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GLOBAL DYNAMICS FOR A DELAYED HEPATITIS C VIRUS INFECTION MODEL

YINGYING ZHAO, ZHITING XU

Abstract. In this paper, we present a delay Hepatitis C virus infection model with Beddington-DeAngelis functional response. We first introduce five reproduction numbers, and then show that the system has five possible equilibria depended on the reproductive numbers. By constructing suitable Lyapunov functionals, the global dynamics for the five equilibria of the model is completely determined by the five reproductive numbers.

1. Introduction

To develop a better understanding of a virus dynamics in vivo, mathematical models have played a significant role. A basic viral infection model proposed by Perelson et al [14, 15] has been widely used for studying the dynamics of infections agents such as hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV, which has the following standard form:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - dT(t) - kT(t)V(t),\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= kT(t)V(t) - \delta T^*(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^*(t) - cV(t),
\end{aligned} \tag{1.1}$$

where T, T^*, V denote the concentration of uninfected cells, infected cells and free virus particles. The uninfected cells are produced at a constant rate λ and die at a per capita rate d. They become infected at a rate proportional kV to the free virus concentration. Infected cells are produced at a rate kTV, and its natural death rate is δT^*. Free viruses are produced by infected cells, which is described by $N\delta T^*$ and die at a per capita rate c.

Note that the immune response after viral infection is universal and necessary to eliminate or control the disease. In most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking infected cells. Let $Y(t)$ be the CTL responses, Nowak and Bangham [13] formulated the following virus

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dynamics model:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - dT(t) - kT(t)V(t),\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= kT(t)V(t) - \delta T^*(t) - pY(t)T^*(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^*(t) - cV(t),\\
\frac{\mathrm{d}Y(t)}{\mathrm{d}t} &= \beta T^*(t)Y(t) - \gamma Y(t),
\end{aligned} \tag{1.2}$$

where infected cells are also killed via mass action kinetics by the CTL immune response, which is described by pYT^*, CTLs are produced at a rate proportional βT^*Y to the abundances of CTLs and infected cells, and die at a per capita rate γ.

In addition, antibody responses, which are implemented by the functioning of immunocompetent B lymphocytes, also play a critical role in preventing and modulating infections. To investigate the highly complex and non-linear interaction between replicating viruses, uninfected cells, infected cells, and different types of immune responses (CTL and antibody), Wodarz [19] developed the following HCV infection model:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - dT(t) - kT(t)V(t),\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= kT(t)V(t) - \delta T^*(t) - pY(t)T^*(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^*(t) - cV(t) - qA(t)V(t),\\
\frac{\mathrm{d}Y(t)}{\mathrm{d}t} &= \beta T^*(t)Y(t) - \gamma Y(t),\\
\frac{\mathrm{d}A(t)}{\mathrm{d}t} &= gA(t)V(t) - bA(t).
\end{aligned} \tag{1.3}$$

Here A denotes the concentration of antibody responses, free virus are also neutralized via mass action kinetics by antibodies, which is described by qAV. The antibody responses are activated at a rate proportional gAV to the abundances of antibodies and free viruses, and die at a per capita rate b. All parameters are positive constants.

Note that model (1.3) ignores the intracellular delay and assumes that cells become productive instantaneously once a virus contacts a cell to infection. However, the intracellular delay may impact infection dynamics significantly. In view of this

observation, Yan and Wang [21] proposed the following model with delay:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - dT(t) - kT(t)V(t),\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= kT(t-\tau)V(t-\tau)e^{-s\tau} - \delta T^*(t) - pY(t)T^*(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^*(t) - cV(t) - qA(t)V(t),\\
\frac{\mathrm{d}Y(t)}{\mathrm{d}t} &= \beta T^*(t)Y(t) - \gamma Y(t),\\
\frac{\mathrm{d}A(t)}{\mathrm{d}t} &= gA(t)V(t) - bA(t).
\end{aligned} \tag{1.4}$$

Here, the production of new virus at time t depends on the population of virus and infected cells at a previous time $t-\tau$, and only a fraction of $e^{-s\tau}$ can survive after the interval τ, where $1/s$ is the average lifetime of infected without reproduction. Yan and Wang [21] have studied the global dynamics of system (1.4).

From system (1.4), we can see that the rate of infection of those viral dynamics models is assumed to bilinear in the virus V and susceptible cells T. However, the actual incidence rate is probably not linear over the entire range of V and T. So it is reasonable to assume that the infection rate of viral infection model is given by saturated infection rate, $\frac{kTV}{1+k_2V}$, where k_2 is positive constant. In addition, because there exists an intracellular phase of a cell and production of new virus particles. In view of the above observation, Wang and Liu [18] considered the viral infection model with saturation infection rate and delay as follows:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - dT(t) - \frac{kT(t)V(t)}{1+k_2V(t)},\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= e^{-s\tau}\frac{kT(t-\tau)V(t-\tau)}{1+k_2V(t-\tau)} - \delta T^*(t) - pY(t)T^*(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^*(t) - cV(t) - qA(t)V(t),\\
\frac{\mathrm{d}Y(t)}{\mathrm{d}t} &= \beta T^*(t)Y(t) - \gamma Y(t),\\
\frac{\mathrm{d}A(t)}{\mathrm{d}t} &= gA(t)V(t) - bA(t).
\end{aligned} \tag{1.5}$$

By constructing Lyapunov functionals, Wang and Liu [18] have studied the global stability of system (1.5).

In this paper, following the line of [18, 21], we assume that the infection rate of the virus dynamics models is given by the Beddington-DeAngelis functional response, $\frac{kTV}{1+k_1T+k_2V}$, where $k_1, k_2 \geq 0$ are constants. Then, we obtain the following viral infection system with a latent period τ and Beddington-DeAngelis functional

response:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= \lambda - dT(t) - f(T(t), V(t)),\\
\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= e^{-s\tau} f(T(t-\tau), V(t-\tau)) - \delta T^*(t) - pY(t)T^*(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\delta T^*(t) - cV(t) - qA(t)V(t),\\
\frac{\mathrm{d}Y(t)}{\mathrm{d}t} &= \beta T^*(t)Y(t) - \gamma Y(t),\\
\frac{\mathrm{d}A(t)}{\mathrm{d}t} &= gA(t)V(t) - bA(t),
\end{aligned} \tag{1.6}$$

with

$$f(T,V) = \frac{kTV}{1 + k_1 T + k_2 V}, \quad k_1 \geq 0,\ k_2 \geq 0,\ (T,V) \in \mathbb{R}^2. \tag{1.7}$$

The functional response $\frac{kTV}{1+k_1T+k_2V}$ was introduced by Beddington [1] and DeAngelis et al.[2]. Obviously, (1.3)-(1.5) can be seen as special cases of (1.6)-(1.7). Other related works contributed to dynamics of the mathematical model with Beddington and DeAngelis functional response; see, for example, [3, 5, 6, 8, 10, 12, 17, 18, 20, 22].

In this paper, we investigate the global dynamics of (1.6)-(1.7) by employing the method using Lyapunov functionals motivated by Huang [5], Korobeinikov [7], Li and Shu [9], Nakata [12], McCluskey [11], Wang and Liu[18], Yan and Wang [21], et al. This paper is organized as follows. In Section 2, we show the positivity and ultimately boundedness of the solutions for (1.6)-(1.7) under suitable initial conditions. In Section 3, we introduce the basic reproduction number for viral infection R_0 and for response reproduction numbers R_1, R_2, R_3, R_4 and derive the existence of the five equilibrium for (1.6)-(1.7). The global stabilities of all equilibrium are given in Section 4. A brief discuss section completes this paper.

2. Basic properties

To study the stability of equilibria and investigate the dynamic of system (1.6)-(1.7), we need to consider a suitable phase space and a bounded feasible region. For $\tau > 0$, we define a Banach space by $\mathcal{C} = \mathcal{C}([-\tau, 0]; \mathbb{R})$, the 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 $\mathcal{C}^+ = \mathcal{C}([-\tau, 0], \mathbb{R}_+)$, where $\mathbb{R}_+ = [0, \infty)$. The initial conditions for system (1.6)-(1.7) are chosen at $t = 0$ as $\varphi \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ \times \mathbb{R}_+$ and $\varphi(0) > 0$. The following lemma establishes the feasible region of the system and shows that the system is well-posed.

Lemma 2.1. *Under the above initial conditions, system* (1.6)-(1.7) *has a unique nonnegative solution, and all solutions are ultimately bounded in* $\mathcal{C} \times \mathbb{R}_+ \times \mathcal{C} \times \mathbb{R}_+ \times \mathbb{R}_+$. *Furthermore, all solutions eventually enter and remain in the following bounded and positively invariant region:*

$$\begin{aligned}
\Gamma = \Big\{ &(T, T^*, V, Y, A) \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ \times \mathbb{R}_+ :\ \|T\| \leq \frac{\lambda}{d} + 1,\ \|T^*\| \leq \frac{\lambda}{d_1} + 1,\\
&\|V\| \leq \frac{N\delta\lambda}{cd_1} + 1,\ \|Y\| \leq \frac{\beta N k \delta \lambda^2}{pcdd_1d_2} e^{-s\tau} + 1,\ \|A\| \leq \frac{gN\delta\lambda}{qd_1d_3} + 1 \Big\},
\end{aligned}$$

where $d_1 = \min\{\delta, d\}$, $d_2 = \min\{\gamma, \delta\}$, $d_3 = \min\{c, b\}$.

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

$$F(\varphi) = \begin{pmatrix} \lambda - d\varphi_1(0) - f(\varphi_1(0), \varphi_3(0)) \\ e^{-s\tau} f(\varphi_1(-\tau), \varphi_3(-\tau)) - \delta\varphi_2(0) - p\varphi_2(0)\varphi_4(0) \\ N\delta\varphi_2(0) - c\varphi_3(0) - q\varphi_5(0)\varphi_3(0) \\ \beta\varphi_2(0)\varphi_4(0) - \gamma\varphi_4(0) \\ g\varphi_5(0)\varphi_3(0) - b\varphi_5(0) \end{pmatrix}.$$

Thus, for all $\varphi \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ \times \mathbb{R}_+$, $F(\varphi)$ is continuous, and Lipschitzian in φ in each compact set in $\mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ \times \mathbb{R}_+$. Hence, there is a unique solution of system (1.6)-(1.7) through $(0, \varphi)$ [4, Theoroms 2.2.1 and 2.2.3]. Note that $F_i(\varphi) \geq 0$ whenever $\varphi \geq 0$ and $\varphi_i(0) = 0$. It then follows from [16, Throem 5.2.1 and Remark 5.2.1] that $\mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ \times \mathbb{R}_+$ is positive invariant.

Next we show that positive solutions of (1.6)-(1.7) are ultimately bounded for $t \geq 0$. From the first equation of (1.6), we obtain $\frac{\mathrm{d}T(t)}{\mathrm{d}t} \leq \lambda - dT(t)$, and thus, $\limsup_{t\to\infty} T(t) \leq \frac{\lambda}{d}$. Adding the first two equations, we then get

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}(T(t) + T^*(t+\tau)) &= \lambda - dT(t) - f(T(t), V(t))(1 - e^{-s\tau}) \\ &\quad - \delta T^*(t+\tau) - pT^*(t+\tau)Y(t+\tau) \\ &\leq \lambda - d_1(T(t) + T^*(t+\tau)). \end{aligned}$$

Thus, $\limsup_{t\to\infty}(T(t) + T^*(t+\tau)) \leq \frac{\lambda}{d_1}$. This relation and the third equation of (1.6) imply

$$\frac{\mathrm{d}}{\mathrm{d}t}V(t) = N\delta T^*(t) - cV(t) - qA(t)V(t) \leq N\delta\frac{\lambda}{d_1} - cV(t),$$

which follows that $\limsup_{t\to\infty} V(t) \leq \frac{N\delta\lambda}{cd_1}$. Also, adding the second and fourth equations of (1.6), we obtain

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}(T^*(t) + \frac{p}{\beta}Y(t)) &= e^{-s\tau} f(T(t-\tau), V(t-\tau)) - \delta T^*(t) - \frac{p}{\beta}\gamma Y(t) \\ &\leq e^{-s\tau} kT(t)V(t) - \delta T^*(t) - \frac{p}{\beta}\gamma Y(t) \\ &\leq e^{-s\tau} k\frac{\lambda}{d}\frac{N\delta\lambda}{cd_1} - d_2\big[T^*(t) + \frac{p}{\beta}Y(t)\big]. \end{aligned}$$

Hence, $\limsup_{t\to\infty}(T^*(t) + \frac{p}{\beta}Y(t)) \leq \frac{Nk\delta\lambda^2}{cdd_1d_2}e^{-s\tau}$.

Similar to the above, we also get

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t}(V(t) + \frac{q}{g}A(t)) &= N\delta T^*(t) - cV(t) - \frac{qb}{g}A(t) \\ &\leq N\delta T^*(t) - d_3(V(t) + \frac{q}{g}A(t)) \\ &\leq N\delta\frac{\lambda}{d_1} - d_3(V(t) + \frac{q}{g}A(t)). \end{aligned}$$

Then, $\limsup_{t\to\infty}(V(t) + \frac{q}{g}A(t)) \leq \frac{N\delta\lambda}{d_1d_3}$. Hence, $T(t)$, $T^*(t)$, $V(t)$, $Y(t)$ and $A(t)$ are ultimately bounded in the bounded feasible and positively invariant region Γ. □

3. Reproductive numbers and equilibria

First of all, we show that system (1.6)-(1.7) has five possible equilibria. For this, we define five threshold parameters, which are also called the reproduction numbers.

The basic reproduction number of system (1.6)-(1.7) is

$$R_0 = \frac{N\lambda k e^{-s\tau}}{c(d+\lambda k_1)}.$$

The CTL immune reproduction number R_1 for system (1.6)-(1.7) is

$$R_1 = \frac{N\lambda k\beta e^{-s\tau}}{\gamma\delta(Nk+Ndk_2-k_1ce^{s\tau})}\Big(1-\frac{1}{R_0}\Big).$$

The antibody immune reproduction number R_2 for system (1.6)-(1.7) is

$$R_2 = \frac{N^2\lambda k g e^{-s\tau}}{bc(Nk+Ndk_2-k_1ce^{s\tau})}\Big(1-\frac{1}{R_0}\Big).$$

The CTL immune competitive reproduction number R_3 for system (1.6)-(1.7) is

$$R_3 = \frac{\lambda\beta^2 kbe^{-s\tau}+k_1g\delta^2\gamma^2e^{s\tau}}{\beta\gamma\delta(gd+kb+k_2bd+\lambda k_1g)},$$

The antibody immune competitive reproduction number R_4 for system (1.6)-(1.7) is

$$R_4 = \frac{Ng\delta\gamma}{\beta bc}.$$

Theorem 3.1. *(i) System* (1.6)-(1.7) *always has an infection free equilibrium* $E_0 = (\frac{\lambda}{d},0,0,0,0)$*;*

(ii) When $R_0>1$*, system* (1.6)-(1.7) *has an immune-free infection equilibrium*

$$E_1 = (T_1, T_1^*, V_1, 0, 0),$$

where

$$\begin{aligned}
T_1 &= \frac{N\lambda+ck_2e^{s\tau}}{Nk+Ndk_2-k_1ce^{s\tau}},\\
T_1^* &= \frac{N\lambda ke^{-s\tau}}{\delta(Nk+Ndk_2-k_1ce^{s\tau})}\Big(1-\frac{1}{R_0}\Big),\\
V_1 &= \frac{N^2\lambda ke^{-s\tau}}{c(Nk+Ndk_2-k_1ce^{s\tau})}\Big(1-\frac{1}{R_0}\Big);
\end{aligned}$$

(iii) When $R_1>1$*, system* (1.6)-(1.7) *has an infection equilibrium with only CTL immune responses* $E_2=(T_2,T_2^*,V_2,Y_2,0)$*, where* T_2 *is the positive root of the following quadric equation:*

$$cdk_1\beta T^2+(\beta cd+kN\delta\gamma+dk_2N\delta\gamma-\lambda k_1\beta c)T-\lambda(\beta c+k_2N\delta\gamma)=0, \tag{3.1}$$

and

$$T_2^*=\frac{\gamma}{\beta},\quad V_2=\frac{N\delta\gamma}{\beta c},\quad Y_2=\frac{\lambda-dT_2-\delta T_2^*e^{s\tau}}{pT_2^*e^{s\tau}};$$

(iv) When $R_2>1$*, system* (1.6)-(1.7) *has an infection equilibrium with only antibody immune responses* $E_3=(T_3,T_3^*,V_3,0,A_3)$*, where* T_3 *is the positive root of the following quadric equation:*

$$gdk_1T^2+(gd+kb+k_2bd-\lambda k_1g)T-\lambda(g+k_2b)=0, \tag{3.2}$$

and

$$T_3^* = \frac{e^{-s\tau}}{\delta} f(T_3, V_3), \quad V_3 = \frac{b}{g}, \quad A_3 = \frac{N(\lambda - dT_3) - cV_3 e^{s\tau}}{qV_3 e^{s\tau}};$$

(v) When $R_3 > 1$ and $R_4 > 1$, system (1.6)-(1.7) has an interior equilibrium with both CTL immune responses and antibody immune responses $E_4 = (T_4, T_4^*, V_4, Y_4, A_4)$, where T_4 is the positive root of the following quadric equation:

$$gdk_1T^2 + (gd + kb + k_2bd - \lambda k_1 g)T - \lambda(g + k_2 b) = 0, \tag{3.3}$$

and

$$T_4^* = \frac{\gamma}{\beta}, \quad V_4 = \frac{b}{g}, \quad Y_4 = \frac{\lambda - dT_4 - \delta T_4^* e^{s\tau}}{pT_4^* e^{s\tau}}, \quad A_4 = \frac{N\delta\gamma g - \beta cb}{\beta qb}.$$

Proof. (i) Obviously, the infection free equilibrium E_0 always exists.

(ii) We show that (1.6)-(1.7) admits an equilibrium $E_1 = (T_1, T_1^*, V_1, 0, 0)$, when $R_0 > 1$, which satisfies

$$\begin{aligned} \lambda - dT_1 - f(T_1, V_1) &= 0, \\ e^{-s\tau} f(T_1, V_1) - \delta T_1^* &= 0, \\ N\delta T_1^* - cV_1 &= 0. \end{aligned} \tag{3.4}$$

From the third equation of (3.4), we obtain $T_1^* = \frac{c}{N\delta} V_1$. Substituting this into the second equation of (3.4), we obtain

$$\frac{kT_1}{1 + k_1T_1 + k_2V_1} e^{-s\tau} = \frac{c}{N}, \tag{3.5}$$

which follows from the first equation of (3.4) that

$$\lambda - dT_1 = f(T_1, V_1) = \frac{c}{N} V_1 e^{s\tau}. \tag{3.6}$$

Combining (3.5) and (3.6), we obtain

$$T_1 = \frac{N\lambda + ck_2 e^{s\tau}}{Nk + Ndk_2 - k_1 ce^{s\tau}}.$$

Here, note that $R_0 > 1$ implies that $Nk + Ndk_2 - k_1 ce^{s\tau} > 0$. Consequently, $T_1 > 0$. Putting T_1 into (3.4), we have

$$V_1 = \frac{N^2 \lambda k e^{-s\tau}}{c(Nk + Ndk_2 - k_1 ce^{s\tau})} \Big(1 - \frac{1}{R_0}\Big),$$

which follows

$$T_1^* = \frac{N\lambda k e^{-s\tau}}{\delta(Nk + Ndk_2 - k_1 ce^{s\tau})} \Big(1 - \frac{1}{R_0}\Big).$$

Hence, if $R_0 > 1$, system (1.6)-(1.7) has an immune-free infection equilibrium $E_1 = (T_1, T_1^*, V_1, 0, 0)$.

(iii) To find the infection equilibrium with only CTL immune responses $E_2 = (T_2, T_2^*, V_2, Y_2, 0)$, we consider the equations

$$\begin{aligned} \lambda - dT - f(T, V) &= 0, \\ e^{-s\tau} f(T, V) - \delta T^* - pYT^* &= 0, \\ N\delta T^* - cV &= 0, \\ \beta T^* Y - \gamma Y &= 0. \end{aligned} \tag{3.7}$$

From the third and fourth equation of (3.7), we obtain

$$T_2^* = \frac{\gamma}{\beta}, \quad V_2 = \frac{N\delta}{c}T_2^* = \frac{N\delta\gamma}{\beta c}.$$

Substituting $V_2 = \frac{N\delta\gamma}{\beta c}$ into the first equation of (3.7), we obtain T_2 satisfies (3.2), thus

$$T_2 = \frac{-b_1 + \sqrt{b_1^2 + 4cdk_1\beta\lambda(\beta c + k_2 N\delta\gamma)}}{2cdk_1\beta},$$

where $b_1 = \beta cd + kN\delta\gamma + dk_2N\delta\gamma - \lambda k_1\beta c$. Obviously $T_2 > 0$. Combining the first and second equation of (3.7), we obtain

$$Y_2 = \frac{\lambda - dT_2 - \delta T_2^* e^{s\tau}}{pT_2^* e^{s\tau}}.$$

Obviously, $\lambda - dT_2 - \delta T_2^* e^{s\tau} > 0$ is equal to the following inequality

$$k_1c\delta\gamma e^{s\tau} + \beta\lambda kNe^{-s\tau} > \beta cd + kN\delta\gamma + \lambda k_1\beta c + dk_2N\delta\gamma.$$

On the other hand, it follows from $R_1 > 1$ that

$$\frac{k_1c\delta\gamma e^{s\tau} + \beta\lambda kNe^{-s\tau}}{\beta cd + kN\delta\gamma + \lambda k_1\beta c + dk_2N\delta\gamma} > 1.$$

Thus, we know that $R_1 > 1$ implies $Y_2 > 0$.

(iv) To find the infection equilibrium with only antibody immune responses $E_3 = (T_3, T_3^*, V_3, 0, A_3)$, we consider the following equations:

$$\begin{aligned} \lambda - dT - f(T,V) &= 0,\\ e^{-s\tau}f(T,V) - \delta T^* &= 0,\\ N\delta T^* - cV - qAV &= 0,\\ gAV - bA &= 0. \end{aligned} \tag{3.8}$$

From the fourth equation of (3.8), we obtain $V_3 = \frac{b}{g}$, Substituting $V_3 = \frac{b}{g}$ into the first equation of (3.8), we obtain $T_3 > 0$ satisfies (3.2). From the second equation of (3.8), we obtain

$$T_3^* = \frac{e^{-s\tau}}{\delta}(\lambda - dT_3) = \frac{e^{-s\tau}}{\delta}f(T_3, V_3) > 0.$$

By (3.8), we also obtain

$$A_3 = \frac{N(\lambda - dT_3) - cV_3e^{s\tau}}{qV_3e^{s\tau}}.$$

On the other hand, $\lambda - dT_3 - \frac{cV_3e^{s\tau}}{N} > 0$ is equivalent to the inequality

$$k_1c^2be^{s\tau} + N^2\lambda gke^{-s\tau} > cN(gd + kb + k_2bd + \lambda k_1g).$$

Obviously, it follows from $R_2 > 1$ that

$$\frac{k_1c^2be^{s\tau} + N^2\lambda gke^{-s\tau}}{cN(gd + kb + k_2bd + \lambda k_1g)} > 1.$$

Thus, we know that $R_2 > 1$ implies $A_3 > 0$.

(v) To find the interior equilibria $E_4 = (T_4, T_4^*, V_4, Y_4, A_4)$, we consider the following equations:

$$\begin{aligned} \lambda - dT - f(T,V) &= 0,\\ e^{-s\tau} f(T,V) - \delta T^* - pYT^* &= 0,\\ N\delta T^* - cV - qAV &= 0,\\ \beta T^* Y - \gamma Y &= 0,\\ gAV - bA &= 0. \end{aligned} \tag{3.9}$$

It follows from (3.9) that

$$T_4^* = \frac{\gamma}{\beta}, \quad V_4 = \frac{b}{g}, \quad A_4 = \frac{N\delta\gamma g - \beta cb}{\beta qb} = \frac{c}{q}(R_4 - 1).$$

Thus, it follows from $R_4 > 1$ that $A_4 > 0$. Substituting $V_4 = \frac{b}{g}$ into the first equation of (3.9), we obtain $T_4 > 0$ satisfies (3.3). From the first and the second equation of (3.9), we obtain

$$Y_4 = \frac{\lambda - dT_4 - \delta T_4^* e^{s\tau}}{pT_4^* e^{s\tau}}.$$

It is not difficult to show that the inequality $\lambda - dT_4 - \delta T_4^* e^{s\tau} > 0$ is equivalent to

$$\lambda kbe^{-s\tau} + k_1 g\delta^2 \frac{\gamma^2}{\beta^2} e^{s\tau} > \frac{\gamma}{\beta}\delta(gd + kb + k_2 bd + \lambda k_1 g).$$

Obviously, $R_3 > 1$ is equal to $\lambda - dT_4 - \delta T_4^* e^{s\tau} > 0$. Consequently, $Y_4 > 0$. □

4. Global stability of the equilibria

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

$$g(x) = x - 1 - \ln x, \quad x \in (0, +\infty).$$

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 4.1. *If $R_0 \leq 1$, then the infection-free equilibrium $E_0 = (\frac{\lambda}{d}, 0, 0, 0, 0)$ is globally asymptotically stable in Γ.*

Proof. Define a Lyapunov functional

$$U_0(t) = \frac{T_0}{1 + k_1 T_0} U_{01}(t) + U_{02}(t),$$

where

$$U_{01}(t) = g\big(\frac{T(t)}{T_0}\big), \quad U_{02}(t) = e^{s\tau} T^*(t) + \frac{e^{s\tau}}{N} V(t) + \int_{t-\tau}^{t} f(T(\theta), V(\theta))\mathrm{d}\theta.$$

Clearly, $U_0(t)$ is non-negative definite in Γ with respect to E_0. Note that

$$\frac{\mathrm{d}U_{01}(t)}{\mathrm{d}t} = \frac{T(t) - T_0}{T_0 T(t)}(\lambda - dT(t) - f(T(t), V(t))).$$

Substituting $\lambda = dT_0$ to the above gives

$$\frac{\mathrm{d}U_{01}(t)}{\mathrm{d}t} = -\frac{d}{T_0 T(t)}(T(t) - T_0)^2 - \Big(\frac{1}{T_0} - \frac{1}{T(t)}\Big) f(T(t), V(t)).$$

Direct computations give

$$\begin{aligned}\frac{\mathrm{d}U_{02}(t)}{\mathrm{d}t} &= e^{s\tau}(e^{-s\tau}f(T(t-\tau),V(t-\tau)) - \delta T^*(t) - pY(t)T^*(t))\\ &\quad + \frac{e^{s\tau}}{N}(N\delta T^*(t) - cV(t) - qA(t)V(t))\\ &\quad + f(T(t),V(t)) - f(T(t-\tau),V(t-\tau))\\ &= -pe^{s\tau}Y(t)T^*(t) - \frac{ce^{s\tau}}{N}V(t) - \frac{qe^{s\tau}}{N}A(t)V(t) + f(T(t),V(t)).\end{aligned}$$

Consequently,

$$\frac{\mathrm{d}U_0(t)}{\mathrm{d}t} = -\frac{d(T(t)-T_0)^2}{(1+k_1T_0)T(t)} + C_0(t),$$

where

$$\begin{aligned}&C_0(t)\\ &= f(T(t),V(t))\Big(1 - \frac{T(t)-T_0}{(1+k_1T_0)T(t)}\Big) - pe^{s\tau}Y(t)T^*(t) - \frac{e^{s\tau}}{N}V(t)(c - qA(t))\\ &= \frac{kT_0}{1+k_1T_0}\frac{V(t)(1+k_1T(t))}{1+k_1T(t)+k_2V(t)} - \frac{ce^{s\tau}}{N}V(t) - pe^{s\tau}Y(t)T^*(t) - \frac{qe^{s\tau}}{N}A(t)V(t)\\ &= (R_0-1)\frac{ce^{s\tau}V(t)(1+k_1T(t))}{N(1+k_1T(t)+k_2V(t))} - \frac{ck_2e^{s\tau}}{N(1+k_1T(t)+k_2V(t))}V^2(t)\\ &\quad - pe^{s\tau}Y(t)T^*(t) - \frac{qe^{s\tau}}{N}A(t)V(t).\end{aligned}$$

Note that $C_0(t) \le 0$ when $R_0 \le 1$. Thus $\frac{\mathrm{d}U_0(t)}{\mathrm{d}t} \le 0$. Let

$$M_0 = \big\{(T(t),T^*(t),V(t),Y(t),A(t)) : \dot{U}_0(t) = 0\big\}.$$

Clearly, $\dot{U}_0(t) = 0$ implies $T(t) = T_0 = \frac{\lambda}{d}$. Thus, $\dot{T}(t) = \lambda - dT_0 - f(T_0,V(t)) = 0$, which gives $V(t) = 0$. Then, $\dot{V}(t) = N\delta T^*(t) = 0$, which gives $T^*(t) = 0$. Clearly, the largest compact invariant set in M_0:

$$M_0 = \big\{(T(t),T^*(t),V(t),Y(t),A(t)) : T(t) = \frac{\lambda}{d}, T^*(t) = V(t) = Y(t) = A(t) = 0\big\}.$$

By the above discussion, in view of the LaSalle invariance principle [4, Theorem 5.3.1], we see that all positive solutions approach the largest compact invariant set E_0 in M_0. Thus, E_0 is globally asymptotically stable in Γ. □

Theorem 4.2. *If $R_1 \le 1 < R_0$ and $R_2 \le 1$, then the immune-free infection equilibrium $E_1 = (T_1, T_1^*, V_1, 0, 0)$ is globally asymptotically stable in Γ.*

Proof. Define a Lyapunov functional

$$U_1(t) = e^{-s\tau}U_{11}(t) + T_1^*g\Big(\frac{T^*(t)}{T_1^*}\Big) + \frac{V_1}{N}g\Big(\frac{V(t)}{V_1}\Big) + \frac{p}{\beta}Y(t) + \frac{q}{Ng}A(t) + \delta T_1^*U_{12}(t),$$

where

$$U_{11}(t) = T(t) - T_1 - \int_{T_1}^{T(t)}\frac{f(T_1,V_1)}{f(\theta,V_1)}\mathrm{d}\theta, \quad U_{12}(t) = \int_{t-\tau}^{t} g\Big(\frac{e^{-s\tau}}{\delta T_1^*}f(T(\theta),V(\theta))\Big)\mathrm{d}\theta.$$

Let

$$H(T) = T - T_1 - \int_{T_1}^{T}\frac{f(T_1,V_1)}{f(\theta,V_1)}\mathrm{d}\theta, \ T \in (0,+\infty).$$

Since

$$\frac{\mathrm{d}H(T)}{\mathrm{d}T} = 1 - \frac{f(T_1, V_1)}{f(T, V_1)},$$

we have

$$\frac{\mathrm{d}H(T)}{\mathrm{d}T} < 0 \text{ for } T \in (0, T_1), \quad \frac{\mathrm{d}H(T)}{\mathrm{d}T} > 0 \text{ for } T \in (T_1, +\infty), \quad \frac{\mathrm{d}H(T_1)}{\mathrm{d}T} = 0.$$

We also have $H(T_1) = 0$. Then $H(T) > 0$ for all $T > 0$. Hence, $U_{11}(t) \geq 0$ for all $t \geq 0$. Obviously, $U_1(t)$ is non-negative definite in Γ with respect to E_1.

First, we calculate $\frac{\mathrm{d}U_{11}(t)}{\mathrm{d}t}$ and $\frac{\mathrm{d}U_{12}(t)}{\mathrm{d}t}$.

$$\frac{\mathrm{d}U_{11}(t)}{\mathrm{d}t} = \Big(1 - \frac{f(T_1, V_1)}{f(T(t), V_1)}\Big)\frac{\mathrm{d}T(t)}{\mathrm{d}t},$$

and

$$\begin{aligned}
\frac{\mathrm{d}U_{12}(t)}{\mathrm{d}t} &= \frac{e^{-s\tau}}{\delta T_1^*}\big(f(T(t), V(t)) - f(T(t-\tau), V(t-\tau))\big) + \ln\frac{f(T(t-\tau), V(t-\tau))}{f(T(t), V(t))} \\
&= \frac{e^{-s\tau}}{\delta T_1^*}\big(f(T(t), V(t)) - f(T(t-\tau), V(t-\tau))\big) + \ln\frac{f(T_1, V_1)}{f(T(t), V_1)} \\
&\quad + \ln\frac{T^*(t)V_1}{T_1^*V(t)} + \ln\frac{V(t)f(T(t), V_1)}{V_1 f(T(t), V(t))} + \ln\frac{T_1^* f(T(t-\tau), V(t-\tau))}{T^*(t)f(T_1, V_1)}.
\end{aligned}$$

Thus

$$\begin{aligned}
\frac{\mathrm{d}U_1(t)}{\mathrm{d}t} &= e^{-s\tau}\Big(1 - \frac{f(T_1, V_1)}{f(T(t), V_1)}\Big)(\lambda - dT(t) - f(T(t), V(t))) \\
&\quad + \Big(1 - \frac{T_1^*}{T^*(t)}\Big)\big(e^{-s\tau}f(T(t-\tau), V(t-\tau)) - \delta T^*(t) - pY(t)T^*(t)\big) \\
&\quad + \frac{p}{\beta}(\beta T^*(t) - \gamma)Y(t) + \frac{q}{Ng}(gV(t) - b)A(t) \\
&\quad + e^{-s\tau}\big(f(T(t), V(t)) - f(T(t-\tau), V(t-\tau))\big) + \delta T_1^*\Big(\ln\frac{f(T_1, V_1)}{f(T(t), V_1)} \\
&\quad + \ln\frac{T^*(t)V_1}{T_1^*V(t)} + \ln\frac{V(t)f(T(t), V_1)}{V_1 f(T(t), V(t))} + \ln\frac{T_1^* f(T(t-\tau), V(t-\tau))}{T^*(t)f(T_1, V_1)}\Big)
\end{aligned}$$

Substituting

$$V_1 = \frac{N^2\lambda k e^{-s\tau}}{c(Nk + Nd - k_1 c e^{s\tau})}\Big(1 - \frac{1}{R_0}\Big)$$

and

$$\lambda = dT_1 + f(T_1, V_1), \quad \delta e^{s\tau}T_1^* = f(T_1, V_1), \quad N\delta T_1^* = cV_1$$

into the above gives

$$\frac{\mathrm{d}U_1(t)}{\mathrm{d}t} = -\frac{de^{-s\tau}(1 + k_2V_1)}{1 + k_1T_1 + k_2V_1}\frac{(T(t) - T_1)^2}{T(t)} + C_1(t),$$

where

$$\begin{aligned}
C_1(t) &= p\Big(T_1^* - \frac{\gamma}{\beta}\Big)Y(t) + \frac{qb}{Ng}\Big(\frac{gV_1}{b} - 1\Big)A(t) \\
&\quad + \delta T_1^*\Big[\ln\frac{f(T(t-\tau), V(t-\tau))}{f(T(t), V(t))} - \frac{V(t)}{V_1} + \frac{f(T(t), V(t))}{f(T(t), V_1)}
\end{aligned}$$

$$+\Big(3-\frac{f(T_1,V_1)}{f(T(t),V_1)}-\frac{T^*(t)V_1}{T_1^*V(t)}-\frac{T_1^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_1,V_1)}\Big)\Big].$$

Next, we claim that $C_1(t)$ is not positive. In fact,

$$\begin{aligned}
C_1(t)&=\frac{p\gamma}{\beta}(R_1-1)Y(t)+\frac{qb}{Ng}(R_2-1)A(t)-\delta T_1^*\Big[g\Big(\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)\\
&\quad+g\Big(\frac{T^*(t)V_1}{T_1^*V(t)}\Big)+g\Big(\frac{V(t)f(T(t),V_1)}{V_1f(T_1,V_1)}\Big)+g\Big(\frac{T_1^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_1,V_1)}\Big)\\
&\quad+1+\frac{V(t)}{V_1}-\frac{f(T(t),V(t))}{f(T(t),V_1)}-\frac{V(t)f(T(t),V_1)}{V_1f(T(t),V(t))}\Big]\\
&=\frac{p\gamma}{\beta}(R_1-1)Y(t)+\frac{qb}{Ng}(R_2-1)A(t)-\delta T_1^*\Big[g\Big(\frac{f(T_1,V_1)}{f(T(t),V_1)}\Big)\\
&\quad+g\Big(\frac{T^*(t)V_1}{T_1^*V(t)}\Big)+g\Big(\frac{V(t)f(T(t),V_1)}{V_1f(T_1,V_1)}\Big)+g\Big(\frac{T_1^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_1,V_1)}\Big)\\
&\quad+\frac{k_2(1+k_1T(t))(V(t)-V_1)^2}{V_1(1+k_1T(t)+k_2V(t))(1+k_1T(t)+k_2V_1)}\Big].
\end{aligned}$$

Clearly, $C_1(t)\le 0$ when $R_1\le 1$ and $R_2\le 1$. Hence, $\frac{\mathrm{d}U_1(t)}{\mathrm{d}t}\le 0$. Let

$$M_1=\Big\{(T(t),T^*(t),V(t),Y(t),A(t)):\dot U_1(t)=0\Big\}.$$

It can be verified from the derivative of $\dot U_1(t)=0$ if and only if $T(t)=T_1$, $V(t)=V_1$, $\frac{T^*(t)V_1}{T_1^*V(t)}=1$. Hence, $T^*(t)=T_1^*$. It follows from the second and the third equation of the model (1.6)-(1.7) that $Y(t)=A(t)=0$. Clearly, the largest compact invariant set in M_1 is

$$\begin{aligned}
&\Big\{(T(t),T^*(t),V(t),Y(t),A(t)):T(t)=T_1,\ T^*(t)=T_1^*,\\
&\quad V(t)=V_1,Y(t)=A(t)=0\Big\}.
\end{aligned}$$

By the LaSalle invariance principle [4, Theorem 5.3.1 5.3.1], we know that, when $R_1\le 1<R_0$ and $R_2\le 1$, the equilibrium E_1 is globally asymptotically stable in Γ. □

Theorem 4.3. *If $R_1>1$ and $R_4\le 1$, then the infection equilibrium $E_2=(T_2,T_2^*,V_2,Y_2,0)$ with only CTL immune responses is globally asymptotically stable in Γ.*

Proof. Define a Lyapunov functional as follows:

$$\begin{aligned}
U_2(t)&=e^{-s\tau}U_{21}(t)+T_2^*g\Big(\frac{T^*(t)}{T_2^*}\Big)+\frac{\delta+pY_2}{N\delta}g\Big(\frac{V(t)}{V_2}\Big)+\frac{pY_2}{\beta}g\Big(\frac{Y(t)}{Y_2}\Big)\\
&\quad+\frac{q}{Ng}\Big(1+\frac{p}{\delta}Y_2\Big)A(t)+(\delta+pY_2)T_2^*U_{22}(t),
\end{aligned}$$

where

$$\begin{aligned}
U_{21}(t)&=T(t)-T_2-\int_{T_2}^{T(t)}\frac{f(T_2,V_2)}{f(\theta,V_2)}\mathrm{d}\theta,\\
U_{22}(t)&=\int_{t-\tau}^{t}g\Big(\frac{e^{-s\tau}}{(\delta+pY_2)T_2^*}f(T(\theta),V(\theta))\Big)\mathrm{d}\theta.
\end{aligned}$$

Obviously, $U_2(t)$ is non-negative definite in Γ with respect to E_2.

Next we calculate the time derivative of $U_2(t)$ along the solution of system. (1.6)-(1.7):

$$\begin{aligned}
&\frac{\mathrm{d}U_2(t)}{\mathrm{d}t}\\
&= e^{-s\tau}\Big(1-\frac{f(T_2,V_2)}{f(T(t),V_2)}\Big)\big(\lambda - dT(t) - f(T(t),V(t))\big)\\
&\quad + \Big(1-\frac{T_2^*}{T^*(t)}\Big)\big(e^{-s\tau}f(T(t-\tau),V(t-\tau)) - \delta T^*(t) - pY(t)T^*(t)\big)\\
&\quad + \frac{\delta+pY_2}{N\delta}\Big(1-\frac{V_2}{V(t)}\Big)\big(N\delta T^*(t) - cV(t) - qA(t)V(t)\big)\\
&\quad + \frac{p}{\beta}\Big(1-\frac{Y_2}{Y(t)}\Big)(\beta T^*(t)-\gamma)Y(t) + \frac{q}{Ng}\Big(1+\frac{p}{\delta}Y_2\Big)(gV(t)-b)A(t)\\
&\quad + e^{-s\tau}\big(f(T(t),V(t)) - f(T(t-\tau),V(t-\tau))\big) + (\delta+pY_2)T_2^*\Big(\ln\frac{f(T_2,V_2)}{f(T(t),V_2)}\\
&\quad + \ln\frac{T^*(t)V_2}{T_2^*V(t)} + \ln\frac{V(t)f(T(t),V_2)}{V_2f(T(t),V(t))} + \ln\frac{T_2^*f(T(t-\tau),V(t-\tau))}{T^*(t)f(T_2,V_2)}\Big).
\end{aligned}$$

Substituting

$$\lambda = dT_2 + f(T_2,V_2), \quad e^{s\tau}(\delta+pY_2)T_2^* = f(T_2,V_2), \quad T_2^* = \frac{\gamma}{\beta}, \quad \frac{T_2^*}{V_2} = \frac{c}{N\delta}$$

into the above gives

$$\frac{\mathrm{d}U_2(t)}{\mathrm{d}t} = -\frac{de^{-s\tau}(1+k_2V_2)}{1+k_1T_2+k_2V_2}\frac{(T(t)-T_2)^2}{T(t)} + C_2(t),$$

where

$$\begin{aligned}
C_2(t) &= \frac{bq}{gN}\Big(1+\frac{p}{\delta}Y_2\Big)\Big(\frac{b}{g}V_2-1\Big)A(t) + (\delta+pY_2)T_2^*\Big[\ln\frac{f(T(t-\tau),V(t-\tau))}{f(T(t),V(t))}\\
&\quad + \Big(3 - \frac{f(T_2,V_2)}{f(T(t),V_2)} - \frac{T^*(t)V_2}{T_2^*V(t)} - \frac{T_2^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_2,V_2)}\Big)\\
&\quad + \Big(-\frac{V(t)}{V_2} + \frac{f(T(t),V(t))}{f(T(t),V_2)}\Big)\Big]\\
&= \frac{bq}{gN}\Big(1+\frac{p}{\delta}Y_2\Big)(R_4-1)A(t) - (\delta+pY_2)T_2^*\Big[g\Big(\frac{f(T_2,V_2)}{f(T(t),V_2)}\Big) + g\Big(\frac{T^*(t)V_2}{T_2^*V(t)}\Big)\\
&\quad + g\Big(\frac{V(t)}{V_2}\frac{f(T(t),V_2)}{f(T(t),V(t))}\Big) + g\Big(\frac{T_2^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_2,V_2)}\Big)\\
&\quad + \frac{k_2(1+k_1T(t))(V(t)-V_2)^2}{V_2(1+k_1T(t)+k_2V(t))(1+k_1T(t)+k_2V_2)}\Big].
\end{aligned}$$

Since $R_4 = \frac{b}{g}V_2$, thus, when $R_4 \le 1$, $C_2(t) \le 0$. Hence, $\frac{\mathrm{d}U_2(t)}{\mathrm{d}t} \le 0$. Let

$$M_2 = \big\{(T(t),T^*(t),V(t),Y(t),A(t)) : \dot{U}_2(t) = 0\big\}.$$

It can be verified from the derivative of $\dot{U}_2(t) = 0$ if and only if

$$V(t) = V_2, \quad \frac{T^*(t)V_2}{T_2^*V(t)} = 1, \quad A(t) = 0.$$

Then, $T^*(t) = T_2^*$. From the first and the second equation of the model (1.6)-(1.7), we have $T(t) = T_2,\ Y(t) = Y_2$. Clearly, the largest compact invariant set in M_2 is

$$\Big\{(T(t), T^*(t), V(t), Y(t), A(t)) : T(t) = T_2, T^*(t) = T_2^*, V(t) = V_2, \\ Y(t) = Y_2, A(t) = 0\Big\}.$$

Hence the LaSalle invariance principle [4, Theorem 5.3.1] implies that the equilibrium E_2 is globally asymptotically stable in Γ when $R_1 > 1$ and $R_4 \le 1$. □

Theorem 4.4. *If $R_2 > 1$ and $R_3 \le 1$, then the infection equilibrium $E_3 = (T_3, T_3^*, V_3, 0, A_3)$ with only antibody immune responses is globally asymptotically stable in Γ.*

Proof. Define a Lyapunov functional

$$U_3(t) = e^{-s\tau}U_{31}(t) + T_3^* g\Big(\frac{T^*(t)}{T_3^*}\Big) + \frac{V_3}{N} g\Big(\frac{V(t)}{V_3}\Big) + \frac{p}{\beta}Y(t) + \frac{q}{Ng} g\Big(\frac{A(t)}{A_3}\Big) \\ + \delta T_3^* U_{32}(t),$$

where

$$U_{31}(t) = T(t) - T_3 - \int_{T_3}^{T(t)} \frac{f(T_3, V_3)}{f(\theta, V_3)}\mathrm{d}\theta, \quad U_{32}(t) = \int_{t-\tau}^{t} g\Big(\frac{e^{-s\tau}}{\delta T_3^*} f(T(\theta), V(\theta))\Big)\mathrm{d}\theta.$$

Obviously, $U_3(t)$ is non-negative definite in Γ with respect to E_3. The time derivative of $U_3(t)$ along the solution of system (1.6)-(1.7) is

$$\begin{aligned}\frac{\mathrm{d}U_3(t)}{\mathrm{d}t} &= e^{-s\tau}\Big(1 - \frac{f(T_3, V_3)}{f(T(t), V_3)}\Big)\big(\lambda - dT(t) - f(T(t), V(t))\big) \\ &\quad + \Big(1 - \frac{T_3^*}{T^*(t)}\Big)\big(e^{-s\tau} f(T(t-\tau), V(t-\tau)) - \delta T^*(t) - pY(t)T^*(t)\big) \\ &\quad + \frac{1}{N}\Big(1 - \frac{V_3}{V(t)}\Big)\Big(N\delta T^*(t) - cV(t) - qA(t)V(t)\Big) \\ &\quad + \frac{p}{\beta}\Big(\beta T^*(t) - \gamma\Big)Y(t) + \frac{q}{Ng}\Big(1 - \frac{A_3}{A(t)}\Big)(gV(t) - b)A(t) \\ &\quad + e^{-s\tau}\big(f(T(t), V(t)) - f(T(t-\tau), V(t-\tau))\big) + \delta T_3^*\Big(\ln\frac{f(T_3, V_3)}{f(T(t), V_3)} \\ &\quad + \ln\frac{T^*(t)V_3}{T_3^* V(t)} + \ln\frac{V(t)f(T(t), V_3)}{V_3 f(T(t), V(t))} + \ln\frac{T_3^* f(T(t-\tau), V(t-\tau))}{T^*(t) f(T_3, V_3)}\Big).\end{aligned}$$

Substituting

$$\lambda = dT_3 + f(T_3, V_3), \quad e^{s\tau}\delta T_3^* = f(T_3, V_3), \quad N\delta T_3^* = (c + qA_3)V_3, \quad V_3 = \frac{b}{g}$$

in the above gives

$$\frac{\mathrm{d}U_3(t)}{\mathrm{d}t} = -\frac{de^{-s\tau}(1 + k_2V_3)}{1 + k_1T_3 + k_2V_3}\frac{(T(t) - T_3)^2}{T(t)} + C_3(t),$$

where

$$\begin{aligned}&C_3(t) \\ &= \frac{p\gamma}{\beta}\Big(\frac{\beta}{\gamma}T_3^* - 1\Big)Y(t) + \delta T_3^*\Big[\ln\frac{f(T(t-\tau), V(t-\tau))}{f(T(t), V(t))} - \frac{V(t)}{V_3} + \frac{f(T(t), V(t))}{f(T(t), V_3)}\end{aligned}$$

$$
\begin{aligned}
&+\Big(3-\frac{f(T_3,V_3)}{f(T(t),V_3)}-\frac{T^*(t)V_3}{T_3^*V(t)}-\frac{T_3^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_3,V_3)}\Big)\Big]\\
&=\frac{p\gamma}{\beta}\Big(\frac{\beta}{\gamma}T_3^*-1\Big)Y(t)-(\delta+pY_3)T_3^*\Big[g\Big(\frac{f(T_3,V_3)}{f(T(t),V_3)}\Big)+g\Big(\frac{T^*(t)V_3}{T_3^*V(t)}\Big)\\
&+g\Big(\frac{V(t)}{V_3}\frac{f(T(t),V_3)}{f(T(t),V(t))}\Big)+g\Big(\frac{T_3^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_3,V_3)}\Big)\\
&+\frac{k_2(1+k_1T(t))(V(t)-V_3)^2}{V_3(1+k_1T(t)+k_2V(t))(1+k_1T(t)+k_2V_3)}\Big].
\end{aligned}
$$

By Theorem 3.1 (iv), we have

$$
T_3=\frac{-b_2+\sqrt{b_2^2+4\lambda gdk_1(g+k_2b)}}{2gdk_1},\quad T_3^*=\frac{e^{-s\tau}}{\delta}(\lambda-dT_3).
$$

where $b_2=gd+kb+k_2bd-\lambda k_1g$.

Obviously, it is not difficult to show that $R_3\le 1$ is equals to $\lambda-dT_3-\delta\frac{\gamma}{\beta}e^{s\tau}\le 0$. We then get

$$
\lambda-dT_3-\delta\frac{\gamma}{\beta}e^{s\tau}=\delta e^{s\tau}\Big(\frac{\lambda-dT_3}{\delta e^{s\tau}}-\frac{\gamma}{\beta}\Big)=\delta e^{s\tau}\Big(T_3^*-\frac{\gamma}{\beta}\Big)\le 0,
$$

which follows $\frac{\beta}{\gamma}T_3^*-1\le 0$. Then we have $C_3(t)\le 0$, if $R_3\le 1$. Hence, $\frac{\mathrm{d}U_3(t)}{\mathrm{d}t}\le 0$. Let

$$
M_3=\big\{(T(t),T^*(t),V(t),Y(t),A(t)):\dot U_3(t)=0\big\}.
$$

It can be verified from the derivative of $\dot U_3(t)=0$ if and only if $T(t)=T_3$, $V(t)=V_3,\frac{T^*(t)V_3}{T_3^*V(t)}=1$, $Y(t)=0$. Then, $T^*(t)=T_3^*$. From the third equation of the model (1.6)-(1.7), we have $A(t)=A_3$. Clearly, the largest compact invariant set in M_3 is

$$
\begin{aligned}
&\Big\{(T(t),T^*(t),V(t),Y(t),A(t)):T(t)=T_3,T^*(t)=T_3^*,V(t)=V_3,\\
&Y(t)=0,\ A(t)=A_3\Big\}.
\end{aligned}
$$

Using the LaSalle invariance principle [4, Theorem 5.3.1], we see that, when $R_2>1$ and $R_3\le 1$, the equilibrium E_3 is globally asymptotically stable in Γ. □

Theorem 4.5. *If $R_3>1$ and $R_4>1$, then the interior equilibrium*

$$
E_4=(T_4,T_4^*,V_4,Y_4,A_4)
$$

with both CTL immune responses and antibody immune responses is globally asymptotically stable in Γ.

Proof. Define a Lyapunov functional

$$
\begin{aligned}
U_4(t)&=e^{-s\tau}U_{41}(t)+T_4^*g\Big(\frac{T^*(t)}{T_4^*}\Big)+\frac{\delta+pY_2}{N\delta}g\Big(\frac{V(t)}{V_4}\Big)+\frac{p}{\beta}g\Big(\frac{Y(t)}{Y_4}\Big)\\
&\quad+\frac{q}{Ng}\Big(1+\frac{pY_4}{\delta}\Big)g\Big(\frac{A(t)}{A_4}\Big)+(\delta+pY_4)T_4^*U_{42}(t),
\end{aligned}
$$

where

$$
\begin{aligned}
U_{41}(t)&=T(t)-T_4-\int_{T_4}^{T(t)}\frac{f(T_4,V_4)}{f(\theta,V_4)}\mathrm{d}\theta,\\
U_{42}(t)&=\int_{t-\tau}^{t}g\Big(\frac{e^{-s\tau}}{(\delta+pY_4)T_4^*}f(T(\theta),V(\theta))\Big)\mathrm{d}\theta.
\end{aligned}
$$

Obviously, the Lyapunov functional $U_4(t)$ is non-negative definite in Γ with respect to E_4. Then the time derivative of $U_4(t)$ along the solution of system (1.6)-(1.7) is

$$\begin{aligned}
&\frac{\mathrm{d}U_4(t)}{\mathrm{d}t}\\
&= e^{-s\tau}\Big(1-\frac{f(T_4,V_4)}{f(T(t),V_4)}\Big)\big(\lambda - dT(t) - f(T(t),V(t))\big)\\
&\quad + \Big(1-\frac{T_4^*}{T^*(t)}\Big)\big(e^{-s\tau}f(T(t-\tau),V(t-\tau)) - \delta T^*(t) - pY(t)T^*(t)\big)\\
&\quad + \frac{\delta+pY_4}{N\delta}\Big(1-\frac{V_4}{V(t)}\Big)\Big(N\delta T^*(t) - cV(t) - qA(t)V(t)\Big)\\
&\quad + \frac{p}{\beta}\Big(1-\frac{Y_4}{Y(t)}\Big)(\beta T^*(t)-\gamma)Y(t) + \frac{q}{Ng}\Big(1+\frac{pY_4}{\delta}\Big)(gV(t)-b)A(t)\\
&\quad + e^{-s\tau}\big(f(T(t),V(t)) - f(T(t-\tau),V(t-\tau))\big) + (\delta+pY_4)T_4^*\Big(\ln\frac{f(T_4,V_4)}{f(T(t),V_4)}\\
&\quad + \ln\frac{T^*(t)V_4}{T_4^*V(t)} + \ln\frac{V(t)f(T(t),V_4)}{V_4f(T(t),V(t))} + \ln\frac{T_4^*f(T(t-\tau),V(t-\tau))}{T^*(t)f(T_4,V_4)}\Big)
\end{aligned}$$

Substituting

$$\lambda = dT_4 + f(T_4,V_4),\quad e^{s\tau}(\delta+pY_4)T_4^* = f(T_4,V_4),\quad N\delta T_4^* = (c+qA_4)V_4,$$
$$T_4^* = \frac{\gamma}{\beta},\quad V_4 = \frac{b}{g},\quad A_4 = \frac{N\delta\gamma g - \beta cb}{\beta qb}$$

into the above gives

$$\frac{\mathrm{d}U_4(t)}{\mathrm{d}t} = -\frac{de^{-s\tau}(1+k_2V_4)}{(1+k_1T_4+k_2V_4)}\frac{(T(t)-T_4)^2}{T(t)} + C_4(t),$$

where

$$\begin{aligned}
C_4(t) &= (\delta+pY_4)T_4^*\Big[\Big(-\frac{V(t)}{V_4} + \frac{f(T(t),V(t))}{f(T(t),V_4)}\Big) + \ln\frac{f(T(t-\tau),V(t-\tau))}{f(T(t),V(t))}\\
&\quad + \Big(3 - \frac{f(T_4,V_4)}{f(T(t),V_4)} - \frac{T^*(t)V_4}{T_4^*V(t)} - \frac{T_4^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_4,V_4)}\Big)\Big]\\
&= -(\delta+pY_4)T_4^*\Big[g\Big(\frac{f(T_4,V_4)}{f(T(t),V_4)}\Big) + g\Big(\frac{T^*(t)V_4}{T_4^*V(t)}\Big)\\
&\quad + g\Big(\frac{V(t)}{V_4}\frac{f(T(t),V_4)}{f(T(t),V(t))}\Big) + g\Big(\frac{T_4^*}{T^*(t)}\frac{f(T(t-\tau),V(t-\tau))}{f(T_4,V_4)}\Big)\\
&\quad + \frac{k_2(1+k_1T(t))(V(t)-V_4)^2}{V_4(1+k_1T(t)+k_2V(t))(1+k_1T(t)+k_2V_4)}\Big].
\end{aligned}$$

Thus $C_4(t)\le 0$. Hence, $\frac{\mathrm{d}U_4(t)}{\mathrm{d}t}\le 0$. Let

$$M_4 = \big\{(T(t),T^*(t),V(t),Y(t),A(t)) : \dot{U}_4(t) = 0\big\}.$$

It can be verified from the derivative of $\dot{U}_4(t)=0$ if and only if

$$T(t) = T_4,\quad V(t) = V_4,\quad \frac{T^*(t)V_4}{T_4^*V(t)} = 1,$$

Therefore, $T^*(t) = T_4^*$. From the second and the third equation of the model (1.6)-(1.7), we have $Y(t) = Y_4$, $A(t) = A_4$. Clearly, the largest compact invariant set in M_4 is

$$\Big\{(T(t), T^*(t), V(t), Y(t), A(t)) : T(t) = T_4, T^*(t) = T_4^*, V(t) = V_4, \\ Y(t) = Y_4, A(t) = A_4\Big\}.$$

Hence, when $R_3 > 1$ and $R_4 > 1$, the equilibrium E_4 is globally asymptotically stable in Γ by the LaSalle invariance principle [4, Theorem 5.3.1]. Thus, the proof is complete. □

Discussion. Many authors had investigated the global dynamics of viral infection models. Korobeinikov [7] studied the basic viral infection model (1.1) using Lyapunov functionals. Nowak and Bangham [13] added the effect of CTLS immune response to the basic virus dynamics model, which exists in many biological organism. Recently, the global dynamics for a delayed viral infection model which has bilinear incidence rate and the saturated infection rate were analyzed by Yan and Wang [21] and Wang and Liu [18], respectively. They all showed that the thresholds parameters work as an important parameter which determines that is globally asymptotically.

In this paper, we assume that the incidence rate of the virus model is described by a Beddington-DeAngelis functional responses. Then we obtained the global dynamics of a delayed differential equations for a virus model with CTL and antibody immune responses. The global stabilities of the infection free equilibrium, the immune free equilibrium, the CTL-activated equilibrium, the antibody-activated equilibrium, and the interior equilibrium of system (1.6)-(1.7) have been completely established by using the Lasalle type theorem. From Theorems 4.1–4.5, we see that the five equilibria are globally asymptotically stable when the five threshold parameters satisfy certain conditions. For cases where system (1.6) has bilinear incidence rate or the saturated infection rate; i.e., for systems (1.4) or (1.5), Theorems 4.1–4.5 reduce to [21, Theorems 4.1–4.5] or [18, Theorems 4.1], respectively. Thus, our analytic results generalize those results in [21, 18].

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Yingying Zhao
School of Mathematical Sciences, South China Normal University, Guangzhou 510631, China
E-mail address: 865564950@qq.com

Zhiting Xu
School of Mathematical Sciences, South China Normal University, Guangzhou 510631, China
E-mail address: xuzhit@126.com