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GLOBAL STABILITY OF A VIRAL INFECTION MODEL WITH TWO DELAYS AND TWO TYPES OF TARGET CELLS*

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Abstract In this paper, incorporating the delay of viral cytopathicity within target cells, we first presented a basic model of viral infection with delay, and then extended it into a model with two delays and two types of target cells. For the models proposed here, both their basic reproduction numbers are found. By constructing Lyapunov functionals, necessary and sufficient conditions ensuring the global stability of the models with delays are given. The obtained results show that, when the basic reproduction number is not greater than one, the infection-free equilibrium is globally stable in the feasible region, which implies that the viral infection goes extinct eventually; when it is greater than one, the infection equilibrium is globally stable in the feasible region, which implies that the viral infection persists in the body of host.

Keywords Viral infection model, delay, equilibrium, global stability.

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1. Introduction

In order to understand the action of in-host free virus on target cells, a number of mathematical models have been used to describe in-host virus dynamics. Nowak et al. [6, 7] proposed one of the earliest of these models

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xv, \\ \frac{dy}{dt} = \beta xv - ay, \\ \frac{dv}{dt} = kay - \gamma v, \end{cases} \tag{1.1}$$

where $x = x(t), y = y(t)$ and $v = v(t)$ are the numbers of uninfected cells, infected cells and viral particles (virions) at time t, respectively. In model (1.1), 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 over the lifetime of a single infected cell, and die at a rate γv. Model (1.1) is a basic model, which has been used widely to investigate infection of some viruses (such as, HIV, HBV, HCV, HLMV, etc.)

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In 1997, Perelson et al. [9] observed that the HIV attack 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[12], peripheral blood mononuclear cells (PBMC)[4], brain[5] and lymph nodes[8]. Then, according to these virological findings, based on model (1.1) some viral dynamical models with two types of target cells were proposed [1, 10, 11], which are expressed by ordinary differential equations.

In [14], Wodarz and Levy pointed out that the term ay in model (1.1) should consist of two parts: one represents the natural death of infected cells, the other is that infected cells are lost due to viral cytopathicity. In this paper, we assume that infected cells burst and then release viral particles (i.e., viral cytopathicity occurs) after uninfected cells were infected by a constant period of time τ, that is, the time period of viral cytopathicity within target cells is τ. So the objective of our work is to investigate the basic virus dynamical model with delay of viral cytopathicity within target cells and further consider the model with two types of target cells and the associated delays.

The global analysis of viral infection models is an important issue for understanding the pathogenesis of in-host free virus. Usually, it is difficult for models of delay differential equations to obtain the global properties. For the models with delays established in this paper, the necessary and sufficient conditions ensuring their global stability are obtained by constructing the Lyapunov functionals.

The paper is organized as follows: In Section 2, we first present a basic model of viral infection with delay of viral cytopathicity, and then extend it into a model with two delays and two types of target cells. In Sections 3 and 4, the global properties of the two models established here are analyzed. The last section is the conclusion.

2. Models

In this section, we present two models of viral infection with delay of viral cytopathicity, in which the infected target cells are the same type and two types, respectively.

When the delay of viral cytopathicity within target cells is τ, and the natural death rate of per target cell is d, the number of infected cells at time t ($t > \tau$) can be represented by

$$y(t) = \int_{t-\tau}^{t} \beta x(\theta) v(\theta) e^{-d(t-\theta)} d\theta, \qquad \text{for} \quad t > \tau, \tag{2.1}$$

where $e^{-d(t-\theta)}$ is the probability that target cells survive from time θ to time t, and $\beta x(\theta) v(\theta) e^{-d(t-\theta)}$ is the number of target cells being infected at time θ and still surviving at time t.

Differentiating $y(t)$ of (2.1) yields

$$\frac{d}{dt} y(t) = \beta x(t) v(t) - \beta e^{-d\tau} x(t-\tau) v(t-\tau) - dy(t),$$

where the term $\beta e^{-d\tau} x(t-\tau) v(t-\tau)$ is the transfer rate of the infected cells being used to produce free virus at time t. Thus the recruitment rate of free virus at time t is $k\beta e^{-d\tau} x(t-\tau) v(t-\tau)$, in which k is the average number of viral particles produced by a infected target cell when viral cytopathicity occurs. It implies that the

recruitment of virus at time t depends on the number of target cells that were newly infected at time $t-\tau$ and are still alive at time t. Therefore, corresponding to the basic viral dynamical model of ordinary differential equations (1.1), incorporating the delay of viral cytopathicity into (1.1) yields the following basic viral dynamical model of delay differential equations

$$\begin{cases} \frac{d}{dt}x(t) = \lambda - dx(t) - \beta x(t)v(t), \\ \frac{d}{dt}y(t) = \beta x(t)v(t) - \beta e^{-d\tau}x(t-\tau)v(t-\tau) - dy(t), \\ \frac{d}{dt}v(t) = k\beta e^{-d\tau}x(t-\tau)v(t-\tau) - \gamma v(t). \end{cases} \tag{2.2}$$

Since the variable y does not appear in the first and the third equations of (2.2), we only focus on the following subsystem of (2.2)

$$\begin{cases} \frac{d}{dt}x(t) = \lambda - dx(t) - \beta x(t)v(t), \\ \frac{d}{dt}v(t) = k\beta e^{-d\tau}x(t-\tau)v(t-\tau) - \gamma v(t), \end{cases} \tag{2.3}$$

which has the same dynamics with system (2.2).

In [2], Elaiw studied the global properties of a viral dynamical model with two types of target cells (CD4+ T cells and macrophages)

$$\begin{cases} \frac{dx_1}{dt} = \lambda_1 - d_1x_1 - \beta_1x_1v, \\ \frac{dy_1}{dt} = \beta_1x_1v - a_1y_1, \\ \frac{dx_2}{dt} = \lambda_2 - d_2x_2 - \beta_2x_2v, \\ \frac{dy_2}{dt} = \beta_2x_2v - a_2y_2, \\ \frac{dv}{dt} = k_1a_1y_1 + k_1a_2y_2 - \gamma v, \end{cases} \tag{2.4}$$

where x_i and y_i $(i = 1, 2)$ are the numbers of uninfected and infected cells for type i, respectively, and all the parameters in (2.4) have the same biological meanings as given in model (1.1). According to the idea of establishing delay differential equations (2.3), corresponding to model (2.4) we can give the following model with two delays and two types of target cells

$$\begin{cases} \frac{d}{dt}x_1(t) = & \lambda_1 - d_1x_1(t) - \beta_1x_1(t)v(t), \\ \frac{d}{dt}x_2(t) = & \lambda_2 - d_2x_2(t) - \beta_2x_2(t)v(t), \\ \frac{d}{dt}v(t) = & k_1\beta_1e^{-d_1\tau_1}x_1(t-\tau_1)v(t-\tau_1) \\ & +k_2\beta_2e^{-d_2\tau_2}x_2(t-\tau_2)v(t-\tau_2) - \gamma v(t), \end{cases} \tag{2.5}$$

where τ_i $(i = 1, 2)$ is the delay of viral cytopathicity within target cells of type i.

For simplicity, letting $b = ke^{-d\tau}, b_1 = k_1e^{-d_1\tau_1}$ and $b_2 = k_2e^{-d_2\tau_2}$, systems (2.3) and (2.5) become

$$\begin{cases} \frac{d}{dt}x(t) = \lambda - dx(t) - \beta x(t)v(t), \\ \frac{d}{dt}v(t) = \beta bx(t-\tau)v(t-\tau) - \gamma v(t), \end{cases} \tag{2.6}$$

and

$$\begin{cases} \frac{d}{dt}x_1(t) = \lambda_1 - d_1x_1(t) - \beta_1x_1(t)v(t), \\ \frac{d}{dt}x_2(t) = \lambda_2 - d_2x_2(t) - \beta_2x_2(t)v(t), \\ \frac{d}{dt}v(t) = \beta_1b_1x_1(t-\tau_1)v(t-\tau_1) + \beta_2b_2x_2(t-\tau_2)v(t-\tau_2) - \gamma v(t), \end{cases} \tag{2.7}$$

respectively. In the following, we will investigate global dynamics of systems (2.6) and (2.7). For models (2.6) and (2.7) or (2.3) and (2.5), all parameters are assumed to be positive.

3. Analysis for system (2.6)

To investigate the dynamics of (2.6), we set a suitable phase space. Denote by $C = C([-\tau, 0], \mathbb{R})$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}$ with norm $\|\phi\| = \sup_{-\tau \le \theta \le 0} |\phi(\theta)|$ for $\phi \in C$. The nonnegative cone of C is defined as $C_+ = C([-\tau, 0], \mathbb{R}_+)$. From the biological meaning, the initial conditions for system (2.6) are given as follows:

$$x(\theta) = \phi_1(\theta), v(\theta) = \phi_2(\theta), \theta \in [-\tau, 0], \tag{3.1}$$

where $\phi_i \in C_+$ and $\phi_i(0) > 0$ for $i = 1, 2$.

The following theorem establishes the non-negativity and boundedness of solutions of (2.6).

Theorem 3.1. *All the solutions* $(x(t), v(t))^T$ *of system* (2.6) *under the initial conditions* (3.1) *are positive on* $[0, +\infty)$ *and ultimately bounded.*

Proof. Assume that there is t_1 ($t_1 > 0$) such that $x(t_1) = 0$, then it follows from $x(0) > 0$ and the continuity of solution of (2.6) that there is $t^* = \inf\{t : t > 0, x(t) = 0\}$ such that $x(t) > 0$ for $t \in [0, t^*)$. So we have $x'(t^*) \le 0$. However, $x'(t^*) = \lambda > 0$. This contradiction implies that $x(t) > 0$ for $t > 0$.

From the last equation of (2.6) we have

$$\begin{aligned} v(t) = & \left[v(0) + \beta b \int_0^t x(\theta - \tau) v(\theta - \tau) e^{\gamma\theta} d\theta\right] e^{-\gamma t} \\ = & \left[v(0) + \beta b \int_{-\tau}^{t-\tau} x(\theta) v(\theta) e^{\gamma(\theta+\tau)} d\theta\right] e^{-\gamma t}. \end{aligned} \tag{3.2}$$

Since $x(t) \ge 0$ and $v(t) \ge 0$ for $-\tau \le t \le 0$, it follows from (3.2) and $v(0) > 0$ that $v(t) > 0$ for $0 \le t < \tau$.

Further, when $\tau \le t < 2\tau$,

$$v(t) = \left\{v(0) + \beta b \left[\int_{-\tau}^{0} U(\theta) d\theta + \int_{0}^{t-\tau} U(\theta) d\theta\right]\right\} e^{-\gamma t},$$

where $U(\theta) = x(\theta) v(\theta) e^{\gamma(\theta+\tau)}$.

Notice that $\int_{-\tau}^{0} U(\theta) d\theta \ge 0$ since $x(\theta) \ge 0$ and $v(\theta) \ge 0$ for $-\tau \le \theta \le 0$, and $\int_{0}^{t-\tau} U(\theta) d\theta \ge 0$ for $\tau \le t < 2\tau$ since $x(\theta) > 0$ and $v(\theta) > 0$ for $0 \le \theta < \tau$, then $v(t) > 0$ also holds true for $\tau \le t < 2\tau$, which implies that $v(t) > 0$ holds true for $0 \le t < 2\tau$.

For a positive integer k, when $k\tau \le t < (k+1)\tau$, from (3.2) we have

$$v(t) = \left\{v(0) + \beta b \left[\int_{-\tau}^{(k-1)\tau} U(\theta) d\theta + \int_{(k-1)\tau}^{t-\tau} U(\theta) d\theta\right]\right\} e^{-\gamma t}.$$

Assume that $v(t) > 0$ for $0 \le t < k\tau$, then the similar inference can show that $v(t) > 0$ for $k\tau \le t < (k+1)\tau$. It follows from mathematical induction that $v(t) > 0$ for $t > 0$.

The positivity of solution of (2.6) is proved completely.

To prove the ultimate boundedness of solution of (2.6), we define a functional $L_{10} = bx(t) + v(t+\tau)$, then the derivative of L_{10} along solutions of (2.6) is given by

$$\frac{dL_{10}}{dt} = b\lambda - bdx(t) - \gamma v(t+\tau) \leq b\lambda - \rho L_{10},$$

where $\rho = \min\{d, \gamma\}$. It follows that $\limsup_{t\to+\infty}[bx(t) + v(t+\tau)] \leq b\lambda/\rho$. Therefore, all the solutions of (2.6) are ultimately bounded.

This completes the proof of Theorem 3.1. □

Additionally, from the first equation of (2.6), for $x(t) > 0$ and $v(t) > 0$ we have $dx(t)/dt < \lambda - dx(t)$, then $\limsup_{t\to+\infty} x(t) \leq \lambda/d$. Thus, the region

$$\Omega_1 = \left\{(x(t), v(t))^T \in C_+^2 : x(t) \leq \lambda/d, bx(t) + v(t+\tau) \leq b\lambda/\rho\right\}$$

is positively invariant with respect to system (2.6). We will analyze the dynamics of system (2.6) on the region Ω_1.

Denote $R_{01} = (\beta b\lambda)/(d\gamma)$, then direct calculation shows that system (2.6) always has the infection-free equilibrium $E_{01}(\lambda/d, 0)$, and that, besides E_{01}, system (2.6) also has a unique infection equilibrium $E_1^*(x^*, v^*)$ in the region Ω_1 as $R_{01} > 1$, where $x^* = \gamma/\beta b$ and $v^* = d(R_{01} - 1)/\beta$.

With respect to the global stability of system (2.6), we have

Theorem 3.2. *For system* (2.6)*, the infection-free equilibrium E_{01} is globally stable on the region Ω_1 as $R_{01} \leq 1$; the infection equilibrium E_1^* is globally stable in the region Ω_1 as $R_{01} > 1$.*

To simplify the proof of the global stability of the infection equilibrium E_1^*, we first introduce an inequality as lemma.

Lemma 3.1. *For n positive numbers c_i $(i = 1, 2, \cdots, n)$, the inequality*

$$n - c_1 - c_2 - \cdots - c_n + \ln(c_1 c_2 \cdots c_n) \leq 0$$

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

Proof. Since $\ln(c_1 c_2 \cdots c_n) = \ln c_1 + \ln c_2 + \cdots + \ln c_n$, then

$$n - c_1 - c_2 - \cdots - c_n + \ln(c_1 c_2 \cdots c_n) = \textstyle\sum_{i=1}^{n} (1 - c_i + \ln c_i).$$

It is easy to see that function $f(x) = 1 - x + \ln x \leq 0$ for $x > 0$ and the equality holds if and only if $x = 1$. Thus Lemma 3.1 holds. □

Proof of Theorem 3.2. To prove the global stability of the infection-free equilibrium E_{01} of (2.6), we define a Lyapunov functional

$$L_{11} = \frac{b}{2}\left(x - \frac{\lambda}{d}\right)^2 + \frac{\lambda}{d}\left[v + \beta b \int_{t-\tau}^{t} x(\theta)v(\theta)d\theta\right],$$

then the derivative of L_{11} along solutions of (2.6) is given by

$$\begin{aligned} \tfrac{dL_{11}}{dt} &= b\left(x - \tfrac{\lambda}{d}\right)(\lambda - dx - \beta xv) + \tfrac{\lambda}{d}(\beta bxv - \gamma v) \\ &= -b(d + \beta v)\left(x - \tfrac{\lambda}{d}\right)^2 + \tfrac{\gamma\lambda}{d}(R_0 - 1)v. \end{aligned}$$

When $R_{01} \leq 1$, $dL_{11}/dt \leq 0$. And it is easy to see that, when $R_{01} \leq 1$, the largest invariant set of system (2.6) on the region $\left\{(x(t), v(t))^T \in \Omega_1 : dL_{11}/dt = 0\right\}$ is the singleton $\{E_{01}\}$. Then it follows by the LaSalle's Invariance Principle[3] that the infection-free equilibrium E_{01} is globally stable on the region Ω_1.

To prove the global stability of the infection equilibrium E_1^*, define a Lyapunov functional

$$\begin{aligned} L_{12} = \quad & m\left(x - x^* - x^* \ln \tfrac{x}{x^*}\right) + \left(v - v^* - v^* \ln \tfrac{v}{v^*}\right) \\ & + r \int_{t-\tau}^{t} \left[\tfrac{x(\theta)v(\theta)}{p} - 1 - \ln \tfrac{x(\theta)v(\theta)}{p}\right] d\theta, \end{aligned}$$

where m, r and p are positive and left unspecified, then the derivative of L_{12} along solutions of system (2.6) is given by

$$\begin{aligned} \tfrac{dL_{12}}{dt} = \quad & m\tfrac{x-x^*}{x}\tfrac{dx(t)}{dt} + \tfrac{v-v^*}{v}\tfrac{dv}{dt} + r\tfrac{d}{dt}\int_{t-\tau}^{t}\left[\tfrac{x(\theta)v(\theta)}{p} - 1 - \ln\tfrac{x(\theta)v(\theta)}{p}\right]d\theta \\ = \quad & m\tfrac{x-x^*}{x}\left[\lambda - dx(t) - \beta x(t)v(t)\right] + \tfrac{v-v^*}{v}\left[\beta b x(t-\tau)v(t-\tau) - \gamma v(t)\right] \\ & + r\left\{\tfrac{1}{p}\left[x(t)v(t) - x(t-\tau)v(t-\tau)\right] + \ln\tfrac{x(t-\tau)v(t-\tau)}{x(t)v(t)}\right\}. \end{aligned}$$

Substituting $d = \lambda/x^* - \beta v^*$ and $\gamma = \beta b x^*$ into dL_{12}/dt yields

$$\begin{aligned} \tfrac{dL_{12}}{dt} = \quad & m\left(\tfrac{x}{x^*} - 1\right)\left[\lambda\left(\tfrac{x^*}{x} - 1\right) - \beta x^* v^*\left(\tfrac{v}{v^*} - 1\right)\right] \\ & + \beta b x^* v^*\left(\tfrac{v}{v^*} - 1\right)\left[\tfrac{x(t-\tau)v(t-\tau)}{x^* v(t)} - 1\right] \\ & + r\left\{\tfrac{1}{p}\left[x(t)v(t) - x(t-\tau)v(t-\tau)\right] + \ln\tfrac{x(t-\tau)v(t-\tau)}{x(t)v(t)}\right\}. \end{aligned}$$

Choosing $m = b, r = \beta b x^* v^*$ and $p = x^* v^*$ gives

$$\begin{aligned} \tfrac{dL_{12}}{dt} = \quad & b d x^*\left(2 - \tfrac{x^*}{x} - \tfrac{x}{x^*}\right) \\ & + \beta b x^* v^*\left[2 - \tfrac{x^*}{x} - \tfrac{x(t-\tau)v(t-\tau)}{x^* v(t)} + \ln\tfrac{x(t-\tau)v(t-\tau)}{x(t)v(t)}\right]. \end{aligned}$$

By the relationship between the arithmetical and geometrical means and Lemma 3.1, we have $dL_{12}/dt \leq 0$, and the equality holds if and only if $x(t) = x^*$ and $v(t) = v(t-\tau)$ for $t > 0$.

Obviously, the largest invariant set of system (2.6) on the region $\left\{(x(t), v(t))^T \in \Omega_1 : dL_{12}/dt = 0\right\}$ is the singleton $\{E_1^*\}$. Therefore, it follows by the LaSalle's Invariance Principle[3] that E_1^* is globally stable in Ω_1 when $R_{01} > 1$.

4. Analysis for system (2.7)

To investigate the dynamics of (2.7), we set a suitable phase space. For $\tau_1 > 0$ and $\tau_2 > 0$, we set $\tau = \max\{\tau_1, \tau_2\}$, and then denote by $C = C([-\tau, 0], \mathbb{R})$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}$ with norm $\|\phi\| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|$ for $\phi \in C$. The nonnegative cone of C is defined as $C_+ = C([-\tau, 0], \mathbb{R}_+)$. From the biological meanings, the initial conditions for system (2.7) are given as follows:

$$x_1(\theta) = \phi_1(\theta), x_2(\theta) = \phi_2(\theta), v(\theta) = \phi_3(\theta), \theta \in [-\tau, 0], \tag{4.1}$$

where $\phi_i \in C_+$ and $\phi_i(0) > 0$ for $i = 1, 2, 3$. Applying the mathematical induction similar to the proof of Theorem 3.1, we can know that, for any solution $(x_1(t), x_2(t), v(t))^T$ of system (2.7) under the initial conditions (4.1), $x_1(t)$, $x_2(t)$ and $v(t)$ are positive for $t > 0$, The proof is omitted here.

We initially consider the ultimate boundedness of solutions of system (2.7).

Theorem 4.1. *For system* (2.7)*, all solutions* $(x_1(t), x_2(t), v(t))^T$ *under the initial conditions* (4.1) *are ultimately bounded.*

Proof. Define a functional $L_{20} = b_1x_1(t-\tau_1) + b_2x_2(t-\tau_2) + v(t)$, then, the derivative of L_{20} along solutions of (2.7) is given by

$$\begin{aligned}\tfrac{dL_{20}}{dt} = \;& (b_1\lambda_1 + b_2\lambda_2) - [b_1d_1x_1(t-\tau_1) + b_2d_2x_2(t-\tau_2) + \gamma v(t)] \\ & \le (b_1\lambda_1 + b_2\lambda_2) - \rho L_{20},\end{aligned}$$

where $\rho = \min\{d_1, d_2, \gamma\}$. Thus,

$$\limsup_{t\to+\infty} [b_1x_1(t-\tau_1) + b_2x_2(t-\tau_2) + v(t)] \le \frac{b_1\lambda_1 + b_2\lambda_2}{\rho} := M.$$

It implies that all solutions of (2.7) are ultimately bounded. The proof is complete. □

Again, from the first two equations of (2.7), for $x_1(t) > 0$, $x_2(t) > 0$ and $v(t) > 0$ we have, respectively,

$$\frac{d}{dt}x_1(t) < \lambda_1 - d_1x_1(t), \quad \text{and} \quad \frac{d}{dt}x_2(t) < \lambda_2 - d_2x_2(t).$$

Then it follows that $\limsup_{t\to+\infty} x_1(t) \le \lambda_1/d_1$ and $\limsup_{t\to+\infty} x_2(t) \le \lambda_2/d_2$. Therefore, the region $\Omega_2 = \{(x_1(t), x_2(t), v(t))^T \in C_+^3 : x_1(t) \le \lambda_1/d_1,\ x_2(t) \le \lambda_2/d_2, b_1x_1(t-\tau_1) + b_2x_2(t-\tau_2) + v(t) \le M\}$ is positively invariant with respect to model (2.7). We will analyze the dynamics of model (2.7) in the region Ω_2.

Obviously, (2.7) always has the infection-free equilibrium $E_{02}(x_{10}, x_{20}, 0)$, where $x_{10} = \lambda_1/d_1$ and $x_{20} = \lambda_2/d_2$. The infection equilibrium (positive equilibrium), $E_2^*(x_1^*, x_2^*, v^*)$, of (2.7) is determined by the following equations

$$\begin{cases} \lambda_1 - d_1x_1 - \beta_1x_1v = 0, \\ \lambda_2 - d_2x_2 - \beta_2x_2v = 0, \\ \beta_1b_1x_1 + \beta_2b_2x_2 - \gamma = 0. \end{cases} \tag{4.2}$$

From the first two equations of (4.2) we have

$$x_1 = \frac{\lambda_1}{d_1 + \beta_1v}, \quad \text{and} \quad x_2 = \frac{\lambda_2}{d_2 + \beta_2v}.$$

Substituting them into the third equation of (4.2) yields

$$\frac{\beta_1b_1\lambda_1}{d_1 + \beta_1v} + \frac{\beta_2b_2\lambda_2}{d_2 + \beta_2v} = \gamma. \tag{4.3}$$

Since the function of v at the left hand side of (4.3) is strictly decreasing, it is easy to see that (4.3) has a positive root if and only if $\beta_1b_1\lambda_1/d_1 + \beta_2b_2\lambda_2/d_2 > \gamma$, and that the positive root is unique, denoted by v^*. Therefore, with respect to the existence of equilibria of (2.7), we have

Theorem 4.2. *Denote*

$$R_{02} = \left(\frac{\beta_1 b_1 \lambda_1}{d_1} + \frac{\beta_2 b_2 \lambda_2}{d_2}\right)\frac{1}{\gamma}, \quad i.e., \quad R_{02} = \frac{\beta_1 b_1 x_{10} + \beta_2 b_2 x_{20}}{\gamma}.$$

Then, when $R_{02} \leq 1$, system (2.7) only has the infection-free equilibrium E_{02}; when $R_{02} > 1$, besides E_{02} system (2.7) also has a unique infection equilibrium $E_2^*(x_1^*, x_2^*, v^*)$, where

$$x_1^* = \frac{\lambda_1}{d_1 + \beta_1 v^*}, \quad x_2^* = \frac{\lambda_2}{d_2 + \beta_2 v^*},$$

and v^* is determined by (4.3).

In the following, we consider the global stability of equilibria of (2.7).

Theorem 4.3. *When $R_{02} \leq 1$, the infection-free equilibrium E_{02} of system (2.7) is globally stable on Ω_2; when $R_{02} > 1$, the infection equilibrium E_2^* of (2.7) is globally stable in the region Ω_2.*

Proof. We first prove the global stability of the infection-free equilibrium E_{02}.

Since $x_{10} = \lambda_1/d_1$ and $x_{20} = \lambda_2/d_2$, system (2.7) can be rewritten as

$$\begin{cases} \frac{d}{dt}x_1(t) = x_1(t)\left\{\lambda_1\left[\frac{1}{x_1(t)} - \frac{1}{x_{10}}\right] - \beta_1 v(t)\right\}, \\ \frac{d}{dt}x_2(t) = x_2(t)\left\{\lambda_2\left[\frac{1}{x_2(t)} - \frac{1}{x_{20}}\right] - \beta_2 v(t)\right\}, \\ \frac{d}{dt}v(t) = \beta_1 b_1 x_1(t-\tau_1)v(t-\tau_1) + \beta_2 b_2 x_2(t-\tau_2)v(t-\tau_2) - \gamma v(t). \end{cases} \tag{4.4}$$

Define a Lyapunov functional

$$L_{21} = \bar{L}_{11} + \bar{L}_{12},$$

where

$$\bar{L}_{11} = b_1\left(x_1 - x_{10} - x_{10}\ln\frac{x_1}{x_{10}}\right) + b_2\left(x_2 - x_{20} - x_{20}\ln\frac{x_2}{x_{20}}\right) + v,$$

and

$$\bar{L}_{12} = \beta_1 b_1 \int_{t-\tau_1}^{t} x_1(\theta)v(\theta)d\theta + \beta_2 b_2 \int_{t-\tau_2}^{t} x_2(\theta)v(\theta)d\theta.$$

Direct calculation shows that the derivative of $\bar{L}_{11}$ along solutions of (4.4) is given by

$$\begin{aligned} \frac{d\bar{L}_{11}}{dt} = \; & b_1\lambda_1\left[x_1(t) - x_{10}\right]\left[\frac{1}{x_1(t)} - \frac{1}{x_{10}}\right] + b_2\lambda_2\left[x_2(t) - x_{20}\right]\left[\frac{1}{x_2(t)} - \frac{1}{x_{20}}\right] \\ & + \left(\beta_1 b_1 x_{10} + \beta_2 b_2 x_{20} - \gamma\right)v(t) + \beta_1 b_1\left[x_1(t-\tau_1)v(t-\tau_1) - x_1(t)v(t)\right] \\ & + \beta_2 b_2\left[x_2(t-\tau_2)v(t-\tau_2) - x_2(t)v(t)\right]. \end{aligned}$$

Since

$$\begin{aligned} \frac{d\bar{L}_{12}}{dt} = \; & \beta_1 b_1\left[x_1(t)v(t) - x_1(t-\tau_1)v(t-\tau_1)\right] \\ & + \beta_2 b_2\left[x_2(t)v(t) - x_2(t-\tau_2)v(t-\tau_2)\right], \end{aligned}$$

the derivative of L_{21} along solutions of (4.4) is

$$\frac{dL_{21}}{dt} = b_1\lambda_1\left[2-\frac{x_{10}}{x_1(t)}-\frac{x_1(t)}{x_{10}}\right]+b_2\lambda_2\left[2-\frac{x_{20}}{x_2(t)}-\frac{x_2(t)}{x_{20}}\right]+\gamma\left(R_{02}-1\right)v(t).$$

According to the property that the arithmetical mean is greater than or equal to the geometrical mean, it follows from $R_{02}\le 1$ that $dL_{21}/dt\le 0$. When $R_{02}<1$, $dL_{21}/dt=0$ if and only if $x_1=x_{10}$, $x_2=x_{20}$ and $v=0$. Thus E_{02} is globally stable in Ω_2 by the Lyapunov Stability Theorem[13]. When $R_{02}=1$, $dL_{21}/dt=0$ if and only if $x_1=x_{10}$ and $x_2=x_{20}$. From the first two equations of (2.7) the largest invariant set of system (2.7) on the set $\{(x_1,x_2,v)\in\Omega_2 : dL_{21}/dt=0\}$ is the singleton $\{E_{02}\}$. Then, it follows by the LaSalle's Invariance Principle[3] that E_{02} is globally stable on Ω_2 when $R_{02}=1$.

Summarizing the inference above, the infection-free equilibrium E_{02} is globally stable on Ω_2 when $R_{02}\le 1$. The proof is complete.

Next, we prove the global stability of the infection equilibrium E_2^*.

For the infection equilibrium $E_2^*(x_1^*,x_2^*,v^*)$, from (4.2) we have

$$\begin{cases} d_1=\frac{\lambda_1}{x_1^*}-\beta_1 v^*,\\ d_2=\frac{\lambda_2}{x_2^*}-\beta_2 v^*,\\ \gamma=\beta_1 b_1 x_1^*+\beta_2 b_2 x_2^*, \end{cases}$$

then (2.7) can be rewritten as

$$\begin{cases} \frac{d}{dt}x_1(t)=x_1(t)\left\{\lambda_1\left[\frac{1}{x_1(t)}-\frac{1}{x_1^*}\right]-\beta_1\left[v(t)-v^*\right]\right\},\\ \frac{d}{dt}x_2(t)=x_2(t)\left\{\lambda_2\left[\frac{1}{x_2(t)}-\frac{1}{x_2^*}\right]-\beta_2\left[v(t)-v^*\right]\right\},\\ \frac{d}{dt}v(t)=v(t)\left\{\beta_1 b_1\left[\frac{x_1(t-\tau_1)v(t-\tau_1)}{v(t)}-x_1^*\right]+\beta_2 b_2\left[\frac{x_2(t-\tau_2)v(t-\tau_2)}{v(t)}-x_2^*\right]\right\}, \end{cases} \tag{4.5}$$

which has the same dynamics as system (2.7) in the interior of the region Ω_2.

Define a Lyapunov functional

$$\begin{aligned} L_{22}= {} & m_1\left[x_1(t)-x_1^*-x_1^*\ln\frac{x_1(t)}{x_1^*}\right]+m_2\left[x_2(t)-x_2^*-x_2^*\ln\frac{x_2(t)}{x_2^*}\right]\\ & +\left[v(t)-v^*-v^*\ln\frac{v(t)}{v^*}\right]+r_1\int_{t-\tau_1}^{t}\left[\frac{x_1(\theta)v(\theta)}{p_1}-1-\ln\frac{x_1(\theta)v(\theta)}{p_1}\right]d\theta\\ & +r_2\int_{t-\tau_2}^{t}\left[\frac{x_2(\theta)v(\theta)}{p_2}-1-\ln\frac{x_2(\theta)v(\theta)}{p_2}\right]d\theta, \end{aligned}$$

where m_i, r_i and p_i $(i=1,2)$ are positive and left unspecified, then the derivative of L_{22} along solutions of (4.5) is given by

$$\begin{aligned} \frac{dL_{22}}{dt}= {} & m_1\left[x_1(t)-x_1^*\right]\left\{\lambda_1\left[\frac{1}{x_1(t)}-\frac{1}{x_1^*}\right]-\beta_1\left[v(t)-v^*\right]\right\}\\ & +m_2\left[x_2(t)-x_2^*\right]\left\{\lambda_2\left[\frac{1}{x_2(t)}-\frac{1}{x_2^*}\right]-\beta_2\left[v(t)-v^*\right]\right\}\\ & +\left[v(t)-v^*\right]\left\{\beta_1 b_1\left[\frac{x_1(t-\tau_1)v(t-\tau_1)}{v(t)}-x_1^*\right]+\beta_2 b_2\left[\frac{x_2(t-\tau_2)v(t-\tau_2)}{v(t)}-x_2^*\right]\right\}\\ & +r_1\left\{\frac{1}{p_1}\left[x_1(t)v(t)-x_1(t-\tau_1)v(t-\tau_1)\right]+\ln\frac{x_1(t-\tau_1)v(t-\tau_1)}{x_1(t)v(t)}\right\}\\ & +r_2\left\{\frac{1}{p_2}\left[x_2(t)v(t)-x_2(t-\tau_2)v(t-\tau_2)\right]+\ln\frac{x_2(t-\tau_2)v(t-\tau_2)}{x_2(t)v(t)}\right\} \end{aligned}$$

$$
\begin{aligned}
= \quad & m_1\lambda_1\left[2-\tfrac{x_1^*}{x_1(t)}-\tfrac{x_1(t)}{x_1^*}\right]+m_2\lambda_2\left[2-\tfrac{x_2^*}{x_2(t)}-\tfrac{x_2(t)}{x_2^*}\right]\\
& -m_1\beta_1x_1^*v^*\left[\tfrac{x_1(t)v(t)}{x_1^*v^*}-\tfrac{x_1(t)}{x_1^*}-\tfrac{v(t)}{v^*}+1\right]\\
& -m_2\beta_2x_2^*v^*\left[\tfrac{x_2(t)v(t)}{x_2^*v^*}-\tfrac{x_2(t)}{x_2^*}-\tfrac{v(t)}{v^*}+1\right]\\
& +\beta_1b_1x_1^*v^*\left[\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1^*v^*}-\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1^*v(t)}-\tfrac{v(t)}{v^*}+1\right]\\
& +\beta_2b_2x_2^*v^*\left[\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2^*v^*}-\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2^*v(t)}-\tfrac{v(t)}{v^*}+1\right]\\
& +r_1\left\{\tfrac{1}{p_1}\left[x_1(t)v(t)-x_1(t-\tau_1)v(t-\tau_1)\right]+\ln\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1(t)v(t)}\right\}\\
& +r_2\left\{\tfrac{1}{p_2}\left[x_2(t)v(t)-x_2(t-\tau_2)v(t-\tau_2)\right]+\ln\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2(t)v(t)}\right\}.
\end{aligned}
$$

In order to eliminate the terms $x_i(t)v(t)$ and $x_i(t-\tau_i)v(t-\tau_i)$ $(i=1,2)$, we need to choose $m_i\beta_i=\beta_ib_i=r_i/p_i$ $(i=1,2)$, that is, $m_i=b_i, r_i=\beta_ib_ip_i$ $(i=1,2)$. Thus, we have

$$\frac{dL_{22}}{dt}=\bar{L}_{21}+\bar{L}_{22},$$

where

$$
\begin{aligned}
\bar{L}_{21}= \quad & b_1\lambda_1\left[2-\tfrac{x_1^*}{x_1(t)}-\tfrac{x_1(t)}{x_1^*}\right]+r_1\ln\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1(t)v(t)}\\
& +\beta_1b_1x_1^*v^*\left[\tfrac{x_1(t)}{x_1^*}-\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1^*v(t)}\right],\\
\bar{L}_{22}= \quad & b_2\lambda_2\left[2-\tfrac{x_2^*}{x_2(t)}-\tfrac{x_2(t)}{x_2^*}\right]+r_2\ln\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2(t)v(t)}\\
& +\beta_2b_2x_2^*v^*\left[\tfrac{x_2(t)}{x_2^*}-\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2^*v(t)}\right].
\end{aligned}
$$

Notice that $\bar{L}_{21}$ can be reexpressed by

$$
\begin{aligned}
\bar{L}_{21}= \quad & 2(b_1\lambda_1-r_1)-b_1(\lambda_1-\beta_1x_1^*v^*)\tfrac{x_1^*}{x_1(t)}-b_1(\lambda_1-\beta_1x_1^*v^*)\tfrac{x_1(t)}{x_1^*}\\
& +2r_1-\beta_1b_1x_1^*v^*\tfrac{x_1^*}{x_1(t)}-\beta_1b_1x_1^*v^*\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1^*v(t)}+r_1\ln\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1(t)v(t)}.
\end{aligned}
$$

When $r_1=\beta_1b_1x_1^*v^*$, that is, $p_1=x_1^*v^*$, using $\lambda_1-\beta_1x_1^*v^*=d_1x_1^*$ yields

$$
\begin{aligned}
\bar{L}_{21}= \quad & b_1d_1x_1^*\left[2-\tfrac{x_1^*}{x_1(t)}-\tfrac{x_1(t)}{x_1^*}\right]\\
& +\beta_1b_1x_1^*v^*\left[2-\tfrac{x_1^*}{x_1(t)}-\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1^*v(t)}+\ln\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1(t)v(t)}\right].
\end{aligned}
$$

Similarly, when $r_2=\beta_2b_2x_2^*v^*$, that is, $p_2=x_2^*v^*$, we have

$$
\begin{aligned}
\bar{L}_{22}= \quad & b_2d_2x_2^*\left[2-\tfrac{x_2^*}{x_2(t)}-\tfrac{x_2(t)}{x_2^*}\right]\\
& +\beta_2b_2x_2^*v^*\left[2-\tfrac{x_2^*}{x_2(t)}-\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2^*v(t)}+\ln\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2(t)v(t)}\right].
\end{aligned}
$$

Summarizing the inference above, when $m_i=b_i, r_i=\beta_ib_ix_i^*v^*$ and $p_i=x_i^*v^*$ $(i=1,2)$,

$$
\begin{aligned}
\tfrac{dL_{22}}{dt}= \quad & b_1d_1x_1^*\left[2-\tfrac{x_1^*}{x_1(t)}-\tfrac{x_1(t)}{x_1^*}\right]+b_2d_2x_2^*\left[2-\tfrac{x_2^*}{x_2(t)}-\tfrac{x_2(t)}{x_2^*}\right]\\
& +\beta_1b_1x_1^*v^*\left[2-\tfrac{x_1^*}{x_1(t)}-\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1^*v(t)}+\ln\tfrac{x_1(t-\tau_1)v(t-\tau_1)}{x_1(t)v(t)}\right]\\
& +\beta_2b_2x_2^*v^*\left[2-\tfrac{x_2^*}{x_2(t)}-\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2^*v(t)}+\ln\tfrac{x_2(t-\tau_2)v(t-\tau_2)}{x_2(t)v(t)}\right].
\end{aligned}
$$

By the relationship between the arithmetical and geometrical means and Lemma 3.1, we have $dL_{22}/dt \leq 0$, and the equality holds if and only if $x_1(t) = x_1^*, x_2(t) = x_2^*, v(t) = v_1(t-\tau_1) = v_2(t-\tau_2)$ for $t > 0$.

Obviously, from the first two equations of system (2.7) the largest invariant set of system (2.7) on the region $\left\{(x_1(t), x_2(t), v(t))^T \in \Omega_2 : dL_{22}/dt = 0\right\}$ is the singleton $\{E_2^*\}$. Therefore, it follows by the LaSalle's Invariance Principle[3] that E_2^* is globally stable in Ω_2 when $R_{02} > 1$.

This completes the proof of Theorem 4.3. □

5. Conclusion

In this paper, assuming that the time period of viral cytopathicity within target cells is a constant number, we incorporated a constant delay into the basic viral dynamical model proposed in [6, 7], established a basic viral dynamical model (2.3) with viral cytopathicity delay, and then extended model (2.3) into the case with two types of target cells. The modeling idea may be applied into the case with $n(n \geq 2)$ types of target cells.

For the two viral infection models with delay proposed here, we found their thresholds determining their dynamics, respectively. By the definition of the basic reproduction number of viral infection, we can know that the obtained thresholds are the basic reproduction numbers of the associated viral infection models, respectively. By constructing Lyapunov functionals, we obtained the main results on the two models: when the basic reproduction number is not greater than one, the infection-free equilibrium is globally stable in the feasible region, which implies that the viral infection goes extinct eventually; when it is greater than one, the infection equilibrium is globally stable in the feasible region, which implies that the viral infection persists in the body of host. Mathematically, the method of constructing Lyapunov functions here is suitable for some delay differential equations of higher order (i.e., the system with $n(n \geq 2)$ types of target cells), and the introduction of Lemma 3.1 may simplify the proof of the global stability.

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