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Effects of HIV infection on CD4+ T-cell population based on a fractional-order model

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Abstract

In this paper, we study the HIV infection model based on fractional derivative with particular focus on the degree of T-cell depletion that can be caused by viral cytopathicity. The arbitrary order of the fractional derivatives gives an additional degree of freedom to fit more realistic levels of CD4+ cell depletion seen in many AIDS patients. We propose an implicit numerical scheme for the fractional-order HIV model using a finite difference approximation of the Caputo derivative. The fractional system has two equilibrium points, namely the uninfected equilibrium point and the infected equilibrium point. We investigate the stability of both equilibrium points. Further we examine the dynamical behavior of the system by finding a bifurcation point based on the viral death rate and the number of new virions produced by infected CD4+ T-cells to investigate the influence of the fractional derivative on the HIV dynamics. Finally numerical simulations are carried out to illustrate the analytical results.

Keywords: fractional derivative; HIV model; finite difference scheme; dynamical analysis

1 Introduction

According to WHO there were approximately 35 million people at the end of 2013 living with HIV with 2.1 million people becoming newly infected in 2013 globally with HIV. HIV belongs to the family of lentiviruses, which means being acting slowly. Lentiviruses cause diseases that progress over a long period disturbing the immune system in humans. HIV produces virus particles by converting viral RNA into DNA in the cell and then making many RNA copies. The transformation is completed with an enzyme named reverse transcriptase. The change from RNA to DNA and back to RNA is substantial and makes fighting against HIV challenging. There is a chance of the virus mutating and there being errors each time when it happens. These copies or virus particles destroy the cell after formation and infecting other cells. Although HIV attacks many different cells, it inflicts the most disorder on the CD4+ T-cells, the main target of CD4+ T-cells is to form the body's overall immune response to external infections. HIV provides the basis to grow acquired immune deficiency syndrome (AIDS). For a person infected from HIV it can take 10-15 years to develop AIDS. On the medical frontier there have been many advances, but still there is no effective cure or vaccine available for HIV. Since the early 1980s, many mathematical models have been developed to better understand the interaction of HIV and the human immune system for the purpose of testing treatment strate-

gies [1–8]. Silva and Torres [9] proposed a population model for TB-HIV/AIDS coinfection transmission dynamics, they applied optimal control theory to TB-HIV/AIDS model to study optimal strategies for the minimization of the number of individuals with TB and AIDS. Recently Rocha *et al.* [10] investigated an HIV optimal control problem with delays in both state and control variables, where the objective is to find the optimal treatment strategy that maximizes the number of CD4+ T-cells and CTL immune response cells, keeping the drug strength low. Luo *et al.* [11] studied bifurcations and stability of an HIV model that incorporates the immune responses. An HIV model including latent infection and antiretroviral therapy is examined by Wang *et al.* [12]. They obtained the global asymptotic stability of the uninfected equilibrium by constructing a Lyapunov function. We refer the reader to the excellent review paper on mathematical modeling of HIV on different phenomena of [13]. Quantitative analysis of HIV-1 replication *in vivo* has made significant contributions to understanding of AIDS pathogenesis and antiretroviral treatment ([4, 14]). For a detailed mathematical analysis on such models, we refer to [15] and [5].

Fractional-order dynamics has recently been a focus of interest because of its appearance in physics, biology and engineering applications. There is a rich literature on the theoretical research of the fractional differential equations. The book of Podlubny [16] provides an overview to the basic theory of fractional differential equations. The monograph by Samko, Kilbas, and Marichev [17] contains remarkably comprehensive theory on the topic of fractional differential equations. Recently, much work has done on modeling the HIV infection with fractional-order derivatives [18–23] and [24]. A fractional-order model retains its memory, which is one of the main characteristic of the fractional-order derivative, while the features of immune response include memory. In [22] a fractional-order time-delay model is investigated which include three types of cells, namely healthy CD4$^+$ T-cells, infected CD4$^+$ T-cells and free HIV virus particles. In [19] the authors introduced fractional orders to the model of HIV-1 whose components are plasma densities of uninfected CD4$^+$ T-cells, they use the generalized Euler method (GEM) and homotopy analysis method (HAM) to approximate the solution. Approximate solutions of fractional-order differential system for modeling human T-cell lymphotropic virus I (HTLV-I) infection of CD4$^+$ T-cells is investigated in [25] using a multi-step generalized differential transform method. Bernstein operational matrices is applied to fractional order HIV model to approximate the solution [26]. Homotopy decomposition method is given in [27] to solve a system of fractional nonlinear differential equations that arise in the model for HIV infection of CD4$^+$ T-cells. Recently, Huo *et al.* [28] studied a fractional-order HIV model to assess the impact of vaccines in a homosexual community. They have shown that the vaccinated reproduction below unity is not a threshold of HIV eradication when effectiveness and the dosage of the vaccines are low. A new critical threshold is derived in order to eradicate the HIV. Recently Pinto *et al.* [29] studied a fractional-order model for HIV infection that includes latently infected cells, macrophages and CTLs. In this paper we propose a finite difference implicit scheme to solve fractional-order HIV model containing four types of populations: uninfected CD4$^+$ T-cells, latently infected, actively infected CD4$^+$ T-cells and HIV virus particles. Further we analyze the dynamics of fractional-order HIV by investigating bifurcation points. The benefit of fractional-order systems is that they permit greater degrees of freedom in the model.

This paper is organized as follows: Section 2 includes generalized HIV model. In Section 3, we introduce implicit scheme for solving the fractional-order HIV-1 infection model. Dynamical behavior of generalized HIV model is investigated in Section 4. In Section 5, we present numerical simulations of the model and discuss the biological significance of the results. A conclusion is given in the last section.

2 Generalized HIV model

The Riemann-Liouville fractional integral $I^\alpha u$ of order $\alpha > 0$ of $u : \mathbb{R}_+ \to \mathbb{R}$ is defined by

$$I^\alpha u(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-s)^{\alpha-1} u(s) \, ds,$$

provided the expression on right hand side is defined. Here Γ denotes the Gamma function [30].

The Caputo fractional derivative $D^\alpha u$ of order α of a continuous function $u : \mathbb{R}_+ \to \mathbb{R}$ is defined by

$$D^\alpha u(t) = \begin{cases} \frac{1}{\Gamma(m-\alpha)} \int_0^t (t-s)^{m-\alpha-1} u^{(m)}(s) \, ds, & m-1 \le \alpha < m, \\ \frac{d^m u(t)}{dt^m}, & m = \alpha. \end{cases}$$

In particular, when $0 < \alpha < 1$, we have

$$D^\alpha u(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-s)^{-\alpha} u'(s) \, ds.$$

We generalize the integer-order model of target cells limited proposed by Perelson *et al.* [31] to fractional order $0 < \alpha < 1$, which involves various types of cells: Let T, T_L and T_A denote the population of uninfected CD4$^+$ T-cells, latently infected and actively infected CD4$^+$ T-cells, respectively. The population of free virus particles is denoted by V. Interaction between these cells is given by the following system:

$$\begin{cases} D^\alpha T = s^\alpha - \mu_T^\alpha T + r^\alpha T(1 - \frac{T+T_L+T_A}{T_{\max}}) - k_1^\alpha TV, & t \ge 0, \\ D^\alpha T_L = k_1^\alpha TV - \mu_T^\alpha T_L - k_2^\alpha T_L, & t \ge 0, \\ D^\alpha T_A = k_2^\alpha T_L - \mu_b^\alpha T_A, & t \ge 0, \\ D^\alpha V = N\mu_b^\alpha T_A - k_1^\alpha VT - \mu_V^\alpha V, & t \ge 0. \end{cases} \quad (1)$$

Note that the units of the fractional differential equation are different, that is, fractional differential equations are expressed with respect to an intrinsic time variable that depends on α [32, 33] instead of the physical time. Thus a reformed parameter has been presented in model (1) to interpret the fractional order. Notice that when $\alpha \to 1$ the fractional HIV model (1) reduces to the classical HIV model.

The first two equations deal with the effects of HIV. Here s^α, corresponds to the s, the source term, from the classical HIV model, r^α corresponding to r represents the rate of growth for the CD4$^+$ cell population and μ_T^α is the analogon to the μ_T, the death rate of uninfected CD4$^+$ T-cells. k_1^α corresponding to k_1 represents the rate at which CD4$^+$ T-cell become infected by virus modeled by mass-action type of term. The dynamical behavior of actively infected T-cells is given in the third equation with k_2^α corresponding to the k_2 rate

at which latently infected cells convert to being actively infected and μ_b^α corresponding to μ_b represents the death rate per cell from the classical HIV model. The last equation models the free infectious virus population. Assume that an actively infected CD4$^+$ T-cell produces N virus particles. The virus production rate is N times μ_b^α. Free virus is expired at a rate $k_1^\alpha V T$ by binding to uninfected CD4$^+$ T-cells. Viral death from the body is represented by $-\mu_v^\alpha V$.

3 Construction of implicit numerical scheme

In this section, we introduce an implicit numerical scheme using a finite difference approximation of the Caputo derivative. Numerous schemes have been developed for the numerical solution of the fractional differential equations [34]. A class of the fractional multi-step method is proposed by Lubich [35] and Galeone and Garrappa [36], the fractional Adams method is proposed by Diethelm *et al.* [37] and Odibat and Momani [3] and Grünwald-Letnikov approximation based on the Grünwald-Letnikov definition of the fractional derivative is addressed in [38] and discussed the analysis of convergence and stability. Baker [39] introduced some numerical methods for the Volterra integral and integro-differential equations.

In this paper, we implement the L1-scheme to approximate the Caputo fractional derivative, which was independently developed and analyzed in [40] and [41]. The L1-scheme is based on a piecewise linear approximation to the fractional derivative. We are in favor of the L1-scheme, because this scheme is derived easily and the coefficients of this scheme have good properties *e.g.* the representation of the coefficients is simple. The L1-scheme has been extensively used in practice and currently it is one of the most efficient numerical methods for solving the time fractional differential equations due to its ease of implementation.

To discretize $D^\alpha f(t)$ based on the L1-scheme, first we defined the temporal size τ and t_n means $n\tau$. Therefore we discretize the Caputo derivative by a finite difference method,

$$
\begin{aligned}
D^\alpha f(t_n) &= \frac{1}{\Gamma(1-\alpha)} \int_0^{t_n} (t_n - s)^{-\alpha} \frac{df(s)}{ds} \, ds \\
&= \frac{1}{\Gamma(1-\alpha)} \sum_{j=0}^{n-1} \int_{t_j}^{t_{j+1}} (t_n - s)^{-\alpha} \frac{f(t_{j+1}) - f(t_j)}{\tau} \, ds + R_t^n \\
&= \frac{\tau^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^{n} b_j^n f(t_j) + R_t^n,
\end{aligned}
\tag{2}
$$

where

$$
b_j^n = \begin{cases}
-(n^{1-\alpha} - (n-1)^{1-\alpha}), & j = 0, \\
(n-j+1)^{1-\alpha} - 2(n-j)^{1-\alpha} + (n-j-1)^{1-\alpha}, & j = 1, 2, \ldots, n-1, \\
1, & j = n.
\end{cases}
$$

Let

$$
\nabla_t^\alpha f(t_n) = \frac{\tau^{-\alpha}}{\Gamma(2-\alpha)} \sum_{j=0}^{n} b_j^n f(t_j), \quad n = 1, 2, \ldots, N,
\tag{3}
$$

Algorithm 1 A modified Jacobi matrix on Newton iteration method

1:	Given $N_{\text{iter}}, \varepsilon$, let $Nd = 1$
2:	if $k > N_{\text{iter}}$ and $\|f(x^{k+1})\| > \|f(x^k)\|$
3:	$Nd := \frac{1}{2} Nd$
4:	end if
5:	if $\det(J(x^k)) < \varepsilon$, %$\varepsilon$ is a sufficiently small positive number
6:	$J(x^k) := Nd \cdot (J(x^k) + I)$, %$I$ is an identity matrix
7:	else
8:	$J(x^k) := Nd \cdot J(x^k)$
9:	end if

then by [41], we have, for $n = 1, 2, \dots, N$,

$$
\left| R_t^n \right| = \left| D^\alpha f(t_n) - \nabla_t^\alpha f(t_n) \right| \leq C \max_{0 \leq t \leq T} \left| \frac{d^2 f(t)}{dt^2} \right| \tau^{2-\alpha},
\tag{4}
$$

for some $C > 0$. The implicit numerical scheme for fractional-order system (1) with finite difference approximation of the Caputo derivative is

$$
\begin{cases}
\nabla_t^\alpha T^n = s^\alpha - \mu_T^\alpha T^n + r^\alpha T^n (1 - \frac{T^n + T_L^n + T_A^n}{T_{\max}}) - k_1^\alpha T^n V^n, \\
\nabla_t^\alpha T_L^n = k_1 T^n V^n - \mu_T^\alpha T_L^n - k_2^\alpha T_L^n, \\
\nabla_t^\alpha T_A^n = k_2^\alpha T_L^n - \mu_b^\alpha T_A^n, \\
\nabla_t^\alpha V^n = N \mu_b^\alpha T_A^n - k_1^\alpha V^n T^n - \mu_V^\alpha V^n,
\end{cases}
\tag{5}
$$

that is,

$$
\begin{cases}
T^n + \sum_{j=0}^{n-1} b_j^n T^j - \tau^\alpha \Gamma(2-\alpha)(s^\alpha - \mu_T^\alpha T^n + r^\alpha T^n (1 - \frac{T^n + T_L^n + T_A^n}{T_{\max}}) - k_1^\alpha T^n V^n) = 0, \\
T_L^n + \sum_{j=0}^{n-1} b_j^n T_L^j - \tau^\alpha \Gamma(2-\alpha)(k_1^\alpha T^n V^n - \mu_T^\alpha T_L^n - k_2^\alpha T_L^n) = 0, \\
T_A^n + \sum_{j=0}^{n-1} b_j^n T_A^j - \tau^\alpha \Gamma(2-\alpha)(k_2^\alpha T_L^n - \mu_b^\alpha T_A^n) = 0, \\
V^n + \sum_{j=0}^{n-1} b_j^n V^j - \tau^\alpha \Gamma(2-\alpha)(N \mu_b^\alpha T_A^n - k_1^\alpha V^n T^n - \mu_V^\alpha V^n) = 0.
\end{cases}
$$

In order to solve the above nonlinear equations, we choose the Newton iteration method

$$
x^{k+1} = x^k - J^{-1}(x^k) f(x^k), \quad k = 0, 1, 2, \dots,
\tag{6}
$$

the initial values are given by $x^0 = (T^0, T_L^0, T_A^0, V^0)$. Furthermore, to ensure the convergence of the Newton iteration method and avoid the Jacobian matrix $J(x^k)$ to be nonsingular, we improve the above method by the Algorithm 1.

4 Dynamical behavior of generalized HIV model

In this section we will analyze the dynamics of the generalized HIV model and examine the effect of the fractional order on the HIV dynamics. For this we find the equilibrium points of (1) by solving the following system:

$$
\begin{cases}
s^\alpha - \mu_T^\alpha T + r^\alpha T (1 - \frac{T + T_L + T_A}{T_{\max}}) - k_1^\alpha TV = 0, \\
k_1^\alpha TV - \mu_T^\alpha T_L - k_2^\alpha T_L = 0, \\
k_2^\alpha T_L - \mu_b^\alpha T_A = 0, \\
N \mu_b^\alpha T_A - k_1^\alpha VT - \mu_V^\alpha V = 0.
\end{cases}
$$

We find that system (1) has two equilibrium points: the uninfected equilibrium points $E_0^\alpha = (T_0, 0, 0, 0)$ and the (positive) infected equilibrium points $E_1^\alpha = (\overline{T}, \overline{T_L}, \overline{T_A}, \overline{V})$ where

$$T_0 = \frac{p + \sqrt{p^2 + 4s^\alpha \gamma}}{2\gamma}, \qquad \overline{T} = \frac{\mu_V^\alpha k_3}{k_1^\alpha (Nk_2^\alpha - k_3)},$$

$$\overline{T_L} = \frac{\mu_V^\alpha \overline{V}}{Nk_2^\alpha - k_3}, \qquad \overline{T_A} = \frac{k_2^\alpha \mu_V^\alpha \overline{V}}{\mu_b^\alpha (Nk_2^\alpha - k_3)}, \qquad \overline{V} = \frac{s^\alpha k_4^2 + pk_4\mu_V^\alpha - \gamma(\mu_V^\alpha)^2}{k_1^\alpha \mu_V^\alpha (k_4 + k_5\mu_V^\alpha)},$$

$$p = r^\alpha - \mu_T^\alpha, \quad \text{and} \quad \gamma = r^\alpha / T_{\max},$$

$$k_4 = k_1^\alpha \left(\frac{Nk_2^\alpha}{k_2^\alpha + \mu_T^\alpha} - 1 \right), \qquad k_3 = k_2^\alpha + \mu_T^\alpha, \qquad k_5 = \frac{\gamma}{k_3} \left(1 + \frac{k_2^\alpha}{\mu_b^\alpha} \right).$$

Theorem 4.1 *The uninfected equilibrium point $E_0^\alpha = (T_0, 0, 0, 0)$ is asymptotically stable if and only if*

$$\mu_V^\alpha > \mu_{\text{crit}}^\alpha = \frac{k_1^\alpha k_2^\alpha T_0 N - k_1^\alpha k_3 T_0}{k_3}.$$

Proof The Jacobian matrix J_1 evaluated at E_0^α for the system (1) is given by

$$J_1 = \begin{pmatrix} -a & -\gamma T_0 & -\gamma T_0 & -k_1^\alpha T_0 \\ 0 & -k_3 & 0 & k_1^\alpha T_0 \\ 0 & k_2^\alpha & -\mu_b^\alpha & 0 \\ 0 & 0 & N\mu_b^\alpha & -k_6 \end{pmatrix},$$

where $k_6 = k_1^\alpha T_0 + \mu_V^\alpha$, $a = -p + 2T_0\gamma$.

The associated characteristic equation is given by

$$(\lambda + a)\left[(\lambda + \mu_b^\alpha)(\lambda + k_3)(\lambda + k_6) - k_1^\alpha k_2^\alpha T_0 N\mu_b^\alpha \right] = 0.$$

Hence

$$\lambda_1 = -a < 0,$$

since substituting the value of T_0, we get $a = \sqrt{p^2 + 4s\gamma} > 0$. Dividing the characteristic equation by $(\lambda + a)$, we obtain

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0,$$

where

$$A_1 = \mu_b^\alpha + k_3 + k_6 > 0,$$

$$A_2 = k_3^\alpha k_6 + \mu_b^\alpha (k_3 + k_6) > 0,$$

$$A_3 = \mu_b^\alpha \left(k_3 k_6 - k_1^\alpha k_2^\alpha T_0 N \right).$$

Using the definition of $\mu_{\text{crit}}^{\alpha}$, we have

$$
\begin{aligned}
A_3 &= \mu_b^{\alpha}\left(k_3 k_6 - k_1^{\alpha} k_2^{\alpha} T_0 N\right) \\
&= \mu_b^{\alpha}\left(k_3\left(k_1^{\alpha} T_0 + \mu_V^{\alpha}\right) - k_1^{\alpha} k_2^{\alpha} T_0 N\right) \\
&= \mu_b^{\alpha} k_3\left(\mu_V^{\alpha} - \left(\frac{k_1^{\alpha} k_2^{\alpha} T_0 N - k_1^{\alpha} k_3 T_0}{k_3}\right)\right) \\
&= \mu_b^{\alpha} k_3\left(\mu_V^{\alpha} - \mu_{\text{crit}}\right).
\end{aligned}
$$

Eigenvalues have a negative real part if and only if the following conditions of the Routh-Hurwitz criteria are satisfied:

$$
A_1, A_3 > 0 \quad \text{and} \quad A_1 A_2 - A_3 > 0.
$$

Here A_1 is positive, being a sum of positive terms,

$$
A_1 A_2 - A_3 = \mu_b^{\alpha}(k_3 + k_6) + \mu_b^{\alpha}\left(k_3^2 + k_6^2 + 2k_3 k_6 + k_1^{\alpha} k_2^{\alpha} T_0 N\right) + k_3 k_6(k_3 + k_6) > 0.
$$

$A_3 > 0$ if and only if

$$
\mu_V^{\alpha} > \mu_{\text{crit}}^{\alpha}. \qquad\qquad \square
$$

Remark 4.1 μ_V^{α} is a bifurcation parameter, transcritical bifurcation occurs as μ_V^{α} passes the point $\mu_{\text{crit}}^{\alpha}$ (see Figure 1). When

$$
\mu_V^{\alpha} > \mu_{\text{crit}}^{\alpha} = \frac{k_1^{\alpha} k_2^{\alpha} T_0 N - k_1^{\alpha} k_3 T_0}{k_3},
$$

the uninfected equilibrium point E_0 is stable and the infected equilibrium point E_1^{α} does not exist (this case is unphysical). When $\mu_V^{\alpha} = \mu_{\text{crit}}^{\alpha}$, the uninfected equilibrium point is neutrally stable. When $\mu_V^{\alpha} < \mu_{\text{crit}}^{\alpha}$, E_0 becomes unstable.

Remark 4.2 Following a similar analysis, we see that a transcritical bifurcation occurs at N_{crit}^{α}, where

$$
N_{\text{crit}}^{\alpha} = \frac{k_3(\mu_V^{\alpha} + k_1^{\alpha} T_0)}{k_1^{\alpha} k_2^{\alpha} T_0}.
$$

If $N < N_{\text{crit}}^{\alpha}$; the uninfected equilibrium point E_0^{α} is stable and the infected equilibrium point E_1^{α} does not exist (this case is unphysical). The uninfected equilibrium point is neutrally stable at $N = N_{\text{crit}}^{\alpha}$. E_0^{α} becomes unstable when $N > N_{\text{crit}}^{\alpha}$.

The Jacobian matrix J_2 evaluated at E_1^{α} for the system (1) is given by

$$
J_2 = \begin{pmatrix}
-\sigma & -\gamma \overline{T} & -\gamma \overline{T} & -k_1^{\alpha} \overline{T} \\
-k_1^{\alpha} \overline{T} & -k_3 & 0 & k_1^{\alpha} \overline{T} \\
0 & k_2^{\alpha} & -\mu_b^{\alpha} & 0 \\
-k_1^{\alpha} \overline{T} & 0 & N \mu_b^{\alpha} & -k_6
\end{pmatrix}, \tag{7}
$$

where $\sigma = -p + 2\gamma\overline{T} + \gamma\overline{T} + k_1\overline{V}$. The characteristic equation associated to the Jacobian matrix is given by

$$\lambda^4 + B_3\lambda^3 + B_2\lambda^2 + B_1\lambda + B_0 = 0, \tag{8}$$

with $B_0 = k_1^\alpha \overline{VT}[k_1^\alpha \mu_b^\alpha(Nk_2^\alpha - k_3^\alpha) + \gamma\mu_V(k_2^\alpha + \mu_b^\alpha)]$, $B_1 = \sigma[k_3k_6 + \mu_b^\alpha(k_3 + k_6)] + k_1^\alpha \overline{VT} \times [\gamma(\mu_V^\alpha + k_2^\alpha + \mu_b^\alpha) - k_1^\alpha(k_3 + \mu_b^\alpha)]$, $B_2 = \sigma(k_3 + k_6 + \mu_b^\alpha) + \mu_b^\alpha(k_3 + k_6) + k_3k_4 + k_1^\alpha \overline{TV}(\gamma - k_1^\alpha)$, $B_3 = \sigma + k_3 + k_6 + \mu_b^\alpha$.

By the Routh-Hurwitz criteria for the stability of fractional-order systems [42], we have the following result for the stability of infected equilibrium.

Theorem 4.2 *The infected equilibrium point $E_1^\alpha = (\overline{T}, \overline{T_L}, \overline{T_A}, \overline{V})$ is locally asymptotically stable if the coefficients of the characteristic polynomial* (8) *evaluated at E_1^α satisfy*

$$B_0 > 0, \qquad B_1 > 0, \qquad B_3 > 0 \quad and \quad B_1B_2B_3 > B_1^2 + B_3^2B_0, \tag{9}$$
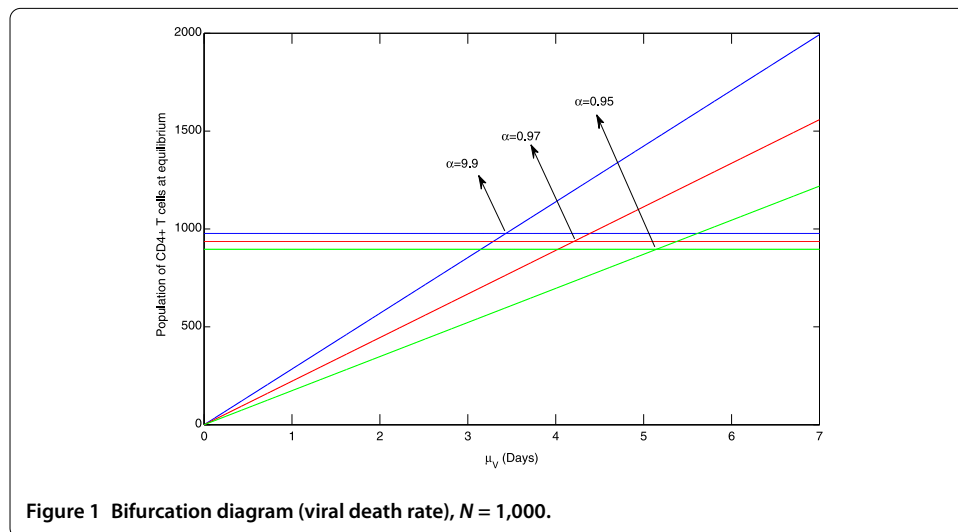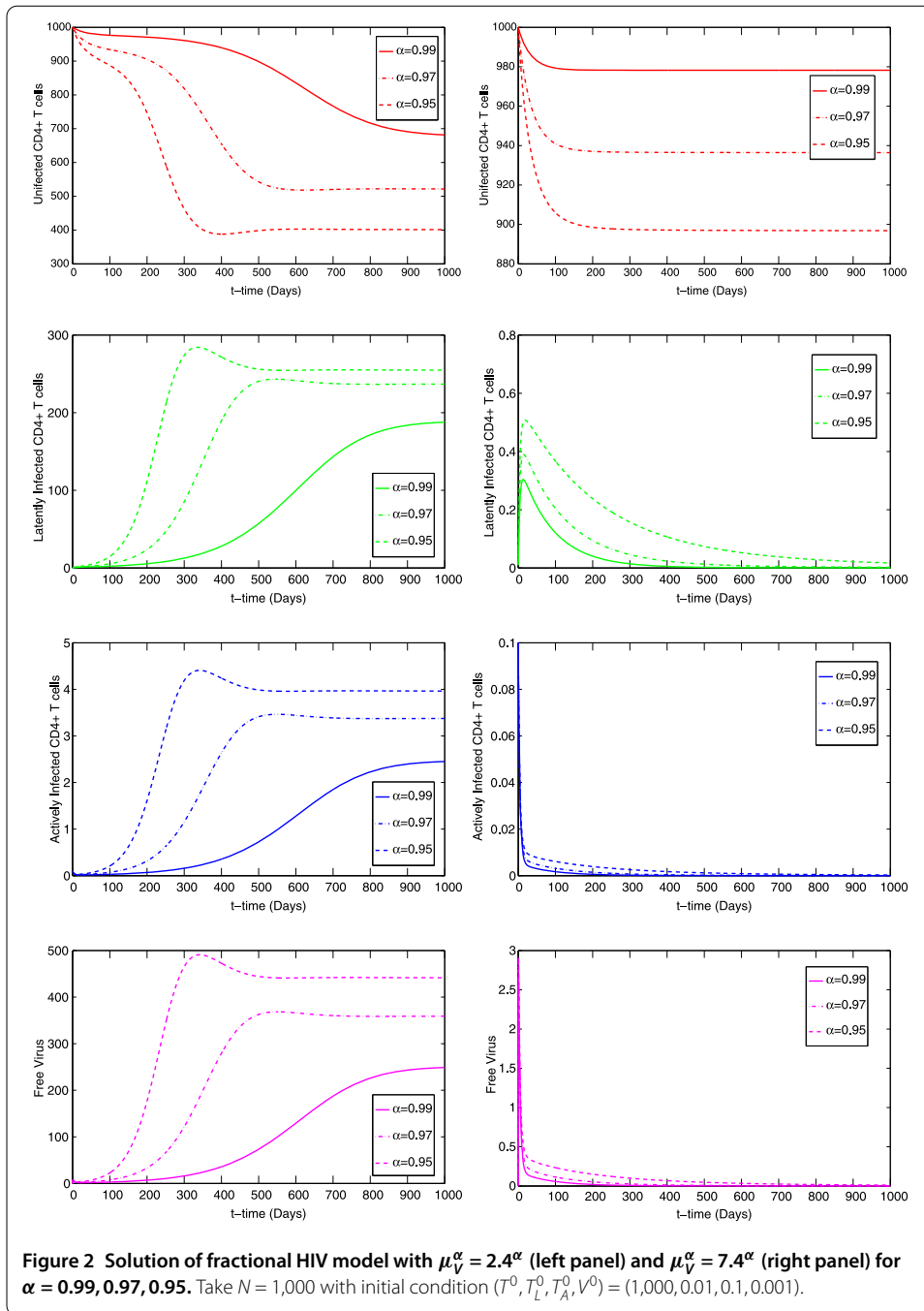
for all $\alpha \in (0, 1]$.

5 Numerical simulations

In this section, numerical simulations are provided to verify the theoretical results established in the previous sections. In the following we will monitor the effect of varying viral death rate and varying number of new virions produced by infected CD4$^+$ T-cells on the dynamical behavior of the fractional model, respectively. The parameters are chosen as in Table 1, unless otherwise stated.

Table 1 HIV model parameters

μ_T^α	μ_b^α	μ_V^α	k_1^α	k_2^α	r^α	N	T_{max}	s^α
0.02^α	0.24^α	2.4^α	$(2.4 \times 10^{-5})^\alpha$	$(3 \times 10^{-3})^\alpha$	0.03	Varies	$1,500$	10^α

Figure 1 Bifurcation diagram (viral death rate), $N = 1,000$.

Figure 2 **Solution of fractional HIV model with $\mu_V^\alpha = 2.4^\alpha$ (left panel) and $\mu_V^\alpha = 7.4^\alpha$ (right panel) for $\alpha = 0.99, 0.97, 0.95$.** Take $N = 1,000$ with initial condition $(T^0, T_L^0, T_A^0, V^0) = (1,000, 0.01, 0.1, 0.001)$.
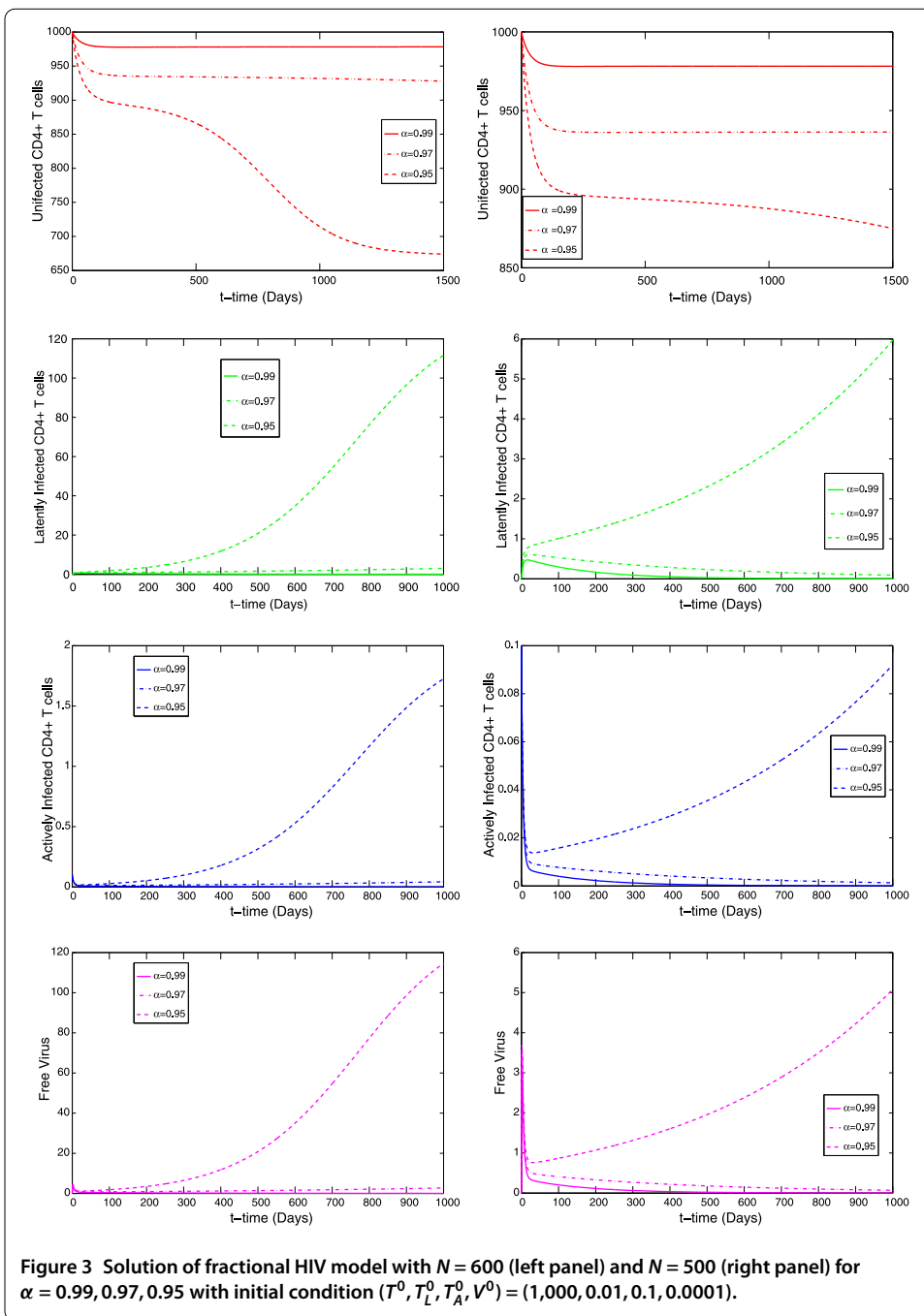
Uninfected equilibria for different fractional orders are as follows:

$$\begin{cases} E_0^\alpha = (978, 0, 0, 0), & \mu_{\text{crit}}^\alpha = 3.4364 & \text{for } \alpha = 0.99, \\ E_0^\alpha = (936, 0, 0, 0), & \mu_{\text{crit}}^\alpha = 4.2059 & \text{for } \alpha = 0.97, \\ E_0^\alpha = (986, 0, 0, 0), & \mu_{\text{crit}}^\alpha = 5.1488 & \text{for } \alpha = 0.95. \end{cases}$$

By Remark 4.1, E_0^α is asymptotically stable when $\mu_V^\alpha = 7.4^\alpha > \mu_{\text{crit}}^\alpha$ and E_0^α become unstable as $\mu_V^\alpha = 2.4^\alpha$ is reduced. Transcritical bifurcation occurs at the point μ_{crit}^α see Figure 1.

Figure 3 Solution of fractional HIV model with $N = 600$ (left panel) and $N = 500$ (right panel) for $\alpha = 0.99, 0.97, 0.95$ with initial condition $(T^0, T_L^0, T_A^0, V^0) = (1{,}000, 0.01, 0.1, 0.0001)$.

The approximate solution for $\alpha = 0.99, 0.97, 0.95$ are displayed in Figure 2, which are in good agreement with the analytical result.

Next we will simulate the fractional system by varying the values of the parameter N and choosing other values from Table 1. By calculation we can obtain

$$
\begin{cases}
E_1^\alpha = (978, 0, 0, 0), & N_{\text{crit}}^\alpha = 694 & \text{for } \alpha = 0.99, \\
E_1^\alpha = (936, 0, 0, 0), & N_{\text{crit}}^\alpha = 559 & \text{for } \alpha = 0.97, \\
E_1^\alpha = (986, 0, 0, 0), & N_{\text{crit}}^\alpha = 450 & \text{for } \alpha = 0.95.
\end{cases}
$$

According to Remark 4.2, $E_0^{0.99}$ is stable but $E_0^{0.97}$ and $E_0^{0.95}$ are unstable when $N = 600$. Next reducing $N = 500$ gives $N < N_{\text{crit}}^{0.99}$ and $N < N_{\text{crit}}^{0.97}$ so $E_0^{0.99}$ and $E_0^{0.97}$ become stable; however, $E_0^{0.95}$ is unstable as shown in Figure 3.
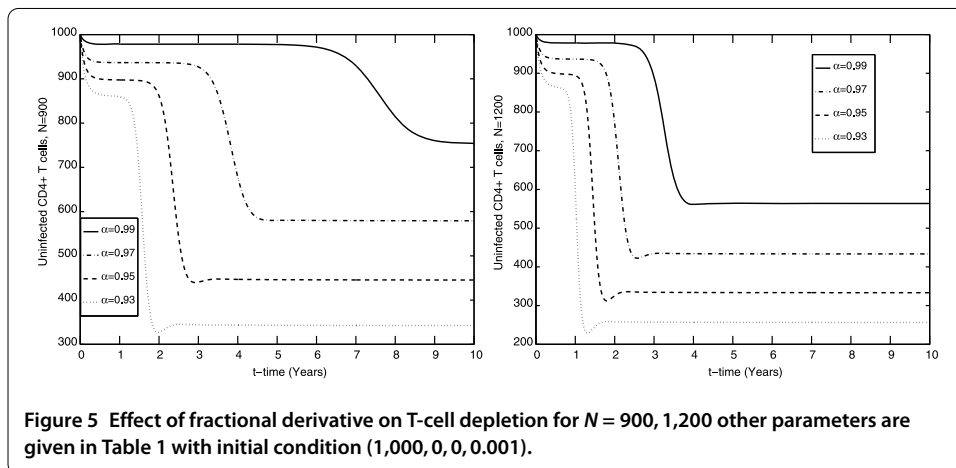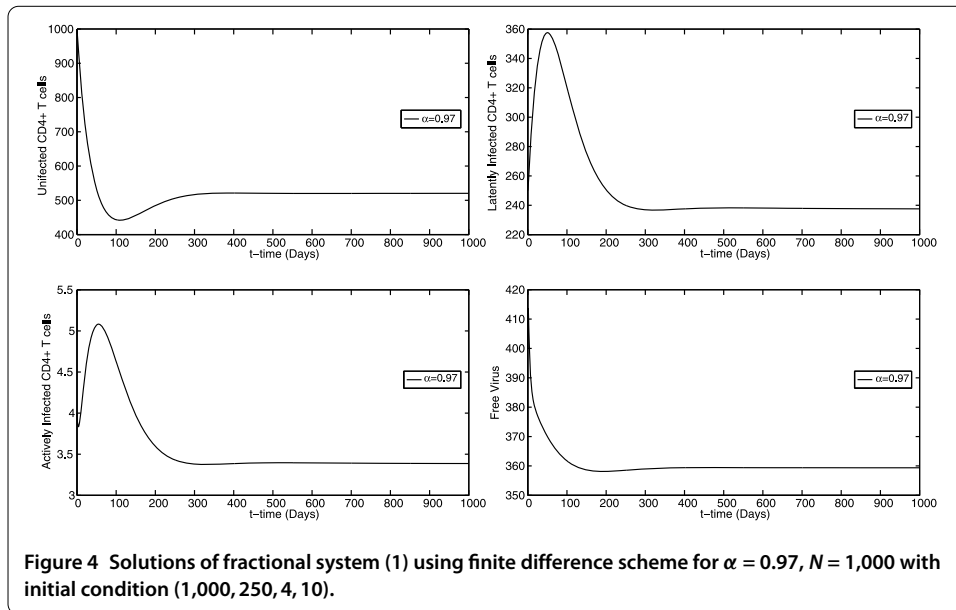
For $\alpha = 0.97$ the coefficients of characteristic polynomial evaluated at infected equilibrium $E_1^\alpha = (520, 236, 3, 359)$ are

$$B_0 = 2.6259 \times 10^{-4} > 0, \qquad B_1 = 0.0197 > 0, \qquad B_3 = 2.6610 > 0,$$

$$B_1 B_2 B_3 = 0.0353 > B_1^2 + B_3^2 B_0 = 0.0022.$$

Hence by Theorem 4.2, $E_1^{0.97}$ is locally asymptotically stable as shown in Figure 4.

The decline in the number of CD4$^+$ T-cells in peripheral blood is used in a clinical setting as indicators of the disease stage. Decreasing fractional order gives rise to larger amounts of CD4$^+$ T-cell depletion as shown in Figure 5.

Figure 4 Solutions of fractional system (1) using finite difference scheme for $\alpha = 0.97$, $N = 1{,}000$ with initial condition $(1{,}000, 250, 4, 10)$.

Figure 5 Effect of fractional derivative on T-cell depletion for $N = 900$, $1{,}200$ other parameters are given in Table 1 with initial condition $(1{,}000, 0, 0, 0.001)$.

6 Conclusion

In this paper, we have investigated a fractional-order HIV model, as a generalization of an integer-order model. The advantage of the generalized model is that the fractional-order system possesses memory, which belongs to the main features of the immune response. An implicit numerical scheme has been proposed for the fractional-order HIV model using a finite difference approximation of the Caputo derivative. We showed that the system possesses two equilibrium points and derived the analytical condition for the stability of uninfected and infected equilibrium points. Further we analyzed the influence of the fractional derivative on the dynamics of system. In many AIDS patients the T-cell level can be depleted <200 mm^{-3} level, on the other hand an integer-order model cannot model this fact using the parameter values in Table 1. However, with the additional degree of freedom of the fractional derivative we can obtain the low CD4$^+$ cell counts seen during the late stages of the disease; see Figure 5. We established that μ_V^α and N are bifurcation parameters, transcritical bifurcation occurs as μ_V^α and N passes the point μ_{crit}^α and N_{crit}^α, respectively. We have shown that the disease can be eradicated by increasing the viral death rate greater than μ_{crit}^α as shown in Figure 2. Another parameter that could play a vital role to control the HIV virus is the number of new virions produced by infected CD4$^+$ T-cells. We found that the virus can be eliminated if N is less than N_{crit}^α, that is, HIV infection will not be sustained if infected cells die without producing an adequate number of viral progeny as demonstrated in Figure 3. Mathematical models can help physicians to choose an optimal dosage and check the effects of their therapeutic action. HIV progression has many variations from patient to patient, which is difficult to capture by an integer-order derivative. The fractional derivative can be varied to best fit the real data according to the progression of different HIV patients. Thus a more reliable model can be obtained by choosing the relevant fractional index according to real data. Consequently, the clinician can recommend administration of drugs or treatment to each individual patient by using the information from the generalized model with the most relevant fractional index.

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