Optimal Design of a Series of CSTRs Performing Reversible Michaelis-Menten Reaction under Specified Temperature Mode

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Abstract A mathematical model is developed for optimal design of a given number of ideal CSTRs operated under specified temperature mode to achieve a certain degree of conversion. The temperature mode of operation for the reactors in series is increasing, decreasing or isothermal. For a selected temperature mode, the absolute temperature difference between the first reactor and the last one is 5, 10 or 20 ^{o}C. The CSTRs operate under steady state conditions and the flow rate throughout the series is constant. The reaction kinetics follows reversible Michaelis-Menten mechanism, while the enzyme i.e. catalyst is soluble and obeys irreversible first order deactivation. The optimal design problem is formulated as an unconstrained minimization problem. The corresponding objective function is set to minimize the total residence time of the reactors in series. As a case study, the isomerization of glucose syrup to fructose, which follows reversible Michaelis-Menten kinetics, is selected. It is found that the optimum total residence time in the presence of enzyme deactivation is almost the same as that without deactivation. And this is, because of a slight drop of glucose isomerase activity.

Keywords: CSTRs Design, Reversible Michaelis-Menten, Enzyme Deactivation, Optimization

التصميم الأمثل لمفاعلات الخزان المستمر المتصلة على التوالي لأجراء تفاعل منعكس (ميكاليز- مينتين) باستخدام نمط حراري محدد.

جمال يونس عبد القادر ابراهيم؛ نعيم محمد الفقير

يهدف هذا البحث إلى وضع نموذج رياضي لإجراء التصميم الأمثل لعدد من مفاعلات الخزان المستمر المثالية المتصلة على التوالي تعمل باستخدام نمط حراري محدد من أجل تحقيق تحول كيماوي معين. النمط الحراري المستخدم لتشغيل هذه المفاعلات هو تدرج حراري متزايد ومتناقص وثابت. لكل نمط حراري سواء كان متزايد اومتناقص استخدم فرق في درجات الحرارة بين المفاعل الأول والأخير 20°م، 10°م ، 5°م. هذه المفاعلات تشغل تحت ظروف الثبات بالنسبة للزمن ومعدل التدفق خلالها, بينما المادة المتفاعلة تستهلك كيماوياً حسب التفاعل المنعكس (ميكاليز- مينتين) بينما فاعلية الأنزيم الذائب في وسط التفاعل السائل نمط حسب اقتران من الدرجة الأولى. الاقتران الرئيسي في عملية المفاضلة الرياضية غير المقيدة يتمثل في إيجاد القيمة الصغرى لزمن المكوث الكلي المثالي للمفاعلات المتصلة على التوالي. وقع الاختيار على تفاعل تحول الجلوكوز بيوكيميائياً إلى فركتوز كحالة دراسية من أجل إجراء الحسابات عددياً. هذا التفاعل يعتبر أحد أهم تفاعلات (ميكاليز- مينتين) المنعكسة حيث وجد لهذا التفاعل بالذات ان زمن المكوث الكلي المثالي للمفاعلات في حالة اعتبار الهبوط في فاعلية الأنزيم الذائب وعدم اخذها بعين الاعتبار تقريبا متساوي لكلا الحالتين.و ذلك بسبب إ نخفاض بسيط في فاعلية الأنزيم الذائب.

1. Introduction

Great attention has been paid to the design and performance of continuous stirred tank reactors (CSTRs) due to the absence of concentration and temperature gradients within these ideal CSTRs. In addition to simple control, CSTR is simple to construct and can handle large throughput feedstocks. This implies that a CSTR is economically feasible [Malcata 1989; Malcata and Cameron, 1992; Lopes and Malcata, 1993; Abu-Reesh, 1996; and Faqir and Abu-Reesh, 1998; Faqir and Attarakih, 1999; Abu-Reesh, 2005]. Reactor performance of a CSTR involves the determination of optimum operating conditions required to improve operational economics and product purity. While optimization of reactor design is related to the determination of the capacity of a CSTR or more reactors in the series required to achieve a specified conversion such that an objective function based on cost or capacity is optimized.

Several literature references are available on the optimal design of a series of CSTRs performing biochemical, liquid phase reaction using soluble enzyme in the liquid phase under steady state conditions [Luyben and Tramper, 1982; Malcata and Cameron, 1992; Lopes and Malcata, 1993; Paiva and Malcata 1993; Abu-Reesh, 1996; Faqir and Attarakih, 1999]. Most of the work on the optimum design of CSTRs in series assumes isothermal mode of operation [Malcata and Cameron, 1992; Lopes and Malcata, 1993; Abu-Reesh, 1996; Faqir and Attarakih, 1999; Abu-Reesh, 2005]. An attempt is made by Paiva and Malcata (1993) to study the effect of temperature on the optimal design of a series of CSTRs performing an enzyme-catalyzed biochemical reaction. The reaction kinetics obeys irreversible Michaelis-Menten mechanism and catalyzed by soluble enzyme in the liquid phase. The enzyme undergoes an irreversible first order thermal deactivation. A suboptimal design is obtained, which is limited only to two reactors in the series.

For enzyme-catalyzed biochemical reaction the enzyme may decay as a result of binding inhibitory and poisonous materials, as well as products, to the enzyme itself. In addition to that, thermal deactivation may take place. The rate of enzyme-catalyzed reactions increases with temperature up to a certain limit, above which, enzyme denaturation may occur. Depending on the exposure time and temperature to which the enzyme is subjected, thermal deactivation of enzyme may be reversible or irreversible [Shuler and Kargi, 1992]. The fact that the enzyme is often subjected to thermal deactivation, the effect of temperature on the design of actual reactor series must be taken into account. This fact is reflected on the residence time of the reactor and consequently in the design of such reactors (see equation (19)).

This paper, based on a master thesis of Ibrahim (2000), deals with the optimal design of a given number of CSTRs connected in series. The reactors are operated under a specified temperature mode to achieve a certain overall substrate conversion. The design equations are derived in terms of intermediate substrate concentrations, operating temperature, enzyme deactivation and the kinetic parameters within each reactor. The reactor design is achieved for a constant volumetric flow rate through the series, and under steady state, nonisothermal conditions. Based on the developed expressions for residence times of each reactor under a specified temperature operation mode, the optimum design is formulated as an unconstrained minimization problem. The design objective function is formulated in terms of the residence time of each reactor and is set to minimize the total residence time of the series. To obtain the minimum total residence time, the necessary conditions of optimality are used. Where a set of highly nonlinear algebraic equations is obtained. This set of equations is derived analytically and solved numerically using the Numerical Algorithms Group (NAG) library. For a local minimum total residence time, the positive definiteness of

the Hessian matrix at the obtained solution is tested numerically by evaluating its corresponding eigenvalues.

2. Mathematical Modeling

By applying material balances on active enzyme and substrate the design equations are derived.

2.1 Rate of Reaction

The reaction, which obeys a reversible Michaelis-Menten kinetics and takes place in the i-th CSTR, can be represented by the following mechanism [Segel, 1975; Bailey and Ollis, 1986]:

$$S + E \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} ES \underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}} P + E \tag{1}$$

The reaction rate of the reversible enzymatic conversion of substrate S to product P, which takes place in the i-th reactor under the assumption of pseudo-steady state, is given by [Segel, 1975; Bailey and Ollis, 1986]:

$$R_i = -\frac{dC_{S,i}}{dt} = \frac{dC_{P,i}}{dt} = \frac{\left(\frac{V_{S,i}}{K_{S,i}}\right)C_{S,i} - \left(\frac{V_{P,i}}{K_{P,i}}\right)C_{P,i}}{1 + \left(\frac{C_{S,i}}{K_{S,i}}\right) + \left(\frac{C_{P,i}}{K_{P,i}}\right)} \tag{2}$$

where

$$V_{S,i} = K_{2,i}C_{E,i} \tag{3}$$

$$V_{P,i} = K_{-1,i}C_{E,i} \tag{4}$$

$$K_{S,i} = \frac{K_{-1,i} + K_{2,i}}{K_{1,i}} \tag{5}$$

$$K_{P,i} = \frac{K_{-1,i} + K_{2,i}}{K_{-2,i}} \tag{6}$$

Note that the above kinetic parameters depend on the operating temperature in the respective reactor. The maximum reaction rates for both substrate and product depend also on the active enzyme concentration in that reactor. For constant-activity enzyme, we can write:

$$V_{S,i} = K_{2,i} C_{E,0} \tag{7}$$

$$V_{P,i} = K_{-1,i} C_{E,0} \tag{8}$$

By using stoichiometry and mathematical manipulations the rate of reaction in the i-th CSTR given by equation (2) can be reduced to the following reversible Michaelis-Menten kinetics [Segel, 1975]:

$$R_i = \frac{V_{m,i}\left(C_{S,i} - C_{S,e,i}\right)}{K_{m,i} + \left(C_{S,i} - C_{S,e,i}\right)} \tag{9}$$

where

$$V_{m,i} = \frac{V_{S,i} K_{P,i}}{K_{P,i} - K_{S,i}} \left(1 + \frac{1}{K_{e,i}}\right) \tag{10}$$

$$K_{m,i} = \frac{K_{S,i} K_{P,i}}{K_{P,i} - K_{S,i}} \left[1 + \left(\frac{K_{e,i}}{K_{P,i}} + \frac{1}{K_{S,i}}\right) C_{S,e,i}\right] \tag{11}$$

$$K_{e,i} = \frac{C_{P,e,i}}{C_{S,e,i}} = \frac{V_{S,i} K_{P,i}}{V_{P,i} K_{S,i}} \tag{12}$$

2.2 Material Balance on Active Enzyme

Since the enzyme does not consume chemically, the total concentration of the enzyme, active and inactive, is constant. The active enzyme concentration in the i-th reactor is decreasing with time, while the inactive concentration is increasing. For irreversible first order enzyme deactivation, the residual activity of the enzyme out of the i-th reactor is given by [Malcata, 1990; Moreira and Malcata, 1996]:

$$A_i = \frac{C_{E,i}}{C_{E,0}} = \frac{1}{\prod_{j=1}^{i}\left(1+\tau_j K_{d,j}\right)} \tag{13}$$

where τ_j is the residence time in the j-th reactor, and K_{dj} is the kinetic constant associated with the deactivation of enzyme in the j-th reactor which depends on temperature according to the Arrhenius law $k_d = k_{d0}e^{-E_a/RT}$.

2.3 Material Balance on Substrate

The reversible Michaelis-Menten rate of reaction, which takes into account enzyme deactivation, can be derived by eliminating the equilibrium constant, K_e , from equation (10) by using equation (12) to get:

$$V_{m,i} = \frac{V_{S,i}K_{P,i} + V_{P,i}K_{S,i}}{K_{P,i} - K_{S,i}} \tag{14}$$

by substituting equations (3) to (6) in equation (14) and performing mathematical manipulations [Ibrahim, 2000] we get,

$$V_{m,i} = K_{v,i}C_{E,i} = \left(\frac{K_{1,i}K_{2,i} - K_{-1,i}K_{-2,i}}{K_{1,i} - K_{-2,i}}\right)C_{E,i} \tag{15}$$

Defining $V_{mo,i}$ as the counterpart of $V_{m,i}$ in the absence of enzyme deactivation as

$$V_{mo,i} = K_{v,i}\ C_{E,0} \tag{16}$$

Substituting equation (16) in equation (15) gives

$$V_{m,i} = V_{mo,i}\frac{C_{E,i}}{C_{E,0}} \tag{17}$$

Substituting equation (17) in equation (9) yields

$$R_i = \frac{V_{mo,i}\left(C_{S,i} - C_{S,e,i}\right)}{K_{m,i} + \left(C_{S,i} - C_{S,e,i}\right)}\frac{C_{E,i}}{C_{E,0}} \tag{18}$$

The substrate material balance on the i-th CSTR under steady state condition and constant volumetric flow rate can be written as $\tau_i = \frac{C_{S,i-1} - C_{S,i}}{R_i}$. Using the rate expression given by equation (18) yields

$$\frac{1}{\tau_i} = \frac{V_{mo,i}\left(C_{S,i} - C_{S,e,i}\right)}{\left(C_{S,i-1} - C_{S,i}\right)\left(K_{m,i} + \left(C_{S,i} - C_{S,e,i}\right)\right)} \frac{C_{E,i}}{C_{E,0}} \tag{19}$$

Defining $\Phi_{S,i} = \frac{C_{S,i}}{C_{S,0}}$; $\Phi_{S,e,i} = \frac{C_{S,e,i}}{C_{S,0}}$; $K_{mn,i} = \frac{K_{m,i}}{C_{S,0}}$; $\gamma_{mo,i} = \frac{V_{mo,i}}{C_{S,0}}$ and substituting equation (13) in equation (19) gives [Ibrahim, 2000]:

$$\tau_i = \frac{1}{\gamma_{mo,i}} \frac{\left[K_{mn,i} + (\Phi_{S,i} - \Phi_{S,e,i})\right](\Phi_{S,i-1} - \Phi_{S,i})\left[\prod_{j=1}^{i}(1 + \tau_j K_{d,j})\right]}{(\Phi_{S,i} - \Phi_{S,e,i})} \tag{20}$$

This expression gives the residence time of the i-th CSTR as a function of the kinetic parameters, the substrate concentrations of both inlet and outlet streams of the i-th reactor, the enzyme deactivation constant and the residence time of all preceding reactors. By defining the normalized deactivation rate constant of the enzyme as $\varepsilon_i = K_{d,i} / \gamma_{mo,i}$ and performing mathematical manipulations [Ibrahim, 2000], the design equation of the i-th CSTR is derived explicitly. This design equation of the i-th CSTR is given by:

$$\tau_i = \frac{\frac{1}{\gamma_{mo,i}} \frac{\left[K_{mn,i} + (\Phi_{S,i} - \Phi_{S,e,i})\right]\left[\Phi_{S,i-1} - \Phi_{S,i}\right]}{\Phi_{S,i} - \Phi_{S,e,i}}}{1 - \sum_{j=1}^{i} \varepsilon_j \frac{\left[K_{mn,i} + (\Phi_{S,j} - \Phi_{S,e,i})\right]\left[\Phi_{S,j-1} - \Phi_{S,j}\right]}{\Phi_{S,j} - \Phi_{S,e,i}}} \tag{21}$$

where ε_j stands for the normalized deactivation kinetic constant of the enzyme in the j-th reactor as defined above.

It is to be noted that the residence time of the i-th reactor given by equation (21) is a function of the kinetic parameters, initial concentration of substrate and substrate concentrations of the i-th and all preceding reactors.

2.4 Optimization of a Series of N CSTRs in the Presence of Enzyme Deactivation

For a specified initial substrate concentration, an overall conversion, and a given number of CSTRs in series, N, the derived design equations are optimized for a specified temperature mode to get the minimum total residence time. The objective function is formulated in terms of the residence time of each reactor and it is given by:

$$Minimize\ \ \tau_T = \sum_{i=1}^{N} \tau_i = \tau_1 + \tau_2 + ... + \tau_N \qquad (22)$$

For unconstrained minimum overall residence time, $\tau_{T,}$ the necessary and sufficient conditions for the above objective function are given by:

(1) For Φ_S^* to be a stationary point it is necessary that, the gradient of $\tau_T(\Phi_S)$ vanishes at Φ_S^*, i.e. $\nabla \tau_T(\Phi_S^*) = 0$.

(2) For Φ_S^* to be a local optimum it is sufficient that, the Hessian matrix, $H(\Phi_S^*)$, is positive definite.

Where Φ_S is a vector of (N-1) dimensionless intermediate substrate concentrations. One of the tests which can be used to verify that, the Hessian matrix, $H(\Phi_S^*)$, is positive definite [Edgar and Himmelblau, 1989], is that all the eigenvalues of the Hessian matrix at the optimum solution should be positive.

The first derivatives of the objective function are obtained by differentiating τ_T, with respect to the intermediate dimensionless concentrations of substrate, $\Phi_{S,j}$, namely

$$\frac{\partial \tau_T}{\partial \Phi_{S,j}} = \frac{\partial}{\partial \Phi_{S,j}}\left(\sum_{i=1}^{N} \tau_i\right) \qquad \text{for } j = 1, \ldots, N\text{-}1 \qquad (23)$$

by performing the differentiation analytically, the following expressions are obtained for the first order derivatives of the design equations [Ibrahim, 2000]:

For i = 1, 2, …., N

For j = 1, 2, … N-1

$$\frac{\partial \tau_T}{\partial \Phi_{S,j}} = \frac{\partial}{\partial \Phi_{S,j}}\left(\sum_{i=1}^{N} \tau_j\right) = -\frac{1}{\gamma_{mo,i}} \frac{\left(1 + K_{mn,i}\dfrac{\Phi_{S,i-1} - \Phi_{S,e,i}}{\left(\Phi_{S,i} - \Phi_{S,e,i}\right)^2}\right)}{1 - \sum_{j=1}^{i} \varepsilon_j \dfrac{\left[K_{mn,j} + \left(\Phi_{S,j} - \Phi_{S,e,j}\right)\right]\left[\Phi_{S,j-1} - \Phi_{S,j}\right]}{\Phi_{S,j} - \Phi_{S,e,j}}} \left[1 + \frac{\varepsilon_i \dfrac{\left[K_{mn,i}\left(\Phi_{S,i} - \Phi_{S,e,i}\right)\right]\left[\Phi_{S,i-1} - \Phi_{S,i}\right]}{\Phi_{S,i} - \Phi_{S,e,i}}}{1 - \sum_{j=1}^{i} \varepsilon_j \dfrac{\left[K_{mn,j} + \left(\Phi_{S,j} - \Phi_{S,e,j}\right)\right]\left[\Phi_{S,j-1} - \Phi_{S,j}\right]}{\Phi_{S,i} - \Phi_{S,e,i}}}\right]$$

$$+ \frac{\dfrac{1}{\gamma_{mo,i+1}}\left(1 + \dfrac{K_{mn,i+1}}{\Phi_{S,i+1} - \Phi_{S,e,i+1}}\right)\left[1 - \sum_{j=1}^{i} \varepsilon_j \dfrac{\left[K_{mn,j} + \left(\Phi_{S,j} - \Phi_{S,e,j}\right)\right]\left[\Phi_{S,j-1} - \Phi_{S,j}\right]}{\Phi_{S,j} - \Phi_{S,e,j}} - \varepsilon_i\left[\Phi_{S,i} - \Phi_{S,i+1}\right]\left(1 + K_{mn,i}\dfrac{\Phi_{S,i-1} - \Phi_{S,e,i}}{\left(\Phi_{S,i} - \Phi_{S,e,i}\right)^2}\right)\right]}{\left(1 - \sum_{j=1}^{i+1} \varepsilon_j \dfrac{\left[K_{mn,j} + \left(\Phi_{S,j} - \Phi_{S,e,j}\right)\right]\left[\Phi_{S,j-1} - \Phi_{S,j}\right]}{\Phi_{S,j} - \Phi_{S,e,j}}\right)^2}$$

$$- \frac{\varepsilon}{\gamma_{mo}} \sum_{k=2}^{N-i} \frac{\left[\left(1 + K_{mn}\dfrac{\Phi_{S,i-1} - \Phi_{S,e}}{\left(\Phi_{S,i} - \Phi_{S,e}\right)^2}\right) - \left(1 + \dfrac{K_{mn}}{\Phi_{S,i+1} - \Phi_{S,e}}\right)\right]\left[\Phi_{S,i+k-1} - \Phi_{S,i+k}\right]\left[K_{mn} + \left(\Phi_{S,i+1} - \Phi_{S,e}\right)\right]}{\left(\Phi_{S,i+K} - \Phi_{S,e}\right)\left[1 - \varepsilon \sum_{j=1}^{i+K} \dfrac{\left[K_{mn} + \left(\Phi_{S,j} - \Phi_{S,e}\right)\right]\left[\Phi_{S,j-1} - \Phi_{S,j}\right]}{\Phi_{S,j} - \Phi_{S,e}}\right]^2}$$

(24)

Note that, i is determined by j which is the subscript of the variable that differentiation is performed with respect to.

The elements of the Hessian matrix, which represent the second order derivatives of the objective function with respect to the intermediate dimensionless concentrations of substrate, are found numerically. This is done by finding the Jacobian matrix of the first order partial derivatives to get:

$$H(\Phi_S)=\begin{bmatrix} \frac{\partial}{\partial\Phi_{S,1}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,1}}\right) & \frac{\partial}{\partial\Phi_{S,1}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,2}}\right) & \cdots & \frac{\partial}{\partial\Phi_{S,1}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,N-1}}\right) \\ \frac{\partial}{\partial\Phi_{S,2}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,1}}\right) & \frac{\partial}{\partial\Phi_{S,2}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,2}}\right) & \cdots & \frac{\partial}{\partial\Phi_{S,2}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,N-1}}\right) \\ \vdots & \vdots & & \vdots \\ \frac{\partial}{\partial\Phi_{S,N-1}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,1}}\right) & \frac{\partial}{\partial\Phi_{S,N-1}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,2}}\right) & \cdots & \frac{\partial}{\partial\Phi_{S,N-1}}\left(\frac{\partial\tau_T}{\partial\Phi_{S,N-1}}\right) \end{bmatrix} \quad (25)$$

To find the optimum solution, we set $(\partial\tau_T / \partial\Phi_{S,j}) = 0$ for j = 1, 2, … N-1, this yields a system of (N-1) nonlinear algebraic equations which is highly nonlinear. This solution should be checked for optimality by determining the positive definiteness of the Hessian matrix of dimension (N-1xN-1) at this solution.

2.5 Optimization of a Series of N CSTRs in the Absence of Enzyme Deactivation

If the rate of deactivation of the enzyme is negligible compared with the overall rate of the enzyme-catalyzed reaction, then

$$\varepsilon_j = \varepsilon_i = \varepsilon_{i+1} = 0 \quad (26)$$

substituting equation (26) in equation (24) gives

$$\frac{\partial\tau_T}{\partial\Phi_{S,j}} = -\frac{1}{\gamma_{mo,i}}\left(1+K_{mn,i}\frac{\Phi_{S,i-1}-\Phi_{S,e,i}}{(\Phi_{S,i}-\Phi_{S,e,i})^2}\right)+\frac{1}{\gamma_{mo,i+1}}\left(1+\frac{K_{mn,i+1}}{\Phi_{S,i+1}-\Phi_{S,e,i+1}}\right) \quad (27)$$

where i = 1,2, ... N and j = 1,2, ... N-1

To optimize, $\frac{\partial\tau_T}{\partial\Phi_{S,j}}$ should be set to zero and $\Phi_{S,i}$ should be replaced by $\Phi^*_{S,i}$,

therefore

$$\frac{1}{\gamma_{mo,i}}\left(1+K_{mn,i}\frac{\Phi_{S,i-1}-\Phi_{S,e,i}}{(\Phi^*_{S,i}-\Phi_{S,e,i})^2}\right)=\frac{1}{\gamma_{mo,i+1}}\left(1+\frac{K_{mn,i+1}}{\Phi_{S,i+1}-\Phi_{S,e,i+1}}\right) \quad (28)$$

Multiplying both sides of equation (28) by $\gamma_{mo,i}$ gives

$$1 + K_{mn,i} \frac{\Phi_{S,i-1} - \Phi_{S,e,i}}{\left(\Phi^{*}_{S,i} - \Phi_{S,e,i}\right)^2} = \frac{\gamma_{mo,i}}{\gamma_{mo,i+1}} \left(1 + \frac{K_{mn,i+1}}{\Phi_{S,i+1} - \Phi_{S,e,i+1}}\right) \tag{29}$$

Define $\gamma_{i} = \frac{\gamma_{mo,i}}{\gamma_{mo,i+1}}$, $\Phi^{*}_{i} = \Phi^{*}_{S,i} - \Phi_{S,e,i}$ and $\Phi_{i+1} = \Phi_{S,i+1} - \Phi_{S,e,i+1}$.

Equation (29) becomes:

$$\frac{(1-\gamma_i)}{K_{mn,i}} + \frac{\Phi_{S,i-1} - \Phi_{S,e,i}}{\Phi^{*2}_{i}} = \gamma_i \frac{K_{mn,i+1}}{K_{mn,i}} \frac{1}{\Phi_{i+1}} \tag{30}$$

Define also $\alpha_i = \frac{(1-\gamma_i)}{K_{mn,i}}$, $\delta_i = \frac{K_{mn,i}}{K_{mn,i+1}}$ and $\beta_i = \frac{\gamma_i}{\delta_i}$. Equation (30) yields

$$(\beta_i - \alpha_i \Phi_{i+1})\Phi^{*2}_{i} = \Phi_{i+1}(\Phi_{S,i-1} - \Phi_{S,e,i}) \tag{31}$$

3. Numerical Example

An important enzymatic reaction, the isomerization of glucose syrup to fructose syrup using isomerase enzyme, is selected as a case study. This reaction follows a reversible Michaelis-Menten kinetics [Illanes et al., 1992]. For which the kinetic parameters are available in the literature for temperature range of 60-80 ^{o}C [Faqir and Abu-Reesh, 1998] and are given as follows:

$$K_P = 1.7539 \times 10^{9} e^{-7360.939/T_k} \tag{32}$$

$$K_S = 431.6294\, e^{-2138.035/T_k} \tag{33}$$

$$V_S = 1.1696798 \times 10^{10}\, e^{-7163.882/T_k} \tag{34}$$

$$V_P = 1.5503 \times 10^{14}\, e^{-10469.39/T_k} \tag{35}$$

$$K_d = 6.2716819 \times 10^{23}\, e^{-20551.81/T_k} \tag{36}$$

$$K_e = 385.7142\, e^{-1996.4/T_k} \tag{37}$$

For the optimal design of a series of CSTRs, a typical feed concentration of glucose $C_{S,0}$ = 2.8 gmol/L and an overall substrate conversion of 90% of the equilibrium are used in the computations [Abu-Reesh and Faqir, 1996].

By considering the purity of the product is determined by the overall conversion, X_N, which is a target value to be achieved using different temperature modes. And the conversion out of any intermediate reactor is governed by the rate of reaction taking place within that reactor, which in turn is affected by the operating temperature of that reactor and the position of that reactor in the series. The value of X_N and the temperatures of the first and last reactors in the series determine the trend of temperature mode i.e. increasing or decreasing that should be selected to meet the required product purity. The overall conversion is taken as a fraction of the equilibrium substrate conversion in the last reactor.

For each reversible reaction of the form $A \Leftrightarrow B$ the equilibrium conversion is a function of operating temperature through the equilibrium constant and is given by:

$$X_e = \frac{K_e}{1 + K_e} \tag{38}$$

The dependence of the equilibrium conversion on temperature as shown by equation (38) yields an equilibrium curve. This curve is used to determine the equilibrium conversion, which represents the maximum conversion, which can be achieved by the reversible reaction and consequently in estimating the temperatures of the intermediate reactors. The intermediate temperatures should have a suitable gradual increase or decrease with respect to the temperature in the first reactor so as to stay as close as possible to the equilibrium curve. This implies reasonable values of the kinetic parameters. This in turn will lead to feasible solutions of the nonlinear algebraic equations and consequently feasible intermediate substrate concentrations

and reasonable values of total residence times can be obtained. Depending on the temperatures of the first and last reactors in addition to the number of reactors, N, an increasing or decreasing temperature mode is selected in order to reach the operating temperature in the last reactor, i.e.

- If $T_1 < T_N$, then an increasing temperature mode is selected
- If $T_1 > T_N$, then a decreasing temperature mode is selected
- If $T_1 = T_N$, then an isothermal temperature mode is selected

Taking into account that, if the feed temperature, T_0, is less than that of the first reactor, T_1, then heating is required, but if $T_0 > T_1$ then cooling should be performed. Based on the operating temperature of the first and last reactors, i.e. the minimum and maximum allowable temperatures in the series, the operating temperature of each intermediate reactor i, T_i, is calculated according to the following relations:

(1) For increasing temperature mode:

$$T_i = T_{min} + \frac{\Delta T}{N-1}(i-1) \qquad i = 2,\ldots, N-1 \tag{39}$$

(2) For decreasing temperature mode:

$$T_i = T_{max} - \frac{\Delta T}{N-1}(i-1) \qquad i = 2,\ldots, N-1 \tag{40}$$

(3) For isothermal temperature mode:

$$T_i = T_{min} = T_{max} \qquad i = 1,\ldots, N \tag{41}$$

where the overall temperature range is given by: $\Delta T = T_{max} - T_{min}$.

5. Results and Discussion

For different number of reactors in series, N, given the operating temperature of the first and last reactors using constant ($\mathbf{A_i}$ =1) or decaying-activity ($\mathbf{A_i}$ <1) enzyme for an overall substrate conversion of 90% of the equilibrium, Tables 1 to 5 show the optimum total residence time expressed in hrs. For the case of N=2 the optimum total

residence time is 0.83 hrs while for N=3 the optimum total residence time is 0.65 hrs without enzyme deactivation. As it can be seen from Table 1 for two CSTRs the total residence time without and with enzyme deactivation is 0.83 hrs and 0.84 hrs respectively. While for N=3 the optimum total residence time is 0.65 hrs with and without enzyme deactivation. The effect of N, number of CSTRs, and operating temperatures of 60, 70, and 80 ^{o}C on the reaction rates within the first and fifth CSTRs are shown in Figures 1 and 2. As it can be seen from the figures as N increases the reaction rate at a given operating temperature in the first and fifth CSTRs increases respectively. And as the temperature increases the reaction rate also increases for any number of reactors in the series. This behavior represents the main reason for decreasing the overall residence time as the number of CSTRs increases (see Tables 1 to 5). This can be explained for the case of increasing temperature mode, as shown by Table 6, for N=2 the optimal residence times are: τ_1^* = 0.20 hrs and τ_2^*=0.63 hrs, whereas the reaction rates in the first and second reactors are 2.50 and 1.52 gmol/L.hr respectively, also the dimensionless substrate concentrations inside the first and second reactors are 0.82 and 0.48 respectively. But for three reactors in series the residence times are: 0.04, 0.22, 0.39 hrs respectively and the reaction rates are: R_1= 3.70, R_2 =3.23 and R_3=1.52 gmol/L.hr, and the dimensionless substrate concentrations are 0.95, 0.69 and 0.48. Notice that the dimensionless substrate concentration inside the first reactor for the case of N=3 is higher than that when N=2. This difference is reflected on the reaction rate which takes place in the first CSTR for N=3 to be higher than that when N=2, because the concentration of the substrate within the first CSTR increases, and this behavior represents the main reason for decreasing the overall residence time as the number of CSTRs increases. Similarily the same explanation is also applicable for the decreasing temperature mode as shown in Table 7. It can be

concluded for both modes that, as the number of reactors, N, increases the rate of reaction, which takes place in any specified reactor increases because the substrate concentration within that reactor is higher.

It is clear that, for the same number of CSTRs and operating conditions, the optimum total residence time in the presence of enzyme deactivation is greater than that without deactivation. Because, according to equation (18), the rate of reaction with enzyme deactivation is less than that without deactivation. But for the isomerization of glucose to fructose using glucose isomerase enzyme, the differences are very small because the enzyme used in our case study needs a very long time to reach an appreciable drop in its activity. Actually the estimated residual activity of the soluble glucose isomerase enzyme using Eq. 13 is almost unity. This is so because the enzyme deactivation constant k_d at 60 ^oC is 0.0009862 (1/hr) while at 80 ^oC is 0.032552 (1/hr) and since the order of magnitude of the total residence is almost 1 hr (Tables 1 through 5) the estimated residual activity at the lower operating temperature of 60 ^oC is almost 1 and at the upper temperature of 80 ^oC is approximately 0.97. Thus there is a slight drop of glucose isomerase activity with temperature and this explains the slight differences in the optimal total residence time solutions.

The developed analysis proves that, for a certain overall temperature difference between the first and last reactors and any number of CSTRs, the optimum total residence time using decreasing temperature mode is smaller than that using increasing temperature mode. But this difference, which is in favor of operation using decreasing temperature mode, is at the expense of overall substrate conversion.

Isothermal design in the presence of enzyme deactivation is performed also for three operating temperatures of 60 ^oC (corresponds to $K_S > K_P$), 80 ^oC (corresponds to $K_S < K_P$), and the critical temperature of 70 ^oC (where $K_S = K_P$). According to Table

8, it can be concluded that, similar to the argument given above, for a certain operating temperature, the optimum total residence time decreases as N increases. Besides, for a certain number of CSTRs, as the operating temperature increases, the optimum total residence time decreases. This is so because as the operating temperature increases the rate of reaction which takes place in each reactor in the series increases (see Table 9). For glucose isomerisation reaction, since the drop in the residual activity of the enzyme out of any reactor within the series is insignificant (see Figure 4), then, the effect of enzyme deactivation is found to be almost negligible.

To check that the computed total residence time is optimal, the Hessian matrix at the computed intermediate dimensionless concentrations of substrate, $\Phi^{*}_{S,i}$ which represent the roots of the system of equations (24), is checked for positive definiteness. The elements of the Hessian matrix are calculated according to equation (25). Table 10 shows the computed eigenvalues of the Hessian matrix for the case in Table 2 in the presence of enzyme deactivation and for a given operating temperature of the first and last reactors in the series to be 60 and 65 respectively. Since the matrix has a dimension of (N-1xN-1), for the case two reactors the computed eigenvalue, e_1, is 26.27; for the case of three reactors e_1 =5.87 and e_1 =39.37 and so on. As it can be seen from Tables 10 through 13 that the computed eigenvalues of the Hessian matrices for all cases are all positive, thus, the computed total residence times are local minima.

5. Conclusions

The main conclusions of this study can be summarized in the following points:

- For both increasing and decreasing operation temperature modes, as the number of CSTRs increases, the overall residence time decreases, and this applies for any temperature difference between the first and last CSTRs.

- For a certain overall temperature difference between the first and the last reactors, and for any number of CSTRs, the overall optimum residence time using decreasing temperature mode is smaller than that using increasing temperature mode, but this difference is at the expense of substrate conversion.

- For any number of CSTRs, the overall optimum residence time in the presence of enzyme deactivation is greater than that when the enzyme does not undergo deactivation as long as there is an appreciable drop in the residual enzyme activity. But for the glucose isomerase enzyme, the differences in the overall optimum residence time are very small because the enzyme needs a very long time to reach an appreciable drop in its activity.

List of Symbols

A_i	[ ]	Residual activity of the enzyme out of i-th reactor
$C_{E,0}$	[mg/L]	Initial concentration of the active enzyme
$C_{P,0}$	[gmol/L]	Initial concentration of product
$C_{P,e}$	[gmol/L]	Product concentration at equilibrium
$C_{S,0}$	[gmol/L]	Initial concentration of substrate
$C_{S,e}$	[gmol/L]	Substrate concentration at equilibrium
E		Enzyme
e_i		The i-th eigenvalue of the Hessian matrix
ES		Enzyme-substrate complex
H		Hessian matrix
K_d	[1/hr]	First order deactivation constant
K_e	[ ]	Equilibrium constant
K_1	[L/mg.hr]	Reaction constant
k_{-1}	[l/hr]	Dissociation constant
K_2	[1/hr]	Reaction constant
k_{-2}	[L/mg.hr]	Dissociation constant
K_m	[gmol/L]	Apparent Michaelis-Menten constant
K_{mn}	[ ]	Dimensionless Michaelis-Menten constant
K_P	[gmol/L]	Michaelis-Menten constant for product
K_S	[gmol/L]	Michaelis-Menten constant for substrate
K_v	[gmol/mg.hr]	Proportionality constant
N	[ ]	Number of reactors in series
P		Product
Q	[L/hr]	Volumetric flow rate
R	[gmol/L.hr]	Rate of reversible Michaelis-Menten reaction
S		Substrate
T	[^oC]	Operating temperature
T_k	[K]	Operating temperature
T_N	[^oC]	Operating temperature of the last reactor
T_1	[^oC]	Operating temperature of the first reactor
V	[L]	Volume of reactor
V_m	[gmol/L.hr]	Maximum apparent reaction rate
V_{mo}	[gmol/L.hr]	Counterpart of V_m in the absence of enzyme deactivation
V_P	[gmol/L.hr]	Maximum reaction rate for product
V_S	[gmol/L.hr]	Maximum reaction rate for substrate
X_N	[ ]	Overall fractional substrate conversion

Greek Symbols

ε	[ ]	Normalized deactivation rate constant of the enzyme
ΔT	[^oC]	Temperature increment between two consecutive reactors
γ_{mo}	[1/hr]	Maximum apparent reaction rate in the absence of enzyme deactivation.
Φ_S	[ ]	Dimensionless substrate concentration
τ	[hr]	Residence time

Superscripts

*	Optimum

Subscripts

d	Deactivation
e	Equilibrium

i	Refers to i-th reactor
j	Refers to j-th reactor
N	Refers to N-th reactor
P	Product
S	Substrate
T	Total or overall
0	Initial

References

1. Abu-Reesh, I.M. 2005. Optimal Design of Continuously Stirred Membrane Reactors in Series Using Michaelis-Menten Kinetics with competitive Product Inhibition: Theoretical Analysis. *Desalination*, **180** (1-3):119-132.

2. Abu-Reesh, I.M. 1996. Optimal Design for CSTR's in Series Using Reversible Michaelis-Menten Reactions. *Bioprocess Engineering*, **15**: 257-264.

3. Abu-Reesh, I.M. and Faqir, N.M. 1996. Simulation of Glucose Isomerase Reactor: Optimum Operation Temperature. *Bioprocess Engineering*, **14**: 205-210.

4. Bailey, J.E and Ollis, D.F. 1986. *Biochemical Engineering Fundamentals*. McGraw-Hill. New York

5. Chen, N. H.1983. *Process Reactor Design*. Allyn and Bacon, Inc, Boston.

6. Constantinides, A. and Mostoufi, N. 1999. *Numerical Methods for Chemical Engineers with MATLAB Applications*. Prentice Hall PTR, New Jersey.

7. Edgar, T.F. and Himmelblau, D.M. 1989. *Optimization of Chemical Processes.* McGraw–Hill, New York.

8. Faqir, N. M. and Abu-Reesh, I.M. 1998. Optimum Temperature Operation Mode for Glucose Isomerase Reactor Operating at Constant Glucose Conversion. *Bioprocess Engineering*, **19**: 11-17.

9. Faqir, N. M. and Attarakih, M.M. 1999. Optimum Design of a Series of CSTRs Performing Reversible Michaelis-Menten Kinetics: A Rigorous Mathematical Study. *Bioprocess Engineering*, **20** (4): 329-335.

10. Fogler, H. S. 1992. *Elements of Chemical Reaction Engineering.* 2nd edition. Prentice Hall International Editions, London

11. Ibrahim, J. Y. 2000. Optimal Design of a Series of CSTRs Performing Reversible Michaelis-Menten Reaction Catalyzed by Soluble Enzyme. M.Sc. Thesis, The University of Jordan, Amman

12. Illanes, A., Zuniga, M.E., Contreras, S. and Guerrero, A. 1992.Reactor Design for the Enzymatic Isomerization of Glucose to Fructose. *Bioprocess Engineering*, **7**: 199-204.

13. Levenspiel O. 1972. *Chemical Reaction Engineer*ing. 2nd edition. John Wiley & Sons, New York.

14. Lopes, I. T and Malcata, F. X. 1993. Optimal Design of a Series of CSTR's for Biochemical Reactions in the Presence of Enzyme Deactivation. *Journal of Chemical Engineering of Japan*, **26** (1): 94-98.

15. Luyben, K.CH.A M. and Tramper, J. 1982. Optimal Design for Continuous Stirred Tank Reactors in Series Using Michaelis-Menten Kinetics. *Biotechnology and Bioengineering*, **24**: 1217-1220.

16. Malcata, F.X. 1989. A Heuristic approach for the economic optimization of a series of CSTR,s performing Michaelis-Menten reactions. *Biotechnology and Bioengineering*, **33**: 251-255.

17. Malcata, F.X. 1990. On the maximum conversion of substrate during biochemical reactions performed by a series of CSTRs in the presence of enzyme deactivation. *Journal of Chemical Engineering of Japan*, **23**: 372-375.

18. Malcata, F.X. and Cameron, D.C. 1992. Optimal Design of a Series of CSTR's Performing Reversible Reactions Catalyzed by Soluble Enzymes: A theoretical Study. *Biocatalysis*, **5**: 233-248.

19. Moreira, N.E and Malcata, F.X. 1996. On the Optimum Distribution of Enzyme Feed in a Cascade of CSTR's Performing an Enzyme-Catalyzed Reaction with Deactivation. *Bioprocess Engineering*, **15**: 301-306.

20. Paiva, A.L. and Malcata, F.X. 1993. Optimal Temperature and Concentration Profiles in a Cascade of CSTR's Performing Michaelis-Menten Reactions with First Order Enzyme Deactivation. *Bioprocess Engineering*, **9**: 77-82.

21. Penny, J. and Lindfield, G.1995. *Numerical Methods Using MATLAB*. Ellis Horwood, New York.

22. Segel, I.H. 1975. *Enzyme Kinetics-Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems.* Wiley, New York.

23. Shuler, L. M and Kargi, F. 1992. *Bioprocess Engineering Basic Concepts*. Prentice Hall, Englewood Cliffs, New Jersey.

24. Wiseman, A. 1985. *Handbook of Enzyme Biotechnology*. 2nd edition. Ellis Horwood Limited, New York. Ontario-Brisbane.

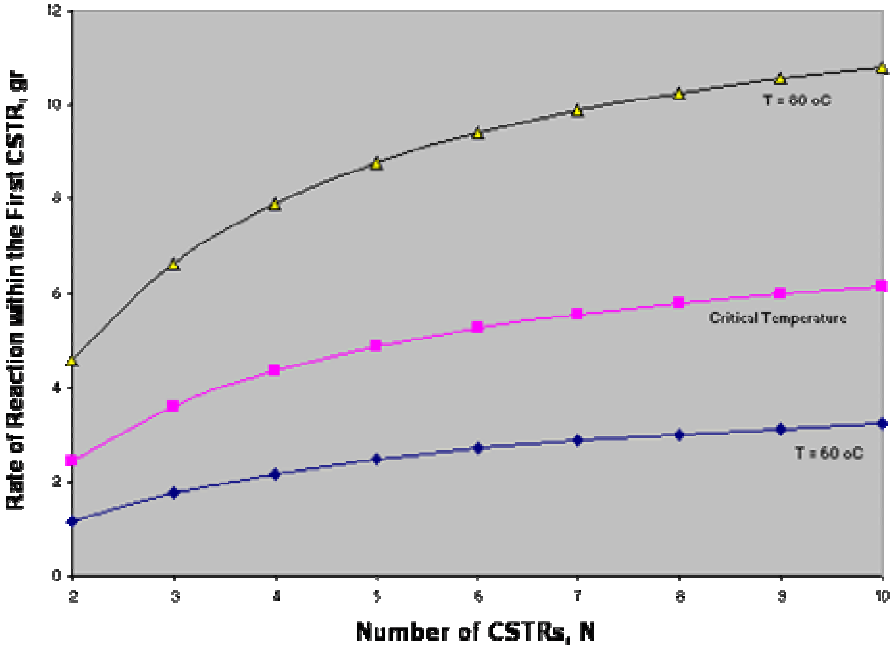

Fig. 1 Rate of reaction within the first CSTR, gmol/L.hr at different temperatures

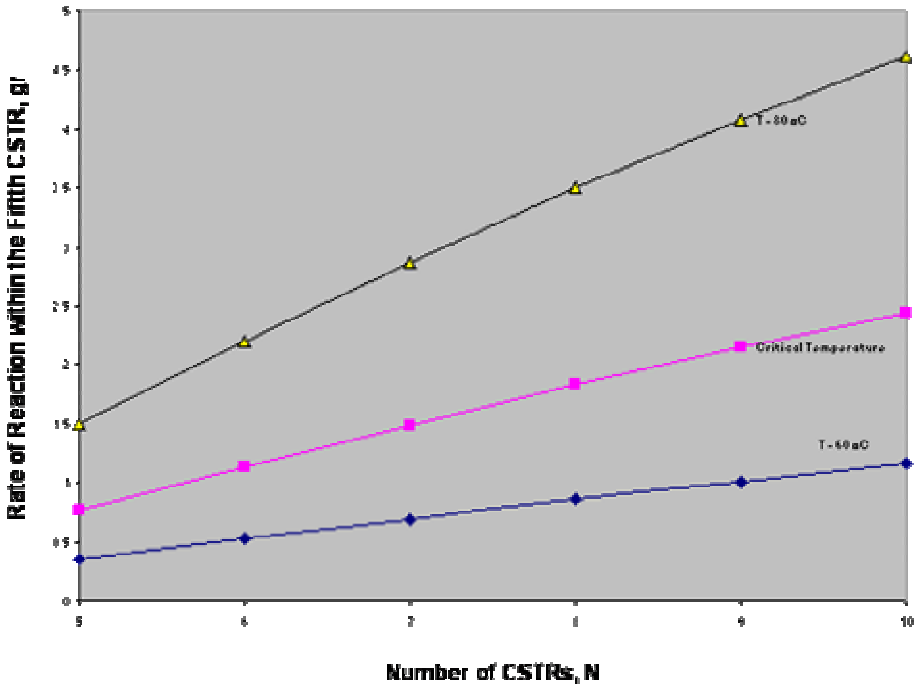

Fig. 2 Rate of reaction within the fifth CSTR, gmol/L.hr at different temperatures

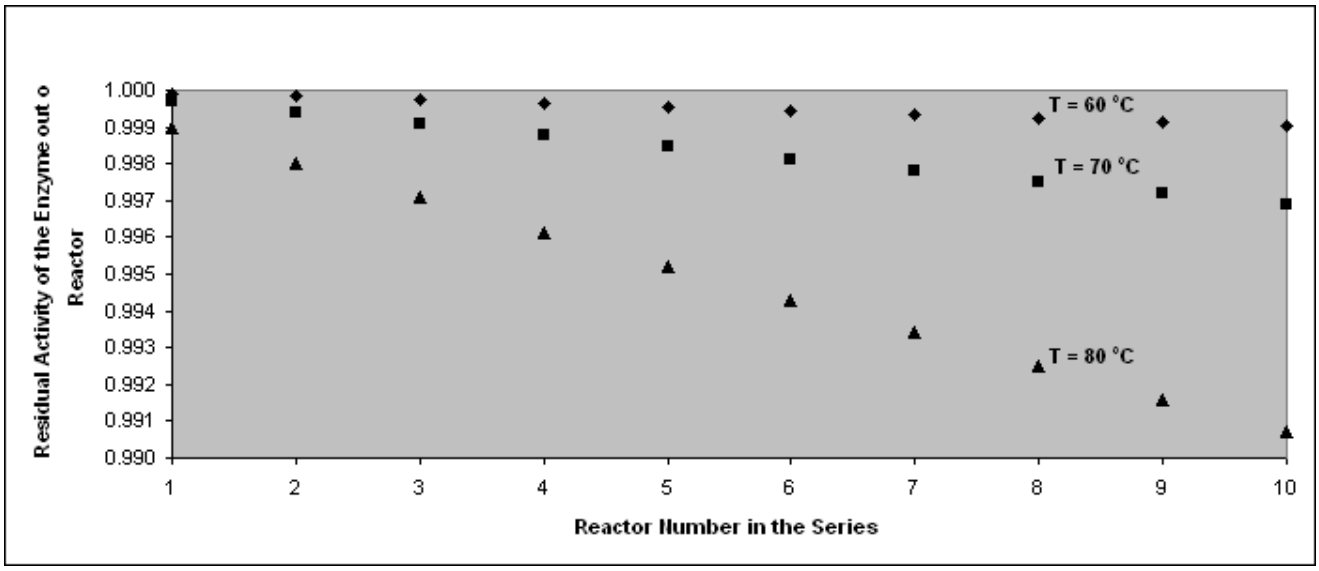

Fig. 3 Residual activity of isomerase out of each reactor within a ten-CSTR-series as a function of temper

Table 1 Comparison study using different operating conditions

X_N : 0.52

Case		N = 2		N = 3		N = 4		N = 5		N = 6		N = 7		
No.	Operating Conditions	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	
I	$A_i = 1$ T_1 : 60 °C T_N : 80 °C	20.00	0.83	10.00	0.65									
II	$A_i < 1$ T_1 : 60 °C T_N : 80 °C	20.00	0.84	10.00	0.65									
III	$A_i = 1$ T_1 : 70 °C T_N : 80 °C	10.00	0.65	5.00	0.52	3.33	0.46	2.50	0.43	2.00	0.41	1.67	0.39	
IV	$A_i < 1$ T_1 : 70 °C T_N : 80 °C	10.00	0.66	5.00	0.52	3.33	0.47	2.50	0.43	2.00	0.41	1.67	0.40	
V	$A_i = 1$ T_1 : 75 °C T_N : 80 °C	5.00	0.56	2.50	0.45	1.67	0.40	1.25	0.38	1.00	0.36	0.83	0.35	
VI	$A_i < 1$ T_1 : 75 °C T_N : 80 °C	5.00	0.56	2.50	0.45	1.67	0.40	1.25	0.38	1.00	0.36	0.83	0.35	

Table 2 Comparison study using different operating conditions

X_N : 0.50

Case		N = 2		N = 3		N = 4		N = 5		N = 6		N = 7		
No.	Operating Conditions	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	
I	$A_i = 1$ T_1 : 70 °C T_N : 75 °C	5.00	0.75	2.50	0.60	1.67	0.54	1.25	0.51	1.00	0.48	0.83	0.47	
II	$A_i < 1$ T_1 : 70 °C T_N : 75 °C	5.00	0.76	2.50	0.60	1.67	0.54	1.25	0.51	1.00	0.49	0.83	0.47	
III	$A_i = 1$ T_1 : 80 °C T_N : 75 °C	5.00	0.50	2.50	0.40	1.67	0.36	1.25	0.34	1.00	0.33	0.83	0.32	
IV	$A_i < 1$ T_1 : 80 °C T_N : 75 °C	5.00	0.51	2.50	0.41	1.67	0.37	1.25	0.34	1.00	0.33	0.83	0.32	

Table 3 Comparison study using different operating conditions

X_N : 0.48

Case		N = 2		N = 3		N = 4		N = 5		N = 6		N = 7		
No.	Operating Conditions	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	
I	$A_i = 1$ T_1 : 60 °C T_N : 70 °C	10.00	1.22	5.00	0.96	3.33	0.85	2.50	0.79	2.00	0.75	1.67	0.72	
II	$A_i < 1$ T_1 : 60 °C T_N : 70 °C	10.00	1.23	5.00	0.97	3.33	0.85	2.50	0.79	2.00	0.75	1.67	0.72	
III	$A_i = 1$ T_1 : 65 °C T_N : 70 °C	5.00	1.04	2.50	0.82	1.67	0.74	1.25	0.69	1.00	0.66	0.83	0.64	
IV	$A_i < 1$ T_1 : 65 °C T_N : 70 °C	5.00	1.04	2.50	0.82	1.67	0.74	1.25	0.69	1.00	0.66	0.83	0.64	
V	$A_i = 1$ T_1 : 80 °C T_N : 70 °C	10.00	0.50	5.00	0.41									
VI	$A_i < 1$ T_1 : 80 °C T_N : 70 °C	10.00	0.51	5.00	0.41									
VII	$A_i = 1$ T_1 : 75 °C T_N : 70 °C	5.00	0.67	2.50	0.54	1.67	0.49	1.25	0.46	1.00	0.44	0.83	0.42	
VIII	$A_i < 1$ T_1 : 75 °C T_N : 70 °C	5.00	0.67	2.50	0.54	1.67	0.49	1.25	0.46	1.00	0.44	0.83	0.42	

Table 4 Comparison study using different operating conditions

X_N : 0.46

Case		N = 2		N = 3		N = 4		N = 5		N = 6		N = 7		
No.	Operating Conditions	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	
I	$A_i = 1$ T_1 : 60 °C T_N : 65 °C	5.00	1.45	2.50	1.14	1.67	1.02	1.25	0.95	1.00	0.91	0.83	0.88	
II	$A_i < 1$ T_1 : 60 °C T_N : 65 °C	5.00	1.45	2.50	1.15	1.67	1.02	1.25	0.95	1.00	0.91	0.83	0.88	
III	$A_i = 1$ T_1 : 70 °C T_N : 65 °C	5.00	0.91	2.50	0.73	1.67	0.66	1.25	0.61	1.00	0.59			
IV	$A_i < 1$ T_1 : 70 °C T_N : 65 °C	5.00	0.92	2.50	0.73	1.67	0.66	1.25	0.62	1.00	0.59			

Table 5 Comparison study using different operating conditions

X_N : 0.44

Case		N = 2		N = 3		N = 4		N = 5		N = 6	
No.	Operating Conditions	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T	**ΔT**	τ^*_T
I	$A_i = 1$ T_1 : 70 °C T_N : 60 °C	10.00	0.89								
II	$A_i < 1$ T_1 : 70 °C T_N : 60 °C	10.00	0.90								
III	$A_i = 1$ T_1 : 65 °C T_N : 60 °C	5.00	1.26	2.50	1.01	1.67	0.90	1.25	0.84	1.00	0.80
IV	$A_i < 1$ T_1 : 65 °C T_N : 60 °C	5.00	1.27	2.50	1.01	1.67	0.90	1.25	0.84	1.00	0.80

Table 6 Comparison study using increasing temperature mode when N=2 & 3

$T_1 = 60\ ^oC$ $T_N = 80\ ^oC$ $A_i = 1$ $X_N = 0.52$

N = 2 & $\Delta T = 20\ ^oC$								N = 3 & ΔT					
$CSTR_1$				$CSTR_2$				$CSTR_1$					
T_1	τ^*_1	R_1	$\Phi^*_{S,1}$	T_2	τ^*_2	R_2	$\Phi^*_{S,2}$	T_1	τ^*_1	R_1	$\Phi^*_{S,1}$	T_2	
60.00	0.20	2.50	0.82	80.00	0.63	1.52	0.48	60.00	0.04	3.70	0.95	70.00	

Table 7 Comparison study using decreasing temperature mode when N=2 & 3

$T_1 = 80\ ^oC$ $T_N = 70\ ^oC$ $A_i = 1$ $X_N = 0.48$

N = 2 & $\Delta T = 10\ ^oC$								N = 3 & ΔT					
$CSTR_1$				$CSTR_2$				$CSTR_1$					
T_1	τ^*_1	R_1	$\Phi^*_{S,1}$	T_2	τ^*_2	R_2	$\Phi^*_{S,2}$	T_1	τ^*_1	R_1	$\Phi^*_{S,1}$	T_2	
80.00	0.38	3.32	0.55	70.00	0.12	0.76	0.52	80.00	0.23	4.69	0.61	75.00	

Table 8 Optimum total residence time expressed in hrs. as a function of number of CSTRs and operating temperature in the presnce of enzyme deactivation

N	T = 60^{O}C	T ≅ 70^{O}C	T = 80^{O}C
2	1.66	0.84	0.47
3	1.31	0.67	0.38
4	1.17	0.60	0.34
5	1.10	0.57	0.32
6	1.05	0.54	0.31
7	1.02	0.53	0.30
8	1.00	0.52	0.30
9	0.98	0.51	0.29
10	0.96	0.50	0.29

Table 9 Rate of Glucose Isomerisation which takes place in the i_th reactor of ten CSTRs in series as a function of temperature in the presence of enzyme deactivation

Reactor	T = 60^{O}C	T ≅ 70^{O}C	T = 80^{O}C
1	3.22	6.13	10.80
2	2.47	4.87	8.78
3	1.91	3.87	7.11
4	1.48	3.07	5.74
5	1.16	2.44	4.61
6	0.91	1.94	3.70
7	0.71	1.54	2.96
8	0.56	1.22	2.37
9	0.44	0.97	1.89
10	0.35	0.77	1.50

Table 10 Computed eigenvalues of the Hessian Matrices in the presence of enzyme deactivation. T_1 : 60^oC & T_N : 65^oC

N	ΔT	e_1	e_2	e_3	e_4	e_5	e_6	e_7	e_8	e_9
2.00	5.00	59.14								
3.00	2.50	13.51	88.42							
4.00	1.67	5.91	24.44	107.62						
5.00	1.25	3.26	12.11	32.34	121.84					
6.00	1.00	2.02	7.52	16.18	39.17	132.87				
7.00	0.83	1.35	5.14	10.32	19.57	45.14	141.72			
8.00	0.71	149.03	0.95	3.69	7.42	12.31	22.64	50.39		
9.00	0.63	155.21	0.69	2.73	5.63	8.90	25.45	14.04	55.05	
10.00	0.56	160.52	0.52	2.08	4.39	6.95	9.99	28.04	15.64	59.20

Table 11 Computed eigenvalues of the Hessian Matrices in the presence of enzyme deactivation. T_1 : 65°C & T_N : 70°C

N	ΔT	e_1	e_2	e_3	e_4	e_5	e_6	e_7	e_8	e_9
2.00	5.00	38.86								
3.00	2.50	8.78	58.21							
4.00	1.67	3.83	16.01	70.90						
5.00	1.25	2.10	7.89	21.29	80.31					
6.00	1.00	1.30	4.88	10.60	25.86	87.60				
7.00	0.83	0.86	3.33	6.72	12.87	29.86	93.45			
8.00	0.71	98.27	0.61	2.38	4.38	8.05	14.94	33.37		
9.00	0.63	102.33	0.44	1.77	3.65	5.78	16.83	9.21	36.47	
10.00	0.56	105.83	0.33	1.34	2.84	4.50	6.51	18.56	39.23	10.29

Table 12 Computed eigenvalues of the Hessian Matrices in the presence of enzyme deactivation. T_1 : 70°C & T_N : 75°C

N	ΔT	e_1	e_2	e_3	e_4	e_5	e_6	e_7	e_8	e_9
2.00	5.00	26.27								
3.00	2.50	5.87	39.37							
4.00	1.67	2.55	10.78	47.97						
5.00	1.25	1.39	5.29	14.41	54.35					
6.00	1.00	0.86	3.26	7.14	17.54	59.29				
7.00	0.83	0.57	2.22	4.50	8.71	20.29	63.25			
8.00	0.71	66.51	0.40	1.59	3.21	5.42	10.13	22.70		
9.00	0.63	69.26	0.29	1.18	2.43	3.87	11.44	6.22	24.82	
10.00	0.56	71.61	26.71	0.22	0.89	1.89	3.00	4.36	12.63	6.97

Table 13 Computed eigenvalues of the Hessian Matrices in the presence of enzyme deactivation. T_1 : 75°C & T_N : 80°C

N	ΔT	e_1	e_2	e_3	e_4	e_5	e_6	e_7	e_8	e_9
2.00	5.00	18.32								
3.00	2.50	4.04	27.38							
4.00	1.67	1.74	7.47	33.35						
5.00	1.25	0.95	3.64	10.02	37.78					
6.00	1.00	0.59	2.24	4.95	12.24	41.21				
7.00	0.83	0.39	1.52	3.10	6.06	14.17	43.96			
8.00	0.71	46.22	0.27	1.09	2.21	3.75	15.87	7.08		
9.00	0.63	48.13	0.20	0.81	1.67	2.67	8.01	4.33	17.37	
10.00	0.56	49.76	18.70	0.15	0.61	1.29	2.06	3.02	4.86	8.86