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Modeling of a control induced system for product formation in enzyme kinetics

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Abstract Double substrate enzyme kinetics has a leading role for product quantification and optimization in different chemical and biochemical sectors. Mathematical approach for controlling these reactions in different stages by suitable parameters adds a new dimension in this interdisciplinary field of research. Applying control theoretic approach in the reversible backward stages of double substrate enzymatic model, time economization with regard to product formation is significant. In this article, we formulate a double substrate mathematical model of enzymatic dynamical reaction system with control measures with a view to observe the effect of changes of these measures with respect to the concentration of substrates, enzyme, complexes and finally product. Here, Pontryagin Minimum Principle is used for observing the effect of control measures in the system dynamics with the help of Hamiltonian. We compare the relevant numerical solutions for the substrates, enzyme, complexes and product concentration profile for a specified time interval with respect to control factors.

Keywords Substrate · Product · Enzyme kinetics · Non-linear reaction equation · Pontryagin Minimum Principle

1 Introduction

Controlling enzymatic reactions in the field of chemical kinetics generates quality product with time economization. Identifying control parameters is thus significant towards formation of product. Chemical kinetics, with the help of biocatalyst like

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enzyme, plays an important role in this aspect. For smooth completion of reaction, enzyme is needed as it acts as a catalyst which increases the rate of a reaction by lowering the free energy of activation of the reaction and gives product without forming any side products. The most important features of enzyme are catalytic power, specificity, regulation and time saving. In the dynamics of enzymatic reaction, enzyme binds target molecules or substrates. This binding occurs through the active sites of enzymes which is the most dynamic part of an enzyme, where substrates bind and undergo a chemical reaction.
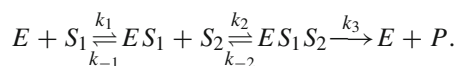
Enzymatic reactions with single substrate or double substrate creates a lot of attention in chemical and biochemical reactions. Among them, double substrate enzymatic kinetic model is more purposeful and applicable. Mathematicians made a significant contribution in this system dynamics for optimization and quantification of product. Introduction of enzyme kinetics with a mathematical bent is elaborately discussed in various books [1–3] and [4]. Dual substrate enzyme kinetic model with control approach glorifies a new dimension of thinking towards chemical engineers, mathematicians, doctors and other academicians relating to the interdisciplinary field of research. So mathematical analysis has an important role in enzymatic reaction environment and helps us to realize the evaluation of control parameters, optimum control of reaction conditions and product optimization in relation to kinetically controlled enzymatic systems. So, mathematical modeling as a reaction engineering principle has been finding a considerable role in enzymatic reactions [5,6] and it is growing in a significant way with the use of bio-catalysis.

The distinctive feature of enzyme kinetics is the formation of enzyme-substrate complex of different nature. In 1902, Brown [7] proposed the existence of an enzyme-substrate complex in a purely kinetic context with a fixed lifetime to form the product. This was the first time that the existence of the complex was proposed in an enzymatic dynamics. Later, this was studied in various disciplines led by the pioneer work of Sharpe and Lotka [8] and Volterra [9] in Epidemiology and Ecology. So enzyme kinetics based on mathematical foundation has an emerging role in the area of double substrate enzymatic system considering control approach.

In our consideration of the enzyme kinetics in this research article, an approach for the development of the enzyme kinetic model with control parameters in different stages of reaction dynamics is introduced. The product formation with a single enzyme by dual substrate is adopted by considering introduction of substrate in the sequence of reactions. With this view, we are trying to establish that by adopting effective control measures in the reversible backward successive stages, time for consumption of substrate is much less as well as product formation will be cost effective.

2 The basic assumptions and formulation of the mathematical model

Here, we are introducing an enzyme kinetic model with two types of substrates and a single enzyme. The kinetic reaction is represented by the following schematic diagram:

$$E + S_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E S_1 + S_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E S_1 S_2 \overset{k_3}{\longrightarrow} E + P.$$

Here S_1 and S_2 are two substrates and E is the enzyme. C_1 i.e., ES_1 and C_2 i.e., ES_1S_2 are the two intermediate enzyme-substrate complexes and P is the product. Here k_1 and k_2 are the rate constants of the formation of the complexes C_1 and C_2 respectively and k_3 is the catalysis rate constant. The rate constant for backward reaction of the complexes C_1 and C_2 are k_{-1} and k_{-2} respectively. In this model, one mole of substrate combining with one mole of enzyme forms one mole of enzyme-substrate complex C_1. This complex (C_1) may decompose back into enzyme E and unmodified substrate S_1 or may combine with substrate S_2 to form enzyme-substrate complex C_2. This complex (C_2) produces the product P or may decompose back into C_1 and S_2 or ES_2 and S_1. Here we assume the first one on the basis of the assumption that the reaction between E and S_1 is faster than that of E and S_2 and hence the binding of E and S_1 is much stronger than that of E and S_2.

Let us assume that s_1, s_2, e_k, c_1, c_2 and p for $[S_1], [S_2], [E], [C_1], [C_2]$ and $[P]$ respectively, where [ ] represents the concentration of a substance. From the Law of Mass Action, the set of nonlinear differential equations describing the above enzymatic reaction is as follows:
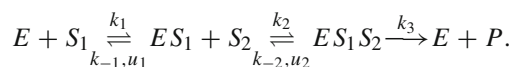
$$\frac{ds_1}{dt} = -k_1 e_k s_1 + k_{-1} c_1,$$

$$\frac{ds_2}{dt} = -k_2 c_1 s_2 + k_{-2} c_2,$$

$$\frac{de_k}{dt} = -k_1 e_k s_1 + k_{-1} c_1 + k_3 c_2,$$

$$\frac{dc_1}{dt} = k_1 e_k s_1 - k_{-1} c_1 - k_2 c_1 s_2 + k_{-2} c_2,$$

$$\frac{dc_2}{dt} = k_2 c_1 s_2 - k_{-2} c_2 - k_3 c_2,$$

$$\frac{dp}{dt} = k_3 c_2, \tag{1}$$

with initial conditions

$$s_1(0) = s_{10}, \quad s_2(0) = s_{20}, \quad e(0) = e_0,$$
$$c_1(0) = 0, \quad c_2(0) = 0 \ \ and \ p(0) = 0, \tag{2}$$

where $k_1, k_2, k_3, k_{-1}, k_{-2}, s_{10}, s_{20}$ and e_0 are positive constants.

Here in this paper, we have introduced two control parameters u_1 and u_2. u_1 is introduced in the first stage of backward reaction and u_2 in the second stage. The corresponding reaction mechanism is given by

$$E + S_1 \underset{k_{-1}, u_1}{\overset{k_1}{\rightleftharpoons}} ES_1 + S_2 \underset{k_{-2}, u_2}{\overset{k_2}{\rightleftharpoons}} ES_1S_2 \overset{k_3}{\longrightarrow} E + P.$$

With these two control parameters taking into consideration and from the Law of Mass Action, we have the following system of nonlinear differential equations:

$$\frac{ds_1}{dt} = -k_1 e_k s_1 + k_{-1}(1 - u_1(t))c_1,$$

$$\frac{ds_2}{dt} = -k_2 c_1 s_2 + k_{-2}(1 - u_2(t))c_2,$$

$$\frac{de_k}{dt} = -k_1 e_k s_1 + k_{-1}(1 - u_1(t))c_1 + k_3 c_2,$$

$$\frac{dc_1}{dt} = k_1 e_k s_1 - k_{-1}(1 - u_1(t))c_1 - k_2 c_1 s_2 + k_{-2}(1 - u_2(t))c_2,$$

$$\frac{dc_2}{dt} = k_2 c_1 s_2 - k_{-2}(1 - u_2(t))c_2 - k_3 c_2,$$

$$\frac{dp}{dt} = k_3 c_2, \tag{3}$$

where

$$s_1(0) = s_{10}, \quad s_2(0) = s_{20}, \quad e(0) = e_0,$$

$$c_1(0) = 0, \quad c_2(0) = 0 \quad \text{and} \quad p(0) = 0, \tag{4}$$

with $k_1, k_2, k_3, k_{-1}, k_{-2}, s_{10}, s_{20}$ and e_0 are positive constants and $0 \leq u_i \leq 1$ for $i = 1, 2$.

3 Theoretical study of the system

Here we want to maximize the product p, so that we define the objective function for the minimization problem as,

$$J(u_1, u_2) = \int_{t_i}^{t_f} \left[A u_1^2(t) + B u_2^2(t) - N p^2(t) \right] dt \tag{5}$$

subject to the state system (3). Here A, B are the weight constant on the benefit of the cost of production and N is the penalty multiplier. The object is to attain the optimal control $u^* = (u_1^*, u_2^*)$ such that

$$J(u_1^*, u_2^*) = min(J(u_1, u_2) : (u_1, u_2) \in U) \; where \; U = U_1 \times U_2,$$
$$U_1 = \left(u_1(t) : u_1 \; is \; measurable \; and \; 0 \leq u_1 \leq 1, t \in [t_i, t_f] \right) \; and$$
$$U_2 = \left(u_2(t) : u_2 \; is \; measurable \; and \; 0 \leq u_2 \leq 1, t \in [t_i, t_f] \right).$$

Here we use "Pontryagin Minimum Principle" [10] to obtain the optimal control u^*.

3.1 Dynamics of the optimal system

For optimal control of the system, we define the Hamiltonian as follows:

$$H = Au_1^2(t) + Bu_2^2(t) - Np^2(t)$$
$$+\xi_1[-k_1 e_k s_1 + k_{-1}(1 - u_1(t))c_1]$$
$$+\xi_2[-k_2 c_1 s_2 + k_{-2}(1 - u_2(t))c_2]$$
$$+\xi_3[-k_1 e_k s_1 + k_{-1}(1 - u_1(t))c_1 + k_3 c_2]$$
$$+\xi_4[k_1 e_k s_1 - k_{-1}(1 - u_1(t))c_1 - k_2 c_1 s_2 + k_{-2}(1 - u_2(t))c_2]$$
$$+\xi_5[k_2 c_1 s_2 - k_{-2}(1 - u_2(t))c_2 - k_3 c_2]$$
$$+\xi_6[k_3 c_2]. \tag{6}$$

The corresponding adjoint equations are given by,

$$\frac{d\xi_1}{dt} = -\frac{\partial H}{\partial s_1}, \quad \frac{d\xi_2}{dt} = -\frac{\partial H}{\partial s_2}, \quad \frac{d\xi_3}{dt} = -\frac{\partial H}{\partial e_k},$$
$$\frac{d\xi_4}{dt} = -\frac{\partial H}{\partial c_1}, \quad \frac{d\xi_5}{dt} = -\frac{\partial H}{\partial c_2}, \quad \frac{d\xi_6}{dt} = -\frac{\partial H}{\partial p},$$

which give,

$$\frac{d\xi_1}{dt} = k_1 e_k(\xi_1 + \xi_3 - \xi_4),$$
$$\frac{d\xi_2}{dt} = k_2 c_1(\xi_2 + \xi_4 - \xi_5),$$
$$\frac{d\xi_3}{dt} = k_1 s_1(\xi_1 + \xi_3 - \xi_4),$$
$$\frac{d\xi_4}{dt} = -k_{-1}(1 - u_1(t))(\xi_1 + \xi_3 - \xi_4) + k_2 s_2(\xi_2 + \xi_4 - \xi_5),$$
$$\frac{d\xi_5}{dt} = -k_{-2}(1 - u_2(t))(\xi_2 + \xi_4 - \xi_5) - k_3(\xi_3 - \xi_5 + \xi_6),$$
$$\frac{d\xi_6}{dt} = 2Np. \tag{7}$$

Using "Pontryagin Minimum Principle", the unconstrained optimal control variables u_1^* and u_2^* satisfy

$$\frac{\partial H}{\partial u_1^*} = \frac{\partial H}{\partial u_2^*} = 0.$$

Now, the Hamiltonian can also be written as,

$$H = Au_1^2(t) + \xi_1 k_{-1}(1 - u_1(t))c_1 + \xi_3 k_{-1}(1 - u_1(t))c_1$$
$$-\xi_4 k_{-1}(1 - u_1(t))c_1 + Bu_2^2(t) + \xi_2 k_{-2}(1 - u_2(t))c_2$$
$$+\xi_4 k_{-2}(1 - u_2(t))c_2 - \xi_5 k_{-2}(1 - u_2(t))c_2$$
$$+terms\ without\ u_1\ and\ u_2.$$

Taking partial derivative of the above expression of H with respect to u_1 and u_2 simultaneously, we have the following results:

$$\frac{\partial H}{\partial u_1^*} = 2Au_1^* - k_{-1}c_1(\xi_1 + \xi_3 - \xi_4) = 0,$$

$$\frac{\partial H}{\partial u_2^*} = 2Bu_2^* - k_{-2}c_2(\xi_2 + \xi_4 - \xi_5) = 0.$$

Thus for the optimal control, we get

$$u_1^*(t) = \frac{k_{-1}c_1(\xi_1 + \xi_3 - \xi_4)}{2A},$$

$$u_2^*(t) = \frac{k_{-2}c_2(\xi_2 + \xi_4 - \xi_5)}{2B}.$$

Due to the boundedness of the standard control, we conclude for the control u_1:

$$u_1^*(t) = \begin{cases} 0, & \frac{k_{-1}c_1(\xi_1+\xi_3-\xi_4)}{2A} \leq 0, \\ \frac{k_{-1}c_1(\xi_1+\xi_3-\xi_4)}{2A}, & 0 < \frac{k_{-1}c_1(\xi_1+\xi_3-\xi_4)}{2A} < 1, \\ 1, & \frac{k_{-1}c_1(\xi_1+\xi_3-\xi_4)}{2A} \geq 1. \end{cases}$$

Hence the compact form of $u_1^*(t)$ is

$$u_1^*(t) = max\left(0, min\left(1, \frac{k_{-1}c_1(\xi_1 + \xi_3 - \xi_4)}{2A}\right)\right).$$

In a similar way we can have the compact form of $u_2^*(t)$ as

$$u_2^*(t) = max\left(0, min\left(1, \frac{k_{-2}c_2(\xi_2 + \xi_4 - \xi_5)}{2B}\right)\right).$$

3.1.1 Uniqueness of the optimal control

Let us suppose that, $(s_1, s_2, e_k, c_1, c_2, p, \xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6)$ and $(\bar{s}_1, \bar{s}_2, \bar{e}_k, \bar{c}_1, \bar{c}_2, \bar{p},$ $\bar{\xi}_1, \bar{\xi}_2, \bar{\xi}_3, \bar{\xi}_4, \bar{\xi}_5, \bar{\xi}_6)$ are two solutions of the system (3), (7).

We consider, $s_1 = e^{\lambda t}p_1, s_2 = e^{\lambda t}p_2, e_k = e^{\lambda t}p_3, c_1 = e^{\lambda t}p_4, c_2 = e^{\lambda t}p_5, p = e^{\lambda t}p_6, \xi_1 = e^{-\lambda t}q_1, \xi_2 = e^{-\lambda t}q_2, \xi_3 = e^{-\lambda t}q_3, \xi_4 = e^{-\lambda t}q_4, \xi_5 = e^{-\lambda t}q_5$ and $\xi_6 = e^{-\lambda t}q_6$.

Similarly, $\bar{s}_1 = e^{\lambda t}\bar{p}_1, \bar{s}_2 = e^{\lambda t}\bar{p}_2, \bar{e}_k = e^{\lambda t}\bar{p}_3, \bar{c}_1 = e^{\lambda t}\bar{p}_4, \bar{c}_2 = e^{\lambda t}\bar{p}_5, \bar{p} = e^{\lambda t}\bar{p}_6, \bar{\xi}_1 = e^{-\lambda t}\bar{q}_1, \bar{\xi}_2 = e^{-\lambda t}\bar{q}_2, \bar{\xi}_3 = e^{-\lambda t}\bar{q}_3, \bar{\xi}_4 = e^{-\lambda t}\bar{q}_4, \bar{\xi}_5 = e^{-\lambda t}\bar{q}_5$ and $\bar{\xi}_6 = e^{-\lambda t}\bar{q}_6$.

We now assume that,

$$u_1 = max\left(0, min\left(1, \frac{k_{-1}c_1(\xi_1 + \xi_3 - \xi_4)}{2A}\right)\right),$$

$$u_2 = max\left(0, min\left(1, \frac{k_{-2}c_2(\xi_2 + \xi_4 - \xi_5)}{2B}\right)\right),$$

$$\bar{u}_1 = max\left(0, min\left(1, \frac{k_{-1}\bar{c}_1(\bar{\xi}_1 + \bar{\xi}_3 - \bar{\xi}_4)}{2A}\right)\right) \; and$$

$$\bar{u}_2 = max\left(0, min\left(1, \frac{k_{-2}\bar{c}_2(\bar{\xi}_2 + \bar{\xi}_4 - \bar{\xi}_5)}{2B}\right)\right).$$

Then we have the following two inequalities,

$$\int_{t_i}^{t_f} (u_1 - \bar{u}_1)^2 \, dt \leq \tilde{C}_1 \left(\frac{k_{-1}}{2A}\right)^2 \int_{t_i}^{t_f} \left[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2\right] dt,$$

$$\int_{t_i}^{t_f} (u_2 - \bar{u}_2)^2 dt \leq \tilde{C}_2 \left(\frac{k_{-2}}{2B}\right)^2 \int_{t_i}^{t_f} \left[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2 + |q_5 - \bar{q}_5|^2\right] dt. \quad (8)$$

Substituting $s_1 = e^{\lambda t} p_1$, $s_2 = e^{\lambda t} p_2$, $e_k = e^{\lambda t} p_3$, $c_1 = e^{\lambda t} p_4$, $c_2 = e^{\lambda t} p_5$, $p = e^{\lambda t} p_6$, $\xi_1 = e^{-\lambda t} q_1$, $\xi_2 = e^{-\lambda t} q_2$, $\xi_3 = e^{-\lambda t} q_3$, $\xi_4 = e^{-\lambda t} q_4$, $\xi_5 = e^{-\lambda t} q_5$ and $\xi_6 = e^{-\lambda t} q_6$ in (3) and (7) we have,

$$\dot{p}_1 + \lambda p_1 = -k_1 e^{\lambda t} p_1 p_3 + k_{-1} p_4 (1 - u_1),$$
$$\dot{p}_2 + \lambda p_2 = -k_2 e^{\lambda t} p_2 p_4 + k_{-2} p_5 (1 - u_2),$$
$$\dot{p}_3 + \lambda p_3 = -k_1 e^{\lambda t} p_1 p_3 + k_{-1} p_4 (1 - u_1) + k_3 p_5,$$
$$\dot{p}_4 + \lambda p_4 = k_1 e^{\lambda t} p_1 p_3 - k_{-1} p_4 (1 - u_1) - k_2 e^{\lambda t} p_2 p_4 + k_{-2} p_5 (1 - u_2),$$
$$\dot{p}_5 + \lambda p_5 = k_2 e^{\lambda t} p_2 p_4 - k_{-2} p_5 (1 - u_2) - k_3 p_5,$$
$$\dot{p}_6 + \lambda p_6 = k_3 p_5,$$
$$\dot{q}_1 - \lambda q_1 = k_1 e^{\lambda t} p_3 (q_1 + q_3 - q_4),$$
$$\dot{q}_2 - \lambda q_2 = k_2 e^{\lambda t} p_4 (q_2 + q_4 - q_5),$$
$$\dot{q}_3 - \lambda q_3 = k_1 e^{\lambda t} p_1 (q_1 + q_3 - q_4),$$
$$\dot{q}_4 - \lambda q_4 = -k_{-1}(1 - u_1)(q_1 + q_3 - q_4) + k_2 p_2 e^{\lambda t} (q_2 + q_4 - q_5),$$
$$\dot{q}_5 - \lambda q_5 = -k_{-2}(1 - u_2)(q_2 + q_4 - q_5) - k_3 (q_3 - q_5 + q_6),$$
$$\dot{q}_6 - \lambda q_6 = 2N e^{2\lambda t} p_6. \quad (9)$$

We have another set of twelve such similar equations for the substitution $\bar{s}_1 = e^{\lambda t} \bar{p}_1$, $\bar{s}_2 = e^{\lambda t} \bar{p}_2$, $\bar{e}_k = e^{\lambda t} \bar{p}_3$, $\bar{c}_1 = e^{\lambda t} \bar{p}_4$, $\bar{c}_2 = e^{\lambda t} \bar{p}_5$, $\bar{p} = e^{\lambda t} \bar{p}_6$, $\bar{\xi}_1 = e^{-\lambda t} \bar{q}_1$, $\bar{\xi}_2 = e^{-\lambda t} \bar{q}_2$, $\bar{\xi}_3 = e^{-\lambda t} \bar{q}_3$, $\bar{\xi}_4 = e^{-\lambda t} \bar{q}_4$, $\bar{\xi}_5 = e^{-\lambda t} \bar{q}_5$ and $\bar{\xi}_6 = e^{-\lambda t} \bar{q}_6$.

Here we subtract the equations for $\bar{s}_1$ from s_1, $\bar{s}_2$ from s_2, $\bar{e}_k$ from e_k, $\bar{c}_1$ from c_1, $\bar{c}_2$ from c_2, $\bar{p}$ from p, $\bar{\xi}_1$ from ξ_1, $\bar{\xi}_2$ from ξ_2, $\bar{\xi}_3$ from ξ_3, $\bar{\xi}_4$ from ξ_4, $\bar{\xi}_5$ from ξ_5 and $\bar{\xi}_6$ from ξ_6. Next, each subtracted equation is multiplied by an appropriate function and then integrated from initial time (t_i) to final time (t_f).

With the help of result (8) we have the following inequalities,

$$\frac{1}{2}(p_1 - \bar{p}_1)^2(t_f) + \lambda \int_{t_i}^{t_f} (p_1 - \bar{p}_1)^2 dt \le \tilde{C}_3 e^{\lambda t_f} \int_{t_i}^{t_f} \Big[|p_1 - \bar{p}_1|^2$$

$$+ |p_3 - \bar{p}_3|^2 \Big] dt + \tilde{C}_4 \int_{t_i}^{t_f} \Big[|p_1 - \bar{p}_1|^2 + |p_4 - \bar{p}_4|^2 \Big] dt$$

$$+ \tilde{C}_4 \left(\frac{k_{-1}}{2A} \right)^2 \int_{t_i}^{t_f} \Big[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2 \Big] dt,$$

$$\frac{1}{2}(p_2 - \bar{p}_2)^2(t_f) + \lambda \int_{t_i}^{t_f} (p_2 - \bar{p}_2)^2 dt \le \tilde{C}_5 e^{\lambda t_f} \int_{t_i}^{t_f} \Big[|p_2 - \bar{p}_2|^2 + |p_4 - \bar{p}_4|^2 \Big] dt$$

$$+ \tilde{C}_6 \int_{t_i}^{t_f} \Big[|p_2 - \bar{p}_2|^2 + |p_5 - \bar{p}_5|^2 \Big] dt + \tilde{C}_6 \left(\frac{k_{-2}}{2B} \right)^2 \int_{t_i}^{t_f} \Big[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2$$

$$+ |q_5 - \bar{q}_5|^2 \Big] dt,$$

$$\frac{1}{2}(p_3 - \bar{p}_3)^2(t_f) + \lambda \int_{t_i}^{t_f} (p_3 - \bar{p}_3)^2 dt$$

$$\le \tilde{C}_7 e^{\lambda t_f} \int_{t_i}^{t_f} \Big[|p_1 - \bar{p}_1|^2 + |p_3 - \bar{p}_3|^2 \Big] dt + \tilde{C}_8 \int_{t_i}^{t_f} \Big[|p_3 - \bar{p}_3|^2 + |p_4 - \bar{p}_4|^2 \Big] dt$$

$$+ \tilde{C}_8 \left(\frac{k_{-1}}{2A} \right)^2 \int_{t_i}^{t_f} \Big[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2 \Big] dt$$

$$+ \tilde{C}_9 \int_{t_i}^{t_f} \Big[|p_3 - \bar{p}_3|^2 + |p_5 - \bar{p}_5|^2 \Big] dt,$$

$$\frac{1}{2}(p_4 - \bar{p}_4)^2(t_f) + \lambda \int_{t_i}^{t_f} (p_4 - \bar{p}_4)^2 dt$$

$$\le \tilde{C}_{10} e^{\lambda t_f} \int_{t_i}^{t_f} \Big[|p_1 - \bar{p}_1|^2 + |p_3 - \bar{p}_3|^2 + |p_4 - \bar{p}_4|^2 \Big] dt$$

$$+\tilde{C_{11}} \int_{t_i}^{t_f} \left[|p_4 - \bar{p}_4|^2\right] dt + \tilde{C_{11}} \left(\frac{k_{-1}}{2A}\right)^2 \int_{t_i}^{t_f} \left[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2\right] dt$$

$$+\tilde{C_{12}} e^{\lambda t_f} \int_{t_i}^{t_f} \left[|p_2 - \bar{p}_2|^2 + |p_4 - \bar{p}_4|^2\right] dt + \tilde{C_{13}} \int_{t_i}^{t_f} \left[|p_5 - \bar{p}_5|^2\right] dt$$

$$+\tilde{C_{13}} \left(\frac{k_{-2}}{2B}\right)^2 \int_{t_i}^{t_f} \left[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2 + |q_5 - \bar{q}_5|^2\right] dt,$$

$$\frac{1}{2}(p_5 - \bar{p}_5)^2(t_f) + \lambda \int_{t_i}^{t_f} (p_5 - \bar{p}_5)^2 dt \le \tilde{C_{14}} e^{\lambda t_f} \int_{t_i}^{t_f} \left[|p_2 - \bar{p}_2|^2 + |p_4 - \bar{p}_4|^2\right.$$

$$\left.+|p_5 - \bar{p}_5|^2\right] dt + \tilde{C_{15}} \left(\frac{k_{-2}}{2B}\right)^2 \int_{t_i}^{t_f} \left[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2 + |q_5 - \bar{q}_5|^2\right] dt$$

$$+\tilde{C_{16}} \int_{t_i}^{t_f} \left[|p_5 - \bar{p}_5|^2\right] dt,$$

$$\frac{1}{2}(p_6 - \bar{p}_6)^2(t_f) + \lambda \int_{t_i}^{t_f} (p_6 - \bar{p}_6)^2 dt \le \tilde{C_{17}} \int_{t_i}^{t_f} \left[|p_5 - \bar{p}_5|^2 + |p_6 - \bar{p}_6|^2\right] dt,$$

$$\frac{1}{2}(q_1 - \bar{q}_1)^2(t_i) + \lambda \int_{t_i}^{t_f} (q_1 - \bar{q}_1)^2 dt \le \tilde{C_{18}} e^{\lambda t_f} \int_{t_i}^{t_f} \left[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2\right] dt,$$

$$\frac{1}{2}(q_2 - \bar{q}_2)^2(t_i) + \lambda \int_{t_i}^{t_f} (q_2 - \bar{q}_2)^2 dt \le \tilde{C_{19}} e^{\lambda t_f} \int_{t_i}^{t_f} \left[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2 + |q_5 - \bar{q}_5|^2\right] dt,$$

$$\frac{1}{2}(q_3 - \bar{q}_3)^2(t_i) + \lambda \int_{t_i}^{t_f} (q_3 - \bar{q}_3)^2 dt \le \tilde{C_{20}} e^{\lambda t_f} \int_{t_i}^{t_f} \left[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2\right] dt,$$

$$\frac{1}{2}(q_4 - \bar{q}_4)^2(t_i) + \lambda \int_{t_i}^{t_f} (q_4 - \bar{q}_4)^2 dt$$

$$\le \tilde{C_{21}} \left(1 + \left(\frac{k_{-1}}{2A}\right)^2\right) \int_{t_i}^{t_f} \left[|q_1 - \bar{q}_1|^2 + |q_3 - \bar{q}_3|^2 + |q_4 - \bar{q}_4|^2\right] dt$$

$$+\tilde{C_{22}} e^{\lambda t_f} \int_{t_i}^{t_f} \left[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2 + |q_5 - \bar{q}_5|^2\right] dt,$$

$$\frac{1}{2}(q_5 - \bar{q}_5)^2(t_i) + \lambda \int_{t_i}^{t_f} (q_5 - \bar{q}_5)^2 dt$$

$$\leq \tilde{C}_{23}\left(1 + \left(\frac{k_{-2}}{2B}\right)^2\right)\int_{t_i}^{t_f}\left[|q_2 - \bar{q}_2|^2 + |q_4 - \bar{q}_4|^2 + |q_5 - \bar{q}_5|^2\right]dt$$

$$+\tilde{C}_{24}\int_{t_i}^{t_f}\left[|q_3 - \bar{q}_3|^2 + |q_5 - \bar{q}_5|^2 + |q_6 - \bar{q}_6|^2\right]dt$$

$$and\ \frac{1}{2}(q_6 - \bar{q}_6)^2(t_i) + \lambda\int_{t_i}^{t_f}(q_6 - \bar{q}_6)^2dt \leq \tilde{C}_{25}e^{2\lambda t_f}\int_{t_i}^{t_f}[|p_6 - \bar{p}_6|^2 + |q_6 - \bar{q}_6|^2]dt.$$

Here the constants $\tilde{C}_1$ to $\tilde{C}_{25}$ depend on the coefficients and the bounds on states and adjoints.

The above twelve inequalities are added and estimated to obtain the following result,

$$\frac{1}{2}\Big[(p_1 - \bar{p}_1)^2(t_f) + (p_2 - \bar{p}_2)^2(t_f) + (p_3 - \bar{p}_3)^2(t_f) + (p_4 - \bar{p}_4)^2(t_f)$$

$$+(p_5 - \bar{p}_5)^2(t_f) + (p_6 - \bar{p}_6)^2(t_f) + (q_1 - \bar{q}_1)^2(t_i) + (q_2 - \bar{q}_2)^2(t_i)$$

$$+(q_3 - \bar{q}_3)^2(t_i) + (q_4 - \bar{q}_4)^2(t_i) + (q_5 - \bar{q}_5)^2(t_i) + (q_6 - \bar{q}_6)^2(t_i)\Big]$$

$$+\lambda\int_{t_i}^{t_f}\Big[(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2$$

$$+(p_5 - \bar{p}_5)^2 + (p_6 - \bar{p}_6)^2 + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2$$

$$+(q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2 + (q_6 - \bar{q}_6)^2\Big]dt$$

$$\leq (\tilde{M}_1 + \tilde{M}_2e^{2\lambda t_f})\int_{t_i}^{t_f}\Big[(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2 + (p_3 - \bar{p}_3)^2$$

$$+(p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2 + (p_6 - \bar{p}_6)^2 + (q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2$$

$$+(q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2 + (q_5 - \bar{q}_5)^2 + (q_6 - \bar{q}_6)^2\Big]dt, \tag{10}$$

where $\tilde{M}_1$ and $\tilde{M}_2$ depend on the coefficients and the bounds of $p_1, p_2, p_3, p_4, p_5, p_6$, q_1, q_2, q_3, q_4, q_5 and q_6.

From the above we have,

$$(\lambda - \tilde{M}_1 - \tilde{M}_2e^{2\lambda t_f})\int_{t_i}^{t_f}\Big[(p_1 - \bar{p}_1)^2 + (p_2 - \bar{p}_2)^2$$

$$+(p_3 - \bar{p}_3)^2 + (p_4 - \bar{p}_4)^2 + (p_5 - \bar{p}_5)^2 + (p_6 - \bar{p}_6)^2$$

$$+(q_1 - \bar{q}_1)^2 + (q_2 - \bar{q}_2)^2 + (q_3 - \bar{q}_3)^2 + (q_4 - \bar{q}_4)^2$$

$$+(q_5 - \bar{q}_5)^2 + (q_6 - \bar{q}_6)^2\Big]dt \leq 0. \tag{11}$$

If we choose λ such that $\lambda > \tilde{M}_1 + \tilde{M}_2$ and $t_f < \frac{1}{2\lambda} \ln(\frac{\lambda - \tilde{M}_1}{\tilde{M}_2})$, then $p_1 = \bar{p}_1, p_2 = \bar{p}_2, p_3 = \bar{p}_3, p_4 = \bar{p}_4, p_5 = \bar{p}_5, p_6 = \bar{p}_6, q_1 = \bar{q}_1, q_2 = \bar{q}_2, q_3 = \bar{q}_3, q_4 = \bar{q}_4, q_5 = \bar{q}_5$ and $q_6 = \bar{q}_6$.

Hence we can conclude that the solution is unique for the time interval $[t_i, t_f]$.

4 Numerical simulation

The dynamics of the double substrate enzymatic reaction system have been analyzed using numerical methods. The concentration of substances s_1, s_2, e_k, c_1, c_2 and p are observed with time in the presence and absence of the control theoretic approach. Here, it may be mentioned that in the system dynamics of enzymatic reaction, first and second steps are reversible and the final stage is irreversible. We analyze the dynamics of the substances for a time period of initial 0.75 h i.e., 45 minutes during which the reaction system progresses continuously as a normal mode. Here, control parameters have been applied in the successive backward reversible stages to observe the effect of concentration of substances with time for significant results. For the better understanding of the control measures on the reaction dynamics, the control variables are introduced during a time period of 30 minutes after completion of initial reaction by 15 minutes. So, two sets of concentration profiles are compared. The kinetic profile diagrams have been analyzed considering the parameter values as $k_1 = 5, k_2 = 5, k_3 = 5, k_{-1} = 1, k_{-2} = 1$. Unit of the parameters k_1 and k_2 is considered as $(\text{moles/l})^{-1} \text{h}^{-1}$ and that of k_3, k_{-1} and k_{-2} is h^{-1}. Numerical values of model parameters, applied in the numerical analysis, have been collected from Alicea [11] and Varadharajan [12].

Figures 1 and 2 represent the concentration profiles of substrates, enzyme, complexes and product of the system dynamics in the absence of the control parameters. It is observed from Fig. 1a that initially rate of consumption of s_1 is higher. After a certain period of time ($t \cong 0.75$ h), it has been almost consumed. As the reaction between enzyme and first substrate (S_1) is faster than that of enzyme and second substrate (S_2), S_2 binds with the first complex (C_1) through the multiple active sites of the enzyme. Due to this reason s_2 takes more time than s_1 for completion of consumption (Fig. 1b). After 45 minutes of reaction time, the concentration of substrates s_1 and s_2 are observed as 0.0283 moles/l and 0.4783 moles/l respectively. Figure 1c repre-
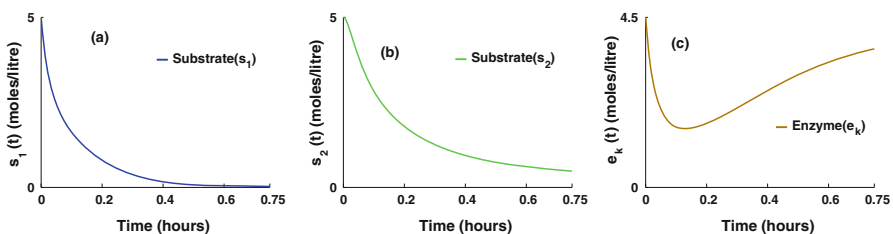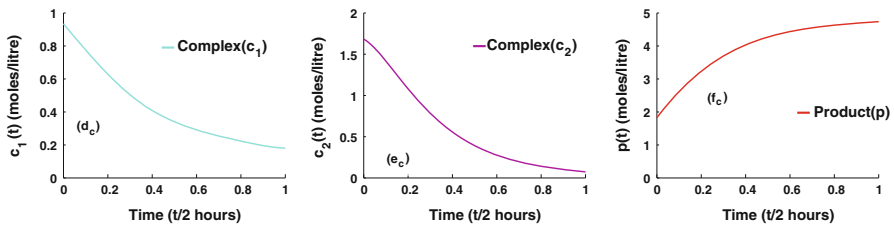

Fig. 1 Normalized concentration profile of the substrates and enzyme as a function of time for various values of reaction parameters (without control)
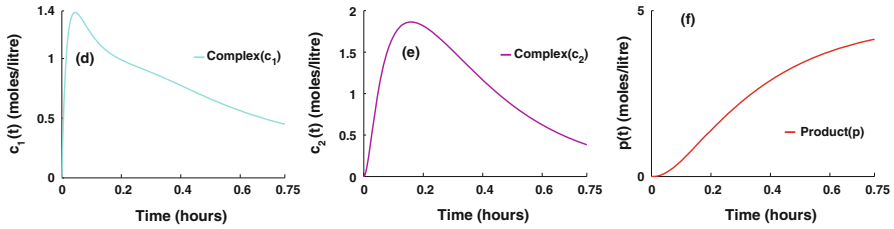
Fig. 2 Normalized concentration profile of the complexes and product as a function of time for various values of reaction parameters (without control)
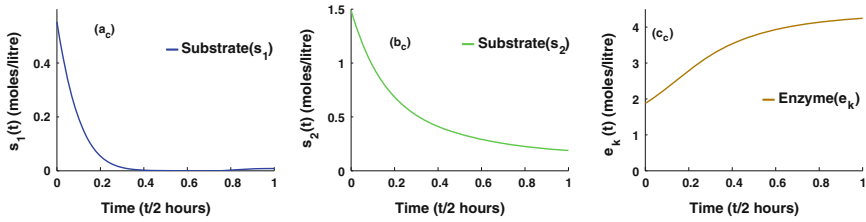
Fig. 3 Normalized concentration profile of the substrates and enzyme as a function of time for various values of reaction parameters (with control)

Fig. 4 Normalized concentration profile of the complexes and product as a function of time for various values of reaction parameters (with control)

sents the concentration profile diagram of enzyme. After the same time interval, the concentration of enzyme is found to be 3.667 moles/l.

It is inferred from Fig. 2d that, the concentration of the first complex c_1 increases gradually form its initial value and reaches a maximum value at a definite time interval. After that, it decreases as it binds with the second substrate to form the second complex. Again the concentration of the second complex c_2 increases (Fig. 2e) as it produces as soon as the first complex is formed. Figure 2f represents the concentration profile of the product p and it is clear from the figure that the product formation continues from the second complex.

Now, control parameters for changing reaction operators have a significant impact on the system dynamics. Figures 3 and 4 characterize the change in concentrations of the substances of the reaction system for a time period of 30 minutes during which a control is applied to the system. Here we see that by applying control approach, both the substrates are consumed within a short period of time as described in Fig. $3a_c$ and $3b_c$. This is due to the fact that applying control measures in the backward reversible

stages indicate prevention of backward reactions. As a result, rate of consumption of substrates are higher. From Fig. 4, it is understandable that the complex concentrations are also decreasing with a higher rate, so that conversion of c_1 to c_2 requires less time and product formation from the complex c_2 indicates time economization. Thus by applying control measures, quantization of product is favorable within a very short period of time.

5 Discussion

In this research article, we have presented a basic mathematical model of enzyme kinetic reaction with two substrates and a single enzyme based on the control theoretic approach. The dynamics of the reaction system depends mainly on the rate of forward reaction, rate of backward reaction and finally rate of formation of product. By implying theoretical control approach, the stability of the complex put together the reaction in such a fashion that the system moves faster toward forward direction than backward. In this way, analysis shows that the time for product formation is minimum and cost effective, when there is no decomposition of enzyme-substrate complex to unmodified substrate.

In our analytical study, Pontryagin Minimum Principle is used with the help of Hamiltonian for this purpose. Analytically we have seen that this optimal control variable is unique and derives the condition for which the system has its unique optimal control variable. Our numerical findings indicate that, introducing control measures in the enzymatic system dynamics, reaction operators are important tools for prevention of backward reversible reaction.

6 Conclusion

In conclusion, we suggest that the proposed model of enzyme kinetics offers flexibility in describing the dynamic reversible change to irreversibility of enzyme substrate reaction. Furthermore, control parameters for changing reaction operators have a significant impact on the system dynamics. As such, the model is more functional and applicable to a wider class of enzymatic reaction systems. The parameters of the model correlate directly with the physical factors that significantly effect reaction dynamics. This way, the model allows more accurate a priori prediction of system kinetics for nonstandard reaction dynamics, both through analytical analysis and using numerical simulation.

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