

Multistage HPM applied to path tracking damped oscillations of a model for HIV infection of CD4⁺ T cells

Research Article

Abstract

The behavior of CD4⁺ T cells infection is modeled by a differential equation system with no exact analytical solution. This work proposes the application of Multistage Homotopy Perturbation Method (MuHPM) to track the path of damped oscillations in the evolution of HIV infection in CD4⁺ T cells. In addition, the paper presents the results which compare the following methods: MuHPM, Modified Variational Iteration Method (MVIM) and HPM, and showing that MuHPM analytical-numerical method is more precise than the other methods, reaching to an adequately plot 70 days of the progress of infection instead of the 0.8 days and 2 days attained by HPM and MVIM methods respectively.

Keywords: HIV model, Homotopy Perturbation Method, Multistage

HPM.x

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1 Introduction

The Human Immunodeficiency Virus (HIV) causes the gradual depletion of $CD4^+$ T cells, which leads patients to acquire AIDS (Acquired Immuno Deficiency Syndrome). Since the cells that HIV invades are essentially lymphocytes $CD4^+$ T, which in human immunity systems are mainly dedicated to fight against diseases, the count of $CD4^+$ T cells is used as primary indicator to measure progression of HIV infection [1]. A series of models have been developed to study HIV virus infection in $CD4^+$ T cells [1, 2, 3, 4, 5, 6]. In [1, 2] a system of nonlinear differential equations, which has no exact analytical solution, is presented. Nowadays, several approximate methods, which allow solving such kind of equations in an exact or approximate form, have been proposed. Among many others, the following can be mentioned: variational approximations method [7, 8], Tanh method [9], exponential function method [10], Adomian decomposition method [11, 12], parametric expansion method [13], homotopy perturbation method (HPM) [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42], and homotopy analysis method (HAM) [43, 44, 45, 46, 47, 48, 49, 50, 51]. From all the methods above mentioned, the HPM method is one of the most widely used because it is a powerful and simple tool which is easier to implement than other used techniques. Firstly proposed by Ji-Huan He [30, 31], homotopy perturbation method was introduced as a tool to approach several kinds of nonlinear problems.

Despite some analytic approximate solutions for HIV differential equation model [1, 2] are reported in [25, 52, 53, 54], these approximations have a limited reach because they do not allow us to appreciate the damped oscillations in the variables of the model. For that reason, the fourth order Runge- Kutta method (RK4) is frequently used for numerical tracking of damped oscillations in the model of HIV infection in $CD4^+$ T cells [1]. This work proposes the multistage homotopy perturbation method (MuHPM) [55], as a numerical-analytical technique for the efficient path tracking of HIV dynamics. In the same manner, the obtained results will be compared with the obtained by RK4, in order to establish that the proposed method can generate a similar accuracy. Moreover, a comparison among the results of applying MuHPM Modified Variational Iteration, (MVIM) [52], and HPM methods [54] is presented, showing that the proposed method is more precise than other methods when a 70 days infection evolution tracking is required.

This paper is organized as follows. Section 2 describes a brief review the basic idea of the Multistage HPM method, while Section 3 presents the model of HIV infection of $CD4^+$ T cells and its solution by the MuHPM method. In Section 4, obtained numerical simulations are shown and their results are discussed. Finally, a brief conclusion is given in Section 5.

2 Introduction to Multistage HPM method

The HPM method [22, 23, 24, 40, 56, 57, 58, 59] is a powerful tool which is used to solve, approximately or exactly, nonlinear differential equations in a systematic and simple way. In this section, the basic concepts for the HPM and the MuHPM procedure will be explored, in order to perform an efficient path tracking of damped oscillations in a model of HIV infection of $CD4^+$ T cells [1, 2].

2.1 Basic idea of HPM method

The basic idea of the HPM method is to introduce an homotopy parameter p , which can take values from 0 to 1. When parameter $p = 0$, the equation is usually reduced to a simple or trivial solution. Then, when p is gradually increased to 1, generating a sequence of deformations where every solution is close to the last one. When eventually $p = 1$, the system takes the original form of the equation,

and the nal stage of deformation provides the desired solution. As shown, only a few iterations are needed to achieve a good accuracy.

The HPM method considers that a nonlinear differential equation can be expressed as

$$A(u) - f(r) = 0, \quad \text{where} \quad r \in \Omega, \quad (2.1)$$

with the boundary condition

$$B\left(u, \frac{\partial u}{\partial \eta}\right) = 0, \quad \text{where} \quad r \in \Gamma, \quad (2.2)$$

where A is a general differential operator, $f(r)$ is a known analytic function, B is a boundary operator, and Γ is the boundary of the domain Ω . The A operator, can usually be divided into two operators, L and N , where L is the linear operator and N is the nonlinear operator. Hence, (2.1) can be rewritten as

$$L(u) + N(u) - f(r) = 0. \quad (2.3)$$

Now, the homotopy function is

$$H(v, p) = (1 - p)[L(v) - L(u_0)] + p(L(v) + N(v) - f(r)) = 0 \quad \text{where} \quad p \in [0, 1] \quad (2.4)$$

where u_0 is the initial approximation of (2.3), which satisfies the boundary conditions, and p is known as the perturbation homotopy parameter. Analysing (2.4), it can be concluded that

$$H(v, 0) = L(v) - L(u_0) = 0, \quad (2.5)$$

$$H(v, 1) = L(v) + N(v) - f(r) = 0. \quad (2.6)$$

We assume that the solution of (2.4) can be written as a power series of p

$$v = p^0 v_0 + p^1 v_1 + p^2 v_2 + \cdots. \quad (2.7)$$

Adjusting $p = 1$ results that the approximate solution for (2.1) is

$$u = \lim_{p \rightarrow 1} v = v_0 + v_1 + v_2 + \cdots. \quad (2.8)$$

The series (2.8) is convergent on most cases [30, 60, 61].

2.2 Basic Procedure of Multistage HPM method

The basic MuHPM [55] algorithm consists in:

1. Setup. $M = (t_f - t_0)/\Delta t$. M is defined as the number of path tracking steps, t_0 is considered as the initial time, t_f the ending time and Δt is the time step size for path tracking.
2. Set $k = 0$.
3. $t^* = t_0 + k\Delta t$ and initial condition $y(t^*) = y_k$.
4. Apply HPM method to obtain an approximate solution $y(t)$ to the nonlinear differential equation.
5. A prediction is performed for $t_{k+1} = t_0 + (k + 1)\Delta t$. That is, $y_{k+1} = y(t_{k+1})$.
6. Update $k = k + 1$.
7. Repeat steps 3, 4, 5 and 6 until $k > M$.

Sym.	Definition for parameters and constants	Value	Units
s	Rate of supply of $CD4^+$ T cells from precursors	0.1	$d^{-1}mm^{-3}$
r	Rate of growth of the $CD4^+$ T cell population	3	d^{-1}
T_{max}	Maximum $CD4^+$ cell population level	1500	mm^{-3}
α	Death rate of uninfected $CD4^+$ cells	0.02	d^{-1}
β	Death rate of infected $CD4^+$ cell population	0.3	d^{-1}
γ	Death rate of free virus	2.4	d^{-1}
k	Rate constant for $CD4^+$ cells becoming infected by free virus	.0027	mm^3d^{-1}
N	Number of free virus produced by lysing a $CD4^+$ cell	10	
r_1	Initial condition $T(0)$	0.1	mm^{-3}
r_2	Initial condition $I(0)$	0	mm^{-3}
r_3	Initial condition $V(0)$	0.1	mm^{-3}

Table 1: Model Parameters (3.1)

3 Solution of Model of HIV infection of $CD4^+$ T cells

In [1, 2] a mathematical model that describes the behavior of the number of infected $CD4^+$ T cells is presented. That model is given by the equations

$$\begin{aligned}
 T' &= s - \alpha T + rT \left(1 - \frac{T + I}{T_{max}}\right) - kVT, \\
 I' &= kVT - \beta I, \\
 V' &= N\beta I - \gamma V,
 \end{aligned}
 \tag{3.1}$$

where initial conditions, parameters and units are dened in Table 1. The parameter values are taken from [52, 54], in order to perform a further numerical comparison with the results presented in this work.

In model (3.1), $T(t)$, $I(t)$ and $V(t)$ corresponds the concentration in the blood of susceptible and infected $CD4^+$ T cells, while $V(t)$ denotes the free HIV virus particles. On the other hand, parameters α , β , and γ are natural turnover rates of uninfected T cells, infected T cells, and virus particles, respectively. The T-cell dynamic is determined by the interactions among susceptible $CD4^+$ T cells, infected $CD4^+$ T cells, and free HIV virus particles. Therefore, the homotopy equation (HPM) can be formulated as

$$\begin{aligned}
 (1 - p)(T' - T'_0) + p(-T' + s - \alpha T + rT \left(1 - \frac{T + I}{T_{max}}\right) - kVT) &= 0, \\
 (1 - p)(I' - I'_0) + p(-I' + kVT - \beta I) &= 0, \\
 (1 - p)(V' - V'_0) + p(-V' + N\beta I - \gamma V) &= 0,
 \end{aligned}
 \tag{3.2}$$

where $T_0(t) = r_1$, $I_0(t) = r_2$ and $V_0(t) = r_3$ fulfil with initial conditions of (3.1).

According to HPM method and equation (2.8), each system variable can be approached as

$$\begin{aligned}
 T &= p^0 T_0 + p^1 T_1 + p^2 T_2 + p^3 T_3 + p^4 T_4 + p^5 T_5 + \cdots, \\
 I &= p^0 I_0 + p^1 I_1 + p^2 I_2 + p^3 I_3 + p^4 I_4 + p^5 I_5 + \cdots, \\
 V &= p^0 V_0 + p^1 V_1 + p^2 V_2 + p^3 V_3 + p^4 V_4 + p^5 V_5 + \cdots.
 \end{aligned}
 \tag{3.3}$$

Substituting (3.3) into (3.2) and rearranging the coefficients of "p" powers, the following system, which includes 15 equations with 15 variables, can be constructed as follows

$$\begin{aligned}
 &T_1' - 1/10 + (1/500)r_1^2 + (1/500)r_1r_2 - (149/50)r_1 \\
 &\quad + (27/1E4)r_1r_3 = 0, \quad T_1(t^*) = 0, \\
 &T_2' + (1/500)r_1I_1 + (27/1E4)T_1r_3 + (1/500)T_1r_2 \\
 &\quad - (149/50)T_1 + (1/250)r_1T_1 + (27/1E4)r_1V_1 = 0, \quad T_2(t^*) = 0, \\
 &T_3' + (1/500)T_1I_1 + (1/500)T_1^2 + (27/1E4)T_2r_3 + (1/500)r_1I_2 + (27/1E4)T_1V_1 \\
 &\quad + (1/500)T_2r_2 + (27/1E4)r_1V_2 - (149/50)T_2 + (1/250)r_1T_2 = 0, \quad T_3(t^*) = 0, \\
 &T_4' + (1/500)r_1I_3 + (1/500)T_1I_2 + (27/1E4)T_2V_1 + (27/1E4)T_3r_3 \\
 &\quad + (1/250)r_1T_3 + (1/250)T_1T_2 - (149/50)T_3 + (27/1E4)T_1V_2 \\
 &\quad + (1/500)T_3r_2 + (1/500)T_2I_1 + (27/1E4)r_1V_3 = 0, \quad T_4(t^*) = 0, \\
 &T_5' + (1/500)T_3I_1 - (149/50)T_4 + (1/500)T_2^2 + (27/1E4)T_2V_2 + (1/500)T_2I_2 \\
 &\quad + (1/250)T_1T_3 + (1/500)T_1I_3 + (27/1E4)T_3V_1 + (1/250)r_1T_4 + (27/1E4)T_4r_3 \\
 &\quad + (27/1E4)T_1V_3 + (1/500)r_1I_4 + (27/1E4)r_1V_4 + (1/500)T_4r_2 = 0, \quad T_5(t^*) = 0, \\
 &I_1' + (3/10)r_2 - (27/1E4)r_1r_3 = 0, \quad I_1(t^*) = 0, \\
 &I_2' - (27/1E4)r_1V_1 + (3/10)I_1 - (27/1E4)T_1r_3 = 0, \quad I_2(t^*) = 0, \\
 &I_3' - (27/1E4)T_2r_3 - (27/1E4)T_1V_1 + (3/10)I_2 - (27/1E4)r_1V_2 = 0, \quad I_3(t^*) = 0, \\
 &I_4' + (3/10)I_3 - (27/1E4)T_1V_2 - (27/1E4)T_3r_3 \\
 &\quad - (27/1E4)r_1V_3 - (27/1E4)T_2V_1 = 0, \quad I_4(t^*) = 0, \\
 &I_5' - (27/1E4)T_3V_1 + (3/10)I_4 - (27/1E4)T_2V_2 - (27/1E4)T_4r_3 \\
 &\quad - (27/1E4)T_1V_3 - (27/1E4)r_1V_4 = 0, \quad I_5(t^*) = 0, \\
 &V_1' + (12/5)r_3 - 3r_2 = 0, \quad V_1(t^*) = 0, \quad V_2' - 3I_1 + (12/5)V_1 = 0, \quad V_2(t^*) = 0, \\
 &V_3' + (12/5)V_2 - 3I_2 = 0, \quad V_3(t^*) = 0, \quad V_4' - 3I_3 + (12/5)V_3 = 0, \quad V_4(t^*) = 0, \\
 &V_5' + (12/5)V_4 - 3I_4 = 0, \quad V_5(t^*) = 0,
 \end{aligned} \tag{3.4}$$

Following the MuHPM method, the step size is assigned to be $\Delta t = 0.1$, initial point $t_i = 0$, ending path tracking point $t_f = 70$ and $M = 700$. After the rst three iterations of MuHPM method, next results are obtained:

1. For $k = 0$. We set $t^* = 0$, $r_1 = 0.1$, $r_2 = 0$ and $r_3 = 0.1$. Solving (3.4) and using (3.3) to obtain segment 0

$$\begin{aligned}
 T_{s0}(t) &= 0.1 + 0.397953t + 0.592849053045t^2 + 0.588718771231t^3 \\
 &\quad + 0.438295158719t^4 + 0.260863294726t^5, \\
 I_{s0}(t) &= 0.000027t + 0.000017273655t^2 - 0.00000840515372595t^3 \\
 &\quad + 0.00000614727820610t^4 - 0.00000283586186805t^5, \\
 V_{s0}(t) &= 0.1 - 0.24t + 0.2880405t^2 - 0.230415126345t^3 \\
 &\quad + 0.138242771942t^4 - 0.0663528421651t^5.
 \end{aligned} \tag{3.5}$$

Evaluating (3.5) at $t = 0.1$, it results in the following prediction: $T_{s0}(0.1) = 0.146358947450$, $I_{s0}(0.1) = 0.00000286491776547$ and $V_{s0}(0.1) = 0.0786631506225$. Besides, (3.5) would be the result of applying the standard HPM method [56] to solve (3.1).

2. For $k = 1$. We set $t^* = 0.1$, $r_1 = T_{s0}(0.1)$, $r_2 = I_{s0}(0.1)$ and $r_3 = V_{s0}(0.1)$. Solving (3.4) and

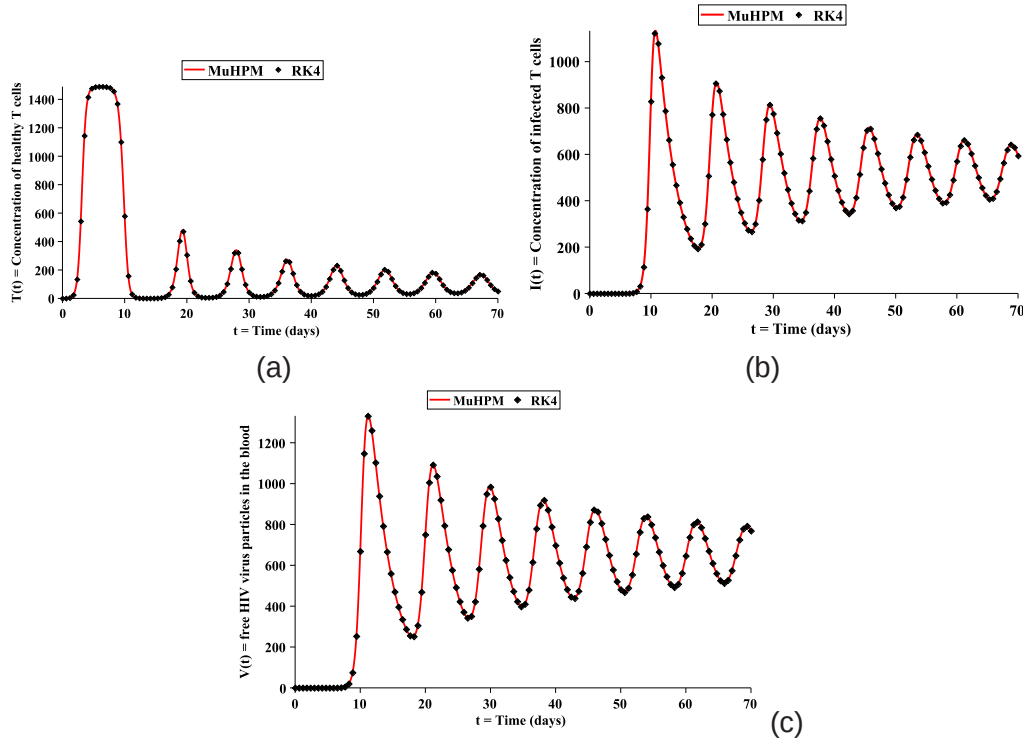


Figure 1: Damped oscillations of a) $T(t)$, b) $I(t)$, and c) $V(t)$. Units: Time is in days and T, I and V are in mm^{-3} .

using (3.3) to obtain segment 1

$$\begin{aligned}
 T_{s_1}(t) &= 0.0999997332523 + .397962630898t + .592602743066t^2 \\
 &\quad + .591949901749t^3 + .414629905334t^4 + .351078486008t^5, \\
 I_{s_1}(t) &= 1.6968\text{E-}12 + 0.270000202\text{E-}4t + 0.172722125\text{E-}4t^2 \\
 &\quad - 0.83858110\text{E-}5t^3 + 0.5999265125\text{E-}5t^4 - 0.2219598720\text{E-}5t^5, \\
 V_{s_1}(t) &= 0.0999999457692 - .239998617212t + .288007524964t^2 \\
 &\quad - .229971204794t^3 + .134844861291t^4 - 0.0521956449518t^5
 \end{aligned} \tag{3.6}$$

Evaluating (3.6) at $t = 0.2$, the following prediction is found: $T_{s_1}(0.2) = 0.208807721334$, $I_{s_1}(0.2) = 0.00000603269631052$ and $V_{s_1}(0.2) = 0.0618798028587$.

- For $k = 2$. We set $t^* = 0.2$, $r_1 = T_{s_1}(0.2)$, $r_2 = I_{s_1}(0.2)$ and $r_3 = V_{s_1}(0.2)$. Then, equation (3.4) is solved, and (3.3) is used to obtain an approximate solution for segment 2. In addition, a further prediction is performed, and parameter k is incremented. This process is repeated until obtain $t^* > t_f$ or $k > M$.

Both, initial condition and predictions of MuHPM process, describe the differential equation trajectory.

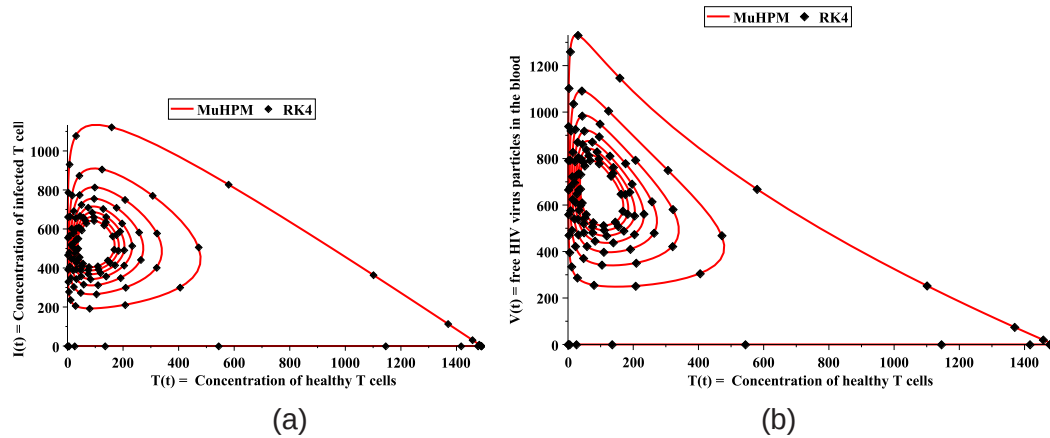


Figure 2: Graphics of concentrations a) $T(t)-I(t)$ and b) $T(t)-V(t)$ for 70 days. Units: T, I and V are in mm^{-3} .

4 Numerical Simulation and Discussion

Figure 1 shows the result of path tracking the iterative process described in the previous section. A high accuracy in the range of 0 to 70 days can be noticed when is compared with the results obtained by employing the fourth order Runge Kutta method (RK4). As expected, the concentration of susceptible CD4^+ T cells $T(t)$, infected CD4^+ T cells $I(t)$, and free HIV virus particles in the blood $V(t)$ behaves as a damped oscillating manner. Similarly, Figures 2(a) and 2(b) show, respectively, the path of $T(t)-I(t)$ and $T(t)-V(t)$ variables, where the damped oscillating behavior can be also appreciated.

On the other hand, tables 2, 3 and 4 present a quantitative comparison among the results of MuHPM, MVIM [52], HPM [54] methods and fourth order Runge-Kutta (RK4) for variables $T(t)$, $I(t)$ and $V(t)$, respectively, and compared with the numerical curve generated by RK4. We can notice that all three methods have similar accuracy until $t = 0.8$. However, HPM and MVIM degrade their accuracy at $t = 0.8$ and $t = 2.0$ respectively. In contrast, MuHPM follows RK4 behavior until $t = 70$, making its results useful for path tracking the damped oscillating behavior of the variables in the HIV model (3.1).

Since MuHPM is a numerical-analytical method that splits the region to be plotted into a series of segments, which are used to obtain a series of analytical approximations (one by each segment), that combination are useful for path following of the nonlinear differential equation trajectories. In addition, MuHPM provides the possibility of knowing valid instant analytical solutions in the vicinity of some given times, which can lead to a better understanding the effects of the model parameter over its dynamic behavior. As future work, the improvement for the obtained segment approximation will be focused, in order to reduce the number of necessary segments to trace the trajectory, which allows increasing the quantitative analysis of the parameter effects over the trajectory in longer periods of time.

5 Conclusions

In this work, an application of MuHPM for path tracking of damped oscillation of HIV infection of CD4^+ T cells was presented. By presented results, It can be established that MuHPM has a good

t	MuHPM	MVIM [52]	HPM [54]	RK4
0.00	0.10000000	0.10000000	0.10000000	0.10000000
0.10	0.14635895	0.1463591	0.1463589	0.14635908
0.20	0.20880772	0.2088081	0.2087991	0.20880807
0.40	0.40623923	0.4062408	0.4056066	0.40624044
0.60	0.76442034	0.7644287	0.7564485	0.76442360
0.80	1.41403830	1.414094	1.364215	1.41404612
1.00	2.59157570	2.591921	2.378679	2.59159323
1.20	4.72392418	4.725783	4.006512	4.72396174
1.40	8.57832730	8.587223	6.521303	8.57840433
1.60	15.52279258	15.56167	10.27357	15.52294312
1.80	27.96135433	28.11961	15.70079	27.96163187
2.00	50.00807072	50.61477	23.3374	50.00854230
3.00	605.32840070	758.3041	121.4166	605.33163787
4.00	1387.07811500	-38782.63	428.183	1387.07909636
5.00	1484.41661850	-1.282298e+07	1179.633	1484.41686125
10.00	578.76850000	-7.535057e+18	31121.36	578.75823022
30.00	42.96200000	-7.954982e+65	6710438	42.97734634
70.00	51.12600000	-8.866339e+159	4.491613e+08	50.72845936

Table 2: Numerical comparison for $T(t)$ obtained by: MuHPM, MVIM [52] , HPM [54] and RK4. Time is in days.

t	MuHPM	MVIM [52]	HPM [54]	RK4
0.00	0.00000000	0.00000000	0.00000000	0.00000000
0.10	0.00000286	0.00000286	0.00000286	0.00000286
0.20	0.00000603	0.00000603	0.00000603	0.00000603
0.40	0.00001316	0.00001315	0.00001315	0.00001316
0.60	0.00002122	0.00002122	0.00002122	0.00002122
0.80	0.00003018	0.00003017	0.00002994	0.00003018
1.00	0.00004004	0.00004002	0.00003918	0.00004004
1.20	0.00005088	0.00005084	0.00004844	0.00005088
1.40	0.00006283	0.00006270	0.00005697	0.00006283
1.60	0.00007608	0.00007574	0.00006354	0.00007608
1.80	0.00009096	0.00009011	0.00006649	0.00009096
2.00	0.00010799	0.00010597	0.00006346	0.00010799
3.00	0.00030568	0.00021559	-0.00018166	0.00030568
4.00	0.00210920	0.00040533	-0.001483771	0.00210924
5.00	0.02011931	0.00074045	-0.005503822	0.02011964
10.00	828.59480000	0.01387534	-0.2285212	828.60463679
30.00	775.29370000	1625.2828	-64.14273	775.28159497
70.00	594.70400000	2.2292957e+13	-4621.433	593.99643299

Table 3: Numerical comparison for $I(t)$ obtained by: MuHPM, MVIM [52] , HPM [54] and RK4. Time is in days.

t	MuHPM	MVIM [52]	HPM [54]	RK4
0.00	0.10000000	0.10000000	0.10000000	0.10000000
0.10	0.07866315	0.07866318	0.07866315	0.07866317
0.20	0.06187980	0.06187991	0.06187825	0.06187984
0.40	0.03829484	0.03829596	0.03819947	0.03829488
0.60	0.02370450	0.02371029	0.02268158	0.02370455
0.80	0.01468033	0.01470042	0.009255115	0.01468036
1.00	0.00910082	0.009157239	-0.0104847	0.00910084
1.20	0.00565326	0.005793751	-0.04982591	0.00565328
1.40	0.00352541	0.003851242	-0.1294878	0.00352542
1.60	0.00221475	0.002938821	-0.2801688	0.00221477
1.80	0.00141046	0.002978637	-0.5450945	0.00141047
2.00	0.00092039	0.0042649	-0.9825656	0.00092040
3.00	0.00032941	0.1364981	-9.17492	0.00032941
4.00	0.00141090	5.40689	-43.55308	0.00141093
5.00	0.01292825	214.2914	-143.6518	0.01292847
10.00	668.78959000	2.095530e+10	-5456.768	668.80004502
30.00	983.98200000	1.916241e+42	-1506366	983.92316539
70.00	769.49000000	1.602369e+106	-1.082777e+08	768.95465807

Table 4: Numerical comparison for $V(t)$ obtained by: MuHPM, MVIM [52] , HPM [54] and RK4. Time is in days.

accuracy for significantly longer periods of time, compared to what is obtained by MVIM and basic HPM methods.

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