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# A Stochastic Cellular Automata Model of Tumor-immune Interaction

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**Keywords**

Cellular Automata,
Immune cells,
Tumor growth,
Growth fraction,
Necrotic fraction.

**Abstract**

Cancer is a leading cause of death in the world. Mathematical and computer models may improve current treatments by helping scientists better understand this disease. They may also introduce new aspects of therapy by predicting the result of changes in microenvironment of the tumor or the interaction between different types of cells. In this paper, a square lattice Cellular Automata model of tumor-immune cell interaction is presented. The state of each tumor cell can be updated according to stochastic rules related to its previous state and the states of its Moore neighborhood. The growth fraction and necrotic fraction are used as output parameters beside a 2-D graphical growth presentation. Our results show that entering immune system not only improves the compatibility of the model with physiological reality which show the impact of immune cells on tumor invasion, but also the results of output parameters are fitter to experimental data.

## 1. Introduction

Accounting for 8.2 million deaths in 2012, cancer is a leading cause of death worldwide. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 within the next two decades [1]. These numbers are expected to grow with time as populations get older in developing countries and better cancer treatments are promoting longer longevity. Therefore, cancer research is a field where most money is spent in today's research [2]. Cancer mortality can be reduced if cases are detected and treated early. Since the treatment of cancers is a challenging issue, different attempts should be considered. Study of tumor growth seems to be useful in understanding cancer in morphological and functional properties [3].

Mathematical and computer modeling may lead to a greater understanding of the dynamics of cancer progression in patients [4]. The understanding of dynamics of formation and cancer growth can give researchers opportunities to try new prevention and treatment solutions [2]. The key characteristics lead to propose and develop a mathematical model are shown in the Figure 1. As it can be seen we emphasized on studying and gathering the knowledge of the system we are going to describe, trying to formulize it by using computational hypothesis, and then making predictions by introducing new concepts. The control of the interacting elements in a tumor is a difficult task in an experimental work. It is also difficult to predict the situation of tumor growth since it is a biological complex system. Hence, mathematical modeling using different methods could be helpful in understanding important features of such a complex system [3]. Using Ordinary or Partial Differential Equations (ODEs or PDEs) is one of these methods. Other approaches like Monte Carlo (MC) and Cellular Automata (CA) in which deterministic or probabilistic methods are employed to obtain a final pattern are also useful.

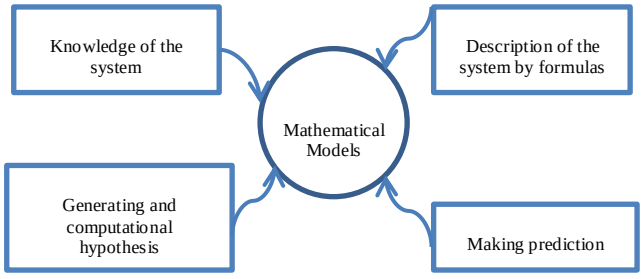


**Figure 1.** Properties of a mathematical model

Since there is not sufficient information about cell-cell and cell-environment interaction, deterministic prediction of the evolution of a tumor seems impossible. Even in *in vitro*

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experiments with well controlled microenvironments, stochastic effects are always present and make prediction difficult [5]. Therefore, most researchers treat the cell dynamic as a stochastic dynamic [6].

Computer simulations have been used to study *in silico* in some of the processes thought to lead to the formation of cancerous masses and have attained good results in explaining some facts observed *in vivo* and *in vitro* tumors [2]. Virtual experiments and simulations give the opportunity to observe effects of different treatments on cancerous cells, and could lead to improve these treatments or suggest new ones [7]. For understanding the *in vivo* behavior of cancer, the fundamental challenge for mathematical simulation is the simplification of the underlying complex processes while maintaining realistic findings [8].

Classical cancer simulation needs solving complicated differential equations which contains time consuming numerical method. Therefore, we consider the concept of cellular automata (CA) to display complex behaviors arising from the interaction among simple components with local connectivity.

CA may be considered as a method for modeling discrete dynamic systems. A CA consists of a discrete system of lattice sites (cells) having various initial values. These cells evolve in discrete time steps as each cell assumes a new state based on the rules i.e. the states of its local neighborhood and a finite number of previous time steps. The neighborhood is described by specifying the set of cells that are the neighbor of a given cell [9].

A CA lattice may be 1-D or multi-dimensional. There are several possible lattices and neighborhood structures for a 2-D CA, i.e., for a square lattice, two types of neighborhoods are typically used; the generalized "Von Neumann" neighborhood and the "Moore" neighborhood (Figure 2) [9].

Square lattices with nearest neighbor interactions are mainly studied in the literature, but triangle and hexagonal lattices are also possible [9].

**Figure 2.** Two kinds of neighborhoods for a central cell: Von Neumann (×) and Moore (●)

Since CA is capable of producing complex patterns by applying simple rules, it is appropriate for expressing many features of self-organizing complex systems which have been applied numerous phenomena in physics, chemistry and biology [10]. Macroscopic tumor growth behavior may be modeled by primarily microscopic data [11] using CA concept.

This paper is organized as follows: First, brief reviews of mathematical and CA models of solid tumor growth are presented. Then, we propose our model based on CA and present the simulation results for tumor progression and compare the simulated results with the *in vivo* experimental results and find that the two are in agreement in many respects. Finally, several conclusions and a discussion are given.

## 2. Mathematical Models

Since biological models are basically multi component chemical reactions, they can be modeled by systems with chemical reactions. With this point of view, the mathematical analysis used in the development of chemistry can be apply as a powerful tool in biological models [11, 12].

It has been shown that the tumor first grows exponentially and then level off to a linear growth [4]. Since avascular tumors receive nutrients (e.g., oxygen and glucose) by diffusion, the diameter to which they may grow is typically limited to several millimeters [13].

One of the first attempts to empirically describe the time-varying volume of a solid tumor is the Gompertz model [14, 15]. Distinct sigmoidal growth curves seen in spheroids also occur in some solid tumors, prompte investigation into whether any appropriate sigmoidal curve could be tempered to describe spheroid growth including other classical continuum tumor growth models such as Van Bertalanffy and logestic family models [16]. Among them, the Gompertz model best fits experimental data [5] which is shown in Eq. (1) as

$$V = V_0\, exp(\tfrac{A}{B}\,[1 - exp(-Bt)]) \qquad (1)$$

where $V_0$ is the volume at time $t = 0$ and $A$ and $B$ are the constant parameters that can be fitted to comply with experimental data [14].

However, real tumors always possess much more complex morphology. Besides, Gompertzian growth models are very limited; they only capture gross features of tumor growth and cannot explain their underlying 'microscopic' mechanisms [14]. Moreover, they cannot predict the effect of chemicals on tumor morphology.

Reaction-diffusion models are another important class of spatial tumor growth models [13]. A tumor growth is usually supposed as a wave traveling phenomenon in these models. This type of diffusion starts by random movement of cancer cells.

Burton [17] was probably the first to propose that diffusion and nutrient concentration limit the growth of solid tumor growth. Since then, numerous models based on spatio-temporal interactions between tumor cell populations and nutrients have been suggested [18]. These mathematical models included lots of large systems of differential equations in order to their special goal of modeling and the level of used details.

### *2.1. Mathematical Models Based on CA*

Here, we particularly concentrate on tumor growth models proposed based on CA. We just review some of important ones. Some of the earliest models were proposed by Düchting [19], with the goal to design a model to study the regulation of disturbed cell renewal through the analysis of two competing populations of cells [10]. A two-dimensional regular 10×10 square lattice with a Von Neumann neighborhood is used in this model. Each lattice site corresponds to a biological cell; and with some deterministic and local transition rules can survive, die or proliferate. If a cell dies, the lattice site becomes empty. The model suffers from the small computational power existing

at that time, which limited the lattice size. Although, scientists present an update to this model with enlarging the lattice to 100×100 sites and introducing extended rules [10].

Qi et al. [20] tried to explain the Gompertz growth curve which characterizes the growth behavior of some tumors by using a 2-D regular square lattice represents the tissue. This model contains four cell types (alive tumor cells, dead tumor cells, normal cells, and an immune cell interacting with a cancer cell) with probabilistic rules. Cells can proliferate, interact with the immune system and dissolve. One disadvantage of this model is that the dissolution of cells does not mimic real biological behavior, since dead tumor cells tend to accumulate, forming a necrotic core [10].

A brain tumor (GBM) growth model with a 3-D Voronoi lattice (see Figure 3) as the tissue was proposed in 2000 by Kansal et al. [21] in order to reproduce the macroscopic structure of a tumor arising from microscopic processes [10]. Each lattice site in this model corresponds to several biological cells. In Figure 3, the inner gray region is composed of necrotic tissue. The cross-hatched layer is composed of living, quiescent (non-proliferative) cells [14]. The authors assume three cell types corresponding to the possible types of malignant cells including the proliferating cells, quiescent cells and necrotic cells. Non-cancerous cells correspond to empty sites of the lattice [10]. The ability of cells to divide is treated by redefining the transition between dividing and non-dividing cells, as the cells attempt to divide, they will search for sufficient space for the new cell, beginning with its neighbors and expanding outwards until they find an empty cell or nothing is found within the proliferation radius. If the cell attempts to divide but cannot find space it is turned into a non-proliferative cell [21].

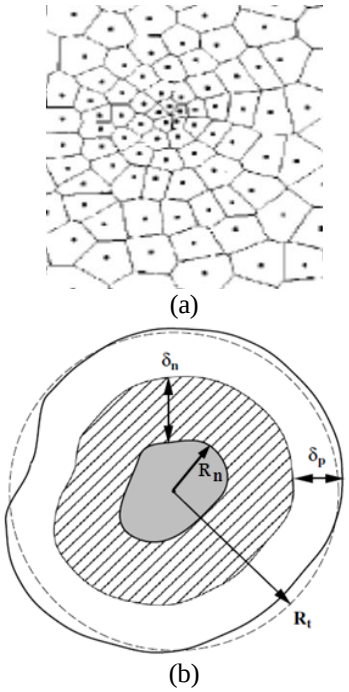



**Figure 3.** (a) A more representative section of the lattice, with the variable density of sites evident, (b) A cross-section of an idealized solid tumor which is used in this model

As the tumor grows, it becomes more difficult for nutrients to reach the core or center of the spheroid since the outer cells tend to consume these nutrients first [18]. Therefore, cells near the core (in the middle layer) can become so deficient that they lose their ability to be proliferative and enter the quiescent stage. Quiescent (non-proliferative) cells are still alive, and can recover with sufficient nutrients [18]. Moreover, the inner core which radius is a function of time in this model is composed of necrotic cells. Since these cells are too far from the nutrients, they are death. The outer shell contains active (proliferate) tumor cells [2]. Proliferative tumor cell is the only type of cells that can cooperate in mitosis.

This model is able to grow from a very small size of roughly 1000 real cells through to a fully developed tumor with 1011 cells [21]. This number of cells requires great computational power and the simulations were run in an IBM SP2 parallel computer [3]. Torquato later expands this model in 2011 [14]. Figure 4 exhibits a cut-away view of a simulated tumor generated from the minimalist CA algorithm [14]. The inner necrotic core is not depicted in this view. The yellow (light gray) region is comprised of non-proliferative cells and the red (dark gray) shell depicts the proliferative cells.

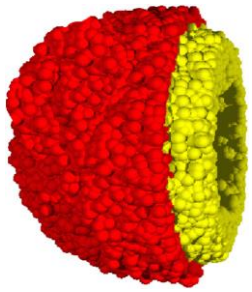


**Figure 4.** A cut-away view of a simulated tumor generated from the minimalist CA algorithm [14].

Another lattice gas cellular automata (LGCA) model of avascular tumor growth with a two-dimensional regular square lattice of 200×200 sites and a von Neumann neighborhood represents the tissue was proposed by Dormann and Deutsch [22]. Each lattice site can accommodate two types of cells -tumor or necrotic cells- that have an orientation expressed by one resting channel (c5) and four velocity channels (c1-c4). Cells can be quiescent, proliferate, die or become necrotic with given probabilities. The probabilities of mitosis, necrosis and apoptosis depend on nutrient concentration and local cell density. Besides, the chemotactic signal produced by necrotic material attracts cancer cells [10]. An example of a cell configuration at a lattice node *r*, is depicted in Figure 5. The dark gray filled circle and the light gray filled circle denote the presence of a tumor and a necrotic cell, respectively [10, 20].

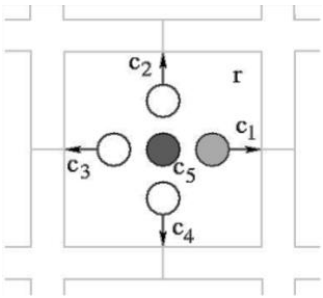



**Figure 5.** Example of a cell configuration at a lattice node *r*

Ghaemi and Sahrokhi [6] used combination of the LGCA and Cellular Potts Model (CPM) according to Dormann and Deutsch's previous model for simulating tumor growth. Later, Ghaemi et al. [3] had considered the effect of nutrient in the tumor growth in order to improve the precision of the model. In addition, they used a simple method for the diffusion step to simplify the model. Therefore, they proposed probabilistic cellular automata on a square lattice for simulating the dynamic of cancer growth in a reaction-diffusion frame. Each cancerous cell can proliferate, be quiescent, or die due to apoptosis or necrosis phenomenon in the reaction step. Moreover, in the reaction step, the three-state Potts model is used for calculating the probabilities [6].

Reis et al. [4] proposed a two-dimensional stochastic CA model to describe avascular solid tumor growth, taking into account both the competition between cancer cells and normal cells for nutrients and/or space and a time-dependent proliferation of cancer cells. A Moore neighborhood with a radius of one and four type of cells including empty site (ES), normal cell (NoC), cancer cell (CC) and necrotic tumor cell (NeC) was used. They assumed that the nutrients are uniformly available over the lattice, and introduced growth potential of normal ($P_{noc}$) and cancer ($P_{cc}$) cells to change the states of each cell. They also considered the probabilities of die due to drug injections in normal and cancer cells by $p_{drugn}$ and $p_{drugc}$, respectively.

## 3. Model Proposal

As we mentioned before, in order to propose a CA model we should introduce its properties (lattice, cell's states, neighborhood, rules, and initial values) one by one. Besides, we assume the growth starts out from a few cells, passes through a multicellular tumor spheroid (MTS) stage (Figure 3(b)) and proceeds to the macroscopic stages. Some of the assumptions used in this article are given in the following.

### *3.1. Lattice*

Here, we propose a probabilistic two-dimensional (L×L) CA model. Besides, we choose a square lattice- the lattice represents a tissue sample- for simplicity.

### *3.2. State Cells*

Each site ($i$,$j$) of the lattice represents some biological cells. The model is composed of six cell population including normal (healthy), proliferative (active) tumor, non-proliferative (quiescent) tumor, necrotic, immune, and dead cells due to the interaction between host immune cells and tumor cells. We briefly will mention them as Em or N, PT, NT, Ne, E, D respectively. In fact, these kind of dead cells because of immune system is considered different from necrotic cells, since necrotic cells cannot digest and solve into the microenvironment. Although dead cells because of the interaction between tumor cells and immune cells can change their state into an empty place/or a normal cell since they can digest.

The state of site ($i$,$j$) of the lattice in our CA model is depicted by $S_{i,j}$.

$$S_{i,j} = \begin{cases} 0 & \text{empty space or normal cell} \\ 1 & \text{proliferative cancer cell} \\ 2 & \text{Immune Cell} \\ 3 & \text{Dead cause of CTLs} \\ 4 & \text{non} - \text{proliferative cancer cell} \\ 5 & \text{necrotic cell} \end{cases} \quad (2)$$

It should be noted that only PT cells can divide. Besides, immune cells can only fight with PT cells.

Since the immune system plays an important role in the growth of avascular tumors, we decided to apply it as an item in our model. Therefore, we consider tumor-immune interaction in our proposed model.

Cytotoxic T lymphocytes (CTLs) infiltrate the tumor and induce apoptosis in the target tumor cells [23]. Depending on the cytokines and other signals presented in the tumor microenvironment, recruited immune cells will either form a pro-tumor immunity or an anti-tumor immunity that we show it stochastically here.

Cytotoxic T cells destroy virally infected cells and tumor cells. They recognize specific antigens to respond to an infection whereas Natural Killer (NK) cells [24] are innate response and do not rely on antigen. Their functionality is similar enough, but the major difference is that the T cells recognize antigens and NK cells do not. That is to say NK cells are the innate defense while cytotoxic T cells are cell-mediated and more specific. Therefore, here we consider cytotoxic T cells in our model.

### *3.3. Neighborhood*

We use Moore neighborhood with a radius of one.

### *3.4. Rule*

#### *3.4.1. For tumor cells*

As lots of models [3, 21], we assume that the nutrients are uniformly available over the lattice. In this respect, lack of nutrients is represented by lack of space in our model. Moreover, we consider a multi-cell spheroid model consists of an outer shell of PT cells, an inner layer of NT cells which are dormant but viable, and a central core of necrotic material.

Each PT cell can proliferate by probability of division p which varies with time and position. Note that, we use an additional parameter - maximum tumor extent ($R_{max}$) - to ensure the results of the model fit Gompertz curve. Therefore, the division probability in the radii greater than $R_{max}$ is zero and the tumor stops growing because of lack of nutrients. So, it reflects the effects of mechanical confinement pressure. The probability of $p$ is obtained by the Eq. (3) [21].

$$p = p_0\left(1 - \frac{r}{R_{\max}}\right) \quad (3)$$

where, $p_0$ is the base probability of division, and $r$ reflects the location of the dividing cell.

PT cells are checked to see if they will attempt to divide. In this case, it should assure that there is an empty place. If there is at least one empty or normal neighbor, PT cell should choose one by probability r1 and it will divide. Therefore, one of the daughter cells will remain in the same position of

the parent. The other one will place in that empty or normal neighbor.

As the tumor grows, it will shape as a multi-cell spheroid. Therefore, we consider a rim of PT cells layer (in the external part of MTS) with a thickness of $\delta_p$ which is obtained using the Eq. (4) [21].

$$\delta_P = b\, R_t^{2/3} \quad (4)$$

where $b$ is a constant parameter, and $R_t$ is the average radius of the tumor calculating by obtaining the external edge of the tumor.

If a PT cell attempts to divide but cannot find empty space it is turned into a NT cell. Therefore, the state of cell will change to 4.

Besides, the thickness of the middle layer in MTS is calculated based on Eq. (5) [21].

$$\delta_n = a\, R_t^{2/3} \quad (5)$$

where $a$ is a constant parameter, and $R_t$ is as mentioned before. We also consider the radius of the inner core (necrotic layer) $R_n$ - which is a function of time – that can be calculated according to the Eq. (6) [21].

$$R_n = R_t - (\delta_n + \delta_p) \quad (6)$$

In conclusion, if an empty (non-tumorous) space is found in a distance less than $\delta_p$, a PT cell can divide. Therefore, the healthy cell in the empty place is turned into a PT cell. Otherwise, the PT cell is turned to NT cell.

Moreover, if the radius of a NT cell is less than $R_n$ (and a distance more than $\delta_n + \delta_p$ from the tumor's edge), it will turn to a necrotic cell because of lack of nutrition. So, its state will change to 5. Besides, Ne cells accumulate in the inner part of the tumor and will not change to any other types of cells. They also will not digest in the encounter of immune system.

This process repeated during time iterations and the type of each cell is updated synchronously.

Figure 6 shows the block diagram of the mode with the general framework, and the change of states for the subroutines.

### *3.4.2. For immune cells*

Three kinds of cells' actions have been considered in this paper. They are respectively cell motion, cell proliferative and cell competition between three kinds of different population cells; tumor cells, normal cells and immune cells. Moreover, there are two kinds of interactions in the model between normal cells and tumor cells, and between tumor cells and immune cells. Here, the second one will be explained, since the first one was represented before.

We mentioned that we have immune (E) cells rather than normal and tumorous cells. E cells can move randomly in our model (we consider the existence of immune cells by probability of k2). If an E cell conflict a PT cell, some situation will happen. The PT cell may die due to cytotoxic T cells (CTLs) by probability k3 and its state will change to 3 which is an unstable state. Then, a dead cell due to CTLs may turn its state to a normal cell with the probability k4. PT cell also can survive and maintain its state.

Otherwise, the immune cell will die and become an empty place. In this case its state will turn to 0.

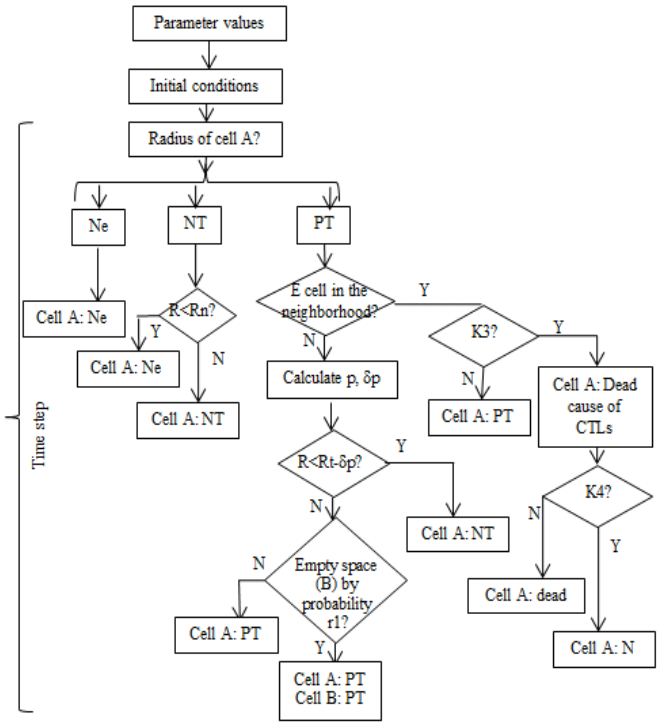



**Figure 6.** Block diagram of the rules of the model for cancer cells

### *3.5. Initial Conditions*

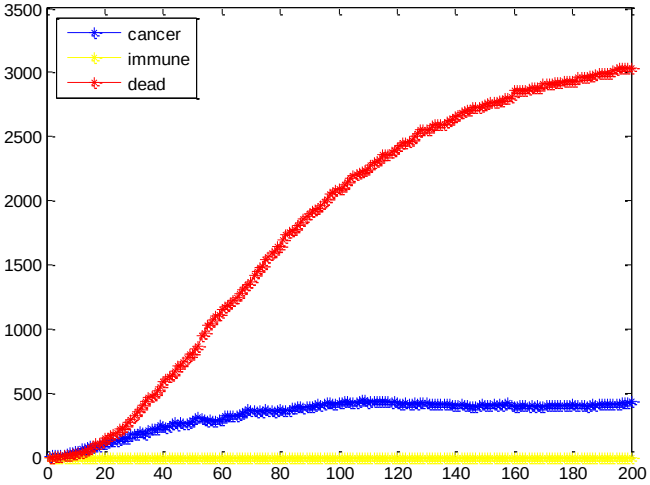
First, we consider whole cells of the tissue as normal with state 0. Then, at the initial condition ($t = 0$); the cells within a fixed initial radius of the center of the lattice are designated proliferative. Therefore, their state changes from 0 to 1. All other cells are supposed as non-tumorous. This was taken from the center of the lattice to ensure better visualization. Besides, we assume some cells of the lattice as immune cells randomly and change their state to 2. Later, we will discuss the results of the simulation both with and without consideration of immune cells. We also report our results by considering $a$=*0.2*, $b$=0.11, $R_{max}$=37.5 in the model. The $a$ and $b$ parameters have been chosen to give a growth history that quantitatively fits the test case.

## 4. Results

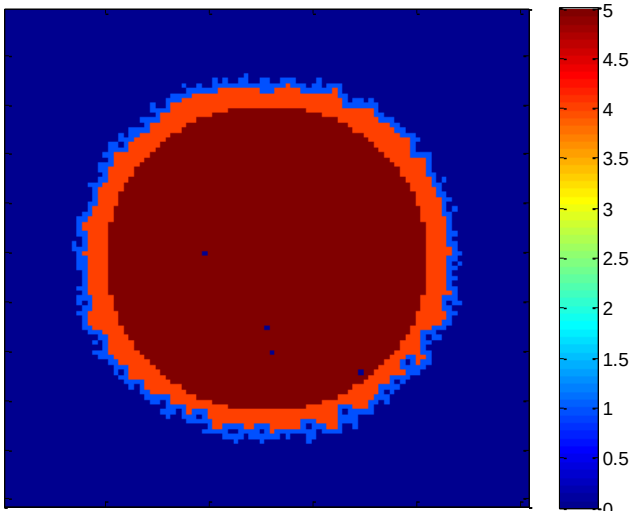
First, we simulate the model without considering any immune cell (i.e. k2=0). Other probabilities and parameters are $L$=100, and $p_0$=0.7.

Figure 7(a) shows the rate of number of necrotic, cancer and immune cells during simulation time iteration. While the effect of immune cells is not considered. As it can be seen, the number of cancer cells increase over time, follow the Gompertz model, and reach a limit of 500 cells. While the number of necrotic cells increase agressively and reach 3000 cells during simulation. Besides, the growth of the tumor can be followed graphically over time in Figure 7(b). The light-blue outer region is comprised of proliferating cells, the light-red region is non-proliferative cells and the dark-red region is necrotic cells. The scales are in millimeters. In fact, It is suggested to observe central cross-sections of the tumor as an output of our simulation to graphically follow the growth of the tumor over time. The numbers on the right

color column in Figures 7 and 8 show the states of the cells as we explained in Eq. (2). It depicts that necrotic cells are labeled with dark-red, non-proliferative tumorous cells with light-red, proliferative tumor cells with light-blue and normal cells with dark-blue.




(a)



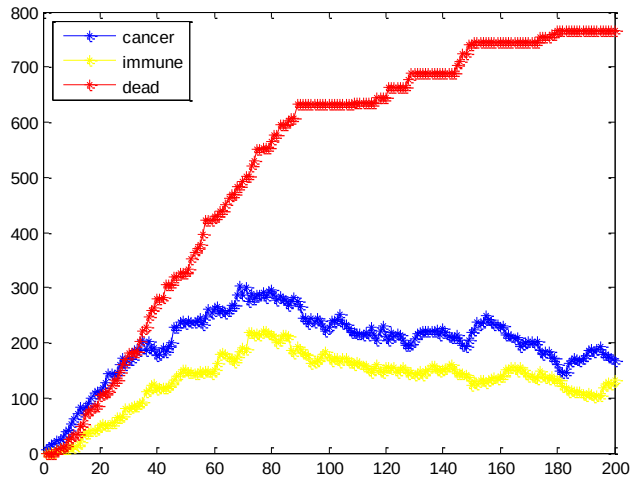

(b)

**Figure 7.** (a) The number of necrotic, cancer, and immune cells during iteration without any immune cell, (b) Snapshot of simulated tumor growth without any immune cell

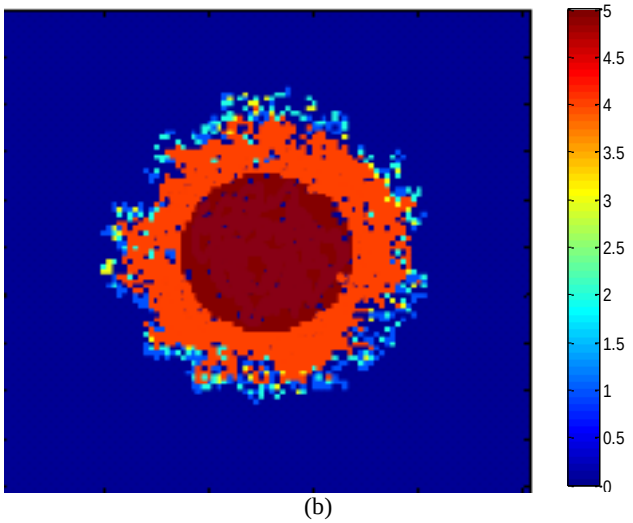
Figure 8 shows the same outputs as Figure 7. The only difference here is that the effect of immune cells has been considered in Figure 8. It seems that the dynamic of the changes of the number of immune cells follows the changes in the number of tumor cells over time.

Comparing Figures 7 and 8, entering immune cells in the system can reduce tumor cells. As we expect, it can be seen that the max cancer cells in a system with immune cells is less than the same ones in a system without E cells. Moreover, it seems that this result is completely the same as the results reported in [21]. Besides, the graphical growth of the tumor with immune cells is less symmetric than the same one in Figure 7. Moreover, it seems immune cells have important impact on tumor invasion and it is compatable with an increasing number of studies have suggested that aberrant infiltration of immune cells into tumor or normal tissues may promote tumor progression, invasion, and metastasis [25].

Table 1 lists the Parameters estimated from fitting the Gompertz model (Eq. (1)) to the number of the PT cells in the model with (w)/without (w.o.) considering immune system, and the E cells. The root-mean-square error (RMSE) is used to evaluate the model fit.




(a)




(b)

**Figure 8.** (a) The number of necrotic, cancer, and immune cells during iteration with adding immune cell in the model (k2=0.1), (b) Snapshot of simulated tumor growth with considering immune cell in the model by setting k2=0.1, k3=0.15, k4=0.35

**Table 1.** Parameters estimated from fitting the Gompertz model to the number of PT, and E cells

| Cell type | $V_0$ | $A$ | $B$ | RMSE (95%) |
|---|---|---|---|---|
| PT (w.o.) | 18.13 | 0.1267 | 0.03982 | 9.403 |
| PT (w) | 7.682 | 0.2281 | 0.06373 | 13.4 |
| E | 1.974 | 0.2492 | 0.05452 | 13.52 |

Figure 9 shows the growth curves of our result in the presence of immune cells comparison with a set of experimental data [26]. The number of tumor cells are normalized for simplicity and each time step in our simulation is considered as 3 hours. Although our results are not the best fitting curve for experimental data, they still show the same dynamic. The circles are experimental data for EMT6/Ro [26]. While, * indicates the result of the present model.

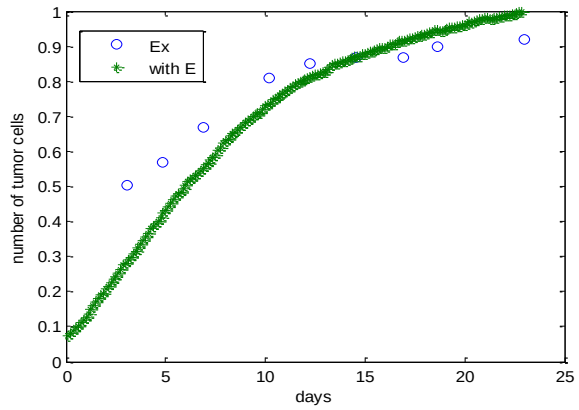



**Figure 9.** The number of tumor cells over time

Moreover, in Figure 10, the results of the simulation are compared with available experimental data [14] for an untreated GBM tumor from medical literature. The parameters compared are growth fraction (the ratio of the number of proliferative cells to the whole tumorous cells), and necrotic fraction (the ratio of the number of necrotic cells to the whole tumorous cells). These data are medically used to determine a tumor's malignancy and the prognosis for its future growth. Since the determination of the exact time of a tumor growth beginning is too difficult, the medical data are listed at fixed radii.

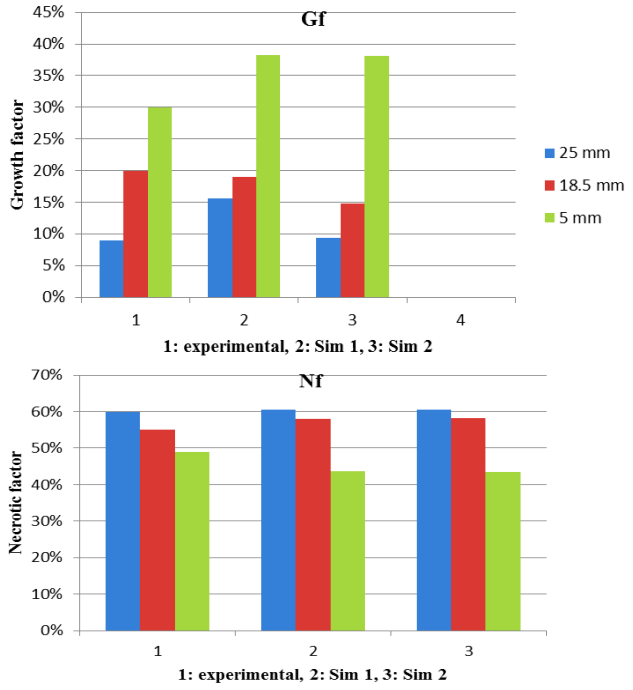



**Figure 10.** Comparison of Growth fraction (Gf) and Necrotic fraction (Nf) of experimental data [14] and simulation results with and without considering immune system effects (Sim 1 and Sim 2, respectively). Sim 1: $p_0$=0.4, Sim 2: $p$=0.5, k2=0.1, k3=0.15, k4=0.15

It is obvious that adding immune system in the model increases the time of run although it considers more reality rather than previous researches. The growth and necrotic fractions of the model in the detect lesion stage ($R_t$=5 mm) are approximately the same in both simulations with and without immune system consideration. The growth fraction of the simulation without involving immune system in the diagnosis stage ($R_t$=18.5 mm) is closer to the value of experimental reports. Although, this is reverse in the dead stage ($R_t$=25 mm).

The necrotic fraction of the model in all stages is approximately the same for both simulations. It arises from the fact that we consider the necrotic radius by equation 6 which is only related to parameters $a$, $b$, and $R_t$. Moreover, the radius doubling time in both simulations are almost the same.

Besides, as we supposed by increasing $p_0$, the time of simulation will reduce but it will ruin the growth and necrotic fractions. Therefore, we should compromise the value of $p_0$ to obtain appropriate values for output parameters to match experimental results. It can be comprehended from Eq. (3) that growth fraction is directly related to $p_0$ and the results confirm it as well. Moreover, it is obvious that growth fraction should be less in the case of interring immune system in each stage ($R_t$=5, 18.5, or 25 mm) of the model. It can be seen that by considering immune system the values of growth and necrotic fraction are much closer to the experimental results, except in diagnosis stage. Besides, the values of radius doubling time in the death stage increases in this case. It also seems that in a model with k2=0, the value of $p_0$ should be reduced to gain the same results of growth and necrotic fraction in a model with involving immune system effects.

## 5. Conclusions

Mathematical models and computer simulations can give researchers opportunities to understand the dynamics of formation and cancer growth. This can help them to find new prevention and treatment solutions. In this article, we introduced a new stochastic CA model of solid tumor growth by considering immune system effects. We mentioned comprehensively each property of CA to propose our model.

The effects of varying the input parameters of the model in order to match previous experimental results are done. Besides, the effect of adding the immune system to the model is discussed. The comparison of our model with and without involving immune system with experimental results is discussed.

Results show that this model adequately fits tentative results reported by scientists. Although considering immune system in the model will rise the simulation time, it is recommended since it adds more physiological details to the model. Besides, the discrete nature of the model enables us to directly simulate more complex physiological situations with only minor alterations. We also observe the effect of immune cells on tumor invation and metastasis, as reported by scientists.

Since immunotherapy is an important type of tumor treatment that uses our body's own immune system to help fight cancer, adding the effects of immune system to the model can help researchers study immunotherapy better. Moreover, the model can be developed to consider metastasis which is an important phenomenon in malignant tumors. The future plan of authors is extending the model to study it under the effect of therapy.

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