Simulation of a Stochastic Cellular Automata HIV/AIDS Model for Investigation of Spatial Pattern Formation Mediated by $CD4^+$ T Cells and HIV Dynamics

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Abstract: As infection of target immune cells by HIV mainly takes place in the lymphoid tissue, cellular automata (CA) models thus represent a significant step of understanding when the infected population is dispersed over the tissue. Motivated by these considerations, we have introduced a stochastic CA model for HIV dynamics and, particularly, explored its spatiotemporal pattern of infection. In good agreement, the model is successful to reproduce the typical evolution of HIV which is observed in the dynamics of $CD4^+$T cells and infected CD^+T cells in infected patients. The geographical result illustrates how infected cell distributions can be dispersed by spatial community. We have found that pattern formation is based on the relationship among cell states, the set of local transition rules, the conditions and the parameters in the system. The main finding is that the characteristics of dead cells barriers, which greatly control pattern formation in our system, take part in limiting the spread of infection, as well as in bringing the system dynamics toward the end phase of the time course of infection.

Key-Words: Stochastic process, Cellular automata, Monte Carlo simulation, HIV, Leukapheresis

1. Introduction

Since the first case was reported in 1981, the infection by the human immunodeficiency virus (HIV), which caused AIDS (the acquired immunodeficiency syndrome), has been actively studied both in the laboratory and with computer modeling in order to understand the different aspects that regulate the virus-host interaction. In recent years, several mathematical models, mainly based on sets of ordinary or partial differential equations (ODE/PDE), have been developed to investigate the dynamics of HIV infection [1-2]. However, these approaches are limited in describing the spatiotemporal averaged behavior and inaccessible to the stochastic properties of HIV dynamics. This is because ODE/PDE approaches describe the system in terms of the average behavior as a whole–body level [3], while the interaction between the virus and host's immunological response tends to be characterized by geometric communities. For example, after HIV enters a human body, the Langheran's cells that reside in the lamina propria subjacent to the vaginal epithelium play a key role in both priming the initial virus-specific immune response and in serving as a carrier for the transport of antigen to the nearest lymphoid station. At the primary phase, HIV is mostly present in several isolated cells and some is exhibited in the germinal centers of a lymph node. Moreover; the follicular dendritic cell (FDC) network in the germinal centers of a lymph node traps and is dominant over the virus in the latency period. These phenomena are associated with an early dramatic decrease in the viral load and replication in the blood compartment. In contrast, an increase in these events are due to the degeneration of this

compartment architecture in the later phase of the disease.

Many articles [4-7] have developed CA models to explain the dynamics of HIV infection. However, few models successfully describe the two time scales and three phase dynamics of HIV infection. For instance, the first model that could be used to describe the three phase dynamics of HIV was presented by Santos *et al*. [4]. The model used a set of 4 different states of CD4 $^+$ T cells which could be healthy, infected – $A1$, infected – $A2$ and dead. Each state was updated according to four simple rules. Although the basic Santos *et al*.'s model produced results that quantitatively matched the three-phase HIV dynamics observed in clinical data, critics raised one particular issue which was that $P_{HIV} = 0.05$ was too large in comparison to clinical findings. Moreover, when P_{HIV} was too much smaller than 0.05, the initial infected peak did not occur in the model, and there was no distinct first phase dynamics. Then, based on the model of Santos *et al*., Sloot *et al*. [8] later investigated further about the model in order to discover the infectious dynamics when the drug treatment was performed. Instead of infecting all eight neighbors of an infected cell, the number of neighbors to be infected was set to N ($0 \le N \le 7$) with the probability P_{resp}, and $N = 8$ with the probability $\left(1 - P_{resp}\right)$ in this work. The number N was used to mimic the drug effectiveness and P_{resp} represented the capability that the patient responds to the treatment. Sloot *et al*. demonstrated that their simulation results showed the temporal behavior of the immune system to drug treatment which corresponds qualitatively to clinical data. They also commented that the value $P_{HIV} = 0.05$ which was used in their work was too large with respect to known clinical data, and suggested that a more realistic value should be $P_{HIV} = 0.05$ instead.

Moreover, another CA model, based upon realistic biological processes, including the virus replication cycle and mechanisms of drug treatment, was recently proposed by Shi *et al*. [5]. The novel approach of the model was that they incorporated the role of latently infected cells in sustaining HIV infection and included the effect of viral load on the infection rate in the model.

Although the previous studies have shown that the typical evolution of HIV could be predicted and examined by CA models, none has yet investigated in detail the spatial distributions of the spread of infection. It therefore becomes our primary objective in this paper to construct a combined version of stochastic cellular automata models proposed by Santos *et al*. [4] and Shi *et al.* [5] in order to study the dynamics of HIV infection which spreads over the lymphoid tissue with parameter values appropriate to the case in which the antigens spread among CD4$^+$T cells. (This idea is supported by the work of Figueirêdo *et al*. [10] which indicates that interaction within the lymph node occurs on an effective surface with a fractional dimension close to two instead of three). This paper aims to explore the spatiotemporal pattern formation of the spreading population, the knowledge of which may improve our understanding of the invasion of HIV in a mesh structure and the mechanisms underlying its dynamical behavior.

2. CA Model and Simulations

Since a lymphoid tissue, the target and major reservoir of HIV [5] has a mesh structure that could be viewed approximately as a rough surface [11] mostly compound with lymphocytes, we focus on a patch of the lymphoid tissue and represent it as a 2-demensional square lattice of grids. Each grid is the position occupied by one state of CD4$^+$T cell whose state could be: healthy (T), infected stage 1 ($A1$), infected stage 2 ($A2$), latently infected ($A0$) or dead (D). The meaning of each state is defined as below:

Healthy cell (T): a cell that stays an uninfected state and is a target of HIV.

Infected cell stage 1 ($A1$): a cell that has been recently infected. It carries new virus particles and has not been recognized by the immune cells. Hence, it could infect the healthy easily.

Infected cell stage 2 ($A2$): an infected cell that has been attacked by the immune cells. This type of cell thus could infect the healthy only in case of their concentration is above some threshold.

Latently infected cell ($A0$): a cell that suddenly become a latent state after it has been infected. Cells in this state cannot be transmitted to other cells.

Dead cell (D): the state of an infected cell that is killed by immune response.

To represent the patch of lymphoid tissue and avoid the finite size effect, we use the periodic boundary condition for the model and set the initial condition so that the healthy CD4$^+$T cells in the system is randomly mixed by a fraction of

infected cell stage 1 ($A1$) with probability P_{HIV} . Then, in the process of simulation, we generate the entire course of HIV progression by changing the state of $CD4^+$ T cells in every time step according to the set of local transition rules shown below.

Description	Parameter	Value/ Condition
Boundary condition	-	periodic
Lattice size, $L \times L$	L	100
Neighboring cells	N	8
Probability of initial $A1$ cells	P_{HIV}	0.005
Probability that a T cell becomes an $A1$ cell	P_{inf}	0.999
Probability that a T cell becomes an $A0$ cell	$1 - P_{inf}$	0.001
Probability that an $A0$ cell is activated	P_{act}	0.0025
Probability that a D cell position is replenished by a T cell	P_{repl}	0.99
Probability that a D cell position is replenished by an $A1$ cell	P_{infec}	-
Number of $A2$ cells in neighborhood to cause the center cell to become infected	R	4
Time delay for an $A1$ cell to become an $A2$ cell	$\tau 1$	4
Time delay during with an $A0$ cell stays inactive	$\tau 2$	30
Simulation time	-	200

Table 1. Model parameters and conditions.

Table 1 lists and all the parameters and conditions used in our model. Each time step of simulation corresponds to one week. The new state of a cell is dictated by the state of its neighbors with the Moore's neighborhood with the neighborhood of range r = 1. The number of neighbors [5] is $(2r+1)^2 - 1$.

The results obtained from our simulations are shown in Figure 1. We note that although the number of free virus particles is seem to be playing a crucial role as proposed by Shi *et al.*, we have ignored this parameter in our model. However, we have assigned it as proportional to the number of infected cells as done by Santos *et al*. instead. Also, our model is operated under the assumption that the percentage of healthy $CD4^+$T cells and the percentage of infected $CD4^+$T cells in our simulation results represent the cell dynamics in the lymphoid tissue and could be related directly to the trend in $CD4^+$T cell count and plasma viremia in blood, respectively, of an HIV infected patient.

The updating rules are as follows.

(1) Rule for Healthy cells

If a healthy cell (T) is in contact with at least one infected cell stage 1 ($A1$) or at least R cells of infected cell stage 2 ($A2$),

(A) The healthy cell becomes an infected cell stage 1 ($A1$) with the probability P_{inf} .

(B) The healthy cell becomes a latently infected cell ($A0$) with the probability $1 - P_{inf}$.

(2) Rule for infected cells stage 1

If an infected cell stage 1 ($A1$) has lived in the system for longer than $\tau 1$ time steps ($t > \tau 1$), the infected cell stage 1 ($A1$) becomes an infected stage 2 cell ($A2$).

Otherwise, it remains the same state.

(3) Rule for infected cells stage 2

An infected cell stage 2 ($A2$) becomes a dead cell (D) at the following step.

(4) Rule for dead cells

A dead cell (D) is replaced by a healthy cell (T) with the probability P_{repl} .

Otherwise it remains unchanged with the probability $1 - P_{repl}$.

(5) Rule for latently infected cells

If a latently infected cell ($A0$) has lived in the system for longer than $\tau 2$ ($t > \tau 2$) time steps, the latently infected cell ($A0$) becomes an infected cell stage 1 ($A1$) with the probability P_{act} . Otherwise, it stays unchanged.

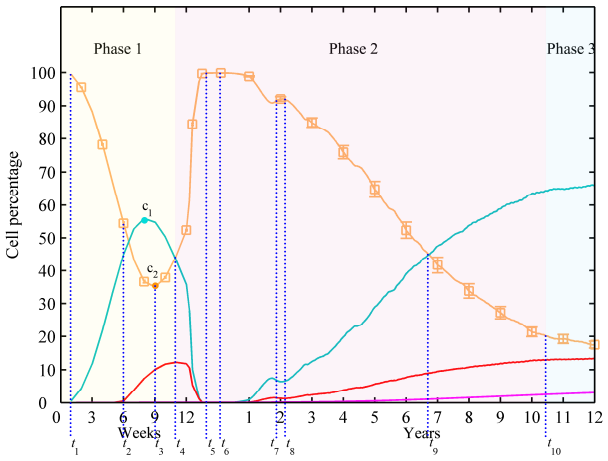

Figure 1. The natural course of HIV dynamics. The results obtained from our simulation averaged over 200 samples and the correlating standard error of the mean (SEM) with $L = 100$, $P_{HIV} = 0.05$, $P_{inf} = 0.999$, $P_{act} = 0.0025$, $P_{repl} = 0.99$, $R_{A2} = 4$, $\tau 1 = 4$, $\tau 2 = 30$. The orange curve corresponds to healthy cells (T), light blue the infected cells $(A1 + A2)$, red the dead cells (D) and violet the latently infected cells $(A0)$. The typical evolution of HIV is represented in two time scales (weeks and years) and divided into three phases, distinguished by the color shaded areas.

3. Results and Discussion

The simulation results are divided into three sections – *Phase 1*, *Phase 2* and *Phase 3* according to the three phases in the dynamics of HIV infection.

Phase 1 – the acute phase of infection (corresponding to the time period from t_1 to t_3 in Figure 1 and to the spatiotemporal patterns seen in Figures 2A-2C)

The beginning configuration (week 1) corresponding to time t_1 depicts a square lattice sheet of healthy $CD4^+T$ cells which is randomly mixed by a fraction of infected $CD4^+T$ cells stage 1 ($A1$) with $P_{HIV} = 0.005$ (Figure 2A). Then, the initial $A1$ cells are going to spread the virus to their healthy neighbors. We could observe the healthy cells surrounding the initial $A1$ cell transforming into an infected cell stage 1, before the initial $A1$ cells becoming weak and transforming into infected cells stage 2 ($A2$) (after $\tau 1$ steps) which characterizes the effect of human immunity to the antigens, dead state (D), and then are replaced by the newly healthy cell in a step by step fashion. These events would give rise to each initial $A1$ cell generating a quadratic band of infected cells, of width $(\tau 1 + 1)$, propagating in all directions in the subsequent time steps, and would lead to a rapid increase in the infected cell population $((A1 + A2))$ generally due to a high replication of HIV causing a rapid decrease in the number of healthy cells (T).

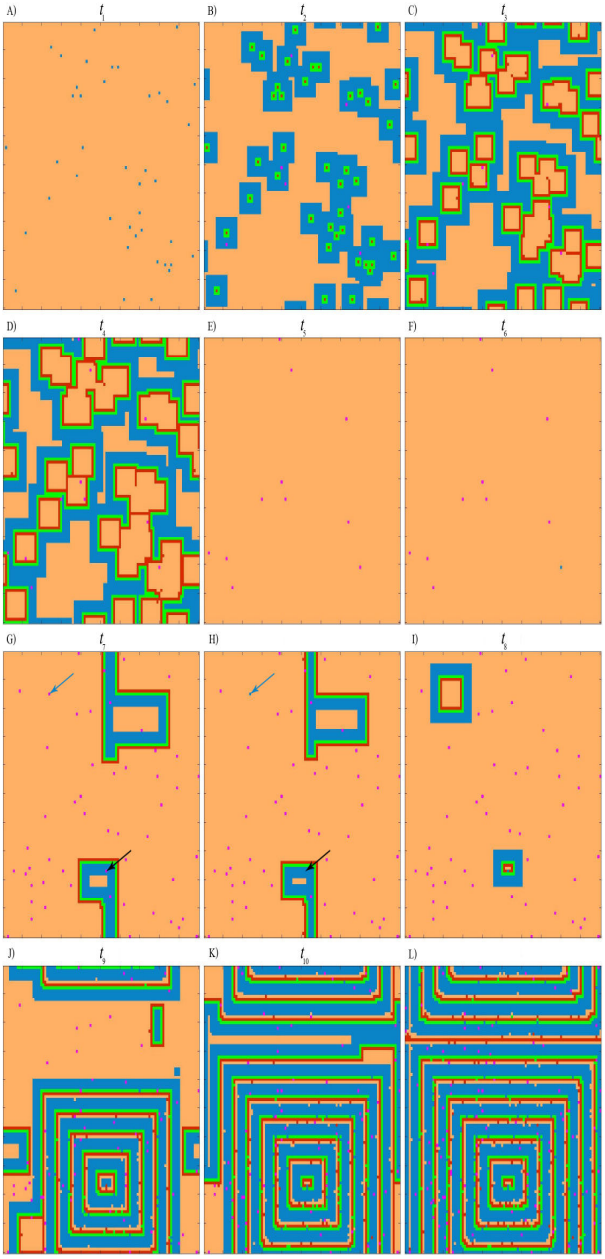

Figure 2. The lattice snapshots. Each grid in the lattice represents one $CD4^+$ T cell position. The orange grid is a healthy (T) position, the blue infected cell stage 1 ($A1$), the green infected cell stage 2 ($A2$), the violet latently infected stage ($A0$) and the red dead cell position (D).

In our model, the distribution of initial $A1$ cells is randomized. We found that if the initial $A1$ cell coordinates are closer together, the $A1$ cells would continually propagate to infect the healthy neighbour cells with each time step, and the outer rings of infected cells $(A1+A2)$ would overlap with each other. The occurrence of these intersections would put a limit on the increment in infected population and confine the level of infected cells $(A1+A2)$ at the initial peak (c_1), when $t = 2\tau 1$.

We have found that, for a fixed initial concentration P_{HIV} of well distributed $A1$ cells, in order for the infection dynamics to attain the highest initial infection peak (c_1), the mean distance between initial $A1$ cells, $\langle d \rangle$, should be not less than $\frac{1}{\sqrt{P_{HIV}}}$.

With our model, the well distributed initial configuration attains the highest initial infection peak when the mean distance between two initial $A1$ cells is at least $\langle d \rangle \approx 14.14$. The eventual pattern of infection is then completely clustered and no overlapping occurs.

The key point of this report is that the wall of dead cells, which we have named a *dead cell barrier*, occurs midway between the infected cells and the new T cell population in every step (see Figure 2C). Due to the Moore's neighborhood with the neighborhood of range r = 1, we emphasize the observation that this *dead cell barrier* would cause the $A1$ cells to infect only the T cells which are located around their outer boundary (outer zone), but definitely could not contaminate the new T cells enclosed inside the inner zone.

Our simulated time course thus shows the decrease in infected cells and the regain of T cells that mimic the initial HIV-specific immune responses, particularly due to HIV specific cytotoxic T lymphocytes (CTLs) [29-32] in real observations.

Phase 2 – the latency/chronic phase of infection (corresponding to the time period t_4 to t_9 in Figure 1 and to the spatiotemporal patterns in Figures 2D-2J)

The beginning of phase 2 is marked by the point in time when T cells and infected cells $(A1+A2)$ intersect, evolving to time t_4 (see also Figure 2D). The broadening of a dead cell barrier is associated with the regain of T cells, while the infected cells are shrinking and are soon cleared out from the lattice. We note that the infected source which originates the wave structure in such a fashion (increase of infected cells, followed by a rapid clearing out) is called "an acute source". This is because it has the same wave structure which is dominant in phase 1. Then, the lattice is left as only a field of healthy cells sparsely mixed with a few latently infected cells ($A0$) (Figure 2E). The lattice would return to a completely healthy state if there is no latent state in this model). The configuration corresponds to time t_5 in the Figure 1 which represented the highest level of T cells (or the highest period), of which percentage varies as P_{inf}.

Phase 3 – on set of AIDS (corresponding to t_{10} in Figure 1 and to the spatiotemporal patterns in Figures 2K-2L)

Figure 2K shows the infectious pattern at the time when the number of T cells has dropped lower than 20% of the total number of cells in lattice. We mark this threshold as the beginning of phase 3 or the onset of AIDS, evolving to time t_{10}. The infectious pattern appears like an invasive wave that eventually covers the entire lattice in such a way that, at every $(\tau 1+3)$ time steps, it would launch a propagating wave front of infected cells of width $\tau 1+1$. Then, the invasive wave covers the whole lattice (see also Figure 2L). The steady state is reached, in which the percentages of each cell state are kept relatively fixed and distribution patterns are unchanged.

4. Conclusion

Because cellular automata (CA) are discrete model that could successfully describe the two time scales (short scale in weeks, long scale in years) and reproduce the three distinctive phases of the HIV infection, we thus have studied the stochastic CA model for HIV dynamics with respect to the spatiotemporal pattern formation of $CD4^+$T cells. From our investigation, we have found the pattern formation is based on the relationship among the cell states, the set of local transition

rules, the conditions and the parameters in the system. Due to the Moore's neighborhood with the neighborhood of range $r = 1$, we have observed that the pattern of infectious wave which propagates in all directions is quadratic. We also have found that the probability of initial $A1$ cells, P_{HIV}, and their distribution effect the percentage of infected cells at the initial peak (c_1). A large P_{HIV} would affect a higher level of infected cells at c_1 than a smaller P_{HIV}. However, for one P_{HIV} value, the system in which the initial $A1$ cells are well distributed at the first configuration would provide a more completely clustered configuration of infection, or a less overlapping one. This would lead to a higher initial infection peak (c_1) in the system than the one in which the seed distributions are crowded.

Moreover, we have found the dead cell barrier is the major control factor in the cells dynamics in our simulations. We have noted that the wall of dead cells would divide the healthy cells (T) into two zones: inner and outer zones of infectious clusters. The outer zone is bounded by infected cells and would be infected at each time step, while the T cells located in the inner zone is bounded by the wall of dead cells and could not be infected. This event causes the accumulation of T cells within the wall of dead cells constantly over time. Specifically, this spatiotemporal pattern formation would cause the rebounding of healthy cells at the early phase of infection in our simulations (and probably so too in those of Santos *et. al.*) which resembles the initial immune response specific to the antigen after the primary attack from HIV.

The knowledge gained from our study may improve our understanding about the invasion of HIV in a mesh structure and the underlying mechanisms which could provide a valuable guide for future research to discover new measures for the prevention and treatment of HIV infection.

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