Mathematical Modeling of Breast Lesion Growth

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Abstract: In this paper, two biologically accurate tumor growth models are presented. These tumor growth models are developed to generate a variety of shapes and growth patterns encountered in benign and malignant breast tumors. In the first tumor growth model, the effect of the nutrient distribution and the heterogeneity in the motion of tumor cells is studied. All tumors generated using this model are spherical in shape. This limits its capability to early stage or benign tumors which tend to be compact in shape. In the second model, the rivalry for nutrients between healthy and tumor cells is represented and its impact on tumor morphology analyzed. It is found that the second model can provide a wide variety of tumor shapes and patterns. This proves the feasibility of using the nutrient rivalry growth model to simulate many kinds of breast tumors including malignant with highly irregular shapes.

Keywords: Tumor growth, mathematical biology, tumor morphology and breast cancer.

1. Introduction

One of the challenges of breast tumor detection is its interdisciplinary nature which requires the integration of knowledge from several fields of engineering, physiology, biology and mathematics. Tumor growth modeling of breast lesions is a classic example of an interdisciplinary area of breast cancer research which has received widespread interest. Accurately modeling tumor growth can provide extensive information regarding tumor growth rates and spatial-temporal tumor patterns. Also, it can shed light on what exactly governs the conversion of a tumor from a dormant benign state into an invasive malignant one [1].

A critical factor which defines the accuracy of a tumor growth model is its ability to generate shapes consistent with histological studies. This fact is emphasized in breast cancer due to the extreme differences that exist between shapes of benign and malignant breast tumors [2]-[3]. Benign tumors tend to be round smooth and compact while malignant tumors tend to have an irregular diffusive shape with several projections[2]-[3]. This necessitates the development of a robust tumor growth model capable of generating the wide variety of shapes encountered in breast lesions.

In this paper, two tumor growth models designed to model biological processes affecting tumor growth are analyzed. In the first model, the effects of the distribution of the nutrient concentration as well as the variation in the mobility of tumor cells are addressed. In the second model, the rivalry for nutrients between healthy and tumor cells is studied. The results obtained from both models are presented and compared in this work.

2. Methodology

In this section, the implementation of the tumor growth models is described. The first model assumes spherical symmetry and assigns different diffusivity values to different tumor cells. The second model does not assume spherical symmetry and it incorporates the interaction between healthy and tumor cells as will be described in the following subsections.

A. Spherical Symmetry-Heterogeneous Diffusivity Tumor Model

The tumor growth model discussed in [4] is selected due to its capability of generating three dimensional tumor shapes with growth patterns matching those obtained *in vitro*. The model also has the advantage of allocating different mobility rates to different tumor cells which allows the modeling of heterogeneous breast tumors with different invasive rates. The effect of nutrients on tumor growth is also included in the model. Two variables are considered; the tumor cell concentration $c(\vec{r},t)$ and the nutrient concentration $u(\vec{r},t)$ to which the tumor is attracted (chemoattractant). The vector radial position is represented by $\vec{r}$. The time is represented as *t*. The model consists of the following two differential equations [4],

$$\frac{\partial u(\vec{r},t)}{\partial t} = \nabla.\left(D_1\left(u(\vec{r},t)\right)\nabla u(\vec{r},t)\right) + gu\left(u_c - u(\vec{r},t)\right) - \nabla\cdot\left(\chi\left(c(\vec{r},t)\right)u(\vec{r},t)\nabla c(\vec{r},t)\right) \tag{1a}$$

$$\frac{\partial c(\vec{r},t)}{\partial t} = \nabla\cdot\left(D_2\nabla u(\vec{r},t)\right) - \alpha u(\vec{r},t)c(\vec{r},t) \tag{1b}$$

where $D_1(u(\vec{r},t))$ is the diffusion profile of tumor cells, D_2 is the diffusivity of the chemoattractant, g is the growth rate of tumor cells, u_c is the maximum tumor cell capacity, α is the nutrient consumption rate and $\chi(c(\vec{r},t))$ is the chemotaxis coefficient. The diffusivity is set equal to [4],

$$D_1\left(u(\vec{r},t)\right) = \frac{D_0}{u+u_0}. \tag{2}$$

This relation was chosen since the model was devised for brain tumors. In brain tumors, cells at the boundaries, where the concentration of tumor cells is low, are more invasive and, hence, will have higher diffusivity. This relation can be easily adapted to model the differential invasive rates in heterogeneous breast tumors discussed in [5], providing another advantage to use of this model.

B. Multiple Nutrients Driven Model

The second tumor growth model is based on the rivalry between cancerous and normal cells for nutrients and its effect on tumor morphology [6]. A further advantage of the second model is that two types of nutrients are considered, one is essential for tumor proliferation $N(\vec{r},t)$ and the other is essential for tumor survival $M(\vec{r},t)$ [6]. The position vector is represented by $\vec{r}$ while *t* represents the time. This model facilitates the study of the interaction between different nutrients. The nutrients diffuse according to the following equations [6],

$$\frac{\partial N(\vec{r},t)}{\partial t} = D\nabla^2 N(\vec{r},t) - \gamma N(\vec{r},t)\sigma_n(\vec{r},t) - \lambda_N\gamma N(\vec{r},t)\sigma_c(\vec{r},t) \tag{3a}$$

$$\frac{\partial M(\vec{r},t)}{\partial t} = D\nabla^2 M(\vec{r},t) - \gamma M(\vec{r},t)\sigma_n(\vec{r},t) - \lambda_M\gamma M(\vec{r},t)\sigma_c(\vec{r},t) \tag{3b}$$

where the parameter D represents the diffusivity of the both nutrients N and M (assumed equal for simplicity) and γ represents the nutrient consumption rate by healthy cells. The concentrations of normal and cancerous cells are represented as $\sigma_n(\vec{r},t)$ and $\sigma_c(\vec{r},t)$, respectively. The parameters λ_N and λ_M are the ratios that describe the tumor cells consumption rates of nutrients $N(\vec{r},t)$ and $M(\vec{r},t)$, respectively [6]. The motion of the tumor cells is attributed to tumor division producing new daughter cells which invade surrounding tissue [6]. Division and consecutively motion is determined by a probabilistic equation which calculates the likeliness for division to occur according to the amount of nutrients $N(\vec{r},t)$ available per each tumor cell [6]. The probability is calculated as [6],

$$P_{div} = 1 - \exp\left[-\left(\frac{N(\vec{r},t)}{\sigma_c \theta_{div}}\right)^2\right] \tag{4}$$

where θ_{div} is a normalization parameter which determines the shape of the Gaussian distribution. If division occurs and the daughter cells are at the boundaries of the tumor they will migrate to an adjacent pixel. Using this mechanism, the tumor can invade surrounding tissue as its growth progresses.

3. Results

In the first model, spherical symmetry is assumed and an infinite source of nutrients is positioned at the boundaries of the discretized domain. The differential equations of (1) and (2) are therefore discretized using the spherical coordinates system. Forward difference is used for time discretizations whilst central difference is used for space discretizations. Adequate normalizations with respect to time, distance, tumor cell density, and chemoattractant density are performed similar to [4]. The growth of the tumor versus normalized time steps is shown throughout the subplots of Figure 1. The figure also shows the spatial distribution of the tumor cells which is highest at the center of the tumor and decays towards the perimeter. The spherical shape is clearly observed in Figure 1.

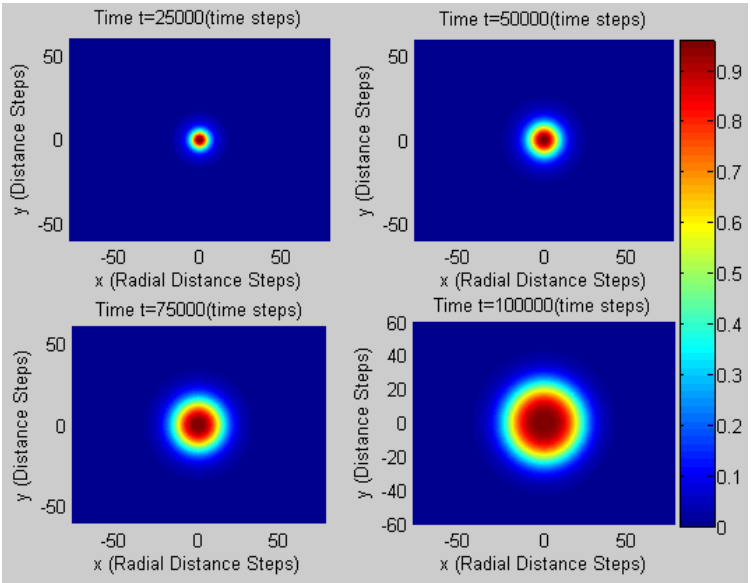

Fig. 1: Progressive tumor growth as generated by the first model.

In the second model, after adequate normalization [6], two dimensional (2D) Cartesian discretization is performed to facilitate the generation of asymmetrical tumor shapes. Forward difference is used for

time derivatives whilst central difference is used for space derivatives. The position vector $\vec{r}$ is discretized into $\vec{r} = (i\Delta, j\Delta)$ where i,j represent the pixel in the 2D domain. The indices i and j have the values $i, j = 0, 1, 2, ..L$ where the grid size is $(L+1)\times(L+1)$. A source of nutrients, such as a blood vessel, is positioned at the right hand side of the grid (at x = 500 steps). For each time step, the nutrient values $N(\vec{r},t)$ and $M(\vec{r},t)$ are updated and each cancer cell would then experience a cell action of either remaining quiescent, dividing or death as in [6]. Different patterns are generated by varying the model parameters as shown in Figure 2-4. The color maps in the figures represent the number of tumor cells at each pixel. The parameter α is simply γ normalized as in [6].

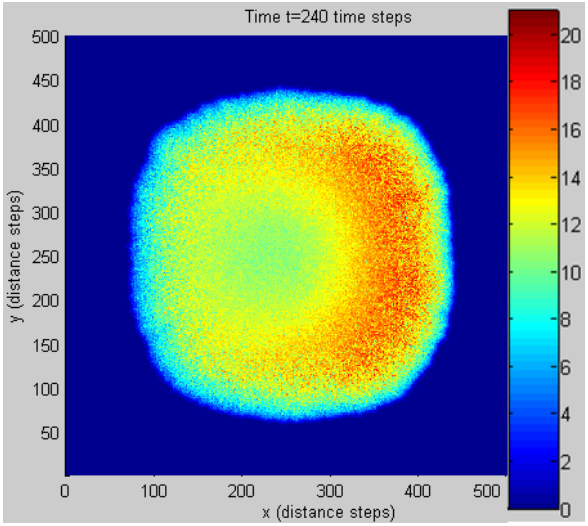

Fig. 2: A highly dense and compact tumor generated using the second model. (α=1/L, λ_N = 25 and λ_M=10)

In Figure 2, a highly dense non-spherical tumor with a compact shape is shown. The high density of this tumor can be observed in the higher cell number in the scale, in comparison to Figures 3 and 4. The wave front of the tumor is shifted towards the right where the nutrient supply is positioned at x=500 steps. This pattern is achieved when the nutrient consumption of tumor cells is not much higher than that of normal cells and therefore λ_N and λ_M are assigned relatively low values.

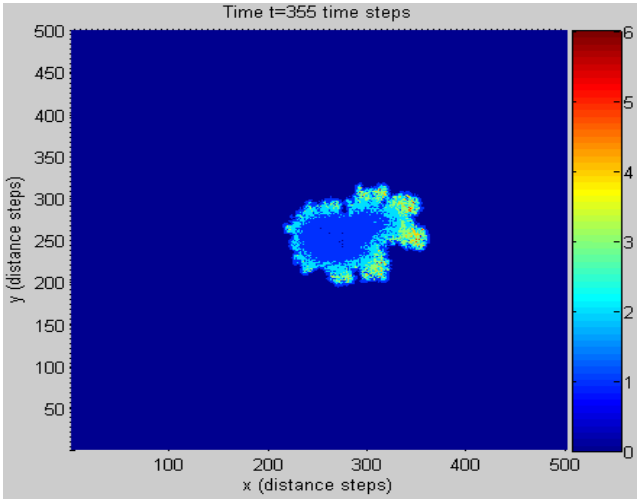

Fig. 3: A tumor with a central necrotic core generated using the second model. (α=4/L, λ_N = 200 and λ_M=80)

The pattern in Figure 3 is generated by increasing the affinity of tumor cells to the nutrient $M(\vec{r},t)$ by setting higher values to the parameter λ_M. This causes tumor cells to consume more of the nutrient $M(\vec{r},t)$ causing its levels to drop which makes tumor cells more likely to die [6]. This explains the central necrotic core (a region with dead tumor cells) shown in Figure 3.

Figure 4 shows a tumor with finger like projections. This pattern is generated by enhancing the rivalry for nutrients between healthy and tumor cells by setting higher values to the parameters α and λ_N.

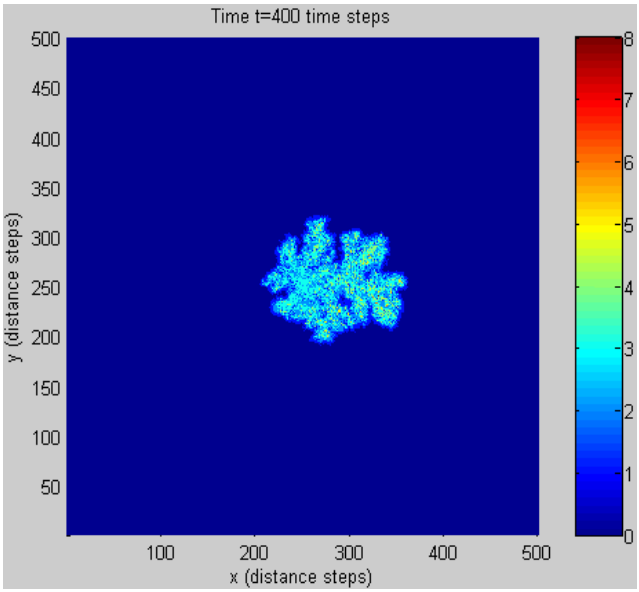

Fig. 4: A tumor with finger like projections generated using the second model. (α=4/L, λ_N = 250 and λ_M=20)

4. Discussion and Conclusions

Tumors have different levels of invasive rates which result in different tumor shapes. The advantage of the first model is providing the mechanism for modeling heterogeneous tumors with different diffusivity rates. The second model, however, shows a capability of generating a wider variety of shapes closely resembling those encountered in histological studies.

A potential application of tumor growth modeling is the electromagnetic imaging and detection of breast tumors. For an imaging algorithm to be efficient it needs testing against biologically accurate model. All of the dimensions, shapes, tissue type, and electrical properties need to be consistent with histological measurements. The shape, in particular, is extremely important due to its significant role in discriminating between malignant and benign breast tumors [3].

The tumor shapes obtained from the growth models are intended for incorporation in electromagnetic imaging algorithms. For example, Artificial Neural Network (ANN) was used for statistical detection of breast tumors [7]. It required hundreds of cases to train the network. Using the presented models, particularly the second one, provides significant help to the ANN detection technique. More importantly, understanding how malignant tumors grow will significantly help breast cancer research in several aspects.

5. Acknowledgements

This work was supported in part by the National Science Foundation Award Number ECS – 0524042 and the University of Arkansas Doctoral Academy Fellowship (DAF).

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