Investigation of Spatial Pattern Formation Involving CD4+ T Cells in HIV/AIDS Dynamics by a Stochastic Cellular Automata Model

Monamorn Precharattana, Wannapong Triampo, Charin Modchang, Darapond Triampo and Yongwimon Lenbury

Abstract— In recent years, discrete models have emerged to play an important role in the study of immune response especially in the problem involving human immunodeficiency virus (HIV) infection, leading to AIDS. As infection of target immune cells by HIV mainly takes place in the lymphoid tissue, cellular automata (CA) models thus represent a significant step toward understanding how the infected population is dispersed. Motivated by these considerations, we introduce a stochastic CA model for HIV dynamics and explore the spatiotemporal pattern of infection. The model is successful in reproducing 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 on cell distributions illustrates how infected cells can be dispersed by spatial communities. We have found the pattern formation is based on the relationship among cell states, the set of local transition rules, the conditions and the parameters in the systems. The main finding is that the emergence of dead cells barriers greatly controls the pattern formation in our system, by limiting infections and the manner in which the infection dynamics is brought to the last phase after the barrier is destroyed.

Keywords—Cellular automata simulation, HIV, Leukapheresis, Monte Carlo, Stochastic process

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I. 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 [1]-[5]. 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 [6]-[8]. However, these approaches are limited in describing the spatiotemporal averaged behavior and inaccessible to the stochastic properties of HIV dynamics. This is because the ODE or PDE approaches describe the system in terms of the average behavior as a whole–body level [9], 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 is due to the degeneration of this compartment architecture in the later phase of the disease.

Many articles [10]-[13] 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 and Coutinho [12]. 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 and Coutinho'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 and Coutinho [12], Sloot *et al.* [14] 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 ($0 \leq N \leq 7$) 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 $P_{HIV} = 0.005$ 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.* [13]. 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 and Coutinho [12] and Shi *et al.* [15] 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.

II. CA MODEL AND SIMULATIONS

Since a lymphoid tissue, the target and major reservoir of HIV [16],[17] has a mesh structure that could be viewed approximately as a rough surface 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 recognized by the immune response. This type of cells thus could infect the healthy ones only in cases where the concentration is above a certain threshold.

Latently infected cell ($A0$): a cell that becomes a cell in the latent state right after it is infected, yetal still be activated after a long period of dormancy to produce infectious particles. Cells in this state cannot transmit the infection to the healthy 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.

Table I Model parameters and conditions.

Description	Parameter	Value/ Condition
Boundary condition	-	Periodic
Lattice size, $L \times L$	L	100
Neighboring cells	N	8
Probability of initial T and $A1$ 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

Table I (Cont.) Model parameters and conditions.

Description	Parameter	Value/ Condition
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
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	$\tau1$	4
Time delay during with an $A0$ cell stays inactive	$\tau2$	30
Number of simulations	-	200

Table I 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 Fig. 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 viral load 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 $\tau1$ time steps ($t > \tau1$), 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 $\tau2$ ($t > \tau2$) time steps, the latently infected cell ($A0$) becomes an infected cell stage 1 ($A1$) with the probability P_{act}.

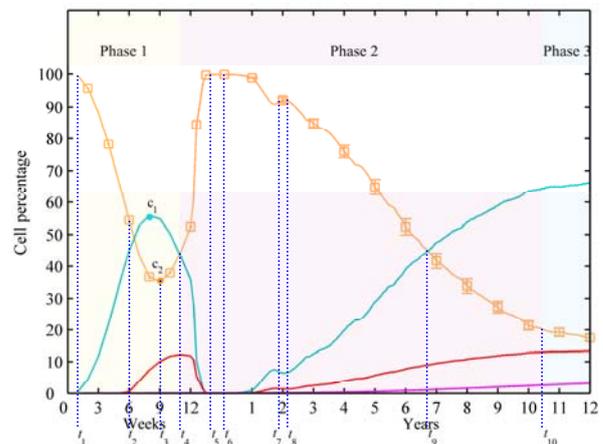Otherwise, it stays unchanged.

Fig. 1 The natural course of HIV dynamics. The results obtained from our simulation averaged over 200 samples with $L = 100$, $P_{HIV} = 0.05$, $P_{inf} = 0.999$, $P_{act} = 0.0025$, $P_{repl} = 0.99$, $R_{A2} = 4$, $\tau1 = 4$, $\tau2 = 30$. The orange curve corresponds to healthy cells (T) with the standard error of the mean (SEM), 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.

III. 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 Fig. 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 (Fig. 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 $\tau1$ 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 ($\tau1+1$), 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).

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 $t = 2\tau1$. With this typical cell state transitions, we note that all cell states appear for the first time concurrently at week $t = \tau1+2$ (see also Figure 3B which corresponds to time t_2 in Figure 2) in which a cluster of infected cells consists of $A1$ cells at P_{inf} = 0.999 and $A0$ cells at a probability 1- P_{inf}, $A2$ cells and dead cells which has replaced the initial $A1$ cells. Afterwards, the dead cells located at the center of an infectious cluster would be later replenished by the newly healthy cells at the probability P_{repl} at time $t = \tau1+3$.

In order to investigate in more detail the effect of initial distributions of $A1$ cells on the level of initial infected peak (c_1), we let the initial configuration be such that the initial $A1$ cells are perfectly distributed among the healthy cells and the healthy cells that are infected would only transform to infected cell stage 1 ($A1$). Under the assumption of no collisions among the expanding areas before the infection reaches the initial peak (c_1), the behavior is completely deterministic and the number of infected cell ($A1+A2$) would grow quadratically with time. The number of infected cells ($A1+A2$) after t iterations is described as

$$P(t = k+1) = (2k+1)^2 P_0 - P(t = k-4) \qquad (1)$$

where P_0 is the initial number of infected cells stage 1, $k = 0$, 1, 2,…, while $P(t < 0)$ is defined to be zero.
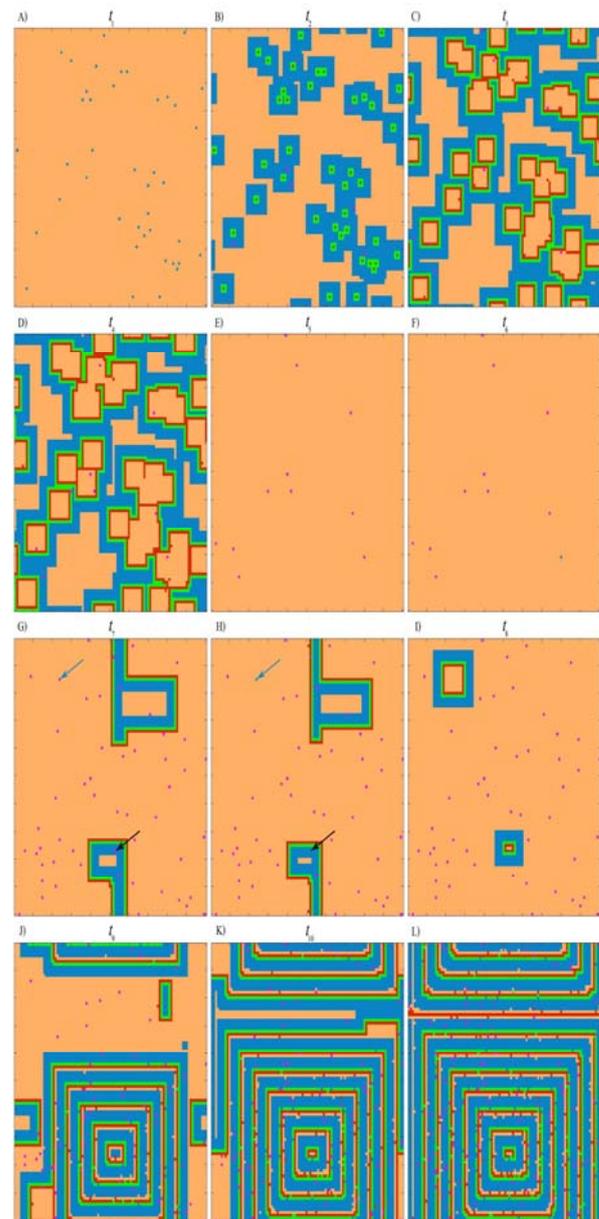

Fig. 2 The lattice snapshots. Each grid in the lattice represents one CD4$^+$ T cell position. The orange grid is a healthy (T) position, the blue infected cell stage 1 ($A1$), the green infected cell stage 2 ($A2$), the violet latently infected stage ($A0$) and the red dead cell position (D).

The term on the left of (1) is the number of infected cells ($A1+A2$) at time t, the first term on the right is the number of all cell states in the square cluster of infection and the second term on the right is the sum of the numbers of dead cell and the newly healthy cell s enclosed in the infectious

cluster at that time. For example, suppose that the system consists of only one initial $A1$ cell ($P_0 = 1$) at the first week. For $k = 0$, the deterministic (1) could be written as $P(t=1) = 1$. Then at week 2 after the virus has spread to neighboring cells, it is found that the infected cells living in the system would be 9 cells due to $k = 1$; $P(t=2) = 9$. Moreover, at week 7 which is the first time that the newly healthy cells replace the dead cells, $k = 6$;

$$P(t=7) = ((2 \times 6) + 1)^2 - P(t=2).$$

So, it was found that the number of infected cells at this time step would be equal to 160 cells.

A comparison of the behavior, during early period, between the infected cell dynamics given by our stochastic model (the short green dashed line) and the graph of infected cell dynamics given by (1) (the blue solid line) is shown in Fig. 4. It can be seen that the level of infected cells at the initial infected peak (c_1) given by our stochastic model is less than that predicted by (1). This is due to the overlap of cells over time arising from the close proximity of initial $A1$ cells.
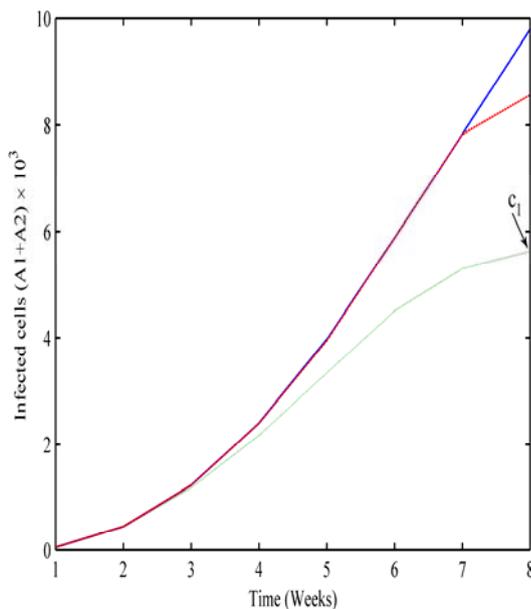

Fig. 4 The number of infected cells ($A1 + A2$) as a function of time during the early phase of infection. A blue line shows the infected dynamics according to the deterministic (1), the green line is obtained from our stochastic simulations when the initial $A1$ cells were randomly distributed and the red line is obtained from our stochastic simulations when the initial $A1$ cells are regularly arranged for which the mean distance between initial $A1$ cells, $\langle d \rangle$, is slightly greater than 14 grids.

This suggests that the level of infected cells at the initial peak (c_1) given by our stochastic model will be closer to that predicted by (1) if the initial $A1$ cells are located sufficiently far from each other which provides the least chance for the

clusters of infection to overlap. In practice, this may be done by reducing the concentration of initial $A1$ cells, (P_{HIV}), or utilizing the well distributed condition for initial $A1$ cells.

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 $\dfrac{1}{\sqrt{P_{HIV}}}$.

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.

To find out what causes T cells to rebound in our model, we consider Fig. 3C which shows the configuration when the young $A1$ cells (located at the rim of a cluster and aged less than $\tau 1$) continually threaten the neighboring cells until the T cells level drops to the lowest point in Phase 1 (c_2) (normally occurring one week after the initial peak of infected cells (c_1) is reached, $t = 2\tau 1 + 1$). We notice in this step the followings.

1) The initial $A1$ cells located at close proximity to each other in week 1 have dispersed until some of border dead cells are in contact with each other. Moreover, some are fused together and disappear. This incident necessitates that the newly healthy area would be situated more and more in the same territory in subsequent time.

2) Moreover, the figure also shows the T cells to be separated in two zones: inside and outside the infectious cluster. The inner zone is the area bounded by the dead cells, while the outer zone is the area bounded by the infected cells and would be infected in the next time step.

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 Fig. 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) in real observations.

As our model is a combination of those by Santos and Cotinho's [12] and Shi *et al.*'s [13], we thus next compare the spatiotemporal pattern formations and the quantitative results in Phase 1 [12],[13].

We found that although Santos and Cotinho's and our work represent the first configuration as a square lattice sheet of healthy CD4+T cells sparsely mixed by the initial $A1$ cells (referred to as *infected - A1* in [12]) at the probability P_{HIV},

the initial $A1$ cells in our model is more widely distributed than Santos Cotinho's. In Santos and Cotinho's model, the configuration holds initial $A1$ cells at 5% of the total number of cells in the system. Our model contains only 0.5% ($P_{HIV} = 0.005$). We choose this value in our work because the observation that one in 10^2 to 10^3 T lymphocyte cells harbor viral DNA during primary infection [18]. We thus concluded that $0.001 \leq P_{HIV} \leq 0.01$ seems to be the correct range [19] and chose to set $P_{HIV} = 0.005$.

Besides, due to their initial number of $A1$ cells being 10 times greater than ours, the initial $A1$ cells thus spread out and then cover almost all of the space within a short time. This event would lead the infected cells reaching the peak (c_1) in 5 week before the newly healthy cell could have been replenished into the system. Their spatiotemporal pattern exhibits a period in which the level of healthy cells drops to nearly 0 after infection which has no supporting clinical data. Unlike their model, at the time when the infected cells level reaches the highest value of Phase 1 (c_1) in our model, the spatiotemporal pattern already shows the occurrence of replenishment by newly healthy cells while the spread of infected cells has not covered the entire space yet (week $t_3 - 1$). This spatiotemporal pattern formation would result in the dynamics of infected cells in our simulation to reach the c_1 position more slowly and at a lower level than given by Santos and Cotinho. Moreover, Shi *et al.*'s model also exhibits a slower progression to a lower peak than in Santos *et al.*'s simulation as well.

Besides, like in Santos and Cotinho's model, this event (the highest level of infected cells) both in Shi *et al.*'s and in ours would affect the number of healthy cells that drops to the lowest point (c_2) in the following step. However, we found that at this point (c_2) the number of remaining healthy cell is $\approx 35\%$ of the total number of cells in our work while, in Shi *et al.*'s, there are only $\approx 20\%$ remaining. Because the general pattern in infected patients [20] it is observed that the number of $CD4^+T$ cells decreases to approximately 50% of the value prior to infection.

We thus would like to observe that our model can reproduce the level of healthy cells at this point that is closer to the clinical value than the other models under discussion (Santos and Cotinho's model and Shi *et al.*'s model). This is because, as stated in the literature [14], Santos and Cotinho used a P_{HIV} which is too large with respect to known clinical data.

Phase 2 – the latency/chronic phase of infection (corresponding to the time period t_4 to t_9 in Fig. 1 and to the spatiotemporal patterns in Fig. 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 Fig. 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 ($A0$) (Fig. 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 Fig. 1 which represented the highest level of T cells (or the highest period), of which percentage varies as P_{inf}.
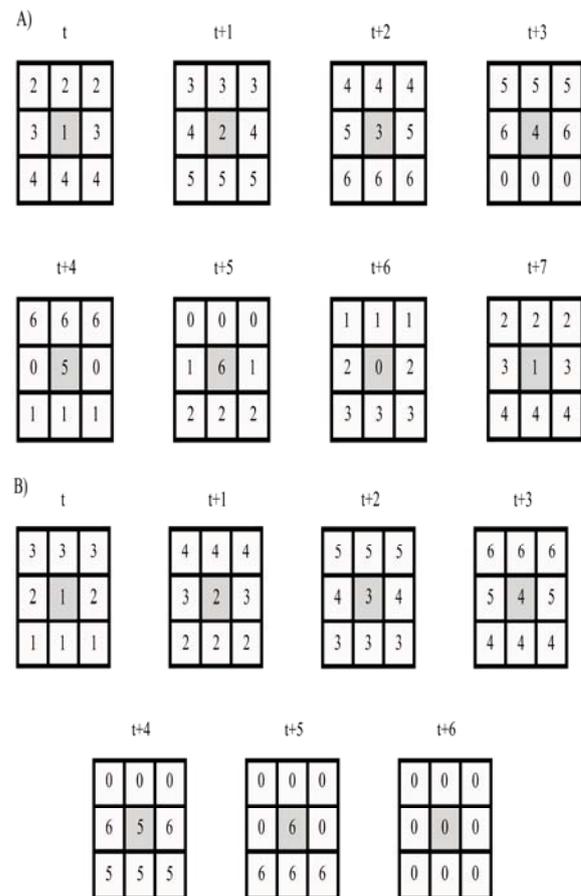

Fig. 5 The local view of a new infected source (the shaded coordinate). 0 = T cell, 1 = 1 week old $A1$ cell, 2 = 2 weeks old $A1$ cell, 3 = 3 weeks old $A1$ cell, 4 = 4 weeks old $A1$ cell, 5 = $A2$ cell, and 6 = D cell.

A) is the case that a latently infected cell is activated on the 3 weeks old $A1$ cells circumference (noticed by there is a state "1" grid between two state "3" grids). It would act as a chronic source initiating the invasive wave over time leading to AIDS (compare t to $t + 7$).

B) is the case that a latently infected cell is activated on the 2 weeks old $A1$ cells circumference. It would act as an acute source originating the propagating wave structure in all

directions, but then soon clear out from the system (clearly seen at $t = t + 6$).

The period that the T cells remains on the high plateau is defined by the time delay during which the $A0$ cell stays inactive ($\tau2$), together with P_{act}, before they are continually reducing again due to the immune response deterioration related to several strategies of HIV to evade the immune response [21]-[23]. However; in our model, we note that this slow decrease in the level in T cells is only determined by the activation of latently infected cells ($A0$).

We also notice that the different environment that $A0$ cell is activated would make the two different kinds of wave structure (Fig. 2G and 2H, evolving to time t_7 in Fig. 2). The $A0$ cell, which is activated among the T cell neighbors (indicated by the blue arrow) or activated on a week or two weeks old $A1$ cells circumference ($t < \tau1 - 1$), would act like the acute source leading a lattice abundant with T cells again and again (more clearly seen in the infectious cluster at the top left corner of Fig. 2I). In contrast, the $A0$ cell, which is activated either on three (or more) weeks old $A1$ cells circumference ($t \geq \tau1 - 1$) (indicated by the black arrow), on $A2$ cells circumference or on the dead cells barrier, would be able to break the wall of dead cells and originate the infectious structure like invasive wave pattern (a repeated wave which is continually emanated from a source, then we obtain a pattern of concentric waves) which, at every $\tau1 + 3$ time steps, propagates the wave structure with its infected wave front of width $\tau1 + 1$ in all directions over time. This event would result in the continuous decrease in T cell population in contrast with an increase in the infected cell population in our simulation over time leading to the last phase of infection eventually (more clearly seen in the bottom cluster of Fig. 2I, corresponding to time t_8 in Fig. 2). We call the source that originates an invasive wave "a chronic source" in our model.

For more understanding of the activation of $A0$ cells leading to the two different kinds of wave structure, please, see the diagrams in Fig. 4 which shows the local view of a new infected source.

As time progresses, Fig. 2J, corresponding to time t_9, shows the step when the infected cells are continually invading the T cells till their levels are overlapping. Then the infected cells dominate over the T cells.

In addition, we found that the dynamics of CD4$^+$T cells reaches the highest point at which the level is approximately 70% of the value prior to infection. None of the models mentioned here- Santos $et\ al$.'s model, Shi $et\ al$.'s model and our model – could reproduce the dynamics in which the healthy level is equal or close to that at this highest point.

Besides, in the models of Santos and Cotinho's, Shi $et\ al$.'s and in ours, the infection originates from the initial $A1$ cells. However, in Santos and Cotinho's model, in the later phase of progression, a new source of infection arises when the dead cell positions can be replaced by healthy cells at the probability P_{repl}. Moreover, each new healthy cell introduced

may be synchronously replaced by an infected cell stage 1 (namely infected- $A1$ in Santos and Cotinho's model) at the probability P_{infec}. Hence, the presence of infected cells will be dictated by the value $P_{newinfec} = P_{repl} \times P_{infec}$ [12]. They also observed that this phenomenon might result from the activation of latently infected CD4$^+$T cells at a random time or the introduction of infected cells from other compartments [12]. In our work and Shi $et\ al$.'s work, a new source of infection is introduced by the activation of latently infected cells ($A0$) at the probability P_{act} at appropriated time (probability $\left(1 - P_{inf}\right) \times P_{act}$).

We also observe that the new source of infection in the later phase, in Santos $et\ al$.'s model and in our model, could generate two different kinds of structures.

The first type of structures corresponds to a wave of infected cells propagating in all directions and then soon disappearing from the lattice, namely an acute source. (For instance the bottom right of Fig. 3b and 3c in Santos and Cotinho's [12] and the top left of Fig. 3I in our simulation). We also compare the mean distances between the new infected sources both in Santos $et\ al$.'s model given by $P_{repl} \times P_{infec}$ and in our model given by $\left(1 - P_{inf}\right) \times P_{act}$ and the mean distance of initial $A1$ sources given by P_{HIV}. Since

$$\left(\left(1 - P_{inf}\right) \times P_{act}\right) < \left(P_{repl} \times P_{infec}\right) \ll P_{HIV}$$

we found that the mean distances between the new sources are greater than that of the initial sources [12]. Moreover, the mean distances between the new sources in our model are larger than those in Santos and Cotinho's work.

The second special structure is generated by a source leading to AIDS, namely a chronic source. In the model of Santos $et.\ al$.'s, This structure occurs when a newly infected cell stage 1 (namely infected- $A1$ in Santos $et\ al$.'s model) is surrounded by at least R dead cells, and the other neighbors are healthy [12], [19]. In contrast, with our model this structure is observed when the latently infected cell ($A0$) is activated two weeks (or more) later than $A1$ cells on the same circumference, or activated on the same circumference of $A2$ cells or D cells. Moreover, this chronic source would launch an invasive wave front of infected cells with width ($\tau1 + 1$) at every ($\tau1 + 3$) time steps both in Santos and Cotinho's model [12] and in our model. Examples of such structures are shown in the top left corner of Fig. 3b and 3c in Santos and Cotinho's [12] and the bottom right corner of Fig. 2I in our simulation).

Phase 3 – onset of AIDS (corresponding to t_{10} in Fig. 1 and to the spatiotemporal patterns in Fig. 2K-2L)

Fig. 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 corresponding to 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 ($\tau1+3$) time steps, it would launch a propagating wave front of infected cells of width $\tau1+1$. Then, the invasive wave covers the whole lattice (see also Fig. 2L). The steady state is reached, in which the percentages of each cell state are kept relatively fixed and distribution patterns are unchanged.

Finally, we also note that in the last phase of infection the spatiotemporal pattern formations show the same pattern in both models - Santos *et al.* and ours, in that the growing structures eventually cover the entire lattice, with the number of cells tending towards steady states until the final average number of the healthy cells is always below the threshold of the CD4$^+$T cell count related to AIDS (more precisely, see Fig. 3d in Santos and Cotinho's [12] and in our Fig. 2L).

We want to highlight that, as seen in [20], in the last phase of infection, the number of CD4$^+$T cells is rapidly decreasing in tending toward zero. However, all of the models under discussion- Santos and Cotinho's , Shi *et al.*'s and ours, this behavior cannot be reproduced. Especially in Shi *et al.*'s model, we observe that the cell dynamics evolves into the steady state too quickly (within 12 years). In our opinion, such quantitative results might be due to the model's sensitivity to the variation of neighbouring cells.

IV. 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 and Cotinho's) which resembles the initial immune response specific to the antigen after the primary attack from HIV.

Besides, we have found the dead cell barrier is the major control dynamics of cells in ours. We have highlighted that the wall of dead cell would divide the healthy cell (T) into two zones: inside and outside of infectious cluster. The outside zone is bounded by infected cells and would be infected at each time step, while the T cells located inside zone is bounded by the wall of dead cell and could not be infected. This event causes the accumulation of T cells within the wall of dead cells constantly over time. For the graph of cell dynamics point of view, this spatiotemporal pattern formation would, especially, cause the rebounding of healthy cells at early phase of infection in ours (so might too in Santos *et. al.*) which resembles the initial immune response specific for the antigen after primary attack from HIV [24].

Moreover, we have found two different kinds of wave structure in the system. The first structure is a band of infected cells, of width $\tau1+1$, propagating in all directions from the source, but when time passes it then soon clears out from the lattice. The feature of this wave pattern is dominant in Phase 1. We thus call the source that originates this kind of wave structure an "acute source". The source of this wave structure is the $A1$ cells which are bounded by the T neighboring cells, or the $A0$ cells that are activated among the T cells or on a week or two weeks old $A1$ cells circumference. The second wave structure is a special kind of structures. It is an invasive wave structure which continually propagates a band of infected cells of width $\tau1+1$ at every $\tau1+3$ time steps in every direction. The source of this kind of wave structures is the $A0$ cell that is activated on either three or more weeks old $A1$ cells circumstance, on $A2$ cells circumstance or on the dead cell barrier. The activation of this kind of source could break the wall of dead cells and then causes the T cells located inside the inner zone to be subsequently infected over time making the pattern of infection like an invasive wave. This spatiotemporal pattern formation results in the continuous reducing of T cell population leading to AIDS in our model which represents the severe deterioration of the immune system within the body [25]. Because the structure of this kind of waves is permanent (from Phase 2 on), we thus name it a "chronic source".

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.

REFERENCES

[1] W. Cavert, D. Notermans, K. Staskus, S. Wietgrefe, M. Zupancic, K. Gebhard, K. Henry, Z. Zhang, R. Mills, H. McDade, "Kinetics of

response in lymphoid tissues to antiretroviral therapy of HIV-1 infection", *Science*, Vol. 276(5314) pp. 960-964, 1997.

[2] A. Haase, K. Henry, M. Zupancic, G. Sedgewick, R. Faust, H. Melroe, W. Cavert, K. Gebhard, K. Staskus, Z. Zhang, "Quantitative image analysis of HIV-1 infection in lymphoid tissue", *Science*, Vol. 274(5289) pp. 985-989, 1996.

[3] B. Betechuoh, T. Tim, T. Marwala, M. Lagazio, "Using genetic algorithms versus line search optimization for HIV predictions", *WSEAS Transactions on Information Science and Applications*, Vol. 3(4) pp. 684-690, 2006.

[4] J. Guardiola, A. Vecchio, "A distributed delay model of viral dynamics", *WSEAS Transactions on biology and biomedicine*, Vol. 2(1) pp. 26-42, 2005.

[5] Y. Kuo, "Plenary lecture 1: nanoparticles for the transport of antiretroviral drugs across the blood-brain barrier: a potential therapy for the acquired immunodeficiency syndrome", *The 3rd WSEAS International Conference on Computational Chemistry*, 2009, pp. 11.

[6] A. Perelson, A. Neumann, M. Markowitz, J. Leonard, D. Ho, "HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time", *Science*, Vol. 271(5255) pp. 1582-1599, 1996.

[7] D. Wodarz, M. Nowak, "Mathematical models of HIV pathogenesis and treatment", *BioEssays*, Vol. 24(12) pp. 1178-1187, 2002.

[8] A. Heydari, M. Farahi A. Heydari, "Chemotherapy in an HIV model by a pair of optimal control", *The 7th WSEAS International Conference on Simulation, Modelling and Optimization*, 2007, pp. 58-63.

[9] A. Perelson, P. Nelson, "Mathematical analysis of HIV-I: dynamics in vivo", *SIAM Review*, Vol. 41(1) pp. 3-44, 1999.

[10] C. Kougias, J. Schulte, "Simulating the immune response to the HIV-1 virus with cellular automata", *Journal of Statistical Physics*, Vol. 60(1) pp. 263-273, 1990.

[11] R. Pandey, "Cellular automata approach to interacting cellular network models for the dynamics of cell population in an early HIV infection", *Physica A: Statistical and Theoretical Physics*, Vol. 179(3) pp. 442-470, 1991.

[12] R. Zorzenon dos Santos, S. Coutinho, "Dynamics of HIV infection: A cellular automata approach", *Physical Review Letters*, Vol. 87(16) 168102–1–4, 2001.

[13] V. Shi, A. Tridane, Y. Kuang, "A viral load-based cellular automata approach to modeling HIV dynamics and drug treatment", *Journal of Theoretical Biology*, Vol. 253(1) pp. 24-35, 2007.

[14] P. Sloot, F. Chen, C. Boucher, "Cellular automata model of drug therapy for HIV infection", *Lecture Notes in Computer Science*, Vol. 2493, pp. 282–293, 2002.

[15] P. Figueirê do, S. Coutinho, R. Zorzenon dos Santos, "Robustness of a cellular automata model for the HIV infection", *Physica A: Statistical Mechanics and its Applications*, Vol. 387(26) pp. 6545-6552, 2008.

[16] G. Pantaleo, C. Graziosi, L. Butini, P. Pizzo, S. Schnittman, D. Kotler, A. Fauci, "Lymphoid organs function as major reservoirs for human immunodeficiency virus", *Proceedings of the National Academy of Sciences*, 1991, Vol. 88(21) pp. 9838.

[17] A. Haase, "Population biology of HIV-1 infection: viral and CD4+ T cell demographics and dynamics in lymphatic tissues", *Annual review of immunology*, Vol. 17(1) pp. 625-656, 1999.

[18] S. M. Schnittman, M. C. Psallidopoulos, H. C. Lane, L. Thompson, M. Baseler, F. Massari, C. H. Fox, N. P. Salzman, A. S. Fauci, "The reservoir for HIV-1 in human peripheral blood is a T cell that maintains expression of CD", *Science*, Vol. 245 (4915) pp. 305-308, 1989.

[19] E. Burkhead, J. Hawkins, D. Molinek, "A Dynamical Study of a Cellular Automata Model of the Spread of HIV in a Lymph Node", *Bulletin of Mathematical Biology*, Vol. 71(1) pp. 25-74, 2009.

[20] G. Pantaleo, C. Graziosi, A. Fauci, "The immunopathogenesis of human immunodeficiency virus infection", *New England Journal of Medicine*, Vol. 328(5) pp. 327-335, 1993.

[21] C. Graziosi, G. Pantaleo, L. Butini, J. Demarest, M. Saag, G. Shaw, "A. Fauci, Kinetics of human immunodeficiency virus type 1 (HIV-1) DNA and RNA synthesis during primary HIV-1 infection", *Proceedings of the National Academy of Sciences of the United States of America*, 1993, Vol. 90(14) pp. 6405.

[22] L. Wagner, O. Yang, E. Garcia-Zepeda, Y. Ge, S. Kalams, B. Walker, M. Pasternack, A. Luster, "β-chemokines are released from HIV-1-specific cytolytic T-cell granules complexed to proteoglycans", *Nature*, Vol. 391(6670) pp. 908-911, 1998.

[23] R. Phillips, S. Rowland-Jones, D. Nixon, F. Gotch, J. Edwards, A. Ogunlesi, J. Elvin, J. Rothbard, C. Bangham, C. Rizza, "Human immunodeficiency virus genetic variation that can escape cytotoxic T cell recognition", *Nature*, Vol. 354(6353) pp. 453, 1991.

[24] G. Pantaleo, C. Graziosi, J. Demarest, L. Butini, M. Montroni, C. Fox, J. Orenstein, D. Kotler, A. Fauci, "HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease", *Nature*, Vol. 362, pp. 355-358, 1993.

[25] P. Goulder, R. Phillips, R. Colbert, S. McAdam, G. Ogg, M. Nowak, P. Giangrande, G. Luzzi, B. Morgan, A. Edwards, "Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS", *Nature medicine*, Vol. 3(2) pp. 212-217, 1997.