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ORIGINAL PAPER

Analytical solution of non-linear enzyme reaction equations arising in mathematical chemistry

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Abstract The boundary value problem in basic enzyme reactions is formulated and approximate expressions for substrate and substrate-enzyme complex are presented. He's Homotopy Perturbation method 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, enzyme- substrate complex and free enzyme are discussed in terms of dimensionless parameters σ, ρ and ε. The obtained concentration results are compared with the numerical solution acquired using Matlab program. They are found to be in satisfactory agreement.

Keywords Enzyme reaction · Non-linear reaction equations · 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 by Rubinow [1], Murray [2], Segel [3] and Roberts [4].

The complexity of biochemical processes is such that the development of a simplifying model is often essential in trying to understand the phenomenon under

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consideration. However, to the best of our knowledge, there were no analytical results available till date that corresponds to the substrate concentration and enzyme-substrate complex concentration and free enzyme concentration for all possible values of dimensionless parameters σ, ρ and ε. 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 σ, ρ and ε.

2 Mathematical formulation and solution of the problem

The enzyme kinetics in biochemical systems have traditionally been modeled 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:

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

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

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

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. he boundary conditions are

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

Adding Eqs. (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 nondimensional variables and parameters,

$$u(\tau) = \frac{s(t)}{s_0}, \quad v(\tau) = \frac{(\mathrm{s_0} + \mathrm{K_m})\, c(t)}{e_0 s_0}, \quad \tau = \frac{t}{t_c} = \mathrm{k_1}\,(\mathrm{s_0} + \mathrm{K_m})\,\mathrm{t},$$
$$\rho = \frac{k_{-1}}{k_2}, \quad K_m = \frac{k_{-1} + k_2}{k_1}, \quad \varepsilon = \frac{e_0}{s_0 + K_m}, \quad \sigma = \frac{s_0}{K_m} \tag{9}$$

With the long or slow timescale, t_s, we nondimensionalise the time by

$$T = \varepsilon(1 + \rho)k_2 t \tag{10}$$

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

$$\frac{du}{dT} = -(1 + \sigma)u + \sigma\, uv + \frac{\rho}{1 + \rho} v \tag{11a}$$

$$\varepsilon \frac{dv}{dT} = (1 + \sigma)u - \sigma\, uv - v \tag{11b}$$

$$u(0) = 1, \quad v(0) = 0 \tag{12}$$

3 Analytical solutions of concentrations of the substrate, enzyme- substrate complex and free enzyme using Homotopy Perturbation method

In recent days, HPM is often employed to solve several analytical problems. In addition, several groups demonstrated the efficiency and suitability of the HPM for solving non-linear equations and other electrochemical problems [5–8]. He et al.[9], used HPM to solve the Lighthill equation, the Duffing equation [10] and the Blasius equation [11]. HPM has also been used to solve non-linear boundary value problems [12], integral equation [13–15], Klein-Gordon and Sine-Gordon equations [16], Emden-Flower type equations [17] and several other problems. From the foretold applications, it is evident that HPM is a powerful tool to solve functional equations. Further, HPM is an accurate and efficient method and this method employs the imbedding parameter p as a small parameter and necessitates only a few iterations to find an asymptotic solution [18]. The HPM is unique in its applicability, accuracy and efficiency. The above system of non-linear equations can be solved analytically in a simple and closed form using Homotopy Perturbation method. (Ref Appendix A). The solutions of the above Eqs. (11a) and (11b) become

$$u(T) = \left\{1 - \frac{1}{(1-\varepsilon(1+\sigma))}\left(1+\frac{\sigma(1+\sigma)}{\varepsilon} - \frac{(1+\sigma)\rho\varepsilon}{(1+\rho)(1-\varepsilon(1+\sigma))}\right)\right\} e^{-(1+\sigma)T} - \frac{1}{(1-\varepsilon(1+\sigma))}\left(\sigma^2 e^{-2(1+\sigma)T} - \frac{\sigma(1+\sigma)e^{-\left(1+\sigma+\frac{1}{\varepsilon}\right)T}}{\varepsilon} - \frac{\varepsilon\rho\, e^{\frac{-T}{\varepsilon}}}{(1+\rho)(1-\varepsilon(1+\sigma))}\right) \tag{13}$$

$$v(T) = \left\{e^{-(1+\sigma)T} - \left(1 - \frac{\sigma\varepsilon}{1-2\varepsilon(1+\sigma)} - \sigma\right) e^{\frac{-T}{\varepsilon}} - \frac{\sigma\varepsilon}{(1-2\varepsilon(1+\sigma))} e^{-2(1+\sigma)T} - \sigma e^{-\left(1+\sigma+\frac{1}{\varepsilon}\right)T}\right\} \tag{14}$$

Equations (13) and (14) represent the analytical expressions of the substrate $u(T)$ and enzyme-substrate $v(T)$ concentration. From the Eq. (6), we can also obtain the dimensionless concentration of enzyme

$$\begin{aligned} E(T) &= e(T)/e_0 = 1 - v(T) \\ &= 1 - \left\{e^{-(1+\sigma)T} - \left(1 - \frac{\sigma\varepsilon}{1-2\varepsilon(1+\sigma)} - \sigma\right) e^{\frac{-T}{\varepsilon}} \right. \\ &\quad \left. - \frac{\sigma\varepsilon}{(1-2\varepsilon(1+\sigma))} e^{-2(1+\sigma)T} - \sigma e^{-\left(1+\sigma+\frac{1}{\varepsilon}\right)T}\right\} \end{aligned} \tag{15}$$

The concentration of the substrate $u(T)$ is maximum when

$$T = \frac{(l_0 + l_1 - l_2 + l_3)\,\varepsilon}{(1+\sigma)\varepsilon\,(l_0 + 2l_1 - l_2) - l_2 + l_3} \tag{16}$$

where

$$l_0 = 1 + \frac{1-\sigma}{(1-\varepsilon(1+\sigma))}\left(\sigma - \frac{\sigma(1+\sigma)}{\varepsilon} - \frac{(1+\sigma)\rho\varepsilon}{(1+\rho)(1-\varepsilon(1+\sigma))}\right)$$
$$l_1 = \frac{-2\sigma^2}{1-\varepsilon(1+\sigma)}, l_2 = \frac{\sigma(1+\sigma)}{\varepsilon(1-\varepsilon(1+\sigma))}, l_3 = \frac{(1+\sigma)\rho\varepsilon}{(1+\rho)(1-\varepsilon(1+\sigma))^2} \quad (17)$$

The concentration of enzyme-substrate complex $v(T)$ is maximum only when time

$$T = -\left\{\frac{\varepsilon(-m_0 + m_1 + m_2 + m_3 - m_4)}{\varepsilon(1+\sigma)(m_0 - 2m_2 - m_3) - m_1 - m_3 + m_4}\right\} \quad (18)$$

Where

$$m_0 = \frac{(1+\sigma)}{1-\varepsilon(1+\sigma)}, \quad m_1 = \frac{1}{(1-\varepsilon(1+\sigma))}\left(1+\sigma - \frac{(1+\sigma)\sigma\varepsilon}{(1-2\varepsilon(1+\sigma))} - \sigma\right)$$
$$m_2 = \frac{(1+\sigma)\sigma}{1-\varepsilon(1+\sigma)}, \quad m_3 = \frac{(1+\sigma)\sigma}{\varepsilon(1-\varepsilon(1+\sigma))}, \quad m_4 = \frac{(1+\sigma)\rho\varepsilon}{(1+\rho)(1-\varepsilon(1+\sigma))^2} \quad (19)$$

4 Numerical simulation

The nonlinear differential Eq. (11) is also solved by using numerical methods. The function ode45 in Matlab software which is a function of solving two-point boundary value problems (BVPs) for ordinary differential equations is used to solve those equations. Its numerical solution is compared with the solution obtained by using Homotopy Perturbation method and it gives a satisfactory result. The Matlab program is also given in Appendix B.

5 Discussion

Equations (13) and (14) are the new and simple analytical expressions of concentrations of the substrate and the enzyme- substrate calculated using Homotopy Perturbation method for the boundary conditions Eq. (12). The dimensionless analytical expressions of concentration $u(T)$, $v(T)$, and $E(T)$ for various values of dimensionless reaction parameters σ, ρ and ε versus the dimensionless distance T compared with numerical solution. From these figures, it is inferred that the value of the concentration of substrate decreases gradually when T increases. The Concentrations of substrate and substrate- enzyme complex reach zero value when $T \geq 5$ for all values of reaction parameters σ , ρ and ε. The concentration of the free enzyme E reaches the constant value when $T \geq 5$ for all values of reaction parameters. When $0.2 \leq T \leq 0.5$, free enzyme attains the minimum value and it reaches one approximately when $T \geq 3$ for small values of σ. Consequently, substrate and enzyme-substrate complex reaches the maximum value from Eqs. (16) and (18). For instance, from these equations $u(T)$ reaches maximum when $T = 0.1841$ and $v(T)$ attains

maximum when $T = 0.7979$ for the values of reaction parameters $\sigma = 0.1$, $\rho = 0.1$ and $\varepsilon = 0.1$ (Figs. 1,2,3,4,5,6,7,8,9,10).

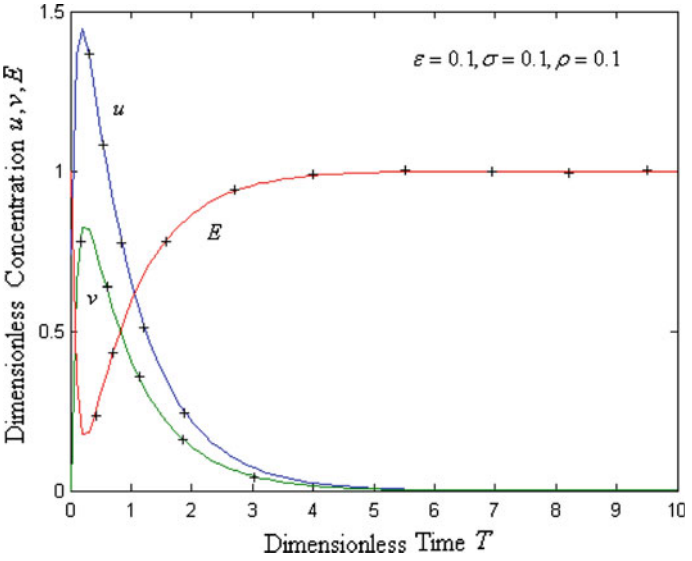

Fig. 1 Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v and enzyme E for $\varepsilon = 0.1$, $\sigma = 0.1$, $\rho = 0.1$. The *curves* are plotted using Eqs. (13), (14) and (16). Here (+) represents the numerical simulation

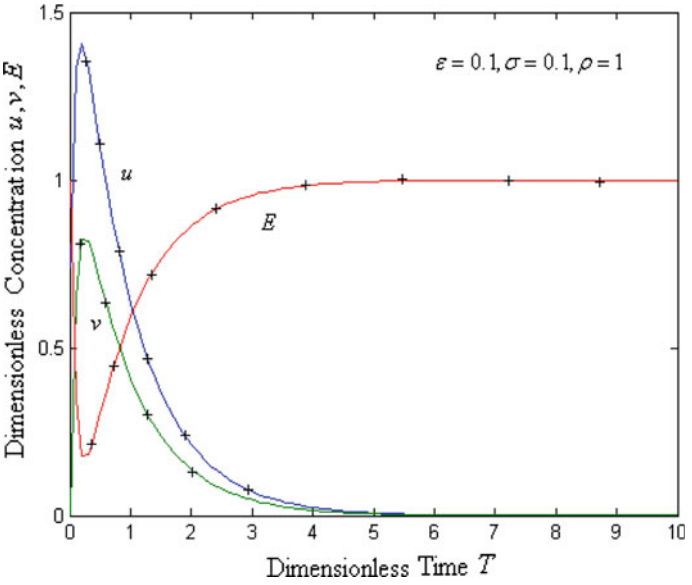

Fig. 2 Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v and enzyme E for $\varepsilon = 0.1$, $\sigma = 0.1$, $\rho = 1$. The *curves* are plotted using Eqs. (13), (14) and (16). Here (+) represents the numerical simulation

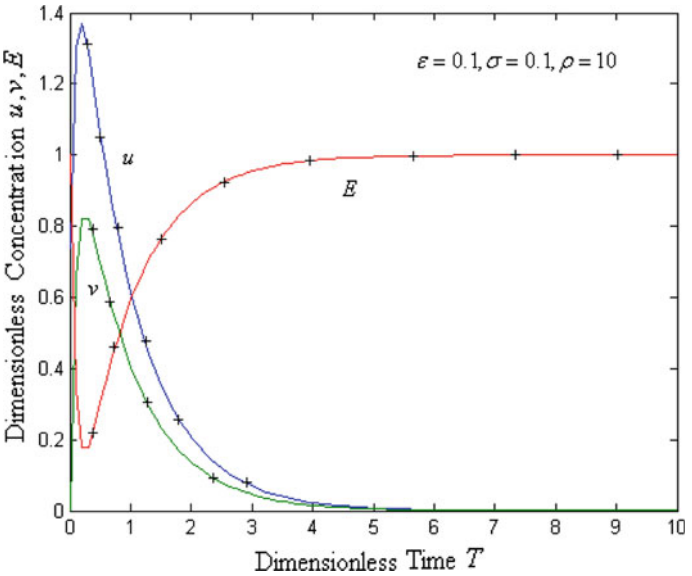

Fig. 3 Profile of the normalized concentrations of the substrate u, enzyme-substrate complex v and enzyme E for $\varepsilon = 0.1$, $\sigma = 0.1$, $\rho = 10$. The *curves* are plotted using Eqs. (13), (14) and (16). Here (+) represents the numerical simulation

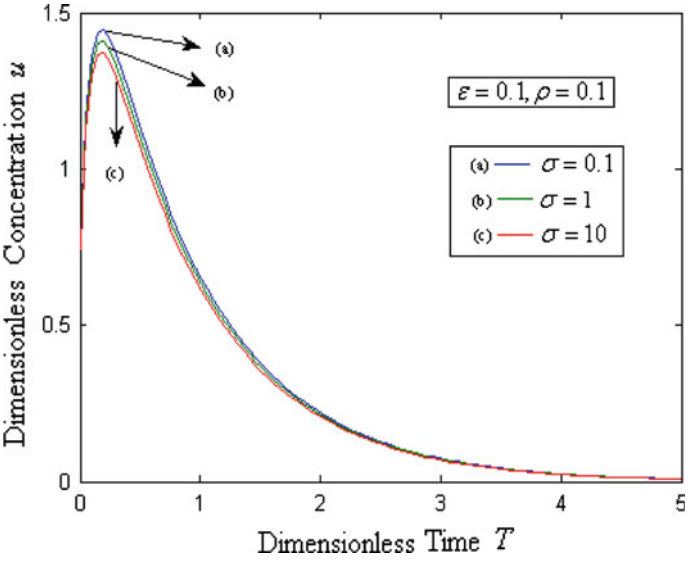

Fig. 4 Profile of the normalized concentrations of the substrate u, for $\varepsilon = 0.1$, $\rho = 0.1$, $\sigma = 0.1,\ 1,\ 10$. The *curves* are plotted using Eq. (13)

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

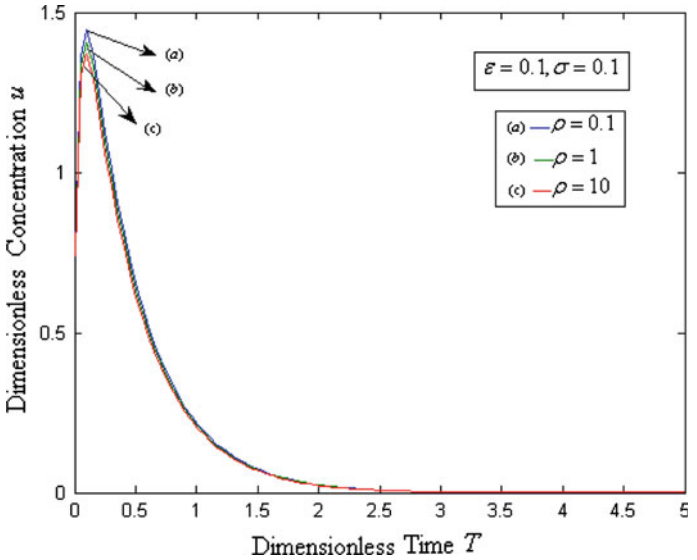

Fig. 5 Profile of the normalized concentrations of the substrate u, for $\varepsilon = 0.1, \sigma = 0.1, \rho = 0.1,\ 1,\ 10$. The *curves* are plotted using Eq. (13)

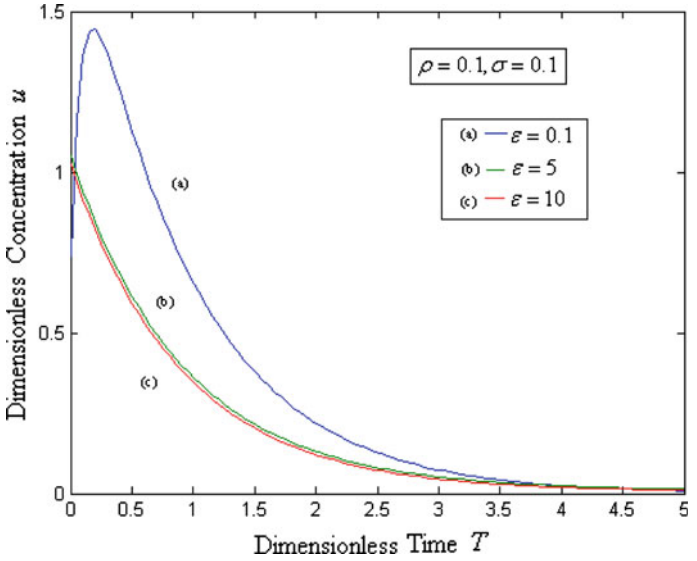

Fig. 6 Profile of the normalized concentrations of the substrate u, for $\rho = 0.1, \sigma = 0.1, \varepsilon = 0.1,\ 5,\ 10$. The *curves* are plotted using Eq. (13)

estimating the concentrations of substrate, enzyme-substrate complex and free enzyme are derived. The pertinent analytical solutions for the substrate, substrate-enzyme complex and free enzyme are discussed in terms of dimensionless parameters σ , ρ and ε.

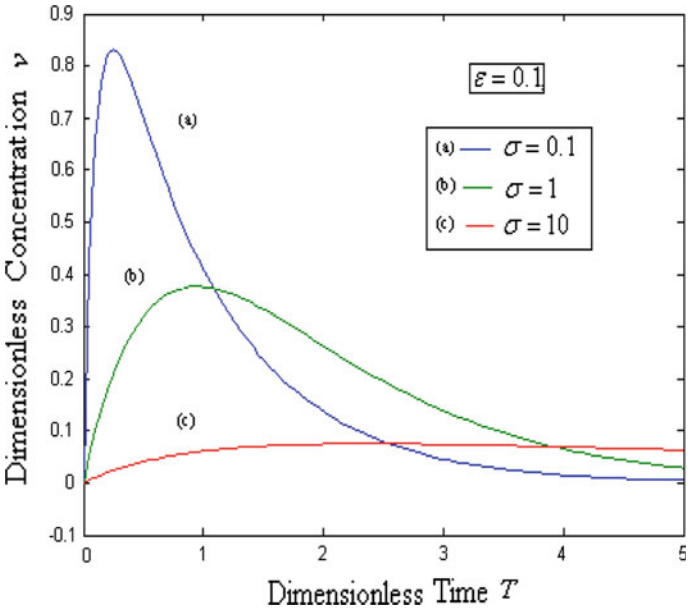

Fig. 7 Profile of the normalized concentrations of the enzyme substrate complex v, for $\varepsilon = 0.1$, $\sigma = 0.1,\ 1,\ 10$. The *curves* are plotted using Eq. (14)

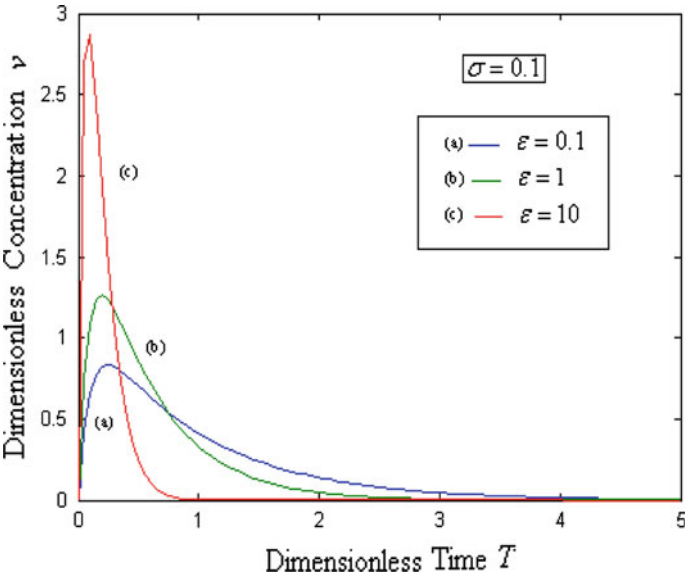

Fig. 8 Profile of the normalized concentrations of the enzyme substrate complex v, for, $\sigma = 0.1$, $\varepsilon = 0.1,\ 1,\ 10$. The *curves* are plotted using Eq. (14)

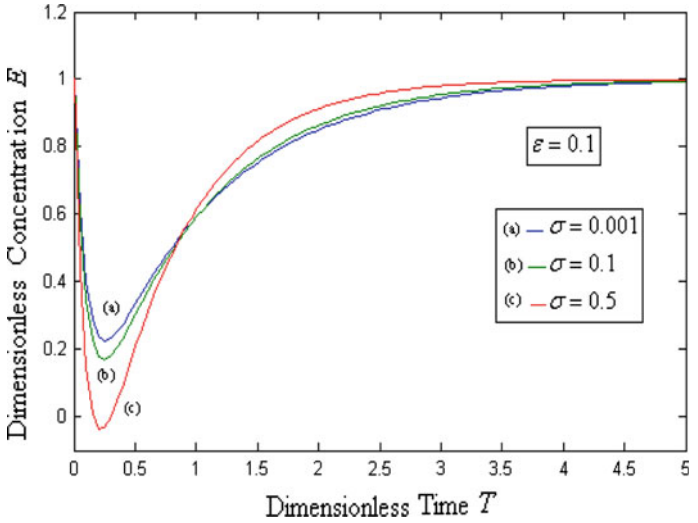

Fig. 9 Profile of the normalized concentrations of the free enzyme E, for $\varepsilon = 0.1, \sigma = 0.001,\ 0.1,\ 0.5$. The *curves* are plotted using Eq. (16)

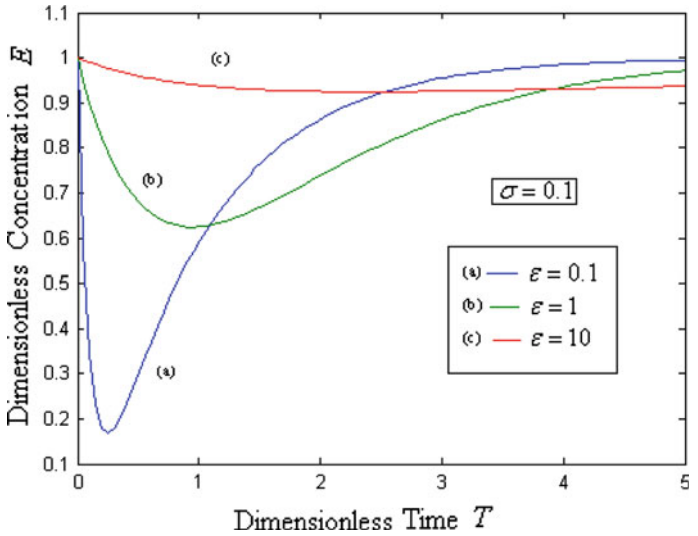

Fig. 10 Profile of the normalized concentrations of the free enzyme E, for $\sigma = 0.1, \varepsilon = 0.1,\ 1,\ 10$. The *curves* are plotted using Eq. (16)

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.

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Appendix A

Solution of the Equation (11a) using Homotopy Perturbation method

In this Appendix, we indicate how Eq. (11a) may be solved using HPM to yield Eq. (4).

$$(1-p)\left[\frac{du}{dT}+(1+\sigma)u\right]+p\left[\frac{du}{dT}+(1+\sigma)u-\sigma uv-\left(\frac{\rho}{1+\rho}\right)v\right]=0 \tag{A1}$$

and the initial approximations are as follows:

$$T=0,\quad u=1 \tag{A2}$$

The approximate solution of (A1) is given by

$$u=u_0+pu_1+p^2u_2+p^3u_3+\cdots \tag{A3}$$

Substituting Eq. (A3) into Eq. (A1) and comparing the coefficients of like powers of p

$$p^0:\frac{du_0}{dT}+(1+\sigma)u_0=0 \tag{A4}$$

$$p^1:\frac{du_1}{dT}+(1+\sigma)u_1-\sigma\, u_0v_0-\left(\frac{\rho}{1+\rho}\right)v_0=0 \tag{A5}$$

and

$$p^2:\frac{du_2}{dT}+(1+\sigma)u_2+\sigma\, u_0v_1+\sigma\, u_1v_0-\left(\frac{\rho}{1+\rho}\right)v_1=0 \tag{A6}$$

Upon solving the Eqs. (A4), (A5) and (A6), and using the boundary condition (A2), we get

$$u_0(T)=e^{-(1+\sigma)T} \tag{A7}$$

$$u_1(T)=0 \tag{A8}$$

and

$$u_2(T)=\left(\frac{-\sigma}{1-\varepsilon(1+\sigma)}+\frac{(1+\sigma)\sigma}{\varepsilon\,(1-\varepsilon(1+\sigma))}\right.$$
$$\left.-(1+\sigma)\left(\frac{\rho}{1+\rho}\right)\frac{\varepsilon}{(1-\varepsilon(1+\sigma))^2}\right)e^{-(1+\sigma)T}+\frac{\sigma e^{-2(1+\sigma)T}}{1-\varepsilon(1+\sigma)}$$

$$-\frac{(1+\sigma)\sigma}{\varepsilon\,(1-\varepsilon(1+\sigma))}e^{-\left(1+\sigma+\frac{1}{\varepsilon}\right)T}+(1+\sigma)\left(\frac{\rho}{1+\rho}\right)Te^{-(1+\sigma)T}$$
$$+(1+\sigma)\left(\frac{\rho}{1+\rho}\right)\frac{\varepsilon}{(1-\varepsilon(1+\sigma))^2}e^{\frac{-T}{\varepsilon}} \tag{A9}$$

Similarly for Eq. (11a)

$$(1-p)\left[\varepsilon\frac{dv}{dT}+v\right]+p\left[\frac{dv}{dT}-(1+\sigma)u+\sigma uv+v\right]=0 \tag{A10}$$

and the initial approximation is as follows:

$$T=0,\quad v=0 \tag{A11}$$

The approximate solution of (A1) is given by

$$v=v_0+pv_1+p^2v_2+p^3v_3+\cdots \tag{A12}$$

Substituting Eq. (A11) into Eq. (A10) and comparing the coefficients of like powers of p

$$p^0:\varepsilon\frac{dv_0}{dT}+v_0=0 \tag{A13}$$
$$p^1:\varepsilon\frac{dv_1}{dT}+v_1-(1+\sigma)u_0-\sigma\,u_0v_0=0 \tag{A14}$$

and

$$p^2:\varepsilon\frac{dv_2}{dT}+v_2-(1+\sigma)u_1+\sigma\,u_1v_0+\sigma\,u_0v_1=0 \tag{A15}$$

Upon solving the Eqs. (A13), (A14) and (A15), and using the boundary conditions (A11), we get

$$v_0(T)=0 \tag{A16}$$
$$v_1(T)=\frac{1+\sigma}{1-\varepsilon(1+\sigma)}\left[e^{-(1+\sigma)T}-e^{\frac{-T}{\varepsilon}}\right] \tag{A17}$$
$$v_2(T)=\left(\frac{(1+\sigma)\sigma\varepsilon}{(1-\varepsilon(1+\sigma))\,(1-2\varepsilon(1+\sigma))}+\frac{\sigma}{(1-2\varepsilon(1+\sigma))}\right)e^{\frac{-T}{\varepsilon}}$$
$$-\frac{(1+\sigma)\sigma\varepsilon}{(1-\varepsilon(1+\sigma))\,(1-2\varepsilon(1+\sigma))}e^{-2(1+\sigma)T}$$
$$-\frac{\sigma}{(1-\varepsilon(1+\sigma))}e^{-\left(1+\sigma+\frac{1}{\varepsilon}\right)T} \tag{A18}$$

According to the HPM, we can conclude that

$$u(T) = \lim_{p \to 1} u(T) = u_0 + u_1 + u_2 \tag{A19}$$

$$v(T) = \lim_{p \to 1} v(T) = v_0 + v_1 + v_2 \tag{A20}$$

Appendix B: (Numerical Simulation Program)

```
function main1
options= odeset('RelTol',1e-6,'Stats','on');
Xo = [1; 0];
tspan = [0,10];
tic
[t,X] = ode45(@TestFunction,tspan,Xo,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)
s2=0.1;e2=0.01;r1=0.1;
dx_dt(1) =-(1+s2)*x(1)+s2*x(1)*x(2)+(r1/(1+r1))*x(2);
dx_dt(2) =(1/e2)*((1+s2)*x(1)-s2*x(1)*x(2)-x(2));
dx_dt = dx_dt';
return
```

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