

STABILITY ANALYSIS OF FRACTIONAL ORDER HIV INFECTION OF CD4⁺T CELLS WITH NUMERICAL SOLUTIONS

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ABSTRACT. In this paper, Mittag-Leffler method has been used to solve a model of HIV infection of CD4⁺ T cells of fractional order . The stability of equilibrium points is studied. The numerical results show that mathematical modeling by fractional ordinary differential equations (FODE) has more advantages than classical integer- order modeling.

1. INTRODUCTION

The HIV infection of CD4⁺T cells model first proposed by Perelson [1]. Mathematical methods have been proven valuable in understanding the dynamics of HIV infection [2-5]. This model is given by three components, the concentration of susceptible CD4⁺T cells, CD4⁺T cells infected by the HIV viruses and free HIV virus particles in blood [6-9]. In healthy person the number of CD4⁺T cells is $\frac{800}{1200}$ mm³. The following three differential equations describe the model.

$$\begin{aligned} dT/dt &= q - \alpha T + rT \left(1 - \frac{T+I}{T_{max}}\right) - kVT \\ dI/dt &= kVT - \beta I, \\ dV/dt &= \mu\beta I - \gamma V \end{aligned} \tag{1.1}$$

Here, R is positive constant, $T(t)$ is the concentration of susceptible CD4⁺T cells, $I(t)$ is CD4⁺T cells infected by the HIV viruses and $V(t)$ is free HIV virus particles in blood. α, β and γ denote natural turnover rates of uninfected T cells, infected T cells and virus particles, respectively. $\left(1 - \frac{T+I}{T_{max}}\right)$ describes the logistic growth of the healthy CD4⁺T cells, the term kVT describes the incidence of HIV infection of healthy CD4⁺T cells. Each infected CD4⁺T cells is assumed to produce μ virus particles during lifetime, including any of its daughter cells. The body is believed to produce CD4⁺T cells from precursors in the bone marrow and thymus at constant rate q . T cells multiply through mitosis with a rate r when T cells are stimulated by antigen or mitogen. T_{max} denotes the maximum CD4⁺T cells concentration in

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the body [6-9]. Fractional calculus (FC) has been extensively applied in many fields [11,12]. Many mathematicians and applied researchers have tried to model real processes using the fractional calculus [13-21]. FODE are naturally related to systems with memory which exists in most biological systems [22]. Also, they are closely related to fractals, which are abundant in biological systems [23]. The major reason of using is that fractional differential equations are naturally related to systems with memory which exists in most biological and systems [24-28]. In other words, calculating time-fractional derivative of a function $f(t)$ at some time $t = t_1$ requires all the previous history, i.e. all $f(t)$ from $t = 0$ to $t = t_1$. Also, using fractional order differential equations can help us to reduce the errors arising from the neglected parameters in modeling real life phenomena [29]. In biology, it has been deduced that the membranes of cells of biological organism have fractional order electrical conductance [11] and then are classified in groups of non-integer order models. Fractional derivatives embody essential features of cell rheological behavior and have enjoyed greatest success in the field of rheology [12]. Some fractional models in HIV proved that fractional models are more approximate than their integer order form. Hence, we propose a system of FODE for modeling HIV infection. We first give the definition of fractional order integration and fractional order differentiation [30]. For the concept of fractional derivative, we will adopt Caputo's definition, which is a modification of the Riemann–Liouville definition and has the advantage of dealing properly with initial value problems

2. FRACTIONAL CALCULUS

In this section, we introduce some basics definitions of fractional calculus.

Definition 2.1.the fractional derivative of $f(x)$ in the caputo sense is defined as:

$$D_*^\alpha f(x) = J^{n-\alpha} D_*^n f(x) = \frac{1}{\Gamma(n-\alpha)} \int_0^x (x-t)^{n-\alpha-1} f^{(n)}(t) dt,$$

for $n - 1 < \alpha \leq n$, $n \in N$, $x > 0$, for the caputo derivative we have $D^\alpha c = 0$, c is constant.

Definition 2.2.Riemann–Liouville fractional integration of order is defined as:

$$J^\alpha f(x) = \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t) dt, \quad \alpha > 0, x > 0$$

$$J^0 f(x) = f(x)$$

Definition 2.3. Riemann–Liouville and Caputo fractional derivatives of order α can be defined which presented in [31] respectively as:

$$D^\alpha f(x) = D^m (J^{m-\alpha} f(x)),$$

$$D_*^\alpha f(x) = J^{m-\alpha} (D^m f(x)),$$

where $m - 1 < \alpha \leq m$, $m \in N$.

Properties of the operator J can be found in [31], we mention only the following:

$$J^\alpha J^\beta f(x) = J^{\alpha+\beta} f(x)$$

$$J^\alpha J^\beta f(x) = J^\beta J^\alpha f(x)$$

$$J^\alpha t^\gamma = \frac{\Gamma(\gamma + 1)}{\Gamma(\alpha + \gamma + 1)} t^{\alpha+\gamma}$$

Definition 2.4. The Caputo fractional derivative of the power function satisfies [31]:

$$D_*^\alpha t^p = \begin{cases} \frac{\Gamma(p+1)}{\Gamma(p-\alpha+1)} t^{p-\alpha} = D^\alpha t^p & , n-1 < \alpha < n, p > n-1, p \in R \\ 0 & , n-1 < \alpha < n, p \leq n-1, p \in R \end{cases}$$

We mention only the following:

(1) interpolation

$$\lim_{\alpha \rightarrow n} D_*^\alpha y(t) = y^{(n)}(t),$$

(2) Linearity

$$D_*^\alpha (ay(x) + bz(t)) = aD_*^\alpha y(x) + bD_*^\alpha z(t).$$

(3) Commutation

$$D_*^\alpha D_*^m f(t) = D_*^{\alpha+m} f(t).$$

Now, we introduce the fractional model of HIV infection of $CD4^+$ T cells : -

$$D^{\alpha_1}(T) = q - \alpha T + rT \left(1 - \frac{T+I}{T_{max}}\right) - kVT,$$

$$D^{\alpha_2}(I) = KVT - \beta I,$$

$$D^{\alpha_3}(V) = \mu\beta I - \gamma V$$

where $\alpha_1, \alpha_2, \alpha_3 > 0$

with initial conditions $T(0) = 0.1, I(0) = 0, V(0) = 0.1$

We will use Mittag-Leffler function method which first introduced by Arafa et al. [10] to obtain the approximate solution of the model (2.1) by using Fractional calculus.

(2.1)

3. MITTAG-LEFFLER FUNCTION METHOD

The Mittag-leffler (1902-1905) functions E_α and $E_{\alpha,\beta}$ [32], defined by the power series as:

$$E_\alpha = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(n\alpha + 1)}, \quad E_{\alpha,\beta} = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(n\alpha + \beta)} \quad \alpha, \beta > 0 \quad (3.1)$$

we will show how to solve nonlinear fractional differential equations (HIV infection of $CD4^+$ T cells model) by using Mittag-Leffler function $E_\alpha(z)$. We suppose that $y_i(t), i = 1, 2, 3, \dots$ are decomposed by an infinite series of components [33]

$$y_i(t) = E_\alpha(a_i t^\alpha) = \sum_{n=0}^{\infty} a_i^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} \quad i = 1, 2, 3, \dots \quad (3.2)$$

$$D^\alpha y_i(t) = \sum_{n=1}^{\infty} a_i^n \frac{t^{(n-1)\alpha}}{\Gamma((n-1)\alpha + 1)} \quad i = 1, 2, 3, \dots \quad (3.3)$$

This are based on the Caputo fractional is derivatives. The convergence of the Mittag Leffler function discussed in [33]

4. EQUILIBRIUM POINTS AND THEIR ASYMPTOTIC STABILITY

We evaluate the equilibrium points and asymptotic stability as in [35]. We suppose that $T(t) = x_1(t)$, $I(t) = x_2(t)$ and $V(t) = x_3(t)$. To evaluate the equilibrium points, let

$$D^\alpha x_i(t) = 0, i = 1, 2, 3$$

Then $(x_1^{eq}, x_2^{eq}, x_3^{eq}) = \left(\frac{r \text{ tmax} - \alpha T_{\text{max}} + \sqrt{\alpha^2 T_{\text{max}}^2 - 2\alpha r T_{\text{max}}^2 + r^2 T_{\text{max}}^2 + 4qr T_{\text{max}}}}{2r}, 0, 0 \right)$,
 $\left(\frac{r \text{ tmax} - \alpha T_{\text{max}} - \sqrt{\alpha^2 T_{\text{max}}^2 - 2\alpha r T_{\text{max}}^2 + r^2 T_{\text{max}}^2 + 4qr T_{\text{max}}}}{2r}, 0, 0 \right)$
 and $\left(\frac{\gamma}{k\mu}, \frac{k^2 \mu^2 q T_{\text{max}} - \gamma^2 r - \alpha T_{\text{max}} \gamma k \mu + T_{\text{max}} \gamma k \mu}{\beta T_{\text{max}} k^2 \mu^2 + \gamma r k \mu}, \frac{\beta T_{\text{max}} q \mu^2 - \beta \gamma^2 r - \alpha \beta \gamma k \mu T_{\text{max}} + \beta \gamma k \mu r T_{\text{max}}}{\gamma^2 r k + \beta \gamma k^2 \mu T_{\text{max}}} \right)$ are the equilibrium points, we take the parameter of this models

For $(x_1^{eq}, x_2^{eq}, x_3^{eq}) = \left(\frac{r \text{ tmax} - \alpha T_{\text{max}} + \sqrt{\alpha^2 T_{\text{max}}^2 - 2\alpha r T_{\text{max}}^2 + r^2 T_{\text{max}}^2 + 4qr T_{\text{max}}}}{2r}, 0, 0 \right)$, we obtain

$$A = \begin{bmatrix} 2.9801 & 0.0001 & 0.0001 \\ 0 & -0.3 & -0.0001 \\ 0 & 3 & -2.4 \end{bmatrix}$$

Its eigenvalues are

$$\lambda_1 = 2.9801 > 0, \lambda_2 = -0.3001 < 0, \lambda_3 = -2.3999 < 0$$

Hence the equilibrium point $(x_1^{eq}, x_2^{eq}, x_3^{eq}) = \left(\frac{r \text{ tmax} - \alpha T_{\text{max}} + \sqrt{\alpha^2 T_{\text{max}}^2 - 2\alpha r T_{\text{max}}^2 + r^2 T_{\text{max}}^2 + 4qr T_{\text{max}}}}{2r}, 0, 0 \right)$ is unstable.

For $(x_1^{eq}, x_2^{eq}, x_3^{eq}) = \left(\frac{r \text{ tmax} - \alpha T_{\text{max}} - \sqrt{\alpha^2 T_{\text{max}}^2 - 2\alpha r T_{\text{max}}^2 + r^2 T_{\text{max}}^2 + 4qr T_{\text{max}}}}{2r}, 0, 0 \right)$, we obtain

$$A = \begin{bmatrix} -2.9801 & -2.9801 & -4.0231 \\ 0 & -0.3 & 4.0231 \\ 0 & 3 & -2.4 \end{bmatrix}$$

Its eigenvalues are

$$\lambda_1 = -2.9801 < 0, \lambda_2 = 2.2793 > 0, \lambda_3 = -4.9793 < 0$$

Hence the equilibrium point $(x_1^{eq}, x_2^{eq}, x_3^{eq}) = \left(\frac{r \text{ tmax} - \alpha T_{\text{max}} - \sqrt{\alpha^2 T_{\text{max}}^2 - 2\alpha r T_{\text{max}}^2 + r^2 T_{\text{max}}^2 + 4qr T_{\text{max}}}}{2r}, 0, 0 \right)$ is unstable.

For $(x_1^{eq}, x_2^{eq}, x_3^{eq}) = \left(\frac{\gamma}{k\mu}, \frac{k^2 \mu^2 q T_{\text{max}} - \gamma^2 r - \alpha T_{\text{max}} \gamma k \mu + T_{\text{max}} \gamma k \mu}{\beta T_{\text{max}} k^2 \mu^2 + \gamma r k \mu}, \frac{\beta T_{\text{max}} q \mu^2 - \beta \gamma^2 r - \alpha \beta \gamma k \mu T_{\text{max}} + \beta \gamma k \mu r T_{\text{max}}}{\gamma^2 r k + \beta \gamma k^2 \mu T_{\text{max}}} \right)$, we obtain

$$A = \begin{bmatrix} -0.1789 & -0.1778 & -0.24 \\ 1.7602 & -0.3 & 0.24 \\ 0 & 3 & -2.4 \end{bmatrix}$$

Its eigenvalues are

$$\lambda_1 = -0.0153 + 0.8417i, \lambda_2 = -0.0153 - 0.8417i, \lambda_3 = -2.8482 < 0$$

$|\arg(\lambda_1)| = 1.58900 > \frac{\alpha\pi}{2}$, $|\arg(\lambda_2)| = 1.58900 > \frac{\alpha\pi}{2}$, where $\alpha = 0.90, 0.99$ and 1 which used in figures 1, 2 and 3. The results show that equilibrium point E_3 is stable according to the results of Matignon [36]. In figures 1, 2 and 3, we show

that fractional order differential equations are, at least, as stable as their integer order fo . In the fractional case $0 < \alpha < 1$.

5. APPLICATION

In this section, we apply Mittag-Leffler method in HIV infection of $CD 4^+ T$ cells model.

$$\begin{aligned} D^{\alpha_1}(T) &= q - \alpha T + rT \left(1 - \frac{T+I}{T_{max}}\right) - kVT, \\ D^{\alpha_2}(I) &= KVT - \beta I, \\ D^{\alpha_3}(V) &= \mu\beta I - \gamma V \end{aligned} \tag{5.1}$$

where $\alpha_1, \alpha_2, \alpha_3 > 0$

$$\text{with initial conditions } T(0) = 0.1, I(0) = 0, V(0) = 0.1 \tag{5.2}$$

By using generalized Mittag-Leffler function method we put

$$\begin{aligned} T(t) &= E_{\alpha}(at^{\alpha}) = \sum_{n=0}^{\infty} a^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} \\ I(t) &= E_{\alpha}(bt^{\alpha}) = \sum_{n=0}^{\infty} b^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} \\ V(t) &= E_{\alpha}(dt^{\alpha}) = \sum_{n=0}^{\infty} d^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} \end{aligned}$$

By using(3.2) and (3.3) into (5.1) when $\alpha_1, \alpha_2, \alpha_3 = \alpha$ we find

$$\begin{aligned} \sum_{n=1}^{\infty} a^n \frac{t^{(n-1)\alpha}}{\Gamma((n-1)\alpha + 1)} - q + \alpha \sum_{n=0}^{\infty} a^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} - r \sum_{n=0}^{\infty} a^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} + \frac{r}{T_{max}} \sum_{n=0}^{\infty} c_1^n t^{n\alpha} + \\ \frac{r}{T_{max}} \sum_{n=0}^{\infty} c_2^n t^{n\alpha} + k \sum_{n=0}^{\infty} c_3^n t^{n\alpha} = 0 \\ \sum_{n=1}^{\infty} b^n \frac{t^{(n-1)\alpha}}{\Gamma((n-1)\alpha + 1)} - k \sum_{n=0}^{\infty} c_3^n t^{n\alpha} + \beta \sum_{n=0}^{\infty} b^n \frac{t^{(n)\alpha}}{\Gamma((n)\alpha + 1)} = 0 \\ \sum_{n=1}^{\infty} d^n \frac{t^{(n-1)\alpha}}{\Gamma((n-1)\alpha + 1)} - \mu\beta \sum_{n=0}^{\infty} b^n \frac{t^{(n)\alpha}}{\Gamma((n)\alpha + 1)} + \gamma \sum_{n=0}^{\infty} d^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} = 0 \end{aligned} \tag{5.4}$$

replace (n) by (n+1) in first sum of (5.4) :

$$\left\{ \sum_{n=1}^{\infty} a^n \frac{t^{(n-1)\alpha}}{\Gamma((n-1)\alpha + 1)} - q + \alpha \sum_{n=0}^{\infty} a^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} - r \sum_{n=0}^{\infty} a^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} + \frac{r}{T_{max}} \sum_{n=0}^{\infty} c_1^n t^{n\alpha} + \right.$$

$$\begin{aligned} & \frac{r}{T_{max}} \sum_{n=0}^{\infty} c_2^n t^{n\alpha} + k \sum_{n=0}^{\infty} c_3^n t^{n\alpha} = 0 \\ & \sum_{n=0}^{\infty} b^{n+1} \frac{t^{n\alpha}}{\Gamma((n-1)\alpha+1)} - k \sum_{n=0}^{\infty} c_3^n t^{n\alpha} + \beta \sum_{n=0}^{\infty} b^n \frac{t^{(n)\alpha}}{\Gamma((n)\alpha+1)} = 0 \tag{5.5} \\ & \sum_{n=0}^{\infty} d^{n+1} \frac{t^{n\alpha}}{\Gamma((n-1)\alpha+1)} - \mu\beta \sum_{n=0}^{\infty} b^n \frac{t^{(n)\alpha}}{\Gamma((n)\alpha+1)} + \gamma \sum_{n=0}^{\infty} d^n \frac{t^{n\alpha}}{\Gamma(n\alpha+1)} = 0 \end{aligned}$$

where

$$\begin{aligned} c_1^n &= \sum_{k=0}^n \frac{a^k a^{n-k}}{\Gamma(k\alpha+1)\Gamma((n-k)\alpha+1)} \\ c_2^n &= \sum_{k=0}^n \frac{a^k b^{n-k}}{\Gamma(k\alpha+1)\Gamma((n-k)\alpha+1)} \\ c_3^n &= \sum_{k=0}^{\infty} \frac{d^k a^{n-k}}{\Gamma(k\alpha+1)\Gamma((n-k)\alpha+1)} \end{aligned}$$

with the coefficient of $t^{n\alpha}$ equal to zero and identifying the coefficients, we obtain :

$$a^{n+1} + (\alpha - r) a^n + \frac{r}{T_{max}} c_1^n \Gamma(n\alpha + 1) + \frac{r}{T_{max}} c_2^n \Gamma(n\alpha + 1) + k c_3^n \Gamma(n\alpha + 1) = 0$$

$$b^{n+1} - k c_3^n \Gamma(n\alpha + 1) + \beta b^n = 0$$

$$d^{n+1} - \mu\beta b^n + \gamma d^n = 0$$

When $n > 0$

when $n = 0$ we obtain :

$$a^1 + (\alpha - r) a^1 + \frac{r}{T_{max}} c_1^0 \Gamma(\alpha + 1) + \frac{r}{T_{max}} c_2^0 \Gamma(n\alpha + 1) + k c_3^0 \Gamma(n\alpha + 1) = q$$

$$b^1 - k c_3^0 \Gamma(\alpha + 1) + \beta b^0 = 0$$

$$d^1 - \mu\beta b^0 + \gamma d^0 = 0.$$

According to Mittag-leffler function by using parameters as $\Gamma(0) = a^0 = 0.1, I(0) = b^0 = 0, V(0) = d^0 = 0.1, q = 0.1, \alpha = 0.02, \beta = 0.3, r = 3, \gamma = 2.4, k = 0.0027, T_{max} = 1500$ and $\mu = 1$, we obtain

$$T(t) = \sum_{n=0}^{\infty} a^n \frac{t^{n\alpha}}{\Gamma(n\alpha+1)} = a^0 + a^1 \frac{t^\alpha}{\Gamma(\alpha+1)} + a^2 \frac{t^{2\alpha}}{\Gamma(2\alpha+1)} + a^3 \frac{t^{3\alpha}}{\Gamma(3\alpha+1)} + \dots \tag{5.6}$$

$$I(t) = \sum_{n=0}^{\infty} b^n \frac{t^{n\alpha}}{\Gamma(n\alpha+1)} = b^0 + b^1 \frac{t^\alpha}{\Gamma(\alpha+1)} + b^2 \frac{t^{2\alpha}}{\Gamma(2\alpha+1)} + b^3 \frac{t^{3\alpha}}{\Gamma(3\alpha+1)} + \dots \tag{5.7}$$

$$V(t) = \sum_{n=0}^{\infty} d^n \frac{t^{n\alpha}}{\Gamma(n\alpha + 1)} = d^0 + d^1 \frac{t^\alpha}{\Gamma(\alpha + 1)} + d^2 \frac{t^{2\alpha}}{\Gamma(2\alpha + 1)} + d^3 \frac{t^{3\alpha}}{\Gamma(3\alpha + 1)} + \dots \quad (5.8)$$

Respectively, $T(t)$, $I(t)$ and $V(t)$ are the approximate solutions of the model. We compare the result with Bessel collocation method and (RK4) method. (See tables 1, 2 and 3)

6. CONCLUSION

In this paper, we applied Mittag-Leffler function method to study HIV infection of $CD 4^+ T$ cells model. We have studied the stability of the model and its numerical solutions. Figures 1, 2 and 3 show that, Fractional order differential equations are, at least, as stable as their integer order counterpart. Tables 1, 2 and 3 show that our method is a very powerful and efficient technique in finding approximate solutions for wide classes of fractional differential equations. Finally, the numerical results show that mathematical modeling by fractional ordinary differential equations (FODE) has more advantages than classical integer-order modeling.

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Table 1 The numerical results of $T(t)$

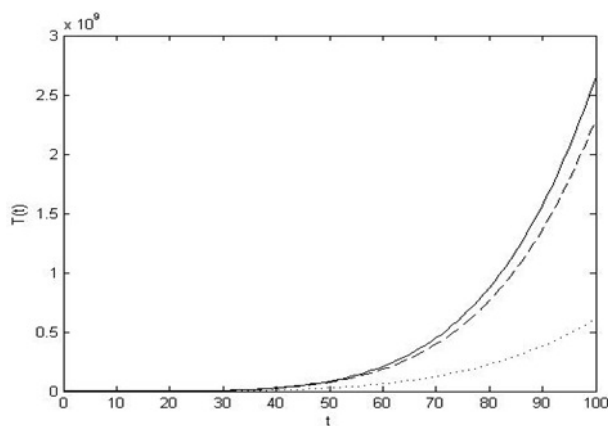
t	Ref[5]	(M-L) $\alpha_1 = 1$	(M-L) $\alpha_1 = 0.99$	$RK4$
0	0.1	0.1	0.1	0.1
0.2	0.2039	0.2087	0.2121	0.2088
0.4	0.3803	0.4030	0.4123	0.4062
0.6	0.6955	0.7363	0.7563	0.7644
0.8	1.2176	1.2789	1.3162	1.4140
1	2.3832	2.1181	2.1804	2.5916

Table2 The numerical results of $I(t)$

t	Ref[5]	(M-L) $\alpha_2 = 1$	(M-L) $\alpha_2 = 0.99$	$RK4$
0	0	0	0	0
0.2	0.6247e-5	0.618 e-5	0.6164e-5	0.6033e-5
0.4	0.1293e-4	0.1341e-4	0.1324e-4	0.1315e-4
0.6	0.2035e-4	0.2170 e-4	0.2083e-4	0.2122e-4
0.8	0.2837e-4	0.3125e-4	0.2855e-4	0.3017e-4
1	0.369e-4	0.3587e-4	0.3598e-4	0.4004e-4

Table3 The numerical results of $V(t)$

t	Ref[5]	(M-L) $\alpha_3=1$	(M-L) $\alpha_3=0.99$	$RK4$
0	0.1	0.1	0.1	0.1
0.2	0.06187991856	0.0618	0.0616	0.0619
0.4	0.03829493490	0.0382	0.0382	0.0383
0.6	0.02370431860	0.0239	0.0237	0.0237
0.8	0.01467956982	0.0164	0.0147	0.0146
1	0.02370431861	0.0166	0.0091	0.0091

FIGURE 1. Solid line represents $T(t)$ in $\alpha_1 = 1$, dashed line represents $T(t)$ in $\alpha_1 = 0.99$ and dotted line $T(t)$ in $\alpha_1 = 0.90$.

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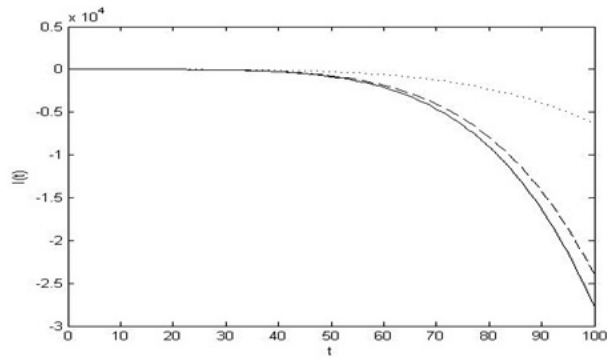


FIGURE 2. Solid line represents $I(t)$ in $\alpha_2 = 1$, dashed line represents $I(t)$ in $\alpha_2 = 0.99$ and dotted line $I(t)$ in $\alpha_2 = 0.90$.

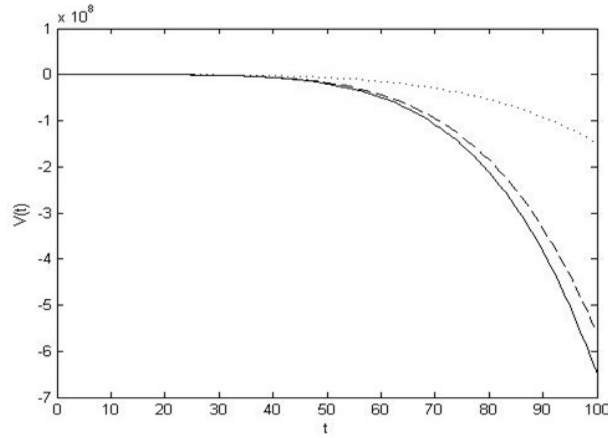


FIGURE 3. Solid line represents $V(t)$ in $\alpha_3 = 1$, dashed line represents $V(t)$ in $\alpha_3 = 0.99$ and dotted line $V(t)$ in $\alpha_3 = 0.90$.