Analysis of A HBV Infection Model with ALT

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***Abstract*—Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. Many hepatitis B virus (HBV) models were set up based on the basic virus infection model (BVIM) introduced by Zeuzem et al. and Nowak et al. But some references have pointed out that the basic infection reproductive number of the BVIM is biologically questionable and given the modified models. And so far, no immune model with alanine aminotransferase (ALT) was given based on the modified models. In this paper one immune models with ALT based on the modified model is discussed. The stability analysis and simulation of the model is also given based on clinical data of ALT and HBV DNA.**

***Keywords*—virus dynamics; stable analysis; ALT**

I. Introduction

Chronic hepatitis B caused by the HBV remains a major global health problem. About 2 billion people have been infected with the virus [1], with 5 million new cases each year [2]. The annual mortality from hepatitis B infection and its sequelae is 1-2 million people worldwide [3]. HBV infection acquired in adult life is often not clinically apparent and most acutely infected adults recover completely from it. Roughly 5%-10% of acutely infected adults become persistently infected by the virus and develop chronic hepatitis [4].

It is currently widely accepted that HBV infection is noncytopathic. Infected hepatocyte are killed not by the virus but by HBV-specific cytotoxic T lymphocytes (CTLs)[5]. Studies in human and animal models provide substantial evidence that viral hepatitis is initiated by an antigen specific antiviral cellular immune response [4].

Most patients with chronic HBV infection require long-term therapy [6], [7]. Effective treatment of chronic HBV patients aims to prevent progression of chronic hepatitis B (CHB) to cirrhosis, hepatocellular carcinoma, and eventually death.

The most commonly used drugs include interferon alpha, peginterferon alfa-2a, and nucleotide such as lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate(DF)[8]. The nucleotide analogues can inhibit viral reverse transcriptase of viral DNA synthesis, while interferon is an immune system modulator. Interferons are not recommended for use in patients with decompensation or immunosuppression, they may have treatment limiting side effects, and they require parenteral administration. Oral nucleosides, although potent, have been limited by the development of resistance mutations in the HBV polymerase reverse transcriptase[9], [10]. Until drug resistance is overcome or more effective and inexpensive therapies are introduced, hepatitis B will remain a major threat to health around the world.

Alanine transaminase (ALT) are chemicals that liver release when they are damaged or sick . ALT in serum is one of the main indicators for inflammatory activity in chronic hepatitis B. Doctors will generally treat patients if their ALT levels are elevated twice above normal. Elevated ALT levels also mean the host's immune system is actively fighting the hepatitis B infection. Paper[9] pointed that during interferon-based therapy, approximately 25%-40% of patients exhibit an ALT flare, which is probably caused by the immune stimulatory effects of interferon. While there is no increased incidence of ALT flares during treatment with nucleos(t)ide analogues, but flares occur in 10%-20% of patients after withdrawal of treatment[12]. Paper [13] reported that host-induced flares, i.e. an ALT flare followed by a decrease in HBV-DNA, are associated with a favorable treatment response.

The use of mathematical models to enhance our understanding of the dynamics of chronic viral infections has proven fruitful. The use of mathematical models to interpret experimental and clinical results has made a significant contribution to the fields of (anti-) HIV, HBV and /or HCV infections[14], [15], [16], [17], [18]. Among those models, the basic virus infection model (BVIM) introduced by Pelson et al.[15] and Nowak et al. [17] is widely used in the studies of virus infection dynamics.

The BVDM was described as follows: .

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

where x, y and v are numbers of uninfected (susceptible) cells, infected cells, and free virus respectively. Uninfected cells are assumed to be produced at the constant rate λ and to die at the rate of dx, and become infected at the rate of βvx , where β is a rate constant describing the infection process. Infected cells are thus produced at the rate of βvx and are assumed to die at the rate ay. Free virus are assumed to be produced from infected cells at the rate of ky and are removed at the rate of μv.

Many subsequent models have adapted the structure of (1)

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to include immune system dynamics [19], [20], [21], [22] and various treatments [23]. The basic infection reproductive number of model (1) is $R_0 = \lambda\beta k/adu$, Paper [24] pointed that the basic infection reproductive number may not be reasonable, for it is proportional to λ/d which represents the number of total cells of the liver, which implies that an individual with a smaller liver maybe more resistant to virus infection than an individual with a larger one.

Paper [24] pointed that the of model (1) is biologically questionable and gave an modified model by using a standard incidence function, and the reproductive number of the modified model is $R_0 = \beta k/au$ which seems more reasonable. Based on paper [24], several models have been considered to describe different aspects of HBV dynamics[25], [26], [27].

In this paper, based on paper [24], we will discuss an immune model with ALT. The model was described as follows:

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta xv}{x+y} \\ \dot{y} = \dfrac{\beta xv}{x+y} - dy - \dfrac{k_1 yz}{x+y} \\ \dot{v} = ky - \mu v \\ \dot{z} = (g + k_2 yz)(1 - z/z_{max}) - d_1 z \\ \dot{u} = s + k_3 z(1 - z/z_{max}) - d_2 u \\ x(0) > 0, y(0) \geq 0, v(0) \geq 0, z(0) \geq 0, u(0) \geq 0 \end{cases} \tag{2}$$

where the meaning of the variables x, y, v and the parameters $\lambda, d, \beta, k, \mu$ are the same as those of BVIM, and we suppose the die rate of infected cell is the same as uninfected cells. z is the number of CTL, u represents the levels of ALT. ALT are assumed to be produced at the constant rate $s(s > 0)$. The constant $d_1, d_2(d_1, d_2 > 0)$ are the death rates of CLT and ALT. The infected cells are killed by the CLT response at a rate $k_1 yz/(x+y)$. CLT proliferation can be described by two terms g and $k_2 yz$, where g represents antigen-independent proliferation, and $k_2 yz$ represents antigen-dependent proliferation. k_3 represents the elevating rate due to the host's immune system's activity. The basic infection reproductive number of model (2) is $R_0 = \beta k/d\mu$. The system (2) has a disease-free equilibrium point $Q_1 = (\lambda/d, 0, 0, z^*, u^*)$, which

$$z^* = g/(d_1 + g/z_{max}), u^* = [s + k_3 z^*(1 - z^*/z_{max})]/d_2.$$

If $R_0 > 1$, system (2) has a unique infection equilibrium point $Q_2 = (x_2, y_2, v_2, z_2, u_2)$, which

$$\begin{aligned} y_2 &= \frac{d_1 z_2 - g(1 - z_2/z_{max})}{k_2 z_2(1 - z_2/z_{max})}, \\ v_2 &= ky_2/\mu, \\ u_2 &= s/d_2 + k_3/d_2 \cdot z_2(1 - z_2/z_{max}). \end{aligned}$$

and x_2, y_2, z_2 satisfy :

$$d{x_2}^2 + (2dy_2 - \lambda)x_2 + (dy_2 - \lambda)y_2 + k_1 y_2 z_2 = 0.$$

II. Analysis of Model (2)

Theorem 2.1: Under the given initial conditions, all solutions of system (2) are positive and there exists an $M > 0$ such that each solution satisfies $x(t) < M, y(t) < M, z(t) < M, u(t) < M, v(t) < M$ after enough large time t.

Proof: First, from [5] , it can be easily seen that the solution of (2) with the given initial condition exists, and is unique. Furthermore, it can also be shown that the solution of (2) is also nonnegative for all $t > 0$.

Now, we prove the boundedness of the solution of (2).

Let $N_1(t) = x(t) + y(t)$, we have

$$\begin{aligned} \dot{N_1} &= \lambda - dx - dy - k_1 yz/(x+y) \\ &\leq \lambda - d(x+y) \\ &= \lambda - dN_1. \end{aligned}$$

A simple comparison argument shows that

$$\limsup_{t\to\infty} (x(t) + y(t)) \leq \lambda/d.$$

Thus, $x(t)$, $y(t)$ are ultimately bounded by $M_1 = \lambda/d$.

From $\dot{v} = ky - \mu v \leq kM_1 - \mu v$, just as above proof, $v(t)$ is also ultimately bounded by $M_2 = kM_1/\mu$.

Let $N_2(t) = 2M_1 y(t) + k_1/k_2 \cdot z(t)$. Note that $x + y \leq 2M_1$ for large t, we have

$$\begin{aligned} \dot{N_2} &= 2M_1\left(\frac{\beta vx}{x+y} - dy - \frac{k_1 yz}{x+y}\right) \\ &\quad + \frac{k_1}{k_2} \cdot [(g + k_2 yz)(1 - z/z_{max}) - d_1 z] \\ &\leq 2M_1\beta v - 2M_1 dy - k_1 yz + \frac{k_1}{k_2} g + k_1 yz - \frac{k_1}{k_2} d_1 z \\ &\leq (2M_1\beta M_2 + \frac{k_1}{k_2} \cdot g) - \min(d, d_1)(2M_1 y + \frac{k_1}{k_2} z) \\ &= (2M_1\beta M_2 + \frac{k_1}{k_2} g) - \min(d, d_1) N_2 \end{aligned}$$

Then N_2 is also ultimately bounded by $(2M_1\beta M_2 + k_1/k_2 \cdot g)/\min(d, d_1)$, So $z(t)$ is also ultimately bounded by some positive M_3.

Obviously $\dot{u} \leq s + k_3 M_3 - d_2 u$. Let $p = s + k_3 M_3$, the above inequality turns to $du/dt \leq p - d_2 u$. Similar to the above proof, we can know that $u(t)$ is also ultimately bounded by some positive M_4. Now let $M = max\{M_1, M_2, M_3, M_4\}$, we have $x(t) < M, y(t) < M, v(t) < M, z(t) < M, u(t) < M$. ■

Let $D = \{(x, y, v, z, u) | 0 < x \leq \dfrac{\lambda}{d}, 0 \leq y, v, z, u \leq M\}$, it is easily to know that D is positive invariant set of system (2).

Theorem 2.2: If $R_0 < 1$, the infection-free equilibrium Q_1 of system (2) is local asymptotically stable.

Proof: The Jacobi matrix of Q_1 is as follows:

$$J\,|_{Q_1} = \begin{pmatrix} -d & 0 & -\beta & 0 & 0 \\ 0 & -d & \beta & 0 & 0 \\ 0 & k & -\mu & 0 & 0 \\ 0 & J_{42} & 0 & -d_1 - g/z_{max} & 0 \\ 0 & 0 & 0 & k_3 - 2k_3 z/z_{max} & -d_2 \end{pmatrix}$$

which $J_{42} = k_2 d_1 g {z_{max}}^2/(z_{max} d_1 + g)^2$. The eigenvalues of $J\,|_{Q_1}$ are:

$$\begin{aligned} \lambda_1 &= -d, \lambda_2 = -d_1 - g/z_{max}, \lambda_5 = -d_2, \\ \lambda_{3,4} &= \frac{-(d+\mu) \pm \sqrt{(d+\mu)^2 - 4(d\mu - \beta k)}}{2} \end{aligned}$$

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It is easy to know $\lambda_1, \lambda_2, \lambda_5$ are less than 0. From $R_0 < 1$, that is $d\mu - \beta k > 0$, the real part of $\lambda_{3,4}$ is negative. Therefore, Q_1 is locally asymptotically stable.

■

Theorem 2.3: If $R_0 < 1$, the infection-free equilibrium Q_1 of system (2) is globally asymptotically stable in D.

Proof: Let

$$V_1(t) = y(t) + \frac{d}{k}v(t).$$

Calculating the derivative of V_1 along the solutions of the model (2) gives

$$\begin{aligned}\dot{V}_1(t) &= \frac{\beta x v}{x+y} - dy - \frac{k_1 y z}{x+y} + \frac{d}{k}(ky - \mu v) \\ &= \frac{\beta x v}{x+y} - \frac{k_1 y z}{x+y} - \frac{d\mu}{k}v \\ &\leqslant \frac{\beta x v}{x+y} - \frac{d\mu}{k}v \\ &= \frac{d\mu}{k}(R_0 - 1)v.\end{aligned}$$

Since $R_0 < 1$, we have $\dot{V}_1(t) \leqslant 0$.

Let $E = \{(x, y, v, z, u)\} | \dot{V}_1(t) = 0$, obviously

$$E \subset \{(x, y, v, z, u) | v(t) = 0\}$$

. Let M be the largest set which is invariant with respect to (2), by the third equation we can know that $y(t) = 0$, so $M = \{(x, y, v, z, u) | y = 0, v = 0\}$. By LaSalle invariance principal, we know

$$\lim_{t\to\infty} y(t) = 0, \quad \lim_{t\to\infty} z(t) = 0,$$

The limit equation of system (2) is

$$\begin{cases} \dot{x} = \lambda - dx \\ \dot{z} = g(1 - z/z_{max}) - d_1 z = g - (g/z_{max} + d_1)z \\ \dot{u} = s + k_3 z(1 - z/z_{max}) - d_2 u \end{cases} \tag{3}$$

From the equation of (3), we easily know

$$\lim_{t\to\infty} x(t) = \frac{\lambda}{d}.$$

$$\lim_{t\to\infty} z(t) = \frac{g}{d_1 + g/z_{max}}.$$

and

$$\lim_{t\to\infty} u(t) = \frac{s + k_3 z^*(1 - z^*/z_{max})}{d_2}.$$

Therefore,

$$(\frac{\lambda}{d}, \frac{g}{d_1 + g/z_{max}}, \frac{s + k_3 z^*(1 - z^*/z_{max})}{d_2})$$

is globally asymptotically stable for model (3). So Q_1 is globally attractive, by the local asymptotical stability of Q_1, we can know Q_1 of system (2) is globally asymptotically stable if $R_0 < 1$. ■

III. Application

Based on model (2), note that adefovir can inhibit viral reverse transcriptase of viral DNA synthesis, we set out the following therapy model with drug adefovir:

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta x v}{x+y} \\ \dot{y} = \dfrac{\beta x v}{x+y} - dy - \dfrac{k_1 y z}{x+y} \\ \dot{v} = (k-p)y - \mu v \\ \dot{z} = (g + k_2 y z)(1 - z/z_{max}) - d_1 z \\ \dot{u} = s + k_3 z(1 - z/z_{max}) - d_2 u \end{cases} \tag{4}$$

which $p (p > 0)$ represents the efficacy of therapy.

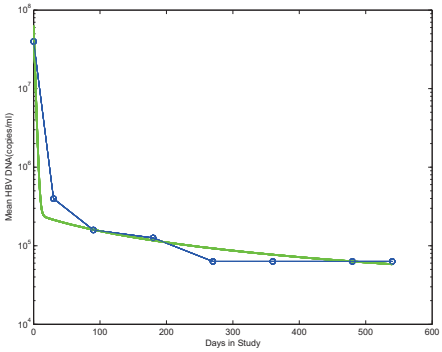

Fig. 1. The simulation of HBV DNA.

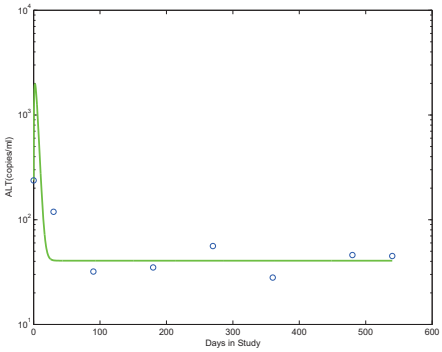

Fig. 2. The simulation of ALT.

we will use our model (4) to simulate the treatment data of HBV infection with drug adefovir reported by [28]. We'll estimate the parameters of system (2) as follows:

1) If the virus is cleared, the infection-free equilibrium $Q_1 = (\lambda/d, 0, 0, z^*, u^*)$ is stable. Thus, we can assume λ/d represents the number of liver cells.
2) A normal human liver contains $\approx 2\times10^{11}$ hepatocytes.[29] A normal patient has about total 3000 ml plasma. Usually, tested virus qualities are in copies/ml. Consequently, we can assume that

$$\lambda/d \approx 2 \times 10^{11}/3000.$$

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3) Since the half-life of a hepatocyte is about half a year,[30] we can assume that

$$d = -\ln(0.5)/100 \approx 0.00693.$$

4) We assume that $\mu = 0.58$, that is equivalent to assume that the half life of a virus is about one day [15]
5) We assume that $d_2 = 0.3466$, that is equivalent the half life of ALT virus is about two days, note that the normal level of ALT is about $40U/L$, so we can choose $s = 14$.
6) Based on the clinical data and numerical simulation, we can select the other parameters as follows.

$$\{\beta,\ k,\ \ k_1,\ p,\ z_{max}\} = \{1.39,\ 3.0,\ 4.8,\ 2.997,\ 1.0e+9\}.$$

$$\{g,\ k_2,\ \ d_1,\ k_3\} = \{0.01,\ 6.0e-10,\ 0.6,\ 45.9\}.$$

The simulation was shown in figure 1 and figure 2. In the two figures, the solid line is the simulation of treatment model based on (4). ∘ stands for clinical data of HBV DNA in figure 1 and ALT in figure 2. From Figure 1 and figure 2 we can see that the simulation of our therapy model is in agreement with the clinical data.

IV. Conclusion

This paper introduces an immune model with HBV about ALT response to HBV. The detailed analysis on the local asymptotic stability and global asymptotic stability of disease-free equilibrium Q_1 is carried out. It is shown that if $R_0 = \beta k/d\mu < 1$, the equilibrium Q_1 is locally and globally asymptotically stable. Base on the immune model with HBV, this paper also set up a therapy model. The simulation of the therapy model shows that our model can fit the clinical data well, of course more data are needed to improve our model.

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