International Mathematical Forum, 5, 2010, no. 61, 3023 - 3029

A Review of Cellular Automata Models of Tumor Growth

Ankana Boondirek

Department of Mathematics, Faculty of Science
Burapha University, Chonburi 20131, Thailand
ankana@buu.ac.th

Wannapong Triampo

Department of Physics, Faculty of Science
Mahidol University, Bangkok 10400, Thailand
R&D Group of Biological and Envionmental Physics
Mahidol University, Bangkok 10400, Thailand

Narin Nuttavut

Department of Physics, Faculty of Science
Mahidol University, Bangkok 10400, Thailand
R&D Group of Biological and Envionmental Physics
Mahidol University, Bangkok 10400, Thailand
Corresponding Author, e-mail: narinnattavut@yahoo.com

Abstract

This review will outline a number of cellular automaton models describing the tumor growth. The review was provided with simulation results demonstrating both growth curves and morphology of tumor. The goal of researchers of CA model of tumor growth is to understand the mechanisms of tumor growth in microscopic scale which generate the tumor morphology from the experimental or clinical data are given. Using the CA model accurately predicts the growth curve as Gompertz curve from the experimental data both *in vitro* and *in vivo* data. The morphology as seen in experimental data will be challenged the modeler to make a novel microscopic model to generate the same tumor morphology. The measurement from tumor including both growth curve and morphology from the different models will be discussed.

Keywords: tumor modeling, cellular automata, stochastic model, fractal boundary, and Gompertz curve

1. Introduction

Probabilistic Cellular Automaton models (CA Models), Individual-based models (IBMs) or agent-based models (ABMs) are artificial ecologies approaches to modeling population dynamics of theoretical ecology Lomnicki[5]; De Angelis et al. [9]; Grimm [15]. The models of population dynamics can be classified by population sizes, space, and time. IBMs are models with discrete in population size as referred in Ludek Berec [7]. The CA models share common characteristics using cellular ‘s rules from cellular or subcellular levels and using stochastic approach see detail in Wolfram [17]. If each individual cell in the cellular‘s rules has behavior and interaction with their environment, the system will be named multi-cellular biological system (MCBS), see Hwang et al [14].

This article aims to review the principle methodology for CA models of tumor growth in MCBS and to emphasize that the most of researchers have attempted to study a microscopic scale to describe the macroscopic characteristic of tumor morphology. The Researchers such as, Qi, et al.[6], Jiang and coworker [19], Boondirek, et al. [2], and Boondirek and Triampo [1], Reis, et al.[10], Smolle and Stettner [12] and Duchting and Vogelsaenger [18] used cellular automaton models to compromise a hybrid of the complex mechanisms of tumor growth and the dynamics of tumor cells such as proliferation, differentiate, move, and lysis will be implement to cellular ‘s rules. To measurement of simulated tumor referred to the experimental or clinical data, such as the different regions of multicellular tumor spheroid, as well as the fractal of tumor boundary were refered by Bru, et al. [3] and Boondirek, et al. [2].

2. The method of CA model and Previous works of tumor growth

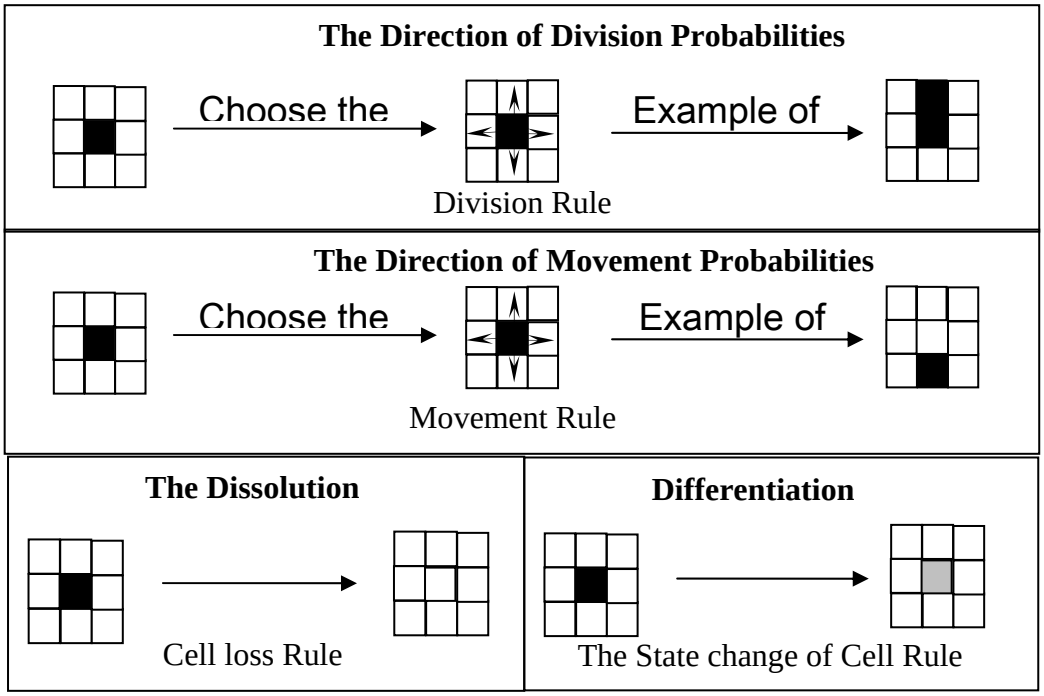
In a cellular automaton modeling, researchers are required to set an initial configuration, design a cell dynamics to be the cellular‘s rule and follow cellular ‘s rule iteratively for each time step. The action’s rules of cell dynamics on two-dimensional square lattice are displayed on Fig 1.

The pioneer research for multi-cellular biological system (MCBS) of tumor growth in three dimensional cubic lattice has been carried out by Duchting and Vogelsaenger [18] to investigate the effects of radio-therapy. Qi, et al. [6] and Boondirek, et al. [2] proposed a two-dimensional cellular automaton model of tumor growth with immune response. The growth curve from their model can give qualitatively the same as the Gompertz curve which describe the growth of tumor *in vivo* or *in vitro* data, see Steel [11], Norton, [13] and Guiot, et al. [8]. Boondirek, et al. [2] also studied several biological effects from clinical trials to the parameters in their kinetic model. The schematic diagram and snapshot of a

simulated tumor with irregular border was shown in Boondirek, et al. [2]. In particular, KikuChi et al. [4] clinically measured the fractal dimension of tumors. Boondirek, et al.[2] measured the fractal measurement of tumor boundary from the simulation results of the tumor boundary in their model as seen in Boondirek, et al. [2] and Jiang et al. [19]. Bru, et al. [3] clinically studied the spatial distribution of cells proliferation in tumors and defined three regions of tumor; innermost, intermediate, and outermost region with using radius as basis see detail in Bru, et al. [3]. Boondirek, et al. [2] also measured the spatial distribution of cells proliferation and concluded that the most of proliferating cells was located in the outermost regions.

Jiang and coworker [19] proposed an MCBS of tumor growth describing the cellular level including cell proliferation, death, and intercellular adhesion on three-dimensional cubic lattice. Snapshots of cross-sectional view of spheroid and the growth curve were depicted in Fig 2 and 3, respectively.

Recently, Boondirek and Triampo [1] have used the cellular ’s rule as seen in Boondirek, et al. [2] to represent tumor cells with immune response on a three-dimensional(3D) CA model with von *Neumann* neighborhood. They modified same cellular ’s rule to include the three-dimensional with 6 nearest neighboring site. This modification makes it possible to observe physical difference appearances such as, with the same set of parameters the simulated tumor in the 3D had more compactness than the simulated tumor in the 2D. The snapshots of cross-sectional view of spheroid and the growth curve were depicted in Boondirek and Triampo [1]



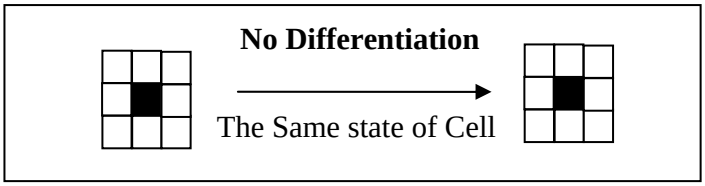


Figure 1 Cell progression. The type of cell dynamics on two-dimensional square lattice with von *Neumann* neighborhood have five rules, i.e., division, move, loss, change and not change state as shown

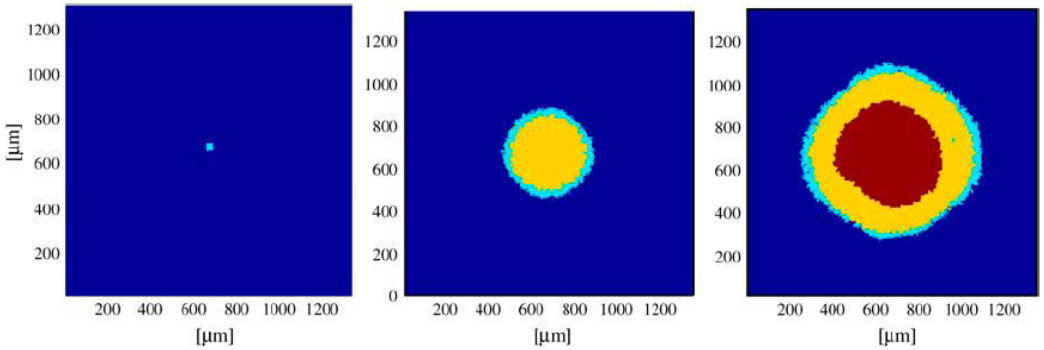


Figure 2 The cross-sectional view of a spheroid at different stages of development from a single cell for 2 days, 10 days, and 18 days, respectively by the left. The colour code is :proliferating, :quiescent, and :necrotic cells (taken from Jiang and coworker [19]).

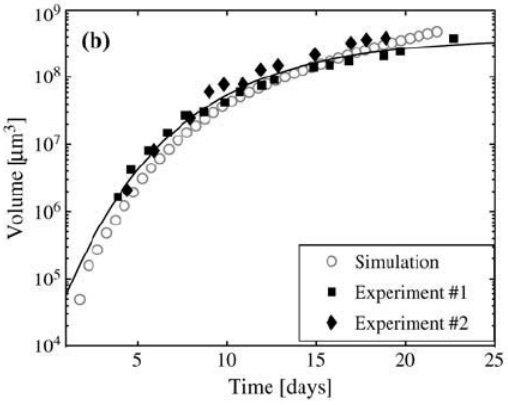


Figure 3 The simulated growth curves of spheroid with 0.08 μm O_2 and 5.5 μm glucose in the medium. The volume of spheroid with time(days) the circles shape are simulation results, the solid diamonds, and the squares shape are experimental data for EMT6/Ro, respectively. The solid lines are the best fit with a Gompertz function for experimental data, more detail see Jiang and coworker [19].

3. Discussion and Conclusion

The purpose of this review is to present cellular automaton models of tumor growth at investigating the results by measurement the evolution of tumor growth. The measurement from tumor both *in vivo* or *in vitro* is both growth curve and morphology. Spatial distribution of the cells is one of the methods for morphology observations and the evolution of tumor growth curve caused by total tumor cell count over time was compared with experimental data. A recent publication by Jiang and coworker [19] shows the three different stages of tumor development. The tumor growth curves could produce the best fit to the growth of spheroids. The tumor shape was shown on the cellular automata grid. The spatial distribution of tumor was caused by the growth dynamics that presented an interaction with tumor cells and their environment. The tumor model, proposed by Boondirek and Triampo [1] emphasized on the parameters involving immune response and the growth curve was fit with experimental growth curves *in vivo* for rat tumors. However, the model proposed of Jiang and coworker [19] was the set of parameters to control spheroid which was *in vitro* experimental and to compare the growth curve of tumor spheroid for EMT6/Ro as detailed in their paper using Gompertz function estimated from experimental data. In similar, simulation results from both CA model used the Gompertz function from experimental data for comparison. The tumor morphology which is proposed by Jiang and coworker [19] explicitly exhibits the layer structure of the three different tumor types as shown in the right picture from the figure 4. Although tumor growth simulation in recent publication cannot answer all aspects of biological activities in tumor cells, it provides scientists to understand mechanism of tumor growth based on basic rules of CA. This could help scientists to detect and recognize early development of tumors which is a key process to treat patients and increase the survival rate. Better and advanced models are being modified from theses research works to compare with clinical data which are progressively made available.

The goal of researchers of CA model of tumor growth is to understand the mechanisms of tumor growth in microscopic scale which generate the tumor morphology from the experimental or clinical data are given. Using the CA model accurately predicts the growth curve as Gompertz curve from the experimental data both *in vitro* and *in vivo* data see Charles [16]. The morphology as seen in experimental data will be challenged the modeler to make a novel microscopic model to generate the same tumor morphology. The measurement from tumor including both growth curve and morphology from the different models will be discussed.

Acknowledgment. This work is partially supported by Faculty of Science, Burapha University, Physics department, Mahidol university, the Thailand Center of Excellence in Physics (ThEP), the Thailand Research Fund (TRF), and the Development Promotion of Science and Technology (DPST),Thailand.

References

[1] A. Boondirek, and W. Triampo, Cancer Research: Computer Simulation of Tumor Growth with Immune Response, Naresuan University Journal, 17, 3 (2009), 196 – 200.

[2] A. Boondirek, Y. Lenbury, J. Wong-ekkabut, W. Triampo, I.M. Tang, and P. Picha,. A Stochastic Model of Cancer Growth with Immune Response, Journal of the Korean Physical Society, 49:4(2006), 1652-1666.

[3] A. Bru, S.Albertos, J.L. Subiza and J.L.Garcia-Asenjo, Biophysic Journal, 85 (2003), 2948.

[4] A. Kikuchi, S. Kozuma, K. Sakamaki, M. Saito, G. Marumo, T. Yasugi, and Y. Taketani, Gynecologic Oncology, 87 (2002), 295-302.

[5] A. Lomnicki, Poppulation ecology from the individual perspective, In: D.L De Angelis, L.T. Gross,(Eds) Individual-based Models and Approaches in Ecology-Populations, Communities and Ecosystems, Chapman&Hall, New York, 1992, 3-17.

[6] A.S. Qi, X. Zheng, C.Y. Du, and B.S. An, A cellular automaton model of cancerous growth, J. theor. Biol., 161 (1993), 1-12.

[7] B. Ludek, Techniques of spatially explicit individual-based models: construction, simulation, and mean-field analysis, Ecological Modelling. 150 (2002), 55.

[8] C. Guiot, P.G. Giorgio, P.P. Degiorgis, P.G. Delsanto, and T. S. Deisboeck, Does tumor growth follow a “universal Law?”, J. theor. Biol., 225 (2003), 147-151.

[9] D.L De Angelis, K.A Rose, and M.A. Huston, Individual-oriented approaches to modeling ecological populations and communities, In: S, Levin,(Ed.), Frontiers in Mathematical Biology, Springer, Berlin, 1994, 390 - 410.

[10] E.A. Reis , L.B.L. Santos, and S.T.R. Pinho, A cellular automata model for avascular solid tumor growth under the effect of theraphy, Physica A. 388 (2009), 1303-1314.

[11] G. G. Steel, Growth Kinetics of Tumors. Oxford: Clarendon Press, 1977.

[12] J. Smolle, and H. Stettner, Computer simulation of tumour cell invasion by a stochastic growth model, J. theor. Biol., 160 (1993), 63-72.

[13] L. Norton, A Gompertzian model of human breast cancer growth, Cancer Res., 48 (1988), 7067-7071.

[14] M. Hwang, M. Garbey, A. Scott, Tran-Son-Tay Bercell, and Roger, Rule-Based Simulation of Multi-Cellular Biological Systems- A Review of Modeling Technique, 2009.

[15] V. Grimm, Ten years of individual-based modeling in ecology: what have we learned and what could we learn in the future, Ecological Modelling, 115 (1999), 129-148.

[16] S. Charles, The Gompertzian View:Norton Honored for Role in Establishing Cancer Treatment Approach, Journal of the National Cancer Institute., 20 (2004), 96.

[17] S. Wolfram, Cellular Automata and Complexity, Addison-Wesley Publishing Company, New York, 1994

[18] W. Duchting, and T. Vogelsaenger, Recent Progress in modeling and simulation of three-dimensional tumor growth and treatment, Biosystems, 18 (1985), 79-91.

[19] Y. Y. Jiang, Y. Pjesivac-Grbovic, J. C. Cantrell, and J.P. Freyer, Biophysic Journal, 89 (2005), 3884-3894.

Received: June, 2010