

## A DELAY VIRUS MODEL WITH BEDDINGTON–DEANGELIS FUNCTIONAL RESPONSE

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*Abstract.* In this paper, we present a delay virus model with Beddington–DeAngelis functional response. We first introduce the basic reproduction number  $R_0$  and the immune response reproduction number  $R_1$ , and then show that the system has three possible equilibria depended on  $R_0$  and  $R_1$ . We further show that the global stability of the disease-free equilibrium  $E_0$ , immune-free equilibrium  $E_1$  and endemic equilibrium  $E_2$  are fully determined by  $R_0$  and  $R_1$ , that is,  $E_0$ ,  $E_1$  and  $E_2$  are globally asymptotically stable when  $R_0 \leq 1$ ,  $R_1 \leq 1 < R_0$ , and  $R_1 > 1$ , respectively.

### 1. Introduction

The mathematical model, based on biological interactions, presents a framework which can be used to obtain new insights and to interpret the mechanisms of virus infections. In the last decades, much has been studied on viral infection model. Considering universal nonlinear infection rate in the process of virus infecting target cells, Huang et al.[3] proposed the following virus dynamics model with Beddington–DeAngelis functional response:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda - dx(t) - f(x(t), v(t)), \\ \frac{dy(t)}{dt} = f(x(t), v(t)) - ay(t), \\ \frac{dv(t)}{dt} = ky(t) - \mu v(t), \end{cases} \quad (1.1)$$

with

$$f(x, v) = \frac{\beta xv}{1 + mx + nv}, \quad m \geq 0, n \geq 0, (x, v) \in \mathbb{R}^2.$$

Here,  $x(t)$ ,  $y(t)$ , and  $v(t)$  represent the populations of uninfected cells, infected target cells, and free virus at time  $t$ , respectively. The positive constant  $\lambda$  is the rate at which new healthy cells are generated. The positive constants  $d$  and  $\beta$  are respectively the

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death rate of uninfected cells and the rate constant characterizing infection of the cells. The function  $f(x, v)$  is the Beddington-DeAngelis functional response developed by Beddington [1] and DeAngelis et al. [2]. The positive constant  $a$  is the death rate of the infected cells due either to virus or the immune system. Free virus is produced from the infected cells at the rate  $ky$ . The positive constant  $\mu$  is the rate at which virus particles are removed from the system.

Note that the immune response after viral infection is universal and necessary to eliminate or control the disease. During the process of viral infection, the host response is induced which is initially rapid and nonspecific (natural killer cells, macrophage cells, etc) and specific (cytotoxic T lymphocyte cells, antibody cell). But, in most virus infections, cytotoxic T lymphocyte (CTL) cells which attack infected cells and antibody cells which attack viruses play a critical part in antiviral defense. In order to investigate the role of the population dynamics of viral infection with CTL response. Letting  $z(t)$  be the concentration of CTLs, Wang et al.[24] modified (1.1) to the following system:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda - dx(t) - f(x(t), v(t)), \\ \frac{dy(t)}{dt} = f(x(t), v(t)) - ay(t) - py(t)z(t), \\ \frac{dv(t)}{dt} = ky(t) - \mu v(t), \\ \frac{dz(t)}{dt} = cy(t)z(t) - bz(t), \end{cases} \quad (1.2)$$

where infected cells  $y(t)$  are removed at a rate  $pz(t)$  by the CTL immune response and the virus-specific CTL cells proliferate at a rate  $cy(t)$  by contact with infected cells, and die at a rate  $bz(t)$ .

System (1.2) always has a disease-free equilibrium  $E_{0(1.2)} = (\frac{\lambda}{d}, 0, 0, 0)$ , which represents the state that the viruses are absent. The basic reproductive number of system (1.2) is

$$R_{0(1.2)} = \frac{\lambda \beta k}{a\mu(d + m\lambda)}.$$

If  $R_{0(1.2)} > 1$ , there exists an immune-free equilibrium  $E_{1(1.2)} = (x_1, y_1, v_1, 0)$ , where

$$\begin{cases} x_1 = \frac{\lambda kn + \mu a}{\beta k + dkn - \mu am}, \\ y_1 = \frac{\lambda \beta k}{a(\beta k + dkn - \mu am)} \left(1 - \frac{1}{R_{0(1.2)}}\right), \\ v_1 = \frac{\lambda \beta k^2}{\mu a(\beta k + dkn - \mu am)} \left(1 - \frac{1}{R_{0(1.2)}}\right), \end{cases}$$

which denotes the state that the viruses are present while the CTL cells are absent.

We introduce an immune response reproduction number [24]:

$$R_{(1.2)}^0 = \frac{\lambda \beta ck}{ab(\beta k + dkn - \mu am)} \left(1 - \frac{1}{R_{0(1.2)}}\right).$$

If  $R_{(1.2)}^0 > 1$ , there exists an endemic equilibrium (called the interior equilibrium)  $E_{2(1.2)} = (x_2, y_2, v_2, z_2)$ , where  $x_2$  is a positive root of the quadric equation:

$$\mu c d m x^2 + (\mu c d + b d k n + \beta b k - \mu \lambda c m) x - \lambda (\mu c + b k n) = 0,$$

and

$$y_2 = \frac{b}{c}, \quad v_2 = \frac{k}{\mu} y_2, \quad z_2 = \frac{\lambda - d x_2 - a y_2}{p y_2}.$$

The endemic equilibrium denotes the state in which both the viruses and CTL cells are present.

Very recently, by constructing Lyapunov functions, Wang et al.[24] have studied the global stability of system (1.2). More specifically, they obtained the global stabilities of the disease-free equilibrium  $E_{0(1.2)}$ , immune-free equilibrium  $E_{1(1.2)}$  and endemic equilibrium  $E_{2(1.2)}$  when  $R_{0(1.2)} \leq 1$ ,  $R_{0(1.2)} > 1$ , and  $R_{(1.2)}^0 > 1$ , respectively; see [24, Theorems 2.1–2.3].

However, system (1.2) ignores the intracellular delay and assume that cells become productive instantaneously once a virus contracted a cell susceptible to infection. In fact, there always exists an intracellular phase of the viral life-cycle, defined as the time between infection of a cell and production of new virus particles [7, 22, 17, 18]. Therefore, in virus dynamics, it has been assumed that new virus particles are produced after the initial infection with a time interval and this leads mathematical models by delay differential equations; see, for example [4, 5, 9, 10, 11, 12, 13, 14, 15, 16, 23, 25, 26].

In this paper, to account for the effect of a latent period for the cell infection in system (1.2), we assume that virus production occurs after virus entry with a constant time lag  $\tau > 0$ . The recruitment of infected cells at time  $t$  is given by  $e^{-\alpha\tau} f(x(t - \tau), v(t - \tau))$ , where  $e^{-\alpha\tau}$  is the probability of surviving from  $t - \tau$  to  $t$  and  $\alpha$  is a constant death rate for infected cells (but not yet virus producing cells). Then, we obtain the following viral infection system with a latent period  $\tau$  and Beddington-DeAngelis functional response:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda - dx(t) - f(x(t), v(t)), \\ \frac{dy(t)}{dt} = e^{-\alpha\tau} f(x(t - \tau), v(t - \tau)) - ay(t) - py(t)z(t), \\ \frac{dv(t)}{dt} = ky(t) - \mu v(t), \\ \frac{dz(t)}{dt} = cy(t)z(t) - bz(t), \end{cases} \tag{1.3}$$

with

$$f(x, v) = \frac{\beta x v}{1 + m x + n v}, \quad m \geq 0, n \geq 0, (x, v) \in \mathbb{R}^2. \tag{1.4}$$

Obviously, (1.1) and (1.2) are the special cases of (1.3)-(1.4), respectively.

Here we investigate the global dynamics of system (1.3)-(1.4). We first introduce the basic reproduction number  $R_0$  and the immune response reproduction number

$R_1$ , and we then show that system (1.3)-(1.4) has three possible equilibria: disease-free equilibrium, immune-free equilibrium and endemic equilibrium; see, Theorem 2.1. Furthermore, by constructing suitable Lyapunov functionals and using the LaSalle invariance principle, we show that the global stability of the equilibria of system (1.3)-(1.4) are fully determined by the threshold parameters  $R_0$  and  $R_1$  defined in section 2, respectively, see, Theorems 3.1.

The paper is organized as follows. In next section, the reproductive numbers are derived and existence of each equilibria is discussed. The global stability of all the equilibria are given in section 3. Finally, we offer a brief discussion in section 4.

### 2. Basic properties

To study the stability of equilibria and investigate the dynamic of system (1.3)-(1.4) when  $\tau \geq 0$ , we need to consider a suitable phase space and a bounded feasible region. For  $\tau > 0$ , denote by  $\mathcal{C} = \mathcal{C}([-\tau, 0]; \mathbb{R})$  the Banach space of continues functions mapping the interval  $[-\tau, 0]$  into  $\mathbb{R}$  with norm  $\|\varphi\| = \sup_{-\tau \leq \theta \leq 0} |\varphi(\theta)|$  for  $\varphi \in \mathcal{C}$ . The nonnegative cone of  $\mathcal{C}$  is defined as  $\mathcal{C}^+ = \mathcal{C}([-\tau, 0], \mathbb{R}_+)$ . The initial conditions for system (1.3)-(1.4) are chosen at  $t = 0$  as  $\varphi \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+$  and  $\varphi(0) > 0$ . The following lemma establishes the feasible region of system (1.3)-(1.4) and shows that the system is well-posed.

LEMMA 2.1. *Under the above initial conditions, system (1.3)-(1.4) has a unique nonnegative solution, and all solutions are ultimately bounded in  $\mathcal{C} \times \mathbb{R} \times \mathcal{C} \times \mathbb{R}$ . Furthermore, all solutions eventually enter and remain in the following bounded and positively invariant region:*

$$\Gamma = \left\{ (x, y, v, z) \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ : \|x\| \leq \frac{\lambda}{d}, \|x + e^{\alpha\tau}y\| \leq \frac{\lambda}{d_1}, \right. \\ \left. \|x + e^{\alpha\tau}y + \frac{a}{k}v\| \leq \frac{\lambda}{d_2}, \|x + e^{\alpha\tau}y + \frac{a}{k}v + \frac{p}{c}e^{\alpha\tau}z\| \leq \frac{\lambda}{d_3} \right\},$$

where  $d_1 = \min\{a, d\}$ ,  $d_2 = \min\{d, a\alpha\tau e^{-\alpha\tau}, \mu\}$ ,  $d_3 = \min\{d, a\alpha\tau e^{-\alpha\tau}, \mu, b\}$ .

*Proof.* For all  $\varphi \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+$ , define

$$F(\varphi) = \begin{pmatrix} \lambda - d\varphi_1(0) + f(\varphi_1(0), \varphi_3(0)) \\ e^{-\alpha\tau}f(\varphi_1(-\tau), \varphi_3(-\tau)) - a\varphi_2(0) - p\varphi_2(0)\varphi_4(0) \\ k\varphi_2(0) - \mu\varphi_3(0) \\ c\varphi_2(0)\varphi_4(0) - b\varphi_4(0) \end{pmatrix}.$$

Thus, for all  $\varphi \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+$ ,  $F(\varphi)$  is continuous, and Lipschitzian in  $\varphi$  in each compact set in  $\mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+$ . Hence, there is a unique solution of system (1.3)-(1.4) through  $(0, \varphi)$  [6, Theorem 2.3.2]. Note that  $F_i(\varphi) \geq 0$  whenever  $\varphi \geq 0$  and  $\varphi_i(0) = 0$ . It then follows from [20, Remark 5.2.1] that  $\mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+$  is positive invariant.

Next we show that positive solutions of (1.3)-(1.4) are ultimately bounded for  $t \geq 0$ . From the first equation of (1.3), we obtain  $\frac{dx(t)}{dt} \leq \lambda - dx(t)$ , and thus  $\limsup_{t \rightarrow \infty} x(t) \leq \frac{\lambda}{d}$ . Adding the first two equations of (1.3), we get

$$\begin{aligned} \frac{d}{dt} \left( x(t) + e^{\alpha\tau}y(t + \tau) \right) &= \lambda - dx(t) - ae^{\alpha\tau}y(t + \tau) - pe^{\alpha\tau}y(t + \tau)z(t + \tau) \\ &\leq \lambda - d_1(x(t) + e^{\alpha\tau}y(t + \tau)). \end{aligned}$$

Thus,

$$\limsup_{t \rightarrow \infty} (x(t) + e^{\alpha\tau}y(t)) \leq \frac{\lambda}{d_1}.$$

Adding the first three equations of (1.3) gives

$$\begin{aligned} \frac{d}{dt} \left( x(t) + e^{\alpha\tau}y(t + \tau) + \frac{a}{k}v(t + \tau) \right) &= \lambda - dx(t) - a(e^{\alpha\tau} - 1)y(t + \tau) - \mu \frac{a}{k}v(t + \tau) \\ &\leq \lambda - dx(t) - a\alpha\tau y(t + \tau) - \mu \frac{a}{k}v(t + \tau) \\ &\leq \lambda - d_2 \left( x(t) + e^{\alpha\tau}y(t + \tau) + \frac{a}{k}v(t + \tau) \right). \end{aligned}$$

Thus,

$$\limsup_{t \rightarrow \infty} \left( x(t) + e^{\alpha\tau}y(t + \tau) + \frac{a}{k}v(t + \tau) \right) \leq \frac{\lambda}{d_2}.$$

Adding all the equations of (1.3), we have

$$\begin{aligned} \frac{d}{dt} \left( x(t) + e^{\alpha\tau}y(t + \tau) + \frac{a}{k}v(t + \tau) + \frac{p}{c}e^{\alpha\tau}z(t + \tau) \right) &= \lambda - dx(t) - a(e^{\alpha\tau} - 1)y(t + \tau) - \mu \frac{a}{k}v(t + \tau) - b \frac{p}{c}e^{\alpha\tau}z(t + \tau) \\ &\leq \lambda - dx(t) - a\alpha\tau y(t + \tau) - \mu \frac{a}{k}v(t + \tau) - b \frac{p}{c}e^{\alpha\tau}z(t + \tau) \\ &\leq \lambda - d_3 \left( x(t) + e^{\alpha\tau}y(t + \tau) + \frac{a}{k}v(t + \tau) + \frac{p}{c}e^{\alpha\tau}z(t + \tau) \right). \end{aligned}$$

Thus,

$$\limsup_{t \rightarrow \infty} \left( x(t) + e^{\alpha\tau}y(t + \tau) + \frac{a}{k}v(t + \tau) + \frac{p}{c}e^{\alpha\tau}z(t + \tau) \right) \leq \frac{\lambda}{d_3}.$$

Therefore,  $x(t)$ ,  $y(t)$ ,  $v(t)$  and  $z(t)$  are ultimately bounded in  $\mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+$ .  $\square$

First of all, we show that system (1.3)-(1.4) has three possible equilibria. For this, we define two threshold parameters, see [24],

$$R_0 = \frac{\lambda \beta k e^{-\alpha\tau}}{\mu a(d + \lambda m)}, \tag{2.1}$$

and

$$R_1 = \frac{\lambda \beta c k e^{-\alpha \tau}}{a b (\beta k + d k n - \mu a m e^{\alpha \tau})} \left( 1 - \frac{1}{R_0} \right), \tag{2.2}$$

$R_0$  and  $R_1$  are respectively called the basic reproduction number and the immune response reproductive number for system (1.3)-(1.4).

**THEOREM 2.1.** *For system (1.3)-(1.4), there exist a disease-free equilibrium*

$$E_0 = (x_0, 0, 0, 0), \quad x_0 = \frac{\lambda}{d},$$

*an immune-free equilibrium  $E_1 = (x_1, y_1, v_1, 0)$ , where*

$$\begin{cases} x_1 = \frac{\lambda k n + \mu a e^{\alpha \tau}}{\beta k + d k n - \mu a m e^{\alpha \tau}}, \\ y_1 = \frac{\lambda \beta k e^{-\alpha \tau}}{a (\beta k + d k n - \mu a m e^{\alpha \tau})} \left( 1 - \frac{1}{R_0} \right), \\ v_1 = \frac{\lambda \beta k^2 e^{-\alpha \tau}}{\mu a (\beta k + d k n - \mu a m e^{\alpha \tau})} \left( 1 - \frac{1}{R_0} \right), \end{cases} \tag{2.3}$$

*if  $R_0 > 1$ , and an endemic equilibrium  $E_2 = (x_2, y_2, v_2, z_2)$ , where  $x_2$  is the positive root of the following quadric equation:*

$$\mu c d m x^2 + (\mu c d + b d k n + \beta b k - \mu \lambda c m) x - \lambda (\mu c + b k n) = 0, \tag{2.4}$$

and

$$y_2 = \frac{b}{c}, \quad v_2 = \frac{b k}{\mu c}, \quad z_2 = \frac{\lambda - d x_2 - a y_2 e^{\alpha \tau}}{p y_2 e^{\alpha \tau}}, \tag{2.5}$$

*if  $R_1 > 1$ .*

*Proof.* Obviously, the disease-free equilibrium  $E_0$  always exists. To find other equilibria, we consider the following equations:

$$\begin{cases} \lambda - d x - f(x, v) = 0, \\ e^{-\alpha \tau} f(x, v) - a y - p y z = 0, \\ k y - \mu v = 0, \\ c y z - b z = 0. \end{cases} \tag{2.6}$$

Assume that there exists an equilibrium  $E_1 = (x_1, y_1, v_1, 0)$  with  $x_1 > 0, y_1 > 0, v_1 > 0$ . From the third equation of (2.6), we get

$$y_1 = \frac{\mu}{k} v_1. \tag{2.7}$$

Substituting (2.7) into the second equation of (2.6) gives

$$\frac{e^{-\alpha \tau} \beta x_1}{1 + m x_1 + n v_1} = \frac{\mu a}{k}, \tag{2.8}$$

which follows from the first equation of (2.6) that

$$\lambda - dx_1 = \frac{\mu a}{k} e^{\alpha\tau} v_1. \tag{2.9}$$

Combining (2.8) and (2.9), we get

$$x_1 = \frac{\lambda kn + \mu a e^{\alpha\tau}}{\beta k + dkn - \mu a m e^{\alpha\tau}},$$

here note that  $R_0 > 1$  implies that  $\beta k + dkn - \mu a m e^{\alpha\tau} > 0$ , thus,  $x_1 > 0$ . Putting  $x_1$  into (2.9), we have

$$v_1 = \frac{\lambda \beta k^2 e^{-\alpha\tau}}{a \mu (\beta k + dkn - \mu a m e^{\alpha\tau})} \left(1 - \frac{1}{R_0}\right),$$

which follows from (2.7) that

$$y_1 = \frac{\lambda \beta k e^{-\alpha\tau}}{a (\beta k + ndk - a m \mu e^{\alpha\tau})} \left(1 - \frac{1}{R_0}\right).$$

It is easy to see that  $y_1$  and  $v_1$  are positive for  $R_0 > 1$ . Consequently, system (1.3)-(1.4) has an immune-free equilibrium  $E_1 = (x_1, y_1, v_1, 0)$  if  $R_0 > 1$ .

Next, we assume that there exists an equilibrium  $E_2 = (x_2, y_2, v_2, z_2)$  with  $x_2 > 0$ ,  $y_2 > 0$ ,  $v_2 > 0$ ,  $z_2 > 0$  if  $R_1 > 1$ . Obviously, from the third and fourth equations of (2.6), respectively, we get

$$y_2 = \frac{b}{c}, \quad v_2 = \frac{k}{\mu} y_2 = \frac{bk}{\mu c}.$$

Substituting  $v_2 = \frac{bk}{\mu c}$  into the first equation of (2.6), we get  $x_2 > 0$  satisfies (2.4). Combining the first two equations of (2.6), we have

$$\lambda - dx_2 = e^{\alpha\tau} y_2 (a + pz_2).$$

Thus,

$$z_2 = \frac{\lambda - dx_2 - ay_2 e^{\alpha\tau}}{p y_2 e^{\alpha\tau}}.$$

Here, we note that the inequality  $\lambda - dx_2 - ay_2 e^{\alpha\tau} > 0$  is equal to

$$\lambda \beta c k e^{-\alpha\tau} + a^2 b \mu m e^{\alpha\tau} - a(\mu \lambda m c + \mu c d + b d n k + \beta k b) > 0.$$

On the other hand, the fact  $R_1 > 1$  implies that

$$\frac{\lambda \beta c k e^{-\alpha\tau} + a^2 b \mu m e^{\alpha\tau}}{a(\mu \lambda m c + \mu c d + b d n k + \beta k b)} > 1,$$

which follows  $z_2 > 0$ .  $\square$

### 3. Global stability of the equilibria

In this section, we consider the global asymptotic stabilities of three equilibria. For convenience, define

$$g(x) = x - 1 - \ln x \text{ for } x \in (0, +\infty),$$

it is easy to see that  $g(x) \geq 0$  for all  $x \in (0, +\infty)$  and  $\min_{0 < x < +\infty} g(x) = g(1) = 0$ .

**THEOREM 3.1.** *For system (1.3)-(1.4),*

- (i) *If  $R_0 \leq 1$ , then the disease-free equilibrium  $E_0$  is globally asymptotically stable in  $\Gamma$ ;*
- (ii) *If  $R_1 \leq 1 < R_0$ , then the immune-free equilibrium  $E_1$  is globally asymptotically stable in  $\Gamma$ ;*
- (iii) *If  $R_1 > 1$ , then the endemic equilibrium  $E_2$  is globally asymptotically stable in  $\Gamma$ .*

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

$$V_1(t) = \frac{x_0}{1 + mx_0} g\left(\frac{x(t)}{x_0}\right) + e^{\alpha\tau}y(t) + \frac{ae^{\alpha\tau}}{k}v(t) + \frac{pe^{\alpha\tau}}{c}z(t) + V_{11}(t),$$

where

$$V_{11}(t) = \int_{t-\tau}^t f(x(\theta), v(\theta))d\theta.$$

Since  $g\left(\frac{x(t)}{x_0}\right)$  is non-negative, Lyapunov functional  $V_1$  is non-negative definite in  $\Gamma$  with respect to  $E_0$ . Note that

$$\frac{dV_{11}(t)}{dt} = f(x(t), v(t)) - f(x(t - \tau), v(t - \tau)).$$

Calculating  $\frac{dV_1(t)}{dt}$  along the solution of (1.3)-(1.4), we have

$$\begin{aligned} \frac{dV_1(t)}{dt} &= \frac{1}{1 + mx_0} \left(1 - \frac{x_0}{x(t)}\right) \left(dx_0 - dx(t) - f(x(t), v(t))\right) \\ &\quad - \frac{\mu ae^{\alpha\tau}}{k}v(t) - \frac{bpe^{\alpha\tau}}{c}z(t) + f(x(t), v(t)) \\ &= -\frac{d(x(t) - x_0)^2}{x(t)(1 + mx_0)} + \frac{1 + mx(t)}{1 + mx_0} \frac{\beta x_0 v(t)}{1 + mx(t) + nv(t)} \\ &\quad - \frac{\mu ae^{\alpha\tau}}{k}v(t) - \frac{bpe^{\alpha\tau}}{c}z(t) \\ &= -\frac{d(x(t) - x_0)^2}{x(t)(1 + mx_0)} + \frac{\mu ae^{\alpha\tau}v(t)(1 + mx(t))}{k(1 + mx(t) + nv(t))} (R_0 - 1) \end{aligned}$$



$$-\frac{\mu b p e^{\alpha \tau}}{k(1+m x(t)+n v(t))} v^2(t)-\frac{b p e^{\alpha \tau}}{c} z(t) .$$

Since  $x(t), y(t), v(t), z(t)$  are positive, it follows from  $R_0 \leq 1$  that  $\frac{dV_1(t)}{dt} \leq 0$ . Hence, every solutions of system (1.3)-(1.4) tends to  $M_0$ , the largest invariant subset of  $\{\frac{dV_1(t)}{dt} = 0\}$  with respect to system (1.3)-(1.4). We show that  $M_0$  consists of only the equilibrium  $E_0$ . Let  $(x(t), y(t), v(t), z(t))$  be the solution with initial function in  $M_0$ . Then, from the invariance of  $M_0$ ,  $x(t) = x_0, v(t) = 0$ , and  $z(t) = 0$  for any  $t$ . Now we have  $\frac{dV(t)}{dt} = 0$  and hence, it follows  $y(t) = 0$  for any  $t$ , from the third equation of (1.3). From the LaSalle invariance principle [6, Corollary 5.3.1], the disease-free equilibrium  $E_0$  is globally asymptotically stable.

(ii) Define a Lyapunov functional as follows:

$$V_2(t) = V_{21}(t) + a y_1 V_{22}(t),$$

where

$$V_{21}(t) = e^{-\alpha t} \left( x(t) - x_1 - \int_{x_1}^{x(t)} \frac{f(x_1, v_1)}{f(\theta, v_1)} d\theta \right) + y_1 g\left(\frac{y(t)}{y_1}\right) + \frac{a v_1}{k} g\left(\frac{v(t)}{v_1}\right) + \frac{p}{c} z(t),$$

and

$$V_{22}(t) = \int_{t-\tau}^t g\left(\frac{e^{-\alpha t}}{a y_1} f(x(\theta), v(\theta))\right) d\theta .$$

Let

$$V_0(x) = x - x_1 - \int_{x_1}^x \frac{f(x_1, v_1)}{f(\theta, v_1)} d\theta \text{ for } x \in (0, +\infty) .$$

Since

$$\frac{dV_0(x)}{dx} = 1 - \frac{f(x_1, v_1)}{f(x, v_1)},$$

we have  $\frac{dV_0(x)}{dx} < 0$  for  $x \in (0, x_1)$ ,  $\frac{dV_0(x)}{dx} > 0$  for  $x \in (x_1, +\infty)$  and  $\frac{dV_0(x_1)}{dx} = 0$ . We also have  $V_0(x_1) = 0$ . Then  $V_0(x) > 0$  for all  $x > 0$ . Hence,  $V_2(t) \geq 0$  for all  $t \geq 0$ . Note that

$$\begin{aligned} \frac{dV_{22}(t)}{dt} &= \frac{e^{-\alpha t}}{a y_1} (f(x(t), v(t)) - f(x(t-\tau), v(t-\tau))) \\ &\quad + \ln \frac{f(x(t-\tau), v(t-\tau))}{f(x(t), v(t))} . \end{aligned}$$

Hence,

$$\begin{aligned} \frac{dV_2(t)}{dt} &= e^{-\alpha t} \left( 1 - \frac{f(x_1, v_1)}{f(x(t), v_1)} \right) \frac{dx(t)}{dt} + \left( 1 - \frac{y_1}{y(t)} \right) \frac{dy(t)}{dt} \\ &\quad + \frac{a}{k} \left( 1 - \frac{v_1}{v(t)} \right) \frac{dv(t)}{dt} + \frac{p}{c} \frac{dz(t)}{dt} + a y_1 \frac{dV_{22}(t)}{dt} . \end{aligned} \tag{3.1}$$

Note that

$$\lambda = dx_1 + ay_1e^{\alpha\tau}, \quad ay_1 = e^{-\alpha\tau}f(x_1, v_1), \quad \frac{y_1}{v_1} = \frac{\mu}{k}.$$

It follows from (3.1) that

$$\begin{aligned} \frac{dV_2(t)}{dt} = & -de^{-\alpha\tau} \frac{(1 + nv_1)(x(t) - x_1)^2}{x(t)(1 + mx_1 + nv_1)} + ay_1 \left[ \ln \frac{f(x(t - \tau), v(t - \tau))}{f(x(t), v(t))} \right. \\ & + \left( 3 - \frac{f(x_1, v_1)}{f(x(t), v_1)} - \frac{y(t)v_1}{y_1v(t)} - \frac{y_1}{y(t)} \frac{f(x(t - \tau), v(t - \tau))}{f(x(t), v(t))} \right) \\ & \left. + \left( -\frac{v(t)}{v_1} + \frac{f(x(t), v(t))}{f(x(t), v_1)} \right) \right] + p \left( y_1 - \frac{b}{c} \right) z(t). \end{aligned}$$

Using the equality

$$\begin{aligned} \ln \frac{f(x(t - \tau), v(t - \tau))}{f(x(t), v(t))} = & \ln \frac{f(x_1, v_1)}{f(x(t), v_1)} + \ln \frac{y(t)v_1}{y_1v(t)} + \ln \frac{1 + mx(t) + nv(t)}{1 + mx_1 + nv_1} \\ & + \ln \frac{y_1}{y(t)} \frac{f(x(t - \tau), v(t - \tau))}{f(x_1, v_1)}, \end{aligned}$$

we obtain

$$\begin{aligned} \frac{dV_2(t)}{dt} = & -de^{-\alpha\tau} \frac{(1 + nv_1)(x(t) - x_1)^2}{x(t)(1 + mx_1 + nv_1)} - ay_1 \left[ g \left( \frac{f(x_1, v_1)}{f(x(t), v_1)} \right) + g \left( \frac{y(t)v_1}{y_1v(t)} \right) \right. \\ & + g \left( \frac{1 + mx(t) + nv(t)}{1 + mx_1 + nv_1} \right) + g \left( \frac{y_1}{y(t)} \frac{f(x(t - \tau), v(t - \tau))}{f(x_1, v_1)} \right) \\ & \left. + \left( 1 + \frac{v(t)}{v_1} - \frac{f(x(t), v(t))}{f(x(t), v_1)} - \frac{1 + mx(t) + nv(t)}{1 + mx_1 + nv_1} \right) \right] - p \left( \frac{b}{c} - y_1 \right) z(t). \end{aligned}$$

Note that

$$1 + \frac{v(t)}{v_1} - \frac{f(x(t), v(t))}{f(x(t), v_1)} - \frac{1 + mx(t) + nv(t)}{1 + mx_1 + nv_1} = \frac{n(v(t) - v_1)^2}{v_1(1 + mx(t) + nv(t))} > 0,$$

and it follows from  $R_1 \leq 1$  that  $cy_1 - b \leq 0$ , i.e.,  $\frac{b}{c} - y_1 \geq 0$ . Then, by the above calculations, we get  $\frac{dV_2(t)}{dt} \leq 0$  holds for  $x(t), y(t), v(t), z(t) > 0$ . It is clear that  $V_2(t) \geq 0$ , and  $V_2(t) = 0$  iff  $x(t) = x_1, y(t) = y_1, v(t) = v_1$  and  $z(t) = 0$ . Hence, every solutions of system (1.3)-(1.4) tends to  $M_1$ , the largest invariant subset of  $\{ \frac{dV_2(t)}{dt} = 0 \}$  with respect to system (1.3)-(1.4). We show that  $M_1$  consists of only the equilibrium  $E_1$ . Let  $(x(t), y(t), v(t), z(t))$  be the solution with initial function in  $M_1$ . Then, from the invariance of  $M_1$ ,  $x(t) = x_1, v(t) = v_1$ , and  $z(t) = 0$  for any  $t$ . Now we have  $\frac{dV(t)}{dt} = 0$  and hence, it follows  $y(t) = 0$  for any  $t$ , from the third equation of (1.3). From the LaSalle invariance principle [6, Corollary 5.3.1], the immune-free equilibrium  $E_1$  is globally asymptotically stable when  $R_1 \leq 1 < R_0$ .

(iii) Define a Lyapunov functional as follows:

$$V_3(t) = V_{31}(t) + y_2(a + pz_2)V_{32}(t),$$

where

$$V_{31}(t) = e^{-\alpha\tau} \left( x(t) - x_2 - \int_{x_2}^{x(t)} \frac{f(x_2, v_2)}{f(\theta, v_2)} d\theta \right) + y_2 g \left( \frac{y(t)}{y_2} \right) + \frac{a + pz_2}{k} v_2 g \left( \frac{v(t)}{v_2} \right) + \frac{pz_2}{c} g \left( \frac{z(t)}{z_2} \right),$$

and

$$V_{32}(t) = \int_{t-\tau}^t g \left( \frac{e^{-\alpha\tau}}{y_2(a + pz_2)} f(x(\theta), v(\theta)) \right) d\theta.$$

Note that

$$\frac{dV_{32}(t)}{dt} = \frac{e^{-\alpha\tau}}{y_2(a + pz_2)} \left( f(x(t), v(t)) - f(x(t - \tau), v(t - \tau)) \right) + \ln \frac{f(x(t - \tau), v(t - \tau))}{f(x(t), v(t))}.$$

Hence

$$\begin{aligned} \frac{dV_3(t)}{dt} &= e^{-\alpha\tau} \left( 1 - \frac{f(x_2, v_2)}{f(x(t), v_2)} \right) \frac{dx(t)}{dt} + \left( 1 - \frac{y_2}{y(t)} \right) \frac{dy(t)}{dt} \\ &+ \frac{a + pz_2}{k} \left( 1 - \frac{v_2}{v(t)} \right) \frac{dv(t)}{dt} \\ &+ \frac{p}{c} \left( 1 - \frac{z_2}{z(t)} \right) \frac{dz(t)}{dt} + y_2(a + pz_2) \frac{dV_{32}(t)}{dt}. \end{aligned} \tag{3.2}$$

Since

$$\begin{aligned} \lambda &= dx_2 + y_2(a + pz_2)e^{\alpha\tau}, \quad \frac{y_2}{v_2} = \frac{\mu}{k}, \quad y_2 = \frac{b}{c}, \\ \beta x_2 v_2 &= e^{\alpha\tau} y_2(a + pz_2)(1 + mx_2 + nv_2), \end{aligned}$$

it follows from (3.2) that

$$\begin{aligned} \frac{dV_3(t)}{dt} &= -de^{-\alpha\tau} \frac{(1 + nv_2)(x(t) - x_2)^2}{x(t)(1 + mx_2 + nv_2)} + y_2(a + pz_2) \left[ \ln \frac{f(x(t - \tau), v(t - \tau))}{f(x(t), v(t))} \right. \\ &+ \left( 3 - \frac{x_2(1 + mx(t) + nv_2)}{x(t)(1 + mx_2 + nv_2)} - \frac{y(t)v_2}{y_2v(t)} - \frac{y_2}{y(t)} \frac{f(x(t - \tau), v(t - \tau))}{f(x_2, v_2)} \right) \\ &\left. + \left( -\frac{v(t)}{v_2} + \frac{f(x(t), v(t))}{f(x(t), v_2)} \right) \right]. \end{aligned}$$

Similarly, using the equality

$$\begin{aligned} \ln \frac{f(x(t - \tau), v(t - \tau))}{f(x(t), v(t))} &= \ln \frac{f(x_2, v_2)}{f(x(t), v_2)} + \ln \frac{y(t)v_2}{y_2v(t)} + \ln \frac{1 + mx(t) + nv(t)}{1 + mx(t) + nv_2} \\ &+ \ln \frac{y_2}{y(t)} \frac{f(x(t - \tau), v(t - \tau))}{f(x_2, v_2)}, \end{aligned}$$

we get

$$\begin{aligned} \frac{dV_3(t)}{dt} = & -de^{-\alpha\tau} \frac{(1+nv_2)(x(t)-x_2)^2}{x(t)(1+mx_2+nv_2)} - y_2(a+pz_2) \left[ g\left(\frac{1+mx(t)+nv(t)}{1+mx(t)+nv_2}\right) \right. \\ & + g\left(\frac{y(t)v_2}{y_2v(t)}\right) + g\left(\frac{f(x_2, v_2)}{f(x(t), v_2)}\right) + g\left(\frac{f(x(t-\tau), v(t-\tau))}{f(x_2, v_2)}\right) \\ & \left. + \left(1 + \frac{v(t)}{v_2} - \frac{f(x(t), v(t))}{f(x(t), v_2)} - \frac{1+mx(t)+nv(t)}{1+mx(t)+nv_2}\right) \right]. \end{aligned}$$

It is easy to see that  $\frac{dV_3(t)}{dt} \leq 0$  holds for  $x(t), y(t), v(t), z(t) > 0$ . Obviously,  $V_3(t) \geq 0$ , and  $V_3(t) = 0$  iff  $x(t) = x_2, y(t) = y_2, v(t) = v_2, z(t) = z_2$ . Hence, every solutions of system (1.3)-(1.4) tends to  $M_2$ , the largest invariant subset of  $\{\frac{dV_2(t)}{dt} = 0\}$  with respect to system (1.3)-(1.4). We show that  $M_2$  consists of only the equilibrium  $E_2$ . Let  $(x(t), y(t), v(t), z(t))$  be the solution with initial function in  $M_2$ . Then, from the invariance of  $M_2$ ,  $x(t) = x_2$ , and  $v(t) = v_2$  for any  $t$ . Now we have  $\frac{dv(t)}{dt} = 0$  and hence, it follows  $y(t) = \frac{\mu v_2}{k} = y_2$  for any  $t$ , from the third equation of (1.3). Similarly, we have  $\frac{dy(t)}{dt} = 0$  and hence, it follows  $z(t) = z_2$  for any  $t$ , from the second equation of (1.3). From the LaSalle invariance principle [6, Corollary 5.3.1], the endemic equilibrium  $E_2$  is globally asymptotically stable when  $R_1 > 1$ .  $\square$

### 4. Discussion

In this paper, following the ideas of Huang et al. [3, 4], Nakata [15], and Wang et al. [24], we also assume that the incidence rate of the virus infection is described by a Beddington-DeAngelis functional response. By introducing a discrete time delay into the functional response  $f(x, v)$ , we then obtain a delay model (1.3)-(1.4). For system (1.3)-(1.4), by Lyapunov functionals and LaSalle invariance principle, we study global dynamics system (1.3)-(1.4). Here, construction of these Lyapunov functionals are all motivated by the works of Huang [3, 4, 5], Korobeinikov [8, 9], Li and Shu [11, 12], McCluskey [13, 14], Nakata [15, 16], Wang et al.[24], and so on.

To analyze the global stability of system (1.3)-(1.4), we define two thresholds parameters, the basic reproduction number  $R_0$  and the immune response reproduction number  $R_1$ , which determine the existence of these equilibria and also fully determine the global stability of system (1.3)-(1.4). The disease-free equilibrium  $E_0$  is globally asymptotically stable if  $R_0 \leq 1$  and the virus are cleared. The infected equilibrium without immune response  $E_1$  is globally asymptotically stable if  $R_1 \leq 1 < R_0$  and the infection becomes chronic but with no persistent immune response. The infected equilibrium with immune response  $E_2$  is globally asymptotically stable if  $R_1 > 1$  and the infection becomes chronic but with immune response.

Note that the Beddington-DeAngelis functional function  $f(x, v) = \frac{\beta xv}{1+mx+nv}$  introduced here includes bilinear rate  $f(x, v) = \beta xv$  from (1.4) with  $m = n = 0$ , and non-linear rate  $f(x, v) = \frac{\beta xv}{1+nv}$  from (1.4) with  $m = 0$  and  $n > 0$ . Therefore, Theorems 3.1 generalize the global stability results in [3, 4, 15, 19]. Moreover, our results improve stability results in [10, 23, 24, 26] and include the main results in [21].

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