Effect of cell-mediated, humoral immune responses on global dynamics of a delayed virus infection model

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1   Introduction

For modeling disease progression scenarios, dividing population into compartments has been recognized as a common approach due to attempts to predict final size of epidemics [10]. With compartments of uninfected cells, infected cells and free virus particles, the dynamics of virus population in vivo has been well-understood from a theoretical point of view by a pioneering work in Nowak and Bangham [13]. In the paper, the modeling framework is based on the construction of ordinary differential equations to invesitgate population dynamics of immune responses on virus load. Many authors have subsequently paid attention to global stability of equilibria of the virus infection models with antiviral immune responses, virus load and its diversity. One of the recent models incorporate the effect humoral immune responses as follows [17].

$$\begin{cases} x'(t) = \lambda - dx(t) - h(x(t), v(t))v(t), \\ y'(t) = e^{-m_1\tau_1}h(x(t-\tau_1), v(t-\tau_1))v(t-\tau_1) - \delta y(t), \\ v'(t) = ke^{-m_2\tau_2}y(t-\tau_2) - cv(t) - qa(t)v(t), \\ a'(t) = ga(t)v(t) - ba(t). \end{cases} \tag{1.1}$$

The variables x, y and v denote the concentration of uninfected cells, infected cells and free virus particles, respectively. The variable a denotes the concentration of B cells.

The nonnegative constant τ_1 (resp. τ_2) denotes the time taken to production of new virus particles since it enters a cell (resp. the time taken to maturation of the newly produced viruses) [14]. The model (1.1) with $h(x,v) = kx$ (i.e., a bilinear incidence $h(x,v)v = kxv$) is equivalent to that in Wang et al. [19, Section 3]. The incidence

Hypothesis	Description
(A_1) $h(x,v) \geq 0$ for all $x,v \geq 0$ and $h(x,v) = 0 \Longleftrightarrow x = 0$ for all $v > 0$	The average number of virus-infected cells is always nonnegative.
(A_2) $\dfrac{\partial h(x,v)}{\partial x} > 0$ for all $x,v \geq 0$	The more the amount of uninfected cells is, then the more the average number of virus-infected cells will be, for a fixed number of free virus particles.
(A_3) $\dfrac{\partial h(x,v)}{\partial v} \leq 0$ for all $x,v \geq 0$	The more the amount of virus is, then the less the average number of virus-infected cells will be, for a fixed number of uninfected cells.
(A_4) $\dfrac{\partial(h(x,v)v)}{\partial v} > 0$ for all $x > 0$ and $v \geq 0$	The more the amount of virus is, then the more the number of cells which are newly infected will be.

Table 1.1: Hypotheses on the function h and the biological meaning for system (1.1)

rate prescribing a rate of newly infected cells per a unit time, is given by the function $h \in C^1(\mathbb{R}_+^2, \mathbb{R})$ satisfying the hypotheses in Table 1.1 [17, **H1-H4**].

In addition, cell-mediated cytotoxic T lymphocytes (CTLs) immune response is also considered as an important factor which determines the dynamics of cell infection (see, e.g., [1,2,4,5] and the references therein). When delays are incorporated in the models, we can observe rich dynamic behaviors; global stability of the equilibria is completely determined by threshold parameters [9,12,15,22], while periodic solutions arise through the Hopf bifurcations describing sustained oscillatory viral loads [3,18,20,23].

Later, the following model is proposed in Yan and Wang [21]:

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

in order to incorporate both cell-mediated and antibody immune responses. The variables x, y, v, z and a denote the concentration of uninfected cells, infected cells, free

virus particles, CTL responses and antibody responses, respectively. Due to the difficulty of finding the actual incidence rate by a concrete form such as bilinear incidence rates, many authors have proposed a general form of nonlinear incidence rates (see, e.g., [7, 8, 20]).

In this paper, the above two considerations in [17, 21] are combined to formulate the model with cell-mediated and antibody responses and nonlinear incidence rates. By means of basic reproduction numbers, we study long-time behavior of virus prevalence in the cells.

The organization of the paper is as follows. In Section 2, we propose the model governed by a system of delay differential equations and define the basic reproduction numbers to investigate the existence of infection equilibria. In Section 3, we establish global stability of four equilibria by Lyapunov functional approach. In Section 4, we provide numerical simulations which display the case that one of the four infection equilibria is globaly stable. In Section 5, we offer concluding remarks with further application of our results.

2 Model and preliminaries

We consider the following model:

$$
\begin{cases}
x'(t) = \lambda - dx(t) - kx(t)f(v(t)), \\
y'(t) = k \displaystyle\int_0^\infty G_1(\tau)x(t-\tau)f(v(t-\tau))\mathrm{d}\tau - \delta y(t) - py(t)z(t), \\
v'(t) = \delta N \displaystyle\int_0^\infty G_2(\tau)y(t-\tau)\mathrm{d}\tau - cv(t) - qa(t)v(t), \\
z'(t) = \beta y(t)z(t) - \gamma z(t), \\
a'(t) = ga(t)v(t) - ba(t).
\end{cases}
\tag{2.1}
$$

The uninfected cells are produced at a constant rate λ and die at a per capita rate d. The infected cells are assumed to die at a rate δ due to the action of virus, each releasing N new virus particles as the lysis of infected cells occurs. Virus particles are cleared from the system at rate c. They are also killed (resp. neutralized) via mass action kinetics by CTLs (resp. antibodies), which is described by pyz (resp. qaz). CTLs are produced at a rate proportional to the abundances of CTLs and infected cells, βyz, 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, gav, and die at a per capita rate b. To account for the time lag between viral entry into a target cell and the production of new virus particles, two distributed intracellular delays are introduced with kernel functions given by $G_i(\tau) = f_i(\tau)e^{-m_i\tau}$, $i = 1, 2$. k is a constant characterizing the infection rate. $G_1(\tau)$ is 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. All the parameters are positive constants. The function $f(\xi)$ is assumed to be locally Lipschitz on $[0, \infty)$ satisfying

$$(H) \quad f(0) = 0, \ f'(\xi) \text{ exists and satisfies } f'(\xi) \geq 0 \text{ and } \left(\frac{f(\xi)}{\xi}\right)' \leq 0 \text{ in } (0, \infty)$$

corresponding to the hypotheses (A_1), (A_3) and (A_4) in Table 1.1. The following assumption on the function G is also used widely in the literatures when describing delay kernels.

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

Let us investigate a suitable phase and a feasible region. Denote non-negative initial functions by

$$
\begin{aligned}
(x(\theta), y(\theta), v(\theta), z(\theta), a(\theta)) &= (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta), \phi_5(\theta)) \\
&= \phi(\theta) \in UC_\psi((-\infty, 0], \mathbb{R}_+^5),
\end{aligned}
\tag{2.2}
$$

where $\mathbb{R}_+^5 = \{(x_1, x_2, \cdots, x_5) \in \mathbb{R}^5 : x_i \geq 0, \ i = 1, 2, \cdots, 5\}$ and

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

$$
\left. \frac{\phi(s)}{\psi(s)} \text{ is uniformly continuous on } (-\infty, 0] \right\}.
$$

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 $\|\cdot\|_\psi$. Moreover, if the function ψ satisfies assumptions (1)-(3), then UC_ψ is an admissible Banach space. Thus, for system (2.1), existence results of Peano type hold (see, for details, Kuang [11, Corollary 5.2]).

It follows from the fundamental theory for integral-differential equations that there exists a $T_\phi > 0$ such that system (2.1) with (2.2) has a unique solution on the interval $[0, T_\phi)$. 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 in time. The proof is omitted because it is quite similar to that in Wang et al. [15, Theorem 2.1].

Theorem 2.1. *Let* $(x(t), y(t), v(t), z(t), a(t))^T$ *be the unique solution to system* (2.1) *with* (2.2). *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* (2.1) *with* $x(t) > 0$, $y(t) > 0$, $v(t) > 0$, $z(t) > 0$ *and* $a(t) > 0$ *are ultimately bounded.*

From Theorem 2.1, we can easily verify that ω-limit sets of system (2.1) are contained in the following bounded feasible region:

$$\Gamma = \left\{ (x, y, v, z, a) \in \mathbb{R}_+^5 : |x| \leq \frac{\lambda}{d}, \; |y|, |z| \leq \frac{\lambda a_1}{\min\{d, \delta, \gamma\}}, \; |v|, |a| \leq \frac{\delta a_2 N \frac{\lambda a_1}{\min\{d, \delta, \gamma\}}}{\min\{c, b\}} \right\}.$$

We can verify that the region Γ is positively invariant with respect to system (2.1).

3 Stability of equilibria

3.1 Basic reproduction numbers and existence of infection (positive) equilibria

An equilibrium (x, y, v, z, a) of system (2.1) satisfies the following equations:

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

It is straightforward to see that system (2.1) always has an infection-free equilibrium $E_0 = (\lambda/d, 0, 0, 0, 0)$. By simple calculation, an immune-free equilibrium exists if and only if the equation:

$$K_1(v) := \frac{ka_1 \lambda f(v)}{d + kf(v)} - \frac{cv}{Na_2} = v\tilde{K}_1(v), \quad \tilde{K}_1(v) = \frac{ka_1 \lambda f(v)}{d + kf(v)} \cdot \frac{1}{v} - \frac{c}{Na_2}$$

has a positive root. Let us 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 the hypothesis (H), we have $\frac{d\tilde{K}_1(v)}{dv} < 0$ and

$$\lim_{v \to +0} \tilde{K}_1(v) = \frac{ka_1 \lambda}{d} f'(0) - \frac{c}{Na_2} = \frac{c}{Na_2}(\Re_0 - 1) > 0$$

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 $\lim_{v \to \infty} \tilde{K}_1(v) = -\frac{c}{Na_2} < 0$. Therefore, $K_1(v) = 0$ has a unique positive root $v = v_1$. By the relation

$$x_1 = \frac{\lambda}{d + kf(v_1)} \text{ and } y_1 = \frac{cv_1}{\delta Na_2},$$

we get an 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 then 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

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

It follows that the equation (3.4) has a unique positive root $x = x_2 \in (0, \lambda/d)$. So 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 then 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

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

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 then get

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

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 $\frac{ka_1 x f(\frac{b}{g})}{\delta} = y_3 = \frac{a_1(\lambda - dx)}{\delta}$ is the number of infected cells at E_3. Denote the CTL immune competitive reproductive number $\Re_3$ for system (2.1) 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 (2.1) is

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

$1/b$ 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.

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 derive the following theorem [15, Theorem 3.1]:

Theorem 3.1. *Let* $\Re_0$, $\Re_1$, $\Re_2$, $\Re_3$ *and* $\Re_4$ *be defined by (3.2), (3.3), (3.6), (3.10) and (3.11), respectively. Then the following statement holds true.*

(i) *System (2.1) always has an infection-free equilibrium* E_0.

(ii) *System (2.1) has an immune-free infection equilibrium* E_1 *when* $\Re_0 > 1$.

(iii) *System (2.1) has an infection equilibrium* E_2 *with only CTL immune responses when* $\Re_1 > 1$.

(iv) *System (2.1) has an infection equilibrium* E_3 *with only humoral immune responses when* $\Re_2 > 1$.

(v) *System (2.1) 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 (2.1) 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 $i = 1, 2$. Let us also 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 (2.1) 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 $g : \mathbb{R}_+ \to \mathbb{R}_+$ has a strict global minimum $g(1) = 0$. Let

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

One can see that $H_i(0) = 1$, $H_i(\infty) = 0$ and $\frac{\mathrm{d}H_i(t)}{\mathrm{d}t} = -g_i(t)$ hold.

3.2 Global stability of the infection-free equilibrium E_0 for the case $\Re_0 \leq 1$

Let us investigate global stability of the infection-free equilibrium E_0 which represents a state that the virus is cleared up. We prove the following theorem [15, Theorem 3.2]:

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 $C((-\infty, 0], \mathbb{R}_+^5)$ as follows:

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

$$(3.13)$$

It is easy to see that $L_{E_0}(x, y, v, z, a)$ reaches its global minimum when the solution is in the infection-free equilibrium E_0, and therefore $L_{E_0}(x, y, v, z, a)$ is a Lyapunov functional. Similar to the arguments in Theorem 3.1 of [22], using integration by parts to the last two terms in (3.13), we obtain the derivative of $L_{E_0}(x, y, v, z, a)$ along the

solution of (3.12) as follows:

$$L'_{E_0}(x, y, v, z, a)$$

$$= -\frac{d}{x(t)}(x(t) - x_0)^2 + kx_0 f(v(t)) - \frac{kp}{\alpha_1}y(t)z(t) - \frac{k\delta c}{\alpha_1\alpha_2}v(t) - \frac{k\delta q}{\alpha_1\alpha_2}a(t)v(t)$$

$$+ \frac{kp}{\alpha_1\beta}(\beta y(t)z(t) - \gamma z(t)) + \frac{k\delta q}{\alpha_1\alpha_2 g}(ga(t)v(t) - ba(t))$$

$$= -\frac{d}{x(t)}(x(t) - x_0)^2 - \frac{kp\gamma}{\alpha_1\beta}z(t) - \frac{k\delta qb}{\alpha_1\alpha_2 g}v(t) + \frac{k\delta c}{\alpha_1\alpha_2}\left(\frac{\lambda\alpha_1\alpha_2}{c\delta d}\frac{f(v(t))}{v(t)} - 1\right)v(t)$$

$$\leq -\frac{d}{x(t)}(x(t) - x_0)^2 - \frac{kp\gamma}{\alpha_1\beta}z(t) - \frac{k\delta qb}{\alpha_1\alpha_2 g}v(t) + \frac{k\delta c}{\alpha_1\alpha_2}\left(\frac{\lambda\alpha_1\alpha_2 f'(0)}{c\delta d} - 1\right)v(t).$$

Therefore, $\Re_0 = \frac{\lambda\alpha_1\alpha_2 f'(0)}{c\delta d} \leq 1$ ensures that $L'_{E_0}(x, y, v, z, a) \leq 0$ for all $x, y, v, z, a \geq 0$. One can see that $L'_{E_0}(x, y, v, z, a) = 0$ if $x(t) = x_0$, $z(t) = 0$, $v(t) = 0$ for $\Re_0 \leq 1$. Hence, every solution of (3.12) tends to M_0, where M_0 is the largest invariant subset in $\{(x, y, v, z, a) \in \Gamma : L'_{E_0}(x, y, v, z, a) = 0\}$ with respect to (3.12). It can be easily verified that M_0 is singleton $\{E_0\}$. This shows that

$$\lim_{t\to\infty}(x(t), y(t), v(t), z(t), a(t)) = E_0.$$

Since

$$L_{E_0}(x, y, v, z, a) \geq x_0 g\left(\frac{x(t)}{x_0}\right) + \frac{k}{\alpha_1}y(t) + \frac{k\delta}{\alpha_1\alpha_2}v(t) + \frac{kp}{\alpha_1\beta}z(t) + \frac{k\delta q}{\alpha_1\alpha_2 g}a(t),$$

E_0 is uniformly stable. □

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

The following lemma plays an important role to prove the globally stability of the infection equilibria.

Lemma 3.1. *Under the hypothesis (H), it holds that $g\left(\frac{f(v^*u)}{f(v^*)}\right) \leq g(u)$ for $u > 0$.*

We prove the following theorem [15, Theorem 3.3]:

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

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

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

$$+ \frac{kp}{\alpha_1\beta}z(t) + \frac{k\delta q}{\alpha_1\alpha_2 g}a(t) + L_1(x, v) + L_2(y), \quad (3.14)$$

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

$$L_1(x,v) = kx_1 f(v_1) \int_0^\infty H_1(\xi) g\left(\frac{x(t-\xi)f(v(t-\xi))}{x_1 f(v_1)}\right) d\xi,$$

and

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

Using integration by parts, we have

$$L_1'(x,v) = kx_1 f(v_1) \int_0^\infty H_1(\xi) \frac{dg\left(\frac{x(t-\xi)f(v(t-\xi))}{x_1 f(v_1)}\right)}{dt} d\xi$$

$$= -kx_1 f(v_1) \int_0^\infty H_1(\xi) \frac{dg\left(\frac{x(t-\xi)f(v(t-\xi))}{x_1 f(v_1)}\right)}{d\xi} d\xi$$

$$= kx(t)f(v(t)) - k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))d\xi$$

$$+ kx_1 f(v_1) \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}d\xi.$$

Similarly, differentiating $L_2(y)$ gives

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

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

$$L_{E_1}'(x,y,v,z,a) = \left(1 - \frac{x_1}{x(t)}\right)x'(t) + \frac{k}{\alpha_1}\left(1 - \frac{y_1}{y(t)}\right)y'(t)$$

$$+ \frac{k\delta}{\alpha_1\alpha_2}\left(1 - \frac{v_1}{v(t)}\right)v'(t) + \frac{kp}{\alpha_1\beta}z'(t) + \frac{k\delta q}{\alpha_1\alpha_2 g}a'(t) + L_1'(x,v) + L_2'(y).$$

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

$$L'_{E_1}(x,y,v,z,a) = -\frac{d}{x(t)}(x(t) - x_1)^2$$

$$+kx_1f(v_1)\left(3 - \frac{x_1}{x(t)} - \frac{v(t)}{v_1} + \frac{f(v(t))}{f(v_1)} - \int_0^\infty g_1(\xi)\frac{x(t-\xi)y_1f(v(t-\xi))}{x_1y(t)f(v_1)}d\xi\right.$$

$$-\int_0^\infty g_2(\xi)\frac{v_1y(t-\xi)}{v(t)y_1}d\xi + \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}d\xi$$

$$\left.+\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}d\xi\right) + \frac{kpy_1}{\alpha_1}z(t) - \frac{kp\gamma}{\alpha_1\beta}z(t) + \frac{k\delta qv_1}{\alpha_1\alpha_2}a(t) - \frac{k\delta qb}{\alpha_1\alpha_2}a(t)$$

$$= -\frac{d}{x(t)}(x(t) - x_1)^2 + kx_1f(v_1)\left[\int_0^\infty g_1(\xi)\left(-g\left(\frac{x_1}{x(t)}\right)\right)\right.$$

$$-g\left(\frac{x(t-\xi)y_1f(v(t-\xi))}{x_1y(t)f(v_1)}\right) - \ln\frac{y_1f(v(t))}{y(t)f(v_1)}\right)d\xi$$

$$\left.+\int_0^\infty g_2(\xi)\left(-g\left(\frac{v_1y(t-\xi)}{v(t)y_1}\right) + \ln\frac{v(t)y_1}{v_1y(t)}\right)d\xi + \frac{f(v(t))}{f(v_1)} - \frac{v(t)}{v_1}\right]$$

$$+\frac{kp\gamma}{\alpha_1\beta}\left(\frac{\beta}{\gamma}y_1 - 1\right)z(t) + \frac{k\delta qb}{\alpha_1\alpha_2 g}\left(\frac{g}{b}v_1 - 1\right)a(t).$$

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

$$L'_{E_1}(x,y,v,z,a)$$

$$\leq -\frac{d}{x(t)}(x(t) - x_1)^2 - kx_1f(v_1)\left[\int_0^\infty g_1(\xi)\left\{g\left(\frac{x_1}{x(t)}\right) + g\left(\frac{x(t-\xi)y_1f(v(t-\xi))}{x_1y(t)f(v_1)}\right)\right\}d\xi\right.$$

$$\left.+\int_0^\infty g_2(\xi)g\left(\frac{v_1y(t-\xi)}{v(t)y_1}\right)d\xi\right] + kx_1f(v_1)\left(\frac{f(v(t))}{f(v_1)} - \ln\frac{f(v(t))}{f(v_1)} - \frac{v(t)}{v_1} + \ln\frac{v(t)}{v_1}\right)$$

$$= -\frac{d}{x(t)}(x(t) - x_1)^2 - kx_1f(v_1)\left[\int_0^\infty g_1(\xi)\left\{g\left(\frac{x_1}{x(t)}\right) + g\left(\frac{x(t-\xi)y_1f(v(t-\xi))}{x_1y(t)f(v_1)}\right)\right\}d\xi\right.$$

$$\left.+\int_0^\infty g_2(\xi)g\left(\frac{v_1y(t-\xi)}{v(t)y_1}\right)d\xi\right] + kx_1f(v_1)(g(F(u_1)) - g(u_1)),$$

where $u_1 = \frac{v(t)}{v_1}$ and $F(u_1) = \frac{f(v(t))}{f(v_1)} = \frac{f(v_1u_1)}{f(v_1)}$. Using Lemma 3.1, one can obtain $g(F(u_1)) - g(u_1) \leq 0$. This implies that $L'_{E_1}(x,y,v,z,a) \leq 0$ and $L'_{E_1}(x,y,v,z,a) = 0$ if $x(t) = x_1$, $x(t - \xi)y_1f(v(t - \xi)) = x_1y(t)f(v_1)$ and $v_1y(t - \xi) = v(t)y_1$ 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

$$0 = \lambda - dx_1 - kx_1f(v(t)), \text{ that is, } f(v(t)) = f(v_1) > 0,$$

which implies that $y(t) = y_1$ and $v(t) = v_1$ from $y_1f(v(t-\xi)) = y(t)f(v_1)$ and $v_1y(t-\xi) = v(t)y_1$ for almost all $\xi \in [0,\infty)$. This yields that $z(t) = 0$ and $a(t) = 0$ from the

equalities:

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

and

$$0 = \delta N a_2 y_1 - c v_1 - q a(t) v_1 = -q a(t) v_1.$$

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

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

E_1 is uniformly stable. $\qquad\qquad\square$

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

We prove the following theorem [15, Theorem 3.4]:

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

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

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

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

$$L_3(x, v) = k x_2 f(v_2) \int_0^\infty H_1(\xi) g\left(\frac{x(t - \xi) f(v(t - \xi))}{x_2 f(v_2)}\right) d\xi,$$

and

$$L_4(y) = k x_2 f(v_2) \int_0^\infty H_2(\xi) g\left(\frac{y(t - \xi)}{y_2}\right) d\xi.$$

Using integration by parts, we obtain

$$L_3'(x,v) = kx(t)f(v(t)) - k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi$$
$$+ kx_2 f(v_2)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi$$

and

$$L_4'(y) = \frac{k(\delta + pz_2)}{\alpha_1}y(t) - \frac{k(\delta + pz_2)}{\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi$$
$$+ kx_2 f(v_2)\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi.$$

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

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

Using the equalities $\lambda = dx_2 + kx_2 f(v_2)$, $\alpha_1 x_2 f(v_2) = \delta y_2 + py_2 z_2$, $\alpha_2 y_2 = cv_2$ and $\beta y_2 z_2 = \gamma z_2$, we obtain

$$L_{E_2}'(x,y,v,z,a) = -\frac{d}{x(t)}(x(t)-x_2)^2 + kx_2 f(v_2)\left(3 - \frac{x_2}{x(t)} - \frac{v(t)}{v_2} + \frac{f(v(t))}{f(v_2)}\right.$$
$$- \int_0^\infty g_1(\xi)\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t)f(v_2)}\mathrm{d}\xi - \int_0^\infty g_2(\xi)\frac{v_2 y(t-\xi)}{v(t)y_2}\mathrm{d}\xi$$
$$+ \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi + \int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\Bigg)$$
$$+ \left(\frac{k\delta qv_2}{\alpha_1\alpha_2} + \frac{kpqz_2 v_2}{\alpha_1\alpha_2} - \frac{kb\delta q}{\alpha_1\alpha_2 g} - \frac{kbpqz_2}{\alpha_1\alpha_2 g}\right)a(t)$$
$$= -\frac{d}{x(t)}(x(t)-x_2)^2$$
$$+ kx_2 f(v_2)\left[\int_0^\infty g_1(\xi)\left(-g\left(\frac{x_2}{x(t)}\right) - g\left(\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t)f(v_2)}\right)\right.\right.$$
$$\left.- \ln\frac{y_2 f(v(t))}{y(t)f(v_2)}\right)\mathrm{d}\xi + \int_0^\infty g_2(\xi)\left(-g\left(\frac{v_2 y(t-\xi)}{v(t)y_2}\right) + \ln\frac{v(t)y_2}{v_2 y(t)}\right)\mathrm{d}\xi$$
$$\left.+ \frac{f(v(t))}{f(v_2)} - \frac{v(t)}{v_2}\right] + \frac{kbq}{\alpha_1\alpha_2 g}(\delta + pz_2)\left(\frac{\alpha_2 g\gamma}{\beta bc} - 1\right)a(t).$$

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

$$L'_{E_2}(x, y, v, z, a)$$

$$\leq -\frac{d}{x(t)}(x(t) - x_2)^2 - kx_2 f(v_2)\left[\int_0^\infty g_1(\xi)\left\{g\left(\frac{x_2}{x(t)}\right) + g\left(\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t)f(v_2)}\right)\right\}\,d\xi\right.$$

$$\left. + \int_0^\infty g_2(\xi)g\left(\frac{v_2 y(t-\xi)}{v(t)y_2}\right)\,d\xi\right] + kx_2 f(v_2)\left(\frac{f(v(t))}{f(v_2)} - \ln\frac{f(v(t))}{f(v_2)} - \frac{v(t)}{v_2} + \ln\frac{v(t)}{v_2}\right)$$

$$= -\frac{d}{x(t)}(x(t) - x_2)^2 - kx_2 f(v_2)\left[\int_0^\infty g_1(\xi)\left\{g\left(\frac{x_2}{x(t)}\right) + g\left(\frac{x(t-\xi)y_2 f(v(t-\xi))}{x_2 y(t)f(v_2)}\right)\right\}\,d\xi\right.$$

$$\left. + \int_0^\infty g_2(\xi)g\left(\frac{v_2 y(t-\xi)}{v(t)y_2}\right)\,d\xi\right] + kx_2 f(v_2)(g(F(u_2)) - g(u_2)),$$

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 Lemma 3.1, one can obtain $g(F(u_2)) - g(u_2) \leq 0$. This implies that $L'_{E_2} \leq 0$ 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

$$L_{E_2}(x, y, v, z, a) \geq x_2 g\left(\frac{x(t)}{x_2}\right) + \frac{k}{\alpha_1}y_2 g\left(\frac{y(t)}{y_2}\right) + \frac{k\delta}{\alpha_1\alpha_2}v_2 g\left(\frac{v(t)}{v_2}\right)$$

$$+ \frac{kp}{\alpha_1\beta}z_2 g\left(\frac{z(t)}{z_2}\right) + \left(\frac{k\delta q}{\alpha_1\alpha_2 g} + \frac{kpqz_2}{\alpha_1\alpha_2 g}\right)a(t),$$

E_2 is uniformly stable. $\qquad\qquad\square$

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

We prove the following theorem [15, Theorem 3.5]:

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

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

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

and

$$L_6(y) = k x_3 f(v_3) \int_0^\infty H_2(\xi) g\left(\frac{y(t-\xi)}{y_3}\right) d\xi.$$

Using integration by parts, we obtain

$$L_5'(x, v) = k x(t) f(v(t)) - k \int_0^\infty g_1(\xi) x(t-\xi) f(v(t-\xi)) d\xi$$
$$+ k x_3 f(v_3) \int_0^\infty g_1(\xi) \ln \frac{x(t-\xi) f(v(t-\xi))}{x(t) f(v(t))} d\xi,$$

and

$$L_6'(y) = \frac{k\delta}{\alpha_1} y(t) - \frac{k\delta}{\alpha_1} \int_0^\infty g_2(\xi) y(t-\xi) d\xi$$
$$+ k x_3 f(v_3) \int_0^\infty g_2(\xi) \ln \frac{y(t-\xi)}{y(t)} d\xi.$$

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

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

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 $ga_3 v_3 = ba_3$. Similar to the discussion in Subsection 3.4, for $\Re_3 = \frac{\beta y_3}{\gamma} \leq 1$, it follows from Lemma 3.1 that $L'_{E_3} \leq 0$ 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 $\xi \in [0,\infty)$. From LaSalle's invariance principle, all solutions of (3.12) are attracted to a point E_3. Thus, the infection equilibrium E_3 is globally asymptotically stable. $\qquad\square$

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

We prove the following theorem [15, Theorem 3.6]:

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 $C((-\infty,0],\mathbb{R}^5_+)$ by

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

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

$$
L_7(x,v) = kx_4 f(v_4)\int_0^\infty H_1(\xi)g\left(\frac{x(t-\xi)f(v(t-\xi))}{x_4 f(v_4)}\right)d\xi,
$$

and

$$
L_8(y) = kx_4 f(v_4)\int_0^\infty H_2(\xi)g\left(\frac{y(t-\xi)}{y_4}\right)d\xi.
$$

Using integration by parts, we obtain

$$
\begin{aligned}
L'_7(x,v) = kx(t)f(v(t)) - k\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))d\xi \\
+ kx_4 f(v_4)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}d\xi
\end{aligned}
$$

and

$$
\begin{aligned}
L'_8(y) = \frac{k(\delta+pz_4)}{\alpha_1}y(t) - \frac{k(\delta+pz_4)}{\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)d\xi \\
+ kx_4 f(v_4)\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}d\xi.
\end{aligned}
$$

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

$$
\begin{aligned}
L'_{E_4}(x, y, v, z, a) &= \left(1 - \frac{x_4}{x(t)}\right) x'(t) + \frac{k}{\alpha_1}\left(1 - \frac{y_4}{y(t)}\right) y'(t) \\
&+ \left(\frac{k\delta}{\alpha_1\alpha_2} + \frac{kpz_4}{\alpha_1\alpha_2}\right)\left(1 - \frac{v_4}{v(t)}\right) v'(t) + \frac{kp}{\alpha_1\beta}\left(1 - \frac{z_4}{z(t)}\right) z'(t) \\
&+ \left(\frac{k\delta q}{\alpha_1\alpha_2 g} + \frac{kpqz_4}{\alpha_1\alpha_2 g}\right)\left(1 - \frac{a_4}{a(t)}\right) a'(t) + L'_7(x, v) + L'_8(y).
\end{aligned}
$$

Using the equalities $\lambda = dx_4 + kx_4 f(v_4)$, $\alpha_1 x_4 f(v_4) = \delta y_4 + py_4 z_4$, $\alpha_2 y_4 = cv_4 + qa_4 v_4$, $\beta y_4 z_4 = \gamma z_4$ and $ga_4 v_4 = ba_4$, we obtain

$$
\begin{aligned}
L'_{E_4}(x, y, v, z, a) &= -\frac{d}{x(t)}(x(t) - x_4)^2 + kx_4 f(v_4)\left(3 - \frac{x_4}{x(t)} - \frac{v(t)}{v_4} + \frac{f(v(t))}{f(v_4)}\right) \\
&- \int_0^\infty g_1(\xi)\frac{x(t-\xi)y_4 f(v(t-\xi))}{x_4 y(t) f(v_4)}d\xi - \int_0^\infty g_2(\xi)\frac{v_4 y(t-\xi)}{v(t)y_4}d\xi \\
&+ \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}d\xi + \int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}d\xi \bigg) \\
&= -\frac{d}{x(t)}(x(t) - x_4)^2 + kx_4 f(v_4)\bigg[\int_0^\infty g_1(\xi)\left(-g\left(\frac{x(t-\xi)y_4 f(v(t-\xi))}{x_4 y(t) f(v_4)}\right)\right. \\
&\left. -g\left(\frac{x_4}{x(t)}\right) - \ln\frac{y_4 f(v(t))}{y(t)f(v_4)}\right)d\xi + \int_0^\infty g_2(\xi)\left(-g\left(\frac{v_4 y(t-\xi)}{v(t)y_4}\right)\right. \\
&\left. + \ln\frac{v(t)y_4}{v_4 y(t)}\right)d\xi + \frac{f(v(t))}{f(v_4)} - \frac{v(t)}{v_4}\bigg].
\end{aligned}
$$

Similar to the discussion in Subsection 3.4, it follows from Lemma 3.1 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 $\xi \in [0, \infty)$. From LaSalle's invariance principle, all solutions of (3.12) are attracted to a point E_4. Thus, the infection equilibrium E_4 is globally asymptotically stable. $\qquad\square$

Remark 3.1. When the inequality:

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

holds, we can rule out the possibility that both of the assumptions $\mathfrak{R}_1 > 1 \geq \mathfrak{R}_4$ of Theorem 3.4 and $\mathfrak{R}_2 > 1 \geq \mathfrak{R}_3$ of Theorem 3.5 hold simultaneously (see, for details, Wang et al. [15, Proposition 3.1]).

4 Discrete-delay model and numerical simulations

In this section, we illustrate our analytical results for the model (2.1) with delay terms discrete as follows:

$$\begin{cases} x'(t) = \lambda - dx(t) - kx(t)\dfrac{v(t)}{1 + \alpha v(t)}, \\ y'(t) = ka_1 x(t - \tau_1)\dfrac{v(t - \tau_1)}{1 + \alpha v(t - \tau_1)} - \delta y(t) - py(t)z(t), \\ v'(t) = \delta N y(t - \tau_2) - cv(t) - qa(t)v(t), \\ z'(t) = \beta y(t)z(t) - \gamma z(t), \\ a'(t) = ga(t)v(t) - ba(t) \end{cases} \tag{4.1}$$

with $\alpha > 0$.

Similar to Theorem 3.2, if $\Re_0 \leq 1$, then the infection-free equilibrium E_0 is globally asymptotically stable. From Theorems 3.3-3.6, the following corollary is derived [15, Corollary 4.1].

Corollary 4.1. Let $\Re_0$, $\Re_1$, $\Re_2$, $\Re_3$ and $\Re_4$ be defined by (3.2), (3.3), (3.6), (3.10) and (3.11), respectively. Then the following statement holds true.

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

Moreover, under the condition $\Re_0 > 1$, the following statement holds 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 $\Re_4 \leq 1$, the infection equilibrium E_2 with only CTL immune response is globally asymptotically stable.

(iv) When $\Re_2 > 1$ and $\Re_3 \leq 1$, the infection equilibrium E_3 with only humoral immune response is globally asymptotically stable.

(v) When $\Re_3 > 1$ and $\Re_4 > 1$, the infection equilibrium E_4 with both CTL response and humoral response is globally asymptotically stable.

For the case $\Re_0 > 1$, let us carry out some computational experiments to investigate the feasibility of the above global stability conditions. We choose the decay rates of virus-specific CTLs γ and antibody responses b as free parameters and fix the other parameter values as:

$$\begin{cases} \lambda = 0.13 \text{ mm}^3 \cdot \text{day}^{-1}, \ d = 0.01 \text{ day}^{-1}, \ k = 0.01 \text{ (mm}^3)^{-1} \cdot \text{day}^{-1}, \\ \delta = 0.01 \text{ day}^{-1}, \ p = 0.1 \text{ (mm}^3)^{-1} \cdot \text{day}^{-1}, \ N = 2, \ c = 0.07 \text{ day}^{-1}, \\ q = 0.03 \text{ (mm}^3)^{-1} \cdot \text{day}^{-1}, \ \beta = 0.02 \text{ (mm}^3)^{-1} \cdot \text{day}^{-1}, \\ g = 0.06 \text{ (mm}^3)^{-1} \cdot \text{day}^{-1}, \ \alpha = 0.01 \text{ (mm}^3)^{-1}, \ a_1 = a_2 = 0.9, \ \tau_1 = \tau_2 = 1 \text{ day}. \end{cases} \tag{4.2}$$
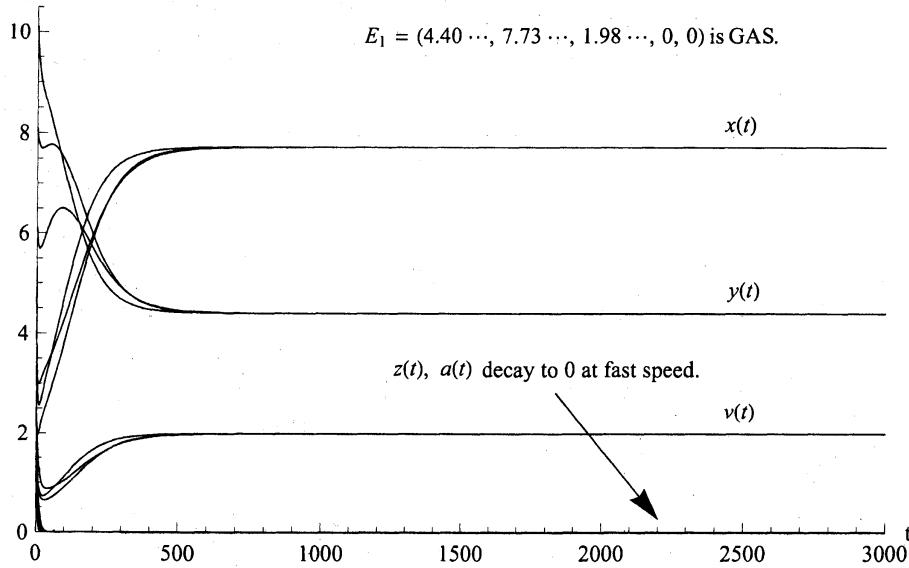
Figure 4.1: The graph trajectory of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $a(t)$ of system (4.1) (the variables $z(t)$ and $a(t)$ decay to 0 at fast speed). For the parameter values in (4.2) with $\gamma = 0.3$ and $b = 0.2$, we have $\Re_1 = 0.51 \cdots \leq 1$, $\Re_2 = 0.59 \cdots \leq 1$ and $E_1 = (4.40 \cdots , 7.73 \cdots , 1.98 \cdots , 0, 0)$. Here, GAS denotes globally asymptotically stable.

For the parameter values, we obtain $\Re_0 = 3.008 \cdots > 1$. First, we consider the case $\alpha = 1.4$. Then, we obtain $\Re_1 = 0.51 \cdots \leq 1$ and $\Re_2 = 0.59 \cdots \leq 1$. 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 and Figure 4.1). Second, we consider the case $\gamma = 0.04$ and $b = 0.2$. Then, we obtain $\Re_1 = 3.86 \cdots > 1$, $\Re_2 = 0.59 \cdots \leq 1$, $\Re_3 = 4.46 \cdots > 1$ and $\Re_4 = 0.15 \cdots \leq 1$. Hence, from the third part of Corollary 4.1, the infection equilibrium E_2 with only CTL immune response is globally asymptotically stable (see also Theorem 3.4 and Figure 4.2). Third, we consider the case $\gamma = 0.3$ and $b = 0.03$. Then, we obtain $\Re_1 = 0.51 \cdots \leq 1$, $\Re_2 = 3.97 \cdots > 1$, $\Re_3 = 0.25 \cdots \leq 1$ and $\Re_4 = 7.71 \cdots > 1$. Hence, 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 and Figure 4.3). Finally, we consider the case $\gamma = 0.04$ and $b = 0.03$. Then, we obtain $\Re_1 = 3.86 \cdots > 1$, $\Re_2 = 3.97 \cdots > 1$, $\Re_3 = 1.94 \cdots > 1$ and $\Re_4 = 1.02 \cdots > 1$. Hence, 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 and Figure 4.4).

5 Discussion

Incorporating cell-mediated and humoral immune responses, we investigate the asymptotic behavior of virus dynamics by a system of delay differential equations. Starting from identifying the basic reproduction numbers for viral infection $\Re_0$, we prove that an infection-free equilibrium E_0 is globally asymptotically stable if and only if $\Re_0 \leq 1$ and establish sufficient conditions under which each of four infection equilibrium is globally asymptotically stable for $\Re_0 > 1$. Recently, in Enatsu et al. [6], the functional methods in Section 3 are applicable to the case where the incidence rate is non-separable with respect to uninfected cells and free virus particles under the hypotheses (A_1)-(A_4). Applying construction methods in [8,9,12,15,22], monotonicity and saturativity of the function $h(x,v)v$ in the four hypotheses, including not only a bilinear incidence rate $h(x,v)v = kxv$, a class of separable incidence rates $h(x,v)v = F(x)G(v)$ but also a standard incidence rate $h(x,v)v = \frac{xv}{x+v}$ and Beddington-DeAngelis functional response $h(x,v)v = \frac{xv}{1+\alpha_1 x+\alpha_2 v}$ ($\alpha_1 > 0$, $\alpha_2 > 0$), play a crucial role to find suitable Lyapunov functionals. We remark that the global stability for each of the four infection equilibria E_i ($i = 1,\ldots,4$) is yet to be completely determined. In contrast to the bifurcation results in the literatures [3,18,20,23], as a future work, we leave an open problem whether or not we can rule out the possibility of Hopf bifurcation when the endemic equilibrium is destabilized.

Acknowledgements

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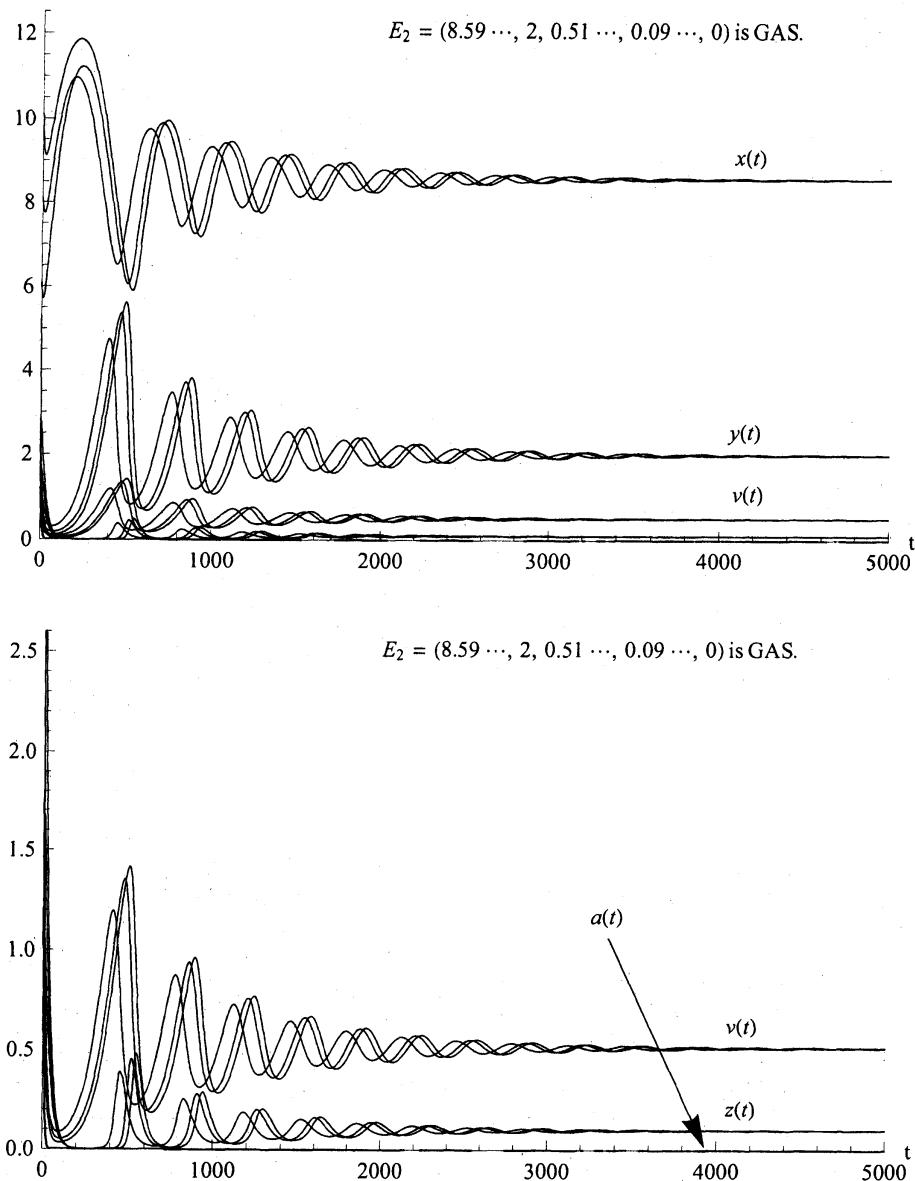
Figure 4.2: The graph trajectory of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $a(t)$ of system (4.1) (the variable $a(t)$ decays to 0 at fast speed). For the parameter values in (4.2) with $\gamma = 0.04$ and $b = 0.2$, we have $\Re_1 = 3.86\cdots > 1$, $\Re_4 = 0.15\cdots \leq 1$ and $E_2 = (8.59\cdots, 2, 0.51\cdots, 0.09\cdots, 0)$. Here, GAS denotes globally asymptotically stable.
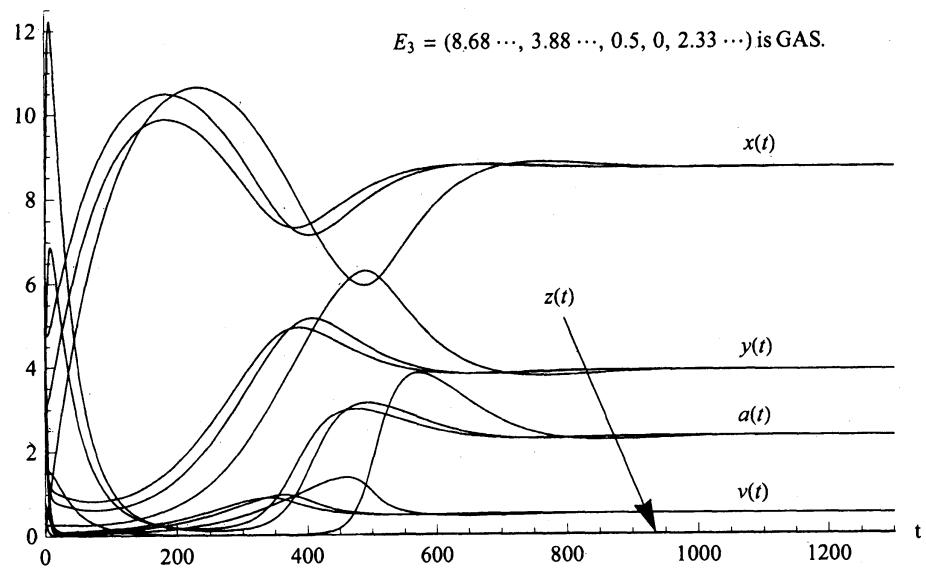
Figure 4.3: The graph trajectory of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $a(t)$ of system (4.1) (the variable $z(t)$ decays to 0 at fast speed). For the parameter values in (4.2) with $\gamma = 0.3$ and $b = 0.03$, we have $\Re_3 = 0.25\cdots \leq 1$, $\Re_2 = 3.97\cdots > 1$ and $E_3 = (8.68\cdots, 3.88\cdots, 0.5, 0, 2.33\cdots)$. Here, GAS denotes globally asymptotically stable.
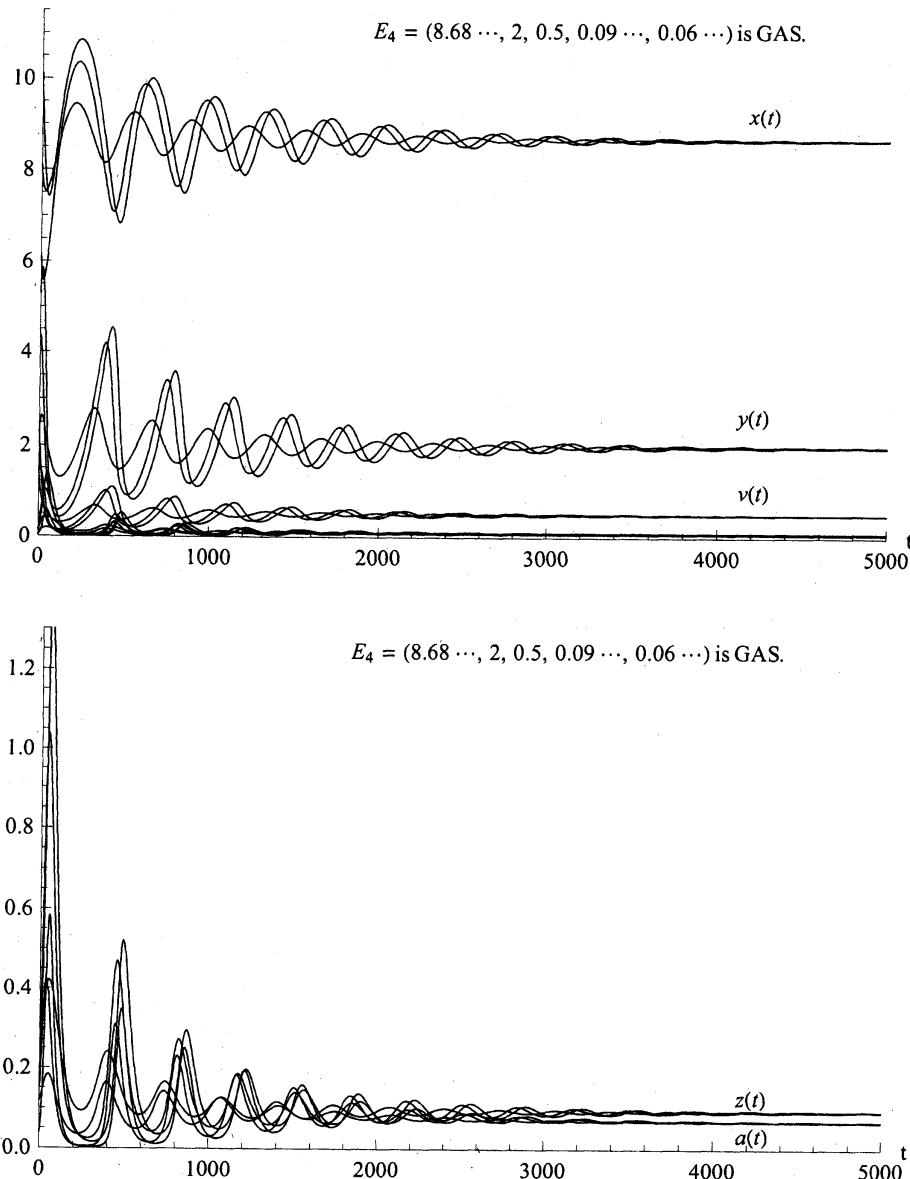
Figure 4.4: The graph trajectory of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $a(t)$ of system (4.1). For the parameter values in (4.2) with $\gamma = 0.04$ and $b = 0.03$, we have $\Re_3 = 1.94\cdots > 1$, $\Re_4 = 1.02\cdots > 1$ and $E_4 = (8.68\cdots, 2, 0.5, 0.06\cdots, 0.09\cdots)$. Here, GAS denotes globally asymptotically stable.