

## IMPACT OF INTRACELLULAR DELAYS AND TARGET-CELL DYNAMICS ON IN VIVO VIRAL INFECTIONS\*

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**Abstract.** The dynamics of an in-host model with general form of target-cell dynamics, nonlinear incidence, and distributed delay are investigated. The model can describe the in vivo infection dynamics of many viruses such as HIV-I, HCV, and HBV. 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 is cleared; if  $R_0 > 1$ , then the infection persists, and the chronic-infection equilibrium is globally asymptotically stable. An implication of our results is that intracellular delays will lead to periodic oscillations in in-host models only with the right kind of target-cell dynamics.

**Key words.** in-host models, target-cell dynamics, intracellular delays, periodic oscillations, global stability, Lyapunov functionals

**AMS subject classifications.** 92D25, 34D23

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### 1. Introduction.

**1.1. Background.** Mathematical models have been developed to describe the in vivo infection process of many viruses such as human immunodeficiency virus type I (HIV-I), hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-cell lymphotropic virus I (HTLV-I) [1, 2, 3, 4, 5, 6, 7]. These *in-host* models are useful for exploring possible mechanisms and outcomes of the viral infection process [1, 2], and for estimating key parameter values such as virion clearance rate, life span of infected cells, and average viral generation time in vivo [3]. Findings from in-host modeling can be used to guide development of efficient antiviral drug therapies [5]. Time delays are intrinsic to the viral infection and replication processes, and they have been incorporated into in-host models [8, 9, 10, 11, 12, 13]. Model analysis has shown that these intracellular delays can cause periodic oscillations through Hopf bifurcations [10, 12, 13]. It is also known that Hopf bifurcations can occur in certain classes of in-host models without intracellular delays, in which the target-cell dynamics have a mitosis component given by a logistic term [14]. It is of interest from both mathematical and biological viewpoints to investigate whether Hopf bifurcations in in-host models are the result of target-cell dynamics, intracellular delays, or a combination of both. Since time delays are known to cause instability and periodic oscillations in dynamical systems, it seems natural to expect that target-cell dynamics and intracellular delays are two independent processes that can lead to Hopf bifurcations. In this paper, using an in-host model with a general form of target-cell dynamics, a general

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form of incidence for the infection, and a general form of intracellular delays, we will show that the occurrence of Hopf bifurcation in in-host viral models depends critically on the target-cell dynamics, not on intracellular delays; if no Hopf bifurcation occurs in an in-host model without delay, incorporating intracellular delays will not produce periodic oscillations.

**1.2. Model derivation.** To incorporate intracellular delays into an in-host model, we briefly summarize the main stages in the infection process of a target cell by a virus and in the viral replication process, as well as the associated time delays. The processes described here are general enough to include RNA viruses such as HIV-I and HCV, as well as certain DNA viruses such as HBV that replicate through reverse transcription.

The first stage of infection is the period between the viral entry of a target cell and integration of viral DNA into the host genome. During this stage, reverse transcription takes place and produces viral DNA from the viral RNA by action of the reverse transcriptase that is part of the viral package. Viral DNAs then need to enter the cell nucleus in order to integrate into the host genome. A target cell in this stage is said to be *infected*. Antiretroviral treatments using reverse transcriptase inhibitors (RTIs) can block the production of viral DNA during this stage. The second stage is the period from the integration of viral DNA to the transcription of viral RNA and translation of viral proteins such as reverse transcriptase, integrase, and protease. This stage typically requires activation of the target cell and can last a variable length of time for individual cells. A target cell in this stage is said to be *actively infected*. Another crucial event in viral replication occurs during this stage: the viral protease needs to cut the long polypeptide chain into individual enzyme components for the translation of viral proteins to be completed. Antiviral treatments using protease inhibitors (PIs) will block the action of protease and thus disrupt the viral replication. Without a functioning protease, an infected target cell will not produce mature viruses and is hence noninfectious. The third stage is the period between the transcription of viral RNA and the release and maturation of virus. During this stage, the virus needs to assemble its package of viral proteins and its lipid envelope near the cell membrane, and then it buds out of the cell. Maturation of viruses can happen inside the target cell or after release. According to these stages, we consider three compartments in the infection process,

$x$  : healthy target cells,  
 $y$  : actively infected target cells,  
 $v$  : mature viruses,

and denote the number of cells or virus particles at time  $t$  in each compartment by  $x(t)$ ,  $y(t)$ ,  $v(t)$ , respectively. In the case of HIV-I infection, the target cells are CD4<sup>+</sup> helper T cells, while in the case of HBV infection, the target cells are hepatocytes in the liver.

To model the delay between viral infection of a healthy target cell and the production of an actively infected target cell, we let  $\tau$  be the random variable that describes the time between viral entry and the transcription of viral RNA (stages 1 and 2) with a probability distribution  $f_1(\tau)$ . We assume that the contacts between viruses and target cells are given by an incidence function  $h(x, v)$ , which also contains the probability of cell entry per contact. Then, newly infected target cells per unit time is given by  $h(x(t), v(t))$ . Since cells infected at time  $t$  will be activated and produce viral materials at time  $t + \tau$ , the number of actively infected target cells at time  $t$  is

given by

$$(1.1) \quad \int_0^\infty e^{-s_1\tau} f_1(\tau) h(x(t-\tau), v(t-\tau)) d\tau.$$

Here, factor  $e^{-s_1\tau}$  accounts for the loss of target cells during time period  $[t-\tau, t]$  due to viral infection. The effect of therapies using RTIs is to reduce the number of actively infected target cells. This effect can be incorporated into the incidence term in (1.1) by multiplying a constant  $0 \leq \alpha_1 \leq 1$  to  $h(x(t), v(t))$  and only including the fraction of target cells that are actively infected. We assume that such a fraction has been absorbed into  $h(x(t), v(t))$ .

To model the delay between viral RNA transcription and viral release and maturation, we let  $\tau_1$  be the random variable that is the time between these two events with a probability distribution  $f_2(\tau_1)$ . Then the mature viral particles produced at time  $t$  are given by

$$(1.2) \quad k \int_0^\infty e^{-s_2\tau} f_2(\tau) y(t-\tau) d\tau.$$

Here, we have suppressed the subindex in  $\tau_1$ . Constant  $k$  is the average number of viruses that bud out from an infected target cell, and  $e^{-s_2\tau}$  accounts for the cell loss during the delay period. PI therapies can render many viruses noninfectious. We can incorporate this effect into the term in (1.2) by multiplying  $k$  by a fraction  $0 \leq \alpha_2 \leq 1$  and only considering mature and infectious viruses. Again, we assume that such a fraction has been absorbed into  $k$ .

The dynamics of healthy target cells in the absence of infection is assumed to satisfy

$$(1.3) \quad x'(t) = n(x(t)),$$

where  $n(x)$  is a general function that accounts for both production and turnover of healthy target cells. Typical assumptions on  $n(x)$  are the following:

$$(H_1) \quad \exists \bar{x} > 0 \text{ such that } n(\bar{x}) = 0 \text{ and } [n(x) - n(\bar{x})](x - \bar{x}) < 0, \quad x \neq \bar{x}.$$

The class of  $n(x)$  that satisfy (H<sub>1</sub>) include both  $n(x) = \lambda - dx$  and  $n(x) = \lambda - dx + rx(1 - x/K)$ , which have been widely used in the literature of population dynamics. Assumption (H<sub>1</sub>) implies that  $x(t) \rightarrow \bar{x}$  as  $t \rightarrow \infty$  in the absence of the viral infection, and  $\bar{x}$  can be regarded as the natural level of target cells in the host body.

Let  $\mu_1$  and  $\mu_2$  be the death rates for the compartments  $y$  and  $v$ , respectively. Then, from preceding discussions, we see that the interactions among  $x(t)$ ,  $y(t)$ , and  $v(t)$  can be described by the following system of differential and integral equations:

$$(1.4) \quad \begin{aligned} x'(t) &= n(x(t)) - h(x(t), v(t)), \\ y'(t) &= \int_0^\infty e^{-s_1\tau} f_1(\tau) h(x(t-\tau), v(t-\tau)) d\tau - \mu_1 y(t), \\ v'(t) &= k \int_0^\infty e^{-s_2\tau} f_2(\tau) y(t-\tau) d\tau - \mu_2 v(t), \end{aligned}$$

with initial conditions  $x(0) > 0$ ,  $y(0) \geq 0$ , and  $v(0) \geq 0$ . We assume that all parameter values are nonnegative and  $\mu_1, \mu_2 > 0$ . Probability distribution functions  $f_1(\tau)$  and

$f_2(\tau)$  are assumed to satisfy  $f_i(\tau) \geq 0$  and  $\int_0^\infty f_i(\tau) d\tau = 1$  for  $i = 1, 2$ . These general distribution functions allow us to include special forms of intracellular delays previously used in the literature. For instance, if  $f_1(\tau) = \delta(\tau - r)$ , then the incidence term becomes  $e^{-s_1\tau} h(x(t-r), v(t-r))$  with a finite delay  $r > 0$ . Similarly, if  $f_2(\tau) = \delta(\tau - r_1)$ , then production of virus will be given by  $ke^{-s_2 r_1} y(t - r_1)$ . If  $f_i(\tau) = \gamma_i e^{-\gamma_i \tau}$ ,  $i = 1, 2$ , then system (1.4) becomes

$$\begin{aligned} x'(t) &= n(x(t)) - h(x(t), v(t)), \\ y'(t) &= \gamma_1 \int_0^\infty e^{-(s_1 + \gamma_1)\tau} h(x(t - \tau), v(t - \tau)) d\tau - \mu_1 y(t), \\ v'(t) &= k\gamma_2 \int_0^\infty e^{-(s_2 + \gamma_2)\tau} y(t - \tau) d\tau - \mu_2 v(t). \end{aligned}$$

We may introduce new variables

$$\begin{aligned} e(t) &= \int_0^\infty e^{-(s_1 + \gamma_1)\tau} h(x(t - \tau), v(t - \tau)) d\tau, \\ z(t) &= \int_0^\infty e^{-(s_2 + \gamma_2)\tau} y(t - \tau) d\tau, \end{aligned}$$

so that  $x, e, y, z, v$  satisfy the following system of ordinary differential equations:

$$\begin{aligned} (1.5) \quad x'(t) &= n(x(t)) - h(x(t), v(t)), \\ e'(t) &= h(x(t), v(t)) - (s_1 + \gamma_1)e(t), \\ y'(t) &= \gamma_1 e(t) - \mu_1 y(t), \\ z'(t) &= y(t) - (s_2 + \gamma_2)z(t), \\ v'(t) &= k\gamma_2 z(t) - \mu_2 v(t). \end{aligned}$$

When the delays are neglected, namely, the average delay  $1/\gamma_i \rightarrow 0$ ,  $i = 1, 2$ , system (1.5) becomes

$$\begin{aligned} (1.6) \quad x'(t) &= n(x(t)) - h(x(t), v(t)), \\ y'(t) &= h(x(t), v(t)) - \mu_1 y(t), \\ v'(t) &= ky(t) - \mu_2 v(t), \end{aligned}$$

which has been well studied in the literature [4, 14, 15, 16] for various forms of  $n(x)$  and  $h(x, v)$ .

**1.3. Earlier results.** We summarize previous studies in the literature related to Hopf bifurcations in in-host models, with specific forms of target-cell dynamics and incidence functions.

(i) Nowak et al. [4] and Korobeinikov [16] considered  $n(x) = \lambda - \mu x$  and  $h(x, v) = \beta xv$  with no intracellular delays. It is shown that no periodic oscillations occur in the model, and all solutions converge to equilibria.

(ii) Nelson and Perelson [11] and Li and Shu [17] considered  $n(x) = \lambda - \mu x$ ,  $h(x, v) = \beta xv$ , a general  $f_1(\tau)$ ,  $f_2(\tau) = \delta(\tau - 0)$ ,  $s_2 = 0$ , and  $s_1 > 0$ . It is shown in [17] that no periodic oscillations occur, and all solutions converge to equilibria.

(iii) Smith and De Leenheer [15] and Wang and Li [14] considered  $n(x) = \lambda - \mu x + rx(1 - \frac{x}{K})$  and  $h(x, v) = \beta xv$  with no intracellular delays. They have shown that periodic oscillations can occur through Hopf bifurcation.

(iv) Culshaw and Ruan [10] and Wang et al. [13] considered  $n(x) = \lambda - \mu x + rx(1 - \frac{x}{K})$ ,  $h(x, v) = \beta xv$ ,  $f_1(\tau) = \delta(\tau - r)$ ,  $f_2(\tau) = \delta(\tau - 0)$ , and  $s_i = 0$ . They have shown that Hopf bifurcation occurs.

In these results, when  $n(x)$  contains a mitosis (logistic) term, Hopf bifurcation occurs with or without intracellular delays; if  $n(x)$  contains no mitosis, Hopf bifurcations do not occur with or without intracellular delays. These studies suggest that occurrence of Hopf bifurcation depends on target-cell dynamics, not the intracellular delays. The question remains of whether periodic oscillations can be induced by intracellular delays alone with more general target-cell dynamics and more general types of delays.

In this paper, for target-cell dynamics described by a general function  $n(x)$ , a general incidence function  $h(x, v)$ , and general delay distributions  $f_i(\tau)$ , we rigorously establish that if Hopf bifurcation does not occur in a model when the delays are absent, then the introduction of intracellular delays will not cause instability or periodic oscillations. The key to establishing these results is to prove the global stability of equilibria, since local stability alone will not rule out existence of periodic solutions.

For model (1.4), we derive the basic reproductive number  $R_0$  and show that  $R_0$  completely determines the global dynamics. More specifically, we prove that if  $R_0 \leq 1$ , the infection-free equilibrium  $E_0$  is globally asymptotically stable, and the virus will be cleared; if  $R_0 > 1$ , all positive solutions converge to the unique chronic-infection equilibrium  $E^*$ . Our global stability result for the chronic-infection equilibrium is new for in-host models with distributed intracellular delays. Our proof utilizes a global Lyapunov functional that is motivated by the work in [18, 19, 20, 21]. The global stability of  $E^*$  rules out any possibility for Hopf bifurcations and existence of sustained oscillations.

Our paper is organized as follows. In the next section, we discuss the feasible region for system (1.4) and derive the basic reproduction number  $R_0$ . Our main results are stated in section 3. In section 4, for special classes of  $n(x)$  and  $h(x, v)$  commonly used in the literature, we show that our main results in section 3 produce sharp threshold results. Mathematical proofs of our main results are given in section 5. A summary and discussion are given in section 6.

**2. Preliminaries.** We assume that  $n(x)$  satisfies assumption (H<sub>1</sub>) with a unique zero  $\bar{x} > 0$ . We make the following assumptions on the incidence function  $h(x, v)$ .

(H<sub>2</sub>)  $h(x, v)$  is continuous;  $h(x, v) \geq 0$  and  $h(x, v) = 0 \iff x = 0$  or  $v = 0$ ; and there exists  $0 < c \leq \infty$  such that

$$(2.1) \quad \lim_{v \rightarrow 0^+} \frac{h(\bar{x}, v)}{v} = c.$$

(H<sub>3</sub>)  $h(x, v) \leq h(\bar{x}, v)$  for  $0 < x \leq \bar{x}$ ,  $v > 0$ ;  $h(x, v) = h(\bar{x}, v) \iff x = \bar{x}$ ; and

$$\sup_{v > 0} \frac{h(\bar{x}, v)}{v} = c.$$

Classes of  $h(x, v)$  that satisfy assumptions (H<sub>1</sub>) and (H<sub>2</sub>) include common incidence functions such as  $h(x, v) = \beta xv$ ,  $h(x, v) = \beta x^p v^q$ , and  $h(x, v) = \beta \frac{x^p}{x^p + A_1} \cdot \frac{v^q}{v^q + A_2}$ ,  $p, q, \beta, A_1, A_2 > 0$ .

We assume that distribution functions  $f_i(r)$ ,  $i = 1, 2$ , satisfy the following condition:

$$(2.2) \quad \int_0^\infty f_i(r) e^{sr} dr < \infty,$$

where  $s$  is a positive number. Define the Banach space of fading memory type [22]

$$(2.3) \quad \mathcal{C} = \left\{ \phi \in C((-\infty, 0], \mathbb{R}) : \phi(r)e^{sr} \text{ is uniformly continuous} \right. \\ \left. \text{for } r \in (-\infty, 0], \text{ and } \sup_{r \leq 0} |\phi(r)|e^{sr} < \infty \right\},$$

with norm

$$\|\phi\|_k = \sup_{r \leq 0} |\phi(r)|e^{sr}.$$

The nonnegative cone of  $\mathcal{C}$  is defined by  $\mathcal{C}^+ = C((-\infty, 0], \mathbb{R}_+)$ . For  $\phi \in \mathcal{C}$ , let  $\phi_t \in \mathcal{C}$  be such that  $\phi_t(s) = \phi(t+s)$ ,  $s \in (-\infty, 0]$ . We consider solutions  $(x_t, y_t, v_t)$  of system (1.4) with initial conditions

$$(2.4) \quad x_0 \in \mathcal{C}^+, \quad y_0 \in \mathcal{C}^+, \quad v_0 \in \mathcal{C}^+.$$

Standard theory of functional differential equations [23] implies that  $(x_t, y_t, v_t) \in \mathcal{C} \times \mathcal{C} \times \mathcal{C}$  for  $t > 0$ . We consider system (1.4) in the phase space

$$(2.5) \quad X = \mathcal{C} \times \mathcal{C} \times \mathcal{C}.$$

**PROPOSITION 2.1.** *For initial conditions in (2.4), solutions of system (1.4) are nonnegative and ultimately uniformly bounded in  $X$ .*

*Proof.* First, we prove that  $x(t) \geq 0$  for all  $t \geq 0$ . Assuming the contrary and letting  $t_1 > 0$  be such that  $x(t_1) < 0$ , set  $t_2 = \inf\{0 < t < t_1 : x(t) < 0\}$ . Then  $x(t_2) = 0$ , and from the first equation of system (1.4) we have  $x'(t_2) = n(0) > 0$ . Hence  $x(t) < 0$  for  $t \in (t_2 - \epsilon, t_2)$  and  $\epsilon > 0$  sufficiently small. This contradicts  $x(t) \geq 0$  for  $t \in (0, t_2]$ . It follows that  $x(t) \geq 0$  for  $t \geq 0$ . Similar arguments can be used to show that  $y(t) \geq 0$ ,  $v(t) \geq 0$  for  $t \geq 0$ .

Assumption (H<sub>1</sub>) and the first equation of (1.4) imply that  $\limsup_{t \rightarrow \infty} x(t) \leq \bar{x}$ . From the first two equations of (1.4) we get

$$\int_0^\infty f_1(\tau)e^{-s_1\tau}x'(t-\tau)d\tau + y'(t) = \int_0^\infty f_1(\tau)e^{-s_1\tau}n(x(t-\tau))d\tau - \mu_1y(t) \leq \bar{\lambda}\beta_1 - \mu_1y(t),$$

where  $\bar{\lambda} = \sup_{x \in [0, \bar{x}]} n(x)$  and

$$(2.6) \quad \beta_1 = \int_0^\infty f_1(\tau)e^{-s_1\tau}d\tau.$$

Let  $e(t) = \int_0^\infty f_1(\tau)e^{-s_1\tau}x(t-\tau)d\tau$ . Then  $e(t) \leq \bar{x}\beta_1$  for  $t \geq 0$ . Choose  $\bar{\mu} \leq \mu_1$  sufficiently small such that  $\bar{x}\bar{\mu} < \bar{\lambda}$ . Then

$$(e(t) + y(t))' \leq \bar{\lambda}\beta_1 - \mu_1y(t) < 2\bar{\lambda}\beta_1 - \bar{\mu}(e(t) + y(t)),$$

and thus  $\limsup_{t \rightarrow \infty} (e(t) + y(t)) \leq \frac{2\bar{\lambda}\beta_1}{\bar{\mu}}$ . Since  $e(t) \geq 0$ , we know  $\limsup_{t \rightarrow \infty} y(t) \leq \frac{2\bar{\lambda}\beta_1}{\bar{\mu}}$ . This relation and the third equation of (1.4) imply

$$v'(t) = k \int_0^\infty f_2(\tau)e^{-s_2\tau}y(t-\tau)d\tau - \mu_2v(t) \leq \frac{2k\bar{\lambda}\beta_1\beta_2}{\bar{\mu}} - \mu_2v(t),$$

and thus  $\limsup_{t \rightarrow \infty} v(t) \leq \frac{2k\bar{\lambda}\beta_1\beta_2}{\mu_2\bar{\mu}}$ , where

$$(2.7) \quad \beta_2 = \int_0^\infty f_2(\tau)e^{-s_2\tau} d\tau.$$

Therefore,  $x(t)$ ,  $y(t)$ , and  $v(t)$  are ultimately uniformly bounded in  $\mathcal{C} \times \mathcal{C} \times \mathcal{C}$ .  $\square$

Proposition 2.1 implies that omega limit sets of system (1.4) are contained in the following bounded feasible region:

$$\Gamma = \left\{ (x, y, v) \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathcal{C}^+ : \|x\| \leq \bar{x}, \|y\| \leq \frac{2\bar{\lambda}\beta_1}{\bar{\mu}}, \|v\| \leq \frac{2k\bar{\lambda}\beta_1\beta_2}{\mu_2\bar{\mu}} \right\}.$$

It can be verified that the region  $\Gamma$  is positively invariant with respect to model (1.4) and that the model is well posed.

System (1.4) always has an infection-free equilibrium  $E_0 = (\bar{x}, 0, 0)$  on the boundary of  $\Gamma$ . A chronic-infection equilibrium  $E^* = (x^*, y^*, v^*)$  in the interior  $\overset{\circ}{\Gamma}$  of  $\Gamma$  must satisfy  $x^*, y^*, v^* > 0$  and

$$(2.8) \quad \begin{aligned} n(x^*) - h(x^*, v^*) &= 0, \\ \beta_1 h(x^*, v^*) - \mu_1 y^* &= 0, \\ k\beta_2 y^* - \mu_2 v^* &= 0. \end{aligned}$$

We will show that, under biologically reasonable conditions, the chronic-infection equilibrium  $E^*$  is unique.

The dynamical outcomes of model (1.4) will be determined by the basic reproduction number  $R_0$ : the average number of actively infected cells that arise from one infectious cell after it is introduced into a population of uninfected cells. One actively infected target cell produces on average  $\frac{k}{\mu_1} \int_0^\infty f_1(\tau)e^{-s_1\tau} d\tau = \frac{k\beta_1}{\mu_1}$  mature viruses during its life span  $\frac{1}{\mu_1}$ . Let  $0 < c < \infty$  be as in (H<sub>2</sub>). Then each virus will infect  $\frac{c}{\mu_2}$  target cells during its life span  $\frac{1}{\mu_2}$ . A newly infected target cell will survive the latent period to become actively infected with a probability  $\beta_2 = \int_0^\infty f_2(\tau)e^{-s_2\tau} d\tau$ . Therefore, the basic reproduction number is given by

$$(2.9) \quad R_0 = \frac{ck \int_0^\infty f_2(\tau)e^{-s_2\tau} d\tau \int_0^\infty f_1(\tau)e^{-s_1\tau} d\tau}{\mu_1\mu_2} = \frac{ck\beta_1\beta_2}{\mu_1\mu_2}.$$

If  $c = \infty$ , we define  $R_0 = \infty$ . Intuitively, the infection and virus will be cleared if  $R_0 < 1$ , and the infection persists if  $R_0 > 1$ . For special forms of intracellular delays, target cell dynamics, and incidence functions, our  $R_0$  in (2.9) agrees with basic reproduction numbers in the literature. In particular, if discrete intracellular delays, bilinear incidence, and linear intrinsic growth functions are used, our  $R_0$  reduces to the basic reproduction number in [17].

**3. Main results.** In the following, we state our main results concerning the global dynamics of (1.4). Proofs will be given in section 5.

**THEOREM 3.1.** *Assume that assumptions (H<sub>1</sub>)–(H<sub>3</sub>) are satisfied.*

(i) *If  $R_0 \leq 1$ , then the infection-free equilibrium  $E_0$  of system (1.4) is globally asymptotically stable in  $\Gamma$ .*

(ii) *If  $R_0 > 1$ , then  $E_0$  is unstable and system (1.4) is uniformly persistent. Furthermore, there exists a chronic-infection equilibrium  $E^*$  in the interior  $\overset{\circ}{\Gamma}$  of  $\Gamma$ .*

**THEOREM 3.2.** *Assume that assumptions (H<sub>1</sub>) and (H<sub>2</sub>) are satisfied and that  $R_0 > 1$ . Suppose a chronic-infection equilibrium  $E^* = (x^*, y^*, v^*)$  and functions  $n(x), h(x, v)$  satisfy the following conditions:*

- (A<sub>1</sub>)  $[n(x) - n(x^*)](x - x^*) < 0$  for  $x \neq x^*, x \in [0, \bar{x}]$ ,
- (A<sub>2</sub>)  $[h(x, v^*) - h(x^*, v^*)](x - x^*) > 0$  for  $x \neq x^*, x \in [0, \bar{x}]$ ,
- (A<sub>3</sub>)  $(\frac{h(x, v)}{h(x, v^*)} - 1)(\frac{v^*}{v} - \frac{h(x, v^*)}{h(x, v)}) \leq 0$  for  $v > 0, x \in [0, \bar{x}]$ .

*Then  $E^*$  is the unique chronic-infection equilibrium and is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .*

Theorems 3.1 and 3.2 imply that, if the basic reproduction number  $R_0 \leq 1$ , then the virus is cleared; if  $R_0 > 1$ , then the infection persists at the unique chronic-infection equilibrium, irrespective of the initial conditions. These results preclude the existence of nonconstant periodic solutions.

We remark that the conclusions of Theorems 3.1 and 3.2 also hold when  $c = \infty$  and  $R_0 = \infty$ . In this case, the infection-free equilibrium  $E_0$  is always unstable, and the unique chronic-infection equilibrium  $E^*$  is always globally stable in  $\overset{\circ}{\Gamma}$ .

Assumptions (H<sub>3</sub>) and (A<sub>1</sub>)–(A<sub>3</sub>) in Theorems 3.1 and 3.2 hold under certain monotonicity conditions that are biologically motivated. More specifically, we have the following result.

**THEOREM 3.3.** *Assume that*

- (1)  $n(x)$  satisfies (H<sub>1</sub>) and is strictly monotonically decreasing for  $x \in [0, \bar{x}]$ ;
- (2)  $h(x, v)$  satisfies (H<sub>2</sub>);
- (3)  $h(x, v)$  is strictly monotonically increasing with respect to  $x$  and  $v$ ;
- (4)  $h(x, v)$  is concave downward with respect to  $v$ .

*Then we have the following:*

(i) *If  $R_0 \leq 1$ , then the infection-free equilibrium  $E_0$  of system (1.4) is globally asymptotically stable in  $\Gamma$ . If  $R_0 > 1$ , then  $E_0$  is unstable.*

(ii) *If  $R_0 > 1$ , then there is a unique chronic-infection equilibrium  $E^*$ , and it is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .*

*Proof.* It is straightforward to verify that conditions in (H<sub>3</sub>), (A<sub>1</sub>), and (A<sub>2</sub>) follow from monotonicity assumptions of Theorem 3.3. We prove that condition (A<sub>3</sub>) or, equivalently, the following relation is also satisfied:

$$(3.1) \quad \begin{aligned} \frac{h(x, v^*)}{h(x, v)} &\geq \frac{v^*}{v} \text{ if } h(x, v^*) \leq h(x, v), \text{ and} \\ \frac{h(x, v^*)}{h(x, v)} &\leq \frac{v^*}{v} \text{ if } h(x, v^*) \geq h(x, v). \end{aligned}$$

Since  $h(x, v)$  is strictly increasing with respect to  $v$ , we know that  $h(x, v^*) < h(x, v)$  if and only if  $v^* < v$ . Therefore, condition (3.1) is equivalent to

$$(3.2) \quad \frac{h(x, v^*)}{h(x, v)} \geq \frac{v^*}{v} \text{ if } v^* \leq v, \quad \text{and} \quad \frac{h(x, v^*)}{h(x, v)} \leq \frac{v^*}{v} \text{ if } v^* \geq v.$$

It is straightforward to verify that relation (3.2) follows from the concavity of  $h(x, v)$  with respect to  $v$ . Therefore, the conclusions of the theorem follows from Theorems 3.1 and 3.2.

**4. Special cases.** The assumptions in Theorems 3.1–3.3 define a special class of functions  $n(x)$  and  $h(x, v)$  for which sharp threshold results hold for system (1.4) and no periodic oscillations occur. In this section, we show that this class contains typical  $n(x)$  and  $h(x, v)$  that have been used in the literature.

**4.1. Special cases for  $n(x)$ .**

*Case 1.*  $n(x) = \Lambda - \mu x$ ,  $\Lambda, \mu > 0$ . In this case,  $n(x)$  is strictly decreasing with respect to  $x$  and satisfies condition (1) of Theorem 3.3.

*Case 2.*  $n(x) = \Lambda - \mu x + rx(1 - \frac{x}{K})$ ,  $\Lambda, \mu, r, K > 0$ .

(a) If  $r \leq \mu$ , then  $n(x)$  is strictly decreasing for  $x \geq 0$  and satisfies condition (1) of Theorem 3.3; see Figure 1(a).

(b) If  $r > \mu$ , then assumption  $(A_1)$  of Theorem 3.2 holds if and only if  $n(x^*) < n(0)$ , namely  $x_1 < x^* < \bar{x}$ , where  $x_1 > 0$  is such that  $n(x_1) = n(0)$ ; see Figure 1(b).

In both Cases 1 and 2, when  $n(x)$  satisfies the assumptions of our theorems, the target-cell dynamics are such that no Hopf bifurcations occur when intracellular delays are not present. In Case 2, if  $r > \mu$  and  $n(x^*) > n(0)$ , namely, if  $x^* \in (0, x_1)$  (Figure 1(b)), assumption  $(A_1)$  of Theorem 3.2 does not hold. It is known that, in this case,  $E^*$  can lose stability and undergoes Hopf bifurcation without intracellular delays [14]. This shows that assumptions on  $n(x)$  in our main results provide sharp criteria for target-cell dynamics that do not produce a Hopf bifurcation in the absence of delays.

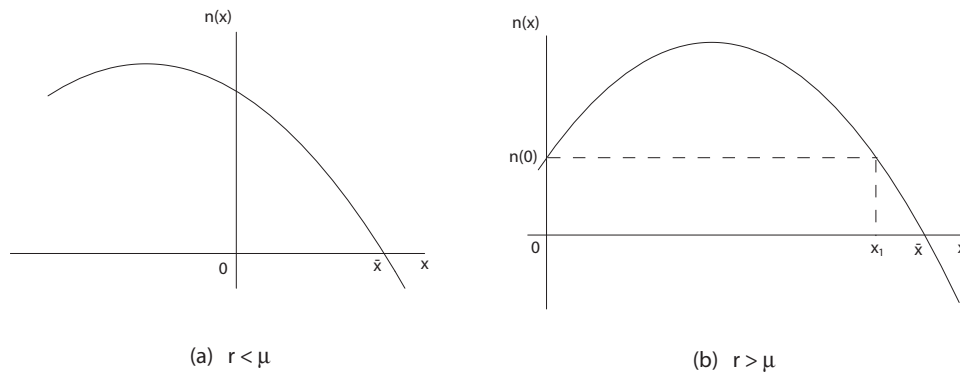


FIG. 1. The graph of  $n(x) = \lambda - \mu x + rx(1 - \frac{x}{K})$ .

**4.2. Special cases for  $h(x, v)$ .** A common form of incidence functions is

$$(4.1) \quad h(x, v) = \beta \frac{x^p}{x^{p_1} + A_1} \frac{v^q}{v^{q_1} + A_2},$$

$\beta, p, q, p_1, q_1 > 0$  and  $A_1, A_2 \geq 0$ . It can be verified that  $h(x, v)$  is strictly monotonically increasing for all  $x$  and  $v$  if one of the following conditions holds:

$(B_1)$   $p_1 \leq p$ ,  $q_1 \leq q$ , and  $A_i > 0$ ,  $i = 1, 2$ ;

$(B_2)$   $p_1 < p$ ,  $q_1 < q$ , and  $A_i \geq 0$ ,  $i = 1, 2$ .

Furthermore,  $h(x, v)$  is concave with respect to  $v$  if  $q_1 \leq q \leq 1$ .

For this form of incidence function, the basic reproductive number  $R_0$  in (2.9) satisfies

$$R_0 = \begin{cases} +\infty & \text{when } q < 1, \\ \frac{ck\beta_1\beta_2}{\mu_1\mu_2} & \text{when } q = 1. \end{cases}$$

Theorem 3.3 leads to the following sharp threshold result.

**THEOREM 4.1.** *Assume that  $n(x)$  satisfies assumption  $(H_1)$  and condition  $(A_1)$ . Let  $h(x, v)$  be given in (4.1) and let it satisfy either  $(B_1)$  or  $(B_2)$ .*

(i) If  $q < 1$ , then  $R_0 = \infty$ , and the infection-free equilibrium  $E_0$  is always unstable. A unique chronic-infection equilibrium  $E^*$  is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .

(ii) If  $q = 1$  and  $R_0 \leq 1$ , then the infection-free equilibrium  $E_0$  is globally asymptotically stable in  $\Gamma$ .

(iii) If  $q = 1$  and  $R_0 > 1$ , then the infection-free equilibrium  $E_0$  is unstable, and a unique chronic-infection equilibrium  $E^*$  is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .

## 5. Proof of main results.

### 5.1. Proof of Theorem 3.1.

(i) Assume that  $R_0 \leq 1$ . To prove global stability of the infection-free equilibrium  $E_0$ , we consider the following Lyapunov functional  $L : \mathcal{C} \times \mathcal{C} \times \mathcal{C} \rightarrow \mathbb{R}$ ,

$$(5.1) \quad \begin{aligned} L(x_t, y_t, v_t) = & y_t(0) + \frac{\mu_1}{k\beta_2} v_t(0) + \frac{\mu_1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2\tau} \int_{-\tau}^0 y_t(s) ds d\tau \\ & + \int_0^\infty f_1(\tau) e^{-s_1\tau} \int_{-\tau}^0 h(x_t(s), v_t(s)) ds d\tau, \end{aligned}$$

with  $x_t(s) = x(t+s)$ ,  $y_t(s) = y(t+s)$ ,  $v_t(s) = v(t+s)$  for  $s \in (-\infty, 0]$ . Calculating the time derivative of  $L$  along a solution of system (1.4), we obtain

$$(5.2) \quad \begin{aligned} L'|_{(1.4)} = & \int_0^\infty f_1(\tau) e^{-s_1\tau} h(x(t-\tau), v(t-\tau)) d\tau - \mu_1 y(t) + \frac{\mu_1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2\tau} y(t-\tau) d\tau \\ & - \frac{\mu_1\mu_2}{k\beta_2} v(t) + \frac{\mu_1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2\tau} y(t) d\tau - \frac{\mu_1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2\tau} y(t-\tau) d\tau \\ & + \int_0^\infty f_1(\tau) e^{-s_1\tau} h(x(t), v(t)) d\tau - \int_0^\infty f_1(\tau) e^{-s_1\tau} h(x(t-\tau), v(t-\tau)) d\tau. \end{aligned}$$

From

$$(5.3) \quad \int_0^\infty f_1(\tau) e^{-s_1\tau} h(x(t), v(t)) d\tau = \beta_1 h(x(t), v(t)),$$

$$(5.4) \quad \frac{\mu_1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2\tau} y(t) d\tau = \mu_1 y(t),$$

we have

$$(5.4) \quad L'|_{(1.4)} = \beta_1 h(x(t), v(t)) - \frac{\mu_1\mu_2}{k\beta_2} v(t) = \frac{\mu_1\mu_2}{k\beta_2} v(t) \left[ \frac{k\beta_1\beta_2}{\mu_1\mu_2} \frac{h(x(t), v(t))}{v(t)} - 1 \right].$$

Using assumptions  $(H_2)$ ,  $(H_3)$ , and the expression of  $R_0$  in (2.9), we obtain

$$\begin{aligned} L'|_{(1.4)} & \leq \frac{\mu_1\mu_2}{k\beta_2} v(t) \left[ \frac{k\beta_1\beta_2}{\mu_1\mu_2} \frac{h(\bar{x}, v(t))}{v(t)} - 1 \right] \\ & \leq \frac{\mu_1\mu_2}{k\beta_2} v(t) \left[ \frac{k\beta_1\beta_2}{\mu_1\mu_2} c - 1 \right] = \frac{\mu_1\mu_2}{k\beta_2} v(t) [R_0 - 1] \leq 0, \end{aligned}$$

and  $L'|_{(1.4)} = 0$  implies that either  $v = 0$  or  $R_0 = 1$  and  $x = \bar{x}$ . Therefore, the maximal compact invariant set in  $\{L'|_{(1.4)} = 0\}$  is the singleton  $\{E_0\}$ . By the LaSalle invariance principle for delay systems (see [23, 24, 25]),  $E_0$  is globally attractive in

$\Gamma$ . Furthermore, it can be verified that  $E_0$  is locally stable using the same proof as that for Corollary 5.3.1 in [23]; see also [26]. Therefore,  $E_0$  is globally asymptotically stable in  $\Gamma$ .

(ii) Assume that

$$R_0 = \frac{ck\beta_1\beta_2}{\mu_1\mu_2} = \frac{k\beta_1\beta_2}{\mu_1\mu_2} \lim_{v \rightarrow 0^+} \frac{h(\bar{x}, v)}{v} > 1.$$

Then there exists  $\tilde{v} > 0$  such that

$$(5.5) \quad \frac{h(\bar{x}, v)}{v} \frac{k\beta_1\beta_2}{\mu_1\mu_2} > 1 \quad \text{for } v \in (0, \tilde{v}).$$

From (5.4), (5.5) and the continuity of  $h(x, v)$ , it follows that  $L'|_{(1.4)} > 0$  in a neighborhood of  $E_0 = (\bar{x}, 0, 0)$ , except for the points with  $v = 0$ . Thus solutions in  $\Gamma$  that start in arbitrarily small neighborhoods of  $E_0$  move away from  $E_0$ , except for those starting in  $X^+ = \{(x_t, 0, 0) \in \mathcal{C} \times \mathcal{C} \times \mathcal{C} : \|x_t\| > 0\}$ , which remain in  $X^+$  and tend to  $E_0$ . Therefore,  $E_0$  is unstable. A similar argument as in the proof of Proposition 3.3 of [27] can show that system (1.4) is uniformly persistent.

Uniform persistence of system (1.4), together with uniform boundedness of solutions in  $\overset{\circ}{\Gamma}$ , implies the existence of a chronic-infection equilibrium  $E^*$  of system (1.4) in  $\overset{\circ}{\Gamma}$  (see Theorem 2.8.6 in [28] or Theorem D.3 in [29]), completing the proof.

**5.2. Proof of Theorem 3.2.** Assume that  $R_0 > 1$ . From Theorem 3.1(ii) we know that a chronic-infection equilibrium  $E^* = (x^*, y^*, v^*)$  exists. We prove that  $E^*$  is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ . In particular, this implies that the chronic-infection equilibrium is unique.

Let

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

Then  $g(z) \geq 0$  for  $z > 0$  and  $g(z) = 0$  if and only if  $z = 1$ . Define a Lyapunov functional  $V : \mathcal{C} \times \mathcal{C} \times \mathcal{C} \rightarrow \mathbb{R}$ ,

$$(5.6) \quad \begin{aligned} V(x_t, y_t, v_t) = & x_t(0) - \int_{x^*}^{x_t(0)} \frac{h(x^*, v^*)}{h(\tau, v^*)} d\tau + \frac{y^*}{\beta_1} g\left(\frac{y_t(0)}{y^*}\right) + \frac{\mu_1 v^*}{k\beta_1\beta_2} g\left(\frac{v_t(0)}{v^*}\right) \\ & + \frac{\mu_1 y^*}{\beta_1^2} \int_0^\infty f_1(\tau) e^{-s_1\tau} \int_{-\tau}^0 g\left(\frac{h(x_t(s), v_t(s))}{h(x^*, v^*)}\right) ds d\tau \\ & + \frac{\mu_1 y^*}{\beta_1\beta_2} \int_0^\infty f_2(\tau) e^{-s_2\tau} \int_{-\tau}^0 g\left(\frac{y_t(s)}{y^*}\right) ds d\tau. \end{aligned}$$

Calculating the time derivative of  $V$  along a positive solution of system (1.4), we obtain

$$\begin{aligned} V'|_{(1.4)} = & n(x(t)) - n(x(t)) \frac{h(x^*, v^*)}{h(x(t), v^*)} + h(x(t), v(t)) \frac{h(x^*, v^*)}{h(x(t), v^*)} \\ & - \frac{y^*}{\beta_1 y(t)} \int_0^\infty f_1(\tau) e^{-s_1\tau} h(x(t-\tau), v(t-\tau)) d\tau + \frac{\mu_1 y^*}{\beta_1} - \frac{\mu_1 \mu_2}{k\beta_1\beta_2} v(t) \\ & - \frac{\mu_1 v^*}{\beta_1 \beta_2 v(t)} \int_0^\infty f_2(\tau) e^{-s_2\tau} y(t-\tau) d\tau + \frac{\mu_1 \mu_2}{k\beta_1\beta_2} v^* \end{aligned}$$

$$\begin{aligned} & -\frac{\mu_1 y^*}{\beta_1^2} \int_0^\infty f_1(\tau) e^{-s_1 \tau} \ln h(x(t), v(t)) d\tau \\ & + \frac{\mu_1 y^*}{\beta_1^2} \int_0^\infty f_1(\tau) e^{-s_1 \tau} \ln h(x(t-\tau), v(t-\tau)) d\tau \\ & - \frac{\mu_1 y^*}{\beta_1 \beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} \ln y(t) d\tau + \frac{\mu_1 y^*}{\beta_1 \beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} \ln y(t-\tau) d\tau. \end{aligned}$$

Using  $\frac{\mu_1 y^*}{\beta_1} = \frac{\mu_1 \mu_2}{k \beta_1 \beta_2} v^* = h(x^*, v^*)$ , we obtain

$$V'|_{(1.4)} = n(x(t)) \left[ 1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} \right] + h(x(t), v(t)) \frac{h(x^*, v^*)}{h(x(t), v^*)} - \frac{h(x^*, v^*)}{v^*} v(t) + h(x^*, v^*) S,$$

where

$$\begin{aligned} S = & 2 - \frac{1}{\mu_1 y(t)} \int_0^\infty f_1(\tau) e^{-s_1 \tau} h(x(t-\tau), v(t-\tau)) d\tau \\ & - \frac{v^*}{y^* \beta_2 v(t)} \int_0^\infty f_2(\tau) e^{-s_2 \tau} y(t-\tau) d\tau \\ & - \frac{1}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} \ln h(x(t), v(t)) d\tau \\ & + \frac{1}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} \ln h(x(t-\tau), v(t-\tau)) d\tau \\ & - \frac{1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} \ln y(t) d\tau + \frac{1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} \ln y(t-\tau) d\tau. \end{aligned}$$

Since  $1 = \frac{1}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} d\tau = \frac{1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} d\tau$  and  $\frac{y^*}{v^*} = \frac{\mu_2}{k \beta_2}$ , we have

$$\begin{aligned} (5.7) \quad S = & \frac{1}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} \left[ 1 - \frac{\beta_1}{\mu_1 y(t)} h(x(t-\tau), v(t-\tau)) - \ln h(x(t), v(t)) \right. \\ & \left. + \ln h(x(t-\tau), v(t-\tau)) \right] d\tau \\ & + \frac{1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} \left[ 1 - \frac{v^* y(t-\tau)}{y^* v(t)} - \ln y(t) + \ln y(t-\tau) \right] d\tau \\ = & \frac{1}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} \left[ \ln \frac{\mu_1 y(t)}{\beta_1 h(x(t), v(t))} - g \left( \frac{\beta_1}{\mu_1 y(t)} h(x(t-\tau), v(t-\tau)) \right) \right] d\tau \\ & + \frac{1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} \left[ \ln \frac{\mu_2 v(t)}{k \beta_2 y(t)} - g \left( \frac{v^* y(t-\tau)}{y^* v(t)} \right) \right] d\tau \\ = & \ln \frac{v(t) h(x^*, v^*)}{v^* h(x(t), v(t))} - \frac{1}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} g \left( \frac{v^* y(t-\tau)}{y^* v(t)} \right) d\tau \\ & - \frac{1}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} g \left( \frac{\beta_1}{\mu_1 y(t)} h(x(t-\tau), v(t-\tau)) \right) d\tau. \end{aligned}$$

Using  $\frac{\mu_1 \mu_2}{k \beta_1 \beta_2} = \frac{h(x^*, v^*)}{v^*}$  and (5.7), we obtain

$$\begin{aligned} V'|_{(1.4)} = & (n(x(t)) - n(x^*)) \left( 1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} \right) + n(x^*) - n(x^*) \frac{h(x^*, v^*)}{h(x(t), v^*)} \\ & + h(x(t), v(t)) \frac{h(x^*, v^*)}{h(x(t), v^*)} - \frac{h(x^*, v^*)}{v^*} v(t) + h(x^*, v^*) \ln \frac{h(x^*, v^*) v(t)}{v^* h(x(t), v(t))} \end{aligned}$$

$$\begin{aligned}
 & - \frac{h(x^*, v^*)}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} g\left(\frac{y^* h(x(t-\tau), v(t-\tau))}{y(t) h(x^*, v^*)}\right) d\tau \\
 & - \frac{h(x^*, v^*)}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} g\left(\frac{v^* y(t-\tau)}{y^* v(t)}\right) d\tau.
 \end{aligned}$$

Since  $n(x^*) = h(x^*, v^*)$ , we have

$$\begin{aligned}
 & n(x^*) - n(x^*) \frac{h(x^*, v^*)}{h(x(t), v^*)} + h(x(t), v(t)) \frac{h(x^*, v^*)}{h(x(t), v^*)} - \frac{h(x^*, v^*)}{v^*} v(t) \\
 & \quad + h(x^*, v^*) \ln \frac{h(x^*, v^*) v(t)}{v^* h(x(t), v(t))} \\
 & = h(x^*, v^*) \left[ 1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} + \frac{h(x(t), v(t))}{h(x(t), v^*)} - \frac{v(t)}{v^*} + \ln \frac{h(x^*, v^*) v(t)}{v^* h(x(t), v(t))} \right] \\
 & = h(x^*, v^*) \left[ \frac{v(t)}{v^*} \left( \frac{h(x(t), v(t))}{h(x(t), v^*)} - 1 \right) \left( \frac{v^*}{v(t)} - \frac{h(x(t), v^*)}{h(x(t), v(t))} \right) \right. \\
 & \quad \left. - g\left(\frac{h(x^*, v^*)}{h(x(t), v^*)}\right) - g\left(\frac{v(t)}{v^*} \frac{h(x(t), v^*)}{h(x(t), v(t))}\right) \right].
 \end{aligned}$$

Therefore,

$$\begin{aligned}
 (5.8) \quad V'|_{(1.4)} & = (n(x(t)) - n(x^*)) \left[ 1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} \right] \\
 & + h(x^*, v^*) \frac{v(t)}{v^*} \left( \frac{h(x(t), v(t))}{h(x(t), v^*)} - 1 \right) \left( \frac{v^*}{v(t)} - \frac{h(x(t), v^*)}{h(x(t), v(t))} \right) \\
 & - h(x^*, v^*) g\left(\frac{h(x^*, v^*)}{h(x(t), v^*)}\right) - h(x^*, v^*) g\left(\frac{v(t)}{v^*} \frac{h(x(t), v^*)}{h(x(t), v(t))}\right) \\
 & - \frac{h(x^*, v^*)}{\beta_1} \int_0^\infty f_1(\tau) e^{-s_1 \tau} g\left(\frac{\beta_1}{\mu_1 y(t)} h(x(t-\tau), v(t-\tau))\right) d\tau \\
 & - \frac{h(x^*, v^*)}{\beta_2} \int_0^\infty f_2(\tau) e^{-s_2 \tau} g\left(\frac{v^* y(t-\tau)}{y^* v(t)}\right) d\tau.
 \end{aligned}$$

From the conditions  $(A_1)$ – $(A_3)$  we know that

$$(5.9) \quad (n(x(t)) - n(x^*)) \left[ 1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} \right] \leq 0,$$

$$(5.10) \quad \left( \frac{h(x(t), v(t))}{h(x(t), v^*)} - 1 \right) \left( \frac{v^*}{v(t)} - \frac{h(x(t), v^*)}{h(x(t), v(t))} \right) \leq 0$$

for  $t \geq 0$ , and the equalities hold only if  $x(t) \equiv x^*$ . Furthermore, the positive definiteness of  $g(z)$  implies  $V'|_{(1.4)} \leq 0$  for all  $(x, y, v) \in \overset{\circ}{\Gamma}$ , and thus omega limit sets of solutions are contained in  $M$ , the largest invariant subset of  $\{V' = 0\}$ . It can be verified that  $V' = 0$  implies

$$x = x^*, \quad \frac{h(x, v)}{h(x, v^*)} = \frac{v}{v^*}, \quad \frac{\beta_1}{ay} h(x, v) = 1, \quad \text{and} \quad \frac{v^* y}{y^* v} = 1.$$

Along a solution in this set we necessarily have

$$x(t) = x^*, \quad x'(t) = y'(t) = v'(t) \equiv 0;$$

namely, the solution must be an equilibrium with  $x = x^*$ . Note that, when  $x^*$  is given, the equilibrium equation (2.8) has a unique solution  $y = y^*, v = v^*$ . Therefore,  $M = \{E^*\}$ . Using the LaSalle invariance principle and a similar argument as in the proof of Theorem 3.1, we can show that the chronic-infection equilibrium  $E^*$  is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ .

**6. Summary and discussion.** For in-host models of viral infection dynamics in vivo, it has been observed that both a mitotic term in the target-cell dynamics and intracellular delays can cause periodic oscillations through Hopf bifurcations. We have investigated, in this paper, whether these two mechanisms can independently lead to periodic oscillations, or more specifically, whether intracellular delays can lead to periodic oscillations without mitosis in the target-cell dynamics.

Using an in-host model with general target-cell dynamics, a general incidence function, and general distributions for intracellular delays, we have rigorously shown that if the target-cell dynamics are such that no Hopf bifurcations occur, introducing intracellular delays into the model will not lead to Hopf bifurcations or periodic oscillations.

Our model is sufficiently general to be applicable to in vivo infection of RNA viruses such as HIV-I and HCV, as well as DNA viruses such as HBV that replicate through reverse transcription. The model can also include effects of antiretroviral therapies using reverse transcriptase inhibitors and protease inhibitors. An implication of our results is that the right kind of target-cell dynamics are essential for sustained oscillations to occur in viral infections. This, however, does not diminish the importance of intracellular delays that are present in viral infection and replication processes; while it is mathematically possible to produce periodic solutions in an in-host model using only a suitable form of target-cell dynamics, intracellular delays may be important biologically for sustained oscillations to occur in vivo. This is in agreement with earlier studies in [12, 13] where it was shown that when both mitosis and intracellular delays are present in an in-host model, Hopf bifurcation occurs in a biologically relevant parameter range. While many in-host models for viral infections show possible parameter regimes for periodic oscillations, clinical data for HIV-I infection rarely show sustained oscillations [10, 30]. Our results imply that the properties of the target-cell dynamics for HIV-1 may have dictated the nonoscillatory nature of the HIV-I infection dynamics. We also note that none of the models discussed in the present paper incorporate immune responses to the viral infection, which should also play a key role in controlling the viral load and in determining outcomes of the viral infection.

Mathematically, our Theorem 3.2 is the first complete result on the global stability of a unique chronic-infection equilibrium for in-host viral models with intracellular delays. The proof relies on the construction of a global Lyapunov functional that is motivated by earlier works in [17]. Establishing global stability is crucial for our study, since local stability cannot rule out periodic solutions far away from equilibria.

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