A Dynamic Model for the Hepatitis B Virus Infection

Changjiang Long , Huan Qi
Institute of Systems Engineering, Huazhong Univ. of Sci. & Tech.
Wuhan, Hubei, 430074, China

and

Sheng-He Huang
Saban Research Institute of Childrens Hospital Los Angeles and the University of Southern California,
Los Angeles, CA 90027, USA

ABSTRACT

According to the pathogenesis of hepatitis B, a mathematical model describing the relationship between hepatitis B virus(HBV) and the cellular immune response to the infection is built based on Nowak's population dynamics model of immune responses to persistent viruses. The model has two possible equilibrium states: complete recovery (HBV will be eliminated from the body entirely), uninfected and infected hepatocytes coexisting state. The stability condition of each equilibrium points is discussed. Different set of parameters satisfied the different conditions is used in the simulation and the results show that the model can interpret the wide variety of clinical manifestations of infection: acute hepatitis, fulminant hepatitis, acute–turn-chronic hepatitis, chronic hepatitis without acute phase, recurring hepatitis, and so on. Both immunomics and infectomics may be involved in the underlying mechanisms. The model suggests that a rapid and vigorous CTL response is required for resolution of HBV infection.

Keywords: Mathematical Model, Hepatitis B Virus, Immune, Infection, Equilibrium.

1. INTRODUCTION

Hepatitis B virus (HBV) infection is an important health problem worldwide. The natural history and outcome of HBV infection is different. In more than 90% of immunocompetent adults who become infected, the immune response is quite vigorous, resulting in acute infections. Acute infections may be clinically silent or produce acute liver inflammation that leads to serious illness, and to fatal fulminant hepatitis in approximately 0.5% of subjects. However, the vast majority of acutely infected adults recover from the disease, controlling virus replication and developing long-lasting immunity. In 5% of HBV-infected immunocompetent adults, and most cases of vertical transmission of HBV, persistent infection and chronic necroinflammatory liver disease evolve which may eventually lead to liver cirrhosis and hepatocarcinoma. Approximately 4% of the world population is persistently infected by HBV. In order to find an efficient way to prevent and treat the infection, it is of great importance to understand both immunomics infectomics (immunoinfectomics) of HBV infection [1, 2]. New techniques in molecular/cellular biology and immunoinfectomics have been crucial in deepening our understanding of immune processes. Most of these new techniques have allowed the isolation of the process or cell under study so that the results can be readily interpretable. At the present time, however, there is an emerging need to understand the system as it functions as a whole and the language of mathematics is the one best suited for this purpose. Mathematical models can serve several distinct purposes. They can be used to analyze experimental results and provide predictions and suggestions for follow-up experiments, or they can attempt to synthesize existing knowledge and provide a theoretical framework for the interpretation of existing paradigms [3].

As cytotoxic T lymphocytes (CTLs) is though to play a critical role in antiviral defense by attacking virus-infected cells in most virus infections, Nowak presented a population dynamics model to explain the dynamics of host cytotoxic T cell response to infectious agents [4]. As the model is in good agreement with the outcome of HIV infection and can interpret the viral load changes after the initiation of antiviral therapy, it is widely used to evaluate the antiviral effectiveness of drug treatment for HIV. And the model is even used in the assessment of the efficiency of antiviral therapy for HBV and HCV [5]-[7]. But the model fails to explain the various outcomes of HBV infection. Payne and Nowak built a cellular model [8]. They assumed that the liver is comprised of two subsets of hepatocytes that respond contrastingly to infection by the virus and that are in different stages of maturation, the less differentiated cells being referred to as R cells (''resistent'' to viral replication) and the more differentiated as S cells (''susceptible'' to viral replication). The R cells have the capacity to divide, but the S cells do not undergo significant further division and the proportion of S cells in an uninfected liver therefore increases with increasing age. The model can be used to account for the wide variety of clinical manifestations of infection and can explain the observed age dependence of the main different outcomes of the disease. But the model has its shortcomings: there is only two stable steady states: (i) uninfected, with only S cells present; (ii) Chronic Persistent Hepatitis, saturated by infected R cells. As the R cell is thought to be the oval cells [9], saturated by R cells means all the cells in the liver are oval cells. But oval cells do not exist in normal liver tissue and only arise after a stressful stimulus such as a mechanical injury or exposure to a carcinogen [10]. So the second state does not exist in clinical.

Aimed at the above shortcomings of Nowak's model, a modified model is proposed. Qualitative analysis and simulation results show that the new model can account for the wide variety of clinical manifestations of HBV infection.

2. MATHEMATICAL MODEL

The model contains five variables, i.e., uninfected hepatocytes (X), infected hepatocytes (Y), total host hepatocytes (N=X+Y), free virus (V) and a CTL response (Z). The changes of population over time can be described by a system of differential equations. Fig.1. is a schematic representation of this model.

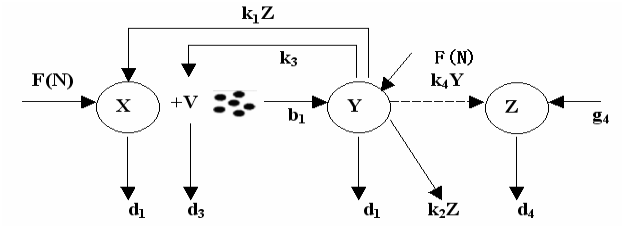

Fig.1. HBV infection model

The corresponding mathematics equations are

$$\begin{aligned} dX/dt &= F(N)X - d_1X - b_1XV + k_1ZY \\ dY/dt &= F(N)Y + b_1XV - d_1Y - (k_1+k_2)ZY \\ dV/dt &= k_3Y - d_3V \\ dZ/dt &= g_4 + k_4YZ - d_4Z \\ N &= X+Y \\ F(N) &= f_1 f_2^2/(f_2^2+N^2) \end{aligned} \quad . \quad (1)$$

where $F(N)$ is the natural growth rate of hepatocyte cells(both infected and uninfected hepatocytes divide at the same rate [11]). It is a monotonically decreasing Hill function [12] and $F(N)=d_1$ 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) [13].

Both uninfected and infected hepatocytes are assured to replicate at rate $F(N)$ and die at rate constant d_1. Infection occurs with rate constant b_1. The model also allows for a component of the death rate of infected cells, k_2Z, due to immune-mediated killing and for noncytolytic clearance of virus from infected cells with rate k_1Z. HBV are produced by infected cells at average rate k_3 per cell and are removed at a rate d_3. 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. g_4 is small. When antigen stimulation is high, we assume $k_4YZ >> g_4$. CTLs decay at rate constant d_4.

3. EQUILIBRIUM POINT ANALYSIS

As the rate of change in the viral concentration will be much faster than that of the cell concentration and we find the V is in direct proportion to Y in the simulation results, so we let $V = k_3Y/d_3$. This will make the qualitatively analysis much easier as the model is reduced. Now the equations can be rewritten as

$$\begin{aligned} dX/dt &= F(N)X - d_1X - b_1k_3YX/d_3 + k_1ZY \\ dY/dt &= F(N)Y + b_1k_3YX/d_3 - d_1Y - (k_1+k_2)ZY \\ dZ/dt &= g_4 + k_4YZ - d_4Z \\ N &= X+Y \\ F(N) &= f_1 f_2^2/(f_2^2+N^2) \end{aligned} \quad . \quad (2)$$

The possible steady states are as follows:

(1) (1，0，g4/d4), (2) ($0, Y_1^*, Z_1^*$) and (3) (X_2^*, Y_2^*, Z_2^*).

We investigate the linear stability by considering small perturbations to the system in the vicinity of the steady state （X^*, Y^*, Z^*） .Let

$X = X^* + x, Y = Y^* + y,$ and $Z = Z^* + z$,

where $x, y, z \to 0$ .Substituting into Eq.(2) and retaining only linear terms, the linearized system can be obtained:

$$\begin{aligned} dx/dt &= (X^*F'(N^*) + F(N^*) - d_1 - b_1k_3Y^*/d_3)x \\ &\quad + [X^*F'(N^*) - b_1k_3X^*/d_3 + k_1Z^*]y + k_1Y^*z \\ dy/dt &= [Y^*F'(N^*) + b_1k_3Y^*/d_3]x + [Y^*F'(N^*) \\ &\quad + F(N^*) + b_1k_3X^*/d_3 - d_1 - (k_1+k_2)Z^*]y - (k_1+k_2)Y^*z \\ dz/dt &= k_4Z^*y + (k_4Y^* - d_4)z \end{aligned} \quad . \quad (3)$$

Where $F'(N^*) = dF(N)/dN\big|_{N=N^*}$.

1) The uninfected state (1，0，g4/d4)

This state satisfies $dX/dt = dY/dt = dZ/dt = 0$, Substituting $X^*=1, Y^*=0, V^*=0, Z^*=d_4/g_4$ into Eq.(3) gives the linearized equations:

$$\begin{aligned} dx/dt &= F'(N^*)x + [F'(N^*) - b_1k_3/d_3 + k_1g_4/d_4]y \\ dy/dt &= (b_1k_3/d_3 - (k_1+k_2)g_4/d_4)y \\ dz/dt &= (k_4g_4/d_4)y - d_4z \end{aligned} \quad . \quad (4)$$

The characteristic equation of (4) is as follows

$$[\lambda - F'(N^*)][\lambda - (b_1k_3/d_3 - (k_1+k_2)g_4/d_4)](\lambda + d_4) = 0 \quad . \quad (5)$$

Since $F'(N) < 0, d_4 > 0$, if $b_1k_3/d_3 < (k_1+k_2)g_4/d_4$, $\lambda_{1,2,3} < 0$ and $x, y, z \to 0$. There will always be stability with respect to perturbations in X, Y, and Z. If the parameters satisfied this situation, HBV will be eliminated from the body entirely soon after the invasion. The larger $(k_1+k_2)g_4/d_4$ is, the less likely that the HBV invasion would be persistent. As k_1+k_2 is the quality index of HBV-specific T cells, the quality of HBV-specific T is the key factor in determining the outcome of HBV infection. $Z^* = g_4/d_4$ is the quantity of the HBV-specific T cells before infection, so vaccination is one of the most important measures in preventing HBV infection. Vaccination can induce immunologic memory, resulting in the increase of memory HBV-specific T cells which are long-lived.

For the case of $b_1k_3/d_3 > (k1+)k_2g_4/d_4$, there will always be instability with respect to perturbations in X ,Y ,and Z. That is to say, if the body is invaded by the HBV and the immune system cannot wipe out the virus, serious problems may appear.

2) All hepatocytes are infected cells （$0, Y_1^*, Z_1^*$）

In this case, $dX/dt = k_1 ZY, as\ k_1, Y, Z > 0, dX/dt > 0.$ $(0, Y_1^*, Z_1^*)$ cannot be an equilibrium point.

3) Uninfected and infected hepatocytes coexisting state (X_2^*, Y_2^*, Z_2^*)

From $dX/dt = dY/dt = dZ/dt = 0$, we can get

$$\begin{aligned} X_2^* &= k_1 d_3 Z_2^* Y_2^* / [d_3 F(N_2^*) - d_1 d_3 - b_1 k_3 Y_2^*] \\ Y_2^* &= (d_4 Z_2^* - g_4)/k_4 \\ Z_2^* &= [F(N_2^*) + b_1 k_3 X_2^*/d_3 - d_1]/(k_1 + k_2) \end{aligned} \quad (6)$$

Substituting (6) into (3) gives the linearized equations

$$\begin{aligned} dx/dt &= [X_2^* F'(N_2^*) - k_1 * Y_2^* Z_2^*]x + (X_2^* F'(N_2^*) + \\ &\quad k_1 Z_2^* - b_1 k_3 X_2^*/d_3) y + k_1 Y_2^* z \\ dy/dt &= [b_1 k_3 Y_2^*/d_3 + Y_2^* F'(N_2^*)]x \\ &\quad + Y_2^* F'(N_2^*) y - (k_1 + k_2) Y_2^* z \\ dz/dt &= k_4 Z_2^* y + (k_4 Y_2^* - d_4) z \end{aligned} \quad (7)$$

The characteristic equation is as follows

$$\lambda^3 + p\lambda^2 + q\lambda + r = 0, \quad (8)$$

where

$$\begin{aligned} p &= -k_4 Y_2^* - F'(N_2^*) X_2^* + k_1 Z_2^* Y_2^* + d_4 - F'(N_2^*) Y_2^* \\ q &= F'(N_2^*)^2 k_4 + [k_3^2 + K_4 F'(N_2^*)] X_2^* Y_2^* - d_4 F'(N_2^*) Y_2^* \\ &\quad + [k_4 k_1 - k_1 F'(N_2^*) + k_2 k_4 + k_1 d_4 - k_1 k_4 Y_2^* \\ &\quad - k_1 F'(N_2^*) Y_2^* - b_1 k_3 k_1 / d_3] Z_2^* Y_2^* \\ r &= -F'(N_2^*) X_2^* k_2 k_4 Y_2^* Z_2^* - b_1^2 k_3 k_4 X_2^* Y_2^{*2}/d_3^2 \\ &\quad + X_2^* Y_2^* b_1^2 k_3^2 d_4 / d_3^2 + k_1 k_4 Y_2^{*3} Z_2^* F'(N_2^*) - Y_2^* Z_2^* b_1 k_3 k_1 d_4 / d_3 \\ &\quad + k_1^2 k_4 Y_2^{*2} Z_2^{*2} - k_1 d_4 F'(N_2^*) Y_2^* Z_2^* - k_1 k_4 F'(N_2^*) X_2^* Z_2^* \\ &\quad - k_1 d_4 Z_2^* Y_2^{*2} F'(N_2^*) + k_1 k_2 k_4 Y_2^{*2} Z_2^{*2}/d_3^2 \end{aligned}$$

When $p > 0, q > 0, r > 0$ and $pq > r$, there are no roots with positive real part [14] .It will be stability with respect to perturbations in (X_2^*, Y_2^*, Z_2^*). In this case, the HBV can invade the body and cause disease. But some times the patient will die before reaching this equilibrium state because of the severe liver dysfunction.

4. SIMULATION

By combining the various conditions 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

f_1=0.04; f_2=1; d_1=0.02(average life span of hepatocyte =50 days) and d_3=0.7(half-life of free virus =1 day).

1) Acute hepatitis

The parameters during the simulation of acute hepatitis are set up as follows

b_1=1.0; k_1=1000; k_2=500; k_3=200;

g_4=0.00003; k_4=1; d_4=0.1; V_0=1e^{-3}.

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 response of CTL to HBV is so rapid and vigorous that 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. Simulation results of acute hepatitis are shown in Fig. 2.

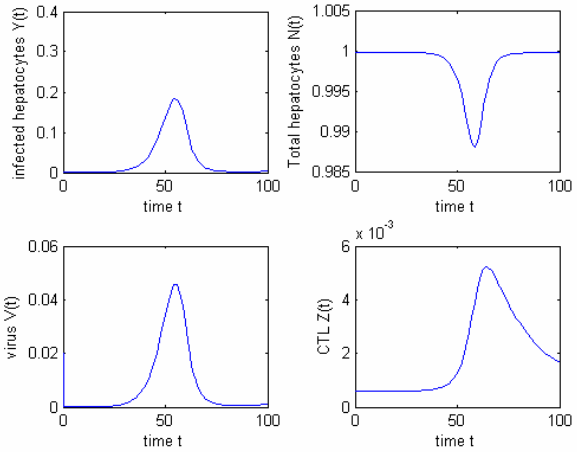

Fig. 2. Acute hepatitis

2) Fulminant hepatitis

The parameters during the simulation of fulminant hepatitis are set up as follows

b_1=10; k_1=50; k_2=1500; k_3=1500;

g_4=0.00001; k_4=0.3; d_4=0.1; V_0=2e^{-2}.

In this case, the virus rapidly replicates and infects almost every hepatocyte cell in the liver. Most infected hepatocytes are destructed due to the vigorous CTL response(k1+k2 is large). Patient with fulminant hepatitis cannot stay at the equilibrium state analyzed in the mathematics model but will die due to the severe liver dysfunction. The mortality of fulminant hepatitis is 60%~90%. Simulation results of fulminant hepatitis are shown in Fig. 3.

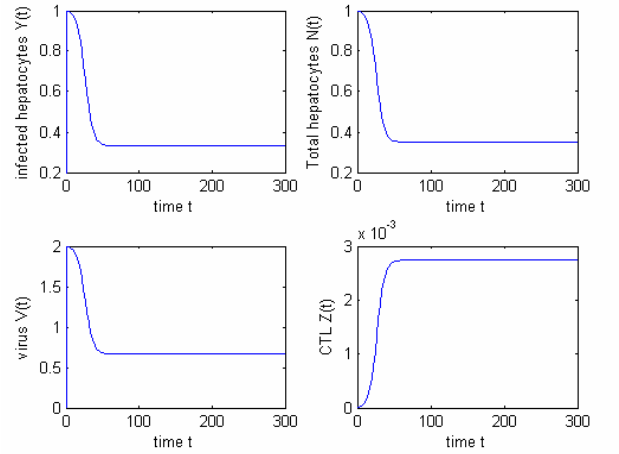

Fig. 3. Fulminant hepatitis

3) Acute–turn-chronic hepatitis

The parameters during the simulation of acute–turn-chronic hepatitis are set up as follows

$$b_1=0.6;\ k_1=50;\ k_2=600;\ k_3=1200;$$

$$g_4=0.00001;\ k_4=0.2;\ d_4=0.1;\ V_0=1e^{-2}.$$

HBV can become a chronic infection when the immune system cannot fight off the hepatitis B 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 CTL 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 Fig. 4.

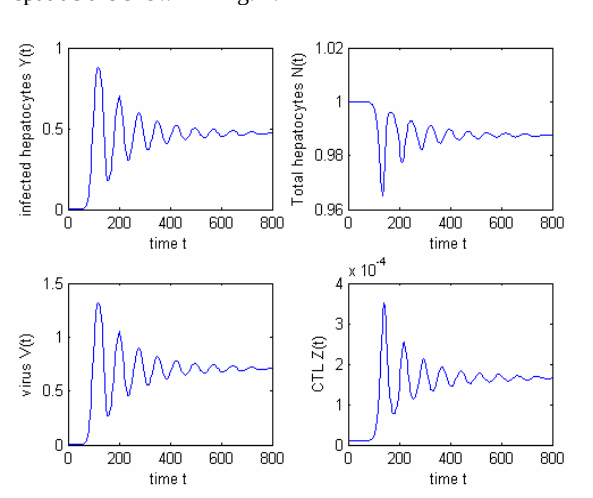

Fig. 4. Acute–turn-chronic hepatitis

4) Chronic hepatitis without acute phase

The parameters during the simulation of chronic hepatitis without acute phase are set up as follows

$$b_1=0.5;\ k_1=100;\ k_2=800;\ k_3=300;$$

$$g_4=0.00001;\ k_4=0.1;\ d_4=0.1;\ V_0=1e^{-2}.$$

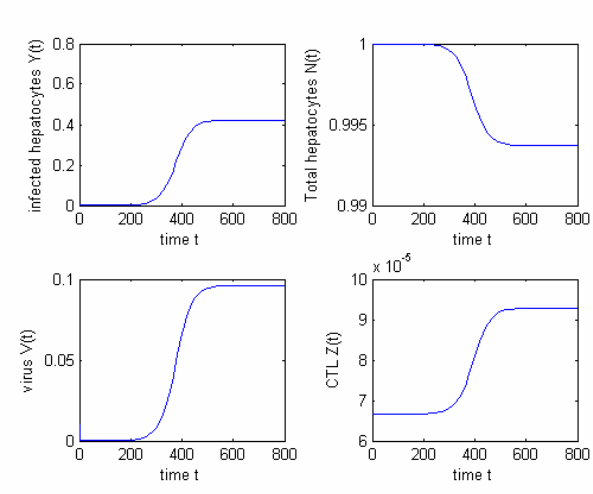

Fig. 5. Chronic hepatitis

Many chronically infected people are asymptomatic and 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 Fig.5.

5) Recurring hepatitis

The parameters during the simulation of Recurring hepatitis are set up as follows

$$b_1=1.0;\ k_1=10;\ k_2=800;\ k_3=800;$$

$$g_4=0.00001;\ k_4=2;\ d_4=0.1;\ V_0=1e^{-2}.$$

The patient may be diagnosed as complete recovery when the viral concentration is at its lowest. 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 Fig. 6.

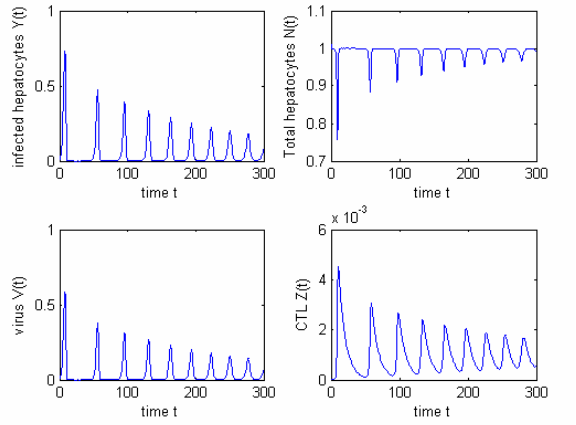

Fig. 6. Recurring hepatitis

6) Asymptomatic chronic hepatitis

The parameters during the simulation of asymptomatic chronic hepatitis are set up as follows

$$b_1=0.01;\ k_1=0;\ k_2=0.001;\ k_3=300;$$

$$g_4=0.00002;\ k_4=0;\ d_4=0.1;\ V_0=2e^{-2};\ X_0=0.98.$$

Vertical transmission of HBV results in milder hepatitis, 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 for 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 Fig. 7.

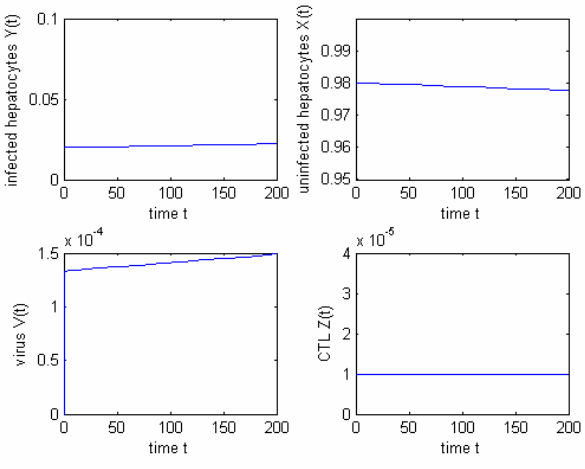

Fig. 7. Asymptomatic hepatitis

5. CONCLUSIONS

According to this model, if the virus has a weak infectious capability (b1 is small) and replicates slowly (k3 is small), the CTL response to HBV is vigorous (k1+k2 is large and $b_1k_3/d_3 < (k_1+k_2)g_4/d_4$) enough to eliminate the virus from the liver entirely and the patient will completely recover after the infection. Otherwise serious problem will be caused.

If the virus with strong infectious capability (b1 is large) replicates rapidly (k3 is large), most hepatocyte cells in the liver will get infected, resulting in massive liver necrosis due to the strong CTL response(k2 is large). The outcome will be fulminant hepatitis.

If the immune system defends against the HBV with a weak ability (k1+k2 is small) and weak CTL level (k4 is small), the infected cells cannot be cleared out entirely. The outcome will be chronic hepatitis.

Though the dynamic behaviors of HBV infection are very complex, this simple model may provide a possible interpretation for the different outcomes of HBV infection. This model can also be applied to fit clinical and immunoinfectomics data for evaluating the interplay between the immune system and virus, thus providing holistic information about the potency of antiviral therapies and guiding development of optimal drug dosages and regimens.

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