

Global Properties for Virus Dynamics Model with Beddington-DeAngelis Functional Response^{*}

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Abstract This paper investigates the global stability of virus dynamics model with Beddington-DeAngelis infection rate. By constructing Lyapunov functions, the global properties have been analyzed. If the basic reproductive ratio of the virus is less than or equal to one, the uninfected steady state is globally asymptotically stable. If the basic reproductive ratio of the virus is more than one, the infected steady state is globally asymptotically stable. The conditions imply that the steady states are always globally asymptotically stable for Holling type II functional response or for a saturation response.

Keyword Virus dynamics; Global Properties; Functional Response; Lyapunov function;

1 Introduction

The model of a parasite with free living stage was introduced by Anderson and May [1], and it was applied to virus dynamics by Nowak and Bangham [2], which is given as the following simple three dimensional model:

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = \beta xv - py, \\ \dot{v} = ky - uv. \end{cases} \quad (1.1)$$

Here x represents the concentration of uninfected CD4⁺T cells at time t , y represents the concentration of infected CD4⁺T cells that produce virus at time t , v represents the concentration of HIV-1 virus at time t . The constant $\lambda(\lambda > 0)$ is the rate at which new CD4⁺T cells are generated. The constant $d(d > 0)$ and $\beta(\beta > 0)$ are the death rate of uninfected CD4⁺T cells and the rate constant characterizing infection of the cells, respectively. The constant $p(p > 0)$ is the death rate of the infected cells due either to the HIV-1 virus or the immune system. Free virus is produced from the infected cells at the rate ky . The constant $u(u > 0)$ is the rate at which HIV-1 virus particles are removed from the system.

Usually the rate of infection in most HIV-1 models is assumed to be bilinear in the virus v and the uninfected CD4⁺T cells x . However, the actual incidence rate is probably not linear over the

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entire range of v and x . Thus, it is reasonable to assume that the infection rate of HIV-1 is given by the Beddington-DeAngelis functional response, $\beta xv/(1 + ax + bv)$, where $a, b \geq 0$ are constants. The functional response $\beta xv/(1 + ax + bv)$ was introduced by Beddington [3] and DeAngelis et al.[4]. 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 virus. When $a > 0, b = 0$, the Beddington-DeAngelis functional response is simplified to Holling type II functional response[5]. And when $a = 0, b > 0$, it expresses a saturation response[6]. In general we consider the model with Beddington-DeAngelis functional response given by

$$\begin{cases} \dot{x} = \lambda - dx - \frac{\beta xv}{1+ax+bv}, \\ \dot{y} = \frac{\beta xv}{1+ax+bv} - py, \\ \dot{v} = ky - uv. \end{cases} \quad (1.2)$$

Here the state variables x, y , and v and parameters λ, β, d, p, k and u have the same biological meanings as in the model (1.1). The initial condition of (1.2) is $x(0) \geq 0, y(0) \geq 0, v(0) \geq 0$.

The local stability of equilibria and the global stability of the uninfected equilibrium of (1.2) have been discussed in [7]. Recently, A. Korobeinikov gave a complete global analysis of virus dynamics on the basic virus dynamical model (1.1) in [8], and constructed Lyapunov functions for the global stability analysis of SIR and SIER epidemiological models with nonlinear transmission in [9] and [10]. Motivated by the works in [9] and [10], in this paper, we will analyse the global stability of the viral free equilibrium and the infected equilibrium by the method of Lyapunov functions.

2 Global asymptotical stability analysis

The basic reproductive ratio of the virus for system (1.2) is $R_0 = \lambda\beta k/(dpu + apu\lambda)$. We will know that if $R_0 \leq 1$, then the uninfected steady state $E_0 = (\lambda/d, 0, 0)$ is the unique steady state; if $R_0 > 1$, then in addition to the uninfected steady state, there is only one infected state $E^* = (x^*, y^*, v^*)$, corresponding to the survival of the free virus, that is given by the following expressions

$$x^* = \frac{\lambda bk + pu}{k\beta + bdk - apu}, \quad y^* = \frac{\lambda\beta k}{p(k\beta + bdk - apu)}\left(1 - \frac{1}{R_0}\right), \quad v^* = \frac{\lambda\beta k^2}{pu(k\beta + bdk - apu)}\left(1 - \frac{1}{R_0}\right).$$

In this section, we consider the global asymptotic stability of the two equilibria.

Theorem. (i) *The uninfected steady state E_0 is globally asymptotically stable, if $R_0 \leq 1$;*
(ii) *The infected steady state E^* is globally asymptotically stable if $R_0 > 1$.*

Proof. (i) Define a Lyapunov function V_1 as follows:

$$V_1(x, y, v) = \frac{x_0}{1 + ax_0} \left(\frac{x}{x_0} - 1 - \ln \frac{x}{x_0} \right) + y + \frac{p}{k}v, \quad (2.3)$$

where $x_0 = \lambda/d$. Calculating the time derivative of $V_1(x, y, v)$ along the positive solutions of model

(1.2), we obtain

$$\begin{aligned}
\frac{dV_1}{dt} &= \frac{1}{1+ax_0}\dot{x} - \frac{1}{1+ax_0}\frac{x_0}{x}\dot{x} + \dot{y} + \frac{p}{k}\dot{v} \\
&= \frac{1}{1+ax_0}\left(\lambda - dx - \frac{\beta xv}{1+ax+bv}\right) - \frac{1}{1+ax_0}\frac{x_0}{x}\left(\lambda - dx - \frac{\beta xv}{1+ax+bv}\right) + \frac{\beta xv}{1+ax+bv} - \frac{pu}{k}v \\
&= \frac{dx_0}{1+ax_0}\left(2 - \frac{x}{x_0} - \frac{x_0}{x}\right) + \frac{\beta xv}{1+ax+bv} + \frac{1}{1+ax_0}\frac{\beta x_0 v}{1+ax+bv} - \frac{1}{1+ax_0}\frac{\beta xv}{1+ax+bv} - \frac{pu}{k}v \\
&= \frac{dx_0}{1+ax_0}\left(2 - \frac{x}{x_0} - \frac{x_0}{x}\right) + \frac{puv(1+ax)}{k(1+ax+bv)}(R_0 - 1) - \frac{pub}{k(1+ax+bv)}v^2.
\end{aligned}$$

Clearly, $V_1(x, y, v)$ is positive definite with respect to $(x - x_0, y, v)$. Furthermore, since

$$\begin{aligned}
2 - \frac{x}{x_0} - \frac{x_0}{x} &< 0 \quad (x \neq x_0), \\
2 - \frac{x}{x_0} - \frac{x_0}{x} &= 0 \quad (x = x_0),
\end{aligned}$$

and $R_0 \leq 1$, we have that $\dot{V}_1(x, y, v) \leq 0$ for all $x, y, v > 0$. Thus, the uninfected steady state E_0 is stable. And $\dot{V}_1(x, y, v) = 0$, when $x = x_0$ and $v = 0$. Let M be the largest invariant set in the set

$$E = \{(x, y, v) | \dot{V}_1(x, y, v) = 0\} = \{(x, y, v) | x = x_0, y \geq 0, v = 0\}.$$

We have from the third equation of (1.2) that $M = \{E_0\}$. It follows from LaSalle invariance principle that the uninfected steady state E_0 is globally asymptotically stable.

(ii) Define a Lyapunov function $V_2(x, y, v)$ as follows:

$$V_2(x, y, v) = x - x^* - \int_{x^*}^x \frac{py^*}{\beta\tau v^*} d\tau + y - y^* - y^* \ln \frac{y}{y^*} \quad (2.4)$$

$$+ \frac{p}{k}\left(1 + \frac{bv^*}{1+ax^*}\right)(v - v^* - \int_{v^*}^v \frac{py^*}{\beta x^* \tau} d\tau). \quad (2.5)$$

$V_2(x, y, v)$ is positive definite with respect to $(x - x^*, y - y^*, v - v^*)$. Calculating the time derivative of $V_2(x, y, v)$ along the positive solutions of model (1.2), satisfies

$$\frac{dV_2}{dt} = \dot{x} + \dot{y} + \frac{p}{k}\left(1 + \frac{bv^*}{1+ax^*}\right)\dot{v} - py^* \frac{1+ax+bv^*}{\beta xv^*} \dot{x} - \frac{y^*}{y} \dot{y} \quad (2.6)$$

$$- \frac{p}{k}\left(1 + \frac{bv^*}{1+ax^*}\right)py^* \frac{1+ax^*+bv}{\beta x^* v} \dot{v} \quad (2.7)$$

$$= \dot{x} + \dot{y} + \frac{p}{k}\dot{v} - py^* \frac{1+ax+bv^*}{\beta xv^*} \dot{x} - \frac{y^*}{y} \dot{y} - \frac{p}{k} \frac{v^*}{v} \dot{v} \quad (2.8)$$

$$= \lambda - dx - \frac{pu}{k}v \quad (2.9)$$

$$- py^* \frac{1+ax+bv^*}{\beta xv^*} \left(\lambda - dx - \frac{\beta xv}{1+ax+bv}\right) \quad (2.10)$$

$$- \frac{y^*}{y} \left(\frac{\beta xv}{1+ax+bv} - py\right) - \frac{p}{k} \frac{v^*}{v} (ky - uv). \quad (2.11)$$

Since (x^*, y^*, v^*) is a positive equilibrium point of (1.2), we have

$$\begin{aligned}\lambda &= dx^* + py^*, \\ pu/k &= py^*/v^*, \\ py^* &= \beta x^* v^*/(1 + ax^* + bv^*).\end{aligned}$$

From the first two equations, the term (2.9) becomes

$$dx^* + py^* - dx - py^* \frac{v}{v^*} \quad (2.12)$$

and from the first and the third equations, the term (2.10) gives

$$-\frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} dx^* - \frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} py^* + \frac{1 + ax + bv^*}{1 + ax^* + bv^*} dx^* + \frac{v}{v^*} \frac{1 + ax + bv^*}{1 + ax + bv} py^*. \quad (2.13)$$

By (2.11), (2.12) and (2.13), we have

$$\begin{aligned}\frac{dV_2}{dt} &= dx^* \left(1 - \frac{x}{x^*} - \frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} + \frac{1 + ax + bv^*}{1 + ax^* + bv^*}\right) \\ &\quad + py^* \left(1 - \frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} + \frac{v}{v^*} \frac{1 + ax + bv^*}{1 + ax + bv}\right) \\ &\quad + py^* \left(1 - \frac{xy^*v}{x^*yv^*} \frac{1 + ax^* + bv^*}{1 + ax + bv}\right) \\ &\quad + py^* \left(1 - \frac{v}{v^*} - \frac{yv^*}{y^*v}\right) \\ &= -\frac{d(1 + bv^*)}{x(1 + ax^* + bv^*)} (x - x^*)^2 + py^* \left(-1 - \frac{v}{v^*} + \frac{v}{v^*} \frac{1 + ax + bv^*}{1 + ax + bv} + \frac{1 + ax + bv}{1 + ax + bv^*}\right) \\ &\quad + py^* \left(4 - \frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} - \frac{xy^*v}{x^*yv^*} \frac{1 + ax^* + bv^*}{1 + ax + bv} - \frac{yv^*}{y^*v} - \frac{1 + ax + bv}{1 + ax + bv^*}\right). \\ &= -\frac{d(1 + bv^*)}{x(1 + ax^* + bv^*)} (x - x^*)^2 - \frac{py^*b(1 + ax)(v - v^*)^2}{v^*(1 + ax + bv)(1 + ax + bv^*)} \\ &\quad + py^* \left(4 - \frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} - \frac{xy^*v}{x^*yv^*} \frac{1 + ax^* + bv^*}{1 + ax + bv} - \frac{yv^*}{y^*v} - \frac{1 + ax + bv}{1 + ax + bv^*}\right).\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, it is clear that

$$4 - \frac{x^*}{x} \frac{1 + ax + bv^*}{1 + ax^* + bv^*} - \frac{xy^*v}{x^*yv^*} \frac{1 + ax^* + bv^*}{1 + ax + bv} - \frac{yv^*}{y^*v} - \frac{1 + ax + bv}{1 + ax + bv^*} \leq 0,$$

and the equality holds only for $x = x^*, y = y^*, v = v^*$.

Therefore, $dV_2/dt \leq 0$ holds for all $x, y, v > 0$. Thus, the infected steady state E^* is stable. And we have $\dot{V}_2(x, y, v) = 0$ if and only if $x = x^*, y = y^*, v = v^*$ holds. The largest compact invariant set in $\Gamma = \{(x, y, v) | \dot{V}_2(x, y, v) = 0\}$ is the singleton $\{E^*\}$. Therefore, the infected steady state E^* is globally asymptotically stable by the LaSalle invariance principle when $R_0 > 1$.

The theorem is proved.

Remark: A Lyapunov function for the model with a general functional response $f(x, v)$ satisfying some conditions is given in [10]. The above theorem proves that E^* is globally asymptotically stable if $R_0 > 1$ by applying the function $V_2(x, y, v)$. Actually, the function $V_2(x, y, v)$ can also be translated into a Kovobeynikov type Lyapunov function.

From the following equations

$$x - x^* - \int_{x^*}^x \frac{py^*}{\frac{\beta\tau v^*}{1+a\tau+bv^*}} d\tau = \frac{1+bv^*}{1+ax^*+bv^*} (x - x^* - x^* \ln \frac{x}{x^*}),$$

$$v - v^* - \int_{v^*}^v \frac{py^*}{\frac{\beta x^* \tau}{1+ax^*+b\tau}} d\tau = \frac{1+ax^*}{1+ax^*+bv^*} (v - v^* - v^* \ln \frac{v}{v^*}),$$

it is easy to know

$$V_2(x, y, v) = \frac{1+bv^*}{1+ax^*+bv^*} (x - x^* - x^* \ln \frac{x}{x^*}) + y - y^* - y^* \ln \frac{y}{y^*} + \frac{p}{k} (v - v^* - v^* \ln \frac{v}{v^*}).$$

3 Discussion

Usually, it is difficult to obtain the global properties of a model with nonlinear functional responses. A. Korobeinikov [8] constructed a class of Lyapunov function and obtained the global stability for the basic HIV model (1.1). D. Li *et al.* [5] and X. Song *et al.* [6] introduced Holling type II functional response and saturation response into HIV-1 infection models, independently. In this paper, a class of more general HIV-1 infection models is considered. Based on the biological meaning, Beddington-DeAngelis functional response, instead of mass action response, is used to describe the infection rate between HIV-1 virus and CD4⁺T cells. Constructing Lyapunov functions, we proved that the uninfected steady state and infected steady state are globally asymptotically stable, depending on the value of the basic reproduction number.

If we compare the model (1.2) with the basic model (1.1), we find that virus load decreases because of the difference of the infection rate. When $a = b = 0$, the model (1.2) coincides with the basic model (1.1), of which unique infected steady state is globally asymptotically stable if $R_0 > 1$; when $a > 0, b = 0$ or $a = 0, b > 0$, the model (1.2) expresses the HIV-1 infection model with Holling type II response or saturation response, of which infected steady state is globally asymptotically stable when it exists (that is when $R_0 > 1$). The theorem obtained in this paper shows that the infected steady state is also globally asymptotically stable for $a \geq 0, b \geq 0$ when $R_0 > 1$.

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