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Global threshold dynamics in a five-dimensional virus model with cell-mediated, humoral immune responses and distributed delays

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Abstract. In this paper, we investigate the dynamics of a five-dimensional virus model with immune responses and an intracellular delay which describes the interactions of the HIV virus, CD4 cells and CTLs within host, which is an improvement of some existing models by incorporating (i) two distributed kernels reflecting the variance of time for virus to invade into cells and the variance of time for invaded virions to reproduce within cells; (ii) a nonlinear incidence function f for virus infections, and (iii) antibody responses, which are implemented by the functioning of immunocompetent B lymphocytes, play a critical role in preventing and modulating infections. By constructing Lyapunov functionals and subtle estimates of the derivatives of these Lyapunov functionals, we show that the global dynamics of the model is determined by the reproductive numbers for viral infection $\Re_0$, for CTL immune response $\Re_1$, for antibody immune response $\Re_2$, for CTL immune competition $\Re_3$ and for antibody immune competition $\Re_4$. The global stability of the model precludes the existence of Hopf bifurcation and other complex dynamical behaviors in long time. Numerical simulations are also performed in order to illustrate the dynamical behavior.

Keywords: Nonlinear infection rate; Intracellular delay; Immune response; Global stability; Lyapunov functional
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1 Introduction

Over recent years, many authors have formulated and studied mathematical models which describe the dynamics of virus population in vivo and these provide insights in our understanding of HIV-1 (human immunodeficiency virus 1) and other viruses, such as HBV (hepatitis B virus) and HCV (hepatitis C virus) (see [11, 12, 16, 17, 22, 23] and the references therein). Mathematical analysis for these models is necessary to obtain an integrated view for the virus dynamics in vivo. In particular, the global stability of a steady state for these models will give us a detailed information and enhances our understanding about the virus dynamics.

During viral infections, it is well-known and pointed out by the work of [45] that antigen-specific immune response after viral infection is universal and necessary for identifying and killing pathogens and infected cells. Antibodies, cytokines, natural killer cells, and T cells are essential components of a normal immune response to a virus. In particular, cytotoxic T lymphocytes (CTLs) play a key role in antiviral defense by attacking virus-infected cell, and it is also believed that they are the main host immune factor that limits the extent of virus replication in vivo and thus determines virus load [43].

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However, in the real virus dynamics, infection processes are not instantaneous. For example, during HIV infection, the intracellular phase is about 0.9 days, but the average half-life of plasma virus is only around 6h [34]. Time delays are usually introduced for the purpose of accurate representations of intracellular phase of the viral life-cycle, defined as the time between infection of a cell and production of new virus particles (see, e.g. [6,11,21,23,30,38,41,44,45]). Thus, delays should be incorporated into the infection equation and/or the virus production equation of a model to account for effect of intracellular delay which leads to mathematical models by delay differential equation (DDE). Many authors have studied the mathematical modelling of viral dynamics with CTL immune response in the literature, which are given by systems of ordinary differential equation (ODE) and DDE (see, e.g., [2,3,8,9] and the references therein). It has been found in [5,40,46] that when a time delay was incorporated into HIV infection models with immune response, very complicated dynamics may occur including stable periodic solutions and chaos.

Arguing that constant delays are not biologically realistic, in [25,29,36], the authors provocated the use of distributed intracellular delays represented by general kernel functions. Nakata [29] investigated the stability of an HIV-1 infection model with immunity mediated and two finite distributed intracellular delays incorporated. Wang et al. [36] and Li and Shu [24] investigated the global stability of an HIV-1 infection model with infinite distributed intracellular delays by constructing Lyapunov functionals.

To investigate effects among incorporating distributed delay into the cell infection equation and another virus production equation and nonlinear incidence rate and a nonlinear removal rate for the infected cells, Yuan and Zou [43] proposed and developed the following mathematical model:

$$\begin{cases} x'(t) &= \mu - kx(t) - \alpha x(t) f(v(t)), \\ y'(t) &= \alpha \displaystyle\int_0^\infty G_1(\tau) x(t-\tau) f(v(t-\tau)) \mathrm{d}\tau - ry(t) - \beta y(t) h(z(t)), \\ v'(t) &= Nr \displaystyle\int_0^\infty G_2(\tau) y(t-\tau) \mathrm{d}\tau - dv(t), \\ z'(t) &= \lambda y(t) - qz(t),\ t > 0, \end{cases} \tag{1.1}$$

where $x(t)$, $y(t)$, $v(t)$ and $z(t)$ represent the concentration of uninfected target cells, productively infected cells, free virus in the serum, and the abundance of virus-specific CTLs, respectively. Uninfected target cells are produced at a constant rate μ and die at a per capita rate k. Infected cells are produced from uninfected cells and virus at rate $\alpha \int_0^\infty G_1(\tau) x(t-\tau) f(v(t-\tau)) \mathrm{d}\tau$, where α is a constant characterizing the infection rate. The infected cells are assumed to die at a rate r (say, via lysis) due to the action of virus, each releasing N new virus particles as the lysis of infected cells occurs. The rate of CTL proliferation is given by λ and decay at rate $qz(t)$ in the absence of stimulation by the infected cells. Infected cells are killed via mass action kinetics by CTLs, which is described by $\beta y(t) h(z(t))$. β accounts for the strength of the lytic component. Virus particles are cleared from the system at rate d. As pointed in [43], the function $f(\xi)$ denotes the force of infection by virus at density ξ, which is locally Lipschitz on $[0, \infty)$ satisfying

$$(\mathbf{A}_1):\ f(0) = 0,\ f'(\xi) \text{ exists and satisfies } f'(\xi) \geq 0 \text{ and } \left(\frac{f(\xi)}{\xi}\right)' \leq 0 \text{ in } (0, \infty).$$

A class of the function f that satisfies $(\mathbf{A}_1)$ include both bilinear incidence $f(\xi) = \xi$, saturated incidence $f(\xi) = \frac{\xi}{1+\alpha\xi}$ and Beddington-DeAngelis functional response $f(\xi) = \frac{\xi}{1+a x+b\xi}$, which have been widely used in the literature of viral dynamics [12,13,17,23,24,31,32,38].

Distributed intracellular delays used here are represented by general kernel functions $G_i(\tau) = f_i(\tau) e^{-m_i \tau}$, $i = 1, 2$. Here the factor $e^{-m_1\tau}$ accounts for the loss of uninfected cells during time interval $[t-\tau, t]$ due to viral infection, and the factor $e^{-m_2\tau}$ accounts for the infected cell loss during the delay period. Probability distribution functions $f_1(\tau)$ and $f_2(\tau)$ are assumed to satisfy $f_i(\tau) \geq 0$ and $\int_0^\infty f_i(\tau) d\tau = 1$ for $i = 1, 2$. $G_1(\tau)$ is the probability that target cells contacted by the virus particles at time $t-\tau$ survived τ time units and become infected at time t and $G_2(\tau)$ is the probability that a cell infected at time $t-\tau$ starts to yield new infectious virus at time t [43]. Assume the kernel functions $G_i(\tau)$, $i = 1, 2$ satisfy

$$(\mathbf{A}_2):\ G_i(\tau) > 0,\ \text{for } \tau > 0,\ \text{and } 0 < a_i := \int_0^\infty G_i(\xi) \mathrm{d}\xi \leq 1,\ i = 1, 2.$$

On the other hand, although the pathogenesis of chronic virus infection is not well understood, there is a consensus that infection damage is immune-mediated [42]. It is also pointed out in [42] that antibody responses, which are implemented by the functioning of immunocompetent B lymphocytes, play a critical role in preventing and modulating infections. More generally, viral infection models have a general immune response, which can have both lytic and non-lytic effector mechanisms. Thus, it is realistic to consider two independent branches of the immune system: one is a lytic branch (such as CTL response), and the other is non-lytic branch (such as antibody response), and assume both branches are stimulated by antigens and suppress the viral population, they are in competition with each other. Therefore, Wodarz [37] presented a mathematical model to study the highly complex and non-linear interaction between replicating viruses,

uninfected cells, infected cells, and different types of immune (CTLs and antibody). To investigate the relation between antiviral immune response and antibody, Yan and Wang [42] developed the model in [37] by incorporating a discrete time delay for production of infected cells. They formulated the following mathematical model:

$$\begin{cases} x'(t) &= \lambda - dx(t) - kx(t)v(t), \\ y'(t) &= kx(t-\tau)v(t-\tau)e^{-s\tau} - \delta y(t) - py(t)z(t), \\ v'(t) &= \delta N y(t) - cv(t) - qa(t)v(t), \\ z'(t) &= \beta y(t)z(t) - \gamma z(t), \\ a'(t) &= ga(t)v(t) - ba(t),\ t > 0, \end{cases} \tag{1.2}$$

where the fraction $e^{-s\tau}$ denotes the survive rate of infected cells after the interval τ, where $1/s$ is the average lifetime of infected cells without reproduction. Virus particles are neutralized via mass action kinetics by antibodies, which is described by $qa(t)v(t)$. CTLs are produced at a rate proportional to the abundances of CTLs and infected cells, $\beta y(t)z(t)$, and die at a per capita rate γ. The antibody responses are activated at a rate proportional to the abundances of antibodies and free viruses, $ga(t)v(t)$, and die at a per capita rate b. All parameters are positive constants.

In this paper, following the line of [42] and [43], we incorporate a continuous distributed delay into the cell infection equation and another distributed intracellular delay in the virus production equation of (1.2). And we incorporate anti-body (humoral) immune response to model (1.1). Moreover, we allow a nonlinear incidence rate for the infected cells. Then, we obtain the following five dimensional viral infection model:

$$\begin{cases} x'(t) &= \lambda - dx(t) - kx(t)f(v(t)), \\ y'(t) &= k\displaystyle\int_0^\infty G_1(\tau)x(t-\tau)f(v(t-\tau))\mathrm{d}\tau - \delta y(t) - py(t)z(t), \\ v'(t) &= \delta N \displaystyle\int_0^\infty G_2(\tau)y(t-\tau)\mathrm{d}\tau - cv(t) - qa(t)v(t), \\ z'(t) &= \beta y(t)z(t) - \gamma z(t), \\ a'(t) &= ga(t)v(t) - ba(t). \end{cases} \tag{1.3}$$

System (1.3) includes many special cases. We summarize previous studies in the literature related to (1.3):

(i) When $p = q = 0$, and $f(\xi) = \xi$ with no intracellular delays, Nowak et al. [32] and Korobeinikov [17] shown that no period oscillations occur in the model, and all solution converge to equilibria. (1.2) with discrete intracellular delay, a general case $f_1(\tau) = f_2(\tau) = \delta(\tau - 0)$ with $\delta(\cdot)$ being the Dirac delta function, $s_1 > 0$, and $s_2 = 0$, system (1.3) reduces to the model studied by Nelson and Perelson [31] and Li and Shu [23]. It is shown in [23] that no period oscillations occur in the model, and all solutions converge to equilibria. Recently, Li and Shu [24] have investigated a viral infection model with a general target cell dynamics, a nonlinear incidence rate and distributed delay. Their results showed that their model always admits an equilibrium which is globally asymptotically stable and it is necessary to have a logistic mitosis term in the target cell dynamics for generating a periodic solution.

(ii) When $f_1(\tau) = f_2(\tau) = \delta(\tau - 0)$, $f(\xi) = \xi$ and CTL activation term $\beta y(t)z(t)$ is replaced by the linear function $\lambda y(t)$ in (1.3), system (1.3) reduces to a class of ordinary differential equations that have been widely studied in literature without antibody immune response (see e.g. [1, 5, 7] and references therein).

(iii) When $p = 0$, Murase et al. [26] and Kajiwara et al. [16] and Wang et al. [39] studied stability of some mathematical models for virus-immune interaction dynamics.

(iv) When $q = 0$, stability analysis for (1.2) with discrete intracellular delay was carried out by Zhu and Zou [45]. Zhu and Zou [45] established global stability of an uninfected equilibrium and obtained sufficient conditions for local asymptotic stability of two infected equilibria. Wang et al. [38] resolved the global stability of endemic equilibrium left as an open problem in [45] by constructing Lyapunov functionals.

Since Yuan and Zou [43] did not consider the humoral immunity (antibody) to the viral infection and Yin and Wang [42] did not address the effect for incorporating distributed delay to global stability of the equilibria for their model, the global dynamics of (1.3) is still unclear and, hence, our primary goal is to carry out a stability analysis of system (1.3). By constructing Lyapunov functionals and subtle estimates of the derivatives of these Lyapunov functionals and using LaSalle's invariance principle, we show that the global dynamics of the model is determined by the reproductive numbers for viral infection $\Re_0$, for CTL immune response $\Re_1$, for antibody immune response $\Re_2$, for CTL immune competition $\Re_3$ and for antibody (humoral) immune competition $\Re_4$. The global stability of the model precludes the existence of Hopf bifurcation and other complex dynamical behaviors. These Lyapunov functions are motivated by the recent works of Korobeinikov [17–19], McCluskey [27, 28], Li and Shu [23, 24], Wang et al. [36, 38], Huang et al. [12, 13], Nakata [29] and Kajiwara et al. [20].

This paper is organized as follows. In Section 2, we consider well-posedness of the model by addressing the non-negativity and boundedness of all solutions. In Section 3, the reproductive numbers are derived and the existence of

equilibrium is discussed. The global stability of all equilibria is investigated in the section. These results are obtained by constructing proper Lyapunov functionals and some subtle estimates of the derivatives of the functionals. In Section 4, we offer numerical simulations to display graph trajectories of (1.3). Biological implications are discussed in Section 5.

2 Non-negativity and boundedness of solutions

For biological reasons, we consider a suitable phase and a feasible region. Denote non-negative initial functions by:

$$\phi(\theta) = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta)) \in UC_\psi((-\infty, 0], \mathbf{R}^5_+), \tag{2.1}$$

where $\mathbf{R}^5_+ = \{(x_1, x_2, x_3, x_4, x_5) : x_i \geq 0,\ i = 1, 2, 3, 4, 5\}$ and

$$UC_\psi((-\infty, 0], \mathbf{R}^5_+) := \left\{ \phi \in C((-\infty, 0], \mathbf{R}^5_+) : \|\phi\|_\psi = \sup_{s \leq 0} \frac{|\phi(s)|}{\psi(s)} < \infty,\ \frac{\phi(s)}{\psi(s)} \text{ is uniformly continuous on } (-\infty, 0] \right\}.$$

Here we assume that $\psi : (-\infty, 0] \longrightarrow [1, \infty)$ satisfies the following properties:

(1) ψ is continuous and nonincreasing on $(-\infty, 0]$ with $\psi(0) = 1$;

(2) $\dfrac{\psi(s+u)}{\psi(s)} \to 1$ uniformly on $(-\infty, 0]$ as $u \to 0^-$;

(3) $\psi(s) \to \infty$ as $s \to -\infty$.

We note that UC_ψ is a Banach space with norm $\|\phi\|_\psi$. Moreover, if the function ψ satisfies assumptions (1)-(3), then UC_ψ is an admissible Banach space. Thus, for system (1.3), well-known Peano type existence results hold, see [14] for details.

It follows from the fundamental theory for integral-differential equations (see, e.g. [4]) that there exists a $T_\phi > 0$ such that system (1.3) with (2.1) has a unique solution on maximal interval $t \in [0, T_\phi)$. The following theorem shows that for positive initial values, the solution remains positive and is bounded, implying $T_\phi = \infty$, that is, the solution exists globally.

Theorem 2.1. *Let $(x(t), y(t), v(t), z(t), a(t))^T$ be the unique solution to system (1.3) with $\phi_i(0) > 0$ $(i = 1, 2, 3, 4, 5)$. Then $x(t), y(t), v(t), z(t)$ and $a(t)$ are positive for all $t > 0$. Moreover, all solutions $(x(t), y(t), v(t), z(t), a(t))^T$ of system (1.3) with $x(t) > 0, y(t) > 0, v(t) > 0, z(t) > 0$ and $a(t) > 0$ are ultimately bounded.*

Proof. First, we prove that $x(t)$ is positive for all $t \geq 0$. On the contrary, we assume that there exists a $t_1 > 0$ such that $x(t_1) = 0$ and $x'(t_1) \leq 0$. From the first equation of system (1.3), we have $x'(t_1) = \lambda > 0$ which is a contradiction. Thus, it follows that $x(t) > 0$ for $t > 0$ as long as $x(t)$ exists.

Using the variation-of-constants formula, we obtain from the second and third equations of system (1.3) that

$$y(t) = e^{-\int_0^t (\delta + pz(s))ds} \left(\phi_2(0) + k \int_0^t \int_0^\infty G_1(\tau) x(s-\tau) f(v(s-\tau)) d\tau e^{\int_0^s (\delta + pz(u))du} ds \right),$$

and

$$v(t) = e^{-\int_0^t (c + qa(s))ds} \left(\phi_3(0) + N\delta \int_0^t \int_0^\infty G_2(\tau) y(s-\tau) d\tau e^{\int_0^s (c+qa(u))du} ds \right).$$

This shows that $y(t)$ and $v(t)$ are non-negative for all $t > 0$.

From the fourth and fifth equations of system (1.3), we have

$$z(t) = \phi_4(0) e^{\int_0^t (\beta y(s) - \gamma)ds}, \text{ and } a(t) = \phi_5(0) e^{\int_0^t (gv(s) - b)ds}.$$

This shows that $z(t), a(t) \geq 0$ for $t > 0$.

Next we show that solutions of (1.3) are ultimately uniformly bounded for $t \geq 0$. It follows from the first equation of system (1.3) that $x'(t) \leq \lambda - dx(t)$. This implies

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

Let

$$L(t) = \int_0^\infty G_1(\tau) x(t-\tau) \mathrm{d}\tau + y(t) + \frac{p}{\beta} z(t),$$

then we can obtain

$$\begin{aligned}L'(t) =& \int_0^\infty G_1(\tau)x'(t-\tau)\mathrm{d}\tau + y'(t) + \frac{p}{\beta}z'(t)\\ =& \int_0^\infty G_1(\tau)[\lambda - dx(t-\tau) - kx(t-\tau)f(v(t-\tau))]d\tau + k\int_0^\infty G_1(\tau)x(t-\tau)f(v(t-\tau))\mathrm{d}\tau - \delta y(t) - \frac{p\gamma}{\beta}z(t)\\ =& \lambda a_1 - d\int_0^\infty G_1(\tau)x(t-\tau)d\tau - \delta y(t) - \frac{p\gamma}{\beta}z(t).\end{aligned}$$

Therefore, we have

$$L'(t) \le \lambda a_1 - sL(t),$$

where $s = \min\{d, \delta, \gamma\}$, and thus $\limsup_{t\to\infty} L(t) \le \frac{\lambda a_1}{s}$. This implies that $L(t)$ is eventually bounded and so is $y(t), z(t)$. Thus, there exists a constant $M > 0$ such that $y(t), z(t) \le M$ for all t.

Let

$$B_1(t) = v(t) + \frac{q}{g}a(t),$$

then we can obtain

$$B_1'(t) \le \ \delta a_2 NM - cv(t) - \frac{qb}{g}a(t).$$

Therefore,

$$B_1'(t) \le \ \delta a_2 NM - \iota B_1(t),$$

where $\iota = \min\{c, b\}$, and thus $\limsup_{t\to\infty} B_1(t) \le \frac{\delta a_2 NM}{\iota}$ and so are $v(t)$ and $a(t)$. Therefore, $x(t), y(t), v(t), z(t)$ and $a(t)$ are ultimately uniformly bounded. □

Theorem 2.1 implies that omega limit sets of system (1.3) are contained in the following bounded feasible region:

$$\Gamma = \left\{(x, y, v, z, a) \in UC_\psi((-\infty, 0], \mathbf{R}_+^5) : \ \|x\| \le \frac{\lambda}{d}, \ \|y\|, \ \|z\| \le M, \ \|v\|, \ \|a\| \le \frac{\delta a_2 NM}{\iota}\right\},$$

where $\|\phi\| = \limsup_{t\to\infty} \phi(t)$. It can be verified that the region Γ is positively invariant with respect to system (1.3).

3 Stability properties of the model

3.1 Reproduction numbers and existence of positive equilibria

The equilibra of system (1.3) satisfy following equalities

$$\begin{cases} \lambda - dx - kxf(v) \ = \ 0, \\ ka_1 xf(v) - \delta y - pyz \ = \ 0, \\ \delta N a_2 y - cv - qav \ = \ 0, \\ \beta yz - \gamma z \ = \ 0, \\ gav - ba \ = \ 0. \end{cases} \tag{3.1}$$

System (1.3) always has an infection-free equilibrium $E_0 = (\lambda/d, 0, 0, 0, 0)$. By simple calculation, we know that the existence of an immune-free equilibrium is equivalent to the existence of a positive root of the equation $K_1(v) = 0$, where

$$K_1(v) = \frac{ka_1\lambda f(v)}{d + kf(v)} - \frac{cv}{Na_2} = vF(v), \ F(v) = \left(\frac{ka_1\lambda f(v)}{d + kf(v)} \cdot \frac{1}{v} - \frac{c}{Na_2}\right).$$

Define the basic reproduction number for viral infection as

$$\Re_0 = \frac{Nk\lambda a_1 a_2 f'(0)}{cd}. \tag{3.2}$$

From assumption $(\mathbf{A}_1)$, we have $F'(v) < 0$ and

$$\lim_{v\to+0} F(v) = \frac{ka_1\lambda}{d}f'(0) - \frac{c}{Na_2} = \frac{c}{Na_2}(\Re_0 - 1) > 0.$$

provided $\Re_0 > 1$. For the both cases $\lim_{v\to\infty} f(v) = \infty$ and $\lim_{v\to\infty} f(v) < \infty$, we have $\lim_{v\to\infty} F(v) = -\frac{c}{Na_2} < 0$. Therefore, the equation $K_1(v) = 0$ has a unique positive root $v = v_1$. By the relation

$$x_1 = \frac{\lambda}{d + kf(v_1)} \text{ and } y_1 = \frac{cv_1}{\delta N a_2},$$

we get immune-free equilibrium $E_1 = (x_1, y_1, v_1, 0, 0)$.

If $z \neq 0$ and $a = 0$, from the fourth equation of (3.1), we can get $y_2 = \frac{\gamma}{\beta} < y_1$, which is denoted by

$$\Re_1 = \frac{\beta y_1}{\gamma} > 1. \tag{3.3}$$

Then the first equation of (3.1) becomes

$$kxf\left(\frac{N\delta a_2\gamma}{\beta c}\right) - \lambda + dx = 0, \tag{3.4}$$

and we have

$$v = \frac{N\delta a_2\gamma}{\beta c} \text{ and } z = \frac{\beta a_1(\lambda - dx)}{p\gamma} - \frac{\delta}{p}. \tag{3.5}$$

It follows that the equation (3.4) has a unique positive root $x = x_2 \in (0, \lambda/d)$. Therefore, if and only if $\Re_1 > 1$, we get the unique equilibrium $E_2 = (x_2, y_2, v_2, z_2, 0)$. Here, $\Re_1$ denotes the average number of the CTL immune cells activated by infected cells when virus infection is successful and humoral immune responses have not been established. Note that y_1 is the number of infected cells at E_1 and $1/r$ is the average life-span of CTL cells.

If $a \neq 0$ and $z = 0$, from the fifth equation of (3.1), we can get $v_3 = \frac{b}{g} < v_1$, which is denoted by

$$\Re_2 = \frac{gv_1}{b} > 1. \tag{3.6}$$

Then the first equation of (3.1) becomes

$$kxf\left(\frac{b}{g}\right) - \lambda + dx = 0, \tag{3.7}$$

and we have

$$y = \frac{a_1(\lambda - dx)}{\delta} \text{ and } a = \frac{Na_1a_2g(\lambda - dx)}{qb} - \frac{c}{q}. \tag{3.8}$$

It follows that the equation (3.7) has a unique positive root $x = x_3 \in (0, \lambda/d)$. So if and only if $\Re_2 > 1$, we get the unique equilibrium $E_3 = (x_3, y_3, v_3, 0, a_3)$. Here, $\Re_2$ denotes the average number of the humoral immune cells activated by virus when virus infection is successful and CTL responses have not been established. Note that v_1 is the number of free viruses at E_1 and $1/b$ is the average life-span of antibody cells.

If $a \neq 0$ and $z \neq 0$, from the forth and fifth equation of (3.1), we can get

$$y_4 = \frac{\gamma}{\beta} \text{ and } v_4 = \frac{b}{g}. \tag{3.9}$$

From the second equation of of (3.1), we can get

$$z = \frac{\delta}{p}\left(\frac{\beta k a_1 x f(\frac{b}{g})}{\gamma\delta} - 1\right).$$

Note that $\frac{ka_1xf(\frac{b}{g})}{\delta} = y_3 = \frac{a_1(\lambda - dx)}{\delta}$ is the number of infected cells at E_3. Denote the CTL immune competitive reproductive number $\Re_3$ for system (1.3) is

$$\Re_3 = \frac{\beta y_3}{\gamma}, \tag{3.10}$$

where $1/\gamma$ is the average life-span of CTL cells. Here, $\Re_3$ denotes the average number of the CTL immune cells activated by infected cells under the condition that humoral immune responses have been established.

From the third equation of of (3.1), we can get

$$a = \frac{c}{q}\left(\frac{g\delta N a_2\gamma}{\beta bc} - 1\right).$$

Note that $\frac{N\delta a_2\gamma}{\beta c}$ is the number of the viruses at E_2. Denote the humoral immune competitive reproductive number $\Re_4$ for system (1.3) is

$$\Re_4 = \frac{gv_2}{b}. \tag{3.11}$$

Note that $1/b$ is the average life-span of antibody cells and thus, $\Re_4$ denotes the average number of the humoral immune cells activated by viruses under the condition that CTL immune responses have been established. We also note that $\Re_4 = \Re_2/\Re_1$ holds true.

When $\Re_3 > 1$ and $\Re_4 > 1$, CTL and humoral immune responses can be established simultaneously, and there exists an interior equilibrium $E_4 = (x_4, y_4, v_4, z_4, a_4)$.

Hence we can state the following theorem:

Theorem 3.1. *Let $\Re_0, \Re_1, \Re_2, \Re_3$ and $\Re_4$ are defined by (3.2), (3.3), (3.6), (3.10) and (3.11).*
(i) System (1.3) always has an infection-free equilibrium E_0;
(ii) System (1.3) has an immune-free infection equilibrium E_1 when $\Re_0 > 1$;
(iii) System (1.3) has an infection equilibrium E_2 with only CTL immune responses when $\Re_1 > 1$;
(iv) System (1.3) has an infection equilibrium E_3 with only humoral immune responses when $\Re_2 > 1$;
(v) System (1.3) has an infection equilibrium E_4 with both CTL responses and humoral immune responses when $\Re_3 > 1$ and $\Re_4 > 1$.

For convenience, we rewrite system (1.3) as

$$\begin{cases} x'(t) &= \lambda - dx(t) - kx(t)f(v(t)), \\ y'(t) &= \alpha_1 \int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi - \delta y(t) - py(t)z(t), \\ v'(t) &= \alpha_2 \int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi - cv(t) - qa(t)v(t), \\ z'(t) &= \beta y(t)z(t) - \gamma z(t), \\ a'(t) &= ga(t)v(t) - ba(t), \end{cases} \tag{3.12}$$

where $\alpha_1 = ka_1, \alpha_2 = N\delta a_2$ and $g_i(\xi) = \frac{G_i(\xi)}{a_i}$ for $i = 1, 2$. Recall that $a_i = \int_0^\infty G_i(\xi)\mathrm{d}\xi$, and thus $\int_0^\infty g_i(\xi)\mathrm{d}\xi = 1$.

The basic reproduction number for (1.3) defined in (3.2) can be rewritten as

$$\Re_0 = \frac{\lambda\alpha_1\alpha_2 f'(0)}{c\delta d}.$$

Throughout the paper, let $g(u) = u - 1 - \ln u$. Note that $g : R_+ \to R_+$ has a strict global minimum $g(1) = 0$. Let

$$H_i(t) = \int_t^\infty g_i(\xi)\mathrm{d}\xi, \quad i = 1, 2.$$

It is easy to see that $H_i(0) = 1, H_i(\infty) = 0, \mathrm{d}H_i(t) = -g_i(t)\mathrm{d}t$.

In what follows, we study the global stability of each equilibrium of system (3.12) by constructing suitable Lyapunov functionals and applying LaSalle's invariance principle.

3.2 Global stability of the infection-free equilibrium for the case $\Re_0 \leq 1$

It was mentioned that the infection-free equilibrium E_0 always exists in the region Γ, which represents that the virus is cleared up. Biologically, the following theorem implies that viral infection is unsuccessful.

Theorem 3.2. *When $\Re_0 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable in the region Γ.*

Proof. Define a Lyapunov functional on $C((-\infty, 0], \mathbf{R}^3_+)$ as follows:

$$\begin{aligned} L_{E_0}(x, y, v) =& x_0 g\left(\frac{x(t)}{x_0}\right) + \frac{k}{\alpha_1}y(t) + \frac{k\delta}{\alpha_1\alpha_2}v(t) \\ &+ k\int_0^\infty H_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi + \frac{k\delta}{\alpha_1}\int_0^\infty H_2(\xi)y(t-\xi)\mathrm{d}\xi. \end{aligned} \tag{3.13}$$

It is easy to see that $L_{E_0}(x, y, v)$ reaches its global minimum when the solution is in the infection-free equilibrium E_0, and therefore $L_{E_0}(x, y, v)$ is a Lyapunov functional. Similar to the arguments in Theorem 3.1 of [43], using integration by parts to the last two terms in (3.13), we obtain the derivative of $L_{E_0}(x, y, v)$ along the solution of (3.12) as follows:

$$\begin{aligned} L'_{E_0}(x, y, v) =& -\frac{d}{x(t)}(x(t) - x_0)^2 + kx_0 f(v(t)) - \frac{kp}{\alpha_1}y(t)z(t) - \frac{k\delta c}{\alpha_1\alpha_2}v(t) - \frac{k\delta q}{\alpha_1\alpha_2}a(t)v(t) \\ =& -\frac{d}{x(t)}(x(t) - x_0)^2 - \frac{kp}{\alpha_1}y(t)z(t) - \frac{k\delta q}{\alpha_1\alpha_2}a(t)v(t) + \frac{k\delta c}{\alpha_1\alpha_2}\left(\frac{\lambda\alpha_1\alpha_2}{c\delta d}\frac{f(v(t))}{v(t)} - 1\right)v(t) \\ \leq& -\frac{d}{x(t)}(x(t) - x_0)^2 - \frac{kp}{\alpha_1}y(t)z(t) - \frac{k\delta q}{\alpha_1\alpha_2}a(t)v(t) + \frac{k\delta c}{\alpha_1\alpha_2}\left(\frac{\lambda\alpha_1\alpha_2 f'(0)}{c\delta d} - 1\right)v(t). \end{aligned}$$

Therefore, $\Re_0 = \frac{\lambda\alpha_1\alpha_2 f'(0)}{c\delta d} \leq 1$ ensures that $L'_{E_0}(x, y, v) \leq 0$ for all $x, y, v \geq 0$. One can see that $L'_{E_0}(x, y, v, z, a) = 0$ if and only if $x(t) = x_0$, $y(t)z(t) = 0$, $a(t)v(t) = 0$, $v(t) = 0$ for $\Re_0 < 1$ and $x(t) = x_0$, $y(t)z(t) = 0$, $a(t)v(t) = 0$ for $\Re_0 = 1$. Hence, every solution of (3.12) tends to M_0, where M_0 is the largest invariant subset in $\{(x, y, v, z, a) \in \Gamma : L'_{E_0}(x, y, v) = 0\}$ with respect to (3.12). It can be easily verified that M_0 is singleton $\{E_0\}$. The global stability of E_0 follows from the classical Lyapunov-LaSalle invariance principle (see, for example, [14]). □

In order to prove the globally stability of the infection equilibria, we need the following lemma.

Lemma 3.1. *Let $F(u)=\frac{f(v^*u)}{f(v^*)}$. If $f(\xi)$ satisfies Assumption (A_1), then*

$$g(F(u))\le g(u),\quad \textit{for}\ \ u>0.$$

3.3 Global stability of the immune-free equilibrium E_1 for the case $\Re_0>1$

Theorem 3.3. *When $\Re_0>1$, $\Re_1\le 1$ and $\Re_2\le 1$, the immune-free infection equilibrium E_1 is globally asymptotically stable.*

Proof. Define a Lyapunov functional on $C((0,+\infty],\mathbf{R}^5_+)$ as follows:

$$L_{E_1}(x,y,v,z,a)=x_1g\Big(\frac{x(t)}{x_1}\Big)+\frac{k}{\alpha_1}y_1g\Big(\frac{y(t)}{y_1}\Big)+\frac{k\delta}{\alpha_1\alpha_2}v_1g\Big(\frac{v(t)}{v_1}\Big)+\frac{kp}{\alpha_1\beta}z(t)+\frac{k\delta q}{\alpha_1\alpha_2 g}a(t)+L_1(x,v)+L_2(y),\quad(3.14)$$

where $L_1(x,v)$ and $L_2(y)$ are defined by

$$L_1(x,v)=kx_1f(v_1)\int_0^\infty H_1(\xi)g\Big(\frac{x(t-\xi)f(v(t-\xi))}{x_1f(v_1)}\Big)\mathrm{d}\xi,$$

and

$$L_2(y)=\frac{k\delta}{\alpha_1}y_1\int_0^\infty H_2(\xi)g\Big(\frac{y(t-\xi)}{y_1}\Big)\mathrm{d}\xi.$$

Obviously, $L_1(x,v)$ and $L_2(y)$ are well-defined and $L_1(x,v),L_2(y)\ge 0$ with the equality holding if and only if $x(t)=x_1$, $y(t)=y_1$, $v(t)=v_1$, $z(t)=a(t)=0$.

Using integration by parts, we have

$$\begin{aligned}L_1'(x,v)=&kx_1f(v_1)\int_0^\infty H_1(\xi)\frac{\mathrm{d}g(\frac{x(t-\xi)f(v(t-\xi))}{x_1f(v_1)})}{\mathrm{d}t}\mathrm{d}\xi\\=&-kx_1f(v_1)\int_0^\infty H_1(\xi)\frac{\mathrm{d}g(\frac{x(t-\xi)f(v(t-\xi))}{x_1f(v_1)})}{\mathrm{d}\xi}\mathrm{d}\xi\\=&kx(t)f(v(t))-k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi+kx_1f(v_1)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi,\end{aligned}$$

Similarly, differentiating $L_2(y)$ gives

$$L_2'(y)=\frac{k\delta}{\alpha_1}y(t)-\frac{k\delta}{\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi+\frac{k\delta}{\alpha_1}y_1\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi.$$

For system (3.12), it is easy to verify that functional $L_{E_1}(x,y,v,z,a)$ satisfies

$$\begin{aligned}L_{E_1}'(x,y,v,z,a)\ =&\ \Big(1-\frac{x_1}{x(t)}\Big)x'(t)+\frac{k}{\alpha_1}\Big(1-\frac{y_1}{y(t)}\Big)y'(t)\\&+\frac{k\delta}{\alpha_1\alpha_2}\Big(1-\frac{v_1}{v(t)}\Big)v'(t)+\frac{kp}{\alpha_1\beta}z'(t)+\frac{k\delta q}{\alpha_1\alpha_2 g}a'(t)+L_1'(x,v)+L_2'(y).\end{aligned}$$

Using the equalities $\lambda=dx_1+kx_1f(v_1)$, $\alpha_1x_1f(v_1))=\delta y_1$ and $\alpha_2y_1=cv_1$, we obtain

$$\begin{aligned}L_{E_1}'(x,y,v,z,a)=&-\frac{d}{x(t)}(x(t)-x_1)^2+kx_1f(v_1)\Big(3-\frac{x_1}{x(t)}-\frac{v(t)}{v_1}+\frac{f(v(t))}{f(v_1)}\\&-\int_0^\infty g_1(\xi)\frac{x(t-\xi)y_1f(v(t-\xi))}{x_1y(t)f(v_1)}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v_1y(t-\xi)}{v(t)y_1}\mathrm{d}\xi\\&+\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi+\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\Big)\\&+\frac{kpy_1}{\alpha_1}z(t)-\frac{kp\gamma}{\alpha_1\beta}z(t)+\frac{k\delta qv_1}{\alpha_1\alpha_2}a(t)-\frac{k\delta qb}{\alpha_1\alpha_2}a(t)\\=&-\frac{d}{x(t)}(x(t)-x_1)^2+kx_1f(v_1)\Big[\int_0^\infty g_1(\xi)\Big(-g\Big(\frac{x_1}{x(t)}\Big)\\&-g\Big(\frac{x(t-\xi)y_1f(v(t-\xi))}{x_1y(t)f(v_1)}\Big)-\ln\frac{y_1f(v(t))}{y(t)f(v_1)}\Big)\mathrm{d}\xi\\&+\int_0^\infty g_2(\xi)\Big(-g\Big(\frac{v_1y(t-\xi)}{v(t)y_1}\Big)+\ln\frac{v(t)y_1}{v_1y(t)}\Big)\mathrm{d}\xi+\frac{f(v(t))}{f(v_1)}-\frac{v(t)}{v_1}\Big]\\&+\frac{kp\gamma}{\alpha_1\beta}\Big(\frac{\beta}{\gamma}y_1-1\Big)z(t)+\frac{k\delta qb}{\alpha_1\alpha_2 g}\Big(\frac{g}{b}v_1-1\Big)a(t).\end{aligned}$$

If $\Re_1 = \frac{\beta}{\gamma} y_1 \le 1$ and $\Re_2 = \frac{g}{b} v_1 \le 1$, we can conclude that

$$\begin{aligned}
L'_{E_1}(x,y,v,z,a) =& -\frac{d}{x(t)}(x(t)-x_1)^2 \\
&- kx_1 f(v_1)\left[\int_0^\infty g_1(\xi)\left(g\left(\frac{x_1}{x(t)}\right)+g\left(\frac{x(t-\xi)y_1 f(v(t-\xi))}{x_1 y(t) f(v_1)}\right)\right)\mathrm{d}\xi + \int_0^\infty g_2(\xi) g\left(\frac{v_1 y(t-\xi)}{v(t) y_1}\right)\mathrm{d}\xi\right] \\
&+ kx_1 f(v_1)\left(\ln\frac{v(t)y_1}{v_1 y(t)} - \ln\frac{y_1 f(v(t))}{y(t) f(v_1)} + \frac{f(v(t))}{f(v_1)} - \frac{v(t)}{v_1}\right) + \frac{kp\gamma}{\alpha_1\beta}(\Re_1 - 1)z(t) + \frac{k\delta qb}{\alpha_1\alpha_2 g}(\Re_2 - 1)a(t) \\
\le& -\frac{d}{x(t)}(x(t)-x_1)^2 \\
&- kx_1 f(v_1)\left[\int_0^\infty g_1(\xi)\left(g\left(\frac{x_1}{x(t)}\right)+g\left(\frac{x(t-\xi)y_1 f(v(t-\xi))}{x_1 y(t) f(v_1)}\right)\right)\mathrm{d}\xi + \int_0^\infty g_2(\xi) g\left(\frac{v_1 y(t-\xi)}{v(t) y_1}\right)\mathrm{d}\xi\right] \\
&+ kx_1 f(v_1)\left(\frac{f(v(t))}{f(v_1)} - \ln\frac{f(v(t))}{f(v_1)} - \frac{v(t)}{v_1} + \ln\frac{v(t)}{v_1}\right) \\
=& -\frac{d}{x(t)}(x(t)-x_1)^2 \\
&- kx_1 f(v_1)\left[\int_0^\infty g_1(\xi)\left(g\left(\frac{x_1}{x(t)}\right)+g\left(\frac{x(t-\xi)y_1 f(v(t-\xi))}{x_1 y(t) f(v_1)}\right)\right)\mathrm{d}\xi + \int_0^\infty g_2(\xi) g\left(\frac{v_1 y(t-\xi)}{v(t) y_1}\right)\mathrm{d}\xi\right] \\
&+ kx_1 f(v_1)(g(F(u_1)) - g(u_1)),
\end{aligned}$$

where $u_1 = \frac{v(t)}{v_1}$ and $F(u_1) = \frac{f(v(t))}{f(v_1)} = \frac{f(v_1 u_1)}{f(v_1)}$. Using the fact in Lemma 3.1, we see that $L'_{E_1}(x,y,v,z,a) \le 0$ and $L'_{E_1}(x,y,v,z,a) = 0$ if $x(t) = x_1$, $x(t-\xi)y_1 f(v(t-\xi)) = x_1 y(t) f(v_1)$ and $v_1 y(t-\xi) = v(t) y_1$ for almost all $\xi \in [0,\infty)$. Again by the Lyapunov-LaSalle invariance principle, all solutions of (3.12) are attracted to M_1, which is the largest invariant subset of $\{(x,y,v,z,a) \in \Gamma : L'_{E_1}(x,y,v,z,a) = 0\}$. Since M_1 is invariant with respect to (3.12), on M_1, we have

$$0 = \lambda - dx_1 - kx_1 f(v(t)), \text{ that is, } f(v(t)) = f(v_1) > 0,$$

which implies that $y(t) = y_1$ and $v(t) = v_1$ from $y_1 f(v(t-\xi)) = y(t) f(v_1)$ and $v_1 y(t-\xi) = v(t) y_1$ for almost all $\xi \in [0,\infty)$. This yields that $z(t) = 0$ and $a(t) = 0$ from the equalities:

$$0 = ka_1 x_1 f(v_1) - \delta y_1 - py_1 z(t) = -py_1 z(t).$$

and

$$0 = \delta N a_2 y_1 - cv_1 - qa(t)v_1 = -qa(t)v_1.$$

Hence, we verify that $M_1 = \{(x_1, y_1, v_1, 0, 0)\}$. This shows that

$$\lim_{t\to\infty}(x(t), y(t), v(t), z(t), a(t)) = E_1.$$

Since

$$L_{E_1}(x,y,v,z,a) \ge x_1 g\left(\frac{x(t)}{x_1}\right) + \frac{k}{\alpha_1} y_1 g\left(\frac{y(t)}{y_1}\right) + \frac{k\delta}{\alpha_1\alpha_2} v_1 g\left(\frac{v(t)}{v_1}\right) + \frac{kp}{\alpha_1\beta} z(t) + \frac{k\delta q}{\alpha_1\alpha_2 g} a(t),$$

E_1 is uniformly stable, which completes the proof. □

Biologically, Theorem 3.3 implies that the infection is successful, but the establishments of both CTLs and antibody immune responses are unsuccessful.

3.4 Global stability of the infection equilibrium E_2 for the case $\Re_1 > 1$

Theorem 3.4. *When $\Re_1 > 1$ and $\Re_4 \le 1$, the infection equilibrium E_2 with only CTL immune response is globally asymptotically stable.*

Proof. Define a Lyapunov functional on $C((-\infty, 0], \mathbf{R}^5_+)$ as follows:

$$\begin{aligned}
L_{E_2}(x,y,v,z,a) =& x_2 g\left(\frac{x(t)}{x_2}\right) + \frac{k}{\alpha_1} y_2 g\left(\frac{y(t)}{y_2}\right) + \left(\frac{k\delta}{\alpha_1\alpha_2} + \frac{kpz_2}{\alpha_1\alpha_2}\right) v_2 g\left(\frac{v(t)}{v_2}\right) \\
&+ \frac{kp}{\alpha_1\beta} z_2 g\left(\frac{z(t)}{z_2}\right) + \left(\frac{k\delta q}{\alpha_1\alpha_2 g} + \frac{kpqz_2}{\alpha_1\alpha_2 g}\right) a(t) + L_3(x,v) + L_4(y),
\end{aligned}$$

where $L_3(x,v)$ and $L_4(y)$ are defined by

$$L_3(x,v)=kx_2f(v_2)\int_0^\infty H_1(\xi)g\Big(\frac{x(t-\xi)f(v(t-\xi))}{x_2f(v_2)}\Big)\mathrm{d}\xi,$$

and

$$L_4(y)=kx_2f(v_2)\int_0^\infty H_2(\xi)g\Big(\frac{y(t-\xi)}{y_2}\Big)\mathrm{d}\xi.$$

Using integration by parts, we can easily obtain

$$L_3'(x,v)=kx(t)f(v(t))-k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi+kx_2f(v_2)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi$$

and

$$L_4'(y)=\frac{k(\delta+pz_2)}{\alpha_1}y(t)-\frac{k(\delta+pz_2)}{\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi+kx_2f(v_2)\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi.$$

Calculating the time derivative of $L_{E_2}(x,y,v,z,a)$ along the solution of (3.12), we have

$$\begin{aligned}L_{E_2}'(x,y,v,z,a)=&\Big(1-\frac{x_2}{x(t)}\Big)x'(t)+\frac{k}{\alpha_1}\Big(1-\frac{y_2}{y(t)}\Big)y'(t)\\&+\Big(\frac{k\delta}{\alpha_1\alpha_2}+\frac{kpz_2}{\alpha_1\alpha_2}\Big)\Big(1-\frac{v_2}{v(t)}\Big)v'(t)+\frac{kp}{\alpha_1\beta}\Big(1-\frac{z_2}{z(t)}\Big)z'(t)\\&+\Big(\frac{k\delta q}{\alpha_1\alpha_2 g}+\frac{kpqz_2}{\alpha_1\alpha_2 g}\Big)a'(t)+L_3'(x,v)+L_4'(y).\end{aligned}$$

Using the equalities $\lambda=dx_2+kx_2f(v_2)$, $\alpha_1x_2f(v_2)=\delta y_2+py_2z_2$, $\alpha_2y_2=cv_2$ and $\beta y_2z_2=\gamma z_2$, we obtain

$$\begin{aligned}&L_{E_2}'(x,y,v,z,a)\\=&-\frac{d}{x(t)}(x(t)-x_2)^2+kx_2f(v_2)\Big(3-\frac{x_2}{x(t)}-\frac{v(t)}{v_2}+\frac{f(v(t))}{f(v_2)}\\&-\int_0^\infty g_1(\xi)\frac{x(t-\xi)y_2f(v(t-\xi))}{x_2y(t)f(v_2)}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v_2y(t-\xi)}{v(t)y_2}\mathrm{d}\xi\\&+\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi+\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\Big)\\&+\Big(\frac{k\delta qv_2}{\alpha_1\alpha_2}+\frac{kpqz_2v_2}{\alpha_1\alpha_2}-\frac{kb\delta q}{\alpha_1\alpha_2 g}-\frac{kbpqz_2}{\alpha_1\alpha_2 g}\Big)a(t)\\=&-\frac{d}{x(t)}(x(t)-x_2)^2+kx_2f(v_2)\Big[\int_0^\infty g_1(\xi)\Big(-g\Big(\frac{x_2}{x(t)}\Big)-g\Big(\frac{x(t-\xi)y_2f(v(t-\xi))}{x_2y(t)f(v_2)}\Big)-\ln\frac{y_2f(v(t))}{y(t)f(v_2)}\Big)\mathrm{d}\xi\\&+\int_0^\infty g_2(\xi)\Big(-g\Big(\frac{v_2y(t-\xi)}{v(t)y_2}\Big)+\ln\frac{v(t)y_2}{v_2y(t)}\Big)\mathrm{d}\xi+\frac{f(v(t))}{f(v_2)}-\frac{v(t)}{v_2}\Big]+\frac{kbq}{\alpha_1\alpha_2 g}(\delta+pz_2)\Big(\frac{\alpha_2g\gamma}{\beta bc}-1\Big)a(t).\end{aligned}$$

If $\Re_4 = \frac{\alpha_2 g\gamma}{\beta bc} \le 1$, we can conclude that

$$\begin{aligned}
L'_{E_2}(x,y,v,z,a) =& -\frac{d}{x(t)}(x(t)-x_2)^2 \\
&- kx_2 f(v_2)\left[\int_0^\infty g_1(\xi)\left(g\left(\frac{x_2}{x(t)}\right)+g\left(\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t) f(v_2)}\right)+\int_0^\infty g_2(\xi)g\left(\frac{v_2 y(t-\xi)}{v(t)y_2}\right)\mathrm{d}\xi\right] \\
&+ kx_2 f(v_2)\left(\ln\frac{v(t)y_2}{v_2 y(t)} - \ln\frac{y_2 f(v(t))}{y(t)f(v_2)} + \frac{f(v(t))}{f(v_2)} - \frac{v(t)}{v_2}\right) + \frac{kbq}{\alpha_1\alpha_2 g}(\delta+pz_2)(\Re_4-1)a(t) \\
\le& -\frac{d}{x(t)}(x(t)-x_2)^2 \\
&- kx_2 f(v_2)\left[\int_0^\infty g_1(\xi)\left(g\left(\frac{x_2}{x(t)}\right)+g\left(\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t) f(v_2)}\right)+\int_0^\infty g_2(\xi)g\left(\frac{v_2 y(t-\xi)}{v(t)y_2}\right)\mathrm{d}\xi\right] \\
&+ kx_2 f(v_2)\left(\frac{f(v(t))}{f(v_2)} - \ln\frac{f(v(t))}{f(v_2)} - \frac{v(t)}{v_2} + \ln\frac{v(t)}{v_2}\right) \\
=& -\frac{d}{x(t)}(x(t)-x_2)^2 \\
&- kx_2 f(v_2)\left[\int_0^\infty g_1(\xi)\left(g\left(\frac{x_2}{x(t)}\right)+g\left(\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t) f(v_2)}\right)+\int_0^\infty g_2(\xi)g\left(\frac{v_2 y(t-\xi)}{v(t)y_2}\right)\mathrm{d}\xi\right] \\
&+ kx_2 f(v_2)(g(F(u_2)) - g(u_2)),
\end{aligned}$$

where $u_2 = \frac{v(t)}{v_2}$ and $F(u_2) = \frac{f(v(t))}{f(v_2)} = \frac{f(v_2 u_2)}{f(v_2)}$. Using the fact in Lemma 3.1, we see that $L'_{E_2} \le 0$ and $L'_{E_2}(x,y,v,z,a) = 0$ if $x(t) = x_2$, $y_2 f(v(t-\xi)) = y(t)f(v_2)$ and $v_2 y(t-\xi) = v(t)y_2$ for almost all $\xi \in [0,\infty)$. Again by the Lyapunov-LaSalle invariance principle, all solutions of (3.12) are attracted to M_2, which is the largest invariant subset of $\{(x,y,v,z,a) \in \Gamma : L'_{E_2}(x,y,v,z,a) = 0\}$. Since M_2 is invariant with respect to (3.12), on M_2, we have

$$0 = \lambda - dx_2 - kx_2 f(v(t)), \text{ that is, } f(v(t)) = f(v_2) > 0,$$

which implies that $y(t) = y_2$, $v(t) = v_2$ from $y_2 f(v(t-\xi)) = y(t)f(v_2)$ and $v_2 y(t-\xi) = v(t)y_2$ for almost all $\xi \in [0,\infty)$. This yields that $z(t) = z_2$ and $a(t) = 0$ from the equalities

$$0 = ka_1 x_2 f(v_2) - \delta y_2 - py_2 z(t) = -py_2(z(t) - z_2).$$

and

$$0 = \delta N a_2 y_2 - cv_2 - qa(t)v_2 = -qa(t)v_2.$$

Hence, we verify that $M_2 = \{(x_2, y_2, v_2, z_2, 0)\}$. This shows that

$$\lim_{t\to\infty}(x(t), y(t), v(t), z(t), a(t)) = E_2.$$

Since

$$L_{E_2}(x,y,v,z,a) \ge x_2 g\left(\frac{x(t)}{x_2}\right) + \frac{k}{\alpha_1}y_2 g\left(\frac{y(t)}{y_2}\right) + \frac{k\delta}{\alpha_1\alpha_2}v_2 g\left(\frac{v(t)}{v_2}\right) + \frac{kp}{\alpha_1\beta}z_2 g\left(\frac{z(t)}{z_2}\right) + \left(\frac{k\delta q}{\alpha_1\alpha_2 g} + \frac{kpqz_2}{\alpha_1\alpha_2 g}\right)a(t),$$

E_2 is uniformly stable, which completes the proof. □

Theorem 3.4 implies that the CTL immune responses are determined, but the viral loads are so small that it can not activate the antibody immune responses.

3.5 Global stability of the infection equilibrium E_3 for the case $\Re_2 > 1$

Theorem 3.5. *When $\Re_2 > 1$ and $\Re_3 \le 1$, the infection equilibrium E_3 with only humoral immune response is globally asymptotically stable.*

Proof. Define a Lyapunov functional on $C((-\infty,0], \mathbf{R}^5_+)$ as follows:

$$L_{E_3}(x,y,v,z,a) = x_3 g\left(\frac{x(t)}{x_3}\right) + \frac{k}{\alpha_1}y_3 g\left(\frac{y(t)}{y_3}\right) + \frac{k\delta}{\alpha_1\alpha_2}v_3 g\left(\frac{v(t)}{v_3}\right) + \frac{kp}{\alpha_1\beta}z(t) + \frac{k\delta q}{\alpha_1\alpha_2 g}a_3 g\left(\frac{a(t)}{a_3}\right) + L_5(x,v) + L_6(y),$$

where $L_5(t)$ and $L_6(t)$ are defined by

$$L_5(x,v) = kx_3 f(v_3)\int_0^\infty H_1(\xi)g\Big(\frac{x(t-\xi)f(v(t-\xi))}{x_3 f(v_3)}\Big)\mathrm{d}\xi,$$

and

$$L_6(y) = kx_3 f(v_3)\int_0^\infty H_2(\xi)g\Big(\frac{y(t-\xi)}{y_3}\Big)\mathrm{d}\xi.$$

Using integration by parts, we can easily obtain

$$L_5'(x,v) = kx(t)f(v(t)) - k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi + kx_3 f(v_3)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi,$$

and

$$L_6'(y) = \frac{k\delta}{\alpha_1}y(t) - \frac{k\delta}{\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi + kx_3 f(v_3)\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi.$$

Calculating the time derivative of $L_{E_3}(x,y,v,z,a)$ along the solution of (3.12), we have

$$\begin{aligned}L_{E_3}'(x,y,v,z,a) =& -\frac{d}{x(t)}(x(t)-x_3)^2 + kx_3 f(v_3)\Big[\int_0^\infty g_1(\xi)\Big(-g\Big(\frac{x_3}{x(t)}\Big) - \ln\frac{y_3 f(v(t))}{y(t)f(v_3)} - g\Big(\frac{x(t-\xi)y_3 f(v(t-\xi))}{x_3 y(t)f(v_3)}\Big)\Big)\mathrm{d}\xi\\ &+\int_0^\infty g_2(\xi)\Big(-g\Big(\frac{v_3 y(t-\xi)}{v(t)y_3}\Big) + \ln\frac{v(t)y_3}{v_3 y(t)}\Big)\mathrm{d}\xi + \frac{f(v(t))}{f(v_3)} - \frac{v(t)}{v_3}\Big] + \frac{kp\gamma}{\alpha_1\beta}\Big(\frac{\beta y_3}{\gamma} - 1\Big)z(t).\end{aligned}$$

Here we use the relation that $\lambda = dx_3 + kx_3 f(v_3)$, $\alpha_1 x_3 f(v_3) = \delta y_3$, $\alpha_2 y_3 = cv_3 + qa_3 v_3$ and $ga_3 v_3 = ba_3$.

If $\Re_3 = \frac{\beta y_3}{\gamma} \le 1$, we can conclude that

$$\begin{aligned}L_{E_3}'(x,y,v,z,a) =& -\frac{d}{x(t)}(x(t)-x_3)^2\\ &- kx_3 f(v_3)\Big[\int_0^\infty g_1(\xi)\Big(g\Big(\frac{x_3}{x(t)}\Big) + g\Big(\frac{x(t-\xi)y_3 f(v(t-\xi))}{x_3 y(t)f(v_3)}\Big)\Big)\mathrm{d}\xi + \int_0^\infty g_2(\xi)g\Big(\frac{v_3 y(t-\xi)}{v(t)y_3}\Big)\mathrm{d}\xi\Big]\\ &+ kx_3 f(v_3)\Big(\ln\frac{v(t)y_3}{v_3 y(t)} - \ln\frac{y_3 f(v(t))}{y(t)f(v_3)} + \frac{f(v(t))}{f(v_3)} - \frac{v(t)}{v_3}\Big) + \frac{kp\gamma}{\alpha_1\beta}(\Re_3 - 1)z(t)\\ \le& -\frac{d}{x(t)}(x(t)-x_3)^2\\ &- kx_3 f(v_3)\Big[\int_0^\infty g_1(\xi)\Big(g\Big(\frac{x_3}{x(t)}\Big) + g\Big(\frac{x(t-\xi)y_3 f(v(t-\xi))}{x_3 y(t)f(v_3)}\Big)\Big)\mathrm{d}\xi + \int_0^\infty g_2(\xi)g\Big(\frac{v_3 y(t-\xi)}{v(t)y_3}\Big)\mathrm{d}\xi\Big]\\ &+ kx_3 f(v_3)\Big(\frac{f(v(t))}{f(v_3)} - \ln\frac{f(v(t))}{f(v_3)} - \frac{v(t)}{v_3} + \ln\frac{v(t)}{v_3}\Big)\\ =& -\frac{d}{x(t)}(x(t)-x_3)^2\\ &- kx_3 f(v_3)\Big[\int_0^\infty g_1(\xi)\Big(g\Big(\frac{x_3}{x(t)}\Big) + g\Big(\frac{x(t-\xi)y_3 f(v(t-\xi))}{x_3 y(t)f(v_3)}\Big)\Big)\mathrm{d}\xi + \int_0^\infty g_2(\xi)g\Big(\frac{v_3 y(t-\xi)}{v(t)y_3}\Big)\mathrm{d}\xi\Big]\\ &+ kx_3 f(v_3)(g(F(w_3)) - g(w_3)),\end{aligned}$$

where $u_3 = \frac{v(t)}{v_3}$ and $F(u_3) = \frac{f(v(t))}{f(v_3)} = \frac{f(v_3 u_3)}{f(v_3)}$. Using the fact in Lemma 3.1, we see that $L_{E_3}' \le 0$ and $L_{E_3}'(x,y,v,z,a) = 0$ if $x(t) = x_3$, $y_3 f(v(t-\xi)) = y(t)f(v_3)$, $v_3 y(t-\xi) = v(t)y_3$ for almost all $\xi \in [0,\infty)$. Similar to the discussion in Subsection 3.4, all solutions of (3.12) are attracted to $M_3 = \{E_3\}$. Thus, it follows from LaSalle's invariance principle that the infection equilibrium E_3 is globally asymptotically stable. This completes the proof. □

Theorem 3.5 means that the antibody immune responses are established, but the infected cells are too weak to stimulate CTL immune responses.

3.6 Global stability of the infection equilibrium E_4 for the case $\Re_3 > 1$ and $\Re_4 > 1$

Theorem 3.6. *When $\Re_3 > 1$ and $\Re_4 > 1$, the infection equilibrium E_4 with both CTL response and humoral response is globally asymptotically stable.*

Proof. Define a Lyapunov functional on $C((-\infty,0],\mathbf{R}^5_+)$ by

$$\begin{aligned}L_{E_4}(x,y,v,z,a) =& x_4 g\Big(\frac{x(t)}{x_4}\Big)+\frac{k}{\alpha_1}y_4 g\Big(\frac{y(t)}{y_4}\Big)+\Big(\frac{k\delta}{\alpha_1\alpha_2}+\frac{kpz_4}{\alpha_1\alpha_2}\Big)v_4 g\Big(\frac{v(t)}{v_4}\Big)\\ &+\frac{kp}{\alpha_1\beta}z_4 g\Big(\frac{z(t)}{z_4}\Big)+\Big(\frac{k\delta q}{\alpha_1\alpha_2 g}+\frac{kpqz_4}{\alpha_1\alpha_2 g}\Big)a_4 g\Big(\frac{a(t)}{a_4}\Big)+L_7(x,v)+L_8(y),\end{aligned}$$

where $L_7(x,v)$ and $L_8(y)$ are defined by

$$L_7(x,v)=kx_4f(v_4)\int_0^\infty H_1(\xi)g\Big(\frac{x(t-\xi)f(v(t-\xi))}{x_4f(v_4)}\Big)\mathrm{d}\xi,$$

and

$$L_8(y)=kx_4f(v_4)\int_0^\infty H_2(\xi)g\Big(\frac{y(t-\xi)}{y_4}\Big)\mathrm{d}\xi.$$

Using integration by parts, we can easily obtain

$$L_7'(x,v)=kx(t)f(v(t))-k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi+kx_4f(v_4)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi$$

and

$$L_8'(y)=\frac{k(\delta+pz_4)}{\alpha_1}y(t)-\frac{k(\delta+pz_4)}{\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi+kx_4f(v_4)\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi.$$

Calculating the derivative of $L_{E_4}(x,y,v,z,a)$ along the solution of (3.12), we have

$$\begin{aligned}L_{E_4}'(x,y,v,z,a) =&\Big(1-\frac{x_4}{x(t)}\Big)x'(t)+\frac{k}{\alpha_1}\Big(1-\frac{y_4}{y(t)}\Big)y'(t)\\ &+\Big(\frac{k\delta}{\alpha_1\alpha_2}+\frac{kpz_4}{\alpha_1\alpha_2}\Big)\Big(1-\frac{v_4}{v(t)}\Big)v'(t)+\frac{kp}{\alpha_1\beta}\Big(1-\frac{z_4}{z(t)}\Big)z'(t)\\ &+\Big(\frac{k\delta q}{\alpha_1\alpha_2 g}+\frac{kpqz_4}{\alpha_1\alpha_2 g}\Big)\Big(1-\frac{a_4}{a(t)}\Big)a'(t)+L_7'(x,v)+L_8'(y).\end{aligned}$$

Using the equalities $\lambda=dx_4+kx_4f(v_4)$, $\alpha_1x_4f(v_4)=\delta y_4+py_4z_4$, $\alpha_2y_4=cv_4+qa_4v_4$, $\beta y_4z_4=\gamma z_4$ and $ga_4v_4=ba_4$, and after long calculation, we obtain

$$\begin{aligned}L_{E_4}'(x,y,v,z,a) =&-\frac{d}{x(t)}(x(t)-x_4)^2+kx_4f(v_4)\Big(3-\frac{x_4}{x(t)}-\frac{v(t)}{v_4}+\frac{f(v(t))}{f(v_4)}\\ &-\int_0^\infty g_1(\xi)\frac{x(t-\xi)y_4f(v(t-\xi))}{x_4y(t)f(v_4)}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v_4y(t-\xi)}{v(t)y_4}\mathrm{d}\xi\\ &+\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi+\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\Big)\\ =&-\frac{d}{x(t)}(x(t)-x_4)^2\\ &+kx_4f(v_4)\Big[\int_0^\infty g_1(\xi)\Big(-g\Big(\frac{x(t-\xi)y_4f(v(t-\xi))}{x_4y(t)f(v_4)}\Big)-g\Big(\frac{x_4}{x(t)}\Big)-\ln\frac{y_4f(v(t))}{y(t)f(v_4)}\Big)\mathrm{d}\xi\\ &+\int_0^\infty g_2(\xi)\Big(-g\Big(\frac{v_4y(t-\xi)}{v(t)y_4}\Big)+\ln\frac{v(t)y_4}{v_4y(t)}\Big)\mathrm{d}\xi+\frac{f(v(t))}{f(v_4)}-\frac{v(t)}{v_4}\Big]\\ =&-\frac{d}{x(t)}(x(t)-x_4)^2\\ &-kx_4f(v_4)\Big[\int_0^\infty g_1(\xi)\Big(g\Big(\frac{x(t-\xi)y_4f(v(t-\xi))}{x_4y(t)f(v_4)}\Big)+g\Big(\frac{x_4}{x(t)}\Big)\Big)\mathrm{d}\xi+\int_0^\infty g_2(\xi)g\Big(\frac{v_4y(t-\xi)}{v(t)y_4}\Big)\mathrm{d}\xi\Big]\\ &+kx_4f(v_4)\Big(\frac{f(v(t))}{f(v_4)}-\ln\frac{f(v(t))}{f(v_4)}-\frac{v(t)}{v_4}+\ln\frac{v(t)}{v_4}\Big)\\ =&-\frac{d}{x(t)}(x(t)-x_4)^2\\ &-kx_4f(v_4)\Big[\int_0^\infty g_1(\xi)\Big(g\Big(\frac{x(t-\xi)y_4f(v(t-\xi))}{x_4y(t)f(v_4)}\Big)+g\Big(\frac{x_4}{x(t)}\Big)\Big)\mathrm{d}\xi+\int_0^\infty g_2(\xi)g\Big(\frac{v_4y(t-\xi)}{v(t)y_4}\Big)\mathrm{d}\xi\Big]\\ &+kx_4f(v_4)(g(F(u_4))-g(u_4)),\end{aligned}$$

where $u_4 = \frac{v(t)}{v_4}$ and $F(u_4) = \frac{f(v(t))}{f(v_4)} = \frac{f(v_4 u_4)}{f(v_4)}$. Using the fact in Lemma 3.1, we see that $L'_{E_4}(x, y, v, z, a) \leq 0$ and $L'_{E_4}(x, y, v, z, a) = 0$ if $x(t) = x_4$, $y_4 f(v(t-\xi)) = y(t) f(v_4)$, $v_4 y(t-\xi) = v(t) y_4$ for almost all $\xi \in [0, \infty)$. Similar to the discussion in Subsection 3.4, all solutions of (3.12) are attracted to $M_3 = \{E_3\}$. Thus, it follows from LaSalle's invariance principle that the infection equilibrium E_4 is globally asymptotically stable. This completes the proof. □

Biologically, Theorem 3.6 implies that susceptible cells, infected cells, free virus particles, CTLs and antibodies coexist in vivo.

Note that we can not rule out the possibility that both of the assumptions $\Re_1 > 1 \geq \Re_4$ of Theorem 3.4 and $\Re_2 > 1 \geq \Re_3$ of Theorem 3.5 hold simultaneously. The following proposition provides a sufficient condition for excluding such a case.

Proposition 3.1. *If*

$$\frac{Nka_1a_2}{c} \frac{\lambda}{d + kf\left(\frac{b}{g}\right)} \frac{f\left(\frac{b}{g}\right)}{\frac{b}{g}} > 1, \tag{3.15}$$

then assumptions $\Re_1 > 1 \geq \Re_4$ of Theorem 3.4 and $\Re_2 > 1 \geq \Re_3$ of Theorem 3.5 do not hold simultaneously.

Proof. On the contrary, we suppose that $\Re_1 > 1 \geq \Re_4$ and $\Re_2 > 1 \geq \Re_3$. Then, we have

$$\begin{aligned} \Re_1 &= \frac{\beta}{\gamma} y_1 > 1 \geq \frac{g}{b} v_2 = \Re_4, \\ \Re_2 &= \frac{g}{b} v_1 > 1 \geq \frac{\beta}{\gamma} y_3 = \Re_3. \end{aligned}$$

Since both of the right-hand sides of the above inequalities are less than 1, we can exchange them and obtain

$$\frac{\beta}{\gamma} y_1 > 1 \geq \frac{\beta}{\gamma} y_3, \quad \frac{g}{b} v_1 > 1 \geq \frac{g}{b} v_2.$$

Hence, recalling that $y_2 = \gamma/\beta$ and $v_3 = b/g$, we have

$$y_1 > y_2 \geq y_3, \quad v_1 > v_3 \geq v_2. \tag{3.16}$$

Considering the case where $a = 0$ in (3.1), we obtain

$$v_2 = \frac{\delta N a_2}{c} y_2. \tag{3.17}$$

Furthermore, considering the case where $z = 0$ in (3.1), we obtain

$$x_3 = \frac{\lambda}{d + kf(v_3)}, \tag{3.18}$$

$$y_3 = \frac{ka_1}{\delta} x_3 f(v_3). \tag{3.19}$$

From (3.16)-(3.19), we have

$$\begin{aligned} v_2 &\geq \frac{\delta N a_2}{c} y_3 \\ &= \frac{\delta N a_2}{c} \frac{ka_1}{\delta} x_3 f(v_3) \\ &= \frac{\delta N a_2}{c} \frac{ka_1}{\delta} \frac{\lambda}{d + kf(v_3)} \frac{f(v_3)}{v_3} v_3 \\ &\geq \frac{\delta N a_2}{c} \frac{ka_1}{\delta} \frac{\lambda}{d + kf\left(\frac{b}{g}\right)} \frac{f\left(\frac{b}{g}\right)}{\frac{b}{g}} v_2. \end{aligned}$$

Hence, dividing the both sides by v_2 yields

$$1 \geq \frac{Nka_1a_2}{c} \frac{\lambda}{d + kf\left(\frac{b}{g}\right)} \frac{f\left(\frac{b}{g}\right)}{\frac{b}{g}},$$

which contradicts with (3.15). □

Note that (3.15) is a sufficient condition for $\Re_0 = Nka_1a_2\lambda/cd > 1$. In fact, if (3.15) holds, then we have from $(\mathbf{A}_1)$ that

$$\begin{aligned} 1 <& \frac{Nka_1a_2}{c}\frac{\lambda}{d+kf\left(\frac{b}{g}\right)}\frac{f\left(\frac{b}{g}\right)}{\frac{b}{g}} \\ \leq& \frac{Nka_1a_2}{c}\frac{\lambda}{d}\lim_{h\to+0}\frac{f(h)}{h} \\ =& \frac{Nka_1a_2}{c}\frac{\lambda}{d}f'(0) = \Re_0. \end{aligned}$$

In the case where $f(v) = v$, condition (3.15) becomes a simpler form. We have the following corollary from Proposition 3.1.

Corollary 3.1. *If $f(v) = v$ and*

$$\frac{Nka_1a_2}{c}\frac{\lambda}{d+k\frac{b}{g}} > 1, \tag{3.20}$$

then assumptions $\Re_1 > 1 \geq \Re_4$ of Theorem 3.4 and $\Re_2 > 1 \geq \Re_3$ of Theorem 3.5 do not hold simultaneously.

4 Numerical Simulations

In this section, we investigate the feasibility of our analytical results for the case $\Re_0 > 1$ for the model (1.3) with discrete delays as follows:

$$\begin{cases} x'(t) &= \lambda - dx(t) - kx(t)f(v(t)), \\ y'(t) &= ka_1x(t-\tau_1)f(v(t-\tau_1)) - \delta y(t) - py(t)z(t), \\ v'(t) &= \delta Na_2y(t-\tau_2) - cv(t) - qa(t)v(t), \\ z'(t) &= \beta y(t)z(t) - \gamma z(t), \\ a'(t) &= ga(t)v(t) - ba(t) \end{cases} \tag{4.1}$$

with $f(v) = \frac{v}{1+\alpha v}$, $\alpha > 0$.

If $\Re_0 \leq 1$, then the infection-free equilibrium E_0 of system (1.3) is globally asymptotically stable. If $\Re_0 > 1$, from Theorems 3.2-3.6, we then obtain the following corollary:

Corollary 4.1. *The following statement holds true.*

(i) *When $\Re_0 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable in the region Γ.*

Moreover, under the condition $\Re_0 > 1$, the following statements hold true.

(ii) *When $\Re_1 \leq 1$ and $\Re_2 \leq 1$, the immune-free infection equilibrium E_1 is globally asymptotically stable.*
(iii) *When $\Re_1 > 1$ and $\Re_2 \leq \Re_1$, the infection equilibrium E_2 with only CTL immune response is globally asymptotically stable.*
(iv) *When $\Re_3 \leq 1$ and $\Re_2 > 1$, the infection equilibrium E_3 with only humoral immune response is globally asymptotically stable.*
(v) *When $\Re_3 > 1$ and $\Re_2 > \Re_1$, the infection equilibrium E_4 with both CTL response and humoral response is globally asymptotically stable.*

Let us carry out some computational experiments for the dynamics of the concentration of uninfected target cells $x(t)$ [cells ml^{-1}], productively infected cells $y(t)$ [cells ml^{-1}], free virus in the serum $v(t)$ [virion cells^{-1}], the abundance of virus-specific $z(t)$ [cells ml^{-1}] and antibodies $a(t)$ [μg]. In order to investigate the feasibility of the above global stability conditions in Corollary 4.1, the decay rates of virus-specific CTLs γ day^{-1} and antibody responses b day^{-1} are chosen as free parameters for the case $\Re_0 > 1$. We fix the parameter values λ, d, k as displayed in Table 1. All the three values, which are used to compare predictions of several models for primary HIV-1 infection, are equivalent to the data from anti-retroviral, drug-naive, HIV-infected patients in Stafford et al. [35]. We also fix the other parameter values as in Table 2 with dimensionless parameters $\alpha = 0.01$ and $a_1 = a_2 = 0.9$. The value of the parameters δ, p, N and the length of time delay τ_1 in Table 2 are used for modeling prediction as best-fit parameter values for viral road data of HIV-infected patients in Table 2 of Pawelek et al. [33]. Under the parameter values in Tables 1 and 2, we obtain $\Re_0 = 19.611\cdots > 1$. First, we consider the case $\gamma = 0.5$ and $b = 2.9$. Then, we obtain $\Re_1 = 0.811\cdots \leq 1$ and $\Re_2 = 0.952\cdots \leq 1$. Hence, from the second part of Corollary 4.1, the immune-free infection equilibrium E_1 is globally asymptotically stable (see also Theorem 3.3). Second, we consider the case $\gamma = 0.2$ and $b = 2.9$. Then, we obtain $\Re_1 = 2.028\cdots > 1$, $\Re_2 = 0.952\cdots \leq 1$ and $\Re_3 = 2.033\cdots > 1$. From the third part of Corollary 4.1, the infection equilibrium E_2 with only CTL immune

Parameter	Value	Unit
λ	46	cells ml-day^{-1}
d	0.0046	day^{-1}
k	4.8×10^{-7}	ml virion-day^{-1}

Table 1: Parameters λ, d, k and their values in Section 4. The value of the above parameters are found in Stafford et al. [35].

Parameter	Value	Unit
δ	0.01	day^{-1}
p	0.00094	ml cells-day^{-1}
N	1261	virion cells^{-1}
c	0.25	day^{-1}
q	0.03	μg-day^{-1}
β	0.01	ml cells-day^{-1}
g	0.0015	cells virion-day^{-1}
τ_1	0.5	day
τ_2	0.5	day

Table 2: Parameters and their values in Section 4. The value of the parameters δ, p, N and τ_1 are found in Pawelek et al. [33].

response is globally asymptotically stable (see also Theorem 3.4). Third, we consider the case $\gamma = 0.5$ and $b = 0.8$. Then, we obtain $\Re_1 = 0.811\cdots \leq 1$, $\Re_2 = 3.453\cdots > 1$ and $\Re_3 = 0.721\cdots \leq 1$. From the fourth part of Corollary 4.1, the infection equilibrium E_3 with only CTL immune response is globally asymptotically stable (see also Theorem 3.5). Finally, we consider the case $\gamma = 0.2$ and $b = 0.8$. Then, we obtain $\Re_1 = 2.028\cdots > 1$, $\Re_2 = 3.453\cdots > 1$ and $\Re_3 = 1.803\cdots > 1$. From the fifth part of Corollary 4.1, the infection equilibrium E_4 with both CTL response and humoral response is globally asymptotically stable (see also Theorem 3.6).

5 Discussion

In this paper, we study global dynamics of delay differential equations for a virus-immune interaction in vivo. Two distributed time delays represent the time needed for infection of cell and virus replication. Stability analysis for (1.3) without humoral immune response was carried out by Yuan and Zou [43], while CTL activation term to the viral infection is assume to $\lambda y(t)$. Our work also extends a model studied by Yan and Wang [42] to incorporate continuous intracellular delay and nonlinear incidence rate.

In order to obtain a comprehensive view for the cell-mediated (CTLs) immune and humoral (antibody) interaction dynamics in vivo, we investigate the global stability of (1.3) by utilizing the method of constructing suitable Lyapunov functionals which are motivated by recent works of Korobeinikov [17–19], McCluskey [27, 28], Li and Shu [23, 24], Wang et al. [36, 38], Huang et al. [12, 13], Nakata [29] and Kajiwara et al. [20]. System (1.3) has five possible equilibria, an infection-free equilibrium, an immune-free equilibrium and three infected equilibria with one immune response or two immune responses.

A combination of the basic reproduction number for viral infection $\Re_0$, for CTL response $\Re_1$, for antibody immune response $\Re_2$, for CTL immune competition $\Re_3$ and for humoral immune competition $\Re_4$ defined by (3.2), (3.3), (3.6), (3.10) and (3.11), respectively, determines the existence of these equilibria. Furthermore, they also determine the global properties of the model. The infection-free equilibrium E_0 is globally asymptotically stable if $\Re_0 \leq 1$ and the viruses are cleared. The immune-free equilibrium E_1 without those two kinds of immune response is globally asymptotically stable if $\Re_0 > 1$, $\Re_1 \leq 1$ and $\Re_2 \leq 1$ and the infection becomes chronic but with no persistent CTL immune response and antibody immune response. The infected equilibrium E_2 with only CTL immune response is globally asymptotically stable if $\Re_1 > 1$ and $\Re_4 \leq 1$ and the infection becomes chronic with persistent CTL immune response, but the viral load can not activate the antibody immune responses. The infected equilibrium E_3 with antibody immune response is globally asymptotically stable if $\Re_2 > 1$ and $\Re_3 \leq 1$ and the infection becomes chronic with persistent antibody immune response, but the infected cells can not stimulate and activate CTL immune responses. If $\Re_3 > 1$ and $\Re_4 > 1$, the CTL and antibody immune responses are all strong enough to be established. E_4 is globally asymptotically stable, that is, susceptible cells, infected cells, free virus particles, CTLs and antibodies coexist in vivo.

From Theorems 3.2–3.6, we see that the distributed delay does not affect the global stability of the equilibria and therefore do not induce periodic oscillation of the solutions, and the possibility of Hopf bifurcations is therefore ruled out.

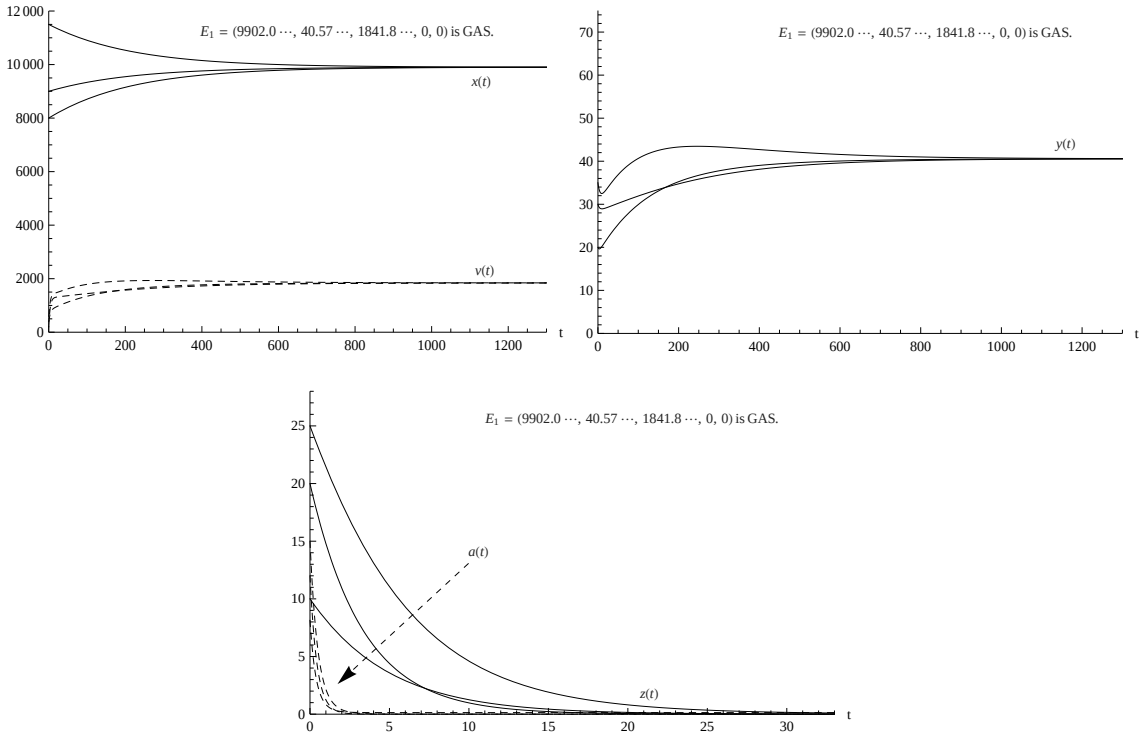

Figure 1: The graph trajectory of $x(t)$, $v(t)$ (Top-left), $y(t)$ (Top-right) and $z(t)$, $a(t)$ (Bottom) of system (4.1). The parameter values are listed in Tables 1 and 2 with $\alpha = 0.01$ and $a_1 = a_2 = 0.9$. For the case $\gamma = 0.5$ and $b = 2.9$, we have $\Re_1 = 0.811\cdots \leq 1$, $\Re_2 = 0.952\cdots \leq 1$ and $E_1 = (9902.0\cdots, 40.57\cdots, 1841.8\cdots, 0, 0)$. Here, GAS denotes globally asymptotically stable.

While viruses can not be eradicated when $\Re_0 > 1$, that is, whether the immune responses are established successfully or not, the patients will follow into a chronic infection.

It is also interesting to see the dynamical behavior if the nonlinear incidence rate $xf(v)$ is changed to either $vf(x)$ or $f(x/v)v$, which is presented in the references [10, 15]. We leave this our future work.

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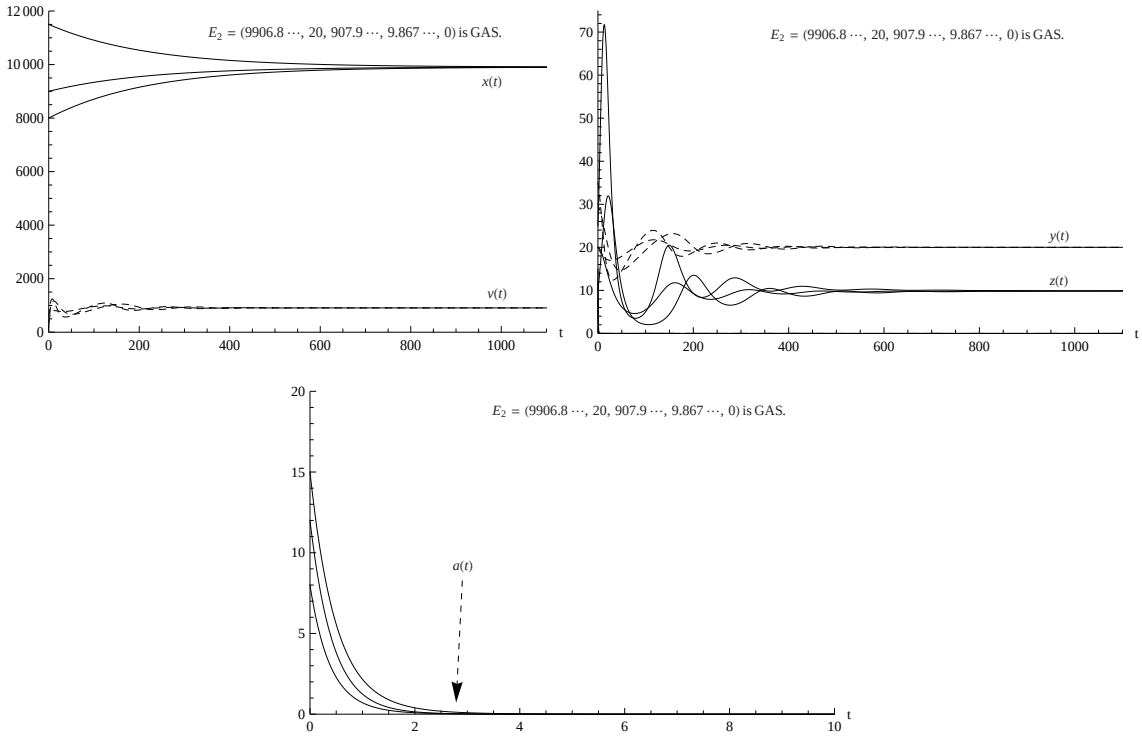

Figure 2: The graph trajectory of $x(t)$, $v(t)$ (Top-left), $y(t)$, $z(t)$ (Top-right) and $a(t)$ (Bottom) of system (4.1). The parameter values are listed in Tables 1 and 2 with $\alpha = 0.01$ and $a_1 = a_2 = 0.9$. For the case $\gamma = 0.2$ and $b = 2.9$, we have $\Re_1 = 2.028\cdots > 1$, $\Re_2 = 0.952\cdots \leq 1$, $\Re_3 = 2.033\cdots > 1$ and $E_2 = (9906.8\cdots, 20, 907.9\cdots, 9.867\cdots, 0)$. Here, GAS denotes globally asymptotically stable.

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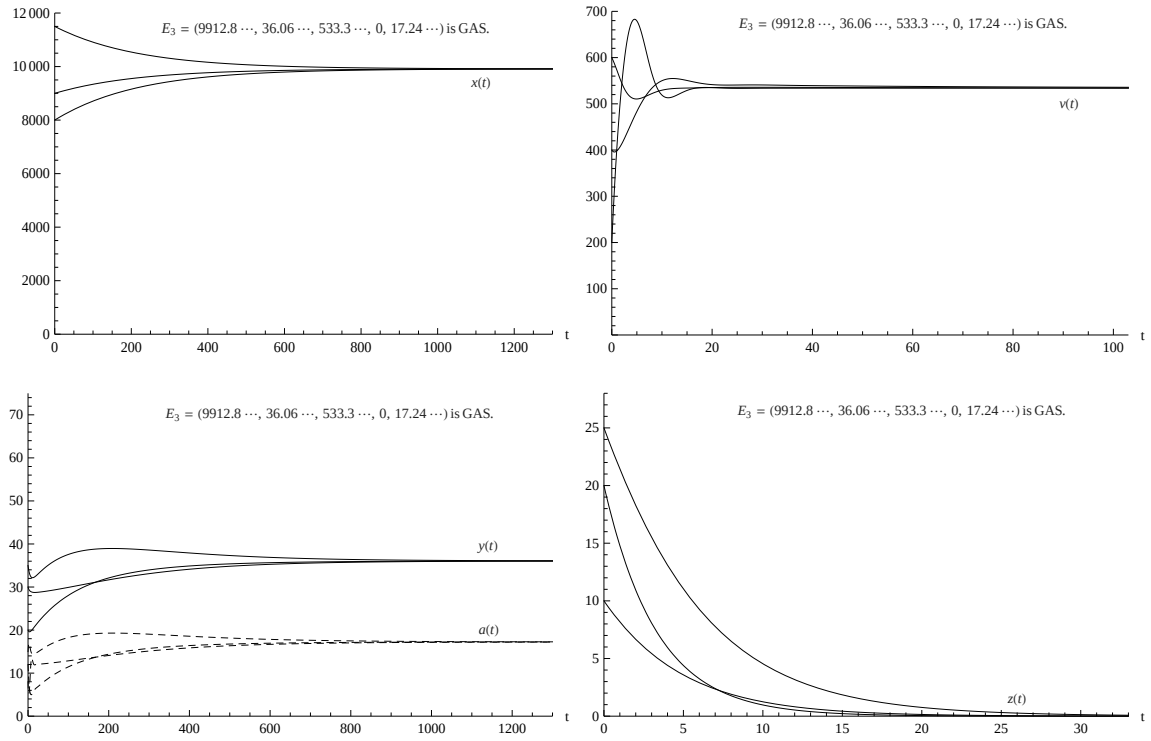

Figure 3: The graph trajectory of $x(t)$ (Top-left), $v(t)$ (Top-right), $y(t)$, $a(t)$ (Bottom-left) and $z(t)$ (Bottom-right) of system (4.1). The parameter values are listed in Tables 1 and 2 with $\alpha = 0.01$ and $a_1 = a_2 = 0.9$. For the case $\gamma = 0.5$ and $b = 0.8$, we have $\Re_1 = 0.811\cdots \leq 1$, $\Re_2 = 3.453\cdots > 1$, $\Re_3 = 0.721\cdots \leq 1$ and $E_3 = (9912.8\cdots, 36.06\cdots, 533.3\cdots, 0, 17.24\cdots)$. Here, GAS denotes globally asymptotically stable.

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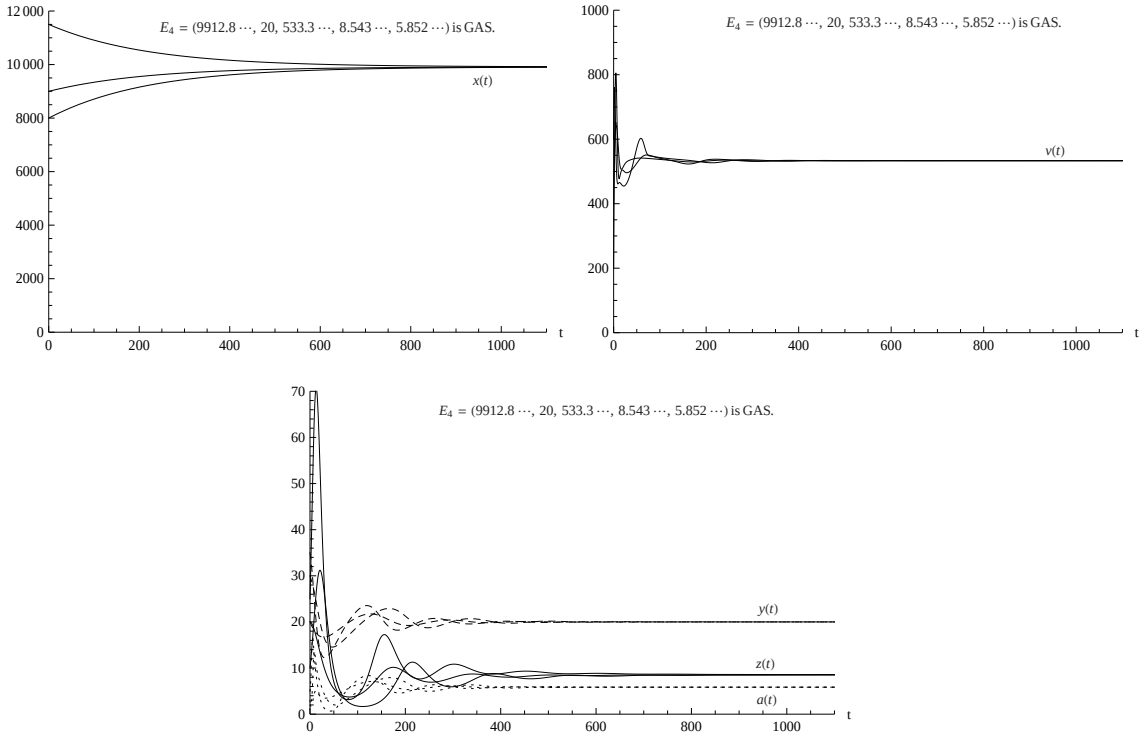

Figure 4: The graph trajectory of $x(t)$ (Top-left), $v(t)$ (Top-right) and $y(t)$, $z(t)$, $a(t)$ (Bottom) of system (4.1). The parameter values are listed in Tables 1 and 2 with $\alpha = 0.01$ and $a_1 = a_2 = 0.9$. For the case $\gamma = 0.2$ and $b = 0.8$, we have $\Re_1 = 2.028\cdots > 1$, $\Re_2 = 3.453\cdots > 1$, $\Re_3 = 1.803\cdots > 1$ and $E_4 = (9912.8\cdots, 20, 533.3\cdots, 8.543\cdots, 5.852\cdots)$. Here, GAS denotes globally asymptotically stable.

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