Proceedings of the 5th WSEAS Int. Conf. on SIMULATION, MODELING AND OPTIMIZATION, Corfu, Greece, August 17-19, 2005 (pp433-438)

CA^2 : Cellular Automata Models and Self-Organized Chaos in Cancer Growth

ADAM V. ADAMOPOULOS
Medical Physics Laboratory, Department of Medicine
Democritus University of Thrace
GR-681 00, Alexandroupolis
HELLAS

Abstract: - CA^2 is a novel computer simulation program to investigate *in silico* population dynamics of cancer growth. The model is based on 2-dimensional generalized and probabilistic cellular automata with fixed lattice structure. The structural elements of the cellular automata are units that simulate real cell dynamics at cellular and inter-celular level. Each artificial unit is a 4-state element and at any instance can be in one of the following conditions: *normal, immature cancer, matured cancer,* or *dead*. Depending on cell's state, a triplet of specific time values are randomly selected and associated with it. This triplet of values corresponds to cell's *lifetime, mature period* and *dissolution time* (if dead). Simulation results of the evolution of cancer growth and the obtained population dynamics are in good agreement with both *in vitro* experiments of cell cultures and statistical (macroscopic) mathematical models of cancer growth. Furthermore, the model provides evidence of emerging non-linear complexity, self-organization and chaotic population dynamics in cancer growth. These features are related to similar observations found in dynamics at cellular and intra-cellular level. Additional evidence for the emergence of self-organized chaos at the systemic level for a growing cancer is provided from the analysis of the underlying dynamics of the biomagnetic activity emitted from various types of cancer lesions. These biomagnetic recordings were obtained using Superconductive Quantum Interference Devices (SQUIDs).

Key-Words: Cancer Growth, Cellular Automata, SQUID biomagnetometer, Biomagnetism in Cancer, Emerging Complexity, Self-Organized Chaos

1 Introduction

Investigation of the dynamics of cancer growth, proliferation and metastasis is of great importance, since it allows to us to study the role of several parameters involved. Early studies concluded to the well-known mathematical model of Gompertz, which in a simple mathematical expression describes the evolution of the volume of a growing and proliferating tumor. In mathematical terms [1], the Gompertzian model can be written as follows:

$$V(t) = V_0 e^{\frac{A}{B}(1-e^{-Bt})} \qquad 1$$

In the above relation, $V(t)$ is the tumor volume at any time t; V_0 is the initial tumor volume ($t = 0$); A and B, are model's positive parameters, with values more or less arbitrarily chosen in order the model to fit given experimental data.

Describing the model of Eq. (1) we could mention that it incorporates exponential growth, but with a time evolving exponent which is zero for $t = 0$ and increases to a saturation value, namely tents to A/B for $t \rightarrow \infty$, or practically, for large values of t (decelerating growth). By plotting $V(t)$ against t, we obtain a *one-modal sigmoid curve*, with rapid increase for small values of t, and a saturation point at $V_0 e^{A/B}$ for large enough values of t.

Despite the fact that there is no doubt that the Gompertzian model is closely related to the realistic behavior of cancer growth, due to its mathematical nature it remains deeply phenomenological and abstractive, lacking of physical interpretation for the parameters A and B, which are of macroscopic and statistical nature. In addition, the Gompertzian model can not incorporate parameters that are related to the micro-structure and the micro-dynamics of cancer growth, which are present at cellular and intra-cellular level. Nor this model takes under consideration that many tumors contain more than one clonal population with different division rates and nutritional needs which can be described

only assuming competition among cellular subpopulations [2].

Except from the above, several mathematical models have been proposed, considering exponential growth, logistic growth [3], incorporating models for the very crucial phenomenon of angiogenesis [4,5], utilizing continuum models governed by reaction-diffusion differential equations [6], description of nutrient distribution with the use of nonlinear partial differential equations [7], even mathematical models of nutrient diffusion, trophoblast invasion [8], cellular necrosis and apoptosis [9], and tumor classification using elasticity theory [10]. Despite their success, the main disadvantage of all these models remains the inability to describe micro-dynamics at cellular and sub-cellular level [11].

More realistic, "bottom-up" approaches that overcome the limitations of the mathematical models are based on cellular automata (CA). Several CA models of cancer growth have been proposed in the past, based on their ability to exhibit global behavior resulting form local interactions, to provide explanation of macroscopic phenomena using discrete, microscopic description, and their adaptability to account as simple-rules-based models of highly complex systems [12-14]. Both 2-dimensional and 3-dimensional CA models of cancer growth have been proposed, providing square or cubic lattice grids of fixed size [15-17]. Moreover, more complex models incorporating variable 3-dimensional lattice have been proposed [18, 19]. All these models were trying to provide answers on subjects such as tumor growth and proliferation, immune response, even cell migration.

Based on our previous work [20, 21], the CA model proposed here is a 2-dimensional approach for the study of cancer growth and proliferation on a fixed size lattice. The model incorporates microscopic parameters referring to cellular generation, maturity, proliferation and death. The exact values of these parameters are individually selected for each one cell. Local interactions are considered that simulate real cellular and inter-cellular behavior. Finally, the model has the ability to study the growth of cellular subpopulations, which were proliferated on the same lattice, but were characterized by different division rates and nutritional needs. Results obtained from the performed computer simulations, shown realistic macroscopic behavior that compares favorably to both experimental data and the findings of other proposed models. These results are discussed in terms of cellular (local) dynamics, as well as global behavior and in terms of emerging features, complex dynamics and self-organization.

2 Methods

Our CA model of cancer growth is based on previous work [21, 22] for cancer growth using a 2-dimensional, rectangular, fixed structured lattice, where each grid point corresponds to a single cell position. The proposed CA is generalized and probabilistic in terms that will be explained in the following. At any instance of time, each cell can be in one of the four following states:

- *Normal*, denoted by N
- *cancer*, denoted by c
- *cancer*, in division phase denoted by C
- *dead*, denoted by D

Thus, the permitted values of each cell are N, c, C or D. Each cell is characterized by a triplet of values:

- *lifetime*, T_L, related to the total period that a specific cell is alive
- *maturity period* or reproduction age, T_R, which is the time necessary a cell to become "mature enough" to divide and proliferate
- *dissolution time*, T_D, the time necessary the remaining of a dead cell to be exported and the specific grid site to be free

Due to the probabilistic nature of the proposed model, the exact values of the triplet (T_L, T_R, T_D) for each cell are individually defined in a random fashion. To be more specific, each one of these values is selected randomly from a range of corresponding permitted values with the use of pseudo-random number generators. In order the model to be able to simulate the evolution of more than one subpopulation, the definition of the triplet of values (T_L, T_R, T_D) of a cell generated after division, takes under consideration the corresponding triplet of values of the original cell. In other words, for the definition of these three vital parameters of each cell inheritance is incorporated. Thus, it can result a number of subpopulations that carry different proliferation and nutritional characteristics that are simultaneously developing and competing on the same lattice.

Finally, the mechanisms of local interactions of the CA that are simulating the real inter- and intra-cellular cellular dynamics are the following:

- N → c : a grid position that was occupied by a normal cell is taken by a new cancer cell
- c → C : an immature cancer cell gets in the proliferation phase
- C → 2c : division of a cancer cell
- c → D : death of an immature cancer cell
- C → D : death of a mature cancer cell
- N → D : death of a normal cell
- D → N : a new normal cell occupies an empty position
- D → c : a new cancer cell occupies an empty grid position

Initially, (for $t = 0$), the CA is consisted of normal cells, except a user-defined number of cells that turned to cancer cells. If the number of cancer cells is more than one for $t = 0$, then a corresponding number of cancer cells subpopulations are evolving simultaneously on the same lattice. The precise grid position of the cancer cell(s) is (are) randomly selected by the simulation program. For each time instance a pictorial representation of the CA is provided, as well as numerical results considering the number of normal cells, immature cancer cells, matured cancer cells and dead cells.

3 Results

The results of two, out of a large number of computer experiments are presented in the following. For better pictorial representation of the CA at each particular time instance, there were used different gray-scale colors to denote the corresponding type of cell on the lattice. Thus:

- *black* denotes mature cancer cells C
- *dark-grey* denotes immature cancer cells c
- *light-grey* denotes normal cells N
- *white* denotes death cells D or empty lattice positions

In Fig. 1 there are shown 6 instances of the obtained simulation results of a CA consisting of 50x50 cells. Starting from the upper-left picture of Fig. 1, a single cell is turned to cancer cell (dark-grey dot) at time $t = 0$. This cancer cell matured and was ready to divide (c → C) at time $t = 10$, as it is shown in upper-right picture (black dot). At the next time step ($t = 11$) the original cancer cell is divided and two cancer cells are shown in middle-left picture (denoted two dark-grey dots). The position of the new cancer cell was selected randomly among the available grid positions surrounding the original cancer cell. At instance for $t = 13$ the new cancer cell dies (white dot at middle-right picture), whereas the original cancer cell remains alive (dark-grey dot at the same picture). The last (lower-left and lower-right) pictures in Fig. 1 represent the death of the original cancer cell, for $t = 18$, before it manage to mature and be divided once more. This result may be unexpected, but however is common behavior in real life. For every organism, generation of a cancer cell from a normal cell, (carcinogenesis), occurs in an every day fashion. However, not all organisms will develop cancer, since as a result of the immune system response, cancer cells die at a very premature level, before they divide and proliferate.

Quite different were the obtained results that are presented in Fig. 2. In that Figure it is shown the evolution of 5 subpopulations of cancer cells. These 5 subpopulations were emerged from 5 cancer cells that appeared for $t = 0$ (upper-left picture). As we have stated before, the particular lattice positions for each one of that 5 cancer cell was chosen randomly by the program. The CA condition for $t = 50$ is shown in the upper-right picture of Fig. 2. Clearly, the 5 original cancer cells have managed to mature, divide and proliferate in the surroundings. Cancer cells are shown to be expanded further for $t = 100$, as it is shown if the lower-left picture of Fig. 2. Almost 50% of the lattice positions are occupied by either mature cancer cells (black dots), or immature cancer cells (dark-gray dots). Finally, $t = 170$ shown in the lower-right picture of Fig. 2, cancer cells have proliferate practically all over CA lattice. Only few grid positions are occupied by normal (light-grey dots) or dead (white dots) cells.

For the latter computer experiment, the evolution of the number of the cancer cells is shown in Fig. 3. The CA considered in that experiment was a 50x50 lattice, that is, it consisted of 2500 grid positions (individual cells). As it is shown in Fig. 3, for small values of time t, the number of cancer cells seems to increase almost exponentially. This is in favorable comparison with the real-life experimental results, and in good agreement with the results of the Gompertz model of (Eq. 1). For $t = 170$ and thereafter up to $t = 300$, the number of cancer cells appears to saturate to a mean value around *2340* cells and small fluctuations are observed above or below that value. Practically, the CA have reached to a dynamical equilibrium condition, with a few cancer cells to die, and a few new-born cancer cells to occupy free lattice positions resulting from the dissolution of a small number of dead cells. The evolution of the dead cells population is shown in

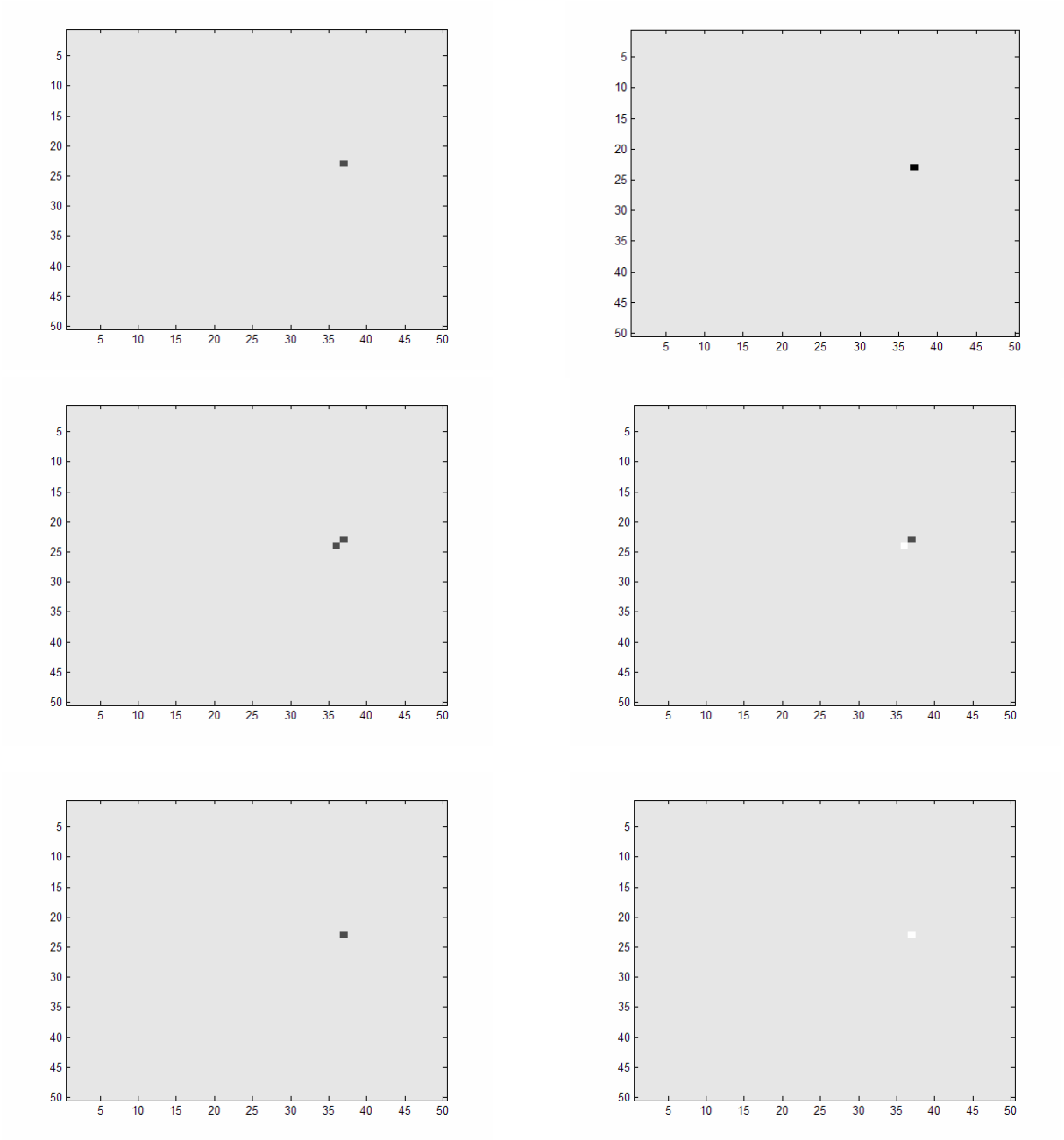

Fig. 1 Evolution of single cancer cell with no proliferation ability

Fig. 4, where after a approximately exponential increase for small values of t a saturation is observed with small fluctuations around a mean value of 160 dead cells.

4 Discussion

The aim of this work was to develop a new software tool named CA^2 for *in silico* investigation of cancer growth [18-21]. CA^2 is a discrete simulation model consisting of elements with real cell-like function. The model is based on generalized, probabilistic cellular automata with a 2 - dimensional fixed (non-variable size) lattice. Each cell is a 4-state element, and may be either a normal cell, or an immature cancer cell, or a mature (dividing) cancer cell, or finally a dead cell. Depending on its state, a cell is characterized of a triplet of values corresponding to three functional parameters: lifetime, maturity time and dissolution time (if dead). The specific values are randomly selected from user-defined ranges. Simulations like the ones presented above are typical results of the model. The obtained results clearly fit the corresponding ones derived from laboratory experiments of cancer cells cultures as well as mathematical models.

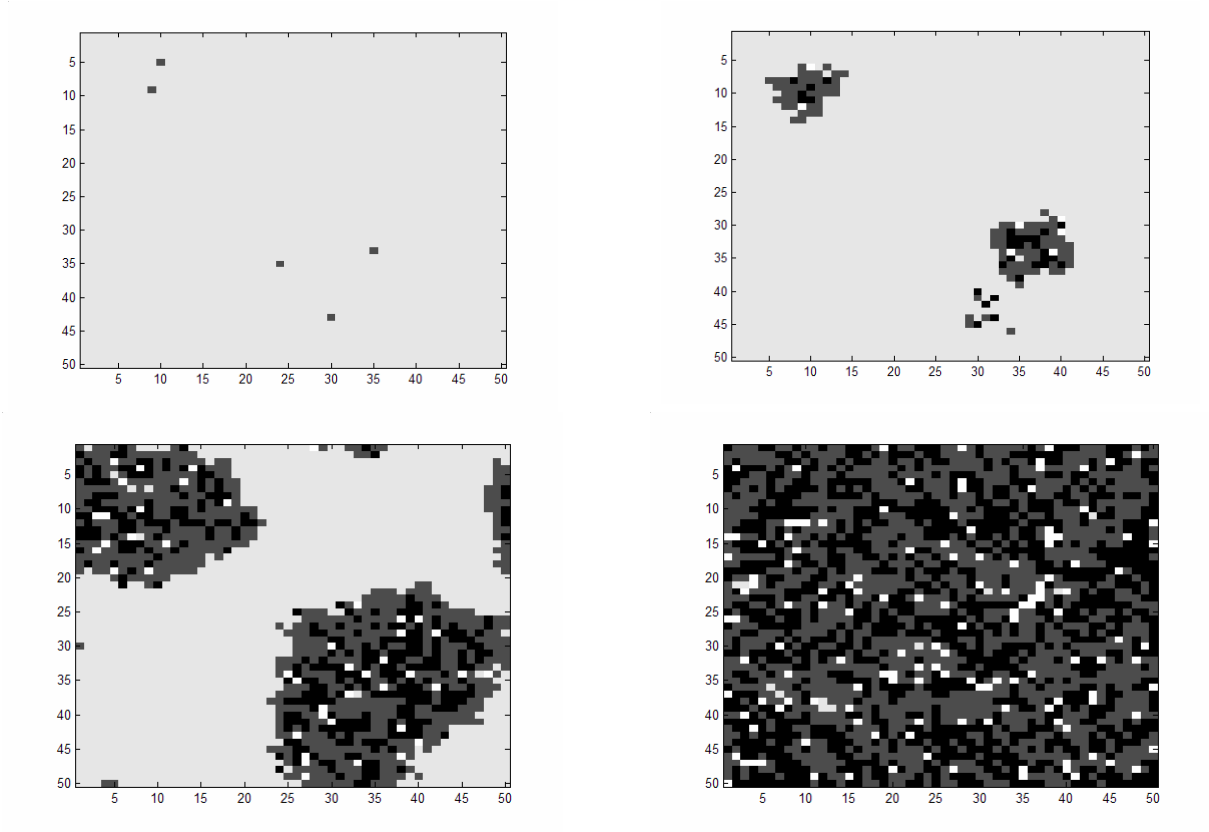

Fig. 2 Evolution of 5 cancer subpopulations on the same CA lattice

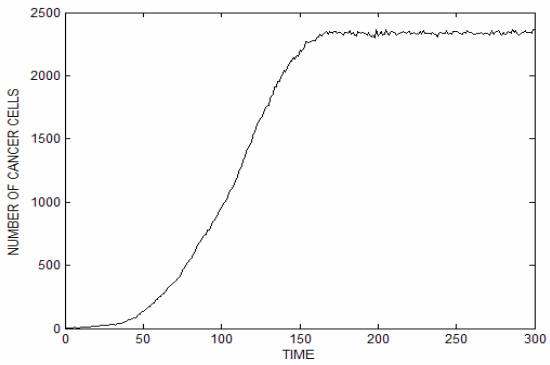

Fig. 3 Evolution of the population of cancer cells

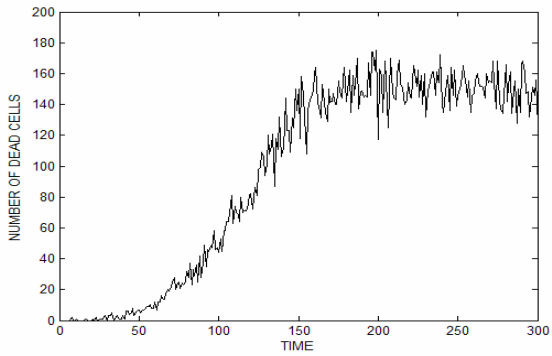

Fig. 4 Evolution of the population of dead cells

As it was shown in Fig. 1, the model is able to provide a simple and realistic explanation for the elimination of cancer cells at their early stage of development, as well as the simultaneous growth of multiple subpopulations on the same lattice (Fig. 2). Finally, the proposed model seems to be in agreement with observations that imply non-linear, complex (chaotic) dynamics and self-organization in cancer growth. This is shown in Fig. 2 where the expansion and proliferation of multiple cancer subpopulations is presented. In addition, the same thing is denoted by the observed stationarity at the population dynamics of the cancer cells (Fig. 3) and the dead cells (Fig. 4). After a short transient phase corresponding to small values of t, both these two populations remain stationary in dynamical equilibrium. These findings provide evidence for emerging non-linear complexity and self-organized chaotic dynamics in cancer growth. This *hypothesis,* proposed for cancer dynamics at sub-cellular and cellular level, [11, 18] seems to stand at the systemic level as well [22-24]. Indeed, non-linear analysis biomagnetic measurements performed in vivo for various types of cancer with the use of SQUIDs indicated the existence of low-dimensional chaotic

dynamics in the biomagnetic activity of these lesions [25-27].

References:

[1] G.G. Steel, *Growth Kinetics of Tumors,* Clarendon Press, 1977.

[2] G.C. Cruywagen, D.E. Woodward, P. Tracqui, G.T. Bartoo, J.D. Murray, & E.C. Alvord, The modeling of diffusive tumours, *J. Biol. Sys.* Vol. 3, 1995, pp. 937-945.

[3] M.W. Retsky, D.E. Swartzendruber, R.H. Wardwell, & P.D. Bame, Is Gompertzian or exponential kinetics a valid description of individual human cancer growth?, *Med Hypoth.*, 1990, 95-106.

[4] M.A.J. Chaplain, & A.R.A. Anderson, Mathematical modeling simulation and prediction of tumor-induced angiogenesis. *Invasion Metastasis,* Vol. 16, 1996, pp. 222-234.

[5] A.R.A. Anderson, & M.A.J. Chaplain, Continuous and discrete mathematical models of tumor-induced angiogenesis, *Bull. Math. Biol.,* Vol. 60, 1998, pp. 857-899.

[6] J.A. Adam, A simplified mathematical model of tumour growth, *Math. Biosc.,* Vol. 81, pp. 229-242.

[7] J.P. Ward & J.R. King, Mathematical Modelling of avascular-tumour growth, *IMA J. Math. Appl. Med. Biol.,* Vol. 14, 1996, pp. 39-69.

[8] P. Trancui, From passive diffusion to active cellular migration in mathematical models of tumour invasion, *Acta Biotheor.,* Vol. 43, 1995, pp. 443-464.

[9] H.M. Byrne, & M.A.J. Chaplain, Necrosis and apoptosis distinct cell loss mechanisms in a mathematical model of avascular tumour growth, *J. Theor. Med.,* Vol. 1, pp. 223-235.

[10] M.A.J. Chaplain, & B.D. Sleeman, Modelling the growth of solid tumours and incorporating a method for their classification using nonlinear elasticity theory, *J. Math. Biol.,* Vol. 31, 1993, 431-479.

[11] V. Quaranta, A.M. Weaver, P.T. Cummings & A.R.A. Anderson, Mathematical Modeling of cancer: The future prognosis and treatment, *Clin. Chim. Acta*, 2005 (to appear).

[12] S.A Kauffan, Emergent properties in random complex automata, *Physica D,* Vol. 10, 1984, pp. 145-156.

[13] S. Wolfram, Cellular automata as models of complexity, *Nature,* Vol. 311, 1984, pp. 419-424.

[14] S. Wolfram, *Theory and Applications of Cellular Automata*, World Scientific, 1986.

[15] W. Duchting, & T. Vogelsaenger, Recent progress in modeling and simulation of three-dimensional tumor growth and treatment, *Biosystems,* Vol. 18, 1985, pp. 79-91.

[16] A.S. Qi, X. Zheng, C.Y. Du & B.S. An, A cellular automaton model of cancerous growth, *Journal of Theoretical Biology,* Vol. 161, 1993, 1-12.

[17] J. Smolle, & H. Stettner, Computer simulation of tumour cell invasion by a stochastic growth model, *Journal of Theoretical Biology,* Vol. 160, 1993, pp. 63-72.

[18] A.R. Kansal, S. Torquato, G.R. Harsh, E.A. Chiocca, & T.S Deisboeck, Simulated brain tumor growth dynamics using a three-dimensional cellular automaton, *Journal of Theoretical Biology,* Vol. 203, 2000, pp. 367- 382.

[19] A.R.A. Anderson, & A. Pitcairn, Application of the hybrid discrete-continuum technique, in: W. Alt, M. Chaplain, M. Griebel & J. Lenz (eds.), Polymer and cell dynamics, Birkhousen, 2003.

[20] A. Adamopoulos, S. Likothanassis, & E. Georgopoulos, Evolving cellular automata to simulate cancer growth, in: Abstract of International Conference on Discrete chaotic dynamics in natural systems (DCDNS), 1998.

[21] A. Adamopoulos, E. Georgopoulos, P. Anninos, & S. Likothanassis, Probabilistic cellular automata to simulate cancer growth, *Physica Medica,* Vol. XV, Nr. 3, 1999, pp. 173-174.

[22] D.A. Rew, Tumour biology, chaos and non-linear dynamics, *Eur. J. Surg. Oncol.,* Vol. 25, 1999, pp. 86-89.

[23] M. Baum, M.A.J. Chaplain, A.R.A. Anderson, M. Douek, & J.S. Vaidya, Does breast cancer exist in a state of chaos, *Eur. J. Canc.,* Vol. 35, Nr. 6, 1999, pp. 886-891.

[24] T. Alacorn, H.M. Byrne, & P.K. Maini, Towards whole-organ modeling of tumour growth, *Prog. Bioph. Molec. Biol.,* Vol. 85, 2004, pp. 451-472.

[25] P.A. Anninos, A. Kotini, N. Koutlaki, A. Adamopoulos, G. Galazios, & P. Anastasiadis, Differential diagnosis of breast lesions, by the use of biomagnetic activity and non-linear analysis, *Eur. J. of Gyn. Oncol.,* Vol. XXI, Nr. 6, 2000, pp. 591-595.

[26] K. Simopoulos, P. Anninos, A. Polychronidis, A. Kotini, A. Adamopoulos, & D. Tamiolakis, Pre- and postsurgical biomagnetic activity in MALT-type gastric lesions, *Acta Radiol.,* Vol. 44, 2003, pp. 1-4.

[27] P. Anninos, I. Papadopoulos, A. Kotini, & A. Adamopoulos, Differential diagnosis of prostate lesions with the use of biomagnetic measurements and non-linear analysis, *Urol. Res.,* Vol. 31, 2003, pp. 32-36.