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A General Fractional-Order Viral Infection Model with Cell-to-Cell Transmission and Adaptive Immunity

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Abstract: We propose a general fractional-order viral infection model with adaptive immune response including both productively infected cells and latently infected cells. This model incorporates two ways of infection, one by virus-to-cell and other by cell-to-cell transmissions, which are modeled by general nonlinear incidence functions. We first show that the proposed model is mathematically and biologically well-posed. Stability analysis of different steady states is explicitly performed and five threshold parameters are identified which determine clearance or maintenance of infection. In addition, we examine the robustness of the model to certain parameters by examining the reproduction numbers. Finally, we present numerical simulations that confirm which our model predicts well the evolution of viral infection.

Keywords: Viral infection, adaptive immunity, Caputo fractional derivative, stability.

1 Introduction

During viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), the adaptive immune response plays a crucial role in the control of infection process. This response is generated by two arms of immunity. The first one based on antibodies, called humoral immunity, is programmed to eradicate viral pathogens, while the second one mediated by Cytotoxic Lymphocytes Cells (CTL), called cellular immunity, is programmed to destroy infected cells. Thus, modeling the role of the immune response in viral infection dynamics have attracted the attention of many researchers during the last years. Some authors have only considered the humoral immunity [1,2,3,4] or cellular immunity [5,6,7,8] and others by both arms of immunity [9,10,11]. Nevertheless, these studies assumed that the infected cells are directly productive and the susceptible host cells become infected only due to virus-to-cell contact. In reality, the viral pathogens can spread by two modes: one by virus-to-cell contact and the other by direct cell-to-cell transmission and, there is also a delay between the moment of infection and the production of virions.

For these reasons, variant mathematical models have been used to study the impact of the immune response in viral infections including the two modes of transmission and the latently infected cells. Guo et al. [12] have studied the global stability of an HIV model with both modes of transmissions by assuming that all the infected cells are productive. In [13], an HIV latent infection model including both modes of transmission has been developed but without immune response. In [14], Hobiny et al. improved the model given in [13] by considering the role of humoral immunity. In the same year, Elaiw et al. [15] developed the model of Guo by considering only the role of CTL immune response. However, all the above models have been formulated by ordinary differential equations (ODEs) in which the memory effect is neglected while the immune response involves memory [16,17,18].

Fractional differential equations (FDEs) are a generalization of ODEs to arbitrary order and they have been used to model real phenomena with memory which exists in most biological systems[19,20,21]. The main advantage of FDEs is

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that involve memory which means that if we want to compute the fractional derivative at a current state $t = t_1$ it is necessary to take into account all the previous complete history from the starting point $t = t_0$ up to the point $t = t_1$. So, modeling viral infection dynamics by FDEs has drawn the attention of several authors [22,23,24,25,26,27,28,29,30,31,32,33,34,35]. Recently, Miao et al. [36] have studied the global dynamics of a fractional-order HIV model with both virus-to-cell and cell-to-cell transmissions but without considering the effect of the immune response. Furthermore, the incidence rate is assumed to be bilinear that is insufficient to describe the infection process in detail [37]. To our knowledge, there have been few fractional viral infection models considering the two modes of transmission and adaptive immunity.

Inspired by the works in [12,13,14,15,36], the main purpose of the current study is to develop a fractional-order viral infection model taking into consideration two modes of infections, two arms of immunity (humoral and cellular), and both latently and actively infected cells. We need to stress that the two modes of transmission considered here are modeled by general incidence functions that generalize the most common types existing in the literature such as bilinear incidence rate, the saturated function, and the Crowley-Martin functional response.

The rest of the paper is organized as follows. In the next section, we present our proposed model and give some properties of the solutions. The existence of equilibria is discussed in section 3 and the global stability is investigated in section 4. In section 5, we examine the sensitivity of the basic reproduction numbers with respect to some parameters of the model. Our theoretical results are illustrated by numerical simulations in section 6.

2 Model formulation and preliminaries

Motivated by the aforementioned discussions, we propose a general viral infection model with two modes of infections, adaptive immune response, and both latently and actively infected cells which is described by the following fractional nonlinear system:

$$\begin{cases} D^{\alpha}x(t) &= \lambda - dx - F(x)[H(v)v + G(y)y], \\ D^{\alpha}l(t) &= (1-\rho)F(x)[H(v)v + G(y)y] - (m+\gamma)l, \\ D^{\alpha}y(t) &= \rho F(x)[H(v)v + G(y)y] + \gamma l - ay - pyz, \\ D^{\alpha}v(t) &= ky - \mu v - qvw, \\ D^{\alpha}w(t) &= gvw - hw, \\ D^{\alpha}z(t) &= cyz - bz, \end{cases} \tag{1}$$

where, the variables $x(t)$, $l(t)$, $y(t)$, $v(t)$, $w(t)$ and $z(t)$ represent the concentrations of susceptible host cells, infected cells in latent stage, productively infected cells, free virus particles, antibodies and CTL cells at time t, respectively. Susceptible host cells are assumed to be produced at a constant rate λ, die at the rate dx and become infected by free virus or by direct contact with an infected cell at the rate $F(x)[H(v)v + G(y)y]$, where the fractions ρ and $1-\rho$ with $\rho \in (0,1)$ are the probabilities that an uninfected cell will transform into a latent or active infected cell, respectively. Latently infected cells die at the rate ml and become productively infected cells at the rate γl. Productively infected cells die at the rate ay and are killed by CTL cells at the rate pyz. Free virus particles are produced from productively infected cells at the rate ky, cleared at the rate μv and are neutralized by antibodies at the rate qvw. Antibodies are activated against the virus at the rate gvw and die at the rate hw. CTL cells develop in response to the productively infected cells at the rate cyz and die at the rate bz.

In (1), we adopt the fractional derivative in the sense of Caputo D^{α}, with $0 < \alpha \leq 1$, defined for an arbitrary function φ by [38]

$$D^{\alpha}\varphi(t) = \frac{1}{\gamma(1-\alpha)} \int_0^t \frac{\varphi^{'}(u)}{(t-u)^{\alpha}} du,$$

to have the same initial conditions as the ODEs. In addition, we mention that system (1) becomes a system formulated by ODEs when $\alpha = 1$.

As in [39,40,41], the functions F, H and G are assumed to be continuously differentiable in $\mathbb{R}_+$ and satisfy the following assumptions:

$$F(0) = 0, \quad F^{'}(x) > 0 \quad \text{for all } x \geq 0, \tag{H_1}$$

$$H(v) > 0 \ \text{ and } \ H^{'}(v) \leq 0, \quad \text{for all } \ v \geq 0, \tag{H_2}$$

$$G(y) > 0, \ \text{ and } \ G^{'}(y) \leq 0, \quad \text{for all } \ y \geq 0. \tag{H_3}$$

Now, we prove that the cell-numbers are non-negative and bounded for all $t \geq 0$. To do so, we assume, for biological reasons, that the initial conditions of (1) are non-negative:

$$x(0) \geq 0, l(0) \geq 0, y(0) \geq 0, v(0) \geq 0, w(0) \geq 0, z(0) \geq 0. \tag{2}$$

Theorem 21 *For any initial conditions satisfying (2), the initial-value problem* (1)-(2) *has a unique solution on* $[0,+\infty)$. *Moreover, this solution remains non-negative and bounded for all* $t \geq 0$.

Proof. According to [42], it is clear that the problem (1)-(2) has a unique local solution.

Next, we show that this solution is non-negative. From (1), we have

$$\begin{aligned}
D^{\alpha}x(t)|_{x=0} &= \lambda \geq 0,\\
D^{\alpha}l(t)|_{l=0} &= (1-\rho)F(x)[H(v)v+G(y)y] \geq 0,\\
D^{\alpha}y(t)|_{y=0} &= \rho F(x)H(v)v+\gamma l \geq 0,\\
D^{\alpha}v(t)|_{v=0} &= ky \geq 0,\\
D^{\alpha}w(t)|_{w=0} &= 0 \geq 0,\\
D^{\alpha}z(t)|_{z=0} &= 0 \geq 0.
\end{aligned}$$

As in [22, Theorem 2.7], we deduce that the solution of (1)-(2) is non-negative.

To establish the boundedness of solutions, it is sufficient to prove the boundedness of the function $T(t)$ defined as

$$T(t) = x(t)+l(t)+y(t)+\frac{a}{2k}v(t)+\frac{aq}{2kg}w(t)+\frac{p}{c}z(t).$$

So, we have

$$\begin{aligned}
D^{\alpha}T(t) &= D^{\alpha}x(t)+D^{\alpha}l(t)+D^{\alpha}y(t)+\frac{a}{2k}D^{\alpha}v(t)+\frac{aq}{2kg}D^{\alpha}w(t)+\frac{p}{c}D^{\alpha}z(t)\\
&= \lambda - dx(t) - ml(t) - \frac{a}{2}y(t) - \frac{a\mu}{2k}v(t) - \frac{aqh}{2kg}w(t) - \frac{pb}{c}z(t)\\
&\leq \lambda - \delta T(t),
\end{aligned}$$

where $\delta = \min\{d, m, \frac{a}{2}, \mu, h, b\}$. Therefore,

$$T(t) \leq T(0)E_{\alpha}(-\delta t^{\alpha}) + \frac{\lambda}{\delta}[1-E_{\alpha}(-\delta t^{\alpha})],$$

where E_{α} is the Mittag-Leffler function [38]. Since $0 \leq E_{\alpha}(-\delta t^{\alpha}) \leq 1$, we get

$$T(t) \leq T(0) + \frac{\lambda}{\delta}.$$

Since the function T is non-negative and written as a linear combination of all the variables of system (1), this implies that the solution of problem (1)-(2) is bounded for $t \geq 0$.

Finally, based on the results in [42, Theorem 3.1 and Remark 3.2], we conclude that the initial value problem (1)-(2) has a unique solution in $[0,+\infty)$. This completes the proof. ■

3 Existence of equilibria

In this section, we discuss the existence of biological equilibria for system (1). It is clear that system (1) has always an infection-free equilibrium $E_0\left(\frac{\lambda}{d},0,0,0,0,0\right)$. Therefore, we define the basic reproduction number of our system (1) as

$$R_0 = R_0^1 + R_0^2, \tag{3}$$

where $R_0^1 = \dfrac{k(\rho m+\gamma)H(0)F(\lambda/d)}{a\mu(m+\gamma)}$ is the basic reproduction number corresponding to the virus-to-cell infection while $R_0^2 = \dfrac{(\rho m+\gamma)G(0)F(\lambda/d)}{a(m+\gamma)}$ is the basic reproduction number corresponding to the cell-to-cell transmission.

To find the other equilibriums, we let the right-hand side of system (1) equal to zero

$$\lambda - dx - F(x)[H(v)v + G(y)y] = 0, \tag{4}$$
$$(1-\rho)F(x)[H(v)v + G(y)y] - (m+\gamma)l = 0, \tag{5}$$
$$\rho F(x)[H(v)v + G(y)y] + \gamma l - ay - pyz = 0, \tag{6}$$
$$ky - \mu v - qvw = 0, \tag{7}$$
$$gvw - hw = 0, \tag{8}$$
$$cyz - bz = 0. \tag{9}$$

The last two equations (8) and (9) imply that $w = 0$ or $v = \dfrac{h}{g}$ and $z = 0$ or $y = \dfrac{b}{c}$. Then we discuss four cases.

Case 1 : If $w = 0$ and $z = 0$. By the equations (4)-(7), we have $l = \dfrac{(1-\rho)(\lambda - dx)}{m+\gamma}$, $y = \dfrac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}$, $v = \dfrac{k(\rho m+\gamma)(\lambda - dx)}{a\mu(m+\gamma)}$ and

$$F(x)\left[kH\left(\frac{k(\rho m+\gamma)(\lambda - dx)}{a\mu(m+\gamma)}\right) + \mu G\left(\frac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}\right)\right] = \frac{a\mu(m+\gamma)}{\rho m+\gamma}. \tag{10}$$

Since $l, y, v \geq 0$, we have $x \leq \dfrac{\lambda}{d}$. Hence, there is no equilibrium when $x > \dfrac{\lambda}{d}$.

Let us define the function Ψ_1 on $\left[0, \dfrac{\lambda}{d}\right]$ by

$$\Psi_1(x) = F(x)\left[kH\left(\frac{k(\rho m+\gamma)(\lambda - dx)}{a\mu(m+\gamma)}\right) + \mu G\left(\frac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}\right)\right] - \frac{a\mu(m+\gamma)}{\rho m+\gamma}.$$

We have $\Psi_1(0) = -\dfrac{a\mu(m+\gamma)}{\rho m+\gamma} < 0$ and $\Psi_1\left(\dfrac{\lambda}{d}\right) = \dfrac{a\mu(m+\gamma)}{\rho m+\gamma}(R_0 - 1)$. Hence if $R_0 > 1$, there exists an equilibrium $E_1(x_1, l_1, y_1, v_1, 0, 0)$ satisfying $x_1 \in \left(0, \dfrac{\lambda}{d}\right)$, $l_1 = \dfrac{(1-\rho)(\lambda - dx_1)}{m+\gamma}$, $y_1 = \dfrac{(\rho m+\gamma)(\lambda - dx_1)}{a(m+\gamma)}$ and $v_1 = \dfrac{k(\rho m+\gamma)(\lambda - dx_1)}{a\mu(m+\gamma)}$.

Case 2 : If $w \neq 0$ and $z = 0$. In this case, $v = \dfrac{h}{g}$. Moreover, the equations (4)-(6) lead to $l = \dfrac{(1-\rho)(\lambda - dx)}{m+\gamma}$, $y = \dfrac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}$ and

$$F(x)\left[\frac{h}{g}H\left(\frac{h}{g}\right) + \frac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}G\left(\frac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}\right)\right] = \lambda - dx. \tag{11}$$

Since $l, y \geq 0$, we have $x \leq \dfrac{\lambda}{d}$. Hence, there is no equilibrium if $x > \dfrac{\lambda}{d}$.

We define the function Ψ_2 on $\left[0, \dfrac{\lambda}{d}\right]$ by

$$\Psi_2(x) = F(x)\left[\frac{h}{g}H\left(\frac{h}{g}\right) + \frac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}G\left(\frac{(\rho m+\gamma)(\lambda - dx)}{a(m+\gamma)}\right)\right] - (\lambda - dx).$$

We have $\Psi_2(0) = -\lambda < 0$ and $\Psi_2\left(\dfrac{\lambda}{d}\right) = F\left(\dfrac{\lambda}{d}\right)\dfrac{h}{g}H\left(\dfrac{h}{g}\right) > 0$. Then from the intermediate value property there exists $x_2 \in \left(0, \dfrac{\lambda}{d}\right)$ such that $\Psi_2(x_2) = 0$. In addition, the equation (8) give $w_2 = \dfrac{\mu}{q}\left(\dfrac{kg(\rho m+\gamma)(\lambda - dx_2)}{ah\mu(m+\gamma)} - 1\right)$. Now, we

introduce the reproduction number for humoral immunity by

$$R_1^w = \frac{kg(\rho m+\gamma)(\lambda - dx_2)}{ah\mu(m+\gamma)},$$

Clearly, when $R_1^w > 1$, it follows that an equilibrium $E_2(x_2, l_2, y_2, v_2, w_2, 0)$ exists and satisfies $x_2 \in \left(0, \frac{\lambda}{d}\right)$, $l_2 = \frac{(1-\rho)(\lambda - dx_2)}{m+\gamma}$, $y_2 = \frac{(\gamma+m\rho)(\lambda - dx_2)}{a(m+\gamma)}$, $v_2 = \frac{h}{g}$ and $w_2 = \frac{\mu}{q}(R_1^w - 1)$.

Case 3 : If $w = 0$ and $z \neq 0$, then $y = \frac{b}{c}$ and from equation (7), we have $v = \frac{kb}{\mu c}$. Using the equations (4)-(6), we get $l = \frac{(1-\rho)(\lambda - dx)}{m+\gamma}$ and

$$F(x)\left[\frac{kb}{\mu c}H\left(\frac{kb}{\mu c}\right) + \frac{b}{c}G\left(\frac{b}{c}\right)\right] = \lambda - dx. \tag{12}$$

Since $l \geq 0$, we have $x \leq \frac{\lambda}{d}$. Then, there is no equilibrium if $x > \frac{\lambda}{d}$.

We define the function Ψ_3 on $\left[0, \frac{\lambda}{d}\right]$ by

$$\Psi_3(x) = F(x)\left[\frac{kb}{\mu c}H\left(\frac{kb}{\mu c}\right) + \frac{b}{c}G\left(\frac{b}{c}\right)\right] - (\lambda - dx).$$

We have $\Psi_3(0) = -\lambda < 0$ and $\Psi_3\left(\frac{\lambda}{d}\right) = F\left(\frac{\lambda}{d}\right)\left[\frac{kb}{\mu c}H\left(\frac{kb}{\mu c}\right) + \frac{b}{c}G\left(\frac{b}{c}\right)\right] > 0$.

Hence, there exists $x_3 \in \left(0, \frac{\lambda}{d}\right)$ such that $\Psi_3(x_3) = 0$. From the equation (9), we get $z_3 = \frac{a}{p}\left(\frac{c(\gamma+\rho m)(\lambda - dx_3)}{ab(m+\gamma)} - 1\right)$.

Then we introduce the reproduction number for cellular immunity as follows

$$R_1^z = \frac{c(\gamma+\rho m)(\lambda - dx_3)}{ab(m+\gamma)}.$$

Hence, when $R_1^z > 1$, there exists an equilibrium $E_3(x_3, l_3, y_3, v_3, 0, z_3)$ satisfying $x_3 \in \left(0, \frac{\lambda}{d}\right)$, $l_3 = \frac{(1-\rho)(\lambda - dx_3)}{m+\gamma}$, $y_3 = \frac{b}{c}$, $v_3 = \frac{kb}{c\mu}$ and $z_3 = \frac{a}{p}(R_1^z - 1)$.

Case 4 : If $w \neq 0$ and $z \neq 0$, we have $y = \frac{b}{c}$, $v = \frac{h}{g}$. From the equations (4)-(6), we obtain $l = \frac{(1-\rho)(\lambda - dx)}{m+\gamma}$ and

$$F(x)\left[\frac{h}{g}H\left(\frac{h}{g}\right) + \frac{b}{c}G\left(\frac{b}{c}\right)\right] = \lambda - dx. \tag{13}$$

Since $l \geq 0$, we have $x \leq \frac{\lambda}{d}$. Hence, there is no equilibrium if $x > \frac{\lambda}{d}$. We introduce the function Ψ_4 on $\left[0, \frac{\lambda}{d}\right]$ by

$$\Psi_4(x) = F(x)\left[\frac{h}{g}H\left(\frac{h}{g}\right) + \frac{b}{c}G\left(\frac{b}{c}\right)\right] - (\lambda - dx).$$

We have $\Psi_4(0) = -\lambda < 0$ and $\Psi_4\left(\frac{\lambda}{d}\right) = F\left(\frac{\lambda}{d}\right)\left[\frac{h}{g}H\left(\frac{h}{g}\right) + \frac{b}{c}G\left(\frac{b}{c}\right)\right] > 0$. Hence, there exists $x_4 \in \left(0, \frac{\lambda}{d}\right)$ such that $\Psi_4(x_4) = 0$. From the last two equations (8) and (9), we get $z_4 = \frac{a}{p}\left(\frac{c(m\rho+\gamma)(\lambda - dx_4)}{ab(m+\gamma)} - 1\right)$ and $w_4 = \frac{\mu}{q}\left(\frac{gkb}{\mu ch} - 1\right)$.

In addition to R_1^z and R_1^w, we define the numbers R_2^z and R_2^w as follows

$$R_2^z = \frac{c(m\rho+\gamma)(\lambda - dx_4)}{ab(m+\gamma)} \quad \text{and} \quad R_2^w = \frac{gkb}{\mu ch}.$$

The first one is the reproduction number for cellular immunity in competition while the second one is the reproduction number for humoral immunity in competition. Finally, we deduce that when $R_2^z > 1$ and $R_2^w > 1$, there exists an equilibrium $E_4(x_4, l_4, y_4, v_4, w_4, z_4)$ satisfying $x_4 \in \left(0, \frac{\lambda}{d}\right)$, $l_4 = \frac{(1-\rho)\lambda - dx_4}{m+\gamma}$, $y_4 = \frac{b}{c}$, $v_4 = \frac{h}{g}$, $w_4 = \frac{\mu}{q}(R_2^w - 1)$ and $z_4 = \frac{a}{p}(R_2^z - 1)$.

We summarize all the previous discussions in the following theorem.

Theorem 31

(i) If $R_0 \leq 1$, then system (1) has always an infection-free equilibrium of the form $E_0(x_0, 0, 0, 0, 0, 0)$, where $x_0 = \frac{\lambda}{d}$.

(ii) If $R_0 > 1$, then system (1) has a unique immune-free infection equilibrium of the form $E_1(x_1, l_1, y_1, v_1, 0, 0)$, where $x_1 \in \left(0, \frac{\lambda}{d}\right)$, $l_1 = \frac{(1-\rho)(\lambda - dx_1)}{m+\gamma}$, $y_1 = \frac{(m\rho+\gamma)(\lambda - dx_1)}{a(m+\gamma)}$ and $v_1 = \frac{k(m\rho+\gamma)(\lambda - dx_1)}{a\mu(m+\gamma)}$.

(iii) If $R_1^w > 1$, then system (1) has a unique infection equilibrium with only humoral immunity of the form $E_2(x_2, l_2, y_2, v_2, w_2, 0)$, where $x_2 \in \left(0, \frac{\lambda}{d}\right)$, $l_2 = \frac{(1-\rho)(\lambda - dx_2)}{m+\gamma}$, $y_2 = \frac{(\gamma+m\rho)(\lambda - dx_2)}{a(m+\gamma)}$, $v_2 = \frac{h}{g}$ and $w_2 = \frac{\mu}{q}(R_1^w - 1)$.

(iv) If $R_1^z > 1$, then system (1) has a unique infection equilibrium with only cellular immunity of the form $E_3(x_3, l_3, y_3, v_3, 0, z_3)$, where $x_3 \in \left(0, \frac{\lambda}{d}\right)$, $l_3 = \frac{(1-\rho)(\lambda - dx_3)}{m+\gamma}$, $y_3 = \frac{b}{c}$, $v_3 = \frac{kb}{c\mu}$ and $z_3 = \frac{a}{p}(R_1^z - 1)$.

(v) If $R_2^z > 1$ and $R_2^w > 1$, then system (1) has a unique infection equilibrium with both humoral and cellular immunity of the form $x_4 \in \left(0, \frac{\lambda}{d}\right)$, $l_4 = \frac{(1-\rho)(\lambda - dx_4)}{m+\gamma}$, $y_4 = \frac{b}{c}$, $v_4 = \frac{h}{g}$, $w_4 = \frac{\mu}{q}(R_2^w - 1)$ and $z_4 = \frac{a}{p}(R_2^z - 1)$.

4 Global stability

In the following section, we study the global stability of the five equilibria. The approach used here is based on the construction of suitable Lyapunov functionals and two lemmas given in [43,44]. In the rest of the paper, we will use the following function $\Phi(x) = x - 1 - \ln x, \forall x > 0$ and the notation $(x(t), l(t), y(t), v(t), w(t), z(t)) = (x, l, y, v, w, z)$.

Theorem 41 *If $R_0 \leq 1$, then the infection-free equilibrium E_0 is globally asymptotically stable.*

Proof. Define the Lyapunov functional $L_0(t)$ as

$$L_0(t) = A\left(x - x_0 - \int_{x_0}^{x} \frac{F(x_0)}{F(s)} ds\right) + \frac{\gamma}{m+\gamma} l + y + \frac{a(1-R_0^2)}{k} v + \frac{aq(1-R_0^2)}{kg} w + \frac{p}{c} z,$$

where $A = \left(\frac{\gamma(1-\rho)}{m+\gamma} + \rho\right)$. From [43], the fractional derivative of $L_0(t)$ along solutions of sytem (1) is estimated as follows

$$\begin{aligned} D^\alpha L_0(t) \leq & A\left(1 - \frac{F(x_0)}{F(x)}\right) D^\alpha x + \frac{\gamma}{m+\gamma} D^\alpha l + D^\alpha y + \frac{a(1-R_0^2)}{k} D^\alpha v \\ & + \frac{aq(1-R_0^2)}{kg} D^\alpha w + \frac{p}{c} D^\alpha z. \end{aligned}$$

Using $\lambda = dx_0$, we obtain

$$\begin{aligned} D^\alpha L_0(t) \leq & dA\left(1 - \frac{F(x_0)}{F(x)}\right)(x_0 - x) + AF(x_0)[H(v)v + G(y)y] + a(1-R_0^2)y - ay \\ & - \frac{a\mu(1-R_0^2)}{k} v - \frac{aqh(1-R_0^2)}{kg} w - \frac{bp}{c} z \\ \leq & dA\left(1 - \frac{F(x_0)}{F(x)}\right)(x_0 - x) + \frac{a\mu}{k}(R_0 - 1)v - \frac{bp}{c} z. \end{aligned}$$

Hence if $R_0 \leq 1$, then $D^\alpha L_0(t) \leq 0$. In addition, the largest invariant set of $\{(x,l,y,v,w,z) \in \mathbb{R}^6_+ : D^\alpha L_0(t) = 0\}$ is the singleton $\{E_0\}$. Therefore, by LaSalle's invariance principle [44], E_0 is globally asymptotically stable when $R_0 \leq 1$. ■

Now, we assume that $R_0 > 1$. In this case, system (1) has four infection equilibrium points $E_i(x_i,l_i,y_i,v_i,w_i,z_i)$, with $i \in \{1,2,3,4\}$. The global stability of these points is achieved by the following assumption on the functions H and G :

$$\begin{aligned}
&\left(1-\frac{H(v)}{H(v_i)}\right)\left(\frac{H(v_i)}{H(v)}-\frac{v}{v_i}\right) \leq 0, \quad \text{for all } v \geq 0,\\
&\left(1-\frac{G(y)}{G(y_i)}\right)\left(\frac{G(y_i)}{G(y)}-\frac{y}{y_i}\right) \leq 0, \quad \text{for all } y \geq 0.
\end{aligned} \tag{H_4}$$

Theorem 42 *Assume that* $R_0 > 1$.

(i) The immune-free infection equilibrium E_1 *is globally asymptotically stable if* $\max\{R_1^w, R_1^z\} \leq 1$.
(ii) The infection equilibrium with only humoral immunity E_2 *is globally asymptotically stable if* $R_1^w > 1$ *and* $R_2^z \leq 1$.
(iii) The infection equilibrium with only cellular immunity E_3 *is globally asymptotically stable if* $R_1^z > 1$ *and* $R_2^w \leq 1$.
(iv) The infection equilibrium with both cellular and humoral immunity E_4 *is globally asymptotically stable if* $\min\{R_2^w, R_2^z\} > 1$.

Proof. At E_1, we consider the Lyapunov functional $L_1(t)$ defined as

$$\begin{aligned}
L_1(t) =& A\left(x - x_1 - \int_{x_1}^{x} \frac{F(x_1)}{F(s)}ds\right) + \frac{\gamma}{m+\gamma} l_1 \Phi\left(\frac{l}{l_1}\right) + y_1 \Phi\left(\frac{y}{y_1}\right)\\
&+ \frac{AF(x_1)H(v_1)v_1}{ky_1} v_1 \Phi\left(\frac{v}{v_1}\right) + \frac{AqF(x_1)H(v_1)v_1}{gky_1} w + \frac{p}{c} z.
\end{aligned}$$

Calculating the fractional derivative of $L_1(t)$ along solutions of system (1), we get

$$\begin{aligned}
D^\alpha L_1(t) \leq& A\left(1-\frac{F(x_1)}{F(x)}\right)(\lambda - dx) - A\left(1-\frac{F(x_1)}{F(x)}\right)F(x)[H(v)v + G(y)y]\\
&+ \frac{\gamma(1-\rho)}{m+\gamma}\left(1-\frac{l_1}{l}\right)F(x)[H(v)v+G(y)y] + \gamma l_1 - ay + ay_1\\
&+ \left(1-\frac{y_1}{y}\right)\rho F(x)[H(v)v+G(y)y] - \gamma l\frac{y_1}{y} + AF(x_1)H(v_1)v_1\frac{y}{y_1}\\
&- AF(x_1)H(v_1)v_1\frac{yv_1}{y_1 v} - \frac{AF(x_1)H(v_1)v_1}{ky_1}\mu v + \frac{AF(x_1)H(v_1)v_1}{ky_1}\mu v_1\\
&+ pz\left(y_1 - \frac{b}{c}\right) + \frac{AqF(x_1)H(v_1)v_1}{ky_1} w\left(v_1 - \frac{h}{g}\right).
\end{aligned}$$

Considering that

$$\lambda = dx_1 + F(x_1)[H(v_1)v_1 + G(y_1)y_1], \gamma l_1 = \frac{\gamma(1-\rho)}{m+\gamma}F(x_1)[H(v_1)v_1 + G(y_1)y_1]$$
and $ay_1 = AF(x_1)[H(v_1)v_1 + G(y_1)y_1]ky_1 = \mu v_1$, we get

$$
\begin{aligned}
D^{\alpha}L_1(t) \leq\, & dA\left(1-\frac{F(x_1)}{F(x)}\right)(x_1-x)+AF(x_1)H(v_1)v_1\left[3-\frac{F(x_1)}{F(x)}+\frac{y}{y_1}-\frac{yv_1}{y_1v}\right.\\
& \left.-\frac{v}{v_1}+\frac{H(v)v}{H(v_1)v_1}\right]+AF(x_1)G(y_1)y_1\left[2-\frac{F(x_1)}{F(x)}+\frac{G(y)y}{G(y_1)y_1}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_1)H(v_1)v_1\left[1-\frac{ly_1}{l_1y}-\frac{y}{y_1}-\frac{F(x)H(v)vl_1}{F(x_1)H(v_1)v_1l}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_1)G(y_1)y_1\left[1-\frac{ly_1}{l_1y}-\frac{y}{y_1}-\frac{F(x)G(y)yl_1}{F(x_1)G(y_1)y_1l}\right]\\
& -\rho F(x_1)H(v_1)v_1\left[\frac{y}{y_1}+\frac{y_1F(x)H(v)v}{yF(x_1)H(v_1)v_1}\right]-\rho F(x_1)G(y_1)y_1\left[\frac{y}{y_1}\right.\\
& \left.+\frac{F(x)g(y)}{F(x_1)G(y_1)}\right]+pz\left(y_1-\frac{b}{c}\right)+\frac{AqF(x_1)H(v_1)v_1}{ky_1}w\left(v_1-\frac{h}{g}\right)\\
\leq\, & dA\left(1-\frac{F(x_1)}{F(x)}\right)(x_1-x)+AF(x_1)H(v_1)v_1\left[\frac{H(v)v}{H(v_1)v_1}-\frac{v}{v_1}-1+\frac{H(v_1)}{H(v)}\right]\\
& +AF(x_1)H(v_1)v_1\left[4-\frac{F(x_1)}{F(x)}+\frac{y}{y_1}-\frac{yv_1}{y_1v}-\frac{H(v_1)}{H(v)}\right]+AF(x_1)G(y_1)y_1\\
& \left[\frac{G(y)y}{G(y_1)y_1}-1+\frac{G(y_1)}{G(y)}\right]+AF(x_1)G(y_1)y_1\left[3-F(x_1)F(x)-\frac{G(y_1)}{G(y)}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_1)H(v_1)v_1\left[1-\frac{ly_1}{l_1y}-\frac{y}{y_1}-\frac{F(x)H(v)vl_1}{F(x_1)H(v_1)v_1l}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_1)G(y_1)y_1\left[1-\frac{ly_1}{l_1y}-\frac{y}{y_1}-\frac{F(x)G(y)yl_1}{F(x_1)G(y_1)y_1l}\right]\\
& -\rho F(x_1)H(v_1)v_1\left[\frac{y}{y_1}+\frac{y_1F(x)H(v)v}{yF(x_1)H(v_1)v_1}\right]-\rho F(x_1)G(y_1)y_1\left[\frac{y}{y_1}\right.\\
& \left.+\frac{F(x)G(y)}{F(x_1)G(y_1)}\right]+pz\left(y_1-\frac{b}{c}\right)+\frac{AqF(x_1)H(v_1)v_1}{ky_1}w\left(v_1-\frac{h}{g}\right)\\
\leq\, & dA\left(1-\frac{F(x_1)}{F(x)}\right)(x_1-x)+AF(x_1)H(v_1)v_1\left[\frac{H(v)v}{H(v_1)v_1}-\frac{v}{v_1}-1+\frac{H(v_1)}{H(v)}\right]\\
& +AF(x_1)G(y_1)y_1\left[\frac{G(y)y}{G(y_1)y_1}-\frac{y}{y_1}-1+\frac{G(y_1)}{G(y)}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_1)H(v_1)v_1\left[5-\frac{F(x_1)}{F(x)}-\frac{yv_1}{y_1v}-\frac{H(v_1)}{H(v)}-\frac{ly_1}{l_1y}-\frac{F(x)H(v)vl_1}{F(x_1)H(v_1)v_1l}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_1)G(y_1)y_1\left[4-\frac{F(x_1)}{F(x)}-\frac{G(y_1)}{G(y)}-\frac{ly_1}{l_1y}-\frac{F(x)G(y)yl_1}{F(x_1)G(y_1)y_1l}\right]\\
& +\rho F(x_1)H(v_1)v_1\left[4-\frac{F(x_1)}{F(x)}-\frac{yv_1}{y_1v}-\frac{H(v_1)}{H(v)}-\frac{F(x)H(v)vy_1}{F(x_1)H(v_1)v_1y}\right]\\
& +\rho F(x_1)G(y_1)y_1\left[3-\frac{F(x_1)}{F(x)}-\frac{G(y_1)}{G(y)}-\frac{F(x)G(y)}{F(x_1)G(y_1)}\right]+pz\left(y_1-\frac{b}{c}\right)\\
& +\frac{AqF(x_1)H(v_1)v_1}{ky_1}w\left(v_1-\frac{h}{g}\right).
\end{aligned}
$$

From the hypothesis (H_1) and the geometric-arithmetic inequality, we get

$$\left(1-\frac{F(x_i)}{F(x)}\right)(x_i-x)\leq 0, \tag{14}$$

and

$$\begin{aligned}
&5-\frac{F(x_i)}{F(x)}-\frac{yv_i}{y_iv}-\frac{H(v_i)}{H(v)}-\frac{ly_i}{l_iy}-\frac{F(x)H(v)vl_i}{F(x_i)H(v_i)v_il}\leq 0,\\
&4-\frac{F(x_i)}{F(x)}-\frac{G(y_i)}{G(y)}-\frac{ly_i}{l_iy}-\frac{F(x)G(y)yl_i}{F(x_i)G(y_i)y_il}\leq 0,\\
&4-\frac{F(x_i)}{F(x)}-\frac{yv_i}{y_iv}-\frac{H(v_i)}{H(v)}-\frac{F(x)H(v)vy_i}{F(x_i)H(v_i)v_iy}\leq 0,\\
&3-\frac{F(x_i)}{F(x)}-\frac{G(y_i)}{G(y)}-\frac{F(x)G(y)}{F(x_i)G(y_i)}\leq 0,
\end{aligned}\tag{15}$$

for all $i\in\{1,2,3,4\}$. The hypothesis (H_4) leads to

$$\begin{aligned}
\left(1-\frac{H(v)}{H(v_i)}\right)\left(\frac{H(v_i)}{H(v)}-\frac{v}{v_i}\right)&=\frac{H(v)v}{H(v_i)v_i}-\frac{v}{v_i}-1+\frac{H(v_i)}{H(v)}\leq 0,\\
\left(1-\frac{G(y)}{G(y_i)}\right)\left(\frac{G(y_i)}{G(y)}-\frac{y}{y_i}\right)&=\frac{G(y)y}{G(y_i)y_i}-\frac{y}{y_i}-1+\frac{G(y_i)}{G(y)}\leq 0.
\end{aligned}\tag{16}$$

In addition, when $R_1^z\leq 1$, E_3 does not exist. Then $(cy-b)z\leq 0$ for all $z>0$. Consequently, $y\leq\frac{b}{c}$ for all $y\geq 0$ which implies $y_1\leq\frac{b}{c}$. By the same reasoning we get $v_1\leq\frac{h}{g}$. Hence if $R_1^z\leq 1$ and $R_1^w\leq 1$, $D^\alpha L_1(t)\leq 0$. Further, the largest invariant set of $\{(x,l,y,v,w,z)\in\mathbb{R}_+^6 : D^\alpha L_1(t)=0\}$ is the singleton $\{E_1\}$. Therefore, by LaSalle's invariance principle, E_1 is globally asymptotically stable when $R^z\leq 1$.

For the equilibrium E_2, we construct the following Lyapunov functional

$$\begin{aligned}
L_2(t)=&A\left(x-x_2-\int_{x_2}^{x}\frac{F(x_2)}{F(s)}ds\right)+\frac{\gamma}{m+\gamma}l_2\Phi\left(\frac{l}{l_2}\right)+y_2\Phi\left(\frac{y}{y_2}\right)\\
&+\frac{AF(x_2)H(v_2)v_2}{ky_2}v_2\Phi\left(\frac{v}{v_2}\right)+\frac{AqF(x_2)H(v_2)v_2}{gky_2}w_2\Phi\left(\frac{w}{w_2}\right)+\frac{p}{c}z.
\end{aligned}$$

The fractional derivative of $L_2(t)$ along solutions of system (1) is given as follows

$$\begin{aligned}
D^\alpha L_2(t)\leq&A\left(1-\frac{F(x_2)}{F(x)}\right)D^\alpha x+\frac{\gamma}{m+\gamma}\left(1-\frac{l_2}{l}\right)D^\alpha l+\left(1-\frac{y_2}{y}\right)D^\alpha y\\
&+\frac{AF(x_2)H(v_2)v_2}{ky_2}\left(1-\frac{v_2}{v}\right)D^\alpha v+\frac{AqF(x_2)H(v_2)v_2}{gky_2}\left(1-\frac{w_2}{w}\right)D^\alpha w+\frac{p}{c}D^\alpha z\\
\leq&A\left(1-\frac{F(x_2)}{F(x)}\right)(\lambda-dx)-A\left(1-\frac{F(x_2)}{F(x)}\right)F(x)[H(v)v+G(y)y]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}\left(1-\frac{l_2}{l}\right)F(x)[H(v)v+G(y)y]+\gamma l_2-ay+ay_2\\
&+\left(1-\frac{y_2}{y}\right)\rho F(x)[H(v)v+G(y)y]-\gamma l\frac{y_2}{y}+AF(x_2)H(v_2)v_2\frac{y}{y_2}\\
&-AF(x_2)H(v_2)v_2\frac{yv_2}{y_2v}-\frac{AF(x_2)H(v_2)v_2}{ky_2}\mu v+\frac{AF(x_2)H(v_2)v_2}{ky_2}\mu v_2\\
&+\frac{AqF(x_2)H(v_2)v_2}{ky_2}v_2w_2-\frac{AqF(x_2)H(v_2)v_2}{ky_2}vw_2-\frac{AqhF(x_2)H(v_2)v_2}{gky_2}w\\
&+\frac{AqhF(x_2)H(v_2)v_2}{gky_2}w_2+pz\left(y_2-\frac{b}{c}\right)
\end{aligned}$$

By taking into account that $\lambda=dx_2+F(x_2)[H(v_2)v_2+G(y_2)y_2]$,
$\gamma l_2=\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)[H(v_2)v_2+G(y_2)y_2]$, $ay_2=AF(x_2)[H(v_2)v_2+G(y_2)y_2]$,

$\mu v_2 = k y_2 - q v_2 w_2$ and $v_2 = \dfrac{h}{g}$, we get

$$
\begin{aligned}
D^{\alpha} L_2(t) \leq\, & dA\left(1-\frac{F(x_2)}{F(x)}\right)(x_2-x)+AF(x_2)H(v_2)v_2\left[3-\frac{F(x_2)}{F(x)}+\frac{y}{y_2}-\frac{yv_2}{y_2v}\right.\\
& \left.-\frac{v}{v_2}+\frac{H(v)v}{H(v_2)v_2}\right]+AF(x_2)G(y_2)y_2\left[2-\frac{F(x_2)}{F(x)}+\frac{G(y)y}{G(y_2)y_2}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)H(v_2)v_2\left[1-\frac{ly_2}{l_2y}-\frac{y}{y_2}-\frac{F(x)H(v)vl_2}{F(x_2)H(v_2)v_2l}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)G(y_2)y_2\left[1-\frac{ly_2}{l_2y}-\frac{y}{y_2}-\frac{F(x)G(y)yl_2}{F(x_2)G(y_2)y_2l}\right]\\
& -\rho F(x_2)H(v_2)v_2\left[\frac{y}{y_2}+\frac{y_2F(x)H(v)v}{yF(x_2)H(v_2)v_2}\right]-\rho F(x_2)G(y_2)y_2\left[\frac{y}{y_2}\right.\\
& \left.+\frac{F(x)G(y)}{F(x_2)G(y_2)}\right]+pz\left(y_2-\frac{b}{c}\right)\\
\leq\, & dA\left(1-\frac{F(x_2)}{F(x)}\right)(x_2-x)+AF(x_2)H(v_2)v_2\left[\frac{H(v)v}{H(v_2)v_2}-\frac{v}{v_2}-1+\frac{H(v_2)}{H(v)}\right]\\
& +AF(x_2)H(v_2)v_2\left[4-\frac{F(x_2)}{F(x)}+\frac{y}{y_2}-\frac{yv_2}{y_2v}-\frac{H(v_2)}{H(v)}\right]+AF(x_2)G(y_2)y_2\\
& \left[\frac{G(y)y}{G(y_2)y_2}-1+\frac{G(y_2)}{G(y)}\right]+AF(x_2)G(y_2)y_2\left[3-F(x_2)F(x)-\frac{G(y_2)}{G(y)}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)H(v_2)v_2\left[1-\frac{ly_2}{l_2y}-\frac{y}{y_2}-\frac{F(x)H(v)vl_2}{F(x_2)H(v_2)v_2l}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)G(y_2)y_2\left[1-\frac{ly_2}{l_2y}-\frac{y}{y_2}-\frac{F(x)G(y)yl_2}{F(x_2)G(y_2)y_2l}\right]\\
& -\rho F(x_2)H(v_2)v_2\left[\frac{y}{y_2}+\frac{y_2F(x)H(v)v}{yF(x_2)H(v_2)v_2}\right]-\rho F(x_2)G(y_2)y_2\left[\frac{y}{y_2}\right.\\
& \left.+\frac{F(x)G(y)}{F(x_2)G(y_2)}\right]+pz\left(y_2-\frac{b}{c}\right)\\
\leq\, & dA\left(1-\frac{F(x_2)}{F(x)}\right)(x_2-x)+AF(x_2)H(v_2)v_2\left[\frac{H(v)v}{H(v_2)v_2}-\frac{v}{v_2}-1+\frac{H(v_2)}{H(v)}\right]\\
& +AF(x_2)G(y_2)y_2\left[\frac{G(y)y}{G(y_2)y_2}-\frac{y}{y_2}-1+\frac{G(y_2)}{G(y)}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)H(v_2)v_2\left[5-\frac{F(x_2)}{F(x)}-\frac{yv_2}{y_2v}-\frac{H(v_2)}{H(v)}-\frac{ly_2}{l_2y}-\frac{F(x)H(v)vl_2}{F(x_2)H(v_2)v_2l}\right]\\
& +\frac{\gamma(1-\rho)}{m+\gamma}F(x_2)G(y_2)y_2\left[4-\frac{F(x_2)}{F(x)}-\frac{G(y_2)}{G(y)}-\frac{ly_2}{l_2y}-\frac{F(x)G(y)yl_2}{F(x_2)G(y_2)y_2l}\right]\\
& +\rho F(x_2)H(v_2)v_2\left[4-\frac{F(x_2)}{F(x)}-\frac{yv_2}{y_2v}-\frac{H(v_2)}{H(v)}-\frac{F(x)H(v)vy_2}{F(x_2)H(v_2)v_2y}\right]\\
& +\rho F(x_2)G(y_2)y_2\left[3-\frac{F(x_2)}{F(x)}-\frac{G(y_2)}{G(y)}-\frac{F(x)G(y)}{F(x_2)G(y_2)}\right]+pz\left(y_2-\frac{b}{c}\right).
\end{aligned}
$$

It is clear that, when $R_2^z \leq 1$, E_4 does not exist. Then $(cy-b)z \leq 0$ for all $z>0$. Consequently, $y \leq \dfrac{b}{c}$ for all $y \geq 0$ which implies $y_2 \leq \dfrac{b}{c}$. From (14)-(16), it holds $D^{\alpha}L_2(t) \leq 0$. In addition, the largest invariant set of $\{(x,l,y,v,w,z) \in \mathbf{R}_+^6 : D^{\alpha}L_2(t)=0\}$ is the singleton $\{E_2\}$. Therefore, E_2 is globally asymptotically stable when $R_2 \leq 1$.

To establish the global stability of E_3, we propose the following Lyapunov functional

$$L_3(t) = A\left(x - x_3 - \int_{x_3}^{x} \frac{f(x_3)}{f(s)}ds\right) + \frac{\gamma}{m+\gamma} l_3 \Phi\left(\frac{l}{l_3}\right) + y_3\Phi\left(\frac{y}{y_3}\right) + \frac{AF(x_3)H(v_3)v_3}{ky_3} v_3\Phi\left(\frac{v}{v_3}\right) + \frac{AqF(x_3)H(v_3)v_3}{gky_3} w + \frac{p}{c}\Phi\left(\frac{z}{z_3}\right).$$

The fractional derivative of $L_3(t)$ along solutions of system (1) is given as follows

$$\begin{aligned} D^\alpha L_3(t) \leq & A\left(1 - \frac{F(x_3)}{F(x)}\right) D^\alpha x + \frac{\gamma}{m+\gamma}\left(1 - \frac{l_3}{l}\right) D^\alpha l + \left(1 - \frac{y_3}{y}\right) D^\alpha y \\ & + \frac{AF(x_3)F(v_3)v_3}{ky_3}\left(1 - \frac{v_3}{v}\right) D^\alpha v + \frac{AqF(x_3)H(v_3)v_3}{gky_3} D^\alpha w + \frac{p}{c}\left(1 - \frac{z_3}{z}\right) D^\alpha z \\ \leq & A\left(1 - \frac{F(x_3)}{F(x)}\right)(\lambda - dx) - A\left(1 - \frac{F(x_3)}{F(x)}\right) F(x)[H(v)v + G(y)y] \\ & + \frac{\gamma(1-\rho)}{m+\gamma}\left(1 - \frac{l_3}{l}\right) F(x)[H(v)v + G(y)y] + \gamma l_3 - ay + ay_3 + py_3 z \\ & + \left(1 - \frac{y_3}{y}\right)\rho F(x)[H(v)v + G(y)y] - \gamma l\frac{y_3}{y} + AF(x_3)H(v_3)v_3\frac{y}{y_3} \\ & - AF(x_3)H(v_3)v_3\frac{yv_3}{y_3 v} - \frac{AF(x_3)H(v_3)v_3}{ky_3}\mu v + \frac{AF(x_3)H(v_3)v_3}{ky_3}\mu v_3 \\ & + \frac{AqF(x_3)H(v_3)v_3}{ky_3} w\left(v_3 - \frac{h}{g}\right) - \frac{pb}{c} z - pyz_3 + \frac{pb}{c} z_3. \end{aligned}$$

By $\lambda = dx_3 + F(x_3)[H(v_3)v_3 + G(y_3)y_3]$, $\gamma l_3 = \frac{\gamma(1-\rho)}{m+\gamma} F(x_3)[H(v_3)v_3 + G(y_3)y_3]$, $ay_3 = AF(x_3)[H(v_3)v_3 + G(y_3)y_3] - py_3z_3$ and $ky_3 = \mu v_3$, we get

$$\begin{aligned} D^\alpha L_3(t) \leq & dA\left(1 - \frac{F(x_3)}{F(x)}\right)(x_3 - x) + AF(x_3)H(v_3)v_3\left[3 - \frac{F(x_3)}{F(x)} + \frac{y}{y_3} - \frac{yv_3}{y_3 v}\right. \\ & \left. - \frac{v}{v_3} + \frac{H(v)v}{H(v_3)v_3}\right] + AF(x_3)G(y_3)y_3\left[2 - \frac{F(x_3)}{F(x)} + \frac{G(y)y}{G(y_3)y_3}\right] \\ & + \frac{\gamma(1-\rho)}{m+\gamma} F(x_3)H(v_3)v_3\left[1 - \frac{ly_3}{l_3 y} - \frac{y}{y_3} - \frac{F(x)H(v)vl_3}{F(x_3)H(v_3)v_3 l}\right] \\ & + \frac{\gamma(1-\rho)}{m+\gamma} F(x_3)G(y_3)y_3\left[1 - \frac{ly_3}{l_3 y} - \frac{y}{y_3} - \frac{F(x)G(y)yl_3}{F(x_3)G(y_3)y_3 l}\right] \\ & - \rho F(x_3)H(v_3)v_3\left[\frac{y}{y_3} + \frac{y_3 F(x)H(v)v}{yF(x_3)H(v_3)v_3}\right] \\ & - \rho F(x_3)G(y_3)y_3\left[\frac{y}{y_3} + \frac{F(x)g(y)}{F(x_3)G(y_3)}\right] + \frac{AqF(x_3)H(v_3)v_3}{ky_3} w\left(v_3 - \frac{h}{g}\right) \end{aligned}$$

$$
\begin{aligned}
D^{\alpha}L_3(t) \leq\, & dA\left(1-\frac{F(x_3)}{F(x)}\right)(x_3-x)+AF(x_3)H(v_3)v_3\left[\frac{H(v)v}{H(v_3)v_3}-\frac{v}{v_3}-1+\frac{H(v_3)}{H(v)}\right]\\
&+AF(x_3)H(v_3)v_3\left[4-\frac{F(x_3)}{F(x)}+\frac{y}{y_3}-\frac{yv_3}{y_3v}-\frac{H(v_3)}{H(v)}\right]+AF(x_3)G(y_3)y_3\\
&\left[\frac{G(y)y}{G(y_3)y_3}-1+\frac{G(y_3)}{G(y)}\right]+AF(x_3)G(y_3)y_3\left[3-F(x_3)F(x)-\frac{G(y_3)}{G(y)}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_3)H(v_3)v_3\left[1-\frac{ly_3}{l_3y}-\frac{y}{y_3}-\frac{F(x)H(v)vl_3}{F(x_3)H(v_3)v_3l}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_3)G(y_3)y_3\left[1-\frac{ly_3}{l_3y}-\frac{y}{y_3}-\frac{F(x)G(y)yl_3}{F(x_3)G(y_3)y_3l}\right]\\
&-\rho F(x_3)H(v_3)v_3\left[\frac{y}{y_3}+\frac{y_3F(x)H(v)v}{yF(x_3)H(v_3)v_3}\right]-\rho F(x_3)G(y_3)y_3\left[\frac{y}{y_3}+\frac{F(x)G(y)}{F(x_3)G(y_3)}\right]\\
&+\frac{AqF(x_3)H(v_3)v_3}{ky_3}w\left(v_3-\frac{h}{g}\right)\\
\leq\, & dA\left(1-\frac{F(x_3)}{F(x)}\right)(x_3-x)+AF(x_3)H(v_3)v_3\left[\frac{H(v)v}{H(v_3)v_3}-\frac{v}{v_3}-1+\frac{H(v_3)}{H(v)}\right]\\
&+AF(x_3)G(y_3)y_3\left[\frac{G(y)y}{G(y_3)y_3}-\frac{y}{y_3}-1+\frac{G(y_3)}{G(y)}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_3)H(v_3)v_3\left[5-\frac{F(x_3)}{F(x)}-\frac{yv_3}{y_3v}-\frac{H(v_3)}{H(v)}-\frac{ly_3}{l_3y}-\frac{F(x)H(v)vl_3}{F(x_3)H(v_3)v_3l}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_3)G(y_3)y_3\left[4-\frac{F(x_3)}{F(x)}-\frac{G(y_3)}{G(y)}-\frac{ly_3}{l_3y}-\frac{F(x)G(y)yl_3}{F(x_3)G(y_3)y_3l}\right]\\
&+\rho F(x_3)H(v_3)v_3\left[4-\frac{F(x_3)}{F(x)}-\frac{yv_3}{y_3v}-\frac{H(v_3)}{H(v)}-\frac{F(x)H(v)vy_3}{F(x_3)H(v_3)v_3y}\right]\\
&+\rho F(x_3)G(y_3)y_3\left[3-\frac{F(x_3)}{F(x)}-\frac{G(y_3)}{G(y)}-\frac{F(x)G(y)}{F(x_3)G(y_3)}\right]+\frac{AqF(x_3)H(v_3)v_3}{ky_3}w\left(v_3-\frac{h}{g}\right).
\end{aligned}
$$

Obviously, when $R_2^w \leq 1$, E_4 does not exist. Then $(gv-h)w \leq 0$ for all $w>0$. Consequently, $v \leq \frac{h}{g}$ for all $v \geq 0$ which implies $v_3 \leq \frac{h}{g}$. From (14)-(16), $D^{\alpha}L_3(t) \leq 0$. It is not hard to see that the largest invariant set of $\{(x,l,y,v,w,z) \in \mathbb{R}_+^6 : D^{\alpha}L_3(t)=0\}$ is the singleton $\{E_3\}$. Hence, we deduce that E_3 is globally asymptotically stable.

For E_4, we propose the following Lyapunov functional

$$
\begin{aligned}
L_4(t) =\, & A\left(x-x_4-\int_{x_4}^{x}\frac{F(x_4)}{F(s)}ds\right)+\frac{\gamma}{m+\gamma}l_4\Phi\left(\frac{l}{l_4}\right)+y_4\Phi\left(\frac{y}{y_4}\right)\\
&+\frac{AF(x_4)H(v_4)v_4}{ky_4}v_4\Phi\left(\frac{v}{v_4}\right)+\frac{AqF(x_4)H(v_4)v_4}{gky_4}w_4\Phi\left(\frac{w}{w_4}\right)+\frac{p}{c}z_4\Phi\left(\frac{z}{z_4}\right).
\end{aligned}
$$

The fractional derivative of $L_4(t)$ along solutions of system (1) is given as follows

$$
\begin{aligned}
D^{\alpha}L_4(t) \leq\, & A\left(1-\frac{F(x_4)}{F(x)}\right)D^{\alpha}x+\frac{\gamma}{m+\gamma}\left(1-\frac{l_4}{l}\right)D^{\alpha}l+\left(1-\frac{y_4}{y}\right)D^{\alpha}y\\
&+\frac{AF(x_4)H(v_4)v_4}{ky_4}\left(1-\frac{v_4}{v}\right)D^{\alpha}v+\frac{AqF(x_4)H(v_4)v_4}{gky_4}\left(1-\frac{w_4}{w}\right))D^{\alpha}w\\
&+\frac{p}{c}\left(1-\frac{z_4}{z}\right)D^{\alpha}z
\end{aligned}
$$

$$
\begin{aligned}
&\leq A\left(1-\frac{F(x_4)}{F(x)}\right)(\lambda-dx)-A\left(1-\frac{F(x_4)}{F(x)}\right)F(x)[H(v)v+G(y)y]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}\left(1-\frac{l_4}{l}\right)F(x)[H(v)v+G(y)y]+\gamma l_4-ay+ay_4+py_4z\\
&+\left(1-\frac{y_4}{y}\right)\rho F(x)[H(v)v+G(y)y]-\gamma l\frac{y_4}{y}+AF(x_4)H(v_4)v_4\frac{y}{y_4}\\
&-AF(x_4)H(v_4)v_4\frac{yv_4}{y_4v}-\frac{AF(x_4)H(v_4)v_4}{ky_4}\mu v+\frac{AF(x_4)H(v_4)v_4}{ky_4}\mu v_4\\
&-\frac{AhF(x_4)H(v_4)v_4}{ky_4}w+\frac{AqF(x_4)H(v_4)v_4}{ky_4}v_4w-\frac{AgF(x_4)H(v_4)v_4}{ky_4}vw_4\\
&+\frac{AhF(x_4)H(v_4)v_4}{ky_4}w_4-\frac{pb}{c}z-pyz_4+\frac{pb}{c}z_4.
\end{aligned}
$$

From $\lambda = dx_4 + F(x_4)[H(v_4)v_4 + G(y_4)y_4]$, $\gamma l_4 = \frac{\gamma(1-\rho)}{m+\gamma}F(x_4)[H(v_4)v_4 + G(y_4)y_4]$, $ay_4 = AF(x_4)[H(v_4)v_4+G(y_4)y_4]-py_4z_4$, $\mu v_4 = ky_4 - qv_4w_4$, $y_4 = \frac{b}{c}$ and $v_4 = \frac{h}{g}$ we get

$$
\begin{aligned}
D^{\alpha}L_4(t) &\leq dA\left(1-\frac{F(x_4)}{F(x)}\right)(x_4-x)+AF(x_4)H(v_4)v_4\left[3-\frac{F(x_4)}{F(x)}+\frac{y}{y_4}-\frac{yv_4}{y_4v}\right.\\
&\left.-\frac{v}{v_4}+\frac{H(v)v}{H(v_4)v_4}\right]+AF(x_4)G(y_4)y_4\left[2-\frac{F(x_4)}{F(x)}+\frac{G(y)y}{G(y_4)y_4}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_4)H(v_4)v_4\left[1-\frac{ly_4}{l_4y}-\frac{y}{y_4}-\frac{F(x)H(v)vl_4}{F(x_4)H(v_4)v_4l}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_4)G(y_4)y_4\left[1-\frac{ly_4}{l_4y}-\frac{y}{y_4}-\frac{F(x)G(y)yl_4}{F(x_4)G(y_4)y_4l}\right]\\
&-\rho F(x_4)H(v_4)v_4\left[\frac{y}{y_4}+\frac{y_4F(x)H(v)v}{yF(x_4)H(v_4)v_4}\right]-\rho F(x_4)G(y_4)y_4\left[\frac{y}{y_4}+\frac{F(x)g(y)}{F(x_4)G(y_4)}\right]\\
&\leq dA\left(1-\frac{F(x_4)}{F(x)}\right)(x_4-x)+AF(x_4)H(v_4)v_4\left[\frac{H(v)v}{H(v_4)v_4}-\frac{v}{v_4}-1+\frac{H(v_4)}{H(v)}\right]\\
&+AF(x_4)H(v_4)v_4\left[4-\frac{F(x_4)}{F(x)}+\frac{y}{y_4}-\frac{yv_4}{y_4v}-\frac{H(v_4)}{H(v)}\right]+AF(x_4)G(y_4)y_4\\
&\left[\frac{G(y)y}{G(y_4)y_4}-1+\frac{G(y_4)}{G(y)}\right]+AF(x_4)G(y_4)y_4\left[3-F(x_4)F(x)-\frac{G(y_4)}{G(y)}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_4)H(v_4)v_4\left[1-\frac{ly_4}{l_4y}-\frac{y}{y_4}-\frac{F(x)H(v)vl_4}{F(x_4)H(v_4)v_4l}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_4)G(y_4)y_4\left[1-\frac{ly_4}{l_4y}-\frac{y}{y_4}-\frac{F(x)G(y)yl_4}{F(x_4)G(y_4)y_4l}\right]\\
&-\rho F(x_4)H(v_4)v_4\left[\frac{y}{y_4}+\frac{y_4F(x)H(v)v}{yF(x_4)H(v_4)v_4}\right]-\rho F(x_4)G(y_4)y_4\left[\frac{y}{y_4}+\frac{F(x)G(y)}{F(x_4)G(y_4)}\right]
\end{aligned}
$$

$$
\begin{aligned}
&\leq dA\left(1-\frac{F(x_4)}{F(x)}\right)(x_4-x)+AF(x_4)H(v_4)v_4\left[\frac{H(v)v}{H(v_4)v_4}-\frac{v}{v_4}-1+\frac{H(v_4)}{H(v)}\right]\\
&+AF(x_4)G(y_4)y_4\left[\frac{G(y)y}{G(y_4)y_4}-\frac{y}{y_4}-1+\frac{G(y_4)}{G(y)}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_4)H(v_4)v_4\left[5-\frac{F(x_4)}{F(x)}-\frac{yv_4}{y_4v}-\frac{H(v_4)}{H(v)}-\frac{ly_4}{l_4y}-\frac{F(x)H(v)vl_4}{F(x_4)H(v_4)v_4l}\right]\\
&+\frac{\gamma(1-\rho)}{m+\gamma}F(x_4)G(y_4)y_4\left[4-\frac{F(x_4)}{F(x)}-\frac{G(y_4)}{G(y)}-\frac{ly_4}{l_4y}-\frac{F(x)G(y)yl_4}{F(x_4)G(y_4)y_4l}\right]\\
&+\rho F(x_4)H(v_4)v_4\left[4-\frac{F(x_4)}{F(x)}-\frac{yv_4}{y_4v}-\frac{H(v_4)}{H(v)}-\frac{F(x)H(v)vy_4}{F(x_4)H(v_4)v_4y}\right]\\
&+\rho F(x_4)G(y_4)y_4\left[3-\frac{F(x_4)}{F(x)}-\frac{G(y_4)}{G(y)}-\frac{F(x)G(y)}{F(x_4)G(y_4)}\right].
\end{aligned}
$$

From (14)-(16), we have $D^\alpha L_4(t)\leq 0$. Furthermore, the largest invariant set of $\{(x,l,y,v,w,z)\in\mathbb{R}^6_+ : D^\alpha L_4(t)=0\}$ is the singleton $\{E_4\}$. Then we conclude that E_4 is globally asymptotically stable. ■

5 Sensitivity analysis and application

Often, susceptible cells became infected by direct contact with productively infected cells or/and free virus particles. Thus, the functions $H(v)$ and $G(y)$ are assumed to depend on the *effective contact rates* β_1 and β_2. For the rest of this work, we chose the following functions F, H and G as

$$
F(x)=x,\quad H(v)=\frac{\beta_1}{1+v},\quad G(y)=\frac{\beta_2}{1+y}, \tag{17}
$$

where $\beta_1>0$ and $\beta_2>0$ denote, respectively, the virus-to-cell infection rate and the cell-to-cell transmission rate. It is easy to check that they satisfy (H_1)-(H_3). So, system (1) becomes as follows:

$$
\begin{cases}
D^\alpha x(t) &= \lambda-dx-\dfrac{\beta_1xv}{1+v}-\dfrac{\beta_2xy}{1+y},\\
D^\alpha l(t) &= (1-\rho)\left[\dfrac{\beta_1xv}{1+v}+\dfrac{\beta_2yv}{1+y}\right]-(m+\gamma)l,\\
D^\alpha y(t) &= \rho\left[\dfrac{\beta_1xv}{1+v}+\dfrac{\beta_2yv}{1+y}\right]+\gamma l-ay-pyz,\\
D^\alpha v(t) &= ky-\mu v-qvw,\\
D^\alpha w(t) &= gvw-hw,\\
D^\alpha z(t) &= cyz-bz.
\end{cases} \tag{18}
$$

With this choice of functions (17), the basic reproduction number R_0 is given by

$$
R_0=\frac{k\lambda\beta_1(\rho m+\gamma)}{ad\mu(m+\gamma)}+\frac{\lambda\beta_2(\rho m+\gamma)}{ad(m+\gamma)}. \tag{19}
$$

5.1 Sensitivity of the thresholds parameters

Sensitivity analysis is an important tool that measures the impact of each parameter on the disease transmission. Sensitivity indices allow us to measure the relative change in a variable when a parameter changes. The normalized forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. So, to determine the robustness of model (18) to some parameter values, we examine the sensitivity of the basic reproduction number R_0 in (19) with respect to these parameters by the so-called *sensitivity index*.

Definition 51 (See [45,46]) *The normalized forward sensitivity index of a variable u, that depends differentially on a parameter p, is defined as*

$$
\Upsilon_p^u:=\frac{\partial u}{\partial p}\times\frac{p}{u}. \tag{20}
$$

Table 1: The normalized forward sensitivity index of R_0

Parameters	Sensitivity index of R_0
β_1	$\Upsilon_{\beta_1}^{R_0} = \frac{k\beta_1}{k\beta_1+\mu\beta_2}$
β_2	$\Upsilon_{\beta_2}^{R_0} = \frac{\mu\beta_2}{k\beta_1+\mu\beta_2}$
γ	$\Upsilon_{\gamma}^{R_0} = \frac{m\gamma(1-\rho)}{(\rho m+\gamma)(m+\gamma)}$
λ	$\Upsilon_{\lambda}^{R_0} = +1$
μ	$\Upsilon_{\mu}^{R_0} = \frac{-k}{k+\mu}$
ρ	$\Upsilon_{\rho}^{R_0} = \frac{m\rho}{m\rho+\gamma}$
m	$\Upsilon_{m}^{R_0} = \frac{m\gamma(\rho-1)}{(\rho m+\gamma)(m+\gamma)}$
k	$\Upsilon_{k}^{R_0} = \frac{k}{k+\mu}$
a	$\Upsilon_{a}^{R_0} = -1$
d	$\Upsilon_{d}^{R_0} = -1$

From (19) and Definition 51, we derive the normalized forward sensitivity index of R_0 with respect to β_1, β_2, γ, λ, μ, ρ, m, k, a, and d in the following Table 1.

Remarks 52 *The effective contact rate is always the most sensitive parameter and have a high impact on the basic reproduction number R_0. Indeed, when $\beta_2 = 0$ ($\beta_1 = 0$), $\Upsilon_{\beta_1}^{R_0}$ ($\Upsilon_{\beta_2}^{R_0}$) is independent of any other parameter with $\Upsilon_{\beta_1}^{R_0} = +1$ ($\Upsilon_{\beta_2}^{R_0} = +1$). Also when $\beta = \beta_1 = \beta_2$, $\Upsilon_{\beta}^{R_0} = +1$.*

Remarks 53 *Likewise, g and c are always the most sensitive parameters and have a high impact on the reproduction numbers for humoral immunity and the reproduction numbers for cellular immunity, respectively. Indeed, $\Upsilon_g^{R_1^w}$, $\Upsilon_g^{R_2^w}$, $\Upsilon_c^{R_1^z}$ and $\Upsilon_c^{R_2^z}$ are independent of any other parameter with $\Upsilon_g^{R_1^w} = +1$, $\Upsilon_g^{R_2^w} = +1$, $\Upsilon_c^{R_1^z} = +1$ and $\Upsilon_c^{R_2^z} = +1$.*

5.2 Numerical simulations

In this subsection, we provide numerical simulations that support our theoretical results. In what follows, we fix the following parameters for a technical reason.

$$\begin{array}{lllllll} \lambda = 1, & d = 1, & \rho = 0.5, & m = 2, & \gamma = 100, & a = 10, \\ p = 1, & k = 10, & \mu = 10, & q = 1, & h = 1, & b = 1. \end{array} \tag{21}$$

Although the choice of parameters in (21) is not based on any observed data, our assumptions for a rough biological justification are as follows.

- –The average life span of the susceptible host cells is $1/d = 1$ (unit time).
- –The total cell concentrations λ/d in the infection-free equilibrium E_0 is normalized as 1.
- –The infected cells experience the latent period with probability $\rho = 0.5$.
- –The average life spans of latent infected cells $1/m$ and productive infected cells $1/a$ are $1/2$ times and $1/10$ times shorter than that of the susceptible host cells, respectively.
- –The average latent period $1/\gamma$ is $1/100$ times shorter than that of the average life span of the susceptible host cells.
- –$k = 10$ viruses are produced by a productive infected cell per unit time.
- –The upper bound k/μ of free virus particles is normalized as 1.
- –The average life spans of antibodies $1/h$ and CTL cells $1/b$ are equal to that of the susceptible host cells.

Moreover, we assume that the initial conditions are fixed as follows

$$x(0) = 0.99,\ l(0) = 0,\ y(0) = 0,\ v(0) = 0.1,\ w(0) = 0.1,\ z(0) = 0.1, \tag{22}$$

and $\beta = \beta_1 = \beta_2$. In what follows, we observe the dynamics of system (1) with different parameter set (β, g, c) and α. For the numerical computation of the Caputo fractional derivative, we use the fractional Euler's method as stated in [47].

Firstly, we set $(\beta, g, c) = (5, 1, 1)$. In this case, we obtain $R_0 \approx 0.9542 < 1$. Hence, by Theorem 41, we see that the infection-free equilibrium E_0 is globally asymptotically stable. In fact, Figure 1 shows that $(v(t), w(t), z(t))$ converges to $(0, 0, 0)$ as time evolves.

Secondly, we set $(\beta, g, c) = (6, 1, 1)$. In this case, we obtain $R_0 \approx 1.1450 > 1$, $R_1^w \approx 0.0767 < 1$ and $R_1^z \approx 0.0849 < 1$. Hence, by Theorem 42 (i), we see that the immune-free infection equilibrium E_1 is globally asymptotically stable. In fact, Figure 2 shows that $(v(t), w(t), z(t))$ converges to $(v_1, 0, 0)$ as time evolves.

Thirdly, we set $(\beta, g, c) = (6, 100, 1)$. In this case, we obtain $R_0 \approx 1.1450 > 1$, $R_1^w \approx 1.0961 > 1$ and $R_1^z \approx 0.0849 < 1$. Hence, by Theorem 42 (ii), we see that the infection equilibrium with only humoral immunity E_2 is globally asymptotically stable. In fact, Figure 3 shows that $(v(t), w(t), z(t))$ converges to $(v_2, w_2, 0)$ as time evolves.

Fourthly, we set $(\beta, g, c) = (6, 1, 100)$. In this case, we obtain $R_0 \approx 1.1450 > 1$, $R_1^w \approx 0.0767 < 1$ and $R_1^z \approx 1.0516 > 1$. Hence, by Theorem 42 (iii), we see that the infection equilibrium with only cellular immunity E_3 is globally asymptotically stable. In fact, Figure 4 shows that $(v(t), w(t), z(t))$ converges to $(v_3, 0, z_3)$ as time evolves.

Finally, we set $(\beta, g, c) = (6, 110, 100)$. In this case, we obtain $R_0 \approx 1.1450 > 1$, $R_2^w \approx 1.1000 > 1$ and $R_2^z \approx 1.0090 > 1$. Hence, by Theorem 42 (iv), we see that the infection equilibrium with both cellular and humoral immunity E_4 is globally asymptotically stable. In fact, Figure 5 shows that $(v(t), w(t), z(t))$ converges to (v_4, w_4, z_4) as time evolves.

6 Conclusion

In this paper, we studied a fractional order viral infection model with the adaptive immunity, latency and general nonlinear incidence functions for both of the virus-to-cell and cell-to-cell transmissions. We obtained five reproduction numbers R_0, R_1^w, R_1^z, R_2^w that determine the existence of five equilibria: the infection-free equilibrium E_0, the immune-free infection equilibrium E_1, the infection equilibrium with only humoral immunity E_2, the infection equilibrium with only cellular immunity E_3 and the infection equilibrium with both humoral and cellular immunity E_4 (see Theorem 31). Moreover, by constructing suitable Lyapunov functionals, we showed that, under assumption (H_4), the reproduction numbers R_0, R_1^w, R_1^z, R_2^w and R_2^z are also the threshold parameters for the global asymptotic stability of the equilibria E_0, E_1, E_2, E_3 and E_4 (see Theorems 41-42). We also performed a sensitivity analysis of these reproduction numbers and numerical simulations to confirm the validity of our theoretical results.

Based on our numerical simulations, we observed that activation of the adaptive immune response decreases viral load to lower levels, but does not eliminate the infection. Besides, we deduce that the order of the fractional derivative α has a remarkable effect on the dynamics of the model. Precisely, a small value of α (long memory) implies a rapid convergence towards equilibrium points.

From our theoretical and numerical results, we conclude that including memory effect, presented by Caputo's derivative, enriches the dynamics of the proposed model and gives more information about the interactions between cells. In our future study, we will extend the proposed fractional-order model by incorporating some effective controlling strategies.

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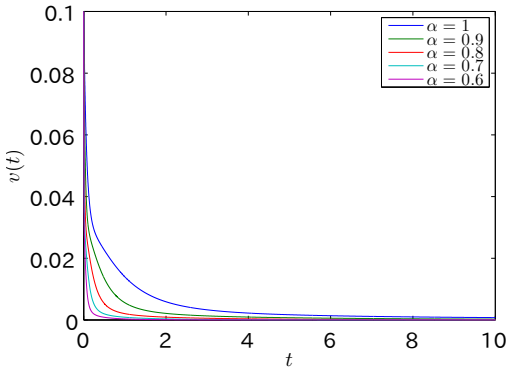
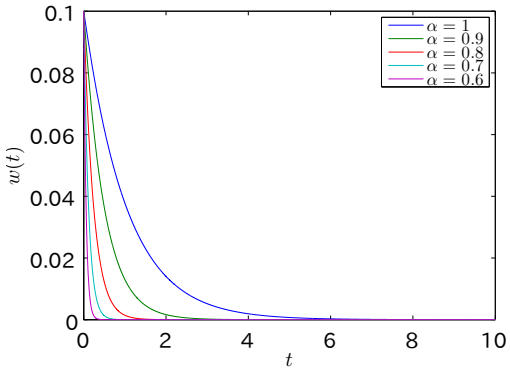


[**Time variation of the concentration of the free virus particles** $v(t)$**.**]



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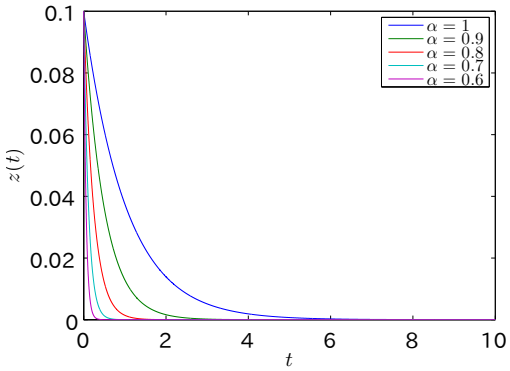
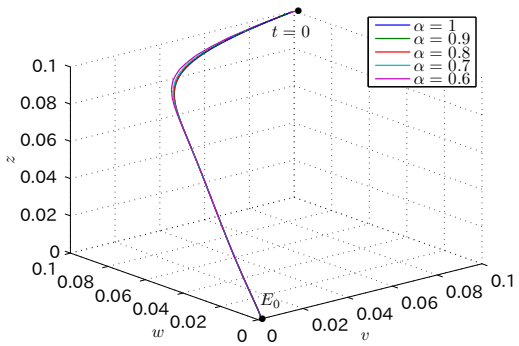
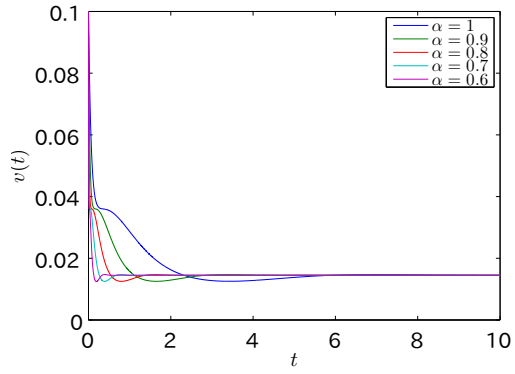


[**Time variation of the concentration of the CTL cells** $z(t)$**.**]

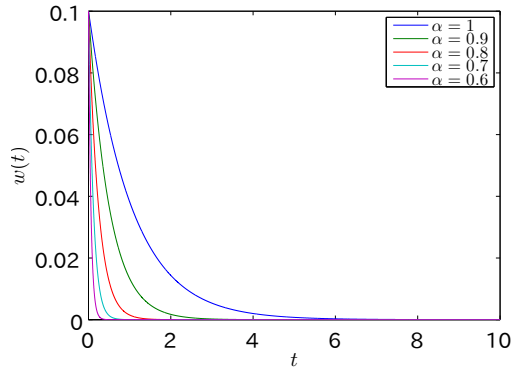


[**3D phase plot of** (v,w,z)**.**]

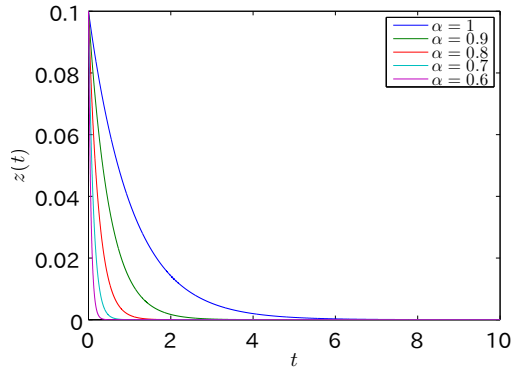
Fig. 1: Dynamics of (v,w,z) **of system** (1) **with** (21)-(22)**,** $(\beta,g,c) = (5,1,1)$ **and** $\alpha = 0.6, 0.7, 0.8, 0.9, 1$ **(**$R_0 \approx 0.9542 < 1$**).**



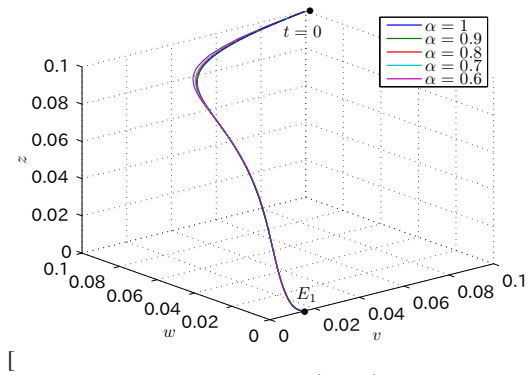
[**Time variation of the concentration of the free virus particles** $v(t)$**.**]



[**Time variation of the concentration of the antibodies** $w(t)$**.**]



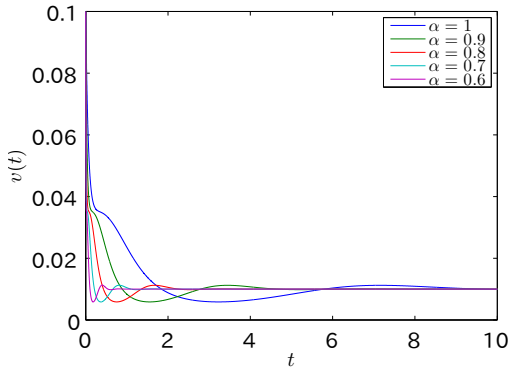
[**Time variation of the concentration of the CTL cells** $z(t)$**.**]



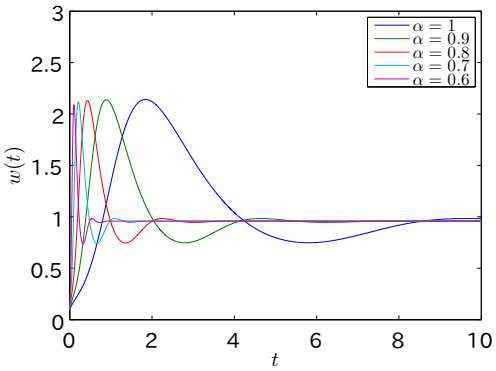
[

3**D phase plot of** (v,w,z)**.**]

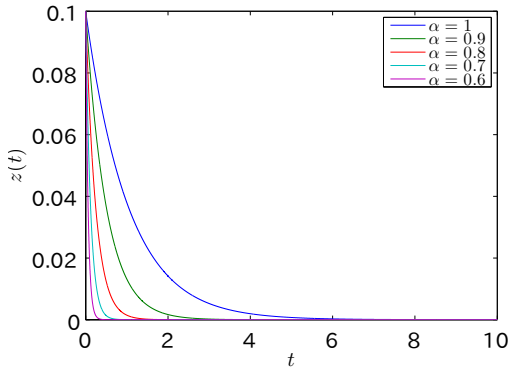
Fig. 2: Dynamics of (v,w,z) **of system** (1) **with** (21)-(22)**,** $(\beta,g,c) = (6,1,1)$ **and** $\alpha = 0.6,0.7,0.8,0.9,1$ **(**$R_0 \approx 1.1450 > 1$**,** $R_1^w \approx 0.0767 < 1$ **and** $R_1^z \approx 0.0849 < 1$**).**



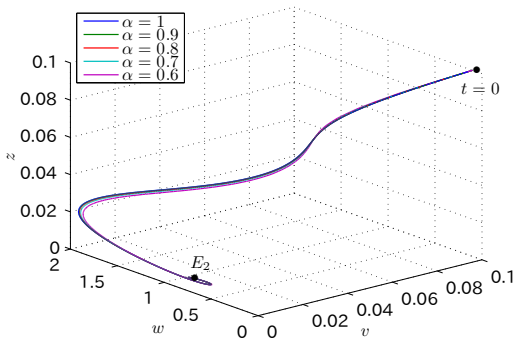
[**Time variation of the concentration of the free virus particles** $v(t)$**.**]



[**Time variation of the concentration of the antibodies** $w(t)$**.**]

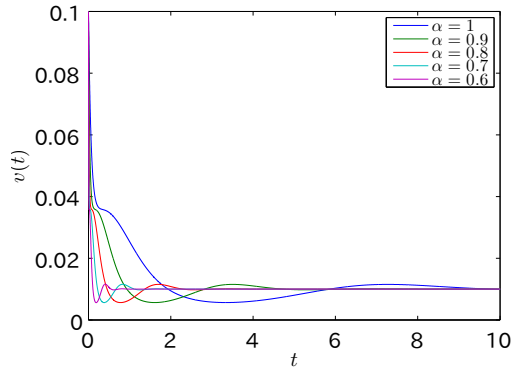


[**Time variation of the concentration of the CTL cells** $z(t)$**.**]

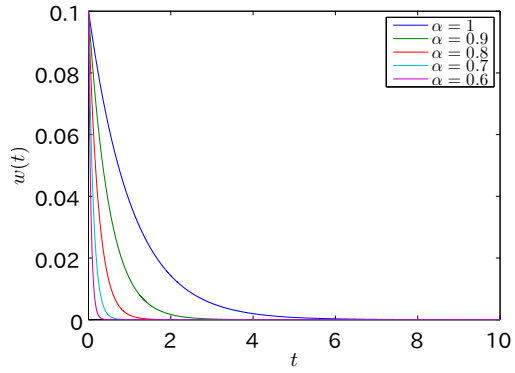


[**3D phase plot of** (v,w,z)**.**]

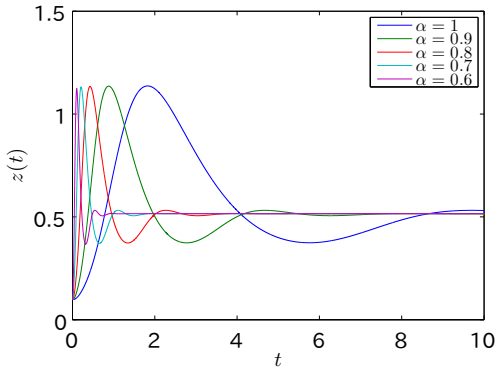
Fig. 3: Dynamics of (v,w,z) **of system** (1) **with** (21)-(22)**,** $(\beta,g,c) = (6,100,1)$ **and** $\alpha = 0.6,0.7,0.8,0.9,1$ **(**$R_0 \approx 1.1450 > 1$**,** $R_1^w \approx 1.0961 > 1$ **and** $R_1^z \approx 0.0849 < 1$**).**



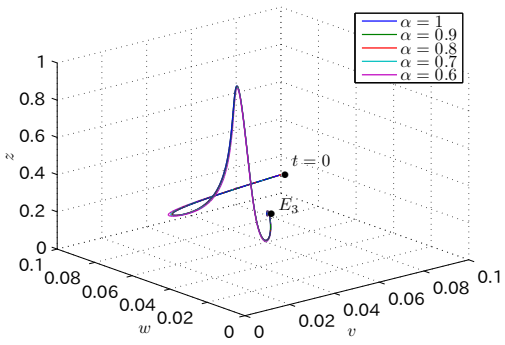
[**Time variation of the concentration of the free virus particles** $v(t)$**.**]



[**Time variation of the concentration of the antibodies** $w(t)$**.**]

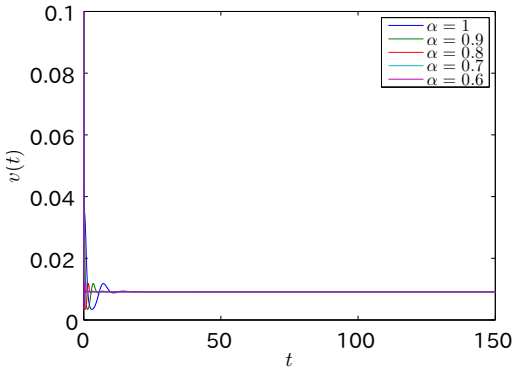


[**Time variation of the concentration of the CTL cells** $z(t)$**.**]

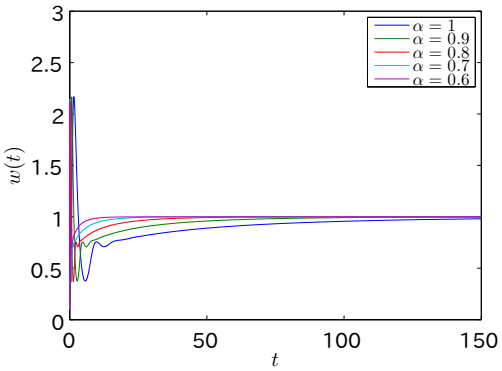


[**3D phase plot of** (v,w,z)**.**]

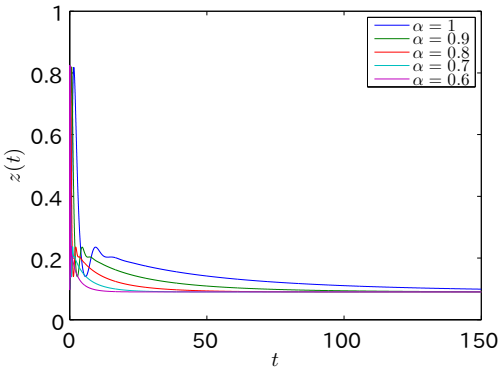
Fig. 4: Dynamics of (v,w,z) **of system** (1) **with** (21)-(22)**,** $(\beta,g,c) = (6,1,100)$ **and** $\alpha = 0.6,0.7,0.8,0.9,1$ **(**$R_0 \approx 1.1450 > 1$**,** $R_1^w \approx 0.0767 < 1$ **and** $R_1^z \approx 1.0516 > 1$**).**



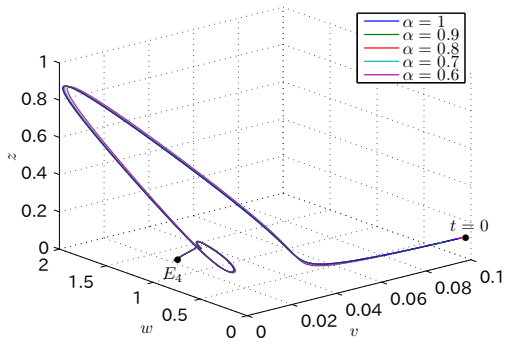
[**Time variation of the concentration of the free virus particles** $v(t)$**.**]



[**Time variation of the concentration of the antibodies** $w(t)$**.**]



[**Time variation of the concentration of the CTL cells** $z(t)$**.**]



[**3D phase plot of** (v,w,z)**.**]

Fig. 5: Dynamics of (v,w,z) **of system** (1) **with** (21)-(22)**,** $(\beta,g,c) = (6,110,100)$ **and** $\alpha = 0.6,0.7,0.8,0.9,1$ **(**$R_0 \approx 1.1450 > 1$**,** $R_2^w \approx 1.1000 > 1$ **and** $R_2^z \approx 1.0090 > 1$**).**

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