Journal of Applied Analysis and Computation
Volume 7, Number 2, May 2017, 532–553
Website:http://jaac-online.com/
DOI:10.11948/2017033

STABILITY AND BIFURCATION ANALYSIS OF A VIRAL INFECTION MODEL WITH DELAYED IMMUNE RESPONSE*

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Abstract In this paper, we study a viral infection model with an immunity time delay accounting for the time between the immune system touching antigenic stimulation and generating CTLs. By calculation, we derive two thresholds to determine the global dynamics of the model, i.e., the reproduction number for viral infection R_0 and for CTL immune response R_1. By analyzing the characteristic equation, the local stability of each feasible equilibrium is discussed. Furthermore, the existence of Hopf bifurcation at the CTL-activated infection equilibrium is also studied. By constructing suitable Lyapunov functionals, we prove that when $R_0 \leq 1$, the infection-free equilibrium is globally asymptotically stable; when $R_0 > 1$ and $R_1 \leq 1$, the CTL-inactivated infection equilibrium is globally asymptotically stable; Numerical simulation is carried out to illustrate the main results in the end.

Keywords Immunity time delay, thresholds, CTL immune response, Hopf bifurcation, global stability.

1. Introduction

Viral infection models have received great attention in recent years [5, 10, 11]. In most virus infections, cytotoxic T lymphocytes play a key role in antiviral defense by attacking virus infected cells. Therefore, in the last few decades, more attention has been paid to the population dynamics of viral infection with CTL response [13,18,21]. In [18], a basic mathematical model describing HIV-1 infection dynamics with CTL immune response is of the form:

$$\begin{aligned} x'(t) &= s - dx(t) - \beta x(t)v(t), \\ y'(t) &= \beta x(t)v(t) - ay(t) - py(t)z(t), \\ v'(t) &= ky(t) - uv(t), \\ z'(t) &= cy(t)z(t) - bz(t), \end{aligned} \tag{1.1}$$

where $x(t)$, $y(t)$, $v(t)$ and $z(t)$ represent the densities of uninfected target cells, infected cells, virions and CTL cells at time t, respectively. Uninfected cells are produced at rate s and die at rate d, and become infected at rate βxv, where β is the constant rate describing the infection process; infected cells are produced at

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*This study was supported by the the Natural Science Foundation of China(11371368).

rate βxv and die at rate ay; free virions are produced from infected cells at rate ky and are removed at rate uv. The parameter p accounts for the strength of the lytic component. The parameter b is the death rate for CTL cells, cyz describes the rate of CTL immune response activated by the infected cells.

In (1.1), the parasite-induced host mortality (parasite virulence) and the reproduction rate of the parasite are assumed to be independent of the infecting parasite dose. In fact, many experiments suggest that, for microparasitic infections, parasitic virulence may increase with the parasite dose, whereas the reproduction rate of the parasite within the host tends to be negatively correlated with the parasite dose [3,7,8,12,14]. Rogeoes et al. [12] proposed a sigmoidal infection model with the dose-dependent virulence in the form of $(d+\alpha v)y$ and the dose-dependent parasite reproduction rate in the form of $c_{max}(1-v/(LD))y$, where c_{max}, α, LD are positive constants and LD denotes the lethal dose that immediately kills a host.

Noting that it is important to choose the infectious rate in modeling viral infection dynamics, since it may allow us to have a more reasonable qualitative description for the dynamics. Experiments reported in [3,12] strongly suggested that the infection rate of the microparasitic infections is an increasing function of the parasite dose, and is usually sigmoidal and shape (see, e.g., [12]). In [14], a more general saturation infection rate $\beta xv^q/(1+\alpha v^p)$ was suggested by Song and Neumann, where q, p and α are positive constants. For $p=1$ and $q=1$, the infectious rate becomes monotone and describes the saturation effect(see, e.g., [9,19]).

Time delays can not be ignored in virus infection models [1,15,16,22,23]. In (1.1), we note that the process of the producing new virus was assumed to occur instantaneously. This is not biologically sensible. In fact, antigenic stimulation generating CTLs may need a period of time τ, i.e. the CTL response at time t may depend on the population of antigen at a previous time $t-\tau$. Kaifa Wang et al. [17] studied the effects of the time delay for immune response on a three-dimensional system with $\dot{z}=cy(t-\tau)-bz$. Assuming that the production of CTLs also depends on the population of CTL cells, Canabarro et al. [2] investigated the effects of a time delay on a four-dimensional system with $\dot{z}=cy(t-\tau)z(t-\tau)-bz$.

Motivated by the works of Nowak and Bangham [18], Regoes et al. [12] and Canabarro et al. [2], in this paper, we are concerned about the effect of time delay and saturation infection rate on the dynamics of a viral infection model. The model is given by

$$
\begin{aligned}
x'(t) &= s - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)},\\
y'(t) &= \frac{\beta x(t)v(t)}{1+\alpha v(t)} - (a+\delta v(t))y(t) - py(t)z(t),\\
v'(t) &= (k-qv(t))y(t) - uv(t),\\
z'(t) &= cy(t-\tau)z(t-\tau) - bz(t),
\end{aligned}
\tag{1.2}
$$

where τ is the time delay of CTL response; δvy represents the dose-dependent virulence and $(k-qv)y$ represents the dose-dependent reproduction rates, respectively. δ and q are positive constants. The initial conditions for system (1.2) take the form:

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

where

$$(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([-\tau, 0], R^4_+),$$
$$R^4_+ = (x_1, x_2, x_3, x_4 : x_i \geq 0, i = 1, 2, 3, 4).$$

This paper is organized as follows. In Section 2, by analyzing the corresponding characteristic equations, we study the local stability of an infection-free equilibrium and a CTL-inactivated infection equilibrium of system (1.2). In Section 3, we discuss the local stability and the existence of Hopf bifurcations at the CTL-activated infection equilibrium. In Section 4, the formulate determining the direction of the Hopf bifurcations on the center manifold are obtained by using the normal form theory and the center manifold theorem due to Hassard et al. [4]. In Section 5, by constructing suitable Lyapunov functionals, we discuss the global stability of the infection-free equilibrium and the CTL-inactivated infection equilibrium, respectively. In Section 6, numerical simulation is carried out to illustrate the main results.

2. Local stability

In this section, by analyzing the corresponding characteristic equations, we discuss the local stability of the infection-free equilibrium and the CTL-inactivated infection equilibrium, respectively.

Clearly, system (1.2) has an infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$, where $x_0 = s/d$.

Let $X = (y, v, z, x)^T$. The system (1.2) can be written to the following form:

$$\frac{dX}{dt} = F(X) - V(x), \tag{2.1}$$

where

$$F(X) = \begin{pmatrix} \frac{\beta x v}{1+\alpha v} \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad V(X) = \begin{pmatrix} (a + \delta v)y + pyz \\ uv - (k - qv)y \\ bz - cy(t-\tau)z(t-\tau) \\ dx + \frac{\beta x v}{1+\alpha v} - s \end{pmatrix}.$$

The Jacobian matrix of $F(X)$ at E_0 is as follows:

$$DF(E_0) = \begin{pmatrix} 0 & \beta x_0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad DV(E_0) = \begin{pmatrix} a & 0 & 0 & 0 \\ -k & u & 0 & 0 \\ 0 & 0 & b & 0 \\ 0 & \beta x_0 & 0 & d \end{pmatrix}.$$

Let

$$F = \begin{pmatrix} 0 & \beta s/d & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} a & 0 & 0 \\ -k & u & 0 \\ 0 & 0 & b \end{pmatrix}.$$

It follows that

$$V^{-1} = \begin{pmatrix} \frac{1}{a} & 0 & 0 \\ \frac{k}{au} & \frac{1}{u} & 0 \\ 0 & 0 & 1/b \end{pmatrix}, \quad FV^{-1} = \begin{pmatrix} \frac{ks\beta}{aud} & \frac{\beta s}{du} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Therefore, the spectral radius of matrix FV^{-1} is the basic reproduction number for viral infection of system (1.2), it follows that

$$R_0 = \frac{ks\beta}{aud}. \tag{2.2}$$

Define the basic reproduction number for CTL immune response as follows:

$$R_1 = \frac{kcus\beta(cu+qb)}{[ud(cu+qb+\alpha kb)+ku\beta b][a(cu+qb)+k\delta b]}. \tag{2.3}$$

If $R_1 \leq 1 < R_0$, $k - qv_1 > 0$, system (1.2) has a CTL-inactivated infection equilibrium $E_1(x_1, y_1, v_1, 0)$ besides the equilibrium E_0, where

$$x_1 = \frac{u(1+\alpha v_1)(a+\delta v_1)}{\beta(k-qv_1)}, \quad y_1 = \frac{uv_1}{k-qv_1},$$

and

$$v_1 = \frac{-U + \sqrt{U^2 + 4aud(du\alpha\delta + u\beta\delta)(R_0 - 1)}}{2(du\alpha\delta + u\beta\delta)}, \tag{2.4}$$

where

$$U = du\delta + adu\alpha + a\beta u + qs\beta.$$

If $R_1 > 1$, system (1.2) has a CTL-activated infection equilibrium $E_2(x_2, y_2, v_2, z_2)$, where

$$x_2 = \frac{s(1+\alpha v_2)}{d(1+\alpha v_2)+\beta v_2}, \quad y_2 = \frac{b}{c}, \quad v_2 = \frac{kb}{cu+qb}, \quad z_2 = \frac{(a+\delta v_2)(R_1-1)}{p}.$$

From (2.2) and (2.3), it is easy to prove that $R_0 > R_1$ always holds.

Theorem 2.1. *If $R_0 \leq 1$, the infection-free equilibrium E_0 of system (1.2) is locally asymptotically stable.*

Proof. The characteristic equation of system (1.2) at E_0 is as follows:

$$(\lambda + d)(\lambda + b)[\lambda^2 + (a+u)\lambda + au - \frac{k\beta s}{d}] = 0. \tag{2.5}$$

For $R_0 < 1$, that is $au - k\beta s/d > 0$. It is easy to prove that all roots of equation (2.5) have negative real parts. By Routh-Hurwitz criterion, the infection-free equilibrium E_0 of system (1.2) is locally asymptotically stable. This completes the proof. □

Lemma 2.1. *$R_1 - 1$ has the same sign as $y_1 - y_2$.*

Proof. From the first equation of system (1.2), we derive that

$$x_2 - x_1 = \frac{\beta s(v_1 - v_2)}{[d(1+\alpha v_2) + \beta v_2][d(1+\alpha v_1) + \beta v_1]}. \tag{2.6}$$

It is clear that $x_2 - x_1$ has the same sign as $v_1 - v_2$.

Noting that the expression of v_1 is equivalent to the following equation

$$(du\alpha\delta + u\beta\delta)v_1^2 + (du\delta + adu\alpha + a\beta u + qs\beta)v_1 + adu - ks\beta = 0. \tag{2.7}$$

From (2.7), it is clear to show that

$$\frac{s\beta(k - qv_1)}{u[d(1+\alpha v_1) + \beta v_1](a + \delta v_1)} = 1.$$

Therefore, we have

$$\begin{aligned} R_1 - 1 &= \frac{\beta s}{u[d(1+\alpha v_2) + \beta v_2]} \frac{k - qv_2}{a + \delta v_2} - \frac{\beta s}{u[d(1+\alpha v_1) + \beta v_1]} \frac{k - qv_1}{a + \delta v_1} \\ &= \frac{\beta s \Big\{ k(ad\alpha + a\beta + d\delta) + adq + (d\alpha\delta + \beta\delta)[kv_1 + (k - qv_1)v_2] \Big\} (v_1 - v_2)}{u(a+\delta v_1)(a + \delta v_2)[d(1 + av_1) + \beta v_1][d(1 + av_2) + \beta v_2]}. \end{aligned}$$

So, $R_1 - 1$ has the same sign as $v_1 - v_2$.

Again from the third equation of system (1.2), we derive that

$$y_1 - y_2 = \frac{uv_1}{k - qv_1} - \frac{uv_2}{k - qv_2} = \frac{ku(v_1 - v_2)}{(k - qv_1)(k - qv_2)}.$$

Therefore, the expressions $v_1 - v_2$ has the same sign as $y_1 - y_2$. This completes the proof. □

Theorem 2.2. *If $R_1 \leq 1 < R_0$, the CTL-inactivated infection equilibrium E_1 of system (1.2) is locally asymptotically stable.*

Proof. The characteristic equation of system (1.2) at E_1 is as follows:

$$(\lambda + b - cy_1 e^{-\lambda\tau})(\lambda^3 + A\lambda^2 + B\lambda + C) = 0, \tag{2.8}$$

where

$$\begin{aligned} A =& qy_1 + u + a + \delta v_1 + \frac{s}{x_1} > 0, \\ B =& (\frac{s}{x_1} + \delta v_1)(qy_1 + u) + (a + \delta v_1)\frac{s}{x_1} + aqy_1 + \frac{a\delta uv_1^2}{1 + \alpha v_1} + \frac{au\alpha v_1}{1 + \alpha v_1} > 0, \\ C =& \frac{s}{x_1}(a + \delta v_1)(qy_1 + u) + \delta uv_1 \frac{s}{x_1} > 0. \end{aligned}$$

We firstly consider the following equation:

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0. \tag{2.9}$$

Since

$$\begin{aligned} AB - C =& \frac{s}{x_1}(qy_1 + u + \frac{s}{x_1})(qy_1 + u) + (qy_1 + u + a + \delta v_1 + \frac{s}{x_1})\delta v_1 qy_1 \\ &+ (qy_1 + u + a + \delta v_1)\delta uv_1 + (qy_1 + u + a + \delta v_1 + \frac{s}{x_1})\frac{au\alpha v_1}{1 + \alpha v_1} \\ &+ (qy_1 + u + a + \delta v_1 + \frac{s}{x_1})[aqy_1 + (a + \delta v_1)\frac{s}{x_1} + \frac{a\delta uv_1^2}{1 + \alpha v_1}] > 0. \end{aligned}$$

Therefore, by Routh-Hurwitz criterion, all roots of equation (2.9) have negative real parts. Now, we discuss the distribution of the roots of the following equation

$$\lambda + b - cy_1 e^{-\lambda\tau} = 0. \tag{2.10}$$

Denote

$$F(\lambda) = \lambda + b - cy_1 e^{-\lambda\tau} = 0.$$

If $i\omega(\omega > 0)$ is a root of Eq. (2.10), separating real and imaginary parts, it follows that

$$\begin{cases} b = cy_1 cos\omega\tau, \\ -\omega = cy_1 \sin\omega\tau. \end{cases} \tag{2.11}$$

Squaring and adding the two equations of (2.11), we obtain that

$$\omega^2 = (b + cy_1)(b - cy_1). \tag{2.12}$$

Therefore, ω^2 has the same sign as $b - cy_1$. Again from Lemma 2.1, we have ω^2 has the same sign as $R_1 - 1$. When $R_1 < 1$, we derive that Eq. (2.12) has no positive roots. Noting that E_1 is globally asymptotically stable when $\tau = 0$, by general theory on characteristic equations of delay differential equations from Kuang [6, Theorem 3.4.1], we see that E_1 is always locally asymptotically stable. This completes the proof. □

3. Hopf bifurcation

In this section, we shall study the existence of the Hopf bifurcation at the activated infection equilibrium $E_2(x_2, y_2, v_2, z_2)$.

The characteristic equation of system (1.2) at the CTL-activated infection equilibrium E_2 is of the form

$$\lambda^4 + p_3\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 - (q_3\lambda^3 + q_2\lambda^2 + q_1\lambda + q_0)e^{-\lambda\tau} = 0, \tag{3.1}$$

where

$$\begin{aligned}
p_3 =& qy_2 + u + b + \frac{s}{x_2} + (s - dx_2)\frac{c}{b}, \\
p_2 =& [\frac{s}{x_2} - (dx_2 - s)\frac{c}{b}](qy_2 + u + b) + b(qy_2 + u) \\
& - \frac{s}{x_2}(dx_2 - s)\frac{c}{b} + (k - qv_2)[\delta y_2 - \frac{\beta x_2}{(1+\alpha v_2)^2}], \\
p_1 =& b[\frac{s}{x_2} - (dx_2 - s)\frac{c}{b}](qy_2 + u) + \frac{s}{x_2}(s - dx_2)\frac{c}{b}(qy_2 + u + b) \\
& + (k - qv_2)[\delta y_2 - \frac{\beta x_2}{(1+\alpha v_2)^2}](\frac{s}{x_2} + b) + \frac{\beta(s - dx_2)(k - qv_2)}{(1+\alpha v_2)^2}, \\
p_0 =& \frac{s}{x_2}(s - dx_2)c(qy_2 + u) + (k - qv_2)[\delta y_2 - \frac{\beta x_2}{(1+\alpha v_2)^2}]\frac{bs}{x_2} + \frac{b\beta(s - dx_2)(k - qv_2)}{(1+\alpha v_2)^2}, \\
q_3 =& b, \quad q_2 = b[\frac{s}{x_2} - (dx_2 - s)\frac{c}{b} + qy_2 + u] - cpy_2z_2, \\
q_1 =& b[\frac{s}{x_2} + (s - dx_2)\frac{c}{b}](qy_2 + u) + \frac{cs}{x_2}(dx_2 - s)
\end{aligned}$$

$$+ b(k - qv_2)[\delta y_2 - \frac{\beta x_2}{(1+\alpha v_2)^2}] - cpy_2z_2(\frac{s}{x_2} + qy_2 + u),$$

$$q_0 = \frac{s}{x_2}(s - dx_2)c(qy_2 + u) + b(k - qv_2)[\delta y_2 - \frac{\beta x_2}{(1+\alpha v_2)^2}]\frac{s}{x_2}$$

$$- (qy_2 + u)cpy_2z_2\frac{s}{x_2} + \frac{\beta b(s - dx_2)(k - qv_2)}{(1+\alpha v_2)^2}.$$

When $\tau = 0$, (3.1) becomes

$$\lambda^4 + (p_3 - q_3)\lambda^3 + (p_2 - q_2)\lambda^2 + (p_1 - q_1)\lambda + p_0 - q_0 = 0. \quad (3.2)$$

Clearly,

$$p_0 - q_0 = (qy_2 + u)cpy_2z_2\frac{s}{x_2} > 0,$$

$$p_3 - q_3 = qy_2 + u + \frac{s}{x_2} + (s - dx_2)\frac{c}{b} > 0.$$

In view of Routh-Hurwitz criterion, all the roots of (3.2) have negative real parts if the following conditions hold

$$(H1) \quad (p_3 - q_3)(p_2 - q_2) - (p_1 - q_1) > 0,$$
$$(p_3 - q_3)(p_2 - q_2)(p_1 - q_1) - (p_3 - q_3)^2(p_0 - q_0) > (p_1 - q_1)^2.$$

Therefore, the CTL-inactivated infection equilibrium E_2 is locally asymptotically stable.

In the following, we investigate the existence of purely imaginary roots to (3.1) following the framework of that in [16].

For $\tau > 0$, if $i\omega(\omega > 0)$ is a root of (3.1), separating real and imaginary parts, it follows that

$$(q_0 - q_2\omega^2)\cos\omega\tau + (q_1\omega - q_3\omega^3)\sin\omega\tau = \omega^4 - p_2\omega^2 + p_0,$$
$$(q_2\omega^2 - q_0)\sin\omega\tau + (q_1\omega - q_3\omega^3)\cos\omega\tau = -p_3\omega^3 + p_1\omega. \quad (3.3)$$

Squaring and adding the two equations of (3.3), we obtain that

$$\omega^8 + G_1\omega^6 + G_2\omega^4 + G_3\omega^2 + G_4 = 0, \quad (3.4)$$

where

$$G_1 = p_3^2 - q_3^2 - 2p_2, \quad G_2 = p_2^2 + 2p_0 - 2p_1p_3 - q_2^2 + 2q_1q_3,$$
$$G_3 = p_1^2 + 2q_0q_2 - 2p_0p_2 - q_1^2, \quad G_4 = p_0^2 - q_0^2.$$

Let $\mu = \omega^2$. Then from (3.4), we have that

$$\mu^4 + G_1\mu^3 + G_2\mu^2 + G_3\mu + G_4 = 0. \quad (3.5)$$

Denote $h(\mu) \equiv \mu^4 + G_1\mu^3 + G_2\mu^2 + G_3\mu + G_4$, then we get

$$h'(\mu) = 4\mu^3 + 3G_1\mu^2 + 2G_2\mu + G_3. \quad (3.6)$$

Assuming that $\mu_1 < \mu_2 < \mu_3 < \mu_4$ are four positive real roots of (3.5), then we derive that (3.4) has four positive real roots:

$$\omega_1 = \sqrt{\mu_1}, \quad \omega_2 = \sqrt{\mu_2}, \quad \omega_3 = \sqrt{\mu_3}, \quad \omega_4 = \sqrt{\mu_4}.$$

From (3.3), we have

$$\cos\omega\tau = \frac{(-q_2\omega_0^2+q_0)(\omega_0^4-p_2\omega_0^2+p_0)+(-q_3\omega_0^3+q_1\omega_0)(-p_3\omega_0^3+p_1\omega_0)}{(-q_2\omega_0^2+q_0)^2+(-q_3\omega_0^3+q_1\omega_0)^2}. \tag{3.7}$$

Assuming that

$$(H2)\quad G_1>0,\quad G_2>0,\quad G_4<0,$$

according to the Inference 2.1 in [20], we derive that (3.4) has a unique positive root ω_0, then (3.1) has a pair of purely imaginary roots $\pm i\omega_0$. Thus, from (3.7) we have

$$\begin{aligned}\tau_k =& \frac{1}{\omega_0}\arccos\Big[\frac{(-q_2\omega_0^2+q_0)(\omega_0^4-p_2\omega_0^2+p_0)+(-q_3\omega_0^3+q_1\omega_0)(-p_3\omega_0^3+p_1\omega_0)}{(-q_2\omega_0^2+q_0)^2+(-q_3\omega_0^3+q_1\omega_0)^2}\Big]\\ &+\frac{2j\pi}{\omega_0},\end{aligned}$$

where $j=0,1,2,\ldots$.

Let $\lambda(\tau)=\alpha(\tau)+i\omega(\tau)$ be the root of (3.1) near $\tau=\tau_k$ satisfying $\alpha(\tau_k)=0,\ \omega(\tau_k)=\omega_k$. Then we have the following result.

Theorem 3.1. *Suppose that $\mu_0=\omega_0^2,\ h'(\mu_0)\neq 0$, where $h'(\mu)$ is defined by (3.6). Then*

$$\frac{d(\alpha(\tau_k)}{d\tau}\neq 0,$$

and $d\alpha(\tau_k)/d\tau$ and $-h'(\mu_0)$ have the same sign.

Proof. Let $\lambda=\lambda(\tau)$, calculating the derivative of (3.1) with respective to τ, we obtain

$$\begin{aligned}&(4\lambda^3+3p_3\lambda^2+2p_2\lambda+p_1)\frac{d\lambda}{d\tau}+[\tau(q_3\lambda^3+q_2\lambda^2+q_1\lambda+q_0)\\ &-(3q_3\lambda^2+2q_2\lambda+q_1)]e^{-\lambda\tau}\frac{d\lambda}{d\tau}=-\lambda(q_3\lambda^3+q_2\lambda^2+q_1\lambda+q_0)e^{-\lambda\tau}.\end{aligned} \tag{3.8}$$

Then we derive from (3.8) that

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1} =& \frac{-3\lambda^4-2p_3\lambda^3-p_2\lambda^2+p_0}{-\lambda^2(\lambda^4+p_3\lambda^3+p_2\lambda^2+p_1\lambda+p_0)}\\ &+\frac{2q_3\lambda^3+q_2\lambda^2-q_0}{-\lambda^2(q_3\lambda^3+q_2\lambda^2+q_1\lambda+q_0)}-\frac{\tau}{\lambda}.\end{aligned}$$

Therefore, we have

$$\begin{aligned}\left[\frac{d(\mathrm{Re}\lambda(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k} =& \frac{(-3\omega_k^4+p_2\omega_k^2+p_0)(\omega_k^4-p_2\omega_k^2+p_0)+2p_3\omega_k^4(p_1-p_3)\omega_k^2}{\omega_k^2(\omega_k^4-p_2\omega_k^2+p_0)^2+\omega_k^4(p_1-p_3\omega_k^2)^2}\\ &+\frac{-2q_3\omega_k^4(q_1-q_3\omega_k^2)+(q_2^2\omega_k^4-q_0^2)}{\omega_k^2(-q_2\omega_k^2+q_0)^2+\omega_k^4(q_1-q_3\omega_k^2)^2}.\end{aligned}$$

Let $\mu_k=\omega_k^2$, from (3.4) and (3.5)

$$(\mu_k^2-p_2\mu_k+p_0)^2+\mu_k(p_1-p_3\mu_k)^2=(-q_2\mu_k^2+q_0)^2+\mu_k(q_1-q_3\mu_k)^2,$$

and

$$p_0^2 - q_0^2 = G_4 = -(\mu_k^4 + G_1\mu_k^3 + G_2\mu_k^2 + G_3\mu_k).$$

Then, we get that

$$\begin{aligned}\left[\frac{d(\mathrm{Re}\lambda(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k} &= \frac{-4\mu_k^4 - 3G_1\mu_k^3 - 2G_2\mu_k^2 - G_3\mu_k}{\mu_k(-q_2\mu_k + q_0)^2 + \mu_k^2(q_1 - q_3\mu_k)^2} \\ &= \frac{-h'(\mu_k)}{(-q_2\mu_k + q_0)^2 + \mu_k(q_1 - q_3\mu_k)^2}.\end{aligned}$$

Therefore,

$$\begin{aligned}\mathrm{sign}\left[\frac{d(\alpha(\tau))}{d\tau}\right]_{\tau=\tau_k} &= \mathrm{sign}\left[\frac{d(Re\lambda(\tau))}{d\tau}\right]_{\tau=\tau_k} \\ &= \mathrm{sign}\left[\frac{-h'(\mu_k)}{(-q_2\mu_k + q_0)^2 + \mu_k(q_1 - q_3\mu_k)^2}\right] \\ &= \mathrm{sign}\left[-h'(\mu_k)\right].\end{aligned}$$

This completes the proof. □

Applying the Hopf bifurcation theorem for functional differential equation [6], we can conclude the existence of a Hopf bifurcation at E_2 as stated in the following theorem.

Theorem 3.2. *Suppose that (3.5) has at least one simple positive root and μ_0 is the last such root. Then there is a Hopf bifurcation for system (1.2) as τ passes through τ_0 leading to a periodic solution that bifurcates from E_2, where*

$$\begin{aligned}\tau_k =& \frac{1}{\sqrt{\mu_0}} \arccos\left[\frac{(-q_2\mu_0 + q_0)(\mu_0^2 - p_2\mu_0 + p_0) + \mu_0(-q_3\mu_0 + q_1)(p_1 - p_3\mu_0)}{(-q_2\mu_0 + q_0)^2 + \mu_0(q_1 - q_3\mu_0)^2}\right] \\ &+ \frac{2j\pi}{\sqrt{\mu_0}}.\end{aligned}$$

4. Direction

In the above sections, we have obtained some conditions under which a family of periodic solutions bifurcate from the positive equilibrium E_2 at the critical value of τ_k. As pointed out in Hassard et al. [4], it is important to determine the direction, stability and period of the periodic solutions bifurcating from the positive equilibrium E_2. In this section, we will study the direction of these Hopf bifurcations and stability of bifurcated periodic solutions arising through Hopf bifurcations. The approach we used here is based on the normal form approach and the center manifold theory introduced by Hassard et al.

Let $u_1(t) = x(t) - x_2$, $u_2(t) = y(t) - y_2$, $u_3(t) = v(t) - v_2$, $u_4(t) = z(t) - z_2$, $\tau = v + \tau_k$. Then system (1.2) is translated into

$$\dot{u}(t) = L_v(u_t) + f(v, u_t), \tag{4.1}$$

where $u(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^T \in R^4$, and $L_v : C \to R^4$, $f : R \times C \to R^4$

are given by

$$L_v(\phi) =(\tau_k+v)\begin{bmatrix} -d-\frac{\beta v_2}{1+\alpha v_2} & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2)-pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2}-\delta y_2 & -py_2 \\ 0 & k-qv_2 & -qy_2-u & 0 \\ 0 & 0 & 0 & -b \end{bmatrix}\begin{bmatrix}\phi_1(0)\\ \phi_2(0)\\ \phi_3(0)\\ \phi_4(0)\end{bmatrix}$$
$$+(\tau_k+v)\begin{bmatrix} 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & cz_2 & 0 & cy_2\end{bmatrix}\begin{bmatrix}\phi_1(-1)\\ \phi_2(-1)\\ \phi_3(-1)\\ \phi_4(-1)\end{bmatrix}, \tag{4.2}$$

and

$$f(v,\phi)=(\tau_k+v)\begin{bmatrix} -\sum\limits_{i+j\geq 2}\frac{1}{i!j!}F_{ij}^{(1)}\phi_1^i(0)\phi_3^j(0) \\ \sum\limits_{i+j\geq 2}\frac{1}{i!j!}F_{ij}^{(1)}\phi_1^i(0)\phi_3^j(0)-\delta\phi_2(0)\phi_3(0)-p\phi_2(0)\phi_4(0) \\ -q\phi_2(0)\phi_3(0) \\ c\phi_2(-1)\phi_4(-1)\end{bmatrix}, \tag{4.3}$$

where

$$F(u_1(t),u_3(t))=\frac{\beta(u_1(t)+x_2)(u_3(t)+v_2)}{1+\alpha(u_3(t)+v_2)},\ F_{ij}^{(1)}=\left.\frac{\partial^{i+j}F(u_1,u_3)}{\partial {u_1}^i\partial {u_3}^j}\right|_{(0,0)},\ i,j\geq 0.$$

By the Riesz representation theorem, there exists a function $\eta(\theta,v)$ of bounded variation for $\theta\in[-1,0]$, such that

$$L_v(\phi)=\int_{-1}^{0}d\eta(\theta,v)\phi(\theta),\quad \phi\in C. \tag{4.4}$$

In fact, we can choose

$$\eta(\theta,v) =(\tau_k+v)\begin{bmatrix} -d-\frac{\beta v_2}{1+\alpha v_2} & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2)-pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2}-\delta y_2 & -py_2 \\ 0 & k-qv_2 & -qy_2-u & 0 \\ 0 & 0 & 0 & -b \end{bmatrix}\delta(\theta)$$
$$-(\tau_k+v)\begin{bmatrix} 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & cz_2 & 0 & cy_2\end{bmatrix}\delta(\theta+1), \tag{4.5}$$

where δ denotes the Dirac delta function. For $\phi \in \big([-1,0], R^4\big)$, define

$$A(v)\phi = \begin{cases} \dfrac{d\phi(\theta)}{d\theta}, & \theta \in [-1,0), \\ \displaystyle\int_{-1}^{0} [d\eta(s,v)]\phi(s), & \theta = 0, \end{cases}$$

and

$$R(v)\phi = \begin{cases} 0, & \theta \in [-1,0), \\ f(v,\phi), & \theta = 0. \end{cases}$$

The system (4.1) is equivalent to

$$\dot{u}(t) = A(v)u_t + R(v)u_t, \tag{4.6}$$

where $u_t(\theta) = u_{t+\theta}$ for $\theta \in [-1,0]$.

For $\psi \in {}^1\big([0,1], (R^4)^*\big)$, define

$$A^*\psi(s) = \begin{cases} -\dfrac{d\psi(s)}{ds}, & s \in (0,1], \\ \displaystyle\int_{-1}^{0} \psi(-t)d\eta(t,0), & s = 0, \end{cases}$$

and a bilinear inner product

$$\langle \psi(s), \phi(\theta) \rangle = \bar{\psi}(0)\phi(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \bar{\psi}(\xi-\theta)d\eta(\theta)\phi(\xi)d\xi, \tag{4.7}$$

where $\eta(\theta) = \eta(\theta, 0)$. Then $A(0)$ and A^* are adjoint operators. By the discussion in section 3, we know that $\pm i\omega_0\tau_k$ are eigenvalues of $A(0)$. Hence, they are also eigenvalues of A^*. We firstly need to compute the eigenvectors of $A(0)$ and A^* corresponding to $i\omega_0\tau_k$ and $-i\omega_0\tau_k$, respectively.

Suppose $q(\theta) = (1, q_1, q_2, q_3)^T e^{i\omega_0\tau_k\theta}$ is the eigenvectors of $A(0)$ corresponding to $i\omega_0\tau_k$, then $A(0)q(\theta) = i\omega_0\tau_k q(\theta)$. Then from the definition of $A(0)$ and (4.2), (4.4) and (4.5), we have

$$\tau_k \begin{bmatrix} -d - \frac{\beta v_2}{1+\alpha v_2} & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2) - pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2} - \delta y_2 & -py_2 \\ 0 & k - qv_2 & -qy_2 - u & 0 \\ 0 & 0 & 0 & -b \end{bmatrix} q(0)$$
$$+ \tau_k \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & cz_2 & 0 & cy_2 \end{bmatrix} q(-1) = i\omega_0\tau_k q(0).$$

For $q(-1) = q(0)e^{-i\omega_0\tau_k}$, then we obtain

$$q_1 = -\frac{(i\omega_0 + qy_2 + u)}{(k - qv_2)}\left(\frac{s}{x_2} + i\omega_0\right)\frac{(1+\alpha v_2)^2}{\beta x_2},$$
$$q_2 = -\left(\frac{s}{x_2} + i\omega_0\right)\frac{(1+\alpha v_2)^2}{\beta x_2},$$
$$q_3 = -\frac{cz_2 e^{-i\omega_0\tau_k}}{i\omega_0 + b - be^{-i\omega_0\tau_k}}\frac{(i\omega_0 + qy_2 + u)}{(k - qv_2)}\left(\frac{s}{x_2} + i\omega_0\right)\frac{(1+\alpha v_2)^2}{\beta x_2}.$$

Similarly, we can obtain the eigenvector $q^*(S) = D(1, {q_1}^*, {q_2}^*, {q_3}^*)e^{i\omega_0\tau_k S}$ of A^* corresponding to $-i\omega_0\tau_k$, where

$${q_1}^* = \left(-i\omega_0 + \frac{s}{x_2}\right)\frac{1+\alpha v_2}{\beta v_2},$$
$${q_2}^* = \frac{(-i\omega_0 + a + \delta v_2 + pz_2)}{(k - qv_2)}\left(-i\omega_0 + \frac{s}{x_2}\right)\frac{1+\alpha v_2}{\beta v_2},$$
$${q_3}^* = \frac{(cz_2 e^{-i\omega_0\tau_k} - py_2)}{(-i\omega_0 + b - be^{-i\omega_0\tau_k})}\left(-i\omega_0 + \frac{s}{x_2}\right)\frac{1+\alpha v_2}{\beta v_2}.$$

In order to assure $\langle q^*(S), q(\theta)\rangle = 1$, we need to determine the value of D. By (4.7), we have

$$\begin{aligned}
&\langle q^*(S), q(\theta)\rangle \\
=&\bar{D}\left\{(1, \bar{q}_1^*, \bar{q}_2^*, \bar{q}_3^*)(1, q_1, q_2, q_3)^T - \chi\right\} \\
=&\bar{D}\left\{1 + q_1\bar{q}_1^* + q_2\bar{q}_2^* + q_3\bar{q}_3^* - \int_{-1}^{0}(1, \bar{q}_1^*, \bar{q}_2^*, \bar{q}_3^*)\theta e^{i\omega_0\tau_k\theta}d\eta(\theta)(1, q_1, q_2, q_3)^T\right\} \\
=&\bar{D}\left\{1 + q_1\bar{q}_1^* + q_2\bar{q}_2^* + q_3\bar{q}_3^* + \tau_k(cz_2\bar{q}_3^* q_1 + cy_2\bar{q}_3^* q_3)e^{i\omega_0\tau_k}\right\},
\end{aligned}$$

where

$$\chi = \int_{-1}^{0}\int_{\xi=0}^{\theta}\bar{D}(1, \bar{q}_1^*, \bar{q}_2^*, \bar{q}_3^*)e^{-i\omega_0\tau_k(\xi-\theta)}d\eta(\theta)(1, q_1, q_2, q_3)^T e^{i\omega_0\tau_k\xi}d\xi.$$

Therefore, we can choose D as

$$D = \frac{1}{1 + q_1\bar{q}_1^* + q_2\bar{q}_2^* + q_3\bar{q}_3^* + \tau_k(cz_2\bar{q}_3^* q_1 + cy_2\bar{q}_3^* q_3)e^{i\omega_0\tau_k}}.$$

Next we will compute the coordinate to describe the center manifold C_0 at $\mu = 0$. Let u_t be the solution of (4.6) when $\mu = 0$. Define

$$z(t) = \langle q^*, u_t\rangle, \quad W(t,\theta) = u_t(\theta) - 2\mathrm{Re}\{z(t)q(\theta)\}, \tag{4.8}$$

on the center manifold C_0. We have

$$W(t,\theta) = W(z(t), \bar{z}(t), \theta),$$

where

$$W(z(t), \bar{z}(t), \theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + \ldots, \tag{4.9}$$

z and $\bar{z}$ are local coordinates for center manifold C_0 in the direction of q^* and $\bar{q}^*$. For solution $u_t \in C_0$ of (4.6), since $\mu = 0$, we have

$$\begin{aligned}\dot{z}(t) &= i\omega_0\tau_k z + \bar{q}^*(0) f\left(0, W(z,\bar{z},0) + 2\mathrm{Re}\{zq(\theta)\}\right) \\ &\triangleq i\omega_0\tau_k z + \bar{q}^*(0) f_0(z,\bar{z}).\end{aligned}$$

We rewrite this equation as

$$\dot{z}(t) = i\omega_0\tau_k z(t) + g(z,\bar{z})(t),$$

where

$$g(z,\bar{z}) = \bar{q}^*(0) f_0(z,\bar{z}) = W(z(t),\bar{z}(t),\theta) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \ldots. \tag{4.10}$$

It follows from (4.8) and (4.9) that

$$\begin{aligned}u_t(\theta) &= W(t,\theta) + 2\mathrm{Re}\{z(t)q(\theta)\} \\ &= W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + (1,q_1,q_2,q_3)^T e^{i\omega_0\tau_k\theta} z \\ &\quad + (1,\bar{q}_1,\bar{q}_2,\bar{q}_3)^T e^{-i\omega_0\tau_k\theta}\bar{z} + \ldots.\end{aligned} \tag{4.11}$$

Furthermore,

$$\begin{aligned}
u_{1t}(0) &= z + \bar{z} + W_{20}{}^{(1)}(0)\frac{z^2}{2} + W_{11}{}^{(1)}(0)z\bar{z} + W_{02}{}^{(1)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|), \\
u_{2t}(0) &= q_1 z + \bar{q}_1\bar{z} + W_{20}{}^{(2)}(0)\frac{z^2}{2} + W_{11}{}^{(2)}(0)z\bar{z} + W_{02}{}^{(2)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|), \\
u_{3t}(0) &= q_2 z + \bar{q}_2\bar{z} + W_{20}{}^{(3)}(0)\frac{z^2}{2} + W_{11}{}^{(3)}(0)z\bar{z} + W_{02}{}^{(3)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|), \\
u_{4t}(0) &= q_3 z + \bar{q}_3\bar{z} + W_{20}{}^{(4)}(0)\frac{z^2}{2} + W_{11}{}^{(4)}(0)z\bar{z} + W_{02}{}^{(4)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|), \\
u_{2t}(-1) &= q_1 e^{-i\omega_0\tau_k} z + \bar{q}_1 e^{-i\omega_0\tau_k}\bar{z} + W_{20}{}^{(2)}(-1)\frac{z^2}{2} + W_{11}{}^{(2)}(-1)z\bar{z} \\
&\quad + W_{02}{}^{(2)}(-1)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|), \\
u_{4t}(-1) &= q_3 e^{-i\omega_0\tau_k} z + \bar{q}_3 e^{-i\omega_0\tau_k}\bar{z} + W_{20}{}^{(4)}(-1)\frac{z^2}{2} + W_{11}{}^{(4)}(-1)z\bar{z} \\
&\quad + W_{02}{}^{(4)}(-1)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|).
\end{aligned}$$

It follows together with (4.3) that

$$\begin{aligned}
g(z,\bar{z}) &= \bar{q}^*(0) f_0(z,\bar{z}) = \bar{q}^*(0) f_0(0,u_t) \\
&= \tau_k \bar{D}(1,\bar{q}_1^*,\bar{q}_2^*,\bar{q}_3^*)\begin{bmatrix} -\sum\limits_{i+j\geq 2}\frac{1}{i!j!}F_{ij}^{(1)}u_{1t}^i(0)u_{3t}^j(0) \\ \sum\limits_{i+j\geq 2}\frac{1}{i!j!}F_{ij}^{(1)}u_{1t}^i(0)u_{3t}^j(0) - \delta u_{2t}(0)u_{3t}(0) - pu_{2t}(0)u_{4t}(0) \\ -qu_{2t}(0)u_{3t}(0) \\ cu_{2t}(-1)u_{4t}(-1)\end{bmatrix}
\end{aligned}$$

$$
\begin{aligned}
&= -\tau_k \bar{D}(1-\bar{q}_1^*)\{F_{11}^{(1)} u_{1t}(0)u_{3t}(0) + \frac{1}{2}F_{20}^{(1)} u_{1t}^2(0) + \frac{1}{2}F_{02}^{(1)} u_{3t}^2(0) \\
&\quad + \frac{1}{2}F_{21}^{(1)} u_{1t}^2(0)u_{3t}(0) + \dots\} - \tau_k \bar{D}\bar{q}_1^* \delta\big(q_1 z + \bar{q}_1 \bar{z} + {W_{20}}^{(2)}(0)\frac{z^2}{2} + {W_{11}}^{(2)}(0) z\bar{z} \\
&\quad + {W_{02}}^{(2)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big) \times \big(q_2 z + \bar{q}_2 \bar{z} + {W_{20}}^{(3)}(0)\frac{z^2}{2} + {W_{11}}^{(3)}(0) z\bar{z} \\
&\quad + {W_{02}}^{(3)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big) - \tau_k \bar{D}\bar{q}_1^* p \times \big(q_1 z + \bar{q}_1 \bar{z} + {W_{20}}^{(2)}(0)\frac{z^2}{2} \\
&\quad + {W_{11}}^{(2)}(0) z\bar{z} + {W_{02}}^{(2)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big) \\
&\quad \times \left(q_3 z + \bar{q}_3 \bar{z} + {W_{20}}^{(4)}(0)\frac{z^2}{2} + {W_{11}}^{(4)}(0) z\bar{z} + {W_{02}}^{(4)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\right) \\
&\quad - \tau_k \bar{D}\bar{q}_2^* q\big(q_1 z + \bar{q}_1 \bar{z} + {W_{20}}^{(2)}(0)\frac{z^2}{2} + {W_{11}}^{(2)}(0) z\bar{z} + {W_{02}}^{(2)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big) \\
&\quad \times \big(q_2 z + \bar{q}_2 \bar{z} + {W_{20}}^{(3)}(0)\frac{z^2}{2} + {W_{11}}^{(3)}(0) z\bar{z} + {W_{02}}^{(3)}(0)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big) \\
&\quad + \tau_k \bar{D}\bar{q}_3^* c\big(q_1 e^{-i\omega_0\tau_k} z + \bar{q}_1 e^{-i\omega_0\tau_k}\bar{z} + {W_{20}}^{(2)}(-1)\frac{z^2}{2} + {W_{11}}^{(2)}(-1) z\bar{z} \\
&\quad + {W_{02}}^{(2)}(-1)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big) \times \big(q_3 e^{-i\omega_0\tau_k} z + \bar{q}_3 e^{-i\omega_0\tau_k}\bar{z} + {W_{20}}^{(4)}(-1)\frac{z^2}{2} \\
&\quad + {W_{11}}^{(4)}(-1) z\bar{z} + {W_{02}}^{(4)}(-1)\frac{\bar{z}^2}{2} + o(\left|(z,\bar{z})^3\right|)\big).
\end{aligned} \tag{4.12}
$$

Comparing the coefficients with (4.10), we have

$$
\begin{aligned}
g_{20} =& -\tau_k \bar{D}\big((1-\bar{q}_1^*)(2F_{11}^{(1)} q_2 + F_{20}^{(1)} + F_{02}^{(1)} {q_2}^2) + 2\bar{q}_2^* q q_1 q_2 + 2\bar{q}_1^* p q_1 q_3 \\
&+ 2\bar{q}_1^*\delta q_1 q_2 - 2\bar{q}_3^* q_1 q_3 c e^{-2i\omega_0\tau_k}\big), \\
g_{11} =& -\tau_k \bar{D}\begin{pmatrix} (1-\bar{q}_1^*)[F_{11}^{(1)}(q_2+\bar{q}_2) + 2F_{20}^{(1)} + 2F_{02}^{(1)} q_2\bar{q}_2] + \bar{q}_1^*\delta(q_1\bar{q}_2 + \bar{q}_1 q_2) \\ +\bar{q}_1^* p(q_1\bar{q}_3 + \bar{q}_1 q_3) + \bar{q}_2^* q(q_1\bar{q}_2 + \bar{q}_1 q_2) - \bar{q}_3^* c e^{-2i\omega_0\tau_k}(q_1\bar{q}_3 + \bar{q}_1 q_3) \end{pmatrix}, \\
g_{02} =& -\tau_k \bar{D}\big((1-\bar{q}_1^*)(2F_{11}^{(1)}\bar{q}_2 + F_{20}^{(1)} + F_{02}^{(1)}\bar{q}_2^2) + 2\bar{q}_2^* q\bar{q}_1\bar{q}_2 + 2\bar{q}_1^* p\bar{q}_1\bar{q}_3 \\
&+ 2\bar{q}_1^*\delta\bar{q}_1\bar{q}_2 - 2\bar{q}_3^*\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k}\big), \\
g_{21} =& \\
-\tau_k \bar{D}&\left[\begin{array}{l} (1-\bar{q}_1^*)\begin{pmatrix} F_{11}^{(1)}(\bar{q}_2 {W_{20}}^{(1)}(0) + 2q_2 {W_{11}}^{(1)}(0)) + \frac{1}{2}F_{20}^{(1)}({W_{20}}^{(1)}(0) + 2{W_{11}}^{(1)}(0)) \\ +\frac{1}{2}F_{02}^{(1)}(2q_2 {W_{11}}^{(3)}(0) + \bar{q}_2 {W_{20}}^{(3)}(0))) + F_{21}^{(1)}(\bar{q}_2 + q_2) \end{pmatrix} \\ +\bar{q}_1^*\delta\left(\bar{q}_2 {W_{20}}^{(2)}(0) + 2q_2 {W_{11}}^{(2)}(0) + \bar{q}_1 {W_{20}}^{(3)}(0) + 2q_1 {W_{11}}^{(3)}(0)\right) \\ +\bar{q}_1^* p\left(\bar{q}_3 {W_{20}}^{(2)}(0) + 2q_3 {W_{11}}^{(2)}(0) + \bar{q}_1 {W_{20}}^{(4)}(0) + 2q_1 {W_{11}}^{(4)}(0)\right) \\ +\bar{q}_2^* q\left(\bar{q}_2 {W_{20}}^{(2)}(0) + 2q_1 {W_{11}}^{(3)}(0) + \bar{q}_1 {W_{20}}^{(3)}(0) + 2q_2 {W_{11}}^{(2)}(0)\right) \\ -\bar{q}_3^* c e^{-i\omega_0\tau_k}\left(\bar{q}_3 {W_{20}}^{(2)}(-1) + 2q_3 {W_{11}}^{(2)}(-1) + \bar{q}_1 {W_{20}}^{(4)}(-1) + 2q_1 {W_{11}}^{(4)}(-1)\right) \end{array}\right].
\end{aligned} \tag{4.13}
$$

Since $w_{20}(\theta)$ and $w_{11}(\theta)$ are in g_{21}, we still need to compute them.

From (4.6) and (4.8), we have

$$
\dot{W} = \dot{u}_t - \dot{z}_t q - \dot{\bar{z}}\bar{q} = \begin{cases} A(0)W - 2\mathrm{Re}\{\bar{q}^*(0) f_0 q(\theta)\}, & \theta \in [-1, 0), \\ A(0)W - 2\mathrm{Re}\{\bar{q}^*(0) f_0 q(0)\} + f_0, & \theta = 0, \end{cases}
$$

$$\triangleq A(0)W + H(z,\bar{z},0), \tag{4.14}$$

Here,

$$H(z,\bar{z},\theta) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \dots. \tag{4.15}$$

Substituting the corresponding series into (4.14) and comparing the coefficients, we have

$$(A(0) - 2i\omega_0\tau_k I)W_{20}(\theta) = -H_{20}(\theta), \quad A(0)W_{11}(\theta) = -H_{11}(\theta). \tag{4.16}$$

From (4.14), we know that for $\theta \in [-1, 0)$,

$$H(z,\bar{z},\theta) = -\bar{q}^*(0)f_0 q(\theta) - q^*(0)\bar{f}_0\bar{q}(\theta) = -g(z,\bar{z})q(\theta) - \bar{g}(z,\bar{z})\bar{q}(\theta). \tag{4.17}$$

Comparing the coefficients with (4.15) gives that

$$H_{20}(\theta) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta), \tag{4.18}$$

and

$$H_{11}(\theta) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta). \tag{4.19}$$

From the definition of A and (4.16) and (4.18), we obtain

$$\dot{W}_{20}(\theta) = 2i\omega_0\tau_k W_{20}(\theta) + g_{20}q(\theta) + \bar{g}_{02}\bar{q}(\theta).$$

For $q(\theta) = (1, q_1, q_2, q_3)^T e^{i\omega_0\tau_k\theta}$, we have

$$W_{20}(\theta) = \frac{ig_{20}}{\omega_0\tau_k}q(0)e^{i\omega_0\tau_k\theta} + \frac{i\bar{g}_{02}}{3\omega_0\tau_k}\bar{q}(0)e^{-i\omega_0\tau_k\theta} + E_1 e^{2i\omega_0\tau_k\theta}, \tag{4.20}$$

where $E_1 = (E_1^{(1)}, E_1^{(2)}, E_1^{(3)}, E_1^{(4)})^T$ is a constant vector.

Similarly, from (4.16) and (4.19), we know

$$W_{11}(\theta) = -\frac{ig_{11}}{\omega_0\tau_k}q(0)e^{i\omega_0\tau_k\theta} + \frac{i\bar{g}_{11}}{\omega_0\tau_k}\bar{q}(0)e^{-i\omega_0\tau_k\theta} + E_2, \tag{4.21}$$

where $E_2(E_2^{(1)}, E_2^{(2)}, E_2^{(3)}, E_2^{(4)})^T$is a constant vector.

In what follows, we shall seek the values of E_1 and E_2. From the definition of $A(0)$ and (4.16), we have

$$\int_{-1}^{0} d\eta(\theta)W_{20}(\theta) = 2i\omega_0\tau_k W_{20}(\theta) - H_{11}(0) \tag{4.22}$$

and

$$\int_{-1}^{0} d\eta(\theta)W_{11}(\theta) = -H_{11}(0), \tag{4.23}$$

where $\eta(\theta) = \eta(0,\theta)$. By (4.14), when $\theta = 0$, we know

$$H_{20}(0) = -g_{20}q(0) - \bar{g}_{02}\bar{q}(0) + \begin{pmatrix} -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 \\ 2F_{11}^{(1)}\bar{q}_2 + F_{20}^{(1)} + F_{02}^{(1)}\bar{q}_2^2 - 2p\bar{q}_1\bar{q}_3 - 2\delta\bar{q}_1\bar{q}_2 \\ -2q\bar{q}_1\bar{q}_2 \\ 2\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k} \end{pmatrix} \tag{4.24}$$

and

$$H_{11}(0) = -g_{11}q(0) - \bar{g}_{11}\bar{q}(0) + \begin{pmatrix} -F_{11}^{(1)}(q_2+\bar{q}_2) - 2F_{20}^{(1)} - 2F_{02}^{(1)}q_2\bar{q}_2 \\ N \\ q(q_1\bar{q}_2+\bar{q}_1q_2) \\ ce^{-2i\omega_0\tau_k}(q_1\bar{q}_3+\bar{q}_1q_3). \end{pmatrix}, \quad (4.25)$$

where

$$N = F_{11}^{(1)}(q_2+\bar{q}_2) + 2F_{20}^{(1)} + 2F_{02}^{(1)}q_2\bar{q}_2 - \delta(q_1\bar{q}_2+\bar{q}_1q_2) - p(q_1\bar{q}_3+\bar{q}_1q_3).$$

Since $i\omega_0\tau_k$ is the eigenvalue of $A(0)$ and $q(0)$ is the corresponding eigenvector, we obtain

$$\left(i\omega_0\tau_k I - \int_{-1}^{0} e^{i\omega_0\tau_k\theta}d\eta(\theta)\right)q(0) = 0$$

and

$$\left(-i\omega_0\tau_k I - \int_{-1}^{0} e^{i\omega_0\tau_k\theta}d\eta(\theta)\right)\bar{q}(0) = 0.$$

Then, substituting (4.20) and (4.24) into (4.22), we obtain

$$\left(2i\omega_0\tau_k I - \int_{-1}^{0} e^{2i\omega_0\tau_k\theta}d\eta(\theta)\right)E_1 = \begin{pmatrix} -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 \\ 2F_{11}^{(1)}\bar{q}_2 + F_{20}^{(1)} + F_{02}^{(1)}\bar{q}_2^2 - 2p\bar{q}_1\bar{q}_3 - 2\delta\bar{q}_1\bar{q}_2 \\ -2q\bar{q}_1\bar{q}_2 \\ 2\bar{q}_1\bar{q}_3ce^{-2i\omega_0\tau_k} \end{pmatrix}.$$

Define

$$T = 2F_{11}^{(1)}\bar{q}_2 + F_{20}^{(1)} + F_{02}^{(1)}\bar{q}_2^2 - 2p\bar{q}_1\bar{q}_3 - 2\delta\bar{q}_1\bar{q}_2.$$

We have

$$\begin{bmatrix} 2i\omega_0 + d + \frac{\beta v_2}{1+\alpha v_2} & 0 & \frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ -\frac{\beta v_2}{1+\alpha v_2} & 2i\omega_0 + (a+\delta v_2) + pz_2 & -\frac{\beta x_2}{(1+\alpha v_2)^2} + \delta y_2 & py_2 \\ 0 & -k + qv_2 & 2i\omega_0 + qy_2 + u & 0 \\ 0 & 0 & 0 & 2i\omega_0 + b \end{bmatrix} E_1$$
$$= \begin{pmatrix} -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 \\ T \\ -2q\bar{q}_1\bar{q}_2 \\ 2\bar{q}_1\bar{q}_3ce^{-2i\omega_0\tau_k} \end{pmatrix}.$$

It follows that

$$E_1^{(1)} = \frac{1}{M_1}\begin{vmatrix} -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 & 0 & \frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ T & 2i\omega_0 + (a+\delta v_2) + pz_2 & -\frac{\beta x_2}{(1+\alpha v_2)^2} + \delta y_2 & py_2 \\ -2q\bar{q}_1\bar{q}_2 & -k+qv_2 & 2i\omega_0 + qy_2 + u & 0 \\ 2\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k} & 0 & 0 & 2i\omega_0 + b \end{vmatrix},$$

$$E_1^{(2)} = \frac{1}{M_1}\begin{vmatrix} 2i\omega_0 + d + \frac{\beta v_2}{1+\alpha v_2} & -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 & \frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ -\frac{\beta v_2}{1+\alpha v_2} & T & -\frac{\beta x_2}{(1+\alpha v_2)^2} + \delta y_2 & py_2 \\ 0 & -2q\bar{q}_1\bar{q}_2 & 2i\omega_0 + qy_2 + u & 0 \\ 0 & 2\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k} & 0 & 2i\omega_0 + b \end{vmatrix},$$

$$E_1^{(3)} = \frac{1}{M_1}\begin{vmatrix} 2i\omega_0 + d + \frac{\beta v_2}{1+\alpha v_2} & 0 & -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 & 0 \\ -\frac{\beta v_2}{1+\alpha v_2} & 2i\omega_0 + (a+\delta v_2) + pz_2 & T & py_2 \\ 0 & -k+qv_2 & -2q\bar{q}_1\bar{q}_2 & 0 \\ 0 & 0 & 2\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k} & 2i\omega_0 + b \end{vmatrix},$$

$$E_1^{(4)} = \frac{1}{M_1}\begin{vmatrix} 2i\omega_0 + d + \frac{\beta v_2}{1+\alpha v_2} & 0 & \frac{\beta x_2}{(1+\alpha v_2)^2} & -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 \\ -\frac{\beta v_2}{1+\alpha v_2} & 2i\omega_0 + (a+\delta v_2) + pz_2 & -\frac{\beta x_2}{(1+\alpha v_2)^2} + \delta y_2 & T \\ 0 & -k+qv_2 & 2i\omega_0 + qy_2 + u & -2q\bar{q}_1\bar{q}_2 \\ 0 & 0 & 0 & 2\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k} \end{vmatrix},$$

where

$$M_1 = \begin{vmatrix} 2i\omega_0 + d + \frac{\beta v_2}{1+\alpha v_2} & 0 & \frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ -\frac{\beta v_2}{1+\alpha v_2} & 2i\omega_0 + (a+\delta v_2) + pz_2 & -\frac{\beta x_2}{(1+\alpha v_2)^2} + \delta y_2 & py_2 \\ 0 & -k+qv_2 & 2i\omega_0 + qy_2 + u & 0 \\ 0 & 0 & 0 & 2i\omega_0 + b \end{vmatrix}.$$

Similarly, substiting (4.21) and (4.25) into (4.23), we get

$$\begin{bmatrix} -d - \frac{\beta v_2}{1+\alpha v_2} & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2) - pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2} - \delta y_2 & -py_2 \\ 0 & k - qv_2 & -qy_2 - u & 0 \\ 0 & 0 & 0 & -b \end{bmatrix} E_1 = \begin{pmatrix} -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 \\ T \\ -2q\bar{q}_1\bar{q}_2 \\ 2\bar{q}_1\bar{q}_3 c e^{-2i\omega_0\tau_k} \end{pmatrix}.$$

Therefore, we obtain

$$E_2^{(1)} = \frac{1}{M_2}\begin{vmatrix} -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ T & -(a+\delta v_2) - pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2} - \delta y_2 & -py_2 \\ -2q\bar{q}_1\bar{q}_2 & k - qv_2 & -qy_2 - u & 0 \\ 2\bar{q}_1\bar{q}_3 ce^{-2i\omega_0\tau_k} & 0 & 0 & -b \end{vmatrix},$$

$$E_2^{(2)} = \frac{1}{M_2}\begin{vmatrix} -d - \frac{\beta v_2}{1+\alpha v_2} & -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & T & \frac{\beta x_2}{(1+\alpha v_2)^2} - \delta y_2 & -py_2 \\ 0 & -2q\bar{q}_1\bar{q}_2 & -qy_2 - u & 0 \\ 0 & 2\bar{q}_1\bar{q}_3 ce^{-2i\omega_0\tau_k} & 0 & -b \end{vmatrix},$$

$$E_2^{(3)} = \frac{1}{M_2}\begin{vmatrix} -d - \frac{\beta v_2}{1+\alpha v_2} & 0 & -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2) - pz_2 & T & -py_2 \\ 0 & k - qv_2 & -2q\bar{q}_1\bar{q}_2 & 0 \\ 0 & 0 & 2\bar{q}_1\bar{q}_3 ce^{-2i\omega_0\tau_k} & -b \end{vmatrix},$$

$$E_2^{(4)} = \frac{1}{M_2}\begin{vmatrix} -d - \frac{\beta v_2}{1+\alpha v_2} & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & -2F_{11}^{(1)}\bar{q}_2 - F_{20}^{(1)} - F_{02}^{(1)}\bar{q}_2^2 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2) - pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2} - \delta y_2 & T \\ 0 & k - qv_2 & -qy_2 - u & -2q\bar{q}_1\bar{q}_2 \\ 0 & 0 & 0 & 2\bar{q}_1\bar{q}_3 ce^{-2i\omega_0\tau_k} \end{vmatrix},$$

where

$$M_2 = \begin{vmatrix} -d - \frac{\beta v_2}{1+\alpha v_2} & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\ \frac{\beta v_2}{1+\alpha v_2} & -(a+\delta v_2) - pz_2 & \frac{\beta x_2}{(1+\alpha v_2)^2} - \delta y_2 & -py_2 \\ 0 & k - qv_2 & -qy_2 - u & 0 \\ 0 & 0 & 0 & -b \end{vmatrix}.$$

Thus, we can determine $W_{20}(\theta)$ and $W_{11}(\theta)$ from (4.20) and (4.21). Furthermore, we can compute g_{21} by (4.13). Thus, we can compute the following values:

$$\begin{aligned} c_1(0) &= \frac{i}{2\omega_0}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}, \\ \mu_2 &= -\frac{\mathrm{Re}\{c_1(0)\}}{\mathrm{Re}\{\lambda'(\tau_k)\}}, \\ \beta_2 &= 2\mathrm{Re}(c_1(0)) \\ T_2 &= -\frac{\mathrm{Im}\{c_1(0)\} + \mu_2 \mathrm{Im}\{\lambda'(\tau_k)\}}{\omega_0\tau_k}, \quad k = 0, 1, 2\ldots, \end{aligned} \tag{4.26}$$

which determine the qualities of bifurcating periodic solution in the center manifold at the critical values τ_k, i.e., μ_2 determines the directions of the Hopf bifurcation: if $\mu_2 > 0(\mu_2 < 0)$, then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_k(\tau < \tau_k)$; β_2 determines the stability of the bifurcating periodic solutions: the bifurcating periodic solutions are stable (unstable) if $\beta_2 < 0(\beta_2 > 0)$; and T_2 determines the period of the bifurcating periodic solutions: the period increase(decrease) if $T_2 > 0(< 0)$.

Theorem 4.1. *The direction of the Hopf bifurcation of system (1.2) at the equilibrium E_2 when $\tau = \tau_k (k = 0, 1, 2, \dots)$ is supercritical(subcritical) and bifurcating periodic solutions on the center manifold are stable(unstable) if $Re(c_1(0)) < 0(> 0)$; particularly, when $\tau = 0$, the stability of bifurcating periodic solutions is the same as that on the center manifold.*

5. Global stability

In this section, we study the global stability of the infection-free equilibrium and the CTL-inactivated infection equilibrium.

Theorem 5.1. *The infection-free equilibrium of system (1.2) is globally asymptotically stable if $R_0 \leq 1$.*

Proof. Define

$$g(x) = x - 1 - \ln x. \tag{5.1}$$

Clearly, for $x \in (0, +\infty)$, $g(x)$ is non-negative and has the global minimum at $x = 1$ and $g(1) = 0$.

Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.2) with initial conditions (1.3).

Define the following Lyapunov functional:

$$V_0(t) = (x - x_0 - x_0 \ln \frac{x}{x_0}) + y + \frac{a}{k} v + \frac{p}{c} z + p \int_{t-\tau}^{t} y(\theta) z(\theta) d\theta. \tag{5.2}$$

Calculating the derivative of $V_0(t)$ along positive solutions of system (1.2), it follows that

$$\begin{aligned} {V'}_0(t) = &\left(1 - \frac{x_0}{x}\right) \left(s - dx - \frac{\beta x v}{1 + \alpha v}\right) + \frac{\beta x v}{1 + \alpha v} \\ &- ay - \delta v y + \frac{a}{k} (ky - qvy - uv) - p y_2 z. \end{aligned} \tag{5.3}$$

On substituting $s = dx_0$ into (5.3), we derive that

$$\begin{aligned} {V'}_0(t) &= dx_0 \left(1 - \frac{x_0}{x}\right) \left(1 - \frac{x}{x_0}\right) - \left(\delta + \frac{aq}{k}\right) vy - p y_2 z + \frac{auv}{k} \left(\frac{k}{au} \frac{\beta x_0}{1 + \alpha v} - 1\right) \\ &= dx_0 \left(1 - \frac{x_0}{x}\right) \left(1 - \frac{x}{x_0}\right) - \left(\delta + \frac{aq}{k}\right) vy - p y_2 z + \frac{auv}{k} \left(\frac{R_0}{1 + \alpha v} - 1\right). \end{aligned} \tag{5.4}$$

Noting that $R_0 \leq 1$, by (5.4) we have that $V_0'(t) \leq 0$. Clearly, it follows from (5.4) that $V_0'(t) = 0$ if and only if $x(t) = x_0$. From Theorem 2.1 E_0 is locally asymptic1ally stable. Accordingly, the global asymptotic stability of E_0 follows LaSalle's invariance principle. This completes the proof. □

Theorem 5.2. *The CTL-inactivated infection equilibrium $E_1(x_1, y_1, v_1, 0)$ of system (1.2) is globally asymptotically stable if $R_1 \leq 1 < R_0$.*

Proof. Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.2) with initial conditions (1.3). Define the following Lyapunov functional:

$$\begin{aligned} V_1(t) =&(x - x_1 - x_1 \ln \frac{x}{x_1}) + (y - y_1 - y_1 \ln \frac{y}{y_1}) + p \int_{t-\tau}^{t} y(\theta)z(\theta)d\theta \\ &+ \frac{1}{uv_1} \left(\frac{\beta x_1 v_1}{1+\alpha v_1} + \delta v_1 y_1 \right) (v - v_1 - v_1 \ln \frac{v}{v_1}) + \frac{p}{c} z. \end{aligned} \tag{5.5}$$

The time derivative of $V_1(t)$ along positive solutions of system (1.2) is given by

$$\begin{aligned} V'_1(t) =& \left(1 - \frac{x_1}{x}\right) (s - dx - \frac{\beta xv}{1+\alpha v}) - py_2 z + pyz \\ &+ (1 - \frac{y_1}{y}) \left(\frac{\beta xv}{1+\alpha v} - ay - \delta vy - pyz \right) \\ &+ \frac{1}{uv_1} \left(\frac{\beta x_1 v_1}{1+\alpha v_1} + \delta v_1 y_1 \right) \left(1 - \frac{v_1}{v}\right) (ky - qvy - uv). \end{aligned} \tag{5.6}$$

On substituting

$$s = dx_1 + \frac{\beta x_1 v_1}{1+\alpha v_1}, \quad a = \frac{\beta x_1 v_1}{1+\alpha v_1} \frac{1}{y_1} - \delta v_1, \quad k = \frac{uv_1}{y_1} + qv_1, \quad y_2 = \frac{b}{c},$$

into (5.6) we derive that

$$\begin{aligned} V'_1(t) =& \left(1 - \frac{x_1}{x}\right) \left(dx_1 - dx + \frac{\beta x_1 v_1}{1+\alpha v_1} - \frac{\beta xv}{1+\alpha v} \right) + \left(1 - \frac{y_1}{y}\right) (\delta v_1 y - \delta vy) \\ &+ (1 - \frac{y_1}{y}) \left(\frac{\beta xv}{1+\alpha v} - \frac{\beta x_1 v_1}{1+\alpha v_1} \frac{y}{y_1} \right) + pz(y_1 - y_2) \\ &+ \frac{1}{uv_1} \left(\frac{\beta x_1 v_1}{1+\alpha v_1} + \delta v_1 y_1 \right) \left(1 - \frac{v_1}{v}\right) \left(\frac{uv_1 y}{y_1} - uv + qv_1 y - qvy \right). \end{aligned}$$

It is equivalent to the following equation:

$$\begin{aligned} V'_1(t) =& -d\frac{(x-x_1)^2}{x} - \frac{\beta x_1 v_1}{1+\alpha v_1} \frac{\alpha (v-v_1)^2}{(1+\alpha v_1)(1+\alpha v)v_1} + pz(y_1 - y_2) \\ &+ \frac{\beta x_1 v_1}{1+\alpha v_1} \left(4 - \frac{xv(1+\alpha v_1)y_1}{x_1 v_1 (1+\alpha v)y} - \frac{yv_1}{y_1 v} - \frac{x_1}{x} - \frac{1+\alpha v}{1+\alpha v_1} \right) \\ &- \frac{qy(v-v_1)^2}{uvv_1} \left(\frac{\beta x_1 v_1}{1+\alpha v_1} + \delta v_1 y_1 \right) + \delta v_1 y \left(2 - \frac{v_1}{v} - \frac{v}{v_1} \right). \end{aligned} \tag{5.7}$$

Noting that $x_1, y_1, v_1 > 0$, $R_1 \leq 1 < R_0$, by Lemma 2.1 we have that $V_1'(t) \leq 0$. Clearly, it follows from (5.7) that $V_1'(t) = 0$ if and only if $x(t) = x_1$, $y(t) = y_1$, $v(t) = v_1$. Moreover, from Theorem 2.2 E_1 is locally asympticlally stable. Accordingly, the global asymptotic stability of E_1 follows LaSalle's invariance principle. This completes the proof. □

6. Example

In this section, we give an example to illustrate the existence of Hopf bifurcation.

Example 6.1. In system (1.2), we choose a set of parameters as follows: $d = 0.5, s = 2, \beta = 2, \alpha = 0.2, a = 0.2, \delta = 0.2, p = 0.2, k = 0.1, q = 0.2, u = 0.2, c = 0.1, b = 0.2$. Then $R_1 = 2.0833 > 1$, system (1.2) has an activated infection equilibrium $E_2(1.7778, 2, 0.333, 1.444)$. By calculating, we derive that system (1.2) undergoes a Hopf bifurcation at τ_k when $\tau = \tau_k \approx 12$. Further, we can calculate the parameters which determine the stability and direction. It follows that $c_1(0) \approx -0.4356+0.0274i$, $\mu_2 = 258.58 > 0$, $\beta_2 = -0.5648 < 0$ and $T_2 = 0.9653 > 0$. Since $\mu_2 > 0$ and $\beta_2 < 0$, the Hopf bifurcation is supercritical and the direction of the bifurcation is $\tau > \tau_k$. Figure 1(A)-(D) denote the projection of the solutions in $(x, y, v) - space$, $(x, y, z) - space$, $(x, v, z) - space$, $(y, v, z) - space$, respectively.

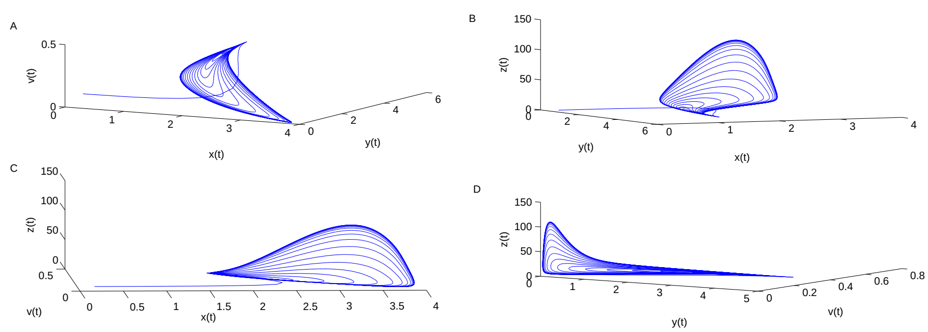

Figure 1. when $R_1 > 1$, the figures (A)-(D) show the trajectories graphs of system (1.2) with $\tau > 12$ in $(x, y, v) - space$, $(x, y, z) - space$, $(x, v, z) - space$, $(y, v, z) - space$, respectively.

References

[1] L. Cai and X. Li, *Stability and Hopf bifurcation in a delayed model for HIV infection of cells*, Chaos, Solitons and Fractals, 2009, 42(1), 1–11.

[2] A. A. Canabarro, I. M. Glria and M. L. Lyra, *Periodic solutions and chaos in a nonlinear model for the delayed cellular immune response*, Physica A, 2004, 342(1-2), 234–241.

[3] D. Ebert, C. Zschokke-Rohringer and H. Carius, *Dose effects and density-dependent regulation of two microparasites of Daphnia magna*, Oecologia, 2000, 12(2), 200–209.

[4] B. Hassard, D. Kazarino and Y. Wan, *Theory and Application of Hopf bifurcation*, Cambridge University Press, Cambridge, 1981.

[5] A. Korobeinikov, *Global properties of basic virus dynamics models*, Bull. Math. Biol., 2004, 66(4), 879–883.

[6] Y. Kuang, *Delay Differential Equations with Applications in Population Dynamics.* Academic Press, New York, 1993.

[7] T. Little and D. Ebert, *The cause of parasitic infection in natural populations of Daphnia*, Proc. R. Soc. Lond. B, 2000, 267(1457), 2037–2042.

[8] A. Mclean and C. Bostock, *Scrapie infections initiated at varying doses: an analysis of 117 titration experiments*, Philos. Trans. R. Soc. Lond. Ser. B, 2000, 355(1400), 1043–1050.

[9] Y. Muroya, Y. Enatsu and H. Li, *Global stability of a delayed HTLV-1 infection model with a class of nonlinear incidence rates and CTLs immune response*, Applied Mathematics and Computation, 2013, 219(21), 10559–10574.

[10] P. W. Nelson and A. S. Perelson, *Mathematical analysis of delay differential equation models of HIV-1 infection*, Math. Biosci., 2012, 179(1), 73–94.

[11] M. A. Nowak and C. R. M. Bangham, *Population dynamics of immune responses to persistent viruses*, Science, 1996, 272(5358), 74–79.

[12] R. Regoes, D. Ebert and S. Bonhoeffer, *Dose-dependent infection rates of parasites produce the Allee effect in epidemiology*, Proc. R. Soc. Lond. Ser. B, 2002, 269(1488), 271–279.

[13] X. Shi and X. Zhou, *Dynamical behavior of a delay virus dynamics model with CTL immune response*, Nonlinear Analysis: Real World Applications, 2010, 11(3), 1795–1809.

[14] X. Song and A.U. Neumann, *Global stability and periodic solution of the viral dynamics*, J. Math. Anal. Appl., 2007, 329(1), 281–297.

[15] C. Sun, Z. Cao and Y. Lin, *Analysis of stability and Hopf bifurcation for a viral infectious model with delay*, Chaos, solitons and Fractals, 2007, 33(1), 234–245.

[16] Z. Wang and R. Xu, *Stability and Hopf bifurcation in a viral infection model with nonlinear incidence rate and delayed immune response*, Commun. Nonlinear Sci. Numer. Simulat., 2012, 17(2), 964–978.

[17] K. Wang, W. Wang and H. Wang, *Complex dynamic behavior in a viral model with delayed immune response*, Physica D, 2007, 226(2), 197–208.

[18] D. Wodarz, *Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses*, Journal of General Virology, 2003. DOI: 10.1099/vir.0.19118-0.

[19] R. Xu, *Global stability of an HIV-1 infection model with saturation infection and intracellular delay*, J. Math. Anal. Appl., 2011, 375(1), 75–81.

[20] T. Zhang, J. Liu and Z. Teng, *Stability of Hopf bifurcations of a delayed SIRS epidemic model with stage structure*, Nonlinear Analysis: Real World Application, 2010, 11(1), 293–306.

[21] X. Zhou, X. Shi and Z. Zhang, *Dynamical behavior of a virus dynamics with CTL immune response*, Applied Mathematics and Computation, 2009, 213(2), 329–347.

[22] H. Zhu, Y. Luo and M. Chen, *Stability and Hopf bifurcation of HIV infection model with CTL response delay*, Computers and Mathematics with Applications, 2011, 62(8), 3091–3102.

[23] H. Zhu and X. Zou, *Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay*, Discrete and Continuous Dynamical Systems-series B, 2009, 12(2), 511–524.