Simulating the Tumor Growth with Cellular Automata Models

S. Zouhri
Université Hassan II-Mohammédia, Faculté des Sciences Ben M'sik Département de Mathématiques, BP.7955, Sidi Othmane, Casablanca, Maroc

S. Saadi
Université Hassan II-Mohammédia, Faculté des Sciences Ben M'sik Département de Mathématiques, BP.7955, Sidi Othmane, Casablanca, Maroc

M. Rachik
Université Hassan II-Mohammédia, Faculté des Sciences Ben M'sik Département de Mathématiques, BP.7955, Sidi Othmane, Casablanca, Maroc

ABSTRACT
In this paper, two types of cellular automata are studied in order to describe the 2-dimensional free growth of an avascular tumor under the effect of a limited nutrient source. On one hand a deterministic cellular automata approach is used. On the other hand a stochastic one is presented. An existing reaction-diffusion model including cell proliferation, motility and death is used. Finally, a numerical simulations that show the difference between these approaches are discussed.

Keywords
Cellular automata (CA), avascular tumor, immune, reaction-diffusion model, stochastic CA, deterministic CA

1. INTRODUCTION
Cellular automata (CA) are mathematical models of systems where time, space and state are discrete. The space is discretized in the cells, each cell can only be in a finite number of states, surrounded by a finite number of cells (neighbours) and changes its state according to its current state, the state of nearest neighbours and local rules. All cells are simultaneously updating and following the same rules.

The CA specificity is its ability to model in a simple formalism a highly complex phenomenon, the distinction between CA and any numerical scheme with a discrete space is the complexity of the system which is modeled in CA from a microscopic level, the level of the cell and rules that provide a physical interpretation. Whereas in a numerical scheme, the complexity of the system is a result of a mapping from a high mathematical abstraction level to a simple form. This is why CA has attracted researchers from various disciplines and its applications have been proposed in different branches of science, such as biology, chemistry, physics, and astronomy. CA have been applied not only to model the world phenomenons but also to be used as an alternative approach to model and simulate systems where partial differential equations (PDEs) become difficult to solve.

In this article, the growth of an avascular tumor is studied by means of CA approach, where the concentrations of nutrients (oxygen, amino acids, glucose, etc.) diffused from the capillary vessel are governed by a reaction - diffusion model [4] considering the cell proliferation, motility, death and competition for nutrients among normal and cancer cells.

Tumor growth has attracted the attention of researchers from many different fields and the description of tumor growth has been presented using partial differential equations or cellular automata (See for example [1] [2]). A variety of mathematical models exist, describing cancer growth in different stage of tumor development, from its initial avascular phase to invasion and metastasis, including different factors such as the interaction between the growing tumor and the immune system (See for example [3), the effect of limited source of nutrient for tumor growth [4], and therapy intervention effect.

This article is organised as follows: In the next section, a CA model is defined, in Section3 a deterministic CA and stochastic CA for tumor growth in the presence of nutrient elements are presented with a number of representative simulations. Finally the difference between the two approaches is discussed in Section 4.

2. CELLULAR AUTOMATA MODEL
A CA is defined by a quadruple A= (T, ξ, v, f) where

T: is a d-dimensional lattice of cells which are arranged depending on space dimension and cell shape. In the infinite case, T = Z^d

ξ: denotes a discrete state set which represents all states likely to be taken by each cell. It is a commutative ring given by

S= {0, 1,…, k-1} in which the usual operations use modular arithmetic.

v: is a function that defines the neighborhood of a cell (c), it is given by :

$$v \quad \begin{array}{l} T \to T^n \\ c \to v(c) = (c_1, c_2, ..., c_n) \end{array}$$

Where cells C_i = 1, 2…, n, are related to **c** by a relationship of proximity, contiguity, influence, and **n** is the size of the v(c) neighborhood

f: is a transition function that calculates the cell state at time

t + 1 in terms of its neighboring states at time t. It can be defined by:

$$f \quad \begin{array}{c} \xi^n \to \xi \\ e_t(v(c)) \to e_{t+1}(c) = f(e_t(v(c\ ))) \end{array}$$

Where e_t (c) is the cell state at time t,

e_t (v(c)) = { e_t ($c^{'}$), $c^{'} \in$ v(c) } is its neighboring state.

The neighborhood plays a very important role in CA; it defines the set of neighboring cells that have an influence on the considered cell. There are two fundamental types of neighborhood that are mainly considered. First there is a Von Neumann neighborhood which comprises the four cells orthogonally surrounding a central cell on a two-dimensional square lattice. A Moore neighborhood comprises the eight surrounding cells and which is used in this work.

3. CA OF CANCER GROWTH

In order to describe the early growth of a 2-dimensional tumor, two types of CA are presented, deterministic and probabilistic one. The deterministic CA describes the effect of a limited nutrient source on tumor growth and on the normal tissue under direct rules; the probabilistic CA describes also the same evolution but furthermore uses probabilistic rules.

3.1 Deterministic CA

The aim is using deterministic-deterministic approach to simulate the tumor growth; this approach consists on presenting the chemical diffusion through deterministic PDEs and the individual cell behavior through a set of direct rules.

Biological background: cancer starts with an uncontrolled growth of mutated cells that disrupts the body tissues, this uncontrolled division leads to the growth of an avascular tumor, if it is not eliminated by the immune system it will then stay dormant or it develops its own blood system by the process of angiogenesis [11]. In this work, an avascular tumor which measures a few millimeters and is not detectable with the medical imaging is considered, in this stage of tumor growth, the tumor does not have its own blood supply, it continues to grow as long as oxygen and nutrients are present in its micro-environment [11], the nutrients necessary for growth are supplied to the tumor via diffusion from distant blood vessels [7]. We use a reaction-diffusion model [4] for an avascular cancer growth including cell proliferation, motility and death. The cell actions (division, migration and death) depend on the nutrient concentration in the local microenvironment, which are diffused from a capillary vessel of the tissue towards the normal and tumor cells. In areas with high nutrient concentration, the tumor cell divides and multiplies, however it migrates from the low nutrient concentration areas, or from the areas when there is a high number of tumor cell.

In this paper the immune response is not considered, a free growth of tumor cells is presented. One of the reasons for considering tumor growth in the absence of immune response is to study the behavior of tumor before including confounding characteristics such as the innate and specific immune response through the immune cells. Another reason is to allow the comparisons of the tumor behaviors in the absence and in the presence of immune response.

The tissue: The tissue is represented by a square lattice of size $(L+1) \times (L+1)$, any site, with coordinates $x = (i, j)$,

$i, j = 0, 1, 2 \ldots L$, is occupied by only one of cell types. The capillary vessel localized at the top of the lattice at $x = 0$, is the only source of nutrient for the tissue cells. The tumor mass may contain different cell [8], we consider only three types: normal, tumor and necrotic cells which are inert. Each grid site may be in a normal state and contains one normal cell, or may be in tumor state, in this case it may contains one or more cancer cells which can pile up in at the same site. Periodic boundary conditions along the horizontal axis are used.

The nutrients model: the nutrient elements are supposed divided into two groups: nutrients essential for cell proliferation and nutrients essential for cell survival. The both nutrient types obey the following diffusion equations:

$$\begin{cases} \dfrac{\partial N}{\partial t} = \nabla^2 N - \alpha^2 NH - \lambda_N \alpha^2 NT \\ \dfrac{\partial M}{\partial t} = \nabla^2 M - \alpha^2 MH - \lambda_M \alpha^2 MT \end{cases}$$

Where ***N*** and ***M*** represent the proliferation nutrient and survival nutrient, respectively, ***H*** is the number of normal cells tissue, ***T*** for tumor cell number. $\boldsymbol{\lambda_N}$ and $\boldsymbol{\lambda_M}$ are the consumption rates of the two chemicals N and M by non-tumor cells, $\lambda_N > \lambda_M$ is used to reflect the excess consumption by the cancer cells of the two types of nutrients. $\boldsymbol{\alpha}$ represents the rate of consumption of nutrient by host cells.

The boundary condition on the capillary vessel is:

$$N(x=0) = M(x=0) = 1;\ N(x, 0) = N(x, L) = 1,$$

and $M(x, 0) = M(x, L) = 1$ corresponding to the periodic boundary conditions along the x-axis; the Neumann boundary condition $\dfrac{\partial N(x=L)}{\partial t} = \dfrac{\partial M(x=L)}{\partial t} = 0$, are imposed to the border of the tissue.

CA Rules: the nutrient elements are governed by deterministic reaction-diffusion equations, the cellular evolution proceeds according to direct rules which are derived from mathematical modeling literature (see for example [4]).

At each time step, each tumor cell is selected to accomplish one of three actions: division, migration or cell death.

Division: the cell division is accomplished when the concentration of nutrients essential for cell proliferation is high; it depends also on the spatial tumor cell position:

- If the selected cell is inside the tumor, the daughter cell will occupy the same mother site, it will pile up at that site, as is shown in Figure 1-a.
- If the selected cell is on the tumor border, his daughter will occupy randomly the nearest site containing a normal or a necrotic cell, as is shown in Figure 1-b.

When the concentration of nutrient essential for cell proliferation is low, the tumor cell becomes necrotic, it loses its ability to divide.

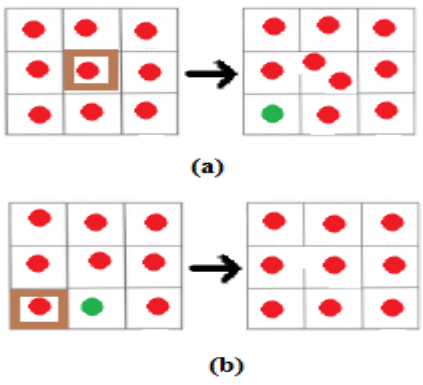


Fig 1 : division rules

Migration: the cell migration is accomplished when the concentration of nutrients essential for cell survival is low, in this case the tumor cell moves away from this area to high nutrient concentration areas. The spatial position of tumor cell defines its way of migration:

- if the selected cell is inside the tumor, it will move to a nearest neighbor site chosen at random, as is shown in figure 2-a.
- if the selected cell is on the tumor border and there is no other cell in the same site, it will migrate by interchanging its position with the position of a normal or a necrotic cell, figure 2-b.
- if the selected cell is on the tumor border and there is another cell in the same site, it will occupy the position of the normal or necrotic closest neighbor cell, this one disappears, figure 2-c.

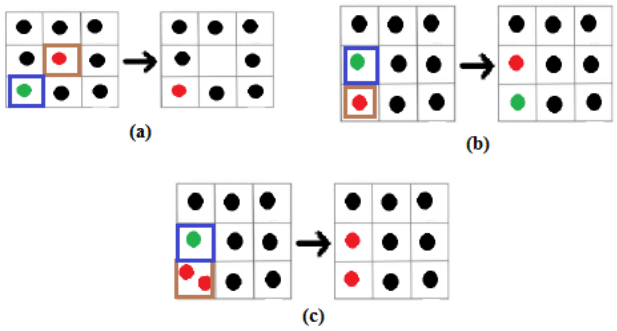


Fig 2 : migration rules

Cell death: the tumor cell dies when the survival nutrient elements are insufficient; in this case it is unable to move to keep alive.

Simulations: We start with one tumor cell grows in the normal tissue in the half of the lattice (x = L/2) and at the distance Y from the capillary vessel which diffuses nutrients to the tissue cells. The CA simulations were implemented using a sequence of steps which are given as the following algorithm:

1) Construct the cell grid, represent the capillary vessel

at x = 0.

2) Assign parameter values; solve the diffusion equations in the steady- state, to obtain initial nutrient concentrations.

3) loop until stop condition is satisfied:

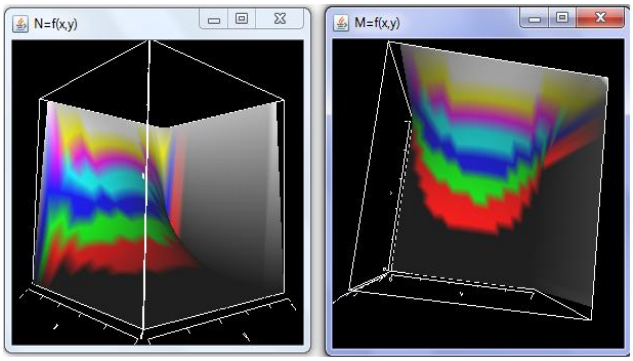
- For each selected cancer cell, define the cell action (division, migration, death) which depends on the calculated nutrient concentration, the action of each cell will be implemented.

If the selected cell divides, then the number of cancer cells increases, on the other hand if the selected cell dies, then the number of cancer cells decreases.

- Update the CA structure according to its changed states

- The time step is iterated and the entire procedure (solution of the diffusion equations and the cell dynamic) is repeated until the stop condition. Each temporal-iteration corresponds to division cycle of tumor cell.

Results: the reaction-diffusion equations have been solved by using a numerical algorithm in addition to the finite difference method, to approximate the derivative of the system, this last could be a set of linear equations, its solution gives at each time step the nutrient concentrations N and M respectively as follows:



- ***Figure 3-a)*** shows a various stages of tumor growth (From the left to the right. We started with a single mutated cancer cell in normal tissue, in a convenable area with high concentration level of nutrients essential for proliferation, the mutated cell divides, grows and leads to a compact tumor with high tumor cell number; similar results are found when the rates of consumption are high.

the rate of consumption is considered in some works such as a key system parameter which defines the relationship between the tumor morphology and the host cell tissue (See [3], [4]), the lower rate consumption refers to a lower competition between the normal and tumor cells for nutrients, which means easy growth of tumor in the absence of immune response in compact morphology, while the higher rate consumption refers to a competition for nutrient elements between the normal and the tumor cells which lead to less compact morphology and less connected cells.

a deterministic approach has not considered the tumor morphology due to the deterministic CA rules, each cell accomplishes its action (division, migration or death) according to nutrient concentration level, its current state and the neighboring state (the 8 surrounding cells) and didn't take into account the total number of tumor cells which changes in every cycle of division in the local microenvironment, neither the nutrient elements consumed. If the migration rule is taken as an example, the tumor cell will migrate not only because the level of survival nutrient elements concentration M is low, but also due to the total tumor cell number in its same area of life which consume at the same time the nutrient elements. Parameter values are: Domain size of 400 elements (H = 400), $\alpha = 1/L$, N = 379, T = 1, $\lambda_N = 100$, $\lambda_M = 10$,

- ***Figure 3-b)*** shows the total number of tumor cells over time.

3.2 Stochastic CA

The aim is using deterministic-stochastic approach to simulate the tumor growth; this approach consists on presenting the chemical diffusion through deterministic PDEs and the individual cell behaviors through a set of probabilistic rules.

CA Rules: The same tissue cells, reaction-diffusion equations for nutrient elements and celular dynamics of the deterministic CA are used for the stochastic CA. the probabilistic rules have been used in order to assign the stochastic nature to the tumor cells.

Division: Tumor cells divide with probability $\mathbf{P_{div}}$ which depends on the ratio of the proliferation nutrient concentration ***N*** present on the microenvironment of the selected cell and the tumor cells T:

$$P_{div} = 1 - \exp\left[-\left(\frac{N}{T\theta_{div}} \right)^2 \right]$$

Migration: Cancer cells migrate with probability $\mathbf{P_{mov}}$, which depends on the survival nutrient concentration M and the tumor cells T presented on the microenvironment of the selected cell:

$$P_{mov} = 1 - \exp\left[-T\left(\frac{M}{\theta_{mov}} \right)^2 \right]$$

Cell death: cancer cells die by becoming a necrotic cell with probability $\mathbf{P_{det}}$ which is determined by the concentration per tumor cell of the survival nutrient M present on the microenvironment of the selected cell:

$$P_{\det} = \exp\left[-\left(\frac{M}{T\theta_{\det}} \right)^2 \right]$$

P_{div}, P_{mov}, $P_{\det}$ are taken from Ferreira et al. [4]

Simulations: We start with one tumor cell grows in the normal tissue in the half of the lattice (x = L/2) and at the distance Y from the capillary vessel which diffuses nutrients to the tissue cells. The CA simulations were implemented using the same deterministic CA algorithms and considering the probability values at each-iteration.

*Results**:***

- Figure 4-a) shows a various stages of tumor growth (From the left to the right). We started with a single cancer cell in the centre of the normal tissue. For low consumption rates, the tumor cell begins with migration action to the high concentration level of nutrients essential for proliferation, once arrived it divides and grows which leads to a compact tumor. The cells in the center of tumor mass die due to the difficulty of nutrients access to that area, it being deprived from nutrient elements which form a necrotic core in the center of tumor, while the tumor cells keep growing whenever are distant from the central area. These tumor characteristics are described mathematically by Chaplain [12] and experimentally by Folkman [13]. Parameter values are: Domain size of 400 elements (H = 400), $\alpha = 1/L$, N = 379,

T = 1, $\lambda_N = 50$, $\lambda_M = 25$, $\theta_{div} = 0.1$, $\theta_{mov} = 1$, $\theta_{\det} = 0.01$.

- Figure 4-b) shows the total number of tumor cells over time, it is noticed that the tumor grows to a certain size and becomes stable, this behavior can be explained by the transition from the dormant avascular state to vascular state and the tumor need to forming a new blood vessels. When the size of tumor is stable that means the tumor is in dormant stage and needs its own vasculature and its own blood supply to stay alive and to invade the surrounding tissue and migrate to distant body parts (the metastasis).

- Figure 5-a): for high consumption rates, the morphology of the tumor becomes less connected and less compact. It is observed also that a necrotic core is beginning to form in the center of the tumor. Parameter values are: Domain size of 400 elements 4mm (H = 400), $\alpha = 19/L$, N = 379, T = 1,

$\lambda_N = 100$, $\lambda_M = 10$, $\theta_{div} = 0.1$, $\theta_{mov} = 1$, $\theta_{\det} = 0.01$.

- Figure 5-b) shows the total number of tumor cells over time, it's less high than the total number of tumor cells in Figure 4-b due to the tumor morphology and competition for nutrients between normal and tumor cells. It is noticed also that the tumor grows to a certain size and becomes stable which means that the tumor is in dormant state.

4. CONCLUSIONS

In this work, the cellular automata approach is used in order to studying the tumor growth; in one hand, the deterministic-deterministic approach is used, which means that the nutrient elements are governed by a deterministic reaction-diffusion PDEs ,and the CA dynamics are defined by a deterministic rules. In the other hand, the use of deterministic-stochastic approach means that a deterministic reaction-diffusion PDEs governs the nutrient elements, and a combination of probabilistic and direct CA rules present the cell dynamics.

In the case of deterministic CA approach, the tumor cells divide and grow when they are present in areas with high concentration levels of nutrient essential for cell proliferation, while the tumor cells migrate from the area with low concentration levels of nutrient essential for cell survival. The tumor cells die when the nutrient elements essential for survival are not sufficient. It is noticed that in deterministic CA approach, the tumor cell action depends only on the concentration of nutrient elements without depending on the total tumor number in the local microenvironment which changes at each division cycle, this number is considered only in PDEs resolution for calculating the nutrient concentration in every tissue site in order to determine the concentration levels of nutrients. If a tumor cell is presented in high concentration level of nutrient elements it will marked for division without taking in account the number of tumor cells consuming nutrient elements in the same time, the direct rules impose on the considered cell to divide without knowing if this cell has consumed enough nutrients and is it able to divide. For this reason, the tumor morphology in deterministic CA is compact even if the rates of consumption are higher or lower.

For stochastic CA approach, the tumor cell action (division, migration, death) depends on the nutrient elements concentration as well as the total number of tumor cell in the local tissue, that is why the tumor morphology has changed for higher and lower consumption rates, also it is noticed that after certain division cycle, the necrotic core in the tumor center has been formed due to insufficient nutrient elements in this area, while this tumor behavior was not noticed for deterministic CA case. Additionally, the tumor cells in Figures 4-b) and 5-b) keep growing to a certain size and become stable in order to move from a dormant avascular state to the vascular state and form its own blood supply to stay alive, however, in deterministic CA case the tumor cells keep growing during the defined division cycle.

The stochastic CA approach sheds light on the tumor behavior and describes the tumor growth in more clearly way than the deterministic approach. This approach will be able to describe clearly the tumor growth when the immune system response and the therapy intervention will be considered?

5. REFERENCES

[1] J.A. Adam and N. Bellomo. A survey of models for tumor-immune system dynamics. Birkhauser, 1997.

[2] T. Alarcon, H.M. Byrne, and P.K. Maini. A cellular automaton model for tumour growth in inhomogeneous environment. J. Theor. Biol., 225, 257-274, 2003.

[3] D.G. Mallet and L.G. de Pillis A cellular automata model of tumor-immune system interactions

[4] S.C. Ferreira Junior, M.L. Martins and M.J. Vilela. A reaction-diffusion model for the growth of avascular tumor

[5] V.A. Kuznetsov. Basic models of tumor-immune system interactions - Identification, analysis and predictions. In J.A. Adam and N. Bellomo (eds), A survey of models for tumor-immune system dynamics. Birkhauser, 1997.

[6] L.G. de Pillis, W. Gu, A.E. Radunskaya (2005). Mixed Immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations

[7] L.G. de Pillis, W. Gu, A.E. Radunskaya (2005). Mixed Immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations

[8] H.M. Byrne. Using mathematics to study solid tumor growth. In Proceedings of the 9th General Meetings of European Women in Mathematics, 81-107.

[9] W.H. Clark, J. Cancer 64, 631 (1991)

[10] S. EL Yacoubi. A mathematical method for control problems on cellular automata models.

[11] M. Turhan Coban. Numerical analysis with java examples.

[12] Helen M. Byrne. Mathematical Biomedicine and modeling avascular tumor growth.

[13] M. A. J. Chaplain. Avascular Growth, Angiogenesis and vascular growth in solid Tumours: the mathematical modelling of the stages of tumour development.

[14] J. Folkman and M. Hochberg. Self-regulation of growth in three dimensions.

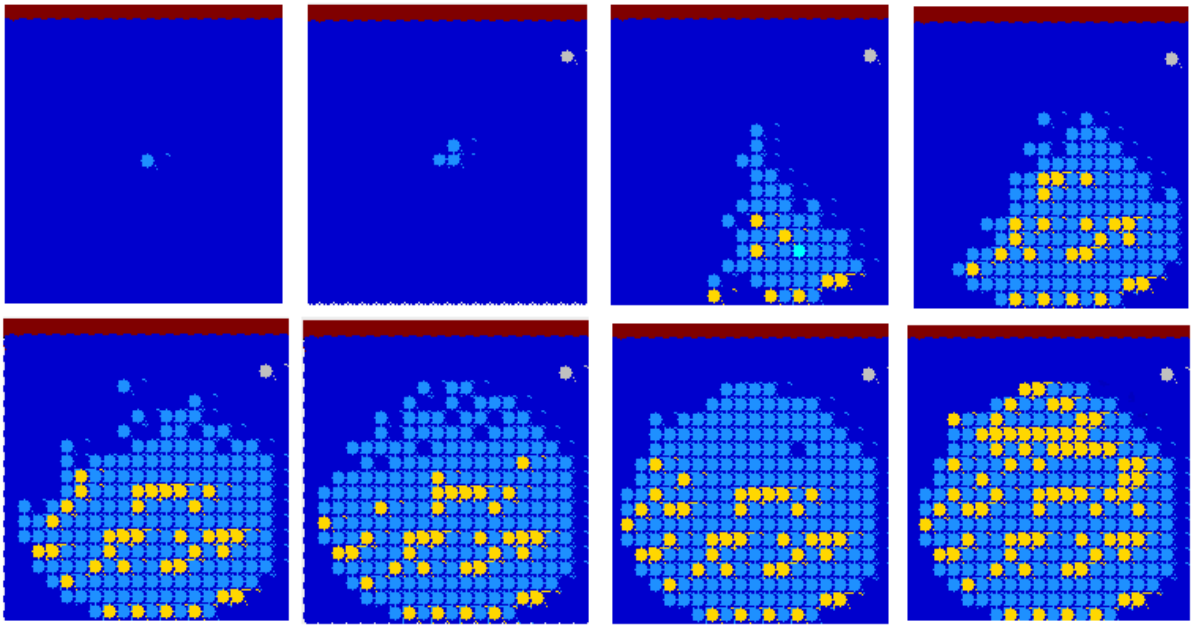


Fig 3-a) : Deterministic CA for tumor growth

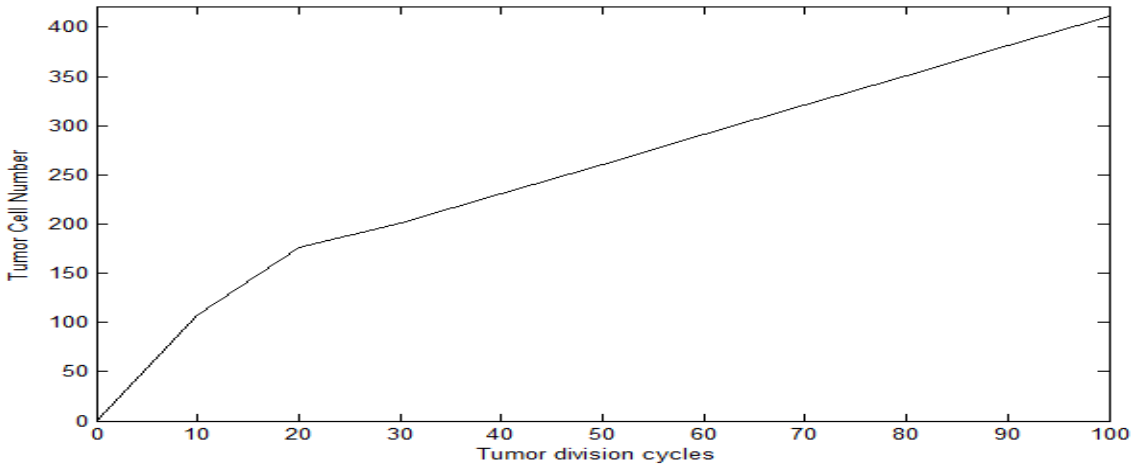


Fig 3-b): Tumor cell count over time

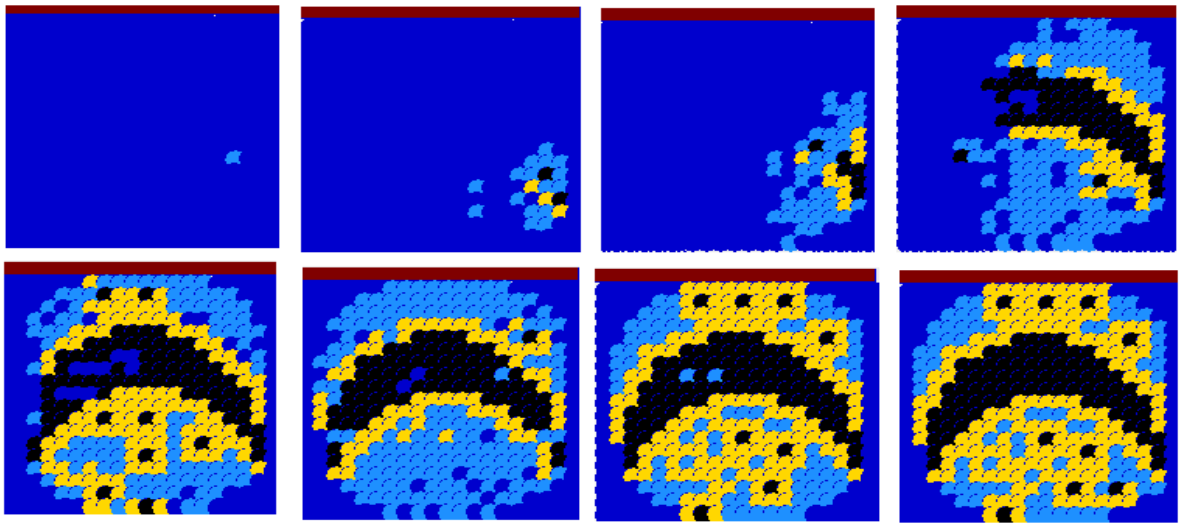


Fig 4-a): Stochastic CA for tumor growth with low consumption rate

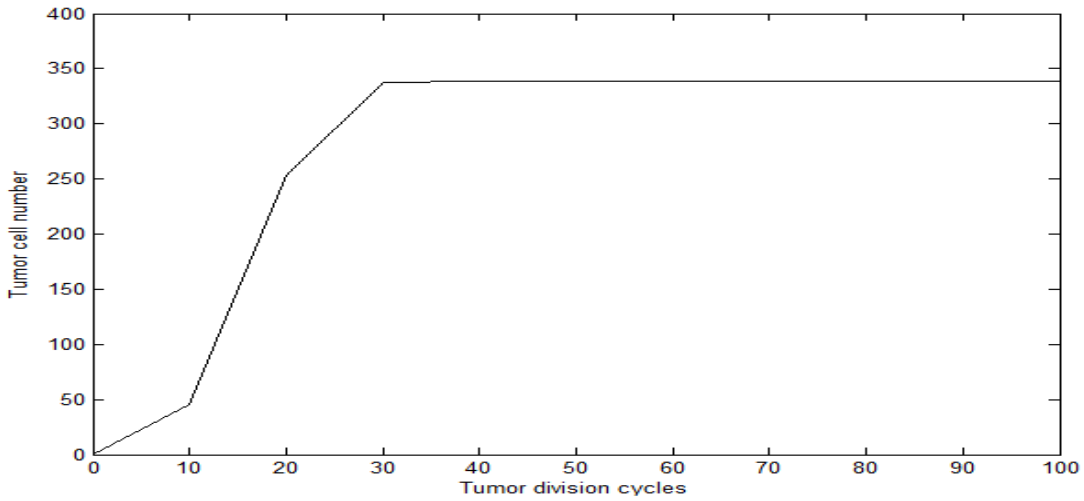


Fig 4-b): Tumor cell count over time

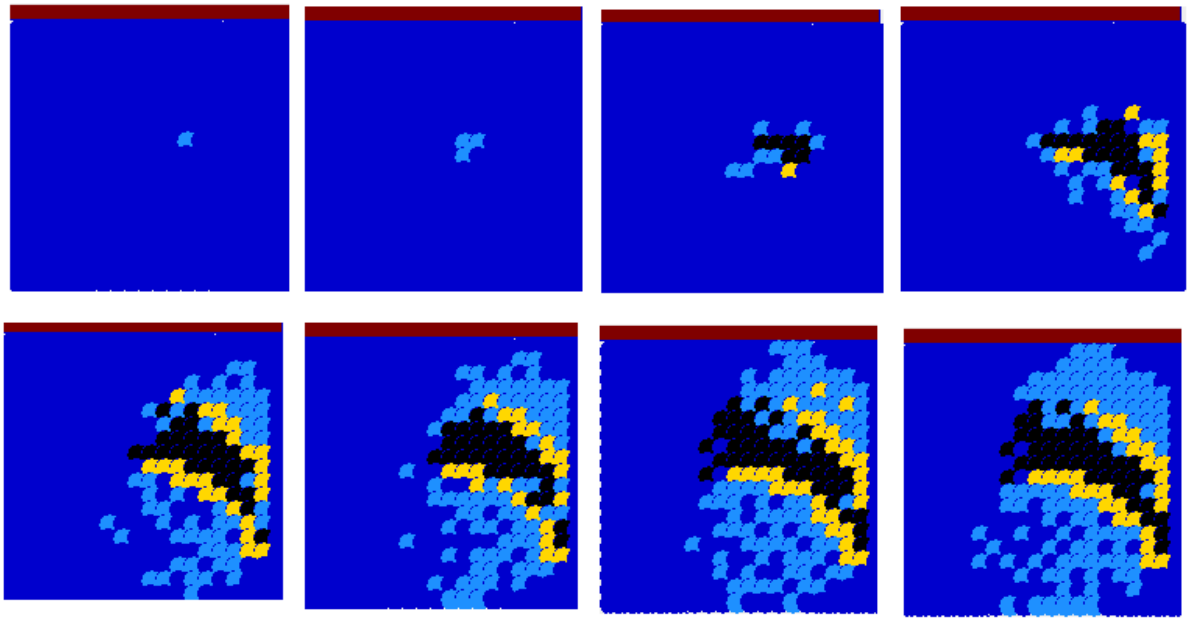


Fig 5-a): Stochastic CA for tumor growth with high consumption rate

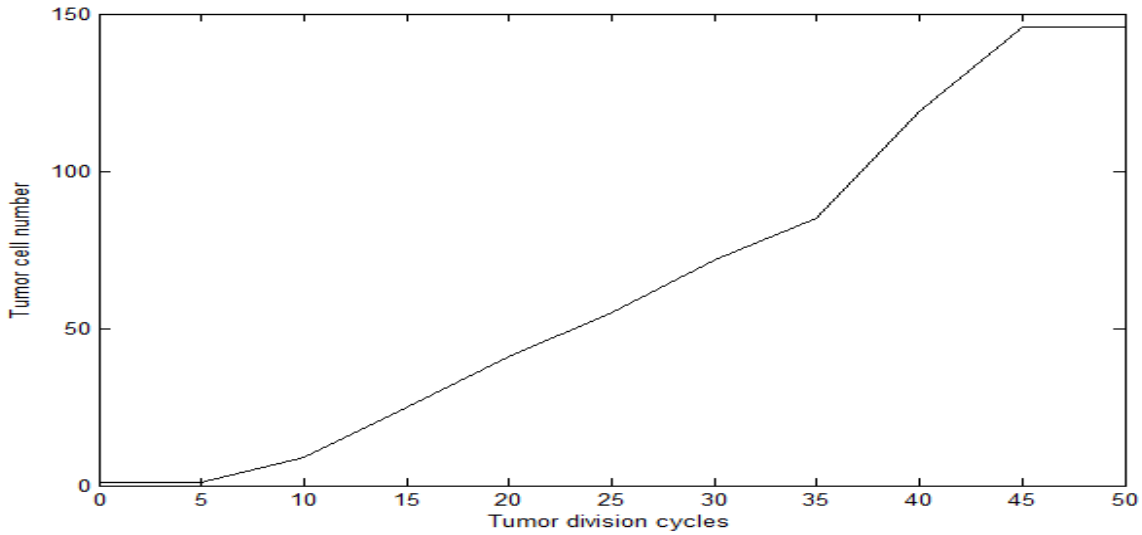


Fig 5-b): Tumor cell count over time