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Research article

Global stability of an HIV infection model with saturated CTL immune response and intracellular delay

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Abstract: In this paper, we consider an HIV infection model with saturated infection rate, intracellular delay and saturated cytotoxic T lymphocyte (CTL) immune response. By calculation, we obtain immunity-inactivated reproduction number \mathscr{R}_0 and immunity-activated reproduction number \mathscr{R}_1 . By analyzing the distribution of roots of the corresponding characteristic equations, we study the local stability of an infection-free equilibrium, an immunity-inactivated equilibrium and an immunity-activated equilibrium of the model. By constructing suitable Lyapunov functionals and using LaSalle's invariance principle, we show that if $\mathscr{R}_0 < 1$, the infection-free equilibrium is globally asymptotically stable; If $\mathscr{R}_1 < 1 < \mathscr{R}_0$, the immunity-inactivated equilibrium is globally asymptotically stable; If $\mathscr{R}_1 > 1$, the immunity-activated equilibrium is globally asymptotically stable; If $\mathscr{R}_1 > 1$, the immunity-activated equilibrium is globally asymptotically stable. Sensitivity analyses are carried out to show the effects of parameters on the immunity-activated reproduction number \mathscr{R}_1 and the viral load.

Keywords: saturated infection rate; intracellular delay; saturated CTL immune response; global stability; Lyapunov functional

1. Introduction

Mathematical modeling and analysis of HIV pathogenesis are crucial in understanding the transmission mechanism of HIV. Many authors are interested in studying the global stability of HIV infection models (see, for example, [1–4]). In addition, the analysis of mathematical models contributes to developing new antiviral drugs and designing effective therapies for HIV infection (see, for example, [5–7]). Since cytotoxic T lymphocytes (CTLs) play a significant role in the within-host anti-HIV defense by attacking infected cells in HIV infection, in 1996, Nowak and Bangham [8] proposed the following HIV model describing the interaction between host cells, free viruses and CTLs:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \dot{v}(t) &= ky(t) - uv(t), \\ \dot{z}(t) &= cy(t)z(t) - bz(t). \end{aligned}$$

$$(1.1)$$

Here, x(t), y(t), v(t) and z(t) are the concentrations of uninfected cells, infected cells, free viruses and CTLs at time *t*, respectively. The parameter λ denotes the production rate of uninfected cells. Uninfected cells, infected cells, free viruses and CTLs die at rate dx(t), ay(t), uv(t) and bz(t), respectively. The term $\beta x(t)v(t)$ is the rate at which uninfected cells are infected by free viruses, and the term py(t)z(t) represents the rate for infected cells to be killed by CTLs. Free viruses are released from infected cells at rate ky(t) and CTL immune response is activated by infected cells at rate cy(t)z(t).

We note that system (1.1) assumes that CTL immune response is activated at bilinear rate. However, in [9], De Boer suggested that bilinear rate cannot model several immune responses that are together controlling a chronic infection, and proposed immune response functions with saturation effect. In [10], Jiang and Wang considered saturated immune response function cy(t)z(t)/(h+z(t)) to replace the bilinear rate, here *h* is a saturation constant.

It is assumed in system (1.1) that as soon as the free viruses enter a target cell, the target cell is immediately infected and new free viruses are produced simultaneously. In [11], a mathematical model with the intracellular phase of the viral life-cycle was first proposed by Herz et al. There is a fixed time delay τ between infection of a cell and production of new free viruses. Some researchers have incorporated the intracellular delay into HIV infection models and investigated the effect of the intracellular delay on HIV infection dynamics (see, for example, [12–15]).

On the other hand, system (1.1) assumes that the infection rate of virus-to-cell is bilinear. In fact, however, in [16], Ebert et al. observed a nonlinear relationship between parasite dose and infection rate in experiments. Furthermore, in [17], Regoes et al. showed that the infection rate is a sigmoidal function. In [18], Song and Neumann considered the infection rate with saturation effect, $\beta x v^p / (1 + \alpha v^q)$, where *p*, *q* and α are positive constants, and investigated the global stability of the viral model with saturated infection rate $\beta x v / (1 + \alpha v)$.

Inspired by the biological reasons mentioned above, in this paper, we study the effect of saturated infection rate, intracellular delay and saturated CTL immune response on the dynamics of HIV infection. To this end, we consider the following delay differential equations:

$$\dot{x}(t) = \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)},$$

$$\dot{y}(t) = \frac{\beta e^{-m\tau} x(t - \tau)v(t - \tau)}{1 + \alpha v(t - \tau)} - ay(t) - py(t)z(t),$$

$$\dot{v}(t) = ky(t) - uv(t),$$

$$\dot{z}(t) = \frac{cy(t)z(t)}{h + z(t)} - bz(t).$$

(1.2)

Here, τ denotes the time between viral entry into a cell and production of free viruses; $e^{-m\tau}$ is the probability of cellular survival from time $t - \tau$ to time t. All parameters of system (1.2) are positive constants.

We assume that the initial condition of system (1.2) satisfies:

$$\begin{aligned} x(\theta) &= \phi_1(\theta), \ y(0) = y^0 > 0, \ v(\theta) = \phi_2(\theta), \ z(0) = z^0 > 0, \\ \phi_1(\theta) &\ge 0, \ \phi_2(\theta) \ge 0, \ \theta \in [-\tau, 0), \ \phi_i(0) > 0 \ (i = 1, 2), \end{aligned}$$
(1.3)

where $(\phi_1(\theta), \phi_2(\theta)) \in \mathbb{C}([-\tau, 0], \mathbb{R}^2_{+0}), \mathbb{R}^2_{+0} = \{(x_1, x_2) : x_i \ge 0, i = 1, 2\}.$

According to the basic theory of functional differential equations [19], we can prove that system (1.2) has a unique solution (x(t), y(t), v(t), z(t)) that satisfies the initial condition (1.3). Furthermore, it is easy to show that under the initial condition (1.3), all solutions of system (1.2) are defined on $[0, +\infty)$ and are positive for all $t \ge 0$.

The main goal of this paper is to make a complete mathematical analysis of system (1.2) and investigate its dynamical behaviors. This paper is organized as follows. In the next section, we calculate the reproduction numbers of system (1.2) and discuss the existence of feasible equilibria. In Section 3, we study the local asymptotic stability of each of feasible equilibria. The global asymptotic stability of each of feasible equilibria is investigated in Section 4. In Section 5, we perform sensitivity analyses to illustrate the effects of parameters on the immunity-activated reproduction number \Re_1 and the viral load.

2. Equilibria and reproduction numbers

It is clear that system (1.2) always admits an infection-free equilibrium $E_0(\lambda/d, 0, 0, 0)$.

Now, we calculate the immunity-inactivated reproduction number of system (1.2). According to the method of next generation matrix proposed by van den Driessche and Watmough [20], we have

$$\mathcal{F} = \begin{pmatrix} \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} ay(t) + py(t)z(t) \\ -ky(t) + uv(t) \end{pmatrix}.$$

Sequentially, we obtain that

$$F = \begin{pmatrix} 0 & \frac{\beta\lambda e^{-m\tau}}{d} \\ 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} a & 0 \\ -k & u \end{pmatrix}.$$

Hence the next generation matrix is

$$FV^{-1} = \begin{pmatrix} \frac{\beta k \lambda e^{-m\tau}}{aud} & \frac{\beta \lambda e^{-m\tau}}{ud} \\ 0 & 0 \end{pmatrix}.$$

We therefore derive the immunity-inactivated reproduction number

$$\mathscr{R}_0 = \rho(FV^{-1}) = \frac{\beta k \lambda e^{-m\tau}}{aud},$$

representing the number of second infected cells produced by a infective cell in a whole susceptible population [20]. It is easy to prove that if $\Re_0 > 1$, system (1.2) has a unique immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0)$, here

$$x_1 = \frac{\lambda(u + \alpha k y_1)}{d(u + \alpha k y_1) + \beta k y_1}, \quad v_1 = \frac{k y_1}{u}, \quad y_1 = \frac{u d(\mathscr{R}_0 - 1)}{k(\alpha d + \beta)}.$$

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$$\mathscr{R}_1 = \frac{cud(\mathscr{R}_0 - 1)}{bkh(\alpha d + \beta)},$$

where \mathscr{R}_1 is called immunity-activated reproduction number of system (1.2). Besides, we can show that if $\mathscr{R}_1 > 1$, system (1.2) has an immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2)$, where

$$x_2 = \frac{(a+pz_2)(cu+\alpha bk(h+z_2))}{c\beta ke^{-m\tau}}, \quad y_2 = \frac{b(h+z_2)}{c}, \quad v_2 = \frac{bk(h+z_2)}{cu},$$

and

$$z_2 = \frac{-(bk(\alpha d + \beta)(a + hp) + cdpu) + \sqrt{\Delta}}{2bpk(\alpha d + \beta)}$$

here,

$$\Delta = (bk(\alpha d + \beta)(a + hp) + cdpu)^2 + 4ab^2k^2hp(\alpha d + \beta)^2(\mathscr{R}_1 - 1).$$

3. Local asymptotic stability

In this section, we study the local dynamics of system (1.2).

Theorem 3.1. If $\mathscr{R}_0 < 1$, the infection-free equilibrium $E_0(\lambda/d, 0, 0, 0)$ of system (1.2) is locally asymptotically stable; if $\mathscr{R}_0 > 1$, E_0 is unstable.

Proof. By calculation, we have the following characteristic equation of system (1.2) at E_0 :

$$(\xi+b)(\xi+d)\left[(\xi+a)(\xi+u) - \frac{\beta k\lambda e^{-(m+\xi)\tau}}{d}\right] = 0.$$
 (3.1)

Clearly, Eq. (3.1) has negative real roots $\xi = -b$ and $\xi = -d$, and other roots are governed by the following equation:

$$(\xi + a)(\xi + u) - \frac{\beta k \lambda e^{-(m+\xi)\tau}}{d} = 0.$$
 (3.2)

Substituting \mathscr{R}_0 into Eq. (3.2), we can rewrite (3.2) as

$$\left(\frac{\xi}{a}+1\right)\left(\frac{\xi}{u}+1\right) = \mathscr{R}_0 e^{-\xi\tau}.$$
(3.3)

Next, we verify that all roots of Eq. (3.3) have negative real parts. By contradiction, let $\xi_1 = \text{Re}\xi_1 + i\text{Im}\xi_1$ with $\text{Re}\xi_1 \ge 0$ be a root of Eq. (3.3). It follows that

$$\left|\frac{\xi_1}{a} + 1\right| \ge 1 > \mathscr{R}_0, \quad \left|\frac{\xi_1}{u} + 1\right| \ge |e^{-\xi_1 \tau}|$$

Further, we have

$$\left| \left(\frac{\xi_1}{a} + 1 \right) \left(\frac{\xi_1}{u} + 1 \right) \right| > |\mathscr{R}_0 e^{-\xi_1 \tau}|,$$

which contradicts (3.3). Hence, we conclude that if $\mathscr{R}_0 < 1$, all roots of Eq. (3.1) have negative real parts. Accordingly, E_0 is locally asymptotically stable. On the other hand, if $\mathscr{R}_0 > 1$, we denote

$$G(\xi) = (\xi + a)(\xi + u) - \frac{\beta k \lambda e^{-(m+\xi)\tau}}{d}.$$
(3.4)

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It is easy to see that $G(0) = au(1 - \Re_0) < 0$ and $G(\xi) \to +\infty$ as $\xi \to +\infty$. Noting that $G(\xi)$ is a continuous function in respect to ξ , it follows that if $\Re_0 > 1$, Eq. (3.1) has a positive real root. Thus, E_0 is unstable.

Theorem 3.2. If $\mathscr{R}_1 < 1 < \mathscr{R}_0$, the immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0)$ of system (1.2) is locally asymptotically stable.

Proof. By calculation, we have the following characteristic equation of system (1.2) at E_1 :

$$\left[\xi - (\frac{cy_1}{h} - b)\right] \left[\left(\xi + d + \frac{\beta v_1}{1 + \alpha v_1}\right) (\xi + a) (\xi + u) - \frac{\beta k x_1 e^{-(m + \xi)\tau}}{(1 + \alpha v_1)^2} (\xi + d) \right] = 0.$$
(3.5)

Since

$$\mathscr{R}_1 = \frac{1}{b}(\frac{cy_1}{h} - b) + 1 < 1, \tag{3.6}$$

Eq. (3.5) has a negative real root $\xi = \frac{cy_1}{h} - b$, and the remaining roots are determined by the following equation:

$$\left(\xi + d + \frac{\beta v_1}{1 + \alpha v_1}\right)(\xi + a)(\xi + u) = (\xi + d)\frac{\beta k x_1 e^{-(m + \xi)\tau}}{(1 + \alpha v_1)^2}.$$
(3.7)

We claim that all roots of Eq. (3.7) have negative real parts. Assume the contrary, Eq. (3.7) has a root $\xi_2 = \text{Re}\xi_2 + i\text{Im}\xi_2$ with $\text{Re}\xi_2 \ge 0$. It is easy to show that

$$|(\xi_2 + a)(\xi_2 + u)| \ge au = \frac{\beta k x_1 e^{-m\tau}}{1 + \alpha v_1} > \frac{\beta k x_1 e^{-m\tau}}{(1 + \alpha v_1)^2}.$$
(3.8)

Furthermore, we have

$$\left|\frac{\xi_2 + d}{\xi_2 + d + \frac{\beta v_1}{1 + \alpha v_1}} \frac{\beta k x_1 e^{-(m + \xi_2)\tau}}{(1 + \alpha v_1)^2}\right| < \frac{\beta k x_1 e^{-m\tau}}{(1 + \alpha v_1)^2},$$

which contradicts (3.7). Consequently, if $\Re_1 < 1 < \Re_0$, all roots of Eq. (3.5) have negative real parts. Accordingly, E_1 is locally asymptotically stable.

Theorem 3.3. If $\mathscr{R}_1 > 1$, the immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2)$ of system (1.2) is locally asymptotically stable.

Proof. The characteristic equation of system (1.2) at E_2 is:

$$\left(\xi + d + \frac{\beta v_2}{1 + \alpha v_2} \right) (\xi + u) \left[\frac{p c y_2 z_2}{h + z_2} + \left(\xi + b - \frac{c h y_2}{(h + z_2)^2} \right) (\xi + a + p z_2) \right]$$

$$= (\xi + d) \left(\xi + b - \frac{c h y_2}{(h + z_2)^2} \right) \frac{\beta k x_2 e^{-(m + \xi)\tau}}{(1 + \alpha v_2)^2}.$$

$$(3.9)$$

In the following, we show that all roots of Eq. (3.9) have negative real parts. If Eq. (3.9) has a root ξ_3 with nonnegative real part, we obtain that

$$\left| \frac{\xi_3 + d}{\xi_3 + d + \frac{\beta v_2}{1 + \alpha v_2}} \left(\xi_3 + b - \frac{chy_2}{(h + z_2)^2} \right) \frac{\beta k x_2 e^{-(m + \xi_3)\tau}}{(1 + \alpha v_2)^2} < \frac{\beta k x_2 e^{-m\tau}}{(1 + \alpha v_2)^2} \left| \xi_3 + b - \frac{chy_2}{(h + z_2)^2} \right|.$$

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From the expression of E_2 , we derive that $u(a + pz_2) = \frac{\beta k x_2 e^{-m\tau}}{1 + \alpha v_2}$. Thus, we have

$$\left| (\xi_{3} + u) \left[\frac{p c y_{2} z_{2}}{h + z_{2}} + \left(\xi_{3} + b - \frac{c h y_{2}}{(h + z_{2})^{2}} \right) (\xi_{3} + a + p z_{2}) \right] \right|$$

$$> u(a + p z_{2}) \left| \xi_{3} + b - \frac{c h y_{2}}{(h + z_{2})^{2}} \right|$$

$$> \frac{\beta k x_{2} e^{-m\tau}}{(1 + \alpha v_{2})^{2}} \left| \xi_{3} + b - \frac{c h y_{2}}{(h + z_{2})^{2}} \right|.$$

$$(3.10)$$

This leads to a contradiction. Therefore, all roots of Eq. (3.9) have negative real parts if $\Re_1 > 1$. Accordingly, E_2 is locally asymptotically stable.

4. Global asymptotic stability

In this section, we establish the global dynamics of system (1.2).

Now, we discuss the boundedness of solutions, and have the following result.

Lemma 4.1. All solutions of system (1.2) with initial condition (1.3) are ultimately bounded for all $t \ge 0$.

Proof. Let (x(t), y(t), v(t), z(t)) be any solution of system (1.2) satisfying the initial condition (1.3). Denote $B(t) = x(t - \tau) + e^{m\tau}y(t)$.

Differentiating B(t) with respect to t, we obtain that

$$\dot{B}(t) = \lambda - dx(t - \tau) - ae^{m\tau}y(t) - pe^{m\tau}y(t)z(t)$$

$$\leq \lambda - [dx(t - \tau) + ae^{m\tau}y(t)]$$

$$\leq \lambda - \min\{a, d\}B(t),$$

which implies that $\limsup_{t\to\infty} B(t) \le \frac{\lambda}{\min\{a,d\}}$. Then x(t) and y(t) are ultimately bounded. From the third and the fourth equations of system (1.2), we derive that

$$\dot{v}(t) = ky(t) - uv(t) \le \frac{ke^{-m\tau}\lambda}{\min\{a,d\}} - uv(t),$$
$$\dot{z}(t) \le cy(t) - bz(t) \le \frac{ce^{-m\tau}\lambda}{\min\{a,d\}} - bz(t),$$

and thus

$$\limsup_{t \to \infty} v(t) \le \frac{k e^{-m\tau} \lambda}{u \min\{a, d\}}, \quad \limsup_{t \to \infty} z(t) \le \frac{c e^{-m\tau} \lambda}{b \min\{a, d\}}$$

Hence v(t) and z(t) are ultimately bounded. Therefore, the positively invariant set for system (1.2) is given by:

$$\mathbf{\Omega} = \left\{ (x, y, v, z) \middle| x + e^{m\tau} y \le \frac{\lambda}{\min\{a, d\}}, v \le \frac{ke^{-m\tau}\lambda}{u\min\{a, d\}}, z \le \frac{ce^{-m\tau}\lambda}{b\min\{a, d\}} \right\}.$$

Next, we define a function $g(x) = x - 1 - \ln x$, where g(1) = 0 and g(x) attains its minimum at x = 1.

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Theorem 4.2. If $\mathscr{R}_0 < 1$, 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) satisfying the initial condition (1.3). Define

$$V_1(t) = x - x_0 - x_0 \ln \frac{x(t)}{x_0} + e^{m\tau} y(t) + \frac{ae^{m\tau}}{k} v(t) + \frac{phe^{m\tau}}{c} z(t) + \int_{t-\tau}^t \frac{\beta x(s)v(s)}{1 + \alpha v(s)} ds,$$

where $x_0 = \lambda/d$. Calculating the time derivative of $V_1(t)$ along positive solutions of system (1.2), we have

$$\begin{split} \dot{V}_{1}(t) = dx_{0} \left(2 - \frac{x(t)}{x_{0}} - \frac{x_{0}}{x(t)} \right) + \frac{\beta x_{0} v(t)}{1 + \alpha v(t)} - \frac{aue^{m\tau}}{k} v(t) - \frac{phbe^{m\tau}}{c} z(t) \\ + pe^{m\tau} \left(\frac{h}{h + z(t)} - 1 \right) y(t) z(t) \\ \leq dx_{0} \left(2 - \frac{x(t)}{x_{0}} - \frac{x_{0}}{x(t)} \right) + (\mathscr{R}_{0} - 1) \frac{aue^{m\tau}}{k} v(t) - \frac{phbe^{m\tau}}{c} z(t) \\ + pe^{m\tau} \left(\frac{h}{h + z(t)} - 1 \right) y(t) z(t). \end{split}$$
(4.1)

Since $\mathscr{R}_0 < 1$, we have $\dot{V}_1(t) \le 0$, and $\dot{V}_1(t) = 0$ if and only if $x = x_0$, y = v = z = 0. It is easy to show that $M_0 = \{E_0\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t)) : \dot{V}_1(t) = 0\}$. In addition, from Theorem 3.1, we know that if $\mathscr{R}_0 < 1$, E_0 is locally asymptotically stable. Thus, by LaSalle's invariance principle [19], we conclude that E_0 is globally asymptotically stable.

Theorem 4.3. If $\mathscr{R}_1 < 1 < \mathscr{R}_0$, the immunity-inactivated 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) satisfying the initial condition (1.3). Define

$$\begin{split} V_2(t) = & x(t) - x_1 - x_1 \ln \frac{x(t)}{x_1} + e^{m\tau} \left(y(t) - y_1 - y_1 \ln \frac{y(t)}{y_1} \right) \\ & + \frac{\beta x_1 v_1}{k y_1 (1 + \alpha v_1)} \left(v(t) - v_1 - v_1 \ln \frac{v(t)}{v_1} \right) + \frac{p e^{m\tau} y_1}{b} z(t) \\ & + \frac{\beta x_1 v_1}{1 + \alpha v_1} \int_{t-\tau}^t g \left(\frac{x(t) v(t) (1 + \alpha v_1)}{x_1 v_1 (1 + \alpha v(t))} \right) ds. \end{split}$$

Differentiating $V_2(t)$ along positive solutions of system (1.2), we obtain that

$$\begin{split} \dot{V}_{2}(t) &= \left(1 - \frac{x_{1}}{x(t)}\right) \left(\lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)}\right) \\ &+ e^{m\tau} \left(1 - \frac{y_{1}}{y(t)}\right) \left(\frac{\beta e^{-m\tau} x(t - \tau)v(t - \tau)}{1 + \alpha v(t - \tau)} - ay(t) - py(t)z(t)\right) \\ &+ \frac{\beta x_{1}v_{1}}{ky_{1}(1 + \alpha v_{1})} \left(1 - \frac{v_{1}}{v(t)}\right) (ky(t) - uv(t)) + \frac{p e^{m\tau} y_{1}}{b} \left(\frac{cy(t)z(t)}{h + z(t)} - bz(t)\right) \\ &+ \frac{\beta x_{1}v_{1}}{1 + \alpha v_{1}} \left[g\left(\frac{x(t)v(t)(1 + \alpha v_{1})}{x_{1}v_{1}(1 + \alpha v(t))}\right) - g\left(\frac{x(t - \tau)v(t - \tau)(1 + \alpha v_{1})}{x_{1}v_{1}(1 + \alpha v(t - \tau))}\right)\right]. \end{split}$$
(4.2)

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Combining $\lambda = dx_1 + \frac{\beta x_1 v_1}{1 + \alpha v_1}$, $\frac{\beta e^{-m\tau} x_1 v_1}{1 + \alpha v_1} = ay_1$ and $ky_1 = uv_1$ with (4.2), we have

$$\dot{V}_{2}(t) = dx_{1} \left(2 - \frac{x(t)}{x_{1}} - \frac{x_{1}}{x(t)} \right) - \frac{\beta x_{1} v_{1}}{1 + \alpha v_{1}} \left[g \left(\frac{x_{1}}{x(t)} \right) + g \left(\frac{v_{1} y(t)}{y_{1} v(t)} \right) \right] - \frac{\beta x_{1} v_{1}}{1 + \alpha v_{1}} \left[g \left(\frac{x(t - \tau) v(t - \tau)(1 + \alpha v_{1}) y_{1}}{x_{1} v_{1}(1 + \alpha v(t - \tau)) y(t)} \right) + g \left(\frac{1 + \alpha v(t)}{1 + \alpha v_{1}} \right) \right] - \frac{\beta x_{1} v_{1}}{1 + \alpha v_{1}} \frac{\alpha (v(t) - v_{1})^{2}}{v_{1}(1 + \alpha v_{1})(1 + \alpha v(t))} + \frac{p e^{m\tau}}{b} \left(\frac{c y_{1}}{h + z(t)} - b \right) y(t) z(t).$$

$$(4.3)$$

From (3.6), we have $\frac{cy_1}{h+z(t)} - b < \frac{cy_1}{h} - b < 0$. Thus $\dot{V}_2(t) \le 0$, and $\dot{V}_2(t) = 0$ if and only if $x = x_1$, $y = y_1$, $v = v_1$, z = 0. It is easy to see that the largest invariant subset of $\{(x(t), y(t), v(t), z(t)) : \dot{V}_2(t) = 0\}$ is the singleton $M_1 = \{E_1\} \subset \Omega$. Furthermore, from Theorem 3.2, we know that if $\Re_1 < 1 < \Re_0$, E_1 is locally asymptotically stable. According to LaSalle's invariance principle [19], E_1 is globally asymptotically stable.

Theorem 4.4. If $\mathscr{R}_1 > 1$, the immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2)$ 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) satisfying the initial condition (1.3). Define

$$\begin{split} V_{3}(t) = & x - x_{2} - x_{2} \ln \frac{x(t)}{x_{2}} + e^{m\tau} \left(y(t) - y_{2} - y_{2} \ln \frac{y(t)}{y_{2}} \right) \\ & + \frac{\beta x_{2} v_{2}}{k y_{2} (1 + \alpha v_{2})} \left(v(t) - v_{2} - v_{2} \ln \frac{v(t)}{v_{2}} \right) + \frac{p e^{m\tau} y_{2}}{b} \left(z(t) - z_{2} - z_{2} \ln \frac{z(t)}{z_{2}} \right) \\ & + \frac{\beta x_{2} v_{2}}{1 + \alpha v_{2}} \int_{t - \tau}^{t} g \left(\frac{x(t) v(t) (1 + \alpha v_{2})}{x_{2} v_{2} (1 + \alpha v(t))} \right) ds. \end{split}$$

Calculating the derivative of $V_3(t)$ along positive solutions of system (1.2), we obtain that

$$\begin{split} \dot{V}_{3}(t) &= \left(1 - \frac{x_{2}}{x(t)}\right) \left(\lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)}\right) \\ &+ e^{m\tau} \left(1 - \frac{y_{2}}{y(t)}\right) \left(\frac{\beta e^{-m\tau} x(t - \tau)v(t - \tau)}{1 + \alpha v(t - \tau)} - ay(t) - py(t)z(t)\right) \\ &+ \frac{\beta x_{2}v_{2}}{ky_{2}(1 + \alpha v_{2})} \left(1 - \frac{v_{2}}{v(t)}\right) (ky(t) - uv(t)) + \frac{p e^{m\tau} y_{2}}{b} \left(1 - \frac{z_{2}}{z(t)}\right) \left(\frac{cy(t)z(t)}{h + z(t)} - bz(t)\right) \\ &+ \frac{\beta x_{2}v_{2}}{1 + \alpha v_{2}} \left[g\left(\frac{x(t)v(t)(1 + \alpha v_{2})}{x_{2}v_{2}(1 + \alpha v(t))}\right) - g\left(\frac{x(t - \tau)v(t - \tau)(1 + \alpha v_{2})}{x_{2}v_{2}(1 + \alpha v(t - \tau))}\right)\right]. \end{split}$$
(4.4)

Substituting $\lambda = dx_2 + \frac{\beta x_2 v_2}{1 + \alpha v_2}$, $\frac{\beta e^{-m\tau} x_2 v_2}{1 + \alpha v_2} = ay_2 + py_2 z_2$, $ky_2 = uv_2$ and $\frac{cy_2 z_2}{h + z_2} = bz_2$ into (4.4), we get

$$\dot{V}_{3}(t) = dx_{2} \left(2 - \frac{x(t)}{x_{2}} - \frac{x_{2}}{x(t)}\right) - \frac{\beta x_{2} v_{2}}{1 + \alpha v_{2}} \left[g\left(\frac{x_{2}}{x(t)}\right) + g\left(\frac{v_{2} y(t)}{y_{2} v(t)}\right)\right] - \frac{\beta x_{2} v_{2}}{1 + \alpha v_{2}} \left[g\left(\frac{x(t - \tau)v(t - \tau)(1 + \alpha v_{2})y_{2}}{x_{2} v_{2}(1 + \alpha v(t - \tau))y(t)}\right) + g\left(\frac{1 + \alpha v(t)}{1 + \alpha v_{2}}\right)\right] - \frac{\beta x_{2} v_{2}}{1 + \alpha v_{2}} \frac{\alpha(v(t) - v_{2})^{2}}{v_{2}(1 + \alpha v(t))} - pe^{m\tau} \frac{(z(t) - z_{2})^{2}}{h + z(t)}y(t).$$
(4.5)

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Obviously, $\dot{V}_3(t) \le 0$ and $\dot{V}_3(t) = 0$ if and only if $x = x_2$, $y = y_2$, $v = v_2$, $z = z_2$. $M_2 = \{E_2\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t)) : \dot{V}_3(t) = 0\}$. From Theorem 3.3, if $\Re_1 > 1$, E_2 is locally asymptotically stable. Hence, using LaSalle's invariance principle [19], we obtain that E_2 is globally asymptotically stable.

5. Sensitivity analyses

In this section, we perform sensitivity analyses to show the effects of parameters β , k, u and c on the immunity-activated reproduction number \Re_1 and the viral load.

We choose the parameter values as follows [21–23]:

$$\lambda = 46 \text{ cells ml}^{-1} \text{ day}^{-1}, \ d = 0.0046 \text{ day}^{-1}, \ \beta = 4.8 \times 10^{-7} \text{ ml virion}^{-1} \text{ day}^{-1}, m = 1.39 \text{ day}^{-1}, \ \tau = 0.5 \text{ day}, \ a = 0.01 \text{ day}^{-1}, \ p = 0.00094 \text{ ml cells}^{-1} \text{ day}^{-1}, k = 11.349 \text{ virion cells}^{-1} \text{ day}^{-1}, \ u = 0.25 \text{ day}^{-1}, \ c = 0.01 \text{ day}^{-1}, \ b = 0.5 \text{ day}^{-1}.$$
(5.1)

Meanwhile, we assume $\alpha = 0.15$ ml virion⁻¹ and h = 0.01 cells ml⁻¹.

First, using the methods of Latin Hypercube Sampling and Partial Rank Correlation Coefficients (PRCCs) developed in [24], we investigate the sensitivity of the immunity-activated reproduction number \mathscr{R}_1 on the parameters β , k, u and c, which have important effects on HIV infection (see Figure 1). From Figure 1, we see that β , k and c are positively correlated with \mathscr{R}_1 while u are negatively correlated with \mathscr{R}_1 . In addition, we obtain that decreasing the activation rate of CTL immune response and the infection rate of virus-to-cell infection can more effectively reduce \mathscr{R}_1 .



Figure 1. Tornado plots of PRCCs in regard to \mathscr{R}_1 with parameter values described in (5.1).

Second, we study the sensitivity of the viral load with respect to the parameters β , k, u and c (see Figure 2). In Figure 2, it is easy to see that β , k and c are positively correlated with the viral load while u are negatively correlated with the viral load. Besides, we get that decreasing the release rate of free viruses or increasing the death rate of free viruses can more effectively reduce the viral load, which is helpful in controling the viral infection.



Figure 2. Tornado plots of PRCCs in regard to the viral load with parameter values described in (5.1).

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Conflict of interest

The authors have no conflicts of interest in this paper.

References

- 1. A. M. Elaiw, Global properties of a class of HIV models, *Nonlinear Anal. RWA*, **11** (2010), 2253–2263.
- L. Wang, M. Y. Li, Mathematical analysis of the global dynamics of a model for HIV infection of CD4⁺ T cells, *Math. Biosci.*, 200 (2006), 44–57.
- 3. L. Cai, X. Li, M. Ghosh, B. Guo, Stability analysis of an HIV/AIDS epidemic model with treatment, *J. Comput. Appl. Math.*, **229** (2009), 313–323.
- 4. J. Xu, Y. Geng, Y. Zhou, Global dynamics for an age-structured HIV virus infection model with cellular infection and antiretroviral therapy, *Appl. Math. Comput.*, **305** (2017), 62–83.
- 5. M. A. Nowak, S. Bonhoeffer, G. M. Shaw, R. M. May, Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations, *J. Theor. Biol.*, **184** (1997), 203–217.
- 6. M. Y. Li, L. Wang, Backward bifurcation in a mathematical model for HIV infection in vivo with anti-retroviral treatment, *Nonlinear Anal. RWA*, **17** (2014), 147–160.

- 7. G. P. Samanta, Permanence and extinction of a nonautonomous HIV/AIDS epidemic model with distributed time delay, *Nonlinear Anal. RWA*, **12** (2011), 1163–1177.
- 8. M. A. Nowak, C. R. M. Bangham, Population dynamics of immune responses to persistent viruses, *Science*, **272** (1996), 74–79.
- 9. R. De Boer, Which of our modeling predictions are robust?, *PLoS Comput. Biol.*, 8 (2012), e1002593.
- 10. C. Jiang, W. Wang, Complete classification of global dynamics of a virus model with immune responses, *Discrete Contin. Dyn. Syst. Ser. B*, **19** (2014), 1087–1103.
- A. V. M. Herz, S. Bonhoeffer, R. M. Anderson, R. M. May, M. A. Nowak, Viral dynamics in vivo: Limitations on estimates of intracellular delay and virus decay, *Proc. Natl. Acad. Sci. USA*, 93 (1996), 7247–7251.
- 12. A. M. Elaiw, I. A. Hassanien, S. A. Azoz, Global stability of HIV infection models with intracellular delays, *J. Korean Math. Soc.*, **49** (2012), 779–794.
- 13. B. Reddy, J. Yin, Quantitative intracellular kinetics of HIV type 1, *AIDS Res. Hum. Retrovir.*, **15** (1999), 273–283.
- A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard, D. D. Ho, HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time, *Science*, 271 (1996), 1582–1586.
- 15. J. E. Mittler, B. Sulzer, A. U. Neumann, A. S. Perelson, Influence of delayed viral production on viral dynamics in HIV-1 infected patients, *Math. Biosci.*, **152** (1998), 143–163.
- 16. D. Ebert, C. D. Zschokke-Rohringer, H. J. Carius, Dose effects and density-dependent regulation of two microparasites of Daphnia magna, *Oecologia*, **122** (2000), 200–209.
- 17. R. R. Regoes, D. Ebert, S. Bonhoeffer, Dose-dependent infection rates of parasites produce the Allee effect in epidemiology, *Proc. R. Soc. Lond. Ser. B*, **269** (2002), 271–279.
- 18. X. Song, A. U. Neumann, Global stability and periodic solution of the viral dynamics, *J. Math. Anal. Appl.*, **329** (2007), 281–297.
- 19. J. K. Hale, S. Verduyn Lunel, *Introduction to Functional Differential Equations*, Springer, New York, 1993.
- 20. P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002), 29–48.
- 21. M. Stafford, L. Corey, Y. Cao, E. Daar, D. Ho, A. Perelson, Modeling plasma virus concentration during primary HIV infection, *J. Theor. Biol.*, **203** (2000), 285–301.
- 22. K. Pawelek, S. Liu, F. Pahlevani, L. Rong, A model of HIV-1 infection with two time delays: Mathematical analysis and comparison with patient data, *Math. Biosci.*, **235** (2012), 98–109.
- 23. J. Wang, M. Guo, X. Liu, Z. Zhao, Threshold dynamics of HIV-1 virus model with cell-to-cell transmission, cell-mediated immune responses and distributed delay, *Appl. Math. Comput.*, **291** (2016), 149–161.
- 24. S. Marino, I. B. Hogue, C. J. Ray, A methodology for performing global uncertainty and sensitivity analysis in systems biology, *J. Theor. Biol.*, **254** (2008), 178–196.

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