On a cellular automaton with time delay for modelling cancer tumors

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Abstract

In this work we considered cellular automaton model with time delay. Time delay included in this model reflects the delay between the time in which the site is affected and the time in which its variable is updated. We analyzed the effect of the rules on the dynamics through the cluster counting. According to this cluster counting, the dynamics behavior is investigated. We verified periodic oscillations same as delay differential equation. We also studied the relation between the time delay in the cell cycle and the time to start the metastasis, using suitable numerical diagnostics.

Motivation

The cancerous tumors dynamics, including their growth, propagation, and treatment, is one of the major problems in mathematical biology. The interest for the problem has led to the formulation of numerous growth models proposed in order to analyze one or several basic features, such as the metastasis, the lack of nutrients, the competition for resources and the cytotoxic activity made by the immune response. Cellular automata are prototypes of spatially extended dynamical systems, that present discrete space and time, as well thus the state variables take on a finite set of discrete values. In recent papers, cellular automata models have been considered to model aspects of tumor growth and therapy and the presence of immune surveillance. A two-dimensional stochastic cellular automata model was proposed to describe avascular solid tumor growth, taking into account both the competition between cancer cells and normal cells for nutrients, space and a time-dependent proliferation of cancerous cells.

In this paper we are to investigate the role of time delay in the cell interaction as a triggering factor for metastasis, by using a modified version of a cellular automaton model for cancer growth proposed by Qi and collaborators[1]. This model also takes into account other microscopic properties, as the proliferation of cancer cells, the cytotoxic effect of the immune system, and the mechanical pressure inside the tumor; so as to reproduce the Gompertz growth of cancer tumors.

Rules

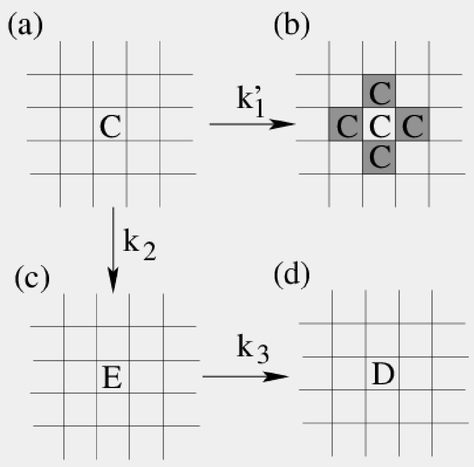

Figure: (a) to (b) describes the possibility of proliferation at one of the shadowed sites occupied by normal cells, (a) to (c) denotes the cytotoxic process and (c) to (d) the complex is replaced by a dead cell.

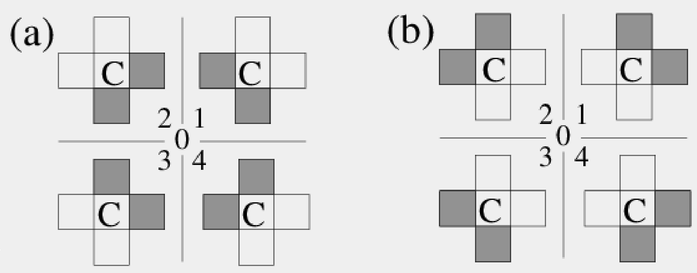

Figure: The number 0 indicates the center of the square lattice, where 1,2,3 and 4 denote the four quadrants. When $\rho(t) \leq \rho_c$ the second daughter cell will occupy one of the two shadowed sites with equal probability, as it is showed in (a), and (b) for $\rho(t) > \rho_c$.

We insert a time delay in the cellular automaton [1] in order to analyze the dynamics behavior of cancerous cells in a tissue. Then, let the cancerous (abnormal) cells, the dead cancerous cells, the effector (cytotoxic) cells (macrophages, etc) and the complexes produced by the cytotoxic process be respectively represented by $\mathbf{C}$, $\mathbf{D}$, $\mathbf{E_0}$, and $\mathbf{E}$. Fig. (1) shows the processes considering the proliferation or dissolution of a cancerous cell. As a matter of fact this process can be depicted by the following reactions:

$$\mathbf{C} \xrightarrow{k_1'(t)} \mathbf{2C}, \tag{1}$$

$$\mathbf{C + E_0} \xrightarrow{k_2} \mathbf{E} \xrightarrow{k_3} \mathbf{E_0 + D}, \tag{2}$$

$$\mathbf{D} \xrightarrow{k_4} \mathbf{normal.} \tag{3}$$

Reaction (1) describes the proliferation of cancerous cells at a time $\mathbf{t}$, with

$$k_1'(t) = k_1\left(1 - \frac{N_c}{\phi}\right), \tag{4}$$

where $\mathbf{k_1(t)}$ is the proliferation rate of cancerous cells, $\mathbf{t}$ is the time, $\mathbf{N_c}$ is the total number of cancerous cells and ϕ is a constant, thus $\mathbf{N_c}$ reaches the maximum ϕ. We can see by Fig. 1(a) to (b) that the cell $\mathbf{C}$ located at site will divide into two and one them will occupy the original position and the other will randomly invade one of the four neighbor sites primarily occupied by normal cell. The first reaction in (2) denotes the cytotoxic process, in that reaction (2) a single effector binds to one abnormal cell in a time. In doing so, there is not cancerous cell proliferation, as it is showed in Fig. 1(b), and there is a probability of a cytotoxic process (Fig. 1c). The second reaction of (2) depicts the dissolution of complexes. In this case the cell died in accordance with a determined probability (Fig. 1d). Equation (3) describes the dissolution of dead cells. The values adopted for the parameters $\mathbf{k_1}$, $\mathbf{k_2}$, $\mathbf{k_3}$ and $\mathbf{k_4}$ are listed in reference [1].

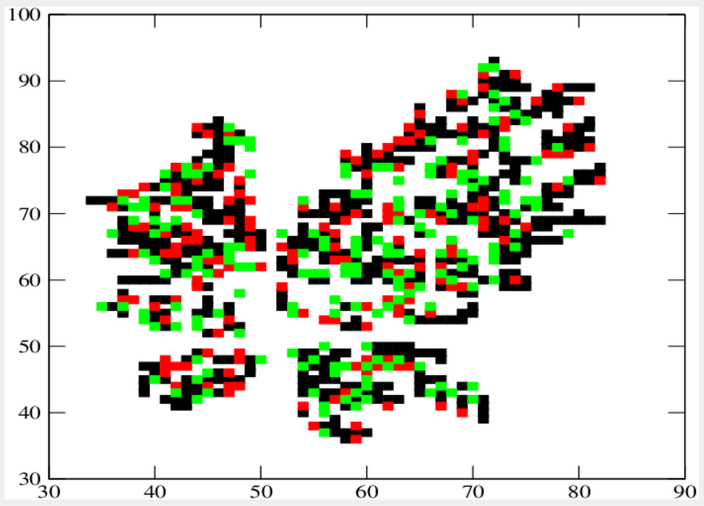

Figure: (Color online) The shape of a tumor $\mathbf{k_1 = 0.74}$, $\mathbf{k_2 = 0.2}$, $\mathbf{k_3 = k_4 = 0.4}$, $\rho_c = \mathbf{3.85}$, $\phi = \mathbf{10^3}$ and $\mathbf{t = 50}$. Black squares represent cancerous cells, red squares are complexes and green squares are the dead cancer cells. The initial configuration is only 5 cancerous cells in the central part of the lattice.

Time Evolution

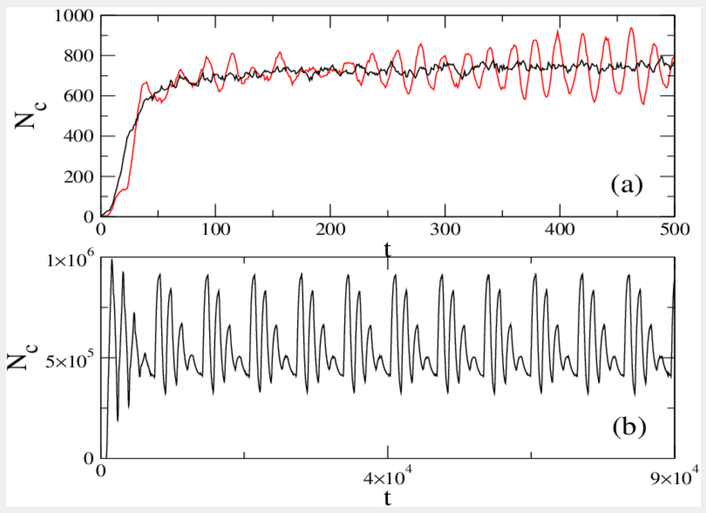

Figure: (Color online) The time evolution of $\mathbf{N_c}$ for $\mathbf{k_1 = 0.74}$, $\mathbf{k_2 = 0.2}$, $\mathbf{k_3 = k_4 = 0.4}$ and $\rho_c = \mathbf{3.85}$. (a) $\mathbf{101 \times 101}$, $\phi = \mathbf{10^3}$, $\tau = \mathbf{0}$ (black line) and $\tau = \mathbf{5}$ (red line), (b) $\mathbf{1301 \times 1301}$, $\tau = \mathbf{850}$ and $\phi = \mathbf{1.7.10^6}$.

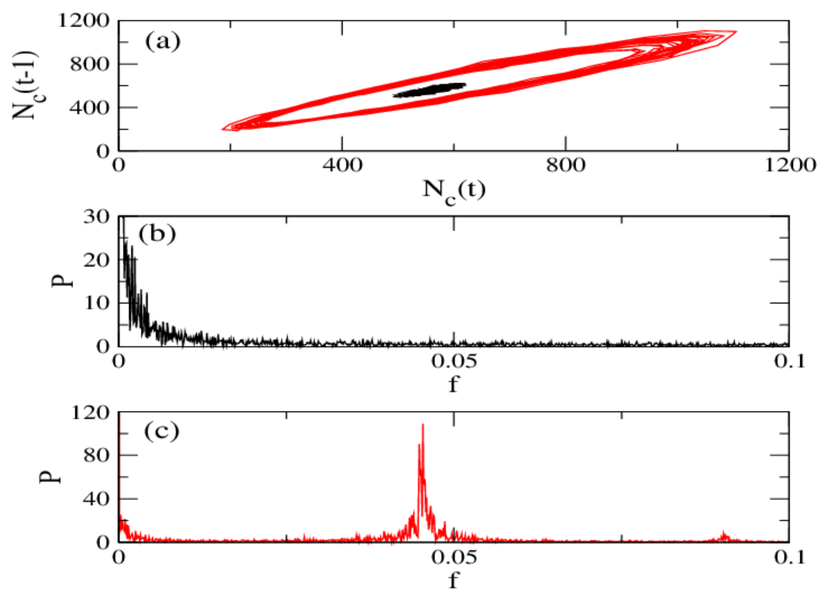

Figure: We consider $\mathbf{k_1 = 0.74}$, $\mathbf{k_2 = 0.2}$, $\mathbf{k_3 = k_4 = 0.4}$ and $\rho_c = \mathbf{3.85}$. (a) Delay plot of the number of cancerous cells showing a non regular behaviour for $\tau = \mathbf{0}$ (black line) and a regular for $\tau = \mathbf{6}$ (red line), as well as the figures (b) and (c) show the respective power spectrum.

Metastasis

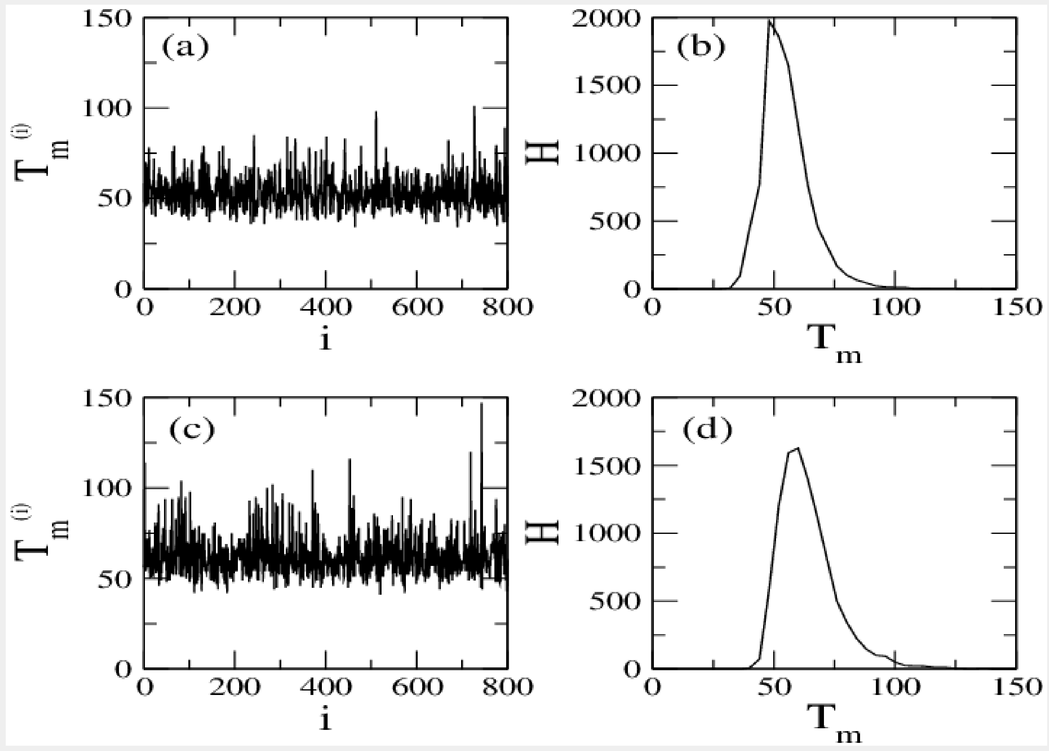

Figure: $\mathbf{T_m^{(i)}}$ versus $\mathbf{i}$ and distribution for (a) and (b) with $\tau = \mathbf{0}$, (c) and (d) with $\tau = \mathbf{10}$. We considered $\mathbf{N = 101}$, $\phi = \mathbf{1000}$, $\rho_c = \mathbf{3.85}$, $\mathbf{k_3 = k_4 = 0.4}$, $\mathbf{k_2 = 0.2}$ and $\mathbf{k_1 = 0.5}$.

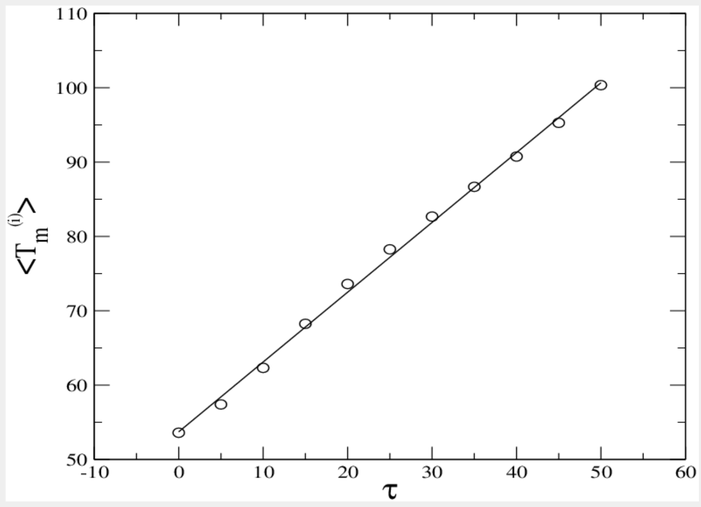

Figure: Average of $\mathbf{T_m^{(i)}}$ varying the time delay, where we considered $\mathbf{k_1 = 0.5}$, $\mathbf{k_2 = 0.2}$, $\mathbf{k_3 = k_4 = 0.4}$, $\rho_c = \mathbf{3.85}$ and $\phi = \mathbf{10^3}$. The solid line is a least-squares with slope≈1.

References

Qi A -S, Zheng X, Du C -Y and An B -S, *A cellular automaton model of cancerous growth*, 1993 Journal of Theoretical Biology **161** 1.