Global dynamics of a cell mediated immunity in viral infection models with distributed delays

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Abstract

In this paper, we investigate global dynamics for a system of delay differential equations which describes a virus-immune interaction in vivo. The model has two distributed time delays describing time needed for infection of cell and virus replication. Our model admits three possible equilibria, an uninfected equilibrium and infected equilibrium with or without immune response depending on the basic reproduction number for viral infection $R_0$ and for CTL response $R_1$ such that $R_1 < R_0$. It is shown that there always exists one equilibrium which is globally asymptotically stable by employing the method of Lyapunov functional. More specifically, the uninfected equilibrium is globally asymptotically stable if $R_0 \leq 1$, an infected equilibrium without immune response is globally asymptotically stable if $R_1 \leq 1 < R_0$ and an infected equilibrium with immune response is globally asymptotically stable if $R_1 > 1$. The immune activation has a positive role in the reduction of the infection cells and the increasing of the uninfected cells if $R_1 > 1$.

Key words: viral infection; global asymptotic stability; Lyapunov functional; immune response

1. Introduction

The mathematical models, based on biological interactions, present a framework which can be used to obtain new insights and to interpret experimental data. Many authors have formulated mathematical models which describe the dynamics of virus population in vivo and these provide advances in our understanding of HIV-1 (human immunodeficiency virus 1) and other viruses, such as HBV (hepatitis B virus) and HCV (hepatitis C virus) (see [1–3, 5–10, 12, 14–25] and the references therein).

During viral infections, the host immune system reacts with antigen-specific immune response. In particular, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking
infected cells. To investigate the relation between antiviral immune response and virus load, Nowak and Bangham [18] developed the following mathematical model.

\[
\begin{align*}
\frac{dx(t)}{dt} &= s - dx(t) - kx(t)v(t), \\
\frac{dy(t)}{dt} &= kx(t)v(t) - \delta y(t) - py(t)z(t), \\
\frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t), \\
\frac{dz(t)}{dt} &= qy(t)z(t) - bz(t),
\end{align*}
\] (1.1)

where \(x(t)\) denotes the concentration of uninfected target cells at time \(t\), \(y(t)\) denotes the concentration of infected cells that produce virus at time \(t\), \(v(t)\) denotes the concentration of virus at time \(t\) and \(z(t)\) denotes the abundance of virus-specific CTLs. Uninfected cells are produced at a constant rate \(s\) and die at rate \(dx(t)\). Infected cells are produced from uninfected cells and virus at rate \(kx(t)v(t)\) and die at rate \(\delta y(t)\). Free virus is produced from uninfected cells at rate \(N\delta y(t)\), where \(N\) denotes the total number of virus particles from one cell, and die at rate \(\mu v(t)\). The rate of CTL proliferation is given by \(qy(t)z(t)\) and decay at rate \(bz(t)\) in the absence of stimulation by the infected cells. Infected cells are killed by CTLs at rate \(py(t)z(t)\). All parameters are positive constant.

Korobeinikov [8] studied global properties of a basic viral infection model which ignores immunity ((1.1) with \(p = 0\)). By assuming that the incidence rate of infection is given by a functional form, more general viral infection models are proposed and investigated (see [6, 9]). Wodarz et al. [23] considered a mathematical model for two types immune responses. Murase et al. [23] studied stability of some mathematical models for virus-immune interaction dynamics. Recently, Prüss et al., [20] showed that (1.1) always admits an equilibrium which is globally asymptotically stable by constructing Lyapunov functions.

On the other hand, in modeling of many biological processes, time delays are usually introduced for the purpose of accurate representations of the phenomena. In virus dynamics, it has been assumed that new virus particles are produced after the initial infection with a time interval and this leads mathematical models by delay differential equations. The estimated values of kinetic parameters are usually changed by these delay differential equations (see [5, 14, 16, 17] and references therein). Mathematical analysis for these models is necessary to obtain an integrated view for the virus dynamics in vivo. In particular, the global stability of a steady state for these models will give us a detailed information and enhances our understanding about the virus dynamics.

In this paper, we introduce distributed (continuous) time delays to (1.1) and study its global dynamics. Let \(h_1\) and \(h_2\) be positive constants and \(f_1(\tau) : [0, h_1] \to \mathbb{R}_+\) and \(f_2(\tau) : [0, h_2] \to \mathbb{R}_+\) be integrable functions with \(\int_0^{h_1} f_1(\tau) d\tau = \int_0^{h_2} f_2(\tau) d\tau = 1\). As in Mittler et al., [14] and Nelson et al., [17], we assume that the infected cells \(y(t)\) appear after the initial infection with a time period \(\tau\) and \(\tau\) is distributed according to \(f_1(\tau)\) over the interval \([0, h_1]\), where \(h_1\) is the limit superior of the infection delay. In addition, we assume that a time is needed for the virus production after a virions enter a cell (see also [12, 24]). Thus, we also assume the production delay \(\tau\), which is distributed according to \(f_2(\tau)\) over the interval \([0, h_2]\), where \(h_2\) is the limit superior of this delay. Then, we obtain the following viral infection model.
\[
\begin{align*}
\frac{dx(t)}{dt} &= s - dx(t) - kx(t)v(t), \\
\frac{dy(t)}{dt} &= k_d \int_{0}^{h_1} f_1(\tau)x(t - \tau)v(t - \tau)d\tau - \delta y(t) - p(t)z(t), \\
\frac{dv(t)}{dt} &= N_d \delta \int_{0}^{h_2} f_2(\tau)y(t - \tau)d\tau - \mu v(t), \\
\frac{dz(t)}{dt} &= qy(t)z(t) - bz(t).
\end{align*}
\] (1.2)

The infection rate \( k_d \) satisfies \( k_d \leq k \) and the total number of virus particles from one cell \( N_d \) satisfies \( N_d \leq N \), if we incorporate the probability of surviving of the infected cells and virus particles between the time for infection and for virus production, respectively.

Stability analysis for (1.2) with discrete intracellular delay was carried out by Li and Shu [10] and Zhu and Zou [25]. Recently, based on Li and Shu [10], Li and Shu [11] has investigated a viral infection model with a general target cell dynamics, a nonlinear incidence rate and distributed delay. Li and Shu [10, 11] showed that their model always admits an equilibrium which is globally asymptotically stable and it is necessary to have a logistic mitosis term in the target cell dynamics for generating a periodic solution. On the other hand, Zhu and Zou [25] established global stability of an uninfected equilibrium and obtained sufficient conditions for local asymptotic stability of two infected equilibria. However, since Li and Shu [10, 11] did not consider the immune response to the viral infection and Zhu and Zou [25] did not address the global stability of the two infected equilibria for their model, the global dynamics of (1.2) is still unclear and, hence, our main aim is to establish the complete global dynamics. We show that (1.2) has three possible equilibria, an uninfected equilibrium and infected equilibrium with or without immune response and always admits one equilibrium which is always globally asymptotically stable. Moreover, it is shown that if the immune response is activated, then the infected equilibrium with immune response is globally stable. This implies that the immune response has a positive role in the reduction of the infected cells.

The paper is organized as follows. In Section 2, we show the positivity and ultimately boundedness of the solutions for (1.2) under suitable initial conditions. Then, we introduce two important parameters, the basic reproduction number for viral infection \( R_0 \) and for CTL response \( R_1 \), defined by (2.4) and (2.5), respectively, and three possible equilibria for (1.2). In Section 3, we establish global asymptotic stability of these equilibria by constructing Lyapunov functional. It is shown that (1.2) always admits one equilibrium which is globally asymptotically stable and, hence, we obtain the complete global dynamics of (1.2). In Section 4, we study discrete delay model which was considered by Zhu and Zou [25] and show that two infected equilibria of their model is not only locally asymptotically stable but also globally asymptotically stable. In Section 5, we offer a brief discussion.

2. Preliminary results

2.1. Positivity and boundedness of the solutions

To investigate the dynamics of (1.2), we set a suitable phase space. Let \( \mathcal{H} = \max \{ h_1, h_2 \} \). We denote by \( C = C([-\mathcal{H}, 0], \mathbb{R}) \) the Banach space of continuous functions mapping the interval \([-\mathcal{H}, 0]\) into \( \mathbb{R} \) equipped with the sup-norm. The nonnegative cone of \( C \) is defined as \( C_+ = C([-\mathcal{H}, 0], \mathbb{R}^+) \). From the biological meanings, the initial conditions for (1.2) are
\[ x(\theta) = \phi_1(\theta), y(\theta) = \phi_2(\theta), v(\theta) = \phi_3(\theta), z(0) = z_0 \text{ for } \theta \in [-\tau, 0], \]  

where \( \phi_i \in C_+, i = 1, 2, 3 \) and \( z_0 \geq 0 \).

**Lemma 2.1** Every solution of (1.2) with (2.1) is nonnegative for \( t > 0 \). Every solution of (1.2) with (2.1) is positive for \( t > \tau \) if \( z_0 > 0 \) and either

i) \( \phi_2(0) + \int_0^{\tau_1} f_1(\tau) \phi_1(-\tau) d\tau > 0 \), or

ii) \( \phi_3(0) + \int_0^{\tau_2} f_2(\tau) \phi_2(-\tau) d\tau > 0 \).

Furthermore, every solution is bounded above by some positive constant for sufficiently large \( t \).

**PROOF.** The solution \((x(t), y(t), v(t), z(t))\) of (1.2) with (2.1) exists and is unique on its maximal interval of existence \((0, \sigma)\) for some \( \sigma > 0 \). We see that \( x(t) > 0 \) for all \( t \in (0, \sigma) \). Indeed, this follows from that \( \frac{dx}{dt} x(t) = s > 0 \) for any \( t \in (0, \sigma) \) when \( x(t) = 0 \) from the first equation of (1.2).

It also holds that

\[ z(t) = z_0 e^{\int_0^t (\alpha(s) - b) ds} \geq 0, \]

if \( z_0 \geq 0 \). In particular, \( z(t) > 0 \) if \( z_0 > 0 \).

Let us show the nonnegativity of \( y(t) \) and \( v(t) \). Since we have

\[ \begin{align*}
  y(t) &= \left( \phi_2(0) + k_d \int_0^t \int_0^{\tau_1} f_1(\tau) x(s-\tau) v(s-\tau) d\tau e^{\int_0^\tau (\delta + p(\zeta)) d\tau} ds \right) e^{-\int_0^t (\delta + p(\zeta)) ds}, \\
  v(t) &= \left( \phi_3(0) + N_d \delta \int_0^t \int_0^{\tau_2} f_2(\tau) y(s-\tau) d\tau e^{\int_0^\tau (\mu) d\tau} ds \right) e^{-\int_0^t (\mu) ds},
\end{align*} \tag{2.2} \]

from (1.2), \( y(t) \geq 0 \) and \( v(t) \geq 0 \) for \( t > 0 \). Now we show \( y(t) > 0 \) and \( v(t) > 0 \) for \( t > \tau \), if i) or ii) holds.

First, we assume that i) holds. Suppose that there exists a \( t_1 \) such that \( y(t_1) = 0 \). Then, from (2.2),

\[ \phi_2(0) + k_d \int_0^{t_1} \int_0^{\tau_1} f_1(\tau) x(s-\tau) v(s-\tau) d\tau e^{\int_0^\tau (\delta + p(\zeta)) d\tau} ds = 0, \]

follows. This leads a contradiction to i). Thus, we obtain

\[ y(t) > 0 \text{ for } t > 0. \tag{2.3} \]

Next, we suppose that there exists a \( t_2 > h_2 \) such that \( v(t_2) = 0 \). Then, from (2.2),

\[ \phi_3(0) + N_d \delta \int_0^{t_2} \int_0^{\tau_2} f_2(\tau) y(s-\tau) d\tau e^{\int_0^\tau (\mu) d\tau} ds = 0, \]

follows. On the other hand, we have

\[ \int_0^t \int_0^{\tau_2} f_2(\tau) y(s-\tau) d\tau ds > 0, \text{ for } t > h_2, \]

by (2.3). This gives a contradiction. Thus, \( v(t) > 0 \) for \( t > h_2 \). Similarly, we see \( v(t) > 0 \) for \( t > 0 \) and \( y(t) > 0 \) for \( t > h_1 \) if ii) holds.

Now we show the boundedness of each solution. Let

\[ G(t) = \frac{k_d}{k} \int_0^{\tau_1} f_1(\tau) x(t-\tau) d\tau + y(t) + \frac{p}{q} z(t), \]

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then we see
\[
\frac{d}{dt} G(t) = \left( \frac{k_d}{k} \int_0^{h_1} f_1(\tau) \left( s - dx(t - \tau) - kx(t - \tau)v(t - \tau) \right) d\tau \right) + \left( k_d \int_0^{h_1} f_1(\tau)x(t - \tau)v(t - \tau) d\tau - \delta y(t) - py(t)z(t) \right) + \left( py(t)z(t) - \frac{p}{q} b z(t) \right)
\]
\[
= \frac{sk_d}{k} - \frac{dk_d}{k} \int_0^{h_1} f_1(\tau)x(t - \tau)d\tau - \delta y(t) - \frac{p}{q} b z(t).
\]
Therefore, it follows that
\[
\frac{d}{dt} G(t) \leq \frac{sk_d}{k} - \min \{d, \delta, b\} G(t),
\]
which implies that \( x(t), y(t) \) and \( z(t) \) are uniformly bounded on \((0, \sigma)\). Then, \( \nu(t) \) is also uniformly bounded on \((0, \sigma)\). Finally, it follows that \((x(t), y(t), v(t), z(t)) \) exists and is unique and positive for any \( t > \bar{t} \). \( \Box \)

**Remark 2.2** \( y(t) \) and \( v(t) \) of (1.2) with (2.1) are identically zero for \( t > 0 \), if
\[
\phi_2(0) = \phi_3(0) = \int_0^{h_1} f_1(\tau) \phi_1(-\tau) \phi_2(-\tau) d\tau = \int_0^{h_2} f_2(\tau) \phi_2(-\tau) d\tau = 0.
\]

### 2.2. Possible equilibria

In this subsection, we show that (1.2) has three possible equilibria. Existence of these equilibria is determined by a combination of two threshold parameters
\[
R_0 = \frac{s}{d N_d}, \quad (2.4)
\]
and
\[
R_1 = \frac{s}{d N_d + \frac{b}{\mu} \delta}, \quad (2.5)
\]

\( R_0 \) and \( R_1 \) are called the basic reproduction number for viral infection and for CTL response, respectively (see Gomez-Acevedo et al. [3]). In particular, \( R_0 \) denotes the average number of secondary virus produced from a single virus for (1.2).

**Theorem 2.3** For (1.2), there exist an uninfected equilibrium
\[
E_0 = (x_0, 0, 0, 0), x_0 = \frac{s}{d}, \quad (2.6)
\]
an infected equilibrium without immune response
\[
E_1 = (x_1^*, y_1^*, v_1^*, 0) = \left( \frac{\mu}{k_d N_d}, \frac{k_d}{k} \left( s - d \frac{\mu}{k_d N_d} \right), \frac{k_d N_d}{k \mu} \left( s - d \frac{\mu}{k_d N_d} \right), 0 \right), \quad (2.7)
\]
if \( R_0 > 1 \), and an infected equilibrium with immune response
\[
E_2 = (x_2^*, y_2^*, v_2^*, z_2^*) = \left( \frac{s}{d + k \frac{N_d \delta}{\mu} \frac{b}{q}}, \frac{b}{\mu} \frac{N_d \delta}{q} \frac{b}{p} \left( \frac{k_d N_d x_2^*}{\mu} - 1 \right) \right), \quad (2.8)
\]
if \( R_1 > 1 \).
PROOF. First of all, we see that (1.2) always has the uninfected equilibrium $E_0$. To find other equilibria, we consider the following equations

\[
\begin{align*}
0 &= s - dx^* - kx^*v^*, \\
0 &= k_d x^*v^* - \delta y^* - p y^*z^*, \\
0 &= N_d \delta y^* - \mu v^*, \\
0 &= qy^*z^* - bz^*.
\end{align*}
\]

(2.9)

Assume that there exists an equilibrium $E_1 = (x_1^*, y_1^*, v_1^*, 0)$ with $x_1^* > 0, y_1^* > 0, v_1^* > 0$. From the third equation of (2.9), we see

\[
y_1^* = \frac{\mu}{N_d \delta} v_1^*.
\]

(2.10)

Substituting (2.10) into the second equation of (2.9) gives

\[
0 = k_d x_1^* v_1^* - \frac{\mu}{N_d} v_1^*.
\]

Hence,

\[
x_1^* = \frac{\mu}{k_d N_d}.
\]

Then from the first equation of (2.9), it follows

\[
v_1^* = \frac{s - dx_1^*}{k x_1^*} = \frac{k_d N_d}{k \mu} \left( s - d \frac{\mu}{k_d N_d} \right).
\]

$\nu_1^*$ and $\nu_1^*$ is positive, if $R_0 > 1$. Consequently, there exists the infected equilibrium $E_1$ if $R_0 > 1$.

Next, we assume that there exists an equilibrium $E_2 = (x_2^*, y_2^*, v_2^*, z_2^*)$ with $x_2^* > 0, y_2^* > 0, v_2^* > 0, z_2^* > 0$. We have

\[
y_2^* = \frac{b}{q} v_2^* = \frac{N_d \delta}{\mu} v_2^*.
\]

(2.11)

from the forth and third equations of (2.9), respectively. Then, we have

\[
x_2^* = \frac{s}{d + k v_2^*} = \frac{s}{d + k \frac{N_d \delta}{\mu} \frac{b}{q}},
\]

(2.12)

and

\[
z_2^* = \frac{k_d x_2^* v_2^* - \delta y_2^*}{p y_2^*},
\]

from the first and second equations of (2.9), respectively. By (2.11) and (2.12), we see

\[
z_2^* = \frac{k_d x_2^* N_d \delta}{p \mu} \left( \frac{\delta}{p} \left( \frac{k_d N_d v_2^*}{\mu} - 1 \right) \right) = \frac{\delta}{p} (R_1 - 1).
\]

Thus, $z_2^*$ is positive if $R_1 > 1$ and, hence, there exists the infected equilibrium with immune response $E_2$. Consequently, the proof is complete. \[\square\]

Remark 2.4 For $R_1 > 1$, there exist three equilibria, $E_0$, $E_1$ and $E_2$. Moreover, we have $x_2^* > x_1^*$ and $y_1^* > y_2^*$, since

\[
x_2^* - x_1^* = \frac{\mu}{k_d N_d} (R_1 - 1) > 0,
\]

and

\[
y_1^* - y_2^* = \frac{k_d}{k \delta} \left( s - d \frac{\mu}{k_d N_d} \frac{k \delta}{k_d} \frac{b}{q} \right) = \frac{k_d}{k \delta} \left( d \frac{\mu}{k_d N_d} + \frac{k \delta}{k_d} \frac{b}{q} \right) (R_1 - 1) > 0.
\]
follows. Therefore, for the equilibrium condition, the immune activation has a positive role in the increasing of the uninfected cells and the reduction of the infected cells. Thus, there exist three possible equilibria depending on the values of $R_0$ and $R_1$ defined by (2.4) and (2.5), respectively. We see that $R_0 > R_1$ always holds.

3. Global asymptotic stability of three equilibria

In this section, we study the global dynamics of (1.2) by employing the method of Lyapunov functional. Lyapunov functionals, we construct here, are inspired by McClusky [13] for SIR epidemic models with distributed delay. From the following result, we see that (1.2) always admits one equilibrium which is globally asymptotically stable and hence, the global dynamics of (1.2) is fully determined by $R_0$ and $R_1$.

**Theorem 3.1**  
(i) If $R_0 \leq 1$, then the uninfected equilibrium $E_0$ for (1.2) is globally asymptotically stable.

(ii) Assume that either i) or ii) in Lemma 2.1 holds. If $R_1 \leq 1 < R_0$, then the infected equilibrium without immune response $E_1$ for (1.2) is globally asymptotically stable.

(iii) Assume that $z_0 > 0$ and either i) or ii) in Lemma 2.1 holds. If $R_1 > 1$, then the infected equilibrium with immune response $E_2$ for (1.2) is globally asymptotically stable.

Before giving the proof of Theorem 3.1, we introduce some notations. In the Lyapunov functionals, the following function is useful.

$$g(x) = x - 1 - \ln x, \text{ for } x \in (0, +\infty).$$

$g(x)$ has the global minimum at $x = 1$ and $g(1) = 0$.

For simplicity, we will use the following notation in the proof

$$\tilde{x}_t = \frac{x(t)}{x_0}, \tilde{x}_{t, \tau} = \frac{x(t - \tau)}{x_0}, \tilde{y}_t = \frac{y(t - \tau)}{y_0}, \tilde{v}_t = \frac{v(t - \tau)}{v_0}, \tilde{z}_t = \frac{z(t)}{z_0},$$

for $\tau \in [0, h]$.

**PROOF.**  
i) We construct the following Lyapunov functional

$$U_0(t) = \frac{k_d}{k} h_1 f_1(\tau) \int_{t-\tau}^{t} x(s)v(s)dsd\tau + \delta \int_{0}^{h_2} f_2(\tau) \int_{t-\tau}^{t} y(s)dsd\tau.$$

**PROOF.**  
i) We construct the following Lyapunov functional

$$U_0(t) = \frac{k_d}{k} h_1 f_1(\tau) \int_{t-\tau}^{t} x(s)v(s)dsd\tau + \delta \int_{0}^{h_2} f_2(\tau) \int_{t-\tau}^{t} y(s)dsd\tau.$$
Next, we obtain
\[
\frac{d}{dt}\left[ x_0 g\left( \frac{x(t)}{x_0} \right) \right] = x_0 \left( 1 - \frac{x_0}{x(t)} \right) (s - dx(t) - kx(t)v(t))
\]
\[
= \left( 1 - \frac{x_0}{x(t)} \right) (dx_0 - dx(t) - kx(t)v(t))
\]
\[
= \left( 1 - \frac{x_0}{x(t)} \right) dx(t) \left( \frac{x_0}{x(t)} - 1 \right) - \left( 1 - \frac{x_0}{x(t)} \right) kx(t)v(t)
\]
\[
= -dx(t) \left( 1 - \frac{x_0}{x(t)} \right)^2 - kx(t)v(t) + kx_0 v(t).
\]
(3.2)

Next, we obtain
\[
\frac{d}{dt}\left( y(t) + \frac{1}{N_d}v(t) + \frac{p}{q}z(t) \right)
\]
\[
= k_d \int_0^{h_1} f_1(\tau) x(t-\tau)v(t-\tau)d\tau - \delta y(t) - py(t)z(t)
\]
\[
+ \frac{1}{N_d} \left( N_d \delta \int_0^{h_2} f_2(\tau)y(t-\tau)d\tau - \mu v(t) \right) + \frac{p}{q} (qy(t)z(t) - bz(t))
\]
\[
= k_d \int_0^{h_1} f_1(\tau) x(t-\tau)v(t-\tau)d\tau - \delta y(t) + \delta \int_0^{h_2} f_2(\tau)y(t-\tau)d\tau - \frac{\mu}{N_d} v(t) - \frac{p}{q} b z(t).
\]
(3.3)

Finally, we obtain
\[
\frac{d}{dt} U_0(t) = k_d \int_0^{h_1} f_1(\tau) (x(t)v(t) - x(t-\tau)v(t-\tau))d\tau + \delta \int_0^{h_2} f_2(\tau)(y(t) - y(t-\tau))d\tau
\]
\[
= k_d \left( x(t)v(t) - \int_0^{h_1} f_1(\tau)x(t-\tau)v(t-\tau)d\tau \right) + \delta \left( y(t) - \int_0^{h_2} f_2(\tau)y(t-\tau)d\tau \right).
\]
(3.4)

Consequently, by adding (3.2), (3.3) and (3.4), we obtain
\[
\frac{d}{dt} U_0(t) = -k_d \frac{d}{k} x(t) \left( 1 - \frac{x_0}{x(t)} \right)^2 + k_d x_0 v(t) - \frac{\mu}{N_d} v(t) - \frac{p}{q} b z(t)
\]
\[
= -k_d \frac{d}{k} x(t) \left( 1 - \frac{x_0}{x(t)} \right)^2 + \left( k_d x_0 - \frac{\mu}{N_d} \right) v(t) - \frac{p}{q} b z(t)
\]
\[
= -k_d \frac{d}{k} x(t) \left( 1 - \frac{x_0}{x(t)} \right)^2 + \frac{\mu}{N_d} (R_0 - 1) v(t) - \frac{p}{q} b z(t) \leq 0, \text{ for } R_0 \leq 1.
\]

Hence, every solution of (1.2) tends to \( M_0 \), where \( M_0 \) is the largest invariant subset in \( \left\{ \frac{dU_0(t)}{dt} = 0 \right\} \) with respect to (1.2). We show that \( M_0 \) consists of only the equilibrium \( E_0 \). Let \( (x(t), y(t), v(t), z(t)) \) be the solution with initial function in \( M_0 \). Then, from the invariance of \( M_0 \), \( x(t) = x_0 \) and \( z(t) = 0 \) for any \( t \). Now we have \( \frac{dx}{dt} x(t) = 0 \) and hence, it follows \( v(t) = 0 \) for any \( t \), from the first equation of (1.2). Then, from the second equation of (1.2), we obtain \( \lim_{t \to +\infty} y(t) = 0 \). Therefore, the uninfected equilibrium \( E_0 \) is globally attractive. Since we have \( \frac{dU_0(t)}{dt} \leq 0 \) for \( R_0 \leq 1 \) and \( U_0(t) \geq U_0(t) - U(t)_0 \), the uninfected equilibrium \( E_0 \) is stable by Hale and Lunel [4, Section 5. Corollary 3.1]. Hence, the uninfected equilibrium \( E_0 \) is globally asymptotically stable for \( R_0 \leq 1 \).

ii) We construct the following Lyapunov functional
\[
U_1(t) = \frac{1}{k_v} g\left( \frac{x(t)}{x_1} \right) + \frac{v_1}{k_d z_1 v_1} g\left( \frac{y(t)}{y_1} \right) + \frac{v_2}{N_d \delta y_1} g\left( \frac{v(t)}{v_1} \right) + \frac{p}{k_d z_1 v_1 q} z(t) + U_1(t),
\]
(3.5)
where
\[ U_1(t) = \int_0^{h_1} f_1(\tau) \int_{t-\tau}^t g \left( \frac{x(s)v(s)}{x^*_1v^*_1} \right) dsd\tau + \int_0^{h_2} f_2(\tau) \int_{t-\tau}^t g \left( \frac{y_1(s)}{y^*_1} \right) dsd\tau. \]

We calculate the time derivative of \( U_1(t) \) along the positive solutions of (1.2) and show that \( \frac{dU_1(t)}{dt} \leq 0 \). First, we have
\[
\frac{d}{dt} \left[ g \left( \frac{x(t)}{x^*_1} \right) \right] = \frac{1}{x^*_1} \left( 1 - \frac{x^*_1}{x(t)} \right) (s - dx(t) - kx(t)v(t)).
\]

Since \( s = dx^*_1 + kx^*_1v^*_1 \) holds, it follows
\[
\frac{d}{dt} \left[ g \left( \frac{x(t)}{x^*_1} \right) \right] = \frac{1}{x^*_1} \left( 1 - \frac{x^*_1}{x(t)} \right) (dx^*_1 + kx^*_1v^*_1 - dx(t) - kx(t)v(t))
= \frac{1}{x^*_1} \left( 1 - \frac{x^*_1}{x(t)} \right) (dx^*_1 - dx(t) + kx^*_1v^*_1 - kx(t)v(t))
= -\frac{dx(t)}{x^*_1} \left( 1 - \frac{x^*_1}{x(t)} \right)^2 + kv^*_1 \left( 1 - \frac{x^*_1}{x(t)} \right) \left( 1 - \frac{x(t)v(t)}{x^*_1v^*_1} \right)
= -\frac{dx(t)}{x^*_1} \left( 1 - \frac{x^*_1}{x(t)} \right)^2 + kv^*_1 \left( 1 - \frac{1}{\bar{x}_k} \right) \left( 1 - \bar{x}_kv_k \right).
\] (3.6)

Secondly, we compute
\[
\frac{d}{dt} \left[ g \left( \frac{y(t)}{y^*_1} \right) \right] = \frac{1}{y^*_1} \left( 1 - \frac{y^*_1}{y(t)} \right) \left( k_d \int_0^{h_1} f_1(\tau) x(t-\tau)v(t-\tau)d\tau - \delta y(t) - py(t)z(t) \right)
= \frac{1}{y^*_1} \left( 1 - \frac{y^*_1}{y(t)} \right) \int_0^{h_1} f_1(\tau) (k_d x(t-\tau)v(t-\tau) - \delta y(t)) d\tau - py(t)z(t).
\]

Since we have \( \delta = \frac{k_d x^*_1 v^*_1}{y^*_1} \), it follows
\[
\frac{d}{dt} \left[ g \left( \frac{y(t)}{y^*_1} \right) \right]
= \frac{k_d x^*_1 v^*_1}{y^*_1} \int_0^{h_1} f_1(\tau) \left( \frac{x(t-\tau)v(t-\tau)}{x^*_1v^*_1} - \frac{y(t)}{y^*_1} \right) d\tau - \frac{1}{y^*_1} \left( 1 - \frac{y^*_1}{y(t)} \right) py(t)z(t)
= \frac{k_d x^*_1 v^*_1}{y^*_1} \int_0^{h_1} f_1(\tau) \left( \frac{x(t-\tau)v(t-\tau)}{x^*_1v^*_1} - \frac{y(t)}{y^*_1} \right) d\tau - \frac{1}{y^*_1} \left( 1 - \frac{y^*_1}{y(t)} \right) py(t)z(t)
= \frac{k_d x^*_1 v^*_1}{y^*_1} \int_0^{h_1} f_1(\tau) \left( \frac{x(t-\tau)v(t-\tau)}{x^*_1v^*_1} - \frac{y(t)}{y^*_1} \right) d\tau - \frac{1}{y^*_1} \left( 1 - \frac{y^*_1}{y(t)} \right) py(t)z(t).
\] (3.7)

Let us calculate the following
\[
\frac{d}{dt} \left[ g \left( \frac{v(t)}{v^*_1} \right) \right] = \frac{1}{v^*_1} \left( 1 - \frac{v^*_1}{v(t)} \right) \left( N_d \delta \int_0^{h_2} f_2(\tau)y(t-\tau)d\tau - \mu v(t) \right).
\]
Since, we have \( \mu = \frac{N_d \delta^* v_1}{v_1} \), it follows

\[
\frac{d}{dt} \left[ g \left( \frac{v(t)}{v_1^*} \right) \right] = \frac{1}{v_1^*} \left( 1 - \frac{v^*_1}{v(t)} \right) \int_0^{h_2} f_2(\tau) \left( N_d \delta y(t-\tau) - N_d \delta y_1^* \frac{v(t)}{v_1^*} \right) d\tau
\]

\[
= N_d \delta y_1^* \frac{1}{v_1^*} \left( 1 - \frac{v^*_1}{v(t)} \right) \int_0^{h_2} f_2(\tau) \left( \frac{y(t-\tau)}{y_1^*} - \frac{v(t)}{v_1^*} \right) d\tau
\]

\[
= N_d \delta y_1^* \left( 1 - \frac{1}{\bar{y}_1} \right) \int_0^{h_2} f_2(\tau) (\tilde{y}_{t,\tau} - \bar{v}_1) d\tau
\]

\[\tag{3.8}\]

Now, we see

\[
\frac{d\tilde{U}_1(t)}{dt} = \int_0^{h_1} f_1(\tau) \left[ g \left( \frac{x(t)v(t)}{x_1^* v_1^*} \right) - g \left( \frac{x(t-\tau)v(t-\tau)}{x_1^* v_1^*} \right) \right] d\tau
\]

\[= \int_0^{h_1} f_1(\tau) (\tilde{x}_1 \tilde{v}_1 - \bar{x}_1 \bar{v}_1) d\tau + \int_0^{h_2} f_2(\tau) (\tilde{y}_{t,\tau} - \bar{v}_1) d\tau.
\] \[\tag{3.9}\]

Consequently, by adding (2.12)-(3.9), we obtain

\[
\frac{d}{dt} U_1(t) = -\frac{d^2(t)}{k_d v_1^* x_1^*} \left( 1 - \frac{x^*_1}{x(t)} \right)^2 + C_1(t, \tau) + C_2(t), \tag{10}\]

where

\[
C_1(t, \tau) = \left( 1 - \bar{x}_1 \bar{v}_1 - \frac{1}{\bar{x}_1} + \bar{v}_1 \right)
\]

\[
+ \int_0^{h_1} f_1(\tau) \left( \tilde{x}_1 \tilde{v}_1 - \frac{\tilde{x}_1 \tau \tilde{v}_1}{\bar{y}_1} - \bar{y}_1 + 1 \right) d\tau + \int_0^{h_2} f_2(\tau) \left( \tilde{y}_{t,\tau} - \bar{v}_1 - \frac{\tilde{y}_{t,\tau}}{\bar{y}_1} + 1 \right) d\tau
\]

\[+ \int_0^{h_1} f_1(\tau) (\tilde{x}_1 \tilde{v}_1 - \bar{x}_1 \bar{v}_1) (\tilde{x}_1 \tilde{v}_1 - \bar{x}_1 \tau \bar{v}_1 \tau + \bar{x}_1 \tau \bar{v}_1 \tau) d\tau.
\] \[\tag{11}\]

and

\[
C_2(t) = -\frac{1}{k_d x_1^* v_1^*} (py(t)z(t) - py_1^* z(t)) + \frac{p}{k_d x_1^* v_1^* q} \left( \frac{d}{dt} z(t) \right)
\]

\[= -\frac{1}{k_d x_1^* v_1^*} (py(t)z(t) - py_1^* z(t)) + \frac{1}{k_d x_1^* v_1^*} \left( \frac{1}{q} \right) (py(t)z(t) - \frac{b}{q} bz(t))
\]

\[= \frac{1}{k_d x_1^* v_1^*} p y^*_1 \left( y^*_1 - \frac{b}{q} \right). \tag{12}\]

Now we claim \( C_2(t) \leq 0 \) for all \( t > 0 \). Since we have \( R_1 \leq 1, s \leq d \frac{\mu}{k_d N_d} + \frac{1}{k_d} \delta^* \frac{h_1}{q} \) holds from (2.4). Then

\[
\frac{k_d}{k_d} \left( s - d \frac{\mu}{k_d N_d} \right) = y^*_1 \leq \frac{b}{q}, \tag{13}\]

10
from (2.7) and hence, \( C_2(t) \leq 0 \).

For \( C_1(t, \tau) \), it holds that

\[
C_1(t, \tau) = \left(1 - \frac{1}{x_i} \right) + \int_0^{h_1} f_1(\tau) \left( -\frac{\hat{x}_i, \tau \hat{y}_i, \tau}{y_i} + 1 \right) \, d\tau + \int_0^{h_2} f_2(\tau) \left( -\frac{\hat{y}_i, \tau}{y_i} + 1 \right) \, d\tau
\]

\[
\quad \quad = \left(1 - \frac{1}{x_i} \right) + \int_0^{h_1} f_1(\tau) \left( -\frac{\hat{x}_i, \tau \hat{y}_i, \tau}{y_i} + 1 \right) \, d\tau + \int_0^{h_2} f_2(\tau) \left( -\frac{\hat{y}_i, \tau}{y_i} + 1 \right) \, d\tau
\]

\[
\quad \quad = \left(1 - \frac{1}{x_i} \right) + \int_0^{h_1} f_1(\tau) \left( -\frac{\hat{x}_i, \tau \hat{y}_i, \tau}{y_i} + 1 + \ln \left(\frac{\hat{x}_i, \tau \hat{y}_i, \tau}{y_i}\right)\right) \, d\tau + \int_0^{h_2} f_2(\tau) \left( -\frac{\hat{y}_i, \tau}{y_i} + 1 + \ln \left(\frac{\hat{y}_i, \tau}{y_i}\right)\right) \, d\tau
\]

\[
\quad \quad = \left(1 - \frac{1}{x_i} + \ln \left(\frac{1}{x_i}\right)\right) - \int_0^{h_1} f_1(\tau) \left( -\frac{\hat{x}_i, \tau \hat{y}_i, \tau}{y_i} \right) \, d\tau - \int_0^{h_2} f_2(\tau) \left( -\frac{\hat{y}_i, \tau}{y_i} \right) \, d\tau \leq 0. \quad (3.15)
\]

Consequently, \( \frac{d C_1(t, \tau)}{dt} \leq 0 \) holds from (3.10), (3.14) and (3.15). Hence, every solution of (1.2) tends to \( M_1 \), where \( M_1 \) is the largest invariant subset in \( \left\{ \frac{d C_1(t, \tau)}{dt} = 0 \right\} \) with respect to (1.2). We show that \( M_1 \) consists of only the equilibrium \( E_1 \). Let \((x(\tau), y(\tau), v(\tau), z(\tau))\) be the solution with initial function in \( M_1 \), then, it holds that

\[
x(\tau) = x_1, \quad \frac{x(t - \tau)v(t - \tau)}{x_1^2 v_1^2} = \frac{y(t)}{y_1^2} \quad \text{for almost} \quad \tau \in [0, h_1] \quad \text{and} \quad \frac{y(t - \tau)}{y_1^2} = \frac{v(t)}{v_1^2} \quad \text{for almost} \quad \tau \in [0, h_2]. \quad (3.16)
\]

From the invariance of \( M_1 \), we have \( \frac{dx}{dt} x(\tau) = 0 \) and it then follows that \( v(\tau) = v_1^* \) for any \( \tau \) from the first equation of (1.2). From (3.16), we obtain \( y(\tau) = y(t - \tau) = y_1^* \) for any \( \tau \) and then, \( z(\tau) = 0 \) follows from the second equation of (1.2). Therefore, the infected equilibrium without immune response \( E_1 \) is globally attractive. Since we have \( \frac{d C_1(t, \tau)}{dt} \leq 0 \) and \( U_1(t) \geq U_1(t) - \bar{U}_1(t) \), the infected equilibrium without immune response \( E_1 \) is stable by Hale and Lunel [4, Section 5, Corollary 3.1]. Hence, the infected equilibrium without immune response \( E_1 \) is globally asymptotically stable for \( R_1 \leq 1 < R_0 \).

iii) We construct the following Lyapunov functional

\[
U_2(t) = \frac{1}{k v_2^2} g \left( \frac{x(t)}{x_2} \right) + \frac{y_2}{k d x_2^2 v_2^2} g \left( \frac{y(t)}{y_2} \right) + \frac{v_2^2}{N_d \delta v_2^2} g \left( \frac{v(t)}{v_2^2} \right) + \frac{p z_2^2}{k_d x_2^2 v_2^2} g \left( \frac{z(t)}{z_2^2} \right) + \bar{U}_2(t),
\]

where

\[
\bar{U}_2(t) = \int_0^{h_1} f_1(\tau) \int_{\tau}^t \left( \frac{x(s) v(s)}{x_2^2 v_2^2} \right) \, ds \, d\tau + \int_0^{h_2} f_2(\tau) \int_{\tau}^t \left( \frac{y(s)}{y_2} \right) \, ds \, d\tau.
\]

Similar to (2.12), we obtain

\[
\frac{d}{dt} \left[ g \left( \frac{x(t)}{x_2} \right) \right] = -\frac{dx(t)}{x_2^2} \left( 1 - \frac{x_1^2}{x(t)^2} \right) + k v_2 \left( 1 - \frac{x_1^2}{x(t)} - \frac{1}{x_1^2} + \frac{1}{x(t)} \right). \quad (3.18)
\]
We also obtain
\[
\frac{d}{dt} \left[ g \left( y(t) \right) \right] = \frac{1}{y^2} \left( 1 - \frac{y^2}{y(t)} \right) \left( k_d \int_{0}^{h_1} f_1(\tau) x(t-\tau) v(t-\tau) d\tau - \delta y(t) - py(t)z(t) \right).
\]

Since we have \( \delta y_2^2 = k_d x_2^2 v_2 - py_2^2 z_2^4 \), it holds
\[
\delta = \frac{1}{y^2} \left( k_d x_2^2 v_2 - py_2^2 z_2^4 \right).
\]

Then
\[
\frac{d}{dt} \left[ g \left( y(t) \right) \right]
= \frac{1}{y^2} \left( 1 - \frac{y^2}{y(t)} \right) \left( k_d \int_{0}^{h_1} f_1(\tau) x(t-\tau) v(t-\tau) d\tau - \frac{1}{y^2} \left( k_d x_2^2 v_2 - py_2^2 z_2^4 \right) y(t) - py(t)z(t) \right)
\]
\[
= \frac{1}{y^2} \left( 1 - \frac{y^2}{y(t)} \right) \left[ \int_{0}^{h_1} f_1(\tau) \left( k_d x(t-\tau) v(t-\tau) - k_d x_2^2 v_2 \frac{y(t)}{y^2} \right) d\tau + \left( pz_2^2 y(t) - py(t)z(t) \right) \right]
\]
\[
= \frac{1}{y^2} \left( 1 - \frac{y^2}{y(t)} \right) \left( k_d x_2^2 v_2 \frac{y(t)}{y^2} \right) d\tau
\]
\[
+ \frac{1}{y^2} \left( 1 - \frac{y^2}{y(t)} \right) \left( pz_2^2 y(t) - py(t)z(t) \right)
\]
\[
= \frac{k_d x_2^2 v_2}{y^2} \left( 1 - \frac{y^2}{y(t)} \right) \int_{0}^{h_1} f_1(\tau) \left( \frac{x(t-\tau) v(t-\tau)}{x_2^2 v_2} - \frac{y(t)}{y^2} \right) d\tau
\]
\[
+ pz_2^2 \left( 1 - \frac{y^2}{y(t)} \right) \left( \frac{y(t)}{y^2} - \frac{y(t)z(t)}{y_2^2} \right)
\]
\[
= \frac{k_d x_2^2 v_2}{y^2} \left( 1 - \frac{1}{y_f} \right) \int_{0}^{h_1} f_1(\tau) \left( \frac{y_f \tau - y_f}{y_f} + 1 \right) d\tau + pz_2^2 \left( \frac{y_f}{y_f} - 1 \right) (1 - \frac{1}{y_f}) \left( y_f - y_f\right).
\]

Similar to (3.8), we also obtain
\[
\frac{d}{dt} \left[ g \left( v(t) \right) \right] = \frac{N_d \delta v_2^2}{v_2^2} \int_{0}^{h_2} f_2(\tau) \left( \frac{y_f}{y_f} - \frac{y_f \tau}{y_f} + 1 \right) d\tau.
\]

Let us calculate
\[
\frac{d}{dt} \left[ g \left( z(t) \right) \right] = \frac{1}{z^2} \left( 1 - \frac{z^2}{z(t)} \right) (qy(t)z(t) - bz(t)) = \frac{1}{z^2} \left( 1 - \frac{z^2}{z(t)} \right) (qy(t)z(t) - qy^2 z(t))
\]
\[
= \frac{z(t)}{z^2} - 1 \right) (qy(t) - qy^2 z(t))
\]
\[
= qy^2 \left( \frac{z(t)}{z^2} - 1 \right) \left( \frac{y(t)}{v_2^2} - 1 \right)
\]
\[
= qy^2 \left( \frac{z(t)}{z^2} - 1 \right) \left( \frac{y(t)}{v_2^2} - 1 \right)
\]
\[
= qy^2 \left( \frac{z(t)}{z^2} - 1 \right) \left( \frac{y(t)}{v_2^2} - 1 \right).
\]

Similar to (3.9), we obtain
\[
\frac{dU_2(t)}{dt} = \int_0^{h_1} f_1(\tau) \left( \bar{x}_r \bar{v}_t - \ln (\bar{x}_r \bar{v}_t) - \bar{x}_r \tau \bar{v}_t \tau + \ln (\bar{x}_r \tau \bar{v}_t) \right) d\tau + \int_0^{h_2} f_2(\tau) \left( \bar{y}_t - \ln \bar{y}_t - \bar{y}_t \tau + \ln \bar{y}_t \tau \right) d\tau.
\] (3.22)

Consequently, by adding (3.18)-(3.22), we obtain
\[
\frac{d}{dt} U_2(t) = - \frac{dx(t)}{x_2^*} \left( 1 - \frac{x_2^*}{x(t)} \right)^2 + C_3(t, \tau),
\] (3.23)

where
\[
C_3(t, \tau)
\]
\[= \left( 1 - \bar{x}_r \bar{v}_t - \frac{1}{x_r} + \bar{v}_t \right)
\]
\[+ \int_0^{h_1} f_1(\tau) \left( \bar{x}_r \tau \bar{v}_t \tau - \bar{y}_t - \bar{x}_r \tau \bar{v}_t + 1 \right) d\tau + \int_0^{h_2} f_2(\tau) \left( \bar{y}_t - \bar{y}_t \tau + 1 \right) d\tau
\]
\[+ \left[ \frac{y_2^*}{k_2 \bar{x}_r \bar{v}_t} (1 - \bar{x}_r) + \frac{p_2^*}{k_2 \bar{x}_r v_2^*} \bar{q} \right] \int_0^{h_1} f_1(\tau) \left( \bar{x}_r \tau \bar{v}_t \tau - \bar{y}_t \bar{v}_t + \ln (\bar{x}_r \tau \bar{v}_t) \right) d\tau + \int_0^{h_2} f_2(\tau) \left( \bar{y}_t - \ln \bar{y}_t + \ln \bar{y}_t \tau \right) d\tau
\]
\[= \left( 1 - \bar{x}_r \bar{v}_t - \frac{1}{x_r} + \bar{v}_t \right)
\]
\[+ \int_0^{h_1} f_1(\tau) \left( \bar{x}_r \tau \bar{v}_t \tau - \bar{y}_t - \bar{x}_r \tau \bar{v}_t + 1 \right) d\tau + \int_0^{h_2} f_2(\tau) \left( \bar{y}_t - \bar{y}_t \tau + 1 \right) d\tau
\]
\[+ \int_0^{h_1} f_1(\tau) \left( \bar{x}_r \tau \bar{v}_t \tau - \bar{y}_t \bar{v}_t + \ln (\bar{x}_r \tau \bar{v}_t) \right) d\tau + \int_0^{h_2} f_2(\tau) \left( \bar{y}_t - \ln \bar{y}_t + \bar{y}_t \tau + \ln \bar{y}_t \tau \right) d\tau.
\]

Similar to (3.11), we see
\[
C_3(t, \tau) = -g \left( \frac{1}{x_r} \right) - \int_0^{h_1} f_1(\tau) g \left( \frac{\bar{x}_r \tau \bar{v}_t \tau}{\bar{y}_t} \right) d\tau - \int_0^{h_2} f_2(\tau) g \left( \frac{\bar{y}_t \tau}{\bar{y}_t} \right) d\tau \leq 0. \] (3.24)

Thus, \( \frac{dU_2(t)}{dt} \leq 0 \) holds from (3.23) and (3.24). Hence, the solution of system (1.2) limit to \( M_2 \), where \( M_2 \) is the largest invariant subset in \( \{ \frac{dU_2(t)}{dt} = 0 \} \) with respect to (1.2). We show that \( M_2 \) consists of only the equilibrium \( E_2 \). Let \( (x(t), y(t), v(t), z(t)) \) be the solution with initial function in \( M_2 \), then it holds that
\[
x(t) = x_2^*, \quad \frac{x(t - \tau)v(t - \tau)}{x_2^* v_2^*} = \frac{y(t)}{y_2^*} \quad \text{for almost } \tau \in [0, h_1] \quad \text{and} \quad \frac{y(t - \tau)}{y_2^*} = \frac{v(t)}{v_2^*} \quad \text{for almost } \tau \in [0, h_2].
\] (3.25)

From the invariance of \( M_2 \), we have \( \frac{dx(t)}{dt} = 0 \) and it then follows that \( v(t) = v_2^* \) for any \( t \) from the first equation of (1.2). From (3.25), we obtain \( y(t) = y(t - \tau) = y_2^* \) for any \( t \) and then, \( z(t) = z_2^* \) follows from the second equation of (1.2). Therefore, the infected equilibrium with immune response \( E_2 \) is globally attractive. Since we have \( \frac{dU_2(t)}{dt} \leq 0 \) and \( U_2(t) \geq U_2(t) - U_2(t) \), the infected equilibrium with immune response \( E_2 \) is stable by Hale and Lunel [4, Section 5, Corollary 3.1]. Hence, the infected equilibrium with immune response \( E_2 \) is globally asymptotically stable for \( R_1 > 1 \).
Finally, the proof of this theorem is complete. \(\square\)

4. Applications

Our approach is applicable for discrete delay models. Zhu and Zou [25] studied the following viral infection model with cell-mediated immunity.

\[
\begin{aligned}
\frac{dx(t)}{dt} &= s - dx(t) - kx(t)v(t), \\
\frac{dy(t)}{dt} &= ke^{-\delta\tau}x(t-\tau)v(t-\tau) - dy(t) - py(t)z(t), \\
\frac{dz(t)}{dt} &= \mu y(t), \\
\end{aligned}
\]

(4.1)

with the initial conditions \(x(\theta) = \phi_1(\theta), y(0) = y_0, v(\theta) = \phi_3(\theta), z(0) = z_0\) for \(\theta \in [-\tau, 0]\), where \(\phi_i(\theta) \in C([-\tau, 0], \mathbb{R}_+), i = 1, 3, y_0 \geq 0\) and \(z_0 \geq 0\). All parameters are positive constant.

For (4.1), similar to (1.2), there exist three possible equilibria. From (2.4) and (2.5), the basic reproduction number for viral infection and for CTL response are given by

\[
\mathcal{R}_0 = \frac{s}{dke^{-\sigma N}} \quad \text{and} \quad \mathcal{R}_1 = \frac{s}{dke^{-\sigma N} + e^{\delta \sigma} b z}.
\]

respectively. There exist the uninfected equilibrium \(E_0(x_0, 0, 0, 0), x_0 = \frac{R}{7}\), the infected equilibrium without immune response \(E_1(x_{01}, y_{01}, 0) (x_{01}, y_{01}, 0 > 0)\) if \(\mathcal{R}_0 > 1\) and the infected equilibrium with immune response \(E_2(x_{02}, y_{02}, 0) (x_{02}, y_{02}, 0 > 0)\) if \(\mathcal{R}_1 > 1\) (see also [25, Section 3]).

Zhu and Zou [25] established the global asymptotic stability of the uninfected equilibrium \(E_0\) for \(\mathcal{R}_0 < 1\). Moreover, they obtained sufficient conditions for the local asymptotic stability of infected equilibria \(E_1\) and \(E_2\) by analysis of associated characteristic equations. Complete global dynamics for (4.1) is not clear and an open problem. However, similar to Theorem 3.1 in Section 3, we establish the following result.

**Theorem 4.1**

i) If \(\mathcal{R}_0 \leq 1\), then the uninfected equilibrium \(E_0\) for (4.1) is globally asymptotically stable.

ii) Assume \(y_0 > 0 + \int_0^\infty f_1(\tau) \phi_1(-\tau) \phi_1(-\tau) d\tau > 0\), \(\phi_3(0) > 0\). If \(\mathcal{R}_1 > 1 < \mathcal{R}_0\), then the infected equilibrium without immune response \(E_1\) for (4.1) is globally asymptotically stable.

iii) Assume \(z_0 > 0\) and either \(y_0 + \int_0^\infty f_1(\tau) \phi_1(-\tau) \phi_1(-\tau) d\tau > 0\), \(\phi_3(0) > 0\). If \(\mathcal{R}_1 < 1\), then the infected equilibrium with immune response \(E_2\) for (4.1) is globally asymptotically stable.

Zhu and Zou [25, Theorems 3.3, 3.4] showed that the infected equilibrium without immune response \(E_1\) is locally asymptotically stable for \(\mathcal{R}_1 < 1 < \mathcal{R}_0\) and the infected equilibrium with immune response \(E_2\) is locally asymptotically stable for \(\mathcal{R}_1 > 1\) if the intracellular delay \(\tau\) satisfies a condition (see [25, Theorem 3.4]). However, by Theorem 4.1, we establish that \(E_1\) is not only locally asymptotically stable but also globally asymptotically stable for \(\mathcal{R}_1 < 1 < \mathcal{R}_0\). Moreover, \(E_2\) is globally asymptotically stable, whenever it exists, that is, \(\mathcal{R}_1 > 1\).

5. Discussion

In this paper, we study global dynamics of delay differential equations for a virus-immune interaction in vivo. Two distributed time delays represent the time needed for infection of cell
and virus replication. Stability analysis for (1.2) with discrete intracellular delay was carried out by Li and Shu [10] and Zhu and Zou [25]. Li and Shu [10] studied aviral infection model which ignores the immune response to the viral infection and showed that their model always admits an equilibrium which is globally asymptotically stable. Recently, Li and Shu [11] has investigated a general viral infection model with distributed delay which also does not incorporate the immune response. Zhu and Zou [25] established global stability of an uninfected equilibrium and obtained sufficient conditions for local asymptotic stability of two infected equilibria when the distributed delay in (1.2) is given by a discrete. Zhu and Zou [25] did not address the global stability of two infected equilibria for their model.

To obtain an integrated view for the virus-immune interaction dynamics in vivo, we investigate the global stability of (1.2) by employing the method of Lyapunov functionals which are motivated by McClusky [13] for delayed epidemic models. (1.2) has three possible equilibria, an uninfected equilibrium and two infected equilibria with or without immune response. A combination of the basic reproduction number for viral infection $R_0$ and for CTL response $R_1$, defined by (2.4) and (2.5), respectively, determine the existence of these equilibria. Moreover, they also fully determine the global dynamics of the model. The uninfected equilibrium $E_0$ is globally asymptotically stable if $R_0 \leq 1$ and the viruses are cleared. The infected equilibrium without immune response $E_1$ is globally asymptotically stable if $R_1 \leq 1 < R_0$ and the infection becomes chronic but with no persistent immune response. The infected equilibrium with immune response $E_2$ is globally asymptotically stable if $R_1 > 1$ and the infection becomes chronic with immune response. Theorem 3.1 is an extension result of the global stability results in Prüss et al. [20] and Li and Shu [10]. Moreover, we improve stability results in Zhu and Zou [25] (see Section 4).

We see that virus eventually persists if $R_0 > 1$, because the infected equilibrium $E_1$ or $E_2$ is globally asymptotically stable in this case. The infected equilibrium without immune response $E_1$ is globally asymptotically stable and the immune response does not work for $R_0 > 1 \geq R_1$. On the other hand, the immune response is activated and there exist two infected equilibria $E_1 = (x_1^*, y_1^*, v_1^*, 0)$ and $E_2 = (x_2^*, y_2^*, v_2^*, z_2^*)$ for $R_1 > 1$. Moreover, in these equilibria, one can see that the relations $x_1^* < x_2^*$ and $y_2^* < y_1^*$ hold due to the effect of immunity (see also Remark 2.4). Therefore, the global stability of $E_2$ for $R_1 > 1$ indicates that the immune activation has a positive role in the reduction of the infected cells and the increasing of the uninfected cells for $R_1 > 1$.

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