much slower than the main reaction. Under this condition, the optimal control can be expressed in terms of a zeroth order solution plus other terms of first and higher orders in the small parameter ϵ. The smaller the value of the parameter ϵ the more accurately the exact solution is approximated by the zeroth order solution. The latter is obtained by setting $\epsilon = 0$ in the system equations and is actually the quasisteady-state solution.

Returning to the original time variable τ and setting $\epsilon = 0$ in Eq. 37 one obtains $d\xi/dt = 0$, i.e., the conversion at the QSS is constant. Also, for $\epsilon = 0$, the state equation (Eq. 26a), or the control law (Eq. 31), yield for the control:

$$Q = a\frac{f(\xi)}{\xi} \tag{38}$$

Thus, by employing the QSS approximation, a control law is obtained according to which the flow rate decreases responding to the decay of activity and in such a way as to maintain the conversion at a quasisteady-state level the optimal value of which, ξ^*, is determined below.

Optimal QSS Conversion

For $\epsilon = 0$, Eq. 26a yields $af = Q\xi$, and substituting this relationship into Eq. 26b the dynamic equation for the activity becomes

$$\frac{da}{d\tau} = -a\epsilon f(\xi) = -\epsilon Q\xi \tag{39}$$

Using the above equation for a change of independent variables from τ to a, neglecting the purging term, allows the performance index to be rewritten in terms of a as:

$$(-J) = \int_{a_{en}}^{a_{min}} \frac{da}{\epsilon} - \int_{a_{en}}^{a_{min}} \frac{c_2}{\epsilon\xi} da + \int_o^{\tau_{en}} c_1 d\tau + \int_{\tau_{en}}^{\tau_f} c_1 d\tau$$

$$= \frac{1}{\epsilon}\left\{\left(1 - \frac{c_2}{\xi}\right)(a_{min} - a_{en}) + \epsilon c_1 \tau_f\right\} \tag{40}$$

In the above equation a_{en} is the activity of the catalyst when the reactor enters QSS operation and τ_{en} the time of entrance into QSS operation. Also a_{min} is the activity at the end of the QSS operation

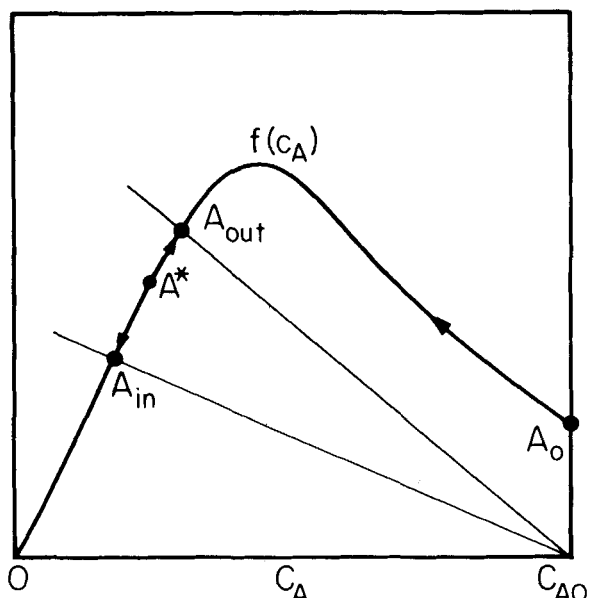**Figure 2. Operation of an enzymatic CSTR under exact and approximate control law for flow rate.**

which in turn is given by $a_{min} = c_1\xi/(f\xi - fc_2)$. Noting that during start-up the activity is given by

$$a = 1 - \epsilon\xi$$

the following expressions can be obtained for the time of entrance into QSS operation, τ_{en}, and the final time τ_f,

$$\tau_{en} = \int_0^\xi \frac{d\xi'}{(1 - \epsilon\xi')f(\xi')}$$

$$\tau_f = \tau_{en} + \frac{ln(a_{en}|a_{min})}{\epsilon f(\xi)} \quad (41)$$

Substituting τ_f from Eq. 41 into Eq. 40 and minimizing $(-J)$ with respect to ξ by setting $d(-J)/d\xi = 0$ gives the desired equation for the optimal value of the conversion, ξ^*:

$$(a_{min} - 1)\frac{c_2}{\xi^{*2}} + \epsilon + \frac{c_1 ln\left[\frac{a_{min}}{1 - \epsilon\xi^*}\right]f_\xi(\xi^*)}{f^2(\xi^*)} = 0 \quad (42)$$

Equation 42 contains ξ^* as the sole unknown and can be solved, once a *design* equation $f(\xi)$ is available to give the conversion of optimal operation ξ^*. The control law of Eq. 38 can then be applied to maintain operation at ξ^* despite changes in the activity. The use of the QSS approximation actually amounts to neglecting the effect of the activity changes on the conversion and varying the flow rate in response to activity changes only, as indicated by Eq. 38. By comparing the control laws for Q of Eq. 38 and 31 it can be seen that the error involved with the use of the QSS is of the order of ϵ, i.e., minimal for small ϵ, and numerical calculations, discussed in the following section, confirm this observation. Figure 2 shows a convenient illustration of the reactor operation when the exact and the approximate solutions are employed for the control. The reactor is initially at point A_0, corresponding to charging the reactor with reactant at concentration c_{A0}. During the start-up in which $Q = 0$, the state travels along the $f(c_A)$ curve till it enters the singular arc at point A_{in}. If the exact solution is applied, the state will move along the singular arc from A_{in} to A_{out} following the control law of Eq. 31. If the QSS solution is employed instead, the control law is given by Eq. 38 which indicates that the flow rate decreases as the activity decays in order to maintain the conversion at some optimal point A^* between A_{in} and A_{out} and determined by Eq. 42.

Case 2: $c_2 = 0$

The cost of the reactant is negligible in this case and Eq. 28 in-

dicates that $(1 + \lambda_1)\xi = 0$. This substituted into Eq. 29 yields $f_\xi = 0$. Therefore, when $c_2 = 0$ the QSS conversion for optimal operation is that for which $f(\xi)$ is maximum. The same conclusion is obtained if the productivity is used as the performance index. It is of interest to notice that when $f_\xi = 0$ the exact solution of the control law given by Eq. 31 reduces to $Q = af/\xi$ which is identical to that of the QSS solution of Eq. 37. Hence, the quasisteady-state solution is indeed the exact solution when $c_2 = 0$ and the kinetics of the deactivation and the main reaction are as indicated in Eqs. 8.

GENERAL CASE

When the kinetics of the deactivation process and the main reaction are not of the form assumed in the previous section, Eqs. 26 are replaced by

$$\epsilon\frac{d\xi}{d\theta} = -Q\xi + af(\xi); \quad \xi(0) = 0 \quad (43a)$$

$$\frac{da}{d\theta} = -ag(\xi); \quad a(0) = 1 \quad (43b)$$

where $f(\xi)$ and $g(\xi)$ are, respectively, the dimensionless forms of the kinetics of the main reaction and the deactivation process, as functions of the conversion ξ.

Following the exact same procedure described previously, one obtains the following expressions for the optimal flow rate:

$$Q = \begin{cases} Q_* = 0 & \text{if} - (1 + \lambda_1)\xi + c_2 > 0 \\ Q^* & \text{if} - (1 + \lambda_1)\xi + c_2 < 0 \\ \dfrac{af}{\xi} + \epsilon \dfrac{gg_\xi\xi - \left(\dfrac{c_2 - \xi}{c_2 f}\right)(gg_\xi f_\xi\xi^2 - fg_\xi^2\xi^2)}{2g_\xi\xi + \xi^2 g_{\xi\xi} - 2\xi^2 f_\xi g_\xi/f} & \\ \quad - [(c_2 - \xi)/c_2 f][f_\xi g_{\xi\xi}\xi^3 - g_\xi f_{\xi\xi}\xi^3] & \\ & \text{if} - (1 + \lambda_1)\xi + c_2 = 0 \end{cases} \quad (44)$$

Notice that when $f = g$, Eq. 44 reduces to the one previously derived for Q, Eq. 31.

The conversion, ξ_{en}, at which the reactor should enter the singular arc is similarly deduced. The same procedure yields the following algebraic equation for ξ_{en}:

$$a_{en}c_2 fg = c_1\xi_{en}^2 g_\xi + (c_2 - \xi_{en})\xi_{en}(fg_\xi - gf_\xi) \quad (45)$$

with the activity, a_{en}, given by:

$$a_{en} = a(\xi_{en}) = 1 - \epsilon\int_0^{\xi_{en}} \frac{g(\xi)}{f(\xi)}d\xi \quad (46)$$

during the start-up period and, therefore, at the entrance to the singular arc, as well. If the kinetics are known, the integral of Eq. 46 can be evaluated to yield a_{en} for use in the estimation of ξ_{en} from Eq. 45.

Finally, in the determination of the optimal QSS conversion the performance index is written as:

$$(-J) = \frac{1}{\epsilon}\left\{\left(\frac{f}{g}\right)(a_{min} - a_{en})\left(1 - \frac{c_2}{\xi}\right) + \epsilon c_1\tau_f\right\} \quad (47)$$

with the final time, τ_f, given by:

$$\tau_f = \int_0^\xi \frac{d\xi'}{af} + \frac{ln(a_{en}|a_{min})}{\epsilon g} \quad (48)$$

and the activity substituted in the integral of Eq. 48 by:

$$a(\xi) = 1 - \epsilon\int_0^\xi \frac{g(\xi')}{f(\xi')}d\xi' \quad (49)$$

For known kinetics $f(\xi)$ and $g(\xi)$, the activity can be estimated as function of the conversion from Eq. 49 and then substituted into Eqs. 48 and 47 to express the performance index as function of ξ. The optimal QSS conversion is then similarly obtained by setting $d(-J)/d\xi = 0$.
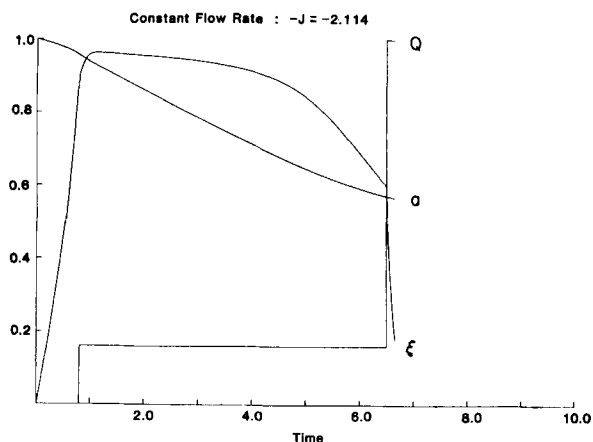
Figure 3. Progress of the activity and conversion with dimensionless time of an enzymatic CSTR: constant flow rate.
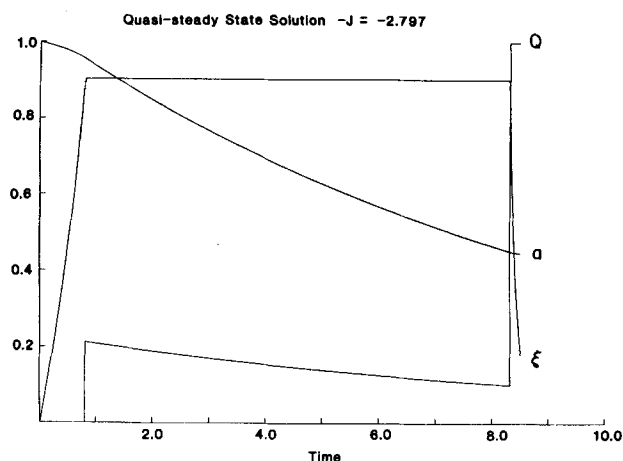

Figure 5. Progress of the activity and conversion with dimensionless time of an enzymatic CSTR: The flow rate follows the solution of the QSS approximation.

DISCUSSION

In order to assess the efficiency of the derived control law and evaluate the improvements over the uncontrolled operation, a test case with the kinetic parameters indicated in Figure 4 was simulated. The performance of the reactor when a constant flow rate is used is shown in Figure 3. When the flow rate varies with time according to the exact or approximate control laws of Eqs. 31 and 38 an improved performance is obtained and Figures 4 and 5, respectively, present the results for the progress of the flow rate, conversion and activity with time for these two cases.

There are various points worth noticing in Figures 3–5. First, the structure of the control law: Initially the flow rate is zero and subsequently it is raised to a value given by Eq. 31 with ξ and a evaluated at the point of entrance to the singular arc as discussed in the previous section. The maximum flow rate Q^* is taken equal to unity and all the other flow rates are scaled accordingly. Second, the performance indices obtained for the exact and the QSS solution are remarkably close. Notice that when the exact solution is employed, the conversion decreases only by a very small amount during operation on the singular arc, thus verifying the validity of the QSS assumption according to which ξ is constant. (This is also reflected in the small difference between the values of the performance indices obtained for the two cases.) Finally, the use of either kind of control law results in substantial improvement over the uncontrolled case. For the example considered, an improvement of 24% is obtained over the case in which the flow rate is initially zero and is raised to a value equal to that given by Eq. 31. The improvement over the uncontrolled case depends on the rate of increase of $f(\xi)$ in the region to the left of the maximum. A rel-

atively flat $f(\xi)$ curve produces rather modest decreases in the performance index when the optimal policy is applied for the flow rate.

The previous observations point to a very convenient control strategy for the enzymatic CSTR under examination: Using kinetic data for the main enzymatic reaction (such data must be available in one form or another for the design of the reactor), the conversion of optimal operation ξ^* is determined. Then the control consists of starting initially with a zero flow rate till a conversion equal to ξ^* is reached and subsequently manipulating the flow rate so that the optimal QSS conversion is maintained. This type of control action can be achieved with simple existing instrumentation, requires the measurement of only one variable and can be incorporated in most operating reactors with minimal modifications. One disadvantage of the above scheme, namely the variable flow rate which may be undesirable for various reasons can easily be avoided by having more than one reactor operating in parallel at the appropriate flow rates and phase lag among them.

The cost of enzyme c_E can be incorporated into the above scheme by redefining the time cost c_1 as $c_1 = c_T = c_{10} + c_E|\tau_f$ where c_{10} is the base daily operating cost and τ_f is the operating time for that particular c_T. QSS optimal operating profile for different c_1 can be obtained by using the method discussed earlier. This calculation also yields the optimal duration of operation, the QSS optimal conversion and the best value of the performance index. These results can be summarized conveniently in graphs similar to Figure 6 which was obtained by using the same kinetic data as before and a value of 0.402 for c_{10}. As expected, an increasing enzyme cost leads to shorter operating periods and smaller
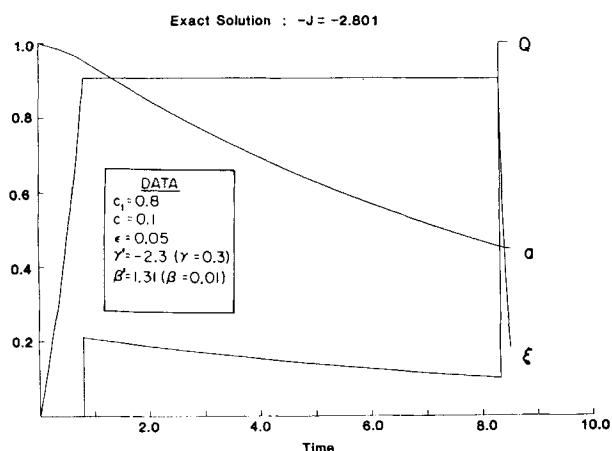

Figure 4. Progress of the activity and conversion with dimensionless time of an enzymatic CSTR: The flow rate follows the exact solution of the optimal control problem.

DATA
$c_1 = 0.8$
$c = 0.1$
$\epsilon = 0.05$
$\gamma' = -2.3$ $(\gamma = 0.3)$
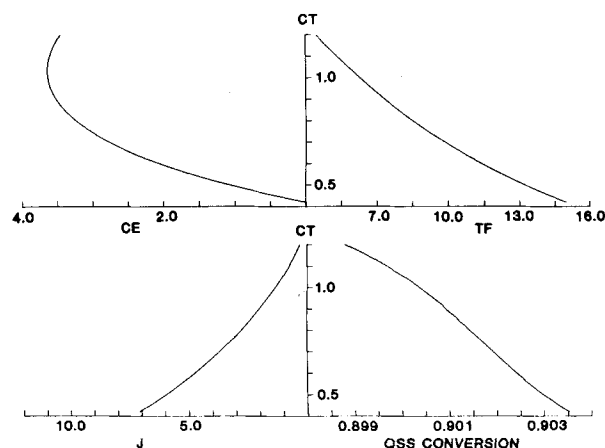$\beta' = 1.31$ $(\beta = 0.01)$

Figure 6. Dependence of the optimal conversion, time of operation and performance index on the enzyme cost.

values for the performance index. Also notice that there is a small region in the values of the enzyme cost where multiple solutions for τ_f and J are possible.

It should also be pointed out that the obtained results are not dependent on the specific kinetics of the main reaction as indicated by Eqs. 44 and 38 which give the control laws in terms of the functions $f(\xi)$ and $g(\xi)$. Any such functions can be used for this purpose and both parallel and series poisoning mechanisms can be treated for the deactivation process. A comparison between the variable flow rate and the other control possibilities mentioned in the introduction is not possible without referring to a specific case and optimizing the various operating parameters in each control mode. However, the simplicity of implementation of the variable flow rate control mode is definitely a strong advantage which can lead to the preference of this control possibility over the others.

ACKNOWLEDGMENT

NOTATION

a	= enzyme activity
A	= dimensionless concentration of A
c_A	= concentration of reactant A
c_B	= concentration of product B
c_1	= dimensionless fixed cost
c_2	= dimensionless reactant cost
c_1'	= fixed costs per unit time
c_2'	= cost per unit gmol of reactant A
c_3	= selling price per gmol of product B
F	= reactor flow rate
f	= dimensionless rate equation of main reaction as function of fractional conversion of A: $f(\xi) = (1 - \xi)/(\xi^2 + \gamma'\xi + \beta')$
f_ξ	= derivative of $f(\xi)$ with respect to ξ
g	= dimensionless rate equation for deactivation process
H	= Hamiltonian function
J	= dimensionless performance index
J'	= dimensional performance index
k	= rate constant of main enzymatic reaction
k_d	= deactivation rate constant
K	= constant in the reaction rate for substrate inhibited kinetics
K_s	= constant in the reaction rate for substrate inhibited kinetics
Q	= dimensionless flow rate
r	= rate of reactant depletion by reaction per unit volume
r_d	= rate of enzyme deactivation per unit volume
u	= control variable in an optimal control problem
u^*	= optimal value of the control variable
V	= reactor volume
x	= state variable in an optimal control problem

Greek Letters

β	= dimensionless equivalent of K (Eq. 7)
γ	= dimensionless equivalent of k_s (Eq. 7)
δ	= defined by boundary condition of Eq. 27b
ϵ	= dimensionless ratio of deactivation and main reaction rate constants
θ	= new dimensionless time scale equal to $\tau\epsilon$
λ	= adjoint variables in an optimal control problem
ν_i	= multipliers in the Hamiltonian Eqs. 18 and 25
ξ	= fractional conversion of the reactant
ξ^*	= optimal value of ξ at quasisteady state
τ	= dimensionless time

Subscripts

f	= final time
0	= feed conditions
en	= conditions of entrance to singular arc

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