Stability properties and Hopf bifurcation of a delayed viral infection model with lytic immune response

Xinyu Song\textsuperscript{a,∗}, Shaoli Wang\textsuperscript{b}, Jing Dong\textsuperscript{c}

\textsuperscript{a} Department of Mathematics, Xinyang Normal University, Xinyang 464000, Henan, PR China
\textsuperscript{b} Faculty of Science, Xi’an Jiaotong University, Xi’an 710049, Shaanxi, PR China
\textsuperscript{c} Department of Mathematics and Computer Science, Xinyang Vocational and Technical College, Xinyang 464000, Henan, PR China

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Abstract

A class of more general delayed viral infection model with lytic immune response is proposed based on some important biological meanings. The effect of time delay on stabilities of the equilibria is given. The sufficient criteria for local and global asymptotic stabilities of the viral free equilibrium and the local asymptotic stabilities of the no-immune response equilibrium are given. We also get the sufficient criteria for stability switch of the positive equilibrium. Numerical simulations are carried out to explain the mathematical conclusions.

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1. Introduction

Mathematical modelling has been proven to be valuable in understanding the dynamics of viral infection. The research of mathematical models can provide insights into the dynamics of viral load in vivo and is very helpful for clinical treatment. Especially, the models of combination therapy provide very important meaning for the cure of HIV, HBV and HCV. However, infection by HIV-1 and HCV has many puzzling quantitative features. For example, there is an average 10 years between infection with the virus and the AIDS in adults. The reason for this time lag remains largely unknown, although it seems tied to changes in the number of circulating \( \text{CD}_4^+ \) T cells. The major target of HIV infection is a class of lymphocytes, or white blood cells, known as \( \text{CD}_4^+ \) T cells. These cells secrete growth and differentiation factors that are required by other cell populations in the immune system, and hence these cells are called “helper T cells”.

Recently, there have been a lot of papers on virus dynamics within-host, some include the immune response directly [1–6], others do not contain the immune response [7–12,14]. During viral infections, the host immune system reacts with innate and antigen-specific immune response. Both types of response can be subdivided broadly into lytic and nonlytic components. Lytic components kill infected cells, whereas the nonlytic inhibit viral replication through soluble mediators. As a part of the innate response, cytotoxic T lymphocytes (CTLs) kill infected cells, whereas antibodies neutralize free virus particles and thus, inhibit the infection of susceptible cells. In addition, \( \text{CD}_4^+ \) and \( \text{CD}_8^+ \) T cells can secrete cytokines that inhibit viral replication (e.g., IFN – \( \gamma \) and tumor necrosis factor \( \alpha \) (TNF – \( \alpha \))). In order to investigate the role of direct lytic and nonlytic inhibition of viral replication by immune cells in viral infections, Bartholdy et al. [1] and Wodarz et al. [4] constructed a mathematical model describing the basic dynamics of the interaction between susceptible host cells, a virus...
population, and immune response, which is described by the following differential equations,

\[
\begin{aligned}
\dot{x} &= s - dx - \frac{\beta xy}{1 + qz}, \\
\dot{y} &= \frac{\beta xy}{1 + qz} - ay - pyz, \\
\dot{z} &= cy - bz,
\end{aligned}
\]

(1.1)

where \( x(t) \) is the number of susceptible host cells, \( y(t) \) is the number of virus population and \( z(t) \) is the number of immune responses; susceptible host cells are generated at a rate \( s \) and die at rate \( dx \) and become infected by virus at rate \( \beta xy \) without the immune response; to model nonlytic antiviral, viral replication is inhibited by the immune response at a rate \( 1 + qz \); infected cells die at a rate \( ay \) and killed by the immune system at a rate \( pyz \) for modelling lytic effector mechanisms; the immune response is assumed to get stronger at a rate proportional to the number of infected cells, \( cy \), and also decay exponentially at a rate proportional to its current strength, \( bz \), the parameter \( p \) expresses the strength of the lytic component, whereas the parameter \( q \) expresses the efficacy of the nonlytic component.

By the similar theoretical analysis to population dynamical systems and epidemic models [13] time delays should be considered in viral models [6,8,12], and N. Burić et al. [15] considered the effects of the time delay for immune response on two-dimensional system which consists of infected cells and CTLs, Canabarro et al. [16] investigated the effects of a time delay on the four-dimensional system with \( \dot{z} = cy(t - \tau)z(t - \tau) - bz \), and Kaifa Wang [6] studied the effects of the time delay for immune response on the three-dimensional system with \( \dot{z} = cy(t - \tau) - bz \).

In this paper, we consider the following model with delay between the time a cell begin to be infected and the time of emission of virus particles from this cell [9,14]. Note that the immune response after viral infection is universal and necessary to eliminate or control the disease. Antibodies, cytokinesis, natural killer cells, and T cells are essential components of a normal immune response to a viral. Indeed, in most viral infections, cytotoxic T lymphocytes (CTLs) play a very important role in antiviral defense by attacking virus infected cells. It is believed that they are the main host immune factor that limits the development of virus replication in vivo and thus determines virus load [2]. Therefore, the population dynamics of viral infection with CTL response has been paid much attention in the last few decades [5,6].

\[
\begin{aligned}
\dot{x} &= s - dx - \beta_{\text{lyt}}x(t - \tau)y(t - \tau) - \beta_{\text{CTL}}xy, \\
\dot{y} &= \beta e^{-\tau t}x(t - \tau)y(t - \tau) - ay - pyz, \\
\dot{z} &= cy - bz,
\end{aligned}
\]

(1.2)

where the state variables \( x, y, \) and \( z \) and the parameters \( s, a, b, d, p \) and \( \beta \) have the same biological meanings as in the model (1.1). In model (1.2) the term \( e^{-\tau t} \) accounts for cells that are infected at time \( t \) but die before becoming productively infected \( \tau \) time units later. The production of CTLs depends not only on the population of infected cells but also depends on the population of CTL cells, then \( \dot{z} = cyz - bz \).

This paper is organized as follows. In the next section, we give the stability analysis of the viral free equilibrium \( E_0 \). In Section 3, local stability analysis of the no-immune response equilibrium \( E_1 \) is presented. Stability analysis and Hopf bifurcation of the positive equilibrium \( E_2 \) are studied in Section 4. Finally, in Section 5 numerical simulations and conclusions are included.

2. Stability analysis of the viral free equilibrium \( E_0 \)

In this section, we shall consider the stability of the viral free equilibrium \( E_0 \) of the system (1.2). Firstly, some preliminaries are provided.

We adopt the following notation: \( \mathbb{R}^3 \) is a three-dimensional real Euclidean space with norm \( |\cdot| \). For \( \tau > 0 \), we denote by \( \mathbb{C} = \mathbb{C}([-\tau, 0], \mathbb{R}^3) \) the Banach space of continuous functions mapping the interval \([−\tau, 0]\) into \( \mathbb{R}^3 \) with the topology of uniform convergence, i.e., for \( \varphi \in \mathbb{C} \), the norm of \( \varphi \) is defined as

\[
\|\varphi\| = \sup_{-\tau \leq \theta \leq 0} \left\{ |\varphi_1(\theta)|, |\varphi_2(\theta)|, |\varphi_3(\theta)| \right\},
\]

where \( \varphi = (\varphi_1, \varphi_2, \varphi_3) \). Further, let \( \mathbb{C}_+ = \mathbb{C}([−\tau, 0], \mathbb{R}^3_+) \).

The initial condition for system (1.2) is given as

\[
\begin{aligned}
x(\theta) = \varphi_1(\theta) &\geq 0, \\
y(\theta) = \varphi_2(\theta) &\geq 0, \\
z(\theta) = \varphi_3(\theta) &\geq 0,
\end{aligned}
\]

\([-\tau \leq \theta \leq 0],
\]

(2.1)

and a solution of system (1.2) is denoted by \( (x(t), y(t), z(t)) \).

Lemma 2.1. Suppose that \( (x(t), y(t), z(t)) \) is a solution of system (1.2) with initial conditions (2.1) then \( x(t) \geq 0, y(t) \geq 0, z(t) \geq 0 \) for all \( t \geq 0 \).
If we denote $R_0 = \frac{\beta^s}{a d} e^{-m\tau}$, $R_0^* = \frac{\beta c s}{a c d + b a \beta} e^{-m\tau}$, then the equilibria of system (1.2) are as follows:

(i) If $R_0^* < R_0 < 1$, then the system (1.2) only has the viral equilibrium $E_0 = (x_0, 0, 0) = \left( \frac{\beta}{a}, 0, 0 \right)$.

(ii) If $R_0 < 1 < R_0^*$, then the system (1.2) has no-immune response equilibrium $E_1 = (x_1, y_1, 0)$ except for $E_0$, where

$$x_1 = \frac{cs}{cd + b\beta}, \quad y_1 = \frac{\beta s e^{-m\tau} - ad}{\beta a}.$$

(iii) If $1 < R_0 < R_0^*$, then the system (1.2) has a positive equilibrium $E_2 = (\bar{x}, \bar{y}, \bar{z})$ except for $E_0$ and $E_1$, where

$$\bar{x} = \frac{cs}{cd + b\beta}, \quad \bar{y} = \frac{b}{c}, \quad \bar{z} = \frac{\beta c e^{-m\tau} - acd - ab\beta}{cdp + bp\beta}.$$

Lemma 2.2. For any solution $(x(t), y(t), z(t))$ of (1.2), we have that

$$\lim \sup_{t \to +\infty} x(t) \leq \frac{s}{d} = x_0.$$

Now, we will begin to analyze the geometric properties of the equilibria of system (1.2). Let $\tilde{E}$ be any arbitrary equilibrium of system (1.2). Then the characteristic equation about $\tilde{E}$ is given by

$$(\lambda + b)(\lambda + d)(\lambda + a - \beta x_0 e^{-m\tau} e^{-\lambda \tau}) = 0. \quad (2.4)$$

It is clear that the transcendental equation (2.4) has negative roots

$$\lambda_1 = -b, \quad \lambda_2 = -d.$$

Next, we shall consider the transcendental equation

$$\lambda + a - \beta x_0 e^{-m\tau} e^{-\lambda \tau} = 0. \quad (2.5)$$

(i) For $\tau = 0$, $R_0$ changes to $R_0' = \frac{\beta}{a d}$. If $R_0' < 1$, we have

$$\lambda_3 = \beta x_0 - a = -a \left( 1 - \frac{\beta}{a d} \right) = -a (1 - R_0') < 0.$$

This shows that Eq. (2.4) has negative real roots for $\tau = 0$. For $\tau > 0$, if (2.5) has complex roots $\lambda = u \pm i \omega$ for some $u > 0$ and $\omega > 0$, then we have

$$u + a = \beta x_0 e^{-(m + u)\tau} \cos \omega \tau, \quad -\omega = \beta x_0 e^{-(m + u)\tau} \sin \omega \tau, \quad (2.6)$$

which implies that

$$(u + a)^2 + \omega^2 = \left( \beta x_0 e^{-(m + u)\tau} \right)^2 = a^2 e^{-2u\tau} R_0^2 < a^2,$$

by $R_0 < 1$. The contradiction shows that any root of (2.5) must have negative real part. Hence, for any time delay $\tau \geq 0$, if $R_0 < 1$, the viral free equilibrium $E_0$ is locally asymptotically stable.

(ii) If $R_0 > 1$, let $f(\lambda) = \lambda + a - \beta x_0 e^{-m\tau} e^{-\lambda \tau}$. Note that $f(0) = a - \beta x_0 e^{-m\tau} = a(1 - R_0) < 0$ 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 one positive root, then the characteristic equation (2.4) has one positive real root. Hence, $E_0$ is unstable.
(iii) To consider the case $R_0 = 1$ and $\tau = 0$, we set $\dot{x} = x - \frac{x^2}{2}$, $\dot{y} = y$, $\dot{z} = z$. Under this transformation, Eq. (1.2) becomes
\[
\begin{align*}
\dot{x} &= -d x - \beta x y - \frac{\beta s}{d} y, \\
\dot{y} &= \beta x y - p z y, \\
\dot{z} &= c y z - b z, \\
\end{align*}
\]
(2.7)
where we substitute $x$, $y$, $z$ for $\dot{x}$, $\dot{y}$, $\dot{z}$. The infection free steady state $E_0$ is shifted to $0 = (0, 0, 0)$. The Jacobian matrix at $0$ of (2.7) is
\[
J = \begin{pmatrix}
-d & -\frac{\beta s}{d} & 0 \\
0 & 0 & 0 \\
0 & 0 & -b
\end{pmatrix},
\]
when $\tau = 0$ and $R_0 = 1$. The matrix $J$ has eigenvalues $-d$, $0$, and $-b$, thus, the center manifold is a curve tangent to the $y$-axis. In order to obtain the approximative expression of the center manifold, we set
\[
\begin{align*}
x &= x_1 y + 2 x_2 y^2 + \mathcal{O}(y^3), \\
\dot{z} &= n_1 + 2 n_2 y^2 + \mathcal{O}(y^3).
\end{align*}
\]
(2.8)
It follows that
\[
\begin{align*}
x' &= x_1 y' + 2 x_2 y y' + \mathcal{O}(y), \\
\dot{z}' &= n_1 y' + 2 n_2 y y' + \mathcal{O}(y).
\end{align*}
\]
(2.9)
In order to find the unknown coefficients, $m_1, m_2, n_1, n_2, \ldots$, we substitute (2.7) and (2.8) into (2.9) and obtain
\[
\begin{align*}
(a + d m_1) y + (\beta m_1 + \beta m_1^2 + d m_2 - p m_1 n_1) y^2 + \mathcal{O}(y^3) &= 0, \\
bn_1 + (b n_2 + b n_1 - p n_1^2) y^2 + \mathcal{O}(y^3) &= 0.
\end{align*}
\]
(2.10)
Comparing the coefficients of $y$, $y^2$ in (2.10), we find that
\[
m_1 = -\frac{a}{d}, \quad n_1 = 0,
\]
\[
m_2 = \frac{\beta a}{d^2} - \frac{\beta a^2}{d^3}, \quad n_2 = 0.
\]
Then, substituting (2.10) into (2.9), we have
\[
y' = -\frac{\beta a}{d} y^2 + \frac{a \beta^2}{d^2} \left(1 - \frac{a}{d}\right) y^3 + \mathcal{O}(y^3).
\]
(2.11)
Clearly, the zero point $y = 0$ of (2.11) is locally asymptotically stable, then the zero point $y = 0$ of (2.9), or equivalently, the zero point $y = 0$ of (1.2) is also locally asymptotically stable. Thus, the infection free steady state $E_0$ is locally asymptotically stable when $\tau = 0$ and $R_0 = 1$.

If $R_0 = 1$ and $\tau > 0$, the transcendental equation (2.5) becomes
\[
g(\lambda) = \lambda + a - ae^{-\tau} e^{-\lambda \tau} = 0.
\]
(2.12)
In fact, if (2.12) has imaginary roots $\lambda = u \pm i \omega$ for some $u \geq 0$, $\omega \geq 0$ and $\tau \geq 0$, from (2.5) we have that
\[
\begin{align*}
u + a &= ae^{-ut - \tau} \cos \omega \tau, \\
-\omega &= ae^{-ut - \tau} \sin \omega \tau,
\end{align*}
\]
(2.13)
which, together with $u \geq 0$, implies that
\[
(u + a)^2 + \omega^2 = a^2 e^{-2(u + m) \tau} \leq a^2.
\]
However, it is easy to check that the above inequality is not true. Hence, it shows that any root of (2.12) has negative real part except $\lambda = 0$, which implies that the trivial solution of the linearized system of (1.2) is stable for any time delay $\tau \geq 0$. Therefore our results in this theorem are proved. □

The following discussions focus on the global asymptotic stability of the viral free equilibrium $E_0$ of system (1.2).

**Theorem 2.2.** If $R_0 < 1$, then the viral free equilibrium $E_0$ of system (1.2) is globally asymptotically stable.
Proof. In fact, from Lemma 2.2, we have that
\[ \limsup_{t \to +\infty} x(t) \leq \frac{s}{d}, \]
from which for sufficiently large \( t \geq t_1 \),
\[ x(t) \leq \frac{s}{d} + \varepsilon, \]
here \( \varepsilon > 0 \) is sufficiently small such that
\[ \beta e^{-m\tau} \left( \frac{s}{d} + \varepsilon \right) < a, \] (2.14)
for \( R_0 < 1 \).

From Lemma 2.1 and the second equation of (1.2), we have that
\[ y'(t) \leq \beta e^{-m\tau} \left( \frac{s}{d} + \varepsilon \right) y(t - \tau) - ay. \]
for \( t \geq t_1 + \tau \). According to [17], and from (2.14), we have
\[ \lim_{t \to +\infty} y(t) = 0. \]
Hence, for sufficiently large \( t \geq t_2 \),
\[ y(t) \leq \eta, \]
here \( \eta > 0 \) is sufficiently small such that \( c\eta - b < 0 \).

From the third equation of (1.2), we have
\[ z'(t) \leq (c\eta - b)z(t), \]
for \( t \geq t_2 \).

In view of \( c\eta - b < 0 \), we have
\[ \lim_{t \to +\infty} z(t) = 0. \]

From the first equation of (1.2), we can also have that
\[ \lim_{t \to +\infty} x(t) = \frac{s}{d}, \]
which shows that \( E_0 \) is a global attractor. By Theorem 2.1(i), it is globally asymptotically stable. \( \square \)

3. Local stability analysis of the no-immune response equilibrium \( E_1 \)

Let us consider local stability of the no-immune response equilibrium \( E_1 \).

Theorem 3.1. If \( R_0 > 1 > R_{0}^* \), then the no-immune response equilibrium \( E_1 \) of system (1.2) is locally asymptotically stable for any \( \tau \geq 0 \). If \( R_0 > R_{0}^* > 1 \), then \( E_1 \) is unstable.

Proof. The characteristic of the linearized system of (1.2) near the no-immune response equilibrium \( E_1 \) is given by
\[ (\lambda + b - cy_1) \left[ \lambda^2 + (a + d + \beta y_1) + a(d + \beta y_1) \right] - (\beta x_1 e^{-m\tau}\lambda + \beta dx_1 e^{-m\tau})e^{-\lambda\tau}. \] (3.1)

One solution of (3.1) is given by
\[ \lambda_1 = cy_1 - b = \frac{R_0 - 1}{a^2\beta(cd + b\beta)}, \] (3.2)
and \( \lambda_1 < 0 \) for \( R_0 > 1 > R_{0}^* \). The other characteristic roots of (3.1) satisfy
\[ g(\lambda, \tau) = \lambda^2 + (a + d + \beta y_1) + a(d + \beta y_1) \right) - (\beta x_1 e^{-m\tau}\lambda + \beta dx_1 e^{-m\tau})e^{-\lambda\tau} = 0. \]

Note that \( \lambda = 0 \) is not root of \( g(\lambda, \tau) = 0 \) for any \( \tau \). If \( \tau = 0 \), we have that
\[ g(\lambda, 0) = \lambda^2 + (a + d + \beta y_1 - \beta x_1)\lambda + ad + a\beta y_1 - d\beta x_1 = 0, \]

where
\[ a + d + \beta y_1 - \beta x_1 = \frac{s\beta}{a} > 0, \]
\[ ad + a\beta y_1 - d\beta x_1 = s\beta - ad > 0, \]
for \( \tau = 0 \) and \( R_0 > 1 \). Hence, all the solutions of \( \phi(\lambda, 0) = 0 \) have negative real part.

For \( \tau > 0 \), letting \( \lambda = i\omega \) for some \( \omega > 0 \), define
\[ h(i\omega, \tau) = -\omega^2 + i\omega(a + d + \beta y_1) + a(d + \beta y_1) - (i\beta x_1 e^{-\omega \tau} \omega + d\beta x_1 e^{-\omega \tau}) e^{-i\omega \tau} = 0. \]

If \( \lambda = i\omega \) is a solution of \( h(i\omega, \tau) = 0 \), then we have
\[ \omega(a + d + \beta y_1) = a(\omega \cos \omega \tau - d \sin \omega \tau), \]
\[ -\omega^2 + ad + a\beta y_1 = a(d \cos \omega \tau + \omega \sin \omega \tau), \]
from which we have
\[ \omega^4 + \omega^2(d + \beta y_1)^2 + a^2\beta^2y_1^2 + 2a^2d\beta y_1 = 0, \]
which is a contradiction.

If \( R_0 > R_0^* > 1 \), from (3.2) we can see that \( \lambda_1 > 0 \), then \( E_1 \) is unstable. This completes the proof. \( \square \)

4. Stability analysis and Hopf bifurcation of the positive equilibrium \( E_2 \)

In this section we will consider the local stability of the positive equilibrium \( E_2 \). It is not easy to find rigorously local stability condition of \( E_2 \). In the following, using stability switch criteria, we try to analyze local stability of \( E_2 \). The criteria can indicate that the stability of a given steady state is simply determined by the graph which is expressed as some functions of \( \tau \) and thus can be easily depicted by Matlab. We will show the stability switch criteria for \( E_2 \).

The characteristic of the linearized system of (1.2) near the infected equilibrium \( E_2 \) is given by
\[ P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda \tau} = 0, \quad (4.1) \]
where
\[ P(\lambda, \tau) = \lambda^3 + b_1(\tau)\lambda^2 + b_2(\tau)\lambda + b_3(\tau), \]
\[ Q(\lambda, \tau) = b_4(\tau)\lambda^2 + b_5(\tau)\lambda, \quad (4.2) \]
and
\[ b_1(\tau) = (d + \beta \bar{y}) + \beta x_1 e^{-\omega \tau}, \]
\[ b_2(\tau) = \beta x_1 e^{-\omega \tau}(d + \beta \bar{y}) + cp\bar{y}\bar{z}, \]
\[ b_3(\tau) = cp\bar{y}\bar{z}(d + \beta \bar{y}), \]
\[ b_4(\tau) = -\beta x_1 e^{-\omega \tau}, \]
\[ b_5(\tau) = -d\beta x_1 e^{-\omega \tau}. \]

When \( \tau = 0 \), Eq. (4.1) becomes
\[ \lambda^3 + a_1(0)\lambda^2 + a_2(0)\lambda + a_3(0) = 0, \]
where
\[ a_1(0) = b_1(0) + b_4(0) = d + \beta \bar{y} > 0, \]
\[ a_2(0) = b_2(0) + b_5(0) = \beta^2\bar{y}\bar{z} + cp\bar{y}\bar{z}, \]
\[ a_3(0) = b_3(0) = cp\bar{y}\bar{z}(d + \beta \bar{y}) > 0, \]
and
\[ a_1(0)a_2(0) - a_3(0) = d\beta^2\bar{y}\bar{z} + \beta^3\bar{y}\bar{z}^2 > 0. \]

From the well-known Routh–Hurwitz criterion, it follows that any root of (4.1) has negative real part for \( \tau = 0 \). Hence we have the following theorem.
Theorem 4.1. If $\tau = 0$ and $R_0^\ast > 1$, then the positive equilibrium $E_2$ of system (1.2) is locally asymptotically stable.

In the following, we investigate the existence of purely imaginary roots $\lambda = i\omega$ ($\omega > 0$) to Eq. (4.1). Eq. (4.1) takes the form of a third-degree exponential polynomial in $\lambda$, with all the coefficients of $P$ and $Q$ depending on $\tau$. Beretta and Kuang [13] established a geometrical criterion which gives the existence of purely imaginary root 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 $\tau \in [0, \tau_{\text{max}})$, where $\tau_{\text{max}}$ is the maximum value which $E_2$ exists.

(a) $P(0, \tau) + Q(0, \tau) \neq 0$.
(b) $P(i\omega, \tau) + Q(i\omega, \tau) \neq 0$.
(c) $\lim_{|\lambda| \to +\infty} \frac{|P(\lambda, \tau)|}{|P(\lambda, \tau)|} = \lim_{|\lambda| \to +\infty} \left| \frac{b_4\lambda^2 + b_5\lambda}{\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3} \right| = \lim_{|\lambda| \to 0} \left| \frac{b_4k + b_5k^2}{1 + b_1k + b_2k^2 + b_3k^3} \right| \left( k = \frac{1}{\lambda} \right) \leq \lim_{|\lambda| \to 0} \left| \frac{b_4k}{1 + b_1k + b_2k^2 + b_3k^3} \right| + \lim_{|\lambda| \to 0} \left| \frac{b_5k^2}{1 + b_1k + b_2k^2 + b_3k^3} \right| = 0.$

Therefore (c) follows.

Let $F$ be defined as in (d). From

$$|P(i\omega, \tau)|^2 = (-\omega^2 + b_2(\tau)\omega)^2 + (-b_1(\tau)\omega^2 + b_3(\tau))^2,$$

and

$$|Q(i\omega, \tau)|^2 = b_4^2(\tau)\omega^4 + b_5^2(\tau)\omega^2,$$

we have

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

where

$$a_1(\tau) = b_1^2(\tau) - 2b_2(\tau) - b_3^2(\tau),$$
$$a_2(\tau) = b_2^2(\tau) - 2b_1(\tau)b_3(\tau) - b_1^2(\tau),$$
$$a_3(\tau) = b_3^2(\tau).$$

It is obvious that property (d) is satisfied. Let $(\omega_0, \tau_0)$ be a point of its domain of definition such that $F(\omega_0, \tau_0) = 0$. We know the partial derivatives $F_\omega$ and $F_\tau$ exist and are continuous in a certain neighborhood of $(\omega_0, \tau_0)$, and $F_\omega(\omega_0, \tau_0) \neq 0$. By Implicit Function Theorem, (e) is also satisfied.
Now let \( \lambda = i\omega \ (\omega > 0) \) be a root of Eq. (4.1), and from which we have that
\[
-b_1(\tau)\omega^2 + b_3(\tau) - (b_4(\tau)\omega^2 \cos(\omega \tau) - b_5(\tau)\omega \sin(\omega \tau)) \\
+ i(-\omega^3 + b_2(\tau)\omega + b_5(\tau)\omega \cos(\omega \tau) + b_4(\tau)\omega^2 \sin(\omega \tau)) = 0.
\]
Hence, we have that
\[
-b_3(\tau) + b_1(\tau)\omega^2 = b_5(\tau)\omega \sin(\omega \tau) - b_4(\tau)\omega^2 \cos(\omega \tau), \\
\omega^3 - b_2(\tau)\omega = b_4(\tau)\omega^2 \sin(\omega \tau) + b_5(\tau)\omega \cos(\omega \tau).
\] (4.3)

From (4.3) it follows that
\[
\sin \omega \tau = \frac{b_4(\tau)\omega^5 + (b_1(\tau)b_5(\tau) - b_2(\tau)b_4(\tau))\omega^3 - b_3(\tau)b_5(\tau)\omega}{b_4(\tau)\omega^4 + b_5(\tau)\omega^2}, \quad (4.4a) \\
\cos \omega \tau = \frac{-b_1(\tau)b_4(\tau)\omega^5 + b_5(\tau)\omega^4 + (b_3(\tau)b_4(\tau) - b_2(\tau)b_5(\tau))\omega^2}{b_4(\tau)\omega^4 + b_5(\tau)\omega^2}. \quad (4.4b)
\]

By the definitions of \( P(\lambda, \tau) \), \( Q(\lambda, \tau) \) as in (4.2), and applying the property (a), (4.4a) and (4.4b) can be written as
\[
\sin \omega \tau = \Im \frac{P(i\omega, \tau)}{Q(i\omega, \tau)} \quad (4.5a)
\]
and
\[
\cos \omega \tau = -\Re \frac{P(i\omega, \tau)}{Q(i\omega, \tau)}, \quad (4.5b)
\]
which yields
\[
|P(i\omega, \tau)|^2 = |Q(i\omega, \tau)|^2.
\]
Assume that $I \in \mathbb{R}^+_{0}$ is the set where $\omega(\tau)$ is a positive root of

$$F(\omega, \tau) = \left| P(i\omega, \tau) \right|^2 - \left| Q(i\omega, \tau) \right|^2$$

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

$$F(\omega, \tau) = 0. \quad (4.6)$$

Let $\omega^2 = h$, then we have that

$$F(h) = h^3 + a_1 h^2 + a_2 h + a_3 = 0, \quad (4.7)$$

where

$$a_1 = b^2 - 2cp\tilde{y} + (d + \beta\tilde{y})^2,$$

$$a_2 = (d + \beta\tilde{y})(b^2 - 2cp\tilde{y}) + cp\tilde{y}(2b\beta\tilde{e}e^{-m\tau}) + \beta^2\tilde{y}^2e^{-2m\tau}(2d + \beta\tilde{y}),$$

$$a_3 = c^2 p^2\tilde{y}^2(2d + \beta\tilde{y})^2. \quad (4.8)$$

Assume that Eq. (4.7) has only one positive real root, we denote by $h_+$ this positive real root. Thus, Eq. (4.6) has only one positive real root $\omega = \sqrt{h_+}$. And the critical values of $\tau$ 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 (4.5).

And the relation between the argument $\theta$ and $\omega\tau$ in (4.5) for $\tau > 0$ must be

$$\omega\tau = \theta + 2n\pi, \quad n = 0, 1, 2, \ldots. \quad (4.9)$$

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

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

where a positive root $\omega(\tau)$ of (4.7) exists in $I$. 

Fig. 2.
Let us introduce the functions $S_n(\tau): I \to R$, 

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

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

**Theorem 4.2.** Assume that $\omega(\tau)$ is a positive root of (4.1) 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

$$\delta(\tau^*) = \text{sign} \left[ F'(\omega(\tau^*, \tau^*)) \right] \text{sign} \left[ \frac{dS_n(\tau)}{d\tau} \bigg|_{\tau = \tau^*} \right].$$  \hspace{1cm} (4.12)

Applying Theorems 4.1 and 4.2 and the Hopf bifurcation theorem for functional differential equation [17], we can conjecture the existence of a Hopf bifurcation as stated in Theorem 4.3.

**Theorem 4.3** *(A conjecture).* For system (1.2), then there exists $\tau^* \in I$, such that the equilibrium $E_2$ is asymptotically stable for $0 \leq \tau < \tau^*$, and becomes unstable for $\tau$ staying in some right neighborhood of $\tau^*$, with a Hopf bifurcation occurring when $\tau = \tau^*$.

### 5. Numerical simulations and conclusions

In order to check our computation, we perform some numerical simulations. We choose a set of parameters as follows: $s = 270$, $d = 0.1$, $\beta = 0.002$, $a = 5$, $p = 0.2$, $c = 0.2$, $b = 0.3$, and $m = 0.001$. Here $x(\theta) = 2500$, $y(\theta) = 2$, $z(\theta) = 2$, $\theta \in [-\tau, 0]$. For the parameter, the trajectory converges to the positive equilibrium at $\tau = 0.241$; a periodic behavior at $\tau = 0.248$; and the trajectory converges to the positive equilibrium again at $\tau = 0.255$.

In this paper, a class of more general viral infection model with time delay and lytic immune response is considered. In the model, the delay between the time a cell begin to be infected and the time of emission of virus particles from this cell is taken into account. Then, a detailed analysis on the local asymptotic stability of the equilibria of the viral infection
model is carried out. It is shown that, if $R_0 < 1$ (hence, $E_1$ and $E_2$ are not feasible), the viral free equilibrium $E_0$ is locally and globally asymptotically stable for any time delay $\tau \geq 0$, and if $R_0 > 1$, then $E_0$ is unstable. If $R_0^* < 1 < R_0$ (hence, $E_2$ is not feasible), then the no-immune response equilibrium $E_1$ is locally asymptotically stable for any time delay $\tau \geq 0$, and if $R_0^* > 1$, then $E_1$ is unstable. If $E_2$ is feasible, i.e., $R_0^* > 1$, and if $\tau = 0$, then the positive equilibrium $E_2$ is asymptotically stable; and for $\tau > 0$, then there will exist $\tau^* \in I$, such that the equilibrium $E_2$ is asymptotically stable for $0 \leq \tau < \tau^*$, and becomes unstable for $\tau$ staying in some right neighborhood of $\tau^*$, with a Hopf bifurcation occurring when $\tau = \tau^*$.

Figs. 1, 2 and 3 have the same parameter values: $s = 270$, $d = 0.1$, $\beta = 0.002$, $a = 5$, $p = 0.2$, $c = 0.2$, $b = 0.3$, and $m = 0.001$. Here $x(\theta) = 2500$, $y(\theta) = 2$, $z(\theta) = 2$, $\theta \in [-\tau, 0]$. In Fig. 1 the trajectory converges to the positive equilibrium at $\tau = 0.241$; Fig. 2 shows a periodic behavior at $\tau = 0.248$; but, in Fig. 3 the trajectory converges to the positive equilibrium again at $\tau = 0.255$.

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