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GLOBAL STABILITY OF A NONLINEAR VIRAL INFECTION MODEL WITH INFINITELY DISTRIBUTED INTRACELLULAR DELAYS AND CTL IMMUNE RESPONSES*

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Abstract. Determining sharp conditions for the global stability of equilibria remains one of the most challenging problems in the analysis of models for the management and control of biological systems. Yet such results are necessary for derivation of parameter thresholds for eradication of pests or clearing infections. This applies particularly to models involving nonlinearity and delays. In this paper, we provide some general results applicable to immune system dynamics: we consider a viral model with general target-cell dynamics, nonlinear incidence functions, state dependent removal functions, infinitely distributed intracellular delays, and the cytotoxic T lymphocyte response (CTL). This general model admits three types of equilibria: infection-free equilibria, CTL-inactivated infection equilibria, and CTL-activated infection equilibria. The model admits two critical values: R_0 (the basic reproduction number for viral infection) and R_1 (the viral reproduction number at the CTL-inactivated infection equilibrium). Under certain assumptions, it is shown that if $R_0 \leq 1$, then the infection-free equilibrium E_0 is globally stable and the viruses are cleared. If $R_1 \leq 1 < R_0$, then there exists a unique CTL-inactivated infection equilibrium E_1 which is globally stable and the infection becomes chronic with no sustained immune response. If $R_1 > 1$, then there is a unique CTL-activated infection equilibrium, which is globally stable implying persistent immune responses. Our results cover and improve many existing ones and include the case when the nonlinear functions are nonmonotone.

Key words. viral infection, immune response, distributed delay, global stability, Lyapunov functional

AMS subject classifications. 92B05, 34D23, 34D20

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1. Introduction.

The global stability of equilibria in models for viral dynamics remains an important and largely open research problem. Such results are necessary to evaluate treatment strategies for infections and to establish thresholds for treatment rates. Several models can be found in the literature to understand the immune response to viral infection. These models propose dynamics for the interactions between target cells, infected cells producing viruses, matured viruses, and immune cells such as Cytotoxic T cells (CTLs). Sufficient conditions for the global stability of the infection-free equilibrium of these models can provide insights on implementing effective antiviral drug therapies to clear viruses [3]. Alternately, if the immune control equilibrium (the equilibrium with a positive level of immune cells) is shown to be globally stable, then it means lifelong immunity can be achieved in the host [14], and no sustained oscillatory viral loads will be observed.

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Most existing viral models consider three main compartments: target cells, infected cells producing viruses, and matured viruses; see, for example, [5, 13, 15, 17, 18, 19, 21, 23, 28, 29, 30, 31]. Some models include intermediate stages such as an exposed stage [7, 8]. A few models also incorporate an immune response as the fourth compartment [22, 26, 27, 34, 35, 37].

In the aforementioned models, intracellular delays in the viral infection and replication, and immune response processes were taken into consideration in [13, 17, 18, 19, 21, 22, 23, 27, 28]. These delays may or may not induce periodic oscillations via Hopf bifurcations; this critically depends on how and in which stages and in what forms the delays are incorporated [4, 13, 18, 19, 20, 21, 27]. Even with no intracellular delays, it is known that some target-cell dynamics can cause sustained oscillations [5, 33].

Earlier models for viral dynamics fit the general form

$$x' = n(x) - h(x, v), \tag{1.1a}$$

$$y' = h\,(x, v) - \mu_1 y - pyz, \tag{1.1b}$$

$$v' = ky - \mu_2 v, \tag{1.1c}$$

$$z' = qyz - \mu_3 z. \tag{1.1d}$$

Here, $n(x)$ models the dynamics of cells in the absence of the virus; $h(x, v)$ is the incidence of new infections; infected cells are removed by CTLs at the rate pyz, produce virions at a rate ky, and die at a per capita rate μ_1; new CTLs are recruited at a rate qyz; and finally, virions are cleared at a per capita rate μ_2, and CTLs die at a per capita rate μ_3. The motivation for the rates of virion production and CTL recruitment is as follows: infected cells are either killed by CTLs or die as they release a burst of k/μ_1 virions which are immediately infectious, leading to the overall production of virions at rate ky; each cell killed by a CTL immediately leads to a recruitment of q/p new CTLs. It is known that there are delays in each connecting step [28]: infected cells can not immediately burst but go through a latent period; released virions may go through a maturation phase outside the cell before becoming infectious; and there is a complex chain of events between CTL attack and subsequent recruitment.

The earliest of these in-host viral models is due to Nowak and Bonhoeffer [30], who set $n(x) = \lambda - \mu x$ and $h(x, v) = \beta xv$. Nelson and Perelson [28] analyzed a model with $n(x) = \lambda - \mu x + rx(1 - x/x_m)$ but without an immune response ($p = q = 0$). Their assumption was that λ is the rate cells emerge from the thymus and the final term is the rate cells increase through mitosis. The addition of the nonlinearity to the model gives rise to Hopf bifurcations and periodic orbits.

The basic model was extended by Herz et al. [12] to include an exposed period. More generally, this can be done by allowing a delay in (1.1b). Li and Shu [19] replaced this equation by

$$y' = f * h\,(x, v) - \mu_1 y,$$

where $f * h(x, v)$ is the convolution

$$(f * h(x, v))\,(t) = \int_0^\infty f(\tau) h(x(t - \tau), v(t - \tau))\, d\tau.$$

More recent work has extended the model to include delays in the maturation of virions and the recruitment of CTLs.

In general, global stability is one of the most difficult problems in the analysis of many classes of biological models and is essential in ruling out other scenarios such as periodic solutions. Unlike local stability, which can be analyzed by studying the distribution of the eigenvalues of the corresponding characteristic equations, there are no standard procedures for establishing global stability. The commonly used methods include Lyapunov functions for systems of ordinary differential equations, Lyapunov functionals for systems of delay differential equations [11], and persistence theory and theory for monotone dynamical systems [32].

In this paper, we aim to establish global stability results and find sufficient conditions under which oscillations are impossible for a viral model with general target-cell dynamics and general forms of delays. We study a model which contains most of the previously mentioned models as special cases. More precisely, we consider the following system of delay-differential equations:

$$x' = n(x) - h(x, v), \tag{1.2a}$$

$$y' = f_1 * (h(x, v)) - \mu_1 g_1(y) - pw(y, z), \tag{1.2b}$$

$$v' = kf_2 * (g_1(y)) - \mu_2 g_2(v), \tag{1.2c}$$

$$z' = qf_3 * (w(y, z)) - \mu_3 g_3(z), \tag{1.2d}$$

where $x(t)$, $y(t)$, $v(t)$, and $z(t)$ denote the concentrations of the uninfected target cells, actively infected target cells, mature viruses, and virus-specific CTLs at time t, respectively. The model consists of the above equations together with suitable initial conditions and the restrictions on the functions given by the six main hypotheses below.

The dynamics of uninfected target cells, x, in the absence of infection is governed by

$$x'(t) = n(x(t)),$$

where $n(x)$ denotes the intrinsic growth rate of uninfected target cells accounting for both production and natural mortality, which is assumed to satisfy the following:

(H_1) $n(x)$ is continuously differentiable, and there exists $\bar{x} > 0$ such that $n(\bar{x}) = 0$, $n(x) > 0$ for $x \in [0, \bar{x})$, and $n(x) < 0$ for $x > \bar{x}$.

Here, $\bar{x}$ is the equilibrium cell density in the absence of infection. Thus (H_1) assumes that the infection-free system has a unique globally asymptotically stable equilibrium. Typical such functions appearing in the literature are $n(x) = \lambda - dx$ and $n(x) = \lambda - dx + rx(1 - x/K)$, where λ, d, r, K are positive real numbers [19, 21, 26, 27, 28, 31].

The incidence of new infections of target cells occurs at a rate $h(x, v)$, which includes the rate of contact between viruses and uninfected target cells as well as the probability of cell entry per contact. The nonlinear incidence function $h(x, v)$ is assumed to satisfy the following conditions:

(H_2) $h(x, v)$ is continuously differentiable; $h(x, v) > 0$ for $x \in (0, \infty)$, $v \in (0, \infty)$ with $h(x, v) = 0$ if and only if $x = 0$ or $v = 0$; $h(x, v) < h(\bar{x}, v)$ for $x \in [0, \bar{x})$, $v \in [0, \infty)$.

The assumptions (H_2) are all quite realistic for infection dynamics and are satisfied by most incidence functions appearing in the literature. The last of these restrictions assumes that for any given viral load, the incidence is greater at the infection-free cell density than at lower cell densities. Many models in the literature make the more restrictive assumption that $h(x, v)$ be increasing in both cell density, x, and viral load, v. Examples include βxv, $\beta x^m v^l$, $\beta x^m v^l / ((x^{m_1} + a_1)(v^{l_1} + a_2))$ with $\beta, a_1, a_2 > 0$, $0 < m_1 \leq m$, and $0 < l_1 \leq l \leq 1$ [5, 19, 26, 27, 28, 31].

The intracellular delay between viral infection of an uninfected target cell and the production of an actively infected target cell is modelled by the distribution f_1. As mentioned above, the incidence of infection at time t is given by the function $h(x(t), v(t))$. However, we include a delay between infection and the the presentation of viral epitopes on the surface of the infected cells such that these cells can be recognized and killed by the CTLs. The rate at which cells are becoming infectious at time t is assumed to be

$$(f_1 * h(x,v))(t) = \int_0^\infty f_1(\tau) h(x(t-\tau), v(t-\tau))\, d\tau,$$

where $f_1(\tau)$ is the probability that an infected cell survives at least τ time units past infection and becomes actively infectious at time τ past infection. Note that this incorporates two, possibly separate, events: first, the "actively infectious" cells are detectable by the CTLs and subject to predation, and second, these cells begin bursting at the rate $\mu_1 g_1(y)$. In reality, it is likely that these are two separate stages: cells becoming detectable by the CTLs as they present viral proteins on their surface, which may then lead to the assembly of virions and bursting. This additional detail is not included in our model.

It is also assumed that the death rates of the actively infected target cells, mature viruses, and CTLs depend on their concentrations. These rates are given by $\mu_1 g_1(y), \mu_2 g_2(v)$, and $\mu_3 g_3(z)$, respectively. Throughout this paper, we assume that these three state-dependent removal functions $g_i, i = 1, 2, 3$, satisfy the following assumptions:

(H_3) g_i is strictly increasing on $[0, \infty)$; $g_i(0) = 0$; $g_i'(0) = 1$; $\lim_{y\to\infty} g_i(y) = +\infty$; and there exists $k_i > 0$ such that $g_i(y) \geq k_i y$ for any $y \geq 0$, $i = 1, 2, 3$.

Thus, μ_1, μ_2, and μ_3 are the per capita clearance rates at low densities for infected cells, free virus, and CTLs, respectively.

Infected cells are assumed to be killed by CTLs at a rate $pw(y, z)$. We make the following assumption on this rate.

(H_4) $w(y, z)$ is continuously differentiable; $\partial w(y, z)/\partial z > 0$ for $y \in (0, \infty)$, $z \in [0, \infty)$; $w(y, z) > 0$ for $y \in (0, \infty)$, $z \in (0, \infty)$ with $w(y, z) = 0$ if and only if $y = 0$ or $z = 0$.

However, the uniqueness and global stability results on the positive equilibrium require the following rather restrictive assumption.

(H_5) $w(y, z) = g_1(y)g_3(z)$.

This is akin to assuming that the attack rate at which CTLs clear infected cells is proportional to the product of the rate these cells clear in the absence of a CTL response and the mortality rate of the CTLs. This restriction excludes the functions that appear in [1] and [6] but is a generalization of the widely used assumption of linear death rates ($g_3(z) = z$) and bilinear CTL induced death rates ($w(y, z) = yz$) that appear in [22, 26, 27, 29, 34, 35, 37].

The ratio of infection rates to clearance rates plays an important role in transmission models. In most models for both disease-transmission and in-host infection, both the incidence term and the clearance rate increase with the level of infection. However, there is also a common but unstated assumption that the ratio of the two is nonincreasing. In our model, this assumption is stated as follows:

(H_6) $h(x, v)/g_2(v)$ is nonincreasing with respect to v for $v \in (0, \infty)$.

To model the delay between viral release and maturation, we use $f_2(\tau)$ to denote the probability a virion released at time $t - \tau$ survives to and becomes infectious at

time t. Then the rate of virion maturation at time t is given by the convolution

$$k\left(f_2 * g_1(y)\right)(t) = k\int_0^\infty f_2(\tau)g_1(y(t-\tau))\,d\tau.$$

Here, k/μ_1 is the average number of virions budding out from a single infected target cell.

To account for the time lag incurred by a sequence of events such as antigenic activation, selection, and proliferation of the CTLs, we let $f_3(\tau)$ be the distribution of delays between cell encounters and subsequent recruitment. Then the rate of CTLs proliferation at time t is given by the convolution

$$q\left(f_3 * w(y,z)\right)(t) = q\int_0^\infty f_3(\tau)w(y(t-\tau),z(t-\tau))\,d\tau.$$

Thus we assume that each effective encounter between a CTL and an infected cell initiates a recruitment of p/q new CTLs which become active after delays distributed according to f_3. Note that this distribution is a product of the probability the cell survives to activation and the probability of activation at a time τ after initiation of the recruitment process. CTLs decay at the rate $\mu_3 g_3(z(t))$ in the absence of viral stimulation.

All parameters in (1.2) are nonnegative, μ_1, μ_2, and μ_3 are positive, and the distributions $f_i(\tau)$ with $i = 1, 2, 3$ are assumed to satisfy

$$f_i(\tau) \geq 0,\ \int_0^\infty f_i(\tau)d\tau \leq 1,\ \text{and}\ \int_0^\infty f_i(\tau)e^{s\tau}d\tau < \infty$$

for some positive s. Here we remark that each $f_i(\tau)$ is the product of a probability density function and survival distribution. So, it is possible to have the total integral along the positive real line being strictly less than one.

Our model, which we refer to as our general model, consists of (1.2) together with assumptions (H_1)–(H_6) and suitable initial conditions. This model is general in the sense that it includes many existing models as special cases. For example, if $p = 0$, $g_1(y) = y$, and $g_2(v) = v$, then the equations of (1.2) reduce to those of the model considered recently in [19]. If $f_1(\tau) = e^{-s_1\tau_1}\delta(\tau - \tau_1)$, $f_2(\tau) = e^{-s_2\tau_2}\delta(\tau - \tau_2)$, $n(x) = \lambda - dx$, $g_2(v) = v$, and $p = 0$, then the model is the same as the one studied in [13]. We will discuss these and other special cases in section 4.

We organize the rest of this paper as follows. Section 2 provides some preliminary results concerning the well-posedness of (1.2) as well as existence and uniqueness of equilibria. Our global stability results are presented in section 3, with proofs postponed to section 5. Some examples allowing nonmonotone nonlinear functions are given in section 4. We summarize our conclusion and discuss our findings in section 6.

2. Preliminaries. For system (1.2), the suitable phase space is

$$\mathcal{C}^4 = \mathcal{C} \times \mathcal{C} \times \mathcal{C} \times \mathcal{C},$$

where $\mathcal{C}$ is the Banach space of fading memory type [2, 16]

$$\mathcal{C} := \left\{ \phi \in C((-\infty, 0], \mathbb{R}) \;\middle|\; \begin{array}{c} \phi(\theta)e^{\alpha\theta}\text{is uniformly continuous} \\ \text{for } \theta \in (-\infty, 0] \text{ and } ||\phi|| < \infty \end{array} \right\},$$

where $\alpha > 0$ is a constant and the norm is defined by $||\phi|| = \sup_{\theta \le 0} |\phi(\theta)| e^{\alpha\theta}$ for $\phi \in \mathcal{C}$. The nonnegative cone of $\mathcal{C}$ is denoted by $\mathcal{C}_+ = \mathcal{C}((-\infty, 0], \mathbb{R}_+)$. We define $\phi_t \in \mathcal{C}$ as $\phi_t(\theta) = \phi(t + \theta)$, $\theta \in (-\infty, 0]$. For any initial condition

$$(x_0, y_0, v_0, z_0) \in \mathcal{C}_+^4 := \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+,$$

the existence and uniqueness of the solution (x_t, y_t, v_t, z_t) of system (1.2) follows from the standard theory of differential equations with infinitely distributed delays [11]. Let

$$\beta_i = \int_0^\infty f_i(\tau) d\tau, \ i = 1, 2, 3. \tag{2.1}$$

Set

$$M_1 := \sup_{x \in [0, \bar{x}]} n(x), \ M_2 := \sup_{y \in [0, \frac{2M_1\beta_1}{\bar{\mu}}]} g_1(y), \ M_3 := \sup_{(x,v) \in [0,\bar{x}] \times [0, \frac{k\beta_2 M_2}{\mu_2 k_2}]} h(x, v)$$

$\bar{\mu} = \min(M_1/\bar{x}, \mu_1 k_1)$, $\tilde{\mu} = \min(\mu_1 k_1, \mu_3 k_3)$, $\bar{y} = 2M_1\beta_1/\bar{\mu}$, $\bar{v} = k\beta_2 M_2/(\mu_2 k_2)$, and $\bar{z} = q\beta_1\beta_3 M_3/(p\tilde{\mu})$, and denote the sets

$$\Gamma = \Big\{(x_0, y_0, v_0, z_0) \in \mathcal{C}_+^4 : ||x_0|| \le \bar{x}, ||y_0|| \le \bar{y}, ||v_0|| \le \bar{v}, \ ||z_0|| \le \bar{z}\Big\},$$
$$Z_1^+ = \{(x_0, 0, 0, 0) \in \mathcal{C}_+^4 : ||x_0|| \ge 0\},$$

and

$$\Omega = \Big\{(x_0, y_0, v_0, z_0) \in \mathcal{C}_+^4 : ||x_0|| \le \bar{x}\Big\}.$$

Using an argument similar to [19, Proposition 2.1], we can prove the following lemma.

LEMMA 2.1. *Assume that* (H_1)–(H_4) *are satisfied, and then the region* Γ *is positively invariant and absorbing in* Ω *with respect to system* (1.2)*, all solutions with initial conditions in* Ω *enter* Γ *in finite time, and all omega limit sets are contained in* Γ.

Under assumption (H_5), the equilibrium equations for (1.2) are given by

$$n(x) = h(x, v), \tag{2.2a}$$
$$\beta_1 h(x, v) = \mu_1 g_1(y) + p g_1(y) g_3(z), \tag{2.2b}$$
$$k\beta_2 g_1(y) = \mu_2 g_2(v), \tag{2.2c}$$
$$q\beta_3 g_1(y) g_3(z) = \mu_3 g_3(z). \tag{2.2d}$$

Clearly, system (1.2) always has an infection-free equilibrium $E_0 = (\bar{x}, 0, 0, 0)$. In addition to E_0, the system may have two types of chronic-infection equilibria $E_1 = (x^*, y^*, v^*, 0)$ and $E_2 = (\hat{x}, \hat{y}, \hat{v}, \hat{z})$ in Γ, where $x^*, y^*, v^*, \hat{x}, \hat{y}, \hat{v}, \hat{z}$ are all strictly positive. We call E_1 a CTL-inactivated equilibrium (CTL-IE) if it exists and E_2 a CTL-activated equilibrium (CTL-AE) if it exists. At a CTL-IE, the infection is persistent with a constant proviral load $v^* > 0$, whereas the CTL response is absent. This corresponds to an asymptomatic carrier. At a CTL-AE, the viral load and the CTL response persist at the level of $\hat{v}$ and $\hat{z}$, respectively.

We define the general reproduction number as

$$R(x, v) = \frac{k\beta_1\beta_2 h(x, v)}{\mu_1\mu_2 g_2(v)},$$

which is the ratio of the per capita production and decay rates of mature viruses at an equilibrium (x, y, v, z) with $z = 0$. In particular, at the infection-free equilibrium, E_0, we denote $R(\bar{x}, 0)$ by R_0 and refer to it as the basic reproduction number for viral infection:

$$R_0 = \frac{k\beta_1\beta_2}{\mu_1\mu_2} \lim_{v\to 0^+} \frac{h(\bar{x}, v)}{g_2(v)} = \frac{k\beta_1\beta_2}{\mu_1\mu_2} \frac{\partial h(\bar{x}, 0)}{\partial v}. \tag{2.3}$$

Assumptions (H_3) imply that g_2 is invertible. Hence from (2.2c)–(2.2d),

$$\hat{v} = g_2^{-1}\left(\frac{k\mu_3\beta_2}{q\mu_2\beta_3}\right). \tag{2.4}$$

Let $H(x) = n(x) - h(x, \hat{v})$. Then $H(0) = n(0) > 0$ and $H(\bar{x}) = -h(\bar{x}, \hat{v}) < 0$. Thus there exists $\hat{x} \in (0, \bar{x})$ such that $H(\hat{x}) = 0$. Existence of $\hat{x}$ and $\hat{v}$ indicates that $R(\hat{x}, \hat{v})$ is well defined, which we denote by R_1 and refer to as the viral reproduction number.

Assumptions (H_2) and (H_6) imply that

$$R_0 = R(\bar{x}, 0) > R(\bar{x}, v) > R(x, v) \quad \text{for} \quad x \in [0, \bar{x}), v \in (0, \bar{v}]. \tag{2.5}$$

In particular, $R_0 > R_1$.

The basic reproduction number for the CTL response R_{CTL} is given by

$$R_{CTL} = \frac{q\beta_3}{\mu_3 g_3'(0)} \frac{\partial w(y^*, 0)}{\partial z} = \frac{q\beta_3}{\mu_3} g_1(y^*), \tag{2.6}$$

which comes from the limiting (linearized) z-dynamics near $z = 0$. The connection between R_{CTL} and R_1 is stated in Remark 3.1 and explored further in section 6.

Remark 2.1. R_{CTL} is the usual reproduction number for the CTL response in the sense that if CTL-IE E_1 is a stable equilibrium of (1.2) with $w(y, z) \equiv 0$, then there is a transcritical bifurcation of (1.2) at $R_{CTL} = 1$ involving the appearance of a CTL-AE E_2.

Before stating results on existence and uniqueness of equilibria, we require two additional assumptions. First, we define the following sets:

$$\begin{aligned} X_n &= \{\xi \in [0, \bar{x}] \mid (n(x) - n(\xi))(x - \xi) < 0 \quad \text{for } x \neq \xi,\ x \in [0, \bar{x}]\}, \\ X_h(v) &= \{\xi \in [0, \bar{x}] \mid (h(x, v) - h(\xi, v))(x - \xi) > 0 \quad \text{for } x \neq \xi,\ x \in [0, \bar{x}]\}, \\ X &= \cap_{v\in(0,\bar{v}]} X_h(v) \cap X_n. \end{aligned}$$

If X_n is nonempty, then there are cell densities at which the net growth rate is lower than the net growth rates at lower densities yet higher than the net growth rates at higher densities.

The theorem below states the conditions for the existence of equilibria for the model. The following assumptions are then used to guarantee the uniqueness of these equilibria.

(A_1) The model (1.2) has a CTL-IE $E_1 = (x^*, y^*, v^*, 0)$ satisfying $x^* \in X$.

(A_2) The model (1.2) has a CTL-AE $E_2 = (\hat{x}, \hat{y}, \hat{v}, \hat{z})$ satisfying $\hat{x} \in X_n \cap X_h(\hat{v})$.

THEOREM 2.2. *Assume that* (H_1)–(H_6) *are satisfied.*

(i) *If* $R_0 \leq 1$, *then* $E_0 = (\bar{x}, 0, 0, 0)$ *is the only equilibrium.*

(ii) *If* $R_1 \leq 1 < R_0$, *then, in addition to* E_0, *there is at least one CTL-IE* $E_1 = (x^*, y^*, v^*, 0)$, *and there are no CTL-AEs.*

(iii) *If $R_1 > 1$, then, in addition to E_0 and at least one CTL-IE E_1, there is at least one CTL-AE $E_2 = (\hat{x}, \hat{y}, \hat{v}, \hat{z})$.*

(iv) *If further, (A_1) holds, then E_1 is the unique CTL-IE of system (1.2).*

(v) *If further, (A_2) holds, then E_2 is the unique CTL-AE of system (1.2).*

Proof. Note that the CTL-IE $E_1 = (x^*, y^*, v^*, 0)$ exists if (x^*, y^*, v^*) satisfies the following equations:

$$n(x) = h(x, v) = \frac{\mu_1}{\beta_1} g_1(y) = \frac{\mu_1 \mu_2}{k\beta_1\beta_2} g_2(v). \tag{2.7}$$

By (H_3), we know that g_2^{-1} exists. Solving $n(x) = \mu_1\mu_2 g_2(v)/(k\beta_1\beta_2)$ for v gives

$$v = \varphi(x) := g_2^{-1}\left(\frac{k\beta_1\beta_2}{\mu_1\mu_2} n(x)\right)$$

with $\varphi(\bar{x}) = 0$, $\varphi(0) = v^0$, where v^0 is the unique positive root of the equation $n(0) = \mu_1\mu_2 g_2(v)/(k\beta_1\beta_2)$. Define

$$G(x) = h(x, \varphi(x)) - \frac{\mu_1\mu_2}{k\beta_1\beta_2} g_2(\varphi(x)).$$

Then $G(0) = -\mu_1\mu_2 g_2(v^0)/(k\beta_1\beta_2) < 0$ and $G(\bar{x}) = h(\bar{x}, 0) - \mu_1\mu_2 g_2(0)/(k\beta_1\beta_2) = 0$. Note that

$$\begin{aligned} G'_-(\bar{x}) &= \frac{\partial h(\bar{x}, 0)}{\partial x} + \frac{\partial h(\bar{x}, 0)}{\partial v}\varphi'(\bar{x}) - \frac{\mu_1\mu_2}{k\beta_1\beta_2} g_2'(0)\varphi'(\bar{x}) \\ &= \frac{\mu_1\mu_2}{k\beta_1\beta_2}\varphi'(\bar{x})\left(\frac{k\beta_1\beta_2}{\mu_1\mu_2}\frac{\partial h(\bar{x}, 0)}{\partial v} - 1\right) = n'(\bar{x})\left(R_0 - 1\right). \end{aligned}$$

Assumption (H_1) implies that $n'(\bar{x}) < 0$. Thus, if $R_0 > 1$, then $G'_-(\bar{x}) < 0$. This implies that there exists $x^* \in (0, \bar{x})$ such that $G(x^*) = 0$. The value of v^* is then given by $\varphi(x^*)$. Assumption (H_3) ensures that the equation $k\beta_2 g_1(y) = \mu_2 g_2(v^*)$ has a unique positive solution y^*. Therefore, E_1 exists if $R_0 > 1$. We next show that $R_0 > 1$ is also a necessary condition for the existence of E_1. For $0 < x < \bar{x}$ and $v > 0$, (2.5) implies that $\mu_1\mu_2 g_2(v) R_0 > k\beta_1\beta_2 h(x, v)$ and thus $\mu_1\mu_2 g_2(v) > k\beta_1\beta_2 h(x, v)$ for $0 < x < \bar{x}$ and $v > 0$ if $R_0 \le 1$. Thus, (2.7) cannot be satisfied and E_1 does not exist if $R_0 \le 1$. This shows that E_1 exists if and only if $R_0 > 1$.

Next we show that if (A_1) holds, then $E_1 = (x^*, y^*, v^*, 0)$ is indeed the unique CTL-IE. Suppose, to the contrary, there exists another CTL-IE $E_1^* = (x^{**}, y^{**}, v^{**}, 0)$. Without of loss of generality, we assume that $x^{**} < x^*$. Then $x^* \in X_n$ implies that $n(x^{**}) > n(x^*)$. This, together with the fact that $k\beta_1\beta_2 n(x^*) = \mu_1\mu_2 g_2(v^*)$, $k\beta_1\beta_2 n(x^{**}) = \mu_1\mu_2 g_2(v^{**})$, and monotonicity of g_2, yields $v^{**} > v^*$. By (H_6), we have $h(x^*, v^{**})/g_2(v^{**}) \le h(x^*, v^*)/g_2(v^*)$. By virtue of $x^{**} < x^*$ and $x^* \in \cap_{v\in(0,\bar{v}]} X_h(v)$, we obtain $h(x^{**}, v^{**}) < h(x^*, v^{**})$ and thus $h(x^{**}, v^{**})/g_2(v^{**}) < h(x^*, v^*)/g_2(v^*)$. On the other hand, it follows from (2.7) that $h(x^{**}, v^{**})/g_2(v^{**}) = h(x^*, v^*)/g_2(v^*) = \mu_1\mu_2/(k\beta_1\beta_2)$. This is a contradiction, and thus E_1 is the unique CTL-IE.

Note that the CTL-AE $E_2 = (\hat{x}, \hat{y}, \hat{v}, \hat{z})$ exists if $(\hat{x}, \hat{y}, \hat{v}, \hat{z}) \in \mathbb{R}^4_+$ satisfies the equilibrium equations (2.2). Equation (2.2d) and (H_3) imply that

$$\hat{y} = g_1^{-1}\left(\mu_3/(q\beta_3)\right). \tag{2.8}$$

Note that the values $\hat{x}$ and $\hat{v}$ used to define R_1 clearly satisfy the equilibrium equations. Solving the second equation of (2.2d) for z yields $\hat{z} = (\beta_1 h(\hat{x},\hat{v}) - \mu_1 g_1(\hat{y}))/(pg_1(\hat{y})) = \mu_1(R_1-1)/p$. Therefore, the CTL-AE $E_2 = (\hat{x},\hat{y},\hat{v},\hat{z})$ exists if and only if $R_1 > 1$.

Next we show that E_2 is the unique CTL-AE if (A_2) holds. Suppose there exists another CTL-AE, $E_2^* = (\hat{x}^*,\hat{y}^*,\hat{v}^*,\hat{z}^*)$. Then, $\hat{y} = \hat{y}^*$ and $\hat{v} = \hat{v}^*$. Again, without loss of generality, we assume that $\hat{x}^* < \hat{x}$. Then $\hat{x} \in X_n$ implies that $n(\hat{x}^*) > n(\hat{x})$. Note that $n(\hat{x}) = h(\hat{x},\hat{v})$ and $n(\hat{x}^*) = h(\hat{x}^*,\hat{v})$, which implies that $h(\hat{x}^*,\hat{v}) > h(\hat{x},\hat{v})$. This contradicts with $\hat{x} \in X_h(\hat{v})$ and hence E_2 is the unique CTL-AE. ∎

3. Global stability results. In this section, we state our main results concerning the global stability of system (1.2), with proofs postponed to section 5. Before stating our main results, we require two additional assumptions. First, we define the following sets.

$$Y_h(x) = \{\zeta \in [0,\bar{v}] \mid (h(x,v) - h(x,\zeta))(v-\zeta) > 0 \quad \text{for } v \neq \zeta,\ v \in [0,\bar{v}]\},$$
$$Y = \cap_{x\in(0,\bar{x}]} Y_h(x).$$

The following assumptions are used to guarantee the global stability of the CTL-IE and CTL-AE.

(B_1) The CTL-IE $E_1 = (x^*,y^*,v^*,0)$ satisfies $v^* \in Y$.

(B_2) The CTL-AE $E_2 = (\hat{x},\hat{y},\hat{v},\hat{z})$ satisfies $\hat{v} \in Y$.

THEOREM 3.1. *Assume that* (H_1)–(H_6) *hold. If* $R_0 \le 1$, *then the infection-free equilibrium* E_0 *of system* (1.2) *is globally asymptotically stable in* Ω; *whereas if* $R_0 > 1$, *then* E_0 *is unstable.*

THEOREM 3.2. *Assume that* (H_1)–(H_6) *hold and that* $R_0 > 1$. *Suppose further that* $E_1 = (x^*,y^*,v^*,0)$ *satisfies* (A_1) *and* (B_1). *If* $R_{CTL} < 1$, *then* E_1 *is locally asymptotically stable, and if* $R_{CTL} > 1$, *then* E_1 *is unstable.*

THEOREM 3.3. *Assume that* (H_1)–(H_6) *hold. Suppose that* $E_1 = (x^*,y^*,v^*,0)$ *satisfies* (A_1) *and* (B_1). *If* $R_1 \le 1 < R_0$, *then* E_1 *is globally asymptotically stable in* $\Omega \setminus Z_1^+$, *and if* $R_1 > 1$, *then* E_1 *is unstable.*

Remark 3.1. By the equilibrium equations, we can rewrite R_1 and R_{CTL} as

$$R_1 = \frac{q\beta_1\beta_3}{\mu_1\mu_3} n(\hat{x}) \quad \text{and} \quad R_{CTL} = \frac{q\beta_1\beta_3}{\mu_1\mu_2} n(x^*).$$

It then follows from Lemma 5.1 that under the assumptions of Theorem 3.2 (also Theorem 3.3), $R_1 > 1 \Leftrightarrow R_{CTL} > 1$, $R_1 < 1 \Leftrightarrow R_{CTL} < 1$, and $R_1 = 1 \Leftrightarrow R_{CTL} = 1$.

It follows from Theorems 2.2, 3.1, and 3.3 that if $R_1 > 1$, then both E_0 and E_1 are unstable and the CTL-AE $E_2 = (\hat{x},\hat{y},\hat{v},\hat{z})$ exists. It has been shown in [4, 20, 36] that a time delay in the CTL response process can induce sustained oscillations through Hopf bifurcation for in-host viral models with CTL responses. Therefore, we only attempt to establish the global stability of the CTL-AE E_2, and we assume that no delay is presented in the CTL response process. That is, we consider system (1.2) with $f_3(\tau) = \delta(\tau)$:

$$x' = n(x) - h(x,v), \tag{3.1a}$$
$$y' = f_1 * (h(x,v)) - \mu_1 g_1(y) - pg_1(y)g_3(z), \tag{3.1b}$$
$$v' = kf_2 * (g_1(y)) - \mu_2 g_2(v), \tag{3.1c}$$
$$z' = qg_1(y)g_3(z) - \mu_3 g_3(z), \tag{3.1d}$$

THEOREM 3.4. *Assume that* (H_1)–(H_6) *hold and that* $f_3(\tau) = \delta(\tau)$. *Further, suppose that* $E_2 = (\hat{x},\hat{y},\hat{v},\hat{z})$ *satisfies* (A_2) *and* (B_2). *If* $R_1 > 1$, *then for system* (3.1), E_2 *is globally asymptotically stable in the interior of* Ω.

Remark 3.2. If $n(x)$ is monotonically decreasing for $x \in [0, \bar{x}]$, then $\{x^*, \hat{x}\} \subset X_n$. If $h(x, v)$ is monotonically increasing with respect to x and v, then $\{x^*, \hat{x}\} \subset \cap_{v\in(0,\bar{v}]} X_h(v)$ and $\{v^*, \hat{v}\} \subset Y$. However, the monotonicity is not necessary for these assumptions to hold. In section 4, we give an example in which $n(x)$ is of logistic type and thus is nonmonotone and $h(x, v)$ is not monotone in v, but (A_1)–(A_2) and (B_1)–(B_2) hold.

4. Examples.

Example 4.1. Consider

$$
\begin{aligned}
x'(t) &= \lambda - dx(t) - \beta \frac{x^m(t)}{(x^{m_1}(t) + a_1)} \frac{v^l(t)}{(v^{l_1}(t) + a_2)},\\
y'(t) &= \beta e^{-s_1\tau_1} \frac{x^m(t-\tau_1)}{(x^{m_1}(t-\tau_1) + a_1)} \frac{v^l(t-\tau_1)}{(v^{l_1}(t-\tau_1) + a_2)} - \mu_1 y(t) - py(t)z(t),\\
v'(t) &= ke^{-s_2\tau_2} y(t-\tau_2) - \mu_2 v(t),\\
z'(t) &= qy(t)z(t) - \mu_3 z(t)
\end{aligned}
\tag{4.1}
$$

with $m_1, l_1, a_1, a_2, s_1, s_2, \tau_1, \tau_2 \geq 0$ and the other parameters being positive.

It can be verified that $h(x, v)$ is strictly monotonically increasing with respect to x and v if one of the following conditions holds:

$$
\begin{aligned}
&(C_1) : m_1 \leq m,\ l_1 \leq l \text{ and } a_i > 0 \text{ for } i = 1, 2;\\
&(C_2) : m_1 < m,\ l_1 < l \text{ and } a_i \geq 0 \text{ for } i = 1, 2.
\end{aligned}
$$

Moreover, $h(x, v)/v$ is nonincreasing in v for $v \in [0, \infty)$ if $l_1 \leq l \leq 1$.

Applying Theorems 3.1–3.4 to system (4.1) yields the following result.

COROLLARY 4.1. *Assume that either* (C_1) *or* (C_2) *is satisfied.*

(i) *If* $l < 1$, *then* $R_0 = +\infty$, *and the infection-free equilibrium* E_0 *of system* (4.1) *is always unstable and system* (4.1) *admits a unique CTL-IE* E_1, *which is globally asymptotically stable in* Ω *if* $R_1 \leq 1$. *If* $R_1 > 1$, *then system* (4.1) *admits a unique CTL-AE* E_2, *which is globally asymptotically stable in the interior of* Ω.

(ii) *If* $l = 1$, *then*

$$
R_0 = \frac{k\beta e^{-s_1\tau_1 - s_2\tau_2}}{\mu_1\mu_2 a_2} \frac{\bar{x}^m}{\bar{x}^{m_1} + a_1},
$$

where $\bar{x} = \lambda/d$. *In this case, if* $R_0 \leq 1$, *then the infection-free equilibrium* E_0 *of system* (4.1) *is globally asymptotically stable in* Ω. *If* $R_1 \leq 1 < R_0$, *then* E_0 *is unstable and the unique CTL-IE* E_1 *is globally asymptotically stable in* $\Omega \setminus Z_1^+$. *If* $R_1 > 1$, *then* E_0 *and* E_1 *are unstable and the unique CTL-AE* E_2 *is globally asymptotically stable in the interior of* Ω.

Remark 4.1. If $m_1 = 0, m = 1, l_1 = l = 1, a_1 = 0$, and $s_1 = s_2 = 0$, then system (4.1) reduces to the system considered in [22] and the global dynamics are completely determined by R_0 and R_1. If $m = l = 1, m_1 = l_1 = 0, a_1 = a_2 = 0, s_2 = 0, \tau_2 = 0$, then (4.1) reduces to the model studied in [37], in which only local stability of E_1 and E_2 was given and their global stability was left open. Corollary 4.1 gives an affirmative answer to the open problem.

Example 4.2. Consider the following system

$$\begin{aligned} x'(t) &= \lambda - dx(t) + rx(t)\left(1 - \frac{x(t)}{K}\right) - \beta x(t)v(t), \\ y'(t) &= \beta e^{-s_1\tau_1}x(t-\tau_1)v(t-\tau_1) - \mu_1 y(t) - py(t)z(t), \\ v'(t) &= ke^{-s_2\tau_2}y(t-\tau_2) - \mu_2 v(t), \\ z'(t) &= qy(t)z(t) \ - \ \mu_3 z(t) \end{aligned} \tag{4.2}$$

with $\tau_1, \tau_2 \geq 0$ and the other parameters being positive.

Clearly, $n(x)$ is a nonmonotone function for positive x if $r > d$. A direct calculation yields

$$\bar{x} = \frac{K(r-d) + \sqrt{K^2(r-d)^2 + 4\lambda rK}}{2r},\ x^* = \frac{\mu_1\mu_2}{\beta k}e^{s_1\tau_1 + s_2\tau_2},$$

$$\hat{v} = \frac{ke^{-s_2\tau_2}\mu_3}{\mu_2 q},\ \hat{x} = \frac{1}{2r}\left(-K(d + \beta\hat{v} - r)) + \sqrt{(K(d+\beta\hat{v}-r))^2 + 4\lambda rK}\right),$$

and

$$R_0 = \frac{k\beta e^{-s_1\tau_1 - s_2\tau_2}}{\mu_1\mu_2}\bar{x},\ \ R_1 = \frac{k\beta e^{-s_1\tau_1 - s_2\tau_2}}{\mu_1\mu_2}\hat{x}.$$

Clearly if $R_1 \leq 1 < R_0$, then (B_1) holds, and (A_1) holds if and only if

$$0 \leq r < \frac{d}{1 - \frac{x^*}{K}}. \tag{4.3}$$

If $R_1 > 1$, then (B_2) holds, and (A_2) holds if and only if

$$0 \leq r < \frac{d}{1 - \frac{\hat{x}}{K}}. \tag{4.4}$$

Therefore, applying Theorems 3.1, 3.3, and 3.4 to system (4.2), we immediately have the following result.

COROLLARY 4.2. *Consider system* (4.2). *If $R_0 \leq 1$, then E_0 is globally asymptotically stable in Ω. If $R_1 \leq 1 < R_0$, then E_0 is unstable, and system* (4.2) *has a unique CTL-IE E_1, which is globally asymptotically stable in $\Omega \setminus Z_1^+$ provided that* (4.3) *is satisfied. If $R_1 > 1$, then E_0 and E_1 are unstable, and system* (4.2) *admits a unique CTL-AE E_2, which is globally asymptotically stable in the interior of Ω provided that* (4.4) *holds.*

Remark 4.2. If (4.3)(resp., (4.4)) is not satisfied, then E_1 (resp., E_2) may become unstable and (4.2) may admit stable periodic solutions (see Figure 4.1). In the case of $p = 0$, the variable z does not appear in the first three equations of system (4.2). The subsystem consisting of the first three equations with $\tau_1 = \tau_2 = 0$ is considered in [5]. It is shown in [5, Theorem 2.1] that E_1 is globally asymptotically stable if $R_0 > 1$ and $0 \leq r \leq d$. Corollary 4.2 relaxes the condition $0 \leq r \leq d$ to (4.3), and when (4.3) is not satisfied, E_1 may lose its stability and Hopf bifurcation may occur inducing stable periodic oscillations.

Example 4.3. Consider

$$\begin{aligned} x'(t) &= \lambda - dx(t) + rx(t)\left(1 - \tfrac{x(t)}{K}\right) - \beta x\left((v-b)e^{-cv} + b\right), \\ y'(t) &= \beta e^{-s_1\tau_1}x(t-\tau_1)\left((v(t-\tau_1) - b)e^{-cv(t-\tau_1)} + b\right) - \mu_1 y(t) - py(t)z(t), \\ v'(t) &= ke^{-s_2\tau_2}y(t-\tau_2) - \mu_2 v(t), \\ z'(t) &= qy(t)z(t) \ - \ \mu_3 z(t), \end{aligned} \tag{4.5}$$

where $b > 0, c > 0$ and the other parameters are the same as in Example 4.2.

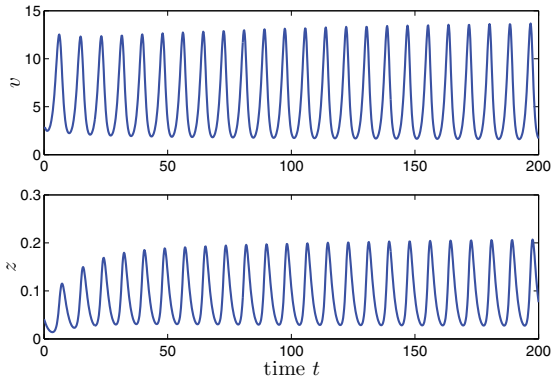

FIG. 4.1. *A numerical solution (the v and z components) of system* (4.2) *with sustained oscillations. Parameter values are $\lambda = 10$ cells $mm^{-3}day^{-1}$, $d = 0.1$ day^{-1}, $r = 0.6$ day^{-1}, $K = 500$ cells mm^{-3}, $\beta = 0.1$ $mm^3 virus^{-1} day^{-1}$, $s_1 = 0.01$ day^{-1}, $\tau_1 = 0.2$ day, $\mu_1 = 0.8$ day^{-1}, $p = 9$ $mm^3 cells^{-1} day^{-1}$, $k = 0.8$ virus $cells^{-1} day^{-1}$, $s_2 = 0.05$ day^{-1}, $\tau_2 = 0.3$ day, $\mu_2 = 3.5$ day^{-1}, $q = 0.03$ $mm^3 cells^{-1} day^{-1}$, and $\mu_3 = 0.75$ day^{-1}. The initial condition is $(x(\theta), y(\theta), v(\theta), z(\theta)) = (\hat{x}/2, \hat{y}/2, \hat{v}/2, \hat{z}/2)$ for $\theta \in [-\tau, 0]$.*

One can verify that (H_1)–(H_6) hold. Direct calculations yield

$$\beta_1 = e^{-s_1\tau_1},\ \beta_2 = e^{-s_2\tau_2},\ \bar{x} = \frac{K(r-d) + \sqrt{K^2(r-d)^2 + 4\lambda r K}}{2r},$$

$$\hat{v} = \frac{k\beta_2\mu_3}{\mu_2 q},\ \hat{x} = \frac{1}{2r}\left(-K(d + \beta h_1(\hat{v}) - r)) + \sqrt{(K(d + \beta h_1(\hat{v}) - r))^2 + 4\lambda r K}\right),$$

and

$$R_0 = \beta\bar{x}(1 + bc)\frac{k\beta_1\beta_2}{\mu_1\mu_2},\quad R_1 = \beta\hat{x}\cdot\frac{k\beta_1\beta_2}{\mu_1\mu_2}\cdot\frac{h_1(\hat{v})}{\hat{v}}.$$

Note that $h_1(v)$ is increasing for $v \in (0, b+1/c)$, and is decreasing for $v > b+1/c$. The maximum of $h_1(v)$ is attained at $v = b + 1/c$. Suppose $\bar{v} > b + 1/c$. (Otherwise, if $\bar{v} < b + 1/c$, then $h(x, v)$ is increasing with respect to v for $v \in (0, \bar{v})$.) Then there exists a $\tilde{v} \in (0, b + 1/c)$ such that $h_1(\tilde{v}) = h_1(\bar{v})$.

If $R_1 \le 1 < R_0$, then x^* is the unique positive solution of the nonlinear equation

$$n(x) = \beta x h_1\left(\frac{k\beta_1\beta_2}{\mu_1\mu_2}n(x)\right),$$

and $v^* = k\beta_1\beta_2 n(x^*)/(\mu_1\mu_2)$. We can further verify that (A_1) holds provided that (4.3) is satisfied, and (B_1) holds if and only if $v^* < \tilde{v}$.

If $R_1 > 1$, then we can verify that (A_2) holds provided that (4.4) is satisfied, and (B_2) holds if and only if $\hat{v} < \tilde{v}$.

Therefore, applying Theorems 3.1, 3.3, and 3.4 to system (4.5), we immediately have the following result.

COROLLARY 4.3. *Consider system* (4.5). *If $R_0 \le 1$, then E_0 is globally asymptotically stable in Ω. If $R_1 \le 1 < R_0$, then E_0 is unstable, and system* (4.5) *has a unique CTL-IE E_1, which is globally asymptotically stable in $\Omega \setminus Z_1^+$ provided that* (4.3) *and $v^* < \tilde{v}$ are satisfied. If $R_1 > 1$, then E_0 and E_1 are unstable, and system* (4.5) *admits a unique CTL-AE E_2, which is globally asymptotically stable in the interior of Ω provided that* (4.4) *and $\hat{v} < \tilde{v}$ hold.*

5. Proofs of main results.

5.1. Proof of Theorem 3.1. Assume that $R_0 \le 1$. Define a Lyapunov functional $L : \Gamma \to \mathbb{R}$ as

$$\begin{aligned} L(x_t, y_t, v_t, z_t) = x_t(0) &- \int_{\bar{x}}^{x_t(0)} \lim_{v\to 0} \frac{h(\bar{x}, v)}{h(\theta, v)}\, d\theta + \frac{1}{\beta_1} y_t(0) + \frac{\mu_1}{k\beta_1\beta_2} v_t(0) + \frac{p}{q\beta_1\beta_3} z_t(0) \\ &+ \frac{1}{\beta_1} \int_0^\infty f_1(\tau) \int_{-\tau}^0 h(x_t(s), v_t(s))\, ds d\tau \\ &+ \frac{\mu_1}{\beta_1\beta_2} \int_0^\infty f_2(\tau) \int_{-\tau}^0 g_1(y_t(s))\, ds d\tau \\ &+ \frac{p}{\beta_1\beta_3} \int_0^\infty f_3(\tau) \int_{-\tau}^0 g_1(y_t(s)) g_3(z_t(s))\, ds d\tau \end{aligned}$$

with $x_t(s) = x(t+s), y_t(s) = y(t+s)$, and $v_t(s) = v(t+s), z_t(s) = z(t+s)$ for $s \in (-\infty, 0]$. Calculating the time derivative of L along a solution of system (1.2) and making use of (2.1) and (H_3), we obtain

$$\begin{aligned} \frac{dL}{dt} &= n(x(t)) \left(1 - \lim_{v\to 0} \frac{h(\bar{x}, v)}{h(x(t), v)}\right) + h(x(t), v(t)) \lim_{v\to 0} \frac{h(\bar{x}, v)}{h(x(t), v)} \\ &\quad - \frac{\mu_1\mu_2}{k\beta_1\beta_2} g_2(v(t)) - \frac{p\mu_3}{q\beta_1\beta_3} g_3(z(t)) \\ &\le n(x(t)) \left(1 - \lim_{v\to 0} \frac{h(\bar{x}, v)}{h(x(t), v)}\right) \\ &\quad + \frac{\mu_1\mu_2}{k\beta_1\beta_2} g_2(v(t)) \left(\frac{k\beta_1\beta_2}{\mu_1\mu_2} \frac{h(x(t), v(t))}{g_2(v(t))} \lim_{v\to 0} \frac{h(\bar{x}, v)}{h(x(t), v)} - 1\right). \end{aligned} \tag{5.1}$$

Assumptions (H_1)–(H_6) imply that $n(x)(1 - \lim_{v\to 0} h(\bar{x}, v)/h(x, v)) \le 0$, and

$$\frac{h(x, v)}{g_2(v)} \lim_{v\to 0} \frac{h(\bar{x}, v)}{h(x, v)} \le \lim_{v\to 0} \frac{h(x, v)}{g_2(v)} \frac{\frac{\partial h(\bar{x}, 0)}{\partial v}}{\frac{\partial h(x, 0)}{\partial v}} = \frac{\partial h(\bar{x}, 0)}{\partial v} \frac{1}{g_2'(0)}.$$

It follows from (2.3) that

$$\frac{dL}{dt} \le \frac{\mu_1\mu_2}{k\beta_1\beta_2} g_2(v(t))\,(R_0 - 1) \le 0 \quad \text{if} \quad R_0 \le 1,$$

and $dL/dt = 0$ implies that $x(t) = \bar{x}$ and $z(t) = 0$ for any $t \ge 0$; it follows from $x'(t) = 0$ and (H_2) that $y(t) = v(t) = 0$ for any $t \ge 0$. Therefore, the maximal compact invariant set in $\{dL/dt = 0\}$ is the singleton $\{E_0\}$. By the LaSalle invariance principle [9, 10, 11], E_0 is globally attractive in Γ. Note that the Lyapunov functional L is positive definite in Γ. It can be verified that E_0 is locally stable using the same proof as that for Corollary 5.3.1 in [11]. Therefore, E_0 is globally asymptotically stable in Γ if $R_0 \le 1$. Finally, E_0 is globally asymptotically stable in Ω since Γ is absorbing in Ω.

Next assume that

$$R_0 = \frac{k\beta_1\beta_2}{\mu_1\mu_2} \lim_{v\to 0^+} \frac{h(\overline{x}, v)}{g_2(v)} > 1.$$

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

$$\frac{h(\overline{x}, v)}{g_2(v)} \frac{k\beta_1\beta_2}{\mu_1\mu_2} > 1 \quad \text{for} \quad v \in (0, \widetilde{v}). \tag{5.2}$$

From (5.1), (5.2), and the continuity of $h(x,v)$, it follows that $dL/dt > 0$ in a neighborhood of $E_0 = (\overline{x}, 0, 0, 0)$, except for the points with $v = 0$. Thus solutions in Γ starting from arbitrarily small neighborhoods of E_0 move away from E_0, except for those starting in $Z_1^+ = \{(x_0, 0, 0, 0) \in \mathcal{C}_+^4 : x_0 \geq 0\}$, which remain in Z_1^+ and tend to E_0. Therefore, E_0 is unstable if $R_0 > 1$.

5.2. Proof of Theorem 3.2. The characteristic equation associated with the linearization of system (1.2) at $(x^*, y^*, v^*, 0)$ is

$$\Delta_1(\xi)\Delta_2(\xi) = 0, \tag{5.3}$$

where $\Delta_1(\xi) = \det \begin{pmatrix} -\xi + n'(x^*) - \frac{\partial h(x^*,v^*)}{\partial x} & 0 & -\frac{\partial h(x^*,v^*)}{\partial v} \\ \frac{\partial h(x^*,v^*)}{\partial x}\hat{f}_1(\xi) & -\xi - \mu_1 g_1'(y^*) & \frac{\partial h(x^*,v^*)}{\partial v}\hat{f}_1(\xi) \\ 0 & k g_1'(y^*)\hat{f}_2(\xi) & -\xi - \mu_2 g_2'(v^*) \end{pmatrix}$, and

$$\Delta_2(\xi) = \xi - q\frac{\partial w(y^*,0)}{\partial z}\hat{f}_3(\xi) + \mu_3 g_3'(0), \tag{5.4}$$

and we have used $\hat{f}_i(\xi)$, $i = 1, 2, 3$, to denote the Laplace transform $\int_0^\infty f_i(\tau)e^{-\xi\tau}\, d\tau$.

If $R_0 > 1$, then (x^*, y^*, v^*) is the unique positive equilibrium of the subsystem of (1.2) consisting of the first three equations with $p = 0$, and (x^*, y^*, v^*) is global asymptotically stable (see [19]), which implies that all eigenvalue of $\Delta_1(\xi) = 0$ have negative real parts. Therefore, E_1 is asymptotically stable if all zeros of $\Delta_2(\xi)$ have negative real parts.

Note that $\Delta_2'(\xi) > 0$. Then $\Delta_2(\xi)$ is an increasing function. Since $\Delta_2(\infty) = \infty$ and $\Delta_2(-\infty) = -\infty$, it follows that $\Delta_2(\xi)$ has exactly one real root, denoted by ξ_0. Next, we claim that if $\Delta_2(a+bi) = 0$ with $b \neq 0$, then $a < \xi_0$. Assume to the contrary that $a \geq \xi_0$, and then we obtain from the real part of the equation $\Delta_2(a + bi) = 0$ that

$$\begin{aligned} a + \mu_3 g_3'(0) &= q\frac{\partial w(y^*,0)}{\partial z}\int_0^\infty f_3(\tau)e^{-a\tau}\cos(b\tau)d\tau \\ &\leq q\frac{\partial w(y^*,0)}{\partial z}\int_0^\infty f_3(\tau)e^{-\xi_0\tau}d\tau = \xi_0 + \mu_3 g_3'(0). \end{aligned}$$

Thus, $a = \xi_0$ and $\cos(b\tau) = 1$. On the other hand, we have $\sin(b\tau)f_3(\tau) = 0$ for all $\tau \geq 0$. It follows from the imaginary part of the equation $\Delta_2(a + bi) = 0$ that

$$b = -q\frac{\partial w(y^*,0)}{\partial z}\int_0^\infty f_3(\tau)e^{-a\tau}\sin(b\tau)d\tau = 0.$$

This leads to a contradiction. Finally, we note that $\Delta_2(0) = \mu_3 g_3'(0)(1 - R_{CTL})$, and then we have $\Delta_2(0) > 0$ if $R_{CTL} < 1$ and $\Delta_2(0) < 0$ if $R_{CTL} > 1$. Then we can easily obtain that if $R_{CTL} < 1$, all eigenvalues of the characteristic equation (5.3) have negative real parts; if $R_{CTL} > 1$, there exists at least one positive eigenvalue. This completes the proof of Theorem 3.2.

5.3. Proof of Theorem 3.3. First, we prove a lemma which will be used in the proof of Theorem 3.3.

LEMMA 5.1. *Suppose that* (H_1), (H_6), (A_1), *and* (B_1) *are satisfied and* $R_0 > 1$. *Then* $x^*, y^*, v^*, \hat{x}, \hat{y}, \hat{v}$ *exist satisfying* $\operatorname{sgn}(\hat{x} - x^*) = \operatorname{sgn}(v^* - \hat{v}) = \operatorname{sgn}(y^* - \hat{y}) = \operatorname{sgn}(R_1 - 1)$.

Proof. It follows from (2.2c) and (2.7) that $g_1(y^*) = \mu_2 g_2(v^*)/(k\beta_2)$, $g_1(\hat{y}) = \mu_2 g_2(\hat{v})/(k\beta_2)$. This, together with ($H_3$), implies that $\operatorname{sgn}(v^* - \hat{v}) = \operatorname{sgn}(y^* - \hat{y})$. Next

we claim

$$\operatorname{sgn}(\hat{x}-x^*)=\operatorname{sgn}(v^*-\hat{v}). \tag{5.5}$$

Suppose this is not true, i.e., $\operatorname{sgn}(\hat{x}-x^*)=\operatorname{sgn}(\hat{v}-v^*)$. Assumptions (A_1)–(B_1) imply that

$$(h(\hat{x},v^*)-h(x^*,v^*))(\hat{x}-x^*)>0,\ (h(\hat{x},\hat{v})-h(\hat{x},v^*))(\hat{v}-v^*)>0.$$

Note that

$$n(\hat{x})-n(x^*)=(h(\hat{x},\hat{v})-h(\hat{x},v^*))+(h(\hat{x},v^*)-h(x^*,v^*)).$$

Thus $\operatorname{sgn}(n(\hat{x})-n(x^*))=\operatorname{sgn}(\hat{x}-x^*)$, which contradicts with (A_1). Therefore (5.5) holds. By (2.7), we obtain

$$R_1-1=\frac{k\beta_1\beta_2}{\mu_1\mu_2}\left(\frac{h(\hat{x},\hat{v})}{g_2(\hat{v})}-\frac{h(\hat{x},v^*)}{g_2(v^*)}+\frac{h(\hat{x},v^*)-h(x^*,v^*)}{g_2(v^*)}\right). \tag{5.6}$$

By (H_6) and (A_1), we have

$$\left(\frac{h(\hat{x},\hat{v})}{g_2(\hat{v})}-\frac{h(\hat{x},v^*)}{g_2(v^*)}\right)(v^*-\hat{v})>0,\ (h(\hat{x},v^*)-h(x^*,v^*))(\hat{x}-x^*)>0.$$

This, together with (5.5) and (5.6), indicates that $\operatorname{sgn}(R_1-1)=\operatorname{sgn}(\hat{x}-x^*)$. ∎

We are now in the position to prove Theorem 3.3. Assume that $R_1\le 1<R_0$. Theorem 2.2 implies that the CTL-IE $E_1=(x^*,y^*,v^*,0)$ exists and is unique. Denote

$$c(\theta)=\theta-1-\ln\theta.$$

Then $c(\theta)\ge 0$ for $\theta>0$ and $c(\theta)=0$ if and only if $\theta=1$. Motivated by the earlier work in [25], we construct a Lyapunov functional $V:\Gamma\to\mathbb{R}$ as

$$\begin{aligned}V(x_t,y_t,v_t,z_t)&=x_t(0)-\int_{x^*}^{x_t(0)}\frac{h(x^*,v^*)}{h(\theta,v^*)}\,d\theta+\frac{1}{\beta_1}\left(y_t(0)-\int_{y^*}^{y_t(0)}\frac{g_1(y^*)}{g_1(\theta)}\,d\theta\right)\\&\quad+\frac{\mu_1}{k\beta_1\beta_2}\left(v_t(0)-\int_{v^*}^{v_t(0)}\frac{g_2(v^*)}{g_2(\theta)}\,d\theta\right)+\frac{p}{q\beta_1\beta_3}z_t(0)\\&\quad+\frac{\mu_1 g_1(y^*)}{\beta_1^2}\int_0^\infty f_1(\tau)\int_{-\tau}^0 c\left(\frac{h(x_t(s),v_t(s))}{h(x^*,v^*)}\right)ds d\tau\\&\quad+\frac{\mu_1 g_1(y^*)}{\beta_1\beta_2}\int_0^\infty f_2(\tau)\int_{-\tau}^0 c\left(\frac{g_1(y_t(s))}{g_1(y^*)}\right)ds d\tau\\&\quad+\frac{p}{\beta_1\beta_3}\int_0^\infty f_3(\tau)\int_{-\tau}^0 g_1(y_t(s))g_3(z_t(s))\,ds d\tau.\end{aligned}$$

It follows from the equilibrium equation (2.7) that the time derivative of V along solutions of system (1.2) is given by

$$\begin{aligned}\frac{dV}{dt}&=n(x(t))\left(1-\frac{h(x^*,v^*)}{h(x(t),v^*)}\right)\\&\quad+h(x(t),v(t))\frac{h(x^*,v^*)}{h(x(t),v^*)}-\frac{h(x^*,v^*)}{g_2(v^*)}g_2(v(t))+S_1+S_2,\end{aligned}$$

where

$$S_1 = \frac{p}{\beta_1} g_1(y^*) g_3(z(t)) - \frac{p\mu_3}{q\beta_1\beta_3} g_3(z(t)) = \frac{p}{\beta_1} g_3(z(t)) \left(g_1(y^*) - g_1(\hat{y})\right),$$

and

$$\begin{aligned}
S_2 = \; & h(x^*, v^*) \Bigg(2 - \frac{1}{\mu_1 g_1(y(t))} \int_0^\infty f_1(\tau) h(x(t-\tau), v(t-\tau)) d\tau \\
& - \frac{k}{\mu_2 g_2(v(t))} \int_0^\infty f_2(\tau) g_1(y(t-\tau)) d\tau - \ln h(x(t), v(t)) \\
& + \frac{1}{\beta_1} \int_0^\infty f_1(\tau) \ln h(x(t-\tau), v(t-\tau)) d\tau - \ln g_1(y(t)) \\
& + \frac{1}{\beta_2} \int_0^\infty f_2(\tau) \ln g_1(y(t-\tau)) d\tau \Bigg) \\
= \; & h(x^*, v^*) \Bigg\{ \frac{1}{\beta_1} \int_0^\infty f_1(\tau) \Bigg[1 - \frac{\beta_1}{\mu_1 g_1(y(t))} h(x(t-\tau), v(t-\tau)) - \ln h(x(t), v(t)) \\
& \qquad + \ln h(x(t-\tau), v(t-\tau)) \Bigg] d\tau \\
& + \frac{1}{\beta_2} \int_0^\infty f_2(\tau) \Bigg[1 - \frac{g_2(v^*) g_1(y(t-\tau))}{g_1(y^*) g_2(v(t))} \\
& \qquad - \ln g_1(y(t)) + \ln g_1(y(t-\tau)) \Bigg] d\tau \Bigg\} \\
= \; & h(x^*, v^*) \ln \frac{h(x^*, v^*) g_2(v(t))}{h(x(t), v(t)) g_2(v^*)} - \frac{h(x^*, v^*)}{\beta_2} \int_0^\infty f_2(\tau) c\left(\frac{g_2(v^*) g_1(y(t-\tau))}{g_1(y^*) g_2(v(t))} \right) d\tau \\
& - \frac{h(x^*, v^*)}{\beta_1} \int_0^\infty f_1(\tau) c\left(\frac{\beta_1 h(x(t-\tau), v(t-\tau))}{\mu_1 g_1(y(t))} \right) d\tau.
\end{aligned}$$

Thus

$$\begin{aligned}
\frac{dV}{dt} = & \left(n(x(t)) - n(x^*)\right) \left(1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} \right) + S_1 + S_3 \\
& - \frac{h(x^*, v^*)}{\beta_1} \int_0^\infty f_1(\tau) c\left(\frac{\beta_1 h(x(t-\tau), v(t-\tau))}{\mu_1 g_1(y(t))} \right) d\tau \\
& - \frac{h(x^*, v^*)}{\beta_2} \int_0^\infty f_2(\tau) c\left(\frac{g_2(v^*) g_1(y(t-\tau))}{g_1(y^*) g_2(v(t))} \right) d\tau,
\end{aligned}$$

where

$$\begin{aligned}
S_3 = & \; h(x^*, v^*) \left[1 - \frac{h(x^*, v^*)}{h(x(t), v^*)} + \frac{h(x(t), v(t))}{h(x(t), v^*)} - \frac{g_2(v(t))}{g_2(v^*)} + \ln \frac{h(x^*, v^*) g_2(v(t))}{h(x(t), v(t)) g_2(v^*)} \right] \\
= & \; h(x^*, v^*) \left[\frac{g_2(v(t))}{g_2(v^*)} \left(\frac{h(x(t), v(t))}{h(x(t), v^*)} - 1 \right) \left(\frac{g_2(v^*)}{g_2(v(t))} - \frac{h(x(t), v^*)}{h(x(t), v(t))} \right) \right. \\
& \left. - c\left(\frac{h(x^*, v^*)}{h(x(t), v^*)} \right) - c\left(\frac{h(x(t), v^*) g_2(v(t))}{h(x(t), v(t)) g_2(v^*)} \right) \right].
\end{aligned}$$

Therefore,

$$\begin{aligned}\frac{dV}{dt} &= (n(x(t)) - n(x^*))\left(1 - \frac{h(x^*,v^*)}{h(x(t),v^*)}\right) + S_1 \\ &\quad + h(x^*,v^*)\frac{g_2(v(t))}{g_2(v^*)}\left(\frac{h(x(t),v(t))}{h(x(t),v^*)} - 1\right)\left(\frac{g_2(v^*)}{g_2(v(t))} - \frac{h(x(t),v^*)}{h(x(t),v(t))}\right) \\ &\quad - h(x^*,v^*)c\left(\frac{h(x^*,v^*)}{h(x(t),v^*)}\right) - h(x^*,v^*)c\left(\frac{h(x(t),v^*)g_2(v(t))}{h(x(t),v(t))g_2(v^*)}\right) \\ &\quad - \frac{h(x^*,v^*)}{\beta_1}\int_0^\infty f_1(\tau)c\left(\frac{\beta_1 h(x(t-\tau),v(t-\tau))}{\mu_1 g_1(y(t))}\right)d\tau \\ &\quad - \frac{h(x^*,v^*)}{\beta_2}\int_0^\infty f_2(\tau)c\left(\frac{g_2(v^*)g_1(y(t-\tau))}{g_1(y^*)g_2(v(t))}\right)d\tau.\end{aligned} \tag{5.7}$$

By (A_1), we have $(n(x(t)) - n(x^*))(1 - h(x^*,v^*)/h(x(t),v^*)) \le 0$. Lemma 5.1 implies that $y^* \le \hat{y}$ if $R_1 \le 1$. It then follows from the monotonicity of g_1 that $S_1 \le 0$ if $R_1 \le 1$. Assumptions (H_6) and (B_1) imply that

$$\left(\frac{h(x(t),v(t))}{h(x(t),v^*)} - 1\right)\left(\frac{g_2(v^*)}{g_2(v(t))} - \frac{h(x(t),v^*)}{h(x(t),v(t))}\right) \le 0 \text{ for } t \ge 0.$$

The positive definiteness of $c(\theta)$ then implies $dV/dt \le 0$ for all $(x_t, y_t, v_t, z_t) \in \Gamma$, and thus the omega limit sets of solutions are contained in K_1, the largest compact invariant subset of $\{dV/dt = 0\}$. It can be verified that $dV/dt = 0$ implies that

$$x = x^*, z = 0, \frac{\beta_1 h(x(t-\tau),v(t-\tau))}{\mu_1 g_1(y(t))} = \frac{g_2(v^*)g_1(y(t-\tau))}{g_1(y^*)g_2(v(t))} = 1 \text{ if } R_1 < 1, \tag{5.8a}$$

$$x = x^*, \frac{\beta_1 h(x(t-\tau),v(t-\tau))}{\mu_1 g_1(y(t))} = \frac{g_2(v^*)g_1(y(t-\tau))}{g_1(y^*)g_2(v(t))} = 1 \text{ if } R_1 = 1. \tag{5.8b}$$

Along a solution in the set defined by (5.8a), we must have

$$x(t) = x^*,\ z(t) = 0,\ x'(t) = y'(t) = v'(t) \equiv 0.$$

Note that if $x(t) = x^*$ and $z(t) = 0$, then $y(t) = y^*, v(t) = v^*$ are determined. If $R_1 = 1$, then along a solution in the set defined in (5.8b), we have $x(t) = x^*,\ x'(t) = v'(t) \equiv 0$, and hence $v(t) = v^*$. This, together with $g_2(v^*)g_1(y(t-\tau))/(g_1(y^*)g_2(v(t))) = 1$ and the monotonicity of g_1, gives $y(t) = y^*$ and hence $y'(t) = 0$. Therefore, $z(t) = 0$ and thus $K_1 = \{E_1\}$ if $R_1 \le 1 < R_0$. The LaSalle invariance principle and a similar argument as in the proof of Theorem 3.1 show that the unique CTL-IE E_1 is globally asymptotically stable in $\Omega \setminus Z_1^+$.

Assume that $R_1 > 1$. Lemma 5.1 implies that $y^* > \hat{y}$. This, together with the monotonicity of g_1, yields that

$$S_1 = \frac{p}{\beta_1} g_3(z(t))\,(g_1(y^*) - g_1(\hat{y})) > 0 \quad \text{for} \quad z > 0. \tag{5.9}$$

By (5.7), (5.9), and the continuity of the functions $n(x), h(x,v), g_i(y) (i = 1,2,3)$, it follows that $dV/dt > 0$ in a neighborhood of $E_1 = (x^*, y^*, v^*, 0)$, except for the points with $x, y, v > 0$ and $z = 0$. Thus solutions in Γ that start in arbitrarily small neighborhoods of E_1 move away from E_1, except for those starting in $Z_2^+ = \{(x_0, y_0, v_0, 0) \in \mathcal{C}_+^4 : ||x_0|| > 0, ||y_0|| > 0, ||v_0|| > 0\}$, which remain in Z_2^+ and tend to E_1. Therefore, E_1 is unstable if $R_1 > 1$. ∎

5.4. Proof of Theorem 3.4. Assume that $R_1 > 1$. The existence and uniqueness of the CTL-AE $E_2 = (\hat{x}, \hat{y}, \hat{v}, \hat{z})$ of system (3.1) follows from Theorem 2.2. Define a Lyapunov functional $U : \Gamma \to \mathbb{R}$

$$
\begin{aligned}
&U(x_t, y_t, v_t, z_t)\\
&\quad = \; x_t(0) - \int_{\hat{x}}^{x_t(0)} \frac{h(\hat{x},\hat{v})}{h(\theta,\hat{v})}\, d\theta + \frac{1}{\beta_1}\left(y_t(0) - \int_{\hat{y}}^{y_t(0)} \frac{g_1(\hat{y})}{g_1(\theta)}\, d\theta\right)\\
&\qquad + \frac{h(\hat{x},\hat{v})}{\mu_2 g_2(\hat{v})}\left(v_t(0) - \int_{\hat{v}}^{v_t(0)} \frac{g_2(\hat{v})}{g_2(\theta)}\, d\theta\right) + \frac{p}{q\beta_1}\left(z_t(0) - \int_{z_2}^{z_t(0)} \frac{g_3(\hat{z})}{g_3(\theta)}\, d\theta\right)\\
&\qquad + \frac{h(\hat{x},\hat{v})}{\beta_1}\int_0^\infty f_1(\tau)\int_{-\tau}^0 c\left(\frac{h(x_t(s), v_t(s))}{h(\hat{x},\hat{v})}\right) ds d\tau\\
&\qquad + \frac{h(\hat{x},\hat{v})}{\beta_2}\int_0^\infty f_2(\tau)\int_{-\tau}^0 c\left(\frac{g_1(y_t(s))}{g_1(\hat{y})}\right) ds d\tau.
\end{aligned}
$$

Making use of (2.2) and noting that

$$
\begin{aligned}
&\frac{1}{\beta_1}\Big(g_1(y(t)) - g_1(\hat{y})\Big)\Big(\mu_1 + p g_3(z(t))\Big)\\
&\quad = h(\hat{x},\hat{v})\left(\frac{g_1(y(t))}{g_1(\hat{y})} - 1\right) + \frac{p}{\beta_1}\Big(g_1(y(t)) - g_1(\hat{y})\Big)\Big(g_3(z(t)) - g_3(\hat{z})\Big),\\
&\qquad \frac{p}{q\beta_1}\Big(z(t) - \hat{z}\Big)\Big(q g_1(y(t)) - \mu_3\Big) = \frac{p}{\beta_1}\Big(z(t) - \hat{z}\Big)\Big(g_1(y(t)) - g_1(\hat{y})\Big),
\end{aligned}
$$

we can express the time derivative of U along a positive solution of system (3.1) as

$$
\frac{dU}{dt} = n(x(t))\left(1 - \frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})}\right) + h(x(t),v(t))\frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})} - \frac{h(\hat{x},\hat{v})}{g_2(\hat{v})} g_2(v(t)) + Q_1,
$$

where

$$
\begin{aligned}
Q_1 = \; & h(\hat{x},\hat{v}) \ln \frac{h(\hat{x},\hat{v}) g_2(v(t))}{h(x(t),v(t)) g_2(\hat{v})} - \frac{h(\hat{x},\hat{v})}{\beta_2}\int_0^\infty f_2(\tau) c\left(\frac{\beta_2 k g_1(y(t-\tau))}{\mu_2 g_2(v(t))}\right) d\tau\\
& - \frac{h(\hat{x},\hat{v})}{\beta_1}\int_0^\infty f_1(\tau) c\left(\frac{h(x(t-\tau), v(t-\tau)) g_1(\hat{y})}{h(\hat{x},\hat{v}) g_1(y(t))}\right) d\tau.
\end{aligned}
$$

Note that $n(\hat{x}) = h(\hat{x},\hat{v})$, and then we have

$$
\begin{aligned}
\frac{dU}{dt} = \; & (n(x(t)) - n(\hat{x}))\left(1 - \frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})}\right) + Q_2\\
& - \frac{h(\hat{x},\hat{v})}{\beta_1}\int_0^\infty f_1(\tau) c\left(\frac{h(x(t-\tau), v(t-\tau)) g_1(\hat{y})}{h(\hat{x},\hat{v}) g_1(y(t))}\right) d\tau\\
& - \frac{h(\hat{x},\hat{v})}{\beta_2}\int_0^\infty f_2(\tau) c\left(\frac{\beta_2 k g_1(y(t-\tau))}{\mu_2 g_2(v(t))}\right) d\tau,
\end{aligned}
$$

where

$$\begin{aligned}Q_2 = {} & n(\hat{x}) - n(\hat{x})\frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})} + h(x(t),v(t))\frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})} \\ & - \frac{h(\hat{x},\hat{v})}{g_2(\hat{v})}g_2(v(t)) + h(\hat{x},\hat{v})\ln\frac{h(\hat{x},\hat{v})g_2(v(t))}{h(x(t),v(t))g_2(\hat{v})} \\ = {} & h(\hat{x},\hat{v})\left[\frac{g_2(v(t))}{g_2(\hat{v})}\left(\frac{h(x(t),v(t))}{h(x(t),\hat{v})}-1\right)\left(\frac{g_2(\hat{v})}{g_2(v(t))}-\frac{h(x(t),\hat{v})}{h(x(t),v(t))}\right)\right. \\ & \left. - c\left(\frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})}\right) - c\left(\frac{h(x(t),\hat{v})g_2(v(t))}{h(x(t),v(t))g_2(\hat{v})}\right)\right].\end{aligned}$$

Thus

$$\begin{aligned}\frac{dU}{dt} = {} & (n(x(t)) - n(\hat{x}))\left(1 - \frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})}\right) \\ & + h(\hat{x},\hat{v})\frac{g_2(v(t))}{g_2(\hat{v})}\left(\frac{h(x(t),v(t))}{h(x(t),\hat{v})}-1\right)\left(\frac{g_2(\hat{v})}{g_2(v(t))}-\frac{h(x(t),\hat{v})}{h(x(t),v(t))}\right) \\ & - h(\hat{x},\hat{v})c\left(\frac{h(\hat{x},\hat{v})}{h(x(t),\hat{v})}\right) - h(\hat{x},\hat{v})c\left(\frac{h(x(t),\hat{v})g_2(v(t))}{h(x(t),v(t))g_2(\hat{v})}\right) \\ & - \frac{h(\hat{x},\hat{v})}{\beta_1}\int_0^\infty f_1(\tau)c\left(\frac{h(x(t-\tau),v(t-\tau))g_1(\hat{y})}{h(\hat{x},\hat{v})g_1(y(t))}\right)d\tau \\ & - \frac{h(\hat{x},\hat{v})}{\beta_2}\int_0^\infty f_2(\tau)c\left(\frac{\beta_2 k g_1(y(t-\tau))}{\mu_2 g_2(v(t))}\right)d\tau.\end{aligned}$$

It follows from (A_2) that $(n(x(t)) - n(\hat{x}))(1 - h(\hat{x},\hat{v})/h(x(t),\hat{v})) \le 0$ for $t \ge 0$, and the equality holds only if $x(t) \equiv \hat{x}$. Assumptions (H_6) and (B_2) imply that

$$\left(\frac{h(x(t),v(t))}{h(x(t),\hat{v})}-1\right)\left(\frac{g_2(\hat{v})}{g_2(v(t))}-\frac{h(x(t),\hat{v})}{h(x(t),v(t))}\right) \le 0.$$

Therefore $dU/dt \le 0$ for all $(x_t, y_t, v_t, z_t) \in \Gamma$, and thus the omega limit sets of solutions are contained in K_2, the largest compact invariant subset of $\{dU/dt = 0\}$. It can be verified that $dU/dt = 0$ implies

$$x(t) = \hat{x}, \quad \frac{h(x(t-\tau),v(t-\tau))g_1(\hat{y})}{h(\hat{x},\hat{v})g_1(y(t))} = \frac{\beta_2 k g_1(y(t-\tau))}{\mu_2 g_2(v(t))} = 1 \ \text{ for } \ \tau \in [0,\infty),$$

and $x'(t) = v'(t) \equiv 0$. Note that once $x(t) = \hat{x}$ is given, $v(t) = \hat{v}$. This, together with $h(x(t-\tau),v(t-\tau))g_1(\hat{y}) = h(\hat{x},\hat{v})g_1(y(t))$ and the monotonicity of g_1, shows that $y(t) = \hat{y}$. Thus,

$$0 = y'(t) = \beta_1 h(\hat{x},\hat{v}) - \mu_1 g_1(\hat{y}) - p g_1(\hat{y}) g_3(z(t)),$$

which implies that $z(t) = \hat{z}$. Therefore, $K_2 = \{E_2\}$ and the global stability of E_2 in the interior of Ω follows from the LaSalle invariance principle and a similar argument as in the proof of Theorem 3.1. ∎

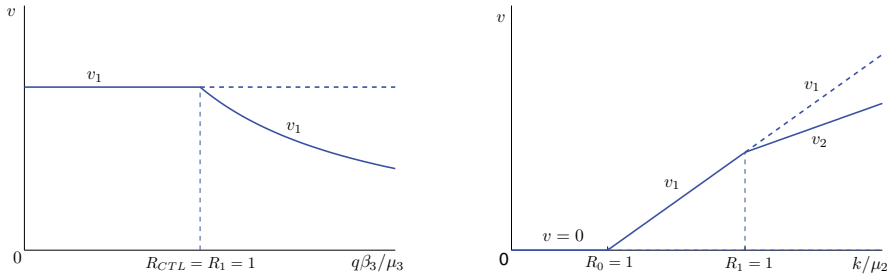

FIG. 6.1. *Equilibrium viral load of system* (4.2) *versus a combination of CTL parameters,* $q\beta_3/\mu_3$ *(left), and a combination of viral parameters,* k/μ_2 *(right).*

6. Conclusion and discussion. In this paper we have considered an in-host model, given by (1.2) together with assumptions (H_1)–(H_6), which describes the dynamics among healthy target cells, actively infected target cells, mature viruses, and virus-specific CTLs. The model allows for very general target-cell dynamics, $n(x)$, including a nonlinear incidence, $h(x, v)$, infinitely distributed intracellular delays, f_i, and state-dependent removal functions, g_i $(i = 1, 2, 3)$. This general model includes many existing models in the literature as special cases.

It is shown that this model admits three types of equilibria: infection-free equilibria, CTL-inactivated equilibria (CTL-IE), and CTL-activated equilibria (CTL-AE). The dynamics of our model are shown to be determined by two critical values: the basic reproduction number for viral infection, R_0, and the viral reproduction number at the CTL-IE, R_1. More precisely, we have proved the following: (i) if $R_0 \leq 1$, then the infection-free equilibrium E_0 is globally stable; (ii) if $R_0 > 1 \geq R_1$ and (A_1) holds, then model (1.2) admits a unique CTL-IE (E_1), which is globally stable provided further that (B_1) holds; (iii) if $R_1 > 1$ and (A_2) holds, then model (1.2) possesses a unique CTL-AE (E_2), which is globally stable provided that (B_2) is further satisfied. For case (i), this means that the viruses are cleared; (ii) implies that the infection becomes chronic with no sustained immune responses; and (iii) indicates that the infection becomes chronic with persistent immune responses.

It is important to note that even though increasing R_1 through the threshold leads to a stability switch from the CTL-IE E_1 to the CTL-AE E_2, this does not imply that the viral load at the equilibrium decreases as R_1 increases across the threshold. Figure 6.1 (left) shows a plot of viral load as a function of $q\beta_3/\mu_3$, a combination of CTL parameters giving a measure of the CTL response. Both R_1 and the CTL reproduction number, R_{CTL}, increase with this parameter combination, and as the two reproduction numbers pass through one, the immune response lowers the equilibrium viral load from v^* to $\hat{v}$. In contrast, Figure 6.1 (right) shows the dependence of the same equilibria, again as both R_1 and R_{CTL} increase through one, but by increasing k/μ_2, which is a combination of viral parameters measuring the virus replication rate. Again, both R_1 and R_{CTL} increase through the threshold as k/μ_2 is increased, and although there is a switch from CTL inactivation to CTL activation as the threshold is crossed, the equilibrium viral load continues to increase. Thus the bifurcation to CTL activation does not imply a reduction in viral load; equilibrium viral loads do not always decrease as R_{CTL}, or R_1, passes through the bifurcation threshold. This suggests that analysis of models for treatment should focus on model outputs such as viral loads and on simple parameter combinations.

Theorems 3.1–3.4 suggest that if (A_1) and (B_1) (or (A_2) and (B_2)) hold, then the intracellular delays (between healthy target cells and actively infected target cells, and between actively infected target cells and mature viruses) do not induce sustained oscillations. However, the values and forms of delays do influence the values of R_0 and R_1 and thus have impacts on the viral dynamics. For instance, considering the general model (4.2) with discrete delays in stages 1 and 2, denoted by τ_1 and τ_2, respectively, the value of R_0 would be lower than one and thus the viruses can be cleared in the host if $\tau_1 + \tau_2$ is large enough. Hence, increasing delays in replication and infection can decrease R_0 and R_1, leading to inability of the virus to invade the host.

Our global stability results cover and improve many existing ones (see Remarks 4.1 and 4.2). Moreover, our results can apply to models with nonmonotone nonlinear functions, for which very limited results have been established. Most existing global stability results for in-host models appearing in the literature require the monotonicity of the nonlinear functions. For example, $h(x, v)$ is assumed to be increasing with respect to x and v in [13]. However, in viral dynamics, monotonicity is often not expected [31]. In this sense, our work is an important extension. A concrete example (Example 4.3) is given to demonstrate the applicability of our results when $n(x)$ and $h(x, v)$ are nonmonotone. As shown in Figure 4.1, if (A_1) (resp., (A_2)) does not hold, then the global stability of E_1 (E_2) is not taken for granted and periodic solutions may exist.

If the distribution functions f_1, f_2, f_3 in our model are chosen as gamma functions, then our model can be rewritten as an ordinary differential equation model with multiple intracellular stages [24]. Our analysis shows that no surprising dynamics will appear if we only let f_1 and f_2 be gamma functions. Note that our global stability result for the CTL-AE E_2 of system (3.1) is established under the assumption that there is no delay in the CTL response. If there is a delay in the CTL immune response, then it is natural to expect that the CTL-AE E_2 is globally stable when the delay is sufficiently small. Deriving conditions (very likely to be delay dependent) for the global stability of (3.1) with a nonzero delay in the CTL response process would be very interesting but challenging, as a large delay may destabilize the CTL-AE leading to stable periodic oscillations [20, 36]. Figure 4.1 suggests that the occurrence of sustained oscillations critically depends on the target-cell dynamics and/or the delay in the CTL response process. This suggests that the system may exhibit rich dynamics beyond globally stable equilibria if f_3 is a gamma function.

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