Cancer Research: Computer Simulation of Tumor Growth with Immune Response

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Received 6 March 2009; accepted 15 December 2009

Abstract

A discrete model for the growth of an avascular tumor on a three-dimensional square lattice has been developed. A cellular automata method for tumor growth based on microscopic description of the immune system response, the cell proliferation, the cell death and its degradation is used to simulate the growth. The Monte-Carlo method is be applied to this model. The results give a growth curve which is shown to qualitatively agree well with experimental result.

Keywords: Cancer modeling; Stochastic model; Cellular automaton model; Gompertz function; Immune response

1. INTRODUCTION

Most tumor growth models (Qi et al., 1993; Kansal et al., 2000; Kansal et al., 2000; Boondirek et al., 2006; Kirschner & Panetta, 1998; Ferreira et al., 1998; Ferreira et al., 1999; Voitikova, 1998; Smolle et al., 1990; Matzavinos & Chaplain, 2004; Duchting & Vogelsaenger, 1981; Bellomo & Preziosi, 2000; Galach, 2003; Alarcon et al., 2003; Buric & Todorovic, 2002) contain several basic features, such as, the cell cycle, the cell proliferation, the lack of nutrients, the competition for resources, and the cytotoxic activity by immune response, etc. All of these features have to be investigated in order to understand the kinetics of tumor growth.

The immune response is one of the most important aspects in the growth of the cancer cells. Many studies have established that the immune response plays the crucial role in eliminating the cancer cells from the healthy tissues (Boondirek et al., 2006; Kirschner & Panetta, 1998; Matzavinos & Chaplain, 2004; Bellomo & Preziosi, 2000; Galach, 2003; Steel, 1977). There have been much interests in using mathematical models to simulate the immune system response (Qi et al., 1993; Boondirek et al., 2006; Kirschner & Panetta, 1998; Voitikova, 1998; Smolle et al., 1990; Matzavinos & Chaplain, 2004; Bellomo & Preziosi, 2000; Galach, 2003; Buric & Todorovic, 2002; Steel, 1977).

The researchers (Qi et al., 1993; Kansal et al., 2000; Kansal et al., 2000; Boondirek et al., 2006; Voitikova, 1998; Smolle et al., 1990; Alarcon et al., 2003; Matzavinos & Chaplain, 2004) have worked on the discrete models that are automaton-based. The cellular automata models, called cellular automaton (CA) models are based on the properties of the actual cells at the microscopic or cellular level. It allows for a more realistic stochastic approach to cancer cell growth. The CA models (Qi et al., 1993; Kansal et al., 2000; Kansal et al., 2000; Boondirek et al., 2006; Voitikova, 1998; Smolle et al., 1990; Duchting & Vogelsaenger, 1981; Alarcon et al., 2003) use cellular level information about the cancer cells to determine the cellular automata's rules.

In 1993, Qi et al. developed a cellular automaton model for cancer growth which does give rise to a Gompertz growth law, an important feature seen in the actual growth of cancer cells. Their model is based on a microscopic description of tumor growth in the presence of immune surveillance. In 2006, Boondirek et al., 2006 developed a microscopic model of tumor growth from Qi et al., 1993 and Kuznetsov & Taylor, 1994 as shown in Figure 1. Their molecular dynamics model (Boondirek et al., 2006) takes into account the tumor cell proliferation, its interaction with the immune system, resulting in either lysis of the proliferating tumor cells or the detachment of immune binding without damaging the tumor cells or the removal of the dead tumor cells.

The major purpose of this research is to extend the CA model of Boondirek et al., 2006 to three-dimensional square lattice to make the model more realistic in spatial distribution with the different starting configuration and rule of the invasion then investigate the simulation results, as well.

Our model and the methodology used are presented in Section 2. In Section 3, we present the simulating results for the tumor progression. In Section 4, conclusions are given.

2. MATERIAL AND METHODS

Lattice system and microscopic dynamics

We have used the cellular automata (CA) approach to study the dynamics of the tumor growth coupled with immune response. A Computer model was developed from the two dimensional square lattice previously published by Boondirek and co-workers

[Boondirek et al., 2006] the three dimensional lattice or cubic lattice due to CA algorithm. In the model, the host tissue is represented by a lattice of size LxLxL. Each site is identified by the coordinates (x_n, y_n, z_n : n = 1, 2, 3, …, L) which are designated by the values either 0, 1, 2, or 3 to specific the cell type normal, tumor, complexes, and dead cell, respectively. We denote the proliferating tumor cells, the dead tumor cells, the cytotoxic lymphocyte and the TICLs-tumor cell complexes by P, D, TICLs, and C, respectively. The kinetics of the tumor development is represented in Figure 1.

$$P \xrightarrow{r'_{prolif.}} 2P$$

$$P+TICLs \underset{r_{detach.}}{\overset{r_{binding}}{\rightleftarrows}} C \xrightarrow{r_{lysis}} D+TICLs$$

$$D \xrightarrow{r_{decay}}.$$

Figure 1. Kinetic mechanisms of development of cancer with immune response (Boondirek et al., 2006).

The parameters $r_{prolif.}$, $r_{binding}$, $r_{detach.}$, r_{lysis} and r_{decay} are the non-negative kinetic constants. $r_{prolif.}$ is the rate of tumor proliferation. $r_{binding}$ is the rate of binding of TICLs to tumor cells. $r_{detach.}$ is the rate of detachment of TICLs from cancer cell without damaging 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. r_{decay} describes dissolution of the dead cancer cells. We define the function $r'_{prolif.}$, in vivo avascular tumor growth rate, as $r'_{prolif.}(t) = r_{prolif.}\left(1 - \frac{P}{K}\right)$, where is the carrying capacity and is the number of proliferating tumor cells, which arises from the limitation on the amount of nutrient that is available for proliferation of cancer cells or from the increasing accumulation of waste product accumulation which causes a decrease in the rate of proliferation of cancer cells (Qi et al., 1993; Boondirek et al., 2006; Bru et al., 2003; Preziosi, 2003). Evidently, $r'_{prolif.}$ decreases when there is an increase in the number of cancer cells. The type of input arises because the proliferating tumor cells are in competition with each other for the limited amount of nutrients available. This will affect the first output of the fist reaction shown in Figure 1. This effect was studied in avascular microscopic tumor growth *in vivo* (Bru et al., 2003; Preziosi, 2003). In the second reaction, the parameter $r_{detach.}$ gives the tumor potential for escaping the host's immune surveillance. $r_{binding}$ is a measure of the TICLs response to the tumor cells r_{lysis} describes the rate of detachment of activated TICLs from tumor cell as an irreversible programming of the tumor cells for lysis. r_{decay} describes the dissolution process in which the 'dead' tumor cells return to the normal tissue.

Cellular automata algorithm

At t = 0, an initial configuration consist of seven cancer cells locating at the center of the normal tissue as shown in Figure 2. Then each time step the CA update rules are applied. The CA rules are applied to each tumorous cell one by one. We select sequentially at random with the same probability and carry out one of the action upon its state as shown in schematic diagram, Figure 4, with the details and flowchart in Boondirek et al, 2006. However, since the tissue model of Boondirek, et al, 2006 is the two dimensional square lattice, with von *Neumann* neighborhood of four nearest neighboring sites. Here we extend to more complicated and realistic model, namely a three dimensional cubic lattice with von *Neumann* neighborhood of six nearest neighboring sites as show in Figure 3. Then by observation with the same set of parameters and carrying capacity the growth pattern in the 3D model is more compact than in the 2D model due to the number of nearest neighboring sites.

Figure 2. An initial configuration of seven cancer cells located at the centre of normal tissue sites.

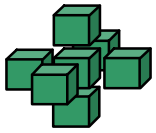
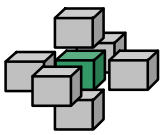


Figure 3. Six nearest-neighboring sites (gray) of the cancer site (green) and the Nearest-neighbor rule. (the so-called von Neumann neighborhoods in 3D)



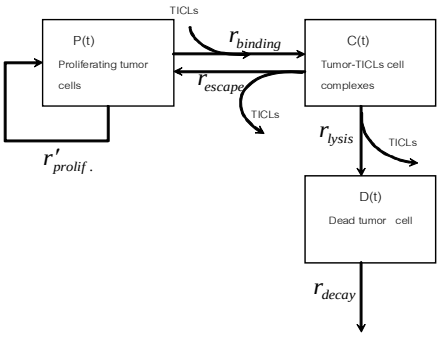


Figure 4. Cell dynamics for tumor growth Schematic diagram of cellular automaton model of tumor growth reveals the possible action, reaction and changing state of each type of tumor cell. P(t) denotes the number of proliferating cells at time t, C(t) denotes the number of TICLs-tumor cell complexes and D(t) denotes the number of dead tumor cells(Boondirek et al., 2006).

3. RESULTS

We have performed simulation according to the dynamics given above. CA simulation is started by placing seven tumor cells in the center of a square lattice, subsequently the invasion of the tumor cells into the rest of the lattice sites which represents the normal tissue occurs. The results of the simulation obtained at time t gives a snapshot of the simulated tumor pattern at time t are shown in Figure 6. As evidently seen three dimensional spatial visualizations of the tumor invasion into the normal tissue generated become greater and greater as time progresses. Quantitatively, we have measured the total number of tumor cells present at time 't' denoted by N(t) which is equal to the sum of P(t), the number of proliferating tumor cells at time t; C(t), the number of TICL (tumor cell complexes) at time t and D(t), the number of dead tumor cells at time t, i.e., N(t) = P(t) + C(t) + D(t). N(t) is a measure of the size of the tumor at time t.

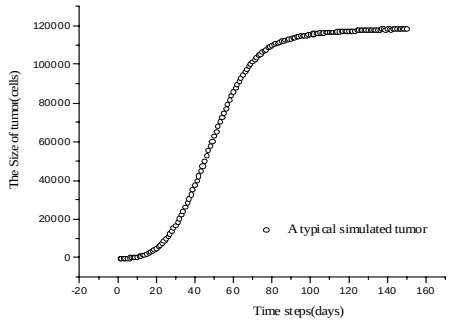


Figure 5. Typical simulated tumor growth curve. The simulation setting is r_{prolif} = 0.85, $r_{binding}$ = 0.1, r_{detach} = 0.35, r_{lysis} = 0.35, r_{decay} = 0.35 and K = 100000.

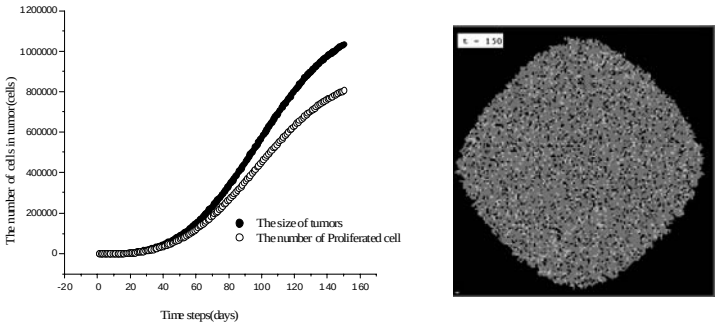


Figure 6. Shows snapshot of tumor(more than million cells) at t =150 on a 151x151x151 cubic lattice and its growth curve with the number of proliferated cells. The parameters setting are rprolif = 0.8, rbinding = 0.15, rdetach = 0.35, rlysis = 0.35, rdecay = 0.35 and K = 1000000. The color code is ■:cancer cell, ■: complexes cell, ■:dead tumor cell, and ■:normal cell, respectively.

Figure 7. represents the comparison between the typical simulated tumor growth curve (circle) and fitted Gompertz growth function. To obtain the fit, we had to normalize the data. This fitting used the Gompertz parameters and which is the growth curve agree well with in vivo experimental results of rat tumor W12a7 as reported by Waliszewski and Konarski, 2002 . The parameter setting is the same simulation as in Figure 6.

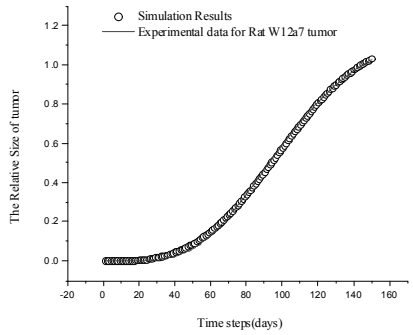


Figure 7. Comparision between the simulated tumor growth (circle) and the experimental growth curves in vivo for rat tumor W12a7 (Waliszewski and Konarski, 2002) with coefficient of nonlinear regression .

4. CONCLUSION

The CA model in three dimensional square lattices of an avascular tumor in the presence of immune response has been studied. The dynamics of the tumor growth based on microscopic description of the immune system response, the cell proliferation, the cell death and its degradation. The Monte-Carlo simulations are then performed to simulate the growth of real tumor. The underlined results showed that the fitted Gompertzian curve could be a good function to describe cancerous growth. In addition, the associated parameters such as varied rbinding , rdetach seem to play a crucial role on how the immune system influences the growth of the tumor. Other comparison measurement between the 3D CA model with the 2D CA model such as space distribution are being in progress.

5. ACKNOWLEDGEMENT

This research work was supported by Faculty of Science, Burapha University, Thailand, the National Center for Genetic Engineering and Biotechnology (BIOTEC), The Thailand Research Fund (TRF), and the Commission on Higher Education (CHE)

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