Tumor Growth Dynamics
A Deterministic and Stochastic Analysis of the Interaction between Normal and Abnormal Cells

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Abstract

We study the interactions between normal and abnormal cell populations as they occur in a tumorous growth. The purpose of our research is determine whether the spatial arrangement of abnormal cells in a tissue is a significant factor governing the spread of the tumor. To this end, we model how normal and abnormal cells compete for nutrients using a deterministic model and a spatial stochastic model. We vary nutrient competition rates as well as drug treatment effects for the two cell populations. The deterministic model indicates how the populations interact without consideration of spatial arrangement, while the stochastic model includes this factor. Our results show that different spatial arrangements of cells may cause significant differences in the growth dynamics of the cells even if the initial population sizes are kept constant. We have found that the spatial model reveals some growth dynamics that the deterministic model overlooks. Therefore it is of interest to obtain more realistic spatial models. For this, we need to focus research on the most distinctive factor of the spatial model: how normal and malignant cells on the boundary of a tumor compete for nutrients.

1 Introduction

Cancer is a seemingly unpredictable illness that is prevalent among adults and children around the world. In fact, one out of every five persons will die as a result of cancer. Cancer begins when normal cells genetically mutate into abnormal cells, which have the mutant gene, oncogene (Alberts 1994). These abnormal cells grow exponentially and take nutrients from their cellular surrounding, which causes nearby normal cells to die.

The mutation of normal cells into abnormal cells can result from many factors, including exposure to the sun, chemical products, water, food, air, etc. However, even "in an environment that is free of mutagens, mutations will occur spontaneously at an estimated rate of about 10^{-6} mutations per gene per cell division- a value set by the fundamental limitations on the accuracy of DNA replication and repair. (Alberts 1994).

The mutation from a normal cell to an abnormal cell is quite unpredictable. From statistical data, it is estimated that somewhere between three and seven consecutive random events of mutations, each of low probability, are typically required to turn normal cells into abnormal cells (Alberts 1994).

After normal cells have mutated into abnormal cells, a tumor may begin to grow, and it eventually starts to vascularize. This enables abnormal cells in the center of a tumor to receive nutrients that would otherwise be available only to the abnormal cells on the surface of the tumor. Vascularization, thus, works as a system of irrigation, which allows the growth of abnormal cells to occur more rapidly than that of normal cells.

Moreover, as a tumor grows, abnormal and normal cells begin to compete for nutrients. Abnormal cells win this competition. They receive more nutrients than normal cells because they grow at a faster rate than normal cells and eventually take up a greater volume than normal cells in their respective, cellular surroundings. This results in a lack of nutrients to normal cells, which causes many of them to eventually die.

Another characteristic of abnormal cell populations that explains their tendency to outgrow normal cell populations is their lack of "contact inhibition." Contact inhibition occurs when normal cell growth ceases due to the spatial accumulation of cells. After a certain density of normal cells is reached, normal cells cease to reproduce. Hence, normal cell growth has a threshold limited to the amount of available space in a specific amount of cellular tissue. Abnormal cells, in contrasts, do not have this threshold; they grow and affect other cells without regard to contact inhibition.

In this paper, we analyze how the two types of cells interact using a deterministic model

and a spatial stochastic model. Comparing the results from the two models allows us to see whether the spatial arrangement of abnormal cells plays a significant role in the development of a tumor. Throughout our paper we describe both the deterministic and stochastic spatial models. We also describe how we determine the parameters. Finally, we present our results and suggestions for further research.

2 Methodology

In our project, we develop a deterministic model and a spatial stochastic model to simulate how normal and abnormal cells in organic tissue interact. The deterministic model shows us how normal and abnormal cells compete with each other without taking into account the spatial arrangement of cells. The stochastic model in contrast, does take this factor into account. Thus, by comparing the two models, we can determine whether the spatial arrangement of cells is a significant factor in studying tumor growth.

In the following sections, we will explain how we establish our two models, the parameters we chose, and how we analyze the two models.

2.1 The Deterministic Model

Our deterministic model is as follows:

$$\frac{dN}{dt} = \lambda_0 N\left(1-\frac{N}{k_0}\right) - \delta_0 N - d_0 N - \frac{AN}{mN+b} \tag{1}$$

$$\frac{dA}{dt} = \lambda_1 A\left(1-\frac{A}{k_1}\right) - \delta_1 A - d_1 A. \tag{2}$$

Interpretation of symbols:

N is the number of normal cells;

A is the number of abnormal cells;

k_0 is a constant;

k_1 is a constant;

λ_0 is the birth rate of normal cells;

λ_1 is the birth rate of abnormal cells;

δ_0 is the death rate of normal cells due to natural death;

δ_1 is the death rate of abnormal cells due to natural death;

d_0 is the death rate of normal cells due to drug treatment;

d_1 is the death rate of abnormal cells due to drug treatment;

ρ is the proportion of abnormal cells that take nutrients from normal cells;

$$\frac{k_0(\lambda_0 - \delta_0 - d_0)}{\lambda_0}$$

is the carrying capacity of the normal cells;

$$\frac{k_1(\lambda_1 - \delta_1 - d_1}{\lambda_1}$$

is the carrying capacity of the abnormal cells;
and

$$\frac{AN}{mN + b}$$

is the number of normal cells that die due "intervascularization".

The carrying capacity for abnormal growth is considered finite because of a phenomena that occurs in neoplasms (or hard tumors). The constants are determined and discussed in the parameter section. When a tumor grows, it vascularizes so that abnormal cells in the center of the growth access nutrients that would otherwise be available only to the abnormal cells on the surface. This system supports abnormal cells in the center of the tumor while the ratio of volume to surface area of the growth is sufficiently large. Otherwise, the system is too inefficient, and the abnormal cells inside the tumor lose in the competition for nutrients and die (Yen 1997). This self-competition for nutrients explains why we modeled the abnormal growth with a carrying capacity. We must mention that the competition for nutrients between normal and abnormal cells does not significantly contribute to abnormal cell death (Velasco 1997). Finally, the rate at which normal cells mutate into abnormal cells is so small, that it is negligible for our purposes (Yen 1997).

2.2 Determining the Parameter Values

The competition factor, $AN/(mN+b)$, tells us the rate of change of normal cells due to competition for nutrients. In Figure 1 we see that when either the populations is low then the competition factor is small. Also when the population of abnormal cells is large then the competition factor is large.

We want the per capita competition factor to reflect some realistic situations. For example, when there is a small number of normal cells then we expect the competition factor to be its greatest. And when the number of normal cells is large then we expect the competition factor to be small.

If we assume that $b = 350$ and $m = 240$ then

$$\frac{A}{mN+b} = \frac{A}{240N+350}$$

is the per capita rate of change of normal cells due to competition of nutrients.

Practically we have control over only the drugs that can be administered to a patient. Consequently, we can control only the variables d_0 and d_1. We researched the other rates and found the birth and death rates of normal and abnormal cells to be:

$\lambda_0 = 7.2\%$ (Fry 1969);

$\delta_0 = 5.3\%$;

$\lambda_1 = 18\%$ (Fry 1969); and

$\delta_1 = 12\%$ (Baserga 1985);

where we have approximated δ_0.

Another significant factor, drug rates, is also considered. For example, the drug Vincristine, has been found to kill abnormal cells at a rate of 4% (Baserga 1982). It has been shown that normal cells are more resistant to certain drugs than abnormal cells. Swan asserts, for example, that "the normal cell population is expected to recover at a much faster rate than the tumor cell population" (Swan 1982).

We know that for our two models to produce results on the same scale we need

$$0 < k_0 < 4910$$

and

$$0 < k_1 < 16920.$$

2.3 The Stochastic Model

For the stochastic model, we set up a 25×25 patch grid. Each patch on the grid has four possible states: E (empty), N (normal cell), A (abnormal cell), or D (dead cell). During the simulation, four basic events can occur: (1) $E \rightarrow N$ (a normal cell is born); (2) $E \rightarrow A$ (an abnormal cell is born); (3) $N \rightarrow E$ or $N \rightarrow D$ (a normal cell dies); and $A \rightarrow E$ or $A \rightarrow D$ (an abnormal cell dies). Selecting the next event on the grid is a four-step process described below.

Step 1: Setting up the weights of each event

To each patch of the grid corresponds a four-component vector containing the weights, of the four basic events. These weights are assigned to each patch with an algorithm that respects the dynamical properties of the deterministic model, while incorporating spatial factors that the deterministic model cannot account for. Specifically, the weight of each event for each patch (referring to the patch as P) is calculated as follows:

$$\begin{aligned}
\text{Weight}(E \rightarrow N) &= \frac{\lambda_0}{8} (\#\text{ of } N \text{ cells in the 8-patch neighborhood of } P) \\
&\quad \text{if state of } P = E. \\
&= 0 \text{ otherwise.} \\
\text{Weight}(E \rightarrow A) &= \frac{\lambda_1}{8} (\#\text{ of } A \text{ cells in the 8-patch neighborhood of } P) \\
\text{Weight}(N \rightarrow E \text{ or } N \rightarrow D) &= (\delta_0 + d_0 + \rho_0) (\#\text{ of } A \text{ cells in the 8-patch neighborhood} \\
&\quad \text{of } P) \text{ if state of } P = N. \\
&= 0 \text{ otherwise.} \\
\text{Weight}(A \rightarrow E \text{ or } A \rightarrow D) &= \delta_1 + d_1 \text{ if state of } P = A \text{ and } \#\text{ of } A \text{ cells in the 8-patch} \\
&\quad \text{neighborhood of } P < 8 \\
&= \delta_1 + d_1 + \rho_0 (\#\text{ of } A \text{ cells in the 24-patch neighborhood} \\
&\quad \text{of } P) \text{ if state of } P = A \text{ and } \#\text{ of } A \text{ cells in the 8-patch} \\
&\quad \text{neighborhood} = 8. \\
&= 0 \text{ otherwise.}
\end{aligned}$$

where ρ_0 is the death rate due to competition for nutrients with abnormal cells.

For example, a section of the grid could look like this:

E	A	A	E	E	N
N	E	A	A	N	E
E	E	N	**E**	N	N
N	E	N	N	E	E
E	N	E	N	E	N
E	E	E	N	N	N

In this case, the weights at the patch containing the bold **E** would be as follows:

$$\begin{aligned} \text{Weight}(E \rightarrow N) &= 5\frac{\lambda_0}{8} \\ \text{Weight}(E \rightarrow A) &= 2\frac{\lambda_1}{8} \\ \text{Weight}(N \rightarrow E) &= 0 \\ \text{Weight}(A \rightarrow E) &= 0. \end{aligned}$$

Events $E \rightarrow N$ and $E \rightarrow A$ would be possible on this patch, while the other two would not.

Step 2: Choosing the time for the next event

Here, we use an exponential function with parameter γ = total event rate. We calculate γ by adding the weights of each event for all the patches in the grid.

Step 3: Choosing the next event

We first add the total weights for each event on the whole grid and place the sums into a 4-element vector. From this weighted vector, we randomly select one of the four events.

Step 4: Choosing a patch for the event

We produce a 625-element vector containing the weight at each patch of the chosen event. From this weighted vector, we randomly select an element, which will correspond to one of the patches on the grid.

Special Cases: There are two special cases to consider. First, when the event $E \rightarrow A$ is chosen on a non-empty patch, "shifting" occurs. For example, if the A below is to reproduce into the space to the left of it, the new A would shift the two other cells one space to the left, until either an empty space is filled, or the edge of the grid is reached.

Second, we incorporate a state D to represent the dead cells in the middle of an abnormal core. The idea behind this is that in real tumor tissue, dead cells in the center of the tumor cannot escape the system. We modeled this as follows. If either an N or A cell dies, and its 8-patch neighborhood is entirely A cells, then it will become a D cell. If at any point, there is

an E patch in the 8-patch neighborhood of a D cell, the D cell will become E. This is simply an updating action and does not count as an event in the stochastic process.

Initial Conditions We begin each simulation with certain arrangements of N and A cells throughout the grid. In most cases, we vary only the spatial arrangement of cells, and not the number of cells of each type. For instance, we keep the N and A count at 156 and 15, respectively, but in one initial condition, we arrange the A cells in one lump, while in the other, we disperse them evenly throughout the grid. In general, we run the simulations until a steady state is reached (1000 frames).

3 Results

3.1 Deterministic Model

After finding reasonable parameter values for our differential equations, we calculated the equilibrium points. We found three equilibria:

$$\begin{aligned} E_0 &= (0,0), \\ E_1 &= \left(\frac{k_0(\lambda_0 - \delta_0 - d_0)}{\lambda_0}, 0\right) \\ E_2 &= \left(0, \frac{k_1(\lambda_1 - \delta_1 - d_1)}{\lambda_1}\right) \end{aligned}$$

Since these are equilibria, if the populations are any of these, the system will not change in time.

Next we found stability at each of these equilibria by linearizing both of our equations and obtaining Jacobian matrices for each equilibria. This allows us to analyze local stability around each equilibrium point by evaluating the trace and the determinant of each Jacobian matrix.

Using the determined parameters, we found equilibria in terms of d_0 and d_1. We carried out the stability analysis also in terms of d_0 and d_1. This allowed us to find conditions on d_0 and d_1 under which we could eradicate the cancer and save normal cells. So we want $N_\infty > 0$ and $A_\infty = 0$ to be stable.

3.2 Stochastic Results

Due to time constraints, we have not run sufficiently many simulations to obtain quantitative results from the stochastic model. However, we have obtained preliminary qualitative results. We have adjusted the death rate due to drugs of abnormal cells so that the total death rate of abnormal cells is similar to the total birth rate of abnormal cells. Using these rates, we have set up two initial conditions (Figure 2 and Figure 3) that differ only in the spatial arrangement of abnormal cells.

In both grids, there are 156 normal cells and 15 abnormal cells. In Figure 2, the abnormal cells are all lumped together in the middle of the grid, while Figure 3 has the abnormal cells dispersed evenly. Running simulations from these initial conditions shows that the lumped cells are more likely to survive. While simulations from Figure 3 results in rapid extinction of abnormal cells (Figure 5), the abnormal cells survive and in fact grow to eventually kill off the normal cells (Figure 4).

This result tells us something interesting about the cellular dynamics of our model. If our model is realistic, this might also suggest a treatment strategy that includes attacking abnormal cells in their weaker state, when they are dispersed. This result could not have been predicted by the non-spatial deterministic model.

4 Discussion

Results from the deterministic model produce a range of values for d_0 and d_1, such that the abnormal cell population can be eliminated while preserving the normal cell population. The stochastic results, on the other hand, show that these values of d0 and d1 are variable, and depend strongly on the spatial arrangement of abnormal cells. The dynamics of abnormal cell growth change considerably when these cells are lumped together compared to when they are dispersed. This fact suggests that a spatial stochastic model is able to produce a more complete picture of normal andabnormal cellular growth dynamics than a non-spatial deterministic one. It is therefore of interest to develop more realistic spatial models. To accomplish this, more needs to be known about the spatial factors in the dynamics of normal and abnormal cell interaction. For example, we need a better estimate of the effect of nutrient competition on the boundary of a tumor, and the extent to which contact inhibition hinders the growth of normal cell populations. We suggest that further research be done in these areas.

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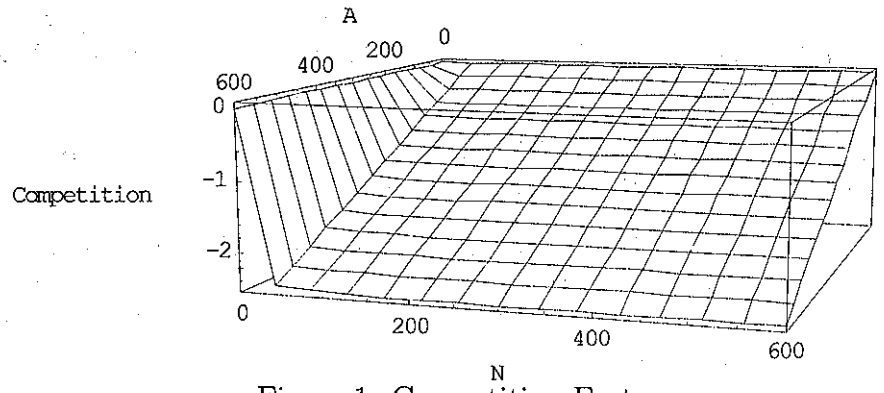

Figure 1: Competition Factor.

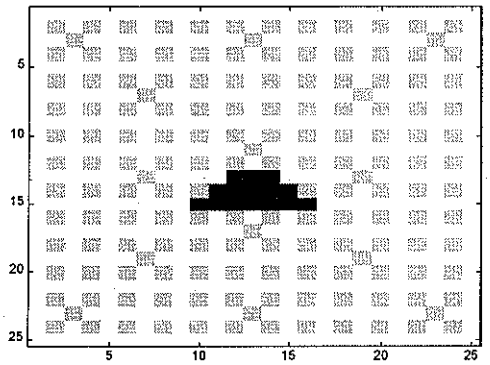

Figure 2: Abnormal cells lumped together in the middle of the grid.

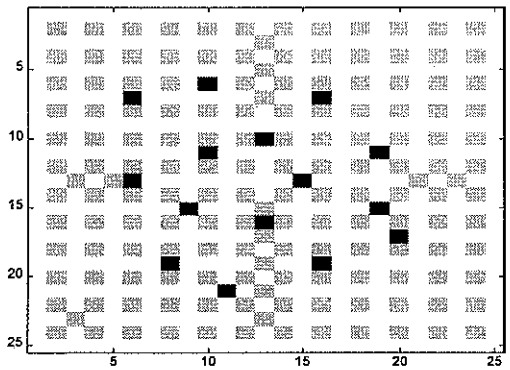

Figure 3: Abnormal cells dispersed evenly.

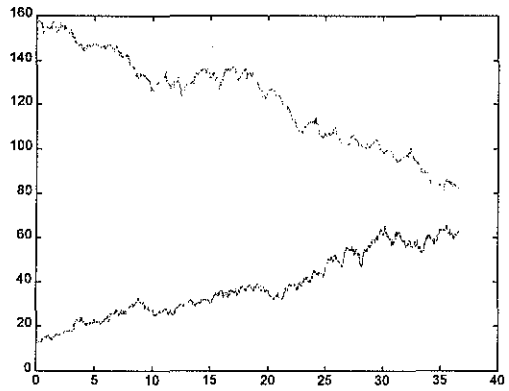

Figure 4: Normal and abnormal cells. Normal cells are extinct.

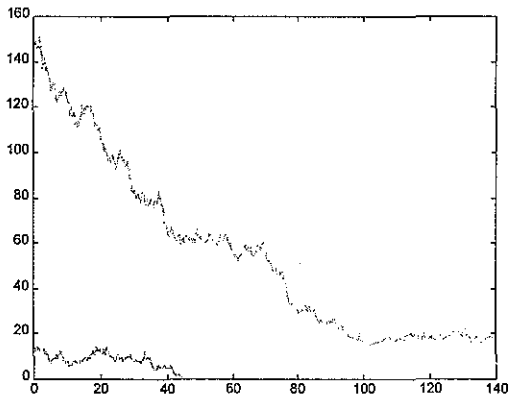

Figure 5: Normal and abnormal cells. Abnormal cells are extinct.