

Research Article

Mathematical Modeling of Cytotoxic Lymphocyte-Mediated Immune Response to Hepatitis B Virus Infection

Changjiang Long,^{1,2} Huan Qi,² and Sheng-Hu Huang^{3,4}

¹ School of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, Hubei 430074, China

² Institute of Systems Engineering, Huazhong University of Science and Technology, Wuhan, Hubei 430074, China

³ The Saban Research Institute, Childrens Hospital Los Angeles, Los Angeles, CA 90027, USA

⁴ University of Southern California University Hospital, Los Angeles, CA 90027, USA

Correspondence should be addressed to Sheng-Hu Huang, shhuang@hsc.usc.edu

Received 1 September 2007; Accepted 23 December 2007

Recommended by Daniel Howard

Nowak's model of the human immunodeficiency virus (HIV) infection has been extensively and successfully used to simulate the interaction between HIV and cytotoxic lymphocyte- (CTL-) mediated immune response. However, this model is not available for hepatitis B virus (HBV) infection. As the enhanced recruitment of virus-specific CTLs into the liver has been an important novel concept in the pathogenesis of hepatitis B, we develop a specific mathematical model analyzing the relationship between HBV and the CTL-mediated immune response, and the indicator of the liver cell damage, alanine aminotransferase (ALT). The stability condition of the complete recovery equilibrium point at which HBV will be eliminated entirely from the body is discussed. A different set of parameters is used in the simulation, and the results show that the model can interpret the wide variety of clinical manifestations of HBV infection. The model suggests that a rapid and vigorous CTL response is required for resolution of HBV infection.

Copyright © 2008 Changjiang Long et al. 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.

1. INTRODUCTION

Infection with the hepatitis B virus (HBV) is a major health problem, which can lead to cirrhosis and primary hepatocellular carcinoma (HCC). More than 2 billion people alive today have been infected by HBV. The population of HBV carrier is about 400 million, of whom 75% are located in Asia. Accordingly, HBV causes approximately 1 million deaths each year worldwide. In China alone, nearly 15 million new infections occur annually, more than 30 million people are chronically infected, and more than 350 thousand of them die each year from cirrhosis and HCC.

In order to find an efficient way to prevent and treat the infection, it is of great importance to understand the immunopathogenesis of HBV. Although molecular techniques have provided fundamental insight into the fine detail of the interaction between HBV and immune system, many biologically important questions are not primarily concerned with the molecular mechanisms of immune recognition but with the population dynamics of the immune response. Mathematical models are always needed to answer these questions.

Studies on humans infected with HIV-1 and macaques infected with simian immunodeficiency virus (SIV) show that cytotoxic lymphocytes (CTLs) are critical in controlling virus replication [1]. Virus mutants of human immunodeficiency virus (HIV) and SIV are able to escape the dominant CTL response and become the major replicating strains in vivo [1]. In contrast to HIV and many other viruses, cell culture systems that allow efficient in vitro infection and passaging of virus are not available for HBV, which is hepatotropic and noncytopathic. Recent studies on HBV pathogenesis in animal models demonstrated that the enhanced recruitment of virus-specific CTLs into the liver cells is critical for the pathogenesis of both HBV infection and hepatocellular carcinoma [2, 3]. The most common mathematical model in HIV infection is presented by Nowak to explain the dynamics of CTL-mediated host immune response to HIV and the pathogenesis of AIDS [4]. Mathematical models, which are not based on CTL-mediated host response, have been proposed for modeling HBV or HCV infection and evaluating the effectiveness of antiviral therapy [5–8]. Even the models describing the interactions between host immune response and

virus were built to explain the mechanism of acute hepatitis [9–11]. However, these models fail to explain the various outcomes of HBV infection [12]. A new mathematical model for dissecting the role of CTL in HBV diseases is needed for the following reasons.

- (1) Being different kinds of viruses, HIV is cytopathic virus and HBV is a noncytopathic virus [12], that is, cells infected by HBV will not be killed by virus directly, cellular function and lifespan of HBV-infected hepatocytes are almost the same as that of the uninfected cells in vitro [13]. The death rate of noncytopathic virus-infected cells in the absence of immunity equals that of uninfected target cells [14]. The lifespan of HBV-infected cells varies greatly in vivo which is mainly due to the strength of the anti-HBV CTL response [15]. CTL will not only kill but also cure the infected hepatocytes by a nonlytic effector mechanism [16, 17]. The effect of CTL response should be considered in the model.
- (2) The non-CTL models ignore the kinetics of hepatocyte replication. Actually, both uninfected and infected hepatocytes can replicate at the same rate [13]. Infected cells are generated not only from normal cells infected by HBV, but also from replication of its own [18, 19].
- (3) In the non-CTL models, the equilibrium abundance of infected cells depends only on the immunological parameters [6]; but in fact the characteristic of HBV also has great influence on the result [12].
- (4) The value of alanine aminotransferase (ALT) in the blood stream is generally taken to be an indicator of the liver cell damage [9]. ALT was not included in the non-CTL models.

2. MATERIALS AND METHODS

2.1. Mathematical models

The model contains six variables, that is, uninfected hepatocytes (X), infected hepatocytes (Y), total host hepatocytes ($N = X + Y$), free virus (V), a CTL response (Z), and ALT. The changes of population over time can be described by a system of differential equations.

The corresponding mathematics equations are

$$\begin{aligned}\frac{dX}{dt} &= F(N)X - d_1X - b_1XV + k_1YZ, \\ \frac{dY}{dt} &= F(N)Y + b_1XV - d_1Y - (k_1 + k_2)YZ, \\ \frac{dV}{dt} &= k_3Y - d_3V, \\ \frac{dZ}{dt} &= (g_4 + k_4YZ) \left(1 - \frac{Z}{Z_{\max}}\right) - d_4Z, \\ \frac{dALT}{dt} &= k_5(d_1X + d_1Y + k_2YZ) - d_5ALT, \\ F(N) &= \frac{d_1}{N^3}, \quad N = X + Y,\end{aligned}$$

$$\begin{aligned}X_0 &= 1, \quad Y_0 = 0, \quad V_0 = 0, \quad Z_0 = \frac{g_4}{d_4}, \\ ALT_0 &= k_5 \frac{d_1}{d_5} d_1, \quad N_0 = 1,\end{aligned}\tag{1}$$

where $F(N)$ is the natural growth rate of hepatocytes. It is a monotonically decreasing function [20]. We took $F(N) = d_1/N^3$ [13]; $F(N) = d_1$ when $N = 1$ (without loss of generality, we take the cell and virus concentrations to be scaled such that in the uninfected system the total cell concentration is $N = 1$ [18, 19]).

Both uninfected and infected hepatocytes replicate at a rate $F(N)$ and die at a rate d_1 , while uninfected ones are infected by virus at a rate b_1XV . The CTL response can activate two different pathways to eliminate a virus, either by killing the infected cells or by eliminating the virus from within the cell without killing it. Infected cells are assumed to be killed by the CTL response at a rate k_2YZ and be cured by the CTL response at a rate k_1YZ . Infected cells produce free virus at a rate k_3Y and free virus particles are removed at a rate d_3V . CTLs proliferation can be described by two terms g_4 and k_4YZ , where g_4 represents antigen-independent proliferation and k_4YZ represents antigen-dependent proliferation. CTLs decay at a rate d_4Z . ALT is generated by the dead hepatocytes at a rate k_5 and decay at a rate d_5 . All the variables and parameters of the above are nonnegative.

2.2. Equilibrium states analysis

There are three possible steady states: Hepatocytes are not infected—the uninfected state, all the hepatocytes are infected—wholly infected state, and the coexisting state—the uninfected and the infected hepatocytes coexist. As these states are too complex to analyze, we only discuss the linear ability of the most concerned state—uninfected state.

As the equation of Z is a logistic model, it will make the expression of the analysis result very complex. To get a meaningful result easy for comparing with the clinical conclusion, we ignore the limitation of Z_{\max} as we only discuss small disturbance to the initial state (the maximum number of specific T-cells can be 10^6 times of its initial number [20]).

As ALT is just an indicator of hepatic injury and do not influence other variables, it is not included in the analysis progress for simplicity.

Then the equations of the system can be rewritten as

$$\begin{aligned}\frac{dX}{dt} &= F(N)X - d_1X - b_1XV + k_1YZ, \\ \frac{dY}{dt} &= F(N)Y + b_1XV - d_1Y - (k_1 + k_2)YZ, \\ \frac{dV}{dt} &= k_3Y - d_3V, \\ \frac{dZ}{dt} &= g_4 + k_4YZ - d_4Z, \\ F(N) &= \frac{d_1}{N^3}, \quad N = X + Y.\end{aligned}\tag{2}$$

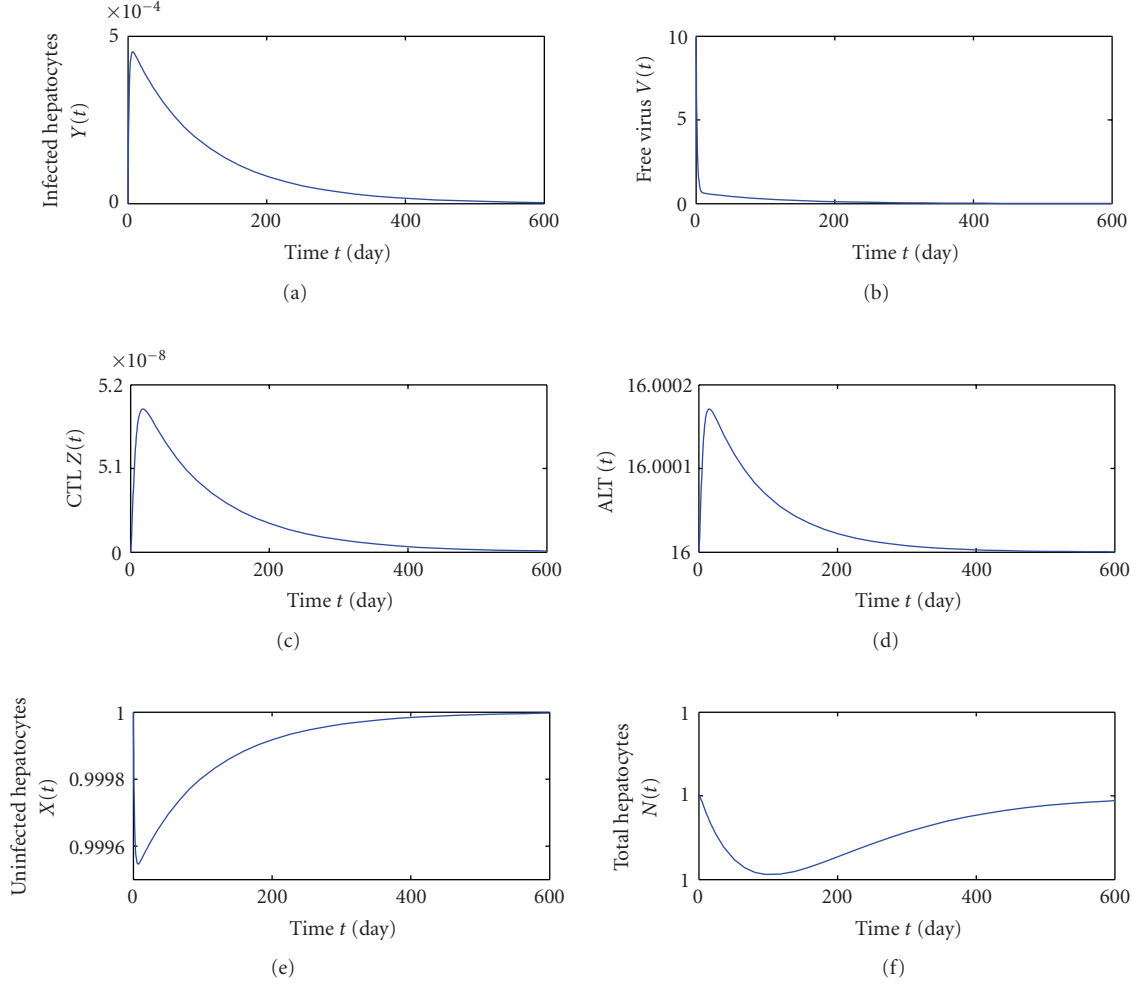


FIGURE 1: Acute hepatitis.

For the uninfected state ($X = 1, Y = 0, V = 0, Z = g_4/d_4$), as it is an equilibrium state, it should satisfy $dX/dt = dY/dt = dV/dt = dZ/dt = 0$, so get the coordinates $(1, 0, 0, g_4/d_4)$. The correspondence Jacobian matrix is

$$\begin{bmatrix} F'(N) & F'(N) + \frac{k_1 g_4}{d_4} & -b_1 & 0 \\ 0 & \frac{-(k_1 + k_2) g_4}{d_4} & b_1 & 0 \\ 0 & k_3 & -d_3 & 0 \\ 0 & \frac{k_4 g_4}{d_4} & 0 & -d_4 \end{bmatrix}. \quad (3)$$

The characteristic equation is

$$(\lambda - F'(N))(\lambda + d_4)(\lambda^2 + (d_3 + \Delta)\lambda + d_3\Delta - b_1k_3) = 0, \quad (4)$$

where

$$\Delta = (k_1 + k_2) \frac{g_4}{d_4},$$

$$\frac{\partial N}{\partial X} = \frac{\partial(X + Y)}{\partial X} = 1; \quad \frac{\partial N}{\partial Y} = \frac{\partial(X + Y)}{\partial Y} = 1,$$

$$\frac{\partial F(N)}{\partial X} = \frac{\partial F(N)}{\partial N} \frac{\partial N}{\partial X} = F'(N), \quad (5)$$

$$\frac{\partial F(N)}{\partial Y} = \frac{\partial F(N)}{\partial N} \frac{\partial N}{\partial Y} = F'(N),$$

$$F'(N) = \frac{\partial F(N)}{\partial N} = \frac{\partial(d_1/N^3)}{\partial N} = \frac{-3d_1}{N^4} = -3d_1.$$

Since $-F'(N) = 3d_1 > 0, d_4 > 0, d_3 > 0, \Delta > 0, d_3 + \Delta > 0$, according to the Routh-Hurwitz criterion [21], if $d_3\Delta - b_1k_3 > 0$, that is,

$$(k_1 + k_2) \frac{g_4}{d_4} > b_1 \frac{k_3}{d_3}, \quad (6)$$

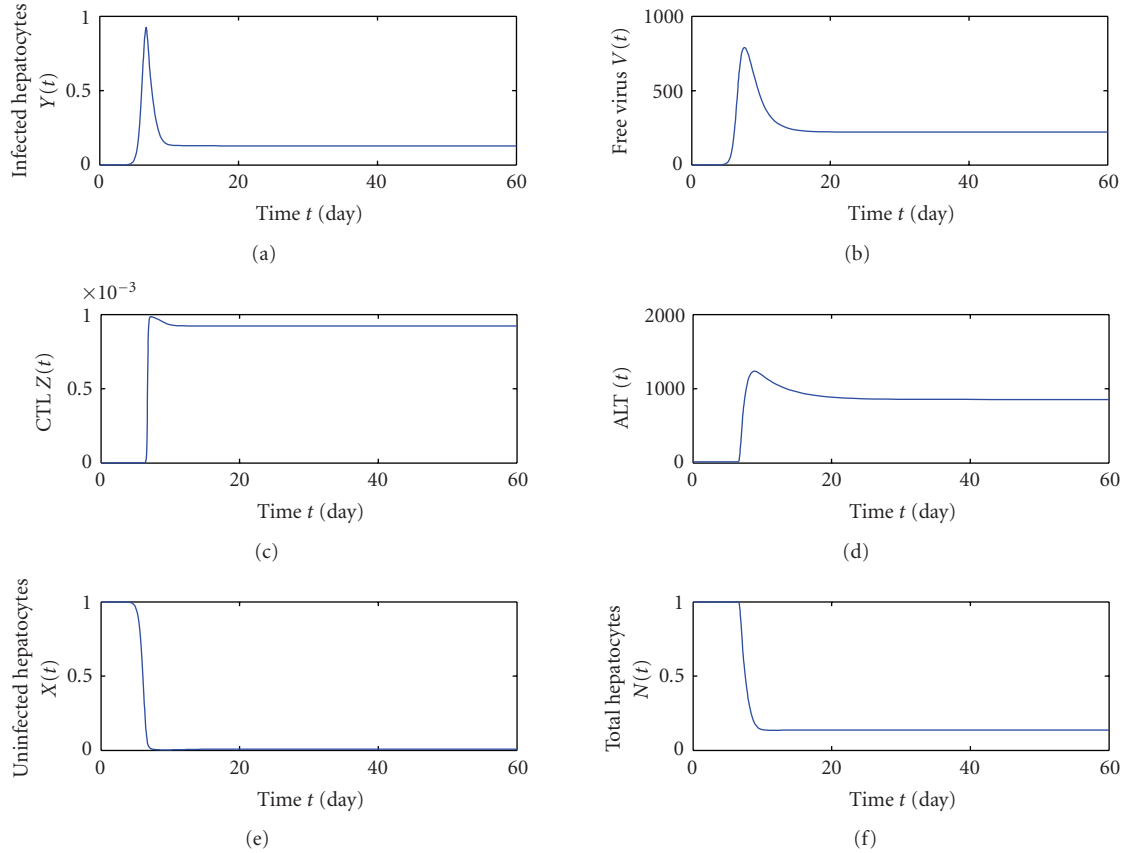


FIGURE 2: Fulminant hepatitis.

there will be linear stability with respect to perturbations in $(1, 0, 0, g_4/d_4)$. The left-hand side of the equation represents the ability of the immune system, k_1 represents the nonlytic ability of CTLs and k_2 represents the lytic ability of CTLs. Also, g_4/d_4 is the initial value of CTLs. The right-hand side of the equation represents the ability of HBV, b_1 represents the infective ability of HBV, k_3 represents the multiplication ability of HBV, and d_3 represents the death rate of HBV. If the left part is bigger than the right part, it means that the immune system is strong enough to eliminate the infection otherwise HBV can invade the body and exist for a long time.

2.3. Simulation

By combining the various results derived in the previous section we can deduce an appropriate parameter set for the simulation of the model.

The parameters (1 time unit = 1 day) are set up as follows: $d_1 = 0.002$ (average life of hepatocyte is about 500 d [13]); $d_3 = 0.58$ (estimated average half-life of free virions is about 1.2 d [22]); $d_4 = 0.2$ (the mean life of CTL is 4–6 d [20]); $d_5 = 0.25$ (average half-life of ALT is between 0.5–5 [13]); $Z_{\max} = 0.001$ there should be no more than 10^8 HBV-specific CTL in the entire body and there are approximately 10^{11} infected hepatocytes in the human liver [23], as we took $N = 1$, so $Z_{\max} = 10^8/10^{11}$; $ALT_0 = 16$ (The normal range for ALT is between 0–40).

3. RESULTS

3.1. Acute hepatitis

HBV can cause acute hepatitis, resulting in short-term inflammation of the liver before the immune system is able to remove the virus from the body. In acutely infected patients who successfully control the virus, the immune response that the patients produce against the viral proteins is polyclonal, multispecific; and the virus is eliminated from the blood and liver entirely. If the maximum damage and the maximum concentration of free virus are low, the disease may come and go without any symptoms, otherwise severe clinical symptoms will be observed.

The parameters during the simulation of acute hepatitis are set up as follows: $d_1 = 0.002$; $b_1 = 3E - 5$; $k_1 = 1E6$; $k_2 = 1E3$; $b_3 = 0.1$; $k_3 = 800$; $d_3 = 0.58$; $g_4 = 1E - 8$; $k_4 = 16$; $d_4 = 0.2$; $k_5 = 2000$; $d_5 = 0.25$; $X_0 = 1$; $Y_0 = 0$; $V_0 = 10$; $Z_0 = 5E - 8$; $ALT_0 = 16$. As the cellular immune response is vigorous and $(k_1 + k_2) (g_4/d_4) = 0.0500 > b_1(k_3/d_3) = 0.0414$, so the immune system is strong enough to eliminate all the infected cells and virus. The number of virus is at its peak at the beginning and then decrease. HBV can only infect a small number of cells. The number of infected cells (4.53×10^{-4}) peaked at 7 days after infection. As the number is so small that the level of serum ALT and the number of total hepatocytes almost

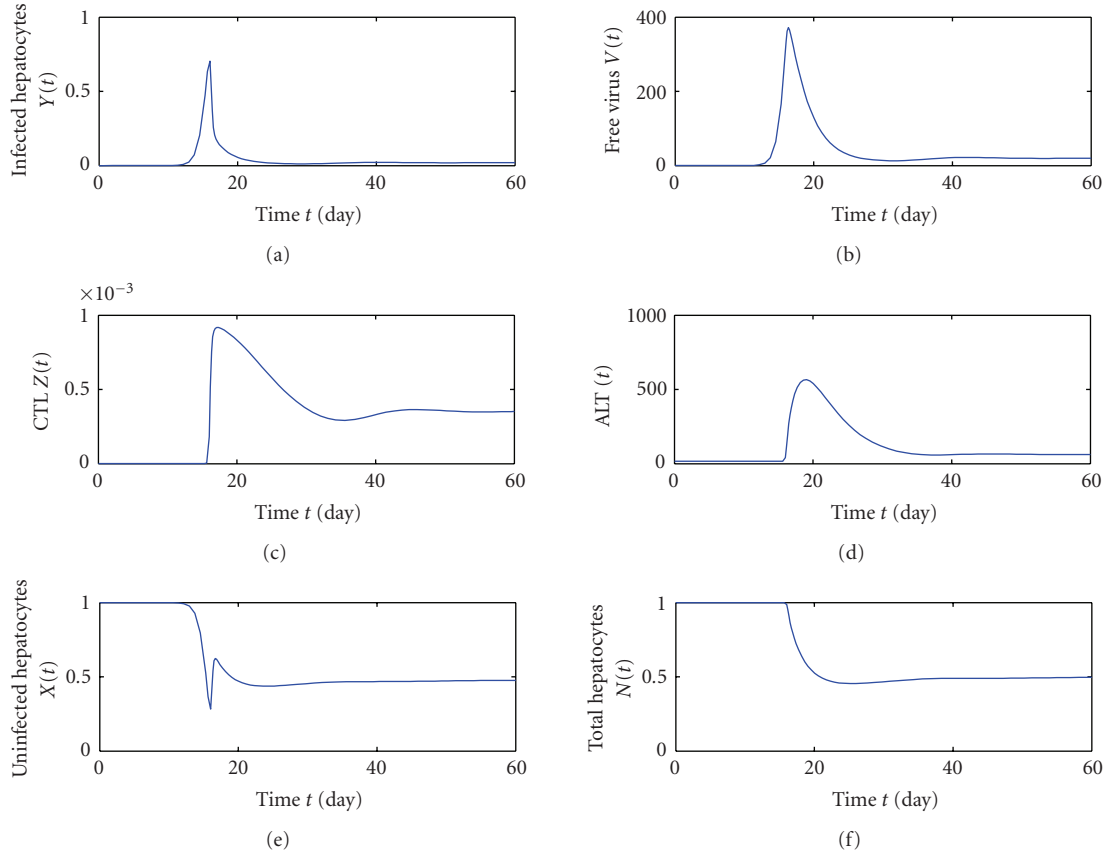


FIGURE 3: Acute-turn-chronic hepatitis.

stay steady when the infected cells are eliminated by the CTLs, viral clearance occur rapidly and efficiently with little evidence of liver disease. Simulation results are shown in Figure 1.

When the $(k_1 + k_2)(g_4/d_4) - b_1(k_3/d_3) < 0$, the cellular immune response is not able to eliminate all the infected hepatocytes, so the virus will be persistent. In this case, if the immune response is strong and many infected cells are killed, it will be chronic hepatitis B. If the immune response is very weak, there will be no symptom. If the virus has a strong infectious capability and the immune response is vigorous but not enough to resolve the infection, it will be fulminant hepatitis.

3.2. Fulminant hepatitis

The parameters during the simulation of fulminant hepatitis are set up as follows: $d_1 = 0.002$; $b_1 = 0.01$; $k_1 = 100$; $k_2 = 900$; $b_3 = 0.1$; $k_3 = 1000$; $d_3 = 0.58$; $g_4 = 1E - 10$; $k_4 = 20$; $d_4 = 0.2$; $k_5 = 2000$; $d_5 = 0.25$; $X_0 = 1$; $Y_0 = 0$; $V_0 = 1E - 5$; $Z_0 = 5E - 8$; $ALT_0 = 16$.

The mortality of fulminant hepatitis is up to 60% ~ 90%. In this case, the virus rapidly replicates and infects every hepatocyte in the liver. Most infected hepatocytes are destructed by the CTLs, resulting in severe liver dysfunction. Simulation results of fulminant hepatitis are shown in Figure 2.

The initiation value of V_0 is set as $10^{-5}(10^6/10^{11})$, as we assume transfusing 100 mL of blood from an inactive carrier whose serum HBV DNA level was about 10^4 copies/mL would deliver $1 \times 10^6(100 \times 10^4)$ particles of HBV into the body.

As shown in Figure 2, hepatitis would outbreak sharply 7 days after the virus entered the body of a host. As the virus has a strong infectious capability ($b_1 = 0.01$) and replicates rapidly ($k_3 = 1000$), 90% of the hepatocytes in the liver will get infected within two days. The total number of HBV particles peaked at 794×10^{11} (equals serum HBV DNA level = 2.6×10^{10} copies/mL). As the cellular immune response is rapidly elicited ($k_4 = 20$), CTLs soon arrive the maximum value. The cytopathic effect of CTLs is more powerful than its noncytopathic effect [$(k_2 = 900) > (k_1 = 100)$]. Most infected cells are killed by CTL directly and this would lead to serious liver necrosis, and the level of ALT starts to rise sharply, it peaks at 1223 at 7 day.

3.3. Acute-turn-chronic hepatitis

The parameters during the simulation of acute-turn-chronic hepatitis are set up as follows: $d_1 = 0.002$; $b_1 = 0.005$; $k_1 = 6000$; $k_2 = 1000$; $b_3 = 0.1$; $k_3 = 600$; $d_3 = 0.58$; $g_4 = 1E - 10$; $k_4 = 16$; $d_4 = 0.2$; $k_5 = 2000$; $d_5 = 0.25$; $X_0 = 1$; $Y_0 = 0$; $V_0 = 1E - 7$; $Z_0 = 5E - 8$; $ALT_0 = 16$.

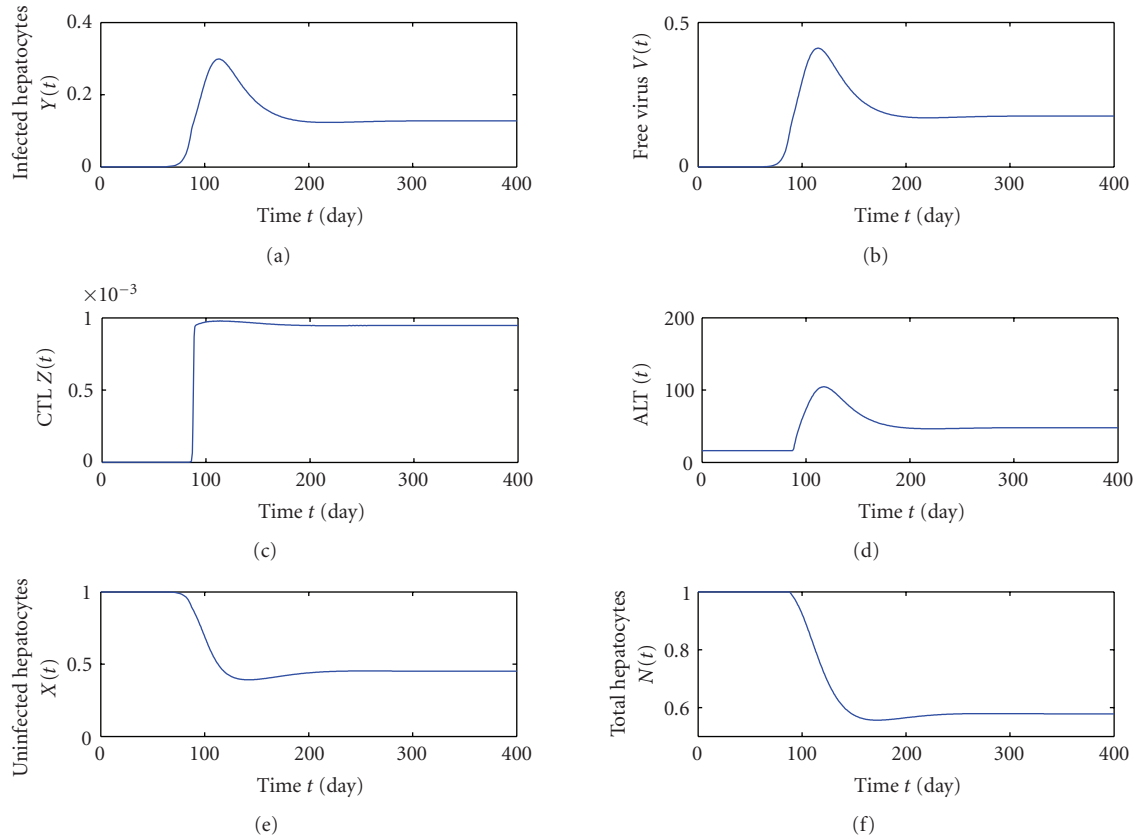


FIGURE 4: Chronic hepatitis.

HBV infection can become a chronic infection when the immune system cannot fight off the virus within six months after infection. It will establish a chronic, lifelong infection in the liver, and will have an enormously increased risk of developing liver cancer. It is well known that the T cell response is much less vigorous in chronically infected patients than it is during acute infection. Simulation results of acute–turn–chronic hepatitis are shown in Figure 3.

The initiation value of V_0 is set as $10^{-7}(10^4/10^{11})$, as we assume transfusing 1 mL of blood from an inactive carrier whose serum HBV DNA level was about 10^4 copies/mL would deliver $1 \times 10^4 = 10^4$ particles of HBV into the body.

The incubation period of hepatitis B caused by the virus or blood transfusions is about 14 to 180 days. As shown in Figure 3, hepatitis would outbreak 16 days after the virus entered the body of a host. Eighty percent of the hepatocytes in the liver would get infected within 16 days, total number of HBV peaked at 371 (equals serum HBV DNA level = 1.2×10^{10} copies/mL). As the cytopathic effect of CTLs is so powerful ($k_2 = 1000$), many infected cells were killed by CTLs, and the level of ALT peaked to 569 at 19 day.

3.4. Chronic hepatitis without acute phase

The parameters during the simulation of chronic hepatitis without acute phase are set up as follows: $d_1 = 0.002$; $b_1 = 0.2$; $k_1 = 100$; $k_2 = 40$; $b_3 = 0.1$; $k_3 = 0.8$; $d_3 = 0.58$; $g_4 =$

$1E-10$; $k_4 = 30$; $d_4 = 0.2$; $k_5 = 2000$; $d_5 = 0.25$; $g_6 = 1E-10$; $X_0 = 1$; $Y_0 = 0$; $V_0 = 1E-8$; $Z_0 = 5E-8$; $ALT_0 = 16$.

Many chronically infected people show little or no clinical signs. The HBV-specific immune response is too weak to eliminate HBV from all infected hepatocytes, but it is strong enough to continuously destroy HBV-infected hepatocytes, maybe resulting in progressive tissue damage and even cancer. Simulation results of chronic hepatitis without acute phase are shown in Figure 4.

The incubation of the Hepatitis B is about 42 to 180 days, average 180 days. The initiation value of V_0 is set as $10^{-8}(10^3/10^{11})$, as we assume that a hypodermic needle carrying HBV-contaminated blood which circulates through the body will spread 10^3 virions. As shown in Figure 4, hepatitis would outbreak 51 days after the virus entered the body. Maximally 35% of the hepatocytes in the liver would get infected, total number of HBV peaked at 0.56 (equals serum HBV DNA level = 1.8×10^7 copies/mL). The level of ALT reaches its peak value (104) at 117 day. The system will arrive its steady state at 175 day, 15% of the hepatocytes in the liver are infected cells, and total number of HBV is 0.24 (equals serum HBV DNA level = 8×10^6 copies/mL) and the ALT level is 48.

3.5. Recurring hepatitis

The parameters during the simulation of recurring hepatitis are set up as follows: $d_1 = 0.002$; $b_1 = 0.0002$; $k_1 = 1000$;

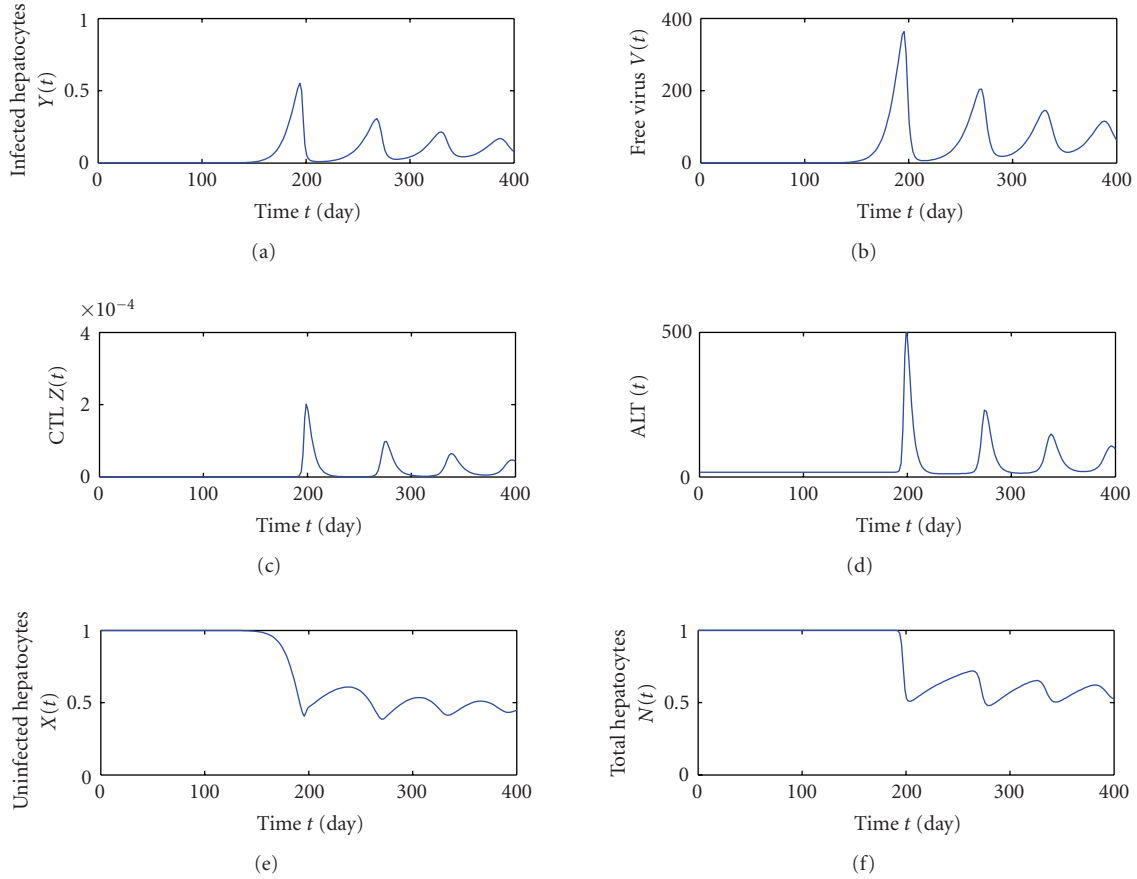


FIGURE 5: Recurring hepatitis.

$k_2 = 2500$; $b_3 = 0.1$; $k_3 = 400$; $d_3 = 0.58$; $g_4 = 1E - 10$; $k_4 = 2.1$; $d_4 = 0.2$; $k_5 = 2000$; $d_5 = 0.25$; $X_0 = 1$; $Y_0 = 0$; $V_0 = 1E - 6$; $Z_0 = 5E - 8$; $ALT_0 = 16$.

When the viral concentration is at its lowest, the patient may be diagnosed as complete recovery; but the virus never completely disappears and an apparent reinfection will soon appear. This recurrence will last for years. The simulation results of recurring hepatitis are shown in Figure 5.

3.6. Asymptomatic chronic hepatitis

The parameters during the simulation of asymptomatic chronic hepatitis are set up as follows: $d_1 = 0.002$; $b_1 = 0.0001$; $k_1 = 1$; $k_2 = 4$; $b_3 = 0.1$; $k_3 = 100$; $d_3 = 0.58$; $g_4 = 1E - 10$; $k_4 = 10$; $d_4 = 0.2$; $k_5 = 2000$; $d_5 = 0.25$; $X_0 = 1$; $Y_0 = 0$; $V_0 = 1E - 7$; $Z_0 = 5E - 8$; $ALT_0 = 16$.

Vertical transmission of HBV results in milder hepatitis in patients with no symptoms. The virus establishes itself in this immunologically immature population and is tolerated so that there will be no adequate immune response. Neonatal tolerance is probably responsible for both the lack of an antiviral immune response and the viral persistence after mother–infant transmission. This is the most common antecedent of persistent HBV infection worldwide. The simulation results of asymptomatic chronic hepatitis are shown in Figure 6.

4. DISCUSSION

The diversity of clinical syndromes and disease manifestations associated with HBV infection strongly suggests that the clinical outcome of this infection is determined by host-virus interactions, especially the quality and vigor of the antiviral immune response produced by the infected host. Most perinatal HBV infections become persistent, presumably due to a suboptimal cellular immune response that destroys some of the infected hepatocytes and does not purge the virus from the remaining infected hepatocytes. It thereby permits the persisting virus to trigger a chronic indolent necroinflammatory liver disease that sets the stage for development of HCC. In contrast, most of the adult onset HBV infections resolve, presumably due to the polyclonal, multispecific cellular immune response that the patients produce against the viral proteins [24].

The qualitative analysis and simulation results suggest the following pattern.

If the cellular immune response is vigorous and satisfied $(k_1 + k_2)g_4/d_4 > b_1k_3/d_3$, the immune system is strong enough to eliminate the infection. Otherwise, chronic hepatitis appears.

If the virus with strong infectious capability (b_1 is large) replicates rapidly (k_3 is large), most hepatocytes in the liver

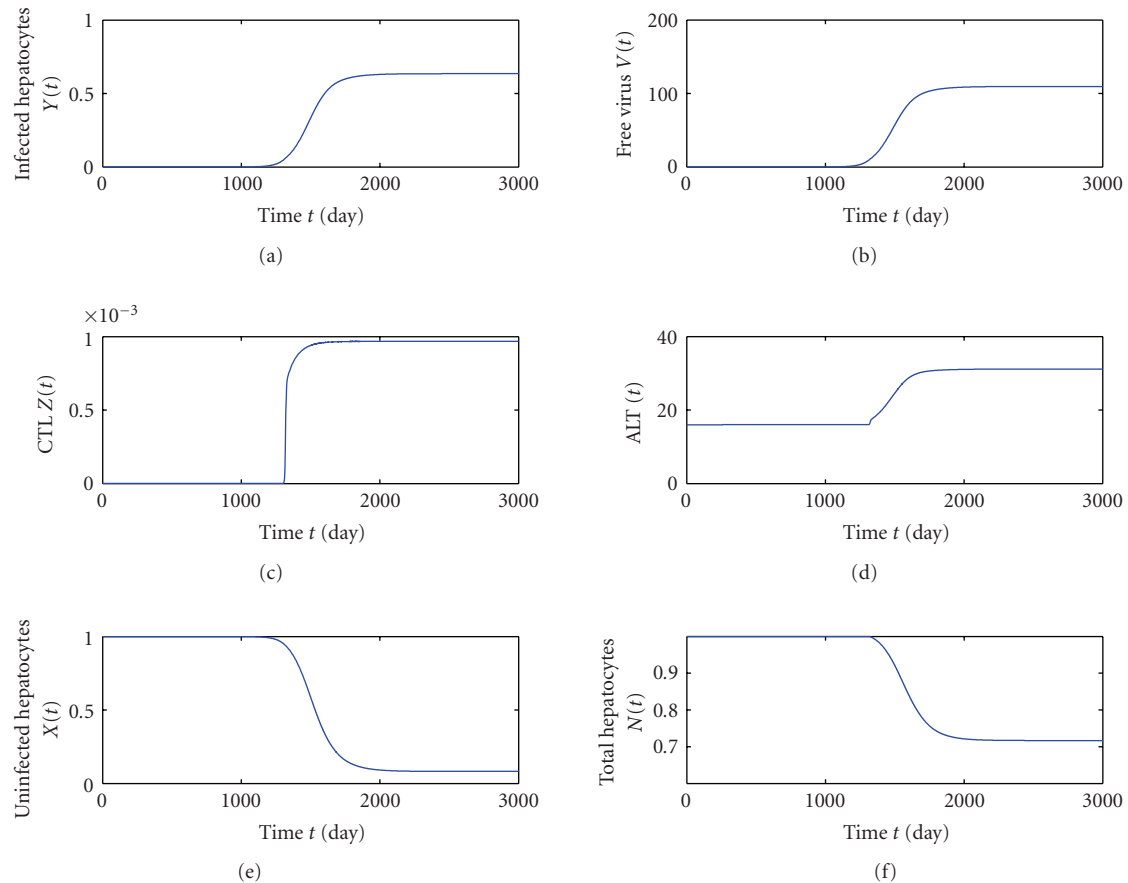


FIGURE 6: Asymptomatic hepatitis.

get infected, resulting in massive liver necrosis due to the strong CTL response. The outcome will be fulminant hepatitis.

If the virus with weak infectious capability replicates slowly, the CTL response to HBV is rapid (k_4 is large) and vigorous ($k_1 + k_2$ is large) enough to eliminate the virus from the blood and liver entirely. The outcome will be acute hepatitis. If the maximum damage and the maximum concentration of free virus are low, the disease may come and go unnoticed, otherwise severe clinical symptoms will be observed.

If the immune system defends against HBV with a weak killing ability ($k_1 + k_2$ is small) and weak CTL level (k_4 is small), the infected cells cannot be cleared out entirely. The outcome will be chronic hepatitis with little or no clinical signs.

This model is able to account for the different outcomes of HBV infection. However, this model can be further improved to explain why many patients with acute hepatitis, whose hepatocytes are almost all infected, can recover, and why many patients with chronic hepatitis B can get rid of HBV when getting older. For the future studies, the model will be applied to fit clinical data for the evaluation of immune states and virus characteristic, thus providing information about the potency of antiviral therapies and guiding the development of optimal drug dosages and regimens.

ACKNOWLEDGMENT

This work was supported by the National Science Foundation of China Grant no. 60774036 (H.Q).

REFERENCES

- [1] P. A. Morel, "Mathematical modeling of immunological reactions," *Frontiers in Bioscience*, vol. 3, no. 3, pp. 338–337, 1998.
- [2] S. M. Ciupe, R. M. Ribeiro, P. W. Nelson, G. Dusheiko, and A. S. Perelson, "The role of cells refractory to productive infection in acute hepatitis B viral dynamics," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 12, pp. 5050–5055, 2007.
- [3] B. Xuli and D. Zhongping, "Advance in viral dynamics of hepatitis B virus infection," *Foreign Medical Science (Section of Virology)*, vol. 11, no. 2, pp. 36–40, 2004.
- [4] M. A. Nowak and C. R. M. Bangham, "Population dynamics of immune responses to persistent viruses," *Science*, vol. 272, no. 5258, pp. 74–79, 1996.
- [5] A. S. Perelson and R. M. Ribeiro, "Hepatitis B virus kinetics and mathematical modeling," *Seminars in Liver Disease*, vol. 24, supplement 1, pp. 11–16, 2004.
- [6] M. A. Nowak, S. Bonhoeffer, A. M. Hill, R. Boehme, H. C. Thomas, and H. Mcdade, "Viral dynamics in hepatitis B virus infection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 9, pp. 4398–4402, 1996.

- [7] R. J. H. Payne, M. A. Nowak, and B. S. Blumberg, "The dynamics of hepatitis B virus infection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 13, pp. 6542–6546, 1996.
- [8] P. Colombatto, L. Civitano, R. Bizzarri, et al., "A multi-phase model of the dynamics of HBV infection in HBeAg-negative patients during pegylated interferon- α 2a, lamivudine and combination therapy," *Antiviral Therapy*, vol. 11, no. 2, pp. 197–212, 2006.
- [9] S. M. Ciupe, R. M. Ribeiro, P. W. Nelson, and A. S. Perelson, "Modeling the mechanisms of acute hepatitis B virus infection," *Journal of Theoretical Biology*, vol. 247, no. 1, pp. 23–35, 2007.
- [10] A. S. Perelson, E. Herrmann, F. Micol, and S. Zeuzem, "New kinetic models for the hepatitis C virus," *Hepatology*, vol. 42, no. 4, pp. 749–754, 2005.
- [11] H. Dahari, M. Major, X. Zhang, et al., "Mathematical modeling of primary hepatitis C infection: noncytolytic clearance and early blockage of virion production," *Gastroenterology*, vol. 128, no. 4, pp. 1056–1066, 2005.
- [12] Y. Ilan, "Immune down regulation leads to up regulation of an antiviral response: a lesson from the hepatitis B virus," *Microbes and Infection*, vol. 4, no. 13, pp. 1317–1326, 2002.
- [13] L. Kangxian, *Hepatitis B Basic Biology and Clinical Science*, People's Medical Publishing House, Beijing, China, 2006.
- [14] D. Wodarz, "Mathematical models of immune effector responses to viral infections: virus control versus the development of pathology," *Journal of Computational and Applied Mathematics*, vol. 184, no. 1, pp. 301–319, 2005.
- [15] M. A. Nowak and M. M. Robert, *Virus Dynamics: Mathematical Principles of Immunology and Virology*, Oxford University Press, New York, NY, USA, 2000.
- [16] A. Bertoletti, M. Maini, and R. Williams, "Role of hepatitis B virus specific cytotoxic T cells in liver damage and viral control," *Antiviral Research*, vol. 60, no. 2, pp. 61–66, 2003.
- [17] L. G. Guidotti, "Pathogenesis of viral hepatitis," *Biological Regulators and Homeostatic Agents*, vol. 17, no. 2, pp. 115–119, 2003.
- [18] R. J. H. Payne, M. A. Nowak, and B. S. Blumberg, "A cellular model to explain the pathogenesis of infection by the hepatitis B virus," *Mathematical Biosciences*, vol. 123, no. 1, pp. 25–58, 1994.
- [19] R. J. H. Payne, M. A. Nowak, and B. S. Blumberg, "Analysis of a cellular model to account for the natural history of infection by the hepatitis B virus and its role in the development of primary hepatocellular carcinoma," *Journal of Theoretical Biology*, vol. 159, no. 2, pp. 215–240, 1992.
- [20] Q. Sheng and D. Chanying, *Nonlinear Models in Immunity*, Shanghai Science & Technology Education Press, Shanghai, China, 1998.
- [21] L. Yun, *Theory for Nonlinear Dynamic System of Modern Mathematics and Its Application*, Communications Press, Beijing, China, 1998.
- [22] J. M. Murray, S. F. Wieland, R. H. Purcell, and F. V. Chisari, "Dynamics of hepatitis B virus clearance in chimpanzees," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 49, pp. 17780–17785, 2005.
- [23] F. V. Chisari, "Viruses, immunity, and cancer: lessons from hepatitis B," *The American Journal of Pathology*, vol. 156, no. 4, pp. 1117–1132, 2000.
- [24] M. Iannacone, G. Sitia, Z. M. Ruggeri, and L. G. Guidotti, "HBV pathogenesis in animal models: recent advances on the role of platelets," *Journal of Hepatology*, vol. 46, no. 4, pp. 719–726, 2007.