

# Optimal Temperature Policy for Immobilized Enzyme Packed Bed Reactor Performing Reversible Michaelis–Menten Kinetics Using the Disjoint Policy

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**Abstract:** The optimal temperature policy that maximizes the time-averaged productivity of a continuous immobilized enzyme packed bed reactor is determined. This optimization study takes into consideration the enzyme thermal deactivation with substrate protection during the reactor operation. The general case of reversible Michaelis–Menten kinetics under constant reactor feed flow rate is assumed. The corresponding nonlinear optimization problem is solved using the calculus of variations by applying the disjoint policy. This policy reduces the optimization problem into a differential-algebraic system, DAE. This DAE system defines completely the optimal temperature–time profiles. These profiles depend on the kinetic parameters, feed substrate concentration, operating period, and the residence time and are characterized by increasing form with time. Also, general analytical expressions for the slopes of the temperature and residual enzyme activity profiles are derived. An efficient solution algorithm is developed to solve the DAE system, which results into a one-dimensional optimization problem with simple bounds on the initial feed temperature. The enzymatic isomerization of glucose into fructose is selected as a case study. The computed productivities are very close to that obtained by numerical nonlinear optimization with simpler problem to solve. Moreover, the computed conversion profiles are almost constant over 90% of the operating periods, thus producing a homogeneous product. © 2002 John Wiley & Sons, Inc. *Biotechnol Bioeng* 77: 163–173, 2002.

**Keywords:** optimal temperature policy; Michaelis–Menten kinetics; disjoint policy

## INTRODUCTION

The problem of optimal operating policy for immobilized enzyme packed bed reactors is a subject of vast operational research due to the economical potential of characterizing such optimal operations. This optimal operating policy can be practically achieved in mainly two control modes of reactor operation. The first one is the control of feed rate to the reactor in such a way that it decreases as function of time in order to compensate

for the loss of enzyme activity. The second mode is the temperature and/or pH profile that is set according to a well-defined time profile (Faqir, 1998; Haas et al., 1974; Kim et al., 1982; Park et al., 1981; Straatsma et al., 1983; Vos and Luyben, 1993). Temperature is one of the most important variables due to its effect on the kinetic parameters, enzyme activity, and substrate protection factor. However, one limitation of this control variable is the narrow range within which enzymes remain active (Lee, 1992). In spite of this, many researchers have used two types of temperature operating policies utilizing the enzymatic isomerization of glucose to fructose as a model system (Abu-Reesh and Faqir, 1996; Faqir, 1998; Hass et al., 1974; Kim et al., 1982; Park et al., 1981; Straatsma et al., 1983). These operating policies are either a rising temperature policy with time to maintain a constant outlet conversion or a constant temperature profile that maximizes the average reactor productivity. Park et al., (1981) studied the temperature control policy for the enzymatic isomerization of glucose to fructose using immobilized glucose isomerase in a continuous packed bed reactor. They found that the average productivity is improved by approximately 8% upon using the optimal increasing temperature policy of operation as compared to the optimum isothermal operation.

Most of the published works on determining the optimum temperature operating policy for continuous packed bed reactors performing reversible Michaelis–Menten kinetics use either Pontryagin's maximum principle or nonlinear programming methods (Faqir, 1998; Haas et al., 1974; Kim et al., 1982; Park et al., 1981; Straatsma et al., 1983; Vos and Luyben, 1993). The main disadvantages of these optimization methods are the tedious formulation and complex solution algorithms used to obtain the desired solution. Moreover, they lack general applicability when applied to the same class of problems.

The present work deals with the optimization of continuous immobilized enzyme packed bed reactors under constant feed flow rate. For such reactors, the optimal

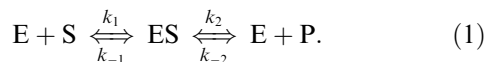
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temperature–time policy is determined such that the time-averaged reactor productivity is maximized. The corresponding nonlinear optimization problem is solved using the calculus of variations and, in particular, by applying the disjoint policy. The problem solution using the disjoint policy proceeds in the most general form to cover any operational problem of immobilized packed bed reactor using reversible Michaelis–Menten kinetics with substrate protection. In this way the optimization problem is reduced to the solution of a differential algebraic system, DAE. Two coupled nonlinear ordinary differential equations plus a nonlinear algebraic equation represent this DAE system. These equations define completely the temperature–time profile over the operating period of the reactor. This profile is optimal and is dependent only on the kinetic parameters, the feed substrate concentration, the operating period, and the residence time. An efficient solution algorithm is developed to solve the DAE system, which results into a one-dimensional optimization problem with simple bounds on the initial feed temperature. The isomerization of glucose to fructose using the immobilized enzyme glucose isomerase (IGI) is chosen as a model system to conduct numerical computations. This reaction is considered as one of the most important industrial applications of immobilized enzyme reactors (Illanes et al., 1992).

## PROBLEM FORMULATION USING THE CALCULUS OF VARIATIONS

### Reaction Kinetics

Most enzyme-catalyzed reactions are reversible in their nature, following a reaction sequence that involves rapid complex formation resulting from enzyme and substrate interaction. This is followed by a slow step with product liberation. When the two steps are reversible, the reaction mechanism is called reversible Michaelis–Menten kinetics and is represented by (Lee, 1992)



The rate of reaction following quasi-steady state mechanism, with no initial product in the feed, is given by (Abu-Reesh and Faqir, 1996; Park et al., 1981)

$$r(C_S) = \frac{V_m(C_S - C_{Se})}{K_m + C_S - C_{Se}}, \quad (2)$$

where

$$K_m = \frac{K_s K_p}{K_p - K_s} \left[ 1 + \left( \frac{K_e}{K_p} + \frac{1}{K_s} \right) \frac{C_{S0}}{1 + K_e} \right];$$

$$V_m = \frac{K_p V_s (1 + K_e)}{(K_p - K_s) K_e};$$

$$K_p = K_{p0} e^{-E_p/RT}; K_s = K_{S0} e^{-E_s/RT};$$

$$V_p = V_{p0} e^{-E_{vp}/RT}; V_s = V_{S0} e^{-E_{vs}/RT}; K_e = K_{e0} e^{-E_e/RT};$$

and further:

$$V_s = C_{E0} K_2; V_p = C_{E0} K_{-1}; K_s = \frac{K_{-1} + K_2}{K_1};$$

$$K_p = \frac{K_{-1} + K_2}{K_{-2}}; K_e = \frac{V_s K_p}{V_p K_s}.$$

Eq. (2) can be rearranged to

$$r(C_S) = \frac{k(C_S - C_{Se})}{1 + K'_m(C_S - C_{Se})}, \quad (3)$$

where  $k = V_m/K_m$  and  $K'_m = 1/K_m$

If it happens at some operating temperature,  $T$ , that  $K_p = K_s$ , then  $K'_m = 0$  and  $V_m \rightarrow \infty$ , but the ratio  $V_m/K_m$  remains finite. Accordingly, Eq. (3) is reduced to a pseudo-first order reversible reaction (Abu-Reesh, 1996; Palazzi and Converti, 1999). At this special case the complex concentration,  $C_{ES}$ , starts from 0 and when  $t \rightarrow \infty$ ,  $C_{ES}$  approaches a constant value. This means that the reversible Michaelis–Menten reaction follows steady state mechanism in both forward and reverse directions and approach equilibrium asymptotically as  $t \rightarrow \infty$  (Keleti, 1986). On the other hand, if  $K_p \neq K_s$ , then the reaction follows steady state kinetics in forward direction but not in the reverse one (Keleti, 1986). Recently, enzyme deactivation with substrate protection is proposed and validated experimentally for a specific case of immobilized glucose isomerase (Chen and Wu, 1987; Houg et al., 1993). For the purpose of general derivation, a first-order reaction mechanism with substrate protection is assumed to describe the thermal deactivation of enzyme. This results in the following rate of residual enzyme activity at any time  $t$  (Chen and Wu, 1987):

$$\frac{da}{dt} = -K_d(1 - \sigma)a \quad \text{at } t = 0, a = 1, \quad (4)$$

where  $K_d$  is the enzyme thermal deactivation rate constant given by

$$K_d = K_{d0} e^{-E_d/RT}, \quad (5)$$

and  $\sigma$  is the substrate protection factor given by (Chen and Wu, 1987; Houg et al., 1993):

$$\sigma = n \frac{K_p \left[ 1 + \frac{S'(1+K_e)}{C_{S0}} \right] + K_s K_e \left[ 1 - \frac{S'(1+K_e)}{K_e C_{S0}} \right]}{K_s K_p \frac{1+K_e}{C_{S0}} + K_p \left[ 1 + \frac{S'(1+K_e)}{C_{S0}} \right] + K_s K_e \left[ 1 - \frac{S'(1+K_e)}{K_e C_{S0}} \right]}, \quad (6)$$

where

$$s' = C_{S0}(x_e - x), \quad x_e = K_e/(1 + K_e), \quad \text{and}$$

$$x = (C_{S0} - C_S)/C_{S0}.$$

The constant  $n$  is a factor used to express the ratio of enzyme–substrate complex to free enzyme deactivation

rate. This value can be determined experimentally for a specific reaction following the mechanism represented by Eq. (1), and it has a value  $0 < n < 1$ . Thus, in the presence of enzyme deactivation and substrate protection the reaction rate becomes

$$r'(x) = r(x) \cdot a. \quad (7)$$

### Mathematical Model

In modeling continuous immobilized enzyme packed bed reactors, the following simplifying assumptions are made (Illanes et al., 1992; Roles and Tilberg, 1979; Vasic-Racki et al., 1991): (1) the flow of substrate through the reactor is ideal plug flow; (2) the immobilized enzyme effectiveness factor is assumed to be unity (no diffusional limitations); (3) the enzyme deactivation is a rather slow process when compared to the mean residence time of reactants; and (4) the residual enzyme activity is considered as a weak function of substrate concentration along the reactor length.

Under these assumed conditions the packed bed design equation is given by (Abu-Reesh and Faqir, 1996; Hass et al., 1974)

$$\frac{\tau}{C_{S0}} = \int_0^x \frac{dx}{r'(x)}, \quad 0 \leq x \leq x_e, \quad (8)$$

where  $\tau$  is the residence time in the reactor, and  $x$  is the substrate conversion. Eq. (8) when combined with Eq. (7) can be reduced to the following algebraic form:

$$\ln(1 - x/x_e) + k\tau a - K'_m C_{S0} x = 0. \quad (9)$$

Eq. (9), the reactor design equation, can be solved for the substrate conversion,  $x$ , at any time,  $t$ , when the reactor is set into operation at a specified feed rate, feed substrate concentration, and temperature. The substrate conversion will decrease as a result of enzyme deactivation as time goes on. This mode of operation necessitates the averaging of conversion over a certain operating period of time,  $t_f$ , beyond which the falling of conversion is no longer acceptable. Practically, the averaging of  $x$  is equivalent to mixing a product of different levels of conversion over the whole operating period. Hence, the production performance of the reactor is measured by the so called the time-averaged productivity defined as

$$\pi(T) = \left( \frac{C_{S0}}{\tau} \right) \left[ \int_0^{t_f} x(t) dt / \int_0^{t_f} dt \right] = \left( \frac{C_{S0}}{\tau} \right) \int_0^1 x(T, (\theta)) d\theta, \quad (10)$$

where  $\theta = t/t_f$ . Note that, for a given packed bed reactor and initial substrate concentration  $C_{S0}$ , the left-hand side of Eq. (9) can be written in the following functional

form  $f(x, T) = 0$ ; accordingly we can write the substrate conversion  $x$  as

$$x = x_e (1 - e^{K'_m C_{S0} x} e^{-k\tau a}). \quad (11)$$

### Optimization Method

The optimal productivity of an immobilized enzyme packed bed reactor performing reversible Michaelis–Menten kinetics with enzyme deactivation represents an optimal-control problem. This optimal productivity results from two opposing phenomena: the rate of reaction and the residual enzyme activity. As a result of temperature increase, the rate of reaction increases while the residual enzyme activity decreases. The result of these phenomena can lead to two optimal operational modes that arise in the operation of packed bed reactors using immobilized enzymes as catalyst. The first is the constant feed rate and constant conversion, where the temperature is increased with time to compensate for the loss of enzyme activity (Faqir and Abu-Reesh, 1998; Hass et al., 1974; Kim et al., 1982; Park et al., 1981). In this mode of operation, the initial temperature must be selected for each operating period, and the temperature must be gradually increased to maintain the desired conversion level. The second mode of operation is the variable conversion and constant feed rate (Faqir, 1998; Hass et al., 1974; Kim et al., 1982; Park et al., 1981; Vos and Luyben, 1993). This mode of operation is characterized by an increasing temperature–time profile starting at the lowest permissible temperature and ending with the highest physically feasible one. These temperature constraints stem from the loss of enzyme stability at high temperature and the risk of microbial contamination at low operating temperature (Illanes et al., 1992). In this operational mode, the objective is to find an optimal policy that maximizes the average conversion (productivity). This is in fact, a defined path that must be described for the operating temperature as a controllable independent variable. This is accomplished by finding the temperature functional that satisfies the necessary and sufficient conditions needed to specify the optimal temperature path. In the present work, the calculus of variations is used to find such an optimal temperature–time profile. The advantage of this approach is that once the solution is obtained it is applicable to an entire class of problems, while the numerical optimization used to find such profiles (Faqir, 1998; Kim et al., 1982; Park et al., 1981) involves sophisticated numerical algorithms.

In the present work, the optimal temperature–time policy maximizing the reactor productivity under the second mode of operation is derived. The objective is to investigate how temperature should be varied with time in order to maximize the time-averaged productivity. For a specified residence time,  $\tau$ , feed flow rate, and a

feed substrate concentration,  $C_{S0}$ , the problem of maximizing the time-averaged productivity is posed as a nonlinear optimization problem:

$$\text{Maximize}_{x,T} \left( \pi(T) = \left( \frac{C_{S0}}{\tau} \right) \int_0^1 x(T(\theta)) d\theta \right) \quad (12)$$

Subject to

$$f(x, T) = \ln(1 - x/x_e) + k\tau a - K'_m S_0 x = 0,$$

$$\frac{da}{d\theta} = -K_d t_f (1 - \sigma) a,$$

$$T^L \leq T \leq T^U, \text{ for all } \theta \in [0, 1],$$

$$0 \leq x \leq x_e, \text{ for all } \theta \in [0, 1].$$

To maximize the productivity,  $\pi(T)$ , given by Eq. (12), we make use of the calculus of variations and, in particular, by applying the disjoint policy (Denn, 1969). According to this policy, the temperature profile,  $T(\theta)$ , is selected in such a way that the integrand at each value of  $\theta$  is maximized. In other words, it is sufficient to maximize  $x(T(\theta))$  in order to find the optimum productivity  $\pi(T)$ . As a result of this policy, the necessary condition of optimality leads to the following differential-algebraic system, DAE (see Appendix 1 for the complete derivation):

$$\frac{dT}{d\theta} = \frac{\tau t_f K_d (1 - \sigma) (\alpha a x_e)}{\tau \alpha x_e a \frac{dk/dT}{k} + \left[ \frac{e^{k\tau a} - \alpha}{k} \right] \frac{dx_e}{dT} - \frac{\alpha C_{S0} x x_e}{k} \frac{dK'_m}{dT}}, \quad (13)$$

where

$$\frac{da}{d\theta} = -t_f K_d (1 - \sigma) a, \quad (14)$$

$$x = x_e (1 - \alpha(x, T) e^{-k\tau a}), \quad (15)$$

$$\text{and } \alpha(x, T) = e^{K'_m C_{S0} x},$$

with the initial conditions

$$T = T_0 \text{ and } a = 1 \text{ at } \theta = 0 \text{ with } T_L \leq T_0 \leq T_U.$$

Note that the disjoint policy has reduced the nonlinear optimization problem given by Eq. (12) into a DAE given by Eqs. (13), (14), and (15). This DAE system consists of a pair of coupled nonlinear ordinary differential equations plus a nonlinear algebraic equation, which defines completely the optimal temperature-time profiles. The initial temperature,  $T_0$ , is chosen such that the solution of Eqs. (13), (14), and (15) will satisfy the optimality condition given by Eq. (19) (see Appendix 1). One way to find  $T_0$  is to solve the DAE system such that the reactor productivity is maximized. This results into a

one-dimensional optimization problem with simple bounds on  $T_0$ , which can be stated as

$$\text{Maximize}_{T^L \leq T_0 \leq T^U} \pi(T_0). \quad (16)$$

The objective function evaluation of the one-dimensional problem requires the solution of one nonlinear algebraic equation plus two ordinary first-order differential equations. Note that numerical algorithms are well established for the solution of the above one-dimensional optimization problem given by Eq. (16) (Edgar and Himmelblau, 1988). Moreover, the disjoint policy has produced the slopes of the temperature and residual enzyme activity profiles explicitly as given by Eqs. (13) and (14). The system of equations, Eqs. (13), (14), and (15), defines completely the optimal temperature-time profiles. The residual enzyme profile is a decreasing profile with respect to time since  $0 \leq \sigma < 1$  (Chen and Wu, 1987), and the temperature profile increases with time ( $dT/d\theta > 0$ ) provided that  $K'_m$  is small which is the case when  $K_s = K_p$ . These facts are evident from Eqs. (13) and (14).

The solution of Eqs. (13), (14), and (15) that satisfy the optimality condition, the residual enzyme activity, and reactor design constraints can be found at each instant of dimensionless time  $\theta$ , specified residence time  $\tau$ , and inlet substrate concentration  $C_{S0}$ . Hence, this solution for the optimum substrate conversion  $x^*$  and operating temperature  $T^*(\theta)$  is optimal if and only if it satisfies the proposed constraints. In this way, the optimum productivity,  $\pi(T)$ , can be generated. However, at small values of  $\theta$ ,  $T^*(\theta)$  might fall below the lower temperature limit,  $T^L$ , and as  $\theta \rightarrow 1$ ,  $T^*(\theta)$  might exceed the upper limit  $T^U$ . In this case,  $T^* = \min(T^U, T^*)$  as  $\theta \rightarrow 1$ , and  $T^* = \max(T^L, T^*)$  as  $\theta \rightarrow 0$ .

Note that Eq. (15) is nonlinear in  $x$ , and hence a suitable iterative technique must be used to solve it. The fixed-point method could be used here effectively if we note that at  $K_s = K_p$ , then  $\alpha = 1$  since  $K'_m = 0$ , and so a good initial guess is obtained from Eq. (15).

The solution algorithm could be summarized as follows:

(1) Choose an initial operating temperature,  $T_0$ , at  $\theta_0$  such that  $T^L \leq T_0 \leq T^U$  and  $a(\theta_0) = 1$  at fixed operating period  $t_f$ . Compute the kinetic parameters and  $x_e$ .

(2) Use the fixed-point algorithm to solve the algebraic Eq. (15) for  $x$  using the initial guess:

$$x_0 = x_e (1 - e^{-k\tau a}).$$

(3) Solve the ordinary differential equations given by Eqs. (13) and (14) using a suitable integration algorithm (for example the 4<sup>th</sup>- and 5<sup>th</sup>-order Runge-Kutta methods) over the interval  $\theta \in [0, 1]$ . At each integration step:

(3.1) Compute the kinetic parameters and  $x_e$ ;

(3.2) Use the fixed-point algorithm to solve the algebraic Eq. (15) for  $x$  using the initial guess:  $x_0 = x_e (1 - e^{-k\tau a})$ ;

(3.3) Compare the computed  $x$  satisfying the design Eq. (9) and the critical value of  $x$  given by  $x = x_c + 1/K'_m C_{S0}$  (see Appendix 1). If they are equal, then the necessary condition for optimality is not satisfied, and hence there is no optimal temperature profile in the entire interval  $\theta \in [0, 1]$ , *STOP*, and try another value of  $t_f$ .

(4) Compute the time-averaged productivity using Eq. (10).

(5) Use quadratic interpolation as a one-dimensional search to update  $T_0$  until the optimal temperature is bracketed within an acceptable tolerance, so that the time-averaged productivity is maximized (Edgar and Himmelblau, 1988).

## NUMERICAL EXAMPLE

The isomerization of glucose to fructose by immobilized glucose isomerase (IGI) is selected as a model system to illustrate the optimal temperature–time profile. This reaction follows reversible Michaelis–Menten kinetics. Chamacho-Rubio et al., (1995) reviewed the vast literature concerning this reaction, which is considered to be the most important industrial application of immobilized enzymes. Chen and Wu (1987) developed a kinetic model for immobilized glucose isomerase with substrate protection. In the present work, the kinetic parameters for this reaction are determined using Chen’s and Wu’s (1987) set of experimental data, where they are correlated with temperature using Arrhenius equation  $K = K_0 e^{-E_a/RT}$ , where  $K$  is a generalized kinetic parameter,  $K_0$  is the pre-exponential factor, and  $E_a$  is the activation energy. The values of the obtained Arrhenius equation constants using least-squares fit are shown in Table I. The values of the kinetic parameters  $K_s$  and  $K_p$  are almost of the same order of magnitude in the range (60–80°C), and they are equal at 70.1°C (Faqir and Attarakih, 1999). In fact this is stated by Chamacho-Rubio et al., (1995) who considered  $K_s$  and  $K_p$  to be equal in magnitude. In this way the reversible Michaelis–Menten kinetics is reduced to a pseudo-first order reversible reaction, a fact that was used by several researchers before Chamacho-Rubio et al., (Roles and Tilberg, 1979; Straatsma et al., 1983; Vos and Luyben, 1993). Actually, Chamacho-Rubio et al., (1995) showed

**Table I.**  $K_0$  and  $E_a/R$  for reaction kinetic parameters (60–80°C).<sup>a</sup>

	$k_0$	$E_a/R$ [K]
$K_s$ [mol/L]	431.63	2138.0
$K_p$ [mol/L]	$1.7539 \times 10^9$	7360.94
$K_c$ [-]	385.71	1996.40
$V_s$ [mol/L·h]	$1.16968 \times 10^{10}$	7163.88
$V_p$ [mol/L·h]	$1.55 \times 10^{14}$	10469.4
$K_d$ [1/h]	$6.2717 \times 10^{23}$	20551.81

<sup>a</sup>Density of the catalyst particle used in calculation = 304.21 g/L (Abu-Reesh and Faqir, 1996, Chen and Wu, 1987).

that the experimental values of the kinetic parameters  $K_s$  and  $K_p$  were invariably close and varied randomly regardless of the operating conditions under which these values had been determined. Palazzi and Converti (1999) experimentally validated an approximate, linearized, and general model for this reaction by utilizing the approximate equality of  $K_s$  and  $K_p$ .

The typical design conditions for immobilized enzyme packed bed reactor used to convert glucose into fructose are (Illanes et al., 1992)  $C_{S0} = 2.8$  mol/L,  $T = 0.5$  and  $1.0$  h,  $T^L = 60^\circ\text{C}$ , and  $T^U = 80^\circ\text{C}$ . The factor,  $n$ , appearing in the substrate protection factor expression is found to be 0.5 for immobilized glucose isomerase enzyme (Chen and Wu, 1987). Different operating periods are used:  $t_f = 50, 100, 250, 500, 750,$  and  $1,000$  h. The optimal initial temperature,  $T_0$ , that maximizes the reactor productivity given by Eq. (10) can be found by solving Eqs. (13), (14), and (15) using the above design conditions. The solution proceeds numerically using the fixed-point iteration method, the fourth- and fifth-order Runge–Kutta methods with variable integration step, and the quadratic interpolation search algorithm (Edgar and Himmelblau, 1988).

For the purpose of method validation, the optimization problem given by Eq. (12) is solved as a nonlinear programming problem, NLP, under constant and variable feed flow rate. In the NLP formulation a piecewise continuous temperature profile with quadratic segments is used. The resulting discretized NLP is solved using GAMS software (Brooke et al., 1992).

## RESULTS AND DISCUSSION

The optimal temperature–time profiles and their corresponding reactor productivities are determined by solving Eqs. (13), (14), and (15) using MATLAB at specified feed substrate concentration  $C_{S0} = 2.8$  mol/L and at constant residence times  $\tau = 0.5$  and  $1$  h. The fixed-point iteration scheme described above is found to converge within 5 iterations per each integration step. Moreover, the necessary condition of optimality,  $(\partial f(x, T)/\partial x)_T \neq 0$  (see Appendix 1), is found to be always satisfied during all numerical examples presented in this work. This means that optimal temperature profiles exist over the entire operating periods ( $t_f = 50, 100, \dots, 1,000$  h) for the given residence times. The reactor operating time period is specified based on the characteristic life curve of the immobilized enzyme (residual enzyme activity curve). The immobilized enzyme is generally replaced before complete loss of its residual activity due to the low enzyme activity and poor reactor performance resulting from prolonged use of the enzyme at high temperatures. Therefore, the usable life of the immobilized enzyme should be equal to or less than the reactor operating period. Thus, the reactor operating time depends on the operating temperature and design criteria. In running an IGI reactor, a high reaction rate and a

**Table II.** Time-averaged productivities for  $\tau = 0.5$  h using the disjoint policy and numerical NLP.

Operating period $t_f$ (h)	Maximum average productivity under temperature-time policy $\pi$ [mol/L·h]	Maximum average productivity under constant optimum temperature policy $\pi$ [mol/L·h]	Optimum temperature $T$ (°C)
50	2.991 (2.990) <sup>a</sup>	2.955	78.5
100	2.805 (2.804) <sup>a</sup>	2.724	74.5
250	2.477 (2.478) <sup>a</sup>	2.374	69.5
500	2.200 (2.196) <sup>a</sup>	2.094	65.5
750	2.032 (2.028) <sup>a</sup>	1.930	63.5
1,000	1.914 (1.910) <sup>a</sup>	1.815	62.0

<sup>a</sup>Productivity using numerical nonlinear programming under constant and variable feed flow rate.

long operational life of the reactor are desired. At a higher operating temperature, the reaction rate is higher, but the deactivation rate of the enzyme is also higher; thus there exists a shorter reactor life. For example, the half life of IGI enzyme is 703 h when running the reactor at 60°C and 21 h at 80°C. While at a final residual enzyme activity of 0.1, the operating time will be 2,335 h and 71 h when the IGI reactor is running at 60 and 80°C, respectively. Therefore, selection of the reactor operating time depends on the relative costs of the enzyme, immobilization support and the operating costs to clean-out the reactor and recharging it with enzyme.

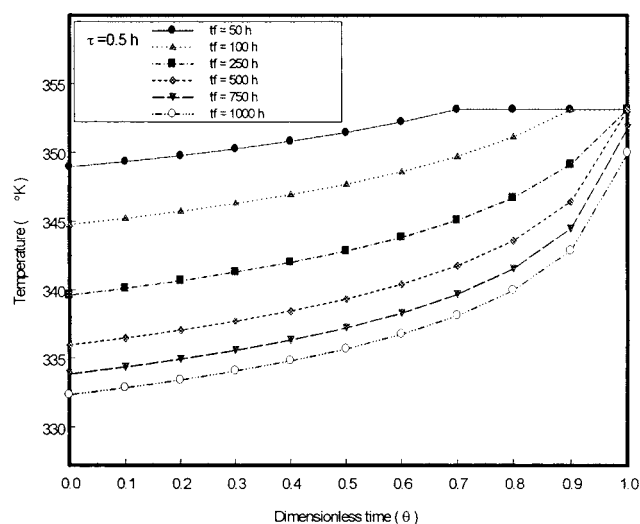
The productivities are compared to that obtained by numerical nonlinear programming under constant and variable feed flow rate at different operating periods as shown in Tables II and III. As it can be seen from the results the productivities are almost the same. Note that the more general optimization problem, where both feed flow rate and temperature would be varied with time is formulated in Appendix 2. Accordingly, the formulated problem is solved as NLP and theoretical analysis based on the disjoint policy is also performed (see Appendix 2). The results show that the more general optimization problem gives the same productivity and temperature

**Table III.** Time-averaged productivities for  $\tau = 1$  h using the disjoint policy and numerical NLP.

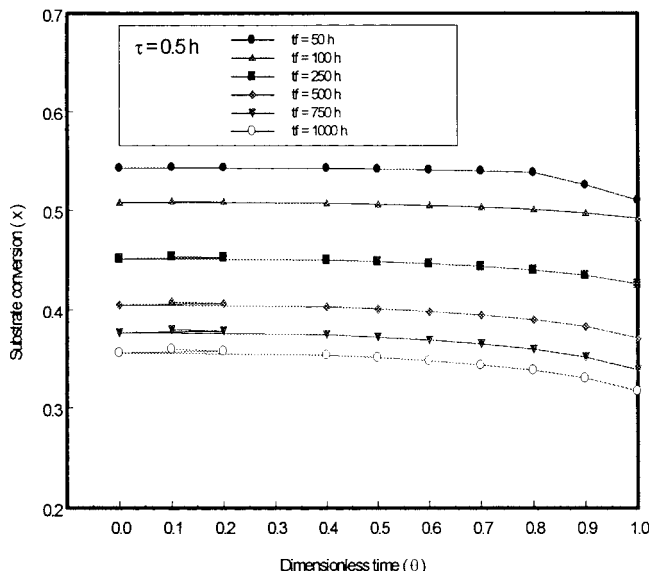
Operating period $t_f$ (h)	Maximum average productivity under temperature-time policy $\pi$ [mol/L·h]	Maximum average productivity under constant optimum temperature policy $\pi$ [mol/L·h]	Optimum temperature $T$ (°C)
50	1.593 (1.592) <sup>a</sup>	1.592	80.0
100	1.545 (1.545) <sup>a</sup>	1.528	76.5
250	1.455 (1.456) <sup>a</sup>	1.420	70.5
500	1.366 (1.364) <sup>a</sup>	1.321	66.0
750	1.304 (1.301) <sup>a</sup>	1.255	64.0
1,000	1.256 (1.253) <sup>a</sup>	1.206	62.0

<sup>a</sup>Productivity using numerical nonlinear programming under constant and variable feed flow rate.

profile to that obtained under constant feed flow rate and varying feed temperature. Also, an improvement is achieved in reactor productivity when compared to the constant optimal temperature policy (Faqr, 1998). A 5% improvement is achieved at longer operating time in comparison with 2% improvement at shorter operating periods. As it can be seen from the results in Tables II and III the productivities are almost the same when operating the reactor at low operating time periods under constant optimal temperature and variable temperature policies. It is noticed that the variable conversion policy of operation is characterized by an increasing temperature-time profiles as found previously by Park et al., (1981). Figures 1, 2, and 3 depict the temperature, conversion, and residual enzyme activity profiles. The temperature profiles hit the upper temperature bound for small operating periods, while it tends to move away from it at long operating periods. This behavior is expected since at long operating periods the immobilized enzyme could not withstand high temperatures for prolonged time without considerable loss of activity. This fact is evident from Figure 3, where the rate of enzyme deactivation increases as the dimensionless time and the operating period increase. The slope of the temperature profiles increases as the dimensionless time and the operating period increase to balance the degradation of conversion due to the loss of enzyme activity by increasing the reaction rate. This is obvious by referring to Figure 2, where the conversion tend to be initially constant and start decreasing, although not so fast, due to the previously buffering effect. This balance of conversion is clear due to the two opposing phenomena; namely the reaction rate and the enzyme activity as shown in Figure 7. The effect of reactor residence time on the operating temperature, conversion, and residual enzyme activity profiles is clear by comparing Figures 1, 2, and 3 ( $\tau = 0.5$  h) and Figures 4, 5, and 6 ( $\tau = 1.0$  h). It is found

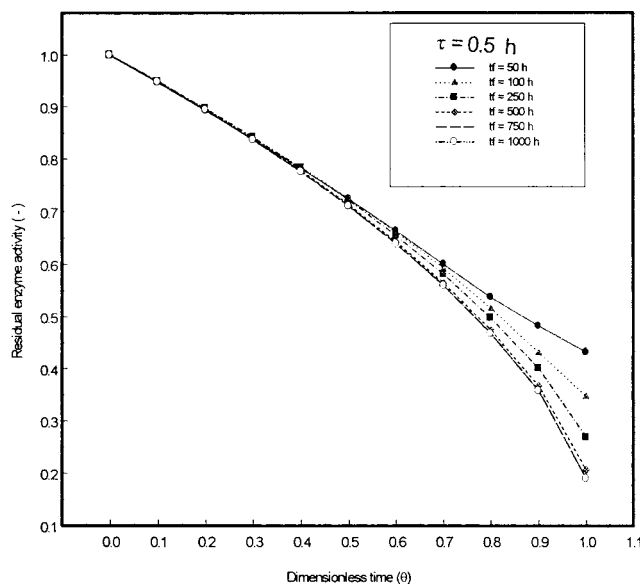


**Figure 1.** Optimal temperature profiles of glucose isomerase reactor under temperature-time policy at residence time of 0.5 h.

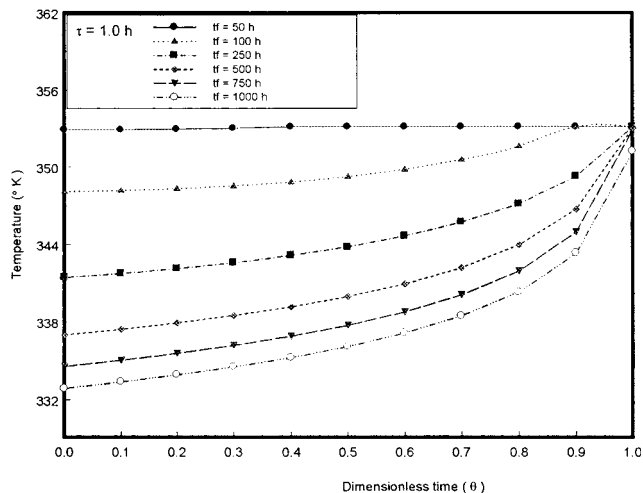


**Figure 2.** Optimal conversion profiles of glucose isomerase reactor under temperature-time policy at residence time of 0.5 h.

that due to larger residence time, the temperature profiles are shifted toward the lower temperature bound to counteract the high rates of enzyme deactivation. It is evident from Figures 2 and 5 that the optimal temperature-time policy tends to keep the conversion constant over almost 90% of the operating period. This behavior is in agreement with the necessary condition of optimality stated by Eq. (19) (see Appendix 1), which means that  $dx/d\theta = 0$ . However, after almost 90% of the operating period, the conversion starts to decrease. This is due to operating the reactor at the constant upper temperature limit, which is shown in Figures 1 and 4. In this



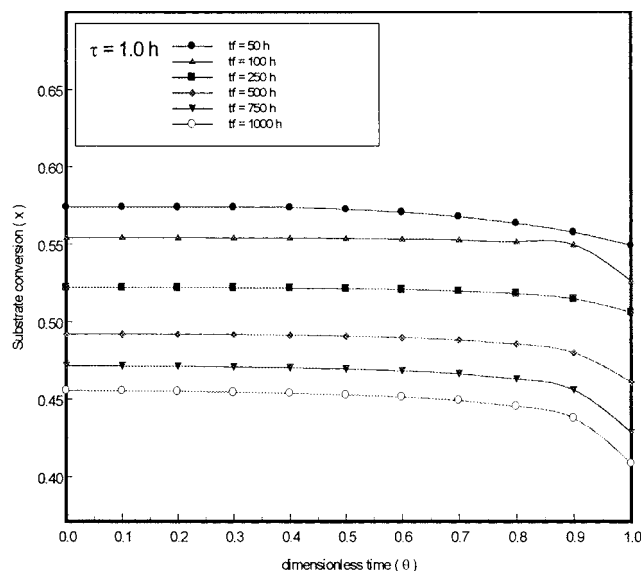
**Figure 3.** Time course of IGI enzyme deactivation of glucose isomerase reactor under optimal temperature-time policy at residence time of 0.5 h.



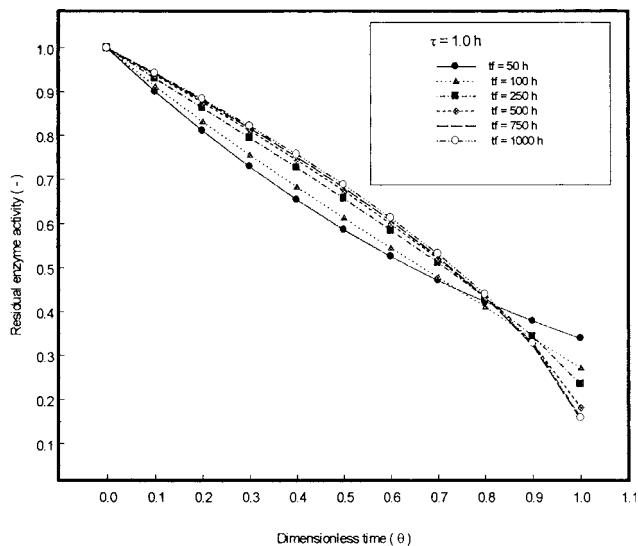
**Figure 4.** Optimal temperature profiles of glucose isomerase reactor under temperature-time policy at residence time of 1.0 h.

way, we could obtain a product with uniform composition that is practically desired.

As can be seen from Figures 1 and 4, the optimal initial temperature decreases exponentially with the operating period and increases as the reactor residence time increases. This behavior is attributed to the same reasons mentioned above. The shape of the residual enzyme activity profiles depends on the shape of the temperature profiles as shown in Figures 1 and 3 for  $\tau = 0.5$  h and in Figures 4 and 6 for  $\tau = 1.0$  h. In Figures 3 and 6 the first two residual enzyme activity profiles which correspond to low operating periods decrease exponentially with time since the corresponding temperature profiles are almost constant, Figures 1 and 4, and become constant at higher dimensionless time



**Figure 5.** Optimal conversion profiles of glucose isomerase reactor under temperature-time policy at residence time of 1.0 h.



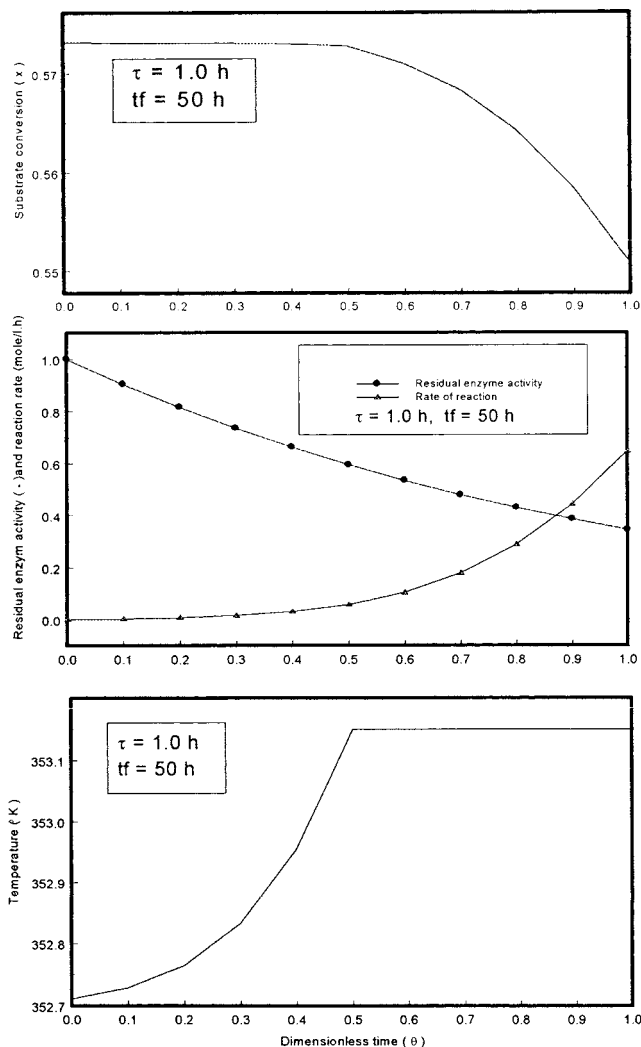
**Figure 6.** Time course of IGI enzyme deactivation of glucose isomerase reactor under optimal temperature-time policy at residence time of 1.0 h.

values. However, the rest of the temperature profiles in Figures 1 and 4 are no longer constant for all dimensionless times, thus resulting in a non-exponential residual enzyme activity decrease.

It is clear that within the numerical accuracy of the two methods (NLP and disjoint policy) that the solutions agree well in describing the optimal temperature policy that maximizes the reactor productivity as shown in Tables II and III. However, in the present work the temperature-time profiles are simply calculated by solving the two nonlinear ordinary differential equations and the nonlinear algebraic equation, which results in less computational steps and hence times. To the best of the author's knowledge, it appears that this method of solution was not tried before; instead, sophisticated nonlinear optimization techniques were used to obtain the optimal temperature control policy in such reactors. From numerical point of view, this method could be easily implemented because of its simplicity when compared to the control function discretization proposed by Cuthrell and Biegler (1987) and Faqir (1998). Here, the objective function and constraints are discretized along the operating time period. Consequently the size of the nonlinear program to solve will be affected by the number and placement of the discretized node points, which in turn will affect the numerical accuracy.

An advantage of the disjoint policy method that it results in an explicit expression for the slopes of both the temperature and the residual enzyme activity profiles. This sheds some light on the characteristics of such profiles without resorting to the numerical solutions, as is required by the other NLP numerical methods.

To account for model uncertainty, if the optimal temperature-time policy is applied to a real process, then further research and experimental work are re-



**Figure 7.** Variation of conversion, residual enzyme activity, and reaction rate due to optimal temperature-time policy of glucose isomerase reactor.

quired. In particular, further experimental work could make the obtained results very practical for industrial application.

## NOMENCLATURE

$a$	residual enzyme activity	[-]
$C$	concentration	[mol/L]
$C_{E0}$	initial concentration of active enzyme	[mol/L]
$C_S$	substrate concentration	[mol/L]
$C_{S0}$	substrate concentration at reactor inlet	[mol/L]
$E$	enzyme	[-]
$E_d$	activation energy of enzyme deactivation reaction	[J/mol]
$E_e$	activation energy of equilibrium	[J/mol]
$E_p$	activation energy of Michaelis-Menten constant for product	[J/mol]
$E_s$	activation energy of Michaelis-Menten constant for substrate	[J/mol]
$E_{vp}$	activation energy of maximum reaction rate for product	[J/mol]



$E_{vs}$	activation energy of maximum reaction rate for substrate	[J/mol]
$k$	pseudo first-order reaction rate	[1/h]
$k_1, k_{-2}$	rate constants	[L/(mol·h)]
$k_{-1}, k_2$	rate constants	[1/h]
$K_e$	equilibrium constant	[-]
$K_d$	enzyme thermal deactivation rate constant	[1/h]
$K_m$	apparent Michaelis–Menten constant	[mol/L]
$K'_m$	reciprocal of $K_m$	[L/mol]
$K_p$	Michaelis–Menten constant for product	[mol/L]
$K_s$	Michaelis–Menten constant for substrate	[mol/L]
$n$	the ratio of enzyme–substrate to free enzyme	[-]
$P$	product	[-]
$R$	ideal gas constant	[J/mol·K]
$r$	reaction rate	[mol/L·h]
$r'$	reaction rate with enzyme deactivation	[mol/L·h]
$s'$	apparent substrate concentration defined as $s' = C_{S0}(x_e - x)$	[mol/L]
$T$	temperature	[K]
$T^L$	lower temperature bound	[K]
$T^U$	upper temperature bound	[K]
$T^*$	optimum temperature	[K]
$t$	time	[h]
$t_f$	reactor operating period	[h]
$V_m$	maximum apparent reaction rate	[mol/L·h]
$V_p$	maximum reaction rate for product	[mol/L·h]
$V_s$	maximum reaction rate for substrate	[mol/L·h]
$x$	substrate conversion	[-]
$x_e$	equilibrium substrate conversion	[-]
$x^*$	optimal substrate conversion	[-]
<hr/>		
<i>Greek Symbols</i>		
$\pi$	time-averaged productivity	[mol/L·h]
$\sigma$	substrate protection factor	[-]
$\tau$	reactor residence time	[h]
$\tau^L$	lower reactor residence time bound	[h]
$\tau^U$	upper reactor residence time bound	[h]
$\theta$	dimensionless operating time	
<hr/>		
<i>Subscripts</i>		
e	equilibrium	
ES	enzyme–substrate complex	
P	product	
s	substrate	
0	initial or pre-exponential factor	

## APPENDIX 1

### Derivation of the Optimal Temperature Profile Using the Disjoint Policy

The value of the productivity,  $\pi(T)$ , depends not only on the set of variables  $x$  and  $T$  but also on an entire function  $T(\theta)$ . Let  $T^*(\theta)$  be the function that maximizes  $\pi(T)$ , then for any permissible function  $T(\theta)$ , and for any small interval  $\Delta\theta$ , we can write:

$$\int_{\theta_1}^{\theta_1 + \Delta\theta} [x(T^*(\theta)) - x(T(\theta))] d\theta \geq 0,$$

where  $\theta_1 \leq \theta \leq \theta_1 + \Delta\theta$ , with an arbitrary  $\theta_1$ . Applying the mean value theorem to the above inequality, we obtain,

$$x(T^*(\theta)) \geq x(T(\theta)) \text{ for all } \theta. \quad (17)$$

This is called the disjoint policy (Denn, 1969). The condition that is implied by Eq. (17) is as to maximize the integral given by Eq. (10), choose the profile,  $T(\theta)$ , that maximizes the integrand at each value of  $\theta$ . Applying this policy to Eq. (10), it is sufficient to maximize  $x(T(\theta))$  in order to find the optimum productivity  $\pi(T)$ . Because  $x$  is an implicit function of  $T$ , the rule of implicit differentiation is used to find  $dx/dT$  at each specified  $\theta$ , then:

$$\frac{dx}{dT} = - \left( \frac{\partial f(x, T)}{\partial T} \right)_x / \left( \frac{\partial f(x, T)}{\partial x} \right)_T. \quad (18)$$

For  $dx/dT$  to vanish we must have

$$\left( \frac{\partial f(x, T)}{\partial T} \right)_x = 0, \quad (19)$$

provided that  $(\partial f(x, T)/\partial x)_T \neq 0$ . When this is applied to Eq. (9), one could obtain  $(\partial f(x, T)/\partial x)_T = -[K'_m C_{S0} + 1/(x_e - x)]$ . Note that  $(\partial f(x, T)/\partial x)_T$  is a function of substrate conversion, since  $K'_m$  and  $x_e$  are functions of temperature only. The expression  $(\partial f(x, T)/\partial x)_T$  is different from zero for the following cases: when  $K_s = K_p$ , it follows that  $K'_m = 0$ ; and when  $K_p > K_s$ , it follows that  $K'_m > 0$ . The only possible case which might make  $(\partial f(x, T)/\partial x)_T$  equal to zero is when  $K'_m < 0$  which corresponds to  $K_p < K_s$ . Accordingly, the corresponding critical value of  $x$  which makes  $(\partial f(x, T)/\partial x)_T = 0$  is given by  $x = x_e + 1/K'_m C_{S0}$ . If it happens that  $(\partial f(x, T)/\partial x)_T = 0$  for certain values of  $K'_m < 0$ , then the necessary condition of optimality given by Eq. (19) will not be satisfied, and hence an optimal solution does not exist. Note that by the chain rule we could write  $dx/d\theta = (dT/d\theta)(dx/dT)$ . Because Eq. (19) states the necessary condition of optimality, then it follows that  $dx/d\theta = 0$  for all  $T(\theta) \leq T^U$ .

The expression of  $(\partial f(x, T)/\partial T)_x$  is also obtained from the expansion of Eq. (9), which results in the following nonlinear algebraic equation:

$$\begin{aligned} \left( \frac{\partial f(x, T)}{\partial T} \right)_x &= (e^{k\tau a} - \alpha) \frac{dx_e}{dT} + \alpha x_e \frac{d}{dT} (k \cdot a) \\ &\quad - \alpha C_{S0} x_e \frac{dK'_m}{dT} = 0, \end{aligned} \quad (20)$$

where

$$\frac{d}{dT} (k \cdot a) = k \frac{da}{dT} + a \frac{dk}{dT}, \quad (21)$$

$$\frac{dK'_m}{dT} = \frac{1}{RT^2} \frac{g_1 \times g_3 - g_2(K_{sp} - 1)(K_e + 1)}{g_1^2}, \quad (22)$$

$$g_1 = K_p + K_{ep} + C_{S0}(K_e + K_{sp}); \quad g_2 = K_p E_p + K_{ep} E_{ep} + C_{S0}(K_e E_e + K_{sp} E_{sp});$$

$$g_3 = (K_{sp} - 1)K_e E_e + (K_e + 1)(K_{sp} E_{sp}); E_{sp} = E_p - E_s; \\ E_{ep} = E_e + E_p;$$

$$K_{ep} = K_e K_p; K_{sp} = K_p / K_s;$$

and

$$\frac{dk}{dT} = \frac{f_1 \times f_2 - (1 + K_e) \times f_3 V_s (1 + K_e)}{f_1^2 RT^2}, \quad (23)$$

where

$$f_1 = K_{se} + K_{se2} + C_{s0} K_{spe} + C_{s0} K_e; f_2 = E_{vs} (1 + K_e) \\ + 2K_e E_e;$$

$$f_3 = K_{se} E_{se} + K_{se2} E_{se2} + C_{s0} (K_e E_e + K_{spe} E_{spe}); \\ E_{se} = E_s + E_e; E_{se2} = E_s + 2E_e;$$

$$E_{spe} = E_s + 2E_e - E_p; K_{se} = K_s K_e;$$

$$K_{se2} = K_s K_e^2; K_{spe} = \frac{K_s K_e^2}{K_p}.$$

$$\frac{dx_e}{dT} = \frac{E_e}{RT^2} \frac{x_e^2}{K_e};$$

and

$$\alpha(x, T) = e^{K_m C_{s0} x}$$

Now, by making use of the chain rule:  $da/d\theta = (dT/d\theta)(da/dT)$ , and by eliminating  $da/dT$  and  $da/d\theta$  between Eqs. (4), (20), and (21) we can obtain the desired result:

$$\frac{dT}{d\theta} = \frac{\tau t_f K_d (1 - \sigma) (\alpha x_e)}{\tau \alpha x_e a \frac{dk/dT}{k} + \left[ \frac{e^{k\tau a} - \alpha}{k} \right] \frac{dx_e}{dT} - \frac{\alpha C_{s0} x_e dK_m}{k dT}},$$

$$\frac{da}{d\theta} = -t_f K_d (1 - \sigma) a,$$

$$x = x_e (1 - \alpha(x, T) e^{-k\tau a}),$$

with the initial conditions

$$T = T_0 \text{ and } a = 1 \text{ at } \theta = 0 \text{ with } T^L \leq T_{s0} \leq T^U.$$

## APPENDIX 2

### General Optimization Problem Formulation

For a given packed bed reactor, this optimization problem corresponds to the case where both flow rate and temperature would be varied with time. In this case the conversion  $x$  is now a function of two undetermined profiles, namely  $x(t)$  and  $\tau(t)$ . Accordingly, the reactor productivity can be written as  $\pi = C_{s0} \int_0^1 \frac{x(T(\theta), \tau(\theta))}{\tau(\theta)} d\theta$ . Let  $\phi = \frac{x(T(\theta), \tau(\theta))}{\tau(\theta)}$ , then the general optimization problem could be written as

$$\text{Maximize}_{x, T, \tau} \left( \pi(T) = C_{s0} \int_0^1 \phi(T(\theta), \tau(\theta)) d\theta \right),$$

subject to the reactor design equation, Eq. (9), residual enzyme activity, Eq. (4); and  $T^L \leq T \leq T^U$ ;  $0 \leq x \leq x_e$ ; and bounds on the reactor residence time  $\tau^L \leq \tau \leq \tau^U$ .

By applying the disjoint policy concept for the above problem, in order to maximize  $\pi$ , it is sufficient to set

$$(\partial\phi/\partial T)_\tau = 0, \quad (24)$$

$$(\partial\phi/\partial\tau)_T = 0. \quad (25)$$

Note that the condition given by Eq. (24) is already derived (see Appendix 1), and the second condition given by Eq. (25) could now be derived for the approximate case of pseudo first-order reversible reaction which corresponds to the case when  $K_p = K_s$ . In this case the conversion  $x$  is given by  $x = x_e (1 - e^{-k\tau a})$ . Accordingly we could obtain the following expression:

$$(\partial\phi/\partial\tau)_T = \frac{x_e}{\tau^2} ((1 + ka\tau)e^{-ka\tau} - 1). \quad (26)$$

As can be seen from Eq. (26), as  $\tau$  goes to 0 the right-hand side goes to  $(-x_e (ka)^2/2)$ , and as  $\tau$  goes to infinity it approaches zero. This means that the function  $\phi$  is monotonically decreasing function with respect to  $\tau$ . So it takes a maximum value only at the lower bound  $\tau^L$ . This in turn states that the optimal residence time profile must be constant with time and be held at its lower bound.

Although the condition given by Eq. (25) is applied to the approximate reaction rate, it is applicable to the exact reaction rate by applying the chain rule, as was done in deriving the condition given by Eq. (24).

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