Research Article

Stability Analysis of an In-Host Viral Model with Cure of Infected Cells and Humoral Immunity

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An in-host viral model with cure of infected cells and humoral immunity is studied. We prove that the stability is completely determined by the basic reproductive number R_0 and show that the infection-free equilibrium E_0 is globally asymptotically stable if and only if $R_0 \leq 1$. Moreover, if $R_0 > 1$, the infection equilibrium is locally asymptotically stable when the time delay τ is small and it loses stability as the length of the time delay increases past a critical value τ_0. Finally, we confirm our analysis by providing several numerical examples.

1. Introduction

The humoral immunity is a kind of immunologic mechanism which uses B lymphocytes to produce antigen to prevent virus and there are evidences to prove that the humoral immunity is more effective than the cell-mediated immune in some infections such as malaria infection [1–3]. Many authors present and develop mathematical systems for the humoral immunity [4–7]. And the cure of virus is also important especially in HBV models [8, 9]. In the present paper, we analyze an in-host viral model with humoral immunity and intracellular delay, and we incorporate a "cure" of infected cells into it. We propose the following system:

$$T'(t) = \Lambda - \beta T(t) V(t) - dT(t) + bI(t),$$

$$I'(t) = \beta T(t) V(t) - (a + b) I(t),$$

$$V'(t) = kI(t) - uV(t) - qB(t) V(t),$$

$$B'(t) = gV(t - \tau) - cB(t),$$

(1)

where T, I, V, and B represent the uninfected cells, the infected cells, the virus, and the B cells, respectively. Λ and d are assumed as the birth rate and death rate of uninfected cells. β is the infection rate and $kI(t)$ represents the number of free virus which is produced during the average infected cell life span. a is the death rate of infected cells and u

represents the death rate of virus. g and c represent the birth rate and death rate of B cells. The B cells neutralization rate is represented by q.

The following form is taken as the initial conditions:

$$T(\theta) = \varphi_1(\theta),$$

$$I(\theta) = \varphi_2(\theta),$$

$$V(\theta) = \varphi_3(\theta),$$

(2)

$$B(\theta) = \varphi_4(\theta)$$

$$\varphi_i(\theta) \geq 0, \quad \theta \in (-\tau, 0), \quad \varphi_i(0) > 0 \ (i = 1, 2, 3, 4),$$

where $(\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta)) \in \mathbb{C}([-\tau, 0], \mathbb{R}_{+0}^4)$, the space of continuous functions mapping the interval $(-\infty, 0]$ into $\mathbb{R}_{+0}^4$, and

$$\mathbb{R}_{+0}^4 = \{(x_1, x_2, x_3, x_4) \mid x_i \geq 0, i = 1, 2, 3, 4\}.$$

(3)

The organization of this paper is as follows. In the next section, we will find threshold parameters R_0 of system (1) and it determines the existence of the equilibriums. In Section 3, by structuring suitable Lyapunov functionals and using LaSalle's invariance principle we attain the global stability of the uninfected equilibrium if $R_0 \leq 1$. In Section 4, we consider the stability of the infected equilibrium and

the occurrence of local Hopf bifurcation. In Section 5, we present the numerical simulations to illustrate our results. Finally, we offer concluding remarks in the last section.

2. Existence of Equilibrium

We can easily find that system (1) always has an uninfected equilibrium $E_0 = (T_0, 0, 0, 0) = ((\Lambda/d), 0, 0, 0)$.

Denote

$$R_0 = \frac{\Lambda k \beta}{ud(a+b)}. \tag{4}$$

We call R_0 the basic reproductive number. It is easy to prove that if $R_0 > 1$, model (1) exist an infected equilibrium $E^*(T^*, I^*, V^*, B^*)$, where

$$
\begin{aligned}
V^* &= \left(\sqrt{(\beta cua - (a+b)dgq)^2 + 4\Lambda gqack\beta^2} \right. \\
&\quad \left. - \beta cua - (a+b)dgq \right) \\
&\quad \times (2a\beta gq)^{-1}, \\
T^* &= \frac{gq(a+b)}{k\beta c}V^* + \frac{u(a+b)}{k\beta}, \\
B^* &= \frac{g}{c}V^*, \\
I^* &= \frac{gq}{kc}V^{*2} + \frac{u}{k}V^*.
\end{aligned}
\tag{5}
$$

3. Global Attraction of Infection-Free Equilibrium

Theorem 1. *The infection-free equilibrium E_0 of system (1) is globally attractive if $R_0 \leq 1$.*

Proof. Let $(T(t), I(t), V(t), B(t))$ be any positive solution of system (1) with initial conditions (2).

Define

$$
\begin{aligned}
L(t) &= \frac{gk}{2q(a+b)} \cdot \frac{(T-T_0)^2}{T_0} \\
&\quad + \frac{bgk}{2q(a+b)(a+d)} \cdot \frac{(T-T_0+I)^2}{T_0} \\
&\quad + \frac{gk}{q(a+b)}I + \frac{g}{q}V + \frac{1}{2}B^2 \\
&\quad + gB\int_{t-\tau}^{t} V(\xi)\,d\xi.
\end{aligned}
\tag{6}
$$

Calculating the derivative of $L(t)$ along positive solutions of system (1) and noting $\Lambda = dT_0$ and $TV(T-T_0) = V(T-T_0)^2 + T_0V(T-T_0)$, it follows that

$$
\begin{aligned}
\dot{L} &= -\left(\frac{gk\beta}{q(a+b)}V + \frac{dgk(a+d)+bdgk}{q(a+b)(a+d)} \right) \\
&\quad \times \frac{(T-T_0)^2}{T_0} - \frac{abgk}{q(a+b)(a+d)}I^2 \\
&\quad - cB^2 + \frac{gu}{q}(R_0-1)V.
\end{aligned}
\tag{7}
$$

If $R_0 \leq 1$, it follows from (7) that $\dot{L} \leq 0$. The solutions are limited to the largest invariant subset M of $\{\dot{L}(t) = 0\}$. It is clear that $\dot{L}(t) = 0$ if and only if $(T, I, V, B) = (T_0, I_0, V_0, B_0)$. So we can obtain the global attraction of E_0 by using LaSalle's invariance principle. This completes the proof. □

4. Permanence of the System for $R_0 > 1$

Theorem 2. *If $R_0 > 1$, the infected equilibrium E^* of system (1) is locally asymptotically stable when $\tau = 0$.*

Proof. The characteristic equation associated with system (1) at E^* is

$$
\begin{aligned}
\lambda^4 &+ m_3\lambda^3 + m_2\lambda^2 \\
&+ m_1\lambda + m_0 + e^{-\lambda\tau}\left(n_2\lambda^2 + n_1\lambda + n_0\right) = 0.
\end{aligned}
\tag{8}
$$

Noting that $T^* = ((gq(a+b))/(k\beta c))V^* + ((u(a+b))/(k\beta))$, $B^* = (g/c)V^*$, we can obtain

$$
\begin{aligned}
m_3 &= a + b + c + d + u + qB^* + \beta V^*, \\
m_2 &= bd + a(d + \beta V^*) \\
&\quad + (u + qB^*)(d + \beta V^*) \\
&\quad + c(a + b + d + u + qB^* + \beta V^*), \\
m_1 &= \frac{(a+c)gq}{c}\beta V^{*2} \\
&\quad + (au + cu + ac)\beta V^* + cd(a+u+b), \\
m_0 &= c(au\beta V^* + aq\beta V^* B^*), \\
n_2 &= gqV^*, \\
n_1 &= gqV^*(a + b + d + \beta V^*), \\
n_0 &= dgq(a+b)V^* + agq\beta V^{*2}.
\end{aligned}
\tag{9}
$$

If $\tau = 0$, (8) becomes

$$\lambda^4 + m_3\lambda^3 + (m_2 + n_2)\lambda^2 + (m_1 + n_1)\lambda + m_0 + n_0 = 0. \tag{10}$$

Then we can obtain $m_0 + n_0 > 0$, $m_1 + n_1 > 0$, $m_2 + n_2 > 0$, and $m_3 > 0$. It follows from Routh-Hurwitz criterion that all roots of (10) have negative real parts when $\tau = 0$. This competes the proof. □

Let $\lambda = iv$ and then substitute it into (8). Separating the real and imaginary parts, we will gain

$$v^4 - m_2 v^2 + m_0 = \left(n_2 v^2 - n_0\right) \cos v\tau - n_1 v \sin v\tau,$$
$$m_3 v^3 - m_1 v = \left(n_2 v^2 - n_0\right) \sin v\tau + n_1 v \cos v\tau. \tag{11}$$

Squaring and adding (11) yield

$$v^8 + \left(m_3^2 - 2m_2\right) v^6$$
$$+ \left(m_2^2 - 2m_1 m_3 + 2m_0 - n_2^2\right) v^4$$
$$+ \left(m_1^2 - 2m_0 m_2 - n_1^2 + 2n_0 n_2\right) v^2 \tag{12}$$
$$+ \left(m_0^2 - n_0^2\right) = 0.$$

Denote

$$G(x) = x^4 + \left(m_3^2 - 2m_2\right) x^3$$
$$+ \left(m_2^2 - 2m_1 m_3 + 2m_0 - n_2^2\right) x^2$$
$$+ \left(m_1^2 - 2m_0 m_2 - n_1^2 + 2n_0 n_2\right) x \tag{13}$$
$$+ \left(m_0^2 - n_0^2\right).$$

We have that

$$G'(x) = 4x^3 + 3\left(m_3^2 - 2m_2\right) x^2$$
$$+ 2\left(m_2^2 - 2m_1 m_3 + 2m_0 - n_2^2\right) x \tag{14}$$
$$+ \left(m_1^2 - 2m_0 m_2 - n_1^2 + 2n_0 n_2\right).$$

Hence if $G(x) = 0$ has a positive root $x = v^2$, then $\lambda = \pm iv$ are a couple of purely imaginary characteristic roots. Moreover, for a real practice model with fully known coefficients, the exactly four roots of $G(x) = 0$ can be numerically calculated with the help of computational software such as Matlab. Let x_i $(1 \leq i \leq k, 1 \leq k \leq 4)$ be the positive roots of $G(x) = 0$ and $v_i = \sqrt{x_i}$.

Solving (11) with respect to τ, we can obtain

$$\tau_i^{(j)} = \frac{1}{v_i} \arccos\left(\left(\frac{n_2 v_i^6 + \left(-n_0 + n_1 m_3 - n_2 m_2\right) v_i^4}{n_1^2 v_i^2 + \left(n_2 v_i^2 - n_0\right)^2}\right)\right.$$
$$\left. + \left(\frac{\left(n_0 m_2 - n_1 m_1 + n_2 m_0\right) v_i^2 - n_0 m_0}{n_1^2 v_i^2 + \left(n_2 v_i^2 - n_0\right)^2}\right)\right)$$
$$+ \frac{1}{v_i} \cdot 2j\pi, \tag{15}$$

where $1 \leq i \leq k$; $1 \leq k \leq 4$; $j = 0, 1, 2, \ldots$. Let

$$\tau_0 = \min\left\{\tau_i^{(j)} \mid 1 \leq i \leq k; j = 0, 1, 2, \ldots\right\}. \tag{16}$$

This means that τ_0 is the least value of τ which can be used to make the characteristic equation have purely imaginary roots.

Theorem 3. $G'(v_i^2)$ and $\mathrm{Re}[d\lambda/d\tau]_{\tau=\tau_i^{(j)}}^{-1}$ have the same sign.

Proof. Let the characteristic equation be in the following form:

$$f(\lambda) + g(\lambda) e^{-\lambda\tau} = 0. \tag{17}$$

We can obviously know from (8) that

$$f(\lambda) = \lambda^4 + m_3 \lambda^3 + m_2 \lambda^2 + m_1 \lambda + m_0,$$
$$g(\lambda) = n_2 \lambda^2 + n_1 \lambda + n_0. \tag{18}$$

Calculating the derivative of (17) with respect to τ, we can obtain that

$$\frac{d\lambda}{d\tau} \left(f'(\lambda) + g'(\lambda) e^{-\lambda\tau} - g(\lambda) e^{-\lambda\tau} \cdot \tau\right)$$
$$= g(\lambda) e^{-\lambda\tau} \cdot \lambda,$$
$$\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_i^{(j)}}^{-1} = \frac{f'(\lambda) + g'(\lambda) e^{-\lambda\tau}}{g(\lambda) e^{-\lambda\tau} \cdot \lambda} - \frac{\tau}{\lambda} \tag{19}$$
$$= \frac{f'(iv_i) + g'(iv_i) e^{-iv_i\tau}}{g(iv_i) e^{-iv_i\tau} \cdot iv_i} - \frac{\tau}{iv_i}.$$

Therefore,

$$\mathrm{Re}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_i^{(j)}}^{-1}$$
$$= \mathrm{Re}\left[\frac{f'(iv_i) + g'(iv_i) e^{-iv_i\tau}}{g(iv_i) e^{-iv_i\tau} \cdot iv_i}\right]$$
$$= \mathrm{Re}\left[\frac{f'(iv_i)}{iv_i \cdot \left(-f(iv_i)\right)} + \frac{g'(iv_i)}{iv_i \cdot g(iv_i)}\right]$$
$$= \mathrm{Re}\left[\frac{1}{iv_i} \cdot \left(\frac{-f'(iv_i) \cdot \overline{f}(iv_i)}{f(iv_i) \cdot \overline{f}(iv_i)} + \frac{g'(iv_i) \cdot \overline{g}(iv_i)}{g(iv_i) \cdot \overline{g}(iv_i)}\right)\right]$$
$$= \mathrm{Re}\left[\frac{1}{iv_i} \cdot \frac{g'(iv_i) \cdot \overline{g}(iv_i) - f'(iv_i) \cdot \overline{f}(iv_i)}{|f(iv_i)|^2}\right]. \tag{20}$$

Obviously,

$$\mathrm{sign}\left(\mathrm{Re}\left[\frac{d\lambda}{d\tau}\right]_{\tau=\tau_i^{(j)}}^{-1}\right)$$
$$= \mathrm{sign}\left(\mathrm{Im}\left(g'(iv_i) \cdot \overline{g}(iv_i) - f'(iv_i) \cdot \overline{f}(iv_i)\right)\right). \tag{21}$$

And after some calculations, we can get

$$\mathrm{Im}\left(g'(iv_i) \cdot \overline{g}(iv_i) - f'(iv_i) \cdot \overline{f}(iv_i)\right)$$
$$= 4v_i^7 + 3\left(-2m_2 + m_3^2\right) v_i^5$$
$$+ 2 \cdot \left(m_2^2 - 2m_1 m_3 + 2m_0 - n_2^2\right) v_i^3 \tag{22}$$
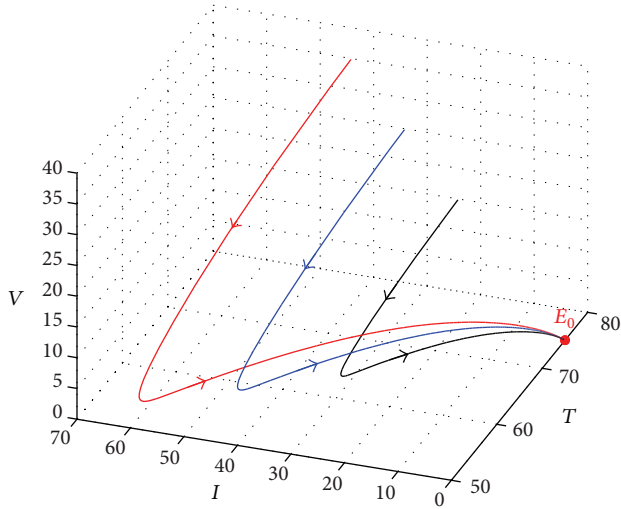$$+ \left(m_1^2 - 2m_0 m_2 - n_1^2 + 2n_0 n_2\right) v_i.$$

FIGURE 1: Equilibrium E_0 is globally asymptotically stable if $R_0 < 1$.

Therefore, $G'(v_i^2)$ and $\text{Re}[d\lambda/d\tau]^{-1}_{\tau=\tau_i^{(j)}}$ have the same sign. This completes the proof. □

Applying Theorems 2 and 3 and the Hopf bifurcation theorem for functional differential equation [10], we derive the existence of a Hopf bifurcation as stated in Theorem 4.

Theorem 4. *Suppose that $G(x) = 0$ has at least one simple positive root and τ_0 is defined in* (16). *Then there is a Hopf bifurcation for the system* (1) *as s passes upwards through τ_0 leading to a periodic solution that bifurcates from E^*, where*

$$\tau_i^{(j)} = \frac{1}{v_i} \arccos\left(\left(\frac{n_2 v_i^6 + (-n_0 + n_1 m_3 - n_2 m_2) v_i^4}{n_1^2 v_i^2 + (n_2 v_i^2 - n_0)^2}\right)\right.$$
$$+ \left.\left(\frac{(n_0 m_2 - n_1 m_1 + n_2 m_0) v_i^2 - n_0 m_0}{n_1^2 v_i^2 + (n_2 v_i^2 - n_0)^2}\right)\right)$$
$$+ \frac{1}{v_i} \cdot 2j\pi, \quad 1 \le i \le k; \quad j = 0, 1, 2, \ldots.$$
$$(23)$$

5. Numerical Examples

Example 1. For system (1), consider all parameters as follows: $a = 0.1$, $b = 0.1$, $\beta = 0.1$, $c = 0.001$, $d = 0.2$, $g = 0.1$, $k = 0.1$, $\lambda = 1$, $q = 0.001$, $u = 10$, and $\tau = 10$. In this case, we can obtain that $R_0 = 0.375 < 1$; the global attraction of the infection-free equilibrium E_0 is illustrated by Figure 1.

Example 2. Consider all parameters of system (1) as follows: $a = 2.41979$, $b = 2.80472$, $\beta = 2.34292$, $c = 2.2057$, $d = 0.9129$, $g = 4.2074$, $k = 2.6415$, $\lambda = 4.60059$, $q = 3.738$, and $u = 1.3978$. In this case, we can obtain that $R_0 = 4.2709 > 1$.

(1) When $\tau = 0.75$, E^* is locally asymptotically stable and the stability is illustrated by Figure 2.
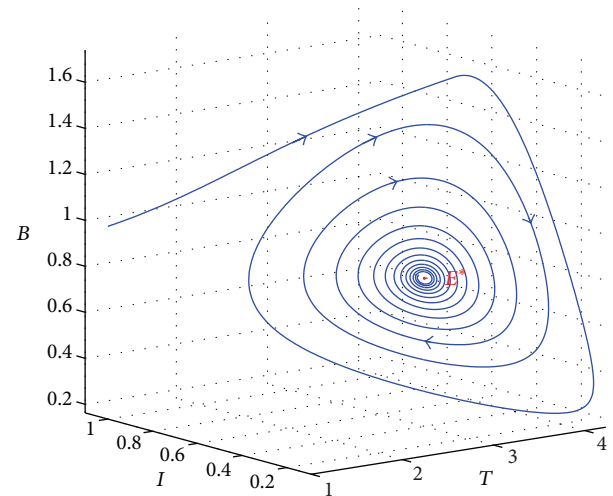

FIGURE 2: Equilibrium E^* is locally asymptotically stable when τ is very small.
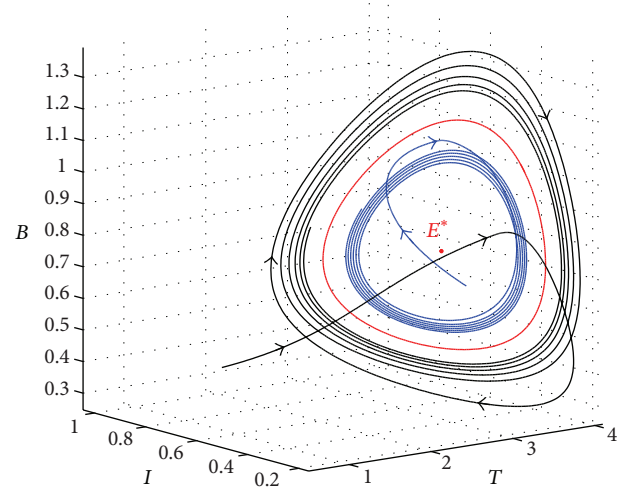

FIGURE 3: Delay can destabilize E^* and lead to Hopf bifurcation when τ increases past a critical value τ_0.

(2) When $\tau = 0.9$, the delay can destabilize E^* and lead to Hopf bifurcation. We will show that in Figure 3.

6. Discussions

In this paper, we consider an in-host viral model humoral immunity. In addition, a "cure" of infected cells is incorporated. Firstly, it has been shown that if the basic reproductive number is less than unity, the infection-free equilibrium E_0 is globally attractive, and the time delay has no effect on the dynamics of the system. Then, a detailed analysis on the local asymptotic stability of the infection equilibrium E^* of the model is carried out. If E^* is feasible, the basic reproduction number of the virus is greater than unity; E^* is globally attractive for any time delay under some parameter conditions. By taking the discrete time delay as a bifurcation parameter, it is shown that this system undergoes a sequence

of Hopf bifurcations and stability switches are observed by using simulations.

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