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STABILITY PROPERTIES AND HOPF BIFURCATION FOR A HEPATITIS B INFECTION MODEL WITH EXPOSED STATE AND HUMORAL IMMUNITY-RESPONSE DELAY

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Abstract. In this paper, a dynamics behavior of a delayed hepatitis B infection model with exposed state and humoral immunity is studied. The basic reproductive number R_0 and humoral immune reproductive number R_1 are introduced. By using suitable Lyapunov functional and LaSalle invariant principle, it is proved that when $R_0 < 1$, the infection-free equilibrium Q_0 is globally asymptotically stable; if $R_1 < 1 < R_0$, the infected equilibrium without immunity Q_1 is globally asymptotically stable. When $R_1 > 1$, the sufficient conditions to the local stability of the infected equilibrium with immunity Q_2 can be obtained. The time delay can change the stability of Q_2 and lead to the existence of Hopf bifurcations. The stabilities of periodic solutions are also investigated. Finally, numerical simulations are carried out.

Keywords: Humoral immunity; Global stability; Lyapunov functional; Hopf bifurcation.

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1. Introduction

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In recent years, considerable attention has been paid to study the mathematical modeling of virus infection, such as the human immunodediciency virus (HIV) and the hepatitis B virus (HBV)(see [1,2,3]). Immunity response plays an important role in resistance to the virus infections, a specific immunity is composed of humoral immunity (B cells) and cellular immunity (T cells). The dynamic models of cellular immunity (see [4,5,6]) and humoral immunity (see [7,8,9]) have all been studied by many people, however, the humoral immunity is more effective than cellular in some infection processes (see [9]). Some researchers have investigated the virus infection model with delay (see [10,11,12,13]). Wang [14] discussed the following model with delayed humoral immunity.

$$\begin{cases} T'(t) = \lambda - \beta T(t)V(t) - dT(t), \\ I'(t) = \beta T(t)V(t) - aI(t), \\ V'(t) = kI(t) - uV(t) - qB(t)V(t), \\ B'(t) = gB(t-\tau)V(t-\tau) - cB(t), \end{cases} \tag{1}$$

where $T(t)$, $I(t)$, $V(t)$ and $B(t)$ denote the concentration of the uninfected cells, the infected, the virus and the B cells at time t, respectively. Constant β is the infection rate of the uninfected cells. Constant λ, k and g are birth rate of the uninfected cells, the virus and the $B(t)$ cells, respectively. Constant d, a, u, and c represent, respectively, the death rate of the uninfected cells, the infected cells, the virus and the B cells. Constant q is removed rate of virus. τ represents the time that antigenic stimulation needs for generating immunity response. [15,16] all considered the exposed state, the infected cells were divided into the latently infected cells (such cells contain the virus but are not producing it) and the actively infected cells (such cells are producing the virus), [15] discussed a HIV infection model and [16] discussed a HBV infection model.

In this paper, based on the model (1), we set up the following model

$$\begin{cases} T'(t) = \lambda - dT(t) - \beta T(t)V(t), \\ E'(t) = \beta T(t)V(t) - aE(t) - kE(t), \\ I'(t) = kE(t) - bI(t), \\ V'(t) = pI(t) - uV(t) - qB(t)V(t), \\ B'(t) = gB(t-\tau)V(t-\tau) - cB(t), \end{cases} \tag{2}$$

where $T(t)$, $V(t)$, $B(t)$, λ, β, d, u, q, g, c, and τ have the same biological meanings as those in the model (1). $E(t)$ and $I(t)$ denote the concentration of the latently infected cells and the actively infected cells, respectively, the latently infected cells convert to actively infected cells with rate constants k. Constant a and b represent, respectively, the death rate of the latently infected cells and the actively infected cells. Constant p is birth rate of the virus.

We denote by C the Banach space of continuous functions $\varphi : [-\tau, 0] \to R^5$ equipped with the suitable sup-norm, let

$$C_+ = \{\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5) \in C, \varphi_i \geq 0 \;\; for\ all \;\; \theta \in [-\tau, 0], i = 1,2,3,4,5\}.$$

The initial conditions for system (2) is given as

$$T(\theta) = \varphi_1(\theta), E(\theta) = \varphi_2(\theta), I(\theta) = \varphi_3(\theta), V(\theta) = \varphi_4(\theta), B(\theta) = \varphi_5(\theta), \theta \in [-\tau, 0].$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5) \in C_+$.

This paper is organized as follows. In section 2, we analyze the global asymptotic stabilities of the infection free equilibrium and the infected equilibrium without B cells response. In section 3, we study the local stability of the infected equilibrium and the existence of Hopf bifurcations. In section 4, we discuss the orbital asymptotic stabilities of the periodic solutions. In section 5, we carry out numerical simulations to illustrate our results. In section 6, we give a brief remark to conclude this work.

2. Global stabilities of two boundary equilibria

2.1. Reproductive numbers and equilibria

As pointed in [17], the basic reproductive number of system (2) is $R_0 = \dfrac{\beta\lambda kp}{udb(k+a)}$, system (2) always has an infection-free equilibrium

$$Q_0 = (T_0, 0, 0, 0, 0) = (\frac{\lambda}{d}, 0, 0, 0, 0).$$

If $R_0 > 1$, in the absence of an immune response, there exists an immune-free infection equilibrium $Q_1 = (T_1, E_1, I_1, V_1, 0)$, where

$$T_1 = \frac{\lambda}{dR_0}, \qquad E_1 = \frac{\lambda(R_0-1)}{(a+k)R_0},$$

$$I_1 = \frac{k\lambda(R_0-1)}{bR_0(a+k)}, \qquad V_1 = \frac{p\lambda k(R_0-1)}{ubR_0(a+k)}.$$

As pointed in [18], if the immune responses can potentially develop, the conditions $gV_1 > c$ must hold. We define the humoral immune reproductive number R_1 as follows,

$$R_1 = \frac{gV_1}{c} = \frac{gp\lambda k(R_0-1)}{cubR_0(a+k)} = \frac{dg}{c\beta} \cdot \frac{\lambda\beta kp - ubd(a+k)}{ubd(a+k)}.$$

When the humoral immune response develops that is $R_1 > 1$, system (2) has an infected equilibrium with humoral immune responses $Q_2 = (T_2, E_2, I_2, V_2, B_2)$, where

$$\begin{aligned}
T_2 &= \frac{\lambda g}{dg+\beta c},\\
E_2 &= \frac{\lambda\beta c}{(a+k)(dg+\beta c)},\\
I_2 &= \frac{kE_2}{b}, \qquad V_2 = \frac{c}{g},\\
B_2 &= \frac{pgI_2}{cq} - \frac{u}{q} = \frac{\lambda\beta gkp - ub(a+k)(dg+\beta c)}{qb(a+k)(dg+\beta c)}.
\end{aligned}$$

Note that $R_1 > 1$ can imply $\lambda\beta gkp > ub(a+k)(dg+\beta c)$, which ensure B_2 be positive.

2.2. The stability of equilibrium

Since R_0 denotes the average number of the free virus released by a infected cell which is infected by the first virus, when $R_0 < 1$, no virus would be released by the infected cell, and the infected people will finally be free of virus infection, when $R_0 > 1$, the number of virus would increase persistently, the infected people would be infected. We use the following the theorem to describe this phenomenon.

Theorem 2.1. *If $R_0 < 1$, the infection-free equilibrium Q_0 of system (2) is globally asymptotically stable. If $R_0 > 1$, Q_0 is unstable.*

Proof. Consider a Lyapunov function

$$\begin{aligned} W_0(t) = {} & T_0[\frac{T(t)}{T_0} - \ln\frac{T(t)}{T_0}] + E(t) + \frac{a+k}{k}I(t) + \frac{b(a+k)}{pk}V(t) + \frac{qb(a+k)}{gpk}B(t) \\ & + \frac{qb(a+k)}{pk}\int_{t-\tau}^{t} B(\theta)V(\theta)d\theta. \end{aligned}$$

Calculating the derivative of $W_0(t)$ along solutions of system (2), we obtain

$$\begin{aligned} W_0'(t) = {} & (1 - \frac{T_0}{T(t)})T'(t) + E'(t) + \frac{a+k}{k}I'(t) + \frac{b(a+k)}{pk}V'(t) \\ & + \frac{qb(a+k)}{gpk}B'(t) + \frac{qb(a+k)}{pk}[B(t)V(t) - B(t-\tau)V(t-\tau)] \\ = {} & (1 - \frac{T_0}{T(t)})[\lambda - dT(t) - \beta T(t)V(t)] + [\beta T(t)V(t) - (a+k)E(t)] \\ & + \frac{a+k}{k}[kE(t) - bI(t)] + \frac{b(a+k)}{pk}[pI(t) - uV(t) - qB(t)V(t)] \\ & + \frac{qb(a+k)}{gpk}[gB(t-\tau)V(t-\tau) - cB(t)] + \frac{qb(a+k)}{pk}[B(t)V(t) - B(t-\tau)V(t-\tau)] \\ = {} & \frac{-d(T(t)-T_0)^2}{T(t)} + \beta T_0 V(t) - \frac{b(a+k)u}{pk}V(t) - \frac{qb(a+k)c}{gpk}B(t) \\ = {} & \frac{-d(T(t)-T_0)^2}{T(t)} + \beta T_0[1 - \frac{(a+k)bu}{\beta T_0 pk}]V(t) - \frac{(a+k)qbc}{gpk}B(t) \\ = {} & \frac{-d(T(t)-T_0)^2}{T(t)} + \beta T_0(1 - \frac{1}{R_0})V(t) - \frac{(a+k)qbc}{gpk}B(t). \end{aligned}$$

Obviously $\frac{-d(T(t)-T_0)^2}{T(t)} \le 0$ and $-\frac{(a+k)qbc}{gpk}B(t) \le 0$. If $R_0 < 1$, $\beta T_0(1-\frac{1}{R_0})V(t) \le 0$, so we have $W_0'(T,E,I,V,\ B) \le 0$ for all $T,E,I,V,B > 0$, therefore the infection-free equilibrium Q_0 is stable. $W_0'(T,E,I,V,B) = 0$, if and only if $T = T_0$, $V = 0$ and $B = 0$. Let M be the largest invariant set in $\{(T,E,I,V,B) \in R^5 \mid W_0(T,E,I,V,B) = 0\}$, then from the second and third equation of system (2) we also obtain $E = I = 0$, so $M = Q_0$. Then we get the global asymptotical stability of Q_0 by the LaSalle' s invariance principle.

The characteristic equation of system (2) at the equilibrium Q_0 is

$$(s+c)(s+d)\{s^3+(a+k+b+u)s^2+[bu+(a+k)(b+u)]s+(a+k)bu(1-R_0)\}=0, \quad (3)$$

clearly, if $R_0>1$, Eq.(3) has a positive real root, and thus Q_0 is unstable. This completes the proof of Theorem 2.1. □

As we pointed above, when $R_0>1$, the infection will existent persistently; when $R_1<1$ the immune response can not potentially develop, so when $R_1<1<R_0$, the infected host would finally be infected without immune, and we use the following theorem to describe this phenomena.

Theorem 2.2. *If $R_1<1<R_0$, the equilibrium Q_1 of system (2) is globally asymptotically stable. If $R_1>1$, Q_1 is unstable.*

Proof. If $R_0>1$, there exists the equilibrium Q_1. Construct a Lyapunov functional

$$\begin{aligned}W_1(t)=&T_1[\frac{T(t)}{T_1}-\ln\frac{T(t)}{T_1}]+E_1[\frac{E(t)}{E_1}-\ln\frac{E(t)}{E_1}]+\frac{a+k}{k}I_1[\frac{I(t)}{I_1}-\ln\frac{I(t)}{I_1}]+\frac{b(a+k)}{pk}V_1[\frac{V(t)}{V_1}\\&-\ln\frac{V(t)}{V_1}]+\frac{qb(a+k)}{gpk}B(t)+\frac{qb(a+k)}{pk}\int_{t-\tau}^{t}B(\theta)V(\theta)d\theta.\end{aligned}$$

The derivative of $W_1(t)$ along the trajectories of system (2) satisfies

$$\begin{aligned}W_1'(t)=&(1-\frac{T_1}{T(t)})T'(t)+(1-\frac{E_1}{E(t)})E'(t)+\frac{a+k}{k}(1-\frac{I_1}{I(t)})I'(t)+\frac{b(a+k)}{pk}(1-\frac{V_1}{V(t)})V'(t)\\&+\frac{qb(a+k)}{gpk}B'(t)+\frac{qb(a+k)}{pk}[B(t)V(t)-B(t-\tau)V(t-\tau)]\\=&(1-\frac{T_1}{T(t)})[\lambda-dT(t)-\beta T(t)V(t)]+(1-\frac{E_1}{E(t)})[\beta T(t)V(t)-(a+k)E(t)]\\&+\frac{a+k}{k}(1-\frac{I_1}{I(t)})[kE(t)-bI(t)]+\frac{b(a+k)}{pk}(1-\frac{V_1}{V(t)})[pI(t)-uV(t)-qB(t)V(t)]\\&+\frac{qb(a+k)}{gpk}[gB(t-\tau)V(t-\tau)-cB(t)]+\frac{qb(a+k)}{pk}[B(t)V(t)-B(t-\tau)V(t-\tau)]\\=&dT_1(2-\frac{T(t)}{T_1}-\frac{T_1}{T(t)})+(a+k)E_1(4-\frac{T_1}{T(t)}-\frac{T(t)}{T_1}\cdot\frac{V(t)}{V_1}\cdot\frac{E_1}{E(t)}-\frac{E(t)}{E_1}\cdot\frac{I_1}{I(t)}\\&-\frac{I(t)}{I_1}\frac{V_1}{V(t)})+\frac{(a+k)c}{gpk}(R_1-1)B(t).\end{aligned}$$

Obviously $2-\frac{T(t)}{T_1}-\frac{T_1}{T(t)}\leq 0$ and $4-\frac{T_1}{T(t)}-\frac{T(t)}{T_1}\cdot\frac{V(t)}{V_1}\cdot\frac{E_1}{E(t)}-\frac{E(t)}{E_1}\cdot\frac{I_1}{I(t)}-\frac{I(t)}{I_1}\frac{V_1}{V(t)}\leq 0$. If $R_1<1$, we have $W_1'(T,E,I,V,B)\leq 0$ for all $T,E,I,V,B>0$, therefore the infected equilibrium without immunity Q_1 is stable. $W_1'(T,E,I,V,B)=0$, if and only if $T=T_1$, $V=V_1$, $E=E_1$, $I=I_1$ and $B=0$, so Q_1 is global asymptotical stability.

The characteristic equation of system (2) at the equilibrium Q_1 take the form

$$(s+c-gV_1e^{-s\tau})H_0(s)=0, \tag{4}$$

where $H_0(s)$ is a polynomial with respect to s. Let $H_1(s)=(s+c-gV_1e^{-s\tau})$. So we have $H_1(0)=c(1-R_1)$ and $\lim_{s\to\infty}H_1(s)>0$. Clearly, if $R_1>1$, equation $H_1(s)=0$ has a positive real root, Eq.(4) has a positive real root, and thus Q_1 is unstable. The proof of Theorem 2.2 is completed. □

3. The positive equilibrium and Hopf bifurcation

When the humoral immune reproductive number $R_1>1$, the virus would stimulate antibody immune response, so the infected one will have a certain immunity, since the proof methods are different, when $\tau=0$ and $\tau>0$. We use Theorem 3.1 and Theorem 3.4 to describe this phenomena.

Theorem 3.1. *If $R_1>1$, the equilibrium Q_2 is locally asymptotically stable when $\tau=0$.*

Proof. The characteristic equation of system (2) at the positive equilibrium Q_2 is

$$\begin{aligned}H(s;\tau)&=s^5+A_1s^4+A_2s^3+A_3s^2+A_4s+A_5+(M_1s^4+M_2s^3+M_3s^2+M_4s+M_5)e^{-s\tau}\\&=0,\end{aligned}\tag{5}$$

where

$$A_1=d+P+a+b+u+Q+c,$$

$$A_2=(d+P)(a+b+c)+(d+P)(u+Q)+ab+ac+bc+(u+Q)(a+b+c),$$

$$A_3=(d+P)(u+Q)(a+b+c)+(d+P)(ab+ac+bc)+(u+Q)(a+b)c+abc,$$

$$A_4=(d+P)(u+Q)(a+b)c+(d+P)abc+Pab(u+Q),$$

$$A_5=Pabc(u+Q),$$

and

$$M_1 = -c,$$

$$M_2 = -c(d+P+a+b+u),$$

$$M_3 = -c((d+P)(a+b)+(d+P)u+(a+b)u+ab),$$

$$M_4 = -c((d+P)(a+b)u+(d+P)ab-abQ),$$

$$M_5 = -c(Pabu-Qabd),$$

$P = \beta V_2$, $Q = qB_2$, and $a = a+k$. If $\tau = 0$, Eq.(5) becomes

$$H(s;0) = s^5 + a_1 s^4 + a_2 s^3 + a_3 s^2 + a_4 s + a_5, \tag{6}$$

where

$$a_1 = A_1 + M_1 = d+P+a+u+b+Q > 0,$$

$$a_2 = A_2 + M_2 = (d+P)(a+b)+(d+P)(u+Q)+ab+(a+b)(u+Q)+cQ > 0,$$

$$a_3 = A_3 + M_3 = (a+b)Qc+(d+P)Qc+(d+P)(a+b)(u+Q)+(d+P)ab > 0,$$

$$a_4 = A_4 + M_4 = (d+P)(a+b)Qc+Pab(u+Q)+abQc > 0,$$

$$a_5 = A_5 + M_5 = Qabc(d+P) > 0.$$

By the Routh-Hurwitz criterion, we know that if

$$\triangle_1 = a_1 > 0,$$

$$\triangle_2 = a_1 a_2 - a_3 > 0,$$

$$\triangle_3 = a_3(a_1 a_2 - a_3) - a_1(a_1 a_4 - a_5) > 0,$$

all roots of Eq.(6) have negative real parts. By some calculations, we obtain that

$$a_1 a_2 - a_3 = B_1 a^2 + B_2 a + B_3 c + B_4,$$

where

$$B_1 = (P+d)^2,$$

$$B_2 = (P+d)(P+Q+d+u)+d(Q+u),$$

$$B_3 = (u+Q)Q,$$

$$B_4 = (P+d)(Q+u)(P+Q+d+u).$$

Hence, we complete the proof for $a_1a_2 - a_3 > 0$, we also obtain that

$$
\begin{aligned}
& a_3(a_1a_2-a_3)-a_1(a_1a_4-a_5) \\
& = D_1a^2c + D_2a^2 + D_3a^3c + D_4a^3 + D_5ac^2 + D_6ac + D_7a + D_8c^2 \\
& \quad + D_9c + D_{10},
\end{aligned}
$$

where

$$
\begin{aligned}
D_1 &= [(P+Q+b+d+u)^2+b](Q+u)Q, \\
D_2 &= (P+Q+b+d+u)(Q+u)[(P+Q+d+u)(P+d)+2bP] \\
&\quad + (P+Q+b+d+u)^2(P+d)b + b(Q+u)(P+d)(Q+u+b), \\
D_3 &= Q(u+Q), \\
D_4 &= P(u+Q)(P+Q+d+u) + [d(Q+u)+b(P+d)](P+Q+b+d+u), \\
D_5 &= Q^2(Q+u), \\
D_6 &= [(P+d)(Q+u)(P+Q+b+d+u)+(Q+b+u)(Q+u)(P+b+d)]Q, \\
D_7 &= (P+d)(Q+b+u)^2[(P+d)(P+Q+b+d+u)+b(Q+u)], \\
D_8 &= (Q+u)(P+b+d)Q^2, \\
D_9 &= Q[b(Q+u+b)(Q+u)(P+b+d)+(Q+u)(P+d)^2(P+Q+b+d+u) \\
&\quad + b(P+d)(Q+u)^2], \\
D_{10} &= b(P+d)(Q+u)(Q+b+u)[(P+d)(P+Q+b+d+u)+b(Q+u)],
\end{aligned}
$$

Hence, we complete the proof for $a_3(a_1a_2-a_3)-a_1(a_1a_4-a_5) > 0$. From the above analysis, the Theorem 3.1 holds.

From Theorem 3.1, when $\tau = 0$, all roots of Eq.(5) lie to the left of imaginary axis. But, as τ is increased from zero, some of the roots may cross the imaginary axis to the right. Then the equilibrium Q_2 becomes unstable. Now we consider the existence of purely imaginary roots to

Eq.(5). We suppose Eq.(5) has a purely imaginary root $s = i\omega(\omega > 0)$. Then we obtain

$$\begin{aligned}
&|i\omega^5 + A_1\omega^4 - iA_2\omega^3 - A_3\omega^2 + iA_4\omega + A_5|^2 \\
&= |M_1\omega^4 - iM_2\omega^3 - M_3\omega^2 + iM_4\omega + M_5|^2 |e^{-i\omega\tau}|^2.
\end{aligned}$$

So we have

$$\omega^{10} + C_1\omega^8 + C_2\omega^6 + C_3\omega^4 + C_4\omega^2 + C_5 = 0, \tag{7}$$

where

$$\begin{aligned}
C_1 &= A_1^2 - 2A_2 - M_1^2, \\
C_2 &= A_2^2 + 2A_4 - 2A_1A_3 - M_2^2 + 2M_1M_3, \\
C_3 &= A_3^2 + 2A_1A_5 - 2A_2A_4 - M_3^2 - 2M_1M_5 + 2M_2M_4, \\
C_4 &= A_4^2 - 2A_3A_5 - M_4^2 + 2M_3M_5, \\
C_5 &= A_5^2 - M_5^2.
\end{aligned}$$

Denote

$$G(x) = x^5 + C_1x^4 + C_2x^3 + C_3x^2 + C_4x + C_5. \tag{8}$$

Therefore, if Eq.(5) has a purely imaginary root $i\omega$, equation

$$G(x) = 0 \tag{9}$$

has a positive real root ω^2.

Suppose that Eq.(8) has $\tilde{n}(1 \le \tilde{n} \le 5)$ positive real roots, which are $x_n(1 \le n \le \tilde{n})$, respectively. So we have

$$\begin{aligned}
\cos(\sqrt{x_n}\tau) &= Q_n \\
&= \frac{(M_3x_n - M_1x_n^2 - M_5)(A_1x_n^2 - A_3x_n + A_5) + x_n(M_2x_n - M_4)(x_n^2 - A_2x_n + A_4)}{(M_3x_n - M_1x_n^2 - M_5)^2 + x_n(M_2x_n - M_4)^2},
\end{aligned}$$

$$\begin{aligned}
\sin(\sqrt{x_n}\tau) &= P_n \\
&= \frac{\sqrt{x_n}(M_2x_n - M_4)(A_1x_n^2 - A_3x_n + A_5) - \sqrt{x_n}(M_3x_n - M_1x_n^2 - M_5)(x_n^2 - A_2x_n + A_4)}{(M_3x_n - M_1x_n^2 - M_5)^2 + x_n(M_2x_n - M_4)^2}.
\end{aligned}$$

Let

$$\tau_n^j = \begin{cases} \dfrac{1}{\sqrt{x_n}}[\arccos(Q_n) + 2j\pi], & if P_n \ge 0, \\ \dfrac{1}{\sqrt{x_n}}[2\pi - \arccos(Q_n) + 2j\pi], & if P_n \le 0, \end{cases} \tag{10}$$

where $1 \leq n \leq \tilde{n}$, and $j = 0, 1, 2, ...$

Then it's easy to show that the characteristic equation $H(s;\tau_n^j) = 0$ has a pair of purly imaginary roots $\pm i\sqrt{x_n}$. For every integer j and $1 \leq n \leq \tilde{n}$, let $s_n^{(j)}(\tau) = \alpha_n^{(j)}(\tau) + i\omega_n^{(j)}(\tau)$ be the root of Eq.(5) near $\tau_n^{(j)}$ satisfying $\alpha_n^{(j)}(\tau_n^{(j)}) = 0$, $\omega_n^{(j)}(\tau_n^{(j)}) = \sqrt{x_n}$. Then we have the following theorem.

Theorem 3.2. $\frac{d\alpha_n^{(j)}}{d\tau}|_{\tau=\tau_n^{(j)}}$ *and* $\frac{dG}{dx}|_{x=x_n}$ *have the same sign.*

Proof. Differentiating Eq.(5) with respect to τ, we get

$$\begin{aligned}
&(5s^4 + 4A_1s^3 + 3A_2s^2 + 2A_3s + A_4)\frac{ds}{d\tau} + (4M_1s^3 + 3M_2s^2 + 2M_3s + M_4)e^{-s\tau}\frac{ds}{d\tau} \\
&- \tau e^{-s\tau}(M_1s^4 + M_2s^3 + M_3s^2 + M_4s + M_5)\frac{ds}{d\tau} - se^{-s\tau}(M_1s^4 + M_2s^3 + M_3s^2 + M_4s + M_5) \\
&= 0.
\end{aligned}$$

This gives

$$\begin{aligned}
(\frac{ds}{d\tau})^{-1} &= \frac{(5s^4 + 4A_1s^3 + 3A_2s^2 + 2A_3s + A_4)}{se^{-s\tau}(M_1s^4 + M_2s^3 + M_3s^2 + M_4s + M_5)} \\
&\quad + \frac{e^{-s\tau}(4M_1s^3 + 3M_2s^2 + 2M_3s + M_4)}{se^{-s\tau}(M_1s^4 + M_2s^3 + M_3s^2 + M_4s + M_5)} - \frac{\tau}{s} \\
&= \frac{5s^4 + 4A_1s^3 + 3A_2s^2 + 2A_3s + A_4}{-s(s^5 + A_1s^4 + A_2s^3 + A_3s^2 + A_4s + A_5)} \\
&\quad + \frac{4M_1s^3 + 3M_2s^2 + 2M_3s + M_4}{s(M_1s^4 + M_2s^3 + M_3s^2 + M_4s + M_5)} - \frac{\tau}{s}.
\end{aligned}$$

By Calculation, we have

$$\begin{aligned}
sign\{\frac{d(Res)}{d\tau}|_{\tau=\tau_n^j}\} &= sign\{Re(\frac{ds}{d\tau})^{-1}|_{\tau=\tau_n^j}\} \\
&= sign\frac{5\omega^8 + (4A_1^2 - 8A_2)\omega^6 + (3A_2^2 + 6A_4 - 6A_1A_3)\omega^4}{\omega^2(\omega^4 - A_2\omega^2 + A_4)^2 + (A_1\omega^4 - A_3\omega^2 + A_5)^2} \\
&\quad + \frac{(2A_3^2 - 4A_2A_4 + 4A_1A_5)\omega^2 + A_4^2 - 2A_3A_5}{\omega^2(\omega^4 - A_2\omega^2 + A_4)^2 + (A_1\omega^4 - A_3\omega^2 + A_5)^2} \\
&\quad + \frac{-4M_1^2\omega^6 + (6M_1M_3 - 3M_2^2)\omega^4 + (4M_2M_4 - 2M_3^2 - 4M_1M_5)\omega^2}{\omega^2(M_2\omega^2 - M_4)^2 + (M_1\omega^4 - M_3\omega^2 + M_5)^2} \\
&\quad + \frac{2M_3M_5 - M_4^2}{\omega^2(M_2\omega^2 - M_4)^2 + (M_1\omega^4 - M_3\omega^2 + M_5)^2}.
\end{aligned}$$

From Eq.(7), we get

$$\omega^2(\omega^4 - A_2\omega^2 + A_4)^2 + (A_1\omega^4 - A_3\omega^2 + A_5)^2 = \omega^2(M_2\omega^2 - M_4)^2 + (M_1\omega^4 - M_3\omega^2 + M_5)^2.$$

It therefore follows that

$$sign\{\frac{d(Res)}{d\tau}|_{\tau=\tau_n^j}\} = sign\{\frac{G'(x_n)}{\omega^2(M_2\omega^2 - M_4)^2 + (M_1\omega^4 - M_3\omega^2 + M_5)^2}\}.$$

Since $x_n > 0$, we conclude that $\frac{d\alpha_n^{(j)}}{d\tau}|_{\tau=\tau_n^{(j)}}$ and $\frac{dG}{dx}|_{x=x_n}$ have the same sign.

Theorem 3.3. *Suppose the characteristic equation is the form*

$$f_0(s) + f_1(s)e^{-s\tau} = 0, \tag{11}$$

where f_0 and f_1 are continuously differentiable with respect to s. One of the roots to Eq.(11) is $s(\tau) = \alpha(\tau) + i\omega(\tau)$, where $s(\tau)$ is continuously differentiable with respects to τ, and satisfy $\alpha(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$ for a positive real number τ_0. Denote

$$\phi(\omega) = |f_0(i\omega)|^2 - |f_1(i\omega)|^2. \tag{12}$$

Then we have

$$sign\{\frac{dRe(s)}{d\tau}|_{\tau=\tau_0}\} = sign\{(\frac{1}{2\omega}\frac{d\phi}{d\omega})|_{\omega=\omega_0}\}.$$

In Theorem 3.3, let

$$f_0(s) = s^5 + A_1s^4 + A_2s^3 + A_3s^2 + A^4s + A_5,$$

$$f_1(s) = M_1s^4 + M_2s^3 + M_3s^2 + M_4s + M_5,$$

then $\phi(\omega) = G(\omega^2)$ where ϕ is defined by Eq.(12) and G is defined by Eq.(8). Thus, Theorem 3.3 implies Theorem 3.2. Applying Theorem 3.2 and the Hopf bifurcation theorem, we obtain the existence of a Hopf bifurcation in the following theorem.

Theorem 3.4. *(1) The equilibrium Q_2 is locally asymptotically stable for any $\tau \geq 0$ if Eq.(9) has no positive real roots.*

(2) If Eq.(9) has some positive real roots, then Q_2 is locally asymptotically stable for $\tau \in [0, \tau_{n_0}^0)$, where

$$\tau_{n_0}^0 = \min\{\tau_n^j | 1 < n < \tilde{n}, j = 0, 1, 2, \cdots\}, \tag{13}$$

where $\tau_n^{(j)}$ *is defined by Eq.(10).*

(3) Furthermore, if x_{n_0} *is a simple root of Eq.(9), there is a Hopf bifurcation for the system (2) as* τ *is increased past* $\tau_{n_0}^{(0)}$.

Proof. (1) is obvious by the above discussion.

By the definition of $\tau_{n_0}^{(0)}$ we know that Eq.(9) has no positive real roots for $\tau \in [0, \tau_{n_0}^{0})$. Namely, there is no crossing for eigenvalues. So the roots of the characteristic Eq.(5) have strictly negative real parts for $\tau \in [0, \tau_{n_0}^{0})$. This completes the proof of (2).

Since x_{n_0} is a simple root of Eq.(9), we know $G'(x_{n_0}) \neq 0$. Then $\frac{d\alpha_{n_0}^{(0)}}{d\tau}|_{\tau=\tau_{n_0}} \neq 0$ from Theorem 3.2. If $\frac{d\alpha_{n_0}^{(0)}}{d\tau}|_{\tau=\tau_{n_0}^{(0)}} < 0$, then the characteristic Eq.(5) has roots with positive real parts when τ is slightly less then $\tau_{n_0}^{(0)}$. It's in contradiction with (2) in Theorem 3.4 that we have proved. So we have $\frac{d\alpha_{n_0}^{(0)}}{d\tau}|_{\tau=\tau_{n_0}^{(0)}} > 0$. When $\tau = \tau_{n_0}$ except for the pair of purely imaginary roots, the remaining roots of Eq.(5) have strictly negative real parts due to Theorem 3.1. This implies the existence of a Hopf bifurcation for the system (2). □

4. Stabilities of the bifurcating periodic solutions

In this section, we analyze the stabilities of the bifurcating periodic solutions by using the method in [19]. We assume

$(H1)$ Eq.(5) has a pair of purely imaginary roots $\pm i\omega_0$ when $\tau = \tau_0$, namely, $\tau_0 \in \{\tau_n^j | 1 \leq n \leq \tilde{n}, j = 0, 1, 2, \cdots\}$;

$(H2)$ ω_0 is a simple root of Eq.(9), in other words, $G'(\omega_0^2) \neq 0$;

$(H3)$ the remaining roots of Eq.(5) have strictly negative real parts.

We use $\mu = \tau - \tau_0$ as a new bifurcation parameter. Then $\mu = 0$ is the Hopf bifurcation value. Let

$$X(t) = (T(t) - T_2, E(t) - E_2, I(t) - I_2, V(t) - V_2, B(t) - B_2)^T$$

and $X_t(\theta) = X(t+\theta)$, where $\theta \in [-\tau, 0]$, so that system (2) can be written as:

$$X'(t) = L_\mu X_t + f(X_t(\cdot), \mu), \tag{14}$$

where $L_\mu \phi = F_1 \phi(0) + F_2 \phi(-\tau)$,

$$F_1 = \begin{bmatrix} -d-\beta V_2 & 0 & 0 & -\beta T_2 & 0 \\ \beta V_2 & -a-k & 0 & \beta T_2 & 0 \\ 0 & k & -b & 0 & 0 \\ 0 & 0 & p & -u-qB_2 & -qV_2 \\ 0 & 0 & 0 & 0 & -c \end{bmatrix}, \quad F_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & gB_2 & gV_2 \end{bmatrix},$$

and

$$f(\phi,\mu) = \begin{bmatrix} -\beta\phi_1(0)\phi_4(0) \\ \beta\phi_1(0)\phi_4(0) \\ 0 \\ -q\phi_4(0)\phi_5(0) \\ g\phi_4(-\tau)\phi_5(-\tau) \end{bmatrix}.$$

Applying the Riese representation theorem, there exists a 5×5 matrix-valued function such that

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

Here we can choose

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

Next we define for $\phi \in C([-\tau,0],R^5)$

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

and

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

Then Eq.(14) becomes

$$X'(\theta) = A(\mu)X_t(\theta) + R(\mu)X_t(\theta).$$

For $\varphi \in C([0,\tau],\ R^5)$, $A^*(0)$ which is the adjoint operator of $A(0)$, is defined by

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

We shall simply write A for $A(0)$, A^* for $A^*(0)$, $\eta(\theta)$ for $\eta(\theta,0)$, and R for $R(0)$. Defined an inner product for $\varphi \in C([0,\tau],R^5)$ and $\phi \in C([0,\tau],R^5)$ as

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

We define $h(\theta)$ and $h^\star(s)$ to be the eigenvectors of A and A^* corresponding to the eigenvalue $i\omega_0$ and $-i\omega_0$, respectively. Namely ,

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

We choose $h(\theta)$ and $h^*(s)$ which satisfy $< h^*, h >= 1$ as

$$h(\theta) = (1,h_2,h_3,h_4,h_5)^T e^{i\omega_0\theta} \ \ and \ \ h^*(s) = D(1,h_2^*,h_3^*,h_4^*,h_5^*)^T e^{i\omega_0 s},$$

where

$$\begin{aligned} h_2 &= -\frac{d+i\omega_0}{a+k+i\omega_0}, \qquad h_3 = -\frac{k(d+i\omega_0)}{(b+i\omega_0)(a+k+i\omega_0)}, \\ h_4 &= -\frac{d+\beta V_2+i\omega_0}{\beta T_2}, \qquad h_5 = \frac{ph_3}{qV_2} - \frac{(u+qB_2+i\omega_0)}{qV_2}h_4, \\ h_2^* &= 1+\frac{d-i\omega_0}{\beta V_2}, \qquad h_3^* = \frac{(a+k-i\omega_0)(d+\beta V_2-i\omega_0)}{k\beta V_2}, \\ h_4^* &= \frac{(b-i\omega_0)(a+k-i\omega_0)(d+\beta V_2-i\omega_0)}{pk\beta V_2}, \quad h_5^* = \frac{qV_2h_4^*}{-c+gV_2+i\omega_0}, \end{aligned}$$

and

$$D = [1+h_2^*\bar{h_2}+h_3^*\bar{h_3}+h_4^*\bar{h_4}+h_5^*\bar{h_5}+\tau_0 e^{i\omega_0\tau_0}h_5^*(\bar{h_4}gB_2+\bar{h_5}gV_2)]^{-1}.$$

Next using the method in [19], we obtain the following coefficients:

$$g_{20} = 2\bar{D}(-\beta h_4 + \beta h_4 \bar{h_2^*} - q h_4 h_5 \bar{h_4^*} + g h_4 h_5 \bar{h_5^*} e^{-2i\omega_0\tau_0}),$$

$$g_{11} = 2\bar{D}[\beta(\bar{h_2^*} - 1)Re(h_4) + (\bar{h_5^*} g - \bar{h_4^*} q)Re(h_4\bar{h}_5)],$$

$$g_{02} = 2\bar{D}(-\beta \bar{h}_4 + \beta \bar{h}_4 \bar{h_2^*} - q \bar{h}_4 \bar{h}_5 \bar{h_4^*} + g \bar{h}_4 \bar{h}_5 \bar{h_5^*} e^{2i\omega_0\tau_0}),$$

$$\begin{aligned} g_{21} = 2\bar{D}\{ & \beta(\bar{h_2^*} - 1)[W_{11}^{(4)}(0) + \frac{1}{2}W_{20}^{(4)}(0) + \frac{1}{2}\bar{h_4}W_{20}^{(1)}(0) + h_4 W_{11}^{(1)}(0)] \\ & - \bar{h_4^*} q[h_4 W_{11}^{(5)}(0) + \frac{1}{2}\bar{h_4}W_{20}^{(5)}(0) + \frac{1}{2}\bar{h_5}W_{20}^{(4)}(0) + h_5 W_{11}^{(4)}(0)] \\ & + g\bar{h_5}^*[(h_4 W_{11}^{(5)}(-\tau_0) + h_5 W_{11}^{(4)}(-\tau_0))e^{-i\omega_0\tau_0} + (\bar{h_4}W_{20}^{(5)}(-\tau_0) + \bar{h_5}W_{20}^{(4)}(-\tau_0))\frac{e^{i\omega_0\tau_0}}{2}]\}, \end{aligned}$$

where

$$W_{20}(\theta) = \frac{ig_{20}}{\omega_0}e^{i\omega_0\theta}h(0) + \frac{i\bar{g}_{02}}{3\omega_0}e^{-i\omega_0\theta}\bar{h}(0) + E_{20}e^{2i\omega_0\theta},$$

$$W_{11}(\theta) = -\frac{ig_{11}}{\omega_0}e^{i\omega_0\theta}h(0) + \frac{i\bar{g}_{11}}{\omega_0}e^{-i\omega_0\theta}\bar{h}(0) + E_{11},$$

$$E_{20} = 2(2i\omega_0 - F_1 - F_2 e^{-2i\omega_0\tau})^{-1}\begin{bmatrix} -2\beta h_4 \\ 2\beta h_4 \\ 0 \\ -2q h_4 h_5 e^{-2i\omega_0\tau} \\ 2g h_4 h_5 e^{-2i\omega_0\tau} \end{bmatrix}$$

and

$$E_{11} = 2(-F_1 - F_2)^{-1}\begin{bmatrix} -\beta Re(h_4) \\ \beta Re(h_4) \\ 0 \\ -qRe(h_4\bar{h_5}) \\ gRe(h_4\bar{h_5}) \end{bmatrix}.$$

Thus far, we figure out g_{20}, g_{11}, g_{02}, and g_{21}. So we can compute the following quantities:

$$c_1(0) = \frac{i}{2\omega_0}(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}) + \frac{g_{21}}{2},$$

$$\mu_2 = -\frac{Re(c_1(0))}{Re(\lambda'(\tau_0))},$$

$$\beta_2 = 2Re(c_1(0)).$$

The signs of μ_2 and β_2 determine the direction of the Hopf bifurcation and the stabilities of bifurcating periodic solutions respectively. From Theorem 3.2, we know

$$sign\{Re\lambda'(\tau_0)\} = sign\{G'(\omega_0)\}.$$

Let $\mu_2^* = -\dfrac{Re(c_1(0))}{G'(\omega_0^2)}$. Then we have the following theorem.

Theorem 4.1. *Assume that $H(1)$, $H(2)$ and $H(3)$ hold.*

(1) If $\mu_2^* > 0$ $(\mu_2^* < 0)$, then the bifurcating periodic solutions exist for $\tau > \tau_0$ $(\tau < \tau_0)$ in a τ_0-neighborhood.

(2) If $\beta_2 < 0$ $(\beta_2 > 0)$, the bifurcating periodic solution are orbitally asymptotically stable as $t \to +\infty$ $(t \to -\infty)$.

It's easy to show that when $\tau_0 = \tau_{n_0}^{(0)}$ where $\tau_{n_0}^{(0)}$ is defined by Eq.(13), the conclusions in (3) of Theorem 3.4 imply that the existence and stabilities of the bifurcating periodic solutions are only determined by $Re(c_1(0))$. Specifically, if $Re(c_1(0)) < 0$, there exist stable periodic solutions for $\tau_0 > \tau_{n_0}^{(0)}$ in a $\tau_{n_0}^{(0)}-$neighborhood.

5. Numerical simulations

In order to check our results, we choose a set of parameters $a = 6.2142 day^{-1}$, $\beta = 1.0903 mm^3 day^{-1}$, $c = 2.4910 day^{-1}$, $d = 1.6964 day^{-1}$, $g = 5.8502 mm^3 day^{-1}$, $k = 6.7965 day^{-1}$, $\lambda = 3.9913 mm^3 day^{-1}$, $u = 5.3556 day^{-1}$, $q = 3.4407 mm^3 day^{-1}$, $b = 1.8042 day^{-1}$, $p = 2.3867 mm^3 day^{-1}$, We can compute $R_0 = 0.5152 < 1$, and $R_1 = 0.1695 < 1$, system (2) has an infection-free equilibrium $Q_0 = (2.3528, 0, 0, 0, 0)$. Hence, by Theorem 2.1, Q_0 is globally asymptotically stable and that the viruses are cleared. Fig.1 demonstrates the above analysis.

In addition to, we choose a set of parameters $a = 6.5718 day^{-1}$, $\beta = 6.8873 mm^3 day^{-1}$, $c = 1.3564 day^{-1}$, $d = 2.4593 day^{-1}$, $g = 5.9402 mm^3 day^{-1}$, $k = 6.7589 day^{-1}$, $\lambda = 7.9037 mm^3 day^{-1}$, $u = 1.2516 day^{-1}$, $q = 6.9692 mm^3 day^{-1}$, $b = 6.1702 day^{-1}$, $p = 5.6224 mm^3 day^{-1}$. We can compute $R_0 = 1.4674 > 1$, and $R_1 = 0.1592 < 1$, and system (2) has an immune-free infection equilibrium $Q_1 = (2.1902, 0.1888, 0.2069, 0.1669, 0)$, which satisfy the condition of Theorem 2.2. Fig.2 demonstrates the result of Theorem 2.2, that Q_1 is globally asymptotically stable.

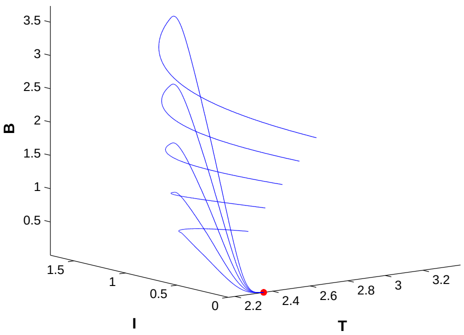

Fig. 1. Stability of the uninfected equilibrium Q_0.

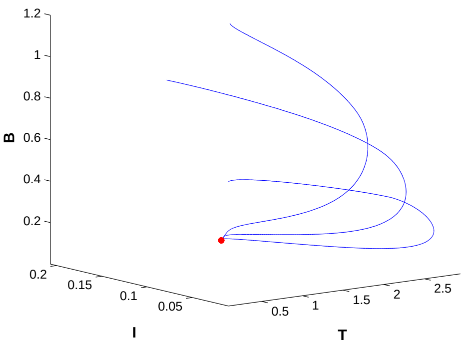

Fig. 2. Stability of the infected equilibrium without immune response equilibrium Q_1

In order to check our results about the existence of Hopf bifurcation, we choose a set of parameters $a = 4.9392 day^{-1}$, $\beta = 2.4842 mm^3 day^{-1}$, $c = 1.6504 day^{-1}$, $d = 0.0940 day^{-1}$, $g = 6.3196 mm^3 day^{-1}$, $k = 2.6057 day^{-1}$, $\lambda = 4.0620 mm^3 day^{-1}$, $u = 1.6065 day^{-1}$, $q = 5.3927 mm^3$ day^{-1}, $b = 2.5210 day^{-1}$, $p = 4.4369 mm^3 day^{-1}$, then we get $R_1 = 5.7400 > 1$, $Q_2 = (5.4688, 0.4702, 0.4860, 0.2612, 1.2334)$, the minimum positive simple real root of (3.4) is $x_1 = 1.8557$. It satisfies the conditions (3) of theorem 3.4. We can calculate that $\tau_1^{(0)} = 0.6079$, Applying theorem 3.4, Q_2 is stable when $\tau < \tau_1^{(0)}$, when $\tau > \tau_1^{(0)}$, then there exist a Hopf bifurcation, the simulation results were shown in Fig.3 and Fig.4. we can compute $c_1(0) = -0.0108 - 0.0062i$, by Theorem 4.1, there is an orbitally asymptotically stable periodic solution when $\tau > \tau_1^{(0)}$. Fig.5 illustrates this fact.

6. Concluding remarks

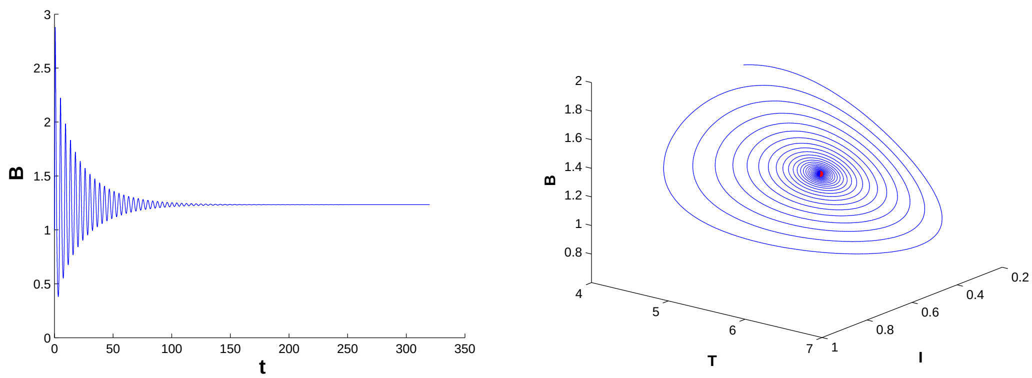

Fig. 3. Stability of Q_2 for $\tau = 0.42 < \tau_1^{(0)}$

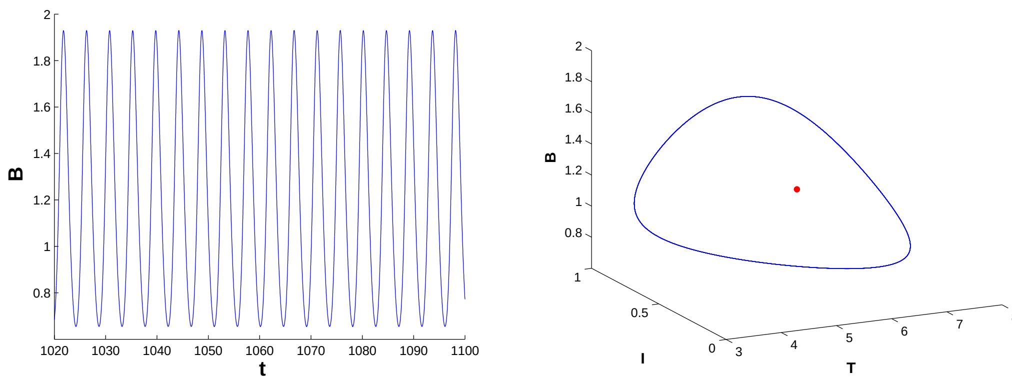

Fig. 4. A stable bifurcating periodic solution when $\tau = 0.68 > \tau_1^{(0)}$

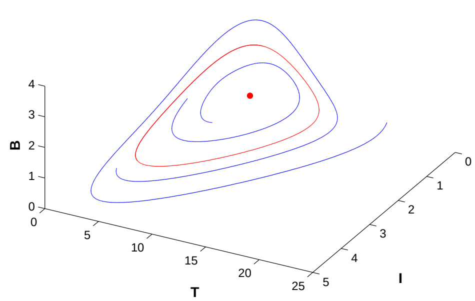

Fig. 5. an orbitally asymptotically stable periodic solution of system (2) when $\tau = 1.6 > \tau_1^{(0)}$

In this parper, we give a virus infection model with delayed humoral immunity. To be more realistic, it is very necessary to introduce the exposed state into the mathematical model. We obtained the basic production ratio R_0 and the immune response reproductive number R_1. By using Lyapunov-LaSalle's invariance principle, we prove the following result: if $R_0 < 1$ the infection-free equilibrium Q_0 is globally asymptotically stable, else unstable; if $R_1 < 1 < R_0$, the infected equilibrium without immunity Q_1 is globally asymptotically stable, else unstable. When $R_1 > 1$, we prove the infected equilibrium with humoral immunity Q_2 is locally asymptotically stable if $\tau = 0$. If characteristic equation about Q_2 has simple positive root, there is a Hopf bifurcation for our system. We also discuss the stability of periodic solutions by the center manifold and canonical form method, simulation results are consistent with our theoretical analysis.

Conflict of Interests

The authors declare that there is no conflict of interests.

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