Proceedings of the 2003 IEEE
International Conference on Robotics,Intelligent Systems and Signal Processing
Changsha, China - October 2003

A Simple Cellular Automaton Model for Tumor-immunity System*

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Abstract

This article builds a sort of immune system model basing on cellular automata method, in order to simulate the immune response to tumor growth. This paper discusses immune-tumor system at the cellular level, based on the simple two-dimensional stochastic discrete cellular automaton model. In this simple three-layer structure designers take into account the features of the immune response, and regard many different kinds of immune cells as the single immune element. The model describes the interaction between cancer and immune cells, and shows immune cells growth around tumor. The authors study the normal cellular automaton model, and design the evolution growth rules. At last we build discrete cellular automaton model of tumor-immune system, and simulate tumor-immune system on computer. The model predicts the dynamics of the tumor-immune system in agreement with Gompertz growth. Via adjusting different parameters of simulating model, the ultimate results indicate the basal behaviors of tumor-immune system exactly.

1 Introduction

Cellular automata (CA) are one of effective methods. CA consist of lots of discrete particles. From the theoretical viewpoint, Neumann and Ulam introduced CA in the late 1940's. John Horton Conway's "game of life" strongly attracted people's attention in the late 1960's. Wolfram did lots of work on non-linear dynamical theory of CA up to 1980's, and made a good base for physics models. As we know, the immune system is a self-organizing complex feedback network in the body. Its main function is one of the body's defenses against tumor. These are some interesting dynamical system problems how to describe the process of tumor-immune system evolution, and how to respond to tumor proliferative in time. Immunoreactions for cancer cells is a sort of emergence property produced by lots of local interaction. Immunity network is unstable and variable according to environmental variety. In recent years, researchers have done a great deal in modeling tumor-immune system, and provided many valuable mathematical models, based on differential equation. In tumor-immune system, there are not only too many serious nonlinear interactions between different components, but also happen large numbers of relevant variety along with time evolution [1]. Those complicated properties finally lead the classical mathematical model to lose the ability of describing the complex process. The purpose of modeling tumor-immune system is to deduce macroscopic properties of a system from element cell interactions. Though we don't know clearly tumor growth process in details, its macroscopic properties still may be observed and described by concrete experiments [2]. Now the problem is how to show complex interactions in tumor-immune system with simple methods. Introducing microscopic local interactions and discrete models make us conveniently and directly describe biological phenomena, and deal with a mass of interactions between microscopic [3]. We usually have interest in macroscopic properties of a system, and don't mind its microscopic origin. In recent years, researchers introduce lots of new methods and technologies into the field of modeling tumor-immune system. The cellular automata approach is one of important modeling branch. Cellular automata (CA) are dynamical computational mathematical systems that are completely discrete in time, space and state. The set of finite states on network node define its dynamical properties. CA is composed into the big system by a very large of components, and has the power of modeling complex system. In contrast to the other computational methods, CA may model and simulate well biological, physical and societal complex phenomena. It possibly replaces differential equations to one of modern modeling methods [4]. Modeling tumor-immunity system is a brand-new research field. To local level CA offers better interaction ability; to macroscopic level it shows the normal phenomena of tumor-immune system. So we choose two dimensional CA approach to design tumor-immunity system program based on rules, and expect CA model to show basal properties of tumor-immunity system growth.

2 Cellular Automata Model

The physical tumor-immunity system is very complex network. Its main properties are described by correlated and simple illuminations [5]. In this article we limit CA model with some hypothesis. Those are:

1. We regard different immune cells, such as B, T, AP, PLB, in tumor-immunity system as the single component cell "immunity cells";

* The project was supported by Beijing natural science foundation (3993010)

2. The model system is composed by three cell population, normal economy cells, abnormal tumor proliferative cells and immunity cells;
3. There are there kinds cells actions. They are respectively cell motion, cell proliferative and cell competition between three kinds of different populational cells;

4. There are two kinds of interactions in the model system between normal cells and tumor cells, and between tumor cells and immunity cells.

According to some necessary hypothesis and simplifications, we studied and built a simple CA model based the cell level. We may define the discrete CA model simulating tumor-immune system growth as quaternary Tumor-Immunity System Cellular Automaton Model (TISCAM):

TISCAM={Cells, CEllSpace, Neighbors, Rule} (1)

where:

(1) Cells: the basal element cell;

(2) CellSpace: the cell space, the set of all cells in TISCAM, include the boundary definition;

(3) Neighbors: Neighbor of TISCAM, the defining field of Rules;

(4) Rules: Evolvement rules of TISCAM.

2. 1 Cells, Cell-Space and Neighbor of TISCAM

Cells are the basal element of TISCAM. Its whole set is the cell space of TISCAM. The cell of TISCAM is a square grid. In normal case the cell space is full of normal healthy economy cells. We define the cell space of TISCAM as two-dimensional coordinate system *O(i,j)*. The cell located at position *(i,j)* of TISCAM is *Cell(i,j)*. The center cell of TISCAM is located at the origin of coordinate system *Cell(0,0)*. We formulate the cell space of TISCAM into:

$$CellSpace = \{Cell(i,j) \mid i,j \in I\} \quad (2)$$

where $I=\{-I_{max}, \cdots, -2, -1, 0, 1, 2, \cdots, I_{max}\}$.

We add a layer cell into the ragged edge of model for making up neighbors of model boundary. The different cell grids define respectively different cell populations. Each cell has many states to represent different cell types. At first normal cells is stroma of model, then tumor mass grows up quickly from one cancer seed located at the center cell grid of model. Abnormal tumor cells infect constantly, and proliferate. Immunity cells spread out random in normal cells of whole model grids. Immunity cells may move freely in normal cells, and there isn't any interaction between immunity cells and normal cells. Immunity cells don't proliferate in model. But immunity cells will be stimulated by abnormal tumor cells growth, and move to tumor cells grids, then interact each other in figure 1.

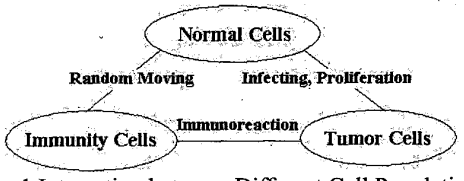


Fig. 1 Interaction between Different Cell Populations

Neighbor of TISCAM is similar with extended Moore neighbor. Neighbor of *Cell(i,j)* in TISCAM is defined as $A_M(i,j)$, and formulate as so:

$$\begin{cases} A_M(i,j) = \{\ Cell(q,r) \mid R(q,r) \le d\} \\ R(q,r) = \sqrt{(q-i)^2 + (r-j)^2} \end{cases} \quad (3)$$

where d is radius of extended Moore neighbor, $A_M(i,j)$is neighbor of *Cell(i,j)* extended Mooreneighbor. Immunity cells may move freely in normal cells. Its immune radius is the radius of Mooreneighbor. The definition of $d^*$and $A^*_M(i,j)$is similar with *Cell(i,j)*'s.

2. 2 Designing Evolvement Rule

Tumor growth is regarded as cells state evolvement in TISCAM. In other words cells evolve slowly according to governing rules from normal cells, to proliferative cells, to non-proliferative cells, and to necrotic cells. Immunity cells freely move into normal cells. Cells evolution in TISCAM depends on states of extended Moore neighbor. It is harmonious relation between immunity cells and normal cells. But it is different from the relation between tumor cells and immunity cells. If it is full of proliferative cells in neighbors of one normal cell at present, then it is very possible this normal cell will evolve into one tumor proliferative cell at next time. Cell states evolve, in turn, from normal cell, proliferative cell, non-proliferative cell to necrotic cell. When tumor cells encounter immunity cells in model, then there will be three possible results. One is Immunity cells win war; another result is that tumor cells kill immunity cells; the third result is they fight and become another different state. We call it as unstable complex state. Some concentric cell shell tissues usually compose the macroscopic idealized solid tumor model. They are, in turn, necrotic cells layer, cell-cycle rest stage G_0 layer and outer proliferative cells layer from inside to outside.

We order the state of *Cell(i,j)* in TISCAM at t time into $s_{i,j}(t)$. There are six values of $s_{i,j}(t)$.

$$s_{ij}(t) \in \{0,1,2,3,4,5\} \quad (4)$$

where $i, j \in I$. their different values as next formula:

States of normal cells:

$\begin{cases} s_{ij}(t)=0: \ Cell(i,j) \text{ is normal cell at } t \text{ time;} \\ s_{ij}(t)=1: \ Cell(i,j) \text{ is immunity cell at } t \text{ time;} \end{cases}$

State of middle cell: $s_{ij}(t)=2:$ *Cell(i,j)* is middle-state cell at t time;

States of abnormal cells:

$\begin{cases} s_{ij}(t)=3: \ Cell(i,j) \text{ is tumor proliferative cell at } t \text{ time;} \\ s_{ij}(t)=4: \ Cell(i,j) \text{ is tumor dormant cell at } t \text{ time;} \\ s_{ij}(t)=5: \ Cell(i,j) \text{ is tumor necro cell at } t \text{ time;} \end{cases}$

TISCAM implements parallel dynamical evolution. In other words at each discrete time t all cells in cell-space of TISCAM evolve simultaneously. Gompertz growth model is very famous in lots of tumor mathematical growth models. Its equation is Eq.5.

$$V(t)=V_0\exp\left(\frac{A}{B}(1-\exp(-Bt))\right) \quad (V(0)=V_0) \qquad (5)$$

where t is time; $V(t)$ is tumor volume at t time; V_0 is initial tumor volume at 0 time; A and B are two constant parameters in model. According to experimental data from medical literatures and discrete Gompertz equation in tumor growth, we design evolving rules of CA, in total four items.

Rule 1, Evolving tumor cells: tumor cells growth obey Gompertz equation. Its basal growth rule is Eq.6.

$$s_{ij}(t+T_0)=\begin{cases} s_{ij}(t) & p_{ij}^{(l)}(t)\le P_{Thr}^{(l)} \\ s_{ij}(t)+1 & p_{ij}^{(l)}(t)>P_{Thr}^{(l)} \end{cases} \qquad (6)$$

Where $i,j=\{-I_{max},\cdots,-2,-1,0,1,2,\cdots,I_{max}\}$; $P_{Thr}^{(l)}$ is evolving threshold probability; $p_{ij}^{(l)}(t)$ is evolving probability of *Cell(i,j)* at t time in TISCAM. We define evolving probability $p_{ij}^{(l)}(t)$ in Eq.7.

$$\begin{cases} p_{ij}^{(l)}(t)=P_0^{(l)}\left(1-\dfrac{r_{ij}(t)}{R_{\max}}\right)\psi(t) \\ \psi(t)=\left(1-\exp\{-\beta^{(l)}r_{ij}(t)\}\right)\left(1-\exp(-\alpha^{(l)}f)\right) \end{cases} \qquad (7)$$

where $r_{ij}=\sqrt{i^2+j^2}$ is distance between *Cell(i,j)* and the center of tumor model; $P_0^{(l)}$ is radical value of evolving probability, and it corresponds to a cell-doubling time of tumor cells; $\alpha^{(l)}$ and $\beta^{(l)}$ is weight coefficient; f is effect factor of *Cell(i,j)*. We define f in Eq.8.

$$f=\sum_{Cell(q,r)\in A_M(i,j)}\frac{1}{d_{ij}^2(q,r)} \qquad (8)$$

where $d_{ij}(q,r)=\sqrt{(q-i)^2+(r-j)^2}$ is distance between *Cell(i,j)* and its neighbor *Cell(q,r)*.

Rule 2, immunity cells randomly move in normal cells: At first every other interval immunity cell choose one of eight directions around the center cell by probability P_{dt}, then walk one unit, namely one grid, along with this chosen direction. If moving probability p is less than threshold value, immunity cell keep initial position. We formulate rule 2 in Eq.9.

$$L(t+T)\xrightarrow{P_{dt}}D_{mov}\xrightarrow{p}\begin{cases} L(t) & p<th \\ L(t)+1 & p\ge th \end{cases} \qquad (9)$$

Where $L(t)$ is cell position; P_{dt} is directional probability; D_{mov} is moving direction; p is cell active probability; th is moving threshold value.

Rule 3, immunoreaction: When tumor cells appear in Moore neighbors of immunity cell, immunity cell directly move into tumor cell grid. It will happen immunoreaction. There are three sorts of immunoreactive results. First, immunity cell kill tumor cell, and cell recover. Second, cancer cell break into defense of immunity cell, and go on infecting, proliferating normal cells. Third, two sorts of cells aren't so strong that they can't defeat rival. So they keep balance each other, and go into middle-stage cell in Eq.10.

$$Tc+Ic\xrightarrow{P_I}\begin{cases} Nc & p_I<Th \\ Mc & p_I=Th \\ Tc & p_I>Th \end{cases} \qquad (10)$$

Where Tc is tumor cell; Ic is immunity cell; Nc is normal cell; Mc is middle-stage cell; P_I is immunoreaction probability; Th is immunoreaction threshold value.

Rule 4, Evolving middle-stage cells: As last sect said, after immunity cells and tumor cells interact each other, one of results is there is middle-stage cells appear in system. We suppose middle-stage cells are very unstable. If sum of normal cells and immunity cells are more than six units in its neighbor, then middle-stage cells will evolve possibly normal cells. Whereas it will be affected by abnormal cells around it, and evolve into tumor cells further in Eq.11.

$$Mc\rightarrow\begin{cases} Nc & Nc+Ic>6 \\ Tc & Tc>3 \end{cases} \qquad (11)$$

Different growth probabilities and parameters of six-states CA model we build are chose from experiment data in medicinal literatures. Considering the model simulating space limits, we adjust suitably them. Uniform distributing random function produces direction probability P_{dt}, active probability p and immunoreaction probability P_I. Other parameters in model are listed in table 1.

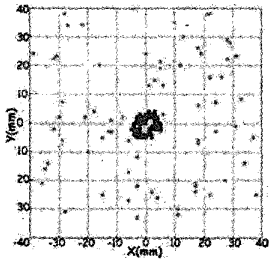
Table 1: parameters of model

Parameters of Model	Parameters Meanings	Value Scope
$P_{Thr}^{(l)}$	Threshold Value of Evolving Probability	0.3 -- 0.6
$P_0^{(l)}$	Radical Value of Evolving Probability	0.0 – 0.5
$\alpha^{(l)}$ and $\beta^{(l)}$	Weight Coefficient	0.0 – 1.0
th	Moving Threshold Value	0.4 – 0.6
Th	Immunoreaction Threshold Value	0.35 – 0.52

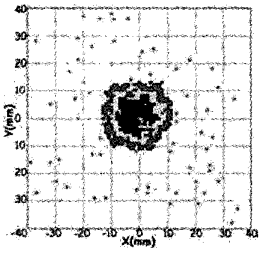
3 Simulations

Gompertz equation provides an approximate description of the tumor growth. We compare the simulating results of CA model with tumor growth volume data of Gompertz equation. The following parameter set was used: R_0=0.1mm, A=0.42mm$^{1/3}$, B=0.11mm$^{1/3}$, R_{max}=37.5mm and cell-doubling time is 4 days[6]. The data set will determine one idealized Gompertz tumor growth curve. Now we give the growth model initial state. (1). Initial discrete time is $t=0$; (2). The initial state value of center cell *Cell(0,0)* of TISCAM is 3; (3). Immunity cells spread out uniformly in cell-space. Its value is 1; (4). The initial state of rest cells is 0.

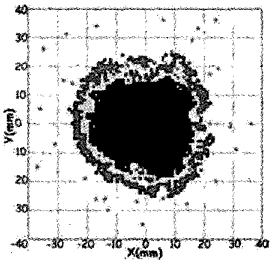
Well we give parameters set of TISCAM. (1). The biggest tumor growth radius is $R_{max}=37.5mm$; (2). The radius of extended Moore neighbor is $d=2$; (3). The radical Value of Evolving Probability is $P_0^{(l)}=0.192$; (4). The threshold Value of Evolving Probability is $P_{Thr}^{(l)}=0.43$; (5). The weight Coefficient is 0.5; (6). The moving threshold value is $th=0.8$; (7). The Immunoreaction threshold Value is $Th=0.5$.



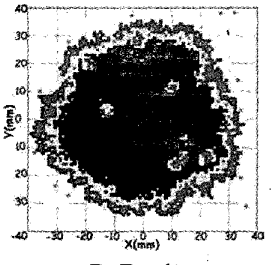
A. Spheriod



B. Detect Lesion



C. Diagnosis



D. Death

Fig. 2: Results of Simulating Tumor-Immunity System

The tumor-immunity system based TISCAM can show very good visual image results of idealized correlate immunoreactions in tumor growth process. We show some section plane snapshots TISCAM simulates four important stages in tumor growth process in Fig. 2. They are respectively spheroid phase, detect lesion phase, diagnosis phase and death phase. We may see the results given by the TISCAM fit the relevant observed tumor growth curves well. The coincidence indicator is surely base of CA modeling meanings.

4 Conclusions

CA is applied into modeling and simulating complex physical system, biological process and societal phenomena. It is an alternation of differential equation modeling. As we know describing tumor growth as complex, dynamic, self-organizing bio-systems is rather than merely focusing on single features [6]. In order to understand complex system, new simulation approaches should be developed. In contrast to conventional differential equation model, CA can simulate well microscopic complex tumor-immunity system in tumor growth process. In this article we developed one tumor-immunity system based on discrete two-dimensional stochastic CA model, and simulated visually immunoreactions in tumor growth process. Modeling tumor-immunity system is the important research field. It combines lots of concepts from many scientific areas such as cancer research, statistical mechanics, applied mathematics and nonlinear dynamical systems [6]. Researching on TISCAM is helpful for forecasting clinical tumor growth process, and help doctors diagnose tumor illness, and improve therapeutic schedule. What we did on TISCAM is simple and idealized case. We neglect many biological factors as complex life phenomena, and set some necessary hypothesis according to our understanding to tumor-immunity system. In other words, our work is just primary explore in this field. The further results will be reported in future.

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