

# A Viral Model with Intracellular Delay and Humoral Immunity

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**Abstract** In this paper, a classical of virus dynamics model with intracellular delay and humoral immunity is introduced. By using suitable Lyapunov functionals and the Lasalle invariant principle, the global stability of the equilibria is proved. Numerical simulations are presented to illustrate our results. The effect of delay and humoral immunity is also discussed.

**Keywords** Viral model · Delay · Humoral immunity · Global stability · Lyapunov functional

**Mathematics Subject Classification** 92D30

## 1 Introduction

The purpose of this paper is to study the following delay virus dynamics model:

$$\begin{cases} x'(t) = \lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}, \\ y'(t) = \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - ay(t), \\ v'(t) = ky(t) - uv(t) - pz(t)v(t), \\ z'(t) = qz(t)v(t) - bz(t), \end{cases} \quad (1.1)$$

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where  $x(t)$  denotes the concentration of the un-infected target cells,  $y(t)$  denotes the concentration of infected cells,  $v(t)$  denotes the concentration of free virus particles,  $z(t)$  denotes the density of the pathogens-specific lymphocytes. Un-infected cells are produced at a constant rate  $\lambda$  and die at rate  $dx(t)$ . Free virus infects un-infected cells to produce infected cells at rate  $\frac{\beta x(t)v(t)}{1+\alpha v(t)}$ . Infected cells die at rate  $ay(t)$ . New virus is produced from infected cells at rate  $ky(t)$  and dies at rate  $uv(t)$ . The pathogens are removed at rate  $pz(t)$  by the immune system. The pathogens-specific lymphocytes proliferate at rate  $qv(t)$  in contact with the pathogens, and die at rate  $b$ . The average life-time of un-infected cells, infected cells, free virus and pathogens-specific lymphocytes are given by  $1/d$ ,  $1/a$ ,  $1/\mu$ ,  $1/b$ , respectively. The average number of virus particles produced over the life-time of a single infected cell is given by  $k/a$ . The parameter  $\tau$  accounts for the time between viral entry into a target cell and the production of new virus particles. The recruitment of virus producing cells at time  $t$  is given by the number of cells that were newly infected at time  $t - \tau$  and are still alive at time  $t$ . Here,  $m$  is assumed to be a constant death rate for infected but not yet virus-producing cells. Thus, the probability of surviving the time period from  $t - \tau$  to  $t$  is  $e^{-m\tau}$ .

When  $\tau = 0$ , (1.1) reduces to the following simple four-dimensional model:

$$\begin{cases} x'(t) = \lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}, \\ y'(t) = \frac{\beta x(t)v(t)}{1+\alpha v(t)} - ay(t), \\ v'(t) = ky(t) - \mu v(t) - pz(t)v(t), \\ z'(t) = qz(t)v(t) - bz(t), \end{cases} \quad (1.2)$$

it has been studied in [1].

For the healthy cell infected with a virus and the virus reproduction cell, there is an intracellular time delay between infection of a cell and production of new virus particles called the latent period (see [2–5]). The delay describes the finite time interval from the time when the infectious virus binds to the receptor of a target cell to the time when the first virion is produced from the same target cell [2]. In reality, there is a time delay between initial viral entry into a cell and subsequent viral production. There has been much work on the effect of intracellular delay accounting for the time between viral entry into a target cell and the production of new virus particles (see [6–13]). Humoral immunity is the aspect of immunity that is mediated by secreted antibodies. In malaria infection the humoral immunity is more effective than cell-mediated immunity [14]. Murase and Kajiwara [12] and Huo et al. [1] consider the effect of the humoral immunity. Many authors have studied the virus model (see [15,16]). In this paper, we incorporate the delay and the humoral immunity and study the global stability of equilibria of (1.1).

The organization of this paper is as follows. In Sect. 2, the positivity and boundedness of solutions of the system (1.1) are presented. The stability analysis for the three equilibria are given in Sect. 3, and some numerical simulations are given in Sect. 4. Finally, a brief discussion of effect of the humoral immunity and the intracellular delay are given in Sect. 5.

## 2 Positivity and Boundedness of Solutions

The initial conditions of (1.1) are given as

$$\begin{aligned}
 x(\theta) &= \varphi_1(\theta), \quad y(\theta) = \varphi_2(\theta), \quad v(\theta) = \varphi_3(\theta), \quad z(\theta) = \varphi_4(\theta), \\
 \varphi_i(\theta) &\geq 0, \quad \theta \in [-\tau, 0], \quad \varphi_i(0) > 0, \quad i = 1, 2, 3, 4,
 \end{aligned}
 \tag{2.1}$$

where  $(\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta)) \in C([- \tau, 0], R^4_{+0})$ , the Banach space of continuous functions mapping the interval  $[-\tau, 0]$  into  $R^4_{+0}$ , where  $R^4_{+0} = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$ . By the fundamental theory of FDEs [17], we know that there is a unique solution  $(x(t), y(t), v(t), z(t))$  of (1.1) with initial condition (2.1).

The following theorem establishes the positivity and boundedness of solutions of (1.1).

**Theorem 1** *Let  $(x(t), y(t), v(t), z(t))$  be any solution of system (1.1) satisfying initial condition (2.1). Then  $x(t), y(t), v(t)$  and  $z(t)$  are all positivity and bounded for all  $t \geq 0$ .*

*Proof* Note that from (1.1), we have

$$\begin{aligned}
 x(t) &= e^{\int_0^t -(d + \frac{\beta v(\xi)}{1 + \alpha v(\xi)}) d\xi} x(0) + \int_0^t \lambda e^{\int_\eta^t -(d + \frac{\beta v(\xi)}{1 + \alpha v(\xi)}) d\xi} d\eta, \\
 y(t) &= y(0)e^{-at} + e^{-at} \int_0^t \frac{\beta x(\eta - \tau)v(\eta - \tau)}{1 + \alpha v(\eta - \tau)} e^{-m\tau} e^{-a(t-\eta)} d\eta, \\
 v(t) &= v(0)e^{-\int_0^t (u + pz(\xi)) d\xi} + e^{\int_0^t -(u + pz(\xi)) d\xi} \int_0^t ky(\eta) e^{\int_\eta^t -(u + pz(\xi)) d\xi} d\eta, \\
 z(t) &= z(0)e^{\int_0^t (qv(\xi) - b) d\xi}.
 \end{aligned}$$

Positivity immediately follows from the above integral forms and initial condition (2.1).

For boundedness of the solution, we define

$$G(t) = qke^{-m\tau} x(t) + qky(t + \tau) + \frac{1}{2}qav(t + \tau) + \frac{1}{2}paz(t + \tau),$$

and  $\gamma = \min\{d, \frac{a}{2}, u, b\}$ . By positivity of the solution, it follows that

$$\begin{aligned}
 G'(t) &= qke^{-m\tau} \left( \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} \right) + qk \left( \frac{\beta e^{-m\tau} x(t)v(t)}{1 + \alpha v(t)} - ay(t + \tau) \right) \\
 &\quad + \frac{1}{2}qa(ky(t + \tau) - uv(t + \tau) - pz(t + \tau)v(t + \tau)) \\
 &\quad + \frac{1}{2}pa(qz(t + \tau)v(t + \tau) - bz(t + \tau))
 \end{aligned}$$

$$\begin{aligned}
 &= qk\lambda e^{-m\tau} - qke^{-m\tau} dx(t) - \frac{1}{2}qkay(t + \tau) \\
 &\quad - \frac{1}{2}qakuv(t + \tau) - \frac{1}{2}pabz(t + \tau) \\
 &< qk\lambda e^{-m\tau} - \gamma G(t).
 \end{aligned}$$

This implies that  $G(t)$  is bounded, and so are  $x(t)$ ,  $y(t)$ ,  $v(t)$  and  $z(t)$ . This completes the proof of the theorem. □

### 3 Equilibria and Global Asymptotically Stability Analysis

From system (1.1), we know that the un-infected steady state is  $E_0 = (x_0, 0, 0, 0) = (\frac{\lambda}{d}, 0, 0, 0)$ . The basic reproduction number is  $R_0 = \frac{k\lambda\beta e^{-m\tau}}{adu}$ . When  $R_0 > 1$ , there is only one un-immune infected steady state  $E_1 = (x_1, y_1, v_1, 0)$  defined by

$$x_1 = \frac{au}{k\beta e^{-m\tau}}(1 + \alpha v_1), \quad y_1 = \frac{u}{k}v_1, \quad v_1 = \frac{d}{\beta + d\alpha}(R_0 - 1).$$

The immune response reproductive ratio is  $R_1 = \frac{qk\lambda\beta e^{-m\tau}}{au(dq + \alpha bd + \beta b)}$ . We will know that if  $R_1 > 1$ , there is only one positive equilibrium point  $E_2 = (x_2, y_2, v_2, z_2)$ , where

$$\begin{aligned}
 x_2 &= \frac{q\lambda + b\lambda\alpha}{dq + bd\alpha + b\beta}, & y_2 &= \frac{b\lambda\beta e^{-m\tau}}{au(dq + bd\alpha + b\beta)}, \\
 v_2 &= \frac{b}{q}, & z_2 &= \frac{u}{p}(R_1 - 1).
 \end{aligned}$$

- Theorem 2** (i) *The un-infected steady state  $E_0$  is globally asymptotically stable, if  $R_0 < 1$ ;*  
 (ii) *The un-immune infected steady state  $E_1$  is globally asymptotically stable, if  $R_0 > 1, R_1 < 1$ ;*  
 (iii) *The immune infected steady state  $E_2$  is globally asymptotically stable, if  $R_1 > 1$ .*

*Proof* (i) Define a Lyapunov function  $V_{00}(t)$  as follows:

$$V_{00}(t) = x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0} + e^{m\tau} y(t) + \frac{a}{k} e^{m\tau} v(t) + \frac{ap}{kq} e^{m\tau} z(t)$$

where  $x_0 = \frac{\lambda}{d}$ .

Calculating the time derivative of  $V_{00}(t)$  along the positive solution of model (1.1), we obtain

$$\begin{aligned}
 V'_{00}(t) &= x'(t) - \frac{x_0}{x(t)} x'(t) + e^{m\tau} y'(t) + \frac{a}{k} e^{m\tau} v'(t) + \frac{ap}{kq} e^{m\tau} z'(t) \\
 &= \left(1 - \frac{x_0}{x(t)}\right) \left(\lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)}\right)
 \end{aligned}$$

$$\begin{aligned}
 & +e^{m\tau} \left( \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - ay(t) \right) \\
 & + \frac{a}{k} e^{m\tau} (ky(t) - uv(t) - pz(t)v(t)) + \frac{ap}{kq} e^{m\tau} (qz(t)v(t) - bz(t)) \\
 = & \left( 1 - \frac{x_0}{x(t)} \right) \left( dx_0 - dx(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} \right) \\
 & + e^{m\tau} \left( \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} - ay(t) \right) \\
 & + \frac{a}{k} e^{m\tau} (ky(t) - uv(t) - pz(t)v(t)) + \frac{ap}{kq} e^{m\tau} (qz(t)v(t) - bz(t)) \\
 = & -\frac{d}{x(t)} (x(t) - x_0)^2 - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} \\
 & + \frac{\beta x_0 v(t)}{1+\alpha v(t)} - \frac{au}{k} e^{m\tau} v(t) - \frac{apb}{kq} e^{m\tau} z(t).
 \end{aligned}$$

Define  $V_0 = V_{00} + \beta \int_{t-\tau}^t \frac{x(s)v(s)}{1+\alpha v(s)} ds$ ,

$$\begin{aligned}
 V'_0 = & -\frac{d}{x(t)} (x(t) - x_0)^2 - \frac{\beta x(t)v(t)}{1+\alpha v(t)} + \frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} + \frac{\beta x_0 v(t)}{1+\alpha v(t)} \\
 & - \frac{au}{k} e^{m\tau} v(t) - \frac{apb}{kq} e^{m\tau} z(t) + \beta \left[ \frac{x(t)v(t)}{1+\alpha v(t)} - \frac{x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} \right] \\
 = & -\frac{d}{x} (x(t) - x_0)^2 + \frac{\beta x_0 v(t)}{1+\alpha v(t)} - \frac{au}{k} e^{m\tau} v(t) - \frac{apb}{kq} e^{m\tau} z(t) \\
 \leq & -\frac{d}{x} (x(t) - x_0)^2 + \beta x_0 v(t) - \frac{au}{k} e^{m\tau} v(t) - \frac{apb}{kq} e^{m\tau} z(t) \\
 = & -\frac{d}{x} (x(t) - x_0)^2 + \frac{au}{k} e^{m\tau} (R_0 - 1)v(t) - \frac{apb}{kq} e^{m\tau} z(t).
 \end{aligned}$$

Since,  $R_0 < 1$ , it follows from LaSalle invariance principle [18, 19] that the uninfected steady state  $E_0$  is globally asymptotically stable, if  $R_0 < 1$ .

(ii) Define a Lyapunov functional  $V_{11}(t)$  as follows:

$$\begin{aligned}
 V_{11}(t) = & x(t) - x_1 - x_1 \ln \frac{x(t)}{x_1} + e^{m\tau} \left( y(t) - y_1 - y_1 \ln \frac{y(t)}{y_1} \right) \\
 & + \frac{a}{k} e^{m\tau} \left( v(t) - v_1 - v_1 \ln \frac{v(t)}{v_1} \right) + \frac{ap}{kq} e^{m\tau} z(t).
 \end{aligned}$$

Calculating the time derivative of  $V_{11}(t)$  along the positive solution of model (1.1), we obtain

$$\begin{aligned}
 V'_{11}(t) = & \left( 1 - \frac{x_1}{x} \right) x'(t) + e^{m\tau} \left( 1 - \frac{y_1}{y} \right) y'(t) \\
 & + \frac{a}{k} e^{m\tau} \left( 1 - \frac{v_1}{v} \right) v'(t) + \frac{ap}{kq} e^{m\tau} z'(t)
 \end{aligned}$$

$$\begin{aligned}
&= \left(1 - \frac{x_1}{x}(t)\right) \left(\lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)}\right) \\
&\quad + e^{m\tau} \left(1 - \frac{y_1}{y}(t)\right) \left(\frac{\beta e^{m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - ay(t)\right) \\
&\quad + \frac{a}{k} e^{m\tau} \left(1 - \frac{v_1}{v}(t)\right) (ky(t) - uv(t)) \\
&\quad - \frac{a}{k} e^{m\tau} \left(1 - \frac{v_1}{v}(t)\right) pz(t)v(t) + \frac{ap}{kq} e^{m\tau} (qz(t)v(t) - bz(t)).
\end{aligned}$$

Since  $E_1$  is an equilibrium point of (1.1), we have

$$\begin{cases} \lambda = dx_1 + \frac{\beta x_1 v_1}{1 + \alpha v_1}, \\ \frac{u}{k} = \frac{y_1}{v_1}, \\ ae^{m\tau} y_1 = \frac{\beta x_1 v_1}{1 + \alpha v_1}. \end{cases}$$

Therefore,

$$\begin{aligned}
V'_{11}(t) &= \left(1 - \frac{x_1}{x(t)}\right) (-d(x(t) - x_1)) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} + \frac{\beta x_1 v_1}{1 + \alpha v_1} \left(1 - \frac{x_1}{x}\right) \\
&\quad + \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} \\
&\quad - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{(1 + \alpha v_1)}{x_1 v_1} \frac{y_1}{y(t)} \frac{x(t-\tau)v(t-\tau)}{(1 + \alpha v(t-\tau))} \\
&\quad - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{v(t)}{v_1} - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{y(t)v_1}{y_1 v(t)} \\
&\quad + \frac{2\beta x_1 v_1}{1 + \alpha v_1} + \frac{ap}{k} e^{m\tau} z(t) \left(v_1 - \frac{b}{q}\right).
\end{aligned}$$

Define,

$$V_1(t) = V_{11}(t) + \beta \int_{t-\tau}^t \left[ \frac{x(s)v(s)}{1 + \alpha v(s)} - \frac{x_1 v_1}{1 + \alpha v_1} - \frac{x_1 v_1}{1 + \alpha v_1} \ln \frac{(1 + \alpha v_1)x(s)v(s)}{x_1 v_1 (1 + \alpha v(s))} \right] ds.$$

Therefore,

$$\begin{aligned}
V'_1(t) &= \left(1 - \frac{x_1}{x(t)}\right) (-d(x(t) - x_1)) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} \\
&\quad + \frac{\beta x_1 v_1}{1 + \alpha v_1} \left(1 - \frac{x_1}{x(t)}\right) + \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} \\
&\quad - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{(1 + \alpha v_1)}{x_1 v_1} \frac{y_1}{y(t)} \frac{x(t-\tau)v(t-\tau)}{(1 + \alpha v(t-\tau))} \\
&\quad - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{v(t)}{v_1} - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{y(t)v_1}{y_1 v(t)} \\
&\quad + \frac{2\beta x_1 v_1}{1 + \alpha v_1} + \frac{ap}{k} e^{m\tau} z(t) \left(v_1 - \frac{b}{q}\right)
\end{aligned}$$

$$\begin{aligned}
 & +\beta \left[ \frac{x(t)v(t)}{1+\alpha v(t)} - \frac{x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} + \frac{x_1 v_1}{1+\alpha v_1} \ln \frac{(1+\alpha v(t))x(t-\tau)v(t-\tau)}{x(t)v(t)(1+\alpha v(t-\tau))} \right] \\
 = & -\frac{d}{x}(x(t) - x_1)^2 - \frac{\beta x_1 v_1}{1 + \alpha v_1} \left[ \frac{x_1}{x(t)} - 1 - \ln \frac{x_1}{x(t)} \right] \\
 & - \frac{\beta x_1 v_1}{1 + \alpha v_1} \left[ \frac{(1 + \alpha v_1) y_1 x(t - \tau) v(t - \tau)}{x_1 v_1 y(t) (1 + \alpha v(t - \tau))} - 1 - \ln \frac{y_1 (1 + \alpha v_1) x(t - \tau) v(t - \tau)}{y(t) x_1 v_1 (1 + \alpha v(t - \tau))} \right] \\
 & - \frac{\alpha \beta x_1 v_1 (v(t) - v_1)^2}{v_1 (1 + \alpha v_1)^2 (1 + \alpha v(t))} \\
 & - \frac{\beta x_1 v_1}{1 + \alpha v_1} \left[ \frac{1 + \alpha v(t)}{1 + \alpha v_1} - 1 - \ln \frac{1 + \alpha v(t)}{1 + \alpha v_1} \right] - \frac{\beta x_1 v_1}{1 + \alpha v_1} \left[ \frac{v_1 y(t)}{y_1 v(t)} - 1 - \ln \frac{v_1 y(t)}{y_1 v(t)} \right] \\
 & + \frac{ap}{k} e^{m\tau} z(t) \left( v_1 - \frac{b}{q} \right).
 \end{aligned}$$

Since the function  $h(i) = 1 - i + \ln i$  ( $i > 0$ ),  $h'(i) = -1 + \frac{1}{i}$ ,  $h''(i) = -\frac{1}{i^2} < 0$ , so  $h(i) \leq 0$  and only  $i = 1$ ,  $h(i) = 0$ . It is clear that

$$R_1 < 1, \text{ so } v_1 - \frac{b}{q} < 0.$$

It follows from LaSalle invariance principle [18, 19] that the un-immune infected steady state  $E_1$  is globally asymptotically stable if  $R_0 > 1$ ,  $R_1 < 1$ . □

(iii) Define a Lyapunov functional  $V_{22}(t)$  as follows:

$$\begin{aligned}
 V_{22}(t) = & x - x_2 - \int_{x_2}^x \frac{ae^{m\tau} y_2}{\frac{\beta\tau v_2}{1+\alpha v_2}} d\tau + e^{m\tau} \left( y - y_2 - y_2 \ln \frac{y}{y_2} \right) \\
 & + \frac{a}{k} e^{m\tau} (1 + \alpha v_2) \left( v - v_2 - \int_{v_2}^v \frac{ae^{m\tau} y_2}{\frac{\beta x_2 \tau}{1+\alpha \tau}} d\tau \right) \\
 & + \frac{ap}{kq} e^{m\tau} \left( z - z_2 - z_2 \ln \frac{z}{z_2} \right).
 \end{aligned}$$

Calculating the time derivative of  $V_{22}(t)$  along the positive solution of model (1.1), we obtain

$$\begin{aligned}
 V'_{22}(t) = & x'(t) + e^{m\tau} y'(t) + \frac{a}{k} e^{m\tau} (1 + \alpha v_2) v'(t) + \frac{ap}{kq} e^{m\tau} z'(t) \\
 & - ae^{m\tau} y_2 \frac{1 + \alpha v_2}{\beta x(t) v_2} x'(t) - e^{m\tau} \frac{y_2}{y} (t) y'(t) \\
 & - \frac{a}{k} e^{m\tau} (1 + \alpha v_2) ae^{m\tau} y_2 \frac{1 + \alpha v(t)}{\beta x_2 v(t)} v'(t) - \frac{ap}{kq} e^{m\tau} \frac{z_2}{z} (t) z'(t) \\
 = & x'(t) + e^{m\tau} y'(t) + \frac{a}{k} e^{m\tau} v'(t) + \frac{ap}{kq} e^{m\tau} z'(t) - ae^{m\tau} y_2 \frac{1 + \alpha v_2}{\beta x(t) v_2} x'(t) \\
 & - e^{m\tau} \frac{y_2}{y} (t) y'(t) - \frac{a}{k} e^{m\tau} \frac{v_2}{v} (t) v'(t) - \frac{ap}{kq} e^{m\tau} \frac{z_2}{z} (t) z'(t)
 \end{aligned}$$

Since  $E_2$  is an equilibrium point of (1.1), we have

$$\begin{cases} \lambda = dx_2 + ae^{m\tau} y_2, \\ ky_2 = uv_2 + pz_2 v_2, \\ ae^{m\tau} y_2 = \frac{\beta x_2 v_2}{1 + \alpha v_2}. \end{cases}$$

Therefore,

$$\begin{aligned} V'_{22}(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} + \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - \frac{au}{k} e^{m\tau} v(t) - \frac{pab}{kq} e^{m\tau} z(t) \\ &\quad - ae^{m\tau} y_2 \frac{1 + \alpha v_2}{\beta x v_2} \left( \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} \right) \\ &\quad - \frac{y_2}{y(t)} e^{m\tau} \left( \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - ay(t) \right) \\ &\quad - \frac{a}{k} e^{m\tau} \frac{v_2}{v(t)} (ky(t) - uv(t) - pz(t)v(t)) - \frac{pa}{kq} e^{m\tau} \frac{z_2}{z(t)} (qz(t)v(t) - bz(t)) \\ &= dx_2 \left( 2 - \frac{x(t)}{x_2} - \frac{x_2}{x(t)} \right) + \frac{\beta x_2 v_2}{1 + \alpha v_2} - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} \\ &\quad + \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - \frac{au}{k} e^{m\tau} v(t) \\ &\quad - \frac{pab}{kq} e^{m\tau} z(t) - \frac{x_2}{x(t)} ae^{m\tau} y_2 + ae^{m\tau} y_2 \frac{v(t)}{v_2} \frac{1 + \alpha v_2}{1 + \alpha v(t)} \\ &\quad - \frac{y_2}{y(t)} e^{m\tau} \left( \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - ay(t) \right) \\ &\quad - \frac{a}{k} e^{m\tau} \frac{v_2}{v(t)} (ky(t) - uv(t) - pz(t)v(t)) - \frac{pa}{kq} e^{m\tau} \frac{z_2}{z(t)} (qz(t)v(t) - bz(t)) \\ &= dx_2 \left( 2 - \frac{x(t)}{x_2} - \frac{x_2}{x(t)} \right) + \frac{\beta x_2 v_2}{1 + \alpha v_2} \left( 1 - \frac{x_2}{x(t)} \right) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} \\ &\quad + \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - \frac{\beta y_2 x(t-\tau)v(t-\tau)}{y(t)(1 + \alpha v(t-\tau))} \\ &\quad + ae^{m\tau} y_2 + \frac{a}{k} e^{m\tau} \left( -uv(t) - kv_2 \frac{y(t)}{v(t)} + uv_2 \right) - \frac{pa}{k} e^{m\tau} z_2 v(t) + \frac{pa}{k} e^{m\tau} z_2 v_2 \\ &= dx_2 \left( 2 - \frac{x(t)}{x_2} - \frac{x_2}{x(t)} \right) + \frac{\beta x_2 v_2}{1 + \alpha v_2} \left( 1 - \frac{x_2}{x(t)} \right) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} \\ &\quad + \frac{\beta x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{(1 + \alpha v_2)}{x_2 v_2} \frac{y_2}{y(t)} \frac{x(t-\tau)v(t-\tau)}{(1 + \alpha v(t-\tau))} + \frac{2\beta x_2 v_2}{1 + \alpha v_2} \\ &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{v(t)}{v_2} - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{y(t)v_2}{y_2 v(t)}. \end{aligned}$$

Define,

$$V_2(t) = V_{22}(t) + \beta \int_{t-\tau}^t \left[ \frac{x(s)v(s)}{1 + \alpha v(s)} - \frac{x_2 v_2}{1 + \alpha v_2} - \frac{x_2 v_2}{1 + \alpha v_2} \ln \frac{(1 + \alpha v_2)x(s)v(s)}{x_2 v_2 (1 + \alpha v(s))} \right] ds.$$



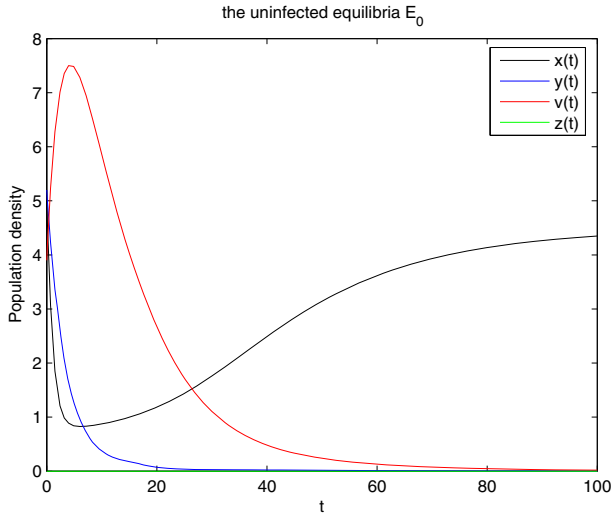
Therefore,

$$\begin{aligned}
 V_2'(t) &= \left(1 - \frac{x_2}{x(t)}\right) (-d(x(t) - x_2)) - \frac{\beta x(t)v(t)}{1 + \alpha v(t)} + \frac{\beta x_2 v_2}{1 + \alpha v_2} \left(1 - \frac{x_2}{x(t)}\right) \\
 &\quad + \frac{\beta x(t - \tau)v(t - \tau)}{1 + \alpha v(t - \tau)} \\
 &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{y_2(1 + \alpha v_2)}{x_2 v_2} \frac{\beta x(t - \tau)v(t - \tau)}{y(t)(1 + \alpha v(t - \tau))} \\
 &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{v(t)}{v_2} - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{y(t)v_2}{y_2 v(t)} \\
 &\quad + \frac{2\beta x_2 v_2}{1 + \alpha v_2} + \frac{ap}{k} e^{m\tau} z(t) \left(v_2 - \frac{b}{q}\right) \\
 &\quad \beta \left[ \frac{x(t)v(t)}{1 + \alpha v(t)} - \frac{x(t - \tau)v(t - \tau)}{1 + \alpha v(t - \tau)} - \frac{x_1 v_1}{1 + \alpha v_1} \ln \frac{(1 + \alpha v(t))x(t - \tau)v(t - \tau)}{x(t)v(t)(1 + \alpha v(t - \tau))} \right] \\
 &= -\frac{d}{x(t)} (x(t) - x_2)^2 \\
 &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \left[ \frac{x_2}{x(t)} - 1 - \ln \frac{x_2}{x(t)} \right] \\
 &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \left[ \frac{y_2(1 + \alpha v_2)x(t - \tau)v(t - \tau)}{x_2 v_2 y(t)(1 + \alpha v(t - \tau))} \right. \\
 &\quad \left. - 1 - \ln \frac{y_2(1 + \alpha v_2)x(t - \tau)v(t - \tau)}{x_2 v_2 y(t)(1 + \alpha v(t - \tau))} \right] \\
 &\quad - \frac{\alpha \beta x_2 v_2 (v(t) - v_2)^2}{v_2(1 + \alpha v_2)^2(1 + \alpha v(t))} \\
 &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \left[ \frac{1 + \alpha v(t)}{1 + \alpha v_2} - 1 - \ln \frac{1 + \alpha v(t)}{1 + \alpha v_2} \right] \\
 &\quad - \frac{\beta x_2 v_2}{1 + \alpha v_2} \left[ \frac{v_2 y(t)}{y_2 v(t)} - 1 - \ln \frac{v_2 y(t)}{y_2 v(t)} \right].
 \end{aligned}$$

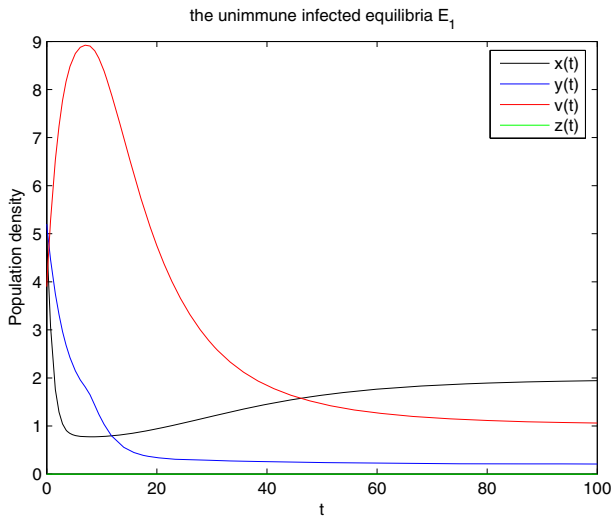
It follows from LaSalle invariance principle [18, 19] that the immune infected steady state  $E_2$  is globally asymptotically stable, if  $R_1 > 1$ . This completes the proof of the theorem.

### 4 Numerical Simulations

In this section, some numerical simulations of system (1.1) are presented for supporting our analytic results. Based on biological meanings of virus dynamics model from papers [5, 8, 10, 11, 16], we have estimated the values of our model parameters as follows:  $\lambda = 0.9, d = 0.2, \beta = 0.3, \alpha = 0.2, a = 0.3, k = 0.5, u = 0.1, p = 0.05, q = 0.2, b = 0.3, m = 0.3, \tau = 15$ . It is obvious that the parameters satisfy (i) of Theorem 2. Then  $E_0$  is globally asymptotically stable (see Fig. 1).



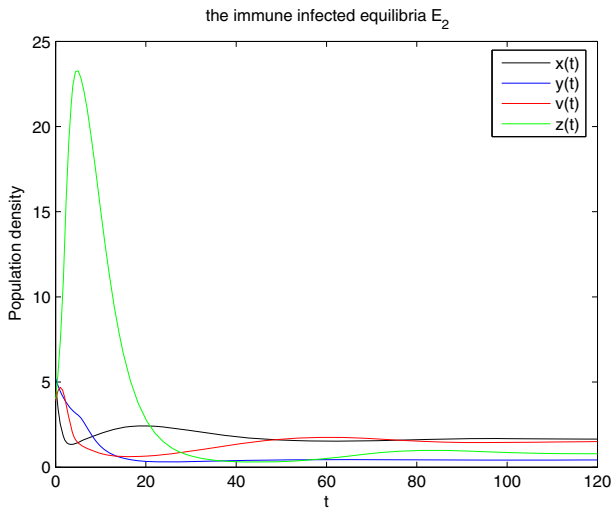
**Fig. 1** When  $\tau = 15$ ,  $R_0 < 1$ , the un-infection steady state  $E_0$  is globally asymptotically stable



**Fig. 2** When  $\tau = 7$ ,  $R_0 > 1$ ,  $R_1 < 1$ , the un-immune infected equilibrium  $E_1$  is globally asymptotically stable

Secondly, we assume that  $\lambda = 0.9, d = 0.2, \beta = 0.3, \alpha = 0.2, a = 0.3, k = 0.5, u = 0.1, p = 0.05, q = 0.2, b = 0.3, m = 0.3, \tau = 7$ . It is obvious that the parameters satisfy (ii) of Theorem 2. Then  $E_1$  is globally asymptotically stable (see Fig. 2).

Finally, we assume that  $\lambda = 0.9, d = 0.2, \beta = 0.3, \alpha = 0.2, a = 0.3, k = 0.5, u = 0.1, p = 0.05, q = 0.2, b = 0.3, m = 0.3, \tau = 5$ . It is obvious that the



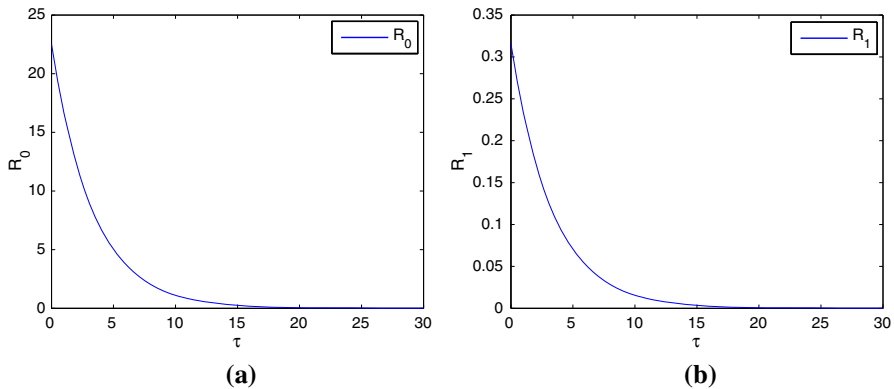
**Fig. 3** When  $\tau = 5$ ,  $R_1 > 1$ , the immune infected equilibrium  $E_2$  is globally asymptotically stable

parameters satisfy (iii) of Theorem 2. Then  $E_2$  is globally asymptotically stable (see Fig. 3).

### 5 Discussion

In this paper, we consider a delay mathematical model with saturation infection and humoral immunity. The global stability of the three equilibria of system (1.1) have been completely established by using suitable Lyapunov functionals and the Lasalle invariant principle. By the (i) of Theorem 2, we see that if  $R_0 < 1$ , the un-infection steady state  $E_0$  is globally asymptotically stable, in this case, the virus is cleared up. By the (ii) of Theorem 2, we see that if  $R_0 > 1$ ,  $R_1 < 1$ , the un-immune infected equilibrium  $E_1$  is globally asymptotically stable. By the (iii) of Theorem 2, we see that if  $R_1 > 1$ , the immune infected equilibrium  $E_2$  is globally asymptotically stable. We know that the global dynamical properties of the model (1.1) depend on the basic reproductive ratio.

The reproductive ratio plays a crucial role for virus infection dynamics. Actually, in model (1.1), the basic reproductive ratio  $R_0$  is a decreasing function on time delay  $\tau$  (see Fig. 4a), the  $R_1$  is also decreasing function on time delay  $\tau$  (see Fig. 4b). When all other parameters are fixed and delay  $\tau$  is sufficiently large,  $R_0$  becomes to be less than one, which makes the un-infection steady state  $E_0$  globally asymptotically stable. The humoral immune does help reduce the virus load and increase the healthy cell population. This can be seen by comparing the virus load components and the healthy cell population components in the un-immune infected equilibrium  $E_1 = (x_1, y_1, v_1, 0)$  and the immune infected equilibrium  $E_2 = (x_2, y_2, v_2, z_2)$ . when  $R_1 > 1$ , simple calculations show that:



**Fig. 4** **a**  $R_0$  is a decreasing function on time delay  $\tau$ , **b**  $R_1$  is a decreasing function on time delay  $\tau$

$$v_1 = \frac{d}{\beta + d\alpha} \left( \frac{\beta\lambda N}{d\mu} - 1 \right) > v_2 = \frac{b}{q},$$

and

$$x_1 = \frac{\mu + \alpha\beta N}{N(\beta + d\alpha)} < x_2 = \frac{q\lambda + b\lambda\alpha}{dq + bd\alpha + b\beta}.$$

By biological meanings, intracellular delay plays a positive role in virus infection process in order to eliminate virus. Sufficiently large intracellular delay makes the virus development slower and the virus has been controlled and disappeared. So this gives us some suggestions on new drugs to prolong the time of infected cells producing virus and to control the load of virus.

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