MicroCASim: An Automata Network Simulator Applied to the Competition Between Microparasites and Host Immune Response

Luciana B. Furlan[1,2], Henrique F. Gagliardi[2,3], Fabrício A.B. da Silva[3], Ivan T. Pisa[1], and Domingos Alves[2]

[1] Departamento de Informática em Saúde (DIS), UNIFESP, São Paulo, SP, Brazil
lubenzoni@yahoo.com.br, ivanpisa@dis.epm.br
[2] Laboratório de Computação Científica Aplicada à Saúde Coletiva (LCCASC),
UNISANTOS, Santos, SP, Brazil
henrique.gagliardi@gmail.com, quiron@unisantos.br
[3] Programa de Mestrado em Informática, UNISANTOS, Santos, SP, Brazil
fabricio@unisantos.br

Abstract. In this work we had developed an alternative model framework to study the concept of immunological memory by proposing as a simplified model for the interaction dynamics between a population of pathogens and the immunological system. The model is based on a probabilistic cellular automata which allows relatively easy inclusion of some of the real immunological systems in a transparently biological manner. The resulting virtual laboratory is called Microscopic Cellular Automata Simulator (*MicroCASim*), a software whose basic idea is to create a tool to assist the visualization of the interaction dynamics of these entities *in silico*.
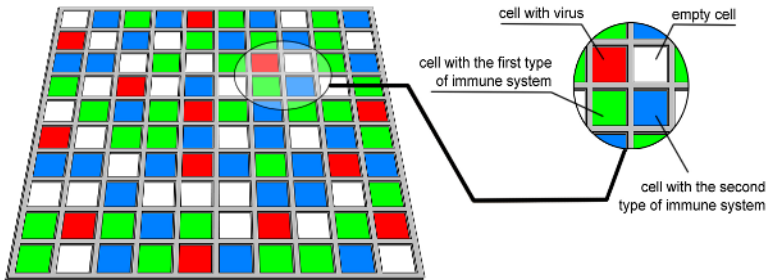
1 Introduction

The antigen-specific mechanisms of lymphocytes (T cells and B cells) are the most advanced and most precise mechanism of host defense. These cells are also responsible for the development of immunological memory, a hallmark of the adaptive immune response. This memory, which stores its encounters with invaders, enables humans to rapidly clear, or even prevent altogether, infection by pathogens which they have been previously infected [1]. Whether such immunity is maintained through constant exposure to infection via long-lived clones of lymphocytes that are able to recognize specific antigens and maintain antibody production in the absence of repeated exposure, or via the persistence of the microparasite at low levels of abundance within the host, remains unclear stil [1].

In the complex area of the interacting immune system, when there is potentially insufficient information available to construct a detailed model, cellular automata can be used [1-3]. There have been few models using the concept of cellular automata, in which the body is depicted as a grid [3,4]. We address this issue by describing in this work the implementation of Microscopic Cellular Automata Simulator (MicroCASim)*,* a software to simulate the competition between the population of *effectors* cells (T and B lymphocytes) and the population of pathogens, based on a generalized

probabilistic cellular automata [4]. The remainder of the paper is organized as follows. In the next Section we present the set of cellular automata rules that govern the interaction of the populations of effectors cells and pathogens. The MicroCASim itself is presented in the Section 3. Finally, some concluding remarks are stated in Section 4.

2   The Alternative Probabilistic Cellular Automata Model

Consider a discrete dynamical system where a population of *N* entities is distributed on the sites of a bi-dimensional square lattice (the virtual lymph node) $M = m_{ij}$ (where *i* and *j* may vary from (1,L) for *L, N = L x L*). Each individual site is assigned to receive three specific attributes: (1) a spatial address or lattice position (*i,j*); (2) a set of possible *occupation states* where each site is either empty or occupied by a T cell, a B cell and a pathogen (Fig. 1), and finally (3) an period τ_i, specifying the number of units of time an entity of type *i* can die.


Fig. 1. Schematic representation of the virtual lymph grid

The dynamics of the system is modeled by three main features: the mobility of its inner elements, the competition between its elements and its reproduction along the time. Mobility is modeled as a diffusion process using the Tofoli-Margolus scheme [5]. We use two diffusion steps within each simulation time step that are defined as follows: the lattice is divided in blocks of 2x2 cells and each block has a p_{RE} probability to rotate 90° and p_T to translate.

The competition is modeled by a predator-pray mechanism of interaction which the effectors cells can kill each virus with an estimated probability when a local contact is established with the pathogen on its neighborhood. In equation 1, we can see the definition of the probability where a virus occupying a site being eliminated due the presence of n_1 effectors cells from type 1 and n_2 from type 2 in its neighborhood:

$$Pc = 1 - (1 - \lambda_1)^{n_1} * (1 - \lambda_2)^{n_2} \tag{1}$$

which λ_i is the probability of a type *i* immune system cell to kill a virus cell and 1- λ_i being the probability of this type of cell to do not kill a virus cell when rounded by n_i cells of type *i*. Therefore, the defined probability in equation 1 is the probability that both immune system cells to eliminate the virus. Schematically, this mechanism works as follows:
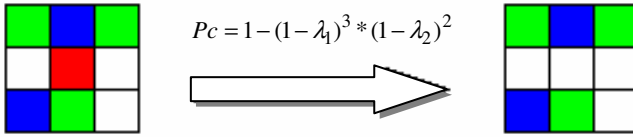
Fig. 2. In the figure we observe that *central cell* changed from a *vírus* to an *empty cell*. The *empty cell* is represented by *white spaces*. Here we have $n_1=3$ and $n_2=2$.

For effectors cells, first we ensure that a constant amount of cells will enter the system after a particular instant of time τ that the first virus has entered in the system and replicated itself. Here, the effectors cells of type i depend on the number of viruses entered the system. The same kind of dependency also occurs for the effectors cells of the type j that depends on the number of effectors cells of type i to enter on the system. After that, this procedure is modified to allow that entrance of effectors cells is proportional to the quantity of virus in the system, i.e.:

$$p_{Ci} = \frac{\rho_1 (N_v + N_{Cj})}{N} \qquad (2)$$

whose ρ_i is a parameter related to the probability of the immune system recognize the virus (eq. 2). The replication can be divided into two phases: virus and immune system replication, which replicates it selves by its own way. Every element of the system has its own time life.

3   The *MicroCASim* Software System

The MicroCASim software system is a simulation environment for the study and analysis of these models with their own probabilistic rules. The simulation was implemented using object oriented methodology and the C++ programming language was chosen for this. The system architecture is composed of four distinct modules: specification, simulation, visualization and analysis. In the specification module the user can configure all the parameters of each available model through a setup window. At each simulation update, the replication, competition and mobility mechanisms of elements are executed, respectively and the resulting data is sent to the visualization module to display the simulation process to the user (Fig. 3).

The visualization module offers also controls to adjust the velocity, simulation animation settings, and a graphic window to visualize simulation current status. Particularly, the Fig. 3 displays a very interesting simulation scenario. We can observe the model with action of a regulatory network with two kinds of immune system cells interacting and a replicating antigen. Its worth to note that there is a stationary behavior due to the coexistence between the B and T cells, which produces in the system an immunological memory effect.

Thus, if the same virus infects again the system, its response will be faster than the previous one, eliminating the menace in a short time. Furthermore, through the analysis module we are able to see the average progression of the infection and the immunological response by generating series of stochastic realizations. Hence, it is possible to sweep all the space of parameters of the present models.

| 8 days | 16 days | 41 days |
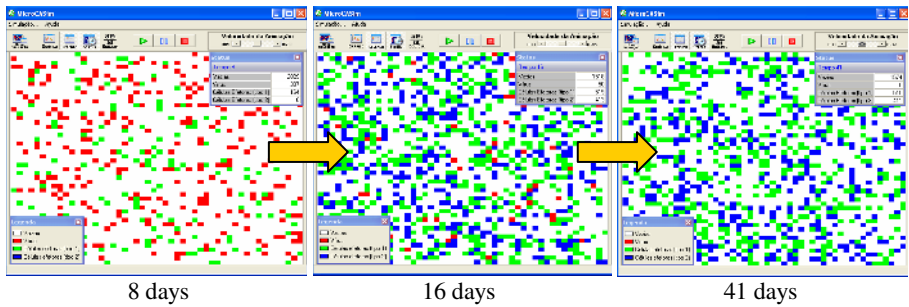
Fig. 3. A model simulation: the model with 3 types of cells

4   Conclusions

The most important feature of the model presented here is the explicitness of individual contact process and mixing. This model is a good platform where to start further expansions like incorporation of various types of interacting immunological entities. Furthermore, owing to its extreme simplicity, this formulation may be useful, in the sense of having the value of an approximation, to tackle problems in immunology.

Acknowledgements

References

1. Anderson, R.M., May, R.M.: Infectious Diseases of Humans. Oxford, U.K.: Oxford University Press (1991).
2. Seiden, P.E., Celada, F.: A model for simulating cognate recognition and response in the immune system. J. Theor. Biol., Vol. 158. (1992) 329-357.
3. Celada, F., Seiden, P.E.: A computer model of cellular interaction in the immune system. Immunology Today, Vol. 13. (1992) 56-62.
4. Alves, D., Hass, V., Caliri, A.: The predictive power of R_0 in an epidemic probabilistic model. Journal of Biological Physics, Vol.29. 1 (2003) 63.
5. Tofoli, T., Margolus, N.: Cellular Automata Machines: A New Environment for Modeling. MIT Press (1987).