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INITIAL NON-LINEAR BOUNDARY VALUE IN ENZYME-SUBSTRATE REACTION PROCESSES - HOMOTOPY PERTURBATION APPROACH

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ABSTRACT

The boundary value problem in basic enzyme reactions is formulated and approximate closed analytical expression of concentrations of substrate, enzyme and substrate-enzyme complex are presented. He's Homotopy perturbation method (HPM) is used to give approximate and analytical solutions of non-linear reaction equations containing a non-linear term related to enzymatic reaction. The pertinent analytical solutions for the substrate, substrate-enzyme complex and free enzyme are discussed in terms of dimensionless parameters a_1, a_2, a_3, a_4 *and* a_5 .

Keywords: *Enzyme catalyzed reaction; Non-linear boundary value problems; Homotopy Perturbation Method; Michaelis-Menten kinetics.*

1. INTRODUCTION:

The vast majority of chemical transformations inside cells are carried out by proteins called enzymes. Enzymes accelerate the rate of chemical reactions (both forward and backward) without being consumed in the process and tend to be very selective, with a particular enzyme accelerating only a specific reaction. Enzymes are important in regulating biological processes, for example, as activators or inhibitors in a reaction. To understand the role of enzyme kinetics, the researcher has to study the rates of reactions, the temporal behaviors of the various reactants and the conditions which influence the enzyme kinetics. Introduction with a mathematical bent is given in the books by Rubinow [1], Murray [2], Segel [3] and Roberts [4].

In the model mechanism one enzyme molecule combines with one substrate molecule; that is, the enzyme has the one binding site. There are many enzymes which have more than one binding site for substrate molecules. For example haemoglobin (Hb), the oxygen-carrying protein in red blood cells, has 4 binding sites for oxygen (O_2) molecules. A reaction between an enzyme and a substrate is described as cooperative if a single enzyme molecule, after binding a substrate molecule at one site can then bind another site. Such phenomenons are common.

Another important cooperative behavior is when an enzyme with several binding sites is such that the binding of one substrate molecule at one site can affect of binding other substrate molecule at another site. This indirect iteration between distinct and specific binding sites is called allostery, or an allosteric effect, and an enzyme exhibiting it, an allosteric enzyme. If a substrate that binds at one site increases the binding activity at another site then the substrate is an activator; if it decreases the activity it is an inhibitor. The detailed mathematical analysis for the kinetics of such allosteric reactions is given briefly in the book by Murray (1997)

Moreover, herein we employ "Homotopy Perturbation Method" (HPM) to solve the non-linear reaction equation. The purpose of this communication is to derive asymptotic approximate expressions for the substrate, enzyme and enzyme-substrate concentrations using Homotopy Perturbation Method for all values of dimensionless reaction diffusion parameters a_1, a_2, a_3, a_4 and a_5 .

2. MATHEMATICAL FORMULATION OF THE PROBLEM AND ANALYSIS:

As an example of cooperative phenomenon we consider the case where an enzyme has two binding sites and calculate an equivalent quasi-steady state approximation and the substrate abstract function. A model for this consists of an enzyme molecule *E* which binds a substrate molecule *S* to form a single bond substrate –enzyme complex C_1. This complex C_1 not only breaks down to form a product *P* and the enzyme *E* again; it can also combine with another

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substrate molecule to form a dual bound substrate-enzyme complex C_2. This C_2 complex breaks down to form the product and the single bound complex C_1. A reaction mechanism for this model is then

$$S + E \underset{k-1}{\overset{k_1}{\Leftrightarrow}} C_1 \overset{k_2}{\rightarrow} E + P, \tag{1}$$

$$S + C_1 \underset{k-3}{\overset{k_3}{\Leftrightarrow}} C_2 \overset{k_4}{\rightarrow} C_1 + P, \tag{2}$$

where the *k*'s are the rate constants. The system of nonlinear equations can be represented in dimensionless form as follows [2]:

$$\frac{du}{dt} = -u + (u - a_3 u + a_1)v + (a_4 + u)w \tag{3}$$

$$\varepsilon \frac{dv}{dt} = u - (u + a_3 u + a_1 + a_2)v + (a_4 + a_5 - u)w \tag{4}$$

$$\frac{\varepsilon\, dw}{dt} = a_3 uv - (a_4 + a_5)w \tag{5}$$

The boundary conditions are

$$w(t) = \frac{a_3}{(a_1 + a_2 - \varepsilon)}\left[\frac{\varepsilon\, e^{-2t}}{a_4 + a_5 - 2\varepsilon} - \frac{\varepsilon\, e^{-\left(\frac{a_1 + a_2 + \varepsilon}{\varepsilon}\right)t}}{(a_4 + a_5 - a_2 - a_1 - \varepsilon)} - \varepsilon\, e^{-\left(\frac{a_4 + a_5}{\varepsilon}\right)t}\left(\frac{1}{a_4 + a_5 - 2\varepsilon} - \frac{1}{a_4 + a_5 - a_2 - a_1 - \varepsilon}\right)\right] \tag{6}$$

where *u*, *v* and *w* represent the dimensional concentrations for the substrate *u*, enzyme-substrate complex *v* and product *w* and a_1, a_2, a_3, a_4 and a_5 are the reaction diffusion parameters .

3. ANALYTICAL SOLUTIONS OF CONCENTRATIONS OF THE SUBSTRATE, SUBSTRATE-ENZYME COMPLEX AND PRODUCT:

Recently, many authors have applied the HPM to various problems and demonstrated the efficiency of the HPM for handling non-linear structures and solving various physics and engineering problems [5-8]. This method is a combination in topology and classic perturbation techniques. Ji Huan He used the HPM to solve the Lighthill equation [9], the Duffing equation [10] and the Blasius equation [11]. The idea has been used to solve non-linear boundary value problems,integral equations and many other problems[11-17]. The HPM is unique in its applicability, accuracy and efficiency. The HPM uses the imbedding parameter *p* as a small parameter and only a few iterations are needed to search for an asymptotic solution. Using this method (see Appendix A), we can obtain the following solution to Eqs.(3) to (5) for the given boundary conditions (Eq.(6)).

$$u(t) = e^{-t} + \frac{\varepsilon e^{t}}{(a_1 + a_2 - \varepsilon)}\left[a_1 t + \frac{\varepsilon}{a_1 + a_2 - \varepsilon}\left(e^{-\left(\frac{a_1 + a_2 - \in}{\varepsilon}\right)t} - 1\right) + (1 - a_3)\left(\frac{\varepsilon}{a_1 + a_2}\left(e^{-\left(\frac{a_1 + a_2}{\varepsilon}\right)t} - 1\right)\right) - e^{-t} + 1\right] \tag{7}$$

$$v(t) = \frac{\varepsilon}{a_1 + a_2 - \varepsilon}\left[e^{-t} - e^{-\left(\frac{a_1 + a_2}{\varepsilon}\right)t}\right] + \frac{(1 + a_3)}{(\varepsilon - a_1 - a_2)}\left[e^{-2t} + e^{-\left(\frac{a_1 + a_2 + \in}{\varepsilon}\right)t} - 2e^{-\left(\frac{a_1 + a_2}{\varepsilon}\right)t}\right] \tag{8}$$

$$w(t) = \frac{a_3}{(a_1 + a_2 - \varepsilon)}\left[\frac{\varepsilon\, e^{-2t}}{a_4 + a_5 - 2\varepsilon} - \frac{\varepsilon\, e^{-\left(\frac{a_1 + a_2 + e}{\varepsilon}\right)t}}{(a_4 + a_5 - a_2 - a_1 - \varepsilon)} - \varepsilon\, e^{-\left(\frac{a_4 + a_5}{\varepsilon}\right)t}\left(\frac{1}{a_4 + a_5 - 2\varepsilon} - \frac{1}{a_4 + a_5 - a_2 - a_1 - \varepsilon}\right)\right] \tag{9}$$

4. DISCUSSION:

Eqs. (7) - (9) represent the most general new approximate analytical expressions for the substrate *u*, enzyme-substrate complex *v* and product *w* for possible values of a_1, a_2, a_3, a_4 and a_5. Figure 1-4 show the analytical expressions of the concentration of substrate *u*, enzyme-substrate complex *v* and product *w* for various values of dimensionless reaction parameters a_1, a_2, a_3, a_4 and a_5 . From these figures, it is inferred that the value of the concentration of substrate decreases gradually from its initial value of the concentration ($u(0) = 1$). The concentration of the product increases slowly from the initial concentration ($w(0) = 0$). The concentration of the product reaches the constant value when τ is large for all values of reaction parameters. Also when the value of the parameters a_1, a_2, a_3, a_4 and a_5 increases, the value of the product decreases. The concentration of the enzyme-substrate complex v increases and reaches the maximum value.

6. CONCLUSION:

Approximate analytical solutions to the non-linear reaction equations are presented using Homotopy Perturbation method. A simple, straight forward and a new method of estimating the concentrations of substrate, enzyme-substrate complex and enzyme are derived. This solution procedure can be easily extended to all kinds of system of coupled non-linear equations with various complex boundary conditions in enzyme-substrate reaction diffusion processes.

APPENDIX (A):

SOLUTION OF THE NONLINEAR THE EQUATIONS USING HOMOTOPY PERTURBATION METHOD

In this appendix, we indicate how Eqs. (3) to (5) may be solved using HPM . To illustrate the basic concepts of this method (HPM), we consider the following non-linear differential equation $L(u) + N(u) - f(r) = 0$ where *L* is a linear operator, *N* is a nonlinear operator, and *f(r)* is a given continuous function**.** We construct a Homotopy $\Omega \times [0,1] \to R$ which satisfies

$$(1-p)\left[\frac{du}{dt} + u\right] + p\left[\frac{du}{dt} + u - (u - a_3 u + a_1)v - (a_4 + u)\right] = 0 \tag{A1}$$

$$(1-p)\left[\varepsilon\frac{dv}{dt} + (a_1 + a_2)v\right] + p\left[\varepsilon\frac{dv}{dt} - u + (1 + a_3)uv + (a_1 + a_2)v - (a_4 + a_5)w + uw\right] = 0 \tag{A2}$$

$$(1-p)\left[\varepsilon\frac{dw}{dt} + (a_4 + a_5)w\right] + p\left[\varepsilon\frac{dw}{dt} + (a_4 + a_5)w - a_3 uv\right] = 0 \tag{A3}$$

The initial approximations are as follows:

$$u(0) = 1, v(0) = 0, w(0) = 0 \tag{A4}$$

The approximate solutions of (A1), (A2) and (A3) are given by

$$u = u_0 + pu_1 + p^2 u_2 + p^3 u_3 + \ldots\ldots \tag{A5}$$

$$v = v_0 + pv_1 + p^2 v_2 + p^3 v_3 + \ldots\ldots \tag{A6}$$

$$w = w_0 + pw_1 + p^2 w_2 + p^3 w_3 + \ldots\ldots \tag{A7}$$

Substituting Equation. (A5), (A6) and (A7) into Equations (A1), (A2) and (A3) and comparing the coefficients of like powers of *p* we obtain the following differential equations.

$$p^0 : \frac{du_0}{dt} + u_0 = 0 \tag{A8}$$

$$p^1 : \frac{du_1}{dt} + u_1 - (a_1 + u_0 - a_3 u_0)v_0 - (a_4 + u_0)w_0 = 0 \tag{A9}$$

$$p^2 : \frac{du_2}{dt} + u_2 - (a_1 + u_0 - a_3 u_0)v_1 + (a_3 u_1 - u_1)v_0 - u_1 w_0 - (a_4 + u_0)w_1 = 0 \tag{A10}$$

and

$$p^0 : \varepsilon \frac{dv_0}{dt} + (a_1 + a_2)v_0 = 0 \tag{A11}$$

$$p^1 : \quad \varepsilon \frac{dv_1}{dt} + (a_1 + a_2)v_1 - (1 + a_3)u_0 v_0 + (u_0 - a_4 - a_5)\mathrm{w}_0 - \mathrm{u}_0 = 0 \tag{A12}$$

$$p^2 : \varepsilon \frac{dv_2}{dt} + (a_1 + a_2)v_2 + (1 + a_3)(u_0 v_1 + u_1 v_0) - u_1 w_0 - (a_4 + a_5 - u_0)w_1 - u_1 = 0 \tag{A13}$$

and

$$p^0 : \quad \varepsilon \frac{dw_0}{dt} + (a_4 + a_5)w_0 = 0 \tag{A14}$$

$$p^1 : \quad \varepsilon \frac{dw_1}{dt} + (a_4 + a_5)w_1 - a_3 u_0 v_0 = 0 \tag{A15}$$

$$p^2 : \quad \varepsilon \frac{dw_2}{dt} + (a_4 + a_5)w_2 - a_3 (u_0 v_1 + u_1 v_0) = 0 \tag{A16}$$

Upon solving the equations (A8)-(A16) and using the boundary conditions (A4), we get

$$u_0 = e^{-t} \tag{A17}$$

$$u_1 = 0 \tag{A18}$$

$$u_2 = \frac{\varepsilon e^t}{(a_1 + a_2 - \varepsilon)}\left[a_1 t + \frac{\varepsilon}{a_1 + a_2 - \varepsilon}\left(e^{-\left(\frac{a_1 + a_2 - \varepsilon}{\varepsilon}\right)t} - 1 \right) + (1 - a_3)\left(\frac{\varepsilon}{a_1 + a_2}\left(e^{-\left(\frac{a_1 + a_2}{\varepsilon}\right)t} - 1 \right) \right) - e^{-t} + 1 \right] \tag{A19}$$

$$v_0 = 0 \tag{A20}$$

$$v_1 = \frac{\varepsilon}{a_1 + a_2 - \varepsilon}\left[e^{-t} - e^{-\left(\frac{a_1 + a_2}{\varepsilon}\right)t} \right] \tag{A21}$$

$$v_2 = \frac{(1 + a_3)}{(\varepsilon - a_1 - a_2)}\left[e^{-2t} + e^{-\left(\frac{a_1 + a_2 + \varepsilon}{\varepsilon}\right)t} - 2e^{-\left(\frac{a_1 + a_2}{\varepsilon}\right)t} \right] \tag{A22}$$

and

$$w_0 = 0 \tag{A23}$$

$$w_1 = 0 \tag{A24}$$

$$w_2 = \frac{a_3}{(a_1+a_2-\varepsilon)}\left[\frac{\varepsilon\, e^{-2t}}{a_4+a_5-2\varepsilon} - \frac{\varepsilon\, e^{-\left(\frac{a_1+a_2+\varepsilon}{\varepsilon}\right)t}}{(a_4+a_5-a_2-a_1-\varepsilon)} - \varepsilon\, e^{-\left(\frac{a_4+a_5}{\varepsilon}\right)t}\left(\frac{1}{a_4+a_5-2\varepsilon} - \frac{1}{a_4+a_5-a_2-a_1-\varepsilon}\right)\right] \quad \text{(A25)}$$

Hence we obtain

$$u = u_0 + u_1 + u_2 \quad \text{(A26)}$$

$$v = v_0 + v_1 + v_2 \quad \text{(A27)}$$

$$w = w_0 + w_1 + w_2 \quad \text{(A28)}$$

Substituting the equations (A17) to (A25) in the above equations we obtain the Eqs. (7) to (9) in the text.

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Fig. 1

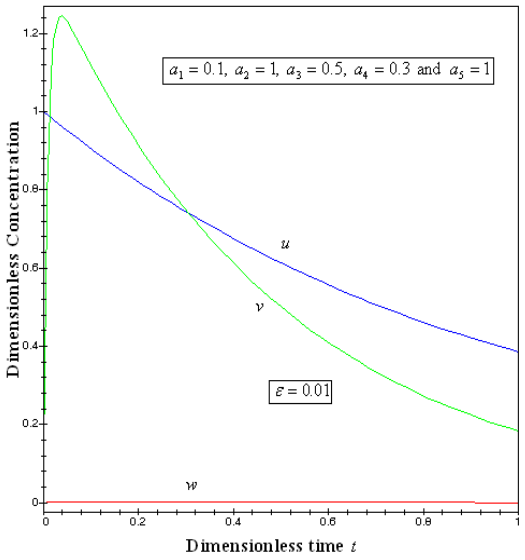

Fig. 2

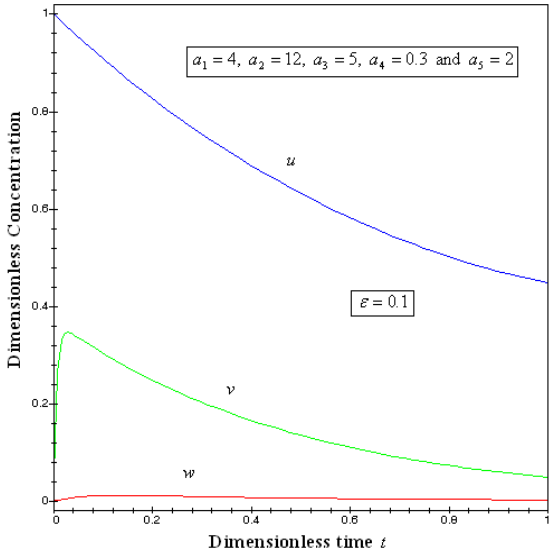

Fig. 3

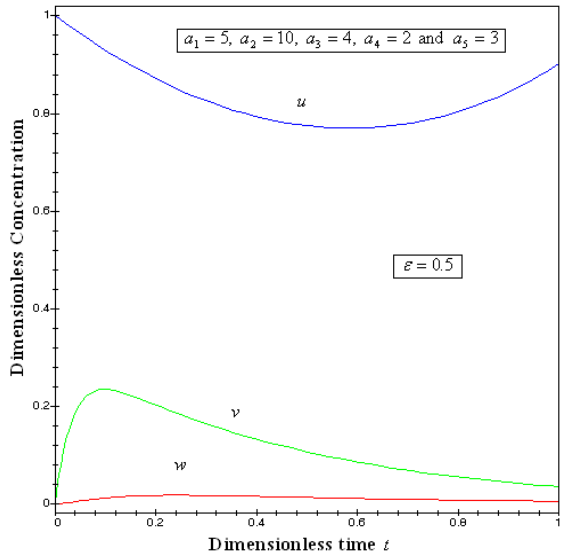

Fig. 4

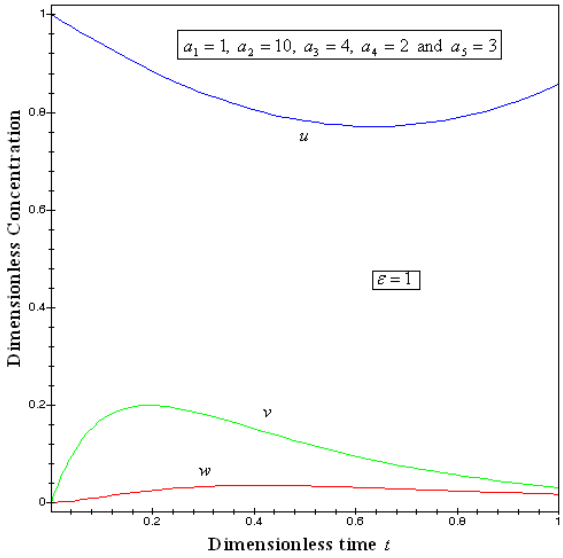

Figure 1-4: Normalised concentration profiles of u, v and w as a function of dimensionless time t.The concentrations are computed using Eqs. (7)-(9) for various values of the ε.

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