Cellular automata model of HIV infection on tilings of the plane

Chris Ormerod

October 13, 2004

Abstract

In this study, we explore the application of R.M.Zorzenon dos Santoses' model of the evolution of Human Immunodeficiency Virus (HIV), to Cellular Automata on different tilings of the plane. We investigate how the geometry of the model changes the overall dynamics of the system. In particular how issues of dimension and different methods of defining nearest neighbours allows us to modify the model to more accurately simulate the underlying system.

1 Introduction

The infection of Human Immunodeficiency Virus (HIV) that leads to Acquired Immunodeficiency (AIDS) has been an area of intense research over the years. We measure the progression of the virus by two factors, the viral load and the number of T helper cells (CD4 T) in the blood. The virus itself shows many of the initial traits of various viral infections. Associated with the progressions are three stages of the infection. The first stage is an initial sharp increase in the viral load followed by a sharp decrease in the viral that lasts 2-6 weeks. The second stage is known as a latency stage where only trace elements of the virus remain. This stage lasts anywhere from one to ten years or more. The difference between HIV and other viral infections is that various other viral infections are completely eliminated whereas HIV remains. The third stage is a gradual build up of the virus coinciding with a decline in CD4 T cell level often leading to the susceptibility to other diseases [11].

Experimental evidence supports the idea that the virus remains inside the Lymph Nodes [3]. Most of the Lymph can be found within the lymph organs, thus the model applied is a simulation of the infection through the lymph nodes. We measure the progression of the virus by two factors, the viral load and the number of healthy lymph cells in the blood. There are two associated time scales with the infection, the initial stages of infection work on a time scale of weeks, whereas the later stages of infection work on a time scale of years.

2 The Abstract Model

The model in question is a Cellular Automata model of HIV infection. This model is highly regarded because of its simplicity and the fact that is has been been the first model of HIV that exhibits the three phase evolution of the viral load while keeping all the parameters constant. Other attempts have been using differential equations such as those in [4] and [3]. This model has also been used to simulate drug therapy for HIV infection [8].

The model itself as proposed in [2] is a model of the infection within the lymph organs. The lymph organs were chosen because evidence suggests most of the infection is within the lymph organs [3]. Although the precise geometry or cell structure of the Lymph nodes is not known, it can be assumed that the cells of the lymph tissue are in a mesh structure. Previous models have approximated the cells within the lymph tissue to be in a square lattice structure. Although this may or may not be indicative of the structure of such a system, it does add a spatial element not evident in most of the previous models. Another desirable feature of the square model is that is is very simple to simulate due to the fact that square arrays are a very basic data structure in computers. The model is a four state model in which each cell in the lattice is in one of the following states

1. Healthy : A cell in this state represents an uninfected cell. This cell has not been affected by the infection.

2. Infected : A cell in this state represents an infected cell.

3. Badly Infected : A cell in this state represents and infected cell that is dying from infection.

4. Dead : A cell in this state represents a cell that has been killed by the virus.

The initial conditions of a lymph node that has been infected is that a very small proportion of the virus can be found. The initial configuration is set such that each cell has a small probability, P_{HIV} of starting off infected otherwise the cell is initially healthy. The original model chose P_{HIV} to be of the order of 0.005. We will assume that initially the infected cells are randomly distributed over the system. Each cell in the lattice is synchronously updated according to the following rules.

1. Rule for Healthy Cells
   (a) If one of the cells nearest neighbours is infected, it will also be infected in the next time step.
   (b) If it has no infected neighbours yet has at least R badly infected neighbouring cells, then it will become infected.
   (c) Otherwise the cell remains healthy.
2. Rule for Infected Cells : If the cell has been infected for τ time steps, it becomes a badly infected cell.
3. Rule for Badly infected Cells: The badly infected cells become dead cells in the next time step.
4. Rule for Dead Cells : A dead cell has a probability of P_{rep} of been replenished. Any replenished cell has a probability of P_{inf} of being infected once it has been replenished.

Typically we assume a high probability of replenishment, thus we choose P_{rep} to be in the order of 0.99. This represents the bodies high ability to recover from infection. The probability that a replenished cell is infected is again chosen to be in accordance to experimental data which suggests that a cell has a one in 10^5 to 10^4 chance of being infected [9]. One criticism of the made in [10] has been that the initial load of 5% was too large, and contrasts with the experimental data [5]. The results obtained from initial loads smaller than that which appeared in [2] led to a discrepancy between the simulations and experimental results. We propose that this disceprancy may be accounted for by artificially adjusting the rate of infection by simulating the infection on different tilings of the plane. By changing the number of nearest neighbours, we effectively increase or decrease an infected cells capacity to spread the infection thus we effectively change the rate of infection.

3 Tilings of the Plane

It is clear that the above model may be applied to tilings of the plain other than square lattices. The only rule that the geometry explicitly affects is the rule that governs the infection of the cells by other infected cells. As of yet, very little research has been done in exploring how one may apply such cellular automata models to different tilings of the plane. Perhaps this is due to the the pure simplicity imposed by data structures in computing, simulations such as these have been restricted to square lattices.Although there is some research in this area, the widely known as their square or one dimensional counterparts. Most notable is the research into cellular automata on different tilings is the work of Morita [6] and Ueno [7] in the area of reversible cellular automata. There are also cellular automata models on hexagonal lattices that are biological in nature concerning the transmission of pheromones within bee hives [12].

Within each model, we may think of these as an arbitrary collection of N cells, but when we consider the geometry of the lattice, this mainly coincides with the question, how do we define the nearest neighbour relations? This factor directly influences the speed at which the infection spreads. We may also think of the variable R to be geometric in nature, as its bounds depends upon the number of neighbours in the system. Varying R well also implicitly alter the rate of infection.

When considering nearest neighbour relations, there are two factors that should be considered. First of all we must consider the dimension of the lattice. In the systems we deal with, the lattices will be from 1 to 3 dimensional. It is not obvious that dimensionality is a factor in the spread of infection under the given rules. If we were to define a metric on the set of cells to be the number of nearest neighbour relations required to get from one cell to another, then a group of n cells in three dimensions are closer together than those in the 2-dimensional case in the sense that the maximal distance between any two cells increases as $\sqrt[3]{n}$ as opposed to $\sqrt{n}$. The other factor is there are many ways in which we may define nearest neighbour relations on any tiling. We may define nearest neighbours to be those:

1. Cells that share a vertex.
2. Cells that share an edge.
3. Cells that share a face.

When considering different shapes of tiles, there were a strong restriction that we placed upon the tilings. We firstly required tilings that somehow admitted a way in which one may define nearest neighbour relations in which each cell had the same number of nearest neighbours. To determine different decompositions of the plane, we draw upon knowledge of Eulers' formula for planar graphs.

$$V - E + F = 2 \tag{1}$$

We will assume we have n cells, where q is the ratio of cells meeting at a vertex, and p is the ratio of edges per face. It is then clear as $F = n$ grows very large, V np/q and E $np/2$. By letting $n \to \infty$ we obtain the formula

$$2p + 2q = qp \tag{2}$$

The square lattice is an example of the case when $q = p = 4$. Another examples of a tiling with the same values for q and p is the well known Penrose tiling. Various other tilings of the plane follow from different values of p and q. We have in this paper restricted much of our attention to the cases where p and q are integers, in which there are a very limited number of tilings possible. The only case we consider in which this is not the case is the pentagonal tiling in which $p = 5$ and $q = 10/3$. There exists analogous decompositions in three and higher dimensions, yet the restrictions imposed limit the number possible decompositions one may consider. For this reason, we have limited our analysis in three dimensions to the cubic lattice, although it would be possible to extend to other lattices such as those considered in [1]. The following table contains those shape of the cells we have considered, the way in which we define the nearest neighbour relations along with the how many nearest neighbours each cell contains.

Shape of Cells	Neighbouring cells share a	Number of Nearest Neighbours
Square	Vertex	8
Square	Edge	4
Triangle	Vertex	12
Triangle	Edge	3
Cube	Vertex	26
Cube	Edge	18
Cube	Face	6
Hexagon	Edge/Face	6
Pentagon	Edge	5

By choosing a tile shape, we may directly alter the speed at which the virus spreads. A statistical argument is given for this in the next section, although intuitively the number of cells one infected cell infects in 1 time step is at most the number of nearest neighbours to that cell.

4 Analysis of the Speed of infection

As with many cellular automata, the complexity of the dynamics is difficult to study. Although direct analysis may be impossible, one can still make probabilistic type arguments concerning various aspects of a cellular automata. In the HIV model studied, one can estimate the speed of infection over different tilings of the plane by determining the probability that upon a single iteration, a healthy cell becomes infected.

Let H be the number of healthy cells, I be the number of infected cells and let B number of badly infected cells. The number of dead cells is given by the relation $n - H - I - B$ where n is the total number of cells. If we let $\bar{H} = \frac{H}{n}$,$\bar{I} = \frac{I}{n}$ and $\bar{B} = \frac{B}{n}$, the probability of a single healthy cell becoming infected is

$$P_{\mathrm{H}\to\mathrm{I}} = f(\bar{I}) + g_R(\bar{B}) - f(\bar{I})g(\bar{B}) \tag{3}$$

where $f(\bar{I})$ is the probability of a single cell healthy becoming infected via contact with an infected cell, and $g_R(\bar{B})$ is the probability of a single healthy cell becoming infected via contact with R or more badly infected cells. The expression for f is given by

$$f(\bar{I}) = 1 - (1 - \bar{I})^N \tag{4}$$

and the expression for g_R is given by

$$g_R(\bar{B}) = \begin{cases} 1 & \text{if } R = 0 \\ 1 - \sum_{i=0}^{R-1} \binom{N}{i} \bar{B}^i (1 - \bar{B})^{N-i} & \text{if } R > 0 \end{cases} \tag{5}$$

Where N is the number of nearest neighbours. If we assume $\bar{B} = 0$ and $\bar{I}$ are very small and $R > 0$, then $g_R(\bar{B}) = 0$, then by expanding (3) to first order we find that $P_{\mathrm{H}\to\mathrm{I}} \approx N\bar{I}$. This tells us an explicit initial dependence on the number of neighbours. Furthermore, if $\bar{B}$ is small then $g_R(\bar{B}) \approx 0$, thus $P_{H\to I} \approx f(\bar{I})$. The short life of badly infected cells suggests that $\bar{B}$ is small, thus this approximation holds for all time.

One problem in using this argument is that it does assume a random distribution of the various types of cells. This may or may not be case in the time evolution of the model. It does however give a rough estimate of the dependence of the speed of the infection with the number of nearest neighbours. Equation (3) also gives an explicit dependence of R on the speed of infection.

5 Results

In order to apply this model to different tilings, we chose to program a new data structure in C++ that was able to easily simulate different shapes. Essentially one can simulate such systems on various n-tuples of lattices, that is a set of lattices with nearest neighbour relations defined between the copies each the lattices. We choose R to be roughly in accordance to the method in [2], that is to say, we choose R so that the cell requires approximately half of it's nearest neighbours to be badly infected in order for the cell itself to be infected upon it's next iteration. We hold all other values constant between different tests, that is to say in each test $P_{\text{HIV}} = 0.005$ in accordance with experimental evidence, P_{rep} is fixed at 0.99 and P_{inf} is fixed at 5×10^{-5}. The first test is the one dimensional model. Figure 1 shows how a much slower rate of infection affects the dynamics of the model.

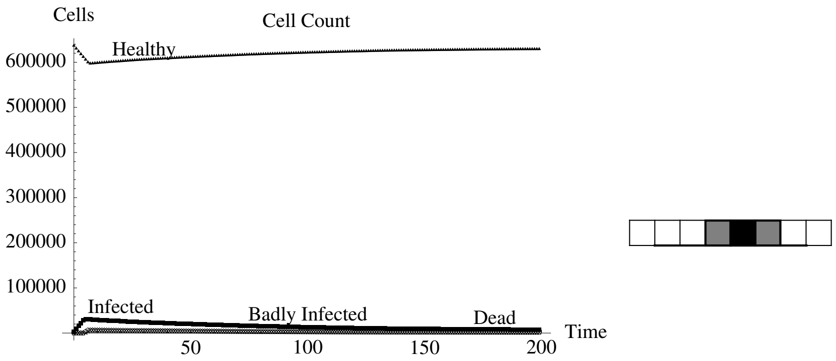

Figure 1: The effect of reducing the number of nearest neighbours to 2. The corresponding neighbourhood is illustrated on the right.

We took a finite periodic 1 dimensional lattice for the above test. The traits that were evident in the original model are not as well pronounced, but we see even in this simple model that there are still features that are similar to experimental evidence. In two dimensions we have a much wider variety of cell configurations to test. In each case we simulate the infection on a sufficiently large finite doubly periodic tessellation of the plane. We start with 2 square lattice models, one in which nearest neighbours are defined by connecting edges, one by connecting vertices yielding 4 and 8 nearest neighbours respectively.

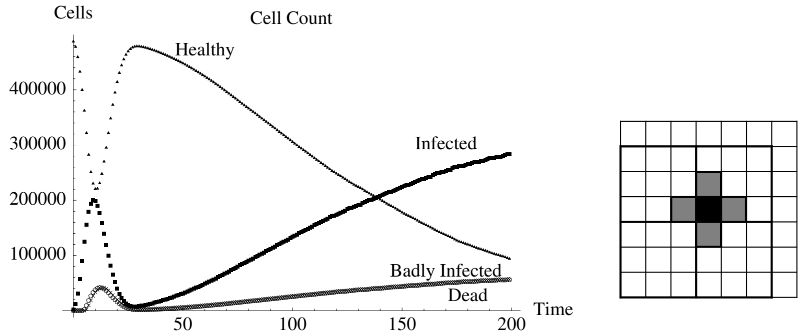

Figure 2: The results of simulating the model on a 2-dimensional square lattice with neighbours defined by connecting edges. This model has 4 nearest neighbours as displayed on the right.

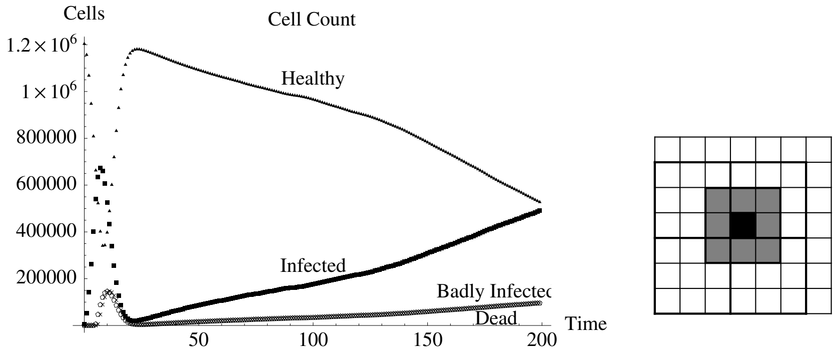

Figure 3: The results of simulating the model on a 2-dimensional square lattice with neighbours defined by vertices. This is essentially the original model.

Secondly we have a triangular tessellation of the plane. Again we test two ways of defining nearest neighbour relations yielding 3 and 12 nearest neighbours respectively. The results of this simulation can be seen in figures 4 and 5.

Essentially the hexagonal tessellation is another lattice, where the nearest neighbours are defined differently from the square case. This model also arises as

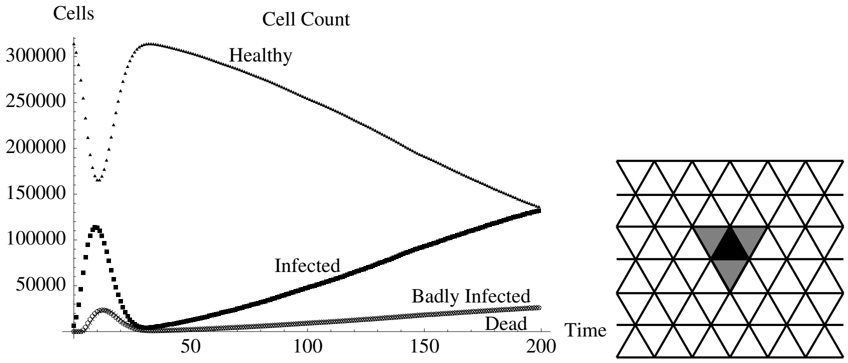

Figure 4: The results of the simulation on a triangular tessellation of the plane. The 4 nearest neighbours are defined in terms of connecting edges as displayed on the right.

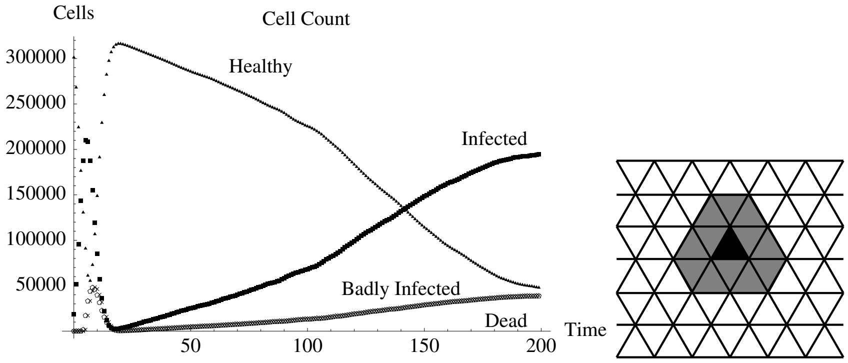

Figure 5: Another result of running the simulation on a triangular tessellation of the plane. The 12 nearest neighbours are defined in terms of connecting vertices as displayed on the right.

the dual of the triangular model. There is one consistent way of defining nearest neighbours yielding 6 nearest neighbours as shown in figure 6.We may also apply the model to tilings of the plane, and we choose a pentagonal tiling as shown in figure 7.

It should be noted that this is not a tessellation of the plane and is the only tiling that is not symmetric. Thus it proved more difficult to program. The above results conclude the tests on 2 dimensional tesselations of the plane consisting

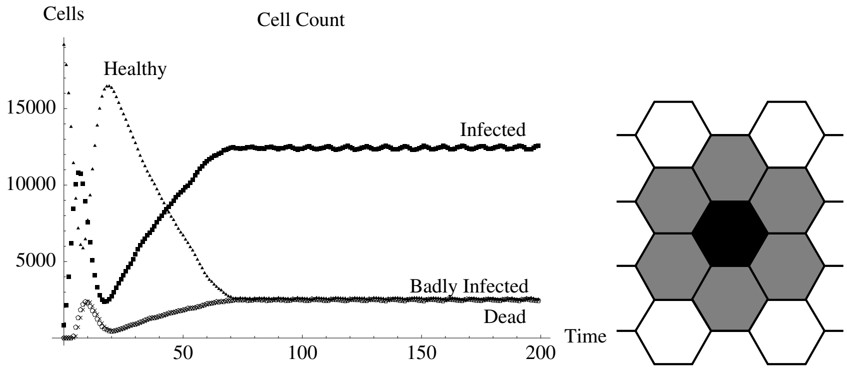

Figure 6: The result of running the simulation on the hexagonal or honeycomb tessellation. There are 6 nearest neighbours as shown on the right.

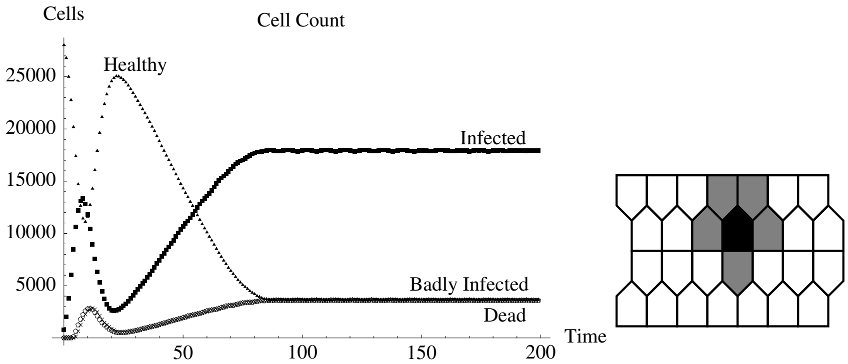

Figure 7: The results of using the pentagonal tiling with the five nearest neighbours seen on the right.

of the regular tesselations and 1 irregular tessellation. We only tested different ways of defining nearest neighbour relations for the typical cubic lattice. This still allowed us to test the difference dimension makes to the dynamics of the model. We choose a finite triply periodic finite 3 dimensional lattice, the three ways of defining nearest neighbour relations are by connecting face, edge and vertex yielding 6,18 and 26 nearest neighbours respectively. The results can be seen in figures 8 and 9.

In figure 9 we notice that when we increase the rate of infection too much, the result is a rapid increase and decrease of the viral load. This corresponds to a

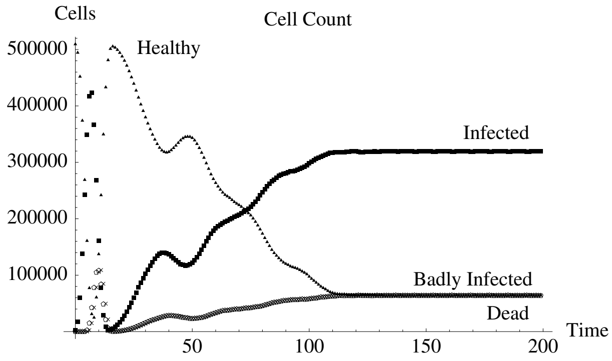

Figure 8: The results of applying the model to a cubic lattice where the 6 nearest neighbours are defined by connecting faces.

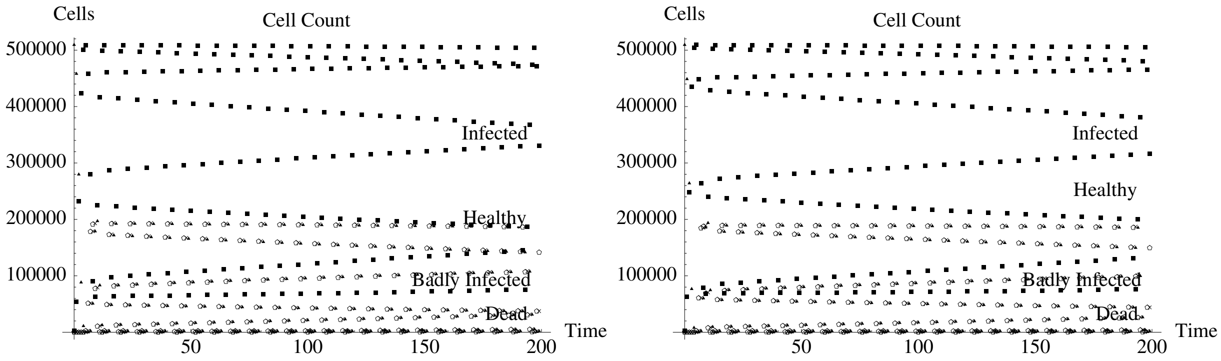

Figure 9: A breakdown of the model as the dynamics become erratic with the increase in speed of the infection. The models above are the square model with nearest neighbours defined by connecting edge on the left, and by connecting vertex on the right.

breakdown of the model.

6 Conclusions

Here we have investigated the affects of simulating a known cellular automata model to different tilings of the plane. The results have been that we have effectively changed the rate of infection of the virus. This in some ways has opened up a new area for biological modelling. Simulations on tilings of the plane may be applied to many biological models, and this is an open area for research. Currently the author knows one model for the spread of cancer that is currently being considered on different tilings of the plane. Even the number of tilings of the plane that admit these Cellular Automata structures is not entirely known. And the question of what decompositions of 3 and higher dimensional space that admit cellular automata structures in the same way, is also a difficult question to answer in general.

References

[1] J. H. Conway and N. J. A. Sloane. *Sphere packings, lattices and groups*, volume 290 of *Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Sciences]*. Springer-Verlag, New York, third edition, 1999. With additional contributions by E. Bannai, R. E. Borcherds, J. Leech, S. P. Norton, A. M. Odlyzko, R. A. Parker, L. Queen and B. B. Venkov.

[2] Rita Maria Zorzenon dos Santos and Sergio Coutinho. Dynamics of hiv infection: A cellular automata approach. *Physical Review Letters*, 87, 2001.

[3] Claire E. Parker Dov J. Stekel and Martin A. Nowak. A model of lymphocyte recirculation. *Immunology Today*, 18(5):216–221., 1997.

[4] R R Farooqi, Z H; Mohler. Distribution models of recirculating lymphocytes. *IEEE Transactions On Bio-Medical Engineering*, 36:355–362, 1989.

[5] A. T. Haase. Population biology of hiv-1 infection: Viral and cd4+ t cell demographics and dynamics in lymphatic tissues. *Annual Review of Immunology*, 17(1):625–656, 1999.

[6] Kenichi Morita Katsunobu Imai. A computation-universal two-dimensional 8-state triangular cellular automaton. *Theoretical Computer Science*, 231:231–191, 2000.

[7] Kenichi Morita and Satoshi Ueno. Computational-universal models of two-dimensional 16-state reversible cellular automata. *IECICE Trans. Inf. and Syst.*, E75-D(1), 1992.

[8] Fan Chen Peter Slot and Charles Boucher. Cellular automata model of drug therapy for hiv infection. *ARCI 2002, LNCS 2493*, 2001.

[9] Wei X.; Ghosh S.K. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature*, 373:117–122., 1995.

[10] Matthew C. Strain and Herbert Levine. Comment on “dynamics of hiv infection: A cellular automata approach”. *Physical Review Letters*, 89, 2002.

[11] S. Baker B.Donovan Tindall, B. Characterization of the acute illness assiciated with human ummunodeficiency virus infection. *Ann. Intern. Med.*, 125:257–264, 1988.

[12] James Watmough. A general model of pheromone transmission within honey bee hives. *J. Theo. Bio.*, 189:159–170., 1997.