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Studies on Population Dynamics Using Cellular Automata

Rosana Motta Jafelice[1] and Patrícia Nunes da Silva[2]
[1]*Federal University of Uberlândia*
Faculty of Mathematics
[2]*State University of Rio de Janeiro*
Department of Mathematical Analysis - IME
Brazil

1. Introduction

In this chapter, we present three cellular automata that simulate the behavior of the population dynamics of three biological systems. They are shaped like a torus in which populations coexist artificially. The first one deals with artificially-living fish divided into two groups: sharks (predators) and fish that are part of their food chain (preys) (Edelstein-Keshet, 1988; Renning, 1999-2000). The second model introduces a simulation of the HIV evolution in the blood stream of positive individuals with no antiretroviral therapy (Jafelice et al., 2009). The last model extends the previous one and considers the HIV dynamics in individuals subject to medical treatment and the monitoring of the medication potency and treatment adhesion (Jafelice et al., 2009). For this purpose, a cellular automata approach coupled with fuzzy set theory is developed to study the HIV evolution. When modeling a physical or biological system there are many decisions to make. One of them is related to the kind of approach to take into account. In the "bottom-up" approach the complex behavior of a system emerges from the interaction of basic components. One might ask if it is possible to describe the behavior of complex systems in this way. As a matter of fact, Banks (1971) makes an interesting remark about how physicists were happy to believe the universe is composed of an enormous number of just three basic components: protons, electrons and neutrons. Modeling biological phenomena by realistic models generally leads to large system of non linear integro- and partial differential equations. One alternative approach is to consider cellular automata (CA) models. The usefulness of the CA models relays on simplicity and uniformity of their cells and also on their potential to model complex systems. The main idea behind cellular automata models is to consider each position (or region) of a spatial domain as a cell to which is attributed a certain state. The state of each cell is modified according to its own state and the states of its neighbor cells. These states are correlated through a number of simple rules that imitates the biological and physical laws that guide the system behavior (Ermentrout & Edelstein-Keshet, 1993). An important aspect in modelling population dynamics is to take into account the effect of the spatial distribution of population on their dynamics. The CA models can capture this effect (e.g. Czaran 1998; Lee et al. 1995).

2. Cellular automata of prey-predator model: Sharks and fish

In this section we discuss a cellular automaton for a predator-prey model proposed by David Wiseman at the University of Western Ontario (see Dewdney 1984). The planet Wa-Tor[1] is a grid shaped like a torus in which coexist artificially fish and sharks. In this planet most of the time fish and sharks move randomly. Fish and sharks can propagate when they have reached the appropriate age. Differently from sharks, fish have a plentiful supply of plankton and sharks have to eat fish in a specific maximal period, otherwise they would starve to death. Thus, the simulation is of a dynamic system of predator-prey type. In his two-dimensional CA, Dewdney (1984) considered a von Neumann neighborhood. That is, each cell is connected with itself and with its four orthogonal neighbors. He compared his results with the theoretical predator-prey relation given by the Lotka-Volterra equations and also with the sizes of the populations of the Canadian lynx and snowshoe hare recorded by the Hudson's Bay Company over almost fifty years. Our results were obtained using a two-dimensional CA with a Moore neighborhood. That is, each cell is connected with itself, with its four orthogonal neighbors and with its four diagonal neighbors. In both cases, just the earlier states of the cell and its neighbors determine the next time step. These kind of automata closely resembles an evolution equation such as partial differential or integral equations. Our results were compared to the Lotka-Volterra classic model (Edelstein-Keshet, 1988; Murray, 1990) and also with the empirical data from the Hudson's Bay Company.

2.1 Realistic example of predator-prey: Hare and lynx at Hudson's Bay

In 1850, the Hudson's Bay Company used to get from trappers pelts of hares and lynxes. The number of hares and lynxes that got into traps were recorded and used by researchers to study competitive interactions models (see Bulmer 1974; Stenseth et al. 1998). It is known that the number of the captured animals is proportional to their population, so researchers found populations statistics for those both species for over a large period. Data on the Canadian hare-lynx system based on the hare and lynx furs records of the Hudson's Bay Company may be found at Elton & Nicholson (1942), Gilpin (1973) and Hewitt (1921). Both populations do not exist independently from one another, because lynxes feed basically from hares. All the records of pelts for each year were analyzed by the ecologist Charles Elton (Elton, 1924) and are presented in the Fig. 1. The figure shows a regular oscillation over ten years in the numbers of both species. They change over 50 fold and up to 100 folds, over the cycle, what makes the amplitude of the oscillation huge. In the next subsections we will see that the classical model presents regular curves and a phase plane that is a perfect cycle while our cellular automaton will present a cycle which will be closer to the Fig. 2. The phase plane graph of a period of thirty years, initiated in 1875, was obtained from the populations data presented in the Fig. 1.

2.2 Classic predator-prey model

The population fluctuations of predators and prey challenged many researchers. What causes the changes in reproduction and survival? Besides the three main factors: food, predation, and social interactions, many other factors might affect these cycles. For instance, Zhang et al. (2007) used partial cross correlation and stepwise multiple regression methods to analyze the effect of climate on the Hudson's Bay Company's hare-lynx system (1847-1903). Their results showed that El Niño/Southern Oscillation has small effects on rates of increase in hare and lynx populations. Krebs et al. (2001) were interested in how changes on food can influence the

[1] The name Wa-Tor comes from Water-Toroidal.

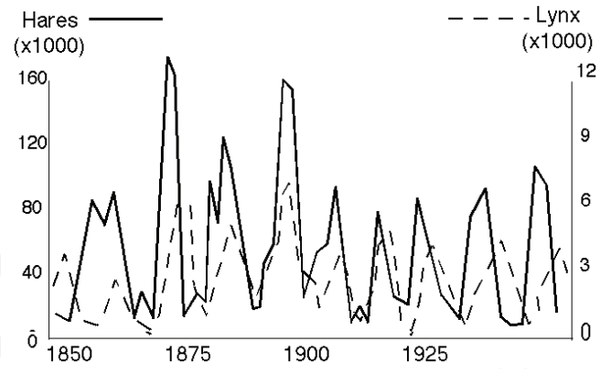


Fig. 1. Hares and lynxes population as a function of time (Renning, 1999-2000).

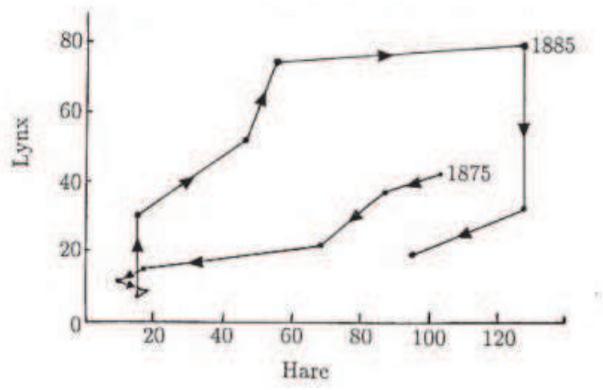


Fig. 2. Detail of the phase plane plot of the data presented in Fig.1 (Murray, 1990).

hare cycle while Stenseth et al. (1999) observed that lynx population dynamics are consistent with a regional structure caused by climatic features.
In order to formulate the interaction between preys and predators, a deterministic model (that became a classic model) was used[2]. It is given by the differential equations system:

$$\begin{aligned} \frac{dx}{dt} &= ax - \alpha xy \\ \frac{dy}{dt} &= -by + \beta xy \end{aligned} \tag{1}$$

In this model, the state variables x and y are, respectively, the number of preys and predators in each instant t. The parameters are:

- a: preys relative growth rate;
- α: predation rate (probability of a predator to kill the prey in each time they encounter);
- b predators mortality rate in the absence of preys;
- β preys conversion rate into predators.

Solving the differential equations with the parameters $a = 0.1$, $\alpha = 0.01$, $b = 0.05$ and $\beta = 0.001$, we obtain the graph of the Fig. 3 and the phase plane, Fig. 4.

[2] See Wangersky (1978) for a review on Lotka-Volterra population models.

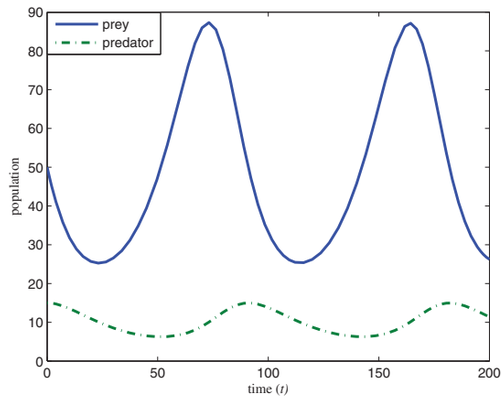


Fig. 3. Solution of the differential equation system.

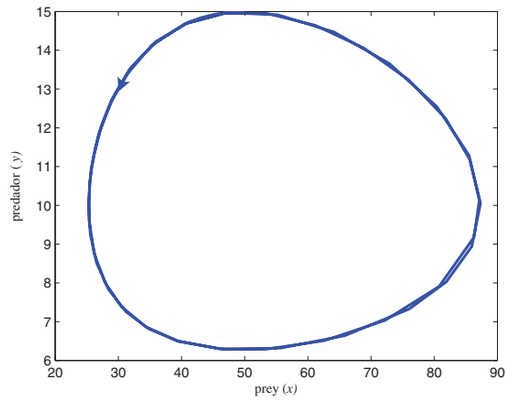


Fig. 4. Phase plane.

Since the classical model ignores spatial correlations it does not take into account important effects that spatial inhomogeneity may cause on the dynamics of the system. Moreover in such a model we do not have any information about the spatial distribution of the populations.

2.3 Description of the cellular automata simulation

The following five parameters need to be chosen to set up a simulation: 1. number of fish; 2. number of sharks; 3. fish reproductive age; 4. sharks reproductive age; 5. sharks starvation period. The initial number of sharks and fish as their respective ages are randomly distributed in a rectangular grid whose opposite sides are identified in pairs. The cells states in the grid are updated according to the local dynamics rules of each cell. For instance, in a 40x40 cell grid, 300 fish and 10 sharks are placed at random positions. All fish and sharks have a reproductive age, i.e., 3 and 10 iterations respectively and sharks starvation period is 3.

2.3.1 Behavior of fish in Wa-Tor

Each fish chooses a free place in its neighborhood, moves and ages there (if all places are occupied, then it remains where it is and ages). When it achieves the reproductive age, it leaves behind a single offspring. They move according to a randomly assigned integer that indicates a direction. More specifically, depending on whether the value of the integer is equal

to 1, 2, 3, 4, 5, 6, 7 or 8, they move north, east, south, west, northeast, northwest, southeast or southwest (Silva & Jafelice, 2010), in the grid, respectively.

2.3.2 Behavior of sharks in Wa-Tor

First, each shark searches for fish in its neighborhood. If there are fish, the shark randomly chooses one, catches it and the variable (starve variable) is set to zero. It goes to the cell of the eaten fish and might propagate if the occasion arises. If it does not find any fish in its neighborhood, it moves like a fish and the starve variable is increased by 1. When the starve variable reaches its maximum (sharks starvation period) the shark dies. Also, sharks reproduction is similar to the fish.

Simulation results of the Wa-Tor system for 200 iterations (or time steps) are depicted in Figs. 5-7. Notice that the behavior of the fish and sharks shown in Fig. 5 are close to the ones in similar phase shown in Fig. 3.

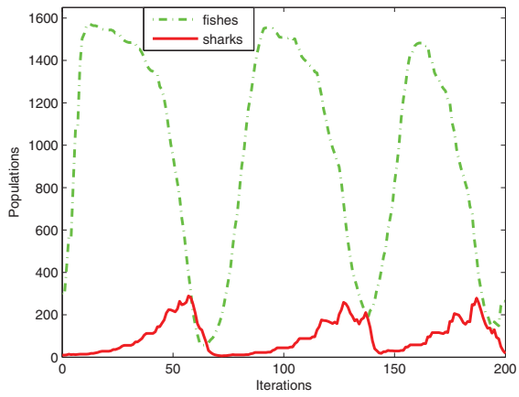


Fig. 5. Wa-Tor simulation results.

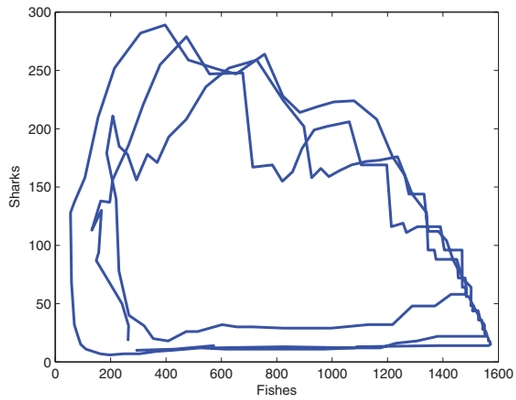


Fig. 6. Phase plan for a simulation in Wa-Tor.

2.4 Computational graphical interface

We have used *Matlab 7.0* to build our computational graphical interface for the Wa-Tor system (see its initial interface in Fig. 8 – (Jafelice & Silva, 2001)). To set up your own simulation,

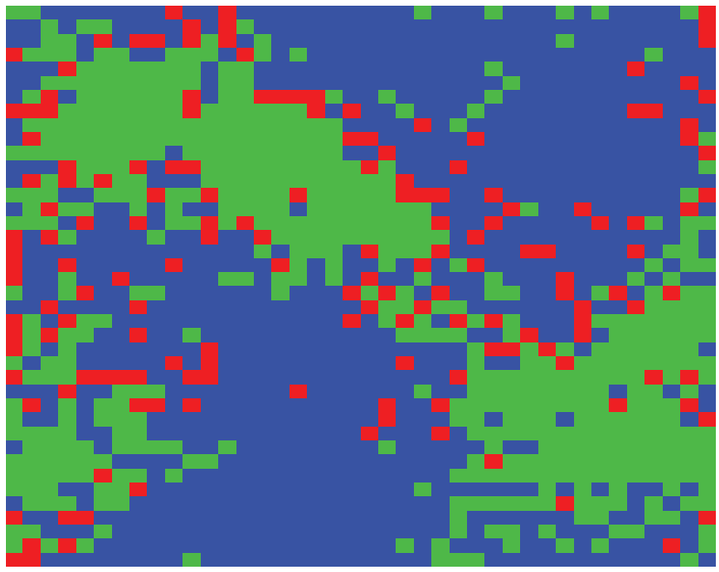


Fig. 7. Snapshot of the cellular automata model output: the blue background is the sea, the fish are in green and the sharks in red.

the following six parameters need to be chosen: 1. number of iterations 2. initial number of fish; 3. initial number of sharks; 4. fish reproductive age; 5. sharks reproductive age; 6. sharks starvation period. It is also possible to run the four simulations listed below with previously assigned parameters:

1. stable ecological cycle
2. fish extinction
3. shark extinction
4. fish and shark extinction.

Furthermore, at the end of each simulation, the graphs of fish and sharks population as a function of time and of the phase plane are plotted.

2.5 Conclusion

This section has introduced a cellular automata approach to a prey-predator dynamics. The obtained results (as well as the Dewdney (1984) ones) resemble the Lotka-Volterra ones but go further. The population fluctuations of fish and shark resemble better the hare and lynx charts than the Lotka-Volterra solutions do. Another interesting feature of the CA model is that it is a spatially distributed prey-predator model. Nowadays, the crucial role of spatial inhomogeneity into the dynamics of biological species has been recognized (see Durrett & Levin (2000), Ermentrout & Edelstein-Keshet (1993) and the references therein for further discussion. See also, Pekalski (2004) for an overview on predator-prey systems approaches and remarks on some open problems). Saila (2009) presents Wa-Tor as a complex adaptive system of interacting autonomous agents and points out that the utility of conventional mathematics in understanding the dynamics of such complex ecosystems is limited. The evolution of the

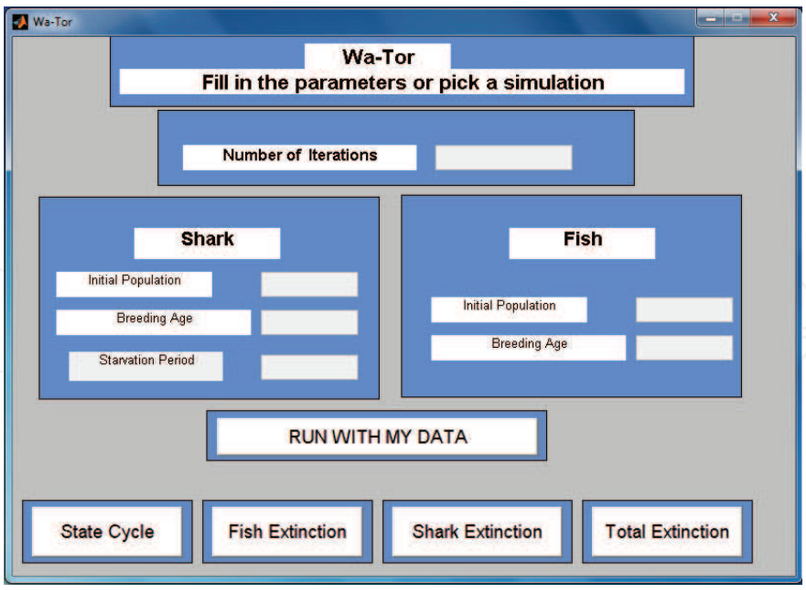


Fig. 8. Computational Graphical Interface of Wa-Tor.

system does not seem to depend on the initial random distribution but the choice of the five initial parameters is a critical point for the future behavior of the system. The model presents a complex behavior and the simulations give a qualitative image of the reality.

Cellular automata models for the Human Immunodeficiency Virus (HIV) infection dynamics are the subject of the next sections. Deciding which are the dynamics rules of each cell demands a deep knowledge on the HIV behavior. HIV is a spherical retrovirus composed of RNA or ribonucleic acid. Its replication occurs within host cells. Three virus proteins are of paramount importance for the replication process: Reverse Transcriptase, Integrase and Protease. After HIV gains entry to its human host, it is disseminated throughout the lymphatic tissues. When HIV reaches the blood stream, it attacks mainly the lymphocyte T of the $CD4+$ type. The quantity of cells $CD4+$ in periphery blood has prognostic implications in HIV infection evolution. The gradual loss of CD4+ T cells to the AIDS-defining level of 200 cells/mm^3 and progressive immune deficiency lead to opportunistic infections that characterizes the HIV infection (Haase, 1999; Hazenberg et al., 2000). Nowadays, the amount of immunocompetent cells is the most clinically used and acceptable measurement during treatment of infected individuals. The antiretroviral treatment works inhibiting both reverse transcriptase and protease. The inhibitions of reverse transcriptase prevents free virus particles to infect $CD4+$ cells. Protease inhibition delays the viral replication, allowing the organism to react naturally. Combination of reverse transcriptase and protease inhibition has led to a substantial improvement in HIV therapy.

Microscopic models for HIV infection dynamics in human individuals provide helpful information to construct cellular automata models, especially when the growth rate of T lymphocyte of $CD4+$, the death rate of infected and non infected cells, free virus load, specific antibodies CTL, interaction rate between non infected cells of the T $CD4+$ and the virus, and the interaction rate between the infected cells of the lymphocyte T of the $CD4+$ and the antibody are constant.

In the next section, we introduce the cellular automaton model for the HIV infection dynamics with no antiretroviral therapy (Jafelice et al., 2009).

3. Cellular automata of the HIV evolution in the blood stream of positive individuals with no antiretroviral therapy

AIDS (Acquired Immunodeficiency Syndrome) has become a worldwide health problem. In countries where AIDS control is poor or even nonexistent, as in some African nations, the HIV-positive population shows high mortality rates. Zorzenon dos Santos & Coutinho (2001) reported a cellular automaton approach to simulate the three-phases patterns of HIV infection consisting of primary response, clinical latency and onset of acquired immunodeficiency syndrome (AIDS). The robustness of the results obtained from their cellular automata model were analyzed in Figueiredo et al. (2008). The CA model from Ueda et al. (2006) considers the diversity exhibited by both HIV and T cells. Their results indicate the diversity of the virus is the major factor affecting the success rate of the escape of HIV from the immune response and they were also able to resemble the incubation time variability observed in vivo. Mielke & Pandey (1998) developed a fuzzy interaction model for mutating HIV with a fuzzy set of 10 interactions for macrophages, helper cells, cytotoxic cells and virion. These models are cellular automata models with no antiretroviral treatment. We consider a cellular automaton to model the behavior of the three-phases pattern of HIV infection which consists of: primary infection, asymptomatic and symptomatic phases for the cells of T lymphocyte of $CD4+$ of the HIV and specific antibodies called CTL. We compare our CA model results with the natural history of HIV infection and also with the HIV dynamics model proposed by Nowak & Bangham (1996).

3.1 Microscopic models of HIV dynamics

Nowak & Bangham (1996) developed three microscopic models for HIV infection dynamics within the organism of human individuals, considering no antiretroviral therapy.
The first model captures the interaction between replicating virus and host cells. In this case, three variables are considered: uninfected cells n, infected cells i and free virus particles v. This model assumes that infected cells are produced from uninfected cells and free virus at rate βnv and die at rate bi. Free virus is produced from infected cells at rate ki and declines at rate sv. Uninfected cells are produced at a constant rate, r, from a pool of precursor cells, and die at rate an. Fig. 9 illustrates the HIV dynamics developed by this model.

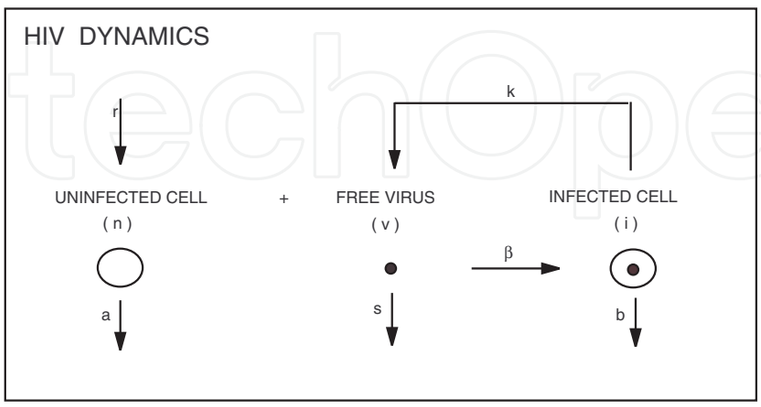


Fig. 9. Microscopic models HIV virus dynamics (Nowak, 1999).

Modeling assumptions lead to the following system of differential equations:

$$\begin{aligned} \frac{dn}{dt} &= r - an - \beta nv \\ \frac{di}{dt} &= \beta nv - bi \\ \frac{dv}{dt} &= ki - sv. \end{aligned} \tag{2}$$

The second model includes immune responses against infected cells, and extends the system of equations (2) adding an equation to describe the immune responses against infected cells:

$$\begin{aligned} \frac{dn}{dt} &= r - an - \beta nv \\ \frac{di}{dt} &= \beta nv - bi - piz \\ \frac{dv}{dt} &= ki - sv \\ \frac{dz}{dt} &= ciz - dz. \end{aligned} \tag{3}$$

The variable z denotes the magnitude of the antibodies CTL (cytotoxic T lymphocyte) – that is, the abundance of virus-specific CTLs. The rate of CTL proliferation in response to antigen is ciz. In the absence of stimulation, CTLs decay at rate dz. Infected cells are killed by CTLs at rate piz. Fig. 10 shows the solution of (3) using the parameters of Table 1 and initial conditions of Table 2, obtained from Caetano & Yoneyama (1999).

$r = 0.3$	$a = 0.1$	$\beta = 1$
$b = 0.01$	$p = 0.03$	$k = 0.5$
$s = 0.01$	$c = 0.01$	$d = 0.01$

Table 1. Parameters of the microscopic HIV model.

$n(0)$	0.99
$i(0)$	0.01
$v(0)$	0.1
$z(0)$	0.01
t initial	0
t final	500 time units

Table 2. Initial conditions of the microscopic HIV model.

From Fig. 10 one can see that, in logarithmic scale, the uninfected cells of $CD4+$ show a rapid decline in the first weeks and a slow recovery when the number of lymphocytes is close to the maximum. The increase in the number of lymphocytes is related to virus replication in the infected cells.
Comparing the solution of system (3), shown in Fig. 10, with the plots of Fig. 11, which gives the dynamics of HIV infection history currently accepted (Coutinho et al., 2001; Perelson & Nelson, 1999; Saag, 1995), we notice that the uninfected cells of $CD4+$ identify with the $CD4+$ level, the free virus with the HIV virus, and the virus-specific CTLs with the HIV

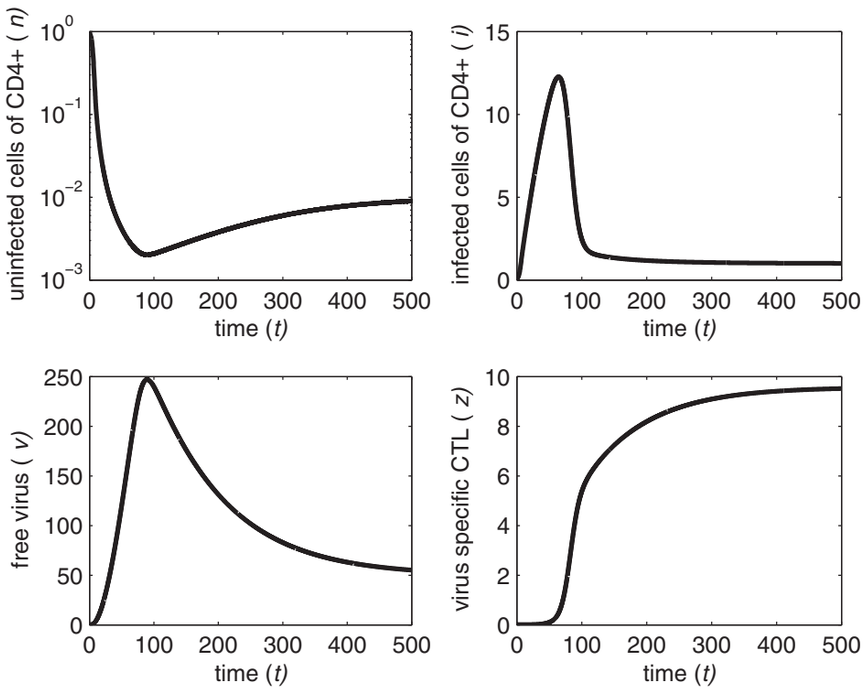


Fig. 10. Solution of the microscopic HIV model (3).

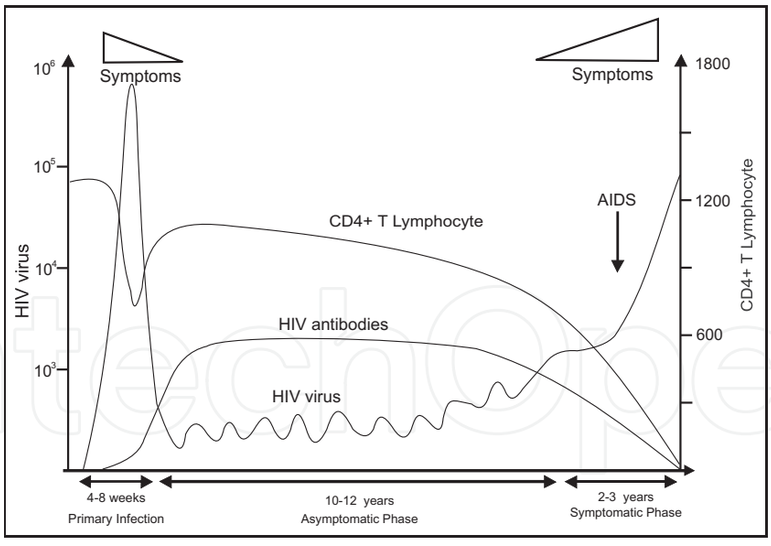


Fig. 11. The natural history of HIV infection dynamics as currently accepted (Coutinho et al., 2001; Perelson & Nelson, 1999; Saag, 1995).

antibodies. This result will help to validate the cellular automata model for individuals under no antiretroviral therapy.

The next section details the Blood-Tor system, the cellular automaton model for the HIV infection dynamics.

4. Blood-Tor system

The name Blood-Tor comes from Bloodstream-Toroidal which is similar to the name of the cellular automaton Wa-Tor, that means Water-Toroidal (Dewdney, 1984; Renning, 1999-2000). The Blood-Tor System (BTS) is shaped like a torus in which coexist artificially uninfected cells, infected cells of lymphocytes T of $CD4+$, free virus particles, and specific antibodies CTL (cytotoxic T lymphocyte) that attack infected cells in an individual blood stream with no antiretroviral therapy. These elements are the same as those associated with the state variables of the differential equation system (3).

4.1 Description of the simulation process

Eleven parameters need to be chosen to set up a simulation run. The parameters are the following:

- number of uninfected cells
- number of infected cells of the lymphocytes T of $CD4+$
- number of free virus particles
- number of specific antibodies CTL (cytotoxic T lymphocyte)
- life span limit of uninfected cells
- life span limit of infected cells
- life span limit of free virus particles
- life span limit of specific antibodies CTL (cytotoxic T lymphocyte)
- infected cells reproductive age
- specific antibodies CTL reproductive age
- uninfected cells production rate

The cells states in the grid are updated according to the local dynamics rules of each cell. For instance, in a 31x31 cell grid 200 uninfected cells, 16 infected cells of the lymphocytes T of $CD4+$, 120 free virus particles and 25 specific antibodies CTL (cytotoxic T lymphocyte) are placed at random positions. All uninfected cells, infected cells of the lymphocytes T of $CD4+$, free virus particles and specific antibodies CTL have a life span set according to a specific time limit. Table 3 gives the values of the life spans. An initially random assortment of ages are distributed to the elements (uninfected cells, infected cells of lymphocytes T of $CD4+$, free virus particles and specific antibodies CTL that attack infected cells) according to their respective life span limits.

cell	uninfected	infected	HIV	CTL
life span limit (iterations)	4	5	3	15

Table 3. Life span limits.

4.1.1 Behavior of uninfected cell of the lymphocytes T of $CD4+$ in BTS

Each uninfected cell of the lymphocytes T of $CD4+$ chooses a free place in its neighborhood, moves and ages there (if all places are occupied, then it remains where it is and ages). They move according to a randomly assigned integer that indicates a direction. More specifically, depending on whether the value of the integer is equal to 0, 1, 2 or 3, they move north, east,

south or west in the grid, respectively. Lymphocytes T of $CD4+$ are produced with a constant rate. During simulation the rate is 18 cells for each iteration. When they reach their life span limit they die.

4.1.2 Behavior of HIV in BTS

First, each HIV searches for uninfected cells of the lymphocytes T of $CD4+$ in its neighborhood. If there are uninfected cells, the HIV randomly chooses one and the cell chosen becomes an infected cell. If there are no uninfected cells, then the HIV chooses a place in its neighborhood and moves and ages there (if all places are occupied, it remains in its place and ages). When HIVs reach their life span limit they die.

4.1.3 Behavior of infected cell of the lymphocytes T of $CD4+$ in BTS

When free HIVs encounter uninfected cells of $CD4+$, the uninfected cells become infected. Those cells begin to replicate HIV when they reach the age of 5 iterations. The simulation program puts a HIV in the position of the infected cell and assigns zero age to the new HIV. They move and age similarly as the uninfected cells lymphocytes T of $CD4+$. After their life span limit, they die.

4.1.4 Behavior of specific antibodies CTL in BTS

Each specific antibody CTL looks for infected cells of the lymphocytes T of $CD4+$ in its neighborhood. When specific antibodies CTL encounter infected cells, the infected cells are destroyed. The specific antibodies CTL move to the cells infected in previous position. The specific antibodies reach the reproduction period after 14 iterations. They move and age similarly as the uninfected cells of lymphocytes T of $CD4+$. After their life span limit, they die.

The Blood-Tor system simulates the dynamics of the evolution of HIV within the blood stream human individual with no treatment.

Fig. 12 shows a snapshot of the Blood-Tor system cellular automaton model. The uninfected cells are shown in blue, the HIVs in black, the infected cells in green, and the antibodies in white. The Blood-Tor simulation system was developed using Matlab 7.0.

Simulation results of the Blood-Tor system (BTS), after 50 iterations (or time steps) are depicted in Fig. 13. Notice that the behavior of the uninfected cells of $CD4+$, infected cells of $CD4+$, free virus, and virus specific antibodies shown in Fig. 13 are close to the ones in similar (asymptomatic) phase shown in Fig. 11. Clearly, BTS does give a good description of the evolution of HIV in the blood stream of human individuals with no treatment.

Next section extends the BTS to encompass the natural phases of HIV dynamics of the Fig. 11.

4.2 Extended Blood-Tor system

To expand the ability of cellular automaton to model the natural history of HIV infection, the Blood-Tor System was extended to include the symptomatic phase behavior, as Fig. 11 suggests.

The cellular automaton that produces the outputs shown in Fig. 13, was modified such that, after a certain number of iterations, antibodies production decrease and, consequently, the number of free virus particles increases. In a grid of 31x31 cells, 120 uninfected cells, 18 infected cells of the lymphocytes T of $CD4+$, 180 free virus particles and 18 specific antibodies CTL (cytotoxic T lymphocyte) were introduced at random positions. All of these cells move

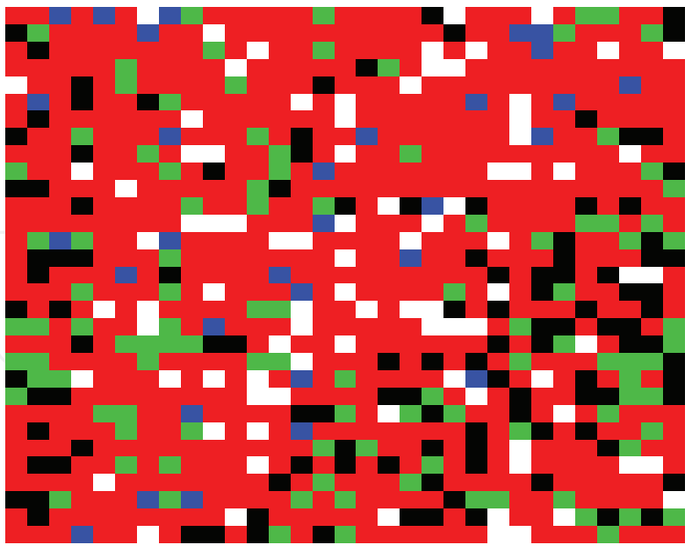


Fig. 12. Snapshot of the cellular automata model output: the red background is the blood stream, the uninfected cells are in blue, the HIV in black, the infected cells in green, and the antibodies in white.

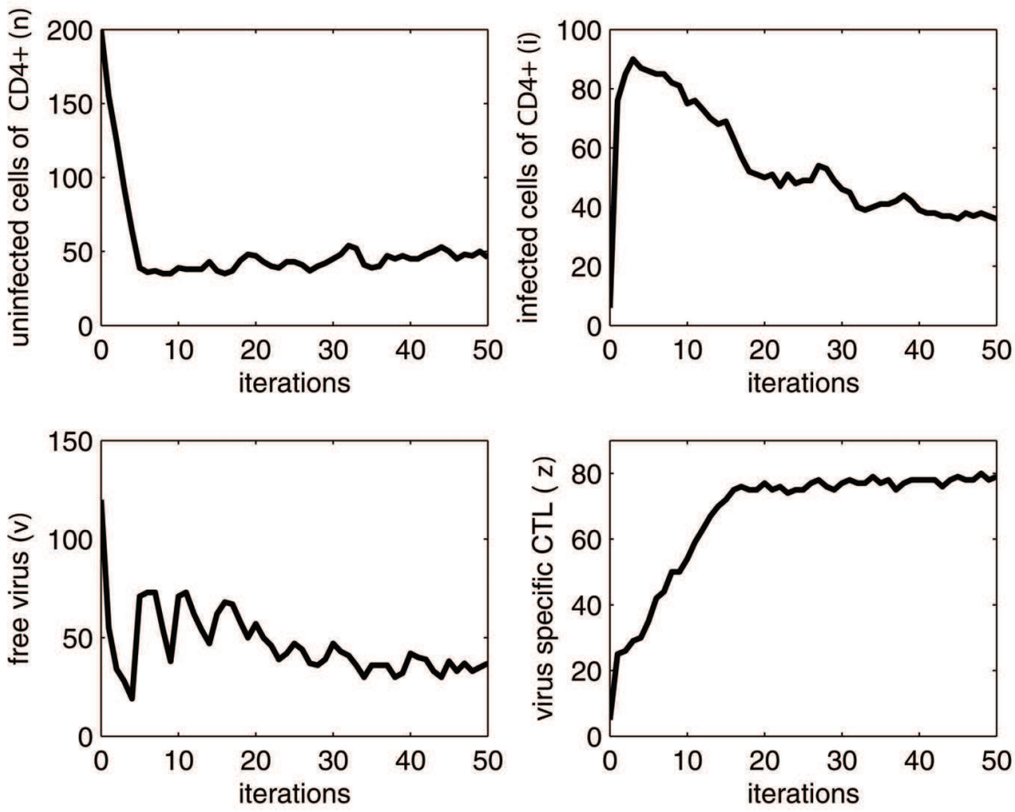


Fig. 13. Blood-Tor system simulation results.

randomly. The time limit of uninfected cells was set to seven (in the previous case it was set at four iterations). If the number of iterations is smaller than 70, then the reproduction time can be chosen as 14 iterations. If the number of iterations is greater than or equal 70, then the reproduction time decreases during the next iterations. If the number of iterations is greater than 90, then the number of uninfected cells placed at each iteration decreases. The result of this choice reflects the failure of the immunological system. That is, the immune system of the human individual looses the capacity to fight the viruses.
The BTS simulation results become, in this case, very close to actual HIV biological dynamics. They show strong qualitative similarities during all the natural history of HIV infection dynamics, as Figs. 11 and 14 clearly show.

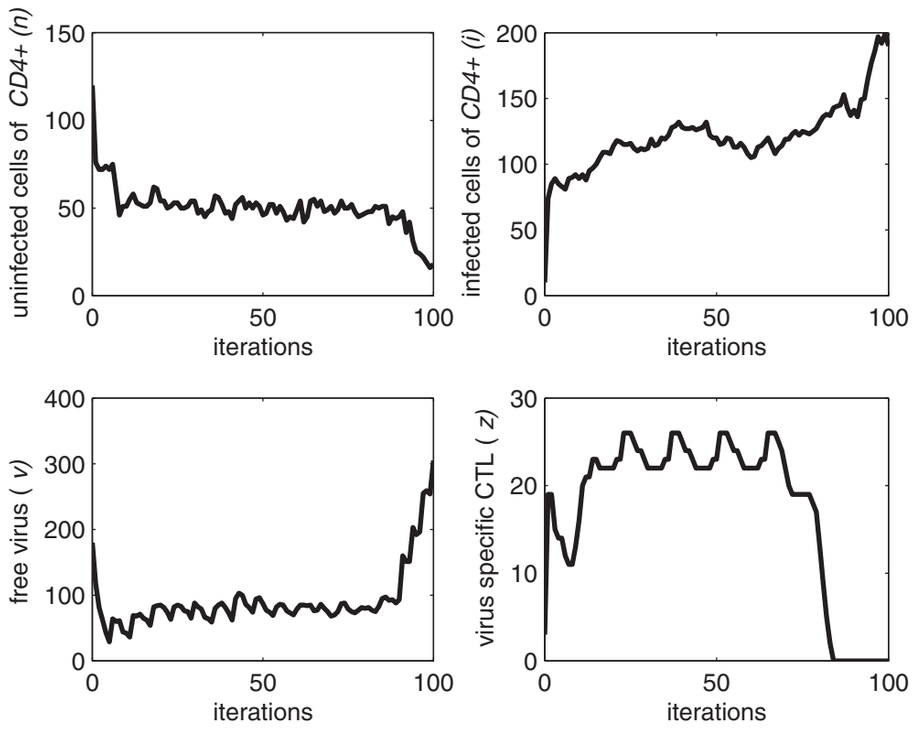


Fig. 14. Extended Blood-Tor system simulation results.

It is well known that AIDS is a disease that can be treated using appropriate drugs, but no absolute cure mechanism has been found yet. Some antiretroviral therapy uses reverse transcriptase inhibitors, others fight against an enzyme that is essential for the formation of infectious virus particles from infected cells called viral protease. All anti-HIV drugs aim at preventing the virus from reproducing, but they do not kill virus particles or infected cells (Nowak, 1999). Inspired in Zorzenon dos Santos & Coutinho (2001) CA model, Sloot et al. (2002) proposed a CA model incorporating drug therapy. Its main ingredients 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. The CA model integrates three different therapy procedures into one model and the simulations show a qualitative correspondence to clinical data. Shi et al. (2008)

presented a CA model for HIV dynamics and drug treatment. It includes the virus replication cycle and mechanisms of drug therapy. Viral load, its effect on infection rate, and the role of latently infected cells in sustaining HIV infection are among the aspects that are explored and incorporated in the model. The dynamics from the model qualitatively match clinical data. In the next section, we present the cellular automaton model for the HIV infection dynamics with antiretroviral therapy (Jafelice et al., 2009).

5. Cellular automata of the HIV evolution in the blood stream of positive individuals with antiretroviral therapy

The Blood-Tor System, detailed in section 4, simulates the behavior of HIV infection dynamics in the blood stream of HIV positive human individuals who have not received any antiretroviral therapy. This section addresses the Bloodstream-Toroidal system when treatment is taken into account. Its purpose is to model and simulate the HIV dynamics in the blood stream of individuals subject to antiretroviral therapy.

To simulate the antiretroviral therapy the BTS system adopts fuzzy parameters due the imprecise nature of how the individuals respond to the antiretroviral therapy. When accounting for antiretroviral therapy, the cellular automaton model assumes that the viruses do not infect all $CD4+$ cells because only a portion of $CD4+$ cells are usually infected. The period of virus replication is delayed, similarly as it happens in positive HIV individuals blood stream. The fuzzy parameters depend on the medication potency and on the adhesion of the individuals to the treatment. Adhesion to treatment means how individuals follow the correct medication prescription of the therapy. Adhesion is a very complex issue because it involves many factors that affect the ability of the individuals to comply with the antiretroviral therapy. Many factors can interfere in the regime prescribed, including the number of hours that individuals sleep, how strict they are with meals, medication schedules and how healthy their social life is. Information about medication potency can be obtained from medical doctors using their knowledge from clinical trials, clinical experience and knowledge published in the relevant literature. Along with clinical experience, the model increases the $CD4+$ level and decreases the viral load to simulate the antiretroviral therapy. The next subsection briefly review the concept of fuzzy set and fuzzy rule-based systems.

5.1 Basic concepts of fuzzy set theory

The literature on uncertainty has grown considerably during these last years, especially in the areas of system modeling, optimization, control, and pattern recognition. Recently, several authors have advocated the use of fuzzy set theory to address epidemiology problems (Barros et al., 2003; Jafelice et al., 2004; 2005; Ortega et al., 2003) and population dynamics (Krivan & Colombo, 1998). Since the advent of the HIV infection, several mathematical models have been developed to describe the HIV dynamics (Murray, 1990; Nowak & Bangham, 1996; Nowak, 1999). Here, we suggest the use of fuzzy set theory (Zadeh, 1965) to deal with the uncertain, imprecise nature of the virus dynamics.

First, we recall that a fuzzy set A on a universal set X is a membership function A that assigns to each element x of X a number $A(x)$ between zero and one to indicate the degree of membership of x in A. Therefore, the membership function of the fuzzy set A is a function $A : X \to [0,1]$. It is interesting to note that a conventional set A on X is a particular instance of a fuzzy set for which the membership function is the characteristic function of A, that is, $\mathcal{X}_A : X \to \{0,1\}$.

Second, we remind the reader that a concept that plays a key role in fuzzy set theory is fuzzy

rule-based systems (FRBS) (Pedrycz & Gomide, 1988). The structure of FRBS is shown in Fig. 15.

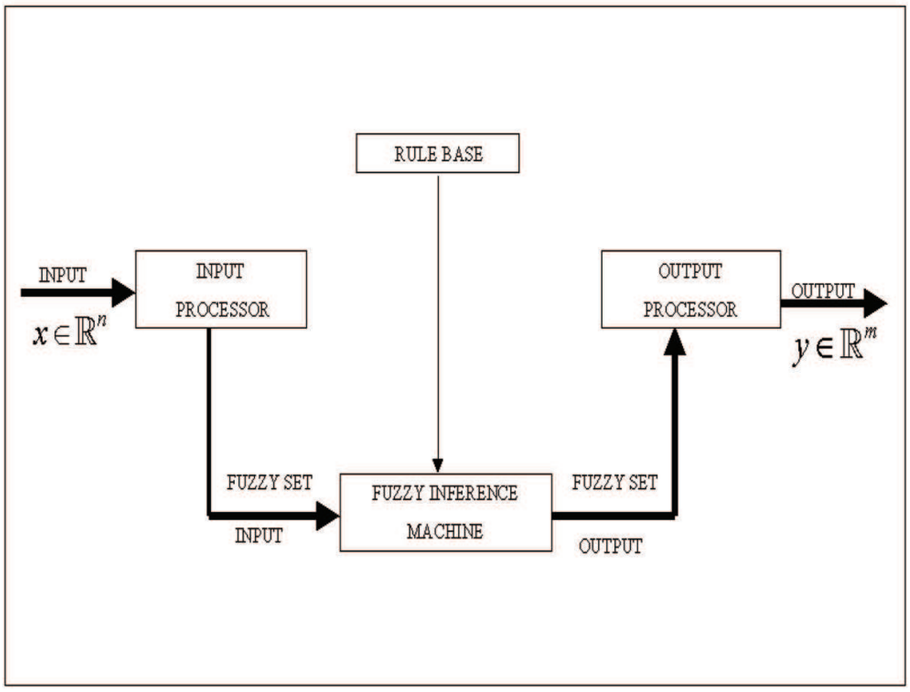


Fig. 15. Structure of fuzzy rule-based systems.

A FRBS has four components: an input processor, a collection of fuzzy rules called fuzzy rule base (or rule base for short), a fuzzy inference machine, and an output processor. These components process real-valued inputs to provide real-valued outputs as follows.

- **Input Processor (Fuzzification).** Here, inputs are encoded into fuzzy sets on the respective universes of the input variables. For numerical inputs, the approach commonly used is to transform a real-valued input into a fuzzy singleton. Expert knowledge plays an important role to build the membership functions for each fuzzy set associated with the inputs.
- **Rule Base.** This a knowledge-encoding component of fuzzy rule-based systems, a collection of fuzzy conditional propositions in the form of If-then rules. Fuzzy rules are an effective mean to encode expert knowledge expressed through linguistic statements. In general, If-then rules describe relationships between linguistic variables such as If *adhesion to treatment* is *low* and *medication potency* is *high* then *period of virus reproduction* is *fast* and *percentage of infected CD4+ cells* is *high*. In fuzzy set theory, a variable (e.g. *adhesion to treatment*) whose value is a linguistic term (e.g. *low*) is called a linguistic variable (Pedrycz & Gomide, 1988).
- **Fuzzy Inference.** The fuzzy inference machine performs approximate reasoning using the compositional rule of inference. A particular form of fuzzy inference that is of interest in this paper is the Mamdani method (Mamdani, 1976; Mamdani & Assilian, 1999), derived from the max-min composition (Pedrycz & Gomide, 1988).

- **Output Processor (Defuzzification).** In fuzzy rule-based systems, the inferred output usually is a fuzzy set. Often, especially in biological systems modeling, we require a real-valued output. The output processor task is to provide real-valued outputs using defuzzification, a process that chooses a real number that is representative of the fuzzy set inferred. A typical defuzzification scheme, the one adopted in this paper, is the centroid or center of mass method (Jafelice et al., 2004).

5.2 Linguistic variables and rule base

Fuzzy set theory is a mathematical tool to model imprecise information and knowledge. In practice, precise values of the number of infected $CD4+$ cells and the period of virus replication with the antiretroviral therapy is uncertain. These values depend on the medication potency and on the individuals adhesion to treatment. Fuzzy rule-based systems (FRBS) is an appropriate approach to address the effect of the treatment in HIV dynamics. The input variables of the FRBS are the adhesion to treatment and the medication potency (Ying et al., 2007). The output variables are the percentage of HIV infected $CD4+$ cells and the period of virus replication. The input and output variables are linguistic variables, denoted as A, M, P and V. Adhesion to treatment (A), medication potency (M) and percentage of infected $CD4+$ cells (P) assume the following linguistic values {*very low*, *low*, *medium*, *high*, *very high*} and the period of virus replication (V) adopts the linguistic values {*very rapid*, *rapid*, *medium*, *slow*, *very slow*}. The membership functions specify the meaning of the linguistic variables, as depicted in Figs. 16, 17, 18 and 19 for *adhesion to treatment*, *medication potency*, *period of virus replication*, and *percentage of CD4+ cells that will be infected*, respectively. The rule base that encodes the relationships between A, M, P and V was constructed using expert medical knowledge. The fuzzy rules are summarized in Tables 4 and 5. The rule base was processed using the Mamdani inference method with centroid defuzzification.

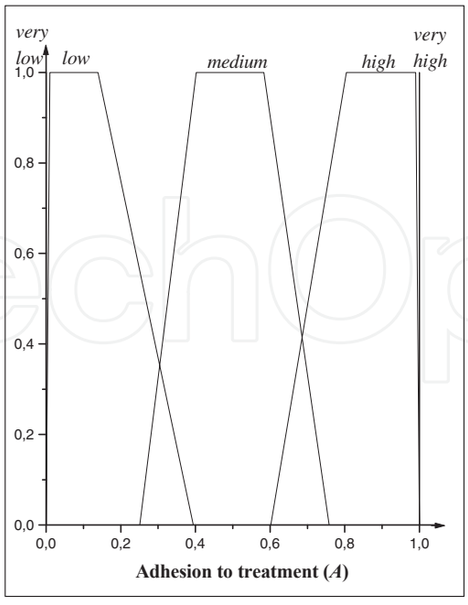


Fig. 16. Membership functions for adhesion to treatment (A).

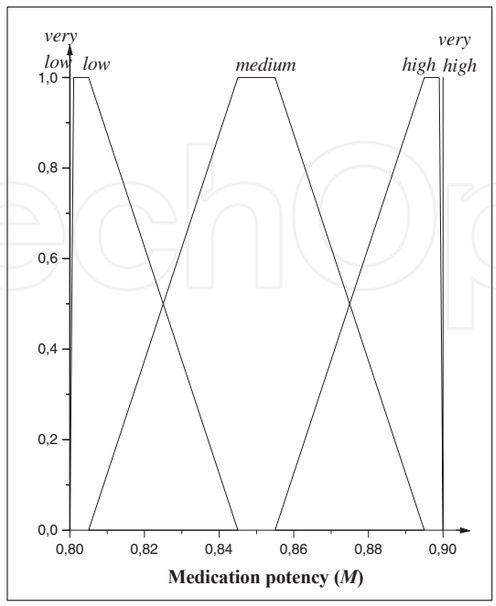


Fig. 17. Membership functions for medication potency (M).

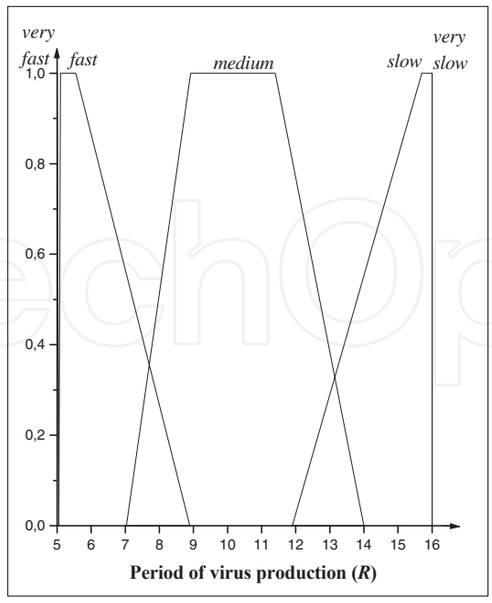


Fig. 18. Membership functions for period of virus replication (R).

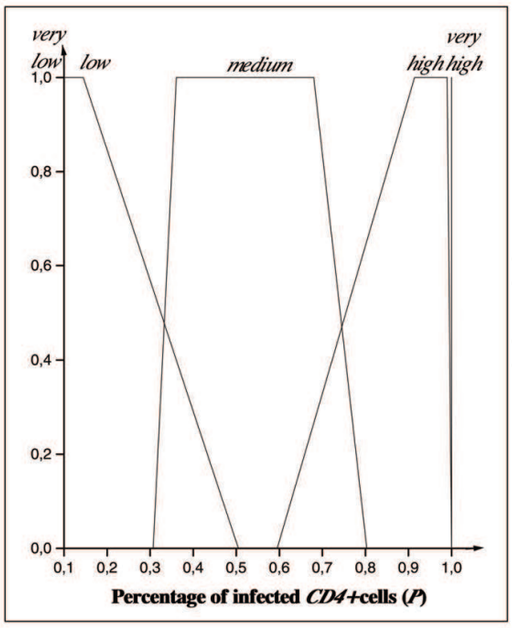


Fig. 19. Membership functions for percentage of $CD4+$ cells that infected (P).

Medication Potency (M) / Adhesion(A)	*very low*	*low*	*medium*	*high*	*very high*
very low	*very high*	*very high*	*very high*	*very high*	*very high*
low	*high*	*high*	*high*	*high*	*high*
medium	*medium*	*high*	*medium*	*high*	*medium*
high	*medium*	*high*	*low*	*low*	*low*
very high	*low*	*low*	*low*	*very low*	*very low*

Table 4. Fuzzy rules for the percentage of $CD4+$ cells that will be infected.

Medicat. Potency (M) / Adhesion(A)	*very low*	*low*	*medium*	*high*	*very high*
very low	*very rapid*	*very rapid*	*very rapid*	*very rapid*	*very rapid*
low	*rapid*	*rapid*	*rapid*	*rapid*	*rapid*
medium	*medium*	*rapid*	*medium*	*rapid*	*medium*
high	*medium*	*rapid*	*medium*	*slow*	*slow*
very high	*rapid*	*medium*	*medium*	*very slow*	*very slow*

Table 5. Fuzzy rules for the period of virus replication.

The cellular automaton model uses the output of the FRBS as follows. The number of HIV in the neighborhood of uninfected $CD4+$ cells is counted at each iteration. The product of the number counted multiplied by the output variable (percentage of $CD4+$ cells) is the number of HIV infected cells. This operation models the action of reverse transcriptase inhibitors. The percentage of $CD4+$ cells depends on the adhesion to treatment and on the potency of the medication. All those processes occur at each iteration. In the cellular automaton representing HIV infection dynamics and untreated HIV positive individuals, an infected cell $CD4+$ releases one virus at an available free place of its neighborhood after 5 iterations. In the

cellular automaton with treatment, the period of virus replication varies from 5 to 16 iterations, which models inhibitors action in delaying viral replication.

6. Simulation of the blood-tor system with treatment

6.1 Analysis of the Solutions

The quantity and specific time limit of uninfected cells, infected cells of the lymphocytes T of $CD4+$, free virus particles and specific antibodies CTL (cytotoxic T lymphocyte) were adjusted for different patients, considering their adhesion to the treatment. Simulation was carried out using the data (treatment adhesion and medication potency) of three HIV positive individuals shown in Table 6. In the table, the parameters of the first, second and third columns correspond to HIV positive individuals whose treatment receives low, medium, and high potency medication and treatment, respectively. The output variable values of the fuzzy rule-based system are shown in Table 7. The first line of the table shows the percentage of the $CD4+$ cells infected, and the second shows the period of virus replication, for the input values of Table 6. The cellular automaton model was ran five times for each patient. Averages are computed at each time instant t. Fig. 20 shows the results. The average of the individuals with the best response to the treatment is depicted in solid line. The dotted line is the average of the individuals with the worst response to the treatment. The behavior of the HIV as well as the behavior of the uninfected cells of type T lymphocyte of $CD4+$ fully agree with the corresponding behaviors reported in Guedj et al. (2007), Filter et al. (2005) and Ouattara et al. (2008). The HIV curve exhibits an asymptotic decay with a positive upper bound. In practice, laboratory exams may not detect the viral load, but indicate that the number of RNA copies of the virus in blood circulation is below the precision of the method used. The precision values are variable. For instance, in the case of the Brazilian public health network, the method currently adopted has the precision of 50 copies$/ml$ (Brazil, 2008). If a patient does not adhere to the treatment, then simulation proceeds as in the no treatment case discussed in section 4.

	First parameter	Second parameter	Third parameter
Medication potency	0.8	0.85	0.9
Adhesion to treatment	0.1	0.6	1

Table 6. Inputs for the FRBS used in simulation.

	First parameter	Second parameter	Third parameter
Percentage of $CD4+$ cells infected	0.85	0.55	0.1
Period of virus replication	6.35	10.37	16

Table 7. Outputs of the FRBS used in simulation.

6.2 Treatment response estimation

Fig. 20 suggests that the treatment response of patient p_s is better than of patient p_f, where p_f and p_s are the data of patients corresponding to first and second parameters of Table 6, respectively. To quantify the treatment response we must define a performance measure. Any of the four (or all, if an appropriate temporal average is chosen) variables, namely, uninfected and infected cells of lymphocyte T $CD4+$, free virus, and specific antibodies, can be considered. For instance, an estimation can be obtained using the a ratio of two variables values. Let us assume that the viral load is the variable revealing the treatment efficiency. Let $\overline{v_{p_1}}$ and $\overline{v_{p_2}}$ the averages of the viral loads of the patient 1 and 2 over the same time interval

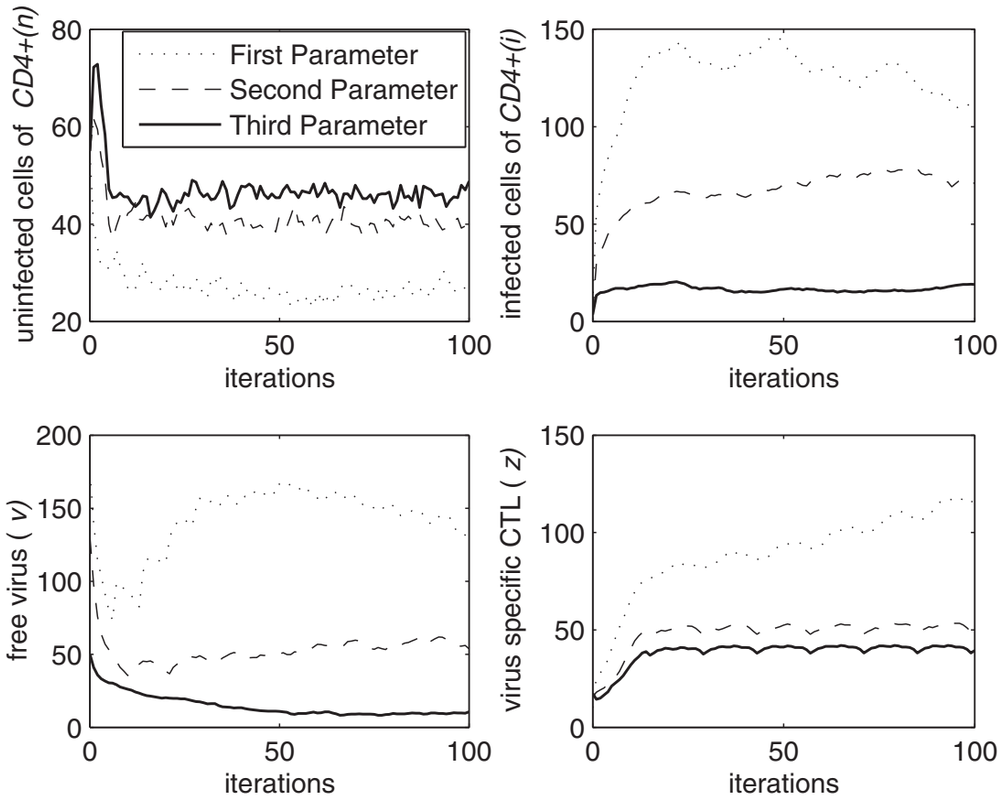


Fig. 20. Averages of the Blood-Tor System with Treatment beginning at $t = 0$.

$\triangle t$. The treatment response (C_r) in terms of the ratio of the averages $\overline{v_{p_1}}$ and $\overline{v_{p_2}}$ signalizes the treatment efficiency. Therefore, we have

$$C_r = \frac{\overline{v_{p_1}}}{\overline{v_{p_2}}} = \frac{\frac{\sum v_{p_1}}{\triangle t}}{\frac{\sum v_{p_2}}{\triangle t}} = \frac{\sum v_{p_1}}{\sum v_{p_2}}. \tag{4}$$

To illustrate the use of (4) with $\triangle t = 100$ we obtain $\overline{v_{p_f}} = 139.24$ and $\overline{v_{p_s}} = 50.71$. The averages $\overline{v_{p_f}}$ and $\overline{v_{p_s}}$ were computed using the outputs of the cellular automaton. Thus, the response ratio between the first and second patient parameters is

$$C_{r_{fs}} = \frac{\overline{v_{p_f}}}{\overline{v_{p_s}}} = \frac{139.24}{50.71} = 2.74.$$

The remaining cases are similar. Notice that, for the example just discussed, patient p_s response is twice as better than patient p_f. The values of $\overline{v_{p_f}}$ and $\overline{v_{p_s}}$ are averages of 30 runs of the model.

6.3 Conclusion

The sections 4 and 5 introduced a cellular automata approach to model HIV positive behavior in two cases: without and with antiretroviral treatment. An interesting characteristic of the

model is its ability to approximate the trajectories of all phases of the HIV history. Most models suggested so far emphasize the asymptomatic phase only. Moreover, the similarity of the solutions of the cellular automata models with the natural history (Fig. 11) gives enough evidence that they reproduce the actual HIV dynamics appropriately. The Blood-Tor System with treatment taken into account approximates the dynamics of HIV infection in the blood stream of HIV positive individuals under antiretroviral therapy. The outputs of the fuzzy rule-based system provide the percentage of infected $CD4+$ cells and the period of virus replication, given information about medication potency and individual adhesion to treatment. Using the outputs of the fuzzy rule-based system, the cellular automaton can be run to reproduce the trajectory of uninfected cells, infected cells of lymphocytes T of $CD4+$, free virus particles and specific antibodies CTL (cytotoxic T lymphocyte).

6.4 Computational graphical interface

We have used *Matlab 7.0* to build our computational graphical interface for the Blood-Tor system (see its initial interface in Fig. 21). To set up your own simulation, the following two

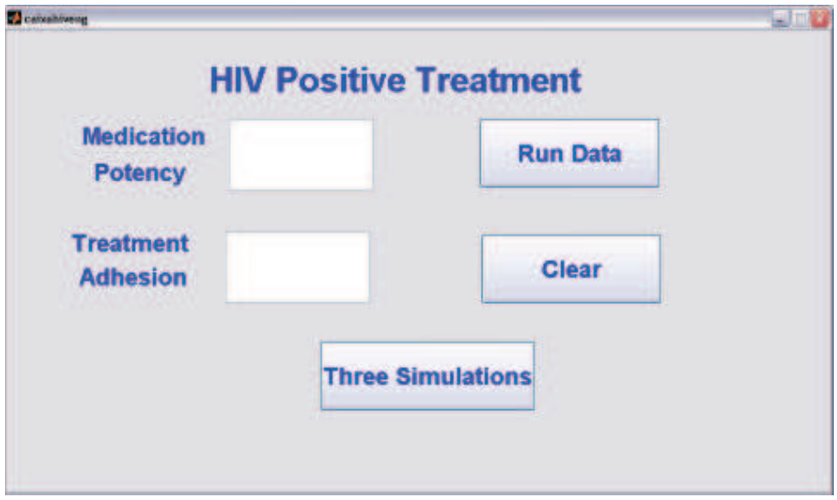


Fig. 21. Computational Graphical Interface of Blood-Tor.

parameters need to be chosen: 1. medication potency; 2. treatment adhesion. Furthermore, at the end of each simulation, the graphs of the uninfected cells of $CD4+$, infected cells of $CD4+$, free virus and virus specific antibodies as a function of time are plotted. If the user press the Three Simulations button, the simulation is carried out using the data (treatment adhesion and medication potency) of three HIV positive individuals shown in Table 6.

7. Conclusion

The interaction of multidisciplinary areas is very important to construct and strength biological mathematical models. For instance, the interaction of mathematical modeling and clinical research was crucial in understanding essential features of the HIV infection dynamics. Identifying that HIV is a dynamic disease which encompass different time scales (hours, days, weeks, months and years) was a conclusion that resulted of mathematical modeling combined with perturbation experiments. It was then to identify that these time scales correspond

to important biological processes underlying HIV infection. This knowledge is associated for instance with the recommendation of changing the treatment from monotherapy to combination antiretroviral. After that, HIV has become a treatable chronic disease, with HIV mortality rates approaching those of the general population. Another important practical message from modeling is the necessity that patients continue with the antiretroviral treatment for a period of at least 2-3 years after virus is no longer detectable in blood (Perelson & Nelson, 1999; Yazdanpanah, 2009). In this context, CA compared to differential equations approaches are better choices for modeling HIV infection since they can deal with the variety of observed time scales and also can incorporate the heterogeneity of populations and the local interactions (Sloot et al., 2002). It also important to address questions concerning the sensitivity to parameters raised for instance by Strain & Levine (2002) on the Zorzenon dos Santos & Coutinho (2001) CA model. Burkhead et al. (2009) presented rigorous mathematical results about the time scales and other dynamical aspects of the last model as well as discussed parameter and model changes and their consequences. They gave explanations for the timing in the model supported by numerical observations. The presented results show that fuzzy set theory is a powerful tool to deal with the uncertain, imprecise nature of the virus dynamics. Besides the discussion on mathematical aspects of the models, it is also important to be aware of questions posed by recent studies on HIV and AIDS. Yazdanpanah (2009) discussed the challenges posed by new antiretroviral agents for the management of treatment-experienced patients. They point out it is important to know how to optimize the pairing and sequencing of recently available antiretroviral agents in order to further improve long-term treatment efficacy in patients with multidrug-resistant HIV infection.

In further researches, a cellular automaton that represents initially the blood stream of an individual HIV positive without treatment and afterwards the same individual with treatment would be our main objective.

8. Acknowledgments

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Cellular automata make up a class of completely discrete dynamical systems, which have became a core subject in the sciences of complexity due to their conceptual simplicity, easiness of implementation for computer simulation, and their ability to exhibit a wide variety of amazingly complex behavior. The feature of simplicity behind complexity of cellular automata has attracted the researchers' attention from a wide range of divergent fields of study of science, which extend from the exact disciplines of mathematical physics up to the social ones, and beyond. Numerous complex systems containing many discrete elements with local interactions have been and are being conveniently modelled as cellular automata. In this book, the versatility of cellular automata as models for a wide diversity of complex systems is underlined through the study of a number of outstanding problems using these innovative techniques for modelling and simulation.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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