Analysis of a HBV Infection Model With Non-cytolytic Cure Process

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***Abstract*—Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. Many models ignore the loss term of free virus particle when it enters the target cell. In this paper, we discuss a virus infection model with the loss term of free virus and the non-cytolytic loss of infected cells. Stable analysis of our model was given. If the basic reproduction number $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable and the virus is cleared; if the basic reproduction number $R_0 > 1$, then the virus would persist in the host.**

***Keywords*—Mathematical model, virus dynamics, stable analysis,**

I. Introduction

The basic models of within-host viral infection, proposed by Nowak and May[1] has been widely used in the studies of HBV and HIV infections. The basic models, describing the dynamics of interaction between uninfected cells $x(t)$, infected cells $y(t)$ and free virus $v(t)$, take the form of

$$\begin{cases} \dot{x} = \lambda - dx - \beta vx \\ \dot{y} = \beta vx - ay \\ \dot{v} = ky - uv \end{cases} \tag{1}$$

uninfected cells are assumed to be produced at the constant rate λ, die at the rate of dx and become infected at the rate of βvx. Infected cells are thus produced at the rate of βvx and die at the rate ay. Free virous are generated from infected cells at the rate of ky and decay at the rate of uv.

Obviously the rate of infection in model (1) is bilinear between the virus v and the uninfected target cells x. Xinyu Song et al.[2] pointed that the saturated mass action $\beta xv^p/(1+)xvp/(1+\alpha v^q)$ can be used for HBV, HCV and HIV infection, and they discussed the special case $\beta xv/(1+)xv/(1+\alpha v)$, Dan Li et al.[3] also used the special saturated mass action $\beta xv/(1+v)$ for HIV infection, Lequan Min et al.[4], [5] used the standard mass action incidences $\beta xv/(x+y)$ for HBV models with, Xiaohong Tian et al.[6] used the standard mass action incidences $\beta xv/(x+y)$ for a time-delay HBV models. Recently, Beddington-DeAngelis functional response $\beta xv/(1+ax+bv)$ was used in paper[7], [8] for HIV infection. Paper [9] used the mass action $\beta vx/(x+v)$ to set up an HBV model. Obviously, the saturated mass action $\beta xv/(1+\alpha v)$ and $\beta xv/(1+v)$ are only the special case of the Beddington-DeAngelis functional response $\beta xv/(1+ax+bv)$, but the mass action $\beta vx/(x+v)$ is not its' special case.

Obviously, as pointed by Leenheer and Smith[10], Nowak and May ignore the loss term βvx which should appear in the v equation, i.e.,

$$\dot{v} = ky - uv - \beta vx \tag{2}$$

representing the loss of free virus particle once it enters the target. On the other hand, paper [11] pointed out that the infected cells can be cured by a non-cytolytic process and recovery into the uninfected cell population, In this paper, considering the loss of viral particles when it enters the target cells and non-cytolytic loss of infected cells, well discuss the model

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta vx}{x+v} + \rho y \\ \dot{y} = \dfrac{\beta vx}{x+v} - ay - \rho y \\ \dot{v} = ky - uv - \dfrac{\beta vx}{x+v}. \end{cases} \tag{3}$$

wherex, y and v are the same as (1), and infected hepatocytes are "cured by non-cytolytic processes at a constant rate ρ per cell. The basic reproduction number of model (3) is $R_0 = \beta(k-a-\rho)/(a+\rho)u$.

our model has two steady states:

$$E_0 = (\lambda/d, 0, 0), E_e = (x_e, y_e, v_e).$$

which

$$\begin{aligned} x_e &= \frac{\lambda(k-a-\rho)}{au(R_0-1)+(k-a-\rho)d} \\ y_e &= \frac{\lambda u(R_0-1)}{au(R_0-1)+(k-a-\rho)d} \\ v_e &= \frac{\lambda(k-a-\rho)(R_0-1)}{au(R_0-1)+(k-a-\rho)d} \end{aligned}$$

Note the biological meaning, E_e does not exist if $R_0 < 1$, and it becomes E_0 when $R_0 = 1$. It is easy to see that $x_e < \lambda/d$ when $R_0 > 1$. This means the infection of the virus will reduce the total number of uninfected cells in host.

The main purpose of this paper is to discuss the globally asymptotical stability of E_0 and E_e. This paper is organized as follows. In Section 2, we give the stable analysis of the infection-free equilibrium of system (3). In Section 3, we give the stable analysis of the endemic steady state. The paper ends with a brief discussion in Section 4.

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II. Stability Analysis of the infection-free steady state

From the first two equations, we can get

$$(x+y)' = \lambda - dx - ay \leq q(x+y)$$

which $q = min\{a, d\}$, so we can get that $x + y \leq \lambda/q$ for large t,from the third equation, it can be easily be seen that $v \leq \lambda k/uq$, so the positive solution of system (3) is ultimately bounded. In the following, we can study the system (3) in the positive invariant set:

$$D = \{(x,\ y,\ v) \in R^3_+ : x + y \leq \lambda/q, v \leq \lambda k/uq\}$$

Theorem 2.1: If $R_0 < 1$, then the disease-free state E_0 is globally asymptotically stable and becomes unstable when $R_0 > 1$.

Proof: First, we will analyze the locally asymptotical stability of E_0. The Jacobian matrix of the vector field corresponding to model (3) is

$$J = \begin{pmatrix} -d - \dfrac{\beta v^2}{(x+v)^2} & p & -\dfrac{\beta x^2}{(x+v)^2} \\ \dfrac{\beta v^2}{(x+v)^2} & -a-p & \dfrac{\beta x^2}{(x+v)^2} \\ -\dfrac{\beta v^2}{(x+v)^2} & k & -u - \dfrac{\beta x^2}{(x+v)^2} \end{pmatrix}. \quad (4)$$

The above Jacobian matrix evaluted at E_0 is

$$J_{E_0} = \begin{pmatrix} -d & p & -\beta \\ 0 & -a-p & \beta \\ 0 & k & -u-\beta \end{pmatrix}. \quad (5)$$

Here $-d < 0$ is an eigenvalue, since the trace of the two-by-two lower right submatrix is negative and the determinant is $(a+p)u(1-R_0)$, if $R_0 < 1$, the remaining two eigenvalues are also negative, so E_0 is locally asymptotically stable. If $R_0 > 1$, there must exist a positive eigenvalue, so E_0 is unstable.

Next, we'll discuss the globally asymptotical stability. Consider the Lyapunov function

$$V_2 = y(t) + \frac{a}{k} v(t).$$

Calculating the derivative of V_2 along the solutions of the model (7) gives

$$\begin{aligned} V_2'(t) &= \frac{\beta xv}{x+v} - \frac{(a+p)u}{k} v - \frac{(a+p)}{k}\frac{\beta xv}{x+v} \\ &= \frac{\beta xv}{x+v}(1 - \frac{a+p}{k}) - \frac{(a+p)u}{k} v \\ &\leqslant \beta v(1 - \frac{a+p}{k}) - \frac{(a+P)u}{k} v \\ &= (1 - \frac{1}{R_0})\frac{\beta(k-a-p)}{k} v \leqslant 0. \end{aligned}$$

Let $E = \{(x,y,v) \in D | V_2'(t) = 0\}$, it is clear that $E \subset \{(x,y,v) \in D | v = 0\}$. Let M be the largest positively invariant subset of the set E,since $v(t) \equiv 0$ in the set M, by the third equation of system (3), we can know $y(t) \equiv 0$, so $M = \{(x,y,v) | v = 0, y = 0\}$, thus by Lyapunov-Lasalle theorem[12], we know $\lim\limits_{t\to\infty} y(t) = 0$, $\lim\limits_{t\to\infty} v(t) = 0$. the limit equation of system (3) is $\dot{x} = \lambda - dx$, and $x(t) = \lambda/d$ is globally asymptotically stable. by the theorem on limiting systems[13] and the locally asymptotical stability, we know E_0 is globally asymptotically stable. ■

III. Stability Analysis of the endemic steady state

A. Local stability of the endemic steady state

We first consider the local stability of the endemic steady state E_e:

Theorem 3.1: If $R_0 > 1$, then the endemic steady state E_e is locally asymptotically stable.

Proof: Note that

$$\frac{v_e}{x_e + v_e} = 1 - \frac{1}{R_0}, \frac{x_e}{(x_e+v_e)^2} = \frac{1}{R_0},$$

the Jacobian matrix of the vector field corresponding to model (3) evaluated at E_e is

$$J_{E_e} = \begin{pmatrix} -d - \beta(1-\frac{1}{R_0})^2 & \rho & -\frac{\beta}{R_0^2} \\ \beta(1-\frac{1}{R_0})^2 & -a-\rho & \frac{\beta}{R_0^2} \\ -\beta(1-\frac{1}{R_0})^2 & k & -u - \frac{\beta}{R_0^2} \end{pmatrix}.$$

The characteristic equation associated with J_{E_e} is given by

$$|lE - J_{E_e}| = l^3 + a_1 l^2 + a_2 l + a_3 = 0, \quad (6)$$

where

$$\begin{aligned} a_1 &= a + \rho + u + d + \frac{\beta}{R_0^2} + \beta(1 - \frac{1}{R_0})^2 > 0, \\ a_2 &= d(a + \rho + u + \frac{\beta}{R_0^2}) + (a+\rho)u(1 - \frac{1}{R_0}) \\ &\quad + \beta a(1 - \frac{1}{R_0})^2 + \beta u(1 - \frac{1}{R_0})^2 > 0, \\ a_3 &= \beta a u(1 - \frac{1}{R_0})^2 + d(a+\rho)u(1 - \frac{1}{R_0}) > 0. \end{aligned}$$

Let

$$\begin{aligned} a_1 &= a + d + C \\ a_2 &= (a+\rho)u(1 - \frac{1}{R_0}) + \beta u(1 - \frac{1}{R_0})^2 + D, \end{aligned}$$

which

$$\begin{aligned} C &= \rho + u + \frac{\beta}{R_0^2} + \beta(1 - \frac{1}{R_0})^2 > 0, \\ D &= d(a + \rho + u + \frac{\beta}{R_0^2}) + \beta a(1 - \frac{1}{R_0})^2 > 0. \end{aligned}$$

then

$$\begin{aligned} a_1 a_2 - a_3 &= d(\beta u(1 - \frac{1}{R_0})^2 + D) \\ &\quad + a(a+\rho)u(1 - \frac{1}{R_0}) + aD + Ca_2 \\ &> 0. \end{aligned}$$

By Routh-Hurwitz criterion, E_e is locally asymptotically stable.

■

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B. Globally asymptotic stability of the disease steady state

In order to prove the global stability, we need to show the uniform persistence of system (3) when $R_0 > 1$. By the theorem 4.3 in paper [14], we choose $X = R^3$ and $E = D$. The maximal invariant set N on the boundary ∂D is the singleton E_0 and is isolated, so the uniform persistence is equivalent to the unstability of E_0. Hence, by theorem 2.1, we know if $R_0 > 1$, the system (3) is uniform persistence. Consequently, there exists a compact absorbing set $K \subset D$[15].

Theorem 3.2: Suppose that $R_0 > 1$, and $\beta < \min(k, a, d)$, then E_e is globally asymptotically stable with initial conditions in int$D$.

Proof: We will prove the result by the theorem 3.5 in paper[16]. The uniform persistence can ensure the existence of the compact absorbing set, combine with the local asymptotical stability, the condition of $H1, H2$ and $H3$ are all satisfied, we need only to show $q < 0$. Let $J^{[2]}$ be the second additive compound matrix of Jacobian (4). Let

$$P = diag(1, \frac{y}{v}, \frac{y}{v}),$$

then

$$P_f P^{-1} = diag(0, \frac{\dot{y}}{y} - \frac{\dot{v}}{v}, \frac{\dot{y}}{y} - \frac{\dot{v}}{v}),$$

where matrix P_f is obtained by replacing each entry p_{ij} of p by its derivative in the direction of solution of (6), furthermore, we have

$$B = P_f P^{-1} + P J^{[2]} P^{-1} = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix},$$

which

$$B_{11} = -d - a - \rho - \frac{\beta v^2}{(x+v)^2},$$
$$B_{12} = (\frac{\beta x^2 v}{(x+v)^2 y}, \frac{\beta x^2 v}{(x+v)^2 y})$$

$$B_{21} = \begin{pmatrix} k\frac{y}{v} \\ \frac{\beta v y}{(x+v)^2} \end{pmatrix},$$

$$B_{22} = \begin{pmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{pmatrix},$$

which

$$\begin{aligned} b_{11} &= \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - d - u - \frac{\beta(v^2 + x^2)}{(x+v)^2}, \\ b_{12} &= \rho, \\ b_{21} &= \frac{\beta v^2}{(x+v)^2}, \\ b_{22} &= \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - a - \rho - u - \frac{\beta . x^2}{(x+v)^2} \end{aligned}$$

Let (w_1, w_2, w_3) denote the vector in $R^3 \cong R \begin{pmatrix} 3 \\ 2 \end{pmatrix}$, the vector normal in R^3 is chosen as

$$|(w_1, w_2, w_3)| = \max\{|w_1|, |w_2| + |w_3|\}.$$

Let μ denote the Lozinskiĭ measure with respect to this norm. Similar to the method used in paper[17], we have estimated that $\mu \leq \sup\{g_1, g_2\}$ where

$$g_1 = \mu_1(B_{11}) + |B_{12}|, \quad g_2 = |B_{21}| + \mu_1(B_{22})$$

here μ_1 denote the Lozinskiĭ measure with respect to l_1 vector norm, $|B_{12}| and |B_{21}|$ are matrix norms with respect to l_1 norm, and

$$\mu_1(B_{11}) = -d - a - \rho - \frac{\beta v^2}{(x+v)^2}, \quad |B_{12}| = \frac{\beta x^2 v}{(x+v)^2 y}$$

Because

$$\frac{\beta v y}{(x+v)^2} \leq \frac{\beta y}{x+v} \leq \frac{\beta y}{v},$$

note that $k > \beta$, we have

$$|B_{21}| = k\frac{y}{v}$$

$$\begin{aligned} \mu_1(B_{22}) &= max\{\frac{\dot{y}}{y} - \frac{\dot{v}}{v} - d - u - \frac{\beta x^2}{(x+v)^2}, \\ &\quad \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - a - u - \frac{\beta x^2}{(x+v)^2}\} \\ &= \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - a - u - \frac{\beta x^2}{(x+v)^2} \end{aligned}$$

$$\begin{aligned} g_1 &= -d - a - \rho - \frac{\beta v^2}{(x+v)^2} + \frac{\beta x^2 v}{(x+v)^2 y} \\ &\leq -d - a - \rho - \frac{\beta v^2}{(x+v)^2} + \frac{\beta x v}{(x+v) y} \\ &= -d - \frac{\beta v^2}{(x+v)^2} + \frac{\dot{y}}{y} \end{aligned}$$

$$\begin{aligned} g_2 &= k\frac{y}{v} + \frac{\dot{y}}{y} - \frac{\dot{v}}{v} - a - u - \frac{\beta x^2}{(x+v)^2} \\ &= \frac{\dot{y}}{y} - a + \frac{\beta x}{x+v} - \frac{\beta x^2}{(x+v)^2} \\ &\leq \frac{\dot{y}}{y} - a + \frac{\beta x}{x+v} \end{aligned}$$

Consequently,

$$\mu(B) \leq sup\{g_1, g_2\} \leq \frac{\dot{y}}{y} - \min(a, d) + \frac{\beta x}{x+v}$$

Along each solution $x(t)$,$y(t)$,$v(t)$ of (3) with $x(0)$,$y(0)$, $v(0) \in D$, we thus have

$$\begin{aligned} \frac{1}{t}\int_0^t \mu(B) ds &\leq \frac{1}{t}\int_0^t (\frac{\dot{y}}{y} - \min(a, d) + \frac{\beta x}{x+v}) ds \\ &\leq \frac{1}{t}\int_0^t (\frac{\dot{y}}{y} - \min(a, d) + \beta) ds \\ &= \frac{1}{t}\lg\frac{y(t)}{y(0)} + \beta - \min(a, d) \end{aligned}$$

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Consequently,

$$\bar{q}_2 = \lim_{t\to\infty} \sup \sup_{x\in K} \frac{1}{t} \int_0^t \mu(B)ds < \frac{\beta - \min(a,d)}{2} < 0.$$

By the theorem 3.5 in paper[16], the disease steady state E_e is globally asymptotically stable, this completes the proof.

■

IV. Concluding remarks

In this paper, we set up a HBV infection model based on saturate infection rate, in the model, we didn't ignore the loss term of free virus particle when it enters the target cell, on the other hand, we also consider the non-cytolytic loss of infected cells. By stable analysis, we can know the infection-free equilibrium is globally asymptotically stable and the virus is cleared if the basic reproduction number $R_0 < 1$, and if the basic reproduction number $R_0 > 1$ and the parameters satisfy $\beta < \min(k, a, d)$, the endemic equilibrium is also globally asymptotically stable.

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