Cellular Automata Simulation Modeling of HIV Infection in Lymph Node and Peripheral Blood Compartments

Sompop Moonchai, Yongwimon Lenbury and Wannapong Triampo

***Abstract*—** Acquired immune deficiency syndrome (AIDS) has been widely considered as the most devastating epidemic. To discover effective therapy for HIV infection, the dynamics of the virus-immune system in the human body have been the subject of intense studies. Since the development of the disease typically exhibits a three phase evolution, that is, an acute phase (measured in days), a chronic phase (measured in weeks) and AIDS (measured in years), the use of ordinary or partial differential equations are inadequate in our attempt to describe the three different time scales in order to simulate the entire course of the HIV infection. Cellular automata simulation approach has become well known as a useful technique to investigate complex biomedical systems in situations where traditional methodologies are difficult or too costly to employ. So far, relatively simple cellular automata models have been proposed to simulate the dynamics of HIV infection in human. Most cellular automata models only considered viral proliferation in the lymph node. However, most clinical indications of AIDS progression are based on blood data, because these data are most easily obtained. Since viral population circulates between lymph node and plasma, viral load in the two compartments are important for the description of HIV infection dynamics. We present here cellular automata simulations of a two-compartment model of HIV proliferation with delay.

***Keywords*—**Cellular Automata, double compartments simulation, HIV proliferation.

I. Introduction

CELLULAR Automata (CA) modeling has been widely used in modeling complex systems. Despite of its simple structure, CA is well suited to describe the propagation phenomena, such as rumor spreading, particle percolation, and disease spreading [1]-[4]. In some practical applications, multiple lattices are needed to simulate in parallel multi-compartmental systems.

In particular, Acquired Immune Deficiency Syndrome (AIDS) has become indisputably the most devastating epidemic so far. The Human Immunodeficiency Virus (HIV) causes AIDS, so that the study of the dynamics of the virus-immune system in the human body is necessary in order to discover a proper therapy for HIV infection and how it might be controlled. Many researchers have used mathematical models to describe the population dynamics of cells involved in the immune response system relevant to HIV proliferation [5]-[10]. Most of these models are based on systems of ordinary differential equations (ODES) and partial differential equations (PDES) [11]-[14]. However, since the development of the disease typically exhibits three phases of infection, that is, an acute phase (measured in days), a chronic phase (measured in weeks), and full blown AIDS (measured in years), the ODES and PDES are insufficient to describe the three different time scales and hard to construct to simulate the entire course of the HIV infection.

In recent years, cellular automata (CA) models have been used in modeling HIV infection model in the lymph node [1], [2]. In 2001, a simple CA model was used to simulate the evolution of HIV infection in the lymph node by Santos and Coutinho (SC-model) [1]. The result of their model was capable of simulating the three phase pattern of HIV dynamics observed in critical data. Later, Sloot *et al.* [2] proposed a CA model to study the dynamics of drug therapy for HIV infection. The CA model was a modification of SC-model. Recently, Veronica Shi *et al.* [3] also formulated a CA model based on SC-model for HIV dynamics and drug treatment. Viral load, its effect on infection rate in the lymph node was included in their CA model.

Most of these CA models only considered the dynamics in the lymph node. However, most clinical indications of progression are based on blood data, because these data are most easily obtained. Since viral population circulates between the lymph node and plasma compartments, viral load in the two compartments are important for the description of the dynamics of HIV infection.

In this paper, by modifying the CA rules based on SC-model, we illustrate the use of double latticed CA simulation to investigate the dynamics of HIV infection in both the

Manuscript received October 29, 2010: Revised version received October 29, 2010. This work was supported by the Center of Excellence in Mathematics, Commission on Higher Education, and Mahidol University. S. Moonchai is with the Department of Mathematics, Faculty of Science, Chiangmai University, Thailand.

Y. Lenbury is with the Department of Mathematics, Faculty of Science, Mahidol University, Bangkok, Thailand and the Centre of Excellence in Mathematics, Commission on Higher Education, 328 Si Ayutthaya Road, Thailand. (corresponding author, phone: 662-201-5340; fax: 662-201-5343; e-mail: scylb@mahidol.ac.th).

W.Triampo is with the R&D Group of Biological and Environmental Physics, Department of Physics, Faculty of Science, Mahidol University, Thailand, Center of Excellence for Vector and Vector-Borne Diseases, Thailand and Thailand Center of Excellence in Physics.

lymph node and blood compartments while the viral loads in the two compartments are continuously updated throughout the simulation. Our model also takes into account a delay τ in the transformation of a newly infected CD4+ T cell that is free to spread the infection, into a final staged infected cell.

II. CA Model of HIV Proliferation

A cellular automaton (CA) is a discrete dynamic system in which space is divided into regular spatial cells, and time progresses in discrete steps. Each cell in the system has one of a finite number of states. The state of each cell is updated according to local rules, that is, the state of a cell at a given time depends on its own state and the states of its neighbors at the previous time step [4].

In this work, the CA model is defined on two coupled square lattices of sizes $L \times L$. The Moore neighborhood is adopted to define the rules. The states of the cells in each of the lattices are updated at each time step in parallel according to the rules, with each time step corresponding to one week. Each site on the lattice is occupied by a cell which is assigned one of the five states that describe the possible states in which those cells may be found: non-activated cells, healthy cells (representing CD4+ T-cells which are the main target of the HIV), infected A_1 cells (corresponding to infected cells that are free to spread the infection), infected A_2 cells (infected cells in the final stage before dying due to the action of the immune system) or dead cells (infected cells killed by the immune response).

In this work, we construct the CA model of HIV infection in two coupled compartments; the lymph node compartment and the peripheral blood compartment. For each compartment, the simulation steps start with N_0 non-activated or non-proliferating cells, H_0 healthy active cells, and a small fraction P_{HIV} of infected A_1 cells (A_{10}), such that $A_{10} = P_{HIV} \cdot H_0$, distributed randomly. These numbers depend on the initial viral load V_0. At each time step, all cells are updated using the rules described below.

The updating rules (modified from SC- model [1]) are as follows.

Rule 1: Updates of non-proliferating cells.

If a non-proliferating cell has non-proliferating cells as neighbors, it may become an active healthy cell at the probability P_{op}, accounting for opportunistic infection, or it remains the same at the probability 1- P_{op}.

If it has a neighbor which is A_1 or A_2 infected, it becomes an active healthy cell, by which the body tries to fight the infection.

Rule 2: Update of healthy cells.

(a) A healthy cell gets infected by coming in contact with a virus at the probability

$$P_v^* = P_v f(V_t) = P_v(1 - e^{-aV_t}). \quad (1)$$

(b) If it has at least one infected A_1 neighbor, it becomes an infected A_1 cell at the probability

$$P_1^* = r_1(1 - P_v^*). \quad (2)$$

(c) If it has no infected A1 neighbor, but has at least R ($2 < R < 8$) infected A_2 neighbors, it becomes an infected A_1 cell at the probability

$$P_2^* = r_2 (1 - r_1)(1 - P_v^*). \quad (3)$$

(d) Otherwise, it remains a healthy cell at the probability

$$1 - P_1^* - P_2^* - P_v^*$$

where $0 < P_1^* + P_2^* + P_v^* < 1$.

Rule 3: Update of infected A_1 cells.

An infected A_1 cell becomes an infected A_2 cell after τ time steps. Thus, infected A_1 cells become infected A_2 cells at different time with a delay of τ.

Rule 4: Update of infected A_1 cells.

Infected A_2 cells become dead cells, corresponding to the depletion of infected cells by the immune response.

Rule 5: Updates of dead cells

(a) Dead cells can be replaced by healthy cells with the probability

$$(1 - P_{infec}) P_{repl}$$

in the next step, or by an infected A_1 cell with the probability

$$P_{infec} P_{repl}.$$

Otherwise, it remains a dead cell at the probability

$$1 - P_{repl}.$$

(b) After step (a), a dead cell can be replaced by an inactivated cell with the probability P_{nona}. Otherwise, it remains a dead cell at the probability

$$1 - P_{nona}.$$

III. Viral Load Simulation

In this CA model, the viral load influences the dynamics of the healthy and infected cells through the probability P_v^*. After all of the five cell states are updated in the two lattices, the viral load in each compartment is calculated using (1)-(2) and the following difference equations which represent the evolution of viral load in the lymph node compartment (with $V_t = V_t^L$) and peripheral blood compartment (with $V_t = V_t^B$) at time *t*.

In the lymph node compartment

$$V_{t+1}^L - V_t^L = pS_L I_t^L + (\alpha \cdot V_t^B - \tilde{V}_L) - c_{LH} H_t^L V_t^L - cV_t^L \quad (4)$$

I_t^L = virus-producing infected cells

$$= A_{1t}^L + A_{2t}^L$$

$$\tilde{V}_L = e\left(V_t^L + \alpha \cdot V_t^B\right)$$

In the blood compartment

$$V_{t+1}^B - V_t^B = pS_B I_t^B + (\tilde{V}_B - V_t^B) - c_{BH} H_t^B V_t^B - cV_t^B \quad (5)$$

I_t^B = virus-producing infected cells = $A_{1t}^B + A_{2t}^B$

$\tilde{V}_B = e\left(\beta \cdot V_t^L + V_t^B\right)$

Δt = 1 week (time step)

Here, A_{1t}^L and A_{2t}^L are the numbers at time t of A_1 and A_2 infected cells in the lymph node, respectively, while A_{1t}^B and A_{2t}^B are the corresponding amounts in the blood compartment. H_t^L and H_t^L are the numbers of healthy cells in the respective compartments at time t, p is the average viral production rate per infected cell , e represents the circulation of virus between the two compartments, and c is the death rate of free virus.

Table I Model parameters in the CA model in the lymph node compartment.

Symbol	Definition	Value [reference]
L	Lattice size	500
N_0	Number of non-activated or non-proliferating cells at $t = 0$	250,000
H_0	Number of healthy active cells at $t = 0$	150,000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [1]
P_{op}	Probability for a nonpro-liferating cell to be replaced with a healthy cell	0.001 (estimated)
P_V	Constant in probability for a healthy cell to come in contact with a virus	0.0004 (estimated)
A	Constant in probability in (1)	1×10^{-15}
r_1	Constant in probability in (2)	0.997 (estimated)
r_2	Constant in probability in (3)	0.997 (estimated)
τ	Time delay for an infected A_1 cell to become an infected A_2 cell	4 [1]
P_{infec}	Probability for a healthy cell to be replaced with an infected A_1 cell	1×10^{-5} [1]
P_{repl}	Probability for a death cell to be replaced with a healthy cell	0.99 [1]
P_{nona}	Probability for a death cell to be replaced with non-activated cells	0.9 (estimated)
R	Number of infected A_2 cells in a cell's neighborhood to induce a healthy cell to become an infected A_1 cell	4 [1]

Since the amount of virus in peripheral blood is measured in milliliters and that in the lymph node is measured in total virus counts, we use conversion factors α (blood to lymph node) and β (lymph node to blood) in (4) and (5) to describe the exchange between the two compartments. We model immune activity in the lymph node and blood with c_{LH} and c_{BH} , respectively. In healthy individuals, total CD4+ T-cell counts are about 2×1011 cells in the lymph node, and 1000 cells/mm3 in the blood [15]. Since each site in the $L\times L$ lattice represents one of the five states of the cells in the two compartments, we convert the numbers of the cells from the CA models to numbers of cells in the body by using the conversion factors S_1 and S_2 for the lymph node and blood, respectively.

Table II Model parameters in the CA model in the blood compartment.

Symbol	Definition	Value [reference]
L	Lattice size	100
N_0	Number of non-activated or non-proliferating cells at $t = 0$	10000
H_0	Number of healthy cells at $t = 0$	5000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [1]
P_{op}	Probability for a non-proliferating cell to be replaced with an active healthy cell	0.001 (estimated)
P_V	Constant in probability for a healthy cell to come in contact with a virus	0.0004 (estimated)
a	Constant in probability in (1)	1×10^{-7}
r_1	Constant in probability in (2)	0.997 (estimated)
r_2	Constant in probability in (3)	0.997 (estimated)
τ	Time delay for an infected A_1 cell to become an infected A_2 cell	4 [1]
P_{infec}	Probability for a healthy cell to be replaced with an infected A_1 cell	1×10^{-5} [1]
P_{repl}	Probability for a death cell to be replaced with a healthy cell	0.99 [1]
P_{nona}	Probability for a death cell to be replaced with a non-activated cell	0.9 (estimated)
R	Number of infected A_2 cells in the neighborhood of a cell to induce a healthy cell to become an infected A_1 cell	4 [1]

To simulate the CA model, all parameters are set up as shown in Tables I-III.

Table III Model parameters in viral load simulation.

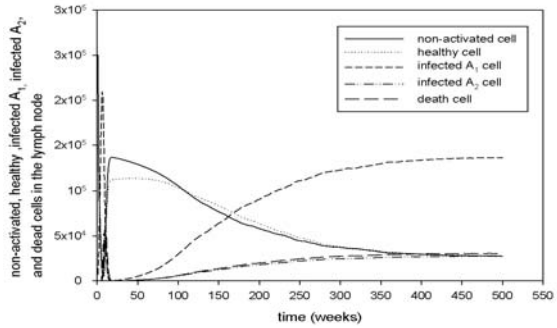
Symbol	Definition	Value [reference]
V_0^B	Palsma virus concentration at $t = 0$	10 [16] (can vary)
V_0^L	Virus concentration in the lymph node at $t = 0$	0
p	Average virion production rate per infected cell	480 [17]
S_L	Scaling factor in the lymph node	$2\times10^{11}/H_0$
S_B	Scaling factor in the blood	$1000/H_0$
c_{LH}	Clearance rate of free virus in the lymph node	0.00001 (estimated)
c_{BH}	Clearance rate of free virus in the blood	0.00001 (estimated)
c	Death rate of free virus	0.3 [17]
e	Circulation fraction of virus between lymph node and blood	0.02 [18]
β	Scaling factor: lymph node $\rightarrow$ blood	2×10^{-7} [16]
α	Scaling factor: blood $\rightarrow$ lymph node	5×10^{6} [16]

IV. Simulation Results

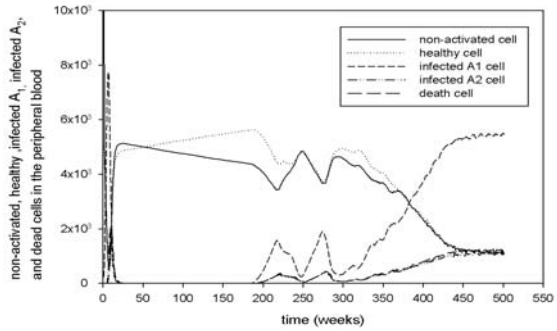
The result of model simulations shows the evolution of the numbers of the non-activated cells, healthy cells, infected A_1 cells, infected A_2 cells, dead cells, viral load in the lymph node and viral load in the peripheral blood.

In Fig. 1, the graphs exhibit three phases of the infection, acute, chronic, and progression to AIDS. The time evolution of healthy cells in the two compartments and the viral load in peripheral blood closely simulate clinical data [19]. In addition, to simulating the dynamics of HIV infection, the model reproduces the two time scales of weeks and years in the graphs.

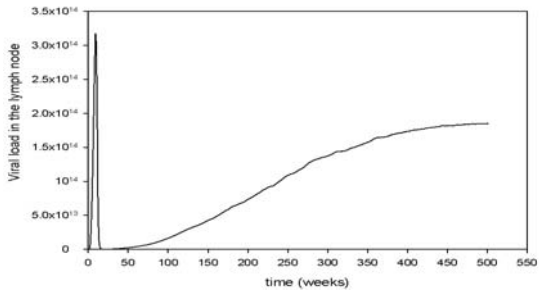
The simulation shown in Fig. 1 uses the parametric values given in Tables I-III which correspond to the case in which a patient eventually succumbs to AIDS in approximately 5-6 years. With different parametric values, the chronic phase may be lengthened.



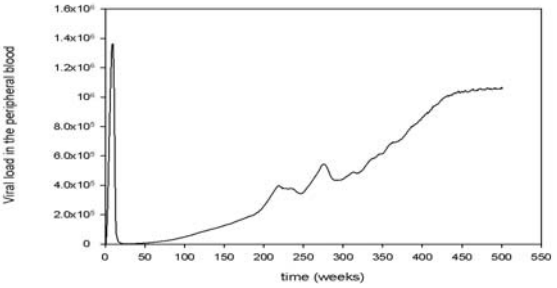
1(a)



1(b)

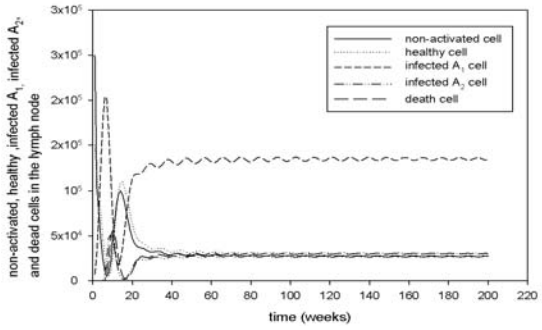


1(c)

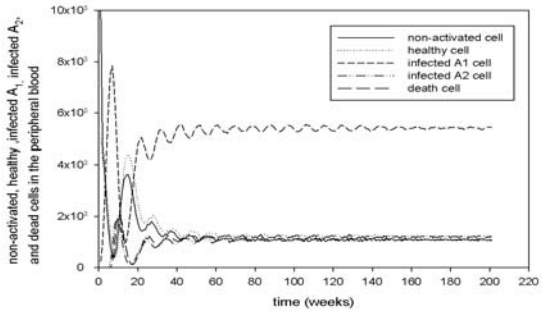


1(d)

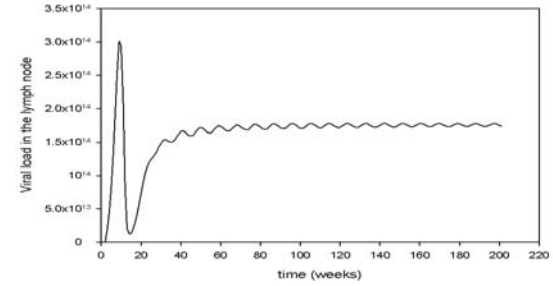
Fig. 1 A simulated evolution of HIV infection without treatment indicates a three phase evolution using the parametric values in Tables I-III. (a), (b) Plots of the numbers of non-activated cells, healthy cells, infected A_1 cells, infected A_2 cells, and dead cells in the lymph node and blood compartments, respectively, (c) viral load in the lymph node compartment, and (d) viral load in the peripheral blood compartment.



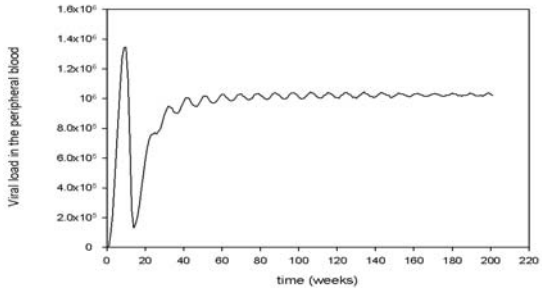
2(a)



2(b)

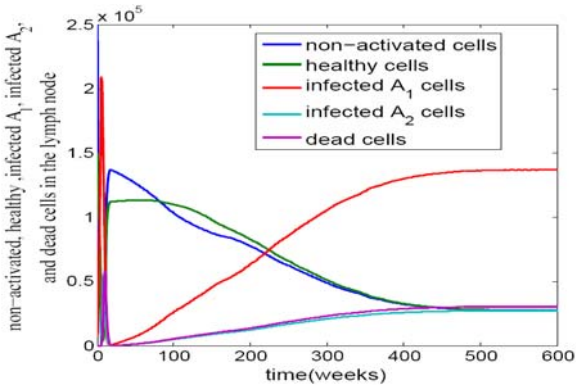


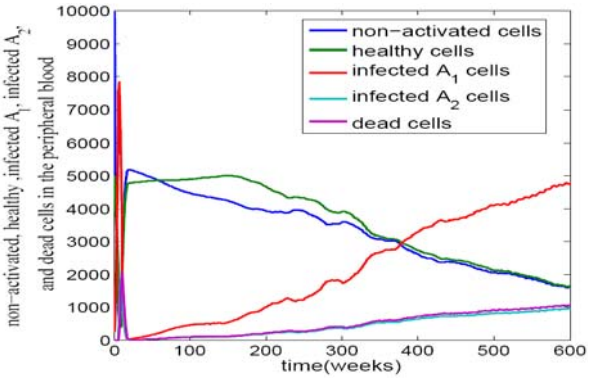
2(c)

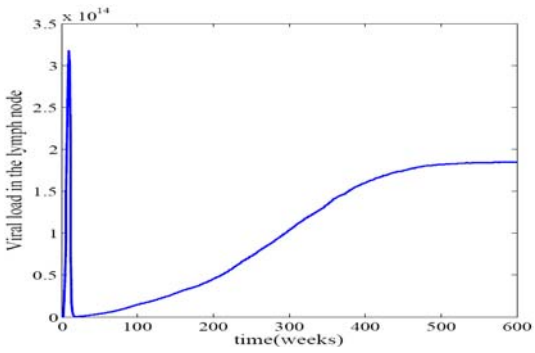


2(d)

Fig. 2 A simulation using probabilities $r_1 = r_2 = 0.9$. (a), (b) Plots of numbers of non-activated cells, healthy cells, infected A_1 cells, infected A_2 cell, and dead cells in the lymph node and blood compartments, respectively, (c) viral load in the lymph node compartment, and (d) viral load in peripheral blood compartment.







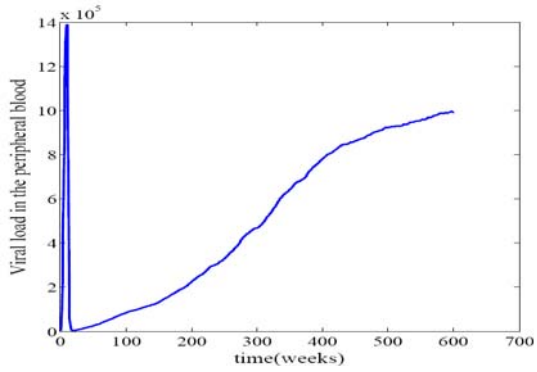


Fig. 3 Evolution of HIV infection averaged over 15 simulations using the parametric values in Tables I-III.

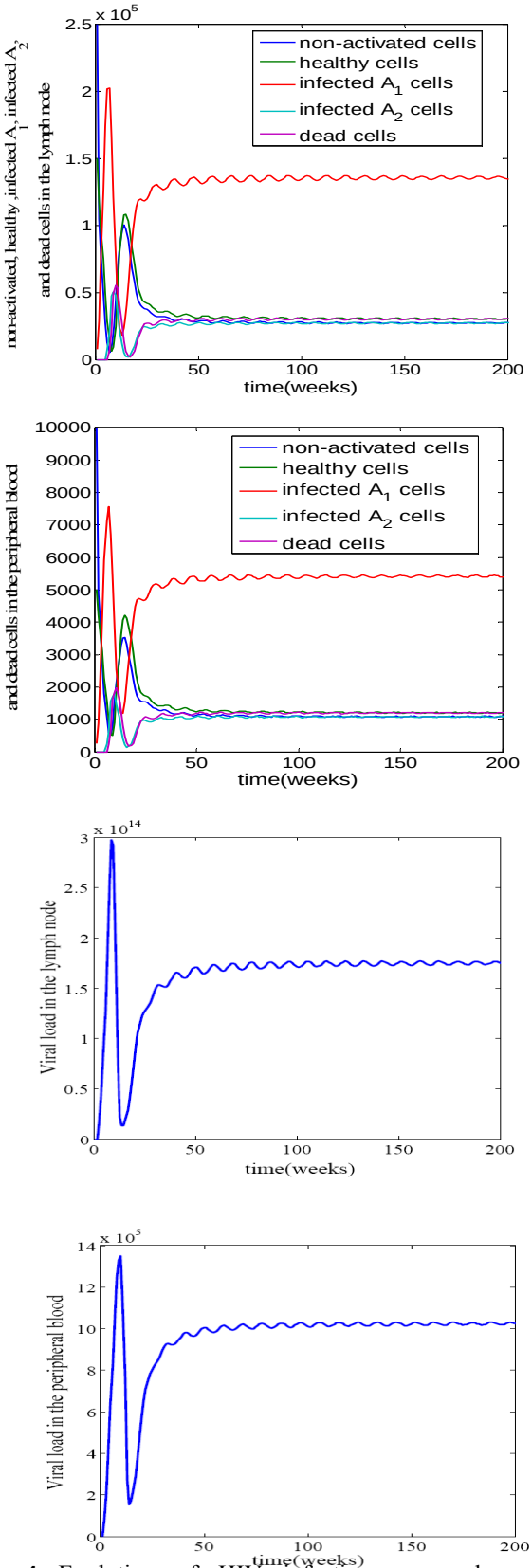
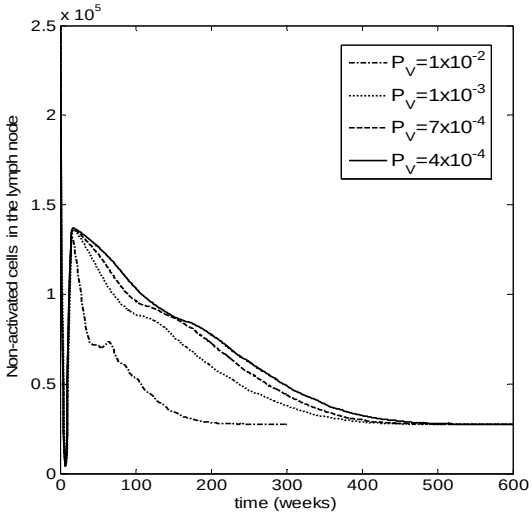


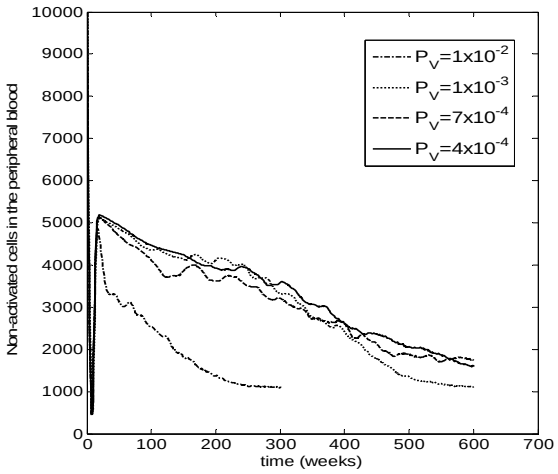
Fig. 4 Evolution of HIV infection averaged over 15 simulations using the parametric values in Tables I-III. but with probabilities $r_1 = r_2 = 0.9$.

In Fig. 2, we show the result of one simulation using $r_1 = r_2 = 0.9$ and the model in this case simulates the progression of a patient who succumbs to AIDS more or less right away.

Fig. 3-4 show the average of 15 simulations of our CA model of HIV infection, using the parameter values in Tables I-III, with $r_1 = r_2 = 0.997$ in Fig. 3, and $r_1 = r_2 = 0.9$ in Fig. 4. We discovered that averaging over a larger number of simulations does not significantly change the averaged behavior of the time courses of the variables tracked by our model. Thus, the number of simulations needs not be greater than 15 in what follows.

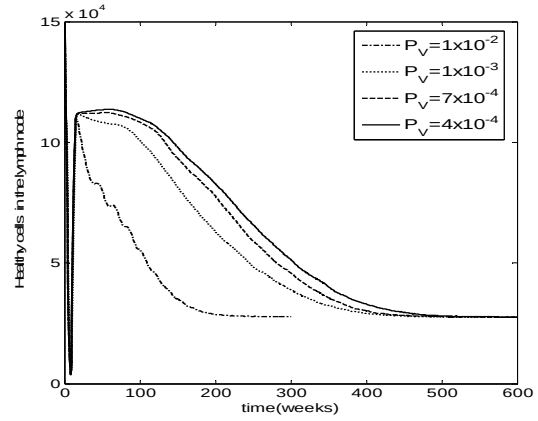


5(a)

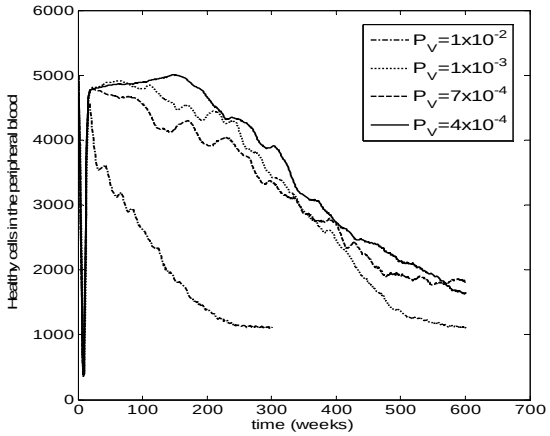


5(b)

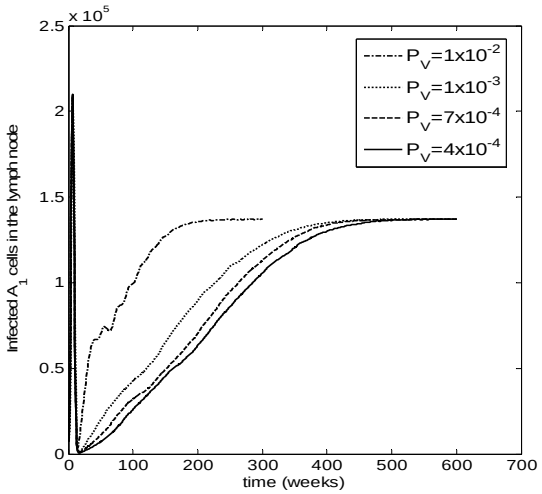
Fig. 5 Evolution of HIV infection from averaging 15 simulations using $r_1 = r_2 = 0.997$ for different values of P_V : (a), (b) the numbers of non-activated cells in the lymph node and peripheral blood, respectively.



6(a)

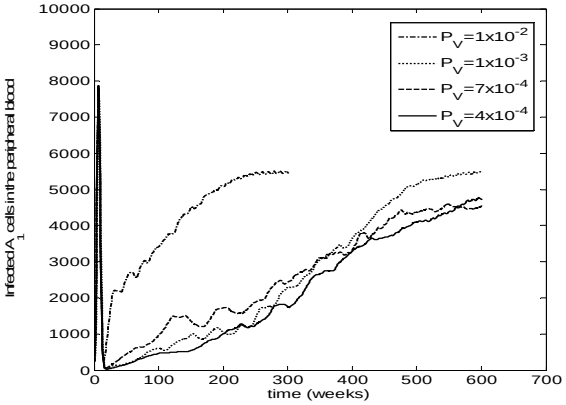


6(b)

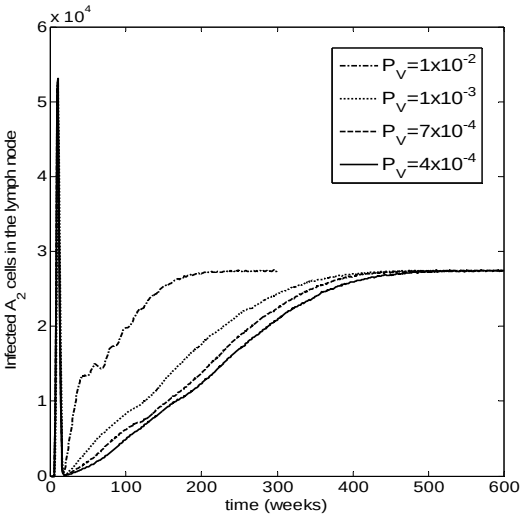


6(c)

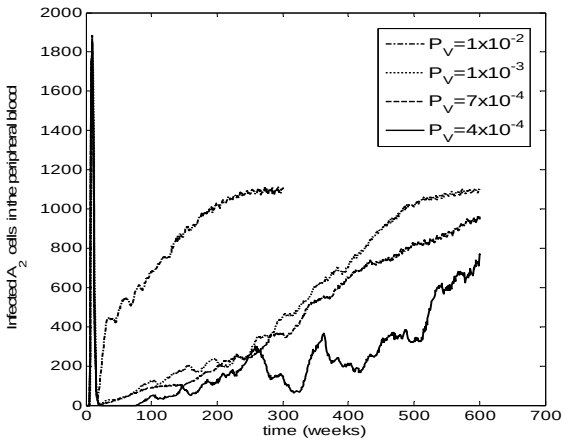
Fig. 6 Evolution of HIV infection from averaging 15 simulations using $r_1 = r_2 = 0.997$ for different values of P_V : (a), (b) the numbers of healthy cells in the lymph node and peripheral blood, respectively, (c) the number of infected A_1 cells in the lymph node.



7(a)

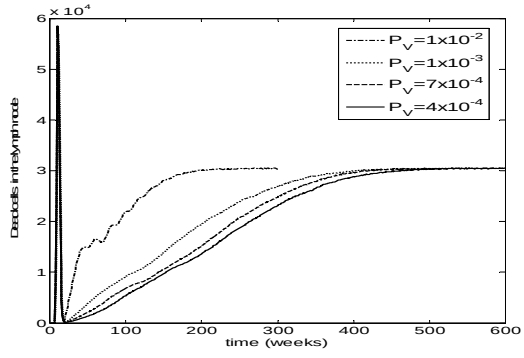


7(b)

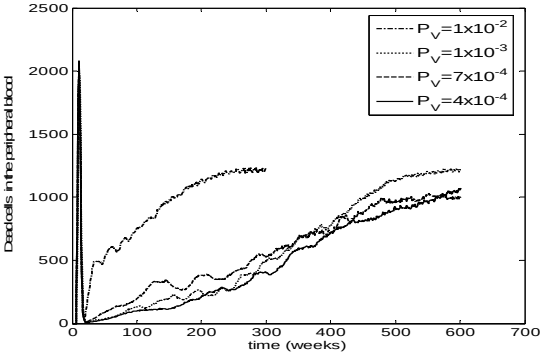


7(c)

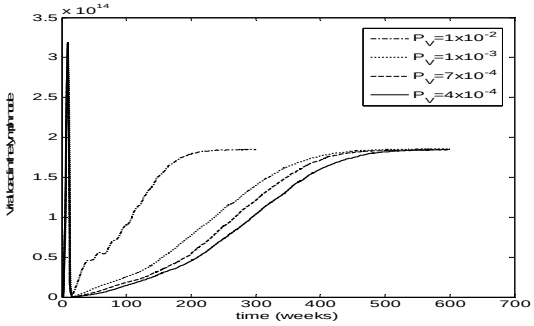
Fig. 7 Evolution of HIV infection from averaging 15 simulations using $r_1 = r_2 = 0.997$ for different values of P_V : (a) the number of infected A_1 cells in the lymph node, (b), (c) the numbers of infected A_2 cells in the lymph node and peripheral blood, respectively.



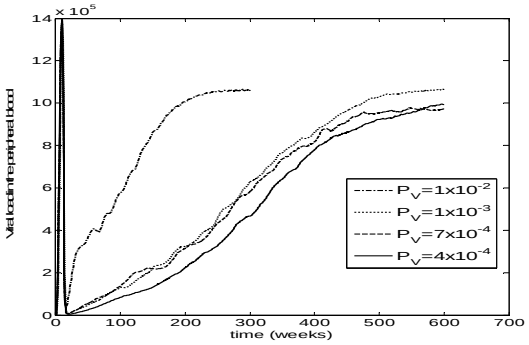
8(a)



8(b)

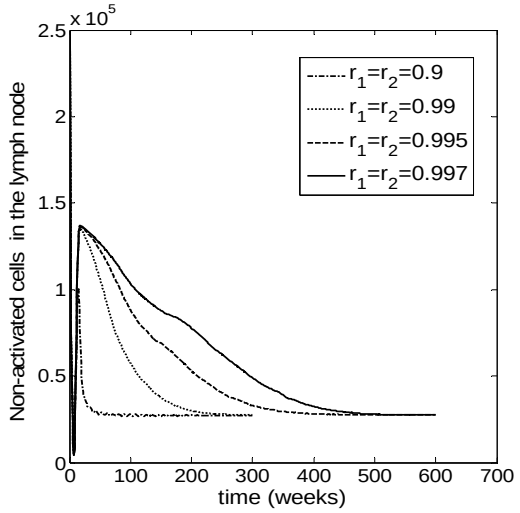


8(c)

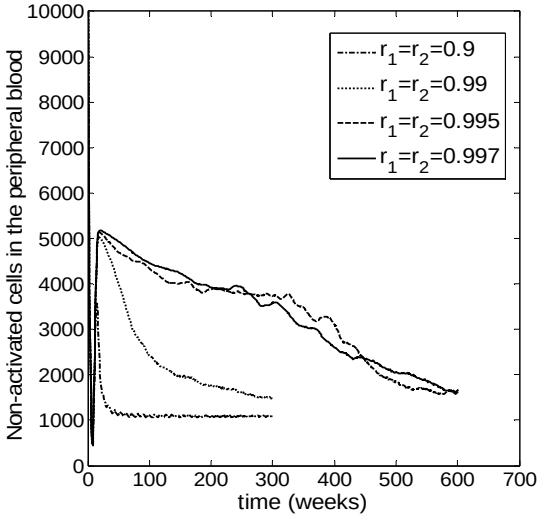


8(d)

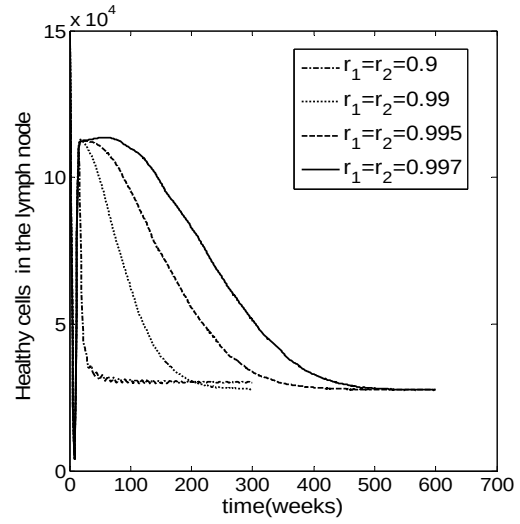
Fig. 8 Evolution of HIV infection from averaging 15 simulations using $r_1 = r_2 = 0.997$ for different values of P_V : (a), (b) numbers of dead cells in the lymph node and peripheral blood, respectively, (c), (d) the viral loads in the lymph node and peripheral blood, respectively.



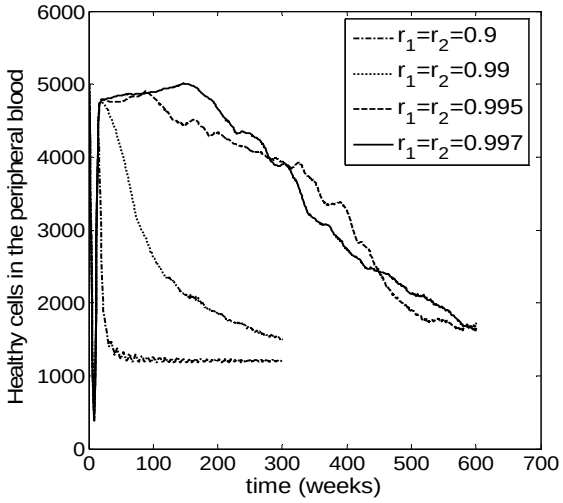
9(a)



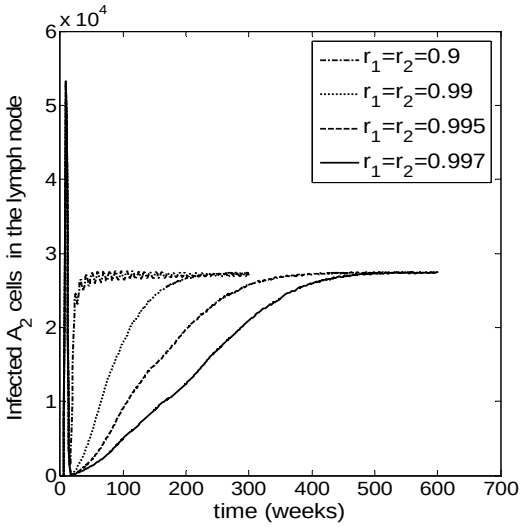
9(b)



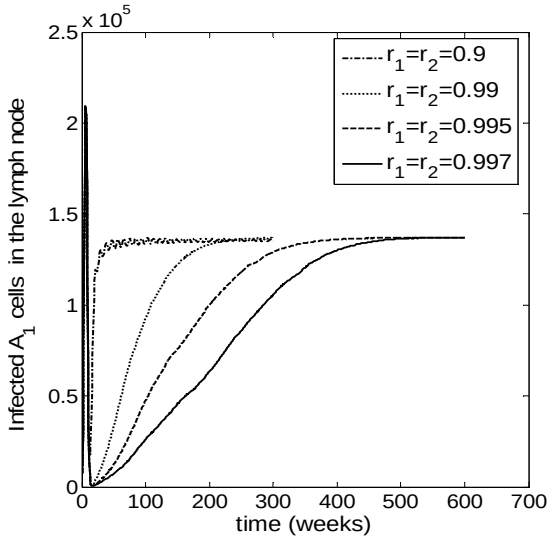
9(c)



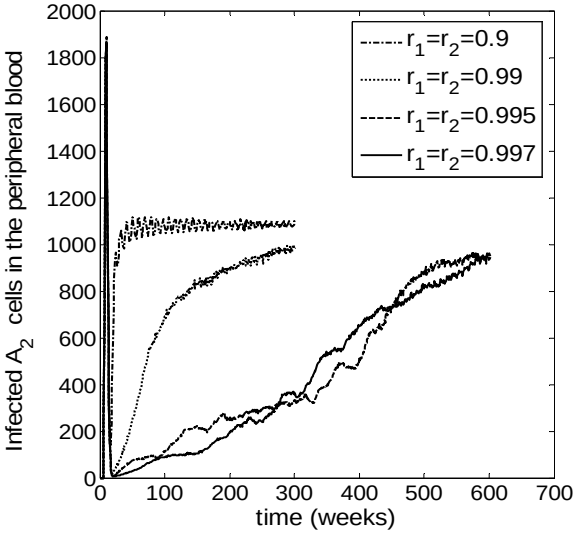
9(d)



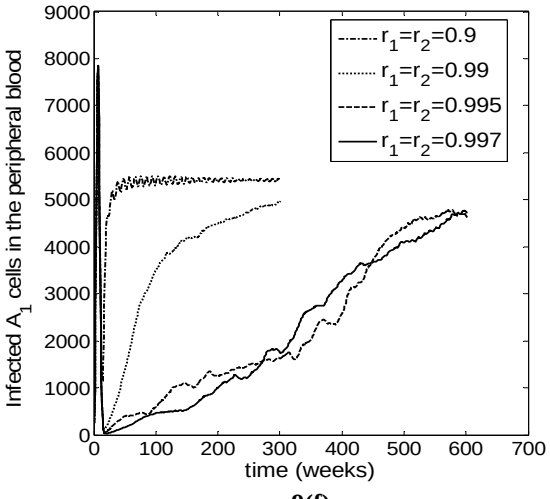
9(g)



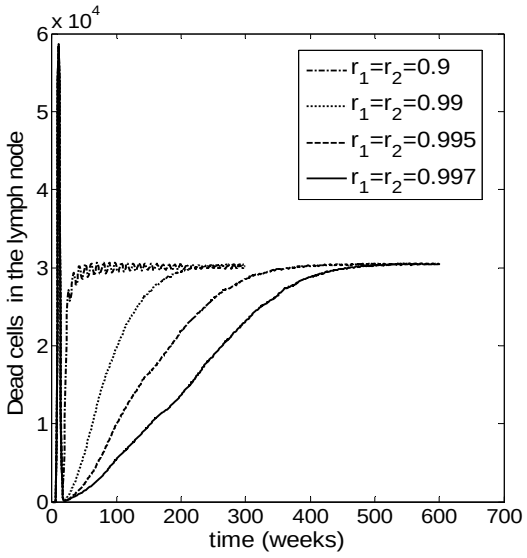
9(e)



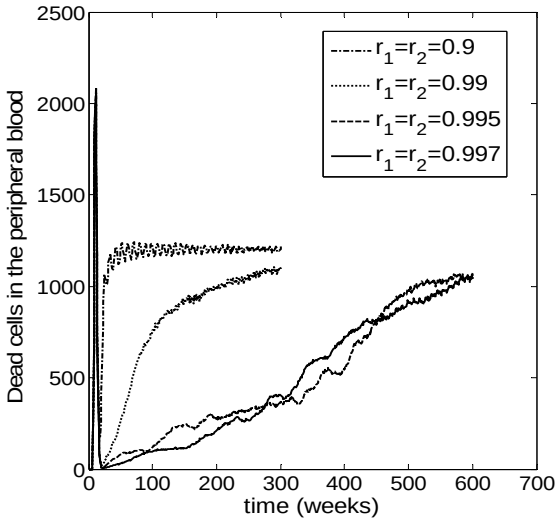
9(h)



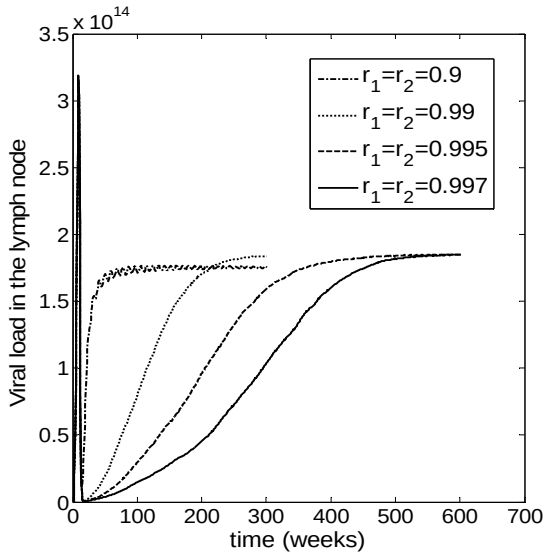
9(f)



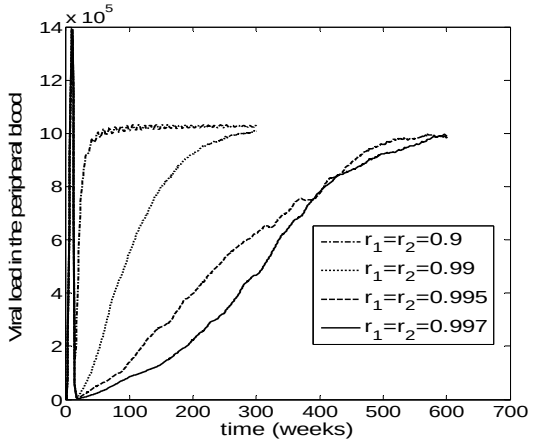
9(i)



9(j)



9(k)



9(l)

Fig. 9 Evolution of HIV infection from averaging 15 simulations with different r_1 and r_2.

Fig. 5-8 show the evolution of HIV infection averaged over 15 simulations using the parameter values in Tables I-III for different values of P_v which represents varying the chances that a cell coming in contact with the virus. We find that a higher P_v leads to a faster progression to full blown AIDS.

Fig. 9 (a)-(l) show the evolution of HIV infection averaged over 15 simulations using the parameter values in Tables I-III for different values of r_1 and r_2 which are related to the chances that a healthy cell is converted to an infected A_1 or A_2 cell. We see that higher r_1 and r_2 means a more lengthy latent phase. This will sound reasonable if we remember that although, with a higher r_1, a healthy cell is infected more readily when it comes into contact with one A_1 infected cell, the chance of its being infected by coming into contact with 2 or more A_2 cells is lower with higher r_1.

V. Conclusion

The model simulation has been carried out by updating each site in two coupled lattices in parallel. Our work is expected to extend the knowledge on the dynamics of HIV infection discovered by earlier researchers on this devastating disease, also see those reported in [20]-[23]. Here, the viral load in each compartment is updated at each time step. The virus is allowed to circulate from the lymph node compartment to the blood compartment whenever the viral load in the blood falls below a fraction *e* of the combined viral load. A delay τ for a highly infectious A_1 cell to become a final staged A_2 cell has been taken into account to make the model more realistic. Moreover, opportunistic infection is considered here to play an essential role in allowing the model to simulate different cases of infection exhibiting different chronic phase durations and eventual progression to full blown AIDS that closely simulate general clinical data.

References

[1] R. M. Zorzenon dos Santos, S. Coutinho, "Dynamics of HIV infection: A cellular automata approach", *Phys. Rev. Lett.*, Vol. 87(16), pp. 168102–1–4, 2001.

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

[3] V. Shi, A. Tridane, Y. Kuang, "A viral load-based cellular automata approach to modeling HIV dynamics and drug treatment", *J. Theor. Biol.*, Vol. 253(1), pp. 24-35, 2008.

[4] S. Wolfram, "Cellular automata as models of complexity", *Nature*, Vol. 311, p. 41924, 1984.

[5] U. Hershberg, Y. Louzoun, H. Atlan, S. Solomon, "HIV time hierarchy: Winning the war while, loosingall the battles", *Physica*, pp. 178–190, 2001.

[6] D. E. Kirschner, G. F. Webb, "A mathematical model of combined drugtherapy of HIV infection", *J. Theoret. Med.*, pp. 25–34, 1997.

[7] A. Mielke, R. B. Pandey, "A computer simulation study of cell population in a fuzzy interaction model for mutating HIV", *Physica A*, Vol. 251, pp. 430–438, 1998.

[8] A. S. Perelson, "Modelling the interaction of the immune system with HIV". In:C. Caastillo-Chavez (ed): Mathematical and Statistical Approaches to AIDS Epidermiology, *Lecture Notes in Biomathematics*, Vol. 83, pp. 350-370, 1989.

[9] N. Stilianakis, C.A.B. Boucher, M.D. De Jong, R. Van Leeuwen, R. Schuurman, R.J. De Boer, "Clinical data sets of HIV-1 reverse transcriptase-resistant mutants explained by a mathematical model", *J. of Virol.*, pp. 161–168, 1997.

[10] D. Wodarz, K. M. Page, R. A. Arnout, A. R. Thomsen, J. D. Lifson, M. A. Nowak, "A new theory of cytotoxic t-lymphocyte memory: implications for HIV treatment", *Philos. Trans. R. Soc. Lond.* (B Biol. Sci.), Vol. 355(1395), pp. 329–343, 2000.

[11] R.J. De Boer, A.S. Perelson, "Target cell limited and immune control models of HIV infection: a comparison", *J. Theor. Biol.*, Vol. 190, pp. 201–214, 1989.

[12] N.M. Dixit, A.S. Perelson, "HIV dynamics with multiple infections of target cells", *Proc. Natl Acad. Sci.*, Vol. 102 (23), pp. 8198–8203, 2005.

[13] D. Kirschner, "Using mathematics to understand HIV immune dynamics", *Nat. Am. Math. Soc.*, Vol. 43 (2), pp. 191-202, 1996.

[14] D. Wodarz, M.A. Nowak, "Mathematical models of virus dynamics and resistance", *J. HIV Ther.*, Vol. 3, pp. 36–41, 1998.

[15] A.T. Haase, "Population biology of HIV-1 infection: viral and CD4+ T cell demographics and dynamics in lymphatic tissues", *Annu. Rev. Immunol.*, Vol. 17, pp. 625–656, 1999.

[16] S. H. Bajaria, G. Webb, M. Cloyd , D. Kirschner, "Dynamics of naive and memory CD4+ T lymphocytes in HIV-1 disease progression", *J Acquir. Immune Defic. Syndr.*, Vol. 30, pp. 41-58, 2002.

[17] P.W. Nelson, J.D. Murray, A.S. Perelson, "A model of HIV-1 pathogenesis that includes an intracellular delay", *Math. Biosci.*, Vol. 163, pp. 201–215, 2000.

[18] D. J. Stekel, C. E. Parker, M. A. Nowak, "A model of lymphocyte recirculation, Immunol. Today", Vol. 18, pp. 216-221, 1997.

[19] A. S. Fauci, G. Pantaleo, S. Stanley, D. Weissman, "Immunopathogenic mecha-nisms of HIV infection", *Ann. Intern. Med.*, Vol. 124, pp. 654-663, 1996.

[20] 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.

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

[22] 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.

[23] 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.