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Dynamics analysis of an HIV infection model with latent reservoir, delayed CTL immune response and immune impairment*

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Abstract. In this paper, we propose an HIV model with latent reservoir, delayed CTL immune response and immune impairment in which both virus-to-cell infection and cell-to-cell viral transmission are considered. By using Lyapunov functionals and LaSalle's invariance principle, it is verified that when time delay is equal to zero, the global threshold dynamics of the model is determined by the basic reproduction ratio. With the help of uniform persistence theory for infinite dimensional systems, we obtain the uniform persistence when the basic reproduction ratio is greater than unity. By choosing time delay τ as a bifurcation parameter and analyzing the corresponding characteristic equation of the system, we establish the existence of Hopf bifurcation at the chronic-infection equilibrium. Numerical simulations are carried out to illustrate the corresponding theoretical results.

Keywords: latent reservoir, cell-to-cell transmission, delayed CTL immune response, immune impairment, stability, Hopf bifurcation.

1 Introduction

The human immunodeficiency virus (HIV) is a lentivirus that causes HIV infection and over time acquired immunodeficiency syndrome (AIDS) [16]. Because of destructiveness and complexity, researchers have been trying to find a way to cure HIV since it was discovered in 1981. Combination antiretroviral therapy (ART) or highly active antiretroviral therapy (HAART) [5] have led to significantly reduced the incidence of HIV related morbidity and mortality. Although the current therapy can reduce plasma virus to undetectable, residual low-level viremia can be detected in most patients using ultrasensitive assays [15]. That is because latently infected cells persist during treatment and release infectious virus when activated by relevant antigens [12].

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To study the effect of latently infected cells on HIV infection dynamics, Rong et al. [18] proposed a mathematical model including uninfected cells $x(t)$, latently infected cells $u(t)$, actively infected cells $y(t)$ and free virus $v(t)$ to describe the effect of latently infected cells on HIV infection dynamics:

$$\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - dx(t) - (1-\epsilon)\beta x(t)v(t),\\
\frac{\mathrm{d}u(t)}{\mathrm{d}t} &= \alpha(1-\epsilon)\beta x(t)v(t) - (\mu+\delta)u(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= (1-\alpha)\beta x(t)v(t) + \delta u(t) - ay(t),\\
\frac{\mathrm{d}v(t)}{\mathrm{d}t} &= Nay(t) - \sigma v(t),
\end{aligned} \tag{1}$$

where uninfected cells are produced at rate λ and die at rate d; β is the infection rate of virus-to-cell infection, α is the fraction of infections that result in latency and ϵ is the efficacy of reverse transcriptase (RT) inhibitors. δ is the rate at which latently infected cells become activated, and μ is the death rate of latently infected cells. a and σ are the death rate of actively infected cells and free virus, respectively. N is the number of virus produced by an infected cells during its life time. All parameters are positive, and $0 < \epsilon < 1$.

It is noted that model (1) includes virus-to-cell infection only. However, cell-to-cell transmission formed by virological synapses has great influence on virus infection, which might be $100-1000$ times faster than cell-free virus spread [14]. Moreover, virus can persist in the presence of antiretroviral therapy that is because cell-to-cell viral transmission permits the transfer of HIV without exposing the virus to extracellular environment [20]. Accordingly, some mathematical analysis of virus model with cell-to-cell viral transmission has been performed. For example, Lai and Zou [11] studied the global dynamics of HIV infection model, which incorporated both virus-to-cell and cell-to-cell viral transmissions.

As is shown in [25], antigen-specific immune response after viral infection is universal and necessary to kill pathogens and infected cells. Faced with HIV infection, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking infected cells, which are the main host immune factor that determines viral load. Furthermore, time delays cannot be ignored in models for immune response [3]. That is because the generation of new CTLs stimulated by antigen needs a period of time τ and it depends on the number of infected cells at time $t-\tau$ [4]. In [22], Wang et al. studied the effects of time delay for immune response on the dynamic of model with

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = cy(t-\tau) - bz(t).$$

However, several studies found that dendritic cells (DCs) are susceptible to HIV infection in vitro, and the modulation of DCs by HIV infection plays a key role in viral pathogenesis [7]. During the course of HIV infection, the number and function of DCs are gradually lost, which engenders some impairment effects for CTL inducement [17]. That

Table 1. The descriptions of parameters in system (2).

Parameters	Biological meaning
λ	The rate of production of uninfected cells
d	The nature death rate of uninfected cells
β_1	The rate of infection by virus-to-cell
β_2	The rate of transmission by cell-to-cell
f	The fraction of infections leading to latency
η	The fraction of infections leading to latency
μ	The death rate of latently infected cells
δ	The rate at which latently infected cells translate to actively infected cells
a	The death rate of actively infected cells
p	The remove rate of actively infected cells due to CTL immune responses
N	The number of virus produced by an infected cells during its life time
σ	The rate of viral clearance
τ	The time delay of CTL immune response
c	The proliferation rate of CTLs
b	The natural death rate of CTLs
m	The rate of immune impairment

is why virus evades immunity and contributes to the development of AIDS eventually [6]. In [23], Wang et al. incorporated immune impairment into viral model, where the specific expression of CTL cells is as follows:

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = cy(t-\tau) - bz(t) - my(t)z(t).$$

In this paper, motivated by the works of Rong et al. [18], Lai and Zou [11], Wang et al. [22] and Wang et al. [23], we are concerned with the effects of latent reservoir, both virus-to-cell and cell-to-cell transmissions, delayed CTL immune response and immune impairment on the dynamics of HIV infection. To this end, we consider the following delayed differential system:

$$\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - dx(t) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t),\\
\frac{\mathrm{d}u(t)}{\mathrm{d}t} &= f\beta_1 x(t)v(t) + \eta\beta_2 x(t)y(t) - (\mu+\delta)u(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= (1-f)\beta_1 x(t)v(t) + (1-\eta)\beta_2 x(t)y(t)\\
&\quad + \delta u(t) - ay(t) - py(t)z(t),\\
\frac{\mathrm{d}v(t)}{\mathrm{d}t} &= Nay(t) - \sigma v(t),\\
\frac{\mathrm{d}z(t)}{\mathrm{d}t} &= cy(t-\tau) - bz(t) - my(t)z(t),
\end{aligned} \tag{2}$$

where $x(t), u(t), y(t), v(t), z(t)$ represent the concentrations of uninfected cells, latently infected cells, actively infected cells, free virus and CTL immune cells at time t, respectively, and other parameters are described in Table 1.

The initial condition for system (2) takes the form

$$\begin{aligned} &x(\theta) = \phi_1(\theta), \qquad u(\theta) = \phi_2(\theta), \\ &y(\theta) = \phi_3(\theta), \qquad v(\theta) = \phi_4(\theta), \qquad z(\theta) = \phi_5(\theta), \\ &\phi_i(\theta) \geqslant 0, \quad \theta \in [-\tau, 0), \quad \phi_i(0) > 0, \quad i = 1, 2, 3, 4, 5, \end{aligned} \tag{3}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta)) \in \mathbb{R} \times \mathbb{R} \times \mathcal{C} \times \mathbb{R} \times \mathbb{R}$, $\mathcal{C} = C([-\tau, 0), \mathbb{R})$ is the Banach space of continuous real-valued functions on the interval $[-\tau, 0]$ with norm $\|\phi\| = \sup_{-\tau \leqslant \theta \leqslant 0} |\phi(\theta)|$. It is well known by the fundamental theory of functional differential equations [8] that system (2) has a unique solution $(x(t), u(t), y(t), v(t), z(t))$ satisfying the initial condition (3).

This paper is organized as follows. In Section 2, we verify the positivity and boundedness of solutions of system (2) with the initial condition (3). In Section 3, we get the reproduction ratio and establish the existence of feasible equilibria of system (2). In Section 4, we investigate the global asymptotic stability of each of feasible equilibria. In Section 5, we analyze the uniform persistence of system (2) when the basic reproduction ratio is greater than unity. In Section 6, we establish the existence of Hopf bifurcation at the chronic-infection equilibrium. In Section 7, we present numerical simulations to illustrate the theoretical results. Besides, we perform a sensitivity analysis of basic reproduction ratio. A brief conclusion of our paper is given in Section 8.

2 Preliminaries

Theorem 1. *Under initial condition in* (3)*, all solutions of system* (2) *are positive and ultimately bounded in* $\mathbb{R} \times \mathbb{R} \times \mathcal{C} \times \mathbb{R} \times \mathbb{R}$.

Proof. First, we prove that $x(t)$ is positive for all $t \geqslant 0$. Indeed, assuming the contrary, let $t_1 \in [0, +\infty)$ be the first time such that $x(t_1) = 0$. By the first equation of system (2), we have $x'(t_1) = \lambda > 0$, and hence $x(t) < 0$ for all $t \in (t_1 - \epsilon, t_1)$, where ϵ is an arbitrarily small positive constant. This contradicts $x(t) > 0$ for $t \in [0, t_1)$. It follows that $x(t) > 0$ for all $t > 0$.

Similarly, we show that $u(t), y(t), v(t)$ and $z(t)$ are positive for all $t \geqslant 0$. Assume the contrary, and let $t_2 > 0$ be the first time such that $y(t_2) = 0$. From the third equation of system (2) we can know $y'(t_2) = (1 - f)\beta_1 x(t_2) v(t_2) + \delta u(t_2)$. Solving $u(t_2), v(t_2)$ from the second and forth equations of system (2), we obtain that

$$u(t_2) = \left[\phi_2(0) + \int_0^{t_2} \left[f\beta_1 x(t) v(t) + \eta\beta_2 x(t) y(t) \right] \mathrm{e}^{(\mu+\delta)t} \, \mathrm{d}t \right] \mathrm{e}^{-(\mu+\delta)t_2},$$

$$v(t_2) = \left[\phi_4(0) + \int_0^{t_2} Na\, y(t) \mathrm{e}^{\delta t} \, \mathrm{d}t \right] \mathrm{e}^{-\delta t_2}.$$

Thus $y'(t_2) > 0$, it follows that $y(t) > 0$ for all $t \geqslant 0$. Accordingly, from the second, forth and fifth equations of system (2) we have

$$u(t) = \left[\phi_2(0) + \int_0^t \left[f\beta_1 x(s)v(s) + \eta\beta_2 x(s)y(s)\right]\mathrm{e}^{(\mu+\delta)s}\,\mathrm{d}s\right]\mathrm{e}^{-(\mu+\delta)t} > 0,$$

$$v(t) = \left[\phi_4(0) + \int_0^t Nay(s)\mathrm{e}^{\delta s}\,\mathrm{d}s\right]\mathrm{e}^{-\delta t} > 0,$$

$$z(t) = \phi_5(0)\mathrm{e}^{\int_0^t (b+my(s))\,\mathrm{d}s} + c\int_0^t y(s-\tau)\mathrm{e}^{-\int_s^t (b+my(\alpha))\,\mathrm{d}\alpha}\,\mathrm{d}s > 0.$$

Next, we show that positive solutions of system (2) are ultimately bounded for $t \geqslant 0$. Adding the first, second and third equations of system (2), we get

$$\begin{aligned}\frac{\mathrm{d}(x(t)+u(t)+y(t))}{\mathrm{d}t} &= \lambda - dx(t) - \mu u(t) - ay(t) - py(t)z(t)\\ &\leqslant \lambda - dx(t) - \mu u(t) - ay(t)\\ &\leqslant \lambda - \min\{a,d,\mu\}\big(x(t)+u(t)+y(t)\big).\end{aligned}$$

Thus $\limsup_{t\to+\infty}(x(t)+u(t)+y(t)) \leqslant \lambda/\min\{a,d,\mu\}$. Therefore, for arbitrarily sufficiently small $\epsilon > 0$, there is a $T > 0$ such that if $t > T$,

$$x(t)+u(t)+y(t) \leqslant \frac{\lambda}{\min\{a,d,\mu\}} + \epsilon.$$

Furthermore, from the forth and fifth equations of (2), for $t > T$,

$$\begin{aligned}\frac{\mathrm{d}v(t)}{\mathrm{d}t} &\leqslant Na\left(\frac{\lambda}{\min\{a,d,\mu\}} + \epsilon\right) - \sigma v(t),\\ \frac{\mathrm{d}z(t)}{\mathrm{d}t} &\leqslant c\left(\frac{\lambda}{\min\{a,d,\mu\}} + \epsilon\right) - bz(t),\end{aligned}$$

which yield

$$\limsup_{t\to+\infty} v(t) \leqslant \frac{Na(\frac{\lambda}{\min\{a,d,\mu\}} + \epsilon)}{\sigma}, \qquad \limsup_{t\to+\infty} v(t) \leqslant \frac{c(\frac{\lambda}{\min\{a,d,\mu\}} + \epsilon)}{b}.$$

For arbitrary sufficiently small $\epsilon > 0$, the inequalities always hold. We conclude that

$$\limsup_{t\to+\infty} v(t) \leqslant \frac{Na\lambda}{\sigma\min\{a,d,\mu\}}, \qquad \limsup_{t\to+\infty} v(t) \leqslant \frac{c\lambda}{b\min\{a,d,\mu\}}.$$

Therefore, the solution of system (2) is ultimately bounded in $\mathbb{R}\times\mathbb{R}\times\mathcal{C}\times\mathbb{R}\times\mathbb{R}$. □

3 Basic reproduction ratio and feasible equilibria

System (2) always has an infection-free equilibrium $E_0(x_0, 0, 0, 0, 0)$, where $x_0 = \lambda/d$. In the following, we will apply the next generation matrix method [21] to compute the basic reproduction ratio of system (2).

The infected compartments in system (2) are u, y and v, ordered (u, y, v). The nonlinear terms with new infection $\mathcal{F}$ and the outflow term $\mathcal{V}$ are given by

$$\mathcal{F} = \begin{pmatrix} f\beta_1 xv + \eta\beta_2 xy \\ (1-f)\beta_1 xv + (1-\eta)\beta_2 xy \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} (\delta+\mu)u \\ -\delta u + ay + pyz \\ -Nay + \sigma v \end{pmatrix}.$$

Evaluating the derivatives of $\mathcal{F}$ and $\mathcal{V}$ at the equilibrium E_0 leads the following matrixes:

$$F = \begin{pmatrix} 0 & \frac{\eta\beta_2\lambda}{d} & \frac{f\beta_1\lambda}{d} \\ 0 & \frac{(1-\eta)\beta_2\lambda}{d} & \frac{(1-f)\beta_1\lambda}{d} \\ 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \delta+\mu & 0 & 0 \\ -\delta & a & 0 \\ 0 & -Na & \sigma \end{pmatrix}.$$

Therefore, we obtain the next-generation matrix

$$FV^{-1} = \begin{pmatrix} \frac{\delta\eta\beta_2\lambda}{ad(\delta+\mu)} + \frac{N\delta f\beta_1\lambda}{d\sigma(\delta+\mu)} & \frac{\eta\beta_2\lambda}{ad} + \frac{Nf\beta_1\lambda}{\sigma d} & \frac{f\beta_1\lambda}{d\sigma} \\ \frac{\delta(1-\eta)\beta_2\lambda}{ad(\delta+\mu)} + \frac{N\delta(1-f)\beta_1\lambda}{d\sigma(\delta+\mu)} & \frac{(1-\eta)\beta_2\lambda}{ad} + \frac{N(1-f)\beta_1\lambda}{\sigma d} & \frac{(1-f)\beta_1\lambda}{d\sigma} \\ 0 & 0 & 0 \end{pmatrix}.$$

One of the eigenvalues of matrix FV^{-1} is 0, the other one gives the basic reproduction ratio of system (2)

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{aN(1-f)\beta_1\lambda + \sigma(1-\eta)\beta_2\lambda}{ad\sigma} + \frac{aN\delta f\beta_1\lambda + \sigma\delta\eta\beta_2\lambda}{ad\sigma(\delta+\mu)}.$$

In addition to the equilibrium E_0, if $\mathcal{R}_0 > 1$, system (2) has an chronic-infection equilibrium $E_1(x_1, u_1, y_1, v_1, z_1)$, where

$$x_1 = \frac{\lambda\sigma}{d\sigma + (\beta_1 Na + \beta_2\sigma)y_1}, \qquad u_1 = \frac{Naf\beta_1\lambda y_1 + \sigma\eta\beta_2\lambda y_1}{(\delta+\mu)(d\sigma + \beta_1 Nay_1 + \beta_2\sigma y_1)},$$
$$v_1 = \frac{aNy_1}{\sigma}, \qquad z_1 = \frac{cy_1}{b+my_1},$$

and y_1 is the unique positive real root of the following algebraic equation:

$$h_2 y^2 + h_1 y + h_0 = 0$$

in which

$$\begin{aligned} h_0 &= -abd\sigma\delta(\mu+\delta)(R_0-1) < 0, \\ h_1 &= (\mu+\delta)[m(1-f)\beta_1\lambda Na + m(1-\eta)\beta_2\lambda\sigma \\ &\quad - adm\sigma - ab(\beta_1 Na + \beta_2\sigma) - cdp\sigma] \\ &\quad + \delta m(Naf\beta_1\lambda + \sigma\eta\beta_2\lambda) > 0, \\ h_2 &= (\mu+\delta)(\beta_1 Na + \beta_2\sigma)(am + cp) > 0. \end{aligned}$$

4 Stability of the equilibria E_0 and E_1

Theorem 2. *If $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0(\lambda/d, 0, 0, 0, 0)$ of system* (2) *is locally asymptotically stable for all $\tau \geqslant 0$; if $\mathcal{R}_0 > 1$, E_0 is unstable.*

Proof. The characteristic equation of system (2) at the equilibrium E_0 is

$$L(s) = (s+d)(s+b)(s^3 + l_2 s^2 + l_1 s + l_0) = 0, \tag{4}$$

where

$$\begin{aligned}
l_0 &= a\sigma(\mu+\delta)(1-R_0) > 0,\\
l_1 &= \big[-\sigma(1-\eta)\beta_2 x_0 - Na(1-f)\beta_1 x_0 + a\sigma\big]\\
&\quad - (1-\eta)\beta_2 x_0(\mu+\delta) - \delta\eta\beta_2 x_0 + a(\mu+\delta) + \sigma(\mu+\delta) > 0,\\
l_2 &= -(1-\eta)\beta_2 x_0 + a + \sigma + \delta + \mu > 0,\\
l_3 &= l_1 l_2 - l_0\\
&= \big[-(1-\eta)\beta_2 x_0 + a + \sigma\big] l_1 + \sigma(\mu+\delta)^2 + \sigma\delta\eta\beta_2 x_0 + \delta f \beta_1 x_0 Na\\
&\quad + (\delta+\mu)\big[-(1-\eta)\beta_2 x_0(\mu+\delta) - \delta\eta\beta_2 x_0 + a(\mu+\delta)\big] > 0.
\end{aligned}$$

By the Routh–Hurwitz criterion, we show that all roots of Eq. (4) have negative real parts. Hence, the infection-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$.

When $\mathcal{R}_0 > 1$, noting that $L(s)$ is a continuous function in respect to s, it is easy to see that

$$L(0) = abd(\mu+\delta)(1-\mathcal{R}_0) < 0, \qquad \lim_{s\to+\infty} L(s) = +\infty,$$

hence Eq. (4) has at least one positive real root, and E_0 is unstable. □

Theorem 3. *Suppose that $f = \eta$. If $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0(\lambda/d, 0, 0, 0, 0)$ of system* (2) *is globally asymptotically stable for all $\tau \geqslant 0$.*

Proof. Let $(x(t), u(t), y(t), v(t), z(t))$ be any positive solution of system (2) with initial condition (3). Define

$$\begin{aligned}
A_1(t) &= x(t) - x_0 - x_0 \ln\frac{x(t)}{x_0} + \frac{\delta}{\delta+\mu(1-\eta)}u(t) + \frac{\delta+\mu}{\delta+\mu(1-\eta)}y(t)\\
&\quad + \frac{\beta_1 x_0}{\sigma}v(t) + \frac{a(\delta+\mu)(1-\mathcal{R}_0)}{c\delta+c\mu(1-\eta)}z(t) + \frac{a(\delta+\mu)(1-\mathcal{R}_0)}{\delta+\mu(1-\eta)}\int_{t-\tau}^{t} y(\theta)\,\mathrm{d}\theta.
\end{aligned}$$

Calculating the derivative of $A_1(t)$ along positive solutions of system (2) and using the equality $\lambda = dx_0$ yields

$$\begin{aligned}
\frac{\mathrm{d}A_1(t)}{\mathrm{d}t} &= dx_0\left(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}\right) - \frac{ab(\delta+\mu)(1-\mathcal{R}_0)}{c\delta+c\mu(1-\eta)}z(t)\\
&\quad - \left[\frac{am(\delta+\mu)(1-\mathcal{R}_0)}{c\delta+c\mu(1-\eta)} + \frac{p(\delta+\mu)}{\delta+\mu(1-\eta)}\right]y(t)z(t).
\end{aligned} \tag{5}$$

It follows from Eq. (5) that $\dot{A}_1(t) \leqslant 0$ if $\mathcal{R}_0 < 1$. Furthermore, $\dot{A}_1(t) = 0$ holds if and only if $x(t) = \lambda/d$, $u(t) = 0$, $y(t) = 0$, $v(t) = 0$ and $z(t) = 0$. It can be verified that $M_0 = \{E_0\} \subset \Omega$ is the largest invariant subset of $\{(x(t), u(t), y(t), v(t), z(t)): \dot{A}_1(t) = 0\}$. By LaSalle's invariance principle, we conclude that the infection-free equilibrium E_0 of system (2) is globally asymptotically stable for all $\tau \geqslant 0$ under the assumption $f = \eta$. □

Theorem 4. *Suppose that $f = \eta$. If $\mathcal{R}_0 > 1$, the chronic-infection equilibrium $E_1(x_1, u_1, y_1, v_1, z_1)$ of system* (2) *is globally asymptotically stable when $\tau = 0$.*

Proof. Let $(x(t), u(t), y(t), v(t), z(t))$ be any positive solution of system (2) with initial condition (3). Define

$$\begin{aligned}\frac{\mathrm{d}A_2(t)}{\mathrm{d}t} &= x(t) - x_1 - x_1 \ln \frac{x(t)}{x_1} + \frac{\delta}{\delta + \mu(1-\eta)}\left(u(t) - u_1 - u_1 \ln \frac{u(t)}{u_1}\right) \\ &\quad + \frac{\delta + \mu}{\delta + \mu(1-\eta)}\left(y(t) - y_1 - y_1 \ln \frac{y(t)}{y_1}\right) \\ &\quad + \frac{\beta_1 x_1}{\sigma}\left(v(t) - v_1 - v_1 \ln \frac{v(t)}{v_1}\right) + \frac{p(\delta+\mu)y_1}{2b(\delta + \mu(1-\eta))z_1}\big(z(t) - z_1\big)^2.\end{aligned}$$

Calculating the derivative of $A_2(t)$ along positive solutions of system (2) yields

$$\begin{aligned}\frac{\mathrm{d}A_2(t)}{\mathrm{d}t} &= \left(1 - \frac{x_1}{x(t)}\right)\big(\lambda - dx(t) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t)\big) \\ &\quad + \frac{\delta}{\delta + \mu(1-\eta)}\left(1 - \frac{u_1}{u(t)}\right)\big(f\beta_1 x(t)v(t) + \eta\beta_2 x(t)y(t) - \mu u(t) + \delta u(t)\big) \\ &\quad + \frac{\delta + \mu}{\delta + \mu(1-\eta)}\left(1 - \frac{y_1}{y(t)}\right) \\ &\quad \times \big((1-f)\beta_1 x(t)v(t) + \delta u(t) + (1-\eta)\beta_2 x(t)y(t) - ay(t) - py(t)z(t)\big) \\ &\quad + \frac{\beta_1 x_1}{\sigma}\left(1 - \frac{v_1}{v(t)}\right)\big(Nay(t) - \sigma v(t)\big) \\ &\quad + \frac{p(\delta+\mu)y_1}{b(\delta + \mu(1-\eta))z_1}(z(t) - z_1)\big(cy(t) - bz(t) - my(t)z(t)\big). \qquad (6)\end{aligned}$$

Substituting equalities $\lambda = dx_1 + \beta_1 x_1 v_1 + \beta_2 x_1 y_1$, $f\beta_1 x_1 v_1 + \eta\beta_2 x_1 y_1 = (\mu + \delta)u_1$, $ay_1 = (1-\eta)\beta_1 x_1 v_1 + (1-\eta)\beta_2 x_1 y_1 + \delta u_1 - py_1 z_1$, $Nay_1 = \sigma v_1$, $cy_1 - my_1 z_1 = bz_1$ into Eq. (6) yields

$$\begin{aligned}\frac{\mathrm{d}A_2(t)}{\mathrm{d}t} &= dx_1\left(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}\right) + \frac{(\delta+\mu)(1-\eta)\beta_2 x_1 y_1}{\delta + \mu(1-\eta)}\left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1}\right) \\ &\quad + \frac{\delta\eta\beta_1 x_1 v_1}{\delta + \mu(1-\eta)}\left(4 - \frac{x_1}{x(t)} - \frac{x(t)v(t)u_1}{x_1 v_1 u(t)} - \frac{y_1 u(t)}{y(t)u_1} - \frac{v_1 y(t)}{v(t)y_1}\right) \\ &\quad + \frac{(\delta+\mu)(1-\eta)\beta_1 x_1 v_1}{\delta + \mu(1-\eta)}\left(3 - \frac{x_1}{x(t)} - \frac{x(t)v(t)y_1}{x_1 v_1 y(t)} - \frac{v_1 y(t)}{v(t)y_1}\right)\end{aligned}$$

$$+\frac{\delta\eta\beta_2 x_1 y_1}{\delta+\mu(1-\eta)}\left(3-\frac{x_1}{x(t)}-\frac{x(t)y(t)u_1}{x_1y_1u(t)}-\frac{y_1u(t)}{y(t)u_1}\right)$$
$$-\frac{p(\delta+\mu)y_1}{b(\delta+\mu(1-\eta))z_1}\big(b+my(t)\big)\big(z(t)-z_1\big)^2. \tag{7}$$

It follows from Eq. (7) that $\dot{A}_2(t)\leqslant 0$. Furthermore, $\dot{A}_2(t)=0$ holds if and only if $x(t)=x_1$, $u(t)=u_1$, $y(t)=y_1$, $v(t)=v_1$ and $z(t)=z_1$. It can be verified that $M_0=\{E_1\}\subset\Omega$ is the largest invariant subset of $\{(x(t),u(t),y(t),v(t),z(t))\colon\ \dot{A}_2(t)=0\}$. By LaSalle's invariance principle, we conclude that the chronic-infection equilibrium E_1 of system (2) is globally asymptotically stable when $\tau=0$ under the assumption $f=\eta$. □

5 Persistence of infection

In this section, we will prove the uniform persistence of system (2) when $\mathcal{R}_0>1$.

Let X be a metric space with metric d. Suppose that X^0 is an open set in X, $X^0\subset X$, $X^0\cap X_0=\emptyset$ and $X^0\cup X_0=X$. Furthermore, $Q(t)$ is a C_0-semigroup of X satisfying

$$Q(t):X^0\to X^0,\ X_0\to X_0. \tag{8}$$

Let $Q_\partial(t)=Q(t)\mid X_0$, and let A_∂ be the global attractor for $Q_\partial(t)$.

Lemma 1. (*See Hale and Waltman* [9].)*Suppose that* $Q(t)$ *satisfies* (8) *and the following conditions are valid*:

(i) $Q(t)$ *is point dissipative in* X.
(ii) *There is a* $t_0\geqslant 0$ *such that* $Q(t)$ *is compact for* $t>t_0$.
(iii) $\widetilde{A}_\partial=\bigcup_{x\in A_\partial}$ *is isolated and has an acyclic covering* $\widetilde{M}=\{M_1,M_2,\dots,M_n\}$.
(iv) $W^s(M_i)\cap X^0=\emptyset$, $i=1,2,\dots,n$.

Then $Q(t)$ *is uniformly persistent in the sense that there exists* $\epsilon>0$ *such that, for any* $x\in X^0$, $\liminf_{x\to+\infty}d(Q(t)X,X_0)\geqslant\epsilon$, *where* d *is the distance of* $Q(t)x$ *from* X_0.

By applying Lemma 1 to system (2), we obtain the following result.

Theorem 5. *If* $\mathcal{R}_0>1$, *system* (2) *is uniformly persistent, i.e., for all solutions of system* (2) *with initial condition* (3), *there exists an* $\epsilon>0$ *such that*

$$\liminf_{t\to+\infty}x(t)\geqslant\epsilon,\qquad \liminf_{t\to+\infty}u(t)\geqslant\epsilon,\qquad \liminf_{t\to+\infty}y(t)\geqslant\epsilon,$$
$$\liminf_{t\to+\infty}v(t)\geqslant\epsilon,\qquad \liminf_{t\to+\infty}z(t)\geqslant\epsilon.$$

Proof. Let $X=C([-\tau,0],R^5_{+0})$. Define

$$X_0=\big\{(\phi_1,\phi_2,\phi_3,\phi_4,\phi_5)\in X\colon\ \phi_2(\theta)\equiv 0,\ \phi_3(\theta)\equiv 0,\ \phi_4(\theta)\equiv 0,\ \phi_5(\theta)\equiv 0\big\},$$
$$X^0=X/X_0.$$

It is easy to see that $X^0 \cap X_0 = \emptyset$ and $X^0 \cup X_0 = X$. Basic analysis of (2) implies that X_0 is a positive invariant set for system (2). The positive invariance of X^0 follows from Theorem 1 and simple analysis of (2) when any initial component is zero. Therefore, (8) is satisfied.

For any initial condition $(\phi_1, \phi_2, \phi_3, \phi_4, \phi_5) \in X$, define $Q(t)$ for $t \geqslant 0$ as

$$Q(t)(\phi_1, \phi_2, \phi_3, \phi_4, \phi_5) := \big(x(t), u(t), y(t), v(t), z(t)\big),$$

where $(x(t), u(t), y(t), v(t), z(t))$ is the solution of (2) with initial condition $(\phi_1, \phi_2, \phi_3, \phi_4, \phi_5)$. Then $\{Q(t)\}_{t\geqslant 0}$ is a C_0-semigroup. By Theorem 1, we have that $Q(t)(\phi_1, \phi_2, \phi_3, \phi_4, \phi_5)$ is dissipative in X and hence condition (i) in Lemma 1 is satisfied.

Next, it is easy to know that the equations in the right-side of system (2) are in C^1, and the solutions of system (2) with initial conditions (3) are ultimately bounded. Condition (ii) in Lemma 1 follows from the smoothing property of solutions of neutral delay differential equations [10] that there is a $t_0 \geqslant 0$ such that $Q(t)$ is compact for $t > t_0$.

Note that system (2) has an unique boundary equilibrium $E_0(\lambda/d, 0, 0, 0, 0)$. For any initial condition $(\phi_1, \phi_2, \phi_3, \phi_4, \phi_5) \in X_0$, we have $u(t) \equiv 0$, $y(t) \equiv 0$, $v(t) \equiv 0$, $z(t) \equiv 0$ for all $t \geqslant 0$ and $x(t) \to \lambda/d$ as $t \to +\infty$. Hence $\{E_0\}$ contains all ω-limit sets in X_0. By Theorem 2, we have that E_0 is unstable if $\mathcal{R}_0 > 1$. Then $\{E_0\}$ is isolated and has an acyclic covering, condition (iii) in Lemma 1 is satisfied.

Since

$$\begin{aligned}\mathcal{R}_0 &= \frac{aN(1-f)\beta_1\lambda + \sigma(1-\eta)\beta_2\lambda}{ad\sigma} + \frac{aN\delta f\beta_1\lambda + \sigma\delta\eta\beta_2\lambda}{ad\sigma(\delta+\mu)} \\ &= \frac{aN\beta_1\lambda[(1-f)\mu+\delta]}{ad\sigma(\delta+\mu)} + \frac{\beta_2\lambda[(1-\eta)\mu+\delta]}{ad\sigma(\delta+\mu)} > 1,\end{aligned}$$

we can choose $\epsilon > 0$ sufficiently small such that

$$\frac{a\sigma(\mu+\delta) + p\sigma\epsilon(\mu+\delta)}{aN\beta_1[(1-f)\mu+\delta] + \beta_2[(1-\eta)\mu+\delta]} < \frac{\lambda}{d} - \epsilon. \tag{9}$$

Now we show that $W^s(E_0) \cap X^0 = \emptyset$. Suppose $W^s(E_0) \cap X^0 \neq \emptyset$, there exists a positive solution $(x(t), u(t), y(t), v(t), z(t))$ such that $(x(t), u(t), y(t), v(t), z(t)) \to (\lambda/d, 0, 0, 0, 0)$ as $t \to 0$. For $\epsilon > 0$ sufficiently small satisfying (9), there is $t_0 > 0$ such that when $t > t_0$, we have $x(t) > \lambda/d - \epsilon$, $z(t) \leqslant \epsilon$. Hence, it follows from system (2) for $t > t_0$,

$$\begin{aligned}\frac{\mathrm{d}u(t)}{\mathrm{d}t} &\geqslant f\beta_1\left(\frac{\lambda}{d}-\epsilon\right)v(t) + \eta\beta_2\left(\frac{\lambda}{d}-\epsilon\right)y(t) - (\mu+\delta)u(t), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} &\geqslant (1-f)\beta_1\left(\frac{\lambda}{d}-\epsilon\right)v(t) + (1-\eta)\beta_2\left(\frac{\lambda}{d}-\epsilon\right)y(t) \\ &\quad + \delta u(t) - ay(t) - py(t)\epsilon, \\ \frac{\mathrm{d}v(t)}{\mathrm{d}t} &= Nay(t) - \sigma v(t).\end{aligned}$$

Consider the following auxiliary system:

$$\begin{aligned}
\frac{\mathrm{d}u_1(t)}{\mathrm{d}t} &= f\beta_1\left(\frac{\lambda}{d}-\epsilon\right)u_3(t)+\eta\beta_2\left(\frac{\lambda}{d}-\epsilon\right)u_2(t)-(\mu+\delta)u_1(t),\\
\frac{\mathrm{d}u_2(t)}{\mathrm{d}t} &= (1-f)\beta_1\left(\frac{\lambda}{d}-\epsilon\right)u_3(t)+(1-\eta)\beta_2\left(\frac{\lambda}{d}-\epsilon\right)u_2(t)\\
&\quad +\delta u_1(t)-(a+p\epsilon)u_2(t),\\
\frac{\mathrm{d}u_3(t)}{\mathrm{d}t} &= Nau_2(t)-\sigma u_3(t).
\end{aligned} \tag{10}$$

Clearly, system (10) has a unique equilibrium $(0,0,0)$. The characteristic equation of (10) at the equilibrium $(0,0,0)$ takes the form

$$G(s)=s^3+g_2s^2+g_1s+g_0=0,$$

where

$$\begin{aligned}
g_0 &= -\left(\frac{\lambda}{d}-\epsilon\right)\big(aN\beta_1\big((1-f)\mu+\delta\big)+\beta_2\big((1-\eta)\mu+\delta\big)\big)\\
&\quad +a\sigma(\delta+\mu)+p\sigma\epsilon(\mu+\delta),\\
g_1 &= -\beta_2(1-\eta)\left(\frac{\lambda}{d}-\epsilon\right)(\mu+\delta)+a(\mu+\delta)+p\epsilon(\mu+\delta)+\sigma(\mu+\delta)\\
&\quad +a\sigma+p\sigma\epsilon-\sigma\beta_2(1-\eta)\left(\frac{\lambda}{d}-\epsilon\right)+Na\beta_1\left(\frac{\lambda}{d}-\epsilon\right)-\delta\eta\beta_2\left(\frac{\lambda}{d}-\epsilon\right),\\
g_2 &= -\beta_2(1-\eta)\left(\frac{\lambda}{d}-\epsilon\right)+a+p\epsilon+\sigma+\mu+\delta.
\end{aligned}$$

If $\mathcal{R}_0>1$, it is easy to see that for real s, $\lim_{s\to+\infty}G(s)=+\infty$, and it follows from Eq. (9) that

$$\begin{aligned}
G(0) &= -\left(\frac{\lambda}{d}-\epsilon\right)\big[aN\beta_1\big((1-f)\mu+\delta\big)+\beta_2\big((1-\eta)\mu+\delta\big)\big]\\
&\quad +\sigma(\delta+\mu)(a+p\epsilon)\\
&< 0.
\end{aligned}$$

Therefore, $G(s)=0$ has at least one positive real root. Hence, the unique equilibrium $(0,0,0)$ is unstable. It follows from that $u_1\to+\infty, u_2\to+\infty$ and $u_3\to+\infty$ as $t\to+\infty$. By comparison, we obtain that $u(t)\to+\infty$, $y(t)\to+\infty$ and $v(t)\to+\infty$ as $t\to+\infty$. This contradicts $\lim_{t\to+\infty}(x(t),u(t),y(t),v(t),z(t))=(\lambda/d,0,0,0,0)$. Hence $W^s(E_0)\cap X^0=\emptyset$, condition (iv) in Lemma 1 is satisfied. This completes the proof. □

6 Hopf bifurcation

In this section, we will identify parameter regimes in which the time delay can destabilize the stability of chronic-infection equilibrium $E_1(x_1,u_1,y_1,v_1,z_1)$ and lead to Hopf bifurcation.

The characteristic equation of system (2) at equilibrium $E_1(x_1, u_1, y_1, v_1, z_1)$ is of the form

$$s^5 + l_4 s^4 + l_3 s^3 + l_2 s^2 + l_1 s + l_0 + \big(h_3 s^3 + h_2 s2 + h_1 s + h_0\big)\mathrm{e}^{-s\tau} = 0, \qquad (11)$$

where

$$\begin{aligned}
l_0 = {} & \frac{-mp\sigma\lambda y_1 z_1}{x_1}(\mu+\delta) - Na\beta_1\lambda\big[\mu(1-f)+\delta\big](b+my_1) - \sigma\delta\eta\beta_2\lambda(b+my_1) \\
& + \frac{\sigma\lambda}{x_1}(b+my_1)(\mu+\delta)(-(1-\eta)\beta_2 x_1 + a + pz_1) \\
& + \delta(Na\beta_1+\sigma\beta_2)(\mu+\delta)u_1(b+my_1) \\
& + (Na\beta_1+\sigma\beta_2)(\mu+\delta)(b+my_1)\big((1-f)\beta_1 x_1 v_1 + (1-\eta)\beta_2 x_1 y_1\big), \\
l_1 = {} & \frac{-mp\lambda y_1 z_1}{x_1}(\sigma+\mu+\delta) - mp\sigma(\mu+\delta)y_1 z_1 \\
& + \sigma(b+my_1)(\mu+\delta)\big[-(1-\eta)\beta_2 x_1 + a + pz_1\big] \\
& + Na\beta_1 x_1(b+my_1)\big[(1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1\big] - Na(1-f)\beta_1\lambda(b+my_1) \\
& + \frac{\sigma\lambda}{x_1}(b+my_1)\big[\mu+\delta-(1-\eta)\beta_2 x_1 + a + pz_1\big] \\
& - \sigma\delta\eta\beta_2 x_1(b+my_1) + \beta_2 x_1(b+my_1+\sigma)(\mu+\delta)\big((1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1\big) \\
& + Na\beta_1 x_1\delta(f\beta_1 v_1 + \eta\beta_2 y_1) \\
& + \beta_2 x_1(b+my_1+\sigma)(\mu+\delta)\big((1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1\big) \\
& - \sigma\delta\eta\beta_2 x_1(b+my_1) + \beta_2 x_1\delta(b+my_1+\sigma)(f\beta_1 v_1 + \eta\beta_2 y_1) \\
& - Na\beta_1 x_1\big(\mu(1-f)+\delta\big)\left(b+my_1+\frac{\lambda}{x_1}\right) \\
& + \frac{\lambda}{x_1}(b+my_1+\sigma)(\mu+\delta)\big[-(1-\eta)\beta_2 x_1 + a + pz_1\big] \\
& + \big[\sigma\beta_2(b+my_1) + Na\beta_1(\mu+\delta)\big]\big[(1-f)\beta_1 x_1 v_1 + (1-\eta)\beta_2 x_1 y_1\big] \\
& - \delta\eta\beta_2\lambda(b+my_1+\sigma), \\
l_2 = {} & \beta_2 x_1\delta(f\beta_1 v_1 + \eta\beta_2 y_1) + \sigma(b+my_1)\left(\frac{\lambda}{x_1} + \mu + \delta - (1-\eta)\beta_2 x_1 + a + pz_1\right) \\
& + Na\beta_1 x_1\big[(1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1\big] \\
& + (b+my_1+\sigma)(\mu+\delta)\big[-(1-\eta)\beta_2 x_1 + a + pz_1\big] \\
& + \frac{\lambda}{x_1}(\mu+\delta)\big(-(1-\eta)\beta_2 x_1 + a + pz_1\big) \\
& + \beta_2 x_1(b+my_1+\sigma)\big[(1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1\big] - mpy_1 z_1\left(\mu+\delta+\frac{\lambda}{x_1}\right) \\
& + \frac{\lambda}{x_1}(b+my_1+\sigma)(\mu+\delta+a+pz_1-\delta\eta\beta_2 x_1)
\end{aligned}$$

$$
\begin{aligned}
&+ \beta_2 x_1(\mu+\delta)\big((1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1 - (1-\eta)\beta_2 x_1\big)\\
&- Na(1-f)\beta_1 x_1\left(b + my_1 + \frac{\lambda}{x_1}\right),\\
l_3 = {}& -mpy_1 z_1 - Na(1-f)\beta_1 x_1 + \frac{\lambda}{x_1}\big[\mu+\delta-(1-\eta)\beta_2 x_1 + a + pz_1\big]\\
&- \delta\eta\beta_2 x_1 + \sigma(b+my_1) + \beta_2 x_1\big[(1-f)\beta_1 v_1 + (1-\eta)\beta_2 y_1\big]\\
&+ (b+my_1+\sigma)\left(\frac{\lambda}{x_1} + \mu + \delta - 1 - (1-\eta)\beta_2 x_1 + a + pz_1\right)\\
&+ (\mu+\delta)\big[-(1-\eta)\beta_2 x_1 + a + pz_1\big],\\
l_4 = {}& b + my_1 + \sigma + \frac{\lambda}{x_1} + \mu + \delta - (1-\eta)\beta_2 x_1 + a + pz_1,
\end{aligned}
$$

$$
h_0 = \frac{cpy_1\sigma\lambda}{x_1}(\mu+\delta), \qquad h_1 = cpy_1\left[\frac{\lambda}{x_1}(\sigma+\mu+\delta) + \sigma(\mu+\delta)\right],
$$

$$
h_2 = cpy_1\left(\sigma+\mu+\delta+\frac{\lambda}{x_1}\right), \qquad h_3 = cpy_1.
$$

When $\tau > 0$, if $\mathrm{i}\omega$ ($\omega > 0$) is a solution of Eq. (11), separating real and imaginary parts, we have

$$
\begin{aligned}
l_4\omega^4 - l_2\omega^2 + l_0 &= \big(h_2\omega^2 - h_0\big)\cos\omega\tau - \big(h_3\omega^3 - h_1\omega\big)\sin\omega\tau,\\
\omega^5 - l_3\omega^3 + l_1\omega &= \big(h_3\omega^3 - h_1\omega\big)\cos\omega\tau + \big(h_2\omega^2 - h_0\big)\sin\omega\tau.
\end{aligned}
\tag{12}
$$

Squaring and adding the two equations of Eq. (12), it follows that

$$
\omega^{10} + k_4\omega^8 + k_3\omega^6 + k_2\omega^4 + k_1\omega^2 + k_0 = 0, \tag{13}
$$

where

$$
\begin{aligned}
&k_0 = l_0^2 - h_0^2, \qquad k_1 = -2l_0l_2 + l_1^2 + 2h_0h_2 - h_1^2,\\
&k_2 = l_2^2 + 2l_0l_4 - 2l_1l_3 - h_2^2 + 2h_1h_3,\\
&k_3 = -2l_2l_4 + l_3^2 + 2l_1 - h_3^2, \qquad k_4 = l_4^2 - 2l_3.
\end{aligned}
$$

Letting $\xi = \omega^2$, Eq. (13) becomes

$$
H(\xi) = \xi^5 + k_4\xi^4 + k_3\xi^3 + k_2\xi^2 + k_1\xi + k_0 = 0. \tag{14}
$$

Suppose now that Eq. (14) has positive real roots. Without loss of generality, we assume that Eq. (14) has m ($1 \leqslant m \leqslant 5$) positive roots denoted respectively as $\xi_1 < \xi_2 < \cdots < \xi_m$. Then Eq. (13) has m positive roots $\omega_j = \sqrt{\xi_j}$ ($1 \leqslant j \leqslant m$). According to Eq. (12), we get

$$
\begin{aligned}
\cos(\omega_j\tau) &= \frac{(l_4\omega_j^4 - l_2\omega_j^2 + l_0)(h_2\omega_j^2 - h_0) + (\omega_j^5 - l_3\omega_j^3 + l_1\omega_j)(h_3\omega_j^3 - h_1\omega_j)}{(h_2\omega_j^2 - h_0)^2 + (h_3\omega_j^3 - h_1\omega_j)^2}\\
&= \varphi(\omega_j).
\end{aligned}
$$

Thus

$$\tau_n^j = \frac{\arccos\varphi(\omega_j)}{\omega_j} + \frac{2n\pi}{\omega_j},$$

where $j = 1, 2, \ldots, m$ and $n \in N^+$. Then $\pm i\omega_j$ are a pair of purely imaginary roots of Eq. (13) with $\tau = \tau_n^j$. Let $s(\tau) = \alpha(\tau) + i\omega(\tau)$ be the root of Eq. (11) satisfying $\alpha(\tau_n^j) = 0$ and $\omega(\tau_n^j) = \omega_j$. Define

$$\tau_0 = \min_{1\leqslant j\leqslant m}\{\tau_{(0)}^j\}, \qquad \omega_0 = \omega_{j0}. \tag{15}$$

Substituting $s(\tau)$ into Eq. (11) and calculating the derivative with respect to τ, we obtain

$$\left(\frac{\mathrm{d}s}{\mathrm{d}\tau}\right)^{-1} = \frac{5s^4 + 4l_4s^3 + 3l_3s^2 + 2l_2s + l_1}{-s(s^5 + l_4s^4 + l_3s^3 + l_2s^2 + l_1s + l_0)} + \frac{3h_3s^2 + 2h_2s + h_1}{s(h_3s^3 + h_2s2 + h_1s + h_0)} - \frac{\tau}{s}.$$

Direct calculation yields

$$\begin{aligned}\left(\frac{\mathrm{d}(\operatorname{Re}s)}{\mathrm{d}\tau}\right)^{-1}\Big|_{\tau=\tau_0} &= \frac{(5\omega_0^4 - 3l_3\omega_0^2 + l_1)(\omega_0^5 - l_3\omega_0^3 + l_1\omega_0)}{(\omega_0^5 - l_3\omega_0^3 + l_1\omega_0)^2 + (l_4\omega_0^4 - l_2\omega_0^2 + l_0)^2} \\ &\quad - \frac{(2l_2\omega_0 - 4l_4\omega_0^3)(l_4\omega_0^4 - l_2\omega_0^2 + l_0)}{(\omega_0^5 - l_3\omega_0^3 + l_1\omega_0)^2 + (l_4\omega_0^4 - l_2\omega_0^2 + l_0)^2} \\ &\quad + \frac{(3h_3\omega_0^2 - h_1)(-h_3\omega_0^3) + h_1\omega_0 + 2h_2\omega_0(-h_2\omega_0^2 + h_0)}{(h_3\omega_0^3 - h_1\omega_0)^2 + (h_0 - h_2\omega_0^2)^2}.\end{aligned}$$

From Eq. (12) we conclude that

$$\left(\omega_0^5 - l_3\omega_0^3 + l_1\omega_0\right)^2 + \left(l_4\omega_0^4 - l_2\omega_0^2 + l_0\right)^2 = \left(h_3\omega_0^3 - h_1\omega_0\right)^2 + \left(h_0 - h_2\omega_0^2\right)^2.$$

Thus

$$\left(\frac{\mathrm{d}(\operatorname{Re}s)}{\mathrm{d}\tau}\right)^{-1}\Big|_{\tau=\tau_0} = \omega_0\frac{H'(\omega_0^2)}{(h_3\omega_0^3 - h_1\omega_0)^2 + (h_0 - h_2\omega_0^2)^2}.$$

Since $\omega_0 > 0$ and $(h_3\omega_0^3 - h_1\omega_0)^2 + (h_0 - h_2\omega_0^2)^2 > 0$, it follows that

$$\operatorname{sign}\left\{\frac{\mathrm{d}(\operatorname{Re}s)}{\mathrm{d}\tau}\Big|_{\tau=\tau_0}\right\} = \operatorname{sign}\left\{\left(\frac{\mathrm{d}(\operatorname{Re}s)}{\mathrm{d}\tau}\right)^{-1}\Big|_{\tau=\tau_0}\right\} = \operatorname{sign}\left\{H'(\omega_0^2)\right\}.$$

From what has been discussed above we have the following result.

Theorem 6. *Let ω_0 and τ_0 be defined by* (15)*. If $\mathcal{R}_0 > 1$, the following conclusions are valid.*

(i) *If Eq.* (14) *has no positive root, the equilibrium E_1 is locally asymptotically stable for $\tau > 0$.*

(ii) *If Eq.* (14) *has at least one positive root, the equilibrium E_1 is locally asymptotically stable for $0 \leqslant \tau < \tau_0$ and becomes unstable for $\tau > \tau_0$. Further, if $H'(\omega_0^2) > 0$, system* (2) *undergoes a Hopf bifurcation at E_1 when $\tau = \tau_0$.*

7 Simulation and discussion

In this section, we want to illustrate the theoretical results for system (2) by numerical simulations. Here we choose initial condition $(20, 0.6, 5, 400, 5)$, and the relevant parameter values of system (2) are listed in Table 2.

We choose parameter values being listed in Table 2. By calculation, we get $\mathcal{R}_0 = 39.9733 > 1$, $\tau_0 = 1.743$, and system (12) has a chronic-infection equilibrium $E_1(21.98, 0.6227, 7.321, 365.1, 11.74)$. From Theorem 6 we derived that the equilibrium E_1 is locally asymptotically stable when $0 \leqslant \tau < \tau_0$ and becomes unstable for $\tau > \tau_0$. Numerical simulations illustrate this fact (see Figs. 1 and 2), and system (2) undergoes a Hopf bifurcation at E_1 when $\tau = \tau_0$ (see Fig. 3).

Table 2. The data of parameters of system (2).

Parameters	values	Unit	Source	Parameters	values	Unit	Source
λ	10	cells/mm^3/day	[24]	a	0.5	day^{-1}	[18]
d	0.03	day^{-1}	[24]	p	0.08	mm^3/cells/day	[23]
β_1	0.001	mm^3/virion/day	[24]	N	200	mm^3/cells/day^{-1}	[24]
β_2	0.01	mm^3/virion/day	[1]	σ	2	day^{-1}	[1]
f	0.001	–	[18]	τ	varied day	Assume	
η	0.003	–	[24]	c	0.65	mm^3/cells/day	[24]
μ	0.01	day^{-1}	[19]	b	0.06	day^{-1}	[24]
δ	0.01	day^{-1}	[19]	m	0.05	cells^{-1}/day	Assume

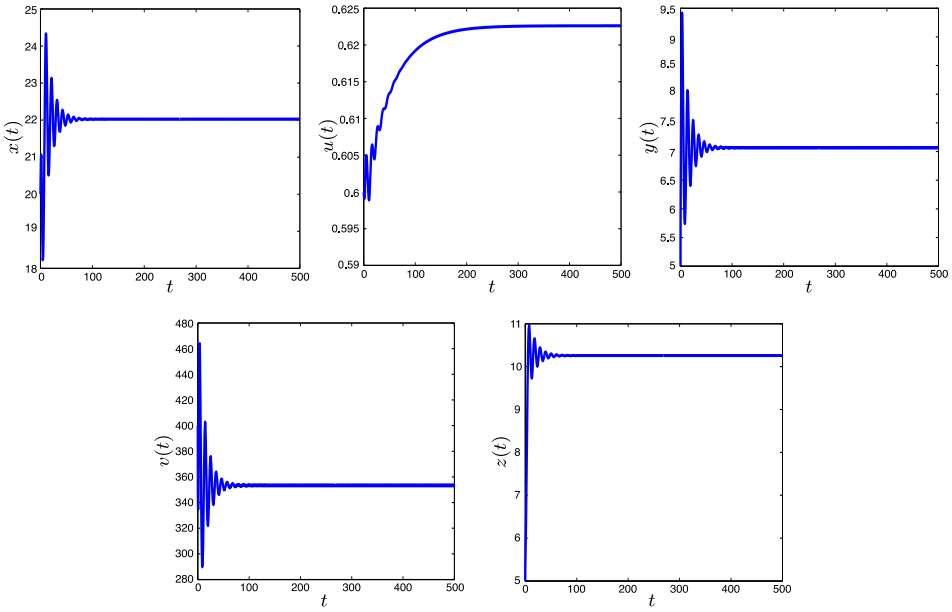

Figure 1. The immune-activated equilibrium $E_1(21.98, 0.6227, 7.321, 365.1, 11.74)$ of system (2) is locally asymptotically stable when $\mathcal{R}_0 > 1$ and $\tau = 1 < \tau_0$.

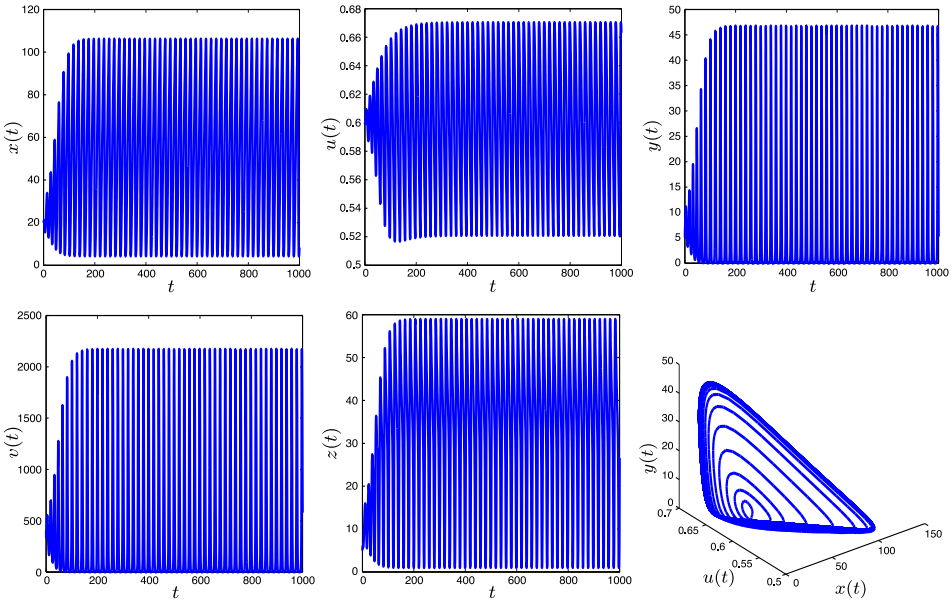

Figure 2. The immune-activated equilibrium $E_1(21.98, 0.6227, 7.321, 365.1, 11.74)$ of system (2) becomes unstable when $\mathcal{R}_0 > 1$ and $\tau = 3 > \tau_0$.

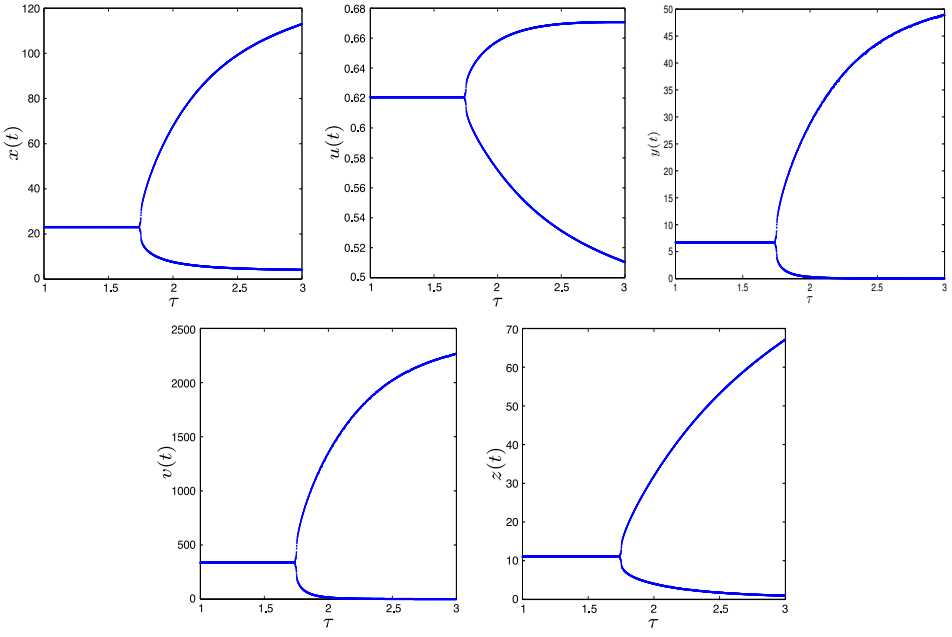

Figure 3. The bifurcation diagram of system (2) when $\lambda = 10$, $d = 0.03$, $\sigma = 2$, $c = 0.065$ and the other parameter values are the same as those in Table 2.

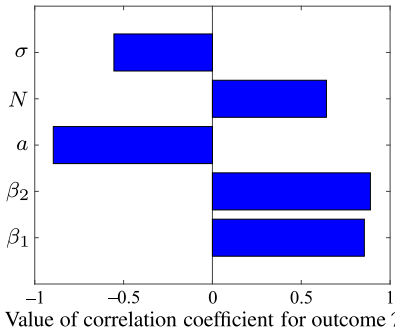

Figure 4. Tornado plot of partial rank correlation coefficients in respect to $\mathcal{R}_0$.

We have shown that the disease will die out if $\mathcal{R}_0 < 1$, and if $\mathcal{R}_0 > 1$, the virus and the CTL cells persist in the host. In addition, as shown in Fig. 3, we see that a threshold τ_0 for the CTL immune delay was identified to characterize the existence of Hopf bifurcation at the chronic-infection equilibrium E^* when the CTL immune delay cross it. This implies that the CTL immune delay τ plays an important role in destabilizing the chronic-infection equilibrium and leading to periodic oscillation.

In terms of the treatment of HIV infection, we pay more attention to antiretroviral therapies, which is directly related to viral production rate and viral remove rate. Besides, it is noted that the antiviral activity of bNAbs results from antigen-binding site-Env interactions that block entry of cell-free virions as well as viral cell-cell transmission in vivo [2]. Since the basic reproduction ratio $\mathcal{R}_0$ is a threshold determining the global dynamics of the model, we analyze the effect of parameters β_1, β_2, a, N and σ on $\mathcal{R}_0$ by LHS with 500 samples and partial rank correlation coefficient [13]. As we can see in Fig. 4, β_1, β_2 and N are positive correlative variables, while others are negative correlative variables.

8 Conclusion

In this paper, we have considered an HIV infection model with latent reservoir, both virus-to-cell and cell-to-cell transmissions, delayed CTL immune response and immune impairment. By a rigorous mathematical analysis, it was shown that the global dynamics of system (2) is completely determined by basic reproduction ratio $\mathcal{R}_0$. Supposing that $f = \eta$, if $\mathcal{R}_0 < 1$, it was verified that the infection-free equilibrium E_0 is globally asymptotically stable, and time delay has no effect on the dynamics of system (2). If $\mathcal{R}_0 > 1$, the infection-free equilibrium E_0 becomes unstable, and the chronic-infection equilibrium E_1 is globally asymptotically stable when $\tau = 0$. On the other hand, the threshold of CTL immune delay is calculated to characterize the existence of Hopf bifurcation at chronic-infection equilibrium E_1 when CTL immune delay crosses it. This implies that the CTL immune delay τ plays an important role in destabilizing the chronic-infection equilibrium and leading to periodic oscillation. Biologically, this explains the sudden jump in viral load among patients with viral suppression under ART when ART is stopped.

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