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Research Article

A Fractional Order Model for Viral Infection with Cure of Infected Cells and Humoral Immunity

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In this paper, we study the dynamics of a viral infection model formulated by five fractional differential equations (FDEs) to describe the interactions between host cells, virus, and humoral immunity presented by antibodies. The infection transmission process is modeled by Hattaf-Yousfi functional response which covers several forms of incidence rate existing in the literature. We first show that the model is mathematically and biologically well-posed. By constructing suitable Lyapunov functionals, the global stability of equilibria is established and characterized by two threshold parameters. Finally, some numerical simulations are presented to illustrate our theoretical analysis.

1. Introduction

The immune response plays an important role to control the dynamics of viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell leukemia virus (HTLV). Therefore, many mathematical models have been developed to incorporate the role of immune response in viral infections. Some of these models considered the cellular immune response mediated by cytotoxic T lymphocytes (CTL) cells that attack and kill the infected cells [1–5] and the others considered the humoral immune response based on the antibodies which are produced by the B-cells and are programmed to neutralize the viruses [6–11]. However, all these models have been formulated by using ordinary differential equations (ODEs) in which the memory effect is neglected while the immune response involves memory [12, 13].

Fractional derivative is a generalization of integer derivative and it is a suitable tool to model real phenomena with memory which exists in most biological systems [14–16]. The fractional derivative is a nonlocal operator in contrast to integer derivative. This means that if we want to compute the fractional derivative at some point $t = t_1$, it is necessary to take into account the entire history from the starting point $t = t_0$ up to the point $t = t_1$. For these reasons, modeling some real process by using fractional derivative has drawn attention of several authors in various fields [17–22]. In biology, it has been shown that the fractional derivative is useful to analyse the rheological proprieties of cells [23]. Furthermore, it has been deduced that the membranes of cells of biological organism have fractional order electrical conductance [24]. Recently, much works have been done on modeling the dynamics of viral infections with FDEs [25–31]. These works ignored the impact of the immune response and the majority of them deal only with the local stability.

In some viral infections, the humoral immune response is more effective than cellular immune response [32]. For this reason, we improve the above ODE and FDE models by proposing a new fractional order model that describes the interactions between susceptible host cells, viral particles, and the humoral immune response mediated by the antibodies; that is,

$$D^{\alpha}x(t) = \lambda - dx - f(x,v)v + \rho l,$$

$$D^{\alpha}l(t) = f(x,v)v - (m+\rho+\gamma)l,$$

$$
\begin{aligned}
D^{\alpha} y(t) &= \gamma l - a y, \\
D^{\alpha} v(t) &= k y - \mu v - q v w, \\
D^{\alpha} w(t) &= g v w - h w,
\end{aligned}
\tag{1}
$$

where $x(t)$, $l(t)$, $y(t)$, $v(t)$, and $w(t)$ are the concentrations of susceptible host cells, latently infected cells (infected cells which are not yet able to produce virions), productive infected cells, free virus particles, and antibodies 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 virus at the rate $f(x, v)v$. Latently infected cells die at the rate ml and return to the uninfected state by loss of all covalently closed circular DNA (cccDNA) from their nucleus at the rate ρl. Productive infected cells are produced from latently infected cells at the rate γl and die at the rate ay. Free virus particles are produced from productive infected cells at the rate ky, cleared at the rate μv, and are neutralized by antibodies at the rate qvw. Antibodies are activated against virus at the rate gvw and die at the rate hw.

In system (1), D^{α} represents the Caputo fractional derivative of order α defined for an arbitrary function φ by

$$
D^{\alpha} \varphi(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{\varphi'(u)}{(t-u)^{\alpha}} du, \tag{2}
$$

with $0 < \alpha \leq 1$ [33]. Further, the infection transmission process in (1) is modeled by Hattaf-Yousfi functional response [34] which was recently used in [35, 36] and has the form $f(x, v) = \beta x/(\alpha_0 + \alpha_1 x + \alpha_2 v + \alpha_3 x v)$, where $\alpha_0, \alpha_1, \alpha_2, \alpha_3 \geq 0$ are the saturation factors measuring the psychological or inhibitory effect and $\beta > 0$ is the infection rate. In addition, this functional response generalizes many common types existing in the literature such as the specific functional response proposed by Hattaf et al. in [37] and used in [2, 31] when $\alpha_0 = 1$; the Crowley-Martin functional response introduced in [38] and used in [39] when $\alpha_0 = 1$ and $\alpha_3 = \alpha_1\alpha_2$; and the Beddington-DeAngelis functional response proposed in [40, 41] and used in [3, 4, 10] when $\alpha_0 = 1$ and $\alpha_3 = 0$. Also, the Hattaf-Yousfi functional response is reduced to the saturated incidence rate used in [9] when $\alpha_0 = 1$ and $\alpha_1 = \alpha_3 = 0$ and the standard incidence function used in [27] when $\alpha_0 = \alpha_3 = 0$ and $\alpha_1 = \alpha_2 = 1$, and it was simplified to the bilinear incidence rate used in [5, 6] when $\alpha_0 = 1$ and $\alpha_1 = \alpha_2 = \alpha_3 = 0$.

On the other hand, system (1) becomes a model with ODEs when $\alpha = 1$, which improves and generalizes the ODE model with bilinear incidence rate [42], the ODE model with saturated incidence rate [43], and the ODE model with specific functional response [44].

The rest of the paper is organized as follows. The next section deals with some basic proprieties of the solutions and the existence of equilibria. The global stability of equilibria is established in Section 3. To verify our theoretical results, we provide some numerical simulations in Section 4, and we conclude in Section 5.

2. Basic Properties and Equilibria

In this section, we will show that our model is well-posed and we discuss the existence of equilibria.

Since system (1) describes the evolution of cells, then we need to prove that the cell numbers should remain nonnegative and bounded. For biological considerations, we assume that the initial conditions of (1) satisfy

$$
\begin{aligned}
x(0) &\geq 0, \\
l(0) &\geq 0, \\
y(0) &\geq 0, \\
v(0) &\geq 0, \\
w(0) &\geq 0.
\end{aligned}
\tag{3}
$$

Then we have the following result.

Theorem 1. *Assume that the initial conditions satisfy (3). Then there exists a unique solution of system (1) defined on* $[0, +\infty)$. *Moreover, this solution remains nonnegative and bounded for all* $t \geq 0$.

Proof. First, system (1) can be written as follows:

$$
D^{\alpha} X(t) = F(X), \tag{4}
$$

where

$$
X(t) = \begin{pmatrix} x(t) \\ l(t) \\ y(t) \\ v(t) \\ w(t) \end{pmatrix}
$$

$$
\text{and } F(X) = \begin{pmatrix} \lambda - dx - f(x, v)v + \rho l \\ f(x, v)v - (m + \rho + \gamma) l \\ \gamma l - a y \\ k y - \mu v - q v w \\ g v w - h w \end{pmatrix}. \tag{5}
$$

It is important to note that when $\alpha = 1$, (4) becomes a system with ODEs. In this case, we refer the reader to [45] for the existence of solutions and to the works [46–50] for the stability of equilibria. In the case of FDEs, we will use Lemma

2.4 in [31] to prove the existence and uniqueness of solutions. Hence, we put

$$\zeta = \begin{pmatrix} \lambda \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$A = \begin{pmatrix} -d & \rho & 0 & 0 & 0 \\ 0 & -(m+\rho+\gamma) & 0 & 0 & 0 \\ 0 & \gamma & -a & 0 & 0 \\ 0 & 0 & k & -\mu & 0 \\ 0 & 0 & 0 & 0 & -h \end{pmatrix} \quad (6)$$

$$\text{and } C = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -q \\ 0 & 0 & 0 & 0 & g \end{pmatrix}.$$

We discuss four cases:

(i) If $\alpha_0 \neq 0$, $F(X)$ can be formulated as follows:

$$F(X) = \zeta + AX + \frac{\alpha_0}{\alpha_0 + \alpha_1 x + \alpha_2 v + \alpha_3 xv} vB_0 X + vCX, \quad (7)$$

where

$$B_0 = \begin{pmatrix} -\frac{\beta}{\alpha_0} & 0 & 0 & 0 & 0 \\ \frac{\beta}{\alpha_0} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}. \quad (8)$$

Hence,

$$\|F(X)\| \leq \|\zeta\| + (\|A\| + \|v\|(\|B_0\| + \|C\|))\|X\|. \quad (9)$$

(ii) If $\alpha_1 \neq 0$, we can write $F(X)$ in the form

$$F(X) = \zeta + AX + \frac{\alpha_1 x}{\alpha_0 + \alpha_1 x + \alpha_2 v + \alpha_3 xv} B_1 X + vCX, \quad (10)$$

where

$$B_1 = \begin{pmatrix} 0 & 0 & 0 & -\frac{\beta}{\alpha_1} & 0 \\ 0 & 0 & 0 & \frac{\beta}{\alpha_1} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}. \quad (11)$$

Moreover, we get

$$\|F(X)\| \leq \|\zeta\| + (\|A\| + \|B_1\| + \|v\|\|C\|)\|X\|. \quad (12)$$

(iii) If $\alpha_2 \neq 0$, we have

$$F(X) = \zeta + AX + \frac{\alpha_2 v}{\alpha_0 + \alpha_1 x + \alpha_2 v + \alpha_3 xv} B_2 X + vCX, \quad (13)$$

where

$$B_2 = \begin{pmatrix} -\frac{\beta}{\alpha_2} & 0 & 0 & 0 & 0 \\ \frac{\beta}{\alpha_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}. \quad (14)$$

Further, we obtain

$$\|F(X)\| \leq \|\zeta\| + (\|A\| + \|B_2\| + \|v\|\|C\|)\|X\|. \quad (15)$$

(iv) If $\alpha_3 \neq 0$, we have

$$F(X) = \zeta + AX + \frac{\alpha_3 xv}{\alpha_0 + \alpha_1 x + \alpha_2 v + \alpha_3 xv} B_3 + vCX, \quad (16)$$

where

$$B_3 = \begin{pmatrix} -\frac{\beta}{\alpha_3} \\ \frac{\beta}{\alpha_3} \\ 0 \\ 0 \\ 0 \end{pmatrix}. \quad (17)$$

Then

$$\|F(X)\| \leq (\|\zeta\| + \|B_3\|) + (\|A\| + \|v\|\|C\|)\|X\|. \quad (18)$$

Hence, the conditions of Lemma 2.4 in [31] are verified. Then system (1) has a unique solution on $[0, +\infty)$. Now, we show the nonnegativity of solutions. By (1), we have

$$\begin{aligned} D^{\alpha}x(t)\big|_{x=0} &= \lambda + \rho l \geq 0, \\ D^{\alpha}l(t)\big|_{l=0} &= f(x,v)\,v \geq 0, \\ D^{\alpha}y(t)\big|_{y=0} &= \gamma l \geq 0, \\ D^{\alpha}v(t)\big|_{v=0} &= ky \geq 0, \\ D^{\alpha}w(t)\big|_{w=0} &= 0 \geq 0. \end{aligned} \tag{19}$$

As in [31, Theorem 2.7], we deduce that the solution of (1) is nonnegative.

Finally, we prove the boundedness of solutions. We define the function

$$T(t) = x(t) + l(t) + y(t) + \frac{a}{2k}v(t) + \frac{aq}{2kg}w(t). \tag{20}$$

Then, we have

$$\begin{aligned} D^{\alpha}T(t) &= D^{\alpha}x(t) + D^{\alpha}l(t) + D^{\alpha}y(t) + \frac{a}{2k}D^{\alpha}v(t) \\ &\quad + \frac{aq}{2kg}D^{\alpha}w(t) \\ &= \lambda - dx(t) - ml(t) - \frac{a}{2}y(t) - \frac{a\mu}{2k}v(t) \\ &\quad - \frac{aqh}{2kg}w(t) \leq \lambda - \delta T(t), \end{aligned} \tag{21}$$

where $\delta = \min\{d, m, a/2, \mu, h\}$. Thus, we obtain

$$T(t) \leq T(0)\,E_{\alpha}\left(-\delta t^{\alpha}\right) + \frac{\lambda}{\delta}\left[1 - E_{\alpha}\left(-\delta t^{\alpha}\right)\right]. \tag{22}$$

Since $0 \leq E_{\alpha}(-\delta t^{\alpha}) \leq 1$, we get

$$T(t) \leq T(0) + \frac{\lambda}{\delta}. \tag{23}$$

This completes the proof. □

Now, we discuss the existence of equilibria. It is clear that system (1) has always an infection-free equilibrium $E_0(\lambda/d, 0, 0, 0, 0)$. Then the basic reproduction number of (1) is as follows:

$$R_0 = \frac{k\beta\lambda\gamma}{a\mu\left(m+\rho+\gamma\right)\left(d\alpha_0 + \lambda\alpha_1\right)}. \tag{24}$$

To find the other equilibria, we solve the following system:

$$\lambda - dx - f(x,v)\,v + \rho l = 0, \tag{25}$$

$$f(x,v)\,v - \left(m+\rho+\gamma\right)l = 0, \tag{26}$$

$$\gamma l - ay = 0, \tag{27}$$

$$ky - \mu v - qvw = 0, \tag{28}$$

$$gvw - hw = 0. \tag{29}$$

From (29), we get $w = 0$ or $v = h/g$. Then we discuss two cases.

If $w = 0$, by (25)-(28), we have $l = (\lambda - dx)/(m+\gamma)$, $y = \gamma(\lambda - dx)/a(m+\gamma)$, $v = k\gamma(\lambda - dx)/a\mu(m+\gamma)$, and

$$f\left(x, \frac{k\gamma\left(\lambda - dx\right)}{a\mu\left(m+\gamma\right)}\right) = \frac{a\mu\left(m+\rho+\gamma\right)}{k\gamma}. \tag{30}$$

Since $l \geq 0$, $y \geq 0$, and $v \geq 0$, then $x \leq \lambda/d$. Consequently, there is no equilibrium when $x > \lambda/d$.

We define the function h_1 on $[0, \lambda/d]$ by

$$h_1(x) = f\left(x, \frac{k\gamma\left(\lambda - dx\right)}{a\mu\left(m+\gamma\right)}\right) - \frac{a\mu\left(m+\rho+\gamma\right)}{k\gamma}. \tag{31}$$

We have $h_1(0) = -a\mu(m+\rho+\gamma)/k\gamma < 0$, $h_1'(x) = \partial f/\partial x - (k\gamma d/a\mu(m+\gamma))(\partial f/\partial v) > 0$, and $h_1(\lambda/d) = (a\mu(m+\rho+\gamma)/k\gamma)(R_0 - 1)$.

Hence if $R_0 > 1$, (30) has a unique root $x_1 \in (0, \lambda/d)$. As a result, when $R_0 > 1$ there exists an equilibrium $E_1(x_1, l_1, y_1, v_1, 0)$ satisfying $x_1 \in (0, \lambda/d)$, $l_1 = (\lambda - dx_1)/(m+\gamma)$, $y_1 = \gamma(\lambda - dx_1)/a(m+\gamma)$, and $v_1 = k\gamma(\lambda - dx_1)/a\mu(m+\gamma)$.

If $w \neq 0$, then $v = h/g$. By (25)-(27), we obtain $l = (\lambda - dx)/(m+\gamma)$, $y = \gamma(\lambda - dx)/a(m+\gamma)$, $w = k\gamma g(\lambda - dx)/aqh(m+\gamma) - \mu/q$, and

$$f\left(x, \frac{h}{g}\right) = \frac{g\left(m+\rho+\gamma\right)}{h\left(m+\gamma\right)}\left(\lambda - dx\right). \tag{32}$$

Since $l \geq 0$, $y \geq 0$, and $w \geq 0$, we have $x \leq \lambda/d - ah\mu(m+\gamma)/dkg\gamma$. Hence, there is no equilibrium if $x > \lambda/d - ah\mu(m+\gamma)/dkg\gamma$.

We define the function h_2 on $[0, \lambda/d - ah\mu(m+\gamma)/dkg\gamma]$ by

$$h_2(x) = f\left(x, \frac{h}{g}\right) - \frac{g\left(m+\rho+\gamma\right)}{h\left(m+\gamma\right)}\left(\lambda - dx\right). \tag{33}$$

We have $h_2(0) = -g\lambda(m+\rho+\gamma)/h(m+\gamma) < 0$, $h_2'(x) = \partial f/\partial x + gd(m+\rho+\gamma)/h(m+\gamma) > 0$, and $h_2(\lambda/d - ah\mu(m+\gamma)/dkg\gamma) = h_1(\lambda/d - ah\mu(m+\gamma)/dkg\gamma)$.

Let us introduce the reproduction number for humoral immunity as follows:

$$R_1 = \frac{gv_1}{h}, \tag{34}$$

which $1/h$ denotes the average life expectancy of antibodies and v_1 is the number of free viruses at E_1. For the biological significance, R_1 represents the average number of the antibodies activated by virus.

If $R_1 < 1$, we have $x_1 > \lambda/d - ah\mu(m+\gamma)/dkg\gamma$ and

$$h_2\left(\frac{\lambda}{d} - \frac{ah\mu\left(m+\gamma\right)}{dkg\gamma}\right) < h_1\left(x_1\right) = 0. \tag{35}$$

Therefore, there is no equilibrium when $R_1 < 1$.

If $R_1 > 1$, then $x_1 < \lambda/d - ah\mu(m+\gamma)/dkg\gamma$ and

$$h_2\left(\frac{\lambda}{d} - \frac{ah\mu\left(m+\gamma\right)}{dkg\gamma}\right) > h_1\left(x_1\right) = 0. \tag{36}$$

In this case, (32) has one root $x_2 \in (0, \lambda/d - ah\mu(m+\gamma)/dkg\gamma)$. Consequently, when $R_1 > 1$, there exists an equilibrium $E_2(x_2, l_2, y_2, v_2, w_2)$ satisfying $x_2 \in (0, \lambda/d - ah\mu(m+\gamma)/dkg\gamma)$, $l_2 = (\lambda - dx_2)/(m+\gamma)$, $y_2 = \gamma(\lambda - dx_2)/a(m+\gamma)$, $v_2 = h/g$, and $w_2 = k\gamma g(\lambda - dx_2)/aqh(m+\gamma) - \mu/q$. When $R_1 = 1$, $E_1 = E_2$.

We summarize the above discussions in the following theorem.

Theorem 2.

(i) *If $R_0 \leq 1$, then system (1) has one infection-free equilibrium of the form $E_0(x_0, 0, 0, 0, 0)$, where $x_0 = \lambda/d$.*

(ii) *If $R_0 > 1$, then system (1) has an infection equilibrium without humoral immunity of the form $E_1(x_1, l_1, y_1, v_1, 0)$, where $x_1 \in (0, \lambda/d)$, $l_1 = (\lambda - dx_1)/(m+\gamma)$, $y_1 = \gamma(\lambda - dx_1)/a(m+\gamma)$, and $v_1 = k\gamma(\lambda - dx_1)/a\mu(m+\gamma)$.*

(iii) *If $R_1 > 1$, then system (1) has an infection equilibrium with humoral immunity of the form $E_2(x_2, l_2, y_2, v_2, w_2)$, where $x_2 \in (0, \lambda/d - ah\mu(m+\gamma)/dkg\gamma)$, $l_2 = (\lambda - dx_2)/(m+\gamma)$, $y_2 = \gamma(\lambda - dx_2)/a(m+\gamma)$, $v_2 = h/g$, and $w_2 = k\gamma g(\lambda - dx_1)/aqh(m+\gamma) - \mu/q$.*

3. Global Stability of Equilibria

In this section, we focus on the global stability of equilibria.

Theorem 3. *If $R_0 \leq 1$, then the infection-free equilibrium E_0 is globally asymptotically stable and it becomes unstable if $R_0 > 1$.*

Proof. The proof of the first part of this theorem is based on the construction of a suitable Lyapunov functional that satisfies the conditions given in [51, Lemma 4.6]. Hence, we define a Lyapunov functional as follows:

$$\begin{aligned} L_0(t) &= \frac{\alpha_0}{\alpha_0 + \alpha_1 x_0} x_0 \Phi\left(\frac{x}{x_0}\right) \\ &\quad + \frac{\rho\alpha_0}{2(d+m+\gamma)(\alpha_0 + \alpha_1 x_0) x_0} (x - x_0 + l)^2 \\ &\quad + l + \frac{m+\rho+\gamma}{\gamma} y + \frac{a(m+\rho+\gamma)}{k\gamma} v \\ &\quad + \frac{aq(m+\rho+\gamma)}{kg\gamma} w, \end{aligned} \tag{37}$$

where $\Phi(x) = x - 1 - \ln(x)$ for $x > 0$. It is not hard to show that the functional L_0 is nonnegative. In fact, the function Φ has a global minimum at $x = 1$. Consequently, $\Phi(x) \geq 0$ for all $x > 0$.

Calculating the fractional derivative of $L_0(t)$ along solutions of system (1) and using the results in [52], we get

$$\begin{aligned} D^\alpha L_0(t) &\leq \frac{\alpha_0}{\alpha_0 + \alpha_1 x_0}\left(1 - \frac{x_0}{x}\right) D^\alpha x \\ &\quad + \frac{\rho\alpha_0}{(d+m+\gamma)(\alpha_0 + \alpha_1 x_0) x_0} (x - x_0 + l) \\ &\quad \cdot (D^\alpha x + D^\alpha l) + D^\alpha l + \frac{m+\rho+\gamma}{\gamma} D^\alpha y \\ &\quad + \frac{a(m+\rho+\gamma)}{k\gamma} D^\alpha v + \frac{aq(m+\rho+\gamma)}{kg\gamma} D^\alpha w. \end{aligned} \tag{38}$$

Using $\lambda = dx_0$, we obtain

$$\begin{aligned} D^\alpha L_0(t) &\leq -\frac{d\alpha_0 (x - x_0)^2}{(\alpha_0 + \alpha_1 x_0) x} - \frac{\alpha_0}{\alpha_0 + \alpha_1 x_0}\left(1 - \frac{x_0}{x}\right) \\ &\quad \cdot f(x, v) v + \frac{\rho\alpha_0}{\alpha_0 + \alpha_1 x_0}\left(1 - \frac{x_0}{x}\right) l \\ &\quad \cdot \frac{\rho\alpha_0 (x - x_0 + l)}{(d+m+\gamma)(\alpha_0 + \alpha_1 x_0) x_0} (d(x_0 - x) \\ &\quad - (m+\gamma) l) + f(x, v) v - \frac{a\mu(m+\rho+\gamma)}{k\gamma} v \\ &\quad - \frac{aqh(m+\rho+\gamma)}{kg\gamma} w \\ &\leq -\left(\frac{1}{x} + \frac{\rho}{(d+m+\gamma) x_0}\right) \frac{d\alpha_0 (x - x_0)^2}{(\alpha_0 + \alpha_1 x_0)} \\ &\quad - \frac{\rho\alpha_0 (m+\gamma) l^2}{(d+m+\gamma)(\alpha_0 + \alpha_1 x_0) x_0} - \frac{\rho\alpha_0 (x - x_0)^2 l}{(\alpha_0 + \alpha_1 x_0) x x_0} \\ &\quad + \frac{a\mu(m+\rho+\gamma)}{k\gamma} (R_0 - 1) v - \frac{aqh(m+\rho+\gamma)}{kg\gamma} w. \end{aligned} \tag{39}$$

Hence if $R_0 \leq 1$, then $D^\alpha L_0(t) \leq 0$. In addition, the equality holds if and only if $x = x_0, l = 0, y = 0, w = 0$, and $(R_0 - 1)v = 0$. If $R_0 < 1$, then $v = 0$. If $R_0 = 1$, from (1), we get $f(x_0, v)v = 0$ which implies that $v = 0$. Consequently, the largest invariant set of $\{(x, l, y, v, w) \in \mathbb{R}^5_+ : D^\alpha L_0(t) = 0\}$ is the singleton $\{E_0\}$. Therefore, by the LaSalle's invariance principle [51], E_0 is globally asymptotically stable.

The proof of the instability of E_0 is based on the computation of the Jacobean matrix of system (1) and the results presented in [53–55]. The Jacobean matrix of (1) at any equilibrium $E(x, l, y, v, w)$ is given by

$$\begin{pmatrix} -d - \frac{\partial f}{\partial x} v & \rho & 0 & -\frac{\partial f}{\partial v} v - f(x, v) & 0 \\ \frac{\partial f}{\partial x} v & -(m+\rho+\gamma) & 0 & \frac{\partial f}{\partial v} v + f(x, v) & 0 \\ 0 & \gamma & -a & 0 & 0 \\ 0 & 0 & k & -\mu - qw & -qv \\ 0 & 0 & 0 & gw & gv - h \end{pmatrix}. \tag{40}$$

We recall that E is locally asymptotically stable if the all eigenvalues ξ_i of (40) satisfy the following condition [53–55]:

$$\left|\arg\left(\xi_i\right)\right| > \frac{\alpha\pi}{2}. \tag{41}$$

From (40), the characteristic equation at E_0 is given as follows:

$$\left(d+\xi\right)\left(h+\xi\right)g_0\left(\xi\right) = 0, \tag{42}$$

where

$$g_0\left(\xi\right) = \left(\left(m+\rho+\gamma\right)+\xi\right)\left(a+\xi\right)\left(\mu+\xi\right) - \frac{k\gamma\beta\lambda}{d\alpha_0+\alpha_1\lambda}. \tag{43}$$

Obviously, (42) has the roots $\xi_1 = -d$ and $\xi_2 = -h$. If $R_0 > 1$, we have $g_0(0) = a\mu(m+\rho+\gamma)(1-R_0) < 0$ and $\lim_{\xi\longrightarrow+\infty} g_0(\xi) = +\infty$. Then, there exists $\xi^* > 0$ satisfying $g_0(\xi^*) = 0$. In addition, we have $|\arg(\xi^*)| = 0 < \alpha\pi/2$. Consequently, when $R_0 > 1$, E_0 is unstable. □

Theorem 4.

(i) *The infection equilibrium without humoral immunity E_1 is globally asymptotically stable if $R_0 > 1$, $R_1 \le 1$, and*

$$R_0 \le 1 + \frac{\left(m+\rho+\gamma\right)\left[\alpha_0 ad\mu\left(m+\rho\right)+dk\lambda\gamma\alpha_2\right]+k\rho\gamma\alpha_3\lambda^2}{a\rho\mu\left(m+\rho+\gamma\right)\left(\alpha_0 d+\lambda\alpha_1\right)}. \tag{44}$$

(ii) *When $R_1 > 1$, E_1 is unstable.*

Proof. Define a Lyapunov functional as follows:

$$\begin{aligned} L_1(t) = {} & \frac{\alpha_0+\alpha_2\nu_1}{\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1} x_1\Phi\left(\frac{x}{x_1}\right) \\ & + l_1\Phi\left(\frac{l}{l_1}\right) \\ & + \frac{\rho\left(\alpha_0+\alpha_2\nu_1\right)}{2\left(d+m+\gamma\right)\left(\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1\right)x_1}\left(x\right. \\ & \left. - x_1 + l - l_1\right)^2 + \frac{m+\rho+\gamma}{\gamma} y_1\Phi\left(\frac{y}{y_1}\right) \\ & + \frac{a\left(m+\rho+\gamma\right)}{k\gamma}\nu_1\Phi\left(\frac{\nu}{\nu_1}\right) + \frac{aq\left(m+\rho+\gamma\right)}{kg\gamma} w. \end{aligned} \tag{45}$$

Calculating the fractional derivative of $L_1(t)$, we get

$$\begin{aligned} D^\alpha L_1(t) = {} & \frac{\alpha_0+\alpha_2\nu_1}{\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1}\left(1-\frac{x_1}{x}\right)D^\alpha x \\ & + \left(1-\frac{l_1}{l}\right)D^\alpha l \\ & + \frac{\rho\left(\alpha_0+\alpha_2\nu_1\right)\left(x-x_1+l-l_1\right)}{\left(d+m+\gamma\right)\left(\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1\right)x_1}\left(D^\alpha x\right. \\ & \left. + D^\alpha l\right) + \frac{m+\rho+\gamma}{\gamma}\left(1-\frac{y_1}{y}\right)D^\alpha y \\ & + \frac{a\left(m+\rho+\gamma\right)}{k\gamma}\left(1-\frac{\nu_1}{\nu}\right)D^\alpha\nu + \frac{aq\left(m+\rho+\gamma\right)}{kg\gamma} w. \end{aligned} \tag{46}$$

Using $\lambda = dx_1+(m+\gamma)l_1$, $f(x_1,\nu_1)\nu_1 = (m+\rho+\gamma)l_1$, $\gamma l_1 = ay_1$, $ky_1 = \mu\nu_1$, and $1-f(x_i,\nu_i)/f(x,\nu_i) = ((\alpha_0+\alpha_2\nu_i)/(\alpha_0+\alpha_1 x_i+\alpha_2\nu_i+\alpha_3 x_i\nu_i))(1-x_i/x)\forall i\in\{1,2\}$, we obtain

$$\begin{aligned} D^\alpha L_1(t) \le {} & d\left(1-\frac{f\left(x_1,\nu_1\right)}{f\left(x,\nu_1\right)}\right)\left(x_1-x\right) + \left(m+\rho+\gamma\right)l_1\left(1-\frac{f\left(x_1,\nu_1\right)}{f\left(x,\nu_1\right)}+\frac{\nu}{\nu_1}\frac{f\left(x,\nu\right)}{f\left(x,\nu_1\right)}\right) + \left(m+\rho+\gamma\right) \\ & \cdot l_1\left(1-\frac{l_1 f\left(x,\nu\right)\nu}{l f\left(x_1,\nu_1\right)\nu_1}\right) + \left(m+\rho+\gamma\right)l_1\left(1-\frac{l y_1}{l_1 y}\right) + \left(m+\rho+\gamma\right)l_1\left(1-\frac{\nu}{\nu_1}-\frac{y\nu_1}{y_1\nu}\right) + \rho\left(l-l_1\right) \\ & \cdot\left(1-\frac{f\left(x_1,\nu_1\right)}{f\left(x,\nu_1\right)}\right) - \frac{\rho\left(\alpha_0+\alpha_2\nu_1\right)\left[d\left(x-x_1\right)^2+\left(m+\gamma\right)\left(l-l_1\right)^2+\left(d+m+\gamma\right)\left(x-x_1\right)\left(l-l_1\right)\right]}{\left(d+m+\gamma\right)\left(\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1\right)x_1} \\ & + \frac{aqh\left(m+\rho+\gamma\right)}{kg\gamma}\left(\frac{g\nu_1}{h}-1\right)w. \end{aligned} \tag{47}$$

Hence,

$$\begin{aligned} D^\alpha L_1(t) \le {} & -\frac{\left(\alpha_0+\alpha_2\nu_1\right)\left(x-x_1\right)^2}{x x_1\left(\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1\right)}\left(\left(dx_1-\rho l_1\right)+\rho l\right. \\ & \left. + \frac{d\rho x}{d+m+\gamma}\right) \\ & - \frac{\rho\left(\alpha_0+\alpha_2\nu_1\right)\left(m+\gamma\right)\left(l-l_1\right)^2}{\left(m+\rho+\gamma\right)\left(\alpha_0+\alpha_1 x_1+\alpha_2\nu_1+\alpha_3 x_1\nu_1\right)x_1} + \left(m+\rho\right. \\ & \left. +\gamma\right)l_1\left(5-\frac{f\left(x_1,\nu_1\right)}{f\left(x,\nu_1\right)}-\frac{l_1 f\left(x,\nu\right)\nu}{l f\left(x_1,\nu_1\right)\nu_1}-\frac{l y_1}{l_1 y}-\frac{y\nu_1}{y_1\nu}\right. \\ & \left. -\frac{f\left(x,\nu_1\right)}{f\left(x,\nu\right)}\right) - \left(m+\rho+\gamma\right)l_1 \end{aligned}$$

$$\cdot \frac{(\alpha_0+\alpha_1 x)(\alpha_2+\alpha_3 x)(v-v_1)^2}{v_1(\alpha_0+\alpha_1 x+\alpha_2 v+\alpha_3 x v)(\alpha_0+\alpha_1 x+\alpha_2 v_1+\alpha_3 x v_1)} + \frac{aqh(m+\rho+\gamma)}{kg\gamma}(R_1-1)w. \tag{48}$$

Using the arithmetic-geometric inequality, we have

$$5-\frac{f(x_i,v_i)}{f(x,v_i)}-\frac{l_i f(x,v)v}{l f(x_i,v_i)v_i}-\frac{l y_i}{l_i y}-\frac{y v_i}{y_i v}-\frac{f(x,v_i)}{f(x,v)} \le 0. \tag{49}$$

Since $R_1 \le 1$, we have $D^\alpha L_1(t) \le 0$ if $dx_1 \ge \rho l_1$. It is easy to see that this condition is equivalent to (44). Furthermore, $D^\alpha L_1(t) = 0$ if and only if $x = x_1, l = l_1, y = y_1, v = v_1$, and $(R_1-1)w = 0$. We discuss two cases: If $R_1 < 1$, then $w = 0$. If $R_1 = 1$, from (1), we get $D^\alpha v_1 = 0 = ky_1 - \mu v_1 - q v_1 w$, and then $w = 0$. Hence, the largest invariant set of $\{(x,l,y,v,w) \in \mathbb{R}^5_+ : D^\alpha L_1(t) = 0\}$ is the singleton $\{E_1\}$. By the LaSalle's invariance principle, E_1 is globally asymptotically stable.

At E_1, the characteristic equation of (40) is given as follows:

$$(g v_1 - h - \xi) g_1(\xi) = 0, \tag{50}$$

where

$$g_1(\xi) = \begin{vmatrix} -d-\frac{\partial f}{\partial x}(x_1,v_1)v_1-\xi & \rho & 0 & -\frac{\partial f}{\partial v}(x_1,v_1)v_1 - f(x_1,v_1) \\ \frac{\partial f}{\partial x}(x_1,v_1)v_1 & -(m+\rho+\gamma)-\xi & 0 & \frac{\partial f}{\partial v}(x_1,v_1)v_1 + f(x_1,v_1) \\ 0 & \gamma & -a-\xi & 0 \\ 0 & 0 & k & -\mu-\xi \end{vmatrix}. \tag{51}$$

We can easily see that (50) has the root $\xi_1 = g v_1 - h$. Then, when $R_1 > 1$, we have $\xi_1 > 0$. In this case, E_1 is unstable. □

Theorem 5. *The infection equilibrium with humoral immunity E_2 is globally asymptotically stable if $R_1 > 1$ and*

$$\rho\beta h \le d(m+\rho+\gamma)(\alpha_0 g+\alpha_2 h)+\rho\lambda(\alpha_1 g+\alpha_3 h). \tag{52}$$

Proof. Consider the following Lyapunov functional:

$$L_2(t) = \frac{\alpha_0+\alpha_2 v_2}{\alpha_0+\alpha_1 x_2+\alpha_2 v_2+\alpha_3 x_2 v_2} x_2 \Phi\left(\frac{x}{x_2}\right) + l_2\Phi\left(\frac{l}{l_2}\right) + \frac{\rho(\alpha_0+\alpha_2 v_2)}{2(d+m+\gamma)(\alpha_0+\alpha_1 x_2+\alpha_2 v_2+\alpha_3 x_2 v_2)x_2}(x - x_2 + l - l_2)^2 + \frac{m+\rho+\gamma}{\gamma} y_2 \Phi\left(\frac{y}{y_2}\right) + \frac{a(m+\rho+\gamma)}{k\gamma} v_2 \Phi\left(\frac{v}{v_2}\right) + \frac{aq(m+\rho+\gamma)}{kg\gamma} \cdot w_2 \Phi\left(\frac{w}{w_2}\right). \tag{53}$$

Computing the fractional derivative of $L_2(t)$ and using $\lambda = dx_2 + (m+\gamma)l_2$, $f(x_2,v_2)v_2 = (m+\rho+\gamma)l_2$, $\gamma l_2 = a y_2$, $k y_2 = (\mu + q w_2)v_2$, and $v_2 = h/g$, we get

$$\begin{aligned} D^\alpha L_2(t) \le{}& d\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}\right)(x_2-x) + (m+\rho+\gamma)l_2\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}+\frac{f(x,v)v}{f(x,v_2)v_2}\right) \\ &+ (m+\rho+\gamma)l_2\left(1-\frac{l_2 f(x,v)v}{l f(x_2,v_2)v_2}\right) + (m+\rho+\gamma)l_2\left(1-\frac{l y_2}{l_2 y}\right) + (m+\rho+\gamma)l_2\left(1-\frac{v}{v_2}-\frac{y v_2}{y_2 v}\right) \\ &+ \rho(l-l_2)\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}\right) \\ &- \frac{\rho(\alpha_0+\alpha_2 v_2)\left[d(x-x_2)^2+(m+\gamma)(l-l_2)^2+(d+m+\gamma)(x-x_2)(l-l_2)\right]}{(d+m+\gamma)(\alpha_0+\alpha_1 x_2+\alpha_2 v_2+\alpha_3 x_2 v_2)x_2} \end{aligned}$$

$$\leq -\frac{(\alpha_0+\alpha_2 v_2)(x-x_2)^2}{x x_2(\alpha_0+\alpha_1 x_2+\alpha_2 v_2+\alpha_3 x_2 v_2)}\left((dx_2-\rho l_2)+\rho l+\frac{d\rho x}{d+m+\gamma}\right)$$
$$-\frac{\rho(\alpha_0+\alpha_2 v_2)(m+\gamma)(l-l_2)^2}{(m+\rho+\gamma)(\alpha_0+\alpha_1 x_2+\alpha_2 v_2+\alpha_3 x_2 v_2)x_2}$$
$$+(m+\rho+\gamma)l_2\left(5-\frac{f(x_2,v_2)}{f(x,v_2)}-\frac{l_2 f(x,v)v}{l f(x_2,v_2)v_2}-\frac{l y_2}{l_2 y}-\frac{y v_2}{y_2 v}-\frac{f(x,v_2)}{f(x,v)}\right)$$
$$-(m+\rho+\gamma)l_2\frac{(\alpha_0+\alpha_1 x)(\alpha_2+\alpha_3 x)(v-v_2)^2}{v_2(\alpha_0+\alpha_1 x+\alpha_2 v+\alpha_3 x v)(\alpha_0+\alpha_1 x+\alpha_2 v_2+\alpha_3 x v_2)}. \quad (54)$$

From (49), we have $D^\alpha L_2(t) \leq 0$ when $dx_2 \geq \rho l_2$. This condition is equivalent to (52). In addition, $D^\alpha L_2(t) = 0$ if $x = x_2, l = l_2, y = y_2$, and $v = v_2$. Further, $D^\alpha v_2 = 0 = ky_2 - \mu v_2 - q v_2 w$; then $w = w_2$. Consequently, the largest invariant set of $\{(x,l,y,v,w) \in \mathbb{R}^5_+ : D^\alpha L_2(t) = 0\}$ is the singleton $\{E_2\}$. By the LaSalle's invariance principle, E_2 is globally asymptotically stable. □

It is important to note that when ρ is sufficiently small or γ is sufficiently large, the two conditions (44) and (52) are satisfied. Then, we have the following corollary.

Corollary 6. *Assume that $R_0 > 1$. When ρ is sufficiently small or γ is sufficiently large, then we have the following:*

(i) *The infection equilibrium without humoral immunity E_1 is globally asymptotically stable if $R_1 \leq 1$.*

(ii) *The infection equilibrium with humoral immunity E_2 is globally asymptotically stable if $R_1 > 1$.*

4. Numerical Simulations

In this section, we validate our theoretical results to HIV infection. Firstly, we take the parameter values as shown in Table 1.

By calculation, we have $R_0 = 0.4274 \leq 1$. Then system (1) has an infection-free equilibrium $E_0(719.4245, 0, 0, 0, 0)$. By Theorem 3, the solution of (1) converges to E_0 (see Figure 1). Consequently, the virus is cleared and the infection dies out.

Now, we choose $\beta = 0.0012$ and we keep the other parameter values. Hence, we obtain $R_0 = 2.137$, $R_1 = 0.8334$, and

$$1+\frac{(m+\rho+\gamma)[\alpha_0 ad\mu(m+\rho)+dk\lambda\gamma\alpha_2]+k\rho\gamma\alpha_3\lambda^2}{a\rho\mu(m+\rho+\gamma)(\alpha_0 d+\lambda\alpha_1)} = 2.5934. \quad (55)$$

Consequently, condition (44) is satisfied. Therefore, the infection equilibrium without humoral immunity $E_1(176.6853, 168.7712, 6.2508, 1666.9, 0)$ is globally asymptotically stable. Figure 2 demonstrates this result. In this case, the infection becomes chronic.

Next, we take $g = 0.0004$ and do not change the other parameter values. In this case, we have $R_1 = 3.3338$, $\rho\beta h = 0.0000024$, and $d(m+\rho+\gamma)(\alpha_0 g+\alpha_2 h)+\rho\lambda(\alpha_1 g+\alpha_3 h) = 0.000006$. Hence, condition (52) is satisfied. Consequently, system (1) has an infection equilibrium with humoral immunity $E_2(423.4261, 92.0442, 3.4090, 500, 245.4473)$ which is globally asymptotically stable. Figure 3 illustrates this result. We can observe that the activation of the humoral immune response increases the healthy cells and decreases the productive infected cells and viral load to a lower levels but it is not able to eradicate the infection.

5. Conclusion

In the present paper, we have studied the dynamics of a viral infection model by taking into account the memory effect represented by the Caputo fractional derivative and the humoral immunity. We have proved that the solutions of the model are nonnegative and bounded which assure the well-posedness. We have shown that the proposed model has three infection equilibriums, namely, the infection-free equilibrium E_0, the infection equilibrium without humoral immunity E_1, and the infection equilibrium with humoral immunity E_2. By constructing suitable Lyapunov functionals, the global stability of these equilibria is fully determined by two threshold parameters R_0 and R_1. More precisely, when $R_0 \leq 1$, E_0 is globally asymptotically stable, whereas if $R_0 > 1$, it becomes unstable and another equilibrium point appears, that is, E_1, which is globally asymptotically stable whenever $R_1 \leq 1$ and condition (44) is satisfied. In the case that $R_1 > 1$, E_1 becomes unstable and there exists another equilibrium point E_2 which is globally asymptotically stable when condition (52) is satisfied. In addition, we remarked that when ρ is sufficiently small or γ is sufficiently large, conditions (44) and (52) are verified, and then the global stability of E_1 and E_2 is characterized only by R_0 and R_1.

From our theoretical and numerical results, we deduce that the order of the fractional derivative α has no effect on the dynamics of the model. However, when the value of α decreases (long memory), the solutions of our model converge rapidly to the steady states (see Figures 1–3). This behavior can be explained by the memory term $1/\Gamma(1-\alpha)(t-u)^\alpha$ included in the fractional derivative which represents

Table 1: Parameter values of system (1).

parameters	values	parameters	values	parameters	values
λ	10	a	0.27	h	0.2
d	0.0139	γ	0.01	g	0.0001
β	0.00024	k	800	α_0	1
ρ	0.01	μ	3	α_1	0.1
m	0.0347	q	0.01	α_2	0.01
		α_3	0.00001		

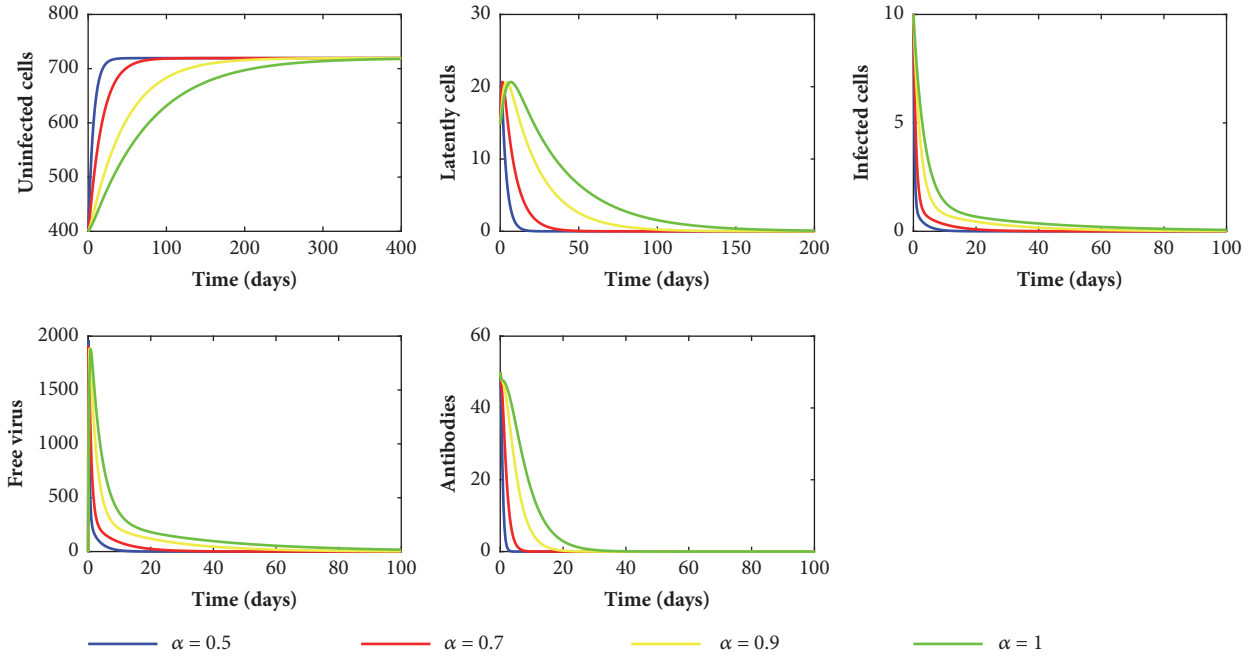

Figure 1: Stability of the infection-free equilibrium E_0.

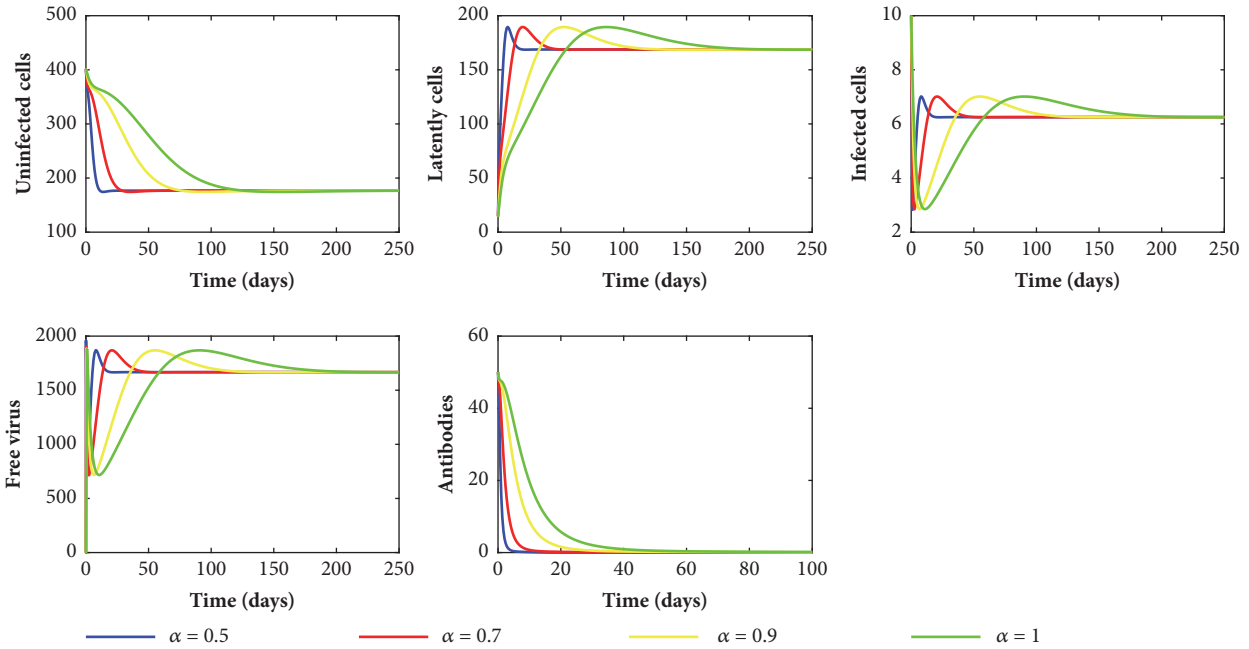

Figure 2: Stability of the infection equilibrium without humoral immunity E_1.

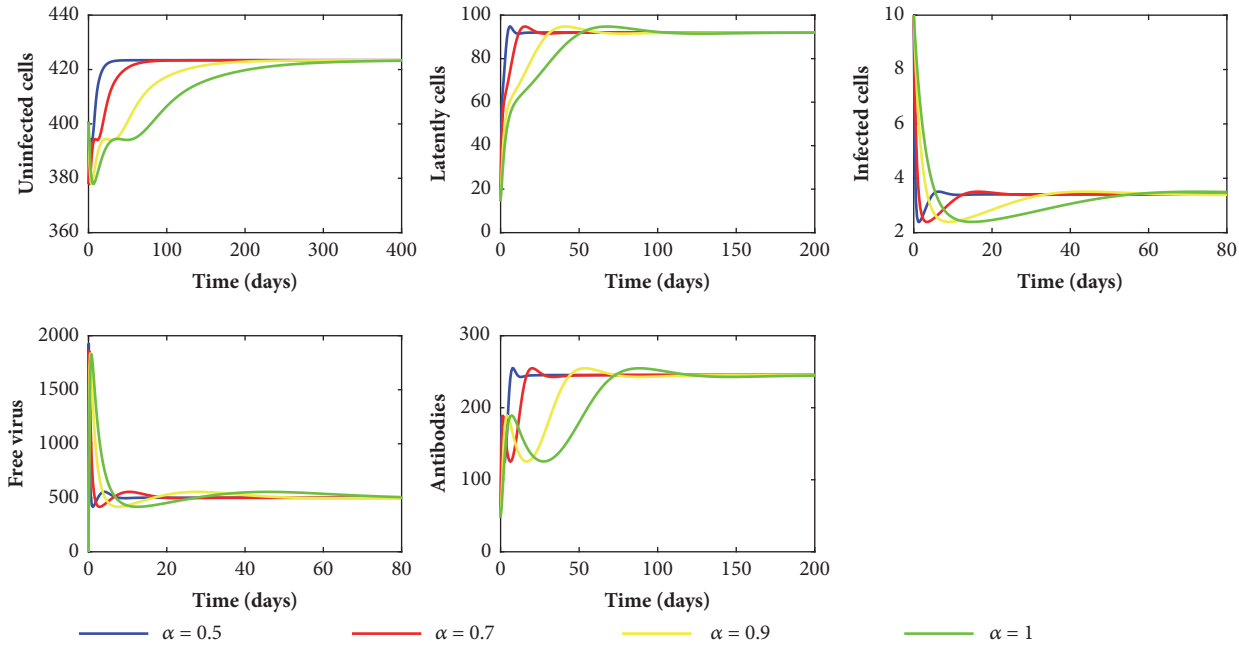

FIGURE 3: Stability of the infection equilibrium with humoral immunity E_2.

the time needed for the interaction between cells and viral particles and the time needed for the activation of humoral immune response. In fact, the knowledge about the infection and the activation of the humoral immune response in an early stage can help us to control the infection.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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