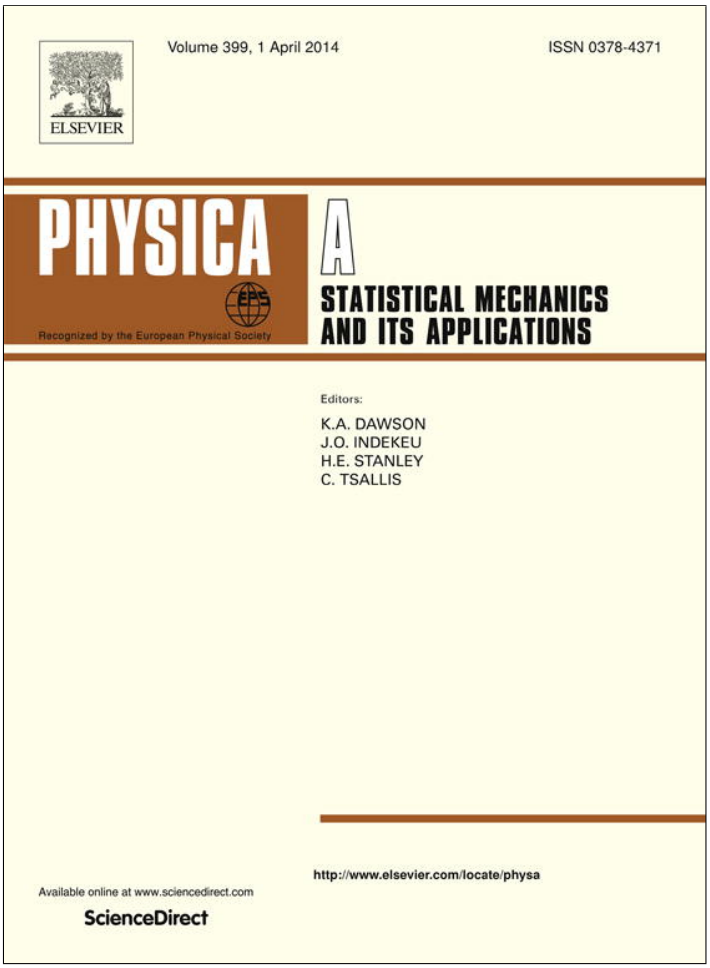

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The 3-dimensional cellular automata for HIV infection

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HIGHLIGHTS

- HIV infection dynamics is discussed with a 3D cellular automata model.
- The model can reproduce the three-phase development of HIV-infected patients.
- The 3D HIV model is more robust on model parameters than the 2D model.
- Occurrence of perpetual pattern drives system from asymptotic state to AIDS state.

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ABSTRACT

The HIV infection dynamics is discussed in detail with a 3-dimensional cellular automata model in this paper. The model can reproduce the three-phase development, i.e., the acute period, the asymptotic period and the AIDS period, observed in the HIV-infected patients in a clinic. We show that the 3D HIV model performs a better robustness on the model parameters than the 2D cellular automata. Furthermore, we reveal that the occurrence of a perpetual source to successively generate infectious waves to spread to the whole system drives the model from the asymptotic state to the AIDS state.

1. Introduction

Nowadays, acquired immunodeficiency syndrome (AIDS) has become one of the main global health problems. Infected by human immunodeficiency virus (HIV), a patient typically shows three-phase pattern development [1]. In the first one month after HIV infection the acute phase occurs with a dramatic increase of virus load in the peripheral blood and a fall of the helper H lymphocytes (CD4 + T cell). Patients usually experience symptoms similar to flu. Then in two or three months the virus load shows a sharp decline with the CD4 + T cell approximately returning to the normal level, and the patients do not perform any clinical symptoms. The patients enter the second phase which is a long period of asymptomatic stage lasting 1–10 years or more. During this asymptomatic phase, instead of being completely eliminated after primary infection, the HIV virus load remains relatively low, while the CD4 + T cells continue to decrease slowly. Finally, the CD4 + T cell population becomes lower than a critical value and the virus load climbs up again, leading to the onset of AIDS in the final phase. In the AIDS phase, the impaired immune system can no longer fight off infections, and the patients die from a variety of infections that would easily be cleared for healthy people.

Since the HIV was isolated in 1983 [2] and found to be the cause of the AIDS in 1984 [3,4], lots of studies have been carried out to understand the complex dynamics between the HIV virus and the immune system. In the immune system, the CD4 + T cells are one of the master regulators for the cytotoxic CD8 + T cells and B cells responding to different types of viruses. The HIV typically infects and kills CD4 + T cells. Therefore, the decline of CD4 + T cells in HIV infection eventually leads to the loss of many cell-mediated immunological functions essential for effective defenses. The patients finally become highly susceptible to any opportunistic infections and malignancies. Secondly, lacking the proof reading mechanism for the reverse

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transcriptase, HIV has a high mutation rate. So HIV can generate highly diverse quasispecies to escape from recognition by host immune effector cells. Although major progresses have been achieved by medical and biological scientists in understanding the complex interaction between HIV and immune cells, the dynamics of the three-phase AIDS development still remains unclear and requires more investigation not only by experiment but also by theoretical modeling.

Several mathematical models using ordinary differential equations have been developed to investigate the dynamics of HIV infection [5–7]. These models have successfully reproduced the three states dynamics and contributed significantly to the understanding of the mechanisms of HIV infection. However, these models could not discuss the spatial behavior and the stochastic effects of HIV dynamics. An HIV model with spatial structure has been studied, indicating that the spatially heterogeneous coupling can change the equilibrium properties of the uncoupled population [8]. The dynamics of HIV infection has also been modeled with grids of conformon-P system, with which the HIV stochastic dynamics can be discussed based on a discrete spatial heterogeneity [9]. Lin and Shuai proposed a stochastic spatial HIV model based on the Monte Carlo approach [10]. With the model, the importance of CD8 + T cells has been assessed in the acute phase.

Dos Santo and Coutinho in 2001 applied a cellular automata (CA) model to discuss the dynamics of HIV infection [11]. The interactions of HIV and immune system are described by a set of simple local transition rules in CA–HIV models, and the model shows a potential for simulating the temporal and spatial dynamics of HIV infection. However, it was soon noted that the original CA–HIV model can only give qualitative agreement with some parameters chosen in a small range [12]. The robustness of the modified CA–HIV model has been simulated against changes in different model parameters [13]. The dynamic behaviors against the different symmetries of the lattices in 2D and 3D CA models have also been investigated [14]. Some rigorous mathematical results about the time scales and other dynamical aspects of the CA–HIV model have been discussed by Burkhead et al. [15].

Recently a two-compartment CA–HIV model has been suggested to discuss the HIV infection between a lymph node and peripheral blood compartments [16]. A non-uniform CA model has been considered to discuss the HIV infection dynamics with three different drug therapies, including mono-therapy, combined drug therapy and highly active antiretroviral therapy HAART [17]. With the CA model, it has also been shown that the effectiveness of the Leukapheresis treatment depends on the starting time and the frequency of the therapy [18]. Besides the HIV dynamics, a simple 2D probability CA model has been introduced to study the dynamics process of hepatitis B virus (HBV) infection, showing that the CA model can successfully reproduce some important features of the HBV disease, such as its wide variety in manifestation and its age dependency [19].

Except the CA–HIV model discussed in Ref. [14], almost all the CA models are utilized on 2 dimensional lattices. In this paper we consider a CA model in 3D lattices to discuss the process of HIV infection for a single lymph node which actually occurs in 3D space. With the 3D CA–HIV model, the dynamics of three typical phases, i.e., the acute phase, asymptomatic period and the AIDS phase, have been studied in detail. We also discuss the robustness of the HIV behavior on the model parameters and the mechanism of the transition from the asymptomatic state to the AIDS phase.

2. Modeling

2.1. Three-dimensional CA model

The 3D CA–HIV model is based on a three-dimensional $L \times L \times L$ cubic lattice. Each cube in the lattice represents a cell. In the 3D CA model, the status of a cube is determined by its 26 neighbors, as shown in Fig. 1 the central red cube surrounded by 26 cubes. Among the 26 cubes, 6 cubes (yellow cubes in Fig. 1) are the nearest neighbors which directly contact the red cube; 12 cubes (green cubes in Fig. 1) are the second nearest neighbors which touch the center cell by line; and 8 cubes (blue cubes in Fig. 1) are the third nearest neighbors which connect the center cell only by a point.

2.2. Updating rules for 4-types of cells

In the model, there are only four types of cells, i.e. healthy cells (H cells), first-stage infected cells (I1 cells), second-stage infected cells (I2 cells) and dead cells (D cells). The H cells represent natural helper T cells, which respond to immunoreaction. However, when a patient carries HIV, H cells will be attacked by HIV then to become the I1 cells. The I2 cells develop from I1 cells. Both I1 and I2 are classified as infected cells, denoted as I = I1 + I2. The D cells are the last state of the infected cells, which are transformed from I2 cells.

In the model the 4 states cells, i.e. H, I1, I2 and D cells, can change their states under certain conditions. Because I1 cells are early infected, they contain more toxicity, so they can infect H cells efficiently. I2 cells are the later state of the infected cells. Hence I2 cells contain less toxicity, and it is less easy for the immune system to detect them. Thus the I2 cells survive longer than I1 cells. According to the dynamics between HIV and immune cells, we set some rules to update the 4 types of cells. Those rules are listed in Table 1 and the transforming relations among the 4 states are shown in Fig. 2.

2.3. Parameter settings

Simulations have been carried out on lattices of size $N = 100 \times 100 \times 100$ with fixed boundary condition. In the model each time step corresponds to one week and so the cell states are updated weekly. At the beginning, we disperse some HIVs randomly over the whole lattices to infect some H cells. Then those infected H cells change to I1 cells with the infecting

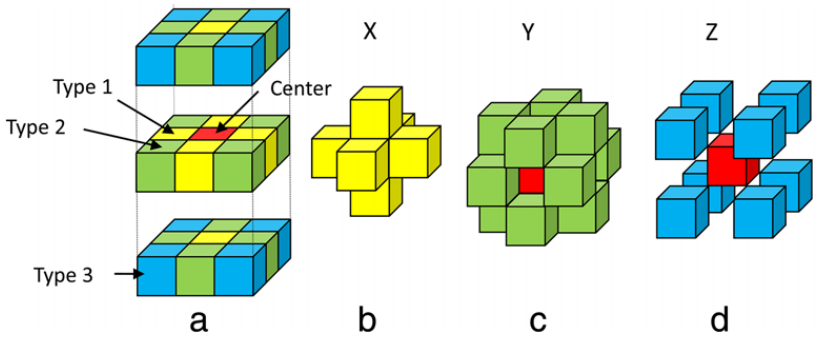

Fig. 1. Red cube is the center cell in the $3 \times 3 \times 3$ lattices. Yellow cubes are the nearest neighbors of the center cube, green cubes are the second nearest neighbors and blue cubes are the third nearest neighbors of the center cube. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

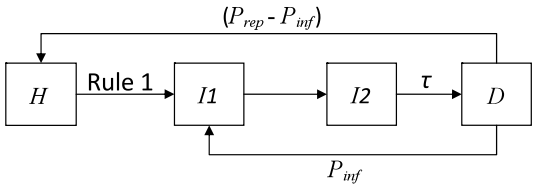

Fig. 2. Transforming relations among 4 types of cells. H cells will change to I1 cells when rule 1 is satisfied. I1 cells will change to I2 cells at next time step. I2 will become D cells after τ steps. D cells will change to I1 with probability P_{inf} or by H with probability $(P_{\text{rep}} - P_{\text{inf}})$ in next step.

Table 1
Updating rules for 4 types of cells.

Rule #	Description of rules
Rule 1	If an H cell satisfies at least one of the rules listed below, it becomes an I1 cell in the next step: (i) At least one I1 cell in the nearest neighbor or the second nearest neighbor; (ii) At least x I2 cells in the nearest neighbor, y I2 cells in the second nearest neighbor, and z I2 cells in the third nearest neighbor.
Rule 2	An I1 cell becomes an I2 cell in the next step.
Rule 3	An I2 cell becomes a D cell after τ steps because of the immune recognition and clear.
Rule 4	A D cell can be replaced by an I1 cell with probability P_{inf} or replaced by an H cell with probability $(P_{\text{rep}} - P_{\text{inf}})$ in the next step.

Table 2
The parameters used for simulations.

Parameter	Value	Description
L	100	Lattice size, total number of cells in the lattice is $L \times L \times L$
P_{HIV}	5×10^{-4}	Probability or percentage of initial healthy cells infected by HIV
P_{rep}	0.99	Probability that a D cell is replenished by an H cell
P_{inf}	9.74×10^{-6}	Probability that a D cell becomes I1
x	5	Number of I2 cells in the nearest neighbor, to make the center cell become infected
y	9	Number of I2 cells in the second nearest neighbor, to make the center cell become infected
z	4	Number of I2 cells in the third nearest neighbor, to make the center cell become infected
τ	2	Time delay for an I2 cell to become a D cell because of immune recognition

percentage P_{HIV}. In the model, $P_{\text{HIV}} = 0.0005$ is typically used. An infected cell may survive 2–6 weeks, so we set $\tau = 2$. The parameters used for simulations are listed in Table 2. Most of them are chosen from the previous models with some modified slightly [11,13,14], and the others, such as x, y, and z, are selected to fit the clinical data.

3. Results

3.1. Three phase dynamics

For the 3D CA–HIV model with the given parameters shown in Table 2, the three typical phases, i.e., the acute phase, asymptomatic period and the AIDS phase, can be observed. Under different initial conditions for H cells infected by HIV, the intervals from the initial infection to the onset of AIDS vary typically from 2 to 20 years. In Fig. 3 some snapshots of the HIV infecting procedure, including acute period from $t = 2$ to 12, latency period from $t = 15$ to 368, and AIDS onset period from $t = 368$ are shown. Fig. 4(a)–(c) show three simulations representing three individuals with AIDS onset occurring at 4, 9 and 16 years after infection.

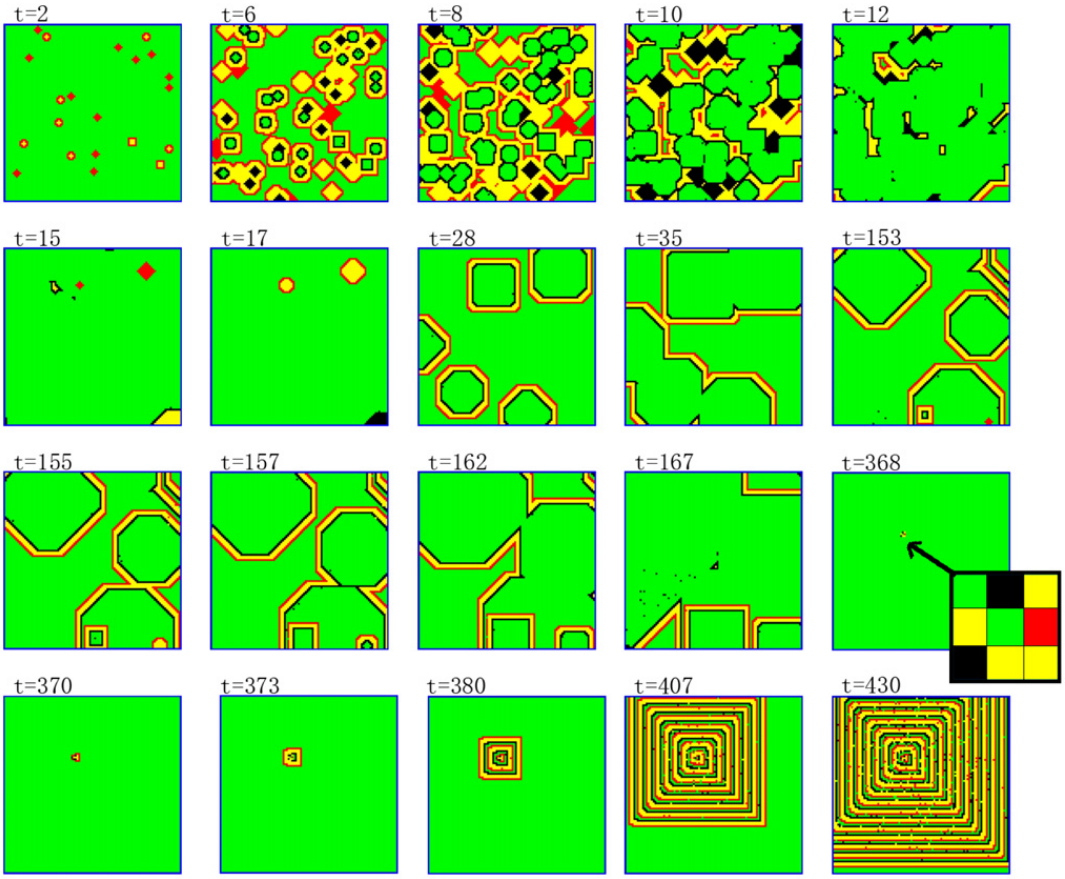

Fig. 3. Snapshots of HIV infecting procedure. Green, red, yellow and black grids correspond to H, I1, I2 and D cells, respectively. The acute period is from $t = 2$ to $t = 12$, latency period from $t = 15$ to $t = 368$, and AIDS onset period from $t = 368$. The inset at $t = 368$ is a kind of perpetual source to induce AIDS onset. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

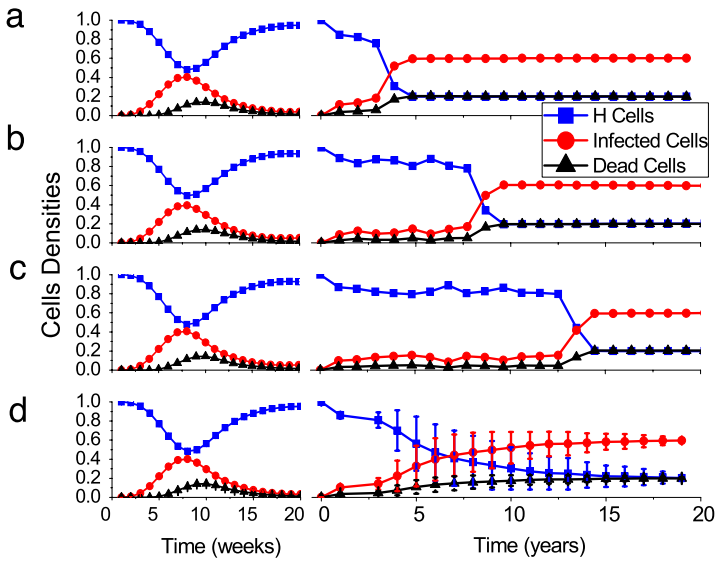

Fig. 4. (a)–(c) Time evolution of healthy cells, infected cells and dead cells in three different cases with AIDS onset occurring at 4, 9 and 16 years after infection. (d) The statistical result of HIV infection averaged over 2000 samples. The error bars are for standard deviations.

The first phase, i.e., the acute period, occurs on initial weeks after infection. In this period, the number of H cells decreases in the first two months and then returns to the normal value in the next two months. After that, the patient goes to the asymptomatic phase in which the system presents antagonism between H cells and I cells: the immune system cannot recognize and kill all infected cells and HIVs cannot infect all immune cells, either. However, when I cells constitute a perpetual structure to keep creating I cells to attack H cells, the number of I cells keeps increasing and becomes out of

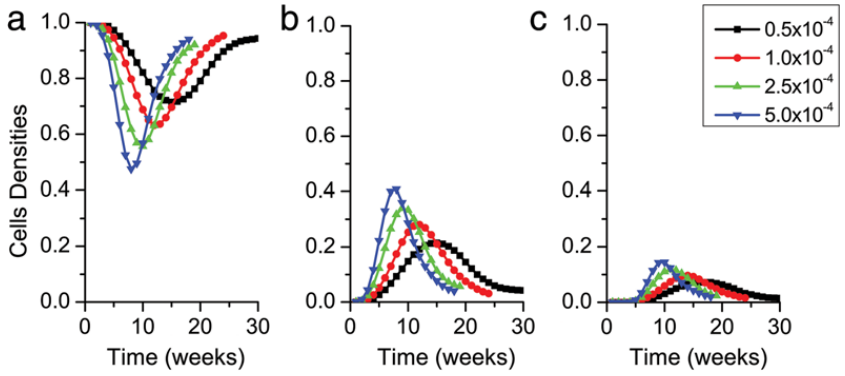

Fig. 5. The average densities of (a) H cells, (b) I cells, and (c) D cells at the acute phase change with time at different probabilities of initially infected cells P_{HIV}.

control. Then the immune system develops into the AIDS phase. In our model, the onset of AIDS is defined when the density of H cells decreases to 0.2.

Fig. 4(d) shows the statistical result over 2000 simulations with random initial infections. The full points stand for average evolution of H cells, I cells and D cells in the CA–HIV system. On an average, the number of H cells decreases gradually and the number of I cells increases slowly after the acute phase. Thus it shows a gradual change from the asymptomatic phase to the AIDS phase (Fig. 4(d)). While at the individual level, the numbers of H and I cells both keep almost constant during the asymptomatic phase, and there is a sharp change of the cell numbers to the onset of AIDS (Fig. 4(a)–(c)). The error bars in Fig. 4(d) stand for standard deviations. One can see that the error bars are typically small in the first three years, indicating all the patients experience the similar process in the first three years. The large error bars found in 4–15 years indicate great diversity in the asymptomatic period due to the stochastic HIV dynamics.

3.2. The acute phase

Given the physical constraints on τ and on the initial infected probability, the dynamics of the acute phase shows that there is an initial drop in the number of healthy cells, and an initial increase in infected cells during the first two months, and then in the next two months most of the cells have been replenished with the healthy cells. The entire acute phase will last about five months, followed by a return to at least 90% of healthy sites in the CA–HIV lattice.

The acute period is shown in Fig. 3 from $t = 2$ to 15. With the CA–HIV model, the propagation of an I1 cell infecting its neighbor cells shows the behavior of a spreading wave. When an I1 cell wave meets the border or another I1 cell wave, the waves disappear. With the one-time-step transformation of I1 to I2, the I1 cell waves are followed by the I2 cell waves. When the I1 waves scan the whole lattices, the peak of acute phase is achieved.

Now we discuss the effect of P_{HIV}, the probability of initially infected cells, on the evolution of acute phase. Simulation results are shown in Fig. 5 with P_{HIV} changing from 5×10^{-5} to 5×10^{-4}. Decreasing P_{HIV} means to decrease the number of initially infected cells. With less initially infected cells, the peak of acute phase occurs at more prolonged time, as shown in Fig. 6. Although the increase of the probability of initially infected cells will shorten the period of the acute phase, our simulation shows that the change of P_{HIV} has little effect on the evolution of asymptomatic phase and the onset of AIDS. Thus the 3D HIV model shows a much better robustness on the probability of initially infected cells than the 2D cellular automata [11,12].

3.3. The asymptomatic phase

As shown in Fig. 4, the density of I cells changes rapidly in the first four months. Actually it is a short time period for the transient process. After the transient phase, the individuals get into a long period of asymptomatic phase. It is a temporal equilibrium state which lets the patient alive with HIV for several years. In this state, as shown in Fig. 4(a)–(c), the density of I cells keeps in a low value of 10% which is typically a little larger than the density of D cells, while the H cells are dominant with a density of about 80%.

However, the D cells can change with a very small probability to I1 cells to induce infectious waves among healthy cells. As shown by the red and yellow lines for the snapshots in Fig. 3 from $t = 15$ to 167 which are in the asymptomatic phase, the infectious wave typically constructs a regular and symmetric shell to spread out before meeting another wave or border. The infectious wave is followed by a wave of D cells. The interior D cell wave acts as a firewall to prevent the infectious wave spreading backward. Then on most sites of D cells, the healthy cells are generated in the next step.

As a result, each grid in the 3D lattice typically shows the following process: it is normally occupied by an H cell. But when an infectious wave is passing by, the H cell becomes I1 cell first and then I2 cell in two time steps. Because of the recognition and killing of the immune system, the I2 cell becomes the D cell in $\tau + 1 = 3$ time steps. Then in the next time step the D cell will be typically replaced by an H cell with $P_{\mathrm{rep}} = 0.99$; otherwise, it will become an I1 cell with a very small

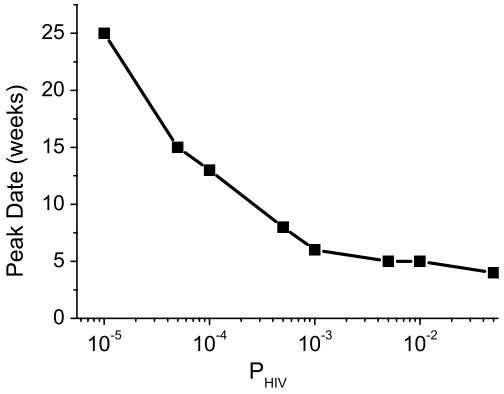

Fig. 6. Relationship between P_{HIV} and peak date. The peak of acute phase shifts to an earlier date with increasing P_{HIV}.

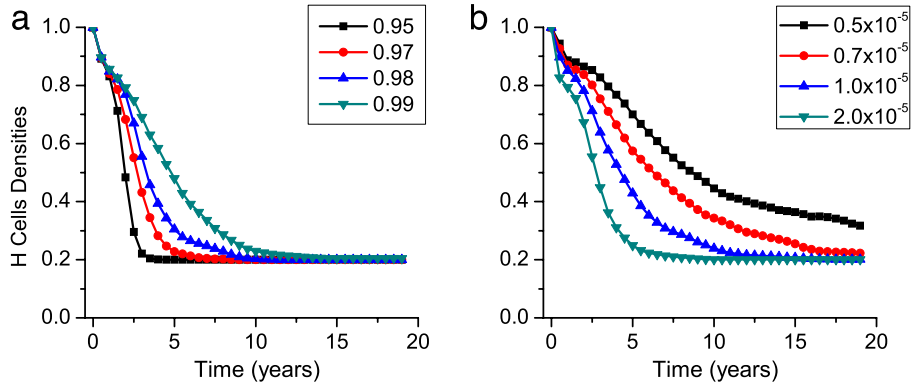

Fig. 7. The average densities of H cells change with time (a) at different P_{rep} levels, or (b) at different P_{inf} levels.

probability $P_{\mathrm{inf}} = 9.74 \times 10^{-6}$. Once an I1 cell occurs, such a single I1 cell typically generates a regular and symmetric wave spreading out into the lattice of H cells.

Now we discuss how the two parameters, i.e. P_{rep} and P_{inf}, affect the asymptomatic phase. The influence of P_{rep} on the HIV dynamics is shown in Fig. 7(a). With a larger value of P_{rep}, which means the more D cells will be replenished with the H cells, the number of H cells decreases slowly. Thus, the increase of the probability that a D cell is replaced by an H cell will lengthen the period of the asymptomatic phase.

The influence of P_{inf} on the HIV dynamics is shown in Fig. 7(b). With a larger value of P_{inf}, which means the more D cells will be replenished with I cells, the number of H cells decreases faster. Thus, the increase of the probability that a D cell is replaced by an I cell will shorten the period of the asymptomatic phase. These results also show that the 3D HIV model is very robust on the model parameters to produce the three phases.

Now we discuss how the rule 1(ii) in Table 1 affects the HIV dynamics. Typically, the density of I2 is about 5%–8% during the asymptomatic phase. Thus, the probability for a lattice to be an I2 cell is less than 10%. According to rule 1(ii), for an H cell to become an I1 cell, it must be surrounded by at least $x = 5$ I2 cells in the nearest neighbor, $y = 9$ I2 cells in the second nearest neighbor, and $z = 4$ I2 cells in the third nearest neighbor. Then the probability to satisfy this condition is a sum of 40 terms with a leading term given by

$$C_6^5 \times C_{12}^9 \times C_8^4 \times 0.1^{18} \times 0.9^8 + (C_6^6 \times C_{12}^9 \times C_8^4 + C_6^5 \times C_{12}^{10} \times C_8^4 + C_6^5 \times C_{12}^9 \times C_8^5) \times 0.1^{19} \times 0.9^7 \approx 4.583 \times 10^{-14}.$$

It is such an extremely small probability for an I1 cell produced via rule 1(ii) per time step even in a $100 \times 100 \times 100$ lattices. However, the rule 1(ii) also affects the HIV dynamics largely.

In Fig. 8, we discuss how the different values of x, y and z modify the period of asymptomatic phase. A general result is that with the increase of x, y or z, which means the decrease of the infecting ability of HIV, the asymptomatic phase becomes longer.

3.4. The onset of AIDS

In our model, the onset of AIDS is defined as when the density of H cells drops to 0.2. The distribution of onset time from the initial infection to the onset of AIDS is plotted in Fig. 9. The distribution shows that the majority of onset time is around 4.5 years and the average onset time is 6.2 years. For different individuals, the onset time varies widely from 1 year to 20 years.

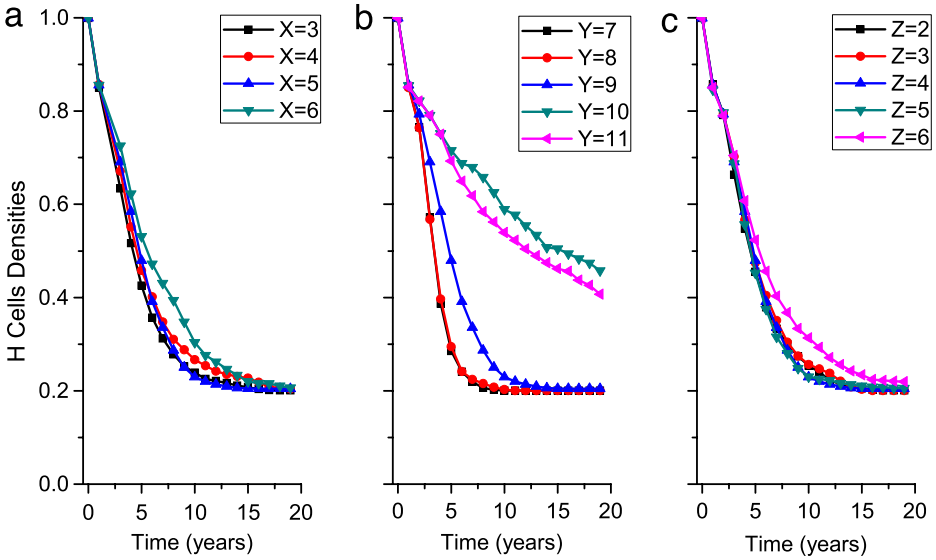

Fig. 8. Modification of x, y, z on the evolution of H cells densities. Average H cells numbers as a function of time at (a) $x = 1, 3, 4, 5$ and 6, (b) $y = 1, 5, 9, 10$, and 12, (c) $z = 1, 2, 4, 5, 6$ and 8. The decrease of x, y or z causes the fast decay of H cells.

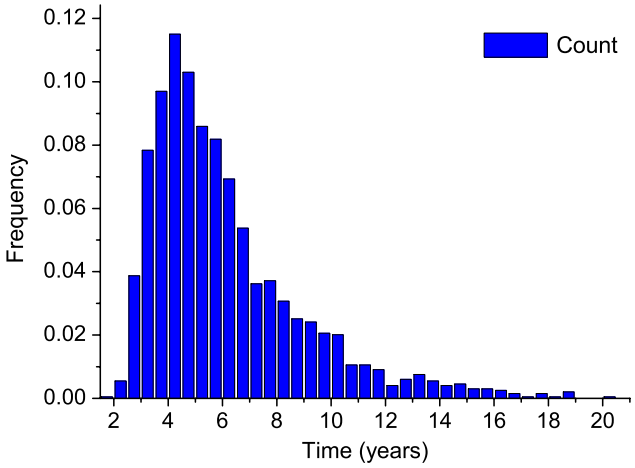

Fig. 9. Distribution of AIDS onset time.

The transition from the asymptomatic phase to the AIDS phase is decided by the occurrence of some special structures. In the asymptomatic phase the number of infected cells randomly oscillates, but it will not increase beyond a threshold. However, once some special structures are constructed in the system, which perpetually generate infectious waves, the AIDS state occurs. An instance is shown in Fig. 10, which is an enlarged part of the inset of Fig. 3 at $t = 368$. At $t = 368$ in Fig. 10, there are only 7 non-healthy cells in the central region and all the other nearby grids in the 3D lattice are H cells. However, updated with time according to the rules given in Table 1, these central grids cannot become D cells simultaneously and then be replaced by H cells. As a result, the grids in this small zone are always partly occupied by infected cells. As a result, such a small zone becomes a perpetual source to successively generate infectious waves to spread out to the system. Then the number of I cells keeps increasing and becomes out of control, giving the onset of AIDS phase.

Another observation in our simulation is that in the asymptomatic phase, a single infected cell typically generates a regular and symmetric wave to infect H cells in the 3D lattice. But with a perpetual source, because there are always several infected cells in the source zone, the generated infectious waves are always irregular and non-smooth.

With the CA model, the AIDS phase is defined after the onset of AIDS. As shown in Fig. 4, another dynamical equilibrium is built up in the AIDS phase, in which the H cells are balanced by the D cells with a density of 20% for them, and the I cells are dominant with a density of 60%. Thus, the CA–HIV model suggests that the AIDS phase is a dynamical equilibrium state, rather than an unstable overflowing process.

4. Discussions

In this paper we study a 3D CA model in detail to investigate the HIV dynamics. The CA–HIV model only considers a few very simple HIV–immune rules which capture the most basic features in the immune–HIV system, and so the model can

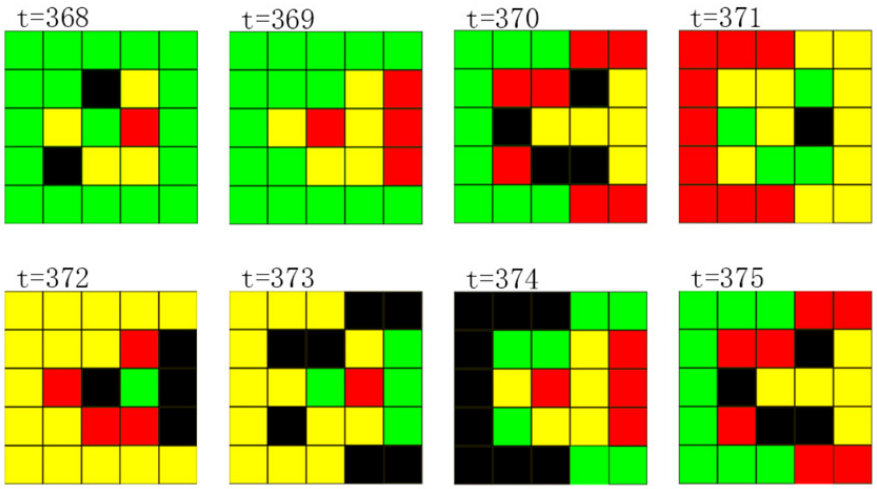

Fig. 10. A perpetually infectious source which is obtained from the inset of Fig. 3 at $t = 368$. At $t = 368$, there are only 7 non-healthy cells in the central region and all the other nearby grids in the 3D lattice are H cells.

reproduce the three-phase development observed in the HIV-infected patients. We show that the 3D HIV model is more robust with the model parameters to reproduce the three stages than the 2D HIV model.

The dynamics of the model has been discussed in detail. In the asymptomatic phase, all the grids are frequently occupied by H cells. But when an infectious wave is passing by, the H cell becomes an I1 cell first, then an I2 cell and a D cell. Finally the D cell typically turns back to an H cell. A single infectious wave which is regular and symmetric is generated occasionally when a D cell becomes an I1 cell with a very small probability. The transition from the asymptomatic phase to the AIDS phase is caused by the occurrence of some special structures. Such a small structure acts as a perpetual source to successively generate infectious waves, which are always irregular and non-smooth, to spread out to the system. The successive waves initiated from the perpetual source give the onset of the AIDS phase. A similar perpetual source has been discussed in the 2D CA–HIV model [11].

In the paper we suggest that the acute state with a short time is a transient process, followed by the asymptotic period which is a temporal equilibrium state. Finally the patient goes to the AIDS phase. It is important to understand that the dynamics in the AIDS phase of the model may have no clinical analog, because a patient is unlikely to survive very far in this stage and the patient will easily die from a variety of normal infections that would easily be cleared for the healthy people. However, it may be of great clinical importance to indicate that the AIDS phase is another dynamical equilibrium state, rather than an unstably overflowing process.

In the model a 3D lattice with $L = 100$ is considered to discuss the immune dynamics in a lymph node. As shown in Fig. 4(d), the model shows large stochasticity in the infected cell number during the asymptomatic phase. The infected cells are given by the infectious waves which are initiated typically by a single infected cell. Such single infected cells are occasionally generated with a very small probability from the dead cells to cause infectious waves, resulting in a large fluctuation of the infected cell number.

The nature of HIV and its interaction with living cells are extremely complex. With the CA–HIV model, we make no attempt to discuss the full HIV dynamics. Only a few very simple rules between immune cells and HIV are considered in the model. As a result, many details could not be discussed, including some that may eventually be important to affect the HIV dynamics, e.g. the mutation of HIV. Our model only consists of 4 types of immune cells in a single lymph node. It has been shown that the viral load affects the HIV–immune interaction [20]. The HIV virus circulation between the lymph node and blood compartments also plays an important role in HIV dynamics [16]. Thus, a more biologically realistic CA model which considers the viral load with the two 3D compartments for the lymph node and plasma may give us more insights on the HIV–immune dynamics.

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