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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

$$\begin{aligned}
\frac{dx(t)}{dt} &= \lambda - dx(t) - \frac{\beta\left(1-\epsilon_{rt}\right)x(t)\,v(t)}{1+mx(t)+nv(t)},\\
\frac{dy(t)}{dt} &= \frac{\beta\left(1-\epsilon_{rt}\right)x(t)\,v(t)}{1+mx(t)+nv(t)} - ay(t) - py(t)\,z(t),\\
\frac{dv(t)}{dt} &= k\left(1-\epsilon_{pi}\right)y(t) - uv(t) - qv(t)\,w(t),\\
\frac{dw(t)}{dt} &= gv(t)\,w(t) - hw(t),\\
\frac{dz(t)}{dt} &= cy(t-\tau)\,z(t-\tau) - bz(t),
\end{aligned} \tag{1}$$

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

$$\begin{aligned}
\frac{dx(t)}{dt} &= s(x) - f(x,v),\\
\frac{dy(t)}{dt} &= e^{-m_1\tau_1} f\left(x\left(t-\tau_1\right), v\left(t-\tau_1\right)\right) - ag_1(y)\\
&\quad - pg_1(y)\, g_4(z),\\
\frac{dv(t)}{dt} &= ke^{-m_2\tau_2} g_1\left(y\left(t-\tau_2\right)\right) - ug_2(v)\\
&\quad - qg_2(v)\, g_3(w),\\
\frac{dz(t)}{dt} &= cg_1\left(y\left(t-\tau_3\right)\right) g_4\left(z\left(t-\tau_3\right)\right) - bg_4(z),\\
\frac{dw(t)}{dt} &= rg_2(v)\, g_3(w) - hg_3(w),
\end{aligned} \tag{2}$$

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 λ, 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 βxv [4, 13], saturated incidence $\beta xv/(1+bv)$ [16], Holling type II functional response $\beta xv/(1+ax)$ [15], and Crowley-Martin incidence $\beta xv/(1+ax+bv+abxv)$ [12, 35], where β, a, and 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 $ag_1(y)$, $ug_2(v)$, $hg_3(w)$, 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 $qg_2(v)g_3(w)$ 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 qvw 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 τ_1. The probability of surviving the time period from $t-\tau_1$ to t is $e^{-m_1\tau_1}$. Let τ_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 delay period. Antigenic stimulation generating CTL cell may need a period of time τ_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, CTL immune competition, and antibody competition, respectively, are calculated. By using Lyapunov functionals 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_3 and E_4 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, and 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_3 and E_4 when $\tau_3 > 0$. It is shown that the Hopf bifurcation and stability switches at these equilibria occur as τ_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 $\|\phi\| = \sup_{-\tau\leq t\leq 0}\{|\phi(t)|\}$ for any $\phi \in C([-\tau, 0], R_+^5)$.

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

$$\begin{aligned}
&\left(x(\theta), y(\theta), v(\theta), z(\theta), w(\theta)\right)\\
&\quad = \left(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta)\right),\\
&\phi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0), \ \phi_i(0) > 0, \ i = 1, 2, 3, 4, 5,
\end{aligned} \tag{3}$$

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 $\overline{x} > 0$ such that $s(\overline{x}) = 0$ and $s'(\overline{x}) < 0$.
- (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 $v \geq 0$; $(d/dx)(\partial f(x,0)/\partial v) \geq 0$ for all $x \geq 0$.

(H_3) $g_i(\xi)$ $(i = 1, 2, 3, 4)$ is strictly increasing on $[0, \infty)$; $\lim_{\xi\to\infty} g_i(\xi) = +\infty$; and there exists $k_i > 0$ such that $g_i(\xi) \geq k_i\xi$ for any $\xi \geq 0$; $g_i(0) = 0$ and $g_i'(0) = 1$.

(H_4) $f(x, v)/g_2(v)$ is nonincreasing with respect to v for $v \in (0, \infty)$.

From (H_1) we easily obtain that $s(x) > 0$ for all $0 < x < \overline{x}$ and $s(x) < 0$ for all $x > \overline{x}$. Assumption (H_1) 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 (H_2) 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 (H_3) 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 $ag_1(y)$, $ug_2(v)$, $hg_3(w)$, and $bg_4(z)$ will increase, and the ratio $g_i(\xi)/\xi$ is no less than a positive constant for $i = 1, 2, 3, 4$. Finally, assumption (H_4) 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 ratio is nonincreasing.

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

Theorem 1. *Assume that (H_1)–(H_4) 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

$$\begin{aligned} s(x) - f(x, v) &= 0, \\ e^{-m_1\tau_1} f(x, v) - ag_1(y) - pg_1(y) g_4(z) &= 0, \\ ke^{-m_2\tau_2} g_1(y) - ug_2(v) - qg_2(v) g_3(w) &= 0, \\ cg_1(y) g_4(z) - bg_4(z) &= 0, \\ rg_2(v) g_3(w) - hg_3(w) &= 0. \end{aligned} \tag{4}$$

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 $s(x) = f(x, v)$, $g_2(v)(u + qg_3(w)) = 0$, $g_4(z) = 0$, and $(rg_2(v) - h)g_3(w) = 0$. Solving these equations, we have $x = \overline{x}$, $v = 0$, $z = 0$, and $w = 0$. 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 $g_3(w) = 0$. Solving these equations, we have $x = \overline{x}$, $v = 0$, $z = 0$, and $w = 0$. 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:

$$s(x) = f(x, v) = ae^{m_1\tau_1} g_1(y) = \frac{aue^{m_1\tau_1+m_2\tau_2}}{k} g_2(v). \tag{5}$$

By (H_3), the inverse function $g_2^{-1}(v)$ exists. Solving $s(x) = (aue^{m_1\tau_1+m_2\tau_2}/k)g_2(v)$, we have $v = \varphi(x) \triangleq g_2^{-1}(ks(x)/aue^{m_1\tau_1+m_2\tau_2})$ with $\varphi(\overline{x}) = 0$ and $\varphi(0) = v^0$, where v^0 is the unique positive root of equation $s(0) = (aue^{m_1\tau_1+m_2\tau_2}/k)g_2(v)$. Define $G(x) = f(x, \varphi(x)) - (aue^{m_1\tau_1+m_2\tau_2}/k)g_2(\varphi(x))$. Then $G(0) = -(aue^{m_1\tau_1+m_2\tau_2}/k)g_2(v^0) < 0$ and $G(\overline{x}) = 0$.

Define the basic reproduction number for viral infection

$$R_0 = \frac{ke^{-m_1\tau_1-m_2\tau_2}}{au} \frac{\partial f(\overline{x}, 0)}{\partial v}. \tag{6}$$

Note that

$$\begin{aligned} &G'(\overline{x}) \\ &= \frac{\partial f(\overline{x}, 0)}{\partial x} + \frac{\partial f(\overline{x}, 0)}{\partial v}\varphi'(\overline{x}) \\ &\quad - \frac{aue^{m_1\tau_1+m_2\tau_2}}{k} g_2'(0)\varphi'(\overline{x}) \\ &= \frac{aue^{m_1\tau_1+m_2\tau_2}}{k}\varphi'(\overline{x}) \left(\frac{k}{aue^{m_1\tau_1+m_2\tau_2}} \frac{\partial f(\overline{x}, 0)}{\partial v} - 1 \right) \\ &= s'(\overline{x}) (R_0 - 1). \end{aligned} \tag{7}$$

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 $v_1 = \varphi(x_1)$. (H_3) ensures that $ke^{-m_2\tau_2} g_1(y) = ug_2(v_1)$ has a unique positive solution $y_1 = g_1^{-1}(ue^{m_2\tau_2} g_2(v_1)/k)$. 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 $E_1^* = (x_1^*, y_1^*, v_1^*, 0, 0)$. Without loss of generality, we assume that $x_1^* < x_1$, and then $s(x_1^*) > s(x_1)$. Meanwhile, $ks(x_1) = aue^{m_1\tau_1+m_2\tau_2} g_2(v_1)$ and $ks(x_1^*) = aue^{m_1\tau_1+m_2\tau_2} g_2(v_1^*)$. By (H_3) and (H_4), 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 $f(x_1, v_1^*) > f(x_1^*, v_1^*)$ and $f(x_1^*, v_1^*)/g_2(v_1^*) < f(x_1, v_1)/g_2(v_1)$. For another, we have $f(x_1^*, v_1^*)/g_2(v_1^*) = f(x_1, v_1)/g_2(v_1)$. This is a contradiction. Thus E_1 is a unique equilibrium.

We consider the existence of infection equilibrium $E_2 = (x_2, y_2, v_2, 0, w_2)$ with only antibody response. It is clear that $v_2 = g_2^{-1}(h/r)$. Define $F(x) = s(x) - f(x, v_2)$. By (H_1) and (H_2), we obtain $F'(x) < 0$. Since $F(0) = s(0) > 0$ and $F(\overline{x}) = s(\overline{x}) - f(\overline{x}, v_2) < 0$, there exists a unique $x_2 \in (0, \overline{x})$ such that $F(x_2) = 0$. Then, we have $y_2 = g_1^{-1}(e^{-m_1\tau_1} f(x_2, v_2)/a)$.

Define the constant

$$R_1 = \frac{ke^{-m_1\tau_1-m_2\tau_2}}{u} \frac{f(x_2, v_2)}{g_2(v_2)}, \tag{8}$$

which is called the antibody response reproductive number of model (2). Solving w_2 from (4), we obtain that

$$w_2 = g_3^{-1}\left(\frac{ke^{-m_2\tau_2}g_1(y_2) - ug_2(v_2)}{qg_2(v_2)}\right) = g_3^{-1}\left(\frac{u(R_1-1)}{q}\right) > 0 \quad \text{if } R_1 > 1. \tag{9}$$

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 $y_3 = g_1^{-1}(b/c)$ and $v_3 = g_2^{-1}(bke^{-m_2\tau_2}/cu)$. Define $F(x) = s(x) - f(x, v_3)$. By (H_1) and (H_2), we obtain $F'(x) < 0$. Since $F(0) = s(0) > 0$ and $F(\overline{x}) = s(\overline{x}) - f(\overline{x}, v_3) < 0$, there exists a unique $x_3 \in (0, \overline{x})$ such that $F(x_3) = 0$.

Define the constant

$$R_2 = \frac{ke^{-m_1\tau_1-m_2\tau_2}}{au}\frac{f(x_3, v_3)}{g_2(v_3)}, \tag{10}$$

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

$$z_3 = g_4^{-1}\left(\frac{e^{-m_1\tau_1}f(x_3, v_3) - ag_1(y_3)}{pg_1(y_3)}\right) = g_4^{-1}\left(\frac{a(R_2-1)}{p}\right) > 0 \quad \text{if } R_2 > 1. \tag{11}$$

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 $y_4 = g_1^{-1}(b/c)$ and $v_4 = g_2^{-1}(h/r)$. Define $F(x) = s(x) - f(x, v_4)$. By (H_1) and (H_2), we obtain $F'(x) < 0$. Since $F(0) = s(0) > 0$ and $F(\overline{x}) = s(\overline{x}) - f(\overline{x}, v_4) < 0$, there exists a unique $x_4 \in (0, \overline{x})$ such that $F(x_4) = 0$.

Define the constants

$$R_3 = \frac{cf(x_4, v_4)}{abe^{m_1\tau_1}}, \qquad R_4 = \frac{kbr}{uche^{m_2\tau_2}}, \tag{12}$$

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 z yields a unique

$$z_4 = g_4^{-1}\left(\frac{e^{-m_1\tau_1}f(x_4, v_4) - ag_1(y_4)}{pg_1(y_4)}\right) = g_4^{-1}\left(\frac{a(R_3-1)}{p}\right) > 0 \quad \text{if } R_3 > 1. \tag{13}$$

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

$$w_4 = g_3^{-1}\left(\frac{ke^{-m_2\tau_2}g_1(y_4) - ug_2(v_4)}{qg_2(v_4)}\right) = g_3^{-1}\left(\frac{u(R_4-1)}{q}\right) > 0 \quad \text{if } R_4 > 1. \tag{14}$$

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

Remark 2. From (H_2) and (H_4), we obtain $R_1 < R_0$ and $R_2 < R_0$. In fact,

$$\begin{aligned} R_1 &= \frac{ke^{-m_1\tau_1-m_2\tau_2}}{u}\frac{f(x_2, v_2)}{g(v_2)} \\ &\le \frac{ke^{-m_1\tau_1-m_2\tau_2}}{u}\lim_{v\to 0^+}\frac{f(x_2, v)}{g_2(v)} \\ &= \frac{ke^{-m_1\tau_1-m_2\tau_2}}{ug_2'(0)}\frac{\partial f(x_2, 0)}{\partial v} < \frac{ke^{-m_1\tau_1-m_2\tau_2}}{ug_2'(0)}\frac{\partial f(\overline{x}, 0)}{\partial v} \\ &= R_0, \\ R_2 &= \frac{ke^{-m_1\tau_1-m_2\tau_2}}{au}\frac{f(x_3, v_3)}{g_2(v_3)} \\ &\le \frac{ke^{-m_1\tau_1-m_2\tau_2}}{au}\lim_{v\to 0^+}\frac{f(x_3, v)}{g_2(v)} \\ &= \frac{ke^{-m_1\tau_1-m_2\tau_2}}{aug_2'(0)}\frac{\partial f(x_3, 0)}{\partial v} < \frac{ke^{-m_1\tau_1-m_2\tau_2}}{aug_2'(0)}\frac{\partial f(\overline{x}, 0)}{\partial v} \\ &= R_0. \end{aligned} \tag{15}$$

3. Stability Analysis

3.1. Stability of Equilibrium E_0

Theorem 3. *(a) If $R_0 \le 1$, 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:

$$\begin{aligned} V_1(t) = x(t) &- \int_{\overline{x}}^{x(t)}\lim_{v\to 0}\frac{f(\overline{x}, v)}{f(\theta, v)}d\theta + e^{m_1\tau_1}y(t) \\ &+ \frac{ae^{m_1\tau_1+m_2\tau_2}}{k}v(t) + \frac{pe^{m_1\tau_1}}{c}z(t) \\ &+ \int_{-\tau_1}^{0} f(x(t+s), v(t+s))\,ds \\ &+ ae^{m_1\tau_1}\int_{-\tau_2}^{0} g_1(y(t+s))\,ds \end{aligned}$$

$$+ pe^{m_1\tau_1}\int_{-\tau_3}^{0} g_1\left(y\left(t+s\right)\right) g_4\left(z\left(t+s\right)\right) ds + \frac{aqe^{m_1\tau_1+m_2\tau_2}}{kr} w\left(t\right). \tag{16}$$

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

$$\begin{aligned}\frac{dV_1\left(t\right)}{dt} &= s\left(x\right)\left(1-\lim_{v\to 0}\frac{f\left(\overline{x},v\right)}{f\left(x,v\right)}\right)+f\left(x,v\right)\\ &\cdot \lim_{v\to 0}\frac{f\left(\overline{x},v\right)}{f\left(x,v\right)}-\frac{aue^{m_1\tau_1+m_2\tau_2}}{k}g_2\left(v\right)-\frac{pbe^{m_1\tau_1}}{c}\\ &\cdot g_4\left(z\right)-\frac{aqhe^{m_1\tau_1+m_2\tau_2}}{kr}g_3\left(w\right)\le\frac{aue^{m_1\tau_1+m_2\tau_2}}{k}\\ &\cdot g_2\left(v\right)\left(\frac{k}{aue^{m_1\tau_1+m_2\tau_2}}\frac{f\left(x,v\right)}{g_2\left(v\right)}\lim_{v\to 0}\frac{f\left(\overline{x},v\right)}{f\left(x,v\right)}-1\right)\\ &+ s\left(x\right)\left(1-\lim_{v\to 0}\frac{f\left(\overline{x},v\right)}{f\left(x,v\right)}\right).\end{aligned} \tag{17}$$

Note that $s(x)(1-\lim_{v\to 0}(f(\overline{x},v)/f(x,v)))\le 0$, and

$$\begin{aligned}\frac{f\left(x,v\right)}{g_2\left(v\right)}\lim_{v\to 0}\frac{f\left(\overline{x},v\right)}{f\left(x,v\right)} &\le \lim_{v\to 0}\frac{f\left(x,v\right)}{g_2\left(v\right)}\frac{\partial f\left(\overline{x},0\right)/\partial v}{\partial f\left(x,0\right)/\partial v}\\ &= \frac{\partial f\left(\overline{x},0\right)}{\partial v}\frac{1}{g_2'\left(0\right)}.\end{aligned} \tag{18}$$

It follows that

$$\frac{dV_1\left(t\right)}{dt}\le\frac{aue^{m_1\tau_1+m_2\tau_2}}{k}g_2\left(v\right)\left(R_0-1\right). \tag{19}$$

Note that $dV_1(t)/dt = 0$ if and only if $x(t)=\overline{x}$, $v(t)=0$, $z(t)=0$, $y(t)=0$, and $w(t)=0$. 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

$$\left(\lambda+hg_3'\left(0\right)\right)\left(\lambda+bg_4'\left(0\right)\right)\left(\lambda-s'\left(\overline{x}\right)\right)f\left(\lambda\right)=0, \tag{20}$$

where

$$\begin{aligned}f\left(\lambda\right) &= \lambda^2+\left(a+u\right)\lambda+au\\ &\quad -k\frac{\partial f\left(\overline{x},0\right)}{\partial v}e^{-\left(m_1+\lambda\right)\tau_1}e^{-\left(m_2+\lambda\right)\tau_2}.\end{aligned} \tag{21}$$

When $R_0>1$, we have $f(0)=au-k(\partial f(\overline{x},0)/\partial v)e^{-m_1\tau_1}e^{-m_2\tau_2}<0$ and $\lim_{\lambda\to+\infty}f(\lambda)=+\infty$. Hence, there is $\lambda>0$ such that $f(\lambda)=0$. Therefore, when $R_0>1$, E_0 is unstable. This completes the proof. □

Remark 4. Theorem 3 shows that if only equilibrium E_0 exists, then it is globally asymptotically stable, and delays τ_1, τ_2, and τ_3 do not impact the stability of E_0.

3.2. Stability of Equilibrium E_1. Firstly, we introduce two lemmas which will be used in the proof of Theorem 7.

Lemma 5. *Suppose that (H_1)–(H_4) hold and $R_0>1$. Let x_2 and v_2 satisfy $g_2(v_2)=h/r$ and $s(x_2)=f(x_2,v_2)$. Then for equilibrium $E_1=(x_1,y_1,v_1,0,0)$, $\operatorname{sign}(x_2-x_1)=\operatorname{sign}(v_1-v_2)=\operatorname{sign}(R_1-1)$.*

Proof. Since $s(x_1)=f(x_1,v_1)$, we have

$$\begin{aligned}s\left(x_2\right)-s\left(x_1\right) &= \left(f\left(x_2,v_2\right)-f\left(x_1,v_2\right)\right)\\ &\quad +\left(f\left(x_1,v_2\right)-f\left(x_1,v_1\right)\right).\end{aligned} \tag{22}$$

By (H_1) and (H_2), we get $\operatorname{sign}(x_2-x_1)=\operatorname{sign}(v_1-v_2)$. Using $(ke^{-m_1\tau_1-m_2\tau_2}/au)(f(x_1,v_1)/g_2(v_1))=1$, we have

$$\begin{aligned}R_1-1 &= \frac{k}{aue^{m_1\tau_1+m_2\tau_2}}\left(\frac{1}{g_2\left(v_2\right)}\left(f\left(x_2,v_2\right)-f\left(x_1,v_2\right)\right)\right.\\ &\quad \left.+\frac{f\left(x_1,v_2\right)}{g_2\left(v_2\right)}-\frac{f\left(x_1,v_1\right)}{g_2\left(v_1\right)}\right).\end{aligned} \tag{23}$$

By (H_2) and (H_4), it follows that $\operatorname{sign}(R_1-1)=\operatorname{sign}(v_1-v_2)$. This completes the proof. □

Lemma 6. *Suppose that (H_1)–(H_4) hold and $R_0>1$. Let x_3, y_3, and v_3 satisfy $g_2(v_3)=kbe^{-m_2\tau_2}/uc$, $g_1(y_3)=b/c$, and $s(x_3)=f(x_3,v_3)$. Then, for equilibrium $E_1=(x_1,y_1,v_1,0,0)$, $\operatorname{sign}(x_3-x_1)=\operatorname{sign}(v_1-v_3)=\operatorname{sign}(y_1-y_3)=\operatorname{sign}(R_2-1)$.*

Proof. Since $g_1(y_1)=(ue^{m_2\tau_2}/k)g_2(v_1)$ and $g_1(y_3)=(ue^{m_2\tau_2}/k)g_2(v_3)$, we have $\operatorname{sign}(v_1-v_3)=\operatorname{sign}(y_1-y_3)$. Since $s(x_1)=f(x_1,v_1)$, one has

$$\begin{aligned}s\left(x_3\right)-s\left(x_1\right) &= \left(f\left(x_3,v_3\right)-f\left(x_3,v_1\right)\right)\\ &\quad +\left(f\left(x_3,v_1\right)-f\left(x_1,v_1\right)\right).\end{aligned} \tag{24}$$

By (H_1) and (H_2), we get $\operatorname{sign}(x_3-x_1)=\operatorname{sign}(v_1-v_3)$, and

$$\begin{aligned}R_2-1 &= \frac{k}{aue^{m_1\tau_1+m_2\tau_2}}\left(\frac{f\left(x_3,v_3\right)}{g_2\left(v_3\right)}-\frac{f\left(x_3,v_1\right)}{g_2\left(v_1\right)}\right.\\ &\quad \left.+\frac{f\left(x_3,v_1\right)-f\left(x_1,v_1\right)}{g_2\left(v_1\right)}\right).\end{aligned} \tag{25}$$

By (H_2) and (H_4), we further have $\operatorname{sign}(R_2-1)=\operatorname{sign}(x_3-x_1)$. This completes the proof. □

Theorem 7. *Let $R_0>1$. (a) If $R_1\le 1$ and $R_2\le 1$, then immune-free equilibrium E_1 is globally asymptotically stable. (b) If $R_1>1$ or $R_2>1$, then E_1 is unstable.*

Proof. Consider conclusion (a). Denote $H(\xi) = \xi - 1 - \ln \xi$ with $\xi \in R_+$. Define a Lyapunov functional $V_2(t)$ as follows:

$$\begin{aligned} V_2(t) &= x(t) - \int_{x_1}^{x(t)} \frac{f(x_1, v_1)}{f(\theta, v_1)}\, d\theta \\ &+ e^{m_1\tau_1}\left(y(t) - \int_{y_1}^{y(t)} \frac{g_1(y_1)}{g_1(\theta)}\, d\theta\right) \\ &+ \frac{ae^{m_1\tau_1+m_2\tau_2}}{k}\left(v(t) - \int_{v_1}^{v(t)} \frac{g_2(v_1)}{g_2(\theta)}\, d\theta\right) \\ &+ \frac{pe^{m_1\tau_1}}{c} z(t) + \frac{aqe^{m_1\tau_1+m_2\tau_2}}{kr} w(t) \\ &+ f(x_1, v_1) \int_{-\tau_1}^{0} H\left(\frac{f(x(t+s), v(t+s))}{f(x_1, v_1)}\right) ds \\ &+ pe^{m_1\tau_1} \int_{-\tau_3}^{0} g_1(y(t+s))\, g_4(z(t+s))\, ds \\ &+ ae^{m_1\tau_1} g_1(y_1) \int_{-\tau_2}^{0} H\left(\frac{g_1(y(t+s))}{g_1(y_1)}\right) ds. \end{aligned} \tag{26}$$

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

$$\begin{aligned} \frac{dV_2(t)}{dt} &= s(x)\left(1 - \frac{f(x_1, v_1)}{f(x, v_1)}\right) \\ &+ f(x, v)\frac{f(x_1, v_1)}{f(x, v_1)} - \frac{aue^{m_1\tau_1+m_2\tau_2}}{k} g_2(v) \\ &+ M_1 + M_2, \end{aligned} \tag{27}$$

where

$$\begin{aligned} M_1 &= pe^{m_1\tau_1} g_1(y_1)\, g_4(z) - \frac{pbe^{m_1\tau_1}}{c} g_4(z) \\ &+ \frac{aqe^{m_1\tau_1+m_2\tau_2}}{k} g_2(v_1)\, g_3(w) - \frac{aqhe^{m_1\tau_1+m_2\tau_2}}{kr} \\ &\cdot g_3(w) = pe^{m_1\tau_1} g_4(z)\left(g_1(y_1) - g_1(y_3)\right) \\ &+ \frac{aqe^{m_1\tau_1+m_2\tau_2}}{k} g_3(w)\left(g_2(v_1) - g_2(v_2)\right), \\ M_2 &= f(x_1, v_1)\Bigg(2 \\ &- \frac{g_1(y_1)\, f(x(t-\tau_1), v(t-\tau_1))}{g_1(y)\, f(x_1, v_1)} \\ &- \frac{g_2(v_1)\, g_1(y(t-\tau_2))}{g_1(y_1)\, g_2(v)} \\ &+ \ln \frac{f(x(t-\tau_1), v(t-\tau_1))}{f(x, v)} \\ &+ \ln \frac{g_1(y(t-\tau_2))}{g_1(y)}\Bigg) = f(x_1, v_1) \\ &\cdot \ln \frac{g_2(v)\, f(x_1, v_1)}{g_2(v_1)\, f(x, v)} - f(x_1, v_1) \\ &\cdot H\left(\frac{g_1(y_1)\, f(x(t-\tau_1), v(t-\tau_1))}{g_1(y)\, f(x_1, v_1)}\right) \\ &- f(x_1, v_1) H\left(\frac{g_2(v_1)\, g_1(y(t-\tau_2))}{g_1(y_1)\, g_2(v)}\right). \end{aligned} \tag{28}$$

Therefore,

$$\begin{aligned} \frac{dV_2(t)}{dt} &= \left(s(x) - s(x_1)\right)\left(1 - \frac{f(x_1, v_1)}{f(x, v_1)}\right) \\ &- f(x_1, v_1) H\left(\frac{g_2(v_1)\, g_1(y(t-\tau_2))}{g_1(y_1)\, g_2(v)}\right) \\ &+ f(x_1, v_1)\frac{g_2(v)}{g_2(v_1)}\left(\frac{f(x, v)}{f(x, v_1)} - 1\right) \\ &\cdot \left(\frac{g_2(v_1)}{g_2(v)} - \frac{f(x, v_1)}{f(x, v)}\right) + M_1 - f(x_1, v_1) \\ &\cdot H\left(\frac{f(x_1, v_1)}{f(x, v_1)}\right) - f(x_1, v_1) \\ &\cdot H\left(\frac{g_2(v)\, f(x, v_1)}{g_2(v_1)\, f(x, v)}\right) - f(x_1, v_1) \\ &\cdot H\left(\frac{g_1(y_1)\, f(x(t-\tau_1), v(t-\tau_1))}{g_1(y)\, f(x_1, v_1)}\right). \end{aligned} \tag{29}$$

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

$$\left(\frac{f(x, v)}{f(x, v_1)} - 1\right)\left(\frac{g_2(v_1)}{g_2(v)} - \frac{f(x, v_1)}{f(x, v)}\right) \le 0 \quad \text{for } t \ge 0. \tag{30}$$

Lemmas 5 and 6 imply that $y_1 \le y_3$ and $v_1 \le v_2$ if $R_1 \le 1$ and $R_2 \le 1$. It then follows from the monotonicity of g_1 and g_2 that $M_1 \le 0$. We have $dV_2(t)/dt \le 0$, 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 $R_0 > 1$, $R_1 \le 1$, and $R_2 \le 1$.

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

$$\left(\lambda + h - rg_2(v_1)\right) f_1(\lambda)\, f_2(\lambda) = 0, \tag{31}$$

where $f_1(\lambda) = \lambda + b - cg_1(y_1)e^{-\lambda\tau_3}$ and

$$f_2(\lambda) = \begin{vmatrix} \lambda - s'(x_1) + \dfrac{\partial f(x_1, v_1)}{\partial x} & 0 & \dfrac{\partial f(x_1, v_1)}{\partial v} \\ -e^{-(m_1+\lambda)\tau_1} \dfrac{\partial f(x_1, v_1)}{\partial x} & \lambda + a g_1'(y_1) & -e^{-(m_1+\lambda)\tau_1} \dfrac{\partial f(x_1, v_1)}{\partial v} \\ 0 & -k e^{-(m_2+\lambda)\tau_2} g_1'(y_1) & \lambda + u g_2'(v_1) \end{vmatrix}. \tag{32}$$

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 $f_1(0) = b - c g_1(y_1) = c(g_1(y_3) - g_1(y_1)) < 0$ and $\lim_{\lambda \to +\infty} f_1(\lambda) = +\infty$. Hence, there is also a positive root λ^* 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 τ_1, τ_2, and τ_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 $R_3 \le 1$. Let $\overline{E_4} = (\overline{x_4}, \overline{y_4}, \overline{v_4}, \overline{z_4}, \overline{w_4})$ be the solution of equation (4) with $\overline{v_4} = g_2^{-1}(h/r)$ and $\overline{y_4} = g_1^{-1}(b/c)$. Then for equilibrium $E_2 = (x_2, y_2, v_2, 0, w_2)$, $y_2 \le \overline{y_4}$.*

Proof. Since $\overline{E_4}$ satisfies (4), we have $\overline{y_4} = g_1^{-1}(b/c)$, $\overline{v_4} = g_2^{-1}(h/r)$, and $\overline{x_4} = x_2$. Compared with E_4, we obtain $\overline{x_4} = x_4$ and $\overline{v_4} = v_4$. When $R_3 \le 1$, we get $\overline{z_4} \le 0$. Since

$$\begin{aligned} e^{-m_1\tau_1} f(x_2, v_2) &= a g_1(y_2), \\ e^{-m_1\tau_1} f(\overline{x_4}, \overline{v_4}) &= a g_1(\overline{y_4}) + p g_1(\overline{y_4}) g_4(\overline{z_4}), \end{aligned} \tag{33}$$

it follows that $y_2 \le \overline{y_4}$ if $R_1 > 1$ and $R_3 \le 1$. This completes the proof. □

Theorem 10. *Let $R_1 > 1$. (a) If $R_3 \le 1$, 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:

$$\begin{aligned} V_3(t) = {} & x(t) - \int_{x_2}^{x(t)} \frac{f(x_2, v_2)}{f(\theta, v_2)}\, d\theta + e^{m_1\tau_1} \left(y(t) - \int_{y_2}^{y(t)} \frac{g_1(y_2)}{g_1(\theta)}\, d\theta \right) \\ & + \frac{f(x_2, v_2)}{g_2(v_2)(u + q g_3(w_2))} \left(v(t) - \int_{v_2}^{v(t)} \frac{g_2(v_2)}{g_2(\theta)}\, d\theta \right) + \frac{p e^{m_1\tau_1}}{c} z(t) \\ & + \frac{q f(x_2, v_2)}{g_2(v_2) r (u + q g_3(w_2))} \left(w(t) - \int_{w_2}^{w(t)} \frac{g_3(w_2)}{g_3(\theta)}\, d\theta \right) + f(x_2, v_2) \\ & \cdot \int_{-\tau_1}^{0} H\left(\frac{f(x(t+s), v(t+s))}{f(x_2, v_2)} \right) ds \\ & + f(x_2, v_2) \int_{-\tau_2}^{0} H\left(\frac{g_1(y(t+s))}{g_1(y_2)} \right) ds \\ & + p e^{m_1\tau_1} \int_{-\tau_3}^{0} g_1(y(t+s)) g_4(z(t+s))\, ds. \end{aligned} \tag{34}$$

Calculating the derivative of $V_3(t)$ along solutions of model (2), we obtain

$$\begin{aligned} \frac{dV_3(t)}{dt} = {} & s(x)\left(1 - \frac{f(x_2, v_2)}{f(x, v_2)}\right) \\ & + f(x, v) \frac{f(x_2, v_2)}{f(x, v_2)} - f(x_2, v_2) \frac{g_2(v)}{g_2(v_2)} \\ & + M_1 + M_2, \end{aligned} \tag{35}$$

where

$$\begin{aligned} M_1 = {} & p e^{m_1\tau_1} g_1(y_2) g_4(z) - \frac{p b e^{m_1\tau_1}}{c} g_4(z) \\ = {} & p e^{m_1\tau_1} g_4(z) (g_1(y_2) - g_1(\overline{y_4})), \\ M_2 = {} & f(x_2, v_2) \ln \frac{g_2(v) f(x_2, v_2)}{g_2(v_2) f(x, v)} - f(x_2, v_2) \\ & \cdot H\left(\frac{g_2(v_2) g_1(y(t-\tau_2))}{g_1(y_2) g_2(v)} \right) - f(x_2, v_2) \\ & \cdot H\left(\frac{g_1(y_2) f(x(t-\tau_1), v(t-\tau_1))}{g_1(y) f(x_2, v_2)} \right). \end{aligned} \tag{36}$$

Therefore,

$$\begin{aligned} \frac{dV_3(t)}{dt} = {} & (s(x) - s(x_2))\left(1 - \frac{f(x_2, v_2)}{f(x, v_2)}\right) \\ & - f(x_2, v_2) H\left(\frac{g_2(v_2) g_1(y(t-\tau_2))}{g_1(y_2) g_2(v)} \right) \\ & + f(x_2, v_2) \frac{g_2(v)}{g_2(v_2)} \left(\frac{f(x, v)}{f(x, v_2)} - 1 \right) \end{aligned}$$

$$\cdot\left(\frac{g_2(v_2)}{g_2(v)}-\frac{f(x,v_2)}{f(x,v)}\right)+pe^{m_1\tau_1}g_4(z)$$
$$\cdot\left(g_1(y_2)-g_1(\overline{y_4})\right)-f(x_2,v_2)$$
$$\cdot H\left(\frac{g_2(v)f(x,v_2)}{g_2(v_2)f(x,v)}\right)-f(x_2,v_2)$$
$$\cdot H\left(\frac{g_1(y_2)f(x(t-\tau_1),v(t-\tau_1))}{g_1(y)f(x_2,v_2)}\right)$$
$$-f(x_2,v_2)H\left(\frac{f(x_2,v_2)}{f(x,v_2)}\right). \tag{37}$$

Note that $(s(x)-s(x_2))(1-f(x_2,v_2)/f(x,v_2))\le 0$, and

$$\left(\frac{f(x,v)}{f(x,v_2)}-1\right)\left(\frac{g_2(v_2)}{g_2(v)}-\frac{f(x,v_2)}{f(x,v)}\right)\le 0 \quad \text{for } t\ge 0. \tag{38}$$

Since $y_2\le\overline{y_4}$, we have $dV_3(t)/dt\le 0$, and $dV_3(t)/dt=0$ 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 $R_1>1$ and $R_3\le 1$.

Next, consider conclusion (b). By computing, the characteristic equation of linearization system of model (2) at E_2 is

$$f_1(\lambda)f_2(\lambda)=0, \tag{39}$$

where $f_1(\lambda)=\lambda+b-ce^{-\lambda\tau_3}g_1(y_2)$ and

$$f_2(\lambda)=\begin{vmatrix} a_{11} & 0 & a_{13} & 0\\ a_{21} & a_{22} & a_{23} & 0\\ 0 & a_{32} & a_{33} & a_{34}\\ 0 & 0 & a_{43} & a_{44}\end{vmatrix}, \tag{40}$$

where

$$a_{11}=\lambda-s'(x_2)+\frac{\partial f(x_2,v_2)}{\partial x},$$
$$a_{13}=\frac{\partial f(x_2,v_2)}{\partial v},$$
$$a_{21}=-e^{-(m_1+\lambda)\tau_1}\frac{\partial f(x_2,v_2)}{\partial x},$$
$$a_{22}=\lambda+ag_1'(y_2),$$
$$a_{23}=-e^{-(m_1+\lambda)\tau_1}\frac{\partial f(x_2,v_2)}{\partial v},$$
$$a_{32}=-ke^{-(m_2+\lambda)\tau_2}g_1'(y_2),$$
$$a_{33}=\lambda+(u+qg_3(w_2))g_2'(v_2),$$
$$a_{34}=qg_2(v_2)g_3'(w_2),$$
$$a_{43}=-rg_2'(v_2)g_3(w_2),$$
$$a_{44}=\lambda+(h-rg_2(v_2))g_3'(w_2). \tag{41}$$

When $R_3>1$, we have $f_1(0)=b-cg_1(y_2)=c(g_1(\overline{y_4})-g_1(y_2))<0$ and $\lim_{\lambda\to+\infty}f_1(\lambda)=+\infty$. Hence, there is also a positive root λ^* 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 $R_3\le 1$ and $R_1>1$, E_2 is globally asymptotically stable, and delays τ_1, τ_2, and τ_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: $\tau_1\ge 0$, $\tau_2\ge 0$, and $\tau_3=0$. Other cases, $\tau_1\ge 0$, $\tau_2\ge 0$, and $\tau_3\ge 0$, are numerically verified for bifurcation phenomena and stability switches of E_3 but the analytic analysis is left as an open problem. Before the proof of theorem, we have the following Lemma.

Lemma 12. *Suppose $R_2>1$ and $R_4\le 1$. Let $\overline{E_4}=(\overline{x_4},\overline{y_4},\overline{v_4},\overline{z_4},\overline{w_4})$ be the solution of (4) with $\overline{v_4}=g_2^{-1}(h/r)$ and $\overline{y_4}=g_1^{-1}(b/c)$. Then for equilibrium $E_3=(x_3,y_3,v_3,z_3,0)$, $v_3\le\overline{v_4}$.*

Proof. Since $\overline{E_4}$ satisfies (4), we have $\overline{y_4}=g_1^{-1}(b/c)$, $\overline{v_4}=g_2^{-1}(h/r)$, and $\overline{x_4}=x_2$. Compared with E_4, we get $\overline{y_4}=y_4$ and $\overline{v_4}=v_4$. When $R_4\le 1$, we obtain $\overline{w_4}<0$. Since

$$ke^{-m_2\tau_2}g_1(y_3)=ug_2(v_3),$$
$$ke^{-m_2\tau_2}g_1(\overline{y_4})=ug_2(\overline{v_4})+qg_2(\overline{v_4})g_3(\overline{w_4}), \tag{42}$$

it follows that $v_3\le\overline{v_4}$ if $R_2>1$ and $R_4\le 1$. This completes the proof. □

Theorem 13. *Let $R_2>1$. (a) If $R_4\le 1$ 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:

$$V_4(t)=x(t)-\int_{x_3}^{x(t)}\frac{f(x_3,v_3)}{f(\theta,v_3)}d\theta+e^{m_1\tau_1}\left(y(t)-\int_{y_3}^{y(t)}\frac{g_1(y_3)}{g_1(\theta)}d\theta\right)+\frac{f(x_3,v_3)}{g_2(v_3)u}\left(v(t)-\int_{v_3}^{v(t)}\frac{g_2(v_3)}{g_2(\theta)}d\theta\right)+\frac{pe^{m_1\tau_1}}{c}\left(z(t)-\int_{z_3}^{z(t)}\frac{g_4(z_3)}{g_4(\theta)}d\theta\right)$$

$$+\frac{qf(x_3,v_3)}{g_2(v_3)ru}w(t)+f(x_3,v_3)\int_{-\tau_1}^{0}H\left(\frac{f(x(t+s),v(t+s))}{f(x_3,v_3)}\right)ds+f(x_3,v_3)\int_{-\tau_2}^{0}H\left(\frac{g_1(y(t+s))}{g_1(y_3)}\right)ds. \tag{43}$$

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

$$\begin{aligned}\frac{dV_4(t)}{dt}&=s(x)\left(1-\frac{f(x_3,v_3)}{f(x,v_3)}\right)+f(x,v)\frac{f(x_3,v_3)}{f(x,v_3)}\\&-f(x_3,v_3)\frac{g_2(v)}{g_2(v_3)}+\frac{qf(x_3,v_3)}{ug_2(v_3)}g_3(w)\\&\cdot(g_2(v_3)-g_2(\overline{v_4}))-f(x_3,v_3)\\&\cdot H\left(\frac{g_2(v_3)g_1(y(t-\tau_2))}{g_1(y_3)g_2(v)}\right)+f(x_3,v_3)\\&\cdot\ln\frac{g_2(v)f(x_3,v_3)}{g_2(v_3)f(x,v)}-f(x_3,v_3)\\&\cdot H\left(\frac{g_1(y_3)f(x(t-\tau_1),v(t-\tau_1))}{g_1(y)f(x_3,v_3)}\right)\\&=(s(x)-s(x_3))\left(1-\frac{f(x_3,v_3)}{f(x,v_3)}\right)-f(x_3,v_3)\\&\cdot H\left(\frac{g_2(v_3)g_1(y(t-\tau_2))}{g_1(y_3)g_2(v)}\right)+f(x_3,v_3)\\&\cdot\frac{g_2(v)}{g_2(v_3)}\left(\frac{f(x,v)}{f(x,v_3)}-1\right)\left(\frac{g_2(v_3)}{g_2(v)}-\frac{f(x,v_3)}{f(x,v)}\right)\\&-f(x_3,v_3)H\left(\frac{f(x_3,v_3)}{f(x,v_3)}\right)-f(x_3,v_3)\\&\cdot H\left(\frac{g_1(y_3)f(x(t-\tau_1),v(t-\tau_1))}{g_1(y)f(x_3,v_3)}\right)\\&-f(x_3,v_3)H\left(\frac{g_2(v)f(x,v_3)}{g_2(v_3)f(x,v)}\right)+\frac{qf(x_3,v_3)}{ug_2(v_3)}\\&\cdot g_3(w)(g_2(v_3)-g_2(\overline{v_4})).\end{aligned} \tag{44}$$

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

$$\left(\frac{f(x,v)}{f(x,v_3)}-1\right)\left(\frac{g_2(v_3)}{g_2(v)}-\frac{f(x,v_3)}{f(x,v)}\right)\le 0 \quad \text{for } t\ge 0. \tag{45}$$

Since $v_3\le\overline{v_4}$, we have $dV_4(t)/dt\le 0$, and $dV_4(t)/dt=0$ 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 $R_4\le 1$.

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

$$(\lambda+h-rg_2(v_3))f(\lambda)=0, \tag{46}$$

where

$$f(\lambda)=\begin{vmatrix}a_{11}&0&a_{13}&0\\a_{21}&a_{22}&a_{23}&a_{24}\\0&a_{32}&a_{33}&0\\0&a_{42}&0&a_{44}\end{vmatrix}, \tag{47}$$

where

$$\begin{aligned}a_{11}&=\lambda-s'(x_3)+\frac{\partial f(x_3,v_3)}{\partial x},\\a_{13}&=\frac{\partial f(x_3,v_3)}{\partial v},\\a_{21}&=-e^{-(m_1+\lambda)\tau_1}\frac{\partial f(x_3,v_3)}{\partial x},\\a_{22}&=\lambda+(a+pg_4(z_3))g_1'(y_3),\\a_{23}&=-e^{-(m_1+\lambda)\tau_1}\frac{\partial f(x_3,v_3)}{\partial v},\\a_{24}&=pg_1(y_3)g_4'(z_3),\\a_{32}&=-ke^{-(m_2+\lambda)\tau_2}g_1'(y_3),\\a_{33}&=\lambda+ug_2'(v_3),\\a_{42}&=-ce^{-\lambda\tau_3}g_4(z_3)g_1'(y_3),\\a_{44}&=\lambda+\left(b-cg_1(y_3)e^{-\lambda\tau_3}\right)g_4'(z_3).\end{aligned} \tag{48}$$

When $R_4>1$, we have $h-rg_2(v_3)=r(g_2(\overline{v_4})-g_2(v_3))<0$. Hence, there is a positive root $\lambda^*=rg_2(v_3)-h$. Therefore, when $R_4>1$, E_3 is unstable for any $\tau_1\ge 0$, $\tau_2\ge 0$, and $\tau_3\ge 0$. 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 $R_2>1$, $R_4\le 1$, and $\tau_3=0$, E_3 is globally asymptotically stable, and delays τ_1 and τ_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: $\tau_1\ge 0$, $\tau_2\ge 0$, and $\tau_3=0$. However, for the cases $\tau_1\ge 0$, $\tau_2\ge 0$, and $\tau_3\ge 0$, 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:

$$\begin{aligned}
V_5(t) &= x(t) - \int_{x_4}^{x(t)} \frac{f(x_4, v_4)}{f(\theta, v_4)}\, d\theta + e^{m_1\tau_1}\left(y(t)\right.\\
&\quad \left. - \int_{y_4}^{y(t)} \frac{g_1(y_4)}{g_1(\theta)}\, d\theta\right)\\
&\quad + \frac{f(x_4, v_4)}{g_2(v_4)(u + qg_3(w_4))}\left(v(t)\right.\\
&\quad \left. - \int_{v_4}^{v(t)} \frac{g_2(v_4)}{g_2(\theta)}\, d\theta\right) + \frac{pe^{m_1\tau_1}}{c}\left(z(t)\right.\\
&\quad \left. - \int_{z_4}^{z(t)} \frac{g_4(z_4)}{g_4(\theta)}\, d\theta\right) + f(x_4, v_4)\\
&\quad \cdot \int_{-\tau_2}^{0} H\left(\frac{g_1(y(t+s))}{g_1(y_4)}\right) ds\\
&\quad + \frac{qf(x_4, v_4)}{g_2(v_4)(u + qg_3(w_4))}\left(w(t)\right.\\
&\quad \left. - \int_{w_4}^{w(t)} \frac{g_3(w_4)}{g_3(\theta)}\, d\theta\right) + f(x_4, v_4)\\
&\quad \cdot \int_{-\tau_1}^{0} H\left(\frac{f(x(t+s), v(t+s))}{f(x_4, v_4)}\right) ds.
\end{aligned} \tag{49}$$

Using the above similar method, we obtain

$$\begin{aligned}
\frac{dV_5(t)}{dt} &= (s(x) - s(x_4))\left(1 - \frac{f(x_4, v_4)}{f(x, v_4)}\right)\\
&\quad - f(x_4, v_4)\left[H\left(\frac{f(x_4, v_4)}{f(x, v_4)}\right)\right.\\
&\quad + H\left(\frac{g_2(v)\, f(x, v_4)}{g_2(v_4)\, f(x, v)}\right)\\
&\quad + H\left(\frac{g_1(y_4)\, f(x(t-\tau_1), v(t-\tau_1))}{g_1(y)\, f(x_4, v_4)}\right)\\
&\quad \left. + H\left(\frac{g_2(v_4)\, g_1(y(t-\tau_2))}{g_1(y_4)\, g_2(v)}\right)\right] + f(x_4, v_4)\\
&\quad \cdot \frac{g_2(v)}{g_2(v_4)}\left(\frac{f(x, v)}{f(x, v_4)} - 1\right)\left(\frac{g_2(v_4)}{g_2(v)} - \frac{f(x, v_4)}{f(x, v)}\right).
\end{aligned} \tag{50}$$

Note that $(s(x) - s(x_4))(1 - f(x_4, v_4)/f(x, v_4)) \le 0$, and

$$\left(\frac{f(x, v)}{f(x, v_4)} - 1\right)\left(\frac{g_2(v_4)}{g_2(v)} - \frac{f(x, v_4)}{f(x, v)}\right) \le 0 \quad \text{for } t \ge 0. \tag{51}$$

Obviously, we have $dV_5(t)/dt \le 0$, and $dV_5(t)/dt = 0$ if and only if $x(t) = x_4$, $y(t) = y_4$, and $v(t) = v_4$. From LaSalle's invariance principle [36], we finally have that E_4 is globally asymptotically stable when $\tau_3 = 0$, $R_3 > 1$, and $R_4 > 1$. 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 $\tau_3 = 0$, E_4 is globally asymptotically stable, and delays τ_1 and τ_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 $\tau_3 = 0$. 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 $\tau_3 > 0$.

Example 17. Corresponding to model (2), we consider the following model:

$$\begin{aligned}
\frac{dx(t)}{dt} &= \lambda - dx(t) + r_1 x\left(1 - \frac{x}{K}\right)\\
&\quad - \beta x(t)\left(\left(v(t) - b_1\right)e^{-c_1 v(t)} + b_1\right),\\
\frac{dy(t)}{dt} &= \beta e^{-m_1\tau_1} x(t-\tau_1)\left(\left(v(t-\tau_1) - b_1\right)e^{-c_1 v(t-\tau_1)} + b_1\right)\\
&\quad - ay(t) - py(t)\, z(t),\\
\frac{dv(t)}{dt} &= ke^{-m_2\tau_2} y(t-\tau_2) - uv(t) - qv(t)\, w(t),\\
\frac{dz(t)}{dt} &= cy(t-\tau_3)\, z(t-\tau_3) - bz(t),\\
\frac{dw(t)}{dt} &= rv(t)\, w(t) - hw(t),
\end{aligned} \tag{52}$$

where $b_1, c_1 > 0$ are constants. We have $s(x) = \lambda - dx(t) + r_1 x(1 - x/K)$, $f(x, v) = \beta x(t)((v(t) - b_1)e^{-c_1 v(t)} + b_1)$, and $g_i(\xi) = \xi$ $(i = 1, 2, 3, 4)$. It can easily verify that (H_1)–(H_4) hold. Taking $\lambda = 10, d = 0.01, r_1 = 0.6, K = 500, \beta = 0.3, c_1 = 0.01, b_1 = 0.01, a = 0.5, p = 1, k = 0.4, u = 3, q = 1, c = 0.1, b = 0.15, m_1 = m_2 = 0.01, g = 1.5, h = 1, \tau_1 = 2$, and $\tau_2 = 5$, choose τ_3 as free parameter. By computing, $R_2 = 34.4139 > 1$, $R_4 = 0.2854 < 1$, and $E_3 = (462.1965, 1.5000, 0.1902, 15.3959, 0)$. From Figures 1–4, we see that as τ_3 increases the complex dynamical behaviors of equilibrium 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 $w(t)$.

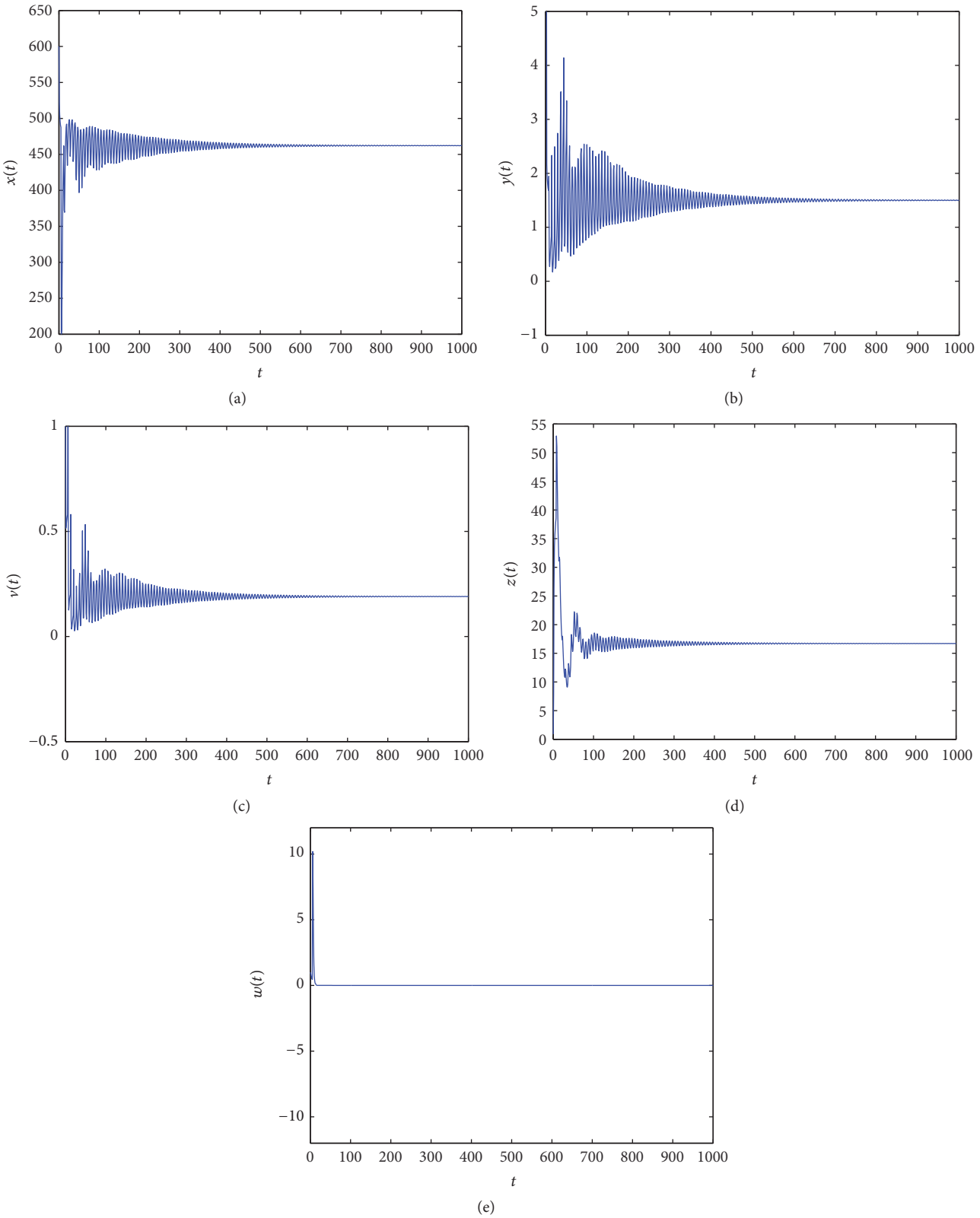

FIGURE 1: Taking $\tau_3 = 0.2$, we have $R_2 = 34.4139 > 1$ and $R_4 = 0.2854 < 1$, and the infection equilibrium E_3 with only CTL response is asymptotically stable.

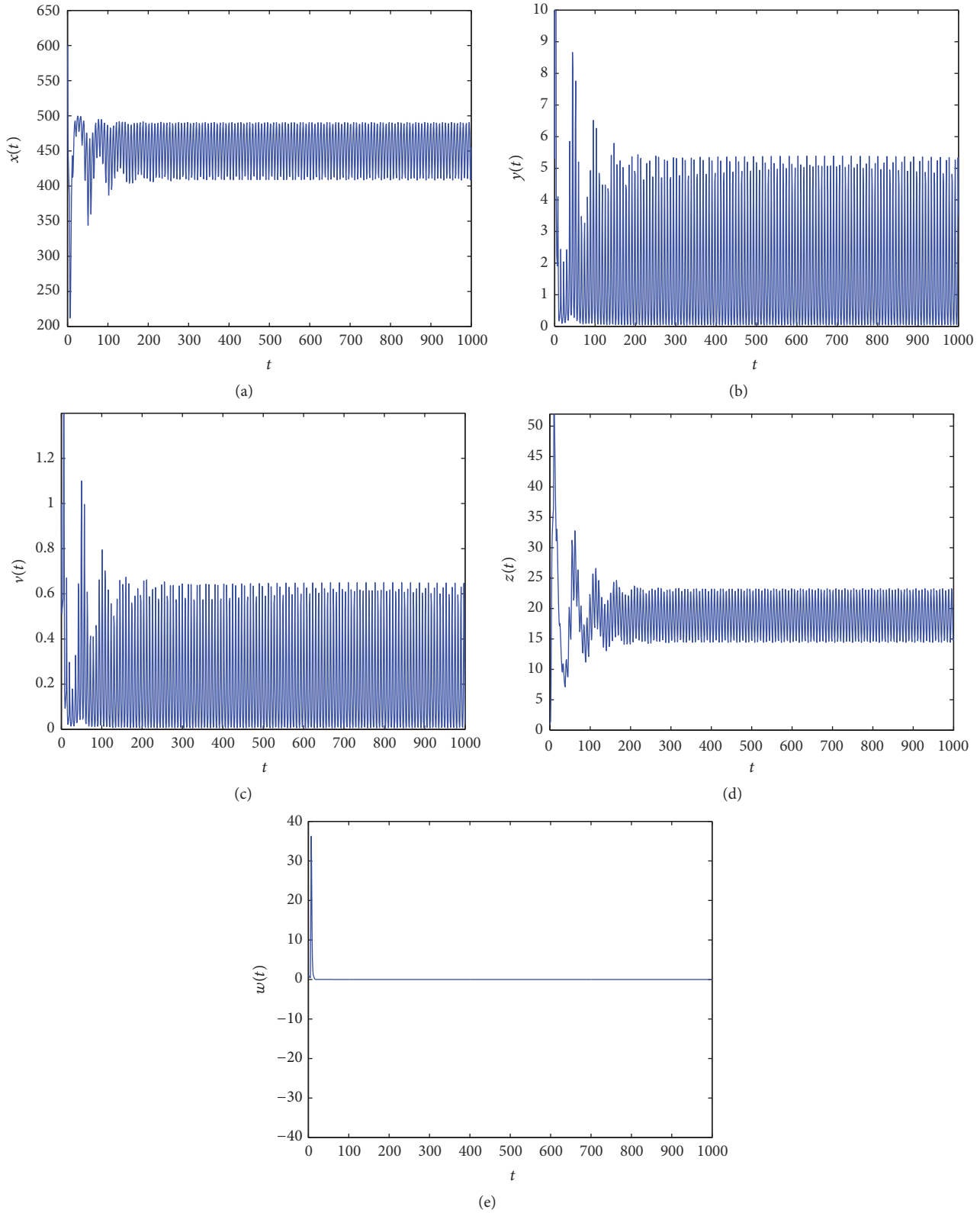

FIGURE 2: Taking $\tau_3 = 2$, we have $R_2 = 34.4139 > 1$ and the Hopf bifurcation at infection equilibrium E_3 with only CTL response occurs.

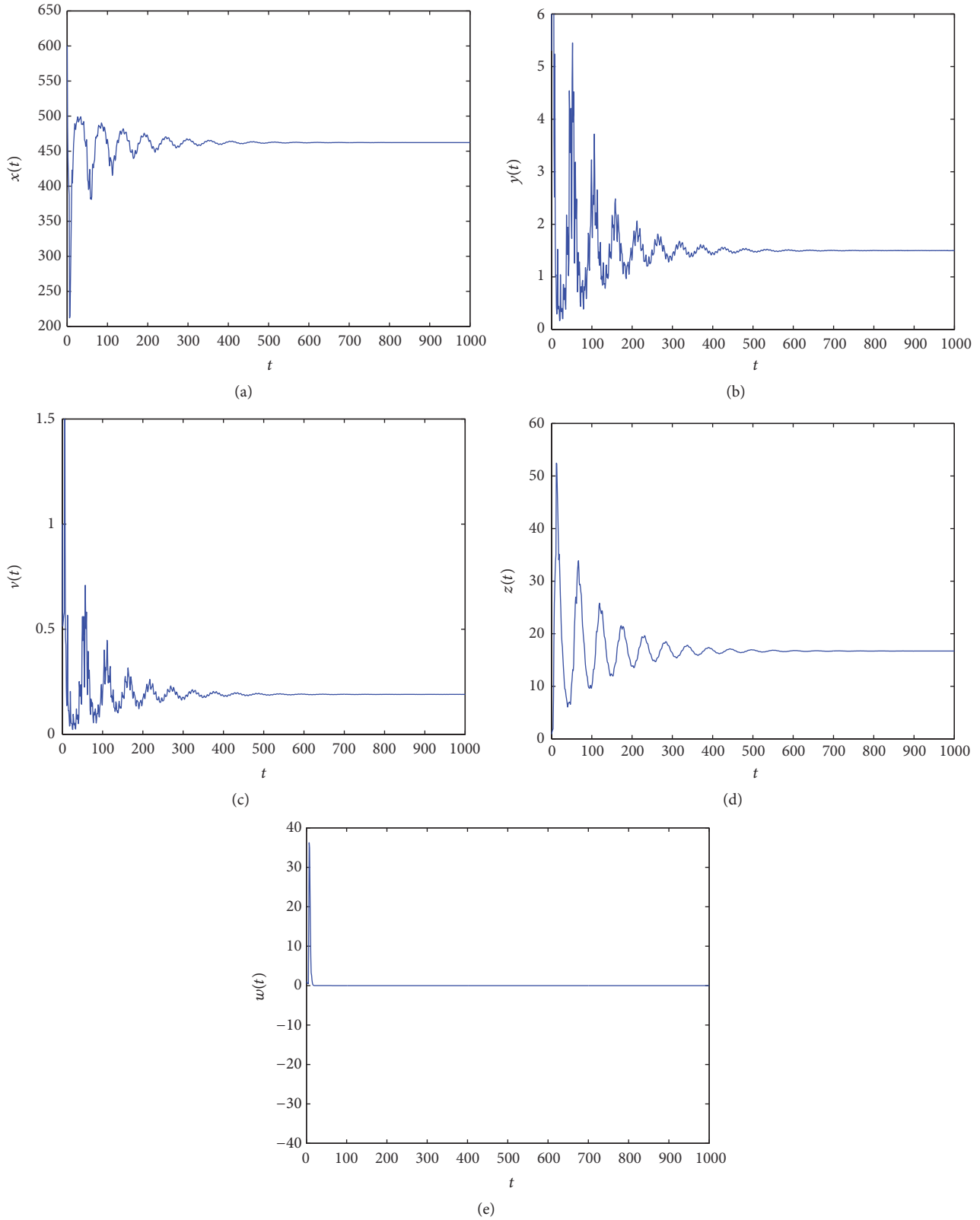

FIGURE 3: Taking $\tau_3 = 4$, we have $R_2 = 34.4139 > 1$ and $R_4 = 0.2854 < 1$, and the infection equilibrium E_3 with only CTL response is asymptotically stable.

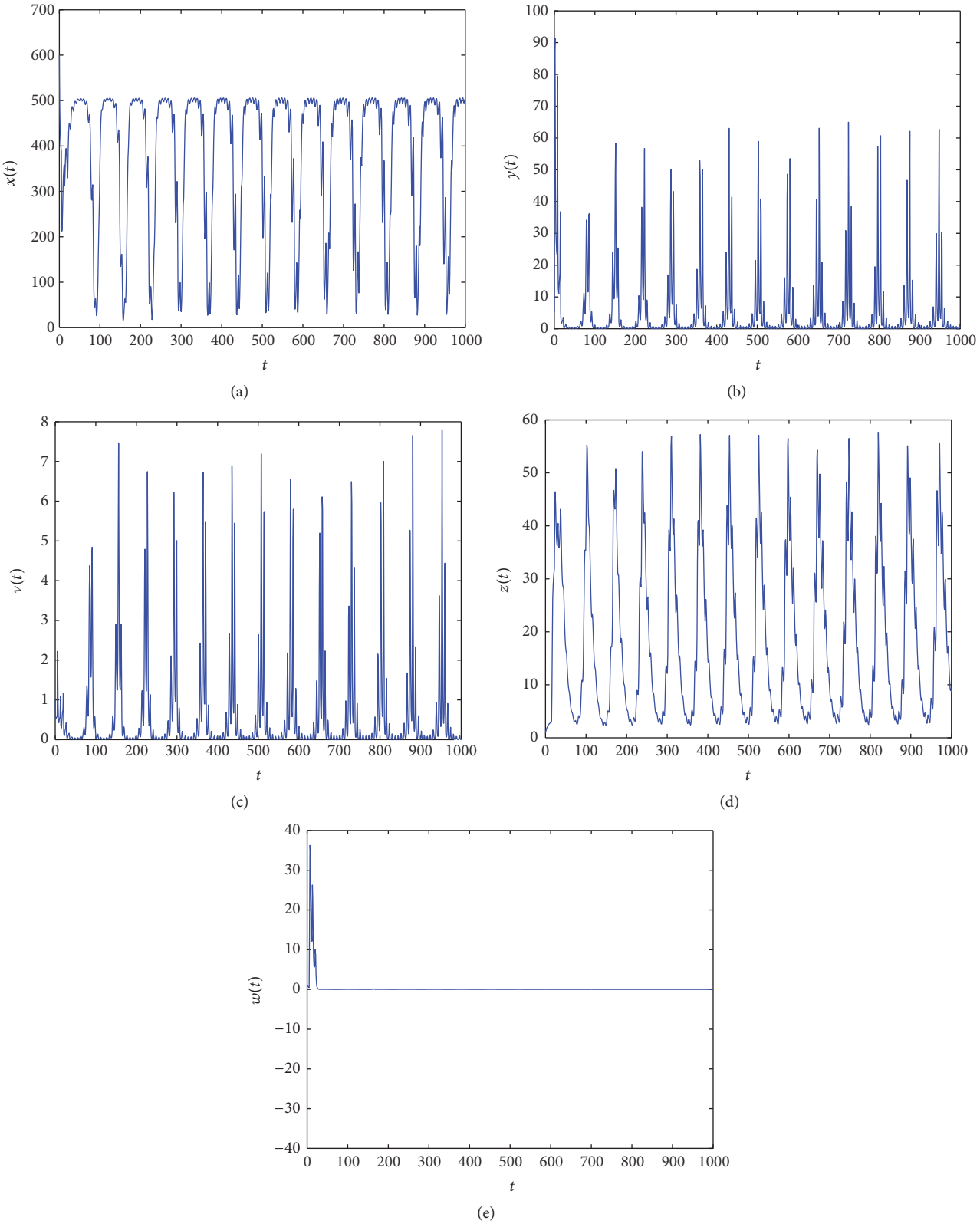

FIGURE 4: Taking $\tau_3 = 15$, we have $R_2 = 34.4139 > 1$ and the Hopf bifurcation at infection equilibrium E_3 with only CTL response occurs.

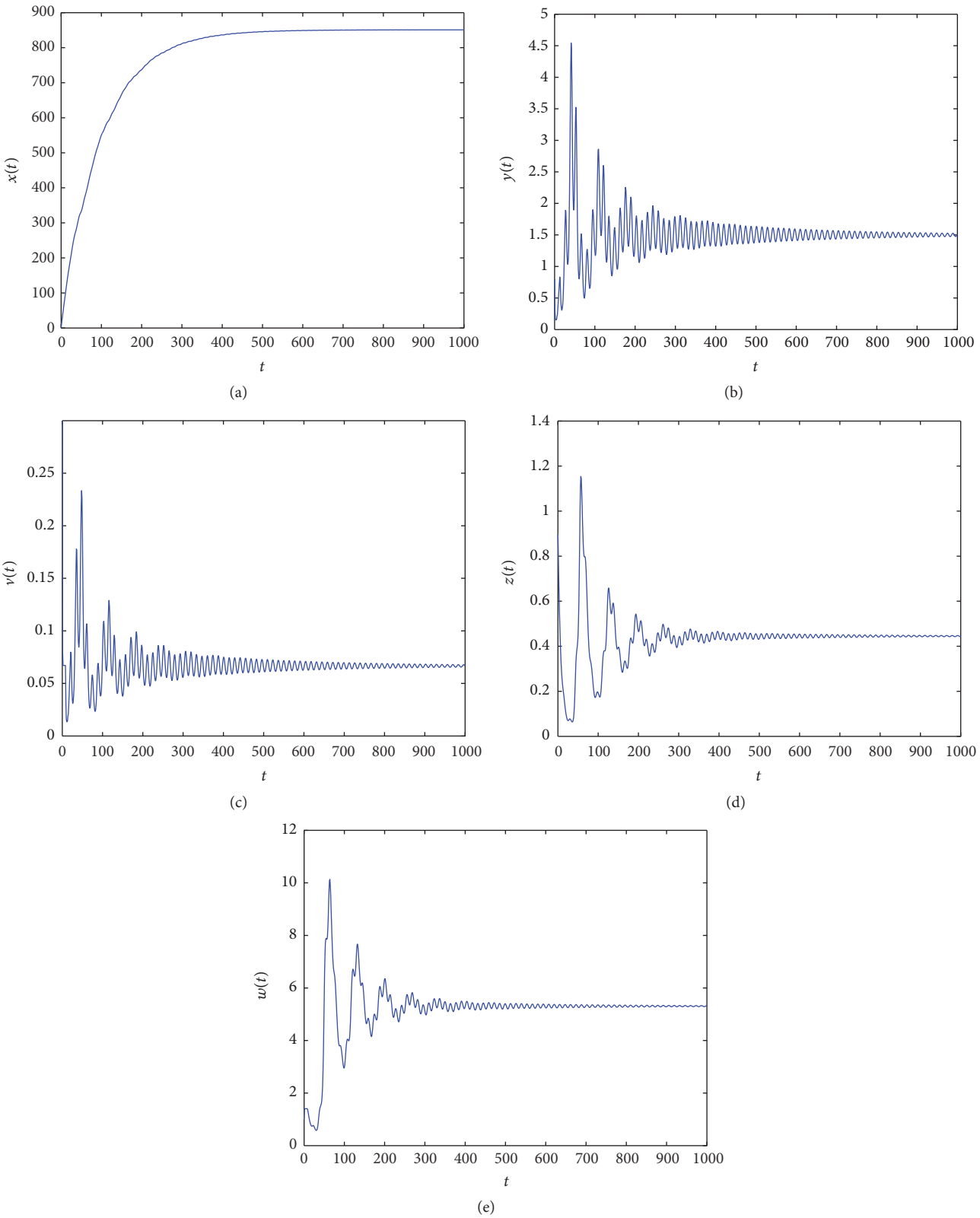

FIGURE 5: Taking $\tau_3 = 0.1$, we have $R_3 = 1.8912 > 1$ and $R_4 = 2.7693 > 1$, and the infection equilibrium E_4 with both CTL and antibody responses is asymptotically stable.

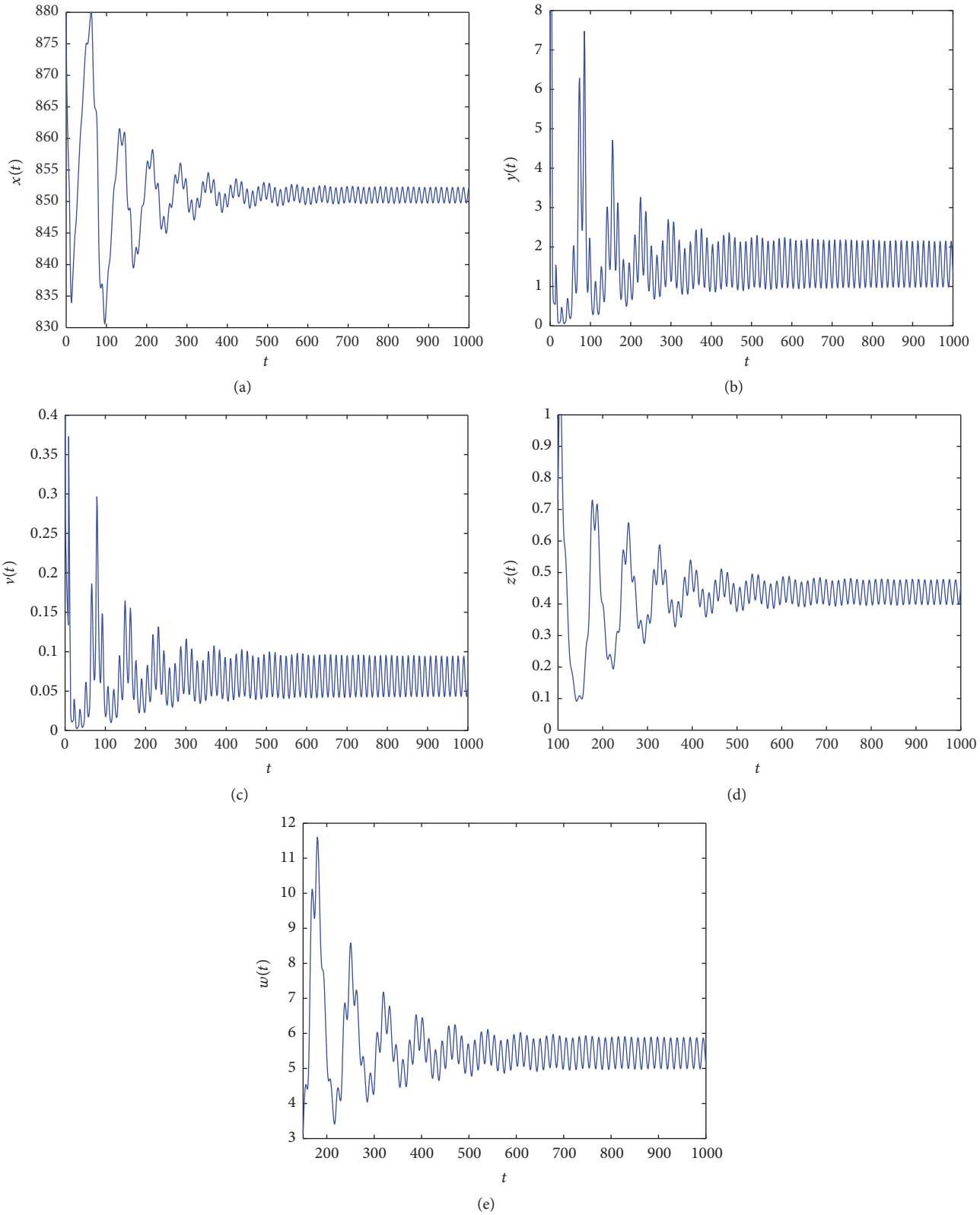

FIGURE 6: Taking $\tau_3 = 2.5$, we have $R_3 = 1.8912 > 1$ and $R_4 = 2.7693 > 1$, and the Hopf bifurcation at infection equilibrium E_4 with both CTL and antibody responses occurs.

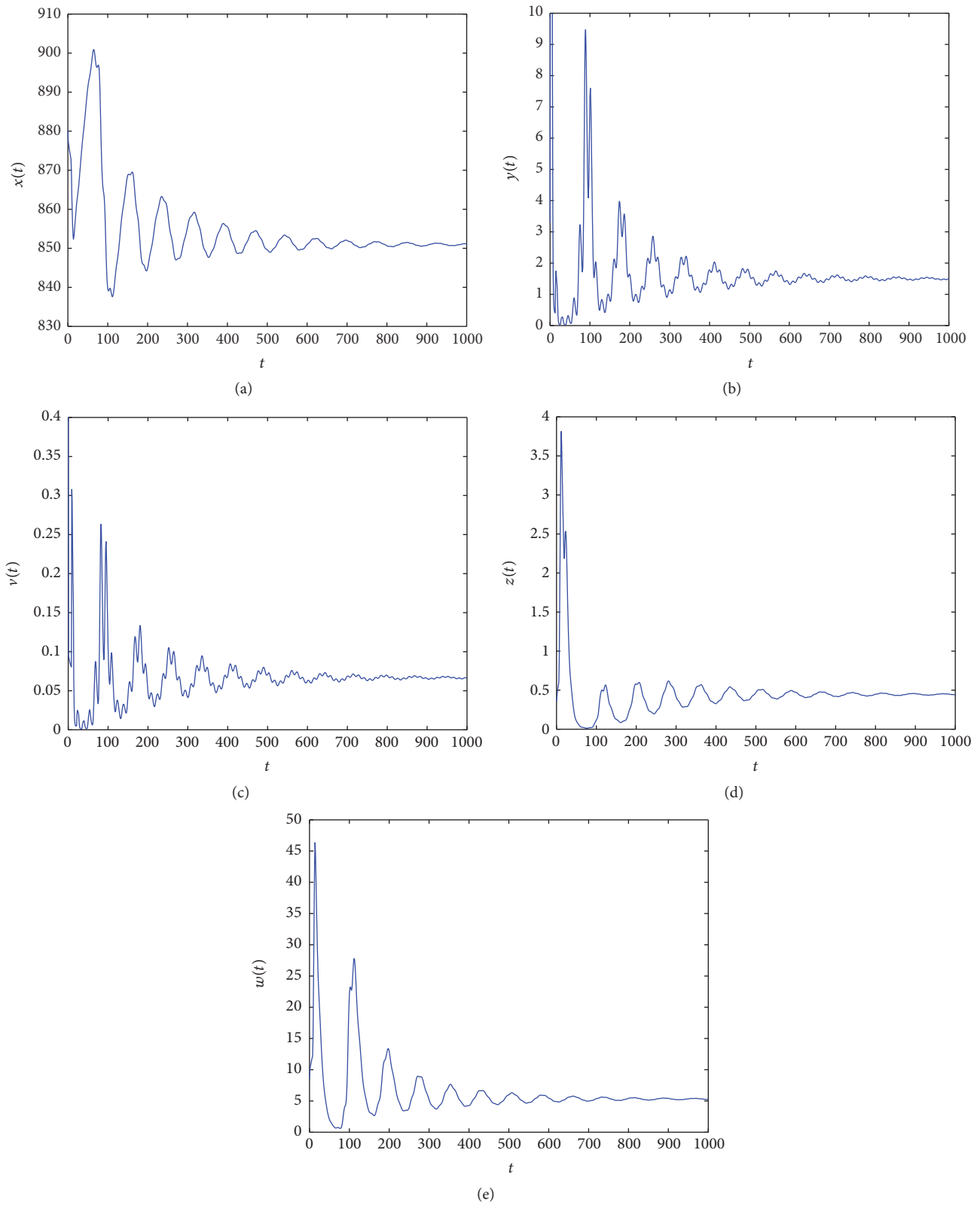

FIGURE 7: Taking $\tau_3 = 6$, we have $R_3 = 1.8912 > 1$ and $R_4 = 2.7693 > 1$, and the infection equilibrium E_4 with both CTL and antibody responses is asymptotically stable.

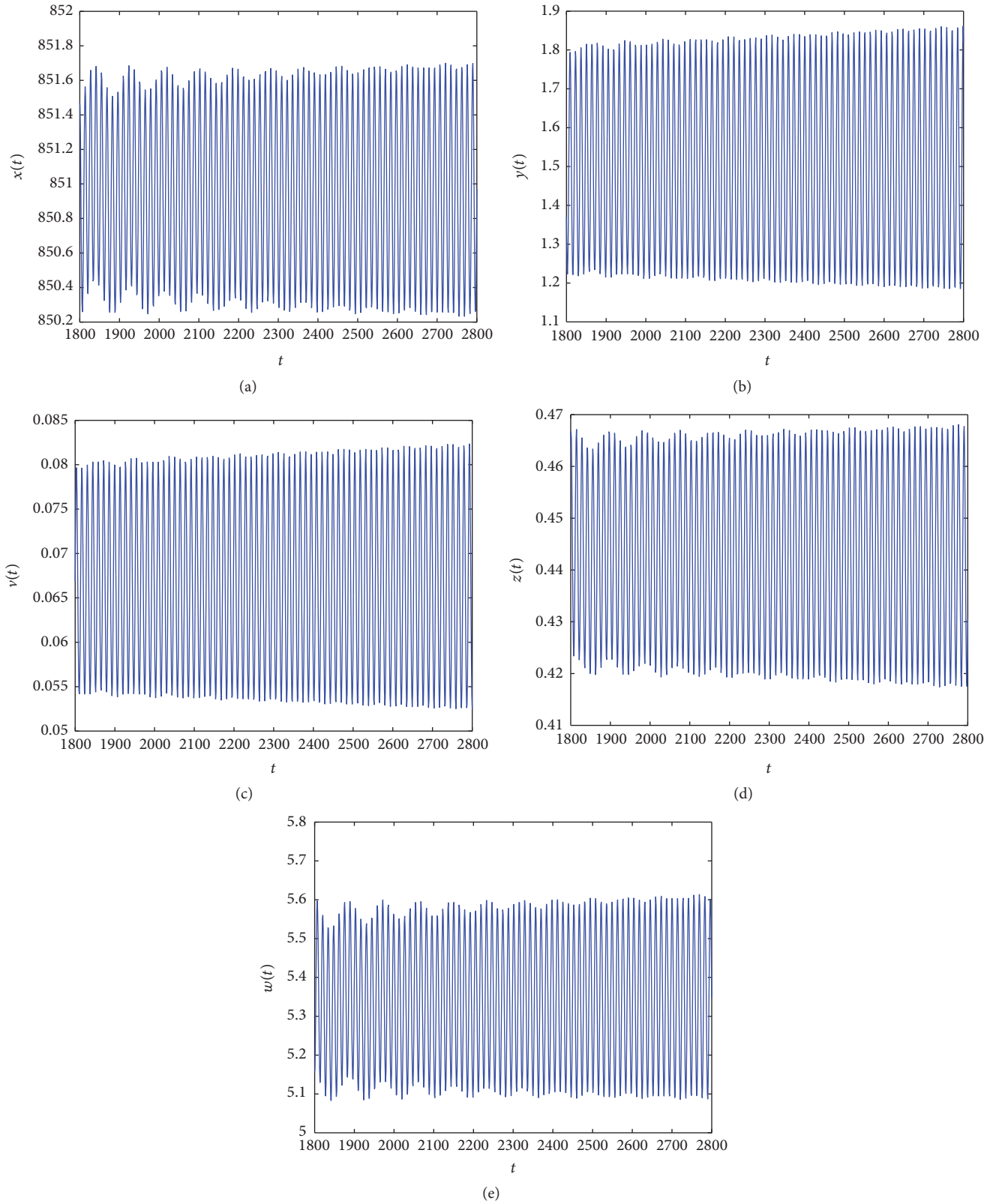

FIGURE 8: Taking $\tau_3 = 16$, we have $R_3 = 1.8912 > 1$ and the Hopf bifurcation at infection equilibrium E_4 with both CTL and antibody responses occurs.

Example 18. Corresponding to model (2), we consider the following model:

$$\begin{aligned}
&\frac{dx(t)}{dt} \\
&= \lambda - dx(t) - \frac{\beta x(t) v(t)}{1 + a_1 x(t) + b_1 v(t) + a_1 b_1 x(t) v(t)}, \\
&\frac{dy(t)}{dt} \\
&= \frac{\beta e^{-m_1 \tau_1} x(t-\tau_1) v(t-\tau_1)}{1 + a_1 x(t-\tau_1) + b_1 v(t-\tau_1) + a_1 b_1 x(t-\tau_1) v(t-\tau_1)} \\
&\quad - ay(t) - py(t) z(t), \\
&\frac{dv(t)}{dt} = k e^{-m_2 \tau_2} y(t-\tau_2) - uv(t) - qv(t) w(t), \\
&\frac{dz(t)}{dt} = cy(t-\tau_3) z(t-\tau_3) - bz(t), \\
&\frac{dw(t)}{dt} = rv(t) w(t) - hw(t),
\end{aligned} \tag{53}$$

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

Taking $\lambda = 10$, $d = 0.01$, $\beta = 0.25$, $a_1 = 0.01$, $b_1 = 0.01$, $a = 0.5$, $p = 1$, $k = 0.4$, $u = 3$, $q = 1$, $c = 0.1$, $b = 0.15$, $m_1 = m_2 = 0.01$, $r = 1.5$, $h = 0.1$, $\tau_1 = 5$, and $\tau_2 = 8$, choose τ_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 τ_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 τ_1, virus replication delay τ_2, and immune response delay τ_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 τ_1, τ_2, and τ_3 play different roles in the stability of the equilibria. Particularly, we see that τ_3 may impact the stability of equilibria E_3 and E_4.

By the analysis, we have shown that when $R_0 \leq 1$, E_0 is globally asymptotically stable, which means that the virus is cleared up. When $R_0 > 1$, $R_1 \leq 1$, and $R_2 \leq 1$, E_1 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 $R_3 \leq 1$, E_2 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 $\tau_3 = 0$, $\tau_1 \geq 0$, and $\tau_2 \geq 0$; when $R_2 > 1$ and $R_4 \leq 1$, E_3 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, $\tau_3 = 0$, $\tau_1 \geq 0$, and $\tau_2 \geq 0$, when $R_3 > 1$ 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 τ_1 and virus replication delay τ_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 τ_1. When all other parameters are fixed and delay τ_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 τ_3 increases. Figures 1–4 indicate that E_3 remains stable as $\tau_3 > 0$ is small, and along with the increase of τ_3, equilibrium E_3 becomes unstable and periodic oscillations appear. It shows that stability switches occur as delay τ_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 τ_3 is small enough, E_4 is asymptotically stable and when τ_3 is increasing, the stability switches occur at equilibrium E_4, and when E_4 is unstable, a Hopf bifurcation occurs. Finally, when τ_3 is enough large, equilibrium E_4 always is unstable. Summarizing these discussions, we have the conclusion that τ_3 affects markedly the stability of equilibria E_3 and E_4. From the numerical simulations, we observe that immune response delay τ_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 τ_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 τ_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 τ_1, τ_2, and τ_3, antibody response delay τ_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_3 and E_4 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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