

Research Article

Dynamics Analysis of an HIV Infection Model including Infected Cells in an Eclipse Stage

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In this paper, an HIV infection model including an eclipse stage of infected cells is considered. Some quicker cells in this stage become productively infected cells, a portion of these cells are reverted to the uninfected class, and others will be latent down in the body. We consider CTL-response delay in this model and analyze the effect of time delay on stability of equilibrium. It is shown that the uninfected equilibrium and CTL-absent infection equilibrium are globally asymptotically stable for both ODE and DDE model. And we get the global stability of the CTL-present equilibrium for ODE model. For DDE model, we have proved that the CTL-present equilibrium is locally asymptotically stable in a range of delays and also have studied the existence of Hopf bifurcations at the CTL-present equilibrium. Numerical simulations are carried out to support our main results.

1. Introduction

In recent years, mathematical models have been done on the viral dynamics of HIV. In the basic mathematical modeling of viral dynamics, the description of the virus infection process has three populations: uninfected target cells, productively infected cells, and free viral particles [1–7]. In this model, infected cells are assumed to produce new virions immediately after target cells are infected by a free virus.

However, there are many biological steps between viral infection of target cells and the production of HIV-1 virions. In 2007, Rong and coworkers [8] studied an extension of the basic model of HIV-1 infection. The main feature of their model is that an eclipse stage for the infected cells is included and a portion of these cells are reverted to the uninfected class. Perelson et al. [9] presented this kind of cell early in 1993. Buonomo and Vergas-De-León [10] have performed the global stability analysis of this model. Perelson et al. [1] put forward another model in 1997. He divided infected cells into two kinds: long-lived productively infected cells and latently infected cells. Latently infected cells are also activated into productively infected cells [11]. Motivated by their work and now we concern the progression of infected cells from this eclipse phase to the productive, and a portion of these cells are reverted to the uninfected class or are latent down in the body.

In most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cells. Therefore, the dynamics of HIV infection with CTL response has received much attention in the past decades, some include the immune response without immune delay [12–15], and others contain immune delay [16–19]. Some HIV infection models with CTL-response describe only the interaction among uninfected target cells, productively infected cells, CTLs [12, 14, 20]. The most basic model can be written as

$$\begin{aligned}\frac{dx}{dt} &= s - dx - \beta xy, \\ \frac{dy}{dt} &= \beta xy - \alpha y - pyz, \\ \frac{dz}{dt} &= f(x, y, z) - rz,\end{aligned}\tag{1}$$

where x , y , and z represent the concentration of uninfected target cells, productively infected cells, CTLs at time t , respectively. Parameters s and d are the birth rate and death rate of uninfected cells, respectively. The uninfected cells become infected at rate of βxy . Productively infected cells are produced at rate βxy , α is the death rate of productively

infected cells, p is the strength of the lytic component, and r is the death rate of CTLs. Function $f(x, y, z)$ describes the rate of immune response activated by the infected cells. Wang et al. [14] assumed that the production of CTLs depends only on the population of infected cells and gave $f(x, y, z) = cy$. Ji et al. [12] assumed that the production of CTLs also depends on the population of CTL cells and chose the former $f(x, y, z) = cyz$.

In this paper, we also consider the dynamics of HIV infection with CTL response and give $f(x, y, z) = cyz$. Meanwhile, our model also concludes an eclipse stage of infected cells. After the eclipse stage, some quicker infected cells which become productively infected cells are obviously attacked by CTLs. Other infected cells which will be reverted to the uninfected class or be latent down in the body do not have the ability to express HIV and will not cause CTL immune response. Therefore, we only take the immune response to productively infected cells into account and ignore the attack to latently infected cells by CTLs. So we get the following ODE:

$$\begin{aligned}\frac{dx}{dt} &= s - \beta xy - dx + \delta w, \\ \frac{dw}{dt} &= \beta xy - (\delta + \eta + q)w, \\ \frac{dy}{dt} &= qw - pyz - \alpha y, \\ \frac{dz}{dt} &= cyz - rz,\end{aligned}\quad (2)$$

where w represents the concentration of infected cells in the eclipse stage at time t . Infected cells in the eclipse phase revert to the uninfected class at a constant rate δ . In addition, they may alternatively progress to the productively infected class at the rate q or die at the rate η . But some authors believe that time delay cannot be ignored in models for immune response [16–19]. In this paper, τ represents CTL-response delay, that is, the time between antigenic stimulation and generating CTLs. We investigated the effect of a time delay on system (2) to obtain the following DDE model:

$$\begin{aligned}\frac{dx}{dt} &= s - \beta xy - dx + \delta w, \\ \frac{dw}{dt} &= \beta xy - (\delta + \eta + q)w, \\ \frac{dy}{dt} &= qw - pyz - \alpha y, \\ \frac{dz}{dt} &= cy(t - \tau)z(t - \tau) - rz.\end{aligned}\quad (3)$$

Our paper is organized as follows: the three equilibriums on system (2) and (3) are given in the next section. In Section 3, the global stability of the ODE model is discussed. The analysis of the stability for this DDE model is carried out in Section 4. Finally, some numerical simulations are carried out to support our analytical results, and some conclusions are presented.

2. The Existence of the Equilibrium of System

In system (2) and (3), the basic reproduction numbers for viral infection and for CTL response are given as follows:

$$\begin{aligned}R_0 &= \frac{qs\beta}{d\alpha(\delta + \eta + q)}, \\ R_1 &= \frac{cqs\beta}{cd\alpha(\delta + \eta + q) + \alpha\beta r(\eta + q)}.\end{aligned}\quad (4)$$

It is clear that $R_0 > R_1$ always holds. For system (2) and (3), there exists three equilibriums.

Theorem 1. For system (2) and (3), the uninfected equilibrium $E_0(s/d, 0, 0, 0)$ always exists;

- (1) if $R_0 > 1$, a CTL-absent infection equilibrium $E_1(x_1, w_1, y_1, z_1)$ exists, where

$$\begin{aligned}x_1 &= \frac{\alpha(\delta + \eta + q)}{\beta q}, \\ w_1 &= \frac{s}{n + q} \left(1 - \frac{1}{R_0}\right), \\ y_1 &= \frac{q}{\alpha} w_1, \quad z_1 = 0;\end{aligned}\quad (5)$$

- (2) if $R_1 > 1$, there exists a CTL-present infection equilibrium $E_2(x_2, w_2, y_2, z_2)$, where

$$\begin{aligned}x_2 &= \frac{c(\delta + \eta + q)}{\beta r} w_2, \\ w_2 &= \frac{s\beta r}{cd(\delta + \eta + q) + \beta r(\eta + q)}, \\ y_2 &= \frac{r}{c}, \quad z_2 = \frac{\alpha}{p}(R_1 - 1).\end{aligned}\quad (6)$$

3. The Global Stability of the ODE Model

The initial conditions for system (2) are given as follows:

$$x(0) > 0, \quad w(0) > 0, \quad y(0) > 0, \quad z(0) > 0. \quad (7)$$

It is clear that all solutions of system (2) are positive for $t > 0$. Before analyzing the stability of system (2), we now show that the solutions of system (2) are bounded.

Theorem 2. Let $(x(t), w(t), y(t), \text{ and } z(t))$ be the solution of system (2) satisfying initial conditions (7), then there exists $M > 0$ such that $x(t) < M$, $w(t) < M$, $y(t) < M$, and $z(t) < M$ hold after sufficiently large time t .

Proof. Let

$$L(t) = x(t) + w(t) + y(t) + \frac{p}{c}z(t), \quad (8)$$

where $k = \min\{d, \eta, \alpha, r\}$. It follows from (2) that

$$\begin{aligned} \frac{dL(t)}{dt} &= s - dx(t) - \eta w(t) - \alpha y(t) - \frac{pr}{c} z(t) \\ &< s - k \left(x(t) + w(t) + y(t) + \frac{p}{c} z(t) \right) \quad (9) \\ &= s - kL(t). \end{aligned}$$

Therefore, $L(t) < s/k + \varepsilon$ for all large t , where ε is an arbitrarily small positive constant. Thus, $x(t) < M$, $w(t) < M$, $y(t) < M$ and $z(t) < M$ for some positive constant M . \square

Theorem 3. If $R_0 < 1$, the uninfected equilibrium E_0 of system (2) is globally asymptotically stable.

Proof. Construct a Lyapunov function

$$\begin{aligned} V_1(x, w, y, z) &= x - x_0 - x_0 \ln \frac{x}{x_0} \\ &\quad + \frac{\delta}{2(d + \eta + q)x_0} [(x - x_0) + w]^2 \\ &\quad + w + \frac{(\delta + \eta + q)}{q} y + \frac{p(\delta + \eta + q)}{cq} z, \end{aligned} \quad (10)$$

where $x_0 = s/d$. The derivative of V_1 along positive solutions of system (2) is given as follows:

$$\begin{aligned} \frac{dV_1}{dt} &= \frac{(x - x_0)}{x} (s - dx - \beta xy + \delta w) \\ &\quad + \frac{\delta}{(d + \eta + q)x_0} (x - x_0 + w) \\ &\quad \times [s - dx - (\eta + q)w] \\ &\quad + \frac{(\delta + \eta + q)}{q} (qw - \alpha y - pyz) \\ &\quad + \beta xy - (\delta + \eta + q)w \\ &\quad + \frac{p(\delta + \eta + q)}{q} yz - \frac{pr(\delta + \eta + q)}{cq} z. \end{aligned} \quad (11)$$

On substituting $s = dx_0$ and $\delta w(x - x_0)/x = -\delta w((x - x_0)^2/xx_0) + \delta w((x - x_0)/x_0)$ into (11), we derive that

$$\begin{aligned} \frac{dV_1}{dt} &= - \left(dx_0 + \delta w + \frac{d\delta x}{d + \eta + q} \right) \frac{(x - x_0)^2}{xx_0} \\ &\quad - \frac{\delta(\eta + q)}{(d + \eta + q)x_0} w^2 \\ &\quad + \frac{\alpha(\delta + \eta + q)}{q} (R_0 - 1)y \\ &\quad - \frac{pr(\delta + \eta + q)}{cq} z. \end{aligned} \quad (12)$$

If $R_0 < 1$, then $dV_1/dt \leq 0$ for all $x > 0$, $w > 0$, $y > 0$ and $z > 0$. So the uninfected equilibrium E_0 is stable. Clearly, it follows from (12) that $dV_1/dt = 0$ if and only if $x = x_0 = s/d$, $w = 0$, $y = 0$, and $z = 0$. Therefore, the largest invariant set in the set $\{(x, w, y, z) \in R_+^4 \mid dV_1/dt = 0\}$ is the singleton $\{E_0\}$. By LaSalle invariance principle, it follows that the equilibrium E_0 is globally asymptotically stable. \square

Theorem 4. For system (2), if $R_1 < 1$ and $1 < R_0 \leq 1 + (\eta + q)/\delta$, CTL-absent infection equilibrium E_1 is globally asymptotically stable.

Proof. Define a Lyapunov function

$$\begin{aligned} V_2(x, w, y, z) &= x - x_1 - x_1 \ln \frac{x}{x_1} \\ &\quad + w - w_1 - w_1 \ln \frac{w}{w_1} + \frac{\beta p x_1 y_1}{c q w_1} z \\ &\quad + \frac{\delta}{2(d + \eta + q)x_1} [(x - x_1) + (w - w_1)]^2 \\ &\quad + \frac{\beta x_1 y_1}{q w_1} \left(y - y_1 - y_1 \ln \frac{y}{y_1} \right). \end{aligned} \quad (13)$$

Calculating the derivative of V_2 along positive solutions of system (2), it follows that

$$\begin{aligned} \frac{dV_2}{dt} &= \left(1 - \frac{x_1}{x} \right) \frac{dx}{dt} + \frac{\beta x_1 y_1}{q w_1} \left(1 - \frac{y_1}{y} \right) \frac{dy}{dt} \\ &\quad + \frac{\delta}{(d + \eta + q)x_1} [(x - x_1) + (w - w_1)] \\ &\quad \times \left(\frac{dx}{dt} + \frac{dw}{dt} \right) + \left(1 - \frac{w_1}{w} \right) \frac{dw}{dt} + \frac{\beta p x_1 y_1}{q c w_1} \frac{dz}{dt} \\ &= \left(1 - \frac{x_1}{x} \right) (s - dx - \beta xy + \delta w) \\ &\quad + \frac{\beta x_1 y_1}{q w_1} \left(1 - \frac{y_1}{y} \right) (qw - \alpha y - pyz) \\ &\quad + \frac{\delta}{(d + \eta + q)x_1} [(x - x_1) + (w - w_1)] \\ &\quad \times [s - dx - (\eta + q)w] \\ &\quad + \left(1 - \frac{w_1}{w} \right) [\beta xy - (\delta + \eta + q)w] \\ &\quad + \frac{\beta p x_1 y_1}{q w_1} yz - \frac{\beta p r x_1 y_1}{c q w_1} z. \end{aligned} \quad (14)$$

At CTL-absent infection equilibrium E_1 , on substituting $s = \beta x_1 y_1 + dx_1 - \delta w_1$, $\alpha = q(w_1/y_1)$, and $\delta + \eta + q = \beta x_1 y_1/w_1$ into (14), we obtain that

$$\begin{aligned} \frac{dV_2}{dt} &= \left(1 - \frac{x_1}{x}\right) [-d(x - x_1) - \beta xy + \beta x_1 y_1 + \delta(w - w_1)] \\ &\quad + \frac{\beta x_1 y_1}{q w_1} \left(1 - \frac{y_1}{y}\right) \left(qw - q w_1 \frac{y}{y_1} - p y z\right) \\ &\quad + \frac{\delta}{(d + \eta + q)} [(x - x_1) + (w - w_1)] \\ &\quad \times [-d(x - x_1) - (\eta + q)(w - w_1)] \\ &\quad + \left(1 - \frac{w_1}{w}\right) \left(\beta xy - \beta x_1 y_1 \frac{w}{w_1}\right) \\ &\quad + \frac{\beta p x_1 y_1}{q w_1} y z - \frac{\beta r p x_1 y_1}{c q w_1} z. \end{aligned} \quad (15)$$

Noting that

$$\begin{aligned} \delta \left(1 - \frac{x}{x_1}\right) (w - w_1) &= -\delta (w - w_1) \frac{(x - x_1)^2}{x x_1} + \frac{\delta}{x_1} (x - x_1) (w - w_1), \end{aligned} \quad (16)$$

therefore,

$$\begin{aligned} \frac{dV_2}{dt} &= - \left(dx_1 - \delta w_1 + \delta w + \frac{d \delta x}{d + \eta + q}\right) \frac{(x - x_1)^2}{x x_1} \\ &\quad - \frac{\delta (\eta + q)}{(d + \eta + q)} (w - w_1)^2 \\ &\quad - \beta x_1 y_1 \left(\frac{x_1}{x} + \frac{y_1 w}{y w_1} + \frac{x y w_1}{x_1 y_1 w} - 3\right) \\ &\quad + \frac{\beta p x_1 y_1}{c q w_1} \left[\frac{d(\delta + \eta + q) + r \beta (\eta + q)}{\beta (\eta + q)}\right] (R_1 - 1) z. \end{aligned} \quad (17)$$

Since $x_1/x + y_1 w/y w_1 + x y w_1/x_1 y_1 w - 3 \geq 0$ and the equality holds if and only if $x = x_1$, $w = w_1$ and $y = y_1$. If $R_0 \leq 1 + (\eta + q)/\delta$, then $dx_1 - \delta w_1 \geq 0$. So, if $R_1 < 1$ and $1 < R_0 \leq 1 + (\eta + q)/\delta$, then $dV_2/dt \leq 0$ for all $x > 0$, $w > 0$, $y > 0$ and $z > 0$. Clearly, it follows from (17) that $dV_2/dt = 0$ if and only if $x = x_1$, $w = w_1$, $y = y_1$, and $z = 0$, thus the largest invariant set in the set $\{(x, w, y, z) \in R_+^4 \mid dV_2/dt = 0\}$ is the singleton $\{E_1\}$. Therefore, the global asymptotic stability of E_1 follows from the LaSalle's invariance principle. \square

Theorem 5. For system (2), if $R_1 > 1$ and $cd(\delta + \eta + q) - r\beta\delta \geq 0$, CTL-present infection equilibrium E_2 is globally asymptotically stable.

Proof. Define a Lyapunov function

$$\begin{aligned} V_3(x, w, y, z) &= x - x_2 - x_2 \ln \frac{x}{x_2} + w - w_2 - w_2 \ln \frac{w}{w_2} \\ &\quad + \frac{\delta}{2(d + \eta + q)x_2} [(x - x_2) + (w - w_2)]^2 \\ &\quad + \frac{\beta x_2 y_2}{q w_2} \left(y - y_2 - y_2 \ln \frac{y}{y_2}\right) \\ &\quad + \frac{\beta p x_2 y_2}{c q w_2} \left(z - z_2 - z_2 \ln \frac{z}{z_2}\right). \end{aligned} \quad (18)$$

Calculating the derivative of V_3 along positive solutions of system (2), we obtain that

$$\begin{aligned} \frac{dV_3}{dt} &= \left(1 - \frac{x_2}{x}\right) \frac{dx}{dt} + \frac{\beta x_2 y_2}{q w_2} \left(1 - \frac{y_2}{y}\right) \frac{dy}{dt} \\ &\quad + \frac{\delta}{(d + \eta + q)x_2} [(x - x_2) + (w - w_2)] \left(\frac{dx}{dt} + \frac{dw}{dt}\right) \\ &\quad + \left(1 - \frac{w_2}{w}\right) \frac{dw}{dt} + \frac{\beta p x_2 y_2}{q c w_2} \left(1 - \frac{z_2}{z}\right) \frac{dz}{dt} \\ &= \left(1 - \frac{x_2}{x}\right) (s - dx - \beta xy + \delta w) \\ &\quad + \frac{\beta x_2 y_2}{q w_2} \left(1 - \frac{y_2}{y}\right) (qw - \alpha y - p y z) \\ &\quad + \frac{\delta}{(u + \eta + q)x_2} [(x - x_2) + (w - w_2)] \\ &\quad \times [s - dx - (\eta + q)w] \\ &\quad + \left(1 - \frac{w_2}{w}\right) [\beta xy - (\delta + \eta + q)w] \\ &\quad + \frac{\beta p x_2 y_2}{q c w_2} \left(1 - \frac{z_2}{z}\right) (c y z - r z). \end{aligned} \quad (19)$$

At CTL-present infection equilibrium E_2 , on substituting $s = \beta x_2 y_2 + dx_2 - \delta w_2$, $\alpha = q(w_2/y_2) - p z_2$, $y_2 = r/c$, and $\delta + \eta + q = \beta x_2 y_2/w_2$ into (19), it follows that

$$\begin{aligned} \frac{dV_3}{dt} &= \left(1 - \frac{x_2}{x}\right) \\ &\quad \times [-d(x - x_2) - \beta xy + \beta x_2 y_2 + \delta(w - w_2)] \end{aligned}$$

$$\begin{aligned}
& + \frac{\beta x_2 y_2}{q w_1} \left(1 - \frac{y_2}{y}\right) \left(q w - q w_2 \frac{y}{y_2} + p y z_2 - p y z\right) \\
& + \frac{\delta}{(d + \eta + q)} [(x - x_2) + (w - w_2)] \\
& \times [-d(x - x_2) - (\eta + q)(w - w_2)] \\
& + \left(1 - \frac{w_2}{w}\right) \left(\beta x y - \beta x_2 y_2 \frac{w}{w_2}\right) \\
& + \frac{\beta p x_2 y_2}{q c w_2} \left(1 - \frac{z_2}{z}\right) (c y z - r z).
\end{aligned} \tag{20}$$

Noting that

$$\begin{aligned}
\delta \left(1 - \frac{x}{x_2}\right) (w - w_2) &= -\delta (w - w_2) \frac{(x - x_2)^2}{x x_2} \\
&+ \frac{\delta}{x_2} (x - x_2) (w - w_2),
\end{aligned} \tag{21}$$

it follows from (20) and (21) that

$$\begin{aligned}
\frac{dV_3}{dt} &= - (dx_2 + \delta (w - w_2)) \frac{(x - x_2)^2}{x x_2} \\
&+ \frac{\delta}{x_2} (x - x_2) (w - w_2) \\
&+ \beta x_2 y_2 \left(1 - \frac{x y}{x_2 y_2} - \frac{x_2}{x} + \frac{y}{y_2}\right) \\
&+ \beta x_2 y_2 \left(\frac{w}{w_2} - \frac{y}{y_2} - \frac{y_2 w}{y w_2} + 1\right) \\
&- \frac{\beta p x_2 y_2}{q w_2} (y - y_2) (z - z_2) \\
&- \frac{\delta}{x_2} \left[\frac{d}{d + \eta + q} (x - x_2)^2 + (x - x_2) \right. \\
&\quad \left. \times (w - w_2) + \frac{\eta + q}{d + \eta + q} (w - w_2)^2 \right] \\
&+ \beta x_2 y_2 \left(\frac{x y}{x_2 y_2} - \frac{w}{w_2} - \frac{x w_2 y}{x_2 y_2 w} + 1\right) \\
&+ \frac{\beta p x_2 y_2}{q w_2} (z - z_2) (y - y_2) \\
&= - \left(dx_2 - \delta w_2 + \delta w + \frac{d \delta x}{d + \eta + q}\right) \frac{(x - x_2)^2}{x x_2} \\
&- \frac{\delta (\eta + q)}{(d + \eta + q)} (w - w_2)^2 \\
&- \beta x_2 y_2 \left(\frac{x_2}{x} + \frac{y_2 w}{y w_2} + \frac{x w_2 y}{x_2 y_2 w} - 3\right).
\end{aligned} \tag{22}$$

Since $x_2/x + y_2 w/y w_2 + x w_2 y/x_2 y_2 w - 3 \geq 0$ and the equality holds if and only if $x = x_2$, $w = w_2$, and $y = y_2$. If $cd(\delta + \eta + q) - r\beta\delta \geq 0$, then $dx_2 - \delta w_2 = ((cd(\delta + \eta + q) - r\beta\delta)/r\beta)w_2 \geq 0$. Therefore, if $R_1 > 1$ and $cd(\delta + \eta + q) - r\beta\delta \geq 0$, it follows from (22) that $dV_3/dt \leq 0$ for all $x > 0$, $w > 0$, $y > 0$, and $z > 0$. Clearly, it follows from (22) that $dV_3/dt = 0$ if and only if $x = x_2$, $w = w_2$, $y = y_2$, and $z = z_2$. So the largest invariant set in the set $\{(x, w, y, z) \in R_+^4 \mid dV_3/dt = 0\}$ is the singleton $\{E_2\}$. By LaSalle invariance principle, we conclude that the equilibrium E_2 is globally asymptotically stable. \square

4. The Stability Analysis of the DDE Model

In this section, we consider the stability of the delay model (3).

Let $C = C([- \tau, 0], R_{+0}^4)$ be the Banach space of continuous functions mapping from the interval $[- \tau, 0]$ to R_{+0}^4 with the topology of uniform convergence, where

$$R_{+0}^4 = \{(x_1, x_2, x_3, x_4) \mid x_i \geq 0, i = 1, 2, 3, 4\}. \tag{23}$$

The initial conditions for system (3) are given as follows:

$$\begin{aligned}
x &= \varphi_1(\theta), \quad w = \varphi_2(\theta), \quad y = \varphi_3(\theta), \\
z &= \varphi_4(\theta), \quad \theta \in [- \tau, 0], \\
x(0) &> 0, \quad w(0) > 0, \quad y(0) > 0, \quad z(0) > 0,
\end{aligned} \tag{24}$$

where $(\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta)) \in C([- \tau, 0], R_{+0}^4)$. It is clear to see that all solutions of system (3) satisfying the initial conditions (24) are positive for all $t \geq 0$. By the similar method to Theorem 2, we can get the following theorem.

Theorem 6. Let $x(t)$, $w(t)$, $y(t)$, and $z(t)$ be the solution of system (3) satisfying the initial conditions (24), then there exists $M > 0$ such that $x(t) < M$, $w(t) < M$, $y(t) < M$, and $z(t) < M$ hold after sufficiently large time t .

Theorem 7. If $R_0 < 1$, the uninfected equilibrium E_0 of system (3) is globally asymptotically stable.

Proof. If $R_0 < 1$, construct a Lyapunov functional

$$\begin{aligned}
W_1(x, w, y, z) &= x - x_0 - x_0 \ln \frac{x}{x_0} \\
&+ \frac{\delta}{2(d + \eta + q)x_0} [(x - x_0) + w]^2 + w \\
&+ \frac{(\delta + \eta + q)}{q} y + \frac{p(\delta + \eta + q)}{cq} z \\
&+ \frac{p(\delta + \eta + q)}{q} \int_{t-\tau}^t y(\theta) z(\theta) d\theta,
\end{aligned} \tag{25}$$

where $x_0 = s/d$. Calculating the derivative of W_1 along positive solutions of system (3), it follows that

$$\begin{aligned} \frac{dW_1}{dt} &= \frac{(x - x_0)}{x} (s - dx - \beta xy + \delta w) \\ &\quad + \frac{\delta}{(d + \eta + q)x_0} (x - x_0 + w) \\ &\quad \times [s - dx - (\eta + q)w] \\ &\quad + \frac{(\delta + \eta + q)}{q} (qw - \alpha y - pyz) + \beta xy \\ &\quad - (\delta + \eta + q)w + \frac{p(\delta + \eta + q)}{q} yz \\ &\quad - \frac{pr(\delta + \eta + q)}{cq} z. \end{aligned} \quad (26)$$

On substituting $s = dx_0$ and $\delta w(x - x_0)/x = -\delta w((x - x_0)^2/xx_0) + \delta w((x - x_0)/x_0)$ into (26), we derive that

$$\begin{aligned} \frac{dW_1}{dt} &= - \left(dx_0 + \delta w + \frac{d\delta x}{d + \eta + q} \right) \\ &\quad \times \frac{(x - x_0)^2}{xx_0} - \frac{\delta w^2 (\eta + q)}{(d + \eta + q)x_0} \\ &\quad + \frac{\alpha(\delta + \eta + q)}{q} (R_0 - 1)y - \frac{pr(\delta + \eta + q)}{cq} z. \end{aligned} \quad (27)$$

If $R_0 < 1$, we have $dW_1/dt \leq 0$ for all $x > 0, w > 0, y > 0$, and $z > 0$. It follows that the uninfected equilibrium E_0 is stable. Clearly, it follows from (27) that $dW_1/dt = 0$ if and only if $x = s/d, w = 0, y = 0$, and $z = 0$. Therefore the largest invariant set in the set $\{(x, w, y, z) \in R_+^4 \mid dW_1/dt = 0\}$ is the singleton $\{E_0\}$. By LaSalle invariance principle [21], we can conclude that the equilibrium E_0 is globally asymptotically stable. \square

From the above analysis, we can obtain that the time delay has no effect on the stability of the uninfected equilibrium E_0 for the DDE model.

Theorem 8. For system (3), if $R_1 < 1$ and $1 < R_0 \leq 1 + (\eta + q)/\delta$, then CTL-absent infection equilibrium E_1 is globally asymptotically stable.

Proof. Define a lyapunov functional

$$\begin{aligned} W_2(x, w, y, z) &= x - x_1 - x_1 \ln \frac{x}{x_1} \\ &\quad + \frac{\beta x_1 y_1}{qw_1} \left(y - y_1 - y_1 \ln \frac{y}{y_1} \right) \end{aligned}$$

$$\begin{aligned} &+ \frac{\delta}{2(d + \eta + q)x_1} [(x - x_1) + (w - w_1)]^2 \\ &+ w - w_1 - w_1 \ln \frac{w}{w_1} \\ &+ \frac{\beta p x_1 y_1}{cq w_1} z + \frac{\beta p x_1 y_1}{q w_1} \int_{t-\tau}^t y(\theta) z(\theta) d\theta. \end{aligned} \quad (28)$$

Calculating the derivative of W_2 along positive solutions of system (3), it follows that

$$\begin{aligned} \frac{dW_2}{dt} &= \left(1 - \frac{x_1}{x} \right) (s - dx - \beta xy + \delta w) \\ &\quad + \frac{\beta x_1 y_1}{q w_1} \left(1 - \frac{y_1}{y} \right) (qw - \alpha y - pyz) \\ &\quad + \frac{\delta}{(d + \eta + q)x_1} [(x - x_1) + (w - w_1)] \\ &\quad \times [s - dx - (\eta + q)w] \\ &\quad + \left(1 - \frac{w_1}{w} \right) [\beta xy - (\delta + \eta + q)w] \\ &\quad - \frac{\beta p r x_1 y_1}{c q w_1} z + \frac{\beta p x_1 y_1}{q w_1} yz. \end{aligned} \quad (29)$$

At CTL-absent infection equilibrium E_1 , on substituting $s = \beta x_1 y_1 + dx_1 - \delta w_1$, $\alpha = q(w_1/y_1)$, and $\delta + \eta + q = \beta x_1 y_1/w_1$ into (29), we obtain that

$$\begin{aligned} \frac{dW_2}{dt} &= \left(1 - \frac{x_1}{x} \right) [-d(x - x_1) - \beta xy + \beta x_1 y_1 + \delta(w - w_1)] \\ &\quad + \frac{\beta x_1 y_1}{q w_1} \left(1 - \frac{y_1}{y} \right) \left(qw - q w_1 \frac{y}{y_1} - pyz \right) \\ &\quad + \frac{\delta}{(d + \eta + q)} [(x - x_1) + (w - w_1)] \\ &\quad \times [-d(x - x_1) - (\eta + q)(w - w_1)] \\ &\quad + \left(1 - \frac{w_1}{w} \right) \left(\beta xy - \beta x_1 y_1 \frac{w}{w_1} \right) \\ &\quad - \frac{\beta r p x_1 y_1}{c q w_1} z + \frac{\beta p x_1 y_1}{q w_1} yz. \end{aligned} \quad (30)$$

It follows from (16) and (30) that

$$\begin{aligned}
 \frac{dW_2}{dt} = & - (dx_1 + \delta(w - w_1)) \frac{(x - x_1)^2}{xx_1} \\
 & + \frac{\delta}{x_1} (x - x_1)(w - w_1) \\
 & + \beta x_1 y_1 \left(1 - \frac{xy}{x_1 y_1} - \frac{x_1}{x} + \frac{y}{y_1} \right) \\
 & + \beta x_1 y_1 \left(\frac{w}{w_1} - \frac{y}{y_1} - \frac{y_1 w}{y w_1} + 1 \right) \\
 & - \frac{\beta x_1 y_1}{q w_1} \left(1 - \frac{y_1}{y} \right) p y z \\
 & + \beta x_1 y_1 \left(\frac{xy}{x_1 y_1} - \frac{w}{w_1} - \frac{x w_1 y}{x_1 y_1 w} + 1 \right) \\
 & - \frac{\delta}{x_1} \left[\frac{d}{d + \eta + q} (x - x_1)^2 + (x - x_1) \right. \\
 & \quad \left. \times (w - w_1) + \frac{\eta + q}{d + \eta + q} (w - w_1)^2 \right] \\
 & - \frac{\beta r p x_1 y_1}{c q w_1} z + \frac{\beta p x_1 y_1}{q w_1} y z \\
 = & - \left(dx_1 - \delta w_1 + \delta w + \frac{d \delta x}{d + \eta + q} \right) \\
 & \times \frac{(x - x_1)^2}{xx_1} - \frac{\delta(\eta + q)}{(d + \eta + q)} (w - w_1)^2 \\
 & - \beta x_1 y_1 \left(\frac{x_1}{x} + \frac{y_1 w}{y w_1} + \frac{x y w_1}{x_1 y_1 w} - 3 \right) \\
 & + \frac{\beta p x_1 y_1}{c q w_1} \left[\frac{d(\delta + \eta + q) + r \beta(\eta + q)}{\beta(\eta + q)} \right] (R_1 - 1) z.
 \end{aligned} \tag{31}$$

Since $x_1/x + y_1 w/y w_1 + x y w_1/x_1 y_1 w - 3 \geq 0$ and the equality holds if and only if $x = x_1$, $w = w_1$, and $y = y_1$. If $R_0 \leq 1 + (\eta + q)/\delta$, then $dx_1 - \delta w_1 \geq 0$. Therefore, if $R_1 < 1$ and $1 < R_0 \leq 1 + (\eta + q)/\delta$, it follows from (31) that $dW_2/dt \leq 0$ for all $x > 0$, $w > 0$, $y > 0$, and $z > 0$. It is readily seen from (31) that $dW_2/dt = 0$ if and only if $x = x_1$, $w = w_1$, $y = y_1$, and $z = 0$. Thus the largest invariant set in the set $\{(x, w, y, z) \in R_+^4 \mid dW_2/dt = 0\}$ is the singleton $\{E_1\}$. Then the global asymptotic stability of E_1 follows from the LaSalle's invariance principle [21]. \square

From the above analysis, we obtain that the time delay has no effect on the stability of the CTL-absent infection equilibrium E_1 for the DDE model. Next, we analyze stability and Hopf bifurcation at the CTL-present equilibrium E_2 .

Firstly, the linearized equations of system (3) at E_2 are given as follows:

$$\begin{aligned}
 \frac{dx}{dt} &= -(\beta y_2 + d)x(t) - \beta x_2 y(t) + \delta w(t), \\
 \frac{dw}{dt} &= \beta y_2 x(t) + \beta x_2 y(t) - (\delta + \eta + q)w(t), \\
 \frac{dy}{dt} &= qw(t) - (\alpha + pz_2)y(t) - py_2 z(t), \\
 \frac{dz}{dt} &= cz_2 y(t - \tau) + cy_2 z(t - \tau) - rz(t).
 \end{aligned} \tag{32}$$

The characteristic equation of system (32) at $O(0, 0, 0, 0)$ takes the form

$$\begin{aligned}
 G(\lambda) &= \lambda^4 + M_1 \lambda^3 + M_2 \lambda^2 + M_3 \lambda + M_4 \\
 &\quad - (N_1 \lambda^3 + N_2 \lambda^2 + N_3 \lambda + N_4) e^{-\lambda \tau} = 0,
 \end{aligned} \tag{33}$$

where

$$\begin{aligned}
 M_1 &= \beta y_2 + d + \delta + \eta + q + \alpha + pz_2 + r, \\
 M_2 &= \beta y_2(\eta + q) + d(\delta + \eta + q) \\
 &\quad + (\beta y_2 + d)(\alpha + pz_2) \\
 &\quad + r(\beta y_2 + d + \delta + \eta + q + \alpha + pz_2), \\
 M_3 &= r[\beta y_2(\eta + q) + d(\delta + \eta + q) \\
 &\quad + (\beta y_2 + d)(\alpha + pz_2)] \\
 &\quad + \beta y_2(\eta + q)(\alpha + pz_2), \\
 M_4 &= r\beta y_2(\eta + q)(\alpha + pz_2), \\
 N_1 &= r, \\
 N_2 &= r(\beta y_2 + d + \delta + \eta + q + \alpha + pz_2) \\
 &\quad - cpy_2 z_2, \\
 N_3 &= r[\beta y_2(\eta + q) + d(\delta + \eta + q) \\
 &\quad + (\beta y_2 + d)(\alpha + pz_2)] \\
 &\quad - cpy_2 z_2(\beta y_2 + d + \delta + \eta + q), \\
 N_4 &= r\beta y_2(\eta + q)(\alpha + pz_2) \\
 &\quad - cpy_2 z_2[\beta y_2(\eta + q) + d(\delta + \eta + q)].
 \end{aligned} \tag{34}$$

Theorem 9. Suppose $\tau = 0$, if $R_1 > 1$, then the CTL-present equilibrium E_2 of system (3) is locally asymptotically stable.

Proof. If $\tau = 0$, (33) becomes

$$\begin{aligned}
 \lambda^4 &+ (M_1 - N_1) \lambda^3 + (M_2 - N_2) \lambda^2 \\
 &+ (M_3 - N_3) \lambda + M_4 - N_4 = 0.
 \end{aligned} \tag{35}$$

Since $R_1 > 1$, $x_2 > 0$, $w_2 > 0$, $y_2 > 0$, and $z_2 > 0$, by the Routh-Hurwitz criteria, it follows that

$$\begin{aligned}
 H_1 &= M_1 - N_1 = \beta y_2 + d + \delta + \eta + q + \alpha + pz_2 > 0, \\
 H_2 &= (M_1 - N_1)(M_2 - N_2) - (M_3 - N_3) \\
 &= [\beta y_2(\eta + q) + d(\delta + \eta + q) \\
 &\quad + (\beta y_2 + d)(\alpha + pz_2) + cpy_2z_2] \\
 &\quad \times (\beta y_2d + \delta + \eta + q + \alpha + pz_2) \\
 &\quad - \beta y_2(\eta + q)(\alpha + pz_2) \\
 &\quad - cpy_2z_2(\beta y_2 + d + \delta + \eta + q) \\
 &= [d(\delta + \eta + q) + (\beta y_2 + d)(\alpha + pz_2)] \\
 &\quad \times [\beta y_2 + d + \delta + \eta + q + \alpha + pz_2] \\
 &\quad + \beta y_2(\eta + q)(\beta y_2 + d + \delta + \eta + q) \\
 &\quad + cpy_2z_2(\alpha + pz_2) > 0, \\
 H_3 &= (M_1 - N_1)[(M_2 - N_2)(M_3 - N_3) \\
 &\quad - (M_1 - N_1)(M_4 - N_4)] - (M_3 - N_3)^2 \\
 &= [\beta y_2(\eta + q) + d(\delta + \eta + q) \\
 &\quad + (\beta y_2 + d)(\alpha + pz_2) + cpy_2z_2] \\
 &\quad \times (\beta y_2 + d + \delta + \eta + q + \alpha + pz_2) \\
 &\quad \times [\beta y_2(\eta + q)(\alpha + pz_2) \\
 &\quad + cpy_2z_2(\beta y_2 + d + \delta + \eta + q)] \\
 &\quad - (\beta y_2 + d + \delta + \eta + q + \alpha + pz_2)^2 \\
 &\quad \times cpy_2z_2[\beta y_2(\eta + q) + d(\delta + \eta + q)] \\
 &\quad - [\beta y_2(\eta + q)(\alpha + pz_2) \\
 &\quad + cpy_2z_2(\beta y_2 + d + \delta + \eta + q)]^2 \\
 &= A(cpy_2z_2)^2 + Bcpy_2z_2 + C,
 \end{aligned} \tag{36}$$

where

$$\begin{aligned}
 A &= (\alpha + pz_2)(\beta y_2 + d + \delta + \eta + q) > 0, \\
 B &= [(\beta y_2 + d)^2 + \beta y_2\delta](\alpha + pz_2) \\
 &\quad \times (\beta y_2 + d + \alpha + pz_2) + [(\beta y_2 + d)^2 + \beta y_2\delta] \\
 &\quad \times \delta(\alpha + pz_2) + (\beta dy_2 + d^2)(\eta + q)(\alpha + pz_2) \\
 &\quad - \beta y_2(\eta + q)^2(\alpha + pz_2),
 \end{aligned}$$

$$\begin{aligned}
 C &= \beta y_2(\eta + q)(\alpha + pz_2)(\beta y_2 + d + \delta + \eta + q) \\
 &\quad \times [\beta y_2(\eta + q) + d(\delta + \eta + q)(\beta y_2 + d)(\alpha + pz_2)] \\
 &\quad + \beta y_2(\eta + q)(\alpha + pz_2)^2 \\
 &\quad \times [d(\delta + \eta + q) + (\beta y_2 + d)(\alpha + pz_2)] > 0.
 \end{aligned} \tag{37}$$

Let

$$\begin{aligned}
 D &= \beta y_2(\eta + q)^2(\alpha + pz_2), \quad h = cpy_2z_2 > 0, \\
 f(h) &= Ah^2 + Bh + C, \\
 g(h) &= Ah^2 - Dh + C.
 \end{aligned} \tag{38}$$

If $g(h) > 0$ for all $h > 0$, then $f(h) > 0$. Since

$$\begin{aligned}
 \Delta_1 &= D^2 - 4AC \\
 &= -4(\alpha + pz_2)^3(\beta y_2 + d + \delta + \eta + q)\beta y_2(\eta + q) \\
 &\quad \times [d(\delta + \eta + q) + (\beta y_2 + d)(\alpha + pz_2)] \\
 &\quad - 4(\alpha + pz_2)^2(\beta y_2 + d + \delta)\beta y_2(\eta + q) \\
 &\quad \times (\beta y_2 + d + \delta + \eta + q) \\
 &\quad \times [\beta y_2(\eta + q) \\
 &\quad + d(\delta + \eta + q)(\beta y_2 + d)(\alpha + pz_2)] \\
 &\quad - 4(\alpha + pz_2)^3(\eta + q)^2\beta y_2(\beta y_2 + d + \delta + \eta + q) \\
 &\quad \times d(\delta + \eta + q)(\beta y_2 + d) \\
 &\quad - 4(\alpha + pz_2)^2(\eta + q)^3(\beta y_2)^2(\beta y_2 + d + \delta) \\
 &\quad - 3[\beta y_2(\eta + q)^2(\alpha + pz_2)]^2 < 0,
 \end{aligned} \tag{39}$$

and $g(0) = C > 0$, it follows that $g(h) > 0$ for all $h > 0$, thus $f(h) > 0$, that is, $H_3 > 0$.

$$\begin{aligned}
 H_4 &= \begin{vmatrix} M_1 - N_1 & M_3 - N_3 & 0 & 0 \\ 1 & M_2 - N_2 & M_4 - N_4 & 0 \\ 0 & M_1 - N_1 & M_3 - N_3 & 0 \\ 0 & 1 & M_2 - N_2 & M_4 - N_4 \end{vmatrix} \\
 &= (M_4 - N_4)H_3.
 \end{aligned} \tag{40}$$

Noting that

$$M_4 - N_4 = cpy_2z_2[\beta y_2(\eta + q) + d(\delta + \eta + q)] > 0, \tag{41}$$

it follows that $H_4 > 0$. Therefore, all the roots of (35) have negative real parts. This completes the proof of Theorem 9. \square

For $\tau = 0$, the all roots of $G(\lambda) = 0$ have negative real roots in Theorem 9. By the continuous dependence of roots

of $G(\lambda) = 0$ on the parameters, it follows that there exists $\bar{\tau} > 0$ such that for $\tau \in [0, \bar{\tau})$, all roots of (33) satisfy

$$G(\lambda) = 0, \quad \operatorname{Re}(\lambda) < 0, \quad \text{for } \tau \in [0, \bar{\tau}), \quad (42)$$

and when $\tau = \bar{\tau}$, $\operatorname{Re}(\lambda) = 0$. To determine $\bar{\tau}$ and the associated purely imaginary roots $\bar{\omega}i$ ($\bar{\omega} > 0$).

Suppose that $\lambda = \omega i$ ($\omega > 0$) is a solution of (33), it follows that

$$\begin{aligned} &\omega^4 - M_1\omega^3i - M_2\omega^2i + M_3\omega i \\ &- (-N_1\omega^3i - N_2\omega^2 + B_3\omega i + B_4)(\cos \omega\tau - i \sin \omega\tau) = 0. \end{aligned} \quad (43)$$

Separating the real and imaginary parts, it follows that

$$\begin{aligned} &(N_4 - N_2\omega^2) \cos \omega\tau + (N_3\omega - N_1\omega^3) \sin \omega\tau \\ &= \omega^4 - M_2\omega^2 + M_4, \\ &(N_1\omega^3 - N_3\omega) \cos \omega\tau + (N_4 - N_2\omega^2) \sin \omega\tau \\ &= M_1\omega^3 - M_3\omega. \end{aligned} \quad (44)$$

From (44), we obtain that

$$\begin{aligned} \cos \omega\tau &= \frac{1}{\Delta} (A_1\omega^6 + A_2\omega^4 + A_3\omega^2 + A_4), \\ \sin \omega\tau &= -\frac{\omega}{\Delta} (B_1\omega^6 + B_2\omega^4 + B_3\omega^2 + B_4), \end{aligned} \quad (45)$$

where

$$\begin{aligned} A_1 &= M_1N_1 - N_2, \\ A_2 &= N_4 + M_2N_2 - M_1N_3 - M_3N_1, \\ A_3 &= M_3N_3 - M_2N_4 - M_4N_2, \quad A_4 = M_4N_4, \\ B_1 &= N_1, \quad B_2 = M_1N_2 - N_3 - M_2N_1, \\ B_3 &= M_2N_3 + M_4N_1 - M_3N_2 - M_1N_4, \\ B_4 &= M_3N_4 - M_4N_3, \\ \Delta &= (N_4 - N_2\omega^2)^2 + (N_3\omega - N_1\omega^3)^2 > 0. \end{aligned} \quad (46)$$

It follows from (44) that

$$\omega^8 + q_1\omega^6 + q_2\omega^4 + q_3\omega^2 + q_4 = 0, \quad (47)$$

where

$$\begin{aligned} q_1 &= M_1^2 - 2M_2 - N_1^2, \\ q_2 &= M_2^2 + 2M_4 - 2M_1M_3 + 2N_1N_3 - M_2^2, \\ q_3 &= M_3^2 - 2M_2M_4 + 2N_2N_4 - M_3^2, \quad q_4 = M_4^2 - N_4^2. \end{aligned} \quad (48)$$

Letting $u = \omega^2$, (47) becomes

$$u^4 + q_1u^3 + q_2u^2 + q_3u + q_4 = 0. \quad (49)$$

Denote $G(u) = u^4 + q_1u^3 + q_2u^2 + q_3u + q_4$. Then we have

$$G'(u) = 4u^3 + 3q_1u^2 + 2q_2u + q_3. \quad (50)$$

Suppose that (49) has positive real roots. Without loss of generality, we assume that it has n ($1 \leq n \leq 4$) positive real roots, defined by $u_1 < u_2 < \dots < u_n$, respectively. Then (47) has n positive real roots

$$\omega_1 = \sqrt{u_1}, \omega_2 = \sqrt{u_2}, \dots, \omega_n = \sqrt{u_n}. \quad (51)$$

From (45), we have

$$\tau_l^j = \frac{1}{\omega_l} \left(\arccos \frac{A_1\omega_l^6 + A_2\omega_l^4 + A_3\omega_l^2 + A_4}{(N_4 - N_2\omega_l^2)^2 + (N_3\omega_l - N_1\omega_l^3)^2} + 2j\pi \right), \quad (52)$$

where $l = 1, 2, \dots, n$, $j = 0, 1, 2, 3, \dots$, then $\pm \omega_l i$ are a pair of purely imaginary roots of (33) with τ_l^j .

Differentiating (33) implicitly with respect to τ , we obtain that

$$\begin{aligned} \left[\frac{d\lambda}{d\tau} \right]^{-1} &= \frac{-(4\lambda^3 + 3M_1\lambda^2 + 2M_2\lambda + M_3)e^{\lambda\tau}}{\lambda(N_1\lambda^3 + N_2\lambda^2 + N_3\lambda + N_4)} \\ &+ \frac{3N_1\lambda^2 + 2N_2\lambda + N_3}{\lambda(N_1\lambda^3 + N_2\lambda^2 + N_3\lambda + N_4)} - \frac{\tau}{\lambda}. \end{aligned} \quad (53)$$

Thus,

$$\begin{aligned} \operatorname{Re} \left[\frac{d\lambda}{d\tau} \right]_{\tau=\tau_l^j}^{-1} &= \frac{1}{\omega_l \Delta} \left\{ (3M_1\omega_l^2 - M_3) \right. \\ &\times \left[(N_1\omega_l^3 - N_3\omega_l) \cos \omega_l\tau \right. \\ &\quad \left. + (N_4 - N_4\omega_l^2) \sin \omega_l\tau \right] \\ &+ (4\omega_l^3 - 2M_2\omega_l) \\ &\times \left[(N_4 - N_2\omega_l^2) \cos \omega_l\tau \right. \\ &\quad \left. - (N_1\omega_l^3 - N_3\omega_l) \sin \omega_l\tau \right] \\ &+ (N_3 - 3N_1\omega_l^2)(N_1\omega_l^3 - N_3\omega_l) \\ &\left. + 2N_2\omega_l(N_4 - N_2\omega_l^2) \right\}. \end{aligned} \quad (54)$$

On substituting (45) into (54), we obtain

$$\begin{aligned} \operatorname{Re} \left[\frac{d\lambda}{d\tau} \right]_{\tau=\tau_l^j}^{-1} &= \frac{1}{\Delta} \left[4\omega_l^6 + 3(M_1^2 - 2M_2 - N_1^2)\omega_l^4 \right. \\ &+ 2(M_2^2 - N_2^2 + 2M_4 + 2N_1N_3 - 2M_1M_3)\omega_l^2 \\ &\left. + M_3^2 - N_3^2 + 2N_2N_4 - 2M_2M_4 \right] = \frac{G'(u_l)}{\Delta}, \end{aligned} \quad (55)$$

where $\Delta = (N_4 - N_2\omega^2)^2 + (N_3\omega - N_1\omega^3)^2 > 0$. If we suppose that $G'(u) \neq 0$, then

$$\begin{aligned} \text{sign} \left\{ \text{Re} \left[\frac{d\lambda}{d\tau} \right]_{\tau=\tau_l'} \right\} &= \text{sign} \left\{ \text{Re} \left[\frac{d\lambda}{d\tau} \right]_{\tau=\tau_l'}^{-1} \right\} \\ &= \text{sign} \left\{ \frac{G'(u_l)}{\Delta} \right\} = \text{sign} \{ G'(u_l) \}. \end{aligned} \quad (56)$$

Applying Theorem 9 and the Hopf bifurcation theorem for functional differential equation [22] from (56), we derive the existence of a Hopf bifurcation as follows.

Theorem 10. Suppose that (49) has at least one simple positive root and \bar{u} is the last such root, then there is a Hopf bifurcation for the system (3) as τ passes upwards through $\bar{\tau}$ leading to a periodic solution that bifurcates from E_2 , where

$$\bar{\tau} = \frac{1}{\bar{\omega}} \left(\arccos \frac{A_1 \bar{\omega}_l^6 + A_2 \bar{\omega}_l^4 + A_3 \bar{\omega}_l^2 + A_4}{(N_4 - N_2 \bar{\omega}_l^2)^2 + (N_3 \bar{\omega}_l - N_1 \bar{\omega}_l^3)^2} + 2j\pi \right). \quad (57)$$

Remark 11. If \bar{u} is the last simple positive root of (49), then we have $G'(\bar{u}) > 0$. From (56), we obtain $\text{Re} [d\lambda/d\tau]_{\tau=\bar{\tau}} > 0$.

Remark 12. In this paper, we construct a few Lyapunov functions (functionals) to prove the global stability of steady states of ODE model (DDE model). This function (functional) can also prove the global stability of steady states of other viral infections models with cure rate [7, 10]. Moreover, the method studying the existence of Hopf bifurcations applies to other viral infections models with immune delay [2, 18, 19].

5. Numerical Simulations

In this section, we perform numerical calculation to support our theoretical analysis of this paper.

Example 13. If we choose parameters $s = 1.5$, $\beta = 0.3$, $\alpha = 0.1$, $p = 0.015$, $c = 0.12$, $r = 0.8$, $d = 0.1$, $\delta = 0.6$, $\eta = 0.4$, and $q = 0.7$, then $R_1 = 1.33 > 1$ and the CTL-present equilibrium $E_2(1.1751, 1.3825, 6.6667, 1.6283)$. From (49), we obtain that

$$u^4 + 10.5385u^3 + 3.9615u^2 + 0.0729u + 0.0151 = 0. \quad (58)$$

Equation (58) has no positive roots, and all roots have negative real parts. Therefore, the equilibrium is locally asymptotically stable for all $\tau \geq 0$ (e.g., $\tau = 1.5$, see Figure 1).

Example 14. If we select parameters $s = 10$, $\beta = 0.1$, $\alpha = 0.4$, $p = 0.3$, $c = 0.5$, $r = 0.9$, $d = 1$, $\delta = 1$, $\eta = 1$, and $q = 4$, then $R_1 = 1.45 > 1$ and the CTL-present equilibrium $E_2(8.8107, 0.2642, 1.7997, 0.6244)$. It follows from (49) that

$$u^4 + 40.7439u^3 + 41.9038u^2 - 1.9589u - 2.0726 = 0. \quad (59)$$

Equation (59) has only one positive real root $u = 0.2217$ and any other roots have negative real parts. Thus,

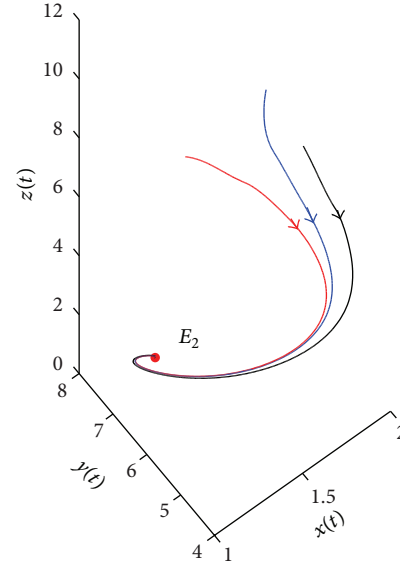


FIGURE 1: The CTL-present infection equilibrium E_2 of system (3) is locally asymptotically stable when $R_1 = 1.33 > 1$ and $\tau = 1.5$.

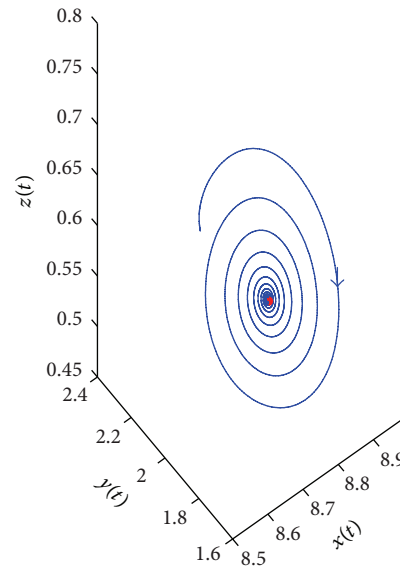


FIGURE 2: The CTL-present infection equilibrium E_2 of system (3) is locally asymptotically stable when $R_1 = 1.45 > 1$ and $\tau = 0.2 < \bar{\tau}$.

$\bar{\omega} = \sqrt{u} = 0.4709$. In addition, it is easy to show that $\bar{\tau} = 0.948$. Therefore, Theorem 10 is satisfied.

If $\tau = 0.2 < \bar{\tau}$, the CTL-present infection equilibrium E_2 of system (3) is locally asymptotically stable (see Figure 2). If $\tau = 5 > \bar{\tau}$, then the CTL-present infection equilibrium E_2 of system (3) becomes unstable, and the Hopf bifurcation occurs (see Figure 3).

6. Conclusion

In this paper, we have studied an HIV infection model including infected cells in an eclipse stage and CTL immune

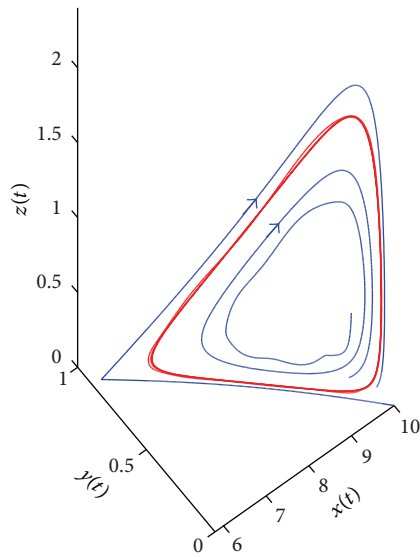


FIGURE 3: The bifurcating periodic solution from the equilibrium E_2 of system (3) occurs when $\tau = 5$.

response. The global stability of the uninfected equilibrium E_0 for system (2) and (3) has been given by the LaSalle's invariance principle when the basic reproductive ratio $R_0 < 1$; it shows that the disease will be controlled. Compared with the earlier modeling studies on the immune response of HIV infection [14, 18, 20], our analysis reveals the existence of a CTL-absent infection equilibrium $E_1(x_1, w_1, y_1, 0)$ when $R_0 > 1$. We also obtained the global asymptotic stability of a CTL-absent infection equilibrium E_1 for system (2) and (3) when $R_1 < 1$ and $1 < R_0 < 1 + (\eta + q)/\delta$. This indicates that there is a persistent HIV infection with no humeral and cellular immune responses. Furthermore, we can see that the time delay has no effect on the stability of the uninfected equilibrium E_0 and CTL-absent infection equilibrium E_1 for the DDE model.

When $R_1 > 1$, we show that the CTL-present infection equilibrium E_2 is locally asymptotically stable when the delay τ is small, and with the increase of the delay τ the stability of E_2 may destabilize and lead to Hopf bifurcation. This suggests that, with the HIV infection developing, the proviral load and CTL frequency can either stabilize at a constant level or show oscillations. Similar phenomenon was also observed in [17–19]. The HIV dynamics model without immune delay is globally stable [14, 15]. In this paper, we show that the HIV infection model including infected cells in an eclipse stage and CTL immune response without immune delay is globally stable; and for the model with immune delay, Hopf bifurcation appears under some conditions.

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