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Analysis of stability and Hopf bifurcation for an HIV infection model with time delay ☆

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Abstract

A class of more general HIV infection models with time delay is proposed based on some important biological meanings. The effect of time delay on stability of the equilibria of the infection model has been studied. And the sufficient criteria for stability switch of the infected equilibrium and the local and global asymptotic stability of the viral-free equilibrium are given. Using the normal form theory and center manifold argument, the explicit formulaes which determine the stability, the direction and the periodic of bifurcating period solutions are derived. Numerical simulations are carried out to explain the mathematical conclusions.

Keywords: HIV infection; Intercelluar delay; Hopf bifurcation; Stability

1. Introduction

HIV (human immunodeficiency virus) has become a global problem. The human suffering due to HIV and AIDS (acquired immunodeficiency syndrome) is enormous. For example, AIDS is now the leading cause of death in Sub-Saharan Africa. Many countries in this region have failed to bring the epidemic under control. It is said that nearly two thirds of the world's HIV positive pepple live in Sub-Saharan Africa. So, in the last decades the infection by HIV, which caused AIDS, has been the subject of most intense studies that encompass diverse fields of scientific research. Although major progress has been achieved by medical and biological researchers in understanding different aspects of the virus–host interaction, the mechanisms by which HIV causes AIDS still remain unexplained.

Mathematical models have been proven to be valuable in understanding the dynamics of HIV infection. Most of them use ordinary (or partial) differential equations to describe different aspects of the dynamics

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of the host–parasite interaction [1–5]. And these models typically consider the dynamics of the $CD4^+$ and virus populations as well as the effects of drug therapy [6]. There are also some models which include an intracellular delay [7–10]. The first model that included this type "intracellular" delay was developed by Herz et al. [11] and assumed that cells became productively infected time units after of HIV initial infection. Patrick et al. extend the development of delay models of HIV infection and treatment to the general case of combination antiviral therapy that is less than completely efficacious. Recently, Xinyu Song et al. [12] had investigated the following viral model with delay:

$$\begin{cases} \dot{T} = s - dT + aT(1 - \frac{T}{T_{\max}}) - bTV, \\ \dot{I} = be^{-m\tau}T(t-\tau)V(t-\tau) - \delta I, \\ \dot{V} = pI - cV, \end{cases} \tag{1.1}$$

where T is the number of target cells, I is the number of infected cells, V is the viral load of the virous, s represents the rate at which new T cells are created from sources, a is the maximum proliferation rate of target cells. $T_{\max}$ is the T population density at which proliferation shuts off. In model (1.1), d is death rate of the T cells, b is the infection rate constant, the term $e^{-m\tau}$ accounts for cells that are infected at time t but die before becoming productively infected τ time units later. δ is the death rate of the infective cells, p is the reproductively rate of the infected cells, and $\frac{p}{\delta}$ is the total number of virions produced by a productively infected cell during its lifetime, c is the clearance rate constant of virions. All the parameters are positive constants.

Xinyu Song et al. had studied the effect of the time delay on the stability of the endemically infected equilibrium, criteria were given to ensure that the infected equilibrium was asymptotically stable for all delay. They also obtained the condition for existence of an orbitally asymptotically stable periodic solutions. All the results were under the case $m = 0$ in system (1.1). And they presented the model (1.1) at last of their paper when $m \neq 0$. But they did not study the model in detail. In this paper, we shall also study the model (1.1). We will analyze the stability of equilibria and Hopf bifurcation. And we will show that when the delay τ passes through a critical value, the endemic equilibrium loses it stability and Hopf bifurcation occurs. Since the coefficients of the corresponding characteristic equation dependent on the delay τ, there are stability switch, and all roots of the characteristic equation have negative real parts when τ large enough. And the direction of Hopf bifurcation and the stability and period of bifurcating periodic solutions on the center manifold are determined.

This paper is organized as follows. In the next section, we give some useful preliminaries. In Section 3, the local and global stability of the viral-free equilibrium are studied. The existence of Hopf bifurcation at the endemic equilibrium are presented in Section 4. In Section 5, the direction of Hopf bifurcation and the stability and period of bifurcating periodic solutions on the center manifold are determined. In Section 6, some numerical simulations are performed to illustrate the analytical results found.

2. Preliminaries

We denote by C the Banach space of continuous functions $\varphi : [-\tau, 0] \to R^3$ with norm

$$\|\varphi\| = \sup_{-\tau \leqslant \theta \leqslant 0} \{|\varphi_1(\theta)|, |\varphi_2(\theta)|, |\varphi_3(\theta)|\},$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3)$. Further, let

$$C_+ = \{\varphi = (\varphi_1, \varphi_2, \varphi_3) \in C : \varphi_i \geqslant 0 \quad \text{for all } \theta \in [-\tau, 0],\ i = 1, 2, 3\}.$$

The initial condition for system (1.1) is given as

$$T(\theta) = \varphi_1(\theta), \quad I(\theta) = \varphi_2(\theta), \quad V(\theta) = \varphi_3(\theta), \quad -\tau \leqslant \theta \leqslant 0, \tag{2.1}$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3)$.

Lemma 2.1. *Suppose that $(T(t), I(t), V(t))$ is a solution of system (1.1) with initial conditions (2.1) then $T(t) \geqslant 0$, $I(t) \geqslant 0$, $V(t) \geqslant 0$ for all $t \geqslant 0$.*

The equilibria of system (1.1) are as follows: $\widehat{E}(\widehat{T},0,0)$ and $\overline{E}(\overline{T},\overline{I},\overline{V})$, where

$$\widehat{T}=\frac{T_{\max}}{2a}\left[a-d+\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}\right],$$
$$\overline{T}=\frac{c\delta}{pb\mathrm{e}^{-m\tau}},$$
$$\overline{I}=\frac{\mathrm{e}^{-m\tau}}{\delta}\left[s-d\overline{T}+a\overline{T}\left(1-\frac{\overline{T}}{T_{\max}}\right)\right],$$
$$\overline{V}=\frac{p\mathrm{e}^{-m\tau}}{c\delta}\left[s-d\overline{T}+a\overline{T}\left(1-\frac{\overline{T}}{T_{\max}}\right)\right].$$

The basic reproductive number is given as

$$R_0=\frac{\widehat{T}}{\overline{T}}.$$

It is easy to prove the following theorem.

Theorem 2.1. *When $R_0\leqslant 1$, then system (1.1) only has the viral-free equilibrium $\widehat{E}$ and when $R_0>1$, the system (1.1) has the endemic equilibrium $\overline{E}$ except for $\widehat{E}$ and $\overline{E}$ is unique.*

Proof. From $\widehat{T}=\frac{T_{\max}}{2a}\left[a-d+\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}\right]$, we can get $s=-(a-d)\widehat{T}+\frac{a\widehat{T}}{T_{\max}}$. Hence,

$$s-d\overline{T}+a\overline{T}\left(1-\frac{\overline{T}}{T_{\max}}\right)=-(a-d)\widehat{T}+(a-d)\overline{T}+\frac{a\widehat{T}^2}{T_{\max}}-\frac{a\overline{T}^2}{T_{\max}}=(\widehat{T}-\overline{T})\left[d-a+\frac{a(\widehat{T}+\overline{T})}{T_{\max}}\right]>0.$$

Then $\overline{I}>0$, $\overline{V}>0$ when $R_0>1$. $\square$

As is obvious for system (1.1), we have the following useful lemma.

Lemma 2.2. *For any solution $(T(t),I(t),V(t))$ of (1.1), we have that*

$$\limsup_{t\to+\infty}T(t)\leqslant\widehat{T}=\frac{T_{\max}}{2a}\left[a-d+\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}\right].$$

3. Stability of the viral-free equilibrium $\widehat{E}$

In this section, we shall consider the stability for the viral-free equilibrium $\widehat{E}$ of system (1.1). We have the following main results.

Theorem 3.1. (1) *If $R_0<1$, $\widehat{E}$ is locally asymptotically stable for any time delay $\tau\geqslant 0$.* (2) *If $R_0>1$, $\widehat{E}$ is unstable for any time delay $\tau\geqslant 0$.* (3) *If $R_0=1$, it is a critical case.*

Proof. By the transformation $\widetilde{T}=T-\widehat{T}$, $\widetilde{I}=I$, $\widetilde{V}=V$, and omitting the tilde ($\sim$), system (1.1) is written as

$$\begin{cases}\dot{T}=(a-d-\frac{2a\widehat{T}}{T_{\max}})T-b\widehat{T}V,\\ \dot{I}=b\mathrm{e}^{-m\tau}\widehat{T}V(t-\tau)-\delta I,\\ \dot{V}=pI-cV,\end{cases}\tag{3.1}$$

whose characteristic equation is

$$\left(\lambda+\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}\right)(\lambda^2+(c+\delta)\lambda+bp\mathrm{e}^{-m\tau}\widehat{T}\mathrm{e}^{-\lambda\tau})=0.\tag{3.2}$$

It is clear that (3.2) has the characteristic root $\lambda = -\sqrt{(a-d)^2 + \frac{4as}{T_{\max}}} < 0$. Next, we shall consider the transcendental polynomial

$$\lambda^2 + (c+\delta)\lambda + c\delta - bpe^{-m\tau}\widehat{T}e^{-\lambda\tau} = 0. \tag{3.3}$$

For $\tau = 0$, we have that $c + d > 0$, $c\delta - bp\widehat{T} > 0$ since $R_0 < 1$. This shows that the roots of (3.2) have negative real parts for $\tau = 0$. If (3.3) has pure imaginary roots $\lambda = \pm i\omega(\omega > 0)$ for some $\omega > 0$ and $\tau > 0$, we have from (3.3) that

$$\begin{cases} -\omega^2 + c\delta = bpe^{-m\tau}\widehat{T}\cos\omega\tau, \\ -\omega(c+\delta) = bpe^{-m\tau}\widehat{T}\sin\omega\tau, \end{cases} \tag{3.4}$$

which implies that

$$\omega^2 = \frac{1}{2}\left[-(c^2+d^2) \pm \sqrt{(c^2+d^2)^2 - 4(c^2\delta^2 - (bpe^{-m\tau}\widehat{T})^2)}\right] < 0,$$

by $R_0 < 1$. The contradiction shows that any root of (3.3) must have negative real part. Hence the viral-free equilibrium $\widehat{E}$ is locally asymptotically stable for any time delay $\tau \geqslant 0$.

If $R_0 > 1$, let $f(\lambda) = \lambda^2 + (c+\delta)\lambda + c\delta - bpe^{-m\tau}\widehat{T}e^{-\lambda\tau} = 0$. Note that $f(0) = c\delta - bpe^{-m\tau}\widehat{T}e^{-\lambda\tau} < 0$ by $R_0 > 1$ and $\lim_{\lambda\to+\infty} f(\lambda) = +\infty$. It follows from the continuity of the function $f(\lambda)$ on $(-\infty, +\infty)$ that the equation $f(\lambda) = 0$ has at least one positive root. Hence, the characteristic Eq. (3.2) has at least one positive real root. Hence, $\widehat{E}$ is unstable.

If $R_0 = 1$, the transcendental polynomial (3.3) becomes

$$g(\lambda) = \lambda^2 + (c+\delta)\lambda + c\delta - c\delta e^{-\lambda\tau} = 0. \tag{3.5}$$

It is clear that $\lambda = 0$ is a simple root of (3.5). We further show that any root of (3.5) must have negative real part except $\lambda = 0$.

In fact, if (3.5) has imaginary roots $\lambda = u \pm i\omega$ for some $u \geqslant 0$, $\omega \geqslant 0$ and $\tau \geqslant 0$, we have from (3.5) that

$$\begin{cases} u^2 - \omega^2 + (c+\delta)u = c\delta e^{-u\tau}\cos\omega\tau, \\ 2u\omega + (c+\delta)\omega = -c\delta e^{-u\tau}\sin\omega\tau \end{cases} \tag{3.6}$$

which, together with $u \geqslant 0$, implies that

$$(u^2 - \omega^2 + (c+\delta)u)^2 + (2u\omega + (a+d)\omega)^2 = c^2\delta^2 e^{-2u\tau} \leqslant c^2\delta^2.$$

However, it is easy to check that the above inequality is not true. Hence, it shows that any root of (3.5) has negative real part except $\lambda = 0$, which implies that the trivial solution of the linearised system (3.1) is stable for any time delay $\tau \geqslant 0$. Therefore our results in this theorem are proved. $\square$

Theorem 3.2

(1) *If* $R_0 < 1$, $\widehat{E}$ *is globally asymptotically stable for any time delay* $\tau \geqslant 0$.
(2) *If* $R_0 = 1$, $\widehat{E}$ *is globally attractive for any time delay* $\tau \geqslant 0$.

Proof. Define

$$G = \{\varphi = (\varphi_1, \varphi_2, \varphi_3) \in C_+ | \widehat{T} \geqslant \varphi_1 \geqslant 0, \varphi_2 \geqslant 0, \varphi_3 \geqslant 0\}.$$

From Lemma 2.2, we see that G attracts all solutions of (1.1). For any $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in G$, let $(T(t), I(t), V(t))$ be the solution of (1.1) with the initial function (2.1). We claim that for any $t \geqslant 0$, $T(t) \leqslant \widehat{T}$. In fact, if there is $t_1 > 0$ such that $T(t_1) > \widehat{T}$ and $\dot{T}(t_1) > 0$, then we have that

$$\dot{T}(t_1) = s - dT(t_1) + aT(t_1)\left(1 - \frac{T(t_1)}{T_{\max}}\right) - bT(t_1)V(t_1) \leqslant -bT(t_1)V(t_1) \leqslant 0.$$

Here we have used $T(t_1) > \widehat{T}$. This is a contradiction to $\dot{T}(t_1) > 0$. The claim is proved. Hence, G is a positively invariant with respect to (1.1). If $R_0 < 1$, let us define a functional W on G as follows:

$$W(t) = \frac{p}{\delta}\varphi_2(0) + \varphi_3(0) + k\int_{-\tau}^{0}\varphi_3(\zeta)\mathrm{d}\zeta, \tag{3.7}$$

here $k > 0$ is a constant to be chosen later. It is clear that $W(\varphi)$ is continuous on the subset G in C_+. From the invariance of G, for any $\varphi \in G$, the solution $(T(t), I(t), V(t))$ of (1.1) with the initial function (2.1) satisfies $T(t) \leqslant \widehat{T}$ for any $t \geqslant 0$. It follows from (1.1) and (3.7) that

$$\begin{aligned}\dot{W}(\varphi)|_{(1.1)} &= \frac{p}{\delta}[b\mathrm{e}^{-m\tau}\varphi_1(-\tau)\varphi_3(-\tau) - \delta\varphi_2(0)] + p\varphi_2(0) - c\varphi_3(0) + k[\varphi_3(0) - \varphi_2(-\tau)]\\ &= \varphi_3(0)(k-c) + \varphi_3(-\tau)\left[\frac{pb}{\delta}\mathrm{e}^{-m\tau}\varphi_1(-\tau) - k\right].\end{aligned}$$

By $R_0 < 1$, we can choose k such that $\frac{pb}{\delta}\mathrm{e}^{-m\tau} < k < c$. Hence, we have that

$$\dot{W}(\varphi)|_{(1.1)} \leqslant \varphi_3(0)(k-c) \tag{3.8}$$

for any $\varphi \in G$. This show that $W(\varphi)$ is a Liapunov function on the subset G in C_+. Define $E = \{\varphi \in G|\{\dot{W}(\varphi)|_{(1.1)}\} = 0\}$. From (3.8), we have that $E \subset \{\varphi \in G|\varphi_3(0) = 0\}$. Let M be the largest set in E which is invariant with respect to (1.1). Clearly, M is not empty since $(\widehat{T}, 0, 0) \in M$. For any $\varphi \in M$, let $(T(t), I(t), V(t))$ be the solution of (1.1) with the initial function (2.1). From the invariance of M, we have that $(T_t, I_t, V_t) \in M \subset E$ for any $t \in R$. Thus $V(t) \to 0$ for any $t \in R$. From the second equation of (1.1), we further have that $I(t) \equiv 0$ as $t \to +\infty$. From the first equation of (1.1) and $V(t) \equiv 0$ for any $t \in R$, we can also show that $T(t) \to \widehat{T}$ as $t \to +\infty$. Hence, the invariance of M implies that $I(t) \equiv 0$ and $T(t) \to \widehat{T}$ for any $t \in R$. Therefore, $M = \{(\widehat{T}, 0, 0)\}$. The classical Liapunov–LaSalle invariance principal shows that $(\widehat{T}, 0, 0)$ is globally attractive. Since it has been shown that, if $R_0 < 1$, $(\widehat{T}, 0, 0)$ is locally asymptotically stable for any time delay $\tau \geqslant 0$. Hence, $(\widehat{T}, 0, 0)$ is global asymptotic stability for any time delay $\tau \geqslant 0$. This proves the conclusion (1).

If $R_0 = 1$, let us consider the following functional on G:

$$W(t) = \frac{p}{\delta}\varphi_2(0) + \varphi_3(0) + \frac{bp}{\delta}\widehat{T}\int_{-\tau}^{0}\varphi_3(\zeta)\,\mathrm{d}\zeta. \tag{3.9}$$

Clearly $W(\varphi)$ is also continuous on subset $\overline{G}$ in C_+. From the invariance of G, for any $\varphi \in G$, the solution $(T(t), I(t), V(t))$ of (1.1) with the initial function (2.1) satisfies $T(t) \leqslant \overline{T}$ for all $t > 0$. From (1.1) and (3.9), we also have that

$$\dot{W}|_{(1.1)} = \frac{pb}{\delta}[\mathrm{e}^{-m\tau}\varphi_1(-\tau) - \widehat{T}]\varphi_3(-\tau).$$

Hence, $W(\varphi)$ is also a Liapunov function on the subset G in C_+. Define $E = \{\varphi \in G|\dot{W}|_{(1.1)} = 0\}$, and we have that $E \subset \{\varphi \in G|\varphi_3(-\tau) = 0 \text{ or } \varphi_1(-\tau) = \widehat{T}\}$. Let M be the largest set in E which is invariant with respect to (1.1). M is not empty. For any $\varphi \in M$, let $(T(t), I(t), V(t))$ be the solution of (1.1) with the initial function (1.1). From the invariance of M, we have that $(T_t, I_t, V_t) \in M \subset E$ for any $t \in R$. Thus, for each $t \in R$, we have that if $T(t-\tau) = \widehat{T}$ for some t, we must have that $V(t-\tau) = 0$ or $T(t-\tau) = 0$ by $T(t) \leqslant \widehat{T}$ and the differentiability of $T(t)$. Hence, the first equation of (1.1) implies that $s - d\widehat{T} + a\widehat{T}(1 - \frac{\widehat{T}}{T_{\max}}) - b\widehat{T}V(t-\tau) = -b\widehat{T}V(t-\tau) = 0$. We must have that $V(t) = 0$. Therefore, we have that $V(t) \equiv 0$ for any $t \in R$. By a completely similar proof as for the case $R_0 < 1$, we can shown that $M = \{(\widehat{T}, 0, 0)\}$. Therefore, it follows from Liapunov–LaSalle invariance principal that $(\widehat{T}, 0, 0)$ is globally attractive for any time delay $\tau \geqslant 0$. This proves the conclusion (2), and completes the proof of the Theorem 3.2. □

4. Stability and Hopf bifurcation at the endemic equilibrium $\overline{E}$

In this section we shall regard τ as a parameter to study the stability of the endemic equilibrium $\overline{E}$ and the existence of Hopf bifurcations.

Firstly, we present the following lemma from [12].

Lemma 4.1. *If* $\tau = 0$, $R_0 > 1$ *and* $(c+\delta)\left(\frac{s}{\overline{T}} + \frac{a\overline{T}}{T_{\max}}\right)\left(\frac{s}{\overline{T}} + \frac{a\overline{T}}{T_{\max}} + c + \delta\right) > pb^2\overline{T}\overline{V}$, *then the positive equilibrium* $\overline{E}$ *is asymptotically stable.*

The characteristic of the linearization of system (1.1) near the endemic equilibrium $\overline{E}$ *is given by*

$$P(\lambda,\tau) + Q(\lambda,\tau)e^{-\lambda\tau} = 0, \tag{4.1}$$

where

$$\begin{aligned} P(\lambda,\tau) &= \lambda^3 + b_1(\tau)\lambda^2 + b_2(\tau)\lambda + b_3(\tau), \\ Q(\lambda,\tau) &= b_4(\tau)\lambda + b_5(\tau), \end{aligned} \tag{4.2}$$

and

$$\begin{aligned} b_1(\tau) &= c + \delta - a + d + \frac{2a\overline{T}}{T_{\max}} + b\overline{V}, \\ b_2(\tau) &= c\delta - (c+\delta)\left(a - d - \frac{2a\overline{T}}{T_{\max}} - b\overline{V}\right), \\ b_3(\tau) &= c\delta\left(d - a + \frac{2a\overline{T}}{T_{\max}} + b\overline{V}\right), \\ b_4(\tau) &= -pbe^{-m\tau}\overline{T} - be^{-m\tau}\overline{V}, \\ b_5(\tau) &= \left(a - d - \frac{2a\overline{T}}{T_{\max}} - b\overline{V}\right)pbe^{-m\tau}\overline{T} - pb^2e^{-m\tau}\overline{T}\overline{V} \\ &= \left(a - d - \frac{2a\overline{T}}{T_{\max}}\right)pbe^{-m\tau}\overline{T}. \end{aligned}$$

When $\tau = 0$, the Eq. (4.1) becomes

$$\lambda^3 + b_1(0)\lambda^2 + (b_2(0) + b_4(0))\lambda + b_3(0) + b_5(0) = 0.$$

From Lemma 4.1, we know that the positive equilibrium $\overline{E}(\overline{T},\overline{I},\overline{V})$ of (1.1) is asymptotically stable.

In the following, we investigate the existence of purely imaginary roots $\lambda = i\omega(\omega > 0)$ to Eq. (1.1). Eq. (1.1) takes the form of a third-degree exponential polynomial in λ, which all the coefficients of P and Q depending on τ. Beretta and Kuang [13] established a geometrical criterion which gives the existence of purely imaginary of a characteristic equation with delay dependent coefficients.

In order to apply the criterion due to Beretta and Kuang [13], we need to verify the following properties for all $\tau \in [0,\tau_{\max})$, where $\tau_{\max}$ is the maximum value which $\overline{E}$ exists.

(a) $P(0,\tau) + Q(0,\tau) \neq 0$;
(b) $P(i\omega,\tau) + Q(i\omega,\tau) \neq 0$;
(c) $\limsup\{|\frac{P(\lambda,\tau)}{Q(\lambda,\tau)}| : |\lambda| \to \infty, Re\lambda \geqslant 0\} < 1$;
(d) $F(\omega,\tau) = |P(i\omega,\tau)|^2 - |Q(i\omega,\tau)|^2$ has a finite number of zeros;
(e) Each positive root $\omega(\tau)$ of $F(\omega,\tau) = 0$ is continuous and differentiable in τ whenever it exists.

Here, $P(\lambda,\tau)$ and $Q(\lambda,\tau)$ are defined as in (4.2).
Let $\tau \in [0,\tau_{\max})$. It is easy to see that

$$P(0,\tau) + Q(0,\tau) = b_3(\tau) + b_5(\tau) = c\delta b\overline{V} > 0.$$

This implies that (4.2) is satisfied. And (b) is obviously true because

$$\begin{aligned} P(i\omega,\tau) + Q(i\omega,\tau) &= -i\omega^3 - b_1(\tau)\omega^2 + ib_2(\tau)\omega + b_3(\tau) + ib_4(\tau)\omega + b_5(\tau) \\ &= [b_3(\tau) + b_5(\tau) - b_1(\tau)\omega^2] + i\omega[b_4(\tau) + b_2(\tau) - \omega^2] \neq 0. \end{aligned}$$

From (4.2) we know that

$$\lim_{|\lambda|\to+\infty}\left|\frac{Q(\lambda,\tau)}{P(\lambda,\tau)}\right| = 0.$$

Therefore (c) follows.

Let F be defined as in (d). From

$$\begin{aligned}|P(\mathrm{i}\omega,\tau)|^2 &= (-\omega^3+b_2(\tau)\omega)^2+(-b_1(\tau)\omega^2+b_3(\tau))^2\\ &= \omega^6+(-2b_2(\tau)+b_1^2(\tau))\omega^4+(b_2^2(\tau)-2b_1(\tau)b_3(\tau))\omega^2+b_3^2(\tau),\end{aligned}$$

and

$$|Q(i\omega,\tau)|^2 = b_4^2(\tau)\omega^2+b_5^2(\tau),$$

we have

$$F(\omega,\tau) = \omega^6+a_1(\tau)\omega^4+a_2(\tau)\omega^2+a_3(\tau),$$

where

$$\begin{aligned}a_1(\tau) &= b_1^2(\tau)-2b_2(\tau),\\ a_2(\tau) &= b_2^2(\tau)-2b_2(\tau)b_1(\tau)-b_4^2(\tau),\\ a_3(\tau) &= b_3^2(\tau)-b_5^2(\tau).\end{aligned}$$

It is obvious that property (d) is satisfied, and by implicit function theorem, (e) is also satisfied.

Now let $\lambda = \mathrm{i}\omega$ $(\omega > 0)$ be a root of Eq. (4.1). Substituting it into Eq. (4.1) and separating the real and imaginary parts yields

$$\begin{aligned}-b_3(\tau)+b_1(\tau)\omega^2 &= b_5(\tau)\sin\omega\tau+b_4(\tau)\omega\cos\omega\tau,\\ \omega^3-b_2(\tau)\omega &= b_4(\tau)\omega\sin\omega\tau-b_5(\tau)\cos\omega\tau.\end{aligned} \tag{4.3}$$

From (4.3) it follows that

$$\sin\omega\tau = \frac{[b_1(\tau)b_4(\tau)-b_5(\tau)]\omega^2+[b_2(\tau)b_5(\tau)-b_3(\tau)b_4(\tau)]\omega}{b_4^2(\tau)\omega^2+b_5^2(\tau)\omega}, \tag{4.4a}$$

$$\cos\omega\tau = \frac{b_3(\tau)b_5(\tau)+[b_2(\tau)b_4(\tau)-b_1(\tau)b_5(\tau)]\omega^2-b_4(\tau)\omega^4}{b_4^2(\tau)\omega^2+b_5^2(\tau)\omega}. \tag{4.4b}$$

By the definitions of $P(\lambda,\tau)$, $Q(\lambda,\tau)$ as in (4.2), and applying the property (a), (4.4) can be written as

$$\sin\omega\tau = \mathrm{Im}\frac{P(\mathrm{i}\omega,\tau)}{Q(\mathrm{i}\omega,\tau)} \tag{4.5a}$$

and

$$\cos\omega\tau = -Re\frac{P(\mathrm{i}\omega,\tau)}{Q(\mathrm{i}\omega,\tau)}, \tag{4.5b}$$

which yields

$$|P(\mathrm{i}\omega,\tau)|^2 = |Q(\mathrm{i}\omega,\tau)|^2.$$

Assume that $I \in R_{+0}$ is the set where $\omega(\tau)$ is a positive root of

$$F(\omega,\tau) = |P(\mathrm{i}\omega,\tau)|^2-|Q(\mathrm{i}\omega,\tau)|^2$$

and for $\tau \notin I$, $\omega(\tau)$ is not definite. Then for all τ in I, $\omega(\tau)$ satisfied

$$F(\omega,\tau) = 0. \tag{4.6}$$

The polynomial function F can be written as $F(\omega,\tau) = h(\omega^2,\tau)$, where h is a third degree polynomial, defined by

$$h(z,\tau) = z^3 + a_1 z^2 + a_2 z + a_3. \tag{4.7}$$

Depending on the determinant of equation

$$h(z,\tau) = z^3 + a_1 z^2 + a_2 z + a_3 = 0, \tag{4.8}$$

$M = \left(\frac{q}{2}\right)^2 + \left(\frac{r}{3}\right)^3$, where $r = a_2 - \frac{1}{3}a_1^2$, $q = \frac{2}{27}a_1^3 - \frac{1}{3}a_1a_2 + a_3$, there are three cases for the solutions of Eq. (4.8).

(i) If $M > 0$, Eq. (4.8) has a real root and a pair of conjugate complex roots. The real root is positive and is given by

$$\mu_1 = \sqrt[3]{-\frac{q}{2} + \sqrt{M}} + \sqrt[3]{-\frac{q}{2} - \sqrt{M}} - \frac{1}{3}a_1.$$

(ii) If $M = 0$, Eq. (3.9) has three real roots, of which two are equal. In particular, if $a_1 > 0$, there exists only one positive root, $\mu_1 = 2\sqrt[3]{-\frac{q}{2}} - \frac{a_1}{3}$; If $a_1 < 0$, there exists a positive root $\mu_1 = 2\sqrt[3]{-\frac{q}{2}} - \frac{a_1}{3}$ for $\sqrt[3]{-\frac{q}{2}} > -\frac{a_1}{3}$, and there exist three positive roots for $\frac{a_1}{6} < \sqrt[3]{-\frac{q}{2}} < -\frac{a_1}{3}$, $\mu_1 = 2\sqrt[3]{-\frac{q}{2}} - \frac{a_1}{3}$, $\mu_2 = \mu_3 = -\sqrt[3]{-\frac{q}{2}} - \frac{a_1}{3}$.

(iii) If $M < 0$, there are three distinct real roots, $\mu_1 = 2\sqrt{\frac{|r|}{3}}\cos(\frac{\varphi}{3}) - \frac{a_1}{3}$, $\mu_2 = 2\sqrt{\frac{|r|}{3}}\cos(\frac{\varphi}{3} + \frac{2\pi}{3}) - \frac{a_1}{3}$, $\mu_1 = 2\sqrt{\frac{|r|}{3}}\cos(\frac{\varphi}{3} + \frac{4\pi}{3}) - \frac{a_1}{3}$, where $\cos\varphi = -\frac{q}{2\sqrt{(\frac{|r|}{3})^3}}$. Furthermore, if $a_1 > 0$, there exists only one positive root. Otherwise, if $a_1 < 0$, there may exist either one or three positive real roots. If there is only one positive real root, it is equal to $\max(\mu_1, \mu_2, \mu_3)$.

Clearly, the number of positive real roots of Eq. (4.8) depends on the sign of a_1. When $a_1 \geqslant 0$, Eq. (4.8) has only one positive real root. Otherwise, there may exist three positive real roots.

It is easy to know that

$$a_1 = b_1^2(\tau) - 2b_2(\tau) = c^2 + \delta^2 + \left(a - d - \frac{2a\overline{T}}{T_{\max}} - b\overline{V}\right)^2 > 0.$$

Hence, Eq. (4.8) has only one positive real root. We denote by z_+ this positive real root. Thus, Eq. (4.6) has only one positive real root $\omega = \sqrt{z_+}$. And the critical values of τ and $\omega(\tau)$ are impossible to solve explicitly, so we shall use the procedure described in Beretta and Kuang [13]. According to this procedure, we define $\theta(\tau) \in [0, 2\pi)$ such that $\sin\theta(\tau)$ and $\cos\theta(\tau)$ are given by the right hand sides of (4.4a) and (4.4b), respectively, with $\theta(\tau)$ given by (4.8). This define $\theta(\tau)$ in a form suitable for numerical evaluation using standard software.

And the relation between the argument θ and $\omega\tau$ in (4.7) for $\tau > 0$ must be

$$\omega\tau = \theta + 2n\pi, \quad n = 0, 1, 2, \ldots \tag{4.9}$$

Hence we can define the maps: $\tau_n : I \to R_{+0}$ given by

$$\tau_n(\tau) := \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}, \quad \tau_n > 0, \ \ n = 0, 1, 2, \ldots, \tag{4.10}$$

where a positive root $\omega(\tau)$ of (4.6) exists in I.

Let us introduce the functions $S_n(\tau) : I \to R$,

$$S_n(\tau) = \tau - \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}, \quad n = 0, 1, 2, \ldots, \tag{4.11}$$

that are continuous and differentiable in τ. Thus, we give the following theorem which is due to Beretta and Kuang [13].

Theorem 4.1. *Assume that $\omega(\tau)$ is a positive root of (4.2) defined for $\tau \in I, I \subseteq R_{+0}$, and at some $\tau^* \in I$, $S_n(\tau^*) = 0$ for some $n \in N_0$. Then a pair of simple conjugate pure imaginary roots $\lambda = \pm i\omega$ exists at $\tau = \tau^*$ which crosses the imaginary axis from left to right if $\delta(\tau^*) > 0$ and crosses the imaginary axis from right to left if $\delta(\tau^*) < 0$, where*

$$\delta(\tau^*) = \mathrm{sign}\{F'_\omega(\omega\tau^*, \tau^*)\}\mathrm{sign}\left\{\left.\frac{\mathrm{d}S_n(\tau)}{\mathrm{d}\tau}\right|_{\tau=\tau^*}\right\}. \tag{4.12}$$

Applying Lemma 4.1 and the Hopf bifurcation theorem for functional differential equation [14], we can conclude the existence of a Hopf bifurcation as stated in the following theorem.

Theorem 4.2. *For system (1.1), there exists $\tau^* \in I$, such that the equilibrium $\overline{E}$ is asymptotically stable for $0 \leqslant \tau < \tau^*$, and becomes unstable for τ staying in some right neighborhood of τ^*, with a Hopf bifurcation occurring when $\tau = \tau^*$.*

5. Direction and stability of the Hopf bifurcation

In the above section, we have obtained some conditions which guarantee that the delay differential equation model of HIV infection of $CD4^+$ T-cells undergoes the Hopf bifurcation at some value of $\tau = \tau^*$. In this section, we shall study the direction, stability and the period of the bifurcating periodic solutions. The approach we used here is based on the normal form approach and the center manifold theory introduced by Hassard et al. [15]. Throughout this section, we always assume that system (1.1) undergoes Hopf bifurcation at the positive equilibrium $\overline{E}(\overline{T}, \overline{I}, \overline{V})$ for $\tau = \tau^*$, and then $\pm\mathrm{i}\omega$ is corresponding purely imaginary roots of the characteristic equation at the positive equilibrium $\overline{E}(\overline{T}, \overline{I}, \overline{V})$.

Let $u_1(t) = T(t) - \overline{T}$, $u_2(t) = I(t) - \overline{I}$, $u_3(t) = V(t) - \overline{V}$, $x_i(t) = u_i(\tau t)$, $(i = 1, 2, 3)$, $\tau = \tau^* + \mu$, system (1.1) is transformed into an functional differential equation (FDE) in $C = C([-1, 0], R^3)$ as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = L_\mu(x_t) + f(\mu, x_t), \tag{5.1}$$

where $x(t) = (x_1(t), x_2(t), x_3(t))^{\mathrm{T}} \in R^3$ and $L\mu : C \to R, f : R \times C \to R$, are given respectively by

$$L_\mu(\phi) = (\tau^* + \mu)\begin{pmatrix} a - d - b\overline{V} - \frac{2a\overline{T}}{T_{\max}} & 0 & -b\overline{T} \\ 0 & -\delta & 0 \\ 0 & p & -c \end{pmatrix}\begin{pmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{pmatrix} + (\tau^* + \mu)\begin{pmatrix} 0 & 0 & 0 \\ b\mathrm{e}^{-m\tau^*}\overline{V} & 0 & b\mathrm{e}^{-m\tau^*}\overline{T} \\ 0 & 0 & 0 \end{pmatrix}\begin{pmatrix} \phi_1(-1) \\ \phi_2(-1) \\ \phi_3(-1) \end{pmatrix}, \tag{5.2}$$

$$f(\mu, \phi) = (\tau^* + \mu)\begin{pmatrix} -\frac{a}{T_{\max}}\phi_1^2(0) - b\phi_1(0)\phi_3(0) \\ b\mathrm{e}^{-m\tau^*}\phi_1(-1)\phi_3(-1) \\ 0 \end{pmatrix}. \tag{5.3}$$

Clearly, L_μ is a linear continuous operator from C to R^3. By the Riesz representation theorem, there exists a matrix components are bounded variation function $\eta(\theta, \mu)$ in $\theta \in [-1, 0]$, such that

$$L_\mu\phi = \int_{-1}^{0} \mathrm{d}\eta(\theta, 0)\phi(\theta) \tag{5.4}$$

for $\phi \in C$.

In fact, we can choose

$$\eta(\theta, \mu) = (\tau^* + \mu)\begin{pmatrix} a - d - b\overline{V} - \frac{2a\overline{T}}{T_{\max}} & 0 & -b\overline{T} \\ 0 & -\delta & 0 \\ 0 & p & -c \end{pmatrix}\begin{pmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{pmatrix}\delta(\theta) - (\tau^* + \mu)\begin{pmatrix} 0 & 0 & 0 \\ b\mathrm{e}^{-m\tau^*}\overline{V} & 0 & b\mathrm{e}^{-m\tau^*}\overline{T} \\ 0 & 0 & 0 \end{pmatrix}\delta(\theta + 1), \tag{5.5}$$

where

$$\delta = \begin{cases} 1, & \theta = 0, \\ 0, & \theta \neq 0. \end{cases}$$

For $\phi \in C^1([-1,0], R^3)$, define

$$A(\mu)\phi = \begin{cases} \frac{\mathrm{d}\phi(\theta)}{\mathrm{d}\theta}, & \theta \in [-1,0), \\ \int_{-1}^{0} \mathrm{d}\eta(\mu,s)\phi(s), & \theta = 0, \end{cases}$$

and

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

Then system (5.1) is equivalent to

$$\dot{x}_t = A(\mu)x_t + R(\mu)x_t, \tag{5.6}$$

where $x_t(\theta) = x(t+\theta)$ for $\theta \in [-1,0]$.

For $\psi \in C^1([-1,0], (R^3)^*)$, define

$$A^*\psi(\xi) = \begin{cases} -\frac{\mathrm{d}\psi(\xi)}{\mathrm{d}\xi}, & \xi \in (0,1], \\ \int_{-1}^{0} \mathrm{d}\eta^{\mathrm{T}}(t,0)\psi(-t), & \xi = 0, \end{cases}$$

and a bilinear inner product

$$\langle \psi(\xi), \phi(\theta) \rangle = \overline{\psi}(0)\phi(0) - \int_{-1}^{0} \int_{\xi-\theta}^{\theta} \overline{\psi}(\zeta - \theta)\mathrm{d}\eta(\theta)\phi(\zeta)\mathrm{d}\zeta, \tag{5.7}$$

where $\eta(\theta) = \eta(\theta, 0)$. Then $A(0)$ and A^* are adjoint operators. By the discussion in Section 4, we know that $\pm i\omega^*\tau^*$ are eigenvalues of $A(0)$. Thus, they are also eigenvalues of A^*. We first need to compute the eigenvector of $A(0)$ and A^* corresponding to $+\mathrm{i}\omega^*\tau^*$ and $-\mathrm{i}\omega^*\tau^*$, respectively.

Suppose that $q(\theta) = (1,\alpha,\beta)^{\mathrm{T}}\mathrm{e}^{\mathrm{i}\omega^*\tau^*\theta}$ is the eigenvector of $A(0)$ corresponding to $+\mathrm{i}\omega^*\tau^*$, then $A(0)q(\theta) = \mathrm{i}\omega^*\tau^*q(\theta)$. It follows from the definition of $A(0)$ and (5.2), (5.4) and (5.5) that

$$\tau^* \begin{pmatrix} \mathrm{i}\omega^* + d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & b\overline{T} \\ 0 & \mathrm{i}\omega^* + \delta & 0 \\ 0 & -p & \mathrm{i}\omega^* + c \end{pmatrix} q(0) = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}.$$

Thus, we can easily obtain $q(0) = (1,\alpha,\beta)^{\mathrm{T}}$, where $\alpha = \frac{\mathrm{i}\omega^*+c}{p}\beta$, $\beta = -\frac{\mathrm{i}\omega^*+d-a+b\overline{V}+\frac{2a\overline{V}}{T_{\max}}}{b\overline{T}}$. Similarly, let $q^*(\xi) = D(1,\alpha^*,\beta^*)\mathrm{e}^{\mathrm{i}\omega^*\tau^*\xi}$ is the eigenvector of A^* corresponding to $-\mathrm{i}\omega^*\tau^*$. By the definition of A^* and (5.2)–(5.4), we can compute $\alpha^* = -\frac{p\beta^*}{\mathrm{i}\omega^*+\delta}$, $\beta^* = \frac{b\overline{T}}{\mathrm{i}\omega^*+c}$. In order to assure $< q^*(\xi), q(\theta) >= 1$, we need to determine the value of D. From (5.7), we have

$$\begin{aligned} \langle q^*(\xi), q(\theta) \rangle &= \overline{D}(1,\overline{\alpha^*},\overline{\beta^*})(1,\alpha,\beta)^{\mathrm{T}} - \int_{-1}^{0}\int_{\zeta=0}^{\theta} \overline{D}(1,\overline{\alpha^*},\overline{\beta^*})\mathrm{e}^{-\mathrm{i}\omega^*\tau^*(\zeta-\theta)}\mathrm{d}\eta(\theta)(1,\alpha,\beta)^{\mathrm{T}}\mathrm{e}^{\mathrm{i}\omega^*\tau^*\zeta}d\zeta \\ &= \overline{D}\left\{1 + \alpha\overline{\alpha^*} + \beta\overline{\beta^*} - \int_{-1}^{0}(1,\overline{\alpha^*},\overline{\beta^*})\theta\mathrm{e}^{\mathrm{i}\omega^*\tau^*\theta}\mathrm{d}\eta(\theta)(1,\alpha,\beta)^{\mathrm{T}}\right\} \\ &= \overline{D}\{1 + \alpha\overline{\alpha^*} + \beta\overline{\beta^*} + (b\mathrm{e}^{-m\tau}\overline{V\alpha^*} + b\mathrm{e}^{-m\tau}\overline{T}\beta\overline{\alpha^*})\tau^*\mathrm{e}^{\mathrm{i}\omega^*\tau^*}\}. \end{aligned}$$

Thus, we can choose D as

$$D = \frac{1}{1 + \alpha\overline{\alpha^*} + \beta\overline{\beta^*} + (b\mathrm{e}^{-m\tau^*}\overline{V}\overline{\alpha^*} + b\mathrm{e}^{-m\tau^*}\overline{T}\beta\overline{\alpha^*})\tau^*\mathrm{e}^{\mathrm{i}\omega^*\tau^*}}.$$

In the remainder of this section, we use the same notations as in [15], we first compute the coordinates to describe the center manifold C_0 at $\mu = 0$. Let x_t be the solution of (5.6) when $\mu = 0$. Define

$$z(t) = \langle q^*, x_t\rangle, \quad W(w,\theta) = x_t(\theta) - 2Re\{z(t)q(\theta)\}. \tag{5.8}$$

On the center manifold C_0 we have

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

where

$$W(z,\bar{z},\theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + W_{30}(\theta)\frac{z^3}{6} + \cdots, \tag{5.9}$$

z and $\bar{z}$ are local coordinates for center manifold C_0 in the direction of q^* and $\overline{q^*}$. Note that W is real if x_t is real. We only consider real solutions. For solution $x_t \in C_0$ of (5.6), since $\mu = 0$, we have

$$\dot{z}(t) = \mathrm{i}\omega^*\tau^*z + \overline{q^*}(0)f(0, W(z,\bar{z},\theta) + 2Re\{zq(\theta)\}) = \mathrm{i}\omega^*\tau^*z + \overline{q^*}(0)f_0(z,\bar{z}).$$

We rewrite this equation as

$$\dot{z}(t) = \mathrm{i}\omega^*\tau^*z(t) + g(z,\bar{z}),$$

where

$$g(z,\bar{z}) = \overline{q^*}(0)f_0(z,\bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots \tag{5.10}$$

It follows from (5.8) and (5.9) that

$$\begin{aligned} x_t(\theta) &= W(t,\theta) - 2Re\{z(t)q(t)\} \\ &= W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + (1,\alpha,\beta)^{\mathrm{T}}\mathrm{e}^{\mathrm{i}\omega^*\tau^*\theta}z + (1,\bar{\alpha},\bar{\beta})^{\mathrm{T}}\mathrm{e}^{-\mathrm{i}\omega^*\tau^*\theta}\bar{z} + \cdots \end{aligned} \tag{5.11}$$

It follows together with (5.3) that

$$\begin{aligned} g(z,\bar{z}) &= \overline{q^*}(0)f_0(z,\bar{z}) = \overline{q^*}(0)f(0,x_t) = \tau^*\overline{D}(1,\overline{\alpha^*},\overline{\beta^*})\begin{pmatrix} -\frac{ax_{1t}^2(0)}{T_{\max}} - bx_{1t}(0)x_{3t}(0) \\ b\mathrm{e}^{-m\tau^*}x_{1t}(-1)x_{3t}(-1) \\ 0 \end{pmatrix} \\ &= \frac{-\tau^*\overline{D}a}{T_{\max}}\left[z + \bar{z} + W_{20}^{(1)}(0)\frac{z^2}{2} + W_{11}^{(1)}(0)z\bar{z} + W_{02}^{(1)}(0)\frac{\bar{z}^2}{2} + o(|(z,\bar{z})^3|)\right]^2 \\ &\quad - b\tau^*\overline{D}\left[z + \bar{z} + W_{20}^{(1)}(0)\frac{z^2}{2} + W_{11}^{(1)}(0)z\bar{z} + W_{02}^{(1)}(0)\frac{\bar{z}^2}{2} + o(|(z,\bar{z})|^3)\right] \\ &\quad \times \left[\beta z + \bar{\beta}\bar{z} + W_{20}^{(3)}(0)\frac{z^2}{2} + W_{11}^{(3)}(0)z\bar{z} + W_{02}^{(3)}(0)\frac{\bar{z}^2}{2} + o(|(z,\bar{z})|^3)\right] \\ &\quad + \tau^*\overline{D}\bar{\alpha}^*b\mathrm{e}^{-m\tau^*}\left[\mathrm{e}^{-\mathrm{i}\omega^*\tau^*}z + \mathrm{e}^{\mathrm{i}\omega^*\tau^*}\bar{z} + W_{20}^{(1)}(-1)\frac{z^2}{2} + W_{11}^{(1)}(-1)z\bar{z} + W_{02}^{(1)}(-1)\frac{\bar{z}^2}{2} + o(|(z,\bar{z})|^3)\right] \\ &\quad \times \left[\beta\mathrm{e}^{-\mathrm{i}\omega^*\tau^*}z + \bar{\beta}\mathrm{e}^{\mathrm{i}\omega^*\tau^*}\bar{z} + W_{20}^{(3)}(-1)\frac{z^2}{2} + W_{11}^{(3)}(-1)z\bar{z} + W_{02}^{(3)}(-1)\frac{\bar{z}^2}{2} + o(|(z,\bar{z})|^3)\right]. \end{aligned} \tag{5.12}$$

Comparing the coefficients with (5.10), we have

$$\begin{aligned}
g_{20} &= 2\tau^*\overline{D}\left(-\frac{a}{2T_{\max}} - \frac{b\beta}{2} + \frac{\bar{\alpha}^* b\beta e^{-m\tau^*}e^{-2i\omega^*\tau^*}}{2}\right),\\
g_{11} &= 2\tau^*\overline{D}\left(-\frac{a}{T_{\max}} - bRe\{\beta\} + \bar{\alpha}^* b e^{-m\tau^*} Re\{\beta\}\right),\\
g_{02} &= 2\tau^*\overline{D}\left(-\frac{a}{2T_{\max}} - \frac{b\bar{\beta}}{2} + \frac{\bar{\alpha}^*\bar{\beta} b e^{-m\tau^*}e^{2i\omega^*\tau^*}}{2}\right),\\
g_{21} &= \tau^*\overline{D}\Bigg[-\frac{a}{T_{\max}}(2W_{11}^{(1)}(0) + \frac{W_{20}^{(1)}(0)}{2}) - b(W_{11}^{(3)}(0) + \frac{W_{20}^{(3)}(0)}{2} + \frac{\bar{\beta}}{2}W_{20}^{(1)}(0)\\
&\quad + \beta W_{11}^{(1)}(0)) + \bar{\alpha}^* b e^{-m\tau^*}\left(e^{-i\omega^*\tau^*}W_{11}^{(3)}(-1) + \frac{e^{i\omega^*\tau^*}}{2}W_{20}^{(3)}(-1)\right.\\
&\quad \left.+\frac{\bar{\beta}e^{i\omega^*\tau^*}}{2}W_{20}^{(1)}(-1) + W_{11}^{(1)}(-1) + \beta e^{i\omega^*\tau^*}e^{-i\omega^*\tau^*}\right)\Bigg].
\end{aligned} \tag{5.13}$$

Since there are $W_{20}(\theta)$ and $W_{11}(\theta)$ in g_{21}, we still need to compute them. From (5.6) and (5.8), we have

$$\dot{W} = \dot{x}_t - \dot{z}q - \dot{\bar{z}}\bar{q} = \begin{cases} AW - 2Re\{\overline{q^*}(0)f_0 q(\theta)\}, & \theta \in [-1,0),\\ AW - 2Re\{\overline{q^*}(0)f_0 q(\theta)\} + f_0, & \theta = 0, \end{cases} \triangleq AW + H(z,\bar{z},\theta), \tag{5.14}$$

where

$$H(z,\bar{z},\theta) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots \tag{5.15}$$

Substituting the corresponding series into (5.14) and comparing the coefficients, we obtain

$$(A - 2i\omega^*\tau^*)W_{20}(\theta) = -H_{20}, \quad AW_{11}(\theta) = -H_{11}, \cdots \tag{5.16}$$

From (5.14), we know that for $\theta \in [-1,0)$,

$$H(z,\bar{z},\theta) = -\overline{q^*}(0)f_0 q(\theta) - q^*(0)\bar{f}_0\bar{q}(\theta) = -g(z,\bar{z})q(\theta) - g(z,\bar{z})\bar{q}(\theta). \tag{5.17}$$

Comparing the coefficients with (5.15) gives that

$$H_{20}(\theta) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta), \tag{5.18}$$

and

$$H_{11}(\theta) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta). \tag{5.19}$$

From (5.16), (5.18), it follows from the definition of A, we get

$$\dot{W}_{20} = 2i\omega^*\tau^* W_{20}(\theta) - H_{20}(\theta) = 2i\omega^*\tau^* W_{20}(\theta) + g_{20}q(\theta) + \bar{g}_{02}\bar{q}(\theta).$$

Notice that $q(\theta) = (1,\alpha,\beta)^{\mathrm{T}}e^{i\omega^*\tau^*\theta}$, hence

$$W_{20}(\theta) = \frac{ig_{20}}{\omega^*\tau^*}q(0)e^{i\omega^*\tau^*\theta} + \frac{i\bar{g}_{02}}{3\omega^*\tau^*}\bar{q}(0)e^{-i\omega^*\tau^*\theta} + E_1 e^{2i\omega^*\tau^*\theta}, \tag{5.20}$$

where $E_1 = (E_1^{(1)}, E_1^{(2)}, E_1^{(3)}) \in R^3$ is a constant vector. Similarly, from (5.16) and (5.19), we obtain

$$W_{11}(\theta) = -\frac{ig_{11}}{\omega^*\tau^*}q(0)e^{i\omega^*\tau^*\theta} + \frac{i\bar{g}_{11}}{\omega^*\tau^*}\bar{q}(0)e^{-i\omega^*\tau^*\theta} + E_2, \tag{5.21}$$

where $E_2 = (E_2^{(1)}, E_2^{(2)}, E_2^{(3)}) \in R^3$ is also a three-dimensional constant vector.

In what follows, we shall seek appropriate E_1 and E_2. From the definition of A and (5.16), we can get

$$\int_{-1}^{0} d\eta(\theta)W_{20}(\theta) = 2i\omega^*\tau^* W_{20}(\theta) - H_{20}(\theta), \tag{5.22}$$

and

$$\int_{-1}^{0} \mathrm{d}\eta(\theta)W_{11}(\theta) = -H_{11}(\theta), \tag{5.23}$$

where $\eta(\theta) = \eta(0,\theta)$. By (5.14), we have

$$H_{20}(\theta) = -g_{20}q(0) - \bar{g}_{20}\bar{q}(0) + 2\tau^* \begin{pmatrix} -\frac{a}{2T_{\max}} - \frac{b\beta}{2} \\ \frac{b\beta \mathrm{e}^{-m\tau^*}\mathrm{e}^{-2\mathrm{i}\omega^*\tau^*}}{2} \\ 0 \end{pmatrix}, \tag{5.24}$$

and

$$H_{11}(\theta) = -g_{11}q(0) - \bar{g}_{11}\bar{q}(0) + 2\tau^* \begin{pmatrix} -\frac{a}{T_{\max}} - bRe\{\beta\} \\ b\mathrm{e}^{-m\tau^*}Re\{\beta\} \\ 0 \end{pmatrix}. \tag{5.25}$$

Substituting (5.20) and (5.24) into (5.22), we obtain

$$\left(2i\omega^*\tau^* I - \int_{-1}^{0} \mathrm{e}^{2\mathrm{i}\omega^*\tau^*\theta}\mathrm{d}\eta(\theta)\right)E_1 = 2\tau^* \begin{pmatrix} -\frac{a}{2T_{\max}} - \frac{b\beta}{2} \\ \frac{b\beta \mathrm{e}^{-m\tau^*}\mathrm{e}^{-2\mathrm{i}\omega^*\tau^*}}{2} \\ 0 \end{pmatrix},$$

which leads to

$$\begin{pmatrix} 2i\omega^* + d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & b\overline{T} \\ 0 & 2\mathrm{i}\omega^* + \delta & 0 \\ 0 & -p & 2\mathrm{i}\omega^* + c \end{pmatrix} E_1 = 2\begin{pmatrix} -\frac{a}{2T_{\max}} - \frac{bRe\{\beta\}}{2} \\ \frac{b\beta \mathrm{e}^{-m\tau^*}\mathrm{e}^{-2i\omega^*\tau^*}}{2} \\ 0 \end{pmatrix}.$$

It follows that

$$E_1^{(1)} = \frac{2}{\Delta}\begin{vmatrix} -\frac{a}{2T_{\max}} - \frac{b\beta}{2} & 0 & b\overline{T} \\ \frac{b\beta \mathrm{e}^{-m\tau^*}\mathrm{e}^{-2\mathrm{i}\omega^*\tau^*}}{2} & 2i\omega^* + \delta & 0 \\ 0 & -p & 2\mathrm{i}\omega^* + c \end{vmatrix},$$

$$E_1^{(2)} = \frac{2}{\Delta}\begin{vmatrix} 2\mathrm{i}\omega^* + d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & -\frac{a}{2T_{\max}} - \frac{b\beta}{2} & b\overline{T} \\ 0 & \frac{b\beta \mathrm{e}^{-m\tau^*}\mathrm{e}^{-2\mathrm{i}\omega^*\tau^*}}{2} & 0 \\ 0 & 0 & 2\mathrm{i}\omega^* + c \end{vmatrix},$$

$$E_1^{(3)} = \frac{2}{\Delta}\begin{vmatrix} 2\mathrm{i}\omega^* + d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & -\frac{a}{2T_{\max}} - \frac{b\beta}{2} \\ 0 & 2\mathrm{i}\omega^* + \delta & \frac{b\beta \mathrm{e}^{-m\tau^*}\mathrm{e}^{-2\mathrm{i}\omega^*\tau^*}}{2} \\ 0 & -p & 0 \end{vmatrix},$$

where

$$\Delta = \begin{vmatrix} 2\mathrm{i}\omega^* + d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & b\overline{T} \\ 0 & 2\mathrm{i}\omega^* + \delta & 0 \\ 0 & -p & 2\mathrm{i}\omega^* + c \end{vmatrix}.$$

Similarly, substituting (5.21) and (5.25) into (5.23), we can get

$$\begin{pmatrix} d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & b\overline{T} \\ -b\mathrm{e}^{-m\tau^*}\overline{V} & \delta & -b\mathrm{e}^{-m\tau^*}\overline{T} \\ 0 & -p & c \end{pmatrix} E_2 = 2\begin{pmatrix} -\frac{a}{T_{\max}} - bRe\{\beta\} \\ b\mathrm{e}^{-m\tau^*}Re\{\beta\} \\ 0 \end{pmatrix},$$

and hence

$$E_2^{(1)} = \frac{2}{\Delta_1}\begin{vmatrix} -\frac{a}{T_{\max}} - bRe\{\beta\} & 0 & b\overline{T} \\ be^{-m\tau^*}Re\{\beta\} & \delta & -be^{-m\tau^*}\overline{T} \\ 0 & -p & c \end{vmatrix},$$

$$E_2^{(2)} = \frac{2}{\Delta_1}\begin{vmatrix} d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & -\frac{a}{T_{\max}} - bRe\{\beta\} & b\overline{T} \\ -be^{-m\tau^*}\overline{V} & be^{-m\tau^*}Re\{\beta\} & -be^{-m\tau^*}\overline{T} \\ 0 & 0 & c \end{vmatrix},$$

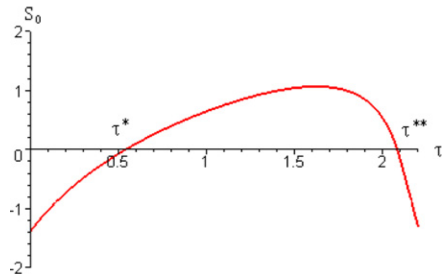

Fig. 1. The distribution of zeros of $s_n(\tau)(n=0)$ corresponding to the equilibrium point $\overline{E}$ of system (1.1).

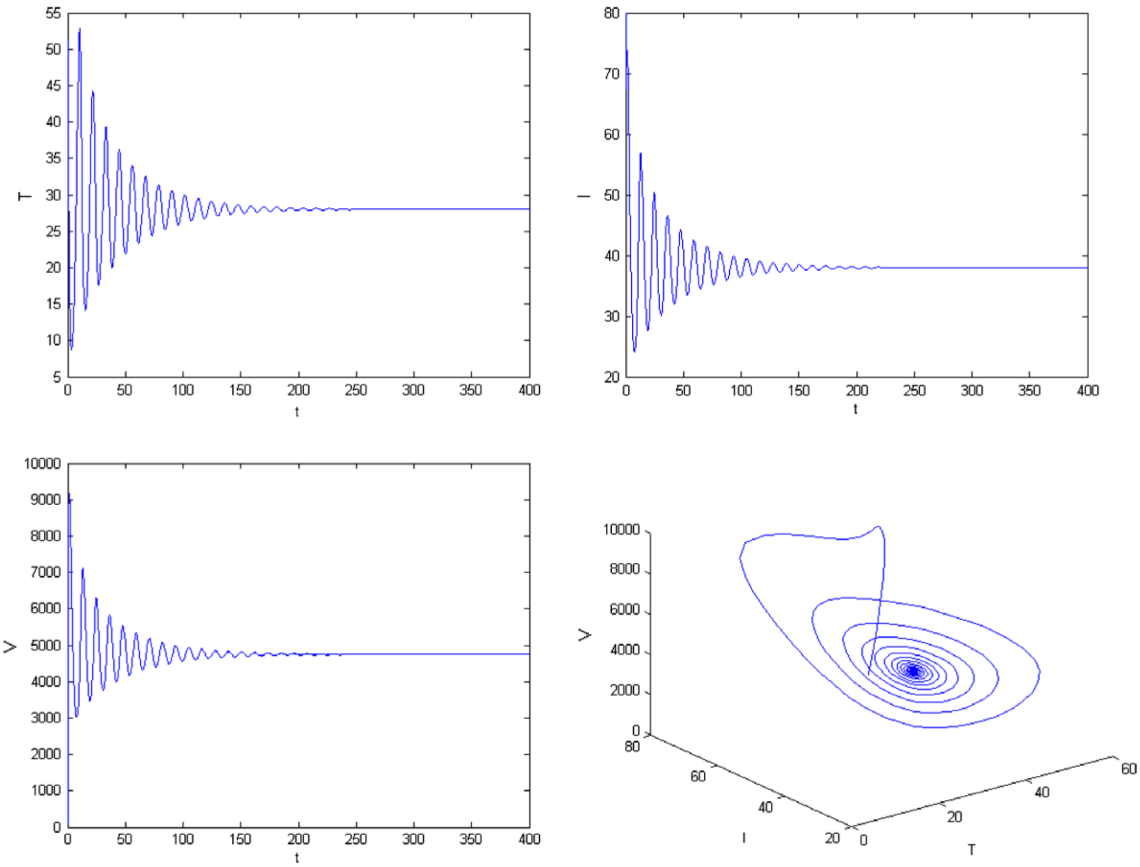

Fig. 2. For the following parameter values, $s=5$, $d=0.01$, $a=0.8$, $b=0.0002$, $T_{\max}=1200$, $\delta=0.4$, $p=1000$, $c=8$, $m=1.4$ and $\tau=0.4$, the positive equilibrium $\widehat{E}(28.01076001, 37.99315970, 4749.144962)$ of system (1.1) is asymptotically stable when $\tau=0.4$. Here $T(\theta)=50$, $I(\theta)=80$, $V(\theta)=100$, $\theta\in[-\tau,0]$.

$$E_2^{(3)} = \frac{2}{\Delta_1}\begin{vmatrix} d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & -\frac{a}{T_{\max}} - bRe\{\beta\} \\ -be^{-m\tau^*}\overline{V} & \delta & be^{-m\tau^*}Re\{\beta\} \\ 0 & -p & 0 \end{vmatrix},$$

where

$$\Delta_1 = \begin{vmatrix} d - a + b\overline{V} + \frac{2a\overline{T}}{T_{\max}} & 0 & b\overline{T} \\ -be^{-m\tau^*}\overline{V} & \delta & -be^{-m\tau^*}\overline{T} \\ 0 & -p & c \end{vmatrix}.$$

Thus, we can determine $W_{20}(\theta)$ and $W_{11}(\theta)$ from (5.20) and (5.21). Furthermore, g_{21} in (5.13) can be expressed by the parameters and delay. Based on the above analysis, we can see that each g_{ij} can be determined by the parameters. Thus we can compute the following quantities:

$$\begin{aligned} c_1(0) &= \frac{\mathrm{i}}{2\omega^*\tau^*}\left(g_{20}g_{11} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}, \\ \mu_2 &= -\frac{Re\{c_1(0)\}}{Re\{\lambda'(\tau^*)\}}, \\ \beta_2 &= 2Re\{c_1(0)\}, \\ T_2 &= -\frac{\mathrm{Im}\{c_1(0)\} + \mu_2\mathrm{Im}\{\lambda'(\tau^*)\}}{\omega^*\tau^*}. \end{aligned} \tag{5.26}$$

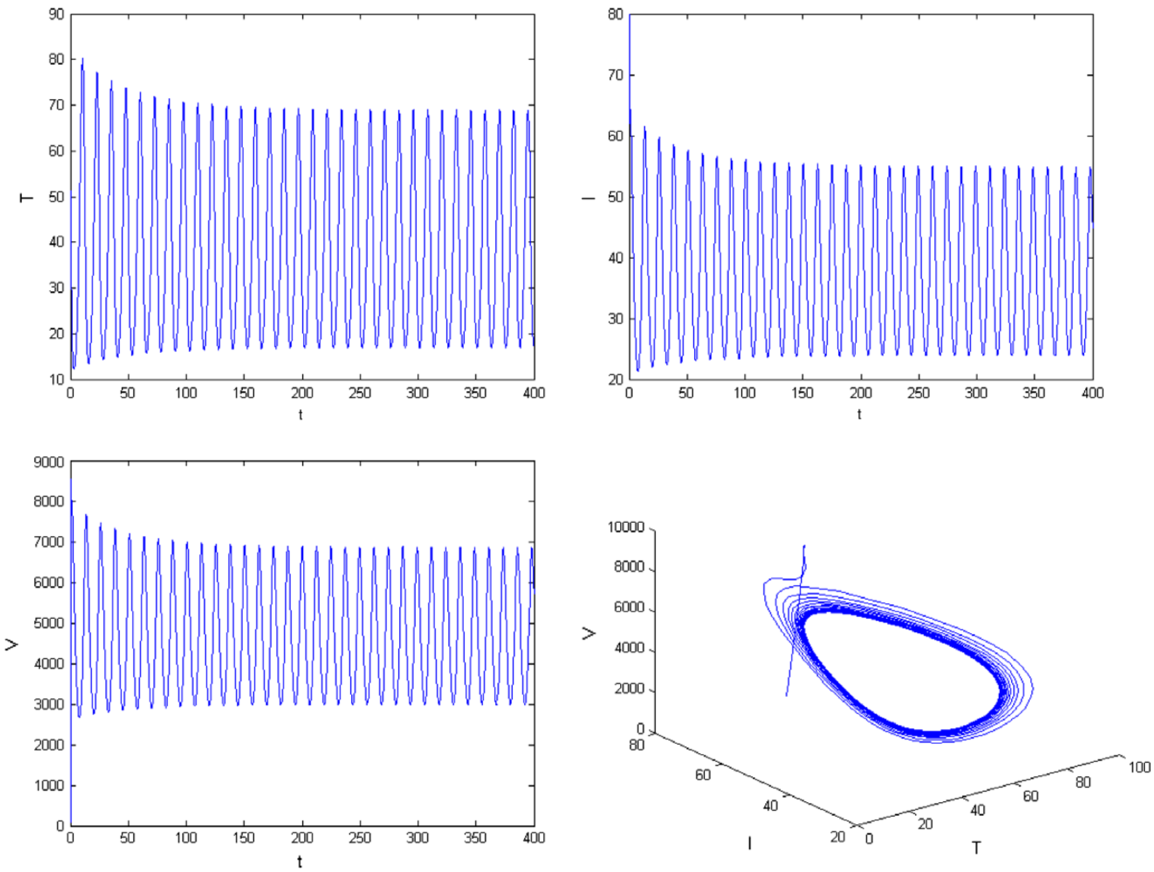

Fig. 3. The time histories and the phase trajectories of the system (1.1) after Hopf bifurcation occurs for the following parameter values: $s = 5$, $d = 0.01$, $a = 0.8$, $b = 0.0002$, $T_{\max} = 1200$, $\delta = 0.4$, $p = 1000$, $c = 8$, $m = 1.4$ and $\tau = 0.6$. Here $T(\theta) = 50$, $I(\theta) = 80$, $V(\theta) = 100$, $\theta \in [-\tau, 0]$.

Hence we have the following theorem by the result of Hassard et al. [15].

Theorem 5.1. *In (5.26), the sign of μ_2 determined the direction of Hopf bifurcation: if $\mu_2 > 0(\mu_2 < 0)$, then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solution exist for $\tau > \tau^*(\tau < \tau^*)$. β_2 determines the stability of the bifurcating periodic solution: the bifurcating periodic solution is stable (unstable) if $\beta_2 < 0(\beta_2 > 0)$ and T_2 determines the period of the bifurcating periodic solution: the period increase (decrease) if $T_2 > 0(T_2 < 0)$.*

6. Numerical simulations

In order to check our computation for Theorem 5.1, we perform some numerical simulations. We choose a set of parameters as follows: $s = 5$, $d = 0.01$, $a = 0.8$, $b = 0.0002$, $T_{\max} = 1200$, $\delta = 0.4$, $p = 1000$, $c = 8$ and $m = 1.4$.

For the above parameters, we draw the graph of S_0 versus τ on I in Fig. 1. One can see that there are two critical values of the delay τ, denoted by τ^* and τ^{**}, and $\tau^* \approx 0.5327$. Simple examination shows that the endemic equilibrium is asymptotically stable for $\tau \in [0, \tau^*)$ (see Fig. 2), and is unstable for $\tau \in (\tau^*, \tau^{**})$.

By using Theorem 4.2, we know that, under the set parameters, when $\tau = \tau^*$, Hopf bifurcation occurs. Furthermore, we can obtain $Re(c_1(0)) < 0$. Therefore, the Hopf bifurcation of system (1.1) at the endemic equilibrium is supercritical and the bifurcating periodic solutions are orbitally asymptotically stable (see Fig. 3).

References

[1] A.S. Perelson, P. Essunger, D.D. Ho, Dynamics of HIV-1 and CD4+ lymphocytes in vivo, AIDS 11 (Suppl. A) (1997) S17–S24.
[2] Xinyu Song, Avidan U. Neumann, Global stability and periodic solution of the viral dynamics, J. Math. Anal. Appl. 329 (2007) 281–297.
[3] X. Wei, S. Ghosh, M. Taylor, V. Johnson, E. Emini, P. Deutsch, J. Lifson, S. Bonhoeffer, M. Nowak, B. Hahn, S. Saag, G. Shaw, Viral dynamics in human immunodeficiency virus type 1 infection, Nature 373 (1995) 117.
[4] K. Wang, W. Wang, X. Liu, Viral infection model with periodic lytic immune response, Chaos Solitons Fract. 28 (2006) 90–99.
[5] R.J. De Boer, A.S. Perelson, Target cell limited and immune control models of HIV infection: a comparison, J. Theor. Biol. 190 (1998) 201–214.
[6] A. Perelson, P. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41 (1) (1999) 3–44.
[7] R.V. Culshaw, S. Ruan, A delay-differential equation model of HIV infection of D4+ T-cells, Math. Biosci. 165 (2000) 27–39.
[8] R.V. Culshaw, S. Ruan, G. Webb, A mathematical model of cell-to-cell HIV-1 that include a time delay, J. Math. Biol. 46 (2003) 425–444.
[9] P.W. Nelson, A.S. Perelson, Mathematical analysis of a delay differential equation models of HIV-1 infection, Math. Biosci. 179 (2002) 73–94.
[10] J. Tam, Delay effect in a model for virus replication, IMA J. Math. Appl. Med. Biol. 16 (1) (1999) 29–37.
[11] A.V.M. Herz, S. Bonhoer, R.M. Anderson, R.M. May, M.A. Nowak, Viral dynamics in vivo: limitations on estimates of intracellular delay and virus decay, Proc. Natl. Acad. Sci. USA 93 (1996) 7247.
[12] X.Y. Song, S.H. Cheng, A delay-differential equation model of HIV infection of $CD4^+$ T-cells, J. Koreal Math. Soc. 42 (5) (2005) 1071–1086.
[13] E. Beretta, Y. Kuang, Geometric stability switch criteria in delay differential systems with delay dependent parameters, SIAM J. Math. Anal. 33 (2002) 1144–1165.
[14] J. Hale, S.M. Verduyn Lunel, Introduction to Functional Differential Equations, Springer-Verlag, 1993.
[15] B.D. Hassard, N.D. Kazariniff, Y.H. Wan, Theory and application of Hopf bifurcation. London Math. Society Lecture, Note Series, 41, Cambridge University Press, 1981.