Mathematical analysis of Biological and Physiological models using the New Homotopy perturbation method

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Abstract

Structural property of biological and physiological model denotes priori review, as it concerns the option of recovering uniquely the unfamiliar global identifiability which is a precondition for well-posed evaluation parameters keeping in mind input–output data, beneath ideal conditions with noise-free observations and error-free model structure. Especially, Computing priori global identifiability is very difficult for nonlinear differential equation models. In this paper, we discussed about two set of nonlinear differential equation models and presented analytical solution for the same model. Here, we employed New Homotopy perturbation method (NHPM) for solving nonlinear systems. Their results were compared with numerical simulation and a satisfactory result was noticed.

Keywords:

Identifiability; Non-linear differential equations; New Homotopy perturbation method; Numerical simulation.

1. Introduction

The parameters characterizing behavior of unobservable features of biological and physiological systems *such as:* the effect of a drug onto an organ its targeting, are usually not agreeable to Direct measurement. This makes there measurement to be approached indirectly as a parameter estimation problem [1, 13]. A dynamic model describing the internal structure of the system is formulated theoretically, based on physical, chemical, conservation and transport laws, *i.e.* enzyme kinetics and pharmacokinetics. These physiological models often use the mathematical form of linear or nonlinear dynamic state-space models, depending on unknown parameters. Generally parameters of these forms are unfamiliar and cannot be fore-précised, and need to be projected from data obtain through observation after conducting an experiment. Variables (inputs and outputs) (I/O) experiments are designed for the purpose of resolving estimation problem which is a vital requirement for parameter estimation to be well posed is

global identifiabiity of the parametric model [1,5,8,13]. This states that, under ideal conditions of noise-free observations and error-free model structure, the unknown parameters of the postulated model can be distinctively recovered from the knowledge of the input–output variables of the designed input–output experiment.

Most essentially we need to note that the property of a priori identifiability regards an ideal context of error-free model structure and noise-free measurements and thus it is a necessary, but not a sufficient condition to ensure that an accurate identification of the model parameters from real input–output data is possible (*e.g.* data may be too noisy or the problem too poorly conditioned, etc.). But, if the parameters of the postulated model are not exclusively identified, even in the theoretical most favorable situation, they will never be identifiable in a practical experiment where model structure misspecification and noise in the dimensions are certainly available. A priori identifiability, the estimates of the parameters which could, sometimes be obtained by some numerical optimization algorithms, will be totally unreliable and random hence not guaranteed. Unfortunately, despite its essential role in parameter identification, identifiability analysis has often been neglected by many researchers. Use of a non-uniquely identifiable model in a clinical setting, may possibly overlook the difference of the normal versus pathological state, eventually leading a physician researcher to draw potentially erroneous eventualities.

In addition to this, identifiability impacts the design of experiments, by providing footprint on the selection of input and output sites to permit unique identifiability [12]. This is particularly useful when dealing with intact physiological systems, where both the number and the location of possible inputs and outputs are always quite limited. It has been shown that *a* priori identifiability results can be used to achieve the formulation of a minimal that is necessary and sufficient for input–output configuration complex experimental design.

Identifiability analysis can be useful also to provide guiding principle to deal with non-identifiability, either providing clues on how to make simpler the model structure or indicating when more information (measured data) are needed for a particular experiment.

Identifiability analysis of nonlinear systems is in universally complicated. Meaning the need for this theory is absolute when dealing with nonlinear models, *i.e.* the Michaelis–Menten equation, is commonly used in modeling say enzyme kinetics and drug metabolism. Unfortunately its applicability has been seriously hampered by the heavy computational burden

of the existing techniques. Specifically, the problem translates mathematically into checking solvability of an unusually large system of non-linear algebraic equations. The number of equations and their degree generally increases with the model order.

In this paper we have discussed about the solutions of two non-linear first order differential equation. Our aim is to giving analytical solution of applicability to models described by (linear and) non-linear models involving polynomial or rational functions, and are initialized at either unknown or known initial conditions.

2. Mathematical formulation of the models

Non-linear systems of differential equation for which the calculation can be done by hand are discussed below.

Model: 1

Two-Compartment model with Michaelis-Menten kinetics are discussed for analytical solution. The model is Mathematically described by the following rational differential equations:

$$\frac{dx_1}{dt} = \frac{-v_{\max}}{(k_m + x_1)} x_1 + u \tag{1}$$

$$\frac{dx_2}{dt} = \frac{v_{\max}}{(k_m + x_1)} x_1 - p_1 x_2 \tag{2}$$

$$y = x_2 \tag{3}$$

Where x_1, x_2 are drug masses in blood and tissues, respectively, u the drug input, y the measured drug output in the blood, p_1 a constant rate parameter and $v_{\max}$ and k_m are the classical Michaelis-Menten parameters.

Model: 2

We have taken very common model in enzyme kinetics and drug metabolism, i.e. the two component open model with Michealis-Menten elimination. The model is mathematically described by the following differential equations.

$$\frac{dx_1}{dt} = -\left(p_{21} + \frac{v_{\max}}{(k_m + x_1)} \right) x_1 + p_{12} x_2 + u_1 \tag{4}$$

$$\frac{dx_2}{dt} = p_{21} x_1 - p_{12} x_2 \tag{5}$$

$$y_1 = x_1 \tag{6}$$

$$y_2 = x_2 \tag{7}$$

Where x_1, x_2 are drug masses in blood and tissues, respectively, u_1 the input , y_1 and y_2 the measured outputs and $p = [p_{21}, p_{12,} v_{\max}, k_m]$ is the unknown parameter vector.

3. Approximate analytical solution of the Biological and Physiological models using the New Homotopy perturbation method

Linear and non-linear phenomena are of fundamental importance in various fields of science and engineering. Most models of real – life problems are still very difficult to solve. Therefore, approximate analytical solutions such as Homotopy perturbation method (HPM) [15-28] were introduced. This method is the most effective and convenient ones for both linear and non-linear equations. Perturbation method is based on assuming a small parameter. The majority of non-linear problems, especially those having strong non-linearity, have no small parameters at all and the approximate solutions obtained by the perturbation methods, in most cases, are valid only for small values of the small parameter. Generally, the perturbation solutions are uniformly valid as long as a scientific system parameter is small. However, we cannot rely fully on the approximations, because there is no criterion on which the small parameter should exist. Thus, it is essential to check the validity of the approximations numerically and/or experimentally. To overcome these difficulties, HPM have been proposed recently. Recently, many authors have applied the Homotopy perturbation method (HPM) to solve the nonlinear boundary value problem in physics and engineering sciences [15,16,22,23]. This method is also used to solve some of the non-linear problem in physical sciences [18-23]. This method is a combination of Homotopy in topology and classic perturbation techniques. Ji-Huan He used to solve the Lighthill equation [18], the Diffusion equation [19] and the Blasius equation [20]. The HPM is unique in its applicability, accuracy and efficiency. The HPM uses the imbedding parameter p as a small parameter, and only a few iterations are needed to search for an asymptotic solution. The approximate analytical solution of eqns.(2)-(7) using the New Homotopy perturbation method [15-28] is given by

For Model-1

$$x_1(t) = \frac{k_m u\left(1 - e^{\left(\frac{-v_{\max} t}{k_m}\right)}\right)}{v_{\max}} \tag{8}$$

$$x_2(t)=\left(\frac{-u}{p_1}-\frac{uk_m}{v_{\max}-p_1k_m}\right)e^{(-p_1t)}+\frac{u}{p_1}+\frac{uk_me^{\left(\frac{-v_{\max}t}{k_m}\right)}}{v_{\max}-p_1k_m} \tag{9}$$

For Model-2

$$x_1(t)=\left[\begin{array}{l} Ae^{-\left(p_{21}+\frac{v_{\max}}{k_m}\right)*t}+\left(\frac{k_mu_1}{v_{\max}+p_{21}k_m}\right)+Ce^{-r*t}-\frac{v_{\max}A^2e^{-2rt}}{k_mr}+ \\ \frac{k_m{u_1}^2v_{\max}}{k_mr(v_{\max}+p_{21})}+\frac{2Av_{\max}u_1te^{-r*t}}{v_{\max}+p_{21}k_m}+\frac{Bp_{12}e^{-p_{12}t}}{p_{21}-p_{12}+\frac{v_{\max}}{k_m}}+\frac{p_{21}p_{12}Ate^{-rt}}{p_{12}-p_{21}-\frac{v_{\max}}{k_m}} \\ +\frac{p_{12}p_{21}k_mu_1}{p_{12}(v_{\max}+p_{21}k_m)+p_{21}+\frac{v_{\max}}{k_m}}+\frac{u_1k_m}{p_{21}k_m+v_{\max}} \end{array}\right] \tag{10}$$

$$x_2(t)=\left[\begin{array}{l} Be^{-p_{12}t}+\frac{p_{21}Ae^{-rt}}{p_{12}-p_{21}-\frac{v_{\max}}{k_m}}+\frac{p_{21}k_mu_1}{p_{12}(v_{\max}+p_{21}k_m)}+De^{-p_{12}t}+ \\ \frac{Ce^{-rt}}{p_{12}-p_{21}+\frac{v_{\max}}{k_m}}+\frac{v_{\max}A^2e^{-2rt}}{(p_{12-}2r)k_m}+\frac{k_m^2u_1^2v_{\max}}{p_{12}k_mr(v_{\max}+p_{21}k_m)}+ \\ \frac{2Av_{\max}u_1te^{-rt}}{(v_{\max}+p_{21}k_m)(p_{12}-r)}+\frac{Bp_{12}te^{-p_1t}}{p_{21}-p_{12}+\frac{v_{\max}}{k_m}}+\frac{p_{12}p_{21}Ate^{-rt}}{(p_{12}-r)\left(p_{12}-p_{21}-\frac{v_{mzx}}{k_m}\right)} \\ +\frac{p_{12}p_{21}k_mu_1}{(p_{12}(v_{\max}+p_{21}k_m)+r)p_{12}}+\frac{u_1k_m}{p_{12}(p_{21}k_m+v_{\max})} \end{array}\right] \tag{11}$$

Where

$$A=a-\frac{k_mu_1}{v_{\max}+p_{21}k_m};\quad B=\left(b-\frac{p_{21}A}{p_{12}-p_{21}-\frac{v_{\max}}{k_m}}-\frac{p_{21}k_mu_1}{p_{12}(v_{\max}+p_{21}k_m)}\right) \tag{12}$$

$$C = \begin{bmatrix} c + \dfrac{v_{\max}\left(a - \dfrac{k_m u_1}{v_{\max} + p_{21}k_m}\right)}{k_m\left(p_{21} + \dfrac{v_{\max}}{k_m}\right)} - \dfrac{k_m u_1^2 v_{\max}}{(v_{\max} + p_{21}k_m)\left(p_{21} + \dfrac{v_{\max}}{k_m}\right)} - \dfrac{Bp_{12}}{p_{21} - p_{12} + \dfrac{v_{\max}}{k_m}} \\ - \dfrac{p_{12}p_{21}k_m u_1}{p_{12}(v_{\max} + p_{21}k_m) + p_{21} + \dfrac{v_{\max}}{k_m}} - \dfrac{k_m u_1}{v_{\max} + p_{21}k_m} \end{bmatrix} \quad (13)$$

$$D = \begin{bmatrix} d - \dfrac{C}{p_{12} - p_{21} + \dfrac{v_{\max}}{k_m}} + \dfrac{v_{\max}A^2}{(p_{12} - 2r)k_m} - \dfrac{k_m u_1^2 v_{\max}}{p_{12}(v_{\max} + p_{21}k_m)r} - \\ \dfrac{p_{21}k_m u_1}{p_{12}(v_{\max} + p_{21}k_m) + r} - \dfrac{u_1 k_m}{p_1(v_{\max} + p_{21}k_m)} \end{bmatrix} \quad (14)$$

$$r = p_2 + \frac{v_{\max}}{k_m}. \quad (15)$$

3.1 Basic concept of Homotopy perturbation method

To explain this method, let us consider the following function:

$$D_o(u) - f(r) = 0, \qquad r \in \Omega \quad (16)$$

with the boundary conditions of

$$B_o\left(u, \frac{\partial u}{\partial n}\right) = 0, \qquad r \in \Gamma \quad (17)$$

where D_o is a general differential operator, B_o is a boundary operator, $f(r)$ is a known analytical function and Γ is the boundary of the domain Ω. In general, the operator D_o can be divided into a linear part L and a non-linear part N. The equation (16) can therefore be written as

$$L(u) + N(u) - f(r) = 0 \quad (18)$$

By the Homotopy technique, we construct a Homotopy $v(r, p) : \Omega \times [0,1] \to \Re$ that satisfies

$$H(v, p) = (1 - p)[L(v) - L(u_0)] + p[D_o(v) - f(r)] = 0. \quad (19)$$

$$H(v, p) = L(v) - L(u_0) + pL(u_0) + p[N(v) - f(r)] = 0. \quad (20)$$

Where $p \in [0, 1]$ is an embedding parameter, and u_0 is an initial approximation of the eqn. (16) that satisfies the boundary conditions. From the eqn. (19) and the eqn. (20), we have

$$H(v,0) = L(v) - L(u_0) = 0 \tag{21}$$

$$H(v,1) = D_o(v) - f(r) = 0 \tag{22}$$

When p=0, then the eqn. (19) and the eqn. (20) become linear equations. When p =1, they become non-linear equations. The process of changing p from zero to unity is that of $L(v) - L(u_0) = 0$ to $D_o(v) - f(r) = 0$. We first use the embedding parameter p as a "small parameter" and assume that the solutions of the eqns. (19) and (20) can be written as a power series in p :

$$v = v_0 + pv_1 + p^2 v_2 + \ldots \tag{23}$$

Setting $p = 1$ results in the approximate solution of the eqn. (16) is

$$u = \lim_{p \to 1} v = v_0 + v_1 + v_2 + \ldots \tag{24}$$

This is the basic idea of the HPM.

3.2 Approximate analytical solution of the nonlinear equations (1) and (2) and (4) and (5) by New Homotopy perturbation method

In this section we derive the analytical expressions for the Model-1 and Model-2 using the New Homotopy perturbation method (NHPM) from eqns. (1) & (2) and (3) & (4) we get the following:

Model-1

$$\frac{dx_1}{dt} = \frac{-v_{\max}}{(k_m + x_1)} x_1 + u \tag{25}$$

$$\frac{dx_2}{dt} = \frac{v_{\max}}{(k_m + x_1)} x_1 - p_1 x_2 \tag{26}$$

$$y = x_2$$

We construct the Homotopy for the above equations as follows:

$$(1-p)\left(\frac{dx_1}{dt} + \frac{v_{\max}}{(k_m + x_1(0))} x_1\right) = p\left(\frac{dx_1}{dt} + \frac{v_{\max}}{(k_m + x_1)} x_1 - u\right) \tag{27}$$

$$(1-p)\left(\frac{dx_2}{dt} + p_1 x_2\right) = p\left(\frac{dx_2}{dt} + p_1 x_2 - \frac{v_{\max}}{(k_m + x_1(0))} x_1\right) \tag{28}$$

The approximate analytical expressions of the eqns. (25) and (26) be

$$x_1 = x_{10} + px_{11} + p^2 x_{12} + \ldots \tag{29}$$

$$x_2 = x_{20} + px_{21} + p^2 x_{22} + \ldots\ldots\ldots \tag{30}$$

Substituting the eqns. (29) and (30) into the eqns. (27) and (28) respectively we get

$$(1-p)\left[\begin{array}{l}\dfrac{d\left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right)}{dt} + \\ \dfrac{v_{\max}}{\left(k_m + x_1(0)\right)} \\ *\left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right)\end{array}\right] = p\left[\begin{array}{l}\dfrac{d\left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right)}{dt} + \\ \dfrac{v_{\max}}{\left(k_m + \left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right)\right)} \\ *\left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right) \\ + u\end{array}\right] \tag{31}$$

$$(1-p)\left[\begin{array}{l}\dfrac{d\left(x_{20} + px_{21} + p^2 x_{22} + \ldots\right)}{dt} + \\ p_1\left(x_{20} + px_{21} + p^2 x_{22} + \ldots\right)\end{array}\right] = p\left[\begin{array}{l}\dfrac{d\left(x_{20} + px_{21} + p^2 x_{22} + \ldots\right)}{dt} + \\ p_1\left(x_{20} + px_{21} + p^2 x_{22} + \ldots\right) - \\ \dfrac{v_{\max}}{\left(k_m + \left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right)\right)} \\ *\left(x_{10} + px_{11} + p^2 x_{12} + \ldots\right)\end{array}\right] \tag{32}$$

Comparing the coefficients of the like powers of p in (32) and (33), we get

$$p^0 : \frac{dx_{10}}{dt} + \frac{v_{\max} x_{10}}{k_m} - u = 0 \tag{33}$$

$$p^0 : \frac{dx_{20}}{dt} + p_1 x_{20} - \frac{v_{\max}}{k_m} x_{10} = 0 \tag{34}$$

The initial approximations are as follows:

$$x_{10}(0) = x_{20}(0) = 0; \qquad x_{1i}(0) = x_{2i}(0) = 0, \ i = 1, 2, 3\ldots\ldots \tag{35}$$

Solving the eqns. (33) and (35) and using the eqn. (35), we can obtain the following results:

$$x_{10}(t) = \frac{k_m u\left(1 - e^{\left(\frac{-v_{\max} t}{k_m}\right)}\right)}{v_{\max}} \tag{36}$$

$$x_{20}(t) = \left(\frac{-u}{p_1} - \frac{u k_m}{v_{\max} - p_1 k_m}\right) e^{(-p_1 t)} + \frac{u}{p_1} + \frac{u k_m e^{\left(\frac{-v_{\max} t}{k_m}\right)}}{v_{\max} - p_1 k_m} \tag{37}$$

According to the HPM, we can conclude that

$$x_1(t) = \lim_{p \to 1} x_{10} \tag{38}$$

$$x_2(t) = \lim_{p \to 1} x_{20} \tag{39}$$

After putting the eqns.(36) into an eqn.(38) and the eqns. (37) into an eqn.(39), we obtain the solutions in the text eqns.(8) and (9) respectively.

Model: 2

$$\frac{dx_1}{dt} = -\left(p_{21} + \frac{v_{\max}}{(k_m + x_1)} \right) x_1 + p_{12} x_2 + u_1 \tag{40}$$

$$\frac{dx_2}{dt} = p_{21} x_1 - p_{12} x_2 \tag{41}$$

$$y_1 = x_1 \tag{42}$$

$$y_2 = x_2 \tag{43}$$

We construct the Homotopy for the above equations as follows.

$$(1-p)\left(\frac{dx_1}{dt} + \left(p_{21} + \frac{v_{\max}}{k_m} \right) x_1 \right) = p\left(\frac{dx_1}{dt} + p_{21} x_1 + \frac{v_{\max}}{(k_m + x_1)} x_1 - u - p_{12} x_2 \right) \tag{44}$$

$$(1-p)\left(\frac{dx_3}{dt} - p_{12} x_2 \right) = p\left(\frac{dx_2}{dt} - p_{21} x_1 + p_{12} x_2 \right) \tag{45}$$

The approximate analytical expressions of the eqns. (25) and (26) be

$$x_1 = x_{10} + p x_{11} + p^2 x_{12} + \ldots \tag{46}$$

$$x_2 = x_{20} + p x_{21} + p^2 x_{22} + \ldots\ldots\ldots \tag{47}$$

Substituting the eqns. (46) and (47) into the eqns. (44) and (45) respectively we get

$$(1-p)\left[\begin{array}{l}\dfrac{d\left(x_{10}+px_{11}+p^2x_{12}+...\right)}{dt}+\\ p_{21}+\dfrac{k_m}{v_{\max}}\left(x_{10}+px_{11}+p^2x_{12}+...\right)\end{array}\right]=\left[\begin{array}{l}\dfrac{d\left(x_{10}+px_{11}+p^2x_{12}+...\right)}{dt}\\ +\dfrac{v_{\max}}{\left(k_m+\left(x_{10}+px_{11}+p^2x_{12}+...\right)\right)}*\\ \left(x_{10}+px_{11}+p^2x_{12}+...\right)\\ +p_{21}\left(x_{10}+px_{11}+p^2x_{12}+...\right)\\ +u-p_{12}\left(x_{20}+px_{21}+p^2x_{22}+...\right)\end{array}\right] \tag{48}$$

$$(1-p)\left[\begin{array}{l}\dfrac{d\left(x_{20}+px_{21}+p^2x_{22}+...\right)}{dt}+\\ p_{12}\left(x_{20}+px_{21}+p^2x_{22}+...\right)\end{array}\right]=p\left[\begin{array}{l}\dfrac{d\left(x_{20}+px_{21}+p^2x_{22}+...\right)}{dt}\\ +p_{12}\left(x_{20}+px_{21}+p^2x_{22}+...\right)\\ -p_{21}\left(x_{10}+px_{11}+p^2x_{12}+...\right)\end{array}\right] \tag{49}$$

Comparing the coefficients of the like powers of p in (48) and (49), we get

$$p^0:\frac{dx_{10}}{dt}+p_{21}x_{10}+\frac{v_{\max}x_{10}}{k_m}-u=0 \tag{50}$$

$$p^0:\frac{dx_{20}}{dt}+p_{12}x_{20}-p_{21}x_{10}=0 \tag{51}$$

$$p^1:\frac{dx_{11}}{dt}+p_{21}x_{11}+\frac{v_{\max}x_{11}}{k_m}-u-\frac{v_{\max}x_{10}{}^2}{k_m}-p_{12}x_{20}=0 \tag{52}$$

$$p^1:\frac{dx_{21}}{dt}+p_{12}x_{21}-p_{21}x_{11}=0 \tag{53}$$

The initial approximations are as follows:

$$x_{10}(0)=a\ ;\ x_{20}(0)=b;\qquad x_{1i}(0)=x_{2i}(0)=0,\ \ i=1,2,3..... \tag{54}$$

Solving the eqns. (50)-(53) and using the initial approximations the eqns. (54), we can obtain the following results

$$x_{10}=Ae^{-\left(p_{21}+\frac{v_{\max}}{k_m}\right)*t}+\left(\frac{k_mu_1}{v_{\max}+p_{21}k_m}\right) \tag{55}$$

$$x_{20}=Be^{-p_{12}t}+\frac{p_{21}Ae^{-rt}}{p_{12}-p_{21}-\frac{v_{\max}}{k_m}}+\frac{p_{21}k_mu_1}{p_{12}\left(v_{\max}+p_{21}k_m\right)} \tag{56}$$

$$x_{11}=\left[\begin{array}{l} Ce^{-r^*t}-\dfrac{v_{\max}A^2e^{-2rt}}{k_m r}+\dfrac{k_m u_1{}^2 v_{\max}}{k_m r(v_{\max}+p_{21})}+\dfrac{2Av_{\max}u_1te^{-r^*t}}{v_{\max}+p_{21}k_m} \\ +\dfrac{Bp_{12}e^{-p_{12}t}}{p_{21}-p_{12}+\dfrac{v_{\max}}{k_m}}+\dfrac{p_{21}p_{12}Ate^{-rt}}{p_{12}-p_{21}-\dfrac{v_{\max}}{k_m}}+\dfrac{p_{12}p_{21}k_m u_1}{p_{12}(v_{\max}+p_{21}k_m)+p_{21}+\dfrac{v_{\max}}{k_m}} \\ +\dfrac{u_1k_m}{p_{21}k_m+v_{\max}} \end{array}\right] \tag{57}$$

$$x_{21}=\left[\begin{array}{l} De^{-p_{12}t}+\dfrac{Ce^{-rt}}{p_{12}-p_{21}+\dfrac{v_{\max}}{k_m}}+\dfrac{v_{\max}A^2e^{-2rt}}{(p_{12-}2r)k_m}+\dfrac{k_m^2u_1^2v_{\max}}{p_{12}k_m r(v_{\max}+p_{21}k_m)}+ \\ \dfrac{2Av_{\max}u_1te^{-rt}}{(v_{\max}+p_{21}k_m)(p_{12}-r)}+\dfrac{Bp_{12}te^{-p_1t}}{p_{21}-p_{12}+\dfrac{v_{\max}}{k_m}}+\dfrac{p_{12}p_{21}Ate^{-rt}}{(p_{12}-r)\left(p_{12}-p_{21}-\dfrac{v_{mzx}}{k_m}\right)} \\ +\dfrac{p_{12}p_{21}k_m u_1}{(p_{12}(v_{\max}+p_{21}k_m)+r)p_{12}}+\dfrac{u_1k_m}{p_{12}(p_{21}k_m+v_{\max})} \end{array}\right] \tag{58}$$

According to the HPM, we can conclude that,

$$x_1(t)=\lim_{p\to 1}x_{10}+x_{11} \tag{59}$$

$$x_2(t)=\lim_{p\to 1}x_{20}+x_{21} \tag{60}$$

After putting the eqns.(54) and (57) into an eqn.(59) and the eqns. (56) and (58) into an eqn.(60), we obtain the solutions in the text eqns.(10) and (11) respectively.

3.3 Matlab/Scilab program to find the solutions of the eqns. (1) and (2) & similarly for the eqns.(4) and (5)

```
function
options= odeset('RelTol',1e-6,'Stats','on');
%initial conditions
x0=[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))
legend('w','x')
ylabel('x')
xlabel('t')
return
function [dx_dt]= TestFunction(t,x)
km=14;vmax=15;p1=28;
dx_dt(1)=((vmax*x(1))/(km+x(1)))+u;
dx_dt(2)=(vmax*x(1)/(km+x(1)))-p1*x(2);
dx_dt = dx_dt';
return
```

4. Numerical simulation

The non-linear first order differential eqns. (1)-(7) for model-I and model-II are solved numerically. The Matlab/Scilab software is used for computing numerical values for the non-linear system of differential equation. We have compared analytical solution with numerical solution and satisfactory results are noted. Comparison of numerical and analytical results is shown in graphs Fig. (1) - (15).

5. Result and discussion

Solution of non-linear differential equations models are discussed in this paper. For getting solution of this system we have employed new Homotopy perturbation method. Analytical solutions are compared with numerical solution using Matlab programm. We have shown the solution as in terms of graphical representation. Figs.(1)-(6) are drawn for Model-1. Figs. (7)-(15) are drawn for Model-2. In Fig.(1)-(2), we have shown that, taking different values for Michaelis-Menten parameters $(v_{\max} \& k_m)$ shall change drug mass level in blood and tissue. That is high values of $(v_{\max} \& k_m)$ will decrease the drug mass level in blood x_1. Taking less value for $v_{\max}$ will be deceasing drug level in tissue $x_2(t)$ which was shown in Fig. (3). Figure

(4) establish that, taking the high value k_m will yield the low drug level in blood tissue $x_2(t)$. Fig.(5) and (6) shows that, dimension less drug masses in blood and tissue $x_1(t), x_2(t)$ for fixed value of Michaelis-Menten parameters $v_{\max}, k_m and\ p_1$. In Fig.(7) and (8) are drawn to represent drug masses in blood and tissue profiles for fixed values of Michaelis-Menten parameters with initial condition as 0.1 and 0 respectively. Fig.(9) and (10) show that, increasing the initial conditions from 0-0.15 , the curve starting at high values and slowly decreasing to low value and then certain it becomes steady state. Figs. (11)-(13) show that, dimension less drug masses in blood and tissue $x_1(t), x_2(t)$ for fixed value of Michaelis-Menten parameters $v_{\max}, k_m, p_{21} and\ p_{12}$. Figure (14) evidently state that, changing the value of Michaelis-Menten parameters $v_{\max}, k_m, p_{21} and\ p_{12}$ doesn't affect the curve of drug masses tissues $x_2(t)$.

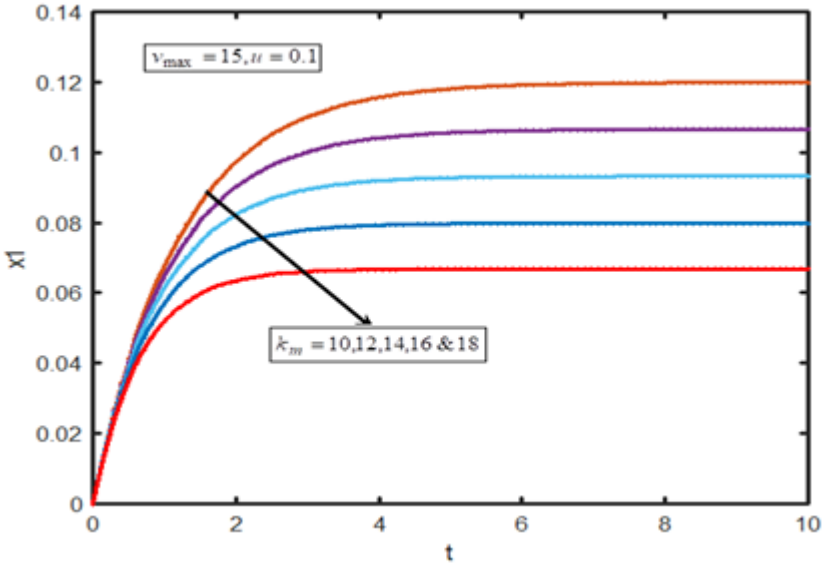

Fig.1: The dimensionless drug masses in blood profiles $x_1(t)$ verses for various values of Michaelis-Menten parameter k_m is plotted using eqn. (8). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

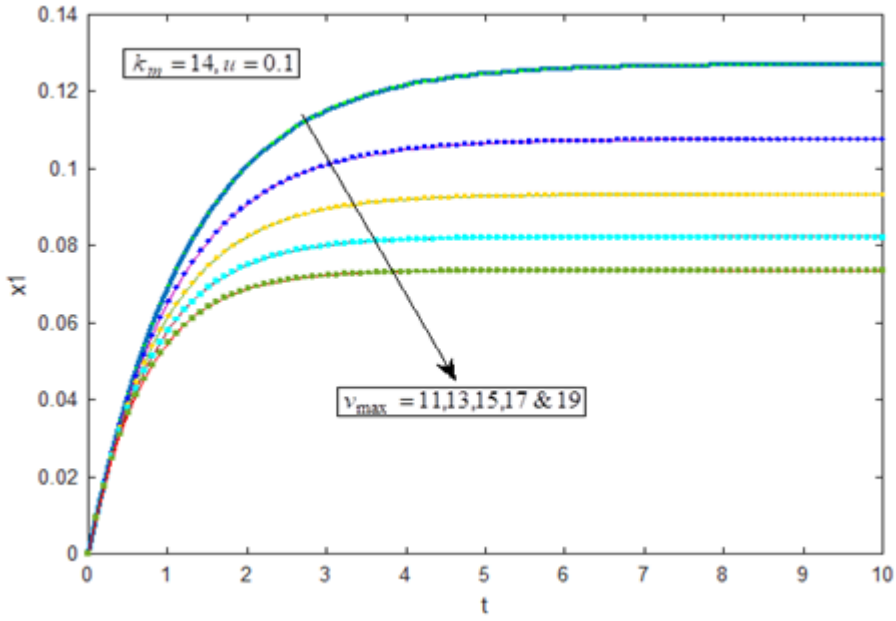

Fig.2: The dimensionless drug masses in blood profiles $x_1(t)$ verses for various values of Michaelis-Menten parameter $v_{\max}$ is plotted using eqn. (8). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

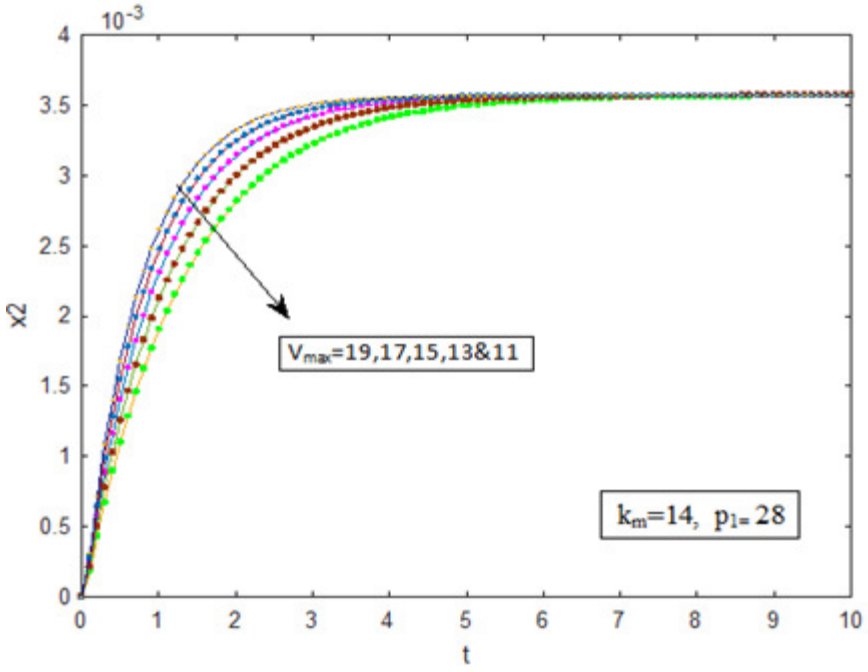

Fig.3: The dimensionless drug masses in tissue profiles $x_2(t)$ verses for various values of Michaelis-Menten parameter $v_{\max}$ is plotted using eqn. (9). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

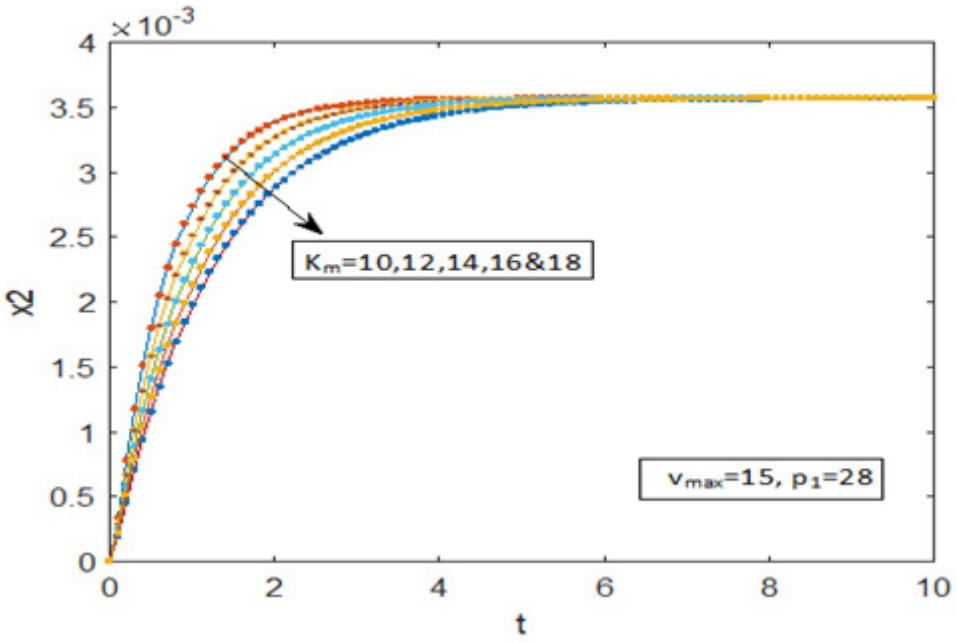

Fig.4: The dimensionless drug masses in tissue profiles $x_2(t)$ verses for various values of Michaelis-Menten parameter k_m is plotted using eqn. (9). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

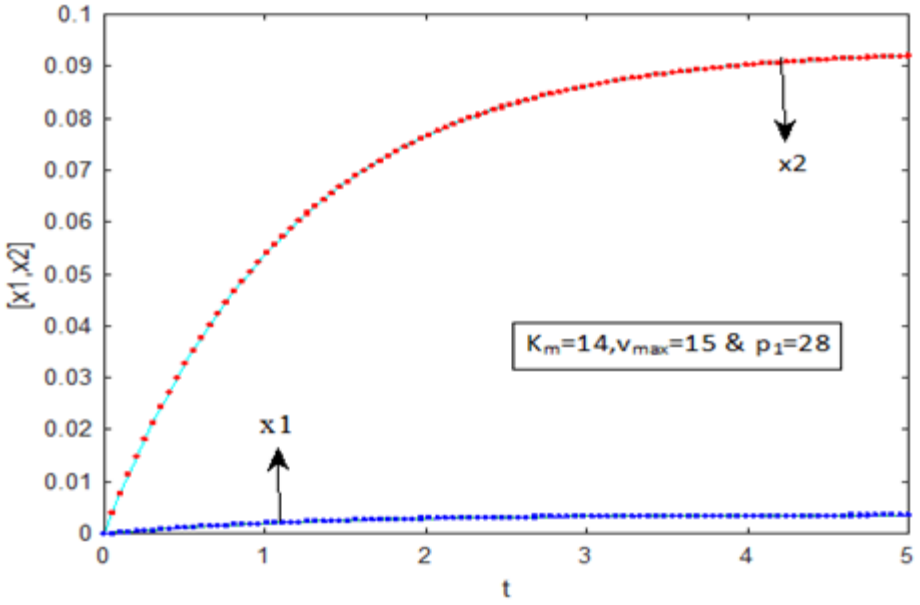

Fig.5: The dimensionless drug masses in blood and tissue profiles $x_1(t) \& x_2(t)$ verses dimensionless time t for fixed values of Michaelis-Menten parameters $v_{\max}, k_m and\ p_1$ are plotted using eqn. (8)-(9). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation..

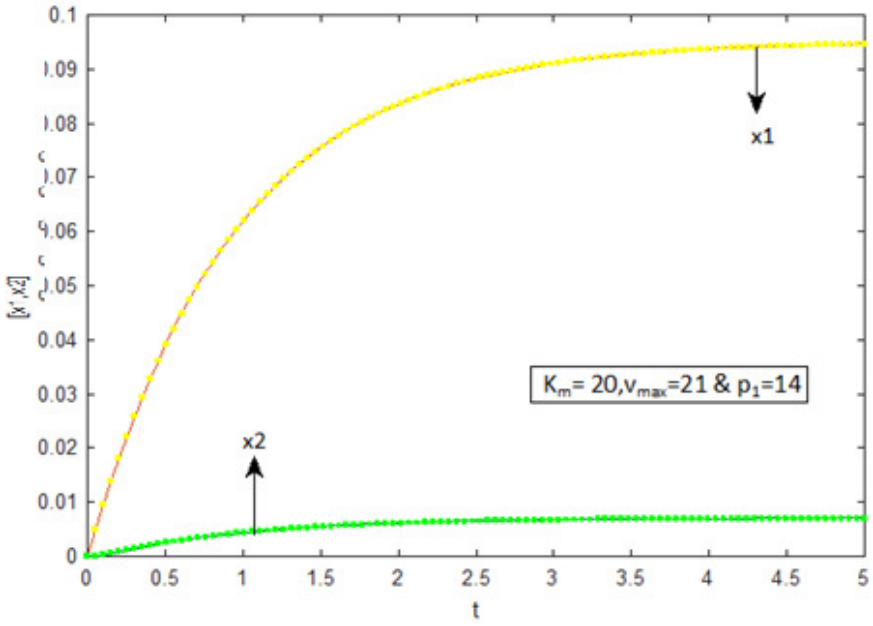

Fig.6: The dimensionless drug masses in blood and tissue profiles $x_1(t) \& x_2(t)$ verses dimensionless time t for fixed values of Michaelis-Menten parameters $v_{\max}, k_m and\ p_1$ are plotted using eqn. (8)-(9). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation..

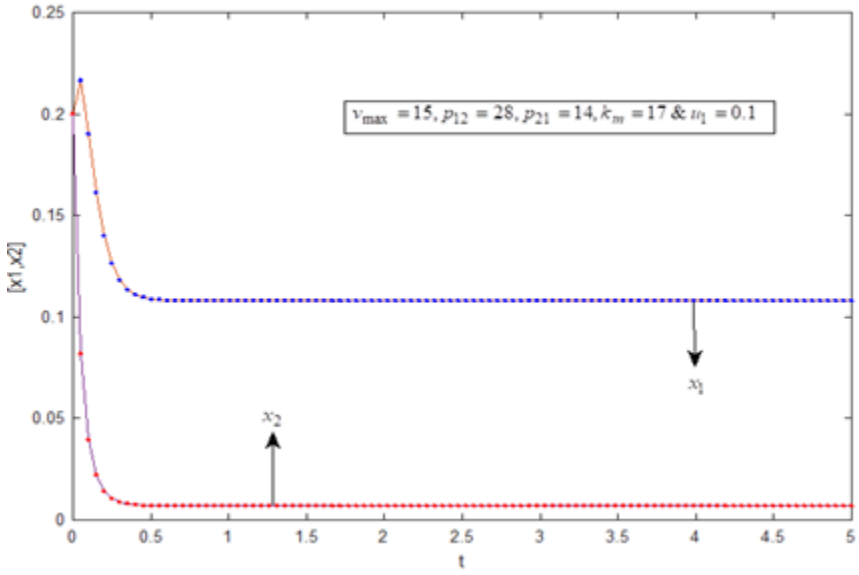

Fig.7: The dimensionless drug masses in blood and tissue profiles $x_1(t) \& x_2(t)$ verses dimensionless time t for fixed values of Michaelis-Menten parameter $v_{\max}, k_m, u_1, p_{21} and\ p_{12}$ are plotted using eqn. (10)-(11). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

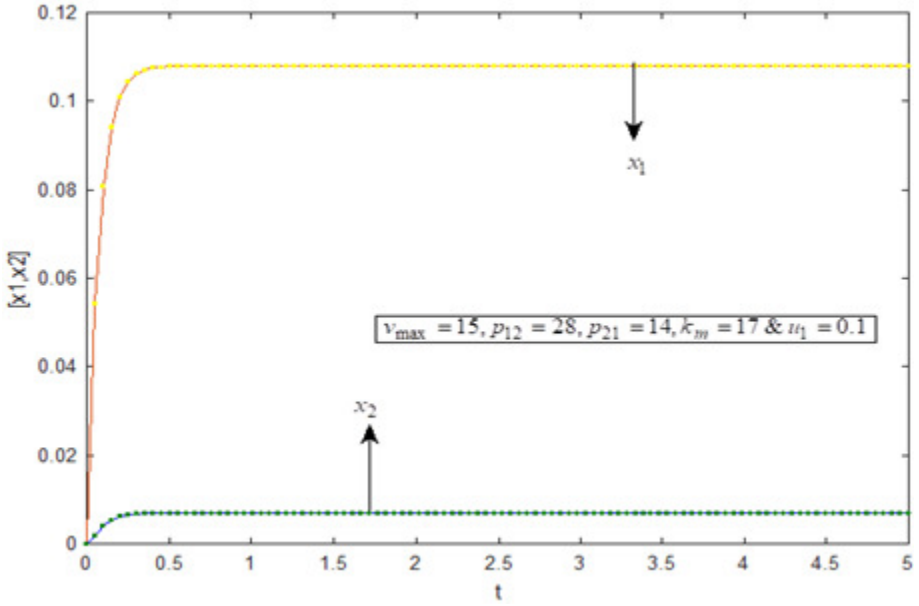

Fig.8: The dimensionless drug masses in blood and tissue profiles $x_1(t) \& x_2(t)$ verses dimensionless time t for fixed values of Michaelis-Menten parameter $v_{\max}, k_m, u_1, p_{21} and\ p_{12}$ are plotted using eqn. (10)-(11). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

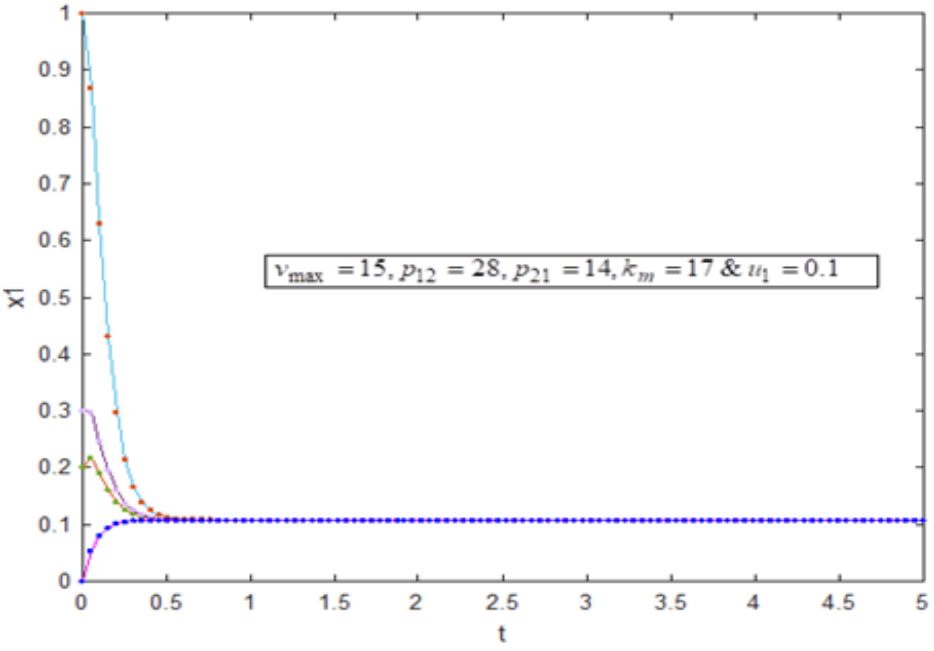

Fig.9: The dimensionless drug mass in blood profiles $x_1(t)$ verses dimensionless time t for varying the initial conditions from 0- 0.15 is plotted using eqn. (10). The key to the graph: solid line represents analytical solution and the dotted line represents the numerical simulation.

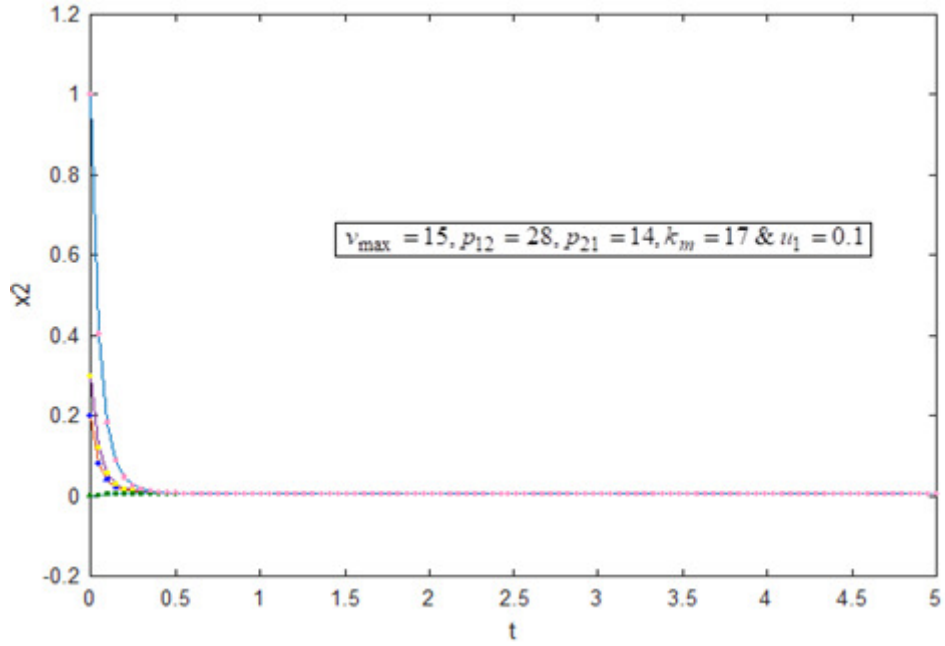

Fig.10: The dimensionless drug mass in tissue profiles $x_2(t)$ verses dimensionless time t for varying the initial conditions from 0- 0.15is plotted using eqn. (11). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

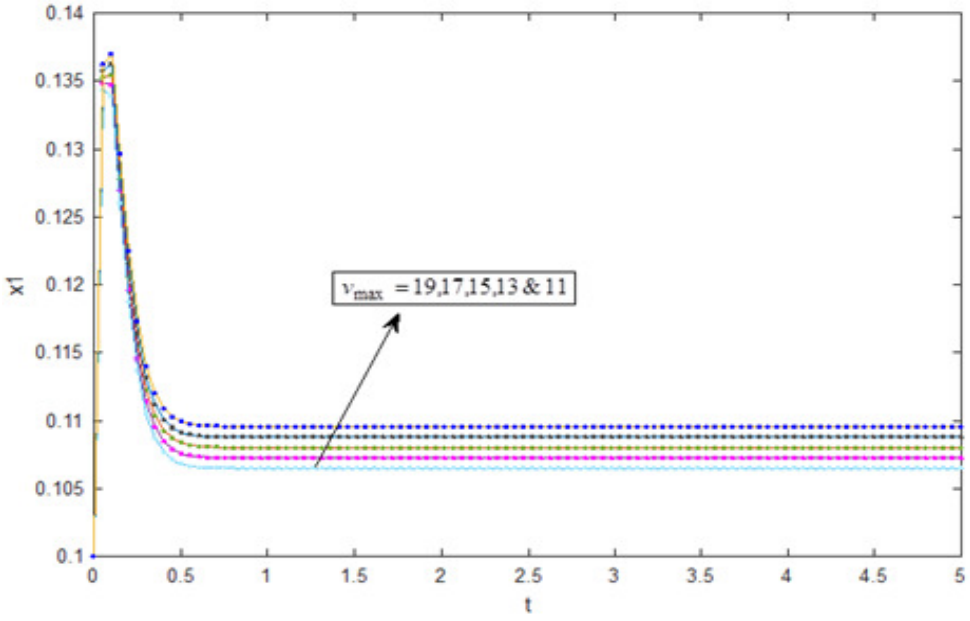

Fig.11: The dimensionless drug mass in tissue profiles $x_2(t)$ verses dimensionless time t for various values of Michaelis-Menten parameter v_{max} is plotted using eqn. (10). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

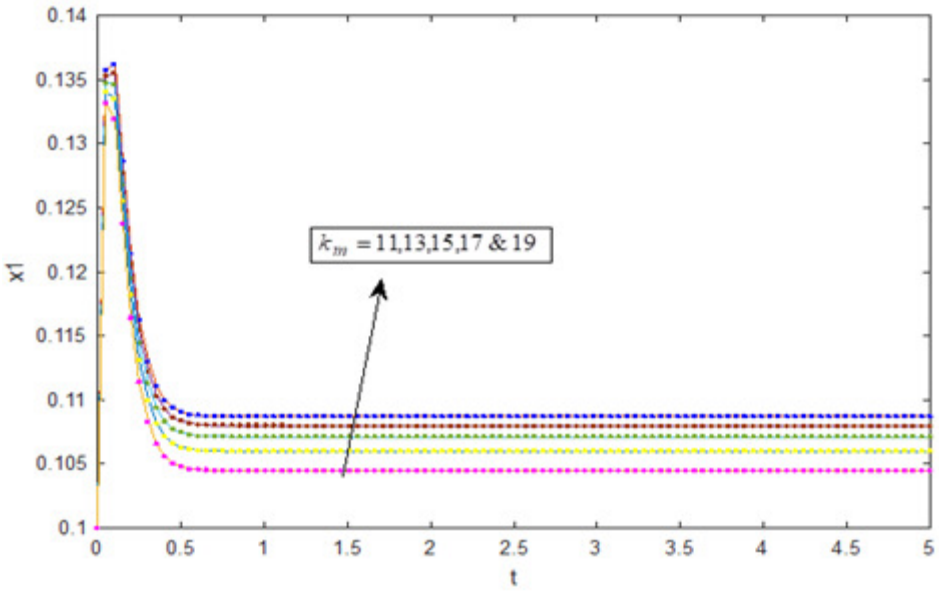

Fig.12: The dimensionless drug mass in tissue profiles $x_1(t)$ verses dimensionless time t for various values of Michaelis-Menten parameter k_m is plotted using eqn. (10). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

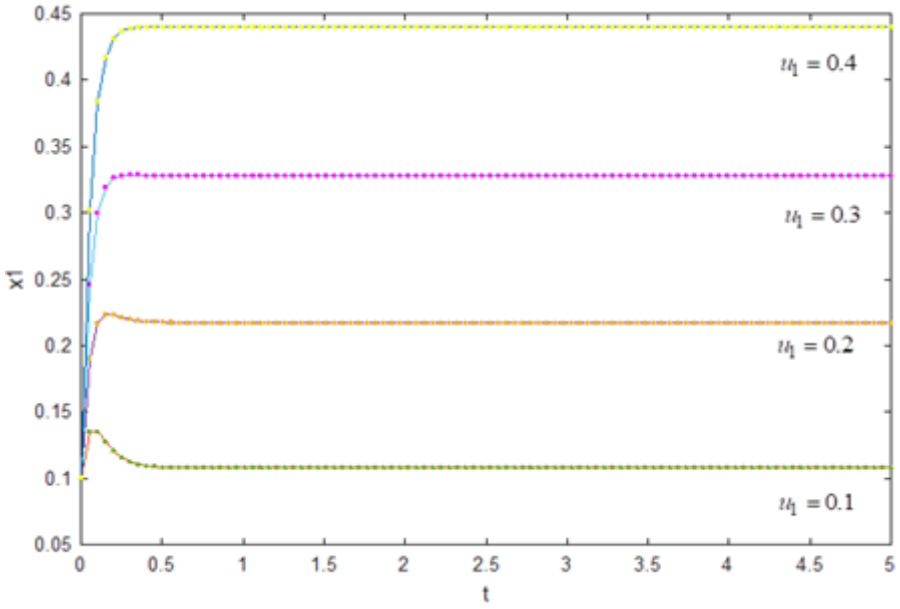

Fig.13: The dimensionless drug mass in tissue profiles $x_1(t)$ verses dimensionless time t for various values of drug input values u_1 is plotted using eqn. (10). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

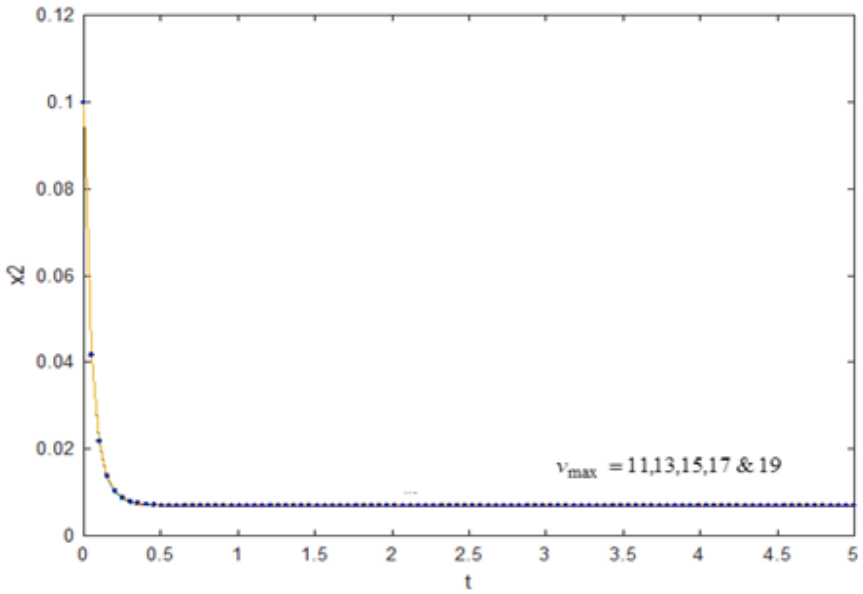

Fig.14: The dimensionless drug mass in tissue profiles $x_2(t)$ verses dimensionless time t for various values of Michaelis-Menten parameter $v_{\max}$ is plotted using eqn. (11). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

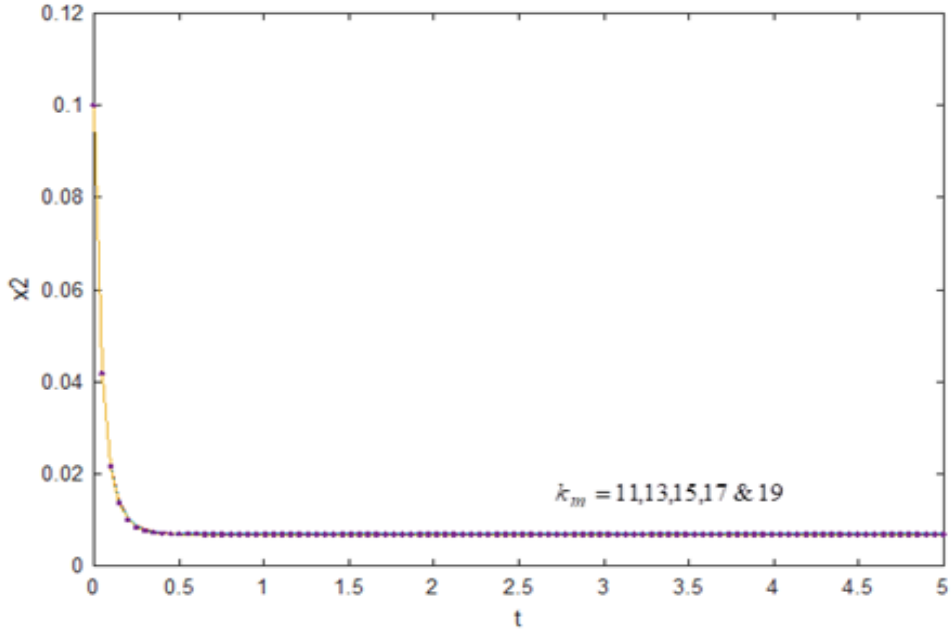

Fig.15: The dimensionless drug mass in tissue profiles $x_2(t)$ verses dimensionless time t for various values of Michaelis-Menten parameter k_m is plotted using eqn. (10). The key to the graph: solid line represents analytical solution and the dotted line represents numerical simulation.

6. Conclusion

In this paper we have described New Homotopy perturbation method (NHPM) , a general asymptotic method assisting biomedical researchers to perform global identifiability analysis for linear and non-linear dynamic models. We discussed about the solution of two non-linear drug masses in blood and tissue profiles to test the global identifiability of biological and physiological systems. The analytical solutions are compared with the numerical solution and satisfactory agreement is noted. The graphical representations also presented for various value of Michaelis-Menten parameters. The New Homotopy perturbation method is a powerful and efficient technique for finding solutions of nonlinear equations. Main concentration of the work is how to employ NHPM technique in non-linear system of differential equations.

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