Bioprocess Engineering 20 (1999) 329 – 335 © Springer-Verlag 1999

Optimum design of a series of CSTRs performing reversible Michaelis-Menten kinetics: a rigorous mathematical study

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Abstract The optimum design of a given number of CSTRs in series performing reversible Michaelis-Menten kinetics in the liquid phase assuming constant activity of the enzyme is studied. In this study, the presence of product in the feed stream to the first reactor, as well as the effect of the product intermediate concentrations in the downstream reactors on the reaction rate are investigated. For a given number of N CSTRs required to perform a certain degree of substrate conversion and under steady state operation and constant volumetric flow rate, the reactor optimization problem is posed as a constrained nonlinear programming problem (NLP). The reactor optimization is based on the minimum overall residence time (volume) of N reactors in series. When all the reactors in series operate isothermally, the constrained NLP is solved as an unconstrained NLP. And an analytical expression for the optimum overall residence time is obtained. Also, the necessary and sufficient conditions for the minimum overall residence time of N CSTRs are derived analytically. In the presence of product in the feed stream, the reversible Michaelis-Menten kinetics shows competitive product inhibition. And this is, because of the increase in the apparent rate constant K'_m that results in a reduction of the overall reaction rate. The optimum total residence time is found to increase as the ratio (ψ_0) of product to substrate concentrations in the feed stream increases. The isomerization of glucose to fructose, which follows a reversible Michaelis-Menten kinetics, is chosen as a model for the numerical examples.

List of symbols

$C_{E,0}$	[mg/l]	initial concentration of active enzyme
C_p	[mole/l]	product concentration
$C_{p,e}$	[mole/l]	product concentration at equilibrium
$C_{p,0}$	[mole/l]	product concentration at the inlet of the first reactor
C_s	[mole/l]	substrate concentration
$C_{s,e}$	[mole/l]	substrate concentration at equilibrium
$C_{s,0}$	[mole/l]	substrate concentration at the inlet of the first reactor
D	[ ]	determinant
HU	[ ]	upper triangular hessain matrix
K_e	[ ]	equilibrium constant
K_m	[mole/l]	apparent Michaelis-Menten constant
K'_m	[ ]	dimensionless Michaelis-Menten constant $(K_m/C_{s,0})$
K_p	[mole/l]	Michaelis-Menten constant for product
K_s	[mole/l]	Michaelis-Menten constant for substrate
K_{-1}, K_2	[h^{-1}]	rate constants
K_1, K_{-2}	[l/mole · h]	rate constants
N	[ ]	number of reactors in series
Q	[l/h]	volumetric flow rate
$R(C_s)$	[mole/l · h]	reaction rate
t	[h]	time
T	[°C]	temperature
V	[l]	reactor volume
V_m	[mole/l · h]	maximum apparent reaction rate
V'_m	[h^{-1}]	apparent reaction rate defined as $(V_m/C_{s,0})$
V_p	[mole/l · h]	maximum reaction rate for product
V_s	[mole/l · h]	maximum reaction rate for substrate
X	[ ]	substrate conversion

Greek symbols

α	[ ]	dimensionless substrate concentration $C_s/C_{s,0}$
α^*	[ ]	dimensionless optimum substrate concentration
τ	[h]	residence time V/Q
τ^*	[h]	optimum residence time
ψ	[ ]	ratio of product to substrate concentrations C_p/C_s

Subscripts

e	equilibrium
i	refers to ith reactor
j	refers to jth reactor
k	order of submatrix
p	product
s	substrate
0	initial

Received: 28 April 1998

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1 Introduction

The problem of reactor optimization can be divided into two major classes, namely reactor design and reactor operation. For a given reactor type of known capacity, optimization of reactor operation involves the determination of optimum operating conditions required to improve operational economics and product yield. While optimization of reactor design involves the determination of the optimum capacity of one or more reactors in series or an arrangement of reactors required to achieve a specified yield such that an objective function based on cost or technological considerations is optimized. Two ideal steady-state flow reactors are known. The first is the plug flow reactor, while the other is called the continuous stirred tank reactor or the CSTR. The CSTR is based on theoretical assumptions of perfect and instantaneous mixing in the tank, which results in perfectly homogeneous reactor contents. For enzyme-catalyzed reaction, the plug flow reactor is much superior than continuous stirred tank reactor. Still the CSTR possess a number of advantages for industrial operation, one major advantage of the CSTR, apart from its simplicity of construction and lower construction cost, is the ease of pH and temperature control facilitated by good mixing [1].

A number of literature references are available on the optimum design of CSTRs in series performing enzyme-catalyzed reactions [2–8]. From the work of Luyben and Tramper [2], who were the first to derive analytical expression to find the minimum overall volume of a series of CSTRs following irreversible Michaelis-Menten kinetics, to the work of Malcata and Cameron [7] and Abu-Reesh [8]. Malcata and Cameron [7] were the first to consider the presence of product in the feed stream when they optimized a series of CSTRs performing reversible enzyme-catalyzed reactions obeying Briggs-Haldane mechanism. But the effects of product intermediate concentrations on the reaction rate for the downstream reactors were not investigated. However, for the general case they were not able to derive an analytical expression for the optimum design of CSTRs in series. Abu-Reesh [8] has optimized a series of CSTRs performing reversible Michaelis-Menten kinetics in the liquid phase. An analytical expression for the optimum overall volume is obtained. But the effects of product in the feed and in the intermediate streams on the reaction rate for the downstream reactors were not investigated.

As mentioned above, literature references are available on the theoretical optimization procedures used for the design of a series of CSTRs performing biochemical reactions. But, all the above references did not rigorously analyze the necessary and sufficient conditions required for the existence of an optimum of an optimization problem of a function of several variables [2–8].

The objective of this paper deals with the derivation of an analytical expression for the optimum design of a series of CSTRs performing a reversible enzyme-catalyzed biochemical reaction obeying Michaelis-Menten kinetics in the liquid phase. The derivation takes into consideration the presence of product in the feed stream to the first reactor as well as the effect of the intermediate product concentrations in the downstream reactors on the reaction rate. For a given number of reactors, the reactor design formulation is posed as a constrained nonlinear programming problem (NLP). The objective function is set to minimize the overall volume (residence time) under steady state operation and constant volumetric flow rate required to perform a certain degree of substrate conversion. For the case of isothermal operation when all the reactors in series operate at constant and identical temperature, the constrained NLP is reduced in size and solved as an unconstrained optimization problem. Solving this reduced NLP as unconstrained optimization problem is proved to be optimal for the constrained case. For a given degree of substrate conversion and a number of CSTR reactors in series operating isothermally, a rigorous mathematical analysis is also developed aimed at establishing the necessary and sufficient conditions required for the existence of a minimum overall reactor volume (residence time).

2 Kinetic model

In general, all reactions catalyzed by enzymes are reversible [7]. A realistic sequence involves the formation of a hybrid substrate and enzyme complex, SE, according to the following reaction mechanism [9, 10]:

$$S + E \underset{k_1}{\overset{k_{-1}}{\Leftrightarrow}} SE \underset{k_2}{\overset{k_{-2}}{\Leftrightarrow}} P + E \quad , \tag{1}$$

where E, S, and P denote the active free enzyme, substrate, and product. Under the assumption of $C_s \gg C_{E,0}$, the net rate of the enzymatic conversion of S to P can be expressed as [9, 10]:

$$R(C_s) = -\frac{dC_s}{dt} = \frac{dC_p}{dt} = \frac{\left(\frac{V_s}{K_s}\right)C_s - \left(\frac{V_p}{K_p}\right)C_p}{1 + \left(\frac{C_s}{K_s}\right) + \left(\frac{C_p}{K_p}\right)} \quad . \tag{2}$$

From the reaction stoichiometry and the presence of product in the feed, the following expression relating the concentrations of substrate and product can be obtained:

$$C_{s,0} + C_{p,0} = C_s + C_p = C_{s,e} + C_{p,e} = C_{s,e}(1 + K_e) \quad , \tag{3}$$

where:

$$C_s = C_{s,0}(1 - X), C_p = C_{p,0} + C_{s,0}X = C_{s,0}(\psi_0 + X) \quad , \tag{4}$$

$$X = \frac{C_{s,0} - C_s}{C_{s,0}} \quad , \tag{5}$$

$$C_{s,e} = \frac{C_{s,0}(1 + \psi_0)}{1 + K_e} \quad , \tag{6}$$

$$\psi_0 = \frac{C_{p,0}}{C_{s,0}} \quad , \tag{7}$$

and ψ_0 denotes the ratio of initial product concentration to initial substrate concentration [11].

The rate expression given by Eq. (2) can be reduced to reversible Michaelis-Menten kinetics as:

$$R(C_s) = \frac{V_m(C_s - C_{s,e})}{K_m + (C_s - C_{s,e})} \quad , \tag{8}$$

where:

$$V_m = \left(\frac{V_s K_p}{K_p - K_s}\right)\left(1 + \frac{1}{K_e}\right) \quad , \tag{9}$$

$$K_m = \left(\frac{K_p K_s}{K_p - K_s}\right)\left[1 + \left(\frac{K_e}{K_p} + \frac{1}{K_s}\right)\left(\frac{C_{s,0}(1+\psi_0)}{1+K_e}\right)\right] \quad , \tag{10}$$

and

$$V_s = C_{E,0}K_2, \; V_p = C_{E,0}K_{-1}, \; K_s = \frac{K_{-1} - K_2}{K_1},$$
$$K_p = \frac{K_{-1} - K_2}{K_{-2}},$$
$$K_e = \frac{V_s K_p}{V_p K_s} = \frac{C_{p,e}}{C_{s,e}} \quad , \tag{11}$$

where V_m, and K_m are apparent rate constants, that are functions of $C_{s,0}, \psi_0$ and temperature and both can have negative values.

3 Optimization of a series of N CSTRs

Consider a series of completely mixed N CSTRs in which a reversible reaction is carried out obeying Michaelis-Menten kinetics. The enzyme concentration is assumed to be identical and remain constant at all times in all reactors i.e. constant activity of the enzyme. The substrate material balance on reactor i under steady state condition and constant volumetric flow rate can be written as:

$$\tau_i = \frac{V_i}{Q} = \frac{(C_{s,i-1} - C_{s,i})}{R(C_{s,i})} \quad i = 1, 2, \ldots, N \quad , \tag{12}$$

where V_i is the volume of reactor i, Q is the volumetric flow rate, $C_{s,i-1}$ is the inlet substrate concentration to reactor i, $C_{s,i}$ is the substrate concentration in reactor i, and τ_i is the residence time in reactor i. Using Eq. (8) for the reaction rate, the residence time in reactor i can be written as:

$$\tau_i = \frac{(C_{s,i-1} - C_{s,i})(K_{m,i} + C_{s,i} - C_{s,e,i})}{V_{m,i}(C_{s,i} - C_{s,e,i})} \quad i = 1, 2, \ldots, N \quad , \tag{13}$$

where:

$$V_{m,i} = \left(\frac{V_s K_p}{K_p - K_s}\right)_i \left(1 + \frac{1}{K_{e,i}}\right) \quad , \tag{14}$$

$$K_{m,i} = \left(\frac{K_p K_s}{K_p - K_s}\right)_i \left[1 + \left(\frac{K_e}{K_p} + \frac{1}{K_s}\right)_i \times \left(\frac{C_{s,i-1}(1+\psi_{i-1})}{1+K_{e,i}}\right)\right] \quad , \tag{15}$$

$$C_{s,e,i} = \frac{C_{s,i-1}(1+\psi_{i-1})}{1+K_{e,i}} \quad , \tag{16}$$

$$\psi_{i-1} = \frac{C_{p,i-1}}{C_{s,i-1}} \quad . \tag{17}$$

For constant volumetric flow rate, the objective function is set to minimize the overall reactor volume, which is equivalent to minimizing the total residence time of all the N CSTRs in series. For a given $C_{s,0}, C_{s,N}$ and ψ_0, the optimization problem can be posed as a constrained nonlinear programming problem (NLP) as follows:

$$\text{Minimize } \tau = \sum_{i=1}^{N} \tau_i \quad . \tag{18}$$

subject to:

$$\tau_i = \frac{(C_{s,i-1} - C_{s,i})(K_{m,i} + C_{s,i} - C_{s,e,i})}{V_{m,i}(C_{s,i} - C_{s,e,i})} \quad i = 1, 2, \ldots, N \quad ,$$

$$V_{m,i} = \left(\frac{V_s K_p}{K_p - K_s}\right)_i \left(1 + \frac{1}{K_{e,i}}\right) \quad i = 1, 2, \ldots, N \quad ,$$

$$K_{m,i} = \left(\frac{K_p K_s}{K_p - K_s}\right)_i \left[1 + \left(\frac{K_e}{K_p} + \frac{1}{K_s}\right)_i \left(\frac{C_{s,i-1}(1+\psi_{i-1})}{1+K_{e,i}}\right)\right] \quad i = 1, 2, \ldots, N \quad ,$$

$$\psi_{i-1} = \frac{C_{p,i-1}}{C_{s,i-1}} \quad i = 2, \ldots, N \quad ,$$

$$C_{s,i} \le C_{s,i-1} \quad i = 1, 2, \ldots, N \quad ,$$

$$C_{s,N} \le C_{s,i} \le C_{s,0} \quad i = 1, 2, \ldots, N-1 \quad .$$

Note that, if the feed to the first reactor is free of product, then $\psi_0 = 0$. But for any reversible reactions to occur in the downstream reactors, the ratio of product to substrate concentrations is different from zero i.e. $\psi_i \neq 0$, $i = 1, 2, \ldots, N-1$. Thus the progress of the reversible reaction could be influenced by this ratio. The apparent rate constant $V_{m,i}$ is a function of temperature only as it can be seen from Eq. (9), since the kinetic parameters are functions only of temperature. Whereas the apparent rate constant $K_{m,i}$ is a function of temperature as well as ψ_{i-1} which in turn is a function of $C_{s,i-1}$ and $C_{p,i-1}$. An overall material balance on reactor i yields:

$$C_{s,i-1} + C_{p,i-1} = C_{s,i} + C_{p,i} = C_{s,e,i} + C_{p,e,i} \quad i = 1, 2, \ldots, N \quad . \tag{19}$$

Using the definition of ψ, Eq. (19) can be written as:

$$C_{s,i-1}(1+\psi_{i-1}) = C_{s,i}(1+\psi_i) = C_{s,e,i}(1+K_{e,i}) \quad i = 1, 2, \ldots, N \quad . \tag{20}$$

Applying Eq. (20) recursively for i equal 1 up to N we obtain:

$$C_{s,0}(1+\psi_0) = C_{s,1}(1+\psi_1) = \ldots = C_{s,N}(1+\psi_N) = C_{s,e,i}(1+K_{e,i}) \quad . \tag{21}$$

From the above relation it can be concluded that $K_{m,i}$ does not depend on the intermediate concentrations $C_{s,i-1}$ and $C_{p,i-1}$. It is only dependent on ψ_0 and temperature. So, we can write:

$$K_{m,i} = K_m = f(T, \psi_0) \qquad i = 1, 2, \ldots, N \ , \tag{22}$$

$$V_{m,i} = V_m = f(T) \qquad i = 1, 2, \ldots, N \ . \tag{23}$$

The same thing could be said about $C_{s,e,i}$ which follows from Eq. (21):

$$C_{s,e,i} = \frac{C_{s,0}(1 + \psi_0)}{1 + K_{e,i}} \qquad i = 1, 2, \ldots, N \ . \tag{24}$$

It follows that:

$$C_{s,e,i} = f(T, \psi_0) \qquad i = 1, 2, \ldots, N \ . \tag{25}$$

So, under isothermal operation when all the reactors in series operate at constant and identical temperature, we can write:

$$C_{s,e,i} = C_{s,e} = f(\psi_0) \qquad i = 1, 2, \ldots, N \ . \tag{26}$$

Thus, for a given $C_{s,0}$, $C_{s,N}$, ψ_0, and under isothermal operation in all reactors, the optimization problem given by Eq. (18) can be reduced in size to:

$$\underset{\substack{\alpha_i \\ 1 \le i \le N-1}}{\text{Minimize}} \ \tau = \sum_{i=1}^{N} \tau_i \ , \tag{27}$$

subject to:

$$\tau_i = \frac{(\alpha_{i-1} - \alpha_i)(K'_m + \alpha_i - \alpha_e)}{V'_m(\alpha_i - \alpha_e)} \qquad i = 1, 2, \ldots, N \ ,$$

$$\alpha_i \le \alpha_{i-1} \qquad i = 1, 2, \ldots, N \ ,$$

$$\alpha_N \le \alpha_i \le 1 \qquad i = 1, 2, \ldots, N-1 \ ,$$

where α_i, α_e and K'_m are dimensionless variables defined as:

$$\alpha_i = \frac{C_{s,i}}{C_{s,0}}, \ K'_m = \frac{K_m}{C_{s,0}}, \ \alpha_e = \frac{C_{s,e}}{C_{s,0}} \ ,$$

and

$$V'_m = \frac{V_m}{C_{s,0}} \ .$$

Note that, the minimum of an unconstrained objective function is the minimum of the same objective function subjected to a set of constraints only if it is feasible i.e. the unconstrained minimum satisfies the set of constraints of the NLP. The above reduced NLP can be solved as an unconstrained optimization problem. And the conditions for minimum overall residence time can be derived using the following theorem. The theorem states the necessary and sufficient conditions required for the existence of a minimum of an unconstrained objective function of several variables [12]:

Theorem 1

Necessary condition:

For the vector of normalized intermediate concentrations, α^*, to be a local minimum, it is necessary that the gradient of the objective function $\tau(\alpha)$ at α^* vanishes i.e.:

$$\nabla\tau(\alpha^*) = 0 \ .$$

Sufficient conditions:

If $\nabla\tau(\alpha^*) = 0$ and $\nabla^2\tau(\alpha^*)$ is positive definite, then α^* is an isolated local minimum of $\tau(\alpha)$.

Where α is a vector of intermediate substrate concentrations of dimension $(N-1 \times 1)$, the gradient $\nabla\tau(\alpha)$ is a vector of dimension $(N-1 \times 1)$, and the hessian $\nabla^2\tau(\alpha)$ is a symmetric matrix of second derivatives of dimension $(N-1 \times N-1)$, and all are defined as:

$$\alpha^T = [\alpha_1 \ \alpha_2 \cdots \alpha_{N-1}] \ ,$$

$$\nabla\tau^T(\alpha) = \left[\frac{\partial\tau}{\partial\alpha_1} \ \frac{\partial\tau}{\partial\alpha_2} \cdot \ \cdot \frac{\partial\tau}{\partial\alpha_{N-1}}\right] \ , \text{ and}$$

$$\nabla^2\tau(\alpha) = \begin{bmatrix} \frac{\partial^2\tau}{\partial\alpha_1^2} & \frac{\partial^2\tau}{\partial\alpha_2\partial\alpha_1} & \cdot & \cdot & \frac{\partial^2\tau}{\partial\alpha_{N-1}\partial\alpha_1} \\ \frac{\partial^2\tau}{\partial\alpha_1\partial\alpha_2} & \frac{\partial^2\tau}{\partial\alpha_2^2} & \cdot & \cdot & \frac{\partial^2\tau}{\partial\alpha_{N-1}\partial\alpha_2} \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \vdots & \vdots & & & \vdots \\ \frac{\partial^2\tau}{\partial\alpha_1\partial\alpha_{N-1}} & \frac{\partial^2\tau}{\partial\alpha_2\partial\alpha_{N-1}} & \cdot & \cdot & \frac{\partial^2\tau}{\partial\alpha_{N-1}^2} \end{bmatrix} \ , \tag{28}$$

where:

$$\frac{\partial\tau}{\partial\alpha_i} = \frac{K'_m}{V'_m}\left[\frac{1}{(\alpha_{i+1} - \alpha_e)} - \frac{(\alpha_{i-1} - \alpha_e)}{(\alpha_i - \alpha_e)^2}\right]$$
$$i = 1, 2, \ldots, N-1 \ , \tag{29}$$

and the hessian matrix is tridiagonal with its elements defined as:

$$\frac{\partial^2\tau}{\partial\alpha_i\partial\alpha_j} = \begin{cases} \dfrac{2K'_m(\alpha_{i-1} - \alpha_e)}{V'_m(\alpha_i - \alpha_e)^3} & \text{if } i = j \\ \dfrac{-K'_m}{V'_m(\alpha_{i+1} - \alpha_e)^2} & \text{if } i - j = 1 \\ \dfrac{-K'_m}{V'_m(\alpha_{i+1} - \alpha_e)^2} & \text{if } i - j = -1 \\ 0.0 & \text{if } |i - j| > 1 \end{cases}$$
$$i, j = 1, 2, \ldots, N-1 \ . \tag{30}$$

For example, if we have 4 CSTRs is series, Eqs. (28) and (30) yield:

$$\nabla^2\tau(\alpha) = \begin{bmatrix} \frac{2K'_m(\alpha_0 - \alpha_e)}{V'_m(\alpha_1 - \alpha_e)^3} & \frac{-K'_m}{V'_m(\alpha_2 - \alpha_e)^2} & 0.0 \\ \frac{-K'_m}{V'_m(\alpha_2 - \alpha_e)^2} & \frac{2K'_m(\alpha_1 - \alpha_e)}{V'_m(\alpha_2 - \alpha_e)^3} & \frac{-K'_m}{V'_m(\alpha_3 - \alpha_e)^2} \\ 0.0 & \frac{-K'_m}{V'_m(\alpha_3 - \alpha_e)^2} & \frac{2K'_m(\alpha_2 - \alpha_e)}{V'_m(\alpha_3 - \alpha_e)^3} \end{bmatrix} \ .$$

for α^* to be a local minimum then according to theorem 1, we must have $\partial\tau/\partial\alpha_i = 0$ for $i = 1, 2, \ldots, N-1$, thus Eq. (29) is reduced to:

$$(\alpha^*_{i-1} - \alpha_e)(\alpha^*_{i+1} - \alpha_e) = (\alpha^*_i - \alpha_e)^2$$
$$i = 1, 2, \ldots, N-1 \ . \tag{31}$$

This equation can be written recursively as [8]:

$$\left(\frac{\alpha^*_i - \alpha_e}{\alpha_0 - \alpha_e}\right) = \left(\frac{\alpha_N - \alpha_e}{\alpha_0 - \alpha_e}\right)^{i/N} \quad i = 1, 2, \ldots, N-1 \ . \tag{32}$$

The optimum residence time τ_i in reactor i is obtained by combining Eqs. (27) and (32) [8]:

$$\tau_i^* = \frac{1}{V'_m}\left[\left(\frac{\alpha_N - \alpha_e}{\alpha_0 - \alpha_e}\right)^{1/N} - 1\right] \times \left[K'_m + (\alpha_0 - \alpha_e)\left(\frac{\alpha_N - \alpha_e}{\alpha_0 - \alpha_e}\right)^{i/N}\right] , \quad (33)$$

and the overall residence time can be written as:

$$\tau^* = \sum_{i=1}^{N} \tau_i^* = \frac{1}{V'_m}\left\{NK'_m\left[\left(\frac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{1/N} - 1\right] + (\alpha_0 - \alpha_N)\right\} . \quad (34)$$

Since the condition expressed by Eq. (34) holds for a minimum as well as for a maximum or a saddle point, then the hessian matrix at the stationary point α^* must be checked. If the hessian matrix $\nabla^2\tau(\alpha^*)$ is positive definite, then α^* corresponds to a local minimum for the unconstrained case. And if the intermediate concentration constraints are satisfied, then it is optimal for the above reduced nonlinear programming problem. The following theorem [12, 13] can be used to establish the positive definiteness of the hessian matrix at the given vector α^*:

Theorem 2:
Either of the following tests is a necessary and sufficient condition for the real symmetric matrix $\nabla^2\tau(\alpha^*)$ to be positive definite:

i All the submatrices of $\nabla^2\tau(\alpha^*)$ must have positive determinants (>0),
ii All the eigenvalues of $\nabla^2\tau(\alpha^*)$ must be positive (>0).

The elements of the hessian matrix $\nabla^2\tau(\alpha^*)$ can be written as follows using Eqs. (30) and (32):

$$\nabla^2\tau(\alpha^*) = H^*_{i,j} = \begin{cases} 2\dfrac{K'_m}{V'_m}\dfrac{1}{(\alpha_0 - \alpha_e)^2}\left(\dfrac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{\frac{2i+1}{N}} & \text{if } i = j, \\ -\dfrac{K'_m}{V'_m}\dfrac{1}{(\alpha_0 - \alpha_e)^2}\left(\dfrac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{\frac{2i+2}{N}} & \text{if } i - j = 1, \\ -\dfrac{K'_m}{V'_m}\dfrac{1}{(\alpha_0 - \alpha_e)^2}\left(\dfrac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{\frac{2i+2}{N}} & \text{if } i - j = -1, \\ 0.0 & \text{if } |i - j| > 1 . \end{cases} \quad (35)$$

The hessian matrix given by Eq. (35) is a real, symmetric and tridiagonal matrix. This matrix can be factorized into lower and upper triangular matrices using Gaussian elimination method without row interchanges [13, 14]. The resulting upper triangular matrix has the following structure:

$$\mathbf{HU}^*_{i,j} = \begin{cases} \left(\dfrac{i+1}{i}\right)\dfrac{K'_m}{V'_m}\dfrac{1}{(\alpha_0 - \alpha_e)^2}\left(\dfrac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{\frac{2i+1}{N}} & \text{if } i = j, \\ 0.0 & \text{if } i - j = 1, \\ -\dfrac{K'_m}{V'_m}\dfrac{1}{(\alpha_0 - \alpha_e)^2}\left(\dfrac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{\frac{2i+2}{N}} & \text{if } i - j = -1, \\ 0.0 & \text{if } |i - j| > 0 , \end{cases} \quad (36)$$

Since the determinant of an upper triangular matrix is the product of its diagonal elements [13, 14], then the determinant of any submatrix $\mathbf{HU}^*_k$ of order k, if no row interchanges has been made, is given by:

$$D_k = (k+1)\left(\frac{K'_m}{V'_m}\frac{1}{(\alpha_0 - \alpha_e)^2}\right)^k \left(\frac{\alpha_0 - \alpha_e}{\alpha_N - \alpha_e}\right)^{\sum_{i=1}^{k}\left(\frac{2i+1}{N}\right)} \quad k = 1, 2, \ldots, N-1 . \quad (37)$$

The ratio $\alpha_0 - \alpha_e/\alpha_N - \alpha_e$ is always greater than zero, because in practice $\alpha_i > \alpha_e$ for i = 1,2,. . .,N. So, the sign of D_k is determined by the sign of the ratio K'_m/V'_m, which depends on the type of reaction and temperature. Using Eqs. (14) and (15) we can write:

$$\frac{K'_m}{V'_m} = \frac{K_s}{V_s}\left[\frac{1 + \left(\frac{K_e}{K_p} + \frac{1}{K_s}\right)\left(\frac{C_{s,0}[1+\psi_0]}{1+K_e}\right)}{1 + \frac{1}{K_e}}\right] . \quad (38)$$

From this relation it is obvious that K'_m/V'_m is always greater than zero and hence D_k is always greater than zero. This completes the proof that satisfies condition (i) of theorem 2, that is; the hessian matrix is positive definite at α^*. So, we can conclude that τ^* is a local minimum of the objective function given by Eq. (27).

4 Numerical examples

One of the famous reversible reactions following Michaelis-Menten kinetics is that of the enzymatic isomerization of glucose to fructose. This reaction occurs in the manufacturing of high fructose corn syrup (HFCS), and approaches equilibrium at relatively low conversions.

Table 1. Kinetic parameters for glucose isomerization reaction at three different conditions assuming initial glucose concentration of 2.8 mole/l [8, 15]

	$K_s = 1.5K_p$	$K_s = K_p$	$K_p = 1.5K_s$
T (°C)	61	70	80
K_s (mole/l)	0.72	0.84	1.011
K_p (mole/l)	0.48	0.84	1.540
K_m (mole/l)	−8.3	−380.2	9.466
V_m (mole/(l · h))	−23.0	−1934.36	90.88
K_e ( )	0.96	1.144	1.349
α_e ( )	0.5	0.4664	0.4256
K'_m ( )	−3.0	−135.78	3.38

Table 2. Optimum intermediate dimensionless concentrations α_i^* evaluated at different temperatures and relative conversion of 90% with S_0 = 2.8 mole/l, ψ_0 = 1 and N = 5

T = 61 °C	T = 70 °C	T = 80 °C
0.817	0.803	0.788
0.702	0.678	0.654
0.629	0.600	0.569
0.583	0.550	0.516
0.554	0.519	0.483

Glucose is usually produced by the enzymatic liquefaction and saccharification of starch at about 60 °C at a typical concentration of 2.8 mole/l [8, 15]. The kinetic parameters of this reaction are shown in Table 1 at different temperatures that are of practical interest [15]. The intermediate substrate concentration given by $(\alpha_i - \alpha_e)/(\alpha_0 - \alpha_e)$ is calculated for substrate conversion of 90% of the equilibrium for a series of N CSTRs [8]. The results shown in Table 2 are for the case of 5 CSTRs in series.

The effect of the presence of product in the feed stream to the first reactor on the optimum total residence time is studied at three different temperatures and different number of reactors in series. The results are shown in Figs. 1, 2, and 3. The elements of the hessian matrix are evaluated in the case of N equal 5 and the conditions for a local minimum are checked. Their corresponding results are shown in Tables 3 and 4 respectively.

Table 4. The eigenvalues of the hessian matrices given in Table 3

T = 61 °C	T = 70 °C	T = 80 °C
9.69	4.27	1.87
39.55	17.44	7.63
117.02	51.6	22.58
392.32	172.99	75.70

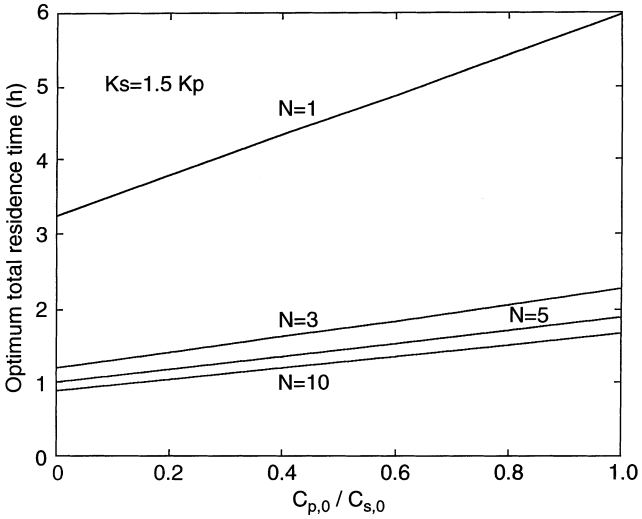

Fig. 1. The optimum total residence time as function of $\psi_0 = C_{p,0}/C_{s,0}$ for N CSTRs in series performing reversible Michaelis-Menten kinetics at T = 61 °C

5 Discussion and conclusions

The analytical expression obtained for the minimum overall residence time of N CSTRs in series operating isothermally and performing reversible Michaelis-Menten kinetics showed that it is a function of several parameters. Such parameters are: the initial and the desired final concentrations of substrate, equilibrium concentration, number of reactors, the apparent kinetic parameters K'_m and V'_m, and the initial ratio of concentrations of substrate and product ψ_0. Also, it is shown that the analytical expression for the optimum intermediate substrate concentration is independent of the apparent kinetic parameters K'_m and V'_m, and the initial ratio of product to substrate concentrations ψ_0.

The necessary condition of a stationary point stated by condition (i) of theorem 1 leads to an analytical expression for the overall residence time. This expression given by Eq. (34) corresponds to a local minimum. Since its corresponding hessian matrix is real, symmetric, tridiagonal and positive definite. This is proved by Eq. (37), where the determinant of any submatrix $\mathbf{HU}_k$ of order k is positive at the optimum intermediate substrate concentration vector α^*. This unconstrained minimum is also optimum for the constrained NLP, since its intermediate substrate concentration constraints are satisfied as it can be seen from Table 2. This is proved to be valid at the practical temperature range of T equal 61 up to 80 °C. For the case of N equal 5 using three different operating temperatures it is shown that all the eigenvalues of the corresponding hessain matrices are positive as shown in Tables 3 and 4, which satisfies also condition (ii) of theorem 2.

Table 3. The hessian matrix given by equation 30 evaluated at different temperatures and relative conversion of 90% with S_0 = 2.8 mole/l, ψ_0 = 1 and N = 5

T = 61 °C				T = 70 °C			
21.76	−17.24	0	0	9.60	−7.60	0	0
−17.24	54.66	−43.31	0	−7.60	24.10	−19.10	0
0	−43.31	137.30	−108.80	0	−19.10	60.54	−47.98
0	0	−108.80	344.87	0	0	−47.98	152.10

T = 80 °C			
4.20	−3.33	0	0
−3.33	10.55	−8.36	0
0	−8.36	26.49	−20.99
0	0	−20.99	66.54

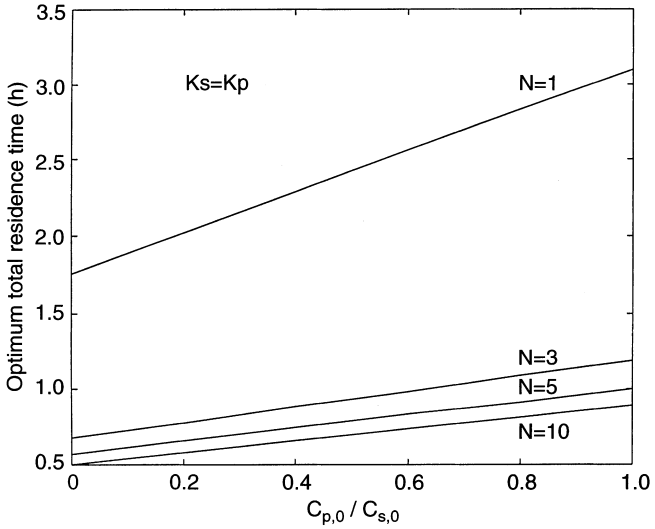

Fig. 2. The optimum total residence time as function of $\psi_0 = C_{p,0}/C_{s,0}$ for N CSTRs in series performing reversible Michaelis-Menten kinetics at $T = 70\,^{\circ}C$

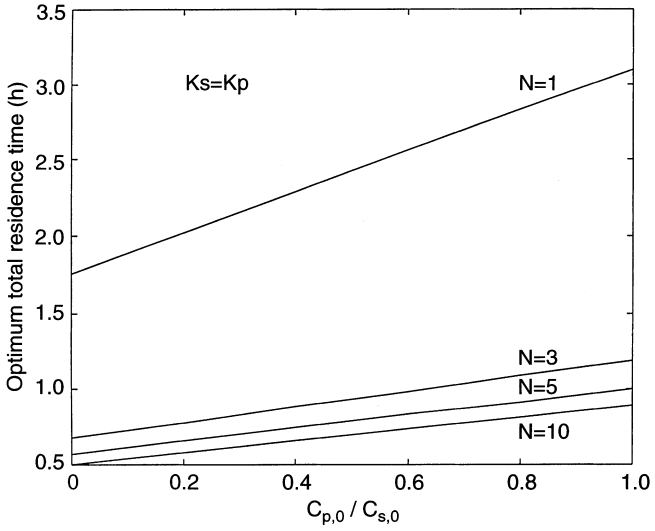

Fig. 3. The optimum total residence time as function of $\psi_0 = C_{p,0}/C_{s,0}$ for N CSTRs in series performing reversible Michaelis-Menten kinetics at $T = 80\,^{\circ}C$

The effect of the presence of product in the feed stream to the first reactor is investigated. It is found that the only kinetic parameter depending on ψ is K'_m where it is dependent on ψ_0 only. The effect of ψ_0 on the optimum overall residence time is shown in Figs. 1, 2, and 3 at different operating temperatures. It is found that as the product concentration in the feed stream increases, the optimum total residence time increases. This behavior is expected since the reaction exhibits competitive product inhibition with net increase of K'_m which results in a reduction of the reaction rate. The effect of the presence of product in the feed stream to the first reactor decreases as the total number of reactors N increases as shown in Figs. 1, 2, and 3. This means that plug flow reactors are not greatly affected by the presence of product in the feed stream, since in the limit as $N \rightarrow \infty$ the CSTRs approach the performance of the plug flow reactor.

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