A SIMULATION MODEL OF TUMOR GROWTH

By

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Abstract

We introduce a new Monte Carlo model for avascular tumor growth. The model is intended to be as realistic as possible and is cell based model. We have developed a two-dimensional lattice Monte Carlo model. The model is complemented by key features such as the explicit presence of nutrient diffusion and consumption, cell growth, cell division and cell death, and the cell-cell interaction. Tuning the parameters of the model can lead to the growth of different tumor morphologies, and can lead to different growth dynamics.

Chapter 1

Introduction

1.1 Motivation for this research

Even if in the past few decades has seen considerable progress in cancer research, cancer is still a timely problem. For instance, according to CCEthiopia, cancer is among the leading cause of illness and death in Ethiopia [1].

In the meantime, the level of cooperation between Biology, Mathematics, and physics has increased. Computer technology is advancing rapidly even as it becomes less expensive, allowing for the implementation of increasingly sophisticated models at lower overall cost. Computer simulations are very important in the case when the experiment is hard to conduct or simulations can be used to explore and gain new insights into new technology, and to estimate the performance of systems too complex for analytical solutions.

A better understanding of the dynamics of tumor formation and its growth are expected from computer models and simulations. The modeling could improve the overall clinical outcome by predicting the results of specific forms of treatment administered at specific time points.

Generally, better tumor models can help to develop more effective treatments by optimizing the existing therapeutic procedures, or even design new ones[2-4].

1.2 General Introduction

1.2.1 Biological Background of Tumor

Under normal conditions, cells in our body grow, divide, die and replace themselves in an orderly and controlled manner. However, if this process gets disturbed (sometimes because of genetic problem), cells can grow uncontrollably without any order. When this happens a tumor arises. Therefore, tumor can be defined as an abnormal mass of tissue, whose growth rate exceeds and is uncoordinated with that of surrounding normal tissues. They usually starts with a single cell due to its unusual response to the genetic order and may slowly develop into cancer.

Tumors can be divided into two classes: benign or malignant depending on their method of growth. Benign tumors are most of the time harmless and, grow by expansion, compressing or displacing surrounding normal tissue, while malignant tumors grow by local infiltration, destroying the tissue which they invade. Benign tumors grow at their site of origin only, but malignant tumors may spread to distant sites, with cells detaching from the primary tumor and migrating to remote sites via the blood stream, in the lymph nodes or across connective tissue. This process is known as metastasis and the secondary tumors formed by this process are called metastases. The majority of deaths from cancer are due to the formation of metastases at sites remote from the primary tumor. Malignant tumors grow faster than benign tumors.

Benign tumors may cause disease by compression of adjacent structures, or in certain circumstances by secretion of hormones. In contrast, malignant tumors always have the potential to cause death as a result of their aggressive growth and invasiveness.

Typically, tumor growth can be divided into three stages: these stages are described as avascular growth, angiogenesis and vascular growth.

1.3 Avascular tumor growth

Avascular tumor growth is the first stage of tumor growth. It is less complex than vascular growth (see section 1.5) and the growth of tumors within this stage is without blood vessels. During this stage, nutrients that enter the tumor are consumed by live, proliferating cells as they diffuse towards the tumor center. As the tumor grows, the amount of nutrient reaching the center decreases as the depth increases until there is insufficient to sustain viable cells. This is because the external nutrients cannot diffuse into the cells in the center. The cells in the center go into a quiescent state. In this state, they are dormant but are able to proliferate again when nutrients become available to them. As the cells on the edge continue to proliferate, i.e. the tumor grows, the proliferating region expands resulting in the formation of a central core of dead (necrotic) cellular material whose size increases as the tumor continues to grow.

Thus, a well-developed avascular tumor comprises an outer rim of nutrient-rich, proliferating cells and a central core of nutrient-starved, necrotic debris. These regions may be separated by a layer of oxygen poor (hypoxic) cells, which are quiescent (viable but none proliferating).

1.4 Angiogenesis

Angiogenesis, the growth of a network of blood vessels, is a crucial component of solid tumor growth, linking the relatively harmless avascular growth phase and the potentially fatal vascular growth phase. This stage is initiated from some of the tumors at the core. These tumors die and release substances known as tumor angiogenic factor (TAFs) by decomposition. When TAFs diffuse to the surrounding vasculature of normal tissue, angiogenesis occurs. In this stage, the vasculature grows toward and into a tumor. Once blood vessels have reached the tumor, the third stage (i.e vascular) begins and then tumor receives a vast amount of nutrient and can grow larger and faster than when it was in the avascular growth stage.

1.5 Vascular Growth

Once a tumor has acquired its own blood supply by angiogenesis, it is able to grow to a large size. There has been relatively little work on this crucial stage of tumor development because of its complexities which arises from:

i) the interaction between angiogenesis and tumor[5-6];

ii) the balance between nutrient delivery by the vasculature and nutrient consumption by the tumor;

iii) the complexities of the immature vascular networks through which the nutrients are delivered, in terms both of their highly tortuous geometry and of the interactions between blood flow and interstitial fluid pressures within the tumor [7];

iv) and the complex micro-environments [8], involving both spatial and temporal variations in oxygen tension and pH in particular, which arise because of non-uniformities in nutrient delivery and waste product removal by the vasculature.

The best way to prevent cancer is preventing angiogenesis from occurring. This is because preventing cancer is difficult once the tumor has obtained a blood supply the tumors can leave its primary location via the circulatory system (metastasis) and settle in multiple areas of the body. The metastatic stage is the final stage of tumor growth, and the most dangerous stage.

1.6 Tumor Growth Models

Generally speaking, the tumor growth models can be divided into two broad categories: discrete and continuum models.

1.6.1 Discrete model

Discrete models are sometimes called cellular and microscopic models. In such kind of model cells are treated as individual entities. One can use this model when the behaviors of individual cell as well as their interaction with other cells and medium which surrounds them are interested to study (e.g. cellular automata model, a lattice Monte Carlo model). Usually, in this type of model, the cells are considered to be points which move on a lattice according to a certain rules. Discrete (individual based) models have found useful application for many physical systems and even simple rules of interaction can give rise to remarkably complex behavior. In particular, individual-based models have found applications in ecology, pattern formation, angiogenesis associated with malignancy are amongst many others [9-10].

1.6.2 Continuum model

These models describe the evolution of the local tumor cell density. Continuum models rely upon a reaction-diffusion equation to account for the tumor propagation. Most continuum biological models have been postulated either by finding certain biologically relevant features from the solutions or making it easier to analyze behavior of solutions using certain mathematical techniques.

Continuum and discrete models address the model building problem from different perspective and depending on the question at hand, one or the other (or both) may be appropriate model frame work to choose for particular problem. These two types of models have their own strengths and weaknesses. For instance, continuum models are suitable for describing large population of cells; while discrete models are often computationally expensive as the population of cells is very large. Discrete models can be related to subcellular mechanisms and data while continuum models are derived making assumptions that are difficult to directly relate to individual cell behavior and continuum model solutions can be expressed in terms of model parameters, while discrete models typically require many computationally intensive simulations to develop insight into system-level behavior. However, by driving continuum models directly from their discrete counterparts, many of the above-mentioned problems of using discrete models can be overcome [11].

1.7 Types of tumor growth

1.7.1 Exponential growth

Exponential growth law is the simplest proliferation law observed at early stages of tumor growth. The first work on an exponentially growing population was performed by Reverend T.R. Malthus in 1798. It is described by differential equation given below.

$$\frac{dN}{dt} = KN \tag{1.7.1}$$

The analytical solution for this differential equation is obviously given as:

$$N(t) = N(0)e^{Kt} \tag{1.7.2}$$

where Eqn.(1.7.2) describes the population density N(t) at any time t as a function of the initial population density N(0) and the constant growth rate K. The value of K depends on the intrinsic aggressiveness of the tumor[12].

1.7.2 Gompertz growth

Since exponential growth has no limit, Malthus work was latter modified by Gompertz(1825). Beyond a certain size, exponential growth slows down gradually and may approach a Malthusian asymptotic rate and is called the growth of Gompertz. Tumors develop, in the Gompertz model, with a growth rate decreasing with tumor growth.

The work by Laird in 1969, based on the kinetics of Gompertz, shows the validity of the kinetics of Gompertz for some tumors. Larid measured the growth of 19 examples of 12 different tumors from the rat, mouse, and rabbit and concluded that this growth model seems to be a general biological characteristic of the growth of tumors[13].

1.8 Previous works and Contribution to cancer research

In this section we will try to mention some of the earlier work that has been done in the field of tumor modeling. We start with the experimental works and then we will finally see what has been done theoretically and computationally (simulations).

Human cancer is probably as old as the human race. It is obvious that cancer did not suddenly start appearing after modernization or industrial revolution. The oldest description of cancer in humans was found in an Egyptian papyrus written between 3000-1500 BC. Hippocrates, the great Greek physician (460-370 B.C), who is called as "the father of medicine " is thought to be the first person to clearly recognize the difference between benign and malignant tumors [14].

The complexity of cancer and its large contribution for most deaths in the world attracted the attention of many researchers. For these reasons, there has been a huge amount of experimental and theoretical researches into this disease and for certain cancer cure rate have improved. Unfortunately, we still do not have full understanding of how this disease progress and how the innumerable process involved combine to initiate cancer and the growth of tumors.

In 1932, Mayneord employed the term "law of growth" for a sarcoma of a rat. Data suggest that each tumor growth can be modeled with a specific equation which can be interpreted in terms of biophysical parameters [15 and reference therein]. In 1988, David Zagag presented a model for the study of tumor angiogenesis within the rabbit brain. The authors reported the sequential growth, histology, tumor neovascularization, and vascular permeability of this tumor following its intracerebral implantation. According to them,

tumor angiogenesis correlates with the rapid and logarithmic intracerebral tumor growth [16]. Recently, the experimental abilities to collect information on the cell-biophysical, cell-biological and cell-kinetic properties have improved significantly.

Significant research has been done in the modeling of tumor using theoretical models and computer simulations. A mathematical model is a representation of a physical, biological, or social system in mathematical language. It allows the tools of mathematics, statistics, and computation to be utilized to understand the system and make quantitative predictions. Most mathematical models involve unknown parameters that must be estimated from observed data. Mathematical models of tumor growth, specially angiogenisis, extends back a number of years [17].

Some of the earliest work in modeling of tumors using a three-dimensional cellular automaton on a cubic lattice was carried out by Düchting and Vogelsaenger for small tumors. These automaton rules were designed to reflect nutritional needs for tumor growth. Other important factors, such as surrounding cells and mechanical pressures, however, remained unconsidered[18].

On the other hand, Zheng considered a two dimensional tumor model that reproduced idealized Gompertz results. However, according to them, cells could only divide if one of their nearest neighbors was empty. This created an unrealistically small fraction of tumor which may divide. In addition, the transition from dividing cells to the resting state was handled in pure stochastic manner, rather than the nutrient-based method[19].

In comparison to the experimental research there has been relatively little theoretical work on tumor growth. It is now being recognized that mathematical modeling and computer simulations may help us to extract the full potential of the vast amounts of data

being generated in the laboratory and provide a framework in which to interpret these results. Modeling may allow the experimental works to be directed in more efficient ways.

Our aim is to develop (i.e. design and implement) a 2D lattice Monte Carlo model based on the biological and physical properties of individual cell (like cell-cell interaction,cell motion) in order to investigate how tumor grows with time under different conditions. Our model includes: cell interaction, motion, growth, division, death as well as nutrition diffusion and consumption. One of the features of our model is that we allow cell division when the local concentration is high. But in most cases, people allow cell division if only the nearest neighbors are empty [see for example 20].

Chapter 2

Models and Methods

2.1 Monte Carlo approach

The Monte Carlo method describes a very broad area of science, in which many processes, physical system and phenomena are simulated by statistical methods employing random numbers. The general idea of Monte Carlo analysis is to create a model, which is as similar as possible to the real physical system of interests, and to create interactions within that system based on known probabilities of occurrence, with random sampling of the probability density functions. As the number of individual events (called histories) increases, the quality of the reported average behavior of the system improves, meaning that the statistical uncertainty decreases.

In a Monte Carlo simulation we attempt to follow the 'time dependence' of a model for which change, or growth, does not proceed in some rigorously predefined fashion (e.g. according to Newton's equations of motion) but rather in a stochastic manner which depends on a sequence of random numbers which is generated during the simulation[21].

Monte Carlo techniques have become one of the most popular tools in different areas of medical and biophysics following the development and subsequent implementation of powerful clinical use. In particular they have been extensively applied to simulate processes involving random behavior and to quantify physical parameters that are difficult or even impossible to calculate analytically or to determine experimentally. The application of Monte Carlo method in medical physics cover almost all topics, including cancer treatment, radiotherapy, radiation protection, intravascular radiation therapy.

In this work, we use a 2D lattice Monte Carlo modeling techniques so that multiple biological parameters could be considered simultaneously, since many parameters involve the use of probability functions in the simulation of tumor growth. The program has been written in the FORTRAN 90 programming language.

In our approach, we consider a 2D square lattice by which a collective of biological cells attached to the lattice sites (i,j) randomly. We model a cellular based model which consists of cell diffusion, nutrition diffusion, cell growth, cell division and cell death. Cell age can be divided into two parts: maturity age (t_{mature}) after which cell has non zero probability of division and critical age after which the cell can have a finite probability of dying per unit time (t_{old}). We start with small number of tumor cells and study tumor growth dynamics under different conditions. For instance, the initial configuration of our system is shown in Fig.2.1.

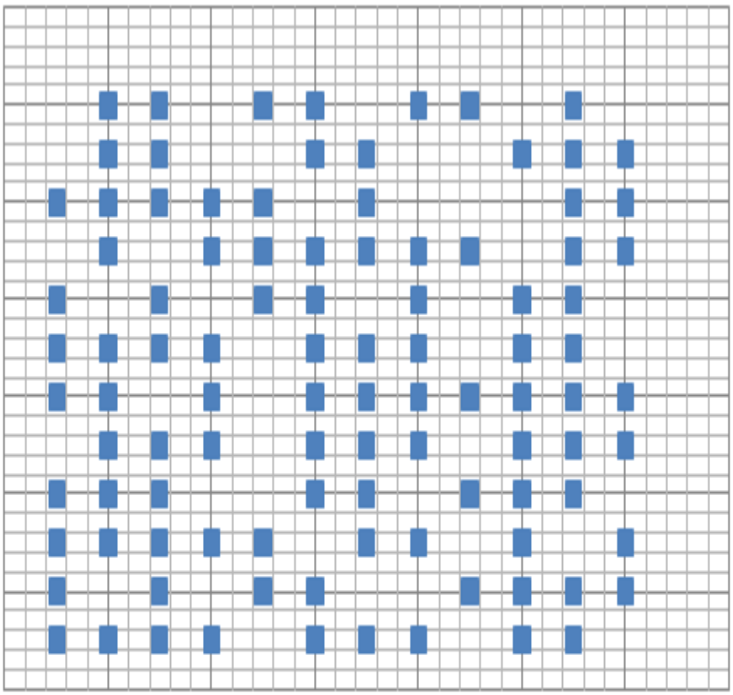

Figure 2.1: Schematic representation of the initial configuration of our model (100 cells) on square lattice.

2.2 Cell diffusion

We randomly select a particle (cell) at a given point (i,j) and this particle has the possibility to jump to the four possible nearest neighbor sites (as shown in Fig.2.2). The jump is accepted only if the conditions imposed by the local rules, such as overlap test, and Metropolis energy tests are satisfied.

2.3 Metropolis Algorithm

When studying systems with many particles, it becomes clear that the number of possible configurations become exceedingly large very quickly. The best way to tackle this problem is to use random sampling, which is done by the Metropolis algorithm. In this method configurations are generated from a previous state using transition probability

which depends on the energy difference between the initial and final state. The sequence of states produced followed by a time ordered path, Monte Carlo time, which is non-deterministic[20]. We consider diffusion to occur via jumps to the nearest neighbor sites with the diffusion probabilities as given below.

$$\rho_{diff} = \begin{cases} 1, & \text{for } \Delta\text{E} \leq 0; \\ e^{-\Delta E}, & \text{for } \Delta\text{E} > 0\ . \end{cases} \tag{2.3.1}$$

Where ΔE is the energy difference between the final and initial states measured in the unit of k_BT.

One of the basic challenges of theoretical model or experimental work of a biological system is that there are many variables on varying scales, some of which can be difficult to measure. But in the case of computer simulation, parameters are most of the time, free parameters. When choosing parameters, the values may be chosen to show qualitative predictions.

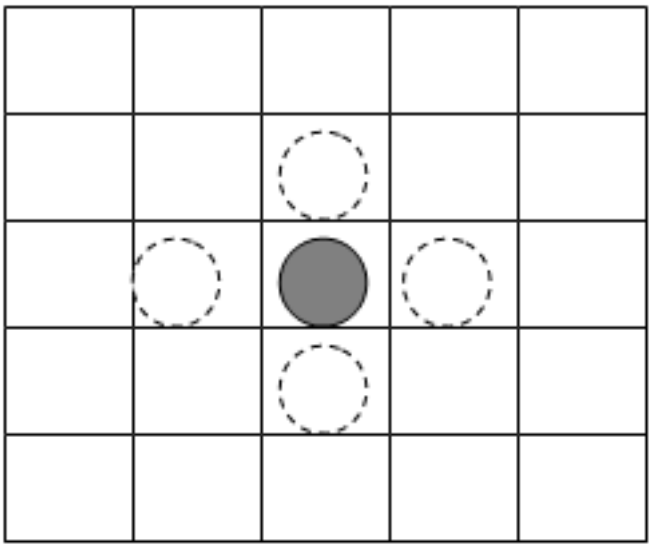

Figure 2.2: An illustration of the four possible nearest neighbor sites. The shaded circle (particle at a site (i,j)) has four possible nearest neighbors (the dashed circles) and jump to these sites is possible.

2.4 Nutrition diffusion

Naturally, tumor cells get nutrient from the surrounding tissue by diffusion. We therefore introduce a reservoir with thickness of n_{box} (n_{box}=20) as shown in Fig.2.3. The nutrient particles are randomly distributed over this reservoir with a constant concentration (ρ_{nut}). Nutrients diffuse in to the tumor tissue from the surrounding tissue (reservoir). We use periodic boundary conditions. Once the particle reaches the site which is already occupied with the cell, it has a non-zero probability to be consumed by the cell. If the nutrient particle is consumed by the cell, then our system automatically replaces the particle by randomly placing one nutrient particle in the reservoir. This is done in order to keep reservoir at constant concentration.

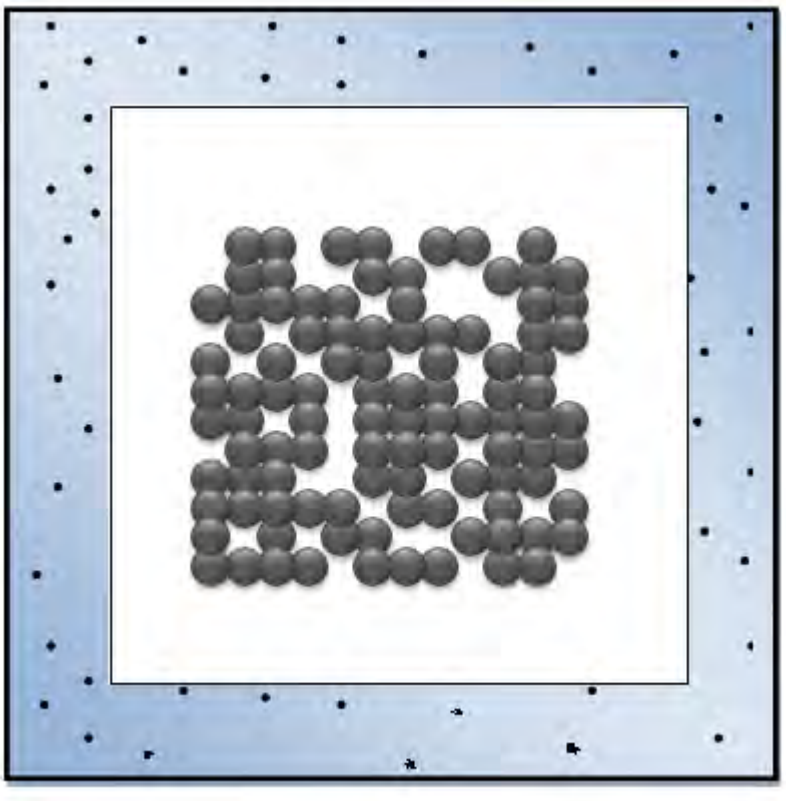

Figure 2.3: Schematic representation of the simulation box. The shaded region is the reservoir with thickness (n_{box}=20) and constant concentration of nutrient particles(dots) and the region with black circles (allowed box (1000×1000) for cell to diffuse).

2.5 Cell growth, division and death

In our model cell growth is simply related to the cell age and nutrition consumption. A cell reaches maturity when its age exceeds minimum value t_{mature}. Once a cell gets enough nutrient and reaches maturity it starts to divide with a given probability (ρ_{div}) depending on local division rules (such as overlap tests,nutrition consumption). The most interesting part of our work during cell division process is when the local concentration is high. In such cases cells may form closed packed patches and division of cells in such patches would be impossible (due to lack of vacant sites) even for small patches, if one does not introduce some prescriptions for global rearrangement of cells after division.

In most cases, people use different strategies to overcome such problem. For example, V.P.Zhadanov [20] considers the cell to be flexible and may change their shapes under contacts. According to them, the cell size is assumed to be slightly larger than the site size but smaller than the distance between the next nearest neighbor sites. The location of cells in next neighbor is allowed. However, such configurations are not favorable, because the cell should be slightly deformed.

We allow local rules for division in order to overcome this problem. During cell division the 'mother' cell and a 'newly born' cell remain in the same site (i.e we allow local overlap without affecting the shape of a cell). We now introduce the effective repulsive interaction (ϵ_{repl})(whose magnitude is large as compared to attractive interaction(ϵ_{att})). This repulsive interaction makes the mother and the newly born cell to repel each other. This process continues until they get separated.

A cell death occurs through two different channels:(i) when the age of the cell exceeds a certain critical time t_{old}, where $t_{old} > t_{mature}$, the cell has finite probability (ρ_{death}) of dying per unit time and (ii) if the amount of nutrients is below the necessary threshold for normal development, proliferating cell becomes quiescent and then die.

2.6 Algorithm of the simulation

With the specification above our Monte Carlo algorithm is as follows:

1. Set up the initial configuration of the system (Fig.2.3) by defining all variables.

2. Generate a random number ρ uniformly between 0 and 1. If (ρ>0.5) perform cell simulation (cell diffusion, division, death)(item 3-6) else perform nutrition diffusion (item 7).

3. A site on the lattice representing the cell is chosen at random. If the selected cell is not mature and the site is occupied by overlapping cell it has the chance to diffuse (item 4) or it has the chance to divide (item 5).

4. The diffusion trial is executed if the selected site is occupied by overlapping cell, and if the selected cell is not mature, if diffusion probability is non-zero. In this case, new site is assigned at random. If the site is vacant, the jump to this site is accepted or rejected by Metropolis test.

5. The division trial is executed with a given probability(ρ_{div}) provided that the selected cell is mature and the site is not occupied by overlapping cell. Division occurs in the same site (overlap is permitted among a mother cell and a newly born cell). Introduce a strong repulsive interaction.

6. Cell death trial is executed with a given probability (ρ_{death}) provided that the cell age exceeds a certain critical age (t_{old}) and there is no sufficient nutrient for the cell

to live and proliferate.

7. Nutrition diffusion:- Select a nutrient particle at random. Assign a new site(using a periodic boundary condition). If the new site is already occupied by a nutrient particle the trial terminates else accept the jump. If jump to the new site is accepted, the nutrient particle has non-zero probability to be consumed. In case the nutrient particle is consumed, automatically replace it in the reservoir in order to keep the reservoir at constant concentration.

Parameter	**Description**
Total number of cell: n_{cell}	Initially we start our simulation with 100 cells
Attractive interaction : ϵ_{att}	A cell-cell attractive interaction energy
Repulsive interaction : ϵ_{repl}	Introduced during cell division (its magnitude is large compared to attractive interaction)
Maturity age: t_{mature}	The probability of cell division is non-zero passed this age
Critical age: t_{old}	The probability of cell death is non-zero passed this age
Nutrition concentration :ρ_{nut}	The concentration is kept constant by using particle reservoir at constant concentration
Division rate : ρ_{div}	Cell division probability per unit time ($\rho_{div} \sim 0.05 - 0.0005$).
Death rate : ρ_{death}	Cell death probability per unit time ($\rho_{death} \sim 0.00005$).

Table 2.1: Main simulation parameters

Chapter 3

Results and Discussion

In this chapter we present our results in three different parts. We first investigate the effect of cell-cell interaction on cell motion by comparing results for different values of cell-cell interaction energy. We then look at the tumor growth dynamics by tuning some parameters of the system, and finish by studying tumor morphology and growth rules.

The simulations are conducted on a 1000×1000 square lattice. We initially place randomly 100 particles (cell) at the center of the box and nutrient particle with a constant concentration in the reservoir of thickness 20 as discussed in chapter 2. The choice of parameter values in the simulation is determined by the particular property which we wish to study. In our lattice Monte Carlo model, time is measured in the so-called Monte Carlo time steps (MCS). One Monte Carlo step means one move attempt per particle (cell) in the system.

3.1 Diffusion

In this section, cell diffusion is investigated for different values of cell-cell interaction energy. We used 10^6 MC time steps in each simulation and performed 1000 runs. The mean square displacement for diffusing particles (cells) is averaged for these 1000 independent runs. In Fig.3.1 we report the results for three different values of cell-cell interaction energy. The data shows that the diffusion coefficient D decreases as the cell-cell interaction energy increases, where D is measured in unit of ((distance)^2 per time) which is set to one. We found D=9.93×10^{-5} for $\epsilon_{att} = 0.0$, D=5.59×10^{-5} for $\epsilon_{att} = -1.5$ and D=5.63×10^{-6} for $\epsilon_{att} = -3.5$.

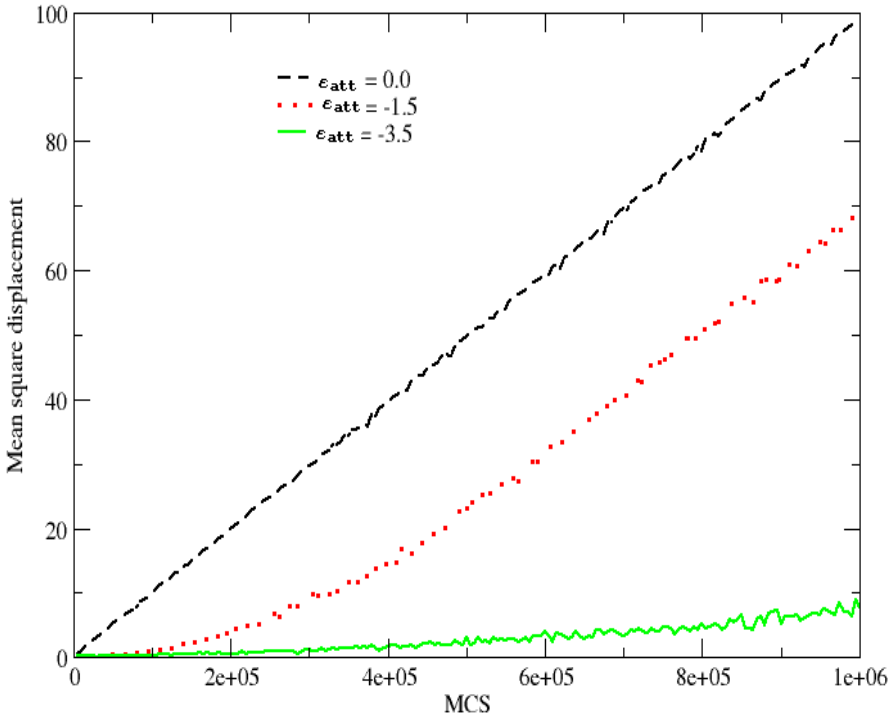

Figure 3.1: Plot of the mean square displacement versus time for three different values of the interaction energy ϵ_{att} for $n_{cell} = 100$.

3.2 Tumor growth dynamics

Several parameters can affect the dynamics of tumor growth. Of all these parameters, the nutrient concentration ρ_{nut} is the most important parameter. In order to show the dependence of tumor growth on the nutrition concentration, we simulated our system for two different concentration. The result from our simulation shows that the tumor growth is strongly affected by nutrition concentration. Fig.3.2 shows the plot of number of cell versus time under different values of ρ_{nut}. As we can see from Fig.3.2, for high concentration ($\rho_{nut} = 0.001$), the tumor grows faster and reaches around 10000 cells after 10^6 MC time steps. For low concentration ($\rho_{nut} = 0.0001$), we get 2650 cells after 10^6 MCTs. This shows that tumor growth is strongly affected by nutrition concentration.

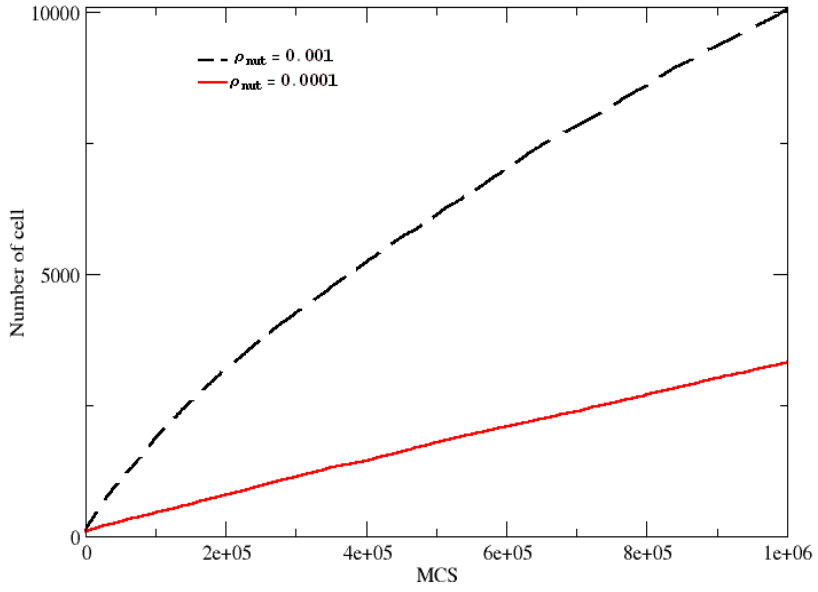

Figure 3.2: Plot of number of cell versus time for two different values of nutrition concentration ρ_{nut}. The set of model parameters used in this particular case are ($\epsilon_{att} = -2.0$, $\epsilon_{repl} = 6.0$, $\rho_{div} = 0.005$, $t_{mature} = 100$ and $t_{old} = 10^5$).

Another parameter which is important for the growth dynamics is the maturity age (t_{mature}). As we said earlier, when a cell grows and reaches t_{mature}, it is allowed to divide with a division probability ρ_{div} per unit time. In Fig.3.3 we show the plots of number of cell per MCS for two different values of t_{mature}. These two values are: $t_{mature} = 10^{-4}\ t_{old}$ and $t_{mature} = 10^{-1}\ t_{old}$ (where t_{old}=10^5 is a critical age after which cell has a non-zero probability to die per unit time), and t_{mature} is the maturity age. For $t_{mature} = 10^{-4}\ t_{old}$ the slope is 4.0×10^{-4} while for $t_{mature} = 10^{-1}\ t_{old}$ is 3.4×10^{-4}. This shows that the slope for the case $t_{mature} = 10^{-4}\ t_{old}$ is greater than for $t_{mature} = 10^{-1}\ t_{old}$.

From Fig.3.3 it can bee seen that the growth is linear. This is because the maturity age (t_{mature}) is not the only condition for cell division. Mature cell has to get enough food to divide. Therefore, the tumor growth is limited by nutrient diffusion. In addition cells have to fulfil the overlap test (i.e overlapped cells are not permitted to divide until they get separated). All these additional conditions make the growth curve linear rather than exponential.

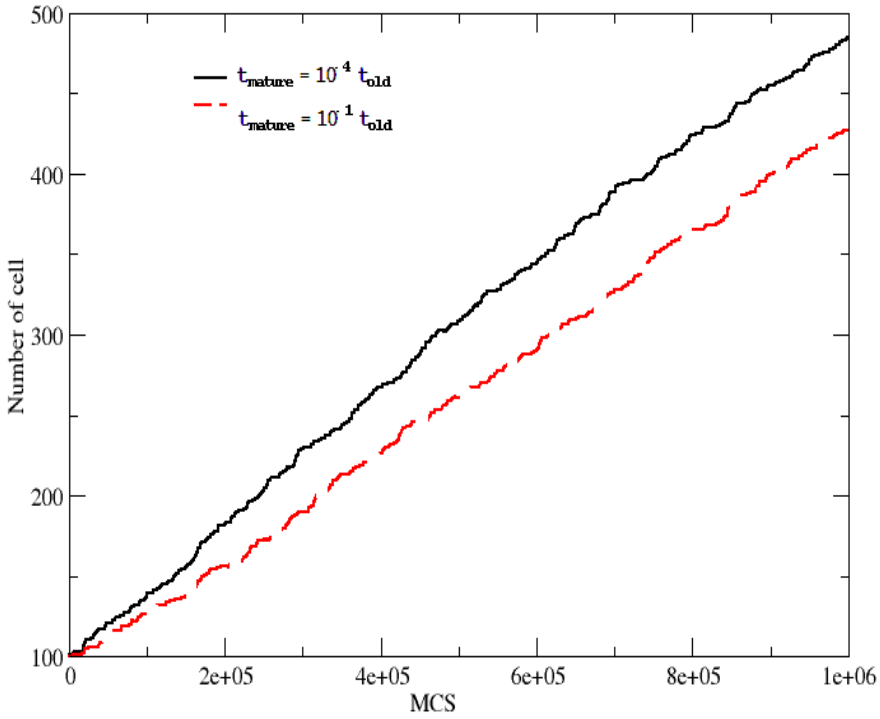

Figure 3.3: Plot of number of cell versus time for two different values of maturity age t_{mature}. The set of parameters ($\epsilon_{att} = -2.0$, $\epsilon_{repl} = 6.0$, $\rho_{div} = 0.0005$, $\rho nut = 0.001$ and $t_{old} = 10^5$) are used in the simulation.

We can also investigate the effect of the repulsive interaction on the growth dynamics. As discussed in our model (Chapter 2), we introduce repulsive interaction during cell division when the local concentration is very high. In such case, overlap among mother cell and newly born cell is permitted and the repulsive interaction makes them to strongly repel each other. This process continues until they get separated. In Fig.3.4 we report the results for two different values of repulsive interaction (ϵ_{repl}). When the repulsive energy is very strong ($\epsilon_{repl} = 8$), the overlapped cells get separated faster than in weak repulsive energy ($\epsilon_{repl} = 4$) situation. Since one of our division criteria is overlap test (overlapped cells should get separated), the system with strong repulsive energy grows faster than when it is in weak repulsive interaction.

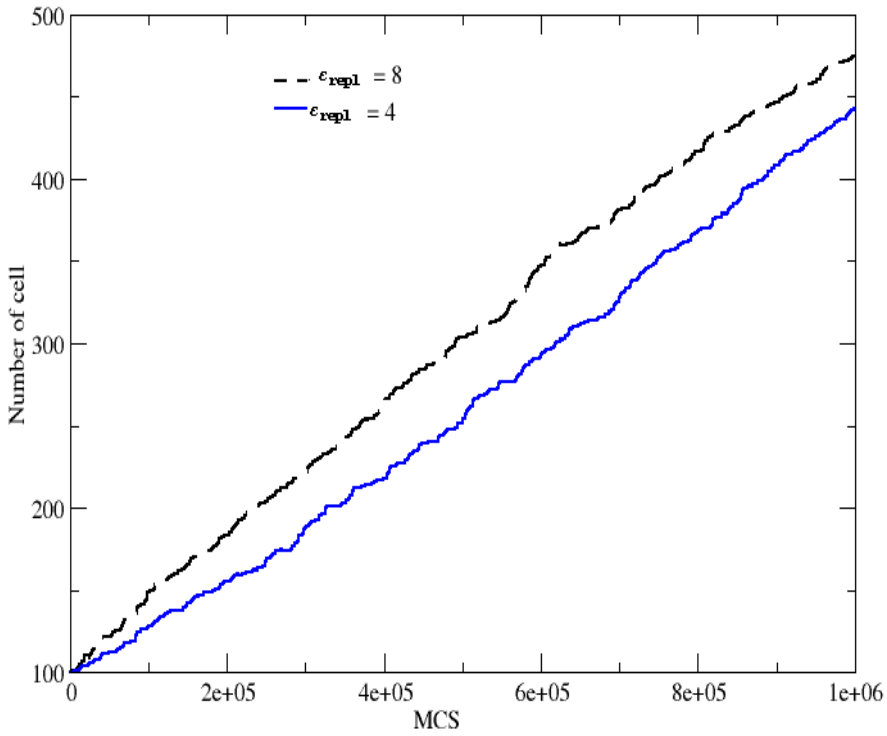

Figure 3.4: Plot of number of cell versus time for two different values of repulsive energy ϵ_{repl}. The set of parameters ($\epsilon_{att} = -2.0$, $t_{mature} = 100$, $\rho_{div} = 0.0005$, $\rho nut = 0.001$ and $t_{old} = 10^5$) are used in the simulation.

Comparisons of Fig.3.3 and Fig.3.4. shows that in both cases the simulation is done at the same nutrition concentration and the plots shows that the effect of maturity age and repulsive interaction energy on tumor growth are similar under the same conditions.

3.3 Tumor morphology and growth rules

In our model we consider necrotic, quiescent, and proliferating cells as distinct cell types. Cells change type in response to a nutrient gradient within the tumor. The concentration of nutrient within the tumor is determined as a function of depth of tumor, where depth is the distance from the core to the periphery of tumor.

Starting with small number of cells, we present how tumor in our simulation evolves with time under different conditions (as described in the model, Chapter 2). Tumor cells consume nutrient. Nutrients diffuse into the tumor tissue from the surrounding tissue. This is modeled by using a nutrient reservoir (placed as shown in Fig.2.3) with a constant nutrient concentration. We use the set of parameters given in the table below (Table 3.1).

Parameter	**value**
ϵ_{att}	-2.0
ϵ_{repl}	4.0
t_{mature}	100
t_{old}	10^5
ρ_{nut}	0.001
ρ_{div}	0.0001

Table 3.1: values of paraments used in section 3.3

Fig.3.5 shows how tumor morphology changes with time. At the early stage of tumor growth, every cell receives sufficient nutrient by diffusion. At this stage almost all cells are proliferating (Fig.3.5 a). Gradually as the tumor grows, supplying the nutrient to the central core by diffusion becomes more and more difficult, so that nutrient concentration at the core diminishes. Quiescent cells then start to emerge at the center of the tumor. This is shown in (Fig.3.5 b-d). The tumor then grows until the inner necrotic core forms. In our model, the necrotic cells are removed from the simulation box.

Therefore, morphology of tumor from our model is characterized as spherical shape by

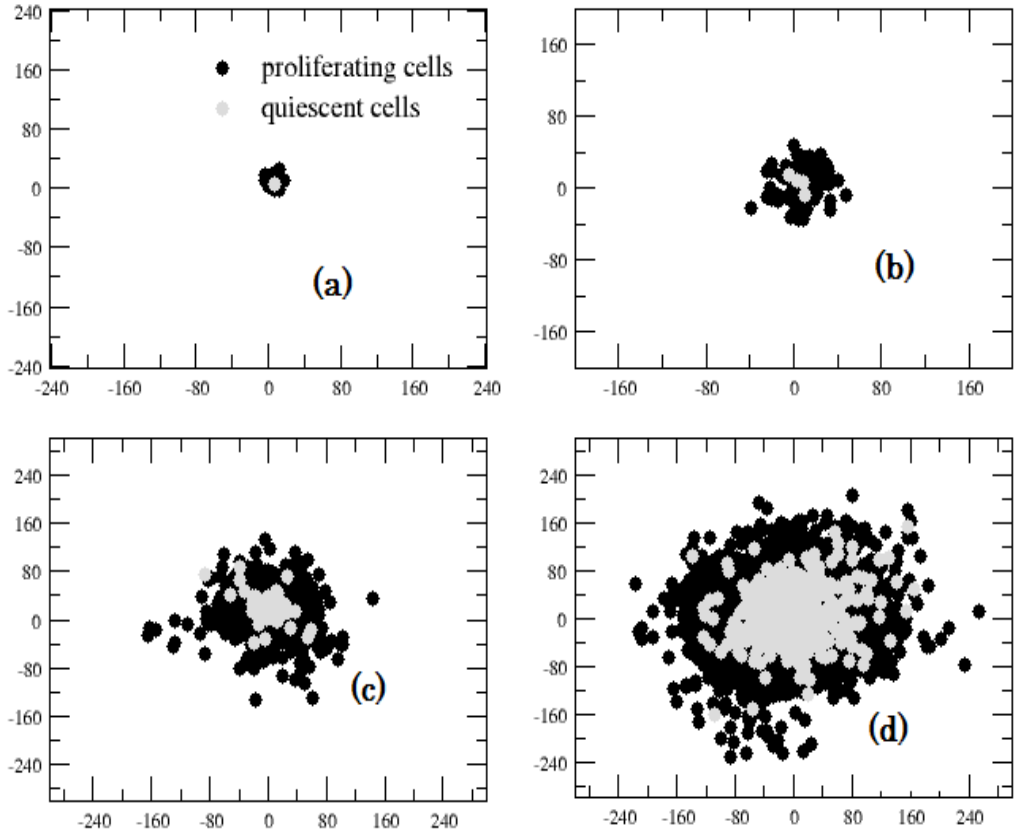

Figure 3.5: Cross section of the simulated tumor at different times showing the proliferating cells (painted black) and quiescent cells (painted light gray).(a) Snapshot at 10^4 time steps, (b) Snapshot at 10^5 time steps, (c) Snapshot at 10^6 time steps and (d) Snapshot at 10^7 time steps

proliferating cells at the edges of the tumor with quiescent cells accumulated at the center (see Fig.3.5 d).

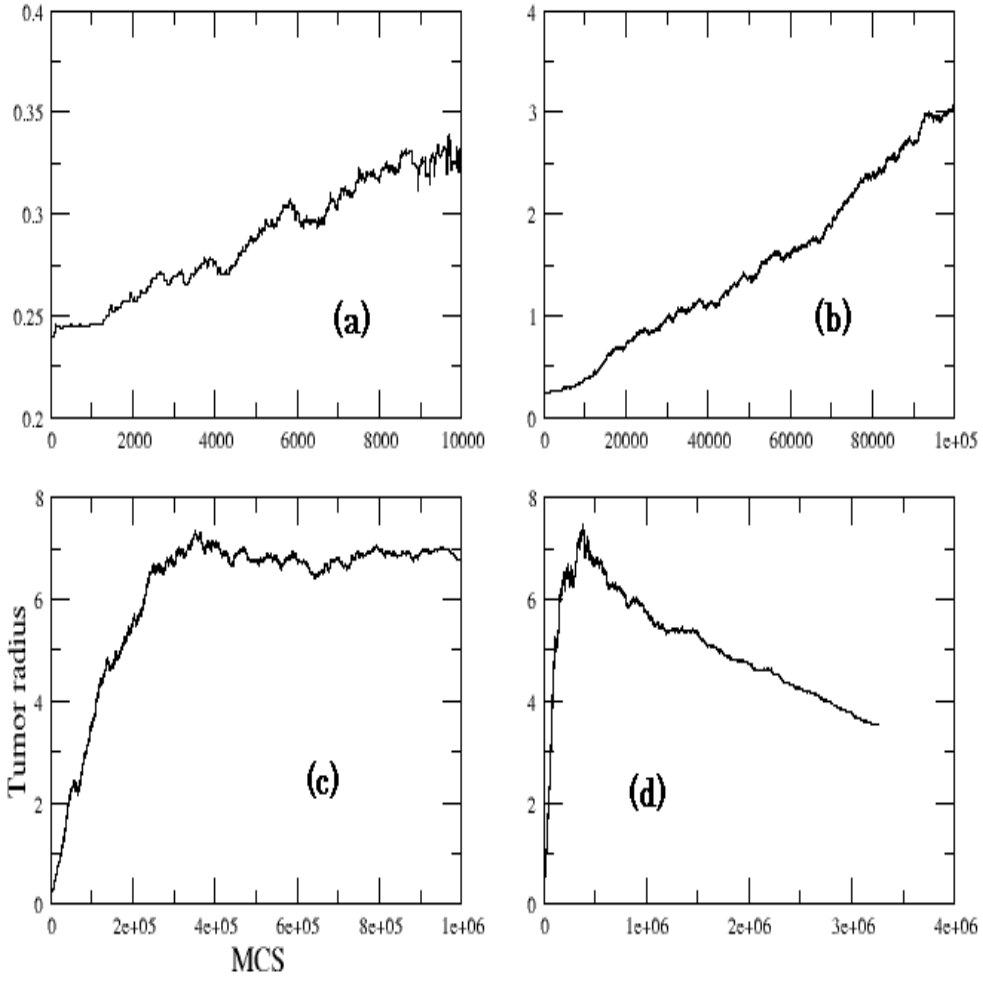

Figure 3.6: Radii of growing tumor versus time;(a) After 10^4 iterations, (b) After 10^5 iterations, (c) After 10^6 iterations and (d) After $4x10^6$ iterations

Fig.3.6 shows the growth curves of tumor discussed in Fig.3.5. The tumor (Fig.3.6 a-b) grows linearly in the initial time for (10^4-10^5 MCS). At about 4×10^4 MCS, the growth curve starts to saturate. This is due to the quiescent cells (Fig.3.6c). Later, the tumor becomes so big that the distance from the edge of the aggregate to the cells at the center is too large for enough nutrient to diffuse to them. After around 10^6 MCS (see Fig.3.6 d) the necrotic core forms and growth starts to slow again. This is due to the removal of necrotic cells from the system. Our results for avascular tumor growth is consistent with experimental evidences.

Once the growth reaches necrotic stage, the growth can no longer increase unless it gets its own nutrient supply. It does this by releasing a chemical called tumor angiogenesis factor (TAF) in to the surrounding tissue. When TAFs diffuse to the surrounding penetrating the tumor mass, angiogenesis occurs and the growth becomes exponential again. We plan to extend our model to include this feature.

Chapter 4

Summary and Conclusion

In this work, we have developed a 2-dimensional tumor growth model using discrete (cell-centered) approach. A tumor growth model algorithm has been designed and implemented using the lattice Monte Carlo method. The model includes key features such as nutrient diffusion and consumption, cell growth, cell division, cell death and cell-cell interaction.

We presented the effect of cell-cell interaction energy on the motion of cells by simulating cell diffusion. Our result shows that as interaction energy becomes stronger the diffusion coefficient decreases.

We have also studied the tumor growth dynamics by tuning some of the parameters of the simulation. The dynamics of tumor growth can be affected by nutrition concentration, maturity age, and repulsive interaction.

Finally, we studied tumor morphologies and growth rules. This has been done by taking snapshots of tumor cross section at different time and by studying (growth curves) tumor radius versus time. Our growth curves best describe the avascular tumor growth.

Future directions:

The tumor growth model developed in this study can be used as robust modeling framework for developing more advanced tumor growth models. consequently, these models can be used to study how tumor angiogenesis factor (TAFs) diffuse, to model tumor angiogeneses and study the effects of individual factors on angiogenesis, understand mechanisms of interaction them and generate experimentally testable hypotheses.

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Declaration

This thesis is my original work, has not been presented for a degree in any other University and that all the sources of material used for the thesis have been dully acknowledged.

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Signature:

Place and time of submission: Addis Ababa University, June 2010

This thesis has been submitted for examination with my approval as University advisor.

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