Kinetics of Hepatitis B Virus Infection: A Cellular Automaton Model Study

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ABSTRACT

We created a simple cellular automata (CA) model for hepatitis B infection dynamics associated with spatial structure performed under various ages of liver tissue correspond to different immune responses in order to study the effect of spatial heterogeneities on the dynamical evolution of a viral infection. The results of the simulations show biphasic nature of viral load decreases, as observed in the acute infection in real state. Our results also confirm the importance of the hepatocyte target cells, the spatial localization, and the local interactions on the dynamics of HBV infection, whereas models based on ordinary differential equations are not considered. Our model is quite simple with four states and only five parameters, however, the dynamics from the model qualitatively equivalent clinical data.

Keyword: Cellular automata, HBV infection, Kinetic model, Dynamical process, Modeling, Viral infections

INTRUDUCTION

Hepatitis B virus (HBV) is a small partially dsDNA virus that infect liver cells (hepatocytes) and can cause both acute and chronic diseases [1]. HBV infects more than 350 million people worldwide [2]. HBV viral load in acute state of infection can reach high levels of viruses which last for several weeks, followed by with HBV infection of a large percentage of hepatocytes [3-6]. Afterwards, viral load decrease, and in 85-95% of actually infected adults the infection is cleared [7, 8]. Although replication of the HBV is only mildly cytopathic toward the host cell, HBV-induced liver damage mediated through the cellular immune response is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma [2, 9].

It is believe that mathematical models have been used to help understand the dynamics of viral infections, such as hepatitis C infection and human immunodeficiency virus [10, 11]. The initial model has been presented by Nowak et al. [12] typically considered uninfected (*T*) and infected (*I*) and free virus (*V*). The model assumed that target cells, i.e., hepatocytes cells in the liver are susceptible to infection, are produced at a constant rate λ, die at per capita rate d, and become infected at a rate *kTV*, proportional to both the target cell concentration and the virus concentration. Also, the infected hepatocytes are produced at rate *kTV* and are considered to die at constant rate δ per cell. During infection, hepatocytes produce virus at rate *p* per infected cells, and virus is cleared at rate *c* per virion.
System's dynamics is governed by the following equations:

$$\frac{dT}{dt} = \lambda - dT - kVT \qquad (1)$$

$$\frac{dI}{dt} = kVT - \delta t \qquad (2)$$

$$\frac{dV}{dt} = pI - cV \qquad (3)$$

The differential equations (DE) assume that various populations of cells and viruses have been homogeneously distributed over the space and time in which the infections take place. Furthermore, these DE models include much more information and parameters that are usually

needed and are difficult to be numerically implemented. Discrete approaches based on cellular automata (CA) have been also proposed to simulate the immune dynamics of particular diseases [13, 14]. CA was introduced by von Neumann to address the question of the logical organization for self-reproduction [15]. Cellular automata are dynamical computational systems that are discrete in space, time and state and whose behavior is specified completely by rules governing local relationships. They are an attempt to simplify the often numerically intractable dynamic simulations into a set of simple rules that mirror intuition and that are easy to compute. As an approach to the modeling of emergent properties of complex systems it has a great benefit in being visually informative of the progress of dynamic events [16]. Ciupe et al. [8, 17] fitted their model based on continuous DE to the date from seven HBV-infected individuals detected at the stage of acute infection. The fits exhibit biphasic decay in the viral load for all patients. Moreover, in other study, Tsiang et al. [9] observed the decline of viral load during treatment with adefovir dipivoxil displayed a biphasic kinetic profile. Their closer examination revealed that although the viral decay was biphasic, the second phase did not plateau, but tended toward zero with time.

The aim of this paper is to study using numerical simulations of CA the different phases of the HBV infection, particularly in the clinical acute period as well as investigate spatial heterogeneities can play an important responsibility in controlling the development of HBV infection and its result. This paper is organized as follow: in section 2, we give a brief description but all the necessary background of the CA approach and our CA model of HBV infection. In this section, we explain the structure and transition rules of the CA model. In sections 3 and 4, we present results from the CA simulations and discuss them against data from clinical observations in the literature. Finally, in the last section conclusion remarks are presented.

MODEL AND METHODS

Before anything else, let us give a brief introduction about CA. CA are one-, two-, or three-dimensional lattice built out of cells. Each cell can be at any given time in one of several possible states. The transitions between states from one time step to the next step depend on the state of the cell and its neighbors. They are determinate by specific rules. The neighborhood is defined arbitrary. As shown in Fig. 1. Neumann and Moore neighborhood are defined four and eight neighbors of the central cell respectively [18].

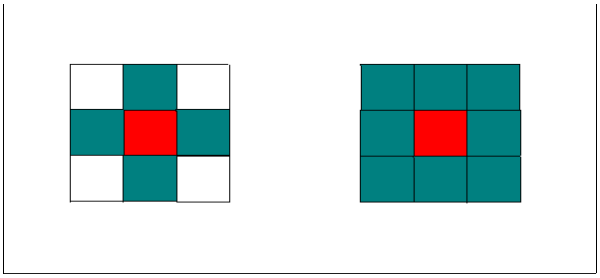

Fig. 1. Von Neumann and Moore neighborhood in left and right respectively.

Cell states of the CA model

We use four cell states in our two-dimensional CA model that characterize the life cycle of hepatocytes as confirmed site for HBV replication [19]. Two types of healthy hepatocytes (*R* and *S*), infected hepatocytes, (*I*), and dead cells (*D*) are considered. The meaning of each of these states is defined as follow:

Healthy (*R)*: the *R* cells have the capacity to divide, being able to differentiate into either *R* cells or *S* cells. The *R* cells are resistance to viral replication.

Healthy (*S*): the *S* cells susceptible to viral replication.

In fact, the *R* and the *S* cells based on London-Blumberg [20] model that the liver tissue is divided to two subsets of hepatocytes in different states of differentiation; these two subsets showed significantly different response to infection by the virus. In other words, the *S* cells are mature hepatocytes and the *R* cells correspond to oval cells [21] that the oval cells can proliferate. Infected (*I*): an infected cell that has been recognized by the immune systems. This type of cell can thus infect

healthy ones only in cause where the concentration is about a certain threshold.

Dead (*D*): the state of an infected cell is killed by the immune responses as cytolytic and noncytolytic mechanisms.

Cell updating rules

The transition (cells updating) rules during each time step of simulations are (See also figure 2):

Healthy R cells

(a) A healthy *R* cell becomes infected if it has as a minimum four infected neighbors. This rule takes into account the spread of the infection that may take place due to cell to cell contact inside liver tissues.

(b) A healthy *R* cell remains in *R* state during τ steps and becomes healthy S cell. This rule reproduces that the healthy *R* cell can be differentiated into *S* cell following by its age is increased as recommended by London-Blumberg model [20].

(c) Otherwise, it remains healthy *R*.

Healthy S cell

(a) A healthy *S* cell becomes infected if it has only one infected neighbors. This rule mimics that the healthy *S* cell is susceptible to infection based on London-Blumberg model [20].

(b) Otherwise, it remains healthy *S*.

***Infected** cell*

An infected cell becomes a dead cell with probability $P_{response}$. This rule mimics that the infected cell is recognized by immune system and the depletion of infected population is happened when immune response is released.

***Dead** cell*

A dead cell has a probability $P_{recovered}$ of being replaced by a new healthy *R* cell, in order to mimics liver cell regeneration and the replacement of the depleted cells by means of healthy *R* cell division.

We represent an individual liver tissue as a simulation of 700×700 lattice grids and an average of 1000 runs correspond to the dynamics of HBV infection for seven cases i.e., seven patients with diverse immune response and various ages (proportion of *R* to *S* cells is different). Each simulation is initialized with healthy R and S cells with various percentages, with small fraction, P_{HBV}, of infected cells, representing the initial infectivity by the HBV that the cells were randomly distributed over the lattice. The state of all cells are updated at each time step depended on the states of its four nearest neighbors and the four next nearest neighbors so called Moore neighborhood (8 nearest-neighbors). Each time step being taken in a unit of one day after infection. The periodic boundary condition was implemented.

All parameters chosen (see in Table 1) are based on experimental data; however, some are chosen to obtain quantitative results that agree firmly with the characteristic dynamics of HBV infection.

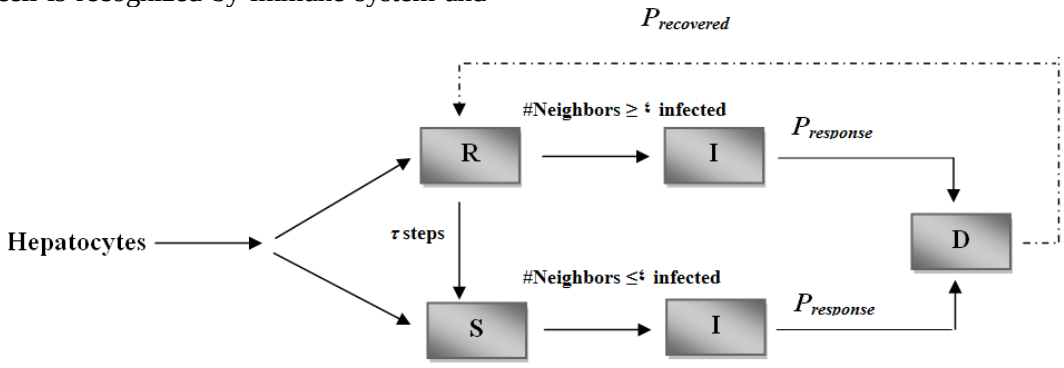

Fig. 2. State transition diagram of cell states. Hepatocyte cells were classified into one of the following states: healthy R, healthy S, infected (I), and Dead (D).

Table 1. The model's default parameters.

Parameters	Explanation	Value	References
L	Lattice size	700	[21-24]
P_{HBV}	Probability or percentage of initial infected cells	0.05	[23]
τ	Time delay for a healthy R cell to become a healthy S cell	4 (day^{-1})	[17]
$P_{response}$	Probability that an infected cell is recognized by immune response	0.01	[8, 17]
$P_{recovered}$	Probability of replacing dead cell with healthy R cell	0.01	[8, 17]

RESULTS

First, as shown in Fig. 3, the evolution of the infected cells can be divided into two different phases. During the initial days after infection, there is an increase in the viral population exponentially as a result of a destruction of the immune cells. To evaluate our model with clinical data, we used of seven cases as different patients with various strength of immune system (various proportions of R cells to S cells). Cases 1 to 7, respectively, 20 to 80 percent of their hepatocytes are composed of healthy R cells. According to the simulation results, the average fraction of infected cells at the peak of infection is near 70% of total hepatocytes and also the results illustrate a biphasic decay pattern in the infected cell population (viral load) in all cases is displayed in Figure 3.

In the second analysis of the model, the change of dead cells is investigated. Figure 4 illustrates the dynamics of dead cells. After the peak, the number of dead cells declines quickly, although with a slower decline in patient 1. Finally, dynamics of healthy hepatocytes (R and S) are shown in figure 5, as can be seen, biphasic change in this population is reasonable with recalling of viral load in figure 3.

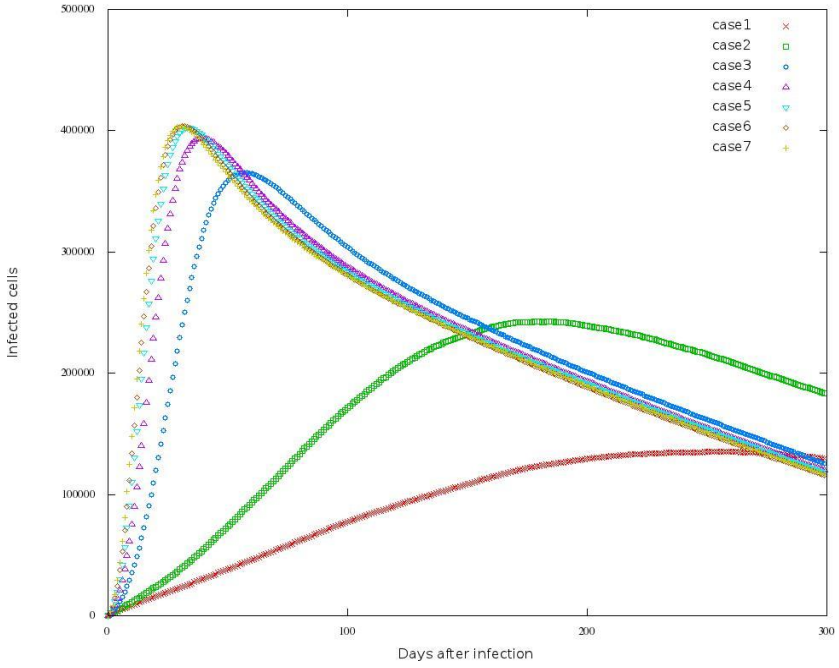

Fig 3. Simulation results for dynamics of infected cells (viral load) averaged over 1000 runs using the parameters mentioned in Table 1. The evolution of the infected population densities exhibits the biphasic behavior observed for infected patients. Different colors correspond to different patients with different immune response**.**

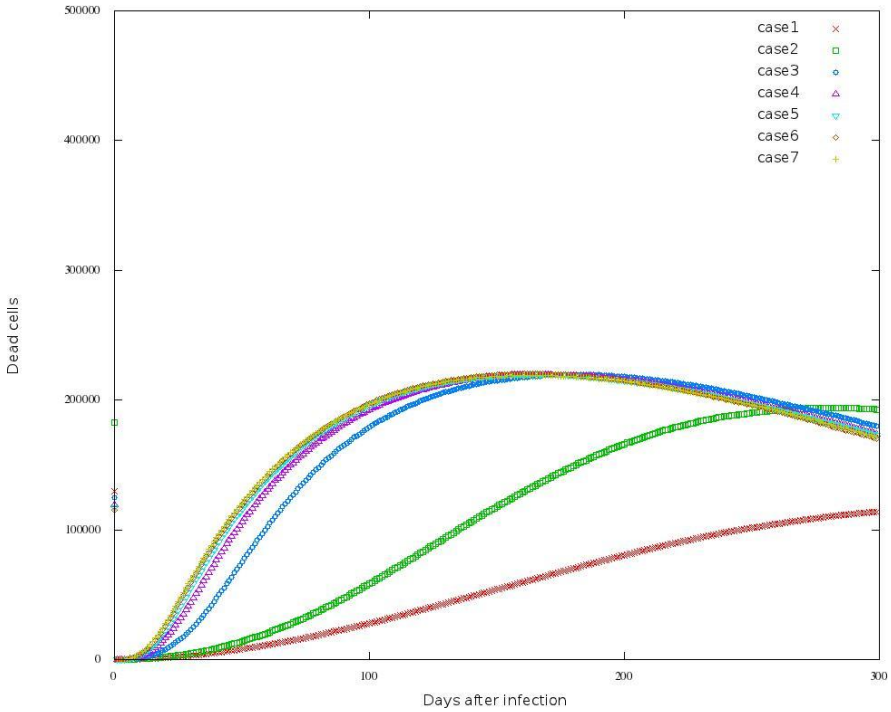

Fig 4. Simulation results for dynamics of dead cells averaged over 1000 runs using the parameters mentioned in Table 1. Different colors correspond to different patients with different immune response.

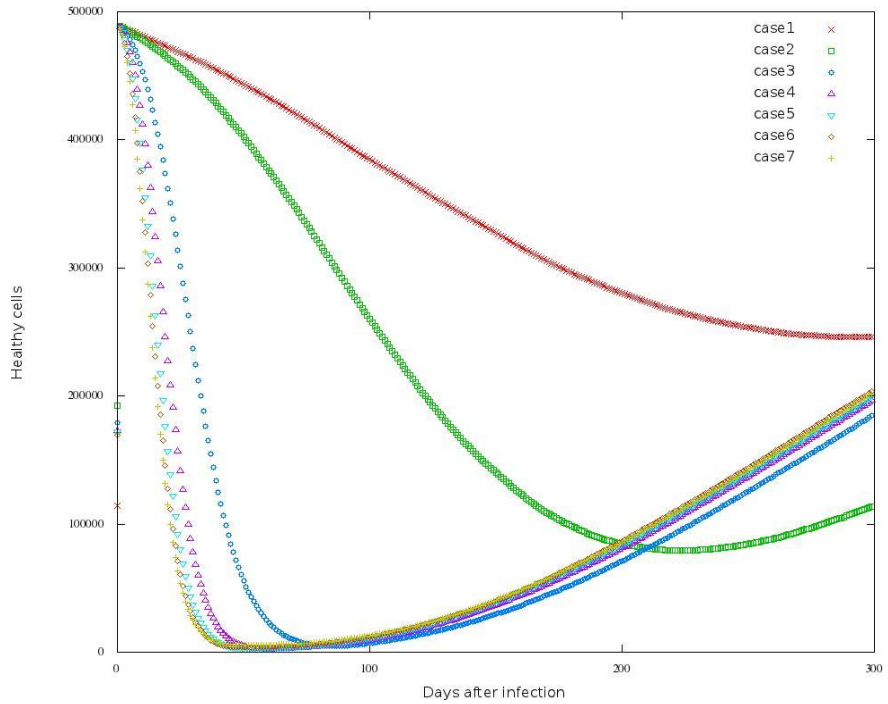

Fig 5. Simulation results for dynamics of healthy cells (viral load) averaged over 1000 runs using the parameters mentioned in Table 1. Different colors correspond to different patients with different immune response.

DISCUSSION

In our study, we explored a simple CA model associated with spatial structure performed under various ages of liver tissue correspond to different immune responses to study the effect of spatial heterogeneities on the dynamical evolution of a viral infection. Subsequently, we chose to parameterize our model to hepatitis B as well as can use this model for other viral infection by modification of the parameters. Our CA model show effectively biphasic nature of viral load decreases, as observed in the acute infection in real state. Our results also confirm the importance of the hepatocyte target cells, the spatial localization, and the local interactions on the dynamics of HBV infection, however, DE models are not considered.

Ciupe at al. [8, 17] as well as Tsiang et al. [9] developed several mathematical models that included additional variables to clearly model the immune system response. They showed initially viral load increases exponentially, reaching a peak. The HBV level then declines in a biphasic manner, and seems to approach a plateau around 6-10 months post-infection. Their fitting procedure resulted in a biphasic decay pattern in the viral load in all patients. Mathematical analysis is difficult due to the complexity of their models, so our simple CA model regenerate the biphasic nature of HBV infection that in accord with the results of mathematical models. The above simulation results are entirely coincident with the experimental findings [8, 17]. We observed in Figure 3, after the peak, the number of infected cells declines quickly.

The clinical studies [8, 17, 25, and 26] are also recorded the alanine aminotransferase (ALT) concentrations as an indicator of hepatocyte death during HBV infection from several patients that infected with the HBV have been shown that initially ALT level increases quickly and then decreases in a biphasic behavior. This correlation between ALT levels as clinically and our computed change in dead population propose that our model is suitably capturing the dynamics of the HBV infection.

CONCLUSION

Our model based on CA approach allows a detailed look at local behavior and spatial structures. We have shown that our CA model which is described by 4 state variables and only 6 parameters is sophisticated enough to reproduce the basic dynamical features of the infection such as the biphasic behavior of viral load and age dependence in relation to various patients.

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