Computational Model of Breast Cancer Tumor Growth

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***Abstract*-Computational methods have been utilized to simulate the growth behavior of a tumor originating near the mandible. Extension of the model to three-dimensions (3D) and adaptation to the case of breast cancer, specifically invasive ductal carcinoma, are discussed.**

I. INTRODUCTION

The area of mathematical modeling of tumor growth has been present for nearly a century. Early formulations were derived in response to gross anatomical observations. The results of such models related cell population and tumor growth kinetics in a format which displayed a chronology of a tumor's life from one cell to clinical detection to an almost certainly lethal mass. Models such as applications of the Gompertz growth equation [1], although describing clinically detectible (radius = 1cm ($\approx 10^9$ cells) or greater) tumor growth remarkably well, failed to account for the growth behaviors from initiation to detection. Of course, at this time, little was known of the underlying biological processes governing tumor growth kinetics, and the nature of early models reflects this fact accordingly.

Since then, cancer research has produced an ever-growing body of knowledge that describes the mechanisms driving tumor growth. Proportionally, mathematicians and biologists alike have shown increasing interests in capturing tumorigenesis formulaically in hopes of garnering some useful results to impact drug treatment strategies and screening methods. Unfortunately, most attempts at modeling tumorigenesis fail to adequately integrate observed biological principles into their models. As such their practical applications are limited. Recently the paradigm of hallmark mutations required by all types of human cancer to progress from benign growths to malignancy was succinctly reviewed [2]. These hallmark mutations which cancer cells can acquire include angiogenesis, ignoring external growth signals, and evasion of programmed cell death among others. It is believed that inclusion of such mutations types into existing modeling techniques such as those in [3, 4] will yield virtual tumor growth for specific cancer types that is comparable to in-vivo observations.

The model put forth by Sansone, et al. in [3, 4] was the starting point for development of the 3D invasive ductal carcinoma model. Their work emphasizes the importance of tissue inhomogeneity in creating nutrient gradients due both to anatomical constraints and variable blood networks as they exist in real physiological systems within the human body. Reference [3] reports results for simulation of two-dimensional (2D) tumor growth near the lower jaw bone (mandible). The drawback to the approach in [3] was the assumption that the tumor, from inception, had already developed all the mutations necessary to invade the surrounding soft tissues and bone.

In reality, the mutations necessary for local tissue invasion can be acquired at different sites on the growing tumor, especially if initial boundaries are present as is true in the case of ductal carcinoma of the breast. This can result in different morphologies during the early stages of tumor growth that are not considered by existing computational simulations for specific types of cancer. Since local tissue invasion is the final stage of tumorigenesis and is thought to be a cooperative effort between previously acquired mutations [2], tumor growth kinetics and morphologies should consequently be affected by the order in which hallmark mutations are acquired. It is the eventual interest of research to explore this hypothesis for the case of ductal carcinoma of the breast.

II. METHODS

As mentioned previously, the starting point for all future work was a confirmation of the model presented in [3] for the case of a malignant neoplasm growing near the jaw bone. This involved implementing the discrete spatiotemporal equations from [3] which governed the growth of the virtual, 2D tumor which were coupled with reaction-diffusion equations describing nutrient sources throughout the region. In reference [3], the tumor's cells are discretized into nodes forming a two-dimensional grid where they can invade surrounding nodes, replicate (mitosis), die (apoptosis) and form necrotic regions, or remain in a quiescent state. The cells gather energy in the form of nutrients from the local blood supply which is present in every node in amounts that can be modeled after reality. In the case of the jaw, nodes that contain active nutrient sources are marrow within the bone, healthy tissues, and nodes which have been invaded by cancerous cells. The 2D grid obeys standard cellular automata (CA) rules such as with periodic boundary conditions. For example, if nutrients from one edge diffuse to a neighboring node that is off the grid, those

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nutrients will diffuse to the appropriate node on the opposing side of the grid.

In the model presented in [3], there are three populations of cells: cancerous cells (c_{ij}^t), necrotic cells (d_{ij}^t), and healthy cells. The subscripts *ij* denote any node location on the 2D grid while *j* are its neighboring nodes. The populations of healthy cells are assumed to diminish proportionally to the number of invading cancerous cells to enter any node ij. The four processes that tumor cells can undergo are diffusion to neighboring nodes, which occurs when there is not enough nutrient (p_{ij}^t) per cancerous cell residing in the node at time t, apoptosis, mitosis, and quiescence. Whether cells from any given node at time step t diffuse is given by the following unit step function:

$$\tilde{\alpha}_{ij}^{i'j'} = \hat{\alpha}_{i'j'}\Theta\left(P_d - \frac{p_{ij}^t}{c_{ij}^t}\right) \tag{1}$$

where the cell diffusion coefficient $\tilde{\alpha}_{i'j'}^{ij}$ is equal to zero when the ratio of nutrient to cancer cell population at node *ij* is greater than the nutrient threshold P_d. This coefficient, along with its neighboring nodes' diffusion coefficients determine the change in cancerous cell population due to cellular motility for every time step.

$$c_{ij}^{t+1} = c_{ij}^t + \sum_{i'j'}^{NN} (\tilde{\alpha}_{i'j'}^{ij} c_{i'j'}^t - \tilde{\alpha}_{ij}^{i'j'} c_{ij}^t) \tag{2}$$

Cancerous cells have a much higher nutrient affinity than healthy cells, which supports rapid proliferation. Depending upon the nutrient uptake, cancerous cells will either replicate, die, or remain quiescent. These processes depend on the amount of nutrient uptake at timestep t by cancer cells at *ij*:

$$\gamma_{ij}^t = \Gamma\delta\left[1 - e^{\left(\frac{p_{ij}^t}{\Gamma\delta \cdot c_{ij}^t}\right)}\right] \tag{3}$$

where Γ is the number of active transporters per cell and δ is the constant nutrient flux per transporter.

The nutrient population p_{ij}^t changes based upon the reaction-diffusion equation

$$p_{ij}^{t+1} = p_{ij}^t + \sum_{i'j'}^{NN} (\alpha_{ij} p_{i'j'}^t - \alpha_{i'j'} p_{ij}^t) - \gamma_{ij}^t c_{ij}^t - \xi_{ij}^t + \psi_{ij}^t \tag{4}$$

where α_{ij} and $\alpha_{i'j'}$ are the nutrient diffusion coefficients for the dominant tissue types at *ij* and *i'j'* respectively, ξ_{ij}^t is the nutrient uptake by healthy cells, which is assumed to be constant for any given tissue type, and ψ_{ij}^t is the restorative function which represents the efforts of the vascular system to maintain equilibrium across capillary boundaries. Increasing cancer cell and necrotic cell populations constrict the vascular presence in each node given by

$$S_{ij}^t = S_{ij}^0 e^{\left[-\left(\frac{c_{ij}^t + d_{ij}^t}{\Omega}\right)\right]} \tag{5}$$

Where Ω is a normalization constant and S_{ij}^0 is the initial capillary surface area for node *ij*.

Programming was done using C++ and visualization of the computational model was implemented with the Python programming language in concert with Blender™ open-source rendering software.

III. PRELIMINARY RESULTS

The 2D results displayed in Fig. 1 for cancer of the jaw show the effects of an inhomogeneous tissue environment on the growing neoplasm.

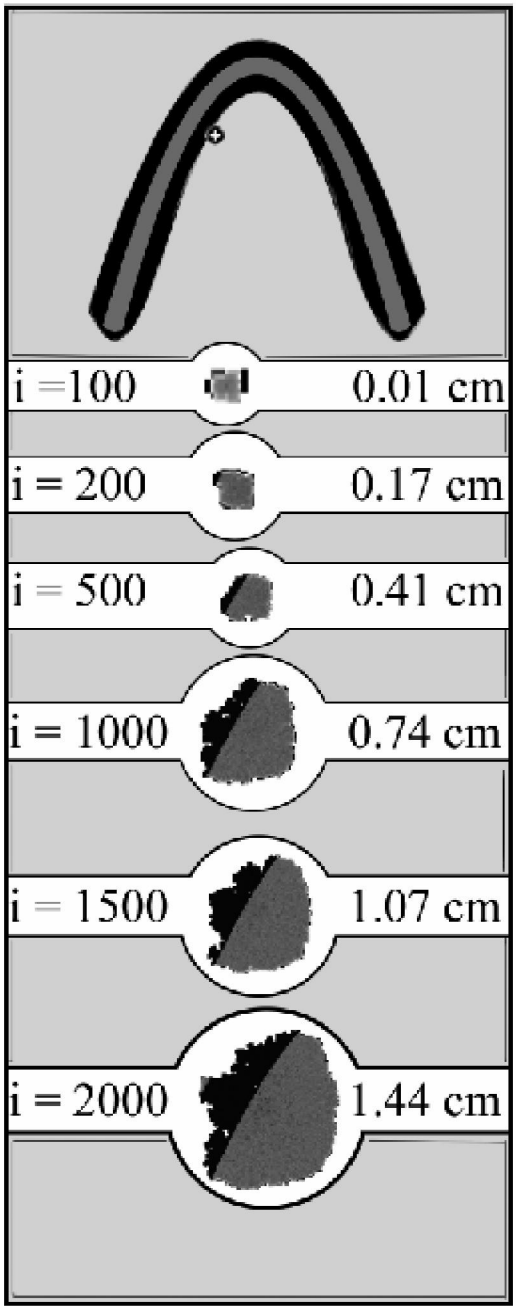

Figure 1. Growth of invasive tumor where [i] = iterations. Lighter grayscale tones indicate higher cancer population.

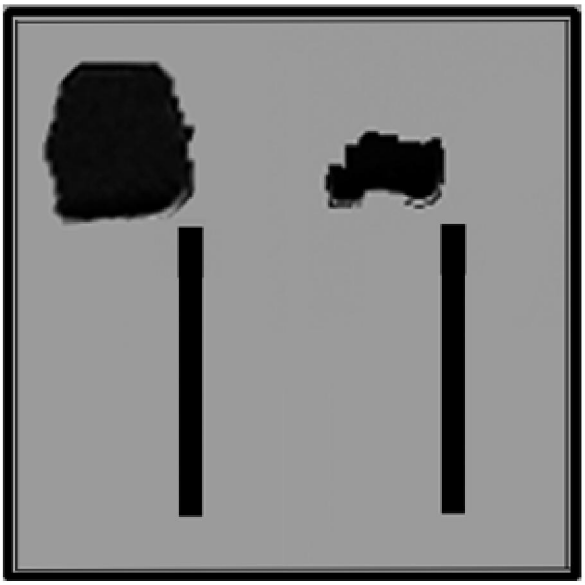

Figure 2. Left tumor, shown after 500 iterations, is faster-growing than right tumor, shown after 1000 iterations.

Nutrient gradients characteristic of those found in the area of the jaw were incorporated into the model. The spatial discretization was over a 1000 x 1000 grid. The characteristic vein underneath the tongue was added to the simulation, and its effects, while not noticeable in Fig. 1, are demonstrated in Fig. 2. In these figures, lighter grayscale tones on the body of the tumor indicate higher cancer populations. Black rectangles indicate location of the additional nutrient source.

The initial cancer seed was placed near the high nutrient gradient that was caused by the additional vascular structure. As seen in Fig. 2, higher population densities occur at the proliferating rims nearest the nutrient source. The nutrient gradient has more effect on the shape of the slow growing tumor because mitosis is favored over diffusion. The slow-growing tumor was assigned fewer nutrient receptors, which in turn lessens its likelihood for diffusion in this model.

IV. Conclusions

The adaptability of the model in [3] and its emphasis on the underlying biological processes involved in governing tumor growth kinetics and shape formation make it an ideal candidate for further investigation. Work is currently being done to adapt this model to 3D. The next step is to computationally simulate the ductal carcinoma growth in the breast that will incorporate characteristics of the tissue environments surrounding the ducts of the breast as well as the inclusion of hallmark mutation acquisition. A recent study suggests that the hallmarks paradigm can be applied to better understand breast cancer [6]. The ability to visualize tumor morphology development at stages that are as yet clinically undetectable will be a powerful tool. With emerging imaging techniques that can accurately reconstruct 3D tumor images, the need to diagnose the images as belonging to malignant or benign growths will be one of the key advantages of such screening technologies. It is believed that this is where a computational model of ductal carcinoma of the breast can help in the fight against breast cancer.

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