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Iterative approximate solutions of kinetic equations for reversible enzyme reactions

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ABSTRACT

We study kinetic models of reversible enzyme reactions and compare two techniques for analytic approximate solutions of the model. Analytic approximate solutions of non-linear reaction equations for reversible enzyme reactions are calculated using the Homotopy Perturbation Method (HPM) and the Simple Iteration Method (SIM). The results of the approximations are similar. The Matlab programs are included in appendices.

Keywords: Enzyme Kinetics; Homotopy Perturbation Method; Iteration Method; Michaelis-Menten Kinetics; Quasi-Steady State Approximation

1. INTRODUCTION

The variety of chemical reactions in a living organism is carried out by enzymes. It appears that the rate of chemical reactions (both forward and backward) is accelerated by enzymes.

They are essential because many chemical reactions occur without the activity of enzymes. Such reactions are linked withan enzyme's active site, and they become a product after a series of stages. These stages are known as the enzymatic mechanism. There are two types of mechanisms, single substrate and multiple substrate mechanisms [1-4]. An important branch of enzymology is enzyme kinetics which is used to study the rate of chemical reactions. Differential equations are used to characterize the enzyme kinetics based on some principles of chemical kinetics [5-8].

The single enzyme reaction is one of the most powerful kinds of kinetic reaction. Simply put, this enzyme reaction is defined as follows:

$$E + S \underset{k_2}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_3} E + P \qquad (1)$$

where the concentrations of enzyme, substrate, enzyme-substrate complex and product are defined by $[E]$, $[S]$, $[ES]$ and $[P]$, respectively. Also, k_1, k_2 and k_3 represent the reaction rate constants. By using the idea of mass action, we can describe the reaction **Eq.1** in terms of a system of non-linear ordinary differential equations [3].

There are varieties of possible simplifications for the system (**Eq.1**) to describe analytic approximate solutions of the system. One of the most common approaches to simplify this system is the use of quasi-steady state approxmation (QSSA). The quasi-steady state assumptions occur as fundamental assumptions for enzyme kinetics, and the history of this subject began 80 years ago. It plays a key role with regard to the analysis of the enzyme kinetic equations [5]. Another simplification is the Michaelis-Menten equation created in 1913which pointed that the enzyme reaction (**Eq.1**) should be $k_2 \gg k_3$, therefore $\frac{[E][S]}{[ES]} = \frac{k_2}{k_1}$. It means that there is equilibrium between $[E]$, $[S]$ and $[ES]$ to produce $[P]$ and $[E]$. In 1925, Briggs and Haldane proposed that the Michaelis-Menten assumption is not always applied. They said that it should be replaced by the assumption that $[ES]$ is present, not necessarily at equilibrium, but in a steady state under condition $[S_0] \gg [E_0]$.This means that the concentrations of $[ES]$ occur as a steady state. This is known as the steady state assumption (SSA) or is sometimes called the quasi-steady state approximation (QSSA), or pseudo-steady sate approximation [9]. The first description of QSS was given by Briggs and Haldane in 1925 [10]. They described the simplest enzyme reaction in **Eq.1**, and pointed out the total concentration of enzyme $[E]$, where $[E]_{tot} = [E] + [ES]$ is a tiny value in comparison with the concentration of substrate $[S]$. Also, they have shown the term of $\frac{d[ES]}{dt}$ is negligible compared to $\frac{d[S]}{dt}$ and $\frac{d[P]}{dt}$. As a result, they found the Michaelis-Menten

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equation, which is a differential equation used to describe the rate of enzymatic reactions. The classical Michaelis-Menten equation is defined as,
$k_1[E][S]=(k_2+k_3)[ES]$, or

$$[ES]=\frac{[E][S]}{k_M+[S]},\frac{\mathrm{d}[P]}{\mathrm{d}t}=k_2[ES]=\frac{k_3[E][S]}{k_M+[S]} \quad (2)$$

where $k_M=\frac{k_2+k_3}{k_1}$ is the Michaelis-Menten constant (for more details see [11]). The purpose of this work is to derive asymptotic approximate expressions for the substrate, product, enzyme and enzyme-substrate concentrations for **Eq.3** by using (HPM) and (SIM), and to point out the similarities and differences between the methods of (HPM) and (SIM) for all values of dimensionless reaction diffusion parameters $\varepsilon,\lambda,\alpha$ and k. Another aim of this project is to find out the appropriate iteration in (SIM) compared to (HPM).

2. MATHEMATICAL FORMULATION

The Michaelis-Menten **Eq.1** was applied by Kuhn in 1924 [12] to several cases of enzyme knetics. The model of biochemical reaction was developed by Briggs and Haldane in 1925 [3]. The model of an enzyme action considers a reaction that includes a substrate [*S*] which binds an enzyme [*E*] reversibly to asubstrate-enzyme [*ES*]. The substrate-enzyme leads reversibly to product [*P*] and enzyme [*E*]. This mechanism is often written as follows:

$$E+S\underset{k_2}{\overset{k_1}{\rightleftarrows}}ES\underset{k_4}{\overset{k_3}{\rightleftarrows}}P+E \quad (3)$$

The mechanism shows the binding of substrate [*S*] and the release of product [*P*] where the free enzyme is [*E*] and the enzyme-substrate complex is [*ES*]. In addition, k_1,k_2,k_3 and k_4 denote the rates of reaction. It is clear from **Eq.3** that substrate binding and product are reversible. The concentration of the reactants in **Eq.3** is denoted by lower case letters:

$$e=[E],s=[S],c=[ES],p=[P] \quad (4)$$

The time of evolution of **Eqs.3** and **4** are found by the law of mass action to obtain the set of system of the following non-linear reaction equations:

$$\frac{\mathrm{d}s}{\mathrm{d}t}=-k_1es+k_2c \quad (5)$$

$$\frac{\mathrm{d}e}{\mathrm{d}t}=-k_1es+(k_2+k_3)c-k_4pe \quad (6)$$

$$\frac{\mathrm{d}c}{\mathrm{d}t}=k_1es-(k_2+k_3)c+k_4pe \quad (7)$$

$$\frac{\mathrm{d}p}{\mathrm{d}t}=k_3c-k_4pe \quad (8)$$

when the initial conditions at $t=0$ are given by

$$e(0)=e_0,s(0)=s_0,c(0)=c_0,p(0)=p_0 \quad (9)$$

Adding **Eqs.6** and **7**, and using initial conditions **Eq.9**, we obtain

$$e+c=e_0 \quad (10)$$

Also, adding **Eqs.5**, **7** and **8**, and using initial conditions **Eq.9**, we get

$$s+c+p=s_0 \quad (11)$$

By using **Eqs.10** and **11**, the system of ordinary differential equations (**Eqs.5-8**) reduce to only two variables, *s* and *c*, as follows:

$$\frac{\mathrm{d}s}{\mathrm{d}t}=-k_1e_0s+(k_1s+k_2)c \quad (12)$$

$$\frac{\mathrm{d}c}{\mathrm{d}t}=k_1e_0s+(k_1s+k_2+k_3)c+k_4(e_0-c)(s_0-s-c) \quad (13)$$

with initial conditions $s(0)=s_0,c(0)=c_0$. By introducing the following parameters:

$$\tau=\frac{k_1e_0t}{\varepsilon},u(\tau)=\frac{s(t)}{s_0},v(\tau)=\frac{c(t)}{e_0},w(\tau)=\frac{p(t)}{e_0},$$

$$E(\tau)=\frac{e(t)}{e_0},\lambda=\frac{k_3}{k_1s_0},k=\frac{k_2+k_3}{k_1s_0},\varepsilon=\frac{e_0}{s_0},\alpha=\frac{k_4}{k_1}, \quad (14)$$

$m=\lambda+\alpha\varepsilon+\alpha.$

We use the dimensionless technique to reduce the number of parameters for the system of **Eqs.12** and **13** and the initial conditions **Eq.9**. This can be represented in dimensionless form as follows:

$$\frac{\mathrm{d}u}{\mathrm{d}\tau}=-\varepsilon u+\varepsilon(u+k-\lambda)v \quad (15)$$

$$\frac{\mathrm{d}v}{\mathrm{d}\tau}=u-(u+k)v+\alpha(1-v)(1-u-\varepsilon v) \quad (16)$$

$$\frac{\mathrm{d}w}{\mathrm{d}\tau}=\alpha u-\alpha(uv+\varepsilon v^2+1) \quad (17)$$

$$u(0)=1,v(0)=0,w(0)=0. \quad (18)$$

In this paper, we estimate the analytic approximate solution for a system of non-linear ODE (**Eqs.15-18)**, by using the methods of (HPM) and (SIM).

3. ANALYTICAL APPROXIMATE SOLUTION USING THE HOMOTOPY PERTURBATION METHOD

The basic idea of the Homotopy-Perturbation Method (HPM) is defined in this section. It is then applied to find the approximate solution of the problem in **Eqs.15-18**. It is considered from the following function:

$$A(x)-f(r)=0,\ r\in\Omega \quad (19)$$

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with the boundary conditions

$$B\left(x,\frac{\partial x}{\partial n}\right)=0,\ \ r\in\Gamma \tag{20}$$

where $A, B, f(r)$ and Γ are general differential operators, boundary operators, a known analytic function, and the boundary of the domain Ω, respectively [13]. The function A consists of linear part L and non-linear part N. So, the **Eq.19** can be written as:

$$L(x)+N(x)-f(x)=0 \tag{21}$$

The Homotopy function is defined by $z(r,q):\Omega\times[0,1]\to R,$ which satisfies

$$H(z,q)=(1-q)\left(L(z)-L(x_0)\right)+q\left(A(z)-f(r)\right)=0, \tag{22}$$

$q\in[0,1], r\in\Omega,$ or

$$H(z,q)=L(z)-L(x_0)+qL(x_0)+q\left(N(x)-f(r)\right) \tag{23}$$

where $q\in[0,1]$ is an embedding parameter. At the same time, x_0 is an initial approximation of **Eq.19**, which satisfies **Eq.20**. Basically, from **Eqs.22** and **23** we can obtain:

$$H(z,0)=L(z)-L(x_0)=0, \tag{24}$$

$$H(z,1)=A(z)-f(r)=0, \tag{25}$$

Changing $z(r,q)$ from x_0 to $x(r)$ depends on the values of q from zero to unity. It is called deformation in the field of topology. At the same time, $L(z)-L(x_0)$ and $A(z)-f(r)$ are called Homotopy. We use q as a small parameter initially, and we defined the **Eqs.22** and **23** as a power series in q:

$$z=z_0+qz_1+q^2z_2+\cdots \tag{26}$$

Let $q=1$ to get the approximate solution of **Eq.19**

$$x=\lim_{q\to1}z=z_0+z_1+z_2+\cdots \tag{27}$$

Thus, HPM includes a combination of the perturbation method and the Homotopy method. **Eqs.15-17** can be solved analytically in a simple and closed form by using the Homotopy Perturbation Method (HPM) (Ref Appendix A). So, the approximate solutions of the system of non-linear differential equations (**Eqs.15** and **16**) become: (see **Eqs.28** and **29**).

The analytic expressions of the substrate $u(\tau)$ and enzyme substrate $v(\tau)$ concentrations can be represented in **Eqs.28** and **29**. The dimensionless concentration of enzyme E can be obtained from **Eqs.10** and **14** as follows:

$$E(\tau)=\frac{e(t)}{e_0}=1-v(\tau) \tag{30}$$

The dimensionless concentration of the product w is obtained either by **Eq.17** as follows:

$$w(\tau)=\int_0^\tau\left(\alpha\left(u(t)-u(t)v(t)-\varepsilon v^2(t)-1\right)+mv(t)\right)\mathrm{d}t \tag{31}$$

or we can use **Eqs.11** and **14** to find the concentration of the product w as follows:

$$w(\tau)=\frac{1-u(\tau)-\varepsilon v(\tau)}{\varepsilon}. \tag{32}$$

The simple analytic approximate solution form of the concentrations of enzyme $E(\tau)$ and product $w(\tau)$ for all values of parameters $\varepsilon,\lambda,\alpha$ and k, are represented in **Eqs.30-32**.

4. SIMPLE ITERATION METHOD

In this section, we use a simple technique to find the analytic approximate solution for the system of **Eqs.15** and **16**. We introduce this method by rewriting **Eqs.15** and **16** as follows:

$$\frac{\mathrm{d}u}{\mathrm{d}\tau}=-\varepsilon u+\varepsilon(k-\lambda)v+\varepsilon uv \tag{33}$$

$$\frac{\mathrm{d}v}{\mathrm{d}\tau}=(1-\alpha)u-(k+\alpha+\alpha\varepsilon)v-(1-\alpha)uv+\alpha\varepsilon v^2+\alpha \tag{34}$$

$$u(\tau)=2\mathrm{e}^{-\varepsilon\tau}+\left(\frac{ab}{c-\varepsilon}+\frac{\alpha\varepsilon}{c}\right)\tau\mathrm{e}^{-\varepsilon\tau}+\frac{abc-a\alpha\varepsilon+a\alpha c}{c(\varepsilon-c)^2}\mathrm{e}^{-c\tau}+\frac{\alpha\varepsilon^2-cb\varepsilon-c\alpha\varepsilon}{c^2(\varepsilon-c)}\mathrm{e}^{(-\varepsilon-c)\tau}+\frac{a\alpha}{c\varepsilon}+\frac{b}{\varepsilon-c}\mathrm{e}^{-2\varepsilon\tau}$$
$$+\left(-1+\frac{a\alpha\varepsilon-abc-ac\alpha}{c(\varepsilon-c)^2}-\frac{a\alpha}{c\varepsilon}+\frac{b}{\varepsilon-c}+\frac{-\alpha\varepsilon^2+bc\varepsilon+c\alpha\varepsilon}{c^2(\varepsilon-c)}\right)\mathrm{e}^{-\varepsilon\tau} \tag{28}$$

$$v(\tau)=\frac{b}{c-\varepsilon}\mathrm{e}^{-\varepsilon\tau}+\frac{bc-\alpha\varepsilon+c\alpha}{c(\varepsilon-c)}\mathrm{e}^{-c\tau}+\left(\frac{b}{c-\varepsilon}+\frac{b\alpha}{c(c-\varepsilon)}\right)\mathrm{e}^{-\varepsilon\tau}+\frac{b^2}{(c-\varepsilon)(c-2\varepsilon)}\mathrm{e}^{-2\varepsilon\tau}+\frac{\alpha}{c}+\frac{b\alpha\varepsilon-cb^2-bc\alpha}{c\varepsilon(\varepsilon-c)}\mathrm{e}^{(-\varepsilon-c)\tau}$$
$$+\left(\frac{b}{\varepsilon-c}+\frac{b^2}{(\varepsilon-c)(c-2\varepsilon)}+\frac{-b\alpha\varepsilon+cb^2+bc\alpha}{c\varepsilon(\varepsilon-c)}+\frac{b\alpha}{c(\varepsilon-c)}\right)\mathrm{e}^{-c\tau} \tag{29}$$

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Let $a=\varepsilon(k-\lambda), b=(1-\alpha)$ and $c=k+\alpha+\alpha\varepsilon$, then the **Eqs.33** and **34** can be written as:

$$\begin{pmatrix} u'_{n+1} \\ v'_{n+1} \end{pmatrix} = A\begin{pmatrix} u_{n+1} \\ v_{n+1} \end{pmatrix} + G(u_n, v_n), \text{ for } n=0,1,2,\cdots \quad (35)$$

where $G(u_n,v_n)=\begin{pmatrix} \varepsilon u_n v_n \\ -bu_n v_n + \alpha\varepsilon u_n^2 + \alpha \end{pmatrix}$ is a non-linear part of the system (**Eq.35**), and $A=\begin{pmatrix} -\varepsilon & a \\ b & -c \end{pmatrix}$ is a matrix of the linear part of the system (**Eq.35**). To evaluatean approximate solution of **Eq.35** with the initial conditions implied by **Eq.18**, we introduce the following steps to approach the approximate solution.

Step 1. For $n=0, u_0(\tau)=1, v_0(\tau)=0$ and, if possible suppose that $\alpha \to 0$ (just in this step). It means we assume the non-linear part of **Eq.35** approaches zero. Consequently, we obtain the following system:

$$\begin{pmatrix} u'_1 \\ v'_1 \end{pmatrix} = A\begin{pmatrix} u_1 \\ v_1 \end{pmatrix} \quad (36)$$

We can solve the system of ordinary differential **Eq.36** analytically [14]. So, the solution of **Eq.36** with initial conditions (**Eq.18**) is

$$\begin{pmatrix} u_1(\tau) \\ v_1(\tau) \end{pmatrix} = \begin{pmatrix} d_2 e^{p_1\tau} + d_3 e^{p_2\tau} \\ d_1 e^{p_1\tau} - d_1 e^{p_2\tau} \end{pmatrix} \quad (37)$$

where p_1 and p_2 are eigenvalues of matrix ***A***, and $d_1=\frac{(p_1+\varepsilon)(p_2+\varepsilon)}{a(p_2-p_1)}, d_2=\frac{(p_2+\varepsilon)}{a(p_2-p_1)}$ and $d_3=\frac{(p_1+\varepsilon)}{(p_2-p_1)}$. We substitute u_1 and v_1 in **Eq.30** and **Eq.32**, then obtain E_1 and w_1, respectively. The behaviour of the components in **Eq.37** are described in **Figures 1-5** (see Appendix C).

Step 2. For $n=1$, and substituting **Eqs.37** in **35**, we obtain the following system of non-linear ODE:

$$\begin{pmatrix} u'_2 \\ v'_2 \end{pmatrix} = A\begin{pmatrix} u_2 \\ v_2 \end{pmatrix} + G(u_1, v_1) \quad (38)$$

It is clear that the system of non-linear differential equations (**Eq.38**) is solved analytically [14]. The solution of the system with initial conditions (**Eq.18**) is obtained as follows:

$$u_2(\tau) = ac_3 e^{p_1\tau} + ac_4 e^{p_2\tau} + d_{22} e^{2p_1\tau} + d_{23} e^{(p_1+p_2)\tau} + d_{24} e^{2p_2\tau} + d_{25} \quad (39)$$

$$v_2(\tau) = c_3(p_1+\varepsilon)e^{p_1\tau} + c_4(p_2+\varepsilon)e^{p_2\tau} + d_{26} e^{2p_1\tau} + d_{27} e^{(p_1+p_2)\tau} + d_{28} e^{2p_2\tau} + d_{29} \quad (40)$$

where $d_{22},\cdots,d_{29}$ and c_3, c_4 are constants. We substitute u_2 and v_2 in **Eqs.30** and **32**, and obtain E_2 and w_2, respectively. The behaviour of concentrations in this step is described in **Figures 6-10** (See Appendix D).

Step 3. For $n=2$, and substituting **Eqs.39** and **40** in **Eq.35**, we get the following system of non-linear ODE:

$$\begin{pmatrix} u'_3 \\ v'_3 \end{pmatrix} = A\begin{pmatrix} u_3 \\ v_3 \end{pmatrix} + G(u_2, v_2) \quad (41)$$

The system of non-linear differential equations (**Eq.41**) is solved analytically. The solution of the system with initial conditions (**Eq.18**) is obtained as follows (see **Eqs.42** and **43**).

Where $d_{90},\cdots,d_{123}$ and c_5, c_6 are constants. We substitute u_3 and v_3 in **Eq.30** and **Eq.32**, and obtain E_3 and w_3, respectively. The behaviour of concentrations in this step is described in **Figures 11-15** (See Appendix E).

On the other hand, we can easily realize that the behaviour of concentrations *u*, *v*, *E* and *w* of (HPM) are described in **Figures 16-20**.

5. ASYMPTOTIC ANALYSIS

An important development of asymptotic analysis was suggested by Kruskal (1963) for differential equations [15]. He defined asymptotology as "the art of describing the behaviour of specified solution (or family of solutions) of a system in limiting case". The following three different conditions can be identified based on the initial ratio $\frac{[E_0]}{[S_0]}$ [16].

1) If the initial concentration of enzyme $[E_0]$ is much greater than the initial concentration of substrate

$$u_3(\tau) = ac_5 e^{p_1\tau} + ac_6 e^{p_2\tau} + d_{90} e^{2p_1\tau} + d_{91} e^{(p_1+p_2)\tau} + d_{92} e^{3p_1\tau} + d_{93} e^{(2p_1+p_2)\tau} + d_{94} e^{(p_1+2p_2)\tau} + d_{95}\tau e^{p_1\tau} + d_{96} e^{p_1\tau} + d_{97} e^{2p_2\tau} + d_{98} e^{3p_2\tau} + d_{99} e^{p_2\tau} + d_{100}\tau e^{p_2\tau} + d_{101} e^{4p_1\tau} + d_{102} e^{(3p_1+p_2)\tau} + d_{103} e^{(2p_1+2p_2)\tau} + d_{104} e^{(p_1+2p_2)\tau} + d_{105} e^{4p_2\tau} + d_{106} \quad (42)$$

$$v_3(\tau) = h_1 c_5 e^{p_1\tau} + h_2 c_6 e^{p_2\tau} + d_{107} e^{2p_1\tau} + d_{108} e^{(p_1+p_2)\tau} + d_{109} e^{3p_1\tau} + d_{110} e^{(2p_1+p_2)\tau} + d_{111} e^{(p_1+2p_2)\tau} + d_{112}\tau e^{p_1\tau} + d_{113} e^{p_1\tau} + d_{114} e^{2p_2\tau} + d_{115} e^{3p_2\tau} + d_{116} e^{p_2\tau} + d_{117}\tau e^{p_2\tau} + d_{118} e^{4p_1\tau} + d_{119} e^{(3p_1+p_2)\tau} + d_{120} e^{(2p_1+2p_2)\tau} + d_{121} e^{(p_1+2p_2)\tau} + d_{122} e^{4p_2\tau} + d_{123} \quad (43)$$

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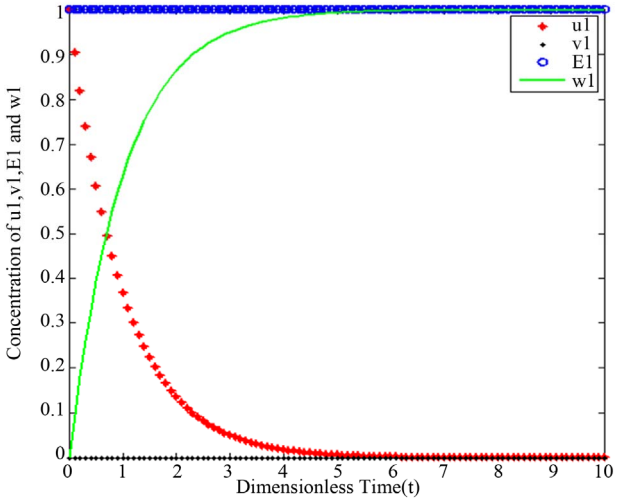

Figure 1. $\varepsilon = 1,\ \alpha = 1,\ \lambda = 0.4$ and $k = 1.3$.

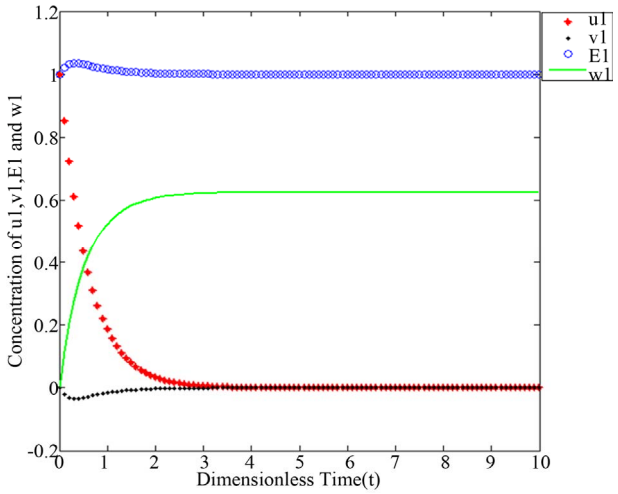

Figure 2. $\varepsilon = 1.6,\ \alpha = 1.3,\ \lambda = 0.9$ and $k = 1.7$.

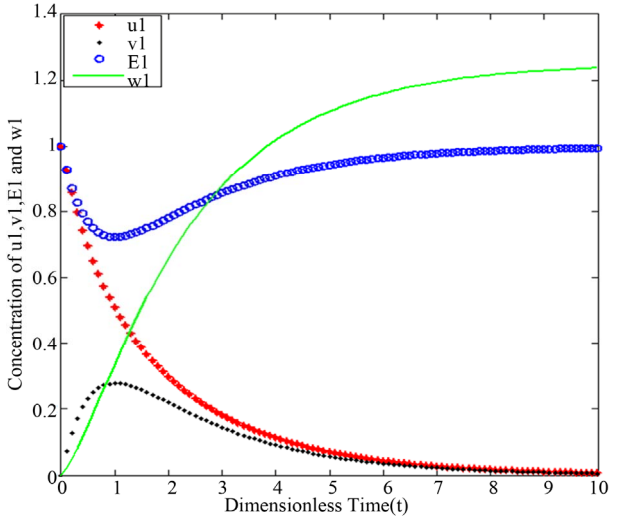

Figure 3. $\varepsilon = 0.8,\ \alpha = 0.3,\ \lambda = 0.9$ and $k = 1.1$.

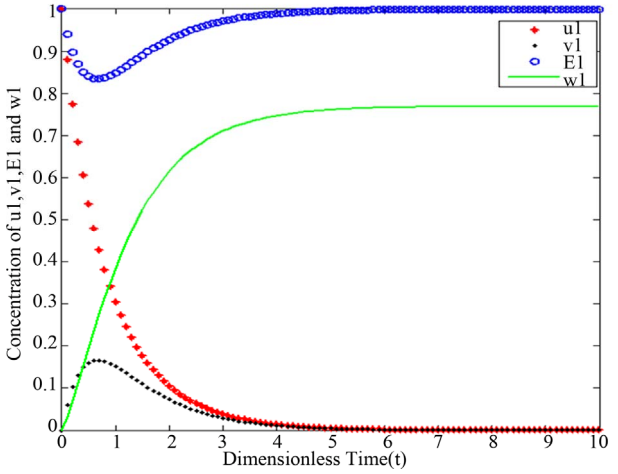

Figure 4. $\varepsilon = 1.3,\ \alpha = 0.3,\ \lambda = 0.9$ and $k = 1.2$.

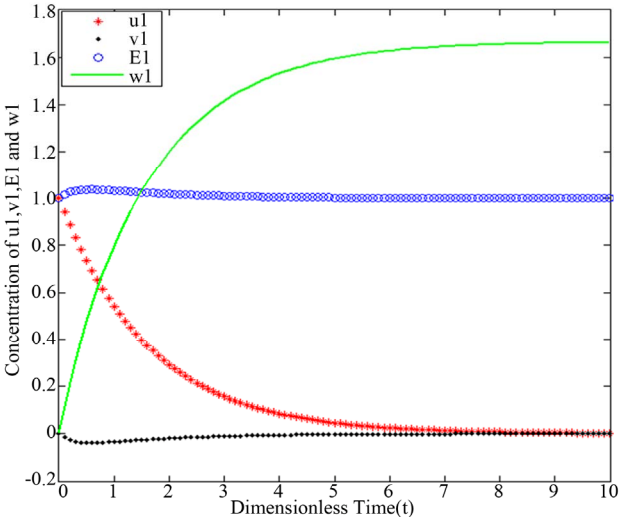

Figure 5. $\varepsilon = 0.6,\ \alpha = 1.2,\ \lambda = 1.2$ and $k = 1.7$.

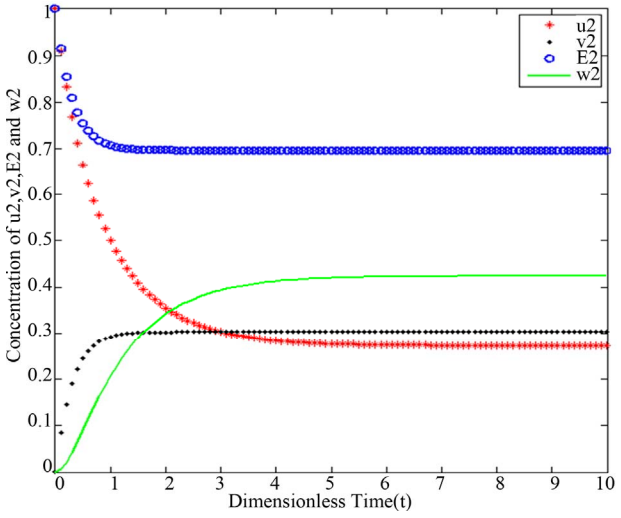

Figure 6. $\varepsilon = 1,\ \alpha = 1,\ \lambda = 0.4$ and $k = 1.3$.

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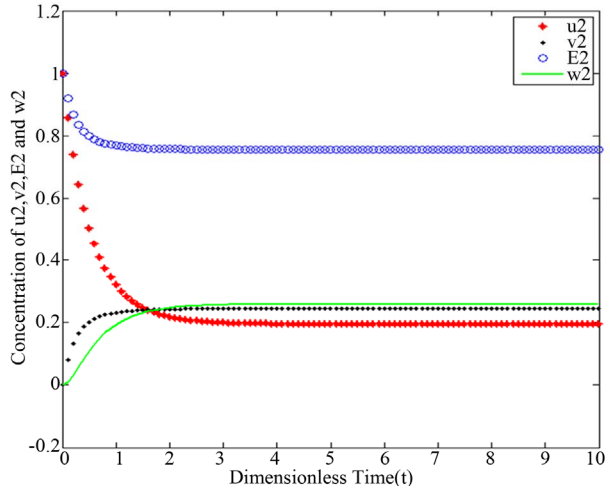

Figure 7. $\varepsilon = 1.6,\ \alpha = 1.3,\ \lambda = 0.9$ and $k = 1.7$.

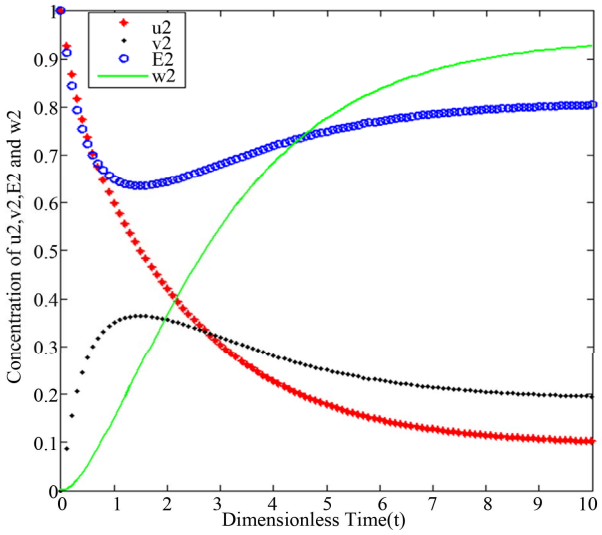

Figure 8. $\varepsilon = 0.8,\ \alpha = 0.2,\ \lambda = 0.6$ and $k = 1.1$.

$[S_0]$. This means that $\frac{[E_0]}{[S_0]} \gg 1$. Also, Schenelland Maini in [2] emphasized that the initial concentration of enzyme greatly exceeds the concentration of substrate, that is $[E_0] \gg [S_0]$. So, from **Eq.14**, we get $\varepsilon > 1$. In this case, the part of the enzyme concentration which binds to the concentration of the substrate is small. This means that there is a free rate of enzyme. This rate is based on the availability of the substrate, and is increased whenever the concentrations of substrate are increased, or by adding additional substrate to the chemical reaction.

2) If the initial concentration of substrate $[S_0]$ is much greater than the initial concentration of enzyme $[E_0]$. This means that $\frac{[E_0]}{[S_0]} \ll 1$. So, from **Eq.14**, we

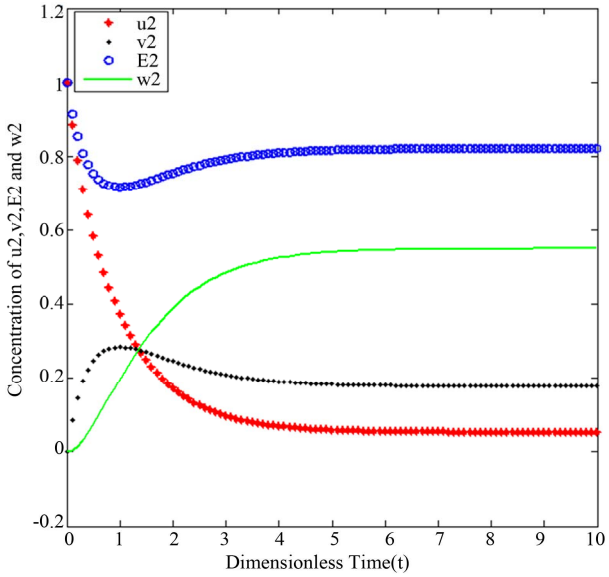

Figure 9. $\varepsilon = 1.3,\ \alpha = 0.3,\ \lambda = 0.9$ and $k = 1.2$.

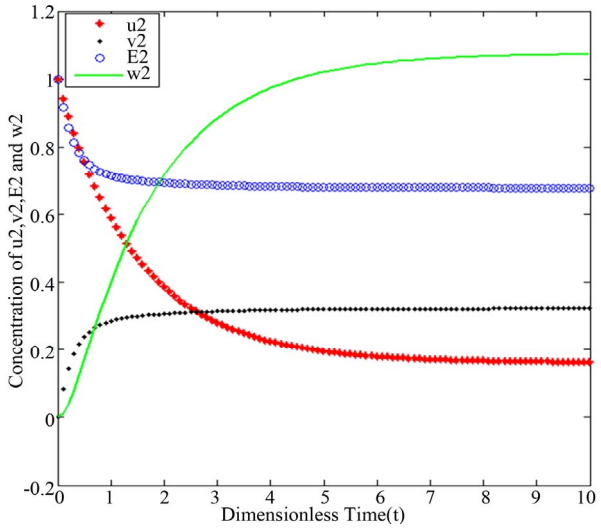

Figure 10. $\varepsilon = 0.6,\ \alpha = 1.2,\ \lambda = 1.2$ and $k = 1.7$.

obtain $\varepsilon < 1$. In this case, there is a small part of substrate that links to the enzyme, while a part of it is free. In this case, enzyme molecules usually bind to substrate molecules which mean that a small amount of enzyme is free. The availability of enzyme in this case depends on this rate, and increases when the rate of enzyme is increased, or by adding some extra enzyme to the chemical reaction.

3) If the initial concentration of enzyme and substrate are equal. This means $\frac{[E_0]}{[S_0]} = 1$, so from **Eq.14**, we get $\varepsilon = 1$. In this case, there are no any free molecules of enzyme or substrate. In other words, all substrate molecules are occupied by the enzyme molecules, and all en-

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zyme molecules are also limited by the number molecules of the substrate. Furthermore, if we look the constant rate of reactions k_4 and k_1 from **Eq.14**, we can define the following conditions:

4) If $k_4 \gg k_1$, then $\alpha > 1$.
5) If $k_4 \ll k_1$, then $\alpha < 1$.
6) If $k_4 \simeq k_1$, then $\alpha \simeq 1$.

In addition, according to the definition of λ and k from **Eq.14**, we obtain $\lambda < k$, because k_3 always has a positive value. As result, we can easily combine the **Conditions 1-6**. We then get the following five basic cases in this paper:

Case 1. The value of $\varepsilon \simeq 1$ and $\alpha \simeq 1$,
Case 2. The value of $\varepsilon > 1$ and $\alpha > 1$,
Case 3. The value of $\varepsilon < 1$ and $\alpha < 1$,
Case 4. The value of $\varepsilon > 1$ and $\alpha < 1$,
Case 5. The value of $\varepsilon < 1$ and $\alpha > 1$.

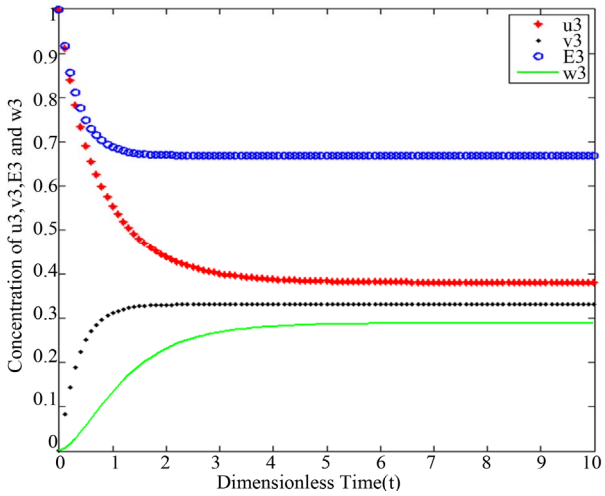

Figure 11. $\varepsilon = 1.001$, $\alpha = 1.001$, $\lambda = 0.4$ and $k = 1.3$.

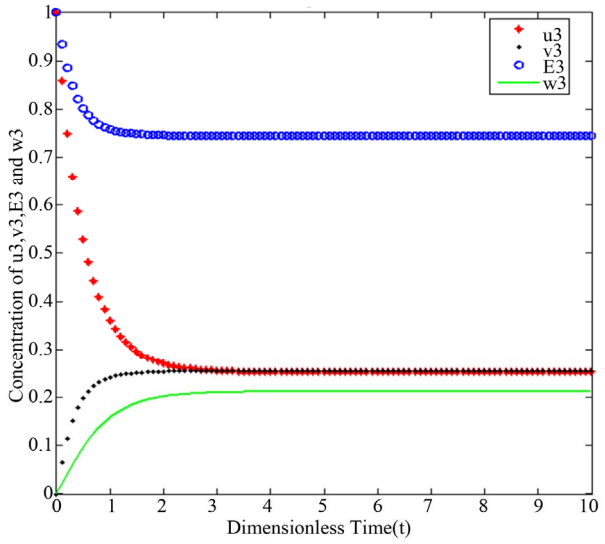

Figure 12. $\varepsilon = 1.6$, $\alpha = 1.3$, $\lambda = 0.9$ and $k = 1.7$.

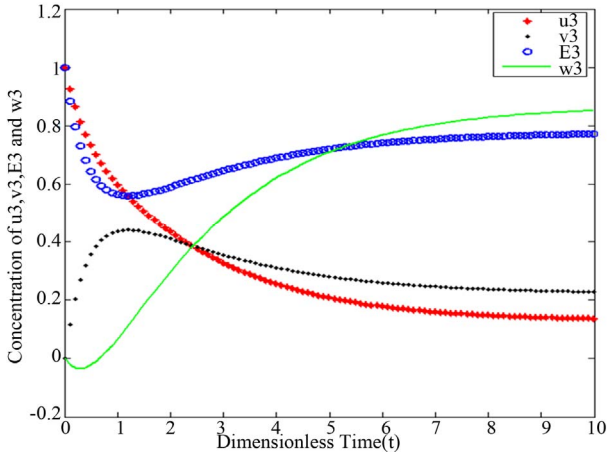

Figure 13. $\varepsilon = 0.8$, $\alpha = 0.2$, $\lambda = 0.6$ and $k = 1.1$.

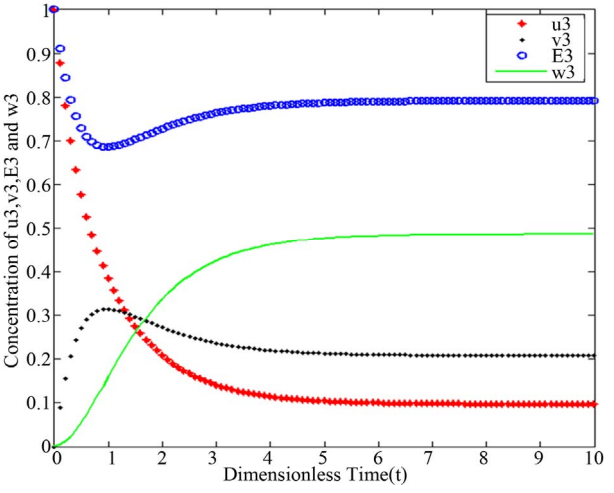

Figure 14. $\varepsilon = 1.3$, $\alpha = 0.3$, $\lambda = 0.8$ and $k = 1.2$.

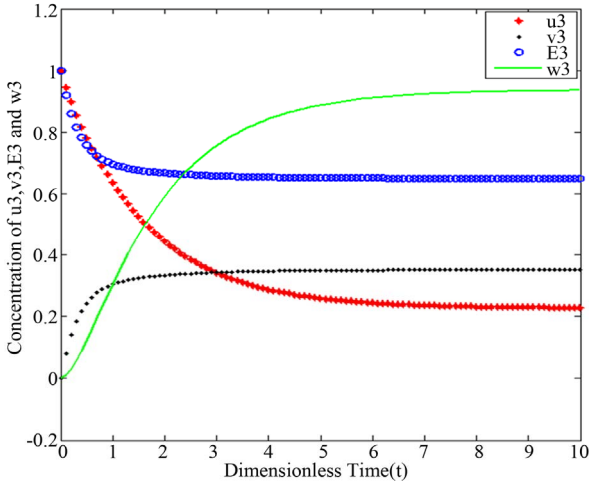

Figure 15. $\varepsilon = 0.6$, $\alpha = 1.2$, $\lambda = 1.2$ and $k = 1.7$.

We apply the above cases separately in the analytic approximate solution for both methods (HPM) and (SIM).

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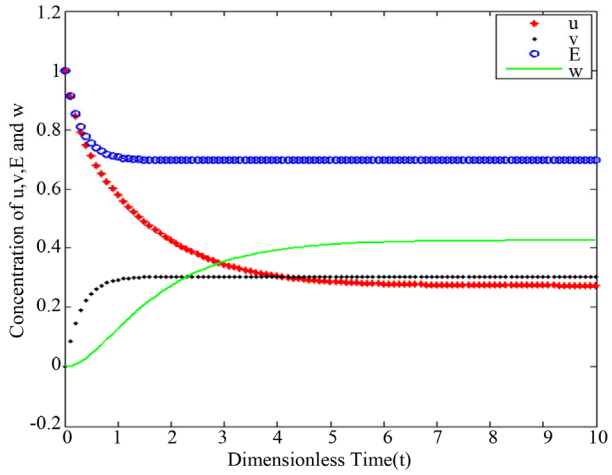

Figure 16. $\varepsilon = 1,\ \alpha = 1,\ \lambda = 0.4$ and $k = 1.3$.

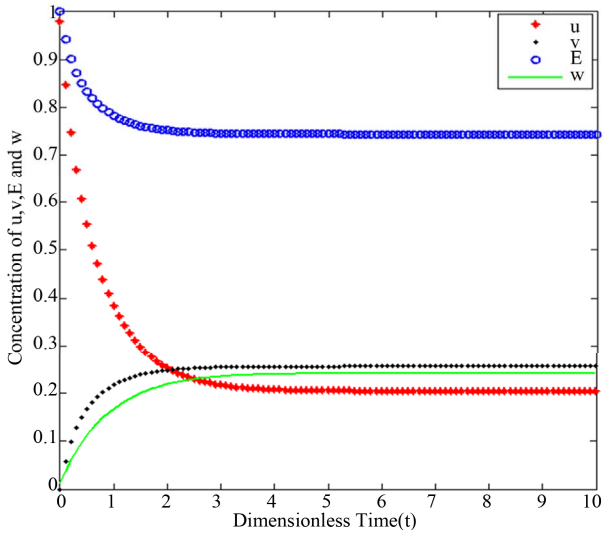

Figure 17. $\varepsilon = 1.6,\ \alpha = 1.3,\ \lambda = 0.9$ and $k = 1.7$.

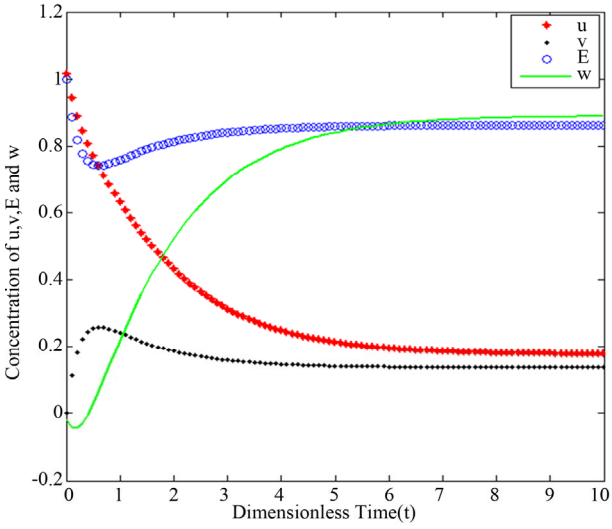

Figure 18. $\varepsilon = 0.8,\ \alpha = 0.6,\ \lambda = 2$ and $k = 3.3$.

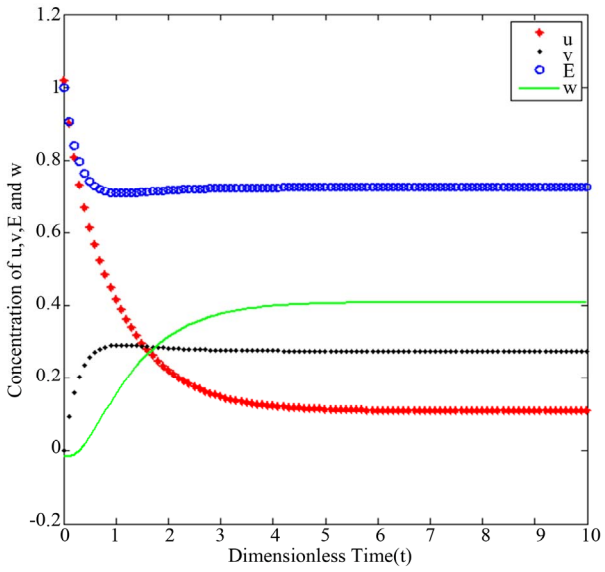

Figure 19. $\varepsilon = 1.3,\ \alpha = 0.9,\ \lambda = 0.8$ and $k = 1.2$.

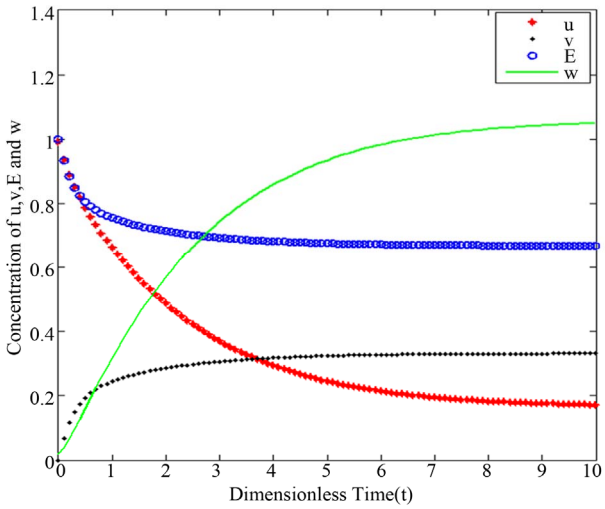

Figure 20. $\varepsilon = 0.6,\ \alpha = 1.2,\ \lambda = 1.2$ and $k = 1.7$.

6. RESULTS AND DISCUSSIONS

The figures in this section are divided in to four groups. The first three groups are related to three iterations of SIM and the last group refers to the HPM. **Figures 1-20** show the analytic approximate solution of substrate u, enzyme E, enzyme-substrate complex v and product w. Each figure in this work corresponds to one case in the previous section. The figures change in terms of the values of the dimensionless parameters $\alpha, \varepsilon, \lambda$ and k. We have applied two different methods which are SIM and HPM to find the analytical approximate solutions for **Eqs.15** and **16**. The HPM has been used by many researchers for the system (**Eq.1**) [1,3,4]. The main purpose of this discussion is to find the similarities and differences between the methods which are

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used in this study. Another purpose is to recognize the best iteration of the SIM compared to the HPM.

There are a variety of data results that tell us the second iteration in our approach (SIM) is similar to HPM. First of all, the second iteration has many significant similarities compared to (HPM), and some of them provide excellent results in terms of our work. For instance, **Figures 6-10** show that the value of the concentration of substrate u slightly decreases from its initial value $(u(0)=1)$ and there are a few changes in the value of the concentration of the enzyme-substrate complex v. Generally, they reach some constant values after $\tau > 4$. Also, in **Figures 16-20**, it appears that the concentration of the components are somewhat similar to those of corresponding **Figures 6-10**. Another example is that the value of the concentration of enzyme E in both sets of figures is more or less is the same, especially in **Cases 1**, **2** and **5**. Another crucial point is that the value of concentration v in **Figure 13** reaches a maximum when $0 < \tau < 2$. Also, in the same interval of time, the value of the concentration v reaches a maximum in **Figure 18** as well. We can also realize that the value of the enzyme in both figures ends up at a minimum value when $0 < \tau < 2$. In addition, **Figures 11-15** and **Figures 16-20** show that there is a gradual decrease in the rate of substrate u between $0 < \tau < 2$ which then levels off after $\tau > 4$. On the other hand, the concentration of the product w slightly increases between $0 < \tau < 2$ in both set of figures, and is likely to remain stable after $\tau > 4$.

However, there are some differences between our simple technique (SIM) and the classical technique (HPM). For example, **Figures 1-5** show that the value of the concentration of substrate u slightly decreases from its initial value $(u(0)=1)$, and there are a few changes in the value of the concentration of the enzyme-substrate complex v. Generally, they become zero after $\tau > 5$. Meanwhile, in **Figures 16-20**, it appears that the concentration of the components do not fall to zero, but instead reach some constant values. Basically, it could be pointed out that the differences between them are small and can be therefore be ignored.

Overall, it can be said that the second and third iterations of SIM are appropriate for obtaining a good approximate solution for our case study. In particular, the results of the second iteration are more fitted to an approximate solution in comparison with the classical technique (HPM). However, although there are some different values in terms of results between HPM and the second iteration method, they are tiny.

Figures 1-5. In these profiles of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w correspond to **Cases 1-5**, respectively. The equations of Step 1 are applied to plot the figures (see Appendix C).

Figures 6-10. In these profiles of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w correspond to **Cases 1-5**, respectively. The equations of Step 2 are applied to plot the Figures (see Appendix D).

Figures 11-15. In these profiles of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w correspond to **Cases 1-5**, respectively. The equations of Step 3 are applied to plot the figures (see Appendix E).

Figures 16-20. In these profiles of the normalized concentrations of the substrate u, enzyme-substrate complex v, enzyme E and product w correspond to **Cases 1-5**, respectively. The **Eqs.28** and **32** are applied to plot the figures (see Appendix A).

7. FINDINGS

We have used the mean of the second norm (**Eq.44**) to find the total differences between the HPM and each iteration of the SIM (see **Tables 1-3**). The rate of convergence between the SIM and the HPM is shown in **Figure 21**. Thus, we use the following equation to find this rate of convergence:

$$\frac{\|f-g\|}{\sqrt{N}} = \sqrt{\frac{\sum_{i=1}^{N} |f_i - g_i|^2}{N}} \tag{44}$$

where f and g are the value of the concentrations of substances u, v, E and w for the SIM and the HPM respectively, and N is the number of timescale iterations. The average norm between the second iteration and HPM is small in value. For instance, the average value of the norm concentration of E is small (equal to 0.02) (see **H-S2** in **Figure 21**). This means that the second iteration method is the most appropriate iteration in this case study in terms of approaching the approximate solution. Although the rate of the second norm for the third iteration is also small (see **H-S3**), but the second iteration method of our work is the best iteration in order to obtain the convergence in terms of the solution in comparison with the classical method (HPM).

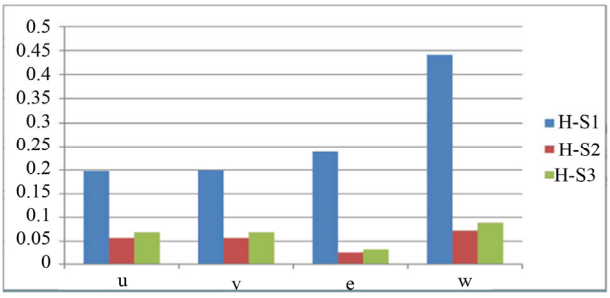

Figure 21. The average value of the second norms convergence between the HPM and the iterations of the SIM.

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Table 1. The average number of second norms between the first iteration (SIM) and HPM, the results are calculated by using Matlab program (see Appendices B and C).

Nor.Con.	Case 1	Case 2	Case 3	Case 4	Case 5	Ave. 1
UU1	0.2674	0.2015	0.1748	0.1655	0.1808	0.1980
VV1	0.2691	0.2031	0.1752	0.1662	0.1838	0.1995
EE1	0.2968	0.2488	0.1472	0.1873	0.3144	0.2389
WW1	0.5633	0.3745	0.3630	0.2911	0.6140	0.4412

Table 2. The average number of second norms between the second iteration (SIM) and HPM, the results are calculated by using Matlab program (see Appendices B and D).

Nor.Con.	Case 1	Case 2	Case 3	Case 4	Case 5	Ave. 2
UU2	0.0361	0.2050	0.0232	0.1411	0.0572	0.0565
VV2	0.0361	0.0251	0.0233	0.1411	0.0572	0.0566
EE2	0	0.0136	0.0255	0.0654	0.0172	0.0243
WW2	0.0336	0.020	0.0525	0.1633	0.0877	0.0719

Table 3. The average number of second norms between the third iteration (SIM) and HPM, the results are calculated by using Matlab program (see Appendices B and E).

Nor.Con.	Case 1	Case 2	Case 3	Case 4	Case 5	Ave. 3
UU3	0.0843	0.0411	0.0470	0.1343	0.0362	0.0686
VV3	0.0844	0.0411	0.0471	0.1344	0.0363	0.0687
EE3	0.0262	0.0094	0.0273	0.0672	0.0326	0.0325
WW3	0.1083	0.0259	0.0824	0.1591	0.0682	0.0888

On the other hand, the differences between our approach (SIM) and the HPM occurred more frequently in the first iteration than in other iterations (see **H-S1** values). It could be said that this iteration is not quite appropriate in this case study. This may be caused by giving the non-linear part in this iteration a zero value (see Step 1).

The blue column (**H-S1**), red column (**H-S2**) and green column (**H-S3**) describe the second norm differences between (HPM) and the iterations of (SIM), respectively. The figure is plotted by using the results of **Tables 1-3**. The second norm differences are represented by *u*, *v*, *E* and *w*.

8. CONCLUSION

The simple iteration method (SIM) and the Homotopy Perturbation Method (HPM) are used to find approximate analytic solutions to non-linear differential **Eqs.15** and **16**. Straightforward methods are derived for estimating the concentrations of substrate *u*, product *w*, enzyme-substrate complex *v* and enzyme *E*. The dimensionless technique applies to reduce the non-linear system of ODE. The HPM was used for a simple enzyme reaction (**Eq.1**) [1,3]. We have used this method for our case study, and have obtained an analytical approximate solution. Furthermore, a simple approach technique (SIM) was applied. This consisted of three iterations (steps). The approximate solution of the second step is similar to the classical method (HPM) (see **Figures 6-10** and **Figures 16-20**). We have also used the idea of the second norm to determine the best iteration for the problem. So, it is clear that the second iteration method is quite similar to the HPM. Consequently, **Figure 21** shows that the second iteration is the appropriate one (see **Figure 21** for the **H-S2** values). Thus, the SIM technique could be applied to some other complex chemical reactions to find appropriate solutions, and to describe the behaviour of their parameters. For example, it could be applied to many open path ways in terms of biochemical reactions [17]. In addition, we highly recommend applying the simple approach (SIM) to describe the approximate solutions of complex enzyme reactions [18], the reaction mechanism of competitive inhibitions, and the reaction scheme of allosteric inhibitions [19].

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Appendix A. This appendix consists of the solution of **Eqs.15** and **16** by using the HPM. Furthermore, this method is used to derive **Eqs.28** and **29** from **Eqs.15** and **16**, let $a=\varepsilon(k-\lambda)$, $b=1-\alpha$ and $c=k+\alpha+\alpha\varepsilon$,

$$(1-q)\left[\frac{\mathrm{d}u}{\mathrm{d}\tau}+\varepsilon u\right]+q\left[\frac{\mathrm{d}u}{\mathrm{d}\tau}+\varepsilon u-av-\varepsilon v\right]=0, \tag{45}$$

$$(1-q)\left[\frac{\mathrm{d}v}{\mathrm{d}\tau}+cv\right]+q\left[\frac{\mathrm{d}v}{\mathrm{d}\tau}-bu+cv+buv-\alpha\varepsilon v^2-\alpha\right]=0, \tag{46}$$

with initial conditions, $u(0)=1, v(0)=0.$ (47)

Thus, by using the HPM [1,3,4], the approximate solution of **Eqs.45** and **46** are:

$$u=u_0+qu_1+q^2u_2+\cdots \tag{48}$$

$$v=v_0+qv_1+q^2v_2+\cdots \tag{49}$$

Substituting the **Eqs.48** and **49** in **Eqs.45** and **46**, and comparing the coefficients of the like power q, we get the following system of ordinary differential equations:

$$q^0:\frac{\mathrm{d}u_0}{\mathrm{d}\tau}+\varepsilon u_0=0, \tag{50}$$

$$q^1:\frac{\mathrm{d}u_1}{\mathrm{d}\tau}+\varepsilon u_1-av_0-\varepsilon u_0v_0=0, \tag{51}$$

$$q^2:\frac{\mathrm{d}u_2}{\mathrm{d}\tau}+\varepsilon u_2-av_1-\varepsilon u_0v_1-\varepsilon u_1v_0=0, \tag{52}$$

$$\text{and.}\quad q^0:\frac{\mathrm{d}v_0}{\mathrm{d}\tau}+cv_0=0, \tag{53}$$

$$q^1:\frac{\mathrm{d}v_1}{\mathrm{d}\tau}+cv_1-bu_0+bu_0v_0-\alpha\varepsilon v_0^2-\alpha=0, \tag{54}$$

$$q^2:\frac{\mathrm{d}v_2}{\mathrm{d}\tau}+cv_2-bu_1+bu_0v_1+bu_1v_0-2\alpha v_0v_1=0, \tag{55}$$

The analytical solutions of **Eqs.50-55** with initial conditions **Eq.47** are:

$$u_0(\tau)=\mathrm{e}^{-\varepsilon\tau} \tag{56}$$

$$u_1(\tau)=\mathrm{e}^{-\varepsilon\tau} \tag{57}$$

$$\text{and,}\quad v_0(\tau)=0, \tag{59}$$

$$v_1(\tau)=\frac{b}{c-\varepsilon}\mathrm{e}^{-\varepsilon\tau}+\frac{bc-\alpha\varepsilon+c\alpha}{c(\varepsilon-c)}\mathrm{e}^{-c\tau}, \tag{60}$$

$$\begin{aligned}v_2(\tau)=&\left(\frac{b}{c-\varepsilon}+\frac{b\alpha}{c(c-\varepsilon)}\right)\mathrm{e}^{-\varepsilon\tau}+\frac{b^2}{(c-\varepsilon)(c-2\varepsilon)}\mathrm{e}^{-2\varepsilon\tau}\\&+\frac{b\varepsilon\alpha-cb^2-cb\alpha}{c\varepsilon(\varepsilon-c)}\mathrm{e}^{(-\varepsilon-c)\tau}+\left(\frac{b}{\varepsilon-c}+\frac{b^2}{(\varepsilon-c)(c-2\varepsilon)}\right.\\&\left.+\frac{-b\varepsilon\alpha+cb^2+cb\alpha}{c\varepsilon(\varepsilon-c)}+\frac{\alpha b}{c(\varepsilon-c)}\right)\mathrm{e}^{-c\tau}+\frac{\alpha}{c}\end{aligned} \tag{61}$$

According to the HPM, we can easily find that

$$u(\tau)=\lim_{q\to1}u(\tau)=u_0+u_1+u_2+\cdots \tag{62}$$

$$\text{and,}\quad v(\tau)=\lim_{q\to1}v(\tau)=v_0+v_1+v_2+\cdots \tag{63}$$

By putting **Eqs.56-58** in **Eq.62** and **Eqs.59-61** in **Eq.63**, we obtain the approximate solution for the system of non-linear ODE equations (**Eqs.15** and **16**) which is described in **Eqs.28** and **29**.

Appendix B. Let $k_1=\varepsilon, k_2=\lambda$, $k_3=\alpha$ and $t=\tau$, and we use the following Matlab programming to plot the functions in **Eqs.28-32**.

$$t=0;\ \text{for}\ i=1{:}101;\ k_1=1;\ k_2=1.2;\ k_3=0.9;\ k=1.3;$$

$$a=k_1\times(k-k_2);b=1-k_3;c=k+k_3\times k_1+k_3;$$

$$\begin{aligned}u_2(\tau)=&\left(\frac{ab}{c-\varepsilon}+\frac{\alpha\varepsilon}{c}\right)\tau\mathrm{e}^{-\varepsilon\tau}+\frac{abc-a\alpha\varepsilon+ac\alpha}{c(\varepsilon-c)^2}\mathrm{e}^{-c\tau}+\frac{\alpha\varepsilon^2-cb\varepsilon-c\alpha\varepsilon}{c^2(\varepsilon-c)}\mathrm{e}^{(-\varepsilon-c)\tau}+\frac{a\alpha}{c\varepsilon}+\frac{b}{\varepsilon-c}\mathrm{e}^{-2\varepsilon\tau}\\&+\left(-1+\frac{a\alpha\varepsilon-abc-ac\alpha}{c(\varepsilon-c)^2}-\frac{a\alpha}{c\varepsilon}+\frac{b}{c-\varepsilon}+\frac{\alpha\varepsilon^2+bc\varepsilon+c\alpha\varepsilon}{c^2(\varepsilon-c)}\right)\mathrm{e}^{-\varepsilon\tau}\end{aligned} \tag{58}$$

$$\begin{aligned}u=&2\times\exp(-k_1\times t)+\left((a\times b)/(c-k_1)+(k_3\times k_1)/c\right)\times t\times\exp(-k_1\times t)+\left(a\times b\times c-a\times k_3\times k_1+a\times k_3\times c\right)/\left(c\times(k_1-c)\wedge2\right)\\&\times\exp(-c\times t)+b/(k_1-c)\times\exp(-2\times k_1\times t)+\left(k_3\times k_1\wedge2-c\times b\times k_1-k_3\times c\times k_1\right)/\left(c\wedge2\times(k_1-c)\right)\\&\times\exp\left((-k_1-c)\times t\right)+(a\times k_3)/(c\times k_1)+\left(-1+(a\times k_1\times k_3-a\times b\times c-a\times k_3\times c)/\left(c\times(k_1-c)\wedge2\right)\right.\\&\left.-(a\times k_3)/(c\times k_1)+b/(c-k_1)+\left(a\times b\times k_1-k_3\times k_1\wedge2+k_3\times c\times k_1\right)/\left(c\wedge2\times(k_1-c)\right)\right)\times\exp(-k_1\times t);\end{aligned}$$

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$$v = b/(c-k_1)\times\exp(-k_1\times t)+\left((c\times b-k_3\times k_1+k_3\times c)/(c\times(k_1-c))\right)\times\exp(-c\times t)$$
$$+k_3/c+\left(b/(c-k_1)+(k_3\times b)/(c\times(c-k_1))\right)\times\exp(-k_1\times t)+\left(b\wedge 2/((c-k_1)\times(c-2\times k_1))\right)\times\exp(-2\times k_1\times t)$$
$$+\left(k_3\times k_1\times b-c\times b\wedge 2-k_3\times c\times b\right)/(c\times k_1\times(k_1-c))\times\exp((-c-k_1)\times t)+\left(b/(k_1-c)+b\wedge 2/((k_1-c)\times(c-2\times k_1))\right)$$
$$+\left(c\times b_2-k_3\times k_1\times b+k_3\times c\times b\right)/(c\times k_1\times(k_1-c))+(k_3\times b)/(c\times(k_1-c))\Big)\times\exp(-c\times t);$$

$$E=1-v;\ w=1/k_1-u/k_1-v;$$

$$A(i)=u;B(i)=v;C(i)=E;D(i)=w;T(i)=t;t=t+0.1;$$

end; plot (*T*,*A*,'*r*',*T*,*B*,'*k*.',*T*,*C*,'*b*.',*T*,*D*,'*g*') *y* label ('Concentration of *u*, *v*, *E* and *w*') *x* label ('Dimensionless Time (*t*)'); axis square.

Appendix C. Let $k_1=\varepsilon, k_2=\lambda$, $k_3=\alpha$ and $t=\tau$, and we use the following Matlab programming to plot the functions of Step 1.

$$t=0;\ \text{for } i=1:101; k_1=1;\ k_2=1.2;\ k_3=0;\ k=1.3;$$

$$a=k_1\times(k-k_2);\ b=1-k_3;\ c=k+k_3+k_3\times k_1;$$

$$p_1=\left(-k_1-c-sqrt\left((k_1+c)\wedge 2-4\times(c\times k_1-a\times b)\right)\right)/2;$$

$$p_2=\left(-k_1-c+sqrt\left((k_1+c)\wedge 2-4\times(c\times k_1-\ a\times b)\right)\right)/2;$$

$$d_2=(p_2+k_1)/(p_2-p_1);d_3=(p_1+k_1)/(p_1-p_2);$$

$$d_1=\left((p_1+k_1)\times(p_2+k_1)\right)/(a\times(p_2-p_1));$$

$$u_1=d_2\times\exp(p_1\times t)+d_3\times\exp(p_2\times t);$$

$$v_1=d_1\times\exp(p_1\times t)-d_1\times\exp(p_2\times t);$$

$$e_1=1-v_1;\ w_1=1/k_1-u_1/k_1-v_1;\ A(i)=u_1;$$

$$B(i)=v_1;C(i)=e_1;D(i)=w_1;T(i)=t;\ t=t+0.1;\ \text{end};$$

plot (*T*,*A*,'*r*',*T*,*B*,'*k*.',*T*,*C*,'*b*.',*T*,*D*,'*g*') *y* label ('Concentration of u_1, v_1, E_1 and w_1') *x* label ('Dimensionless Time (*t*)'); axis square.

Appendix D. Let $k_1=\varepsilon, k_2=\lambda$, $k_3=\alpha$ and $t=\tau$, and we use the following Matlab programming to plot the functions in Step 2.

$$t=0;\ \text{for } i=1:101;\ k_1=1;\ k_2=1.2;\ k_3=0.2;\ k=1.3;$$

$$a=k_1\times(k-k_2);\ b=1-k_3;\ c=k+k_3+k_3\times k_1;$$

$$p_1=\left(-k_1-c-sqrt\left((k_1+c)\wedge 2-4\times(c\times k_1-a\times b)\right)\right)/2;$$

$$p_2=\left(-k_1-c+sqrt\left((k_1+c)\wedge 2-4\times(c\times k_1-a\times b)\right)\right)/2;$$

$$d_2=(p_2+k_1)/(p_2-p_1);d_3=(p_1+k_1)/(p_1-p_2);$$

$$d_1=\left((p_1+k_1)\times(p_2+k_1)\right)/(a\times(p_2-p_1));$$

$$d_4=k_1\times d_2\times d_1;d_5=(-k_1\times d_2\times d_1)+(k_1\times d_3\times d_1);$$

$$d_6=-k_1\times d_3\times d_1;\ d_7=(-b\times d_2\times d_1)+(k_3\times k_1\times d_1\wedge 2;$$

$$d_8=(b\times d_2\times d_1)-(b\times d_3\times d_1)-(2\times k_3\times k_1\times d_1\wedge 2);$$

$$d_9=(b\times d_3\times d_1)+(k_3\times k_1\times d_1\wedge 2);$$

$$d_{10}=(p_2+k_1)/(a\times(p_2-p_1));d_{11}=-1/(p_2-p_1);$$

$$d_{12}=(p_1+k_1)/(a\times(p_1-p_2));d_{13}=1/(p_2-p_1);$$

$$d_{14}=(d_4\times d_{10}+d_{11}\times d_7)/p_1;d_{15}=(d_{10}\times d_5+d_{11}\times d_8)/p_2;$$

$$d_{16}=(d_{10}\times d_6+d_{11}\times d_9)/(2\times p_2-p_1);d_{17}=(-k_3\times d_{11})/p_1;$$

$$d_{18}=(d_{12}\times d_4+d_{13}\times d_7)/(2\times p_1-p_2);\ d_{19}=(d_{12}\times d_5+d_{13}\times d_8)/p_1;$$

$$d_{20}=(d_{12}\times d_6+d_{13}\times d_9)/p_2;\ d_{21}=(-k_3\times d_{13})/p_2;$$

$$d_{22}=a\times d_{14}+a\times d_{18};d_{23}=a\times d_{15}+a\times d_{19};$$

$$d_{24}=a\times d_{16}+a\times d_{20};\ d_{25}=a\times d_{17}+a\times d_{21};$$

$$d_{26}=(p_1+k_1)\times d_{14}+(p_2+k_1)\times d_{18};$$

$$d_{27}=(p_1+k_1)\times d_{15}+(p_2+k_1)\times d_{19};$$

$$d_{28}=(p_1+k_1)\times d_{16}+(p_2+k_1)\times d_{20};$$

$$d_{29}=(p_1+k_1)\times d_{17}+(p_2+k_1)\times d_{21};$$

$$c_3=(1-d_{22}-d_{23}-d_{24}-d_{25})/a-\left(a\times(d_{26}+d_{27}+d_{28}+d_{29})+(p_1+k_1)\times(1-d_{22}-d_{23}-d_{24}-d_{25})\right)/(a\times(p_1-p_2));$$

$$c_4=\left(a\times(d_{26}+d_{27}+d_{28}+d_{29})+(p_1+k_1)\times(1-d_{22}-d_{23}-d_{24}-d_{25})\right)/(a\times(p_1-p_2));$$

$$u_2=c_3\times a\times\exp(p_1\times t)+c_4\times a\times\exp(p_2\times t)+d_{22}\times\exp(2\times p_1\times t)+d_{23}\times\exp((p_1+p_2)\times t)+d_{24}\times\exp(2\times p_2\times t)+d_{25};$$

$$v_2=c_3\times(p_1+k_1)\times\exp(p_1\times t)+c_4\times(p_2+k_1)\times\exp(p_2\times t)+d_{26}\times\exp(2\times p_1\times t)+d_{27}$$
$$\times\exp((p_1+p_2)\times t)+d_{28}\times\exp(2\times p_2\times t)+d_{29};$$

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$$e_2 = 1 - v_2; w_2 = 1/k_1 - u_2/k_1 - v_2;$$

$$A(i) = u_2;\ B(i) = v_2;\ C(i) = e_2; D(i) = w_2; T(i) = t; t = t + 0.1;$$

end; plot (*T*,*A*,'*r*',*T*,*B*,'*k*.',*T*,*C*,'*b*.',*T*,*D*,'*g*') *y* label ('Concentration of u_2, v_2, E_2 and w_2') *x* label ('Dimensionless Time (*t*)'); axis square.

Appendix E. Let $k_1 = \varepsilon, k_2 = \lambda,\ k_3 = \alpha$ and $t = \tau$, and we use the following Matlab programming to plot the functions in Step 3.

$$t = 0;\ \text{for } i = 1{:}101;\ k_1 = 1;\ k_2 = 1.2;\ k_3 = 0.2;\ k = 1.4;$$

$$a = k_1 \times (k - k_2);\ b = 1 - k_3;\ c = k + k_3 + k_3 \times k_1;$$

$$p_1 = \left(-k_1 - c - sqrt\left((k_1 + c)\wedge 2 - 4 \times (c \times k_1 - a \times b)\right)\right)/2;$$

$$p_2 = \left(-k_1 - c + sqrt\left((k_1 + c)\wedge 2 - 4 \times (c \times k_1 - a \times b)\right)\right)/2;$$

$$d_2 = (p_2 + k_1)/(p_2 - p_1);\ d_3 = (p_1 + k_1)/(p_1 - p_2);$$

$$d_1 = ((p_1 + k_1) \times (p_2 + k_1))/(a \times (p_2 - p_1));$$

$$d_4 = k_1 \times d_2 \times d_1; d_5 = (-k_1 \times d_2 \times d_1) + (k_1 \times d_3 \times d_1);$$

$$d_6 = -k_1 \times d_3 \times d_1;\ d_7 = (-b \times d_2 \times d_1) + (k_3 \times k_1 \times d_1 \wedge 2);$$

$$d_8 = (b \times d_2 \times d_1) - (b \times d_3 \times d_1) - (2 \times k_3 \times k_1 \times d_1 \wedge 2);$$

$$d_9 = (b \times d_3 \times d_1) + (k_3 \times k_1 \times d_{12}); d_{10} = (p_2 + k_1)/(a \times (p_2 - p_1));$$

$$d_{11} = -1/(p_2 - p_1); d_{12} = (p_1 + k_1)/(a \times (p_1 - p_2));$$

$$d_{13} = 1/(p_2 - p_1); d_{14} = (d_4 \times d_{10} + d_{11} \times d_7)/p_1;$$

$$d_{15} = (d_{10} \times d_5 + d_{11} \times d_8)/p_2;$$

$$d_{16} = (d_{10} \times d_6 + d_{11} \times d_9)/(2 \times p2 - p1); d_{17} = (-k_3 \times d_{11})/p_1;$$

$$d_{18} = (d_{12} \times d_4 + d_{13} \times d_7)/(2 \times p_1 - p_2);$$

$$d_{19} = (d_{12} \times d_5 + d_{13} \times d_8)/p_1; d_{20} = (d_{12} \times d_6 + d_{13} \times d_9)/p_2;$$

$$d_{21} = (-k_3 \times d_{13})/p_2;\ d_{22} = a \times d_{14} + a \times d_{18};$$

$$d_{23} = a \times d_{15} + a \times d_{19};\ d_{24} = a \times d_{16} + a \times d_{20};$$

$$d_{25} = a \times d_{17} + a \times d_{21}; d_{26} = (p_1 + k_1) \times d_{14} + (p_2 + k_1) \times d_{18};$$

$$d_{27} = (p_1 + k_1) \times d_{15} + (p_2 + k_1) \times d_{19};$$

$$d_{28} = (p_1 + k_1) \times d_{16} + (p_2 + k_1) \times d_{20};$$

$$d_{29} = (p_1 + k_1) \times d_{17} + (p_2 + k_1) \times d_{21};$$

$$c_3 = (1 - d_{22} - d_{23} - d_{24} - d_{25})/a - (a \times (d_{26} + d_{27} + d_{28} + d_{29}) + (p_1 + k_1) \times (1 - d_{22} - d_{23} - d_{24} - d_{25}))/(a \times (p_1 - p_2));$$

$$c_4 = (a \times (d_{26} + d_{27} + d_{28} + d_{29}) + (p_1 + k_1) \times (1 - d_{22} - d_{23} - d_{24} - d_{25}))/(a \times (p_1 - p_2));$$

$$d_{30} = k_1 \times c_{32} \times a \times (p_1 + k_1) + k_1 \times d_{22} \times d_{29} + k_1 \times d_{26} \times d_{25};$$

$$d_{31} = k_1 \times c_3 \times c_4 \times a \times (p_2 + k_1) + k_1 \times c_4 \times c_3 \times a \times (p_1 + k_1) + k_1 \times d_{23} \times d_{29} + k_1 \times d_{25} \times d_{27};$$

$$d_{32} = k_1 \times c_3 \times a \times d_{26} + k_1 \times c_3 \times (p_1 + k_1) \times d_{22};$$

$$d_{33} = k_1 \times c_3 \times a \times d_{27} + k_1 \times c_4 \times a \times d_{26} + k_1 \times c_4 \times (p_2 + k_1) \times d_{22} + k_1 \times c_3 \times (p_1 + k_1) \times d_{23};$$

$$d_{34} = k_1 \times c_3 \times a \times d_{28} + k_1 \times c_4 \times a \times d_{27} + k_1 \times c_4 \times (p_2 + k_1) \times d_{23} + k_1 \times c_3 \times (p_1 + k_1) \times d_{24};$$

$$d_{35} = k_1 \times c_3 \times a \times d_{29} + k_1 \times c_3 \times (p_1 + k_1) \times d_{25};$$

$$d_{36} = k_1 \times c_4 \wedge 2 \times a \times (p_2 + k_1) + k_1 \times d_{24} \times d_{29} + k_1 \times d_{25} \times d_{28};$$

$$d_{37} = k_1 \times c_4 \times a \times d_{28} + k_1 \times c_4 \times (p_2 + k_1 \times d_{24};$$

$$d_{38} = k_1 \times c_4 \times a \times d_{29} + k_1 \times c_4 \times (p_2 + k_1) \times d_2;$$

$$d_{39} = k_1 \times d_{22} \times d_{26};\ d_{40} = k_1 \times d_{22} \times d_{27} + k_1 \times d_{23} \times d_{26};$$

$$d_{41} = k_1 \times d_{22} \times d_{28} + k_1 \times d_{23} \times d_{27} + k_1 \times d_{24} \times d_{26};$$

$$d_{42} = k_1 \times d_{23} \times d_{28} + k_1 \times d_{24} \times d_{27};$$

$$d_{43} = k_1 \times d_{24} \times d_{28}; d_{44} = k_1 \times d_{25} \times d_{29};$$

$$d_{45} = -b \times d_{30}/k_1 + k_3 \times k_1 \times c_3 \wedge 2 \times (p_1 + k_1) \wedge 2 + k_3 \times k_1 \times d_{26} \times d_{29} + k_3 \times k_1 \times d_{29} \times d_{26};$$

$$d_{46} = -b \times d_{31}/k_1 + k_3 \times k_1 \times c_3 \times c_4 \times (p_1 + k_1) \times (p_2 + k_1) + k_3 \times k_1 \times c_3 \times c_4 \times (p_1 + k_1) \times (p_2 + k_1) + k_3 \times k_1 \times d_{27} \times d_{29} + k_3 \times k_1 \times d_{27} \times d_{29};$$

$$d_{47} = -b \times d_{32}/k_1 + k_3 \times k_1 \times c_3 \times d_{26} \times (p_1 + k_1) + k_3 \times k_1 \times c_3 \times d_{26} \times (p_1 + k_1);$$

$$d_{48} = -b \times d_{33}/k_1 + k_3 \times k_1 \times c_3 \times d_{27} \times (p_1 + k_1) + k_3 \times k_1 \times c_4 \times d_{26} \times (p_2 + k_1);$$

$$d_{49} = -b \times d_{34}/k_1 + k_3 \times k_1 \times c_3 \times d_{28} \times (p_1 + k_1) + k_3 \times k_1 \times c_4 \times d_{27} \times (p_2 + k_1) + k_3 \times k_1 \times c_4 \times d_{27} \times (p_2 + k_1) + k_3 \times k_1 \times c_3 \times d_{28} \times (p_1 \times k_1);$$

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$$d_{50} = -b \times d_{35} / k_1 + k_3 \times k_1 \times c_3 \times d_{29} \times (p_1 + k_1) + k_3 \times k_1 \times c_3 \times d_{29} \times (p_1 \times k_1);$$

$$d_{51} = -b \times d_{36} / k_1 + k_3 \times k_1 \times c_4 \wedge 2 \times (p_2 + k_1) + k_3 \times k_1 \times d_{28} \times d_{29} + k_3 \times k_1 \times d_{28} \times d_2;$$

$$d_{52} = -b \times d_{37} / k_1 + k_3 \times k_1 \times c_4 \times d_{28} \times (p_2 + k_1) + k_3 \times k_1 \times c_4 \times d_{28} \times (p_2 + k_1);$$

$$d_{53} = -b \times d_{38} / k_1 + k_3 \times k_1 \times c_4 \times d_{29} \times (p_2 + k_1) + k_3 \times k_1 \times c_4 \times d_{29} \times (p_2 + k_1);$$

$$d_{54} = -b \times d_{39} / k_1 + k_3 \times k_1 \times (d_{26}) \wedge 2;$$

$$d_{55} = -b \times d_{40} / k_1 + k_3 \times k_1 \times d_{26} \times d_{27} + k_3 \times k_1 \times d_{26} \times d_{27};$$

$$d_{56} = -b \times d_{41} / k_1 + k_3 \times k_1 \times d_{26} \times d_{28} + k_3 \times k_1 \times (d_{27}) \wedge 2 + k_3 \times k_1 \times d_{26} \times d_{28};$$

$$d_{57} = -b \times d_{42} / k_1 + k_3 \times k_1 \times d_{27} \times d_{28} + k_3 \times k_1 \times d_{27} \times d_{28};$$

$$d_{58} = -b \times d_{43} / k_1 + k_3 \times k_1 \times (d_{28}) \wedge 2;$$

$$d_{59} = -b \times d_{44} / k_1 + (d_{29}) \wedge_2 + k_3; d_{60} = (d_{10} \times d_{30} + d_{11} \times d_{45}) / (p_1);$$

$$d_{61} = (d_{10} \times d_{31} + d_{11} \times d_{46}) / (p_2);$$

$$d_{62} = (d_{10} \times d_{32} + d_{11} \times d_{47}) / (2 \times p_1);$$

$$d_{63} = (d_{10} \times d_{33} + d_{11} \times d_{48}) / (p_1 + p_2);$$

$$d_{64} = (d_{10} \times d_{34} + d_{11} \times d_{49}) / (2 \times p_2);$$

$$d_{65} = (d_{10} \times d_{35} + d_{11} \times d_{50});$$

$$d_{66} = (d_{10} \times d_{36} + d_{11} \times d_{51}) / (-p_1 + 2 \times p_2);$$

$$d_{67} = (d_{10} \times d_{37} + d_{11} \times d_{52}) / (-p_1 + 3 \times p_2);$$

$$d_{68} = (d_{10} \times d_{38} + d_{11} \times d_{53}) / (-p_1 + p_2);$$

$$d_{69} = (d_{10} \times d_{39} + d_{11} \times d_{54}) / (3 \times p_1);$$

$$d_{70} = (d_{10} \times d_{40} + d_{11} \times d_{55}) / (2 \times p_1 + p_2);$$

$$d_{71} = (d_{10} \times d_{41} + d_{11} \times d_{56}) / (p_1 + 2 \times p_2);$$

$$d_{72} = (d_{10} \times d_{42} + d_{11} \times d_{57}) / (3 \times p_2);$$

$$d_{73} = (d_{10} \times d_{43} + d_{11} \times d_{58}) / (-p_1 + 4 \times p_2);$$

$$d_{74} = (d_{10} \times d_{44} + d_{11} \times d_{59}) / (-p_1);$$

$$d_{75} = (d_{12} \times d_{30} + d_{13} \times d_{45}) / (2 \times p_1 - p_2);$$

$$d_{76} = (d_{12} \times d_{31} + d_{13} \times d_{46}) / (p_1);$$

$$d_{77} = (d_{12} \times d_{32} + d_{13} \times d_{47}) / (3 \times p_1 - p_2);$$

$$d_{78} = (d_{12} \times d_{33} + d_{13} \times d_{48}) / (2 \times p_1);$$

$$d_{79} = (d_{12} \times d_{34} + d_{13} \times d_{49}) / (p_1 + p_2);$$

$$d_{80} = (d_{12} \times d_{35} + d_{13} \times d_{50}) / (p_1 - p_2);$$

$$d_{81} = (d_{12} \times d_{36} + d_{13} \times d_{51}) / (p_2);$$

$$d_{82} = (d_{12} \times d_{37} + d_{13} \times d_{52}) / (2 \times p_2);$$

$$d_{83} = (d_{12} \times d_{38} + d_{13} \times d_{53});$$

$$d_{84} = (d_{12} \times d_{39} + d_{13} \times d_{54}) / (4 \times p_1 - p_2);$$

$$d_{85} = (d_{12} \times d_{40} + d_{13} \times d_{55}) / (3 \times p_1);$$

$$d_{86} = (d_{12} \times d_{41} + d_{13} \times d_{56}) / (2 \times p_1 + p_2);$$

$$d_{87} = (d_{12} \times d_{42} + d_{13} \times d_{57}) / (p_1 + 2 \times p_2);$$

$$d_{88} = (d_{12} \times d_{43} + d_{13} \times d_{58}) / (3 \times p_2);$$

$$d_{89} = (d_{12} \times d_{44} + d_{13} \times d_{59}) / (-p_2);$$

$$d_{90} = a \times d_{60} + a \times d_{75}; d_{91} = a \times d_{61} + a \times d_{76};$$

$$d_{92} = a \times d_{62} + a \times d_{77}; d_{93} = a \times d_{63} + a \times d_{78};$$

$$d_{94} = a \times d_{64} + a \times d_{79}; d_{95} = a \times d_{65};$$

$$d_{96} = a \times d_{80}; \; d_{97} = a \times d_{66} + a \times d_{81};$$

$$d_{98} = a \times d_{67} + a \times d_{82}; \; d_{99} = a \times d_{68}; \; d_{100} = a \times d_{83};$$

$$d_{101} = a \times d_{69} + a \times d_{84}; d_{102} = a \times d_{70} + a \times d_{85};$$

$$d_{103} = a \times d_{71} + a \times d_{86}; \; d_{104} = a \times d_{72} + a \times d_{87};$$

$$d_{105} = a \times d_{73} + a \times d_{88}; \; d_{106} = a \times d_{74} + a \times d_{89};$$

$$h_1 = p_1 + k_1; \; h_2 = p_2 + k_1; d_{107} = h_1 \times d_{60} + h_2 \times d_{75};$$

$$d_{108} = h_1 \times d_{61} + h_2 \times d_{76}; \; d_{109} = h_1 \times d_{62} + h_2 \times d_{77};$$

$$d_{110} = h_1 \times d_{63} + h_2 \times d_{78}; \; d_{111} = h_1 \times d_{64} + h_2 \times d_{79};$$

$$d_{112} = h_1 \times d_{65}; \; d_{113} = h_2 \times d_{80}; d_{114} = h_1 \times d_{66} + h_2 \times d_{81};$$

$$d_{115} = h_1 \times d_{67} + h_2 \times d_{82}; d_{116} = h_1 \times d_{68}; \; d_{117} = h_2 \times d_{83};$$

$$d_{118} = h_1 \times d_{69} + h_2 \times d_{84}; \; d_{119} = h_1 \times d_{70} + h_2 \times d_{85};$$

$$d_{120} = h_1 \times d_{71} + h_2 \times d_{86}; d_{121} = h_1 \times d_{72} + h_2 \times d_{87};$$

$$d_{122} = h_1 + d_{92} + d_{93} + d_{94} + d_{96} + d_{97} + d_{98} + d_{99} + d_{101} + d_{102} + d_{103} + d_{104} + d_{105} + d_{106};$$

$$N = d_{107} + d_{108} + d_{109} + d_{110} + d_{111} + d_{113} + d_{114} + d_{115} + d_{116} + d_{118} + d_{119} + d_{120} + d_{121} + d_{122} + d_{123};$$

$$c_5 = ((1 - M) \times h_2 + a \times N) / (a \times (h_2 - h_1));$$

$$c_6 = -N / h_2 - (h_1 / h_2) \times c_5;$$

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$$u_3 = c_5 \times a \times \exp(p_1 \times t) + c_6 \times a \times \exp(p_2 \times t) + d_{90} \times \exp((2 \times p_1) \times t) + d_{91} \times \exp((p_1 + p_2) \times t)$$
$$+ d_{92} \times \exp((3 \times p_1) \times t) + d_{93} \times \exp((2 \times p_1 + p_2) \times t) + d_{94} \times \exp((p_1 + 2 \times p_2) \times t) + d_{95} \times t \times \exp((p_1) \times t)$$
$$+ d_{96} \times \exp((p_1) \times t) + d_{97} \times \exp((2 \times p_2) \times t) + d_{98} \times \exp((3 \times p_2) \times t) + d_{99} \times \exp((2 \times p_2) \times t)$$
$$+ d_{100} \times t \times \exp((2 \times p_2) \times t) + d_{101} \times \exp((4 \times p_1) \times t) + d_{102} \times \exp((3 \times p_1 + p_2) \times t) + d_{103} \times \exp((2 \times p_1 + 2 \times p_2) \times t)$$
$$+ d_{104} \times \exp((p_1 + 3 \times p_2) \times t) + d_{105} \times \exp((4 \times p_2) \times t) + d_{106};$$

$$v_3 = c_5 \times h_1 \times \exp(p_1 \times t) + c_6 \times h_2 \times \exp(p_2 \times t) + d_{107} \times \exp((2 \times p_1) \times t) + d_{108} \times \exp((p_1 + p_2) \times t)$$
$$+ d_{109} \times \exp((3 \times p_1) \times t) + d_{110} \times \exp((2 \times p_1 + p_2) \times t) + d_{111} \times \exp((p_1 + 2 \times p_2) \times t) + d_{112} \times t \times \exp((p_1) \times t)$$
$$+ d_{113} \times \exp((p_1) \times t) + d_{114} \times \exp((2 \times p_2) \times t) + d_{115} \times \exp((3 \times p_2) \times t) + d_{116} \times \exp((2 \times p_2) \times t)$$
$$+ d_{117} \times t \times \exp((2 \times p_2) \times t) + d_{118} \times \exp((4 \times p_1) \times t) + d_{119} \times \exp((3 \times p_1 + p_2) \times t) + d_{120} \times \exp((2 \times p_1 + 2 \times p_2) \times t)$$
$$+ d_{121} \times \exp((p_1 + 3 \times p_2) \times t) + d_{122} \times \exp((4 \times p_2) \times t) + d_{123};$$

$e_3 = 1 - v_3;\ w_3 = 1/k_1 - u_3/k_1 - v_3; A(i) = u_3; B(i) = v_3;$

$C(i) = e_3;\ D(i) = w_3;\ T(i) = t;\ t = t + 0.1;$

end; plot (*T*,*A*,'*r*',*T*,*B*,'*k.*',*T*,*C*,'*b.*',*T*,*D*,'*g*') *y* label ('Concentration of u_3, v_3, E_3 and w_3') *x* label ('Dimensionless Time (*t*)'); axis square.

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