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STABILITY PROPERTIES OF A DELAYED VIRAL INFECTION MODEL WITH LYTIC IMMUNE RESPONSE†

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Abstract. In this paper, a class of more general delayed viral infection model with lytic immune response is proposed by Song et al.[1] ([Journal of Mathematical Analysis Application 373 (2011), 345-355). We derive the basic reproduction numbers R_0 and R_0^* for the viral infection, and establish that the global dynamics are completely determined by the values of R_0 and R_0^*. If $R_0 \leq 1$, the viral-free equilibrium E_0 is globally asymptotically stable; if $R_0^* \leq 1 < R_0$, the immune-free equilibrium E_1 is globally asymptotically stable; if $R_0^* > 1$, the chronic-infection equilibrium E_2 is globally asymptotically stable by using the method of Lyapunov function.

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1. Introduction

Mathematical models can provided insights into the dynamics of viral load in vivo. A basic viral infection model([2]) has been widely used for studying the dynamics of infections agents such as hepatitis B virus(HBV), hepatitis C virus(HCV), and human immunodeficiency virus(HIV). This is because these mathematical models may play a significant role in the development of a better understanding of the disease and the various drug therapy strategies used against it([3-5]).

Recently, there have been a lot of papers on virus dynamics with in-host, some include the immune response directly [2,3,5-11], others do not contain the immune response [12-19]. During viral infections, the host immune system reacts

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with innate and antigen-specific immune response. Both types of response can be subdivided broadly into lytic and non-lytic components. Lytic components kill infected cells, whereas the non-lytic inhibit viral replication through soluble mediators. As a part of the innate response, cytotoxic T lymphocytes (CTLs) kill infected cells, whereas antibodies neutralize free virus particles and thus, inhibit the infection of susceptible cells. In addition, $CD4^+$ and $CD8^+$ T cells can secrete cytokines that inhibit viral replication(e.g., IFN-γ and tumor necrosis factor α(TNF-α)). In order to investigate the role of direct lytic and non-lytic inhibition of viral replication by immune cells in viral infections, Bartholdy et al. [6] and Wodarz et al. [9] constructed a mathematical model describing the basic dynamics of the interaction between susceptible host cells, a virus population, and immune response, which is shown graphically in Fig.1 and described by the following differential equations:

$$\begin{cases} \dot{x} = s - dx - \dfrac{\beta xy}{1+qz}, \\ \dot{y} = \dfrac{\beta xy}{1+qz} - ay - pyz, \\ \dot{z} = cy - bz, \end{cases} \tag{1.1}$$

where x is the number of susceptible host cells, y is the number of virus population and z is the number of immune response; susceptible host cells are generated at a rate s, die at a rate dx and become infected by virus at a rate βxy. Virus replication is inhibited by the immune response at a rate $1+qz$; infected cells die at a rate ay and killed by the immune system at a rate pyz. This corresponds to lytic effector mechanisms; the immune response is assumed to get stronger at a rate proportional to the number of infected cells, cy, and also decays exponentially at a rate proportional to its current strength, bz. Note that the variable z represents overall immunity that can be generated in response to a virus infection. The parameter p expresses the strength of the lytic component, whereas the parameter q expresses the efficacy of the non-lytic component.

By the similar theoretical analysis to population dynamical systems and epidemic models [18], time delays should be considered in viral models [11,13,17], and N.Burić et al. [20] condidered the effects of the time delay for immune response on two-dimensional system which consists of infected cells and CTLs, Canabarro et al. [21] investigated the effects of a time delay on the four-dimensional system with $\dot{z} = cy(t-\tau)z(t-\tau) - bz$, and Wang et al. [11] studied the effects of the time delay for immune response on the three-dimensional system with $\dot{z} = cy(t-\tau) - bz$.

Note that the immune response after viral infection is universal and necessary to eliminate or control the disease. Antibodies cytokinesis, natural killer cells, and T cells are essential components of a normal immune response to a viral. Indeed, in most viral infections, cytotoxic T lymphocytes (CTLs) play a very important role in antiviral defense by attacking virus infected cells. It is believed that they are the main host immune factor that limits the development of virus

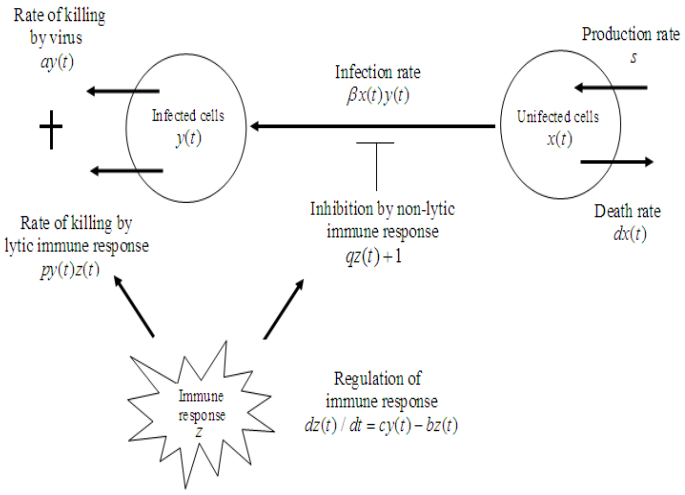

Fig. 1 Schematic representation of the mathematical model (1.1)

replication in vivo and thus determines virus load [7]. Therefore, the population dynamics of viral infection with CTL response has been paid much attention in the last few decades [10,11]. In this paper, we consider the following model with delay between the time a cell begin to be infected and the time of emission of virus particles from this cell [1,14,19].

$$\begin{cases} \dot{x} = s - dx - \beta xy, \\ \dot{y} = \beta e^{-m\tau} x(t-\tau)y(t-\tau) - ay - pyz, \\ \dot{z} = cyz - bz, \end{cases} \tag{1.2}$$

where the state variables x, y, z and the parameters s, a, b, c, d, p and β have the same biological meanings as in the model (1.1). In model (1.2), the term $e^{-m\tau}$ accounts for cells that are infected at time t but die before becoming productively infected τ time units later. The production of CTLs depends not only on the population of infected cells but also depends on the population of CTL cells, then $\dot{z} = cyz - bz$.

This paper is organized as follows: In the next section, we give the existences of the equilibria and basic reproduction number. In Section 3, the global dynamics are established. Biological implications of our results are discussed in Section 4.

2. Equilibria and positive invariance

If we denote the basic reproduction number of model (1.2) as

$$R_0 = \frac{\beta s e^{-m\tau}}{ad},$$

and the immune response reproduction number of model (1.2) as

$$R_0^* = \frac{\beta c s e^{-m\tau}}{acd + ab\beta},$$

then the equilibria of system (1.2) as follows:

(i) if $R_0^* < R_0 < 1$, then system (1.2) only has the viral-free equilibrium $E_0 = (x_0, 0, 0) = (\frac{s}{d}, 0, 0)$;

(ii) if $R_0^* < 1 < R_0$, then system (1.2) has immune-free equilibrium $E_1 = (x_1, y_1, 0)$ except for E_0, where

$$x_1 = \frac{cs}{cd + b\beta}, \quad y_1 = \frac{\beta s e^{-m\tau} - ad}{\beta a} = \frac{d}{\beta}(R_0 - 1);$$

(iii) if $1 < R_0^* < R_0$, then system (1.2) has a positive equilibrium $E_2 = (\overline{x}, \overline{y}, \overline{z})$ except for E_0 and E_1, where

$$\overline{x} = \frac{cs}{cd + b\beta}, \quad \overline{y} = \frac{b}{c}, \quad \overline{z} = \frac{\beta s c e^{-m\tau} - acd - ab\beta}{cdp + bp\beta} = \frac{a}{p}(R_0^* - 1).$$

Next, we show that model (1.2) is biologically acceptance in the sense that no population goes negative.

To study the stability of equilibria and investigate the dynamics of model (1.2) when $\tau \geq 0$, we need to consider a suitable phase space and a feasible region. For $\tau > 0$, we denote by $C = C([-\tau, 0], R^3)$ the Banach space of continuous functions mapping from the interval $[-\tau, 0]$ to R equipped with the sup-norm $\|\varphi\| = \sup\limits_{-\tau \leq \theta \leq 0} \{|\varphi_1(\theta)|, |\varphi_2(\theta)|, |\varphi_3(\theta)|\}$, where $\varphi = (\varphi_1, \varphi_2, \varphi_3)$. Further, the nonnegative cone of C is defined as $C^+ = C([-\tau, 0], R_+^3)$.

The initial condition for system (1.2) is given as

$$x(\theta) = \varphi_1(\theta) \geq 0, \quad y(\theta) = \varphi_2(\theta) \geq 0, \quad z(\theta) = \varphi_3(\theta) \geq 0, \quad -\tau \leq \theta \leq 0, \quad (2.1)$$

and a solution of system (1.2) is denoted by $(x(t), y(t), z(t))$.

The following result establish the positivity and boundedness of solution for system (1.2) with initial condition (2.1).

Theorem 2.1. *Under the above initial condition (2.1), then $x(t), y(t)$ and $z(t)$ are all non-negative and bounded for all $t \geq 0$ at which the solution exists.*

Proof. From system (1,2), we have

$$\begin{aligned} x(t) &= x(0)e^{-\int_0^t (d+\beta y(\xi))d\xi} + \int_0^t s e^{-\int_\eta^t (d+\beta y(\xi))d\xi} d\eta, \\ y(t) &= y(0)e^{-\int_0^t (a+pz(\xi))d\xi} + \int_0^t \beta x(\eta-\tau)y(\eta-\tau)e^{-m\tau} e^{-\int_\eta^t (a+pz(\xi))d\xi} d\eta, \\ z(t) &= z(0)e^{\int_0^t (cy(\xi)-b)d\xi}. \end{aligned} \tag{2.2}$$

Positivity immediately follows from the above integral forms (2.2) and initial condition (2.1).

For boundedness of the solution, we define

$$G(t) = \frac{ce^{-m\tau}}{a}x(t) + \frac{c}{a}y(t+\tau) + \frac{p}{a}z(t+\tau),$$

and $\gamma = \min\{d, a, b\}$.

By non-negativity of the solution, it follows that

$$\dot{G}(t) = \frac{cse^{-m\tau}}{a} - \frac{dce^{-m\tau}}{a}x(t) - cy(t+\tau) - \frac{pb}{a}z(t+\tau) \le \frac{cse^{-m\tau}}{a} - \gamma G(t).$$

This implies that $G(t)$ is bounded, and so are $x(t)$, $y(t)$ and $z(t)$. This completes the proof. □

3. Global dynamics

3.1. Global stability of the viral-free equilibrium E_0. In the following, we can obtain globally stability of E_0 when $R_0 \le 1$ by using a Lyapunov function.

Theorem 3.1. *The viral-free equilibrium E_0 is globally asymptotically stable if $R_0 \le 1$.*

Proof. Define a Lyapunov function

$$L_0 = L_0(x_t, y(t), z_t) = x_t(0) - x_0 \ln\frac{x_t(0)}{x_0} + e^{m\tau}y(t) + \frac{pe^{m\tau}}{c}z_t(0) + \beta\int_{-\tau}^0 x_t(\theta)y_t(\theta)d\theta, \tag{3.1}$$

where $x_t(\theta) = x(t+\theta), z_t(\theta) = z(t+\theta)$ for $\theta \in [-\tau, 0]$. Therefore, $x(t) = x_t(0), z(t) = z_t(0)$ in this notation.

Noting that $f(u) = u - \ln u,\ u \in R_+$ has the global minimum at $u = 1$ and $f(1) = 1$, we have

$$x_t(0) - x_0 \ln\frac{x_t(0)}{x_0} = x_0\left(\frac{x_t(0)}{x_0} - \ln\frac{x_t(0)}{x_0}\right) > x_0.$$

The Lyapunov function L_0 is non-negative definite in the bouned feasible region with respect to the viral-free equilibrium E_0. Calculating the time derivative of L_0 along the positive solution of model (1.2), we can obtain

$$\begin{aligned} \dot{L}_0\Big|_{(1.2)} &= \dot{x}(t) - \frac{x_0}{x(t)}\dot{x}(t) + e^{m\tau}\dot{y}(t) + \frac{pe^{m\tau}}{c}\dot{z}(t) + \beta xy - \beta x(t-\tau)y(t-\tau) \\ &= s - dx(t) - \frac{x_0}{x(t)}(s - dx(t) - \beta x(t)y(t)) - ay(t)e^{m\tau} - \frac{pbe^{m\tau}}{c}z(t). \end{aligned} \tag{3.2}$$

Note that $s = dx_0,\ R_0 = \dfrac{\beta s e^{-m\tau}}{ad}$, from (3.2), we get

$$\begin{aligned}\dot{L}_0\Big|_{(1.2)} &= dx_0(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}) + (\beta x_0 - ae^{m\tau})y(t) - \frac{pbe^{m\tau}}{c}z(t)\\ &= dx_0(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}) + ae^{m\tau}(R_0 - 1)y(t) - \frac{pbe^{m\tau}}{c}z(t).\end{aligned} \tag{3.3}$$

Since $2 - \dfrac{x(t)}{x_0} - \dfrac{x_0}{x(t)} \le 0$ and $R_0 \le 1$, we can obtain that $\dot{L}_0\Big|_{(1.2)} \le 0$ for all $x(t), y(t), z(t) \ge 0$, and $\dot{L}_0\Big|_{(1.2)} \equiv 0$ if and only if $(x, y, z) = (x_0, 0, 0)$. Then the globally asymptotical stability of E_0 follows from Lyapunov LaSalle Invariance Principle([22]). □

3.2. Global stability of the immune-free equilibrium E_1. In this subsection, when $R_0^* \le 1 < R_0$, then we can establish the following result for the immune-free equilibrium E_1.

Theorem 3.2. *The immune-free equilibrium E_1 is globally asymptotically stable if $R_0^* \le 1 < R_0$.*

Proof. Let $g(u) = u - 1 - \ln u$, and define a Lyapunov function

$$\begin{aligned}L_1 &= L_1(x_t, y(t), z_t) = x_1 g(\frac{x_t(0)}{x_1}) + y_1 e^{m\tau} g(\frac{y(t)}{y_1}) + \frac{pe^{m\tau}}{c}z_t(0)\\ &\quad + \beta x_1 y_1 \int_{-\tau}^{0} g(\frac{x_t(\theta)y_t(\theta)}{x_1 y_1})d\theta.\end{aligned} \tag{3.4}$$

Calculating the time derivative of L_1 along the positive solutions of model (1.2), we have

$$\begin{aligned}\dot{L}_1\Big|_{(1.2)} &= \dot{x}(t) - \frac{x_1}{x(t)}\dot{x}(t) + e^{m\tau}(\dot{y}(t) - \frac{y_1}{y(t)}\dot{y}(t)) + \frac{pe^{m\tau}}{c}\dot{z}(t) + \beta x(t)y(t)\\ &\quad - \beta x(t-\tau)y(t-\tau) - \beta x_1 y_1 \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}\\ &= s - dx(t) - \frac{x_1}{x(t)}(s - dx(t) - \beta x(t)y(t)) - ay(t)e^{m\tau} - \frac{y_1}{y(t)}\beta x(t-\tau)y(t-\tau)\\ &\quad + ay_1 e^{m\tau} + py_1 z(t)e^{m\tau} - \frac{pbe^{m\tau}}{c}z(t) - \beta x_1 y_1 \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}.\end{aligned} \tag{3.5}$$

Using $s = dx_1 + \beta x_1 y_1,\ \beta x_1 y_1 = a y_1 e^{m\tau},\ R_0^* = \dfrac{\beta c s e^{-m\tau}}{acd + ab\beta}$, from (3.5), we have

$$\begin{aligned}
\dot{L}_1\Big|_{(1.2)} &= dx_1(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}) + \beta x_1 y_1(2 - \frac{x_1}{x(t)}) + (\beta x_1 - a e^{m\tau}) y(t) \\
&\quad + pz(t)e^{m\tau}(y_1 - \frac{b}{c}) - \frac{y_1}{y(t)}\beta x(t-\tau)y(t-\tau) - \beta x_1 y_1 \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)} \\
&= dx_1(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}) + pz(t)e^{m\tau}\cdot\frac{dc + b\beta}{\beta c}(R_0^* - 1) \\
&\quad + \beta x_1 y_1\Big(2 - \frac{x_1}{x(t)} - \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}\Big) - \frac{y_1}{y(t)}\beta x(t-\tau)y(t-\tau) \\
&= dx_1(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}) + pz(t)e^{m\tau}\cdot\frac{dc + b\beta}{\beta c}(R_0^* - 1) \\
&\quad - \beta x_1 y_1\Big[g(\frac{x(t-\tau)y(t-\tau)}{x_1 y(t)}) + \ln\frac{x(t-\tau)y(t-\tau)}{x_1 y(t)} + g(\frac{x_1}{x(t)}) + \ln\frac{x_1}{x(t)} \\
&\quad + \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}\Big] \\
&= dx_1(2 - \frac{x(t)}{x_1} - \frac{x_1}{x(t)}) + pz(t)e^{m\tau}\cdot\frac{dc + b\beta}{\beta c}(R_0^* - 1) \\
&\quad - \beta x_1 y_1\Big[g(\frac{x(t-\tau)y(t-\tau)}{x_1 y(t)}) + g(\frac{x_1}{x(t)})\Big]..
\end{aligned}$$

Noting that $2 - \dfrac{x(t)}{x_1} - \dfrac{x_1}{x(t)} \le 0,\ R_0^* \le 1$, and $g(u):\ R_+ \to R$ has the global minimum at $u = 1$ and $g(1) = 0$. Hence, $x_1, y_1 > 0$ ensures that $\dot{L}_1\Big|_{(1.2)} \le 0$, and $\dot{L}_1\Big|_{(1.2)} \equiv 0$ if and only if $(x, y, z) = (x_1, y_1, 0)$. Then the globally asymptotical stability of E_1 follows from Lyapunov LaSalle Invariance Principle([22]). □

3.3. Global stability of the positive equilibrium E_2. Lastly, we consider the case $1 < R_0^* < R_0$, then discuss the stability of the positive (chronic-infection) equilibrium E_2.

Theorem 3.3. *The positive equilibrium E_2 is globally asymptotically stable when $1 < R_0^* < R_0$ hold.*

Proof. Let $g(u) = u - 1 - \ln u$, and define a Lyapunov function

$$\begin{aligned}
L_2 &= L_2(x_t, y(t), z_t) = \overline{x}g(\frac{x_t(0)}{\overline{x}}) + \overline{y}e^{m\tau}g(\frac{y(t)}{\overline{y}}) + \frac{p\overline{z}e^{m\tau}}{c}g(\frac{z_t(0)}{\overline{z}}) \\
&\quad + \beta\overline{xy}\int_{-\tau}^{0} g(\frac{x_t(\theta)y_t(\theta)}{\overline{xy}})d\theta.
\end{aligned} \tag{3.6}$$

Calculating the time derivative of L_2 along the positive solutions of model (1.2), we obtain

$$\begin{aligned}\dot{L}_2\Big|_{(1.2)} &= \dot{x}(t) - \frac{\overline{x}}{x(t)}\dot{x}(t) + e^{m\tau}(\dot{y}(t) - \frac{\overline{y}}{y(t)}\dot{y}(t)) + \frac{p\overline{z}e^{m\tau}}{c}(\dot{z}(t) - \frac{\overline{z}}{z(t)}\dot{z}(t))\\ &\quad \beta x(t)y(t) - \beta x(t-\tau)y(t-\tau) - \beta\overline{x}\overline{y}\ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}\\ &= s - dx(t) - \frac{\overline{x}}{x(t)}(s - dx(t) - \beta x(t)y(t)) - ay(t)e^{m\tau}\\ &\quad -\frac{\overline{y}}{y(t)}\beta x(t-\tau)y(t-\tau) + a\overline{y}e^{m\tau} + p\overline{y}z(t)e^{m\tau} - \frac{pbe^{m\tau}}{c}z(t) - py(t)\overline{z}e^{m\tau}\\ &\quad +\frac{pbe^{m\tau}}{c}\overline{z} - \beta\overline{x}\overline{y}\ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}\\ &= s - dx(t)\frac{\overline{x}}{x(t)}s + d\overline{x} + (\beta\overline{x} - ae^{m\tau} - p\overline{z}e^{m\tau})y(t) + a\overline{y}e^{m\tau} + \frac{pb\overline{z}e^{m\tau}}{c} + p\overline{y}z(t)e^{m\tau}\\ &\quad -\frac{pbe^{m\tau}}{c}z(t) - \frac{\overline{y}}{y(t)}\beta x(t-\tau)y(t-\tau) - \beta\overline{x}\overline{y}\ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}.\end{aligned} \tag{3.7}$$

Noting that

$$s = d\overline{x} + \beta\overline{x}\overline{y}, \quad \overline{y} = \frac{b}{c}, \quad \beta\overline{x}\overline{y} = (a\overline{y} + p\overline{y}\overline{z})e^{m\tau}$$

then from (3.7), we get

$$\begin{aligned}\dot{L}_2\Big|_{(1.2)} &= d\overline{x}(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}) + \beta\overline{x}\overline{y}(2 - \frac{\overline{x}}{x(t)} - \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)})\\ &\quad +p(\overline{y} - \frac{b}{c})e^{m\tau}z(t) - \frac{\overline{y}}{y(t)}\beta x(t-\tau)y(t-\tau)\\ &= d\overline{x}(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}) - \beta\overline{x}\overline{y}\Big[g(\frac{x(t-\tau)y(t-\tau)}{\overline{x}\overline{y}(t)}) + \ln\frac{x(t-\tau)y(t-\tau)}{\overline{x}\overline{y}(t)}\\ &\quad +g(\frac{\overline{x}}{x(t)}) + \ln\frac{\overline{x}}{x(t)} + \ln\frac{x(t)y(t)}{x(t-\tau)y(t-\tau)}\Big]\\ &= d\overline{x}(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}) - \beta\overline{x}\overline{y}\Big[g(\frac{x(t-\tau)y(t-\tau)}{\overline{x}\overline{y}(t)}) + g(\frac{\overline{x}}{x(t)})\Big].\end{aligned}$$

Since $2 - \dfrac{x(t)}{\overline{x}} - \dfrac{\overline{x}}{x(t)} \le 0$ and $g(u) :\ R_+ \to R$ has the global minimum $u = 1$ and $g(1) = 0$. Hence, $\overline{x}, \overline{y}, \overline{z} > 0$ ensures that $\dot{L}_2\Big|_{(1.2)} \le 0$. By Theorem 5.3.1 of ([22]), it can be verified that $\dot{L}_2\Big|_{(1.2)} \equiv 0$ if and only if $(x, y, z) = (\overline{x}, \overline{y}, \overline{z})$. Then the globally asymptotical stability of E_2 follows from Lyapunov LaSalle Invariance Principle ([22]). □

As a corollary, Theorem 3.3 implies that no sustained oscillation can occur in our model (1.2).

Corollary 3.1. *Assume $1 < R_0^* < R_0$. For $m \ge 0$ and $\tau > 0$, system (1.2) has no non-constant periodic solutions.*

4. Conclusions

In paper [1], Authors Song et al. have obtained the following results only:

(1) the viral-free equilibrium E_0 of system (1.2) is indeed globally asymptotically stable if $R_0 < 1$;

(2) if $R_0 > 1 > R_0^*$, then the immune-free response equilibrium E_1 of system (1.2) is locally asymptotically stable for any $\tau \geq 0$;

(3) if $\tau = 0$ and $R_0^* > 1$, then the positive equilibrium E_2 of system (1.2) is locally asymptotically stable;

(4) a conjecture: if $\tau > 0$, then there will exists $\tau^* \in I$, such that the equilibrium E_2 is asymptotically stable for $0 \leq \tau < \tau^*$, and becomes unstable for τ staying in some right neighborhood of τ^*, with a Hopf bifurcation occurring when $\tau = \tau^*$, where the forms of $\tau^*,\ I$ are defined in [1].

However, in present paper, we have rigorously established the global dynamics of model (1.2):

(a) if $R_0 \leq 1$, then all solutions converge to the viral-free equilibrium E_0;

(b) if $R_0^* \leq 1 < R_0$, then the immune-free equilibrium E_1 is globally asymptotically stable;

(c) if $R_0^* > 1$, then all positive solutions converge to the chronic-infection equilibrium E_2, where the forms of $R_0,\ R_0^*,\ E_0,\ E_1,\ E_2$ are defined as the same as in [1].

Our result establishing that no sustained-oscillation regime exists without cell division even in the presence of intracellular delays is of particular interest in this context, it shows that target-cell dynamics plays a crucial role in the dynamics of viral infection in vivo. Mathematically, Theorem 3.3 is the complete result on the global stability of the chronic-infection equilibrium for the virus infection models with intracellular delays τ. The global stability result is essential for our conclusion that the delay τ does not produce periodic oscillations for all positive values of parameters.

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