Double Compartment CA Simulation of Drug Treatments Inhibiting HIV Growth and Replication at Various Stages of Life Cycle

Sompop Moonchai, and Yongwimon Lenbury

***Abstract*—**Although there is no cure for AIDS at this time, intense research efforts have yielded several treatments that may be relied upon to delay HIV progression and improve the quality of life of those who have become symptomatic. Human immunodeficiency virus (HIV) infection typically follows a three phase pattern; the primary response phase, the clinical latency phase, and the final phase of onset of acquired immunodeficiency syndrome (AIDS). In order to test the efficiency of different protocols in drug therapy for HIV patients, it is important to have a realistic model which reliably simulates the course of the infection which exhibits two drastically different time scales, days and decades. The classical ordinary or partial differential equations have been found to be inadequate in coping with such extreme spread in time scales. In this paper, we employ a two-compartment Cellular Automata (CA) model to study the dynamics of drug therapy of HIV infection. The levels of healthy an infected CD+T cells are tracked in both the lymph node and peripheral blood compartments coupled and updated simultaneously with each time step. The viral loads in the two compartments are also updated through a system of difference equations. The cell update rules in the CA model are modified to simulate the impacts of therapeutic measures where various types of antiretroviral drugs are applied to inhibit the growth and replication of HIV at various stages of its life cycle. By adjusting the rules to update the cells in the CA lattice, it becomes possible to study the efficacies of different treatment strategies or drugs of choice, as well as the repercussion of drug resistance over time.

***Keywords*—**human immunodeficiency virus, Cellular Automata (CA) model, drug therapy, drug resistance.

I. Introduction

HUMAN immunodeficiency virus (HIV) is a member of the retrovirus family that causes a condition called acquired immunodeficiency syndrome (AIDS) [1, 2] in which the human's immune system begins to fail. Once this stage in the progression of the disease is reached, the infected person becomes susceptible to life-threatening opportunistic infections. Within the infected person's bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

Since the Human Immunodeficiency Virus causes a lethal disease with such an insidious time course, the study of the dynamics and pharmacokinetics of the virus-immune system in the human body is necessary in order to discover a proper therapeutic strategy for HIV infection and discover how the disease might be controlled. Development of reliable models to simulate the course of HIV infection can be an important and crucial component in the pharmacological research for effective HIV treatments.

Recently, it has been discovered that cellular CA modelling technique offers a more suitable tool for the study of the progress of the disease since it can accommodate the drastically different time scales exhibited in the entire course of HIV infection. Classical attempts at modelling based on systems of ordinary differential equations (ODES) and partial differential equations (PDES) have been found inadequate for the task 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 development to full blown AIDS (measured in years).

In recent years, a few cellular CA models have been developed to model HIV infection in the lymph node [3-5]. In 2002, Sloot et al. reported on a non-uniform CA model which studies the dynamics of drug therapy in HIV infection [4]. Their model was employed to simulate four phases of infection dynamics; acute, chronic, drug treatment response, and onset of AIDS. Their results indicated that both simulations (with or without treatment) evolved toward to same steady state. Three different drug therapies were investigated, mono-therapy, combined drug therapy, and highly active antiretroviral treatment (HAART).

More recently, Shi et al. developed a CA model to study the effect of drug treatment of HIV, incorporating the virus replication cycle and the role of viral load and latently infected cells in sustaining HIV infection [1]. Drug treatment combinations with reverse transcriptase inhibitors and protease inhibitors are simulated with various drug efficacies.

Reverse transcriptase inhibitors (RTIs) are a class of antiretroviral drug used to treat HIV infection. When HIV infects a cell, reverse transcriptase copies the viral single

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stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA. This allows transcription and translation to occur in the host's cells in order to reproduce the virus. The role of RTIs is to block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA. HIV is thus prevented from multiplying.

Antiretroviral drugs inhibit the growth and replication of HIV at various stages of its life cycle. RTIs come in three forms. The first is the nucleotide analog reverse transcriptase inhibitors (NRTIs), sometimes called "nukes", which work by blocking an enzyme (reverse transcriptase) crucial to the production and replication of HIV. The second form is the nucleoside analog reverse transcriptase inhibitors (NNRTIs), sometimes referred to as Non-Nucleoside Analogs or "non-nukes", which operates by preventing the enzyme from converting RNA to DNA, and prevents the genetic material of the HIV virus from being incorporated into the healthy genetic material of the cell. Thus, they render it impossible for the cell to produce a new virus. Finally protease inhibitors (PIs) work by interfering with the enzyme HIV protease. HIV replication is thus interrupted at a later stage in its life cycle, causing HIV particles in the body to become structurally disorganized and noninfectious [6].

Most CA models so far 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 both compartments are important for the description of the dynamics of HIV infection.

In our earlier paper [7], the CA rules based on those utilized by Santos and Coutinho in their CA model [5] were modified to construct a double latticed CA model to investigate the dynamics of HIV infection in both the lymph node and blood compartments while the viral loads in the two compartments are continuously updated throughout the simulation. The 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.

In this paper, different forms of drug therapy are simulated by incorporating its effects in the cell update rules of the double compartment CA model we developed in [7]. First, we investigate the action of medication by drugs in the group of protease inhibitors which cause some HIV particles to become structurally disorganized and non-infectious. We then utilize a modified set of cell update rules to simulate the action of drugs in the group which work by blocking reverse transcriptase's enzymatic function occurring in the host's cells so that viral DNA synthesis is blocked. By appropriately adjusting the rules to update the cells in the two CA lattices, the lattice representing the lymph node tissue and that for the peripheral blood compartment, it becomes possible to study the efficacies of different treatment options or drugs of choice, as well as the repercussion of drug resistance over time.

II. CA Model and Simulations

Here, we employ a CA model which 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, active healthy cells (representing CD4+ T-cells which are the main target of the HIV), infected A1 cells (corresponding to infected cells that are free to spread the infection), infected A2 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 simulating the CA model of HIV infection in two coupled compartments, for each compartment, the simulation steps start with N0 non-activated or non-proliferating cells, H0 healthy active cells, and a small fraction P_{HIV} of infected A1 cells (A10), 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 efficacy of drug use in the protease inhibitor group is reflected in the probability P_d appearing below in ***Rule 2*** for the updates of healthy cells. It reduces the chance that a healthy cell is infected by the virus into an A1 infected cell. The definitions and values of all the parameters and probabilities used in these rules are given in Tables 1-2.

The updating rules are as follows.

Rule 1**:** Updates of non-proliferating cells.
(a) If a non-proliferating cell has non-assigned slots 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}.
(b) 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) An active healthy cell gets infected by coming in contact with a virus at the probability

$$P_v^* = (1 - P_d) P_v f(V_t) = (1 - P_d) P_v (1 - e^{-a V_t^L}) . \qquad (1)$$

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

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

Table 1. 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	250,000

	$t = 0$	
H_0	Number of healthy active cells at $t = 0$	200,000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [5]
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	0.001 (estimated)
A	Constant in probability in Eq. (1)	1×10^{-15}
r_1	Constant in probability in Eq. (2)	0.997 (estimated)
r_2	Constant in probability in Eq. (3)	0.997 (estimated)
τ	Time delay for an infected A_1 cell to become an infected A_1 cell	4 [5]
P_{infec}	Probability for a healthy cell to be replaced with an infected A_1 cell	1×10^{-5} [5]
P_{repl}	Probability for a death cell to be replaced with a healthy cell	0.99 [5]
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 neighbourhood to induce a healthy cell to become an infected A_1 cell	4 [5]

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

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

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

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

where $0 < P_1^* + P_2^* + P_v^* < 1$ and P_d is a drug effectiveness, $0 \le P_d \le 1$.

***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 $(1 - P_{\text{infec}})P_{\text{repl}}$ in the next step, or by an infected A_1 cell with the probability $P_{\text{infec}}P_{\text{repl}}$. Otherwise, it remains a dead cell at probability $1 - P_{\text{repl}}$.

(b) After step (a), dead cells can be replaced by an inactivated cell with probability P_{inc}. Otherwise, it remains a dead cell at the probability $1 - P_{\text{inc}}$.

Table 2. 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 $t = 0$	10,000
H_0	Number of healthy cells at $t = 0$	5,000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [5]
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	0.001 (estimated)
A	Constant in probability in Eq. (1)	1×10^{-7}
r_1	Constant in probability in Eq. (2)	0.997 (estimated)
r_2	Constant in probability in Eq. (3)	0.997 (estimated)
τ	Time delay for an infected A_1 cell to become an infected A_2 cell	4 [5]
P_{infec}	Probability for a healthy cell to be replaced with an infected A_1 cell	1×10^{-5} [3]
P_{repl}	Probability for a death cell to be replaced with a healthy cell	0.99 [3]
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 [5]

The same rules are applied to update the cells in the lattice for the peripheral blood compartment.

III. Viral Load Determinations

The viral load influences the dynamics of the healthy and infected cells through the probability P_v^*. Following what has

been done in our earlier work [7], after all of the five cell states are updated in the two lattices, the virus presence in each compartment is calculated using Eq. (1)-(2) and the following difference equations which represent the evolution of viral load in the lymph node compartment (with Vt = V_t^L) and peripheral blood compartment (with Vt = V_t^B) at time t.

In the lymph node compartment

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

where

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)

As in [7], A_{1t}^L and A_{2t}^L are the numbers at time t of A1 and A2 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 active 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.

The values of the parameters appearing in Eq. 4-5 used in our simulations are given in Table 3.

The value of drug efficacy probability P_d is varied in the simulation shown in Figures 1-6. The healthy cells, the infected A1 cells, the infected A2 cells, and the viral load in the lymph node are shown in Figures 1-3, comparing no-treatment course of infection to effects of treatments at various drug efficacies. The levels of these cell types in the peripheral blood are shown in Figures 4-6.

We observe in these simulation samples that the application of anti-viral drugs exert a marked effect only briefly immediately after the beginning of drug use. The drug seems to eventually become less effective in the long run, however high its efficacy is, even though its use has not been terminated, as long as 100% efficacy can not be assured ($P_d \neq 1$). Our simulations indicate that the virus will be able to adjust quite quickly to the drugs attempt at blocking its infection of the healthy cells whose level of healthy cells still drops to a low level, and those of infected cells and viral load still rise to unhealthily high levels. However, these levels do stabilize to steady state levels, which could be controllable. In contrast, the patient free of therapy shows a continued drop in the level of healthy cells, and non-stabilizing rise in the levels of infected cells and viral load in the blood compartment.

IV. Drug Efficacies with Resistance

To investigate the possible long term consequences of drug resistance at different drug efficacies, we replace P_d, in the updating rule, which incorporates the effect of drug therapy in fighting HIV infection, by

$$P_d = \mu e^{-\eta(t-T_d)}$$

with $0 \le \mu \le 1$, $T_d = 300$, and $\eta = 0.001$. This means that as time progresses, the given drug loses its ability to fight the virus in an exponential fashion.

Table 3. Model parameters in viral load simulation.

Symbol	Definition	Value [reference]
V_0^B	Plasma virus concen-tration at $t = 0$	10 [8] (can vary)
V_0^L	Virus concentration in the lymph node at $t = 0$	0
p	Average virion production rate per infected cell	480 [9]
S_L	Scaling factor in the lymph node	$2\times10^{11}/H_0$ (estimated)
S_B	Scaling factor in the blood	$1,000/H_0$ (estimated)
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	Free virus death rate	0.3 [9]
e	Circulation fraction of virus between lymph node and blood	0.02 [10]
β	Scaling factor: lymph node $\rightarrow$ blood	2×10^{-7} [8]
α	Scaling factor: lymph node $\rightarrow$ blood	5×10^{6} [8]

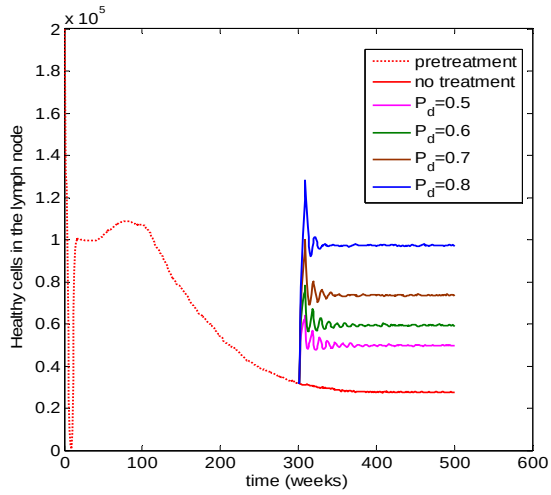


Figure 1

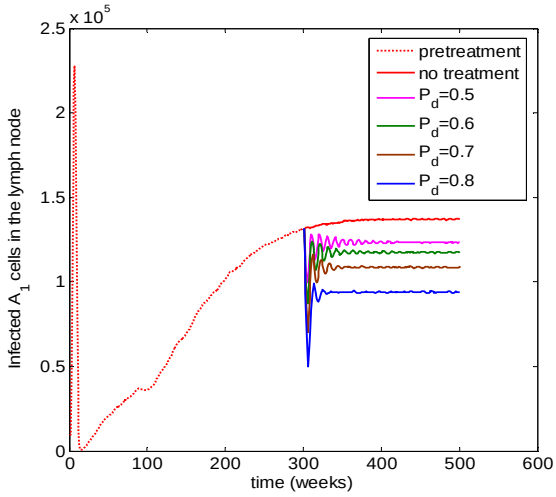


Figure 2

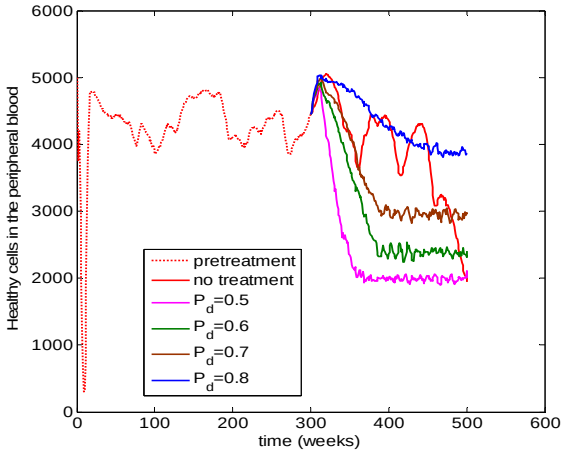


Figure 3

In Figures 7-9, we see the comparison of effects of drug treatment at different resistance values of μ. The drug efficacy wears off with time and the healthy cells settle to a lower steady state level than the case where drug resistance is not under display. The A1 infected cells and viral load are seen to settle to higher steady state levels than those in the case where drug resistance is not incorporated. The curves are averages over 10 simulations. No significant difference has been observed in the curves when averaged over a higher number of simulations.

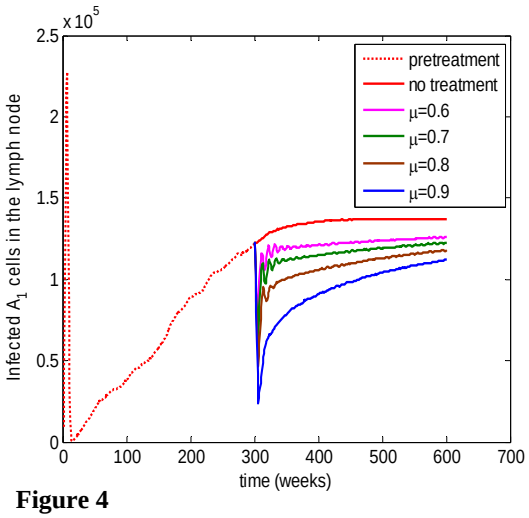


Figure 4

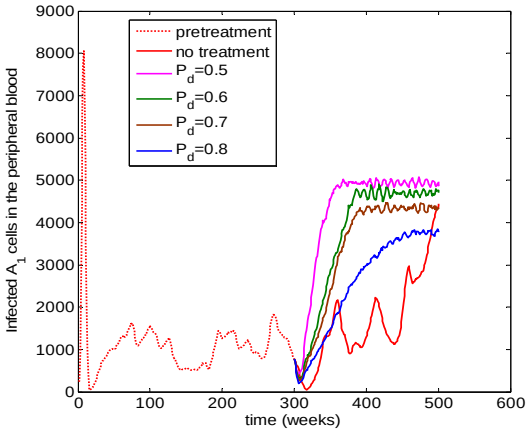
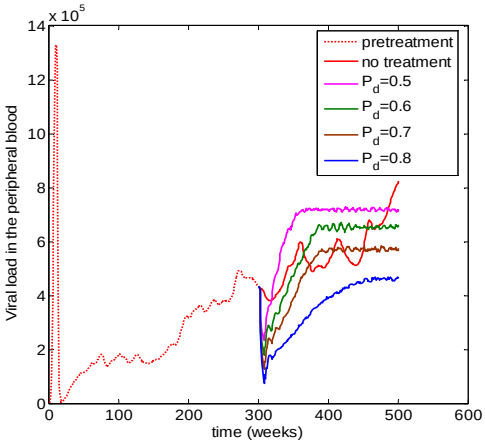


Figure 5



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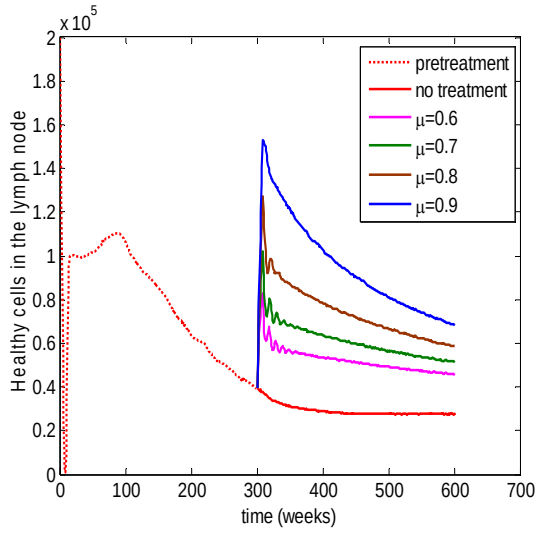

Figure 7

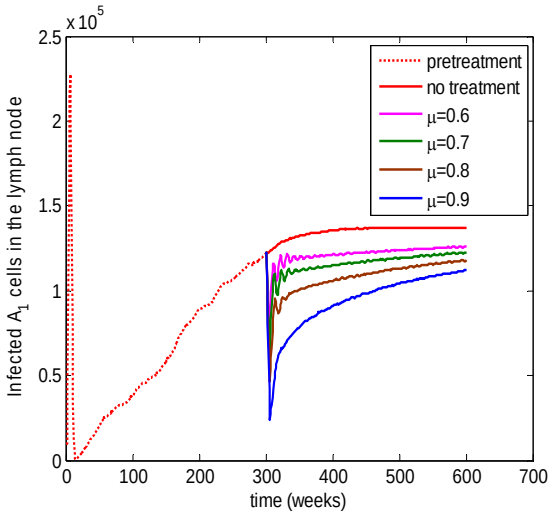

Figure 8

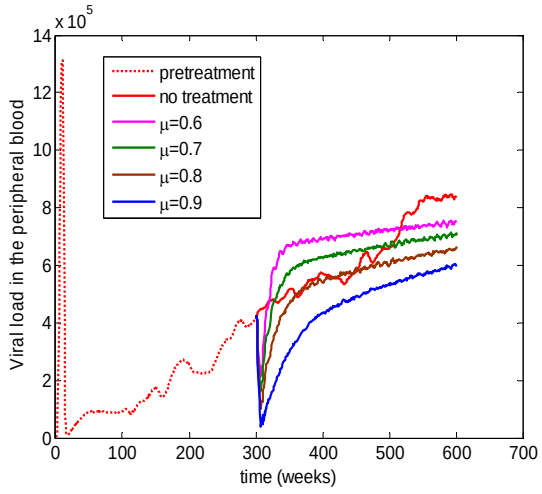

Figure 9

V. Action of NRTIs/NNRTIs

To simulate the efficacy of reverse transcriptase inhibitors in the form of NRTIs or NNRTIs, we adjust the cell update rules as follows.

***Rule 1*:** Updates of non-proliferating cells.

(a) If a non-proliferating cell has non-assigned slots 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}.

(b) 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

$$P_v^* = P_v f(V_t) = P_v(1 - e^{-aV_t^L}). \quad (6)$$

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

$$P_1^* = r_1(1 - P_v^*). \quad (7)$$

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

$$P_2^* = r_2(1 - r_1)(1 - P_v^*). \quad (8)$$

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

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

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

(e) After step (d), an infected A_1 cell remains an infected A_1 cell at the probability $1 - P_d$ .Otherwise, it becomes a healthy cell.

(f) After step (e), a healthy cell can be replaced by an infected A_1 cell with probability $1 - P_c$.

Otherwise, it remains a healthy cell at the probability P_c in the next time step**,** where P_c is probability that reverse transcription is not completed and P_d is a drug efficacy of reverse transcriptase inhibitor, $0 \le P_d \le 1$.

***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_2 cells.

Infected A_2 cells become dead cells in the next time step, 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 $P_{\text{infec}}P_{\text{repl}}$. Otherwise, it remains a dead cell at probability $1 - P_{\text{repl}}$.

(b) After step (a), dead cells can be replaced by an inactivated cell with probability P_{inc}. Otherwise, it remains a dead cell at the probability $1 - P_{\text{inc}}$.

The parametric values used in our simulations in this case are given in Tables 4-5.

Table 4. Model parameters in the CA model in the lymph node compartment.

Symbol	Value in lymph node [reference]	Value in blood [reference]
L	500	200
N_0	250,000	40,000
H_0	120,000	30,000
P_{HIV}	0.05 [1]	0.05 [1]
P_{op}	0.001 (estimated)	0.001 (estimated)
P_v	0.00045 (estimated)	0.0025 (estimated)
a	5×10^{-16}	4×10^{-8}
r_1	0.997 (estimated)	0.997 (estimated)
r_2	0.997 (estimated)	0.997 (estimated)
τ	4 [1]	4 [1]
P_{infec}	1×10^{-5} [1]	1×10^{-5} [1]
P_{repl}	0.99 [1]	0.99 [1]
P_{nona}	0.9 (estimated)	0.9 (estimated)
R	4 [1]	4 [1]
P_d	0.5-0.9	0.5-0.9
P_c	0.5-0.99	0.8-0.99

Figures 10-12 show the simulated results in the lymph node and blood compartments when P_c is set equal to 0.99, while P_d is varied from 0.5 to 0.9.

Figures 13-18 show the simulation results when P_d is fixed at 0.9, while P_c is varied between 0.5 and 0.99. The curves have been obtained from averaging over 20 simulations. No observable difference was found when averaged over higher number of simulations.

Table 5. Model parameters in viral load simulation.

Symbol	Definition	Value [reference]
V_0^B	Plasma virus concentration at $t = 0$	10 [8] (can vary)
V_0^L	Virus concentration in the lymph node at $t = 0$	0
p	Average virion production rate per infected cell	480 [9]
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 [9]
e	Circulation fraction of virus between lymph node and blood	0.02 [10]
β	Scaling factor: lymph node $\rightarrow$ blood	2×10^{-7} [8]
α	Scaling factor: lymph node $\rightarrow$ blood	5×10^{6} [8]

Since the simulated curves in the lymph node and the peripheral blood compartments are qualitatively similar, we only show the simulated curves in the lymph node for some quantities, and in the blood compartment for others.

We observe in these figures that when the efficacies P_c and P_d are sufficiently high, this type of drug treatment affects a clear improvement in the course of infection: the levels of viral load and infected cells drops drastically and remain significantly lower than those of the no-treatment case, while the level of healthy cells rises to reach and remain at a level significantly higher than the no-treatment case.

Thus, our simulations appear to indicate that this form of drug choice can be expected to be more effective than the use of protease inhibitors simulated in the previous section.

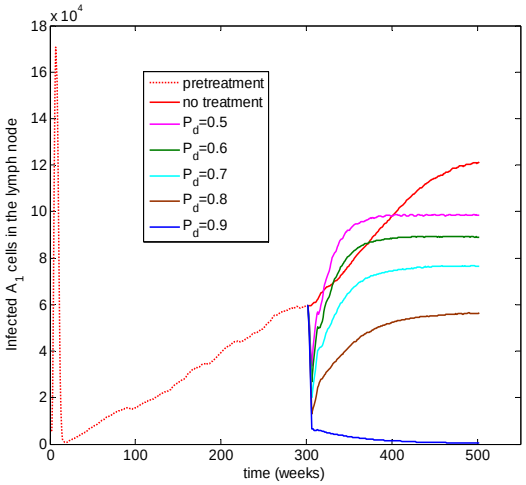

Figure 10

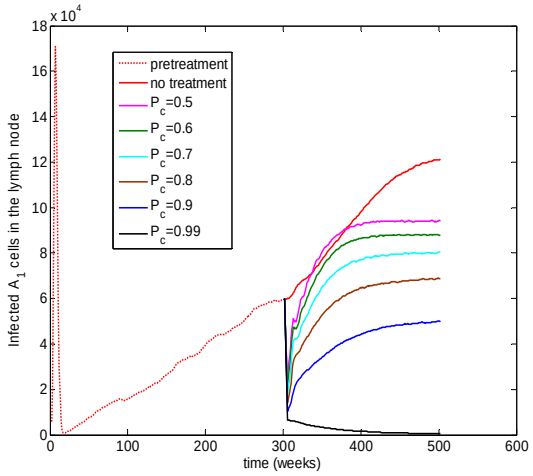

Figure 13

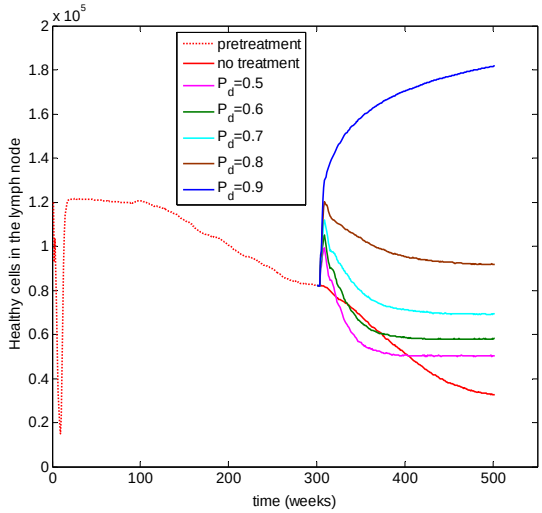

Figure 11

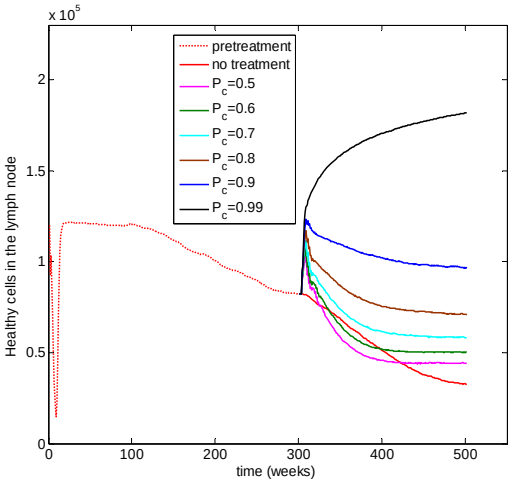

Figure 14

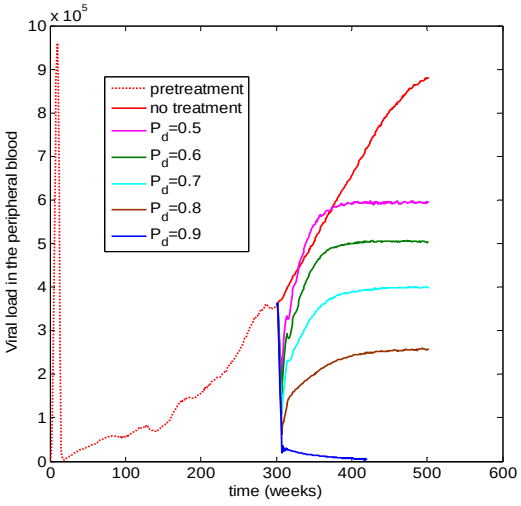

Figure 12

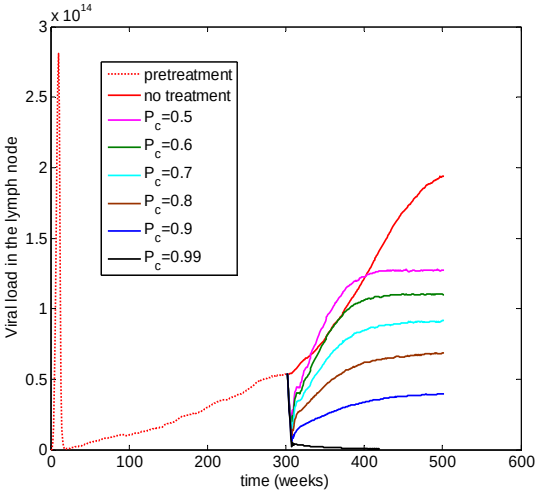

Figure 15

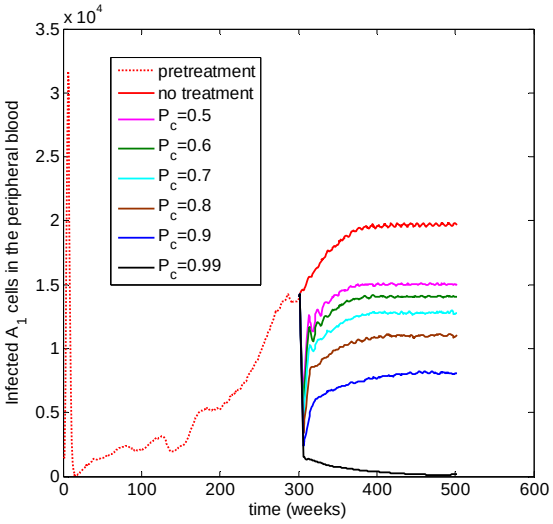

Figure 16

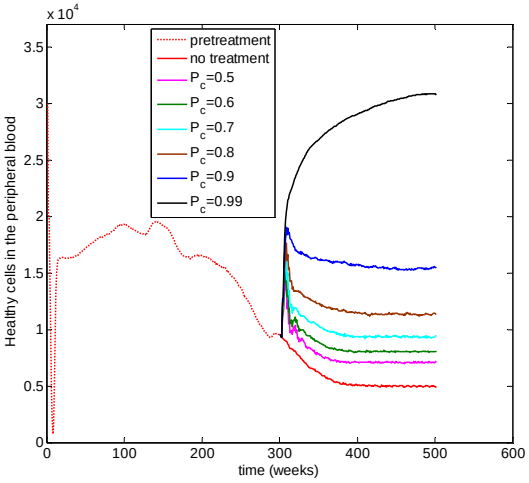

Figure 17

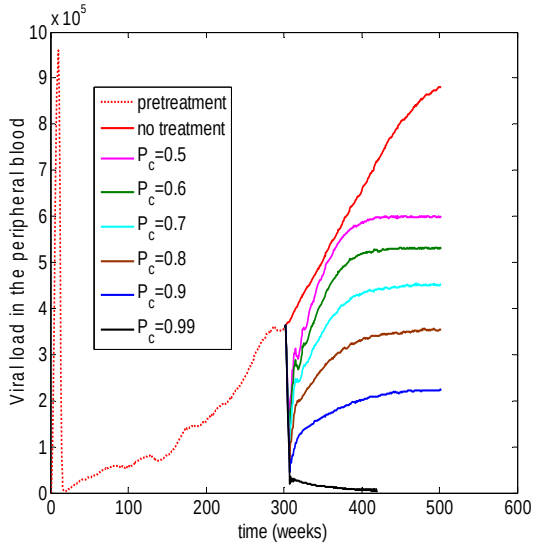

Figure 18

VI. Conclusion

The simulations of our CA model allow us to investigate the effects of drug efficacies and drug resistance on the development of HIV infection. Effects of different types of drugs targeting different infection mechanisms, such as the use of drug treatment combinations with reverse transcriptase inhibitors and protease inhibitors may be simulated subject to various drug efficacies. Our study indicates that he drugs which cause the virus to become structurally disorganized and hence less infectious lead to better improvement in the lymph node than in the peripheral blood compartment. On the other hand, drugs which work by blocking the enzyme reverse transcriptase crucial for the production and replication of the virus lead to more observable improvements in the blood compartment than in the lymph node. Moreover, the latter drug type seems to be more efficient in fighting the infection.

It would seem that our results differ qualitatively from those of Sloot et al. [4] in that the non-treated and treated curves simulated with our model do not converge to the same steady state. The same can be observed in the case where drug resistance is assumed to take place. In our opinion, our result is more reasonable as it suggests that even though drug treatment does not effectively annihilate the infection altogether, and even with the ensuing drug resistance, the patients benefit from the treatment to a certain extent over not being given any treatment at all.

Of course, the applications of drug treatment at different points in time in a patient course of HIV infection is expected to lead to different outcomes. Simulations can be further carried out to determine the optimal point in time during the course of infection at which drug treatment should be started.

Effects of different types of drugs targeting different infection mechanisms, such as the use of drug treatment combinations with reverse transcriptase inhibitors and protease inhibitors may be simulated subject to various drug efficacies. The outcomes of these different drug choices or combinations could be compared in order for proper prognosis and decisions can be made by the physicians on the best course of action to be taken for their patients under their care.

Acknowledgment

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