Global Stability of in-host Viral Model with Humoral Immunity and Beddington-DeAngelis Functional Response

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***Abstract*- In this paper, we have considered an in-host viral model with humoral immunity and Beddington-DeAngelis functional response. For this model, we constructed suitable Lyapunov functional and used LaSalle invariance, we obtained the global stability of three equilibriums which depend on two threshold parameters R_0 and R_1, that is, if $R_0 \le 1$, the infected-free equilibrium E_0 is globally asymptotically stable; if $R_1 \le 1 < R_0$, the infected equilibrium without B cells response E_1^* is globally asymptotically stable; and if $R_1 > 1$, the infected equilibrium with B cells response E_2^* is globally asymptotically stable, too. Finally, numerical simulations are carried out to support our main results.**

Keywords*- *Global Stability; Delay; Humoral Immunity; Lyapunov Functional

I. INTRODUCTION

Over the past several years, the studies of mathematical models with humoral immunity have received much attention in [1, 3, 13, 17, 22]. Virus dynamics is an important method for the research on proliferation of virus in the host of parasitic. It shows the parasitic process of the virus, reveals the law and predicts the trend of development via qualitative analysis. As a result, it can offer people the theoretical basis for decision-making on prevention and control. The adaptive immune response is intermediated by lymphocytes, that is to say, humoral and cellular immunity. The humoral immunity is more effective than the cell-intermediated immune in malaria infection. In [19], the author studied the global stability of in-host viral model with humoral model, which can be simply written as

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - dT(t) - \beta V(t)T(t), \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = \beta V(t)T(t) - \delta I(t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = N\delta I(t) - cV(t) - qB(t)V(t), \\ \dfrac{\mathrm{d}B(t)}{\mathrm{d}t} = gB(t)V(t) - \mu B(t), \end{cases} \tag{1.1}$$

where the parameter T denotes the uninfected cells, I denotes the infected cells, V denotes virus, B denotes the B cells. Λ is the birth rate of uninfected cells and d is the death rate of uninfected cells. β is the infection rate, N is the average number of virus particles produced over the lifetime of a single infected cells, and δ is the death rate of infected cells. And the virus dies at rate cV, g and μ are the birth rate and death rate of B cells respectively.

In reality, since the incidence rates are probably not strictly linear in each variable over the entire range of V and T. In [8, 9], Huang, Ma and Takeuchi have studied the viral model with Beddingtou-DeAngelis functional response and have studied the global properties of the model. Recently, it also has been realized that time delay should be taken into consideration [7, 14, 15].

Motivated by [7-9, 14, 15, 23], in this paper, we will incorporate the Beddingtou-DeAngelis functional response and distributed intracellular delays in model (1.1). So, we get this following model:

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - dT(t) - \dfrac{\beta V(t)T(t)}{1 + aT(t) + bV(t)}, \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = \beta \int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau} \dfrac{V(t-\tau)T(t-\tau)}{1 + aT(t-\tau) + bV(t-\tau)}\mathrm{d}\tau - \delta I(t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = N\delta \int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau} I(t-\tau)\mathrm{d}\tau - cV(t) - qB(t)V(t), \\ \dfrac{\mathrm{d}B(t)}{\mathrm{d}t} = gB(t)V(t) - \mu B(t), \end{cases} \tag{1.2}$$

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where the parameters $\Lambda, d, \beta, N, \delta, c, g, \mu$ and the variables T, I, V, B are the same as defined in model (1.1), a, b, m_1 and m_2 are the positive constants. In this model, the cells which are infected at time $t-\tau$ begin producing virus at the time t, and τ is distributed according to a probability $f_1(\tau)$. And m_1 is a constant death rate for infected which is not yet virus-producing cells. So the possibility of surviving from the time $t-\tau$ to the time t is $\mathrm{e}^{-m\tau}$. In the same as the above explanation, the virus also has this similar situation. In (1.2), the delay kernel, $f_i:[0,\infty)\to[0,\infty), i=1,2$, and these two functions are piecewise continuous and also satisfy the following properties:

$$\int_0^\infty f_i(\tau)\,\mathrm{d}\tau = 1, \int_0^\infty \tau f_i(\tau)\,\mathrm{d}\tau < \infty, i=1,2.$$

With initial conditions as follows:

$$\begin{aligned} &T(\theta)=\varphi_1(\theta), I(\theta)=\varphi_2(\theta), V(\theta)=\varphi_3(\theta), B(\theta)=\varphi_4(\theta),\\ &\varphi_i(\theta)\ge 0, \theta\in(-\infty,0), \varphi_i(0)>0 (i=1,2,3,4), \end{aligned} \tag{1.3}$$

where $(\varphi_1(\theta),\varphi_2(\theta),\varphi_3(\theta),\varphi_4(\theta))\in C\left((-\infty,0], R_{+0}^4\right)$ are continuous function mapping the interval $(-\infty,0]$ into R_{+0}^4, and $R_{+0}^4=\{(x_1,x_2,x_3,x_4)\mid x_i\ge 0, i=1,2,3,4\}$.

The purpose of this paper is to carry out a complete mathematical analysis of system (1.2) and investigate its global stability. Our paper is organized as follows: The equilibriums of system (1.2) and two threshold parameters R_0 and R_1 are given in Section 2. In Section 3, we used the suitable Lyapunov functional and LaSalle invariance principle to analyze the global stability of the three equilibriums. In Section 4, numerical simulations are carried out to support our analytical results. And the paper ends with a brief remark to conclude our work in Section 5.

II. THE EXISTENCE OF EQUILIBRIUM

In this section, we will discuss the equilibrium and get the basic reproduction number R_0 and the immune response reproduction ratio R_1.

From the system (1.2), it always has an infection-free equilibrium $E_0(T_0^*,0,0,0)$, where $T_0^*=\dfrac{\Lambda}{d}$. Next, we denote

$$F_1=\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\,\mathrm{d}\tau,\ \ F_2=\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}\,\mathrm{d}\tau,\ R_0=\frac{N\Lambda\beta F_1F_2}{c(a\Lambda+d)}.$$

When $R_0>1$, we can obtain the only one infected equilibrium without B cells response $E_1^*(T_1^*,I_1^*,V_1^*,0)$, where

$$T_1^*=\frac{c+Nb\Lambda F_1F_2}{NF_1F_2(\beta+bd)-ac},\ \ I_1^*=\frac{N\Lambda\beta F_1^2F_2}{\delta\left[NF_1F_2(\beta+bd)-ac\right]}\left(1-\frac{1}{R_0}\right),\ V_1^*=\frac{N^2\Lambda\beta F_1^2F_2^2}{c\left[NF_1F_2(\beta+bd)-ac\right]}\left(1-\frac{1}{R_0}\right).$$

Finally, we discuss the infected equilibrium with B cells response $E_2^*(T_2^*,I_2^*,V_2^*,B_2^*)$. Since

$$\begin{cases} \Lambda-dT_2^*-\dfrac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}=0,\\ F_1\dfrac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}-\delta I_2^*=0,\\ F_2N\delta I_2^*-cV_2^*-qB_2^*V_2^*=0,\\ gB_2^*V_2^*-\mu B_2^*=0, \end{cases} \tag{2.1}$$

we can obtain $I_2^*=\dfrac{F_1\left(\Lambda-dT_2^*\right)}{\delta}$ from the first two equations, in order to ensure $I_2^*>0$, we need $0<T_2^*<\dfrac{\Lambda}{d}$. Evidently $V_2^*=\dfrac{\mu}{g}>0$. Form the above third equation, we can obtain that

$$B_2^*=N\delta F_2\frac{g}{q\mu}I_2^*-\frac{c}{q}=\frac{\Lambda NgF_1F_2}{q\mu}-\frac{c}{q}-\frac{dNgF_1F_2T_2^*}{q\mu},$$

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so $B_2^* > 0$ if and only if $T_2^* < \frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}$. In summary, E_2^* exists if and only if $0 < T_2^* < \frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}$, we denote

$$G(T) = \frac{\beta \frac{\mu}{g} T}{1 + aT + b\frac{\mu}{g}} - \Lambda + dT,$$

and it satisfies $G(T_2^*) = 0$, and $G(T)$ is an increasing function about T. As $G(0) = -\Lambda < 0$, if $0 < \frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}$, E_2^* exists if and only if $G\left(\frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}\right) > 0$, that is

$$G(\frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}) = \frac{\beta \frac{\mu}{g}(\frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2})}{1 + a(\frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}) + b\frac{\mu}{g}} - \frac{c\mu}{NgF_1F_2} > 0.$$

So we denote

$$R_1 = \frac{\frac{\beta NF_1F_2}{c}\left(\frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}\right)}{1 + a\left(\frac{\Lambda}{d} - \frac{c\mu}{dNgF_1F_2}\right) + b\frac{\mu}{g}},$$

where R_1 called the immune response reproduction ratio, when $R_1 > 1$, $E_2^*(T_2^*, I_2^*, V_2^*, B_2^*)$ exists, where

$$T_2^* = \frac{(a\Lambda - \beta V_2^* - d - bdV_2^*) + \sqrt{(\beta V_2^* + d + bdV_2^* - a\Lambda)^2 + 4ad\Lambda(1 + bV_2^*)}}{2ad},$$

$$I_2^* = \frac{F_1}{\delta}\left[\Lambda - \frac{(a\Lambda - \beta V_2^* - d - bdV_2^*) + \sqrt{(\beta V_2^* + d + bdV_2^* - a\Lambda)^2 + 4ad\Lambda(1 + bV_2^*)}}{2a}\right], V_2^* = \frac{\mu}{g},$$

$$B_2^* = \frac{1}{qV_2^*}\left[NF_1F_2(\Lambda - \frac{(a\Lambda - \beta V_2^* - d - bdV_2^*) + \sqrt{(\beta V_2^* + d + bdV_2^* - a\Lambda)^2 + 4ad\Lambda(1 + bV_2^*)}}{2a}) - cV_2^*\right].$$

III. THE GLOBAL STABILITY OF EQUILIBRIUM

In this section, we discuss the global stability of each equilibrium by means of using suitable Lyapunov functional and LaSalle invariance principle for system (1.2).

Theorem 3.1 Let $(T(t), I(t), V(t), B(t))$ be the solutions of system (1.2). There exists an $M > 0$ such that $T(t) < M, I(t) < M, V(t) < M, B(t) < M$ hold after sufficiently large time t.

Proof. Let $N_1(t) = \int_0^\infty f_1(\tau) e^{-m_1\tau} T(t-\tau)\,\mathrm{d}\tau + I(t),$

$$\begin{aligned}\frac{\mathrm{d}N_1(t)}{\mathrm{d}t} &= \int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\left[\Lambda - dT(t-\tau) - \frac{\beta V(t-\tau)T(t-\tau)}{1 + aT(t-\tau) + bV(t-\tau)}\right]\mathrm{d}\tau + \beta\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1 + aT(t-\tau) + bV(t-\tau)}\mathrm{d}\tau - \delta I(t) \\ &= \Lambda\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\,\mathrm{d}\tau - d\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}T(t-\tau)\mathrm{d}\tau - \delta I(t) \\ &\le \Lambda - n_1 N_1(t),\end{aligned}$$

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where $n_1 = \min\{d, \delta\}$. So $\limsup_{t\to\infty} N_1(t) \le \frac{\Lambda}{n_1} \le M_1$, thus we can get $T(t) < M_1, I(t) < M_1$. And next we denote $N_2(t) = V(t) + \frac{q}{g} B(t)$,

$$\frac{\mathrm{d}N_2(t)}{\mathrm{d}t} = N\delta \int_0^\infty f_2(\tau) e^{-m_2\tau} I(t-\tau)\,\mathrm{d}\tau - cV(t) - \mu\frac{q}{g}B(t) \le N\delta M_1 - n_2 N_2(t),$$

where $n_2 = \min\{c, \mu\}$. So $\limsup_{t\to\infty} N_2(t) \le \frac{N\delta M_1}{n_2} = M_2$, thus we can get $V(t) < M_2, B(t) < M_2$. This completes the proof.

Theorem 3.2 For system (1.2), if the basic reproduction ratio $R_0 \le 1$, the disease-free equilibrium E_0 is globally asymptotically stable.

Proof. Let $(T(t), I(t), V(t), B(t))$ be any positive solution of system (1.2) with initial conditions (1.3). We define Lyapunov functional $V_0(t) = V_{01}(t) + V_{02}(t)$, where

$$V_{01}(t) = \frac{1}{1+aT_0^*}(T - T_0^* - T_0^* \ln\frac{T}{T_0^*}) + \frac{1}{F_1} I + \frac{1}{NF_1F_2} V + \frac{q}{NgF_1F_2} B,$$

$$V_{02}(T) = \frac{\beta}{F_1}\int_0^\infty f_1(\tau)\,\mathrm{e}^{-m_1\tau} \int_{t-\tau}^{t} \frac{V(s)T(s)}{1+aT(s)+bV(s)}\,\mathrm{d}s\,\mathrm{d}\tau + \frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\,\mathrm{e}^{-m_2\tau}\int_{t-\tau}^{t} I(s)\,\mathrm{d}s\,\mathrm{d}\tau.$$

The derivative of $V_0(t)$ along positive solutions of system (1.2) is as follows

$$\begin{aligned}
\frac{\mathrm{d}V_{01}(t)}{\mathrm{d}t} &= \frac{1}{1+aT_0^*}(1-\frac{T_0^*}{T})\frac{\mathrm{d}T}{\mathrm{d}t} + \frac{1}{F_1}\frac{\mathrm{d}I}{\mathrm{d}t} + \frac{1}{NF_1F_2}\frac{\mathrm{d}V}{\mathrm{d}t} + \frac{q}{NgF_1F_2}\frac{\mathrm{d}B}{\mathrm{d}t} \\
&= \frac{1}{1+aT_0^*}(1-\frac{T_0^*}{T})(\Lambda - dT - \frac{\beta VT}{1+aT+bV}) + \frac{1}{F_1}\left[\beta\int_0^\infty f_1(\tau)\,\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\,\mathrm{d}\tau - \delta I(t)\right] \qquad (3.1)\\
&\quad + \frac{1}{NF_1F_2}\left[N\delta\int_0^\infty f_2(\tau)\,\mathrm{e}^{-m_2\tau} I(t-\tau)\,\mathrm{d}\tau - cV - qBV\right] + \frac{q}{NgF_1F_2}(gBV - \mu B),
\end{aligned}$$

On substituting $\Lambda = dT_0^*$ into (3.1), we can derive that

$$\begin{aligned}
\frac{\mathrm{d}V_{01}(t)}{\mathrm{d}t} &= -\frac{d(T-T_0^*)^2}{T(1+aT_0^*)} - \frac{1}{1+aT_0^*}\frac{\beta VT}{1+aT+bV} + \frac{1}{1+aT_0^*}\frac{\beta T_0^*}{1+aT+bV}V \\
&\quad + \frac{\beta}{F_1}\int_0^\infty f_1(\tau)\,\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\,\mathrm{d}\tau - \frac{\delta}{F_1}I + \frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\,\mathrm{e}^{-m_2\tau} I(t-\tau)\,\mathrm{d}\tau \\
&\quad - \frac{c}{NF_1F_2}V - \frac{\mu q}{NgF_1F_2}B,
\end{aligned}$$

$$\begin{aligned}
\frac{\mathrm{d}V_{02}(t)}{\mathrm{d}t} &= \frac{\beta}{F_1}\int_0^\infty f_1(\tau)\,\mathrm{e}^{-m_1\tau}\left[\frac{V(t)T(t)}{1+aT(t)+bV(t)} - \frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\right]\mathrm{d}\tau + \frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\,\mathrm{e}^{-m_2\tau}\left[I(t) - I(t-\tau)\right]\mathrm{d}\tau \\
&= \frac{\beta VT}{1+aT+bV} - \frac{\beta}{F_1}\int_0^\infty f_1(\tau)\,\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\,\mathrm{d}\tau + \frac{\delta}{F_1}I - \frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\,\mathrm{e}^{-m_2\tau} I(t-\tau)\,\mathrm{d}\tau.
\end{aligned}$$

So we can get

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$$\frac{\mathrm{d}V_0(t)}{\mathrm{d}t}=\frac{\mathrm{d}V_{01}(t)}{\mathrm{d}t}+\frac{\mathrm{d}V_{02}(t)}{\mathrm{d}t}$$
$$=-\frac{d(T-T_0^*)^2}{T(1+aT_0^*)}+\frac{(1+aT)V}{1+aT+bV}(\frac{\beta T_0^*}{1+aT_0^*}-\frac{c}{NF_1F_2})-\frac{bc}{NF_1F_2(1+aT+bV)}V^2-\frac{\mu q}{NgF_1F_2}B.$$

Noting that $\frac{\beta T_0^*}{1+aT_0^*}=\frac{\beta\Lambda}{d+a\Lambda}, \frac{c}{NF_1F_2}=\frac{\beta\Lambda}{(d+a\Lambda)R_0}$, it follows that

$$\frac{\mathrm{d}V_0(t)}{\mathrm{d}t}=-\frac{d(T-T_0^*)^2}{T(1+aT_0^*)}+\frac{(1+aT)V}{(1+aT+bV)}\frac{\beta\Lambda}{(d+a\Lambda)}(1-\frac{1}{R_0})-\frac{bc}{NF_1F_2(1+aT+bV)}V^2-\frac{\mu q}{NgF_1F_2}B, \tag{3.2}$$

If $R_0\le 1$, it follows from (3.2) that $\frac{\mathrm{d}}{\mathrm{d}t}V_0(t)\le 0$. And we can clearly obtain that $\frac{\mathrm{d}}{\mathrm{d}t}V_0(t)=0$ if and only if $(T,I,V,B)=(T_0^*,0,0,0)$. By LaSalle invariance principle, the infection-free equilibrium E_0 is globally asymptotically stable.

Theorem 3.3 For system (1.2), if the basic reproduction ratio R_0 and the immune response reproductive ratio R_1 satisfy $R_1\le 1<R_0$, the infected equilibrium without B cells response E_1^* is globally asymptotically stable.

Proof. Let $(T(t),I(t),V(t),B(t))$ be any positive solution of system (1.2). We construct Lyapunov functional

$$V_1(t)=V_{11}(t)+V_{12}(t),$$

where

$$V_{11}(t)=\frac{1+bV_1^*}{1+aT_1^*+bV_1^*}(T-T_1^*-T_1^*\ln\frac{T}{T_1^*})+\frac{1}{F_1}(I-I_1^*-I_1^*\ln\frac{I}{I_1^*})+\frac{1}{NF_1F_2}(V-V_1^*-V_1^*\ln\frac{V}{V_1^*})+\frac{q}{NgF_1F_2}B,$$

$$V_{12}(t)=\frac{\beta}{F_1}\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\int_{t-\tau}^t\left[\frac{V(s)T(s)}{1+aT(s)+bV(s)}-\frac{V_1^*T_1^*}{1+aT_1^*+bV_1^*}-\frac{V_1^*T_1^*}{1+aT_1^*+bV_1^*}\ln\frac{V(s)T(s)(1+aT_1^*+bV_1^*)}{(1+aT(s)+bV(s))V_1^*T_1^*}\right]\mathrm{d}s\,\mathrm{d}\tau$$
$$+\frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}\int_{t-\tau}^t\left[I(s)-I_1^*-I_1^*\ln\frac{I(s)}{I_1^*}\right]\mathrm{d}s\,\mathrm{d}\tau.$$

By calculating the derivative of $V_1(t)$ along positive solutions of system (1.2), it follows that

$$\frac{\mathrm{d}V_{11}(t)}{\mathrm{d}t}=-\frac{d(1+bV_1^*)(T-T_1^*)^2}{T(1+aT_1^*+bV_1^*)}+\frac{\beta V_1^*T_1^*}{1+aT_1^*+bV_1^*}\left[1-\frac{T_1^*(1+aT+bV_1^*)}{T(1+aT_1^*+bV_1^*)}+\frac{V(1+aT+bV_1^*)}{V_1^*(1+aT+bV)}\right]$$
$$-\frac{\beta VT}{1+aT+bV}+\frac{\beta}{F_1}\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau-\frac{\delta}{F_1}I(t)$$
$$-\frac{1}{F_1}\frac{I_1^*}{I}\beta\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau+\frac{\delta}{F_1}I_1^*+\frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)\mathrm{d}\tau-\frac{c}{NF_1F_2}V-\frac{q}{NF_1F_2}BV$$
$$-\frac{\delta}{F_1F_2}\frac{V_1^*}{V}\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)\mathrm{d}\tau+\frac{c}{NF_1F_2}V_1^*+\frac{q}{NF_1F_2}V_1^*B+\frac{q}{NF_1F_2}BV-\frac{\mu q}{NgF_1F_2}B.$$

$$\frac{\mathrm{d}V_{12}(t)}{\mathrm{d}t}=\frac{\beta VT}{1+aT+bV}-\frac{\beta}{F_1}\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau+\frac{1}{F_1}\frac{\beta V_1^*T_1^*}{1+aT_1^*+bV_1^*}\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\ln\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau$$
$$-\frac{\beta V_1^*T_1^*}{1+aT_1^*+bV_1^*}\ln\frac{VT}{1+aT+bV}+\frac{\delta}{F_1}I(t)-\frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)d\tau$$
$$+\frac{\delta}{F_1F_2}\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}\ln I(t-\tau)\mathrm{d}\tau-\frac{\delta}{F_1}I_1^*\ln I(t).$$

So we can get

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$$\begin{aligned}\frac{\mathrm{d}V_1(t)}{\mathrm{d}t} &= -\frac{d(1+bV_1^*)(T-T_1^*)^2}{T(1+aT_1^*+bV_1^*)} + \frac{\beta V_1^* T_1^*}{1+aT_1^*+bV_1^*}\left[1-\frac{T_1^*(1+aT+bV_1^*)}{T(1+aT_1^*+bV_1^*)}+\ln\frac{T_1^*(1+aT+bV_1^*)}{T(1+aT_1^*+bV_1^*)}\right] \\ &+ \frac{\beta V_1^* T_1^*}{1+aT_1^*+bV_1^*}\frac{1}{F_1}\int_0^\infty f_1(\tau)\mathrm{e}^{-m_1\tau}\left[1-\frac{I_1^* V(t-\tau)T(t-\tau)(1+aT_1^*+bV_1^*)}{IT_1^* V_1^*(1+aT(t-\tau)+bV(t-\tau))}\right. \\ &\left.+\ln\frac{I_1^* V(t-\tau)T(t-\tau)(1+aT_1^*+bV_1^*)}{IT_1^* V_1^*(1+aT(t-\tau)+bV(t-\tau))}\right]d\tau + \frac{\delta}{F_1}I_1^*\frac{1}{F_2}\int_0^\infty f_2(\tau)\mathrm{e}^{-m_2\tau}\left[1-\frac{V_1^* I(t-\tau)}{VI_1^*}+\ln\frac{V_1^* I(t-\tau)}{VI_1^*}\right]\mathrm{d}\tau \\ &+ \frac{\beta V_1^* T_1^*}{1+aT_1^*+bV_1^*}\left[1-\frac{1+aT+bV}{1+aT+bV_1^*}+\ln\frac{1+aT+bV}{1+aT+bV_1^*}\right] - \frac{\beta V_1^* T_1^*}{(1+aT_1^*+bV_1^*)}\frac{b(1+aT)(V_1^*-V)^2}{V_1^*(1+aT+bV)(1+aT+bV_1^*)} \\ &+ \frac{q}{NF_1F_2}(V_1^*-\frac{\mu}{g})B. \end{aligned} \tag{3.3}$$

We need to prove that

$$V_1^* - \frac{\mu}{g} \le 0\,. \tag{3.4}$$

It follows from (2.1) that $V_1^* = \frac{NF_2F_1}{c}\left(\Lambda - dT_1^*\right)$, the inequality (3.4) is equivalent to

$$T_1^* \ge \frac{\Lambda}{d} - \frac{c\mu}{gdNF_2F_1}\,. \tag{3.5}$$

On substituting $T_1^* = \frac{c+Nb\Lambda F_1F_2}{NF_1F_2(\beta+bd)-ac}$ into (3.5), the inequality (3.5) is equivalent to

$$c+Nb\Lambda F_1F_2 \ge \left(\frac{\Lambda}{d}-\frac{c\mu}{gdNF_2F_1}\right)\left(NF_1F_2(\beta+bd)-ac\right). \tag{3.6}$$

Clearly, the inequality (3.6) is equivalent to

$$1 \ge \frac{\frac{NF_1F_2\beta}{c}\left(\frac{\Lambda}{d}-\frac{c\mu}{gdNF_2F_1}\right)}{1+a\left(\frac{\Lambda}{d}-\frac{c\mu}{gdNF_2F_1}\right)+\frac{b\mu}{g}}, \tag{3.7}$$

that is, $R_1 = \frac{\frac{NF_1F_2\beta}{c}\left(\frac{\Lambda}{d}-\frac{c\mu}{gdNF_2F_1}\right)}{1+a\left(\frac{\Lambda}{d}-\frac{c\mu}{gdNF_2F_1}\right)+\frac{b\mu}{g}} \le 1$, if $R_1 \le 1 < R_0$, it follows from (3.3) and the above calculation that $\frac{\mathrm{d}}{\mathrm{d}t}V_1(t) \le 0$.

We can clearly obtain that $\frac{\mathrm{d}}{\mathrm{d}t}V_1(t) = 0$ if and only if $(T,I,V,B) = (T_1^*, I_1^*, V_1^*, 0)$. By LaSalle invariance principle, we can obtain that E_1^* is globally asymptotically stable.

Theorem 3.4 For system (1.2), if the basic reproduction ratio $R_1 > 1$, then the infected equilibrium with B cells response E_2^* is globally asymptotically stable;

Proof. We define Lyapunov functional $V_2(t) = V_{21}(t) + V_{22}(t)$, where

$$V_{21}(t) = \frac{1+bV_2^*}{1+aT_2^*+bV_2^*}(T-T_2^*-T_2^*\ln\frac{T}{T_2^*}) + \frac{1}{F_1}(I-I_2^*-I_2^*\ln\frac{I}{I_2^*}) + \frac{1}{NF_1F_2}(V-V_2^*-V_2^*\ln\frac{V}{V_2^*}) + \frac{q}{NgF_1F_2}(B-B_2^*-B_2^*\ln\frac{B}{B_2^*}),$$

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$$V_{22}(t)=\frac{\beta}{F_1}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\int_{t-\tau}^{t}\left[\frac{V(s)T(s)}{1+aT(s)+bV(s)}-\frac{V_2^*T_2^*}{1+aT_2^*+bV_2^*}-\frac{V_2^*T_2^*}{1+aT_2^*+bV_2^*}\ln\frac{V(s)T(s)(1+aT_2^*+bV_2^*)}{(1+aT(s)+bV(s))V_2^*T_2^*}\right]\mathrm{d}s\,\mathrm{d}\tau$$
$$+\frac{\delta}{F_1F_2}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}\int_{t-\tau}^{t}\left[I(s)-I_2^*-I_2^*\ln\frac{I(s)}{I_2^*}\right]\mathrm{d}s\,\mathrm{d}\tau.$$

We calculate the derivative of $V_2(t)$ along positive solutions of system (1.2), and it follows that

$$\frac{\mathrm{d}V_{21}(t)}{\mathrm{d}t}=-\frac{d(1+bV_2^*)(T-T_2^*)^2}{T(1+aT_2^*+bV_2^*)}+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\left[1-\frac{T_2^*(1+aT+bV_2^*)}{T(1+aT_2^*+bV_2^*)}+\frac{V(1+aT+bV_2^*)}{V_2^*(1+aT+bV)}\right]-\frac{\beta VT}{1+aT+bV}$$
$$+\frac{\beta}{F_1}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau-\frac{\delta}{F_1}I(t)-\frac{1}{F_1}\frac{I_2^*}{I}\beta\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau+\frac{\delta}{F_1}I_2^*$$
$$+\frac{\delta}{F_1F_2}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)\mathrm{d}\tau-\frac{c}{NF_1F_2}V-\frac{q}{NF_1F_2}BV-\frac{\delta}{F_1F_2}\frac{V_2^*}{V}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)\mathrm{d}\tau+\frac{c}{NF_1F_2}V_2^*+\frac{q}{NF_1F_2}V_2^*B$$
$$+\frac{q}{NF_1F_2}BV-\frac{\mu q}{NgF_1F_2}B-\frac{q}{NF_1F_2}B_2^*V+\frac{\mu q}{NgF_1F_2}B_2^*,$$

$$\frac{\mathrm{d}V_{22}(t)}{\mathrm{d}t}=\frac{\beta VT}{1+aT+bV}-\frac{\beta}{F_1}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau+\frac{1}{F_1}\frac{\beta V_2^*T_2^*}{(1+aT_2^*+bV_2^*)}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\ln\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau$$
$$-\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\ln\frac{VT}{1+aT+bV}+\frac{\delta}{F_1}I(t)-\frac{\delta}{F_1F_2}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)\mathrm{d}\tau-\frac{\delta}{F_1}I_2^*\ln I(t)+\frac{\delta}{F_1F_2}I_2^*\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}\ln I(t-\tau)\mathrm{d}\tau,$$

$$\frac{\mathrm{d}V_2(t)}{\mathrm{d}t}=-\frac{d(1+bV_2^*)(T-T_2^*)^2}{T(1+aT_2^*+bV_2^*)}+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\left[1-\frac{T_2^*(1+aT+bV_2^*)}{T(1+aT_2^*+bV_2^*)}+\frac{V(1+aT+bV_2^*)}{V_2^*(1+aT+bV)}\right]$$
$$+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\left[-\ln\frac{VT}{1+aT+bV}+\frac{1}{F_1}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\ln\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau\right]$$
$$+\left[-\frac{I_2^*}{I}\frac{\beta}{F_1}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\frac{V(t-\tau)T(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)}\mathrm{d}\tau+\frac{\delta}{F_1}I_2^*\right]+\frac{1}{NF_1}\left[-\frac{N\delta}{F_2}\frac{V_2^*}{V}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}I(t-\tau)\mathrm{d}\tau+\frac{c}{F_2}V_2^*\right]$$
$$+\frac{\delta}{F_1}I_2^*\left[-\ln I(t)+\frac{1}{F_2}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}\ln I(t-\tau)\mathrm{d}\tau\right]+\frac{\mu q}{NgF_1F_2}B_2^*-\frac{1}{NF_2}(\frac{c}{F_1}+\frac{qB_2^*}{F_1})V$$

$$=-\frac{d(1+bV_2^*)(T-T_2^*)^2}{T(1+aT_2^*+bV_2^*)}+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\left[1-\frac{T_2^*(1+aT+bV_2^*)}{T(1+aT_2^*+bV_2^*)}+\ln\frac{T_2^*(1+aT+bV_2^*)}{T(1+aT_2^*+bV_2^*)}\right]$$
$$+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\frac{1}{F_1}\int_0^{\infty} f_1(\tau)\mathrm{e}^{-m_1\tau}\left[1-\frac{I_2^*V(t-\tau)T(t-\tau)(1+aT_2^*+bV_2^*)}{IT_2^*V_2^*(1+aT(t-\tau)+bV(t-\tau))}\right.$$
$$\left.+\ln\frac{I_2^*V(t-\tau)T(t-\tau)(1+aT_2^*+bV_2^*)}{IT_2^*V_2^*(1+aT(t-\tau)+bV(t-\tau))}\right]d\tau+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\frac{1}{F_2}\int_0^{\infty} f_2(\tau)\mathrm{e}^{-m_2\tau}\left[1-\frac{V_2^*I(t-\tau)}{VI_2^*}+\ln\frac{V_2^*I(t-\tau)}{VI_2^*}\right]\mathrm{d}\tau$$
$$+\frac{\beta V_2^*T_2^*}{1+aT_2^*+bV_2^*}\left[1-\frac{1+aT+bV}{1+aT+bV_2^*}+\ln\frac{1+aT+bV}{1+aT+bV_2^*}\right]-\frac{\beta V_2^*T_2^*}{(1+aT_2^*+bV_2^*)}\frac{b(1+aT)(V_2^*-V)^2}{V_2^*(1+aT+bV)(1+aT+bV_2^*)}.$$

Noting that T_2^*, I_2^*, V_2^* and B_2^* are positive, we obtain that $\frac{\mathrm{d}V_2(t)}{\mathrm{d}t}\le 0$. So, we can clearly obtain that $\frac{\mathrm{d}}{\mathrm{d}t}V_2(t)=0$ if and only if $(T,I,V,B)=(T_2^*,I_2^*,V_2^*,B_2^*)$. By LaSalle invariance principle E_2^* is globally asymptotically stable.

IV. SIMULATION

In order to support our analytical results of this paper, we use Matlab software to carry out some numerical simulations.

Example 4.1. For system (1.2), we choose the following set of biologically feasible parameter values $\Lambda=1, d=0.01, \beta=0.05,\ a=0.0001, b=0.005, \delta=30.4, N=2, c=15, q=4.2, m_1=0.4, m_2=0.5, g=0.8, u=1,\ \tau=1.15$ and $f_1(\tau)=f_2(\tau)=\delta(u-\tau)$, we have $R_0=0.2345<1$ and the disease-free equilibrium $E_0(\frac{\Lambda}{d},0,0,0)=E_0(100,0,0,0)$ is globally asymptotically stable. Its phase diagram is illustrated in Fig. 1. Numerical calculations show that the equilibrium E_0 is

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globally asymptotically stable, and the disease will be controlled.

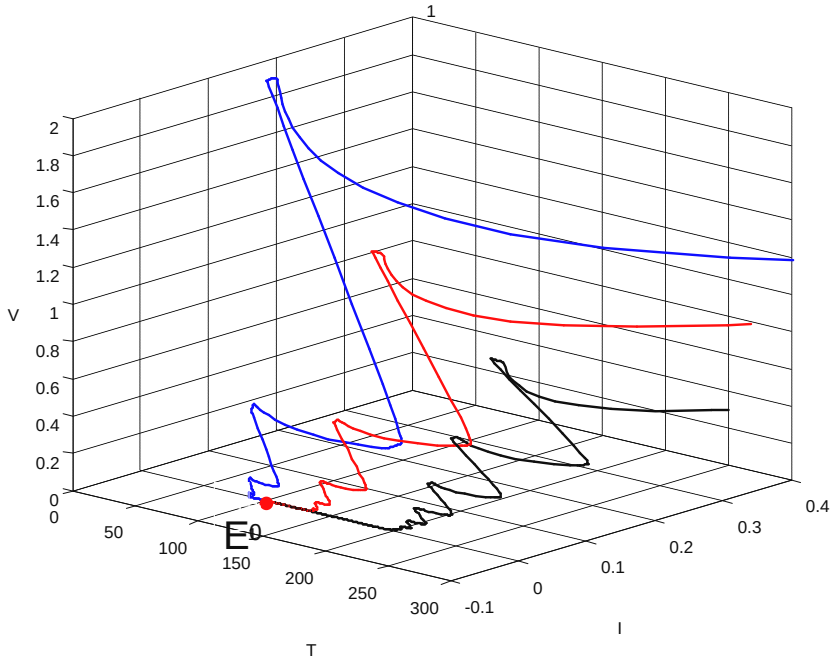

Fig. 1 Equilibrium E_0 is stable

Example 4.2. For system (1.2), we select the following set of biologically feasible parameter values $\Lambda = 2, d = 0.01, \beta = 0.1, a = 0.0001, b = 6, \delta = 0.2, N = 2, c = 3.2, q = 4.2, m_1 = 0.4, m_2 = 0.5, g = 5, u = 1, \tau = 1.15$ and $f_1(\tau) = f_2(\tau) = \delta(u - \tau)$, by calculation, we can obtain $R_0 = 4.3774 > 1$ and $R_1 = 0.9390 < 1$, and the infected equilibrium without B cells response $E_1^*(T_1^*, I_1^*, V_1^*, 0) = E_1^*(103.4423, 3.0478, 0.2144, 0)$ is globally asymptotically stable. Its phase diagram is illustrated in Fig. 2. Numerical calculations show that the equilibrium E_1^* is globally asymptotically stable; there exists the disease without B cells response. That is to say, the diseases without B cells response ultimately tend to be stable as time increases.

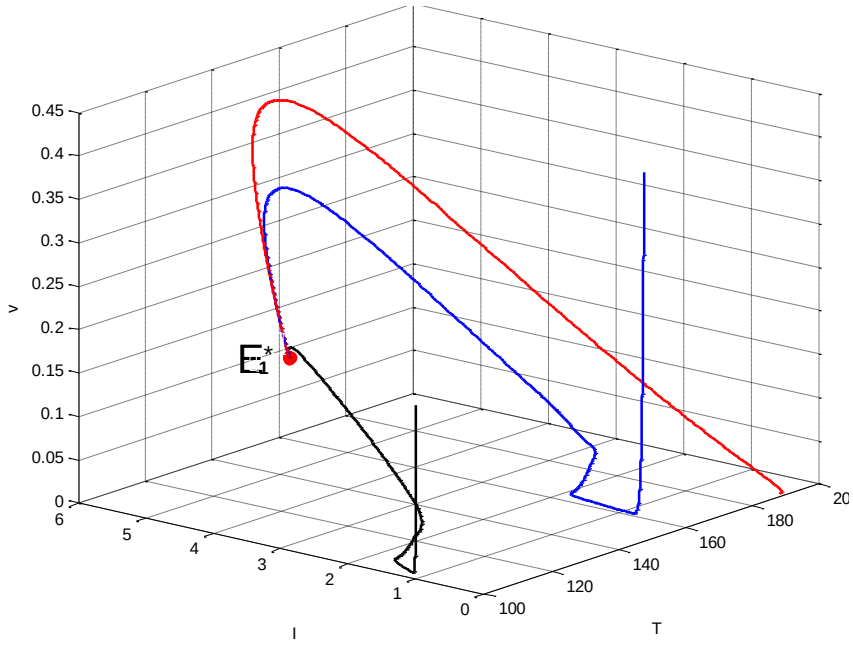

Fig. 2 Equilibrium E_1^* is stable

Example 4.3. For system (1.2), we take the following set of biologically feasible parameter values $\Lambda = 2, d = 0.01, \beta = 0.1, a = 0.001, b = 3, \delta = 0.2, N = 2, c = 1.5, q = 4.2, m_1 = 0.4, m_2 = 0.5, g = 5, u = 1, \tau = 1.15$ and $f_1(\tau) = f_2(\tau) = \delta(u - \tau)$, at present, $R_1 = 4.25 > 1$, and the infected equilibrium with B cells response $E_2^*(T_2^*, I_2^*, V_2^*, B_2^*) = E_2^*(91.6494, 3.4201, 0.2000, 0.5593)$ is

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globally asymptotically stable. Its phase diagram is illustrated in Fig. 3. Numerical calculations show that the equilibrium E_2^* is globally asymptotically stable; there exists the disease with B cells response. That is to say, the diseases with B cells response ultimately tend to be stable as time increases.

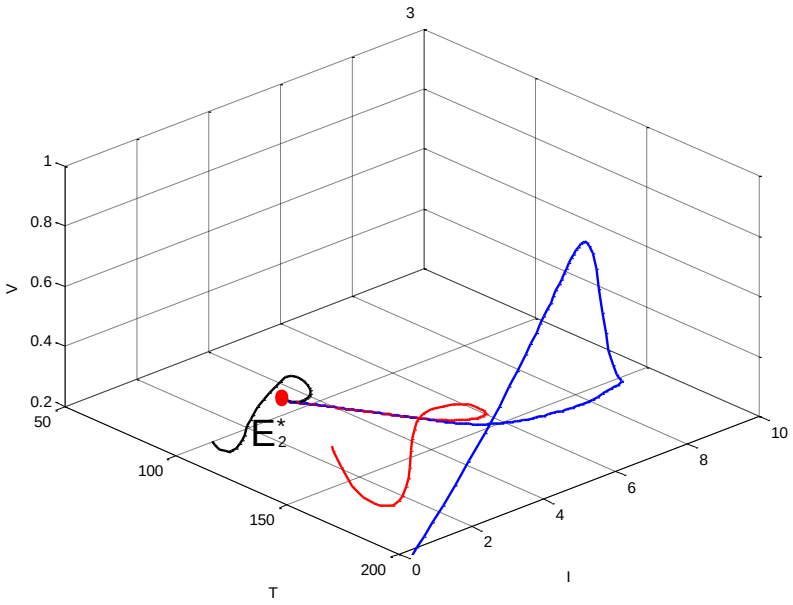

Fig. 3 Equilibrium E_2^* is stable

V. CONCLUSIONS

Recently, in order to characterize the relationship between humoral immune response and virus load, many authors studied on this type of models for the humoral immunity [1-6, 10, 13, 16-18, 20-24]. Especially consider the more general epidemic and virus dynamic models with nonlinear functional response in [11, 12]. Our paper presents a study of in-host viral model with humoral immunity and Beddington-DeAngelis functional response. In this model, we investigated the global stability of the infection-free equilibrium, the infected equilibrium without B cells response and the infected equilibrium with B cells response of system (1.2) by using the Layapunov-Lasalle invariance principle. Through the above analysis, we obtained that if $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable; On the other hand, if $R_1 \le 1 < R_0$, the infected equilibrium without B cells response E_1^* is globally asymptotically stable; At last, we obtained that if $R_1 > 1$, the infected equilibrium with B cells response E_2^* is globally asymptotically stable. From the discussion above, we can see that the intracellular delay plays a very important role in virus infection process, sufficiently large intracellular delay makes the virus development slower and the virus has been controlled and disappeared, it can not produce periodic oscillations and also there is no possibility of the existence of the Hopf bifurcations.

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