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Complete global dynamics of a delayed viral infection model with lytic and nonlytic effectors

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Abstract. We perform the global stability analysis for a viral infection model with two types of immune response. The model is formulated as a system of delay differential equations. We determine the global dynamics in terms of the basic reproduction number using Lyapunov functionals. Our results on the global stability of the infected equilibrium answer the conjecture offered in the paper [K. Wang, W. Wang and X. Liu, *Comput. Math. Appl.* **51** (2006) 1593-1610].

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1 Introduction

Mathematical models have a role to develop our better understanding of a virus dynamics in vivo. Several mathematical models have been proposed in order to expect the dynamics of virus population since a basic viral infection model was formulated by Nowak and Bangham [14]. Those models provide advances in our understanding of HIV-1 (human immunodeficiency virus 1) and other viruses, such as HBV (hepatitis B virus) and HCV (hepatitis C virus) (see [6,10,12] and the references therein).

Wodarz *et al.* [18] proposed a mathematical model describing interaction between viral dynamics and the immune response. The authors analyzed equilibrium condition of the mathematical model in order to investigate which type of immune response is required against different types of viral infection. Wang *et al.* [16] mathematically investigated the dynamics of the model. They proved that the infection free equilibrium is globally asymptotically stable if the basic reproduction number is less than or equal to one and that the infected equilibrium is locally asymptotically stable if the basic reproduction number is greater than one. By using a Lyapunov function they obtained a sufficient condition for the global stability of the infected equilibrium. In particular, they proved that when there is no nonlytic effector the infected equilibrium is globally asymptotically stable, see Corollary 3.2 in [16]. Their numerical studies indicated that the infected equilibrium seems to be globally asymptotically stable, even if the nonlytic component is available. Thus they offered a conjecture on the global asymptotic stability of the infected equilibrium.

In virus dynamics it has been reported that new virus particles are not instantaneously produced after the initial infection, see [6, 10, 12, 13]. This motivates us to employ mathematical models by delay differential equations. The estimated values of kinetic parameters are usually changed by these delay differential equations, see [6,12]. Mathematical analysis for the models may be helpful to obtain an integrated view for the virus dynamics.

In this paper we formulate the viral infection model with lytic and nonlytic responses by a system of delay differential equations, based on the mathematical model in Wodarz *et al.* [18]. Via constructing Lyapunov functionals we prove that the global dynamics can be completely determined by the basic reproduction number.

The organization of this paper is as follows. In Section 2 we introduce the mathematical model derived in Wodarz *et al.* [18], which is a system of ordinary differential equations. Assuming that virus particles are not produced instantaneously,

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we formulate a system of delay differential equations. We prove existence of positive solutions under suitable initial conditions and existence of equilibria. In Section 3 we analyze dynamics of the model. We prove that the infection free equilibrium is globally asymptotically stable if the basic reproduction number is less than or equal to one and that the infected equilibrium is globally asymptotically stable if the basic reproduction number is greater than one. Furthermore we provide a proof for the permanence of the infected cell population when the nonlytic immune response is available. In Section 5 we discuss our results.

2 Delayed viral infection dynamics with lytic and nonlytic immune effectors

Wodarz *et al.* [18] proposed the following mathematical model for viral infection dynamics with lytic and nonlytic immune responses:

$$\begin{cases} \dfrac{dx(t)}{dt} = \lambda - dx(t) - \dfrac{\beta x(t)y(t)}{1+qz(t)}, \\ \dfrac{dy(t)}{dt} = \dfrac{\beta x(t)y(t)}{1+qz(t)} - ay(t) - py(t)z(t), \\ \dfrac{dz(t)}{dt} = cy(t) - bz(t). \end{cases} \tag{2.1}$$

Here $x(t)$, $y(t)$ and $z(t)$ denote the number of susceptible host cells, the number of infected cells, which produce virus particles, and the number of immune cells at time t, respectively. The number of produced susceptible cells per unit of time and the mortality rate of the susceptible cells is given by λ and d, respectively. Antiviral immune effector mechanism is divided into lytic and nonlytic. Lytic components kill infected cells whereas the nonlytic components inhibit viral replication through soluble mediators. The number of produced infected cells per unit of time at time t is given by $\beta x(t)y(t)/(1+qz(t))$, where viral replication is inhibited by the nonlytic antiviral activity, where q take into account the strength of the nonlytic component. Infected cells are killed by the lytic immune response at rate $pz(t)$, where p denotes the strength of the lytic component. The mortality rate of infected cells is a. The number of produced immune cells per unit of time and the mortality rate of immune cells are given by $cy(t)$ and b, respectively. We assume that every parameter is positive except p and q and that p and q are nonnegative constants.

We assume that virus production occurs after the virus entry by a constant delay τ. Then the number of produced infected cells per unit of time at time t is given as

$$\frac{\beta e^{-\delta\tau} x(t-\tau)y(t-\tau)}{1+qz(t-\tau)},$$

where $e^{-\delta\tau}$ is the survival probability of infected but not yet virus-producing cells. We obtain the following delayed viral infection model:

$$\begin{cases} \dfrac{dx(t)}{dt} = \lambda - dx(t) - \dfrac{\beta x(t)y(t)}{1+qz(t)}, \\ \dfrac{dy(t)}{dt} = \dfrac{\beta e^{-\delta\tau} x(t-\tau)y(t-\tau)}{1+qz(t-\tau)} - ay(t) - py(t)z(t), \\ \dfrac{dz(t)}{dt} = cy(t) - bz(t). \end{cases} \tag{2.2}$$

2.1 Existence and uniqueness of positive solution

For the system (2.2) we set a suitable phase space. We denote by $C = C([-\tau, 0], \mathbb{R}^3)$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^3$ equipped with the sup-norm. The nonnegative cone of C is defined as $C_+ = C([-\tau, 0], \mathbb{R}^3_+)$. The initial condition for (2.2) is given by $(x, y, z)(\theta) = \phi(\theta)$ for $\theta \in [-\tau, 0]$, where $\phi \in C_+$.

Lemma 2.1. *System (2.2) generates a unique solution defined on $t \in (0, \infty)$. For $\phi \in C_+$ one has $x(t) > 0$, $y(t) \geq 0$ and $z(t) \geq 0$ for $t \in (0, \infty)$. If we assume further that either $\phi_2(0) > 0$ or there exists $\theta \in [-\tau, 0)$ such that $\phi_1(\theta)\phi_2(\theta) > 0$ then $y(t) > 0$ and $z(t) > 0$ for $t \in [\tau, \infty)$.*

Proof. Since the right hand side of system (2.2) is locally Lipschitzian on C_+, there exists $\alpha > 0$ such that system (2.2) has a unique local solution on $(0, \alpha)$, see Theorem 2.3, Chapter 2 in [5]. We prove that $x(t) > 0$, $y(t) \geq 0$ and $z(t) \geq 0$ for $t \in (0, \alpha)$. It is straightforward to show that $x(t) > 0$ for all $t \in (0, \alpha)$, because $\frac{dx(t)}{dt} = \lambda > 0$ if $x(t) = 0$. Consider the case $\alpha \leq \tau$. Integrating the second equation of system (2.2) from 0 to t, we get

$$y(t) = \phi_2(0) e^{-\int_0^t a + pz(s)ds} + \beta e^{-\delta\tau} \int_0^t \frac{\phi_1(\theta-\tau)\phi_2(\theta-\tau)}{1+q\phi_3(\theta-\tau)} e^{-\int_\theta^t a+pz(s)ds} d\theta, \tag{2.3}$$

which yields $y(t) \geq 0$ for $t \in (0, \alpha)$. Next, integrating the third equation of system (2.2) from 0 to t, we obtain

$$z(t) = \phi_3(0)e^{-bt} + \int_0^t cy(\theta)e^{-b(t-\theta)}d\theta, \tag{2.4}$$

which yields $z(t) \geq 0$ for $t \in (0, \alpha)$. For the case $\alpha > \tau$, one can obtain the nonnegativity by the method of steps with (2.3) and (2.4). Thus $x(t) > 0$, $y(t) \geq 0$ and $z(t) \geq 0$ for all $t \in (0, \alpha)$. Now we show the global existence of the solution, i.e., $\alpha = +\infty$. One has $x(t) \leq \max\left\{\phi_1(0), \frac{\lambda}{d}\right\}$ for $t \in (0, \alpha)$. Formulas of (2.3) and (2.4) imply boundedness of y and z for $t \leq \tau$. For $t > \tau$ we define

$$N(t) := x(t-\tau) + e^{\delta\tau}y(t) + \frac{ae^{\delta\tau}}{2c}z(t).$$

Then we get

$$\begin{aligned}\frac{d}{dt}N(t) =& \lambda - dx(t-\tau) - \frac{ae^{\delta\tau}}{2}y(t) - py(t)z(t) - \frac{ae^{\delta\tau}}{2c}bz(t)\\ \leq& \lambda - \min\left\{d, \frac{a}{2}, b\right\}N(t).\end{aligned}$$

This implies that the solution is bounded on $(0, \alpha)$. Therefore, we can take $\alpha = +\infty$ by continuation of the solution, see Chapter 2 in [5]. Finally, again using the formulas of (2.3) and (2.4), strict positivity of y and z can be shown. □

2.2 Existence of equilibria

System (2.2) always has an infection free equilibrium given as $\left(\frac{\lambda}{d}, 0, 0\right)$. To show the existence of an infected equilibrium we define the basic reproduction number as

$$R_0 := \frac{\lambda\beta e^{-\delta\tau}}{da}. \tag{2.5}$$

The basic reproduction number denotes the expected number of the infected cells produced by one infected cell in the expected life-time in the initial infection. We introduce the following result.

Theorem 2.1. *Let us assume that $R_0 > 1$ holds. Then (2.2) admits a unique infected equilibrium, where every component is strictly positive.*

Proof. We assume that there exists an equilibrium. We denote it by (x, y, z). Then the third equation of (2.2) implies

$$y = \frac{b}{c}z. \tag{2.6}$$

The first equation of (2.2) and (2.6) give

$$x = \lambda\left(d + \frac{\beta\frac{b}{c}z}{1+qz}\right)^{-1}. \tag{2.7}$$

We define

$$H(z) := \frac{\beta e^{-\delta\tau}\lambda}{d(1+qz) + \beta\frac{b}{c}z} - a - pz \text{ for } z > 0.$$

From the second equation of (2.2), we consider the existence of positive roots of $H(z) = 0$. It is straightforward to see that H is a strictly monotone decreasing function with respect to z. Since we have

$$\lim_{z\to+0} H(z) = \beta e^{-\delta\tau}\frac{\lambda}{d} - a = a\left(R_0 - 1\right) > 0$$

there exists a unique positive root of $H(z)$, which is the third component of the infected equilibrium. Then the first and second components are given as (2.7) and (2.6), respectively. □

3 Global dynamics analysis

In this section we analyze global dynamics of (2.2). We divide the section into two parts for the case, $q = 0$, i.e., no nonlytic immune response, and for the case $q > 0$, i.e., nonlytic immune response is available, while we always assume $p \in [0, \infty)$. To analyze global stability of equilibria we construct Lyapunov functionals. For Lyapunov functionals, we define a function

$$g(x) := x - 1 - \ln x \tag{3.1}$$

defined on $(0, \infty)$. One can see that $x = 1$ is a strict global minimum for $g(x)$ and $g(1) = 0$ holds. In the proofs we use the notation $x_t(\theta) = x(t+\theta)$ for $\theta \in [\tau, 0]$ as usual in the theory of functional differential equations, see e.g [5].

In the following, we restrict our attention to the positive solution. Thus we can redefine the initial condition as $(x, y, z)(\theta) = \phi(\theta)$ with $\phi_i(\theta) > 0$ for $i \in \{1, 2, 3\}$ and $\theta \in [-\tau, 0]$.

3.1 Viral dynamics without nonlytic immune response

First we analyze global dynamics of (2.2) for a special case. We assume that there is no nonlytic immune effector, i.e., $q = 0$. We provide a threshold result in terms of the basic reproduction number.

Theorem 3.1. *Let us assume that $R_0 \leq 1$ holds. Then the infection free equilibrium of (2.2) is globally asymptotically stable. If $R_0 > 1$ then the infected equilibrium is globally asymptotically stable.*

Proof. We define

$$G := \{\varphi \in C_+ | \varphi_i(\theta) > 0,\ i \in \{1,2,3\},\ \theta \in [-\tau, 0]\}.$$

First, we assume $R_0 \leq 1$. We denote $\frac{\lambda}{d}$ by x_0. For $\varphi \in G$ we define

$$V(\varphi) := x_0 g\left(\frac{\varphi_1(0)}{x_0}\right) + e^{\delta\tau}\varphi_2(0) + \beta V_-(\varphi) + \frac{pe^{\delta\tau}}{c}\frac{1}{2}(\varphi_3(0))^2, \tag{3.2}$$

where

$$V_-(\varphi) := \int_{-\tau}^{0} \varphi_1(\theta)\varphi_2(\theta)d\theta.$$

We show that

$$\frac{d}{dt}V(x_t, y_t, z_t) \leq 0, \tag{3.3}$$

where (x_t, y_t, z_t) is a solution of (2.2). Since it holds $\lambda = dx_0$, we calculate

$$\begin{aligned}
\frac{d}{dt}g\left(\frac{x(t)}{x_0}\right) =& \frac{1}{x_0}\left(1 - \frac{x_0}{x(t)}\right)(dx_0 - dx(t) - \beta x(t)y(t)) \\
=& \left(1 - \frac{x_0}{x(t)}\right)\left\{d\left(1 - \frac{x(t)}{x_0}\right) - \beta\frac{x(t)}{x_0}y(t)\right\} \\
=& -\frac{d}{x_0 x(t)}(x(t) - x_0)^2 - \beta\frac{x(t)}{x_0}y(t) + \beta y(t).
\end{aligned} \tag{3.4}$$

We calculate

$$\frac{d}{dt}V_-(x_t, y_t, z_t) = x(t)y(t) - x(t-\tau)y(t-\tau) \tag{3.5}$$

and

$$\begin{aligned}
\frac{d}{dt}\frac{1}{2}(z(t))^2 =& z(t)(cy(t) - bz(t)) \\
=& cz(t)y(t) - b(z(t))^2.
\end{aligned} \tag{3.6}$$

Combining (3.4), (3.5) and (3.6), we obtain

$$\begin{aligned}
\frac{d}{dt}V(x_t, y_t, z_t) =& -\frac{d}{x(t)}(x(t) - x_0)^2 - \beta x(t)y(t) + \beta x_0 y(t) \\
&+ e^{\delta\tau}\left(\beta \mathrm{e}^{-\delta\tau}x(t-\tau)y(t-\tau) - ay(t) - py(t)z(t)\right) \\
&+ \beta\left(x(t)y(t) - x(t-\tau)y(t-\tau)\right) + \frac{pe^{\delta\tau}}{c}\left\{cz(t)y(t) - b(z(t))^2\right\} \\
=& -\frac{d}{x(t)}(x(t) - x_0)^2 + \left(\beta x_0 - ae^{\delta\tau}\right)y(t) - \frac{bpe^{\delta\tau}}{c}(z(t))^2.
\end{aligned} \tag{3.7}$$

Since we have that $R_0 \leq 1$, it follows that $\beta x_0 - ae^{\delta\tau} \leq 0$. Thus, from (3.7), we obtain (3.3). We define a set

$$\overline{G} := \{\varphi \in G | V(\varphi) \leq V(\phi)\},$$

where $\phi = (x_0, y_0, z_0)$. One can see that $\overline{G}$ is closed and positively invariant. Thus the closure of $\overline{G}$ is itself and $\overline{G}$ contains (x_t, y_t, z_t) for all $t > 0$. Since V is continuous on $\overline{G}$, V is a Lyapunov functional on G (see Chapter 5.3 in [5]). We define the set

$$E := \{\varphi \in \overline{G} | \dot{V}_{(2.2)}(\varphi) = 0\}.$$

Then we get

$$E = \left\{\varphi \in \overline{G} | \varphi_1(0) = x_0,\ \varphi_3(0) = 0\right\}.$$

Let M be the largest subset in E that is invariant with respect to (2.2). By LaSalle's invariant principle, the solution tends to M, see Theorem 3.2, Chapter 5.3 in [5]. We show that M consists only of the infection free equilibrium. From the invariance of M, one has $(x_t, y_t, z_t)(\phi) \in M \subset E$ for $t > 0$. Then it follows $x_t = \hat{x}_0$ and $z_t = \hat{0}$, where $\hat{}$ denotes an inclusion $\mathbb{R} \to C$. From the first equation of system (2.2), we obtain $y_t = \hat{0}$. Thus, M consists only of the infection free equilibrium. Hence, every solution tends to the infection free equilibrium. By applying Theorem 2.1, Chapter 5.3 in [5] one can show that the infection free equilibrium is uniformly stable.

Next we assume $R_0 > 1$. We denote the infected equilibrium by (x^*, y^*, z^*). For $\varphi \in G$ we define a functional as

$$U(\varphi) = x^* g\left(\frac{\varphi_1(0)}{x^*}\right) + y^* e^{\delta\tau} g\left(\frac{\varphi_2(0)}{y^*}\right) + \beta x^* y^* U_-(\varphi) + \frac{p e^{\delta\tau}}{c} U_+(\varphi_3(0)), \tag{3.8}$$

where

$$U_-(\varphi) = \int_{-\tau}^{0} g\left(\frac{\varphi_1(\theta)}{x^*}\frac{\varphi_2(\theta)}{y^*}\right) d\theta \text{ and } U_+(\varphi_3(0)) = \frac{1}{2}\left(\varphi_3(0) - z^*\right)^2.$$

We now show that

$$\frac{d}{dt} U(x_t, y_t, z_t) \leq 0. \tag{3.9}$$

In the following we drop $*$ from the notation: x^*, y^* and z^*. Since one has

$$\lambda = dx + \beta xy$$

from the equilibrium condition, we calculate that

$$\begin{aligned}
\frac{d}{dt} g\left(\frac{x(t)}{x}\right) =& \frac{1}{x}\left(1 - \frac{x}{x(t)}\right)\left(\lambda - dx(t) - \beta x(t) y(t)\right) \\
=& \left(1 - \frac{x}{x(t)}\right)\left\{d\left(1 - \frac{x(t)}{x}\right) + \beta y\left(1 - \frac{x(t)}{x}\frac{y(t)}{y}\right)\right\} \\
=& -\frac{d}{x x(t)}\left(x(t) - x\right)^2 + \beta y\left(1 - \frac{x(t)}{x}\frac{y(t)}{y} - \frac{x}{x(t)} + \frac{y(t)}{y}\right).
\end{aligned} \tag{3.10}$$

We secondly calculate that

$$\begin{aligned}
\frac{d}{dt} g\left(\frac{y(t)}{y}\right) &= \frac{1}{y}\left(1 - \frac{y}{y(t)}\right)\left(\beta e^{-\delta\tau} x(t-\tau) y(t-\tau) - a y(t) - p y(t) z(t)\right) \\
&= \left(\frac{y(t)}{y} - 1\right)\left(\beta e^{-\delta\tau} x \frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)} - a - p z(t)\right).
\end{aligned}$$

Substituting $a = \beta e^{-\delta\tau} x - pz$ gives

$$\begin{aligned}
\frac{d}{dt} g\left(\frac{y(t)}{y}\right) =& \beta e^{-\delta\tau} x\left(\frac{y(t)}{y} - 1\right)\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)} - 1\right) - p\left(\frac{y(t)}{y} - 1\right)\left(z(t) - z\right) \\
=& \beta e^{-\delta\tau} x\left(\frac{x(t-\tau)y(t-\tau)}{xy} - \frac{y(t)}{y} - \frac{x(t-\tau)y(t-\tau)}{xy(t)} + 1\right) - pz\left(\frac{y(t)}{y} - 1\right)\left(\frac{z(t)}{z} - 1\right).
\end{aligned} \tag{3.11}$$

We calculate

$$\frac{d}{dt} U_-(x_t, y_t, z_t) = g\left(\frac{x(t)}{x}\frac{y(t)}{y}\right) - g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\right) \tag{3.12}$$

and get

$$\begin{aligned}
\frac{d}{dt} U_+(z(t)) &= \left(z(t) - z\right)\left(c y(t) - b z(t)\right) \\
&= \left(z(t) - z\right)\left\{c\left(y(t) - y\right) - b\left(z(t) - z\right)\right\} \\
&= cyz\left(\frac{z(t)}{z} - 1\right)\left(\frac{y(t)}{y} - 1\right) - bz^2\left(\frac{z(t)}{z} - 1\right)^2.
\end{aligned} \tag{3.13}$$

Combining (3.10), (3.11), (3.12) and (3.13), we obtain

$$\begin{aligned}
\frac{d}{dt}U(x_t,y_t,z_t) =& -\frac{d}{x(t)}\left(x(t)-x\right)^2+\beta xy\left[\left(1-\frac{x(t)}{x}\frac{y(t)}{y}-\frac{x}{x(t)}\right)\right.\\
&+\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}-\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\right)+1\\
&\left.+\left\{g\left(\frac{x(t)}{x}\frac{y(t)}{y}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\right)\right\}\right]-\frac{pbe^{\delta\tau}}{c}z^2\left(\frac{z(t)}{z}-1\right)^2\\
=& -\frac{d}{x(t)}\left(x(t)-x\right)^2+\beta xy\left\{-g\left(\frac{x(t)}{x}\frac{y(t)}{y}\right)-g\left(\frac{x}{x(t)}\right)\right.\\
&+g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\right)\\
&\left.+g\left(\frac{x(t)}{x}\frac{y(t)}{y}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\right)\right\}-\frac{pbe^{\delta\tau}}{c}z^2\left(\frac{z(t)}{z}-1\right)^2\\
=& -\frac{d}{x(t)}\left(x(t)-x\right)^2+\beta xy\left\{-g\left(\frac{x}{x(t)}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\right)\right\}-\frac{pbe^{\delta\tau}}{c}z^2\left(\frac{z(t)}{z}-1\right)^2. \qquad (3.14)
\end{aligned}$$

Hence we get (3.9). We define a set

$$\overline{G}:=\{\varphi\in G|U(\varphi)\le U(\phi)\}.$$

One can see that $\overline{G}$ is closed and positively invariant. Thus the closure of $\overline{G}$ is itself and $\overline{G}$ contains (x_t,y_t,z_t) for all $t>0$. Since U is continuous on $\overline{G}$, U is a Lyapunov functional on G. We define the set

$$E=\left\{\varphi\in\overline{G}|\dot{U}_{(2.2)}(\varphi)=0\right\}.$$

We get

$$E=\left\{\varphi\in\overline{G}\Big|\varphi_1(0)=x,\ \varphi_3(0)=z,\ \frac{\varphi_1(-\tau)\varphi_2(-\tau)}{x\varphi_2(0)}=1\right\}.$$

Let M be the largest subset in E that is invariant with respect to (2.2). Then, by LaSalle's invariant principle, the solution tends to M. As in the case $R_0\le 1$ one can prove that M consists only of the infected equilibrium. Thus every solution tends to the infected equilibrium. By applying Theorem 2.1, Chapter 5.3 in [5], the infected equilibrium is uniformly stable. □

3.2 Viral dynamics with nonlytic immune response

We analyze the global dynamics of (2.2) with $q>0$. It is convenient to transform a variable as

$$u(t):=1+qz(t).$$

Then we obtain the following system:

$$\begin{cases}
\dfrac{dx(t)}{dt}=\lambda-dx(t)-\dfrac{\beta x(t)y(t)}{u(t)},\\
\dfrac{dy(t)}{dt}=\dfrac{\beta e^{-\delta\tau}x(t-\tau)y(t-\tau)}{u(t-\tau)}-\left(h+ru(t)\right)y(t),\\
\dfrac{du(t)}{dt}=sy(t)-bu(t)+b,
\end{cases} \qquad (3.15)$$

where

$$h:=a-\frac{p}{q},\ r:=\frac{p}{q}\text{ and }s:=qc.$$

It is a direct consequence from Theorem 2.1 that the infection free equilibrium $(\frac{\lambda}{d},0,1)$ always exists whereas the infected equilibrium exists if $R_0>1$.

First we prove that the infection free equilibrium is globally asymptotically stable if $R_0\le 1$.

Theorem 3.2. *Let us assume that $R_0\le 1$ holds. Then the infection free equilibrium of (3.15) is globally asymptotically stable.*

Proof. We define the set as

$$G := \{\varphi \in C_+ | \varphi_i(\theta) > 0,\ i \in \{1,2\},\ \varphi_3(\theta) > 1,\ \theta \in [-\tau, 0]\}. \tag{3.16}$$

For $\varphi \in G$ we define

$$V(\varphi) := x_0 g\left(\frac{\varphi_1(0)}{x_0}\right) + e^{\delta\tau}\varphi_2(0) + \frac{\beta x_0}{s} g\left(\varphi_3(0)\right) + \beta V_-(\varphi) + \frac{re^{\delta\tau}}{s} V_+(\varphi_3(0)), \tag{3.17}$$

where

$$V_-(\varphi) := \int_{-\tau}^{0} \frac{\varphi_1(\theta)\varphi_2(\theta)}{\varphi_3(\theta)} d\theta \text{ and } V_+(u) := \frac{1}{2}(u-1)^2.$$

We show that

$$\frac{d}{dt} V(x_t, y_t, u_t) \leq 0. \tag{3.18}$$

Since it holds $\lambda = dx_0$, we calculate that

$$\begin{aligned}
\frac{d}{dt} g\left(\frac{x(t)}{x_0}\right) =& \frac{1}{x_0}\left(1 - \frac{x_0}{x(t)}\right)\left(dx_0 - dx(t) - \frac{\beta x(t) y(t)}{u(t)}\right) \\
=& \left(1 - \frac{x_0}{x(t)}\right)\left\{d\left(1 - \frac{x(t)}{x_0}\right) - \frac{\beta}{x_0}\frac{x(t)y(t)}{u(t)}\right\} \\
=& -\frac{d}{x_0 x(t)}\left(x(t) - x_0\right)^2 - \beta\frac{x(t)}{x_0}\frac{y(t)}{u(t)} + \beta\frac{y(t)}{u(t)}.
\end{aligned} \tag{3.19}$$

We compute that

$$\begin{aligned}
\frac{d}{dt} g\left(u(t)\right) =& \left(1 - \frac{1}{u(t)}\right)\left(sy(t) - bu(t) + b\right) \\
=& sy(t) - s\frac{y(t)}{u(t)} - b\frac{(u(t)-1)^2}{u(t)}.
\end{aligned} \tag{3.20}$$

Finally, we calculate

$$\frac{d}{dt} V_-(x_t, y_t, u_t) = \frac{x(t)y(t)}{u(t)} - \frac{x(t-\tau)y(t-\tau)}{u(t-\tau)} \tag{3.21}$$

and

$$\begin{aligned}
\frac{d}{dt} V_+(u(t)) =& (u(t)-1)(sy(t) - bu(t) + b) \\
=& su(t)y(t) - sy(t) - b(u(t)-1)^2.
\end{aligned} \tag{3.22}$$

Combining (3.19), (3.20), (3.21) and (3.22), we obtain

$$\begin{aligned}
\frac{d}{dt} V\left(x_t, y_t, u_t\right) =& -\frac{d}{x(t)}\left(x(t) - x_0\right)^2 - \beta x(t)\frac{y(t)}{u(t)} + \beta x_0 \frac{y(t)}{u(t)} \\
&+ e^{\delta\tau}\left(\frac{\beta \mathrm{e}^{-\delta\tau} x(t-\tau)y(t-\tau)}{u(t-\tau)} - hy(t) - ry(t)u(t)\right) \\
&+ \frac{\beta x_0}{s}\left\{sy(t) - s\frac{y(t)}{u(t)} - b\frac{(u(t)-1)^2}{u(t)}\right\} + \beta\left(\frac{x(t)y(t)}{u(t)} - \frac{x(t-\tau)y(t-\tau)}{u(t-\tau)}\right) \\
&+ \frac{re^{\delta\tau}}{s}\left\{su(t)y(t) - sy(t) - b\left(u(t)-1\right)^2\right\} \\
=& -\frac{d}{x(t)}\left(x(t) - x_0\right)^2 + \left\{\beta x_0 - (h+r)e^{\delta\tau}\right\} y(t) - b\left(\frac{\beta x_0}{su(t)} + \frac{re^{\delta\tau}}{s}\right)\left(u(t)-1\right)^2.
\end{aligned} \tag{3.23}$$

Since we have that $R_0 \leq 1$, it follows that $\beta x_0 - (h+r)e^{\delta\tau} \leq 0$. Thus, from (3.23), we obtain (3.18). We define a set

$$\overline{G} := \{\varphi \in G | V(\varphi) \leq V(\phi)\}.$$

One can see that $\overline{G}$ is closed and positively invariant. Thus the closure of $\overline{G}$ is itself and $\overline{G}$ contains (x_t, y_t, u_t) for all $t > 0$. Since V is continuous on $\overline{G}$, V is a Lyapunov functional on G. We define the set

$$E := \{\varphi \in \overline{G} | \dot{V}_{(3.15)}(\varphi) = 0\}.$$

Then we get

$$E = \left\{\varphi \in \overline{G} | \varphi_1(0) = x_0,\ \varphi_3(0) = 1\right\}.$$

Let M be the largest subset in E that is invariant with respect to (2.2). Then, by LaSalle's invariant principle, the solution tends to M. As in the proof of Theorem 3.1 one can prove that M consists only of the infection free equilibrium. Thus every solution tends to the infected equilibrium. By applying Theorem 2.1, Chapter 5.3 in [5], the infected equilibrium is uniformly stable. □

We now consider the global dynamics for $R_0 > 1$. First we prove that the system is permanent. Biologically, this implies that the virus can persist in the host cell population for any initial conditions. We derive a priori bounds for the solution.

Proposition 3.1. *It holds that*

$$\limsup_{t\to\infty} (x(t), y(t), u(t)) \leq \left(\frac{\lambda}{d}, \frac{\lambda e^{-\delta\tau}}{\min\{d, h+r\}}, 1 + \frac{s}{b}\frac{\lambda e^{-\delta\tau}}{\min\{d, h+r\}}\right),$$

where the inequality is the componentwise inequality.

Proof. Since it holds that

$$\frac{d}{dt}x(t) \leq \lambda - dx(t),$$

we get the bound for $\limsup_{t\to\infty} x(t)$. Similarly it holds

$$\frac{d}{dt}\left(x(t-\tau)e^{-\delta\tau} + y(t)\right) \leq \lambda e^{-\delta\tau} - \min\{d, h+r\}\left(x(t-\tau)e^{\delta\tau} + y(t)\right),$$

we have the bound for $\limsup_{t\to\infty} y(t)$. By

$$\limsup_{t\to\infty} u(t) \leq 1 + \frac{s}{b}\limsup_{t\to\infty} y(t)$$

we obtain the bound for $\limsup_{t\to\infty} u(t)$. □

We define a set as

$$\Gamma := \left\{\phi \in C_+ | \phi_1(\theta) \leq \frac{\lambda}{d},\ \phi_2(\theta) \leq \frac{\lambda e^{-\delta\tau}}{\max\{d, h+r\}},\ \phi_3(\theta) \leq U,\ \theta \in [-\tau, 0]\right\},$$

where

$$U := 1 + \frac{s}{b}\frac{\lambda e^{-\delta\tau}}{\min\{d, h+r\}}.$$

Then, similar to the proof of Lemma 3 in [2], one can derive the following proposition.

Proposition 3.2. *The set Γ is positively invariant for the system (3.15) and attracts all solutions of the system (3.15).*

We prepare some elementary results which will be used in the proof for the permanence of the system (3.15). We denote by (x^*, y^*, u^*) the infected equilibrium of (3.15). For $\gamma \in (0, 1)$ we define

$$k_1(\gamma) := b - s\gamma\frac{y^*}{u^*},\ k_2(\gamma) := \beta\gamma\frac{y^*}{u^*}.$$

We prove the following lemma:

Lemma 3.1. *Let us assume that $R_0 > 1$ holds. For any $\gamma \in (0, 1)$ one has that $k_1(\gamma) > 0$ and that*

$$U > u^* > \frac{b}{k_1(\gamma)},\ \frac{\lambda}{d + k_2(\gamma)} > x^*. \tag{3.24}$$

Proof. We use the equilibrium conditions of (3.15). Using the third equation one can estimate

$$k_1(\gamma) > b - s\frac{y^*}{u^*} = \frac{b}{u^*}.$$

Thus we get $k_1(\gamma) > 0$ and $u^* > \frac{b}{k_1(\gamma)}$. From the first equation it holds

$$\frac{\beta x^* y^*}{u^*} = \lambda - dx^*.$$

Since we have $u^* > 1$, the second equations of (3.15) implies

$$y^* < \frac{(\lambda - dx^*)\, e^{-\delta\tau}}{h+r} < \frac{\lambda e^{-\delta\tau}}{\min\{d, h+r\}}.$$

Then, from the third equations of (3.15), we get

$$u^* = 1 + \frac{s}{b} y^* < U.$$

Using the first equation of (3.15) we have

$$0 = \lambda - dx^* - \frac{\beta x^* y^*}{u^*} < \lambda - (d + k_2(\gamma))\, x^*,$$

from which we obtain the second part of (3.24). □

For $\gamma \in (0,1)$, by (3.24) in Lemma 3.1, we can define positive constants

$$\rho_1(\gamma) := -\frac{1}{k_1(\gamma)} \ln \frac{u^* - \frac{b}{k_1(\gamma)}}{U - \frac{b}{k_1(\gamma)}},$$
$$\rho_2(\gamma) := -\frac{1}{d + k_2(\gamma)} \ln \left(1 - \frac{x^*(d + k_2(\gamma))}{\lambda}\right).$$

By straightforward calculations one can obtain

Lemma 3.2. *Let us assume that $R_0 > 1$ holds. Fix $\gamma \in (0,1)$ arbitrarily. The following inequalities hold:*

$$U e^{-k_1(\gamma)t} + \frac{b}{k_1(\gamma)} \left(1 - e^{-k_1(\gamma)t}\right) \le u^* \text{ for } t \ge \rho_1(\gamma)$$

and

$$\frac{\lambda}{d + k_2(\gamma)} \left\{1 - e^{-(d+k_2(\gamma))t}\right\} \ge x^* \text{ for } t \ge \rho_2(\gamma).$$

Then we prove

Theorem 3.3. *Let us assume that $R_0 > 1$ holds. For any solution of system (3.15), it holds that*

$$\liminf_{t \to +\infty} y(t) \ge \sup_{\gamma \in (0,1)} \gamma \frac{y^*}{u^*} e^{-(h+rU)(\rho(\gamma)+\tau)}, \tag{3.25}$$

where

$$\rho(\gamma) := \max\{\rho_1(\gamma), \rho_2(\gamma)\}.$$

Proof. From Proposition 3.2 it is enough to consider the solution with initial conditions satisfying $\phi = (x_0, y_0, u_0) \in \Gamma$. Then one has

$$u(t) \le U \text{ for } t > 0 \tag{3.26}$$

by Proposition 3.2. We choose a constant $\gamma \in (0,1)$ arbitrarily. We define

$$l(\gamma) := \gamma \frac{y^*}{u^*}.$$

First we prove

Proposition 3.3. *There exists t_0 such that for $t \ge t_0$ either*

$$\text{(i) } \frac{y(t)}{u(t)} \ge l(\gamma) \text{ or}$$
$$\text{(ii) } \frac{y(t)}{u(t)} \text{ oscillates about } l(\gamma).$$

Proof. Suppose that there exists t_0 such that

$$\frac{y(t_0)}{u(t_0)} = l(\gamma) \text{ and } \frac{y(t)}{u(t)} < l(\gamma) \text{ for any } t > t_0. \tag{3.27}$$

In order to lead a contradiction we estimate $x(t)$ and $u(t)$. Since (3.27) implies that

$$y(t) < l(\gamma)u(t) \text{ for any } t > t_0,$$

from the third equation of (3.15) one has

$$\frac{du(t)}{dt} < -k_1(\gamma)u(t) + b \text{ for any } t > t_0.$$

Then we get

$$u(t) < u(t_0)e^{-k_1(\gamma)(t-t_0)} + \frac{b}{k_1(\gamma)}\left(1 - e^{-k_1(\gamma)(t-t_0)}\right),\ t > t_0.$$

Since we have (3.26), it holds that $u(t_0) \leq U$. By Lemma 3.2 we obtain that

$$u(t) < u^* \text{ for any } t > t_0 + \rho_1(\gamma). \tag{3.28}$$

From the first equation of (3.15), it follows that

$$\frac{dx(t)}{dt} > \lambda - (d + k_2(\gamma))\, x(t) \text{ for any } t > t_0.$$

Then one has

$$\begin{aligned} x(t) &> x(t_0)e^{-(d+k_2(\gamma))(t-t_0)} + \frac{\lambda}{d + k_2(\gamma)}\left\{1 - e^{-(d+k_2(\gamma))(t-t_0)}\right\} \\ &> \frac{\lambda}{d + k_2(\gamma)}\left\{1 - e^{-(d+k_2(\gamma))(t-t_0)}\right\},\ t > t_0. \end{aligned} \tag{3.29}$$

By Lemma 3.2 we obtain that

$$x(t) > x^* \text{ for any } t > t_0 + \rho_2(\gamma). \tag{3.30}$$

We define a positive constant as

$$\underline{y} := \min_{\theta \in [0,\tau]} y(t_0 + \rho(\gamma) + \theta).$$

We claim that

$$y(t) \geq \underline{y} \text{ for any } t > t_0 + \rho(\gamma) + \tau. \tag{3.31}$$

Suppose that there exists $T > 0$ such that $y(t_0 + \rho(\gamma) + \tau + \theta) \geq \underline{y}$ for $\theta \in [0, T]$ and $y(L) = \underline{y}$ with $\frac{dy}{dt}(L) < 0$, where $L := t_0 + \rho(\gamma) + \tau + T$. Then one has

$$\frac{dy(L)}{dt} \geq \left\{\frac{\beta e^{-\delta\tau}x(L-\tau)}{u(L-\tau)} - (h + ru(L))\right\}\underline{y}.$$

Since (3.30) implies that $x(L-\tau) > x^*$ and (3.28) implies $u(L-\tau) < u^*$ and $u(L) < u^*$, using the equilibrium condition, it holds that

$$\frac{\beta e^{-\delta\tau}x(L-\tau)}{u(L-\tau)} - (h + ru(L)) > \frac{\beta e^{-\delta\tau}x^*}{u^*} - (h + ru^*) = 0.$$

Hence $\frac{dy(L)}{dt} > 0$ follows, which is a contradiction. Thus (3.31) holds. For $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in C_+$ with $\varphi_3(\theta) > 1$ for $\theta \in [-\tau, 0]$ we define a functional as

$$W(\varphi) := \varphi_2(0) + \beta e^{-\delta\tau}\int_{-\tau}^{0} \frac{\varphi_1(\theta)\varphi_2(\theta)}{\varphi_3(\theta)} d\theta. \tag{3.32}$$

For $t > t_0 + \rho(\gamma) + \tau$ we compute

$$\begin{aligned} \frac{d}{dt}W(x_t, y_t, u_t) =& \frac{\beta e^{-\delta\tau}x(t-\tau)y(t-\tau)}{u(t-\tau)} - (h + ru(t))\, y(t) + \beta \mathrm{e}^{-\delta\tau}\left(\frac{x(t)y(t)}{u(t)} - \frac{x(t-\tau)y(t-\tau)}{u(t-\tau)}\right) \\ =& \left\{\frac{\beta e^{-\delta\tau}x(t)}{u(t)} - (h + ru(t))\right\} y(t). \end{aligned}$$

Since one has (3.29), we can estimate $x(t)$ as $x(t) > \underline{x}(\gamma) > x^*$, where

$$\underline{x}(\gamma) := \frac{\lambda}{d + k_2(\gamma)} \left\{ 1 - e^{-(d+k_2(\gamma))(\rho(\gamma)+\tau)} \right\}.$$

Then one has

$$\frac{d}{dt} W(x_t, y_t, u_t) > \left\{ \frac{\beta e^{-\delta\tau} \underline{x}(\gamma)}{u^*} - (h + ru^*) \right\} \underline{y} > 0$$

for $t > t_0 + \rho(\gamma) + \tau$. Thus it follows that $\lim_{t\to+\infty} W(t) = +\infty$. However, Proposition 3.1 implies boundedness of W, which leads to a contradiction. Thus the claim is proved. □

If (i) holds, then it holds that $\liminf_{t\to+\infty} y(t) \geq l(\gamma)$. Thus we obtain (3.25). We consider the case (ii). We choose t_j, $j \in \{1, 2\}$ such that $t_0 \leq t_1 < t_2$,

$$\frac{y(t_j)}{u(t_j)} = l(\gamma),\ j \in \{1, 2\} \text{ and } \frac{y(t)}{u(t)} < l(\gamma) \text{ for any } t \in (t_1, t_2). \tag{3.33}$$

Finally we prove

Proposition 3.4. *It holds that*

$$y(t) > l(\gamma) e^{-(h+rU)(\rho(\gamma)+\tau)} \text{ for any } t \in (t_1, t_2). \tag{3.34}$$

Proof. From (3.26), one has $u(t) \leq U$ for $t \geq t_0$. Then, by the second equation of system (3.15), we have that

$$\frac{dy(t)}{dt} \geq -(h + rU)\, y(t) \text{ for any } t \geq t_0.$$

Since $y(t_1) = l(\gamma)u(t_1) \geq l(\gamma)$, it follows that

$$y(t) \geq l(\gamma) e^{-(h+rU)(t-t_1)} \text{ for } t \in (t_1, t_2).$$

If $t_2 < t_1 + \rho(\gamma) + \tau$, we obtain (3.34). Consider the case $t_2 \geq t_1 + \rho(\gamma) + \tau$. We define

$$\nu(\gamma) := l(\gamma) e^{-(h+rU)(\rho(\gamma)+\tau)}.$$

Suppose that there exists T such that $y(t) > \nu(\gamma)$ for $t \in (t_1, t_1 + \rho(\gamma) + \tau + T)$ and $y(L) = \nu(\gamma)$ with $\frac{dy(L)}{dt} < 0$, where $L := t_1 + \rho(\gamma) + \tau + T$. Since we have (3.33), as in the proof of Proposition 3.3, we again obtain that

$$u(t) < u^* \text{ for } t > t_1 + \rho_1(\gamma)$$

and that

$$x(t) > x^* \text{ for } t > t_1 + \rho_2(\gamma).$$

Then, we obtain that

$$\begin{aligned} \frac{dy(L)}{dt} &> \left\{ \frac{\beta e^{-\delta\tau} x(L-\tau)}{u(L-\tau)} - (h + ru(L)) \right\} \nu(\gamma) \\ &> \left\{ \frac{\beta e^{-\delta\tau}}{u^*} x^* - (h + ru^*) \right\} \nu(\gamma) \\ &= 0, \end{aligned}$$

which leads a contradiction. Thus, (3.34) holds. □

Since we chose γ arbitrarily and the right hand side in (3.34) is continuous with respect to γ, we obtain the estimation (3.25). □

Finally we prove the global asymptotic stability of the infected equilibrium.

Theorem 3.4. *Let us assume that $R_0 > 1$ holds. Then the infected equilibrium of (3.15) is globally asymptotically stable.*

Proof. For $\varphi \in G$, which is defined in (3.16), we define a functional as

$$U(\varphi) := x^* g\left(\frac{\varphi_1(0)}{x^*}\right) + y^* e^{\delta\tau} g\left(\frac{\varphi_2(0)}{y^*}\right) + \frac{\beta x^*}{s} g\left(\frac{\varphi_3(0)}{u^*}\right) + \frac{\beta x^* y^*}{u^*} U_-(\varphi) + \frac{r e^{\delta\tau}}{s} U_+(\varphi_3(0)), \tag{3.35}$$

where

$$\begin{aligned} U_-(\varphi) &:= \int_{-\tau}^{0} g\left(\frac{\varphi_1(\theta)}{x^*}\frac{\varphi_2(\theta)}{y^*}\frac{u^*}{\varphi_3(\theta)}\right) d\theta, \\ U_+(u) &:= \frac{1}{2}\left(u - u^*\right)^2. \end{aligned}$$

We show that

$$\frac{d}{dt} U(x_t, y_t, u_t) \le 0. \tag{3.36}$$

In the following we drop $*$ from the notation: x^*, y^* and u^*. Since one has

$$\lambda = dx + \beta \frac{xy}{u}$$

from the equilibrium condition, we calculate that

$$\begin{aligned} \frac{d}{dt} g\left(\frac{x(t)}{x}\right) =& \frac{1}{x}\left(1 - \frac{x}{x(t)}\right)\left(\lambda - dx(t) - \frac{\beta x(t) y(t)}{u(t)}\right) \\ =& \left(1 - \frac{x}{x(t)}\right)\left\{ d\left(1 - \frac{x(t)}{x}\right) + \frac{\beta y}{u}\left(1 - \frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)}\right)\right\} \\ =& -\frac{d}{x x(t)}\left(x(t) - x\right)^2 + \frac{\beta y}{u}\left(1 - \frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)} - \frac{x}{x(t)} + \frac{y(t)}{y}\frac{u}{u(t)}\right). \end{aligned} \tag{3.37}$$

We secondly calculate that

$$\begin{aligned} \frac{d}{dt} g\left(\frac{y(t)}{y}\right) =& \frac{1}{y}\left(1 - \frac{y}{y(t)}\right)\left\{\frac{\beta e^{-\delta\tau} x(t-\tau) y(t-\tau)}{u(t-\tau)} - \left(h + r u(t)\right) y(t)\right\} \\ =& \left(\frac{y(t)}{y} - 1\right)\left\{\frac{\beta e^{-\delta\tau} x}{u}\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\frac{u}{u(t-\tau)} - \left(h + r u \frac{u(t)}{u}\right)\right\}. \end{aligned}$$

Substituting $h = \beta e^{-\delta\tau}\frac{x}{u} - ru$ gives

$$\begin{aligned} \frac{d}{dt} g\left(\frac{y(t)}{y}\right) =& \left(\frac{y(t)}{y} - 1\right)\left\{\frac{\beta e^{-\delta\tau} x}{u}\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\frac{u}{u(t-\tau)} - 1\right) - ru\left(\frac{u(t)}{u} - 1\right)\right\} \\ =& \frac{\beta e^{-\delta\tau} x}{u}\left(\frac{x(t-\tau)y(t-\tau)}{xy}\frac{u}{u(t-\tau)} - \frac{y(t)}{y} - \frac{x(t-\tau)y(t-\tau)}{xy(t)}\frac{u}{u(t-\tau)} + 1\right) - ru\left(\frac{y(t)}{y} - 1\right)\left(\frac{u(t)}{u} - 1\right). \end{aligned} \tag{3.38}$$

We calculate that

$$\frac{d}{dt} g\left(\frac{u(t)}{u}\right) = \frac{1}{u}\left(1 - \frac{u}{u(t)}\right)\left(s y(t) - b u(t) + b\right).$$

Since we have

$$b = bu - sy, \tag{3.39}$$

it holds

$$\begin{aligned} \frac{d}{dt} g\left(\frac{u(t)}{u}\right) =& \frac{1}{u}\left(1 - \frac{u}{u(t)}\right)\left\{ sy\left(\frac{y(t)}{y} - 1\right) - bu\left(\frac{u(t)}{u} - 1\right)\right\} \\ =& \frac{sy}{u}\left(\frac{y(t)}{y} - 1 - \frac{y(t)}{y}\frac{u}{u(t)} + \frac{u}{u(t)}\right) - b\frac{u}{u(t)}\left(\frac{u(t)}{u} - 1\right)^2. \end{aligned} \tag{3.40}$$

We calculate

$$\frac{d}{dt} U_-(x_t, y_t, u_t) = g\left(\frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)}\right) - g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\frac{u}{u(t-\tau)}\right). \tag{3.41}$$

Using (3.39) again we get

$$\begin{aligned}\frac{d}{dt}U_+(u(t)) =& (u(t)-u)\,(sy(t)-bu(t)+b)\\ =& (u(t)-u)\,\{s(y(t)-y)-b(u(t)-u)\}\\ =& syu\left(\frac{u(t)}{u}-1\right)\left(\frac{y(t)}{y}-1\right)-bu^2\left(\frac{u(t)}{u}-1\right)^2. \end{aligned} \tag{3.42}$$

Thus, combining (3.37), (3.38), (3.40), (3.41) and (3.42), we obtain

$$\begin{aligned}\frac{d}{dt}U(x_t,y_t,u_t) =& -\frac{d}{x(t)}\,(x(t)-x)^2+\frac{\beta xy}{u}\left[\left(1-\frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)}-\frac{x}{x(t)}\right)\right.\\ &+\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\frac{u}{u(t-\tau)}-\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\frac{u}{u(t-\tau)}\right)+\frac{u}{u(t)}\\ &\left.+\left\{g\left(\frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\frac{u}{u(t-\tau)}\right)\right\}\right]\\ &-\frac{b}{s}\left(\beta x\frac{u}{u(t)}+re^{\delta\tau}u^2\right)\left(\frac{u(t)}{u}-1\right)^2\\ =& -\frac{d}{x(t)}\,(x(t)-x)^2+\frac{\beta xy}{u}\left\{-g\left(\frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)}\right)-g\left(\frac{x}{x(t)}\right)\right.\\ &+g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\frac{u}{u(t-\tau)}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\frac{u}{u(t-\tau)}\right)\\ &\left.+g\left(\frac{u}{u(t)}\right)+g\left(\frac{x(t)}{x}\frac{y(t)}{y}\frac{u}{u(t)}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y}\frac{u}{u(t-\tau)}\right)\right\}\\ &-\frac{b}{s}\left(\beta x\frac{u}{u(t)}+re^{\delta\tau}u^2\right)\left(\frac{u(t)}{u}-1\right)^2\\ =& -\frac{d}{x(t)}\,(x(t)-x)^2+\frac{\beta xy}{u}\left\{-g\left(\frac{x}{x(t)}\right)-g\left(\frac{x(t-\tau)}{x}\frac{y(t-\tau)}{y(t)}\frac{u}{u(t-\tau)}\right)\right\}\\ &+\frac{\beta xy}{u}g\left(\frac{u}{u(t)}\right)-\frac{b}{s}\left(\beta x\frac{u}{u(t)}+re^{\delta\tau}u^2\right)\left(\frac{u(t)}{u}-1\right)^2. \end{aligned} \tag{3.43}$$

Since it holds that

$$\frac{(x-1)^2}{x}-g\left(\frac{1}{x}\right)=g(x)\geq 0 \text{ for } x\in(0,\infty),$$

one has

$$g\left(\frac{u}{u(t)}\right)\leq\frac{u}{u(t)}\left(\frac{u(t)}{u}-1\right)^2.$$

Then it holds that

$$\frac{\beta xy}{u}g\left(\frac{u}{u(t)}\right)-\frac{b}{s}\left(\beta x\frac{u}{u(t)}+re^{\delta\tau}u^2\right)\left(\frac{u(t)}{u}-1\right)^2\leq\left\{\beta x\left(\frac{y}{u}-\frac{b}{s}\right)\frac{u}{u(t)}-\frac{bre^{\delta\tau}u^2}{s}\right\}\left(\frac{u(t)}{u}-1\right)^2.$$

One can see that (3.39) implies that

$$\frac{y}{u}-\frac{b}{s}=\frac{sy-bu}{su}=-\frac{b}{su}<0.$$

Thus, we get (3.36). We define a set

$$\overline{G}:=\{\varphi\in G|U(\varphi)\leq U(\phi)\}.$$

As in the proof of Theorem 3.2 one can see that U is a Lyapunov functional on G. We define the set

$$E:=\{\varphi\in\overline{G}|\dot{U}_{(3.15)}(\varphi)=0\}.$$

Then we get

$$E=\left\{\varphi\in\overline{G}|\varphi_1(0)=x,\ \varphi_3(0)=u,\ \frac{\varphi_1(-\tau)\varphi_2(-\tau)u}{x\varphi_2(0)\varphi_3(-\tau)}=1\right\}.$$

Let M be the largest subset in E that is invariant with respect to (2.2). Then, by LaSalle's invariant principle, the solution tends to M. As in the proof of Theorem 3.1 one can prove that M consists only of the infected equilibrium. Thus every solution tends to the infected equilibrium. By applying Theorem 2.1, Chapter 5.3 in [5], the infected equilibrium is uniformly stable. □

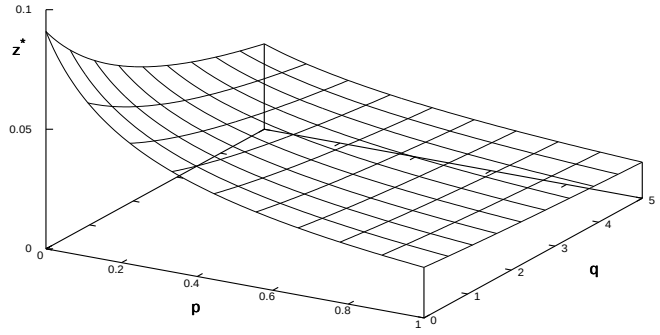

Figure 1: Surface plot of $z^*(p,q)$ with respect to $0 < p \leq 1$ and $0 < q \leq 5$ for the parameter values $\lambda = 0.3$ day^{-1}, $\beta = 0.027$ mm day^{-1}, $d = 0.02$ day^{-1}, $a = 0.1$ day^{-1}, $c = 1$ day^{-1}, $b = 2.4$ day^{-1}, $\delta = 0.02$ and $\tau = 0.1$ day. For this case, we have $R_0 = 4.0419\cdots > 1$.

4 Biological findings

In Section 3 we showed that the basic reproduction number given as in (2.5) has a critical role to determine the dynamics of (2.2) for any strength of lytic and nonlytic immune activities. The basic reproduction number denotes the expected number of the infected cells produced by one infected cell in the expected life-time in a completely susceptible cell population, see [3] in the context of the infectious disease in human population. One can see that the value of the basic reproduction number decreases as the length of the delay increases. It has a clear meaning that, if the length of the delay is large, infected cells may die before it spreads virus due to the small survival probability in the latent period between the infection phase and the virus-producing phase. It is also natural that the strength of immune effector does not change the value of the basic reproduction number, since the basic reproduction number measures a possibility of successful invasion of the virus in a completely susceptible cell population, where no active immune cells exist.

The strength of lytic and nonlytic component monotonically change the number of cells at the infected equilibrium. To show that we assume that the basic reproduction number is greater than one and we choose p and q as free parameters. From the proof of Theorem 2.1, we see that the number of immune cells at the equilibrium is determined by the equation:

$$H(p,q,z) = 0,$$

where

$$H(p,q,z) = \frac{\beta e^{-\delta\tau}\lambda}{d(1+qz)+\beta\frac{b}{c}z} - a - pz,\ (p,q,z) \in \mathbb{R}^3_+.$$

We denote the unique equilibrium of the immune cells by a function $z^*(p,q)$ which satisfies $H(p,q,z^*(p,q)) = 0$. By an application of the implicit function theorem, it is straightforward to prove

$$\frac{\partial z^*}{\partial p}(p,q) < 0,\ \frac{\partial z^*}{\partial q}(p,q) < 0 \text{ for any } (p,q) \in \mathbb{R}^2_+.$$

Thus the number of immune cells at the equilibrium decreases with respect to p and q, see Figure 1. Since the number of infected cells at the equilibrium is linearly dependent on the number of the immune cells, see (2.6), it also decreases with respect to p and q. Hence, large strength of immune effectors regulates the number of both immune cells and infected cells at the equilibrium. From (2.7) the number of susceptible cells at the equilibrium is given as

$$x^*(p,q) := \lambda\left(d + \frac{\beta\frac{b}{c}z^*(p,q)}{1+qz^*(p,q)}\right)^{-1}.$$

Using the chain rule of differentiation, one can obtain that

$$\frac{\partial x^*}{\partial p}(p,q) > 0,\ \frac{\partial x^*}{\partial q}(p,q) > 0 \text{ for any } (p,q) \in \mathbb{R}^2_+.$$

Thus the number of susceptible cells at the equilibrium increases with respect to p and q, see Figure 2. One can conclude that the immune effector has a positive role for the number of susceptible cells at the equilibrium.

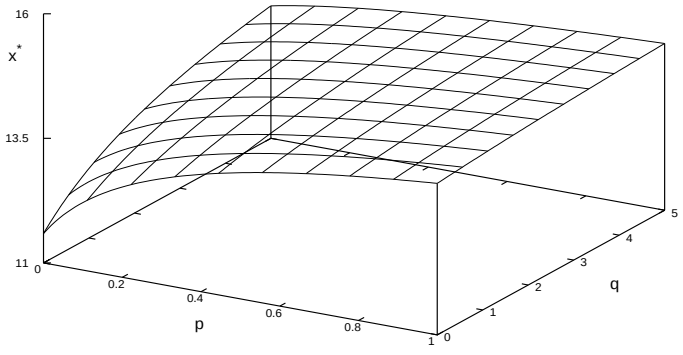

Figure 2: Surface plot of $x^*(p,q)$ with respect to $0 < p \leq 1$ and $0 < q \leq 5$ for the parameter values $\lambda = 0.3$ day^{-1}, $\beta = 0.027$ mm day^{-1}, $d = 0.02$ day^{-1}, $a = 0.1$ day^{-1}, $c = 1$ day^{-1}, $b = 2.4$ day^{-1}, $\delta = 0.02$ and $\tau = 0.1$ day. For this case, we have $R_0 = 4.0419\cdots > 1$.

5 Discussion

The authors in [18] formulated the mathematical model (2.1) by a system of ordinary differential equations to investigate the effect of two different immune responses. Stability of equilibria of (2.1) was investigate in [16]. It was not clear that if the nonlytic immune response changes the global stability of the infected equilibrium, though their numerical studies suggested that the infected equilibrium is always globally stable. Thus they left a conjecture on the global stability. In this paper we formulate (2.2) by introducing virus replication delay. We prove that for any strength of the nonlytic component the basic reproduction number determines the equilibrium that is globally asymptotically stable: if the basic reproduction number is less than or equal to one then the infection free equilibrium is globally asymptotically stable while if the basic reproduction number is greater than one then the infected equilibrium is globally asymptotically stable. Thus we can say that the nonlytic immune response does not change the qualitative dynamics. Since one can easily see that this threshold type result holds for a special case, $\tau = 0$, the conjecture offered in [16] is affirmatively solved: the infected equilibrium is always globally stable if the basic reproduction number is greater than one. For the global stability results we construct Lyapunov functionals and apply LaSalle's invariant principle. The essential idea behind the construction of the Lyapunov functionals and the calculation of the time derivative is firstly introduced in the paper [9] for a delayed epidemiological model. Here we carefully designed Lyapunov functionals for a specific nonlinearity by immune cells appeared in the incidence rate.

We also prove the permanence of the infected cell population when nonlytic immune effector is available, i.e., $q > 0$. We modify the proof in [15, 17] for (2.2). Since the application of the approach in [15, 17] was not clear due to the nonlinearity in the infectious incidence rate, we have decided to put the proof for the permanence. Since permanence implies ultimate survival of the interested population, it has been an important concept in mathematical biology, see e.g. [4, 7], in particular, when it is difficult to analyze global stability of a positive equilibrium. Wang [17] provided an elementary proof for the permanence of a delayed epidemic model. One important aspect of the approach is that we can get the explicit formula to estimate the lower bound of the solution.

Since we tried to avoid technical difficulty, with keeping the essential ideas on the proofs, we have concentrated on the constant delay model (2.2). However, it may be not a difficult task to construct similar Lyapunov functionals for (2.2) with distributed delay, instead of the constant delay, see [9, 11] for the treatment for distributed delay models.

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