A delayed viral infection model with antibody immune response

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Abstract: In this paper, we investigate the dynamical behavior of a virus infection model with antibody immune response and distributed intracellular delays. The incidence rate of the infection is given by Beddington-DeAngelis 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 stability of the model is completely determined by two threshold numbers, the basic reproduction number R_0 and the antibody immune response reproduction number R_1. We have proven that if $R_0 \le 1$, then the uninfected steady state is globally asymptotically stable (GAS), if $R_1 \le 1 < R_0$, 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.
[Alhejelan, A., Elaiw, A.M. and Alghamdi M.A. **A delayed viral infection model with antibody immune response.** *Life Sci J* 2013;10(4):695-700]. (ISSN:1097-8135). http://www.lifesciencesite.com. 88

Keywords: Virus dynamics; Antibody immune response; Global stability; Lyapunov functional.

1. Introduction

Recently, the study of population dynamics of infectious diseases has attracted the interest of many mathematicians. Several mathematical models have been proposed to describe the viral infection process such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell leukemia virus type I (HTLV-I), [1]-[25]. These models can capture some essential features of the immune system and are able to produce a variety of immune responses, many of which are observed experimentally and clinically. Mathematical models can also be used to guide the development of efficient antiviral drug therapies. B cells, cytokines, natural killer cells, and T cells are essential components of a normal immune response to a virus. The antibody immune response is an important part of the immune system. The B cells create the antibodies which clear antigens circulating in blood and lymph. The antibody immune is more effective than the cell-mediated immune in some diseases like in malaria infection [26]. Mathematical models for virus dynamics with the antibody immune response have been developed in [27]-[37]. The basic virus dynamics model with antibody immune response was introduced by Murase et. al. [28] as:

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

$$\dot{y}(t) = \beta x(t)v(t) - \delta y(t), \quad (2)$$

$$\dot{v}(t) = N\delta y(t) - cv(t) - qv(t)z(t), \quad (3)$$

$$\dot{z}(t) = rv(t)z(t) - \mu z(t), \quad (4)$$

where $x(t), y(t), v(t)$ and $z(t)$ are the populations of the uninfected target cells, infected cells, viruses and antibody immune cells at time t, respectively; λ and d are the birth 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 death rate constant of the virus. The viruses are cleared by antibodies with rate $qv(t)z(t)$. The antibody immune cells are proliferated at a rate $rv(t)z(t)$ and die at rate $\mu z(t)$.

Model (1)-(4) is based on the assumption that the infection could occur and 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 the 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. [9]-[16]). In these papers, the viral infection models are presented without taking into consideration the antibody immune response. In [32] and [37], the global stability of viral infection models with antibody immune response and with discrete-time delays has been studied.

In model (1)-(4), the infection rate is assumed to be bilinear in x and v. However, the actual incidence rate is probably not linear over the entire range of x and v [38], [39], [41]. In [36] and [37], a virus infection model with antibody immune response and with saturated infection rate of the form $\beta xv/(1+\alpha v)$, was suggested where α is a positive constant. However, the time delay was not considered in [36] and [37]. Huang and Takeuchi [40] investigated a viral infection model with Beddington-DeAngelis functional response, $\beta xv/(1+\gamma x+\alpha v)$ where α and γ are positive constants. However, the antibody immune response was not included.

Our primary goal is to propose a virus infection model with antibody immune response. The infection rate is given by Beddington-DeAngelis functional response. We incorporate two types of distributed delays into the model to account the time delay between the time that uninfected cells are contacted by the virus particle and the time the emission of infectious (matures) virus particles. The global stability of the model is established using Lyapunov functionals, which is similar in nature to those used in [41]-[42]. We prove that the global dynamics of the model is determined by the basic reproduction number R_0 and the antibody immune response reproduction number R_1. We have proven that if $R_0 \le 1$, then the uninfected steady state is globally asymptotically stable (GAS), if $R_1 \le 1 < R_0$, 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 mathematical model of viral infection with Beddington-DeAngelis functional response which describes the interaction of the virus with the uninfected cells, taking into account the antibody immune response.

$$\dot{x}(t) = \lambda - dx(t) - \frac{\beta x(t)v(t)}{1+\gamma x(t)+\alpha v(t)}, \tag{5}$$

$$\dot{y}(t) = \int_0^h f(\tau)e^{-m\tau}\frac{\beta x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}d\tau - \delta y(t), \tag{6}$$

$$\dot{v}(t) = N\delta\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv(t) - qv(t)z(t), \tag{7}$$

$$\dot{z}(t) = rv(t)z(t) - \mu z(t), \tag{8}$$

where α and γ are positive constants, and all the variables and other parameters of the model have the same meanings as given in (1)-(4). To account for the time lag between viral contacting the uninfected cell and the production of new virus particles, two types of distributed intracellular delays are introduced. It assumed that, the target cells are contacted by the virus particles at time $t-\tau$ becomes infected cells at time where τ is a random variable with a probability distribution $f(\tau)$ over the interval [0] and is limit superior of this delay. The factor $e^{-m\tau}$ account for the probability of surviving the time period of delay, where 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 where τ is distributed according to a probability distribution $g(\tau)$ over the interval [0] and 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 a constant. The probability distribution functions $f(\tau)$ and $g(\tau)$ are assumed to satisfy $f(\tau) > 0$ and $g(\tau) > 0$ and

$$\int_0^h f(\tau)d\tau = \int_0^\omega g(\tau)d\tau = 1$$

$$\int_0^h f(u)e^{su}du < \infty, \quad \int_0^\omega g(u)e^{su}du < \infty, \quad s > 0$$

Let

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

Then, $0 < F \le 1, \quad 0 < G \le 1$.

The initial conditions for system (5)-(8) take the form

$$\begin{aligned} &x(\theta) = \phi_1(\theta), \quad y(\theta) = \phi_2(\theta),\\ &v(\theta) = \phi_3(\theta), \quad z(\theta) = \phi_4(\theta),\\ &\phi_j(\theta) \ge 0, \quad \theta \in [-\rho, 0), j = 1,\ldots 4\\ &\phi_j(0) > 0, \quad j = 1,\ldots 4 \end{aligned} \tag{9}$$

Where $\rho = \max\{h, \omega\}$,

$$(\varphi_1(\theta),\ldots,\varphi_4(\theta)) \in C([-\rho,0], R_+^4)$$

where $C([-\rho,0], R_+^4)$, is the Banach space of continuous functions mapping the interval $[-\rho,0]$, into R_+^4.

Proposition 1. Let $(x(t), y(t), v(t), z(t))$, be any solution of system (5)-(8) satisfying the initial conditions (9), then $x(t), y(t), v(t)$ and $z(t)$ are all non-negative for $t \ge 0$, and ultimately bounded.

Proof. The poof is similar to the Proposition 1 in [34].

3. Steady states

We de.ne the basic reproduction number for system (5)-(8) as:

$$R_0 = \frac{NFG\beta x_0}{c(1+\gamma x_0)}$$

It is clear that, system (5)-(8) 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 $E_1(x_1,y_1,v_1,0)$ where

$$x_1 = \frac{(NFG\alpha\lambda + c)x_0}{NFG\alpha\lambda + c + c(1+\gamma x_0)(R_0-1)},$$

$$y_1 = \frac{NF^2G\beta\lambda x_0}{\delta[NFG\alpha\lambda + c + c(1+\gamma x_0)(R_0-1)]}(1-\frac{1}{R_0})$$

$$v_1 = \frac{N^2F^2G^2\beta\lambda x_0}{c[NFG\alpha\lambda + c + c(1+\gamma x_0)(R_0-1)]}(1-\frac{1}{R_0})$$

Moreover, the system has an infected steady state with immune response $E_2(x_2,y_2,v_2,z_2)$ define as:

$$x_2 = \frac{1}{2\gamma}(-\chi + \sqrt{\chi^2 + 4\gamma x_0(1+\alpha v_2)})$$

$$y_2 = \frac{F\beta x_2 v_2}{\delta[1+\gamma x_2 + \alpha v_2]}, \quad v_2 = \frac{\mu}{r}, z_2 = \frac{c}{q}(1-R_1),$$

where $\xi = \alpha + \frac{\beta}{d}$, $(1+\xi v_2) - \gamma x_0$ and R_1 is the antibody immune response reproduction number which is given by:

$$R_1 = \frac{NFG\beta x_2}{c(1+\gamma x_2 + \alpha v_2)}$$

It is clear that $x_2 > 0, y_2 > 0$ and $v_2 > 0$, moreover, if $R_1 > 1$ then $z_2 > 0$. Since $0 < x_2 \le x_0$ and $v_2 > 0$, then

$$R_1 = \frac{NFG\beta x_2}{c(1+\gamma x_2 + \alpha v_2)} \le \frac{NFG\beta x_0}{c(1+\gamma x_0)} = R_0.$$

From 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 $E_2(x_2,y_2,v_2,z_2)$.

4. Global stability

In this section, we prove the global stability of the steady states of system (5)-(8) employing the method of Lyapunov functional which is used in [42] for SIR epidemic model with distributed delay. Next we shall use the following notation: $u = u(t),$, for any $u \in \{x,y,v,z\}$. We also define a function $H:(0,\infty)\to[0,\infty)$ as $H(u) = u - 1 - \ln u.$ It is clear that $H(u) \ge 0$ for any $u > 0$ and H has the global minimum $H(1) = 0$.

Theorem 1. If $R_0 \le 1$; then E_0 is GAS.

Proof. Define a Lyapunov functional W_0 as follows:

$$W_0 = NFG\left[\frac{x_0}{(1+\gamma x_0)}H\left(\frac{x}{x_0}\right) + \frac{1}{F}y\right.$$
$$+ \frac{\beta}{F}\int_0^h f(\tau)e^{-m\tau}\int_0^\tau \frac{x(t-\theta)v(t-\theta)}{1+\gamma x(t-\theta)+\alpha v(t-\theta)}d\theta d\tau$$
$$\left. + \frac{\delta}{FG}\int_0^\omega g(\tau)e^{-n\tau}\int_0^\tau y(t-\theta)d\theta d\tau\right] + v + \frac{q}{r}z. \qquad (10)$$

The time derivative of W_0 along the trajectories of (5)-(8) satisfies:

$$\frac{dW_0}{dt} = NFG\left[\frac{x_0}{(1+\gamma x_0)}\left(1-\frac{x_0}{x}\right)\left(\lambda - dx - \frac{\beta xv}{1+\gamma x+\alpha v}\right)\right.$$
$$+ \frac{\beta}{F}\int_0^h f(\tau)e^{-m\tau}\frac{x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}d\tau - \frac{\delta}{F}y$$
$$+ \frac{\beta}{F}\int_0^h f(\tau)e^{-m\tau}\left(\frac{xv}{1+\gamma x+\alpha v} - \frac{x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}\right)d\tau$$
$$\left. + \frac{\delta}{FG}\int_0^\omega g(\tau)e^{-n\tau}(y - y(t-\tau))d\tau\right]$$
$$+ N\delta\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv - qvz + qvz - \frac{q\mu}{r}z. \qquad (11)$$

Collecting terms of (11) we get**:**

$$\frac{dW_0}{dt} = NFG\left[-\frac{d(x-x_0)^2}{(1+\gamma x_0)x} - \frac{\beta xv}{(1+\gamma x_0)(1+\gamma x+\alpha v)}\right.$$
$$\left. + \frac{\beta x_0 v}{(1+\gamma x_0)(1+\gamma x+\alpha v)} - \frac{\beta xv}{1+\gamma x+\alpha v}\right] - cv - \frac{q\mu}{r}z.$$
$$= -\left[NFGd\frac{(x-x_0)^2}{(1+\gamma x_0)x} + \frac{c\alpha v^2 R_0}{(1+\gamma x+\alpha v)} + \frac{q\mu}{r}z\right] + cv(R_0-1). \qquad (12)$$

From Eq. (12) we can see that if $R_0 \le 1$ then $\frac{dW_0}{dt} = 0$ for all $x,v,z > 0$. One can easily show that $\frac{dW_0}{dt} = 0$ if and only if $x = x_0, y = 0, v = 0, z = 0$ From LaSalle's Invariance Principle, E_0 is GAS.

Theorem 2. If $R_1 \le 1 < R_0$, then E_1 is GAS.

Proof. We construct the following Lyapunov functional

$$W_1 = NFG\left[x - x_1 - \int_{x_1}^{x}\frac{x_1(1+\gamma\eta+\alpha v_1)}{\eta(1+\gamma x_1+\alpha v_1)}d\eta + \frac{1}{F}H\left(\frac{y}{y_1}\right)\right.$$
$$+\frac{\beta}{F}\frac{x_1v_1}{(1+\gamma x_1+\alpha v_1)}\int_0^h f(\tau)e^{-m\tau}$$
$$\int_0^\tau H\left(\frac{x(t-\theta)v(t-\theta)(1+\gamma x_1+\alpha v_1)}{x_1v_1(1+\gamma x(t-\theta)+\alpha v(t-\theta))}\right)d\theta d\tau$$
$$\left.+\frac{\delta y_1}{FG}\int_0^\omega g(\tau)e^{-n\tau}\int_0^\tau H\left(\frac{y(t-\theta)}{y_1}\right)d\theta d\tau\right] + v_1H\left(\frac{v}{v_1}\right)+\frac{q}{r}z.$$

The time derivative of W_1 along the trajectories of (5)-(8) satisfies

$$\frac{dW_1}{dt} = NFG\left[\left(1-\frac{x_1(1+\gamma x+\alpha v_1)}{x(1+\gamma x_1+\alpha v_1)}\right)\left(\lambda - dx - \frac{\beta xv}{1+\gamma x+\alpha v}\right)\right.$$
$$+\frac{1}{f}(1-\frac{y_1}{y})\left(\beta\int_0^h f(\tau)e^{-m\tau}\frac{x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}d\tau-\delta y\right)$$
$$+\frac{\beta}{F}\int_0^h f(\tau)e^{-m\tau}\left(\frac{xv}{1+\gamma x+\alpha v}-\frac{x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}\right.$$
$$\left.\left.+\frac{x_1v_1}{1+\gamma x_1+\alpha v_1}\ln\left(\frac{x(t-\tau)v(t-\tau)(1+\gamma x+\alpha v)}{xv(1+\gamma x(t-\tau)+\alpha v(t-\tau))}\right)\right)d\tau\right.$$
$$\left.+\frac{\delta}{FG}\int_0^\omega g(\tau)e^{-n\tau}\left(y-y(t-\tau)+y_1\ln\left(\frac{y(t-\tau)}{y}\right)\right)d\tau\right]$$
$$+\left(1-\frac{v_1}{v}\right)\left(N\delta\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv - qvz\right)$$
$$+qvz - \frac{q\mu}{r}z.$$

Using the steady state conditions for E_1 we obtain:

$$\frac{dW_1}{dt} = NFG\left[-d(x-x_1)\left(1-\frac{x_1(1+\gamma x+\alpha v_1)}{x(1+\gamma x_1+\alpha v_1)}\right)\right.$$
$$+\frac{\beta x_1v_1}{(1+\gamma x_1+\alpha v_1)}-\frac{\beta x_1v_1}{(1+\gamma x_1+\alpha v_1)}\frac{x_1(1+\gamma x+\alpha v_1)}{x(1+\gamma x_1+\alpha v_1)}$$
$$-\frac{\beta x_1v_1}{(1+\gamma x_1+\alpha v_1)}\frac{v(1+\gamma x+\alpha v_1)}{v_1(1+\gamma x_1+\alpha v_1)}$$
$$-\frac{1}{F}\frac{\beta x_1v_1}{(1+\gamma x_1+\alpha v_1)}\int_0^h f(\tau)e^{-m\tau}\frac{y_1x(t-\tau)v(t-\tau)(1+\gamma x_1+\alpha v_1)}{yx_1v_1(1+\gamma x(t-\tau)+\alpha v(t-\tau))}d\tau$$
$$+\frac{1}{F}\frac{\beta x_1v_1}{(1+\gamma x_1+\alpha v)_1}\int_0^h f(\tau)e^{-m\tau}\ln\left(\frac{x(t-\tau)v(t-\tau)(1+\gamma x+\alpha v)}{xv(1+\gamma x(t-\tau)+\alpha v(t-\tau))}\right)d\tau$$
$$\left.+\frac{\delta y_1}{FG}\int_0^\omega g(\tau)e^{-n\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau-\frac{\delta y_1}{FG}\int_0^\omega g(\tau)e^{-n\tau}\frac{v_1y(t-\tau)}{vy_1}d\tau\right]$$
$$-cv+cv_1-qvz+qv_1z+qvz-\frac{q\mu}{r}z.$$
$$=NFG\left[-\frac{d(x-x_1)^2(1+\alpha v_1)}{x(1+\gamma x_1+\alpha v_1)}-\frac{\delta y_1}{F}\frac{\alpha(1+\gamma x)(v-v_1)^2}{v_1(1+\gamma x+\alpha v)(1+\gamma x+\alpha v_1)}\right.$$
$$-\frac{\delta y_1}{F}H\left(\frac{x_1(1+\gamma x+\alpha v_1)}{x(1+\gamma x_1+\alpha v_1)}\right)-\frac{\delta y_1}{F}H\left(\frac{1+\gamma x+\alpha v}{1+\gamma x+\alpha v_1}\right)$$
$$-\frac{\beta x_1v_1}{(1+\gamma x_1+\alpha v_1)}\frac{v(1+\gamma x+\alpha v_1)}{v_1(1+\gamma x_1+\alpha v_1)}$$
$$-\frac{\delta y_1}{F}\int_0^h f(\tau)e^{-m\tau}H\left(\frac{y_1x(t-\tau)v(t-\tau)(1+\gamma x_1+\alpha v_1)}{yx_1v_1(1+\gamma x(t-\tau)+\alpha v(t-\tau))}\right)d\tau$$
$$\left.-\frac{\delta y_1}{FG}\int_0^\omega g(\tau)e^{-n\tau}H\left(\frac{v_1y(t-\tau)}{vy_1}\right)d\tau\right]+q(v_1-\frac{\mu}{r})z.$$

Similar to the proof of Theorem 2 of [35] we can show that if $R_1\le 1$, then $v_1\le\frac{\mu}{r}=v_2$. Hence, if $R_0>1$ then $x_1,y_1,v_1>0$; and if $R_1\le 1$, then $\frac{dW_1}{dt}=0$ for all $x,y,v>0$. One can easily show that $\frac{dW_1}{dt}\le 0$ at E_1. LaSalle's Invariance Principle implies global stability of E_1.

Theorem 3. If $R_1>1$, then E_2 is GAS.

Proof. We construct the following Lyapunov functional

$$W_2 = NFG\left[x - x_2 - \int_{x_2}^{x}\frac{x_2(1+\gamma\eta+\alpha v_2)}{\eta(1+\gamma x_2+\alpha v_2)}d\eta + \frac{1}{F}H\left(\frac{y}{y_2}\right)\right.$$
$$+\frac{\beta}{F}\frac{x_2v_2}{(1+\gamma x_2+\alpha v_2)}\int_0^h f(\tau)e^{-m\tau}$$
$$\int_0^\tau H\left(\frac{x(t-\theta)v(t-\theta)(1+\gamma x_2+\alpha v_2)}{x_2v_2(1+\gamma x(t-\theta)+\alpha v(t-\theta))}\right)d\theta d\tau$$
$$\left.+\frac{\delta y_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}\int_0^\tau H\left(\frac{y(t-\theta)}{y_2}\right)d\theta d\tau\right]$$
$$+v_2H\left(\frac{v}{v_2}\right)+\frac{q}{r}z_2H\left(\frac{z}{z_2}\right).$$

The time derivative of W_2 along the trajectories of (5)-(8) satisfies

$$\frac{dW_2}{dt} = NFG\left[\left(1-\frac{x_2(1+\gamma x+\alpha v_2)}{x(1+\gamma x_2+\alpha v_2)}\right)\left(\lambda - dx - \frac{\beta xv}{1+\gamma x+\alpha v}\right)\right.$$
$$+\frac{1}{f}(1-\frac{y_2}{y})\left(\beta\int_0^h f(\tau)e^{-m\tau}\frac{x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}d\tau-\delta y\right)$$
$$+\frac{\beta}{F}\int_0^h f(\tau)e^{-m\tau}\left(\frac{xv}{1+\gamma x+\alpha v}-\frac{x(t-\tau)v(t-\tau)}{1+\gamma x(t-\tau)+\alpha v(t-\tau)}\right.$$
$$\left.\left.+\frac{x_2v_2}{1+\gamma x_2+\alpha v_2}\ln\left(\frac{x(t-\tau)v(t-\tau)(1+\gamma x+\alpha v)}{xv(1+\gamma x(t-\tau)+\alpha v(t-\tau))}\right)\right)d\tau\right.$$
$$\left.+\frac{\delta}{FG}\int_0^\omega g(\tau)e^{-n\tau}\left(y-y(t-\tau)+y_2\ln\left(\frac{y(t-\tau)}{y}\right)\right)d\tau\right]$$
$$+\left(1-\frac{v_2}{v}\right)\left(N\delta\int_0^\omega g(\tau)e^{-n\tau}y(t-\tau)d\tau - cv - qvz\right)$$
$$+\left(1-\frac{z_2}{z}\right)\left(qvz-\frac{q\mu}{r}z\right).$$

Using the steady state conditions for E_2 we obtain:

$$\frac{dW_2}{dt} = NFG\left[-d(x-x_2)\left(1-\frac{x_2(1+\gamma x+\alpha v_2)}{x(1+\gamma x_2+\alpha v_2)}\right)\right.$$
$$+\frac{\beta x_2v_2}{(1+\gamma x_2+\alpha v_2)}-\frac{\beta x_2v_2}{(1+\gamma x_2+\alpha v_2)}\frac{x_2(1+\gamma x+\alpha v_2)}{x(1+\gamma x_2+\alpha v_2)}$$
$$-\frac{\beta x_2v_2}{(1+\gamma x_2+\alpha v_2)}\frac{v(1+\gamma x+\alpha v_2)}{v_1(1+\gamma x_2+\alpha v_2)}$$
$$-\frac{1}{F}\frac{\beta x_2v_2}{(1+\gamma x_2+\alpha v_2)}v_2\int_0^h f(\tau)e^{-m\tau}\frac{y_2x(t-\tau)v(t-\tau)(1+\gamma x_2+\alpha v_2)}{yx_2v_2(1+\gamma x(t-\tau)+\alpha v(t-\tau))}d\tau$$
$$+\frac{1}{F}\frac{\beta x_2v_2}{(1+\gamma x_2+\alpha v_2)}v_2\int_0^h f(\tau)e^{-m\tau}\ln\left(\frac{x(t-\tau)v(t-\tau)(1+\gamma x+\alpha v)}{xv(1+\gamma x(t-\tau)+\alpha v(t-\tau))}\right)d\tau$$
$$\left.+\frac{\delta y_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau-\frac{\delta y_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}\frac{v_2y(t-\tau)}{vy_2}d\tau\right]$$
$$-cv+cv_2-qvz+qv_2z+qvz-qvz_2-\frac{q\mu}{r}z+\frac{q\mu}{r}z_2.$$

$$= NFG\left[-\frac{d(x-x_2)^2(1+\alpha v_2)}{x(1+\gamma x_2+\alpha v_2)}-\frac{\delta y_2}{F}\frac{\alpha(1+\gamma x)(v-v_2)^2}{v_2(1+\gamma x+\alpha v)(1+\gamma x+\alpha v_2)}\right.$$
$$-\frac{\delta y_2}{F}H\left(\frac{x_2(1+\gamma x+\alpha v_2)}{x(1+\gamma x_2+\alpha v_2)}\right)-\frac{\delta y_2}{F}H\left(\frac{1+\gamma x+\alpha v}{1+\gamma x+\alpha v_2}\right)$$
$$-\frac{\delta y_2}{F}\int_0^h f(\tau)e^{-m\tau}H\left(\frac{y_2x(t-\tau)v(t-\tau)(1+\gamma x_2+\alpha v_2)}{yx_2v_2(1+\gamma x(t-\tau)+\alpha v(t-\tau))}\right)d\tau$$
$$\left.-\frac{\delta y_2}{FG}\int_0^\omega g(\tau)e^{-n\tau}H\left(\frac{v_2y(t-\tau)}{vy_2}\right)d\tau\right].$$

Hence, if $R_1>1$ then $x_2,y_2,v_2,z_2>0$; and if $R_1>1$, then $\frac{dW_2}{dt}=0$ for all $x,y,v>0$. One can easily show that $\frac{dW_2}{dt}\le 0$ at E_2. LaSalle's Invariance Principle implies global stability of E_2.

5. Conclusion

In this paper, we have proposed a virus infection model describing the interaction of the virus with uninfected cell taking into account the Beddington-DeAngelis infection rate. Two types of distributed time delays describing time needed for infection of target cell and virus replication have been incorporated into the model. Using the method of Lyapunov functional, we have establish that the global dynamics are determined be 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 basic reproduction number R_1 for B cells response determines whether a persistent B cells response can be established. If $R_0\le 1$, the uninfected steady state E_0 is GAS, and the viruses are cleared. If $R_1\le 1<R_0$, the infected steady state without B cells response E_1 is GAS, and the infection becomes chronic but with no persistent B cells response. If $R_1>1$, the infected steady state with B cells response E_2 is GAS, and the infection is chronic with persistent B cells response.

6.Acknowledgements

This article was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah. The authors, therefore, acknowledge with thanks DSR technical and financial support.

References

1. M.A. Nowak, and R.M. May, .Virus dynamics: Mathematical Principles of Immunology and Virology, Oxford Uni., Oxford, 2000.
2. M.A. Nowak, C.R.M. Bangham, Population dynamics of immune responses to persistent viruses, Science, 272 (1996), 74-79.
3. A.M. Elaiw, Global properties of a class of HIV models, Nonlinear Anal. Real World Appl., 11(2010), 2191-3286.
4. A.M. Elaiw, and X. Xia, HIV dynamics: Analysis and robust multirate MPC-based treatment schedules, J. Math. Anal. Appl., 356 (2009), 285-301.
5. A.M. Elaiw and S.A. Azoz, Global properties of a class of HIV infection models with Beddington-DeAngelis functional response, Mathematical Methods in the Applied Sciences 36 (2013), 383-394.
6. A.M. Elaiw, Global properties of a class of virus infection models with multitarget cells, Nonlinear Dynamics., 69 (2012), 423-35.
7. A.M. Elaiw and A.M. Shehata, Stability and feedback stabilization of HIV infection model with two classes of target cells, Discrete Dynamics in Nature and Society, 2012 (2012), Article ID 963864.
8. A.S. Perelson, and P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev., 41 (1999) 3-44.
9. A.M. Elaiw, I.A. Hassanien, and S.A. Azoz, Global stability of HIV infection models with intracellular delays, J. Korean Math. Soc. 49 (2012), No. 4, pp. 779-794.
10. A.M. Elaiw and M.A. Alghamdi, Global properties of virus dynamics models with multitarget cells and discrete-time delays, Discrete Dynamics in Nature and Society, 2011, Article ID 201274.
11. A.M. Elaiw and A.S. Alsheri, Global dynamicsof HIV infection of CD4+ T cells and macrophages, Discrete Dynamics in Nature and Society 2013, (2013) Article ID 264759.
12. A.M. Elaiw, Global dynamics of an HIV infection model with two classes of target cells and distributed delays, Discrete Dynamics in Nature and Society, 2012 (2012), Article ID 253703.
13. M.A. Obaid, Global analysis of a virus infection model with multitarget cells and distributed intracellular delays, Life Science Journal, 9,no. 4, pp. 1500-1508, 2012.
14. A.S. Alsheri, A.M. Elaiw and M. A. Alghamdi, Global dynamics of two target cells HIV infection model with Beddington-DeAngelisfunctional response and delay-discrete or distributed, Journal of Computational Analysisand Applications, (in press).
15. A.M. Elaiw, A. S. Alsheri and M. A. Alghamdi, Global properties of HIV infection models with nonlinear incidence rate and delay-discrete or distributed, Journal of Computational Analysis and Applications, (in press).

16. A.M. Elaiw and M. A. Alghamdi, Global analysisfor delay virus infection model with multitarget cells, Journal of Computational Analysis and Applications, (in press).
17. M.A. Nowak, S. Bonhoeffer, A. M. Hill, Viral Dynamics in Hepatitis B Virus Infection, Proc. Natl. Acad. Sci. USA, 93 (1993), 4398-4402.
18. A.U. Neumann, N.P. Lam, H. Dahari, D.R. Gretch, T.E. Wiley, T.J. Layden, and A.S. Perelson, Hepatitis C viral dynamics in vivo and the antiviral e¢ cacy of interferon-alpha therapy, Science, 282 (1998), 103-107.
19. E. M. Elsayed, Solutions of rational difference system of order two, Math. Comp. Mod., 55(2012), 378--384.
20. E. M. Elsayed, Solution and attractivity for arational recursive sequence, Dis. Dyn. Nat. Soc., 2011, (2011)Article ID 982309, 17 pages.
21. E. M. Elsayed, Behavior and expression of the solutions of some rational difference equations,J. Comp. Anal. Appl., 15 (1) (2013), 73.
22. Korobeinikov, Global properties of infectious disease models with nonlinear incdence, Bull. Math. Biol., 69 (2007), 1871-1886.
23. G. Huang, Y. Takeuchi, and W. Ma, Lyapunov functionals for delay differential equations model of viral infection, SIAM J. Appl. Math., 70 (2010), 2693.2708.
24. Korobeinikov, Global properties of basic virus dynamics models, Bull. Math. Biol. 66 (2004), 879-883.
25. Michael Y. Li, Hongying Shu, Global dynamics of a mathematical model for HTLV-I infection of CD4+ T cells with delayed CTL response, Nonlinear Anal. Real World Appl., 13 (2012), 1080-1092.
26. J.A. Deans, S. Cohen, Immunology of malaria, Ann. Rev. Microbiol. 37 (1983), 25-49.
27. R.M. Anderson, R.M. May, and S. Gupta, Non-linear phenomena in host-parasite interactions, Parasitology, 99 (1989), 59.79.
28. Murase, T. Sasaki, and T. Kajiwara, Stability analysis of pathogen-immune interaction dynamics, J. Math. Biol., 51 (2005), 247.267.
29. D. Wodarz, M. M. Robert, and A. N. Martin, The role of antigen-independent persistence of memory cytotoxic T lymphocytes, Int. Immunol., 12 (2000), 467.477.
30. C. Chiyaka, W. Garira, and S. Dube, Model lingimmune response and drug therapy in humanmalaria infection, Comput. Math. Method. Med.,9 (2008), 143.163.
31. A.S. Perelson, Modelling viral and immune system dynamics, Nature Rev. Immunol. 2 (2002), 28.36.
32. S. Wang, D. Zou, Global stability of in host viral models with humoral immunity and intracellulardelays, J. Appl. Math. Mod., 36 (2012), 1313-1322.
33. Alhejelan and A. M. Elaiw, Global dynamicsof virus infection model with humoral immune response and distributed delays, Journal. Of Computational Analysis and Applications, (inpress).
34. M. Elaiw, A. Alhejelan and M. A. Alghamdi, Global dynamics of virus infection model with antibody immune response and distributed delays, Discrete Dyn. Nat. Soc., 2013, Article ID781407.
35. M. Elaiw, A. Alhejelan and M. A. Alghamdi, Global stability of a delayed virus dynamics model with humoral immunity and Crowley-Martin functional response, Discrete Dyn. Nat. Soc. (submitted).
36. H. F. Huo, Y. L. Tang, and L. X. Feng, A virus dynamics model with saturation infection and humoral immunity, Int. J. Math. Anal., 6 (2012), 1977-1983.
37. X. Wang, S. Liu, A class of delayed viral models with saturation infection rate and immune response, Math. Meth. Appl. Sci., 36, (2013),125-142.
38. Korobeinikov, Global properties of infectious disease models with nonlinear incdence, Bull.Math. Biol., 69 (2007), 1871-1886.
39. G. Huang, Y. Takeuchi, and W. Ma, Lyapunov functionals for delay di¤erential equations modelof viral infection, SIAM J. Appl. Math., 70(2010), 2693-2708.
40. G.Ma. Huang, W.B., Takeuchi, Y., Global properties for virus dynamics model with Beddington-DeAngelis functional response.Appl. Math. Lett., 22 (2009), 1690-1693.
41. A.M. Elaiw and M. A. Alghamdi Global stability of a viral dynamics model with multi-target cellsand nonlinear incidence rate, Life Science Journal, (in press).
42. C.C. McCluskey, Complete global stability for anSIR epidemic model with delay-distributed or discrete, Nonlinear Anal. Real World Appl., 11(2010), 55-59.

11/12/2013