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*Research article*

# Mathematical analysis of an HIV model with latent reservoir, delayed CTL immune response and immune impairment

**Ning Bai and Rui Xu***

Complex Systems Research Center, Shanxi University, Taiyuan 030006, China

* **Correspondence:** Email: xurui@sxu.edu.cn, rxu88@163.com.

**Abstract:** In this paper, an in-host HIV infection model with latent reservoir, delayed CTL immune response and immune impairment is investigated. By using suitable Lyapunov functions and LaSalle's invariance principle, it is shown that when time delay is equal to zero, the immunity-inactivated reproduction ratio is a threshold determining the global dynamics of the model. By means of the persistence theory for infinite dimensional systems, it is proven that if the immunity-inactivated reproduction ratio is greater than unity, the model is permanent. Choosing time delay as the bifurcation parameter and analyzing the corresponding characteristic equation of the linearized system, the existence of a Hopf bifurcation at the immunity-activated equilibrium is established. Numerical simulations are carried out to illustrate the theoretical results and reveal the effects of some key parameters on viral dynamics.

**Keywords:** latent reservoir; delayed CTL immune response; immune impairment; Lyapunov functions; Hopf bifurcation

## 1. Introduction

Combination antiretroviral therapy or highly active antiretroviral therapy (HAART) have led to a substantial reduction in the incidence of HIV-related morbidity and mortality [1,2]. HAART consisting of at least three different drugs has proved to be effective in suppressing the plasma viral load of most patients to below 50 RNA copies/ml, which is the detection limit of current standard assays [3]. However, this does not mean that virus replication has been completely suppressed by the therapy [4–6]. Even in patients whose plasma viral level has been below the detection limit for many years, a low level of viremia can be detected in plasma by more sensitive assays [7]. Studies have shown that this phenomenon may be related to the continuous release of virus particles, which are produced by activating latently infected cells [8]. In the past decades, the activation of latently infected cells has been incorporated into the modelling of HIV infection [9–13].

Rong et al. [13] considered a mathematical model including uninfected CD4$^+$ T cells $T$, latently infected CD4$^+$ T cells $L$, actively infected CD4$^+$ T cells $T^*$ and free virus $V$ to explore a hypothesis about latently infected cell activation under the effect of therapy. The model takes the following form:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - d_T T - (1-\varepsilon)kVT,\\
\frac{\mathrm{d}L(t)}{\mathrm{d}t} &= \alpha_L(1-\varepsilon)kVT - d_L L - aL,\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= (1-\alpha_L)(1-\varepsilon)kVT - \delta T^* + aL,\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^* - cV.
\end{aligned} \tag{1.1}$$

In (1.1), $\lambda$ is the production rate of uninfected cells, $d_T$ is the death rate coefficient of uninfected cells, $k$ is the infection rate coefficient at which uninfected cells are infected by free virus, and $\varepsilon$ ($0 \le \varepsilon \le 1$) is an overall therapy efficacy. $\alpha_L$ is the proportion of cells progress from uninfected to latently infected, $a$ is the rate coefficient at which latently infected cells translate to actively infected cells, and $d_L$ is the death rate coefficient of latently infected cells. $\delta$ is the death rate coefficient of actively infected cells, $N$ is the number of virus particles produced by an actively infected cell during its life time, and $c$ is the rate coefficient at which free virus is cleared.

Noting that in system (1.1), the cytotoxic T-lymphocyte (CTL) immune response is ignored. Faced with viral infection, the immune system has a strong CTL immune response, which attacks actively infected cells to reduce viral load and protect infected individuals from virus-related diseases [14, 15]. In addition, it is noteworthy that the generation of CTL cells at time $t$ may depend on the number of actively infected cells at time $t-\tau$, where the nonnegative constant $\tau$ represents a time delay of CTL immune response. Accordingly, a large number of HIV infection models with CTL immune response given by delay differential equations have been studied by several scholars, mainly focusing on the effect of time delay on the dynamics of the model, bifurcations, and several complex dynamical behaviors (see, for example, [16–18]). In [17], Wang et al. proposed a viral model with delayed immune response, where the specific expression of CTL cells is as follows:

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

in which $y$ and $z$ represent the numbers of actively infected cells and CTL cells, respectively. The parameters $c$ and $b$ are the coefficients of proliferation rate and dacay rate of CTL cells, respectively.

Furthermore, in most viral infection models, it is assumed that the presence of antigen can only simulate the immune response, and ignore the immune impairment. In fact, several human pathogens have the ability to suppress immune responses, allowing them to establish a persistent and productive infection that eventually lead to diseases [19–21]. Under this assumption, many researchers have carried out further researches on HIV infection [22–24], which helps us to understand the biological interactions between virus and immune system. In [24], Wang et al. considered a delayed viral model with immune impairment, where the specific expression of CTL cells is as follows:

$$\dot{z}(t) = cy(t-\tau) - bz(t) - myz.$$

Motivated by the works of Rong et al. [13] and Wang et al. [24], in the present paper, we are concerned with the joint effects of latent reservoir, delayed CTL immune response and immune

impairment on the transmission dynamics of HIV infection. To this end, we consider the following delay differential equations:

$$\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - dx(t) - \beta x(t)v(t),\\
\frac{\mathrm{d}u(t)}{\mathrm{d}t} &= q\beta x(t)v(t) - (\mu+\delta)u(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= (1-q)\beta x(t)v(t) + \delta u(t) - ay(t) - py(t)z(t),\\
\frac{\mathrm{d}v(t)}{\mathrm{d}t} &= Nay(t) - \sigma v(t),\\
\frac{\mathrm{d}z(t)}{\mathrm{d}t} &= cy(t-\tau) - bz(t) - my(t)z(t).
\end{aligned} \tag{1.2}$$

In [25], Wodarz et al. found that the decay rate of free virus is much faster than that of infected cells. This allows us to make a quasi steady-state assumption: $dv/dt = 0$, which implies $v = Nay/\sigma$, in other words, the number of free virus is proportional to the number of actively infected cells. Therefore, the number of actively infected cells $y(t)$ can also be considered as a measure of free virus $v(t)$, then system (1.2) can be described as the following system:

$$\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - dx(t) - \beta x(t)y(t),\\
\frac{\mathrm{d}u(t)}{\mathrm{d}t} &= q\beta x(t)y(t) - (\mu+\delta)u(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= (1-q)\beta x(t)y(t) + \delta u(t) - ay(t) - py(t)z(t),\\
\frac{\mathrm{d}z(t)}{\mathrm{d}t} &= cy(t-\tau) - bz(t) - my(t)z(t),
\end{aligned} \tag{1.3}$$

where the descriptions of all variables and parameters in system (1.3) are shown in Table 1, and values of all parameters are positive constants.

For system (1.3), the suitable phase space is $\mathbb{R}\times\mathbb{R}\times C\times\mathbb{R}$, where $C = C([-\tau,0],\mathbb{R})$ is the Banach space of all continuous functions mapping the interval $[-\tau,0]$ into $\mathbb{R}$, with norm $\|\phi\| = \sup_{-\tau\le\theta\le 0}|\phi(\theta)|$ for $\phi\in C$. The nonnegative cone of $C$ is $C^+ = C([-\tau,0],\mathbb{R}_+)$. The initial condition for system (1.3) takes the form

$$\begin{aligned}
&x(\theta) = \varphi_1(\theta), \quad u(\theta) = \varphi_2(\theta), \quad y(\theta) = \varphi_3(\theta), \quad z(\theta) = \varphi_4(\theta),\\
&\varphi_i(\theta) \ge 0, \quad \theta\in[-\tau,0), \quad \varphi_i(0) > 0, \quad i = 1,2,3,4.
\end{aligned} \tag{1.4}$$

It is well-known by the fundamental theory of functional differential equations [26], system (1.3) has a unique solution $(x(t),u(t),y(t),z(t))$ satisfying initial condition (1.4).

The organization of this paper is as follows. In section 2, we show the positivity and boundedness of solutions of system (1.3), and establish the existence of feasible equilibria of system (1.3). In section 3, we investigate the global asymptotic stability of each of feasible equilibria. In section 4, we verify that system (1.3) is permanent if the immunity-activated equilibrium exists. In section 5, we establish the existence of Hopf bifucation at the immune-activated equilibrium. In section 6, we present numerical

simulation to illustrate the theoretical results, and explore the effects of some key parameters on viral dynamics by sensitivity analysis. The paper ends with a brief conclusion in section 7.

**Table 1.** The descriptions of all variables and parameters in system (1.3).

| Variables | Biological meaning |
|---|---|
| $x(t)$ | The number of uninfected $CD4^+$ T cells at time $t$ |
| $u(t)$ | The number of latently infected $CD4^+$ T cells at time $t$ |
| $y(t)$ | The number of actively infected $CD4^+$ T cells at time $t$ |
| $z(t)$ | The number of CTL cells at time $t$ |
| Parameters | Biological meaning |
| $\lambda$ | The production rate of uninfected cells |
| $d$ | The nature death rate coefficient of uninfected cells |
| $\beta$ | The infectious transmissibility coefficient |
| $q$ | The proportion of cells progress from uninfected to latently infected |
| $\mu$ | The natural death rate coefficient of latently infected cells |
| $\delta$ | The rate coefficient at which latently infected cells translate to actively infected cells |
| $a$ | The natural death rate coefficient of actively infected cells |
| $p$ | The remove rate coefficient of actively infected cells due to CTL immune responses |
| $\tau$ | The time delay of CTL immune response |
| $c$ | The proliferation rate coefficient of CTL cells |
| $b$ | The dacay rate coefficient of CTL cells |
| $m$ | The rate coefficient of immune impairment |

## 2. Preliminaries

In this section, we demonstrate that system (1.3) with initial condition (1.4) is well-posed, and establish the existence of feasible equilibria.

### *2.1. Positivity and boundedness of solutions*

**Theorem 2.1.** *All solutions of system* (1.3) *with initial condition* (1.4) *are defined on* $[0, +\infty)$ *and remain positive for all* $t \geq 0$ *in* $\mathbb{R} \times \mathbb{R} \times C \times \mathbb{R}$.

**Proof**. Firstly, we prove that $x(t)$ is positive for all $t \geq 0$. Assume the contrary and let $t_1 > 0$ be the first time such that $x(t_1) = 0$. Then from the first equation of system (1.3), we have $\dot{x}(t_1) = \lambda > 0$, which indicates that $x(t) < 0$ for $t \in (t_1 - \varepsilon_1, t_1)$, where $\varepsilon_1$ is an arbitrarily small positive constant. This contradicts with the fact of $x(t) > 0$ for all $t \in [0, t_1)$. It follows that $x(t) > 0$ for all $t \geq 0$.

Similarly, we show that $u(t)$, $y(t)$ and $z(t)$ are positive for all $t \geq 0$. Assume the contrary and let $t_2 > 0$ be the first time such that $y(t_2) = 0$. Then from the third equation of system (1.3), we have $\dot{y}(t_2) = \delta u(t_2)$. Solving $u(t)$ in the second equation of system (1.3), we obtain

$$u(t_2) = \left(\varphi_2(0) + q\beta \int_0^{t_2} x(s)y(s)e^{(\mu+\delta)s}\mathrm{d}s\right) e^{-(\mu+\delta)t_2} > 0,$$

which yields $\dot{y}(t_2) > 0$. It follows that $y(t) > 0$ for all $t \geq 0$. Accordingly, from the second and fourth equations of system (1.3), we get

$$u(t) = \left(\varphi_2(0) + q\beta \int_0^t x(s)y(s)e^{(\mu+\delta)s}\mathrm{d}s\right)e^{-(\mu+\delta)t} > 0,$$

and

$$z(t) = \varphi_4(0)e^{-\int_0^t (b+my(s))\mathrm{d}s} + c\int_0^t y(\xi-\tau)e^{-\int_\xi^t (b+my(s))\mathrm{d}s}\mathrm{d}\xi > 0,$$

respectively. This completes the proof.

**Theorem 2.2.** *Any positive solution of system* (1.3) *is ultimately bounded, and the following set*

$$\Omega = \left\{(x,u,y,z) \in \mathbb{R}_+ \times \mathbb{R}_+ \times C^+ \times \mathbb{R}_+ : \|x+u+y\| \leq \frac{\lambda}{\min\{d,\mu,a\}},\ \|z\| \leq \frac{c\lambda}{b\min\{d,\mu,a\}}\right\},$$

*is positively invariant for system* (1.3).

**Proof**. Define $B(t) = x(t)+u(t)+y(t)$. Calculating the derivative of $B(t)$ in respect to $t$ along positive solution of system (1.3), it follows that

$$\dot{B}(t) = \lambda - dx(t) - \mu u(t) - ay(t) - py(t)z(t) \leq \lambda - \min\{d,\mu,a\}B(t),$$

which yields

$$\begin{aligned}\limsup_{t\to+\infty} B(t) &\leq \frac{\lambda}{\min\{d,\mu,a\}}\\ &= \text{Production rate of uninfected CD4}^+ \text{ T cells}\\ &\quad \times \max\{\text{Lifespan of uninfected, latently infected or actively infected CD4}^+ \text{ T cells}\}.\end{aligned}$$

Hence, for $\varepsilon > 0$ sufficiently small, there is a $T_1 > 0$ such that if $t > T_1$,

$$x(t) + u(t) + y(t) = B(t) \leq \frac{\lambda}{\min\{d,\mu,a\}} + \varepsilon.$$

Furthermore, we derive from the fourth equation of system (1.3), for $t > T_1 + \tau$,

$$\dot{z}(t) = cy(t-\tau) - bz(t) - my(t)z(t) \leq \frac{c\lambda}{\min\{d,\mu,a\}} + c\varepsilon - bz(t),$$

which yields

$$\limsup_{t\to+\infty} z(t) \leq \frac{c\lambda}{b\min\{d,\mu,a\}} + \frac{c\varepsilon}{b}.$$

Since this inequality holds true for arbitrary $\varepsilon > 0$ sufficiently small, we conclude that

$$\limsup_{t\to+\infty} z(t) \leq \frac{c\lambda}{b\min\{d,\mu,a\}}.$$

Therefore, $x(t)$, $u(t)$, $y(t)$ and $z(t)$ are uniformly ultimately bounded. This completes the proof.

*2.2. Reproduction ratio and feasible equilibria*

System (1.3) is an autonomous differential equation system with a fixed time delay. It always admits a unique infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$, where $x_0 = \lambda/d$. In the following, applying the method in Diekmann et al. [27] and van den Driessche et al. [28], we compute the immunity-inactivated reproduction ratio $\mathcal{R}_0$ of system (1.3).

The infected compartments in system (1.3) are $u$ and $y$, ordered $(u, y)$. The nonlinear terms with new infection $\mathcal{F}$ and the outflow term $\mathcal{V}$ are given by

$$\mathcal{F} = \begin{pmatrix} q\beta xy \\ (1-q)\beta xy \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\mu+\delta)u \\ -\delta u + ay + pyz \end{pmatrix}.$$

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

$$F = \begin{pmatrix} 0 & \frac{q\beta\lambda}{d} \\ 0 & \frac{(1-q)\beta\lambda}{d} \end{pmatrix}, \quad V = \begin{pmatrix} \mu+\delta & 0 \\ -\delta & a \end{pmatrix}.$$

Therefore, we obtain the following next-generation matrix

$$FV^{-1} = \begin{pmatrix} \frac{q\beta\lambda\delta}{ad(\mu+\delta)} & \frac{q\beta\lambda}{ad} \\ \frac{(1-q)\beta\lambda\delta}{ad(\mu+\delta)} & \frac{(1-q)\beta\lambda}{ad} \end{pmatrix}.$$

One of the eigenvalues of matrix $FV^{-1}$ is 0, the other one gives the immunity-inactivated reproduction ratio of system (1.3)

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{(1-q)\beta\lambda}{ad} + \frac{q\beta\lambda\delta}{ad(\mu+\delta)},$$

where $\rho(FV^{-1})$ denotes the spectral radius of matrix $FV^{-1}$. Besides, $\mathcal{R}_0$ represents the number of newly actively infected CD4$^+$ T cells generated from one actively infected CD4$^+$ T cell in a totally susceptible cells during its lifespan.

It is easy to see that if $\mathcal{R}_0 > 1$, in addition to the equilibrium $E_0$, system (1.3) has an immunity-activated equilibrium $E^* = (x^*, u^*, y^*, z^*)$, where

$$x^* = \frac{\lambda}{d+\beta y^*}, \quad u^* = \frac{q\beta\lambda y^*}{(\mu+\delta)(d+\beta y^*)}, \quad z^* = \frac{cy^*}{b+my^*},$$

and $y^*$ is a unique positive real root of the following algebraic equation:

$$A_1 y^2 + A_2 y + A_3 = 0,$$

in which

$$\begin{aligned} A_1 &= \beta(\mu+\delta)(am+pc) > 0, \\ A_2 &= mad(\mu+\delta)(1-\mathcal{R}_0) + (\mu+\delta)(ab\beta + dpc), \\ A_3 &= bad(\mu+\delta)(1-\mathcal{R}_0) < 0. \end{aligned}$$

## 3. Global stability

In this section, by using suitable Lyapunov functionals and LaSalle's invariance principle, we are concerned with the global asymptotic stability of each of feasible equilibria to system (1.3).

**Theorem 3.1.** *If $\mathcal{R}_0 \leq 1$, then the infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$ of system* (1.3) *is globally asymptotically stable for any time delay $\tau \geq 0$.*

**Proof**. Let $(x(t), u(t), y(t), z(t))$ be any positive solution of system (1.3) with initial condition (1.4). Define

$$W_1(t) = x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0} + \frac{\delta}{\mu(1-q)+\delta} u(t) + \frac{\mu+\delta}{\mu(1-q)+\delta} y(t) + \frac{\varepsilon}{c} z(t) + \varepsilon \int_{t-\tau}^{t} y(\theta) d\theta, \tag{3.1}$$

where $\varepsilon = \frac{\beta\lambda}{d}\left(\frac{1}{\mathcal{R}_0} - 1\right) \geq 0$ and $\lambda = dx_0$. Calculating the derivative of $W_1(t)$ along positive solutions of system (1.3), it follows that

$$\begin{aligned} \dot{W}_1(t) =& -\frac{d}{x(t)}(x(t) - x_0)^2 - \frac{\beta\lambda}{d}\left(\frac{1}{\mathcal{R}_0} - 1 - \frac{\varepsilon d}{\beta\lambda}\right) y(t) - \frac{\varepsilon b}{c} z(t) - \left(\frac{p(\mu+\delta)}{\mu(1-q)+\delta} + \frac{\varepsilon m}{c}\right) y(t) z(t) \\ =& -\frac{d}{x(t)}(x(t) - x_0)^2 - \frac{\varepsilon b}{c} z(t) - \left(\frac{p(\mu+\delta)}{\mu(1-q)+\delta} + \frac{\varepsilon m}{c}\right) y(t) z(t). \end{aligned} \tag{3.2}$$

It follows from (3.2) that $W_1'(t) \leq 0$. By Theorem 5.3.1 in reference [29], solutions limit to $\mathcal{M}_1$, the largest invariant subset of $\{(x(t), u(t), y(t), z(t)) : W_1'(t) = 0\}$. Clearly, we see from (3.2) that $W_1'(t) = 0$ if and only if $x = x_0$ and $z = 0$. Noting that $\mathcal{M}_1$ is invariant, for each element in $\mathcal{M}_1$, we have $x(t) = x_0$ and $z(t) = 0$. It follows from the first equation of system (1.3) that $0 = x'(t) = -\beta x_0 y(t)$, which yields $y(t) = 0$. Furthermore, it follows from the third equation of system (1.3) that $0 = y'(t) = \delta u(t)$, which leads to $u(t) = 0$. Hence, $W_1'(t) = 0$ if and only if $x(t) = x_0$, $u(t) = 0$, $y(t) = 0$ and $z(t) = 0$. Accordingly, $E_0$ is globally asymptotically stable follows from LaSalle's invariance principle. This completes the proof.

**Theorem 3.2.** *If $\mathcal{R}_0 > 1$, then the equilibrium $E_0$ is unstable and the immunity-activated equilibrium $E^* = (x^*, u^*, y^*, z^*)$ of system* (1.3) *is globally asymptotically stable when $\tau = 0$.*

**Proof**. The characteristic equation of system (1.3) at the equilibrium $E_0$ is

$$(s+d)(s+b)\left[s^2 + \left(\mu + \delta + a + \frac{(q-1)\beta\lambda}{d}\right) s + a(\mu+\delta)(1-\mathcal{R}_0)\right] = 0. \tag{3.3}$$

It is clear that (3.3) always has two negative real roots $\lambda_1 = -d$, $\lambda_2 = -b$, and other roots are determined by the following equation:

$$f(s) = s^2 + \left(\mu + \delta + a + \frac{(q-1)\beta\lambda}{d}\right) s + a(\mu+\delta)(1-\mathcal{R}_0) = 0. \tag{3.4}$$

If $\mathcal{R}_0 > 1$, it is easy to see that

$$f(0) = a(\mu+\delta)(1-\mathcal{R}_0) < 0 \quad \text{and} \quad \lim_{s\to+\infty} f(s) = +\infty.$$

Noting that $f(s)$ is a continuous function in respect to $s$, so (3.4) has at least one positive real root. Accordingly, (3.3) has at least one positive real root, and $E_0$ is unstable.

Let $(x(t), u(t), y(t), z(t))$ be any positive solution of system (1.3) with initial condition (1.4). Define

$$\begin{aligned} W_2(t) =& x(t) - x^* - x^* \ln \frac{x(t)}{x^*} + \frac{\delta}{\mu(1-q)+\delta}\left(u(t) - u^* - u^* \ln \frac{u(t)}{u^*}\right) \\ &+ \frac{\mu+\delta}{\mu(1-q)+\delta}\left(y(t) - y^* - y^* \ln \frac{y(t)}{y^*}\right) + \frac{\mu+\delta}{\mu(1-q)+\delta}\frac{p}{2(c-mz^*)}(z(t)-z^*)^2. \end{aligned} \tag{3.5}$$

Calculating the derivative of $W_2(t)$ along positive solutions of system (1.3), it follows that

$$\begin{aligned} \dot{W}_2(t) =& \left(1 - \frac{x^*}{x(t)}\right)(\lambda - dx(t) - \beta x(t)y(t)) \\ &+ \frac{\delta}{\mu(1-q)+\delta}\left(1 - \frac{u^*}{u(t)}\right)(q\beta x(t)y(t) - (\mu+\delta)u(t)) \\ &+ \frac{\mu+\delta}{\mu(1-q)+\delta}\left(1 - \frac{y^*}{y(t)}\right)((1-q)\beta x(t)y(t) + \delta u(t) - ay(t) - py(t)z(t)) \\ &+ \frac{(\mu+\delta)}{\mu(1-q)+\delta}\frac{p}{c-mz^*}(z(t)-z^*)(cy(t) - bz(t) - my(t)z(t)). \end{aligned} \tag{3.6}$$

On substituting

$$\begin{aligned} &\lambda = dx^* + \beta x^* y^*, \\ &(\mu+\delta)u^* = q\beta x^* y^*, \\ &ay^* = (1-q)\beta x^* y^* + \delta u^* - py^* z^*, \\ &cy^* = bz^* + my^* z^* \end{aligned} \tag{3.7}$$

into (3.6), we have

$$\begin{aligned} \dot{W}_2(t) =& -\frac{d}{x(t)}(x(t)-x^*)^2 + \frac{(\mu+\delta)(1-q)\beta x^* y^*}{\mu(1-q)+\delta}\left(2 - \frac{x^*}{x(t)} - \frac{x(t)}{x^*}\right) \\ &+ \frac{\delta q\beta x^* y^*}{\mu(1-q)+\delta}\left(3 - \frac{x^*}{x(t)} - \frac{y^*}{y(t)}\frac{u(t)}{u^*} - \frac{x(t)}{x^*}\frac{y(t)}{y^*}\frac{u^*}{u(t)}\right) \\ &- \frac{\mu+\delta}{\mu(1-q)+\delta}\frac{p}{c-mz^*}(b+my(t))(z(t)-z^*)^2. \end{aligned} \tag{3.8}$$

It follows from (3.8) that $W_2'(t) \le 0$. By Theorem 5.3.1 in reference [29], solutions limit to $\mathcal{M}_2$, the largest invariant subset of $\{(x(t), u(t), y(t), z(t)) : W_2'(t) = 0\}$. Clearly, we see from (3.8) that $W_2'(t) = 0$ if and only if $x = x^*$, $u = u^*$, $y = y^*$ and $z = z^*$. Accordingly, the global asymptotic stability of $E^*$ follows from LaSalle's invariance principle. This completes the proof.

## 4. Permanence

In this section, we explore the permanence of system (1.3) referring to the persistence theory on infinite dimensional systems developed by Hale and Waltman [30].

Let $X$ be a complete metric space with metric d. Assume that $T$ is a continuous mapping from $[0, +\infty) \times X$ into $X$ with the following properties:

$$T_t \circ T_s = T_{t+s}, \quad T_0(x) = x, \quad t, s \geq 0, \quad x \in X,$$

where $T_t(x) = T(t, x)$. The distance $\mathrm{d}(x, Y)$ from a point $x \in X$ to a subset $Y$ of $X$ is defined by

$$\mathrm{d}(x, Y) = \inf_{y \in Y} \mathrm{d}(x, y).$$

Recall that the positive orbit $\gamma^+(x)$ through $x$ is defined as $\gamma^+(x) = \cup_{t \geq 0} T(t)x$, and its $\omega$-limit set is $\omega(x) = \cap_{s \geq 0} \overline{\cup_{t \geq s} \{T(t)x\}}$. Define $W^s(A)$ the strong stable set of a compact invariant set $A$ as

$$W^s(A) = \{x : x \in X, \omega(x) \neq \emptyset, \omega(x) \subset A\}.$$

Suppose that $X^0$ is an open set in $X$, $X_0 \subset X$, $X^0 \cap X_0 = \varnothing$ and $X^0 \cup X_0 = X$. Moreover, $T(t)$ is a $C_0-$semigroup of $X$ satisfying

$$T(t) : X^0 \longrightarrow X^0, \quad T(t) : X_0 \longrightarrow X_0. \tag{4.1}$$

Let $T_\partial(t) = T(t)|X_0$, and $A_\partial$ be the global attractor for $T_\partial(t)$. The following result is provided.

**Lemma 4.1.** *Suppose that $T(t)$ satisfies* (4.1) *and the following conditions (Hale & Waltman [30]):*

*(i) There is a $t_0 \geq 0$ such that $T(t)$ is compact for $t > t_0$.*

*(ii) $T(t)$ is point dissipative in $X$.*

*(iii) $\widetilde{A_\partial} = \bigcup_{x \in A_\partial} \omega(x)$ is isolated and has an acyclic covering $\widetilde{M}$, where $\widetilde{M} = \{M_1, M_2, \cdots, M_n\}$.*

*(iv) $W^s(M_i) \cap X^0 = \varnothing$, $i = 1, 2, \cdots, n$.*

*Then $X_0$ is a uniform repeller with respect to $X^0$, that is, there is an $\varepsilon_0 > 0$ such that for any $x \in X^0$, $\liminf_{t \to +\infty} d(T(t)x, X_0) \geq \varepsilon_0$, where $d$ is the distance of $T(t)x$ from $X_0$.*

We are now in a position to state and prove our result on the permanence of system (1.3) with initial condition (1.4).

**Theorem 4.1.** *If $\mathcal{R}_0 > 1$, then system* (1.3) *is permanent.*

**Proof**. Let $X = C([-\tau, 0], R^4_{+0})$. Define

$$\begin{aligned} X_0 =& \{(\phi_1, \phi_2, \phi_3, \phi_4) \in C([-\tau, 0], R^4_{+0}) : \phi_1(\theta) \geq 0, \phi_2(\theta) \equiv 0, \phi_3(\theta) \equiv 0, \phi_4(\theta) \equiv 0\}, \\ X^0 =& X/X_0. \end{aligned}$$

It is easy to see that $X^0 \cap X_0 = \varnothing$ and $X^0 \cup X_0 = X$. For any $(\phi_1, \phi_2, \phi_3, \phi_4)$ in $X$, define $T(t)$ for $t \geq 0$ as $T(t)(\phi_1, \phi_2, \phi_3, \phi_4) = (x(t), u(t), y(t), z(t))$, where $(x(t), u(t), y(t), z(t))$ is a solution of system (1.3) with initial condition $(\phi_1, \phi_2, \phi_3, \phi_4)$. Then $\{T(t)\}_{t \geq 0}$ is a $C_0-$semigroup generated by system (1.3). By the definition of $X^0$ and $X_0$, we verify that $X$, $X^0$ and $X_0$ are all positively invariant.

According to Theorem 2.2, we obtain that condition (ii) of Lemma 4.1 is satisfied. Noting that the functions in right side of system (1.3) are in $C^1$ and the solution of system (1.3) with initial condition (1.4) is ultimately bounded, using the smoothing property of solutions of delay differential equations introduced in Kuang (Theorem 2.8) [31], it follows that condition (i) of Lemma 4.1 is satisfied.

Note that system (1.3) admits one boundary equilibrium $E_0 = (\lambda/d, 0, 0, 0)$ in $X_0$. For any solution of system (1.3) with initial condition $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in X_0$, we have $u(t) = 0$, $y(t) = 0$, $z(t) = 0$ and $x(t) \to \lambda/d$ as $t \to \infty$. Hence $\{E_0\}$ contains all $\omega-$limit sets in $X_0$. By Theorem 3.2, $E_0$ is unstable if $\mathcal{R}_0 > 1$. Accordingly, $\{E_0\}$ is isolated and has an acyclic covering satisfying the condition (iii) in Lemma 4.1.

We now show that $W^s(E_0) \cap X^0 = \varnothing$. Assume $W^s(E_0) \cap X^0 \neq \varnothing$. Then there is a positive solution $(x(t), u(t), y(t), z(t))$ with $\lim_{t\to+\infty}(x(t), u(t), y(t), z(t)) = (\lambda/d, 0, 0, 0)$. Since $\mathcal{R}_0 > 1$, we can choose $\varepsilon_1 > 0$ sufficiently small satisfying

$$\frac{\lambda}{d} - \varepsilon_1 > \frac{a(\mu+\delta)}{\beta[(1-q)\mu+\delta]} + \frac{p(\mu+\delta)\varepsilon_1}{\beta[(1-q)\mu+\delta]}. \tag{4.2}$$

For $\varepsilon_1 > 0$ sufficiently small satisfying (4.2), there is a $t_0 > 0$ such that if $t > t_0$, we have

$$x(t) > \frac{\lambda}{d} - \varepsilon_1 \quad \text{and} \quad z(t) \le \varepsilon_1.$$

Hence, it follows from system (1.3) that, for $t > t_0$,

$$\begin{aligned}
\frac{du(t)}{dt} &\ge q\beta\left(\frac{\lambda}{d} - \varepsilon_1\right)y(t) - (\mu+\delta)u(t),\\
\frac{dy(t)}{dt} &\ge (1-q)\beta\left(\frac{\lambda}{d} - \varepsilon_1\right)y(t) + \delta u(t) - ay(t) - p\varepsilon_1 y(t).
\end{aligned}$$

Consider the following auxiliary system

$$\begin{aligned}
\frac{du_1(t)}{dt} &= q\beta\left(\frac{\lambda}{d} - \varepsilon_1\right)y_1(t) - (\mu+\delta)u_1(t),\\
\frac{dy_1(t)}{dt} &= (1-q)\beta\left(\frac{\lambda}{d} - \varepsilon_1\right)y_1(t) + \delta u_1(t) - ay_1(t) - p\varepsilon_1 y_1(t).
\end{aligned} \tag{4.3}$$

Clearly, $(0, 0)$ is the unique equilibrium of system (4.3). The characteristic equation of system (4.3) at the equilibrium $(0, 0)$ is

$$g(s) = s^2 + G_1 s + G_2 = 0,$$

where

$$\begin{aligned}
G_1 &= \mu + \delta + a + p\varepsilon_1 - (1-q)\beta\left(\frac{\lambda}{d} - \varepsilon_1\right),\\
G_2 &= (\mu+\delta)(a+p\varepsilon_1) - \beta\left(\frac{\lambda}{d} - \varepsilon_1\right)((1-q)\mu+\delta).
\end{aligned}$$

It is easy to see that $G_2 < 0$ when $\mathcal{R}_0 > 1$. Accordingly, $g(s) = 0$ has at least one positive root $\lambda^*$. In this case, $u_1 \to \infty$ and $y_1 \to \infty$ as $t \to \infty$. By comparison arguments, it is shown that $u \to \infty$ and $y \to \infty$ as $t \to \infty$. This contradicts $\lim_{t\to+\infty}(x(t), u(t), y(t), z(t)) = (\lambda/d, 0, 0, 0)$. Hence, we have $W^s(E_0) \cap X^0 = \varnothing$ satisfying the condition (iv) in Lemma 4.1. This completes the proof.

## 5. Hopf bifurcation

In this section, we are concerned with the effect of time delay $\tau$ on the stability of the immunity-activated equilibrium $E^* = (x^*, u^*, y^*, z^*)$.

The characteristic equation of system (1.3) at the equilibrium $E^*$ is

$$s^4 + h_3 s^3 + h_2 s^2 + h_1 s + h_0 + (l_2 s^2 + l_1 s + l_0)e^{-s\tau} = 0, \tag{5.1}$$

where

$$\begin{aligned}
h_0 =&\beta^2 x^* y^* (b + my^*)[\delta + (1-q)\mu] - pmy^* z^* (\mu + \delta)(d + \beta y^*),\\
h_1 =&(d + \beta y^*)(b + my^*)\left(\mu + \delta + \frac{\delta u^*}{y^*}\right) + \beta^2 x^* y^* [\delta + (1-q)(\mu + b + my^*)]\\
&- pmy^* z^* (\mu + \delta + d + \beta y^*),\\
h_2 =&(b + d + my^* + \beta y^*)\left(\mu + \delta + \frac{\delta u^*}{y^*}\right) + (d + \beta y^*)(b + my^*) + \beta^2 x^* y^* (1-q) - pmy^* z^*,\\
h_3 =&\mu + \delta + d + b + my^* + \beta y^* + \frac{\delta u^*}{y^*},\\
l_0 =&pcy^* (\mu + \delta)(d + \beta y^*),\\
l_1 =&pcy^* (\mu + \delta + d + \beta y^*),\\
l_2 =&pcy^*.
\end{aligned}$$

When $\tau > 0$, if $s = \mathrm{i}\omega$ ($\omega > 0$) is a root of characteristic equation (5.1), separating real and imaginary parts, we have

$$\begin{aligned}
\omega^4 - h_2\omega^2 + h_0 =& -l_1\omega \sin\omega\tau + (l_2\omega^2 - l_0)\cos\omega\tau,\\
h_3\omega^3 - h_1\omega =&(l_2\omega^2 - l_0)\sin\omega\tau + l_1\omega\cos\omega\tau.
\end{aligned} \tag{5.2}$$

Squaring and adding the two equations of (5.2), it follows that

$$\omega^8 + C_3\omega^6 + C_2\omega^4 + C_1\omega^2 + C_0 = 0, \tag{5.3}$$

where

$$C_0 = h_0^2 - l_0^2, \quad C_1 = h_1^2 + 2l_0l_2 - 2h_0h_2 - l_1^2, \quad C_2 = h_2^2 + 2h_0 - 2h_1h_3 - l_2^2, \quad C_3 = h_3^2 - 2h_2.$$

Letting $z = \omega^2$, (5.3) becomes

$$h(z) = z^4 + C_3 z^3 + C_2 z^2 + C_1 z + C_0 = 0. \tag{5.4}$$

Denote

$$P = \frac{8C_2 - 3C_3^2}{16}, \quad Q = \frac{C_3^3 - 4C_3C_2 + 8C_1}{32}, \quad D_0 = \frac{Q^2}{4} + \frac{P^3}{27},$$

and

$$z_1^* = -\frac{C_3}{4} + \sqrt[3]{-\frac{Q}{2} + \sqrt{D_0}} + \sqrt[3]{-\frac{Q}{2} - \sqrt{D_0}}, \quad D_0 > 0,$$
$$z_2^* = \max\left\{-\frac{C_3}{4} - 2\sqrt[3]{\frac{Q}{2}}, -\frac{C_3}{4} + \sqrt[3]{\frac{Q}{2}}\right\}, \quad D_0 = 0,$$
$$z_3^* = \max\left\{-\frac{C_3}{4} - 2Re\{\xi\}, -\frac{C_3}{4} + 2Re\{\xi\nu\}, -\frac{C_3}{4} + 2Re\{\xi\overline{\nu}\}\right\}, \quad D_0 < 0,$$

where $\nu = (-1 + \sqrt{3}\mathrm{i})/2$ and $\xi$ is one of cubic roots of the complex number $-Q/2 + \sqrt{D_0}$. By [32], we have the following results.

**Lemma 5.1.** *For polynomial equation* (5.4)*, the following conclusions are valid (Yan & Li [32]):*

*(i) If $C_0 < 0$, then* (5.4) *at least has one positive root.*

*(ii) Assume that $C_0 \geq 0$, then* (5.4) *has no positive roots if one of the following conditions holds:*
*(1) $D_0 > 0$ and $z_1^* < 0$;*
*(2) $D_0 = 0$ and $z_2^* < 0$;*
*(3) $D_0 < 0$ and $z_3^* < 0$.*

*(iii) Assume that $C_0 \geq 0$, then* (5.4) *at least has one positive root if one of the following conditions holds:*
*(1) $D_0 > 0$, $z_1^* > 0$ and $h(z_1^*) < 0$;*
*(2) $D_0 = 0$, $z_2^* > 0$ and $h(z_2^*) < 0$;*
*(3) $D_0 < 0$, $z_3^* > 0$ and $h(z_3^*) < 0$.*

Without loss of generality, we assume that (5.4) has four positive real roots, which are denoted as $z_1$, $z_2$, $z_3$ and $z_4$, respectively. Then (5.3) has positive roots $\omega_k = \sqrt{z_k}$ $(k = 1, 2, 3, 4)$. From (5.2) we have

$$\tau_k^{(n)} = \frac{1}{\omega_k}\arccos\left[\frac{(\omega_k^4 - h_2\omega_k^2 + h_0)(l_2\omega_k^2 - l_0) + l_1\omega_k(h_3\omega_k^3 - h_1\omega_k)}{(l_2\omega_k^2 - l_0)^2 + l_1^2\omega_k^2}\right] + \frac{2n\pi}{\omega_k},$$

where $k = 1, 2, 3, 4$ and $n = 1, 2, \cdots$. Therefore, (5.1) has a pair of purely imaginary roots of the form $\pm\omega_k\mathrm{i}$ with $\tau = \tau_k^{(n)}$. Let $s(\tau) = \psi(\tau) + \mathrm{i}\omega(\tau)$ be a root of (5.1) satisfying $\psi(\tau_k^{(n)}) = 0$, $\omega(\tau_k^{(n)}) = \omega_k$. Denote

$$\tau_0 = \min_{k\in\{1,2,3,4\}}\{\tau_k^{(0)}\}, \quad \omega_0 = \omega_{k0}. \tag{5.5}$$

Differentiating (5.1) with respect $\tau$, it follows that

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

Hence, a direct calculation shows that

$$\begin{aligned}\operatorname{sign}\left\{\frac{\mathrm{d}(\mathrm{Re}s)}{\mathrm{d}\tau}\right\}_{s=\mathrm{i}\omega_0} =& \operatorname{sign}\left\{\mathrm{Re}\left(\frac{\mathrm{d}s}{\mathrm{d}\tau}\right)^{-1}\right\}_{s=\mathrm{i}\omega_0}\\ =& \operatorname{sign}\Bigg\{\frac{(h_1-3h_3\omega_0^2)(h_1-h_3\omega_0^2)+(2h_2-4\omega_0^2)(-\omega_0^4+h_2\omega_0^2-h_0)}{(h_1\omega_0-h_3\omega_0^3)^2+(-\omega_0^4+h_2\omega_0^2-h_0)^2}\\ &-\frac{l_1^2+2l_2^2\omega_0^2-2l_0l_2}{l_1^2\omega_0^2+(l_0-l_2\omega_0^2)^2)}\Bigg\}.\end{aligned}$$

We derive from (5.2) that

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

Hence, it follows that

$$\operatorname{sign}\left\{\frac{\mathrm{d}(\mathrm{Re}s)}{\mathrm{d}\tau}\right\}_{s=\mathrm{i}\omega_0}=\operatorname{sign}\left\{\frac{4\omega_0^6+3C_3\omega_0^4+2C_2\omega_0^2+C_1}{l_1^2\omega^2+(l_0-l_2\omega^2)^2)}\right\}=\operatorname{sign}\left\{\frac{h'(\omega_0^2)}{l_1^2\omega_0^2+(l_0-l_2\omega_0^2)^2}\right\}.$$

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

**Theorem 5.1.** *Let $\omega_0$ and $\tau_0$ be defined by* (5.5). *Assumed that $\mathcal{R}_0>1$, we have*

*(i) the equilibrium $E^*$ is locally asymptotically stable for all $\tau\geq 0$ if the condition as stated in Lemma 4.1(ii) is satisfied.*

*(ii) the equilibrium $E^*$ is locally asymptotically stable for $\tau\in[0,\tau_0)$ if the condition as stated in Lemma 4.1(i) or Lemma 4.1(iii) is satisfied.*

*(iii) system* (1.3) *undergoes a Hopf bifurcation at the equilibrium $E^*$ when $\tau=\tau_0$ if the condition as stated in (ii) is satisfied and $h'(\omega_0^2)>0$.*

## 6. Numerical simulation

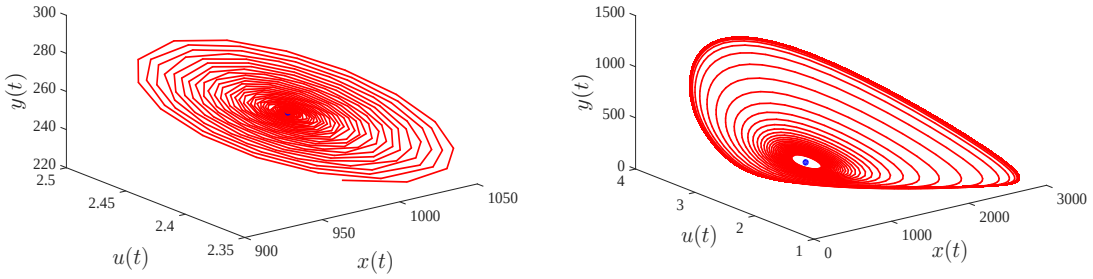
In this section, numerical simulations will be given to illustrate the theoretical results in Theorem 5.1, and sensitivity analysis is used to determine key parameters affecting HIV infection. In addition, parameter values of system (1.3) are listed in Table 2.

**Table 2.** Parameter values of system (1.3) used in numerical simulations.

| Parameters | Values | Units | Sources | Parameters | Values | Units | Sources |
|---|---|---|---|---|---|---|---|
| $\lambda$ | 270 | cells day$^{-1}$ | [24] | $d$ | 0.02 | day$^{-1}$ | [24] |
| $\beta$ | 0.001 | cells$^{-1}$ day$^{-1}$ | Assumed | $q$ | 0.001 | – | [13] |
| $\mu$ | 0.004 | day$^{-1}$ | [13] | $\delta$ | 0.1 | day$^{-1}$ | [13] |
| $a$ | 0.8 | day$^{-1}$ | [24] | $p$ | 0.04 | cells$^{-1}$ day$^{-1}$ | [24] |
| $c$ | 0.025 | day$^{-1}$ | Assumed | $b$ | 0.2 | day$^{-1}$ | Assumed |
| $m$ | 0.005 | cells$^{-1}$ day$^{-1}$ | Assumed | $\tau$ | – | day | Variable |

### 6.1. *Dynamics of system* (1.3)

We choose parameter values as listed in Table 2. By calculation, we get $\mathcal{R}_0 = 16.8744 > 1$, $\omega_0 = 0.4838$, $\tau_0 = 3.7708$ and $h'(\omega_0^2) = 0.0593 > 0$. In this case, Theorem 5.1 ensures that the equilibrium $E^* = (973.1423, 2.4090, 257.4517, 4.3276)$ is locally asymptotically stable if $\tau < \tau_0$, unstable if $\tau > \tau_0$, and system (1.3) undergoes a Hopf bifurcation at $E^*$ when $\tau = \tau_0$. Figure 1 shows the phase diagram of system (1.3) with initial conditions $x(0) = 873.1423$, $u(0) = 1.4090$, $y(0) = 207.4517$ and $z(0) = 3.3276$. It is worth mentioning that the solutions of all variables in system (1.3) are created by the command of dde23 in Matlab. Figure 1(a) shows that the solution of system (1.3) approaches $E^*$ as $t$ goes to infinity when $\tau = 3.5$, and Figure 1(b) illustrates that $E^*$ losses its stability when $\tau = 4$. When $\tau$ varies from 3 to 5, the bifurcation diagram of system (1.3) is shown in Figure 2. From Figure 2, we obtain that the time delay $\tau$ can cause the equilibrium $E^*$ to be unstable when $\tau$ crosses $\tau_0$ to the right. It should be noted that the bifurcation diagram of system (1.3) is created by integrating the differential equation forward in time and plotting the maximum and minimum values of the periodic solutions using Matlab.




(a) $\tau = 3.5 < \tau_0$ (b) $\tau = 4 > \tau_0$

**Figure 1.** The temporal solution found by numerical integration of system (1.3) with initial condition $x(0) = 873.1423$, $u(0) = 1.4090$, $y(0) = 207.4517$, $z(0) = 3.3276$, and parameter values are listed in Table 2, in which (a) $\tau = 3.5 < \tau_0$ and (b) $\tau = 4 > \tau_0$.

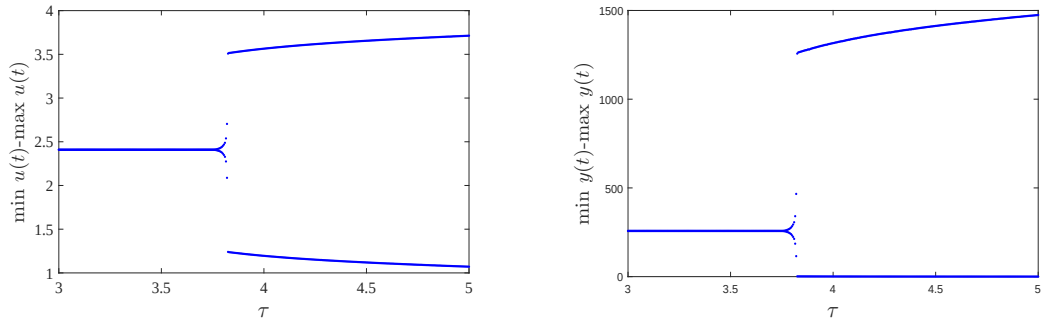



**Figure 2.** The bifurcation diagram of system (1.3) with the initial condition $x(0) = 873.1423$, $u(0) = 1.4090$, $y(0) = 207.4517$, $z(0) = 3.3276$. Parameter $\tau$ varies from 3 to 5, and other parameters are listed in Table 2.

### 6.2. *Sensitivity analysis*

Studies have shown that the new generation of broadly neutralizing anti-HIV antibodies (bNAbs) can suppress new infection by blocking entry of virions, and current inducers can activate the latently infected cells both *in vitro* and *in vivo* [33]. More specifically, in our model, bNAbs mainly influence parameter $\beta$, and inducers affect parameter $\delta$. Therefore, in this subsection, we analyze the effect of parameters $\beta$ and $\delta$ on HIV infection.

From Theorems 3.1, 3.2 and 5.1, the immunity-inactivated reproduction ratio $\mathcal{R}_0$ is a threshold to determined whether actively infected cell dies out or prevails. Hence, we first explore the effects of parameters $\beta$ and $\delta$ on $\mathcal{R}_0$ by Latin hypercube sampling with 1000 samples and Partial Rank Correlation Coefficient (see Figure 3). Figure 3 shows the Partial Rank Correlation Coefficients of $\mathcal{R}_0$ in respect to $\beta$ and $\delta$, which implies that $\beta$ and $\delta$ are both positive correlative variables with $\mathcal{R}_0$, and $\beta$ contributes more to $\mathcal{R}_0$ compared to $\delta$.

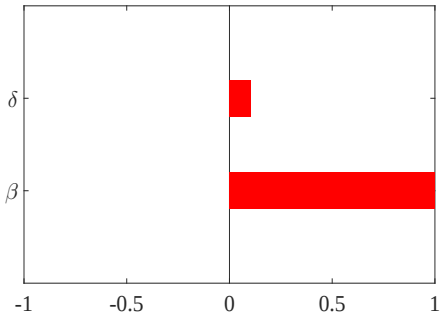
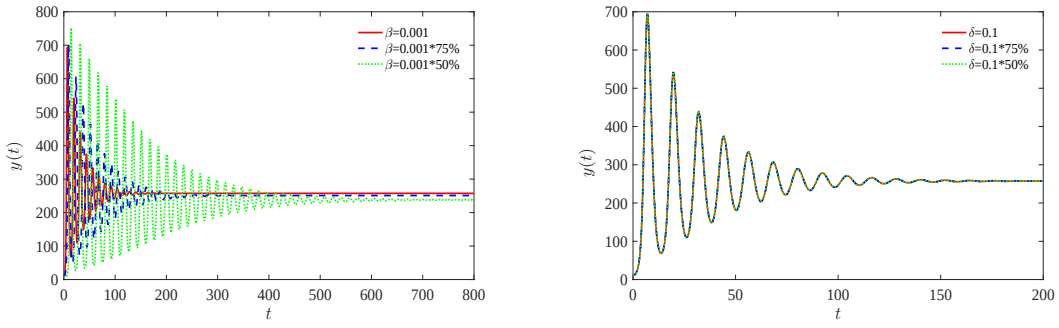



**Figure 3.** The tornado chart of PRCC for coefficients associated with $\mathcal{R}_0$.

Then, we perform the effects of $\beta$ and $\delta$ on the number of actively infected cells by decreasing the same proportion of parameter values (see Figure 4). As shown from Figure 4, decreasing the values of $\beta$ are more conducive to reduce the number of actively infected cells, while the values of $\delta$ has little effect, which is in agreement with Figure 3.




(a) (b)

**Figure 4.** The effects of the parameters $\beta$ and $\delta$ on the number of actively infected cells with initial condition $x(0) = 873.1423$, $u(0) = 1.4090$, $y(0) = 207.4517$, $z(0) = 3.3276$, $\tau = 2.5$ and other parameters are listed in Table 2.

## 7. Conclusions and discussion

In this paper, we consider an HIV infection model with latent reservoir, delayed CTL immune response and immune impairment. Assuming that the number of actively infected cells $y(t)$ can be considered as a measure of free virus $v(t)$, then system (1.2) can be transformed into system (1.3). By a vigorous mathematical analysis, the threshold dynamics of system (1.3) is established and it can be determined by the immunity-inactivated reproduction ratio $\mathcal{R}_0$. If $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0$ of system (1.3) is globally asymptotically stable for any CTL immune delay $\tau \geq 0$. If $\mathcal{R}_0 > 1$, the immunity-activated equilibrium $E^*$ of system (1.3) is globally asymptotically stable when CTL immune delay $\tau = 0$. In addition, we see that a threshold $\tau_0$ for the CTL immune delay was identified to characterize the existence of Hopf bifurcation at the immunity-activated equilibrium $E^*$ when the CTL immune delay cross it. This implies that the introduction of the CTL immune delay $\tau$ plays an important role in destabilizing the the immunity-activated equilibrium and leading to periodic oscillation. Numerical simulations vividly illustrate our main results of stability analysis for system (1.3). In addition, we perform the sensitivity analysis of threshold parameters $\mathcal{R}_0$ and the number of actively infected cells $y$ in respect to the parameters $\beta$ and $\delta$, which provides some suggestions for clinical treatment of HIV-associated diseases.

If the latent reservoir is not considered in our model, then system (1.3) becomes the model proposed in [24], the specific form is as follows:

$$\begin{aligned} \frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - dx(t) - \beta x(t)y(t), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} &= \beta x(t)y(t) - ay(t) - py(t)z(t), \\ \frac{\mathrm{d}z(t)}{\mathrm{d}t} &= cy(t-\tau) - bz(t) - my(t)z(t), \end{aligned} \tag{7.1}$$

where the descriptions of all variables and parameters in system (7.1) are consistent with system (1.3). By calculation, the immunity-inactivated reproduction ratio of system (7.1) is given as $\mathcal{R}_0 = \lambda\beta/(ad)$. Compared with the works in [24], it is found that incorporating the latent reservoir into an in-host HIV infection model could reduce the immunity-inactivated reproduction ratio, but the dynamics of the model does not change. If the latent reservoir and immune impairment are not considered in our model, then system (1.3) becomes the model proposed in [17]. Compared with the works in [17], it is found that the immune delay could cause stable switching even if the latent reservoir and immune impairment are not considered in the HIV infection model.

In addition, studies have found that uninfected cells can be infected through indirect virus-to-cell infection or direct cell-to-cell transmission [34, 35]. Combining both virus-to-cell infection and cell-

to-cell transmission into the model considered in this paper, we obtain the following system

$$\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= \lambda - dx(t) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t),\\
\frac{\mathrm{d}u(t)}{\mathrm{d}t} &= f\beta_1 x(t)v(t) + \eta\beta_2 x(t)y(t) - (\delta+\mu)u(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= (1-f)\beta_1 x(t)v(t) + (1-\eta)\beta_2 x(t)y(t) + \delta u(t) - ay(t) - py(t)z(t),\\
\frac{\mathrm{d}v(t)}{\mathrm{d}t} &= Nay(t) - \sigma v(t),\\
\frac{\mathrm{d}z(t)}{\mathrm{d}t} &= cy(t-\tau) - bz(t) - my(t)z(t).
\end{aligned} \tag{7.2}$$

It may be difficult to study the dynamics of system (7.2) without any assumptions, which is also what we need to break through in the future.

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## Conflict of interest

All authors declare no conflicts of interest in this paper.

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