

Research Article

Global Analysis of a Model of Viral Infection with Latent Stage and Two Types of Target Cells

Shuo Liu,¹ Lina Ma,² Jianquan Li,³ and Qingbo Zhao¹

¹ School of Biomedical Engineering, The Fourth Military Medical University, Xi'an 710032, China

² College of Mathematics and Information Science, Shaanxi Normal University, Xi'an 710062, China

³ College of Science, Air Force Engineering University, Xi'an 710051, China

Correspondence should be addressed to Jianquan Li; jianq.li@263.net

Received 23 June 2013; Accepted 8 September 2013

Academic Editor: Fernando Simões

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By introducing the probability function describing latency of infected cells, we unify some models of viral infection with latent stage. For the case that the probability function is a step function, which implies that the latency period of the infected cells is constant, the corresponding model is a delay differential system. The model with delay of latency and two types of target cells is investigated, and the obtained results show that when the basic reproduction number is less than or equal to unity, the infection-free equilibrium is globally stable, that is, the in-host free virus will be cleared out finally; when the basic reproduction number is greater than unity, the infection equilibrium is globally stable, that is, the viral infection will be chronic and persist in-host. And by comparing the basic reproduction numbers of ordinary differential system and the associated delayed differential system, we think that it is necessary to elect an appropriate type of probability function for predicting the final outcome of viral infection in-host.

1. Introduction

The dynamical models of virus infection have played an important role in understanding the action of in-host free virus on target cells. Nowak et al. [1, 2] proposed one of the earliest of these models:

$$\begin{aligned}x' &= \lambda - dx - \beta xv, \\y' &= \beta xv - ay, \\v' &= kay - \gamma v,\end{aligned}\tag{1}$$

where $x = x(t)$, $y = y(t)$, and $v = v(t)$ are the concentrations of uninfected cells, infected cells, and viral particles (virions) at time t , respectively. In model (1), uninfected target cells are assumed to be produced at a constant rate λ and die at a rate dx . Infection of target cells by in-host free virus is assumed to occur at a bilinear rate βxv . Infected cells are lost at a rate ay . Free virus are produced by infected cells at a rate kay in which k is the average number of viral particles produced by a single infected cell over its lifetime and die at a rate γv .

Model (1) is a basic model of viral infection, which has been used widely to investigate infection of some viruses (such as, HIV, HBV, HCV, and HLTV). However, following infection of virus, within a cell the provirus may remain latent, giving no sign of its presence for months or years [3]. According to this fact, in order to investigate HIV-1 dynamics in vivo, Perelson et al. incorporated the latently infected cells into the basic model (1) [4, 5]. It implies that the development of infected cell should include latent and active two stages. That is, once infected, a cell first becomes a latently infected cell, but does not produce virus; after a period of time a latently infected cell turns active and begins to produce virus. The global stability of some ODE models of viral infection with latent stage is considered in [6, 7].

In 1997, Perelson et al. [8] observed that HIV attacks two types of target cells, $CD4^+$ T cells and macrophages. On the other hand, it was also detected that, except for liver tissue, HCV may be produced in some extrahepatic tissues, such as bone marrow [9], peripheral blood mononuclear cells (PBMC) [10], brain [11], and lymph nodes [12]. Then, according to these virological findings, based on model (1),

some viral dynamical models with two types of target cells were proposed [5, 13, 14], which are all expressed by ordinary differential equations.

Since the dynamics of viral infection in-host is not well understood, in order to investigate the mechanism of viral infection, some reasonable assumptions are often incorporated into mathematical models describing the interaction between target cells and viral particles. In this paper, we first introduce the probability functions describing the latency of infected cells to unify some models of viral infection with latent stage and then analyze dynamics of viral infection model with constant latency period and two types of target cells. The discussed model is a system of delay differential equations.

The organization of this paper is as follows. In Section 2, we unify some models of viral infection with latent stage by introducing the probability function describing latency of infected cells and propose a model of virus infection with latent delay and two types of target cells. The global stability is analyzed in Section 3. At last, the conclusion on the model is summarized, and the basic reproduction numbers of ordinary differential system and the associated delay differential system are compared.

2. Models

Let $Q(t)$ for $t \geq 0$ denote the probability that an infected cell is in the latent stage at least t time units before becoming the actively infected cell, and then, when the infection rate of virus is assumed to be $\beta x(t)v(t)$, the concentration of the latently infected cells at time t can be expressed by the following equation:

$$w(t) = w_0(t) + \int_0^t \beta x(\theta) v(\theta) Q(t - \theta) e^{-d(t-\theta)} d\theta, \quad (2)$$

where $w_0(t)$ is the concentration of the latently infected cells which are in the latent stage at time 0 and still at the same state at time t . Function $w_0(t)$ is a nonnegative, non-increasing, and piecewise continuous function. Thus, when incorporating the latent stage of infected cells into the basic model (1), we have the model of viral infection with latent stage:

$$\begin{aligned} x' &= \lambda - dx - \beta xv, \\ w(t) &= w_0(t) + \int_0^t \beta x(\theta) v(\theta) Q(t - \theta) e^{-d(t-\theta)} d\theta, \\ y' &= F(x, y, w) - ay, \\ v' &= kay - \gamma v, \end{aligned} \quad (3)$$

where the term $F(x, y, w)$ in the third equation of (3) represents the recruitment rate of actively infected cells; its expression should depend on the form of function $Q(t)$.

Usually, function $Q(t)$ is elected as one of the following two types, the exponential function (i.e., $Q(t) = \exp(-\varepsilon t)$) and the step function (i.e., $Q(t)$ equals to 1 for $t \in [0, \tau]$ and 0 for $t \in [\tau, +\infty)$) [15, 16]. Here, the exponential function

means that the transfer of the infected cells from the latent state to the active one follows the exponential distribution, and the step function means that the time length of staying at the latent state for the infected cells is constant τ and that they become active after the time period τ . It is easy to know that the average latency period of the infected cells is $1/\varepsilon$ for the exponential function and τ for the step function.

When $Q(t) = \exp(-\varepsilon t)$, (2) becomes

$$w(t) = w_0 e^{-(d+\varepsilon)t} + \int_0^t \beta x(\theta) v(\theta) e^{-(d+\varepsilon)(t-\theta)} d\theta, \quad (4)$$

where w_0 is the concentration of the latently infected cells at $t = 0$, then we have

$$w'(t) = \beta x(t) v(t) - (d + \varepsilon) w(t). \quad (5)$$

From the equation of w , we know that the removed rate of the latently infected cells is $(d + \varepsilon)w$, where d is the death rate coefficient of uninfected cells; then εw is the infection-induced transfer rate to actively infected cells, that is, $F(x, y, w) = \varepsilon w$. So, system (3) becomes

$$\begin{aligned} x' &= \lambda - dx - \beta xv, \\ w' &= \beta xv - (d + \varepsilon) w, \\ y' &= \varepsilon w - ay, \\ v' &= kay - \gamma v. \end{aligned} \quad (6)$$

When $Q(t)$ is a step function, that is,

$$Q(t) = \begin{cases} 1 & \text{for } t \in [0, \tau), \\ 0 & \text{for } t \in [\tau, +\infty), \end{cases} \quad (7)$$

$w_0(t) = 0$ for $t \geq \tau$. Thus, for $t \geq \tau$ the integral equation (2) becomes

$$w(t) = \int_{t-\tau}^t \beta x(\theta) v(\theta) e^{-d(t-\theta)} d\theta. \quad (8)$$

It is equivalent to the following delay differential equation:

$$w'(t) = \beta x(t) v(t) - \beta e^{-d\tau} x(t - \tau) v(t - \tau) - dw(t), \quad (9)$$

with $w(0) = \int_{-\tau}^0 \beta x(\theta) v(\theta) e^{d\theta} d\theta$, where the term $\beta e^{-d\tau} x(t - \tau) v(t - \tau)$ represents the recruitment rate of the actively infected cells for $t > \tau$. Thus, when investigating the long-term behavior of model (3), the corresponding model with constant latent period is given by

$$\begin{aligned} x' &= \lambda - dx - \beta xv, \\ w' &= \beta xv - \beta e^{-d\tau} x(t - \tau) v(t - \tau) - dw, \\ y' &= \beta e^{-d\tau} x(t - \tau) v(t - \tau) - ay, \\ v' &= kay - \gamma v. \end{aligned} \quad (10)$$

From the inference above, we may see that models (6) and (10) can be unified into model (3) and are two special cases

of (3). This is due to the introduction of the probability function $Q(t)$. Global properties of models (6) and (10) were investigated in [6, 17], respectively.

When considering the case that virus attacks two types of target cells, we denote the corresponding quantities by the same letters as model (3) with the subscript 1 or 2. The subscript represents the type of target cells. Thus, we have the following model with latent stage and two types of target cells:

$$\begin{aligned}
 x_1' &= \lambda_1 - d_1 x_1 - \beta_1 x_1 v, \\
 w_1(t) &= w_{10}(t) \\
 &+ \int_0^t \beta_1 x_1(\theta) v(\theta) Q_1(t - \theta) e^{-d_1(t-\theta)} d\theta, \\
 y_1' &= F_1(x_1, y_1, w_1) - a_1 y_1, \\
 x_2' &= \lambda_2 - d_2 x_2 - \beta_2 x_2 v, \\
 w_2(t) &= w_{20}(t) \\
 &+ \int_0^t \beta_2 x_2(\theta) v(\theta) Q_2(t - \theta) e^{-d_2(t-\theta)} d\theta, \\
 y_2' &= F_2(x_2, y_2, w_2) - a_2 y_2, \\
 v' &= k_1 a_1 y_1 + k_2 a_2 y_2 - \gamma v.
 \end{aligned} \tag{11}$$

Similarly, when the probability functions in (11) are exponential function, model (11) can become

$$\begin{aligned}
 x_1' &= \lambda_1 - d_1 x_1 - \beta_1 x_1 v, \\
 w_1' &= \beta_1 x_1 v - (d_1 + \varepsilon_1) w_1, \\
 y_1' &= \varepsilon_1 w_1 - a_1 y_1, \\
 x_2' &= \lambda_2 - d_2 x_2 - \beta_2 x_2 v, \\
 w_2' &= \beta_2 x_2 v - (d_2 + \varepsilon_2) w_2, \\
 y_2' &= \varepsilon_2 w_2 - a_2 y_2, \\
 v' &= k_1 a_1 y_1 + k_2 a_2 y_2 - \gamma v.
 \end{aligned} \tag{12}$$

Its dynamical behavior was analyzed in [7].

When the probability functions in (11) are step function, for $t > \tau := \max\{\tau_1, \tau_2\}$, model (11) can become

$$\begin{aligned}
 x_1'(t) &= \lambda_1 - d_1 x_1(t) - \beta_1 x_1(t) v(t), \\
 w_1'(t) &= \beta_1 x_1(t) v(t) - \beta_1 e^{-d_1 \tau_1} x_1(t - \tau_1) \\
 &\quad \times v(t - \tau_1) - d_1 w_1(t), \\
 y_1'(t) &= \beta_1 e^{-d_1 \tau_1} x_1(t - \tau_1) v(t - \tau_1) - a_1 y_1(t),
 \end{aligned}$$

$$\begin{aligned}
 x_2'(t) &= \lambda_2 - d_2 x_2(t) - \beta_2 x_2(t) v(t), \\
 w_2'(t) &= \beta_2 x_2(t) v(t) - \beta_2 e^{-d_2 \tau_2} x_2(t - \tau_2) \\
 &\quad \times v(t - \tau_2) - d_2 w_2(t), \\
 y_2' &= \beta_2 e^{-d_2 \tau_2} x_2(t - \tau_2) v(t - \tau_2) - a_2 y_2(t), \\
 v' &= k_1 a_1 y_1(t) + k_2 a_2 y_2(t) - \gamma v(t).
 \end{aligned} \tag{13}$$

For system (13), variables w_1 and w_2 do not appear in the equations of x_i , y_i ($i = 1, 2$), and v , then denoting $b_1 = e^{-d_1 \tau_1}$, and $b_2 = e^{-d_2 \tau_2}$, gives a subsystem of (13) as follows:

$$\begin{aligned}
 x_1'(t) &= \lambda_1 - d_1 x_1(t) - \beta_1 x_1(t) v(t), \\
 y_1'(t) &= \beta_1 b_1 x_1(t - \tau_1) v(t - \tau_1) - a_1 y_1(t), \\
 x_2'(t) &= \lambda_2 - d_2 x_2(t) - \beta_2 x_2(t) v(t), \\
 y_2' &= \beta_2 b_2 x_2(t - \tau_2) v(t - \tau_2) - a_2 y_2(t), \\
 v' &= k_1 a_1 y_1(t) + k_2 a_2 y_2(t) - \gamma v(t).
 \end{aligned} \tag{14}$$

In this paper, we will investigate the global behaviors of system (14).

For system (14), we set a suitable phase space. Denote the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into \mathbb{R}^5 with the sup-norm for $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5)^T \in C$ by $C = C([-\tau, 0], \mathbb{R}^5)$, where $\tau = \max\{\tau_1, \tau_2\}$. The nonnegative cone of C is defined as $C_+ = C([-\tau, 0]; \mathbb{R}_+^5)$. From the biological meaning, the initial conditions for system (14) are given as follows:

$$\begin{aligned}
 x_1(\theta) &= \phi_1(\theta), \quad y_1(\theta) = \phi_2(\theta), \quad x_2(\theta) = \phi_3(\theta), \\
 y_2(\theta) &= \phi_4(\theta), \quad v(\theta) = \phi_5(\theta), \quad \theta \in [-\tau, 0],
 \end{aligned} \tag{15}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta))^T \in C_+$ and $\phi_i(0) > 0$, $i = 1, 2, 3, 4, 5$.

Under the initial conditions (15), it is easy to see that all solutions of system (14) are positive on $[0, +\infty)$. Furthermore, we have the following statement with respect to the boundedness of solutions of system (14).

Theorem 1. *All solutions of system (14) under the initial conditions (15) are ultimately bounded.*

Proof. Define a Lyapunov functional $L_{01} = b_1 x_1(t) + y_1(t + \tau_1)$ then from the first two equations of (14), we have

$$\begin{aligned}
 L_{01}' &= b_1 \lambda_1 - [b_1 d_1 x_1(t) + a_1 y_1(t + \tau_1)] \\
 &\leq b_1 \lambda_1 - \rho_1 L_{01},
 \end{aligned} \tag{16}$$

where $\rho_1 = \min\{d_1, a_1\}$. It follows that $\limsup_{t \rightarrow +\infty} [b_1 x_1(t) + y_1(t + \tau_1)] \leq b_1 \lambda_1 / \rho_1$, that is, for any positive number ε there is $T_1 > 0$ such that $b_1 x_1(t) + y_1(t + \tau_1) < b_1 \lambda_1 / \rho_1 + \varepsilon$ for $t > T_1$.

Similarly, from the third and fourth equations of (14) we know that for any positive number ε there is $T_2 > 0$ such that $b_2 x_2(t) + y_2(t + \tau_2) < b_2 \lambda_2 / \rho_2 + \varepsilon$ for $t > T_2$, where $\rho_2 = \min\{d_2, a_2\}$.

Therefore, for $t > T = \max\{T_1 + \tau, T_2 + \tau\}$, we have $y_1(t) < b_1 \lambda_1 / \rho_1 + \varepsilon$ and $y_2(t) < b_2 \lambda_2 / \rho_2 + \varepsilon$. Thus, from the last equation of (14), it follows that

$$v'(t) < k_1 a_1 \left(\frac{b_1 \lambda_1}{\rho_1} + \varepsilon \right) + k_2 a_2 \left(\frac{b_2 \lambda_2}{\rho_2} + \varepsilon \right) - \gamma v(t), \quad (17)$$

for $t > T$. It implies that

$$\limsup_{t \rightarrow +\infty} v(t) \leq \frac{1}{\gamma} \left[k_1 a_1 \left(\frac{b_1 \lambda_1}{\rho_1} + \varepsilon \right) + k_2 a_2 \left(\frac{b_2 \lambda_2}{\rho_2} + \varepsilon \right) \right]. \quad (18)$$

Summarizing the above inference, Theorem 1 holds. \square

Since the positive number ε in the proof of Theorem 1 is arbitrary, we can know that the set

$$\Omega = \left\{ x^T(t) \in C_+ : b_i x_i(t) + y_i(t + \tau_i) \leq \frac{b_i \lambda_i}{\rho_i}, i = 1, 2, v(t) \leq \bar{v} \right\} \quad (19)$$

is positively invariant to system (14), where $x(t) = (x_1(t), y_1(t), x_2(t), y_2(t), v(t))$, $\bar{v} = (k_1 a_1 b_1 \lambda_1 / \rho_1 + k_2 a_2 b_2 \lambda_2 / \rho_2) / \gamma$. Therefore, we will consider system (14) on the set Ω .

3. Global Stability

In this section, we will investigate the existence and stability of equilibria of system (14).

Obviously, (14) always has the infection-free equilibrium $E_0(x_{10}, 0, x_{20}, 0, 0)$, where $x_{10} = \lambda_1 / d_1$ and $x_{20} = \lambda_2 / d_2$. The infection equilibrium $E^*(x_1^*, y_1^*, x_2^*, y_2^*, v^*)$ ($v^* > 0$) is determined by the following equations:

$$\begin{aligned} \lambda_1 - d_1 x_1 - \beta_1 x_1 v &= 0, \\ \beta_1 b_1 x_1 v - a_1 y_1 &= 0, \\ \lambda_2 - d_2 x_2 - \beta_2 x_2 v &= 0, \\ \beta_2 b_2 x_2 v - a_2 y_2 &= 0, \\ k_1 a_1 y_1 + k_2 a_2 y_2 - \gamma v &= 0. \end{aligned} \quad (20)$$

From the first and third equations of (20), we have

$$x_1 = \frac{\lambda_1}{d_1 + \beta_1 v}, \quad x_2 = \frac{\lambda_2}{d_2 + \beta_2 v}, \quad (21)$$

respectively. Substituting them into the second and fourth equations of (20) yields

$$y_1 = \frac{\beta_1 b_1 \lambda_1 v}{a_1 (d_1 + \beta_1 v)}, \quad y_2 = \frac{\beta_2 b_2 \lambda_2 v}{a_2 (d_2 + \beta_2 v)}, \quad (22)$$

respectively. When $v \neq 0$, substituting the above y_1 and y_2 into the last equation of (20) gives

$$\frac{k_1 \beta_1 b_1 \lambda_1}{d_1 + \beta_1 v} + \frac{k_2 \beta_2 b_2 \lambda_2}{d_2 + \beta_2 v} = \gamma. \quad (23)$$

Since the function of v at the left hand side of (23) is strictly decreasing, it is easy to see that (23) has a positive root if and only if $k_1 \beta_1 b_1 \lambda_1 / d_1 + k_2 \beta_2 b_2 \lambda_2 / d_2 > \gamma$ and that the positive root is unique, denoted by v^* . Therefore, with respect to the existence of equilibria of (14), we have the following result.

Theorem 2. Denote

$$R_0 = \left(\frac{k_1 \beta_1 b_1 \lambda_1}{d_1} + \frac{k_2 \beta_2 b_2 \lambda_2}{d_2} \right) \frac{1}{\gamma}; \quad (24)$$

then, when $R_0 \leq 1$, system (14) only has the infection-free equilibrium $E_0(x_{10}, 0, x_{20}, 0, 0)$, where $x_{10} = \lambda_1 / d_1$ and $x_{20} = \lambda_2 / d_2$; when $R_0 > 1$, besides E_0 , system (14) also has a unique infection equilibrium $E^*(x_1^*, y_1^*, x_2^*, y_2^*, v^*)$, where

$$\begin{aligned} x_1^* &= \frac{\lambda_1}{d_1 + \beta_1 v^*}, & x_2^* &= \frac{\lambda_2}{d_2 + \beta_2 v^*}, \\ y_1^* &= \frac{\beta_1 b_1 \lambda_1 v^*}{a_1 (d_1 + \beta_1 v^*)}, & y_2^* &= \frac{\beta_2 b_2 \lambda_2 v^*}{a_2 (d_2 + \beta_2 v^*)}, \end{aligned} \quad (25)$$

and v^* is determined by (23).

Note that R_0 is the basic reproduction number describing the viral infection within host.

In the following, we consider the global stability of equilibria of (14).

In order to simplify the proof of the global stability of the infection equilibrium E^* , we first introduce an inequality as lemma, which was proved in [18].

Lemma 3. For n positive numbers c_i ($i = 1, 2, \dots, n$), the inequality

$$n - c_1 - c_2 - \dots - c_n + \ln(c_1 c_2 \dots c_n) \leq 0 \quad (26)$$

is true, and the equality holds if and only if $c_1 = c_2 = \dots = c_n = 1$.

Theorem 4. When $R_0 \leq 1$, the infection-free equilibrium E_0 of system (14) is globally stable on Ω ; when $R_0 > 1$, the infection equilibrium E^* of (14) is globally stable in the region Ω .

Proof. In order to prove the global stability of the infection-free equilibrium E_0 of (14), we define a Lyapunov function:

$$\begin{aligned} L_{11} &= k_1 b_1 \left(x_1 - x_{10} - x_{10} \ln \frac{x_1}{x_{10}} \right) + k_1 y_1 \\ &\quad + k_2 b_2 \left(x_2 - x_{20} - x_{20} \ln \frac{x_2}{x_{20}} \right) + k_2 y_2 + v, \end{aligned} \quad (27)$$

then

$$\begin{aligned}
 \frac{dL_{11}}{dt} &= k_1 b_1 (x_1 - x_{10}) \left(\frac{\lambda_1}{x_1} - d_1 - \beta_1 v \right) \\
 &\quad + k_1 [\beta_1 b_1 x(t - \tau_1) v(t - \tau_1) - a_1 y_1] \\
 &\quad + k_2 b_2 (x_2 - x_{20}) \left(\frac{\lambda_2}{x_2} - d_2 - \beta_2 v \right) \\
 &\quad + k_2 [\beta_2 b_2 x(t - \tau_2) v(t - \tau_2) - a_2 y_2] \\
 &\quad + k_1 a_1 y_1 + k_2 a_2 y_2 - \gamma v \\
 &= k_1 b_1 (x_1 - x_{10}) \left[\lambda_1 \left(\frac{1}{x_1} - \frac{1}{x_{10}} \right) - \beta_1 v \right] \\
 &\quad + k_1 [\beta_1 b_1 x(t - \tau_1) v(t - \tau_1) - a_1 y_1] \\
 &\quad + k_2 b_2 (x_2 - x_{20}) \left[\lambda_2 \left(\frac{1}{x_2} - \frac{1}{x_{20}} \right) - \beta_2 v \right] \\
 &\quad + k_2 [\beta_2 b_2 x(t - \tau_2) v(t - \tau_2) - a_2 y_2] \\
 &\quad + k_1 a_1 y_1 + k_2 a_2 y_2 - \gamma v \\
 &= k_1 b_1 \lambda_1 \left(2 - \frac{x_1}{x_{10}} - \frac{x_{10}}{x_1} \right) \\
 &\quad + k_2 b_2 \lambda_2 \left(2 - \frac{x_2}{x_{20}} - \frac{x_{20}}{x_2} \right) \\
 &\quad + k_1 b_1 \beta_1 [x_1(t - \tau_1) v(t - \tau_1) - x_1(t) v(t)] \\
 &\quad + k_2 b_2 \beta_2 [x_2(t - \tau_2) v(t - \tau_2) - x_2(t) v(t)] \\
 &\quad + (k_1 b_1 \beta_1 x_{10} + k_2 b_2 \beta_2 x_{20} - \gamma) v.
 \end{aligned} \tag{28}$$

Let $L_1 = L_{11} + k_1 b_1 \beta_1 \int_{t-\tau_1}^t x_1(\theta) v(\theta) d\theta + k_2 b_2 \beta_2 \int_{t-\tau_2}^t x_2(\theta) v(\theta) d\theta$; then

$$\begin{aligned}
 \frac{dL_1}{dt} &= k_1 b_1 \lambda_1 \left(2 - \frac{x_1}{x_{10}} - \frac{x_{10}}{x_1} \right) \\
 &\quad + k_2 b_2 \lambda_2 \left(2 - \frac{x_2}{x_{20}} - \frac{x_{20}}{x_2} \right) + \gamma (R_0 - 1) v,
 \end{aligned} \tag{29}$$

where $R_0 = (k_1 b_1 \beta_1 x_{10} + k_2 b_2 \beta_2 x_{20})/\gamma$ is used.

It is easy to see that $2 \leq x_i/x_{i0} + x_{i0}/x_i$ ($i = 1, 2$), then $dL_1/dt \leq 0$ as $R_0 \leq 1$. Note that, for $R_0 < 1$, $dL_1/dt = 0$ if and only if $x_i = x_{i0}$ ($i = 1, 2$) and $v = 0$; for $R_0 = 1$, $dL_1/dt = 0$ if and only if $x_i = x_{i0}$ ($i = 1, 2$). No matter the case $R_0 < 1$ or $R_0 = 1$, the largest invariant set of (14) on the set Ω is the singleton $\{E_0\}$. Since any solution of (14) is bounded, it follows from the Lyapunov-LaSalle Invariance Principle for functional differential equations that the infection-free equilibrium E_0 is globally stable on the set Ω when $R_0 \leq 1$ [19].

In order to prove the global stability of the infection equilibrium $E^*(x_1^*, y_1^*, x_2^*, y_2^*, v^*)$, define the following Lyapunov functions and functionals:

$$\begin{aligned}
 L_{21} &= k_1 b_1 \left(x_1 - x_1^* - x_1^* \ln \frac{x_1}{x_1^*} \right) \\
 &\quad + k_1 \left(y_1 - y_1^* - y_1^* \ln \frac{y_1}{y_1^*} \right), \\
 L_{22} &= k_2 b_2 \left(x_2 - x_2^* - x_2^* \ln \frac{x_2}{x_2^*} \right) \\
 &\quad + k_2 \left(y_2 - y_2^* - y_2^* \ln \frac{y_2}{y_2^*} \right), \\
 L_{23} &= \left(v - v^* - v^* \ln \frac{v}{v^*} \right),
 \end{aligned} \tag{30}$$

$$\begin{aligned}
 L_{24} &= k_1 b_1 \beta_1 x_1^* v^* \\
 &\quad \times \int_{t-\tau_1}^t \left[\frac{x_1(\theta) v(\theta)}{x_1^* v^*} - 1 - \ln \frac{x_1(\theta) v(\theta)}{x_1^* v^*} \right] d\theta \\
 &\quad + k_2 b_2 \beta_2 x_2^* v^* \\
 &\quad \times \int_{t-\tau_2}^t \left[\frac{x_2(\theta) v(\theta)}{x_2^* v^*} - 1 - \ln \frac{x_2(\theta) v(\theta)}{x_2^* v^*} \right] d\theta.
 \end{aligned}$$

According to (20), we have

$$\begin{aligned}
 d_1 &= \frac{\lambda_1}{x_1^*} - \beta_1 v^*, \\
 a_1 &= \frac{\beta_1 b_1 x_1^* v^*}{y_1^*}, \\
 d_2 &= \frac{\lambda_2}{x_2^*} - \beta_2 v^*, \\
 a_2 &= \frac{\beta_2 b_2 x_2^* v^*}{y_2^*}, \\
 \gamma &= \frac{k_1 a_1 y_1^*}{v^*} + \frac{k_2 a_2 y_2^*}{v^*}.
 \end{aligned} \tag{31}$$

Then, system (14) can be rewritten as

$$\begin{aligned}
 x_1'(t) &= x_1(t) \left[\lambda_1 \left(\frac{1}{x_1(t)} - \frac{1}{x_1^*} \right) - \beta_1 (v(t) - v^*) \right], \\
 y_1'(t) &= \beta_1 b_1 y_1(t) \left[\frac{x_1(t - \tau_1) v(t - \tau_1)}{y_1(t)} - \frac{x_1^* v^*}{y_1^*} \right], \\
 x_2'(t) &= x_2(t) \left[\lambda_2 \left(\frac{1}{x_2(t)} - \frac{1}{x_2^*} \right) - \beta_2 (v(t) - v^*) \right], \\
 y_2'(t) &= \beta_2 b_2 y_2(t) \left[\frac{x_2(t - \tau_2) v(t - \tau_2)}{y_2(t)} - \frac{x_2^* v^*}{y_2^*} \right], \\
 v'(t) &= v(t) \left[k_1 a_1 \left(\frac{y_1(t)}{v(t)} - \frac{y_1^*}{v^*} \right) + k_2 a_2 \left(\frac{y_2(t)}{v(t)} - \frac{y_2^*}{v^*} \right) \right].
 \end{aligned} \tag{32}$$

By using $\lambda_1 = d_1 x_1^* + \beta_1 x_1^* v^*$ and $\lambda_2 = d_2 x_2^* + \beta_2 x_2^* v^*$, direct computations show that

$$\begin{aligned}
 L'_{21} &= k_1 b_1 d_1 x_1^* \left(2 - \frac{x_1^*}{x_1} - \frac{x_1}{x_1^*} \right) \\
 &\quad + k_1 b_1 \beta_1 x_1^* v^* \left(2 - \frac{x_1^*}{x_1} - \frac{x_1 v}{x_1^* v^*} + \frac{v}{v^*} \right) \\
 &\quad + k_1 b_1 \beta_1 x_1^* v^* \left[\frac{x_1 (t - \tau_1) v (t - \tau_1)}{x_1^* v^*} - \frac{y_1}{y_1^*} \right. \\
 &\quad \left. - \frac{x_1 (t - \tau_1) y_1^* v (t - \tau_1)}{x_1^* y_1 v^*} \right], \\
 L'_{22} &= k_2 b_2 d_2 x_2^* \left(2 - \frac{x_2^*}{x_2} - \frac{x_2}{x_2^*} \right) \\
 &\quad + k_2 b_2 \beta_2 x_2^* v^* \left(2 - \frac{x_2^*}{x_2} - \frac{x_2 v}{x_2^* v^*} + \frac{v}{v^*} \right) \\
 &\quad + k_2 b_2 \beta_2 x_2^* v^* \left[\frac{x_2 (t - \tau_2) v (t - \tau_2)}{x_2^* v^*} - \frac{y_2}{y_2^*} \right. \\
 &\quad \left. - \frac{x_2 (t - \tau_2) y_2^* v (t - \tau_2)}{x_2^* y_2 v^*} \right], \\
 L'_{23} &= k_1 a_1 y_1^* \left(\frac{y_1}{y_1^*} - \frac{y_1 v^*}{y_1^* v} - \frac{v}{v^*} + 1 \right) \\
 &\quad + k_2 a_2 y_2^* \left(\frac{y_2}{y_2^*} - \frac{y_2 v^*}{y_2^* v} - \frac{v}{v^*} + 1 \right), \\
 L'_{24} &= k_1 b_1 \beta_1 x_1^* v^* \left[\frac{x_1 v}{x_1^* v^*} - \frac{x_1 (t - \tau_1) v (t - \tau_1)}{x_1^* v^*} \right. \\
 &\quad \left. + \ln \frac{x_1 (t - \tau_1) v (t - \tau_1)}{x_1 (t) v (t)} \right] \\
 &\quad + k_2 b_2 \beta_2 x_2^* v^* \left[\frac{x_2 v}{x_2^* v^*} - \frac{x_2 (t - \tau_2) v (t - \tau_2)}{x_2^* v^*} \right. \\
 &\quad \left. + \ln \frac{x_2 (t - \tau_2) v (t - \tau_2)}{x_2 (t) v (t)} \right].
 \end{aligned} \tag{33}$$

Let $L_2 = L_{21} + L_{22} + L_{23} + L_{24}$, then

$$\begin{aligned}
 L'_2 &= k_1 b_1 d_1 x_1^* \left(2 - \frac{x_1^*}{x_1} - \frac{x_1}{x_1^*} \right) + k_2 b_2 d_2 x_2^* \left(2 - \frac{x_2^*}{x_2} - \frac{x_2}{x_2^*} \right) \\
 &\quad + k_1 b_1 \beta_1 x_1^* v^* \left[3 - \frac{x_1^*}{x_1 (t)} - \frac{x_1 (t - \tau_1) y_1^* v (t - \tau_1)}{x_1^* y_1 v^*} \right. \\
 &\quad \left. - \frac{y_1 (t) v^*}{y_1^* v (t)} + \ln \frac{x_1 (t - \tau_1) v (t - \tau_1)}{x_1 (t) v (t)} \right]
 \end{aligned}$$

$$\begin{aligned}
 &+ k_2 b_2 \beta_2 x_2^* v^* \left[3 - \frac{x_2^*}{x_2 (t)} - \frac{x_2 (t - \tau_2) y_2^* v (t - \tau_2)}{x_2^* y_2 v^*} \right. \\
 &\quad \left. - \frac{y_2 (t) v^*}{y_2^* v (t)} + \ln \frac{x_2 (t - \tau_2) v (t - \tau_2)}{x_2 (t) v (t)} \right].
 \end{aligned} \tag{34}$$

According to the relationship between the arithmetic and the associated geometric means and Lemma 3, $dL_2/dt \leq 0$ and $dL_2/dt = 0$ if and only if $x_1 = x_1^*$, $x_2 = x_2^*$, $y_1/y_1^* = y_2/y_2^* = v(t)/v^* = v(t - \tau_1)/v^* = v(t - \tau_2)/v^*$. It is easy to see that the largest invariant set of (14) on the set $\{(x_1, y_1, x_2, y_2, v) \in \Omega : dL_2/dt = 0\}$ is the singleton $\{E^*\}$. Since any solution of (14) is bounded, it follows from the Lyapunov-LaSalle Invariance Principle for functional differential equations that the infection equilibrium E^* is globally stable on the set Ω when $R_0 > 1$ [19]. \square

4. Discussion

In this paper, we first present the probability function describing the latency of the infected cells such that some models of viral infection with latent stage are unified. When the function is an exponential one, the associated model is a system of ordinary differential equations; when the function is a step function, the associated one is a delay differential system. Both of the two types of models have the similar dynamical behaviors. That is, when the basic reproduction number is less than or equal to unity, the infection-free equilibrium is globally stable, which implies that the in-host free virus will be cleared out finally; when the basic reproduction number is greater than unity, the infection equilibrium is globally stable, which implies that the viral infection will be chronic and persist in-host [6, 7, 17]. But there is a difference between the basic reproduction numbers for the two types of models.

In fact, for ordinary differential systems (6) and (12), the basic reproduction numbers are

$$R_{01}^{(O)} = \frac{\beta \lambda k \varepsilon}{d \gamma (d + \varepsilon)}, \tag{35}$$

$$R_{02}^{(O)} = \left[\frac{\beta_1 \lambda_1 k_1 \varepsilon_1}{d_1 (d_1 + \varepsilon_1)} + \frac{\beta_2 \lambda_2 k_2 \varepsilon_2}{d_2 (d_2 + \varepsilon_2)} \right] \frac{1}{\gamma},$$

respectively [6, 7]. For delay differential systems (10) and (13) (or (14)), the basic reproduction numbers are

$$R_{01}^{(D)} = \frac{\beta \lambda k e^{-d\tau}}{d \gamma}, \tag{36}$$

$$R_{02}^{(D)} = \left[\frac{\beta_1 \lambda_1 k_1 e^{-d_1 \tau_1}}{d_1} + \frac{\beta_2 \lambda_2 k_2 e^{-d_2 \tau_2}}{d_2} \right] \frac{1}{\gamma},$$

respectively, where $R_{01}^{(D)}$ was obtained in [17]; $R_{02}^{(D)}$ is R_0 in this paper.

According to the definition of probability function of staying in the latent stage, for the two common types of probability functions, exponential function and step function, we

assume that the associated average latent periods of infected cells are equal, that is, $\tau = 1/\varepsilon$. Then, the basic reproduction numbers of ordinary differential systems (6) and (12) can be rewritten by

$$R_{01}^{(O)} = \frac{\beta\lambda k}{d\gamma(1+d\tau)}, \quad (37)$$

$$R_{02}^{(O)} = \left[\frac{\beta_1\lambda_1k_1}{d_1(1+d_1\tau_1)} + \frac{\beta_2\lambda_2k_2}{d_2(1+d_2\tau_2)} \right] \frac{1}{\gamma},$$

respectively.

From the inequality $1/(1+u) > e^{-u}$ for $u > 0$, it follows that

$$R_{01}^{(O)} > R_{01}^{(D)}, \quad R_{02}^{(O)} > R_{02}^{(D)}. \quad (38)$$

They imply that for certain models of viral infection, the basic reproduction number of ordinary differential system may be greater than that of delay differential system. It is well known that the basic reproduction number usually determines dynamics of models of viral infection. Therefore, the difference between the basic reproduction numbers of the different types of models reminds us that it is necessary to elect an appropriate type of probability function, when predicting the final outcome of viral infection in-host.

Acknowledgments

The authors would like to thank the referees for their valuable comments. This work was partially supported by the National Natural Science Foundation of China (nos. 11071256, 11171267, and 11371369).

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