The influence of antiretroviral treatment in a fractional-order model of HIV infection

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Abstract

In this article, we provide the fractional-order model for HIV infection of CD4+ T cells that accounts for the therapeutic impact of antiretroviral drugs. To get a numerical answer to this kind of issue, the Generalized Euler Method (GEM) is used. The Caputo sense is used to describe fractional derivatives.

1. Introduction

CD4+ T lymphocytes are the most common kind of white blood cell in the immune system [2, 3, 26, and 27]. HIV is a retrovirus that specifically targets these cells. HIV may infect more than only human cells, although wreaks havoc on CD4+ T cells by inducing their decrease and death, which weakens the immune system [20-25]. The dynamics of HIV infection may be better understood with the use of mathematical models [5, 6, 15, 18, and 19]. Human immunodeficiency virus (HIV) plasma virus load is rapidly reduced after anti-viral medication therapy. The HIV infection is treated with reverse transcriptase inhibitors (RTIs) [23, 24]. Reverse transcriptase is a viral DNA polymerase enzyme necessary for retrovirus reproduction, and RTIs block [23] its function. Antiviral drugs that inhibit reverse transcriptase are effective against HIV-1 because they prevent infection of healthy cells [25, 26]. Assuming that the treatment is not completely successful, the authors of [25] postulated that some infected cells in the pre-RT class would revert back to the uninfected class while the rest would complete reverse transcription, become productively infected, and create virus. Under these conditions, they built a mathematical model of primary infection with RT inhibitor. For this reason, the next model is an extension of the one shown in [25]:

$$\begin{aligned} D^{\alpha}(T) &= s - kLT - \mu T + (\eta\epsilon + b)I \\ D^{\alpha}(I) &= kLT - (\mu_1 + \epsilon + b)I \\ D^{\alpha}(V) &= (1-\eta)\epsilon I - \delta V \\ D^{\alpha}(L) &= N\delta V - cL \end{aligned} \qquad (1)$$

where $0 < \alpha \leqslant 1$.

Density of susceptible CD4+ T cells is represented by T, density of infected CD4+ T cells before to reverse transcription (pre-RT class) is represented by I, and density of activated CD4+ T cells is represented by V in the aforementioned Class of CD4+ T cells infected with HIV in which reverse transcription has been completed (post-RT class) and which may replicate the virus. The density of the virus is denoted by the symbol V. The infected cells enter a stage called pre-RT after infection. Infected cells enter pre-RT class I soon after infection and exit pre-RT class to post-RT class at a rate e. The virus may replicate within these infected cells and spread to other cells. In light of what has been said above, we hypothesize that in the presence of RT inhibitor, some number of cells, denoted by g eye, migrates back to the uninfected class, while the remaining number, denoted by (1 g) eI, migrates

to the post-RT class and becomes productively infected. CD4+ T cell influx (s), natural cell death (l), CD4+ T cell interaction infection (k), infected cell death (l1), CD4+ T cell transition from pre-RT to post-RT (e), and reversion of infected cells to uninfected cells (b) owing to incomplete reverse transcription (23,25).
Actively infected cell death, which may include T cell bursting, is represented by the parameter d, viral clearance is denoted by the parameter c, and the number of infected cells is given by the value N. quantification of how many virus particles each infected cell produces. Here is how the remainder of the paper is structured. Fractional calculus as a notion is introduced in Section 2, followed by the Generalized Euler method (GEM) in Section 3. In Section 4, we talk about the system's non-negative solutions. Section 5 covers stability and equilibrium point analysis. In Chapter 6, we show the numerical findings of the proposed issue (1).

2. Fractional calculus

Many disciplines make substantial use of fractional calculus (FC) [4, 7]. Many mathematicians and scientists in the applied sciences have attempted to use fractional calculus to create models of real-world processes. Fractional-order dynamical analysis of electrical impedances in plants was performed by Jesus, Machado, and Cunha [11, 12]. Using fractional-order mathematics, Mestrovic, Spastic, and Atanackovic modeled human root dentin [20]. A fractional-order electrical conductance [4] has been inferred for biological cell membranes, which leads to their further classification into non-integer order model classes. The most significant advances in theology have been made using fractional derivatives [7], since they capture key aspects of cellular rheological activity. Furthermore, it has been shown that there are benefits to using fractional ordinary differential equations (FODE) in mathematical modeling rather than the more traditional integer order modeling [9]. The primary justification for their use is that fractional differential equations have a natural connection to systems with memory, which is present in almost all biological and other systems [1-4].
That is, you need to know everything about the function f (t) up to and including time t= t1 in order to compute the time-fractional derivative of f (t) at that time. t= t1. Additionally, modeling real-world phenomena with fractional-order differential equations can help us cut down on errors caused by overlooked variables [6]. Biological systems typically feature some form of memory, and FODE are thus naturally related to such systems. Also, fractals, which are common in living things, share a close relationship with them [8]. For all practical purposes, fractional-order differential equations are at least as stable as their integer-order counterparts. We therefore propose a framework of FODE models for HIV transmission. First, we define integration and differentiation at the fractional order [10]. To properly handle initial value problems, we will use a modified version of the Riemann-Lowville definition that we will call "Caputo's definition" for the concept of fractional derivative.

This section provides a definition for the Riemann-Lowville fractional integration of order a.

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

Definition 2.2. Riemann–Lowville and Caputo fractional derivatives of order a can be defined respectively as follows:

$$D^{\alpha} f(x) = D^{m}(J^{m-\alpha} f(x)), \tag{2}$$
$$D_*^{\alpha} f(x) = J^{m-\alpha}(D^{m} f(x)) \tag{3}$$

where

$$m-1 < \alpha \leqslant m, \quad m \in N$$

Properties of the operator JA can be found in [4, 5], we mention only the following:

$$(1)\ J^{\alpha}J^{\beta}f(x) = J^{\alpha+\beta}f(x) \quad (4)$$

$$(2)\ J^{\alpha}J^{\beta}f(x) = J^{\beta}J^{\alpha}f(x) \quad (5)$$

$$(3)\ J^{\alpha}t^{\gamma} = \frac{\Gamma(\gamma+1)}{\Gamma(\alpha+\gamma+1)}t^{\alpha+\gamma},\quad \alpha>0,\ \gamma>-1,\ t>0 \quad (6)$$

3. Generalized Euler Method (GEM)

Non-linear fractional differential equations typically lack analytic solutions [16, 17], necessitating the use of approximations and numerical methods to solve them. Decomposition Analysis (ADM) and the variation iteration method (VIM) are relatively new approaches that provide an approximate analytical solution to linear and non-linear problems; these methods are useful for scientists and applied mathematicians because they allow them to see the symbolic terms of analytic solutions right away, while also providing numerical approximate solutions. There has been progress in using the VIM ADM for both linear and nonlinear issues in recent years. However, the standard homogony perturbation method (HPM) [14] cannot solve the problem for larger time, and in fact the solution of the chaotic system using HPM is an open problem; these methods are effective for small time, i.e. t 1 [9,10].

However, there are edge cases where these methods provide a good approximation over a broad period of time (t). A few the literatures present numerical methods for solving fractional differential equations. However, many of these approaches are only applicable to very restricted classes of differential equations, such as linear equations. Our numerical approach to solving initial value problems with Caputo derivatives is based on the generalized Euler's method derived by Doubt and Momani [16, 17]. This approach is a modern extension of Euler's method. To illustrate, let's think about the initial value problem.

$$D_*^{\alpha}y(t) = f(t,y(t)),\quad y(0)=y_0,\quad 0<\alpha\leqslant 1,\ t>0 \quad (7)$$

$$y(t) = y(t_0) + \left(D_*^{\alpha}y(t)\right)(t_0)\frac{t^{\alpha}}{\Gamma(\alpha+1)} + \left(D_*^{2\alpha}y(t)\right)(c_1) \times \frac{t^{2\alpha}}{\Gamma(2\alpha+1)} \quad (8)$$

When $\left(D_*^{\alpha}y(t)\right)(t_0) = f(t_0,y(t_0))$ and $h = t_1$ are substituted into Eq. (8), the result is an expression for $y(t_1)$:

$$y(t_1) = y(t_0) + f(t_0,y(t_0))\frac{h^{\alpha}}{\Gamma(\alpha+1)} + \left(D_*^{2\alpha}y(t)\right)(c_1)\frac{h^{2\alpha}}{\Gamma(2\alpha+1)}$$

If the step size h is chosen small enough, then we may neglect the second-order term (involving h2a) and get

$$y(t_1) = y(t_0) + \frac{h^{\alpha}}{\Gamma(\alpha+1)}f(t_0,y(t_0))$$

The process is repeated and generates a sequence of points that approximates the solution y (t). The general Formula for generalized Euler's method (GEM) when

$t_{j+1} = t_j + h$ is

$$y(t_{j+1}) = y(t_j) + \frac{h^\alpha}{\Gamma(\alpha+1)} f(t_j, y(t_j)) \qquad (9)$$

for $j = 0, 1, \ldots, k-1$. It is clear that if $\alpha = 1$, then the generalized Euler's method (9) reduces to the classical Euler's method.

4. Non-negative solutions

Denote $R_+^4 = \{X \in R^4 : X \geqslant 0\}$, and $X(t) = (T, I, V, L)^T$.

For the proof of the non-negative solution, consider the following theorem and corollary:
Theorem 1 (Generalized mean value theorem).

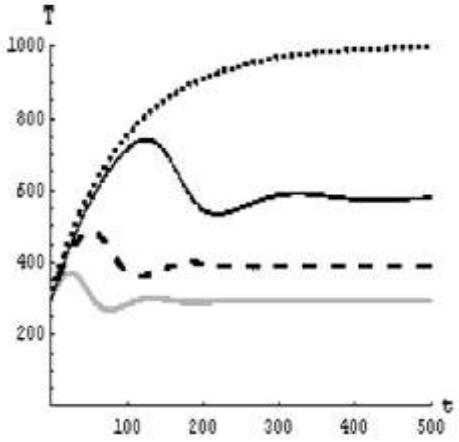
Let $f(x) \in C(0, a]$ *and* $D^\alpha f(x) \in C(0, a]$, *for* $0 < \alpha \leqslant 1$. *Then we have*

$$f(x) = f(0+) + \frac{1}{\Gamma(\alpha)} (D^\alpha f)(\xi)(x)^\alpha$$

with $0 \leqslant \xi \leqslant x$, $\forall x \in (0, a]$.

Proof. Proof is given in [16]. □

Corollary 1.1. *Suppose that* $f(x) \in C[0, a]$ *and* $D^\alpha f(x) \in C(0, a]$ *for* $0 < \alpha \leqslant 1$. *It is clear from theorem 1.1 that if* $D^\alpha f(x) \geqslant 0$, $\forall x \in (0, a)$, *then* $f(x)$ *is non-decreasing and if* $D^\alpha f(x) \leqslant 0$, $\forall x \in (0, a)$ *then* $f(x)$ *is non-increasing for all* $x \in [0, a]$.



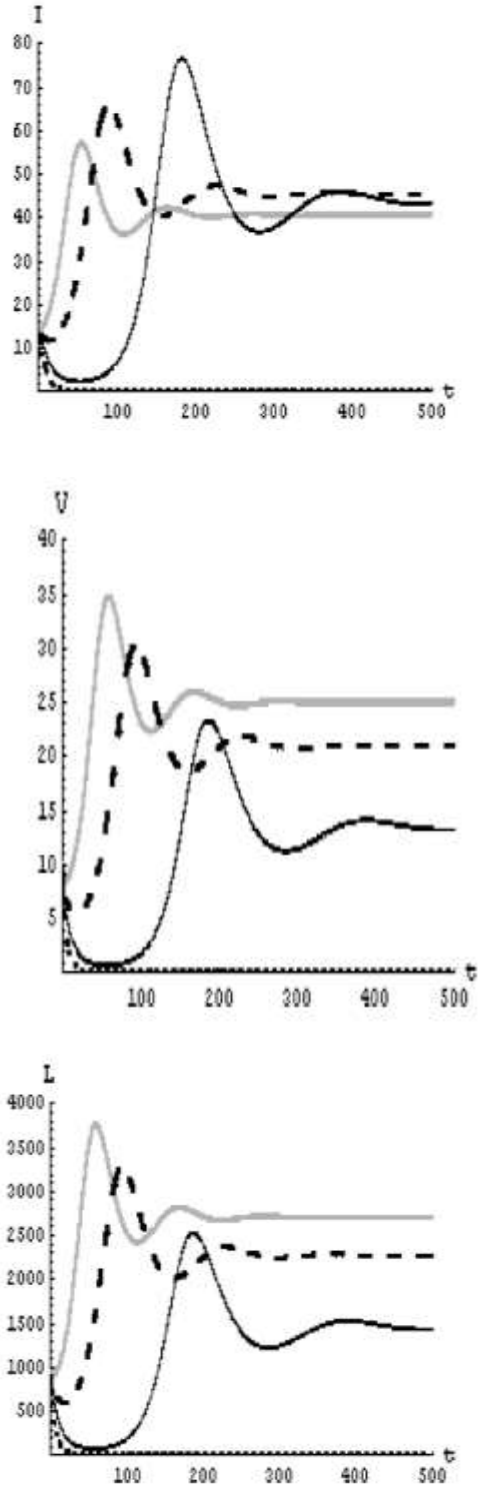


Fig. 1 The densities of the susceptible CD4+ T cells T(t), infected CD4+ T cells I(t)in pre-RT class, density of infected CD4+ T cells V(t) in post-RT class, and the virus density L(t) when a= 1. The gray line (g= 0.6), the dashed line (g= 0.7), black solid line (g =0.8), the dotted line (g= 0.9).

Proof. This is clear from Theorem 1.1 [6]. □

Theorem 2. *There is a unique solution* $X(t) = (T, I, V, L)^T$ *for* (1) *at* $t \geqslant 0$ *and the solution will remain in* R_+^4.

Proof. The existence and uniqueness of the solution of the initial value problem (2.2) in (0, 1) can be obtained from [13, Theorem 3.1 and Remark 3.2]. Now we will show that R4 þ is positively invariant domain:

$$D^1T|_{T=0} = S + (\eta\epsilon + b)I \geqslant 0$$
$$D^1I|_{I=0} = kLT \geqslant 0$$
$$D^1V|_{V=0} = (1-\eta)\epsilon I \geqslant 0$$
$$D^1L|_{L=0} = N\delta V \geqslant 0$$

From Corollary 1.1, the solution will remain in R_+^4. □

5. Equilibrium points and stability

The equilibrium points of the given integer system (1), i.e., when a = 1, were derived by the authors in [25]. The fractional-order system (1)'s equilibrium points are evaluated by

$$D^{\alpha}(T) = 0$$
$$D^{\alpha}(I) = 0$$
$$D^{\alpha}(V) = 0$$
$$D^{\alpha}(L) = 0$$

Then we will have the same results in [20] as follows

$$E_1 = \left(\frac{s}{\mu}, 0, 0, 0\right) \text{ and } E_2 = (\overline{T}, \overline{I}, \overline{V}, \overline{L})$$

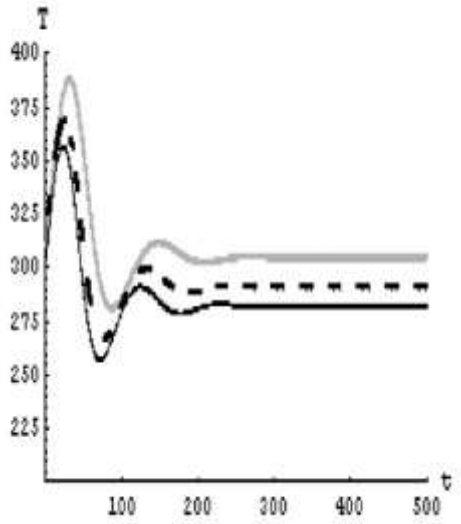
where

$$\overline{T} = \frac{(\mu_1 + \epsilon + b)c}{NK\epsilon(1-\eta)}, \quad \overline{I} = \frac{s - T\mu}{\epsilon(1-\eta) + \mu_1}, \quad \overline{V} = \frac{(1-\eta)\epsilon T_1^*}{\delta},$$
$$\overline{L} = \frac{NT^*\delta}{c}$$

It is required that the eigenvalues ki of the Jacobean matrices of E1 and E2 meet the criterion for the local asymptotic stability of the equilibrium points. j > a p 2 | ki > j this proves that differential equations of fractional order are at least as stable as their integer order counterparts.

7. Conclusion

In this research, we used the Generalized Euler method (GEM) as a viable starting point for investigating the treatment of human T-cell lymph tropic virus type I (HIV-I) infection.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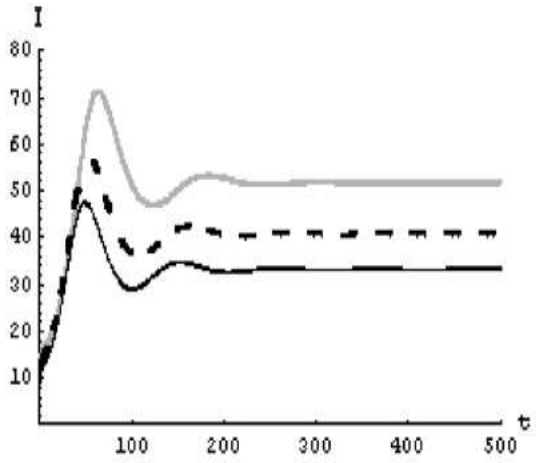
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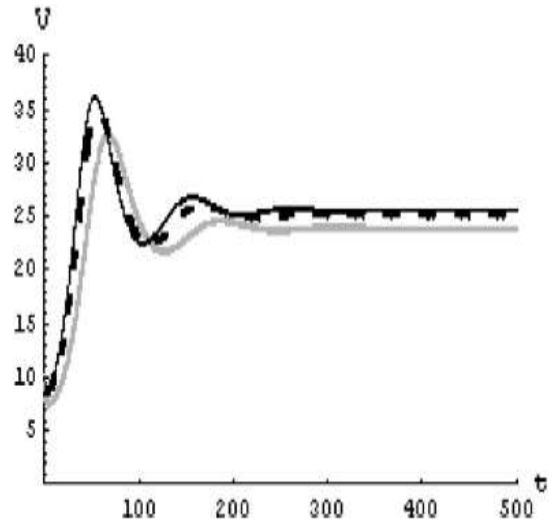
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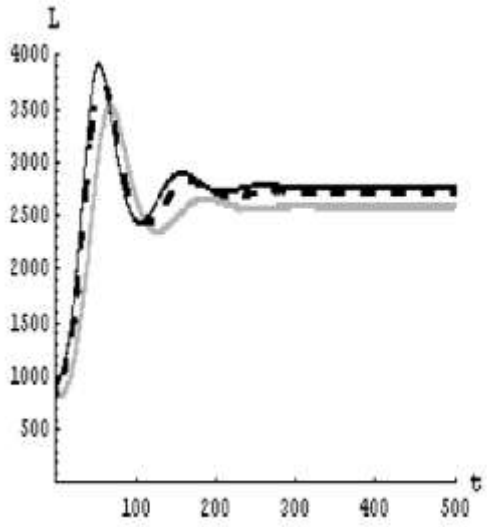

Fig. 4 Densities of susceptible CD4(+) T cells T(t), infected CD4(+) T cells I(t) in the pre-RT class, infected CD4(+) T cells V(t) in the post-RT class, and viral density L(t) for a= 1 (the grey line), a=0.99 (the dotted line), and a= 0.98 (the black solid line). T lymphocytes CD4+. Changes in viral load may be seen between the 0.6 and 0.8 levels of CD4+ T cells rise when g is raised, and the ratio between the two rises (see Fig. 1). Increases in a have a greater effect on viral load than increases in e (see Fig. 2). Same set of inputs as before, this time for b= 0–0.1. A constant g of 0.6 and an equal but opposite e of 0.4 is maintained. Fig. 3 displays the data. The correlation between a rise in b and an increase in CD4+ T cells and a fall in viral load is clear. Since we now know the concentrations of susceptible CD4+ T cells T(t), infected CD4+ T cells I(t), and free HIV virus particles V(t) in the blood, we can use affix 1 to convert the solution of the fractional model (1) Ta(t), Ia(t), Va(t), La(t) back to the original form T(t), Ia(t), V(t), L(t) (see Fig. 4). Finally, we hope that our study is a beginning toward investigating techniques of solution for such equations (analytical and numerical) in light of the recent emergence of fractional differential equations as models in various domains of applied mathematics.

References

[1] E. Ahmed, A.M.A. El-Sayed, H.A.A. El-Saka, Equilibrium points, stability and numerical solutions of fractional-order predator–prey and rabies models, J. Math. Anal. Appl. 325 (2007) 542–553.

[2] A.A.M. Arafa, S.Z. Rida, M. Khalil, Fractional modeling dynamics of HIV and CD4+ T-cells during primary infection, Nonlinear Biomed. Phys. 6 (2012) 1–7.

[3] A.A.M. Arafa, S.Z. Rida, M. Khalil, The effect of anti-viral drug treatment of human immunodeficiency, Appl. Math. Modell. 37 (2013) 2189–2196.

[4] K.S. Cole, Electric conductance of biological systems, in: Proc. Cold Spring Harbor Symp. Quant. Biol, Cold Spring Harbor, New York, 1993, pp. 107–116.

[5] R.V. Culshaw, S. Ruan, A delay-differential equation model of HIV infection of CD4+ T -cells, Math. Biosci. 165 (2000) 27–39.

[6] Y. Ding, Haiping Ye, A fractional-order differential equation model of HIV infection of CD C T-cells, Math. Comput. Modell. 50 (2009) 386–392.

[7] V.D. Djordjevic´ , J. Jaric´ , B. Fabry, J.J. Fredberg, D. Stamenovic´ , Fractional derivatives embody essential features of cell rheological behavior, Ann. Biomed. Eng. 31 (2003) 692– 699.

[8] A.M.A. El-Sayed, S.Z. Rida, A.A.M. Arafa, On the solutions of time-fractional bacterial chemotaxis in a diffusion gradient chamber, Int. J. Nonlinear Sci. 7 (2009) 485–492.

[9] A.M.A. El-Sayed, A.E.M. El-Mesiry, H.A.A. El-Saka, Numerical solution for multi-term fractional (arbitrary) orders differential equations, Comput. Appl. Math. 23 (2004) 33–54.

[10] I. Hashim, O. Abdulaziz, S. Momani, Homotopy analysis method for fractional IVPs, Commun. Nonlinear Sci. Numer. Simul. 14 (2009) 674–684.

[11] I.S. Jesus, J.A.T. Machado, J.B. Cunha, Fractional electrical impedances in botanical elements, J. Vib. Control 14 (2008) 1389–1402.

[12] I.S. Jesus, J.A.T. Machado, J.B. Cunha, Fractional order electrical impedance of fruits and vegetables, in: Proceedings of the 25th IASTED International Conference Modeling, Identification, and Control, February 6–8, 2006, Lanzarote, Canary Islands, Spain, 2006.
[13] W. Lin, Global existence theory and chaos control of fractional differential equations, J. Math. Anal. Appl. 332 (2007) 709–726.
[14] M. Merdan, Tahir Khan Yev, Homotopy perturbation method for solving viral dynamical model, C.U¨ . Fen-EdebiyatFaku¨ ltesi, Fen BilimleriDergisi 31 (2010) 65–77.
[15] P.W. Nelson, A.S. Perelson, Mathematical analysis of delay differential equation models of HIV-1 infection, Math. Biosci. 179 (2002) 73.