Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

MBE, 17(5): 4384–4405.
DOI: 10.3934/mbe.2020242
Received: 14 April 2020
Accepted: 08 June 2020
Published: 22 June 2020

Research article

Stability and Hopf bifurcation in a virus model with self-proliferation and delayed activation of immune cells

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Abstract: A new mathematical model was proposed to study the effect of self-proliferation and delayed activation of immune cells in the process of virus infection. The global stability of the boundary equilibria was obtained by constructing appropriate Lyapunov functional. For positive equilibrium, the conditions of stability and Hopf bifurcation were obtained by taking the delay as the bifurcation parameter. Furthermore, the direction and stability of the Hopf bifurcation are derived by using the theory of normal form and center manifold. These results indicate that self-proliferation intensity can significantly affect the kinetics of viral infection, and the delayed activation of immune cells can induce periodic oscillation scenario. Along with the increase of delay time, numerical simulations give the corresponding bifurcation diagrams under different self-proliferation rates, and verify that there exists stability switch phenomenon under some conditions.

Keywords: viral infection; self-proliferation; delayed activation of immune cells ; global stability; Hopf bifurcation; stability switch

1. Introduction

Recently, different kinds of viral infection such as HIV (human immunodeficiency virus), HCV (hepatitis C virus) and HBV (hepatitis B virus) have received many attention. Different mathematical models have been formulated to describe the dynamics of virus population in vivo [1–6]. The basic viral infection model of within-host can be described by the following three dimensional system [7]:

$$\begin{cases} \dfrac{dx}{dt} = s - \beta xv - d_1 x, \\ \dfrac{dy}{dt} = \beta xv - d_2 y, \\ \dfrac{dv}{dt} = ky - uv. \end{cases} \tag{1.1}$$

Here $x(t), y(t)$, and $v(t)$ represent uninfected target cells, infected cells and free virus, respectively. Uninfected cells are produced at a constant rate s, die at rate d_1x, and become infected at rate βxv. Infected cells are produced at rate βxv and die at rate by. Free virus are produced from infected cells at rate ky and die at rate uv. It was showed that, for system (1.1), there exist a critical threshold named as the basic reproduction number of virus $R_0 = \frac{\beta sk}{d_1 d_2}$ to determine its global dynamical behavior [8].

During viral infections, the adaptive immune response is mediated by lymphocytes expressing antigen specific receptors, T and B lymphocytes, namely, humoral and cellular immunity. To study the population dynamics of immune response, Nowak et al. [9] introduced the CTL population into system (1.1) and obtain the following four dimensional system:

$$\begin{cases} \dfrac{dx}{dt} = s - \beta xv - d_1 x, \\ \dfrac{dy}{dt} = \beta xv - d_2 y - pyz, \\ \dfrac{dv}{dt} = ky - uv, \\ \dfrac{dz}{dt} = cyz - d_3 z. \end{cases} \tag{1.2}$$

Here $z(t)$ denotes CTLs, which is produced at rate cyz because of the stimulation of infected cells, and die at rate d_3z. The infected cells are eliminated by CTLs at rate pyz. Following [9], many authors present and develop mathematical models for the cell-mediated immune response [10–13] and the humoral immunity [14–17].

Recently study indicates that the self-proliferation of immune cells can not be neglected besides the stimulation of infected cells. In order to mimic the spontaneous proliferation of CTLs, a logistic proliferation term for CTLs was incorporated in virus infection models in [18], where a rigorous mathematical analysis of the effect of self-proliferation of CTLs on the dynamics of viral infection is necessary. In order to understand the effect of self-proliferation and delayed activation of immune cells in a virus model, we propose the following virus infection model:

$$\begin{cases} \dfrac{dx}{dt} = s - \beta xv - d_1 x, \\ \dfrac{dy}{dt} = \beta xv - d_2 y - pyz, \\ \dfrac{dv}{dt} = ky - uv, \\ \dfrac{dz}{dt} = cy(t-\tau)z(t-\tau) + rz(1 - \dfrac{z}{m}) - d_3 z. \end{cases} \tag{1.3}$$

Here the logistic proliferation term $rz(1 - z/m)$ describes the self-proliferation of CTLs, in which parameter r denotes a per capita self-proliferation rate, and m means the capacity of CTLs population. Time delay term $cy(t - \tau)z(t - \tau)$ represents a sequence of events such as antigenic activation and selection. It has been shown that time delays cannot be ignored in models for viral immune response including intracellular delay during viral infection [19–22] and time delay of CTLs stimulating proliferation [23, 24].

Note that the turnover of virus is much faster than that of infection cells within-host [25, 26]. A plausible quasi steady-state assumption is proposed to mimic the fast time-scale [27, 28]. In other

words, v can be replaced by $\frac{ky}{u}$ in (1.3). Let $\hat{\beta} = \frac{\beta k}{u}$ and also note as β to simplify the parameter, system (1.3) can be written as:

$$\begin{cases} \dfrac{dx}{dt} = s - \beta xy - d_1 x, \\ \dfrac{dy}{dt} = \beta xy - d_2 y - pyz, \\ \dfrac{dz}{dt} = cy(t-\tau)z(t-\tau) + rz(1 - \dfrac{z}{m}) - d_3 z. \end{cases} \tag{1.4}$$

This paper is organized as follows. In section 2, some preliminary results are obtained, including non-negativity and boundedness of the solution of system (1.4), the existence of equilibria under different self-proliferation intensities of CTLs. Section 3 investigate the local and global stability of the boundary equilibria. Section 4 study the effects of delayed activation of immune cells on the existence of Hopf bifurcation. The direction and stability of Hopf bifurcation is investigated in section 5. Some numerical simulations are given to quantify the impact of self-proliferation and delayed activation of CTLs in section 6. Finally, some conclusions and discusses are presented in section 7.

2. Preliminary results

In this section, we first discuss the non-negativity and boundedness of solutions of system (1.4). For $\tau > 0$, let $C = C([-\tau, 0], \mathbb{R}^3_+)$ denote the Banach space of continuous function mapping the interval $[-\tau, 0]$ into $\mathbb{R}^3_+$ with the topology of uniform convergence. The initial conditions are given by

$$x(\xi) = \phi_1(\xi), y(\xi) = \phi_2(\xi), z(\xi) = \phi_3(\xi) \tag{2.1}$$

with $\phi_i(\xi) \geq 0, \xi \in [-\tau, 0]$ and $\phi_i(0) > 0$ $(i = 1, 2, 3)$.

Theorem 2.1. *The solutions of system (1.4) satisfying the initial conditions (2.1) are non-negative and ultimately bounded.*

Proof. We first define the right-hand side function of system (1.4) as

$$G(t, K(t)) = \begin{pmatrix} s - \beta xy - d_1 x \\ \beta xy - d_2 y - pyz \\ cy(t-\tau)z(t-\tau) + rz(1 - \dfrac{z}{m}) - d_3 z \end{pmatrix},$$

where $K(t) = (K_1(t), K_2(t), K_3(t))^T$ and $K_1(t) = x$, $K_2(t) = y$, $K_3(t) = z$. It is obvious that the function $G(t, K(t))$ is locally Lipschitz and by the standard theory of functional differential equation, we know that there exists a unique solution for a given initial conditions. To prove the non-negativity of solutions of system (1.4), we first prove the non-negativity over the time interval $[0, \tau]$. Considering the right-hand side functions of system (1.4) over the time interval $[0, \tau]$, we have

$$G(t, K(t)) = \begin{pmatrix} G_1(t, K(t)) \\ G_2(t, K(t)) \\ G_3(t, K(t)) \end{pmatrix}_{K_i(t)=0} = \begin{pmatrix} s \\ 0 \\ cy(t-\tau)z(t-\tau) \end{pmatrix} = \begin{pmatrix} s \\ 0 \\ c\phi_2(\xi)\phi_3(\xi) \end{pmatrix},$$

where $\xi \in [-\tau, 0]$. Note that the positivity of parameters and nonnegativity of initial functions. It can be seen from the above expression that each component $G_i(t, K(t)) \geq 0$. It follows that the solutions of system (1.4) remain nonnegative in $[0, \tau]$. Similarly, we can repeat the process over $[\tau, 2\tau]$ and so on by using the method of steps [29], it can be proved that for any finite interval $[0, t]$, the solutions of system (1.4) remains non-negative.

Now we consider the boundeness of the solutions. Define a new variable $X(t) = x(t)+y(t)+\frac{p}{c}z(t+\tau)$, and let $d = \min\{1, d_1, d_2\}$. By the non-negativity of the solutions of system (1.4), we have

$$\begin{aligned}
\frac{dX}{dt} &= s - d_1 x - d_2 y + \frac{pr}{c} z(t+\tau)\Big(1 - \frac{z(t+\tau)}{m}\Big) - d_3 z(t+\tau) \\
&= s - d_1 x - d_2 y - \frac{p}{c} z(t+\tau) + \frac{p}{c} z(t+\tau)\Big(1 + r - \frac{rz(t+\tau)}{m}\Big) - d_3 z(t+\tau) \\
&\leq s - d_1 x - d_2 y - \frac{p}{c} z(t+\tau) + \frac{pm(1+r)^2}{4rc} \\
&\leq s + \frac{pm(1+r)^2}{4rc} - dX(t). \qquad (2.2)
\end{aligned}$$

Taking $M = s + \frac{pm(1+r)^2}{4rc}$, we know $\limsup_{t\to\infty} X(t) \leq \frac{M}{d}$. So the solutions of system(1.4) are ultimately bounded. □

The equilibria of (1.4) are the solutions of the following algebraic equations:

$$\begin{cases} s - \beta xy - d_1 x = 0, \\ \beta xy - d_2 y - pyz = 0, \\ cyz + rz(1 - \frac{z}{m}) - d_3 z = 0. \end{cases} \qquad (2.3)$$

It is easy to see that system (1.4) always has infection-free equilibrium $E_0^{yz} = (x_0, 0, 0)$, where $x_0 = \frac{s}{d_1}$. According to the definition in [30], we obtain the basic reproduction number of virus $R_0 = \frac{\beta s}{d_1 d_2}$. Now we define $x_1 = \frac{d_2}{\beta}, y_1 = \frac{d_1(R_0-1)}{\beta}, x_2 = \frac{s}{d_1}, z_2 = \frac{m(r-d_3)}{r}$. Based on (2.3), after some simple calculations, it is easy to get the following results.

Proposition 2.2. *(i) Suppose that $R_0 > 1$. The immunity-inactivated infection equilibrium $E_0^z = (x_1, y_1, 0)$ always exists. Especially, besides E_0^z, an infection-free but immunity-activated equilibrium $E_0^y = (x_2, 0, z_2)$ will appear if $r > d_3$. (ii) Suppose that $0 \leq r \leq d_3$. If $R_0 > 1 + \frac{\beta(d_3-r)}{cd_1}$, system (1.4) has a unique immunity-activated infection equilibrium $E_1^* = (x_1^*, y_1^*, z_1^*)$, where*

$$x_1^* = \frac{d_2 + pz_1^*}{\beta}, \qquad y_1^* = \frac{rz_1^* + m(d_3 - r)}{mc},$$

and z_1^* is the unique positive root of the quadratic equation $A_1 z^2 + B_1 z + C_1 = 0$, in which

$$A_1 = -pr\beta, B_1 = -(d_2 r\beta + pmcd_1 + \beta pm(d_3 - r)), C_1 = mcd_1 d_2(R_0 - 1) - \beta m d_2(d_3 - r).$$

(iii) Suppose that $r > d_3$. *If* $R_0 > 1 + \dfrac{pm(r-d_3)}{rd_2}$, *system (1.4) has a unique immunity-activated infection equilibrium* $E_2^* = (x_2^*, y_2^*, z_2^*)$, *where*

$$x_2^* = \frac{s}{d_1 + \beta y_2^*}, \qquad z_2^* = \frac{m(cy_2^* + r - d_3)}{r},$$

and y_2^* *is the unique positive root of the quadratic equation* $A_2y^2 + B_2y + C_2 = 0$, *in which*

$$A_2 = pmc\beta, B_2 = pm\beta(r-d_3) + d_2r\beta + pmcd_1, C_2 = -rd_1d_2(R_0 - 1) + pmd_1(r-d_3).$$

3. Global stability analysis of boundary equilibria

In order to study the stability of equilibrium, we linearize system (1.4) about one equilibrium $E^* = (x^*, y^*, z^*)$ and obtain the following linear system

$$\begin{cases} \dfrac{dx}{dt} = (-\beta y^* - d_1)x - \beta x^* y, \\ \dfrac{dy}{dt} = \beta y^* x + (\beta x^* - d_2 - pz^*)y - py^* z, \\ \dfrac{dz}{dt} = cz^* y(t-\tau) + cy^* z(t-\tau) + (r - d_3 - \dfrac{2rz^*}{m})z. \end{cases} \tag{3.1}$$

When $r = 0$, it follows from the study of Michael Y. Li and Hongying Shu [23] that time delay τ does not change the stability of the boundary equilibria.

When $r > 0$, by using the linear system (3.1) and constructing Lyapunov function, we can obtain the following results.

Proposition 3.1. *Suppose that* $0 < r < d_3$. *Then we have*

(i) The infection-free equilibrium E_0^{yz} *is globally asymptotically stable if* $R_0 < 1$, *and it is unstable when* $R_0 > 1$.

(ii) The immunity-inactivated infection equilibrium E_0^z *is globally asymptotically stable if* $1 < R_0 < 1 + \dfrac{\beta(d_3 - r)}{cd_1}$, *and it is unstable when* $R_0 > 1 + \dfrac{\beta(d_3 - r)}{cd_1}$.

Proof. (i) By the linear system (3.1), we can obtain the characteristic equation of system(1.4) at E_0^{yz} as

$$(\lambda + d_1)(\lambda - (r - d_3))(\lambda + d_1d_2(1 - R_0)) = 0. \tag{3.2}$$

So the eigenvalues are

$$\lambda_1 = -d_1 < 0, \lambda_2 = r - d_3 < 0, \lambda_3 = d_1d_2(R_0 - 1).$$

As a result, if $R_0 < 1$, the infection-free equilibrium E_0^{yz} is locally asymptotically stable, and E_0^{yz} is unstable if $R_0 > 1$.

In order to obtain the global stability of equilibrium E_0^{yz}, we consider a Lyapunov function given by

$$L_1 = x - x_0 - x_0 \ln \frac{x}{x_0} + y + \frac{p}{c}z + p\int_{-\tau}^{0} y(t+\theta)z(t+\theta)d\theta.$$

Taking the time derivative of L_1 along the solution of system (1.4), we have

$$\begin{aligned}\frac{dL_1}{dt} &= (1-\frac{x_0}{x})(s-\beta xy-d_1x)+\beta xy-d_2y-pyz\\ &\quad+\frac{p}{c}[cy(t-\tau)z(t-\tau)+rz(1-\frac{z}{m})-d_3z]+pyz-py(t-\tau)z(t-\tau)\\ &= -\frac{d_1(x-x_0)^2}{x}+(\beta x_0-d_2)y+\frac{p}{c}(r-d_3)z-\frac{prz^2}{cm}\\ &= -\frac{d_1(x-x_0)^2}{x}+d_2(R_0-1)y+\frac{p}{c}(r-d_3)z-\frac{prz^2}{cm}.\end{aligned}$$

Notice that $r < d_3$ and $R_0 < 1$. We have $L_1^{'} \leq 0$ for all $x(t), y(t), z(t) > 0$, and $L_1^{'} = 0$ only if $x = x_0$, $y = 0$ and $z = 0$. It can be verified that the maximal compact invariant set in $L_1^{'} = 0$ is the singleton E_0^{yz}. By the LaSalle's invariance principle, we know the infection-free equilibrium E_0^{yz} is globally asymptotically stable.

(ii) The characteristic equation of system(1.4) at E_0^z is

$$(\lambda^2+d_1R_0\lambda+\beta^2x_1y_1)(\lambda-(r-d_3+cy_1e^{-\lambda\tau}))=0. \tag{3.3}$$

When $\tau = 0$ and $R_0 < 1+\dfrac{\beta(d_3-r)}{cd_1}$, the roots of (3.3) are negative. When $\tau > 0$, the local stability of equilibrium E_0^z is solely determined by

$$\lambda-(r-d_3+cy_1e^{-\lambda\tau})=0. \tag{3.4}$$

Let $\lambda = i\omega(\tau)(\omega(\tau) > 0)$ be the root of Eq (3.4). Separating real and imaginary parts yields

$$\begin{cases} d_3-r = cy_1\cos(\omega\tau),\\ \omega = cy_1\sin(\omega\tau).\end{cases} \tag{3.5}$$

Squaring and adding Eq (3.5) gives

$$\omega^2-(cy_1)^2+(d_3-r)^2=0.$$

Note that

$$(cy_1)^2-(d_3-r)^2=\left(\frac{cd_1(R_0-1)}{\beta(d_3-r)}\right)^2-1<0$$

if $R_0 < 1+\dfrac{\beta(d_3-r)}{cd_1}$. Then we konw that (3.3) has no root that can across the imaginary axis, which indicate that the immunity-inactivated infection equilibrium E_0^z is locally asymptotically stable when $R_0 < 1+\dfrac{\beta(d_3-r)}{cd_1}$.

In order to obtain the global stability of E_0^z, we construct the following Lyapunov functions:

$$L_2 = x-x_1-x_1\ln\frac{x}{x_1}+y-y_1-y_1\ln\frac{y}{y_1}+\frac{p}{c}z+p\int_{-\tau}^{0}y(t+\theta)z(t+\theta)d\theta.$$

Taking the time derivative of L_2 along the solution of system(1.4), we get

$$\begin{aligned}\frac{dL_2}{dt} &= (1-\frac{x_1}{x})(s-\beta xy-d_1x)+(1-\frac{y_1}{y})(\beta xy-d_2y-pyz)\\ &\quad+\frac{p}{c}(cy(t-\tau)z(t-\tau)+rz(1-\frac{z}{m})-d_3z)+pyz-py(t-\tau)z(t-\tau)\\ &= s-d_1x-s\frac{x_1}{x}+\beta x_1y+d_1x_1-d_2y-\beta xy_1+d_2y_1+py_1z+\frac{p}{c}(r-d_3)z-\frac{prz^2}{cm}.\end{aligned}$$

Using $s=\beta x_1y_1+d_1x_1$ and $d_2=\beta x_1$, we have

$$\begin{aligned}\frac{dL_2}{dt} &= (d_1x_1+\beta x_1y_1)(2-\frac{x}{x_1}-\frac{x_1}{x})+p(y_1-\frac{d_3-r}{c})z-\frac{prz^2}{cm}\\ &= (d_1x_1+\beta x_1y_1)(2-\frac{x}{x_1}-\frac{x_1}{x})+\frac{pd_1}{\beta}(R_0-1-\frac{\beta(d_3-r)}{cd_1})z-\frac{prz^2}{cm}.\end{aligned}$$

Using the LaSalle's invariance principle, we can obtain that E_0^z is globally asymptotically stable. □

Proposition 3.2. *Suppose that $r=d_3$. Then we have*

(i) The infection-free equilibrium E_0^{yz} is globally asymptotically stable if $R_0<1$, and it is unstable when $R_0>1$.

(ii) The immunity-inactivated infection equilibrium E_0^z is unstable as long as it appears, i.e., $R_0>1$.

Proof. (i) The characteristic equation of system (1.4) at E_0^{yz} is

$$\lambda(\lambda+d_1)(\lambda+d_1d_2(1-R_0))=0. \tag{3.6}$$

So the eigenvalues are

$$\lambda_1=0,\lambda_2=-d_1<0,\lambda_3=d_1d_2(R_0-1).$$

So if $R_0<1$, the infection-free equilibrium E_0^{yz} is locally asymptotically stable and if $R_0>1$, the equilibrium E_0^{yz} is unstable.

In order to obtain the global stability of E_0^{yz}, we construct the following Lyapunov functions:

$$L_3=x-x_0-x_0\ln\frac{x}{x_0}+y+\frac{p}{c}z+p\int_{-\tau}^{0}y(t+\theta)z(t+\theta)d\theta.$$

Taking the time derivative of L_3 along the solution of system (1.4), we have

$$\begin{aligned}\frac{dL_3}{dt} &= (1-\frac{x_0}{x})(s-\beta xy-d_1x)+\beta xy-d_2y-pyz\\ &\quad+\frac{p}{c}(cy(t-\tau)z(t-\tau)-\frac{rz^2}{m})+pyz-py(t-\tau)z(t-\tau)\\ &= -\frac{d_1(x-x_0)^2}{x}+(\beta x_0-d_2)y-\frac{prz^2}{cm}\\ &= -\frac{d_1(x-x_0)^2}{x}+d_2(R_0-1)y-\frac{prz^2}{cm}.\end{aligned}$$

Using the LaSalle's invariance principle, we can obtain that E_0^{yz} is globally asymptotically stable.

(ii)The characteristic equation of system (1.4) at E_0^z is

$$(\lambda^2 + d_1R_0\lambda + \beta^2 x_1 y_1)(\lambda - cy_1 e^{-\lambda\tau}) = 0. \tag{3.7}$$

It can be showed that there exist positive real root for the characteristic Eq (4.3), which indicates that the infection-free equilibrium E_0^z is unstable. This completes the proof. □

Proposition 3.3. *Suppose that $r > d_3$. Then we have*

(i) The infection-free equilibrium E_0^{yz} is unstable.

(ii) The immunity-inactivated infection equilibrium E_0^z is unstable.

(iii) If $R_0 < 1 + \frac{pm(r-d_3)}{rd_2}$, the infection-free equilibrium E_0^y is locally asymptotically stable, moreover if $R_0 < 1$, the infection-free equilibrium E_0^y is globally asymptotically stable; if $R_0 > 1 + \frac{pm(r-d_3)}{rd_2}$, E_0^y is unstable.

Proof. (i) The characteristic equation of system (1.4) at E_0^{yz} is

$$(\lambda + d_1)(\lambda - (r - d_3))(\lambda + d_1d_2(1 - R_0)) = 0. \tag{3.8}$$

So the eigenvalues are

$$\lambda_1 = -d_1, \lambda_2 = r - d_3, \lambda_3 = d_1d_2(R_0 - 1).$$

It follows from $\lambda_2 = r - d_3 > 0$ that the infection-free equilibrium E_0^{yz} is always unstable. So we can easily get the infection-free equilibrium E_0^{yz} is always unstable when $\tau > 0$.

(ii) The characteristic equation of system (1.4) at E_0^z is

$$(\lambda^2 + d_1R_0\lambda + \beta^2 x_1 y_1)(\lambda - (r - d_3 + cy_1 e^{-\lambda\tau})) = 0. \tag{3.9}$$

Note that $r > d_3$. It can be shown that there exist positive real root for the characteristic equation above, which indicates that the immunity-inactivated infection equilibrium E_0^z is unstable.

(iii) The characteristic equation of system (1.4) at E_0^y is

$$(\lambda + d_1)(\lambda + r - d_3)(\lambda - \frac{s\beta}{d_1} + d_2 + \frac{pm(r-d_3)}{r}) = 0. \tag{3.10}$$

The eigenvalues are

$$\lambda_1 = -d_1, \lambda_2 = -(r - d_3), \lambda_3 = \frac{s\beta}{d_1} - d_2 - \frac{pm(r-d_3)}{r}.$$

Note that

$$\frac{s\beta}{d_1} - d_2 - \frac{pm(r-d_3)}{r} = d_2(R_0 - 1) - \frac{pm(r-d_3)}{r} < 0 \Leftrightarrow R_0 < 1 + \frac{pm(r-d_3)}{rd_2}.$$

Thus, the infection-free equilibrium E_0^y is locally asymptotically stable if $R_0 < 1 + \frac{pm(r-d_3)}{rd_2}$, and E_0^y is unstable if $R_0 > 1 + \frac{pm(r-d_3)}{rd_2}$.

In order to obtain the global stability of E_0^y, we construct the following Lyapunov function:

$$L_4 = x - x_2 - x_2 \ln \frac{x}{x_2} + y + \frac{p}{c}(z - z_2 - z_2 \ln \frac{z}{z_2}) + \frac{p}{c}z + p\int_{-\tau}^{0} y(t+\theta)z(t+\theta)d\theta.$$

Taking the time derivative of L_4 along the solution of system (1.4) and using a computation process similar to that of Theorem 3.9, we have

$$\begin{aligned}\frac{dL_4}{dt} &= (1 - \frac{x_2}{x})(s - \beta xy - d_1 x) + \beta xy - d_2 y - pyz \\ &\quad + \frac{p}{c}(1 - \frac{z_2}{z})\Big(cy(t-\tau)z(t-\tau) + rz(1 - \frac{z}{m}) - d_3 z\Big) \\ &= -\frac{d_1(x - x_2)^2}{x} + d_2(R_0 - 1)y - \frac{pz_2 y(t-\tau)z(t-\tau)}{z} - \frac{rp}{cm}(z - z_2)^2.\end{aligned}$$

Thus, $\frac{dL_4}{dt} \le 0$ if $R_0 < 1$, and $\frac{dL_4}{dt} = 0$ only if $x = x_2, y = 0$ and $z = z_2$, i.e., the maximal invariant subset in $\{(x, y, z) : \frac{dL_4}{dt}\Big|_{(1.4)} = 0\}$ is the singleton $\{E_0^y\}$. As a result, E_0^y is globally asymptotically stable based on the LaSalle's invariance principle. This complete the proof. □

Remark 3.4. From Proposition 3.1 to Proposition 3.3, we can see that the delay τ does not affect the stability of infection-free equilibrium E_0^{yz}, E_0^y and immune-unactivated E_0^z equilibrium.

4. Stability of positive equilibrium and Hopf bifurcation

In this section, we take the discrete delay τ as a bifurcation parameter and show that when the positive equilibrium E_2^* loses its stability and a Hopf bifurcation appears when the delay τ passes through a critical value. We point out there also exists a Hopf bifurcation at positive equilibrium E_1^* as the delay τ passes through a critical value and the proof is similar.

The characteristic equation of system (1.4) at E_2^* is

$$\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 + (C_1\lambda^2 + C_2\lambda + C_3)e^{-\lambda\tau} = 0, \tag{4.1}$$

where

$$\begin{aligned}B_1 &= \frac{2rz_2^*}{m} - r + d_3 + d_1 + \beta y_2^*, \qquad B_2 = (d_1 + \beta y_2^*)(\frac{2rz_2^*}{m} - r + d_3) + \beta^2 x_2^* y_2^*, \\ B_3 &= (\frac{2rz_2^*}{m} - r + d_3)\beta^2 x_2^* y_2^*, \qquad C_1 = -cy_2^*, \\ C_2 &= -(d_1 + \beta y_2^*)cy_2^* + pcy_2^* z_2^*, \qquad C_3 = -cy_2^*\beta^2 x_2^* y_2^* + (d_1 + \beta y_2^*)pcy_2^* z_2^*.\end{aligned}$$

When $\tau = 0$, the characteristic equation of system (1.4) at E_2^* is

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0,$$

where

$$A_1 \equiv B_1 + C_1 = d_1 + \beta y_2^* + cy_2^* + r - d_3 > 0,$$

$$A_2 \equiv B_2 + C_2 = (d_1 + \beta y_2^*)(cy_2^* + r - d_3) + \beta^2 x_2^* y_2^* + pcy_2^* z_2^* > 0,$$
$$A_3 \equiv B_3 + C_3 = pcy_2^* z_2^*(d_1 + \beta y_2^*) + (cy_2^* + r - d_3)\beta^2 x_2^* y_2^* > 0.$$

After some calculations, we have

$$A_1A_2 - A_3 = (cy_2^* + r - d_3)(pcy_2^* z_2^* + (d_1 + \beta y_2^*)^2) + (d_1 + \beta y_2^*)(\beta^2 x_2^* y_2^* + (cy_2^* + r - d_3)^2) > 0.$$

It follows from the Routh-Hurwitz criterion that E_2^* is locally asymptotically stable when time delay is absent.

When $\tau > 0$, putting $\lambda = i\omega$ into characteristic Eq (4.1) and separating real and imaginary parts, we have

$$B_1\omega^2 - B_3 = (C_3 - C_1\omega^2)\cos(\omega\tau) + C_2\omega\sin(\omega\tau), \tag{4.2}$$

$$\omega^3 - B_2\omega = -(C_3 - C_1\omega^2)\sin(\omega\tau) + C_2\omega\cos(\omega\tau). \tag{4.3}$$

Since $\sin^2(\omega\tau) + \cos^2(\omega\tau) = 1$, squaring and adding the two Eqs (4.2) and (4.3), we have

$$\omega^6 + p_1\omega^4 + p_2\omega^2 + p_3 = 0, \tag{4.4}$$

where

$$p_1 = B_1^2 - 2B_2 - C_1^2,$$
$$p_2 = B_2^2 + 2C_1C_3 - C_2^2 - 2B_1B_3,$$
$$p_3 = B_3^2 - C_3^2.$$

Let $u = \omega^2$, Eq (4.4) becomes

$$G(u) = u^3 + p_1u^2 + p_2u + p_3 = 0. \tag{4.5}$$

If Eq (4.5) has a positive real root u, the characteristic Eq (4.1) has a purely imaginary root $i\omega = i\sqrt{u}$; otherwise, Eq (4.1) has no purely imaginary root.

Note that

$$G'(u) = 3u^2 + 2p_1u + p_2. \tag{4.6}$$

Let

$$\Delta = p_1^2 - 3p_2.$$

Then we know that $G(u)$ is monotonically increasing if $\Delta \le 0$, which indicates that Eq (4.5) has no positive root when $p_3 \ge 0$ and $\Delta \le 0$.

If $\Delta > 0$, the function $G(u)$ has two critical points

$$u^* = \frac{-p_1 + \sqrt{\Delta}}{3}, \qquad u^{**} = \frac{-p_1 - \sqrt{\Delta}}{3}.$$

Thus we know that Eq (4.5) has unique positive root u_0 with $G'(u_0) > 0$ if one of the following two conditions hold:

(H_1) $\Delta > 0$, $p_3 < 0$, $u^{**} < 0$ and $u^* > 0$;
(H_2) $\Delta > 0$, $p_3 < 0$, $u^* > 0$ and $G(u^{**}) < 0$.
Equation (4.5) has two positive roots $u_1 < u_2$ with $G'(u_1) < 0$ and $G'(u_2) > 0$ if the following assumption is satisfied:
(H_3) $\Delta > 0$, $p_3 > 0$, $u^* > 0$ and $G(u^*) < 0$.

Let $\omega_k = \sqrt{u_k}, k = 0, 1, 2$. It follows from Eqs (4.2) and (4.3) that the value of τ associated with the purely imaginary root $i\omega_k$ should satisfy

$$(B_1\omega_k^2 - B_3)(C_3 - C_1\omega_k^2) + (\omega_k^3 - B_2\omega_k)C_2\omega_k = ((C_3 - C_1\omega_k^2)^2 + C_2^2\omega_k^2)\cos(\omega_k\tau).$$

For $k = 0, 1, 2$, we define

$$\tau_n^k = \frac{1}{\omega_k}\arccos\Big(\frac{(B_1\omega_k^2 - B_3)(C_3 - C_1\omega_k^2) + (\omega_k^3 - B_2\omega_k)C_2\omega_k}{(C_3 - C_1\omega_k^2)^2 + C_2^2\omega_k^2}\Big) + \frac{2n\pi}{\omega_k}, n = 0, 1, 2\cdots. \tag{4.7}$$

Then at increasing sequences of τ values,

$$\begin{aligned}
&\tau_0^0 < \tau_1^0 < \tau_2^0 < \cdots < \tau_n^0 \cdots,\\
&\tau_0^1 < \tau_1^1 < \tau_2^1 < \cdots < \tau_n^1 \cdots,\\
&\tau_0^2 < \tau_1^2 < \tau_2^2 < \cdots < \tau_n^2 \cdots,
\end{aligned}$$

Eq (4.1) has purely imaginary roots $i\omega_k, k = 0, 1, 2$.

Now we consider the transversality conditions associated with Hopf bifurcation. Substituting $\lambda(\tau)$ into Eq (4.1) and differentiating the resulting equation in τ, we obtain

$$\begin{aligned}
\Big(\frac{d\lambda}{d\tau}\Big)^{-1} &= \frac{3\lambda^2 + 2B_1\lambda + B_2 + (2C_1\lambda + C_2)e^{-\lambda\tau} + (C_1\lambda^2 + C_2\lambda + C_3)\cdot(-\tau)e^{-\lambda\tau}}{\lambda e^{-\lambda\tau}(C_1\lambda^2 + C_2\lambda + C_3)}\\
&= \frac{(3\lambda^2 + 2B_1\lambda + B_2)e^{\lambda\tau}}{\lambda(C_1\lambda^2 + C_2\lambda + C_3)} + \frac{2C_1\lambda + C_2}{\lambda(C_1\lambda^2 + C_2\lambda + C_3)} - \frac{\tau}{\lambda}.
\end{aligned}$$

which indicates that

$$\begin{aligned}
\operatorname{sign}\Big\{\frac{d(\mathrm{Re}\lambda)}{d\tau}\Big\}\Big|_{\lambda=i\omega_k} &= \operatorname{sign}\Big\{\mathrm{Re}\Big(\frac{d\lambda}{d\tau}\Big)^{-1}\Big\}\Big|_{\lambda=i\omega_k}\\
&= \operatorname{sign}\Big\{\frac{3\omega_k^4 + 2(B_1^2 - 2B_2 - C_1^2)\omega_k^2 + (B_2^2 + 2C_1C_3 - C_2^2 - 2B_1B_3)}{(C_3 - C_1\omega_k^2)^2 + C_2^2\omega_k^2}\Big\}\\
&= \operatorname{sign}\Big\{\frac{G'(\omega_k^2)}{(C_3 - C_1\omega_k^2)^2 + C_2^2\omega_k^2}\Big\}.
\end{aligned}$$

Since $G'(u_0) > 0$, $G'(u_1) < 0$ and $G'(u_2) > 0$, then for $n = 0, 1, 2, ...$, we have

$$\operatorname{sign}\Big\{\frac{d(\mathrm{Re}\lambda)}{d\tau}\Big|_{\tau=\tau_n^k}\Big\} = \operatorname{sign}\Big\{\mathrm{Re}\Big(\frac{d\lambda}{d\tau}\Big)^{-1}\Big|_{\tau=\tau_n^k}\Big\} > 0, (k = 0, 2),$$

and

$$\operatorname{sign}\Big\{\frac{d(\mathrm{Re}\lambda)}{d\tau}\Big|_{\tau=\tau_n^k}\Big\} = \operatorname{sign}\Big\{\mathrm{Re}\Big(\frac{d\lambda}{d\tau}\Big)^{-1}\Big|_{\tau=\tau_n^k}\Big\} < 0, (k = 1).$$

Then we know that at each τ_n^0 and τ_n^2, $n = 0, 1, 2, \cdots$, a pair of characteristic roots of Eq (4.1) cross the imaginary axis to the right. At each τ_n^1, $n = 0, 1, 2, \cdots$, a pair of characteristic roots of Eq (4.1) cross the imaginary axis to the left. Then the transversality condition required by the Hopf bifurcation theorem is satisfied.

Note that $\omega_k = \sqrt{u_k}$ and $u_1 < u_2$. We have $\omega_1 < \omega_2$, which indicates that

$$\tau_n^1 - \tau_{n-1}^1 = \frac{2\pi}{\omega_1} > \frac{2\pi}{\omega_2} = \tau_n^2 - \tau_{n-1}^2, n = 0, 1, 2....$$

Then there exists a positive integer k such that

$$\tau_0^2 < \tau_0^1 < \tau_1^2 < \tau_1^1 \cdots < \tau_k^2 < \tau_{k+1}^2 < \tau_k^1.$$

We thus obtain the following result.

Theorem 4.1. *For system (1.4), we have*

(i) If $\Delta \leq 0$ and $p_3 \geq 0$ holds, E_2^* is asymptotically stable for all $\tau > 0$.

(ii) If one of the conditions (H_1) and (H_2) holds, E_2^* is asymptotically stable when $\tau \in [0, \tau_0^0)$ and unstable when $\tau > \tau_0^0$, that is system (1.4) undergoes a Hopf bifurcation at E_2^* when $\tau = \tau_0^0$.

(iii) If the condition (H_3) holds, system (1.4) undergoes a Hopf bifurcation at E_2^* along two sequences of τ values $\tau_n^{1,2}$, $n = 0, 1, 2....$ Furthermore there exists a positive integer k such that E_2^* is stable when

$$\tau \in [0, \tau_0^2) \cup (\tau_0^1, \tau_1^2) \cup \cdots\cdots \cup (\tau_{k-1}^1, \tau_k^2);$$

E_2^* is unstable when

$$\tau \in (\tau_0^2, \tau_0^1) \cup (\tau_1^2, \tau_1^1) \cup \cdots\cdots \cup (\tau_{k-1}^2, \tau_{k-1}^1) \cup (\tau_k^2, +\infty).$$

5. Direction and stability of the Hopf bifurcation

In the previous section, we know that system (1.4) undergoes a Hopf bifurcation at E_2^* along some sequences of τ values. Let τ^* be one of the Hopf bifurcation points. As pointed out in Hassard et al. [31], it is interesting to determine the direction, stability and period of these periodic solutions.

Let $\mu = \tau - \tau^*$, and then μ is new bifurcation parameter of the system. Define

$$X(t) = (x - x_2^*, y - y_2^*, z - z_2^*)^{\mathrm{T}}, X_t(\theta) = X(t + \theta), \theta \in [-\tau, 0].$$

System (1.4) may be written as:

$$X^{'}(t) = L_\mu X_t + f(X_t(.), \mu), \quad L_\mu \phi = F_1 \phi(0) + F_2 \phi(-\tau), \tag{5.1}$$

where

$$f(\phi, \mu) = \begin{bmatrix} -\beta\phi_1(0)\phi_2(0) \\ \beta\phi_1(0)\phi_2(0) - p\phi_2(0)\phi_3(0) \\ c\phi_2(-\tau)\phi_3(-\tau) - \dfrac{r}{m}{\phi_3}^2(0) \end{bmatrix},$$

$$F_1 = \begin{bmatrix} -\beta y_2^* - d_1 & -\beta x_2^* & 0 \\ \beta y_2^* & -d_2 - pz_2^* & -py_2^* \\ 0 & 0 & r - d_3 - \dfrac{2rz_2^*}{m} \end{bmatrix},$$

and

$$F_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & cz_2^* & cy_2^* \end{bmatrix}.$$

By Riesz representation theorem, there exists a matrix $\eta(\theta, \mu) : [-\tau, 0] \to \mathbb{R}^3$ whose components are bounded variation functions such that

$$L_\mu \phi = \int_{-\tau}^{0} d\eta(\theta, \mu)\phi(\theta),$$

where

$$d\eta(\theta, \mu) = F_1 \delta(\theta) d\theta + F_2 \delta(\theta + \tau) d\theta$$

and $\delta(\theta)$ is the Dirac delta function.

For $\phi \in C([-\tau, 0], R^3)$, we define

$$A(\mu)\phi(\theta) = \begin{cases} \dfrac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau, 0), \\ \displaystyle\int_{-\tau}^{0} d\eta(\xi, \mu)\phi(\xi), & \theta = 0, \end{cases}$$

and

$$R(\mu)\phi(\theta) = \begin{cases} 0, & \theta \in [-\tau, 0), \\ f(\phi, \mu), & \theta = 0. \end{cases}$$

Then system (1.4) is equivalent to the following operator equation

$$X_t^{'}(\theta) = A(\mu)X_t(\theta) + R(\mu)X_t(\theta). \tag{5.2}$$

For $\varphi \in C([0, \tau], R^3)$, we define the adjoint operator of $A(0)$ as $A^*(0)$,where

$$A^*(0)\varphi(s) = \begin{cases} -\dfrac{d\varphi(s)}{ds}, & s \in (0, \tau], \\ \displaystyle\int_{-\tau}^{0} d\eta^{\mathrm{T}}(\xi, 0)\phi(-\xi), & s = 0. \end{cases}$$

For the convenience of research, we simply write A for $A(0)$, A^* for $A^*(0)$, R for $R(0)$, $\eta(\theta)$ for $\eta(\theta, 0)$, for $\varphi \in C([0, \tau], R^3)$ and $\phi \in C([-\tau, 0], R^3)$.

Define a bilinear form as

$$\langle \varphi, \phi \rangle = \bar{\varphi}^{\mathrm{T}}(0)\phi(0) - \int_{\theta=-\tau}^{0} \int_{\xi=0}^{\theta} \bar{\varphi}^{\top}(\xi - \theta) d\eta(\theta)\phi(\xi) d\xi.$$

Let $q(\theta)$ and $q^*(s)$ to be the eigenvectors of matric A and A^* corresponding to eigenvalue $i\omega_0$ and $-i\omega_0$, respectively. Then

$$Aq(\theta) = i\omega_0 q(\theta), \qquad A^* q^*(s) = -i\omega_0 q^*(s).$$

We can choose appropriate $q(\theta)$ and $q^*(s)$ such that $< q(\theta), q^*(s) >= 1$,
where

$$q(\theta) = (1, q_2, q_3)^{\mathrm{T}} e^{i\omega_0\theta}, \quad q^*(s) = D(1, q_2^*, q_3^*)^{\mathrm{T}} e^{i\omega_0 s},$$

and

$$q_2 = \frac{\beta y_2^* + d_1 + i\omega_0}{-\beta x_2^*}, \qquad q_3 = \frac{\beta^2 y_2^* x_2^* + (\beta y_2^* + d_1 + i\omega_0)(d_2 + p z_2^* + i\omega_0)}{p y_2^* \beta x_2^*},$$
$$q_2^* = \frac{\beta y_2^* + d_1 - i\omega_0}{\beta y_2^*}, \qquad q_3^* = \frac{[\beta^2 y_2^* x_2^* + (\beta y_2^* + d_1 - i\omega_0)(d_2 + p z_2^* - i\omega_0)]e^{i\omega_0\tau^*}}{c\beta y_2^* z_2^*}.$$

Note that

$$\begin{aligned}
< q, q^* > &= \bar{D}\bar{q}^{\mathrm{T}}(0)q^*(0) - \int_{\theta=-\tau^*}^{0}\int_{s=0}^{\theta} \bar{D}\bar{q}^{\mathrm{T}}(s-\theta)d\eta(\theta)q^*(s)ds \\
&= \bar{D}(1 + \bar{q}_2 q_2^* + \bar{q}_3 q_3^* - \int_{\theta=-\tau^*}^{0}\int_{s=0}^{\theta} (1, \bar{q}_2, \bar{q}_3)e^{-(s-\theta)i\omega_0}(1, q_2^*, q_3^*)^{\mathrm{T}} e^{i\omega_0 s} ds d\eta(\theta)) \\
&= \bar{D}(1 + \bar{q}_2 q_2^* + \bar{q}_3 q_3^* - \int_{\theta=-\tau^*}^{0} (c\bar{q}_2 z^* + c q_3^* y^*)\theta e^{i\omega_0\theta} d\eta(\theta)) \\
&= \bar{D}(1 + \bar{q}_2 q_2^* + \bar{q}_3 q_3^* + (c\bar{q}_2 z^* + c q_3^* y^*) q_3^* \tau^* e^{i\omega_0\tau^*}).
\end{aligned}$$

Then we can choose $\bar{D}$ as

$$\bar{D} = [1 + \bar{q}_2 q_2^* + \bar{q}_3 q_3^* + (c\bar{q}_2 z_2^* + c q_3^* y_2^*) q_3^* \tau^* e^{i\omega_0\tau^*}]^{-1}$$

such that $< q(\theta), q^*(s) >= 1$.

According to the notations in Hassard et al. [31], we need to compute the center manifold C_0 at $\mu = 0$. Let u_t be the solution of Eq (5.1) when $\mu = 0$ and define

$$Z(t) =< q^*, u_t >, \quad W(t, 0) = u_t(0) - 2Re\{Z(t)q(\theta)\}. \tag{5.3}$$

On the center manifold C_0, we have $W(t, 0) = W(Z(t), \bar{Z}(t), \theta)$, where

$$W(Z, \bar{Z}, \theta) = W_{20}(\theta)\frac{Z^2}{2} + W_{11}(\theta)Z\bar{Z} + W_{02}(\theta)\frac{\bar{Z}^2}{2} + \cdots,$$

Z and $\bar{Z}$ are local coordinates for center manifold C_0 in the direction of q^* and $\bar{q}^*$. Note that if X_t is real, W is real. We only consider the real solutions. For the solution of the Eq (5.1) $X_t \in C_0$, we have

$$\dot{Z}(t) = i\omega Z + \bar{q}^*(\theta)f(0, W(Z, \bar{Z}, \theta)) + 2\mathrm{Re}\{Zq(\theta)\} \triangleq i\omega Z + \bar{q}^*(0)f_0(Z, \bar{Z}).$$

Now we rewrite this equation as $\dot{Z}(t) = i\omega Z + g(Z, \bar{Z})$, where

$$g(Z, \bar{Z}) = \bar{q}^*(0)f_0(Z, \bar{Z}) = g_{20}\frac{Z^2}{2} + g_{11}Z\bar{Z} + g_{02}\frac{\bar{Z}^2}{2} + g_{21}\frac{Z^2\bar{Z}}{2} + \cdots. \tag{5.4}$$

Note that $u_t(\theta) = W(t,\theta) + Zq(\theta) + \bar{Z}\bar{q}(\theta)$. We have

$$\begin{aligned}
&g(Z,\bar{Z}) = \bar{q}^*(0)f_0(Z,\bar{Z})\\
&= \bar{D}\{-\beta u_{1t}(0)u_{2t}(0) + q_2^*(\beta u_{1t}(0)u_{2t}(0) - pu_{2t}(0)u_{3t}(0)) + q_3^*(cu_{2t}(-\tau)u_{3t}(-\tau) - \frac{r}{m}u_{3t}^2(0))\}\\
&= \bar{D}\Big\{(q_2^* - \beta)(Z + \bar{Z} + W_{20}^{(1)}(0)\frac{Z^2}{2} + W_{11}^{(1)}(0)Z\bar{Z} + W_{02}^{(1)}(0)\frac{\bar{Z}^2}{2})(q_2Z + \bar{q}_2\bar{Z} + W_{20}^{(3)}(0)\frac{Z^2}{2}\\
&+ W_{11}^{(3)}(0)Z\bar{Z} + W_{02}^{(3)}(0)\frac{\bar{Z}^2}{2}) - pq_2^*(q_2Z + \bar{q}_2\bar{Z} + W_{20}^{(2)}(0)\frac{Z^2}{2} + W_{11}^{(2)}(0)Z\bar{Z} + W_{02}^{(2)}(0)\frac{\bar{Z}^2}{2})(q_3Z\\
&+ \bar{q}_3\bar{Z} + W_{20}^{(3)}(0)\frac{Z^2}{2} + W_{11}^{(3)}(0)Z\bar{Z} + W_{02}^{(3)}(0)\frac{\bar{Z}^2}{2}) + q_3^*c(q_2Ze^{-i\omega_0\tau} + \bar{q}_2\bar{Z}e^{-i\omega\tau} + W_{20}^{(2)}(-\tau)\frac{Z^2}{2}\\
&+ W_{11}^{(2)}(-\tau)Z\bar{Z} + W_{02}^{(2)}(-\tau)\frac{\bar{Z}^2}{2})(q_4Ze^{-i\omega_0\tau} + \bar{q}_4\bar{Z}e^{-i\omega\tau} + W_{20}^{(3)}(-\tau)\frac{Z^2}{2} + W_{11}^{(3)}(-\tau)Z\bar{Z}\\
&+ W_{02}^{(3)}(-\tau)\frac{\bar{Z}^2}{2}) - \frac{r}{m}q_3^*(q_3Z + \bar{q}_3\bar{Z} + W_{20}^{(3)}(0)\frac{Z^2}{2} + W_{11}^{(3)}(0)Z\bar{Z} + W_{02}^{(3)}(0)\frac{\bar{Z}^2}{2})^2\Big\}.
\end{aligned}$$

Comparing the coefficients with Eq (5.4), we have

$$\begin{aligned}
g_{20} &= 2\bar{D}\{(q_2^* - \beta)q_2 + q_3^*q_2q_3ce^{-2i\omega\tau} - q_2^*q_2q_3p - \frac{r}{m}q_3^*q_3^2\},\\
g_{11} &= 2\bar{D}\{(q_2^* - \beta)\mathrm{Re}\{q_2\} + q_3^*c\mathrm{Re}\{\bar{q}_2q_3\}e^{-2i\omega\tau} - q_2^*p\mathrm{Re}\{\bar{q}_2q_3\} - \frac{r}{m}q_3^*q_3\bar{q}_3\},\\
g_{02} &= 2\bar{D}\{(q_2^* - \beta)\bar{q}_2 + q_3^*\bar{q}_2\bar{q}_3ce^{-2i\omega\tau} - q_2^*\bar{q}_2\bar{q}_3p - \frac{r}{m}q_3^*\bar{q}_3{}^2\},\\
g_{21} &= 2\bar{D}\Big\{(q_2^* - \beta)(W_{11}^{(2)}(0) + \frac{W_{20}^{(2)}(0)}{2} + \frac{\bar{q}_2W_{20}^{(1)}(0)}{2} + q_2W_{11}^{(1)}(0))\\
&\quad + q_3^*c(q_2e^{-i\omega\tau}W_{11}^{(3)}(-\tau) + q_3e^{-i\omega\tau}W_{11}^{(2)}(-\tau) + \frac{\bar{q}_2W_{20}^{(3)}(-\tau)}{2}e^{-i\omega\tau} + \frac{\bar{q}_3W_{20}^{(2)}(-\tau)}{2}e^{-i\omega\tau})\\
&\quad - q_2^*p(q_2W_{11}^{(3)}(0) + \frac{\bar{q}_2W_{20}^{(3)}(0)}{2} + \frac{\bar{q}_3W_{20}^{(2)}(0)}{2} + q_3W_{11}^{(2)}(0))\\
&\quad - \frac{r}{m}q_3^*(2q_3W_{11}^{(3)}(0) + \bar{q}_3W_{20}^{(3)}(0))\Big\}.
\end{aligned} \tag{5.5}$$

It remains to compute $W_{11}(0)$ and $W_{20}(0)$ in g_{21}. From Eqs (5.2) and (5.3), we have

$$\dot{W} = \dot{x}_t - \dot{Z}q - \overline{\dot{Z}q} = \begin{cases} AW - 2\mathrm{Re}\{\bar{q}^*(0)f_0q(\theta)\}, & \theta \in [-1,0),\\ AW - 2\mathrm{Re}\{\bar{q}^*(0)f_0q(0)\} + f_0, & \theta = 0. \end{cases} \tag{5.6}$$

We rewrite the Eq (5.6) as

$$\dot{W} \triangleq AW + H(Z,\bar{Z},\theta) \tag{5.7}$$

where

$$H(Z,\bar{Z},\theta) = H_{20}(\theta)\frac{Z^2}{2} + H_{11}(\theta)Z\bar{Z} + H_{02}(\theta)\frac{\bar{Z}^2}{2} + \cdots.$$

Thus

$$(A - 2i\omega)W_{20}(\theta) = -H_{20}(\theta), \quad AW_{11}(\theta) = -H_{11}(\theta). \tag{5.8}$$

From Eq (5.7), we know that for $\theta \in [-1, 0)$

$$H(Z, \bar{Z}, \theta) = -\bar{q}^*(0) f_0 q(\theta) - q^*(0) \bar{f}_0 \bar{q}(\theta) = -gq(\theta) - \bar{g}\bar{q}(\theta).$$

Comparing the coefficients with Eq (5.8), we obtain

$$H_{20}(\theta) = -g_{20} q(\theta) - \bar{g}_{20} \bar{q}(\theta), \tag{5.9}$$

$$H_{11}(\theta) = -g_{11} q(\theta) - \bar{g}_{11} \bar{q}(\theta). \tag{5.10}$$

From Eqs (5.8) and (5.9) and the definition of A, we have

$$\dot{W}_{20}(\theta) = 2i\omega W_{20}(\theta) + g_{20} q(\theta) + \bar{g}_{02} \bar{q}(\theta),$$

where $q(\theta) = (1, q_2, q_3)^{\mathrm{T}} e^{i\theta\omega\tau}$. Hence

$$W_{20}(\theta) = \frac{ig_{20}}{\omega} e^{i\omega\theta} q(0) + \frac{i\bar{g}_{02}}{3\omega} e^{-i\omega\theta} \bar{q}(0) + E_{20} e^{2i\omega\theta}$$

where

$$E_{20} = 2(2i\omega - F_1 - F_2 e^{-2i\omega\tau})^{-1} \begin{bmatrix} -\beta q_2 \\ \beta q_2 - p q_2 q_3 \\ c q_2 q_3 e^{-2i\omega\tau} - \dfrac{r}{m} q_3^2 \end{bmatrix}.$$

Similarly, from Eqs (5.8) and (5.10) we obtain

$$W_{11}(\theta) = \frac{ig_{11}}{\omega} e^{i\omega\theta} q(0) + \frac{i\bar{g}_{11}}{\omega} e^{-i\omega\theta} \bar{q}(0) + E_{11},$$

where

$$E_{11} = 2(-F_1 - F_2)^{-1} \begin{bmatrix} -\beta Re\{q_2\} \\ \beta Re\{q_2\} - p Re\{q_2 \bar{q}_3\} \\ c Re\{q_2 \bar{q}_3\} - \dfrac{r}{m} \{q_3^2\} \end{bmatrix}.$$

So far, we have calculated g_{20}, g_{11}, g_{02}, g_{21} in Eq (5.5) and then we can obtain

$$\begin{aligned} c_1(0) &= \frac{i}{2\omega}\Big(g_{11} g_{20} - 2 \mid g_{11} \mid^2 - \frac{\mid g_{02} \mid^2}{3}\Big) + \frac{g_{21}}{2}, \\ \nu_2 &= -\frac{\mathrm{Re}(c_1(0))}{\mathrm{Re}(\lambda'(\tau^*))}, \\ \beta_2 &= 2\mathrm{Re}(c_1(0)), \\ T_2 &= \frac{-(\mathrm{Im}\{c_1(0)\} + \nu_2 \mathrm{Im}\{\lambda'(\tau^*)\})}{\omega}. \end{aligned} \tag{5.11}$$

It is well known that ν_2 and β_2 will determine the direction and stability of the Hopf bifurcation, and T_2 determines the period of the bifurcated periodic solutions, respectively. In particular, the Hopf bifurcation is supercritical (subcritical) if $\nu_2 > 0 (\nu_2 < 0)$, and the bifurcated periodic solutions exist for $\tau > \tau_0 (\tau < \tau_0)$. The bifurcated periodic solutions are stable (unstable) if $\beta_2 < 0$ ($\beta_2 > 0$) and the period will become longer (shorter) if $T_2 > 0$ ($T_2 < 0$).

6. Numerical simulations

In this section, we carry out some numerical simulations to display some qualitative behaviours of system (1.4). Table 1 lists the values or ranges of parameters for system (1.4) referring to [21].

We first study the effect of logistic growth on the dynamics of system (1.4). According to the ranges of parameters in Table 1, we take the following parameters

$$s = 10, \beta = 0.02, d_1 = 0.2, d_2 = 0.5, d_3 = 0.2, p = 0.05, c = 0.4, m = 20. \tag{6.1}$$

Figure 1 presents the bifurcation diagrams of the solutions for system (1.4) with respect to τ and different logistic growth rate r. One can see that the positive equilibrium E_1^* of system (1.4) is local asymptotically stable when $\tau < \tau^* = 0.8$ and the bifurcated periodic solutions occurs through Hopf bifurcations when $\tau > \tau^*$. Similarly, the positive equilibrium $E_2^* = (49.42, 0.12, 9.77)$ of system (1.4) is local asymptotically stable when $\tau = 8 < \tau^* = 8.655$ and the bifurcated periodic solutions occur through Hopf bifurcations when $\tau = 9 > \tau^*$. At the same time, one can note that, except $r = 0$, the values of Hopf bifurcation points increase with the increase of r. On the other hand, the amplitude of the bifurcated periodic solution increase with the increase of time delay τ and decrease with the increase of r.

Table 1. Meanings and units of parameters.

Parameters	Descriptions	Ranges	Units
s	Source rate of uninfected cell	1–10	cells $\text{mL}^{-1}\text{day}^{-1}$
β	Virus-to-cell infection rate	0.00025–0.5	mL $\text{virion}^{-1}\text{day}^{-1}$
p	Predation rate of infection cell by CTLs	$1–4.048 \times 10^{-4}$	mL $\text{cell}^{-1}\text{day}^{-1}$
r	Breath rate of CTLs	0.0051–3.912	mL $\text{cell}^{-1}\text{day}^{-1}$
m	Capacity of immune cells	6.25–235999.9	mL cell^{-1}
c	Development rate of CTLs	0.0051–3.912	mL $\text{cell}^{-1}\text{day}^{-1}$
d_1	Death rate of uninfected cell	0.007–0.1	day^{-1}
d_2	Death rate of infected cell	0.2–0.3	day^{-1}
d_3	Death rate of immune cell	0.001–0.3	day^{-1}

Figure 2 presents phase diagrams of the solutions for system (1.4) with $r = 0.3$ and different values of τ. One can see that the positive equilibrium $E_2^* = (49.42, 0.12, 9.77)$ is local asymptotically stable when $\tau = 8 < \tau^* = 8.655$ and the bifurcated periodic solutions occur through Hopf bifurcations when $\tau = 9 > \tau^*$. Furthermore, using the given parameter values (6.1), we can obtain $c_1(0) = -19.651 + 26.769i$ by some calculations and then we know that $\mu_2 > 0, \beta_2 < 0, T_2 < 0$ by (5.11). According to the conclusion in [31], we know that the Hopf bifurcation at $\tau^* = 8.655$ is supercritical, and the bifurcating periodic solution is stable.

In order to investigate the stability switch of equilibrium, we take the following parameters

$$s = 10, \beta = 0.2, d_1 = 0.2, d_2 = 0.3, d_3 = 0.2, p = 0.05, c = 0.5, r = 1.6, m = 50. \tag{6.2}$$

We obtain there exists positive equilibrium $E_2^* = (18.8775, 1.6487, 69.5102)$ and the characteristic equation of system (1.4) have two pure virtual roots $\omega_1 = 0.4464$ and $\omega_2 = 1.4748$. Then by (4.7) we

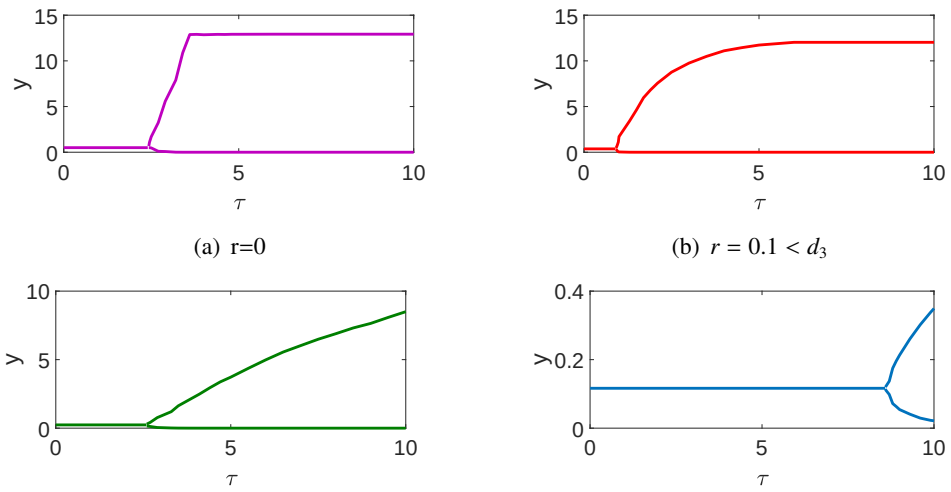
get

$$\tau_0^1 = 0.8365, \tau_1^1 = 8.1911, \tau_2^1 = 12.4513;$$

and

$$\tau_0^2 = 3.9309, \tau_1^2 = 14.9113.$$

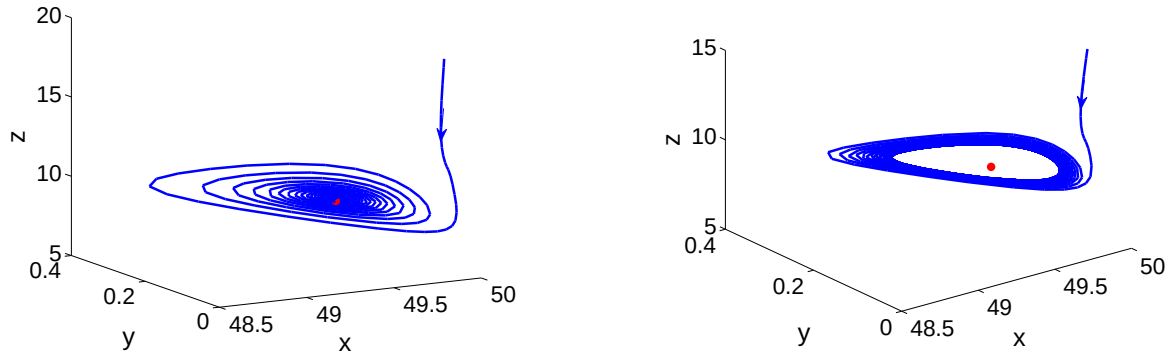
Noting that $\tau_1^2 > \tau_2^1$, we know that E_2^* is asymptotically stable when $\tau \in [0, \tau_0^1) \cup (\tau_0^2, \tau_1^1)$ and is unstable when $\tau \in (\tau_0^1, \tau_0^2) \cup (\tau_1^1, +\infty)$. Figure 3 presents time series diagrams of the solutions for system (1.4) with different values of τ. One can see that there exists stability switch of equilibrium E_2^* as τ increases and some periodic solutions are bifurcated by Hopf bifurcation.



(a) r=0 (b) $r = 0.1 < d_3$

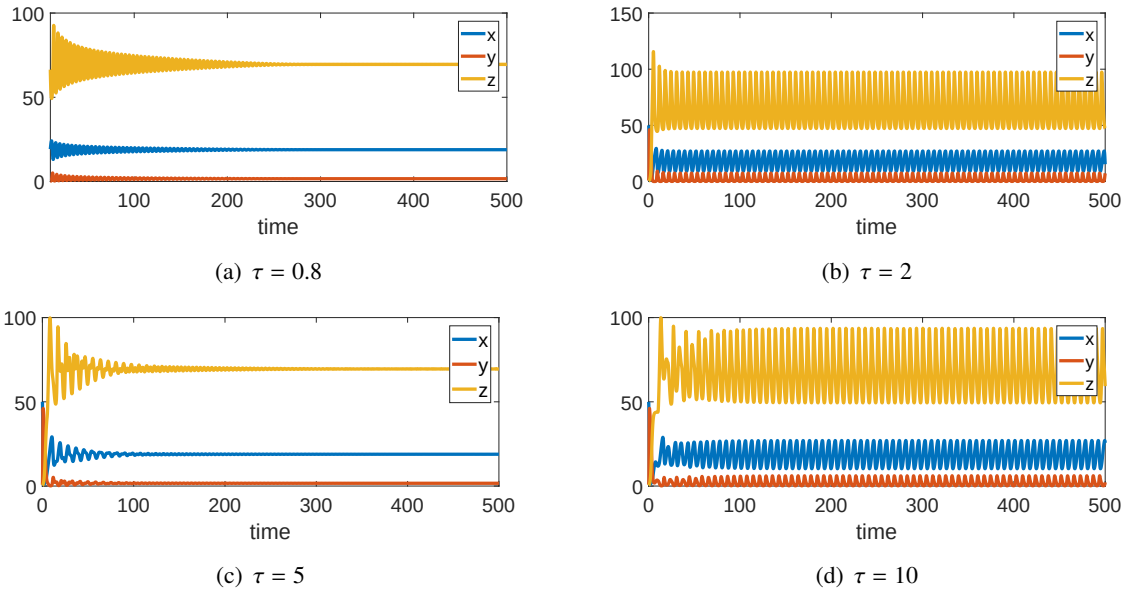
(c) $r = d_3$ (d) $r = 0.3 > d_3$

Figure 1. Bifurcation diagrams of system (1.4) with respect to τ and different r. Parameter values are given by (6.1).



(a) $r = 0.3, \tau = 8$ (b) $r = 0.3, \tau = 9$

Figure 2. Phase diagrams of the solutions for system (1.4) with $r = 0.3$ and different values of τ. The other parameters values are given by (6.1).



(a) $\tau = 0.8$ (b) $\tau = 2$

(c) $\tau = 5$ (d) $\tau = 10$

Figure 3. Time series diagrams of the solutions for system (1.4) showing stability switch with increase of τ. Parameter values are given by (6.2).

Table 2. Global properties of system (1.4) with $\tau > 0$.

Case	Conditions	Equilibria and its stability
$r = 0$	$R_0 < 1$	E_0^{yz} is GAS
	$1 < R_0 < 1 + \frac{\beta d_3}{cd_1}$	E_0^{yz} is US, E_0^z is GAS
	$R_0 > 1 + \frac{\beta d_3}{cd_1}$	E_0^{yz} and E_0^z are US, E^* (Hopf)
$r < d_3$	$R_0 < 1$	E_0^{yz} is GAS
	$1 < R_0 < 1 + \frac{\beta(d_3-r)}{cd_1}$	E_0^{yz} is US, E_0^z is GAS
	$R_0 > 1 + \frac{\beta(d_3-r)}{cd_1}$	E_0^{yz} and E_0^z are US, E^* (Hopf)
$r = d_3$	$R_0 < 1$	E_0^{yz} is GAS
	$R_0 > 1$	E_0^{yz} and E_0^z are US, E^* (Hopf)
$r > d_3$	$R_0 < 1$	E_0^{yz} is US, E_0^y is GAS
	$1 < R_0 < 1 + \frac{pm(r-d_3)}{rd_2}$	E_0^{yz} and E_0^z are US, E_0^y is GAS
	$R_0 > 1 + \frac{pm(r-d_3)}{rd_2}$	E_0^{yz} , E_0^z and E_0^y are US, E^* (Hopf)

Note: GAS means globally asymptotically stable; US means unstable.

7. Conclusions and discussions

In this paper, a viral infection model with self-proliferation of cytotoxic T lymphocytes (CTLs) and activation time delay of immune cells is proposed. We mainly focus on two topics. First, we study the global dynamics of system (1.4) through constructing appropriate Lyapunov functions. Then we examine the impact of the activation time delay of immune cells on the existence of periodic solutions. The global dynamical properties of system (1.4) can be summarized in the following

Table 2. Numerical simulations verify the theoretical analyses. In particular, we find that for different values of the delay in CTL response, the system can stabilize at the positive equilibrium when the delay is small, or stabilize at a stable periodic oscillation when the delay is large. The amplitudes of bifurcated periodic solutions increase with the increase of activation time delay of immune cells and decrease with the increase of r (Figure 1). It is also found that there exists stability switch phenomenon under some conditions (Figure 3). The results indicate that the self-proliferation intensity and activation time delay of immune cells can significantly affect the kinetics of viral infection.

Some aspects of the viral infection problem remain to be studied in the future. For instance, we plan to extend our analysis to global Hopf bifurcation analysis. Some other factors that influence the dynamics of viral infection including the heterogeneity of space and movement of cells may be investigated.

Acknowledgments

The authors would like to thank the reviewers and the editor for their careful reading, helpful comments and suggestions that greatly improved the paper. This work is supported by the National Natural Science Foundation of China (Grant Nos. 11701472, 11771448, 11871403).

Conflict of interest

The authors declare that they have no conflict of interest.

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