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A Stochastic Model of Tumor Growth With Immune Response: Three Dimensional Cubic Lattice

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Abstract

A stochastic cellular automata (CA) model of tumor growth in a cubic lattice was studied. The dynamics of tumor growth was incorporated to describe tumor cell invasion of normal tissue. Five input parameters controlling the scenario of what may happen when tumor cells invade normal tissue were used: proliferation rate, tumor-immune binding and association rate, cell lysis, and decay. Monte Carlo simulations based on a CA model were performed. The simulation results provided growth curves highly dependent on the controlled parameters. Comparisons between experimental results from the computer simulation and clinical results are discussed.

Keywords: *stochastic model, cellular automaton model, tumor growth model, tumor – immune competition*

1 Introduction

Combining a self-organizing complex dynamic system and computational model has been a great challenge in interdisciplinary research, especially in medical, mathematics, and biophysics research. The development of tumor growth modeling using theoretical models, a mathematical approach, and computer simulations has been done for more than two decades; see details in [1]. Here, an automaton–based method was established to explain the self-organizing dynamics of cells in discrete nature; i.e., where a cellular automaton (CA) or individual-based model is the main focus (see various CA models in [2]). The CA models carried out the simulation results by using computer implementation as per the evolutionary experiments *in-machina,* which were introduced in 1987 by Agur [3]. The Agur model describes the immune system with deterministic rules for cells, molecules, and their interaction by performing computer simulation experiments on a two dimensional cellular automata.

Some of the CA models of tumor growth were carried out by Duchting and Vogelsaenger [4], who describe the cell-cycle of tumor cell dynamics on a cubic lattice. Qi and coworker [5] established a CA model which describes tumor growth under the influence of immune response and mechanical pressure to tumor on a two-dimensional cellular automata model on a square lattice. Their model simulates the growth curves as a Gompertz-like curve and compares them with the experimental data. In general, the Gompertz curve is commonly used and is an important feature noticed during *in vivo* tumor growth. In 2006, Boondirek et al. [6] added the detachment of immune binding, without damaging cancer cells, to the microscopic model of [5], yielding a trend of growth curve that was shown to qualitatively agree well with experimental animal tumor growth. Boondirek and Triampo (BT)[7] have recently used the kinetic model with five parameters, as in [6], on a three dimensional cubic lattice that reproduced Gompertz curves. In addition, the simulation results showed that the qualitative growth curve and the experimental growth curves *in vivo* for rat tumor W12a7 were in agreement, see details in [7].

The microscopic model takes into account the proliferation of tumor cells and their interaction with the immune response, resulting in either lysis of the proliferating tumor cells or the detachment of immune binding without damaging the tumor cells or removing the dead tumor cells from the tissue. According to the above description, we may revise the notation of the proliferating tumor cells, the dead tumor cells, the tumor infiltrating cytotoxic lymphocyte(TICLs) and the TICLs-tumor cell complexes as: *P*, *D*, *TICLs*, and *C*, respectively. Where the five parameters $r_{prolif.}$, $r_{binding}$, $r_{detach.}$, r_{lysis}, and r_{decay} are the non-negative kinetic constants, we define the function $r'_{prolif.}$, or the *in vivo* avascular tumor growth rate, as $r'_{prolif.}(t) = r_{prolif.}\left(1 - \frac{P}{K}\right)$, and $P(t)$ as the number of proliferating tumor cells, where K is the carrying capacity, see details in [6].

The aim of this research was to use the model of [7] to create a three dimensional lattice to predict tumor growth by investigating the effects of the immune system, as done previously. This model is believed to be relatively more realistic than those of the two dimensional model. To investigate the immune influences on tumor growth, we varied the escape and binding parameters in the microscopic model and studied the growth of the tumor from the simulated growth curves. Additionally, comparisons between the simulation results and some biological effects from clinical studies have been discussed.

2 Method

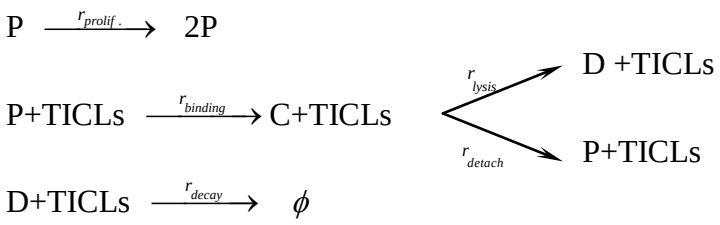

Fig. 1 The fundamental features of development of cancer with immune response, where P, TICLs, C and D denote proliferating cell, effectors, cancer-TICLs cells complex, and dead cancer cell.

The BT model being used to formulate the nutrient-limited growth of an avascular tumor growth took into account the competition between the immune system and tumor cells [7] as shown in Fig. 1, and was applied to a three dimensional model. The Monte Carlo computer simulations were performed to investigate the effects of parameters at the microscopic scale. $r_{prolif.}$ is the rate of tumor proliferation. The binding parameters, $r_{binding}$ is the rate at which the TILCs form lymphocyte tumor cell complexes; see more details in [9]. The higher binding rate indicates the ability of immune cells to bind with the cancer cells and become cell complexes. $r_{detach.}$ is the rate of detachment of TICLs from cancer cells without damaging the cells; r_{lysis} is the rate of detachment of TICLs from dead tumor cells, due to the irreversible programming of the tumor cells for lysis. Zheng and coworker [10] produced experimental data that led them to draw the conclusion that induction of the apoptosis of tumor cells can enhance antitumor efficacy. r_{decay} describes the dissolution of the dead cancer cells. Some key results are presented here and discussed.

3 Simulation Results

We set the five input parameters and ran simulations. To obtain a primary understanding of the dynamic changes, a spatial visualization of the tumor spreading on the cubic lattice is presented in Fig. 2. Fig.2a) shows the cross-central section of the tumor at time step 10 and 50. The boundary shows a roughly circular shape in which the proliferating tumor cells (see color details) are most likely to locate at the rim of the tumor. The spatial distribution of proliferated cells in the simulated tumor can be measured by [6], with a comparison to the *in vivo* experiment by Bru et al. [12]. Additionally, the fractal structure as seen in the snapshot cross-section tumor can be characterized by fractal dimension, as shown in [6].

Since the parameter space is very big and requires very rigorous analysis to identify the parameter ranges, we consequently used parameter values that were more or less the same as those studied in ref [7]. To gain more insight into the tumor dynamics quantitatively, the growth curve of the tumor was numerically obtained. It appears that the Gompertz-like curve appears a good fit for our data, as shown in Fig.2(b).

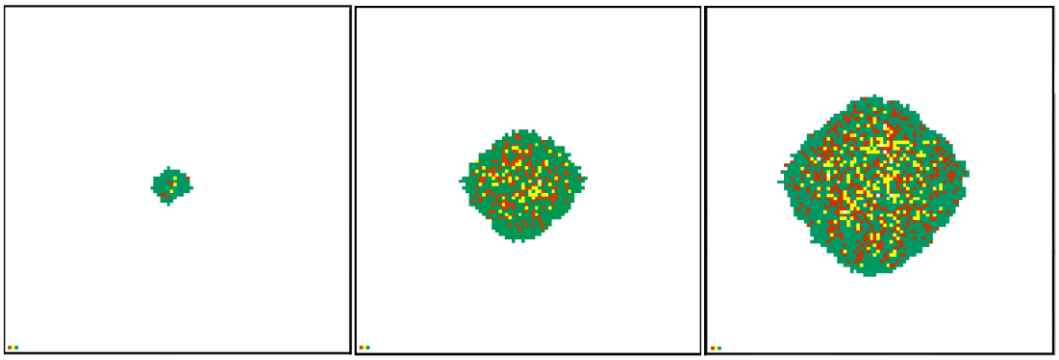

Fig.2(a) Snapshots of a cross-central section of simulated tumor on 101x101x101 cubic lattices with time progression at time steps 10, 30 and 50. The parameter settings are $r_{prolif.} = 0.8$, $r_{binding} = 0.05$, $r_{detach.} = 0.05$, $r_{lysis} = 0.05$, $r_{decay} = 0.05$, and $K = 10^5$. The color code is ■: proliferating tumor cell, ■: TICLs-tumor cell complexes, ■ : dead tumor cell, and □: normal cell.

To connect our computer model with the real world system, we compared our results with the clinical data by Matzavinos and Chaplain [8]. It appears that they are at least in qualitative good agreement. This could relate to the possibility that cytokines in the immune system are the reason for increased binding and lysis rate in the microscopic model. To understand more about this issue, we therefore changed the values of the binding, escape, and lysis parameters and investigated the trend of the growth curves by comparative study. Some of the results are presented in Fig. 3 and 4.

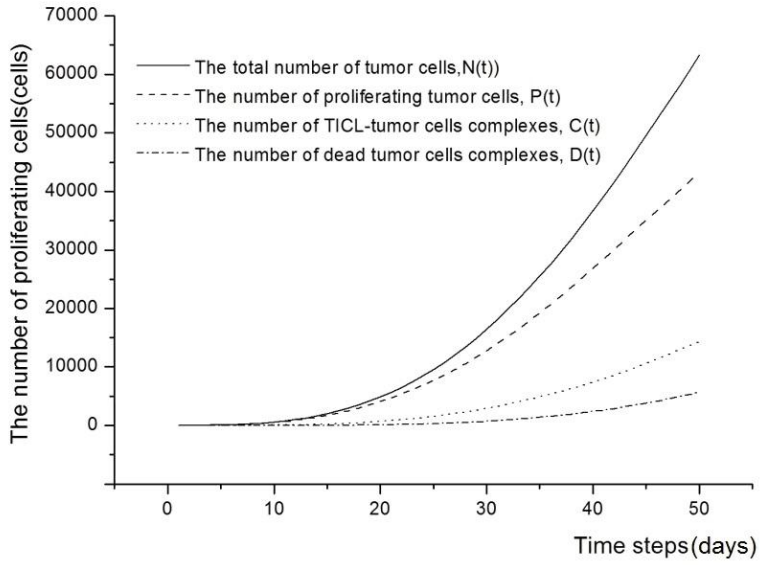

Fig. 2(b) Time evolutions of the total number of tumor cells (solid line), the number of proliferating cells (long dash), the number of TICLs-tumor cells (dot), and the number of dead tumor cells (dash dot), using the same parameters as in Fig. 2(a) with the same computer run-time.

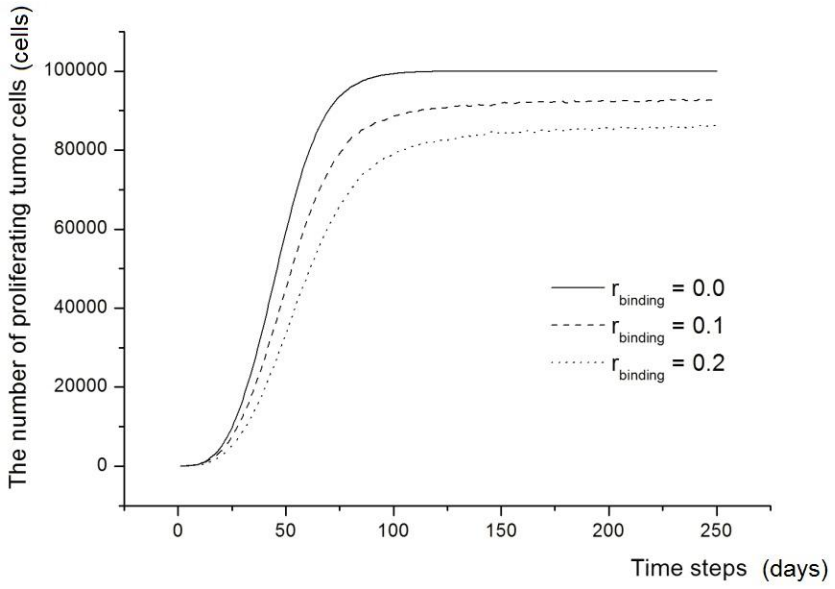

Fig. 3 The influences of $r_{binding}$ on the aggressive growth of the tumor. This figure shows the plots of the time evolution of the proliferating number of tumor cells by

varying the value of $r_{binding}$ from 0.0 to 0.2 in steps of 0.1 while fixing the other values at $r_{prolif.} = 0.8$, $r_{detach.} = 0.35$, $r_{lysis} = 0.35$, $r_{decay} = 0.2$, and $K = 10^5$.

We varied $r_{binding}$ from 0.0 to 0.1 to 0.2 and fixed the other parameters to see how this changed the proliferating growth curves. It was found that the higher binding rate decreases the aggressiveness of the tumor. Fig. 3, clearly shows that the higher binding rate results in a lower saturated size of proliferating tumor. Alternatively, we varied r_{lysis} from 0.0 to 0.1 to 0.2 and fixed the other parameters to see the change of the proliferating growth curve and found that the higher lysis rate also results in a lower saturated size of the proliferating tumor as shown in Fig. 4. This seems to indicate that the comparison between simulation results of our model and some clinical trials agrees well.

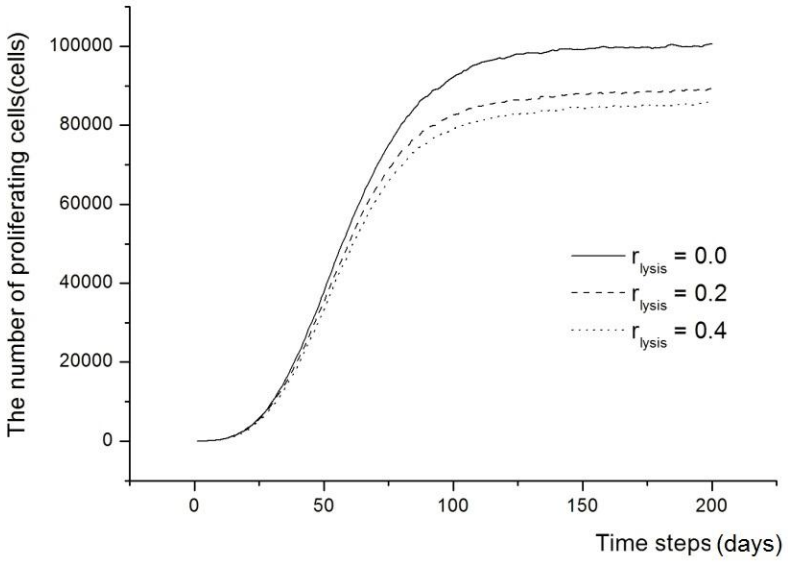

Fig. 4 The influences of r_{lysis} on the aggressive growth of the tumor. This figure shows the plots of the time evolution of the proliferating number of tumor cells by varying the value of r_{lysis} from 0.0 to 0.4 in steps of 0.2, while fixing the other values at $r_{prolif.} = 0.8$, $r_{binding} = 0.2$, $r_{detach.} = 0.35$, $r_{decay} = 0.2$, and $K = 10^5$.

4 Conclusion

This article presented an extension of earlier work by [7] to show the time evolution visual configurations of a cross-section of simulated tumors for tumor-immune response dynamics on a 101x101x101 cubic lattice. To gain insight into

how controlled parameters may affect the evolution of proliferating tumor growth, Monte Carlo simulations were performed which focused on the change of the proliferation, binding, and lysis parameters which influence the proliferating growth rate of a tumor. This was to see how the immune system responds to the growth of tumor. Specifically we investigated the proliferating growth curves after varying the $r_{binding}$, and it was found that our simulation results agree well with those obtained from clinical studies of tumor-immune response. Since the microscopic model of tumor growth may exhibit other complex behaviors relating to cell motility [11] or when mechanical pressure is applied [5], further exploration needs to be done.

5 Open Problem

The microscopic model of tumor growth may exhibit other complex behaviors such as the mechanical pressure as in [5], also the movement of proliferating cell or cell motility, see Gerlee and Anderson[11].

The spatial distribution of proliferated cell in simulated tumor can be measured by [6] with comparison to *in vivo* experiment by Bru et al. [12].

Additionally, the fractal structure as seen in the snapshot cross-section tumor can be characterized by fractal dimension senses as shown in [6].

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