

Global Dynamics of an In-host Viral Model with Intracellular Delay

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Abstract The dynamics of a general in-host model with intracellular delay is studied. The model can describe *in vivo* infections of HIV-I, HCV, and HBV. It can also be considered as a model for HTLV-I infection. We derive the basic reproduction number R_0 for the viral infection, and establish that the global dynamics are completely determined by the values of R_0 . If $R_0 \leq 1$, the infection-free equilibrium is globally asymptotically stable, and the virus are cleared. If $R_0 > 1$, then the infection persists and the chronic-infection equilibrium is locally asymptotically stable. Furthermore, using the method of Lyapunov functional, we prove that the chronic-infection equilibrium is globally asymptotically stable when $R_0 > 1$. Our results shows that for intercellular delays to generate sustained oscillations in in-host models it is necessary have a logistic mitosis term in target-cell compartments.

Keywords In-host models · Intracellular delays · Global stability · Lyapunov functionals

1. Introduction

Much interest has been devoted to mathematical modeling of *in vivo* dynamics of viral infections. These in-host models are formulated to explore possible mechanisms and dynamical behaviors of the viral infection process (Perelson et al., 1993; Perelson and Nelson, 1999). They can be used to estimate key parameter values for the viral infection such as virion clearance rate, infected cell life-span, and viral generation time (Perelson et al., 1996), and to guide development of efficient anti-viral drug therapies (Bonhoeffer et al., 1997).

A basic in-host compartmental model of viral dynamics contains three compartments: the population of uninfected target cells, $x(t)$, infected target cells that produce virus, $y(t)$, and free virus particles, $v(t)$. Uninfected target cells are assumed to be produced at

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a constant rate λ and die at rate $dx(t)$. Infection of target cells by free virus is assumed to occur at rate $\beta x(t)v(t)$. Infected cells die at rate $ay(t)$. New virus are produced from infected cells at rate $ky(t)$ and die at rate $uv(t)$. The average life-time of uninfected cells, infected cells, and free virus is thus given by $1/d$, $1/a$, and $1/u$, respectively. The average number of virus particles produced over the lifetime of a single infected cell (the burst size) is given by k/a .

The preceding assumptions lead to the following system of differential equations

$$\begin{aligned}x'(t) &= \lambda - dx(t) - \beta x(t)v(t), \\y'(t) &= \beta x(t)v(t) - ay(t), \\v'(t) &= ky(t) - uv(t).\end{aligned}\tag{1}$$

System (1) has been derived to model *in vivo* dynamics of HIV-1, HBV, and other virus (Perelson et al., 1993, 1996; Bonhoeffer et al., 1997; Perelson and Nelson, 1999; Nowak and May, 2000; Tuckwell and Wan, 2004; Nowak et al., 1996). It can also be considered as a model for the HTLV-I infection if $x(t)$, $y(t)$, and $v(t)$ are regarded as healthy, latently infected, and actively infected $CD4^+$ T cell pools (Nowak and Bangham, 1996; Wang et al., 2002). It has been shown (e.g. in Nowak et al., 1996), the basic reproductive number of the virus for system (1) is given as $R_0 = \frac{\lambda k \beta}{d a u}$, which describes the average number of newly infected cells generated from one infected cell at the beginning of the infection process. An illustration of R_0 is given in Fig. 2. If $R_0 \leq 1$, the infection-free equilibrium $E_0 = (\frac{\lambda}{d}, 0, 0)$ is locally asymptotically stable and the virus will be cleared; if $R_0 > 1$, then a unique chronic-infection equilibrium $E_1 = (\bar{x}, \bar{y}, \bar{v})$, $\bar{x}, \bar{y}, \bar{v} > 0$, exists and is locally asymptotically stable. The virus establish themselves among the target cells and infection becomes chronic. In Smith and De Leenheer (2003), Korobeinikov (2004), Wang and Li (2006), global dynamics of system (1) are established: the system is infection free if $R_0 \leq 1$, and if $R_0 > 1$, then the chronic-infection equilibrium is globally asymptotically stable. Divisions of activated target cells have been incorporated into the basic model (1) in such a way that the target cells satisfy the following set of equations (Perelson et al., 1993; Perelson and Nelson, 1999; Smith and De Leenheer, 2003; Wang and Li, 2006)

$$\begin{aligned}x'(t) &= \lambda + r_1 x(t) \left[1 - \frac{x(t) + y(t)}{K} \right] - dx(t) - \beta x(t)v(t), \\y'(t) &= \beta x(t)v(t) - r_2 y(t) \left[1 - \frac{x(t) + y(t)}{K} \right] - ay(t).\end{aligned}$$

It has been shown (e.g. in Wang and Li, 2006) that addition of cell divisions, as modeled by logistic terms, can destabilize the chronic-infection equilibrium and lead to sustained oscillations.

In the basic model (1), no distinction is made between target cells infected by the virus and virus producing target cells; they are both labeled $y(t)$. To account for the time between viral entry into a target cell and the production of new virus particles, typically lasts for around 1 day for the HIV-I infection (Dixit et al., 2004), models that include time delays have been developed and investigated (Herz et al., 1996;

Mittler et al., 1998; Nelson et al., 2000; Culshaw and Ruan, 2000; Nelson and Perelson, 2002; Dixit et al., 2004; Wang et al., 2009). One distinct feature of delay differential equation models is that delays typically destabilize an otherwise stable equilibrium and cause sustained oscillation through Hopf bifurcations. In recent studies of in-host viral model with intracellular delay and cell divisions (Culshaw and Ruan, 2000; Wang et al., 2009), it is shown that sustained oscillation can occur for realistic parameter values. The paper Wang et al. (2009) also contains a updated review of literature of in-host viral modeling. Regarding periodic oscillations in in-host models, it is known that such oscillations can occur in ODE models with cell divisions, and they can also occur in delayed models with cell divisions. It is not known, however, if periodic oscillations can be caused by intracellular delays without cell divisions. This motivates our study in the present paper. By rigorously establishing the global dynamics of a general viral model with intracellular delay and without cell divisions, we show that no sustained oscillations are possible in the model.

To incorporate the intracellular phase of the virus life-cycle, we assume that virus production occurs after the virus entry by a constant delay τ . The recruitment of virus-producing cells at time t is given by the number of cells that were newly infected at time $t - \tau$ and are still alive at time t . If we assume a constant death rate s for infected but not yet virus-producing cells, the probability of surviving the time period from $t - \tau$ to t is $e^{-s\tau}$. A transfer diagram for the transmission of viral infection is shown in Fig. 1. We thus arrive at the following model:

$$\begin{aligned} x'(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ y'(t) &= \beta x(t - \tau)v(t - \tau)e^{-st} - ay(t), \\ v'(t) &= ky(t) - uv(t). \end{aligned} \tag{2}$$

Division of target cells is not included in model (2) since we are interested in the effects of intracellular delays alone. The delay is incorporated in the same way as in Herz et al. (1996), Wang et al. (2009). Possible cell death during the delay phase is considered in model (2) while it was not assumed in Wang et al. (2009). Delays with general exponential distribution were considered in Nelson and Perelson (2002). In contrast, delays in model (2) satisfy a delta-type distribution. Many previous in-host models considered the effects of anti-viral drug therapies such as HAART (Bonhoeffer et al., 1997; Nelson et al., 2000; Nelson and Perelson, 2002; Wang et al., 2009). We note that model (2)

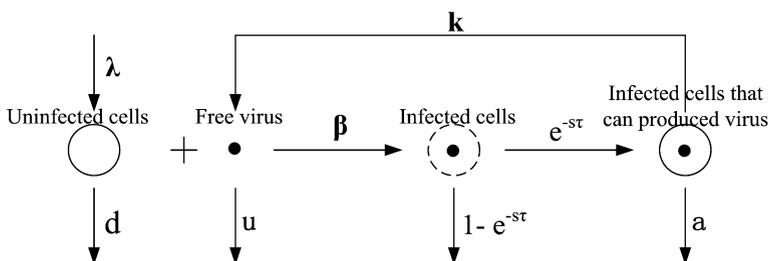


Fig. 1 Transfer diagram for model (2).

is mathematically equivalent to these models by allowing the transmission coefficient β to include a reduction due to the effect of reverse transcriptase inhibitors, and allow virus production coefficient k to include a reduction caused by protease inhibitors (c.f. Wang et al., 2009). Our results on the global dynamics of model (2) can readily apply to these models with anti-viral therapies. In all previous studies of delayed viral models, only local stabilities were investigated for the chronic-infection equilibrium. However, to rule out the existence of periodic solutions, it is necessary to establish the global stability of the chronic-infection equilibrium.

In the present paper, our primary goal is to carry out complete mathematical analysis of system (2) and establish its global dynamics. First of all, we derive the basic reproductive number R_0 as given in (3). We show that R_0 is a decreasing function of the delay τ . This implies that ignoring the intracellular delay will overestimate the basic reproduction number. We show that the basic reproductive number R_0 completely determines the global dynamics of model (2). More specifically, if $R_0 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable, and the virus will be cleared; if $R_0 > 1$, a unique chronic-infection equilibrium E_1 is locally asymptotically stable and all positive solutions converge to E_1 . Our global-stability result for the chronic-infection equilibrium is the first in the literature for in-host models with intracellular delays. The proof utilizes a global Lyapunov functional that is motivated by the work in McCluskey (2009, 2010). The global stability of E_1 rules out any possibility for Hopf bifurcations and existence of sustained oscillations.

Our paper is organized as follows. In the next section, the basic reproduction number R_0 is derived and the existence of equilibria in the feasible region is discussed. In Section 3, the global dynamics when $R_0 \leq 1$ are established. In Section 4, we prove our main result, global stability of the chronic-infection equilibrium when $R_0 > 1$. Biological implications of our results are discussed in Section 5.

2. Equilibria and basic reproductive number

In system (2), without infection ($y = 0, v = 0$), uninfected target cells stabilizes at the equilibrium $x_0 = \frac{\lambda}{a}$. The basic reproductive number R_0 for in-host models (Perelson et al., 1993; Nowak and May, 2000) measures the average number virus-producing target cells produced by an single virus-producing target cell during its entire infectious period in an entirely uninfected target-cell population. As illustrated in Fig. 2, the basic reproductive

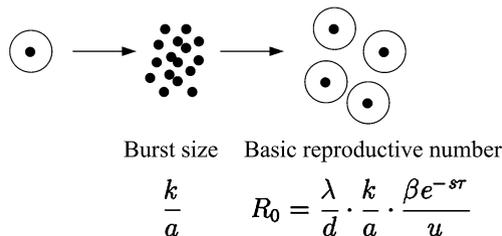


Fig. 2 An illustration of the basic reproduction ratio in model (2).

number R_0 for system (2) is given by

$$R_0 = \frac{k}{a} \cdot \frac{\beta e^{-s\tau}}{u} \cdot \frac{\lambda}{d}. \tag{3}$$

In (3), each virus-producing target cell produces $\frac{k}{a}$ virus particles over its entire infectious period $\frac{1}{a}$, and each virus infects $\frac{\beta}{u}$ target cells over the life span $\frac{1}{u}$, and of the newly infected target cells, a fraction of $e^{-s\tau}$ survives the delay period τ to become virus producing. When no intracellular delay is considered ($\tau = 0$), our R_0 reduces to the basic reproduction number for model (1). If the cell death during the delay is ignored ($s = 0$), our R_0 agrees with the basic reproduction number in Culshaw and Ruan (2000), Wang et al. (2009) when no cell division is present. We see that, if $s > 0$, R_0 is a decreasing function of the delay τ . An implication of this is that, if cells die during the delay period, an intracellular delay decreases R_0 , and thus ignoring the intracellular delay in a viral model will overestimate R_0 .

The equilibrium equations are

$$\begin{aligned} \lambda - d\bar{x} - \beta\bar{x}\bar{v} &= 0, \\ \beta\bar{x}\bar{v}e^{-s\tau} - a\bar{y} &= 0, \\ k\bar{y} - u\bar{v} &= 0. \end{aligned} \tag{4}$$

If $R_0 \leq 1$, an infection-free equilibrium $E_0 = (x_0, 0, 0)$ is the only equilibrium, corresponding to the extinction of free virus. If $R_0 > 1$, in addition to the infection-free equilibrium, there is a unique positive (chronic-infection) equilibrium $E_1 = (\bar{x}, \bar{y}, \bar{v})$, where

$$\bar{x} = \frac{au}{\beta k} e^{s\tau}, \quad \bar{y} = \frac{d\mu}{\beta k} (R_0 - 1), \quad \bar{v} = \frac{d}{\beta} (R_0 - 1). \tag{5}$$

To study the stability of equilibria and investigate the dynamics of system (2) when $\tau \geq 0$, we need to consider a suitable phase space and a feasible region. For $\tau > 0$, we denote by $\mathcal{C} = \mathcal{C}([-\tau, 0], \mathbb{R})$ 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 $\phi \in \mathcal{C}$. The nonnegative cone of \mathcal{C} is defined as $\mathcal{C}^+ = \mathcal{C}([-\tau, 0], \mathbb{R}_+)$. The initial conditions for system (2) are chosen at $t = 0$ as $\varphi \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+$ and $\varphi(0) > 0$. We present the preliminary results for system (2) in the following.

Proposition 2.1. *Under the above initial conditions, all solutions of system (2) are positive and ultimately bounded in $\mathcal{C} \times \mathbb{R} \times \mathcal{C}$.*

Proof: First, we prove that $x(t)$ is positive for all $t \geq 0$. Assuming the contrary, and letting $t_1 > 0$ be the first time such that $x(t_1) = 0$, then by the first equation of system (2) we have $x'(t_1) = \lambda > 0$, and hence $x(t) < 0$ for $t \in (t_1 - \epsilon, t_1)$, where $\epsilon > 0$ is sufficiently small. This contradicts $x(t) > 0$ for $t \in [0, t_1)$. It follows that $x(t) > 0$ for $t > 0$. Similarly, we can show the solutions $y(t), v(t)$ of system (2) are positive for $t > 0$ under positive initial conditions. In fact, assuming the contrary, and letting $t_2 > 0$ be the first time such that $v(t_2) = 0$, then by the third equation of system (2) we have $v'(t_2) = ky(t_2)$. Solving

$y(t)$ in the second equation of (2), we have

$$y(t_2) = \left(y(0) + \int_0^{t_2} \beta x(\theta - \tau)v(\theta - \tau)e^{-s\tau} e^{a\theta} d\theta \right) e^{-at_2} > 0.$$

It follows that $v'(t_2) > 0$, and hence $v(t)$ is positive, and

$$y(t) = \left(y(0) + \int_0^t \beta x(\theta - \tau)v(\theta - \tau)e^{-s\tau} e^{a\theta} d\theta \right) e^{-at} > 0.$$

From the first equation of (2), we obtain $x'(t) \leq \lambda - dx(t)$, and thus $\limsup_{t \rightarrow \infty} x(t) \leq \frac{\lambda}{d}$. Adding the first two equations of (2), we get

$$\begin{aligned} (x(t) + y(t + \tau))' &= \lambda - dx(t) - ay(t + \tau) + \beta x(t)v(t)(e^{-s\tau} - 1) \\ &\leq \lambda - \tilde{\mu}(x(t) + y(t + \tau)), \end{aligned}$$

where $\tilde{\mu} = \min\{d, a\}$. Thus, $\limsup_{t \rightarrow \infty} (x(t) + y(t + \tau)) \leq \frac{\lambda}{\tilde{\mu}}$. This relation and the third equation of (2) imply

$$v'(t) = ky(t) - uv(t) \leq k \frac{\lambda}{\tilde{\mu}} - uv(t),$$

and $\limsup_{t \rightarrow \infty} v(t) \leq \frac{k\lambda}{u\tilde{\mu}}$. Therefore, $x(t)$, $y(t)$ and $v(t)$ are ultimately bounded in $\mathcal{C} \times \mathbb{R} \times \mathcal{C}$. □

The dynamics of system (2) can be analyzed in the following bounded feasible region

$$\Gamma = \left\{ (x, y, v) \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ : \|x\| \leq \frac{\lambda}{d}, \|x + y\| \leq \frac{\lambda}{\tilde{\mu}}, \|v\| \leq \frac{k\lambda}{u\tilde{\mu}} \right\}.$$

Furthermore, the region Γ is positively invariant with respect to model (2) and the model is well posed.

3. Global dynamics when $R_0 \leq 1$

Intuitively, if $R_0 < 1$, the virus will not spread since an infected cell produces on average less than one secondary infection. In this section, we rigorously show that when $R_0 \leq 1$, the infection-free equilibrium E_0 is locally asymptotically stable, and all solutions in Γ converge to E_0 in the $\mathcal{C} \times \mathbb{R} \times \mathcal{C}$ topology.

Translating the equilibrium E_0 of system (2) to the origin, we let $x_1(t) = x(t) - x_0$, $y_1(t) = y(t)$, $v_1(t) = v(t)$. Then system (2) becomes

$$\begin{aligned} x_1'(t) &= -dx_1(t) - \beta x_0 v_1(t) - \beta x_1(t)v_1(t), \\ y_1'(t) &= -ay_1(t) + \beta x_0 e^{-s\tau} v_1(t - \tau) + \beta x_1(t - \tau)v_1(t - \tau)e^{-s\tau}, \\ v_1'(t) &= ky_1(t) - uv_1(t). \end{aligned} \tag{6}$$

The characteristic equation associated with the linearization of system (6) at $(0, 0, 0)$ is

$$(\mu + d)[\mu^2 + (a + u)\mu + au - k\beta x_0 e^{-s\tau} e^{-\mu\tau}] = 0. \tag{7}$$

One of the characteristic roots is $\mu_1 = -d < 0$, and the equilibrium $(0, 0, 0)$ is asymptotically stable if all roots of

$$\mu^2 + (a + u)\mu + au - k\beta x_0 e^{-s\tau} e^{-\mu\tau} = 0 \tag{8}$$

have negative real parts. It can be verified that all roots of Eq. (8) with $\tau = 0$ have negative real parts if $R_0 < 1$. Now, let us consider the distribution of the roots of Eq. (8) when $\tau > 0$.

Suppose $i\omega$ ($\omega > 0$) is a root of Eq. (8). Substituting $i\omega$ ($\omega > 0$) into Eq. (8) and separating the real and imaginary parts gives

$$\begin{aligned} -\omega^2 + au &= k\beta x_0 e^{-s\tau} \cos \omega\tau, \\ (a + u)\omega &= -k\beta x_0 e^{-s\tau} \sin \omega\tau, \end{aligned}$$

which imply

$$\omega^4 + (a^2 + u^2)\omega^2 + a^2u^2 - k^2\beta^2x_0^2e^{-2s\tau} = 0. \tag{9}$$

Noticing that $a^2u^2 - k^2\beta^2x_0^2e^{-2s\tau} > 0$ when $R_0 < 1$ and that $a^2 + u^2 > 0$, we know Eq. (9) have no positive solutions. This shows that Eq. (8) has no purely imaginary roots for all $\tau > 0$. A continuity argument shows that no roots of Eq. (8) can cross the imaginary axis, and has to remain to the left of imaginary axis for all $\tau \geq 0$. We arrive at the following result.

Proposition 3.1. *Suppose $R_0 < 1$. Then the infection-free equilibrium E_0 is locally asymptotically stable.*

A stronger result can be established using a Lyapunov functional. In the following, we show that when $R_0 \leq 1$, E_0 is globally asymptotically stable in Γ .

Theorem 3.2. *Suppose $R_0 \leq 1$. Then the infection-free equilibrium E_0 is globally asymptotically stable in Γ .*

Proof: Define a Lyapunov functional $L : \mathcal{C} \times \mathbb{R} \times \mathcal{C} \rightarrow \mathbb{R}$

$$L(x_t, y(t), v_t) = x_t(0) - x_0 \ln \frac{x_t(0)}{x_0} + e^{s\tau} y(t) + \frac{ae^{s\tau}}{k} v_t(0) + \beta \int_{-\tau}^0 x_t(\theta) v_t(\theta) d\theta. \tag{10}$$

Here, $x_t(\theta) = x(t + \theta)$, $v_t(\theta) = v(t + \theta)$ for $\theta \in [-\tau, 0]$. Therefore, $x(t) = x_t(0)$, $v(t) = v_t(0)$ in this notation.

Since $f(z) = z - \ln z$, $z \in \mathbb{R}_+$, has the global minimum at $z = 1$ 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 functional L is non-negative definite in Γ with respect to the infection-free equilibrium $E_0 = (x_0, 0, 0)$.

Calculating the time derivative of L along solutions of system (2), we obtain

$$\begin{aligned} L'|_{(2)} &= \lambda - dx(t) - \frac{\lambda x_0}{x(t)} + dx_0 + \beta x_0 v(t) - \frac{au}{k} e^{s\tau} v(t) \\ &= dx_0 \left(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)} \right) + \frac{au}{k} e^{s\tau} (R_0 - 1)v(t). \end{aligned} \tag{11}$$

The arithmetical mean is greater than or equal to the geometrical mean, and the function

$$\frac{x(t)}{x_0} + \frac{x_0}{x(t)} - 2$$

is non-negative for all $x(t) > 0$, and it is equal to zero if and only if $x = x_0$. Since $x(t), y(t), v(t)$ are positive, it follows from $R_0 \leq 1$ that $L' \leq 0$, and $L' = 0$ if and only if $(x, y, v) = (x_0, 0, 0)$. Then the globally asymptotical stability of E_0 follows from the Lyapunov–LaSalle invariance principle (Hale and Verduyn Lunel, 1993). \square

4. Global dynamics when $R_0 > 1$

First, we show that the infection-free equilibrium E_0 is unstable when $R_0 > 1$.

Proposition 4.1. *Suppose $R_0 > 1$. Then the infection-free equilibrium E_0 is unstable.*

Proof: Considering the same Lyapunov functional L in the previous section, and relation (11), when $R_0 > 1$ and $\|x_t(0) - x_0\|$ is sufficiently small, we can show that $L'|_{(2)} > 0$. Therefore, the infection-free equilibrium E_0 is unstable by the standard Lyapunov instability theorem (Hale, 1977). \square

The following discussions focus on the stability of the chronic-infection equilibrium E_1 . First of all, we translate the equilibrium E_1 of system (2) to the origin. Let $x_2(t) = x(t) - \bar{x}$, $y_2(t) = y(t) - \bar{y}$, $v_2(t) = v(t) - \bar{v}$. Then system (2) becomes

$$\begin{aligned} x_2'(t) &= -(d + \beta \bar{v})x_2(t) - \beta \bar{x}v_2(t) - \beta x_2(t)v_2(t), \\ y_2'(t) &= -ay_2(t) + \beta \bar{v}e^{-s\tau}x_2(t - \tau) + \beta \bar{x}e^{-s\tau}v_2(t - \tau) \\ &\quad + \beta e^{-s\tau}x_2(t - \tau)v_2(t - \tau), \\ v_2'(t) &= ky_2(t) - uv_2(t). \end{aligned} \tag{12}$$

The linearization of (12) at the origin is

$$\begin{aligned}x_2'(t) &= -(d + \beta\bar{v})x_2(t) - \beta\bar{x}v_2(t), \\y_2'(t) &= -ay_2(t) + \beta\bar{v}e^{-s\tau}x_2(t - \tau) + \beta\bar{x}e^{-s\tau}v_2(t - \tau), \\v_2'(t) &= ky_2(t) - uv_2(t),\end{aligned}\tag{13}$$

whose characteristic equation is given by

$$\mu^3 + a_1\mu^2 + a_2\mu + a_3 + (b_1\mu + b_2)e^{-\mu\tau} = 0,\tag{14}$$

where $b_1 = -au < 0$, $b_2 = -adu < 0$,

$$\begin{aligned}a_1 &= a + u + d + \beta\bar{v} > 0, & a_2 &= au + (d + \beta\bar{v})(a + u) > 0, \\a_3 &= au(d + \beta\bar{v}) > 0.\end{aligned}$$

Note that a_i ($i = 1, 2, 3$) are all dependent on the delay τ , since \bar{x} and \bar{v} include τ .

Equation (14) takes the general form

$$P(\mu, \tau) + Q(\mu, \tau)e^{-\mu\tau} = 0\tag{15}$$

with

$$P(\mu, \tau) = \mu^3 + a_1(\tau)\mu^2 + a_2(\tau)\mu + a_3(\tau), \quad Q(\mu, \tau) = b_1\mu + b_2.\tag{16}$$

When $\tau = 0$, Eq. (15) becomes

$$\mu^3 + a_1(0)\mu^2 + (a_2(0) + b_1)\mu + (a_3(0) + b_2) = 0.$$

Noticing that

$$\begin{aligned}a_1(0) &> 0, & a_2(0) + b_1 &> 0, & a_3(0) + b_2 &> 0, \\a_1(0)(a_2(0) + b_1) - (a_3(0) + b_2) &> 0,\end{aligned}$$

Routh–Hurwitz criterion implies that all roots of Eq. (15) with $\tau = 0$ have negative real parts. Hence, we get the following conclusion.

Lemma 4.2. *Suppose $R_0 > 1$. Then the chronic-infection equilibrium $E_1 = (\bar{x}, \bar{y}, \bar{v})$ of system (2) is locally asymptotically stable when $\tau = 0$.*

In the following, for $\tau > 0$, we investigate the existence of purely imaginary roots $\mu = i\omega$ ($\omega > 0$) to Eq. (15).

Let $\mu = i\omega$ ($\omega > 0$) be a root of Eq. (15). Substituting it into Eq. (15) and separating the real and imaginary parts yield

$$\begin{aligned}\omega^3 - a_2(\tau)\omega &= b_1\omega \cos \omega\tau - b_2 \sin \omega\tau, \\a_1(\tau)\omega^2 - a_3(\tau) &= b_1\omega \sin \omega\tau + b_2 \cos \omega\tau.\end{aligned}\tag{17}$$

Let

$$\begin{aligned}
 F(\omega, \tau) &= |P(i\omega, \tau)|^2 - |Q(i\omega, \tau)|^2 \\
 &= \omega^6 + c_1(\tau)\omega^4 + c_2(\tau)\omega^2 + c_3(\tau), \\
 c_1(\tau) &= a_1^2(\tau) - 2a_2(\tau), \quad c_2(\tau) = a_2^2(\tau) - 2a_1(\tau)a_3(\tau) - b_1^2, \\
 c_3(\tau) &= a_3^2(\tau) - b_2^2.
 \end{aligned}$$

Then $i\omega$ ($\omega > 0$) is a root of Eq. (15) if and only if $F(\omega, \tau) = 0$. The polynomial function F can be written as

$$F(\omega, \tau) = h(\omega^2, \tau),$$

where h is a third-degree polynomial defined by

$$h(z, \tau) := z^3 + c_1(\tau)z^2 + c_2(\tau)z + c_3(\tau). \tag{18}$$

Noticing that

$$\begin{aligned}
 c_1(\tau) &= a^2 + u^2 + (d + \beta\bar{v})^2 > 0, \\
 c_2(\tau) &= (a^2 + u^2)(d + \beta\bar{v})^2 > 0, \\
 c_3(\tau) &= a^2u^2\beta\bar{v}(2d + \beta\bar{v}) > 0,
 \end{aligned}$$

for all $\tau > 0$, Eq. (18) has no positive roots, and thus the characteristic equation (14) has no purely imaginary roots.

In addition, $P(0, \tau) + Q(0, \tau) = a_3(\tau) + b_2(\tau) > 0$ for all $\tau \geq 0$ implies that 0 is not the root of Eq. (14). Summarizing the discussion above, we have the following conclusion.

Proposition 4.3. *Suppose $R_0 > 1$. Then the chronic-infection equilibrium E_1 is locally asymptotically stable.*

Using a global Lyapunov function, we can establish the following global-stability result for the chronic-infection equilibrium E_1 . The detailed proof is mathematically technical and will be given in the Appendix.

Theorem 4.4. *Suppose $R_0 > 1$. Then the chronic-infection equilibrium E_1 is locally asymptotically stable, and all solutions in Γ with positive initial conditions converge to E_1 in $C \times \mathbb{R} \times C$ topology.*

As a corollary, Theorem 4.4 implies that no sustained oscillations can occur in model (2).

Corollary 4.5. *Assume $R_0 > 1$. For $s \geq 0$ and $\tau > 0$, system (2) has no non-constant periodic solutions.*

We remark that results in Theorem 4.4 and Corollary 4.5 hold even when $s = 0$, since coefficients of the characteristic equation (14) do not depend explicitly on $e^{-s\tau}$ and V

in (A.1) continues to be a Lyapunov functional when $s = 0$. In particular, Hopf bifurcations will not occur in delayed models of Culshaw and Ruan (2000), Wang et al. (2009) when no cell divisions are considered.

5. Summary and discussions

Mathematical models are used to provide insights into the mechanisms and dynamics of the progression of viral infection *in vivo*. Several studies have shown that sustained oscillations in the form of periodic solutions can exist in in-host models with cell divisions (Wang and Li, 2006) or with both intra-cellular delays and cell divisions (Culshaw and Ruan, 2000; Wang et al., 2009). Since time delays are known to cause sustained oscillations, it is of both mathematical and biological interest to investigate if the sustained oscillations observed in Culshaw and Ruan (2000), Wang et al. (2009) can be the result of intra-cellular delays alone.

We have carried out complete analysis for an in-host model with intra-cellular delays, system (2). We have rigorously established the global dynamics of model (2): if the basic reproduction number $R_0 \leq 1$, then all solutions converge to the infection-free equilibrium E_0 ; if $R_0 > 1$, then all positive solutions converge to the chronic-infection equilibrium E_1 . As a result, no non-constant periodic solutions can exist for all positive values of parameters. An implication of our result is that the underlying mechanism for sustained oscillations in in-host viral models is the target cell divisions, rather than intra-cellular delays.

Intra-cellular delays are nonetheless important for modeling the viral dynamics *in vivo*. It is shown in Wang et al. (2009) that the inclusion of intra-cellular delays and target cells divisions allow sustained oscillations to occur for biologically realistic parameter values. Another importance of intracellular delay is that, as we show in (3), it can reduce the basic reproduction number R_0 if cell die during the delay period. As a consequence, ignoring the delay will produce overestimation of R_0 . It also is worth mentioning that, while mathematical models with intracellular delays have predicted the possibility of sustained oscillations in viral infection of target cells (Culshaw and Ruan, 2000; Wang et al., 2009), experimental data on HIV infection of CD4⁺ T cells *in vivo* have failed to detect such oscillations (Brebán and Blower, 2006). Our result establishing that no sustained-oscillation regime exists without cell division even in the presence of intra-cellular delays is of particular interest in this context; together with the result in Wang and Li (2006), it shows that target-cell dynamics plays a crucial role in the dynamics of viral infection *in vivo*.

Mathematically, Theorem 4.4 is the first complete result on the global stability of the chronic-infection equilibrium for in-host models with intracellular delays. The global stability result is essential for our conclusion that the delay does not produce periodic oscillations; local stability analysis or partial results on global stability will not rule out the possibility of Hopf bifurcations.

The intracellular delays incorporated in model (2) has a step-function distribution. It remains to be seen if Hopf bifurcations can occur if intracellular delays with other types of distribution functions are incorporated into the model.

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Appendix: Proof of Theorem 4.4

We assume that $R_0 > 1$ so that the chronic-infection equilibrium E_1 is the only equilibrium in the interior of the feasible region Γ . Since the local stability of E_1 is established in Proposition 4.3, it suffices to show that all positive solutions in Γ converge to E_1 . We achieve this by constructing a global Lyapunov functional.

Let

$$g(z) = z - 1 - \ln z.$$

Define a Lyapunov functional $V : \mathcal{C} \times \mathbb{R} \times \mathcal{C} \rightarrow \mathbb{R}$

$$\begin{aligned} V(x_t, y(t), z_t) = & \bar{x} g\left(\frac{x_t(0)}{\bar{x}}\right) + \bar{y} e^{s\tau} g\left(\frac{y(t)}{\bar{y}}\right) \\ & + \frac{a\bar{v}}{k} e^{s\tau} g\left(\frac{v_t(0)}{\bar{v}}\right) + \beta\bar{x}\bar{v} \int_{-\tau}^0 g\left(\frac{x_t(\theta)v_t(\theta)}{\bar{x}\bar{v}}\right) d\theta. \end{aligned} \quad (\text{A.1})$$

Calculating the time derivative of V along the positive solutions of system (2), we obtain

$$\begin{aligned} V'|_{(2)} = & \lambda - dx(t) - \beta x(t)v(t) - \lambda \frac{\bar{x}}{x} + d\bar{x} + \beta\bar{x}v(t) + \beta x(t-\tau)v(t-\tau) \\ & - ae^{s\tau}y(t) - \beta\bar{y} \frac{x(t-\tau)v(t-\tau)}{y(t)} + ae^{s\tau}\bar{y} + ae^{s\tau}y(t) - \frac{au}{k} e^{s\tau}v(t) \\ & - ae^{s\tau}\bar{v} \frac{y(t)}{v(t)} + \frac{au}{k} e^{s\tau}\bar{v} + \beta x(t)v(t) - \beta x(t-\tau)v(t-\tau) \\ & - \beta\bar{x}\bar{v} \ln x(t)v(t) + \beta\bar{x}\bar{v} \ln x(t-\tau)v(t-\tau). \end{aligned}$$

Using $\lambda = d\bar{x} + \beta\bar{x}\bar{v}$, $\beta\bar{x}\bar{v} = a\bar{y}e^{s\tau}$, $\beta\bar{x} = \frac{au}{k} e^{s\tau}$, we obtain

$$\begin{aligned} V'|_{(2)} = & d\bar{x} \left[2 - \frac{x(t)}{\bar{x}} - \frac{\bar{x}}{x(t)} \right] + \beta\bar{x}\bar{v} - \frac{\beta\bar{x}^2\bar{v}}{x(t)} + \beta\bar{x}v(t) - \beta\bar{y} \frac{x(t-\tau)v(t-\tau)}{y(t)} \\ & + ae^{s\tau}\bar{y} - \frac{au}{k} e^{s\tau}v(t) - a\bar{v}e^{s\tau} \frac{y(t)}{v(t)} + \frac{au\bar{v}}{k} e^{s\tau} \\ & - \beta\bar{x}\bar{v} \ln x(t)v(t) + \beta\bar{x}\bar{v} \ln x(t-\tau)v(t-\tau) \end{aligned}$$

$$\begin{aligned}
&= d\bar{x} \left[2 - \frac{x(t)}{\bar{x}} - \frac{\bar{x}}{x(t)} \right] \\
&\quad - \beta\bar{x}\bar{v}g \left(\frac{\bar{y}x(t-\tau)v(t-\tau)}{\bar{x}\bar{v}y(t)} \right) - \beta\bar{x}\bar{v} \ln \frac{x(t-\tau)v(t-\tau)\bar{y}}{\bar{x}\bar{v}y(t)} \\
&\quad - \beta\bar{x}\bar{v}g \left(\frac{\bar{x}}{x(t)} \right) - \beta\bar{x}\bar{v} \ln \frac{\bar{x}}{x(t)} - \beta\bar{x}\bar{v}g \left(\frac{\bar{v}y(t)}{\bar{y}v(t)} \right) - \beta\bar{x}\bar{v} \ln \frac{y(t)\bar{v}}{\bar{y}v(t)} \\
&\quad - \beta\bar{x}\bar{v}(\ln x(t)v(t) + \ln x(t-\tau)v(t-\tau)) \\
&= d\bar{x} \left[2 - \frac{x(t)}{\bar{x}} - \frac{\bar{x}}{x(t)} \right] - \beta\bar{x}\bar{v}g \left(\frac{\bar{y}x(t-\tau)v(t-\tau)}{\bar{x}\bar{v}y(t)} \right) \\
&\quad - \beta\bar{x}\bar{v}g \left(\frac{\bar{x}}{x(t)} \right) - \beta\bar{x}\bar{v}g \left(\frac{\bar{v}y(t)}{\bar{y}v(t)} \right).
\end{aligned}$$

We note that $g : \mathbb{R}_+ \rightarrow \mathbb{R}$ has the global minimum at $z = 1$ and $g(1) = 0$. Hence, $\bar{x}, \bar{y}, \bar{v} > 0$ ensures $\frac{dV}{dt} \leq 0$. By Theorem 5.3.1 of Hale and Verduyn Lunel (1993), solutions limit to M , the largest invariant subset of $\{\frac{dV}{dt} = 0\}$. It can be verified that $\frac{dV}{dt} = 0$ if and only if $x = \bar{x}$ and $\frac{\bar{y}x(t-\tau)v(t-\tau)}{\bar{x}\bar{v}y(t)} = \frac{\bar{v}y(t)}{\bar{y}v(t)} = 1$. For each element of M , we have $x = \bar{x}$ and $x'(t) = 0$, since M is invariant. Using the first equation of system (2), we obtain

$$0 = x'(t) = \lambda - d\bar{x} - \beta\bar{x}v(t).$$

This gives $v(t) = \frac{\lambda - d\bar{x}}{\beta\bar{x}} = \bar{v}$, and then $y(t) = \bar{y}$ from $\frac{\bar{v}y(t)}{\bar{y}v(t)} = 1$. Therefore, $\frac{dV}{dt} = 0$ if and only if $(x, y, v) = (\bar{x}, \bar{y}, \bar{v})$. Therefore, all solutions in Γ with positive initial conditions converge to E_1 by the LaSalle invariance principle (Hale and Verduyn Lunel, 1993).

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