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MODELING OF A DELAY INDUCED BIOCHEMICAL SYSTEM FOR PRODUCT OPTIMIZATION

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Abstract. Enzymatic reactions occur through active sites of enzymes, which combine with the substrates to form intermediate complexes and subsequently lead to product. Transformation from one intermediate to another requires time dependent conformational changes of complexes. These changes are thus often accompanied by some time delay during formation of product. Time delay due to conformational changes can be avoided by controlling suitable reaction parameters, which are better identified by mathematical modeling. In this research article, we have proposed a delay differential equation model of enzymatic reaction system and analyzed the dynamics of the system critically from analytical and numerical points of view. It has been observed that time delay affects the stability and performance characteristics of the system. A control induced delay differential equation model is derived to reduce the delay induced instability of the system which contributes product optimization.

Keywords. Biochemical reaction; Oscillation; Time delay; Delay differential equation; Optimal control approach.

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1. Introduction

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In biochemical system, reactions are generally catalyzed by enzymes for smooth conversion of substrates to product. Enzymes are very much selective in nature where a particular enzyme generally accelerates only a specific reaction. Enzyme works on the basis of binding target molecules or substrates through the active sites which is the most vibrant part of an enzyme. After binding with the substrate, it forms enzyme-substrate complex and finally transformed into product through enzyme-product complex. Existence of an enzyme-substrate complex in enzymatic reactions is first proposed by Brown in 1902 [1]. Later, it is shown that formation of complex by the interaction of substrate and enzyme is a reversible process [2]. Transformation of enzyme-substrate complex to enzyme-product complex involves conformational changes accompanied by some time delay which reduces the optimal conversion [3–5]. So most of the enzymatic reactions are not instantaneous and natural time delay is also observed in the evolution of cell states [6, 7].

Formation, stability and conformational changes of intermediate complexes affect the rate of reaction, nature of product and conversion efficiency of biochemical reactions. One of the most important aspects of enzyme kinetics is the formation and retention of intermediate complexes of different nature including time delay. The time delay in reaction system has been studied through mathematical modeling by many researchers [8–10]. It has been proposed that Ninio [11] first constructed a delayed enzyme-substrate reaction by sequence of conventional elementary steps. Hinch and Schnell [12] studied the distribution of delay by the number of intermediates between reactant mixing and product formation in enzyme kinetic reactions. Albornoz and Parravano [13] proposed continuous delayed models for large enough number of substrate molecules in enzyme kinetic reactions. Their models consider the time that elapses from the moment enzyme-substrate complex forms until the moment a product molecule is released. It has also been shown that delay differential equations exhibit a comparatively complex dynamical behavior than ordinary differential equations since a delay may cause an equilibrium state to lose its stability and makes the system oscillatory [14–17].

Controlling or minimization of time delay in biochemical system is the key factor for product optimization through mathematical concepts . Control measure in this regard in intermediate stages of conformational change contributes appreciably for economization of time as well as smooth completion of product in system kinetics [18–20]. Here, we initially formulate a mathematical model of enzymatic reactions considering the intermediate conversion of enzyme-substrate complex to enzyme-product complex. In this stage of conformational change, we introduce time delay to study the effect on concentrations of different components of the system. To make this enzymatic process more realistic and to optimize the formation of product, optimal control theory has been introduced in the delayed model for that particular stage. We have discussed about stability of both the non-delayed and delayed system. "Pontryagin Minimum Principle" is applied to determine the optimal control. We solve both the models from numerical point of view. Stability analysis shows that the non-delayed system is globally asymptotically stable where as the delayed system is locally asymptotically stable for all values of delay. Our numerical results reveal that the product in biochemical system can be optimized by reducing delay time with the understanding of control based modeling technique.

2. Mathematical Model Formulation

The schematic diagram of a basic enzymatic reaction, proposed by Michaelis and Menten [2], can be represented as follows,

$$S + E \rightleftharpoons ES \rightarrow E + P,$$

where S is the substrate, E is the enzyme, ES is the enzyme-substrate complex and P is the product. We want to extend the above schematic diagram with the assumption that the complex ES is converted to the enzyme-product complex EP. All reactions which are catalyzed by enzymes are reversible and this could play a prominent role in biochemistry [21]. We consider that the stage of product formation from EP complex is reversible. The extended schematic diagram thus can be represented by [3–5],

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} EP \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E + P,$$

where S, E, ES, EP and P are the substrate, enzyme, enzyme-substrate intermediate complex (represented by C_1), enzyme-product intermediate complex (C_2) and the product respectively. The rate constants for the formation of C_1 and C_2 are denoted by k_1 and k_2 respectively and k_3

is the catalysis rate constant. k_{-1} and k_{-2} are the rate constants for backward reactions of C_1 and C_2 respectively and k_{-3} is the rate constant for backward reactions of E and P. The above diagram demonstrates that one mole of substrate S combines with one mole of enzyme E to form C_1. This complex (C_1) may convert to C_2 through some conformational changes or may decompose back into unmodified substrate S and enzyme E. Finally, C_2 is either converted to the product P and makes the enzyme free or revert back into C_1.

Considering s, e_k, c_1, c_2 and p as the concentrations of S, E, ES, EP and P respectively, from the law of mass action, the non-linear system of differential equations for the above enzymatic reaction may be enunciated as follows:

$$\begin{aligned}
\frac{ds}{dt} &= -k_1 e_k s + k_{-1} c_1, \\
\frac{de_k}{dt} &= -k_1 e_k s + k_{-1} c_1 + k_3 c_2 - k_{-3} e_k p, \\
\frac{dc_1}{dt} &= k_1 e_k s - k_{-1} c_1 - k_2 c_1 + k_{-2} c_2, \\
\frac{dc_2}{dt} &= k_2 c_1 - k_{-2} c_2 - k_3 c_2 + k_{-3} e_k p, \\
\frac{dp}{dt} &= k_3 c_2 - k_{-3} e_k p,
\end{aligned} \tag{1}$$

with the initial conditions,

$$e_k(0) = e_{k0},\ s(0) = s_0,\ c_1(0) = 0,\ c_2(0) = 0,\ p(0) = 0. \tag{2}$$

From the above system, we have

$$\begin{aligned}
\frac{ds}{dt} + \frac{dp}{dt} - \frac{de_k}{dt} &= 0, \\
\frac{dc_1}{dt} + \frac{dc_2}{dt} + \frac{de_k}{dt} &= 0.
\end{aligned} \tag{3}$$

From relation (3) with help of initial conditions (2), we have the following relations.

$$\begin{aligned}
s + p - e_k &= s_0 - e_{k0}, \\
c_1 + c_2 + e_k &= e_{k0}.
\end{aligned} \tag{4}$$

Using (4), system (1) can be reduced to a three dimensional model given below,

$$\begin{aligned}
\frac{de_k}{dt} &= -\{k_1(s_0-e_{k0}+e_k)+k_3\}e_k+(k_{-1}-k_3)c_1+(k_1-k_{-3})e_kp+k_3e_{k0},\\
\frac{dc_1}{dt} &= \{k_1(s_0-e_{k0}+e_k)-k_{-2}\}e_k-(k_{-1}+k_2+k_{-2})c_1-k_1e_kp+k_{-2}e_{k0},\\
\frac{dp}{dt} &= -k_3(c_1+e_k)-k_{-3}e_kp+k_3e_{k0},
\end{aligned} \tag{5}$$

with initial conditions,

$$e_k(0)=e_{k0},\ c_1(0)=0,\ p(0)=0. \tag{6}$$

2.1. Theoretical Study of System (5)

Here we determine the equilibrium point of system (5) and discuss the stability of the system around it.

2.1.1. Equilibria and Stability

In this section, we only consider positive equilibrium point of the system and its stability. The system (5) possesses the following interior equilibria $E^*(e_k^*, c_1^*, p^*)$, where

$$c_1^*=\frac{k_{-2}(e_{k0}-e_k^*)}{k_2+k_{-2}},\ p^*=\frac{k_2k_3(e_{k0}-e_k^*)}{(k_2+k_{-2})k_{-3}e_k^*}$$

and e_k^* satisfies the following equation,

$$\Lambda_1 e_k^{*2}+\Lambda_2 e_k^*-\Lambda_3 = 0. \tag{7}$$

The coefficients Λ_1, Λ_2 and Λ_3 are given by,

$$\begin{aligned}
\Lambda_1 &= k_1(k_2+k_{-2})k_{-3},\\
\Lambda_2 &= k_1(k_2+k_{-2})k_{-3}(s_0-e_{k0})+k_1k_2k_3+k_{-1}k_{-2}k_{-3},\\
\Lambda_3 &= (k_1k_2k_3+k_{-1}k_{-2}k_{-3})e_{k0}.
\end{aligned}$$

2.1.2. Existence Condition

Positive equilibrium point E^* exists if e_k^* satisfies the following condition,

$$e_{k0}-e_k^*>0.$$

2.1.3. Stability Analysis

Here we discuss about stability of the equilibrium point E^*. The jacobian matrix $J(e_k^*, c_1^*, p^*)$ about the equilibrium point $E^*(e_k^*, c_1^*, p^*)$ is $[m_{ij}], i, j = 1, 2, 3$, where

$$
\begin{aligned}
m_{11} &= -\{k_1(s^* + e_k^*) + k_{-3}p^* + k_3\}, \\
m_{12} &= k_{-1} - k_3, \\
m_{13} &= (k_1 - k_{-3})e_k^*, \\
m_{21} &= k_1(s^* + e_k^*) - k_{-2}, \\
m_{22} &= -(k_{-1} + k_2 + k_{-2}), \\
m_{23} &= -k_1 e_k^*,\ m_{31} = -(k_3 + k_{-3}p^*), \\
m_{32} &= -k_3,\ m_{33} = -k_{-3}e_k^*.
\end{aligned} \tag{8}
$$

The characteristic equation of system (5) is

$$\xi^3 + A_1\xi^2 + A_2\xi + A_3 = 0, \tag{9}$$

where the coefficients are given by,

$$
\begin{aligned}
A_1 &= -(m_{11} + m_{22} + m_{33}), \\
A_2 &= m_{22}m_{33} - m_{32}m_{23} + m_{11}m_{22} - m_{21}m_{12} + m_{11}m_{33} - m_{31}m_{13}, \\
A_3 &= -[m_{11}(m_{22}m_{33} - m_{32}m_{23}) - m_{12}(m_{21}m_{33} - m_{31}m_{23}) \\
&\quad + m_{13}(m_{21}m_{32} - m_{31}m_{22})].
\end{aligned}
$$

It is clear from the expressions of A_1, A_3 and $A_1A_2 - A_3$ (given in Appendix A) that the coefficients of (9) always satisfy the Routh-Hurwitz conditions i.e.,

$$A_1 > 0,\ A_3 > 0 \text{ and } A_1A_2 - A_3 > 0. \tag{10}$$

Thus, we have the following proposition.

Proposition 1. *The equilibrium point $E^*(e_k^*, c_1^*, p^*)$ is locally asymptotically stable.*

2.1.4. Global Stability

Now, we want to show that the equilibrium point $E^*(e_k^*, c_1^*, p^*)$ is globally asymptotically stable. Let us formulate the following Lyapunov function,

$$L(e_k, c_1, p) = \frac{1}{2}\{v_1 e_k^2 + v_2 c_1^2 + v_3 p^2\}, \tag{11}$$

where $v_i > 0$, $(i = 1, 2, 3)$ is to be determined suitably. The derivative of L along the solution of $\dot{X}(t) = J(e_k^*, c_1^*, p^*)X(t)$, where $X(t) = (e_k(t), c_1(t), p(t))^T$, is given by,

$$\begin{aligned} \frac{dL}{dt} &= v_1 e_k \dot{e_k} + v_2 c_1 \dot{c_1} + v_3 p \dot{p} \\ &= v_1 m_{11} e_k^2 + (v_1 m_{12} + v_2 m_{21}) e_k c_1 + (v_1 m_{13} + v_3 m_{31}) e_k p \\ &\quad + v_2 m_{22} c_1^2 + v_3 m_{33} p^2 + (v_2 m_{23} + v_3 m_{32}) c_1 p, \end{aligned} \tag{12}$$

where $\dot{e_k} = \frac{de_k}{dt}$, $\dot{c_1} = \frac{dc_1}{dt}$, $\dot{p} = \frac{dp}{dt}$ and m_{ij}'s $(i, j = 1, 2, 3)$ are given by equation (8).
The symmetric matrix corresponding to $\frac{dL}{dt}$ is given by,

$$\Upsilon = \frac{1}{2}\begin{pmatrix} 2v_1 m_{11} & v_1 m_{12} + v_2 m_{21} & v_1 m_{13} + v_3 m_{31} \\ v_1 m_{12} + v_2 m_{21} & 2v_2 m_{22} & v_2 m_{23} + v_3 m_{32} \\ v_1 m_{13} + v_3 m_{31} & v_2 m_{23} + v_3 m_{32} & 2v_3 m_{33} \end{pmatrix}.$$

The equilibrium point E^* is globally asymptotically stable if $\frac{dL}{dt}$ is negative definite i.e., if matrix Υ is negative definite. This follows if $2v_1 m_{11} < 0$, $4v_1 v_2 m_{11} m_{22} - (v_1 m_{12} + v_2 m_{21})^2 > 0$ and $|\Upsilon| < 0$, where $|\Upsilon|$ is determinant of matrix Υ. Hence, we have the following proposition.

Proposition 2. *The equilibrium point $E^*(e_k^*, c_1^*, p^*)$ is globally asymptotically stable for suitably chosen positive values of v_1, v_2 and v_3 satisfying $4v_1 v_2 m_{11} m_{22} - (v_1 m_{12} + v_2 m_{21})^2 > 0$ and $|\Upsilon| < 0$.*

2.2. The Model with Delay

The mathematical model (1) does not involve any time delay. Since the process is not instantaneous, as it takes time to form the complex EP from the complex ES, we assume that there is a delay in the intermediate step $ES \overset{\tau}{\rightleftharpoons} EP$ [3–5].

The dependency of one chemical component on the history of another chemical component can also force the system into oscillation. When this dependency is distributed and it is taken into consideration, model (1) reduces to a system of delay differential equations. However, introduction of delay into system (1) may produce spontaneous oscillation [22].

Incorporating delay in the model equations (1), we get the following delay induced system,

$$\begin{aligned}
\frac{ds(t)}{dt} &= -k_1e_k(t)s(t)+k_{-1}c_1(t),\\
\frac{de_k(t)}{dt} &= -k_1e_k(t)s(t)+k_{-1}c_1(t)+k_3c_2(t)-k_{-3}e_k(t)p(t),\\
\frac{dc_1(t)}{dt} &= k_1e_k(t)s(t)-k_{-1}c_1(t)-k_2c_1(t)+k_{-2}c_2(t),\\
\frac{dc_2(t)}{dt} &= k_2c_1(t-\tau)-k_{-2}c_2(t)-k_3c_2(t)+k_{-3}e_k(t)p(t),\\
\frac{dp(t)}{dt} &= k_3c_2(t)-k_{-3}e_k(t)p(t),
\end{aligned} \tag{13}$$

along with initial conditions,

$$s(\theta)=s_0>0,\ e_k(\theta)=e_{k0}>0,\ c_1(\theta)=0,\ c_2(\theta)=0,\ p(\theta)=0,\ \theta\in[-\tau,0]. \tag{14}$$

Here we also have the following relation,

$$\frac{ds(t)}{dt}+\frac{dp(t)}{dt}-\frac{de_k(t)}{dt} = 0. \tag{15}$$

Using initial conditions (14) and the relation (15), from (13), we have

$$\begin{aligned}
\frac{ds(t)}{dt} &= -k_1\{s(t)+p(t)+e_{k0}-s_0\}s(t)+k_{-1}c_1(t),\\
\frac{dc_1(t)}{dt} &= k_1\{s(t)+p(t)+e_{k0}-s_0\}s(t)-(k_{-1}+k_2)c_1(t)+k_{-2}c_2(t),\\
\frac{dc_2(t)}{dt} &= k_2c_1(t-\tau)-(k_{-2}+k_3)c_2(t)\\
&\quad +k_{-3}\{s(t)+p(t)+e_{k0}-s_0\}p(t),\\
\frac{dp(t)}{dt} &= k_3c_2(t)-k_{-3}\{s(t)+p(t)+e_{k0}-s_0\}p(t),
\end{aligned} \tag{16}$$

with initial conditions

$$s(\theta)=s_0,\ c_1(\theta)=0,\ c_2(\theta)=0,\ p(\theta)=0,\ \text{where } \theta\in[-\tau,0].$$

2.3. Length of Delay and Stability of the System

Let us define $\bar{s}(t) = s(t) - s^*$, $\bar{c}_1(t) = c_1(t) - c_1^*$, $\bar{c}_2(t) = c_2(t) - c_2^*$, $\bar{p}(t) = p(t) - p^*$. The linearized form of the system (16) about (e_k^*, c_1^*, p^*) is,

$$
\begin{aligned}
\frac{d\bar{s}(t)}{dt} &= -k_1(s^* + e_k^*)\bar{s}(t) + k_{-1}\bar{c}_1(t) - k_1 s^* \bar{p}(t), \\
\frac{d\bar{c}_1(t)}{dt} &= k_1(s^* + e_k^*)\bar{s}(t) - (k_{-1} + k_2)\bar{c}_1(t) + k_{-2}\bar{c}_2(t) + k_1 s^* \bar{p}(t), \\
\frac{d\bar{c}_2(t)}{dt} &= k_2\bar{c}_1(t-\tau) + k_{-3}p^*\bar{s}(t) - (k_{-2} + k_3)\bar{c}_2(t) + k_{-3}(e_k^* + p^*)\bar{p}(t), \\
\frac{d\bar{p}(t)}{dt} &= -k_{-3}p^*\bar{s}(t) + k_3\bar{c}_2(t) - k_{-3}(e_k^* + p^*)\bar{p}(t). \qquad (17)
\end{aligned}
$$

Now we express system (17) in matrix form as follows:

$$
\frac{d}{dt}\begin{pmatrix} \bar{s}(t) \\ \bar{c}_1(t) \\ \bar{c}_2(t) \\ \bar{p}(t) \end{pmatrix} = B_1 \begin{pmatrix} \bar{s}(t) \\ \bar{c}_1(t) \\ \bar{c}_2(t) \\ \bar{p}(t) \end{pmatrix} + B_2 \begin{pmatrix} \bar{s}(t-\tau) \\ \bar{c}_1(t-\tau) \\ \bar{c}_2(t-\tau) \\ \bar{p}(t-\tau) \end{pmatrix},
$$

where

$$
B_1 = \begin{pmatrix} -k_1(s^* + e_k^*) & k_{-1} & 0 & -k_1 s^* \\ k_1(s^* + e_k^*) & -(k_{-1} + k_2) & k_{-2} & k_1 s^* \\ k_{-3}p^* & 0 & -(k_{-2} + k_3) & k_{-3}(e_k^* + p^*) \\ -k_{-3}p^* & 0 & k_3 & -k_{-3}(e_k^* + p^*) \end{pmatrix}
$$

and

$$
B_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & k_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.
$$

The characteristic equation of system (17) is given by,

$$
\triangle(\xi) = |\, \xi I - B_1 - e^{-\xi\tau}B_2 \,| = 0,
$$

$$
\text{i.e., } \xi^4 + a_{11}\xi^3 + a_{12}\xi^2 + a_{13}\xi + a_{14} + (a_{15}\xi^2 + a_{16}\xi - a_{14})e^{-\xi\tau} = 0. \qquad (18)
$$

Here,

$$
\begin{aligned}
a_{11} &= a_{21}+a_{22}\\
a_{12} &= a_{23}+a_{21}a_{22}+a_{24}+a_{25},\\
a_{13} &= a_{21}a_{23}+a_{22}a_{24}+a_{25}a_{29}+a_{26},\\
a_{14} &= a_{23}a_{24}-a_{15}a_{25},\\
a_{15} &= -k_{-2}k_2,\\
a_{16} &= a_{15}a_{27}-a_{28}, \qquad (19)
\end{aligned}
$$

where

$$
\begin{aligned}
a_{21} &= k_{-1}+k_2+k_1(s^*+e_k^*),\\
a_{22} &= k_{-2}+k_3+k_{-3}(e_k^*+p^*),\\
a_{23} &= k_{-3}k_{-2}(e_k^*+p^*),\\
a_{24} &= k_1k_2(s^*+e_k^*),\\
a_{25} &= -k_{-3}k_1s^*p^*,\\
a_{26} &= -k_{-3}k_{-2}k_{-1}p^*,\\
a_{27} &= k_1(s^*+e_k^*)+k_{-3}(e_k^*+p^*),\\
a_{28} &= k_1k_2k_3s^*,\\
a_{29} &= k_{-2}+k_2. \qquad (20)
\end{aligned}
$$

For $\tau>0$, we study the nature of roots of the equation (18) analytically to ensure the stability of the delay model. The characteristic equation (18) is transcendental for $\tau>0$. It is not possible to apply R-H criterion to this equation.

We have shown that the coefficients of the non-delayed system always satisfy the Routh-Hurwitz conditions. Hence, roots of it have negative real parts. Since the characteristic equation (18) is a continuous function of τ, there is continuity in the eigenvalues for $\tau>0$. Rouche's Theorem [23] and the continuity of the eigenvalues assure that the roots of equation (18) have positive real parts if and only if the roots are purely imaginary. We study if equation (18) has purely imaginary roots or not.

Let $\lambda = \eta(\tau) + i\omega(\tau)$ be a root of equation (18), where $\eta(\tau)$ and $\omega(\tau)$ depend on the delay τ. $\eta(0) < 0$ since the equilibrium point E^* of (5) is stable. E^* remains stable for sufficiently small positive values of τ as by continuity $\eta(\tau) < 0$ for such values of τ [24, 25]. The equilibrium point E^* loses its stability if there exists some $\tau_c > 0$ so that $\eta(\tau_c) = 0$ and $\lambda = i\omega(\tau_c)$ is a purely imaginary root of equation (18) and becomes unstable when $\eta(\tau)$ becomes positive. We show that the characteristic equation (18) has no purely imaginary root for all values of τ i.e., E^* is always stable.

Suppose $\xi = i\omega(\tau)$ is a root of the equation (18). Then,

$$\omega^4 - ia_{11}\omega^3 - a_{12}\omega^2 + ia_{13}\omega + a_{14} + (-a_{15}\omega^2 + ia_{16}\omega - a_{14})(\cos\omega\tau - i\sin\omega\tau) = 0. \tag{21}$$

Separating real and imaginary parts we obtain the following equations,

$$\begin{aligned} \omega^4 - a_{12}\omega^2 + a_{14} &= (a_{15}\omega^2 + a_{14})\cos\omega\tau - a_{16}\omega\sin\omega\tau, \\ a_{11}\omega^3 - a_{13}\omega &= (a_{15}\omega^2 + a_{14})\sin\omega\tau + a_{16}\omega\cos\omega\tau. \end{aligned} \tag{22}$$

Squaring and adding the above two equations we get,

$$\omega^8 + \alpha_1\omega^6 + \alpha_2\omega^4 + \alpha_3\omega^2 = 0, \tag{23}$$

where

$$\begin{aligned} \alpha_1 &= a_{11}^2 - 2a_{12}, \\ \alpha_2 &= a_{12}^2 + 2a_{14} - 2a_{11}a_{13} - a_{15}^2, \\ \alpha_3 &= a_{13}^2 - 2a_{12}a_{14} - 2a_{15}a_{14} - a_{16}^2. \end{aligned} \tag{24}$$

Let us consider, $v = \omega^2$. Then equation (23) becomes,

$$F(v) = v^4 + \alpha_1 v^3 + \alpha_2 v^2 + \alpha_3 v = 0. \tag{25}$$

Here $v = 0$ is a root of equation (25) i.e., ξ is not a purely imaginary root of (18). So, rest of study depends on the following cubic equation,

$$F_R(v) = v^3 + \alpha_1 v^2 + \alpha_2 v + \alpha_3 = 0. \tag{26}$$

It is clear from the expressions of α_1, α_2 and α_3 (given in Appendix A) that all of these coefficients are positive for all parameter values. Roots of the equation $\frac{dF_R(v)}{dv} = 0$ i.e., of

$$3v^2 + 2\alpha_1 v + \alpha_2 = 0 \tag{27}$$

can be represented as

$$v_{1,2} = \frac{-\alpha_1 \pm \sqrt{\alpha_1^2 - 3\alpha_2}}{3}. \tag{28}$$

Both of v_1 and v_2 are negative as $\alpha_2 > 0$ implies that $\sqrt{\alpha_1^2 - 3\alpha_2} < \alpha_1$. Hence, equation (27) has no positive roots. Thus, equation (26) has no positive roots as $F_R(0) = \alpha_3 > 0$.
This implies that there is no ω so that $i\omega$ is a root of the characteristic equation (18). Hence, the real parts of all the roots of (18) are negative for all $\tau > 0$. We thus have the following proposition.

Proposition 3. *The equilibrium point $E^*(e_k^*, c_1^*, p^*)$ is locally asymptotically stable for all delay $\tau > 0$.*

3. The Optimal Control Problem

Now, we are introducing control input $u(t)$ to reduce the delay induced instability of the system. Thus $u(t)$ is introduced in the stage $ES \rightleftharpoons EP$ where there is a delay in forward reaction. This is shown by the following schematic diagram,

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2,\ \tau,\ u(t)}{\rightleftharpoons}} EP \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E + P.$$

Here $u(t)$ represents control input with values normalized between 0 and 1. $u(t) = 1$ represents the maximal use of control and $u(t) = 0$ signifies no control. The control measure stands for reaction temperature, pressure, enzyme concentration, activation energy etc. [26]. Introducing control parameter into the model (13), we get the following system,

$$
\begin{aligned}
\frac{ds(t)}{dt} &= -k_1 e_k(t)s(t) + k_{-1}c_1(t), \\
\frac{de_k(t)}{dt} &= -k_1 e_k(t)s(t) + k_{-1}c_1(t) + k_3 c_2(t) - k_{-3}e_k(t)p(t), \\
\frac{dc_1(t)}{dt} &= k_1 e_k(t)s(t) - k_{-1}c_1(t) - (1-u(t))k_2 c_1(t) + k_{-2}c_2(t), \\
\frac{dc_2(t)}{dt} &= (1-u(t))k_2 c_1(t-\tau) - k_{-2}c_2(t) - k_3 c_2(t) + k_{-3}e_k(t)p(t), \\
\frac{dp(t)}{dt} &= k_3 c_2(t) - k_{-3}e_k(t)p(t),
\end{aligned} \tag{29}
$$

with initial conditions $s(\theta) = s_0 > 0,\ e_k(\theta) = e_{k0} > 0,\ c_1(\theta) = 0,\ c_2(\theta) = 0,\ p(\theta) = 0$, where $\theta \in [-\tau, 0]$.

We want to maximize the product and minimize the cost of product formation. So, we define the cost function for the minimization problem as,

$$
J(u(t)) = \int_{t_i}^{t_f} [Au^2(t) - Bp^2(t)]dt \tag{30}
$$

subject to the state system (29). The parameter A represents the weight constant on the benefit of the cost of production and B is the penalty multiplier. Our aim is to find the optimal control $u^*(t)$ such that

$$
J(u^*(t)) = min\ (J(u) : u \in U),
$$

where $U = (u(t) :\ u$ is measurable and $0 \le u \le 1,\ t \in [t_i, t_f])$.

3.1. Optimality System

Pontryagin Minimum Principle with delay provides necessary conditions for an optimal control problem. The Hamiltonian (H) given by,

$$\begin{aligned}
H &= Au^2(t) - Bp^2(t) \\
&+\xi_1\{-k_1e_k(t)s(t)+k_{-1}c_1(t)\} \\
&+\xi_2\{-k_1e_k(t)s(t)+k_{-1}c_1(t)+k_3c_2(t)-k_{-3}e_k(t)p(t)\} \\
&+\xi_3\{k_1e_k(t)s(t)-k_{-1}c_1(t)-(1-u(t))k_2c_1(t)+k_{-2}c_2(t)\} \\
&+\xi_4\{(1-u(t))k_2c_1(t-\tau)-k_{-2}c_2(t)-k_3c_2(t)+k_{-3}e_k(t)p(t)\} \\
&+\xi_5\{k_3c_2(t)-k_{-3}e_k(t)p(t)\}.
\end{aligned} \tag{31}$$

Applying Pontryagin Minimum Principle with delay [27–29], we obtain the following theorem.

Theorem 3.1. *If the objective cost function $J(u^*(t))$ over U is minimum for the optimal control $u^*(t)$ corresponding to the interior equilibrium (s^*, e_k^*, c_1^*, c_2^*, p^*) then there exist adjoint variables $\xi_1,\ \xi_2,\ \xi_3,\ \xi_4$ and ξ_5 which satisfy the following system of equations:*

$$\begin{aligned}
\frac{d\xi_1}{dt} &= k_1e_k(\xi_1+\xi_2-\xi_3), \\
\frac{d\xi_2}{dt} &= k_1s(\xi_1+\xi_2-\xi_3)+k_{-3}p(\xi_5-\xi_4), \\
\frac{d\xi_3}{dt} &= -k_{-1}(\xi_1+\xi_2-\xi_3)+(1-u(t))k_2\xi_3 \\
&\quad +k_2\chi_{[0,t_f-\tau]}(t)\{u(t+\tau)-1\}\xi_4(t+\tau), \\
\frac{d\xi_4}{dt} &= k_{-2}(\xi_4-\xi_3)-k_3(\xi_2-\xi_4+\xi_5), \\
\frac{d\xi_5}{dt} &= 2Bp+k_{-3}e_k(\xi_2-\xi_4+\xi_5),
\end{aligned} \tag{32}$$

with the transversality condition satisfying $\xi_i(t_f)$=0 (i=1, 2, 3, 4, 5).
Moreover, the optimal control is given by,

$$u^*(t) = max(0,\ min(1,\ \tfrac{k_2\{c_1(t-\tau)\xi_4(t)-c_1(t)\xi_3(t)\}}{2A})).$$

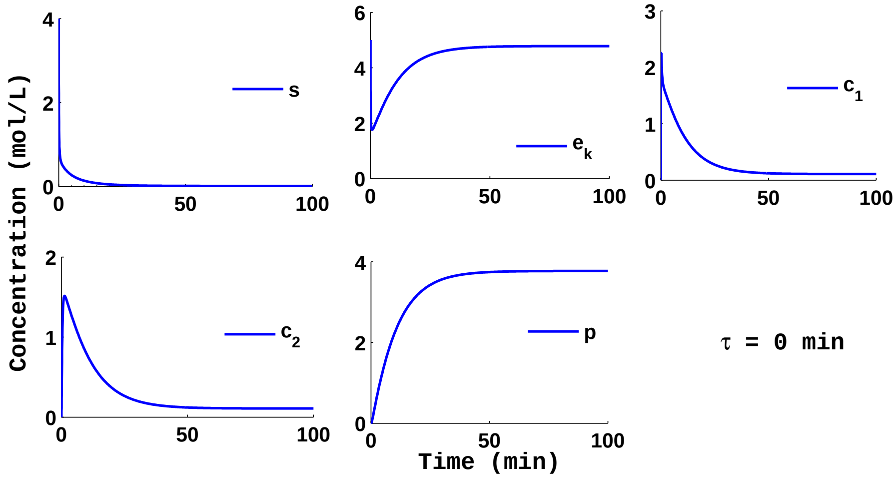

FIGURE 1. Concentration profiles of substances of the ODE model (1) using the parameter values as in Table 1.

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin Minimum Principle with delay such that

$$\begin{aligned}
\frac{d\xi_1}{dt}(t) &= -\frac{\partial H}{\partial s}(t),\ \frac{d\xi_2}{dt}(t) = -\frac{\partial H}{\partial e_k}(t),\\
\frac{d\xi_3}{dt}(t) &= -\frac{\partial H}{\partial c_1}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial H}{\partial c_1}(t+\tau),\\
\frac{d\xi_4}{dt}(t) &= -\frac{\partial H}{\partial c_2}(t),\ \frac{d\xi_5}{dt}(t) = -\frac{\partial H}{\partial p}(t),
\end{aligned} \tag{33}$$

with $\xi_i(t_f) = 0, i = 1,\ 2,\ 3,\ 4,\ 5.$

From (33) we get the adjoint equations as,

$$\begin{aligned}
\frac{d\xi_1}{dt} &= k_1 e_k(\xi_1 + \xi_2 - \xi_3),\\
\frac{d\xi_2}{dt} &= k_1 s(\xi_1 + \xi_2 - \xi_3) + k_{-3} p(\xi_5 - \xi_4),\\
\frac{d\xi_3}{dt} &= -k_{-1}(\xi_1 + \xi_2 - \xi_3) + (1 - u(t))k_2\xi_3\\
&\quad + k_2\chi_{[0,t_f-\tau]}(t)\{u(t+\tau) - 1\}\xi_4(t+\tau),\\
\frac{d\xi_4}{dt} &= k_{-2}(\xi_4 - \xi_3) - k_3(\xi_2 - \xi_4 + \xi_5),\\
\frac{d\xi_5}{dt} &= 2Bp + k_{-3} e_k(\xi_2 - \xi_4 + \xi_5).
\end{aligned} \tag{34}$$

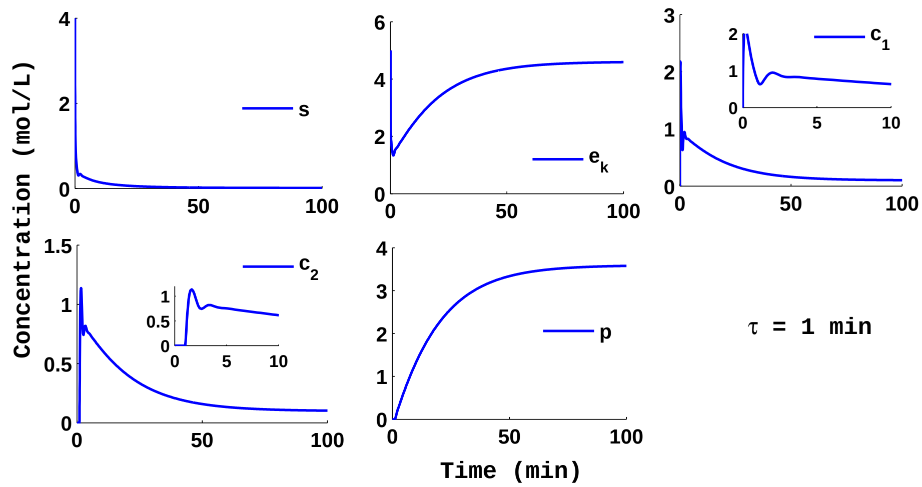

FIGURE 2. Concentration profiles of substances of the DDE system (13) for $\tau = 1$ min and other parameter values are as given in Table 1.

According to Pontryagin Minimum Principle, the unconstrained optimal control variables $u^*(t)$ satisfies

$$\frac{\partial H}{\partial u^*}(t) = 0.$$

This implies,

$$\frac{\partial H}{\partial u^*}(t) = 2Au(t) + k_2 c_1(t)\xi_3(t) - k_2 c_1(t-\tau)\xi_4(t) = 0. \tag{35}$$

Due to the boundedness of the standard control,

$$u^*(t) = \begin{cases} 0, & \frac{k_2\{c_1(t-\tau)\xi_4(t) - c_1(t)\xi_3(t)\}}{2A} \leq 0; \\ \frac{k_2\{c_1(t-\tau)\xi_4(t) - c_1(t)\xi_3(t)\}}{2A}, & 0 < \frac{k_2\{c_1(t-\tau)\xi_4(t) - c_1(t)\xi_3(t)\}}{2A} < 1; \\ 1, & \frac{k_2\{c_1(t-\tau)\xi_4(t) - c_1(t)\xi_3(t)\}}{2A} \geq 1. \end{cases}$$

Hence, the compact form of $u^*(t)$ is given by,

$$u^*(t) = max(0,\ min(1,\ \frac{k_2\{c_1(t-\tau)\xi_4(t) - c_1(t)\xi_3(t)\}}{2A})). \tag{36}$$

Thus equation (29) together with equation (34) and (36) represent the optimality system.

4. Numerical Simulation

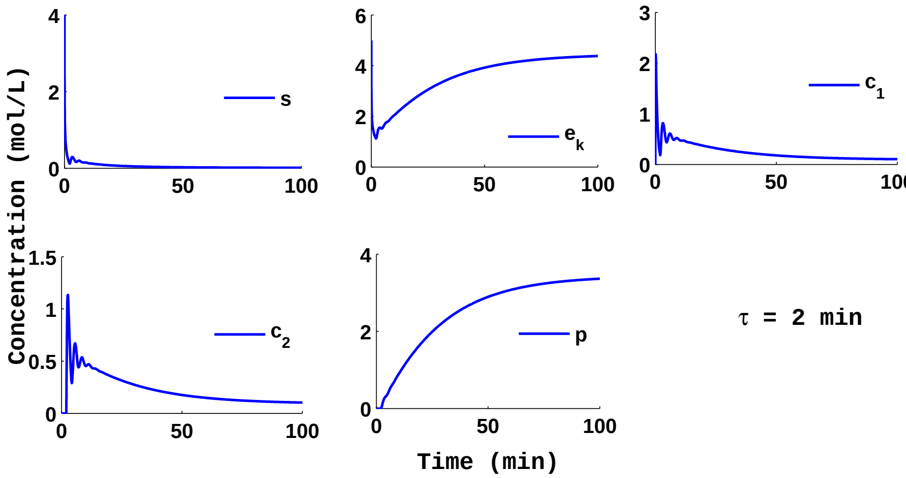

FIGURE 3. Concentration profiles of substances of the DDE system (13) for $\tau = 2$ min and other parameter values are as given in Table 1.

TABLE 1. Parameters used in numerical calculation

Parameter	Definition	Recommended Value with Unit
k_1	Forward rate constant for the formation of enzyme-substrate complex C_1	2.7 $(\text{mol/l})^{-1}\text{min}^{-1}$
k_{-1}	Rate constant for backward reaction of C_1	1.5 min^{-1}
k_2	Forward rate constant for the formation of enzyme-product complex C_2	2 min^{-1}
k_{-2}	Rate constant for backward reaction of C_2	0.5 min^{-1}
k_3	Forward rate constant for the formation of the product P	1.3 min^{-1}
k_{-3}	Rate constant for backward reaction of product P and enzyme E	0.0012 $(\text{mol/l})^{-1}\text{min}^{-1}$

In this section, the dynamics of reaction system kinetics are analyzed numerically based on the analytical results. We present some numerical results of system (1) and (13). The present study also deals with the application of optimum control in model (13) of the enzyme kinetic

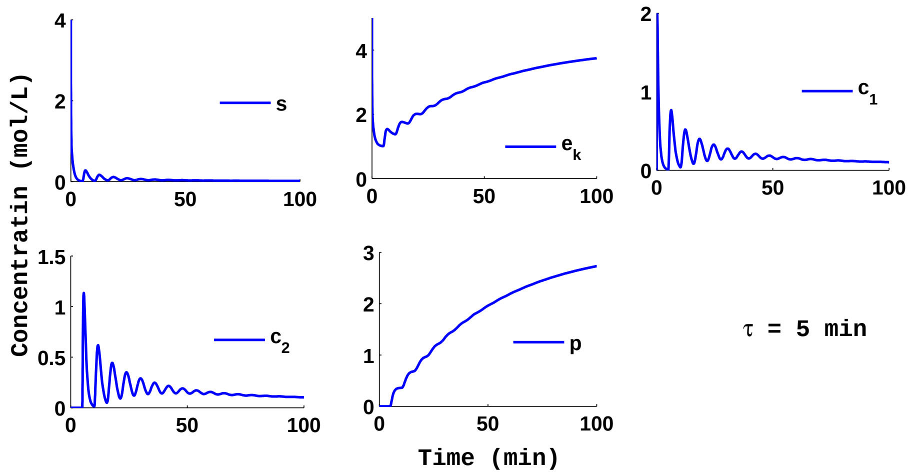

FIGURE 4. Concentration profiles of substances of the DDE system (13) for $\tau = 5$ min and other parameter values are as given in Table 1.

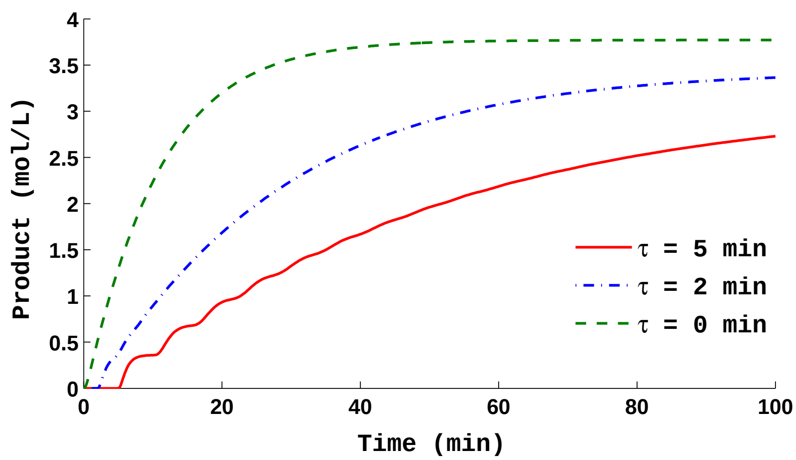

FIGURE 5. Concentration profiles of product of the DDE system (13) for $\tau = 0, 2, 5$ and other parameter values are as given in Table 1.

system. The analytical results of optimal control are satisfied by numerical simulation using MATLAB.

Concentration profiles of the substances of system (1) are represented by Figure 1. The parameter values are considered as shown in Table 1. Here ideal reaction conditions are considered i.e., there is no delay in the system. Figure 1 reveals that the substrate concentration falls off with time and becomes zero as it is consumed with the progress of the reaction. This is due to

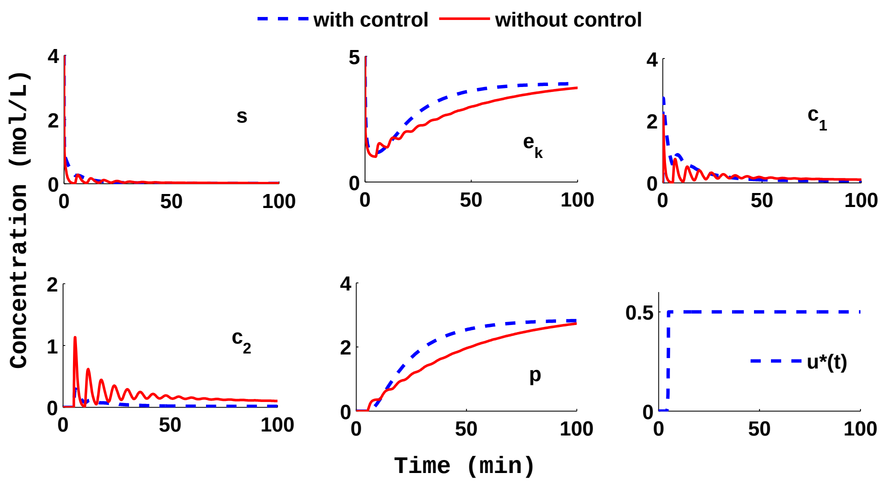

FIGURE 6. The system dynamics under the influence of optimal control $u^*(t)$ with $\tau = 5$ min. Solid line indicates "without control" and dotted line indicates "with control".

the initial higher rate of collision between substrate and enzyme which gradually slows down with time. Consumption of higher rate of substrate concurrently reduces enzyme concentration (e_k) as the reaction proceeds and is recovered at the end of the reaction. Initial formation of the complexes C_1 and C_2 is higher. After a certain time, concentrations of both the complexes decrease with time due to conversion of C_1 to C_2 and that of C_2 to E and P. Product concentration increases smoothly from the beginning of the reaction.

Figure 2 displays concentration profiles of the substances in presence of delay $(\tau = 1)$. It has been observed from the figure that initial oscillation diminishes after 5 minutes of reaction. Duration of oscillation increases with increment of time delay which persists for longer time as observed in Figure 3 and 4. So product formation takes more time in delayed system. This is due to the fact that delay effect on reaction rate directs the conversion of ES to EP for a longer time which results unnecessary presence of enzyme-substrate complex. So, concentration of product decreases significantly which has been shown in Figure 5.

Figure 6 exhibits the behavior of the delayed system (13) under the influence of optimal control $u^*(t)$. Here, it can be seen from the figure (Figure 6) that application of control measures in the delayed system minimizes the oscillations of intermediate complexes which enhances product optimization. So, control approach in the delayed biochemical system improves the product formation.

5. Discussion and Conclusion

In this research article, we have proposed a delay induced mathematical model of a biochemical system for better realization of it along with the non-delayed system. We show by constructing a Lyapunov function that the non-delayed system is globally asymptotically stable.The delayed system is locally asymptotically stable for all values of time delay τ. The delayed model has been solved numerically using MATLAB. It is seen that time lag can produce major changes in the behavior of a delayed model rather than ordinary model. We have observed from the model analysis that the delay induced system takes higher time for product formation. This is due to the fact that longer delay time for conformational changes reduces the rate of formation of product. Introduction of optimal control to this system shows that the solution trajectories approach towards a stable region which actually directs the higher rate of product formation from enzyme-product intermediate complex.

In conclusion, the proposed delay induced mathematical model is much more realistic. It provides an idea to understand the dynamics of delay induced enzymatic system. This study will help the future researchers regarding the time delay in suitable phases of biochemical system and product optimization.

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Appendix A The expressions A_1, A_3 and $A_1A_2 - A_3$ are as follows:

$$
\begin{aligned}
A_1 &= k_1(s^* + e_k^*) + k_{-3}(e_k^* + p^*) + k_{-1} + k_{-2} + k_2 + k_3, \\
A_3 &= k_{-3}k_1(k_{-2} + k_2)(s^* + e_k^* + p^*)e_k^* + k_{-3}k_{-2}k_{-1}e_k^* + k_1k_2k_3e_k^*, \\
A_1A_2 - A_3 &= \{k_1(s^* + e_k^*) + k_{-3}(e_k^* + p^*) + k_{-1} + k_{-2} + k_2 + k_3\}. \\
&\quad \{(k_{-1} + k_{-2} + k_2)k_{-3}e_k^* + k_{-3}(k_{-1} + k_{-2} + k_2)p^* + k_1(k_{-2} \\
&\quad + k_2 + k_3 + k_{-3}e_k^*)(s^* + e_k^*) + k_{-3}k_1e_k^*p^* + k_3(k_{-1} + k_2) + k_{-1}k_{-2}\} \\
&\quad - \{k_{-3}k_1(k_{-2} + k_2)(s^* + e_k^* + p^*)e_k^* + k_{-3}k_{-2}k_{-1}e_k^* + k_1k_2k_3e_k^*\}. \qquad (37)
\end{aligned}
$$

Thus, from the relations (37), A_1, A_3 and $A_1A_2 - A_3$ are obviously always positive.

Expressions of the coefficients α_1, α_2, α_3 of equation (25) are given by,

$$\begin{aligned}
\alpha_1 &= \{k_{-1}+k_2+k_1(s^*+e_k^*)\}^2+\{k_{-2}+k_3+k_{-3}(e_k^*+p^*)\}^2 \\
&\quad -2k_{-3}k_{-2}(e_k^*+p^*)-2k_1k_2(s^*+e_k^*)+2k_{-3}k_1s^*p^*, \\
\alpha_2 &= \{k_{-3}k_{-2}(e_k^*+p^*)+k_{-2}k_{-1}+k_{-1}k_3+k_{-3}k_{-1}(e_k^*+p^*)+k_{-2}k_2+k_2k_3 \\
&\quad +k_{-3}k_2(e_k^*+p^*)+k_{-2}k_1(s^*+e_k^*)+k_1k_3(s^*+e_k^*)+k_{-3}k_1(e_k^*+p^*)e_k^* \\
&\quad +k_{-3}k_1s^*e_k^*+k_1k_2(s^*+e_k^*)\}^2+2k_{-3}k_{-2}k_1k_2(s^*+e_k^*+p^*)e_k^*-k_{-2}^2k_2^2 \\
&\quad -2\{k_{-2}+k_{-1}+k_2+k_3+k_1(s^*+e_k^*)+k_{-3}(e_k^*+p^*)\}.\{k_{-3}k_{-2}k_{-1}e_k^* \\
&\quad +k_{-3}k_{-2}k_2(e_k^*+p^*)+k_{-3}k_{-2}k_1(e_k^*+p^*)e_k^*+k_{-3}k_{-2}k_1s^*e_k^* \\
&\quad +k_{-2}k_1k_2(s^*+e_k^*)+k_1k_2k_3(s^*+e_k^*)+k_{-3}k_1k_2(s^*e_k^*+p^*)e_k^*\}, \\
\alpha_3 &= \{k_{-3}k_{-2}k_{-1}e_k^*+k_{-3}k_{-2}k_2e_k^*+k_{-3}k_{-2}k_2p^*+k_{-3}k_{-2}k_1(s^*+e_k^*+p^*)e_k^* \\
&\quad +k_{-2}k_1k_2(s^*+e_k^*)+k_1k_2k_3(s^*+e_k^*)+k_{-3}k_1k_2(s^*+e_k^*+p^*)e_k^*\}^2 \\
&\quad +2k_{-3}k_{-2}^2k_1k_2^2(s^*+e_k^*+p^*)e_k^*-\{k_{-2}k_1k_2(s^*+e_k^*)+k_{-3}k_{-2}k_2(e_k^*+p^*) \\
&\quad +k_1k_2k_3s^*\}^2-2k_{-3}k_{-2}k_1k_2(s^*+e_k^*+p^*)e_k^*.\{k_{-3}k_{-2}(e_k^*+p^*) \\
&\quad +k_1k_2(s^*+e_k^*)+k_{-2}k_{-1}+k_{-1}k_3+k_{-3}k_{-1}(e_k^*+p^*)+k_{-2}k_2+k_2k_3 \\
&\quad +k_{-3}k_2(e_k^*+p^*)+k_{-2}k_1(s^*+e_k^*)+k_1k_3(s^*+e_k^*) \\
&\quad +k_{-3}k_1(s^*+e_k^*+p^*)e_k^*\}. \qquad (38)
\end{aligned}$$

It is easy to understand from (38) that all of α_1, α_2 and α_3 are always positive.