แบบจำลองสโตแคสติกเซลลูลาร์ออโตมาตาสำหรับการเจริญของเนื้องอกที่ไม่มีหลอดเลือดกับการเฝ้าระวังเพื่อตอบสนองในการต่อต้านเซลล์เนื้องอก : บนตาข่ายลูกบาศก์

A Stochastic Cellular Automata Model for Avascular Tumor Growth with Surveillance of an Immune Response Against the Tumorous Cells : on a Cubic Lattice

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บทคัดย่อ

แบบจำลองจลนพลศาสตร์สำหรับการเจริญของเนื้องอกที่ไม่มีหลอดเลือดได้ถูกนำเสนอ แบบจำลองได้รวมกลไกเฝ้าระวังของภูมิคุ้มกันที่รับรู้ถึงเซลล์มะเร็งและทำให้เซลล์อ่อนแอด้วยปฏิกิริยารวมตัวเฉพาะ โดยการหลอมรวมเป็นสารเชิงซ้อนของเซลล์เนื้องอกที่แพร่กระจายกับภูมิคุ้มกัน ซึ่งประกอบไปด้วยเซลล์มะเร็งทั้งหลายและสารส่งผลที่ทำให้เกิดปฏิกิริยาเคมีของภูมิคุ้มกันที่มีพิษต่อเซลล์ (เอฟเฟคเตอร์) ได้แก่ เซลล์ หรือ ชีวเคมี ซึ่งนำไปสู่กระบวนการตายแบบแตกตัวของเซลล์มะเร็ง แบบจำลองนี้ได้รวมแสดงถึงความเป็นไปได้ของเซลล์มะเร็งที่จะหลบหลีกปฏิกิริยาเคมีของภูมิคุ้มกันหลังจากที่ถูกหลอมรวมเป็นสารเชิงซ้อนแล้ว หรือการตายของเซลล์แต่ไม่แตกตัวอันเนื่องมาจากการด้อยประสิทธิภาพของภูมิคุ้มกัน แบบจำลองสโตแคสติกเซลลูลาร์ออโตมาตาบนตาข่ายลูกบาศก์ถูกใช้เพื่อศึกษากลไกของแบบจำลองจลนพลศาสตร์ดังกล่าว ผลที่ได้จากการจำลองนี้ เช่น เส้นโค้งการเจริญของเนื้องอกจะถูกอธิบายตามจลนพลศาสตร์ในระดับขนาดเล็กมาก การวิเคราะห์ความไวต่อผลกระทบของพารามิเตอร์ จากการเปลี่ยนแปลงทางสัณฐานของเนื้องอกจำลอง ซึ่งวัดจากการกระจายของเซลล์เนื้องอกที่แพร่กระจายบนตาข่ายลูกบาศก์ พบว่าการเพิ่มของอัตราการพักตัวของเซลล์เนื้องอกได้นำไปสู่การเพิ่มของความหนาแน่นของเซลล์มะเร็งที่แพร่กระจายได้ในบริเวณด้านนอกสุด

คำสำคัญ : แบบจำลองสโตแคสติก, การจำลองการเจริญของเนื้องอกด้วยโปรแกรมคอมพิวเตอร์, แบบจำลองบนตาข่ายลูกบาศก์, การเจริญของเนื้องอกกับการตอบสนองของภูมิคุ้มกัน

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Abstract

A kinetic model for avascular tumor growth is presented. The model includes an immune surveillance mechanism that recognizes the cancerous cell and makes the cell susceptible to certain binding reactions. The particular binding interactions of interest are those that lead to the formation of tumor-immune complexes consisting of the cancerous cells and cytotoxic agents (effectors) such as cells or biochemical which can cause the apoptosis of the cancerous cells. The model allows for the possibility of the cancerous cells escaping the immune activity after the binding reactions have occurred, or dying but not undergoing apoptosis when the immune agents are ineffectual. A stochastic cellular automata model on a three-dimensional cubic lattice is used to implement the kinetic model. The simulation results, such as the growth curves are explained at a kinetic microscopic scale. The sensitivity analysis of the effects on parameters from the morphologies of simulated tumors by measuring the spatial distribution of proliferating cells will be presented. The model shows that an increase in the dormancy rate leads to an increase in the density of the proliferating cells in the outermost region.

Keywords : stochastic model, *in silico* model of tumor growth, model on a cubic lattice, tumor growth with immune response

Introduction

Cancer is the un-controlled growth of cells. The transformation of a cell from a normal one to a malignant one is the consequence of the expression of genes called oncogenes. The cells with these oncogenes have the ability to invade the space occupied by healthy cells and evidently cause their death. The immune system which attacks the cancerous cells is a complex one. Evidence has been accumulating that the immune system (cytotoxic agents such as the CD8+, the T cells, the NK cells or the phagocytes) of the body can eliminate the malignant cells after they are identified as such. Its essential function is to suppress the cancer growth in both *in vivo* and *in vitro* (details are given in Abbas & Lichtman, 2011; Kasiske *et al*., 2004; Le Mire *et al*., 2006; Kataki *et al*., 2002; Hanahan & Weinberg, 2011; Mocellin *et al*., 2005; Gajewski *et al*., 2013; Nieswandt *et al*., 1999; Parish, 2003).

In tumor biology, the first response of the immune system is to identify a cell as being cancerous. This is done by the antigen presenting cells (APC's) and occurs at the beginning of the immune surveillance steps. The APC's recognizes the foreign antigens on the surface of the cancerous cells and present them to the T cells. This causes the immune cells to recognize and mark them as being cancerous cells. After this recognition step, the cancerous cells form into cancer–complexes with the immunity agents. They can remain as malignant tumor by evading the immune system or they can become necrosis cells (Hanahan & Weinberg, 2011; Mocellin *et al*., 2005; Gajewski *et al*., 2013; Nieswandt *et al*., 1999; Parish, 2003). Only after apoptosis (disintegration or fragmentation

of the nuclear DNA of the cell) new cells be able to grow into the space since it would be vacant. Here we introduce what we call an effective immune response and an ineffective immune response, i.e., the removal (elimination) or non removal of the necrosis cells. The explanations of the effective and ineffective immune response to show its critical role in the immune system to control the tumor, is given in Hanahan & Weinberg, 2011; Mocellin *et al*., 2005; Parish, 2003. The cancer growth *in vivo* is complicated and not fully understood. Eftimie and coworkers (Eftimie *et al*., 2011) have pointed out that the micro-environment of the tumor cells includes the immune cells, the fibroblasts factors, the endothelial cells, the extracellular matrix, signaling molecules (chemokines and cytokines) and the growth factors (including cytokines and etc.). The interactions between the tumor cells and the other component of the tumor microenvironment are complex and evolve with time, i.e., they are kinetic in nature. To understanding of the interplay of these factors on the growth of cancerous cells, various mathematical descriptions of what might be happening have been given and reviewed in Eftimie *et al*., 2011 and Preziosi, 2003. The cellular automata (CA) model is one of these mathematical methods which might be suitable for studying the convergent behavior of microscopic interaction processes discrete in time and which involve different cell types (Qi *et al*., 1993; Boondirek *et al*., 2006; Boondirek & Triampo, 2009; Boondirek *et al*., 2011; Matzavinos *et al*., 2004; de Pillis *et al*., 2005).

Over the last decade, a number of computational methods have also been proposed to explain cancer growth which takes into account the response of the immune system, and are given in Qi *et al*., 1993; Boondirek *et al*., 2006; Boondirek & Triampo, 2009; Boondirek *et al*., 2011; Matzavinos et al., 2004; de Pillis et al., 2005; Mallet & de Pillis, 2006. Qi and coworkers (Qi, *et al*., 1993) proposed a kinetic model to explain the tumor growth using the cellular dynamics which included an immune response. They employed the stochastic cellular automata (SCA) approach to the tumor growth on a two dimensional square lattice. They simulated the growth curves for different sets of parameter values. Their simulated curves were Gompertz-like, similar to the shapes of the growth curves of avascular tumor observed experimentally (Steel, 1977 and Norton, 1988).

In 2006, Boondirek and coworkers (Boondirek, *et al*., 2006) examined the effects of allowing for avoidance of the immune surveillance by the cancerous cells had been observed by Hanahan & Weinberg, 2011; Kuznetsov *et al*., 1994. They considered the case where the SCA was used to simulate the cancer growth on a two dimensional square lattice. In a later study, Boondirek and Triampo (Boondirek & Triampo, 2009) extended their earlier study to a SCA simulation of the cancerous growth on a three dimensional cubic lattice by having more than one million cells. The simulated results were then compared with some experimental results via Gompertz parameters. Boondirek and coworkers (Boondirek *et al*., 2011) extended the work so that a sensitivity analysis could be performed for some parameter values to explore the efficacy of the parameter values used and how they might relate to the experimental observation.

The aim of the present research is to apply the SCA to a three dimensional cubic lattice using a kinetic model which includes several details for the role of the tumor – immune interaction on the growth of tumors to the published research work from Boondirek and Triampo (Boondirek & Triampo, 2009). The role of the interactions has emerged from the studies of the clinical, experimental data, and mathematical models see Abbas & Lichtman, 2011; Kasiske *et al*., 2004; Le Mire *et al*., 2006; Kataki *et al*., 2002; Hanahan & Weinberg, 2011; Mocellin *et al*., 2005; Gajewski *et al*., 2013; Nieswandt *et al*., 1999; Parish, 2003; Qi, Zheng *et al*., 1993; Boondirek *et al*., 2006; Boondirek & Triampo, 2009; Matzavinos *et al*., 2004; de Pillis *et al*., 2005; Mallet & de Pillis, 2006; Kuznetsov *et al*., 1994. A simulation of the tumor growth is presented. Finally, a sensitivity analysis is performed to see the effects of the dormant parameter values on the growth curves, the spatial distributions of proliferating cells after variation of the parameter values will be observed and compared with the experimental research by Bru *et al*., 2004.

Methods

Materials and Methods

Outline of the SCA model

We propose a kinetic model to describe the avascular tumor growth which includes an immune surveillance, and can lead either to an effective or an in-effective immune response. The chart flow for the model is given in Fig. 1. The first reaction describes the proliferation of tumor cells by mitosis where the proliferation rate of the *in vivo* tumor growth is assumed to have a logistical form of $r_{\text{prolif.}} = r_p(1 - \frac{T}{T_{\max}})$, this is a function of proliferating parameter, r_p, and the number of tumor cells, T. $T_{\max}$ is the carrying maximum number of tumorous or proliferating cells due to the limitation caused by the restriction of oxygen and nutrients (Qi, Zheng *et al*., 1993; Boondirek *et al*., 2006; Boondirek & Triampo, 2009; Matzavinos *et al*., 2004).

$$T \xrightarrow{r_{\text{prolif.}}} 2T$$

$$T + E \underset{r_{\text{evade}}}{\overset{r_{\text{recognize}}}{\rightleftharpoons}} C \xrightarrow{r_{\text{cytotoxic}}} D + E \begin{cases} \xrightarrow{r_{\text{domant}}} D^* + E^* \\ \xrightarrow{r_{\text{decay}}} E \end{cases}$$

Figure 1 The kinetic model of cancer cells with immune surveillance and suppression. T, C, D, and D^* denotes the number of tumor, tumor-immune complexes, dead tumor (necrosis) cells and dormant cells, respectively. By E and E^* denotes the effective and ineffective immune agents, respectively.

The second reaction arises when the immune system recognizes an invasive cell as being a cancerous cell by sensing certain biochemical sites (protein sites) on the surface of the cancerous cell.

As we briefly mentioned, in tumor biology the immune's role is carried out by antigen presenting cells (APC's). The APC's are initially present themselves to the T cells which then replicates the APC's. The newly replicated APC's can then combine with another protein to form an effector cell. These effector cells can efficiently combine with the tumor cells having the antigens that the APC's had identified at first to form the tumor-immune complex C . The rate at which this occurs is called the recognition rate of the immune surveillance. It has a logistic form given by $r_{\text{recognize}} = r_{\text{r}}(1 - \frac{C(t-1)}{C_{\max}})$, where r_{r} is the recognition parameter and $C(t-1)$ is the number of tumor–immune complexes cells formed after the cell is tagged at the former time step, and $C_{\max}$ is the carrying capacity (maximum number) for the effector cells which can recognize the tumor cells. The tumor-immune complexes can lose the tag at an evading rate, r_{evade}. The effectors cells are the agents which causes the deaths of cancerous cells but not their disintegration. The rate at which the tumor–immune complexes cells is transformed into a dead tumor cell by cytotoxic activity of the effector cells is denoted with cytotoxic rate, $r_{\text{cytotoxic}}$. The final reaction leads to two possible results by the decay and dormant rate. The results of the tumor-immune complexes cell during this reaction are either an effective immune agent or a dormant dead cell and an ineffective immune agent, respectively. A disintegration of the cancerous cells by apoptosis is occurred by an effective immune agent with the decay rate, r_{decay}. But, when the immune agent is ineffective leads the dead tumor cell cannot to undergo programmed disintegration (apoptosis)). The rate at which the second outcome occurs is given by the dormant rate, r_{domant}. E and E^* denote the effective immune cells (agents) and ineffective immune cells (agents), respectively.

Figure 2 The figure shows the initial condition of the seven proliferative cells in the middle of the cubic lattice for the application of the rules for our CA. This CA 's rule uses von – Neumann neighborhood for dynamical change, the six nearest neighboring cells of the middle one (the unseen middle cell) are located around the middle one, which can be seen.

The method of the SCA model

(1) The model formulation

The biological assumptions were taken into account when developing the kinetic model. The assumptions are based on both the clinical and experimental data on the tumor growth when the effects of the immune system is taken into account given in Abbas & Lichtman, 2011; Kasiske *et al*., 2004; Le Mire *et al*., 2006; Kataki *et al*., 2002; Hanahan & Weinberg, 2011; Mocellin *et al*., 2005; Gajewski *et al*., 2013; Nieswandt *et al*., 1999; Parish, 2003 and on the mathematical models given in Eftimie *et al*., 2011; Preziosi, 2003; Qi, Zheng *et al*., 1993; Boondirek *et al*., 2006; Boondirek & Triampo, 2009; Matzavinos *et al*., 2004; de Pillis *et al*., 2005; Mallet & de Pillis, 2006; Kuznetsov *et al*., 1994. The assumptions are as follows:

1. Tumor is the uncontrolled growth of cells. They can divide by mitosis only if they have enough food and space to grow by increasing the number of tumor cell. They will divide into two daughter tumor cells with a proliferation rate, $r_{\text{prolif.}}$.

2. The immune system is based on three mechanisms to control the tumor growth,

   (i) a recognition mechanism of the proliferating tumor cells which allows them to combine with various agents of the immune system to form into tumor–complexes cells,

   (ii) a cytotoxic mechanism which leads the agents to kill the cancerous cells, and

   (iii) an apoptosis mechanism which causes the dead tumor cells to undergo apoptosis (or programmed disintegration).

3. At the recognition stage, the proliferating cancerous cells are recognized by immune surveillance at the recognize rate, $r_{\text{recognize}}$. These then form into tumor-immune complexes cells with agents of the immune system.

4. The cancerous cells can escape from tumor–immune complexes cells to be cancerous one if the immune surveillance of the proliferative cancerous cells is ineffective. This occurs at an evading rate, r_{evade}.

5. When the immune response within tumor–immune complexes cells is effective, the cytotoxic activity between the cancerous tumor and the immunity agents will lead to the death of the cancerous cells. This will occur at the cytotoxic rate, $r_{\text{cytotoxic}}$.

6. When the immune response within tumor-immune complexed, it cannot lead to the apoptosis of the dead cancerous cell, the dead cell is left in a dormant state. It still occupies the space with the inefficiency immune agent. The rate at which this happens is given by dormancy rate, r_{dormant}.

7. When the immune response is effective, the mechanism for apoptosis is turned on and the dead cell disintegrates, freeing up the space. The rate at which this occurs is denoted as the decay rate, r_{decay}.

(2) The Algorithm for the SCA model

The tissue is modeled as a three dimensional cubic lattice having the size, $L \times L \times L$. The details of algorithm for a simulation can be described as the following steps.

Step I. The initial time step: $t = 0$

The initial condition in CA model is for seven proliferating tumor cells, which are located at the center of the cubic lattice as seen in Fig. 2. The values of the parameters $r_p, r_r, r_{evade}, r_{cytotoxic}, r_{dormant}, r_{decay}, C_{max}$, and T_{max} are chosen. The initial values of the parameters need to satisfy the conditions that each rate must be in the range between 0 and 1, and satisfy the kinetic model in Fig. 1, that is

$$r_p + r_r \leq 1,\ r_{evade} + r_{cytotoxic} \leq 1,\ r_{dormant} + r_{decay} \leq 1.$$

The initial configuration for tumor and complexes cells is $T(0) = 7$ and $C(0) = 0$.

Step II. The next time step: $t = t + 1$, starting at $t = 1$

Here, we describe the details of the automata-based model. The updating in SCA model is done synchronously in discrete space and time with von Neumann neighborhood. The states of each site on the cubic lattice are updated at most once per time step. The dynamics of cells is determined by a random number chosen, on the occupations of the surrounding space and on the values of the parameter rates as dictated by the schematics diagram, shown in Fig.3.

For each proliferating tumor cell at time step *t*, the proliferation and recognition rate are first calculated and then a cancerous cell is randomly picked one by one with the equal probability until all cells in the simulated tumor at time *t* are picked. Then a random number is generated and depending on the occupation condition of space surrounding the cell, and depending on the value of the random number one of the following changes to the state of that particular cell will be made until all of the cancerous cells present at time t have been changed,:

(i) Change the number of complex cells, *C* with a probability given be the recognition rate, $r_{recognize}$ during the immune surveillance stage. The recognition rate is calculated by

$$r_{recognize} = r_r\left(1 - \frac{C(t-1)}{C_{max}}\right),$$

where $C(t-1)$ is the number of complexes cells in the former time step.

(ii) Duplicate two daughters' tumor cells with the probability of the proliferation rate, $r_{\text{prolif.}}(t)$, if there is at least one vacant nearest neighboring site to the tumor cell site. The nearest neighboring of each tumor cell can be seen in Fig. 2. The proliferation rate is calculated from

$$r_{\text{prolif.}} = r_p\left(1 - \frac{T(t-1)}{T_{\max}}\right),$$

where $T(t-1)$ is the number of tumorous cells in the former time step. The daughter's cell can be placed in only one cell in the nearest vacant neighboring site of the tumor cell with equal probability.

(iii) Remain in the same state with a probability given by

$$1 - (r_{\text{recognize}}(t) + r_{\text{prolif.}}(t)),$$

which shows that the probability depends on the proliferation rate of specific tumor cell, the recognition rate of immune surveillance and the lack of space for tumor to proliferate.

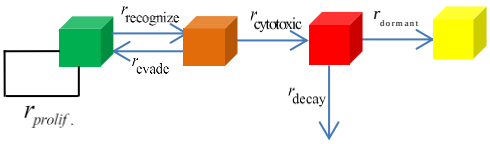


Figure 3 The diagram is representing the tumor cell dynamics with immune competition from the kinetic model. (= proliferative tumor cell, = complexes cell, = dead tumor cell, and = dormant cell).

Next, for each complexes cell at time *t*, we first pick a random number and then calculate the evasion rate and the cytotoxic rate and then make one of three possible decisions:

(i) Change the complex to be a dead tumor cell with a probability given by the cytotoxic rate, $r_{\text{cytotoxic}}$. This result occurs when the immune surveillance is effective.

(ii) Change to the complex to be proliferative cell with a probability given by the evasion rate, r_{evade}. This results lead to the escape of the tumor cell from the cancer-immune complex.

(iii) Keep in the same state with the probability of $1 - (r_{\text{cytotoxic}} + r_{\text{evade}})$.

For each dead tumor cell at time *t*, we again picked a random number, calculate the dormancy rate and decay rate and then make the decision which can lead to two possible outcomes:

(i) Change to state to be vacant with the probability of decay rate, r_{decay} . This is caused by an effective immune response. This results in a vacant space into which a new cell (both normal and cancerous) can move into.

(ii) Change to state to be dormant cell with the probability given by the dormancy rate, $r_{dormant}$. This is due to an ineffective immune response which does not cause the dead tumor cells to disintegrate and be removed from the tissues.

Technically, all cells are randomly selected one by one with equal probability and a decision is made to undertake one of the possible steps that can be taken depending on the value of a new random number which has generated. We progress iteratively in time step by changing $t = t + 1$ and determine the number (size) of tumorous cells, $N(t) = T(t) + C(t) + D(t) + D^*(t)$, where $T(t), C(t), D(t), D^*(t)$ are the number of tumor cells, of tumor-complexes cells, of dead tumor cells and of the dormant cells at time t .

Step III. The step II is repeated in self-organizing method until the desired number of time steps is reached. At this point, we have a simulated tumor whose growth pattern is determined stochastically.

Results

We have written a program source code to implement the SCA model by using the algorithms described above. To see the results of our studies, we have simulated the tumor growth at different times and looked at growth patterns as a function of time. In Fig. 4(a), we plot the numbers of cancerous (tumorous) cells and prolife-rating cells as functions of time, while in Fig. 4(b), we have plotted the numbers of proliferating cells and of tumor-immune complexes. The values of the parameters used in the simulations are given in the figure captions of Fig. 4(a). The Fig. 4(a) and 4(b) shows the results from one simulation with 250 time step and 350 time step, respectively. We see that the simulation yields a Gompertz like curve. As is well known, the Gompertz growth curve has been most used to fit the experimental data for *in vivo* tumor growth (Steel, 1977; Norton, 1988; Demicheli *et al*., 1991; Cameron *et al*., 2001). In Fig. 4(a) is a plot of the time evolution of the tumor size, the size of a tumor reflects the number of tumorous cells, $N(t)$. Fig. 4(c) shows the snapshot of simulated tumor at t = 25, 100, 200, and 250 time steps. The simulated tumors consist of four types of tumorous cell: proliferative tumor cells, tumor- immune complexes cells, dead tumor cells, and dormant cells.

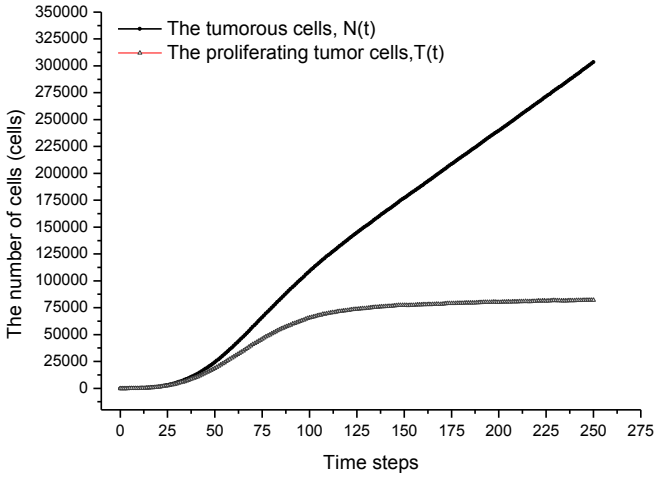


Fig. 4(a) Plots of time evolutions of the number of tumorous cells and number of proliferating cells from the parameter setting is $r_{\mathrm{p}} = 0.5, r_{\mathrm{r}} = 0.05, r_{\mathrm{evade}} = 0.1, r_{\mathrm{cytotoxic}} = 0.4, r_{\mathrm{dormant}} = 0.3,\ r_{\mathrm{decay}} = 0.5,$ and $T_{\max} = C_{\max} = 100\ 000$.

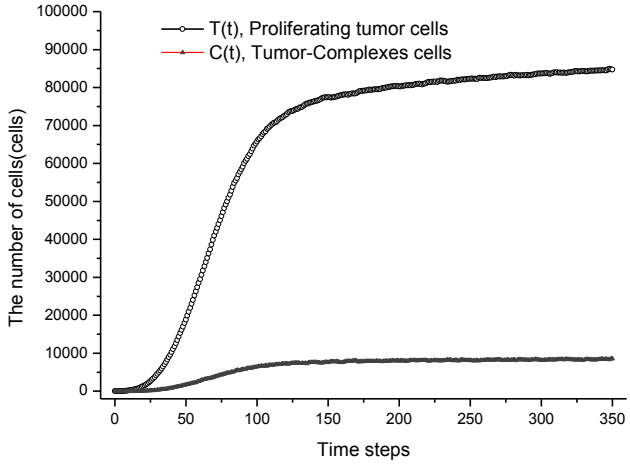
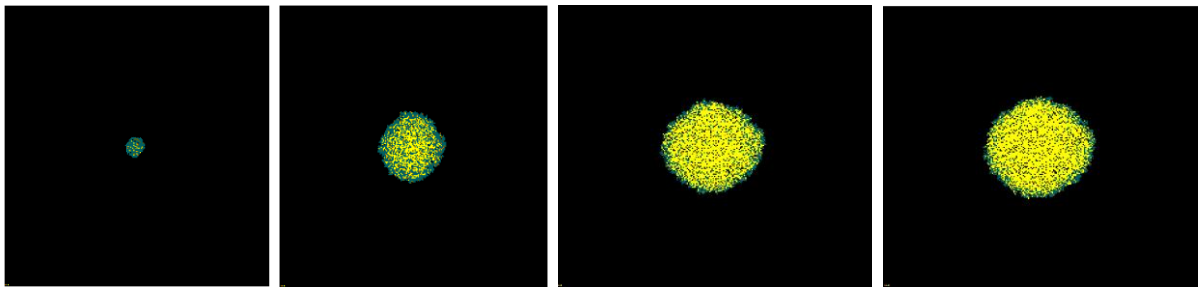


Fig. 4(b) Plots of time evolutions of the number of proliferating cells and number of tumor-immune complexes cells. The parameter setting is the same as in Fig. 4(a).



$t = 25$ $t = 100$ $t = 200$ $t = 250$

Fig. 4(c) The snapshot of simulated tumor shows the evolution of tumor size were generated by the SCA model hybrid the kinetic reaction is typically, shown on a 151x151 lattice. Typical simulated tumor after time steps of 25, 100, 200, and 250, respectively. The simulation setting is the same as Fig. 4(a). The simulated tumor with the four tumorous cell types, proliferative tumor cells, tumor-immune complex cells, dead tumor cells, and dormant cells with the different color green, brown, red, yellow, respectively. (= proliferative tumor cell, = complexes cell, = dead tumor cell, and = dormant cell).

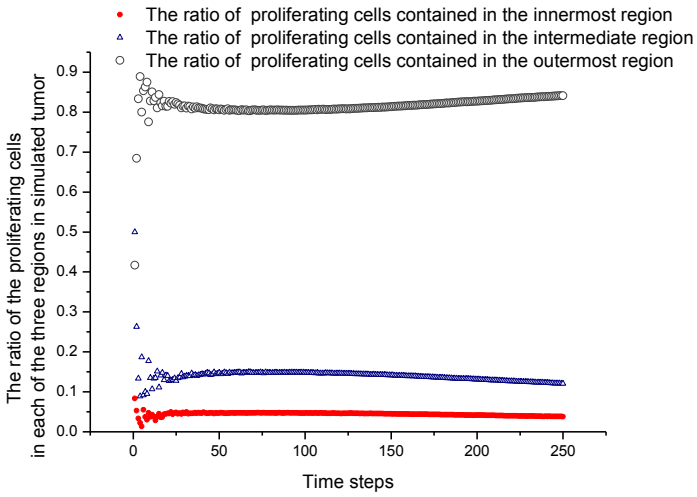


Fig. 4(d) Typical plots of the time evolution to show the ratio between the number of proliferated cells and the number of tumorous cells in the innermost, intermediate, and outermost region as defined by Bru and coworkers (Bru *et al*., 2004). The values of the parameters are the same as those used in Fig. 4(a).

They are color coded in the Fig. 3. Bru and coworkers (Bru *et al*., 2004) defined three regions in the avascular tumor. With the average radius of tumor being R and r_i as the distance of a proliferating cell i from the center of tumor, a cell is located in the innermost regions when r_i was in the range $0 \le r_i < \frac{R}{2}$, the cell is in the intermediate regions when r_i is in the range $\frac{R}{2} \le r_i < \frac{4R}{5}$ and the cell is in the outermost regions when r_i was in the range $r_i \ge \frac{4R}{5}$. Bru and coworkers (Bru *et al*., 2004) measured the number of proliferating cells in the three regions in a human colon adenocarcinoma tumor. Fig. 4(d) shows plots of the time evolution of the ratio of the number of proliferated cells and the number of tumorous cells in the innermost, intermediate, and outermost region as defined by Bru *et al*., 2004.

To see the effects changing the dormancy rate $\mathrm{r}_{\mathrm{dormant}}$ on the growth of the cancerous tumor, we have simulated the growth when $\mathrm{r}_{\mathrm{dormant}}$ has been varied but the values of the other parameters have kept constant at the values given in the caption of Fig. 5(a). Fig. 5(a) shows the simulated tumor growth curves when the dormancy rate is varied from 0.00 to 0.06 in steps of 0.02. Snapshots of the cross sections of the simulated tumor are shown in Fig. 5(b). We see that the morphologies of simulated tumors exhibit different amounts of dormant cells in the tumor and the spatial distribution of proliferating cells changes when $\mathrm{r}_{\mathrm{dormant}}$ is increased. We see that increasing $\mathrm{r}_{\mathrm{dormant}}$ will cause increases in the number of dormant cells in the inner and intermediate regions inside the simulated tumor. This leads to the result that most of the proliferating cells will be located at the perimeter of the simulated tumor cell clusters.

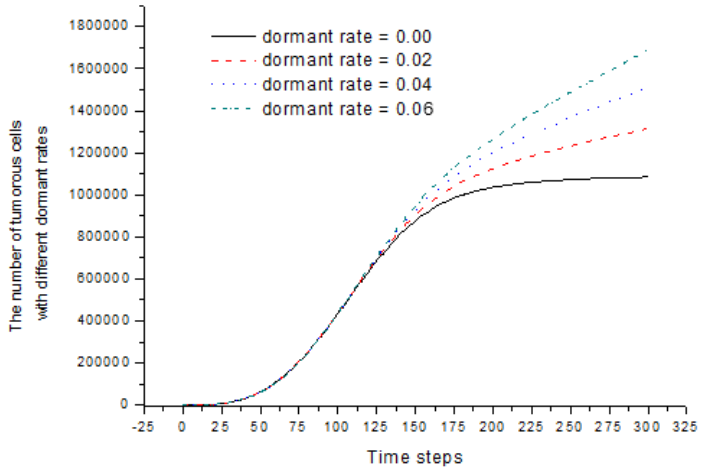


Fig. 5(a) The simulated tumor growth curves when the dormancy rate is changed. The simulated growth curves are for $\mathrm{r}_{\mathrm{dormant}}$ being increased from 0.00 to 0.06 in steps of 0.02, with the carrying capacities being $T_{\max} = C_{\max} = 1\ 000\ 000$ and the values of the other rates are $r_{\mathrm{p}} = 0.7, r_{\mathrm{r}} = 0.05,$ and $r_{\mathrm{evade}} = 0.1, r_{\mathrm{cytotoxic}} = 0.4,\ r_{\mathrm{decay}} = 0.5.$

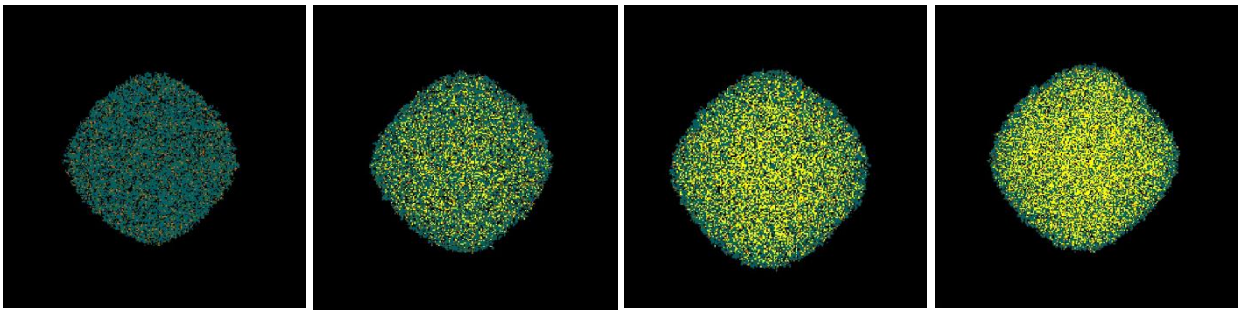


Fig.5(b) The snapshots of the cross sections of the simulated tumor which were generated by the SCA are shown on a 271×271 lattice after 300 time steps. The tumors seen are the simulated tumors when the dormancy rate is increased from 0.00 to 0.06 in steps of 0.02 from the left to right.

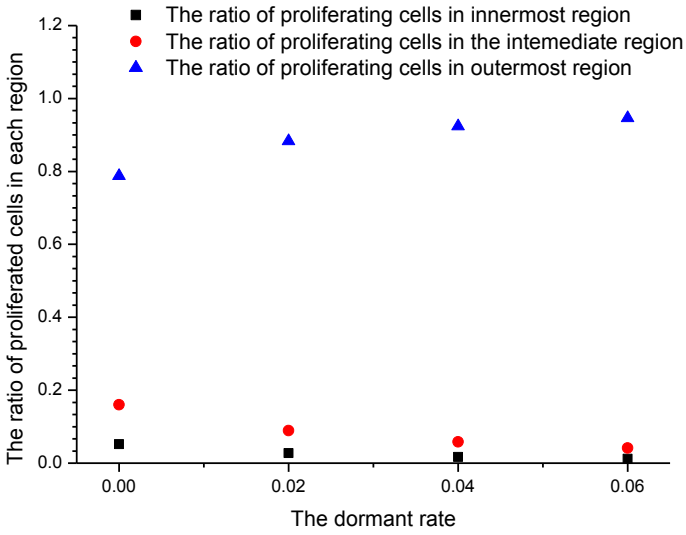


Fig. 5(c) The spatial distribution of simulated tumor using the same values of the parameters used to obtain Fig. 5(a). This figure shows the averaged ratio of the number of proliferating cells and the number of tumorous cells as the number of time steps is increased from 250 to 300.

This is in agreement with the findings of Bru and coworkers (Bru *et al.*, 2004) who found that the outermost regions of a tumor contained the proliferating tumor cells. They found the ratio of proliferating cancer cells found in the three regions of tumor to be in order 80:14:6 where the ratio is for outermost to innermost, meaning that most of the cancer growth is taking place in the outer layer. This expected since any cells in the innermost layer do not have many vacant spaces next to them and they would not be proliferating.

Discussion

We carry out a sensitivity analysis of the dormancy parameter since this parameters affects the spatial distribution of proliferating cells within the tumor. This is done by varying the value of the dormancy ratio from 0.00 to 0.06 in steps of 0.02 and determining the increases in the numbers of proliferating cell in the three regions when the number of time steps to increase from 250 to 300. The results of these determinations are plotted in Fig. 5(c) which shows that the ratio of the number of proliferating tumor and the number of tumorous cells in each region tends to asymptotical limits as dormancy rate increases and that the end result of an increase in the dormancy rate will increase the number of proliferating cells in the outermost region. This is in agreement with the conclusion of Bru and coworkers (Bru *et al*., 2004).

Conclusions

In this research, we have studied the growth of cancerous avascular tumors by simulating its growth with a model which includes interactions between the cancerous cells and different parts of the immune system. The interactions are based on what has actually been seen clinically. These include the observations that one of the task of the immune response is to survey and identify which of the cells is cancerous. The same mechanisms that leads to the identification of the cancerous cells also lead to the formation of cancer-immune complexes which have important roles in causing the cytotoxic activity (death but no disintegration of the cell) and apoptosis (death and disintegration). Apoptosis makes it possible for a different cancerous cell to proliferate through mitosis (the process which leads a cell to separate into two daughter cells). Without the apoptosis mechanism activated by an effective immune response, a dead cell will becomes a dormant cell preventing new cells from moving into its space. The model also includes the possibility that the cancerous cell can escape from the complex and proliferate again by activating the escape mechanism in the proliferating cancer cells.

Altogether there are six transition rates: a rate for recognizing a cancerous cell, a rate of proliferation, a rate for a cancerous cell to escape (evade) from the tumor-immune complex, a rate for cytotoxic activity to take hold, a rate for a dead cell to be become dormant, and a rate for the disintegration of a dead cancerous cell. The decisions as to what cellular transitions are determined by picking random numbers and establishing the rules for the taking the different choices. The entire process leads to stochastic cellular automata (SCA) approach.

We have applied our cellular automata model to a cubic lattice and have simulated the growth of the tumor. We find that the growth curves of the different types of cancerous cells; proliferating cells, dormant cells, dead tumor cells and tumor-immune cell complexes appear as Gompertz–like curves, which is the shape of the experimental growth curves of human colon adenocarcinoma tumor obtained by Bru and coworkers (Bru *et al*.,

2004). Our computer simulations, Figs. 5(b) and 5(c), also show that the densities of the proliferating cells is the greatest in the outermost region of the cancerous cells which is also agree with Bru and coworkers (Bru *et al*., 2004) observed.

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