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MATHEMATICAL ANALYSIS OF AN ALLOSTERIC ACTIVATION OF AN ENZYME

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Abstract:

In this research paper, the Homotopy analysis method is adopted to study the problem of the allosteric of an enzyme with a boundary condition analytically. We have developed a mathematical model that simulates the allosteric regulation for activation of an enzyme. These mechanisms are converted by celebrator into ordinary differential equations (ODEs) solvable by analytically. This governing equation is a first order non-linear boundary value problem over a semi-infinite interval. General non-linear mathematical expressions can be assigned to all structure definition items. Further the graphical representations of the dimensionless dependent variables x_1 *and* x_2 *will be investigated. Our analytical results are compared with the satisfactory agreement is noted. The Homotopy analysis method can be easily extended to solve other non-linear initial and numerical solution of optimal control problems.*

Index Terms: Allosteric Activation of Enzyme, Modeling of Physiological Systems, Identification, Non-Linear Differential Equation & Homotopy Analysis Method

1. Introduction:

Direct control of enzyme activity can be exerted by the binding of small molecules such as substrates or effectors (activators and inhibitors) to catalytic or regulatory sites on the enzyme. It can also be achieved by modification of the enzyme molecules, through either covalent changes(hydrolysis, phosphorylation, etc) or no covalent changes (polymerization-depolymerization, etc).This article will concentrate on general theories and experimental manifestations of regulatory enzymes, with special emphasis on equilibrium and kinetic analysis of the molecular interactions involved in the regulatory process. A few illustrative examples are discussed. Regulation through covalent modifications of enzymes and by the interaction of enzymes with membranes is not discussed. The most important issue a number of recent reviews are available that supplement that the material presented here (1-10) in physiological modeling is therefore the determination of a suitable mathematical representation of the true system. Practical simulation of systems behavior is usually performed by numerical integration of the model's ODE. An important aspect in simulation studies is the determination of sensitivities of a system's characteristics with respect to perturbations in model variables. Physiological models of metabolic and pharmacokinetic systems are based on physical and biochemical laws that govern the transport and reaction of substances, e.g.mass balance and law of mass action. Most of the problem and scientific phenomena such as physical problems, fluid mechanics, engineering application and chemical physics it can be described through non-linear equations. Except the limited number of problems most of them do not have an exact solution. This method is applied o solve the linear and non-linear problems. The concept of Homotopy analysis method was first introduced by Liao in 1992 [11-14] is method offers highly accurate successive approximations of the solution. Howarth [15] developed this method for the solution of the laminar boundary-layer equation they applied the method, Chen et.al [16] and [17] developed this method for partial differential equations and obtained closed form series solution for linear and non-linear initial value problems.

2. Mathematical Formulation of the Problem:

To illustrate the flexibility of PANSYM for defining model structures, the example considered in the following will be based on simple enzyme reactions, which do not strictly fit in with compartmental or 'linear' structures, as explicitly considered in the development of this software. In particular, it will be shown that parameterized block representation of simple standard reactions can be used for building a model-definition dictionary, which can be viewed as an extension of the existing modeling tools of PANSYM.

Let as consider first the following simple reaction, which may describe an allosteric activation of an eqn. (5)

$$E_i + A \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} E \qquad (1)$$

Where E_i and E are the inactive and active forms of an enzyme, respectively, and A is the activator. The differential equations for this reaction are:

$$\frac{d[E_i]}{dt} = -k_1[E_i][A] + k_{-1}[E] \qquad (2)$$

$$\frac{d[A]}{dt} = -k_1[E_i][A] + k_{-1}[E] \qquad (3)$$

$$\frac{d[E]}{dt} = -k_1[E_i][A] - k_{-1}[E] \qquad (4)$$

Which differ from each other only by a sign change and represent the basis of more complex models that might include exogenous inputs or loss of substances. It can be noted that the structure of this model cannot be represented as a conventional compartmental model, because of the bond between E_i and A. Nevertheless we may express the kinetics of E_i and E as a compartmental model with control, and add the constraint on the kinetics of A.If we denote with x_1 ,x_2 and x_3 the concentrations $[E_i]$,$[A]$ and $[E]$, respectively, and with km_1 the rate constant k_{-1},then the structure of this reaction can be defined, according to the model definition rules described previously, by the following list of statements:

$$[k_{31} = k_1 * x_2, a_{21} = -k_{31}, k_{13} = kml, a_{23} = k_{13}] \qquad (5)$$

Note that symbol k_1 for parameter k_1 is acceptable, since it cannot be misinterpreted as a structural parameter k_{ij}, which requires two indices. A parameterized block definition of eqn.(5),which generalizes the definitions of coupled sets of differential equations of the type (2)-(4),could be give. Where A and E represent index numbers of state variables $[E_i][A]$ and $[E]$, respectively.

In particular, the generation and solution of differential or algebraic equations has not been implemented, and algebraic constraints must be explicitly incorporated into definitions of systems. As an example let as consider the introduction of a conservation law for reaction (1) by assuming that the total amount of bound and unbound activating enzyme can be considered constant, i.e. $[A]+[E]=[A]_0$ =constant. The system (2-4) can be simplified by eliminating $[A]$and thus eqn. (3), as follows:

$$\frac{d[E_i]}{dt} = -k_1[E_i]([A]_0 - [E]) + k_{-1}[E] \quad (6)$$

$$\frac{d[E]}{dt} = -k_1[E_i]([A]_0 - [E]) - k_{-1}[E] \quad (7)$$

The corresponding parameterized block definition, which is based on compartmental structural parameters alone where A_0 represents the constant $[A]_0$.

3. Solution of the Non-Linear Boundary Value Problem Using the Homotopy Analysis Method:

HAM is a non-perturbative analytical method for obtaining series solutions to non-linear equations and has been successfully applied to numerous problems in science and engineering [18-37]. In comparison with other perturbative and non perturbative analytical methods, HAM offers the ability to adjust and control the convergence of a solution via the so-called convergence-control parameter. Because of this, HAM has proved to be the most effective method for obtaining analytical solutions to highly non-linear differential equations. Previous applications of HAM have mainly focused on non-linear differential equations in which the non-linearity is a polynomial in terms of the unknown function and its derivatives. Our results show that even in this case, HAM yields excellent results.

Liao [18-23] proposed a powerful analytical method for non-linear problems, namely the Homotopy analysis method. This method provides an analytical solution in terms of an infinite power series. However, there is a practical need to evaluate this solution and to obtain numerical values from the infinite power series. In order to investigate the accuracy of the Homotopy analysis method (HAM) solution with a finite number of terms, the system of differential equations were solved. The Homotopy analysis method is a good technique comparing to another perturbation method. The Homotopy analysis method contains the auxiliary parameter h, which provides us with a simple way to adjust and control the convergence region of solution series. The analytical solution of the eqns. (6) and (7) using the Homotopy analysis method is as follows:

$$x_1 = ce^{-aA_0t} - h\left(acd\left[\frac{e^{(-aA_0+b-a)t}}{-aA_0+b-a}\right] - \frac{acd}{(-aA_0+b-a)}e^{-at}\right) \quad (8)$$

$$x_2 = de^{(b-a)t} - h\left(acd\left[\frac{e^{(-aA_0-b-a)t}}{-aA_0-b-a}\right] - \frac{acd}{(-aA_0-b-a)}e^{-bt}\right) \quad (9)$$

4. Results and Discussion:

Figure 1-3 represents the (x_1) versus the dimensionless time (t). From Fig.1 it is evident that when the (k) decreases the corresponding (x_1) increases for some fixed value of the (a) and (b). From Fig.2 shows that when the (b) decreases the corresponding (x_1) increases in some fixed value of (a) and (k). From Fig. 3 it is inferred that when the (a) increases the corresponding (x_1) increases for some fixed value of (b) and (k). Figure 4-6 represents the (x_2) versus the dimensionless time (t). From Fig. 4 shows that when the (k) increases the corresponding (x_2) increases in some fixed value of (a) and (b). From Fig.5 shows that when the (b) increases the corresponding (x_2) increases in some fixed value of (a) and (k). From Fig. 6 it is inferred that when the (a) decreases the corresponding (x_2) increases for some fixed value of (b) and (k). Figure 7-15 represents the (x_1) and (x_2) versus the dimensionless time (t). From Fig. 7 -9 shows that when the (x_1) decreases and (x_2) increases in some fixed value of (a) and (b) and for some value of (k). From Fig. 9-12 inferred that when the (x_1) decreases and (x_2) increases in some fixed value of (a) and (k) and for some value of (b). From Fig. 13-15 depicts that when the (x_1) increases and (x_2) decreases in some fixed value of (b) and (k) and for some value of (a).

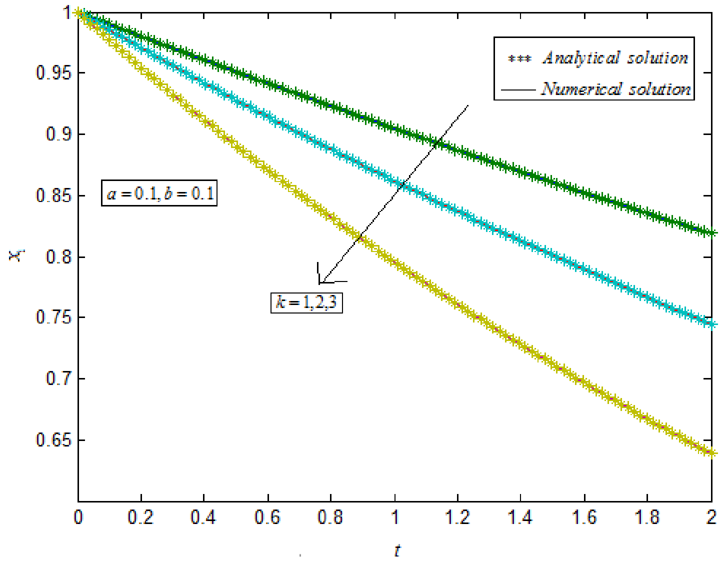

Figure 1: (x_1) versus dimensionless time (t). The curves are plotted using the eqn.(8) for various values of dimensionless parameter (k) and some fixed value of the dimensionless parameters (a) and (b).

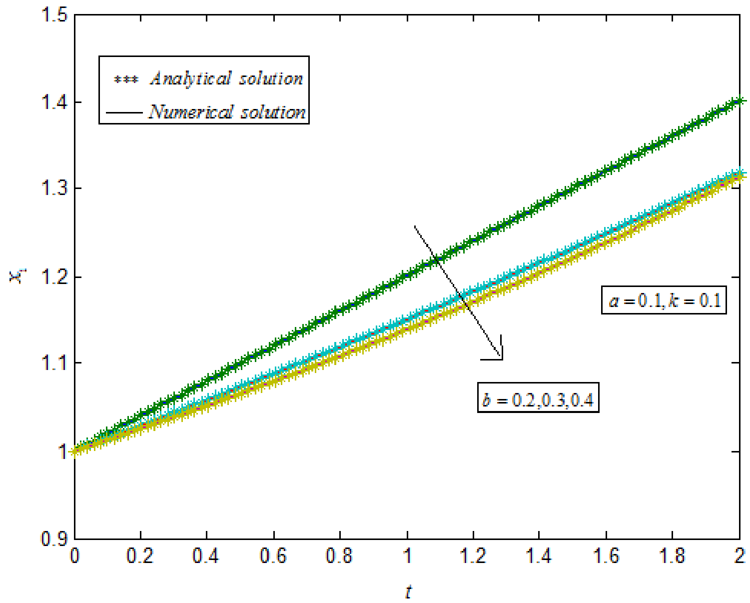

Figure 2: (x_1) versus dimensionless time (t). The curves are plotted using the eqn.(8) for various values of dimensionless parameter (b) and some fixed value of the dimensionless parameters (a) and (k).

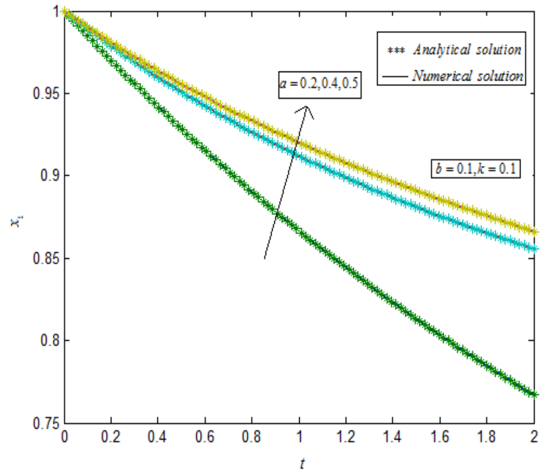

Figure 3: (x_1) versus dimensionless time (t). The curves are plotted using the eqn.(8) for various values of dimensionless parameter (a) and some fixed value of the dimensionless parameters (b) and (k).

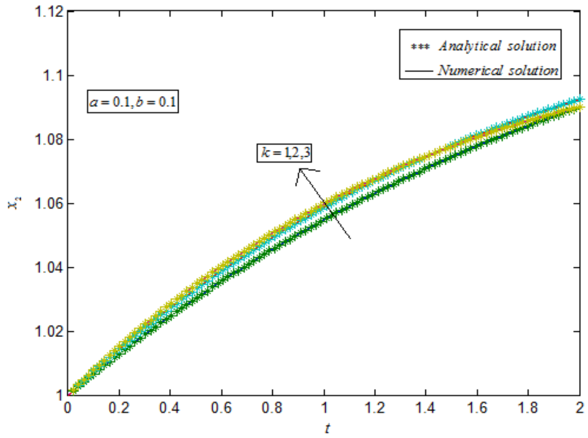

Figure 4: (x_2) versus dimensionless time (t). The curves are plotted using the eqn.(9) for various values of dimensionless parameter (k) and some fixed value of the dimensionless parameters (a) and (b).

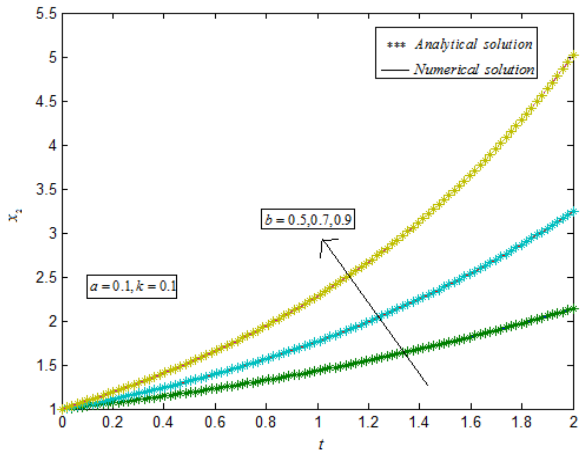

Figure 5: (x_2) versus dimensionless time (t). The curves are plotted using the eqn.(9) for various values of dimensionless parameter (b) and some fixed value of the dimensionless parameters (a) and (k).

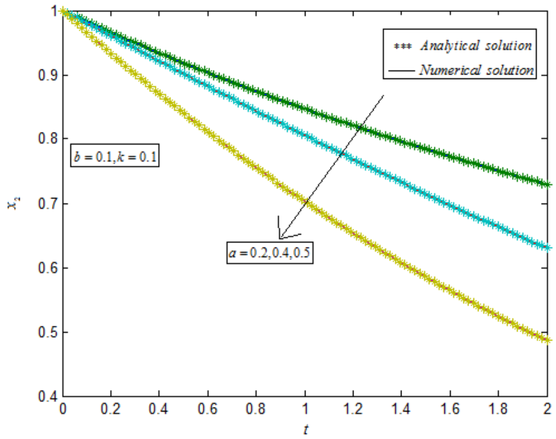

Figure 6: (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (9) for various values of dimensionless parameter (a) and some fixed value of the dimensionless parameters (b) and (k).

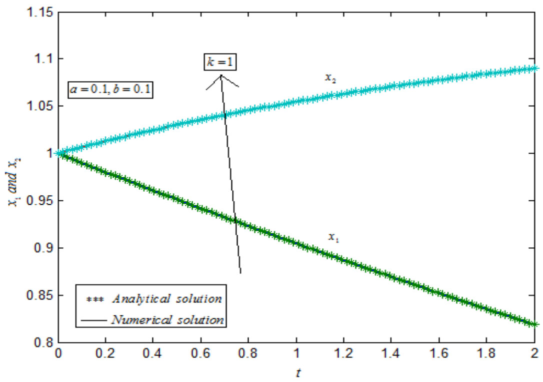

Figure 7: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (k) and some fixed value of the dimensionless parameters (a) and (b).

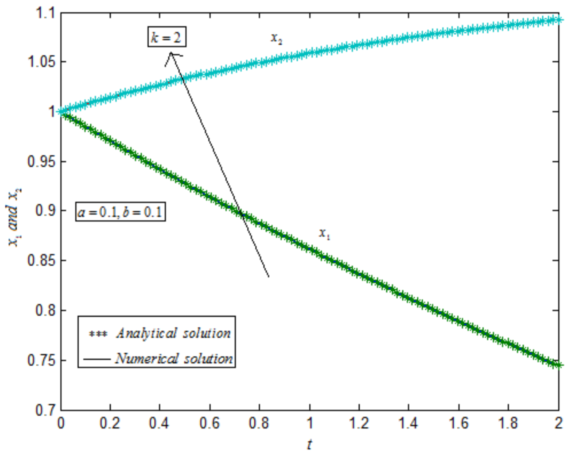

Figure 8: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (k) and some fixed value of the dimensionless parameters (a) and (b).

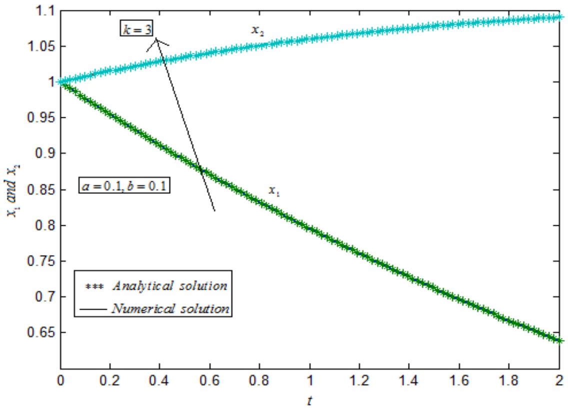

Figure 9: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (k) and some fixed value of the dimensionless parameters (a) and (b).

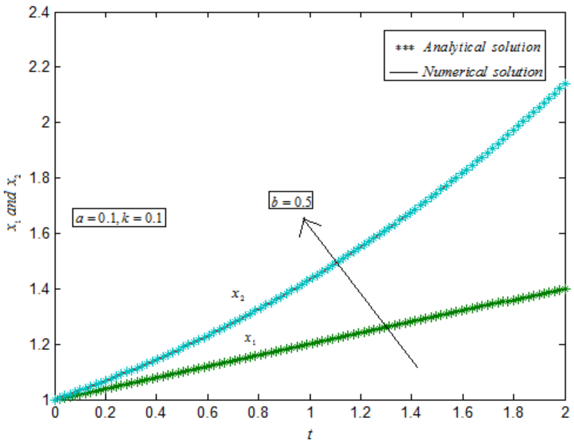

Figure 10: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (b) and some fixed value of the dimensionless parameters (a) and (k).

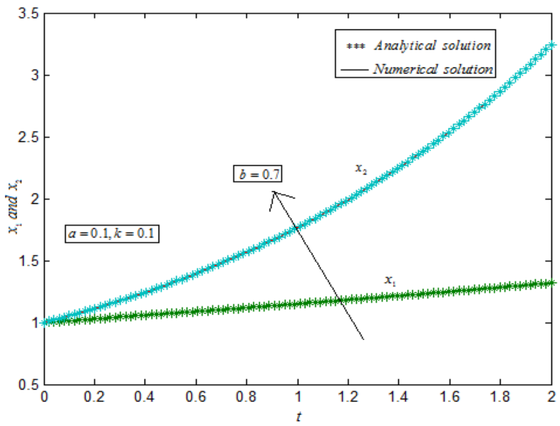

Figure 11: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (b) and some fixed value of the dimensionless parameters (a) and (k).

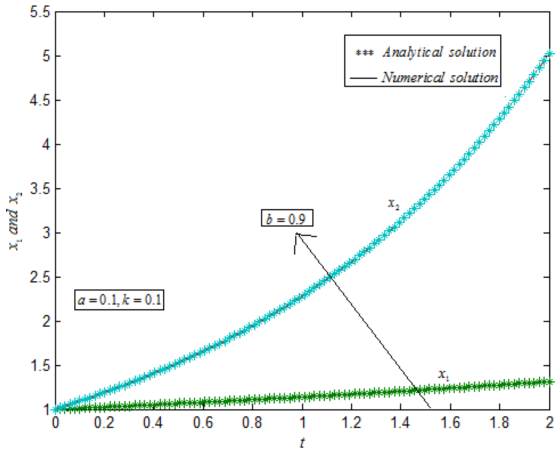

Figure 12: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (b) and some fixed value of the dimensionless parameters (a) and (k).

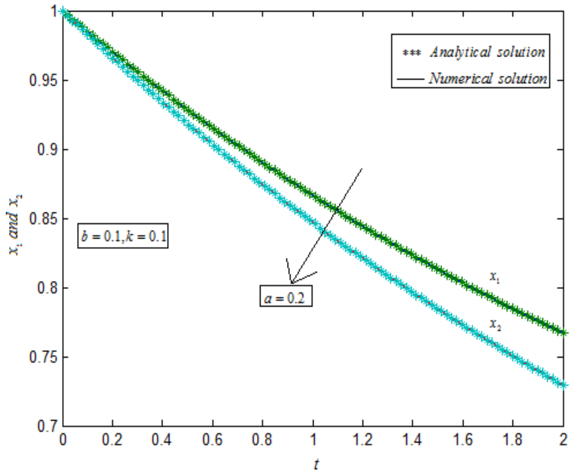

Figure 13: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (a) and some fixed value of the dimensionless parameters (b) and (k).

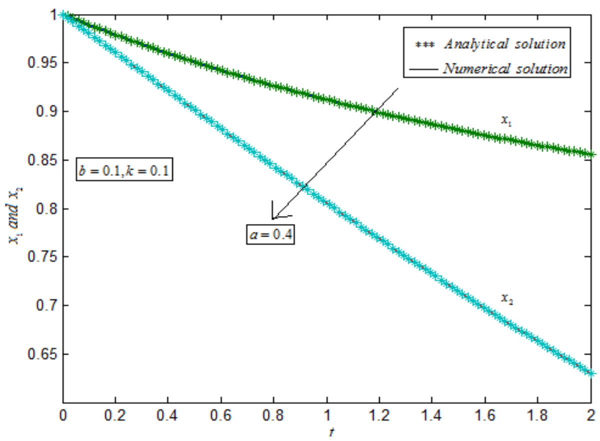

Figure 14: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (a) and some fixed value of the dimensionless parameters (b) and (k).

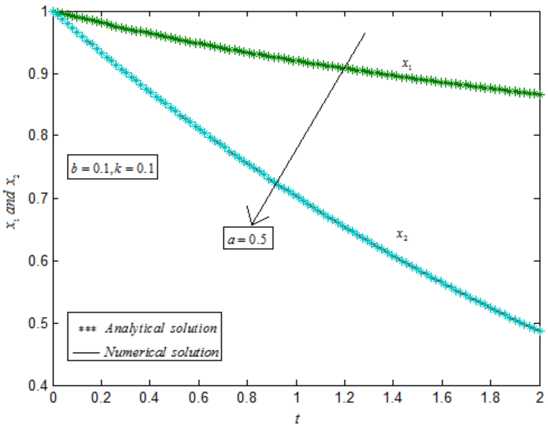

Figure 15: (x_1) and (x_2) versus dimensionless time (t). The curves are plotted using the eqn. (8) and (9) for various values of dimensionless parameter (a) and some fixed value of the dimensionless parameters (b) and (k).

5. Conclusion:

In this study, the Homotopy analysis method (HAM) has been applied to solve non-linear differential equation arising in allosteric of an enzyme with a boundary condition analytically. The analytical expressions time dependent have been derived by the Homotopy analysis method. Comparison of the results obtained by HAM with those of numerical showed efficiency of this method to solve strong non-linear differential equations. Further the graphical representations of the dimensionless time dependent variables x_1 and x_2 have been investigated. This method can be easily extended to solve the non-linear initial and boundary value problems in computer methods in optimal control problems.

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Appendix: A

Basic Concept of the Homotopy Analysis Method [8-27]:

Consider the following differential equation:

$$N[u(t)] = 0 \quad (A.1)$$

Where N is a nonlinear operator, t denotes an independent variable, u (t) is an unknown function. For simplicity, we ignore all boundary or initial conditions, which can be treated in the similar way. By means of generalizing the conventional Homotopy method, Liao (2012) constructed the so-called zero-order deformation equation as:

$$(1-p)L[\varphi(t;p)-u_0(t)] = phH(t)N[\varphi(t;p)] \quad (A.2)$$

where $p\in$ [0,1] is the embedding parameter, $h \neq 0$ is a nonzero auxiliary parameter, $H(t) \neq 0$ is an auxiliary function, L an auxiliary linear operator, u_0 (t) is an initial guess of $u(t)$, $\varphi(t:p)$ is an unknown function. It is important to note that one has great freedom to choose auxiliary unknowns in HAM. Obviously, when $p=0$ and $p=1$, it holds:

$$\varphi(t;0)=u_0(t) \text{ and } \varphi(t;1)=u(t) \quad (A.3)$$

Respectively. Thus, as p increases from 0 to 1, the solution $\varphi(t;p)$ varies from the initial guess to the solution u (t). Expanding $\varphi(t;p)$ in Taylor series with respect to p, we have:

$$\varphi(t;p)=u_0(t)+\sum_{m=1}^{+\infty}u_m(t)p^m \quad (A.4)$$

Where

$$u_m(t)=\frac{1}{m!}\frac{\partial^m\varphi(t;p)}{\partial p^m}\Big|_{p=0} \quad (A.5)$$

If the auxiliary linear operator, the initial guess, the auxiliary parameter h, and the auxiliary function are so properly chosen, the series (A.4) converges at p =1 then we have:

$$u(t)=u_0(t)+\sum_{m=1}^{+\infty}u_m(t). \quad (A.6)$$

Differentiating (A.2) for m times with respect to the embedding parameter p, and then setting p = 0 and finally dividing them by m!, we will have the so-called *mth* -order deformation equation as:

$$L[u_m-\chi_m u_{m-1}] = hH(t)\Re_m(\vec{u}_{m-1}) \quad (A.7)$$

Where

$$\Re_m(\vec{u}_{m-1})=\frac{1}{(m-1)!}\frac{\partial^{m-1}N[\varphi(t;p)]}{\partial p^{m-1}} \quad (A.8)$$

And

$$\chi_m=\begin{cases}0, & m\le 1,\\ 1, & m>1.\end{cases} \quad (A.9)$$

Applying L^{-1} on both side of equation (A7), we get

$$u_m(t)=\chi_m u_{m-1}(t)+hL^{-1}[H(t)\Re_m(\vec{u}_{m-1})] \quad (A10)$$

In this way, it is easily to obtain u_m for $m\ge 1$, at M^{th} order, we have

$$u(t) = \sum_{m=0}^{M} u_m(t) \tag{A.11}$$

When $M \to +\infty$, we get an accurate approximation of the original equation (A.1). For the convergence of the above method we refer the reader to Liao [3]. If equation (A.1) admits unique solution, then this method will produce the unique solution.

Appendix: B

Approximate Analytical Expression of the Non-Linear Differential Equations (8) and (16) Using the Modified Homotopy Analysis Method:

We indicate how the eqns. (21) and (22) are derived in this paper. To find the solution of the eqns. (8) and (16) we construct the Homotopy are as follows:

$$(1-p)f''' = hp\left[-k_1[E_i]([A]_0-[E])+k_{-1}[E]\right] \tag{B.1}$$

$$(1-p)\theta'' = hp\left[-k_1[E_i]([A]_0-[E])-k_{-1}[E]\right] \tag{B.2}$$

The approximate analytical solution of the eqns. (6) and (7) are as follows:

$$f = f_0 + pf_1 + p^2 f_2 + \ldots \tag{B.3}$$

$$\theta = \theta_0 + p\theta_1 + p^2\theta_2 + \ldots \tag{B.4}$$

Substituting the eqn. (B.3) into an eqn.(B.1) and (B.4) into an eqn.(B.2) we get

$$(1-p)\left[\frac{d(f_0+pf_1+\ldots)}{dt}\right] = hp\left[\frac{d(f_0+pf_1+\ldots)}{dt}+\frac{1}{2}(f_0+pf_1+\ldots)\left(\frac{d(f_0+pf_1\ldots)}{dt}\right)\right] \tag{B.5}$$

$$(1-p)\left[\frac{d(\theta_0+p\theta_1+\ldots)}{dt}\right] = hp\left[\frac{d(\theta_0+p\theta_1+\ldots)}{dt}+\frac{1}{2}Pr(f_0+pf_1+\ldots)\left(\frac{d(\theta_0+p\theta_1+\ldots)}{dt}\right)\right] \tag{B.6}$$

Comparing the coefficients of like powers of p in the eqns. (B.5) and (B.6) we get,

$$p^0: \frac{dx_{10}}{dt} + ax_{10}A_0 = 0 \tag{B.7}$$

$$p^0: \frac{dx_{20}}{dt} - (b-a)x_{20} = 0 \tag{B.8}$$

$$p^1: \frac{dx_{11}}{dt} + ax_{11} - ax_{10}x_{20} + bx_{20} \tag{B.9}$$

$$p^1: \frac{dx_{21}}{dt} + (b-a)x_{21} + ax_{10}A_0 \tag{B.10}$$

The initial approximations are as follows:

$$x_1(0) = a_0 \quad x_2(0) = b_0 \tag{B.11}$$

$$f_i(0),\ f_i'(0) = 0,\ \lim_{\tau\to\infty} f_i'(\tau) = 1 \tag{B.12}$$

Solving the eqns. (B.7) - (B.10) and using the boundary condition (B.11) and (B.12) we obtain the following results:

For this HAM solution, we choose the initial guesses in the following form which satisfies the eqn. (B.11).

$$x_1 = ce^{-aA_0t} \tag{B.13}$$

$$x_2 = de^{(b-a)t} \tag{B.14}$$

By solving the eqns. (B.9) and (B.10) using the eqn. (B.12), we can obtain the following results

$$\frac{dx_{11}}{dt} = ce^{-aA_0 t} - h\left(acd\left[\frac{e^{(-aA_0+b-a)t}}{-aA_0+b-a}\right] - \frac{acd}{(-aA_0+b-a)}e^{-at}\right) \tag{B.15}$$

$$\frac{dx_{21}}{dt} = de^{(b-a)t} - h\left(acd\left[\frac{e^{(-aA_0-b-a)t}}{-aA_0-b-a}\right] - \frac{acd}{(-aA_0-b-a)}e^{-bt}\right) \tag{B.16}$$

According to the HAM, we can conclude that

$$f = \lim_{p\to 1}(x_1) = f_0 + f_1 \tag{B.17}$$

$$\theta = \lim_{p\to 1}(x_2) = \theta_0 + \theta_1 \tag{B.18}$$

After putting the eqns. (B.13), (B.15) into an eqn. (B.17) and the eqns. (B.14), (B.16) into an eqn. (B.18), we obtain the solution in the text as given in the eqns.

Appendix: C

Matlab/Scilab program to solve the non-linear differential eqns.(6) and (7):

```
function
options= odeset('RelTol',1e-6,'Stats','on');
%initial conditions
x0 = [1;1];
tspan = [0,2];
tic
[t,x] = ode45(@TestFunction,tspan,x0,options);
toc
figure
hold on
plot(t, x(:,1))
plot(t, x(:,2))
legend('x1','x2')
ylabel('x')
xlabel('t')
return
function [dx_dt]= TestFunction(t,x)
a=0.1;b=0.1;h=-1;u=1;
dx_dt(1)=-a*x(1)*u-a*x(1)*x(2)+b*x(2);
dx_dt(2)=-a*x(1)*u-a*x(1)*x(2)-b*x(2);
dx_dt = dx_dt';
return
```