Global Properties of an Improved Hepatitis B Virus Model with Beddington-DeAngelis Infection Rate and CTL Immune Response

Zhengzhi Cao

School of Statistics and Applied Mathematics,
Anhui University of Finance and Economics, Bengbu, China

Copyright ©2014 Zhengzhi Cao. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

This paper investigates the global stability of an improved hepatitis B virus model with Beddington-DeAngelis infection rate. CTL immune response is studied by constructing Lyapunov functions. If the basic production number is less than or equal to one, the uninfected steady state is globally asymptotically stable. If the basic production number is more than one, the immune-free equilibrium is globally asymptotically stable. If the immune response reproduction number is more than one, the endemic equilibrium is globally asymptotically stable.

Keywords: Virus dynamics, CTL immune response, Beddington-DeAngelis, Lyapunov function, Global stability

1 Introduction

In the past decades, there has been much interest in mathematical modeling of HIV dynamics [11-12]. Clearly, we are now able to understand the dynamics of infections at the cellular level. Of the many different mechanisms of the immune system, defenses against viral infections are of interest because many of the diseases caused by them, e.g. hepatitis B and AIDS, are chronic and incurable

[10].

To model the immune response during a viral infection, researchers first consider the basic interactions between the immune system and the virus using the following system of differential equations [1, 3]. Then we introduce the model constructed by Nowak and Bangham [9].

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = \beta xv - ay - pyz, \\ \dot{v} = ky - uv, \\ \dot{z} = cyz - bz, \end{cases} \quad (1.1)$$

where susceptible cells x are produced at a constant rate λ , die at a density-dependent rate dx , and become infected with a rate βxv ; infected cells y are produced at rate βxv and die at a density-dependent rate ay ; free virus particles v are released from infected cells at a rate ky and die at a rate uv . z is the concentration of CTLs. Infected cells y are removed at a rate pyz by the CTL immune response and the virus-specific CTL cells proliferate at a rate cy by contact with infected cells, and die at a rate bz .

In addition, we take the non cytolytic mechanisms of CTL cells into consideration, and build the following model:

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv + qyz, \\ \dot{y} = \beta xv - ay - (p + q)yz, \\ \dot{v} = ky - uv, \\ \dot{z} = cyz - bz, \end{cases} \quad (1.2)$$

the bilinear term qyz represents the CTL cells cure the infected hepatocytes by a nonlytic effectors mechanism [8].

It is true that the rate of infection in most virus dynamics models is assumed to be bilinear in the virus v and susceptible cells x . However, the actual incidence rate is probably not linear over the entire range of v and x . Thus, it is reasonable to assume that the infection rate of HIV-1 is given by Beddington-DeAngelis functional response, $\frac{\beta xv}{1 + mx + nv}$, $m, n \geq 0$. The functional response $\frac{\beta xv}{1 + mx + nv}$ was introduced by Beddington [2] and DeAngelis et al. [4].

In general we incorporate a Beddington-DeAngelis into the model (1.2) and construct the following model:

$$\begin{cases} \dot{x} = \lambda - dx - \frac{\beta xv}{1 + mx + nv} + qyz, \\ \dot{y} = \frac{\beta xv}{1 + mx + nv} - ay - (p + q)yz, \\ \dot{v} = ky - uv, \\ \dot{z} = cyz - bz, \end{cases} \quad (1.3)$$

here the state variable x, y, v, z and parameters $\lambda, d, \beta, q, a, p, k, u, c, b$ have the same biological meanings as in the model (1.2). The initial condition of (1.3) is $x(0) \geq 0, y(0) \geq 0, v(0) \geq 0, z(0) \geq 0$.

2 Global asymptotical stability

Note that the basic reproductive ratio of the system (1.3) is $R_0 = \lambda\beta k / (dau + au\lambda m)$.

From (1.3), we can obtain that

(i) if $R_0 \leq 1$, then the uninfected steady state $E_0 = (\lambda/d, 0, 0, 0)$ is the unique steady state, called the infection-free equilibrium.

(ii) if $R_0 > 1$, $R^* \leq 1$, then in addition to the uninfected steady state, there exists an immune-free equilibrium $E_1 = (x_1, y_1, v_1, z_1)$, here

$$x_1 = \frac{\lambda kn + au}{k\beta + ndk - aum}, \quad y_1 = \frac{\lambda k\beta}{a(k\beta + ndk - aum)} \left(1 - \frac{1}{R_0}\right), \quad v_1 = \frac{\lambda k^2 \beta}{au(k\beta + ndk - aum)} \left(1 - \frac{1}{R_0}\right)$$

We define an immune response reproduction number $R^* = cy_1/b$. If $R_0 > 1$, the infected cell for per unit time is $\lambda k\beta(1 - 1/R_0) / (ak\beta + andk - a^2 um)$, in spite of CTL immune response. CTL cells reproduced by infected cells stimulating per unit time is cy_1 . The CTL load of a cell during the life cycle is cy_1/b .

(iii) if $R^* > 1$, corresponding to the survival of the virus and CTL cells, there is an endemic equilibrium $E^* = (x^*, y^*, v^*, z^*)$, here

$$x^* = \frac{-(d + ndv^* + \beta v^* - \lambda m) + \sqrt{(d + ndv^* + \beta v^* - \lambda m)^2 + 4md(\lambda + \lambda nv^*)}}{2dm}$$

$$y^* = \frac{b}{c}, \quad v^* = \frac{k}{u} y^*, \quad z^* = \frac{\lambda - dx^* - ay^*}{py^*}$$

In this section, we consider the global asymptotical stability of these three equilibria.

Theorem 2.1 *The infection-free equilibrium E_0 is globally asymptotically stable if*

$$R_0 \leq 1.$$

Proof. Define a Lyapunov function L_1 as follows:

$$L_1(x, y, v, z) = \frac{1}{1+mx_0} \left(x - x_0 - x_0 \ln \frac{x}{x_0} \right) + y + \frac{a}{k} v + \frac{p}{c} z. \quad (2.1)$$

where $x_0 = \lambda/d$, along the positive solutions of model (1.3), we calculating the time derivative of $L_1(x, y, v, z)$, then

$$\begin{aligned} \frac{dL_1}{dt} &= \frac{1}{1+mx_0} \dot{x} - \frac{1}{1+mx_0} \frac{x_0}{x} \dot{x} + \dot{y} + \frac{a}{k} \dot{v} + \frac{p}{c} \dot{z} \\ &= \frac{1}{1+mx_0} \left(\lambda - dx - \frac{\beta xv}{1+mv+nv} + qyz \right) - \frac{1}{1+mx_0} \frac{x_0}{x} \left(\lambda - dx - \frac{\beta xv}{1+mv+nv} + qyz \right) \\ &\quad + \frac{\beta xv}{1+mv+nv} - ay - (p+q)yz + \frac{a}{k} (ky - uv) + \frac{p}{c} (cyz - bz) \\ &= \frac{dx_0}{1+mx_0} \left(2 - \frac{x}{x_0} - \frac{x_0}{x} \right) + \frac{auv(1+mx)}{1+mv+nv} (R_0 - 1) - \frac{aunv^2}{k+mkv+nkv} - qyz \frac{x_0}{x} - \frac{auv}{k} - \frac{pbz}{c}. \end{aligned}$$

Thus, since $2 - \frac{x}{x_0} - \frac{x_0}{x} \leq 0$ and $R_0 \leq 1$, we find that $\dot{L}_1(x, y, v, z) \leq 0$ for all

$x, y, v, z \geq 0$, the infection-free equilibrium E_0 is stable. For $\dot{L}_1(x, y, v, z) = 0$, when $x = x_0$ and $v = z = 0$. Set M be the largest invariant set in the set

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

It is clear that $M = \{E_0\}$. The global asymptotical stability of E_0 follows from LaSalle invariance principle [5].

Theorem 2.2 *The immune-free equilibrium E_1 is globally asymptotically stable if $R_0 > 1$, $R^* \leq 1$.*

Proof. Define a Lyapunov function L_2 as follows:

$$L_2(x, y, v, z) = x - x_1 - \int_{x_1}^x \frac{ay_1}{v_1 \beta s} ds + y - y_1 - y_1 \ln \frac{y}{y_1} + \frac{a}{k} \left(v - v_1 - v_1 \ln \frac{v}{v_1} \right) + \frac{p+q}{c} z. \quad (2.2)$$

Obviously, $L_2(x, y, v, z)$ is positive define with respect to $(x - x_1, y - y_1, v - v_1, z)$. Along the positive solutions of model (1.3), we calculating the time derivative of $L_2(x, y, v, z)$, we obtain

$$\frac{dL_2}{dt} = \dot{x} + \dot{y} - ay_1 \frac{1+mx+nv}{\beta xv_1} \dot{x} - \frac{y_1}{y} \dot{y} + \frac{a}{k} \left(\dot{v} - \frac{v_1}{v} \dot{v} \right) + \frac{p+q}{c} \dot{z}$$

$$\begin{aligned}
&= \lambda - dx - ay - pyz - ay_1 \frac{1+mx+nv_1}{\beta xv_1} \left(\lambda - dx - \frac{\beta xv}{1+mx+nv} + qyz \right) \\
&\quad - \frac{y_1}{y} \left[\frac{\beta xv}{1+mx+nv} - ay - (p+q)yz \right] + \frac{a}{k} (ky - uv) - \frac{a}{k} \frac{v_1}{v} (ky - uv) + \frac{p+q}{c} (cyz - bz).
\end{aligned}$$

Since (x_1, y_1, v_1, z_1) is a positive equilibrium point of (1.3), we have

$$\begin{aligned}
\lambda &= dx_1 + ay_1, \\
au/k &= ay_1/v_1, \\
ay_1 &= \beta x_1 v_1 / (1 + mx_1 + nv_1)
\end{aligned}$$

Thus, we obtain

$$\lambda - dx - \frac{auv}{k} = dx_1 + ay_1 - dx - ay_1 \frac{v}{v_1} \quad (2.3)$$

What's more,

$$\begin{aligned}
&- ay_1 \frac{1+mx+nv_1}{\beta xv_1} \left(\lambda - dx - \frac{\beta xv}{1+mx+nv} + qyz \right) \\
&= - \frac{x_1}{x} \frac{1+mx+nv_1}{1+mx_1+nv_1} (dx_1 + ay_1 - dx) + ay_1 \frac{v}{v_1} \frac{1+mx+nv_1}{1+mx+nv} - ay_1 \frac{1+mx+nv_1}{\beta xv_1} qyz \\
&\quad - \frac{y_1}{y} \left(\frac{\beta xv}{1+mx+nv} - ay - pyz \right) \quad (2.4)
\end{aligned}$$

Then, we get

$$\begin{aligned}
\frac{dL_2}{dt} &= dx_1 \left(1 - \frac{x}{x_1} - \frac{x_1}{x} \frac{1+mx+nv_1}{1+mx_1+nv_1} + \frac{1+mx+nv_1}{1+mx_1+nv} \right) + ay_1 \left(1 - \frac{y_1 xv}{yx_1 v_1} \frac{1+mx_1+nv_1}{1+mx+nv} \right) \\
&\quad + ay_1 \left(1 - \frac{y_1 xv}{yx_1 v_1} \frac{1+mx_1+nv_1}{1+mx+nv} \right) + ay_1 \left(1 - \frac{v}{v_1} - \frac{yv_1}{y_1 v} \right) - ay_1 \frac{1+mx+nv_1}{\beta xv_1} qyz + qy_1 z \\
&\quad + qz \left(y_1 - \frac{b}{c} \right) + qyz + ay_1 \left(1 - \frac{x_1}{x} \frac{1+mx+nv_1}{1+mx_1+nv_1} + \frac{v}{v_1} \frac{1+mx+nv_1}{1+mx+nv} \right) + pz \left(y_1 - \frac{b}{c} \right) \\
&= \frac{d(nv_1+1)}{x(1+mx_1+nv_1)} (x-x_1)^2 - ay_1 \frac{n(1+mx)(v-v_1)^2}{v_1(1+mx+nv)(1+mx_1+nv_1)} \\
&\quad + ay_1 \left(4 - \frac{x_1}{x} \frac{1+mx+nv_1}{1+mx_1+nv_1} - \frac{y_1 xv}{yx_1 v_1} \frac{1+mx+nv_1}{1+mx_1+nv_1} - \frac{yv_1}{y_1 v} - \frac{1+mx+nv}{1+mx+nv_1} \right) \\
&\quad + qyz \left(1 - \frac{x_1}{x} \frac{1+mx+nv_1}{1+mx_1+nv_1} \right) - pz \left(y_1 - \frac{b}{c} \right) - qz \left(y_1 - \frac{b}{c} \right). \quad (2.5)
\end{aligned}$$

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

$$4 - \frac{x_1}{x} \frac{1+mx+nv_1}{1+mx_1+nv_1} - \frac{y_1 xv}{yx_1 v_1} \frac{1+mx+nv_1}{1+mx_1+nv_1} - \frac{yv_1}{y_1 v} - \frac{1+mx+nv}{1+mx+nv_1} \leq 0$$

and the equality holds only for $x = x_1, y = y_1, v = v_1, z = z_1$. From $R^* \leq 1$, we have $cy_1 - b \leq 0$, then $pz(y_1 - b/c) \leq 0, qz(y_1 - b/c) \leq 0$.

Therefore, $dL_2/dt \leq 0$ holds for all $x, y, v, z > 0$. Thus, the immune-free equilibrium E_1 is stable. And we have $L_2(x, y, v, z) = 0$ if and only if $x = x_1, y = y_1, v = v_1, z = z_1$ and $R^* = 1$. The largest compact invariant set in $M = \{(x, y, z) | L_2(x, y, v, z) = 0\}$ is $\{E_1\}$. Therefore, the immune-free equilibrium E_1 is globally asymptotically stable by the LaSalle invariance principle [5].

Theorem 2.3 *The endemic equilibrium E_1 is globally asymptotically stable if $R^* > 1$.*

Proof. Define a Lyapunov function L_3 as follows:

$$L_3(x, y, v, z) = x - x^* \int_{x^*}^x \frac{ay^* + (p+q)y^*z^*}{\beta v_1 s} ds + y - y^* - y^* \ln \frac{y}{y^*} \\ + \frac{p+q}{c} \left(z - z^* - z^* \ln \frac{z}{z^*} \right) + \frac{a + (p+q)z^*}{k} \left(v - v^* - v^* \ln \frac{v}{v^*} \right). \quad (2.6)$$

Along the positive solutions of model (1.3), we calculating the time derivative of $L_3(x, y, v, z)$, we obtain

$$\frac{dL_3}{dt} = \dot{x} + \dot{y} - [ay^* + (p+q)y^*z^*] \frac{1+mx+nv^*}{\beta xv^*} \dot{x} - \frac{y^*}{y} \dot{y} + \frac{a + (p+q)z^*}{k} \left(\dot{v} - v \frac{v^*}{v} \dot{v} \right) \\ + \frac{p+q}{c} \left(\dot{z} - \frac{z^*}{z} \dot{z} \right) \quad (2.7)$$

Clearly,

$$\lambda = dx^* + ay^* + py^*z^*, \beta x^*v^* = [ay^* + (p+q)y^*z^*](1+mx^*+nv^*), \frac{u}{k} = \frac{y^*}{v^*}$$

It follows from (2.7), we obtain

$$\frac{dL_3}{dt} = \lambda - dx - ay - pyz - \frac{x^*}{x} \frac{1+mx+nv^*}{1+mx^*+nv^*} (\lambda - dx) + \frac{a + (p+q)z^*}{k} (ky - uv) \\ - \frac{a + (p+q)z^*}{k} \frac{v^*}{v} (ky - uv) + \frac{p+q}{c} (cyz - bz) - \frac{p+q}{c} \frac{z^*}{z} (cyz - bz) \\ + [ay^* + (p+q)y^*z^*] \frac{1+mx+nv^*}{\beta xv^*} \left(\frac{\beta xv}{1+mx+nv} - qyz \right) \\ - \frac{y^*}{y} \left(\frac{\beta xv}{1+mx+nv} - ay - (p+q)yz \right). \quad (2.8)$$

Note that,

$$-\frac{y^*}{y} \left[\frac{\beta x v}{1+mx+nv} - ay - (p+q)yz \right] = -[ay^* + (p+q)y^*z^*] \frac{y^*xv}{yx^*v^*} \frac{1+mx+nv^*}{1+mx^*+nv^*} + ay^* + (p+q)y^*z^*.$$

$$\frac{a+(p+q)z^*}{k} (ky-uv) = ay + (p+q)yz^* - ay^* \frac{v}{v^*} - (p+q)y^*z^* \frac{v}{v^*}.$$

$$\frac{a+(p+q)z^*}{k} \frac{v^*}{v} (ky-uv) = ay \frac{v^*}{v} - (p+q)yz^* \frac{v^*}{v} + ay^* + (p+q)y^*z^*.$$

Hence,

$$\begin{aligned} \frac{dL_3}{dt} &= dx^* \left(1 - \frac{x}{x^*} - \frac{x^*}{x} \frac{1+mx+nv^*}{1+mx^*+nv^*} + \frac{1+mx+nv^*}{1+mx^*+nv^*} \right) \\ &\quad + [ay^* + (p+q)y^*z^*] \left(1 - \frac{x^*}{x} \frac{1+mx+nv^*}{1+mx^*+nv^*} + \frac{v}{v^*} \frac{1+mx+nv^*}{1+mx+nv} \right) \\ &\quad + [ay^* + (p+q)y^*z^*] \left(1 - \frac{xy^*v}{x^*yv^*} \frac{1+mx^*+nv^*}{1+mx+nv} \right) + [ay^* + (p+q)y^*z^*] \left(1 - \frac{v}{v^*} - \frac{yv^*}{y^*v} \right) \\ &\quad - (ay^* + (p+q)y^*z^*) \frac{1+mx+nv^*}{\beta xv^*} qyz. \\ &= -\frac{d(1+nv^*)}{x(1+mx^*+nv^*)} (x-x^*)^2 - [ay^* + (p+q)y^*z^*] \frac{n+(1+mx)(v-v^*)^2}{(1+mx+nv)(1+mx^*+nv^*)v^*} \\ &\quad + [ay^* + (p+q)y^*z^*] \left(4 - \frac{x^*}{x} \frac{1+mx+nv^*}{1+mx^*+nv^*} - \frac{xy^*v}{x^*yv^*} \frac{1+mx^*+nv^*}{1+mx+nv} - \frac{yv^*}{y^*v} - \frac{1+mx+nv}{1+mx+nv^*} \right) \\ &\quad - [ay^* + (p+q)y^*z^*] \frac{1+mx+nv^*}{\beta xv^*} qyz. \end{aligned} \tag{2.9}$$

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

$$4 - \frac{x^*}{x} \frac{1+mx+nv^*}{1+mx^*+nv^*} - \frac{xy^*v}{x^*yv^*} \frac{1+mx^*+nv^*}{1+mx+nv} - \frac{yv^*}{y^*v} - \frac{1+mx+nv}{1+mx+nv^*} \leq 0$$

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

It follows from (2.9) that $dL_3/dt \leq 0$ holds for all $x, y, v, z > 0$. And we have $L_3(x, y, v, z) = 0$ if and only if $x = x^*, y = y^*, v = v^*$. The largest compact invariant set in $M = \{(x, y, z) | L_2(x, y, v, z) = 0\}$ is the singleton $\{E^*\}$. Therefore, the endemic equilibrium E^* is globally asymptotically stable by the LaSalle invariance principle [5]. The theorems are proved.

3 Discussion

Korobeinikov [6-7] constructed a class of Lyapunov function. In [13], they proved global stability of the virus model with the incidence rate $\beta x^p y^q$ and they have presented a global analysis of model (1.1) by Lyapunov functions. In present paper, a class of more general HIV-1 infection model with Beddington-DeAngelis incidence rate and CTL immune response is considered.

References

- [1] R. Anderson, R. May, Infectious Diseases of Humans: Dynamics and Control, *Oxford University Press*, 1991.
- [2] J.R. Beddington, Mutual interference between parasites or predators and its effect on searching efficiency, *J. Anim.Ecol.* 44 (1975), 331–340.
- [3] R. De Boer, A. Perelson, Target cell limited and immune control models of HIV infection: a comparison, *Journal of Theoretical Biology* , 190 (3) (1998), 201–214.
- [4] D.L. DeAngelis, R.A. Goldstein, R.V. O'Neill, A model for tropic interaction. *Ecology*, 56(1975), 881–892.
- [5] J.K. Hale, Verduyn Lunel, Introduction to FunctionalDifferential Equations. *Springer*, New York, 1993.
- [6] A. Korobeinikov, Global properties of basic virus dynamics models, *Bull. Math. Biol*, 66(2004), 879-883.
- [7] A. Korobeinikov, P.K.A. Maini, Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence, *Math. Biosc.* 1 (2004), 57-60.
- [8] C. Long, H. Qi, S.H. Huang, Mathematical modeling of cytotoxic lymphocyte-mediated immune responses to hepatitis B virus infection. *J. Biomed. Biotechnol.*38(2008), 1573–1585.
- [9] M. Nowak, C.R.M. Bangham, Population dynamics ofimmune responses to persistent viruses, *Science*, 272(1996), 74–79.

- [10] M. Nowak, R. May, Virus Dynamics, Oxford University Press, 2000.
- [11] A. Perelson, P. Nelson, Mathematical models of HIV dynamics in vivo, *SIAM Rev*, 41(1999), 3-44.
- [12] A. Perelson, A. Neumann, M. Markowitz, J. Leonard, HIV-1 dynamics in vivo: vision clearance rate, infected cell life-span, and viral generation time. *Science*, 271(1996),1582–1586.
- [13] X. Wang, Y.D. Tao, Lyapunov function and global proper-ties OS virus dynamics with CTL immune response. *Int. J. Biomath*, 4(2008), 443-448.

Received: June 12, 2014