Global stability and Hopf bifurcation of an HIV-1 infection model with saturation incidence and delayed CTL immune response

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**Abstract**

In this paper, an HIV-1 infection model with saturation incidence and time delay due to the CTL immune response is investigated. By analyzing corresponding characteristic equations, the local stability of each of feasible equilibria and the existence of Hopf bifurcation at the CTL-activated infection equilibrium are established, respectively. By means of Lyapunov functionals and LaSalle's invariance principle, it is shown that the infection-free equilibrium is globally asymptotically stable when the basic reproduction ratio is less than unity. When the immune response reproductive ratio is less than unity and the basic reproductive ratio is greater than unity, the CTL-inactivated infection equilibrium of the system is globally asymptotically stable.

1. Introduction

Mathematical modelling combined with experimental measurements has yielded important insights into HIV-1 pathogenesis and has enhanced progress in the understanding of HIV-1 infection and drug therapies. In most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by providing a cell-mediated response to specific foreign antigens associated with cells. For HIV-1 infection, the main clinical indicators of that HIV-1 positive patient are in the follow up both the viral load and the CD4+ T cells count in blood plasma, therapy is started, make a portion to the immune cells to be toxic thereby introducing toxicity in the immune system of the individual [11]. Therefore, the immune response after viral infection is universal and necessary to eliminate or control the disease.

Recently, great attention has been paid to mathematical modelling of virus infection with immune response (see, for example, [1,7,12,14,15,17]). Cao et al. [3] have shown that CTL immune responses are often associated with better virus control and slower disease progression during the early stage of HIV infection. Considering the effect of the population dynamics of viral infection with CTL immune response, Nowak and Bangham [8] investigated the following HIV-1 infection model:

*[This work was supported by the National Natural Science Foundation of China (Nos. 11371368, 11071254), the Natural Science Foundation of Hebei Province of China under Grant (No. A2014506015) and the Natural Science Foundation for Young Scientists of Hebei Province, China (No. A2013506012) and the Science Research Foundation of Shijiazhuang Mechanical Engineering College, China (No. YJXM12010).]

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http://dx.doi.org/10.1016/j.amc.2014.03.091

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\[ \begin{aligned}
  x(t) &= \dot{x} - dx(t) - \beta x(t)v(t), \\
  y(t) &= \beta x(t)v(t) - ay(t) - py(t)z(t), \\
  v(t) &= ky(t) - u v(t), \\
  z(t) &= cy(t)(z(t) - bz(t)),
\end{aligned} \]

where \( x(t), \ y(t), \ v(t), \) and \( z(t) \) represent the densities of uninfected target cells, infected cells, virions, and CTL cells at time \( t \), respectively. Uninfected cells are produced at a rate \( \lambda \), die at rate \( dx \), and become infected cells at rate \( \beta x v \). Infected cells are produced at rate \( \beta x \), die at rate \( ay \) and are removed at rate \( pyz \) by the CTL immune response. Free viruses are produced from infected cells at rate \( ky \) and are removed at rate \( uv \). The virus-specific CTL cells proliferate at rate \( cyz \) by contact with infected cells, and die at rate \( bz \).

We note that in model (1.1), time delay for immune response is ignored. In reality, as argued by Canabarro et al. [2] and Wang et al. [15], antigenic stimulation generating CTLs may need a period of time \( \tau \), i.e., the CTL response at time \( t \) may depend on the population of antigen at a previous time \( t - \tau \). In [2], Canabarro et al. considered a non-linear model of the cellular immune response that includes a time-delay in the initiation of CTL cells production. Meanwhile, the time evolution of the population of CTL cells \( z \) is governed by the following delayed non-linear differential equation:

\[ \dot{z}(t) = cy(t - \tau)(z(t) - \tau) - bz(t), \]

where the parameter \( \tau \) is the time delay of CTL response. By numerical simulations, Canabarro et al. observed the emergence of oscillatory and chaotic behavior.

Furthermore, it is assumed in model (1.1) that the infection process follows the principle of mass action [9], namely, the infection rate per host and per virus is a constant. However, experiments reported in [4] have shown that the infection rate of microparasitic infections is an increasing function of the parasite dose, and is usually sigmoidal in shape. In [10], Regoes et al. replaced the mass-action infection rate with a dose-dependent infection rates. In [13], Song and Neumann suggested a more general saturated infection rate \( \beta x v^p/(1 + \alpha v^q) \), where \( p, q \) and \( \alpha \) are positive constants.

Motivated by the works of Canabarro et al. [2] and Song and Neumann [13], in this paper, we are concerned with the combined effects of saturation incidence, CTL immune response and time delay due to the CTL immune response on the global dynamics of HIV-1 infection. To this end, we consider the following delay differential equations

\[ \begin{aligned}
  \dot{x}(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)}, \\
  \dot{y}(t) &= \frac{\beta x(t)v(t)}{1 + \alpha v(t)} - ay(t) - py(t)z(t), \\
  \dot{v}(t) &= ky(t) - u v(t), \\
  \dot{z}(t) &= cy(t - \tau)(z(t) - \tau) - bz(t).
\end{aligned} \]

The initial conditions for system (1.2) take the form

\[ \begin{aligned}
  x(\theta) &= \phi_1(\theta), & y(\theta) &= \phi_2(\theta), & v(\theta) &= \phi_3(\theta), & z(\theta) &= \phi_4(\theta), \\
  \phi_i(\theta) &\geq 0, & \theta &\in [-\tau, 0], & \phi_i(0) &> 0 & (i = 1, 2, 3, 4),
\end{aligned} \]

where \( \phi_i(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta) \in C([-\tau, 0], \mathbb{R}^+_{\theta}), \) here \( \mathbb{R}^+_{\theta} = \{x_1, x_2, x_3, x_4 : x_i \geq 0, i = 1, 2, 3, 4\} \).

It is easy to show that all solutions of system (1.2) with initial condition (1.3) are defined on \([0, +\infty)\) and remain positive for all \( t \geq 0 \).

The organization of this paper is as follows. In the next section, by analyzing the corresponding characteristic equations, we study the local stability of each of feasible equilibria of system (1.2). In Section 3, by using suitable Lyapunov functionals and LaSalle's invariance principle, we establish sufficient conditions for the global stability of infection-free equilibrium and CTL-inactivated infection equilibrium of system (1.2), respectively. In Section 4, we carry out a numerical example to illustrate the main theoretical results. Finally, a brief remark is given in Section 5 to conclude this work.

2. Local stability and Hopf bifurcation

In this section, we study the local stability of each of feasible equilibria of system (1.2) by analyzing the corresponding characteristic equations, respectively.

System (1.2) always has an infection-free equilibrium \( E_0(\lambda/d, 0, 0, 0) \). Denote

\[ \mathcal{R}_0 = \frac{\beta k}{ad}, \quad \mathcal{R}_1 = \frac{ck\beta}{a(du + bk(d^2 + \beta))}. \]

Here, \( \mathcal{R}_0 \) is called the basic reproduction ratio of model (1.2) which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process, and \( \mathcal{R}_1 \) is called the immune response reproduction ratio which expresses the CTL load during the lifespan of a CTL cell.
It is easy to show that if $R_0 > 1$, system (1.2) has a CTL-inactivated infection equilibrium $E_1(x_1, y_1, v_1, 0)$, where
\[ x_1 = \frac{au}{bk}(1 + x v_1), \quad y_1 = \frac{b}{k} v_1, \quad v_1 = \frac{-jk - adu}{au(xd + \beta)}.
\]
Further, if $R_1 > 1$, system (1.2) has a unique CTL-activated infection equilibrium $E^* (x^*, y^*, v^*, z^*)$, where
\[ x^* = \frac{u(cu + bk\alpha)}{cdu + bk(xd + \beta)}, \quad y^* = \frac{b}{c}, \quad v^* = \frac{bk}{cu}, \quad z^* = \frac{a}{p}(R_1 - 1).
\]

Theorem 2.1. For system (1.2), we have

(i) If $R_0 < 1$, the infection-free equilibrium $E_0(\lambda/d, 0, 0, 0)$ is locally asymptotically stable and is unstable if $R_0 > 1$.

(ii) If $R_1 < 1 < R_0$, the CTL-inactivated infection equilibrium $E_1(x_1, y_1, v_1, 0)$ is locally asymptotically stable and is unstable if $R_1 > 1$.

Proof. The characteristic equation of system (1.2) at the infection-free equilibrium $E_0$ is of the form
\[(s + b)(s + d)^2 + (a + u)s + au(1 - R_0)] = 0. \tag{2.1}\]
Clearly, Eq. (2.1) always have two negative real roots $s_1 = -b, s_2 = -d$. If $R_0 < 1$, it is easy to show that roots of $s^2 + (a + u)s + au(1 - R_0) = 0$ have only negative real parts. Accordingly, the equilibrium $E_0$ of system (1.2) is locally asymptotically stable. If $R_0 > 1$, Eq. (2.1) has at least one positive real root. Therefore, $E_0$ is unstable.

The characteristic equation of system (1.2) at the CTL-inactivated infection equilibrium $E_1$ takes the form
\[(s + b - cy_1e^{-st})(s^3 + g_2s^2 + g_1s + g_0) = 0, \tag{2.2}\]
where
\[g_0 = \frac{auv_1}{1 + x v_1}(xd + \beta), \quad g_1 = (a + u)\left(\frac{d + \beta v_1}{1 + x v_1}\right) + \frac{au x v_1}{1 + x v_1}, \quad g_2 = a + d + u + \frac{\beta v_1}{1 + x v_1}.
\]
Obviously, the equation $s^3 + g_2s^2 + g_1s + g_0 = 0$ always have three negative real roots. Let $s + b - cy_1e^{-st} = 0$. If $R_1 > 1$, it is easy to show that, for $s$ real,
\[f(s) = (b + \frac{cd u}{k(xd + \beta)})(1 - R_1) < 0, \quad \lim_{s \to \infty} f(s) = +\infty.
\]
Hence, $f(s) = 0$ has at least one positive real root. Therefore, $E_1$ is unstable. If $R_1 < 1$, we now claim that roots of $f(s) = 0$ have only negative real parts. Suppose that $\text{Re}(s) \geq 0$. It then follows from Eq. (2.2) that
\[\text{Re}(s) \geq \left[\frac{cjk - adu}{abk(xd + \beta)}e^{-s}\cos(\text{Re}(s)) - 1\right] \leq \frac{cd u + bk(xd + \beta)}{k(xd + \beta)}(R_1 - 1) < 0,
\]
which leads to a contradiction. Thus, we have $\text{Re}(s) < 0$. Hence, if $R_1 < 1 < R_0$, the equilibrium $E_1$ is locally asymptotically stable. \(\square\)

We now study the local stability of the CTL-activated infection equilibrium $E^*$ of system (1.2).

The characteristic equation of system (1.2) at the CTL-activated infection equilibrium $E^*$ takes the form
\[s^4 + p_3s^3 + p_2s^2 + p_1s + p_0 + (q_1s^3 + q_2s^2 + q_1s + q_0)e^{-st} = 0. \tag{2.3}\]
where
\[p_0 = b(a + px^*u)(d + \frac{\beta v}{1 + xv^*}) - bd\frac{kpx}{(1 + xv^*)^2},
\]
\[p_1 = b(a + px^*u) + b(a + px^*u + b(a + px^* + u)(d + \frac{\beta v}{1 + xv^*}) - (b + d)\frac{kpx}{(1 + xv^*)^2},
\]
\[p_2 = (a + px^*)u + b(a + px^* + u)(a + b + px^* + u)(d + \frac{\beta v}{1 + xv^*}) - \frac{kpx}{(1 + xv^*)^2},
\]
\[p_3 = a + b + px^* + u + d + \frac{\beta v}{1 + xv^*},
\]
\[q_0 = bd\frac{kpx}{(1 + xv^*)^2} - abu(d + \frac{\beta v}{1 + xv^*}),
\]
\[q_1 = \frac{kpx}{(1 + xv^*)^2} - abu(b(a + u)(d + \frac{\beta v}{1 + xv^*}),
\]
\[q_2 = -b(a + u + d + \frac{\beta v}{1 + xv^*}), \quad q_3 = -b.
\]
When \( \tau = 0 \), Eq. (2.3) reduces to
\[
s^4 + (p_3 + q_3)s^3 + (p_2 + q_2)s^2 + (p_1 + q_1)s + p_0 + q_0 = 0. \tag{2.4}
\]
Denote
\[
\begin{align*}
\Delta_1 &= p_3 + q_3, \\
\Delta_2 &= (p_3 + q_3)(p_2 + q_2) - (p_1 + q_1), \\
\Delta_3 &= (p_1 + q_1)(p_2 + q_2)(p_3 + q_3) - (p_0 + q_0)(p_1 + q_1)^2 - (p_1 + q_1)^2.
\end{align*}
\]
A direct calculation shows that
\[
\begin{align*}
\Delta_1 &= a + \frac{bpz^* + a + bpz}{1 + bvp^*} \left[ d + u + \frac{bvp}{1 + bvp} \right], \\
\Delta_2 &= \left[ a + \frac{bpz^* + a + bpz}{1 + bvp^*} \left[ d + u + \frac{bvp}{1 + bvp} \right] \right] + \left( d + u + \frac{bvp}{1 + bvp} \right) \left[ a + \frac{bpz^* + a + bpz}{1 + bvp} \right] > 0.
\end{align*}
\]
\[
\Delta_3 = bpz^* \left[ a + \frac{bpz^*}{1 + bvp^*} \right] \left[ d + u + \frac{bvp}{1 + bvp} \right] + bpz \left[ d + u + \frac{bvp}{1 + bvp} \right] \left[ a + \frac{bpz^* + a + bpz}{1 + bvp} \right] + \left[ a + \frac{bpz^*}{1 + bvp^*} \right] \left[ d + u + \frac{bvp}{1 + bvp} \right] + \left[ a + \frac{bpz^* + a + bpz}{1 + bvp} \right] > 0.
\]

Hence, by Routh-Hurwitz criterion, when \( \tau = 0 \), we see that the equilibrium \( E^* \) is locally asymptotically stable if \( \Delta_1 > 0 \); and \( E^* \) is unstable if \( \Delta_1 < 0 \).

Substituting \( \lambda = i\omega (\omega > 0) \) into Eq. (2.3) and separating the real and imaginary parts, one obtains that
\[
\begin{align*}
\omega^6 &= -p_2\omega^2 + p_0 = (q_3\omega^3 - q_1\omega) \sin \omega \tau + (q_2\omega^2 - q_0) \cos \omega \tau, \\
-\omega^2 &= p_1\omega^4 + p_0\omega = (q_3\omega^3 - q_1\omega) \cos \omega \tau - (q_2\omega^2 - q_0) \sin \omega \tau. \tag{2.5}
\end{align*}
\]
Squaring and adding the two equations of (2.5), it follows that
\[
\omega^6 + h_3\omega^6 + h_2\omega^4 + h_1\omega^2 + h_0 = 0, \tag{2.6}
\]
where
\[
\begin{align*}
h_0 &= p_0^2 - q_0^2, & h_1 &= p_1^2 - q_1^2 + 2q_0q_2 - 2p_0p_2, \\
h_2 &= p_2^2 + q_2^2 + 2p_0 + 2q_1q_3 - 2p_1p_3, & h_3 &= p_3^2 + q_3^2 - 2p_2.
\end{align*}
\tag{2.7}
\]
Letting \( z = \omega^2 \), Eq. (2.6) can be written as
\[
h(z) := z^4 + h_3z^3 + h_2z^2 + h_1z + h_0 = 0. \tag{2.8}
\]
Denote
\[
P = \frac{8h_2 - 3h_3^2}{16}, \quad Q = \frac{h_3^3 - 4h_2h_3 + 8h_1}{32}, \quad D_0 = \frac{Q^2 + P^3}{4}.
\]
and define
\[
\begin{align*}
\delta &= \frac{h_3}{4} + \sqrt{-\frac{3}{4} + \sqrt{D_0}} + \sqrt{-\frac{3}{4} - \sqrt{D_0}}, & \text{if } D_0 > 0, \\
\delta^* &= \max \left\{ -\frac{h_3}{4} - 2\sqrt{\frac{3}{4} - \frac{h_3}{8}} - \sqrt{-\frac{3}{4} - \sqrt{D_0}} \right\}, & \text{if } D_0 = 0, \\
\delta^* &= \max \left\{ -\frac{h_3}{4} + 2 \text{Re} (\delta), -\frac{h_3}{4} + 2 \text{Re} (\delta^*) \right\}, & \text{if } D_0 = 0.
\end{align*}
\]
where \( \delta \) is one of cube roots of the complex number \( -Q/2 + \sqrt{D_0} \), and \( \delta = -1/2 + (\sqrt{3}/2)i \).

By a similar argument as that in [16], we have the following result.
Lemma 2.1 [16]. For the polynomial Eq. (2.8), the following results hold true:

(i) If \( h_0 < 0 \), then Eq. (2.8) has at least one positive root.
(ii) If \( h_0 > 0 \), then Eq. (2.8) has no positive root if one of the following conditions holds:
   (1) \( D_0 > 0 \) and \( z_1 < 0 \);
   (2) \( D_0 = 0 \) and \( z_1 < 0 \);
   (3) \( D_0 < 0 \) and \( z_1 < 0 \).
(iii) If \( h_0 > 0 \), then Eq. (2.8) has at least one positive root if one of the following conditions holds:
   (1) \( D_0 > 0 \), \( z_1 > 0 \) and \( h(z_1) < 0 \);
   (2) \( D_0 = 0 \), \( z_1 > 0 \) and \( h(z_1) < 0 \);
   (3) \( D_0 < 0 \), \( z_1 > 0 \) and \( h(z_1) < 0 \).

Noting that
\[
\tau = (a + pz^2)^2 + u^2 + \left( d + \frac{\beta vy}{1 + 2\nu}\right)^2 + \frac{2k\beta x^2}{(1 + 2\nu)^2} > 0,
\]
without loss of generality, we may assume that Eq. (2.8) has three positive roots denoted respectively as \( z_1, z_2 \) and \( z_3 \). Then Eq. (2.7) has three positive roots \( \omega_k = \sqrt{\tau_k} \) (\( k = 1, 2, 3 \)). From (2.5), we have
\[
\tau_k^{(0)} = \frac{1}{\omega_k} \text{arcsin} \left[ \frac{(\omega_k^4 - p_2 \omega_k^2 + p_0)(q_3 \omega_k^2 - q_1 \omega_k) + (p_3 \omega_k^2 - p_1 \omega_k)(q_2 \omega_k^2 - q_0)}{(q_3 \omega_k^2 - q_1 \omega_k)^2 + (q_2 \omega_k^2 - q_0)^2} + 2\tau \right],
\]
where \( k = 1, 2, 3; \ j = 0, 1, \ldots \). Then \( \pm \omega_k \) is a pair of purely imaginary roots of Eq. (2.3) with \( \tau = \tau_k^{(0)} \). Define
\[
\tau_0 = \tau_k^{(0)} = \min_{k=1,2,3} \left\{ \tau_k^{(0)} \right\}, \quad \omega_0 = \omega_{k_0}.
\]
Let \( s(t) = \xi(t) + i\alpha(t) \) be a root of Eq. (2.3) satisfying \( \xi(t) = 0, \alpha(t) = \omega_0 \).

Differentiating the two sides of Eq. (2.3) with respect to \( t \), it follows that
\[
\frac{d\xi}{dt} = -\frac{4s^3 + 3ps^2 + 2ps + p_1}{s(s^2 + sp^2 + ps^2 + p_0)} + \frac{3q_3s^2 + 2qq_1s + q_0}{s(q_3s^2 + q_2s^2 + q_1s + q_0)} \frac{\tau}{s}.
\]

A direct calculation shows that
\[
\text{sign} \left( \frac{d(\text{Re}s)}{dt} \right)_{t=\tau_0} = \text{sign} \left( \text{Re} \left( \frac{d\xi}{dt} \right)^{-1} \right)_{t=\tau_0} = \text{sign} \left[ \frac{4p_0^2 + 3(p_2 - 2p_1) \omega_0^2 + 2(p_3 + 2p_0 - 2p_1) \omega_0^2 + 2p_0 p_2}{(p_3 \omega_0^2 - p_1)^2 \omega_0^2 + (p_2 \omega_0^2 + p_0)^2} + \frac{-3q_3 \omega_0^2 + 2(q_1 q_3 - q_1^2) \omega_0^2 + 2q_0 q_0 - q_1^2}{(q_3 \omega_0^2 - q_1)^2 \omega_0^2 + (q_0 - q_2 \omega_0^2)^2} \right].
\]

From Eq. (2.6), we get
\[
(p_3 \omega_0^2 - p_1) \omega_0^2 + (\omega_0^2 - p_2 \omega_0^2 + p_0)^2 = (q_3 \omega_0^2 - q_1)^2 \omega_0^2 + (q_0 - q_2 \omega_0^2)^2.
\]
It therefore follows that
\[
\text{sign} \left( \frac{d(\text{Re}s)}{dt} \right)_{t=\tau_0} = \text{sign} \left[ \frac{\hat{h}(z_k)}{(q_3 \omega_0^2 - q_1)^2 \omega_0^2 + (q_0 - q_2 \omega_0^2)^2} \right].
\]
Since \( z_k > 0 \), we conclude that \( \text{Re} \left[ d\xi(t)dt \right]_{t=\tau_0} \) and \( \hat{h}(z_k) \) have the same sign.

Noting that when \( \tau = 0 \), the CTL-activated infection equilibrium \( E^* \) of system (1.2) is locally asymptotically stable if \( \tau > 1 \), from what has been discussed above, we have the following results.

Theorem 2.2. Let \( \tau_k^{(0)} \) and \( \omega_0 \) be defined by (2.9) and (2.10), respectively. If \( \tau > 1 \).

(i) the CTL-activated infection equilibrium \( E^* \) of system (1.2) is locally asymptotically stable for all \( \tau \geq 0 \) if \( h_0 \geq 0 \) and one of the following conditions is satisfied:
   (1) \( D_0 > 0 \) and \( z_1 < 0 \);
   (2) \( D_0 = 0 \) and \( z_1 < 0 \);
   (3) \( D_0 < 0 \) and \( z_1 < 0 \).
(ii) the CTL-activated infection equilibrium \( E^* \) is asymptotically stable for \( \tau \in (0, \tau_0) \) if \( h_0 < 0 \) or \( h_0 \geq 0 \) and one of the following conditions holds:
(1) $D_0 > 0$, $z_i^* > 0$ and $h(z_i^*) < 0$;
(2) $D_0 = 0$, $z_i^* > 0$ and $h(z_i^*) < 0$;
(3) $D_0 < 0$, $z_i^* > 0$ and $h(z_i^*) < 0$.

(iii) system (1.2) undergoes a Hopf bifurcation at CTL-activated infection equilibrium $E^*$ when $\tau = \tau_k^0$ ($j = 0, 1, 2, \ldots$) if the conditions as stated in (ii) are satisfied and $h'(z_k) \neq 0$.

3. Global stability

In this section, we are concerned with the global stability of infection-free equilibrium $E_0$ and the CTL-inactivated infection equilibrium $E_1$ of system (1.2), respectively. The strategy of proofs is to use suitable Lyapunov functionals and LaSalle’s invariance principle.

**Theorem 3.1.** If $\mathcal{R}_0 < 1$, then the infection-free equilibrium $E_0(\lambda/d, 0, 0, 0)$ of system (1.2) is globally asymptotically stable.

**Proof.** Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.2) with initial conditions (1.3). Denote $x_0 = \lambda/d$.

Define
\[
V_1(t) = x - x_0 - x_0 \ln \frac{x}{x_0} + y + \frac{a}{k} v + \frac{p}{c} z + p \int_{t-\tau}^{t} y(\theta) z(\theta) d\theta.
\]
(3.1)

Calculating the derivative of $V_1(t)$ along positive solutions of system (1.2), it follows that
\[
\frac{d}{dt} V_1(t) = \left(1 - \frac{x_0}{x}ight) \left[ -d(x-x_0) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \frac{\beta x(t)v(t)}{1+\alpha v(t)} - \frac{a}{k} v(t) - \left(1 - \mathcal{R}_0\right)v(t) - \frac{bp}{c} z(t) \right]
\]
(3.2)

On substituting $\lambda = \alpha x_0$ into (3.2), we obtain that
\[
\frac{d}{dt} V_1(t) = \left(1 - \frac{x_0}{x}\right) \left[ -d(x-x_0) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \frac{\beta x(t)v(t)}{1+\alpha v(t)} - \frac{a}{k} v(t) - \frac{bp}{c} z(t) \right]
\]
(3.3)

It follows from (3.3) that $V'_1(t) < 0$. By Theorem 5.3.1 in [6], solutions limit to $\mathcal{M}_t$, the largest invariant subset of $\{V'_1(t) = 0\}$.

Clearly, we obtain from (3.3) that $V'_1(t) = 0$ if and only if $x = x_0$, $v = 0$, and $z = 0$. Noting that $\mathcal{M}_t$ is invariant, for each element in $\mathcal{M}_t$, we have $v = 0$, $v' = 0$. It therefore follows from the third equation of system (1.2) that
\[
0 = v'(t) = ky(t),
\]
which yields $y = 0$. Hence, $V'_1(t) = 0$ if and only if $(x, y, v, z) = (x_0, 0, 0, 0)$. Accordingly, the global asymptotic stability of $E_0$ follows from LaSalle’s invariance principle for delay differential equations (see, for example, Haddock and Terjéki [5]). □

**Theorem 3.2.** If $\mathcal{R}_1 < 1 < \mathcal{R}_0$, the CTL-inactivated infection equilibrium $E_1(x_1, y_1, v_1, 0)$ of system (1.2) is globally asymptotically stable.

**Proof.** Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.2) with initial conditions (1.3).

Define
\[
V_2(t) = x(t) - x_1 - x_1 \ln \frac{x(t)}{x_1} + y(t) - y_1 - y_1 \ln \frac{y(t)}{y_1} + \frac{a}{k} \left(\frac{v(t) - v_1}{v_1} - \frac{v(t)}{v_1} \ln \frac{v(t)}{v_1}\right) + \frac{p}{c} z(t) + p \int_{t-\tau}^{t} y(\theta) z(\theta) d\theta.
\]
(3.4)

Calculating the derivative of $V_2(t)$ along positive solutions of system (1.2), we derive that
\[
\frac{d}{dt} V_2(t) = \left(1 - \frac{x_1}{x(t)}\right) \left[ -d(x-x_1) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \left(1 - \frac{y_1}{y(t)}\right) \left(\frac{\beta x(t)v(t)}{1+\alpha v(t)} - ay(t) - py(t)z(t)\right) \right]
\]
\[
+ \frac{a}{k} \left(1 - \frac{v_1}{v(t)}\right) [ky(t) - u v(t)] - \frac{bp}{c} z(t) + py(t)z(t) = \left(1 - \frac{x_1}{x(t)}\right) \left[ -d(x-x_1) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \frac{\beta x_1 v_1}{1+\alpha v_1} \right]
\]
\[
+ \left(1 - \frac{y_1}{y(t)}\right) \left[\frac{\beta x(t)v(t)}{1+\alpha v(t)} - ay(t) - py(t)z(t)\right] - \frac{a}{k} v(t) - \frac{y_1}{v_1} v(t) - \frac{bp}{c} z(t).
\]
(3.5)

Noting that $\beta x_1 v_1/(1+\alpha v_1) = ay_1 = au v_1/k$, it follows from (3.5) that
\[
\frac{d}{dt} V_2(t) = -\frac{d}{x(t)} (x(t) - x_1)^2 - p \left( \frac{b}{c} - y_1 \right) z(t) + \frac{\beta x_1 y_1}{1 + x_1 v_1} + \frac{\beta x_1 y_1}{1 + x_1 v_1} - \frac{x_1}{1 + x_1 v_1} - \frac{\beta x_1 y_1}{1 + x_1 v_1} \frac{y_1(t)}{y_1(t)}
\]

We therefore derive from (3.5) that
\[
\frac{d}{dt} V_2(t) = -\frac{d}{x(t)} (x(t) - x_1)^2 - \frac{x_1}{1 + x_1 v_1} y_1(t) \left( \frac{x(t)}{y_1(t)} \right) - \frac{x_1}{1 + x_1 v_1} \frac{y_1(t)}{y_1(t)} - \frac{1 + x_1 v_1}{1 + x_1 v_1} \leq 0.
\]

Since the arithmetic mean is greater than or equal to the geometric mean, it is clear that
\[
4 - \frac{x_1}{x(t)} - \frac{y_1}{x(t)} \left( \frac{x(t)}{y(t)} \right) + \frac{x_1}{1 + x_1 v_1} \frac{y_1(t)}{y_1(t)} - \frac{1 + x_1 v_1}{1 + x_1 v_1} \leq 0,
\]
and the equality holds only for \(x = x_1, y = y_1, v = v_1\). Hence, if \(\mathcal{R}_1 < 1 < \mathcal{R}_0\), we have that \(V_2(t) \leq 0\). By Theorem 5.3.1 in [6], solutions limit to \(\mathcal{M}\), the largest invariant subset of \(\{V_2(t) = 0\}\). Clearly, it follows from (3.6) that \(V_2(t) = 0\) if and only if \((x, y, v, z) = (x_1, y_1, v_1, 0)\). Note that if \(\mathcal{R}_1 < 1 < \mathcal{R}_0\), \(E_1\) is locally asymptotically stable. Using a similar argument as that in the proof of Theorem 3.1 and LaSalle’s invariance principle, the global asymptotic stability of \(E_1\) follows. 

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**Fig. 1.** The temporal solution found by numerical integration of system (1.2) with \(a = 2, b = 0.3, c = 0.2, d = 0.01, k = 25, p = 0.05, u = 10, x = 0.01, \beta = 0.002, \lambda = 1000, (\phi_1, \phi_2, \phi_3, \phi_4) = (1000, 5.5, 100)\). When \(\tau = 0.2 < \tau_0 = 0.2321\), the CTL-activated infection equilibrium \(E^*\) of system (1.2) is stable.
4. Numerical simulations

In this section, we give a numerical example to illustrate the main results in Section 2.

Example 1. In system (1.2), let $a = 2.3, b = 0.3, c = 0.2, d = 0.01, k = 25, p = 0.05, u = 10, \alpha = 0.01, \beta = 0.002, \lambda = 1000$. It is easy to show that $R_1 \approx 139.8601 > 1$ and $h_0 = -23.1880 < 0$. $z_1 = 1.5776$. $h'(z_1) \neq 0$. In this case, system (1.2) has a CTL-activated infection equilibrium $E^*$ of system (1.2) that loss its stability and a Hopf bifurcation occurs.

5. Conclusions

In this paper, we have investigated the global stability and Hopf bifurcation of an HIV-1 infection model with CTL immune response and time delay representing the effective delay between the antigenic stimulation and the immune system actually producing new CTL cells. By using suitable Lyapunov functionals and LaSalle’s invariance principle, we studied the global asymptotic stability of infection-free equilibrium and CTL-inactivated infection equilibrium of system (1.2). By Theorem 3.1, we see that if the basic reproductive ratio $R_0$ is less than unity, the infection-free equilibrium $E_0$ is globally asymptotically stable. In this case, the virus is finally cleared up. By Theorem 3.2, we know that if the immune response reproductive ratio $R_1$ satisfies $R_1 < 1 < R_0$, the CTL-inactivated infection equilibrium $E_1$ is globally asymptotically stable. In this case, the
infection becomes chronic but without CTL immune response. We would like to mention it is interesting to study here that if \( R_1 > 1 \), whether the equilibrium \( E^- \) is globally asymptotically stable when it is locally stable. We leave this for our future work.

References