Studying the correlation between the extracellular environment and the diffusion processes in tumor growth.

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Abstract— **The tumor behavior is understood as a complex dynamical system encountering many different scales. Following the principles of Jiang et.al, we also employ a multiscale model, where the environment of a tumor, at the extracellular level is described by reaction diffusion, while at the cellular level an agent based model is applied. We further extend this model by employing a health function, which describes at every time step the health state of any tumor cell. This health function takes into account the biological and biochemical micro environment. A stochastic function is applied to model the mitosis process of proliferating tumor cells.**

I. Introduction

CANCER perhaps is the most serious of modern deceases which causes one of every four deaths in the US [1]. Even though new tools and methods are developed every year to solve this nowadays problem, there still remains much to be done on the subject of developing modeling tools for tumor growth. A main category of models that are employed in this field are the continuum models, see for eg. [2-4], where, the tumor is considered to be homogenous and continuous averaging out the effects of individual cells. Its growth is described through the evolution of its boundary. Another category consist the discrete models where the behavior of the tumor is determined by the interaction of individual cells with each other and the microenvironment. Recently, discrete-numerical models [5-6] are taking much attention due to the increase in computer power that is available nowadays. In these numerical models the same biological processes are described using mathematical tools that are available from numeric and discrete methods. Our approach is mainly numerical and we attempt to bring together the advantages of both of these categories. The proposed model implements the different processes of cellular lifecycle at the scale each of these processes using appropriately numerical and stochastic methods in its various scales. Thusly the proposed model is a multiscale model for tumor growth.

The present manuscript first provides a short description of the model that was used as a starting point, then we describe the proposed model in each of its scales and biological processes, and lastly we demonstrate the results that were produced until now and offer some conclusions.

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II. Brief description of Jiang's Model

According to Jiang et. al. [7] "the multiscale cellular model takes into account three levels. At the cellular level, a discrete lattice Monte Carlo model considers cell growth, proliferation, death, and intercellular adhesion. At the sub-cellular level, a simplified boolean protein expression regulatory network controls cell-cycle arrest. At the extracellular level, a system of differential equations describes diffusion, consumption, and production of nutrients, metabolites, growth promoters, and inhibitors. The three levels are closely integrated. The model parameters are obtained from previous multi cellular spheroid experiments."

III. Proposed model

A. Biochemical environment

Following the above scheme, the biochemical environment surrounding the cells is determined from the concentrations of five -parameters: oxygen, glucose, (the nutrients), waste, growth factors and inhibitor factors. All of these biochemical substances are either provided by the tumor environment, (oxygen and glucose) and are consumed from the cells or they are produced from the cells and are removed through the environment (waste, growth factors and inhibitor factors). Propagation of these biochemical factors through the cell colony is modeled by reaction – diffusion equations. A Dirichlet boundary condition is applied to the boundary of the extracellular tumor environment for all of these factors.

B. Cellular model

Each cell is represented by a set of variables that they uniquely characterize it [8]. These are: the location and the state of each cell (proliferating, quiescent and necrotic). In extent to existing models we introduce a health level function h, which takes positive real values. This arbitrary introduced function represents the overall condition of each cell of the tumor and is correlated with the equivalent amount of Adenosine 5-triphosphate (ATP) molecules of each cell [9]. Initially we consider one cell that is placed in the center of the extracellular environment and is considered

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to be a quiescent tumor cell. This cell is assigned of a health level equal to the value one, corresponding to the normalized health level value of normal tissue cells and thusly to the normal amount of ATP molecules of the cells. As the simulation time progresses and nutrition becomes available for each cell through the environment, each cell then adds or retracts from its previous health level. Where the health level function, h, of each cell is given by: $h_{t+1}=f(h_t, C_O, C_G, C_W, C_{GF}, C_{GI})$, and the corresponding variables are: h_t - health level at time t, and C_O, C_G, C_W, C_{GF}, C_{GI} are the concentrations for oxygen, glucose, waste, growth factors and growth inhibitor factors respectively. The function f identifies explicitly the influence of the concentration of biochemical factors on the future health state of each cell. In the case where the health level of a cell increases more than the threshold value, i.e. takes values greater than 1.2, the state of this cell changes to proliferating. On the contrary, in the case that the health level decreases bellow a critical value, i.e. takes values smaller than 0.4, then this cell is characterized as necrotic and an apoptosis mechanism is implemented in the proposed model that removes the cell after a time period. The health level is representing the in vivo behavior of cells, where cells with high amount of ATP are able to use this intracellular energy to perform various metabolic tasks such as mitosis, while other cells low in ATP restrict cellular functionality. Also, depending on the h_t variable, the function f carries information with respect to the metabolism rates of each cell. It is noted that cancer cells of different states metabolize at different rates [7]. We give bellow, as they were adopted from Jiang et al., the characteristic values of metabolic rates:

TABLE I
CANCER CELLS METABOLISM RATES.

Health - State	Oxygen	Glucose	Waste	Growth factor	Inhb. factor
(1.2,∞) Prolif.	108	162	240	1	0
[0.4,1.2] Quies.	50	80	110	0.5	1
(0,0.4) Necrotic	0	0	0	0	2
	mM/h/ cm^3	mM/h/ cm^3	mM/h/ cm^3	%/h/cm^3	%/h/cm^3

Accordingly, these biochemical factors are considered to diffuse at specific rates:

TABLE II
BIOCHEMICAL FACTORS DIFFUSION CONSTANTS.

	Oxygen	Glucose	Waste	Growth factor	Inhib. factor
Diff. constant	5.94×10^{-2}	1.52×10^{-3}	2.124×10^{-3}	10^{-6}	10^{-6}
cm^2/h					

C. Numerical solutions

Given the tumor geometry (i.e. the location and state of each cell of the tumor as well as the extracellular boundary) as along with the production – consumption rates of the biochemical factors, we are able to produce a set of numerical results that describe the concentration of each of these factors at any point in space and time. The numerical scheme and the solutions for all the biochemical factors of the models at every iteration are provided through COMSOL [11] by employing a reaction - diffusion model. The reaction - diffusion equations that produce the values of the concentration field for each of the biochemical factors are:

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (-D_i \nabla c_i) = Q_j$$

In addition to the geometry and the boundary conditions the variables that are considered for deriving the numerical solutions are:

c_i: concentration of biochemical factor 'i'

t: time.

D_i: diffusion coefficient of biochemical factor 'i'

Q_j: rate of production-consumption of biochemical factor 'j' dependant on each cells state (Table I).

D. Cellular movement

In our proposed model each proliferating cell moves following the gradient of the nutrient-waste function m at its position in space time: $\vec{m} = m(\nabla C_O, \nabla C_G, \nabla C_W)$, while quiescent cells remain at a constant location and necrotic cells abide to the n-body - Barnes–Hut movement algorithm [10]. This movement forces the necrotic cells that are produced at the boundary between the necrotic and the quiescent region, to move towards the center of the tumor until they have been depleted and removed from the model. This prevents the formation of empty space at the very center of the necrotic region. Both proliferating and necrotic cells are allowed to travel freely inside the extracellular environment.

E. Mitosis

As simulation time progresses the possibility for each cell to undergo mitosis changes according to its health level and to the biochemical environment. The function that describes mitosis of a proliferating cancer cell is stochastic and the probability of mitosis for each cell is: $P_{mitosis} = p(h_t, C_{GF}, C_{GI}, \mu)$ where μ corresponds to the number of phenotype mutations. Once a mother cell undergoes mitosis, the two daughter cells occupy the same space at that time iteration and they are able to move freely thereafter. Also the health factor of mother cells is equally divided between the two daughters upon mitosis. With mitosis, each daughter cell has a probability to increase its number of phenotype mutations. This μ variable is included in the model, in order to represent the evolution of cancer in more aggressive forms over time.

This process as it was described explicitly above, has been motivated from the work of R.A. Alexander et al. [12] and it is considered to describe comprehensively the biological phenomenon of mitosis.

IV. RESULTS

Based on the aforementioned configuration and methodology we produce a number of simulations that show

correlation between the geometry of the extracellular environment and the progress of tumor growth. Our aim in the present work is to study the response of the proposed model to different reaction - diffusion processes considered for the bio-chemical factors.

Considering isotropic diffusion, simulations of spherical and circular environments obtain isotropically growing tumors, allowing occasionally small fluctuations on the boundary of each region. These fluctuations appear to be oscillating around a specific value that the boundary gets at each region which is also predicted by other analytical models [13,14]. This reassures the validity of the proposed model and enables us to apply it in more complex extracellular environments. The following figures demonstrate instances of simulated tumors in various extracellular environment geometries. In these figures the centers or the cores of the simulated cells appear as circles. The colors red, blue and black represent centers of cells that are proliferating, quiescent or necrotic, respectively. The first figure shows a state of equilibrium that is reached from a tumor that grows inside a circular extracellular environment. The boundaries of each region are defined and on the outer boundary of the tumor as well as in the border that separates the proliferating and quiescent regions some oscillation is noticed.

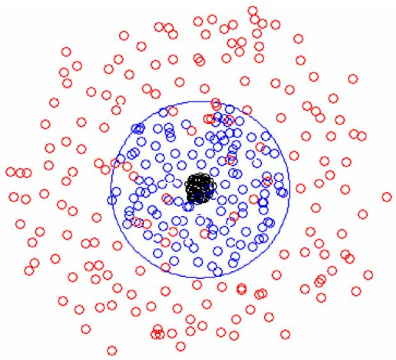

Fig. 1. Instance of a tumor growing inside a circular extracellular environment. Borders of all regions form homocentric circles with small oscillations at the border resulting a tumor that has reached a steady state. The necrotic region is well formed and the border outside witch all cells have access to enough nutrition to be in proliferating state is also noted.

Next we study simulations of square and cubic extracellular environment that develop anisotropic growth with preferable directions. These preferable directions are in accordance with the expected growth pattern which has been assumed and are produced as a result of the feeding function f that is being used, the gradient of the biochemical factors that participate and the geometry of the extracellular environment. The simulated cells will try to move with a velocity that has the same direction as the gradient of the nutrition conditions. Proliferating cells that are closer to the extracellular border will increase their health value rapidly while others that are further away will struggle as a result of poorer biochemical conditions. The second figure demonstrates such a simulation where the preferable growth directions on the horizontal and vertical axis of tumor growth are apparent. The specific tumor grows inside a square extracellular environment and has a starting point at the center of the square.

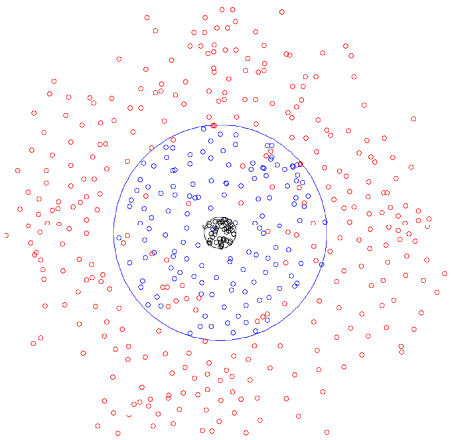

Fig. 2. Instance of a tumor growing inside a cubic extracellular environment. Reader can observe the preferable directions of tumor growth along both axis.

Elliptical and ellipsoid extracellular boundaries produce various growth patterns that are dependent on the eccentricity of the extracellular boundary [15,16]. Again the same observed behavior as the one in the square and cubic extracellular environments can be noticed which can be justified by employing the aforementioned arguments. Proliferating cells that are closer to the extracellular ellipsoid will have access to a richer biochemical environment and thus will undergo mitosis earlier than those proliferating cells that are far away. In figure 3 we demonstrate an instance of a tumor growth in the interior of an ellipsoid extracellular environment. It can be noticed that the tumor grows with apparent preferable directions in such a way that it forms a non-confocal ellipsoids which exhibit noticeable fluctuations of their boundary.

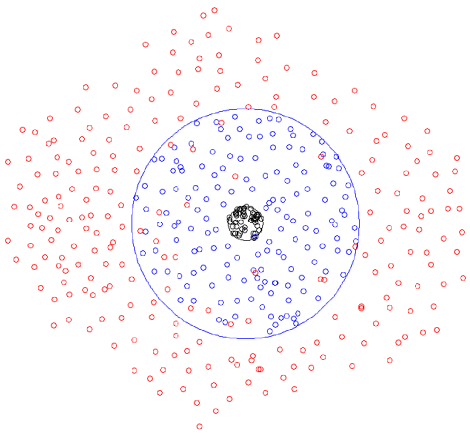

Fig. 3. Instance of a tumor growing inside an elliptical extracellular environment. The tumor grows inside a ellipsoid extracellular environment with a vertical long axis and demonstrates horizontal preference.

In all previous simulations the diffusions process was considered isotropic. Assuming now non-isotropic diffusion, simulations of spherical and circular environments produce tumor growth patterns that are similar to those produced considering isotropic diffusion of elliptical or ellipsoid extracellular environment.

Furthermore, non-isotropic diffusion simulations of elliptical or ellipsoid extracellular environment, show that the tumor growth pattern depends on the inner product of the unit vectors that are considered in the minor semi axis of the extracellular environment and the diffusion direction.

Using anisotropic diffusion, simulations produce chaotic tumor growth without any distinct pattern formation.

It's worth mentioning that in the performed simulations only cancer tumors that evolve in a spherical or circular extracellular environment and exhibit isotropic growing, reach a steady state or . In these virtual tumors occupies a certain area and their borders oscillate over time, around a certain value. In the elliptical and ellipsoidal extracellular environments correlation between eccentricity of the extracellular environment and the possibility is perceived for the tumor to reach a steady state. Following the proposed methodology, we show that only the extracellular environments that are having small eccentricity can produce steady state avascular tumors.

Moreover, simulations of square, cubic, elliptical, ellipsoidal extracellular environments as well as simulations considering non-isotropic diffusion don't grow tumors that can reach at a steady state.

Finally, no strong correlation has been noticed between the different geometrical shapes assumed for the cells and the evolution of tumor domains.

V. Conclusions

Following the principles of Jiang et.al [7] and inspired from the work of R.A. Alexander et al. [12], we employ a multiscale model of avasular cancer tumor growth, where the environment of a tumor, is described at the extracellular level by reaction-diffusion partial differential equations, and at the cellular level by a stochastic and agent based model. The proposed model also employs, a health function that describes, at every time step, the health state of each tumor cell and it is directly correlated to the amount of Adenosine 5-triphosphate molecules of each cell.

The proposed model predicts that avascular tumors that are growing within a circular or spherical extracellular environment are likely to reach and oscillate around equilibrium. The area of the tissue domain occupied by the tumor varies proportionally to the amount of nutrition that it is provided to the tumor through the extracellular environment. Elliptic extracellular environments characterized by small eccentricity grow tumors that reach at a state of instant stability. Different extracellular environments result in cancer tumors that are growing towards preferable directions and do not exhibit any stability.

These are preliminary qualitative results obtained from the simulations based on the proposed model that aim to reveal and investigate the role that the different biological parameters play in the tumor growth. Our results have to be validated with medical data which can provide also realistic values for the parameters involved in the model.

Once the proposed model has been medically approved at the present stage of tumor growth,, the next step is the attempt to extend it so that it will take into account angiogenesis as well as the effect of chemotherapy drugs.

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