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DYNAMICS OF FRACTIONAL ORDER MODEL OF HIV INFECTION ON $CD4^+T$ -CELLS WITH DRUG ANALYSIS

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Abstract. In this paper, we consider a four-compartmental model of HIV infection on $CD4^+T$ -cells with drug therapy in order to study the transmission dynamics of disease. We examine the qualitative behaviour of the model and analyze the sufficient criteria for the stability. In addition, we introduce a Caputo derivative fractional order model and numerical simulations are carried out to illustrate the analytical results.

Keywords: HIV; AIDS; $CD4^+T$ cells; fractional order differential equation; ART; AZT.

2020 AMS Subject Classification: 97M60, 34D20, 34C23.

1. INTRODUCTION

The Human Immunodeficiency Virus (HIV) primarily infects $CD4^+T$ cells. Acquired immunodeficiency syndrome (AIDS) is the advanced stage of HIV infection, which damages the body's ability to fight other infections. Antiretroviral therapy (ART) of HIV/AIDS requires treating two or more antiviral medications concurrently, which improves the patients' immune system and extends their life.

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Reverse transcriptase inhibitors and protease inhibitors are two commonly known drugs. By inhibiting the reverse transcription of HIV RNA into its proviral DNA, reverse transcriptase inhibitors block the new infection. Whilst by disabling enzymes required for viral protein production and assembly, protease inhibitors prevent the production of new infectious virus particles.

Mathematical model plays an effective and efficient way to interpret the dynamics of HIV infection on $CD4^+$ T cells and antiretroviral therapy effect, to reduce HIV viral load. The drug therapy model was transformed from ordinary differential equations to fractional differential equations due to their association with memory systems in biological systems [1].

The fractional differentiation defined as $\mathcal{D}_t^\alpha = \frac{d^\alpha}{dt^\alpha}$, if $\alpha > 0$ and fractional integral defined as $\mathcal{D}_t^\alpha = \int_a^t (d\tau)^\alpha$, if $\alpha < 0$. There are three types of general fractional differential integrals: Grunwald-Letnikov, Riemann-Liouville, and Caputo derivatives[2], [3]. We proposed the Caputo fractional order differential model for drug therapy. The efficacy of HIV medication therapy A.A.M Arafa, S.Z.Ridha, and M. Khalil discuss the plasma densities of uninfected $CD4^+$ T-cells and infected cells devoid of viruses[4].

Around one million individuals will pass away from HIV-related illnesses globally in 2020. 28 million people have access to ARVs (antiretroviral medications) by the end of 2021. With 2 million new HIV infections recorded and an estimated 38 million individuals living with the virus worldwide in 2020, AIDS-related illnesses claimed the lives of 680,000 people. A. J. Ferrari and E. A. Santillan Marcus conducted a study on HIV infection in $CD4^+$ T-cells, as well as the impact of treatment on infected patients. Their research resulted in the identification of model solutions pertaining to existence, uniqueness, positive invariant, and stability aspects [5]. P.K. Srinivastava, M. Banerjee, and Peeyush Chandra explored drug treatment modeling for HIV/AIDS disease. They specifically analyzed the impact of reverse transcriptase inhibitors on the dynamics of HIV. Additionally, a straightforward model for HIV infection was examined by Alans S. Perelson, Denise E. Kirchner, and Rob De. Boer. Furthermore, the authors investigated different dynamic characteristics of HIV infection in $CD4^+$ T-cells.

In this study, zidovudine and azidothymidine are administered as part of the HIV infection therapy combined with the protease inhibitor m_p and the reverse transcription inhibitor m_{rt} .

The ordinary $CD4^+T$ -cell counting is 500-1400 cells/cubic a blood millimetre. Antiretroviral therapy becomes necessary for the patient when there is a decline in the count of $CD4^+T$ -cells [6]. This study focuses on the spread of HIV, which is depicted using a four compartmental model. The basic reproduction number \mathfrak{R}_0 is determined through the next generation matrix. If $\mathfrak{R}_0 \leq 1$, the system is locally asymptotically stable. The drugs, protease inhibitor m_p and reverse transcription inhibitor m_{rt} are shown to effectively reduce HIV plasma levels and increase the count of $CD4^+T$ -cells, leading to improved life expectancy for HIV/AIDS patients.

2. MATHEMATICAL MODEL FORMULATION

2.1. HIV Virus Transmission with $CD4^+T$ - cells. Consider the following model,

$$(1) \quad \left\{ \begin{array}{l} \frac{dA}{dt} = l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_A A - kDA, \\ \frac{dI}{dt} = (1 - m_{rt}) kDA - \delta I, \\ \frac{dD}{dt} = (1 - m_p) N \delta I - cD, \\ \frac{dS}{dt} = m_p N \delta I - cS. \end{array} \right.$$

where, A -non-infected $CD4^+T$ cells, I -Infected $CD4^+T$ cells, D -Infectious viruses, S -Non infectious viruses, I - $CD4^+T$ cells source, δ -Infected cells death rate, k -Viral activity rate, N -Bursting cells, d_A -Death rate of target cell, A_{max} -Maximum $CD4^+T$ - cell, p -Growth rate of $CD4^+T$ cells, c - Rate of clearance virus, m_p -Protease inhibitor drugs and m_{rt} -Reverse transcriptase drugs.

$$\frac{dA}{dt} = l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_A A - kDA.$$

Disease free virus with initial conditions are, $A(0) = A_0, I(0) = 0, D(0) = 0, S(0) = 0$.

$$A_0 = \frac{A_{max}}{2p} \left[(p - d_A) + \sqrt{(p - d_A)^2 + \frac{4pl}{A_{max}}} \right].$$

3. PRELIMINARIES

3.1. Invariant Region.

Theorem 1. *The solution $x(t) = (A, I, D, S)^T$ to the equation (1) on $t \geq 0$ and R_+^4 . Further more $A(t)$, $I(t)$, $D(t)$ and A_{max} are bounded.*

Proof. System of mathematical model equation (1) is unique but not existence. The R_+^4 is a non negative.

Invariant region:

$$\begin{aligned} \frac{dA}{dt} \Big|_{A=0} &= l \geq 0, \\ \frac{dI}{dt} \Big|_{I=0} &= (1 - m_{rt})kDA \geq 0, \\ \frac{dD}{dt} \Big|_{D=0} &= (1 - m_p)N\delta I \geq 0, \\ \frac{dS}{dt} \Big|_{S=0} &= m_p N \delta I \geq 0. \end{aligned}$$

From equation (1) we see that

$$\begin{aligned} \frac{dA_{tot}}{dt} &= l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_A A - kDA, \\ &\quad + (1 - m_{rt})kDA - \delta I + (1 - m_p)N\delta I - cD, \\ &= l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_A A - m_{rt}kDA \\ &\quad - \delta I + N\delta I - m_p N \delta I - cD, \\ &= l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - (1 - N + m_p N)\delta I \\ &\quad - (d_A + m_{rt}kD)A - cD. \end{aligned}$$

$$\frac{dA_{tot}}{dt} > l + pA \left[1 - \frac{A+I+D}{A_{max}} \right],$$

$$A_{tot} = A + I + D,$$

$$A_{tot} = A_{max},$$

$$\frac{dA_{tot}}{dt} > l \geq 0.$$

3.2. Equilibrium Point and Asymptotic Stability.

In this section, the equilibrium points are given by solving,

$$\frac{dA}{dt} = 0, \frac{dI}{dt} = 0, \frac{dD}{dt} = 0, \frac{dS}{dt} = 0.$$

By [7], we obtain equilibrium points E_0 and \bar{E} are given below:

$$E_0 = (A, 0, 0, 0) \text{ and } \bar{E} = (\bar{A}, \bar{I}, \bar{D}, \bar{S})$$

where,

$$\begin{aligned} \bar{A} &= \frac{c}{N(1-m_p)(1-m_{rt})}, \\ \bar{I} &= \frac{c\bar{D}}{(1-m_p)N\delta}, \\ \bar{D} &= \frac{[l + (p - d_A)A]A_{max} - pA^2}{A[p_c + (p + kA_{max})(1-m_p)N\delta]}, \\ \bar{S} &= \frac{m_p\bar{D}}{1-m_p}. \end{aligned}$$

□

3.3. Uninfected Steady State. The Jacobian matrix $J(E_0)$ provides an estimation for the dis-infected steady state E_0 , based on the system of equation (1).

$$J(E_0) = \begin{bmatrix} p - d_A - \frac{2pA_0}{A_{max}} & \frac{pA_0}{A_{max}} & -\frac{pA_0}{A_{max}} - kA_0 & 0 \\ 0 & -\delta & k(1-m_{rt})A_0 & 0 \\ 0 & (1-m_p)N\delta & -c & 0 \\ 0 & m_pN\delta & 0 & -c \end{bmatrix}.$$

Eigenvalues can be evaluated by solving the characteristic equation $\det(\lambda I - J(E_0)) = 0$.

We have,

$$\left(\lambda - p + d_A + \frac{2pA_0}{A_{max}} \right) (\lambda^3 + C_1^* \lambda^2 + C_2^* \lambda + C_3^*) = 0.$$

$$C_1^* = \delta + 2c,$$

$$C_2^* = c^2 + 2\delta c - (1-m_p)(1-m_{rt})N\delta kA_0,$$

$$C_3^* = (1-m_p)(1-m_{rt})N\delta kA_0.$$

Then, the eigenvalues are,

$$\begin{aligned}\lambda_1 &= p - d_A - \frac{2pA_0}{A_{max}}, \\ \lambda_2 &= (1 - m_{rt})(1 - m_p)N\delta kA_0 - \delta c, \\ \lambda_3 &= -kc(1 - m_{rt})A_0, \\ \lambda_4 &= -c.\end{aligned}$$

The Jacobian matrix of \bar{E} is given, and the linearization system of equation (1), (2), (3) and (4) at \bar{E} .

$$J(\bar{E}) = \begin{bmatrix} L & \frac{-pA}{A_{max}} & \frac{-pA}{A_{max}} & 0 \\ (1 - m_{rt})kD & -\delta & (1 - m_{rt})kA & 0 \\ 0 & (1 - m_p)N\delta & -c & 0 \\ 0 & m_p N\delta & 0 & -c \end{bmatrix}.$$

Let $L = d_A + kD + \frac{2pA + pI + pD}{T_{max}} - p$.

The Characteristic equation for matrices is, $\det(\lambda - J(\bar{E})) = 0$.

Therefore, $(\lambda + c)(\lambda^3 + C_1\lambda^2 + C_2\lambda + C_3) = 0$.

where,

$$\begin{aligned}C_1 &= L + \delta + c, \\ C_2 &= \delta c - (1 - m_{rt})(1 - m_p)kNA\delta + Lc + L\delta + \frac{pA}{A_{max}}kD, \\ C_3 &= L[\delta c - (1 - m_{rt})(1 - m_p)kNA\delta] + (1 - m_{rt})kD \left[\frac{pAc}{A_{max}} + \frac{pA}{A_{max}}(1 - m_p)N\delta \right].\end{aligned}$$

3.4. Proposition 1. [8] If all the eigenvalues $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ of Jacobian (\bar{E}) satisfied the condition $|\arg(\lambda)| > \frac{\alpha\pi}{2}$, then an Infected steady state $\bar{E} = (\bar{A}, \bar{I}, \bar{D}, \bar{S})$ is asymptotically stable.

$$T(P) = \begin{bmatrix} 1 & C_1 & C_2 & C_3 & 0 \\ 0 & 1 & C_1 & C_2 & C_3 \\ 3 & 2C_1 & C_2 & 0 & 0 \\ 0 & 3 & 2C_1 & C_2 & 0 \\ 0 & 0 & 3 & 2C_1 & C_2 \end{bmatrix}.$$

$$T(P) = 18C_1C_2C_3 + (C_1C_2)^2 - 4C_3C_1^3 - 4C_2^3 - 27C_3^2.$$

3.5. Proposition 2. [9, 10, 11] If $T(P)$ is non-negative, then Routh-Hurwitz conditions are satisfied, infected steady state $\bar{E} = (\bar{A}, \bar{I}, \bar{D}, \bar{S})$ is asymptotically stable.

(i) $T(P) > 0, C_1 > 0, C_3 > 0, C_1C_2 > C_3$.

(ii) $T(P) < 0, C_1 \geq 0, C_2 \geq 0$.

(iii) $T(P) < 0, C_1 > 0, C_2 > 0, C_1C_2 = C_3$.

(iv) The infected steady state \bar{E} is unstable if satisfied condition $T(P) < 0, C_1 < 0, C_2 < 0$.

3.6. Reproduction Number \mathfrak{R}_0 . In this section, we obtain the reproduction number [12, 13],

The Model is given as follows:

$$\begin{cases} \frac{dA}{dt} = l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_A A - kDA, \\ \frac{dI}{dt} = (1 - m_{rt}) kDA - \delta I, \\ \frac{dD}{dt} = (1 - m_p) N \delta I - cD, \\ \frac{dS}{dt} = m_p N \delta I - cS. \end{cases}$$

Now,

$$\mathcal{F} = \begin{bmatrix} (1 - m_{rt}) kDA \\ 0 \end{bmatrix} \text{ and } \mathcal{V} = \begin{bmatrix} \delta I \\ -(1 - m_p) N \delta I + cD \end{bmatrix}.$$

Where,

$$X = (I, D) = (x_1, x_2).$$

Hence,

$$F = \begin{bmatrix} 0 & (1 - m_{rt}) kA \\ 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} \delta & 0 \\ -(1 - m_p) N \delta & c \end{bmatrix}.$$

Therefore, $\rho(FV^{-1})$ is given below,

$$\rho(FV^{-1}) = \left(\frac{1}{c} \right) (1 - m_{rt}) (1 - m_p) N kA.$$

Hence the reproduction number is,

$$\mathfrak{R}_0 = \left(\frac{1}{c}\right) (1 - m_{rt}) (1 - m_p) NkA.$$

Definition 1. [14] Let $h(\tau) \in R^K$, for the fractional differential α is non integer, then the Caputo derivative is defined by ${}^C \mathcal{D}_\tau^\alpha h(\tau) = \frac{1}{\Gamma k - \alpha} \int_0^\tau \frac{(\tau - \zeta)^{k-\alpha} (h^k)(\zeta)}{\tau - \zeta} d\zeta$. Here $k = [\alpha] + 1$ with $[\alpha]$ is the integer part of real number α . obviously ${}^C \mathcal{D}_\tau^\alpha h(\tau) \rightarrow h'(\tau)$ as $\alpha \rightarrow 1$.

Definition 2. [15] The function f from positive real number (R^+) to real number (R) and fractional order of integral $\alpha > 0$ is defined as $\mathcal{I}^\alpha(h(\tau)) = \frac{1}{\Gamma k - \alpha} \int_0^\tau \frac{(\tau - \zeta)^\alpha h(\zeta)}{\tau - \zeta} d\zeta$. Here $\tau > 0$ and $0 < \alpha < 1$.

Properties

- (i) ${}^C \mathcal{D}_\tau^\alpha h(\tau) * \mathcal{I}^\alpha(h(\tau)) = 1$,
- (ii) ${}^C \mathcal{D}_t^{\alpha-1} \frac{dI}{dt} = {}^C \mathcal{D}_t^\alpha$,
- (iii) ${}^C \mathcal{D}_\tau^{\alpha+\beta} h(\tau) = {}^C \mathcal{D}_\tau^\alpha h(\tau) * {}^C \mathcal{D}_\tau^\beta h(\tau)$,
- (iv) $\mathcal{I}^{\alpha+\beta}(h(\tau)) = \mathcal{I}^\alpha(h(\tau)) * \mathcal{I}^\beta(h(\tau))$.

4. MAIN RESULTS

4.1. Fractional order Mathematical Model Formulation: System of model equation non infected $CD4^+T$ -cells, productively infected $CD4^+T$ -cells, infected virus and non infected virus denoted by A, I, D, S and this model obtained from mathematical biology J.D.murray. In dynamics of uninfected $CD4^+T$ cells . The system of mathematical model equation is given as follows:

$$(2) \quad \left\{ \begin{array}{l} \frac{dA}{dt} = l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_A A - kDA, \\ \frac{dI}{dt} = (1 - m_{rt}) kDA - \delta I, \\ \frac{dD}{dt} = (1 - m_p) N \delta I - cD, \\ \frac{dS}{dt} = m_p N \delta I - cS. \end{array} \right.$$

subject to initial condition $A(0) = A_0 \geq 0, I(0) = I_0 \geq 0, D(0) = D_0 \geq 0, S(0) = S_0 \geq 0$. The Caputo fractional time derivative is used to illustrate the dynamics of $CD4^+T$ - cells for the HIV

model in fractional form, The time-dependent kernel has been presented $k(t - \tau) = \frac{1}{\Gamma\alpha - 1}(t - \tau)^{\alpha-2}$ [16][17],[18].

$$\left\{ \begin{array}{l} \frac{dA}{dt} = \int_{t_0}^t k(t - \tau) \left[l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_{AA} - kDA \right] d\tau, \\ \frac{dI}{dt} = \int_{t_0}^t k(t - \tau) [(1 - m_{rt})kDA - \delta I] d\tau, \\ \frac{dD}{dt} = \int_{t_0}^t k(t - \tau) [(1 - m_p)N\delta I - cD] d\tau, \\ \frac{dS}{dt} = \int_{t_0}^t k(t - \tau) [m_p N\delta I - cS] d\tau. \end{array} \right.$$

[14][10] Apply the Caputo type derivative have order $\alpha - 1$,

$$\left\{ \begin{array}{l} {}^C \mathcal{D}_t^{(\alpha-1)} \frac{dA}{dt} = {}^C D_t^{(\alpha-1)} I^{-(\alpha-1)} \left[l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_{AA} - kDA \right], \\ {}^C \mathcal{D}_t^{(\alpha-1)} \frac{dI}{dt} = {}^C D_t^{(\alpha-1)} I^{-(\alpha-1)} [(1 - m_{rt})kDA - \delta I], \\ {}^C \mathcal{D}_t^{(\alpha-1)} \frac{dD}{dt} = {}^C D_t^{(\alpha-1)} I^{-(\alpha-1)} [(1 - m_p)N\delta I - cD], \\ {}^C \mathcal{D}_t^{(\alpha-1)} \frac{dS}{dt} = {}^C D_t^{(\alpha-1)} I^{-(\alpha-1)} [m_p N\delta I - cS]. \end{array} \right.$$

The operator ${}^C \mathcal{D}_t^{(\alpha-1)}$ and $\mathcal{I}_t^{-(\alpha-1)}$ are reciprocal together,

$$(3) \quad \left\{ \begin{array}{l} {}^C \mathcal{D}_t^\alpha = \left[l + pA \left[1 - \frac{A+I+D}{A_{max}} \right] - d_{AA} - kDA \right], \\ {}^C \mathcal{D}_t^\alpha = [(1 - m_{rt})kDA - \delta I], \\ {}^C \mathcal{D}_t^\alpha = [(1 - m_p)N\delta I - cD], \\ {}^C \mathcal{D}_t^\alpha = [m_p N\delta I - cS]. \end{array} \right.$$

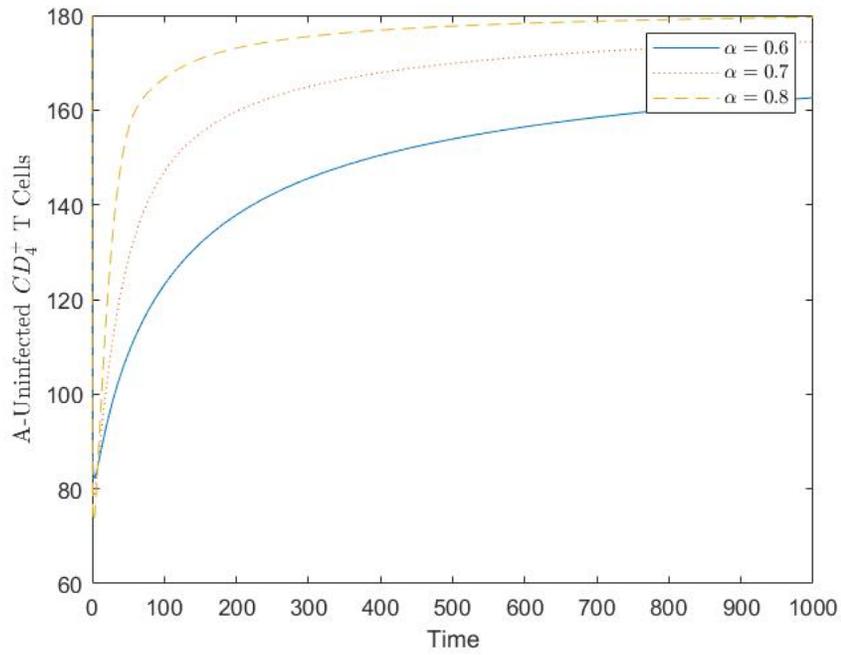
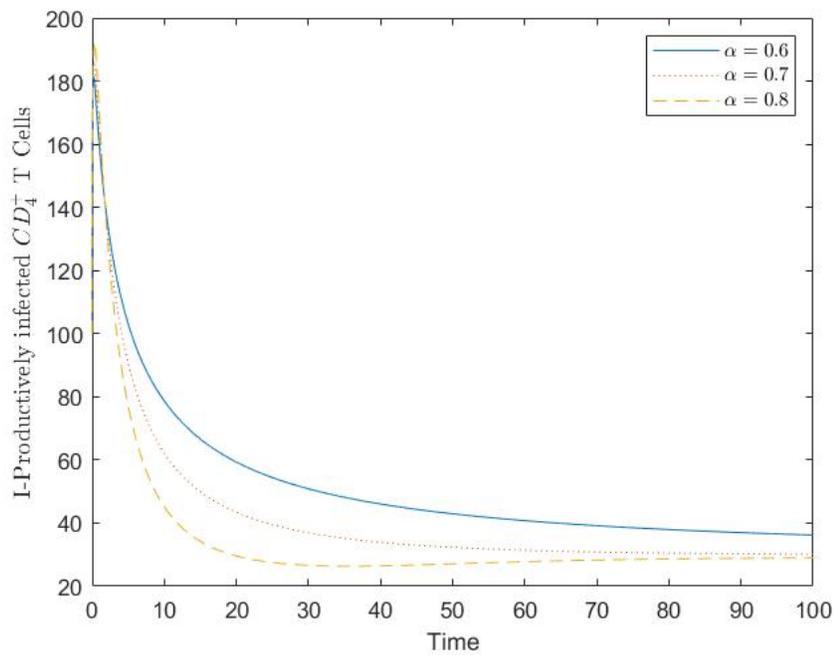
5. NUMERICAL SIMULATION

In this section, we explore the dynamic behaviour of our model (1) by changing the derivative order to a non-integer value. The numerical simulation is performed by Adams Bashforth method using MATLAB [19] and time interval taken time $t = [0, 100]$ days. The α value has been taken 0.6, 0.7 and 0.8 respectively. From the Figure (1)-(4), the trajectory of non-infected

$CD4^+T$ -cells (A), productively infected $CD4^+T$ -cells (I), infected virus (D) and non infected virus (S) are provided. In the figure (1), uninfected $CD4^+T$ -cells time limit has been taken $t = [0, 1000]$. The graph has been obtained from the numerical values from Table 1 and use MATLAB simulation. The system of equation (1) has modified incase A_{max} and $A + I + D$ values are equal and considered the combination of drug therapy, protease inhibitor drugs $m_p = 1$ and reverse transcriptase inhibitor drugs $m_{rt} = 1$. If the system of model equations are $A + I + D = A_{max}$, $m_{rt} = 1$ and $m_p = 1$, then Figure 5-8, illustrates the trajectory respectively.

TABLE 1. Description of Parameters

Description	symbol	Values
Non infected $CD4^+T$ -cells	A	180 mm^{-3}
Infected $CD4^+T$ -cells	I	0.02 day^{-1}
Infectious Viruses	D	$1.34 \times 10^3 \text{ virons}$
Noninfectious Viruses	S	0.0001 virons
$CD4^+$ cell source	l	$10 \text{ mm}^{-3} \text{ day}^{-1}$
Mortality rate of infected cells	δ	0.5 day^{-1}
Virul activity rate	k	$3.45 \times 10^{-5} \text{ ml}^{-1}$
Bursting cells	N	$480 \text{ virons cell}^{-1}$
Mortality rate of Target cell	d_A	0.03 day^{-1}
Maximum $CD4^+T$ -cell	A_{max}	1600 mm^{-3}
Rate of growth $CD4^+T$ -cell	p	0.04 day^{-1}
Rate of clearance virus	c	3 day
Protease inhibitor drugs	m_p	$0 \leq m_p \leq 1$
Reverse transcriptase drugs	m_{rt}	$0 \leq m_{rt} \leq 1$

FIGURE 1. $A(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 1000]$.FIGURE 2. $I(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.

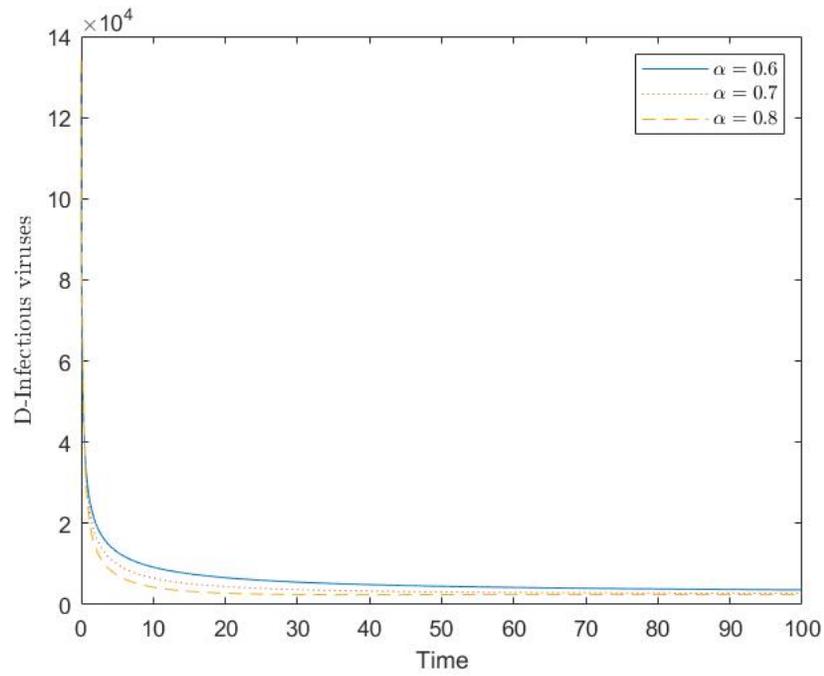


FIGURE 3. $D(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.

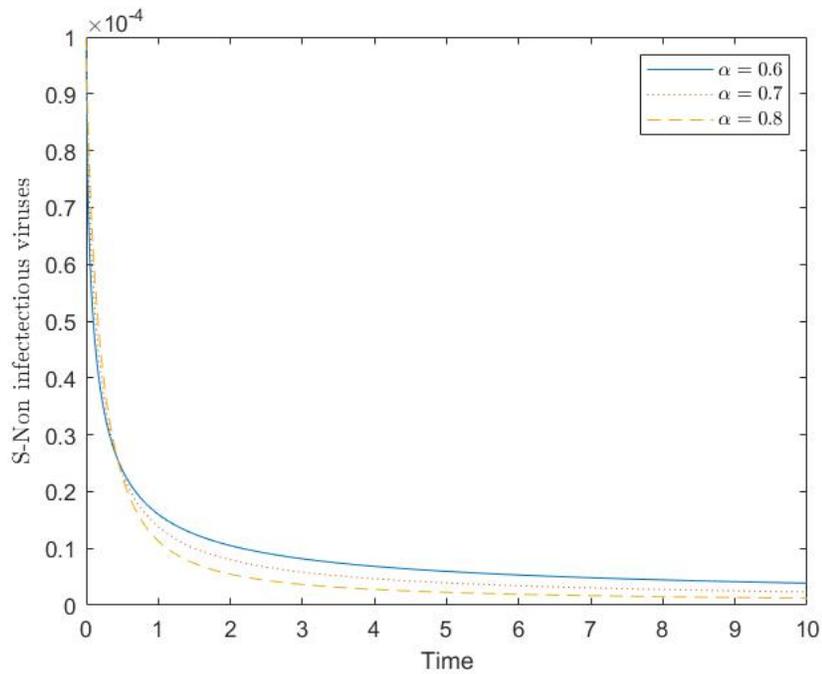


FIGURE 4. $S(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.

The system has changed as,

$$(4) \quad \left\{ \begin{array}{l} {}^C \mathcal{D}_t^\alpha A = l - d_A A - kDA, \\ {}^C \mathcal{D}_t^\alpha I = -\delta I, \\ {}^C \mathcal{D}_t^\alpha D = -cD, \\ {}^C \mathcal{D}_t^\alpha S = N\delta I - cS. \end{array} \right.$$

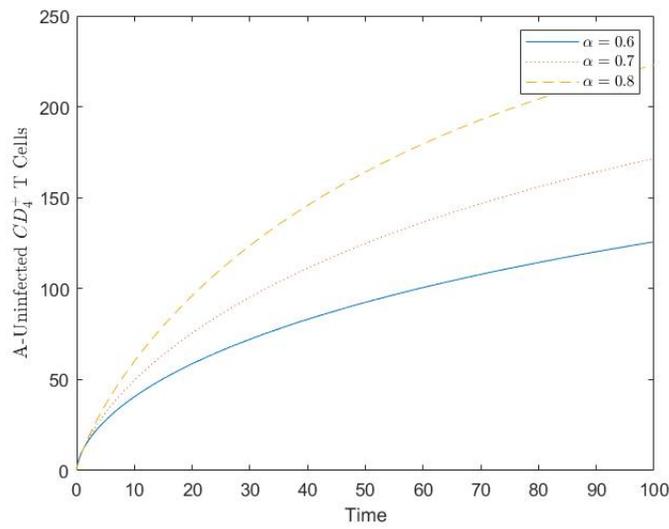


FIGURE 5. $A(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.

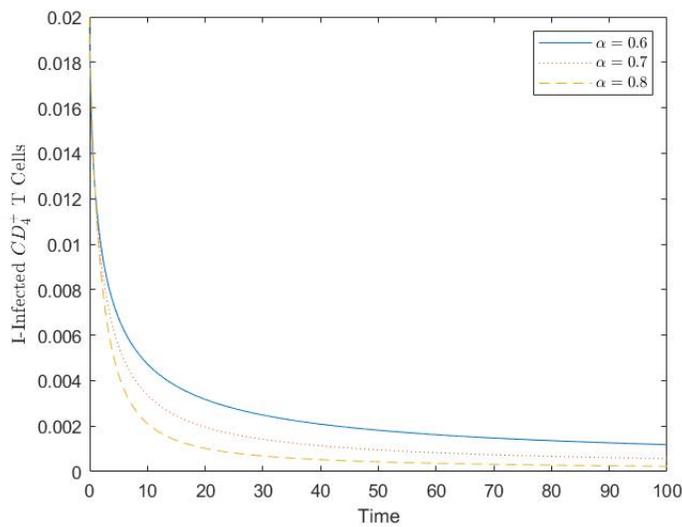
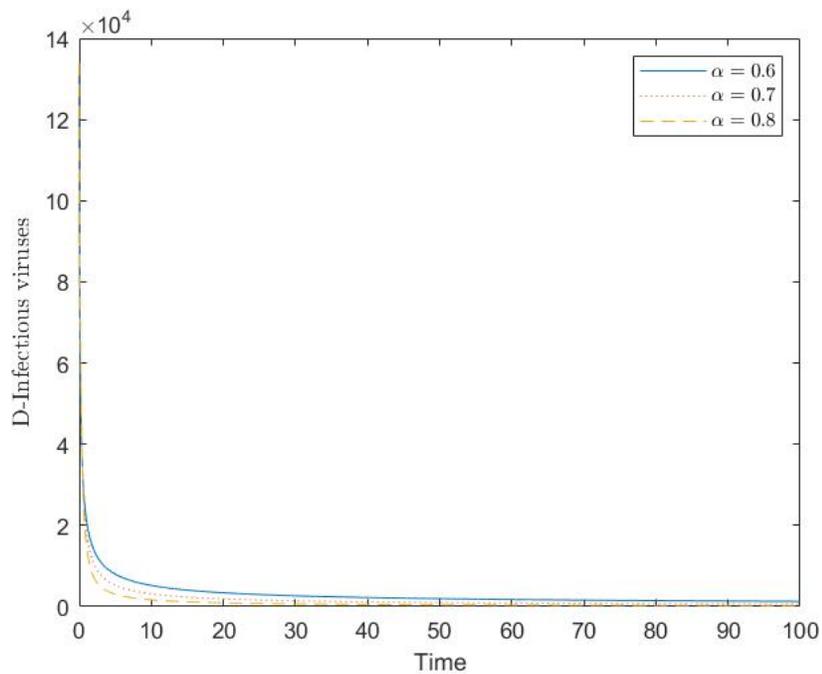
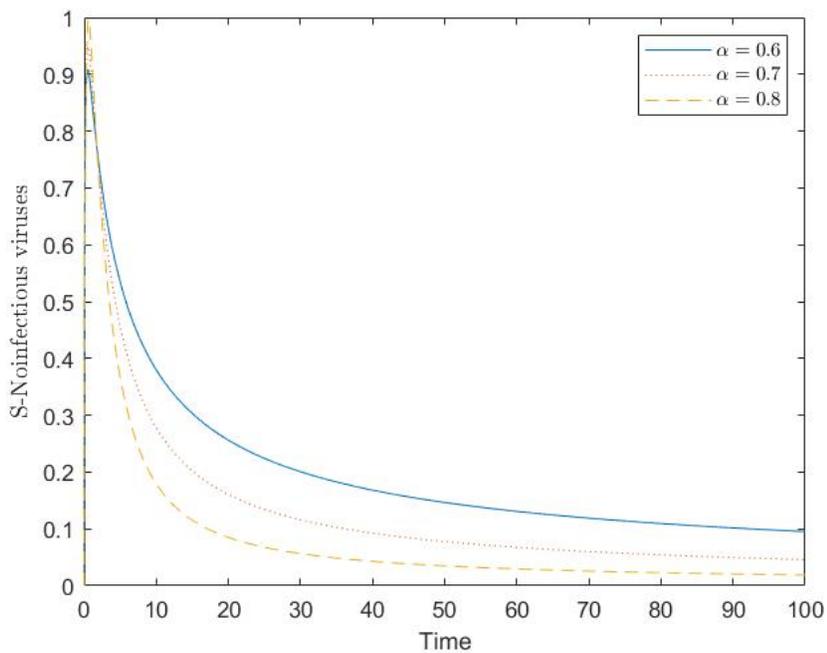


FIGURE 6. $I(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.

FIGURE 7. $D(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.FIGURE 8. $S(t)$ for $\alpha \in 0.6, 0.7, 0.8$ and $t \in [0, 100]$.

Reproduction number $\mathfrak{R}_0 = \left(\frac{1}{c}\right) (1 - m_{rt}) (1 - m_p) NkA$. Consider Table 1 and $\mathfrak{R}_0 = 0.9936$. By the Proposition (1), Routh-Hurwitz criteria are satisfied. Hence, $C_1 = 3.1287 > 0, C_2 = 0.2853 > 0, C_3 = 0.0569 > 0, C_1 C_2 > C_3$ satisfied and $T(P) = -3.1464 < 0$. Therefore, infected steady state \bar{E} asymptotically stable.

6. CONCLUSION

We have established that the transmission of the HIV virus involving $CD4^+$ T-cells applies to both the disease-free equilibrium and the endemic equilibrium. Furthermore, by introducing a Caputo derivative fractional order model, we expand the scope of our analysis and provide numerical simulations to illustrate our analytical findings. This study contributes to a deeper understanding of HIV dynamics and provides the potential insights for the development of effective treatment strategies.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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