Research Article

Global Stability of Delayed Viral Infection Models with Nonlinear Antibody and CTL Immune Responses and General Incidence Rate

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The dynamical behaviors for a five-dimensional viral infection model with three delays which describes the interactions of antibody, cytotoxic T-lymphocyte (CTL) immune responses, and nonlinear incidence rate are investigated. The threshold values for viral infection, antibody response, CTL immune response, CTL immune competition, and antibody competition, respectively, are established. Under certain assumptions, the threshold value conditions on the global stability of the infection-free, immune-free, antibody response, CTL immune response, and interior equilibria are proved by using the Lyapunov functionals method, respectively. Immune delay as a bifurcation parameter is further investigated. The numerical simulations are performed in order to illustrate the dynamical behavior of the model.

1. Introduction

In recent years, many authors have formulated and studied mathematical models which describe the dynamics of virus population in vivo. These provide insights in our understanding of HIV (human immunodeficiency virus) and other viruses, such as HBV (hepatitis B virus) and HCV (hepatitis C virus) [1–34]. In particular, the global stability of steady states for these models will give us a detailed information and enhance our understanding about the viral dynamics.

During viral infections, the immune system reacts against virus. The antibody and CTL play the crucial roles in preventing and modulating infections. The antibody response is implemented by the functioning of immunocompetent B lymphocytes. The CTL immune response has the ability to suppress the virus replication in vivo. Hence, in order to prevent virus infection, an effective vaccine needs both strong neutralizing antibody and CTL immune responses [1, 2, 14, 18–23, 25–32]. Based on these, it is of interest for us to investigate whether sustained oscillations are the result of delayed viral infection model. This provides us with the motivation to conduct our work. In [2], Balasubramaniam et al. developed the viral infection model by incorporating immune delays and Beddington-DeAngelis incidence rate

\[
\frac{dx(t)}{dt} = \lambda - dx(t) - \frac{\beta(1 - \epsilon_{nt}) x(t) v(t)}{1 + mx(t) + nv(t)},
\]

\[
\frac{dy(t)}{dt} = \frac{\beta(1 - \epsilon_{nt}) x(t) v(t)}{1 + mx(t) + nv(t)} - ay(t) - py(t) z(t),
\]

\[
\frac{dv(t)}{dt} = k\left(1 - \epsilon_{pi}\right) y(t) - uv(t) - qv(t) w(t),
\]

\[
\frac{dw(t)}{dt} = gv(t) w(t) - hw(t),
\]

\[
\frac{dz(t)}{dt} = cy(t - \tau) z(t - \tau) - bz(t),
\]

where \(x, y, v, w,\) and \(z\) denote the concentrations of susceptible host cells, infected cells, free virus, antibody responses, and CTL immune responses, respectively. The local and global stability of the infection-free equilibrium and infected equilibrium and the existence of Hopf bifurcation are...
obtained. Furthermore, by using the Nyquist criterion, the estimation of the length of the delay to preserve stability of the infected equilibrium is obtained.

Motivated by the work in [1, 2, 20, 21], in the present paper we propose a general viral infection model with three time delays which describes the interactions of antibody, CTL immune responses, and nonlinear incidence rate

\[
\frac{dx(t)}{dt} = s(x) - f(x, v),
\]

\[
\frac{dy(t)}{dt} = e^{-m_1 \tau_1} f(x(t - \tau_1), v(t - \tau_1)) - ag_1(y) - pg_1(y)g_4(z),
\]

\[
\frac{dv(t)}{dt} = ke^{-m_2 \tau_2}g_1(y(t - \tau_2)) - ug_2(v) - qg_2(v)g_3(w),
\]

\[
\frac{dz(t)}{dt} = cg_1(y(t - \tau_3))g_4(z(t - \tau_3)) - bg_4(z),
\]

\[
\frac{dw(t)}{dt} = rg_2(v)g_3(w) - hg_3(w),
\]

where \(s(x)\) denotes the intrinsic growth rate of uninfected target cells accounting for both production and natural mortality. In the literature of virus dynamics, the typical forms of the growth rate are \(s(x) = \lambda - dx \) and \(s(x) = \lambda - dx + rx(1 - x/K)\), where \(\lambda, d, r, K\) are positive real numbers [4–13, 15, 16, 18, 20–23, 26–32, 34].

We assume that the incidence of new infections of target cells occurs at a rate \(f(x, v)\). This form of incident rate is general to encompass several forms such as bilinear incidence \(\beta x v[4, 13]\), saturated incidence \(\beta x v/(1 + bv) [16]\), Holling type II functional response \(\beta x v/(1 + ax) [15]\), and Crowley-Martin incidence \(\beta x v/(1 + ax + bx + abxv) [12, 35]\), where \(\beta, a, b\) are positive constants.

It is also assumed that the death rates of the infected target cells, viruses, antibody, and CTLs depend on their concentrations. These rates are given by \(aq_1(y), uq_2(v), hq_3(w), \) and \(bg_4(z)\), respectively. The neutralization rate of viruses and the activation rate of B cells are proportional to the product of the removal rates of the viruses and B cells. Let \(qg_3(v)g_3(w)\) and \(rg_2(v)g_3(w)\) be the neutralization rate of viruses and activation rate of B cells, respectively. The typical forms can be seen as \(gvw\) and \(rvw\) [1, 2, 20, 21, 31, 32]. Accordingly, let \(pg_1(y)g_4(z)\) and \(cg_1(y)g_4(z)\) be the killing rate of infected cells and the birth rate of the CTL cells, respectively. The typical forms are \(pyz\) and \(cyz\) that appear in several papers [1, 2, 14, 20, 22, 27, 30, 34].

For model (2), based on the epidemiological background, we assume that virus production occurs after the virus entry by the time delay \(\tau_1\). The probability of surviving the time period from \(t - \tau_1\) to \(t\) is \(e^{-m_1 \tau_1}\). Let \(\tau_2\) be the maturation time of the newly produced viruses. The constant \(e^{-m_2 \tau_2}\) denotes the surviving rate of virus during the time period. Antigenic stimulation generating CTL cell may need a period of time \(\tau_3\).

In this paper, our purpose is to investigate the dynamical properties of model (2), including the local and global stability of equilibria. The reproduction numbers for viral infection, antibody response, CTL immune response, and antibody competition, respectively, are calculated. By using Lyapunov functional and LaSalle’s invariance principle, the threshold conditions for the global asymptotic stability of infection-free equilibrium \(E_0\), immune-free equilibrium \(E_1\), infection equilibrium \(E_2\) only with antibody response, and infection equilibrium \(E_3\) only with CTL immune response and infection equilibrium \(E_4\) with both antibody and CTL immune responses when the delay \(\tau_3 = 0\), respectively, are established. By using the linearization method, the instability of equilibria \(E_0, E_1, E_2,\) and \(E_3\), respectively, is also established. Furthermore, by using the numerical simulation method, we will discuss the existence of the Hopf bifurcation and stability switches at equilibria \(E_1\) and \(E_2\) when \(\tau_3 > 0\).

The organization of this paper is as follows. In the next section, the basic properties of model (2) for the positivity and boundedness of solutions, the threshold values, and the existence of equilibria are discussed. In Section 3, the threshold conditions on the global stability and instability of equilibria \(E_0, E_1, E_2\) are proved. When \(\tau_3 = 0\), the threshold conditions on the global stability and instability for equilibria \(E_3\) and \(E_4\) are stated and proved. In Section 4, the numerical simulations are given to further discuss the stability of equilibria \(E_1\) and \(E_2\) when \(\tau_3 > 0\). It is shown that the Hopf bifurcation and stability switches at these equilibria occur as \(\tau_3\) increases. In the last section, we offer a brief conclusion.

2. Preliminaries

Let \(\tau = \max(\tau_1, \tau_2, \tau_3)\) and \(R^5 = \{(x_1, x_2, x_3, x_4, x_5) : x_i \geq 0, i = 1, 2, \ldots, 5\}\). \(C([-\tau, 0], R^5)\) denotes the space of continuous functions mapping interval \([-\tau, 0]\) into \(R^5\) with norm \(\|f\| = \sup_{-\tau \leq t \leq 0} \|f(t)\|\) for any \(f \in C([-\tau, 0], R^5)\).

The initial conditions for any solutions of model (2) are given as follows:

\[
(x(\theta), y(\theta), v(\theta), z(\theta), w(\theta)) = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta)), \quad \phi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0], \quad \phi_i(0) > 0, \quad i = 1, 2, 3, 4, 5,
\]

where \((\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta)) \in C([-\tau, 0], R^5)\). By the fundamental theory of functional differential equation [36], model (2) admits a unique solution \((x(t), y(t), v(t), z(t), w(t))\) satisfying initial conditions (3).

In this paper, we firstly introduce the following assumptions:

\((H_1)\) \(s(x)\) is continuously differentiable. There exists \(\exists x > 0\) such that \(s'(x) = 0\) and \(s''(x) < 0\).

\((H_2)\) \(f(x, v)\) is continuously differentiable; \(f(x, v) > 0\) for \(x \in (0, \infty), v \in (0, \infty)\); \(f(x, v) = 0\) if and only if \(x = 0\) or \(v = 0\); \(\partial f(x, v)/\partial x \geq 0\) and \(\partial f(x, v)/\partial v \geq 0\) for all \(x \geq 0\) and \(v \geq 0\); \((d/dx)(\partial f(x, v)/\partial v) \geq 0\) for all \(x \geq 0\).
(H₃) \( g_3(\xi) \) \((i = 1, 2, 3, 4)\) is strictly increasing on \([0, \infty)\); 
\[ \lim_{\xi \to \infty} g_3(\xi) = +\infty; \]
and there exists \( k_i > 0 \) such that 
\[ g_3(\xi) \geq k_i \xi \] for any \( \xi \geq 0; g_3(0) = 0 \) and \( g'_3(0) = 1. \)

(H₄) \( f(x, v)/g_2(v) \) is nonincreasing with respect to \( v \) for \( v \in (0, \infty). \)

From (H₁) we easily obtain that \( s(x) > 0 \) for all \( 0 < x < \overline{x} \) and \( s(x) < 0 \) for all \( x > \overline{x} \). Assumption (H₂) shows that the number of healthy cells \( x \) has a maximum capacity \( \overline{x} \) in the absence of infection. When \( x < \overline{x} \), \( s(x) \) has a positive growth; if \( x > \overline{x} \) it has a negative growth. Assumption (H₃) implies that there are no new infected cells (i.e., \( f(x, v) = 0 \)) without healthy cells \((x = 0)\) or virus \((v = 0)\). The higher the number of healthy cells \( x \) is, the higher the number of healthy cells \( x \) which are infected in the unit time will be. Similarly, the higher the amount of virus \( v \) is, the higher the number of healthy cells \( x \) which are infected in the unit time will be. Assumption (H₄) assumes that the death rates of the infected target cells \( y \), virus \( v \), antibodies \( w \), and CTLs \( z \) depend on their concentrations. If these numbers \( y, v, w, z \) increase, the corresponding rates \( ag_1(y), ug_2(v), hg_2(w), \) and \( bg_3(z) \) will increase, and the ratio \( g_3(\xi)/\xi \) is less than a positive constant for \( i = 1, 2, 3, 4 \). Finally, assumption (H₅) indicates that both the rate of new infections of target cells and the virus clearance rate increase according to the level of virus. However, the corresponding rate is nonincreasing.

Using an argument similar to [14] we have the following result.

**Theorem 1.** Assume that (H₁)-(H₄) hold. Let \((x(t), y(t), v(t), z(t), w(t))\) be the solution of model (2) with initial conditions (3); then \((x(t), y(t), v(t), z(t), w(t))\) is positive and ultimately bounded.

Next, we discuss the existence and uniqueness of equilibria of model (2). We know that any equilibrium \( E = (x, y, v, z, w) \) of model (2) satisfies

\[
\begin{align*}
    s(x) - f(x, v) &= 0, \\
    e^{-m_1 t} f(x, v) - ag_1(y) - pg_1(y) g_4(z) &= 0, \\
    ke^{-m_2 t} g_1(y) - u g_2(v) - q g_2(v) g_3(w) &= 0, \\
    c g_1(y) g_4(z) - bg_3(z) &= 0, \\
    rg_2(v) g_3(w) - hg_2(w) &= 0.
\end{align*}
\]

It is clear from (4) that model (2) has a unique infection-free equilibrium \( E_0 = (\overline{x}, 0, 0, 0, 0) \). When \( y = 0 \), from (4) we have \( s(x) = f(x, v), g_2(v) (u + q g_4(w)) = 0, g_4(z) = 0 \), and \( rg_2(v) - h g_2(w) = 0. \) Solving these equations, we have \( x = \overline{x}, v = 0, z = 0, w = 0 \). When \( v = 0 \), from (4) we have \( s(x) = 0, g_1(y) (a + pg_4(z)) = 0, g_1(y) = 0, g_4(z) = 0, \) and \( g_2(w) = 0. \) Solving these equations, we have \( x = \overline{x}, v = 0, z = 0, w = 0. \) Therefore, besides equilibrium \( E_0, \) model (2) only has the following four possible equilibria:

\[ E_1 = (x_1, y_1, v_1, 0, 0), E_2 = (x_2, y_2, v_2, 0, w_2), E_3 = (x_3, y_3, v_3, z_3, 0), \]
and \( E_4 = (x_4, y_4, v_4, z_4, w_4). \)

The existence of immune-free equilibrium \( E_1 = (x_1, y_1, v_1, 0, 0) \) is equivalent to the existence of positive solution \((x_1, y_1, v_1)\) of the following equations:

\[
    s(x) = f(x, v) = ae^{m_1 t} g_1(y) = \frac{aue^{m_1 t + m_2 z}}{k} g_2(v). \tag{5}
\]

By (H₃), the inverse function \( g_2^{-1}(v) \) exists. Solving

\[ s(x) = \left( au e^{m_1 t + m_2 z} / k \right) g_2(v), \]
we have \( v = \varphi(x) = \varphi^{-1}(k s(x) / au e^{m_1 t + m_2 z}) \) with \( \varphi(\overline{x}) = 0 \) and \( \varphi(0) = \varphi^0 \), where \( \varphi^0 \) is the unique positive root of equation \( s(0) = \left( au e^{m_1 t + m_2 z} / k \right) g_2(v) \). Define \( G(x) = f(x, \varphi(x)) - \left( au e^{m_1 t + m_2 z} / k \right) g_2(\varphi(x)) \). Then \( G(0) = \left( au e^{m_1 t + m_2 z} / k \right) g_2(\varphi^0) < 0 \) and \( G(\overline{x}) = 0 \).

Define the basic reproduction number for viral infection

\[
    R_0 = \frac{ke^{m_1 t - m_2 z}}{au} \frac{\partial f(x, 0)}{\partial v}. \tag{6}
\]

Note that

\[
    G'(\overline{x}) = \frac{\partial f(x, 0)}{\partial x} + \frac{\partial f(x, 0)}{\partial v} \varphi'(\overline{x}) + \frac{aue^{m_1 t + m_2 z}}{k} g_2'(0) \varphi'(\overline{x}) - \frac{aue^{m_1 t + m_2 z}}{k} \frac{\partial f(x, 0)}{\partial v} \tag{7}
\]

Thus, if \( R_0 > 1 \), then \( G'(\overline{x}) < 0 \). This implies that there exists \( x_1 \in (0, \overline{x}) \) such that \( G(x_1) = 0 \). The value of \( v_1 \) is given by \( v_1 = \varphi(x_1) \). (H₄) ensures that \( ke^{m_1 t} g_1(y) = u g_2(v_1) \) has a unique positive solution \( y_1 = g_1^{-1}(u e^{m_1 t} g_2(v_1)/k) \). Therefore, \( E_1 \) exists if \( R_0 > 1 \).

Next we show that \( E_1 = (x_1, y_1, v_1, 0, 0) \) is a unique immune-free equilibrium. Otherwise, there exists another \( E' = (x'_1, y'_1, v'_1, 0, 0) \). Without loss of generality, we assume that \( x'_1 < x_1 \), and then \( s(x'_1) > s(x_1) \). Meanwhile, \( ks(x_1) = au e^{m_1 t + m_2 z} g_2(v_1) \) and \( ks(x'_1) = au e^{m_1 t + m_2 z} g_2(v'_1) \). By (H₃) and (H₄), we have \( v'_1 > v_1 \) and \( f(x_1, v'_1)/g_2(v'_1) \leq f(x_1, v_1)/g_2(v_1) \). Since \( x'_1 < x_1 \), we obtain \( f(x_1, v'_1) > f(x'_1, v'_1) \). Thus \( E_1 \) is a unique equilibrium.

We consider the existence of infection equilibrium \( E_2 = (x_2, y_2, v_2, 0, 0) \) with only antibody response. It is clear that \( v_2 = \varphi^{-1}(h/r) \). Define \( F(x) = f(x, 0) - f(x, v_2) \). By (H₄) and (H₂), we obtain \( F(x) < 0 \). Since \( F(0) = s(0) > 0 \) and \( F(\overline{x}) = s(\overline{x}) - \overline{x} - v_2 < 0 \), there exists a unique \( x_2 \in (0, \overline{x}) \) such that \( F(x_2) = 0 \). Then, we have \( v_2 = g_1^{-1}(e^{-m_1 t} f(x_2, v_2)/a) \).

Define the constant

\[
    R_1 = \frac{ke^{m_1 t - m_2 z}}{u} \frac{f(x_2, v_2)}{g_2'(v_2)}. \tag{8}
\]
which is called the antibody response reproductive number of model (2). Solving $w_1$ from (4), we obtain that

$$w_1 = g_3^{-1} \left( \frac{ke^{-m_1 \tau_1} g_1 (y_2) - u g_2 (v_2)}{q g_2 (v_2)} \right)$$

$$= g_3^{-1} \left( \frac{u (R_1 - 1)}{q} \right) > 0 \text{ if } R_1 > 1. \quad (9)$$

Therefore, $E_2$ exists and is unique if $R_1 > 1$.

We consider the existence of infection equilibrium $E_3 = (x_3, y_3, v_3, z_3, 0)$ with only CTL immune response. From the third and fourth equations of (4), we obtain unique $y_3 = g_3^{-1} (b/c)$ and $v_3 = g_2^{-1} (b k e^{-m_2 \tau_2} / c v)$. Define $F(x) = s(x) - f(x, y_3)$. By $(H_1)$ and $(H_2)$, we obtain $F'(x) < 0$. Since $F(0) = s(0) > 0$ and $F(\infty) = s(\infty) - f(\infty, v_3) < 0$, there exists a unique $x_3 \in (0, \infty)$ such that $F(x_3) = 0$.

Define the constant

$$R_2 = \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{au} f (x_3, v_3) g_2 (v_3), \quad (10)$$

which is called the CTL immune response reproductive number of model (2). Solving the second equation for $x$ yields

$$z_3 = g_4^{-1} \left( \frac{e^{m_1 \tau_1} f (x_3, v_3) - a g_1 (y_3)}{p g_1 (y_3)} \right)$$

$$= g_4^{-1} \left( \frac{a (R_2 - 1)}{p} \right) > 0 \text{ if } R_2 > 1. \quad (11)$$

Therefore, $E_3$ exists and is unique if $R_2 > 1$.

Lastly, we consider the existence of infection equilibrium $E_4 = (x_4, y_4, v_4, z_4, w_4)$ with both antibody and CTL immune responses. From the fourth and fifth equation of (4), we obtain unique $y_4 = g_3^{-1} (b/c)$ and $v_4 = g_2^{-1} (h/r)$. Define $F(x) = s(x) - f(x, y_4)$. By $(H_1)$ and $(H_2)$, we obtain $F'(x) < 0$. Since $F(0) = s(0) > 0$ and $F(\infty) = s(\infty) - f(\infty, v_4) < 0$, there exists a unique $x_4 \in (0, \infty)$ such that $F(x_4) = 0$.

Define the constants

$$R_3 = \frac{cf (x_4, v_4)}{a b c e^{m_1 \tau_1}}, \quad R_4 = \frac{k b r}{u c h e^{m_2 \tau_2}}, \quad (12)$$

which are called the CTL immune response competitive reproductive number and the antibody response competitive reproductive number of model (2), respectively. Solving the second equation for $x$ yields a unique

$$z_4 = g_4^{-1} \left( \frac{e^{m_1 \tau_1} f (x_4, v_4) - a g_1 (y_4)}{p g_1 (y_4)} \right)$$

$$= g_4^{-1} \left( \frac{a (R_3 - 1)}{p} \right) > 0 \text{ if } R_3 > 1. \quad (13)$$

Solving the third equation for $w$, we further obtain a unique

$$w_4 = g_3^{-1} \left( \frac{ke^{-m_1 \tau_1} g_1 (y_4) - u g_2 (v_4)}{q g_2 (v_4)} \right)$$

$$= g_3^{-1} \left( \frac{u (R_4 - 1)}{q} \right) > 0 \text{ if } R_4 > 1. \quad (14)$$

Therefore, $E_4$ exists and is unique if $R_3 > 1$ and $R_4 > 1$.

Remark 2. From $(H_3)$ and $(H_4)$, we obtain $R_1 < R_0$ and $R_2 < R_0$. In fact,

$$R_1 = \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{u} f (x_3, v_3) g_2 (v_3)$$

$$\leq \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{u} \lim_{v \to 0^+} f (x_3, v) g_2 (v)$$

$$= \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{u} \frac{\partial f (x_3, 0)}{\partial v} < \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{u} \frac{\partial f (\infty, 0)}{\partial v}$$

$$= R_0, \quad (15)$$

$$R_2 = \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{au} f (x_3, v_3) g_2 (v_3)$$

$$\leq \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{au} \lim_{v \to 0^+} f (x_3, v) g_2 (v)$$

$$= \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{au} \frac{\partial f (x_3, 0)}{\partial v} < \frac{ke^{-m_1 \tau_1 - m_2 \tau_3}}{au} \frac{\partial f (\infty, 0)}{\partial v}$$

$$= R_0.$$

3. Stability Analysis

3.1. Stability of Equilibrium $E_0$

Theorem 3. (a) If $R_0 \leq 1$, then infection-free equilibrium $E_0$ is globally asymptotically stable.

(b) If $R_0 > 1$, then $E_0$ is unstable.

Proof. Consider conclusion (a). Define a Lyapunov functional $V_1(t)$ as follows:

$$V_1 (t) = x (t) - \int_{0}^{t} \int_{0}^{\infty} \lim_{v \to 0^+} f (\theta , v) d \theta + e^{\sigma_1 \tau_1} y (t)$$

$$+ \frac{ae^{m_1 \tau_1 + m_2 \tau_3}}{k} v (t) + \frac{pe^{m_1 \tau_1}}{c} z (t)$$

$$+ \int_{0}^{\tau_1} \int_{0}^{\infty} f (x (t + s), v (t + s)) ds$$

$$+ ae^{m_1 \tau_1} \int_{0}^{\tau_1} g_1 (y (t + s)) ds$$
\[ + \frac{pe^{m_1s}}{kr} \int_{\tau_3}^{0} g_1(y(t+s))g_4(z(t+s)) ds + \frac{ae^{m_1s+mr_2s}}{kr} w(t). \]

Calculating the time derivative of \( V_1(t) \) along solutions of model (2), we obtain

\[ \frac{dV_1(t)}{dt} = s(x) \left( 1 - \lim_{v \to 0} f(\bar{x}, v) \right) + f(x, v) \]

\[ + \lim_{v \to 0} \int_0^v g_1(y(t+s))g_4(z(t+s)) ds + \frac{ae^{m_1s+mr_2s}}{kr} w(t). \]

(16)

It follows that

\[ \frac{dV_1(t)}{dt} \leq \frac{ae^{m_1s+mr_2s}}{k} g_2(v) (R_0 - 1). \]

(19)

Note that \( V_1(t)/dt = 0 \) if and only if \( x(t) = \bar{x} \), \( y(t) = 0 \), \( z(t) = 0 \), \( w(t) = 0 \). So, the maximal compact invariant set in \( \{(x, y, v, z, w) \in R^5_+ : dV_1(t)/dt = 0\} \) is singleton \( E_0 \). By LaSalle's invariance principle [36], \( E_0 \) is globally asymptotically stable.

Next, we consider conclusion (b). By computing the characteristic equation of the linearization system of model (2) at \( E_0 \) is

\[ (\lambda + h\tilde{g}'(0))(\lambda + b\tilde{g}'(0))(\lambda - s'(\bar{x}))f(\lambda) = 0, \]

(20)

where

\[ f(\lambda) = \lambda^3 + (a + u)\lambda + au \]

\[ - k \frac{\partial f(\bar{x}, v)}{\partial v} e^{-(m_1s+s_1r_1s)} e^{-(m_2s+s_2r_2s)}. \]

(21)

When \( R_0 > 1 \), we have \( f(0) = au - k(\partial f(\bar{x}, v)/\partial v) e^{-(m_1s+s_1r_1s)} e^{-(m_2s+s_2r_2s)} < 0 \) and \( \lim_{s \to \infty} f(\lambda) = -\infty \). Hence, there is \( \lambda > 0 \) such that \( f(\lambda) = 0 \). Therefore, when \( R_0 > 1 \), \( E_0 \) is unstable. This completes the proof. \( \square \)

Remark 4. Theorem 3 shows that if only equilibrium \( E_0 \) exists, then it is globally asymptotically stable, and delays \( \tau_1 \), \( \tau_2 \), and \( \tau_3 \) do not impact the stability of \( E_0 \).
Proof. Consider conclusion (a). Denote $H(\xi) = \xi - 1 - \ln \xi$ with $\xi \in \mathbb{R}_+$. Define a Lyapunov functional $V_2(t)$ as follows:

$$V_2(t) = x(t) - \int_{0}^{t} f(x_1, v_1) d\theta + e^{m_1 t} y(t) - \int_{0}^{t} g_1(y_1) \frac{g_2(v_1)}{g_1(\theta)} d\theta + \frac{ae^{m_1 t + m_2 t \tau}}{k} \left( v(t) - \int_{0}^{t} g_2(v_1) \frac{g_1(y_1)}{g_2(\theta)} d\theta \right) + \frac{pe^{m_1 t}}{c} z(t) + \frac{aqe^{m_1 t + m_2 t \tau}}{kr} w(t).$$

(26)

Calculating the derivative of $V_2(t)$ along solutions of model (2), we obtain

$$\frac{dV_2(t)}{dt} = s(x) \left( 1 - \frac{f(x_1, v_1)}{f(x, v)} \right) + f(x, v) \frac{f(x_1, v_1)}{f(x, v)} - \frac{ae^{m_1 t + m_2 t \tau}}{k} g_2(v) + M_1 + M_2,$$

(27)

where

$$M_1 = pe^{m_1 t} g_1(y_1) g_4(z) - \frac{phe^{m_1 t}}{c} g_4(z) + \frac{aqe^{m_1 t + m_2 t \tau}}{k} g_2(v_1) g_3(w) - \frac{aqhe^{m_1 t + m_2 t \tau}}{kr},$$

$$M_2 = f(x_1, v_1) \left( 2 - \frac{g_1(y_1) f(x(t - \tau_1), v(t - \tau_1))}{g_1(y_1) f(x_1, v_1)} - \frac{g_2(v_1) g_1(y(t - \tau_2))}{g_1(y_1) g_2(v)} \right).$$

Therefore,

$$\frac{dV_2(t)}{dt} = (s(x) - s(x_1)) \left( 1 - \frac{f(x_1, v_1)}{f(x, v)} \right) - f(x_1, v_1) H \left( \frac{g_2(v_1) g_1(y(t - \tau_2))}{g_1(y_1) g_2(v)} \right) + \frac{f(x, v)}{f(x_1, v_1)} \left( \frac{g_2(v_1)}{g_2(v_1)} - \frac{f(x_1, v_1)}{f(x, v)} \right) + M_1 - f(x_1, v_1)$$

(29)

Note that $(s(x) - s(x_1))(1 - f(x_1, v_1)/f(x_1, v_1)) \leq 0$, and

$$\left( \frac{f(x, v)}{f(x_1, v_1)} - 1 \right) \left( \frac{g_2(v_1)}{g_2(v_1)} - \frac{f(x_1, v_1)}{f(x, v)} \right) \leq 0$$

(30)

for $t \geq 0$.

Lemmas 5 and 6 imply that $y_1 \leq y_3$ and $v_1 \leq v_2$ if $R_1 \leq 1$ and $R_2 \leq 1$. It then follows from the monotonicity of $g_1$ and $g_2$ that $M_1 \leq 0$. We have $dV_2(t)/dt \leq 0$, and $dV_2(t)/dt = 0$ if and only if $x(t) = x_1, y(t) = y_1, v(t) = v_1, z(t) = 0$, and $w(t) = 0$. From LaSalle’s invariance principle [36], we finally have that equilibrium $E_1$ of model (2) is globally asymptotically stable when $R_0 > 1, R_1 \leq 1$, and $R_2 \leq 1$.

Next, consider conclusion (b). By computing, the characteristic equation of the linearization system of model (2) at $E_1$ is

$$(\lambda + h - rg_2(v_1)) f_1(\lambda) f_2(\lambda) = 0,$$

(31)

where $f_1(\lambda) = \lambda + b - cg_1(y_1)e^{-\lambda \tau_2}$ and
When $R_1 > 1$, we have $h - r g_2(v_1) = r(g_2(v_2) - g_2(v_1)) < 0$. Hence, there is a positive root $\lambda^* = r g_2(v_1) - h$. When $R_2 > 1$, we have $f_1(0) = b - c g_1(y_1) = c(g_1(y_2) - g_1(y_1)) < 0$ and $\lim_{\lambda \to +\infty} f_1(\lambda) = +\infty$. Hence, there is also a positive root $\lambda^*$ such that $f_1(\lambda^*) = 0$. Therefore, when $R_1 > 1$ or $R_2 > 1$, $E_1$ is unstable. This completes the proof.

Remark 8. Theorem 7 shows that if only equilibria $E_0$ and $E_1$ exist, then $E_1$ is globally asymptotically stable, and delays $\tau_1$, $\tau_2$, and $\tau_3$ do not impact the stability of $E_1$.

3.3. Stability of Equilibrium $E_2$. We firstly have the following Lemma.

**Lemma 9.** Suppose $R_1 > 1$ and $R_3 \leq 1$. Let $\bar{E}_4 = (\bar{x}_4, \bar{y}_4, \bar{v}_4, \bar{z}_4)$, $\bar{w}_4$ be the solution of equation (4) with $\bar{v}_4 = g_2^{-1}(h/r)$ and $\bar{y}_4 = g_1^{-1}(b/c)$. Then for equilibrium $E_2 = (x_2, y_2, v_2, 0, w_2, z_2)$, $\bar{w}_4 \leq 0$.

Proof. Since $E_4$ satisfies (4), we have $\bar{y}_4 = g_1^{-1}(b/c)$, $\bar{v}_4 = g_2^{-1}(h/r)$, and $\bar{x}_4 = x_2$. Compared with $E_4$, we obtain $\bar{y}_4 = x_4$ and $\bar{v}_4 = v_4$. When $R_3 \leq 1$, we get $\bar{w}_4 \leq 0$. Since
\[
e^{-m \tau_1} f(x_2, v_2) = g_1(y_2),
\]
\[
e^{-m \tau_1} f(x_4, v_4) = g_1(y_4) + p g_1(y_4) g_4(z),
\]
then it follows that $y_2 \leq \bar{y}_4$ if $R_1 > 1$ and $R_3 \leq 1$. This completes the proof.

**Theorem 10.** Let $R_3 > 1$. (a) If $R_1 \leq 1$, then antibody response equilibrium $E_2$ is globally asymptotically stable.

(b) If $R_3 > 1$, then $E_2$ is unstable.

Proof. Consider conclusion (a). Define a Lyapunov functional $V_3(t)$ as follows:
\[
V_3(t) = x(t) - \int_{\tau_2}^{\tau(t)} f(x_2, v_2) \frac{g_1(y_2)}{g_1(y_\theta)} d\theta + e^{m \tau_1} \left( \int_{y_2}^{y(t)} \frac{g_1(y_2)}{g_1(y_\theta)} d\theta \right) + \frac{f(x_2, v_2)}{g_2(v_2)(u + q g_5(w_2))} \left( v(t) - \int_{v_2}^{v(t)} \frac{g_2(v_2)}{g_2(\theta)} d\theta \right) + \frac{p e^{m \tau_1}}{c} z(t) + \frac{q f(x_2, v_2)}{g_2(v_2) r(u + q g_5(w_2))} \left( w(t) - \int_{w_2}^{w(t)} \frac{g_2(w_2)}{g_2(\theta)} d\theta \right).
\]
Calculating the derivative of $V_3(t)$ along solutions of model (2), we obtain
\[
dV_3(t) = s(x) \left( 1 - \frac{f(x_2, v_2)}{f(x, v_2)} \right) + f(x_2, v_2) \frac{g_1(y_2)}{g_1(y_2)} \left( v(t) - \int_{v_2}^{v(t)} \frac{g_2(v_2)}{g_2(\theta)} d\theta \right) + \frac{p e^{m \tau_1}}{c} z(t) + \frac{q f(x_2, v_2)}{g_2(v_2) r(u + q g_5(w_2))} \left( w(t) - \int_{w_2}^{w(t)} \frac{g_2(w_2)}{g_2(\theta)} d\theta \right).
\]
\begin{equation}
\begin{aligned}
&\left(\frac{g_2(v_2)}{g_2(v)} - \frac{f(x, v_2)}{f(x, v)}\right) + pe^{m_1\tau_1}g_4(x) \\
&\left(g_1(y_2) - g_1(\bar{y}_2)\right) - f(x_2, v_2) \\
&H\left(\frac{g_2(v)f(x, v_2)}{g_2(v_2)f(x, v)}\right) - f(x_2, v_2) \\
&H\left(\frac{g_1(y_2)f(x(t - \tau_1), v(t - \tau_1))}{g_1(y)f(x_2, v_2)}\right) \\
&- f(x_2, v_2)H\left(\frac{f(x_2, v_2)}{f(x, v_2)}\right),
\end{aligned}
\tag{37}
\end{equation}

Note that \((s(x) - s(x)) (1 - f(x_2, v_2)/f(x, v_2)) \leq 0\), and
\begin{equation}
\left(\frac{f(x, v)}{f(x, v_2)} - 1\right) \left(\frac{g_2(v_2)}{g_2(v)} - \frac{f(x, v_2)}{f(x, v)}\right) \leq 0
\end{equation}
for \(t \geq 0\).

Since \(y_2 \leq \bar{y}_2\), we have \(dV_2(t)/dt \leq 0\), and \(dV_2(t)/dt = 0\) if and only if \(x(t) = x_2\), \(y(t) = y_2\), \(v(t) = v_2\), and \(z(t) = 0\). From LaSalle’s invariance principle [36], we finally have that \(E_2\) is globally asymptotically stable when \(R_3 > 1\) and \(R_4 \leq 1\).

Next, consider conclusion (b). By computing the characteristic equation of linearization system of model (2) at \(E_1\) is
\begin{equation}
f_1(\lambda)f_2(\lambda) = 0,
\end{equation}
where \(f_1(\lambda) = \lambda + b - ce^{\lambda \tau_2}g_1(y_2)\) and
\begin{equation}
f_2(\lambda) = \begin{bmatrix}
a_{11} & 0 & a_{13} \\
a_{21} & a_{22} & a_{23} \\
0 & a_{32} & a_{33} & a_{34}
\end{bmatrix},
\end{equation}
where
\begin{align*}
a_{11} &= \lambda - s'(x_2) + \frac{df(x_2, v_2)}{dx}, \\
a_{13} &= \frac{df(x_2, v_2)}{dv}, \\
a_{21} &= -e^{-(m_1+\lambda)\tau_2}\frac{df(x_2, v_2)}{dx}, \\
a_{22} &= \lambda + ag_1(y_2), \\
a_{23} &= -e^{-(m_1+\lambda)\tau_2}\frac{df(x_2, v_2)}{dv}, \\
a_{32} &= -ke^{-(m_3+\lambda)\tau_3}g_1'(y_2), \\
a_{33} &= \lambda + (u + qg_3(w_2))g_2'(v_2), \\
a_{34} &= qg_2(v_2)g_3'(w_2),
\end{align*}
\begin{align*}
a_{43} &= -rg_2'(v_2)g_3(w_2), \\
a_{44} &= \lambda + (h - rg_2(v_2))g_3'(w_2).
\end{align*}
(41)

When \(R_3 > 1\), we have \(f_1(0) = b - cg_1(y_2) = c(g_1(\bar{y}_2) - g_1(y_2)) < 0\) and \(\lim_{t \to +\infty} f_1(\lambda) = +\infty\). Hence, there is also a positive root \(\lambda^*\) such that \(f_1(\lambda^*) = 0\). Therefore, when \(R_3 > 1\), \(E_2\) is unstable. This completes the proof.

Remark 11. Theorem 10 shows that if only equilibria \(E_0, E_1,\) and \(E_2\) exist, then when \(R_3 \leq 1\) and \(R_4 > 1\), \(E_2\) is globally asymptotically stable, and delays \(\tau_1, \tau_2,\) and \(\tau_3\) do not impact the stability of \(E_2\).

3.4. Stability of Equilibrium \(E_3\). On the stability analysis of equilibrium \(E_3\), we only discuss the following case: \(\tau_1 \geq 0\), \(\tau_2 \geq 0\), and \(\tau_3 = 0\). Other cases, \(\tau_1 \geq 0, \tau_2 \geq 0,\) and \(\tau_3 \geq 0\), are numerically verificed for bifurcation phenomena and stability switches of \(E_3\) but the analytic analysis is left as an open question. Before the proof of the theorem, we have the following Lemma.

Lemma 12. Suppose \(R_3 > 1\) and \(R_4 < 1\). Let \(E_4 = (x_4, y_4, v_4, w_4)\) be the solution of (4) with \(\bar{y}_4 = g_1^{-1}(b/c)\) and \(\bar{y}_4 = g_1^{-1}(b/c)\). Then for equilibrium \(E_3 = (x_3, y_3, v_3, z_3, 0), v_3 \leq \bar{y}_4\).

Proof. Since \(E_4\) satisfies (4), we have \(\bar{y}_4 = g_1^{-1}(b/c), v_4 = g_2^{-1}(h/r),\) and \(x_4 = x_2\). Compared with \(E_3\), we get \(\bar{y}_4 = y_4\) and \(v_4 = v_4\). When \(R_4 \leq 1\), we obtain \(\bar{y}_4 < 0\). Since
\begin{align*}
ke^{m_2\tau_2}g_1(y_3) &= u_2 g_2'(v_3), \\
ke^{m_2\tau_2}g_1(\bar{y}_4) &= u_2 g_2'(v_4) + qg_2(v_4)g_3(w_4),
\end{align*}
(42)
it follows that \(v_3 \leq \bar{y}_4\) if \(R_2 > 1\) and \(R_4 \leq 1\). This completes the proof.

Theorem 13. Let \(R_3 \geq 1\). (a) If \(R_4 \leq 1\) and \(\tau_3 = 0\), then infection equilibrium \(E_3\) with only CTL response is globally asymptotically stable.
(b) If \(R_4 > 1\), then \(E_3\) is unstable.

Proof. We first consider conclusion (a). Define a Lyapunov functional \(V_4(t)\) as follows:
\begin{align*}
V_4(t) &= x(t) - \int^{x(t)}_{x_3} f(x_3, v_3) \, d\theta \\
&\quad + e^{m_2\tau_2} f(y(t) - \int^{y(t)}_{y_3} g_1(y_3) / g_1(\theta) \, d\theta) \\
&\quad + f(x_3, v_3) u (v(t) - \int_{v_3}^{v(t)} g_2(v_3) / g_2(\theta) \, d\theta) \\
&\quad + pe^{m_2\tau_2} c (z(t) - \int_{z_3}^{z(t)} g_3(z_3) / g_3(\theta) \, d\theta).\end{align*}

\begin{align*}
a_{43} &= -rg_2'(v_2)g_3(w_2), \\
a_{44} &= \lambda + (h - rg_2(v_2))g_3'(w_2).
\end{align*}
+ \frac{qf(x_3, v_3)}{g_2(v_3)}ru(t)
+ f(x_3, v_3) \int_{-\tau_1}^{0} H \left( \frac{f(x(t+s), v(t+s))}{f(x_3, v_3)} \right) ds
+ f(x_3, v_3) \int_{-\tau_1}^{0} H \left( \frac{g_1(y(t+s))}{g_1(y_3)} \right) ds.

(43)

Calculating the derivative of $V_4(t)$ along solutions of model (2), we obtain that

$$
\frac{dV_4(t)}{dt} = s(x) \left( 1 - \frac{f(x_3, v_3)}{f(x, v_3)} \right) + f(x, v) \frac{f(x_3, v_3)}{f(x, v_3)}
- f(x_3, v_3) \frac{g_2(v)}{g_2(v_3)} + \frac{qf(x_3, v_3)}{ug_2(v_3)} g_3(w)
\cdot \frac{\left( g_2(v) - g_2(T) \right) - f(x_3, v_3)}{g_2(v_3)}
\cdot H \left( \frac{g_2(v_3) g_1(y(t - \tau_1))}{g_1(y_3) g_2(v_3)} \right) + f(x_3, v_3)
\cdot \left( s(x) - s(x_3) \right) \left( 1 - \frac{f(x_3, v_3)}{f(x, v_3)} \right) - f(x_3, v_3)
\cdot H \left( \frac{g_2(v_3) g_1(y(t - \tau_1))}{g_1(y_3) g_2(v_3)} \right) + f(x_3, v_3)
\cdot \frac{g_2(v)}{g_2(v_3)} \left( \frac{f(x, v)}{f(x_3, v_3)} - 1 \right) \left( \frac{g_2(v)}{g_2(v)} - \frac{f(x_3, v_3)}{f(x, v)} \right)
- f(x_3, v_3) H \left( \frac{f(x_3, v_3)}{f(x, v_3)} \right) - f(x_3, v_3)
\cdot H \left( \frac{g_1(y_3) f(x(t - \tau_1), v(t - t_1))}{g_1(y_3) f(x_3, v_3)} \right)
- f(x_3, v_3) H \left( \frac{g_2(v)}{g_2(v_3)} \right) \frac{g_1(y_3) f(x_3, v_3)}{g_2(v_3) f(x_3, v)} + \frac{qf(x_3, v_3)}{ug_2(v_3)}
\cdot g_3(w) \left( g_2(v_3) - g_2(T) \right).

Note that $s(x) - s(x_3)(1 - f(x_3, v_3)/f(x, v_3)) \leq 0$, and

$$
\left( \frac{f(x, v)}{f(x_3, v)} - 1 \right) \left( \frac{g_2(v_3)}{g_2(v_3)} - \frac{f(x_3, v_3)}{f(x, v)} \right) \leq 0
$$

(45)

for $t \geq 0$.

Since $v_3 \leq T$, we have $dV_4(t)/dt \leq 0$, and $dV(t)/dt = 0$ if and only if $x(t) = x_3$, $y(t) = y_3$, $v(t) = v_3$, and $w(t) = 0$. From LaSalle’s invariance principle [36], we finally have that $E_3$ is globally asymptotically stable when $\tau_3 = 0$, $R_0 > 1$, $R_2 > 1$, and $R_3 \leq 1$.

Next, we consider conclusion (b). By computing, the characteristic equation of the linearization system of model (2) at $E_3$ is

$$
(\lambda + h - rg_2(v_3)) f(\lambda) = 0,
$$

(46)

where

$$
f(\lambda) = \begin{pmatrix}
a_{11} & a_{13} & 0 \\
a_{21} & a_{22} & a_{23} & a_{24} \\
0 & a_{32} & a_{33} & 0 \\
0 & a_{42} & 0 & a_{44}
\end{pmatrix},
$$

(47)

where

$$
a_{11} = \lambda - s'(x_3) + \frac{df(x_3, v_3)}{dx},
$$

$$
a_{13} = \frac{df(x_3, v_3)}{dv},
$$

$$
a_{21} = -e^{-(m_1 + \lambda) \tau_1} \frac{df(x_3, v_3)}{dx},
$$

$$
a_{22} = \lambda + (a + pg_4(z_3)) g_1'(y_3),
$$

$$
a_{23} = -e^{-(m_1 + \lambda) \tau_1} \frac{df(x_3, v_3)}{dv},
$$

$$
a_{24} = pg_1(y_3) g_4'(z_3),
$$

$$
a_{32} = -ke^{-(m_2 + \lambda) \tau_2} g_4'(z_3),
$$

$$
a_{33} = \lambda + ug_2'(v_3),
$$

$$
a_{42} = -ce^{-\lambda \tau_3} g_4(z_3) g_4'(z_3),
$$

$$
a_{44} = \lambda + (b - cg_1(y_3) - e^{-\lambda \tau_3}) g_4(z_3).
$$

When $R_4 > 1$, we have $h - rg_2(v_3) = r(g_2(T) - g_2(v_3)) < 0$. Hence, there is a positive root $\lambda^* = rg_2(v_3) - h$. Therefore, when $R_4 > 1$, $E_3$ is unstable for any $\tau_1 \geq 0$, $\tau_2 \geq 0$, and $\tau_3 \geq 0$. This completes the proof.

Remark 14. Theorem 13 shows that if only equilibria $E_0$, $E_1$, $E_2$, and $E_3$ exist, then when $R_2 > 1$, $R_3 \leq 1$, and $\tau_3 = 0$, $E_3$ is globally asymptotically stable, and delays $\tau_1$ and $\tau_2$ do not impact the stability of $E_3$.

3.5. Stability of Equilibrium $E_4$. On the stability analysis of equilibrium $E_4$, we here only discuss the following case: $\tau_1 \geq 0$, $\tau_2 \geq 0$, and $\tau_3 = 0$. However, for the cases $\tau_1 \geq 0$, $\tau_2 \geq 0$, and $\tau_3 \geq 0$, the theoretical analysis is very complicated. We will give numerical analysis for this case in the next section.

Theorem 15. If $\tau_3 = 0$, $R_3 > 1$, and $R_4 > 1$, then infection equilibrium $E_4$ with both antibody and CTL immune responses is globally asymptotically stable.
Proof. Define a Lyapunov functional \( V_5(t) \) as follows:
\[
V_5(t) = x(t) - \int_{x_4}^{x(t)} \frac{f(x_4, v_4)}{f(\theta, v_4)} d\theta + e^{m_1 \tau_1} \left( y(t) - \int_{y_4}^{y(t)} \frac{g_1(y_4)}{g_1(\theta)} d\theta \right)
+ \frac{f(x_4, v_4)}{g_2(v_4)} \left( v(t) - \int_{v_4}^{v(t)} \frac{g_1(v_4)}{g_1(\theta)} d\theta \right) + \frac{e^{m_2 \tau_2}}{c} \left( z(t) - \int_{z_4}^{z(t)} \frac{g_1(z_4)}{g_1(\theta)} d\theta \right)
- \int_{w_4}^{w(t)} \frac{g_1(w_4)}{g_1(\theta)} d\theta + f(x_4, v_4)
- \int_{u_4}^{u(t)} \frac{g_1(u_4)}{g_1(\theta)} d\theta + f(x_4, v_4)
+ \int_{-\tau_1}^{0} H \left( \frac{g_1(y(t+s))}{g_1(y_4)} \right) ds
+ \frac{q f(x_4, v_4)}{g_2(v_4)} \left( \frac{f(x_4, v_4)}{f(x_4, v_4)} \right)
+ H \left( \frac{g_2(v)}{g_2(v_4)} \right) f(x, v) \cdot \frac{g_2(v_4)}{g_2(v_4)} f(x, v_4)
+ \frac{g_1(y_4)}{g_1(\theta)} f(x(t-\tau_1), v(t-\tau_1))
+ \frac{g_1(y_4)}{g_1(\theta)} f(x(t-\tau_2), v(t-\tau_2)) \right)
+ f(x_4, v_4)
+ \frac{g_2(v_4)}{g_2(v_4)} \left( f(x, v) - \int_{f(x, v_4)}^{f(x, v_4)} -1 \right) \left( \frac{g_2(v_4)}{g_2(v_4)} - \frac{f(x, v_4)}{f(x, v)} \right).
\]

Using the above similar method, we obtain
\[
\frac{dV_5(t)}{dt} = (s(x) - s(x_4)) \left( 1 - \frac{f(x_4, v_4)}{f(x_4, v_4)} \right)
- f(x_4, v_4) \left[ \frac{f(x_4, v_4)}{f(x_4, v_4)} \right]
+ H \left( \frac{g_2(v)}{g_2(v_4)} \right) f(x, v) \cdot \frac{g_2(v_4)}{g_2(v_4)} f(x, v_4)
+ \frac{g_1(y_4)}{g_1(\theta)} f(x(t-\tau_1), v(t-\tau_1))
+ \frac{g_1(y_4)}{g_1(\theta)} f(x(t-\tau_2), v(t-\tau_2)) \right)
\]

Note that \((s(x) - s(x_4))(1 - f(x_4, v_4))/f(x_4, v_4)\) ≤ 0, and
\[
\frac{f(x, v)}{f(x, v_4)} - 1 \left( \frac{g_2(v_4)}{g_2(v)} - \frac{f(x, v_4)}{f(x, v)} \right) ≤ 0
\]
for \(t ≥ 0\).

Obviously, we have \(dV_5(t)/dt ≤ 0\), and \(dV_5(t)/dt = 0\) if and only if \(x(t) = x_4, y(t) = y_4, v(t) = v_4\). From LaSalle’s invariance principle [36], we finally have that \(E_4\) is globally asymptotically stable when \(r_3 = 0, R_3 > 1, R_4 > 1\). This completes the proof.

Remark 16. Theorem 15 shows that if equilibria \(E_0, E_1, E_2, E_3,\) and \(E_4\) exist, then when \(R_3 > 1, R_4 > 1,\) and \(r_3 = 0, E_4\) is globally asymptotically stable, and delays \(r_1\) and \(r_2\) do not impact the stability of \(E_4\).

4. Numerical Simulations

In the above section, we obtain the global asymptotic stability of equilibria \(E_3\) and \(E_4\) when the delay \(r_3 = 0\). In this section, by using the numerical simulation, it is shown that the Hopf bifurcation and stability switches occur at equilibria \(E_3\) and \(E_4\) in the case \(r_3 > 0\).

Example 17. Corresponding to model (2), we consider the following model:
\[
\frac{dx(t)}{dt} = \lambda - dx(t) + r_1 x \left( 1 - \frac{x}{K} \right)
- \beta x(t) \left( \left( v(t) - b_4 \right) e^{-r_4} \eta(t) - b_1 \right),
\frac{dy(t)}{dt} = \beta e^{-m_1 r_1} x(t - r_1) - ay(t) - py(t) z(t),
\frac{dv(t)}{dt} = ke^{-m_2 r_1} y(t - r_2) - uv(t) - qv(t) w(t),
\frac{dz(t)}{dt} = cy(t - r_3) z(t - r_3) - bz(t),
\frac{dw(t)}{dt} = rv(t) w(t) - hw(t),
\]
where \(b_1, c_1 > 0\) are constants. We have \(s(x) = \lambda - dx(t) + r_1 x(1 - x/K), f(x, v) = \beta x(t)(v(t) - b_4) e^{-r_4} \eta(t) + b_1),\) and \(g_k(\xi) = \xi (k = 1, 2, 3, 4).\) It can easily verify that \((H_1)-(H_2)\) hold. Taking \(\lambda = 10, d = 0.01, r_1 = 0.6, K = 500, \beta = 0.3, c_1 = 0.01, b_1 = 0.01, a = 0.5, p = 1, k = 0.4, u = 3, q = 1, c = 0.1, b = 0.15, m_1 = m_2 = 0.01, g = 1.5, h = 1, r_1 = 2,\) and \(r_2 = 5,\) choose \(r_3\) as free parameter. By computing, \(R_3 = 34.4139 > 1, R_4 = 0.2854 < 1,\) and \(E_3 = (462.1965, 1.5000, 0.1902, 15.3959, 0).\) From Figures 1–4, we see that as \(r_3\) increases the complex dynamical behaviors of equilibriu \(E_3\) occur.

In Figures 1–8, we denote by (a) the time-series of \(x(t)\), by (b) the time-series of \(y(t)\), by (c) the time-series of \(v(t)\), by (d) the time-series of \(z(t)\), and by (e) the time-series of \(w(t)\).
Figure 1: Taking $\tau_3 = 0.2$, we have $R_2 = 34.4139 > 1$ and $R_4 = 0.2854 < 1$, and the infection equilibrium $E_3$ with only CTL response is asymptotically stable.
Figure 2: Taking \( \tau_3 = 2 \), we have \( R_2 = 34.4139 > 1 \) and the Hopf bifurcation at infection equilibrium \( E_3 \) with only CTL response occurs.
Figure 3: Taking $\tau_3 = 4$, we have $R_2 = 34.4139 > 1$ and $R_4 = 0.2854 < 1$, and the infection equilibrium $E_3$ with only CTL response is asymptotically stable.
Figure 4: Taking $\tau_3 = 15$, we have $R_2 = 34.4139 > 1$ and the Hopf bifurcation at infection equilibrium $E_3$ with only CTL response occurs.
Figure 5: Taking $\tau_3 = 0.1$, we have $R_3 = 1.8912 > 1$ and $R_4 = 2.7693 > 1$, and the infection equilibrium $E_4$ with both CTL and antibody responses is asymptotically stable.
Figure 6: Taking $\tau_3 = 2.5$, we have $R_3 = 1.8912 > 1$ and $R_4 = 2.7693 > 1$, and the Hopf bifurcation at infection equilibrium $E_4$ with both CTL and antibody responses occurs.
Figure 7: Taking $\tau_3 = 6$, we have $R_3 = 1.8912 > 1$ and $R_4 = 2.7693 > 1$, and the infection equilibrium $E_4$ with both CTL and antibody responses is asymptotically stable.
Figure 8: Taking $\tau_3 = 16$, we have $R_3 = 1.8912 > 1$ and the Hopf bifurcation at infection equilibrium $E_4$ with both CTL and antibody responses occurs.
Example 18. Corresponding to model (2), we consider the following model:

\[
\begin{align*}
\frac{dx(t)}{dt} &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + a_1 x(t) + b_1 v(t) + a_2 b_2 x(t)v(t)}, \\
\frac{dy(t)}{dt} &= \frac{\beta e^{-m_v} x(t-\tau_1) v(t-\tau_1)}{1 + a_1 x(t-\tau_1) + b_1 v(t-\tau_1) + a_2 b_2 x(t-\tau_1)v(t-\tau_1)} - ay(t) - py(t)z(t), \\
\frac{dv(t)}{dt} &= ke^{-m_T}y(t-\tau_2) - uv(t) - qv(t)w(t), \\
\frac{dz(t)}{dt} &= cy(t-\tau_3)z(t-\tau_3) - bz(t), \\
\frac{dw(t)}{dt} &= rv(t)w(t) - hw(t),
\end{align*}
\]

where \(a_1, b_1 > 0\) are constants. We have \(s(x) = \lambda - dx(t)\), \(f(x, v) = \beta x(t)v(t)/(1 + a_1 x(t) + b_1 v(t) + a_2 b_2 x(t)v(t))\), and \(g_i(t) = \xi (i = 1, 2, 3, 4)\). It is easily verified that \((H_1)-(H_4)\) hold.

Taking \(\lambda = 10, d = 0.01, \beta = 0.25, a_1 = 0.01, b_1 = 0.01, a = 0.5, p = 1, k = 0.4, u = 3, q = 1, c = 0.1, b = 0.15, m_1 = m_3 = 0.01, r = 1.5, h = 0.1, \tau_1 = 5, \text{ and } \tau_2 = 8\), choose \(\tau_3\) as free parameter. By computing, \(R_3 = 1.8912 > 1\), \(R_4 = 2.7693 > 1\), and \(E_4 = (850.8857, 1.5000, 0.6667, 0.4456, 5.3039)\). From Figures 5–8, we see that as \(\tau_3\) increases the complex dynamical behaviors of equilibrium \(E_4\) occur.

5. Discussion

In this paper we have considered an in-host model with intracellular delay \(\tau_1\), virus replication delay \(\tau_2\), and immune response delay \(\tau_3\), given by (2) together with assumptions \((H_1)-(H_4)\), which describes the dynamics among uninfected cells, infected cells, virus, CTL responses, and antibody responses. The model allows for general target-cell dynamics \(s(x)\), including a nonlinear incidence \(f(x, v)\), discrete delays, and state-dependent removal functions \(g_i (i = 1, 2, 3, 4)\). This general model includes many existing models in the literature as special cases. Dynamical analysis of model (2) shows that \(\tau_1, \tau_2, \text{ and } \tau_3\) play different roles in the stability of the equilibria. Particularly, we see that \(\tau_3\) may impact the stability of equilibria \(E_3, E_4\).

By the analysis, we have shown that when \(R_0 \leq 1\), \(E_4\) is globally asymptotically stable, which means that the virus is cleared up. When \(R_0 > 1, R_1 \leq 1, \text{ and } R_2 \leq 1\), \(E_3\) is globally asymptotically stable, which means that the infection is successful, but the establishments of both antibody and CTLs immune responses are unsuccessful. When \(R_1 > 1\) and \(R_2 \leq 1\), \(E_3\) is globally asymptotically stable, which implies that the antibody response is established, but the infected cells are too weak to stimulate CTL immune response. With respect to the analysis of \(E_3\), we consider special cases \(\tau_3 = 0, \tau_1 \geq 0, \text{ and } \tau_2 \geq 0\); when \(R_0 > 1 \text{ and } R_4 \leq 1\), \(E_4\) is globally asymptotically stable, which means that the CTL immune response is determined, but the viral loads are so small that it cannot activate the antibody response. About the stability of \(E_4\), we have obtained that for special case, \(\tau_3 = 0, \tau_1 \geq 0, \text{ and } \tau_2 \geq 0, \text{ when } R_0 > 1 \text{ and } R_4 > 1\), \(E_4\) is globally asymptotically stable, that is, susceptible cells, infected cells, free virus, CTLs, and antibodies coexist in vivo.

Based on Theorems 13 and 15, we obtain that the intracellular delay \(\tau_1\) and virus replication delay \(\tau_2\) for model (2) do not cause Hopf bifurcation. Moreover, \(R_0\) plays a crucial role in virus infection dynamics. Actually, in model (2), \(R_0\) is a decreasing function on time delay \(\tau_1\). When all other parameters are fixed and delay \(\tau_1\) is sufficiently large, \(R_0\) becomes less than one, only infection-free equilibrium \(E_0\) exists, and the virus is cleared in the host. By biological meanings, intracellular delay plays a positive role in virus infection process in order to eliminate virus. Sufficiently large intracellular delay makes the virus development slower and the virus has been controlled and disappeared. This gives us some suggestions on new drugs to prolong the time of infected cells producing virus. However, by the recent research of Li and Shu [37], in the case of the coexistence of mitosis rate of the target cells and an intracellular delay in the viral infection model, the intracellular delay produces Hopf bifurcation only when the mitosis rate is sufficiently large.

When \(\tau_3 > 0\), by numerical simulations, it is shown that the Hopf bifurcation and stability switches occur at equilibria \(E_3\) and \(E_4\) as \(\tau_3\) increases. Figures 1–4 indicate that \(E_3\) remains stable as \(\tau_3 > 0\) is small, and along with the increase of \(\tau_3\), equilibrium \(E_3\) becomes unstable and periodic oscillations appear. It shows that stability switches occur as delay \(\tau_3\) increases. Similarly, from Figures 5–8, we see that along with the increases of \(\tau_3 > 0\) the dynamical behaviors of model (53) at equilibrium \(E_4\) appear as very large diversification. Particularly, when \(\tau_3\) is small enough, \(E_4\) is asymptotically stable and when \(\tau_3\) is increasing, the stability switches occur at equilibrium \(E_4\), and when \(E_4\) is unstable, a Hopf bifurcation occurs. Finally, when \(\tau_3\) is enough large, equilibrium \(E_4\) always is unstable. Summarizing these discussions, we have the conclusion that \(\tau_3\) affects markedly the stability of equilibria \(E_3\) and \(E_4\). From the numerical simulations, we observe that immune response delay \(\tau_3\) can cause Hopf bifurcation. Upon primary infection, the sustained oscillations from the Hopf bifurcation imply that the pathogen may not always be cleared entirely with the CTL responses which usually occur in a few days after serum conversion. As the increase of immune delay \(\tau_3\), we know that the drug prevents virus from continuing through their cell cycle, thus trapping them at some point during interphase, where the cells die from natural causes. Then susceptible cells, infected cells, free virus, CTLs, and antibodies reach a stable level in the host. When immune delay \(\tau_3\) continuously increases, the activation of the immune cell is to fight against the malignant virus cells. Thus susceptible cells, infected cells, free virus, CTLs, and antibodies exhibit sustained periodic oscillations in the chronic phase of infection. This explains the fact that the immune response delay plays negative roles in controlling disease progression.
Observing all obtained results in this paper, we can directly put forward the following open questions which need to be further studied in the future.

For one, in addition to $\tau_1$, $\tau_2$, and $\tau_3$, antibody response delay $\tau_4$ is also considered, whether the results obtained in this paper can be extended to a virus infection model with nonlinear incidence rate and four time delays. For another, we obtain the Hopf bifurcation and stability switches at equilibria $E_1$ and $E_2$ for model (2) only by using the numerical simulation method for special examples (52) and (53). Up to now, the theoretical analysis and results in this aspect are few and rough. Therefore, a systemic and complete theoretical analysis and results will be a very estimable and significative subject.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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