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Research Article

Constructing Lyapunov functionals for a delayed viral infection model with multitarget cells, nonlinear incidence rate, state-dependent removal rate

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Abstract

For a viral infection model with multitarget cells, nonlinear incidence rate, state-dependent removal rate and distributed delays, we analyze the global asymptotic behavior of its solutions. In this model, the rate of contact between viruses and uninfected target cells and state-dependent removal rate of infected cells depend on general nonlinear functions. The basic reproduction number for the model is discussed. Under certain assumptions, it is shown that if $\Re_0 \leq 1$, then the infection-free equilibrium P_0 is globally stable and the viruses are cleared; If $\Re_0 > 1$, then there is a unique infection equilibrium, which is globally stable implying the infection becomes chronic. The global stability results are achieved by appealing to the direct Lyapunov method.

Keywords: Viral infection model, nonlinear incidence rates, state-dependent removal rate, Lyapunov functionals, global stability.
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1. Introduction

In recent years, the study of HIV infection model have attracted the attention of mathematicians and biologists. Some basic dynamical properties, such as positive invariance properties, boundedness of the

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model solutions, local stability, uniform persistence and global stability are important from the view of realistic situation. They ensure that whether the viruses are cleared or not.

Since the pioneering frame work of [1, 2, 8, 17, 18], many works have focused on the global stability of equilibria in viral dynamical models, which play a crucial role in implementing effective antiviral drug therapies to clear viruses [1] and evaluating treatment strategies for infections and to establish thresholds for treatment rates.

Systems of differential equations are also used as HIV infection model with transitions between uninfected cells and infected cells. The classical HIV infection divided the cells population into following three main compartments depending on cell status, target cells, infected cells producing viruses, matured virus particles, and its concentrations are denoted by $x(t)$, $y(t)$ and $v(t)$, respectively. Dynamics behaviors for the interactions between target cells, infected cells producing viruses, matured viruses and immune cells are investigated by many authors in the literature, [1, 8, 10, 11, 12, 17, 18, 19, 23, 26, 28]. These models focused on two dynamics scenarios: (i) whether the viruses are cleared; (ii) whether life long infection-free can be achieved in the host, or sustained oscillatory viral loads phenomenon occurs.

Bilinear incidence rate associated with the mass action principle is insufficient to describe the infection process in detail. To model the realistic situation, many authors are devoted to nonlinear incidence rate, the rate of contact between viruses and uninfected target cells, The following incidence rate is proposed in the literature, e.g., Holling type II functional response, $\frac{\beta xv}{1+\alpha x}$ [13], Beddington-DeAngelis functional response, $\frac{\beta xv}{1+ax+bv}$ [9, 16], $c(x)f(v)$ [7], and $F(x,v)$ [10, 19].

Delay differential equations (DDEs) frequently provide quite realistic models in mathematical biology in general. [8] first incorporated an intracellular delay to analyze the data from infected patients and clinical experiment. Subsequently, there are two delays incorporate intracellular delays into viral infection model. One is the delay between viral infection of a healthy target cell and the production of an actively infected target cell (it is known as infection delay); the other is the delay between viral RNA transcription and viral release and maturation (it is known as maturation delay). We refer the reader to discrete delays [15, 16, 28], finite distributed delays [16, 25] and infinite distributed delays [14, 19, 23].

With the deepening of the research and more recent findings, it is evidenced that interactions of some types of viruses inside the human body attack more than one class of target cells. The viral infection models describing the interaction of the virus with more than one class of target cells can be found in the literature, such as [3, 4, 6, 18, 21] and references cited therein. In these models, HIV attack two classes of target cells, $CD4^+$ T cells and macrophages. We would like to mention a recent work of Elaiw [4], where the virus particles is assumed to infect n classes of target cells. The model with multitarget cells and two types of discrete-time delays, infection delays, τ_i, and maturation delays, ω_i, $i = 1, 2, \ldots, n$ investigated (may be the first) in [4] is given by the following system of delay differential equations:

$$\begin{cases} \dfrac{dx_i(t)}{dt} = \lambda_i - d_i x_i(t) - \beta_i x_i(t) v(t), \\ \dfrac{dy_i(t)}{dt} = e^{-m_i\tau_i}\beta_i x_i(t-\tau_i) v(t-\tau_i) - b_i y_i(t), \\ \dfrac{dv(t)}{dt} = \displaystyle\sum_{i=1}^{n} e^{-n_i\omega_i} k_i y_i(t-\omega_i) - cv(t), \end{cases} \tag{1.1}$$

where for $i = 1, 2, \ldots, n$, λ_i, d_i and β_i represent the rates of which new target cells are generated, the death rate constants, and the infection rate constants, respectively. The infected cells die with rate constants b_i. The virus particles are produced by the infected cells with rate constants k_i, and are cleared with rate constant c. m_i is the constant death rate for infected target cells of class i, but not yet virus-producing cells. $e^{-m_i\tau_i}$ represents the survival probability of newly infected cells for the time period from $t-\tau_i$ to t due to viral infection. $e^{-n_i\omega_i}$ represents the survival probability of an immature virus for the time period from $t-\omega_i$ to t, where n_i is constant.

Motivated by the above works, in the present paper, we introduce a virus infection model with multitarget cells, nonlinear incidence rate, nonlinear death rates of the infected target cells (depend on

its concentrations) and two kinds of finite distributed delays. The model to be studied takes the following form:

$$\begin{cases} \dfrac{dx_i(t)}{dt} = s - d_i x_i(t) - h_i(x_i(t), v(t)), \\ \dfrac{dy_i(t)}{dt} = \displaystyle\int_0^{a_i} f_i(\tau) e^{-m_i\tau} h_i(x_i(t-\tau), v(t-\tau)) d\tau - b_i G(y_i(t)), \\ \dfrac{dv(t)}{dt} = \displaystyle\sum_{i=1}^{n} k_i \int_0^{a_i} g_i(\tau) e^{-n_i\tau} G(y_i(t-\tau)) d\tau - cv(t), \end{cases} \tag{1.2}$$

where $x_i(t)$ and $y_i(t)$ represent the concentrations of the uninfected target cells and infected cells of class i, respectively, $v(t)$ is the concentration of the free virus particles. The incidence of new infections of class i between viruses and uninfected target cells occurs at a rate $h_i(x_i(t), v(t))$. The death rates of the infected target cells of class i depends on its concentrations which is given by $G(y_i(t))$. a_i is the limit superior of the infection and maturation delay. Factor $e^{-m_i\tau}$ and $e^{-n_i\tau}$ account for the loss of target cells due to viral infection and the loss of infected target cells during time period $[t-\tau, t]$, respectively. $f_i(\tau)$ and $g_i(\tau)$ denote the probability distribution of random variable τ.

The object of this paper is to establish global stability results and find sufficient conditions under which sustained oscillations of viral loads are impossible for a viral model with multitarget cells, nonlinear incidence rate, nonlinear death rates of the infected target cells and general forms of delays. Since local stability alone will not rule out existence of periodic solutions, to overcome this difficulty, it is necessary to rigorously establish the global stability of equilibria. Our global stability result for the infection equilibrium is new for in-host models with finite distributed intracellular delays. Our proof utilizes the Lyapunov method motivated by the work in [3, 9, 10, 12, 14, 15, 16, 19, 20, 21, 22, 23, 24, 25, 26, 27].

Our paper is organized as follows. In the next section, we discuss some preliminary results concerning the well-posedness of system (1.2) as well as existence and of equilibria, and derive the basic reproduction number $\Re_0$. Our main results, global stability results, are stated in section 3, which is a sharp threshold result under certain conditions. One example allowing $n = 1$ is given in Section 4.

2. Preliminaries

2.1. Basic assumptions

In this subsection, the restrictions on the functions $h_i(x_i(t), v(t))$ and $G(y_i(t))$ in system (1.2) are common and can be found in [10, 19]. We assume that the functions $h_i(x_i(t), v(t))$ and $G(y_i(t))$ in system (1.2) are always positive, differentiable, and monotonically increasing with respect to variables $x_i > 0$, $y_i > 0$, and $v > 0$, respectively, and $h_i(x_i(t), v(t))$ is concave with respect to v. To be specific, we have the following assumption:

Assumption 2.1. *Consider system* (1.2)*, for $i = 1, 2, \ldots, n$, we make the following assumptions on nonlinear functions h_i and G:*

(i) *Nonlinear incidence functions $h_i(x_i(t), v)$ are continuously differentiable; $h_i(x_i(t), v(t))$, $\frac{\partial h_i(x_i(t), v(t))}{\partial v}$, $\frac{\partial h_i(x_i(t), v(t))}{\partial x_i}$ and $-\frac{\partial h_i^2(x_i(t), v(t))}{\partial v^2}$ are positive for any $x_i(t) \in (0, \infty)$, $v \in (0, \infty)$; $h_i(x_i(t), v(t)) = 0$ if and only if $x_i(t) = 0$ or $v = 0$; $\frac{\partial h_i(x_i(t), 0)}{\partial v} > 0$ for $x_i(t) > 0$ and $v(t) > 0$.*

(ii) *State-dependent removal function G satisfies: $G(0) = 0$, $G'(y_i(t)) > 0$ for $y_i(t) > 0$ and there exists $M_i > 0$ such that $G(y_i(t)) \geq M_i y_i(t)$ for $y_i(t) > 0$. Further, $\lim\limits_{y_i \to +\infty} G(y_i(t)) = +\infty$.*

(iii) *$\frac{\partial h_i(x_i(t), 0)}{\partial v(t)}$ is increasing with respect to $x_i(t) > 0$.*

(iv) *Probability distributions functions $f_i(\tau), g_i(\tau) \in [0, a_i] \to R^+$, where a_i is the limit superior of the infection and maturation delay. Further, $\int_0^{a_i} f_i(\tau) d\tau = \int_0^{a_i} g_i(\tau) d\tau = 1$, and $\int_0^{a_i} f_i(\tau) e^{sr} dr, \int_0^{a_i} g_i(\tau) e^{sr} dr < \infty$, where s is a positive constant.*

(i) of Assumptions 2.1 are all biologically relevant for realistic infection dynamics and are fulfilled 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.
(ii) of Assumptions 2.1 is mathematical required for the existence of infection equilibrium. From (iv) of Assumptions 2.1, it follows that $f_i(\tau)e^{-m_i\tau}$ and $g_i(\tau)e^{-n_i\tau}$ are the product of a probability density function and survival distribution, respectively. So for $i = 1, 2, \ldots, n$, it is possible to have the total integral along the positive real line being strictly less than one, that is, $0 < \int_0^{a_i} f_i(\tau)e^{-m_i\tau}d\tau \leq 1$ and $0 < \int_0^{a_i} g_i(\tau)e^{-n_i\tau}d\tau \leq 1$.

2.2. Non-negativity and boundedness of solutions

The initial conditions for system (1.2) take the form:

$$\begin{cases} x_i(\theta) = \phi_i(\theta),\ y_i(\theta) = \psi_i(\theta),\ v(\theta) = \chi(\theta), \\ \phi_i(\theta),\ \psi_i(\theta),\ \chi(\theta) \geq 0,\ \theta \in [-\tau, 0], \\ \phi_i(0),\ \psi_i(0),\ \chi(0) > 0,\ i = 1, 2, 3, \ldots, n, \end{cases} \tag{2.1}$$

where $(\phi_i(\theta), \psi_i(\theta), \chi(\theta)) \in \mathcal{C}([-\tau, 0], \mathrm{R}_+^{2n+1})$. In the following, we establish the non-negativity and boundedness of solutions of (1.2).

Theorem 2.2. *For $i = 1, 2, \ldots, n$, let $(x_i(t), y_i(t), v(t))$ be any solutions of system (1.2) satisfying the initial conditions (2.1), then $x_i(t), y_i(t), v(t)$ are all non-negative for $t > 0$ and ultimately bounded.*

Proof. First, for $i = 1, 2, \ldots, n$, we prove that $x_i(t) > 0$ for all $t \geq 0$. Assume the contrary and let $t_0 > 0$ be such that $x_i(t_0) < 0$. Set $t_{01} = \inf\{0 < t < t_0 : x_i(t) < 0\}$. Then $x_i(t_{01}) = 0$, and from the first equation of system (1.2) we have $\frac{dx_i(t_{01})}{dt} = s > 0$. Hence $x(t) < 0$ for $t \in (t_{01} - \epsilon, t_{01})$ and $\epsilon > 0$ sufficiently small. This contradicts $x(t) \geq 0$ for $t \in (0, t_{01}]$. It follows that for $i = 1, 2, \ldots, n$, $x_i(t) > 0$ for $t \geq 0$.

Furthermore, if there exists $t_1 > 0$, such that $y_i(t_1) = 0$, and $y_i(t) > 0$ for all $t \in (0, t_1)$. By the second equation of system (1.2), we can easily obtain $\frac{dy_i(t_1)}{dt} \geq -b_iG(y_i(t_1)) = 0$. This is a contradiction to the assumption of $\frac{dy_i(t_1)}{dt} < 0$. Hence, $y_i(t) > 0$, for all $t \geq 0$. Finally, by the last equation of system (1.2), we have

$$v(t) = e^{-ct}\left(v(0) + \int_0^t e^{cs}\sum_{i=1}^n k_i \int_0^{a_i} g_i(\tau)e^{-n_i\tau}G(y_i(s-\tau))d\tau ds\right).$$

Hence, $v(t) \geq 0$, for all $t \geq 0$.

Next we show that the solution is ultimately bounded. It follows from the first equation of system (1.2) that

$$\frac{dx_i(t)}{dt} \leq s - d_ix_i(t).$$

Thus $\limsup_{t\to\infty} x_i(t) \leq s/d_i$ and $x_i(t)$ is ultimately bounded. Let

$$V_i(t) = \int_0^{a_i} f_i(\tau)e^{-m_i\tau}x_i(t-\tau)d\tau + y_i(t),\ i = 1, 2, \ldots, n,$$

then a time derivative of $V_i(t)$ along the trajectories of system (1.2) satisfies

$$\begin{aligned} \frac{dV_i(t)}{dt} &= \int_0^{a_i} f_i(\tau)e^{-m_i\tau}\Big(s - d_ix_i(t-\tau) - h_i(x_i(t-\tau), v(t-\tau))\Big)d\tau \\ &\quad + \int_0^{a_i} f_i(\tau)e^{-m_i\tau}h_i(x_i(t-\tau), v(t-\tau))d\tau - b_iG(y_i(t)) \\ &= s\beta_i - d_i\int_0^{a_i} f_i(\tau)e^{-m_i\tau}x_i(t-\tau)d\tau - b_iG(y_i(t)), \end{aligned}$$

where β_i is defined by

$$\beta_i = \int_0^{a_i} f_i(\tau) e^{-m_i \tau} d\tau. \tag{2.2}$$

It follows from (ii) of Assumption 2.1 that $G(y_i(t)) \geq M_i y_i(t)$. Thus,

$$\frac{dV_i(t)}{dt} \leq s\beta_i - \varrho_i V_i(t),$$

where $\varrho_i = \min\{d_i, b_i M_i\}$. It follows that $\limsup_{t\to\infty} V_i(t) \leq \frac{s\beta_i}{\varrho_i}$.

Since $x_i(t) \geq 0$, we know that $\limsup_{t\to\infty} y_i(t) \leq \frac{s\beta_i}{\varrho_i}$. Consequently, from the third equation of (1.2), we obtain that for any $\varepsilon > 0$, there exists $T > 0$ such that for $t > T$,

$$\frac{dv(t)}{dt} \leq \sum_{i=1}^{n} k_i \eta_i G\left(\frac{s\beta_i}{\varrho_i} + \varepsilon\right) - cv(t),$$

immediately follows, where η_i is defined by

$$\eta_i = \int_0^{a_i} g_i(\tau) e^{-n_i \tau} d\tau. \tag{2.3}$$

It follows that $\limsup_{t\to\infty} v(t) \leq \frac{\sum_{i=1}^{n} k_i \eta_i G\left(\frac{s\beta_i}{\varrho_i}+\varepsilon\right)}{c}$. Therefore, $x_i(t), y_i(t)$ and $v(t)$ are ultimately uniformly bounded on $(0, \infty)$. □

Theorem 2.2 implies that omega limit sets of system (1.2) are contained in the following bounded feasible region:

$$\Gamma = \left\{\phi_i(\theta), \psi_i(\theta), \chi(\theta) \in \mathcal{C}([-\tilde{h}, 0], \mathbb{R}_+^{2n+1}) : \ \|x_i(t)\| \leq s/d_i, \right.$$
$$\left. \|y_i(t)\| \leq \frac{s\beta_i}{\varrho_i}, \ \|v(t)\| \leq \frac{\sum_{i=1}^{n} k_i \eta_i G\left(\frac{s\beta_i}{\varrho_i}\right)}{c}, \ i = 1, 2, \ldots, n \right\}.$$

It can be verified that the region Γ is positively invariant with respect to model (1.2) and that the model is well-posed.

2.3. Reproduction numbers and steady states

The basic reproduction number of the virus for system (1.2) is

$$\Re_0 = \sum_{i=1}^{n} \Re_i, \tag{2.4}$$

where

$$\Re_i = \frac{\beta_i \eta_i k_i}{b_i c} \cdot \frac{\partial h_i(x_i^0, 0)}{\partial v}$$

and β_i, η_i are defined in (2.2) and (2.3), respectively. We will know that if $\Re_0 \leq 1$, then infection-free equilibrium $P^0 = (x_1^0, 0, \ldots, x_n^0, 0, 0)$, $x_i^0 = s/d_i$, is the unique steady state. If $\Re_0 > 1$, the system (1.2) has an infection equilibrium $P^* = (x_1^*, y_1^*, \ldots, x_n^*, y_n^*, v^*)$, which satisfies:

$$\begin{cases} s - d_i x_i^* = h_i(x_i^*, v^*), \\ b_i G(y_i^*) = \beta_i h_i(x_i^*, v_i^*), \\ cv^* = \sum_{i=1}^{n} \eta_i k_i G(y_i^*). \end{cases} \tag{2.5}$$

In the following, we get a lemma which gives the existence condition of a positive equilibrium.

Lemma 2.3. *Suppose that the functions $h_i(x_i(t), v(t))$ and $G(y_i)$ satisfy the Assumption 2.1. If $\Re_0 > 1$, then there exists an infection equilibrium*

$$P^* = (x_1^*, y_1^*, x_2^*, y_2^*, \ldots, x_i^*, y_i^*, v^*).$$

Proof. Let the right-hand sides of the three equations in system (1.2) equal zero, and we have that

$$s - d_i x_i = h_i(x_i, v) = \frac{b_i G(y_i)}{\beta_i} = \frac{b_i c v - b_i \sum\limits_{j=1, j\neq i}^{n} \eta_j k_j G(y_j)}{\beta_i k_i \eta_i}. \tag{2.6}$$

After substituting the expression of x_i by v, we obtain the following equation for v:

$$H_i(v) = h_i\left(\frac{s\beta_i k_i \eta_i - b_i c v + b_i \sum\limits_{j=1, j\neq i}^{n} \eta_j k_j G(y_j)}{d_i \beta_i k_i \eta_i}, v\right) - \frac{b_i c v - b_i \sum\limits_{j=1, j\neq i}^{n} \eta_j k_j G(y_j)}{\beta_i k_i \eta_i} = 0. \tag{2.7}$$

It is obvious that $H_i(0) = 0$, and when $v = v_0 = \frac{s k_i \beta_i \eta_i + b_i \sum\limits_{j=1, j\neq i}^{n} \eta_j k_j G(y_j)}{b_i c}$, $H_i(v_0) = h_i(0, v_0) - s = -s < 0$. Since $H_i(v)$ is continuous for $v \geq 0$, it gives that

$$\begin{aligned} H_i'(0) &= \lim_{v \to 0^+} \frac{H_i(v) - H_i(0)}{v} \\ &= \frac{\partial h_i(x_i^0, 0)}{\partial v} - \frac{b_i c}{k_i \beta_i \eta_i} - \frac{b_i c}{d_i k_i \beta_i \eta_i} \frac{\partial h_i(x_i^0, 0)}{\partial x_i} \\ &= \frac{b_i c}{k_i \beta_i \eta_i}(\Re_i - 1). \end{aligned}$$

Thus, $\Re_i > 1$ ensures that $H_i'(0) > 0$, and there exists some $v^* \in (0, v_0)$ such that $H_i(v^*) = 0$ for $\Re_0 > 1$. Knowing the value of v^*, from the monotonicity of the function $G(y_i)$ and (2.6), the values of x_i^* and y_i^* can be computed. In fact, it is easy to check that $g_i(x_i) = s - d_i x_i - h_i(x_i, v^*)$ has a positive solution x_i^* since $g_i(0) > 0$ and $g_i(\infty) = -\infty$. Further, note that

$$f_i(y_i) = G(y_i) - \frac{c v^* - \sum\limits_{j=1, j\neq i}^{n} \eta_j k_j G(y_j)}{k_i \eta_i} = 0$$

has a positive solution, since $f_i(0) = -\frac{c v^*}{k_i \eta_i} < 0$ and

$$\lim_{y_i \to +\infty} f_i(y_i) = \lim_{y_i \to +\infty} G(y_i) - \frac{s\beta_i}{b_i} \to \infty.$$

Therefore, we have proved the existence of the infection equilibrium P^* for system (1.2) under condition $\Re_0 > 1$. □

3. Main Results

In this section, we consider the global asymptotic stability of the two equilibria. Throughout the paper, for easy to notation, we adopt $H(s) = s - 1 - \ln s \geq H(1) = 0$ to simplify many of the expressions which follow.

Theorem 3.1. *Consider system* (1.2) *and $\Re_0$ is defined by* (2.4). *Suppose Assumption 2.1 holds and $\Re_0 \leq 1$, then the infection-free equilibrium P^0 of* (1.2) *is globally asymptotically stable.*

Proof. For $i = 1, 2, \ldots, n$, we define a Lyapunov functional $L_0(x_i, y_i, v)$ as follows:

$$L_0(x_i, y_i, v) = \sum_{i=1}^{n} \frac{\beta_i \eta_i k_i}{b_i} \left[x_i - x_i^0 - \int_{x_i^0}^{x_i} \lim_{v \to 0} \frac{h_i(x_i^0, v)}{h_i(\theta, v)} d\theta + \frac{y_i}{\beta_i} + \frac{1}{\beta_i} W_1 + \frac{b_i}{\beta_i \eta_i} W_2 \right] + v(t),$$

where β_i and η_i are defined in (2.2) and (2.3), and

$$W_1 = \int_0^{a_i} f_i(\tau) e^{-m_i \tau} \int_0^{\tau} h_i(x_i(t-s), v(t-s)) ds d\tau,$$
$$W_2 = \int_0^{a_i} g_i(\tau) e^{-n_i \tau} \int_0^{\tau} G(y_i(t-s)) ds d\tau.$$

The functional L_0 is non-negative defined with respect to the infection-free equilibrium $P^0 = (x_1^0, 0, \ldots, x_n^0, 0, 0)$, which is a global minimum. Calculating the time derivative of W_1 and W_2, we have

$$\begin{aligned} \frac{dW_1}{dt} &= \beta_i h_i(x_i, v) - \int_0^{a_i} f_i(\tau) e^{-m_i \tau} h_i(x_i(t-\tau), v(t-\tau)) d\tau, \\ \frac{dW_2}{dt} &= \eta_i G(y_i) - \int_0^{a_i} g_i(\tau) e^{-n_i \tau} G(y_i(t-\tau))) d\tau. \end{aligned}$$

Calculating the time derivative of L_0 along solutions of system (1.2) gives

$$\begin{aligned} \frac{dL_0(x_i, y_i, v)}{dt} = & \sum_{i=1}^{n} \frac{\beta_i \eta_i k_i}{b_i} d_i x_i \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \to 0} \frac{h_i(x_i^0, v)}{h_i(x_i, v)} \right) \\ & + cv \left(\sum_{i=1}^{n} \frac{\beta_i \eta_i k_i}{b_i} \frac{h_i(x_i, v)}{cv} \lim_{v \to 0} \frac{h_i(x_i^0, v)}{h_i(x_i, v)} - 1 \right). \end{aligned}$$

From (i) of Assumption 2.1, it follows that $\left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \to 0} \frac{h_i(x_i^0, v)}{h_i(x_i, v)} \right) \leq 0$, and

$$\frac{h_i(x_i(t), v)}{v} \lim_{v \to 0} \frac{h_i(x_i^0, v)}{h_i(x_i, v)} \leq \lim_{v \to 0} \frac{h_i(x_i, v)}{v} \cdot \frac{\frac{\partial h_i(x_i^0, 0)}{\partial v}}{\frac{\partial h_i(x_i, 0)}{\partial v}} = \frac{\partial h_i(x_i^0, 0)}{\partial v}.$$

Hence we have

$$\frac{dL_0(x_i, y_i, v)}{dt} \leq \sum_{i=1}^{n} \frac{\beta_i \eta_i k_i}{b_i} d_i x_i \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \to 0} \frac{h_i(x_i^0, v)}{h_i(x_i, v)} \right) + cv(\Re_0 - 1),$$

Thus, $\Re_0 \leq 1$ ensures that $\frac{dL_0(x_i, y_i, v)}{dt} < 0$ for all $x_i > 0$, $y_i > 0$, and $v > 0$. And $\frac{dL_0(x_i, y_i, v)}{dt} = 0$ if and only if $x_i = x_i^0$, $v = 0$ for $\Re_0 \leq 1$. It is easy to show that $P^0 = (x_1^0, 0, \ldots, x_n^0, 0, 0)$ is the largest invariant set in $\{(x_i, y_i, v) \mid \frac{dL_0(x_i, y_i, v)}{dt} = 0\}$. By LaSalle's invariance principle, the equilibrium $P^0 = (x_1^0, 0, \ldots, x_n^0, 0, 0)$ is globally asymptotically stable. This completes the proof. □

Theorem 3.2. *Consider system* (1.2) *and* $\Re_0$ *are defined by* (2.4). *Suppose Assumption 2.1 holds true, the* P^* *of* (1.2) *is a unique infection equilibrium and is globally asymptotically stable if* $\Re_0 \geq 1$.

Proof. Define a Lyapunov functional $L_1(x_i, y_i, v)$ as follows:

$$L_1(x_i, y_i, v) = \sum_{i=1}^{n} \frac{\beta_i \eta_i k_i}{b_i} \left[x_i - x_i^* - \int_{x_i^*}^{x_i} \frac{h_i(x_i^*, v^*)}{h_i(\theta, v^*)} d\theta + \frac{1}{\beta_i} \left(y_i - y_i^* - \int_{y_i^*}^{y_i} \frac{G(y_i^*)}{G(\theta)} \right) d\theta \right.$$

$$+\frac{h_i(x_i^*,v^*)}{\beta_i}U_1+\frac{b_iG(y_i^*)}{\beta_i\eta_i}U_2\Big]+v^*H\left(\frac{v}{v^*}\right),$$

where

$$U_1=\int_0^{a_i}f_i(\tau)e^{-m_i\tau}\int_0^{\tau}H\left(\frac{h_i(x_i(t-\theta),v(t-\theta))}{h_i(x_i^*,v^*)}\right)d\theta d\tau,$$
$$U_2=\int_0^{a_i}g_i(\tau)e^{-n_i\tau}\int_0^{\tau}H\left(\frac{G(y_i(t-\theta))}{G(y_i^*)}\right)d\theta d\tau.$$

Calculating the time derivative of U_1 and U_2, we have

$$\frac{dU_1}{dt}=\int_0^{a_i}f_i(\tau)e^{-m_i\tau}\left(\frac{h_i(x_i,v)}{h_i(x_i^*,v^*)}-\frac{h_i(x_i(t-\tau),v(t-\tau))}{h_i(x_i^*,v^*)}+\ln\frac{h_i(x_i(t-\tau),v(t-\tau))}{h_i(x_i,v)}\right)d\tau,$$
$$\frac{dU_2}{dt}=\int_0^{a_i}g_i(\tau)e^{-n_i\tau}\left(\frac{G(y_i)}{G(y_i^*)}-\frac{G(y_i(t-\tau))}{G(y_i^*)}+\ln\frac{G(y_i(t-\tau))}{G(y_i)}\right)d\tau.$$

Calculating the time derivative of $L_1(x_i,y_i,v)$ along solutions of system (1.2) yields

$$\frac{dL_1(x_i,y_i,v)}{dt}=\sum_{i=1}^{n}\frac{\beta_i\eta_ik_i}{b_i}\Big[d_i(x_i^*-x_i)\left(1-\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right)+h_i(x_i^*,v^*)\left(1-\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right)$$
$$+h_i(x_i,v)\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}-\frac{h_i(x_i^*,v^*)}{v^*}v+h_i(x_i^*,v^*)S_1\Big],$$

where

$$\begin{aligned}S_1=&\ 2-\frac{1}{b_iG(y_i)}\int_0^{a_i}f_i(\tau)e^{-m_i\tau}h_i(x_i(t-\tau),v(t-\tau))d\tau\\&-\frac{v^*}{G(y_i^*)\eta_i(t)v}\int_0^{a_i}g_i(\tau)e^{-n_i\tau}G(y_i(t-\tau))d\tau-\ln h_i(x_i,v)\\&+\frac{1}{\beta_i}\int_0^{a_i}f_i(\tau)e^{-m_i\tau}\ln h_i(x_i(t-\tau),v(t-\tau))d\tau-\ln G(y_i)\\&+\frac{1}{\eta_i}\int_0^{a_i}g_i(\tau)e^{-n_i\tau}\ln G(y_i(t-\tau))d\tau\\=&\ \ln\frac{v(t)h_i(x_i^*,v^*)}{v^*h_i(x_i,v)}-\frac{1}{\eta_i}\int_0^{a_i}g_i(\tau)e^{-n_i\tau}H\left(\frac{v^*G(y_i(t-\tau))}{G(y_i^*)v}\right)d\tau\\&-\frac{1}{\beta_i}\int_0^{a_i}f_i(\tau)e^{-m_i\tau}H\left(\frac{\beta_i}{b_iG(y_i)}h_i(x_i(t-\tau),v(t-\tau))\right)d\tau.\end{aligned}$$

It follows that

$$\begin{aligned}\frac{dL_1(x_i,y_i,v)}{dt}=&\sum_{i=1}^{n}\frac{\beta_i\eta_ik_i}{b_i}\Big[d_i(x_i^*-x_i)\left(1-\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right)+h_i(x_i^*,v^*)\left(1-\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right)\\&+h_i(x_i,v)\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}-\frac{h_i(x_i^*,v^*)}{v^*}v+h_i(x_i^*,v^*)\ln\frac{v(t)h_i(x_i^*,v^*)}{v^*h_i(x_i,v)}\\&-\frac{h_i(x_i^*,v^*)}{\beta_i}\int_0^{a_i}f_i(\tau)e^{-m_i\tau}H\left(\frac{G(y_i^*)h_i(x_i(t-\tau),v(t-\tau))}{G(y_i)h_i(x_i^*,v^*)}\right)d\tau\\&-\frac{h_i(x_i^*,v^*)}{\eta_i}\int_0^{a_i}g_i(\tau)e^{-n_i\tau}H\left(\frac{v^*G(y_i(t-\tau))}{G(y_i^*)v}\right)d\tau\Big]\\=&\sum_{i=1}^{n}\frac{\beta_i\eta_ik_i}{b_i}\Big[d_i(x_i^*-x_i)\left(1-\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right)\end{aligned}$$

$$
\begin{aligned}
&+ h_i(x_i^*, v^*)\frac{v}{v^*}\left(\frac{h_i(x_i,v)}{h_i(x_i,v^*)} - 1\right)\left(\frac{v^*}{v} - \frac{h_i(x_i,v^*)}{h_i(x_i,v)}\right)\\
&- h_i(x_i^*, v^*)H\left(\frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right) - h_i(x_i^*, v^*)H\left(\frac{v}{v^*}\frac{h_i(x_i,v^*)}{h_i(x_i,v)}\right)\\
&- \frac{h_i(x_i^*,v^*)}{\eta_i}\int_0^{a_i} g_i(\tau)e^{-n_i\tau}H\left(\frac{v^*G(y_i(t-\tau))}{G(y_i^*)v}\right)d\tau\\
&- \frac{h_i(x_i^*,v^*)}{\beta_i}\int_0^{a_i} f_i(\tau)e^{-m_i\tau}H\left(\frac{G(y_i^*)h_i(x_i(t-\tau),v(t-\tau))}{G(y_i)h_i(x_i^*,v^*)}\right)d\tau\Bigg].
\end{aligned}
$$

By (i) of Assumption 2.1, the following inequality holds:

$$
(x_i^* - x_i)\left(1 - \frac{h_i(x_i^*,v^*)}{h_i(x_i,v^*)}\right) \le 0. \tag{3.1}
$$

Furthermore, from the concavity and monotonicity of the function $h_i(x_i, v)$ on v, the inequalities

$$
\begin{cases}
1 \ge \frac{h_i(x_i,v)}{h_i(x_i,v^*)} \ge \frac{v}{v^*}, & for \quad 0 \le v \le v^*,\\
1 \le \frac{h_i(x_i,v)}{h_i(x_i,v^*)} \le \frac{v}{v^*}, & for \quad v \ge v^*.
\end{cases} \tag{3.2}
$$

hold, which in turn implies that

$$
\left(\frac{v^*}{v} - \frac{h_i(x_i,v^*)}{h_i(x_i,v)}\right)\left(\frac{h_i(x_i,v)}{h_i(x_i,v^*)} - 1\right) \le 0. \tag{3.3}
$$

Therefore, $\frac{dL_1(x_i,y_i,v)}{dt} \le 0$ holds for all $x_i, y_i, v > 0$. Thus, the infection equilibrium P^* is stable. And we have $\frac{dL_1(x_i,y_i,v)}{dt} = 0$ if and only if $x_i = x_i^*$, $y_i = y_i^*$ and $v = v^*$ hold. The largest compact invariant set in $\{(x_i, y_i, v) \mid \frac{dL_1(x_i,y_i,v)}{dt} = 0\}$ is the singleton $\{P^*\}$. Therefore, the infection equilibrium P^* is globally asymptotically stable by the LaSalle's invariance principle when $\Re_0 > 1$. This completes the proof. □

4. Special case when n=1

For $n = 1$, system (1.2) becomes

$$
\begin{cases}
\dot{x}(t) = s - dx(t) - h(x(t), v(t)),\\
\dot{y}(t) = \displaystyle\int_0^a f(\tau)e^{-m\tau}h(x(t-\tau), v(t-\tau))d\tau - bG(y(t)),\\
\dot{v}(t) = k\displaystyle\int_0^a g(\tau)e^{-n\tau}G(y(t-\tau))d\tau - cv(t),
\end{cases} \tag{4.1}
$$

where $\beta = \int_0^a f(\tau)e^{-m\tau}d\tau$ and $\eta = \int_0^a g(\tau)e^{-n\tau}d\tau$.

Here the state variables x, y and v and parameters $s, d, \beta, \eta, b, m, n, k, c$, $h(\cdot,\cdot)$ and $G(\cdot)$ have the similar biological meanings as in the system (1.2). We also assume that the functions $h(x, v)$ and $G(y)$ in system (4.1) are always positive, differentiable, and monotonically increasing for all $x > 0$, $y > 0$, and $v > 0$ and that $h(x, v)$ is concave with respect to v. The well-posedness of system (4.1) can be achieved by similar arguments as in section 2.

The basic reproduction number of the virus for system (4.1) is $\Re_0^1 = \frac{\beta\eta k}{bc} \cdot \frac{\partial h(x^0,0)}{\partial v}$. We will know that if $\Re_0^1 \le 1$, then infection-free equilibrium $E^0 = (x^0, 0, 0)$, $x^0 = s/d$, is the unique equilibrium; if $\Re_0^1 > 1$, then in addition to the uninfected steady state, there exists an infection equilibrium $E^* = (x^*, y^*, v^*)$. The initial conditions for system (4.1) take the form:

$$
\begin{gathered}
x(\theta) = \phi_1(\theta), \quad y(\theta) = \phi_2(\theta), \quad v(\theta) = \phi_3(\theta),\\
\phi_i(\theta) \ge 0, \quad \theta \in [-\tau, 0], \quad \phi_i(0) > 0, \ i = 1, 2, 3,
\end{gathered}
$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta)) \in \mathcal{C}([-\tau, 0], \mathrm{R}^3_{+0})$.

Theorem 4.1. *Consider system* (4.1). *Assume that Assumption 2.1 holds true for* $i = 1$, *the we have the following statements:*

(i) *The infection-free equilibrium* E^0 *of* (4.1) *is globally asymptotically stable if* $\Re_0^1 \leq 1$;

(ii) *The infection equilibrium* E^* *of* (4.1) *is globally asymptotically stable if* $\Re_0^1 > 1$.

Proof. (i) Define a Lyapunov functional L_0 as follows:

$$L^0(x,y,v) = \frac{\beta\eta k}{b}\left[x - x^0 - \int_{x^0}^{x} \lim_{v\to 0}\frac{h(x^0,v)}{h(\theta,v)}d\theta + \frac{y}{\beta} + \frac{1}{\beta}W_1 + \frac{b}{\beta\eta}W_2\right] + v. \tag{4.2}$$

where β and η are defined by (2.2) and (2.3) for $i = 1$, and

$$W_3 = \int_0^a f(\tau)e^{-m\tau}\int_0^\tau h(x(t-s),v(t-s))dsd\tau,$$
$$W_4 = \int_0^a g(\tau)e^{-n\tau}\int_0^\tau G(y(t-s))dsd\tau.$$

The functional $L^0(x,y,v)$ is non-negative defined with respect to the infection-free equilibrium $E^0 = (x^0, 0, 0)$, which is a global minimum. Calculating the time derivative of W_3 and W_4, we have

$$\frac{dW_3}{dt} = \beta h(x,v) - \int_0^a f(\tau)e^{-m\tau}h(x(t-\tau),v(t-\tau))d\tau,$$
$$\frac{dW_4}{dt} = \eta G(y) - \int_0^a g(\tau)e^{-n\tau}G(y(t-\tau)))d\tau.$$

Calculating the time derivative of $L^0(x,y,v)$ along solutions of system (4.1) gives

$$\frac{dL^0(x,y,v)}{dt} = \frac{\beta\eta k}{b}dx\left(\frac{x^0}{x} - 1\right)\left(1 - \lim_{v\to 0}\frac{h(x^0,v)}{h(x,v)}\right) + cv\left(\frac{\beta\eta k}{b}\frac{h(x,v)}{cv}\lim_{v\to 0}\frac{h(x^0,v)}{h(x,v)} - 1\right).$$

Similarly, we have $\left(\frac{x^0}{x} - 1\right)\left(1 - \lim_{v\to 0}\frac{h(x^0,v)}{h(x,v)}\right) \leq 0$, and

$$\frac{h(x,v)}{v}\lim_{v\to 0}\frac{h(x^0,v)}{h(x,v)} \leq \lim_{v\to 0}\frac{h(x,v)}{v}\cdot\frac{\frac{\partial h(x^0,0)}{\partial v}}{\frac{\partial h(x,0)}{\partial v}} = \frac{\partial h(x^0,0)}{\partial v}.$$

Then

$$\frac{dL^0(x,y,v)}{dt} \leq \frac{\beta\eta k}{b}dx\left(\frac{x^0}{x} - 1\right)\left(1 - \lim_{v\to 0}\frac{h(x^0,v)}{h(x,v)}\right) + cv(\Re_0^1 - 1),$$

where

$$\Re_0^1 = \frac{\beta\eta k}{bc}\cdot\frac{\partial h(x^0,0)}{\partial v}.$$

Thus, $\Re_0^1 \leq 1$ ensures that $\frac{dL^0(x,y,v)}{dt} < 0$ for all $x > 0$, $y \geq 0$, and $v > 0$. And $L_0' = 0$ if and only if $x = x^0$, $v = 0$ for $\Re_0^1 \leq 1$. It is easy to show that $E^0 = (x^0, 0, 0)$ is the largest invariant set in $\{(x,y,v) \mid \frac{dL^0(x,y,v)}{dt} = 0\}$. By LaSalle's invariance principle, the equilibrium $E^0 = (x^0, 0, 0)$ is globally asymptotically stable.

(ii) Define a Lyapunov functional $L^1(x,y,v)$ as follows:

$$L^1(x,y,v) = \frac{\beta\eta k}{b}\left[x - x^* - \int_{x^*}^{x}\frac{h(x^*,v^*)}{h(\theta,v^*)}d\theta + \frac{1}{\beta}(y - y^* - \int_{y^*}^{y}\frac{G(y^*)}{G(\theta)})d\theta\right. \tag{4.3}$$
$$\left. + \frac{h(x^*,v^*)}{\beta}U_3 + \frac{bG(y^*)}{\beta\eta}U_4\right] + v^*H\left(\frac{v}{v^*}\right). \tag{4.4}$$

Here, we give

$$U_3 = \int_0^a f(\tau)e^{-m\tau}\int_0^\tau H\left(\frac{h(x(t-\theta),v(t-\theta))}{h(x^*,v^*)}\right)d\theta d\tau,$$
$$U_4 = \int_0^a g(\tau)e^{-n\tau}\int_0^\tau H\left(\frac{G(y(t-\theta))}{G(y^*)}\right)d\theta d\tau.$$

Calculating the time derivative of U_3 and U_4, we have

$$\frac{dU_3}{dt} = \int_0^a f(\tau)e^{-m\tau}\left(\frac{h(x,v)}{h(x^*,v^*)} - \frac{h(x(t-\tau),v(t-\tau))}{h(x^*,v^*)} + \ln\frac{h(x(t-\tau),v(t-\tau))}{h(x,v)}\right)d\tau,$$
$$\frac{dU_4}{dt} = \int_0^a g(\tau)e^{-n\tau}\left(\frac{G(y)}{G(y^*)} - \frac{G(y(t-\tau))}{G(y^*)} + \ln\frac{G(y(t-\tau))}{G(y)}\right)d\tau.$$

Calculating the time derivative of $L^1(x,y,v)$ along solutions of system (4.1),

$$\frac{dL^1(x,y,v)}{dt} = \gamma\Bigg[d(x^*-x)\left(1-\frac{h(x^*,v^*)}{h(x,v^*)}\right) + h(x^*,v^*)\left(1-\frac{h(x^*,v^*)}{h(x,v^*)}\right) + h(x,v)\frac{h(x^*,v^*)}{h(x,v^*)} - \frac{h(x^*,v^*)}{v^*}v + h(x^*,v^*)S_2\Bigg],$$

where

$$\begin{aligned}
S_2 = {} & 2 - \frac{1}{bG(y)}\int_0^a f(\tau)e^{-m\tau}h(x(t-\tau),v(t-\tau))d\tau \\
& - \frac{v^*}{G(y^*)\eta v}\int_0^a g(\tau)e^{-n\tau}G(y(t-\tau))d\tau - \ln h(x,v) \\
& + \frac{1}{\beta}\int_0^a f(\tau)e^{-m\tau}\ln h(x(t-\tau),v(t-\tau))d\tau \ln G(y) \\
& + \frac{1}{\eta}\int_0^a g(\tau)e^{-n\tau}\ln G(y(t-\tau))d\tau \\
= {} & \ln\frac{vh(x^*,v^*)}{v^*h(x,v)} - \frac{1}{\eta}\int_0^a g(\tau)e^{-n\tau}H\left(\frac{v^*G(y(t-\tau))}{G(y^*)v}\right)d\tau \\
& - \frac{1}{\beta}\int_0^a f(\tau)e^{-m\tau}H\left(\frac{\beta}{bG(y)}h(x(t-\tau),v(t-\tau))\right)d\tau.
\end{aligned}$$

We have

$$\begin{aligned}
\frac{dL^1(x,y,v)}{dt} = {} & \frac{\beta\eta k}{b}\Bigg[d(x^*-x)\left(1-\frac{h(x^*,v^*)}{h(x,v^*)}\right) + h(x^*,v^*)\left(1-\frac{h(x^*,v^*)}{h(x,v^*)}\right) \\
& + h(x,v)\frac{h(x^*,v^*)}{h(x,v^*)} - \frac{h(x^*,v^*)}{v^*}v + h(x^*,v^*)\ln\frac{vh(x^*,v^*)}{v^*h(x,v)} \\
& - \frac{h(x^*,v^*)}{\beta}\int_0^a f(\tau)e^{-m\tau}H\left(\frac{G(y^*)h(x(t-\tau),v(t-\tau))}{G(y)h(x^*,v^*)}\right)d\tau \\
& - \frac{h(x^*,v^*)}{\eta}\int_0^a g(\tau)e^{-n\tau}H\left(\frac{v^*G(y(t-\tau))}{G(y^*)v}\right)d\tau\Bigg] \\
= {} & \frac{\beta\eta k}{b}\Bigg[d(x^*-x)\left(1-\frac{h(x^*,v^*)}{h(x,v^*)}\right) \\
& + h(x^*,v^*)\frac{v}{v^*}\left(\frac{h(x,v)}{h(x,v^*)}-1\right)\left(\frac{v^*}{v}-\frac{h(x,v^*)}{h(x,v)}\right)
\end{aligned}$$

$$
\begin{aligned}
&- h(x^*, v^*)H\left(\frac{h(x^*, v^*)}{h(x, v^*)}\right) - h(x^*, v^*)H\left(\frac{v}{v^*}\frac{h(x, v^*)}{h(x, v)}\right) \\
&- \frac{h(x^*, v^*)}{\eta}\int_0^a g(\tau)e^{-n\tau}H\left(\frac{v^*G(y(t-\tau))}{G(y^*)v}\right)d\tau \\
&- \frac{h(x^*, v^*)}{\beta}\int_0^a f(\tau)e^{-m\tau}H\left(\frac{G(y^*)h(x(t-\tau), v(t-\tau))}{G(y)h(x^*, v^*)}\right)d\tau\Bigg].
\end{aligned}
$$

The following inequality holds true:

$$
(x^* - x)(1 - \frac{h(x^*, v^*)}{h(x, v^*)}) \leq 0. \tag{4.5}
$$

Furthermore, from the concavity and monotonicity of the function $h(x, v)$ on v, the inequalities

$$
\begin{cases}
1 \geq \frac{h(x,v)}{h(x,v^*)} \geq \frac{v}{v^*}, & \text{for} \quad 0 \leq v \leq v^*, \\
1 \leq \frac{h(x,v)}{h(x,v^*)} \leq \frac{v}{v^*}, & \text{for} \quad v \geq v^*.
\end{cases} \tag{4.6}
$$

hold, which implies that

$$
\left(\frac{v^*}{v} - \frac{h(x, v^*)}{h(x, v)}\right)\left(\frac{h(x, v)}{h(x, v^*)} - 1\right) \leq 0. \tag{4.7}
$$

Therefore, $\frac{dL^1(x,y,v)}{dt} \leq 0$ holds for all $x, y, v > 0$. Thus, the infection equilibrium E^* is stable. And we have $\frac{dL^1(x,y,v)}{dt} = 0$ if and only if $x = x^*$, $y = y^*$ and $v = v^*$ hold. The largest compact invariant set in $\{(x, y, v) \mid \frac{dL^1(x,y,v)}{dt} = 0\}$ is the singleton $\{E^*\}$. Therefore, the infection equilibrium E^* is globally asymptotically stable by the LaSalle's invariance principle when $\Re_0^1 > 1$. This completes the proof. □

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