Optimal control of a fractional-order enzyme kinetic model[*]

by

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Abstract: Enzymes play a significant role in controlling the characteristics of various chemical and biochemical reactions. They act as catalysts that increase the rate of reaction without undergoing any change in quantity. Enzymatic reactions occur through the active sites, which combine with the substrates to form intermediate complexes, subsequently leading to products. An enzyme having two active sites can show cooperative phenomena. Against this background, an enzyme-kinetic mathematical model is formulated using fractional order derivatives. Optimal control mechanism has been incorporated into the fractional-order model system to maximize the product output. Euler-Lagrange optimality conditions are derived for the FOCP (fractional order control problem) using maximum principle. Numerical iterative schemes have been developed to solve the fractional order optimal control problem through Matlab.

Keywords: enzyme kinetics, cooperative phenomenon, fractional derivative, mathematical modeling, Hamiltonian, optimal control problem

1. Introduction

Enzymes are proteins, which exist in nature, and which act as catalysts in biochemical reactions. They reduce the activation energy of reactions and accelerate the rate of reaction. Moreover, they are selective in nature, i.e. a particular enzyme accelerates only a specific reaction. The dynamic part of an enzyme

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is the active site, through which it binds with target molecules or substrates. After binding with substrate, an enzyme-substrate complex is formed, which is then either reverted back to unmodified substrate and enzyme or is transformed into product. Regarding the cooperative behavior of enzymes, enzyme may bind with another substrate molecule if it has more than one active site (Rubinow, 1975; Murray, 1989).

In biological essence, enzymes may have multiple binding sites which react with the substrate molecules. A single enzyme molecule with two active sites can bind with a substrate molecule at one site and another substrate molecule at the other active site. The binding of one substrate molecule at one active site has a significant effect on the binding of another substrate molecule at another active site (allosteric site). This type of binding between distinct and specific sites is called allosteric effect or cooperative phenomenon and the respective enzyme is called an allosteric enzyme (Murray, 1989). Mathematical modeling provides a framework for investigating the mechanism of cooperation in, for instance, hemoglobin (Antonini and Brunori, 1971; Henry et al., 2002; Szabo and Karplus, 1972).

Analysis of enzyme kinetics, described by the mathematical models, is considered in different studies, reported in the literature (Segel, 1980; Roberts, 1977). Ordinary differential equations (ODEs) are used to describe the dynamics of enzymatic reactions in biochemical systems. These equations are based on the law of mass action (Roy et al., 2013). The product obtained by application of this type of simple mechanism may not always secure the optimum course of the reaction process. Reaction conditions are maintained or controlled so as to get the optimum process control that is analyzed and designed with the use of optimal control theory. Mathematical study helps to find the most appropriate reaction conditions for process optimization (Nandi et al., 2013; Al Basir et al., 2015).

Contemporary research articles demonstrate that fractional order differential equations (FDEs) are a powerful tool for modelling the dynamics of enzymatic processes under difficult reaction conditions (Magin, 2006; Sabatier et al., 2007). Fractional derivatives can represent the non-local property, thereby providing an excellent mechanism for describing the dynamical behavior of various chemical and biochemical systems. There are several research articles on application of FDEs in biochemical or chemical reactions. Magin has used fractional derivatives and fractional integrals to describe the stress-strain relationship in biomaterials (Magin, 2006). Craiem et al. (2008) applied fractional calculus to model arterial viscoelasticity. Abdullah (2011) has used fractional differential equations to model the Michaelis-Menten reaction in a 2D region.

In addition, many researchers describe the non-local property and the memory effect using the fractional differential operator (Sun et al., 2011; Du et al.,

2013). In particular, Magin has provided a simple but illustrative example of the memory effect of fractional derivative. Therefore, the fractional derivative oriented models are more accurate in their description capacity (Magin, 2006). Theoretical developments are also in progress for more extensive use of this tool in science and engineering. Toledo-Hernandez et al. (2014a) have shown the feasibility and capabilities of fractional calculus as a tool for modeling dynamic systems in the area of process systems engineering. They have proposed a model for the fermentation problem using fractional calculus as a modeling tool and used experimental data to establish the validity of the model in biochemical reaction (Toledo-Hernandez et al., 2014b).

In other fields, the applications of fractional calculus are developed as extensions of the well established mathematical models that are based upon ordinary differential equations. Therefore, in those cases it is important to understand how to properly fractionalize these classical models using different definitions (Rana et al., 2013; Roy et al., 2013).

Optimal control problems, involving the use of fractional derivatives, have been extensively studied in the literatures (Sabatier Agrawal and Teneiro-Machado, 2007; Agarwal, 2008). Several references and classical books provide the theoretical basis and fundamentals for this area (Sethi and Thompson, 2000; Stengel, 1994). Interesting and promising applications of fractional calculus have been proposed in the area of process control (Moreau et al., 2008; Delavari et al., 2013). However, in the area of optimal control, the fractional calculus literature is quite limited. Agrawal (2008) derived the optimality conditions for the fractional order optimal control problems (FOCP) for single state and control variable. Further, Agrawal (2008) provided the Euler-Lagrange equations for the FOCP, based on the Riemann-Liouville definition of fractional derivative. Agrawal, Defterli and Babanu (2010) and Ding, Wang and Ye (2012) have derived the optimality conditions for several state and control variables using Caputo definitions.

In this research article, we propose an enzyme-kinetic mathematical model of fractional order. We also incorporate optimal control mechanism in our fractional-order model system to optimize the respective process. Maximum principle is used to solve the optimum control problem using Hamiltonian. Numerical iterative schemes are developed to get approximate analytical solution for the model system and also for the fractional optimal control problem. Numerical simulation has also been performed with the use of Matlab programming in order to illustrate the analytical results.

2. The fractional derivatives

To analyze the dynamical behavior of a fractional system it is necessary to use an appropriate definition of the fractional derivative. In fact, the definition of

the fractional order derivative is not unique, and there exist several of them, including Grünwald-Letnikov, Riemann-Liouville, Weyl, Riesz, and the Caputo representation. In the Caputo case, the derivative of a constant is zero and we can properly define the initial conditions for the fractional differential equations, so that they can be handled analogously to the classical integer case. Caputo derivative implies a memory effect by means of a convolution between the integer order derivative and a power of time (Ahmed, 2013; Toledo-Hernandez et al., 2014a,b; Aguilar et al., 2014).

The right-sided Caputo fractional derivative and the Riemann-Liouville fractional derivative are defined in the book by Li and Zeng (Li and Zeng, 2015). The left-sided Caputo fractional derivative can be defined as:

$$
{}_a^C D_t^\alpha g(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{g^{(n)}(s)}{(t-s)^{\alpha-n+1}} ds. \tag{1}
$$

The right-sided Caputo fractional derivative is defined as:

$$
{}_t^C D_b^\alpha g(t) = \frac{(-1)^n}{\Gamma(n-\alpha)} \int_t^b \frac{g^{(n)}(s)}{(t-s)^{\alpha-n+1}} ds, \tag{2}
$$

where α is the order of the derivative and $n-1 < \alpha < n$, Γ denotes the gamma function, and n is considered as an integer.

The left-sided Riemann-Liouville fractional derivative is defined as:

$$
{}_a D_t^\alpha g(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_a^t \frac{g(s)}{(t-s)^{\alpha-n+1}} ds. \tag{3}
$$

Furthermore, the right-sided Riemann-Liouville fractional derivative is defined as:

$$
{}_t D_b^\alpha g(t) = \frac{(-1)^n}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_t^b \frac{g(s)}{(t-s)^{\alpha-n+1}} ds, \tag{4}
$$

where α is the order of the derivative and $n-1 < \alpha < n$, Γ denotes the gamma function, and n is considered as an integer, while $a > 0$, $b > 0$ are constants.

Next, the definition of the fractional derivative due to Grünwald-Letnikov (GL) for FODEs is expressed as follows:

$$
{}_{GL} D_t^\alpha g(t) = \lim_{h \to 0} h^{-\alpha} \sum_{i=0}^{[(t-\alpha)/h]} (-1)^i \binom{\alpha}{i} g(t-ih). \tag{5}
$$

After some simplifications, the GL definition can be modified into the following form:

$$
{}_{GL} D_t^\alpha x(t_m) = h^{-\alpha} \sum_{i=0}^m v_i^{(\alpha)} x_{m-i}. \tag{6}
$$

Here, h denotes the size of the time step and v_i^α are the Grünwald-Letnikov coefficients that are given through the expression below:

$$v_i^\alpha = (1 - (1 + \alpha)/i)v_{i-1}^\alpha, \ i = 0, 1, 2, ... \text{ and } v_0^\alpha = h^{-\alpha}. \tag{7}$$

The definition of the fractional derivative $D_t^\alpha g(t)$ is also constructed on the basis of the finite differences of an equidistant grid in $[0, t]$. In each and every finite interval (ϕ, t), $t \leqslant T$, it is assumed that the function $g(\omega)$ satisfies some smoothness conditions. The considered grid is as follows:

$$0 = \omega_0 \leq \omega_1 \leq \omega_2 \leq ... \leq t = \omega_{n+1} = (n+1)h, \tag{8}$$

where $\omega_{n+1} - \omega_n = h$.

By applying the general definition of finite differences and with the help of the GL definition, we obtain

$$\frac{1}{h^\alpha}\Delta_h^\alpha g(t) = \frac{1}{h^\alpha}\Big(g(\omega_{n+1}) - \sum_{\zeta=1}^{n+1} k_\zeta^\alpha g(\omega_{n+1-\zeta})\Big), \tag{9}$$

where

$$k_\zeta^\alpha = -(1)^{\zeta-1}\binom{\alpha}{\zeta}. \tag{10}$$

In general, the GL definition is a transposition of the Euler mechanism to the fractional-order differential equations. If $\alpha \to 1$, then the general implicit or explicit Euler procedure is achieved. If we compare this with the linear multi-step methods, then the totality of divided differences leads to a lengthy process (Podlubny and Chen, 2007).

We use the notation of the operator D_t^α for left-Caputo and $D_{t_f}^\alpha$ for right-Caputo derivative throughout the article.
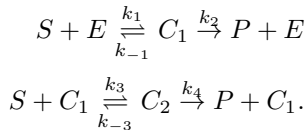
3. The fractional-order model

Typical simulation and optimization models for reactive biological systems do not necessary follow the classical mass-action law, but include equations involving empirical or semi-empirical expressions (Toledo-Hernandez et al., 2014a). By applying the memory effect to the dynamics of such systems, the kinetics of those reactive systems can also be accurately represented by using fractional calculus, yielding forms similar to those obtained by the law of mass action. The following assumptions are adopted in the formulation of the mathematical model:

An enzyme molecule (E) having a double active site can bind with a substrate molecule S to form a single bound substrate-enzyme complex C_1. This complex C_1 may break down to form a product P or can combine with another substrate

molecule to form a dual bound substrate-enzyme complex C_2. This C_2 complex breaks down to form the product P, and the single bound complex C_1 (Murray, 1989; Henry et al., 2002).

Based on the above assumptions, the reaction mechanism for this model can be given schematically by:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \overset{k_2}{\rightarrow} P + E$$

$$S + C_1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \overset{k_4}{\rightarrow} P + C_1.$$

Here k_i's are the rate constants. The concentrations of the reactants and products are denoted by lower case letters. So, $s = [S], e = [E], c_1 = [C_1], c_2 = [C_2]$ and $p = [P]$ where $[\,]$ denotes the concentration of the reactants.

With the assumptions here adopted, the integer order model can therefore be formulated as:

$$
\begin{aligned}
\frac{ds}{dt} &= -k_1 se + (k_{-1} - k_3 s)c_1 + k_{-3}c_2 \\
\frac{dc_1}{dt} &= k_1 se - (k_{-1} + k_2 + k_3 s)c_1 + (k_{-3} + k_4)c_2 \\
\frac{dc_2}{dt} &= k_3 sc_1 - (k_{-3} + k_4)c_2 \\
\frac{de}{dt} &= -k_1 se + (k_{-1} + k_2)c_1 \\
\frac{dp}{dt} &= k_2 c_1 + k_4 c_2,
\end{aligned}
$$

$$(11)$$

with initial conditions: $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$, and $p(0) = 0$.

The physicochemical nature of biological processes involves, in this case, the dynamic behavior of the processes with memory. Microorganism activity forms the major source for enzymes. Enzymes (generally proteins) are catalysts that help to convert substrates into products and are particularly efficient at speeding up biological reactions. Microorganism growth depends on the medium, in which the microorganisms are located. The dynamic behavior of living microorganisms is affected by a number of factors (substrate concentration, medium conditions, etc.) and they will adapt to changes in their environment. Thus, we can assume that the dynamic behavior of a living microorganism does not depend only on conditions existing at the current point in time, but also on the states of the entire system at earlier points. Therefore, the dynamics of biological reactions can, in general, involve memory effects (Ahmed, 2013; Toledo-Hernandez et al.,

2014a,b).

Based on the above prerequisites, the fractional order model is thus formulated as:

$$
\begin{aligned}
D_t^\alpha s &= -k_1 se + (k_{-1} - k_3 s)c_1 + k_{-3}c_2 \\
D_t^\alpha c_1 &= k_1 se - (k_{-1} + k_2 + k_3 s)c_1 + (k_{-3} + k_4)c_2 \\
D_t^\alpha c_2 &= k_3 s c_1 - (k_{-3} + k_4)c_2 \\
D_t^\alpha e &= -k_1 se + (k_{-1} + k_2)c_1 \\
D_t^\alpha p &= k_2 c_1 + k_4 c_2,
\end{aligned}
\tag{12}
$$

with initial conditions: $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$, and $p(0) = 0$.

The above system can be written down in the matrix form as below:

$$
D_t^\alpha x(t) = f(x(t)),
\tag{13}
$$

with $x(0) = x_0$ as the initial conditions.

Here, $x = (s, e, c_1, c_2, p)^T$ and $f = (f_1, f_2, f_3, f_4, f_5)^T$, where $f_i, i = 1, \ldots, 5$ are the right hand sides of the system (12).

4. Non-negative solutions

Initially, we prove the non-negativity of the solutions. Next, we show that the solution $x(t)$, with $x(0) > 0$, is always positive, whenever the solution exists and the solutions will remain in $\Re_+^5$, where $\Re_+^5 = \{x \in \Re^5 : x \geq 0\}$ and $x(t) = (s(t), c_1(t), c_2(t), e(t), p(t))^T$.

For the proof of the theorem about the nonnegativity of solutions, we need the following Lemma (see Odibat and Shawagfeh, 2007) :

LEMMA 1 *(Generalized Mean Value Theorem): Let $f(x) \in C[a, b]$ and $D_t^\alpha \in C(a, b]$ for $0 < \alpha \leq 1$, then we have*

$$
f(x) = f(a) + \frac{1}{\Gamma(\alpha)} D_t^\alpha f(\xi)(x - a)^\alpha,
\tag{14}
$$

with $0 \leq \xi \leq x$, for all $x \in (a, b]$.

REMARK 1 *With $f(x) \in C[0, b]$ and $D_t^\alpha \in C(a, b]$ for $0 < \alpha \leq 1$ it is clear from Lemma 1 that if $D_t^\alpha \geq 0$, for all $x \in (0, b)$, then the function f is non decreasing, and if $D_t^\alpha \leq 0$, for all $x \in (0, b)$, then the function f is non increasing for all $x \in [0, b]$.*

THEOREM 1 *There is a unique solution $x(t) = (s(t), c_1(t), c_2(t), e(t), p(t))^T$ for the initial value problem given by (12) and the solution remains in $\Re_+^5$.*

Proof: The existence and uniqueness of the solution of (12) in $(0, \infty)$ can be established by Theorem 3.1 and Remark 3.2 of Lin (2007). We need to show that the domain $\Re_+^5$ is positively invariant.
Since

$$
\begin{aligned}
D_t^\alpha s|_{s=0} &= (k_{-1}c_1 + k_{-3}c_2 \geq 0, \\
D_t^\alpha c_1|_{c_1=0} &= k_1 se + (k_{-3} + k_4)c_2 \geq 0, \\
D_t^\alpha c_2|_{c_2=0} &= k_3 sc_1 \geq 0, \\
D_t^\alpha e|_{e=0} &= (k_{-1} + k_2)c_1 \geq 0, \\
D_t^\alpha p|_{p=0} &= k_2 c_1 + k_4 c_2 \geq 0,
\end{aligned}
$$

by Remark 1, the solution will remain in $\Re_+^5$. So we can say that on each hyperplane, bounding the non-negative orthant, the vector field points into $\Re_+^5$. Therefore, the domain $\Re_+^5$ is a positively invariant region.   □

5. The fractional optimal control problem (FOCP)

5.1. Formulation

Optimal control is a useful tool for appropriate steering of a chemical or bio-chemical system. By applying the methods of optimal control, the time dependent profiles of the control variable are determined to optimize a particular performance. In the present article, as product formation constitutes a fast irreversible step and complexes are formed in a reversible manner, so control measures are being applied in the case of both backward reversible stages for production process optimization. In this way, backward reactions can be reduced to some extent, and hence we can increase the rate of forward reaction. Ultimately, this leads to product output optimization. The system with the application of control can be represented schematically as:

$$
S + E \underset{k_{-1},u}{\overset{k_1}{\rightleftharpoons}} C_1 \overset{k_2}{\rightarrow} P + E
$$
$$
S + C_1 \underset{k_{-3},u}{\overset{k_3}{\rightleftharpoons}} C_2 \overset{k_4}{\rightarrow} P + C_1. \tag{15}
$$

Here, $u(t)$ represents control input with values normalized between 0 and 1. This means that $u(t) = 1$ represents the maximal use of control and $u(t) = 0$ signifies no control. The control measure can be realized through reaction temperature, pressure, enzyme concentration, activation energy etc. (Roy et al., 2014; Basir and Roy, 2015). By applying the control $u(t)$ at the reversible steps, the system

(12) becomes a controlled system, which is now written down as below:

$$
\begin{aligned}
D_t^\alpha s &= -k_1 se + \{u(t)k_{-1} - k_3 s\}c_1 + u(t)k_{-3}c_2 \\
D_t^\alpha c_1 &= k_1 se - \{u(t)k_{-1} + k_2 + k_3 s\}c_1 + (u(t)k_{-3} + k_4)c_2 \\
D_t^\alpha c_2 &= k_3 sc_1 - \{u(t)k_{-3} + k_4\}c_2 \\
D_t^\alpha e &= -k_1 se + \{u(t)k_{-1} + k_2\}c_1 \\
D_t^\alpha p &= k_2 c_1 + k_4 c_2,
\end{aligned}
\tag{16}
$$

with initial conditions: $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$ and $p(0) = 0$. The system (16) is the state system and the derivative is taken in the left-Caputo sense. The control–induced system can be written down in the matrix form as:

$$
D_t^\alpha x(t) = f(x(t), u(t)),
\tag{17}
$$

where $x(t) \equiv (s(t), e(t), c_1(t), c_2(t), p(t))^T$ is the state vector, $u(t)$ is the control variable and t is time. We want to maximize the product amount (p), while keeping cost as low as possible. We thus formulate the objective function as:

$$
\begin{aligned}
J(u) &= \int_{t_i}^{t_f} [u^2(t) - p^2(t)]dt \\
&= \int_{t_i}^{t_f} g(x(t), u(t))dt
\end{aligned}
\tag{18}
$$

say,

where t_i stands for initial time and t_f for final time. Our aim is to find the optimal control $u(t)$ for the system (16) such that minimizes the functional $J(u)$ and hence to optimize the product volume (p).

5.2. The optimality of the system

Ding, Wang and Ye (2012) and Agrawal, Defterli and Baleanu (2010) have presented a general formulation and the derivation of the optimality conditions for a FOCP for several state and control variables. Here, we have solved our FOCP using the results from these articles. There is no difficulty in using the respective principle in case of fractional ordered system (Agrawal, Defterli and Baleanu, 2010).

We formulate the Hamiltonian as below

$$
H(u(t), x(t), \lambda(t)) = g(x(t), u(t)) + \lambda^T f(x(t), u(t)).
\tag{19}
$$

The co-state system with λ as the costate vector can be obtained by the following relation:

$$
D_{t_f}^\alpha \lambda = \frac{\partial H}{\partial x} = \frac{\partial g}{\partial x} + \lambda^T \frac{\partial f}{\partial x}, \text{ with boundary conditions } \lambda_i(t_f) = 0.
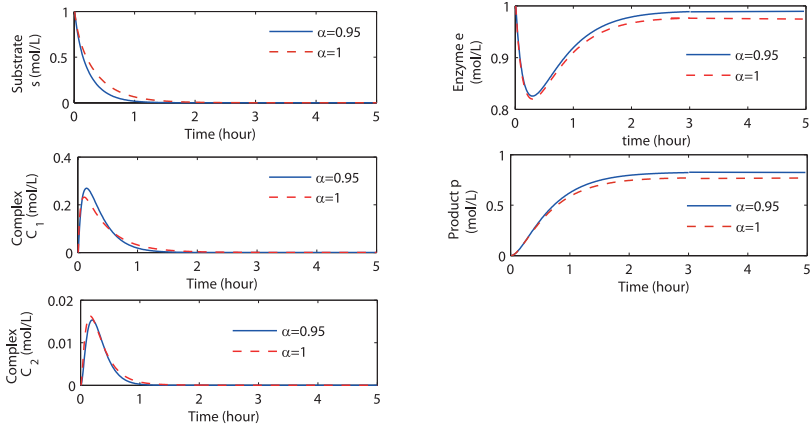\tag{20}
$$

Figure 1. Numerical solutions of the fractional model of the system for different values of α and other parameters as given in Table 1

The optimal control function $u(t)$ satisfies the following relation:

$$\frac{\partial H}{\partial u} = \frac{\partial g}{\partial u} + \lambda^T \frac{\partial f}{\partial u} = 0. \tag{21}$$

The Euler-Lagrange optimality conditions for the FOCP with Caputo fractional derivatives are given by relations (20) and (21). It can be noted that if the order of the fractional derivatives (α) becomes equal to 1, the above system of equations reduces to the classical optimality condition for an optimal control problem.

Here,

$$\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)^T, \quad f = (f_1, f_2, f_3, f_4, f_5)^T, \quad f_i, i = 1 - 5$$

are the right hand sides of the system (16). Using the optimality conditions given by equations (20) and (21), the Euler-Lagrange optimality conditions that minimize the objective functional (18) are obtained as follows:

The adjoint system is obtained as:

$$
\begin{aligned}
D_{t_f}^\alpha \lambda_1 &= -\lambda_1(k_1 e + k_3 c_1) - \lambda_2(k_3 c_1 - k_1 e) \\
&\quad + \lambda_3 k_3 c_1 - \lambda_4 k_1 e \\
D_{t_f}^\alpha \lambda_2 &= \lambda_1(k_{-1}u(t) - k_3 s) - \lambda_2(k_{-1}u(t) + k_2 \\
&\quad + k_3 s) + \lambda_3 k_3 s + \lambda_4[k_{-1}u(t) + k_2] + \lambda_5 k_2 \\
D_{t_f}^\alpha \lambda_3 &= \lambda_1 u(t) k_{-3} + (\lambda_2 - \lambda_3)(u(t)k_{-3} + k_4) + \lambda_5 k_4 \\
D_{t_f}^\alpha \lambda_4 &= (-\lambda_1 + \lambda_2 - \lambda_4)k_1 s \\
D_{t_f}^\alpha \lambda_5 &= -2p, \tag{22}
\end{aligned}
$$

with the boundary conditions: $\lambda_i(t_f) = 0, \quad i = 1, 2, 3, 4, 5.$

From relations (19) and (21), we get the expression for the optimal control function as:

$$u(t) = \frac{k_{-1}c_1(\lambda_1 + \lambda_4 - \lambda_2) + k_{-3}c_2(\lambda_1 + \lambda_2 - \lambda_3)}{2}. \tag{23}$$

Due to boundedness of the optimal control we have:

$$u(t) = min\{max\{\frac{k_{-1}c_1(\lambda_1 + \lambda_4 - \lambda_2) + k_{-3}c_2(\lambda_1 + \lambda_2 - \lambda_3)}{2}, 0\}, 1\}. \tag{24}$$

Equation (16), together with equations (22) and (23), represent the FOCP. Thus, the optimality system constitutes a two-point boundary value problem including a set of fractional order differential equations.

Table 1: Values of the parameters used in the model equation

Parameter	Assigned values	Units
k_1	3	$mol\ L^{-1}\ hour^{-1}$
k_2	3	$hour^{-1}$
k_3	0.6	$mol\ L^{-1}\ hour^{-1}$
k_4	3	$hour^{-1}$
k_{-1}	1	h^{-1}
k_{-3}	1	$hour^{-1}$

6.   Numerical simulation

In previous sections, we have presented some analytical results related to the fractional mathematical model (12). We have shown that solutions of the system are non-negative and remain always in $\Re_+^5$. Next, we have incorporated optimal control with respect to the formulated fractional model to optimize the product generation process. In this section, we explore the numerical simulation of the fractional model system and FOCP against the outlook of the analytical results. We apply numerical techniques for the cases of fractional-order differential equations to achieve approximate solutions. There are few analytical and numerical methods for solving the fractional differential equations. We have developed iterative schemes to solve the fractional order systems and proceed through Matlab using the schemes.

The main objective of this study is to show the effect of memory (α) on enzymatic system and to find out the optimal control profile $u(t)$ to minimize the reverse reaction of enzyme substrate complex in order to optimize the product generation process. Numerically, we have tried to solve the fractional model system (16) and the fractional optimal control problem. The solution has been displayed in respective figures.
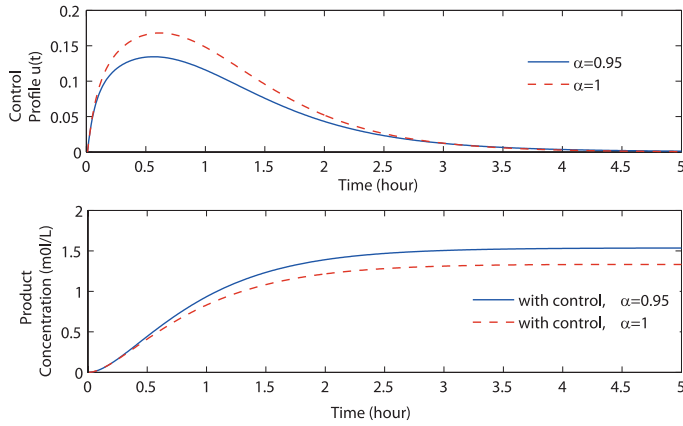
Figure 2. Numerical solution of the FOCP for $\alpha = 0.95$ and $\alpha = 1$ and other parameter values as in Table 1

Numerical simulation of the fractional system (12)

The following numerical scheme is developed for solving the fractional model (12):

$$s(i) = [-k_1 s(i-1)e(i-1) + k_{-1}c_1(i-1) - k_3 s(i-1)c_1(i-1) + k_{-3}c_2(i-1)]h^\alpha$$
$$-\sum_{j=1}^{i} m(j)s(i-j),$$

$$c_1(i) = [k_1 s(i)e(i-1) - k_{-1}c_1(i-1) - k_2 c_1(i-1) - k_3 s(i)c_1(i-1)$$
$$+k_{-3}c_2(i-1) + k_4 c_2(i-1)]h^\alpha - \sum_{j=1}^{i} m(j)c_1(i-j),$$

$$c_2(i) = [k_3 s(i)c_1(i) - k_{-3}c_2(i-1) - k_4 c_2(i-1)]h^\alpha - \sum_{j=1}^{i} m(j)c_2(i-j),$$

$$e(i) = [-k_1 c_1(i) + k_{-1}s(i)e(i-1) + k_2 c_1(i)]h^\alpha - \sum_{j=1}^{i} m(j)e(i-j),$$

$$p(i) = [-k_2 c_1(i) + k_4 c_2(i)]h^\alpha - \sum_{j=1}^{i} m(j)p(i-j).$$

The last term of the above equations stands for memory. The parameter $m(j)$ is defined as $m(0) = 1$ and $m(j) = (1 - \frac{1+\alpha}{j})m(j-1)$, $j \geq 1$. Here, $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$, and $p(0) = 0$ are the initial conditions, and h is the time step length, and we take h=0.05.
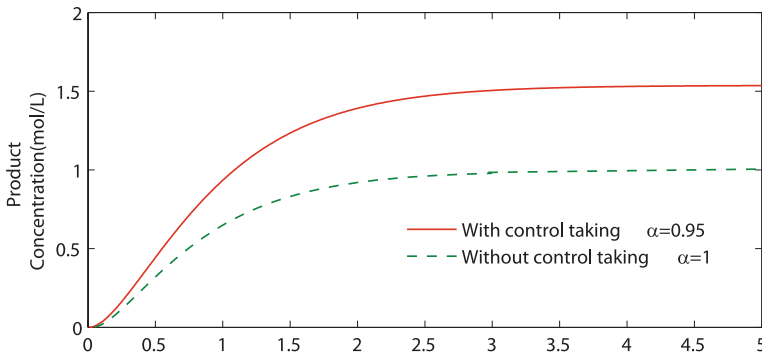

Figure 3. Comparison between two concentrations of product (p) in two cases: (case I) with control, taking $\alpha = 0.95$, and (case II) without control, taking $\alpha = 1$

The solution trajectory of the system (12) is plotted in Fig. 1. Here, we take $e(0) = 1\ mol/L$, $s(0) = 1\ mol/L$, and see that the substrate concentration decreases with time. This is due to the fact that as the substrate is consumed gradually by the binding sites of the enzymes and as the reaction progresses, single bound enzyme-substrate complex is restricted as to reverting back due to the application of control variable in this step. Rather, complex C_1 has a stronger tendency to form the product and to bind with another substrate molecule (due to the allosteric nature), so as to form the double bounded enzyme-substrate complex, i.e. the second complex, C_2. As the second complex is formed from the first one, it takes some time period to reach the maximum, after which the volumes of both complexes gradually fall off. The enzyme, which is consumed during the process, is recuperated back at the end of the reaction. The product (p), which is obtained from the two stages of the reaction, displays a continuous rise in concentration, this concentration becoming stable at the end of reaction.

Numerical simulation of the FOCP

We have provided here the iterative scheme for solving the FOCP (the system (16), (22) and (23)). The FOCP is a two point boundary value problem with the state and adjoint systems. The state system is an initial value whereas adjoint system is a boundary value problem. We proceed through Matlab using the iterative scheme described below.

We perform forward integration of the state variables from t_0 to t_f and similarly, using the final condition $\lambda(t_f) = 0$, we perform the backward integration of the adjoint variables λ_i from t_f to t_0.

The state system (16) can be solved by the following iterative scheme, developed for this purpose:

$$s(i) = [-k_1 s(i-1)e(i-1) + uk_{-1}c_1(i-1) - k_3 s(i-1)c_1(i-1) + uk_{-3}c_2(i-1)]$$

$$h^\alpha - \sum_{j=1}^{i} m(j)s(i-j),$$

$$c_1(i) = [k_1 s(i)e(i-1) - uk_{-1}c_1(i-1) - k_2 c_1(i-1) + uk_{-3}c_2(i-1) + k_4 c_2(i-1)]$$

$$h^\alpha - \sum_{j=1}^{i} m(j)c_1(i-j),$$

$$c_2(i) = [k_3 s(i)c_1(i) - uk_{-3}c_2(i-1) - k_4 c_2(i-1)]h^\alpha - \sum_{j=1}^{i} m(j)c_2(i-j),$$

$$e(i) = [-k_1 s(i)e(i-1) + uk_{-1}s(i)e(i-1) + k_2 c_1(i)]h^\alpha - \sum_{j=1}^{i} m(j)e(i-j),$$

$$p(i) = [k_2 c_1(i) + k_4 c_2(i)]h^\alpha - \sum_{j=1}^{i} m(j)p(i-j).$$

Here, $s(i)$ is the value of $s(t)$ at the ith iteration. The last term of the above equations stands for memory. Here, $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$, and $p(0) = 0$ are the initial conditions, and h is the time step length, and we take $h=0.05$. Also, the parameter $m(j)$ is defined as $m(0) = 1$ and $m(j) = (1 - \frac{1+\alpha}{j})m(j-1)$, $j \geq 1$.

The optimal control is updated by the scheme given below:

$$u = min\{max\{\frac{k_{-1}c_1(i)(\lambda_1 + \lambda_4 - \lambda_2) + k_{-3}c_2(i)(\lambda_1 + \lambda_2 - \lambda_3)}{2}, 0\}, 1\}.$$

The adjoint system (22) is solved backward-in-time with terminal conditions $\lambda_i(t_f) = 0$ using the following iterative scheme:

$$\lambda_1(i) = [-\lambda_1(i-1)\{k_1 e(i) + k_3 c_1(i)\} - \lambda_2(i-1)(k_3 c_1(i) - k_1 e(i))$$
$$+ \lambda_3(i-1)(k_3 c_1(i)) - \lambda_4(i)k_1 e(i)]h^\alpha - \sum_{j=1}^{i} m(j)\lambda_1(i-j),$$

$$\lambda_2(i) = [\lambda_1(i)(uk_{-1}c_2 - k_3 s(i)) - \lambda_2(i-1)(uk_{-1}c_2 + k_2 + k_3 s(i))$$
$$+ \lambda_3(i)k_3 s(i) + \lambda_4(i)(-uk_{-1}c_2 + k_2) + \lambda_5(i)k_2]h^\alpha - \sum_{j=1}^{i} m(j)\lambda_2(i-j),$$

$$\lambda_3(i) = [\lambda_1(i)uk_{-3} + (\lambda_2(i) - \lambda_3(i))(k_4 + uk_{-3}) + \lambda_5(i)k_4]h^\alpha - \sum_{j=1}^{i} m(j)\lambda_3(i-j),$$

$$\lambda_4(i) = [-\lambda_1(i) + \lambda_2(i) - \lambda_4(i)k_1 s(i)]h^\alpha - \sum_{j=1}^{i} m(j)\lambda_4(i-j),$$

$$\lambda_5(i) = [-2p(i)]h^\alpha - \sum_{j=1}^{i} m(j)\lambda_5(i-j).$$

The FOCP is solved in Matlab using the two iterative schemes given above. We solve the state system by forward iteration method and the adjoint system by backward iteration method, alternatively.

The optimal control approach applied to fractional differential equation (FDS) and the effect of control are shown in Fig. 2 for different values of α. The figure reveals the changes in concentration by using two different values of the parameter α and other parameters as given in Table 1.

Figures 2 represent the variation of the system dynamics considering different control approaches (OCP and FOCP) with respect to a definite time interval. Here we observe the changes in concentration of the product, induced by varying the value of α. The control profile of the system is also plotted for different values of α. It is seen that control applied to the system is reduced if we consider the memory effect by taking the fractional order model.

In Fig. 3, we have compared the concentrations of product obtained from the integer order system and from the fractional system to see the combined effect of memory and optimal control on the system. We compare the concentrations of the desired product (p) for two cases: case I: at optimum condition, taking $\alpha = 0.95$, and case II: at $\alpha = 1$, when no control is applied to the system. This figure shows that concentration depends strongly on the parameter α, i.e. the order of the system. Taking into account the memory and control, it can be seen that the rate of production has also increased significantly.

7.   Discussion

In this article, we have proposed a fractional order model of the enzymatic reaction system. Fractional optimal control problem (FOCP) for the enzyme-kinetic system is formulated, meant to optimize the process of product generation. Necessary conditions (Euler-Lagrange optimality conditions) have been given for the optimality of the fractional optimal control problem. Numerical simulation has been displayed to illustrate the main results obtained using numerical iterative schemes.

Control applied in the first, reversible stage actually directs the reaction faster in the forward direction. By applying control in the backward reaction stage, we get earlier binding between the initial complex and substrate in the remaining active site, which ultimately yields the product in shorter time. The action of control causes that all the substrate eventually becomes product, due to the irreversibility, while the enzyme is free and the complex concentration tends to zero. Numerical analysis of the fractional order enzymatic system gives a better understanding for the FOCP with respect to optimization of the production process.

8.   Conclusion

The dynamical behavior of a biological reaction systems depends on memory. Fractional-order mathematical models are endowed with memory. Therefore, fractional-order model is more realistic than the integer-order models. The fractional optimal control problem is solved numerically and it offers better prediction concerning the product generation optimization. Thus, our analytical and numerical analysis would be helpful for experimental researchers in predicting the dynamics of biochemical reacting systems. It can be expected that the proposed fractional order model and the control theoretic approach can be successfully applied to experimental investigations.

Acknowledgments

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