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Three-Dimensional Cellular Automaton for Modeling the Hepatitis B Virus Infection

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ABSTRACT

Hepatitis B is considered as the most common hepatic in the world and may lead to cirrhosis and liver cancer. It is caused by the hepatitis B virus, which attacks and can damage the liver. In this paper we investigate a new mathematical model to study the dynamic process of HBV infection on the liver. This model is based on a three dimensional cellular automaton, which is composed of four state variables. The model takes into account the heterogeneous feature and the spatial localization of the population studied. Furthemore, since the virus doesn't remain only on the liver surface but penetrates into the organ, our model describes better the behavior of interactions between cells and hepatitis B virus in the liver than the previous works found in the literature, which have used only two cellular automata in their models.

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1. INTRODUCTION

Currently, hepatitis B virus (HBV) infection is considered as a major global health problem because it is a potentially life-threatening viral infection that can cause illness and even death. It can lead to cirrhosis and liver cancer. From the World Health Organization (WHO), more than 240 million people have chronic (long-term) liver infections, and about 600.000 people die every year due to the acute or chronic consequences of hepatitis B [1]. The most infected infants and children develop chronic. The hepatitis B is transmitted through blood, unprotected sex, sharing or reuse of contaminated needles, and vertically from mother to her newborn during childbirth.

Therefore, many mathematical models have been developed in order to understand the dynamics of HBV infection and help the responsible for public health to make the right decisions. The most of these models are

based on ordinary differential equations (ODEs) or partial differential equations (PDEs) and they have good explained different aspects of the dynamics of the virus [2, 3, 4, 5].

For instance in [2], Yousfi et al. have investigated a new model that described the interactions between HBV, liver cells (hepatocytes), and the adaptive immune response. They found that a disease free steady state, which its local stability called also the basic infection reproduction number is characterized as usual by R_0 smaller than one and the existence of four endemic steady states when this number greater than one. In [3], Cupe et al. have presented a model baesd on PDEs. They have focused on HBV dynamics during the acute phases of the infection and analyzed the immune reponses mechanisms which play an important role in determining whether the infection will be cleared or become chronic. They found that after the peak in viral load the cell-mediated immune response plays an important role in controlling the virus. Khabouze et al. have introduced in [4] an improved HBV model which is based on a nonlinear system of differential equations with standard incidence function, cytotoxic T lymphocytes (CTL) immune response, and took into account the effect of the export of precursor CTL cells from the thymus and the role of cytolytic and noncytolytic mechanisms. Using the characteristic equations, the authors found the local stability of the disease-free equilibrium and the chronic infection equilibrium. Furthermore, they used the direct Lyapunov method and the geometrical approach to establish the global stability respectively of the disease-free equilibrium and of the chronic infection equilibrium.

Although, in all these works the authors assumed that various populations of cells and viruses have been homogeneously distributed over the space and time in which the infection takes place. However, in the reality the virus infection system is not homogeneous and the populations of viruses and cells are not uniformly mixed.

To overcome this problem, there are a few works in the literature [6, 7] which have studied the dynamic process of HBV infection by considering the inhomogeneous feature. Their models are based on the approach of Cellular Automata. Xiao et al. have introduced in [6] a 2-D simple probability Cellular Automaton to model the HBV infection. Their model took into account the existence of type of HBV infectious and non-infectious particles. They claimed that the spatial characteristics play a nontrivial role in the development of HBV infection and that the infected cells propagate in all directions stochastically under the condition of a probability cellular automaton model. In the work of Gharib-Zahedi et al. [7], a 2-D simple CA has been presented, which contains four state variables. The authors performed their experiment under various ages of liver tissue correspond to different immune responses. They asserted that the CA can reproduce the basic dynamical features of the infection.

All these previous works have good described the interactions between the hepathocytes cells and HBV during the infection taking into account to the heterogeneity of the population studied, however the virus doesn't remain only on the liver surface but penetrates into it. Therfore there is a need to construct a model based on cellular automata approach which takes also account into the the volumetric character of the liver.

In this paper, we present a three dimensional cellular automaton (CA) that models the interaction between the hepatocyte cells and the infected cells during the infection with hepatitis B in the liver. The manuscript is organized as follows: In second section an overview of CA will be presented. Our model based on three dimensional CA to simulate the HBV infection will be described in section three. The simulation of the model and the results are given in section four. A brief discussion and concluding remarks round up the paper.

2. FORMULATION OF THE MODEL

In this section, we recall the fundamental hypothesis of Blumberg and London cited in [8]. Then we give an overview on cellular automata and at the end we present our model based on three dimensional cellular automaton.

2.1 London and Blumberg microscopic model

Our CA model is based on the fundamental hypothesis from the study of London and Blumberg described in [8] which supposed that the liver is composed of two subsets of hepatocytes in various states of differentiation that react meaningfully opposed to infection by the virus. The termed R cells which are resitant to the viral replication and thve susceptible cells wich have been termed S cells. The hypothesis of the autors implies that the R cells are not only able to divide further but can also differentiate into either R cells or S cells, whereas the S cells will have only a limited capacity for division and can only produce more S cells.

2.2 Overview of cellular automata

Cellular automata are discrete dynamical systems, whose behavior is completely specfied by the terms of a local relation and variable states, namely the values associated with locations of grid cells in the case of two dimensional CA or cube cells in the case of three dimensional CA are driven by simple rules that depend on the

states of the neighbors of each variable. They describe the behavior of discrete systems in space, time, and state. Many epidemic complex systems containing several discrete elements with local interactions have been well modeled by the CA. For example in [9], the authors have modeled the complex interactions between the host cells, the virus and the adaptive immune response by the infection with HIV using a two dimensional CA.

Furthermore The Cellular automata have been successfully applied in various felds such as medicine, engineering, physics and biology. Due to their conceptual simplicity, ease of implementation for the numerical simulation, and the ability to expose a variety of complex behavior, the CA are a class of completely distinct dynamical systems, which has become a central topic in the sciences of complexity.

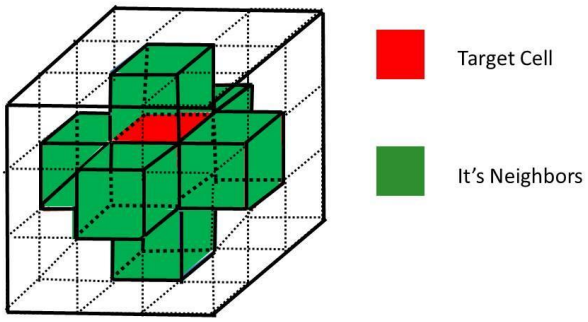


Figure 1: Illustration of target red cell with it's green direct neighbors in a 3-D Cellular Automaton

Three-dimensional cellular automata are discrete dynamical system formed of a finite number $LxLxL$ of cells which are arranged uniformly in a cubic lattice. Each small cube in the lattice represents a cell which is endowed with a state (fro m a finite set of states), that can change after each time step accordingly to a local transition rule. The new state of a target cell at time t depends on it's state and the states of the neighborhood cells at the previous time step $t-1$. As shown in Figure 1. The central red cube (cell) surrounded by 26 cubes. Among the 26 cubes, 6 cubes, the green cubes are the nearest neighbors which directly contact the red cube. More precisely, a CA is defined by a 4-tuple (C, Q, N, δ), where C represents the cells positions defined as follows:

$$C = \{(i, j, k), 1 \leq i \leq L, 1 \leq j \leq L, 1 \leq k \leq L\}$$

is the finite set of states whose elements are all possible states of the cells. The neighborhood set is defining by the following indices set:

$$V = \{(\alpha_k, \beta_k, \lambda_k), 1 \leq k \leq n\} \subset \mathbb{Z} \times \mathbb{Z} \times \mathbb{Z}.$$

The neighborhood of the cell (i, j, k) is the set

$$V_{ijk} = \{(i-1, j, k), (i+1, j, k), (i, j-1, k), (i, j+1, k), (i, j, k-1), (i, j, k+1)\},$$

as shown in figure 1.

Finaly, the transition function is defined as follows:

$$\delta^t_{ijk} = \delta(\delta^{t-1}_{i+\alpha_1 j+\beta_1 k+\lambda_1}, ..., \delta^{t-1}_{i+\alpha_n j+\beta_n k+\lambda_n}) \in Q,$$

Where δ^t_{ijk} is the state of the cell (i, j, k) at time t.

2.3 The proposed model

Our model is based on a three dimensional celluar automaton which is composed of four state variables: (1) **Hepatocytes healty (R)** cells, that have the capacity to divide, being able to differentiate into either R cells or S cells and are resistance to viral replication. (2) **The hepatocytes healty (S)** cells susceptible to viral replication. (3) The third state represents **the infected hepatocytes (I)**, which are the results of the infection of either the R cells or the S cells with the HBV. We note that the roles of the virus particles and the immune responses are in an implicit manner considered. (4) **Dead cell (D)**: an infected cell that had been killed by the immune responses as cytolytic and noncytolytic mechanisms or any kind of cells which reaches the end of its lifetime. We note that the infection occurs when there is 100% contact between the hepathocytes healty cells and the virus. Thus, the neighbors of each cell are cells in its right and left side, the top and bottom of the

cell and cells in front and behind the cell. A second remark is that the time step in our model is one day. The figure 2 illustrates graphically the updating rules of all cells. In the next paragraph we describe explicitly these rules:

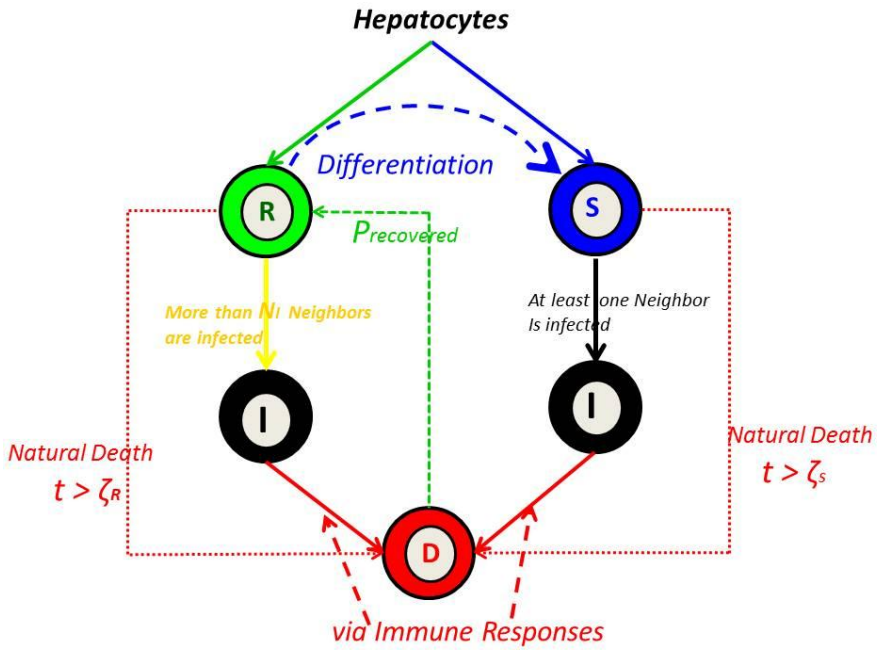


Figure 2: Graph of the cellular automata that illustrates the interactions of different cells in the liver by the HBV infection

Update of healty R cells:

- The healty R cells are randomly distributed in the cube. As recommended by Blumberg-London [8], these cells can be differentiated into either R cells or S cells, and the proportion of S cells in a liver is approximately constant within a time frame. Then they became healthy S cell randomly as needed to maintain the ratio of all R cells to all S cells invariable.
- If a healty R cell has as a minimum N_R number of infected neighbors with $N_R \leq 6$, then it will be infected and becomes an infected cell. Ever this number the bigger more the cell is resistant. This rule describes the event of the spread of the HBV infection which occurs by the contact between healty R cells and infected cells.
- After each time step the age of a healthy Rcell increases by one and dies when it reachs its lifespan τ_R. This explains the natural death of the healty hepathocyte R cell. The production of The R cells is guaranteed by the recovery of dead cells with the probability $P_{recovered}$.

Update of healty cells S:

- A healthy *S* cell is produced by the the differentiation of a healty R cell. If there is at least one infected cell in its neighborhood, it becomes infected. Based on London-Blumberg model [8], this rule mimics that the healthy *S* cell is more susceptible to infection.
- The healty hepathocyte S cell ages by one after each time step. Its dies, when the end of its lifespan τ_S is reached.

Update of infected cells I:

The Infected cell I is produced by the infection process either from the healthy R cell or S cell. It ages after each iteration and dies due to the immune response process after a given lifespan time.

Update of death cells D:

- When healthy R, healthy S or infected cells reach their lifespan time they become a dead cell.
- To maintain the same size of the the liver in frame the dead cells are replaced by new healty R cell with probability $P_{recovered}$.

3. SIMULATION AND RESULTS

To simulate our model we have developed a program with C++ language and the graphical library Opengl. As presented in Figure 3, the user can instantly view the interaction between different cell types. Uninfected heapathocytes R cells, uninfected heapathocytes S cells, infected heapathocytes cells and dead cells are modeled respectively by green, blue, black and red small cubes as shown in Figure 3.

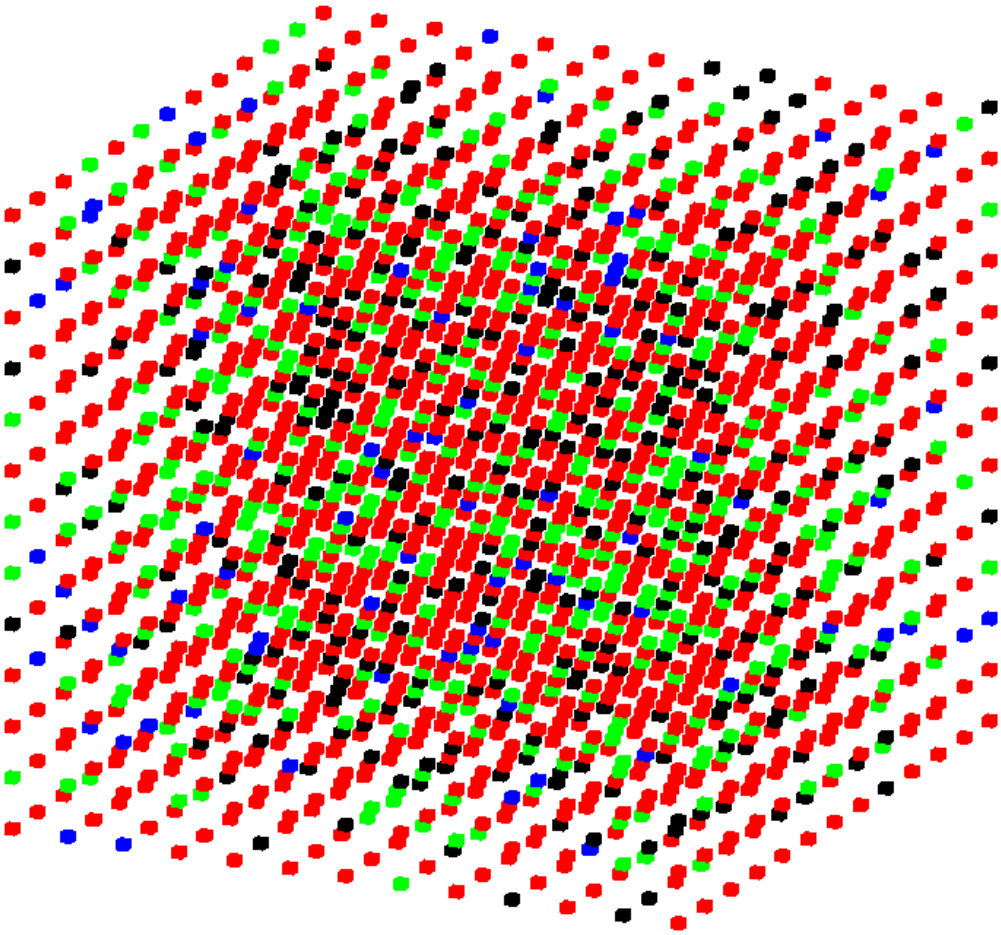
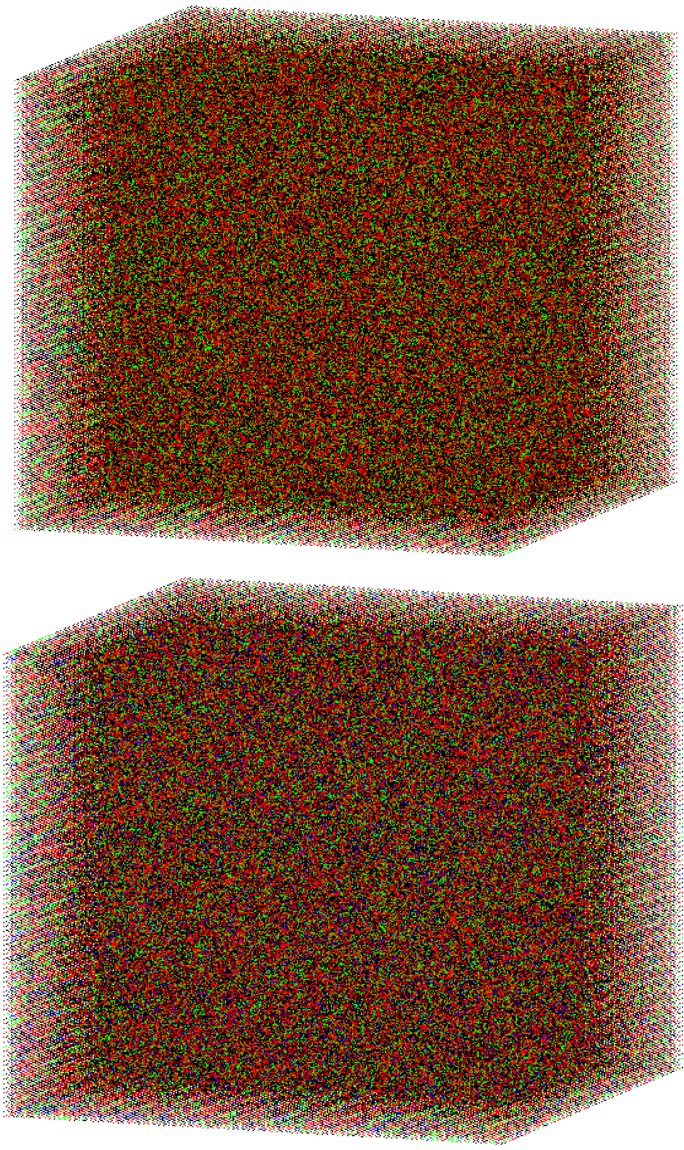


Figure 3: A snapshot of the modeled part of liver (about 13*13*13 cells) using a 3-D cellular automaton

The cells are randomly populated on the cube, which represents a part of the liver in order to ensure the real dynamic behavior of these cells. Each cell is assigned a random age between 0 and its lifespan inclusively, which is incremented after each iteration. Each iteration corresponds to a time step. We choose one day as time step. We run the program several times with different initial configurations of input parameters values. In each initial configuration there is a differents proportions of healty R cells to S healty cells. We suppose that the liver is infected with probability P_{HBV}. The updating of each cell from the cube according to the rules described above is synchronously. About the lifespan of different infected hepatocytes, the numbers of copies of cccDNA in infected hepatocytes, which means the production of infected cells and the immune response, there are no convinced medicinal experiment data [10]. We have considered a cube of 55x55x55 cells to model an infected liver which is distributed randomly. Table1 lists values and definitions of parameters used in this model

Table 1: Model parameters and values

Parameters	Definitions	Values	References
$LxLxL$	Cube size	$1.25 *10^6$	Ad hoc
R	The number of R cells	20%-80%	Ad hoc
P_{HBV}	Probabilty of initial infected cells	0.05	[6-7-8]
$P_{recovered}$	Probabilityof recovered dead cell	0.99	[6,7]
τ_R	Life span of R cells	48	[7]
τ_S	Life span of S cells	48	[7]
τ_I	Life span of Infected I cells	6	[7]
N_i	Number of iterations	240	Ad hoc
N_R	Number of infected neighbors	5	Ad hoc



(a)

(b)

Figure 4: A snapshot of the 3-d CA with about $1.6*10^6$ cells to simulate a part of the liver (a) Initial Infected liver (b) after 150 days

Depending on the states of the tangent six neighbors of a given cell and also on it state a cell's state is updated at each iteration. Each simulation is initialized with healthy R and S cells with various percentages. The results show that by changing the number of the heapathocytes S cells increasly the number load viral increases and

the number of the healty cells in the liver deacreases as shown in figure 5. This explains the fact that a child with small liver is more susceptible to the HBV than an adult.

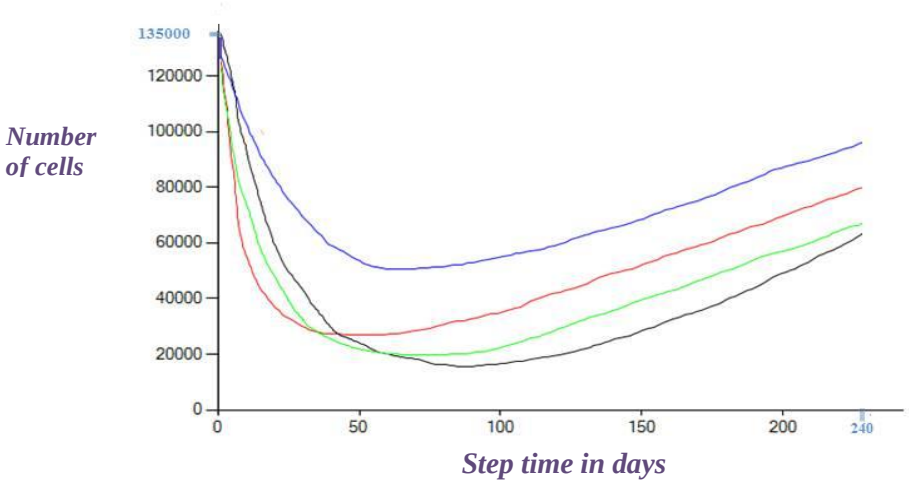


Figure 5: The curves of the heapthocytes with differents quantities of the heapthocytes S cells. **Bleu** 20%, **red** 40%, **green** 60% and **black** 80%

3. CONCLUSION

In the current paper, we propose a new mathematical model based on CA approach to simulate the interaction between the heapathocytes healty cells and the infected heapathocytes by HBV infection. Our model simulates the behavior of cells by using a three dimensional CA, which is composed of four state variables, namely the states for healty heapathocytes R cells, healty heapathocytes S cells, infected cells and the dead. We have implemented a program with c++ language and Opengl to experiment and test our model. The experiment is realized for different liver size by changing the number of heapthocytes S cells. The results demonstrated that the model agrees with natural development of the HBV infection as known. To improve our model we will introduce a study about the number of infected cells in a neighborhood of either the heapathocytes R cells or the heapathocytes S cells also the introduction explicitly the state variables for virus and immune responses is considered as challenge to realize.

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