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Research Article

Caputo Fractional Order Nonlinear Incidence HIV Infection Model with Optimal Control

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Abstract: Examining mathematical models is a crucial aspect of research in comprehending the dynamics and managing the transmission of Human Immunodeficiency Virus (HIV). This study presents a Caputo fractional order HIV infection model with optimal control. We demonstrate that this model exhibits solutions that are always nonnegative. Additionally, we provide a comprehensive examination of the elasticity of both zero disease and viral-persistence equilibrium location. We also delve into the numerical method proposed by Atanackovic and Stanckovic for solving Generalized Inverse Method and provide numerical simulations to validate the findings.

***Keywords*:** caputo fractional differential equations, stability, sensitivity, optimal control, numerical solutions

MSC: 34A08, 37N25

1. Introduction

A large number of cells that are essential to the body's defense are destroyed by the Human Immunodeficiency Virus (HIV), which is the cause of AIDS. These cells are referred to as CD4 cells or T cells [1–4]. When HIV infiltrates a T cell, it transforms the cell into a production center for the virus, compelling it to generate countless copies of the virus. These copies then go on to infect other T cells. The body finds it harder and harder to stay healthy as time goes on because the immune system becomes weaker due to the decrease in T cells. HIV can enter the human body through a number of different channels, including intercourse, blood transfusions, contaminated needles, and mother-to-child transmission. This viral disease appears to be the main cause of AIDS, a disorder that compromises the immune system of humans and causes opportunistic infections in the body that can be fatal [5]. The vast majority of research on infections with HIV models has focused on integer-order ordinary (or delay) differential equations [6, 7]. In contrast, the literature has explored diverse control problems and applied various control theories to HIV-immune systems, as exemplified by works such as [8–11]. Many of these control problems involve control difficulties such as feedback control and optimal control techniques utilizing mathematical models, which have been confined to integer-order ordinary derivative models or delay derivative models, as demonstrated by [12, 13].

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Currently, interest in estimating evidence-based processes employing fractional derivative equations (FDEs) has increased, resulting in intriguing findings, as highlighted by [14–16]. Ding and Ye, in their studies presented in [17], introduced fractional-order derivatives into a T-cell HIV infection model and conducted a thorough analysis of equilibrium stability. However, it is worth noting that epidemiological optimal control constraints incorporating fractional-order derivatives in output and input variables are relatively uncommon in existing body of knowledge. Fractional calculus is a well-established mathematical concept that extends the traditional operations of differentiation and integration from whole numbers to non-integer values. According to [15], Leibniz in 1,695 initially introduced the idea of fractional calculus.

A fractional-order differential equation serves as an alternative to primarily nonlinear ordinary differential equations [18]. For an extended period, it received little attention due to its complexity and limited application background. However, in recent decades, its use in modeling various phenomena across multiple fields of science and engineering and has proven beneficial. Fractional-order differentiations have garnered significant interest for their precise representation of different nonlinear phenomena [19–21]. In recent years, fractional differential equations have been employed in several scientific disciplines and numerous theoretical and practical models [22–24]. These equations are particularly applicable to various natural phenomena, where they demonstrate greater validity and adaptability. The fractional-order system offers increased degrees of freedom, which helps minimize errors from neglected parameters. Consequently, more researchers are exploring the qualitative characteristics and numerical solutions related to fractional-order virus infection models [25–27]. Furthermore, it also provides a strong application of memory, which is a key hereditary trait in the immune response, is being explored. Key concepts in cellular structures, like fractals, are often linked to fractional-order differential equations. Recently, fractional calculus (FC) has gained popularity across various disciplines. Numerous mathematicians and applied researchers have sought to model real-world processes utilizing fractional calculus. For instance, Hashish and Ahmed introduced a fractional-order model involving two immune effectors attacking an antigen. In rheology, significant achievements have been made using fractional derivatives that capture vital aspects of cell rheological behavior. Building on these findings, this study employs fractional-order differential equations to represent the dynamics of HIV infections at the cellular level. Furthermore, we examine the impact of antiretroviral drug therapy and dietary supplements in managing the levels of infected cells and virus.

The paper is organized as follows. In section 2, a brief discussion of fractional-order calculus is presented. The model with initial values is derived in section 3. The non-negative solution of the model is presented in section 4. In section 5, we established the existence of the model equilibria and analyzed the local stability of the model. Sensitivity analysis of the model parameters on the basic reproduction number is discussed in section 6. Optimal control strategies and numerical methods are discussed in sections 7 and 8 respectively. Numerical solutions of the mathematical model are given in section 9. Finally, discussion of results and conclusion are presented in section 10.

2. Fractional calculus

This section presents definitions of fractional-order differentiation pertaining to the concept of fractional derivatives. The model is developed using the Caputo and Riemann-Liouville definitions [33]. The primary benefit of Caputo's definition is that the initial conditions for fractional differential equations using Caputo derivatives resemble those of classical differential equations.

Definition 2.1 The Riemann-Liouville (R-L) fractional integral operator of order $\delta > 0$ of a function $k : R^+ \longrightarrow R$ is defined as

$$I^{\delta}k(\chi) = \frac{1}{\Gamma(\delta)} \int_0^{\chi} (\chi - \omega)^{\delta-1} k(\omega) d\omega. \tag{1}$$

Here $\Gamma(\cdot)$ is the Euler Gamma function which is defined as

$$\Gamma(m) = \int_0^{\infty} \omega^{m-1} e^{-\omega} d\omega. \tag{2}$$

This function is a generalization of a factorial in the following form:

$$\Gamma(m) = (m-1)! \tag{3}$$

Definition 2.2 ([33]) The Caputo (C) fractional derivative of order $\delta > 0,\ m-1,\ \delta < m,\ m \in M$ is defined as

$$D^{\delta} k(\omega) = I^{m-\delta} D^{m} k(\omega) = \frac{1}{\Gamma(m-\delta)} \int_0^{\omega} \frac{k^{(m)}(r)}{(\omega - r)^{\delta+1-m}} dr, \tag{4}$$

where the function $k(\omega)$ has absolutely continuous derivatives up to order $(m-1)$. In particular, when $0 < \delta < 1$, one has

$$D^{\delta} k(\omega) = \frac{1}{\Gamma(1-\delta)} \int_0^{\omega} \frac{k'(R)}{(\omega - r)^{\delta}} dr. \tag{5}$$

We make use of Caputo fractional derivative definition in this paper. The main advantage of Caputo's definition is that the initial condition for fractional differential equations with Caputo derivatives takes the same form as the classical differential equations.

3. Mathematical model derivation

In this work, we develop a fractional-order mathematical model for HIV infection, based on the foundational HIV model by Culshaw, Ruan, and Spiteri [34]. This model outlines the transmission dynamics of HIV at the cellular level and consists of three populations: uninfected cells, $\mathrm{u}(\omega)$; concentration of infected cells, $\mathrm{c}(\omega)$ and concentration of virus $\mathrm{v}(\omega)$. Uninfected cells produced at a rate η, die at a rate ϕ and become infected at a rate ζ. The concentration of virus is considered proportional to the level of infected cells. Infected cells die at a rate of θ. Viruses are produced at a rate of τ and decay at a rate of σ. These assumptions result in the following integer-order system of differential equations:

$$\begin{aligned} \frac{d\mathrm{u}}{d\omega} &= \eta - \phi \mathrm{u} - \zeta \mathrm{uv}, \\ \frac{d\mathrm{c}}{d\omega} &= \zeta \mathrm{uv} - \theta \mathrm{c}, \\ \frac{d\mathrm{v}}{d\omega} &= \tau \mathrm{c} - \sigma \mathrm{v}, \end{aligned} \tag{6}$$

where $\mathrm{u}(0) = \mathrm{u}_0$, $\mathrm{c}(0) = \mathrm{c}_0$, $\mathrm{v}(0) = \mathrm{v}_0$, are the initial conditions.

Considering the above model, introducing the fractional order, gives

$$D^{\delta}\mathrm{u} = \eta^{\delta} - \phi^{\delta}\mathrm{u} - \zeta^{\delta}\mathrm{uv},$$

$$D^{\delta}\mathrm{c} = \zeta^{\delta}\mathrm{uv} - \theta^{\delta}\mathrm{c}, \tag{7}$$

$$D^{\delta}\mathrm{v} = \tau^{\delta}\mathrm{c} - \sigma^{\delta}\mathrm{v},$$

with initial conditions

$$\mathrm{u}(0) = \mathrm{u}_0,\ \mathrm{c}(0) = \mathrm{c}_0,\ \mathrm{v}(0) = \mathrm{v}_0, \tag{8}$$

and D^{δ} is the Caputo derivative.

Definition 3.1 ([28]) The discriminant $D(k)$ of a polynomial

$$k(y) = y^n + a_1 y^{n-1} + a_2 y^{n-2} + \cdots + a_n \tag{9}$$

is defined by $D(k) = (-1)^{n(n-1)/2} Q(k,\ k')$, where k' is the derivative of k. If $q(y) = y^l + c_1 y^{l-1} + c_2 y^{l-2} + \cdots + c_n$, $Q(k,\ q)$ is the determinant of the corresponding Sylvester $(n+l) \otimes (n+l)$ matrix. The Sylvester matrix is formed by filling the matrix beginning with the upper left corner with the coefficients of $k(y)$ and then shifting down one row and one column to the right side. The process is then repeated for the coefficients of $q(y)$.

Lemma 1 ([33]) For the polynomial equation,

$$R(\lambda) = \lambda^n + d_1\lambda^{n-1} + d_2\lambda^{n-2} + \cdots + d_n = 0, \tag{10}$$

the conditions displayed below make all the roots of (10) satisfy (12):

· For $n = 1$, the condition for (10) is $d_1 > 0$.

· For $n = 2$, the conditions for (10) are either Routh-Hurwitz conditions or $d_1 < 0$, $4d_2 > (d_1)^2$,

$$\left| \tan^{-1}\left(\frac{\sqrt{4d_2 - (d_1)^2}}{d_1} \right) \right| > \frac{\delta\pi}{2};$$

· For $n = 3$, if the discriminant of $R(\lambda),\ D(R)$ is positive, then Routh-Hurwitz conditions are the necessary and sufficient conditions for (10), i.e.

$$d_1 > 0,\ d_3 > 0,\ d_1 d_2 > d_3 \text{ if } D(R) > 0.$$

· If $D(R) < 0,\ d_1 \geq 0,\ d_3 > 0,\ \delta < 2/3$, then the condition (10) is satisfied. Also if $D(R) < 0$, $d_1 < 0$, $d_2 < 0$, $\delta > 2/3$, then all roots of $R(\lambda) = 0$ satisfies $|arg(\lambda)| < \delta\pi/2$.

· If $D(R) < 0$, $d_1 > 0$, $d_2 > 0$, $d_1 d_2 = d_3$ then condition (10) is satisfied for all $\delta \in [0,\ 1)$.

· For general n, $d_n > 0$ is a necessary condition for condition (10) to be satisfied.

4. Non-negative solution

Let $R_+^3 = Z \in R^3 : Z \geq 0$ and $Z(\omega) = (\mathrm{u}(\omega)),\ \mathrm{c}(\omega),\ \mathrm{v}(\omega)))^T$.

We use the following theorem to proof the nonnegative solutions of the system.

Theorem 4.1 (Generalized mean value theorem [36]). Let the function $k(y) \in C[\delta_1,\ \delta_2]$ and $D^\delta k(y) \in C(\delta_1,\ \delta_2]$ for $0 < \delta \leq 1$ and $\delta_1,\ \delta_2 \in \mathbb{R}$ then we have

$$k(y) = k(\delta_1) + \frac{1}{\Gamma(\delta)} D^\delta k(\xi)(y-\delta_1)^\delta \quad \forall y \in (\delta_1,\ \delta_2],$$

where $0 < \xi \leq y$.

Remark 1 Suppose that $k(y) \in C[g,\ h]$ and $D^\delta k(y) \in C[g,\ h]$, for $0 < \delta \leq 1$. It is clear from Lemma 1 that if $D^\delta k(y) \geq 0,\ \forall y \in (g,\ h)$, then $k(y)$ is nondecreasing for each $y \in [g,\ h]$. If $D^\delta k(y) \leq 0,\ \forall y \in (g,\ h)$, then $k(y)$ is nonincreasing for each $y \in [g,\ h]$.

We now prove the main theorem.

Theorem 4.2 There is a unique solution for the initial value problem in (7) and (8) and the solution remains in R_+^3.

Proof. From Theorem 3.1 and Remark 3.2 of [37], we obtain the solution on $(0,\ \infty)$ solving the initial value problem (7) with (8) which is not only existent but also unique. Next, we will show the nonnegative orthant R_+^3 is a positively invariant region. What is needed for this is to show that, on each hyperplane bounding the nonnegative orthant, the vector field points into R_+^3. From (7), we find

$$D^\delta \mathrm{u}|_{\mathrm{u}=0} \geq \eta^\delta,\ \ D^\delta \mathrm{c}|_{\mathrm{c}=0} \geq \zeta^\delta \mathrm{uv},\ \ D^\delta \mathrm{v}|_{\mathrm{v}=0} \geq \tau^\delta \mathrm{c}.$$

By Remark 1, the solution will remain in R_+^3. □

5. Equilibrium points and stability

In this section, we examine the stability of Caputo's fractional order HIV infection model.

To ascertain the equilibria of model (7), we set

$$D^\delta \mathrm{u}(\omega) = 0,\ D^\delta \mathrm{c}(\omega) = 0,\ \text{and}\ D^\delta \mathrm{v}(\omega) = 0.$$

The model (7) has two equilibrium points, the disease-free equilibrium.

$H_0 = [\mathrm{u} = \dfrac{\eta^\delta}{\phi^\delta},\ \mathrm{c} = 0,\ \mathrm{v} = 0]$ and the viral-persistence equilibrium

$$H_1 = \left[\mathrm{u}^* = \frac{\sigma^\delta \theta^\delta}{\zeta^\delta \tau^\delta},\ \mathrm{c}^* = \frac{\zeta^\delta \tau^\delta \eta^\delta - \phi^\delta \sigma^\delta \theta^\delta}{\zeta^\delta \theta^\delta \tau^\delta},\ \mathrm{v}^* = \frac{\zeta^\delta \tau^\delta \eta^\delta - \phi^\delta \sigma^\delta \theta^\delta}{\zeta^\delta \sigma^\delta \theta^\delta}\right].$$

The basic reproductive number $\mathscr{R}_0$ of system (7) is defined as

$$\mathscr{R}_0 = \frac{\zeta^\delta \eta^\delta \tau^\delta}{\phi^\delta \sigma^\delta \theta^\delta}. \tag{11}$$

The $\mathscr{R}_0$ describes the average number of newly generated infected cells from one infected cell at the beginning of the infection process. The biological interpretation is that when $\mathscr{R}_0 < 1$, the infected cells and the viral dies off but when $\mathscr{R}_0 > 1$, the infected cells and the viral exists.

The Jacobian matrix of the system (7) evaluated at the disease-free equilibrium H_0 is as follows:

$$J(H_0) = \begin{pmatrix} -\phi^{\delta} & 0 & -\dfrac{\zeta^{\delta}\eta^{\delta}}{\phi^{\delta}} \\ 0 & -\theta^{\delta} & \dfrac{\zeta^{\delta}\eta^{\delta}}{\phi^{\delta}} \\ 0 & \tau^{\delta} & -\sigma^{\delta} \end{pmatrix}.$$

Theorem 5.1 The disease-free equilibrium of system (7) is asymptotically stable if $\mathscr{R}_0 < 1$.

Proof. The disease-free equilibrium point, H_0, is asymptotically stable if the eigenvalues, Λ_i, $i = 1,\ 2,\ 3$, of $J(H_0)$ satisfy the following conditions [28–35]:

$$|arg\Lambda_i| > \delta\frac{\pi}{2}. \tag{12}$$

The eigenvalues of the Jacobian matrix above, using $|\Lambda I - J(H_0)| = 0$ gives the characteristic equation

$$(\Lambda + \phi^{\delta})\left(\phi^{\delta}\Lambda^2 + \Lambda(D+E) + \frac{1}{\phi^{\delta}}DE - F\right) = 0, \tag{13}$$

where

$$D = \phi^{\delta}\theta^{\delta},\ \ E = \phi^{\delta}\sigma^{\delta},\ \ F = \tau^{\delta}\eta^{\delta}\zeta^{\delta}.$$

The roots of the characteristic equation are

$$\Lambda_1 = -\phi^{\delta},$$

$$\Lambda_{2,\,3} = \frac{-(D+E) \pm \sqrt{(D+E)^2 - 4\phi^{\delta}(\frac{1}{\phi^{\delta}}DE - F)}}{2\phi^{\delta}}.$$

It is obvious that, $D+E > 0$ and if $DE > \phi^{\delta}F$, then all the eigenvalues, $\Lambda_i,\ i = 1,\ 2,\ 3$ satisfies the condition given by (12).

We now consider the endemic stability of the system.

The Jaccobian is

$$J(H_1) = \begin{pmatrix} -\zeta^{\delta}\mathrm{v}^* - \phi^{\delta} & 0 & -\zeta^{\delta}\mathrm{u}^* \\ \zeta^{\delta}\mathrm{v}^* & -\theta^{\delta} & \zeta^{\delta}\mathrm{u}^* \\ 0 & \tau^{\delta} & -\sigma^{\delta} \end{pmatrix}.$$

The characteristic polynomial of the linearizes system is

$$R(\Lambda) = \Lambda^3 + C_1\Lambda^2 + C_2\Lambda + C_3 = 0$$

where

$$C_1 = \frac{1}{8}\left(4\zeta^{\delta}\mathrm{v}^* + 4\phi^{\delta} + 4\sigma^{\delta} + 4\theta^{\delta}\right),$$

$$C_2 = \frac{1}{8}\left(\zeta^{\delta}(2\sigma^{\delta}\mathrm{v}^* + 2\theta^{\delta}\mathrm{v}^* - 2\tau^{\delta}\mathrm{u}^*) + \sigma^{\delta}(2\phi^{\delta} + 2\theta^{\delta}) + 2\phi^{\delta}\theta^{\delta}\right),$$

$$C_3 = \frac{1}{8}\left(\zeta^{\delta}(\sigma^{\delta}\theta^{\delta}\mathrm{v}^* - \phi^{\delta}\tau^{\delta}\mathrm{u}^*) + \phi^{\delta}\sigma^{\delta}\theta^{\delta}\right).$$

Let $D(R)$ be the discriminant of the polynomial R, then based on the definition, we obtain the discriminant of R as

$$D(R) = -\begin{vmatrix} 1 & C_1 & C_2 & C_3 & 0 \\ 0 & 1 & C_1 & C_2 & C_3 \\ 3 & 2\,C_1 & C_2 & 0 & 0 \\ 0 & 3 & 2\,C_1 & C_2 & 0 \\ 0 & 0 & 3 & 2\,C_1 & C_2 \end{vmatrix}$$

$$= 18C_1C_2C_3 + (C_1C_2)^3 - 4C_1^3C_3 - 4C_2^3 - 27C_3^2.$$

By using condition (3) in Lemma 1 and (12), we have the following theorem.

Theorem 5.2 Consider system (7). Under the condition of $\mathscr{R}_0 > 1$,

· If the discriminant of $R(\lambda)$, $D(R)$ is positive, that is, $D(R) > 0$, then the viral-persistent equilibrium H_1 is locally asymptotically stable for $0 < \delta \leq 1$;

· If $D(R) < 0$, then the viral-persistent equilibrium H_1 is locally asymptotically stable for $0 < \delta < \frac{2}{3}$.

6. Sensitivity analysis for $\mathscr{R}_0$

This section explores how $\mathscr{R}_0$ responds to variations in parameters to identify which parameter changes most significantly and could lead to effective disease control.

The normalized forward-sensitivity index of a variable G with respect to a parameter w (or the elasticity of G with respect to w) is defined as

$$F_w^G = \frac{w}{G} \cdot \frac{\partial G}{\partial w}.$$

This index indicates how sensitive G is to changes of parameter w. Precisely, a positive or negative index indicates that an increase in the parameter value results in an increase or decrease of G [38]. We derive the sensitivity of $\mathscr{R}_0$ with respect to ζ^δ, η^δ, τ^δ, ϕ^δ, σ^δ and θ^δ as shown in Figure 1.

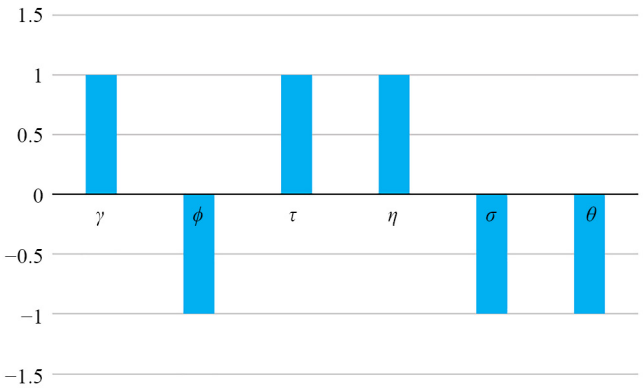

Figure 1. Sensitivity indices for $\mathscr{R}_0$ against model parameters

One sees that viral infection of healthy cells (ζ^δ), per capita rate of HIV virus production (τ^δ) and rate of healthy cells production (η^δ) have sensitivity index of +1. This means that increasing or (decreasing) these parameters by 10%, will lead to a corresponding 10% increase or (decreases) in $\mathscr{R}_0$. Conversely, the death rate of healthy cells (ϕ^δ), death rate of infected cells (θ^δ) and decay rate of virus (σ^δ) have sensitivity index of -1. This means that increasing or (decreasing) these parameters by 10%, will lead to a corresponding 10% decreases or (increases) in $\mathscr{R}_0$. The above remarks suggest that control strategies that effectively reduce the infection rate of healthy cells (ζ^δ) and per capita rate of HIV virus production (τ^δ) can control the disease. From a medical viewpoint, antiretroviral therapy and dietary supplement can reduce the infection rate of healthy cells and viral production. In section 7, we discuss the effect of antiretroviral therapy (w_1) and dietary supplement (w_2).

7. Optimal control strategies

In this section, we extend our model in equation (14) by introducing two time-dependent control measures, namely $w_1(\omega)$ (Antiretroviral drugs therapy) and $w_2(\omega)$ (Dietary supplements). It is assumed that the concentration of infected cells is reduced by the factor $(1 - w_1(\omega))$ as HIV patients undergo antiretroviral drug therapy. Furthermore, the concentration of virus is reduced by a factor of $(1 - w_2(\omega))$ as HIV patients take in dietary supplements to boost their immune cells. The model system (14) becomes

$$\begin{aligned} D^\delta \mathrm{u} &= \eta^\delta - \phi^\delta \mathrm{u} - \zeta^\delta \mathrm{uv}(1 - w_1(\omega)), \\ D^\delta \mathrm{c} &= \zeta^\delta \mathrm{uv}(1 - w_1(\omega)) - \theta^\delta \mathrm{c}, \end{aligned} \tag{14}$$

$$D^{\delta}\mathrm{v} = \tau^{\delta}\mathrm{c}(1 - w_2(\omega)) - \sigma^{\delta}\mathrm{v},$$

with the given objective function

$$J(w_1,\ w_2) = \int_0^T (q_1\mathrm{c} + q_2\mathrm{v} + q_3 w_1^2 + q_4 w_2^2) d\omega, \tag{15}$$

where c is the concentration of infected cells and v is the concentration of virus. T is the final time and the coefficients $q_1,\ q_2,\ q_3,\ q_4$ are positive weights. Our aim is to minimize the concentration of infected cell and virus while minimizing the cost of control $w_1,\ w_2$. Thus, we search for an optimal control $w_1^*,\ w_2^*$, such that

$$J(w_1^*,\ w_2^*) = \min_{w_1,\ w_2} \{J(w_1,\ w_2) | w_1,\ w_2 \in \Omega\} \tag{16}$$

where the control set is $\Omega = \{(w_1,\ w_2) | w_i :\ [0,\ T] \longrightarrow [0,\ \infty)$ Lebesgue measurable, $i = 1,\ 2,\ \}$.

The terms $q_1\mathrm{c}$ and $q_2\mathrm{v}$ represent the cost of reducing the concentration of infected cells and virus respectively, while $q_3 w_1^2$ is the cost of antiretroviral drug therapy and also, $q_4 w_2^2$ is the cost of dietary supplements. The necessary conditions that an optimal control must satisfy come from the Pontryagins Minimum Principle [39]. This principle converts Equations (14) and (15) into a problem of point-wise minimizing a Hamiltonian H with respect to $(w_1,\ w_2)$ stated as follows:

$$\begin{aligned} H =& q_1\mathrm{c} + q_2\mathrm{v} + q_3 w_1^2 + q_4 w_2^2 \\ &+ \lambda_{\mathrm{u}}\left\{ \eta^{\delta} - \phi^{\delta}\mathrm{u} - \zeta^{\delta}\mathrm{uv}(1 - w_1(\omega)) \right\} \\ &+ \lambda_{\mathrm{c}}\left\{ \zeta^{\delta}\mathrm{uv}(1 - w_1(\omega)) - \theta^{\delta}\mathrm{c} \right\} \\ &+ \lambda_{\mathrm{v}}\left\{ \tau^{\delta}\mathrm{c}(1 - w_2(\omega)) - \sigma^{\delta}\mathrm{v} \right\}, \end{aligned}$$

where λ_{u}, λ_{c}, and λ_{v}, adjoint variables or co-state variables [39]

$$\begin{cases} -\dfrac{d\lambda_{\mathrm{u}}}{d\omega} = \dfrac{\partial H}{\partial \mathrm{u}} = \lambda_{\mathrm{u}}(-\phi^{\delta} - \zeta^{\delta}\mathrm{v}(1 - w_1)) + \lambda_{\mathrm{c}}\zeta^{\delta}\mathrm{u}(1 - w_1) \\ -\dfrac{d\lambda_{\mathrm{c}}}{d\omega} = \dfrac{\partial H}{\partial \mathrm{c}} = q_1 - \lambda_{\mathrm{c}}\theta^{\delta} + \lambda_{\mathrm{v}}\tau^{\delta}(1 - w_2) \\ -\dfrac{d\lambda_{\mathrm{v}}}{d\omega} = \dfrac{\partial H}{\partial \mathrm{v}} = q_2 - \lambda_{\mathrm{u}}\zeta^{\delta}\mathrm{u}(1 - w_1) + \lambda_{\mathrm{c}}\zeta^{\delta}\mathrm{u}(1 - w_1) - \lambda_{\mathrm{v}}\sigma^{\delta} \end{cases} \tag{17}$$

The transversality conditions are

$$\lambda_{\mathrm{u}}(\omega) = \lambda_{\mathrm{c}}(\omega) = \lambda_{\mathrm{v}}(\omega) = 0.$$

On the interior of the control set, where $0 < w_i < 1$, for $i = 1,\ 2$ we have

$$\frac{\partial H}{\partial w_1} = \zeta^{\delta}\mathrm{vu}\lambda_{\mathrm{u}} - \zeta^{\delta}\mathrm{vu}\lambda_{\mathrm{c}} + 2q_3 w_1 = 0,$$

$$\frac{\partial H}{\partial w_2} = -\tau^{\delta}\mathrm{c}\lambda_{\mathrm{v}} + 2q_4 w_2 = 0.$$

We obtain

$$w_1 = -\frac{1}{2}\frac{\zeta^{\delta}\mathrm{uv}(\lambda_{\mathrm{u}} - \lambda_{\mathrm{c}})}{q_3},$$

$$w_2 = \frac{1}{2}\ \frac{\lambda_{\mathrm{v}}\tau^{\delta}\mathrm{c}}{q_4}.$$

Theorem 7.1 The optimal control $(w_1^*,\ w_2^*)$ that minimizes $J(w_1,\ w_2)$ over $\mathscr{U}$ is given by

$$w_1^* = \max\left\{0,\ \min\left(1,\ -\frac{1}{2}\ \frac{\zeta^{\delta}\mathrm{uv}(\lambda_{\mathrm{u}} - \lambda_{\mathrm{c}})}{q_3}\right)\right\},$$

$$w_2^* = \max\left\{0,\ \min\left(1, \frac{1}{2}\frac{\lambda_{\mathrm{v}}\tau^{\delta}\mathrm{c}}{q_4}\right)\right\},$$

where $\lambda_{\mathrm{u}},\ \lambda_{\mathrm{c}}$, and λ_{v} are the adjoint variables satisfying (17) and the following transversality conditions: $\lambda_{\mathrm{u}}(\omega) = \lambda_{\mathrm{c}}(\omega) = \lambda_{\mathrm{v}}(\omega) = 0$ and

$$w_1^* = \begin{cases} 0 & \text{if } w_1 \leq 0 \\ w_1, & \text{if } 0 < w_1 < 1 \\ 1, & \text{if } w_1, \geq 1 \end{cases} \quad w_2^* = \begin{cases} 0 & \text{if } w_2 \leq 0 \\ w_2, & \text{if } 0 < w_2 < 1 \\ 1, & \text{if } w_2, \geq 1 \end{cases}$$

8. Numerical method

Atanackovic and Stankovic [40] introduced a numerical method to solve the single linear FDE. Some few years later, they developed a method again to solve the nonlinear FDE [40]. It was shown that the fractional derivative of a function $k(\omega)$ with order δ satisfying $0 < \delta < 1$ may be expressed as

$$D^{\delta}k(\omega) = \frac{1}{\Gamma(2-\delta)} \times \left\{ \frac{k^{(1)}(\omega)}{\omega^{\delta-1}} \left[1 + \sum_{p=1}^{\infty} \frac{\Gamma(p-1+\delta)}{\Gamma(\delta-1)p!} \right] - \left[\frac{\delta-1}{\omega^{\delta}} k(\omega) + \right. \right.$$

$$\left. \left. \sum_{p=2}^{\infty} \frac{\Gamma(p-1+\delta)}{\Gamma(\delta-1)(p-1)!} \times \left(\frac{k(\omega)}{\omega^{\delta}} + \frac{V_p(k)(\omega)}{\omega^{p-1+\delta}} \right) \right] \right],$$

where

$$V_p(k)(\omega) = -(p-1) \int_0^{\omega} \nu^{p-2} k(\nu) d\nu, \quad p = 2,\ 3,\ \ldots, \tag{18}$$

with the following properties:

$$\frac{d}{d\omega} V_p(k) = -(p-1)\omega^{p-2} k(\omega), \quad p = 2,\ 3,\ \ldots, \tag{19}$$

We approximate $D^{\delta}k(\omega)$ by using P terms in the sums appearing in (18) as follows:

$$D^{\delta}k(\omega) = \frac{1}{\Gamma(2-\delta)} \times \left\{ \frac{k^{(1)}(\omega)}{\omega^{\delta-1}} \left[1 + \sum_{p=1}^{P} \frac{\Gamma(p-1+\delta)}{\Gamma(\delta-1)m!} \right] - \left[\frac{\delta-1}{\omega^{\delta}} k(\omega) + \right. \right.$$

$$\left. \left. \sum_{p=2}^{P} \frac{\Gamma(p-1+\delta)}{\Gamma(\delta-1)(p-1)!} \times \left(\frac{k(\omega)}{\omega^{\delta}} + \frac{V_p(k)(\omega)}{\omega^{p-1+\delta}} \right) \right] \right].$$

We can rewrite the above equation as follows:

$$D^{\delta}k(\omega) \simeq \Omega(\delta,\ \omega, P)k^{(1)}(\omega) + \Theta(\delta,\ \omega,\ P)k(\omega) + \sum_{p=2}^{P} A(\delta,\ \omega,\ P) \frac{V_p(k)(\omega)}{\omega^{p-1+\delta}}, \tag{20}$$

where

$$\Omega(\delta,\ \omega,\ P) = \frac{1 + \sum_{p=1}^{P} \frac{\Gamma(p-1+\delta)}{\Gamma(\delta-1)p!}}{\Gamma(2-\delta)\omega^{\delta-1}},$$

$$R(\delta,\ \omega) = \frac{1}{\omega^{\delta}\Gamma(2-\delta)},$$

$$A(\delta,\ \omega,\ p) = -\frac{\Gamma(p-1+\delta)}{\Gamma(2-\delta)\Gamma(\delta-1)(p-1)!},$$

$$\Theta(\delta,\ \omega,\ P) = R(a,\ \omega) + \sum_{p=2}^{P} \frac{A(\delta,\ \omega,\ p)}{\omega^{\delta}}. \tag{21}$$

We set

$$\begin{aligned}
&\Theta_1(\omega) = \mathrm{u}(\omega), \qquad \Theta_p(\omega) = V_p(\mathrm{u})(\omega) \\
&\Theta_{P+1}(\omega) = \mathrm{c}(\omega), \qquad \Theta_{P+p}(\omega) = V_p(\mathrm{c})(\omega) \\
&\Theta_{2P+1}(\omega) = \mathrm{v}(\omega), \qquad \Theta_{2P+p}(\omega) = V_p(\mathrm{v})(\omega) \\
&\text{for} \quad p = 2,\ 3,\ \ldots
\end{aligned} \tag{22}$$

From equation (7), we can rewrite in the following form:

$$\begin{aligned}
&\Omega(\delta,\ \omega,\ P)\Theta_1' + \Phi(\delta,\ \omega,\ P)\Theta_1(\omega) + \sum_{p=2}^{P} A(\delta,\ \omega,\ p)\frac{\Theta_p(\omega)}{\omega^{p-1+\delta}} \\
=&\eta^{\delta} - \phi^{\delta}\Theta_1(\omega) - \zeta^{\delta}\Theta_1(\omega)\Theta_{2P+1}(\omega), \\
&\Omega(\delta,\ \omega,\ P)\Theta_{P+1}'(\omega) + \Phi(\delta,\ \omega,\ P)\Theta_{P+1}(\omega) + \sum_{p=2}^{P} A(\delta,\ \omega,\ P)\frac{\Theta_{P+p}(\omega)}{\omega^{p-1+\delta}} \\
=&\zeta^{\delta}\Theta_1(\omega)\Theta_{2P+1}(\omega) - \theta^{\delta}\Theta_{P+1}(\omega), \\
&\Omega(\delta,\ \omega,\ P)\Theta_{2P+1}'(\omega) + \Phi(\delta,\ \omega,\ P)\Theta_{2P+1}(\omega) + \sum_{p=2}^{P} A(\delta,\ \omega,\ P)\frac{\Theta_{2P+p}(\omega)}{\omega^{p-1+\delta}} \\
=&\tau^{\delta}\Theta_{P+1}(\omega) - \sigma^{\delta}\Theta_{2P+1}(\omega),
\end{aligned} \tag{23}$$

where

$$\Theta_p(\omega) = -(p-1)\int_0^{\omega} \varepsilon^{p-2}\mathrm{u}(\varepsilon)d\varepsilon,$$

$$\Theta_{P+p}(\omega) = -(p-1)\int_0^{\omega} \varepsilon^{p-2}\mathrm{c}(\varepsilon)d\varepsilon,$$

$$\Theta_{2P+p}(\omega) = -(p-1)\int_0^{\omega} \varepsilon^{p-2}\mathrm{v}(\varepsilon)d\varepsilon,$$

$$p = 2,\ 3,\ ...,\ P. \tag{24}$$

Now we can rewrite (20) and (23) as

$$\Theta_1' = \frac{1}{\Omega(\delta,\ \omega,\ P)}\left[\eta^{\delta} - \left(\phi^{\delta} + \zeta^{\delta}\Theta_{2P+1}(\omega) + \Phi(\delta,\ \omega,\ P)\right)\Theta_1(\omega) - \sum_{p=2}^{P} A(\delta,\ \omega,\ P)\frac{\Theta_p(\omega)}{\omega^{p-1+\delta}}\right],$$

$$\Theta_p'(\omega) = -(p-1)\omega^{p-2}\Theta_1(\omega), \quad p = 2,\ 3,\ \ldots,\ P,$$

$$\Theta_{P+1}' = \frac{1}{\Omega(\delta,\ \omega,\ P)}\left[\zeta^{\delta}\Theta_1(\omega)\Theta_{2P+1}(\omega) - (\theta^{\delta} + \Phi(\delta,\ \omega,\ P))\Theta_{P+1}(\omega)\right.$$

$$\left. - \sum_{p=2}^{P} A(\delta,\ \omega,\ P)\frac{\Theta_{P+p}(\omega)}{\omega^{p-1+\delta}}\right], \tag{25}$$

$$\Theta_{P+p}'(\omega) = -(p-1)\omega^{p-2}\Theta_{P+1}(\omega), \quad p = 2,\ 3,\ \ldots,\ P,$$

$$\Theta_{2P+1}' = \frac{1}{\Omega(\delta,\ \omega,\ P)}\left[\tau^{\delta}\Theta_{P+1}(\omega) - (\sigma^{\delta} + \Phi(\delta,\ \omega,\ P))\Theta_{2P+1}(\omega)\right.$$

$$\left. - \sum_{p=2}^{P} A(\delta,\ \omega,\ P)\frac{\Theta_{2P+p}(\omega)}{\omega^{p-1+\delta}}\right],$$

$$\Theta_{2P+p}'(\omega) = -(p-1)\omega^{p-2}\Theta_{2P+1}(\omega), \quad p = 2,\ 3,\ \ldots,\ P,$$

with initial conditions

$$\Theta_1(\omega) = \mathrm{u}_0, \quad \Theta_p(\delta) = 0, \quad p = 2,\ 3,\ \ldots,\ P,$$

$$\Theta_{P+1}(\omega) = \mathrm{c}_0, \quad \Theta_{P+p}(\omega) = 0, \quad p = 2,\ 3,\ \ldots,\ P, \tag{26}$$

$$\Theta_{2P+1}(\omega) = \mathrm{v}_0, \quad \Theta_{2P+p}(\omega) = 0, \quad p = 2,\ 3,\ \ldots,\ P.$$

The numerical solution of the system of ordinary differential equations (25) with the initial conditions (26) could be solved by using the famous Runge-Kutta fourth order method.

9. Numerical simulation and discussion

By implementing the Generalized Euler Method (GEM) [27], we simulate model (7) with the parameter values as indicated in Table 1. Using the parameter values in Table 1, we have $\mathscr{R}_0 = 10.0$ and $D(R) = -0.0006188 < 0$ which indicates that the viral-persistence equilibrium H_1 is locally asymptotically stable for $0 < \delta < \frac{2}{3}$. It can be observed that, compared with the case of order $\delta = 0.85$, the trajectory of the model with order $\delta = 0.95$ is closer to the trajectory of the model with the integer-order 1. That is, the farther from δ to 1, the bigger of the trajectory difference between them as in Figure 4. By comparing the numerical results with the existing work, it can be observed that the non-integer order method of modeling is more efficient and reliable than the integer order modeling. The advantage of the non-integer order over the integer order is that it keeps memory of the data.

Table 1. Parameter values

Parameter	Discription	Value [41]
η^δ	Rate of healthy cells production	8 cells/day
ϕ^δ	Death rate of healthy cells	0.1 cells/day
ζ^δ	Infection rate of virus on healthy cells	0.0025
θ^δ	Death rate of infected cells	0.2 cells/day
τ^δ	Per capita rate of HIV viral load production	0.1/day
σ^δ	Decay rate of virus	0.01/day

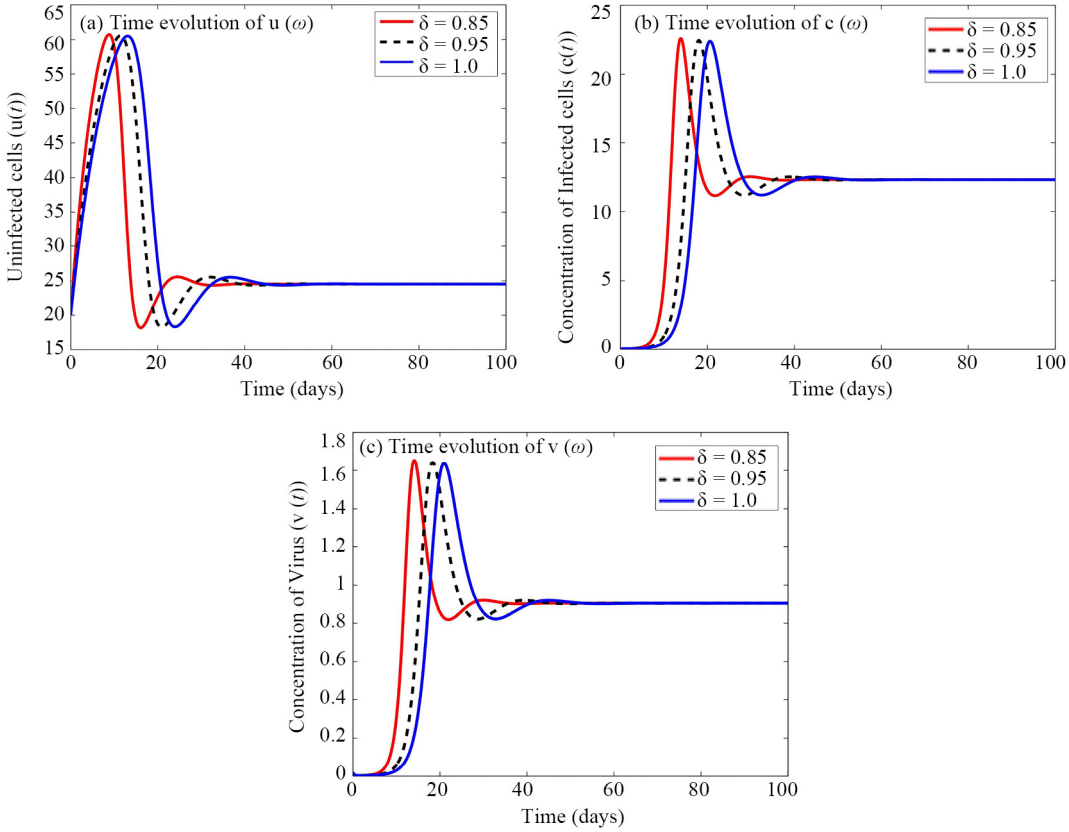

Figure 2. The time evolution of the trajectory of system (7) for uninfected cells u(ω), concentration of infected cells c(ω), and the concentration of virus v(ω), respectively, with respect to $\delta = 0.85$, $\delta = 0.95$, and $\delta = 1$, in condition of $D(R) > 0$

Figure 3 shows that the viral-persistence equilibrium H_1 is asymptotically stable for $0 < \delta < \frac{2}{3}$ and there exists the limit circle for $\delta > \frac{2}{3}$.

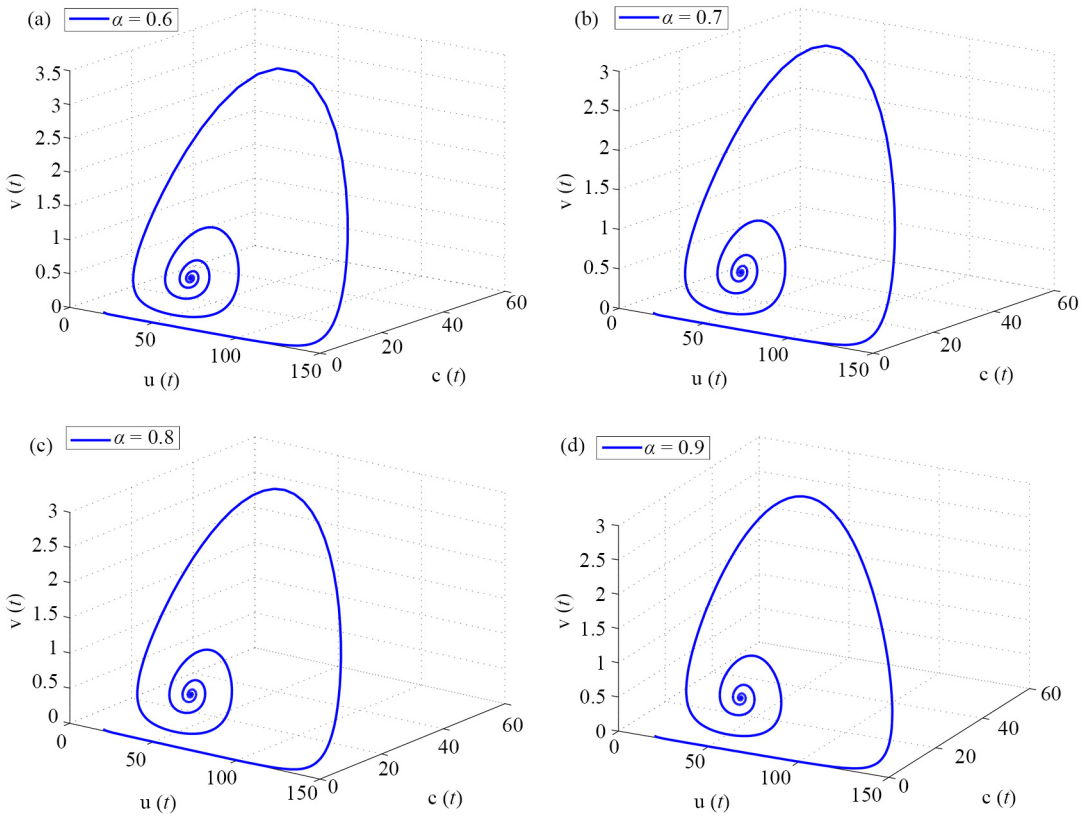

Figure 3. The three-dimensional diagrams show the approximate solutions of u(ω), c(ω) and v(ω) for $\delta = 0.6$, $\delta = 0.7$, $\delta = 0.8$, and $\delta = 0.9$ in condition of $D(R) < 0$

9.1 *The effects of optimal integrated controls on the concentration of infected cells and virus*

Figure 4 (a) shows a substantial difference in concentration of infected cells with and without using controls. Without using controls, the concentration of infected cells increases and reaches a higher peak, while in the controlled case, the concentration of infected cells decreases rapidly and reaches a lower peak. This suggests that antiretroviral drug therapy and dietary supplements minimize the infected cells in HIV patients. Similarly, Figure 4 (b) also indicates a reduction in the concentration of virus in HIV patients due to antiretroviral drug therapy and dietary supplements compared with the uncontrolled case.

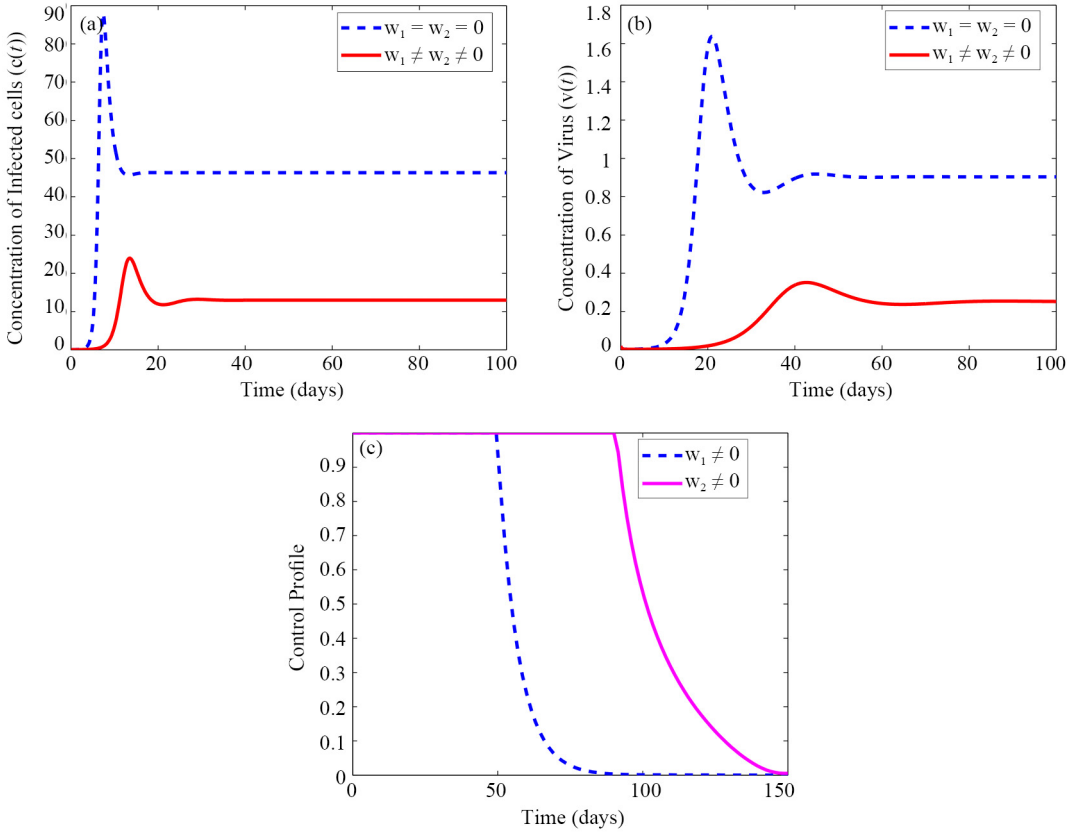

Figure 4. Simulations showing the effect of w_1 (antiretroviral drug therapy) and w_2 (dietary supplements) on (a) concentration of infected cells, (b) concentration of virus. The optimal control profile of w_1 (antiretroviral drugs therapy) and w_2 (dietary supplements) is simulated in (c)

10. Conclusion

Microbiological systems inherently possess fractal structures, closely associated with non-integer (fractional) order differential equations. This paper builds on the integer-order HIV model proposed by Culshaw and Ruan [12], utilizing fractional differential equations to examine HIV infection dynamics at the cellular level to produce results that are more reflective of biological realities. Modeling the transmission dynamics of HIV disease mathematically helps to provide suitable control strategies to defend against the disease. We chose the relevant fractional index according to available real data to obtain a more reliable model that can be used to study the progression of different HIV patients. Our results reveal that the fractional order model possesses non-negative solutions which are needed in any dynamical system. We studied the stability behavior of the disease-free and viral-persistence equilibrium of the system (7). We found that the stability of the disease-free equilibrium is locally asymptotically stable if the basic reproduction number of viruses is less than one ($\mathscr{R}_0 < 1$). However, when the basic reproduction number of viruses is more than one ($\mathscr{R}_0 > 1$), the disease-free equilibrium is unstable. In the condition of $\mathscr{R}_0 > 1$ when discriminant of the characteristic polynomial of the linearized system is positive $D(R) > 0$, the virus persistent equilibrium is locally asymptotically stable for $0 < \delta \leq 1$, while when $D(R) < 0$, the viral-persistence equilibrium is stable only for $0 < \delta < \frac{2}{3}$. By using numerical simulation on our parameter values, we found $D(R) < 0$ which means that virus persistence equilibrium is stable for $0 < \delta < \frac{2}{3}$. The simulation also indicates that the farther from δ to 1, the bigger of their trajectory difference in the system. These results indicate that the fractional order model is a generalization of the classical differential equation. Thus the integer-order model can be viewed as a special case from the non-integer order model. The viral-persistence equilibrium (H_1) has a limit circle for $\delta > \frac{2}{3}$. We analyzed

the sensitivity of the basic reproductive number ($\mathscr{R}_0$) to the parameter values. We found that increasing or (decreasing) the rate of viral infection of healthy cells (ζ^δ) and per capita rate of HIV virus production (τ^δ) lead to a corresponding increase or (decreases) in $\mathscr{R}_0$. Which means that strategies that effectively reduce the infection rate of healthy cells (ζ^δ) and per capita rate of HIV virus production (τ^δ) can control the disease. We, therefore, examined the effect of antiretroviral therapy (w_1) and dietary supplement (w_2) on the control of the disease. Using these control parameters, the concentration of virus and infected cells decreases rapidly and reaches a lower peak compared to uncontrolled cases. In this paper, we introduce the Caputo fractional order nonlinear incidence in modeling HIV infection at the cellular level with optimal control. Through theoretical analysis and numerical simulations, it is illustrated that fractional-order HIV model is a generalization of the classical integer order HIV model. The limitation of the fractional model is that it may not have solutions that you can express in terms of elementary functions and it requires substantial mathematical machinery to understand them at any depth. This work provides useful insight into the fractal dynamical behavior of HIV disease and control strategies which can aid research effort in this field. The significance of the findings indicates how effective and reliable in modeling HIV infectious disease at the cellular level can easily be controlled by the implementation of the fractional order differential models. Also, the findings revealed that the application of fractional derivative aid in the introduction of memory effects into the mathematical models, which is critical for efficiently predicting the behavior of physical systems with memory effects. In the near future, we intend to apply real data-set to both model (6) and model (7) in order to make comparison for the integer-order model and the fractional-order model.

Data availability statement

The data collected for this study can be obtained from the first author upon a reasonable request.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of the research article.

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