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# 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.

## 1. Introduction

The cancerous tumors dynamics, including their growth, propagation, and treatment, is one of the major problems in mathematical biology [1]. The interest for the problem has led to the formulation of numerous growth models [2], which have been proposed in order to analyze one or several basic features, such as the metastasis [3], the lack of nutrients [4], the competition for resources and the cytotoxic activity made by the immune response [5].

In human cancers, the mean cell division cycle time is a relevant measure due to the difference that we find in patients and the region affected by cancer. The range average cycle time varies from 2 days to several weeks with a mean of approximately 6 days [6]. Cell division cycle can be divided into 4 distinct phases, such as  $G_1$ -phase, DNA synthesis or  $S$ -phase,  $G_2$ -phase and mitosis or  $M$ -phase. The duration of  $S$ -phase,  $G_2$ -phase and  $M$ -phase is relatively short, most cancerous cells in a patient's tumor are in  $G_1$ -phase. Bertalanffy and collaborators [7] investigated the cell cycle of Ehrlich tumor cell populations. Ehrlich tumors are neoplastic cell populations frequently employed in cancer research, due to the fast proliferation. They transplanted primary Ehrlich ascites tumors to a great variety of mice, and observed that the  $S$ -phase duration seems to center around 9 hours,  $G_2$ -phase may be around an hour and the mitosis ranged from 30 to 75 minutes. Some studies showed that most Ehrlich tumor cell lines pass through at least a brief  $G_1$  phase which lasts about 3 to 6 hours. Besides the experimental evidence in DNA synthesis, there is an equation used to described the fraction of the Ehrlich cell cycle [8].

Experiences have shown the effect of various chemotherapeutic agents on metastasis, and the relationship between cell cycle and tumor growth. One element that has received attention in recent years is the selenoprotein. Mice injected with this element presented a pronounced reduction in tumor progression and metastasis in colon and prostate [9]. Moreover, experimental observations have shown that selenium can inhibit cell cycle progression in human prostate cancer [10].

Continuous and discrete models are types of approaches used to describe the cancerous growth. The mathematical modelling of cancer growth and therapy can be done using many tools, as ordinary and partial differential equations [11]. However, discrete models such as cellular automata have been used as well chiefly, because they can be formulated in a rather simple way by specifying the types of cells involved and their evolution through rules connecting the cells and their neighbors [12].

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 [13]. They have been used on self-organization studies in dynamical systems, as cancerous cells proliferation [14], traffic flow [15], neural network [16], ecosystems [17], and spatial pattern formation [18].

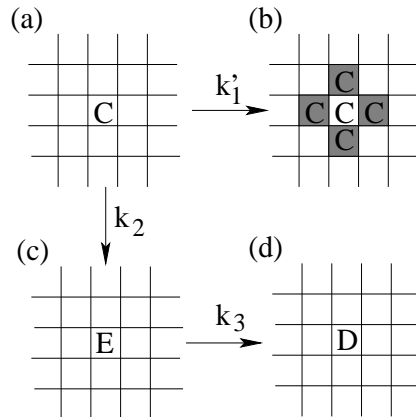
From cellular automata models, one is able to investigate how global (macroscopic) behavior of cell assemblies as tumors are affected by changes in local (microscopic) properties of the cell interaction with its surrounding medium [19]. One macroscopic property of tumors is the metastasis, or the ability to migrate to other parts of the body through the lymphatic system or the bloodstream, causing the appearance of secondary tumors in other organs. The mechanisms triggering the appearance of metastasis are not well-known presently, but one possible factor involved is some change in the interaction between the cells at the microscopic level [20, 21].

In recent papers, cellular automata models have been considered to model aspects of tumor growth and therapy [22] and the presence of immune surveillance [23], as well as to study the role of acidity in tumor growth [24]. Tumor-induced angiogenesis has also been modelled using a cellular automaton approach [25]. 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 [26].

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 [23]. 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.

In the Qi and collaborators model the cancer cell mitosis is instantaneous, what is obviously a simplifying assumption [23]. Accordingly, we introduced a time delay in our modified model as a parameter representing the time it takes for a cancer cell to undergo mitosis [27, 28]. As we shall see, on varying this time delay it is possible to trigger the formation of metastases. This is consistent with similar findings for delay differential equation models of tumor evolution. Hence, we claim that the same outcome would be exhibited by other similar cellular automata models of cancer growth, so that our result is quite general in spite of having been observed in a particular model.

This paper is organized as follows: in Section 2 we introduce the cellular automaton with emphasis on the time delay in proliferation. Section 3 shows the results obtained with the varying of the cellular automaton model parameters that influence the dynamics behavior using the cluster counting. The last section presents the conclusions.



**Figure 1.** (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.

## 2. Cellular automaton with time delay

In this study we insert a time delay in the cellular automaton [23] 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  $C$ ,  $D$ ,  $E_0$ , and  $E$ . 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:



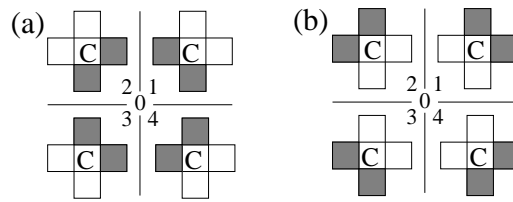
Reaction (1) describes the proliferation of cancerous cells at a time  $t$ , with

$$k'_1(t) = k_1 \left( 1 - \frac{N_c}{\phi} \right), \quad (4)$$

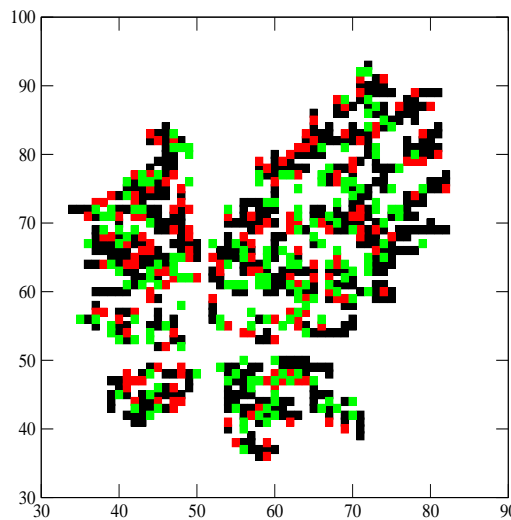
where  $k_1(t)$  is the proliferation rate of cancerous cells,  $t$  is the time,  $N_c$  is the total number of cancerous cells and  $\phi$  is a constant, thus  $N_c$  reaches the maximum  $\phi$ . We can see by Fig. 1(a) to (b) that the cell  $C$  located at site will divide into two and one them 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  $k_1$ ,  $k_2$ ,  $k_3$  and  $k_4$  are listed in reference [23]. To overcome the lack of the experimental data for  $k_4$ , it is possible to consider the value in the wide range (0.1-0.4).

The density of cancerous cells  $\rho(t)$  describes the effect of the mechanical pressure on cancer development,

$$\rho(t) = \frac{N'}{R^2}, \quad (5)$$



**Figure 2.** 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  $\rho(t) > \rho_c$ .



**Figure 3.** (Color online) The shape of a tumor  $k_1 = 0.74$ ,  $k_2 = 0.2$ ,  $k_3 = k_4 = 0.4$ ,  $\rho_c = 3.85$ ,  $\phi = 10^3$  and  $t = 50$ . 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.

where  $N' = N_c + N_E + N_D$ ,  $R = (\sum R_{ij})/N'$  and  $R_{ij}$  depicts the distance from the site  $(i, j)$  occupied by a cancerous cell to the origin. Considering a critical value of  $\rho(t)$ ,  $\rho(t) = \rho_c$ , we have that if  $\rho(t) \leq \rho_c$ , the second daughter cell resulting from the proliferation can only occupy one of the inside nearest neighboring sites occupied by normal cell (Fig. 2a), if  $\rho(t) > \rho_c$ , the second daughter cell may invade outside nearest neighboring sites with normal cell (Fig. 2b). This way we used equal probability of the second daughter to occupy one of the two possible neighboring sites.

The shape of the tumor is shown by Fig. 3 for  $k_1 = 0.4$ ,  $k_2 = 0.1$ ,  $k_3 = k_4 = 0.35$ ,  $\rho_c = 3.7$ ,  $\phi = 10^3$  and  $t = 50$ . We consider at  $t = 0$ , 5 cancerous cells in the central part of the square lattice  $101 \times 101$  and all of the remaining sites are occupied by normal cells. The black, red and green colors denote  $C$ ,  $E$  and  $D$ , respectively. The white region represents the normal tissue and we can see that the tumor is irregular at each lattice site

We include a time delay  $\tau$  in proliferation rate of cancerous cells  $k_1'(t - \tau)$  and density of cancerous cells  $\rho(t - \tau)$ , in order to consider the delay between the time at which a cancerous cell commences mitosis and the time at which the daughter cell is produced.

Fig. (4a) shows the curves of  $N_c$  versus  $t$  for  $\tau = 0$  (black line) and  $\tau = 5$  (red line). It is seen that the curves reach their average maxima simultaneously. Thus, results given by the model

fit the relevant observed cancer growth curves. The model may describe the Gompertz growth of a cancer [29], as a matter of fact its algebraic is

$$V = V_0 \exp \left\{ \frac{A}{B} [1 - \exp(-Bt)] \right\}, \quad (6)$$

where  $V$  is the volume of the tumor,  $A$  and  $B$  are parameters,  $t$  is the time and  $V_0$  denotes the initial volume. The parameters are obtained as a result of experimental data.

At  $\tau = 5$  an periodic oscillation of amplitude occurs, furthermore the value of  $\tau$  to occur oscillatory behavior of  $N_c$  depends on the network size. Due to this fact, we can see in the Fig. (4b) a periodic oscillation for a network with  $N = 1301$  considering  $\tau = 850$ . In a model of delay differential equations proposed by Banerjee and Sarkar [30] it was presented the existence of periodic solutions, that is, tumor levels oscillated around a fixed point in absence of treatment. This phenomenon is known as Jeff's Phenomenon [31], and it has been observed clinically.

The value of  $\tau$  may cause oscillations due to the competition between  $k_1$  and  $k_2$ . Moreover, there is a critical value of  $\tau$  for which the network presents  $N_c = 0$  after a transient time, i.e., the proliferation of cancerous cells ceases.

Fig. (4b) shows that the amplitude of the oscillations increases when we increase the network size. This behavior occurs due to the fact that  $\phi$  may be increased, and  $N_c$  reaches the maximum  $\phi$ . The amplitude of the oscillations does not increase when the network size increases and the  $\phi$  is maintained constant.

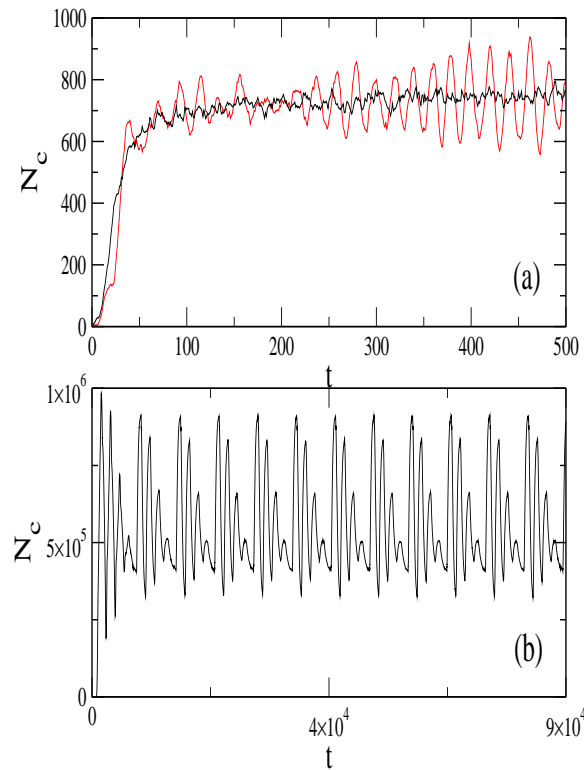
In Fig. (5a) we plot each value of the time series of number of cancerous cells versus a time-delayed version, by plotting  $(N_c(t), N_c(t-1))$ . This is called a delay-coordinate reconstruction, or delay plot. At  $\tau = 0$  a small and irregular oscillation of the values of  $N_c$  can be observed in Fig. (5a) (black line), whereas for  $\tau = 6$  the red line reproduces a regular behavior. Fig. (5b) and (5c) show the power spectrum analysis for  $\tau = 0$  and  $\tau = 6$ , respectively. The power spectrum analysis is used to detect periodic behavior, indeed for  $\tau = 6$  (Fig. 5c) there is a periodic behavior with a value of frequency around 0.045. By the way, oscillatory behavior occurs in delay differential equation due to a Hopf-bifurcation. The delay in differential equation model for tumor growth is used to study the effects and interactions between tumor cells and immune cells [30][32][33].

### 3. Cluster

In each cell growth pattern, a cluster is defined as any set of interconnected cells which is physically isolated from any other group of cells on the pattern. We use the Hoshen-Kopelman method to study the number of clusters of the cancerous cells in the cellular automaton. Hoshen and Kopelman introduced in 1976 a breakthrough algorithm for cluster analysis in percolation phenomena [34]. Cluster size distribution of cellular aggregates was also used to characterize the growth patterns of established normal and cancer cell lines, cultured in mono-layer and collagen gel [35].

Fig. (6) shows the time evolution of the number of clusters  $\eta$  for two different values of the proliferation rate of cancerous cells  $k_1$ . As we observe the maximum average value of  $\eta$  increases with the rate  $k_1$ , although the time for achieving maximum decreases. By the way, when a time delay is included it is possible to occur a periodic oscillation in the values of  $\eta$ . However, the main result is the difference in the values of number of the cancerous cells varying the rate  $k_1$ . In preliminary injection experiments with a mouse bronchogenic carcinoma [36], a known metastasizable tumor, it was shown that metastasizability is exhibited by viable tumor cells in clumps and not by discrete single cells.

In many cancer cases, the cancer spreads from the one site to another physiological organ via the blood stream or via the lymphatic system. This processes is known as metastasis [37]. Tumor metastasis consists of a series of discrete biological processes that move tumor cells from



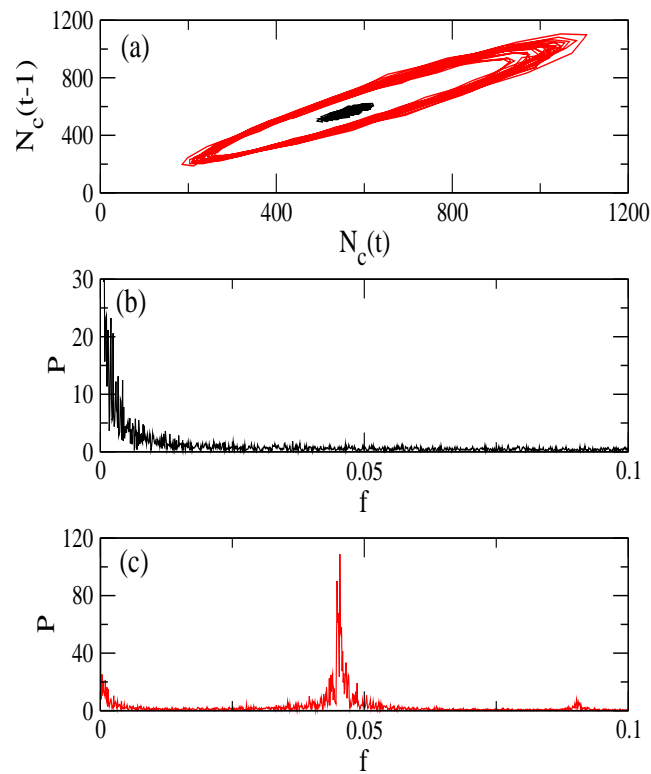
**Figure 4.** (Color online) The time evolution of  $N_c$  for  $k_1 = 0.74$ ,  $k_2 = 0.2$ ,  $k_3 = k_4 = 0.4$  and  $\rho_c = 3.85$ . (a)  $101 \times 101$ ,  $\phi = 10^3$ ,  $\tau = 0$  (black line) and  $\tau = 5$  (red line), (b)  $1301 \times 1301$ ,  $\tau = 850$  and  $\phi = 1.7 \cdot 10^6$ .

the primary site to a distant location [38]. When tumor cells metastasize, the new tumor is called a secondary or metastatic tumor. Metastatic tumors are very common in the late stages of cancer. It is sometimes the case where the secondary tumor is one that is fatal. Cells that metastasize are basically of the same kind as those in the original tumor. We considered that the metastasis occurs when the value  $\eta$  is greater than a critical value  $\eta^*$ .

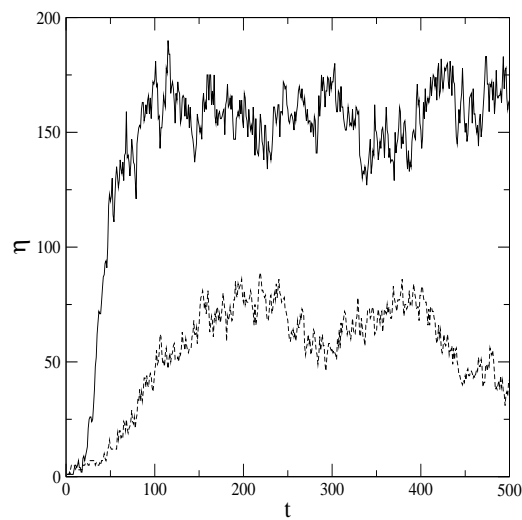
Fig. (7) represents the probability of a cytotoxic process versus proliferation rate of cancerous cells exhibiting a gray region where the metastasis occurs. For this reason, by Fig. (7), the metastasis only can occur for values of  $k_1$  and  $k_2$  in the gray region when the cellular automaton presents  $\eta > \eta^*$ , so that we fix  $\eta^*$  equal 50.

Let us fix  $\eta$  at a value, say  $\eta = \eta^* = 50$ , and vary the parameter  $k_1$  to analyze the behavior of the time to start the metastasis  $T_m$ , that is, the time to the number of clusters attains the critical value  $\eta^*$ . We analyze the values of the  $T_m$  for different seeds of the random number generator due to the fact the proliferation be probabilistic, then we consider several time evolutions with different initial random seeds to verify the behavior of  $T_m^{(i)}$  at each seed  $i$ . This probabilistic behavior may be related to dependence of the cancerous growth on the manner and speed with which it adapts to changes in its surroundings and composition.

Fig. (8a) shows that the values of  $T_m^{(i)}$  behave asynchronously, on the other hand, in Fig. (8c) we can see spikes with amplitudes higher than the case without time delay in proliferation. Moreover, increasing  $\tau$  the spikes increase its amplitude and quantity. In fact, if we plot the distribution it is possible to observe that the time to start the metastasis  $T_m$  increases with the time delay, in accordance with the distribution in Fig. (8d) which has a minor area and a shift

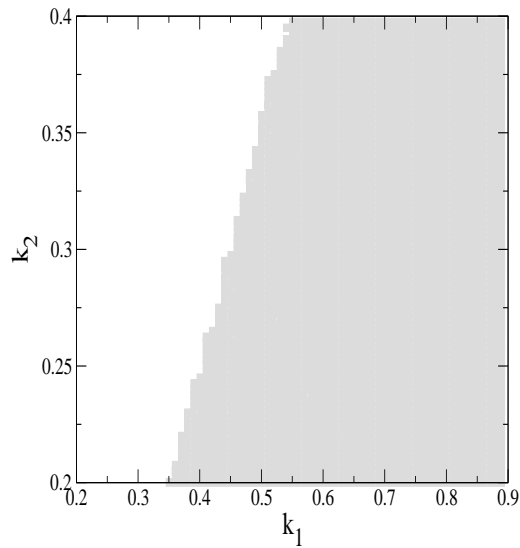


**Figure 5.** (Color online) We consider  $k_1 = 0.74$ ,  $k_2 = 0.2$ ,  $k_3 = k_4 = 0.4$  and  $\rho_c = 3.85$ . (a) Delay plot of the number of cancerous cells showing a non regular behaviour for  $\tau = 0$  (black line) and a regular for  $\tau = 6$  (red line), as well as the figures (b) and (c) show the respective power spectrum.

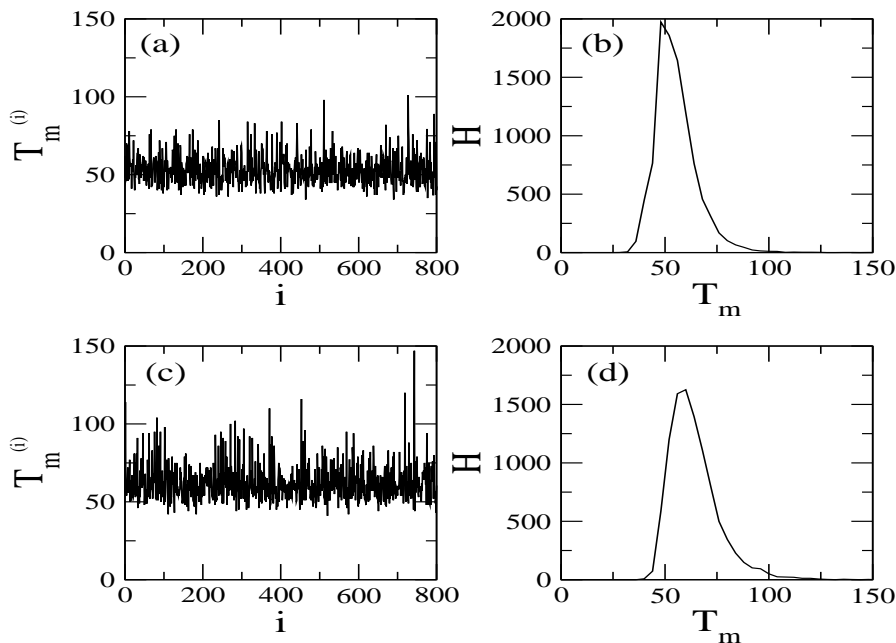


**Figure 6.** Time series of the number of clusters for  $N = 101$ ,  $\tau = 0$ ,  $\phi = 1000$ ,  $\rho_c = 3.85$ ,  $k_2 = 0.2$ ,  $k_3 = k_4 = 0.4$ ,  $k_1 = 0.74$  (continuous line) and  $k_1 = 0.4$  (dashed line).





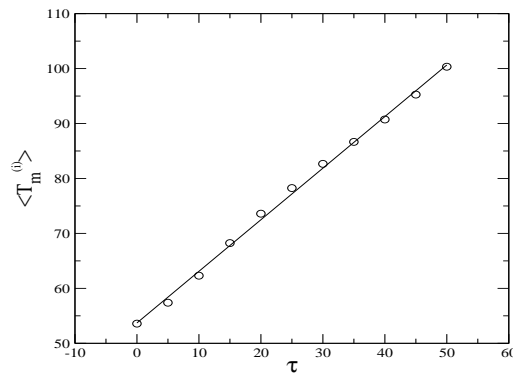
**Figure 7.**  $k_2$  versus  $k_1$  for  $N = 101$ ,  $\phi = 1000$ ,  $\rho_c = 3.85$ ,  $k_3 = k_4 = 0.4$  and  $\eta^* = 50$ . Gray region represents the values which metastasis occurs ( $\eta > \eta^*$ ).



**Figure 8.**  $T_m^{(i)}$  versus  $i$  and distribution for (a) and (b) with  $\tau = 0$ , (c) and (d) with  $\tau = 10$ . We considered  $N = 101$ ,  $\phi = 1000$ ,  $\rho_c = 3.85$ ,  $k_3 = k_4 = 0.4$ ,  $k_2 = 0.2$  and  $k_1 = 0.5$ .

to right compared with distribution of the Fig. (8c), as a result of major values of  $T_m^{(i)}$ . In order to obtain a time delay in the metastasis it is necessary to consider a time delay in proliferation.

In Fig. (9) we have plotted the average time to start the metastasis versus the time delay, where our results for the average was taken by considering different initial condition profiles. We can observed the tendency of the time to start the metastasis increases when the time delay increases. This behaviour may occur as a result of chemotherapeutic agents. There are agents



**Figure 9.** Average of  $T_m^{(i)}$  varying the time delay, where we considered  $k_1 = 0.5$ ,  $k_2 = 0.2$ ,  $k_3 = k_4 = 0.4$ ,  $\rho_c = 3.85$  and  $\phi = 10^3$ . The solid line is a least-squares with slope  $\approx 1$ .

that inhibit cell cycle, as well as they are used to increase the time to start the metastasis [10].

#### 4. Conclusions

In this paper we studied some aspects of the cancerous growth dynamics displayed by a cellular automaton, also we analyzed the metastasis starting time from a primary to a secondary cellular automaton varying parameters of the system. With a time delay in proliferation we observed periodic behavior of the number of the cancerous cells for some parameter values. This behavior may explain periodic tumors whose growth is uncorrelated with the administration of chemotherapy, more commonly referred to as Jeff's Phenomenon.

We considered the number of clusters as a critical parameter to start the metastasis. We have found that the metastasis starting time increases when a time delay in proliferation is introduced in the model. The results suggested that the metastasis starting time increases when cancerous cell division is not instantaneous.

The model with a time delay introduced in proliferation has more complex dynamics than the model without time delay, such as oscillatory behavior and time delay in the metastasis, as well as it reproduces same periodic oscillations as delay differential equation.

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