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Research Article

Analysis of a viral infection model with immune impairment and cure rate

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Abstract

In this paper, the dynamics behavior of a delayed viral infection model with immune impairment and cure rate is studied. It is shown that there exists three equilibria. By analyzing the characteristic equations, the local stability of the infection-free equilibrium and the immune-exhausted equilibrium of the model are established. In the following, the stability of the positive equilibrium is studied. Furthermore, we investigate the existence of Hopf bifurcation by using a delay as a bifurcation parameter. Finally, numerical simulations are carried out to explain the mathematical conclusions. ©2016 All rights reserved.

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1. Introduction

Mathematical models of epidemic and viral dynamics have attracted much attention in recent years. A proper model may play a significant role in the development of a better understanding of the disease and the various drug therapy strategics used against it. There has been much interest in mathematical modeling of viral dynamics within-host.

During the process of viral infection, as soon a virus invades host cells, Cytotoxic T Lymphocyte (CTL) cells which attack infected cells play an important role in responding to the aggression. In order to investigate the role of the population dynamics of viral infection with CTL response, Nowak and Bangham [10] constructed a mathematical model that describes the basic dynamics of the interaction between activated $CD4^+$ T cells $x(t)$, infected $CD4^+$ T cells $y(t)$, viruses $v(t)$ and immune cells $z(t)$. There are three kinds

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of models that describe the interaction between a virus population $y(t)$ and the number of CTL cells $z(t)$ [3, 4, 11]: a self-regulating CTL response $z' = c - bz$, a linear CTL response $z' = cy - bz$, and a nonlinear CTL response $z' = cyz - bz$. Besides, Bartholdy et al. [2] and Wodarz et al. [16] found that the turnover of free virus is much faster than that of infected cells, which allowed them to make a quasi-steady state assumption: $v'(t) = 0$, that is, the amount of free virus is simply proportional to the number of infected cells. Furthermore, time delays should be considered in viral models, especially the delay between viral appearance and the production of new immune particles. A delayed viral infection model with immune response is given by Xie et al. [17]

$$\begin{cases} x'(t) = s - dx(t) - \beta x(t)y(t), \\ y'(t) = \beta x(t)y(t) - ay(t) - py(t)z(t), \\ z'(t) = cy(t-\tau)z(t-\tau) - bz(t), \end{cases} \tag{1.1}$$

where activated $CD4^+$ T cells are produced at a constant rate s, decay at a rate d, and can become infected at a rate that is proportional to the number of infected $CD4^+$ T cells $y(t)$ with a transmission rate constant β. The infected $CD4^+$ T cells are assumed to decay at the rate of a and kill at a rate p by the CTL responses. The CTL responses proliferate at a rate proportional to the number of infected $CD4^+$ T cells at a previous time $cy(t-\tau)z(t-\tau)$ and decay at a rate b. Furthermore, τ is the time delay of CTL responses.

However, there are numerous experimental results suggesting that the virus generates mutants which escape from specific immune responses [5, 7]. For example, during the course of HIV-1 infection, the modulation of dendritic cells by HIV infection is a key aspect in viral pathogenesis. It contributes to viral evasion from immunity because the dysfunction of dendritic cells engenders some impairment effects for CTL inducement [12], and Regoes et al. provided some models with immune impairment. Iwasa et al. [8] discovered the existence of so-called Risky threshold and Immunodeficiency threshold on the impairment rate. The former implies that immune system may collapse when the impairment rate of HIV exceeds the threshold value. The latter implies that the immune system always collapses when the impairment rate exceeds the value. Wang et al. [15] considers the following DDE model with an immune impairment term myz.

$$\begin{cases} x'(t) = s - dx(t) - \beta x(t)y(t), \\ y'(t) = \beta x(t)y(t) - ay(t) - py(t)z(t), \\ z'(t) = cy(t-\tau) - bz(t) - my(t)z(t), \end{cases} \tag{1.2}$$

where m denotes the immune impairment rate.

In addition, the consideration of cure rate of infected cells is another innovation in the modeling for viral dynamics. Recently, this cure of infected cells is considered by several works [6, 14]. On the basis of the system (1.2), we investigate the viral model as follows:

$$\begin{cases} x'(t) = s - dx(t) - \beta x(t)y(t) + \rho y(t), \\ y'(t) = \beta x(t)y(t) - (a+\rho)y(t) - py(t)z(t), \\ z'(t) = cy(t-\tau)z(t-\tau) - bz(t) - my(t)z(t), \end{cases} \tag{1.3}$$

where the state variables x, y, z and the parameters s, d, β, a, p, c, b and m have the same biological meanings as in the model (1.1) and (1.2). ρ is the rate of cure. We assume that each infected cell revert to the uninfected state at a rate ρ. Suppose $c > m$ in this paper.

The initial conditions for system (1.3) take the form

$$\begin{aligned} &x(\theta) = \varphi_1(\theta), \quad y(\theta) = \varphi_2(\theta), \quad z(\theta) = \varphi_3(\theta), \\ &\varphi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0], \quad \varphi_i(0) > 0 \quad (i = 1, 2, 3), \end{aligned} \tag{1.4}$$

where $(\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta)) \in C([-\tau, 0], R^3_{+0})$. We denote by $C = C([-\tau, 0], R^3_{+0})$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R^3_{+0} with the topology of uniform convergence, where $R^3_{+0} = \{(x_1, x_2, x_3) | x_i \geq 0, i = 1, 2, 3\}$.

In this paper, our focus is to study dynamics of model (1.3). In the next Section, the conditions for existence of equilibria and the boundedness of solutions are derived. By analyzing the corresponding characteristic equations, we study the local asymptotic stability of the infection-free equilibrium and the immune-exhausted equilibrium of system (1.3) in Section 3. In the following section, we discuss the global stability of the infection-free equilibrium by means of suitable Lyapunov functional and LaSalle invariance principle in this section. We analyze the local stability of the positive equilibrium and the existence of the Hopf bifurcation occurring at the positive equilibrium in Section 4. Finally, some numerical simulations are given in Section 5.

2. The existence of equilibria and the boundedness of solutions

In this section, we study the equilibrium of system (1.3). Denote

$$\Re_0 = \frac{\beta s}{(a+\rho)d}, \qquad \Re_1 = \frac{\beta[(c-m)s+\rho b]}{(a+\rho)[(c-m)d+\beta b]},$$

where $\Re_0$ is called the basic reproduction number, that is "the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual" [1]; $\Re_1$ is called the basic reproductive number eith immune response of model (1.3). It is easy to show the following conclusions.

Theorem 2.1 ([1])**.**

(1) If $\Re_0 < 1$ and $\Re_1 < 1$, system (1.3) only has an infection-free equilibrium $E_0(x_0, 0, 0)$, where $x_0 = \frac{s}{d}$.

(2) If $\Re_0 > 1$ and $\Re_1 < 1$, in addition to the infection-free equilibrium E_0, system (1.3) has another equilibrium $E_1(x_1, y_1, 0)$ corresponding to the survival of free virus and the extinction of CTL. It is called as immune-exhausted equilibrium, where $x_1 = \frac{a+\rho}{\beta}$ and $y_1 = \frac{s\beta-(a+\rho)d}{a\beta}$.

(3) If $\Re_0 > 1$ and $\Re_1 > 1$, in addition to the infection-free equilibrium E_0, system (1.3) has another infected equilibrium $E_2(x_2, y_2, z_2)$ corresponding to the survival of free virus and CTL, where $x_2 = \frac{(c-m)s+b\rho}{(c-m)d+b\beta}$, $y_2 = \frac{b}{c-m}$ and $z_2 = \frac{\beta x_2-(a+\rho)}{p}$.

Next, we prove all solutions of system (1.3) are positive and ultimately bounded.

Theorem 2.2. *Under the above initial conditions (1.4), all solutions of system (1.3) are positive and there exists a positive constant M such that each solution satisfies $x(t) < M, y(t) < M, z(t) < M$ after sufficiently large time t.*

Proof. By the second and third equations of system (1.3) we have

$$y(t) = y(0)e^{\int_0^t(\beta x(\theta)-(a+\rho)-pz(\theta))d\theta}.$$

By (1.4), $y(t) > 0$ for all $t > 0$.

From (1.4), on the interval $0 \le t \le \tau$, $y(t-\tau) \ge 0, z(t-\tau) \ge 0$, so we have

$$z'(t) = cy(t-\tau)z(t-\tau) - bz(t) - my(t)z(t) \ge -(b+my(t))z(t), \quad 0 \le t \le \tau,$$

According to comparison theorem, $z(t) \ge z(0)e^{\int_0^t -(b+my(\theta))d\theta} > 0$, for $0 \le t \le \tau$. By using the method of steps, we have $z(t) > 0$ for all $t > 0$.

Further, we show $x(t) > 0$. If not, then we let $t_1 > 0$ be the first time such that $x(t_1) = 0$. By the first equation of system (1.3), we have $x'(t_1) = s + \rho y(t_1) > 0$. That means $x(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, where ε is an arbitrarily small positive constant. This leads to a contradiction. It follows that $x(t)$ is always positive.

Next, we prove the ultimate boundedness of solutions of (1.3). Let $N(t) = x(t) + y(t) + \frac{p}{2c}z(t+\tau)$. Since all solutions of (1.3) are positive, we have

$$\begin{aligned} N'(t) &= s - dx(t) - ay(t) - \frac{p}{2}y(t)z(t) - \frac{pb}{2c}z(t+\tau) - \frac{pm}{2c}y(t+\tau)z(t+\tau) \\ &\leq s - dx(t) - ay(t) - \frac{pb}{2c}z(t+\tau) \leq s - qN, \end{aligned}$$

where $q = \min\{d, a, b\}$. Therefore, $N(t) < \frac{s}{q} + \varepsilon$ for all large t, ε is an arbitrarily small positive constant. Thus, there exists some positive constant M such that $x(t) < M, y(t) < M, z(t) < M$ after sufficiently large time t. □

3. The stability analysis of infection-free equilibrium and the immune-exhausted equilibrium

In the following, we will discuss the local stability of infection-free equilibrium and the immune-exhausted equilibrium for system (1.3) by analyzing the corresponding characteristic equations.

For simplicity, let $\overline{E} = (\overline{x}, \overline{y}, \overline{z})$ is the arbitrarily equilibrium of system (1.3), then the characteristic equation about $\overline{E}$ is given by

$$\begin{vmatrix} \lambda + d + \beta\overline{y} & \beta\overline{x} - \rho & 0 \\ -\beta\overline{y} & \lambda - \beta\overline{x} + (a+\rho) + p\overline{z} & p\overline{y} \\ 0 & m\overline{z} - c\overline{z}e^{-\lambda\tau} & \lambda + b + m\overline{y} - c\overline{y}e^{-\lambda\tau} \end{vmatrix} = 0. \tag{3.1}$$

Theorem 3.1. *If $\Re_0 < 1$ and $\Re_1 < 1$, then the infection-free equilibrium $E_0(x_0, 0, 0)$ is locally asymptotically stable, and E_0 is unstable if $\Re_0 > 1$.*

Proof. By (3.1), the characteristic equation about E_0 is

$$(\lambda + d)(\lambda + b)(\lambda - \frac{\beta s}{d} + a + \rho) = 0. \tag{3.2}$$

It is clear that Eq. (3.2) has eigenvalues $\lambda_1 = -d < 0, \lambda_2 = -b < 0$ and $\lambda_3 = \frac{\beta s}{d} - (a + \rho)$.

If $\Re_0 < 1$, then $\lambda_3 < 0$, therefore E_0 is locally asymptotically stable.

If $\Re_0 > 1$, then $\lambda_3 > 0$, so E_0 is unstable. □

Theorem 3.2. *If $\Re_0 > 1$ and $\Re_1 < 1$, then the immune-exhausted equilibrium $E_1(x_1, y_1, 0)$ is locally asymptotically stable, and E_1 is unstable if $\Re_0 > 1$ and $\Re_1 > 1$.*

Proof. By (3.1), the characteristic equation about E_1 is

$$[\lambda^2 + (d + \beta y_1)\lambda + a\beta y_1](\lambda + b + my_1 - cy_1e^{-\lambda\tau}) = 0.$$

It is easy to see that $\lambda_1 + \lambda_2 = -(d + \beta y_1) < 0$, $\lambda_1\lambda_2 = a\beta y_1 > 0$, then $\lambda_1 < 0$, $\lambda_2 < 0$, and λ_3 is determined by the following equation

$$f(\lambda) \equiv \lambda + b + my_1 - cy_1e^{-\lambda\tau} = 0. \tag{3.3}$$

If $\Re_0 > 1$, $\Re_1 < 1$ and $\tau = 0$, then $\lambda_3 = (c - m)y_1 - b = (c - m)\frac{s\beta - (a+\rho)d}{a\beta} - b < (c - m)\frac{s\beta - d\beta x_2}{(\beta x_2 - \rho)\beta} - b = 0$. Therefore, if $\tau = 0$, $\Re_0 > 1$ and $\Re_1 < 1$, E_1 is locally asymptotically stable.

If $\tau > 0$, let $i\omega(\omega > 0)$ is a solution of Eq. (3.3). On substituting $\lambda = i\omega$ into Eq. (3.3) and separating real and imaginary parts, we have

$$\begin{cases} \omega = -cy_1 \sin(\omega\tau), \\ b + my_1 = cy_1 \cos(\omega\tau). \end{cases} \tag{3.4}$$

Squaring and adding the two equations of (3.4), we derive that

$$\omega^2 = [(c-m)y_1 - b][(c+m)y_1 + b].$$

From $\Re_0 > 1$ and $\Re_1 < 1$, we have $(c-m)y_1 - b < 0$. This leads to a contradiction. So, Eq. (3.3) has no pure imaginary root. Therefore, E_1 is locally asymptotically stable for all $\tau \geq 0$.

If $\Re_0 > 1$ and $\Re_1 > 1$, then $f(0) = b - (c-m)y_1 < 0$, $\lim_{\lambda\to\infty} f(\lambda) = +\infty$. Hence, Eq. (3.3) has at least one positive real root. So the immune-exhausted equilibrium E_1 is unstable. □

Next, we study the global stability of infection-free equilibrium E_0 of system (1.3).

Theorem 3.3. *If $\Re_0 < 1$, $\Re_1 < 1$ and $d < a, d < b$, then the infection-free equilibrium $E_0(x_0, 0, 0)$ is globally asymptotically stable.*

Proof. Define Lyapunov functional

$$V(t) = y(t) + \frac{p}{c-m}z(t) + \frac{cp}{c-m}\int_{t-\tau}^{t} y(\theta)z(\theta)\mathrm{d}\theta.$$

Taking derivative of $V(t)$ along the positive solutions of the system (1.3), we get

$$\begin{aligned} V'(t) =& (\beta x(t) - a - \rho)y(t) + (\frac{cp}{c-m} - \frac{mp}{c-m} - p)y(t)z(t) - \frac{pb}{c-m}z(t) \\ <& (\frac{s\beta}{q} - a - \rho)y(t). \end{aligned}$$

Obviously, $V'(t) = 0$ if and only if $y(t) = 0$, by the Lasalle invariance principle we have $\lim_{t\to\infty} y(t) = 0$. Hence, the limit equation of system (1.3) is

$$x'(t) = s - dx(t). \tag{3.5}$$

Note that the equilibrium of Eq. (3.5) is $x = \frac{s}{d}$ which is globally asymptotically stable. Thus, by the limit equation we get $E_0(x_0, 0, 0)$ is globally attractive. It is proved that E_0 is locally asymptotically stable by the Theorem 3.1 when $\Re_0 < 1$ and $\Re_1 < 1$. Therefore, E_0 is globally asymptotically stable. □

4. The stability of infected equilibrium and Hopf bifurcation

The characteristic equation of system (1.3) about E_2 is given by

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

where

$$P(\lambda) = \lambda^3 + b_1\lambda^2 + b_2\lambda + b_3, \quad Q(\lambda) = b_4\lambda^2 + b_5\lambda + b_6,$$

and

$$\begin{aligned} &b_1 = b + d + (m+\beta)y_2, \quad b_2 = (b+my_2)(d+\beta y_2) - mpy_2z_2 + \beta^2x_2y_2 - \rho\beta y_2, \\ &b_3 = (\beta^2x_2y_2 - \rho\beta y_2)(b+my_2) - mpy_2z_2(d+\beta y_2), \quad b_4 = -cy_2, \\ &b_5 = cpy_2z_2 - cy_2(d+\beta y_2), \quad b_6 = cpy_2z_2(d+\beta y_2) - c\beta^2x_2y_2^2 + c\rho\beta y_2^2. \end{aligned}$$

When $\Re_1 > 1$ and $\tau = 0$, Eq. (4.1) becomes

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0, \tag{4.2}$$

where

$$\begin{aligned}
A =& b_1 + b_4 = b + d + (m+\beta)y_2 - cy_2 = d + \beta y_2 > 0,\\
B =& b_2 + b_5\\
=& (b + my_2)(d + \beta y_2) - mpy_2z_2 + \beta^2 x_2 y_2 - \rho\beta y_2 + cpy_2z_2 - cy_2(d + \beta y_2)\\
=& bpz_2 + (\beta x_2 - \rho)\beta y_2 > 0.\\
C =& b_3 + b_6\\
=& (\beta^2 x_2 y_2 - \rho\beta y_2)(b + my_2) - mpy_2z_2(d + \beta y_2) + cpy_2z_2(d + \beta y_2)\\
& - c\beta^2 x_2 y_2^2 + c\rho\beta y_2^2\\
=& bpz_2(d + \beta y_2) > 0.\\
AB - C =& (d + \beta y_2)[bpz_2 + \beta y_2(\beta x_2 - \rho)] - bpz_2(d + \beta y_2)\\
=& \beta y_2(\beta x_2 - \rho)(d + \beta y_2) > 0.
\end{aligned}$$

By directly calculating, we have $\beta x_2 - \rho > 0$. According to Routh-Hurwitz criterion, we know that all roots of (4.2) have negative real part. Hence, the infected equilibrium $E_2(x_2, y_2, z_2)$ is locally asymptotically stable when $\tau = 0$.

Therefore, we have the following Theorem.

Theorem 4.1. *If $\tau = 0$, $\Re_0 > 1$ and $\Re_1 > 1$, then the infected equilibrium $E_2(x_2, y_2, z_2)$ is locally asymptotical stable.*

In order to investigate the locally asymptotically stable of E_2 for $\tau > 0$, we will apply the following result that has been proposed by Boese (1992) [9].

Lemma 4.2 ([9])**.** *Consider Eq.* (4.1)*, where $P(\lambda)$ and $Q(\lambda)$ are analytic functions and* $\mathrm{Re}\lambda > 0$ *and satisfy the following conditions:*

(1) $P(\lambda)$ and $Q(\lambda)$ have no common imaginary root;
(2) $\overline{P(-iy)} = P(iy)$, $\overline{Q(-iy)} = Q(iy)$ for real y;
(3) $P(0) + Q(0) \neq 0$;
(4) $\limsup\{|\frac{Q(\lambda)}{P(\lambda)}| : |\lambda| \to \infty, Re\lambda \geq 0\} < 1$;
(5) $F(y) \equiv |P(-iy)|^2 - |Q(-iy)|^2$ for real y has at most a finite number of real zeros.

Then the following statements are true.

(a) If $F(y) = 0$ has no positive roots, then no stability switch may occur.
(a) If $F(y) = 0$ has at least one positive root and each of them is simple, then as τ increases, a finite number of stability switches may occur, and eventually the considered equation becomes unstable.

In the following, we check Eq. (4.1) satisfying Lemma 4.2. Obviously,

$$P(i\omega) + Q(i\omega) = -(b_1 + b_4)\omega^2 + b_3 + b_6 + i\omega(-\omega^2 + b_2 + b_5) \neq 0.$$

This implies condition (1) of Lemma 4.2 is satisfied. And condition (2) is true, for

$$\overline{P(-i\omega)} = -i\omega^3 - b_1\omega^2 + ib_2\omega + b_3 = P(i\omega), \quad \overline{Q(-i\omega)} = -b_4\omega^2 + ib_5\omega + b_6 = Q(i\omega).$$

We have

$$P(0) + Q(0) = b_3 + b_6 > 0, \qquad \limsup_{\lambda\to\infty} |\frac{Q(\lambda)}{P(\lambda)}| = \frac{b_4\lambda^2 + b_5\lambda + b_6}{\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3} = 0 < 1.$$

Condition (3) and (4) are also true. To determine the stability of the equilibrium E_2, the existence of positive roots of the following equation needs to be analyzed

$$F(\omega) \equiv |P(-i\omega)|^2 - |Q(-i\omega)|^2 = \omega^6 + a_1\omega^4 + a_2\omega^2 + a_3 = 0, \tag{4.3}$$

where $a_1 = b_1^2 - 2b_2 - b_4^2, \quad a_2 = b_2^2 - 2b_1b_3 - b_5^2 + 2b_4b_6, \quad a_3 = b_3^2 - b_6^2.$

Let $h = \omega^2$, we denote

$$G(h) \equiv h^3 + a_1h^2 + a_2h + a_3 = 0. \tag{4.4}$$

Then

$$G'(h) = 3h^2 + 2a_1h + a_2 = 0. \tag{4.5}$$

Thus Eq. (4.5) has two real roots $h_1 = \frac{-a_1+\sqrt{\triangle}}{3}$ and $h_2 = \frac{-a_1-\sqrt{\triangle}}{3}$, where $\triangle = a_1^2 - 3a_2$.

Now, we introduce the following results which were proved by Song and Yuan [13].

Lemma 4.3 ([13]). *For the polynomial Eq.* (4.4)*, we have the following results:*

(1) If $a_3 < 0$, then (4.4) *has at least one positive root.*

(2) If $a_3 \geq 0$, and $\triangle \leq 0$, then (4.4) *has no positive root.*

(3) If $a_3 \geq 0$, and $\triangle > 0$, then (4.4) *has positive root if and only if $h_1 = \frac{-a_1-\sqrt{\triangle}}{3} > 0$ and $G(h_1) \leq 0$.*

From Lemma 4.3, we know that if $a_3 \geq 0$, and $\triangle = a_1^2 - 3a_2 \leq 0$, then Eq. (4.4) has no positive root. If $a_3 \geq 0$, $a_1 > 0$ and $a_2 > 0$, then Eq. (4.4) also has no positive root. Hence, we can conclude the following theorem.

Theorem 4.4. *Suppose that $\Re_0 > 1$, $\Re_1 > 1$, if $a_1 > 0$, $a_2 > 0$ and $a_3 \geq 0$, or $a_3 \geq 0$ and $\triangle \leq 0$, then the infected equilibrium $E_2(x_2, y_2, z_2)$ is locally asymptotically stable for $\tau > 0$.*

In the following, we study the Hopf bifurcation of the infected equilibrium. We assume that for some $\tau > 0$, $i\omega(\omega > 0)$ is a root of (4.1). On substituting $\lambda = i\omega$ into Eq. (4.1) and separating real and imaginary parts, we have

$$\begin{cases} b_3 - b_1\omega^2 = -(b_6 - b_4\omega^2)\cos\omega\tau - b_5\omega\sin\omega\tau, \\ b_2\omega - \omega^3 = (b_6 - b_4\omega^2)\sin\omega\tau - b_5\omega\cos\omega\tau. \end{cases} \tag{4.6}$$

Squaring and adding the two equations of (4.6), then ω satisfies Eq. (4.3). Let $h = \omega^2$, then h satisfies Eq. (4.4).

From Lemma 4.3, we know that if $a_1 > 0$, $a_2 > 0$ and $a_3 < 0$, then Eq. (4.4) has at least one positive root. Under the condition, if $h \geq 0$, then $G'(h) > 0$. That is to say, $G(h)$ is monotone increasing in $h \in [0, +\infty)$. Thus, there is a unique positive ω_0 satisfying (4.1), i.e. the characteristic Eq. (4.1) has a pair of purely imaginary roots of the form $\pm i\omega_0$. From (4.6), we get the corresponding $\tau_n > 0$ such that the characteristic Eq. (4.1) has a pair of purely imaginary roots $\pm i\omega_0$, where

$$\tau_n = \frac{1}{\omega_0}\arccos\frac{(b_1\omega_0^2 - b_3)(b_6 - b_4\omega_0^2) + b_5\omega_0(\omega_0^3 - b_2\omega_0)}{(b_6 - b_4\omega_0^2)^2 + (b_5\omega_0)^2} + \frac{2n\pi}{\omega_0}, \quad n = 0, 1, 2, \cdots.$$

In the following, we will prove that

$$\frac{\mathrm{d}(\mathrm{Re}\lambda)}{\mathrm{d}\tau}|_{\tau=\tau_n} > 0.$$

This will signify that there exists at least one eigenvalue with positive real part for $\tau > \tau_n$.

Differentiating (4.1) with respect to τ, we get

$$(3\lambda^2+2b_1\lambda+b_2)\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}+(2b_4\lambda+b_5)e^{-\lambda\tau}\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}$$
$$-\tau(b_4\lambda^2+b_5\lambda+b_6)e^{-\lambda\tau}\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}-\lambda(b_4\lambda^2+b_5\lambda+b_6)e^{-\lambda\tau}=0.$$

This gives

$$\begin{aligned}(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau})^{-1}&=\frac{3\lambda^2+2b_1\lambda+b_2}{\lambda e^{-\lambda\tau}(b_4\lambda^2+b_5\lambda+b_6)}+\frac{2b_4\lambda+b_5}{\lambda(b_4\lambda^2+b_5\lambda+b_6)}-\frac{\tau}{\lambda}\\&=\frac{2\lambda^3+b_1\lambda^2-b_3}{-\lambda^2(\lambda^3+b_1\lambda^2+b_2\lambda+b_3)}+\frac{b_4\lambda^2-b_6}{\lambda^2(b_4\lambda^2+b_5\lambda+b_6)}-\frac{\tau}{\lambda}.\end{aligned}$$

By calculation, we have

$$\begin{aligned}\mathrm{sign}\{\frac{\mathrm{d}(\mathrm{Re}\lambda)}{\mathrm{d}\tau}\}_{\tau=\tau_n}&=\mathrm{sign}\{\mathrm{Re}(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau})^{-1}\}_{\lambda=i\omega_0}\\&=\mathrm{sign}\{\frac{2\omega_0^6+(b_1^2-2b_2-b_4^2)\omega_0^4-(b_3^2-b_6^2)}{\omega_0^2[(b_6-b_4\omega_0^2)^2+(b_5\omega_0)^2]}\}\\&=\mathrm{sign}\{\frac{2\omega_0^6+a_1\omega_0^4-a_3}{\omega_0^2[(b_6-b_4\omega_0^2)^2+(b_5\omega_0)^2]}\}.\end{aligned}$$

By $a_1=b_1^2-2b_2-b_4^2>0,\quad a_3=b_3^2-b_6^2<0$, we get $\frac{\mathrm{d}(\mathrm{Re}\lambda)}{\mathrm{d}\tau}|_{\tau=\tau_n}>0$.

This root of characteristic Eq. (4.1) crosses the imaginary axis from the left to the right as τ continuously varies from a number less than τ_n to one greater than τ_n. Therefore, the transversal condition holds and the conditions for Hopf bifurcation are then satisfied at $\tau=\tau_n$. Then, from the above analysis, we can conclude the following theorem.

Theorem 4.5. *Assume that $\Re_0>1, R_1>1$, $a_1>0$, $a_2>0, a_3<0$ and ω_0 is the first positive root of Eq. (4.3), then the infected equilibrium $E_2(x_2,y_2,z_2)$ is locally asymptotically stable when $\tau<\tau_0$ and unstable when $\tau>\tau_0$, where*

$$\tau_0=\frac{1}{\omega_0}\arccos\frac{(b_1\omega_0^2-b_3)(b_6-b_4\omega_0^2)+b_5\omega_0(\omega_0^3-b_2\omega_0)}{(b_6-b_4\omega_0^2)^2+(b_5\omega_0)^2}.$$

Furthermore, when $\tau=\tau_0$, system (1.3) undergoes a Hopf bifurcation to periodic solutions at the infected state E_2.

5. Numerical simulations

To demonstrate the theoretical results obtained in this paper, we will give some numerical simulations.

Example 5.1. $s=80$; $\beta=0.001$; $d=0.1$; $\rho=0.2$; $a=0.8$; $p=0.1$; $c=0.003$; $b=0.1$; $m=0.001$ and $\tau=3$. Through calculation, we get $R_0=0.8<1$ and $R_1=0.6<1$, system (1.3) only has an infection-free equilibrium $E_0(800,0,0)$. Hence, according to Theorem 3.1, E_0 is locally asymptotically stable (see Fig. 1 (a)-(c) and (d)).

Example 5.2. $s=80$; $\beta=0.002$; $d=0.1$; $\rho=0.1$; $a=0.8$; $p=0.1$; $c=0.003$; $b=0.1$; $m=0.001$ and $\tau=3$. Through calculation, we get $R_0=1.78>1$ and $R_1=0.94<1$, then in addition to the infection-free equilibrium E_0, system (1.3) has another equilibrium $E_1(450,43.75,0)$. According to Theorem 3.2, the immune-exhausted equilibrium $E_1(450,43.75,0)$ is locally asymptotically stable. For this case (see Fig. 2 (a)-(c) and (d)).

Example 5.3. $s=80$; $\beta=0.01$; $d=0.1$; $\rho=0.05$; $a=0.8$; $p=0.1$; $c=0.01$; $b=0.1$; $m=0.007$ and $\tau=1$. Through calculation, we get $R_0=9.411765>1$ and $R_1=2.2171946>1$, then system (1.3) has another infected equilibrium $E_2(188.461538,33.33,10.346754)$. Besides, we get $a_3=0.006889>0$ and $\triangle=a_1^2-3a_2=-0.020931<0$, according to Theorem 4.4, E_2 is locally asymptotically stable. For this case (see Fig. 3 (a)-(c) and (d)).

Remark 5.4. As is well-known, the infection rate β of susceptible host cells by the virus, the cure rate ρ of infected cells and the rate of immune response c play a critical role in virus infections model (1.3). In Example 5.1, we select a set of parameters, and the $\beta = 0.001$ is small, the cure rate $\rho = 0.2$ is larger, system (1.3) only has an infection-free equilibrium E_0, Fig.1 shows E_0 is locally asymptotically stable corresponding to the extinction of free virus. In Example 5.2, increasing the infection rate of susceptible host cells to $\beta = 0.002$ and decreasing the cure rate to $\rho = 0.1$, other parameters are the same as Example 5.1, system (1.3) has immune-exhausted equilibrium E_1, Fig.2 shows the E_1 is locally asymptotically stable which means that the survival of free virus and the extinction of CTL. In Example 5.3, we further increase β to 0.001, decrease ρ to 0.05 and increase the rate of immune response to $c = 0.01$. System (1.3) has an infection equilibrium E_2, Fig.3 shows the E_2 is locally asymptotically stable which means that the survival of free virus and CTL.

Example 5.5. $s = 500$; $\beta = 0.005$; $d = 0.5$; $\rho = 2$; $a = 2$; $p = 0.5$; $c = 0.03$; $b = 0.09$; $m = 0.02$. Here, $R_0 = 1.25 > 1$, $R_1 = 1.1880734 > 1$, $a_1 = 0.320144 > 0, a_2 = 0.0393182 > 0$, $a_3 = -0.00434 < 0$, which satisfy the conditions of Theorem 4.5. Hence, we shall utilize these values to work out the critical time delay preserving stability or not. Through calculation, we obtain the critical time delay $\tau_0 = 1.30270806$. Therefore, the infected equilibrium $E_2(950.45872, 9, 1.504587)$ remains locally asymptotically stable for $\tau = 1 < \tau_0$ (see Fig. 4 (a)-(c) and (d)), while for $\tau = 2 > \tau_0$, E_2 is unstable. (see Fig. 5 (a)-(c) and (d)).

Remark 5.6. Time delays cannot be ignored in models for immune response, in Example 5.5, we indicate that the effects of the time delay for immune response can affect the dynamic behavior of system (1.3). Indeed, Fig. 4 shows the infected equilibrium E_2 remains stable at low values of time delay, while it becomes unstable if time delay τ exceeds a certain threshold τ_0, we can observe periodic oscillations emerge(see Fig. 5).

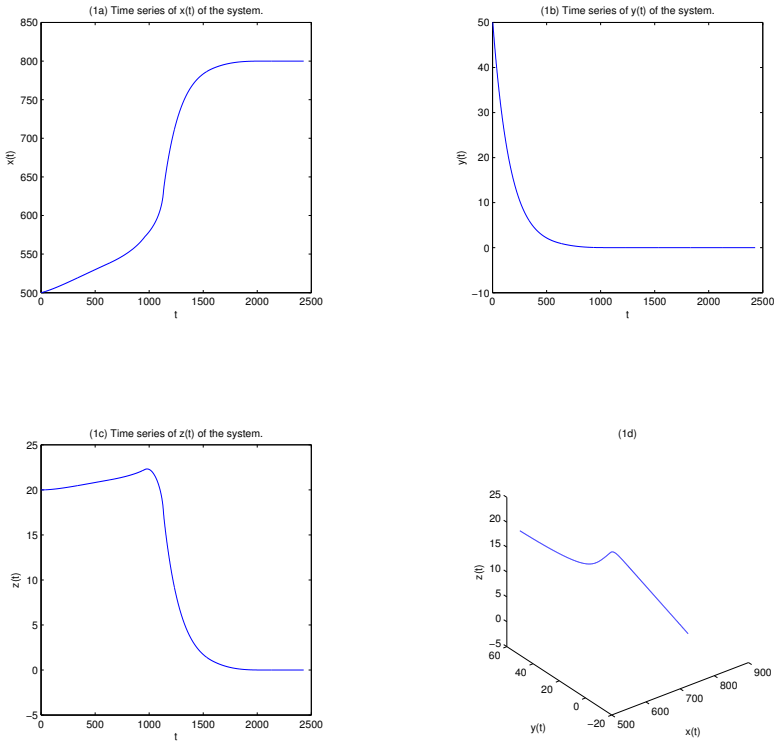

Figure 1: $R_0 = 0.8 < 1$ and $R_1 = 0.6 < 1$, the infection-free equilibrium $E_0(800, 0, 0)$ is locally asymptotically stable.

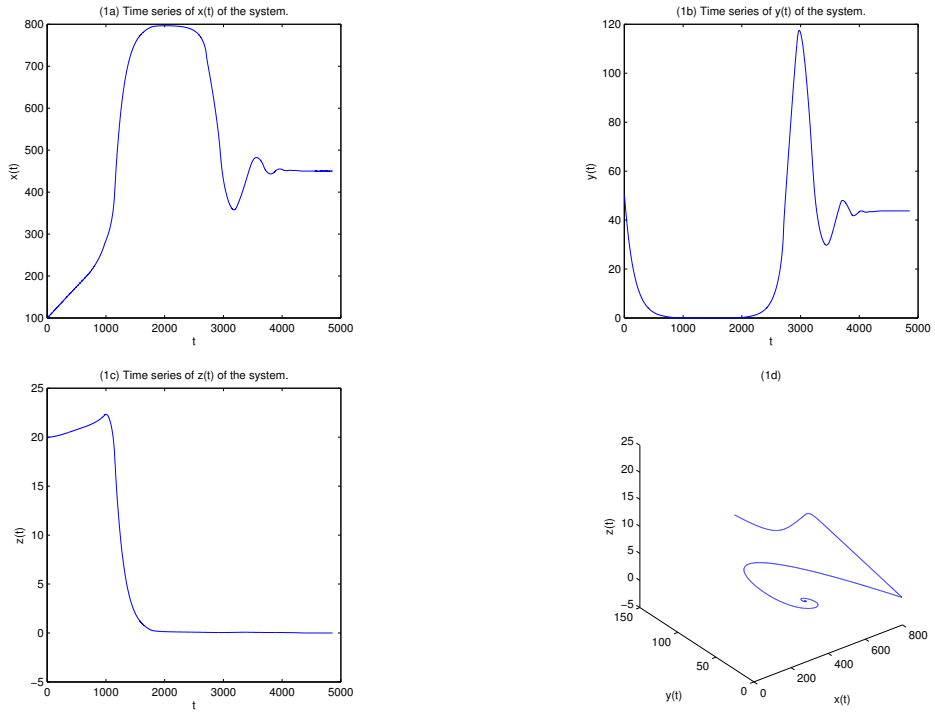

Figure 2: $R_0 = 1.78 > 1$ and $R_1 = 0.94 < 1$, the immune-exhausted equilibrium $E_1(450, 43.75, 0)$ is locally asymptotically stable.

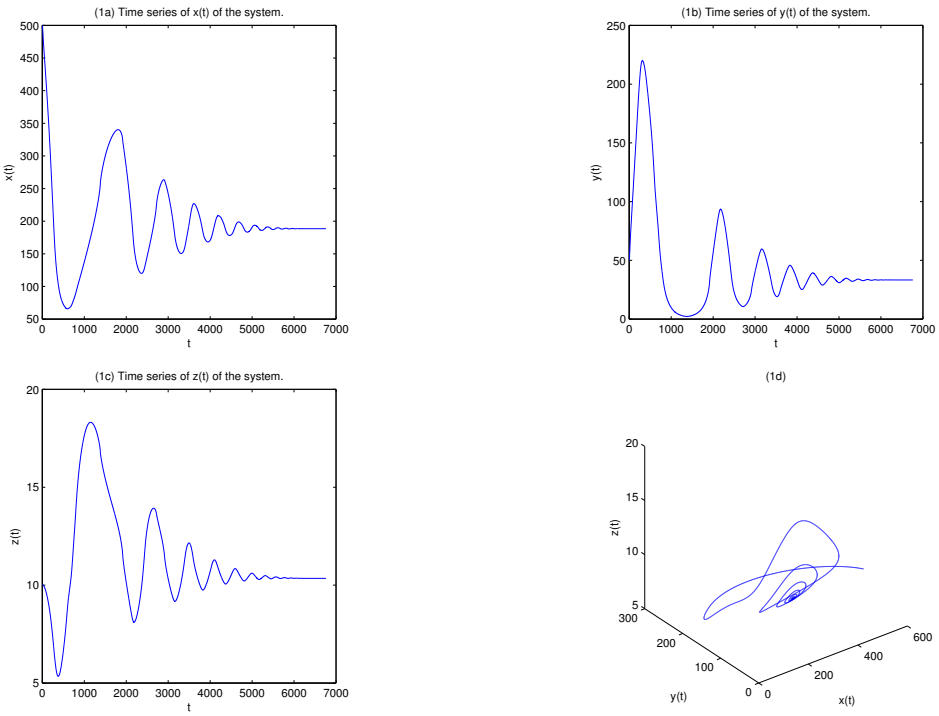

Figure 3: $R_0 = 9.411765 > 1$, $R_1 = 2.2171946 > 1$, $a_3 = 0.006889 > 0$ and $\triangle = a_1^2 - 3a_2 = -0.020931 < 0$, the infected equilibrium $E_2(188.461538, 33.33, 10.346754)$ is locally asymptotically stable for $\tau \geq 0$.

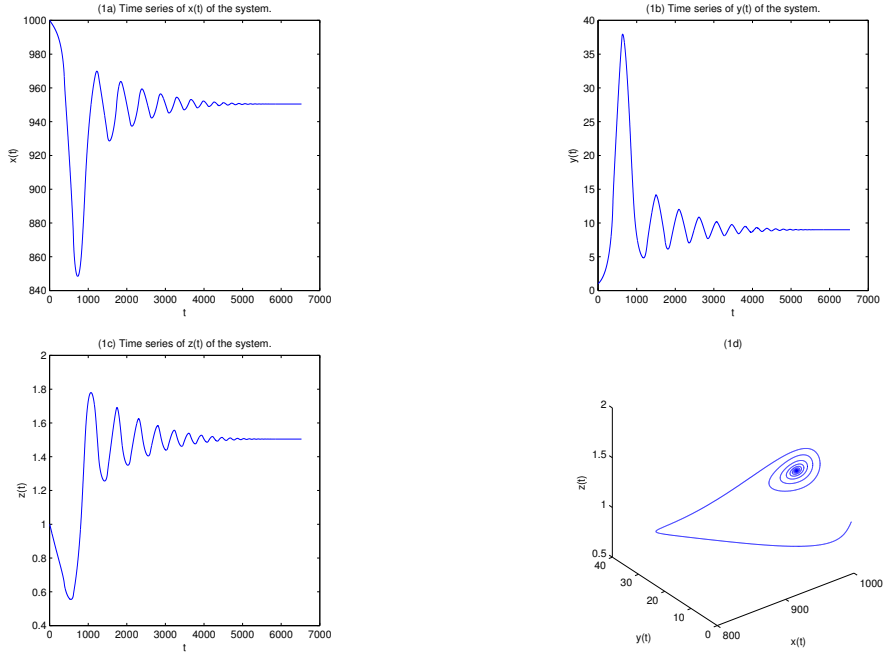

Figure 4: $R_0 = 1.25 > 1$, $R_1 = 1.1880734 > 1$, $a_1 = 0.320144 > 0, a_2 = 0.0393182 > 0$, $a_3 = -0.00434 < 0$, $\tau_0 = 1.30270806$, $\tau = 1 < \tau_0$, the infected equilibrium $E_2(950.45872, 9, 1.504587)$ remains locally asymptotically stable.

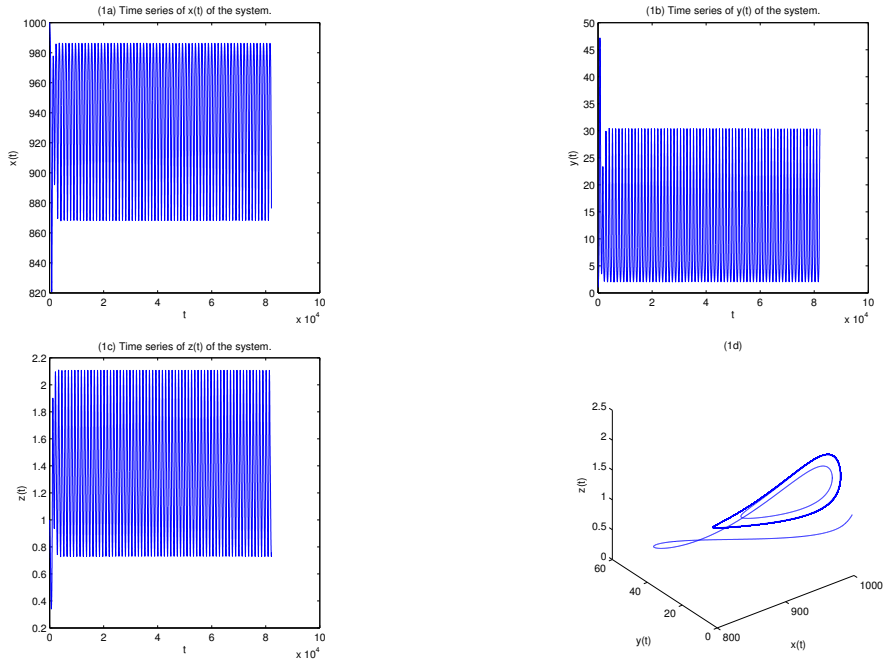

Figure 5: $R_0 = 1.25 > 1$, $R_1 = 1.1880734 > 1$, $a_1 = 0.320144 > 0, a_2 = 0.0393182 > 0$, $a_3 = -0.00434 < 0$, $\tau_0 = 1.30270806$, $\tau = 2 > \tau_0$, the infected equilibrium $E_2(950.45872, 9, 1.504587)$ is unstable.

6. Conclusion

In this paper, we have studied a delayed viral infection model with immune impairment and cure rate. There exist three equilibria: infection-free equilibrium $E_0(x_0, 0, 0)$, immune-exhausted equilibrium $E_1(x_1, y_1, 0)$, and the positive equilibrium $E_2(x_2, y_2, z_2)$. By analyzing the model, we obtained the basic reproduction number $\Re_0$ and the immune response basic reproduction number $\Re_1$. By analyzing the char-

acteristic equations, the local stability of all equilibria of the model are investigated. By choosing delays as parameters, we obtain the local stability and existence of Hopf bifurcation of the endemic equilibrium. At the same time, some Hopf bifurcation values are also obtained, that is, the system can produce stable periodic solutions under some conditions, which has very significative sense in biology. This shows that the system has richer dynamic behavior with the change of τ.

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