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# Modelling of Non Linear Enzyme Reaction Process Using Variational Iteration Method

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**ABSTRACT**

*A mathematical model for the nonlinear enzymatic reaction process is discussed. An approximate analytical expression of concerntrations of substrate, enzyme-substrate and product are obtained using variational iteration method (VIM). The main objective is to propose an analytical solution to nonlinear differential equations. Furthermore, in this work the numerical stimulation of the problem is also reported using Scilab/Matlab program. An agreement between analytical solution and numerical results is noted.*

***Keywords:*** *Mathematical modeling, enzyme Kinetics, Nonlinear equations, enzyme substrate, variational iteration method.*

## I. INTRODUCTION

Enzyme kinetics is the study of the chemical reactions that are catalysed by enzymes. In enzyme kinetics, the reaction rate is measured and the effects of varying the conditions of the reaction are investigated. An initial-rate equation for a single-substrate noncooperative enzyme-catalyzed reaction is relating to the initial velocity and initial substrate concentration;

$v = V_{max}[S]/(K_m + [S])$, where v is the initial velocity of the reaction, $V_{max}$ is the maximum velocity, [S] is the initial substrate concentration. The rate of reaction when the enzyme is saturated with substrate is the maximum rate of reaction, $V_{max}$. The relationship between rate of reaction and concentration of substrate depends on the affinity of the enzyme for its substrate.

As enzyme-catalysed reactions are saturable, their rate of catalysis does not show a linear response to increasing substrate. If the initial rate of the reaction is measured over a range of substrate concentrations [S], the reaction rate ($v$) increases as [S] increases. However, as [S] gets higher, the enzyme becomes saturated with substrate and the rate reaches $V_{max}$, the enzyme's maximum rate. In the first moment after an enzyme is mixed with substrate, no product has been formed and no intermediates exist. The study of the next few milliseconds of the reaction is called pre-steady-state kinetics also referred to as Burst kinetics. Pre-steady-state kinetics is therefore concerned with the formation and consumption of enzyme–substrate intermediates (such as ES or E*) until their steady-state concentrations are reached.

Stoyan Rangelov et al. [2] develope a model of the transient kinetics of laccase-catalyzed oxidation of phenol at micromolar concentrations. The feasibility of this approach can be explored by modeling transient kinetics, particularly in the low substrate concentration range, where the model may be used to predict the quantity of enzyme and time required to achieve a particular level of conversion of a target compound. Gang Li et al. [3] discuss a kinetic model for analysis of physical tunnels in sequentially acting enzymes with direct proximity channeling.

A diffusion-reaction model showed that simply reducing the diffusion distance does not improve the global catalytic efficiency of a coupled reaction, rather, a physical tunnel between two consecutive active sites of

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enzymes. Pengcheng Zhang and Buyun Wang [4] discuss a kinetics modeling on the inhibition of glucose on cellulosome of clostridium thermocellum.
Glucose was found to be an inhibitor for cellulosome based on the kinetics analysis. Manimozhi, and Rajendran [5] derive the nonsteady-state analytical solution for surface enzyme kinetics. A mathematical modeling of real-time surface Plasmon resonance(SPR) imaging measurements of surface enzymatic reactions on DNA microarrays are examined using a kinetics model that couples the contribution of both enzyme adsoption and surface enzyme reaction kinetics. Manimozhi et al.[6] obtain the expresion of steady-state substrate concerntration in the action of biosensor response at mixed enzyme kinetics and diffusion limitation in the case of substrate inhibition.
This model is based on non-stationary diffusion equation containing a non-linear term related to non-Michalies-Menten kinetics of the enzymatic reaction. Meena et al. [7] discuss mathematical modeling of enzyme kinetics reaction mechanisms and obtain the simple analytical solutions of non-linear reaction equation. In this paper we have obtained the analytical solution of nonlinear equation using variational iteration method. Rahamahunissa and Rajendran [8] applied the he's variational iteration method in nonlinear boundary value problems in enzyme-substrate reaction diffusion processes. In this communication He's variational iteration metod is implemented to give approximate an analytical solutions of non-linear reaction diffusion equations containing a non-linear term related to Michalies-Menten kinetic of the enzymatic reaction.

**Nomenclature and units**

$[E]$: Enzyme concentration ($\mu M$)

$[C]$: Enzyme-substrate complex ($\mu M$)

$[S]$: Substrate concerntrtion ($\mu M$)

$[E_0]$: Initial enzyme concerntrtion ($\mu M$)

$k_M$: Michaelis-menten constant

$[s_0]$: Initial substrate concentration ($\mu M$)

$k_1, k_2, k_3$: positive rate constant (none)

$\lambda_1, \lambda_2, \lambda_3, \varepsilon$ Reaction diffusion parameter (none)

$u$: Dimensionless substrate concentration (none)

$v$: Dimensionless enzyme concentration (none)

$w$: Dimensionless product concentration (none)

$t$: Time(sec)

$\tau$: Dimensionless time (none)

## II. MATHEMATICAL FORMULATION OF THE PROBLEM

The typical notation of the enzyme catalyzed reaction with one substrate can be given as

$$A + E \underset{K_2}{\overset{K_1}{\leftrightarrow}} X \underset{K_4}{\overset{K_3}{\leftrightarrow}} P + E \tag{1}$$

where $A$ is substrate, $E$ is enzyme, $X$ is enzyme-substrate complex, and $P$ is free enzyme product. The kinetic equations for the above reactions can represented as follows [1]:

$$\frac{d(A)}{dt} = k_2(X) - k_1(A)(E), \tag{2}$$

$$\frac{d(E)}{dt} = (k_2 + k_3)(X) - (k_1(A) + k_4(P))(E), \tag{3}$$

$$\frac{d(X)}{dt} = (k_1(A) + k_4(P))(E) - (k_2 + k_3)(X), \tag{4}$$

$$\frac{d(P)}{dt} = k_3(X) - k_4(P)(E) \tag{5}$$

The more general form of (2-5) can be written in the form of

$$\frac{d(A)}{dt} = v_2 - v_1, \tag{6}$$

$$\frac{d(E)}{dt} = v_2 + v_3 - v_1 - v_4, \tag{7}$$

$$\frac{d(X)}{dt} = v_1 + v_4 - v_2 - v_3, \tag{8}$$

$$\frac{d(P)}{dt} = v_3 - v_4. \tag{9}$$

Where

$$v_1 = k_1(A)(E), v_2 = k_2(X), v_3 = k_3(X), v_4 = k_4(P)(E) \tag{10}$$

The initial condition are as follows:

$$\text{At } t = 0, \quad (A) = A_0, \quad (E) = E_0, \quad (X) = 0, \quad (P) = 0. \tag{11}$$

The concentration of the reactants in (6-9) is denoted by lower cases letters

$$s = (A) \quad e = (E), \quad c = (X) \quad p = (P) \tag{12}$$

The law of mass action leads to the system of following non-linear kinetic equation:

$$\frac{ds}{dt} = -k_1 se + k_2 c \tag{13}$$

$$\frac{de}{dt} = -k_1 se + k_2 c + k_3 c - k_4 pe \tag{14}$$

$$\frac{dp}{dt} = k_3 c - k_4 pe \tag{15}$$

$$\frac{dc}{dt} = k_1 se - k_2 c - k_3 c + k_4 pe \tag{16}$$

with the initial conditions

$$s(0) = s_0, \quad e(0) = e_0, \quad p(0) = 0, \quad c(0) = 0. \tag{17}$$

Adding (14) and (16), we get

$$\frac{de}{dt} + \frac{dc}{dt} = 0. \tag{18}$$

Using the initial conditions (17), we obtain

$$e(t) + c(t) = e_0. \tag{19}$$

The solid phase equation for the enzyme with the indicating concentration of the substrate is described by the following equation (13-16):

$$\frac{ds}{dt} = -k_1 se_0 + k_1 sc + k_2 c \tag{20}$$

$$\frac{de}{dt} = k_1 se_0 - k_1 sc - k_2 c - k_3 c + k_4 pe_0 - k_4 sc, \tag{21}$$

$$\frac{dp}{dt} = k_3 c - k_4 pe_0 - k_4 pc \tag{22}$$

The initial conditions for this equation are given by

$$s(0) = s_0, \quad c(0) = 0, \quad p(0) = 0. \tag{23}$$

By introducing the following set of non-dimensional variables and parameters,

$$\tau = \frac{k_1 e_0 t}{\varepsilon}, u(\tau) = \frac{s(t)}{s_0}, v(\tau) = \frac{c(t)}{s_0}, w(\tau) = \frac{P(t)}{s_0},$$
$$\lambda_1 = \frac{k_2}{k_1 s_0}, \lambda_2 = \frac{k_3}{k_1 s_0}, \lambda_3 = \frac{k_4}{k_1}, \varepsilon = \frac{e_0}{s_0}, \eta = \lambda_1 + \lambda_2. \tag{24}$$

the nonlinear reaction-diffusion Eqns. (20-22) are expressed in the following non-dimensional form as:

$$\frac{du}{d\tau} = -\varepsilon u + uv + \lambda_1 v \tag{25}$$

$$\frac{dv}{d\tau} = \varepsilon u - \eta v + \lambda_3 \varepsilon\omega - uv - \lambda_3 v \tag{26}$$

$$\frac{dw}{d\tau} = \lambda_2 v - \lambda_3 \varepsilon\omega + \lambda_3 v\omega \tag{27}$$

with the dimensionless initial conditions:

$$u(0) = 1, v(0) = 0, w(0) = 0 \tag{28}$$

**2.1 Analytical expression of concentrations of substrate, enzyme substrate and product**

The normalized concentrations of the substrate are presented in Eqns. (20-22) defines the initial and boundary value problem [8]. The variational iteration method [9-10] is used to give the approximate solutions of the non-linear Eqns. (25-27). Using VIM (refer Appendix 2), we can obtain the concentrations of substrate, enzyme substrate and product by solving the the Eqns. (25-27). The analytical expression of dimensionless concentration of the substrate $u(\tau)$ is,

$$u(\tau) = e^{-\varepsilon\tau} + \left[ \frac{e^{-\varepsilon\tau}}{(-\varepsilon + \lambda_3 + \eta)\varepsilon} \left\{ \frac{e^{-\varepsilon\tau}}{\varepsilon} - \frac{e^{-(\lambda_{3+\eta})\tau}}{(\lambda_3 + \eta)} \right\} + \frac{e^{-\varepsilon\tau}}{\varepsilon(-\varepsilon + \lambda_3 + \eta)} \left\{ -\frac{1}{\varepsilon} + \frac{1}{(\lambda_3 + \eta)} \right\} \right]$$
$$+ \left[ \frac{\lambda_1}{-\varepsilon + \lambda_3 + \eta} \left\{ \frac{-e^{-\varepsilon\tau}}{\varepsilon} + \frac{e^{-(\lambda_{3+\eta})\tau}}{(\lambda_3 + \eta)} \right\} + \frac{\lambda_1 e^{-\varepsilon\tau}}{-\varepsilon + \lambda_3 + \eta} \left\{ \frac{-1}{\varepsilon} + \frac{1}{(\lambda_3 + \eta)} \right\} \right] \tag{29}$$

The analytical expression of dimensionless concentration of the enzyme substrate $v(\tau)$ is

$$v(\tau) = \frac{\varepsilon}{(-\varepsilon + \lambda_3 + \eta)}(e^{-\varepsilon\tau} - e^{-(\lambda_3+\eta)\tau})$$
$$- \left( \frac{\varepsilon}{(\lambda_3 + \eta)(-\varepsilon + \lambda_3 + \eta)}(e^{-\varepsilon\tau} - e^{-(\lambda_3+\eta)\tau}) \right) + \left( \frac{-e^{-\varepsilon\tau}}{(\lambda_3+\eta)} + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)} \right)$$
$$+ \left( \frac{\varepsilon\eta}{(\lambda_3 + \eta)(-\varepsilon + \lambda_3 + \eta)}\left(\frac{e^{-\varepsilon\tau}}{-\varepsilon} + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)}\right) - \frac{\varepsilon\eta\, e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda_3 + \eta)}\left(\frac{1}{-\varepsilon} + \frac{1}{(\lambda_3 + \eta)}\right) \right)$$
$$+ \left( \frac{\lambda_3\varepsilon}{\lambda_3 + \eta} \left( \frac{\lambda_2 v}{\lambda_3(\varepsilon - v)}\left(1 + \frac{e^{-\lambda_3(\varepsilon-v)\tau}}{\lambda_3(\varepsilon - v)}\right) \right) - \frac{\lambda_3\varepsilon\, e^{-(\lambda_3+\eta)\tau}}{\lambda_3 + \eta} \left( \frac{\lambda_2 v}{\lambda_3(\varepsilon - v)}\left(1 + \frac{1}{\lambda_3(\varepsilon - v)}\right) \right) \right) \tag{30}$$
$$- \left( \frac{e^{-\varepsilon\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)}\left(\frac{e^{-\varepsilon\tau}}{\varepsilon} - \frac{e^{-\lambda_3(\varepsilon-v)\tau}}{\lambda_3(\varepsilon - v)}\right) + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)}\left(\frac{1}{-\varepsilon} + \frac{1}{\lambda_3(\varepsilon - v)}\right) \right)$$
$$- \left( \frac{\varepsilon}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)}\left(\frac{e^{-\varepsilon\tau}}{-\varepsilon} + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)}\right) - \frac{\varepsilon\, e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)}\left(\frac{1}{-\varepsilon} + \frac{1}{\lambda 3 + \eta}\right) \right)$$

The analytical expression of dimensionless concentration of the product $w(\tau)$ can be obtained as

$$w(t)=\frac{\varepsilon\lambda_2}{(-\varepsilon+\lambda_3+\eta)}\left[\frac{e^{-\varepsilon t}+e^{-\lambda_3\varepsilon t}}{-\varepsilon+\lambda_3\varepsilon}-\left(\frac{e^{-(\lambda_3+\eta)t}+e^{-\lambda_3\varepsilon t}}{-(\lambda_3+\eta)+\lambda_3\varepsilon}\right)\right]$$

$$-\left[\begin{array}{l}\frac{\lambda_2\varepsilon}{\lambda_3\varepsilon(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{e^{-\varepsilon\tau}}{\varepsilon^2}-\frac{e^{-\lambda_3\varepsilon\tau}}{(\lambda_3\varepsilon)^2}\right)-\frac{1}{-(\lambda_3+\eta)+\lambda_3\varepsilon}\left(\frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)^2}-\frac{e^{-\lambda_3\varepsilon\tau}}{(\lambda_3\varepsilon)^2}\right)\\ -\frac{\lambda_2\varepsilon\,e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{1}{\varepsilon^2}-\frac{1}{(\lambda_3\varepsilon)^2}\right)-\frac{1}{-(\lambda_3+\eta)+\lambda_3\varepsilon}\left(\frac{1}{(\lambda_3+\eta)^2}-\frac{1}{(\lambda_3\varepsilon)^2}\right)\end{array}\right]$$

$$+\frac{\lambda_2\varepsilon}{(\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left[\left(\frac{-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)}\right)-e^{-\lambda_3\varepsilon\tau}\left(\frac{-1}{\varepsilon}+\frac{1}{(\lambda_3+\eta)}\right)\right]$$

$$-\left[\begin{array}{l}\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-e^{-B\tau}}{(\lambda_3+\eta)}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)\right\}\\ -e^{-\lambda_3\varepsilon\tau}\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{-1}{\varepsilon}+\frac{1}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-1}{(\lambda_3+\eta)}+\frac{1}{\lambda_3\varepsilon}\right)\right\}\end{array}\right]$$

$$+\left[\begin{array}{l}\frac{1}{(-\varepsilon+\lambda_3+\eta)}\left(\frac{-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta}\right)\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(-\frac{e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-e^{-B\tau}}{(\lambda_3+\eta)}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)\right\}\\ -\frac{e^{-\lambda_3\varepsilon\tau}}{(-\varepsilon+\lambda_3+\eta)}\left(\frac{-1}{\varepsilon}+\frac{1}{(\lambda_3+\eta}\right)\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{-1}{\varepsilon}+\frac{1}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-1}{(\lambda_3+\eta)}+\frac{1}{\lambda_3\varepsilon}\right)\right\}\end{array}\right]$$

(31)

## III. NUMERICAL SIMULATION

The non-linear differential equations (25-27) for the given initial – boundary conditions are being solved numerically. The function pdex, in MATLAB software which is a function of solving the initial – boundary value problems for non-linear ordinary differential equations is used to solve this equation. Dimensionless concentration of substrate $u(\tau)$, enzyme-substrate $v(\tau)$ and product $w(\tau)$ are compared with stimulation results for various dimensionless time$\tau$ are kinetic parameters using Eqns. (29-31) in Fig. 1. Satisfactory aggrement is noted. Matlab programme is also given in Appendix 3.

## IV. DISCUSSION

Equations (29-31) are the new and simple analytical expressions of concentrations of substrate, enzyme-substrate and product for all values of parameter. Fig. 2 represent dimensionless concentration of substrate $u(\tau)$ versus dimensionless time $\tau$ for various values of parameter using equation (29). From the figure it is inferd that the concentration of substrate decreases gradually from its initial value and reaches the steady state value for all values of parameter $\lambda_1, \lambda_2, \lambda_3$ and $\varepsilon$. This due to consumption of substrate in the enzyme reaction. The variation of concentration of the enzyme substrate with respect to time for various values of parameter is represented in Fig. 3. From the figure it is observed that the enzyme-substrate increases absurdly and reaches the maximum value when time $0.1<\tau<0.2$ and then decreases slowly. Fig. 4 represent the dimensionless concentration of product $w(\tau)$ versus dimensionless time $\tau$ and for various values of all other parameter. From this figure it is noted that the concentration of the product increases when the dimensionless parameter $\varepsilon$, $\eta$ and $\lambda_1, \lambda_2, \lambda_3$ decreases.

## V. CONCLUSION

Approximate analytical solutions to the non-linear reaction equations are presented using variational iterational method. A simple, straight forward and a application of new method of estimating the concerntrations of substrate, enzyme substrate and product 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.

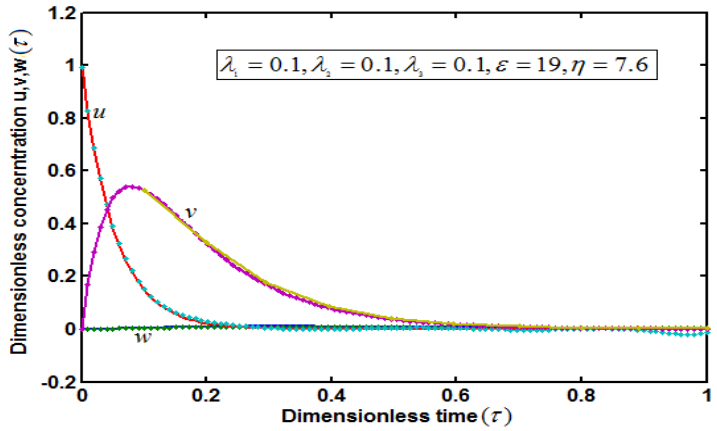
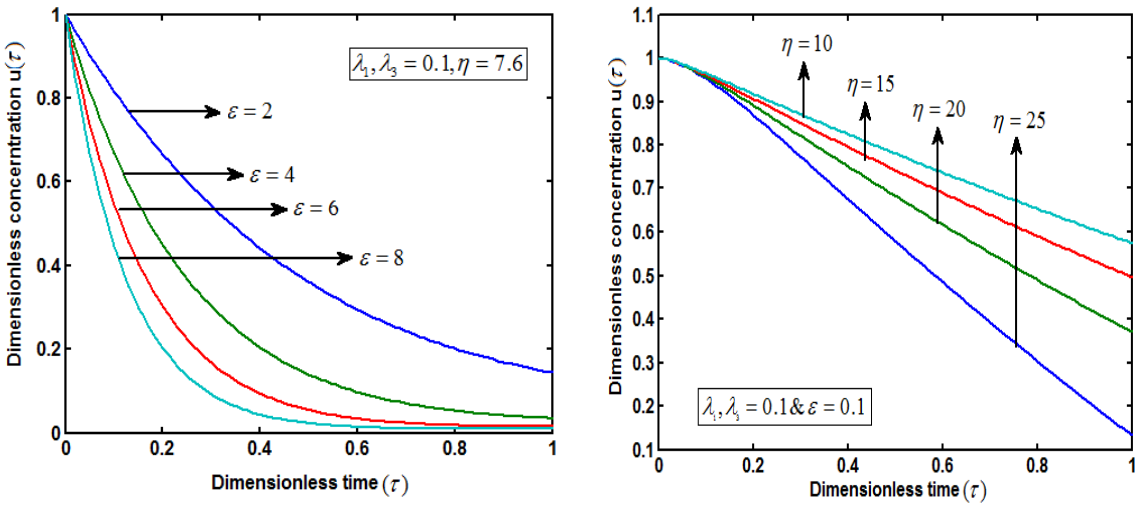



**Fig. 1.** Plot of dimensionless concentration of $u(\tau), v(\tau)$ and $w(\tau)$ versus dimensionless time $\tau$ for some fixed values of parameters $\lambda_1 = 0.1, \lambda_2 = 0.1, \lambda_3 = 0.1, \varepsilon = 19, \eta = 7.6$ using Eqns. (29)- (31). The key the graph:(_) represents the Eqns. (29)- (31) and (…) represents the numerical results.

(a) (b)




(c)

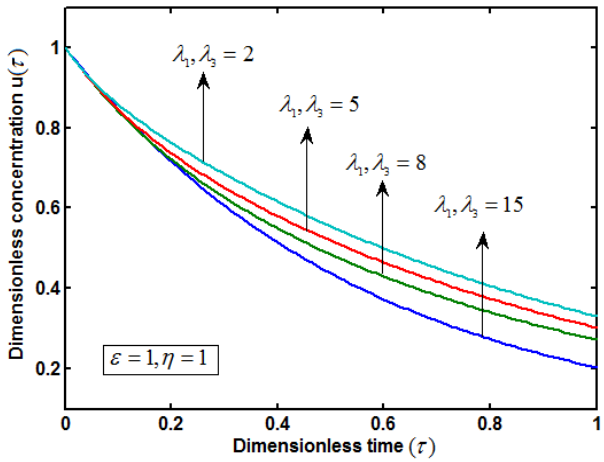



**Fig. 2.** Plot of dimensionless concentration of $u(\tau)$ versus dimensionless time $\tau$ for various values of the parameter (a) $\varepsilon$ , (b) $\eta$ , (c) $\lambda_2$ , $\lambda_3$ and for some fixed values of parameters $(a)\lambda_1, \lambda_3 = 0.1, \eta = 7.6$ $(b)\lambda_1, \lambda_3 = 0.1, \varepsilon = 0.1$ $(c)\varepsilon = 1, \eta = 1$ using Eqn. (29).

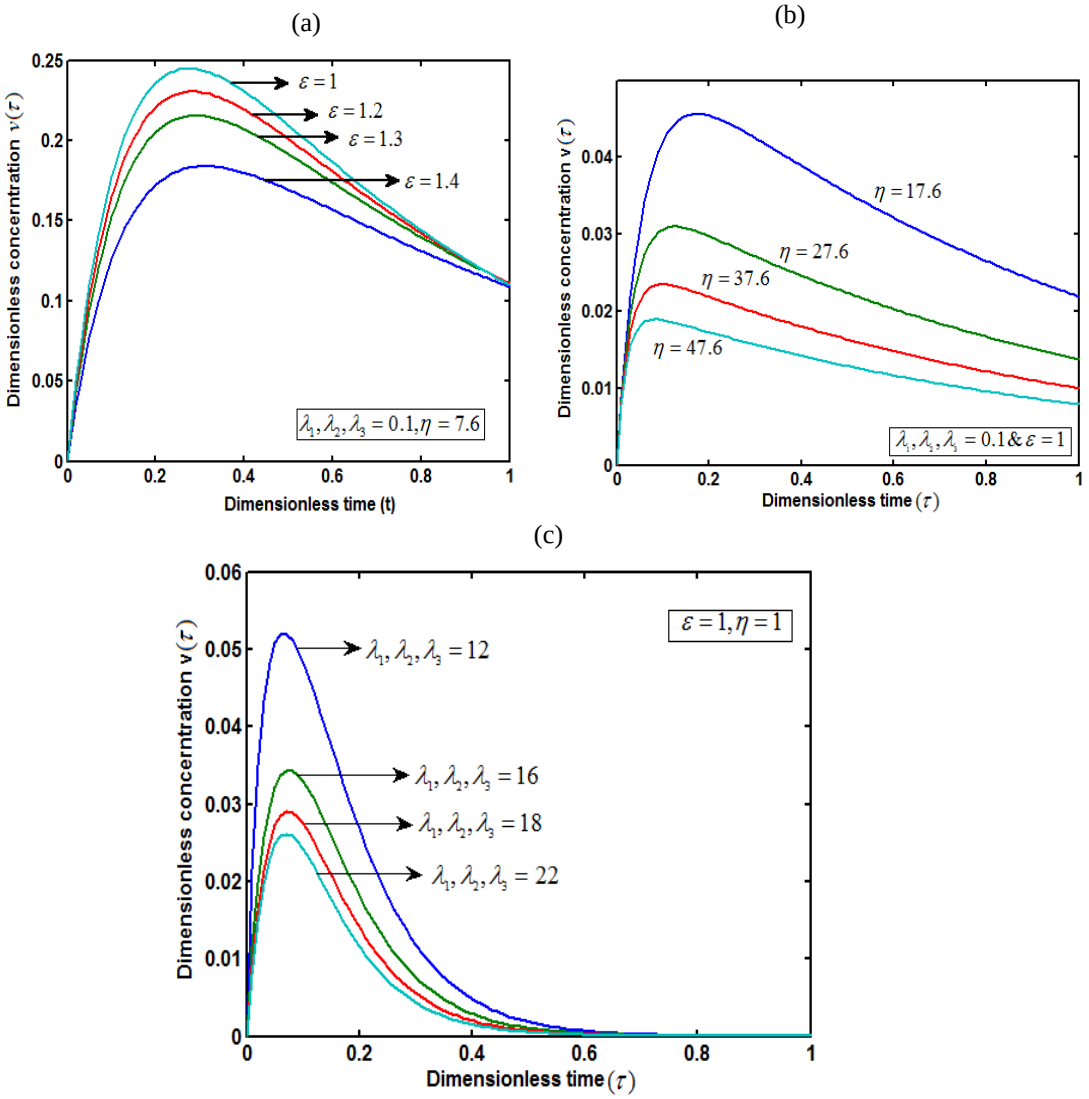
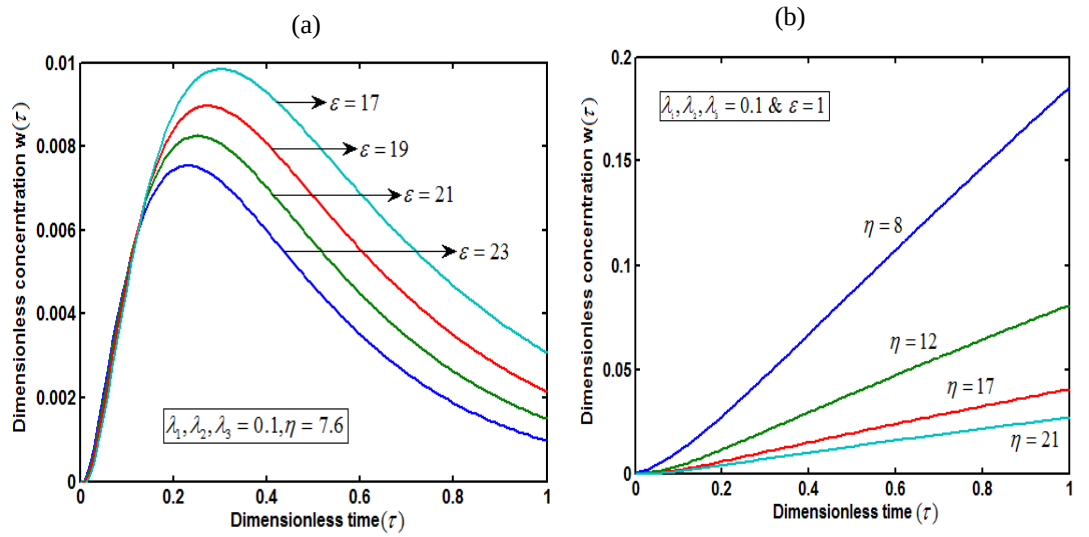



**Fig. 3.** Plot of dimensionless concentration of $v(\tau)$ versus dimensionless time $\tau$ for various values of the parameter (a) $\varepsilon$ , (b) $\eta$ , (c) $\lambda_1, \lambda_2, \lambda_3$ ,and for some fixed values of parameters $(a)\lambda_1, \lambda_2, \lambda_3 = 0.1, \eta = 7.6,\ (b)\lambda_1, \lambda_2, \lambda_3 = 0.1, \varepsilon = 1,\ (c)\varepsilon = 1, \eta = 1$ using Eqn. (30).



(c)

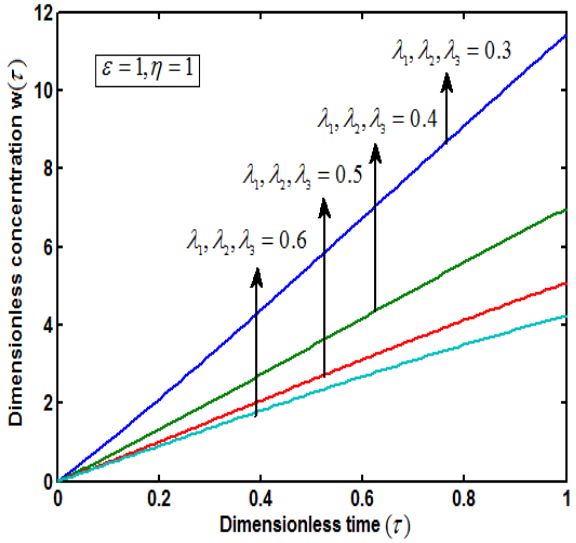



**Fig. 4** Plot of dimensionless concentration of product $w(\tau)$ versus dimensionless time $\tau$ for various values of the parameter (a) $\varepsilon$ , (b) $\eta$ , (c) $\lambda_1, \lambda_2, \lambda_3$ ,and for some fixed values of parameters $(a)\lambda_1, \lambda_2, \lambda_3 = 0.1, \eta = 7.6,\ (b)\lambda_1, \lambda_2, \lambda_3 = 0.1, \varepsilon = 1,\ (c)\varepsilon = 1, \eta = 1$ using Eqn. (31).

**Appendix 1: Basic Ideas of variational iteration method**

To illustrate the basic concepts of variational iteration method (VIM), we consider the following nonlinear partial differential equation:

L[u(x)]+N[u(x)]=g(x) (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:

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

where $\lambda$ is a general Lagrange multiplier which can be identified optimally via variation theory, $u_n$ is the nth approximate solution, and $\tilde{u}_n$ denotes a restricted variation,

i.e., $\delta\tilde{u}_n = 0$. (A3)

**Appendix 2: Analytical solution of nonlinear equation using variation iteration method**

The equation (25) is

$$\frac{du}{dt} + \varepsilon u - uv - \lambda_1 v = 0 \quad \text{(A4)}$$

The lagrange multiplier $\mu_1 = e^{\varepsilon(s-\tau)}$ (A5)

General form of VIM is

$$u_{n+1} = u_n - \int_0^\tau \mu_1 \left[u'_n + \varepsilon u_n - u_n v_n - \lambda_1 v_n\right] ds \quad \text{(A6)}$$

Solving the above equations and using the boundary conditions, we have

$$u_0(\tau) = e^{-\varepsilon\tau} \quad \text{(A7)}$$

$$u_1(\tau) = \left[ \frac{e^{-\varepsilon\tau}}{(-\varepsilon + \lambda_3 + \eta)\varepsilon} \left\{ \frac{e^{-\varepsilon\tau}}{\varepsilon} - \frac{e^{-(\lambda_{3+\eta})\tau}}{(\lambda_3 + \eta)} \right\} + \frac{e^{-\varepsilon\tau}}{\varepsilon(-\varepsilon + \lambda_3 + \eta)} \left\{ -\frac{1}{\varepsilon} + \frac{1}{(\lambda_3 + \eta)} \right\} \right]$$

$$+ \left[ \frac{\lambda_1}{-\varepsilon + \lambda_3 + \eta} \left\{ \frac{-e^{-\varepsilon\tau}}{\varepsilon} + \frac{e^{-(\lambda_{3+\eta})\tau}}{(\lambda_3 + \eta)} \right\} + \frac{\lambda_1 e^{-\varepsilon\tau}}{-\varepsilon + \lambda_3 + \eta} \left\{ \frac{-1}{\varepsilon} + \frac{1}{(\lambda_3 + \eta)} \right\} \right] \quad \text{(A8)}$$

The equation (26) is given by

$$\frac{dv}{dt} - \varepsilon u + \eta v - \lambda_3 \varepsilon w + uv + \lambda_3 v = 0 \quad \text{(A9)}$$

The Lagrange multiplier is, $\mu_2 = e^{(\lambda_3+\eta)(s-\tau)}$ (A10)

General form of VIM is

$$v_{n+1} = v_n(\tau) - \int_0^\tau \mu_2 \left[ v'_n(s) - \varepsilon u_n(s) + \eta v_n(s) - \lambda_3 \varepsilon w_n(s) + u_n(s) v_n(s) + \lambda_3 v_n(s) \right] ds \quad \text{(A11)}$$

Solving the above equations and using the boundary conditions, we have

$$v_0(\tau) = \frac{\varepsilon}{-\varepsilon + \lambda 3 + \eta} (e^{-\varepsilon\tau} - e^{-\lambda_3(\varepsilon - v)\tau}) \quad \text{(A12)}$$

$$\begin{aligned} v_1(\tau) = &- \left( \frac{\varepsilon}{(\lambda_3 + \eta)(-\varepsilon + \lambda_3 + \eta)} (e^{-\varepsilon\tau} - e^{-(\lambda_3+\eta)\tau}) \right) + \left( \frac{-e^{-\varepsilon\tau}}{(\lambda_3+\eta)} + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)} \right) \\ &+ \left( \frac{\varepsilon\eta}{(\lambda_3 + \eta)(-\varepsilon + \lambda_3 + \eta)} \left( \frac{e^{-\varepsilon\tau}}{-\varepsilon} + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)} \right) - \frac{\varepsilon\eta\, e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda_3 + \eta)} \left( \frac{1}{-\varepsilon} + \frac{1}{(\lambda_3+\eta)} \right) \right) \\ &+ \left( \frac{\lambda_3\varepsilon}{\lambda_3 + \eta} \left( \frac{\lambda_2 v}{\lambda_3(\varepsilon - v)} \left( 1 + \frac{e^{-\lambda_3(\varepsilon-v)\tau}}{\lambda_3(\varepsilon - v)} \right) \right) - \frac{\lambda_3\varepsilon\, e^{-(\lambda_3+\eta)\tau}}{\lambda_3 + \eta} \left( \frac{\lambda_2 v}{\lambda_3(\varepsilon - v)} \left( 1 + \frac{1}{\lambda_3(\varepsilon - v)} \right) \right) \right) \\ &- \left( \frac{e^{-\varepsilon\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)} \left( \frac{e^{-\varepsilon\tau}}{\varepsilon} - \frac{e^{-\lambda_3(\varepsilon-v)\tau}}{\lambda_3(\varepsilon - v)} \right) + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)} \left( \frac{1}{-\varepsilon} + \frac{1}{\lambda_3(\varepsilon - v)} \right) \right) \\ &- \left( \frac{\varepsilon}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)} \left( \frac{e^{-\varepsilon\tau}}{-\varepsilon} + \frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)} \right) - \frac{\varepsilon\, e^{-(\lambda_3+\eta)\tau}}{(\lambda_3 + \eta)(-\varepsilon + \lambda 3 + \eta)} \left( \frac{1}{-\varepsilon} + \frac{1}{\lambda 3 + \eta} \right) \right) \end{aligned} \quad \text{(A13)}$$

The equation (27) is

$$\frac{dw}{dt} - \lambda_2 v + \lambda_3 \varepsilon w - \lambda_3 v w = 0 \quad \text{(A14)}$$

The lagrange multiplier is, $\mu_3 = e^{\lambda_3(s-\tau)}$ (A15)

General form of VIM is

$$w_{n+1} = w_n - \int_0^\tau \mu_3 \left[ w'_n(s) - \lambda_2 v_n(s) + \lambda_3 \varepsilon w_n(s) - \lambda_3 v_n(s) w_n(s) \right] ds \quad \text{(A16)}$$

Solving the above equations and using the boundary conditions, we have

$$w_0(\tau) = \frac{\varepsilon\lambda_2}{(-\varepsilon + \lambda_3 + \eta)} \left[ \frac{e^{-\varepsilon t} + e^{-\lambda_3\varepsilon t}}{-\varepsilon + \lambda_3\varepsilon} - \left( \frac{e^{-(\lambda_3+\eta)t} + e^{-\lambda_3\varepsilon t}}{-(\lambda_3 + \eta) + \lambda_3\varepsilon} \right) \right] \quad \text{(A17)}$$

$$w_1(t) = -\begin{bmatrix} \frac{\lambda_2\varepsilon}{\lambda_3\varepsilon(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{e^{-\varepsilon\tau}}{\varepsilon^2}-\frac{e^{-\lambda_3\varepsilon\tau}}{(\lambda_3\varepsilon)^2}\right)-\frac{1}{-(\lambda_3+\eta)+\lambda_3\varepsilon}\left(\frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)^2}-\frac{e^{-\lambda_3\varepsilon\tau}}{(\lambda_3\varepsilon)^2}\right) \\ -\frac{\lambda_2\varepsilon\, e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{1}{\varepsilon^2}-\frac{1}{(\lambda_3\varepsilon)^2}\right)-\frac{1}{-(\lambda_3+\eta)+\lambda_3\varepsilon}\left(\frac{1}{(\lambda_3+\eta)^2}-\frac{1}{(\lambda_3\varepsilon)^2}\right) \end{bmatrix}$$

$$+\frac{\lambda_2\varepsilon}{(\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left[\left(\frac{-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta)}\right)-e^{-\lambda_3\varepsilon\tau}\left(\frac{-1}{\varepsilon}+\frac{1}{(\lambda_3+\eta)}\right)\right]$$

$$-\begin{bmatrix} \left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-e^{-B\tau}}{(\lambda_3+\eta)}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)\right\} \\ -e^{-\lambda_3\varepsilon\tau}\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{-1}{\varepsilon}+\frac{1}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-1}{(\lambda_3+\eta)}+\frac{1}{\lambda_3\varepsilon}\right)\right\} \end{bmatrix}$$

$$+\begin{bmatrix} \frac{1}{(-\varepsilon+\lambda_3+\eta)}\left(\frac{-e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-(\lambda_3+\eta)\tau}}{(\lambda_3+\eta}\right)\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(-\frac{e^{-\varepsilon\tau}}{\varepsilon}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-e^{-B\tau}}{(\lambda_3+\eta)}+\frac{e^{-\lambda_3\varepsilon\tau}}{\lambda_3\varepsilon}\right)\right\} \\ -\frac{e^{-\lambda_3\varepsilon\tau}}{(-\varepsilon+\lambda_3+\eta)}\left(\frac{-1}{\varepsilon}+\frac{1}{(\lambda_3+\eta}\right)\left\{\frac{\lambda_2\varepsilon}{(-\varepsilon+\lambda_3\varepsilon)(-\varepsilon+\lambda_3+\eta)}\left(\frac{-1}{\varepsilon}+\frac{1}{\lambda_3\varepsilon}\right)-\frac{1}{(-(\lambda_3+\eta)+\lambda_3\varepsilon)}\left(\frac{-1}{(\lambda_3+\eta)}+\frac{1}{\lambda_3\varepsilon}\right)\right\} \end{bmatrix} \quad \text{(A18)}$$

By considering two iteration

$u(\tau) \approx u_0(\tau) + u_1(\tau)$,

$v(\tau) \approx v_0(\tau) + v_1(\tau)$,

$w(\tau) \approx w_0(\tau) + w_1(\tau)$.

we can obtain the equations (29) - (31) in the text.

**Appendix 3 scilab/Matlab program for the numerical solution of equations (25) – (27)**

```
function graphmain3
options= odeset('RelTol',1e-6,'stats','on');
X0=[1;0;0];
tspan=[0,1];
tic
[t,X]=ode45(@TestFunction,tspan,X0,options);
toc
figure
hold on
plot(t,X(:,1),'*');
plot(t,X(:,2),'.');
plot(t,X(:,3),'+');
legend('x1','x2','x3')
ylabel('x')
xlabel('t')
return
function [dx_dt]=TestFunction(t,x)
e=1,c3=0.1,n=1,c1=0.1,c2=0.001
,c2=0.001;
dx_dt(1)=-e*x(1)+x(1)*x(2)+c1*x(2);
dx_dt(2)=e*x(1)-n*x(2)+c3*e*x(3)-x(1)*x(2)-c3*x(2);
dx_dt(3)=c2*x(2)-c3*e*x(3)+c3*x(2)*x(3);
dx_dt = dx_dt';
return
```

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