

GLOBAL STABILITY ANALYSIS AND PERMANENCE FOR AN HIV-1 DYNAMICS MODEL WITH DISTRIBUTED DELAYS*

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Abstract This paper mainly investigates the global asymptotic stabilities of two HIV dynamics models with two distributed intracellular delays incorporating Beddington-DeAngelis functional response infection rate. An eclipse stage of infected cells (i.e. latently infected cells), not yet producing virus, is included in our models. For the first model, it is proven that if the basic reproduction number R_0 is less than unity, then the infection-free equilibrium is globally asymptotically stable, and if R_0 is greater than unity, then the infected equilibrium is globally asymptotically stable. We also obtain that the disease is always present when R_0 is greater than unity by using a permanence theorem for infinite dimensional systems. What is more, a n-stage-structured HIV model with two distributed intracellular delays, which is the extension to the first model, is developed and analyzed. We also prove the global asymptotical stabilities of two equilibria by constructing suitable Lyapunov functionals.

Keywords HIV model, Global stability analysis, Beddington-DeAngelis functional response, distributed intracellular delays, uniformly persistent.

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1. Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that infects the human cells which deal with the immune system. HIV viruses destroy CD4 T cells in vivo and decrease the resistance of the immune system. HIV dynamics within a host depend on the HIV replication resulting into dynamics of the infected and uninfected cells. Many mathematical models have been developed to understand the interaction of the HIV infection and the immune system [4, 7, 15, 19]. Nowak and his cooperators in [19] consider one basic HIV model which included populations of three components: normal CD4 T-cells, infected CD4 T-cells and free HIV viruses. Many studies have showed that upon infection and transcription of viral RNA into cell DNA, a fraction of CD4 T-cells fail to actively produce virus until they are activated (an eclipse stage) [4, 5, 20]. Therefore, it is necessary that the latent stage

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of infected CD4 T-cells should be considered during the interaction. Especially, Elaiw and Azoz consider one HIV infection model with latently infected cells and Beddington-DeAngelis functional response in [4]. Moreover, there is an intracellular time delay between infection of a cell and production of new virus particles [8,9,11]. The infected cells would not change into productively infected cells in the same time. Distributed intracellular delays can describe continuous time delays between viral infection and production. Many papers consider viral dynamics models with distributed intracellular delays [13,17,24,25,29]. Dynamic behaviors for the basic HIV model with infinite distributed intracellular delays are researched in [1,13,25].

Motivated by the above works and features of HIV infection, we propose one model with two distributed delays, which is described by the following equations

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)}, \quad (1.1)$$

$$\frac{dz(t)}{dt} = \int_0^\infty f(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau - \delta z(t) - \mu z(t), \quad (1.2)$$

$$\frac{dy(t)}{dt} = \mu z(t) - ay(t), \quad (1.3)$$

$$\frac{dv(t)}{dt} = p \int_0^\infty g(\tau)y(t-\tau)d\tau - rv(t). \quad (1.4)$$

The state variables $x(t)$, $y(t)$, $z(t)$ and $v(t)$ represent the concentrations of uninfected CD4 T cells, productively infected cells, infected cells in the eclipse stage and HIV virus, respectively. The uninfected CD4 T cells are produced at a rate λ and die at the rate d (average life span of cells), and become latently infected cells at the rate $\frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)}$, the Beddington-DeAngelis functional response [7,15,27]. Parameter μ is the rate at which latently infected cells become productively infected cells and these cells die at the rate δ (average life span of cells in the eclipse state). The productively infected cells are produced at rate $\mu z(t)$ and are removed at rate $ay(t)$. HIV viruses are produced by the actively infected cells with rate constant p and are removed with constant rate r . The intracellular delay τ , allowing to be infinite because of drugs resistant strains, describes the periods between HIV viruses to enter infected cells and the infected cells start to become latently infected cells or the periods between latently infected cells become actively infected cells and actively infected cells start to produce new viral particles. The two distributed intracellular delays are introduced with the kernel functions given by $f(\tau) = f_1(\tau)e^{-\mu_1\tau}$, $g(\tau) = g_1(\tau)e^{-\mu_2\tau}$, where μ_1 and μ_2 are the per capita loss rates for the uninfected CD4 T-cells due to viral infection and HIV viruses during time interval $[t-\tau, t]$. $f(\tau)$ accounts for the probability that target cells contacted by the virus particles at time $t-\tau$ and become latently infected cells at time t , and $g(\tau)$ accounts for the probability that a cell productively infected at time $t-\tau$ starts to yield new infectious virus at time t . The nonnegative functions $f_1(\tau)$ and $g_1(\tau)$ are incorporated to describe the probability distribution for the two processes and are assumed to satisfy

$$\int_0^\infty f_1(\tau)d\tau = 1, \quad \int_0^\infty g_1(\tau)d\tau = 1.$$

Suppose all the parameters are nonnegative and the initial conditions

$$x(t) = \psi_1(t) \geq 0, z(t) = \psi_2(t) \geq 0, y(t) = \psi_3(t) \geq 0, v(t) = \psi_4(t) \geq 0, \quad (1.5)$$

where $\psi_i(t) \in C((-\infty, 0], R_+)$ ($i = 1, 2, 3, 4$), $R_+ = [0, \infty)$ and $t \in (-\infty, 0]$.

Because of existence of the infinite delay, we consider Banach phase space [9, 24, 25]:

$$C^* = \{\phi \in C((-\infty, 0], R) \mid \phi(\theta)e^{\omega\theta} \text{ is uniformly continuous for } \theta \\ \text{and } \sup_{\theta \leq 0} |\phi(\theta)| e^{\omega\theta} < \infty\},$$

where $\omega > 0$ is a constant and the norm is defined $\|\phi\| = \sup_{\theta \leq 0} |\phi(\theta)|e^{\omega\theta}$.

Denote $C_+^* = \{\phi \in C^* \mid \phi(\theta) \geq 0 \text{ for all } \theta \leq 0\}$. Here we suppose the initial conditions for system (1.1-1.4) are given

$$\psi_i(t) \in C_+^* (i = 1, 2, 3, 4). \quad (1.6)$$

When $f_1(\tau) = g_1(\tau) = \delta(\tau - 0)$ with $\delta(\cdot)$ being the Dirac delta function, system (1.1-1.4) reduces to system in [4]. When $f_1(\tau) = \delta(\tau - \tau_1)$ and $g_1(\tau) = \delta(\tau - 0)$, system (1.1-1.4) reduces to a similar model with a single discrete delay [27]. When $f_1(\tau) = \delta(\tau - \tau_1)$ and $g_2(\tau) = \delta(\tau - \tau_2)$, system (1.1-1.4) reduces to a similar model with two discrete delays in [28] where the authors established global stabilities of two equilibria by constructing Lyapunov functionals. It is obvious that system (1.1-1.4) includes a simple three-dimensional model ($\alpha = \gamma = 0$) studied in works [13, 25] where global stabilities of equilibria have been obtained as well. Moreover, our system includes another system with delay functions $f(\tau) = \frac{\tau^{n-1}}{(n-1)!b^n} e^{-\frac{\tau}{b}} e^{-\mu_1\tau}$ and $g(\tau) = \frac{\tau^{n-1}}{(n-1)!b^n} e^{-\frac{\tau}{b}} e^{-\mu_2\tau}$, where $\frac{\tau^{n-1}}{(n-1)!b^n} e^{-\frac{\tau}{b}}$ is a gamma distribution function, and $\int_0^\infty \frac{\tau^{n-1}}{(n-1)!b^n} e^{-\frac{\tau}{b}} d\tau = 1$ [18].

The main purpose of this paper is to analyse global properties for system (1.1-1.4) and explore the impact of distributed intracellular delays on the dynamical behavior of the system. In addition, we study the conditions under which diseases will die out. We begin model analysis with proving the positivity of the solutions, boundedness of the solutions, and uniform persistence of the system. We also prove that global stabilities of two equilibria only depend on the basic reproduction number by constructing suitable Lyapunov functionals which are motivated by the recent works [7, 12, 13, 16, 23, 25]. The paper is ordered as follows: equilibria, properties analysis and uniform persistence are studied in Section 2. Global asymptotic stabilities of two equilibria are discussed by constructing suitable Lyapunov functionals in Section 3. The n-stage-structured model for HIV infection is studied in Section 4. Discussion and conclusion in Section 5.

2. Properties analysis and uniform persistence

First, we establish the nonnegativity and boundedness of solutions of system (1.1-1.4) in the following analysis.

Proposition 2.1. *Let $(x(t), z(t), y(t), v(t)) \in \mathbf{R}^4$ be any solution of system (1.1-1.4) satisfying the initial conditions (1.5) and (1.6), then $x(t), z(t), y(t)$, and $v(t)$ are all nonnegative for $t > 0$ and are ultimately bounded.*

Proof. The methods are similar to those in the article [14]. Assume that there exists $t > 0$ at which $x(t), z(t), y(t)$ or $v(t)$ is equal to 0. Denote

$$t^* = \min\{t > 0 \mid x(t)z(t)y(t)v(t) = 0\}.$$

If $x(t^*) = 0$, it follows that

$$\frac{dx(t)}{dt}\Big|_{t=t^*} = \lambda > 0.$$

That means $x(t) < 0$ for $t \in (t^* - \varepsilon, t^*)$, where $\varepsilon > 0$ is sufficiently small. That is in contradiction with $x(t) > 0$ for $t \in (0, t^*)$. Thus $x(t) > 0$ for all $t \geq 0$. If $z(t^*) = 0$, it follows that $x(t^*) > 0, y(t^*) \geq 0$ and $v(t^*) \geq 0$ when $t \in [0, t^*]$. Then for $t \in [0, t^*]$, we can easily obtain $\frac{dz(t)}{dt} \geq -\delta z(t) - \mu z(t)$. It follows that

$$z(t) \geq z(0)e^{-(\delta+\mu)t}.$$

This is a contradiction to the assumption of $z(t^*) = 0$. Hence, $z(t) > 0$ for all $t \geq 0$. Similarly, we can obtain $y(t) > 0$ and $v(t) > 0$ for all $t \geq 0$. Solutions remain positive for positive initial conditions. It follows from the equation (1.1) that $\frac{dx(t)}{dt} \leq \lambda - dx(t)$. Thus, we get

$$\limsup_{t \rightarrow \infty} x(t) \leq \frac{\lambda}{d}.$$

That means $x(t)$ is ultimately bounded. For convenience of notations, we set

$$b_1 = \int_0^\infty f(\tau) d\tau, \quad b_2 = \int_0^\infty g(\tau) d\tau.$$

From the equation (1.2), we can obtain

$$\frac{dz(t)}{dt} \leq \frac{\beta\lambda}{d\gamma} b_1 - (\mu + \delta)z(t).$$

Thus, we obtain $\limsup_{t \rightarrow \infty} z(t) \leq \frac{\beta\lambda b_1}{d\gamma(\mu + \delta)}$. This implies that $z(t)$ is also ultimately bounded. By a similar argument, we can obtain

$$\limsup_{t \rightarrow \infty} y(t) \leq \frac{\beta\lambda b_1 \mu}{d\gamma(\mu + \delta)a}, \quad \limsup_{t \rightarrow \infty} v(t) \leq \frac{\beta\lambda b_1 \mu p b_2}{d\gamma(\mu + \delta)ar}.$$

Therefore, $y(t)$ and $v(t)$ are both ultimately bounded. This completes the proof. \square

From biological considerations, we study system (1.1-1.4) in the closed set:

$$P = \left\{ (x(t), z(t), y(t), v(t)) \in R_+^4; \|x\| \leq \frac{\lambda}{d}, \|z\| \leq \frac{\beta\lambda b_1}{d\gamma(\mu + \delta)}, \right. \\ \left. \|y\| \leq \frac{\beta\lambda b_1 \mu}{d\gamma(\mu + \delta)a}, \|v\| \leq \frac{\beta\lambda b_1 \mu p b_2}{d\gamma(\mu + \delta)ar} \right\},$$

where R_+^4 denotes the non-negative cone. Proposition 2.1 implies that the omega limit sets of system (1.1-1.4) are contained in the region P . Obviously, solutions of system (1.1-1.4) remain nonnegative for nonnegative initial conditions. So P is a positively invariant set with respect to system (1.1-1.4). In the following, we will investigate dynamic behavior on P .

We note that the basic reproduction number R_0 for the system is given by

$$R_0 = \frac{\mu p \lambda \beta b_1 b_2}{ar(\mu + \delta)(d + \alpha \lambda)}.$$

The basic reproduction number R_0 represents the average number of secondary cases generated by an infected case throughout its infection period.

The steady states (equilibria) of system (1.1-1.4) satisfy the following equations:

$$\begin{cases} \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)} = 0, \\ \frac{b_1 \beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)} - (\delta + \mu)z(t) = 0, \\ \mu z(t) - ay(t) = 0, \\ b_2 py(t) - rv(t) = 0. \end{cases}$$

We obtain that the equations always have an infection-free equilibrium $E_0(x_0, 0, 0, 0)$, where $x_0 = \frac{\lambda}{d}$. Meanwhile, if $R_0 > 1$ we obtain that the equations have only one infected equilibrium $E^*(x^*, z^*, y^*, v^*)$ where

$$x^* = \frac{\mu\gamma\lambda pb_1 b_2 + ar(\delta + \mu)}{\mu\beta pb_1 b_2 + \mu d\gamma pb_1 b_2 - \alpha ar(\delta + \mu)}, z^* = \frac{b_1(\lambda - dx^*)}{\delta + \mu}, y^* = \frac{\mu z^*}{a}, v^* = \frac{pb_2 y^*}{r}.$$

We will establish the uniform persistence of system (1.1-1.4) and start with the definition.

Definition 2.1. System (1.1-1.4) is said to be uniformly persistent if there exists a constant $m > 0$ such that each positive solution $(x(t), z(t), y(t), v(t))$ with initial conditions (1.5) and (1.6) satisfies ([3, 25, 26])

$$\min\{\liminf_{t \rightarrow \infty} x(t), \liminf_{t \rightarrow \infty} z(t), \liminf_{t \rightarrow \infty} y(t), \liminf_{t \rightarrow \infty} v(t)\} \geq m.$$

In order to study the permanence of system (1.1-1.4), we present the persistence theory on infinite dimensional systems from [6]. The persistence theory and techniques we are using have been recently employed in [10, 22, 25]. First, we introduce some concepts, notations and terminology. Denote by $T(t), t \geq 0$, the family of solution operators corresponding to system (1.1-1.4). We also denote $X = (C_+^*)^4$ and the positive orbit $\gamma^+(x)$ through $x \in X$ is defined as $\gamma^+(x) = \cup_{t \geq 0} \{T(t)x\}$. Consider any arbitrary non-negative solution $x_t = x(t + \theta), z_t = z(t + \theta), y_t = y(t + \theta)$, and $v_t = v(t + \theta)$ for $\theta \leq 0$, where the initial functions satisfy $(\psi_1(\theta), \psi_2(\theta), \psi_3(\theta), \psi_4(\theta)) \in X$. The ω -limit set $\omega(x)$ of x consists of $y \in X$ such that there exists a sequence $t_n \rightarrow \infty$ as $n \rightarrow \infty$ with $T(t_n)x \rightarrow y$ as $n \rightarrow \infty$. The semi-group $T(t)$ (that is $T(0) = I, T(s+t) = T(s)T(t)$, for $s, t \geq 0$, and $T(t)x$ is continuous in x, t) is said to be asymptotically smooth, if for any bounded subset U of X , for which $T(t)U \subseteq U$ for any $t \geq 0$, there exists a compact set Υ such that $d(T(t)U, \Upsilon) \rightarrow 0$ as $t \rightarrow \infty$. Let $T_b(t)$ be $T(t)$ restricted to X_0 and A_b be the global attractor for $T_b(t)$.

Lemma 2.1 ([10, 22, 25]). *Suppose that we have the following conditions:*

- (1) $X^0 \subset X$ is open and dense in X with $X_0 \cup X^0 = X$ and $X_0 \cap X^0 = \Phi$;
- (2) the solution operators $T(t)$ satisfy $T(t) : X_0 \rightarrow X_0, T(t) : X^0 \rightarrow X^0$;
- (3) $T(t)$ is point dissipative in X ;
- (4) $\gamma^+(U)$ is bounded in X if U is bounded in X ;
- (5) $T(t)$ is asymptotically smooth;
- (6) $\Lambda = \cup_{x \in A_b} \omega(x)$ is isolated and has an acyclic covering N , where $N = \{N_1, N_2, \dots$

$\cdot, N_n\}$; (γ) for each $N_i \in N$, we have $W^s(N_i) \cap X^0 = \Phi$, where W^s refers to the stable set.

Then, $T(t)$ is a uniform repeller with respect to X^0 , i.e. there is an $\eta > 0$ such that for any $x \in X^0$, $\liminf_{t \rightarrow \infty} d(T(t)x, X_0) \geq \eta$.

Proposition 2.2. Assume that $R_0 > 1$, then the disease is endemic and system (1.1-1.4) is uniformly persistent.

Proof. From the equation (1.1), one can show that

$$\lambda - dx(t) \geq \frac{dx(t)}{dt} \geq \lambda - \left(d + \frac{\beta}{\gamma}\right)x(t),$$

hence, by integration for $t \geq 0$ and the initial condition $x(0)$, we have

$$\frac{\lambda}{d} + (x(0) - \frac{\lambda}{d})e^{-dt} \geq x(t) \geq \frac{\lambda}{d + \frac{\beta}{\gamma}} + (x(0) - \frac{\lambda}{d + \frac{\beta}{\gamma}})e^{-(d + \frac{\beta}{\gamma})t}.$$

This leads to $x(t)$ is uniformly bounded away from zero and has positive ultimate lower boundary. That is, there exists a constant $\eta_1 = \frac{\lambda}{d + \frac{\beta}{\gamma}} > 0$ such that $\liminf_{t \rightarrow \infty} x(t) \geq \eta_1$. Thus we will prove that other three variables have positive ultimate lower boundary. Let

$$X^0 = \{(x(t), z_t(\theta), y_t(\theta), v_t(\theta)) \mid z_t(\theta), y_t(\theta), v_t(\theta) > 0 \text{ for some } \theta < 0\},$$

$$X_0 = \{(x(t), z_t(\theta), y_t(\theta), v_t(\theta)) \mid z_t(\theta) = 0, \text{ or } y_t(\theta) = 0, \text{ or } v_t(\theta) = 0 \text{ for any } \theta \leq 0\}.$$

In the following, we verify that the conditions in Lemma 2.1 are satisfied. It is straightforward to see that the conditions (1) and (2) are satisfied. From Proposition 2.1, we obtain that $T(t)$ is point dissipative in X . So the condition (3) is satisfied. Let U be a bounded set of X , and $B > 0$ be such that for any $(\sigma, \sigma_2, \sigma_3, \sigma_4) \in U$, $\sigma < B$ and $\|\sigma_i\| \leq B, i = 2, 3, 4$. Denote $\varphi(s) := Be^{\omega s}, s \leq 0$. Consider the solution $\bar{x}(t), \bar{z}(t), \bar{y}(t)$, and $\bar{v}(t)$ with initial condition $x(0) = B, z_0 = y_0 = v_0 = \varphi$. For any solution $x(t), z(t), y(t)$, and $v(t)$ with initial solution from U , we can obtain that $x(t) < \bar{x}(t), z(t) < \bar{z}(t), y(t) < \bar{y}(t)$, and $v(t) < \bar{v}(t)$ for $t \geq 0$. Indeed, let t_0 is the smallest t such that $v(t) = \bar{v}(t), x(t) \leq \bar{x}(t), z(t) \leq \bar{z}(t)$, and $y(t) \leq \bar{y}(t)$ for all $t \in [0, t_0]$. Therefore, we obtain $v'(t_0) > \bar{v}'(t_0)$ and

$$\int_0^\infty g(\tau)y(t-\tau)d\tau > \int_0^\infty g(\tau)\bar{y}(t-\tau)d\tau.$$

This is a contradiction to $y(t) \leq \bar{y}(t)$. So we have $v(t) < \bar{v}(t)$ for $t \geq 0$. Similarly, we have $x(t) < \bar{x}(t), z(t) < \bar{z}(t)$ and $y(t) < \bar{y}(t)$ for $t \geq 0$. As a result of all this, we get that $T(t)$ is monotone. Using the arguments of Proposition 2.1, we obtain $\bar{x}(t), \bar{z}(t), \bar{y}(t)$ and $\bar{v}(t)$ are bounded and dominate every solution with initial data from U . Hence, we obtain the condition (4). Next we show that $T(t)$ is asymptotically smooth. Let

$$M := \max\left\{\frac{\lambda}{d}, \frac{\beta\lambda b_1}{d\gamma(\mu + \delta)}, \frac{\beta\lambda b_1 a}{d\gamma(\mu + \delta)\mu}, \frac{\beta\lambda b_1 a p b_2}{d\gamma(\mu + \delta)\mu r}\right\}.$$

We define a set Υ by

$$\Upsilon := \{\phi \in C^* \mid \sup_{s \leq 0} \phi(s)e^{\frac{\omega s}{2}} \leq M\}.$$

We obtain that Υ is compact set in C^* from Lemma 3.2 of the paper [2]. Let x_t, z_t, y_t and v_t be the segment of solution with initial condition lying in an arbitrary bounded set $U \in X$. We will show that $\lim_{t \rightarrow \infty} d(x_t, \Upsilon) = 0$. z_t, y_t , and v_t can be derived analogously. we can obtain that there exists a $T > 0$ such that $x(t) \leq M$ for $t \geq T$ and $x(t) = M$ or $x(t) < M$ for $t > 0$ from Proposition 2.1. We first consider the case $x(t) = M$ for $t > 0$ and denote K be the maximum of $x(t)$ on $[0, T]$ and define the function $\psi^t(s)$ for $t > T$

$$\psi^t(s) = \begin{cases} x(t+s)e^{-\frac{\omega s}{2}}, & T-t \leq s \leq 0, \\ Me^{-\frac{\omega s}{2}}, & s \leq T-t. \end{cases}$$

Thus, we have $\psi^t(s) \in \Upsilon$ and

$$\lim_{t \rightarrow \infty} d(x_t, \Upsilon) \leq \lim_{t \rightarrow \infty} d(x_t, \psi^t) = \sup_{s \leq 0} |x_t(s) - \psi^t(s)| e^{\omega s}.$$

Separating to the intervals $[T-t, 0]$, $[-t, T-t]$ and $[-\infty, -t]$, we obtain

$$\begin{aligned} \sup_{T-t \leq s \leq 0} |x_t(s) - \psi^t(s)| e^{\omega s} &= 0, \\ \sup_{-t \leq s \leq T-t} |x_t(s) - \psi^t(s)| e^{\omega s} &\leq (Ke^{\omega T} + Me^{\frac{\omega T}{2}})e^{-\frac{\omega t}{2}}, \\ \sup_{s \leq -t} |x_t(s) - \psi^t(s)| e^{\omega s} &\leq (\|x_0\| + M)e^{-\omega t}. \end{aligned}$$

Thus, we get that $\lim_{t \rightarrow \infty} d(x_t, \Upsilon) = 0$ and $T(t)$ is asymptotically smooth. The case $x(t) < M$ for $t > 0$ can be treated similarly. Thus, we verified the condition (5). Regarding (6), we can obtain that $\Lambda = E_0$ and isolated. The covering is simple $N = E_0$, which is acyclic (there is no orbit that connects E_0 to itself in X_0).

At last, we prove that $W^s(E_0) \cap X^0 = \Phi$. Suppose it is not true, i. e. there exists a solution $u_t \in X^0$ such that

$$\lim_{t \rightarrow \infty} x(t) = x_0 = \frac{\lambda}{d}, \lim_{t \rightarrow \infty} z(t) = 0, \lim_{t \rightarrow \infty} y(t) = 0, \lim_{t \rightarrow \infty} v(t) = 0.$$

Then for any sufficient small $\epsilon > 0$, there is $T_1(\epsilon)$ large enough, such that $x(t) > \frac{\lambda}{d} - \epsilon$, $z(t) < \epsilon$, $y(t) < \epsilon$, and $v(t) < \epsilon$ for all $t \geq T_1(\epsilon)$. When $R_0 > 1$, for the given $\epsilon > 0$, we have

$$\frac{\mu p(\frac{\lambda}{d} - \epsilon)\beta b_1 b_2}{ar(\mu + \delta)(1 + \alpha(\frac{\lambda}{d} - \epsilon) + \gamma\epsilon)} > 1.$$

There exists a T_2 such that

$$\frac{\mu p(\frac{\lambda}{d} - \epsilon)\beta \int_0^{T_2} f(\tau) d\tau \int_0^{T_2} g(\tau) d\tau}{ar(\mu + \delta)(1 + \alpha(\frac{\lambda}{d} - \epsilon) + \gamma\epsilon)} > 1.$$

$$\frac{dz(t)}{dt} \geq \int_0^{T_2} f(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau - \delta z(t) - \mu z(t).$$

For the given T_2 , there exists a $T_3 > \max\{T_1, T_2\}$ such that $x(t-\tau) \geq x_0 - \epsilon$, for any $t > T_3$ and $\tau \in [0, T_2]$, we have

$$\frac{dz(t)}{dt} \geq \beta(x_0 - \epsilon) \int_0^{T_2} f(\tau) \frac{v(t-\tau)}{1 + \alpha(x_0 - \epsilon) + \gamma v(t-\tau)} d\tau - \delta z(t) - \mu z(t).$$

What is more, we get

$$\frac{dz(t)}{dt} \geq \frac{\beta(x_0 - \epsilon)}{1 + \alpha(x_0 - \epsilon) + \gamma\epsilon} \int_0^{T_2} f(\tau)v(t - \tau)d\tau - \delta z(t) - \mu z(t).$$

Also, we obtain

$$\frac{dv(t)}{dt} \geq p \int_0^{T_2} g(\tau)y(t - \tau)d\tau - rv(t).$$

By the mean value theorem for integrals we obtain that there is a ξ_t such that

$$\int_0^{T_2} f(\tau)v(t - \tau)d\tau = v(\xi_t) \int_0^{T_2} f(\tau)d\tau,$$

where $t - T_3 \leq \xi_t \leq t$. Thus, we have

$$\frac{dz(t)}{dt} \geq \frac{\beta(x_0 - \epsilon)}{1 + \alpha(x_0 - \epsilon) + \gamma\epsilon} v(\xi_t) \int_0^{T_2} f(\tau)d\tau - \delta z(t) - \mu z(t).$$

Meanwhile we also consider

$$\begin{aligned} \frac{dy(t)}{dt} &= \mu z(t) - ay(t), \\ \frac{dv(t)}{dt} &\geq p \int_0^{T_2} g(\tau)y(t - \tau)d\tau - rv(t). \end{aligned}$$

If $z(t), y(t), v(t) \rightarrow 0$, as $t \rightarrow +\infty$, then by a standard comparison argument and the nonnegativity, the solution $(z_c(t), y_c(t), v_c(t))$ of

$$\begin{aligned} \frac{dz_c(t)}{dt} &= \frac{\beta(x_0 - \epsilon)}{1 + \alpha(x_0 - \epsilon) + \gamma\epsilon} v_c(\xi_t) \int_0^{T_2} f(\tau)d\tau - \delta z_c(t) - \mu z_c(t), \\ \frac{dy_c(t)}{dt} &= \mu z_c(t) - ay_c(t), \\ \frac{dv_c(t)}{dt} &= p \int_0^{T_2} g(\tau)y_c(t - \tau)d\tau - rv_c(t), \end{aligned}$$

with initial conditions $z_c(t) = z_c(T_3), y_c(t) = y_c(T_3), v_c(t) = v_c(T_3)$, has to convergence to 0 as well. However, we define the function

$$\begin{aligned} G(t) &= \int_0^{T_2} g(\tau)z_c(t - \tau)d\tau + \frac{\mu + \delta}{\mu} \int_0^{T_2} g(\tau)y_c(t - \tau)d\tau + \frac{(\mu + \delta)a}{\mu p} v_c(t) \\ &\quad + \frac{(\mu + \delta)ar}{\mu p} \int_{\xi_t}^t v_c(s)ds. \end{aligned}$$

Therefore, we can obtain $\lim_{t \rightarrow \infty} G(t) = 0$. On the other hand, differentiating with respect to time gives

$$G'(t) = \left[\frac{(\frac{\lambda}{d} - \epsilon)\beta \int_0^{T_2} f(\tau)d\tau \int_0^{T_2} g(\tau)d\tau}{1 + \alpha(\frac{\lambda}{d} - \epsilon) + \gamma\epsilon} - \frac{(\mu + \delta)ar}{\mu p} \right] v_c(\xi_t) \geq 0.$$

Therefore, $G(t)$ goes to infinity or approaches a positive limit as $t \rightarrow \infty$ which is a contradiction to $\lim_{t \rightarrow \infty} G(t) = 0$. Thus, $W^s(E_0) \cap X^0 = \Phi$ is satisfied. By

Lemma 2.1, $T(t)$ is a uniform repeller with respect to X^0 . That is, we obtain that there exists $\eta_2 > 0$ for initial condition $\phi \in X_0$ such that

$$\liminf_{t \rightarrow \infty} x(t) \geq \eta_2, \liminf_{t \rightarrow \infty} z(t) \geq \eta_2, \liminf_{t \rightarrow \infty} y(t) \geq \eta_2, \liminf_{t \rightarrow \infty} v(t) \geq \eta_2.$$

So, we denote $\eta = \min\{\eta_1, \eta_2\}$ and obtain

$$\liminf_{t \rightarrow \infty} x(t) \geq \eta, \liminf_{t \rightarrow \infty} z(t) \geq \eta, \liminf_{t \rightarrow \infty} y(t) \geq \eta, \liminf_{t \rightarrow \infty} v(t) \geq \eta.$$

That shows that system (1.1-1.4) is uniformly persistent. This completes the proof. \square

The uniform persistence of system (1.1-1.4) shows that the disease will not only exist in every subpopulation but in fact the number of individuals in each group will always remain beyond a certain positive level.

3. Global stability of the equilibria

In this section, we would consider the global asymptotic stability of the two equilibria of system (1.1-1.4). We would apply the Lyapunov functional and the LaSalle invariance principle to establish global dynamical properties for the delay differential equations.

Theorem 3.1. *If $R_0 \leq 1$, the infection-free equilibrium $E_0(x_0, 0, 0, 0)$ of system (1.1-1.4) is globally asymptotically stable.*

Proof. Define a Lyapunov functional $V_1(t)$ as follows:

$$\begin{aligned} V_1(t) \equiv V_1((x(t), z(t), y(t), v(t))) &= \frac{b_1 b_2}{1 + \alpha x_0} (x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0}) + b_2 z(t) \\ &+ \frac{(\mu + \delta) b_2}{\mu} y(t) + \frac{a(\mu + \delta)}{\mu p} v(t) + b_2 U_1(t) + \frac{(\mu + \delta) a}{\mu} U_2(t), \end{aligned}$$

where

$$\begin{aligned} U_1(t) &= \int_0^\infty \phi_1(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau, \quad \phi_1(t) = \int_t^\infty f(\tau) d\tau, \\ U_2(t) &= \int_0^\infty \phi_2(\tau) y(t-\tau) d\tau, \quad \phi_2(t) = \int_t^\infty g(\tau) d\tau. \end{aligned}$$

It is easily seen that $V_1(t) \geq 0$ for all $(x(t), z(t), y(t), v(t)) > 0$ and $V_1(t) = 0$ if and only if $x(t) = x_0$ and $y(t) = z(t) = v(t) = 0$. Calculating the derivative of $V_1(t)$ with respect to time t along positive solutions of system (1.1-1.4), it follows that

$$\begin{aligned} \frac{dV_1(t)}{dt} &= \frac{b_1 b_2}{1 + \alpha x_0} \left(1 - \frac{x_0}{x(t)}\right) \frac{dx(t)}{dt} + b_2 \frac{dz(t)}{dt} + \frac{b_2(\mu + \delta)}{\mu} \frac{dy(t)}{dt} \\ &+ \frac{a(\mu + \delta)}{\mu p} \frac{dv(t)}{dt} + b_2 \frac{dU_1(t)}{dt} + \frac{(\mu + \delta) a}{\mu} \frac{dU_2(t)}{dt}. \end{aligned}$$

Therefore, we obtain

$$\frac{dV_1(t)}{dt} = \frac{b_1 b_2}{1 + \alpha x_0} \left(1 - \frac{x_0}{x(t)}\right) (\lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)})$$

$$+b_2\left(\int_0^\infty \frac{f(\tau)\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}d\tau - \delta z(t) - \mu z(t)\right) + \frac{b_2(\mu+\delta)}{\mu}(\mu z(t) - ay(t)) \\ + \frac{a(\mu+\delta)}{\mu p}\left(p\int_0^\infty g(\tau)y(t-\tau)d\tau - rv(t)\right) + b_2\frac{dU_1(t)}{dt} + \frac{(\mu+\delta)a}{\mu}\frac{dU_2(t)}{dt}.$$

Using integration by parts, we calculate the derivative of $U_1(t)$,

$$\frac{dU_1(t)}{dt} = \frac{d}{dt}\int_0^\infty \phi_1(\tau)\frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}d\tau \\ = \int_0^\infty \phi_1(\tau)\frac{d}{dt}\left[\frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}\right]d\tau \\ = -\int_0^\infty \phi_1(\tau)\frac{d}{d\tau}\left[\frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}\right]d\tau \\ = -\phi_1(\tau)\frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}\Big|_{\tau=0}^\infty + \int_0^\infty \frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}d\phi_1(\tau).$$

Noting that

$$\lim_{\tau\rightarrow\infty}\phi_1(\tau) = 0, \phi_1(0) = b_1, \text{ and } d\phi_1(\tau) = -f(\tau)d\tau,$$

we obtain

$$\frac{dU_1(t)}{dt} = b_1\frac{\beta x(t)v(t)}{1+\alpha x(t)+\gamma v(t)} - \int_0^\infty f(\tau)\frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)}d\tau.$$

Similarly, we have

$$\frac{dU_2(t)}{dt} = b_2y(t) - \int_0^\infty g(\tau)y(t-\tau)d\tau.$$

Thus, we get

$$\frac{dV_1(t)}{dt} = -\frac{b_1b_2d(x(t)-x_0)^2}{(1+\alpha x_0)x(t)} - \frac{b_1b_2}{1+\alpha x_0}\left(1-\frac{x_0}{x(t)}\right)\frac{\beta x(t)v(t)}{1+\alpha x(t)+\gamma v(t)} \\ + \frac{b_1b_2\beta x(t)v(t)}{1+\alpha x(t)+\gamma v(t)} - \frac{ar(\mu+\delta)}{\mu p}v(t) \\ = -\frac{b_1b_2d(x(t)-x_0)^2}{x(t)(1+\alpha x_0)} + b_1b_2\frac{1+\alpha x(t)}{1+\alpha x_0}\frac{\beta x_0v(t)}{1+\alpha x(t)+\gamma v(t)} - \frac{ar(\mu+\delta)}{\mu p}v(t) \\ \leq -\frac{b_1b_2d(x(t)-x_0)^2}{x(t)(1+\alpha x_0)} + \frac{ar(\mu+\delta)}{\mu p}(R_0-1)v(t).$$

So, it follows that $\frac{dV_1(t)}{dt} \leq 0$ if $R_0 \leq 1$. It is clear that the infection-free equilibrium $E_0(x_0, 0, 0, 0)$ is stable. Let M be the largest compact invariant set in the set

$$\{(x(t), z(t), y(t), v(t)) \in \mathbf{R}^4 \mid \frac{dV_1(t)}{dt} = 0\} \\ = \{(x(t), z(t), y(t), v(t)) \in \mathbf{R}^4 \mid x(t) = x_0, v(t) = 0, z(t) \geq 0, y(t) \geq 0\}.$$

From system (1.1-1.4), we obtain that the largest compact invariant set is the singleton $\{E_0\}$. Accordingly, it follows from Lyapunov-LaSalle invariance principle that $E_0(x_0, 0, 0, 0)$ is globally asymptotically stable when $R_0 \leq 1$. \square

Theorem 3.2. *If $R_0 > 1$, the infected equilibrium $E^*(x^*, z^*, y^*, v^*)$ of system (1.1-1.4) is globally asymptotically stable.*

Proof. Define a Lyapunov functional $V_2(t)$ as follows:

$$\begin{aligned} V_2(t) = & b_1 b_2 (x(t) - x^* - \int_{x^*}^{x(t)} \frac{(1 + \alpha s + \gamma v^*) x^*}{(1 + \alpha x^* + \gamma v^*) s} ds) + b_2 (z(t) - z^* - z^* \ln \frac{z(t)}{z^*}) \\ & + \frac{(\mu + \delta) b_2}{\mu} (y(t) - y^* - y^* \ln \frac{y(t)}{y^*}) + \frac{a(\mu + \delta)}{\mu p} (v(t) - v^* - v^* \ln \frac{v(t)}{v^*}) \\ & + \frac{(\mu + \delta) z^*}{b_1} b_2 U_3(t) + (\mu + \delta) z^* U_4(t), \end{aligned}$$

where

$$\begin{aligned} U_3(t) = & \int_0^\infty \phi_1(\tau) \left[\frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} - 1 \right. \\ & \left. - \ln \frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} \right] d\tau, \\ U_4(t) = & \int_0^\infty \phi_2(\tau) \left[\frac{y(t - \tau)}{y^*} - 1 - \ln \frac{y(t - \tau)}{y^*} \right] d\tau. \end{aligned}$$

Calculating the derivative of $V_2(t)$ with respect to time t along positive solutions of system (1.1-1.4), it follows that

$$\begin{aligned} \frac{dV_2(t)}{dt} = & b_1 b_2 \left(1 - \frac{x^*}{x(t)} \frac{1 + \alpha x(t) + \gamma v^*}{1 + \alpha x^* + \gamma v^*} \right) \frac{dx(t)}{dt} + b_2 \frac{z(t) - z^*}{z(t)} \frac{dz(t)}{dt} \\ & + \frac{(\mu + \delta) b_2}{\mu} \frac{y(t) - y^*}{y(t)} \frac{dy(t)}{dt} + \frac{a(\mu + \delta)}{\mu p} \frac{v(t) - v^*}{v(t)} \frac{dv(t)}{dt} \\ & + \frac{(\mu + \delta) z^*}{b_1} b_2 \frac{dU_3(t)}{dt} + (\mu + \delta) z^* \frac{dU_4(t)}{dt}. \end{aligned}$$

We calculate the derivative of $U_3(t)$,

$$\begin{aligned} \frac{dU_3(t)}{dt} = & \frac{d}{dt} \int_0^\infty \phi_1(\tau) \left[\frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} - 1 \right. \\ & \left. - \ln \frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} \right] d\tau \\ = & - \int_0^\infty \phi_1(\tau) \frac{d}{d\tau} \left[\frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} - 1 \right. \\ & \left. - \ln \frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} \right] d\tau. \end{aligned}$$

Using integration by parts, we obtain

$$\begin{aligned} \frac{dU_3(t)}{dt} = & -\phi_1(\tau) \left[\frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} - 1 \right. \\ & \left. - \ln \frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} \right] \Big|_{\tau=0}^\infty \\ & + \int_0^\infty \left[\frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^* (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} - 1 \right. \end{aligned}$$

$$\begin{aligned}
& -\ln \frac{b_1 \beta x(t-\tau)v(t-\tau)}{(\mu+\delta)z^*(1+\alpha x(t-\tau)+\gamma v(t-\tau))}]d\phi_1(\tau) \\
= & b_1 \left[\frac{b_1 \beta x(t)v(t)}{(\mu+\delta)z^*(1+\alpha x(t)+\gamma v(t))} - 1 - \ln \frac{b_1 \beta x(t)v(t)}{(\mu+\delta)z^*(1+\alpha x(t)+\gamma v(t))} \right] \\
& - \int_0^\infty f(\tau) \left[\frac{b_1 \beta x(t-\tau)v(t-\tau)}{(\mu+\delta)z^*(1+\alpha x(t-\tau)+\gamma v(t-\tau))} - 1 \right. \\
& \left. - \ln \frac{b_1 \beta x(t-\tau)v(t-\tau)}{(\mu+\delta)z^*(1+\alpha x(t-\tau)+\gamma v(t-\tau))} \right] d\tau.
\end{aligned}$$

Using integration by parts, meanwhile we calculate the derivative of $U_4(t)$,

$$\frac{dU_4(t)}{dt} = b_2 \left[\frac{y(t)}{y^*} - 1 - \ln \frac{y(t)}{y^*} \right] - \int_0^\infty g(\tau) \left[\frac{y(t-\tau)}{y^*} - 1 - \ln \frac{y(t-\tau)}{y^*} \right] d\tau.$$

At the infected equilibrium E^* , we have

$$\lambda = dx^* + \frac{\beta x^* v^*}{1 + \alpha x^* + \gamma v^*}, \frac{\beta b_1 x^* v^*}{1 + \alpha x^* + \gamma v^*} = (\delta + \mu)z^*, \mu z^* = ay^*, pb_2 y^* = rv^*.$$

Thus, we obtain

$$\begin{aligned}
\frac{dV_2(t)}{dt} = & 4(\mu+\delta)z^*b_2 - (\mu+\delta)z^*b_2 \frac{(1+\alpha x(t)+\gamma v^*)x^*}{(1+\alpha x^*+\gamma v^*)x(t)} \\
& - b_2 \int_0^\infty f(\tau) \frac{z^*}{z(t)} \frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha x(t-\tau)+\gamma v(t-\tau)} d\tau - (\mu+\delta)z^*b_2 \frac{y^*z(t)}{y(t)z^*} \\
& - (\mu+\delta)z^*b_2 \frac{v(t)}{v^*} - (\mu+\delta)z^* \int_0^\infty g(\tau) \frac{y(t-\tau)v^*}{y^*v(t)} d\tau \\
& + \frac{(\mu+\delta)z^*}{b_1} b_2 \int_0^\infty f(\tau) \ln \left[\frac{x(t-\tau)v(t-\tau)}{(1+\alpha x(t-\tau)+\gamma v(t-\tau))} \frac{(1+\alpha x(t)+\gamma v(t))}{x(t)v(t)} \right] d\tau \\
& + (\mu+\delta)z^*b_2 \frac{v(t)}{v^*} \frac{1+\alpha x(t)+\gamma v^*}{1+\alpha x(t)+\gamma v(t)} + (\mu+\delta)z^* \int_0^\infty g(\tau) \ln \frac{y(t-\tau)}{y(t)} d\tau.
\end{aligned}$$

Note that:

$$\begin{aligned}
\ln \left[\frac{x(t-\tau)v(t-\tau)}{(1+\alpha x(t-\tau)+\gamma v(t-\tau))} \frac{(1+\alpha x(t)+\gamma v(t))}{x(t)v(t)} \right] &= \ln \frac{x^*}{x(t)} \frac{1+\alpha x(t)+\gamma v^*}{1+\alpha x^*+\gamma v^*} \\
+ \ln \frac{zy^*}{z^*y} + \ln \frac{yv^*}{y^*v} + \ln \frac{z^*x(t-\tau)v(t-\tau)(1+\alpha x^*+\gamma v^*)}{z^*v^*[(1+\alpha x(t-\tau)+\gamma v(t-\tau))]} &+ \ln \frac{1+\alpha x(t)+\gamma v(t)}{1+\alpha x(t)+\gamma v^*}.
\end{aligned}$$

Therefore, we obtain

$$\begin{aligned}
\frac{dV_2(t)}{dt} = & -\frac{b_1 b_2 d(1+\gamma v^*)}{x(t)(1+\alpha x^*+\gamma v^*)} (x(t)-x^*)^2 \\
& + (\mu+\delta)z^*b_2 \left(1 - \frac{x^*}{x(t)} \frac{1+\alpha x(t)+\gamma v^*}{1+\alpha x^*+\gamma v^*} + \ln \frac{x^*}{x(t)} \frac{1+\alpha x(t)+\gamma v^*}{1+\alpha x^*+\gamma v^*} \right) \\
& + (\mu+\delta)z^*b_2 \left(1 - \frac{z(t)y^*}{z^*y(t)} + \ln \frac{z(t)y^*}{z^*y(t)} \right) \\
& + (\mu+\delta)z^* \int_0^\infty g(\tau) \left[1 - \frac{y(t-\tau)v^*}{y^*v(t)} + \ln \frac{y(t-\tau)v^*}{y^*v(t)} \right] d\tau
\end{aligned}$$

$$\begin{aligned}
& + \frac{(\mu + \delta)z^*}{b_1} b_2 \int_0^\infty f(\tau) \left[1 - \frac{z^* x(t-\tau) v(t-\tau) (1 + \alpha x^* + \gamma v^*)}{z x^* v^* [(1 + \alpha x(t-\tau) + \gamma v(t-\tau))]} \right. \\
& \left. + \ln \frac{z^* x(t-\tau) v(t-\tau) (1 + \alpha x^* + \gamma v^*)}{z x^* v^* [(1 + \alpha x(t-\tau) + \gamma v(t-\tau))]} \right] d\tau \\
& + (\mu + \delta) z^* b_2 \left(1 - \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^*} \right) + \ln \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^*} \\
& + (\mu + \delta) z^* b_2 \left(-1 - \frac{v(t)}{v^*} + \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^*} \right) + \frac{v(t)}{v^*} \frac{1 + \alpha x(t) + \gamma v^*}{1 + \alpha x(t) + \gamma v(t)}.
\end{aligned}$$

By calculating we have

$$\begin{aligned}
& (\mu + \delta) z^* \left(-1 - \frac{v(t)}{v^*} + \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^*} \right) + \frac{v(t)}{v^*} \frac{1 + \alpha x(t) + \gamma v^*}{1 + \alpha x(t) + \gamma v(t)} \\
& = - \frac{(\mu + \delta) z^* \gamma (1 + \alpha x(t))}{v^* (1 + \alpha x(t) + \gamma v^*) (1 + \alpha x(t) + \gamma v(t))} (v(t) - v^*)^2.
\end{aligned}$$

As we know function $f(x) = 1 - x + \ln x$ is always non-positive for $x > 0$, and $f(0) = 0$ if and only if $x = 1$. Noting that $x^*, z^*, y^*, v^* > 0$, it is easy to see that $\frac{dV_2(t)}{dt} \leq 0$ and $\frac{dV_2(t)}{dt} = 0$ if and only if $x(t) = x^*, z(t) = z^*, y(t) = y^*, v(t) = v^*$. From Lyapunov-LaSalle invariance principle, it shows that E^* is globally asymptotically stable when $R_0 > 1$. This completes the proof. \square

4. N-stage-structured model for HIV infection

In this section, we consider a n-stage-structured model of latently infected cells with two distributed delays. The model is described by

$$\frac{dx(t)}{dt} = \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)}, \quad (4.1)$$

$$\frac{dz(t)}{dt} = \int_0^\infty f(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau - \delta z(t) - \mu z(t), \quad (4.2)$$

$$\frac{dy_1(t)}{dt} = \mu z(t) - a_1 y_1(t), \quad (4.3)$$

$$\frac{dy_i(t)}{dt} = c_i y_{i-1}(t) - a_i y_i(t), \quad (4.4)$$

$$\frac{dv(t)}{dt} = p \int_0^\infty g(\tau) y_n(t-\tau) d\tau - rv(t), \quad (4.5)$$

where $i = 2, \dots, n$. $y_i(t)$ ($i = 2, \dots, n-1$) denote a class of infected cells that are not yet producing virus, i.e. cells in the eclipse phase (stage-structured model). Parameters a_i ($i = 1, \dots, n$) and c_i ($i = 2, \dots, n$) are assumed to be positive. Also, we suppose that $c_i < a_{i-1}$ according to the biological meanings. Denote the basic reproduction number of system (4.1-4.5) as

$$R_1 = \frac{\mu \lambda \beta p b_1 b_2}{\prod_{i=1}^n a_i r (\mu + \delta) (d + \alpha \lambda)},$$

where we denote $c_1 = 1$. System (4.1-4.5) always has an infection-free equilibrium $E_{00}(x_0, 0, \dots, 0)$, where $x_0 = \frac{\lambda}{d}$, and has only one infected equilibrium

$E^+(x^+, z^+, y_1^+, \dots, y_n^+, v^+)$ if $R_1 > 1$, where

$$x^+ = \frac{\mu\gamma\lambda p + \frac{\prod_{i=1}^n a_i}{\prod_{i=1}^n c_i} r(\mu + \delta)}{\mu\beta p + \mu d\gamma p - \alpha \frac{\prod_{i=1}^n a_i}{\prod_{i=1}^n c_i} r(\mu + \delta)}, z^+ = \frac{dx^+}{\mu + \delta} \left(\frac{\lambda}{dx^+} - 1 \right), y_1^+ = \frac{\mu z^+}{a_1},$$

$$y_i^+ = \frac{c_i y_{i-1}^+}{a_i} (i = 2, \dots, n), v^+ = \frac{p y_n^+}{r}.$$

Theorem 4.1. *If $R_1 \leq 1$, the infection-free equilibrium E_{00} of system (4.1-4.5) is globally asymptotically stable.*

Proof. Define a Lyapunov functional $V_3(t)$ as follows:

$$V_3(t) = \frac{b_1 b_2}{1 + \alpha x_0} (x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0}) + b_2 z(t) + \frac{(\mu + \delta) b_2}{\mu} y_1(t)$$

$$+ \sum_{i=2}^n \frac{(\mu + \delta) b_2}{\mu} \frac{\prod_{s=1}^{i-1} a_s}{\prod_{s=2}^i c_s} y_i(t) + \frac{(\mu + \delta)}{\mu p} \frac{\prod_{i=1}^n a_i}{\prod_{i=1}^n c_i} v(t)$$

$$+ b_2 U_5(t) + \frac{(\mu + \delta)}{\mu} \frac{\prod_{i=1}^n a_i}{\prod_{i=1}^n c_i} U_6(t),$$

where

$$U_5(t) = U_1(t) = \int_0^\infty \phi_1(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau, \quad \phi_1(t) = \int_t^\infty f(\tau) d\tau,$$

$$U_6(t) = \int_0^\infty \phi_2(\tau) y_n(t-\tau) d\tau, \quad \phi_2(t) = \int_t^\infty g(\tau) d\tau.$$

Similarly, we have

$$\frac{dU_5(t)}{dt} = b_1 \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)} - \int_0^\infty f(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau,$$

$$\frac{dU_6(t)}{dt} = b_2 y_n(t) - \int_0^\infty g(\tau) y_n(t-\tau) d\tau.$$

Calculating the derivative of $V_3(t)$, it follows that

$$\frac{dV_3(t)}{dt} = \frac{b_1 b_2}{1 + \alpha x_0} \left(1 - \frac{x_0}{x(t)} \right) (\lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)})$$

$$+ b_2 \left(\int_0^\infty f(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau - \delta z(t) - \mu z(t) \right)$$

$$+ \frac{(\mu + \delta) b_2}{\mu} (\mu z(t) - a_1 y_1(t)) + \sum_{i=2}^n \frac{(\mu + \delta) b_2}{\mu} \frac{\prod_{s=1}^{i-1} a_s}{\prod_{s=2}^i c_s} (b_i y_{i-1}(t) - a_i y_i(t))$$

$$+ \frac{(\mu + \delta) \frac{\prod_{i=1}^n a_i}{\prod_{i=1}^n c_i}}{\mu p} \left(p \int_0^\infty g(\tau) y_n(t-\tau) d\tau - r v(t) \right)$$

$$+ b_1 b_2 \frac{\beta x(t)v(t)}{1 + \alpha x(t) + \gamma v(t)} - b_2 \int_0^\infty f(\tau) \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha x(t-\tau) + \gamma v(t-\tau)} d\tau$$

$$+ \frac{(\mu + \delta) \frac{\prod_{i=1}^n a_i}{\prod_{i=1}^n c_i}}{\mu} [b_2 y_n(t) - \int_0^\infty g(\tau) y_n(t-\tau) d\tau].$$

Then, we have

$$\begin{aligned} \frac{dV_3(t)}{dt} &= -\frac{b_1 b_2 d(x(t) - x_0)^2}{x(t)(1 + \alpha x_0)} + b_1 b_2 \frac{1 + \alpha x(t)}{1 + \alpha x_0} \frac{\beta x_0 v(t)}{1 + \alpha x(t) + \gamma v(t)} \\ &\quad - \frac{r(\mu + \delta) \prod_{i=1}^n a_i}{\mu p} v(t) \\ &\leq -\frac{b_1 b_2 d(x(t) - x_0)^2}{x(t)(1 + \alpha x_0)} + \frac{r(\mu + \delta) \prod_{i=1}^n a_i}{\mu p} (R_1 - 1)v(t). \end{aligned}$$

So, it follows that $\frac{dV_3(t)}{dt} \leq 0$ if $R_1 \leq 1$. It is clear that $E_{00}(x_0, 0, \dots, 0, 0)$ is globally asymptotically stable when $R_1 \leq 1$ from Lyapunov-LaSalle invariance principle. \square

Theorem 4.2. *If $R_1 > 1$, the infected equilibrium $E^+(x^+, z^+, y_1^+, \dots, y_n^+, v^+)$ of system (4.1-4.5) is globally asymptotically stable.*

Proof. Define a Lyapunov functional $V_4(t)$ as follows:

$$\begin{aligned} V_4(t) &= b_1 b_2 (x(t) - x^+ - \int_{x^+}^{x(t)} \frac{(1 + \alpha s + \gamma v^+) x^+}{(1 + \alpha x^+ + \gamma v^+) s} ds) + b_2 (z(t) - z^+ - z^+ \ln \frac{z(t)}{z^+}) \\ &\quad + \frac{(\mu + \delta) b_2}{\mu} (y_1(t) - y_1^+ - y_1^+ \ln \frac{y_1(t)}{y_1^+}) \\ &\quad + \sum_{i=2}^n \frac{(\mu + \delta) b_2}{\mu} \frac{\prod_{s=1}^{i-1} a_s}{\prod_{s=2}^i c_s} (y_i(t) - y_i^+ - y_i^+ \ln \frac{y_i(t)}{y_i^+}) \\ &\quad + \frac{(\mu + \delta) \prod_{i=1}^n a_i}{\mu p \prod_{i=1}^n c_i} (v(t) - v^+ - v^+ \ln \frac{v(t)}{v^+}) \\ &\quad + \frac{(\mu + \delta) z^+}{b_1} b_2 U_7(t) + (\mu + \delta) z^+ U_8(t), \end{aligned}$$

where

$$\begin{aligned} U_7(t) &= \int_0^\infty \phi_1(\tau) \left[\frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^+ (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} - 1 \right. \\ &\quad \left. - \ln \frac{b_1 \beta x(t - \tau) v(t - \tau)}{(\mu + \delta) z^+ (1 + \alpha x(t - \tau) + \gamma v(t - \tau))} \right] d\tau, \\ U_8(t) &= \int_0^\infty \phi_2(\tau) \left[\frac{y_n(t - \tau)}{y_n^+} - 1 - \ln \frac{y_n(t - \tau)}{y_n^+} \right] d\tau \\ \phi_1(t) &= \int_t^\infty f(\tau) d\tau, \phi_2(t) = \int_t^\infty g(\tau) d\tau. \end{aligned}$$

Calculating the derivative of $V_4(t)$, it follows from the same methods in Theorem 3.2 that

$$\begin{aligned} \frac{dV_4(t)}{dt} &= -\frac{b_1 b_2 d(1 + \gamma v^+)}{1 + \alpha x^+ + \gamma v^+} (x(t) - x^+)^2 \\ &\quad + (\mu + \delta) z^+ b_2 \left(1 - \frac{x^+}{x(t)} \frac{1 + \alpha x(t) + \gamma v^+}{1 + \alpha x^+ + \gamma v^+} + \ln \frac{x^+}{x(t)} \frac{1 + \alpha x(t) + \gamma v^+}{1 + \alpha x^+ + \gamma v^+} \right) \\ &\quad + (\mu + \delta) z^+ b_2 \left(1 - \frac{z(t) y_1^+}{z^+ y_1(t)} + \ln \frac{z(t) y_1^+}{z^+ y_1(t)} \right) \end{aligned}$$

$$\begin{aligned}
& + \sum_{i=1}^{n-1} (\mu + \delta) z^+ b_2 \left(1 - \frac{y_i(t) y_{i+1}^+}{y_i^+ y_{i+1}(t)} + \ln \frac{y_i(t) y_{i+1}^+}{y_i^+ y_{i+1}(t)} \right) \\
& + (\mu + \delta) z^+ \int_0^\infty g(\tau) \left[1 - \frac{y_n(t-\tau) v^+}{y_n^+ v(t)} + \ln \frac{y_n(t-\tau) v^+}{y_n^+ v(t)} \right] d\tau \\
& + \frac{(\mu + \delta) z^+}{b_1} b_2 \int_0^\infty f(\tau) \left[1 - \frac{z^+ x(t-\tau) v(t-\tau) (1 + \alpha x^+ + \gamma v^+)}{z x^+ v^+ [(1 + \alpha x(t-\tau) + \gamma v(t-\tau))]} \right. \\
& \left. + \ln \frac{z^+ x(t-\tau) v(t-\tau) (1 + \alpha x^+ + \gamma v^+)}{z x^+ v^+ [(1 + \alpha x(t-\tau) + \gamma v(t-\tau))]} \right] d\tau \\
& + (\mu + \delta) z^+ b_2 \left(1 - \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^+} \right) + \ln \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^+} \\
& + (\mu + \delta) z^+ b_2 \left(-1 - \frac{v(t)}{v^+} + \frac{1 + \alpha x(t) + \gamma v(t)}{1 + \alpha x(t) + \gamma v^+} \right) + \frac{v(t)}{v^+} \frac{1 + \alpha x(t) + \gamma v^+}{1 + \alpha x(t) + \gamma v(t)}.
\end{aligned}$$

Thus, it follows that

$$\frac{dV_4(t)}{dt} \leq 0.$$

It is clear that $E^+(x^+, z^+, y_1^+, \dots, y_n^+, v^+)$ is globally asymptotically stable when $R_1 > 1$. We complete the proof. \square

5. Discussion and conclusion

In the present paper, we have proposed two mathematical models which includes two distributed intracellular delays. Meanwhile, we use the Beddington-DeAngelis functional response as nonlinear incidence rate. Here we introduce two general distributed delays with infinite delays. For the first model, we first derive that the solutions are all nonnegative and ultimately bounded for all $t > 0$. We also obtain the basic reproduction number $R_0 > 1$ which can determine global dynamics of the model and investigate uniform persistence of the model. What is more, we obtain global asymptotical stabilities of two equilibria by using the Lyapunov functional method. Our results imply that HIV virus can be eliminated at last if $R_0 \leq 1$. HIV virus will persist in vivo if $R_0 > 1$. Our conclusions show that time delay has no effect on the global asymptotic stability of the model. In addition, for the n-stage-structured model of latently infected cells, we calculate the basic reproduction number and derive that two equilibria are globally asymptotically stable by constructing proper Lyapunov functionals. It shows that multistage delays cannot change global asymptotic stability under some conditions.

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