Cellular Automata Model of Drug Therapy for HIV Infection

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Abstract. In this study, we employ non-uniform Cellular Automata (CA) to simulate drug treatment of HIV infection, where each computational domain may contain different CA rules, in contrast to normal uniform CA models. Ordinary (or partial) differential equation models are insufficient to describe the two extreme time scales involved in HIV infection (days and decades), as well as the implicit spatial heterogeneity [4,3, 10]. R.M.Zorzenon dos Santose [13] (2001) reported a cellular automata approach to simulate three-phase patterns of human immunodeficiency virus (HIV) infection consisting of primary response, clinical latency and onset of acquired immunodeficiency syndrome (AIDS), Here we report a related model. We developed a non-uniform CA model to study the dynamics of drug therapy of HIV infection, which simulates four- phases (acute, chronic, drug treatment responds and onset of AIDS). Our results indicate that both simulations (with and without treatments) evolve to the relatively same steady state (characteristic of Wolfram's class II behaviour). Three different drug therapies (mono-therapy, combined drug therapy and highly active antiretroviral therapy HAART) can also be simulated in our model. Our model for prediction of the temporal behaviour of the immune system to drug therapy qualitatively corresponds to clinical data.

1 Introduction

1.1 Biological Background of HIV Infection

The infection of human immunodeficiency virus (HIV), causing AIDS (acquired immunodeficiency syndrome), is almost invariably a progressive, lethal disease with insidious time course. Currently, clinicians identified two common laboratory markers for detection of disease progression (the amount of virus (HIV-RNA) and the number of T helper cells (CD4 T cells) in blood. Immune response for typical virus infection varies from days to weeks, but HIV infection typically follows a three-phase pattern (See also Fig. 1).

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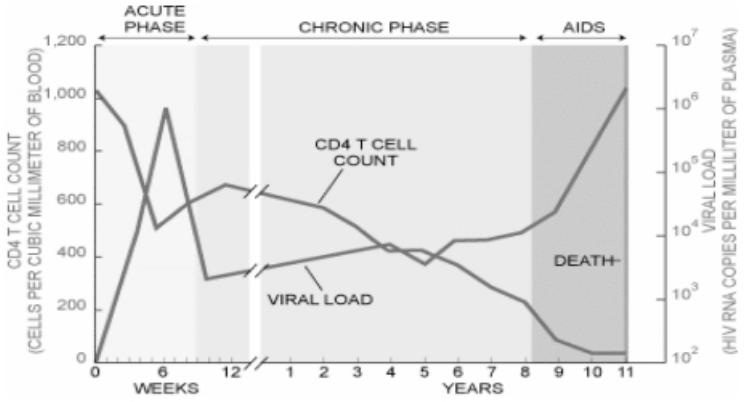

Fig. 1. Common pattern of HIV infection in a typical untreated patient indicates a three-phase evolution. The two lines represent CD4 T cell count and viral load respectively. (Image: Bryan Christie, July 1998 Scientific American)

- During a few weeks (varying from two to six weeks), a transient and dramatic jump of plasma virion level is present with a marked decrease of immune cell count (CD4 T helper cells), following by a sharp decline.
- In the subsequent chronic phase (varying from one to ten or more years, on average eight to ten years), the immune system partially eliminates the HIV virus and the rate of viral production reaches a lower, but relatively steady, state that varies greatly from patient to patient. Their apparent good health continues because CD4 T cell levels remain high enough to preserve defensive responses to other pathogens. But over time, CD4 T cell concentrations gradually fall.
- An outbreak of the virus (varying from one to two years), together with constitutional symptoms and onslaught by opportunistic diseases, cause death [2].

1.2 Biological Background of Drug Therapy of HIV Infection

A vaccine would certainly be ideal for preventing infection by HIV and thus for avoiding AIDS when immunity is severely impaired. The near-term prospects for a vaccine are poor due to error occurrence during each transcription of HIV. Therefore, for the immediate future, many scientists are concentrating on improving the therapy.

- Currently, there are fifteen drugs licensed for treatment of individuals infected with HIV. These drugs belong to two classes, one inhibiting the viral enzyme reverse transcriptase and the other inhibiting the viral protease. These drugs are used in combination therapy to maximally inhibit viral replication and decrease HIV-RNA to below levels of detection levels (currently

defined as below 50 copies per ml) in blood. In one class, the nucleoside analogues resemble the natural substances that become building blocks of HIV-DNA; and when reverse transcriptase tries to add the drugs to a developing strand of HIV-DNA, the drugs prevent completion of the strand. The other agent in this class, non-nucleoside reverse transcriptase inhibitors, composed of other kinds of substances, constitute the second class of anti-retrovirals. The other class, the protease inhibitors, blocks the active, catalytic site of the HIV protease, thereby preventing it from cleaving newly made HIV proteins.

- HIV therapy is classified into three classes: mono-therapy, combined therapy and triple therapy. Mono-therapy (such as based on reverse transcriptase inhibitor) or combined drug therapy (reverse transcriptase and protease inhibitors) are considered to suppress the viral multiplication. Because of incompletely blocking the replication pathway and occasionally creation of a resistant virus strain, the CD4 T counts will come back to the pre-treatment baseline within many weeks (Fig. 2). The problem of drug resistance in the treatment has become an increasing significant barrier in the effectiveness of AIDS immune-therapy.
- Currently, there is no single class of drug that can completely prevent HIV from replicating. Treatment with drug combinations is in only 50% of the cases successful in inhibiting viral replication to undetectable levels. In the remaining 50% of cases viruses can be detected with a reduced sensitivity to one or more drugs from the patients regimen. Theory and clinical trials indicate that the best way to achieve maximum viral suppression is through highly active anti-retroviral therapy (HAART), which consists of triple therapy including two nucleoside analogues and a protease inhibitor.

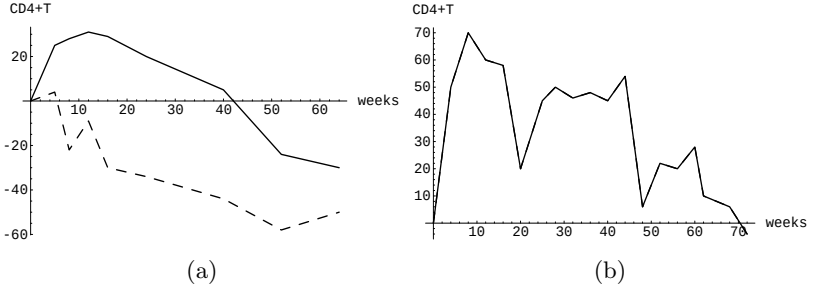

Fig. 2. Clinical data for mono-therapy (CD4 + T count is compared with baseline): (a) This study administered patients either with a placebo control (hash line) or AZT (solid line) for 62 weeks. The treatment started when CD4 T counts were between 200 and 500/ml [1]. (b) The results indicated that the effects of mono-therapy AZT on non-progressors can not be sustained above base line for more than 70 weeks [9].

1.3 Uniform and Non-uniform CA

Cellular automata (CA) provide us with a means to model complex dynamical phenomena by reformulating the macroscopic behaviour into microscopic and mesoscopic rules that are discrete in space and time. The states of the discrete elements (cells) organised in a regular grid, are updated synchronously according to a uniform local interaction rule [8]. Uniform CAs have three notable features: massive parallelism, locality of cellular interactions and simplicity of cells (finite state machines). Non-uniform CAs have first been investigated by Vichniac [11] who discussed a one-dimension CA in which a cell probabilistically selects one of two rules, at each time step. In this study, we use non-uniform CAs to explore the huge space of this complex system. The three essential CA features are preserved in this non-uniform model.

1.4 Computational Task and Related Work

Modelling the population dynamics of cells in immune response relevant to HIV has recently attracted a considerable interest [2,3,5,6,7,12]. Currently, the only two ways to model this dynamics of the immune response with respect to the pathology and therapy of HIV infection are analytic PDE and ODE models and cellular automata models. Analytical approaches are successful to describe different aspects of HIV infection dynamics [4,3,6]. But they have strong limitations to describe the two time scales observed in the time course of infection in term of weeks and years and have serious difficulties in exploiting spatial information. Cellular automata are recently regarded as a good strategy to model this spatial-temporal dynamics with emphasis on local interactions. Mielke et al., developed a fuzzy interaction model for mutating HIV with a fuzzy set of 10 interactions for macrophages, helper cells, cytotoxic cells and virion [5]. Hershberg et al., (2001) indicated, using a microscopic simulation, that the time course of AIDS is determined by the interactions of the virus and the immune cells in the shape space of antigens, and that it is the virus's ability to move more rapidly in this space (its high mutability) which cause the time course and eventual "victory" of the disease [2]. This model clearly showed the three stages of the disease. A simple set of CA rules was used to model the evolution of HIV infection by Zorenon dos Santos et al. (2001). The three phase patterns were also presented and the results indicated that the infected cells organise themselves into spatial structures, which are responsible for the decrease in the concentration of uninfected cells, leading to AIDS [13]. This CA model inspires the drug therapy simulation presented here. In this model we can investigate the HIV infection dynamics with therapy using microscopic simulations. The main ingredients in our model are destruction of previously emerged spatial patterns (wave-like and solid-like structures) and reconstruction of new spatial patterns (wave-like structures) due to incorporation of the drug therapy concept. In the sequel we will refer to the Zorenon dos Santos's model as the HIV Infection Model (HI model) and our model as the Drug Therapy of HIV Infection Model (DTHI model).

2 The Computational Model

Here we illustrate the basic concepts of DTHI. The first subsection introduces shortly the context of the problem, including the models of ODE/ PDE. The second section presents the CA rules and corresponding description for mimicked biological concepts in the HI model as well as the correctness for one of rules. The third section defines our DTHI model.

2.1 The Problem of Modelling Drug Therapy

With continuous progress of medical and biological research, three kinds of therapy have been gradually developed. The long-term survival with combined drug therapy is considered to be longer than with mono-therapy. The appearance of resistance virus against HAART is apparently much longer than with combined drug therapy. Up to now, the extension of long-term survival with HAART is not yet known. Mathematical ODE/PDE models have difficulties to simulate the four phases (acute, chronic, drug treatment responds and AIDS) in one model but have also difficulties to unify three therapies into one model. Because these models could not describe two kinds of time scales (weeks in primary response and years in the clinical latency and AIDS) which might be related to two kinds of interactions: one local and fast, and the other long-ranged and slow [13].

2.2 The HI Model

Here we first review the rules and biological descriptions of HIV infection model (HI) with Moore neighbourhood and periodic boundary from reference [13].

[Rule 1] Update of a healthy cell.
(a) If it has at least one infected-A1 neighbour, it becomes an infected-A1 cell.
- The spread of the HIV infection by contact before the immune system had developed its specific response against the virus.

(b) If it has no infected-A1 neighbour but does have at least R $(2 < R < 8)$ infected-A2 neighbours, it becomes infected-A1.
- Before dying, infected-A2 cells may contaminate a healthy cell if their concentration is above some threshold.

(c) Otherwise it stays healthy.

[Rule 2] An infected-A1 cell becomes an infected-A2 cell after τ time steps.
- An infected cell is the one against which the immune response has developed a response hence its ability to spread the infection is reduced. The τ represents the time required for the immune systems to develop a specific response to kill an infected cell. A time delay is requested for each cell because each new infected cell carry a different lineage (strain) of the virus. This is the way to incorporate the mutation rate of the virus in this model. On the average, one mutation is produced in one generation due to the error occurrence during HIV transcription. Assume that mutation in each trial is varied in this model due to the stochastic characteristics.

[Rule 3] Infected-A2 cells become dead cells.
- The depletion of the infected cells by the immune response.

[Rule 4]
(a) Dead cells can be replaced by healthy cells with probability p_{repl} in the next step ($p_{repl} = 99\%$) or remain dead with probability 1 - p_{repl}.
- The replenishment of the depleted cells mimics the high ability of the immune system to recover from the immuno-suppression generated by infection. As a consequence, it will also mimic some diffusion of the cells in the tissue.

(b) Each new healthy cell introduced, may be replaced by an infected-A1 cell with probability p_{infec} ($p_{infec} = 10^{-5}$).
- The introduction of new infected cells in the system, either coming from other compartments of the immune system or from the activation of the latent infected cells.

2.3 The DTHI Model

Based on the model summarized above, we incorporate the drug therapy process into the CA model for drug therapy. All approved anti-HIV, or anti-retroviral, drugs attempt to block viral replication within cells by inhibiting either reverse transcriptase or the HIV protease. In addition to the 'delayed' infection modelled in Rule 1b and the latent infection in Rule 4b, the main source of HIV infection in the HI model is Rule 1a. We limit the range of HIV infection (infected A1 cells) by giving a rank level N ($0 \leq N \leq 7$). This mimics the principle that the drug prevents the virus from replication, resulting in less efficient infection. N represents the effectiveness of each drug. The bigger N, the less efficient the drug. Different drug therapies are modelled by different response functions P_{resp} over the time. P_{resp} represents the response function for each drug therapy, which have effects on the infected A1 cells after the starting of a drug therapy. This models the fact that the drug therapy will not immediately influence all of infected A1, but rather it will affect part of them at each time step. Over time these effects of drug therapy can (and will) decay. At the same time, this also mimics the concept of drug resistant virus strains.

[Modified Rule 1 (a)] Update of a healthy cell:
If there is one A1 neighbour during the time of drug therapy, N ($0 \leq N \leq 7$) neighbour healthy cells become infected-A1 in the next time steps with probability p_{resp}. Otherwise, all of eight neighbours become infected-A1 cells. N is related to effectiveness of each drug. Non-uniform CA rules is used when the therapy starts. At the time step t_c during the therapy, $p_{resp}(t_c)$ infected-A1 cells have rank N and $1 - p_{resp}(t_c)$ infected-A1 cells have the max rank eight.

[Modified Rule 3] We propose to adapt Rule 3 by adding 'In The Next Time Step'. This mimics the fact that infected-A2 cell will also be present in the lymph-node for a short time but with less infection ability, compared to infected-A1 cells.

[The rest of rules] don't change.

3 Results

3.1 DTHI Model Simulations

To repeat the HI model, we use the same parameters as reference [13], using a Moore neighbourhood, periodic boundary conditions on a lattice of 700 sites, initial infected A1 cells (with $P_{HIV} = 0.05$), $\tau = 4$ and $R = 4$. Because the delay parameter τ may vary from 2 to 6 weeks, and the number of infected-A2 neighbours vary from 3 to 7 due to some of threshold. In Fig. 3, we show the densities of healthy, infected (A1 and A2) and dead cells using the modified Rule 3 with the other rules the same as in the HI paper. The results are averaged over 500 simulations. The variance which do not show in this paper is consistent with Fig. 2 in reference [13]. The reason to do this modification of the Rule 3 comes from two facts. Analytically, infected A2 cells will be only present transiently in the lattice during execution of a set of rules if we don't modify Rule 3. Infected A1 cells, however do have an opportunity to be present because of its related τ time steps. Moreover, there is hardly opportunity for Rule 1b to contribute. As a consequence the evolution speed with which the cells enter the AIDS phase is too fast, without correction and Rule 1b has no chance to be activated. Our simulations show that the density of the dead cells in Fig. 3 are shifted one time step with respected to the results shown in reference [13]. This results in a required conservation of densities of healthy, infected and dead cells, normalized to unity in each time step.

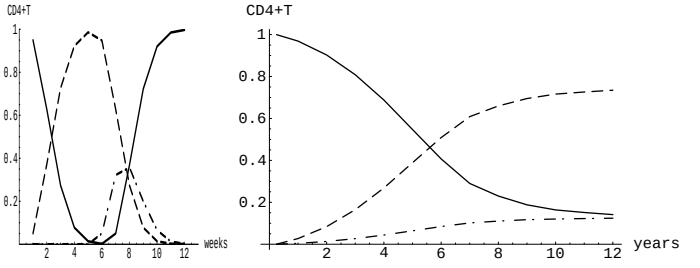

Fig. 3. Three-phase dynamics with two time scales (weeks and years) were obtained which were primary response (within 12 weeks), clinical latency (within 10 years) and AIDS (steady state after 10 years). The solid, hash and hash-dot lines represent healthy, infected (A1 and A2) and dead cells respectively. The density of dead cells shifted one time step, compared with the result of HI model. The evolution speed of cells with corrected rule was consistent with the result of HI model, but was slower than the result without correction.

3.2 Introduction of Drug Therapy into the DTHI Model

In the previous sections we introduced new rules to model the response of the system to drug therapy. In figure 4 four different time scales (weeks and years) can be observed. The data shown were averaged over 500 simulations. The first acute phase indicates the fast proliferation of the original HIV strains before the actual immune system response. This phase ends when specific immune response occurs for these strains. The next phase, the chronic phase that takes years, is the phase where the viral load increases slowly and CD4 counts decrease slowly. When CD4 T counts drop to a certain level (normal 200 to 500 counts per ml), the drug therapy is started. In this phase, virus replication is blocked and CD4 T counts increase. Once resistant strains against the drugs evolve, the last phase of the disease occurs disrupting the whole immune system.

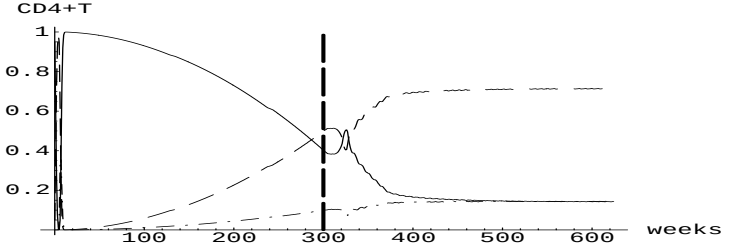

Fig. 4. Four-phase dynamics with two time scales (weeks and years) were obtained, which were qualitatively comparable with clinical data. The solid, hash and hash-dot lines represent healthy, infected (A1 and A2) and dead cells respectively. The vertical hash line indicates the starting point of the therapy. The profile indicated that after primary response, the CD4 T cells decreased gradually in the latency period. Once the therapy started, CD4 T cell count increased due to the drug therapy. Finally they evolved into AIDS state due to the resistance against drug.

Our simulation results indicate that the extension of long-term survival is dependent on the drug effectiveness (N) and the response function (P_{resp}). The high quality of the drug (modelled by small N) efficiently prevents the virus from replication, and thus few resistant new viruses are generated. As a consequence, a relatively prolonged long-term survival is obtained such as shown for $N = 0$ in Fig. 5. We can also simulate HAART treatment by selecting a suitable P_{resp} response function in our model such as $P_{resp}2$ and $P_{resp}3$ in Fig. 6.

In our simulation model, we get insights into local behaviour and spatial structures. Two typical spatial structures wave-like (left structure) and solid-like structures (right structure) are shown in Fig. 7a. The solid-like structures spread in all directions and wave-like structures generate a propagating front wave with width τ+1." After the therapy started, original spatial structures disappeared

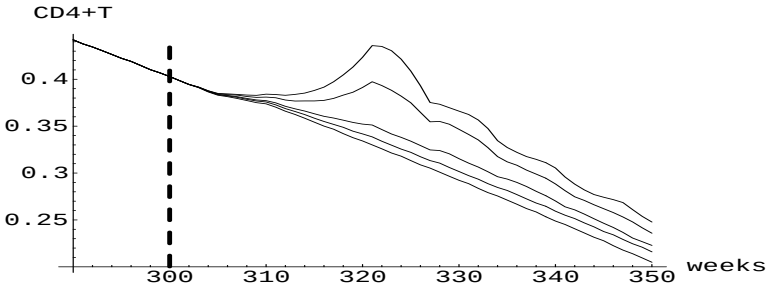

Fig. 5. Different drug effectiveness with the same response function (P_{resp}) was observed, which were $N = 0$, $N = 1$, $N = 4$, $N = 7$ and no treatment locating from the top to the bottom in the figure respectively. The results here qualitatively simulated mono-therapy and combined therapy.

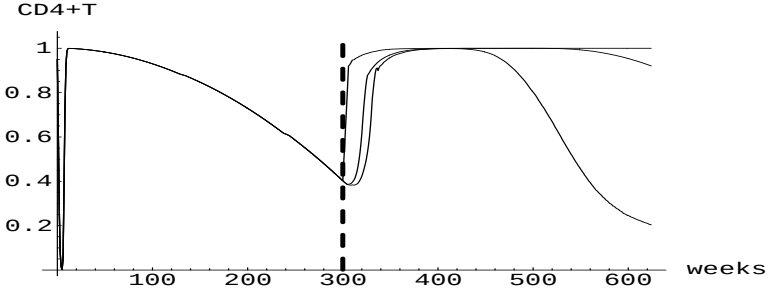

Fig. 6. Different response functions (P_{resp}) with the same drug effectiveness ($N = 0$) were obtained, which were P_{resp1},P_{resp2} and P_{resp3} locating from the top to the bottom of the figure respectively. $P_{resp}1$ simulated the completely recovering therapy. $P_{resp}2$ and $P_{resp}3$ simulated the current HAART therapy. Vertical hash line represents the starting of the therapy.

due to the limitation of infection, and only new resistant virus against drug were left in the lattice (Fig. 7b). They developed and formed new virus sources wave-like structures (Fig. 7c). Eventually, they evolved into AIDS phase. Only wave-structures were left and covered the whole lattice. The steady states was reached, in which the concentrations of each cell were kept relatively fixed and patterns of structures were unchanged (Wolframs class II behaviour) (Fig. 7d).

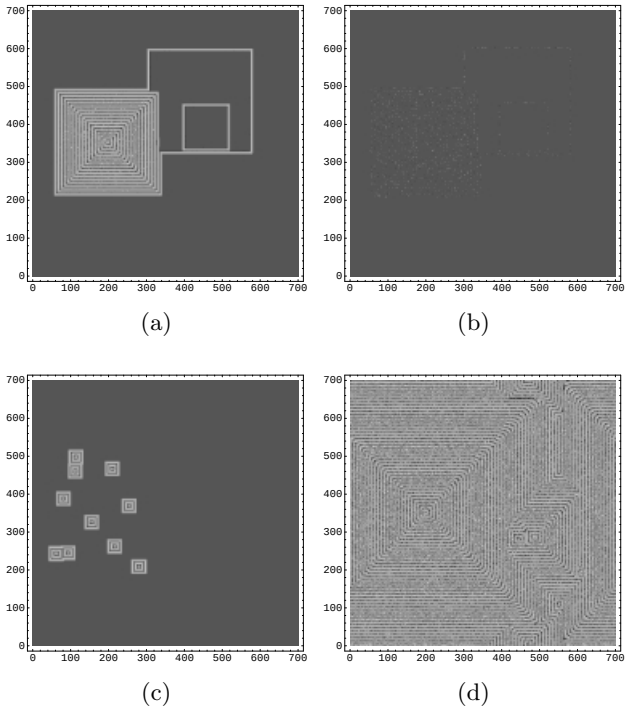

Fig. 7. Four snapshots of the whole lattice (700 X 700) at different time steps in the trial of Fig. 5 ($P_{resp}3$), simulated by the DTHI model. The dark grey, light grey, white and black represent healthy, infected A1, infected A2 and dead cells respectively. Figures (a) to (d) indicated time steps 300, 400, 500 and 600 respectively. The treatment starts at 300 time steps.

4 Discussions and Conclusions

The main success of the present model is the adequate modelling of the four-phases of HIV infection with different time scales into one model. Moreover, we could also integrate all of the three different therapy procedures into one model. The simulations show a qualitative correspondence to clinical data. During the phase of drug therapy response, temporal fluctuations for $N > 3$ were observed, this is due to the relative simple form of the response distribution function (P_{resp}) applied to the drug effectiveness parameter N at each time-step. Our simulation results indicate that, in contrast to ODE/PDE, our model supports a more flexible approach to mimic different therapies through the use of mapping the parameter space of P_{resp} to clinical data. P_{resp} is different functions of time step, corresponding to different therapies. In this paper, we employ different constant P_{resp} over time step for mono-/combined therapy and linear P_{resp} over time step for HAART therapy. Therefore there is ample room to incorporate

biologically more relevant response functions into the model. This future work requires in depth investigation of the parameter space of P_{resp}.

The results from Fig. 3 with respect to the amount of CD4 T counts are not completely supported by clinical data. The number of CD4 T cells should completely go down at least to a level that is undetectable. We will investigate the influence of P_{resp} on the steady state in our model. The chosen value of P_{HIV} in this paper ($P_{HIV} = 0.05$) is too large with respect to data known for clinic. A more realistic value would be 1 infected cell per 10^2 to 10^3 cells, resulting in $P_{HIV} = 0.005$. This effect will also be investigated. Clinical data indicate a increased sensitivity of T-cells over time, probably due to activation of the immune system. This will be modelled by making P_{infec} a function of the number of infected cells. Finally, it is known that in the early stages of infection, virus replication is confined to monocytic white blood cells. Only in later stages, CD4 T cells will become the new target cells. This trophysm effect will be studied in the future.

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References

1. M.A. Fischl, D.D. Richman, Hansen. N., A.C. Collier, J.T. Carey, M.F. Para, W.D. Hardy, R. Dolin, W.G. Powderly, J.D. Allan, and et al. The safety and efficacy of azt in the treatment of subjects with mildly symptomatic HIV type 1. *Annals Int. Med.*, pages 727–737, 1990.
2. U. Hershberg, Y. Louzoun, H. Atlan, and S. Solomon. HIV time hierarchy: Winning the war while, loosing all the battles. *Physica.*, pages 178–190, 2001.
3. D. E. Kirschner and G. F. Webb. A mathematical model of combined drug therapy of HIV infection. *J. Theoret. Med.*, pages 25–34, 1997.
4. D. E. Kirschner and G. F. Webb. Understanding drug resistance for mono-therapy treatment of HIV infection. *Bull. Math. Biol.*, pages 763–185, 1997.
5. A. Mielke and R. B. Pandey. A computer simulation study of cell population in a fuzzy interaction model for mutating HIV. *Physica A*, 251:430–438, 1998.
6. 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, Springer-Verlag*, 83:350–370, 1989.
7. N. Stilianakis, C.A.B. Boucher, M.D. De Jong, R. Van Leeuwen, R. Schuurman, and R.J. De Boer. Clinical data sets of HIV-1 reverse transcriptase-resistant mutants explained by a mathematical model. *J. of Virol.*, pages 161–168, 1997.
8. T. Toffoli and N. Margolus. *Cellular Automata Machines.* Cambridge, Massachusetts: The MIT Press, 1987.
9. S. Vella, M. Giuliano, L.G. Dally, M.G. Agresti, C. Tomino, M. Floridia, A. Chiesi, V. Fragola, M. Moroni, M. Piazza, and et al. Long-term follow-up of zidovudine therapy in asymptomatic HIV infection: results of a multicenter cohort study. *J. AIDS.*, pages 31–38, 1994.
10. D. Verotta and F. Schaedeli. Non-linear dynamics models characterising long- term virological data from aids clinical trials. *Math. Biosci.*, pages 1–21, 2002.

11. G. Y. Vichniac, P. Tamayo, and H. Hartman. Annealed and quenched inhomogeneous cellular automata. *J. Statistical Phys.*, 45:875–883, 1986.
12. D. Wodarz, K. M. Page, R. A. Arnout, A. R. Thomsen, J. D. Lifson, and M. A. Nowak. A new theory of cytotoxic t-lymphocyte memory: implications for hiv treatment. *Philos. Trans. R. Soc. Lond. (B Biol. Sci.)*, 355(1395):329–343, 2000.
13. R. M. Zorzenon dos Santos and S. Coutinho. Dynamics of HIV infection: A cellular automata approach. *Phys. Rev. Lett.*, 87(16):168102–1–4, 2001.