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Analysis of a fractional order HIV-1 infection model with saturated immune response

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ABSTRACT

Human immunodeficiency virus type 1 (HIV-1) infection is studied in this paper using a fractional order mathematical model. The model is made up of a set of four nonlinear diff erential equations that account for two forms of infection transmission (cell-to-cell and virus-to-cell) as well as a saturated immune response.The positivity and boundedness of the fractional order model solutions are studied. The values of equilibrium points and two fundamental threshold parameters have been computed. In addition, we proved global asymptotic stability for the model equilibrium points given. To corroborate the analytical conclusions and investigate the model's dynamical behavior, numerical simulations were used.

1 INTRODUCTION

Human immunodeficiency virus type-1 (HIV-1) is a retrovirus that induces acquired immunodeficiency syndrome (AIDS). HIV-1 targets CD4+ T cells, which are the most numerous white blood cells in the host immune system and play a crucial role in protecting the body from infection. The first case of HIV infection was identified in 1981 and since then HIV has become one of the most deadly infections in the world and has a devastating impact on human health and even life [1]. For a decade, it was thought that the spread of HIV-1 in hosts was primarily due to free circulation of virus particles, with a repeated process consisting of virus attachments to T cells. However recent studies have shown that the infection can also be passed directly from infected cells to susceptible cells.

In order to gain a better understanding of virus dynamics within the host and to predict how antiviral treatment effectiveness will affect the course of an infection,

mathematical models of HIV-1 dynamics have developed into useful tools (see e.g. [2]-[6]). These models originally comprised a set of ordinary differential equations, and they have proven useful for comprehending the dynamics of HIV infection ([7] and [8]). However, recent research has shown that models based on fractional order differential equations (FODS) can accurately capture many viral infection-related events. According to Rossikhin [9], fractals that seem to be prevalent in biological systems are related to fractional order differential equations. Fractional calculus was initially only used in pure mathematics studies until the 1990s when it was applied to issues in nature and society. Additionally, fractional-order electrical conductivity has been discovered in the cell membranes of living things. Scientists have given modeling in the fractional order more attention as a result of the thorough investigation of dynamical issues [10]– [14].

All models mentioned in previous papers that studied HIV infection did not take into account the effect of CTLs. Cytotoxic T lymphocytes (CTLs) are an important and necessary component of innate immunological opposition to infection and disease management. It play a critical role in protecting the body from the viral load by eliminating infected cells during HIV infection. As a result, CTLs are thought to be the primary host immunological component determining the viral load. From this point of view, the effect of CTLs on models of HIV was considered in many publications [15]-[18], these papers considered only the interaction between the HIV particales and only one target cell which is CD$\mathbf{4}^{+}$T cells. Due to recent studies that have proven that the infection can also be transmitted directly from infected cells to susceptible cells, then two forms of disease transmission: virus-to-cell and cell-to-cell was presented [19], [20] and [21]. All previous articles assumed that the CTL immune response is represented by a bilinear function, while the number of infected cells when reaches a certain level, the rate of CTL cell production often stops rising and enters a saturation condition. Therefore, De Boer [22] asserted that the bilinear rate cannot represent many immune responses that are working together to manage chronic infection and suggested an immune response function based on a competitive saturation term. Then [23]-[27] opted for the saturated CTL response function.

Motivated by above biological reasons, in this paper we consider a within-host HIV-1 infection model, the model presented by four fractional order differential equations. The proposed model is a modification for the model presented by Wang et al. [23]. The authors in [23] studied the effect of the Cytotoxic T lymphocytes (CTLs) immune response as a saturated term on HIV dynamics when infections being a result of interaction with virus particles but in these study we considered both virus-to-cell and cell-to-cell transmissions. This manuscript is structured as follows: In Section 2, we provide a definition of fractional-order derivatives and theorems related to them. In Section 3, we present our HIV-1 infection model. In Section 4 we analyze the local stability for equilibrium points using characteristic equations. As for Section 5, we use Lyapunov method and apply LaSalle's invariance principle to prove the global asymptomatic stability

for equilibrium points. We review the numerical simulations of the system in the last section.

2 MAIN CONCEPTS OF FRACTIONAL CALCULUS

In this part, we explain the fundamental concepts and lemma of fraction calculus, which is an essential tool in modeling biological system processes and may offer a precise description not only of the disease's current condition but also of all its historical stages.

Definition 1 Define a function $f:[0,\infty) \longrightarrow R$, then fractional integral of it of order $\alpha \in (0,1]$ given as follows:

$$I^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-x)^{\alpha-1} f(x) dx,$$

where $\Gamma(\alpha)$ is the gamma function [28], and the Caputo fractional derivative of order α is given by:

$$D^{\alpha} f(t) = I^{n-\alpha} D^{n} f(t), \tag{1}$$

where $n-1 < \alpha \leq n$ and f (t) is a continuous function [29]. Particularly, when $0 < \alpha \leq 1$, one has

$$D^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(x)}{(t-x)^{\alpha}} dx,$$

for more properties of the fraction order derivatives (see e.g. [30] and [31]).

Lemma 1 *Consider a fractional order system*

$$D^{\alpha}(x) = f(x), \quad x(0) = x_0, \tag{2}$$

where $0 < \alpha \leq 1$ *and* $x \in \{R^n\}$, *evaluate the equilibrium points of system (2) by letting* $D^{\alpha}(x) = 0$, *if all eigenvalues* λ_i *of the system's Jacobian matrix evaluated at the equilibrium points fulfil the following criterion, then these points are locally asymptotically stable: [32]*

$$|arg(\lambda_i)| > \alpha \frac{\pi}{2}. \tag{3}$$

3 HIV MODEL DESCRIPTION

For the biological and mathematical justifications mentioned above, we suggest a fractional-order model explain the dynamics of HIV-1 infection including two classes of transmissions: virus-to-cell and cell-to-cell incidence as well as a saturating CTL

immunological response as follows:

$$D^{\alpha}T(t) = \Lambda - dT(t) - \beta T(t)V(t) - kT(t)T^{*}(t), \tag{4}$$

$$D^{\alpha}T^{*}(t) = \beta T(t)V(t) + kT(t)T^{*}(t) - \Delta T^{*}(t) - qT^{*}(t)Z(t), \tag{5}$$

$$D^{\alpha}V(t) = nT^{*}(t) - cV(t), \tag{6}$$

$$D^{\alpha}Z(t) = \frac{mT^{*}(t)Z(t)}{h+Z(t)} - bZ(t), \tag{7}$$

where $T(t)$, $T^{*}(t)$, $V(t)$ and $Z(t)$ are respectively the concentrations of uninfected cells, infected cells, HIV-1 particles and CTL immune response cells at time t. The uninfected cells are restored at rate Λ, become infected at rate $\beta TV + kTT^{*}$ and die at rate dT. CTL kills infected cells by rate $qT^{*}Z$ and it perish at a rate of ΔT^{*}. Virus particles proliferate at rate nT^{*} and die at rate cV. CTL cells multiply at rate $\frac{mT^{*}Z}{h+Z}$, it die by bZ rate, where m and h are constants, see Figure 1 for further explanation on the interaction of the variables represented in the model (4)-(7).

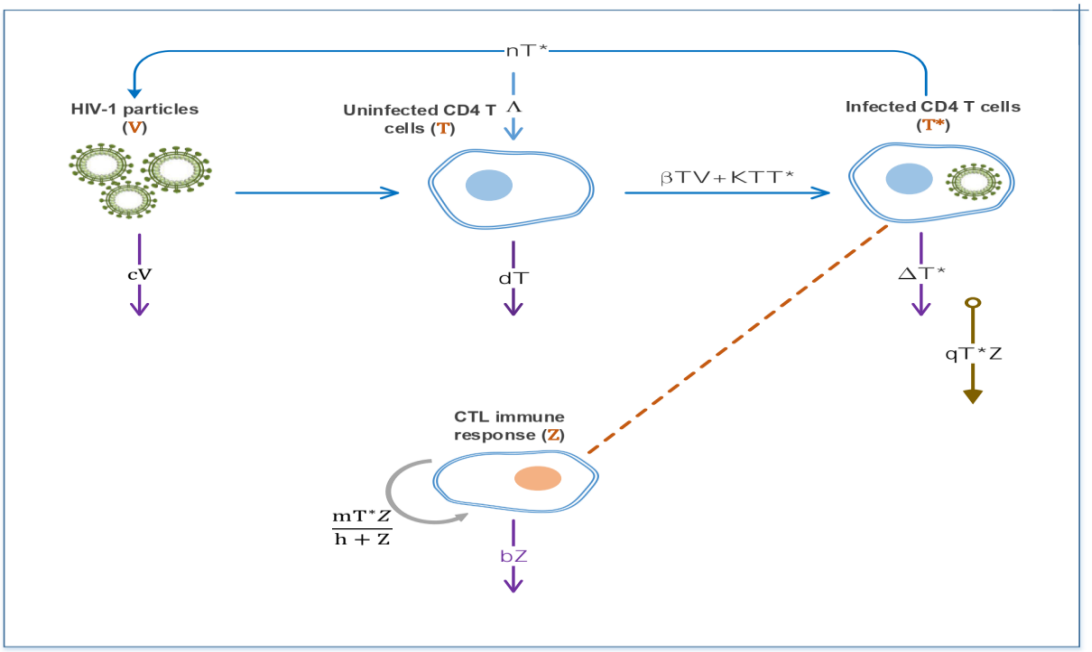

Figure 1: Schematic diagram for HIV-1 model (4)-(7)

3.1 Basic properties

In this part, we shall look at the non-negativity and finiteness of model (4)-(7) solutions.

Lemma 2 *For the model (4)-(7), a non-negative invariant compact set* Π *exists such that*

$$\Pi = \{(T, T^*, V, Z) \in \mathbb{R}^4_{\geq 0} : 0 \leq T,\ T^* \leq l_1,\ 0 \leq V \leq l_2,\ 0 \leq Z \leq l_3\}. \quad (8)$$

Proof. It is obvious that

$$D^\alpha T|_{(T=0)} = \Lambda > 0,$$

$$D^\alpha T^*|_{(T^*=0)} = \beta TV \geq 0, \qquad \text{for all } T, V \geq 0,$$

$$D^\alpha V|_{(V=0)} = nT^* \geq 0, \qquad \text{for all } T^* \geq 0,$$

$$D^\alpha Z|_{(Z=0)} = 0.$$

This supports the non-negatively invariant feature of Π for the model (4)-(7).
Let $Q = T + T^* + \frac{\Delta}{2n}V + \frac{qh}{m}Z$, then

$$D^\alpha Q = \Lambda - dT - \frac{\Delta}{2}T^* - qT^*Z - \frac{\Delta c}{2n}V + \frac{qhT^*Z}{h+Z} - \frac{qbh}{m}Z$$

$$= \Lambda - dT - \frac{\Delta}{2}T^* - \frac{qT^*Z^2}{h+Z} - \frac{\Delta c}{2n}V - \frac{qbh}{m}Z$$

$$\leq \Lambda - \sigma\left(T + T^* + \frac{\Delta}{2n}V + \frac{qh}{m}Z\right) = \Lambda - \sigma Q,$$

where, $\sigma = \min\{d, \frac{\Delta}{2}, c, b\}$. Then

$$Q(t) \leq e^{-\sigma t}\left(Q(0) - \frac{\Lambda}{\sigma}\right) + \frac{\Lambda}{\sigma}.$$

This yields to $0 \leq Q(t) \leq l_1$ for all $t \geq 0$ when $Q(0) \leq l_1$, where $l_1 = \frac{\Lambda}{\sigma}$. As a result of this, $0 \leq T(t), T^*(t) \leq l_1, 0 \leq V(t) \leq l_2$ and $0 \leq Z(t) \leq l_3$ for all $t \geq 0$ if $T(0) + T^*(0) + \frac{\Delta}{2n}V(0) + \frac{qh}{m}Z(0) \leq l_1$, where $l_2 = \frac{2n\Lambda}{\Delta\sigma}$ and $l_3 = \frac{m\Lambda}{qh\sigma}$. This proves the boundedness of T, T^*, V and Z.

The equilibrium points existence for the system (4)-(7) will be introduced in the following lemma:

Lemma 3 *Suppose that* $R_0 > 0$ *and* $R_1 > 0$ *be the fundamental threshold parameters of the model (4)-(7), then*

(i) *if* $R_0 \leq 1$, *then there is just one equilibrium point* Γ_0 *exists,*
(ii) *if* $R_0 > 1$ *and* $R_1 < 1$, *therefore two equilibrium points* Γ_0 *and* Γ_1 *exist.*
(iii) *if* $R_1 > 1$, *therefore three equilibrium points* Γ_0, Γ_1 *and* Γ_2 *exist.*

Proof. To obtain equilibrium points of the model (4)-(7), we put $D^{\alpha}T = D^{\alpha}T^{*} = D^{\alpha}V = D^{\alpha}Z = 0,$ then

$$0 = \Lambda - dT - \beta TV - kTT^{*}, \tag{9}$$

$$0 = \beta TV + kTT^{*} - \Delta T^{*} - qT^{*}Z, \tag{10}$$

$$0 = nT^{*} - cV, \tag{11}$$

$$0 = \frac{mT^{*}Z}{h+Z} - bZ. \tag{12}$$

From Eq. (12), we have two possibilities $Z = 0$ or $mT^{*} = b(h + Z)$ and if $Z = 0$ then Eq. (11) gives us

$$V = \frac{n}{c}T^{*}.$$

Substitute into Eq. (10), we get the equation

$$\left[\beta\frac{n}{c}T + kT - \Delta\right]T^{*} = 0.$$

If $T^{*} = 0$, then the model (4)-(7) has only uninfected equilibrium point $\Gamma_0 = (T_0, 0,0,0)$, where $T_0 = \frac{\Lambda}{d}$. If $\beta\frac{n}{c}T + kT - \Delta = 0$ and substitute into Eq. (9), the model has an immune absence equilibrium point $\Gamma_1 = (T_1, T_1^{*}, V_1, 0)$, where

$$T_1 = \frac{\Delta c}{(\beta n + kc)}, \qquad T_1^{*} = \frac{dc}{\beta n + kc}\left[\frac{(\beta n + kc)T_0}{\Delta c} - 1\right], \qquad V_1 = \frac{n}{c}T_1^{*}.$$

As a result, we may establish basic reproduction number for the system (4)-(7) by

$$\mathrm{R}_0 = \frac{(\beta n + kc)T_0}{\Delta c}.$$

So we can rewrite elements of Γ_1 as

$$T_1 = \frac{T_0}{\mathrm{R}_0}, \qquad T_1^{*} = \frac{dc}{\beta n + kc}(\mathrm{R}_0 - 1), \qquad V_1 = \frac{n}{c}T_1^{*}.$$

Hence, if $\mathrm{R}_0 \leq 1$, system (4)-(7) is stable and has a unique steady state Γ_0 and when $\mathrm{R}_0 > 1$, the system has two equilibrium points Γ_0 and Γ_1, note that when $\mathrm{R}_0 > 1$, the virus and infected cells are present, but the immune response is not presented. Also, we have an immune present equilibrium point $\Gamma_2 = (T_2, T_2^{*}, V_2, Z_2)$ when the second possibility $mT^{*} = b(h + Z)$ is realized, then

$$T_2^{*} = \frac{b}{m}(h + Z_2), \qquad V_2 = \frac{n}{c}T_2^{*} = \frac{nb}{mc}(h + Z_2). \tag{13}$$

By substituting into Eq. (9), we obtain

$$T_2 = \frac{\Lambda}{d+\frac{\Delta b \mathrm{R}_0}{mT_0}(h+Z_2)}, \tag{14}$$

therefore from Eq. (10), we have

$$\left(\frac{b}{m}\frac{(\beta n + kc)}{c}\frac{\Lambda}{d+\frac{\Delta b \mathrm{R}_0}{mT_0}(h+Z_2)} - \frac{\Delta b}{m} - \frac{qb}{m}Z_2\right)(h+Z_2) = 0.$$

If $h + Z_2 \neq 0$, then we get

$$\frac{\Lambda(\beta n + kc)}{c} - (\Delta + qZ_2)\left(d + \frac{\Delta b \mathrm{R}_0}{mT_0}(h+Z_2)\right) = 0.$$

The previous equation can be simplified to the form

$$\frac{\Delta q b \mathrm{R}_0}{mT_0}Z_2^2 + \left(\frac{\Delta^2 b \mathrm{R}_0}{mT_0} + qd + \frac{qhb\Delta \mathrm{R}_0}{mT_0}\right)Z_2 + \Lambda\left[\frac{m}{bh}\frac{dc(\mathrm{R}_0-1)}{(\beta n+kc)} - 1\right] = 0. \tag{15}$$

The last equation has a positive real root when $\frac{m}{bh}\frac{dc(\mathrm{R}_0-1)}{(\beta n+kc)} - 1 > 0$, so we can define a second threshold parameter R_1 as

$$\mathrm{R}_1 = \frac{m}{bh}\frac{dc(\mathcal{R}_0-1)}{(\beta n+kc)} = \frac{mT_1^*}{bh}.$$

When $\mathrm{R}_1 > 1$, there exist three equilibrium points Γ_0, Γ_1 and Γ_2, where Γ_2 is given by Eqs. (13) and (14) and Z_2 is determined from Eq. (15) by

$$Z_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A},$$

where,

$$A = \frac{\Delta q b \mathrm{R}_0}{mT_0},$$

$$B = \frac{\Delta^2 b \mathrm{R}_0}{mT_0} + qd + \frac{qhb\Delta \mathrm{R}_0}{mT_0},$$

$$C = \Lambda\left[\frac{m}{bh}\frac{dc(\mathrm{R}_0-1)}{(\beta n+kc)} - 1\right].$$

Where Γ_2 represents the state in which CTLs immune response is present.

4 LOCAL CHARACTERISTICS

This section demonstrates the results of stability in the local case. The Jacobian matrix that corresponds to the system (4)-(7) is

$$J=\begin{pmatrix} -d-\beta V-kT^{*} & -kT & -\beta T & 0 \\ \beta V+kT^{*} & kT-\Delta-qZ & \beta T & -qT^{*} \\ 0 & n & -c & 0 \\ 0 & \frac{mZ}{h+Z} & 0 & \frac{mhT^{*}}{(h+Z)^{2}}-b \end{pmatrix}. \tag{16}$$

Theorem 1 *The system (4)-(7) has equilibrium point* Γ_0 *is locally asymptotically stable if* $R_0<1$.

Proof. For equilibrium point Γ_0, the characteristic equation of the matrix (16) is given by follows:

$$|J-rI|=\begin{vmatrix} -d-r & -kT_0 & -\beta T_0 & 0 \\ 0 & kT_0-\Delta-r & \beta T_0 & 0 \\ 0 & n & -c-r & 0 \\ 0 & 0 & 0 & -b-r \end{vmatrix}=0. \tag{17}$$

It has been decreased to

$$(r+d)(r+b)((r+c)(kT_0-\Delta-r)+n\beta T_0)=0. \tag{18}$$

Clearly, Eq. (18) has the roots $r_1=-d<0$ and $r_2=-b<0$, which are negative, and the remaining roots are specified by

$$r^2+a_1r+a_2=0,$$

where,

$$a_1=(c+\Delta-kT_0),\quad a_2=c(\Delta-kT_0)-\beta nT_0,$$

if $a_1>0$ and $a_2>0$, then $R_0<1$, which means $r_3<0$ and $r_4<0$, is the required and sufficient condition to ensure Γ_0 local stability.

Theorem 2 *The equilibrium point* Γ_1 *of system (4)-(7) is locally asymptotically stable if* $R_1<1<R_0$.

Proof. The characteristic equation of the matrix (16) at the equilibrium point Γ_1 is as follows:

$$\begin{vmatrix} -d-\beta V_1-kT_1^{*}-r & -kT_1 & -\beta T_1 & 0 \\ \beta V_1+kT_1^{*} & kT_1-\Delta-r & \beta T_1 & -qT_1^{*} \\ 0 & n & -c-r & 0 \\ 0 & 0 & 0 & \frac{mT_1^{*}}{h}-b-r \end{vmatrix}=0, \tag{19}$$

it follows that,

$$\left(\frac{mT_1^*}{h} - b - r\right)\begin{vmatrix} -d - \beta V_1 - kT_1^* - r & -kT_1 & -\beta T_1 \\ \beta V_1 + kT_1^* & kT_1 - \Delta - r & \beta T_1 \\ 0 & n & -c - r \end{vmatrix} = 0.$$

Hence,

$$\left(\frac{mT_1^*}{h} - b - r\right)(r^3 + e_1 r^2 + e_2 r + e_3) = 0. \tag{20}$$

It is clear that, one of the roots of (20) is $r = \frac{mT_1^*}{h} - b = b(\mathrm{R}_1 - 1)$, which is a negative if $\mathrm{R}_1 < 1$. The remaining roots of (20) can be obtained from the following equation:

$$p(r) = r^3 + e_1 r^2 + e_2 r + e_3 = 0, \tag{21}$$

where,

$$e_1 = d + \beta V_1 + kT_1^* + c + \Delta - kT_1,$$

$$e_2 = (d + \beta V_1 + kT_1^*)(c + \Delta - kT_1) + c(\Delta - kT_1) - n\beta T_1 + kT_1(\beta V_1 + kT_1^*),$$

$$e_3 = (d + \beta V_1 + kT_1^*)[c(\Delta - kT_1) - n\beta T_1] + kT_1 c(\beta V_1 + kT_1^*) + n\beta T_1(\beta V_1 kT_1^*).$$

The discriminant $D(p)$ of $p(r)$ given in (21) is:

$$D(p) = \begin{pmatrix} 1 & e_1 & e_2 & e_3 & 0 \\ 0 & 1 & e_1 & e_2 & e_3 \\ 3 & 2e_1 & e_2 & 0 & 0 \\ 0 & 3 & 2e_1 & e_2 & 0 \\ 0 & 0 & 3 & 2e_1 & e_2 \end{pmatrix} = 18e_1e_2e_3 + (e_1e_2)^2 - 4e_3(e_1)^3 - 4(e_2)^3 - 27(e_3)^2.$$

According to [33], for the fractional Routh-Hurwitz criteria, equilibrium point Γ_1 is locally asymptotically stable if $\mathrm{R}_1 < 1 < \mathrm{R}_0$ and one of the following criteria are met.

(i) $D(p) > 0, e_1 > 0, e_3 > 0, e_1e_2 > e_3$;

(ii) $D(p) < 0, e_1 \geq 0, e_2 \geq 0, e_3 > 0,\ for\ \alpha < 2/3$;

(iii) $D(p) < 0, e_1 > 0, e_2 > 0, e_1e_2 = e_3\ \ for\ \alpha \in (0,1)$.

5 GLOBAL CHARACTERISTICS

In this section, we shall prove globally asymptotical stability of Γ_0, Γ_1 and Γ_2 of model (4)-(7).

Theorem 3 *For model (4)-(7), if* $R_0 < 1$, *then* Γ_0 *is globally asymptotically stable.*

Proof. Let us define a Lyapunov function $L_0(T, T^*, V, Z)$ as:

$$L_0(T, T^*, V, Z) = T - T_0 - T_0 \ln \frac{T}{T_0} + T^* + \frac{\beta T_0}{c} V + \frac{qh}{m} Z$$

Clearly $L_0(T, T^*, V, Z) > 0$ for all $T, T^*, V, Z > 0$ and $L_0(T_0, 0,0,0) = 0$. Calculating $\frac{d^\alpha L_0}{dt^\alpha}$ along the model (4)-(7), we obtain

$$D^\alpha L_0 = \left(1 - \frac{T_0}{T}\right)[\Lambda - dT - \beta TV - kTT^*] + \beta TV + kTT^* - \Delta T^* - qT^* Z + \frac{\beta T_0}{c}[nT^* - cV] + \frac{qh}{m}\left[\frac{mT^* Z}{h + Z(t)} - bZ(t)\right].$$

Using $\Lambda = dT_0$, we get

$$D^\alpha L_0 = dT_0\left(2 - \frac{T_0}{T} - \frac{T}{T_0}\right) + \left[kT_0 + \frac{\beta n T_0}{c} - \Delta\right]T^* - qT^* Z + \frac{qhT^* Z}{h + Z} - \frac{qhb}{m} Z$$

$$= \frac{-d(T - T_0)^2}{T} + \Delta(\mathrm{R}_0 - 1)T^* - \frac{qT^* Z^2}{h + Z} - \frac{qhb}{m} Z.$$

Clearly if $\mathrm{R}_0 < 1$, then $D^\alpha L_0 \leq 0$ for all $T, T^*, V, Z > 0$. Moreover $D^\alpha L_0 = 0$ if and only if $T(t) = T_0$, $T^*(t) = 0$ and $Z(t) = 0$. Let $\mathcal{F}_0 = \{(T, T^*, V, Z): D^\alpha L_0 = 0\}$ and $\mathcal{F}'_0$ be the largest invariant subset of $\mathcal{F}_0$. The model (4)-(7) solutions tend to $\mathcal{F}'_0$. For each element in $\mathcal{F}'_0$ we have $T(t) = T_0$, $T^*(t) = 0$ and $Z(t) = 0$. Thus Eq. (6) yields

$$D^\alpha V(t) = 0 = nT^*(t) - cV(t).$$

Hence $V(t) = 0$. Consequently, $\mathcal{F}'_0$ only includes one point $\Gamma_0 = (T_0, 0,0,0)$. According to LaSalle's invariance principle (LIP), Γ_0 is GAS when $\mathrm{R}_0 < 1$.

Theorem 4 *For the model (4)-(7),* Γ_1 *is globally asymptomatic stable if* $R_1 < 1 < R_0$.

Proof. Constructing a Lyapunov function $L_1(T, T^*, V, Z)$ as:

$$L_1(\mathrm{T}, T^*, \mathrm{V}, \mathrm{Z}) = T - T_1 - T_1 \ln \frac{T}{T_1} + T^* - T_1^* - T_1^* \ln \frac{T^*}{T_1^*} + \frac{\beta T_1}{c}\left[V - V_1 - V_1 \ln \frac{V}{V_1}\right] + \frac{qT_1^*}{b} Z$$

Clearly $L_1(T,T^*,V,Z) > 0$ for all $T,T^*,V,Z > 0$ and $L_1(T,T^*,V,Z) = 0$ only when $T = T_1, T^* = T_1^*, V = V_1, Z = Z_1$. Moreover

$$D^\alpha L_1 = \left(1-\frac{T_1}{T}\right)[\Lambda - dT - \beta TV - kTT^*] + \left(1-\frac{T_1^*}{T^*}\right)[\beta TV + kTT^* - qT^*Z] + \frac{\beta T_1}{c}\left(1-\frac{V_1}{V}\right)[nT^* - cV] + \frac{qT_1^*}{b}\left[\frac{mT^*Z}{h+Z} - bZ\right]$$

$$= \left(1-\tfrac{T_1}{T}\right)(\Lambda - dT) + \beta T_1 V + kT_1T^* - \Delta T^* - qT^*Z - \tfrac{T_1^*}{T^*}(\beta TV + kTT^*) + \Delta T_1^* + qT_1^*Z + \tfrac{\beta T_1}{c}nT^* - \beta T_1 V - \tfrac{\beta T_1 V_1}{cV}nT^* + \beta T_1 V_1 + \tfrac{qT_1^*}{b}\tfrac{mT^*Z}{h+Z} - qT_1^*Z. \quad (22)$$

Applying the steady state conditions for Γ_1:

$$\Lambda = dT_1 + \beta T_1 V_1 + kT_1T_1^*,$$

$$\Delta T_1^* = \beta T_1 V_1 + kT_1T_1^*,$$

$$nT_1^* = cV_1,$$

we get

$$D^\alpha L_1 = d\left(2 - \tfrac{T_1}{T} - \tfrac{T}{T_1}\right) + \beta T_1 V_1\left(3 - \tfrac{T_1}{T}\right) + kT_1T_1^*\left(2 - \tfrac{T_1}{T}\right) - \tfrac{T^*}{T_1^*}[\beta T_1 V_1 + kT_1T_1^*] + kT_1T^* - qT^*Z - \tfrac{T_1^*}{T^*}\beta TV - kTT_1^* + \beta T_1 V_1 \tfrac{T^*}{T_1^*} - \beta T_1 V_1 \tfrac{V_1 T^*}{VT_1^*} + \tfrac{qT_1^*}{b}\tfrac{mT^*Z}{h+Z}. \quad (23)$$

Eq. (23) can be simplified to

$$D^\alpha L_1 = d\left(2 - \frac{T_1}{T} - \frac{T}{T_1}\right) + \beta T_1 V_1\left[3 - \frac{T_1}{T} - \frac{T_1^*TV}{T^*T_1V_1} - \frac{T^*V_1}{T_1^*V}\right]$$

$$+kT_1T_1^*\left(2 - \frac{T_1}{T} - \frac{T}{T_1}\right) + \frac{qhT^*Z}{h+Z}(\mathrm{R}_1 - 1) - \frac{qT^*Z^2}{h+Z}.$$

Applying the relationship of geometrical and arithmetical means, we are able to write

$$2 \le \frac{T_1}{T} + \frac{T}{T_1},$$

$$3 \le \frac{T_1}{T} + \frac{T_1^*TV}{T^*T_1V_1} + \frac{T^*V_1}{T_1^*V},$$

and if $\mathrm{R}_1 < 1$, we get that $D^\alpha L_1 \le 0$ and $D^\alpha L_1 = 0$ at the point $(T_1, T_1^*, V_1, 0)$. Let $\mathcal{F}'_1$ be the largest invariant subset of the set $\{(T,T^*,V,Z): D^\alpha L_1 = 0\}$. The model solutions therefore tend to $\mathcal{F}'_1$. Since it is obvious that $\mathcal{F}'_1$ includes the single point Γ_1 so global asymptotic stability of Γ_1 results from (LIP).

Theorem 5 *For the model (4)-(7), if Γ_2 exists then it is global asymptomatic stable.*
Proof. Constructing a function $L_2(T,T^*,V,Z)$ as:

$$L_2(T,T^*,V,Z) = T - T_2 - T_2\ln\frac{T}{T_2} + T^* - T_2^* - T_2^*\ln\frac{T^*}{T_2^*} + \frac{\beta T_2}{c}\left[V - V_2 - V_2\ln\frac{V}{V_2}\right] + \frac{qT_2^*}{b}\left[Z - Z_2 - Z_2\ln\frac{Z}{Z_2}\right].$$

Clearly, $L_2(T,T^*,V,Z) > 0$ for all $T,T^*,V,Z > 0$ and $L_2(T_2,T_2^*,V_2,Z_2) = 0$. Moreover,

$$D^\alpha L_2 = \left(1 - \frac{T_2}{T}\right)[\Lambda - dT - \beta TV - kTT^*] + \left(1 - \frac{T_2^*}{T^*}\right)[\beta TV + kTT^* - \Delta T^* - qT^*Z] + \frac{\beta T_2}{c}\left(1 - \frac{V_2}{V}\right)[nT^* - cV] + \frac{qT_2^*}{b}\left(1 - \frac{Z_2}{Z}\right)\left[\frac{mT^*Z}{h+Z} - bZ\right]$$

$$= \left(1 - \frac{T_2}{T}\right)(\Lambda - dT) + kT_2T^* - \Delta T^* - qT^*Z - \frac{T_2^*}{T^*}(\beta TV + kTT^*) + \Delta T_2^* + \frac{\beta T_2}{c}nT^* - \frac{\beta T_2V_2}{cV}nT^* + \beta T_2V_2 + \frac{qT_2^*}{b}\frac{mT^*Z}{h+Z} - \frac{qT_2^*}{b}\frac{mT^*Z_2}{h+Z} + qT_2^*Z_2. \quad (24)$$

Implementing conditions of the equilibrium point Γ_2, we get:

$$\Lambda = dT_2 + \beta T_2V_2 + kT_2T_2^*,$$

$$(\Delta + qZ_2)T_2^* = \beta T_2V_2 + kT_2T_2^*,$$

$$nT_2^* = cV_2,$$

$$\frac{m}{b}T_2^* = h + Z_2,$$

we get

$$D^\alpha L_2 = d\left(2 - \frac{T_2}{T} - \frac{T}{T_2}\right) + \beta T_2V_2\left(3 - \frac{T_2}{T} - \frac{T_2^*TV}{T^*T_2V_2}\right) + kT_2T_2^*\left(2 - \frac{T_2}{T} + \frac{T^*}{T_2^*} - \frac{T}{T_2}\right) - \Delta T^* - qT^*Z_2 - qT^*(Z - Z_2) + \beta T_2V_2\frac{T^*}{T_2^*} - \beta T_2V_2\frac{V_2T^*}{VT_2^*} + \frac{qT_2^*}{b}\frac{mT^*(Z-Z_2)}{h+Z}. \quad (25)$$

Eq. (25) can be simplified to

$$D^\alpha L_2 = d\left(2 - \frac{T_2}{T} - \frac{T}{T_2}\right) + \beta T_2V_2\left[3 - \frac{T_2}{T} - \frac{T_2^*TV}{T^*T_2V_2} - \frac{T^*V_2}{T_2^*V}\right] + kT_2T_2^*\left(2 - \frac{T_2}{T} - \frac{T}{T_2}\right) - \frac{qT^*(Z - Z_2)^2}{h+Z}.$$

Applying the relationship of geometrical and arithmetical means, we get $D^\alpha L_2 \le 0$ and $D^\alpha L_2 = 0$ at the point (T_2,T_2^*,V_2,Z_2). Let $\mathcal{F}'_2$ be the most extensive invariant subset of the set $\{(T,T^*,V,Z): D^\alpha L_2 = 0\}$. Consequently, the model solutions tend to $\mathcal{F}'_2$. There is no doubt that $\mathcal{F}'_2$ includes a single point Γ_2 and this ensure global asymptotic stablility of Γ_2 as a result of (LIP).

6 NUMERICAL SIMULATIONS AND DISSECTION

To validate our theoretical findings, we provide various instances and run numerical simulations in this section. MATLAB is used to run the numerical computations. Using the parameters values listed in Table 1, we will carry out numerical simulations for the system (4)-(7). We will pick the following three beginning conditions:

IC1: $T(0) = 900,\ T^*(0) = 50,\ V(0) = 100,\ Z(0) = 5.5,$

IC2: $T(0) = 600,\ T^*(0) = 30,\ V(0) = 50,\ Z(0) = 4.5,$ and

IC3: $T(0) = 300,\ T^*(0) = 20,\ V(0) = 30,\ Z(0) = 3.5.$

6.1 Stability behavior of equilibrium points

Taking $\alpha = 0.97$ and according to Table 1. While the parameters β, k and m are varied as following:

Case (i): Stability of Γ_0: If $\beta = 0.001,\ k = 0.0008$ and $m = 0.03$ then we find that $R_0 = 0.6598 < 1$. According to Lemma 3, the system has a single equilibrium point $\Gamma_0 = (1300,0,0,0)$. As shown in Figure 2, the numerical outcomes confirm theoretical outcomes of Theorem 3 and the solutions of the system approach to Γ_0 for all **IC1**-**IC3**.

Case (ii): Stability of Γ_1: If $\beta = 0.003$, $k = 0.002$ and $m = 0.03$, then $R_1 = 0.6290 < 1 < R_0 = 1.7713$. Clearly, $\Gamma_1 = (733.9450,45.2844,21.2271,0)$ exists and is globally asymptotic stable, and this support the findings in Theorem 4. This is shown in Figure 3. In this case, we can observe that when β and k increase, the concentration of uninfected cells decreases while concentration of infected cells and pathogens increases and the CTL immune response is unstimulated.

Case (iii): Stability of Γ_2: If $\beta = 0.003,\ k = 0.002$ and $m = 0.3$ then $R_1 = 6.2895 > 1$. Figure 4 show that $\Gamma_2 = (775.040,39.563,18.021,3.645)$ exists and is globally asymptotic stable, which corresponds with Theorem 5. Therefore, chronic HIV infection with CTL-mediated immune response has been achieved.

6.2 The influence of production rate m of CTL

Parameter values in Table 1 are used with $\beta = 0.005,\ k = 0.008,\ \alpha = 0.97,$ considering **IC2** and different values of m. We demonstrated in Figure 5 that increasing the CTL response parameter m can reduce the number of infected cells and HIV viral load while increasing the concentration of uninfected cells.

6.3 The influence of CTL killing rate q

Using Table 1 and taking $\beta = 0.005,\ k = 0.008,\ m = 0.3,\ \alpha = 0.97,$ with

different values of q, Figure 6 indicates that increasing the CTL killing rate q can reduce the HIV viral level and increasing the concentration of uninfected cells.

6.4 The influence of fractional-order agent α on stability of equilibrium points

Consider another group of initial conditions as **IC4:** $T(0) = 600$, $T^*(0) = 20$, $V(0) = 80$, $Z(0) = 5$. Figures 7 and 8 show the effect of fractional-order α on the system solutions for examples **Case(i)** and **Case(iii)** in the previous Subsection 6.1. According to the numerical simulations with the comparison between the results of the fractional order and integer model, if $R_0 < 1$ and the fractional-order agent α value increases, uninfected cells increase accordingly, while the remaining concentrations approach zero. While the fractional order parameter α has no effect on the global dynamics of our model if $R_0 > 1$, but it can affect the time for arriving to the steady states and reduces the oscillations. The fractional-order enhances the dynamics of the system and increases stability region of the equilibrium points.

Parameter	Value	Description
Λ	260	Production rate of uninfected CD4 T cells
d	0.2	Death rate of uninfected cells
β	varied	Infection rate by free virus
k	varied	Cell-to-cell viral transmissions rate
Δ	2.5	Death rate of infected CD4 T cells
q	0.04	Rate of killed infected cells by CTLs
n	1.5	proliferation rate of free virus
c	3.2	Clearance of viral load
m	*varied*	Production rate of CTLs by infected cells
h	0.8	Saturation constant
b	2.7	Death rate of CTLs cells

Table 1: Parameters values of the model (4)-(7).

7 CONCLUSION

In this paper, HIV type 1 infection model with saturated CTL immune response beside to two types of transmission have been considered. We proved that the proposed model solutions are bounded. We proved that the model exists with three possible

equilibrium points: an infection-free equilibrium Γ_0, an immune-free equilibrium Γ_1, an infection equilibrium with CTL response Γ_2, depending on the threshold parameters. We presented two threshold parameters: the basic reproductive rate of HIV-1 infection R_0 and the CTL immune reproductive rate R_1. These govern the dynamic behaviour of the model as well as whether or not the equilibrium point exists. In order to verify the theoretical findings and investigate how the fractional-order affects the model solutions and the system's dynamic behavior, we lastly conducted some numerical computations. We have assumed in this paper that HIV-1 attacks only one target cell which is $CD4^+$ T cells, but some studies have shown that the virus attacks multiple target cells so the work can be improved by considering the infection between the virus and two targets cells or more. We will keep these points in mind for future work.

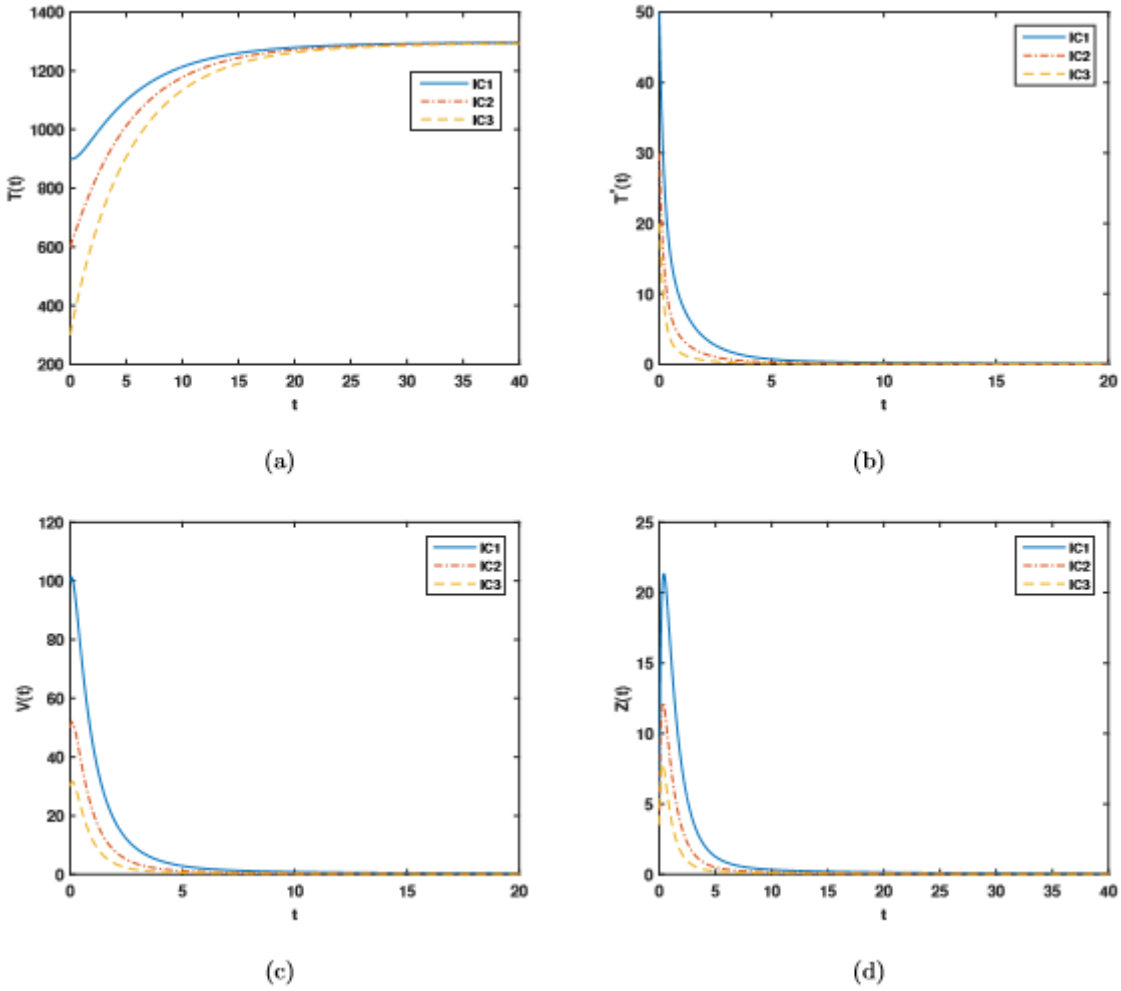

Figure 2: System (4)-(7) state trajectories with $R_0 = 0.6598 < 1$ and initial conditions IC1-IC3.

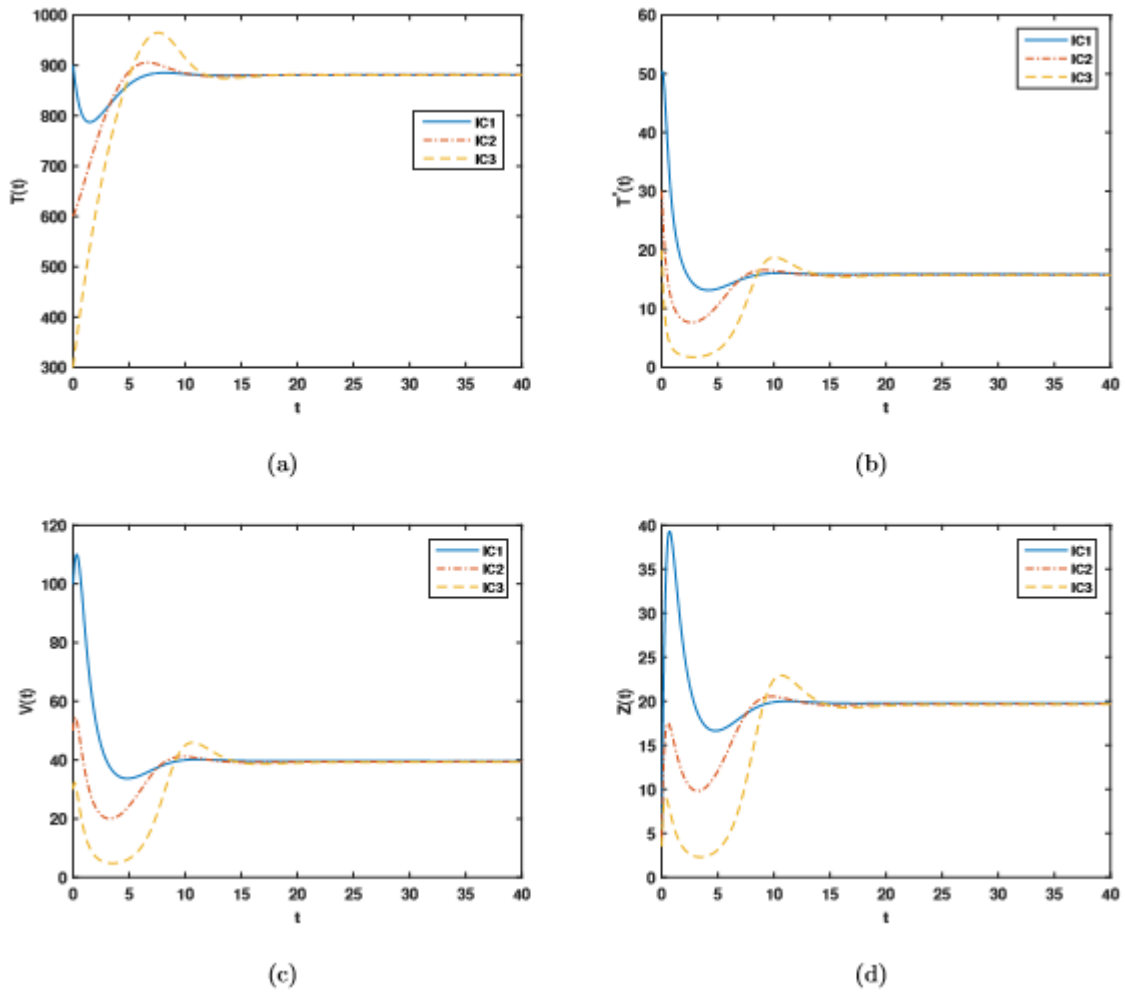

Figure 3: System (4)-(7) state trajectories with $R_1 = 0.6290 < 1 < R_0 = 1.7713 > 1$ and initial conditions IC1-IC3.

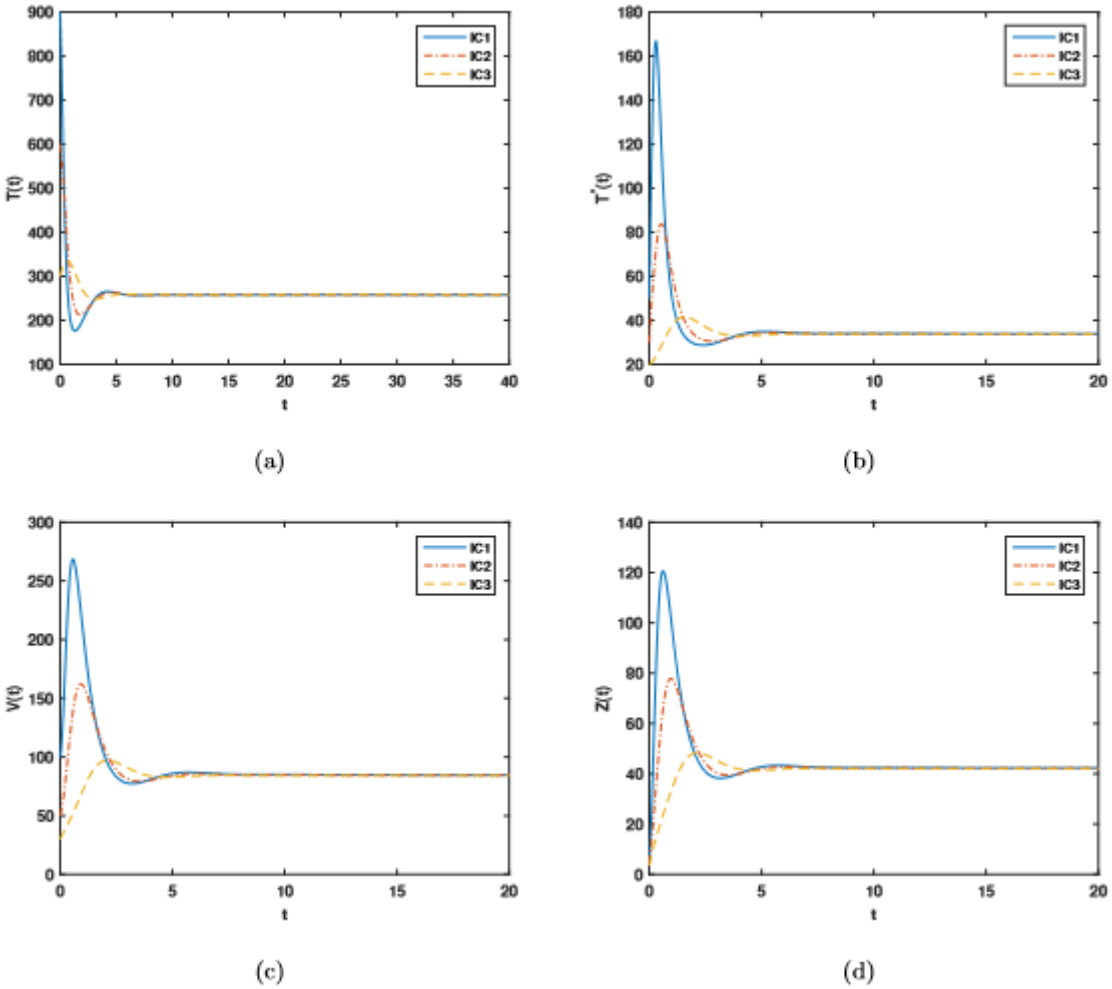

Figure 4: System (4)-(7) state trajectories with $R_1 = 6.2895 > 1$ and initial conditions IC1-IC3.

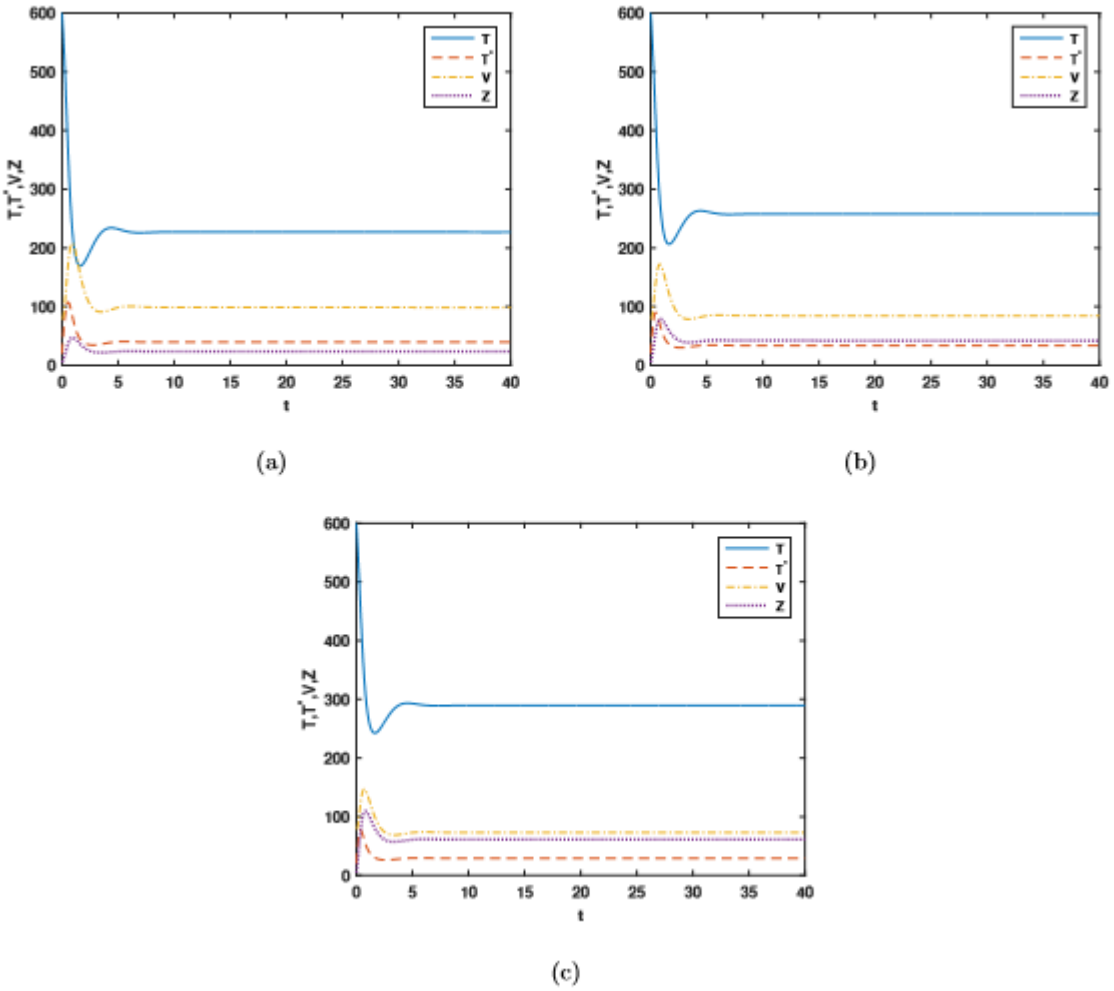

Figure 5: The influence of CTL response rate m. (a) $m = 0.3$, (b) $m = 1.3$ and (c) $m = 2.3$

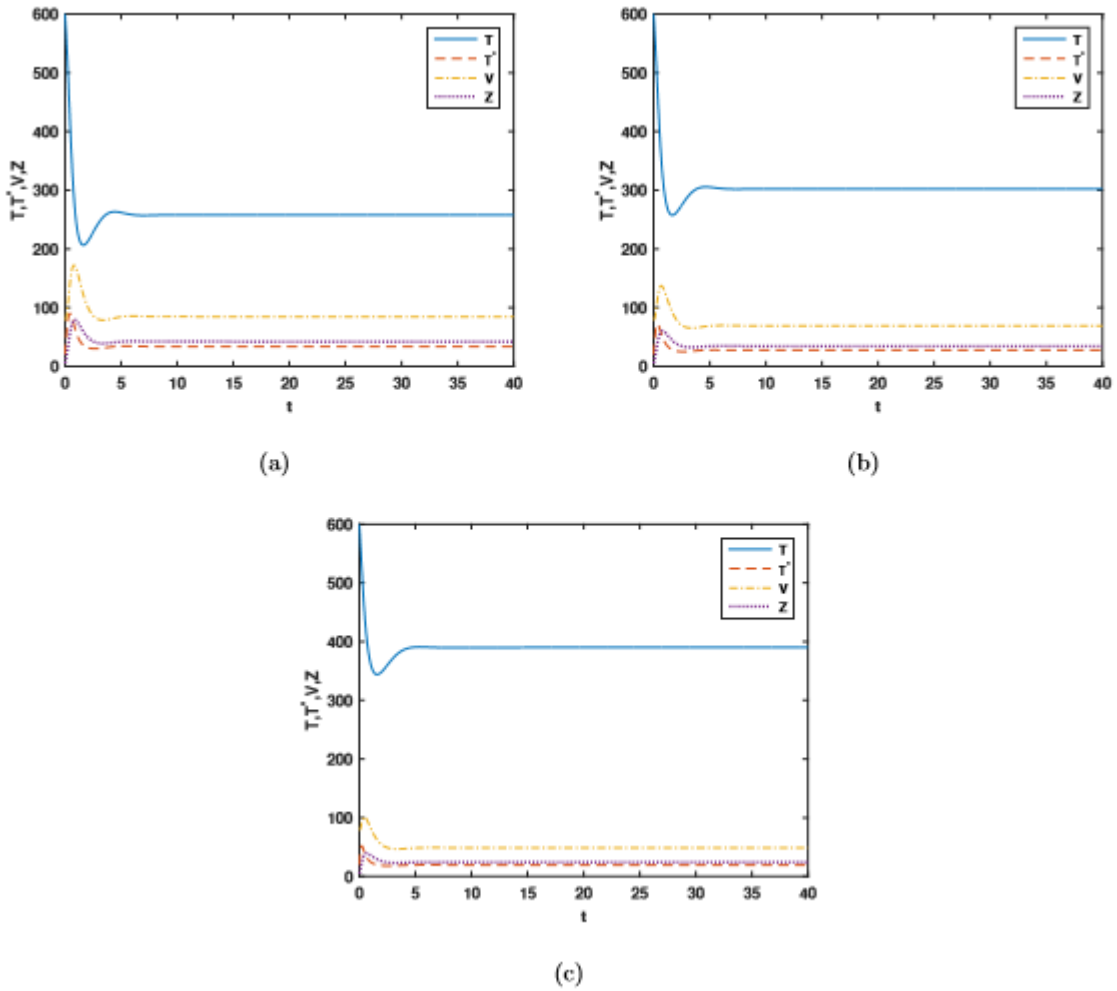

Figure 6: The influence of CTL killing rate q. (a)$q = 0.04$, (b)$q = 0.08$ and (c)$q = 0.2$

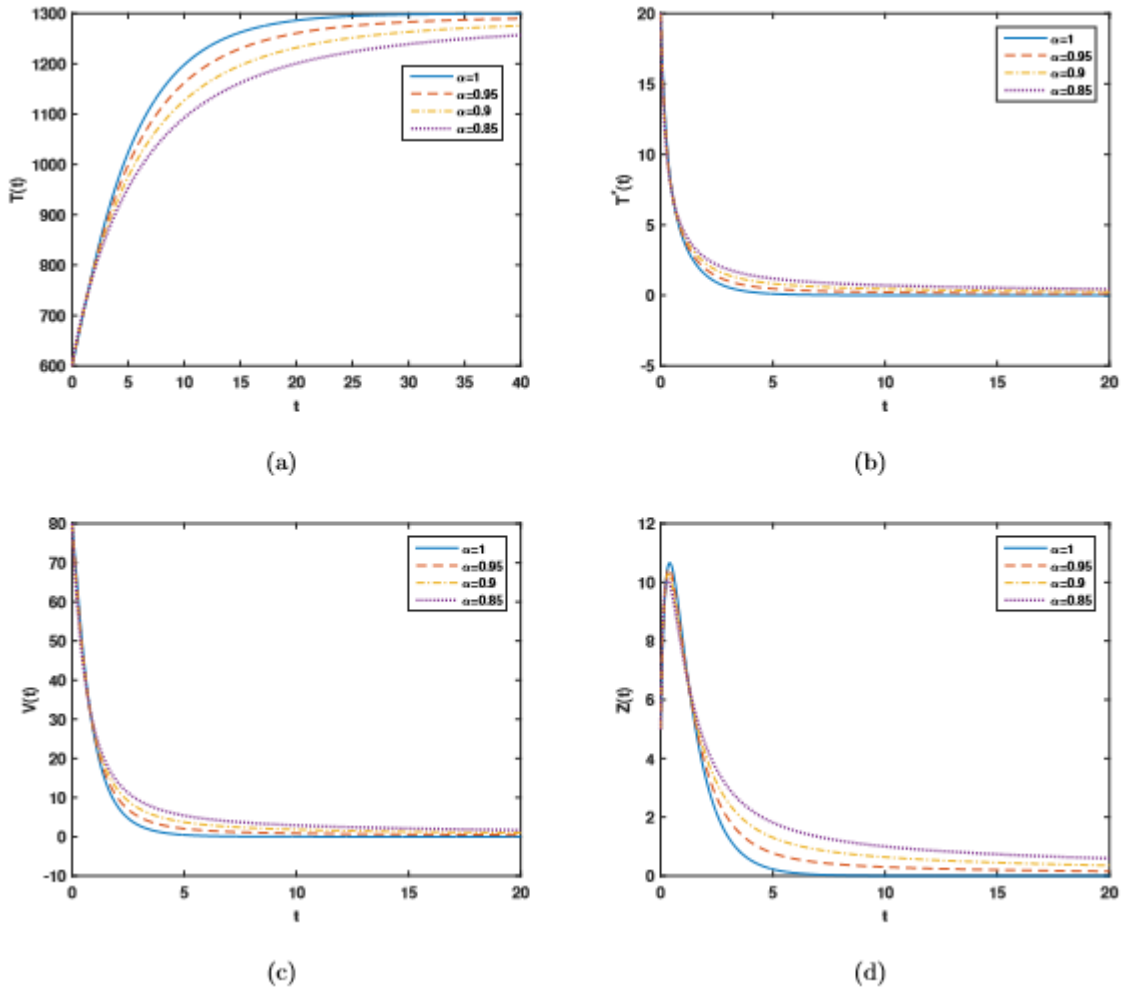

Figure 7: System (4)-(7) state trajectories with the initial conditions (600,20,80,5) and different values of α when $R_0 = 0.6598 < 1$.

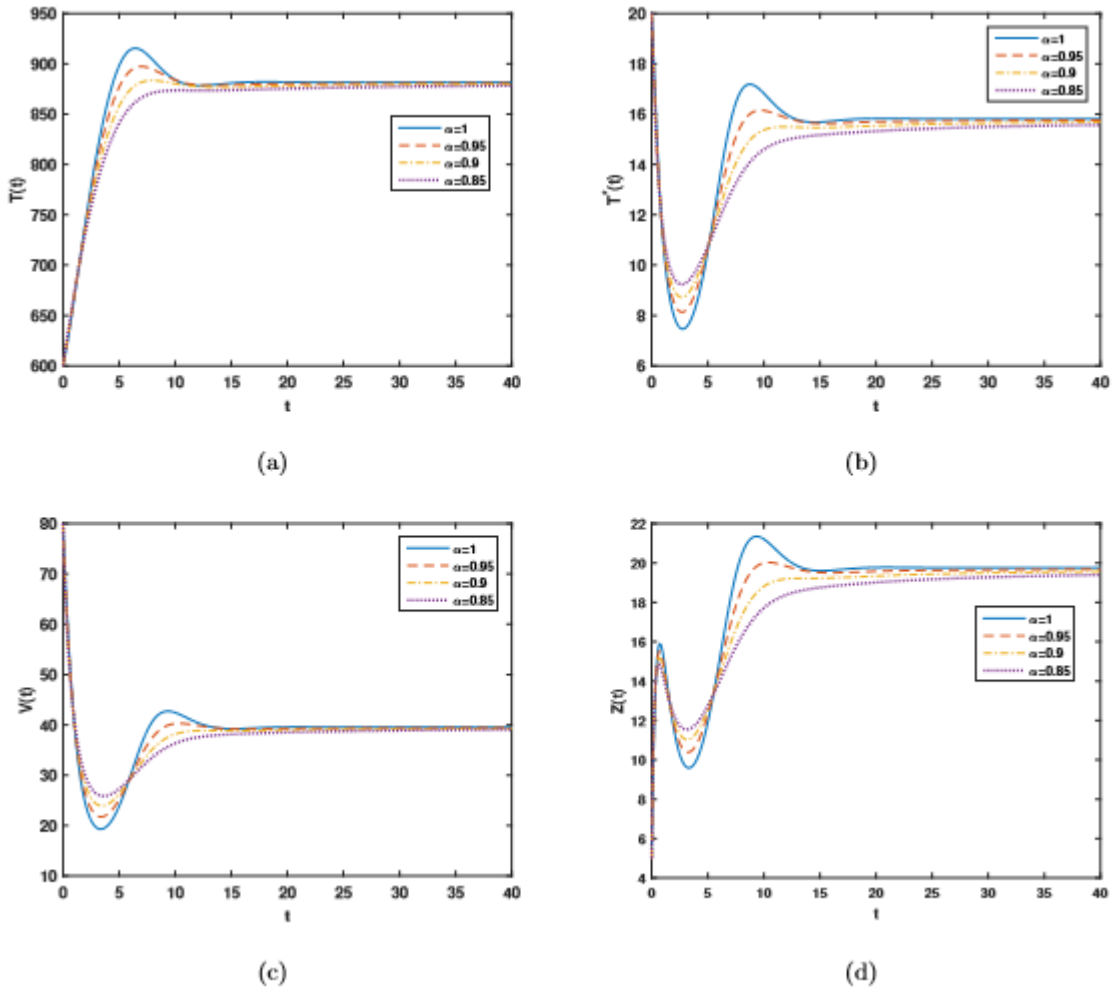

Figure 8: System (4)-(7) state trajectories with the initial conditions (600,20,80,5) and different values of α when $R_1 = 6.2895 > 1$.

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