Stability Analysis and Optimal Control of a Fractional Order Model for HIV Infection

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Abstract: In this article, a mathematical model of HIV infection is developed using fractional-order differential equation consisting uninfected $CD4^+T$ cells, infected $CD4^+T$ cells and CTL effectors (i.e. immune response cells). The fractional order model possesses non-negative solutions. The system has three equilibria: infection-free equilibrium, infected equilibrium and CTL equilibrium. Stability conditions of the model system around the equilibria are derived. Numerically it is observed that the system is Global MittagLeffler stabile. Moreover, the necessary conditions for the optimality of the system are derived whose fractional derivative is described in the Riemann and Caputo sense. Using an objective functional, the fractional optimal control problem is solved with minimal dosage of anti-HIV drugs with an aim to minimize the infectious viral load and count of infected $CD4^+T$ cells. Efficient numerical technique is provided for solving the FOCP. Numerical simulation has been done to elucidate the analytical results.

Key–Words: HIV, $CD4^+T$ cell, Immune system, Fractional-Order Differential Equations (FODEs), Memory, Optimal Drug therapy, Fractional Optimal Control Problem (FOCP).

1 Introduction

HIV is an infection that is accompanied by a reflective depletion in the number of $CD4^+T$ lymphocytes. They spread in human body through human by sexual contact, through blood (through transfusion, blood products or contaminated needs) or from mother to child and appear to cause AIDS This serious disease destroys the immune system of human being which produce life-threatening opportunistic infections in the body [1]. In human immune system HIV infects primary cell such as helper T-cell, dendritic cells and macrophages. When $CD4^+T$ - cell numbers decline below a threshold level, cell-mediated immunity is lost and the body becomes increasingly susceptible to infections [2].

Large amount of work on modeling the HIV infection has been done restricting to integer-order ordinary (or delay) differential equations [3, 4]. On the other hand, different control problems have been addressed in the literature and various existing control theories have been applied to HIV-immune systems [5, 6, 7]. Many control problems are addressed in the literature to HIV-immune systems, such as feedback control, optimal control using mathematical models which are restricted to integer order ordinary [8] or delay differential equations [9]. Recently, the problem of modeling real processes using fractional differential equations (FDEs) has started to draw attention leading to inspiring results [10]. Ding and Ye introduced the fractional order into a model of HIV infection of T-cells and carried out a detailed analysis on the stability of equilibrium [11, 12]. However, epidemiology optimal control problems with fractional derivative in both state and control variables are very rare.

Fractional calculus is a classical mathematical notion and a generalization of the integer-order differentiation and integration to arbitrary non-integer order. The conception of fractional calculus is firstly projected by Leibniz in 1695 [13]. Fractional-order differential equation is considered as an alternative model to especially non-linear ordinary differential equations [14]. Due to its complexity and lack of application background, it did not attract much attention for a long time. In recent decades, fractional-order differential equations have been proved to be valuable tools in the modeling of many phenomena in various elds of science and engineering Fractional order differentiations have gained a lot of attention due to its ability to provide an exact description of different

nonlinear phenomena [15, 16, 17].

In recent years, the application of fractional differential equations has been found in different fields of sciences as well as in many scientific and practical models [18, 19, 20]. Fractional differential equations are applied in many natural phenomena in which case these equations have more validity and adaptation to the natural phenomena. The advantage of fractional-order system is that it allows greater degrees of freedom in the system. More and more researcher begin to study the qualitative properties and numerical solutions of fractional-order virus infection models [21, 22, 23].
. Furthermore it also provides a commanding implementation of memory, which is one of the hereditary characteristic in most of the main features of immune response. The major concepts in cell-biological structures like fractals is usually related with the fractional-order differential equations [24, 12]. Recently, fractional calculus (FC) has been extensively applied in many fields [25, 26]. Many mathematicians and applied researchers have tried to model real processes using the fractional calculus [10, 20]. A fractional-order example of two immune effectors attacking an antigen was proposed by Hashish and Ahmed [27]. Fractional derivatives embody essential features of cell rheological behavior and have enjoyed greatest success in the field of rheology [28].

In this article, considering the mathematical model presented in [8], the fractional order HIV-immune system with memory is proposed. Here, a fractional ordered optimal control problem for HIV-model in both state and control variables is proposed and solved, where the objective is to find the optimal dosing for drug that maximizes the number of infected CD4$^+$T cells, as well as CTL immune response cells. Detailed analysis of the stability of equilibrium is carried out. Numerical simulations are done using iterative schemes through Matlab.

2 The Fractional Derivatives

Here, the definitions of fractional-order differentiation are provided for the concept of fractional derivative. Caputo and Riemann-Liouville definitions [29] are used to developed the model.

Definition 1. *Caputo fractional derivative can be defined as:*

$$ {}_a^C D_t^\alpha g(t) = \frac{1}{\Gamma(n-\alpha)} \int_a^t \frac{g^{(n)}(s)}{(t-s)^{\alpha-n+1}} ds \qquad (1) $$

where α is the order of the derivative and $n-1 < \alpha < n$, Γ is symbolized as the gamma function and n is considered as an integer.

Definition 2. *Riemann-Liouville fractional derivative is defined as:*

$$ {}_a D_t^\alpha g(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_a^t \frac{g(s)}{(t-s)^{\alpha-n+1}} ds \qquad (2) $$

where α is the order of the derivative and $n-1 < \alpha < n$, Γ is symbolized as the gamma function and n is considered as an integer and $a > 0$, $b > 0$ are constants.

3 Mathematical model derivation

In this work, a fractional order mathematical model of HIV infection is proposed in the context of antiviral treatment technique. The base model was formulated by Culshaw, Ruan and Spiteri [8]. The model consists of three populations: uninfected CD4$^+$ T cells, x(t); infected CD4$^+$ T cells, y(t) and CTL effectors (immune response cells), z(t). Uninfected CD4$^+$ T cells produced at a rate a and die at a rate δ, and become infected at a rate β. The viral load is considered proportional to the level of infected cells. b is the decay rate of Infected cells and ρ is killing rate by CTL effectors. Proliferation of the CTL population is given by $cxyz$ and is assumed to be proportional with both virus load, y(t) and the number of uninfected CD4$^+$ T cells, x(t). CTL effectors have a death rate m. Based on the above assumptions, the following integer order mathematical model [8] is obtained:

$$ \begin{aligned} \frac{dx}{dt} &= a - \delta x - \beta xy, \\ \frac{dy}{dt} &= \beta xy - by - \rho yz, \\ \frac{dz}{dt} &= cxyz - mz, \end{aligned} \qquad (3) $$

where $x(0) = x_0$, $y(0) = y_0$, $z(0) = z_0$ are initial conditions.

Considering the above model, the following fractional order model is proposed:

$$ \begin{aligned} D_t^\alpha x &= a - \delta x - \beta xy, \\ D_t^\alpha y &= \beta xy - by - \rho yz, \\ D_t^\alpha z &= cxyz - mz, \end{aligned} \qquad (4) $$

where $x(0) = x_0$, $y(0) = y_0$, $z(0) = z_0$ are initial conditions and D_t^α is the Caputo derivative.

4 Some basic properties

In this section, the existence and uniqueness of solution of the system (4) are analysed. The system (4) can be written in the following form:

$$D_t^\alpha v(t) = f(t, v(t)),\ 0 < \alpha \leq 1, \tag{5}$$

where $f(t, v) = (f_1, f_2, f_3)^T$ and $v(0) = (x(0), y(0), z(0))$ as initial conditions, where the derivative is in Left-Caputo sense. Here, f_1, f_2, f_3 are right hand side of system (7), i.e., $f_1 = a - \delta x - \beta xy$ etc. The function $f(v, t) : \mathbb{R} \times \mathbb{R}^d \longrightarrow \mathbb{R}^d$ defines a vector field with dimension $d \geq 1$.

4.1 Non-negative solutions

Initially, the non-negativity of the solutions is shown. Next, it is shown that the solution x(t), with $x(0) > 0$, is always positive whenever the solution exists and the solutions will remain in $\mathbb{R}^3_+$, where $\mathbb{R}^3_+ = \{x \in \mathbb{R}^3 : x \geq 0\}$ and $x(t) = (x(t), y(t), z(t))^T$.

Theorem 3. *There is a unique solution $u(t) = (x(t), y(t), z(t))^T$ for the initial value problem given by (12) and the solution remains in $\mathbb{R}^3_+$.*

Proof. For the proof of the theorem about nonnegative solutions, the following Lemma is needed:

Lemma 1 (Generalized Mean Value Theorem): Let $f(x) \in C[a, b]$ and $D_t^\alpha \in C(a, b]$ for $0 < \alpha \leq 1$, then

$$f(x) = f(a) + \frac{1}{\Gamma(\alpha)} D_t^\alpha f(\xi)(x - a)^\alpha, \tag{6}$$

with $0 \leq \xi \leq x$, for all $x \in (a, b]$.

Remark 1: $f(x) \in C[0, b]$ and $D_t^\alpha \in C(a, b]$ for $0 < \alpha \leq 1$ then it is clear from Lemma 1 that if $D_t^\alpha \geq 0$, for all $x \in (0, b)$ then the function f is non decreasing and if $D_t^\alpha \leq 0$ for all $x \in (0, b)$ then the function f is non increasing for all $x \in [0, b]$.

The existence and uniqueness of the solution of (4) in (0, ∞) can be established by Theorem 3.1 and Remark 3.2 of [30]. The remaining tusk is to show that the domain $\Re^3_+$ is positively invariant.
Now, since

$$\begin{aligned} D_t^\alpha x|_{x=0} &= a > 0, \\ D_t^\alpha y|_{y=0} &= 0, \\ D_t^\alpha z|_{z=0} &= 0, \end{aligned} \tag{7}$$

by Remark 1 and Lemma 1 above, the solution of the system will remain in $\mathbb{R}^3_+$. Thus it can be said that on each hyperplane bounding the nonnegative orthant, the vector field points into $\mathbb{R}^3_+$ and thus the the domain $\mathbb{R}^3_+$ is a positively invariant region. □

4.2 Equilibria and Stability

Stability analysis is one of the most important factors to study the fractional-order differential systems, which has been investigated by many researchers [31, 32, 33] to obtain important results about stability of the systems.

To evaluate the equilibrium points, we set

$$\begin{aligned} D_t^\alpha x &= 0, \\ D_t^\alpha y &= 0, \\ D_t^\alpha z &= 0. \end{aligned}$$

Then the system posses three equilibria, viz

i. infection-free equilibrium: $E_0 = (\frac{a}{\delta}, 0, 0)$,

ii. infected equilibrium: $E_1 = (\frac{b}{\beta}, \frac{a\beta}{b\beta} - \frac{\delta}{\beta}, 0)$ and

iii. CTL equilibrium: $E^* = (\frac{ac-\beta m}{c\delta}, \frac{m\delta}{ac-\beta m}, \frac{\beta(ac-\beta m)}{\rho c\delta} - \frac{a}{\rho})$.

It is cleared that infected equilibrium E_1 exists if $a\beta - b\delta > 0$ and E^* is stable if $ac - \beta m > 0$.

4.3 Stability analysis

Now, the Jacobian matrix at the equilibrium point $E(x, y, z)$ is given by,

$$M = [m_{ij}] = \begin{bmatrix} -\delta - \beta y & -\beta x & 0 \\ \beta y & \beta x - b - \rho z & -\rho y \\ cyx & cxz & cxy - m \end{bmatrix}.$$

Then the characteristic equation of the system at the equilibrium point (x, y, z) is given by,

$$\lambda^3 + \kappa_1 \lambda^2 + \kappa_2 \lambda + \kappa_3 = 0, \tag{8}$$

where

$$\begin{aligned} \kappa_1 &= -[m_{11}x^2 + m_{22}x^2 + m_{33}], \\ \kappa_2 &= [m_{12}m_{21} - m_{11}m_{22} + m_{23}m_{32} \\ &\quad -m_{11}m_{33} - m_{22}m_{33}], \\ \kappa_3 &= [m_{12}m_{23}m_{31} - m_{11}m_{23}m_{32} \\ &\quad -m_{12}m_{21}m_{33} + m_{11}m_{22}m_{33}]. \end{aligned}$$

The eigenvalues of Jacobian matrix evaluated at the uninfected steady state E_0 are given by: $-\delta, \frac{\beta a}{\delta} - b, -m$. Thus E_0 is stable if $\beta a - \delta b < 0$ and in that case E_1 will not exist.

The characteristic equation of the system at the equilibrium point E_1 is given by:

$$M = [m_{ij}] = \begin{bmatrix} -d-(\frac{a\beta}{b}-\delta) & -\frac{\beta b}{\beta} & 0 \\ (\frac{a\beta}{b}-\delta) & \frac{b\beta}{\beta}-b & -\rho(\frac{a\beta}{b\beta}-\frac{\delta}{\beta}) \\ \frac{bc}{\beta}(\frac{a\beta}{b\beta}-\frac{\delta}{\beta}) & 0 & \frac{cb}{\beta}(\frac{a\beta}{b\beta}-\frac{\delta}{\beta})-m \end{bmatrix}.$$

$$(\lambda - \frac{\beta ac - \beta^2 m - bc\delta}{\beta^2})(b\lambda^2 + a\beta\lambda + ab\beta - b^2\delta) = 0. \quad (9)$$

Proposition 4. *The steady state E_1 is asymptotically stable if all of the eigenvalues λ_i of $J(E_1)$ satisfy: $|arg(\lambda_i)| > \frac{\alpha\pi}{2}$, i = 1, 2, 3.*

The characteristic equation of the system at the equilibrium point E^* is given by:

$$\lambda^3 + \sigma_1\lambda^2 + \sigma_2\lambda + \sigma_3 = 0, \quad (10)$$

where

$$\begin{aligned} \sigma_1 &= \frac{\delta ac}{ac - \beta m}, \\ \sigma_2 &= \frac{(\beta ac - bc\delta + \delta\beta^2 - \beta^2 m)m}{c\delta}, \\ \sigma_3 &= \frac{m(\beta ac - \beta^2 m - ac\delta)}{c}. \end{aligned} \quad (11)$$

Proposition 5. *The CTL equilibrium state E^* is asymptotically stable if all of the eigenvalues λ_i of $J(E^*)$ satisfy: $|arg(\lambda_i)| > \frac{\alpha\pi}{2}$, i = 1, 2, 3.*

The discriminant of the polynomial $g(\lambda)$ is denoted by $D(\varepsilon)$. Now, if $g(\lambda) = \lambda^3 + \sigma_1\lambda^2 + \sigma_2\lambda + \sigma_3 = 0$, then

$$D(\varepsilon) = -\begin{vmatrix} 1 & \sigma_1 & \sigma_2 & \sigma_3 & 0 \\ 0 & 1 & \sigma_1 & \sigma_2 & \sigma_3 \\ 3 & 2\sigma_1 & \sigma_2 & 0 & 0 \\ 0 & 3 & \sigma_1 & \sigma_2 & 0 \\ 0 & 0 & 3 & 2\sigma_1 & \sigma_2 \end{vmatrix}$$

$$= 18\sigma_1\sigma_2\sigma_3 + (\sigma_1\sigma_2)^2 - 4\sigma_1^3\sigma_3 - 4\sigma_2^3 - 27\sigma_3^2.$$

Proposition 6. *If E^* exists in R^3_+, then:*

i. *If the discriminant $D(\varepsilon)$ is positive and Routh-Hurwitz criterion are satisfied, i.e., $D(\varepsilon) > 0$, $\sigma_1 > 0$, $\sigma_3 > 0$ and $\sigma_1\sigma_2 > \sigma_3$, then the interior equilibrium point E^* is locally asymptotically stable.*

ii. *If $D(\varepsilon) < 0$, $\sigma_1 > 0$, $\sigma_2 > 0$, $\sigma_1\sigma_2 = \sigma_3$ and $\alpha \in [0.5, 1)$, then the interior equilibrium point E^* is locally asymptotically stable.*

iii. *If $D(\varepsilon) < 0$, $\sigma_1 < 0$, $\sigma_2 < 0$ and $\alpha > 2/3$, then the interior equilibrium point E^* is unstable.*

5 The fractional optimal control problem (FOCP)

Here, the aim is to maximise levels of healthy CD 4^+ T cells, as well as levels of CTLs (immune response cells) and to keep cost $J(u)$ as measured in terms of chemotherapy strength, a combination of duration and intensity as low as possible. The control function is denoted by $u(t)$ with values normalised between 0 and 1, where u(t) = 1 represents totally effective chemotherapy and u(t) = 0 represents no treatment. Introducing $u(t)$, the following state system is obtained:

$$\begin{aligned} D_t^\alpha x &= a - \delta x - (1-u)\beta xy, \\ D_t^\alpha y &= (1-u)\beta xy - by - \rho yz, \\ D_t^\alpha z &= cxyz - mz, \end{aligned} \quad (12)$$

where $x(0) = x_0$, $y(0) = y_0$, $z(0) = z_0$ are initial conditions and D_t^α is indicated as the Caputo fractional derivative. The above system can be written in matrix form as below

$$D_t^\alpha v = f(v(t), u(t)),$$

where, $v = [x, y, z]$. Mathematically, the optimal control problem is formulated as:

$$\text{Max } J(u) = \int_0^{t_f} (x + z - \frac{Pu^2}{2})dt, \quad (13)$$
subject to the system (12).

Here, the aim is to find the optimal control function $u^*(t)$ for the system (12) that minimizes the functional $J(u)$. Basically $u(t)$ stands for the effect of drug and it lies between 0 and 1 [35].

5.1 The Euler-Lagrange optimality conditions for the FOCP

The general formulation and the derivation of the Euler-Lagrange optimality conditions for a Fractional Optimal Control Problem can be presented using the following control induced system:

$$D_t^\alpha v = f(v, u, t),\ x(0) = x_0, \quad (14)$$

where, $x(t)$ is the state vector, $u(t)$ stands for the control parameter and t is the time. The objective functional can be taken as

$$J(u) = \int_0^{t_f} g(v, u, t)dt,$$

Now, the control problem can be described as:

$$\text{Maximize } J(u) = \int_0^{t_f} g(v, u, t)dt,$$
subject to the system (14).

The adjoint system with ξ as the adjoint vector is given by:

$$D_{t_f}^\alpha \xi = \frac{\partial g}{\partial x} + \xi^T \frac{\partial f}{\partial x},\ \xi(t_f) = 0. \quad (15)$$

The optimal control $u^*(t)$ satisfies the following equation:

$$\frac{\partial g}{\partial u^*} + \xi^T \frac{\partial f}{\partial u^*} = 0. \quad (16)$$

The Euler-Lagrange optimality conditions for the FOCP with Caputo fractional derivatives is given by (14), (15), and (16). Note that when (α) becomes 1, the above FOCP becomes a classical optimal control problem.

Now, the optimal control problem given in (13) can be solved using the above results. The Hamiltonian function for our control problem is formulated as:

$$H = g + \xi^T f, \quad (17)$$

with $g = x + z - \frac{Pu^2}{2}$, $\xi = (\xi_1, \xi_2, \xi_3)$, $f = (f_1, f_2, f_3)^T$, $f_i, i = 1, 2, 3$ are the right sides of system (12). Using the optimality conditions given by equations (14), (15) and (16), the Euler-Lagrange optimality conditions that minimize the objective functional (13) can be obtained.

The state system has already been given by (12). Using relations above, the adjoint system is derived as:

$$\begin{aligned} D_{t_f}^\alpha \xi_1 &= 1 - \delta\xi_1 y(1-u)(\beta\xi_1 - \beta\xi_2) + cyz\xi_3, \\ D_{t_f}^\alpha \xi_2 &= -x(1-u)(\beta\xi - \beta\xi_2) - b\xi_2 + \rho z\xi_2 \\ &\quad + cxz\xi_3, \\ D_{t_f}^\alpha \xi_3 &= 1 - \rho y\xi_2 + cxy\xi_3 - m\xi_3, \end{aligned} \quad (18)$$

with the boundary conditions: $\xi_i(t_f) = 0$, where i = 1,2,3.
From equation (16) and equation (17), the expression for optimal control function is obtained as:

$$u^*(t) = \frac{xy(\beta\xi_1 - \beta\xi_2)}{P}. \quad (19)$$

For the boundedness of the optimal control, $u^*(t)$ takes the form

$$u^*(t) = max\left\{min\left\{\frac{xy(\beta\xi_1 - \beta\xi_2)}{P}, 1\right\}, 0\right\}. \quad (20)$$

replacing $u(t)$ by $u^*(t)$ in system (12) and (18) the desired FOCP can be obtained.

6 Numerical Results and Discussion

In this section, numerical simulations of the fractional model system and FOCP are presented. Iterative scheme are developed to solve the fractional order systems through Matlab using these schemes.

6.1 Numerical solution of system (4)

The following numerical scheme is developed for solving the fractional model system (equation (4)):

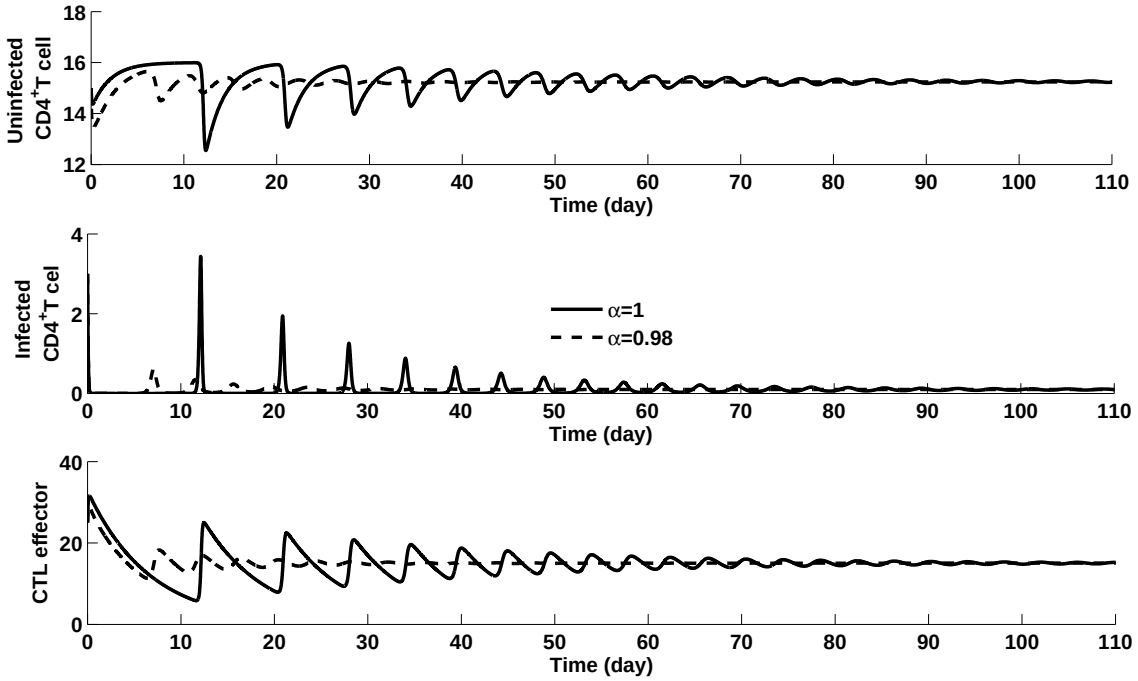

Figure 1: Solution of the system without control for different value of α.

$$
\begin{aligned}
x(i) &= [a-\delta x(i-1)-\beta x(i-1)y(i-1)]h^{\alpha} \\
&\quad -\sum_{j=1}^{i} c(j)x(i-j), \\
y(i) &= [\beta x(i)y(i-1)-by(i-1)-\rho y(i-1)z(i \\
&\quad -1)]h^{\alpha}-\sum_{j=1}^{i} c(j)x(i-j), \\
z(i) &= [cx(i)y(i)z(i-1)-mz(i-1)]h^{\alpha} \\
&\quad -\sum_{j=1}^{i} c(j)z(i-j),
\end{aligned}
$$

The last term of the above equations stands for memory i.e. history function. The parameter $c(j)$ is defined as $c(0)=1$ and $c(j)=(1-\frac{1+\alpha}{j})c_{j-1}, j\geq 1$ and $L(0)=L_0$, $M(0)=M_0$, $C(0)=C_0$, $K(0)=K_0$ are the initial conditions.

Some numerical simulations are done through Matlab using the above iterative scheme for phase-plane analysis of systems of fractional differential equations. The Matlab code is developed from the code given in [20, 36]. In Figure 1, the behaviour of the system (4) is shown for different values of α. A phase portrait of the system is shown in (x- y- z) plane (Figure 2). It can be concluded from these figures that fractional ordered system attains steady-state more quickly than integer order system. Some numerical simulations are done through Matlab using the above iterative scheme for phase-plane analysis of systems of fractional differential equations. In Figure 1, the behaviour of the system (4) is shown for different values of α. A phase portrait of the system is shown in (x- y- z) plane (Figure 2). It can be concluded from these figures that fractional ordered system attains steady-state more quickly than integer order system. In Figure 3, solution trajectories are drawn for different initial conditions. The system converges to the same solution. According to [34], the system is Globally MittagLeffler stabile (see Figure 3).

6.2 Numerical solution of the FOCP

The optimality system constitute a two-point boundary value problem including a set of fractional-order differential equations. The state system (13) is an initial value and adjoint system (19) is a boundary value problem. The state system is solved by forward iteration method and the costate system is by backward integration method by the following code through Matlab.

i. The state system is solved using the iterative

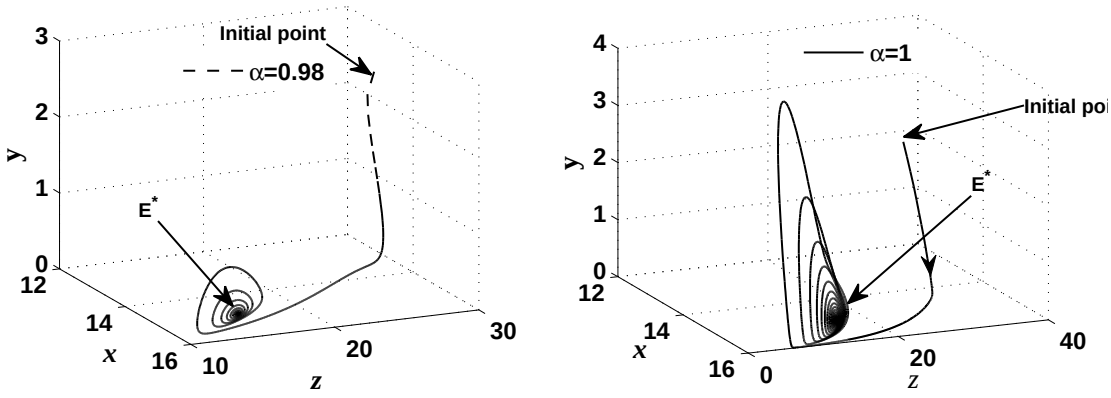

Figure 2: Phase portrait of the system without control for different value of α.

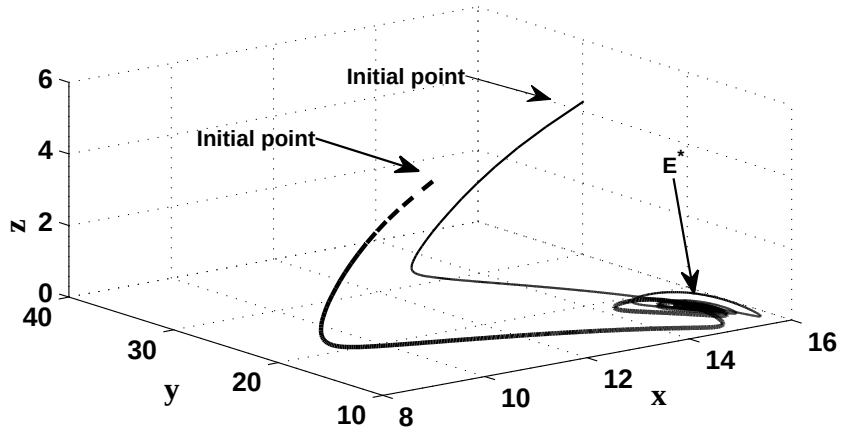

Figure 3: Global MittagLeffler stability: Phase portrait of the system without control for different initial conditions.

scheme below:

$$\begin{aligned} x(i) &= [a-\delta x(i-1)-(1-u)\beta x(i-1)y(i-1)]h^{\alpha} - \sum_{j=1}^{i} c(j)x(i-j), \\ y(i) &= [(1-u)\beta x(i)y(i-1)-by(i-1)-\rho y(i-1)z(i-1)]h^{\alpha} - \sum_{j=1}^{i} c(j)y(i-j), \\ z(i) &= [cx(i)y(i)z(i-1)-mz(i-1)]h^{\alpha} - \sum_{j=1}^{i} c(j)z(i-j). \end{aligned}$$

Here, $s(i)$ is the value of $s(t)$ at i^{th} iteration. The last term of the above equations stands for memory. Here, $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$ and $p(0) = 0$ are the initial conditions and h is the time step length. Also, the parameter $m(j)$ is defined as $m(0) = 1$ and $m(j) = (1-\frac{1+\alpha}{j})m(j-1), j \geq 1$.

ii. The optimal control is updated by the scheme below:

$$u^*(i) = \max\{\min\{u, 1\}, 0\}, \qquad (21)$$

where, $u = \frac{x(i)y(i)(\beta\xi_1(i-1)-\beta\xi_2(i-1))}{P}$.

iii. The adjoint system (19) is solved backward-in-time with terminal conditions $\xi_i(t_f) = 0$ using the following iterative scheme:

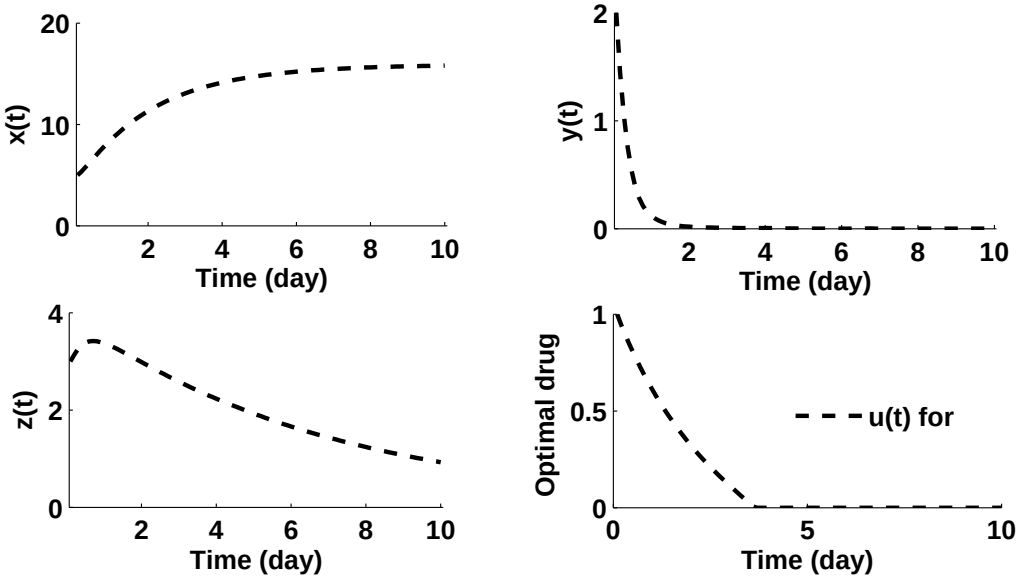

Figure 4: Dynamics of the system with control for the value of $\alpha = 0.98$.

Table 1: List of parameters used for numerical simulations [8, 9].

Parameter	Definition	Value (unit)
a	source rate of CD4$^+$T cells	8 cells/day
δ	decay rate of CD4$^+$T cells	0.1 cells/day
β	rate CD4+T cells become infected	0.0025
ρ	rate at which infected cells are killed by CTLs	1/day
c	immune response activation rate	0.1/day
b	death rate infected CD4$^+$T cells, not by CTL killing	0.2 cells/day

$$
\begin{aligned}
\xi_1(i) &= 1-\delta\xi_1(i-1)y(i)(1-u)[\beta\xi_1(i-1)-\beta\xi_2(i-1)]+cy(i)z(i)\xi_3(i-1)-\sum_{j=1}^{i}c(j)x(i-j),\\
\xi_2(i) &= -x(i)(1-u)[\beta\xi_1(i)-\beta\xi_2(i-1)]-b\xi_2(i-1)+\rho z(i)\xi_2(i-1)+cx(i)z(i)\xi_3(i-1)-\sum_{j=1}^{i}c(j)y(i-j),\\
\xi_3(i) &= 1-\rho y(i)\xi_2(i)+cx(i)y(i)\xi_3(i-1)-m\xi_3(i-1)-\sum_{j=1}^{i}c(j)z(i-j). \qquad (22)
\end{aligned}
$$

The Matlab code for solving the FOCP is derived using the code as given in [20, 36].

Numerical simulation results have been exploited graphically to illustrate the main results. In Figure 3, solution of the optimality system and optimal profile of drug (i.e. $u^*(t)$) is displayed. It is seen that the dosing starts from its boundary value of $u = 1$ that corresponding to treatment at full strength and drops sharply to zero before 4 days. It is also seen from Figure 3 that the optimal drug dosing has a significant effect on healthy CD4$^+$T cells as well as immune response cells (CTL). Infection level is decreased but never eradicated. Here, it is observed from Figure 4 that for $\alpha = 0.95$, comparatively high drug is required rather than $\alpha = 0.98$ and $\alpha = 1$. That means, if FOCP is used rather than OCP, high drug should be required to control the system. Our results demonstrate that once the virus is controlled to very low levels the drug

dosage can be reduced. Under such circumstances side effects of the therapy can also be reduced.

It is observed that immune response (i.e. z(t)) is always maintained at a positive level. It is never eradicated. When the infection is low, the immune response is not needed at such high levels and this is why it very low. The initial decrease in the control occurs at roughly the same time as the immune response is high. This indicates that during periods of effective immune responsiveness, less medication is needed to control infection. Also strategy that enhance a patient's natural immune response may be beneficial as an alternative to quite high levels of drug therapy.

Comparing our results with the results as established in [8], we find that our control profile for optimal drug is different from drugs used to control systems. However, we observe that our control actually decreases after initiation of treatment and remain close to nil after four days. This initial drop is directly dependent upon the action of the immune response, which occurs shortly after treatment initiation in response to the high infection level. This indicates that enhancement of the immune response by means other than continual administration of anti-HIV drugs should be considered seriously in a clinical setting. Treatment strategies such as interruption of drug therapy to allow the immune response to rebuild should also be considered. This can be tested clinically through drug trials.

7 Conclusion

Biological systems have fractal structures and they have very close ties with fractional differential equations. Thus using fractional differential equations for these systems can produce more natural results. A mathematical model determines the transmission dynamics of HIV disease and helps to find a suitable control technic to defend this disease. The fractional derivative can be used to fit the real data according to the progression of different HIV patients. A more reliable model can be obtained by choosing the relevant fractional index according to available real data.

In this research article, the integer order model as proposed by Culshaw and Ruan [8] is modified to a system of fractional differential equations. It is seen that the fractional order model possesses non-negative solutions which are needed in any population dynamics. Using stability analysis on a fractional-order system, a sufficient condition on the parameters for the stability of the steady states is derived. It is also seen numerically that the system is Globally Mittag-Leffler stabile. Moreover, necessary conditions for the optimality of a fractional optimal control problem are derived. It is established that if the infection is controlled to very low levels the drug dosage can be reduced and the side effects due to the therapy can also be reduced. In this way, the fractional-order optimal control approach can improve the quality of the treatment.

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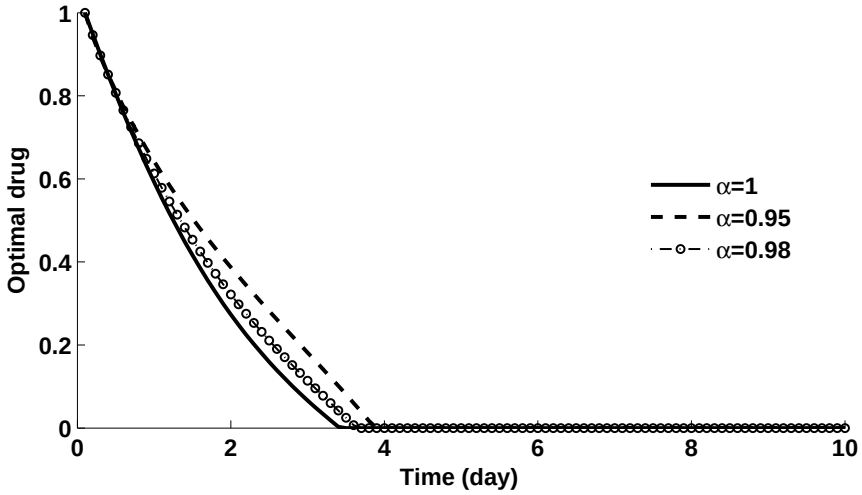

Figure 5: Optimal control for different value of α is plotted.

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