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Global dynamics of an age-structured in-host viral infection model with humoral immunity

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Abstract

An age-structured in-host viral infection model with humoral immunity, consisting of partial differential and ordinary differential equations, is investigated. By calculation we get the basic reproduction number $\Re_0$ and the immune-activated reproduction number $\Re_1$. By analyzing the characteristic equations, the local stability of an infection-free steady state, an immune-inactivated infected steady state and an immune-activated infected steady state of the model is established. By using suitable Lyapunov functionals and LaSalle's invariance principle, it is proved that if $\Re_0 < 1$, the infection-free steady state is globally asymptotically stable; if $\Re_1 < 1 < \Re_0$, the immune-inactivated infected steady state is globally asymptotically stable; and if $\Re_1 > 1$, the immune-activated infected steady state is globally asymptotically stable. Numerical simulations are carried out to illustrate the theoretical results.

MSC: 92D30; 34D23; 34K20

Keywords: age of infection; stability; Lyapunov functionals; LaSalle's invariance principle

1 Introduction

The adaptive immune system, also known as the acquired immune system, is mainly composed of two parts, cellular immunity and humoral immunity. Humoral immunity is mediated by macromolecules such as antibodies, complement proteins, and certain antimicrobial peptides. These macromolecules are produced by a special kind of leukocyte, the B lymphocyte. The principal function of B cells is to make these macromolecules against soluble antigens. So humoral immunity can be more effective than cellular immunity in some infections, such as malaria [1]. To investigate the role of humoral immunity in infection, many authors have presented and developed mathematical models [2–7]. Murase *et al.* introduced a basic in-host viral model with humoral immunity response in [5]:

$$\frac{dx(t)}{dt} = s - dx(t) - \beta x(t)v(t),$$
$$\frac{dy(t)}{dt} = \beta x(t)v(t) - \delta y(t),$$

$$\begin{aligned} &\frac{dv(t)}{dt} = ky(t) - uv(t) - pv(t)z(t), \\ &\frac{dz(t)}{dt} = cv(t)z(t) - bz(t). \end{aligned} \tag{1.1}$$

In system (1.1), $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are the densities of uninfected cells, infected cells, viruses, and B cells at time t, respectively. s and d are the birth rate and death rate of uninfected cells. β is the infection rate. k is the average virion production rate of infected cells. δ is the death rate of infected cells, u is the death rate of the virus. c, b, and p are the birth rate, death rate, and neutralized rate of B cells, respectively.

In [8] Nelson *et al.* suggested that the death rate of infected cells should vary over their life span and the virion production rate is initially low and increases with the age of infection. Further, they introduced an age-structured HIV infection model taking the following form:

$$\begin{aligned} &\dot{x}(t) = s - dx(t) - \beta x(t)v(t), \\ &\frac{\partial y(a,t)}{\partial a} + \frac{\partial y(a,t)}{\partial t} = -\delta(a)y(a,t), \\ &\dot{v}(t) = \int_0^\infty k(a)y(a,t)\,da - uv(t). \end{aligned} \tag{1.2}$$

In system (1.2), $x(t)$ and $v(t)$ denote the densities of uninfected target T cells and infectious free virions at time t, respectively. $y(a,t)$ denotes the density of infected T cells of infection age a at time t. The definitions of the various parameters in system (1.2) are listed in Table 1.

In their model, the production rate of viral particles and the death rate of productively infected cells are allowed to vary and depend on two general functions of age. These assumptions are reasonable and the supporting evidence can be found in the recent research of Reilly *et al.* and Gilchrist *et al.* in [9, 10]. Nelson *et al.* analyzed the local stability of the equilibria of the age-structured HIV infection model when they introduced it. Later Huang *et al.* established the global asymptotic stability of the equilibria by using suitable Lyapunov functionals and Lasalle's invariance principle in [11]. Recently, in [12] Wang *et al.* analyzed an age-structured HIV infection model with saturation infection rate, their result is an extension to the work of Nelson *et al.* and Huang *et al.*

Motivated by the basic in-host viral model with humoral immunity response introduced in [5] and work of Nelson *et al.* in [8], in this paper, we study an age-structured in-host

Table 1 Biological definitions of parameters

Parameter	Biological definition
a	Age of infection
s	Recruitment rate of healthy T cells
d	Per capita death rate of uninfected cells
β	Rate at which an uninfected cell becomes infected by an infectious virus
$k(a)$	Virion production rate of an infected cell with age a
$\delta(a)$	Age-dependent per capita death rate of infected cells
u	Clearance rate of virions

viral infection model with humoral immunity, the model takes the following form:

$$\begin{aligned}
&\dot{x}(t) = s - dx(t) - \beta x(t)v(t),\\
&\frac{\partial y(a,t)}{\partial t} + \frac{\partial y(a,t)}{\partial a} = -\delta(a)y(a,t),\\
&\dot{v}(t) = \int_0^\infty k(a)y(a,t)\,da - uv(t) - pv(t)z(t),\\
&\dot{z}(t) = cv(t)z(t) - bz(t),
\end{aligned} \tag{1.3}$$

with boundary condition

$$y(0,t) = \beta x(t)v(t) \tag{1.4}$$

and initial condition

$$x(0) = x_s, \qquad y(a,0) = y_s(a), \qquad v(0) = v_s, \qquad z(0) = z_s. \tag{1.5}$$

In system (1.3), $y(a,t)$ is the density of infected cells of infection age a at time t, $k(a)$ is the virion production rate of infected cells with infection age a, $\delta(a)$ is the age-dependent per capita death rate of infected cells. The definitions of $x(t)$, $v(t)$, $z(t)$, and the other parameters are the same as in system (1.1). To make the model biologically meaningful, we assume:

(H1) $a \geq 0$, $s > 0$, $d > 0$, $\beta > 0$, $u > 0$, $p > 0$, $c > 0$, $b > 0$.

(H2) $\delta(a)$ is bounded and $\delta(a) > \delta_{\min}$ for some positive constant $\delta_{\min}$ for all $a \geq 0$.

(H3) $k(a)$ is bounded and there exists a maximum age a^+ for the virion production such that $k(a) > 0$ for $0 < a < a^+$, $k(a) = 0$ for $a \geq a^+$.

(H4) $x_s > 0$, $y_s(a) \geq 0$, $v_s > 0$, $z_s \geq 0$.

According to (H1)-(H4), it is easy to see that system (1.3) with boundary condition (1.4) and initial condition (1.5) has a unique nonnegative solution.

2 Local stability

Denote

$$N = \int_0^\infty k(a)\sigma(a)\,da, \tag{2.1}$$

where

$$\sigma(a) = e^{-\int_0^a \delta(\varepsilon)\,d\varepsilon}.$$

N stands for the total number of viral particles produced by an infected cell in its lifespan. According to (H3), N also takes the form

$$N = \int_0^{a^+} k(a)\sigma(a)\,da.$$

By calculation we know that the infection-free steady state of system (1.3) is $E_0(s/d, 0, 0, 0)$. If the basic reproduction number $\Re_0 = \beta sN/du > 1$, there exists an immune-inactivated

infected steady state $E_1^*(x_1^*, y_1^*(a), v_1^*, 0)$, in which

$$x_1^* = \frac{u}{\beta N}, \qquad y_1^*(a) = \frac{(\beta sN - du)\sigma(a)}{\beta N}, \qquad v_1^* = \frac{\beta sN - du}{\beta u}.$$

If the immune-activated reproduction number $\Re_1 = \beta csN/(cdu + \beta bu) > 1$, there exists an immune-activated infected steady state $E_2^*(x_2^*, y_2^*(a), v_2^*, z_2^*)$, in which

$$x_2^* = \frac{cs}{cd + \beta b}, \qquad y_2^*(a) = \frac{\beta bs\sigma(a)}{cd + \beta b}, \qquad v_2^* = \frac{b}{c}, \qquad z_2^* = \frac{\beta csN - cdu - \beta bu}{p(cd + \beta b)}.$$

Theorem 2.1 *The infection-free steady state E_0 is locally asymptotically stable if $\Re_0 < 1$.*

Proof Linearizing system (1.3) about E_0 and defining the perturbation variables

$$x_1(t) = x(t) - \frac{s}{d}, \qquad y_1(a,t) = y(a,t), \qquad v_1(t) = v(t), \qquad z_1(t) = z(t),$$

we obtain

$$\begin{aligned}
&\dot{x}_1(t) = -dx_1(t) - \frac{\beta s}{d} v_1(t),\\
&\frac{\partial y_1(a,t)}{\partial a} + \frac{\partial y_1(a,t)}{\partial t} = -\delta(a) y_1(a,t),\\
&\dot{v}_1(t) = \int_0^\infty k(a) y_1(a,t)\,da - uv_1(t),\\
&\dot{z}_1(t) = -bz_1(t),
\end{aligned} \tag{2.2}$$

and

$$y_1(0,t) = \frac{\beta s}{d} v_1(t). \tag{2.3}$$

Look for non-trivial solutions of (2.2) and (2.3) of the form

$$x_1(t) = c_{11}e^{\lambda t}, \qquad y_1(a,t) = y_1^0(a)e^{\lambda t}, \qquad v_1(t) = c_{21}e^{\lambda t}, \qquad z_1(t) = c_{31}e^{\lambda t}. \tag{2.4}$$

Substituting (2.4) into (2.2) and (2.3), it follows that

$$\begin{aligned}
&(\lambda + d)c_{11} = -\frac{\beta s}{d} c_{21},\\
&\frac{dy_1^0(a)}{da} = -\big(\delta(a) + \lambda\big) y_1^0(a),\\
&(\lambda + u)c_{21} = \int_0^\infty k(a) y_1^0(a)\,da,\\
&c_{31}\lambda = -bc_{31},\\
&y_1^0(0) = \frac{\beta s}{d} c_{21}.
\end{aligned} \tag{2.5}$$

Integrating the second equation of (2.5) from 0 to a yields

$$y_1^0(a) = y_1^0(0)e^{-\int_0^a (\lambda + \delta(\varepsilon))\,d\varepsilon}. \tag{2.6}$$

We derive from the fifth equation of (2.5) and (2.6) that

$$y_1^0(a) = \frac{\beta s}{d} c_{21} e^{-\int_0^a (\lambda+\delta(\varepsilon))\,d\varepsilon}. \tag{2.7}$$

Then substituting (2.7) and the fourth equation of (2.5) into the third equation of (2.5), we obtain the characteristic equation

$$(\lambda + b)\left(\frac{N}{\int_0^\infty k(a) e^{-\int_0^a (\lambda+\delta(\varepsilon))\,d\varepsilon}\,da} \cdot \frac{\lambda + u}{u} - \Re_0 \right) = 0. \tag{2.8}$$

Clearly, $\lambda = -b$ is a negative real root of equation (2.8). We claim that if $\Re_0 < 1$, all roots of equation (2.8) have negative real parts. Otherwise, equation (2.8) has at least one root satisfying $\mathrm{Re}\lambda \geq 0$, in this case

$$\begin{aligned} \Re_0 &= \left| \frac{N}{\int_0^\infty k(a) e^{-\int_0^a (\lambda+\delta(\varepsilon))\,d\varepsilon}\,da} \cdot \frac{\lambda + u}{u} \right| \\ &= \left| \frac{\int_0^\infty k(a) e^{-\int_0^a \delta(\varepsilon)\,d\varepsilon}\,da}{\int_0^\infty e^{-a\lambda} k(a) e^{-\int_0^a \delta(\varepsilon)\,d\varepsilon}\,da} \right| \cdot \left| \frac{\lambda + u}{u} \right| \geq 1. \end{aligned}$$

It contradicts with $\Re_0 < 1$. Therefore, all roots of equation (2.8) have negative real parts. Accordingly, E_0 is locally asymptotically stable if $\Re_0 < 1$. □

Theorem 2.2 *The immune-inactivated infected steady state E_1^* is locally asymptotically stable if $\Re_1 < 1 < \Re_0$.*

Proof Linearizing system (1.3) about E_1^* and defining the perturbation variables

$$x_2(t) = x(t) - x_1^*, \qquad y_2(a,t) = y(a,t) - y_1^*(a), \qquad \nu_2(t) = \nu(t) - \nu_1^*, \qquad z_2(t) = z(t),$$

we obtain

$$\begin{aligned} &\dot{x}_2(t) = \left(-d - \beta \nu_1^*\right) x_2(t) - \beta x_1^* \nu_2(t), \\ &\frac{\partial y_2(a,t)}{\partial a} + \frac{\partial y_2(a,t)}{\partial t} = -\delta(a) y_2(a,t), \\ &\dot{\nu}_2(t) = \int_0^\infty k(a) y_2(a,t)\,da - u\nu_2(t) - p\nu_1^* z_2(t), \\ &\dot{z}_2(t) = \left(c\nu_1^* - b\right) z_2(t), \end{aligned} \tag{2.9}$$

and

$$y_2(0,t) = \beta x_1^* \nu_2(t) + \beta \nu_1^* x_2(t). \tag{2.10}$$

We look for non-trivial solutions of (2.9) and (2.10) of the form

$$x_2(t) = c_{12} e^{\lambda t}, \qquad y_2(a,t) = y_2^0(a) e^{\lambda t}, \qquad \nu_2(t) = c_{22} e^{\lambda t}, \qquad z_2(t) = c_{32} e^{\lambda t}. \tag{2.11}$$

By using a similar method to the proof of Theorem 2.1, we obtain the characteristic equation

$$\left(\frac{\lambda+u}{u}-\frac{\lambda+d}{\lambda+d+\beta v_1^*}\cdot\frac{\int_0^\infty k(a)e^{-\int_0^a(\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da}{\int_0^\infty k(a)e^{-\int_0^a\delta(\varepsilon)\,d\varepsilon}\,da}\right)\left(\lambda-cv_1^*+b\right)=0. \tag{2.12}$$

Obviously, $\lambda = cv_1^* - b = (\Re_1 - 1)(cd + \beta b)/\beta$ is a root of equation (2.12), and it is negative when $\Re_1 < 1$. We claim that if $\Re_1 < 1 < \Re_0$, all roots of equation (2.12) have negative real parts. Otherwise, equation (2.12) has at least one root satisfying $\mathrm{Re}\lambda \geq 0$, in this case

$$\frac{\lambda+u}{u}=\frac{\lambda+d}{\lambda+d+\beta v_1^*}\cdot\frac{\int_0^\infty k(a)e^{-\int_0^a(\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da}{\int_0^\infty k(a)e^{-\int_0^a\delta(\varepsilon)\,d\varepsilon}\,da}.$$

However,

$$\begin{aligned}&\left|\frac{\lambda+u}{u}\right|\geq 1,\\&\left|\frac{\lambda+d}{\lambda+d+\beta v_1^*}\cdot\frac{\int_0^\infty k(a)e^{-\int_0^a(\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da}{\int_0^\infty k(a)e^{-\int_0^a\delta(\varepsilon)\,d\varepsilon}\,da}\right|\\&\quad=\left|\frac{\lambda+d}{\lambda+d+\beta v_1^*}\right|\cdot\left|\frac{\int_0^\infty k(a)e^{-\int_0^a(\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da}{\int_0^\infty k(a)e^{-\int_0^a\delta(\varepsilon)\,d\varepsilon}\,da}\right|<1.\end{aligned}$$

A contradiction occurs. Thus, all roots of equation (2.12) have negative real parts, E_1^* is locally asymptotically stable if $\Re_1 < 1 < \Re_0$. □

Theorem 2.3 *The immune-activated infected steady state E_2^* is locally asymptotically stable if $\Re_1 > 1$.*

Proof Linearizing system (1.3) about E_1^* and defining the perturbation variables

$$\begin{aligned}&x_3(t)=x(t)-x_2^*,\qquad y_3(a,t)=y(a,t)-y_2^*(a),\\&v_3(t)=v(t)-v_2^*,\qquad z_3(t)=z(t)-z_2^*,\end{aligned}$$

we obtain

$$\begin{aligned}&\dot{x}_3(t)=\left(-d-\beta v_2^*\right)x_3(t)-\beta x_2^* v_3(t),\\&\frac{\partial y_3(a,t)}{\partial a}+\frac{\partial y_3(a,t)}{\partial t}=-\delta(a)y_3(a,t),\\&\dot{v}_3(t)=\int_0^\infty k(a)y_3(a,t)\,da-\left(u+pz_2^*\right)v_3(t)-pv_2^*z_3(t),\\&\dot{z}_3(t)=cz_2^*v_3(t),\end{aligned} \tag{2.13}$$

and

$$y_3(0,t)=\beta x_2^* v_3(t)+\beta v_2^* x_3(t). \tag{2.14}$$

We look for non-trivial solutions of (2.13) and (2.14) of the form

$$x_3(t) = c_{13}e^{\lambda t}, \qquad y_3(a,t) = y_3^0(a)e^{\lambda t}, \qquad v_3(t) = c_{23}e^{\lambda t}, \qquad z_3(t) = c_{33}e^{\lambda t}. \tag{2.15}$$

Substituting (2.15) into (2.13) and (2.14), it follows that

$$\begin{aligned}
&c_{13}\lambda = \big(-d - \beta v_2^*\big)c_{13} - \beta x_2^* c_{23},\\
&\frac{dy_3^0(a)}{da} = -\big(\delta(a) + \lambda\big)y_3^0(a),\\
&c_{23}\lambda = \int_0^\infty k(a)y_3^0(a)\,da - \big(u + pz_2^*\big)c_{23} - pv_2^* c_{33},\\
&c_{33}\lambda = cz_2^* c_{23},\\
&y_3^0(0) = \beta x_2^* c_{23} + \beta v_2^* c_{13}.
\end{aligned} \tag{2.16}$$

We derive from the second and the fifth equations of (2.16) that

$$y_3^0(a) = \big(\beta x_2^* c_{23} + \beta v_2^* c_{13}\big)e^{-\int_0^a (\delta(\varepsilon)+\lambda)\,d\varepsilon}. \tag{2.17}$$

Substituting the first and the fourth equations of (2.16) into the third equation of (2.16), we get the characteristic equation

$$\begin{aligned}
&\lambda\big(\lambda + u + pz_2^*\big)\big(\lambda + d + \beta v_2^*\big) + cpv_2^* z_2^*\big(\lambda + d + \beta v_2^*\big)\\
&\quad = \lambda(\lambda + d)\beta x_2^* \int_0^\infty k(a)e^{-\int_0^a (\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da.
\end{aligned} \tag{2.18}$$

Noting that $\lambda = 0$ and $\lambda = -d - \beta v_2^*$ are not roots of equation (2.18), (2.18) can also be written as

$$\lambda + u + pz_2^* + \frac{cpv_2^* z_2^*}{\lambda} = \frac{(\lambda + d)\beta x_2^*}{\lambda + d + \beta v_2^*} \int_0^\infty k(a)e^{-\int_0^a (\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da. \tag{2.19}$$

Substituting $x_2^* = cs/(cd + \beta b)$, $v_2^* = b/c$, $z_2^* = (\beta csN - cdu - \beta bu)/p(cd + \beta b)$ into (2.19), we have

$$\frac{\beta csN}{cd + \beta b} + \frac{\lambda^2 + pbz_2^*}{\lambda} = \frac{\lambda + d}{\lambda + d + \beta v_2^*} \frac{\beta cs}{cd + \beta b} \int_0^\infty k(a)e^{-\int_0^a (\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da. \tag{2.20}$$

We claim that if $\Re_1 > 1$, all roots of equation (2.20) have negative real parts. Otherwise, equation (2.20) has at least one root satisfying $\lambda = \alpha + \gamma i$ ($\alpha > 0$ or $\alpha = 0$, $\gamma \neq 0$), in this case

$$\begin{aligned}
&\left|\frac{\lambda + d}{\lambda + d + \beta v_2^*} \frac{\beta cs}{cd + \beta b} \int_0^\infty k(a)e^{-\int_0^a (\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da\right|\\
&\quad = \frac{\beta cs}{cd + \beta b}\left|\frac{\lambda + d}{\lambda + d + \beta v_2^*}\right|\left|\int_0^\infty k(a)e^{-\int_0^a (\delta(\varepsilon)+\lambda)\,d\varepsilon}\,da\right| < \frac{\beta csN}{cd + \beta b},
\end{aligned}$$

while

$$\begin{aligned}\left|\frac{\beta csN}{cd+\beta b}+\frac{\lambda^2+pbz^*}{\lambda}\right| &= \left|\frac{\beta csN}{cd+\beta b}+\frac{\alpha^2-\gamma^2+2\alpha\gamma i+pbz^*}{\alpha+\gamma i}\right| \\ &= \left|\frac{\beta csN}{cd+\beta b}+\frac{\alpha(\alpha^2+\gamma^2+pbz^*)+(\alpha^2\gamma+\gamma^3-pbz^*\gamma)i}{\alpha^2+\gamma^2}\right| \\ &\geq \frac{\beta csN}{cd+\beta b}.\end{aligned}$$

The contradiction is obvious. Thus, all roots of equation (2.20) have negative real parts, E_2^* is locally asymptotically stable if $\Re_1 > 1$. □

3 Global stability

In this section, we study the global asymptotic stability of each steady state of system (1.3). The strategy of proofs is to use Lyapunov functionals.

Theorem 3.1 *The infection-free steady state E_0 is globally asymptotically stable if $\Re_0 < 1$.*

Proof Denote

$$f(a) := \int_a^\infty k(\theta)e^{-\int_a^\theta \delta(\varepsilon)\,d\varepsilon}\,d\theta \quad \left(= \int_a^{a^+} k(\theta)e^{-\int_a^\theta \delta(\varepsilon)\,d\varepsilon}\,d\theta\right). \tag{3.1}$$

Note that $f(a) > 0$ for all $0 < a < a^+$. It is easy to show from (3.1) that $f(0) = N, f(a^+) = 0$. Further, the derivative of $f(a)$ satisfies

$$f'(a) = \delta(a)f(a) - k(a). \tag{3.2}$$

Let $(x(t), y(a,t), v(t), z(t))$ be any solution of system (1.3) with boundary condition (1.4) and initial condition (1.5). Define

$$V_1(t) = \left(x(t) - x_0 - x_0 \ln\frac{x(t)}{x_0}\right) + \frac{1}{N}\int_0^{a^+} f(a)y(a,t)\,da + \frac{1}{N}v(t) + \frac{p}{cN}z(t).$$

It is easy to see that $V_1(t)$ is nonnegative and E_0 is a global minimum of $V_1(t)$. Calculating the derivative of $V_1(t)$ along the solutions of system (1.3), we have

$$\frac{dV_1(t)}{dt} = \left(1-\frac{x_0}{x}\right)\frac{dx(t)}{dt} + \frac{1}{N}\int_0^{a^+} f(a)\frac{\partial y(a,t)}{\partial t}\,da + \frac{1}{N}\frac{dv(t)}{dt} + \frac{p}{cN}\frac{dz(t)}{dt}. \tag{3.3}$$

Substituting $s = dx_0$ and (3.2) into (3.3), we get

$$\begin{aligned}\frac{dV_1(t)}{dt} &= \left(1-\frac{x_0}{x(t)}\right)\big(dx_0 - dx(t) - \beta x(t)v(t)\big) \\ &\quad - \frac{1}{N}\int_0^{a^+} f(a)\left(\frac{\partial y(a,t)}{\partial a} + \delta(a)y(a,t)\right)da \\ &\quad + \frac{1}{N}\left(\int_0^{a^+} k(a)y(a,t)\,da - uv(t) - pv(t)z(t)\right)\end{aligned}$$

$$
\begin{aligned}
&+\frac{p}{cN}\big(cv(t)z(t)-bz(t)\big)\\
=&-\frac{d}{x(t)}\big(x(t)-x_0\big)^2+\beta x_0 v(t)-\beta x(t)v(t)\\
&-\frac{1}{N}\int_0^{a^+} f(a)\left(\frac{\partial y(a,t)}{\partial a}+\delta(a)y(a,t)\right)da\\
&+\frac{1}{N}\int_0^{a^+} k(a)y(a,t)\,da-\frac{u}{N}v(t)-\frac{bp}{cN}z(t). \qquad (3.4)
\end{aligned}
$$

Using integration by parts and $f(0)=N, f(a^+)=0$, $y(0,t)=\beta x(t)v(t)$, we have

$$
\begin{aligned}
\int_0^{a^+} f(a)\frac{\partial y(a,t)}{\partial a}\,da &= f\big(a^+\big)y\big(a^+,t\big)-f(0)y(0,t)-\int_0^{a^+} f'(a)y(a,t)\,da\\
&=-\beta N x(t)v(t)-\int_0^{a^+} f'(a)y(a,t)\,da. \qquad (3.5)
\end{aligned}
$$

Substituting (3.5) into (3.4) yields

$$
\begin{aligned}
\frac{dV_1(t)}{dt} =& -\frac{d}{x(t)}\big(x(t)-x_0\big)^2+\beta x_0 v(t)-\frac{1}{N}\int_0^{a^+} f(a)\delta(a)y(a,t)\,da\\
&+\frac{1}{N}\int_0^{a^+}\big(\delta(a)f(a)-k(a)\big)y(a,t)\,da+\frac{1}{N}\int_0^{a^+} k(a)y(a,t)\,da\\
&-\frac{u}{N}v(t)-\frac{bp}{cN}z(t)\\
=&-\frac{d}{x(t)}\big(x(t)-x_0\big)^2+\frac{u}{N}(\Re_0-1)v(t)-\frac{bp}{cN}z(t).
\end{aligned}
$$

Therefore, $\Re_0<1$ ensures that $V_1'(t)\le 0$ holds true. By Theorem 5.3.1 in [13], solutions limit to $\mathcal{M}$, the largest invariant subset of $\{V_1'(t)=0\}$. Clearly, $V_1'(t)=0$ if and only if $x(t)=x_0$, $v(t)=0$, $z(t)=0$. Noting that $\mathcal{M}$ is invariant, for each element in $\mathcal{M}$, we have $v(t)=0$, $z(t)=0$, $v'(t)=0$. We therefore derive from the third equation of system (1.3) that $y(a,t)=0$. Hence, $V_1'(t)=0$ if and only if $(x(t),y(a,t),v(t),z(t))=(x_0,0,0,0)$. Accordingly the global asymptotic stability of E_0 follows from LaSalle's invariance principle. This completes the proof. □

Theorem 3.2 *The immune-inactivated infected steady state E_1^* is globally asymptotically stable if $\Re_1<1<\Re_0$.*

Proof Let $(x(t),y(a,t),v(t),z(t))$ be any solution of system (1.3) with boundary condition (1.4) and initial condition (1.5). Define

$$
\begin{aligned}
V_2(t)=&\left(x(t)-x_1^*-x_1^*\ln\frac{x(t)}{x_1^*}\right)\\
&+\frac{1}{N}\int_0^{a^+} f(a)y_1^*(a)\left(\frac{y(a,t)}{y_1^*(a)}-1-\ln\frac{y(a,t)}{y_1^*(a)}\right)da\\
&+\frac{1}{N}\left(v(t)-v_1^*-v_1^*\ln\frac{v(t)}{v_1}\right)+\frac{p}{cN}z(t),
\end{aligned}
$$

where $f(a)$ is defined in (3.1). It is easy to see that $V_2(t)$ is nonnegative and E_1^* is a global minimum. Calculating the derivative of $V_2(t)$ along the solutions of system (1.3), we have

$$\begin{aligned}\frac{dV_2(t)}{dt} &= \left(1-\frac{x_1^*}{x(t)}\right)\big(s-dx(t)-\beta x(t)v(t)\big)\\ &\quad+\frac{1}{N}\int_0^{a^+} f(a)\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\frac{\partial y(a,t)}{\partial t}\,da\\ &\quad+\frac{1}{N}\left(1-\frac{v_1^*}{v(t)}\right)\left(\int_0^{\infty} k(a)y(a,t)\,da-uv(t)-pv(t)z(t)\right)\\ &\quad+\frac{p}{cN}\big(cv(t)z(t)-bz(t)\big).\end{aligned}$$

By using $s = dx^* + \beta x^* v^*$, we have

$$\begin{aligned}\frac{dV_2(t)}{dt} &= \left(1-\frac{x_1^*}{x(t)}\right)\big(dx_1^*-dx(t)+\beta x_1^* v_1^*-\beta x(t)v(t)\big)\\ &\quad-\frac{1}{N}\int_0^{a^+} f(a)\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\left(\frac{\partial y(a,t)}{\partial a}+\delta(a)y(a,t)\right)da\\ &\quad+\frac{1}{N}\left(1-\frac{v_1^*}{v(t)}\right)\left(\int_0^{a^+} k(a)y(a,t)\,da-uv(t)-pv(t)z(t)\right)\\ &\quad+\frac{p}{cN}\big(cv(t)z(t)-bz(t)\big)\\ &= -\frac{d}{x(t)}\big(x_1^*-x(t)\big)^2+\left(1-\frac{x_1^*}{x(t)}\right)\big(\beta x_1^* v_1^*-\beta x(t)v(t)\big)\\ &\quad-\frac{1}{N}\int_0^{a^+} f(a)\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\left(\frac{\partial y(a,t)}{\partial a}+\delta(a)y(a,t)\right)da\\ &\quad+\frac{1}{N}\left(\int_0^{a^+} k(a)y(a,t)\,da-uv(t)\right)\\ &\quad-\frac{1}{N}\frac{v_1^*}{v(t)}\left(\int_0^{a^+} k(a)y(a,t)\,da-uv(t)-pv(t)z(t)\right)\\ &\quad-\frac{bp}{cN}z(t).\end{aligned}\tag{3.6}$$

Note that

$$\frac{d}{da}\left(\frac{y(a,t)}{y_1^*(a)}-1-\ln\frac{y(a,t)}{y_1^*(a)}\right)=\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\left(\frac{y_a(a,t)}{y_1^*(a)}-\frac{y(a,t)y_{1a}^*(a)}{[y_1^*(a)]^2}\right),\tag{3.7}$$

here $y_a(a,t) = \partial y(a,t)/\partial a$ and $y_{1a}^*(a) = dy_1^*(a)/da$. Since

$$y_a^*(a) = -\delta(a)y^*(a),\tag{3.8}$$

substituting (3.8) into (3.7) yields

$$\begin{aligned}\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\frac{\partial y(a,t)}{\partial a} &= y_1^*(a)\frac{d}{da}\left(\frac{y(a,t)}{y_1^*(a)}-1-\ln\frac{y(a,t)}{y_1^*(a)}\right)\\ &\quad+\delta(a)y_1^*(a)-\delta(a)y(a,t).\end{aligned}\tag{3.9}$$

Using integration by parts, it follows from (3.9) that

$$\begin{aligned}
&\int_0^{a^+} f(a)\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\frac{\partial y(a,t)}{\partial a}\,da \\
&\quad = f\left(a^+\right)y_1^*\left(a^+\right)\left(\frac{y(a^+,t)}{y_1^*(a^+)}-1-\ln\frac{y(a^+,t)}{y_1^*(a^+)}\right)-f(0)y_1^*(0)\left(\frac{y(0,t)}{y_1^*(0)}-1-\ln\frac{y(0,t)}{y_1^*(0)}\right) \\
&\qquad -\int_0^{a^+}\left(\frac{y(a,t)}{y_1^*(a)}-1-\ln\frac{y(a,t)}{y_1^*(a)}\right)\left(f'(a)y_1^*(a)+f(a)y_{1a}^*(a)\right)da \\
&\qquad +\int_0^{a^+} f(a)\left(\delta(a)y_1^*(a)-\delta(a)y(a,t)\right)da. \qquad (3.10)
\end{aligned}$$

Noting that

$$\begin{aligned}
&f(0)=N, \qquad f\left(a^+\right)=0,\\
&y_1^*(0)=\beta x_1^*\nu_1^*,\\
&y(0,t)=\beta x\nu,\\
&y_{1a}^*(a)=-\delta(a)y_1^*(a),\\
&f'(a)=\delta(a)f(a)-k(a),
\end{aligned}$$

we have

$$\begin{aligned}
&f(0)y_1^*(0)\left(\frac{y(0,t)}{y_1^*(0)}-1-\ln\frac{y(0,t)}{y_1^*(0)}\right)=N\beta x_1^*\nu_1^*\left(\frac{x\nu}{x_1^*\nu_1^*}-1-\ln\frac{x\nu}{x_1^*\nu_1^*}\right),\\
&f\left(a^+\right)y^*\left(a^+\right)\left(\frac{y(a^+,t)}{y_1^*(a^+)}-1-\ln\frac{y(a^+,t)}{y_1^*(a^+)}\right)=0, \qquad (3.11)\\
&f'(a)y_1^*(a)+f(a)y_{1a}^*(a)=-k(a)y_1^*(a).
\end{aligned}$$

Further, we obtain

$$\begin{aligned}
&\int_0^{a^+} f(a)\left(1-\frac{y_1^*(a)}{y(a,t)}\right)\left(\frac{\partial y(a,t)}{\partial a}+\delta(a)y(a,t)\right)da \\
&\quad =-N\beta x_1^*\nu_1^*\left(\frac{x\nu}{x_1^*\nu_1^*}-1-\ln\frac{x\nu}{x_1^*\nu_1^*}\right) \\
&\qquad +\int_0^{a^+}\left(\frac{y(a,t)}{y_1^*(a)}-1-\ln\frac{y(a,t)}{y_1^*(a)}\right)k(a)y_1^*(a)\,da. \qquad (3.12)
\end{aligned}$$

We derive from (3.6) and (3.12) that

$$\begin{aligned}
\frac{dV_2(t)}{dt} &= -\frac{d}{x(t)}\left(x_1^*-x(t)\right)^2+\left(1-\frac{x_1^*}{x(t)}\right)\left(\beta x_1^*\nu_1^*-\beta x(t)\nu(t)\right)\\
&\quad +\beta x_1^*\nu_1^*\left(\frac{x\nu}{x_1^*\nu_1^*}-1-\ln\frac{x\nu}{x_1^*\nu_1^*}\right)\\
&\quad -\frac{1}{N}\int_0^{a^+}\left(\frac{y(a,t)}{y_1^*(a)}-1-\ln\frac{y(a,t)}{y_1^*(a)}\right)k(a)y_1^*(a)\,da
\end{aligned}$$

$$+\frac{1}{N}\left(\int_0^{a^+} k(a)y(a,t)\,da - uv(t)\right)$$
$$-\frac{1}{N}\frac{v_1^*}{v(t)}\left(\int_0^{a^+} k(a)y(a,t)\,da - uv(t) - pv(t)z(t)\right) - \frac{bp}{cN}z(t). \tag{3.13}$$

Noting that $uv_1^* = \int_0^\infty k(a)y_1^*(a)\,da = \beta x_1^* v_1^* N$, we have

$$\begin{aligned}\frac{dV_2(t)}{dt} =& -\frac{d}{x(t)}\left(x_1^* - x(t)\right)^2\\ &-\frac{1}{N}\int_0^{a^+}\left(\frac{v_1^* y(a,t)}{y_1^*(a)v(t)} - 1 - \ln\frac{v_1^* y(a,t)}{y_1^*(a)v(t)}\right)k(a)y_1^*(a)\,da\\ &-\beta x_1^* v_1^*\left(\frac{x_1^*}{x(t)} - 1 - \ln\frac{x_1^*}{x(t)}\right) + \frac{pz(t)}{N}\left(v_1^* - \frac{b}{c}\right).\end{aligned}$$

Since

$$\frac{pz(t)}{N}\left(v_1^* - \frac{b}{c}\right) = \left(\frac{(\beta sN - du)}{\beta u} - \frac{b}{c}\right)\frac{pz(t)}{N} = (\Re_1 - 1)(cdu + \beta bu)\frac{pz(t)}{\beta cuN},$$

$V_2'(t) \le 0$ if $\Re_1 < 1 < \Re_0$. By Theorem 5.3.1 in [13], solutions limit to $\mathcal{M}$, the largest invariant subset of $\{V_2'(t) = 0\}$. It is readily seen that $V_2' = 0$ if and only if $x(t) = x_1^*$, $y(a,t) = y_1^*(a)$, $v(t) = v_1^*$, $z(t) = 0$. We have proved in Theorem 2.2 that E_1^* is locally asymptotically stable if $\Re_1 < 1 < \Re_0$, then the global asymptotic stability of E_1^* follows. □

Theorem 3.3 *The immune-activated infected steady state E_2^* is globally asymptotically stable if $\Re_1 > 1$.*

Proof Let $(x(t), y(a,t), v(t), z(t))$ be any solution of system (1.3) with boundary condition (1.4) and initial condition (1.5). Define

$$\begin{aligned}V_3(t) =& \left(x(t) - x_2^* - x_2^*\ln\frac{x(t)}{x_2^*}\right)\\ &+\frac{1}{N}\int_0^{a^+} f(a)y_2^*(a)\left(\frac{y(a,t)}{y_2^*(a)} - 1 - \ln\frac{y(a,t)}{y_2^*(a)}\right)da\\ &+\frac{1}{N}\left(v(t) - v_2^* - v_2^*\ln\frac{v(t)}{v_2^*}\right) + \frac{p}{cN}\left(z(t) - z_2^* - z_2^*\ln\frac{z(t)}{z_2^*}\right),\end{aligned}$$

where $f(a)$ is defined in (3.1). It is easy to see that $V_3(t)$ is nonnegative and E_2^* is a global minimum. Calculating the derivative of $V_3(t)$ along the solutions of system (1.3), we have

$$\begin{aligned}\frac{dV_3(t)}{dt} =& \left(1 - \frac{x_2^*}{x(t)}\right)\left(s - dx(t) - \beta x(t)v(t)\right)\\ &+\frac{1}{N}\int_0^{a^+} f(a)\left(1 - \frac{y_2^*(a)}{y(a,t)}\right)\frac{\partial y(a,t)}{\partial t}\,da\\ &+\frac{1}{N}\left(1 - \frac{v_2^*}{v(t)}\right)\left(\int_0^\infty k(a)y(a,t)\,da - uv(t) - pv(t)z(t)\right)\\ &+\frac{p}{cN}\left(1 - \frac{z_2^*}{z(t)}\right)\left(cv(t)z(t) - bz(t)\right).\end{aligned}$$

By using $s = dx_2^* + \beta x_2^* v_2^*$, we obtain

$$\begin{aligned}
\frac{dV_3(t)}{dt} &= \left(1 - \frac{x_2^*}{x(t)}\right)\left(dx_2^* + \beta x_2^* v_2^* - dx(t) - \beta x(t)v(t)\right) \\
&\quad - \frac{1}{N}\int_0^{a^+} f(a)\left(1 - \frac{y_2^*(a)}{y(a,t)}\right)\left(\frac{\partial y(a,t)}{\partial a} + \delta(a)y(a,t)\right) da \\
&\quad + \frac{1}{N}\left(1 - \frac{v_2^*}{v(t)}\right)\left(\int_0^{\infty} k(a)y(a,t)\,da - uv(t) - pv(t)z(t)\right) \\
&\quad + \frac{p}{cN}\left(1 - \frac{z_2^*}{z(t)}\right)\left(cv(t)z(t) - bz(t)\right) \\
&= -\frac{d}{x(t)}\left(x_2^* - x(t)\right)^2 + \left(1 - \frac{x_2^*}{x(t)}\right)\left(\beta x_2^* v_2^* - \beta x(t)v(t)\right) \\
&\quad - \frac{1}{N}\int_0^{a^+} f(a)\left(1 - \frac{y_2^*(a)}{y(a,t)}\right)\left(\frac{\partial y(a,t)}{\partial a} + \delta(a)y(a,t)\right) da \\
&\quad + \frac{1}{N}\left(\int_0^{\infty} k(a)y(a,t)\,da - uv(t)\right) \\
&\quad - \frac{1}{N}\frac{v_2^*}{v(t)}\left(\int_0^{\infty} k(a)y(a,t)\,da - uv(t) - pv(t)z(t)\right) \\
&\quad - \frac{p}{cN}\left(cv(t)z_2^* - bz_2^*\right) - \frac{bp}{cN}z(t). \qquad (3.14)
\end{aligned}$$

By using a similar method to (3.7)-(3.12), we derive from (3.14) that

$$\begin{aligned}
\frac{dV_3(t)}{dt} &= -\frac{d}{x(t)}\left(x_2^* - x(t)\right)^2 + \left(1 - \frac{x_2^*}{x(t)}\right)\left(\beta x_2^* v_2^* - \beta x(t)v(t)\right) \\
&\quad + \beta x_2^* v_2^*\left(\frac{xv}{x_2^* v_2^*} - 1 - \ln\frac{xv}{x_2^* v_2^*}\right) \\
&\quad - \frac{1}{N}\int_0^{a^+}\left(\frac{y(a,t)}{y_2^*(a)} - 1 - \ln\frac{y(a,t)}{y_2^*(a)}\right)k(a)y_2^*(a)\,da \\
&\quad + \frac{1}{N}\left(\int_0^{a^+} k(a)y(a,t)\,da - uv(t)\right) \\
&\quad - \frac{1}{N}\frac{v_2^*}{v(t)}\left(\int_0^{a^+} k(a)y(a,t)\,da - uv(t) - pv(t)z(t)\right) \\
&\quad - \frac{p}{cN}\left(cv(t)z_2^* - bz_2^*\right) - \frac{bp}{cN}z(t). \qquad (3.15)
\end{aligned}$$

Substituting $uv_2^* = \int_0^{a^+} k(a)y_2^*(a)\,da - pv_2^* z_2^* = \beta x_2^* v_2^* N - pv_2^* z_2^*$ and $v_2^* = b/c$ into (3.15), we have

$$\begin{aligned}
\frac{dV_3(t)}{dt} &= -\frac{d}{x(t)}\left(x_2^* - x(t)\right)^2 - \beta x_2^* v_2^*\left(\frac{x_2^*}{x(t)} - 1 - \ln\frac{x_2^*}{x(t)}\right) \\
&\quad - \int_0^{a^+}\left(\frac{v_2^* y(a,t)}{y_2^*(a)v(t)} - 1 - \ln\frac{v_2^* y(a,t)}{y_2^*(a)v(t)}\right)k(a)y_2^*(a)\,da.
\end{aligned}$$

Therefore, $\Re_1 > 1$ ensures that $V_3'(t) \le 0$ holds true. By Theorem 5.3.1 in [13], solutions of (1.3) are limited to $\mathcal{M}$, the largest invariant subset of $\{V_3'(t) = 0\}$. Using a similar argument

to that in the proof of Theorem 3.1, we know that the equality $V_3'(t) = 0$ holds true if and only if $x(t) = x_2^*$, $y(a,t) = y_2^*(a)$, $v(t) = v_2^*$, $z(t) = z_2^*$. By LaSalle's invariance principle, the global asymptotic stability of E_2^* follows. This completes the proof. □

4 Numerical simulations

In this section, we give some numerical examples to illustrate the theoretical results obtained in Sections 2 and 3. The mean methods are discretizing the equations and using eulerian difference method. The value of integral terms is obtained by Simpson's rule.

Usually, there is an incubation period after the cells are infected. In this period, the death rate of the cells is not changed and the infected cells do not produce virion. Later there is an outbreak period, in this period the infected cells begin to produce virion and the production rate increases, and the death rate of infected cells also rapidly increases. After the outbreak period, the death rate and the virion production rate of the infected cells tend to be stable. Considering these properties we assume that the death rate $\delta(a)$ and the virion production rate $k(a)$ of the infected cells take the forms

$$\delta(a) = \begin{cases} 0.03, & 0 \le a \le 10; \\ 0.03 + 0.005(a-10)e^{-0.009(a-25)^2}, & 10 < a \le 40; \\ 0.05, & 40 < a \le a^+, \end{cases}$$

and

$$k(a) = \begin{cases} 0, & 0 \le a \le 10; \\ 30(a-10)e^{-0.05(a-25)^2}, & 10 < a \le 40; \\ 0.012, & 40 < a \le a^+, \end{cases}$$

where the maximum age of the cells a^+ is supposed to be 300 days. The initial value is supposed to be

$$x_s = 800, \qquad v_s = 100, \qquad y_s(a) = 50(a+3)e^{-0.2(a+3)}, \qquad z_s = 300.$$

We will take a day as the unit time and plot the solutions of system (1.3) from 0 to 600 days.

Example 1 In system (1.3), we choose $s = 20$, $d = 0.03$, $\beta = 0.00024$, $u = 30$, $p = 0.5$, $c = 0.000005$, $b = 0.07$. In this case $\Re_0 = 0.5626 < 1$. By Theorem 3.1, the infection-free steady state $E_0(s/d, 0, 0, 0)$ is globally asymptotically stable, where $s/d = 666.67$. (See Figure 1.)

Example 2 In system (1.3), we choose $s = 30$, $d = 0.03$, $\beta = 0.00024$, $u = 18$, $p = 0.5$, $c = 0.000005$, $b = 0.07$. In this case $\Re_0 = 1.4064 > 1$, $\Re_1 = 0.1153 < 1$. By Theorem 3.2, the immune-inactivated infected steady state $E_1^*(x_1^*, y_1^*(a), v_1^*, 0)$ is globally asymptotically stable, where $x_1^* = 711.04$, $y_1^*(a) = 8.66\sigma(a)$, $v_1^* = 507.98$. (See Figure 2.)

Example 3 In system (1.3), we choose $s = 20$, $d = 0.03$, $\beta = 0.00024$, $u = 8$, $p = 0.1$, $c = 0.01$, $b = 2$. In this case $\Re_1 = 1.8186 > 1$. By Theorem 3.3, the immune-activated infected steady state $E_2^*(x_2^*, y_2^*(a), v_2^*, z_2^*)$ is globally asymptotically stable, where $x_2^* = 574.41$, $y_2^*(a) = 2.76\sigma(a)$, $v_2^* = 200$, $z_2^* = 65.4878$. (See Figure 3.)

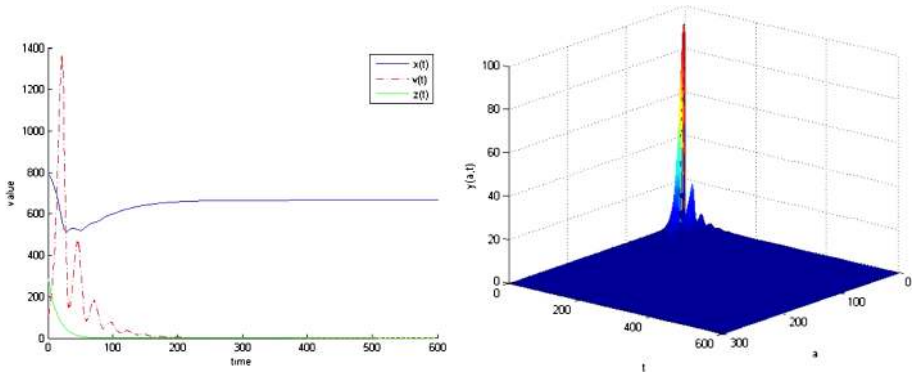

Figure 1 Example 1. $\Re_0 = 0.5626 < 1$. The infection-free steady state E_0 is globally asymptotically stable.

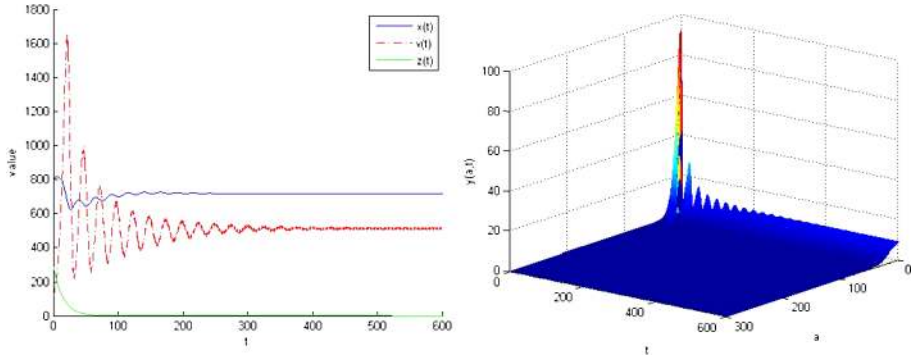

Figure 2 Example 2. $\Re_0 = 1.4064 > 1$, $\Re_1 = 0.1153 < 1$. The immune-inactivated infected steady state E_1^* is globally asymptotically stable.

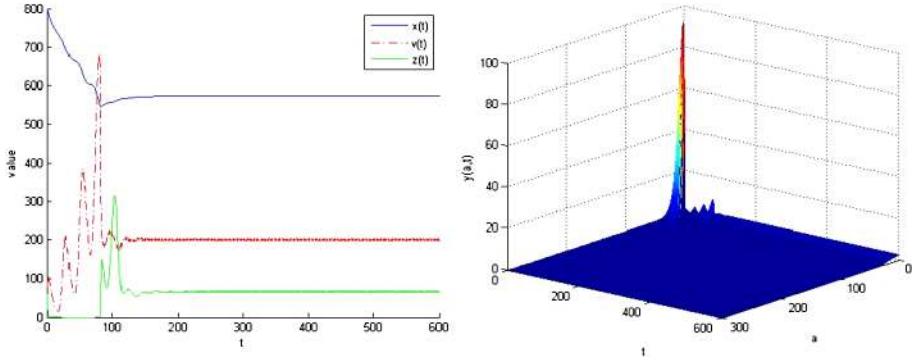

Figure 3 Example 3. $\Re_1 = 1.8186 > 1$. The immune-activated infected steady state E_2^* is globally asymptotically stable.

The results of numerical simulation are accord with theorems and the eventual number of each variable in simulation is approximate to the theoretical value. Comparing the results of Example 2 and Example 3 we can find that the densities of infectious free virion and infected T cells are lower when $\Re_1 > 1$, the humoral immunity is activated. Comparing

the results of Example 3 and Example 1 we can see that although the humoral immunity is activated, the density of uninfected target T cells of E_2^* is lower than that of E_0.

5 Conclusions

In this paper, we formulated an in-host viral infection model, in which the influence of humoral immunity and the infection age of the infected cells are considered. Using the method of Lyapunov functionals and LaSalle's invariance principle, we got the conclusions that the global dynamics of the model is determined by the basic reproduction number and the immune-activated reproduction number; if $\Re_0 < 1$, the infection-free steady state is globally asymptotically stable; if $\Re_1 < 1 < \Re_0$, the immune-inactivated infected steady state is globally asymptotically stable; and if $\Re_1 > 1$, the immune-activated infected steady state is globally asymptotically stable. Comparing the expressions of immune-inactivated infected steady state with immune-activated infected steady state, we saw that $v_1^* - v_2^* = (\Re_1 - 1)\frac{cdu+\beta bu}{\beta cu}$, so humoral immunity has a positive role in the reduction of the virus. Moreover, analyzing the immune-activated reproduction number $\Re_1$, we found the parameter c (the birth rate of B cells) effects the value of $\Re_1$ a lot. The birth rate of B cells reflects the sensibility of humoral immunity to the virus; generally speaking it can be greatly improved by vaccination.

To illustrate the theoretical results, we did some numerical simulations. Our simulation results confirmed the analytic results. Figures 1-3 showed the stability of E_0, E_1^*, E_2^*, respectively, and by comparison we saw the effect of humoral immunity in the reduction of virus.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript

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References

1. Deans, JA, Cohen, S: Immunology of malaria. Annu. Rev. Microbiol. **37**, 25-49 (1983)
2. Inoue, T, Kajiawara, T, Sasaki, T: Global stability of models of humoral immunity against multiple viral strains. Journal of Biological Dynamics **4**, 282-295 (2010)
3. Kajiwara, T, Sasaki, T: A note on the stability analysis of pathogen-immune interaction dynamics. Discrete Contin. Dyn. Syst., Ser. B **4**, 615-622 (2004)
4. Nowak, MA, Bangham, CRM: Population dynamics of immune responses to persistent viruses. Science **272**, 74-79 (1996)
5. Murase, A, Sasaki, T, Kajiwara, T: Stability analysis of pathogen-immune interaction dynamics. J. Math. Biol. **51**, 247-267 (2005)
6. Perelson, AS: Modelling viral and immune system dynamics. Nat. Rev. Immunol. **2**, 28-36 (2002)
7. Wang, S, Zou, D: Global stability of in-host viral models with humoral immunity and intracellular delays. Appl. Math. Model. **36**, 1313-1322 (2012)
8. Nelson, PW, Gilchrist, MA, Coombs, D, Hyman, JM, Perelson, AS: An age-structured model of HIV infection that allow for variations in the production rate of viral particles and the death rate of productively infected cells. Math. Biosci. Eng. **1**, 267-288 (2004)
9. Reilly, C, Wietgrefe, S, Sedgewick, G, Haase, A: Determination of simmian immunodeficiency virus production by infected activated and resting cells. AIDS **21**, 163-168 (2007)
10. Gilchrist, MA, Coombs, D, Perelson, AS: Optimizing within-host viral fitness: infected cell lifespan and virion production rate. J. Theor. Biol. **229**, 281-288 (2004)
11. Huang, G, Liu, X, Takeuchi, Y: Lyapunov functions and global stability for age-structured HIV infection model. SIAM J. Appl. Math. **72**, 25-38 (2004)
12. Wang, J, Zhang, R, Kuniya, T: Mathematical analysis for an age-structured HIV infection model with saturation infection rate. Electron. J. Differ. Equ. **2015**, 33 (2015)
13. Hale, JK, Lunel, SV: Introduction to Functional Differential Equations. Springer, New York (1993)