On the Diversity of HIV using Cellular Automata Approach

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Abstract

Diversity of HIV (Human Immunodeficiency Virus) in vivo has been reported. In this study, we propose a CA (Cellular Automata) model about interaction between the immune system and HIV, and examine the effect of this diversity. Originality of our CA model is that it has not only four states (HIV, Virgin, Dead, Infect) but diversity of HIV and T-Cells. Growing maximum value of the diversity, we performed computer simulation with the CA model. The results demonstrated that growth of the diversity have an effect on cell population and simulations steps. Additionally, we observed CA state corresponds to infection, incubation period and development of AIDS. In on our CA model, it is demonstrate that the diversity of HIV is the major factor which HIV can escape the immune response.

Keywords: Cellular automata, HIV, Immune system

1 introduction

From the late in the 1980s, many active researches about infection of HIV (Human Immunodeficiency Virus) and development of AIDS (Acquired Immunodeficiency Syndrome) are current in progress. Medical works have been reported diversity of HIV which is due to its high mutation rate and variability in HIV-specific T cell epitope sequences [1, 2, 3], but its functionality to develop HIV infection against the immune response is not clear in vivo. Nowak and May have proposed a mathematical model considered with diversity of HIV strains[4]. According the model, there exists *antigenic diversity threshold* of HIV.

On the other hand, many scientists and engineers have proposed CA (cellular automata) model to investigate physical, chemical, life, traffic and economical processes. Advantage of CA model is that can simplify complicated interaction into local interaction.

Since it is considered to that the immune system responses based on local interaction between immune cells and antigens [5], many CA models about HIV infection has been proposed [6, 7, 8, 9, 10, 11, 12].

But until now, no work has focused on diversity of HIV with CA model. In this study, we proposed CA model considering diversity of HIV and investigated its behavior.

2 Model

We consider two-dimensional CA, the cells of which being arranged in a square lattice. Each cell has four states (*HIV, Virgin, Dead, Infect*) and *Type i* ($i = 0, 1, 2, \cdots, T_{max} - 1$) as follows:

- *HIV[i]:* A state being HIV type *i* which is from outside the body, other lymphocyte or host cell. Although there exists only one HIV strain (*HIV[0]*) at the beginning of infection, it mutates into strain *HIV[1], HIV[2], $\cdots$, or* $HIV[T_{max} - 1]$ in each proliferate process.
- *Virgin[i]:* Uninfected healthy host cell which can only response and eliminate against $Infect[i]$.
- *Dead:* Nothing exists. After moving $HIV[i]$ or $Infect[i]$ was eliminated.
- *Infect[i]:* A state corresponds to host cell ($Virgin[*]$) infected by $HIV[i]$.

$HIV[*], Virgin[*]$ and $Infect[*]$ imply any type of HIV, host cell and infected cell respectively. T_{max} stands for anti-

genic diversity of HIV and the immune system in the CA model. In fact, this is the originality of our model.

Parameters of the model are maximum value of the diversity of HIV, T_{max} and small initial infection fracture $pHIV$. The initial CA configuration is composed of $Virgin[*]$ with $pHIV$ of $HIV[0]$. Type i and the placement chosen randomly.

In one time step the entire lattice is updated in a synchronized parallel way, according to the rules described below. The updated state of a cell is dependent on the states of its *Moore* neighbors in a square lattice.

We determine this process will continue until all the $HIV[*]$ and $Infect[*]$ or $Virgin[*]$ is eliminated.

Rule 1 *Moving of HIV:* If $HIV[*]$ has at least one $Virgin[*]$ or *Dead* neighbor, it becomes *Dead* with probability (the number sum of $Virgin[*]$ and *Dead*)/8. This rule represents that HIV moves to the cite nothing exists or infects to another virgin host cell.

Rule 2 *Being infected of virgin host cell with HIV:* If $Virgin[*]$ has at least one $HIV[i]$, it becomes $Infect[i]$ with probability (the number of $HIV[i]$)/8. This rule represents that virgin host cell is infected with HIV.

Rule 3 *Mutation and emergence of HIV:* **(a)** If *Dead* has at least one $Infect[*]$, it becomes $HIV[*]$ since HIV mutates before emergence, with probability (the number of $Infect[*]$)/8 . This rule represents that HIV emerges from infected host cell. **(b)** If *Dead* has at least one $HIV[i]$, it becomes $HIV[i]$ with probability (the number of $HIV[i]$)/8. This rule represents that moving of HIV from another cite.

Rule 4 *Update of infected cell:* **(a)** If $Infect[*]$ has at least one $Virgin[i]$, it becomes $Virgin[i]$ with probability (the number of $Virgin[i]$)/8. This rule represents that infected cell is eliminated by type i activated virgin host cell. **(b)** Otherwise it becomes $HIV[i]$ since HIV eliminate infected cell.

We performed computer simulations of the model, using periodic boundary condition, on a 100×100 lattice, $pHIV = 0.05$ with T_{max} from 1 to 35. For each T_{max}, we performed 1000 times trial runs.

3 Results and Discussion

Fig. 1 and 2 show the relation between average number of cells and *antigenic diversity* of HIV, T_{max}. $HIV[*]$,$Empty$ increased with T_{max}. In addition, decrease of $Virgin[*]$ was also observed. Mutation of HIV in vivo has been reported. From these results, it seem to suggest that *antigenic diversity* of HIV has great effect on the model.

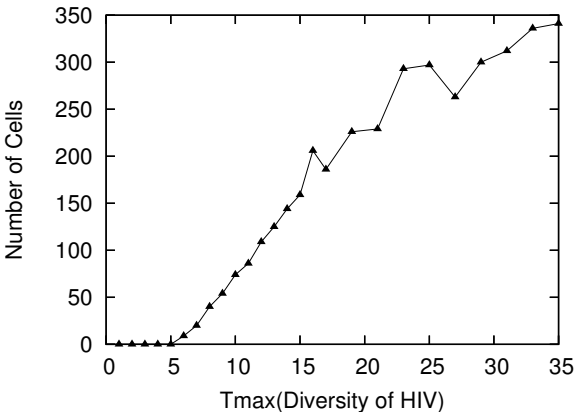

Figure 1: Average number of $HIV[*]$ cells versus T_{max}.

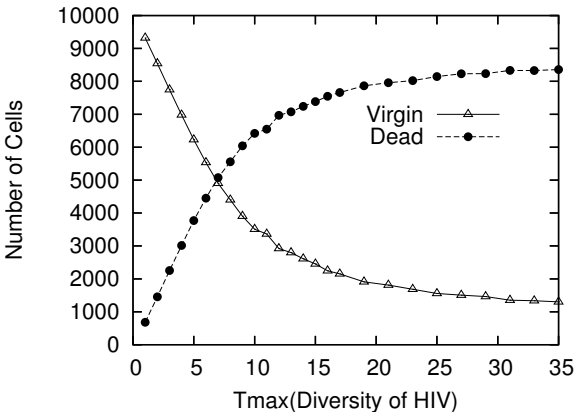

Figure 2: Average number of $Virgin[*]$ and $Empty$ cells versus T_{max}.

Fig. 3 shows the relation between average simulation steps and T_{max}. The simulation steps increased with T_{max}. Long time incubation period of HIV has been known. This result corresponds to HIV infect phenomenon in vivo.

Main points are described below:

First, since the decrease of $Virgin[*]$ depend on HIV infection in the model, the situation that immune system cannot response was assumed to be due to increase of *antigenic diversity* of HIV (Fig. 1, 2). In detail, if no responsible immune cells exist on its *Moore* neighbors, HIV can escape the immune response in the CA model.

Second, Fig. 3 points out that long time steps were needed to stop simulation in the situation high *antigenic diversity* of HIV.

Fig. 1-3 indicate only average value of 1000 times runs.

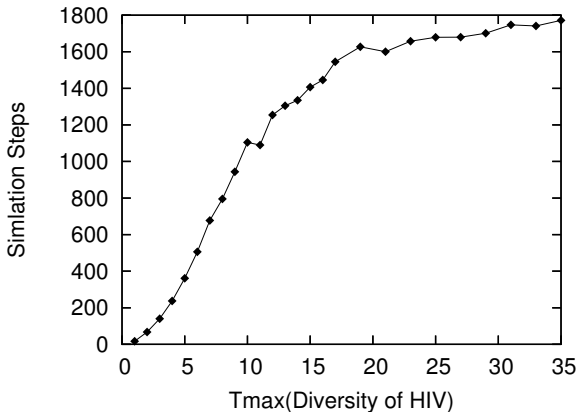

Figure 3: Average simulation steps versus T_{max}.

Since the CA model is not deterministic, the simulation result of one trial run (namely whether HIV is control or not) is not depend on parameters. Fig. 4-6 show the time-evolution of CA state. In early stage (Fig. 4), a volume of $Infect[*]$ was observed. This state seem to correspond to initial infection. In contrast, only a few $Infect[*]$ cells was observed in fig. 5. This state seem to correspond to incubation period in which being controlled of $HIV[*]$. Moreover, since CA is filled with *Dead* in fig. 6, this state seem to correspond to *break down* of the immune system, that is AIDS.

4 Conclusion

In this study, we modeled the interaction between HIV and the immune system with CA approach to examine the effect of antigenic diversity of HIV. We make a point that CA approach which is based on local interaction is very useful to investigate the interaction between HIV and the immune system.

Our CA model contrasts with deterministic model because simulation result of each trial runs is different at same parameters. Since all the HIV carrier don't have an onset of AIDS; variety of time in incubation period has reported, this property of CA model is correspond with phenomenon in vivo.

Originality of out CA model is that takes into consideration of antigenic diversity of HIV. We have taken *antigenic diversity* of HIV as parameter. Simulation results suggest that increase of *antigenic diversity* of HIV has great impact on the immune system.

By taking account for *antigenic diversity* in CA model, we make a point that HIV which has diversity can escape from local immune response and proliferate.

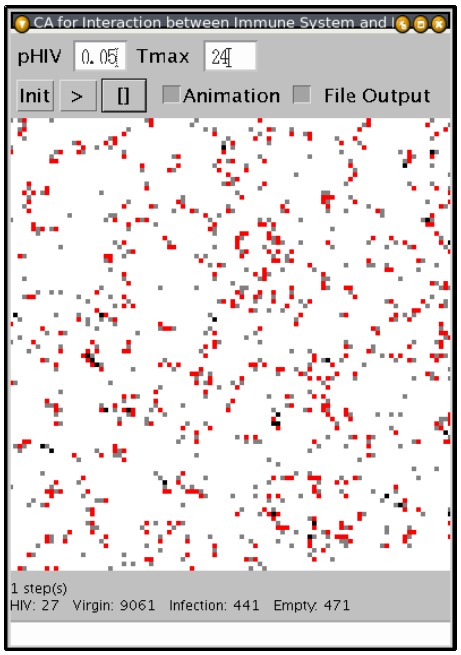

Figure 4: Snapshot of CA state at step 1. Red: $Infect[*]$, Black: $HIV*$, White: $Virgin[*]$, Gray: *Dead*. Parameters are: $T_{max} = 24, pHIV = 0.05$

These results depend on that interaction between HIV and the immune system is sum of local interactions. We are currently performing studies to determine CA model to compute Moore neighbor. Therefore, it is interesting to change condition of neighbor.

Further studies to analyze development of *antigenic diversity* of HIV and pattern which is formulated by CA are required.

In summary, the present work shows that the the CA model taking account for *antigenic diversity* of HIV can examine interaction between HIV and the immune system successfully.

Acknowledgments

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References

[1] A. S. De Groot *et al.*, "Engineering immunogenic consensus T helper epitopes for a cross-clade HIV vaccine," *Methods*, vol. 34, no. 4, pp. 476–487, 2004.

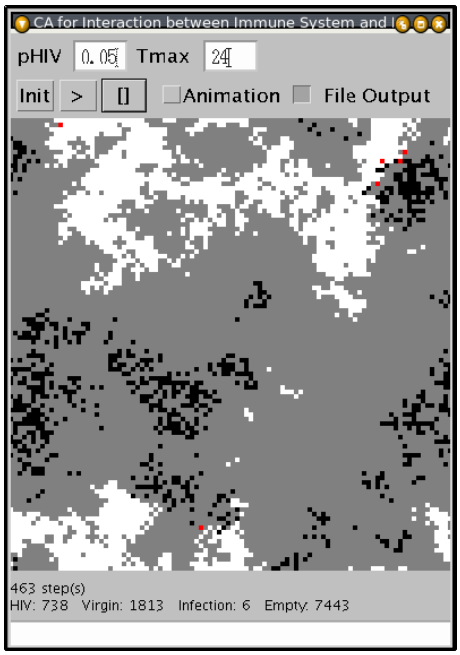

Figure 5: Snapshot of CA state at step 463. Parameters are same to Fig. 4

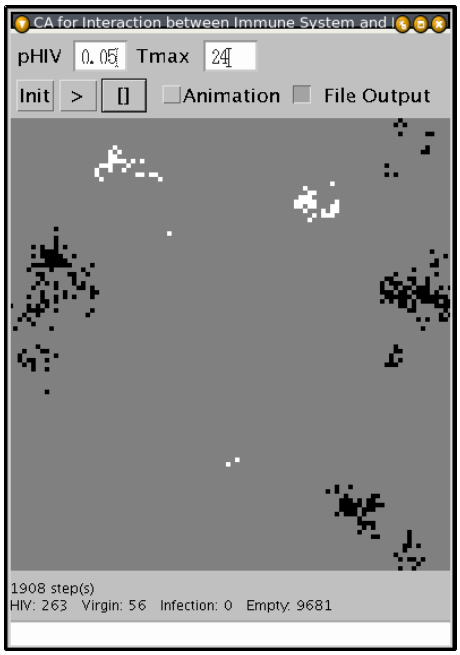

Figure 6: Snapshot of CA state at step 1908. Parameters are same to Fig. 4

[2] D. Turner *et al.*, "Variability in the PR and RT genes of HIV-1 isolated from recently infected subjects," *Antiviral Chemistry & Chemotherapy*, vol. 15, pp. 255–259, September 2004.

[3] P. J. R. Goulder *et al.*, "Evolution and transmission of stable CTL escape mutations in HIV infection," *Nature*, vol. 412, pp. 334–338, July 2001.

[4] M. A. Nowak *et al.*, "Antigenic diversity thresholds and the development of AIDS," *Science*, vol. 254, pp. 963–969, Novemver 1991.

[5] N. K. Jerne, "The immune system," *Scientific American*, vol. 229, no. 1, pp. 52–60, 1973.

[6] R. B. Pandey and D. Stauffer, "Immune response via interacting three dimensional network of cellular automata," *Le Journal de Physique*, vol. 50, pp. 1–10, January 1989.

[7] R. B. Pandey, "Cellular automata approach to interacting cellular network models for the dynamics of cell population in an early HIV infection," *Physica A*, vol. 179, no. 3, pp. 442–470, 1991.

[8] R. M. Z. dos Santos and S. Coutinho, "Dynamics of HIV infection: A cellular automata approach," *Physical Review Letters*, vol. 87, no. 16, pp. 168102–1–168102–4, 2001.

[9] F. Kougias and J. Schulte, "Simulating the immune response to the HIV–1 virus with cellular automata," *Journal of Statistical Physics*, vol. 60, no. 1/2, pp. 263–273, 1990.

[10] P. Sloot, F. Chen, and C. Boucher, "Cellular automata model of drug therapy for HIV infection," in *ACRI* (S. Bandini, B. Chopard, and M. Tomassini, eds.), vol. 2493 of *Lecture Notes in Computer Science*, pp. 282–293, Springer, 2002.

[11] R. B. Pandey and D. Stauffer, "Metastability with probabilistic cellular automata in an HIV infection," *Journal of Statistical Physics*, vol. 61, no. 1/2, pp. 235–240, 1990.

[12] T. Tomé and J. R. D. de Felício, "Probabilistic cellular automaton describing a biological immune system," *Physical Review E*, vol. 53, no. 4, pp. 3976–3981, 1995.