Research Article

Global Dynamics of Virus Infection Model with Antibody Immune Response and Distributed Delays

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We present qualitative behavior of virus infection model with antibody immune response. The incidence rate of infection is given by saturation functional response. Two types of distributed delays are incorporated into the model to account for the time delay between the time when uninfected cells are contacted by the virus particle and the time when emission of infectious (matures) virus particles. Using the method of Lyapunov functional, we have established that the global stability of the steady states of the model is determined by two threshold numbers, the basic reproduction number R_0 and antibody immune response reproduction number R_1 . We have proven that if $R_0 \leq 1$, then the uninfected steady state is globally asymptotically stable (GAS), if $R_1 \leq 1 < R_0$, then the infected steady state without antibody immune response is GAS, and if $R_1 > 1$, then the infected steady state with antibody immune response is GAS.

1. Introduction

In the past ten years there has been a growing interest in modeling viral infections for the study and characterization of host infection dynamics. The mathematical models, based on biological interactions, present a framework which can be used to obtain new insights into the viral dynamics and to interpret experimental data. Many authors have formulated mathematical models to describe the population dynamics of several viruses such as, human immunodeficiency virus (HIV) [1–14], hepatitis B virus (HBV) [15, 16], and hepatitis C virus (HCV) [17, 18]. During viral infections, the host immune system reacts with antigen-specific immune response. In particular, B cells play a critical role in antiviral defense by attacking free virus particles by making antibodies to clear antigens circulating in blood and lymph. The antibody immune response is more effective than the cell-mediated immune in some diseases like in malaria infection [19].

Mathematical models for virus dynamics with the antibody immune response have been developed in [20–26]. The

basic virus dynamics model with antibody immune response was introduced by Murase et al. [21] as

$$\begin{aligned}\dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta x(t)v(t) - \delta y(t), \\ \dot{v}(t) &= N\delta y(t) - cv(t) - qv(t)z(t), \\ \dot{z}(t) &= rv(t)z(t) - \mu z(t),\end{aligned}\tag{1}$$

where $x(t)$, $y(t)$, $v(t)$, and $z(t)$ represent the populations of uninfected cells, infected cells, virus, and B cells at time t , respectively; λ and d are the recruited rate and death rate constants of uninfected cells, respectively; β is the infection rate constant; N is the number of free virus produced during the average infected cell life span; δ is the death rate constant of infected cells; c is the clearance rate constant of the virus; r and μ are the recruited rate and death rate constants of B cells; and q is the B cells neutralization rate. Model (1) is based on the assumption that the infection could occur and that the viruses are produced from infected cells instantaneously, once the

uninfected cells are contacted by the virus particles. Other accurate models incorporate the delay between the time viral entry into the uninfected cell and the time the production of new virus particles, modeled with discrete time delay or distributed time delay using functional differential equations (see e.g., [7–14, 27]). In [7–14, 27], the viral infection models are presented without taking into consideration the antibody immune response. In [25, 28], global stability of viral infection models with antibody immune response and discrete delays has been studied.

In model (1) the infection rate is assumed to be bilinear in x and v however, this bilinear incidence rate associated with the mass action principle is insufficient to describe the infection process in detail [29, 30]. For example, a less than linear response in v could occur due to saturation at high virus concentration, where the infectious fraction is high so that exposure is very likely. Thus, it is reasonable to assume that the infection rate is given by saturation functional response [31]. In [26], a virus infection model with antibody immune response and with saturation incidence rate has been considered. However, the time delay was not considered.

In this paper, we assume that the infection rate is given by saturation functional response. We incorporate two types of distributed delays into the model to account for the time delay between the time when uninfected cells are contacted by the virus particle and the time of emission of infectious (matures) virus particles. The global stability of this model is established using Lyapunov functionals, which are similar in nature to those used in [32]. We prove that the global dynamics of this model is determined by the basic reproduction number R_0 and antibody immune response reproduction number R_1 . If $R_0 \leq 1$, then the uninfected steady state is globally asymptotically stable (GAS), if $R_1 \leq 1 < R_0$, then the infected steady state without antibody immune response is GAS, and if $R_1 > 1$, then the infected steady state with antibody immune response is GAS.

2. The Model

In this section we propose a delay mathematical model of viral infection with saturation functional response which describes the interaction of the virus with uninfected and infected cells, taking into account the effect of antibody immune response. Consider

$$\dot{x}(t) = \lambda - dx(t) - \frac{\beta x(t) v(t)}{1 + \alpha v(t)}, \quad (2)$$

$$\dot{y}(t) = \beta \int_0^h f(\tau) e^{-m\tau} \frac{x(t-\tau) v(t-\tau)}{1 + \alpha v(t-\tau)} d\tau - \delta y(t), \quad (3)$$

$$\dot{v}(t) = N\delta \int_0^\omega g(\tau) e^{-n\tau} y(t-\tau) d\tau - cv(t) - qv(t)z(t), \quad (4)$$

$$\dot{z}(t) = rv(t)z(t) - \mu z(t), \quad (5)$$

where α is a positive constant, and all the variables and parameters of the model have the same meanings as given in model (1). To account for the time lag between viral

contacting a target cell and the production of new virus particles, two distributed intracellular delays are introduced. It is assumed that the uninfected cells that are contacted by the virus particles at time $t - \tau$ become infected cells at time t , where τ is a random variable with a probability distribution $f(\tau)$ over the interval $[0, h]$ and h is limit superior of this delay. The factor $e^{-m\tau}$ accounts for the probability of surviving the time period of delay, where m is the death rate of infected cells but not yet virus producer cells. On the other hand, it is assumed that a cell infected at time $t - \tau$ starts to yield new infectious virus at time t where τ is distributed according to a probability distribution $g(\tau)$ over the interval $[0, \omega]$ and ω is limit superior of this delay. The factor $e^{-n\tau}$ accounts for the probability of surviving during the time period of delay, where n is constant. All the parameters are supposed to be positive.

The probability distribution functions $f(\tau)$ and $g(\tau)$ are assumed to satisfy $f(\tau) > 0$ and $g(\tau) > 0$, and

$$\begin{aligned} \int_0^h f(\tau) d\tau &= \int_0^\omega g(\tau) d\tau = 1, \\ \int_0^h f(u) e^{su} du &< \infty, \quad \int_0^\omega g(u) e^{su} du < \infty, \end{aligned} \quad (6)$$

where s is a positive number. Then

$$\begin{aligned} 0 &< \int_0^h f(\tau) e^{-m\tau} d\tau \leq 1, \quad \text{for } m \geq 0, \\ 0 &< \int_0^\omega g(\tau) e^{-n\tau} d\tau \leq 1, \quad \text{for } n \geq 0. \end{aligned} \quad (7)$$

Let $F = \int_0^h f(\tau) e^{-m\tau} d\tau$ and $G = \int_0^\omega g(\tau) e^{-n\tau} d\tau$. The initial conditions for system (2)–(5) take the form

$$\begin{aligned} x(\theta) &= \varphi_1(\theta), \quad y(\theta) = \varphi_2(\theta), \\ v(\theta) &= \varphi_3(\theta), \quad z(\theta) = \varphi_4(\theta), \\ \varphi_j(\theta) &\geq 0, \quad \theta \in [-\rho, 0], \quad j = 1, \dots, 4, \\ \varphi_j(0) &> 0, \quad j = 1, \dots, 4, \end{aligned} \quad (8)$$

where $\rho = \max\{h, \omega\}$, $(\varphi_1(\theta), \varphi_2(\theta), \dots, \varphi_4(\theta)) \in C([-\rho, 0], \mathbb{R}_+^4)$, where $C([-\rho, 0], \mathbb{R}_+^4)$ is the Banach space of continuous functions mapping the interval $[-\rho, 0]$ into $\mathbb{R}_+^4$. By the fundamental theory of functional differential equations [33], system (2)–(5) has a unique solution satisfying the initial conditions (8).

2.1. Nonnegativity and Boundedness of Solutions. In the following, we establish the nonnegativity and boundedness of solutions of (2)–(5) with initial conditions (8).

Proposition 1. *Let $(x(t), y(t), v(t), z(t))$ be any solution of (2)–(5) satisfying the initial conditions (8); then $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are all nonnegative for $t \geq 0$ and ultimately bounded.*

Proof. First, we prove that $x(t) > 0$ for all $t \geq 0$. Assume that $x(t)$ loses its non-negativity on some local existence interval

$[0, \ell]$ for some constant ℓ , and let $t_1 \in [0, \ell]$ be such that $x(t_1) = 0$. From (2) we have $\dot{x}(t_1) = \lambda > 0$. Hence, $x(t) > 0$ for some $t \in (t_1, t_1 + \varepsilon)$, where $\varepsilon > 0$ is sufficiently small. This leads to contradiction, and hence $x(t) > 0$ for all $t \geq 0$. Now from (3), (4), and (5) we have

$$\begin{aligned} y(t) &= y(0)e^{-\delta t} + \beta \int_0^t e^{-\delta(t-\eta)} \\ &\quad \times \int_0^h f(\tau) e^{-m\tau} \frac{x(\eta-\tau)v(\eta-\tau)}{1+\alpha v(\eta-\tau)} d\tau d\eta, \\ v(t) &= v(0)e^{-\int_0^t (c+qz(\xi))d\xi} \\ &\quad + N\delta \int_0^t e^{-\int_\eta^t (c+qz(\xi))d\xi} \\ &\quad \times \int_0^\omega g(\tau) e^{-m\tau} y(\eta-\tau) d\tau d\eta, \\ z(t) &= z(0)e^{-\int_0^t (\mu-rv(\xi))d\xi}, \end{aligned} \quad (9)$$

confirming that $y(t) \geq 0$, $v(t) \geq 0$, and $z(t) \geq 0$ for all $t \in [0, \rho]$. By a recursive argument, we obtain $y(t) \geq 0$, $v(t) \geq 0$, and $z(t) \geq 0$ for all $t \geq 0$.

Next we show the boundedness of the solutions. From (2) we have $\dot{x}(t) \leq \lambda - dx(t)$. This implies $\limsup_{t \rightarrow \infty} x(t) \leq \lambda/d$. Let $X(t) = \int_0^h f(\tau) e^{-m\tau} x(t-\tau) d\tau + y(t)$; then

$$\begin{aligned} \dot{X}(t) &= \int_0^h f(\tau) e^{-m\tau} \left(\lambda - dx(t-\tau) \right. \\ &\quad \left. - \frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} \right) d\tau \\ &\quad + \int_0^h f(\tau) e^{-m\tau} \frac{\beta x(t-\tau)v(t-\tau)}{1+\alpha v(t-\tau)} d\tau - \delta y(t) \\ &= \lambda \int_0^h f(\tau) e^{-m\tau} d\tau - d \\ &\quad \times \int_0^h f(\tau) e^{-m\tau} x(t-\tau) d\tau - \delta y(t) \\ &\leq \lambda \int_0^h f(\tau) e^{-m\tau} d\tau - \sigma_1 \\ &\quad \times \left[\int_0^h f(\tau) e^{-m\tau} x(t-\tau) d\tau + y(t) \right] \\ &\leq \lambda - \sigma_1 X(t), \end{aligned} \quad (10)$$

where $\sigma_1 = \min\{d, \delta\}$. Hence, $\limsup_{t \rightarrow \infty} X(t) \leq L_1$, where $L_1 = \lambda/\sigma_1$. Since $\int_0^h f(\tau) e^{-m\tau} x(t-\tau) d\tau > 0$, then

$\limsup_{t \rightarrow \infty} y(t) \leq L_1$. On the other hand, let $Z(t) = v(t) + (q/r)z(t)$; then

$$\begin{aligned} \dot{Z}(t) &= N\delta \int_0^\omega g(\tau) e^{-m\tau} y(t-\tau) d\tau - cv(t) - \frac{q\mu}{r} z(t) \\ &\leq N\delta L_1 \int_0^\omega g(\tau) e^{-m\tau} d\tau - \sigma_2 \left(v(t) + \frac{q}{r} z(t) \right) \\ &= N\delta L_1 \int_0^\omega g(\tau) e^{-m\tau} d\tau - \sigma_2 Z(t) \leq N\delta L_1 - \sigma_2 Z(t), \end{aligned} \quad (11)$$

where $\sigma_2 = \min\{c, \mu\}$. Hence, $\limsup_{t \rightarrow \infty} Z(t) \leq L_2$, where $L_2 = N\delta L_1/\sigma_2$. Since $v(t) \geq 0$, and $v(t) \geq 0$, then $\limsup_{t \rightarrow \infty} v(t) \leq L_2$ and $\limsup_{t \rightarrow \infty} z(t) \leq L_2$.

Therefore, $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are ultimately bounded. $\square$

2.2. Steady States. We define the basic reproduction number for system (2)–(5) as

$$R_0 = \frac{NFG\beta\lambda}{cd}, \quad (12)$$

and the antibody immune response reproduction number

$$R_1 = \frac{R_0}{1 + ((\mu\alpha d + \mu\beta)/rd)}. \quad (13)$$

Clearly $R_1 < R_0$. It can be seen that system (2)–(5) has an uninfected steady state $E_0 = (x_0, 0, 0, 0)$, where $x_0 = \lambda/d$. In addition to E_0 , the system has an infected steady state without immune response $E_1(x_1, y_1, v_1, 0)$ and infected steady state with immune response $E_2(x_2, y_2, v_2, z_2)$, where

$$\begin{aligned} x_1 &= \frac{x_0(1+\alpha v_1)}{R_0}, & y_1 &= \frac{c}{N\delta G} v_1, \\ v_1 &= \frac{d}{\alpha d + \beta} (R_0 - 1), \\ x_2 &= \frac{\lambda}{d + (\beta v_2/(1+\alpha v_2))}, \\ y_2 &= \frac{F\beta\lambda v_2}{\delta(d(1+\alpha v_2) + \beta v_2)}, \\ v_2 &= \frac{\mu}{r}, & z_2 &= \frac{c}{q} (R_1 - 1). \end{aligned} \quad (14)$$

From the above we have the following:

- (i) if $R_0 > 1$, then there exists a positive steady state $E_1(x_1, y_1, v_1, 0)$;
- (ii) if $R_1 > 1$, then there exists a positive steady state $E_2(x_2, y_2, v_2, z_2)$.

3. Global Stability

In this section, we prove the global stability of the steady states of system (2)–(5) employing the method of Lyapunov

functional which is used in [32] for SIR epidemic model with distributed delay. Next we will use the following notation: $b = b(t)$ for any $b \in \{x, y, v, z\}$. We also define a function $H : (0, \infty) \rightarrow [0, \infty)$ as

$$H(b) = b - 1 - \ln(b). \quad (15)$$

It is clear that $H(b) \geq 0$ for any $b > 0$ and H has the global minimum $H(1) = 0$.

Theorem 2. *If $R_0 \leq 1$, then E_0 is GAS.*

Proof. Define a Lyapunov functional W_0 as follows:

$$\begin{aligned} W_0 = NFG & \left[x_0 H\left(\frac{x}{x_0}\right) + \frac{1}{F} y + \frac{\beta}{F} \right. \\ & \times \int_0^h f(\tau) e^{-m\tau} \\ & \times \int_0^\tau \frac{x(t-\theta)v(t-\theta)}{1+\alpha v(t-\theta)} d\theta d\tau \\ & \left. + \frac{\delta}{FG} \int_0^\omega g(\tau) e^{-n\tau} \int_0^\tau y(t-\theta) d\theta d\tau \right] + v + \frac{q}{r} z. \end{aligned} \quad (16)$$

The time derivative of W_0 along the trajectories of (2)–(5) satisfies

$$\begin{aligned} \frac{dW_0}{dt} = NFG & \left[\left(1 - \frac{x_0}{x}\right) \left(\lambda - dx - \frac{\beta x v}{1 + \alpha v}\right) \right. \\ & + \frac{\beta}{F} \int_0^h f(\tau) e^{-m\tau} \frac{x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} d\tau - \frac{\delta}{F} y \\ & + \frac{\beta}{F} \int_0^h f(\tau) e^{-m\tau} \\ & \times \left(\frac{x v}{1 + \alpha v} - \frac{x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} \right) d\tau \\ & \left. + \frac{\delta}{FG} \int_0^\omega g(\tau) e^{-n\tau} (y - y(t-\tau)) d\tau \right] \\ & + N\delta \int_0^\omega g(\tau) e^{-n\tau} y(t-\tau) d\tau \\ & - cv - qvz + qvz - \frac{q\mu}{r} z \\ = NFG & \left[-d \frac{(x - x_0)^2}{x} + \frac{\beta x_0 v}{1 + \alpha v} \right] - cv - \frac{q\mu}{r} z \\ = -NFGd & \frac{(x - x_0)^2}{x} - cv \\ & + cv \frac{R_0(1 + \alpha v - \alpha v)}{1 + \alpha v} - \frac{q\mu}{r} z \\ = -\frac{NFGd}{x} & (x - x_0)^2 + cv(R_0 - 1) \\ & - \frac{R_0 c \alpha v^2}{1 + \alpha v} - \frac{q\mu}{r} z. \end{aligned} \quad (17)$$

If $R_0 \leq 1$, then $dW_0/dt \leq 0$ for all $x, v, z > 0$. By Theorem 5.3.1 in [33], the solutions of system (2)–(5) limit to M , the largest invariant subset of $\{dW_0/dt = 0\}$. Clearly, it follows from (17) that $dW_0/dt = 0$ if and only if $x = x_0$, $v = 0$, and $z = 0$. Noting that M is invariant for each element of M , we have $v = 0$, and $z = 0$, and then $\dot{v} = 0$. From (4) we derive that

$$0 = \dot{v} = N\delta \int_0^\omega g(\tau) e^{-n\tau} y(t-\tau) d\tau. \quad (18)$$

This yields $y = 0$. Hence, $dW_0/dt = 0$ if and only if $x = x_0$, $y = 0$, $v = 0$, and $z = 0$. From LaSalle's Invariance Principle, E_0 is GAS. $\square$

Theorem 3. *If $R_1 \leq 1 < R_0$, then E_1 is GAS.*

Proof. We construct the following Lyapunov functional:

$$\begin{aligned} W_1 = NFG & \left[x_1 H\left(\frac{x}{x_1}\right) + \frac{1}{F} y_1 H\left(\frac{y}{y_1}\right) \right. \\ & + \frac{1}{F} \frac{\beta x_1 v_1}{(1 + \alpha v_1)} \\ & \times \int_0^h f(\tau) e^{-m\tau} \\ & \times \int_0^\tau H\left(\frac{x(t-\theta)v(t-\theta)(1 + \alpha v_1)}{x_1 v_1 (1 + \alpha v(t-\theta))}\right) d\theta d\tau \\ & + \frac{\delta y_1}{FG} \int_0^\omega g(\tau) e^{-n\tau} \int_0^\tau H\left(\frac{y(t-\theta)}{y_1}\right) d\theta d\tau \left. \right] \\ & + v_1 H\left(\frac{v}{v_1}\right) + \frac{q}{r} z. \end{aligned} \quad (19)$$

The time derivative of W_1 along the trajectories of (2)–(5) is given by

$$\begin{aligned} \frac{dW_1}{dt} = NFG & \left[\left(1 - \frac{x_1}{x}\right) \right. \\ & \times \left(\lambda - dx - \frac{\beta x v}{1 + \alpha v} \right) + \frac{1}{F} \left(1 - \frac{y_1}{y}\right) \\ & \times \left(\beta \int_0^h f(\tau) e^{-m\tau} \frac{x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} d\tau - \delta y \right) \\ & + \frac{\beta}{F} \int_0^h f(\tau) e^{-m\tau} \\ & \times \left(\frac{x v}{1 + \alpha v} - \frac{x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \frac{x_1 v_1}{1 + \alpha v_1} \right. \\ & \left. \times \ln \left(\frac{x(t-\tau)v(t-\tau)(1 + \alpha v)}{x v (1 + \alpha v(t-\tau))} \right) \right) d\tau \end{aligned}$$

$$\begin{aligned}
& + \frac{\delta}{FG} \int_0^\omega g(\tau) e^{-n\tau} \\
& \quad \times \left(y - y(t-\tau) + y_1 \ln \left(\frac{y(t-\tau)}{y} \right) \right) d\tau \Big] \\
& + \left(1 - \frac{v_1}{v} \right) \left(N\delta \int_0^\omega g(\tau) e^{-n\tau} y(t-\tau) d\tau \right. \\
& \quad \left. - cv - qzv \right) + qvz - \frac{q\mu}{r} z.
\end{aligned} \tag{20}$$

Using the steady state conditions for E_1 :

$$\begin{aligned}
\lambda &= dx_1 + \frac{\beta x_1 v_1}{1 + \alpha v_1}, \\
\delta y_1 &= F \frac{\beta x_1 v_1}{1 + \alpha v_1}, \\
cv_1 &= N\delta G y_1,
\end{aligned} \tag{21}$$

we have

$$\begin{aligned}
\frac{dW_1}{dt} &= NFG \left[-d \frac{(x-x_1)^2}{x} + \frac{\beta x_1 v_1}{1 + \alpha v_1} \right. \\
&\quad - \frac{\beta x_1 v_1}{1 + \alpha v_1} \frac{x_1}{x} + \frac{\beta x_1 v}{1 + \alpha v} - \frac{1}{F} \frac{\beta x_1 v_1}{(1 + \alpha v_1)} \\
&\quad \times \int_0^h f(\tau) e^{-m\tau} \\
&\quad \times \frac{y_1 x(t-\tau) v(t-\tau) (1 + \alpha v_1)}{y x_1 v_1 (1 + \alpha v(t-\tau))} d\tau \\
&\quad + \frac{\delta}{F} y_1 + \frac{1}{F} \frac{\beta x_1 v_1}{1 + \alpha v_1} \\
&\quad \times \int_0^h f(\tau) e^{-m\tau} \\
&\quad \times \ln \left(\frac{x(t-\tau) v(t-\tau) (1 + \alpha v)}{x v (1 + \alpha v(t-\tau))} \right) d\tau \\
&\quad + \frac{\delta y_1}{FG} \int_0^\omega g(\tau) e^{-n\tau} \ln \left(\frac{y(t-\tau)}{y} \right) d\tau \Big] \\
&+ N\delta y_1 \int_0^\omega g(\tau) e^{-n\tau} \frac{v_1 y(t-\tau)}{v y_1} d\tau \\
&- cv + cv_1 + qv_1 z - \frac{q\mu}{r} z.
\end{aligned} \tag{22}$$

Using the following equalities:

$$\begin{aligned}
& \ln \left(\frac{x(t-\tau) v(t-\tau) (1 + \alpha v)}{x v (1 + \alpha v(t-\tau))} \right) \\
&= \ln \left(\frac{y_1 x(t-\tau) v(t-\tau) (1 + \alpha v_1)}{y x_1 v_1 (1 + \alpha v(t-\tau))} \right) \\
&\quad + \ln \left(\frac{x_1}{x} \right) + \ln \left(\frac{v_1 y}{v y_1} \right) + \ln \left(\frac{1 + \alpha v}{1 + \alpha v_1} \right), \\
& \ln \left(\frac{y(t-\tau)}{y} \right) = \ln \left(\frac{v_1 y}{v_1 y} \right) + \ln \left(\frac{v_1 y(t-\tau)}{v y_1} \right),
\end{aligned} \tag{23}$$

then collecting terms of (22), we obtain

$$\begin{aligned}
\frac{dW_1}{dt} &= NFG \left[-d \frac{(x-x_1)^2}{x} - \frac{\delta y_1}{F} \left(\frac{x_1}{x} - 1 - \ln \frac{x_1}{x} \right) \right. \\
&\quad + \frac{\delta y_1}{F} \frac{v(1 + \alpha v_1)}{v_1 (1 + \alpha v)} - \frac{\delta y_1}{F^2} \\
&\quad \times \int_0^h f(\tau) e^{-m\tau} \\
&\quad \times \left(\frac{y_1 x(t-\tau) v(t-\tau) (1 + \alpha v_1)}{y x_1 v_1 (1 + \alpha v(t-\tau))} - 1 \right. \\
&\quad \left. \left. - \ln \left(\frac{y_1 x(t-\tau) v(t-\tau) (1 + \alpha v_1)}{y x_1 v_1 (1 + \alpha v(t-\tau))} \right) \right) d\tau \right. \\
&\quad - \frac{\delta y_1}{FG} \int_0^\omega g(\tau) e^{-n\tau} \\
&\quad \times \left(\frac{v_1 y(t-\tau)}{v y_1} - 1 \right. \\
&\quad \left. \left. - \ln \left(\frac{v_1 y(t-\tau)}{v y_1} \right) \right) d\tau \right. \\
&\quad \left. + \frac{\delta y_1}{F} \left(\ln \left(\frac{1 + \alpha v}{1 + \alpha v_1} \right) - \frac{v}{v_1} \right) \right] \\
&\quad + qz \left(v_1 - \frac{\mu}{r} \right) \\
&= NFG \left[-d \frac{(x-x_1)^2}{x} + \frac{\delta y_1}{F} \right. \\
&\quad \times \left(-1 + \frac{v(1 + \alpha v_1)}{v_1 (1 + \alpha v)} - \frac{v}{v_1} + \frac{1 + \alpha v}{1 + \alpha v_1} \right) \\
&\quad - \frac{\delta y_1}{F} H \left(\frac{x_1}{x} \right) - \frac{\delta y_1}{F^2}
\end{aligned}$$

$$\begin{aligned}
& \times \int_0^h f(\tau) e^{-m\tau} \\
& \quad \times H\left(\frac{y_1 x(t-\tau) v(t-\tau) (1+\alpha v_1)}{y x_1 v_1 (1+\alpha v(t-\tau))}\right) d\tau \\
& - \frac{\delta}{FG} y_1 \int_0^\omega g(\tau) e^{-n\tau} H\left(\frac{v_1 y(t-\tau)}{v y_1}\right) d\tau \\
& - \frac{\delta y_1}{F} H\left(\frac{1+\alpha v}{1+\alpha v_1}\right) + qz\left(v_1 - \frac{\mu}{r}\right) \\
& = NFG \left[-d \frac{(x-x_1)^2}{x} - \frac{\delta y_1}{F} \frac{\alpha(v-v_1)^2}{v_1 (1+\alpha v) (1+\alpha v_1)} \right. \\
& \quad - \frac{\delta y_1}{F} H\left(\frac{x_1}{x}\right) - \frac{\delta y_1}{F^2} \\
& \quad \times \int_0^h f(\tau) e^{-m\tau} \\
& \quad \times H\left(\frac{y_1 x(t-\tau) v(t-\tau) (1+\alpha v_1)}{y x_1 v_1 (1+\alpha v(t-\tau))}\right) d\tau \\
& \quad - \frac{\delta}{FG} y_1 \int_0^\omega g(\tau) e^{-n\tau} H\left(\frac{v_1 y(t-\tau)}{v y_1}\right) d\tau \\
& \quad \left. - \frac{\delta y_1}{F} H\left(\frac{1+\alpha v}{1+\alpha v_1}\right) \right] \\
& + \frac{qd}{\alpha d + \beta} \left(1 + \frac{\mu \alpha d + \mu \beta}{rd}\right) (R_1 - 1) z.
\end{aligned} \tag{24}$$

Thus, if $R_0 > 1$, then x_1, y_1 , and $v_1 > 0$, and hence, if $R_1 \leq 1$, then $dW_1/dt \leq 0$ for all $x, y, v > 0$. By Theorem 5.3.1 in [33], the solutions of system (2)–(5) limit to M , the largest invariant subset of $\{dW_1/dt = 0\}$. It can be seen that $dW_1/dt = 0$ if and only if $x = x_1, v = v_1$, and $H = 0$; that is,

$$\begin{aligned}
\frac{y_1 x(t-\tau) v(t-\tau) (1+\alpha v_1)}{y x_1 v_1 (1+\alpha v(t-\tau))} &= \frac{v_1 y(t-\tau)}{v y_1} = 1 \\
&\text{for almost all } \tau \in [0, \rho].
\end{aligned} \tag{25}$$

From (25), if $v = v_1$, then $y = y_1$, and hence dW_1/dt equals zero at E_1 . LaSalle's Invariance Principle implies global stability of E_1 . $\square$

Theorem 4. *If $R_1 > 1$, then E_2 is GAS.*

Proof. We construct the following Lyapunov functional:

$$\begin{aligned}
W_2 &= NFG \left[x_2 H\left(\frac{x}{x_2}\right) + \frac{1}{F} y_2 H\left(\frac{y}{y_2}\right) \right. \\
&\quad \left. + \frac{1}{F} \frac{\beta x_2 v_2}{(1+\alpha v_2)} \right]
\end{aligned}$$

$$\begin{aligned}
& \times \int_0^h f(\tau) e^{-m\tau} \\
& \quad \times \int_0^\tau H\left(\frac{x(t-\theta) v(t-\theta) (1+\alpha v_2)}{x_2 v_2 (1+\alpha v(t-\theta))}\right) d\theta d\tau \\
& + \frac{\delta y_2}{FG} \int_0^\omega g(\tau) e^{-n\tau} \int_0^\tau H\left(\frac{y(t-\theta)}{y_2}\right) d\theta d\tau \\
& + v_2 H\left(\frac{v}{v_2}\right) + \frac{q}{r} z_2 H\left(\frac{z}{z_2}\right).
\end{aligned} \tag{26}$$

The time derivative of W_2 along the trajectories of (2)–(5) is given by

$$\begin{aligned}
\frac{dW_2}{dt} &= NFG \left[\left(1 - \frac{x_2}{x}\right) \left(\lambda - dx - \frac{\beta x v}{1+\alpha v}\right) + \frac{1}{F} \left(1 - \frac{y_2}{y}\right) \right. \\
&\quad \times \left(\beta \int_0^h f(\tau) e^{-m\tau} \frac{x(t-\tau) v(t-\tau)}{1+\alpha v(t-\tau)} d\tau - \delta y \right) \\
&\quad + \frac{\beta}{F} \int_0^h f(\tau) e^{-m\tau} \\
&\quad \times \left(\frac{x v}{1+\alpha v} - \frac{x(t-\tau) v(t-\tau)}{1+\alpha v(t-\tau)} + \frac{x_2 v_2}{1+\alpha v_2} \right. \\
&\quad \left. \left. \times \ln \left(\frac{x(t-\tau) v(t-\tau) (1+\alpha v)}{x v (1+\alpha v(t-\tau))} \right) \right) d\tau \right. \\
&\quad + \frac{\delta}{FG} \int_0^\omega g(\tau) e^{-n\tau} \\
&\quad \times \left(y - y(t-\tau) \right. \\
&\quad \left. + y_2 \ln \left(\frac{y(t-\tau)}{y} \right) \right) d\tau \left. + \left(1 - \frac{v_2}{v}\right) \right. \\
&\quad \times \left(N\delta \int_0^\omega g(\tau) e^{-n\tau} y(t-\tau) d\tau - cv - qzv \right) \\
&\quad \left. + \left(1 - \frac{z_2}{z}\right) \left(qvz - \frac{q\mu}{r} z\right) \right].
\end{aligned} \tag{27}$$

Using the steady state conditions for E_2 :

$$\begin{aligned}
\lambda &= dx_2 + \beta \frac{x_2 v_2}{1+\alpha v_2}, \\
cv_2 &= NFG \left(\frac{\delta}{F} y_2 \right) - qv_2 z_2, \\
\mu &= rv_2,
\end{aligned} \tag{28}$$

we obtain

$$\begin{aligned}
\frac{dW_2}{dt} = & NFG \left[-d \frac{(x - x_2)^2}{x} + \frac{\beta x_2 v_2}{1 + \alpha v_2} \right. \\
& - \frac{\beta x_2 v_2}{1 + \alpha v_2} \frac{x_2}{x} + \frac{\beta x_2 v}{1 + \alpha v} - \frac{1}{F} \frac{\beta x_2 v_2}{1 + \alpha v_2} \\
& \times \int_0^h f(\tau) e^{-m\tau} \\
& \times \frac{y_2 x(t - \tau) v(t - \tau) (1 + \alpha v_2)}{y x_2 v_2 (1 + \alpha v(t - \tau))} d\tau \\
& + \frac{\delta}{F} y_2 + \frac{1}{F} \frac{\beta x_2 v_2}{1 + \alpha v_2} \\
& \times \int_0^h f(\tau) e^{-m\tau} \\
& \times \ln \left(\frac{x(t - \tau) v(t - \tau) (1 + \alpha v)}{x v (1 + \alpha v(t - \tau))} \right) d\tau \\
& + \frac{\delta y_2}{FG} \int_0^\omega g(\tau) e^{-n\tau} \ln \left(\frac{y(t - \tau)}{y} \right) d\tau \Big] \\
& - N\delta y_2 \int_0^\omega g(\tau) e^{-n\tau} \frac{v_2 y(t - \tau)}{v y_2} d\tau - cv \\
& + cv_2 + qv_2 z - qvz_2 - \frac{q\mu}{r} z + \frac{q\mu}{r} z_2.
\end{aligned} \tag{29}$$

Using the following equalities:

$$\begin{aligned}
cv &= cv_2 \frac{v}{v_2} = NFG \left(\frac{\delta}{F} y_2 \frac{v}{v_2} \right) - qvz_2, \\
\ln \left(\frac{x(t - \tau) v(t - \tau) (1 + \alpha v)}{x v (1 + \alpha v(t - \tau))} \right) \\
&= \ln \left(\frac{y_2 x(t - \tau) v(t - \tau) (1 + \alpha v_2)}{y x_2 v_2 (1 + \alpha v(t - \tau))} \right) \\
&\quad + \ln \left(\frac{x_2}{x} \right) + \ln \left(\frac{v_2 y}{v y_2} \right) + \ln \left(\frac{1 + \alpha v}{1 + \alpha v_2} \right), \\
\ln \left(\frac{y(t - \tau)}{y} \right) &= \ln \left(\frac{v y_2}{v_2 y} \right) + \ln \left(\frac{v_2 y(t - \tau)}{v y_2} \right),
\end{aligned} \tag{30}$$

and collecting terms of (29), we obtain

$$\begin{aligned}
\frac{dW_2}{dt} = & NFG \left[-d \frac{(x - x_2)^2}{x} - \frac{\delta y_1}{F} \left(\frac{x_2}{x} - 1 - \ln \frac{x_2}{x} \right) \right. \\
& + \frac{\delta y_2}{F} \frac{v(1 + \alpha v_2)}{v_2 (1 + \alpha v)} - \frac{\delta y_2}{F^2}
\end{aligned}$$

$$\begin{aligned}
& \times \int_0^h f(\tau) e^{-m\tau} \\
& \times \left(\frac{y_2 x(t - \tau) v(t - \tau) (1 + \alpha v_2)}{y x_2 v_2 (1 + \alpha v(t - \tau))} - 1 \right. \\
& \quad \left. - \ln \left(\frac{y_2 x(t - \tau) v(t - \tau) (1 + \alpha v_2)}{y x_2 v_2 (1 + \alpha v(t - \tau))} \right) \right) d\tau \\
& - \frac{\delta y_2}{FG} \int_0^\omega g(\tau) e^{-n\tau} \left(\frac{v_2 y(t - \tau)}{v y_2} - 1 \right. \\
& \quad \left. - \ln \left(\frac{v_2 y(t - \tau)}{v y_2} \right) \right) d\tau \\
& + \frac{\delta y_2}{F} \left(\ln \left(\frac{1 + \alpha v}{1 + \alpha v_2} \right) - \frac{v}{v_2} \right) \Big] \\
= & NFG \left[-d \frac{(x - x_2)^2}{x} - \frac{\delta y_2}{F} \frac{\alpha(v - v_2)^2}{v_2 (1 + \alpha v) (1 + \alpha v_2)} \right. \\
& - \frac{\delta y_2}{F} H \left(\frac{x_2}{x} \right) - \frac{\delta y_2}{F^2} \\
& \times \int_0^h f(\tau) e^{-m\tau} \\
& \times H \left(\frac{y_2 x(t - \tau) v(t - \tau) (1 + \alpha v_2)}{y x_2 v_2 (1 + \alpha v(t - \tau))} \right) d\tau \\
& - \frac{\delta}{FG} y_2 \int_0^\omega g(\tau) e^{-n\tau} H \left(\frac{v_2 y(t - \tau)}{v y_2} \right) d\tau \\
& \left. - \frac{\delta y_2}{F} H \left(\frac{1 + \alpha v}{1 + \alpha v_2} \right) \right].
\end{aligned} \tag{31}$$

Thus, if $R_1 > 1$, then x_2, y_2, v_2 , and $z_2 > 0$ and $dW_2/dt \leq 0$. By Theorem 5.3.1 in [33], the solutions of system (2)–(5) limit to M , the largest invariant subset of $\{dW_2/dt = 0\}$. It can be seen that $dW_2/dt = 0$ if and only if $x = x_2, v = v_2$, and $H = 0$; that is,

$$\begin{aligned}
\frac{y_2 x(t - \tau) v(t - \tau) (1 + \alpha v_2)}{y x_2 v_2 (1 + \alpha v(t - \tau))} &= \frac{v_2 y(t - \tau)}{v y_2} = \frac{1 + \alpha v}{1 + \alpha v_2} = 1 \\
&\text{for almost all } \tau \in [0, \rho].
\end{aligned} \tag{32}$$

Then from (32) $y = y_2$, and hence $dW_2/dt = 0$ at the steady state E_2 . LaSalle's Invariance Principle implies global stability of E_2 . $\square$

4. Conclusion

In this paper, we have proposed a virus infection model which describes the interaction of the virus with the uninfected and infected cells taking into account the antibody immune response. The infection rate is given by saturation functional response. Two types of distributed time delays have been

incorporated into the model to describe the time needed for infection of uninfected cell and virus replication. Using the method of Lyapunov functional, we have established that the global dynamics of the model is determined by two threshold parameters R_0 and R_1 . The basic reproduction number viral infection R_0 determines whether a chronic infection can be established, and the antibody immune response reproduction number R_1 determines whether a persistent antibody immune response can be established. We have proven that if $R_0 \leq 1$, then the uninfected steady state is GAS, and the viruses are cleared. If $R_1 \leq 1 < R_0$, then the infected steady state without antibody immune response is GAS, and the infection becomes chronic but without persistent antibody immune response. If $R_1 > 1$, then the infected steady state with antibody immune response is GAS, and the infection is chronic with persistent antibody immune response. We note that the effect of the time delay appears in the parameters F and G . Since $0 < F \leq 1$ and $0 < G \leq 1$, then the intracellular delay can reduce the parameters R_0 and R_1 . As a consequence, ignoring the delay will produce overestimation of R_0 .

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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