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Mathematical modelling of enzyme kinetics reaction mechanisms and analytical solutions of non-linear reaction equations

A. Meena · A. Eswari · L. Rajendran

Abstract   The boundary value problem in basic enzyme reactions is formulated and approximate expressions for substrate and product concentrations are presented. He's variational iteration method is used to give approximate and analytical solutions of non-linear reaction equations containing a non-linear term related to enzymatic reaction. The relevant analytical solutions for the substrate, enzyme, substrate-enzyme and product concentration profiles are discussed in terms of dimensionless reaction diffusion parameters K, λ and ε.

Keywords   Enzyme kinetics · Non-linear reaction equations · Variational iteration 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 behaviours 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] . The purpose of this communication is to derive asymptotic approximate expressions for the substrate, product,

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enzyme and enzyme-substrate concentrations using variational iteration method for all values of dimensionless reaction diffusion parameters K, λ and ε.

2 Mathematical formulation and solution of the problem

The enzyme kinetics in biochemical systems have traditionally been modelled by ordinary differential equations which are based solely on reactions without spatial dependence of the various concentrations. The model for an enzyme action, first elucidated by Michaelis and Menten suggested the binding of free enzyme to the reactant forming an enzyme-reactant complex. This complex undergoes a transformation, releasing the product and free enzyme. The free enzyme is then available for another round of binding to a new reactant. Traditionally, the reactant molecule that binds to the enzyme is termed the substrate S, and the mechanism is often written as:

$$E + S \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} ES \overset{k2}{\rightarrow} E + P \tag{1}$$

This mechanism illustrates the binding of substrate S and release of product P. E is the free enzyme and ES is the enzyme-substrate complex. k_1, k_{-1} and k_2 denote the rates of reaction of these three processes. Note that substrate binding is reversible but product release is not. The concentration of the reactants in the Eq. (1) is denoted by lower case letters

$$s = [S], \quad e = [E], \quad c = [SE], \quad p = [P] \tag{2}$$

The law of mass action leads to the system of following non-linear reaction equations [2]

$$\frac{ds}{dt} = -k_1 es + k_{-1} c \tag{3a}$$

$$\frac{de}{dt} = -k_1 es + (k_{-1} + k_2) c \tag{3b}$$

$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2) c \tag{3c}$$

$$\frac{dp}{dt} = k_2 c \tag{3d}$$

where k_1 is the forward rate of ES complex formation and k_{-1} is the backward rate constant. The boundary conditions are

$$s(0) = s_0, \quad e(0) = e_0, \quad c(0) = 0, \quad p(0) = 0. \tag{4}$$

Adding equations (3b) and (3c), we get,

$$de/dt + dc/dt = 0 \tag{5}$$

Using the initial conditions (4) we obtain

$$e(t) + c(t) = e_0 \tag{6}$$

with this, the system of ordinary differential equations reduce to only two, for s and c, namely

$$\frac{ds}{dt} = -k_1 e_0 s + (k_1 s + k_{-1})c, \tag{7}$$

$$\frac{dc}{dt} = k_1 e_0 s - (k_1 s + k_{-1} + k_2)c, \tag{8}$$

with initial conditions $s(0) = s_0$, $c(0) = 0$. By introducing the following parameters

$$\tau = \frac{k_1 e_0 t}{\varepsilon}, \quad u(\tau) = \frac{s(t)}{s_0}, \quad v(\tau) = \frac{c(t)}{e_0}, \quad w(\tau) = \frac{p(t)}{e_0}$$

$$\lambda = \frac{k_2}{k_1 s_0}, \quad k = \frac{k_{-1} + k_2}{k_1 s_0}, \quad \varepsilon = \frac{e_0}{s_0} \tag{9}$$

the system of Eqs. (7) and (8) and the initial conditions [Eqs. (4)] can be represented in dimensionless form as follows:

$$\frac{du}{d\tau} = -u\varepsilon + \varepsilon(u + k - \lambda)v, \tag{10a}$$

$$\frac{dv}{d\tau} = u - (u + k)v \tag{10b}$$

$$\frac{dw}{d\tau} = \lambda v \tag{10c}$$

$$u(0) = 1, \quad v(0) = 0, \quad w(0) = 0 \tag{11}$$

The above system of non-linear equations can be solved analytically in a simple and closed form using variational iteration method [5–10] (Ref Appendix A). The solutions of the above Eqs. 10a and 10b become

$$u(\tau) = e^{-\varepsilon\tau} - \frac{e^{-\varepsilon\tau}}{k(k-\varepsilon)^2}\left[e^{-k\tau}\varepsilon^2 - k\varepsilon\{\varepsilon(\lambda - k)\tau + e^{-\varepsilon\tau} + e^{-k\tau}\}\right.$$

$$+ k\{ke^{-\varepsilon\tau} + \varepsilon(\lambda - k)k\tau + \varepsilon(\lambda - k)e^{(\varepsilon - k)\tau}\} - (\varepsilon - k)^2$$

$$\left. - \varepsilon(\lambda - k)k\right] \tag{12}$$

$$v(\tau) = \frac{e^{-\varepsilon\tau} - e^{-k\tau}}{k - \varepsilon} - \frac{e^{-k\tau}}{k - \varepsilon}\left[\frac{(e^{-k\tau} - 1)}{\varepsilon} + \frac{(e^{(k-2\varepsilon)\tau} - 1)}{k - 2\varepsilon}\right] \tag{13}$$

Equations (12) and (13) represent the analytical expressions of the substrate $u(\tau)$ and enzyme-substrate $v(\tau)$ concentration. From the Eq. (6), we can also obtain the dimensionless concentration of enzyme

$$E(\tau) = e(t)/e_0 = 1 - v(\tau) \tag{14}$$

Equation (3d) is uncoupled with the first three equations. The dimensionless concentration of the product is given by

$$
w(\tau) = \lambda \int_0^\tau v(t')dt'
$$

$$
= \frac{\lambda}{k-\varepsilon}\left[\frac{e^{-k\tau}-1}{k}+\frac{1-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-2k\tau}(1-2e^{k\tau})+1}{2k\varepsilon}+\frac{1}{k-2\varepsilon}\left(\frac{e^{-2\varepsilon\tau}-1}{2\varepsilon}\right.\right.
$$
$$
\left.\left.+\frac{1-e^{-k\tau}}{k}\right)\right] \tag{15}
$$

Equations (14) and (15) represent the new analytical expressions of the concentrations of enzyme $E(\tau)$ and product $w(\tau)$ for all values of parameters k, λ and ε

3 Discussion

Figures 1, 2, 3 and 4 show the analytical expressions of concentrations of substrate u, enzyme E, enzyme-substrate complex v and product w for various values of dimensionless reaction parameters k, λ and ε. 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 substrate becomes zero when $\tau \geq 4$. (see
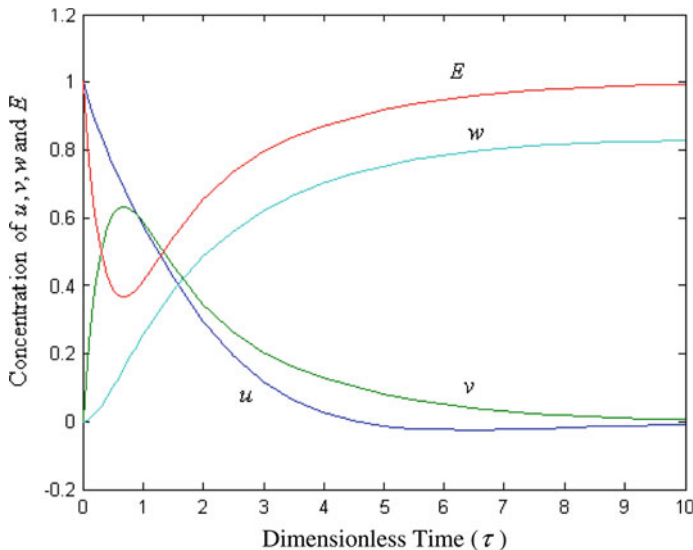

Fig. 1 Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w for $k = 1$, $\varepsilon = 0.6$, and $\lambda = 0.5$. The curves are plotted using Eqs. (12)–(15)
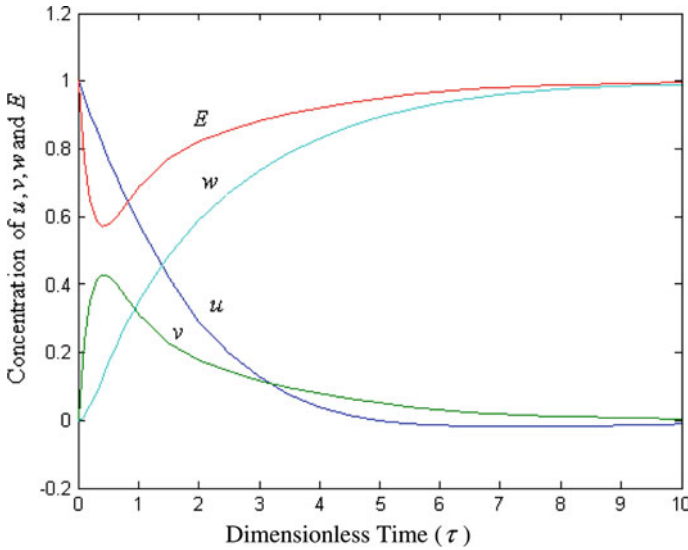
Fig. 2 Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w for $k = 2, \varepsilon = 0.5,$ and $\lambda = 1$. The curves are plotted using Eqs. (12)–(15)
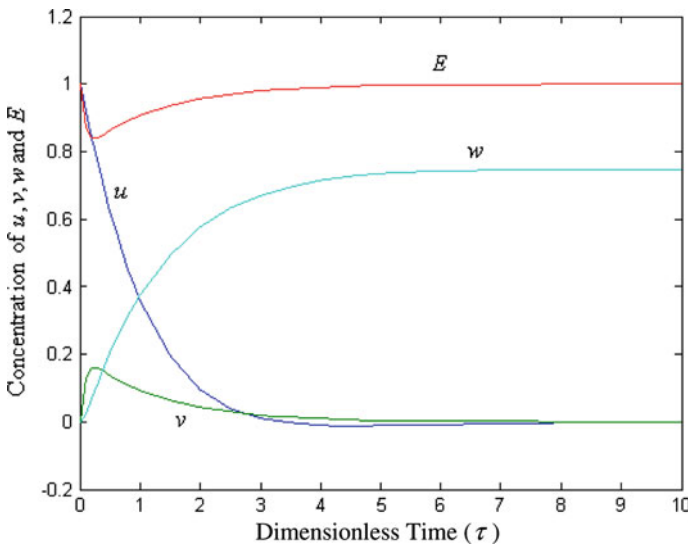

Fig. 3 Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w for $k = 5, \varepsilon = 0.8$ and $\lambda = 3$. The curves are plotted using Eqs. (12)–(15)

left hand side of Figs. 1 and 2). The concentration of the product increases slowly from the initial concentration ($w(0) = 0$). The concentration of the product reaches the constant value when $\tau \geq 6$ for all values of reaction parameters. Also when the value of the parameters k, λ and ε increases, the value of the product decreases. When $0.2 \leq \tau \leq 0.5$, enzyme reaches the minimum value and enzyme- substrate reaches

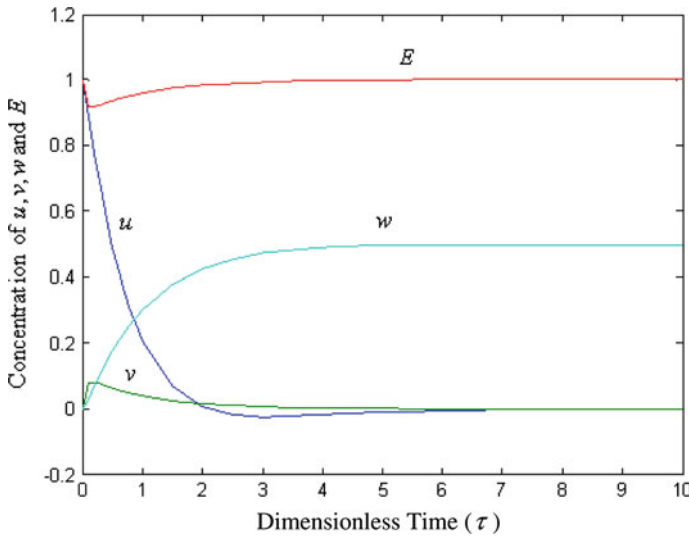**Fig. 4** Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w for $k = 10$, $\varepsilon = 1$ and $\lambda = 5$. The curves are plotted using Eqs. (12)–(15)

the maximum value. Concentrations of enzyme- substrate and substrate reach zero value when $\tau \geq 5$ for all values of reaction parameters. The concentration of substrate u reaches the steady-state value ($u = 0$) when $\tau \geq 3$.

4 Conclusion

Approximate analytical solutions to the non-linear reaction equations are presented using variational iteration method. A simple, straight forward and a new method of estimating the concentrations of substrate, product, 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 [11].

Appendix A

In this appendix, we derive the general solution of non-linear reaction Eq. (10) using He's variational iteration method. To illustrate the basic concepts of variational iteration method (VIM), we consider the following non-linear partial differential equation [6–10]

$$L[u(x)] + N[u(x)] = g(x) \tag{A1}$$

where L is a linear operator, N is a nonlinear operator, and $g(x)$ is a given continuous function. According to the variational iteration method, we can construct a correct functional as follows [9]

$$u_{n+1}(x) = u_n(x) + \int_0^x \lambda \big[L[u_n(\tau)] + N[\tilde{u}_n(\tau)] - g(\tau)\big]d\tau \tag{A2}$$

where λ is a general Lagrange multiplier which can be identified optimally via variational theory, u_n is the nth approximate solution, and $\tilde{u}_n$ denotes a restricted variation, i.e., $\delta\tilde{u}_n = 0$. In this method, a trail function (an initial solution) is chosen which satisfies given boundary conditions. Using above variation iteration method we can write the correction functional of Eq. (10) as follows

$$\begin{aligned} u_{n+1}(\tau) = u_n(\tau) \\ + \int_0^x \lambda_1 \left[u_n'(\xi) + \varepsilon u_n(\xi) - \varepsilon k \widetilde{v_n(\xi)} + \varepsilon\lambda \widetilde{v_n(\xi)} - \widetilde{\varepsilon u_n(\xi)v_n(\xi)} \right] d\xi \end{aligned} \tag{A3}$$

$$v_{n+1}(\tau) = v_n(\tau) + \int_0^x \lambda_2 \left[v_n'(\xi) - \widetilde{u_n(\xi)} + k v_n(\xi) + \widetilde{u_n(\xi)v_n(\xi)} \right] d\xi \tag{A4}$$

Taking variation with respect to the independent variable u_n and v_n, we get

$$\begin{aligned} \delta u_{n+1}(\tau) = \delta u_n(\tau) \\ + \delta \int_0^x \lambda_1 \left[u_n'(\xi) + \varepsilon u_n(\xi) - \varepsilon k \widetilde{v_n(\xi)} + \varepsilon\lambda \widetilde{v_n(\xi)} - \widetilde{\varepsilon u_n(\xi)v_n(\xi)} \right] d\xi \end{aligned} \tag{A5}$$

$$\delta v_{n+1}(\tau) = \delta v_n(\tau) + \delta \int_0^x \lambda_2 \left[v_n'(\xi) - \widetilde{u_n(\xi)} + k v_n(\xi) + \widetilde{u_n(\xi)v_n(\xi)} \right] d\xi \tag{A6}$$

where λ_1 and λ_2 are general Lagrangian multipliers, u_0 and v_0 are initial approximations or trial functions, $\widetilde{u_n(\xi)}$, $\widetilde{\varepsilon(\lambda - k)v_n(\xi)}$ and $\widetilde{u_n(\xi)v_n(\xi)}$ are considered as restricted variations i.e $\delta\tilde{u}_n = 0$, $\delta\tilde{v}_n = 0$ and $\delta\tilde{u}_n\tilde{v}_n = 0$. Making the above correction functional (A5) and (A6) stationary, noticing that $\delta u_n(0) = 0$, $\delta v_n(0) = 0$ and $\delta u_n(0)v_n(0) = 0$.

$$\delta u_n : 1 + \lambda_1(\xi)|_{\xi=\tau} = 0, \delta v_n : 1 + \lambda_2(\xi)|_{\xi=\tau} = 0 \qquad \text{(A7)}$$

$$\delta u_n : -\lambda_1'(\xi) + \varepsilon\lambda(\xi)\big|_{\xi=\tau}, \delta v_n : -\lambda_2'(\xi) + k\lambda(\xi)\big|_{\xi=\xi} = 0 \qquad \text{(A8)}$$

The above equations are called Lagrange-Euler equations. The Lagrange multipliers, can be identified as

$$\begin{aligned} \lambda_1(\xi) &= -e^{\varepsilon(\xi-\tau)} \\ \lambda_2(\xi) &= -e^{k(\xi-\tau)} \end{aligned} \qquad \text{(A9)}$$

substituting the Lagrangian multipliers and $n = 0$ in the iteration formula [Eqs. (A3) and (A4)] we obtain,

$$u_1(x) = u_0(x) - \int_0^\tau e^{\varepsilon(\xi-\tau)} \left[u_0'(\xi) + \varepsilon u_0(\xi) - \varepsilon u_0(\xi)v_0(\xi) - \varepsilon k v_0(\xi) \right.$$
$$\left. + \varepsilon\lambda v_0(\xi) \right] d\xi \qquad \text{(A10)}$$

$$v_1(x) = v_0(x) - \int_0^\tau e^{k(\xi-\tau)} \left[v_0'(\xi) - u_0'(\xi) + u_0(\xi)v_0(\xi) + k v_0(\xi) \right] d\xi$$
$$\text{(A11)}$$

Assuming that its initial approximate solution which satisfies the boundary condition (11) have the form

$$\begin{aligned} u_0(x) &= e^{-\varepsilon\tau} \\ v_0(x) &= (e^{-\varepsilon\tau} - e^{-k\tau})/(k - \varepsilon) \end{aligned} \qquad \text{(A12)}$$

By the iteration formula (A10) and (A11) we have the Eqs. (12) and (13) in the text.

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