Cellular Automata Simulation of Interrupted Plasma Aphaeresis on AIDS Patients: Investigating Effects of Different Clearance Rate

Sompop Moonchai, Yongwimon Lenbury

***Abstract*—**The use of a combination of three or more antiretroviral drugs, called the Highly Active Antiretroviral Therapy (HAART), has been found to keep the viral load of HIV in the patient's body at a controllable level as well as improve the immune system. However, if HAART is abandoned, a rebound of plasma viral load occurs which led us to believe that the use of this treatment is associated with metabolic side effects in human, including increased risk for opportunistic infections. In order to avoid the problems with drug treatment, an alternative treatment by Aphaeresis has been suggested. In plasma aphaeresis, the virus in the large molecular components of plasma are removed from a patient after which the small molecular components of plasma and cell components of blood are returned to the patient. Several studies seem to suggest that plasma aphaeresis could be a good treatment for AIDS patients with peripheral polyneuropathy since plasma pheresis has been found to be capable of reducing a patient's plasma viral load to half of the original load. In this paper, we modify the CA rules based on the CA model of Moonchai and Lenbury [1] to investigate the action of plasma aphaeresis therapy on the CD4+ T cells and viral load in both the lymph node and blood compartments. Effects of different clearance rates of plasma aphaeresis therapy are investigated.

***Keywords*—**Human immunodeficiency virus, HIV infection, Cellular Automata, plasmapheresis treatment.

I. Introduction

COMPUTER simulation modeling has become increasingly important in decision making in modern medicine. Admittedly, clinical studies, in particular large-scale randomized controlled trials, remain the main source of information for decision makers. However, modeling is gaining acceptance as a valuable tool to provide information on long-term medical and socio-economical outcomes. Computer simulation models can provide information for health care decision makers and allow them to make the most informed choices between available treatments protocols. For such reasons, the health care industry is relying more and more on modeling to make well informed decisions.

Acquired Immune Deficiency Syndrome (AIDS), due to the Human Immunodeficiency Virus (HIV), widely recognized as one of the most devastating epidemic, has affected people all over the world. According to a recent report [2], by the end of 2009 the number of people living with HIV reached 33.3 million and 1.8 million deaths were linked to AIDS [2]. HIV destroys CD4+ T cell lymphocytes of the human immune system of the person infected with the virus, causing the immune system to weaken or become immune deficient. As has now become well known, HIV infection typically follows a three phase pattern, that is, the primary response phase (acute phase), the clinical latency phase (chronic phase), and the final phase of onset of AIDS. Although there is no cure for AIDS so far, a variety of drugs can be used to slow the progress of the disease by decreasing the rate of viral growth or replication or the recovery of CD4+ T cell lymphocytes. Antiretroviral drugs are the main alternative treatment for HIV infection and AIDS. Highly Active Antiretroviral Therapy (HAART) is a combination of three or more antiretroviral drugs, which is, during treatment, effective in controlling the viral loads of HIV in the patient's body at a low level and improving the immune system [3], [4]. However, on interrupting HAART there is a rebound of plasma viral loads [5] so that the use of this treatment has been linked to metabolic side effects in humans [6]. There are evidence that such patients may be at increased risk for opportunistic infections [7]. Thus, in order to avoid the problems with drug treatment, an alternative treatment is needed.

Aphaeresis has for some time been used effectively in the treatment of hepatitis C infection [8]-[10], cancer [11] and HIV infection [12]. Plasma aphaeresis is a process in which the virus in the large molecular components of plasma are removed from a patient while the small molecular components of plasma and cell components of blood are returned to the patient. Several studies suggest that plasma aphaeresis may offer a good alternative for the treatment of AIDS patients with peripheral polyneuropathy [13]–[15]. A study by Ramratnam et al. [12] showed that plasma aphaeresis can

S. Moonchai is with the Department of Mathematics, Faculty of Science, Chiengmai University, Chiengmai, and the Centre of Excellence in Mathematics, THAILAND (e-mail: tumath@gmail.com).

Y. Lenbury is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok, and the Centre of Excellence in Mathematics, Thailand (corresponding author, phone: 662-201-5448; fax: 662-201-5343; e-mail: scylb@yahoo.com).

reduce the viral load to half of the original load in the blood. However, plasma virus rebounds at baseline load after the end of aphaeresis [12]. Since the viral population circulates between the lymph node and plasma compartments, the viral load influences the dynamics of HIV infection. Therefore, in order to use the plasma aphaeresis treatment, it is essential to study the effect of this technique on the dynamics of viral load in both the lymph node and blood compartments as well as the development of the virus-immune response in the human body.

Many researchers have used mathematical models to describe the population dynamics of cells involved in the immune response system relevant to HIV proliferation [16-22]. Most models are based on systems of ordinary differential equations (ODES) and partial differential equations (PDES) [21], [24]-[26]. However, since the development of the disease typically exhibits three phases of infection, these models are insufficient to describe the three different time scales and hard to construct to simulate the entire course of the HIV infection.

Recently, cellular automata (CA) models have become useful in modelling HIV infection in the lymph node [27]-[29]. Although these CA models have been capable of simulating the three phase pattern of HIV dynamics observed clinically, most of these CA models only incorporated the lymph node compartment into the simulation. However, most clinical studies follow the disease progression based on blood data. Since viral population circulates between the lymph node and plasma compartments, viral load in both compartments are vital for the accurate diagnostic description of the dynamics of HIV progression. For this reason, Moonchai and Lenbury [1,] [30] have proposed a double latticed CA simulation model to investigate the dynamics of HIV infection in both the lymph node and blood compartments.

In this paper, we modify the CA rules based on the CA model of Moonchai and Lenbury [1] in order to investigate the effect, on the CD4+ T cell count and viral load in both the lymph node and blood compartments, of different clearance rates in plasma aphaeresis treatment, by incorporating its application in the viral load model in blood compartment. Extending the work presented in [31], apart from discovering the effect of different treatment protocols on the outcome of the plasma aphaeresis therapy, we also simulate the case where the treatment is abandoned after a sufficiently long period of treatment.

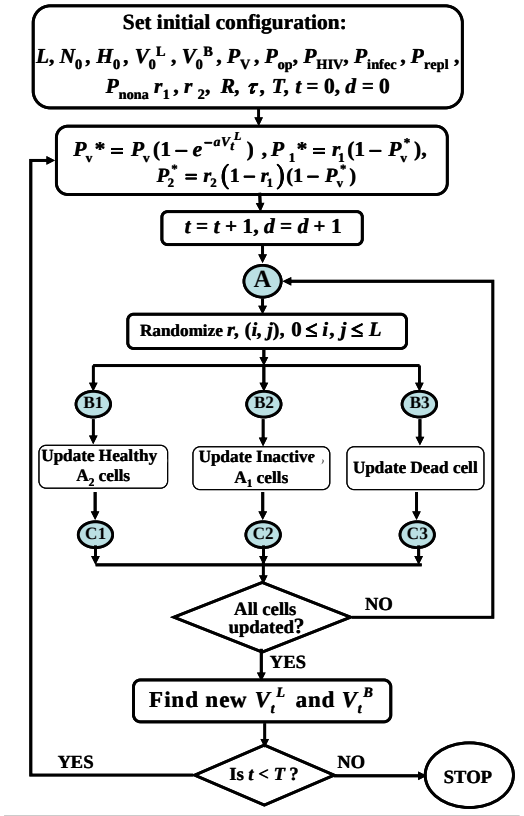
II. CA Model of HIV Infection

As detailed in [32], cellular automata (CA) models are discrete mathematical models in which space is divided into regular spatial cells, and time progresses in discrete steps. Each cell has one of a finite number of states. The state of each cell is updated according to given local rules, that is, the state of a cell at a given time depends on its own state and the states of its neighbours at the previous time step [31].

In this work, based on the CA model of Moonchai and Lenbury [1], we construct a CA model of HIV infection in the lymph node and the peripheral blood compartments or lattices under plasma aphaeresis therapy.

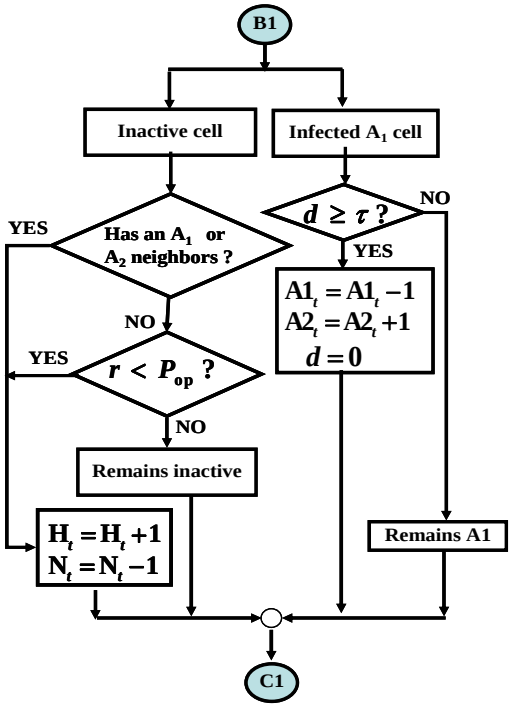
Model simulations have been performed in MATLAB, and averaged over 15 runs for each configuration. In each compartment, the CA model is defined on a square lattice of size $L \times L$, assuming the Moore's neighborhood using a neighborhood of range 1. The states of the cells in each of the lattices are updated at each time step in parallel according to given rules, each time step corresponding to one week.

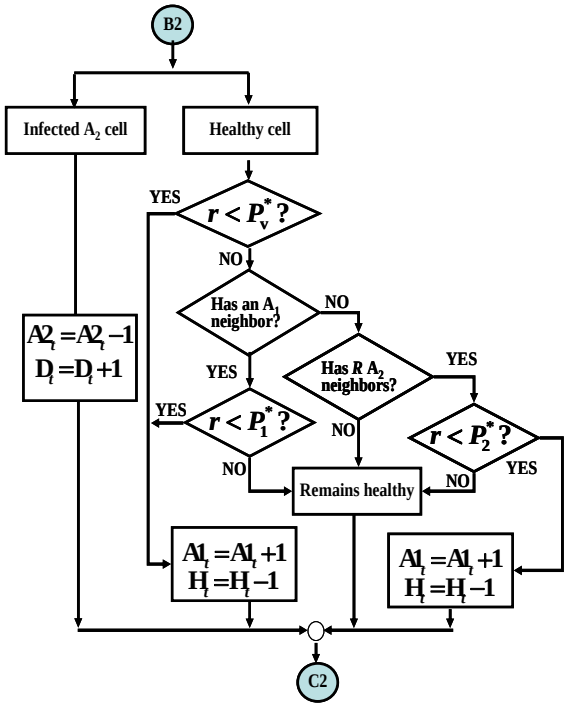
Each site on the lattice is occupied by a cell which is assigned one of the five states that describe the possible states in which those cells may be found: non-activated cells, active healthy cells (representing $CD4^+$ T cells which are the main target of the HIV), infected A_1 cells (being infected cells that are free to spread the infection), infected A_2 cells (corresponding to infected cells in the final stage of infection before dying due to the action of the immune response) or dead cells. The simulation steps start with N_0 non-activated cells, H_0 healthy active cells, and a small fraction P_{HIV} of infected A_1 cells (A_{10}), such that $A_{10} = P_{\mathrm{HIV}} \cdot H_0$, distributed randomly.



$\mathbf{N}_t$ - number of inactive cells at time t
$\mathbf{H}_t$ - number of healthy cells at time t
$\mathbf{A1}_t$ - number of infected A_1 cells at time t
$\mathbf{A2}_t$ - number of infected A_2 cells at time t
$\mathbf{D}_t$ - number of dead cells at time t

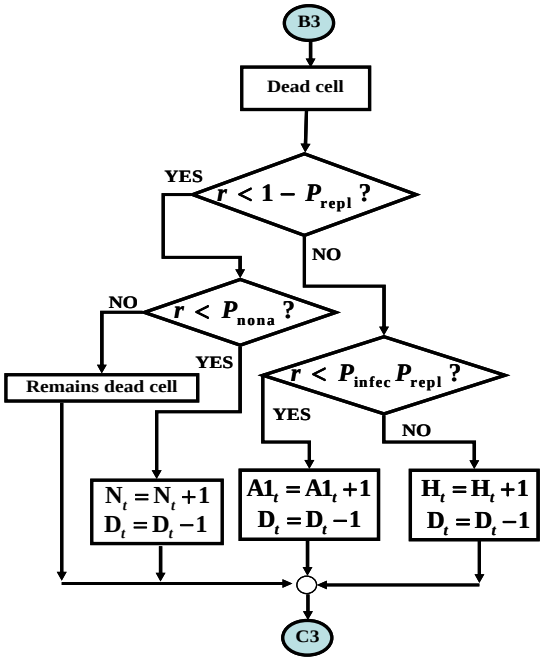
Flowchart 1. The algorithm to update all cells in each compartment (continued in Flowchart 2.).





$\mathbf{N}_t$	- number of inactive cells at time t
$\mathbf{H}_t$	- number of healthy cells at time t
$\mathbf{A1}_t$	- number of infected A_1 cells at time t
$\mathbf{A2}_t$	- number of infected A_2 cells at time t
$\mathbf{D}_t$	- number of dead cells at time t

Flowchart 2. The detail in the algorithm to update all cells in each compartment (continued from Flowchart 1).



Flowchart 3. The detail in the algorithm to update all cells in each compartment (continued from Flowchart 2).

Table 1. Model parameters in the CA model in the lymph node.

Symbol	Definition	Value [reference]
L	Lattice size	500
N_0	Number of nonactivated or nonproliferating 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 [26]
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	0.00045 (estimated)
a	Constant in P_v *	1×10^{-16}
r_1	Constant in P_1 *	0.997 (estimated)
r_2	Constant in P_2 *	0.997 (estimated)
τ	Time delay for an infected A_1 cell to become an infected A_1 cell	4 [26]
P_{infec}	Probability for a healthy cell to be replaced with an infected A_1 cell	1×10^{-5} [26]
P_{repl}	Probability for a death cell to be replaced with a healthy cell	0.99 [26]
P_{nona}	Probability for a death cell to be replaced with nonactivated 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 [26]

Table 2. Model parameters in the CA model in the blood compartments.

Symbol	Definition	Value [reference]
L	Lattice size	100
N_0	Number of nonactivated or nonproliferating cells at $t = 0$	10,000
H_0	Number of healthy active cells at $t = 0$	4,000
P_{HIV}	Probability or percentage of initial infected cells	0.05 [26]
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	0.0025 (estimated)
a	Constant in P_v*	1×10^{-8}
r_1	Constant in P_1*	0.997 (estimated)
r_2	Constant in P_2*	0.997 (estimated)
τ	Time delay for an infected A_1 cell to become an infected A_1 cell	4 [26]
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 [26]
P_{nona}	Probability for a death cell to be replaced with nonactivated 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 [26]

At each time step, all cells are updated using the rules given in [1] and [30]. That is, each of the cells is updated according the rules which are described in Flowcharts 1-3. The same rules are applied to update the cells in both the lymph node lattice and the peripheral blood lattice.

The parameter values appearing in the flowcharts used in our simulations are given in Tables 1-2.

III. Model for Viral Load

In our CA model, the dynamics of the healthy and infected cells are influenced by the viral load through the probability P_{V}^{*}. We calculate the viral load in the lymph node compartment (V_t^L) and peripheral blood compartment (V_t^B) at time t by using the following difference equations.

In the lymph node compartment

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

where

I_t^L = virus-producing infected cells

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

In the blood compartment

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

$$V_{t+\Delta t}^{B} - V_t^{B} = pS_B I_t^{B} + (\tilde{V}_B - V_t^{B}) - c_{BH} H_t^{B} V_t^{B} - cV_t^{B} + F(t) \qquad (2)$$

where

$$F(t) = \begin{cases} -\varepsilon\ V_t^B, & t = T_0 + k\Delta T, k = 0,1,2,\ldots \\ 0, & \text{otherwise} \end{cases} \qquad (3)$$

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)

ΔT = duration of a break between treatments

Table 3. Definition and values of model parameters in the viral load simulation.

Symbol	Definition	Value [reference]
V_0^B	Plasma virus concentration at $t = 0$	10 [21] (can vary)
V_0^L	Virus concentration in the lymph node at $t = 0$	0
p	Average virion production rate per infected cell	480 [22]
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 [22]
e	Circulation fraction of virus between lymph node and blood	0.02 [23]
β	Scaling factor: lymph node→ blood	2×10^{-7} [21]
α	Scaling factor: lymph node→ blood	5×10^{6} [21]
ε	Clearance rate of free virus due to plasma pheresis.	0.5-0.7
T_0	Time at start of treatment	402, 282
ΔT	Duration of breaks from treatment	4

In Eq. (1)–(3), 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. H_t^L and H_t^B are the numbers of healthy cells in the respective compartments at time t, p is the average virion production rate per infected cell, e represents the circulation of virus between the two compartments, c is the death rate of free virus, and ε is the rate of free virus clearance due to the removal by plasma aphaeresis treatment.

IV. Result and Discussion

The values of the parameters appearing in (1)-(3) used in our viral load simulations are given in Table 3. Some of the values in these tables are the same as those used in [29]-[30], but some have been adjusted for more realistic simulation outcomes. The model has been simulated at different rates of free virus clearance ε due to plasma aphaeresis treatment. Averages over 15 simulations have been obtained using the parametric values in Tables 1 and 2. When ε is set to zero, the model then in fact simulates the no treatment case.

First, we simulate treatment which starts at two different stages of the disease, one of which starts at week 402 (the final phase of the disease progression), the other at week 282 (the end point of the clinical latency phase). The plasma aphaeresis therapy is simulated by varying the value of the clearance rate ε and performed at a frequency of every 4 weeks. The plots seen in Fig.1 show the dynamics of healthy cells, infected A_1 cells, infected A_2 cells, and dead cells in the lymph node and blood compartments under the no treatment condition. All these graphs exhibit three phases of the disease progression.

Fig. 2-3 show the effect of the plasma aphaeresis treatment on healthy cells and viral load, respectively, in the lymph node and blood compartments. In Fig. 2-3, the treatment is started at $T_0 = 402$. In the peripheral blood, it can be observed that the level of healthy cells becomes higher than the no treatment level for a short duration after the treatment has been preformed, while the viral load becomes lower during treatment. During the 4 week breaks from treatment rebounds in the viral load to levels higher than the no treatment levels are evident, which may lead to serious complications. There is the risk that the treated patient could be more vulnerable to opportunistic infection during these times than an untreated patient. Although the healthy cells curve is observed to become higher than the no treatment curve, the difference is in the order of 10^3 cells which is not, in our opinion, very significant.

In Fig. 4-5, on the other hand, where the treatment is initiated much earlier in the course of infection, $T_0 = 282$, the viral load does not appear to rebound to levels higher than the no treatment level, at least if the treatment is kept up long enough. The simulated curves of treated patients all drop below that of the untreated patient during the treatment, and remain at the lower levels even during the 4 week breaks after the treatment has been kept up for a while. Although the level of healthy cells in the peripheral blood compartment is higher during treatment, the difference is again in the order of 10^3 cells. From this simulation results, we may be able to deduce that the plasma aphaeresis treatment could be more beneficial to the patient if it is initiated at an earlier stage in the progression of HIV infection.

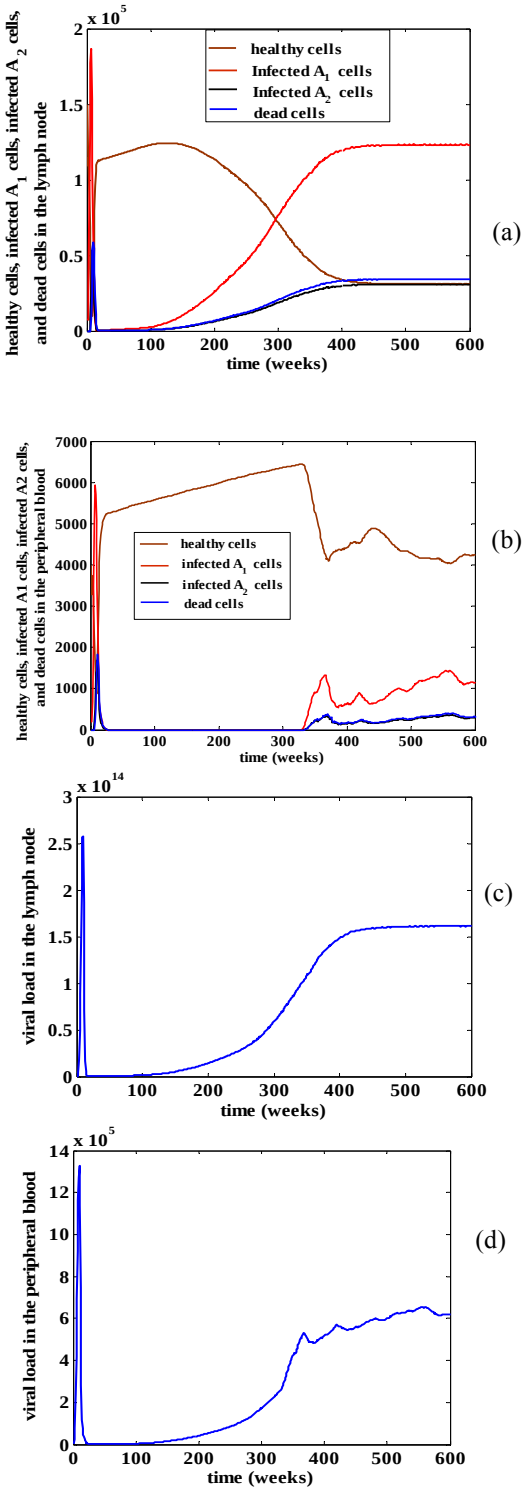


Fig 1. Simulated dynamics, under the no treatment condition, of (a) healthy cells, infected A_1 cells, infected A_2 cells, and dead cells in the lymph node, and (b) in the blood compartments (c) viral load in the lymph node compartment, and (d) in the peripheral blood compartment.

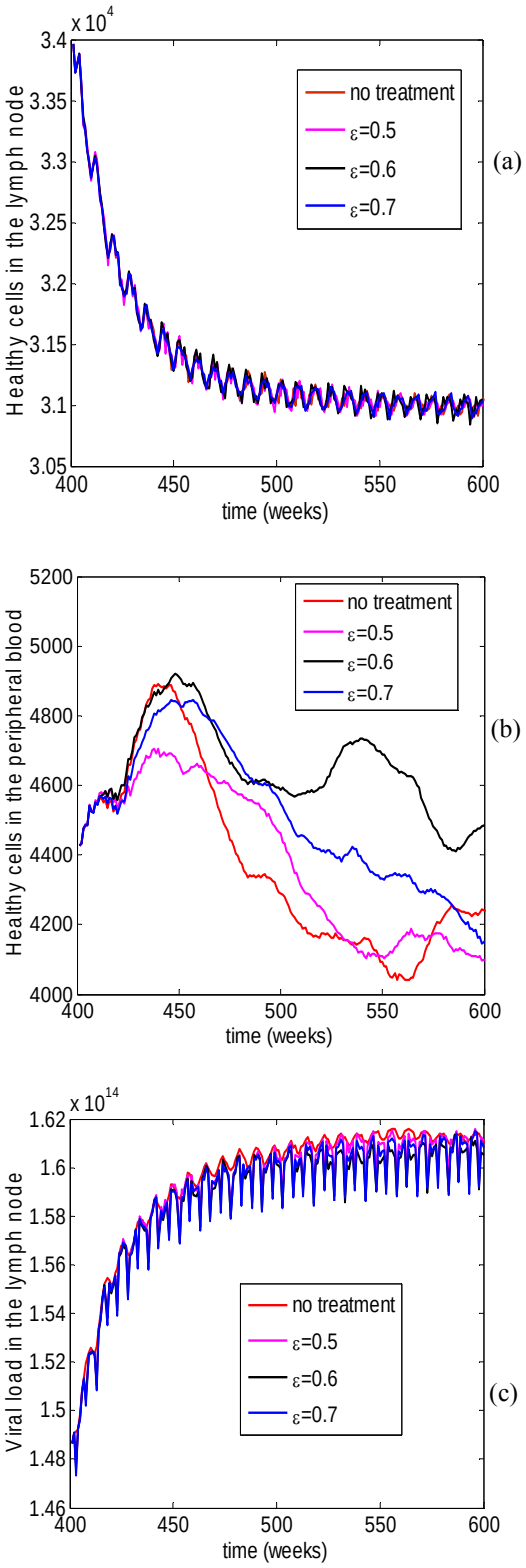


Fig. 2. Simulation of the HIV infection, under plasma aphaeresis treatment started at week 402, showing levels of (a) healthy cells in lymph node, (b) healthy cells in the peripheral blood (c) viral load in the lymph node (plots previously shown in Proceedings paper by Moonchai and Lenbury [31].)

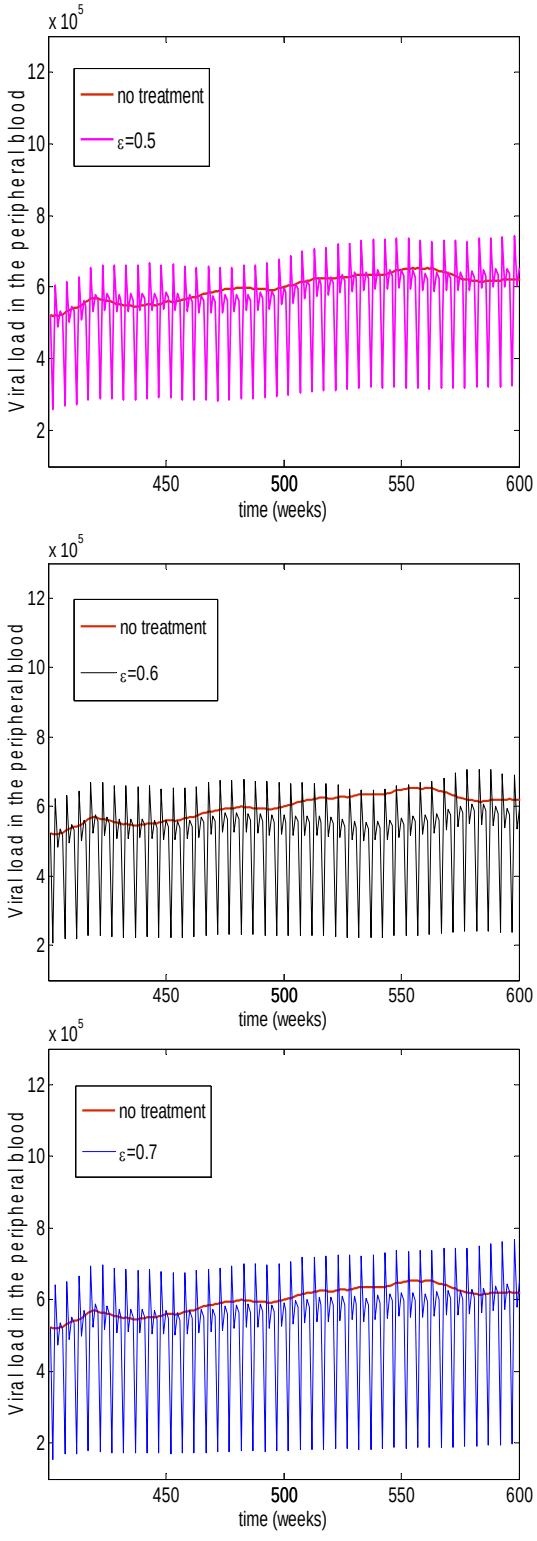
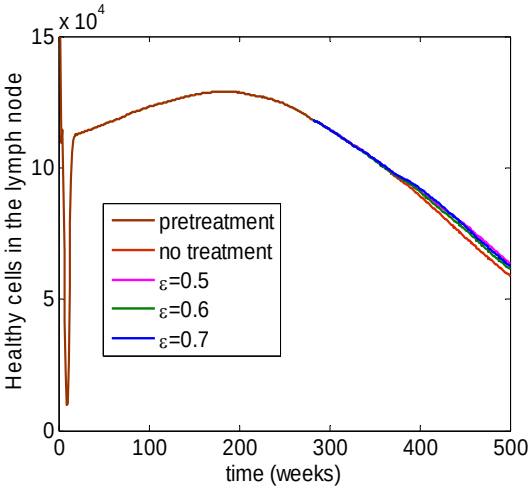
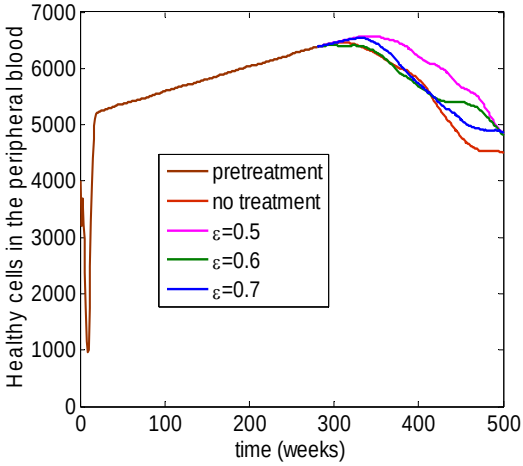


Fig. 3. Simulation of the HIV infection, under plasma aphaeresis treatment started at week 402, showing level of viral load in the peripheral blood for different values of ε (plots previously shown in Proceedings paper by Moonchai and Lenbury [31].)





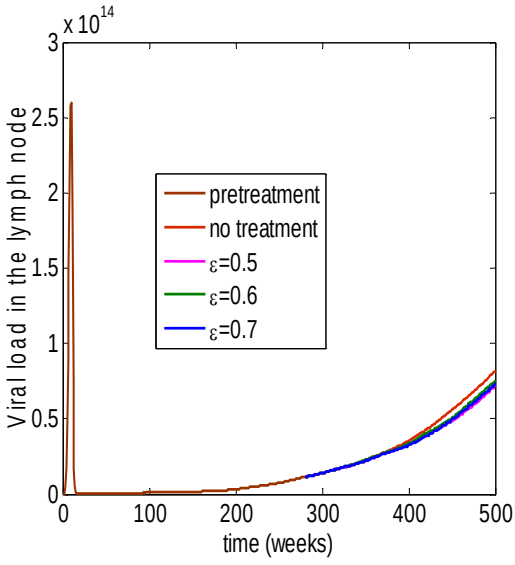
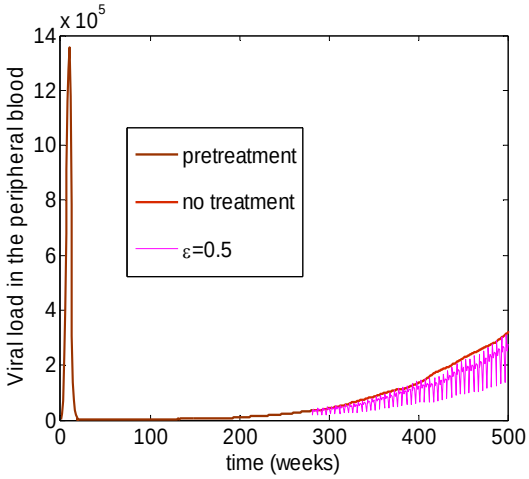
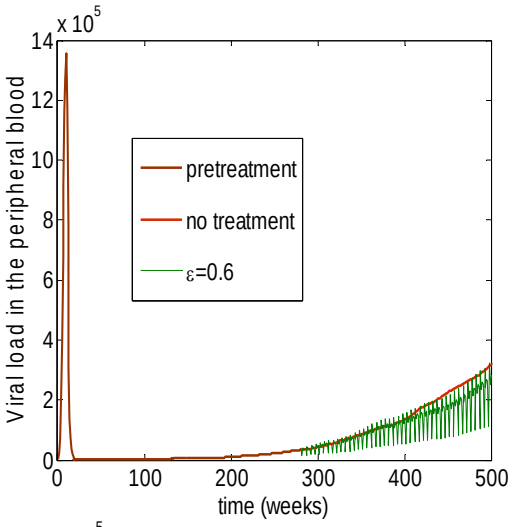


Fig. 4. Simulation of the HIV infection, under plasma aphaeresis treatment started at week 282, showing levels of (a) healthy cells in lymph node, (b) healthy cells in the peripheral blood (c) viral load in the lymph node (plots previously shown in Proceedings paper by Moonchai and Lenbury [31].)





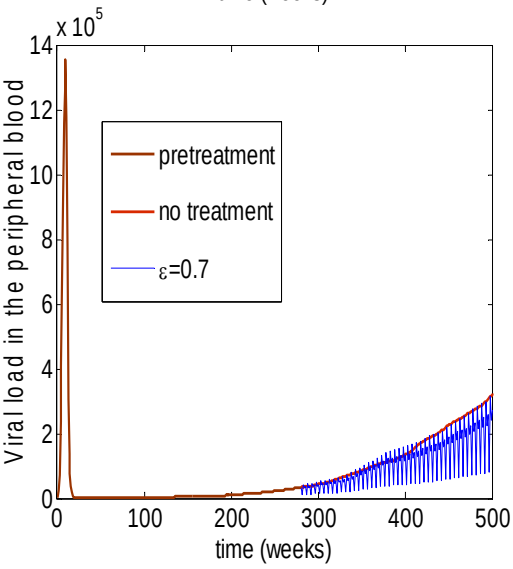


Fig. 5. Simulation of the HIV infection, under plasma aphaeresis treatment started at week 282, showing level of viral load in the peripheral blood for different values of ε (plots previously shown in Proceedings paper by Moonchai and Lenbury [31].)

Fig. 6-7 show the evolution of HIV infection for different values of ε in which treatment is abandoned after week 452. The result indicates that viral load rebounds to values no different from the no treatment case after treatment ceases. The simulated dynamics of healthy cells in the peripheral blood, seen in Fig. 6 b), exhibits interesting development after treatment cessation. For a certain period after the treatment has been abandoned, healthy cells in treated patients seem to maintain a higher level in the blood compartment than that of the untreated patient (the red curve). This may be taken to reflect in favour of the treatment by plasma aphaeresis under our investigation.

However, this favourable condition appears, at least in this particular simulation result shown here, to last for only a relatively short period after the treatment has been abandoned. In fact, the black curve corresponding to the higher clearance rate $\varepsilon = 0.6$ is observed to drop to a dangerously low level which could mean a critical situation for the patient. We observe in our simulation results, some of which are shown above, that under treatment the developments of the healthy cells in the lymph node and the blood compartments do not follow similar patterns. The level of healthy cells stays continuously high in the lymph node compartment, which would lead us to conclude that the monthly treatment can keep the patient in a better condition even during the breaks from treatments. However, if the blood compartment is also taken into consideration, such conclusion cannot be made, since the level of healthy cells fluctuates more significantly here. This illustrates the advantage of using a double compartment instead of a single compartment CA simulation model.

Moreover, we have investigated what will happen if the treatment is abandoned after a period of time has passed. This is in fact what happens in real practices where a number of patients do no maintain rigorous treatment schedule, for reasons of financial problems, or inconvenience. Some patients break away from treatment for lengthy periods, instead of keeping up with the regular schedule of treatment at once every month. Some drop out of the program and become untraceable. To expect all patients to subject themselves at a strictly regular treatment schedule is not always plausible.

Our simulation shown in Fig. 6-7 illustrates a possible outcome of abandoning treatment for a lengthy period which could possibly have ominous outcome. This may be attributed to the fact that plasma aphaeresis for a short period leads to a fast drop in the viral load in the peripheral blood. The natural compensation mechanism would lead to a fast transfer of viral load from the lymph node compartment to the blood compartment to compensate for the recognized drop in its level. Such fast transfer is what leads to the rebound of the viral load which can overshoot the normal level of the no treatment case. If this happens when the healthy cell levels are already low and the viral load is already dangerously high, it could lead to a complete failure in the immune system and development to symptoms of full blown AIDS.

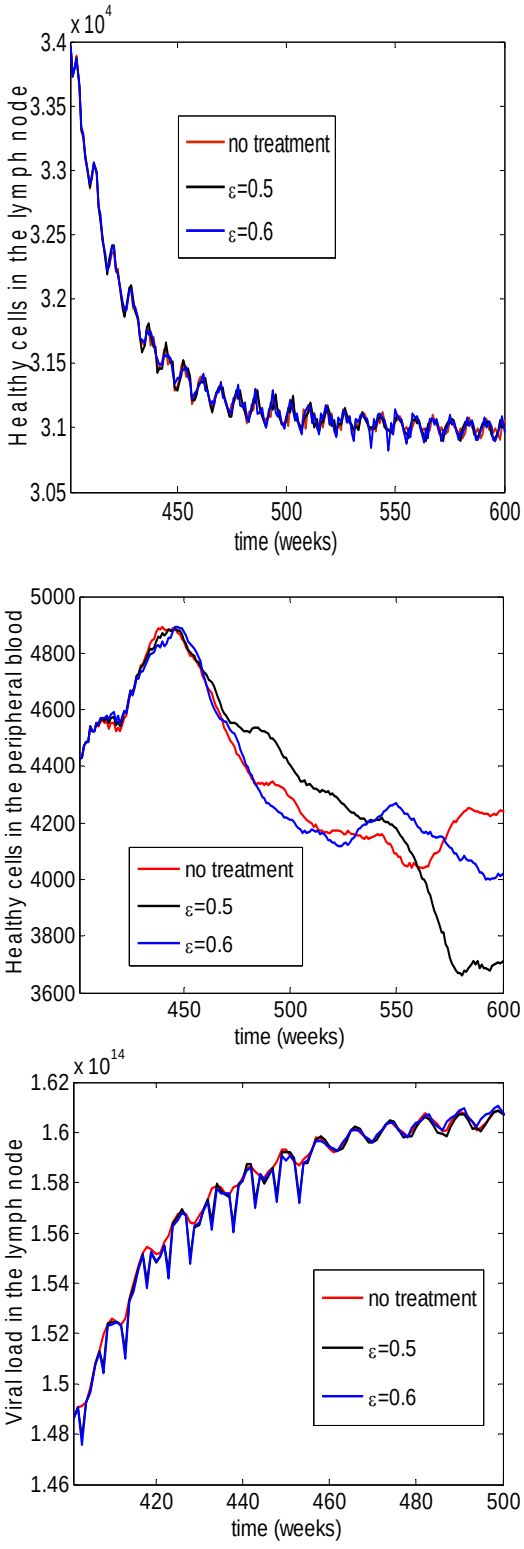


Fig. 6. Simulated evolution under the plasmapheresis treatment started at week 402 for different values of ε. The treatment is interrupted at week 452. (a), (b) Plots of the numbers of healthy cells in the lymph node and blood compartments, respectively, (c) viral load in the lymph node compartment.

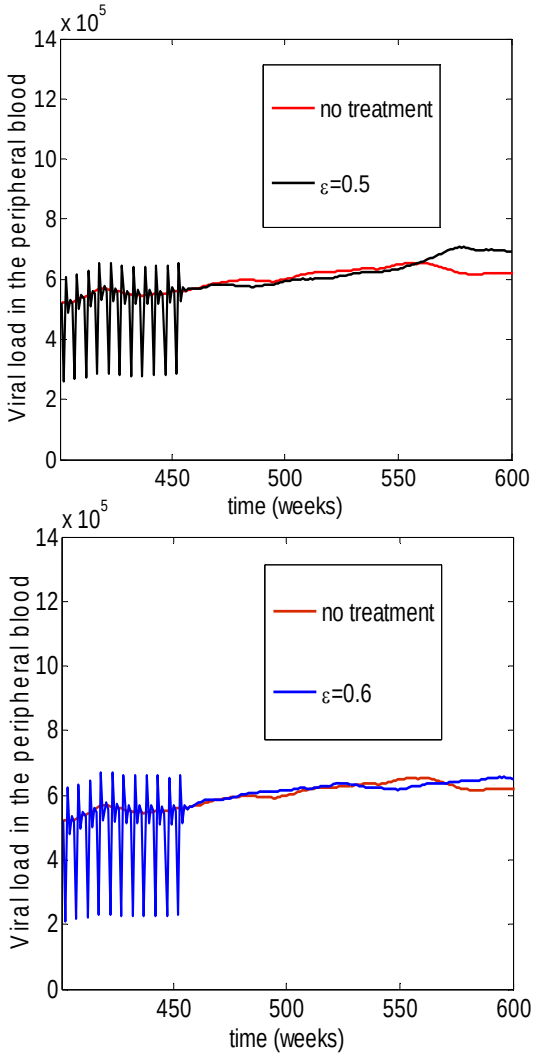


Fig. 7. Simulated evolution of viral load in the blood compartment under the plasma aphaeresis treatment started at week 402 for different values of ε . The treatment is interrupted at week 452.

Again, we emphasize the advantage of having simulation results in both the lymph node and the blood compartments in comparison, since without the evidence of evolution of the healthy cells and viral load in the blood compartment, the artefacts we have been able to observe in our arguments above would not have been clearly identified.

In light of our simulations presented here, the outcome of the treatment with plasma aphaeresis, although appearing promising if the treatment could be instituted on a patient at an early enough stage of infection, is still doubtful especially in the long run, or if the treatment is not maintained in a continual fashion. Impacts of the frequency and the duration of treatment or the breaks from treatments still need to be investigated further. These factors can potentially affect significantly the outcomes of such treatment. Moreover, for the same reason, it cannot be concluded with certainty that plasma aphaeresis therapy offers a better treatment for HIV patients than HAART since the same rebounding of viral load is observed in both treatments.

The impacts of different clearance rates can only be observed clearly in Fig. 5, where a higher clearance rate leads to lower viral load during treatments and does not rebound back to as high a level. However, the difference in its impact cannot be as clearly seen in the simulated curves of the healthy cells in the lymph node or the blood.

V. Conclusion

We have utilized the technique of cellular automata simulation with double lattice to simulate the impacts of plasma aphaeresis treatment on patients infected with HIV. Effects of various clearance rates on the treatment outcome have been investigated. The treatment started earlier stages of infection appears to yield better result on the treated patients compared to the untreated case. Moreover, treatment interruptions are observed to possibly be potentially harmful to the patient once they have gone through a period of treatments.

To be further investigated is the benefit of combining plasma aphaeresis and HAART, a possible therapy which might overcome some of the reservations we have in the case where the two treatment methods are performed separately.

Although this investigation has yielded several valuable insights, the results are still not definitely conclusive. Due to the probabilistic nature of the infectious process, the disease progression is highly non-deterministic. More simulations are needed and further in depth investigation with careful analyses of the simulation results is necessary. It is clear, however, that the technique of CA modeling and simulation offers a promising tool for the investigation of such complicated process involving multiple probabilistic events.

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