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Research Article

Global Dynamics of a Delayed HIV-1 Infection Model with CTL Immune Response

Yunfei Li, Rui Xu, Zhe Li, and Shuxue Mao

Institute of Applied Mathematics, Shijiazhuang Mechanical Engineering College, Shijiazhuang 050003, China

Correspondence should be addressed to Yunfei Li, liyunfei2009@126.com

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A delayed HIV-1 infection model with CTL immune response is investigated. By using suitable Lyapunov functionals, it is proved that the infection-free equilibrium is globally asymptotically stable if the basic reproduction ratio for viral infection is less than or equal to unity; if the basic reproduction ratio for CTL immune response is less than or equal to unity and the basic reproduction ratio for viral infection is greater than unity, the CTL-inactivated infection equilibrium is globally asymptotically stable; if the basic reproduction ratio for CTL immune response is greater than unity, the CTL-activated infection equilibrium is globally asymptotically stable.

1. Introduction

Recently, many mathematical models have been developed to describe the infection with HIV-1 (human immunodeficiency virus 1). By investigating these models, researchers have gained much important knowledge about the HIV-1 pathogenesis and have enhanced progress in the understanding of HIV-1 infection (see, e.g., [1–4]). It is pointed out by the work of [5] that immune response is universal and necessary to eliminate or control the disease during viral infections. In particular, as a part of innate response, cytotoxic T lymphocytes (CTLs) play a particularly important role in antiviral defense by attacking infected cells. Thus, many authors have studied the mathematical modelling of viral dynamics with CTL immune response (see, e.g., [5–9]). In [7], Nowak and Bangham considered an HIV-1 infection model with CTL immune response which is described by the following differential equations:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \dot{v}(t) &= ky(t) - uv(t), \\ \dot{z}(t) &= cy(t)z(t) - bz(t), \end{aligned} \tag{1.1}$$

where $x(t)$, $y(t)$, $v(t)$, and $z(t)$ represent the densities of uninfected target cells, infected cells, virions, and CTL cells at time t, respectively. Uninfected cells are produced at rate λ, die at rate d, and become infected cells at rate βxv. Infected cells are produced from uninfected cells at rate βxv and die at rate a. The parameter p accounts for the strength of the lytic component. Free virions are produced from uninfected cells at rate ky and are removed at rate u. The parameter b is the death rate for CTLs, and cyz describes the rate of CTL immune response activated by the infected cells.

Moreover, infection rate plays an important role in the modelling of epidemic dynamics. Holling type-II functional response seems more reasonable than the bilinear incidence rate (see, [10]). In [11], by stability analysis, Song and Avidan obtained that the system with the bilinear incidence rate was an extreme case of the model with Holling type-II functional response term.

In [3, 4, 7], the researchers used ordinary differential equations to describe different aspects of the dynamics of the viral infections. However, in the real virus dynamics, infection processes are not instantaneous. Time delays are usually introduced for the purpose of accurate representations of this phenomena (see, e.g., [6, 12–17]). As pointed out in [12], there is a time delay between initial viral entry into a cell and subsequent viral production, and the effect of saturation infection of an HIV-1 model was studied. By using the Lyapunov-LaSalle type theorem, sufficient conditions were derived for the global stability of the infection-free equilibrium and the chronic-infection equilibrium. In addition, there is also a period between virions that have created within a cell, and the new virions are released from the cell (see, e.g., [6, 13, 17]). In [13], Zhu and Zou studied an HIV-1 model with discrete delays and found that large delays can help eliminate the virus. To the best of our knowledge, there are few works on the dynamics of HIV-1 system with CTL immune response, Holling type-II functional response, and two kinds of discrete delays. Therefore, we are concerned with the effect of the above factors on system (1.1).

Motivated by the works of Nowak and Bangham [7], Song and Avidan [11], in the present paper, we consider the following delay differential equations:

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)},\\
\dot{y}(t) &= \frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - ay(t) - py(t)z(t),\\
\dot{v}(t) &= ky(t-\tau_2) - uv(t),\\
\dot{z}(t) &= cy(t)z(t) - bz(t),
\end{aligned} \tag{1.2}$$

where the parameters have the same meanings as in system (1.1), τ_1 represents the time between viral entry into a target cell and the production of new virus particles and τ_2 stands for a virus production period for new virions to be produced within and released from the infected cells.

The initial conditions for system (1.2) take the form

$$\begin{aligned}
&x(\theta) = \phi_1(\theta), \quad y(\theta) = \phi_2(\theta), \quad v(\theta) = \phi_3(\theta), \quad z(\theta) = \phi_4(\theta),\\
&\phi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0], \quad \phi_i(0) > 0 \quad (i = 1, 2, 3, 4),
\end{aligned} \tag{1.3}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([-\tau, 0], \mathbb{R}^4_{+0})$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^4_{+0}$, where $\tau = \max\{\tau_1, \tau_2\}$, $\mathbb{R}^4_{+0} = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$.

It is well known by the fundamental theory of functional differential equations [18] that system (1.2) has a unique solution $(x(t), y(t), v(t), z(t))$ satisfying the initial conditions (1.3). It is easy to show that all solutions of system (1.2) with initial conditions (1.3) are defined on $[0, +\infty)$ and remain positive for all $t > 0$.

This paper is organized as follows. In Section 2, by analyzing the basic reproduction ratio for viral infection and CTL immune response, the existence of three equilibria is established. Moreover, the ultimate boundedness of the solutions for system (1.2) is presented. In Section 3, by means of suitable Lyapunov functionals and LaSalle's invariant principle, we discuss the global stability of the infection-free equilibrium, the CTL-inactivated infection equilibrium, and the CTL-activated infection equilibrium, respectively. In Section 4, we carry out some numerical examples to illustrate the theoretical results. Finally, a discussion is given in Section 5 to end this work.

2. Preliminary Results

In this section, we discuss the existence of three equilibria and prove that all the solutions are positive and bounded.

Clearly, system (1.2) always has an infection-free equilibrium $E_0 = (x_0, 0, 0, 0) = (\lambda/d, 0, 0, 0)$.

Denote

$$\mathcal{R}_0 = \frac{k\lambda\beta}{adu}, \qquad \mathcal{R}_1 = \frac{ck\lambda\beta}{a(bk\beta + cdu + bdk\alpha)}. \tag{2.1}$$

Here, $\mathcal{R}_0$ and $\mathcal{R}_1$ are called the basic reproduction ratios for viral infection and CTL immune response of system (1.2), respectively. It is easy to see that $\mathcal{R}_0 > \mathcal{R}_1$ always holds. If $\mathcal{R}_0 > 1$, system (1.2) has a CTL-inactivated infection equilibrium $E_1 = (x_1, y_1, v_1, z_1)$ besides the equilibrium E_0, where

$$x_1 = \frac{au}{k\beta}(1 + \alpha v_1), \qquad y_1 = \frac{u}{k}v_1, \qquad v_1 = \frac{d}{\beta + d\alpha}(\mathcal{R}_0 - 1), \qquad z_1 = 0. \tag{2.2}$$

If $\mathcal{R}_1 > 1$, system (1.2) has a CTL-activated infection equilibrium $E_2 = (x_2, y_2, v_2, z_2)$ besides the equilibrium E_0 and E_1, where

$$x_2 = \frac{\lambda(1 + \alpha v_2)}{\beta v_2 + d(1 + \alpha v_2)}, \qquad y_2 = \frac{b}{c}, \qquad v_2 = \frac{bk}{cu}, \qquad z_2 = \frac{a}{p}(\mathcal{R}_1 - 1). \tag{2.3}$$

Theorem 2.1. *Supposing that $(x(t), y(t), v(t), z(t))$ is a solution of system (1.2) with initial conditions (1.3), then there exists $M > 0$, such that all the solutions satisfy $x(t) < M$, $y(t) < M$, $v(t) < M$, $z(t) < M$ for sufficiently large time t.*

Proof. Let

$$N(t) = x(t - \tau_1) + y(t) + \frac{a}{2k}v(t + \tau_2) + \frac{p}{c}z(t), \qquad \delta = \min\left\{d, \frac{a}{2}, u, b\right\}. \tag{2.4}$$

Since all solutions of system (1.2) are positive, simple calculation leads to

$$\begin{aligned}\frac{d}{dt}N(t) &= \lambda - dx(t-\tau_1) - \frac{\beta x(t-\tau_1)}{1+\alpha v(t-\tau_1)} + \frac{\beta x(t-\tau_1)}{1+\alpha v(t-\tau_1)} - ay(t) - py(t)z(t) \\ &\quad + \frac{a}{2k}\left(ky(t) - uv(t+\tau_2)\right) + \frac{p}{c}\left(cy(t)z(t) - bz(t)\right) \\ &= \lambda - dx(t-\tau_1) - \frac{a}{2}y(t) - \frac{au}{2k}v(t+\tau_2) - \frac{bp}{c}z(t) \\ &\le \lambda - \delta N(t).\end{aligned} \tag{2.5}$$

Therefore, we get $N(t) < (\lambda/\delta) + \varepsilon \triangleq M$ for sufficiently large time t, where ε is an arbitrarily small positive constant. Finally, all the solutions of system (1.2) are ultimately bounded by some positive constant. This completes the proof. □

3. Global Stability

In this section, we study the global stability of each equilibrium of system (1.2) by using suitable Lyapunov functionals which are inspired by Xu [12] and McCluskey [19] and LaSalle's invariant principle.

Define the following function:

$$g(x) = x - 1 - \ln x. \tag{3.1}$$

Clearly, for $x \in (0, +\infty)$, $g(x)$ has the minimum at $x = 1$ and $g(1) = 0$.

Theorem 3.1. *If $\mathcal{R}_0 \le 1$, the infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$ of system (1.2) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.2) with initial conditions (1.3). Define the following Lyapunov functional:

$$V_0(t) = x(t) - x_0 \ln\frac{x(t)}{x_0} + y(t) + \frac{a}{k}v(t) + \frac{p}{c}z(t) + \beta\int_{t-\tau_1}^{t}\frac{x(\theta)v(\theta)}{1+\alpha v(\theta)}d\theta + a\int_{t-\tau_2}^{t}y(\theta)d\theta. \tag{3.2}$$

Calculating the derivative of $V_0(t)$ along positive solutions of system (1.2), it follows that

$$\begin{aligned}\frac{d}{dt}V_0(t) &= \left(1 - \frac{x_0}{x(t)}\right)\left(\lambda - dx(\mathrm{t}) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right) + \frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - ay(t) \\ &\quad - py(t)z(t) + \frac{a}{k}\left(ky(t-\tau_2) - uv(t)\right) + \frac{p}{c}\left(cy(t)z(t) - bz(t)\right) \\ &\quad + \frac{\beta x(t)v(t)}{1+\alpha v(t)} - \frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} + ay(t) - ay(t-\tau_2) \\ &= \left(1 - \frac{x_0}{x(t)}\right)\left(dx_0 - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right) + \frac{\beta x(t)v(t)}{1+\alpha v(t)} - \frac{au}{k}v(t) - \frac{bp}{c}z(t) \\ &= -\frac{d}{x(t)}(x(t)-x_0)^2 - \frac{bp}{c}z(t) - \left(\frac{au}{k} - \frac{\beta x_0}{1+\alpha v(t)}\right)v(t).\end{aligned} \tag{3.3}$$

Noting that $\mathcal{R}_0 \le 1$, we obtain $(au/k)-(\beta x_0/(1+\alpha v(t))) \ge (au/k)-(\beta\lambda/d) = (au/k)(1-\mathcal{R}_0) \ge 0$. Hence, from (3.3), we have $V_0'(t) \le 0$. By Theorem 5.3.1 in [18], solutions limit to $\mathcal{M}_0$, the largest invariant subset of $\{V_0'(t) = 0\}$. Let $(x(t), y(t), v(t), z(t))$ be the solution with initial function in $\mathcal{M}_0$. Then, from the invariance of $\mathcal{M}_0$, we obtain $x(t) = x_0$, $v(t) = 0$, and $z(t) = 0$ for any t. Further, from the third equation of system (1.2), we obtain $y(t) = 0$. Accordingly, it follows from LaSalle's invariance principal that the infection-free equilibrium E_0 is globally asymptotically stable for any positive time delays. This completes the proof. □

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

Proof. Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.2) with initial conditions (1.3). Define the following Lyapunov functional:

$$V_1(t) = x_1 g\left[\frac{x(t)}{x_1}\right] + y_1 g\left[\frac{y(t)}{y_1}\right] + \frac{\beta x_1 v_1^2}{k y_1(1+\alpha v_1)} g\left[\frac{v(t)}{v_1}\right] + \frac{p}{c} z(t) + V_{11}(t) + V_{12}(t), \tag{3.4}$$

where

$$\begin{aligned} V_{11}(t) &= \frac{\beta x_1 v_1}{1+\alpha v_1} \int_{t-\tau_2}^{t} g\left[\frac{y(\theta)}{y_1}\right] d\theta, \\ V_{12}(t) &= \frac{\beta x_1 v_1}{1+\alpha v_1} \int_{t-\tau_1}^{t} g\left[\frac{x(\theta)v(\theta)(1+\alpha v_1)}{x_1 v_1(1+\alpha v(\theta))}\right] d\theta. \end{aligned} \tag{3.5}$$

For clarity, we will calculate the derivatives of $g[x(t)/x_1]$, $g[y(t)/y_1]$, $g[v(t)/v_1]$, $z(t)$, $V_{11}(t)$, and $V_{12}(t)$ along positive solutions of system (1.2), respectively.

Since $\lambda = dx_1 + \beta x_1 v_1/(1+\alpha v_1)$ holds, it follows that

$$\begin{aligned} \frac{d}{dt}\left[g\left(\frac{x(t)}{x_1}\right)\right] &= \frac{1}{x_1}\left(1-\frac{x_1}{x(t)}\right)\left[\lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right] \\ &= \left(1-\frac{x_1}{x(t)}\right)\left[dx_1 - dx(t) + \frac{\beta x_1 v_1}{1+\alpha v_1} - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right] \\ &= -\frac{dx(t)}{x_1}\left(1-\frac{x_1}{x(t)}\right)^2 + \frac{1}{x_1}\left(1-\frac{x_1}{x(t)}\right)\left[\frac{\beta x_1 v_1}{1+\alpha v_1} - \frac{\beta x(t)v(t)}{1+\alpha v(t)}\right] \\ &= -\frac{dx(t)}{x_1}\left(1-\frac{x_1}{x(t)}\right)^2 + \frac{1}{x_1}\frac{\beta x_1 v_1}{1+\alpha v_1}\left(1-\frac{x_1}{x(t)}\right)\left[1-\frac{x(t)v(t)}{1+\alpha v(t)}\frac{1+\alpha v_1}{x_1 v_1}\right] \\ &= -\frac{dx(t)}{x_1}\left(1-\frac{x_1}{x(t)}\right)^2 \\ &\quad + \frac{1}{x_1}\frac{\beta x_1 v_1}{1+\alpha v_1}\left[1-\frac{x_1}{x(t)}-\frac{x(t)v(t)}{1+\alpha v(t)}\frac{1+\alpha v_1}{x_1 v_1}+\frac{v(t)}{1+\alpha v(t)}\frac{1+\alpha v_1}{v_1}\right]. \end{aligned} \tag{3.6}$$

Noting that $a = \beta x_1 v_1 / y_1(1 + \alpha v_1)$, we get that

$$\begin{aligned}
\frac{d}{dt}\left[g\left(\frac{y(t)}{y_1}\right)\right] &= \frac{1}{y_1}\left(1 - \frac{y_1}{y(t)}\right)\left[\frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - ay(t) - py(t)z(t)\right] \\
&= \frac{1}{y_1}\left(1 - \frac{y_1}{y(t)}\right)\left[\frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - \frac{\beta x_1 v_1}{1+\alpha v_1}\frac{y(t)}{y_1} - py(t)z(t)\right] \\
&= \frac{1}{y_1}\left(1 - \frac{y_1}{y(t)}\right)\left[\frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - \frac{\beta x_1 v_1}{1+\alpha v_1}\frac{y(t)}{y_1}\right] - \frac{py(t)z(t)}{y_1}\left(1 - \frac{y_1}{y(t)}\right) \\
&= \frac{1}{y_1}\frac{\beta x_1 v_1}{1+\alpha v_1}\left[\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_1}{x_1 v_1} - \frac{y(t)}{y_1}\right. \\
&\qquad \left. - \frac{y_1}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_1}{x_1 v_1} + 1\right] - \frac{py(t)z(t)}{y_1} + pz(t).
\end{aligned} \tag{3.7}$$

Since $u = ky_1/v_1$ holds, it follows that

$$\begin{aligned}
\frac{d}{dt}\left[g\left(\frac{v(t)}{v_1}\right)\right] &= \frac{1}{v_1}\left(1 - \frac{v_1}{v(t)}\right)\left[ky(t-\tau_2) - uv(t)\right] \\
&= \frac{1}{v_1}\left(1 - \frac{v_1}{v(t)}\right)\left[ky(t-\tau_2) - \frac{ky_1}{v_1}v(t)\right] \\
&= \frac{ky_1}{v_1}\left(1 - \frac{v_1}{v(t)}\right)\left[\frac{y(t-\tau_2)}{y_1} - \frac{v(t)}{v_1}\right] \\
&= \frac{ky_1}{v_1}\left[\frac{y(t-\tau_2)}{y_1} - \frac{v_1}{v(t)}\frac{y(t-\tau_2)}{y_1} - \frac{v(t)}{v_1} + 1\right].
\end{aligned} \tag{3.8}$$

Calculating the derivatives of $V_{11}(t)$ and $V_{12}(t)$ shows that

$$\begin{aligned}
\frac{d}{dt}V_{11}(t) &= \frac{\beta x_1 v_1}{1+\alpha v_1}\left[\frac{y(t)}{y_1} - \frac{y(t-\tau_2)}{y_1} + \ln\frac{y(t-\tau_2)}{y_1} - \ln\frac{y(t)}{y_1}\right], \\
\frac{d}{dt}V_{12}(t) &= \beta\left[\frac{x(t)v(t)}{1+\alpha v(t)} - \frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} + \frac{x_1 v_1}{1+\alpha v_1}\ln\frac{x(t-\tau_1)v(t-\tau_1)(1+\alpha v(t))}{x(t)v(t)(1+\alpha v(t-\tau_1))}\right].
\end{aligned} \tag{3.9}$$

We therefore derive from (3.6)–(3.9) that

$$\begin{aligned}
\frac{d}{dt}V_1(t) &= -dx(t)\left(1-\frac{x_1}{x(t)}\right)^2 - \frac{\beta x_1 v_1}{1+\alpha v_1}\left[\frac{x_1}{x(t)} - 1 - \ln\frac{x_1}{x(t)}\right] \\
&\quad - \frac{\beta x_1 v_1}{1+\alpha v_1}\left[\frac{1+\alpha v(t)}{1+\alpha v_1} - 1 - \ln\frac{1+\alpha v(t)}{1+\alpha v_1}\right] \\
&\quad - \frac{\beta x_1 v_1}{1+\alpha v_1}\left[\frac{v_1}{v(t)}\frac{y(t-\tau_2)}{y_1} - 1 - \ln\frac{v_1}{v(t)}\frac{y(t-\tau_2)}{y_1}\right] \\
&\quad - \frac{\beta x_1 v_1}{1+\alpha v_1}\left[\frac{y_1}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_1}{x_1 v_1} - 1\right. \\
&\qquad \left. - \ln\left(\frac{y_1}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_1}{x_1 v_1}\right)\right] \\
&\quad - \frac{\alpha\beta x_1 (v(t)-v_1)^2}{(1+\alpha v_1)^2(1+\alpha v(t))} + p\left(y_1 - \frac{b}{c}\right)z(t) \\
&= -dx(t)\left(1-\frac{x_1}{x(t)}\right)^2 - \frac{\alpha\beta x_1 (v(t)-v_1)^2}{(1+\alpha v_1)^2(1+\alpha v(t))} + p\left(y_1 - \frac{b}{c}\right)z(t) \\
&\quad - \frac{\beta x_1 v_1}{1+\alpha v_1} g\left[\frac{v_1 y(t-\tau_2)}{y_1 v(t)}\right] - \frac{\beta x_1 v_1}{1+\alpha v_1} g\left[\frac{x_1}{x(t)}\right] - \frac{\beta x_1 v_1}{1+\alpha v_1} g\left[\frac{1+\alpha v(t)}{1+\alpha v_1}\right] \\
&\quad - \frac{\beta x_1 v_1}{1+\alpha v_1} g\left[\frac{y_1}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_1}{x_1 v_1}\right].
\end{aligned} \tag{3.10}$$

Noting that $\mathcal{R}_1 \le 1$, we derive that $y_1 - b/c = ((bk\beta + cdu + bdk\alpha)/ck(\beta + d\alpha))(R_1 - 1) \le 0$. Hence, from (3.10), we have $V_1'(t) \le 0$. Similar to Theorem 3.1, solutions limit to $\mathcal{M}_1$, the largest invariant subset of $\{V_1'(t) = 0\}$. Let $(x(t), y(t), v(t), z(t))$ be the solution with initial function in $\mathcal{M}_1$. Then, we obtain that

$$x(t) = x_1, \qquad v(t) = v_1, \qquad z(t) = 0, \qquad \frac{v_1 y(t-\tau_2)}{y_1 v(t)} = \frac{y_1}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_1}{x_1 v_1} = 1. \tag{3.11}$$

It is readily to show that $x(t) = x(t-\tau_1) = x_1$, $y(t) = y(t-\tau_2) = y_1$, $v(t) = v(t-\tau_1) = v_1$, and $z(t) = 0$ for any t. Thus, it follows from LaSalle's invariance principal that the CTL-inactivated infection equilibrium E_1 is globally asymptotically stable for any positive time delays. This completes the proof. □

Theorem 3.3. *If $\mathcal{R}_1 > 1$, the CTL-activated infection equilibrium E_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) with initial conditions (1.3). We construct the following Lyapunov functional:

$$V_2(t) = x_2 g\left[\frac{x(t)}{x_2}\right] + y_2 g\left[\frac{y(t)}{y_2}\right] + \frac{\beta x_2 v_2^2}{k y_2(1+\alpha v_2)} g\left[\frac{v(t)}{v_2}\right] + \frac{p z_2}{c} g\left[\frac{z(t)}{z_2}\right] + V_{21}(t) + V_{22}(t), \tag{3.12}$$

where

$$V_{21}(t) = \frac{\beta x_2 v_2}{1+\alpha v_2}\int_{t-\tau_2}^{t} g\left[\frac{y(\theta)}{y_2}\right]d\theta,$$
$$V_{22}(t) = \frac{\beta x_2 v_2}{1+\alpha v_2}\int_{t-\tau_1}^{t} g\left[\frac{x(\theta)v(\theta)(1+\alpha v_2)}{x_2 v_2(1+\alpha v(\theta))}\right]d\theta. \tag{3.13}$$

Next, we will calculate the derivatives of $g[x(t)/x_2]$, $g[y(t)/y_2]$, $g[v(t)/v_2]$, $g[z(t)/z_2]$, $V_{21}(t)$, and $V_{22}(t)$ along positive solutions of system (1.2), respectively.

Similar to (3.6), we derive that

$$\begin{aligned}\frac{d}{dt}\left[g\left(\frac{x(t)}{x_2}\right)\right] &= -\frac{dx(t)}{x_2}\left(1-\frac{x_2}{x(t)}\right)^2 \\ &\quad + \frac{1}{x_2}\frac{\beta x_2 v_2}{1+\alpha v_2}\left[1-\frac{x_2}{x(t)}-\frac{x(t)v(t)}{1+\alpha v(t)}\frac{1+\alpha v_2}{x_2 v_2}+\frac{v(t)}{1+\alpha v(t)}\frac{1+\alpha v_2}{v_2}\right].\end{aligned} \tag{3.14}$$

Noting that $a = \beta x_2 v_2/y_2(1+\alpha v_2) - p z_2$, it follows that

$$\begin{aligned}\frac{d}{dt}\left[g\left(\frac{y(t)}{y_2}\right)\right] &= \frac{1}{y_2}\left(1-\frac{y_2}{y(t)}\right)\left[\frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - a y(t) - p y(t) z(t)\right] \\ &= \frac{1}{y_2}\left(1-\frac{y_2}{y(t)}\right)\left[\frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - \frac{\beta x_2 v_2}{1+\alpha v_2}\frac{y(t)}{y_2} + p z_2 y(t) - p y(t) z(t)\right] \\ &= \frac{1}{y_2}\frac{\beta x_2 v_2}{1+\alpha v_2}\left(1-\frac{y_2}{y(t)}\right)\left[\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_2}{x_2 v_2} - \frac{y(t)}{y_2}\right] \\ &\quad + \frac{p y(t)}{y_2}\left(1-\frac{y_2}{y(t)}\right)(z_2 - z(t)) \\ &= \frac{1}{y_2}\frac{\beta x_2 v_2}{1+\alpha v_2}\left[\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_2}{x_2 v_2} - \frac{y(t)}{y_2}\right. \\ &\qquad \left. - \frac{y_2}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_2}{x_2 v_2} + 1\right] + \frac{p}{y_2}(y(t)-y_2)(z_2 - z(t)).\end{aligned} \tag{3.15}$$

Similar to (3.8), we get that

$$\frac{d}{dt}\left[g\left(\frac{v(t)}{v_2}\right)\right] = \frac{k y_2}{v_2}\left[\frac{y(t-\tau_2)}{y_2} - \frac{v_2}{v(t)}\frac{y(t-\tau_2)}{y_2} - \frac{v(t)}{v_2} + 1\right]. \tag{3.16}$$

Calculating the derivative of $g[z(t)/z_2]$ shows that

$$\begin{aligned}\frac{d}{dt}\left[g\left(\frac{z(t)}{z_2}\right)\right] &= \frac{1}{z_2}\left(1-\frac{z_2}{z(t)}\right)\left(cy(t)z(t)-bz(t)\right)\\ &= \frac{1}{z_2}\left(1-\frac{z_2}{z(t)}\right)\left(cy(t)z(t)-cy_2z(t)\right)\\ &= \frac{c}{z_2}\left(z(t)-z_2\right)\left(y(t)-y_2\right).\end{aligned} \tag{3.17}$$

Similar to (3.9), it follows that

$$\begin{aligned}\frac{d}{dt}V_{21}(t) &= \frac{\beta x_2 v_2}{1+\alpha v_2}\left[\frac{y(t)}{y_2}-\frac{y(t-\tau_2)}{y_2}+\ln\frac{y(t-\tau_2)}{y_2}-\ln\frac{y(t)}{y_2}\right],\\ \frac{d}{dt}V_{22}(t) &= \beta\left[\frac{x(t)v(t)}{1+\alpha v(t)}-\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}+\frac{x_2v_2}{1+\alpha v_2}\ln\frac{x(t-\tau_1)v(t-\tau_1)(1+\alpha v(t))}{x(t)v(t)(1+\alpha v(t-\tau_1))}\right].\end{aligned} \tag{3.18}$$

We therefore derive from (3.14)–(3.18) that

$$\begin{aligned}\frac{d}{dt}V_2(t) &= -dx(t)\left(1-\frac{x_2}{x(t)}\right)^2-\frac{\alpha\beta x_2(v(t)-v_2)^2}{(1+\alpha v_2)^2(1+\alpha v(t))}\\ &\quad-\frac{\beta x_2v_2}{1+\alpha v_2}g\left[\frac{y_2}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_2}{x_2v_2}\right]\\ &\quad-\frac{\beta x_2v_2}{1+\alpha v_2}g\left[\frac{x_2}{x(t)}\right]-\frac{\beta x_2v_2}{1+\alpha v_2}g\left[\frac{1+\alpha v(t)}{1+\alpha v_2}\right]\\ &\quad-\frac{\beta x_2v_2}{1+\alpha v_2}g\left[\frac{v_2y(t-\tau_2)}{y_2v(t)}\right].\end{aligned} \tag{3.19}$$

Hence, from (3.19), we get $V_2'(t)\le 0$. Similar to Theorem 3.1, solutions limit to $\mathcal{M}_2$, the largest invariant subset of $\{V_2'(t)=0\}$. Let $(x(t),y(t),v(t),z(t))$ be the solution with initial function in $\mathcal{M}_2$. Then, it holds that

$$x(t)=x_2,\qquad v(t)=v_2,\qquad \frac{y_2}{y(t)}\frac{x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)}\frac{1+\alpha v_2}{x_2v_2}=\frac{v_2y(t-\tau_2)}{y_2v(t)}=1. \tag{3.20}$$

It is easy to show that $x(t)=x(t-\tau_1)=x_2$, $y(t)=y(t-\tau_2)=y_2$, and $v(t)=v(t-\tau_1)=v_2$ for any time t. Moreover, from the second equation of system (1.2), we obtain $z(t)=z_2$. Therefore, it follows from LaSalle's invariance principal that the CTL-activated infection equilibrium E_2 is globally asymptotically stable for any positive time delays. This completes the proof. □

4. Numerical Simulations

In the following, we give three examples to illustrate the main theoretical results above. All the parameters were obtained from [9, 16, 20].

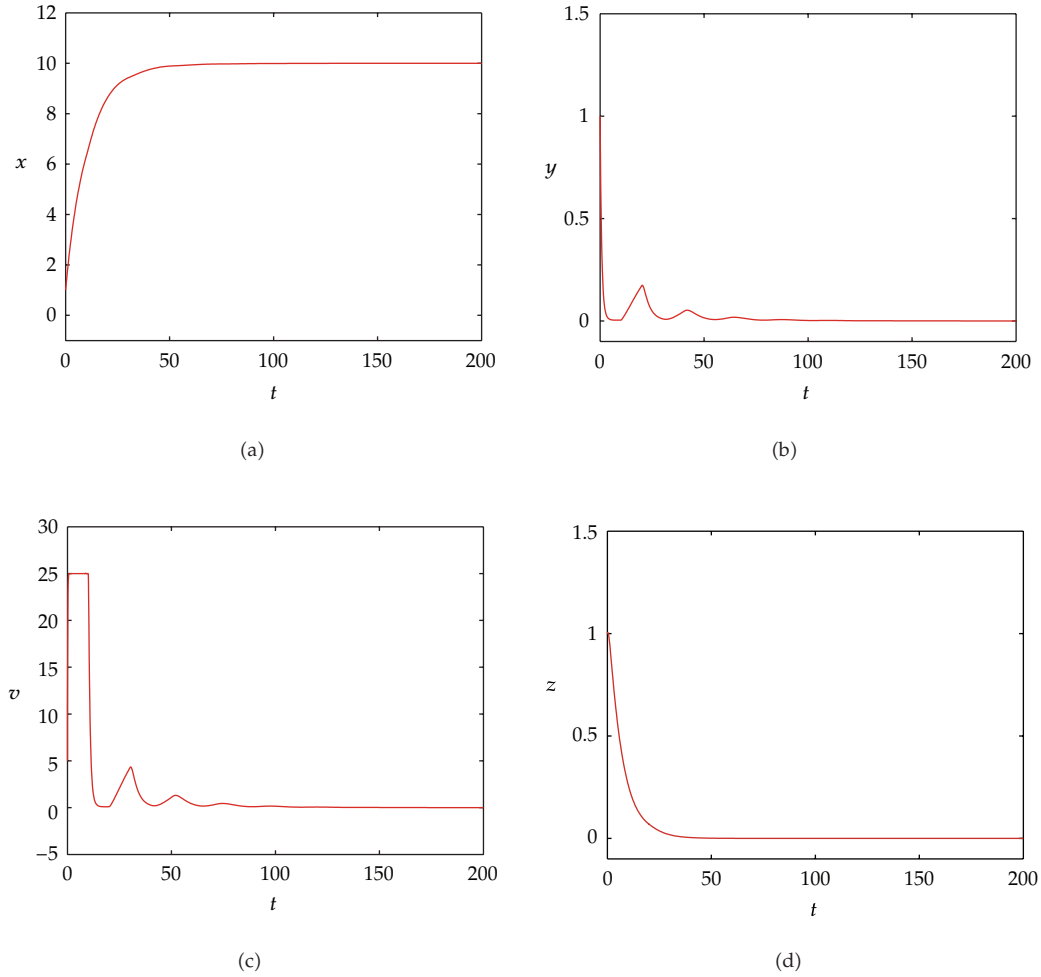

Figure 1: The infection-free equilibrium E_0 of system (1.2) is globally asymptotically stable. Here $\tau_1 = 10$, $\tau_2 = 10$, and the initial value is $(x_0 = 1, y_0 = 1, v_0 = 5, z_0 = 1)$.

Example 4.1. In system (1.2), we choose $\lambda = 1$, $d = 0.1$, $\beta = 0.0005$, $\alpha = 0.000001$, $a = 0.3$, $p = 1$, $k = 200$, $u = 8$, $c = 0.2$, $b = 0.15$, and $\tau_1 = 10$, $\tau_2 = 10$. It is easy to show that $\mathcal{R}_0 = 0.833 < 1$, and that system (1.2) has an infection-free equilibrium $E_0 = (10, 0, 0, 0)$. By Theorem 3.1, we get that the infection-free equilibrium E_0 of system (1.2) is globally asymptotically stable. Numerical simulation illustrates this fact (see Figure 1).

Example 4.2. In system (1.2), we set $\lambda = 2$, $d = 0.09$, $\beta = 0.0006$, $\alpha = 0.000001$, $a = 0.3$, $p = 1$, $k = 240$, $u = 8$, $c = 0.1$, $b = 0.3$, and $\tau_1 = 5$, $\tau_2 = 9$. It is easy to show that $0.8333 = \mathcal{R}_1 \leq 1 < \mathcal{R}_0 = 1.3333$, and that system (1.2) has a CTL-inactivated infection equilibrium $E_1 = (16.6675, 1.6664, 49.9925, 0)$. By Theorem 3.2, we obtain that the CTL-inactivated infection equilibrium E_1 of system (1.2) is globally asymptotically stable. Numerical simulation illustrates our result (see Figure 2).

Example 4.3. In system (1.2), let $\lambda = 5$, $d = 0.02$, $\beta = 0.009$, $\alpha = 0.000001$, $a = 0.25$, $p = 1$, $k = 240$, $u = 5$, $c = 0.1$, $b = 0.15$, and $\tau_1 = 4$, $\tau_2 = 2$. It is easy to show that $\mathcal{R}_1 = 12.9341 > 1$, and then

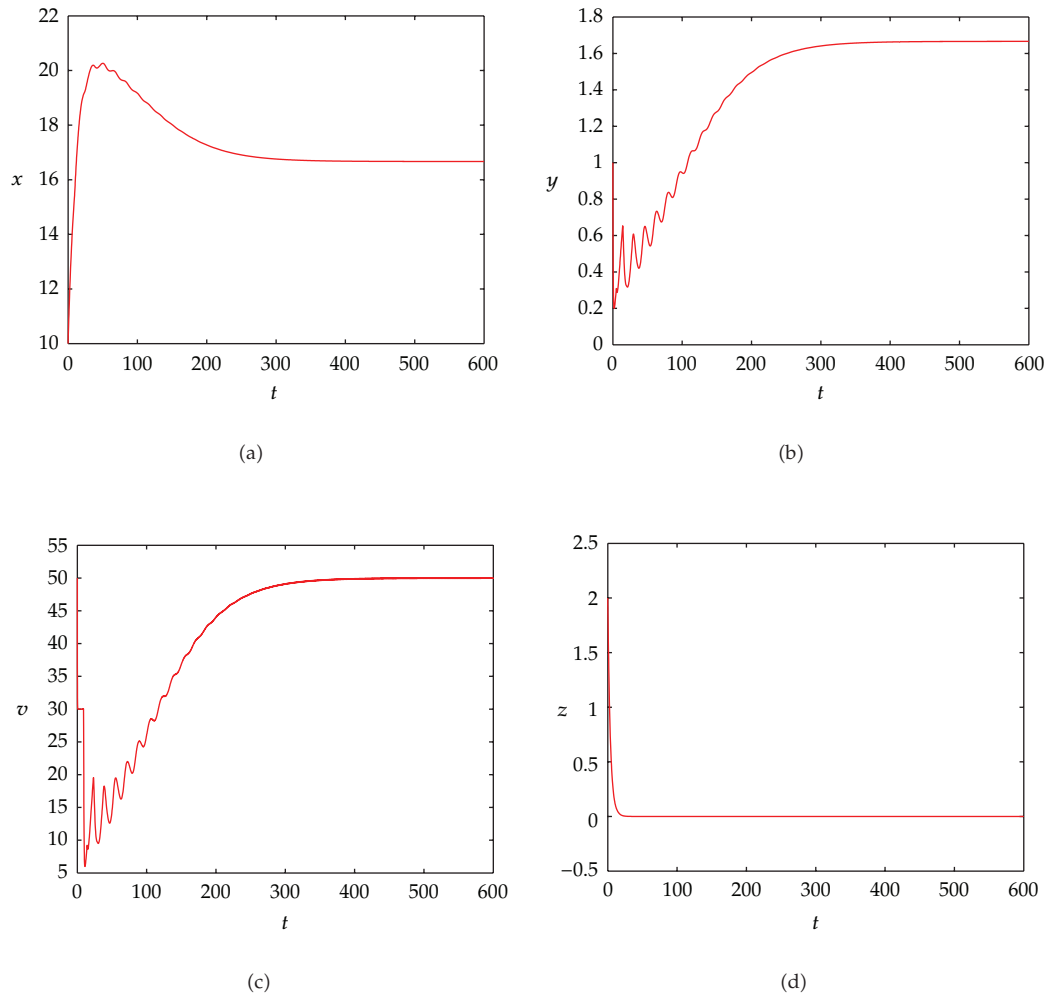

Figure 2: The CTL-inactivated infection equilibrium E_1 of system (1.2) is globally asymptotically stable. Here $\tau_1 = 5$, $\tau_2 = 9$, and the initial value is $(x_0 = 10,\ y_0 = 1,\ v_0 = 50,\ z_0 = 2)$.

system (1.2) has a CTL-activated infection equilibrium $E_2 = (7.4856, 1.5000, 72.0000, 2.9835)$. By Theorem 3.3, we get that the CTL-activated infection equilibrium E_2 of system (1.2) is globally asymptotically stable. Numerical simulation illustrates this fact (see Figure 3).

5. Discussion

In this paper, we have studied the global dynamics of a delayed HIV-1 infection model with CTL immune response. By constructing suitable Lyapunov functionals, sufficient conditions have been derived for the global stability of three equilibria. It is easy to show that if the basic reproduction ratio for viral infection $\mathcal{R}_0 \leqslant 1$, infection-free equilibrium E_0 is globally asymptotically stable, and the virus is cleared up; if the basic reproduction ratio for CTL immune response $\mathcal{R}_1$ satisfies $\mathcal{R}_1 \leq 1 < \mathcal{R}_0$, the equilibrium E_1 is globally asymptotically stable, and the infection becomes chronic but without CTL immune response; if $\mathcal{R}_1 > 1$,

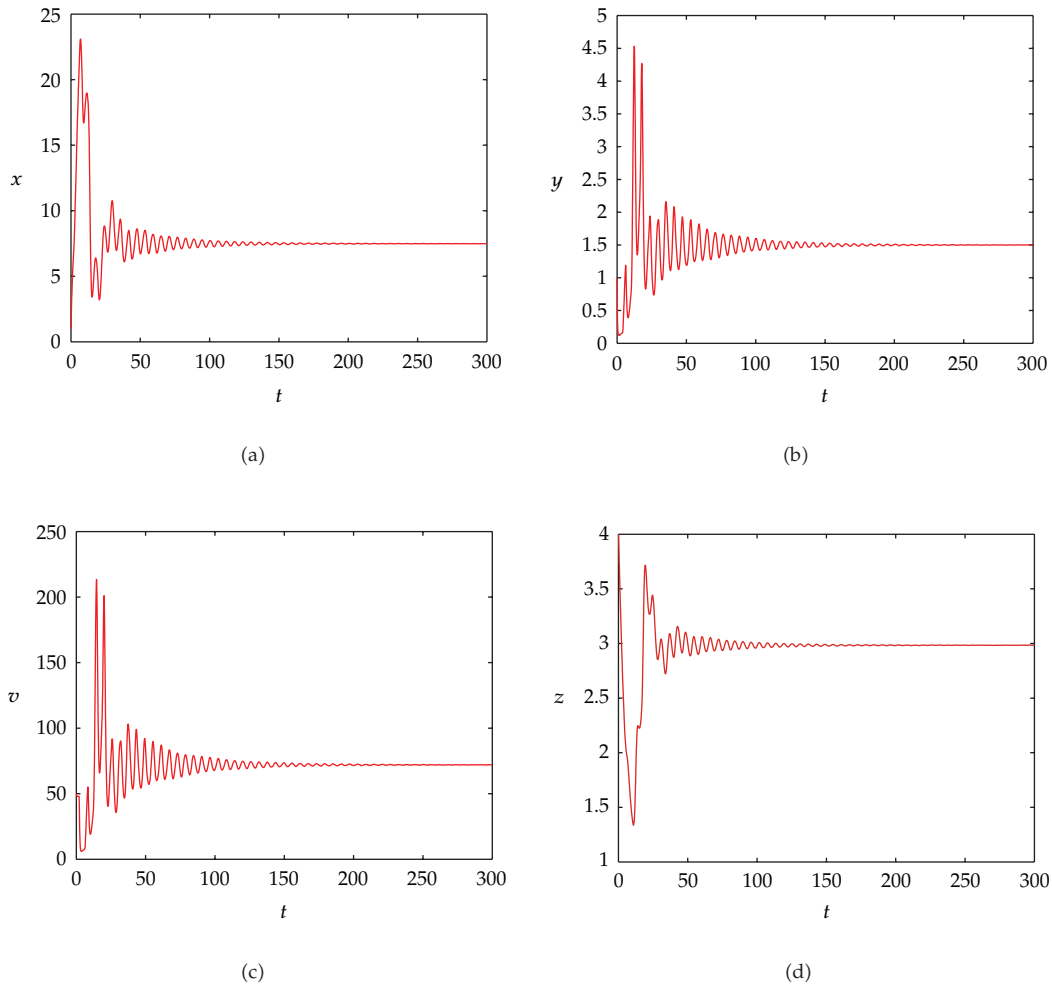

Figure 3: The CTL-activated infection equilibrium E_2 of system (1.2) is globally asymptotically stable. Here $\tau_1 = 4$, $\tau_2 = 2$, and the initial value is $(x_0 = 1, y_0 = 1, v_0 = 50, z_0 = 4)$.

system (1.2) has a CTL-activated infection equilibrium E_2 besides E_0 and E_1, which is globally asymptotically stable, and the infection turns to chronic with CTL immune response.

From Theorems 3.1, 3.2, and 3.3, we see that the delays τ_1 and τ_2 do not affect the global stability of the feasible equilibria and therefore do not induce periodic oscillations, and the possibility of Hopf bifurcations is therefore ruled out. On the other hand, if the basic reproduction ratio for CTL immune response $\mathcal{R}_1 > 1$, we can get

$$y_1 - y_2 = \frac{kb\beta + cdu + kbd\alpha}{ck(\beta + d\alpha)}(\mathcal{R}_1 - 1) > 0, \qquad v_1 - v_2 = \frac{kb\beta + cdu + kbd\alpha}{cu(\beta + d\alpha)}(\mathcal{R}_1 - 1) > 0, \quad (5.1)$$

which shows that the number of infected cells and virions of the equilibrium E_1 is greater than the number of those of the equilibrium E_2. Hence, the CTL immune response plays an important role in the reduction of the infected cells and the free virions.

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