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Mathematical Modeling of Biosensors: Enzyme-substrate Interaction and Biomolecular Interaction

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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, 1975), (Murray, 1989), (Segel, 1980) and (Roberts, 1977). Biosensors are analytical devices made up of a combination of a specific biological element, usually an enzyme that recognizes a specific analyte (substrate) and the transducer that translates the biorecognition event into an electrical signal (Tuner et al., 1987; Scheller et al., 1992). Amperometric biosensors may utilize one, two, three or multi enzymes (Kulys, 1981). The classical example of mono enzyme biosensor might be the biosensor that contains membrane with immobilized glucose oxidase. The glucose oxidase specifically oxidizes glucose to hydrogen peroxide that is determined ampero-metrically on platinum electrode (Kulys, 1981). The amperometric biosensors measure the current that arises on a working electrode by direct electrochemical oxidation or reduction of the biochemical reaction product. The current is proportionate to the concentration of the target analyte. The biosensors are widely used in clinical diagnostics, environment monitoring, food analysis and drug detection because they are reliable, highly sensitive and relatively cheap. However, amperometric biosensors possess a number of serious drawbacks.

One of the main reasons that restrict the wider use of the biosensors is the relatively short linear range of the calibration curve (Nakamura et al., 2003). Another serious drawback is the instability of bio-molecules. These problems can be partially solved by the application of an additional outer perforated membrane (Tuner et al., 1987; Scheller et al., 1992; Wollenberger et al., 1997). To improve the productivity and efficiency of a biosensor design as well as to optimize the biosensor configuration a model of the real biosensor should be built (Amatore et al., 2006; Stamatin et al., 2006). Modeling of a biosensor with a perforated

membrane has been already performed by Schulmeister and Pfeiffer (Schulmeister et al., 1993). The proposed one-dimensional-in-space (1-D) mathematical model does not take into consideration the geometry of the membrane perforation and it also includes effective diffusion coefficients. The quantitative value of diffusion coefficients is limited, for one dimensional model (Schulmeister et al., 1993). Recently, a two-dimensional-in-space (2-D) mathematical model has been proposed taking into consideration the perforation geometry (Baronas et al., 2006; Baronas, 2007). However, a simulation of the biosensor action based on the 2-D model is much more time-consuming than a simulation based on the corresponding 1-D model. This is especially important when investigating numerically peculiarities of the biosensor response in wide ranges of catalytically and geometrical parameters. The multifold numerical simulation of the biosensor response based on the 1-D model is much more efficient than the simulation based on the corresponding 2-D model.

1.1 Biomolecule model and Enzyme substrate interaction

A Biomolecular interaction is a central element in understanding disease mechanisms and is essential for devising safe and effective drugs. Optical biosensors usually involves biomolecular interaction, they are very often used for affinity relation test.

The catalytic event that converts substrate to product involves the formation of a transition state. The complex, when substrate S and enzyme E combine, is called the enzyme substrate complex C, etc. Enzyme interfaced biosensors involve enzyme-substrate interaction, two significant applications are: monitoring of human glucose and monitoring biochemical reaction at a single cell level. Normally, we have two ways to set up experiments for biosensors: free enzyme model and immobilized enzyme model. The mathematical and computational model for these two models are very similar, at here we are going to investigate the free enzyme model. Recently (Yupeng Liu et al., 2008) investigate the problem of optimizing biosensor design using an interdisciplinary approach which combines mathematical and computational modeling with electrochemistry and biochemistry techniques. Yupeng Liu and Qi Wang developed a model for enzyme-substrate interaction and a model for biomolecular interaction and derived the free enzyme model for the non-steady state using simulation result. To my knowledge no rigorous analytical solutions of free enzyme model under steady-state conditions for all values of reaction/diffusion parameters γ_E, γ_S and γ_P have been reported. The purpose of this communication is to derive asymptotic approximate expressions for the substrate, product, enzyme and enzyme-substrate concentrations using variational iteration method for all values of dimensionless reaction diffusion parameters γ_S, γ_E and γ_P.

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:

$$E + S \underset{k-1}{\overset{k_1}{\leftrightarrow}} C \xrightarrow{kcat} E + P \tag{1}$$

This mechanism illustrates the binding of substrate S and release of product P. E is the free enzyme and C is the enzyme-substrate complex. k_1, k_{-1} and k_{cat} 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 equation (1) is denoted by lower case letters

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

The law of mass action leads to the system of following non-linear reaction equations [15]

$$D_S \frac{d^2 s}{dx^2} - k_1 es + k_{-1} c \quad = 0 \tag{3}$$

$$D_e \frac{d^2 e}{dx^2} - k_1 es + (k_{-1} + k_{cat}) c \ = 0 \tag{4}$$

$$D_c \frac{d^2 c}{dx^2} + k_1 es - (k_{-1} + k_{cat}) c \ = 0 \tag{5}$$

$$D_p \frac{d^2 p}{dx^2} + k_{cat} c = 0 \tag{6}$$

where k_1 is the forward rate of complex formation and k_{-1} is the backward rate constant. All species are considered to have an equal diffusion coefficient ($D_s = D_p = D_e = D_c = D$). The boundary conditions are

$$\frac{ds}{dx} = 0,\ \frac{dp}{dx} = 0,\ \frac{de}{dx} = 0,\ \frac{dc}{dx} = 0, \text{ when } t > 0 \text{ and } x = 0 \tag{7}$$

$$s = s_0,\ \frac{dp}{dx} = 0,\ \frac{de}{dx} = 0,\ \frac{dc}{dx} = 0, \text{ when } t > 0 \text{ and } x = L \tag{8}$$

Adding Eqs. (4) and (5), we get,

$$d^2 e / dx^2 \ + d^2 c / dx^2 = 0 \tag{9}$$

Using the boundary conditions and from the law of mass conservation, we obtain

$$e = e_0 - c \tag{10}$$

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

$$D \frac{d^2 s}{dx^2} - k_1 e_0 s + (k_1 s + k_{-1}) c = 0 \tag{11}$$

$$D\frac{d^2c}{dx^2} + k_1 e_0 s - (k_1 s + k_{-1} + k_{cat})c = 0 \tag{12}$$

By introducing the following parameters

$$u = \frac{s}{s_0},\ v = \frac{c}{e_0},\ w = \frac{p}{e_0},\ X = \frac{x}{L},\ \gamma_S = \frac{k_{-1}L^2}{D},\ \gamma_E = \frac{k_1 s_0 L^2}{D},\ \gamma_P = \frac{k_{cat}L^2}{D} \tag{13}$$

Now the given two differential equations reduce to the following dimensionless form (Yupeng Liu et al., 2008):

$$\frac{d^2u}{dX^2} - \gamma_E u + (\gamma_S + \gamma_E u)v = 0 \tag{14}$$

$$\frac{d^2v}{dX^2} + \gamma_E u - (\gamma_S + \gamma_E u + \gamma_P)v = 0 \tag{15}$$

$$\frac{d^2w}{dX^2} + \gamma_P v = 0 \tag{16}$$

where γ_E, γ_S and γ_P are the dimensionless reaction diffusion parameters. These equations must obey the following boundary conditions:

$$\frac{du}{dX} = 0,\ \frac{dv}{dX} = 0,\ \frac{dw}{dX} = 0 \text{ when } X = 0 \tag{17}$$

$$u = 1,\ \frac{dv}{dX} = 0,\ \frac{dw}{dX} = 0 \text{ when } X = 1 \tag{18}$$

3. Variational iteration method

The variational iteration method (He, 2007, 1999; Momani et al., 2000; Abdou et al., 2005) has been extensively worked out over a number of years by numerous authors. variational iteration method has been favourably applied to various kinds of nonlinear problems (Abdou et al., 2005; He et al., 2006). The main property of the method is in its flexibility and ability to solve nonlinear equations (Abdou et al., 2005). Recently (Rahamathunissa and Rajendran, 2008) and (Senthamarai and Rajendran, 2010) implemented variational iteration method to give approximate and analytical solutions of nonlinear reaction diffusion equations containing a nonlinear term related to Michaelis-Menten kinetic of the enzymatic reaction. More recently (Manimozhi et al., 2010) solved the non-linear partial differential equations in the action of biosensor at mixed enzyme kinetics using variational iteration method. (Loghambal and Rajendran, 2010) applied the method for an enzyme electrode where electron transfer is accomplished by a mediator reacting in a homogeneous solution. (Eswari and Rajendran, 2010) solved the coupled non linear diffusion equations analytically for the transport and kinetics of electrodes and reactant in the layer of modified electrode. Besides its mathematical importance and its links to other branches of mathematics, it is widely used in all ramifications of modern sciences. In this method the solution procedure is

very simple by means of Variational theory and only few iterations lead to high accurate solution which are valid for the whole solution domain. The basic concept of Variational iteration method is given in Appendix A.

4. Analytical solution of the concentration and current using Variational iteration method

Using variational iteration method (He, 2007, 1999) (refer Appendix A), the concentration of the substrate and the enzyme-substrate are

$$\begin{aligned} u(X) = 1 - a + 0.5\gamma_E\left[1 + ab - b - (\gamma_S / \gamma_E)b - a\right]X^2 + 0.083\gamma_E\left[2a - 1 - ab - (\gamma_S / \gamma_E)\right]X^4 \\ + 0.1\gamma_E\left[1 - a + (\gamma_S / \gamma_E)\right]X^5 - 0.03\gamma_E\left[1 + (\gamma_S / \gamma_E)\right]X^6 + 0.05a\gamma_E X^7 - 0.02a\gamma_E X^8 \end{aligned} \tag{14}$$

$$\begin{aligned} v(X) = {} & b + 0.5\gamma_E\left[b - ab + \left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right)b - 1 + a\right]X^2 + \\ & + 0.083\gamma_E\begin{bmatrix}\left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right) \\ -2a + 1 + ab\end{bmatrix}X^4 \\ & + 0.1\gamma_E\left[a - 1 - \left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right)\right]X^5 + \\ & + 0.03\gamma_E\left[1 + \left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right)\right]X^6 \\ & - 0.05a\gamma_E X^7 + 0.02a\gamma_E X^8 \end{aligned} \tag{15}$$

where

$$a = \frac{7}{5}\left[\frac{\gamma_S + \gamma_P - 29\gamma_E + 30b(\gamma_S + \gamma_P + \gamma_E)}{\gamma_E(28b - 27)}\right] \tag{16}$$

$$\begin{aligned} b = {} & \frac{1}{2}\left[\left(2100(\gamma_S + \gamma_E) + 10500\gamma_P\right)\gamma_E\right]^{-1} \\ & \text{x}\begin{bmatrix} 9820\gamma_E\gamma_P - 25200\gamma_S + 2000\gamma_S\gamma_E + 4100{\gamma_E}^2 + 25200\gamma_P - 20(1595160\gamma_E\gamma_S\gamma_P + \\ 3175200\ (\gamma_E\gamma_S + \gamma_E\gamma_P + \gamma_P\gamma_S) + 1587600({\gamma_E}^2 + {\gamma_P}^2 + {\gamma_S}^2). + 3175200\gamma_P\gamma_S \\ +112564{\gamma_E}^2\gamma_P\gamma_S - 786240{\gamma_E}^2\gamma_P + 1325520\gamma_E{\gamma_P}^2 + 276676{\gamma_E}^2{\gamma_P}^2 - 1676{\gamma_E}^3\gamma_P \\ +269640\gamma_E{\gamma_S}^2 + 274680\gamma_S{\gamma_E}^2 + 11449{\gamma_E}^2{\gamma_S}^2 + 428{\gamma_E}^3\gamma_S + 5040{\gamma_E}^3 + 4{\gamma_E}^4)^{1/2} \end{bmatrix} \end{aligned} \tag{17}$$

Equations (14), (15), (16) and (17) represent the analytical expressions of the substrate $u(X)$ and enzyme-substrate $v(X)$ concentration. From the equation (15), we can also obtain the dimensionless concentration of enzyme

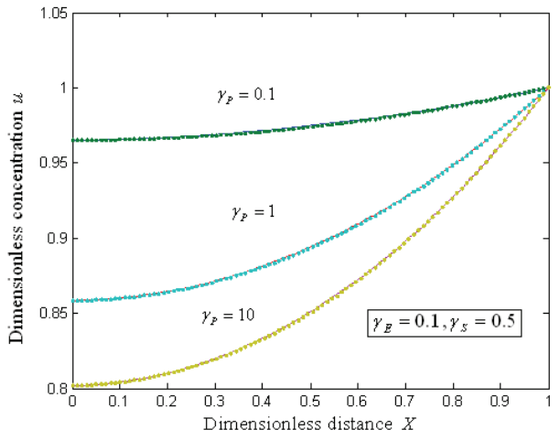
$$\begin{aligned} e(X) = {} & e(t) / e_0 = 1 - v(\tau) \\ & = 1 - b + 0.5\gamma_E\left[b - ab + \left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right)b - 1 + a\right]X^2 + 0.083\gamma_E\begin{bmatrix}\left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right) \\ -2a + 1 + ab\end{bmatrix}X^4 \\ & + 0.1\gamma_E\left[a - 1 - \left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right)\right]X^5 + 0.03\gamma_E\left[1 + \left((\gamma_S / \gamma_E) + (\gamma_P / \gamma_E)\right)\right]X^6 \\ & - 0.05a\gamma_E X^7 + 0.02a\gamma_E X^8 \end{aligned} \tag{18}$$

The dimensionless concentration of the product is given by

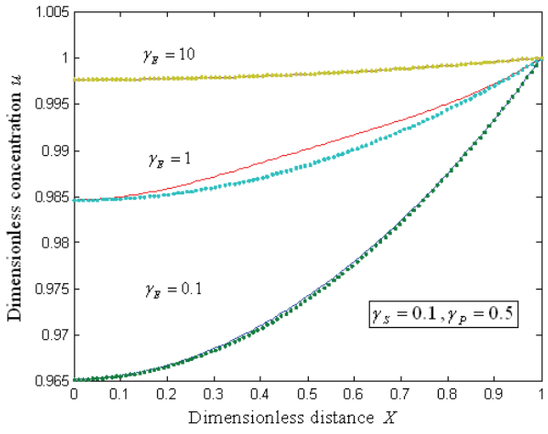
$$w(X) = 0.0335X^2 + 0.0167\gamma_P X^2 - 0.0333X^2(X-1)^2 - 0.0667X^3 - 0.0833\gamma_P X^4 + 0.0333X^4 + 0.1000\gamma_P X^5 - 0.00033\gamma_P X^6 \quad (19)$$

5. Numerical simulation

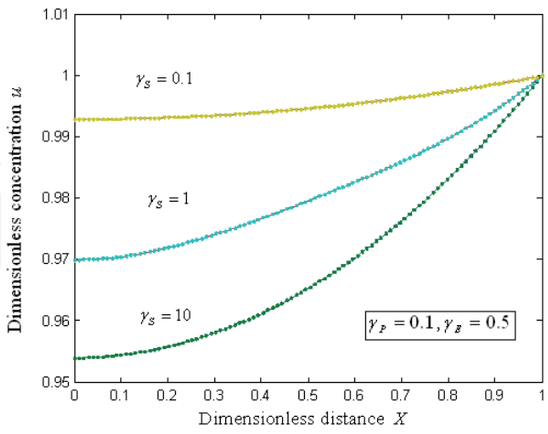
The non-linear differential equations (14-16) are solved by numerical methods. The function pdex4 in SCILAB software which is a function of solving the boundary value problems for differential equation is used to solve this equation. Its numerical solution is compared with variational iteration method in Figure 1*a*-c, 2*a*-c, 3 and it gives a satisfactory result for various values of γ_E, γ_S and γ_P. The SCILAB program is also given in Appendix C.



(a)



(b)



(c)

Fig. 1. Profile of the normalized concentrations of the substrate u, were computed using equation (14) for various values of γ_S, γ_E and γ_P when the reaction/diffusion parameters (a) $\gamma_E = 0.1$, $\gamma_S = 0.5$ (b) $\gamma_S = 0.1$, $\gamma_P = 0.5$ (c) $\gamma_P = 0.1$, $\gamma_E = 0.5$. The key to the graph: (__) represents the Eq. (14) and (.) represents the numerical results.

6. Results and discussion

Equations (14) and (15) are the new and simple analytical expressions of normalized concentration profiles for the substrate $u(X)$ and enzyme-substrate $v(X)$. The approximate solutions of second order differential equations describing the transport and kinetics of the enzyme and the substrate in the diffusion layer of the electrode are derived.

Fig. 1a-c, we present the series of normalized concentration profile for a substrate $u(X)$ as a function of the reaction/diffusion parameters γ_E, γ_S and γ_P. From this figure1a, it is inferred that, the value of $u \approx 1$ for all small values of γ_P, γ_E. Also the value of u increases when γ_P decreases when γ_E and γ_S small. Similarly, in fig1b, it is evident that the value of concentration increases when γ_E increases for small values of γ_S and γ_P. Also value of concentration of substrate increases when γ_S decreases (Refer fig1*c*).

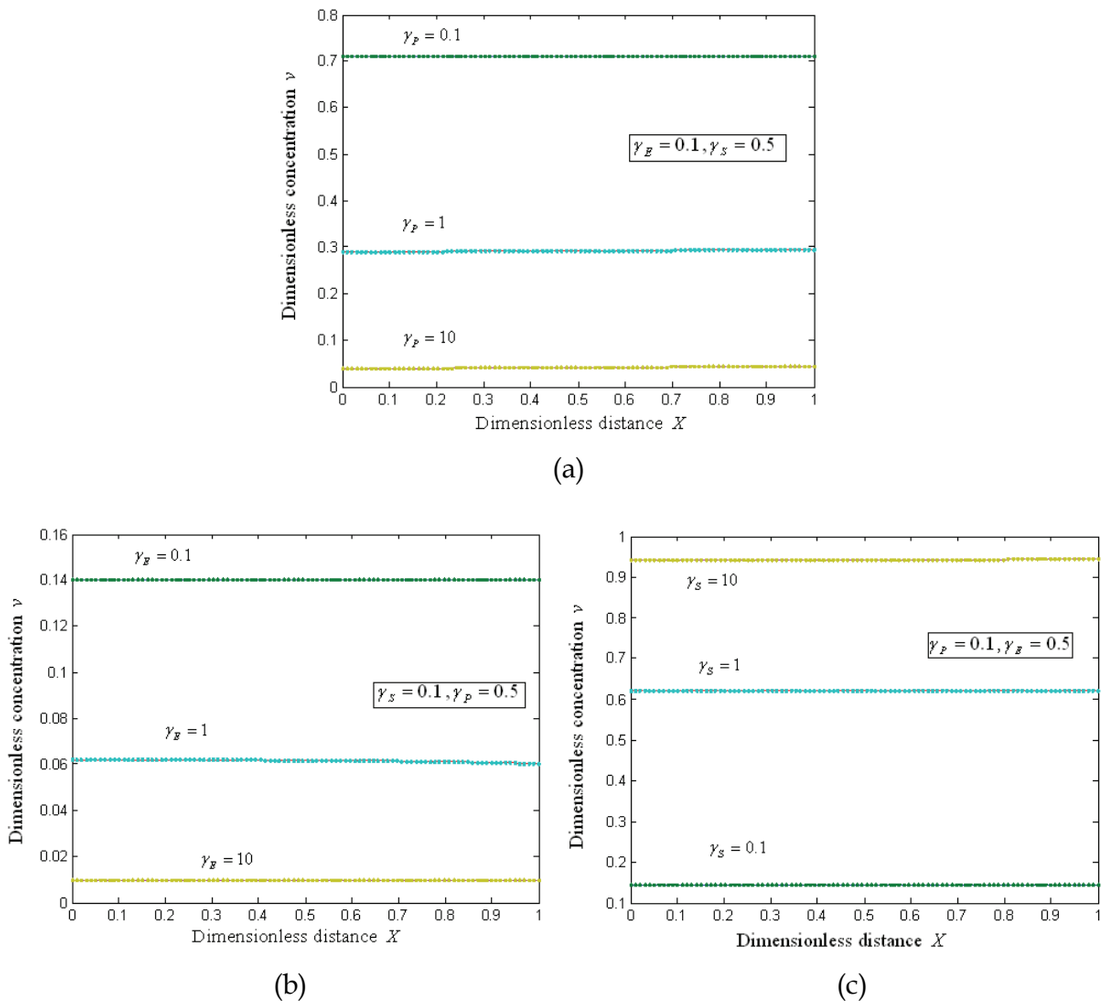


Fig. 2. Profile of the normalized enzyme-substrate complex v, were computed using equation (15) for various values of γ_S, γ_E and γ_P when the reaction/diffusion parameters (a) $\gamma_E = 0.1$, $\gamma_S = 0.5$ (b) $\gamma_S = 0.1$, $\gamma_P = 0.5$ (c) $\gamma_P = 0.1$, $\gamma_E = 0.5$. The key to the graph: (__) represents the Eq. (14) and (…) represents the numerical results.

Fig. 2*a-c* shows the normalized steady-state concentration of enzyme-substrate $v(X)$ versus the dimensionless distance X for various values of dimensionless parameters γ_E, γ_S and γ_P. From these figure, it is obvious that the values of the concentration $v(X)$ reaches the constant value for various values of γ_E, γ_S and γ_P. In figure 2*a-b*, the value of enzyme-substrate $v(X)$ decreases when the value of γ_P and γ_E are increases for $\gamma_E = 0.1, \gamma_S = 0.5$ and $\gamma_S = 0.1, \gamma_P = 0.5$. In Fig. 2*c*, the concentration $v(X)$ increases when γ_S increases.

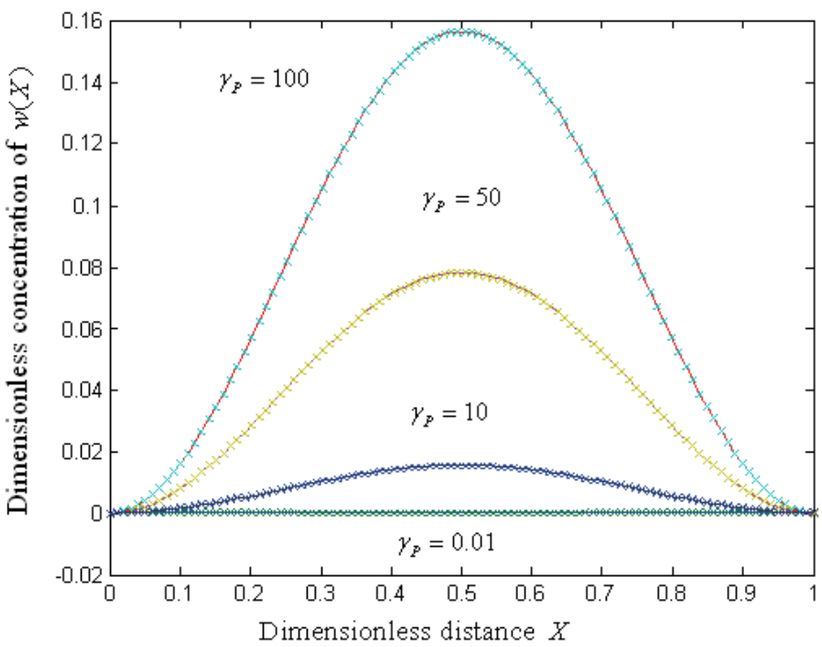


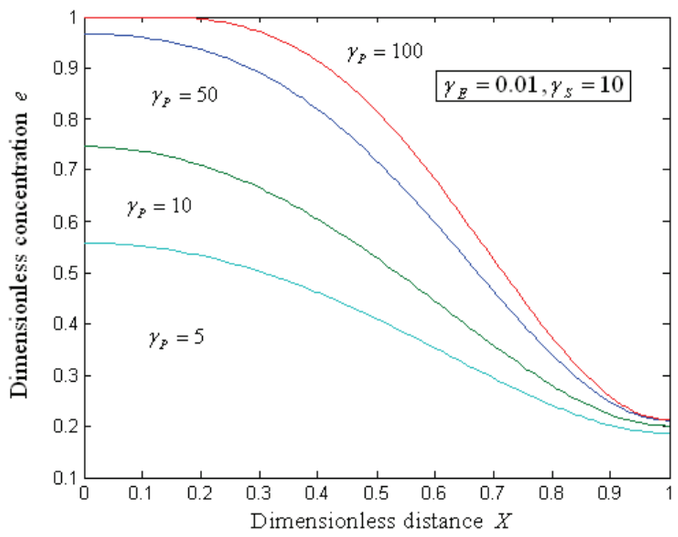
Fig. 3. Profile of the normalized concentration of product w for various values of γ_P. The curves are plotted using equation (19). The key to the graph: (__) represents the Eq. (19) and (++) represents the numerical results.

Fig. 3 shows the dimensionless concentration profile of product $w(X)$ using Eq. (20) for all various values of γ_P. Thus it is concluded that there is a simultaneous increase in the values of the concentration of $w(X)$ as well as in γ_P. Also the value of concentration is equal to zero when $X = 0$ and 1. From the Fig. 3, it is also inferred that, the concentration $w(X)$ increases slowly and then reaches the maximum value at $X = 0.5$ and then decreases slowly. In the Figs. 1*a-c*, 2*a-c* and 3 our steady-state analytical results (Eqs. (14, 15, 19)) are compared with simulation program for various values of γ_E, γ_S and γ_P.
In Fig. 4*a-b*, we present the dimensionless concentration profile for an enzyme as a function of dimensionless parameters for various values of γ_E, γ_S and γ_P. From this figure, it is confirmed that the value of the concentration increases when the value of γ_P increases for various values of γ_E and γ_S.

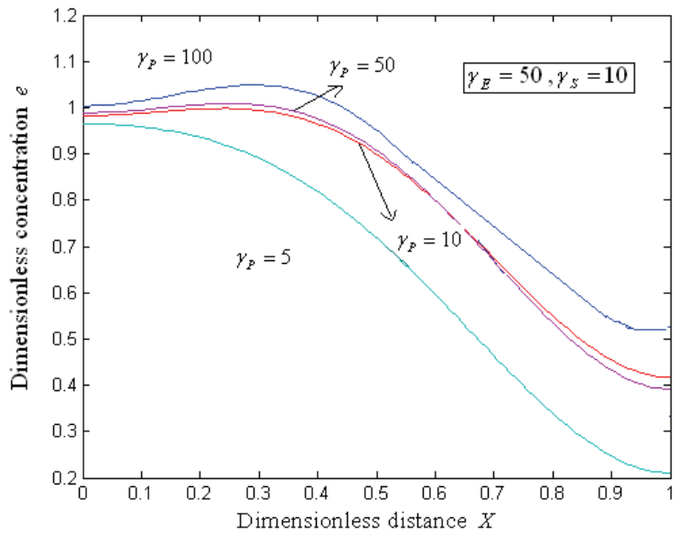
7. Conclusion

In this paper, the coupled time-independent nonlinear reaction/diffusion equations have been formulated and solved analytically 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. we have presented analytical expressions corresponding to the concentration of the substrate and concentration of the enzyme-substrate complex and enzyme interms of the parameters, γ_E, γ_S and γ_P. Moreover, we have also reported a simple and closed form of an analytical expression for the steady state concentration of the product for different values of the parameter γ_P. 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 (Baronas et al., 2008).



(a)



(b)

Fig. 4. Profile of the normalized concentration enzyme e for various values of γ_S,γ_E and γ_P when the reaction/diffusion parameters (a) $\gamma_E = 0.01$, $\gamma_S = 10$ (b) $\gamma_E = 50$, $\gamma_S = 10$. The curves are plotted using equations (18).

Appendix A

In this appendix, we derive the general solution of non-linear reaction eqns. (14) to (16) 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 (Scheller et al., 1992; Wollenberger et al., 1997; Nakamura et al., 2003; Amatore et al., 2006)

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

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 [10]

$$u_{n+1}(X) = u_n(X) + \int_0^x \lambda \left[L\left[u_n(\xi)\right] + N[\tilde{u_n}(\xi)] - g(\xi) \right] d\xi \tag{A2}$$

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 eqn. (10) as follows

$$u_{n+1}(X) = u_n(X) + \int_0^x \lambda_1 \left[u''_n(\xi) - \gamma_E \widetilde{u_n(\xi)} + \gamma_S \widetilde{v_n(\xi)} + \widetilde{\gamma_E u_n(\xi) v_n(\xi)} \right] d\xi \tag{A3}$$

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

$$w_{n+1}(X) = w_n(X) + \int_0^x \lambda_3 \left[w''_n(\xi) + \gamma_P \widetilde{v_n(\xi)} \right] d\xi \tag{A5}$$

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

$$\delta u_{n+1}(X) = \delta u_n(X) + \delta \int_0^x \lambda_1 \left[u''_n(\xi) - \gamma_E \widetilde{u_n(\xi)} + \gamma_S \widetilde{v_n(\xi)} + \widetilde{\gamma_E u_n(\xi) v_n(\xi)} \right] d\xi \tag{A6}$$

$$\delta v_{n+1}(X) = \delta v_n(X) + \delta \int_0^x \lambda_2 \left[v''_n(\xi) + \gamma_E \widetilde{u_n(\xi)} - \gamma_S \widetilde{v_n(\xi)} + \widetilde{\gamma_E u_n(\xi) v_n(\xi)} \right] d\xi \tag{A7}$$

$$\delta w_{n+1}(X) = \delta w_n(X) + \delta \int_0^x \lambda_3 \left[w''_n(\xi) + \gamma_P \widetilde{v_n(\xi)} \right] d\xi \tag{A8}$$

where λ_1 and λ_2 are general Lagrangian multipliers, u_0 and v_0 are initial approximations or trial functions, $\widetilde{u_n(\xi)}$, $\widetilde{v_n(\xi)}$ 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 $\delta u_n(0)v_n(0) = 0$.

$$\delta u_n : 1 + \lambda_1(\xi)\big|_{\xi=\tau} = 0 \,,\ \delta v_n : 1 + \lambda_2(\xi)\big|_{\xi=\tau} = 0 \tag{A9}$$

$$\delta u_n : -\lambda_1'(\xi) + \varepsilon\lambda(\xi)\ \big|_{\xi=\tau} \,,\ \delta v_n : -\lambda_2'(\xi) + k\lambda(\xi)\big|_{\xi=\xi} = 0 \tag{A10}$$

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

$$\lambda_1(\xi) = \lambda_2(\xi) = \lambda_3(\xi) = \xi - X \tag{A11}$$

Substituting the Lagrangian multipliers and n = 0 in the iteration formula (eqns. (A3) and (A4)) we obtain,

$$u_1(X) = u_0(X) + \int_0^x (\xi - X)\left[u''_0(\xi) - \gamma_E u_0(\xi) + \gamma_S v_0(\xi) + \gamma_E u_0(\xi)v_0(\xi)\right] d\xi \tag{A12}$$

$$v_1(X) = v_0(X) + \int_0^x (\xi - X)\left[v''_0(\xi) + \gamma_E u_0(\xi) - (\gamma_S + \gamma_P)v_0(\xi) + \gamma_E u_0(\xi)v_0(\xi)\right] d\xi \tag{A13}$$

$$w_1(X) = w_0(X) + \int_0^x (\xi - X)\left[w''_0(\xi) + \gamma_P v_0(\xi)\right] d\xi \tag{A14}$$

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

$$\begin{aligned} u_0(x) &= 1 - a + aX^2 \\ v_0(x) &= b + X^2(X-1)^2 \\ w_0(x) &= b_1 X^2(X-1)^2 \end{aligned} \tag{A15}$$

By the iteration formula (A10) and (A11) we obtain the equations (14) and (15) in the text.

Appendix B

function pdex4

```
m = 0;
x = linspace(0,1);
t = linspace(0,1000);
sol = pdepe(m,@pdex4pde,@pdex4ic,@pdex4bc,x,t);
u1 = sol(:,:,1);
```

```
u2 = sol(:,:,2);
u3 = sol(:,:,3);
figure
plot(x,u1(end,:))
title('Solution at t = 2')
xlabel('Distance x')
ylabel('u1(x,2)')
figure
plot(x,u2(end,:))
title('Solution at t = 2')
xlabel('Distance x')
ylabel('u2(x,2)')
figure
plot(x,u3(end,:))
title('Solution at t = 2')
xlabel('Distance x')
ylabel('u3(x,2)')
% --------------------------------------------------------------
function [c,f,s] = pdex4pde(x,t,u,DuDx)
c = [1; 1; 1];
f = [1; 1; 1] .* DuDx;
l=1;
m=1;
n=10;
F=-m*u(1)+(l+m*u(1))*u(2);
F1=m*u(1)-(l+m*u(1)+n)*u(2);
F2=n*u(2);
s=[F; F1; F2];
% --------------------------------------------------------------
function u0 = pdex4ic(x);
u0 = [1; 0; 1];
% --------------------------------------------------------------
function [pl,ql,pr,qr] = pdex4bc(xl,ul,xr,ur,t)
pl = [0; 0; 0];
ql = [1; 1; 1];
pr = [ur(1)-1; 0; 0];
qr = [0; 1; 1];
```

Appendix C

Nomenclature and units

Symbol	Meaning	Usual dimension
s	Concentration of the substrate	mole cm $^{-3}$
c	Concentration of the enzyme-substrate complex	mole cm $^{-3}$

e	Concentration of the enzyme	mole cm^{-3}
p	Concentration of the product	mole cm^{-3}
s_0	Bulk concentration of the substrate	mole cm^{-3}
e_0	Bulk concentration of the enzyme	mole cm^{-3}
D_S	Diffusion coefficient of the substrate	$cm^2\ sec^{-1}$
D_C	Diffusion coefficient of the enzyme-substrate complex	$cm^2\ sec^{-1}$
D_e	Diffusion coefficient of the enzyme	$cm^2\ sec^{-1}$
D_P	Diffusion coefficient of the product	$cm^2\ sec^{-1}$
D	Diffusion coefficient	$cm^2\ sec^{-1}$
x	Distance	cm
L	Length	cm
k_1	The forward rate of complex formation.	sec^{-1}
k_{-1}	The backward rate constant	sec^{-1}
k_{cat}	The rate of catalytic reaction	sec^{-1}
u	Dimensionless concentration of substrate	None
v	Dimensionless concentration of enzyme-substrate complex	None
w	Dimensionless concentration of product	None
γ_E ,γ_S,γ_P	Dimensionless reaction/diffusion parameter	None

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A biosensor is a detecting device that combines a transducer with a biologically sensitive and selective component. Biosensors can measure compounds present in the environment, chemical processes, food and human body at low cost if compared with traditional analytical techniques. This book covers a wide range of aspects and issues related to biosensor technology, bringing together researchers from 12 different countries. The book consists of 20 chapters written by 69 authors and divided in three sections: Biosensors Technology and Materials, Biosensors for Health and Biosensors for Environment and Biosecurity.

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