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MATHEMATICAL EXPRESSIONS OF MAMILLARY MODEL OF FOUR COMPARTMENTS

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Abstract:

In this study we can determine the structural identifiability of certain in vitro nonlinear pharmacokinetic models is provided. The major components of identifiability analysis are determining the identifiable parameter combinations and the functional forms for the dependencies between unidentifiable parameters. There are several numerical approaches to determining identifiability of different equation models have been developed. Mass of the substances can shown graphically. The Homotopy analysis method can be easily extended to solve other non-linear initial and numerical solutions of four components.

Index Terms: Compartmental Models, Structural Identifiability, Numerical Simulation & Homotopy Analysis Method

1. Introduction:

In this paper we investigated in medicine is a pharmacokinetic measurement of the volume of plasma that is completely cleared off a substance per unit. The usual units are mL/min. The total body clearance will be equal to the renal clearance, hepatic clearance although of many drugs the clearance is at most synonymous with renal clearance each substance has a specific clearance that depends on its filtration characteristics. A blood clot is a ticked mass in the blood formed by tiny substances called platelets. A group or layer of cells that platform specific function muscle tissue is a group of muscle cells. Human body tissue consist of groups of cells with a similar structure working with together for a specific function .we are composed of several types of human body tissue. In general ,these physiological models take the mathematical form of linear or nonlinear dynamic state –space models ,depending on unknown parameter .In common case of model unidentifiability, a key concept in identifiability analysis is that identifiable combinations C. Cobelli.et.al[1,2].Many different analytical approaches to structural identifiability have been developed. [3-4]. Most numerical approaches to identifiability provide only local information about the parameter they are often more computationally tractable [5]. It is desired to investigate the nonlinear kinetics of in vitro hepatic uptake the OATP substrate pitavastin and quantity the mechanics present numerically [6]. In the model derived as in most biomedical system modelling. In the model parameter have biological meaning and it is desired to establish whether it is possible to estimate their values from experimental data [7]. This is an important but often overlooked theoretical to experiment design, system identification, and parameter estimation. Such analysis is highly relevant to large scale, highly complex systems, which are typical and chemical kinetics and system biology [8-9]. If all the unknown parameter s are globally identifiable, the system model is structurally globally identifiable.

2. Mathematical Modulation of the Problem:

It has been shown that the construction of the characteristic set ignores the initial conditions .however in the fortune circumstances of the initial conditions ,the data available to solve the identifiably problem should include also this knowledge.

In this case we assume that $l,(l \leq n)$,initial condition of a dynamical model of order n are known .To check if the corresponding states are algebraically observable .to do this one has to verify if the derivatives of these state components appears or not in the corresponding l of the characteristic set .if not the above states are algebraically observable and we produce with the identically test as follows the polynomial time $t = 0$ and set equal to their corresponding known values .Note that the right hand members of these polynomial function of p with coefficient of the data $X_0, \dot{u}(0), \ddot{u}(0)\ldots.. y(0), \dot{y}(0), \ddot{y}(0)\ldots$ for example we have four eqn.

$$\dot{x}_1 = -(k_{21} + k_{31} + k_{41} + k_{01})x_1 + k_{12}x_2 + k_{13}x_3 + k_{14}x_4 + u \;\; ; \; x_1(0) = x_{10} \quad (1)$$

$$\dot{x}_2 = k_{21}x_1 - k_{12}x_2 \;\; ; \;\; x_2(0) = x_{20} \quad (2)$$

$$\dot{x}_3 = k_{31}x_1 - k_{13}x_3 ; \quad x_3(0) = x_{30} \quad (3)$$

$$\dot{x}_4 = k_{41}x_1 - k_{14}x_4 ; \quad x_4(0) = x_{40} \quad (4)$$

3. Solution of the Non-Linear Differential Equations Using the Homotopy Analysis Method:

HAM is a non-perturbative analytical method for obtaining series solutions to nonlinear equations and has been successfully applied to numerous problems in science and engineering [9-31]. In comparison with other perturbative and non-perturbative analytical methods, HAM offers the ability to adjust and control the convergence of a solution via the so-called convergence-control parameter. Because of this, HAM has proved to be the most effective method for obtaining analytical solutions to highly non-linear differential equations. Previous applications of HAM have mainly focused on non-linear differential equations in which the non-linearity is a polynomial in terms of the unknown function and its derivatives. As seen in (1), the non-linearity presents in the form of non-linear terms, and thus, poses a greater challenge with respect to finding approximate solutions analytically. Our results show that even in this case, HAM yields excellent results.

Liao [17-25] proposed a powerful analytical method for non-linear problems, namely the Homotopy analysis method. This method provides an analytical solution in terms of an infinite power series. However, there is a practical need to evaluate this solution and to obtain numerical values from the infinite power series. In order to investigate the accuracy of the Homotopy analysis method (HAM) solution with a finite number of terms, the system of differential equations were solved. The Homotopy analysis method is a good technique comparing to another perturbation method. The Homotopy analysis method contains the auxiliary parameter h, which provides us with a simple way to adjust and control the convergence region of solution series. The approximate analytic solution of the eqns. (7)-(9) by using the HAM is as follows:

$$
\begin{aligned}
x_1(t) = & -\frac{u}{R} + ae^{-Rt} + \frac{ue^{-Rt}}{R} + h\left[\frac{-be^{-k12t} - ce^{-k13t} - de^{-k14t}}{R}\right] - h\left[\frac{b+c+d}{R}\right]e^{-Rt} \\
& + \frac{\left[\begin{array}{l} (h+1)h\left(-be^{-k12t} - ce^{-k13t} - de^{-k14t}\right) \\ + h^2\left(-\frac{1}{2}ut^2 + \frac{ae^{-Rt}}{R^2} + \frac{ue^{-Rt}}{R^3}\right)\left(k_{21} + k_{31} + k_{41}\right) \\ - h^2\left(-\frac{a}{R} - \frac{u}{R^2}\right)\left(-\frac{k_{21}e^{-k12t}}{k_{12}} - \frac{k_{31}e^{-k13t}}{k_{13}} - \frac{k_{41}e^{-k14t}}{k_{14}}\right) \end{array}\right]}{R} \\
& - \frac{\left[\begin{array}{l} (h+1)h(-b-c-d) + h^2\left(-\frac{1}{2}ut^2 + \frac{a}{R^2} + \frac{u}{R^3}\right)\left(k_{21} + k_{31} + k_{41}\right) \\ - h^2\left(-\frac{a}{R} - \frac{u}{R^2}\right)\left(-\frac{k_{21}}{k_{12}} - \frac{k_{31}}{k_{13}} - \frac{k_{41}}{k_{14}}\right) \end{array}\right]}{R}
\end{aligned} \qquad (5)
$$

$$
\begin{aligned}
x_2(t) = & \, be^{-k12t} + h\left[\frac{k_{21}}{k_{12}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - h\left[\frac{k_{21}}{k_{12}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k12t} \\
& + (h+1)h\left[\frac{k_{21}}{k_{12}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - (h+1)h\left[\frac{k_{21}}{k_{12}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k12t}
\end{aligned} \qquad (6)
$$

$$
\begin{aligned}
x_3(t) = & \, ce^{-k13t} + h\left[\frac{k_{31}}{k_{13}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - h\left[\frac{k_{31}}{k_{13}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k13t} \\
& + (h+1)h\left[\frac{k_{31}}{k_{13}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - (h+1)h\left[\frac{k_{31}}{k_{13}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k13t}
\end{aligned} \qquad (7)
$$

$$
\begin{aligned}
x_4(t) = & \, ce^{-k14t} + h\left[\frac{k_{41}}{k_{14}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - h\left[\frac{k_{41}}{k_{14}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k14t} \\
& + (h+1)h\left[\frac{k_{41}}{k_{14}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - (h+1)h\left[\frac{k_{41}}{k_{14}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k14t}
\end{aligned} \qquad (8)
$$

4. Result and Discussion:

Figure 1-4 represents Mass of the substance in the blood $(\dot{x}_1)$ versus time (t) From Fig.1, it is evident that when the k_{12} increases the corresponding Mass of the substance in the blood $(\dot{x}_1)$ also increases in some fixed values of other parameters $k_{13,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig.2, it is observed that when the k_{13} increases the corresponding Mass of the substance in the blood $(\dot{x}_1)$ also increases in some fixed values of other parameters $k_{12,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig.3, it shows that when the k_{14} increases the corresponding Mass of the substance in the blood $(\dot{x}_1)$ also increases in some fixed values of other parameters $k_{12,}k_{13},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig.4, it is evident that when the k_{01} increases the corresponding Mass of the substance in the blood $(\dot{x}_1)$ also increases in some fixed values of other parameters $k_{12,}k_{13},k_{14,}k_{21,,}k_{31,}k_{41,}u$. Figure 5-8 represents Mass of the substance in the tissue $(\dot{x}_2)$ versus time (t). From Fig.5, it is evident that when the k_{12} increases the corresponding Mass of the substance in the blood $(\dot{x}_2)$ also decreases in some fixed values of other parameters $k_{13,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig.6, it is observed that when the k_{13} increases the corresponding Mass of the substance in the tissue $(\dot{x}_2)$ also decreases in some fixed values of other parameters $k_{12,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig.7, it shows that when the k_{14} increases the corresponding Mass of the substance in the tissue $(\dot{x}_2)$ also increases in some fixed values of other parameters $k_{12,}k_{13},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig.8, it is evident that when the k_{01} increases the corresponding Mass of the substance in the tissue $(\dot{x}_2)$ also decreases in some fixed values of other parameters $k_{12,}k_{13},k_{14,}k_{21,,}k_{31,}k_{41,}u$.

Figure 9-12 represents $(\dot{x}_3)$ versus time $(\dot{t})$. From Fig .9, it is evident that when the k_{12} increases the corresponding $(\dot{x}_3)$ also increases in some fixed values of other parameters $k_{13,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig .10, it observed that when the k_{13} increases the corresponding $(\dot{x}_3)$ is decreases in some fixed values of other parameters $k_{12,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig .11, it is evident that when the k_{14} increases the corresponding $(\dot{x}_3)$ also increases in some fixed values of other parameters $k_{12,}k_{13},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig .12, it is evident that when the k_{01} increases the corresponding $(\dot{x}_3)$ also increases in some fixed values of other parameters $k_{12,}k_{13},k_{14,}k_{21,,}k_{31,}k_{41,}u$.

Figure 13-16 represents $(\dot{x}_4)$ versus time $(\dot{t})$. From Fig .13, it is evident that when the k_{12} increases the corresponding $(\dot{x}_4)$ also increases in some fixed values of other parameters $k_{13,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$ .From Fig .14, it observed that when the k_{13} increases the corresponding $(\dot{x}_4)$ is decreases in some fixed values of other parameters $k_{12,}k_{14},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig .15, it is shows that when the k_{14} increases the corresponding $(\dot{x}_4)$ also decreases in some fixed values of other parameters $k_{12,}k_{13},k_{01,}k_{21,,}k_{31,}k_{41,}u$. From Fig .16, it is evident that when the k_{01} increases the corresponding $(\dot{x}_4)$ also decreases in some fixed values of other parameters $k_{12,}k_{13},k_{14,}k_{21,,}k_{31,}k_{41,}u$.

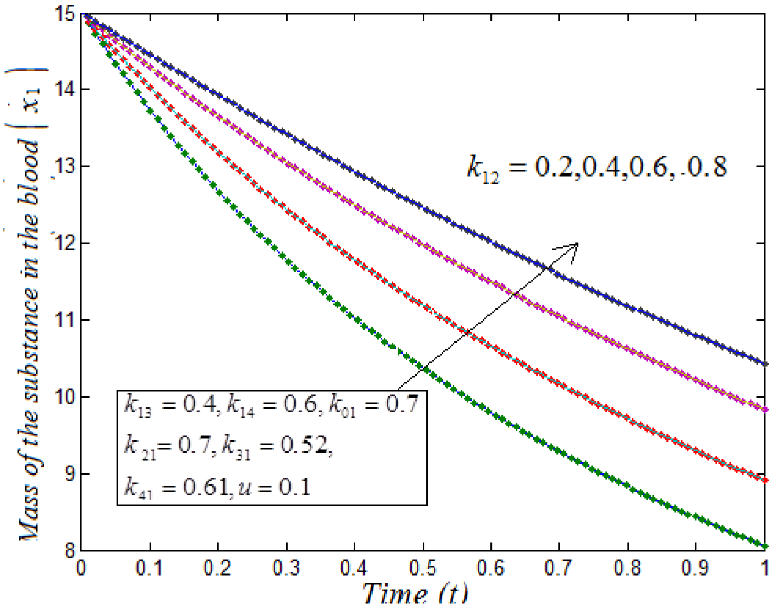

Figure 1: Mass of the substance in the blood $(\dot{x}_1)$ versus time (t).The curves are plotted using the eqn.(5) for various value of k_{12} and in some fixed value of the other dimensionless parameter $k_{13,} k_{14,} k_{01,} k_{21}, k_{31}, k_{41}, u$,when $k_{13} = 0.4, k_{14} = 0.6, k_{01} = 0.7, k_{21} = 0.7,\ k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = -0.82$ Here (....) represents numerical simulation and (___) represents HAM solution.

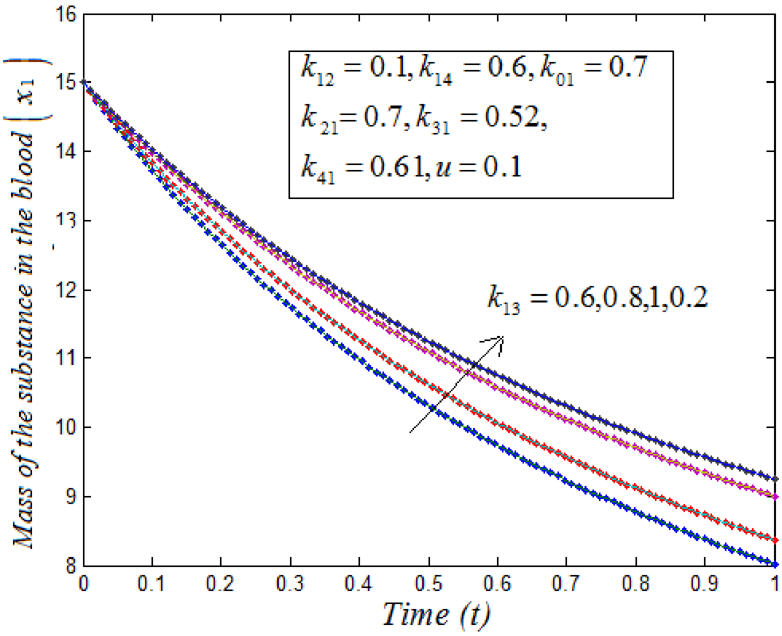

Figure 2: Mass of the substance in the blood $(\dot{x}_1)$ versus time (t).The curves are plotted using the eqn.(5) for various value of k_{13} and in some fixed values of the other dimensionless parameters $k_{12,} k_{14,} k_{01,} k_{21}, k_{31}, k_{41}, u$, when $k_{14} = 0.4, k_{12} = 0.1, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52,\ k_{41} = 0.61, u = 0$, with $h = 0.8$ Here (....) represents numerical simulation and (___) represents HAM solution.

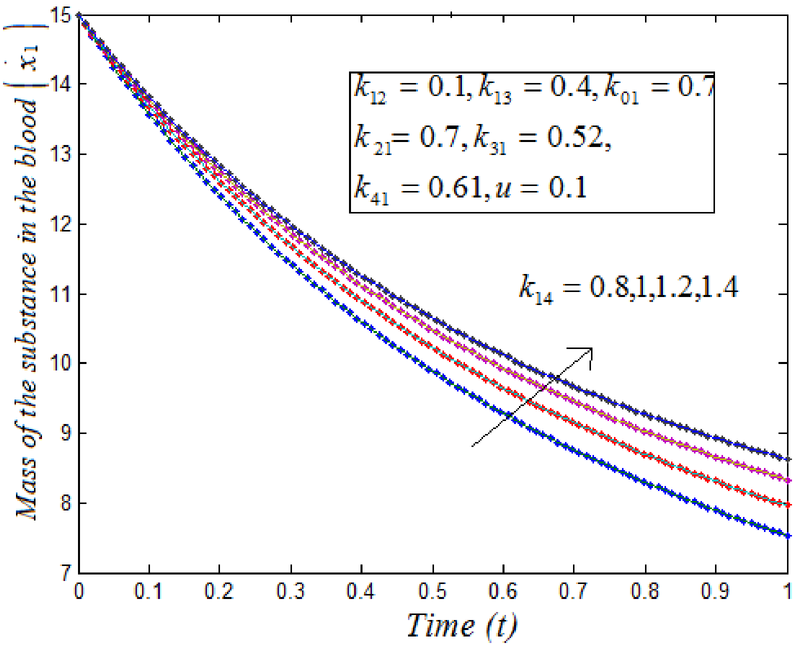

Figure 3: Mass of the substance in the blood $(\dot{x}_1)$ versus time (t). The curves are plotted using the eqn.(5) for various value of k_{14} and in some fixed values of the other dimensionless parameters $k_{12,}k_{13,}k_{01,}k_{21},k_{31},k_{41},u$, when $k_{13}=0.4, k_{12}=0.1, k_{01}=0.7, k_{21}=0.7, k_{31}=0.52,$ $k_{41}=0.61, u=0.1$ with $h=0.87$ Here (....) represents numerical simulation and (____) represents HAM solution.

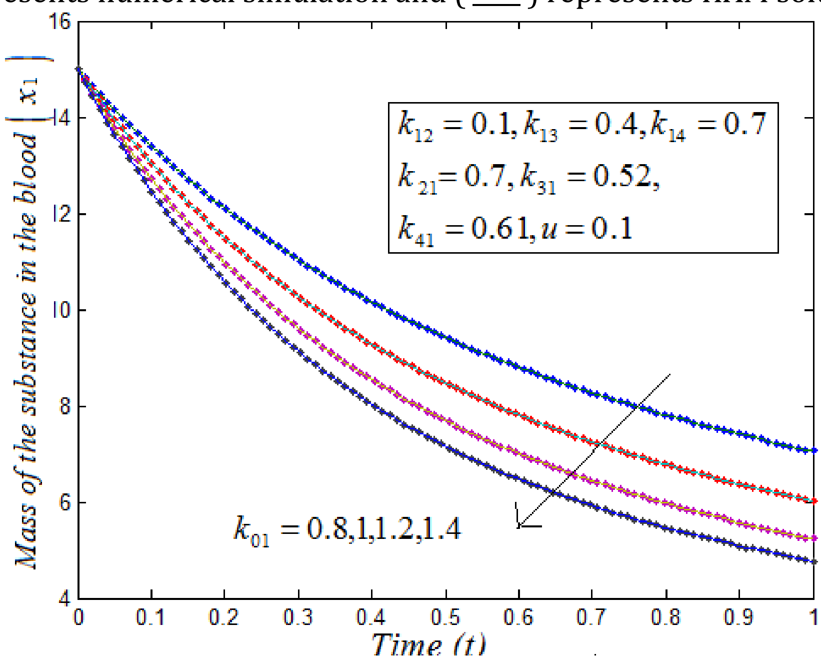

Figure 4: Mass of the substance in the blood $(\dot{x}_1)$ versus time (t). The curves are plotted using the eqn.(5) for various value of k_{01} and in some fixed values of the other dimensionless parameters $k_{12,}k_{13,}k_{14,}k_{21},k_{31},k_{41},u$, when $k_{13}=0.4, k_{12}=0.1, k_{14}=0.6, k_{21}=0.7, k_{31}=0.52,$ $k_{41}=0.61, u=0.1$ with $h=-0.5$. Here (....) represents numerical simulation and (____) represents HAM solution.

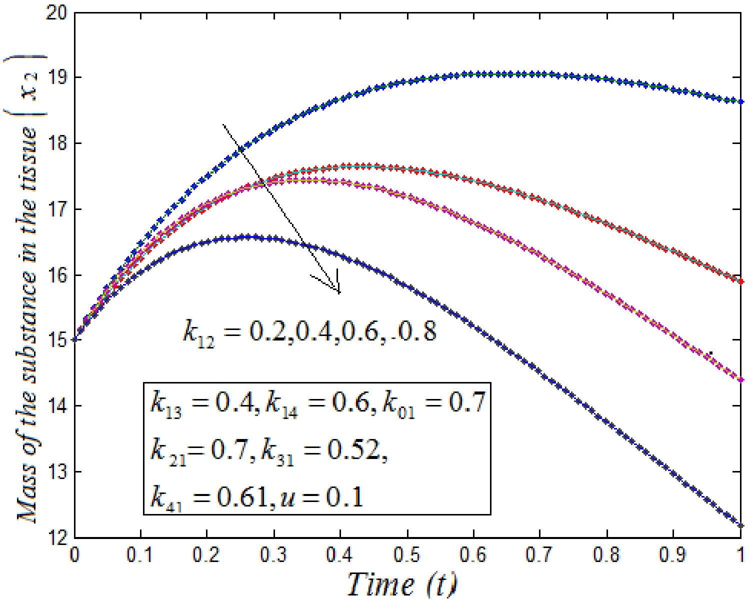

Figure 5: Mass of the substance in the tissue $(\dot{x}_2)$ versus time (t). The curves are plotted using the eqn.(6) for various value of k_{12} and some in fixed values of the other dimensionless parameters $k_{13}, k_{14}, k_{01}, k_{21}, k_{31}, k_{41}, u$, when $k_{13} = 0.4, k_{14} = 0.6, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = -0.270$ Here (....) represents numerical simulation and (____) represents HAM solution.

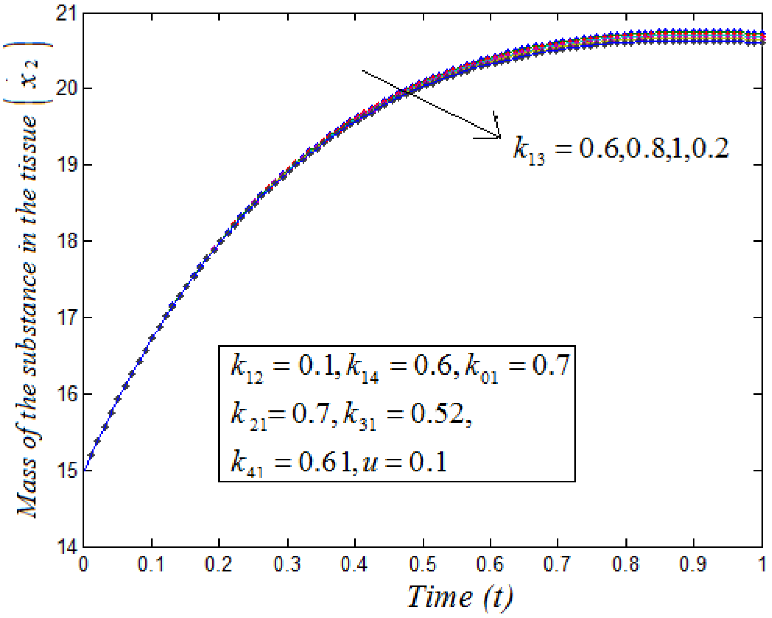

Figure 6: Mass of the substance in the tissue $(\dot{x}_2)$ versus time (t). The curves are plotted using the eqn.(6) for various value of k_{13} and in some fixed values of the other dimensionless parameters $k_{12}, k_{14}, k_{01}, k_{21}, k_{31}, k_{41}, u$, when $k_{14} = 0.4, k_{12} = 0.1, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.01$. Here (....) represents numerical simulation and (____) represents HAM solution.

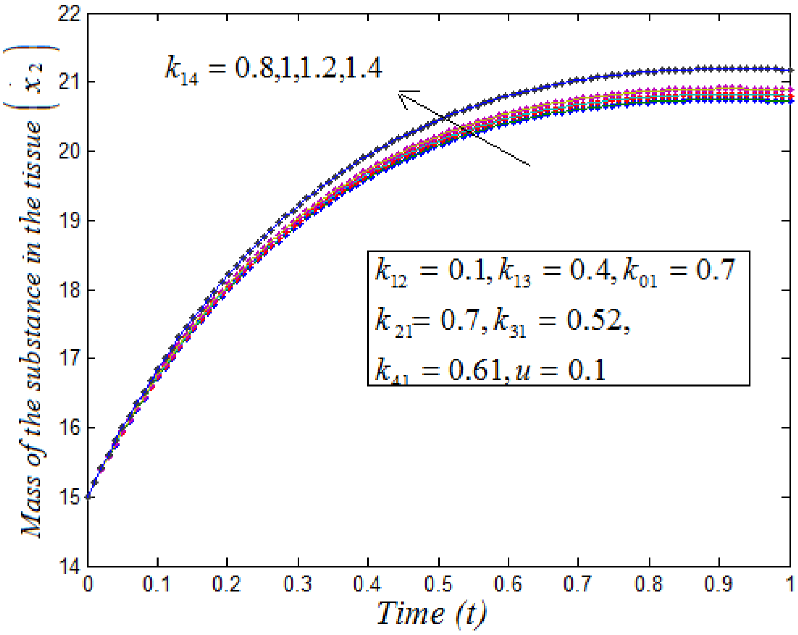

Figure 7: Mass of the substance in the tissue $(\dot{x}_2)$ versus time (t). The curves are plotted using the eqn.(1) for various value of k_{14} and in some fixed value of the other dimensionless parameters $k_{12}, k_{13}, k_{01}, k_{21}, k_{31}, k_{41}, u$, when $k_{13} = 0.4, k_{12} = 0.1, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = -0.102$ Here (....) represents numerical simulation and (____) represents HAM solution.

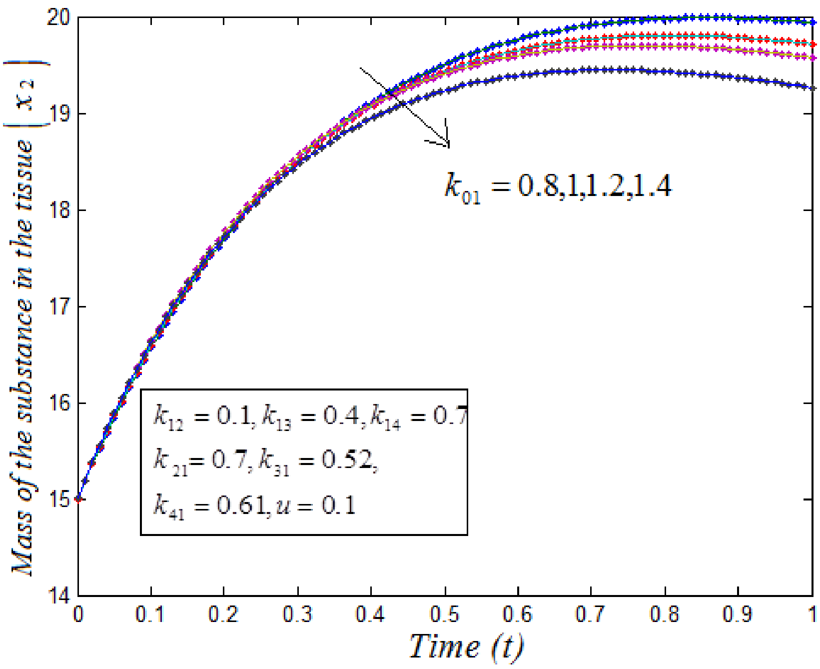

Figure 8: Mass of the substance in the tissue $(\dot{x}_2)$ versus time (t). The curves are plotted using the eqn.(6) for various value of k_{01} and in some fixed values of the other dimensionless parameters $k_{12}, k_{13}, k_{14}, k_{21}, k_{31}, k_{41}, u$, when $k_{13} = 0.4, k_{12} = 0.1, k_{14} = 0.6, k_{21} = 0.7, k_{31} = 0.52,$ $k_{41} = 0.61, u = 0.1$ with $h = 0.09$. Here (....) represents numerical simulation and (____) represents HAM solution.

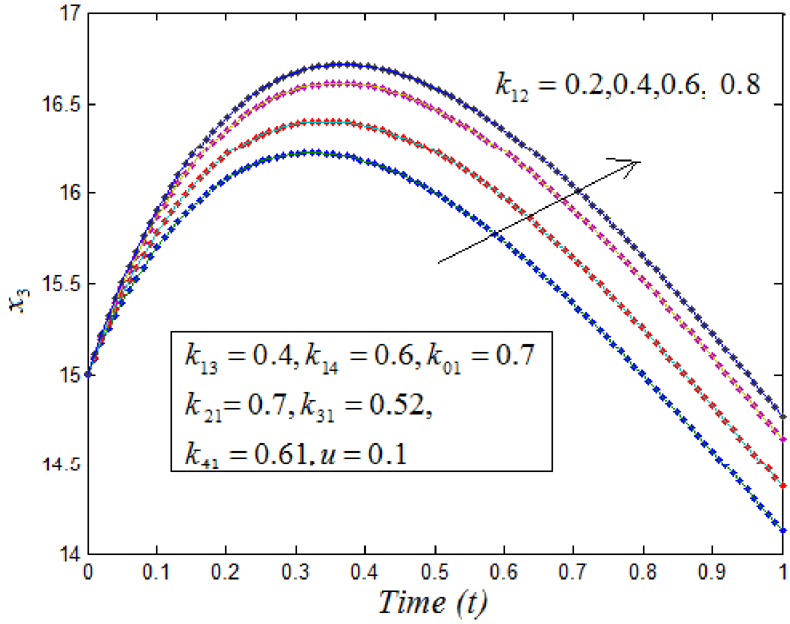

Figure 9: $(\dot{x}_3)$ versus time (t).The curves are plotted using the eqn.(7) for various value of k_{12} and in some fixed values of the other dimensionless parameters $k_{13}, k_{14}, k_{01}, k_{21}, k_{31}, k_{41}, u$, when $k_{13} = 0.4, k_{14} = 0.6, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.407$. Here (....) represents numerical simulation and (____) represents HAM solution.

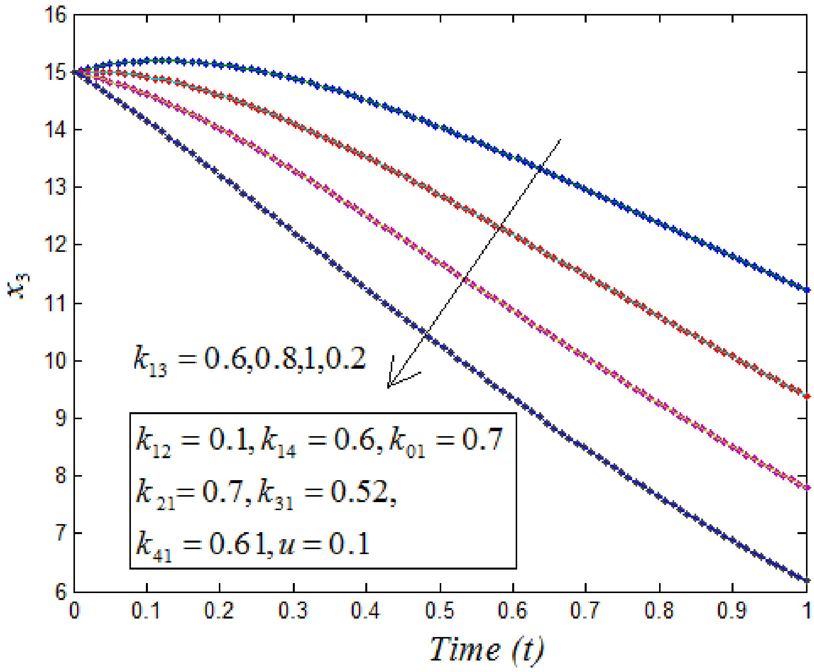

Figure 10: $(\dot{x}_3)$ versus time (t).The curves are plotted using the eqn.(7) for various value of k_{13} and in some fixed values of the other dimensionless parameters $k_{12}, k_{14}, k_{01}, k_{21}, k_{31}, k_{41}, u$ $k_{14} = 0.4, k_{12} = 0.1, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.54$. Here (....) represents numerical simulation and (____) represents HAM solution.

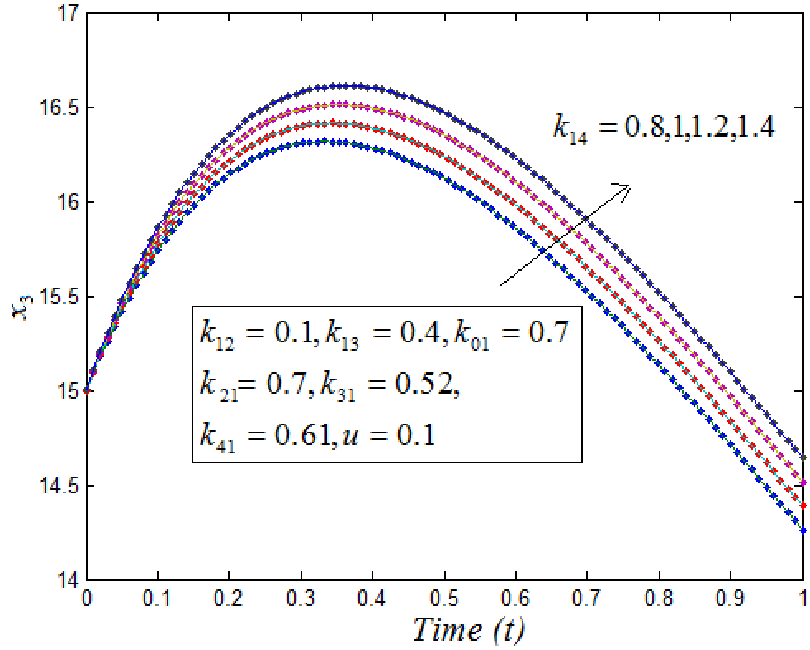

Figure 11: $(\dot{x}_3)$ versus time (t). The curves are plotted using the eqn.(7) for various value of k_{14} and in some fixed values of the other dimensionless parameters $k_{12}, k_{13}, k_{01}, k_{21}, k_{31}, k_{41}, u$, when $k_{13} = 0.4, k_{12} = 0.1, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.4$. Here (....) represents numerical simulation and (____) represents HAM solution.

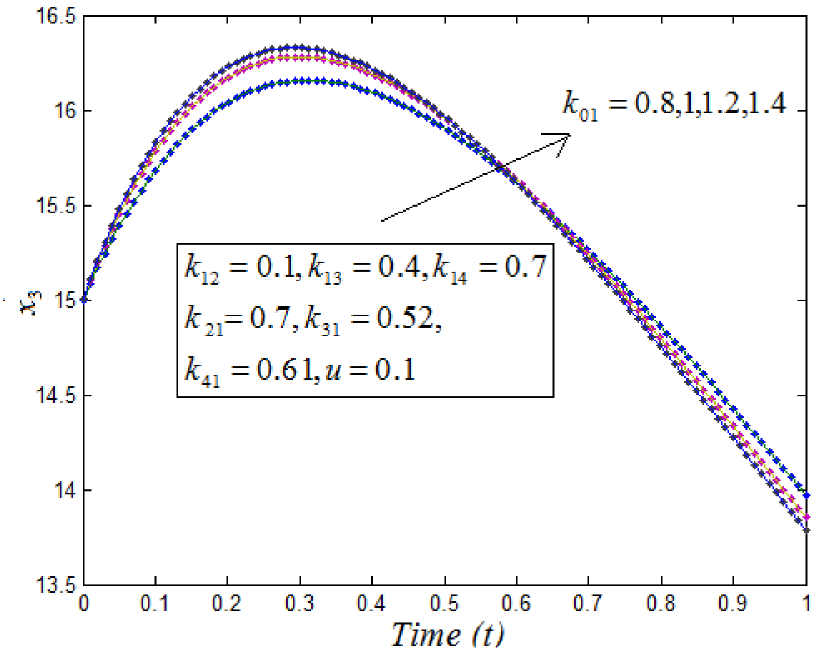

Figure 12: $(\dot{x}_3)$ versus time (t). The curves are plotted using the eqn.(1) for various value of k_{01} and in some fixed values of the other dimensionless parameters $k_{12}, k_{13}, k_{14}, k_{21}, k_{31}, k_{41}, u$, when $k_{13} = 0.4, k_{12} = 0.1, k_{14} = 0.6, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.39$. Here (....) represents numerical simulation and (____) represents HAM solution.

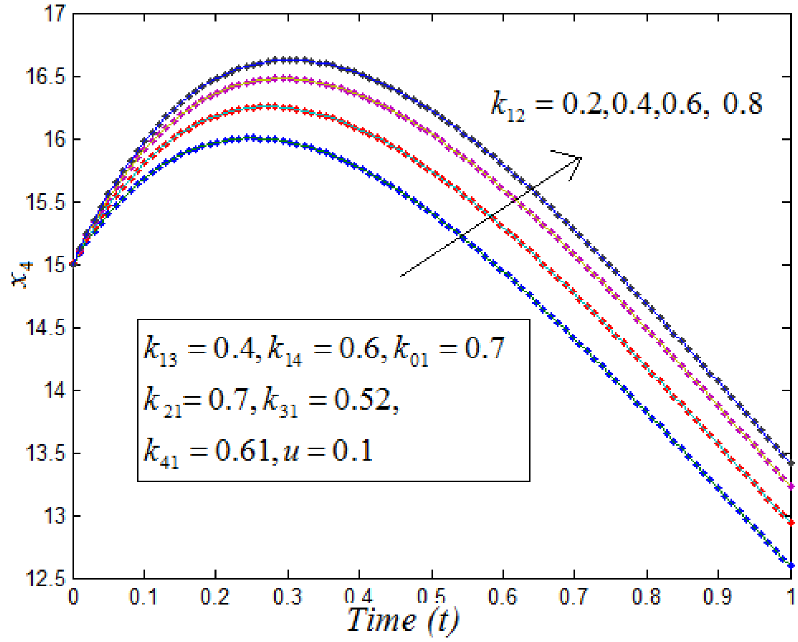

Figure 13: $(\dot{x}_3)$ versus time (t).The curves are plotted using the eqn.(8) for various value of k_{01} and in some fixed values of the other dimensionless parameters $k_{12}, k_{13}, k_{14}, k_{21}, k_{31}, k_{41}, u$,when $k_{13} = 0.4, k_{12} = 0.1, k_{14} = 0.6, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.67$. Here (....) represents numerical simulation and (____) represents HAM solution.

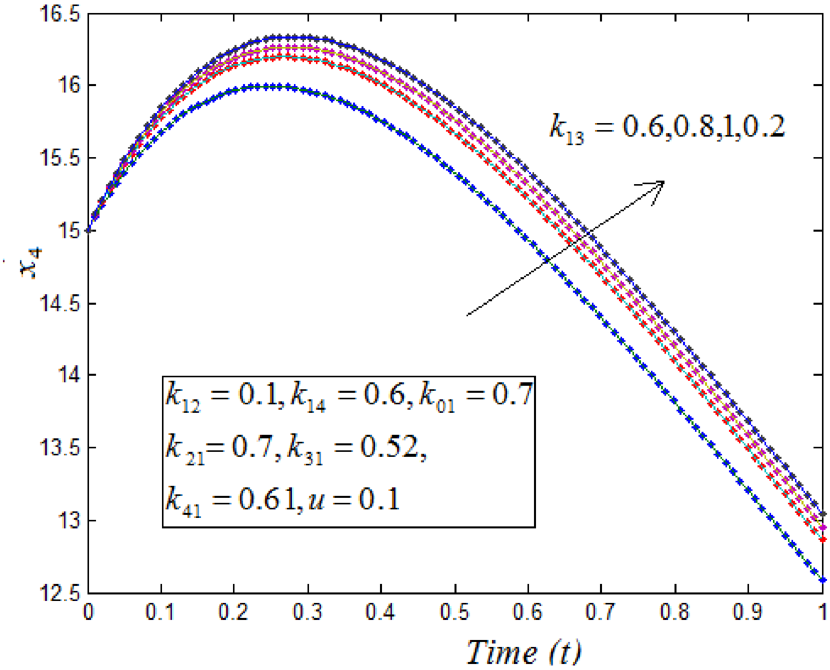

Figure 14: $(\dot{x}_4)$ versus time (t).The curves are plotted using the eqn.(8) for various value of k_{12} and in some fixed values of the other dimensionless parameters $k_{13}, k_{14}, k_{01}, k_{21}, k_{31}, k_{41}, u$,when $k_{13} = 0.4, k_{14} = 0.6, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.62$. Here (....) represents numerical simulation and (____) represents HAM solution.

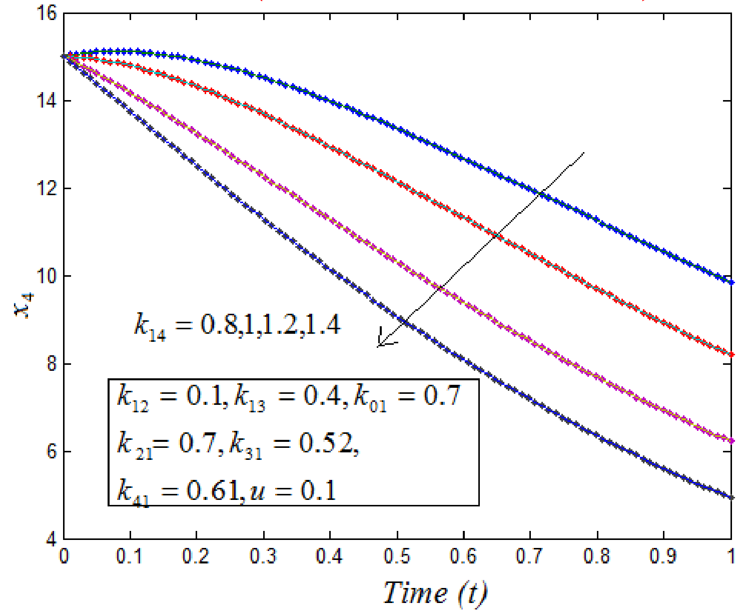

Figure 15: (x_3) versus time (t).The curves are plotted using the eqn.(8) for various value of k_{14} and in some fixed values of the other dimensionless parameters $k_{12}, k_{13}, k_{01}, k_{21}, k_{31}, k_{41}, u$,when $k_{13} = 0.4, k_{12} = 0.1, k_{01} = 0.7, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.87$. Here (....) represents numerical simulation and (____) represents HAM solution.

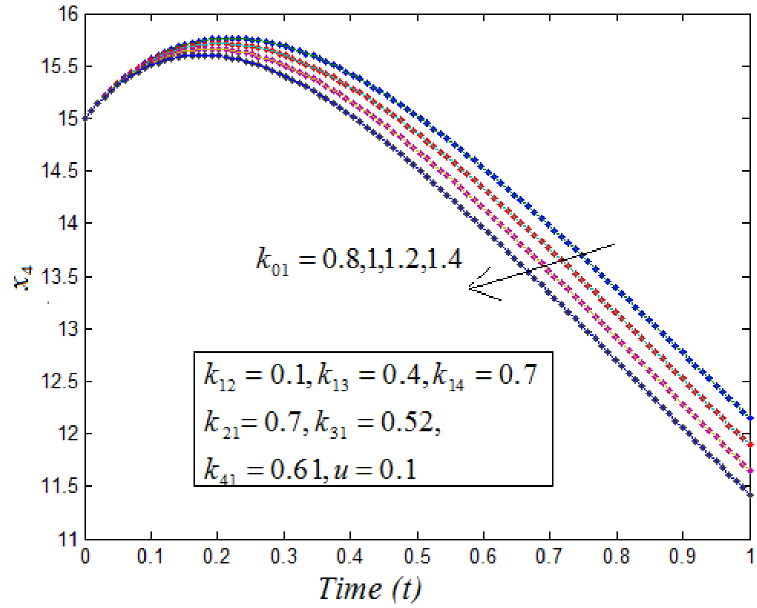

Figure 16: (x_4) versus time (t).The curves are plotted using the eqn.(8) for various value of k_{01} and in some fixed values of the other dimensionless parameters $k_{12}, k_{13}, k_{14}, k_{21}, k_{31}, k_{41}, u$,when $k_{13} = 0.4, k_{12} = 0.1, k_{14} = 0.6, k_{21} = 0.7, k_{31} = 0.52, k_{41} = 0.61, u = 0.1$ with $h = 0.52$. Here (....) represents numerical simulation and (____) represents HAM solution.

5. Conclusion:

In this paper discussed about the mathematical expression for mamilary of four compartments. The approximated analytical expressions for mamillary of four compartments are derived by using the Homotopy analysis method. Further our analytical results are compared with the numerical simulation and a satisfactory agreement is noted. This method can be easily extended to solve the other nonlinear initial and boundary value problems in the fields of science and technology.

6. Acknowledgement:

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Appendix: A

Basic Concept of the Homotopy Analysis Method:

Consider the following differential equation:

$$N[u(t)] = 0 \qquad \text{(A.1)}$$

Where N is a nonlinear operator, t denotes an independent variable, $u(t)$ is an unknown function. For simplicity, we ignore all boundary or initial conditions, which can be treated in the similar way. By means of generalizing the conventional Homotopy method, Liao (2012) constructed the so-called zero-order deformation equation as:

$$(1-p)L[\varphi(t;p)-u_0(t)] = phH(t)N[\varphi(t;p)] \qquad \text{(A.2)}$$

where $p \in [0,1]$ is the embedding parameter, $h \neq 0$ is a nonzero auxiliary parameter, $H(t) \neq 0$ is an auxiliary function, L an auxiliary linear operator, $u_0(t)$ is an initial guess of $u(t)$, is an unknown function. It is important to note that one has great freedom to choose auxiliary unknowns in HAM. Obviously, when $p=0$ and $p=1$, it holds

$$\varphi(t;0)=u_0(t) \text{ and } \varphi(t;1)=u(t) \qquad \text{(A.3)}$$

respectively. Thus, as p increases from 0 to 1, the solution $\varphi(t;p)$ varies from the initial guess $u_0(t)$ to the solution $u(t)$. Expanding $\varphi(t;p)$ in Taylor series with respect to p, we have:

$$\varphi(t;p)=u_0(t)+\sum_{m=1}^{+\infty}u_m(t)p^m \qquad \text{(A.4)}$$

Where

$$u_m(t)=\frac{1}{m!}\frac{\partial^m\varphi(t;p)}{\partial p^m}\Big|_{p=0} \qquad \text{(A.5)}$$

If the auxiliary linear operator, the initial guess, the auxiliary parameter h, and the auxiliary function are so properly chosen, the series (A.4) converges at $p=1$ then we have:

$$u(t)=u_0(t)+\sum_{m=1}^{+\infty}u_m(t). \qquad \text{(A.6)}$$

Differentiating (A.2) for m times with respect to the embedding parameter p, and the n setting $p = 0$ and finally dividing them by m, we will have the so-called mth-order deformation equation as:

$$L[u_m-\chi_m u_{m-1}]=hH(t)\Re_m(\vec{u}_{m-1}) \qquad \text{(A.7)}$$

Where

$$\Re_m(\vec{u}_{m-1})=\frac{1}{(m-1)!}\frac{\partial^{m-1}N[\varphi(t;p)]}{\partial p^{m-1}} \qquad \text{(A.8)}$$

$$\text{and } \chi_m=\begin{cases}0, & m\le 1,\\ 1, & m>1.\end{cases} \qquad \text{(A.9)}$$

Applying L^{-1} on both side of equation (A7), we get

$$u_m(t)=\chi_m u_{m-1}(t)+hL^{-1}[H(t)\Re_m(\vec{u}_{m-1})] \qquad \text{(A.10)}$$

In this way, it is easily to obtain u_m for $m\ge 1$, at M^{th} order, we have

$$u(t)=\sum_{m=0}^{M}u_m(t) \qquad \text{(A.11)}$$

when $M\to+\infty$, we get an accurate approximation of the original equation (A.1). For the convergence of the above method we refer the reader to Liao [20]. If equation (A.1) admits unique solution, then this method will produce the unique solution.

Appendix: B

Approximate Analytical Expression of the Non - Linear Differential Equations (7) and (8) Using the Homotopy Analysis Method:

In this appendix, we derive the analytical expressions for (5-8) using the HAM. The eqns. (1-4) can be written as

$$\frac{d\dot{x}_1}{dt}+(k_{21}+k_{31}+k_{41}+k_{01})x_1-k_{12}x_2-k_{13}x_3-k_{14}x_4-u=0 \quad \text{(B.1)}$$

$$\frac{d\dot{x}_2}{dt}-k_{21}x_1+k_{12}x_2=0 \quad \text{(B.2)}$$

$$\frac{d\dot{x}_3}{dt}-k_{31}x_1+k_{13}x_3=0 \quad \text{(B.3)}$$

$$\frac{d\dot{x}_4}{dt}-k_{41}x_1+k_{14}x_4=0 \quad \text{(B.4)}$$

We construct the Homotopy analysis for the eqns.(B.1) to(B.4) are as follows:

$$(1-p)\left[\frac{dx_1}{dt}+(k_{21}+k_{31}+k_{41}+k_{01})x_1-u\right]$$
$$=hp\left[\frac{d\dot{x}_1}{dt}+(k_{21}+k_{31}+k_{41}+k_{01})x_1-k_{12}x_2-k_{13}x_3-k_{14}x_4-u\right] \quad \text{(B.5)}$$

$$(1-p)\left[\frac{dx_2}{dt}+k_{12}x_2\right]=hp\left[\frac{dx_2}{dt}-k_{21}x_1+k_{12}x_2\right] \quad \text{(B.6)}$$

$$(1-p)\left[\frac{dx_3}{dt}+k_{13}x_3\right]=hp\left[\frac{dx_3}{dt}-k_{31}x_1+k_{13}x_3\right] \quad \text{(B.7)}$$

$$(1-p)\left[\frac{dx_4}{dt}+k_{14}x_4\right]=hp\left[\frac{dx_4}{dt}-k_{41}x_1+k_{14}x_4\right] \quad \text{(B.8)}$$

The approximate analytical solution of the eqn. (B.1) - (B.4) are as follows:

$$x_1=x_{10}+px_{11}+p^2x_{12}.... \quad \text{(B.9)}$$

$$x_2=x_{20}+px_{21}+p^2x_{22}.... \quad \text{(B.10)}$$

$$x_3=x_{30}+px_{31}+p^2x_{32}.... \quad \text{(B.11)}$$

$$x_4=x_{40}+px_{41}+p^2x_{42}.... \quad \text{(B.12)}$$

Substituting the eqns. (B.9)-(B.12) into the eqn. (B.5)-(B.8) we get

$$(1-p)\left[\frac{d(x_{10}+px_{11}+p^2x_{12}...)}{dt}+(k_{21}+k_{31}+k_{41}+k_{01})(x_{10}+px_{11}+p^2x_{12}...)-u\right]$$
$$=hp\left[\begin{array}{l}\frac{d(x_{10}+p\dot{x}_{11}+p^2x_{12}...)}{dt}\\+(k_{21}+k_{31}+k_{41}+k_{01})(x_{10}+px_{11}+p^2x_{12}...)\\-k_{12}(x_{20}+px_{21}+p^2x_{22}...)-k_{13}(x_{30}+px_{31}+p^2x_{32}...)\\-k_{14}(x_{40}+px_{41}+p^2x_{42}...)-u\end{array}\right] \quad \text{(B.13)}$$

$$(1-p)\left[\frac{d(x_{20}+px_{21}+p^2x_{22}...)}{dt}+k_{12}(x_{20}+px_{21}+p^2x_{22}...)\right]$$
$$=hp\left[\frac{d(x_{20}+px_{21}+p^2x_{22}...)}{dt}-k_{21}(x_{10}+px_{11}+p^2x_{12}...)+k_{12}(x_{20}+px_{21}+p^2x_{22}...)\right] \quad \text{(B.14)}$$

$$(1-p)\left[\frac{d\left(x_{30}+px_{31}+p^2x_{32}...\right)}{dt}+k_{13}\left(x_{30}+px_{31}+p^2x_{32}...\right)\right]$$
$$=hp\left[\frac{d\left(x_{30}+px_{31}+p^2x_{32}...\right)}{dt}-k_{31}\left(x_{10}+px_{11}+p^2x_{12}...\right)+k_{13}\left(x_{30}+px_{31}+p^2x_{32}...\right)\right] \quad (B.15)$$

$$(1-p)\left[\frac{d\left(x_{40}+px_{41}+p^2x_{42}...\right)}{dt}+k_{14}\left(x_{40}+px_{41}+p^2x_{42}...\right)\right]$$
$$=hp\left[\frac{d\left(x_{40}+px_{41}+p^2x_{42}...\right)}{dt}-k_{41}\left(x_{10}+px_{11}+p^2x_{12}...\right)+k_{14}\left(x_{40}+px_{41}+p^2x_{42}...\right)\right] \quad (B.16)$$

Comparing the coefficients of p^0, p^1, p^2 in the eqns. (B.7) and (B.8) we get,

$$p^0:\frac{dx_{10}}{dt}+\left[k_{21}+k_{31}+k_{41}+k_{01}\right]x_{10}+u=0 \quad (B.17)$$

$$p^0:\frac{dx_{20}}{dt}+k_{12}x_{20}=0 \quad (B.18)$$

$$p^0:\frac{dx_{30}}{dt}+k_{13}x_{30}=0 \quad (B.19)$$

$$p^0:\frac{dx_{40}}{dt}+k_{14}x_{40}=0 \quad (B.20)$$

$$p^1:\frac{dx_{11}}{dt}+\left[k_{21}+k_{31}+k_{41}+k_{01}\right]x_{11}-h\left[k_{12}x_{20}+k_{13}x_{30}+k_{14}x_{40}\right]=0 \quad (B.21)$$

$$p^1:\frac{dx_{21}}{dt}+k_{12}x_{21}-h\left[k_{21}x_{10}\right]=0 \quad (B.22)$$

$$p^1:\frac{dx_{31}}{dt}+k_{13}x_{31}-h\left[k_{31}x_{10}\right]=0 \quad (B.23)$$

$$p^1:\frac{dx_{41}}{dt}+k_{14}x_{41}-h\left[k_{41}x_{10}\right]=0 \quad (B.24)$$

$$p^2:\frac{dx_{12}}{dt}+\left[k_{21}+k_{31}+k_{41}+k_{01}\right]x_{12}$$
$$-\left[(h+1)h\left[k_{12}x_{20}+k_{13}x_{30}+k_{14}x_{40}\right]\right]+h^2\left[k_{21}x_{21}+k_{31}x_{31}+k_{41}x_{41}\right]=0 \quad (B.25)$$

$$p^2:\frac{dx_{22}}{dt}+k_{12}x_{22}-(h+1)h\left[k_{21}x_{11}\right]=0 \quad (B.26)$$

$$p^2:\frac{dx_{32}}{dt}+k_{13}x_{32}-(h+1)h\left[k_{31}x_{11}\right]=0 \quad (B.27)$$

$$p^2:\frac{dx_{42}}{dt}+k_{14}x_{42}-(h+1)h\left[k_{41}x_{11}\right]=0 \quad (B.28)$$

The initial approximations are as follows:

$$\frac{dx_{10}}{dt}(0)=a,\frac{dx_{20}}{dt}(0)=b,\frac{dx_{30}}{dt}(0)=c,\frac{dx_{10}}{dt}(0)=d \quad (B.29)$$

$$\frac{dx_{ij}}{dt}(0)=0,\frac{dx_{ij}}{dt}(0)=0,\frac{dx_{ij}}{dt}(0)=0,\frac{dx_{ij}}{dt}(0)=0 \quad i=1,2,3,4.... \quad j=1,2,3,4.... \quad (B.30)$$

Solving the eqns.(B.17)-(B.28) using the boundary conditions (B.29) and (B.30). We obtain the following results,

$$x_{10} = -\frac{u}{R} + ae^{-Rt} + \frac{ue^{-Rt}}{R} \quad (B.31)$$

$$x_{11} = h\left[\frac{-be^{-k12t} - ce^{-k13t} - de^{-k14t}}{R}\right] - h\left[\frac{b+c+d}{R}\right]e^{-Rt} \quad (B.32)$$

$$x_{12} = \frac{\begin{bmatrix}(h+1)h\left(-be^{-k12t} - ce^{-k13t} - de^{-k14t}\right) + h^2\left(-\frac{1}{2}ut^2 + \frac{ae^{-Rt}}{R^2} + \frac{ue^{-Rt}}{R^3}\right)(k_{21}+k_{31}+k_{41}) \\ -h^2\left(-\frac{a}{R} - \frac{u}{R^2}\right)\left(-\frac{k_{21}e^{-k12t}}{k_{12}} - \frac{k_{31}e^{-k13t}}{k_{13}} - \frac{k_{41}e^{-k14t}}{k_{14}}\right)\end{bmatrix}}{R} - \frac{\begin{bmatrix}(h+1)h(-b-c-d) + h^2\left(-\frac{1}{2}ut^2 + \frac{a}{R^2} + \frac{u}{R^3}\right)(k_{21}+k_{31}+k_{41}) \\ -h^2\left(-\frac{a}{R} - \frac{u}{R^2}\right)\left(-\frac{k_{21}}{k_{12}} - \frac{k_{31}}{k_{13}} - \frac{k_{41}}{k_{14}}\right)\end{bmatrix}e^{-Rt}}{R} \quad (B.33)$$

$$x_{20} = be^{-k12t} \quad (B.34)$$

$$x_{21} = h\left[\frac{k_{21}}{k_{12}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - h\left[\frac{k_{21}}{k_{12}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k12t} \quad (B.35)$$

$$x_{22} = (h+1)h\left[\frac{k_{21}}{k_{12}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - (h+1)h\left[\frac{k_{21}}{k_{12}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k12t} \quad (B.36)$$

$$x_{30} = ce^{-k13t} \quad (B.37)$$

$$x_{31} = h\left[\frac{k_{31}}{k_{13}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - h\left[\frac{k_{31}}{k_{13}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k13t} \quad (B.38)$$

$$x_{32} = (h+1)h\left[\frac{k_{31}}{k_{13}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - (h+1)h\left[\frac{k_{31}}{k_{13}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k13t} \quad (B.39)$$

$$x_{40} = be^{-k14t} \quad (B.40)$$

$$x_{41} = h\left[\frac{k_{41}}{k_{14}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - h\left[\frac{k_{41}}{k_{14}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k14t} \quad (B.41)$$

$$x_{42} = (h+1)h\left[\frac{k_{41}}{k_{14}}\left(-\frac{u}{R}t - \frac{ae^{-Rt}}{R} - \frac{ue^{-Rt}}{R^2}\right)\right] - (h+1)h\left[\frac{k_{41}}{k_{14}}\left(-\frac{a}{R} - \frac{u}{R^2}\right)\right]e^{-k14t} \quad (B.42)$$

According to the HAM, we conclude that

$$x_1 = \lim_{p\to\infty} x_1(t) = x_{10} + x_{11} + x_{12} \quad (B.43)$$

$$x_2 = \lim_{p\to\infty} x_2(t) = x_{20} + x_{21} + x_{22} \quad (B.44)$$

$$x_3 = \lim_{p\to\infty} x_3(t) = x_{30} + x_{31} + x_{32} \quad (B.45)$$

$$x_4 = \lim_{p\to\infty} x_4(t) = x_{40} + x_{41} + x_{42} \quad (B.46)$$

After putting eqns. (B.31)- (B.42) into the eqns. (B.43)- (B.46), we obtain the solution in the text as given in the eqns.(5)-8)

Appendix: C

Scilab Program to Find the Solutions of the Equations (1)-(4):

```
function  sum1
options= odeset('RelTol',1e-6,'Stats','on');
%initial conditions
x0 = [15; 15; 15; 15];
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))
%plot(t, x(:,4))
legend('x','y','z')
ylabel('x')
xlabel('t')
return
function [dx_dt]= TestFunction(t,x)
k12=0.1;k13=0.4;k14=0.6;k01=0.7;k21=0.7;k31=0.52,k41=0.61,u=0.1;
dx_dt(1)= -(k21+k31+k41+k01)*x(1)+k12*x(2)+k13*x(3)+k14*x(4)+u;
dx_dt(2)=k21*x(1)-k12*x(2);
dx_dt(3)=k31*x(1)-k13*x(3);
dx_dt(4)=k41*x(1)-k14*x(4);
dx_dt = dx_dt';
return
```

Appendix: D

Nomenclature:

$\dot{x}_1$	Mass of the substance in the blood
x_2	Mass of the substance in the tissue
t	Time
u	Blood volume