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STABILITY OF HUMORAL IMMUNITY VIRUS INFECTION MODEL WITH GENERAL INCIDENCE RATE AND DISTRIBUTED DELAYS

A. M. ELAIW, A. ALHEJELAN, AND A. M. SHEHATA

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Abstract. In this paper, we investigate the global stability of a virus infection model with humoral immune response and distributed intracellular delays. The incidence rate of infection is given by general functional response. The model has two types of distributed time delays which describe the time needed for infection of uninfected cell and virus replication. Lyapunov functionals are constructed and LaSalle's invariance principle is used to establish the global asymptotic stability of all steady states of the model. We have proven that, if the basic reproduction number R_0 is less than or equal unity, then the uninfected steady state is globally asymptotically stable (GAS), and if the humoral immune response reproduction number R_1 is less than or equal unity and $R_0 > 1$, then the infected steady state without humoral immune response exists and it is GAS, and if $R_1 > 1$, then the infected steady state with humoral immune response exists and it is GAS. Numerical simulations have been carried out with a specific form of the incidence rate function. We have shown that, both the numerical and theoretical results are consistent.

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Keywords: virus dynamics, intracellular delay, global stability, humoral immunity, Lyapunov functional

1. INTRODUCTION

Recently, several mathematical models have been proposed and developed to understand the interaction of virus and target cells, such as human immunodeficiency virus (HIV) (see [3,4,6–11,13,15,16,23,25,26,29,31,32]), hepatitis B virus (HBV) [21,28,33], hepatitis C virus (HCV) [27] and [38] and human T cell leukemia HTLV [22], etc. Mathematical modeling and model analysis of the viral infection process are helpful for estimating key parameter values, and guiding development efficient anti-viral drug therapies. Immunity is a biological term that describes a state of having sufficient biological defenses to avoid infection, disease or other unwanted biological invasion. 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 [5]. Mathematical models for virus dynamics with humoral immune response have been developed in [1, 2, 12, 14, 19, 24, 30, 34, 36].

The basic virus dynamics model with humoral immune response was introduced by Murase et. al. [24] as:

$$\dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t), \tag{1.1}$$
$$\dot{y}(t) = \beta x(t)v(t) - ay(t), \tag{1.2}$$
$$\dot{v}(t) = Nay(t) - cv(t) - qv(t)z(t), \tag{1.3}$$
$$\dot{z}(t) = rv(t)z(t) - \mu z(t), \tag{1.4}$$

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 is the rate at which new uninfected cells are generated from the body; d is the natural death rate constant of uninfected cells; β is the infection rate constant; N is the number of free viruses produced during the average infected cell life span; a is the death rate constant of infected cells; c is the clearance rate constant of the virus particles; r and μ are the proliferation rate and death rate constants of B cells; q is the B cells neutralize rate. Note that the forenamed system (1.1)-(1.4) does not contain an intracellular time delay between the infection of a cell and the production of new virus particles, despite the fact that intracellular delay actually exists (see e.g. [4, 6, 7, 9–11, 13, 15, 16, 23]). Further, the infection rate is assumed to be bilinear in x and v, but many researches suggested that the bilinear incidence rate associated with the mass action principle is insufficient to describe the infection process in detail (see e.g. [18, 20]). Thus, it is reasonable to assume that the infection rate is given by nonlinear incidence rate. The incidence rate has been considered in the viral infection models with humoral immune response by different forms as: saturated incidence rate, $\frac{\beta xv}{1+\alpha v}$ where $\alpha \geq 0$ [12, 36], Beddington-DeAngelis functional response, $\frac{\beta xv}{1+\gamma x+\alpha v}$, $\alpha, \gamma \geq 0$ [14, 37], and general form, $\Phi(x, v)v$ [35]. In [35], model with discrete time delay has been investigated.

In this paper, we propose a virus infection model with humoral immune response and with general incidence rate. We incorporate two types of distributed delays into this model to account the time delay between the time that target cells are contacted by the virus particles and the time the emission of infectious (matures) virus particles. The global stability of this model is established using Lyapunov functionals and LaSalle's invariance principle. We prove that the global dynamics of this model is determined by the basic reproduction number R_0 and humoral 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 humoral immune response exists and it is GAS, and if $R_1 > 1$, then the infected steady state with humoral response exists and it is GAS. Numerical simulations is carried out to confirm our theoretical results.

2. The Model

In this section, we propose a mathematical model of virus infection which describes the interaction of the virus with target cells, taking into account the humoral immune response.

$$\dot{x}(t) = \lambda - dx(t) - \Phi(x(t), v(t))v(t), \tag{2.1}$$

$$\dot{y}(t) = \int_0^h f(\tau)e^{-m\tau}\Phi(x(t-\tau), v(t-\tau))v(t-\tau)d\tau - ay(t), \tag{2.2}$$

$$\dot{v}(t) = Na\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv(t) - qv(t)z(t), \tag{2.3}$$

$$\dot{z}(t) = rv(t)z(t) - \mu z(t). \tag{2.4}$$

All the variables and parameters of the model have the same meanings as given in section 1. To account for the time lag between viral contacting an uninfected cell and the production of new virus particles, two distributed intracellular delays are introduced. It assumed that the uninfected cells 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 $e^{-m\tau}$ account 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 $e^{-n\tau}$ account for the probability of surviving the time period of delay, where n is a constant. The incidence rate is given by a general function $\Phi(x,v)v$ where $\Phi \in C^1([0,\infty)\times[0,\infty),\mathbb{R})$ and satisfies the following assumptions [35]:

Assumption A1. $\Phi(x,v) > 0$ for all $x > 0$, $v > 0$, and $\Phi(0,v) = 0$.

Assumption A2. $\dfrac{\partial\Phi(x,v)}{\partial x} > 0$ for all $x > 0$ and $v > 0$.

Assumption A3. $\dfrac{\partial\Phi(x,v)}{\partial v} < 0$ for all $x > 0$ and $v > 0$.

Assumption A4. $\dfrac{\partial(\Phi(x,v)v)}{\partial v} > 0$ for all $x > 0$ and $v > 0$.

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

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

where s is a positive number. Then

$$0 < \int_0^h f(\tau)e^{-m\tau}d\tau \leq 1,\ 0 < \int_0^\omega g(\tau)e^{-n\tau}d\tau \leq 1, \quad m,n \geq 0.$$

Let us denote:

$$F = \int_0^h f(\tau)e^{-m\tau}d\tau, \qquad G = \int_0^\omega g(\tau)e^{-n\tau}d\tau.$$

The initial conditions for system (2.1)-(2.4) take the form

$$\begin{aligned} x(\theta) &= \varphi_1(\theta),\ y(\theta) = \varphi_2(\theta), \\ v(\theta) &= \varphi_3(\theta),\ z(\theta) = \varphi_4(\theta), \\ \varphi_j(\theta) &\geq 0,\ \theta \in [-\rho, 0),\ \ j = 1,...,4, \\ \varphi_j(0) &> 0,\ j = 1,...,4, \end{aligned} \tag{2.5}$$

where $\rho = \max\{h,\omega\}$, $(\varphi_1(\theta),\varphi_2(\theta),\varphi_3(\theta),\varphi_4(\theta)) \in C([-\rho,0],\mathbb{R}^4_+)$, 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 [17], system (2.1)-(2.4) has a unique solution satisfying the initial conditions (2.5).

2.1. *Non-negativity and boundedness of solutions*

In the following, we establish the non-negativity and boundedness of solutions of (2.1)-(2.4) with initial conditions (2.5).

Proposition 1. *Assume that Assumption A1 is satisfied. Let $(x(t), y(t), v(t), z(t))$ be any solution of (2.1)-(2.4) satisfying the initial conditions (2.5), then $x(t), y(t), v(t)$ and $z(t)$ are all non-negative 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 Eq. (2.1) 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 Eqs. (2.2)-(2.4) we have

$$y(t) = y(0)e^{-at} + \int_0^t e^{-a(t-\eta)} \int_0^h f(\tau)e^{-m\tau}\Phi(x(\eta-\tau), v(\eta-\tau))v(\eta-\tau)d\tau d\eta,$$

$$v(t) = v(0)e^{-\int_0^t (c+qz(\xi))d\xi} + Na \int_0^t e^{-\int_\eta^t (c+qz(\xi))d\xi} \int_0^\omega g(\tau)e^{-n\tau}y(\eta-\tau)d\tau d\eta,$$

$$z(t) = z(0)e^{-\int_0^t (\mu - rv(\xi))d\xi},$$

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 of the system. From Eq. (2.1) we have $\dot{x}(t) \leq \lambda - dx(t)$ and thus $\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{d}$. Let $X_1(t) = \int_0^h f(\tau)e^{-m\tau} x(t-\tau)d\tau + y(t)$, then

$$\begin{aligned}
\dot{X}_1(t) &= \int_0^h f(\tau)e^{-m\tau}\left(\lambda - dx(t-\tau) - \Phi(x(t-\tau), v(t-\tau))v(t-\tau)\right)d\tau \\
&\quad + \int_0^h f(\tau)e^{-m\tau}\Phi(x(t-\tau), v(t-\tau))v(t-\tau)d\tau - ay(t), \\
&= \lambda\int_0^h f(\tau)e^{-m\tau}d\tau - d\int_0^h f(\tau)e^{-m\tau}x(t-\tau)d\tau - ay(t) \\
&\leq \lambda\int_0^h f(\tau)e^{-m\tau}d\tau - \sigma_1\left[\int_0^h f(\tau)e^{-m\tau}x(t-\tau)d\tau + y(t)\right] \\
&= \lambda\int_0^h f(\tau)e^{-m\tau}d\tau - \sigma_1 X_1(t) \leq \lambda - \sigma_1 X_1(t),
\end{aligned}$$

where $\sigma_1 = \min\{d, a\}$. Hence $\limsup_{t\to\infty} X_1(t) \leq L_1$, where $L_1 = \dfrac{\lambda}{\sigma_1}$. Since $\int_0^h f(\tau)e^{-m\tau}x(t-\tau)d\tau > 0$, then $\limsup_{t\to\infty} y(t) \leq L_1$. On the other hand, let $X_2(t) = v(t) + \frac{q}{r}z(t)$, then

$$\begin{aligned}
\dot{X}_2(t) &= Na\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv(t) - \frac{q\mu}{r}z(t) \\
&\leq NaL_1\int_0^\omega g(\tau)e^{-n\tau}d\tau - \sigma_2\left(v(t) + \frac{q}{r}z(t)\right)
\end{aligned}$$

$$= NaL_1 \int_0^{\omega} g(\tau)e^{-n\tau}d\tau - \sigma_2 X_2(t) \leq NaL_1 - \sigma_2 X_2(t),$$

where $\sigma_2 = \min\{c, \mu\}$. Hence $\limsup_{t\to\infty} X_2(t) \leq L_2$, where $L_2 = \dfrac{NaL_1}{\sigma_2}$. Since $v(t) \geq 0$ and $y(t) \geq 0$, then $\limsup_{t\to\infty} v(t) \leq L_2$ and $\limsup_{t\to\infty} z(t) \leq L_3$, where $L_3 = \frac{r}{q}L_2$. Therefore, $x(t), y(t), v(t)$ and $z(t)$ are ultimately bounded. □

2.2. *Steady states*

We define the basic reproduction number for system (2.1)-(2.4) as

$$R_0 = \frac{NFG\Phi(x_0, 0)}{c},$$

where $x_0 = \lambda/d$. To calculate the steady state, we let the right-hand side of Eqs. (2.1)-(2.4) be zero:

$$\lambda - dx - \Phi(x, v)v = 0, \tag{2.6}$$

$$F\Phi(x, v)v - ay = 0, \tag{2.7}$$

$$NaGy - cv - qvz = 0, \tag{2.8}$$

$$rvz - \mu z = 0. \tag{2.9}$$

From (2.9), either $z = 0$ or $z \neq 0$. If $z = 0$, then from (2.6)-(2.8) we get

$$y = \frac{F(\lambda - dx)}{a} = \frac{c}{NaG}v, \qquad v = \frac{NFG(\lambda - dx)}{c}. \tag{2.10}$$

Substituting from (2.10) into (2.7) we get:

$$\left[\Phi\left(x, \frac{NFG(\lambda - dx)}{c}\right) - \frac{c}{NFG}\right]v = 0. \tag{2.11}$$

Eq. (2.11) has two possible solutions $v = 0$ or $v \neq 0$. If $v = 0$, then from Eqs. (2.6) and (2.7), we get $x = x_0$ and $y = 0$ which leads to the uninfected steady state $E_0(x_0, 0, 0, 0)$. If $v \neq 0$, then we have

$$\Phi\left(x, \frac{NFG(\lambda - dx)}{c}\right) - \frac{c}{NFG} = 0.$$

Let

$$M(x) = \Phi\left(x, \frac{NFG(\lambda - dx)}{c}\right) - \frac{c}{NFG}.$$

From Assumptions A1 and A2, function $M(x)$ is strictly increasing with respect to x. Moreover, $M(0) = \Phi(0, \frac{NFG\lambda}{c}) - \frac{c}{NFG} = -\frac{c}{NFG} < 0$. Also, $M(x_0) = \Phi(x_0, 0) - \frac{c}{NFG} = \frac{c}{NFG}(R_0 - 1)$. Therefore, if $R_0 > 1$, then there exist a unique $x_1 \in (0, x_0)$ such that $M(x_1) = 0$. From Eq. (2.10) we obtain $y_1 > 0$ and $v_1 > 0$.

It follows that, if $R_0 > 1$, then there is an infected steady state without immune response $E_1(x_1, y_1, v_1, 0)$.
The other possibility of Eq. (2.9) $z \neq 0$ leads to

$$v_2 = \frac{\mu}{r}, \quad y_2 = \frac{F\Phi(x_2, v_2)v_2}{a}, \quad z_2 = \frac{NFG\Phi(x_2, v_2)}{q} - \frac{c}{q}.$$

Let

$$M_1(x) = \lambda - dx - \Phi(x, v_2)v_2.$$

From Assumptions A1 and A2, function M_1 is strictly decreasing with respect to x. We have also $M_1(0) = \lambda > 0$ and $M_1(x_0) = -\Phi(x_0, v_2)v_2 < 0$. Thus, there exist a unique $x_2 \in (0, x_0)$ such that $M_1(x_2) = 0$. Now we are ready to define the humoral immune response reproduction number as:

$$R_1 = \frac{NFG\Phi(x_2, v_2)}{c}.$$

Hence, z_2 cab be rewritten as $z_2 = \frac{c}{q}(R_1 - 1)$. It follows that, if $R_1 > 1$, then there is an infected steady state with immune response $E_2(x_2, y_2, v_2, z_2)$.

From above we have the following result.

Lemma 1. *Assume that Assumptions A1 and A2 are satisfied and*
(i) if $R_0 \leq 1$, then there exists only one positive steady state E_0,
(ii) if $R_0 > 1$, then there exist two positive steady states E_0 and E_1, and
(iii) if $R_1 > 1$, then there exist three positive steady states E_0, E_1 and E_2.

2.3. *Global stability*

In this section, we prove the global stability of the steady states of system (2.1)-(2.4) employing the method of Lyapunov functional and LaSalle's invariance principle. Next we shall use the following notation: $u = u(t)$, for any $u \in \{x, y, v, z\}$. Throughout the paper, we let

$$H(u) = u - 1 - \ln u.$$

where $H : (0, \infty) \to [0, \infty)$, $H(u) \geq 0$ for any $u > 0$ and H has the global minimum $H(1) = 0$.

Theorem 1. *If Assumptions A1-A3 hold true and $R_0 \leq 1$, then E_0 is GAS.*

Proof. Define a Lyapunov functional W_0 as follows:

$$W_0 = NFG\left[x - x_0 - \int_{x_0}^{x} \frac{\Phi(x_0, 0)}{\Phi(\eta, 0)} d\eta + \frac{1}{F} y \right.$$
$$\left. + \frac{1}{F} \int_0^h f(\tau) e^{-m\tau} \int_0^\tau \Phi(x(t-\theta), v(t-\theta)) v(t-\theta) d\theta d\tau \right.$$

$$+\frac{a}{FG}\int_0^{\omega} g(\tau)e^{-n\tau}\int_0^{\tau} y(t-\theta)d\theta d\tau\Bigg]+v+\frac{q}{r}z. \tag{2.12}$$

The time derivative of W_0 along the trajectories of (2.1)-(2.4) satisfies

$$\begin{aligned}
\frac{dW_0}{dt} &= NFG\Bigg[\left(1-\frac{\Phi(x_0,0)}{\Phi(x,0)}\right)(\lambda-dx-\Phi(x,v)\,v)\\
&\quad+\frac{1}{F}\int_0^{h} f(\tau)e^{-m\tau}\Phi(x(t-\tau),v(t-\tau))v(t-\tau)d\tau-\frac{a}{F}y\\
&\quad+\frac{1}{F}\int_0^{h} f(\tau)e^{-m\tau}\left(\Phi(x,v)v-\Phi(x(t-\tau),v(t-\tau))v(t-\tau)\right)d\tau\\
&\quad+\frac{a}{FG}\int_0^{\omega} g(\tau)e^{-n\tau}(y-y(t-\tau))d\tau\Bigg]\\
&\quad+Na\int_0^{\omega} g(\tau)e^{-n\tau}y(t-\tau)d\tau-cv-qvz+qvz-\frac{q\mu}{r}z,\\
&=\frac{NFGd}{\Phi(x,0)}(x_0-x)\left(\Phi(x,0)-\Phi(x_0,0)\right)\\
&\quad+\left(NFG\Phi(x,v)\frac{\Phi(x_0,0)}{\Phi(x,0)}-c\right)v-\frac{q\mu}{r}z,\\
&=\frac{NFGd}{\Phi(x,0)}(x_0-x)\left(\Phi(x,0)-\Phi(x_0,0)\right)+c\left(R_0\frac{\Phi(x,v)}{\Phi(x,0)}-1\right)v-\frac{q\mu}{r}z.
\end{aligned} \tag{2.13}$$

From Assumptions A2-A3 we have

$$(x_0-x)\left(\Phi(x,0)-\Phi(x_0,0)\right)\le 0,\quad x\in(0,x_0],$$

$$\Phi(x,v)\le\Phi(x,0),\quad x,v>0$$

Therefore, if $R_0\le 1$, we get $R_0\frac{\Phi(x,v)}{\Phi(x,0)}\le 1$ and then $\frac{dW_0}{dt}\le 0$ for all $x,v,z>0$. By Theorem 5.3.1 in [17], the solutions of system (2.1)-(2.4) limit to M, the largest invariant subset of $\left\{\frac{dW_0}{dt}=0\right\}$. Clearly, it follows from (2.13) that $\frac{dW_0}{dt}=0$ 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 $z = 0$, then $\dot{v} = 0$. From Eq. (2.3) we drive that

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

This yields $y = 0$. Hence $\frac{dW_0}{dt} = 0$ if and only if $x = x_0$, $y = 0$, $v = 0$ and $z = 0$. From LaSalle's invariance principle, E_0 is GAS. □

Theorem 2. *If Assumptions A1-A4 hold true and $R_1 \leq 1 < R_0$, then E_1 is GAS.*

Proof. We construct the following Lyapunov functional

$$\begin{aligned} W_1 = NFG \Bigg[& x - x_1 - \int_{x_1}^{x} \frac{\Phi(x_1, v_1)}{\Phi(\eta, v_1)} d\eta + \frac{1}{F} y_1 H\left(\frac{y}{y_1}\right) \\ & + \frac{\Phi(x_1, v_1) v_1}{F} \int_0^h f(\tau) e^{-m\tau} \int_0^{\tau} H\left(\frac{\Phi\left(x(t-\theta), v(t-\theta)\right) v(t-\theta)}{\Phi(x_1, v_1) v_1}\right) d\theta d\tau \\ & + \frac{a y_1}{FG} \int_0^{\omega} g(\tau) e^{-n\tau} \int_0^{\tau} H\left(\frac{y(t-\theta)}{y_1}\right) d\theta d\tau \Bigg] + v_1 H\left(\frac{v}{v_1}\right) + \frac{q}{r} z. \end{aligned} \tag{2.14}$$

The time derivative of W_1 along the trajectories of (2.1)-(2.4) is given by

$$\begin{aligned} \frac{dW_1}{dt} = NFG \Bigg[& \left(1 - \frac{\Phi(x_1, v_1)}{\Phi(x, v_1)}\right) (\lambda - dx - \Phi(x, v) v) \\ & + \frac{1}{F} \left(1 - \frac{y_1}{y}\right) \left(\int_0^h f(\tau) e^{-m\tau} \Phi(x(t-\tau), v(t-\tau)) v(t-\tau) d\tau - ay \right) \\ & + \frac{1}{F} \int_0^h f(\tau) e^{-m\tau} \left(\Phi(x, v) v - \Phi(x(t-\tau), v(t-\tau)) v(t-\tau) \right. \\ & \left. + \Phi(x_1, v_1) v_1 \ln\left(\frac{\Phi(x(t-\tau), v(t-\tau)) v(t-\tau)}{\Phi(x, v) v}\right)\right) d\tau \\ & + \frac{a}{FG} \int_0^{\omega} g(\tau) e^{-n\tau} \left(y - y(t-\tau) + y_1 \ln\left(\frac{y(t-\tau)}{y}\right)\right) d\tau \Bigg] \\ & + \left(1 - \frac{v_1}{v}\right) \left(Na \int_0^{\omega} g(\tau) e^{-n\tau} y(t-\tau) d\tau - cv - qvz \right) + qvz - \frac{q\mu}{r} z. \end{aligned} \tag{2.15}$$

Using the steady state conditions for E_1:

$$\lambda = dx_1 + \frac{a}{F}y_1, \quad F\Phi(x_1,v_1)v_1 = ay_1, \quad cv_1 = NaGy_1,$$

we have

$$\begin{aligned}\frac{dW_1}{dt} = NFG\Bigg[&d(x_1-x)\left(1-\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}\right)+\frac{a}{F}y_1\\
&-\frac{a}{F}y_1\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}+\frac{a}{F}y_1\frac{\Phi(x,v)v}{\Phi(x,v_1)v_1}\\
&-\frac{a}{F^2}y_1\int_0^h f(\tau)e^{-m\tau}\frac{y_1\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_1,v_1)v_1}d\tau+\frac{a}{F}y_1\\
&+\frac{a}{F^2}y_1\int_0^h f(\tau)e^{-m\tau}\ln\left(\frac{\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{\Phi(x,v)v}\right)d\tau\\
&+\frac{ay_1}{FG}\int_0^\omega g(\tau)e^{-n\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau-\frac{ay_1}{FG}\int_0^\omega g(\tau)e^{-n\tau}\frac{v_1y(t-\tau)}{vy_1}d\tau\\
&-\frac{a}{F}y_1\frac{v}{v_1}+\frac{a}{F}y_1\Bigg]+q\left(v_1-\frac{\mu}{r}\right)z. \qquad (2.16)\end{aligned}$$

Using the following equalities:

$$\begin{aligned}\ln\left(\frac{\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{\Phi(x,v)v}\right) &= \ln\left(\frac{y_1\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_1,v_1)v_1}\right)\\
&\quad+\ln\left(\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}\right)+\ln\left(\frac{\Phi(x,v_1)}{\Phi(x,v)}\right)+\ln\left(\frac{v_1y}{vy_1}\right),\\
\ln\left(\frac{y(t-\tau)}{y}\right) &= \ln\left(\frac{vy_1}{v_1y}\right)+\ln\left(\frac{v_1y(t-\tau)}{vy_1}\right),\end{aligned}$$

we obtain

$$\begin{aligned}\frac{dW_1}{dt} = NFG\Bigg[&d(x_1-x)\left(1-\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}\right)-\frac{ay_1}{F}\left(\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}-1-\ln\left(\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}\right)\right)\\
&+\frac{ay_1}{F}\left(\frac{\Phi(x,v)v}{\Phi(x,v_1)v_1}-\frac{v}{v_1}+\frac{\Phi(x,v_1)}{\Phi(x,v)}-1\right)\\
&-\frac{ay_1}{F}\left(\frac{\Phi(x,v_1)}{\Phi(x,v)}-1-\ln\left(\frac{\Phi(x,v_1)}{\Phi(x,v)}\right)\right)\\
&-\frac{ay_1}{F^2}\int_0^h f(\tau)e^{-m\tau}\left(\frac{y_1\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_1,v_1)v_1}-1\right.\end{aligned}$$

$$-\ln\left(\frac{y_1\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_1,v_1)v_1}\right)\Bigg)d\tau$$
$$-\frac{ay_1}{FG}\int_0^{\omega} g(\tau)e^{-n\tau}\left(\frac{v_1y(t-\tau)}{vy_1}-1-\ln\left(\frac{v_1y(t-\tau)}{vy_1}\right)\right)d\tau\Bigg]+q\left(v_1-\frac{\mu}{r}\right)z. \tag{2.17}$$

Eq. (2.17) can be rewritten as:

$$\begin{aligned}\frac{dW_1}{dt} = NFG\Bigg[&\frac{d}{\Phi(x,v_1)}(x_1-x)\left(\Phi(x,v_1)-\Phi(x_1,v_1)\right)\\
&+\frac{\Phi(x_1,v_1)}{\Phi(x,v)\Phi(x,v_1)}\left(\Phi(x,v)-\Phi(x,v_1)\right)\left(\Phi(x,v)v-\Phi(x,v_1)v_1\right)\\
&-\frac{ay_1}{F}H\left(\frac{\Phi(x_1,v_1)}{\Phi(x,v_1)}\right)-\frac{ay_1}{F}H\left(\frac{\Phi(x,v_1)}{\Phi(x,v)}\right)\\
&-\frac{ay_1}{F^2}\int_0^{h} f(\tau)e^{-m\tau}H\left(\frac{y_1\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_1,v_1)v_1}\right)d\tau\\
&-\frac{ay_1}{FG}\int_0^{\omega} g(\tau)e^{-n\tau}H\left(\frac{v_1y(t-\tau)}{vy_1}\right)d\tau\Bigg]\\
&+qz\left(v_1-\frac{\mu}{r}\right).\end{aligned} \tag{2.18}$$

From Assumptions A3-A4, we have

$$(x_1-x)\left(\Phi(x,v_1)-\Phi(x_1,v_1)\right)\le 0,$$
$$\left(\Phi(x,v)-\Phi(x,v_1)\right)\left(\Phi(x,v)v-\Phi(x,v_1)v_1\right)\le 0.$$

Now we show that if $R_1\le 1$ then $v_1\le\frac{\mu}{r}=v_2$. Let $R_0>1$, then we want to show that

$$sgn\left(x_2-x_1\right)=sgn\left(v_1-v_2\right)=sgn\left(R_1-1\right).$$

From Assumptions A2-A4, for $x_1,x_2,v_1,v_2>0$, we have:

$$\left(\Phi(x_2,v_1)-\Phi(x_1,v_1)\right)(x_2-x_1)>0, \tag{2.19}$$
$$\left(\Phi(x_2,v_2)v_2-\Phi(x_2,v_1)v_1\right)(v_2-v_1)>0, \tag{2.20}$$
$$\left(\Phi(x_2,v_2)-\Phi(x_2,v_1)\right)(v_1-v_2)>0. \tag{2.21}$$

Suppose that, $sgn\left(x_2-x_1\right)=sgn\left(v_2-v_1\right)$. Using the conditions of the steady states E_1 and E_2 we have

$$\begin{aligned}(\lambda-dx_2)-(\lambda-dx_1)&=\Phi(x_2,v_2)v_2-\Phi(x_1,v_1)v_1\\
&=\Phi(x_2,v_2)v_2-\Phi(x_2,v_1)v_1+\left[\Phi(x_2,v_1)-\Phi(x_1,v_1)\right]v_1,\end{aligned}$$

but

$$[(\lambda - dx_2) - (\lambda - dx_1)](x_1 - x_2) = d(x_2 - x_1)^2 > 0. \tag{2.22}$$

Then from (2.19) and (2.20) we get:

$$sgn(x_1 - x_2) = sgn(x_2 - x_1),$$

which leads to contradiction. Thus, $sgn(x_2 - x_1) = sgn(v_1 - v_2)$. Using the steady state conditions for E_1 we have $\frac{NFG\Phi(x_1,v_1)}{c} = 1$, then

$$\begin{aligned} R_1 - 1 &= \frac{NFG}{c}(\Phi(x_2,v_2) - \Phi(x_1,v_1)) \\ &= \frac{NFG}{c}(\Phi(x_2,v_2) - \Phi(x_2,v_1) + \Phi(x_2,v_1) - \Phi(x_1,v_1)) \\ &= \frac{NFG}{c}[\Phi(x_2,v_2) - \Phi(x_2,v_1) + \Phi(x_2,v_1) - \Phi(x_1,v_1)]. \end{aligned}$$

From (2.19) and (2.21), we get

$$sgn(R_1 - 1) = sgn(v_1 - v_2).$$

Hence, if $R_0 > 1$, then $x_1, y_1, v_1 > 0$, and if $R_1 \le 1$, then $v_1 \le v_2 = \frac{\mu}{r}$ and $\frac{dW_1}{dt} \le 0$ for all $x, y, v, z > 0$. By Theorem 5.3.1 in [17], the solutions of system (2.1)-(2.4) limit to M, the largest invariant subset of $\left\{\frac{dW_1}{dt} = 0\right\}$. It can be seen that $\frac{dW_1}{dt} = 0$ if and only if $x = x_1, v = v_1, z = 0$ and $H = 0$ i.e.

$$\frac{y_1\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_1,v_1)v_1} = \frac{v_1 y(t-\tau)}{v y_1} = 1 \text{ for almost all } \tau \in [0,\rho]. \tag{2.23}$$

From Eq. (2.23), if $v = v_1$ then $y = y_1$ and hence $\frac{dW_1}{dt}$ equal to zero at E_1. LaSalle's invariance principle implies global stability of E_1. □

Theorem 3. *If Assumptions A1-A4 hold true and $R_1 > 1$, then E_2 is GAS.*

Proof. We construct the following Lyapunov functional

$$\begin{aligned} W_2 = NFG\Bigg[& x - x_2 - \int_{x_2}^{x} \frac{\Phi(x_2,v_2)}{\Phi(\eta,v_2)} d\eta + \frac{1}{F} y_2 H\left(\frac{y}{y_2}\right) \\ & + \frac{\Phi(x_2,v_2)v_2}{F} \int_0^h f(\tau) e^{-m\tau} \int_0^\tau H\left(\frac{\Phi(x(t-\theta),v(t-\theta))v(t-\theta)}{\Phi(x_2,v_2)v_2}\right) d\theta d\tau \\ & + \frac{a y_2}{FG} \int_0^\omega g(\tau) e^{-n\tau} \int_0^\tau H\left(\frac{y(t-\theta)}{y_2}\right) d\theta d\tau \Bigg] + v_2 H\left(\frac{v}{v_2}\right) + \frac{q}{r} z_2 H\left(\frac{z}{z_2}\right). \end{aligned} \tag{2.24}$$

Calculating the time derivative of W_2 along the solution of (2.1)-(2.4) we obtain

$$\begin{aligned}\frac{dW_2}{dt} = NFG\Bigg[&\left(1-\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\right)(\lambda - dx - \Phi(x,v)v)\\ &+\frac{1}{F}\left(1-\frac{y_2}{y}\right)\left(\int_0^h f(\tau)e^{-m\tau}\Phi(x(t-\tau),v(t-\tau))v(t-\tau)d\tau - ay\right)\\ &+\frac{1}{F}\int_0^h f(\tau)e^{-m\tau}\left(\Phi(x,v)v - \Phi(x(t-\tau),v(t-\tau))v(t-\tau)\right.\\ &\left.+\Phi(x_2,v_2)v_2\ln\left(\frac{\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{\Phi(x,v)v}\right)\right)d\tau\\ &+\frac{a}{FG}\int_0^\omega g(\tau)e^{-n\tau}\left(y - y(t-\tau) + y_2\ln\left(\frac{y(t-\tau)}{y}\right)\right)d\tau\Bigg]\\ &+\left(1-\frac{v_2}{v}\right)\left(Na\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv - qvz\right)\\ &+\left(1-\frac{z_2}{z}\right)\left(qvz - \frac{q\mu}{r}z\right). \end{aligned} \tag{2.25}$$

Applying $\lambda = dx_2 + \Phi(x_2,v_2)v_2$ we obtain

$$\begin{aligned}\frac{dW_2}{dt} = NFG\Bigg[&d(x_2-x)\left(1-\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\right) + \Phi(x_2,v_2)v_2 - \Phi(x_2,v_2)v_2\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\\ &+\Phi(x,v)v\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\\ &-\frac{1}{F}\Phi(x_2,v_2)v_2\int_0^h f(\tau)e^{-m\tau}\frac{y_2\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_2,v_2)v_2}d\tau + \frac{a}{F}y_2\\ &+\frac{1}{F}\Phi(x_2,v_2)v_2\int_0^h f(\tau)e^{-m\tau}\ln\left(\frac{\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{\Phi(x,v)v}\right)d\tau\\ &+\frac{ay_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau - \frac{ay_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}\frac{v_2y(t-\tau)}{vy_2}d\tau\Bigg]\\ &-cv + cv_2 + qv_2z - qvz_2 - \frac{q\mu}{r}z + \frac{q\mu}{r}z_2. \end{aligned} \tag{2.26}$$

Using the steady state conditions of E_2

$$F\Phi(x_2,v_2)v_2 = ay_2, \quad cv_2 = NaGy_2 - qv_2z_2, \quad \mu = rv_2,$$

and the following equalities:

$$cv = cv_2\frac{v}{v_2} = NFG\left(\frac{a}{F}y_2\frac{v}{v_2}\right) - qvz_2,$$

$$\ln\left(\frac{\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{\Phi(x,v)v}\right) = \ln\left(\frac{y_2\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_2,v_2)v_2}\right) + \ln\left(\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\right) + \ln\left(\frac{\Phi(x,v_2)}{\Phi(x,v)}\right) + \ln\left(\frac{v_2y}{vy_2}\right),$$

$$\ln\left(\frac{y(t-\tau)}{y}\right) = \ln\left(\frac{vy_2}{v_2y}\right) + \ln\left(\frac{v_2y(t-\tau)}{vy_2}\right),$$

we obtain

$$\begin{aligned}\frac{dW_2}{dt} = NFG\Bigg[&d(x_2-x)\left(1-\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\right) - \frac{ay_2}{F}\left(\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)} - 1 - \ln\left(\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\right)\right)\\ &- \frac{ay_2}{F^2}\int_0^h f(\tau)e^{-m\tau}\left(\frac{y_2\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_2,v_2)v_2} - 1\right.\\ &\left.- \ln\left(\frac{y_2\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_2,v_2)v_2}\right)\right)d\tau\\ &- \frac{ay_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}\left(\frac{v_2y(t-\tau)}{vy_2} - 1 - \ln\left(\frac{v_2y(t-\tau)}{vy_2}\right)\right)d\tau\\ &- \frac{ay_2}{F}\left(\frac{\Phi(x,v_2)}{\Phi(x,v)} - 1 - \ln\left(\frac{\Phi(x,v_2)}{\Phi(x,v)}\right)\right)\\ &+ \frac{ay_2}{F}\left(\frac{\Phi(x,v)v}{\Phi(x,v_2)v_2} + \frac{\Phi(x,v_2)}{\Phi(x,v)} - \frac{v}{v_2} - 1\right)\Bigg].\end{aligned} \tag{2.27}$$

We can rewrite (2.27) as

$$\begin{aligned}\frac{dW_2}{dt} = NFG\Bigg[&\frac{d}{\Phi(x,v_2)}(x_2-x)\left(\Phi(x,v_2)-\Phi(x_2,v_2)\right) - \frac{ay_2}{F}H\left(\frac{\Phi(x_2,v_2)}{\Phi(x,v_2)}\right)\\ &- \frac{ay_2}{F^2}\int_0^h f(\tau)e^{-m\tau}H\left(\frac{y_2\Phi(x(t-\tau),v(t-\tau))v(t-\tau)}{y\Phi(x_2,v_2)v_2}\right)d\tau\\ &- \frac{ay_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}H\left(\frac{v_2y(t-\tau)}{vy_2}\right)d\tau - \frac{ay_2}{F}H\left(\frac{\Phi(x,v_2)}{\Phi(x,v)}\right)\\ &+ \frac{\Phi(x_2,v_2)}{\Phi(x,v)\Phi(x,v_2)}\left(\Phi(x,v)-\Phi(x,v_2)\right)\left(\Phi(x,v)v-\Phi(x,v_2)v_2\right)\Bigg].\end{aligned} \tag{2.28}$$

From Assumptions A3-A4, we have

$$(x_2 - x)\left(\Phi(x, v_2) - \Phi(x_2, v_2)\right) \leq 0,$$
$$\left(\Phi(x, v) - \Phi(x, v_2)\right)\left(\Phi(x, v)v - \Phi(x, v_2)v_2\right) \leq 0.$$

Therefore, $\frac{dW_2}{dt} \leq 0$. One can easily show that $\frac{dW_2}{dt} = 0$ occurs at E_2. LaSalle's invariance principle implies global stability of E_2. □

3. Numerical results and discussions

In this section we first show two special forms of the general function $\Phi(x, v)$ which satisfy Assumptions A1-A4, then perform some numerical simulations for model (2.1)-(2.4) in case of discrete-time delays. Function $\Phi(x, v)$ can be chosen as:

(1) Beddington-DeAngelis functional response:

$$\Phi_1(x, v) = \frac{\beta x}{1 + \gamma x + \alpha v},$$

where $\alpha, \gamma \geq 0$. We have the following

$$\Phi_1(x, v) > 0 \text{ for all } x > 0, v > 0, \text{ and } \Phi_1(0, v) = 0,$$
$$\frac{\partial \Phi_1(x, v)}{\partial x} = \frac{\beta\,(1 + \alpha v)}{(1 + \gamma x + \alpha v)^2} > 0 \text{ for all } v > 0,$$
$$\frac{\partial \Phi_1(x, v)}{\partial v} = \frac{-\beta \alpha x}{(1 + \gamma x + \alpha v)^2} < 0 \text{ for all } x > 0,$$
$$\frac{\partial\left(\Phi_1(x, v)v\right)}{\partial v} = \frac{\beta x(1 + \gamma x)}{(1 + \gamma x + \alpha v)^2} > 0 \text{ for all } x > 0.$$

Then function $\Phi(x, v)$ satisfies Assumptions A1-A4 and the global stability results presented in Theorems 1-3 are valid.

(2) Crowley-Martin functional response:

$$\Phi_2(x, v) = \frac{\beta x}{(1 + \gamma x)(1 + \alpha v)}.$$

Function Φ_2 satisfies the following:

$$\Phi_2(x, v) > 0 \text{ for all } x > 0, v > 0, \text{ and } \Phi_2(0, v) = 0,$$
$$\frac{\partial \Phi_2(x, v)}{\partial x} = \frac{\beta}{(1 + \alpha v)(1 + \gamma x)^2} > 0 \text{ for all } v > 0,$$
$$\frac{\partial \Phi_2(x, v)}{\partial v} = \frac{-\beta \alpha x}{(1 + \alpha v)^2(1 + \gamma x)} < 0 \text{ for all } x > 0,$$
$$\frac{\partial\left(\Phi_2(x, v)v\right)}{\partial v} = \frac{\beta x}{(1 + \alpha v)^2(1 + \gamma x)} > 0 \text{ for all } x > 0.$$

Thus Assumption A1-A4 hold true and Theorems 1-3 are applicable.

Next, we shall perform simulation studies for the model (2.1)-(2.4) with function $\Phi_2(x,v)$ and with particular distribution functions $f(\tau)$ and $g(\tau)$. All computations are carried out by MATLAB. We are going to choose the probability distribution functions $f(\tau)$ and $g(\tau)$ as $f(\tau)=\delta(\tau-\tau_1)$ and $g(\tau)=\delta(\tau-\tau_2)$, where $\delta(.)$ is the dirac delta function, τ_1 and τ_2 are constants and $\tau_1\in[0,h],\tau_2\in[0,\omega]$. We can see that, from the properties of dirac delta function, as h and ω tend to ∞,

$$\int_0^\infty f(\tau)d\tau=\int_0^\infty g(\tau)d\tau=1,$$

$$F=\int_0^\infty \delta(\tau-\tau_1)e^{-m\tau}d\tau=e^{-m\tau_1},$$

$$G=\int_0^\infty \delta(\tau-\tau_2)e^{-n\tau}d\tau=e^{-n\tau_2}.$$

Moreover, we have

$$\int_0^\infty \delta(\tau-\tau_1)e^{-m\tau}\Phi_2\left(x\left(t-\tau\right),v\left(t-\tau\right)\right)v\left(t-\tau\right)d\tau$$

$$=e^{-m\tau_1}\Phi_2\left(x\left(t-\tau_1\right),v\left(t-\tau_1\right)\right)v\left(t-\tau_1\right),$$

$$\int_0^\infty \delta(\tau-\tau_2)e^{-n\tau}y\left(t-\tau\right)d\tau=e^{-n\tau_2}y\left(t-\tau_2\right).$$

Using these choices, model (2.1)-(2.4) becomes

$$\dot{x}(t)=\lambda-dx(t)-\frac{\beta x(t)v(t)}{(1+\gamma x(t))(1+\alpha v(t))},\tag{3.1}$$

$$\dot{y}(t)=e^{-m\tau_1}\frac{\beta x(t-\tau_1)v(t-\tau_1)}{(1+\gamma x(t-\tau_1))(1+\alpha v(t-\tau_1))}-ay(t),\tag{3.2}$$

$$\dot{v}(t)=Nae^{-n\tau_2}y(t-\tau_2)-cv(t)-qv(t)z(t),\tag{3.3}$$

$$\dot{z}(t)=rv(t)z(t)-\mu z(t).\tag{3.4}$$

As a result, the parameters R_0 and R_1 become

$$R_0=\frac{e^{-(m\tau_1+n\tau_2)}N\beta x_0}{c(1+\gamma x_0)},$$

$$R_1=\frac{e^{-(m\tau_1+n\tau_2)}N\beta x_2}{c(1+\gamma x_2)(1+\alpha v_2)},$$

where

$$x_2 = \frac{1}{2\gamma(1+\alpha v_2)}\left(\gamma x_0(1+\alpha v_2) - (1+\zeta v_2) + \sqrt{[(1+\zeta v_2) - \gamma x_0(1+\zeta v_2)]^2 + 4\gamma x_0(1+\alpha v_2)^2}\right),$$

$$v_2 = \mu/r,$$

and $\zeta = \alpha + \frac{\beta}{d}$.

Now we will perform some numerical simulations to testify our theoretical results. The values of the parameters of model (3.1)-(3.4) are given in Table 1.

TABLE 1. The values of the parameters of model (3.1)-(3.4).

Parameter	Value	Parameter	Value	Parameter	value
λ	10	a	0.1	μ	0.1
d	0.01	N	10	m	1
β	Varied	c	3	n	3.4
γ	0.0001	q	0.01	τ_1	1
α	0.0001	r	Varied	τ_2	1.2

Now, we study the following cases:

- $R_0 \leq 1$. We choose, $\beta = 0.001$ and $r = 0.01$. Using these data, we compute $R_0 = 0.0188$ and $R_1 = 0.0101$. According to Theorem 1, E_0 is GAS. Figures 1-4 show that, the numerical results are consistent with Theorem 1. We can see that, the concentration of uninfected cells is increased and converged to its normal value $\frac{\lambda}{d} = 1000$, while the concentrations of infected cells, free viruses and B cells are decaying and approaching zero. In this case the viruses can be cleared from the body.
- $R_1 \leq 1 < R_0$. We take $\beta = 0.1$ and $r = 0.01$. In this case, $R_0 = 1.8848$ and $R_1 = 0.0205$. From Theorem 2, E_1 is GAS. Figures 1-4 show that the numerical results are consistent with Theorem 2. We can see that, the trajectory of the system will tend to the infected steady state without humoral immune response $E_1(506.77, 18.1449, 0.1023, 0)$, and the infection becomes chronic but with no persistent humoral immune response.
- $R_1 > 1$. We choose, $\beta = 0.1$ and $r = 1$. Then, we compute $R_0 = 1.8848$ and $R_1 = 1.0107$. From Theorem 3, E_2 is GAS. Figures 1-4 demonstrate that, our simulations are consistent with the theoretical results of Theorem 3. We observe that, the trajectory of the system will tend to the infected steady state with humoral immune response $E_2(512.4948, 17.9343, 0.1, 3.2238)$. Then, the infection becomes chronic but with persistent humoral immune response. From Figures 1 and 3 we observe that, if $R_1 > 1$ the humoral immune response reduce the concentration of free viruses and increase the concentration of uninfected cells.

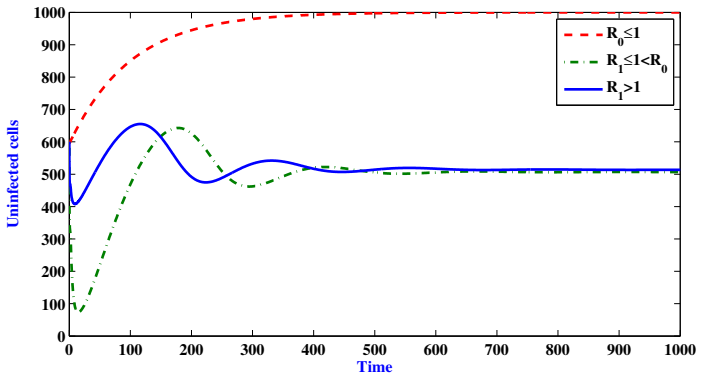

FIGURE 1. Evaluation of uninfected cells.

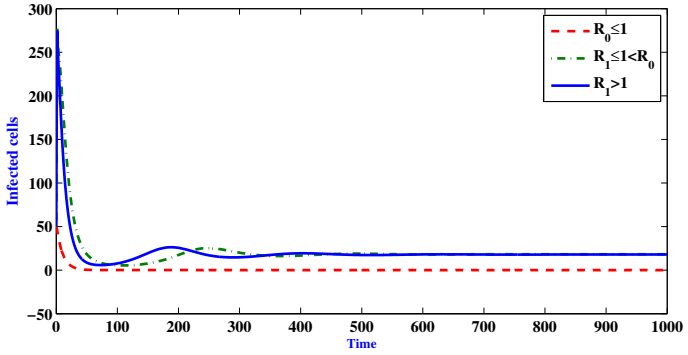

FIGURE 2. Evaluation of infected cells.

We note that, the values of the parameters q, r and μ have no impact on the value of R_0, since R_0 is independent of those parameters. This fact seems to suggest that, humoral immune response do not play a role in eliminating the viruses. From above we can see that, R_1 can be increased by increasing the parameter r. When we compare the cases $R_1 \leq 1 < R_0$ and $R_1 > 1$, we can see that, the presence of humoral immune response (i.e. $R_1 > 1$) reduce the concentration of free viruses and infected cells and increase the concentration of uninfected cells. It means that, the humoral immune response can play an important role in controlling the infection.

4. CONCLUSION

In this paper, we have proposed a virus infection model describing the interaction of the virus with target cell taking into account the humoral immune response. The

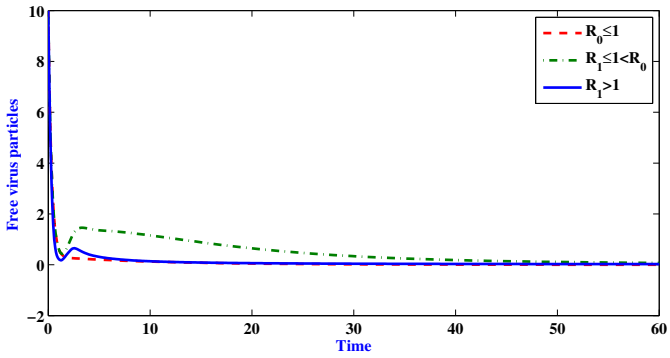

FIGURE 3. Evaluation of free virus particles.

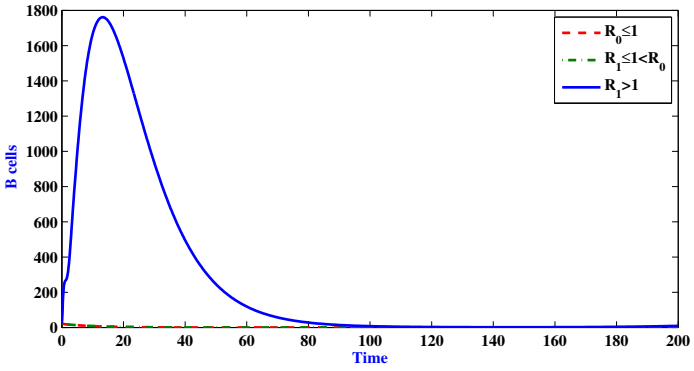

FIGURE 4. Evaluation of B cells.

infection rate is given by a general function. Two types of distributed time delays describing the time needed for infection of target cell and virus replication have been incorporated into the model. 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. We have proven that if $R_0 \leq 1$, then the uninfected steady state E_0 is GAS, and the viruses are cleared, if $R_1 \leq 1 < R_0$, then the infected steady state without humoral immune response E_1 is GAS, and the infection becomes chronic but with no persistent B cells response, and if $R_1 > 1$, then the infected steady state with B cells response E_2 is GAS, and the infection is chronic with persistent B cells response. Numerical simulations have been performed for the virus dynamics model with discrete-time delays and special form of the function $\Phi(x, v)$. Our simulation results confirm the theoretical results given in Theorems 1-3.

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Authors' addresses

A. M. Elaiw
King Abdulaziz University, Department of Mathematics, Faculty of Science, P.O. Box 80203, Jeddah 21589, Saudi Arabia
E-mail address: a_m_elaiw@yahoo.com

A. Alhejelan
King Abdulaziz University, Department of Mathematics, Faculty of Science, P.O. Box 80203, Jeddah 21589, Saudi Arabia

Qassim University, Department of Mathematics, Faculty of Arts and Science Buraidah, P. O. Box 0001, Buridah, Saudi Arabia
E-mail address: am-math@outlook.com

A. M. Shehata
Al-Azhar University, Faculty of Science, Mathematics Department, Assiut 71511, Egypt
E-mail address: ah_moukh81@yahoo.com