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A 3D Cellular Automaton for Cell Differentiation in a Solid Tumor with Plasticity

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A model with spherical symmetry is proposed. We analyze the appropriate parameters of cell differentiation for different kinds of cells (Cancer Stem Cells (CSC) and Differentiated Cells (DC)). The plasticity (capacity to return from a DC to its previous state of CSC) is taken into account. Following this hypothesis, the dissemination of CSCs to another organ is analyzed. The location of the cells in the tumor and the plasticity range for possible metastasis is discussed.

Keywords: Cellular automaton; cellular differentiation; cancer; tumor; cancer stem cells; plasticity.

1. Introduction

The theory of Cancer Stem Cells (CSCs) has been discussed for many years in academic books, journals and reviews. The role of CSCs is fundamental in the formation,[1] aggressiveness,[2] growth rates,[3] relapse and metastasis.[4] Similar to normal cells, the CSCs can be self-renewing or differentiated by a hierarchical structure.[5] Depending on the affected organ, there are several types of tumor cells. In this case, we will study only CSC and differentiated cells (DC) (regardless of the sub-stage, i.e. fully differentiated cells).

The cancerous cells form accumulations (spherical in many cases[6]) which disturb the normal function of the site where they are generated.[1] These cells can spread and disperse in another organ and create metastasis. In many cases, they are intercepted by the immune system to avoid metastasis,[4] but the CSCs can overcome this in many cases, generating a new tumor in a new organ.

The CSCs do not generate metastasis in every organ, but there are some organs that are more susceptible than others. This is seen in the theory of CSC Markers,[7]

where the compatibility of certain organs is related with the capacity to store different types of CSC. Our main objective is to study and analyze the process of cell differentiation of CSCs, moreover, to determine the amount of cells located in the periphery of the tumor since they are more likely to detach, disperse and settle in other organs.

In this work, we propose a 3D cellular automaton simulation of the evolution of cancer cells differentiated, considering the plasticity and its relation with the generation of metastasis.

This paper is organized as follows: in Sec. 2, we introduce the cancer cells differentiation description for the adopted model and the automaton rules. The parameters used are shown in Sec. 3. Section 4 is devoted to the analysis of this model and the plasticity range estimation. In Sec. 5, we analyze the plasticity and its relation with the metastasis. Finally, in Sec. 6, we summarize some conclusions.

2. Cell Differentiation in Cancer Cells Automaton Rules

2.1. *Cell differentiation for cancer*

For cancerous cells, a hierarchical structure exists, similar to normal cells, where the division occurs by a regulation that depends on its cellular lineage.[8]

Nowadays, the plasticity in CSC is not completely understood. The clonal evolution and CSC models require that the hierarchy in the CSC must have a bidirectional transformation between the CSCs and the tumor differentiated cell DCs.[9] This CSC model is based on the traditional one, considering the dynamic of self-renewal,[10] plasticity and differentiated CSCs.[11]

Starting from a CSC, there are three possible ways to differentiate according with the hierarchical structure as shown in Fig. 1.

(1) Symmetric division of CSC: A CSC can divide itself in two equal CSCs.
(2) Asymmetric division: A CSC can divide itself in a CSC and a DC.
(3) Plasticity: A DC can come back from its previous stage of CSC.

Then, three populations are involved in this model:

(a) CSC: Cancer Stem Cells.
(b) DC: Differentiated Cells (we do not take into account intermediate stages).
(c) PCSC: CSCs from DC by plasticity.

In this model, we do not considerate apoptosis, since it is not relevant for our purposes, we focus in the search of parameters in the differentiation of cancer cells.

2.2. *3D automaton rules*

The cellular automaton models allow the characterization of spatial properties. In a cellular automaton model, as usual, space and time are divided into cells with discrete steps. Each cell relates to neighboring cells directly at a defined time step.[12]

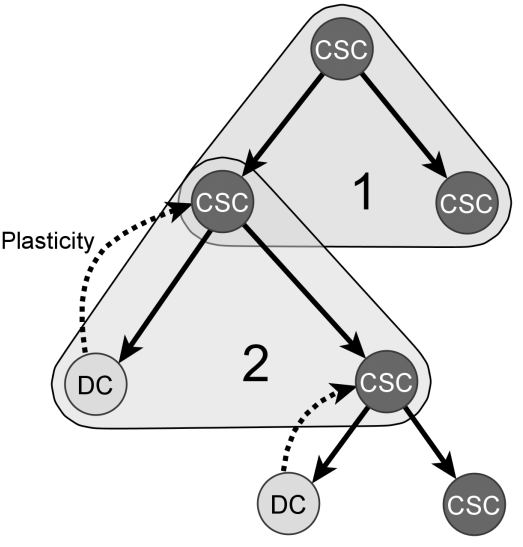


Fig. 1. Hierarchical structure. Sector 1 is the representation of the symmetric division and 2 is for asymmetrical division.

For this model, the following are the structural rules of the system:

(i) Initially empty the cubic space with only one CSC in the center.
(ii) The system evolves in discrete times (steps) $T = 300$, with steps $t = 1, 2, 3, \ldots, T$.
(iii) Each cell interacts with its nearest neighbors (26 boxes).

For the cellular division, the rules are given as follows:

(i) If one of the neighboring cells is empty and ζ (random number with uniform distribution between 0 and 1) is less than β (differentiation parameter that we will find) then the symmetric contiguous cell is differentiated.
(ii) If $\zeta < \lambda$ then it CSC is equally divided. λ is the CSC's auto-renewal parameter.
(iii) If the above happens, and if $\zeta < \gamma$ and is a DC, then it will go back to a previous stage of CSC (plasticity). γ is the plasticity parameter.

3. Methodology

We will search the parameters β, λ and γ in order to represent a real model that can be used in different scenarios. These values must be according to those found in the literature. The population of CSCs must be between 0.6% and 1% (over the total number of cancer cells (N)) on average for the majority of solid tumors.[13] Also, these parameters have to reach a plateau in their time series of cell proportions (CSC/N, DC/N and PCSC/N, respectively).

On the other hand, these parameters have to show a plateau in their time series. The final percentage of CSCs will be approximately 0.8%, which is a mean value of amount of CSCs in a organ.

Under these considerations, there may be several groups of parameters which may be considered correct.

We have chosen, for simplicity, the following group of parameters:

- $\beta = 0.1$
- $\lambda = 0.001 = \beta/100$.

These values correspond to a model without plasticity ($\gamma = 0$). For the different γ values, the final number of CSCs will be different, affecting the trend in stem cells to generate metastasis in other organs. The γ parameter is found when the rest of the parameters (β and λ) remain constant. This is obtained assuming that when plasticity is considered, the final percentage of CSCs must be equal to or less than 1%.

It is important to clarify that more than 500 simulations were performed for each change of the parameters. MathWorks MATLAB®[14] was the software used.

4. Analysis

In Fig. 2, the evolution (without plasticity) for the cellular automaton is depicted, showing the spherical symmetry of the tumor. It is worth to note in Fig. 3(a), the stationary trend of the time series. The low proportion of CSCs makes them difficult

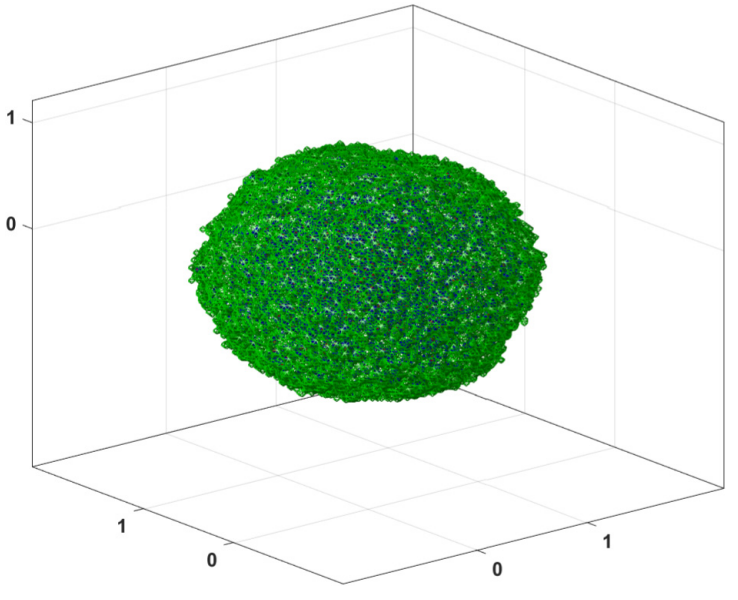
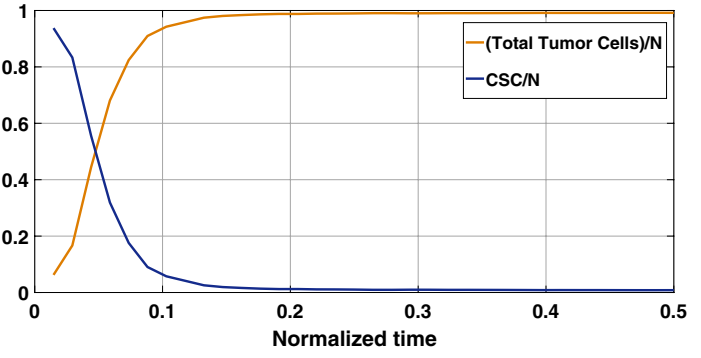
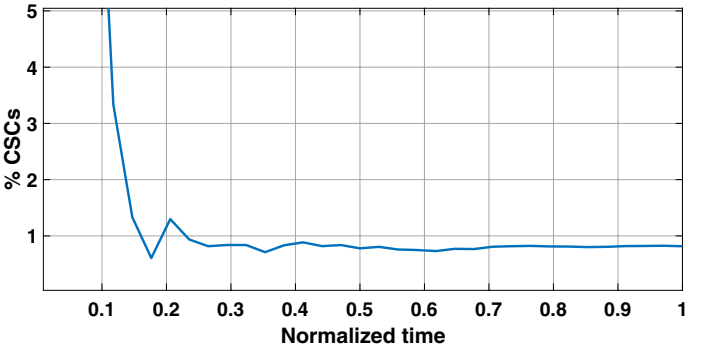


Fig. 2. Simulation of cellular automaton without plasticity. The value in the three coordinates is the normalized radius.



(a) Percentage of CSCs



(b) Percentage of CSCs

Fig. 3. (a) Time series of CSCs and Total Cells, we can see that the proportion of CSCs is considerably lower than the total of cancer cells. (b) Percentage of CSCs without plasticity.

to observe in Fig. 2. Figure 3(b) shows the time series of CSCs, where a plateau is reached in 0.8% of total cancer cells in the system.

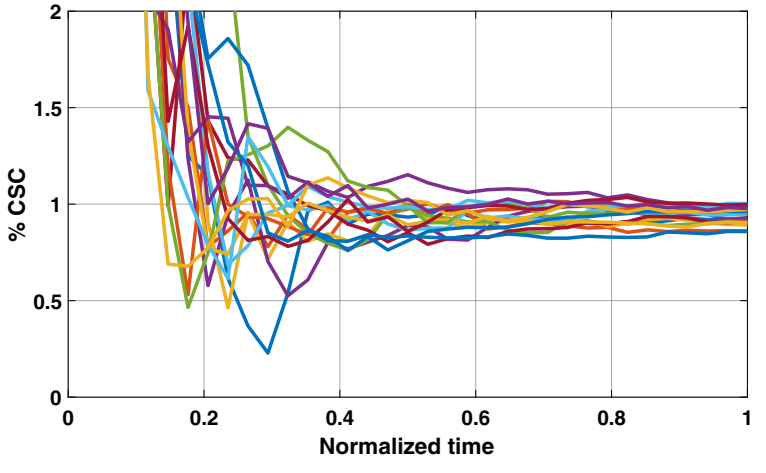
The evolution time and the mean radius of the tumor have been normalized, because they depend on the kind of tumor.[15,16] This will be our starting point for finding γ. The interval of seeking it will be in increments of 10^{-7}, having as restriction that the proportion of CSCs will be (at most) close to 1%.

4.1. *Plasticity (γ) range*

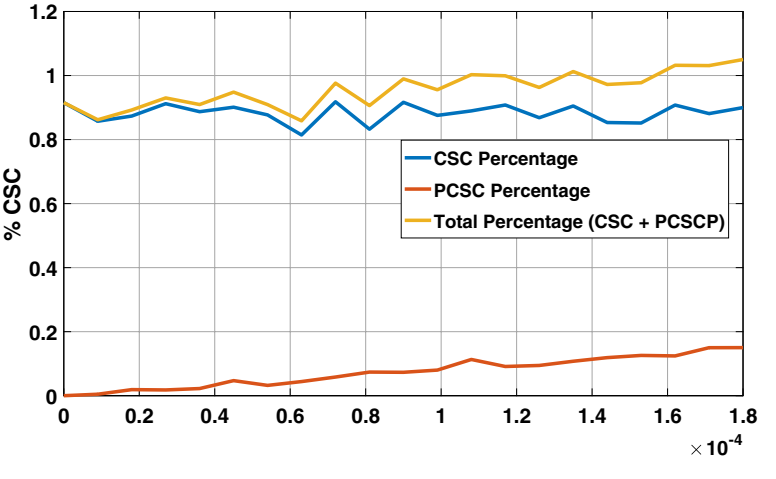
The simulations were performed in order to find the range of plasticity γ, under the restriction of the maximum percentage of CSCs in the system, this range is

$$\text{Plasticity} : 0 \leq \gamma \leq 0.00018.$$

Figure 4(a) shows the time series for several plasticity values, reaching a plateau near 1% of CSCs. Figure 4(b) shows the proportion of CSCs coming from plasticity (PCSC) or by mitosis, where the growth of cells in function of γ is clear.



(a) CSCs for different values of γ



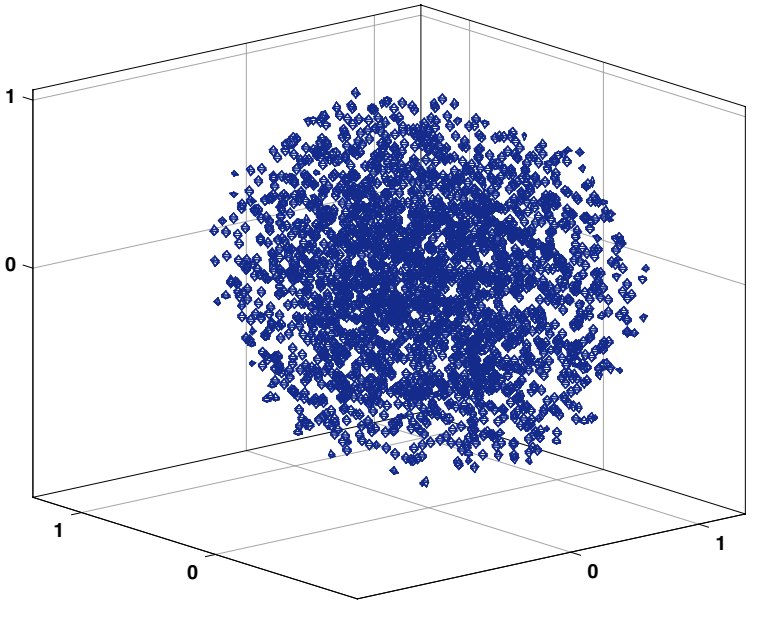
(b) CSCs vs. γ

Fig. 4. (a) Time Series of CSCs for different values of plasticity γ. (b) Percentage of CSCs with plasticity.

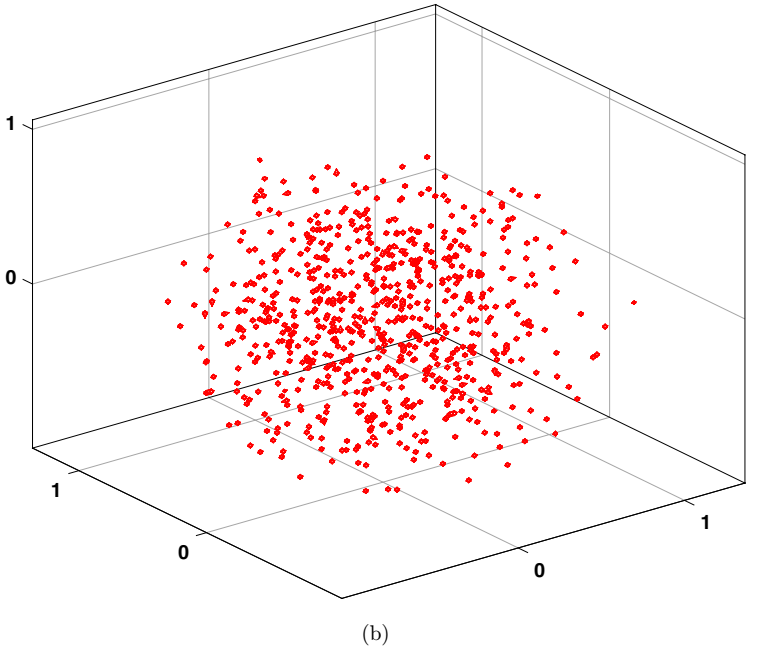
4.2. *Spatial visualization of CSCs*

As the number of CSCs and PCSCs in the system is very small, it is quite hard to visualize them. Therefore, we analyze the time series and spatial distribution (as a function on the radius) of a proportion of them. Dependence with the radius (with or without of plasticity) shows an increase in the whole tumor. For simplicity, we will show the simulation for the highest value of plasticity (Figs. 4 and 5).

The distribution is homogeneous for every radius of the spherical tumor, which is relevant and important to understand why tumors relapse[17] (tumor initiation after some therapy) and why some tumors produce metastasis due to CSC migration.[18]



(a)



(b)

Fig. 5. (a) Spatial distribution of CSCs for the highest value of γ. (b) Spatial distribution of PCSCs (CSCs by plasticity) for the same value of γ. The value in the three coordinates is the normalized radius.

5. Tendency Towards Metastasis

Metastasis is the spread of Circulating Tumor Cells (CTC) from a site (called *primary*) to another nearby or distant site by different ways (through either the bloodstream or the lymphatic system).[19,20] The factors can be different depending on the organ and its initial localization.

As discussed previously, we consider crucial to understand the metastasis process the location of the CSCs location in the tumor. The periphery is the most important site to analyze considering the potential migration from that site.[21]

To quantify the relation between the proportion of CSCs, we analyze this portion of the tumor between

$$0.95 \leq R \leq 1 \quad \text{(The radius } R \text{ is normalized)}.$$

This implies the Peripheral Volume Ratio (PVR) of

$$\text{PVR} = 1 - \frac{4/3\pi(0.95R)^3}{4/3\pi R^3} = 1 - 0.857375 = 0.14265,$$

resulting in $1/7$ of the whole volume of the tumor. Such volume portion is most likely to spread its cells through the blood vessels or lymph nodes that surround it. In Fig. 6, the proportion of CSCs is shown for the highest value of plasticity (orange) and without it (blue). As can be observed, this proportion is higher, around 12%, than without plasticity (near to 7.5%).

Therefore, the cells that are in the tumor border will have more chances to migrate and generate metastasis.[22] Moreover, if the plasticity is taken into account, it is greater.

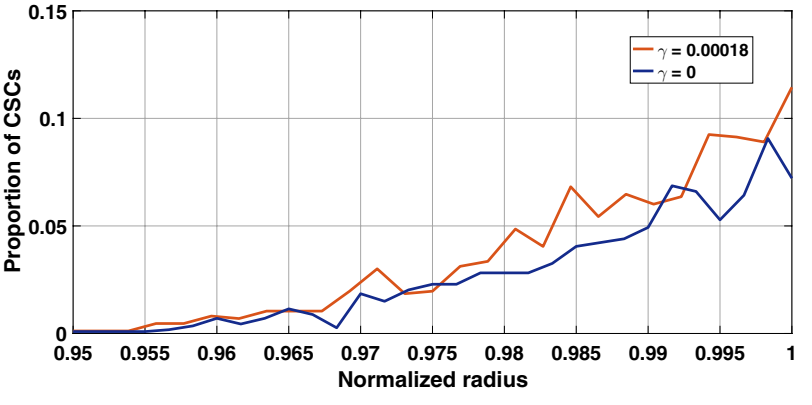


Fig. 6. (Color online) Proportion of CSCs in the final slice of the tumor. In orange with $\gamma = 0.00018$, in blue without plasticity.

6. Conclusion

Today, the study of cell differentiation and their results establish new foundations and bridges between theoretical and experimental research.[23,24] The statistics of current clinical data has shown that the CSCs are responsible for growth, recurrence and metastasis of the tumor after treatment or therapy.

In order to understand, complement and characterize (under experimental data from bibliography) the cancer cell differentiation, we proposed and built a theoritical model based in cellular automaton with spherical symmetry and taking into account plasticity (γ) from DCs. The range found for the plasticity in the system is according to the data given in the literature,[13,25,26] and this promotes a new window for the study of therapies against to cancer.[27,28]

The relation with metastasis is developed, principally, in the periphery of the tumor as well as its proportion of CSCs (PVR) for the two extremes values of γ. In conclusion, the plasticity has an important role since it increases the possibility of dissemination of CSCs to other organs.

Moreover, if we emphasize the existence of information about average diameters in solid tumors (in the pre-metastasis stage)[29] and that the model is dimensionless, this can be extrapolated easily to several specific tumors as those that we can observe in Table 1. This is an important tool because with scale changes real tumors could be represented.

A future investigation is to understand the miRNA expressions for several types and stages of cancer, analyzing their incidence on the cells with plasticity and generate control, fundamentally, in relapse or metastasis.

Table 1. Average diameters for some solid tumors.

Organ	Average diameter (cm.)
Breast	0,2
Lung	7
Uterus	4
Testicle	4,5
Thiroyd	2
Melanoma	0,4
Pancreas	2
Colon/Rectum	4
Bladder	0,8

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