

Using Mathematical Model to Depict the Immune Response to Hepatitis B Virus Infection

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Abstract

A simplified mathematical model of immune responds to Hepatitis B Virus (HBV) infection is presented. This focuses on the control of the infection by the interferons, the innate and adaptive immunity. The model was compartmentalized as appropriate and the resulting model equations were solved numerically. A mathematical analysis of the model shows that both disease-free and endemic equilibrium point exist and we derive conditions for their stability. We perform sensitivity analysis on the model parameters, to account for the variability and speed of adaptation.

Keywords: Immune system, Immunity, Immune response, Hepatitis B, Numerical result, Stability analysis, Compartmentalized

1. Introduction

Hepatitis B is a liver infection caused by the Hepatitis B Virus (HBV). It can be a serious disease that can lead to cirrhosis (scarring of the liver) and/or liver cancer. Most people who get the disease recover from it and can never get it again, that is they get permanent immunity. However, about 10% of people who get hepatitis B will go on to have chronic infection (long-term infection) and can pass it on to others (be carriers). The younger a person is when infected, the more likely he or she is to go on to have chronic infection and to develop serious liver disease.

The HBV is spread by direct contact with blood, semen, vaginal and other body fluids of an infected person. Sharing needles to inject drugs or having sex with an infected person can spread the virus. Health care workers who get struck with contaminated needles can also get infected if they are not protected by immunity, such as by immunization or vaccination. Pregnant women who have the virus in their blood can pass it on to their babies at birth (vertical transmission). The virus can also spread by sharing personal items such as toothbrush, razor, or anything else that may have blood on it.

Patients infected with HBV may develop one of two types of anti-HBV immune responses. The first is an effective anti-viral response that suppresses viral growth as the result of both non-specific (innate) as well as specific (adaptive) immunity. After early actions of natural killer (NK) cells, NK T cells and antiviral cytokines, individuals with acute self-limited HBV infection mount a vigorous polyclonal and multi-specific Th and CTL response to epitopes within the HBV-envelope, nucleocapsid and polymerase proteins. The peptides are presented to the T cells by professional antigen-presenting cells (APC) and on the surface of infected hepatocytes in the context of a MHC class I molecule. The response is readily detectable in peripheral blood (Maini et al., 2000; Rehmann et al., 1996; Livingston et al., 1997; Guidotti et al., 1994). Upon recognition of viral peptides CTL acquire the capacity to either cure HBV-infected cells via a non-cytopathic, cytokinemediated inhibition of HBV replication, or to kill them via perforin-Fas ligand and TNF α -mediated death pathways (Rehmann et al., 2000; Ganem et al., 1982; Guidotti et al., 1999; Heise et al., 1999). Both effector functions have been observed during resolution of acute HBV and this type 1 T-cell (Th1) response persists even after clinical recovery (Guidotti et al., 2000). In contrast, the second type of anti-HBV immune response is an ineffective one. The HBV-specific immune response is weak, antigenically restricted or undetectable in the blood of chronically infected patients, although individual HBV-specific T-cell clones have been isolated and expanded from liver biopsies (Barnaba et

al., 1989; Ferrari et al., 1987). As HBV is considered a non-cytopathic virus and the degree of intrahepatic inflammatory leukocytic infiltrate is regarded as the histological hallmark of the severity of chronic hepatitis B, it has been postulated that the HBV-specific immune response is too weak to eliminate HBV from all infected hepatocytes, but sufficiently strong to continuously destroy HBV-infected hepatocytes and to induce chronic inflammatory liver disease in persistently infected individuals.

In this paper we construct a simplified, biologically justified, mathematical model of the dynamics of HBV infection and the human immune response to such infection. We focus on three important components of the immune response; the interferon and cellular components of innate immunity and the adaptive immunity. All of these have the same goal of limiting the concentration of the virus and the damage to the system. They achieve this goal using different strategies: interferon immunity by removing the substrate that the virus needs for reproduction (i.e., the healthy cells), cellular immunity by removing the source of new viruses (i.e., the infected cells), and adaptive immunity by lowering the effective concentration of the virus.

2. Mathematical Model Formulation

We note that a number of assumptions in the model are strong simplifications of our knowledge of immune physiology.

1. We assume that the system is healthy, thus free of all infection such as HIV, Influenza, etc. We now introduce HBV and looked at the dynamics.
2. The populations of cells and virus are assumed to be uniformly distributed over the system at all times.
3. It is also assumed that time rate of change of any model variable is determined by the present value of all variables.
4. We do not account for the intermediate steps in the production of effector cells and plasma cells such as Th1 and Th2 helper cells and B-cells.
5. We do not consider time delays in the reproduction of cellular components.

For the model of human immune response against HBV infection, we consider a simplified model of population-dynamics type which consists of the following interactions (see Figure 1)(Baris et al., 1998): The liver cells are assumed to be in one of four possible states: healthy (H), infected (I), dead (D), or resistant (R) to infection. The total number of liver cells (i.e., $H + I + D + R$) is assumed constant. The virus particles (V) interact with healthy cells and infect them. Infected cells release new virus particles upon their death. Proliferation of healthy cells causes regeneration and decrease in the proportion of dead cells. Dead cells stimulate the activation of APC (M). APC stimulate the production of interferon α and β (F) that interact with healthy cells and convert them to a resistant state. APC also stimulate the proliferation of effector cells (E) that destroy infected cells. Finally, they stimulate the production of plasma cells (P) which, in turn, produce antibodies (A) that neutralize (kills) virus. This neutralization is modulated by the antigenic compatibility (S) between virus and antibodies currently produced by the organism. S quantifies the affinity between antibodies and virus. These interactions are used in the construction of a system of 10-dimensional ordinary differential equations describing the dynamics of the main variables, which correspond to the components of the immune response shown in figure 1.

$$\frac{dV}{dt} = \alpha I - \varepsilon SAV - \theta HV - \lambda V \quad (1)$$

$$\frac{dH}{dt} = \pi D(H + R) + \sigma R - \varphi VH - \beta FH \quad (2)$$

$$\frac{dI}{dt} = \varphi VH - \mu EI - \tau I \quad (3)$$

$$\frac{dM}{dt} = (\vartheta D + \chi V)(1 - M) - \gamma M \quad (4)$$

$$\frac{dF}{dt} = \psi M + \delta I - \eta HF - \xi F \quad (5)$$

$$\frac{dR}{dt} = \beta FH - \sigma R \quad (6)$$

$$\frac{dE}{dt} = \varepsilon ME - \rho IE + \omega(1 - E) \quad (7)$$

$$\frac{dP}{dt} = \phi MP + \kappa(1 - P) \quad (8)$$

$$\frac{dA}{dt} = \varrho P - \varepsilon SAV - \zeta A \quad (9)$$

$$\frac{dS}{dt} = rP(1 - S) \quad (10)$$

where

$$D = 1 - H - R - I \tag{11}$$

The variable D serves as a marker for tissue damage (Hayden et al., 1998) and an indicator of the severity of disease. The system (1)-(11) is nondimensionless. The nondimensionless here means that, since we do not know the actual values of the variable, we assume these values to be in proportions.

The interactions are based on clonal selection theory, mass-action kinetics, characteristics of interactions and the birth-death balances of populations of cells and molecules.

2.1 Stability analysis

Equilibrium of the model

Let Eq(V*, H*, I*, M*, F*, R*, E*, P*, A*, S*) be the equilibrium points of the system described by equations (1)-(10). At equilibrium, the LHS of the ten equations constituting the system of equation are zeros, we have

$$\frac{dV}{dt} = \frac{dH}{dt} = \frac{dI}{dt} = \frac{dM}{dt} = \frac{dF}{dt} = \frac{dR}{dt} = \frac{dE}{dt} = \frac{dP}{dt} = \frac{dA}{dt} = \frac{dS}{dt} = 0$$

Hence, the system of equation becomes:

$$\left. \begin{aligned} \alpha I - \varepsilon SAV - \theta HV - \lambda V &= 0 \\ \pi D(H + R) + \sigma R - \varphi VH - \beta FH &= 0 \\ \varphi VH - \mu EI - \tau I &= 0 \\ (\theta D + \chi V)(1 - M) - \gamma M &= 0 \\ \psi M + \delta I - \eta HF - \xi F &= 0 \\ \beta FH - \sigma R &= 0 \\ \varepsilon ME - \rho IE + \omega(1 - E) &= 0 \\ \phi MP + \kappa(1 - P) &= 0 \\ \varrho P - \varepsilon SAV - \zeta A &= 0 \\ rP(1 - S) &= 0 \end{aligned} \right\} \tag{12}$$

Clearly, at the disease-free environment, $V = I = M = F = R = E = P = A = S = 0$ and $H = 1$. So, the disease-free equilibrium is (0, 1, 0, 0, 0, 0, 0, 0, 0, 0). However, for the endemic equilibrium, we solve equation (12) for V, H, I, M, F, R, E, P, A and S respectively. This gives

$$\begin{aligned} V &= \frac{\alpha I}{\varepsilon SA + \theta H + \lambda} = V^* & H &= \frac{\pi DR + \sigma R}{\varphi V + \beta F - \pi D} = H^* \\ I &= \frac{\varphi VH}{\mu E + \tau} = I^* & M &= \frac{\theta D + \lambda V}{\theta D + \lambda V + \delta} = M^* \\ F &= \frac{\psi M - \delta I}{\eta H + \xi} = F^* & R &= \frac{\beta FH}{\sigma} = R^* \\ E &= \frac{\omega}{\rho I + \omega - \varepsilon M} = E^* & P &= \frac{\kappa}{\kappa - \phi M} = P^* \\ A &= \frac{\varrho P}{\varepsilon S V - \zeta} = A^* & S &= \frac{rP}{rP} = 1 = S^* \end{aligned}$$

Thus, we can take our endemic equilibrium as (V*, H*, I*, M*, F*, R*, E*, P*, A*, S*). An analysis of the local stability of each of the two equilibriums enables us to identify condition under which a behavior of HBV infection can be established. The local stability may be determined first by linearizing the system of equation and taking the eigenvalues of the Jacobian matrix. The Jacobian of the HBV model is in equation (13) below:

$$J = \begin{pmatrix} J_{1,1} & J_{1,2} & J_{1,3} & 0 & 0 & 0 & 0 & 0 & 0 & J_{1,10} \\ J_{2,1} & J_{2,2} & 0 & 0 & J_{2,5} & J_{2,6} & 0 & 0 & 0 & 0 \\ J_{3,1} & J_{3,2} & J_{3,3} & 0 & 0 & 0 & J_{3,7} & 0 & 0 & 0 \\ J_{4,1} & 0 & 0 & J_{4,4} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & J_{5,2} & J_{5,3} & J_{5,4} & J_{5,5} & 0 & 0 & 0 & 0 & 0 \\ 0 & J_{6,2} & 0 & 0 & J_{6,5} & J_{6,6} & 0 & 0 & 0 & 0 \\ 0 & 0 & J_{7,3} & J_{7,4} & 0 & 0 & J_{7,7} & 0 & 0 & 0 \\ 0 & 0 & 0 & J_{8,4} & 0 & 0 & 0 & J_{8,8} & 0 & 0 \\ J_{9,1} & 0 & 0 & 0 & 0 & 0 & 0 & J_{9,8} & J_{9,9} & J_{9,10} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{10,8} & 0 & J_{10,10} \end{pmatrix} \tag{13}$$

$$\begin{array}{ll}
 J_{1,1} = -\varepsilon SA - \theta H - \lambda & J_{5,4} = \psi \\
 J_{1,2} = -\theta V & J_{5,5} = -\eta H - \xi \\
 J_{1,3} = \alpha & J_{6,2} = \beta F \\
 J_{1,10} = -\varepsilon AV & J_{6,5} = \beta H \\
 J_{2,1} = -\varphi H & J_{6,6} = -\sigma \\
 J_{2,2} = \pi D - \varphi - \beta F & J_{7,3} = -\rho E \\
 J_{2,5} = -\beta H & J_{7,4} = \epsilon E \\
 J_{2,6} = \pi D + \sigma & J_{7,7} = \epsilon M - \rho I - \omega \\
 J_{3,1} = \varphi H & J_{8,4} = \phi P \\
 J_{3,2} = \varphi V & J_{8,8} = \phi P - \kappa \\
 J_{3,3} = -\mu E - \tau & J_{9,1} = -\varepsilon SA \\
 J_{3,7} = -\mu I & J_{9,8} = \varrho \\
 J_{4,1} = \chi - \chi M & J_{9,9} = -\varepsilon SV - \zeta \\
 J_{4,4} = \vartheta D - \chi V - \sigma & J_{9,10} = -\varepsilon AV \\
 J_{5,2} = -\eta F & J_{10,8} = r - rS \\
 J_{5,3} = \delta & J_{10,10} = -rP
 \end{array}$$

with

At the disease-free equilibrium, (0, 1, 0, 0, 0, 0, 0, 0, 0, 0) the Jacobian matrix becomes

$$J^0 = \begin{pmatrix}
 -\theta - \lambda & 0 & \alpha & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 -\varphi & \pi D - \varphi & 0 & 0 & 0 & \pi D + \sigma & 0 & 0 & 0 & 0 \\
 \varphi & 0 & -\tau & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 \chi & 0 & 0 & \vartheta D - \sigma & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & \delta & \psi & -\eta - \xi & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & \beta & -\sigma & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & \omega & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\kappa & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \varrho & -\zeta \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & r & 0
 \end{pmatrix}$$

The eigenvalues of the Jacobian matrix J^0 can be determined by solving root of the characteristic equation

$$|J^0 - aI| = 0$$

$$\begin{vmatrix}
 -\theta - \lambda - a & 0 & \alpha & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 -\varphi & \pi D - \varphi - a & 0 & 0 & 0 & \pi D + \sigma & 0 & 0 & 0 & 0 \\
 \varphi & 0 & -\tau - a & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 \chi & 0 & 0 & \vartheta D - \sigma - a & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & \delta & \psi & -\eta - \xi - a & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & \beta & -\sigma - a & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & \omega - a & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\kappa - a & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \varrho & -\zeta - a \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & r & -a
 \end{vmatrix} = 0$$

Hence the eigenvalues are $(-\lambda, \pi D - \varphi, -\tau, \vartheta D - \sigma, -\eta - \xi, -\sigma, -\omega, -\kappa, -\zeta, 0)$. We admits that the eigenvalues, are all real and negative iff $\pi D < 0$ and $\vartheta D < 0$, and hence the fixed point is asymptotically stable. We find that, with the exception of a small number of cases, the system remains stable under perturbations of the parameters of the system.

Similarly, for the endemic equilibrium $(V^*, H^*, I^*, M^*, F^*, R^*, E^*, P^*, A^*, S^*)$. We form an associated Jacobian matrix J^* and obtaining the eigenvalues as usual from $|J^* - aI| = 0$. Results in characteristics polynomial of the form $a^{10} + b_1 a^9 + b_2 a^8 + \dots + b_9 a^1 + b_{10} = 0$ where b_1, b_2, \dots, b_{10} depend on the various combination of the model parameter values. In this case the ten eigenvalues could be negative, positive, zeros, or any combination of the three alternatives. Thus, the endemic equilibrium could be stable, unstable, or saddle.

3. Numerical Results

Simulations

The simulations were conducted using MATLAB program. We take or derive all parameters from the literature; the time courses of variables were obtained by numerical integration using parameters provided in Table 1. Model parameters were

adjusted so that the response of the naive host to the standard initial conditions satisfies the following criteria, extracted from available experimental and clinical data (Bocharov et al., 1994).

Standard Behavior

The standard behavior describes the course of infection in a naive host. We assume that initially the host has no dead, infected or resistant cells, no interferon molecules, and no activated APC (i.e., $H(0) = 0.59$, $I(0) = 0$, $M(0) = 0$, $F(0) = 0$, $R(0) = 0$). The initial levels of effectors, plasma cells, and antibodies are assumed to be at this values (i.e., $E(0) = 0.1$, $P(0) = 0.1$, $A(0) = 0.1$). In a naive host, we assume that $S(0) = 0.1$ which corresponds to a relatively low compatibility with the virus strain, that may have resulted from previous exposure to HBV and subsequent genetic drift. In the typical course of acute HBV Infection, the initial concentration of aerosol delivered virus particles that the host receives is about 106 particle per ml on day 0, corresponding to $V(0) = 0.01$ in our dimensionless system.

Interferon response comes into play once the virus peaks at day 3 making most of the cells resistant to infection. Interferon level is increased by 280 fold peaking approximately at day 3. Plasma cells are produced after 4 days peaking at 7 days, before virus-specific antibodies are detectable, in accord with empirical observations (Ada et al., 1986). Antibody production by plasma cells begins at day 4. There is a $11.8 * 10^8$ fold increase in the amount of antibodies when the adaptive immune response comes into play to remove all viral particles and generate immune memory. Furthermore, antigenic compatibility is increasing monotonically starting right after when the adaptive immunity is activated (after day 3) and the antibodies are capable of inhibiting viral particles with 80% probability after 20 day of infection (Tamura and Kutara, 2004).

From fig. 1 (a). After a time lag of 2 days post-infection the virus begin to replicate in the system. From days 2 to 3 the production rate of viral particle by the infected cell break sharply to a maximum level of about 270 cells on day 3. Between days 3 and 20 nearly all viral cells are neutralized by specific antibodies and some also die out. The model indicates that the number of viral particle declines from 270 cells on day 3 of the immune response.(b) The healthy cell gradually increase from day 0 of no infection. After a time lag of 1 day post-infection, the cells decline exponentially to 0 by days 2 and 3 when the healthy cells loses their resistance to infection. After day 3 the cell increases exponentially when there is a transition of the healthy cells into resistant cells by the interferons.

In fig. 2 (c). After a time lag of 1 day post-infection the infected begin to replicate in the system. From days 1 to 3 the infected cell break sharply to a maximum level of about 0.8 cells on day 2. Between days 3 and 20 nearly all infected cells are neutralized by specific antibodies and some also die out. The model indicates that the number of viral particle declines from 0.8 cells on day 3 of the immune response. (d) The APC act as signal sensor. Upon the death of some infected cell, the APC is activated by day 1 and increase exponentially by day 1 and so doing it stimulate the interferon immunity, the innate and adaptive immunity when it peak at 0.9 by day 3 and then gradually decline exponentially by days 3 to 7 when the virus is in control.

From fig. 3 (e) and (f). The interferon is stimulated by APC by day 1 and increase exponentially by day 1 and peak at 280 by day 3 and then gradually decline exponentially by days 3 to 7 while doing this there is a transition of healthy cells to resistant cells which also increase exponentially by day 3 and peak at 0.24 by day 5 and then gradually decline exponentially by days 5 to 10 when the virus is in control.

From fig. 4 (g). Effector cells are stimulated by APC, appears around day 4 post-infection reach a peak of $2.1 * 10^5$ by day 6 and decline exponentially. (h) Plasma cell are stimulated by APC, migrate into the infected tissues much faster than their proliferation, appears around day 4 post-infection reach a peak of $17.8 * 10^8$ by day 7 and decline exponentially.

In fig. 5 (i). Antibodies appears around day 4 post-infection reach a peak of $11.5 * 10^8$ by day 9 and then decline exponentially at rate of ζ (rate constant of natural death of antibodies). (j) This indicates a calculation with an increasing binding affinity of the antibody and the virus from days 0 and 2.

3.1 Sensitivity analysis

Sensitivity analysis is used to determine how sensitive a model is to changes in the value of the parameters of the model and to changes in the structure of the model. In this paper, we focus on parameter sensitivity. Parameter sensitivity is usually performed as a series of tests in which the modeler sets different parameter values to see how a change in the parameter causes a change in the dynamic behavior of the system.

Sensitivity to interferon response

The parameters ψ and β characterize the interferon production rate constant and the rate constant of induction of resistant state in cells, respectively. If ψ increased or lowered from its standard value, disease always develops for standard values of $V(0)$ and $S(0)$. However, when β is high, the host remains asymptotic. Damage increases if either ψ or β is decreased. Very low values of ψ or β result in excessive damage (over 50%) which may presumably lead to secondary infections or death (Iwasaki et al., 1977). When the interferon production rate constant is two times bigger than the baseline value (i.e., when $\psi=5,000$), then the host remains contagious for about 3-5 days. When this rate is two times less than the baseline

(i.e., when $\psi=1,250$) then the contagious period is about 2-3 days. So, the difference in the length of infectious period is significant for various levels of innate immune response.

Even in the absence of an innate response (when $\psi=0$ and $\beta=0$), the disease is eventually healed by the adaptive immune response and the organism will approach the healthy state.

Sensitivity to cellular component of innate immunity

The parameters ϵ and μ stand for the rate constant of production of effector cells and rate constant of removal of infected cells by effectors, respectively. For sufficiently large ϵ or μ , the host is able to clear the disease without symptoms and typical disease conditions, given the standard initial immunity and standard initial amount of the virus. At low values of ϵ or μ , the symptoms last longer. When ϵ is high, the resulting maximum damage, is large and may result in death. On the other hand, when μ is high, we observe lower damage of cells. Even under a significant decrease in μ , maximum damage will stay under 50% and hence a decrease in μ has no effect on the mortality.

Even in the absence of a cellular response (when $\epsilon=0$ and $\mu=0$), virus is eventually cleared by the innate and adaptive immune responses and the organism will approach the healthy state.

Sensitivity to adaptive response

Activation of adaptive immune response is slower than activation of cellular and interferon components of innate immunity. The parameters ϕ , ρ and ϵ stand for the plasma cell production rate constant, antibody production rate constant and the rate constant of neutralization of HBV by antibodies. For sufficiently large ϕ , ρ or ϵ , the host is able to clear infection without symptoms. The duration of illness does not depend on ϕ , ρ or ϵ . Damage is lower with higher ρ , while damage is insensitive to the two other rate constants. Variations in ϕ , ρ or ϵ never result in excessive damage. With higher ρ , the contagious period is significantly shorter.

In summary, ϵ only affects the onset of the disease, while ϕ affects only virus shedding at the peak. The system is much more sensitive to the ρ .

4. Discussion

We derived and analyzed a mathematical model to better understand the immune response to HBV infection. We used this model to compare strategies for HBV control for two representative areas which include innate and adaptive immunity.

Mathematically, we modeled the immune response to HBV as a 10 - dimensional system of ordinary differential equations. We first showed the existence of the equilibrium point, thus disease-free and endemic. The equilibrium point with no virus, $(0, 1, 0, 0, 0, 0, 0, 0, 0, 0)$, is locally asymptotically stable.

Analysis of the adaptive immune response revealed that whenever there is sufficient antibody response with enough specificity, the dynamics will restore health, irrespective of the intensity of the innate responses and of the trajectory followed by the disease. However, if memory cells cannot produce sufficiently compatible antibodies against the HBV particles initially (very low $S(0)$) or cannot improve the antigenic compatibility sufficiently rapidly (S is not increasing during the disease), there is transition of the system to a chronic state.

5. Conclusion

The resulting model equations were solved numerically and the results were presented graphically based on our simulations. Our results show that although each component of innate and adaptive immune response contributes to the recovery of HBV infection, the simulations suggest that, in the absence of one component of innate immunity, the remaining two defense mechanisms are sufficient for viral clearance. For example, when cellular component are not involved in viral clearance, antibodies (sufficient in the amount and affinity) on their own can mediate clearance of hepatitis B (Scherle et al., 1992). The cellular response can also be sufficient to clear the HBV infection from an individual (Asquith et al., 2003). In the absence of adaptive immunity, the viral load is brought down to very low levels, although not completely cleared, which is supported by experiments showing that in some circumstances antibody response is necessary to clear the infection (Iwasaki et al., 1977). For example, in nude mice without antibodies the viral particles survive with chronic infection (Scherle et al., 1992). After transferring T helper cells into the infected mice that promotes antibody response, the disease is completely cleared (Iwasaki et al., 1977; Scherle et al., 1992). Therefore, one can conclude that innate defense mechanisms are not capable of curing the disease on their own in the absence of antibody response, and can only reduce the disease to a chronic state. Most importantly, we also showed that the disease-free equilibrium is stable while the endemic equilibrium may or may not be stable depending on the various values of the model parameters.

References

- Ada, G.L., Jones, P.D. (1986). The immune response to influenza infection. *Curr. Top. Microbiol. Immunol.*, 128, 1-54.
- Asquith B., Bangham C. R. (2003). An introduction to lymphocyte and viral dynamics: the power and limitations of mathematical analysis. *Proc. Biol. Sci.*, 720, 1651-1657.

- Baris H. (2007). Mathematical Modeling Of Virus Dynamics In Immunology. *J. Immunol.*, 144, 8-19.
- Barnaba V., Franco A., Alberti A., Balsano C., Benvenuto R., Balsano F. (1989). Recognition of hepatitis B virus envelope proteins by liver-infiltrating T lymphocytes in chronic HBV infection. *J. Immunol.*, 143, 2650-2655.
- Bocharov, G.A., Romanyukha, A.A. (1994). Mathematical model of antiviral immune response.III. Influenza A virus infection. *J. Theor. Biol.*, 167, 323-360
- Ferrari C., Penna A., Giuberti T. (1987). Intrahepatic, nucleocapsid antigen-specific T cells in chronic active hepatitis B. *J. Immunol.*, 139, 2050-2058.
- Ganem D. (1982). Persistent infection of humans with hepatitis B virus: mechanisms and consequences. *Rev. Infect. Dis.*, 4, 1026-1047.
- Guidotti L.G., Rochford R., Chung J., Shapiro M., Purcell R., Chisari F.V. (1999) Viral clearance without destruction of infected cells during acute HBV infection. *Science*, 284, 825-829.
- Guidotti L.G., Ando K., Hobbs M.V. (1994). Cytotoxic T lymphocytes inhibit hepatitis B virus gene expression by a noncytolytic mechanism in transgenic mice. *Proc. Natl. Acad. Sci. USA*, 91, 3764-3768.
- Guidotti L.G., Chisari F.V. (2000). Cytokine-mediated control of viral infections. *Virology*, 273, 221-227.
- Heise T., Guidotti L.G., Cavanaugh V.J., Chisari F.V. (1999). Hepatitis B virus RNA-binding proteins associated with cytokine-induced clearance of viral RNA from the liver of transgenic mice. *J. Virol.*, 73, 474-481.
- Hayden, F.G., Fritz, R., Lobo, M.C., Alvord, W., Strober, W., Straus, S.E. (1998). Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J. Clin. Invest.*, 101, 643-649.
- Iwasaki, T., Nozima, T. (1977). Defense mechanisms against primary influenza virus infection in mice. I. The roles of interferon and neutralizing antibodies and thymus dependence of interferon and antibody production. *J. Immunol.*, 118, 256-263.
- Keenan, K.P., Combs J.W., McDowell E.M. (1982). Regeneration of hamster tracheal epithelium after mechanical injury. I. Focal lesions: quantitative morphologic study of cell proliferation. *Virchows Arch. B Cell Pathol. Incl. Mol. Pathol.*, 41, 193-214.
- Livingston B.D., Crimi C., Grey H. (1997). The hepatitis B virus specific CTL responses induced in humans by lipopeptide vaccination are comparable to those elicited by acute viral infection. *J. Immunol.*, 159, 1383-1392.
- Maini M.K., Boni C., Lee C.K. (2000). The role of virus-specific CD8(+) cells in liver damage and viral control during persistent hepatitis B virus infection. *J. Exp. Med.*, 191, 1269-1280.
- Maini M.K., Reignat S., Boni C., Ogg G.S., King A.S., Malacarne F. (2000). T cell receptor usage of virus-specific CD8 cells and recognition of viral mutations during acute and persistent hepatitis B virus infection. *Eur. J. Immunol.*, 30, 3067-3078.
- Marchuk, G.I., Petrov, R.V., Romanyukha, A.A., Bocharov, G.A. (1991). Mathematical model of antiviral immune response. I. Data analysis, generalized picture construction and parameters evaluation for hepatitis B. *J. Theor. Biol.*, 151, 1-40.
- Rehermann B. (2000). Intrahepatic T cells in hepatitis B: viral control versus liver cell injury. *J. Exp. Med.*, 191, 1263-1268.
- Rehermann B., Lau D., Hoofnagle J.H., Chisari F.V. (1996). Cytotoxic T lymphocyte responsiveness after resolution of chronic hepatitis B virus infection. *J. Clin. Invest.*, 97, 1655-1665.
- Scherle, P.A., Palladino, G., Gerhard, W. (1992). Mice can recover from pulmonary influenza virus infection in the absence of class I-restricted cytotoxic T cells. *J. Immunol.*, 148, 212-217.
- Tamura, S., and Kurata, T. (2004). Defence mechanisms against influenza virus infection in the respiratory tract mucosa. *Jpn. J. Infect. Dis.*, 57, 236-247.
- Zdanor, V. M., Bakrinskaja, A. G. (1969). *Myxoviruses Reproduction*. Medicina.Moscow, Russia.

Table 1. Model parameters used for the modeling

| Parameters | Value | Discription | Source |
|---------------|-------|--|-----------------------|
| α | 100 | rate constant of HBV | Zdanov et. al. 1969 |
| ε | 146.2 | rate constant of neutralization of HBV by antibodies | Bocharov et. al. 1994 |
| θ | 1.02 | rate constant of absorption of HBV by infected cells | Bocharov et. al. 1994 |
| λ | 1.7 | rate constant of nonspecific HBV removal | Bocharov et. al. 1994 |
| π | 4 | rate constant of regeneration | Keenan et. al. 1982 |
| σ | 1 | rate constant of cell's viron resistance state decay | Marchuk et. al. 1991 |
| φ | 0.34 | rate constant of cell infected by HVB | Marchuk et. al. 1991 |
| β | 0.01 | rate constant of cells virus resistant state induction | Bocharov et. al. 1994 |
| μ | 0.066 | rate constant of infected cell that CTL damages | Bocharov et. al. 1994 |
| τ | 0.5 | rate constant of infection cell damage by cytophthicity of HBV | Zdanov et. al. 1969 |
| ϑ | 1 | rate constant of stimulation of antigen presenting cell by dead cell | Marchuk et. al. 1991 |
| χ | 0.037 | rate constant of stimulation of antigen presenting cell by virus particle | Marchuk et. al. 1991 |
| γ | 1 | rate constant of stimulated state lose of antigens presenting cell | Marchuk et. al. 1991 |
| ψ | 2500 | Interferon (IFN) production rate per APC | Bocharov et. al. 1994 |
| δ | 200 | Interferon (IFN) production rate per infected cell | Baris et. al. 1998 |
| η | 17 | rate constant of cell that IFN bind | Bocharov et. al. 1994 |
| ξ | 8 | rate constant of IFN's natural decay | Bocharov et. al. 1994 |
| ϵ | 8.3 | rate constant of stimulation of effector cell | Marchuk et. al. 1991 |
| ρ | 2.72 | rate constant of death of effector by lytic interaction with infected cell | Bocharov et. al. 1994 |
| ω | 0.4 | rate constant of natural death of effector cell | Marchuk et. al. 1991 |
| ϕ | 11.5 | rate constant of plasma cell production | Marchuk et. al. 1991 |
| κ | 0.4 | rate constant of natural death of plasma cell | Marchuk et. al. 1991 |
| ϱ | 0.43 | antibody production rate per plasma cell | Marchuk et. al. 1991 |
| ζ | 0.43 | rate constant of natural death of antibodies | Marchuk et. al. 1991 |
| r | 3e-1 | rate constant for S variable | Baris et. al. 1998 |

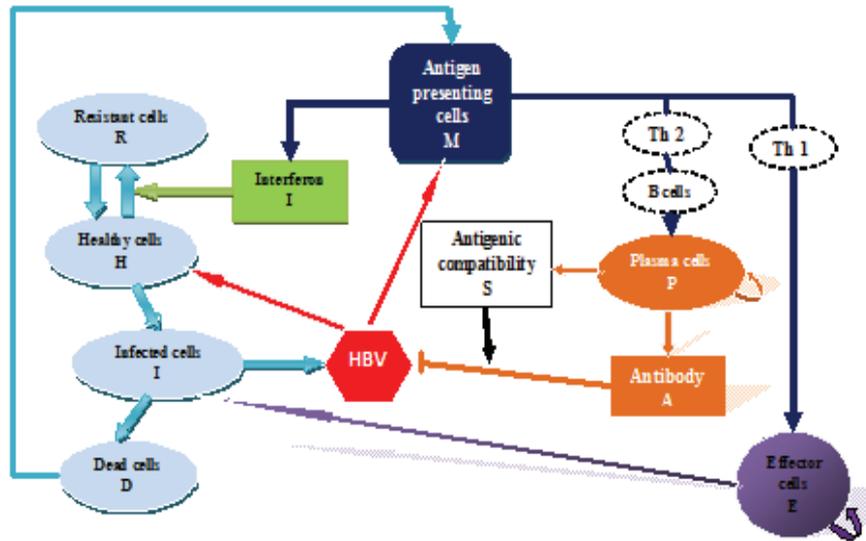


Figure 1. Schematic representation of interactions included in the model

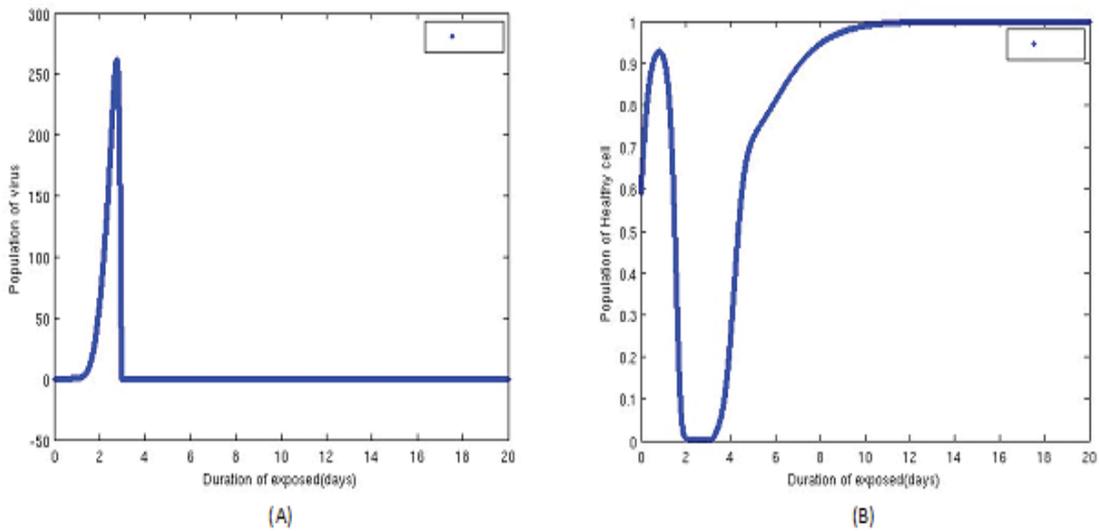


Figure 2. Virus and Healthy cells

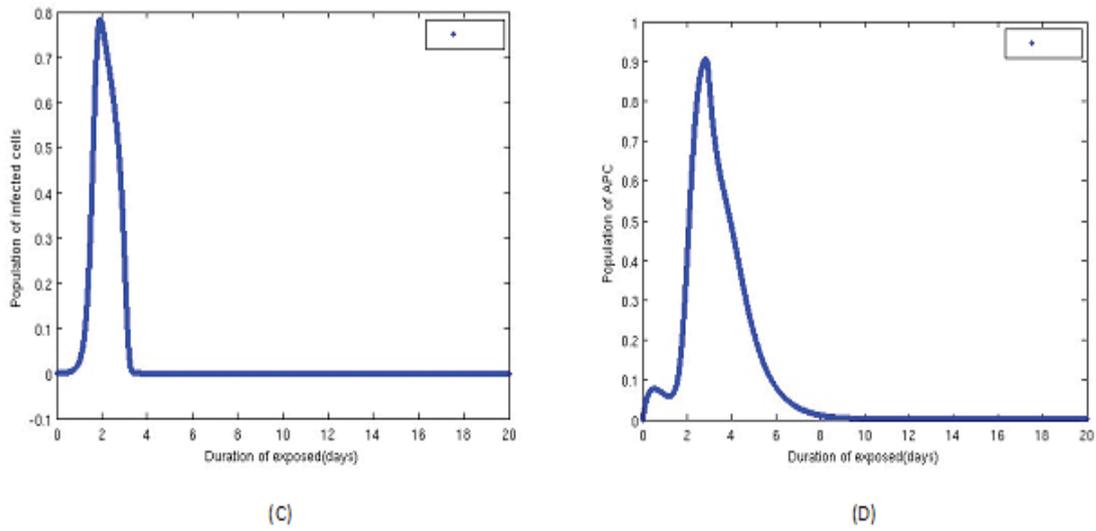


Figure 3. Infected cells and Activation antigen presenting cell(APC)

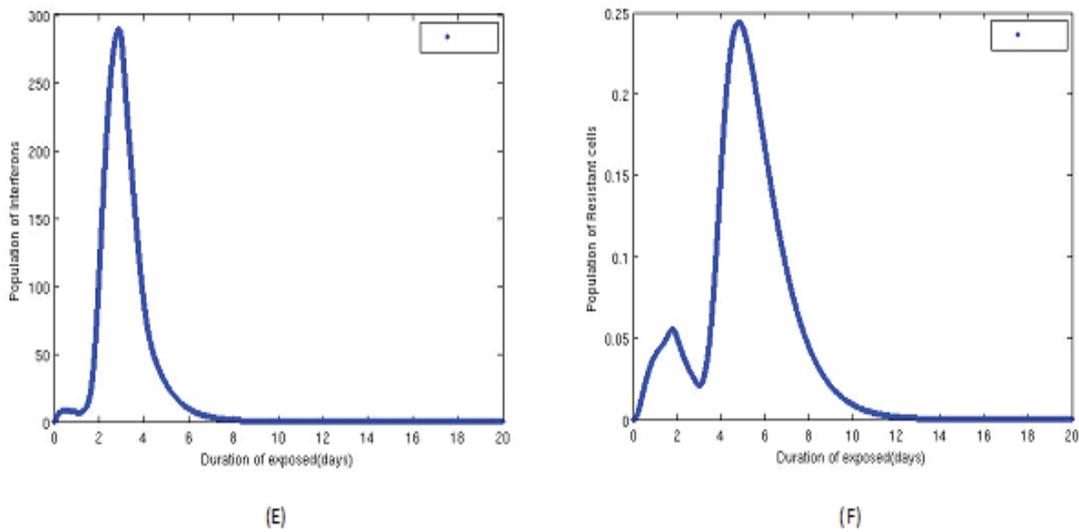


Figure 4. Interferons and Resistant cells

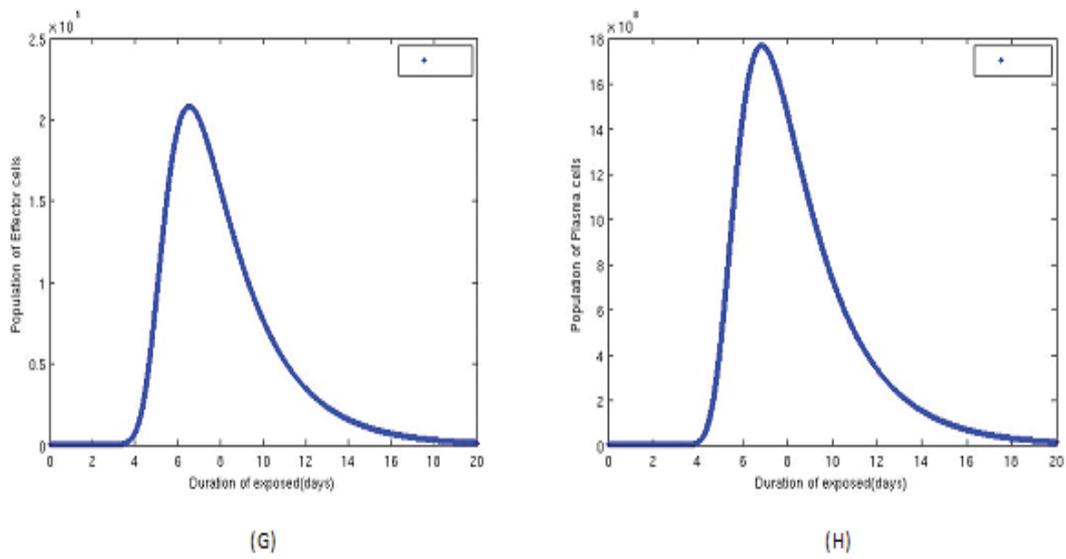


Figure 5. Effector cells and Plasma cells

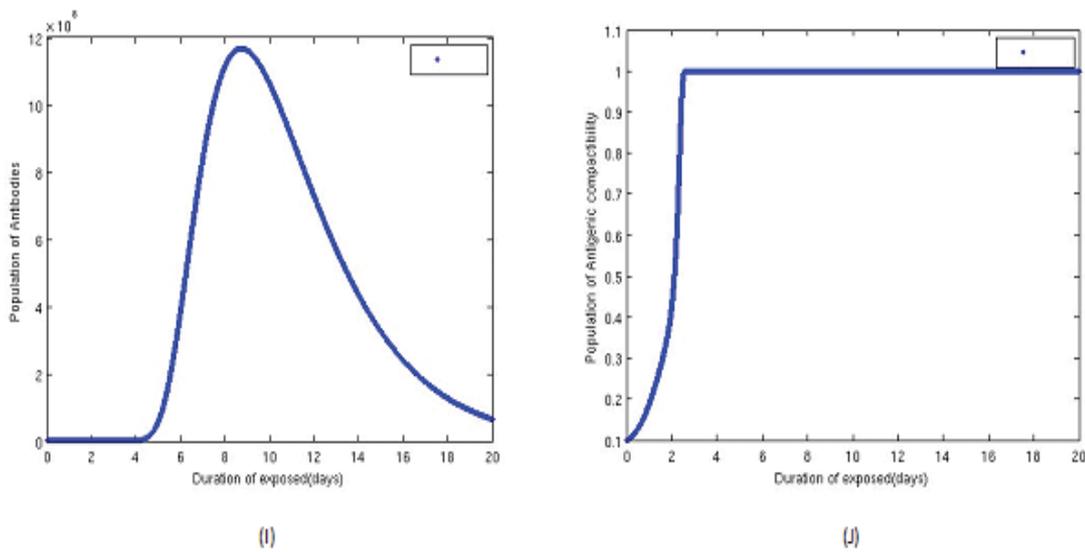


Figure 6. Antibodies and Antigenic compatibility