Research Article

Stability Analysis for Viral Infection Model with Multitarget Cells, Beddington-DeAngelis Functional Response, and Humoral Immunity

Xinxin Tian¹ and Jinliang Wang^{1,2}

¹School of Mathematical Science, Heilongjiang University, Harbin 150080, China

²School of Mathematics and Statistics, Southwest University, Chongqing 400715, China

Correspondence should be addressed to Jinliang Wang; jinliangwang@aliyun.com

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We formulate a $(2n + 2)$ -dimensional viral infection model with humoral immunity, n classes of uninfected target cells and n classes of infected cells. The incidence rate of infection is given by nonlinear incidence rate, Beddington-DeAngelis functional response. The model admits discrete time delays describing the time needed for infection of uninfected target cells and virus replication. By constructing suitable Lyapunov functionals, we establish that the global dynamics are determined by two sharp threshold parameters: $\mathfrak{R}_0$ and $\mathfrak{R}_1$. Namely, a typical two-threshold scenario is shown. If $\mathfrak{R}_0 \leq 1$, the infection-free equilibrium P_0 is globally asymptotically stable, and the viruses are cleared. If $\mathfrak{R}_1 \leq 1 < \mathfrak{R}_0$, the immune-free equilibrium P_1 is globally asymptotically stable, and the infection becomes chronic but with no persistent antibody immune response. If $\mathfrak{R}_1 > 1$, the endemic equilibrium P_2 is globally asymptotically stable, and the infection is chronic with persistent antibody immune response.

1. Introduction

In the study of mathematical models of infectious diseases *in vivo*, it is an important problem to predict whether the infection disappears or the pathogens and the immune system persist. In general, the mathematical models of infectious diseases *in vivo* have a general immune response. For instance, CTLs can kill infected cells or they can secrete soluble factors, which can inhibit viral replication. Another immune response to viral infection is antibody immune response (humoral immunity), which is widely developed to analyze the dynamics of infections agents such as HIV and malaria (see, e.g., [1, 2]).

The basic viral infection model with antibody immunity response studied by Kajiwara and Sasaki [3] takes the following four-dimensional nonlinear differential equations:

$$x'(t) = \lambda - dx(t) - \beta x(t)v(t),$$

$$y'(t) = \beta x(t)v(t) - py(t),$$

$$v'(t) = ky(t) - \mu v(t) - qv(t)w(t),$$

$$w'(t) = gv(t)w(t) - hw(t),$$

(1)

where the uninfected $CD4^+$ T cells, $x(t)$, are produced at a constant rate of λ , die at a rate of d , and become infected at a rate of βxv . The infected cells, $y(t)$, are produced at a rate of βxv . β and p are the infection rate and death rate of infected cells, respectively. Free virus particles, $v(t)$, are released from infected cells at a rate of k . μ is the death rate of virus. $w(t)$ denotes the density of the antibody immune response (B cells). g and μ are the birth rate and death rate of B cells. q is the B cells neutralization rate.

In [3], Kajiwara and Sasaki studied the local stability of the equilibria of system (1). But local stability is not equivalent to global stability. The question of global stability in population models is a very interesting mathematical problem. Many authors have studied the global stability of virus dynamics models without delay using the second Lyapunov method. The Lyapunov function candidate for population biology

models is the Volterra-type function which was applied in literatures [4–9] to prove global stability of the steady states of viral infections models with discrete intracellular delay and distributed delay. But they all ignore the antibody immune response. In [8], Wang and Zou investigated the dynamical behavior of in-host viral models with humoral immunity and intracellular delays. By means of constructing suitable Lyapunov functionals and Lasalle invariance principles, they established the global dynamics by two sharp thresholds.

Most of the existing delayed HIV infection models are based on the assumption that the virus attacks one class of target cells, $CD4^+$ T cells. In [10, 11], an HIV model with two target cells, $CD4^+$ T cells and macrophages, has been proposed. Recently, a series of work [12–17] has been done for HIV models with two target cells with discrete-time and distributed delays. Lyapunov functionals are proved to be effective tool to establish the global asymptotic stability of their steady states [18–20].

Let $x_i(t)$ and $y_i(t)$ be the populations of the uninfected target cells and infected cells of class i , respectively, and let $v(t)$ be the population of the virus particles. The basic virus infection model with multitarget cells proposed by Elaiw [15] takes the following form of ordinary differential equations:

$$\begin{aligned}\frac{dx_i(t)}{dt} &= \lambda_i - d_i x_i(t) - \beta_i x_i(t) v(t), \\ \frac{dy_i(t)}{dt} &= \beta_i x_i(t) v(t) - p_i y_i(t), \\ \frac{dv(t)}{dt} &= \sum_{i=1}^n k_i y_i(t) - cv(t),\end{aligned}\quad (2)$$

where, for $i = 1, 2, \dots, n$, λ_i , d_i , and β_i represent the rates of which new target cells are generated, the death rate constants, and the infection rate constants, respectively. The infected cells die with rate constants p_i . The virus particles are produced by the infected cells with rate constants k_i and are cleared with rate constant c .

From system (2), the rate of infection of these viral dynamics models is assumed to be bilinear in the virus v and the uninfected $CD4^+$ T cells x_i . However, the actual incidence rate is probably not linear over the entire range of v and x_i . Thus, it is reasonable to assume that the infection rate of viral infection model is given by the Beddington-DeAngelis functional response, $\beta_i x_i v / (1 + a_i x_i + b_i v)$, where $a_i, b_i \geq 0$ [7, 21]. Time delays are intrinsic to the viral infection and replication processes, since antigenic stimulation generating immune response may need a period of time. Let parameter τ account for the time between viral entry into a target cell and the production of new virus particles. The recruitment of virus-producing cells at time t is given by the number of cells that were newly infected at time $t - \tau$ and are still alive at time t . Let m_i be a constant rate for infected but not yet virus-producing cells; the probability of surviving the time period from $t - \tau$ to t is $e^{-m_i \tau}$.

Combining model (1), model (2), and the preceding assumptions above, we arrive at the following viral infection model:

$$\begin{aligned}x_i'(t) &= \lambda_i - d_i x_i(t) - \frac{\beta_i x_i(t) v(t)}{1 + a_i x_i(t) + b_i v(t)}, \\ y_i'(t) &= \frac{\beta_i e^{-m_i \tau} x_i(t - \tau) v(t - \tau)}{1 + a_i x_i(t - \tau) + b_i v(t - \tau)} - p_i y_i(t), \\ v'(t) &= \sum_{i=1}^n k_i y_i(t) - \mu v(t) - qv(t) w(t),\end{aligned}\quad (3)$$

$$w'(t) = gv(t) w(t) - hw(t).$$

Here the state variables x_i , y_i , v , and w and parameters $\lambda_i, d_i, \beta_i, m_i, p_i, k_i, \mu, q, g$, and h have the same biological meanings as in the systems (1) and (2). a_i and b_i are constant.

For system (3), we derive the basic reproductive number $\mathfrak{R}_0$ and antibody immune activation number $\mathfrak{R}_1$ and show that $\mathfrak{R}_0$ and $\mathfrak{R}_1$ completely determine the global dynamics. The global stability result for the equilibria is new for in-host models with Beddington-DeAngelis functional response, antibody immune response, and intracellular delays. Our proof utilizes a global Lyapunov functional that is motivated by the earlier works mentioned above. The global stability of equilibria rules out any possibility for Hopf bifurcations and existence of sustained oscillations.

The paper is organized as follows. Section 2 is devoted to showing the positivity and ultimate boundedness of the solutions for (1) under suitable initial conditions. Then, we introduce threshold parameter, the basic reproduction number for viral infection $\mathfrak{R}_0$, antibody immune response reproduction number $\mathfrak{R}_1$, and three possible equilibria for (3). In Section 3, we establish global asymptotic stability of infection-free equilibrium by constructing Lyapunov functional. For a special case $i = 1$, we give the proof of global stability of equilibria for a 4-dimensional model in Section 4. We provide some numerical simulations which confirm our analysis in Section 5. In the last section, we offer a brief discussion.

2. Preliminaries

The initial conditions for system (3) take the following form:

$$\begin{aligned}x_i(\theta) &= \phi_i(\theta), \quad y_i(\theta) = \psi_i(\theta), \\ v(\theta) &= \chi(\theta), \quad w(\theta) = \varphi(\theta), \\ \phi_i(\theta), \psi_i(\theta), \chi(\theta), \varphi(\theta) &\geq 0, \quad \theta \in [-\tau, 0], \\ \phi_i(0), \psi_i(0), \chi(0), \varphi(0) &> 0, \quad i = 1, 2, 3, \dots, n,\end{aligned}\quad (4)$$

where $(\phi_i(\theta), \psi_i(\theta), \chi(\theta), \varphi(\theta)) \in \mathcal{C}([-\tau, 0], R_+^{2n+2})$.

2.1. Nonnegativity and Boundedness of Solutions. In the following, we establish the nonnegativity and boundedness of solutions of (3).

Theorem 1. Let $(x_i(t), y_i(t), v(t), w(t))$ be any solution of system (3) satisfying the initial conditions (4); then $x_i(t)$, $y_i(t)$, $v(t)$, and $w(t)$ are all nonnegative for $t > 0$ and are ultimately bounded.

Proof. First, for $i = 1, 2, \dots, n$, we prove that $x_i(t) > 0$ for all $t \geq 0$. Assume the contrary and let $t_0 > 0$ be such that $x_i(t_0) < 0$. Set $t_{01} = \inf\{0 < t < t_0 : x_i(t) < 0\}$. Then $x_i(t_{01}) = 0$, and from the first equation of system (3) we have $x'_i(t_{01}) = \lambda_i > 0$. Hence $x(t) < 0$ for $t \in (t_{01} - \epsilon, t_{01})$ and $\epsilon > 0$ sufficiently small. This contradicts $x(t) \geq 0$ for $t \in (0, t_{01}]$. It follows that, for $i = 1, 2, \dots, n$, $x_i(t) > 0$ for $t \geq 0$.

Furthermore, if there exists $t_1 > 0$, such that $y_i(t_1) = 0$, and $y_i(t) > 0$ for all $t \in (0, t_1)$, then by the second equation of system (3), we can easily obtain $y'_i(t) \geq -p_i y_i(t)$. And it follows that $y_i(t) \geq e^{-p_i t}$ for all $t \geq 0$. This is a contradiction to the assumption of $y_i(t_1) = 0$. Hence, $y_i(t) > 0$, for all $t \geq 0$.

Finally, if there exists $t_2 > 0$, such that $v(t_2) = 0$, and $v(t) > 0$, for $t \in (0, t_2)$, then by the forth equation of system (3), we have $v'(t) \geq -uv(t) - qv(t)w(t)$. And it follows that $v(t) \geq e^{-(u+q)w(t)}$ for all $t \geq 0$. This contradicts with the assumption of $v(t_2) = 0$. Hence, $v(t) > 0$, for all $t \geq 0$. Similarly, we have $w(t) > 0$, for $t \in (0, t_3)$.

Next we show that the solution is ultimately bounded. It follows from the first equation of system (3) that

$$x'_i(t) \leq \lambda_i - d_i x_i(t). \quad (5)$$

Thus $\limsup_{t \rightarrow \infty} x_i(t) \leq \lambda_i/d_i$ and $x_i(t)$ is ultimately bounded. Let

$$X_i = e^{-m_i \tau} x_i(t - \tau) + y_i(t); \quad (6)$$

then

$$X'_i(t) \leq \lambda_i e^{-m_i \tau} - \sigma_i X_i(t), \quad (7)$$

where $\sigma_i = \min\{d_i, p_i\}$. It follows that $\limsup_{t \rightarrow \infty} X_i \leq M_1$, where $M_1 = \lambda_i e^{-m_i \tau}/\sigma_i$. This in turn implies, by the nonnegativity of $x_i(t)$ and $y_i(t)$, that $\limsup_{t \rightarrow \infty} y_i \leq M_1$ and $y_i(t)$ is ultimately bounded. On the other hand, from the third equation of system (3) we have

$$v'(t) \leq \sum_{i=1}^n k_i M_1 - uv - qvw; \quad (8)$$

then $\limsup_{t \rightarrow \infty} v(t) \leq M_2$, where $M_2 = \sum_{i=1}^n (k_i M_1/u)$ and $v(t)$ is ultimately bounded. Let $V = v + w$; then

$$V' \leq \sum_{i=1}^n k_i y_i - uv - (dM_2 + h)w, \quad (9)$$

where $d = \min\{q, g\}$; then let $m = \min\{u, dM_2 + h\}$; then

$$V' \leq \sum_{i=1}^n k_i y_i - mV. \quad (10)$$

It follows that $\limsup_{t \rightarrow \infty} V \leq M_3$, where $M_3 = (\sum_{i=1}^n k_i y_i)/m$. This in turn implies, by the nonnegativity of $v(t)$ and $w(t)$, that $\limsup_{t \rightarrow \infty} w(t) \leq M_3$ and $w(t)$ is ultimately bounded. $\square$

2.2. Reproduction Numbers and Steady States. The basic reproductive number of the virus for system (3) is

$$\mathfrak{R}_0 = \sum_{i=1}^n R_i, \quad (11)$$

where $R_i = \lambda_i \beta_i k_i e^{-m_i \tau} / (d_i p_i \mu + a_i p_i \mu \lambda_i)$. We will know that if $\mathfrak{R}_0 \leq 1$, then infection-free equilibrium $P_0 = (x_i^0, 0, 0, 0)$, $x_i^0 = \lambda_i/d_i$, is the unique steady state. If $\mathfrak{R}_0 > 1$, then in addition to the uninfected steady state there exists an immune-free equilibrium $P_1 = (x_i^1, y_i^1, v^1, 0)$, corresponding to the situation that infection becomes chronic but with no persistent antibody immune response, which is given by the following expressions:

$$\begin{aligned} x_i^1 &= \frac{\sum_{i=1}^n (\lambda_i b_i k_i - \lambda_i k_i \beta_i) + d_i p_i \mu e^{m_i \tau} + \lambda_i k_i \beta_i}{d_i (k_i \beta_i + \sum_{i=1}^n b_i d_i k_i - a_i p_i \mu e^{m_i \tau})}, \\ y_i^1 &= \frac{\sum_{i=1}^n \beta_i e^{-m_i \tau} k_i \lambda_i - d_i p_i \mu - a_i p_i \mu \lambda_i}{\sum_{i=1}^n p_i k_i d_i b_i + \beta_i k_i p_i - p_i^2 a_i \mu e^{m_i \tau}} (R_i - 1), \end{aligned} \quad (12)$$

$$v^1 = \sum_{i=1}^n \frac{k_i}{\mu} \left(\frac{\sum_{i=1}^n \beta_i e^{-m_i \tau} k_i \lambda_i - d_i p_i \mu - a_i p_i \mu \lambda_i}{\sum_{i=1}^n p_i k_i d_i b_i + \beta_i k_i p_i - p_i^2 a_i \mu e^{m_i \tau}} \right) (R_i - 1).$$

Now, we introduce an antibody immune response reproduction number:

$$\begin{aligned} \mathfrak{R}_1 &= \sum_{i=1}^n \frac{\mu \left(\sum_{i=1}^n p_i k_i d_i b_i + \beta_i k_i p_i - p_i^2 a_i \mu e^{m_i \tau} \right)}{g k_i \left(\sum_{i=1}^n \beta_i e^{-m_i \tau} k_i \lambda_i - d_i p_i \mu - a_i p_i \mu \lambda_i \right)} (g v^1 - h) + 1. \end{aligned} \quad (13)$$

Further, if

$$\mathfrak{R}_0 > 1 + \sum_{i=1}^n \frac{\mu \left(\sum_{i=1}^n p_i k_i d_i b_i + \beta_i k_i p_i - p_i^2 a_i \mu e^{m_i \tau} \right) h}{g k_i \left(\sum_{i=1}^n \beta_i e^{-m_i \tau} k_i \lambda_i - d_i p_i \mu - a_i p_i \mu \lambda_i \right)}, \quad (14)$$

system (3) also has an endemic equilibrium $P_2 = (x_i^*, y_i^*, v^*, w^*)$, where

$$\begin{aligned} x_i^* &= \left(a_i \lambda_i - d_i - \frac{b_i d_i h}{g} - \frac{\beta_i h}{g} \right. \\ &\quad \left. + \left(\left(a_i \lambda_i - d_i - \frac{b_i d_i h}{g} - \frac{\beta_i h}{g} \right)^2 \right. \right. \\ &\quad \left. \left. + 4a_i d_i \lambda_i + \frac{4\lambda_i b_i h a_i d_i}{g} \right)^{1/2} \right) \\ &\quad \times (2a_i d_i)^{-1}, \\ v^* &= \frac{h}{g}, \end{aligned} \quad (15)$$

$$y_i^* = \frac{\beta_i e^{-m_i \tau} x_i^* v^*}{p_i (1 + a_i x_i^* + b_i v^*)}, \quad w^* = \sum_{i=1}^n \frac{k_i g y_i^*}{q h} - \frac{\mu}{q}.$$

It follows from

$$\mathfrak{R}_1 = \mathfrak{R}_0 - \sum_{i=1}^n \frac{\mu \left(\sum_{i=1}^n p_i k_i d_i b_i + \beta_i k_i p_i - p_i^2 a_i \mu e^{m_i \tau} \right) h}{g k_i \left(\sum_{i=1}^n \beta_i e^{-m_i \tau} k_i \lambda_i - d_i p_i \mu - a_i p_i \mu \lambda_i \right)} \quad (16)$$

that $\mathfrak{R}_1 > 1$ is equivalent to $gv^1/h > 1$. The latter gv^1/h can be regarded as the immune activation effector. It is reasonable that immune response is activated in the case where $\mathfrak{R}_1 > 1$.

3. Main Results

In this section, we consider the global asymptotic stability of the three equilibria. Throughout the paper, for easy notation, we adopt $H(s) = s - 1 - \ln s \geq H(1) = 0$ to simplify many of the expressions which follow.

Theorem 2. Consider system (3) and $\mathfrak{R}_0$ is defined by (11). The infection-free equilibrium P_0 of (3) is globally asymptotically stable if $\mathfrak{R}_0 \leq 1$.

Proof. Define a Lyapunov functional L_0 as follows:

$$L_0 = \sum_{i=1}^n \frac{x_i^0}{1 + a_i x_i^0} e^{-m_i \tau} H\left(\frac{x_i}{x_i^0}\right) + y_i + \frac{p_i}{k_i} v + \frac{p_i q}{k_i g} w + \beta_i e^{-m_i \tau} \int_{t-\tau}^t \frac{x_i(\theta) v(\theta)}{1 + a_i x_i(\theta) + b_i v(\theta)} d\theta. \quad (17)$$

Using $\lambda_i = d_i x_i^0$ and calculating the time derivative of L_0 along (3) yield

$$\begin{aligned} L'_0 &= \sum_{i=1}^n \left[\frac{e^{-m_i \tau}}{1 + a_i x_i^0} \left(1 - \frac{x_i^0}{x_i(t)} \right) x'_i(t) + y'_i(t) \right. \\ &\quad + \frac{\beta_i e^{-m_i \tau} x_i v}{1 + a_i x_i + b_i v} - \frac{\beta_i e^{-m_i \tau} x_i(t-\tau) v(t-\tau)}{1 + a_i x_i(t-\tau) + b_i v(t-\tau)} \Big] \\ &\quad + \frac{p_i}{k_i} v'(t) + \frac{p_i q}{k_i g} w'(t) \\ &= \sum_{i=1}^n \left[-\frac{d_i e^{-m_i \tau}}{x_i(1 + a_i x_i^0)} (x_i - x_i^0)^2 \right. \\ &\quad - \frac{\beta_i e^{-m_i \tau} x_i v}{(1 + a_i x_i^0)(1 + a_i x_i + b_i v)} - \frac{p_i \mu}{k_i} v - \frac{p_i q h}{k_i g} w \\ &\quad + \frac{\beta_i e^{-m_i \tau} x_i^0 v}{(1 + a_i x_i^0)(1 + a_i x_i + b_i v)} + \frac{\beta_i e^{-m_i \tau} x_i v}{1 + a_i x_i + b_i v} \Big] \\ &= \sum_{i=1}^n -\frac{d_i e^{-m_i \tau}}{x_i(1 + a_i x_i^0)} (x_i - x_i^0)^2 + (\mathfrak{R}_0 - 1) v \\ &\quad - \sum_{i=1}^n \frac{b_i \beta_i e^{-m_i \tau} x_i^0}{(1 + a_i x_i^0)(1 + a_i x_i + b_i v)} v^2 - \frac{p_i q h}{k_i g} w. \end{aligned} \quad (18)$$

Thus, $\mathfrak{R}_0 \leq 1$ ensures that $L'_0 < 0$ for all $x_i > 0$, $y_i \geq 0$, $v > 0$, and $w > 0$. And $L'_0 = 0$ if and only if $x_i = x_i^0$, $v = w = 0$ for $\mathfrak{R}_0 \leq 1$. It is easy to show that $P_0 = (x_i^0, 0, 0, 0)$ is the largest invariant set in $\{(x_i, y_i, v, w) \mid L'_0 = 0\}$. By LaSalle invariance principle, the equilibrium $P_0(x_i^0, 0, 0, 0)$ is globally asymptotically stable. This completes the proof. $\square$

Theorem 3. Consider system (3) and $\mathfrak{R}_0$ and $\mathfrak{R}_1$ are defined by (11) and (13). The immune-free equilibrium P_1 of (3) is globally asymptotically stable if $\mathfrak{R}_1 \leq 1 < \mathfrak{R}_0$.

Proof. Define a Lyapunov functional L_1 as follows:

$$L_1 = \sum_{i=1}^n \left[\frac{x_i^1 (1 + b_i v^1) e^{-m_i \tau}}{1 + a_i x_i^1 + b_i v^1} H\left(\frac{x_i}{x_i^1}\right) + y_i H\left(\frac{y_i}{y_i^1}\right) + p_i y_i^1 \int_{t-\tau}^t H\left(\frac{x_i(\theta) v(\theta)}{1 + a_i x_i(\theta) + b_i v(\theta)} \times \frac{1 + a_i x_i^1 + b_i v^1}{x_i^1 v^1}\right) d\theta \right] \quad (19)$$

$$+ \frac{p_i v^1}{k_i} H\left(\frac{v}{v^1}\right) + \frac{p_i q}{k_i g} w.$$

The derivative of L_1 is given by

$$\begin{aligned} L'_1 &= \sum_{i=1}^n \left[\frac{(1 + b_i v^1) e^{-m_i \tau}}{1 + a_i x_i^1 + b_i v^1} \left(1 - \frac{x_i^1}{x_i} \right) x'_i + \left(1 - \frac{y_i^1}{y_i} \right) y'_i \right. \\ &\quad + \frac{\beta e^{-m_i \tau} x_i v}{1 + a_i x_i + b_i v} - \frac{\beta e^{-m_i \tau} x_i(t-\tau) v(t-\tau)}{1 + a_i x_i(t-\tau) + b_i v(t-\tau)} \\ &\quad + p_i y_i^1 \ln \frac{x_i(t-\tau) v(t-\tau)}{x_i v} \\ &\quad \times \frac{1 + a_i x_i + b_i v}{1 + a_i x_i(t-\tau) + b_i v(t-\tau)} \Big] \\ &\quad + \frac{p_i}{k_i} \left(1 - \frac{v^1}{v} \right) v' + \frac{p_i q}{k_i g} w' \\ &= \sum_{i=1}^n \left[-\frac{d_i (1 + b_i v^1) e^{-m_i \tau}}{x_i (1 + a_i x_i^1 + b_i v^1)} (x_i - x_i^1)^2 \right. \\ &\quad + p_i y_i^1 \left[1 - \frac{x_i^1 (1 + a_i x_i + b_i v^1)}{x_i (1 + a_i x_i^1 + b_i v^1)} \right. \\ &\quad \left. \left. + \ln \frac{x_i^1 (1 + a_i x_i + b_i v^1)}{x_i (1 + a_i x_i^1 + b_i v^1)} \right] \right] \end{aligned}$$

$$\begin{aligned}
& + p_i y_i^1 \\
& \times \left[1 - \frac{y_i^1 (1 + a_i x_i^1 + b_i v^1) x_i(t-\tau) v(t-\tau)}{y_i x_i^1 v^1 (1 + a_i x_i(t-\tau) + b_i v(t-\tau))} \right. \\
& \quad \left. + \ln \frac{y_i^1 (1 + a_i x_i^1 + b_i v^1) x_i(t-\tau) v(t-\tau)}{y_i x_i^1 v^1 (1 + a_i x_i(t-\tau) + b_i v(t-\tau))} \right] \\
& + p_i y_i^1 \left[1 - \frac{v^1 y_i}{y_i^1 v} + \ln \frac{v^1 y_i}{y_i^1 v} \right] \\
& + p_i y_i^1 \left[1 - \frac{1 + a_i x_i + b_i v}{1 + a_i x_i + b_i v^1} + \ln \frac{1 + a_i x_i + b_i v}{1 + a_i x_i + b_i v^1} \right] \\
& \quad - \frac{p_i y_i^1 b_i (1 + a_i x_i) (v - v^1)^2}{v^1 (1 + a_i x_i + b_i v) (1 + a_i x_i + b_i v^1)} \Bigg] \\
& + \frac{p_i q (g v^1 - h)}{k_i g} w.
\end{aligned} \tag{20}$$

In the above calculations, we used the equations $\lambda_i = d_i x_i^1 + (\beta_i x_i^1 v^1 / (1 + a_i x_i^1 + b_i v^1))$, $\sum_{i=1}^n k_i y_i^1 = u v^1$, and $\beta_i e^{-m_i \tau} x_i^1 v^1 / (1 + a_i x_i^1 + b_i v^1) = p_i y_i^1$.

Further, $\mathfrak{R}_1 \leq 1 < \mathfrak{R}_0$ is equivalent to $v^1 \leq h/g$. Hence L'_1 is always nonpositive under the condition $\mathfrak{R}_1 \leq 1 < \mathfrak{R}_0$, and $L'_1 = 0$ if and only if $x_i = x_i^1$, $y_i/y_i^1 = v/v^1$, and $w = 0$ for $\mathfrak{R}_1 < 1$ or $x_i = x_i^1$, $y_i/y_i^1 = v/v^1$ for $\mathfrak{R}_1 = 1$. Similarly, it follows from LaSalle invariance principle that the immune-free equilibrium P_1 is globally asymptotically stable. This completes the proof. $\square$

Theorem 4. Consider system (3) and $\mathfrak{R}_1$ is defined by (13). The endemic equilibrium P_2 of (3) is globally asymptotically stable if $\mathfrak{R}_1 > 1$.

Proof. Define a Lyapunov functional L_2 as follows:

$$\begin{aligned}
L_2 = & \sum_{i=1}^n \left[\frac{x_i^* (1 + b_i v_i^*) e^{-m_i \tau}}{1 + a_i x_i^* + b_i v^*} H \left(\frac{x_i}{x_i^*} \right) + y_i^* H \left(\frac{y_i}{y_i^*} \right) \right. \\
& + p_i y_i^* \int_{t-\tau}^t H \left(\frac{x_i(\theta) v(\theta)}{1 + a_i x_i(\theta) + b_i v(\theta)} \right. \\
& \quad \left. \times \frac{1 + a_i x_i^* + b_i v^*}{x_i^* v^*} \Bigg) d\theta \Bigg] \\
& + \frac{p_i v^*}{k_i} H \left(\frac{v}{v^*} \right) + \frac{p_i q w^*}{k_i g} H \left(\frac{w}{w^*} \right).
\end{aligned} \tag{21}$$

The derivative of L_2 is given by

$$\begin{aligned}
L'_2 = & \sum_{i=1}^n \left[\frac{e^{-m_i \tau} (1 + b_i v^*)}{1 + a_i x_i^* + b_i v^*} \left(1 - \frac{x_i^*}{x_i} \right) x'_i + \left(1 - \frac{y_i^*}{y_i} \right) y'_i \right. \\
& + \frac{\beta_i e^{-m_i \tau} x_i v}{1 + a_i x_i + b_i v} - \frac{\beta_i e^{-m_i \tau} x_i(t-\tau) v(t-\tau)}{1 + a_i x_i(t-\tau) + b_i v(t-\tau)} \\
& + p_i y_i^* \ln \frac{x_i(t-\tau) v(t-\tau)}{x_i v} \\
& \times \frac{1 + a_i x_i + b_i v}{1 + a_i x_i(t-\tau) + b_i v(t-\tau)} \Bigg] \\
& + \frac{p_i}{k_i} \left(1 - \frac{v^*}{v} \right) v' + \frac{p_i q}{k_i g} \left(1 - \frac{w^*}{w} \right) w' \\
= & \sum_{i=1}^n \left[- \frac{d_i (1 + b_i v^*) e^{-m_i \tau}}{x_i (1 + a_i x_i^* + b_i v^*)} (x_i - x_i^*)^2 \right] \\
& + \sum_{i=1}^n p_i y_i^* \left[1 - \frac{x_i^* (1 + a_i x_i + b_i v^*)}{x_i (1 + a_i x_i^* + b_i v^*)} \right. \\
& \quad \left. + \ln \frac{x_i^* (1 + a_i x_i + b_i v^*)}{x_i (1 + a_i x_i^* + b_i v^*)} \right] \\
& + \sum_{i=1}^n p_i y_i^* \left[1 - \frac{y_i^* (1 + a_i x_i^* + b_i v^*) x_i(t-\tau) v(t-\tau)}{y_i x_i^* v^* (1 + a_i x_i(t-\tau) + b_i v(t-\tau))} \right. \\
& \quad \left. + \ln \frac{y_i^* (1 + a_i x_i^* + b_i v^*) x_i(t-\tau) v(t-\tau)}{y_i x_i^* v^* (1 + a_i x_i(t-\tau) + b_i v(t-\tau))} \right] \\
& - \sum_{i=1}^n \frac{p_i y_i^* b_i (1 + a_i x_i) (v - v^*)^2}{v^* (1 + a_i x_i + b_i v) (1 + a_i x_i + b_i v^*)} \\
& + \sum_{i=1}^n p_i y_i^* \left[1 - \frac{v^* y_i}{y_i^* v} + \ln \frac{v^* y_i}{y_i^* v} \right] \\
& + \sum_{i=1}^n p_i y_i^* \left[1 - \frac{1 + a_i x_i + b_i v}{1 + a_i x_i + b_i v^*} + \ln \frac{1 + a_i x_i + b_i v}{1 + a_i x_i + b_i v^*} \right].
\end{aligned} \tag{22}$$

Therefore, $L'_2 \leq 0$ holds for all $x_i, y_i, v, w > 0$. Thus, the endemic equilibrium P_2 is stable. And we have $L'_2 = 0$ if and only if $x_i = x_i^*$, $y_i = y_i^*$, $v = v^*$, and $w = w^*$ hold. The largest compact invariant set in $\{(x_i, y_i, v, w) \mid L'_2 = 0\}$ is the singleton $\{P_2\}$. Therefore, the endemic equilibrium P_2 is globally asymptotically stable by the LaSalle invariance principle when $\mathfrak{R}_1 > 1$. This completes the proof. $\square$

4. Special Case When $i = 1$

For $i = 1$, system (3) becomes

$$\begin{aligned} x'(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)}, \\ y'(t) &= \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)} - py(t), \\ v'(t) &= ky(t) - \mu v(t) - qv(t)w(t), \\ w'(t) &= gv(t)w(t) - hw(t). \end{aligned} \quad (23)$$

Here the state variables x , y , v , and w and parameters λ , d , β , a , b , m , p , k , μ , q , g , and h have the similar biological meanings as in the system (3).

The basic reproductive number of the virus for system (23) is $\mathfrak{R}_0^1 = \lambda \beta k e^{-m\tau} / (dp\mu + ap\mu\lambda)$. We will know that if $\mathfrak{R}_0^1 \leq 1$, then infection-free equilibrium $P_0 = (x_0, 0, 0, 0)$, $x_0 = \lambda/d$, is the unique steady state; if $\mathfrak{R}_0^1 > 1$, then in addition to the uninfected steady state there exists an immune-free equilibrium $E_1 = (x_1, y_1, v_1, 0)$, corresponding to the situation that infection becomes chronic but with no persistent antibody immune response, which is given by the following expressions:

$$\begin{aligned} x_1 &= \frac{\lambda bk + pue^{m\tau}}{k\beta + bdk - ap\mu e^{m\tau}}, \\ y_1 &= \frac{dp\mu + ap\mu\lambda}{p(k\beta + bdk - ap\mu e^{m\tau})} (\mathfrak{R}_0^1 - 1), \\ v_1 &= \frac{k(dp\mu + ap\mu\lambda)}{p\mu(k\beta + bdk - ap\mu e^{m\tau})} (\mathfrak{R}_0^1 - 1). \end{aligned} \quad (24)$$

Now, we introduce an antibody immune response reproduction number:

$$\mathfrak{R}_1^1 = \frac{p\mu(k\beta + bdk - ap\mu e^{m\tau})}{gk(dp\mu + ap\mu\lambda)} (gv_1 - h) + 1. \quad (25)$$

Further, if

$$\mathfrak{R}_0^1 > 1 + \frac{p\mu(k\beta + bdk - ap\mu e^{m\tau})h}{gk(dp\mu + ap\mu\lambda)}, \quad (26)$$

system (3) also has an endemic equilibrium $E_2 = (x_2, y_2, v_2, w_2)$, where

$$\begin{aligned} x_2 &= \left(a\lambda - d - \frac{bdh}{g} - \frac{\beta h}{g} \right. \\ &\quad \left. + \sqrt{\left(a\lambda - d - \frac{bdh}{g} - \frac{\beta h}{g} \right)^2 + 4ad\lambda + \frac{4\lambda bhad}{g}} \right) \\ &\quad \times (2ad)^{-1}, \\ v_2 &= \frac{h}{g}, \quad y_2 = \frac{\beta e^{-m\tau} x_2 v_2}{p(1 + ax_2 + bv_2)}, \quad w_2 = \frac{kgy_2}{qh} - \frac{\mu}{q}. \end{aligned} \quad (27)$$

It follows from

$$\mathfrak{R}_1^1 = \mathfrak{R}_0^1 - \frac{p\mu(k\beta + bdk - ap\mu e^{m\tau})h}{gk(dp\mu + ap\mu\lambda)} \quad (28)$$

that $\mathfrak{R}_1^1 > 1$ is equivalent to $gv_1/h > 1$. The latter gv_1/h can be regarded as the immune activation effector. It is reasonable that immune response is activated in the case where $\mathfrak{R}_1^1 > 1$.

The initial conditions for system (23) take the following form:

$$\begin{aligned} x(\theta) &= \phi_1(\theta), \quad y(\theta) = \phi_2(\theta), \\ v(\theta) &= \phi_3(\theta), \quad w(\theta) = \phi_4(\theta), \end{aligned} \quad (29)$$

$$\phi_i(\theta) \geq 0, \quad \theta \in [-\tau, 0], \quad \phi_i(0) > 0, \quad i = 1, 2, 3, 4,$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in \mathcal{C}([-\tau, 0], R_{+0}^4)$.

Theorem 5. Consider system (23).

- (i) The infection-free equilibrium E_0 of (23) is globally asymptotically stable if $\mathfrak{R}_0^1 \leq 1$.
- (ii) The immune-free equilibrium E_1 of (23) is globally asymptotically stable if $\mathfrak{R}_1^1 \leq 1 < \mathfrak{R}_0^1$.
- (iii) The endemic equilibrium E_2 of (23) is globally asymptotically stable if $\mathfrak{R}_1^1 > 1$.

Proof. Consider the following.

Proof of (i) of Theorem 5. Define a Lyapunov functional L_0 as follows:

$$L_0 = \frac{x_0}{1 + ax_0} e^{-m\tau} H\left(\frac{x}{x_0}\right) + y + \frac{p}{k}v + \frac{pq}{kg}w \quad (30)$$

$$+ \beta e^{-m\tau} \int_{t-\tau}^t \frac{x(\theta)v(\theta)}{1 + ax(\theta) + bv(\theta)} d\theta.$$

Using $\lambda = dx_0$ and calculating the time derivative of U_0 along (23), we have

$$\begin{aligned} U'_0 &= \frac{e^{-m\tau}}{1 + ax_0} \left(1 - \frac{x_0}{x(t)} \right) x'(t) + y'(t) + \frac{p}{k}v'(t) \\ &\quad + \frac{pq}{kg}w'(t) + \frac{\beta e^{-m\tau} xv}{1 + ax + bv} \\ &\quad - \frac{\beta e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)} \\ &= - \frac{de^{-m\tau}}{x(1 + ax_0)} (x - x_0)^2 - \frac{\beta e^{-m\tau} xv}{(1 + ax_0)(1 + ax + bv)} \\ &\quad - \frac{p\mu}{k}v - \frac{pqh}{kg}w + \frac{\beta e^{-m\tau} x_0 v}{(1 + ax_0)(1 + ax + bv)} \\ &\quad + \frac{\beta e^{-m\tau} xv}{1 + ax + bv} \end{aligned}$$

FIGURE 1: Trajectories of $x(t)$, $x(t)$, $x(t)$, $w(t)$ for $\mathfrak{R}_0^1 = 0.215743$, $\mathfrak{R}_1^1 = 0.127203$, and $E_0 = (10^4, 0, 0, 0)$ are globally asymptotically stable. $x(t)$, $y(t)$, $v(t)$, and $w(t)$ versus t are illustrated by (a), (b), (c), and (d).

$$\begin{aligned}
 &= -\frac{de^{-m\tau}}{x(1+ax_0)}(x-x_0)^2 + \frac{p\mu v(1+ax)}{k(1+ax+bv)}(\mathfrak{R}_0-1) \\
 &\quad - \frac{p\mu b}{k(1+ax+bv)}v^2 - \frac{pqh}{kg}w.
 \end{aligned} \tag{31}$$

Thus, $\mathfrak{R}_0^1 \leq 1$ ensures that $U'_0 < 0$ for all $x > 0$, $y \geq 0$, $v > 0$, and $w > 0$. And $U'_0 = 0$ if and only if $x = x_0$, $v = w = 0$ for $\mathfrak{R}_0^1 \leq 1$. It is easy to show that $E_0(x_0, 0, 0, 0)$ is the largest invariant set in $\{(x, y, v, w) \mid U'_0 = 0\}$. By LaSalle invariance principle, the equilibrium $E_0(x_0, 0, 0, 0)$ is globally asymptotically stable.

Proof of (ii) of Theorem 5. Define a Lyapunov functional L_1 as follows:

$$\begin{aligned}
 U_1 &= \frac{x_1(1+bv_1)e^{-m\tau}}{1+ax_1+bv_1}H\left(\frac{x}{x_1}\right) \\
 &\quad + y_1H\left(\frac{y}{y_1}\right) + \frac{pv_1}{k}H\left(\frac{v}{v_1}\right) + \frac{pq}{kg}w \\
 &\quad + py_1 \int_{t-\tau}^t H\left(\frac{x(\theta)v(\theta)}{1+ax(\theta)+bv(\theta)} \frac{1+ax_1+bv_1}{x_1v_1}\right) d\theta.
 \end{aligned} \tag{32}$$

The derivative of U_1 is given by

$$\begin{aligned}
 U'_1 &= \frac{(1+bv_1)e^{-m\tau}}{1+ax_1+bv_1} \left(1 - \frac{x_1}{x}\right)x' + \left(1 - \frac{y_1}{y}\right)y' \\
 &\quad + \frac{p}{k} \left(1 - \frac{v_1}{v}\right)v' + \frac{pq}{kg}w' + \frac{\beta e^{-m\tau}xv}{1+ax+bv} \\
 &\quad - \frac{\beta e^{-m\tau}x(t-\tau)v(t-\tau)}{1+ax(t-\tau)+bv(t-\tau)} \\
 &\quad + py_1 \ln \frac{x(t-\tau)v(t-\tau)}{xv} \frac{1+ax+bv}{1+ax(t-\tau)+bv(t-\tau)} \\
 &= -\frac{d(1+bv_1)e^{-m\tau}}{x(1+ax_1+bv_1)}(x-x_1)^2 + \frac{pq(gv_1-h)}{kg}w \\
 &\quad + py_1 \left[1 - \frac{x_1(1+ax+bv_1)}{x(1+ax_1+bv_1)} + \ln \frac{x_1(1+ax+bv_1)}{x(1+ax_1+bv_1)}\right]
 \end{aligned}$$

FIGURE 2: Trajectories of $x(t)$, $y(t)$, $v(t)$, $w(t)$ for $\mathfrak{R}_0^1 = 1.07872$, $\mathfrak{R}_1^1 = 0.982187$, and $E_1 = (9924.5, 34.7292, 1576.57, 0)$ are globally asymptotically stable. $x(t)$, $y(t)$, $v(t)$, and $w(t)$ versus t are illustrated by (a), (b), (c), and (d).

$$\begin{aligned}
& + py_1 \left[1 - \frac{y_1 (1 + ax_1 + bv_1) x(t - \tau) v(t - \tau)}{yx_1 v_1 (1 + ax(t - \tau) + bv(t - \tau))} \right. \\
& \quad \left. + \ln \frac{y_1 (1 + ax_1 + bv_1) x(t - \tau) v(t - \tau)}{yx_1 v_1 (1 + ax(t - \tau) + bv(t - \tau))} \right] \\
& + py_1 \left[1 - \frac{v_1 y}{y_1 v} + \ln \frac{v_1 y}{y_1 v} \right] \\
& + py_1 \left[1 - \frac{1 + ax + bv}{1 + ax + bv_1} + \ln \frac{1 + ax + bv}{1 + ax + bv_1} \right] \\
& - \frac{py_1 b (1 + ax) (v - v_1)^2}{v_1 (1 + ax + bv) (1 + ax + bv_1)}.
\end{aligned} \tag{33}$$

In the above calculations, we used the equations $\lambda = dx_1 + (\beta x_1 v_1 / (1 + ax_1 + bv_1))$, $ky_1 = uv_1$, and $\beta e^{-m\tau} x_1 v_1 / (1 + ax_1 + bv_1) = py_1$.

Further, $\mathfrak{R}_1^1 \leq 1 < \mathfrak{R}_0^1$ is equivalent to $v_1 \leq h/g$. Hence U_1' is always nonpositive under the condition $\mathfrak{R}_1^1 \leq 1 < \mathfrak{R}_0^1$, and $U_1' = 0$ if and only if $x = x_1$, $y/y_1 = v/v_1$, and $w = 0$ for $\mathfrak{R}_1^1 < 1$ or $x = x_1$, $y/y_1 = v/v_1$ for $\mathfrak{R}_1^1 = 1$. Similarly,

it follows from LaSalle invariance principle that the immune-free equilibrium E_1 is globally asymptotically stable. $\square$

Proof of (iii) of Theorem 5. Define a Lyapunov functional U_2 as follows:

$$\begin{aligned}
U_2 &= \frac{x_2 (1 + bv_2) e^{-m\tau}}{1 + ax_2 + bv_2} H\left(\frac{x}{x_2}\right) + y_2 H\left(\frac{y}{y_2}\right) \\
&+ \frac{pv_2}{k} H\left(\frac{v}{v_2}\right) + \frac{pqw_2}{kg} H\left(\frac{w}{w_2}\right) \\
&+ py_2 \int_{t-\tau}^t H\left(\frac{x(\theta) v(\theta)}{1 + ax(\theta) + bv(\theta)} \frac{1 + ax_2 + bv_2}{x_2 v_2}\right) d\theta.
\end{aligned} \tag{34}$$

The derivative of U_2 is given by

$$\begin{aligned}
U_2' &= \frac{e^{-m\tau} (1 + bv_2)}{1 + ax_2 + bv_2} \left(1 - \frac{x_2}{x}\right) x' + \left(1 - \frac{y_2}{y}\right) y' \\
&+ \frac{p}{k} \left(1 - \frac{v_2}{v}\right) v' + \frac{pq}{kg} \left(1 - \frac{w_2}{w}\right) w'
\end{aligned}$$

FIGURE 3: Trajectories of $x(t)$, $y(t)$, $v(t)$, $w(t)$ for $\mathfrak{R}_0^1 = 2.15743$ and $\mathfrak{R}_1^1 = 2.05092$, and $E_2 = (9818.03, 83.7059, 1933.33, 8.0456)$ are globally asymptotically stable. $x(t)$, $y(t)$, $v(t)$, and $w(t)$ versus t are illustrated by (a), (b), (c), and (d).

$$\begin{aligned}
& + \frac{\beta e^{-m\tau} x v}{1 + ax + bv} - \frac{\beta e^{-m\tau} x(t-\tau) v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)} \\
& + py_2 \ln \frac{x(t-\tau) v(t-\tau)}{x v} \frac{1 + ax + bv}{1 + ax(t-\tau) + bv(t-\tau)} \\
& + py_2 \left[1 - \frac{v_2 y}{y_2 v} + \ln \frac{v_2 y}{y_2 v} \right] \\
& + py_2 \left[1 - \frac{1 + ax + bv}{1 + ax + bv_2} + \ln \frac{1 + ax + bv}{1 + ax + bv_2} \right]. \\
& = - \frac{d(1 + bv_2) e^{-m\tau}}{x(1 + ax_2 + bv_2)} (x - x_2)^2 \\
& + py_2 \left[1 - \frac{x_2(1 + ax + bv_2)}{x(1 + ax_2 + bv_2)} + \ln \frac{x_2(1 + ax + bv_2)}{x(1 + ax_2 + bv_2)} \right] \\
& + py_2 \left[1 - \frac{y_2(1 + ax_2 + bv_2) x(t-\tau) v(t-\tau)}{yx_2 v_2(1 + ax(t-\tau) + bv(t-\tau))} \right. \\
& \quad \left. + \ln \frac{y_2(1 + ax_2 + bv_2) x(t-\tau) v(t-\tau)}{yx_2 v_2(1 + ax(t-\tau) + bv(t-\tau))} \right] \\
& - \frac{py_2 b(1 + ax)(v - v_2)^2}{v_2(1 + ax + bv)(1 + ax + bv_2)}
\end{aligned} \tag{35}$$

Therefore, $U_2' \leq 0$ holds for all $x, y, v, w > 0$. Thus, the endemic equilibrium E_2 is stable. And we have $U_2' = 0$ if and only if $x = x_2$, $y = y_2$, $v = v_2$, and $w = w_2$ hold. The largest compact invariant set in $\{(x, y, v, w) \mid U_2' = 0\}$ is the singleton $\{E_2\}$. Therefore, the endemic equilibrium E_2 is globally asymptotically stable by the LaSalle invariance principle when $\mathfrak{R}_1^1 > 1$. This completes the proof.

5. Numerical Example

We now carry out some numerical simulations to support our theoretic results for the dynamics of the concentration of uninfected target cells $x(t)$ [cells mL^{-1}], productively infected cells $y(t)$ [cells mL^{-1}], free virus in the serum $v(t)$ [virion cells mL^{-1}] antibodies $w(t)$ [μg]. We set $m = 0$ and $\tau = 0.5$ for the sake of simplification. The values of the parameters $\lambda, d, \beta,$

p, k, μ, q, g , and h are found in Pawelek et al. [22] and Wang et al. [23].

Parameters in Figure 1 are $\lambda = 46$ cells mL^{-1} , $d = 0.0046$ day^{-1} , $\beta = 4.8 \times 10^{-7}$ mL virion- day^{-1} , $a = 0.01$, $b = 0.005$, $p = 0.01$ day^{-1} , $k = 11.349$ day^{-1} , $\mu = 0.25$ day^{-1} , $q = 0.03$, $g = 0.0015$, and $h = 2.9$ day^{-1} . In this case, we obtain $\mathfrak{R}_0^1 = 0.215743$ and $\mathfrak{R}_1^1 = 0.127203$. From (i) of Theorem 5, $E_0 = (10^4, 0, 0, 0)$ is globally asymptotically stable.

Parameters in Figure 2 are $\lambda = 46$ cells mL^{-1} , $d = 0.0046$ day^{-1} , $\beta = 2.4 \times 10^{-7}$ mL virion- day^{-1} , $a = 0.01$, $b = 0.005$, $p = 0.01$ day^{-1} , $k = 11.349$ day^{-1} , $\mu = 0.25$ day^{-1} , $q = 0.03$, $g = 0.0015$, and $h = 2.9$ day^{-1} . In this case, we obtain $\mathfrak{R}_0^1 = 1.07872$ and $\mathfrak{R}_1^1 = 0.982187$. From (ii) of Theorem 5, $E_1 = (9924.5, 34.7292, 1576.57, 0)$ is globally asymptotically stable.

Parameters in Figure 3 are $\lambda = 46$ cells mL^{-1} , $d = 0.0046$ day^{-1} , $\beta = 4.8 \times 10^{-6}$ mL virion- day^{-1} , $a = 0.01$, $b = 0.005$, $p = 0.01$ day^{-1} , $k = 11.349$ day^{-1} , $\mu = 0.25$ day^{-1} , $q = 0.03$, $g = 0.0015$, and $h = 2.9$ day^{-1} . In this case, we obtain $\mathfrak{R}_0^1 = 2.15743$ and $\mathfrak{R}_1^1 = 2.05092$. From (iii) of Theorem 5, $E_2 = (9818.03, 83.7059, 1933.33, 8.0456)$ is globally asymptotically stable.

6. Conclusions and Discussion

From Theorem 2 we can see that

$$v^1 - v^* = \sum_{i=1}^n \frac{k_i \sum_{j=1}^n \beta_j e^{-m_i \tau} k_j \lambda_i - d_i p_i \mu - a_i p_i \mu \lambda_i}{\mu \sum_{i=1}^n p_i k_i d_i b_i + \beta_i k_i p_i - a_i p_i^2 \mu e^{m_i \tau}} \quad (36)$$

$$\times (\mathfrak{R}_1 - 1) > 0,$$

so the antibody immune response has a positive role in reduction of the virus. Huang et al. [7] investigated the global dynamics of basic in-host dynamics model with Beddington-DeAngelis infection rate. But their models did not conclude immune response and intracellular delay. On the other hand, we improve the results in [8] from bilinear incidence rate to Beddington-DeAngelis incidence rate. It is similar to the well-known Holling type II functional response but has an extra term bv in the denominator which models mutual interference between viruses. When $a > 0$, $b = 0$, the Beddington-DeAngelis functional response is simplified to Holling type II functional response [21]. When $a = 0$, $b > 0$, it expresses a saturation response; our model will reduce to the model studied in [9].

Conflict of Interests

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

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References

- [1] C. Chiyaka, W. Garira, and S. Dube, "Modelling immune response and drug therapy in human malaria infection," *Computational and Mathematical Methods in Medicine*, vol. 9, no. 2, pp. 143–163, 2008.
- [2] A. S. Perelson, "Modelling viral and immune system dynamics," *Nature Reviews Immunology*, vol. 2, no. 1, pp. 28–36, 2002.
- [3] T. Kajiwarra and T. Sasaki, "A note on the stability analysis of pathogen-immune interaction dynamics," *Discrete and Continuous Dynamical Systems Series B*, vol. 4, no. 3, pp. 615–622, 2004.
- [4] A. Korobeinikov, "Global properties of basic virus dynamics models," *Bulletin of Mathematical Biology*, vol. 66, no. 4, pp. 879–883, 2004.
- [5] C. C. McCluskey, "Complete global stability for an SIR epidemic model with delay—distributed or discrete," *Nonlinear Analysis: Real World Applications*, vol. 11, no. 1, pp. 55–59, 2010.
- [6] M. Y. Li and H. Shu, "Impact of intracellular delays and target-cell dynamics on in vivo viral infections," *SIAM Journal on Applied Mathematics*, vol. 70, no. 7, pp. 2434–2448, 2010.
- [7] G. Huang, W. Ma, and Y. Takeuchi, "Global properties for virus dynamics model with Beddington-DeAngelis functional response," *Applied Mathematics Letters*, vol. 22, no. 11, pp. 1690–1693, 2009.
- [8] S. Wang and D. Zou, "Global stability of in-host viral models with humoral immunity and intracellular delays," *Applied Mathematical Modelling*, vol. 36, no. 3, pp. 1313–1322, 2012.
- [9] X. Wang and S. Liu, "A class of delayed viral models with saturation infection rate and immune response," *Mathematical Methods in the Applied Sciences*, vol. 36, no. 2, pp. 125–142, 2013.
- [10] D. S. Callaway and A. S. Perelson, "HIV-1 infection and low steady state viral loads," *Bulletin of Mathematical Biology*, vol. 64, no. 1, pp. 29–64, 2002.
- [11] A. S. Perelson and P. W. Nelson, "Mathematical analysis of HIV-1 dynamics in vivo," *SIAM Review*, vol. 41, no. 1, pp. 3–44, 1999.
- [12] A. M. Elaiw and X. Xia, "HIV dynamics: analysis and robust multirate MPC-based treatment schedules," *Journal of Mathematical Analysis and Applications*, vol. 359, no. 1, pp. 285–301, 2009.
- [13] A. M. Elaiw, "Global properties of a class of HIV models," *Nonlinear Analysis: Real World Applications*, vol. 11, no. 4, pp. 2253–2263, 2010.
- [14] 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*, vol. 2011, Article ID 201274, 19 pages, 2011.
- [15] A. M. Elaiw, "Global properties of a class of virus infection models with multitarget cells," *Nonlinear Dynamics*, vol. 69, no. 1-2, pp. 423–435, 2012.

- [16] 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*, vol. 36, no. 4, pp. 383–394, 2013.
- [17] A. Elaiw, I. Hassanien, and S. Azoz, "Global stability of HIV infection models with intracellular delays," *Journal of the Korean Mathematical Society*, vol. 49, no. 4, pp. 779–794, 2012.
- [18] J. Wang and L. Guan, "Global stability for a HIV-1 infection model with cell-mediated immune response and intracellular delay," *Discrete and Continuous Dynamical Systems B*, vol. 17, no. 1, pp. 297–302, 2012.
- [19] J. Wang, G. Huang, and Y. Takeuchi, "Global asymptotic stability for HIV-1 dynamics with two distributed delays," *Mathematical Medicine and Biology*, vol. 29, no. 3, pp. 283–300, 2012.
- [20] J. Wang, G. Huang, Y. Takeuchi, and S. Liu, "Sveir epidemiological model with varying infectivity and distributed delays," *Mathematical Biosciences and Engineering*, vol. 8, no. 3, pp. 875–888, 2011.
- [21] D. Li and W. Ma, "Asymptotic properties of a HIV-1 infection model with time delay," *Journal of Mathematical Analysis and Applications*, vol. 335, no. 1, pp. 683–691, 2007.
- [22] K. A. Pawelek, S. Liu, F. Pahlevani, and L. Rong, "A model of HIV-1 infection with two time delays: mathematical analysis and comparison with patient data," *Mathematical Biosciences*, vol. 235, no. 1, pp. 98–109, 2012.
- [23] J. Wang, J. Pang, T. Kuniya, and Y. Enatsu, "Global threshold dynamics in a five-dimensional virus model with cell-mediated, humoral immune responses and distributed delays," *Applied Mathematics and Computation*, vol. 241, pp. 298–316, 2014.