Investigating Effects of Drug Therapy for HIV Infection by Double Compartments Cellular Automata Simulations

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Abstract: - The progress of 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. Drug therapy is then simulated by incorporating its effects in the update rules of the CA model. 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.

Key-Words: - human immunodeficiency virus, Cellular Automata (CA) model, drug therapy, drug resistance.

1 Introduction

The Human Immunodeficiency Virus (HIV) causes AIDS, a lethal disease with 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 realized that models based on systems of ordinary differential equations (ODES) and partial differential equations (PDES) are 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 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 [1-3]. In 2002, Sloot et al. reported on a non-uniform CA model which studies the dynamics of drug therapy in HIV infection [2]. In their model, each computational domain may contain different CA rules. The model was then 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.

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.

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In our earlier paper [4], the CA rules based on those utilized by Santos and Coutinho in their CA model [3] 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 drug therapies are simulated by incorporating its effects in the update rules of the double compartment CA model we developed in [4]. By 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 strategies or drugs of choice, as well as the repercussion of drug resistance over time.

2 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 neighbourhood 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 simulating the CA model of HIV infection in two coupled compartments, 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 drug efficacy 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 neighbours, 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 neighbour 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

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

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

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

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

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

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

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

where $0 < P_1^* + P_2^* + P_v^* < 1$ 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 $1 - P_{\text{repl}}$.

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

3 Viral Load Determinations

The viral load influences the dynamics of the healthy and infected cells through the probability P_v^*. Following the work done in our earlier work [5], after all of the five cell states are updated in the two lattices, the viral load 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 $V_t = V_t^L$) and peripheral blood compartment (with $V_t = V_t^B$) at time *t*.

In the lymph node compartment

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

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 [5], 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.

The values of the parameters appearing in Eq. 1-2 used in our simulations are given in Table 3.

The value of drug efficacy probability P_d is varied in the simulations 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 compartment are shown in Figures 4-6.

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 $t = 0$	250,000
H_0	Number of healthy active cells at $t = 0$	200,000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [3]
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 [3]
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 non-activated cells	0.9 (estimated)
R	Number of infected A_2 cells in a cell neighbour-hood to induce a healthy cell to become an infected A_1 cell	4 [3]

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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 $t=0$	10000
H_0	Number of healthy cells at $t=0$	5000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [3]
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 [3]
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 [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 [3]

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.

4 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	Palsma virus concentration at $t=0$	10 [5] (can vary)
V_0^L	Virus concentration in the lymph node at $t=0$	0
p	Average virion production rate per infected cell	480 [6]
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	Free virus death rate	0.3 [6]
e	Circulation fraction of virus between lymph node and blood	0.02 [7]
β	Scaling factor: lymph node$\rightarrow$ blood	2×10^{-7} [5]
α	Scaling factor: lymph node$\rightarrow$ blood	5×10^{6} [5]

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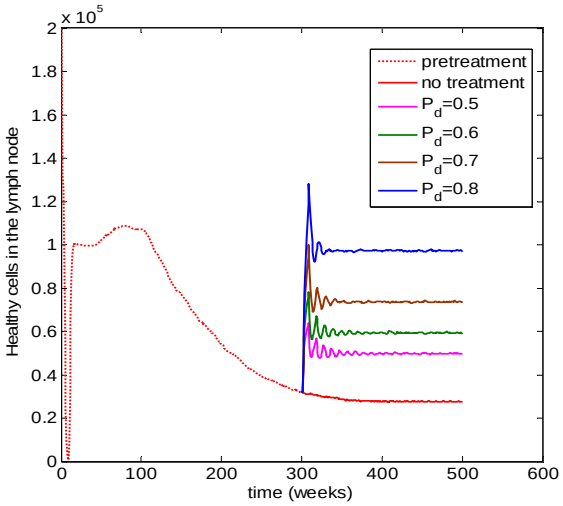

Figure 1

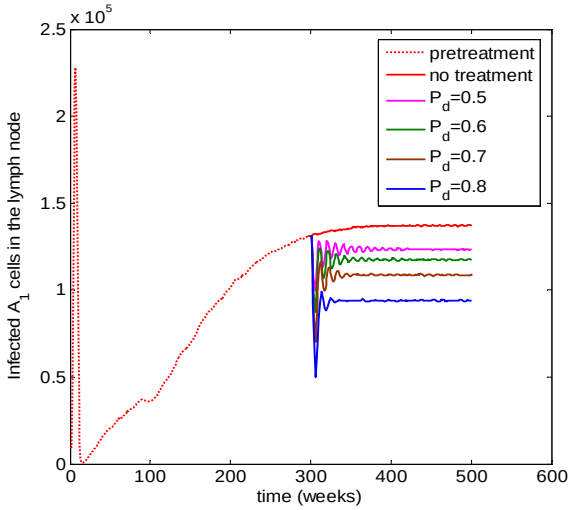

Figure 2

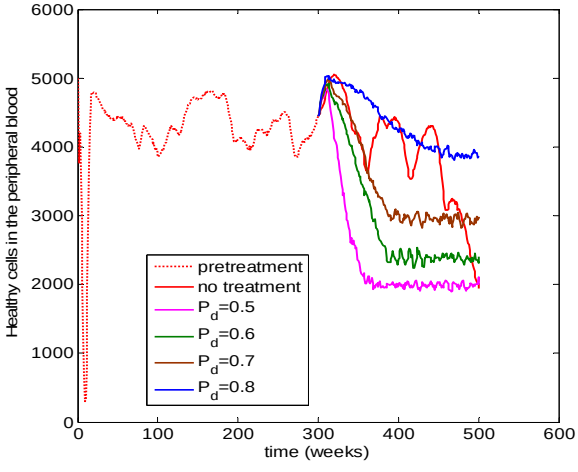

Figure 3

In Figures 7-9, we see the comparison of simulation results at different 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.

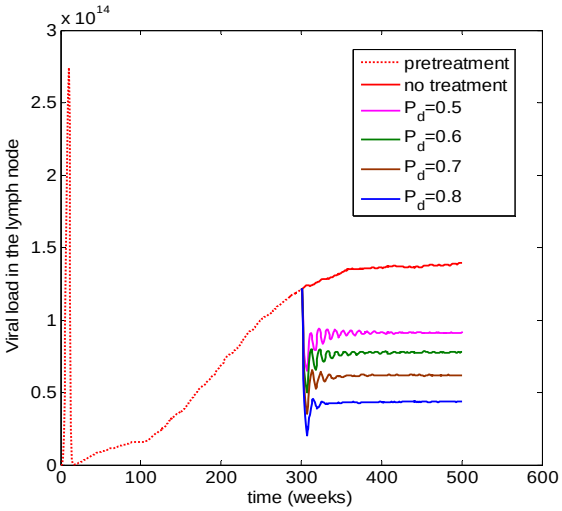

Figure 4

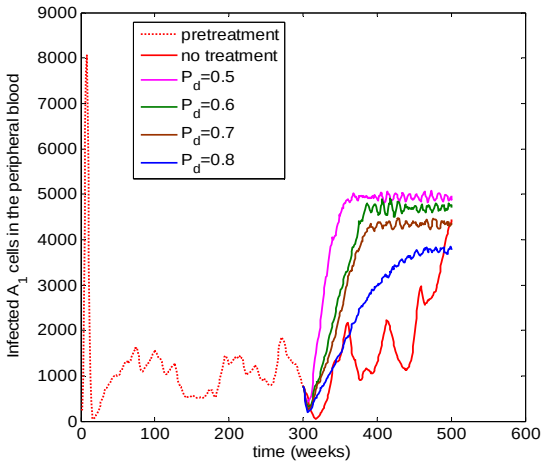

Figure 5

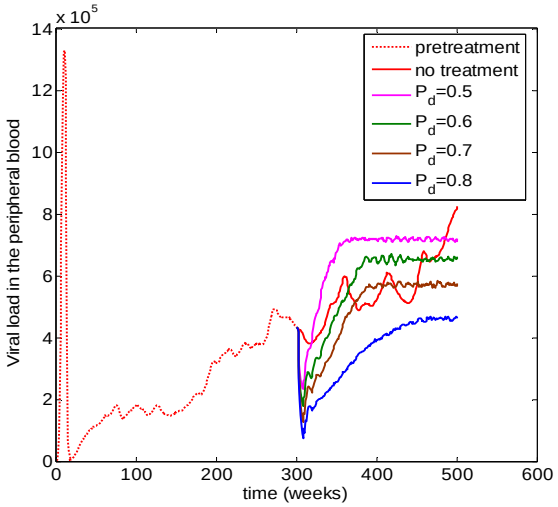

Figure 6

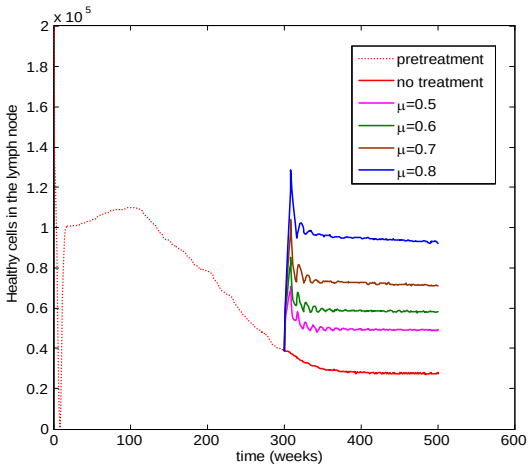

Figure 7

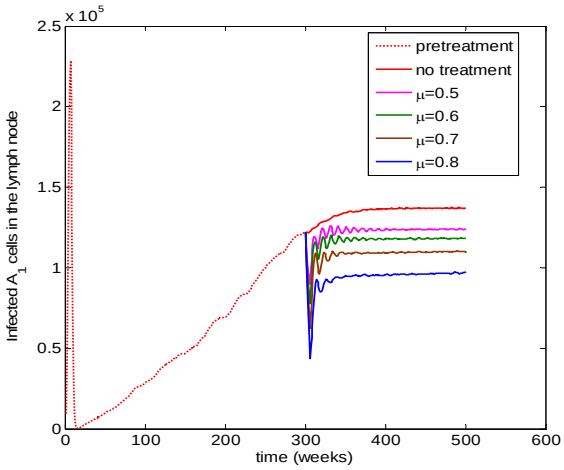

Figure 8

5 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. 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.

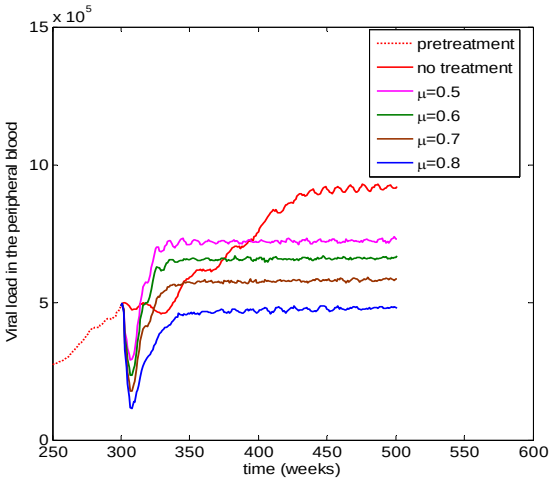

Figure 9

5 Acknowledgement

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