

Modeling the Adaptive Immune Response in HIV Infection Using a Cellular Automata

Khabouze Mostafa¹, Hattaf Khalid², Yousfi Noura³

^{1,3}Department of Mathematics and Computer Science, Faculty of Sciences
Ben M' Sik, Hassan II University, P.O Box 7955 Sidi Othman,
Casablanca, Morocco

¹Khabouzemostafa@gmail.com

³nourayousfi@hotmail.com

²Regional Centre for Careers Education and Training (CRC CET), Derb Ghalef,
Casablanca, Morocco

²k.Hattaf@yahoo.fr

Abstract: *The public health issues have a lot of importance in our society, particularly the Human Immunodeficiency Virus (HIV) infection. Many models based on ordinary differential equations (ODEs) or partial differential equations (PDEs) have explained different aspects of the dynamics of the virus-immune system interaction. Although, they assume that various populations of cells and viruses have been homogeneously distributed over the space and time in which the infection takes place. In this paper, we present a cellular automaton (CA) that models the interaction between the cytotoxic T lymphocytes (CTLs) Cells and the immunoglobulin of the immune system and HIV in blood stream. Our approach is based on simple calculation rules that are easy to implement. The results of our (CA), taking into account the role of the two components of the adaptive immune system to overcome HIV infection reproduces the acute stage and the beginning of the second phase of the HIV infection development.*

Keywords: CTLs, Antibodies, HIV, Cellular Automata.

1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) which is caused by the propagation of the HIV infection has become a worldwide health problem, because yearly it is responsible for millions of deaths in the globe. When HIV infects the body, it is propagated throughout the lymphatic tissues. When it reaches the blood stream its main target is the lymphocyte-T CD4+ (CD4) cells. On the other side, the body triggers the adaptive immune response, which is characterized in two ways: cellular immune response and humoral immune response in order to eradicate this strange object. The humoral response is characterized by the production of antibodies by certain directed lymphocytes against all viral proteins. Antibodies, also called immunoglobulin, are proteins synthesized by the B lymphocytes. Generally an HIV-infected patient develops a high concentration of anti HIV antibodies between one and three months after infection [1]. The cellular response is based on direct action by some CD8+ T-lymphocytes (called cytotoxic) and eliminates infected cells directly. They are cells charged to maintain the integrity of the cellular populations by destroying the cells infected by viruses, the cells modified by a change, like the cancer cells, or the grafted cells. They intervene in immunity with cellular mediation. The cytotoxic T lymphocytes are one of the main mechanisms involved in viral control [2]. The HIV infection is detected by the laboratory

observation of the amount of virus HIV-RNA and the number of the helper cells CD4 in blood. Clinically, it is known that the HIV infection exhibits three phases [3, 4], the primary phase, which is described by relatively short period of time (in days), after the virus invaded the body, a notable decrease of the immune cell count CD4, following by a sharp decline with an increase of the amount of the virus. The clinical latency phase measured from one to ten years, in this phase, the immune system reduces the virus and the rate of viral production reaches a lower level for a long time. The third phase of the infection is characterized when the level of the concentration of the T cells is lower than a critical value (about 30%). Figure 1 shows the natural history of HIV infection dynamics as currently accepted by [4]. Recently, many researchers have used mathematical models [5, 6, 7, 8] in order to understand the mechanism of the dynamics involved in the interaction between the acquired immune system and the HIV infection. Most of these models have been done using ODEs or PDEs approaches [9, 10, 11, 12, 13]. For example in [12, 13], Hattaf and Yousfi presented models which have good explained different aspects of the dynamics of the HIV immune system interaction. Although, they assumed that various populations of cells and viruses have been homogeneously distributed over the space and time in which the infection takes place and they describe the system using continuous functions. Due to the discrete nature and the inhomogeneity of the biological entities involved in the phenomena, we propose in this paper a model

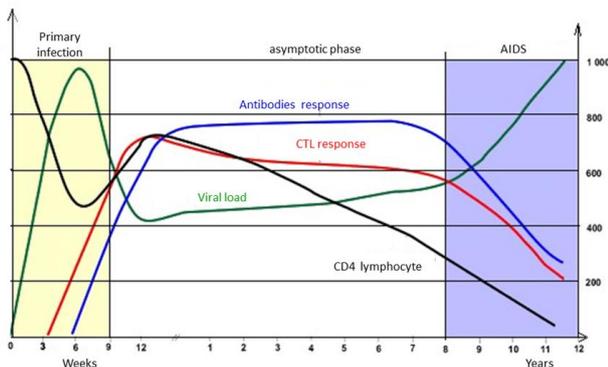


Figure 1: The natural history of HIV infection [4].

to simulate the dynamic interaction between the adaptive immune system and the HIV infection based on a cellular automaton (CA). To explain this dynamics of HIV infection, many authors [14, 15, 16, 17, 18, 19] have developed different CA models. The popular of them was presented in [14], the authors built a CA with four states to model the evolution of the HIV infection, namely the healthy, the first infected phase, the second infected phase, the phase before the cell dies and the dead state. Their model matched the clinically experienced three phases of the HIV infection. In [15], the CA proposed by Santos et al. was extended to study the dynamics of the drug therapy in HIV infection. The model simulated the four phases of infection dynamics with drug treatment: acute, chronic, drug treatment response and the onset of AIDS. Shi et al. proposed in [16], a CA model for HIV dynamics by including the virus replication cycle and a mechanism for drug therapy. They assumed that the viral load is strictly proportional to the number of infected cells. Recently, Precharattana et al. presented in [17], a CA model by introducing explicitly the role of the dendritic and CD8+ cells from the immune system. Their CA model reproduced the acute phase of the HIV infection. The majority of these CA models studied the dynamics in the lymph node. However, most clinical indications of progressing are based on blood data, because these data are most easily obtained. Furthermore the bloodstream Toroidal can be model with a 2-D CA because it is shaped like a torus in which coexists all type of cells [18, 19]. Therefore it is useful to consider the dynamics in the plasma compartments. Thus, in our model, we consider cells from blood stream to study HIV infection. In [18, 19], Jafelice et al. built a two-dimensional CA to describe and understand the interaction between HIV and the immune system based on blood data. Nevertheless, they considered only the cellular response from the immune system. The novelty of our model is that takes also into account of the humoral response, which has a crucial role in the adaptive immune system. Our spatially structured model represents an important step forward in understanding the virus infection from the dynamic point of view and allows a detailed look at local behavior. The simulation results show that our model reproduces the evolution of the HIV infection without medical treatment, in particular, the acute stage. This paper is organized as follows: In next Section, an overview of CA and a definition of bidimensional CA is given. The proposed model is introduced in section 3. The results and some graphical simulations are shown in section 4. Finally, in the last section

the conclusion and future work are presented.

2. Overview of Cellular Automata

Cellular automata (CA) are discrete dynamical systems, whose behavior is completely specified by the terms of a local relation and variable states, namely the values associated with locations of grid cells are driven by simple rules that depend on the states of the neighbors of each variable. They describe the behavior of discrete systems in space, time, and state. Many epidemic complex systems containing several discrete elements with local interactions have been well modeled by the CA [18, 19]. They have been successfully applied in various fields such as finance, medicine, engineering, physics and biology. For example, in medicine, the CA have been widely used in medical diagnostics, detection and evaluation of medical conditions and cost estimation of treatment [22, 23, 24]. Due to their conceptual simplicity, ease of implementation for the numerical simulation, and the ability to expose a variety of complex behavior, the CA are a class of completely distinct dynamical systems, which has become a central topic in the sciences of complexity. In the 1950s von Neumann and Ulam introduced the CA in order to model a massively parallel and complex system such as the brain. The method became popular in the 1970s with the “Game of Life” of John Conway, popularized by Martin Gardner [25]. In his books, Wolfram [26, 27] presented a large study of properties of CA.

3. The Model

Cellular In order to model the life cycle of the interaction between the acquired immune system and the HIV infection in blood data, we use a two-dimensional CA which can simulate the bloodstream toroidal system. The set of states is composed of six states, namely, the uninfected cell state (T), the infected cell state (I), the state represented by free HIV (V), antibody (AB), the CTL (CTL), and the death state (D). In the next section we describe the behavior of each cell and the rules of the update of the state covered by each of them after one iteration. Due to the kind of contact between different particles (cells), we use in this CA the Neumann Neighborhood with radius one.

Update of uninfected cells (T): A specific number of uninfected cells will be randomly distributed over the grid. Such cells become infected if there is a virus in their neighborhood, otherwise they age after each iteration with one and die if they reach their lifespan τ_T . After each iteration such cells are produced with a giving rate Pr_T and are randomly distributed.

Update of infected cells (I): The infected cells are produced by the presence of virus in the neighborhood of uninfected cells. They become a free virus (HIV) with a given probability p or they age after each iteration and die 4 with probability $(1-p)$, when they reach their lifespan τ_I . An infected cell will be killed by a CTL existing in its neighborhood.

Update of free virus (V): When the HIV invades the body, it searches for uninfected cells (CD4) in its neighborhood. When it meets one of them, the host cell (T) becomes infected. The virus ages and can be either died when it reaches its lifespan τ_V or can be neutralized by the presence of an antibody in its neighborhood.

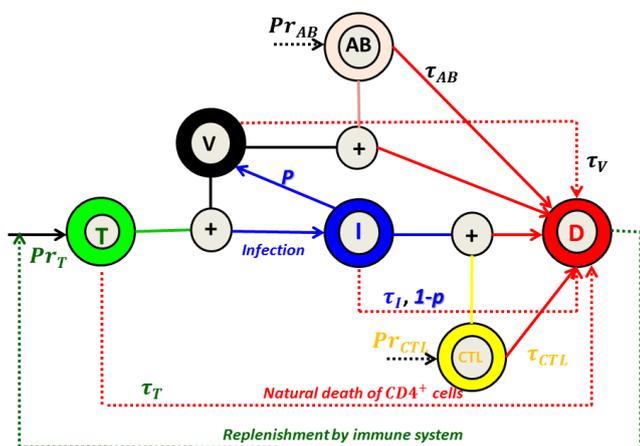


Figure 2: Graph of the cellular automata that illustrates the interaction of different cells in the blood stream by the HIV infection with Pr_x and τ_x are respectively the production rate and the life span time of a cell of type x

Update of CTLs (CTL): The CTLs kill the HIV found in their neighborhood. After each iteration, they are produced with rate Pr_{CTL} and randomly distributed and they age by one. When they reach their lifespan τ_{CTL} , they die.

Update of antibodies (AB): The main role of the particular antibodies is to control the HIV. They eradicate each particle of the virus found in their neighborhood, and like the CTL, they age by one after each iteration and die when their lifespan τ_{AB} is reached. After each iteration they are produced with rate Pr_{AB}

Update of dead cells (D): We assume that dead cells in the blood stream can become uninfected cells due to the replenishment process. For testing and illustrating the working of our CA we present in the next section a simulation.

4. Simulation and Results

For the simulation of our model we have developed a program with C Sharp language. We have used the data grid view as structure of data to represent the 2-D CA. Uninfected cells, infected cells, free virus particles, CTLs and antibodies are represented respectively by green, blue, black, yellow and white colors. The user can instantly view the interaction between different cell types as represented in Figure 3. To ensure the dynamic of the behavior of cells as in the real case, they are randomly distributed on the grid.

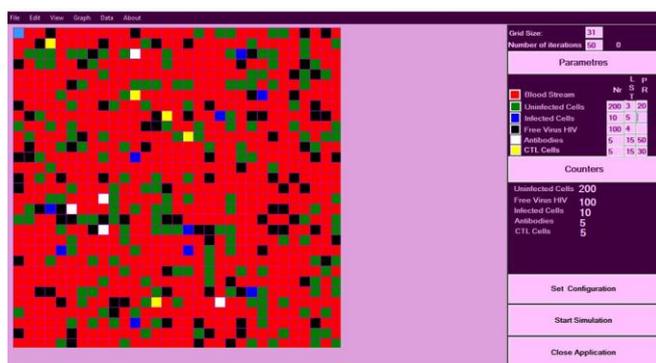


Figure 3: A snapshot of the software that simulates the interaction between the adaptive immune cells and the HIV infection are randomly distributed on the grid.

We note that each iteration corresponds to a week's time. We run the program several times with different initial configurations of input parameter values. We have considered a square grid of size 31x31 and we have chosen the values of the following parameters:

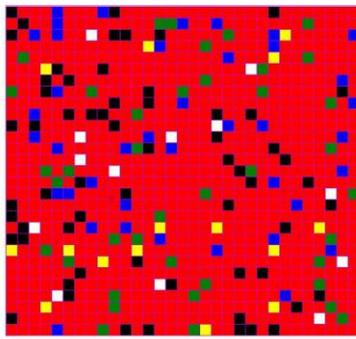
- The start number of uninfected cells CD4, which are target of the virus, is equal to 200.
- The number of infected CD4 cells is about 0.05 % [14] of the healthy cells.
- The number of free virus particles: we have considered that the virus exists in the body and we have taken 0.5% [Ad-hoc] of the host cells.
- The initial number of the cytotoxic T lymphocytes is 5 [Ad-hoc].

Table1: Model parameters used for the cellular automata

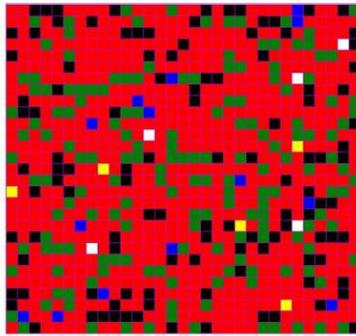
Parameter	Definition	Value	Reference
L	Lattice size, with $L*L$ is the total number of cells in the Lattice	31	Ad hoc
P	The probability that an infected cell becomes a virus	0.99	Ad hoc
τ_T	Lifespan time of uninfected Cells	3	[18, 19]
Pr_T	Production rate of uninfected Cells	20	Ad hoc
N_T	Initial number of uninfected Cells	200	[18, 19]
τ_I	Life span of infected cells	5	[18, 19]
τ_{AB}	Life span of antibodies	15	Ad hoc
Pr_{AB}	Production rate of antibodies	50	Ad hoc
τ_{CTL}	Lifespan time of CTLs	15	[18, 19]
Pr_{CTL}	Production rate of CTLs	30	Ad hoc
τ_V	Life span of free virus Cells	4	[18, 19]
N_i	Number of iterations	50	[18, 19]

- The start number of specific antibodies is the same as of the number of CTLs equals to 5 [Adhoc].

Table1 lists values and definition of parameters used in this model. The CA based model, that describes the behavior of the interaction between the adaptive immune system and HIV is simulated. Figure 4-a shows the initial configuration of cell states. Figure 4-b describes the state of the CA after two months. There is an increase in the number of antibodies and CTLs and a decline in number of other cells. As shown in figure 5-a, the evolution of the uninfected cells can be divided into two different phases. During the first days after infection, there is an exponentially decrease of the number of CD4, which corresponds to the acute phase of the HIV infection. After the fifth week, the number of uninfected cells starts to stabilize and it remains at the same level during the next months with a slight change that is the latency phase.



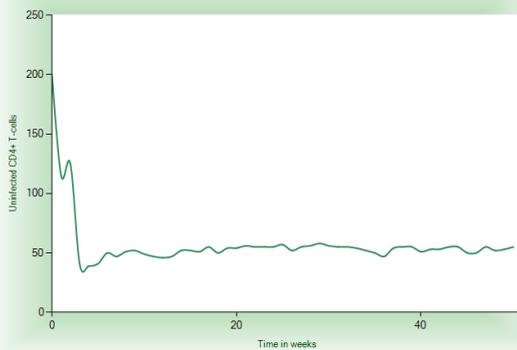
(a)



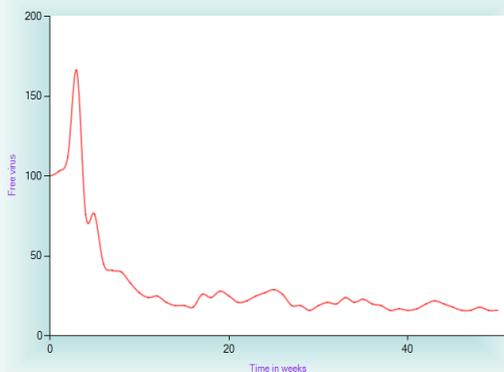
(b)

Figure 4: Snapshots of states of CA: (a) Start state, (b) State after two months.

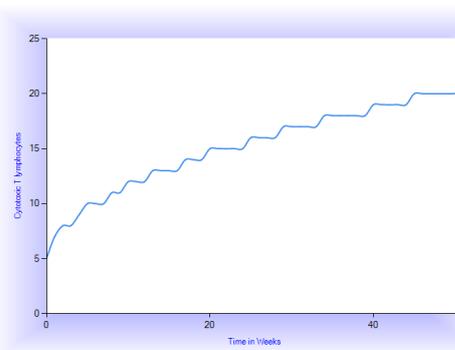
The curve of development of viral load in the body is increased during the first weeks as described in figure 5-b. It reaches its peak in the 5th week, which it corresponds to the minimum point of the number of uninfected cells.



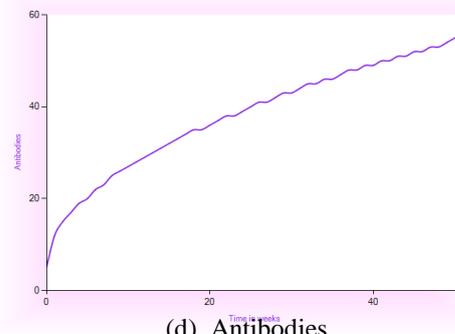
(a) Uninfected CD4+



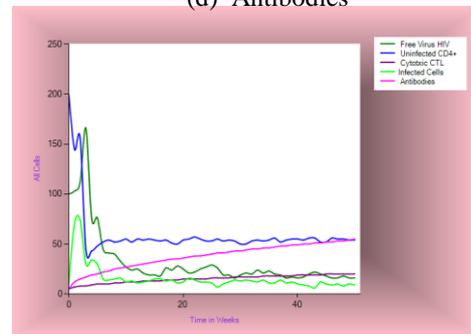
(b) Free Virus



(c) CTLs



(d) Antibodies



(e) All Cells

Figure 5: Simulation results of the CA based model

Afterwards, the evolution of the infection has become more stable with a small change, which it explains the beginning of the second phase of the infection. The viral load is created by the proliferation of the infected cells, thus the evolution of these last over the time is nearly the same as of the development of the viral load with a step time (one week) backward. After the invasion of HIV in the human body, the immune system triggers cellular response via antibodies to attack the virus and humoral response with CTLs to clean the body from infected cells and limit the spread of the HIV. Figure 5-c and figure 5-d shows respectively the evolution of the CTLs and the antibodies over time. The numbers of these two last increase and multiply over time. That is the normal behavior of the acquired immune system. Figure 5-e includes the development of all cells. The simulation results show good agreement with the behavior that is observed in practice as shown in figure 1, which implies that Cellular Automata is an effective analyzing method in the simulation of strategic decision for drug treatments.

5. Conclusion and Future Work

In this present paper, we propose a new mathematical model based on CA approach to simulate the interaction between the adaptive immune system and the HIV. In our model we introduced the role of the CTLs and the antibodies to achieve

respectively the infected cells and the free virus. Since viral propagation and the immune response are fundamentally local, these features are of central importance. Our spatially explicit model takes into account the local interactions and the spatial inhomogeneity unlike to the well-mixed population model. Our CA is composed of six states to describe the dynamic of the HIV infection. We have developed software with an interface to instantaneous visualization that simulates the comportment of HIV and the immune system to illustrate and validate our model. The simulations obtained seem to be in agreement with the expected behavior of a real infection as shown in figure 1. In the next step we intend to extend our model for taking account of medical treatment. Also, we plan to improve our model by doing research on the values of the input parameters closer to reality. As third idea, we would perform the run time of our program involving parallel programming with GPUs and the programming language CUDA in order to consider a larger number of cells and to study the infection for years (larger number of iterations).

References

- [1] Moore, J., Sattentau, Q., Wyatt, R. Sodroski, J. *Probing the structure of the human immunodeficiency virus surface glycoprotein gp120 with a panel of monoclonal antibodies.* Journal of Virology 68, 469484. 1994.
- [2] Streeck, H., Jolin, J., Qi, Y., Yassine-Diab, B., Johnson, R., Kwon, D., et al. *HIV-1-specific CD8+ T cell responses during primary infection are major determinants of the viral set point and loss of CD4+ T cells.* Journal of Virology 83, 76417648. 2009.
- [3] Pantaleo G, Graziosi C, Fauci AS. *New concepts in the immunopathogenesis of human immunodeficiency virus infection.* N Engl J Med. 1993 Feb 4; 328(5):327-35.
- [4] J. Drylewicz, *Dynamical modelling of host-pathogen interaction applied to primary HIV infection.* PhD thesis, available online: <http://tel.archives-ouvertes.fr/tel-00433430> 2009. Accessed: Sept.10, 2013.
- [5] Isham V. *Mathematical modelling of the transmission dynamics of HIV infection and AIDS.* *Mathematical and Computer Modelling*, Volume 12, Issue 9, 1989, Page 1187.
- [6] Jennifer Ng, Orav E J. *A generalized chain binomial model with application to HIV infection.* *Mathematical Biosciences*, Volume 101, Issue 1, September 1990, Pages 99-119.
- [7] Yates A, Chan C W, Callard R E, George A J T, Stark J. *An Approach to Modelling in Immunology.* *Briefings in Bioinformatics* (2001) 245-257.
- [8] Hraba T, Dolezal J, Celikovský S. *Model-Based Analysis of CD4+ Lymphocyte Dynamics In HIV Infected Individuals.* *Immunobiology*, Volume 181, Issue 1, August 1990, Pages 108-118.
- [9] Kirschner D, Perelson A. *A Model for the Immune System Response to HIV: AZT Treatment Studies.* In: Arino O, Axelrod D, Kimmel M, Langlais M (eds): *Mathematical Population Dynamics: Analysis of Heterogeneity and Theory of Epidemics* (Wuerz Publishing, Winnipeg, 1995) pp. 295-310.
- [10] Kirschner D. *Using mathematics to understand HIV immune dynamics.* *AMS Notices* pp.191-202, February 1996.
- [11] Nowak M. A., Bangham C. R. M. *Population Dynamics of Immune Responses to Persistent Viruses.* *Science* 272(5258). (1996). pages 7479.
- [12] Hattaf K. and Yousfi N., *Dynamics of HIV infection model with therapy and cure rate.* *International Journal of Tomography and Statistics.* vol. 16. no. 11. pp. 7480, 2011.
- [13] Hattaf K. and Yousfi N. *Optimal Control of a Delayed HIV Infection Model with Immune Response Using an Efficient Numerical Method.* *ISRN Biomathematics.* Volume 2012 (2012), Article ID 215124, 7 pages. .
- [14] Zorzenon dos Santos R. M. and Coutinho S., *Dynamics of HIV infection: A cellular automata approach.* *Phys. Rev. Lett.*, 87(16):16810214, 2001. .
- [15] P. Sloom, F. Chen, C. Boucher, *Cellular automata model of drug therapy for HIV infection.* In: *Lecture Notes in Computer Science*, Springer-Verlag, Berlin, 2002, pp. 282-293.
- [16] V. Shi, A. Tridane, Y. Kuang, *A viral load-based cellular automata approach to modeling HIV dynamics and drug treatment.* *J. Theor. Biol.* 253 (2008) 2435. .
- [17] M. Precharattana, and W. Triampo. *Stochastic cellular automata for HIV infection with effects of cell-mediated immunity.* *Proceedings of The 2012 World Congress in Computer Science, Computer Engineering, and Applied Computing.* Available online: Accessed: Jan.10.2014. <http://worldcomp.org/p2012/CSC2.html>.
- [18] R. M. Jafelice, B.F.Z. Bechara, L.C. Barros, R.C. Bassanezi, F. Gomide, *Cellular automata with fuzzy parameters in microscopic study of positive HIV individuals, Mathematical and Computer Modelling.* Volume 50, Issues 12, July 2009, Pages 3244.
- [19] Jafelice R. M. and Nunes da Silva P., *Studies on Population Dynamics Using Cellular Automata. Cellular Automata - Simplicity Behind Complexity*, Dr. Alejandro Salcido (Ed.), ISBN: 978-953-307-230-2, InTech, DOI: 10.5772/15939, 2011.
- [20] X. Xiao, S. Shao, and K. Chou, *A probability cellular automaton model for hepatitis. B viral infections*, *BBRC* 342 (2006), 605-610.
- [21] C. Wan, Y. Liu, X.Tu, Y. Zhang, J. Xu, D. Lin, J.Luo, F. Chen, H. Wu, *A cellular automaton model of Schistosoma japonicum infection.* *Acta Tropica*, Volume 126, Issue 3, June 2013, Pages 256-264.
- [22] J. E. Schmitz, A. R. Kansal, S. Torquato, *A Cellular Automaton Model of Brain Tumor Treatment and Resistance.* *Journal of Theoretical Medicine* Volume 4, Pages 223-239, 2002.
- [23] F. Barigou, B. Atmani, B. Beldjilali, *Using a Cellular Automaton to Extract Medical Information from Clinical Reports.* *Journal of Information Processing Systems*, 2012, 8(1), pp. 67-84.
- [24] B. Placzek, *Rough sets in identification of cellular automata for medical image processing.* *Journal of medical informatics and technologies* Vol. 22. 2013.
- [25] Gardner, M., *Mathematical Games: The Fantastic Combinations of John Conways New Solitaire Game Life.* *Scientific American.* 223 (October 1970): 120-123.
- [26] Wolfram, S. *Universality and complexity in cellular automata.* *Physica* 10D, 1 1984.
- [27] Wolfram, S. *A New Kind of Science.* Wolfram Media, January 2002.