

Review of "A Multiscale Model for Tumor Growth"

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1 Introduction

Cancer is believed to be responsible for one of every five deaths in Western countries and therefore is among the major killers in the developed world. Because of this modeling cancer has become one of the most active areas within the mathematical and theoretical biology communities. Broadly speaking, we can divide these efforts into two approaches: continuum models, mathematically formulated in terms of partial differential equations (PDEs), and discrete cellular automaton (CA) models.

Typically, tumor growth is divided into three stages. First, the tumor develops avascularly, or in the absence of a blood supply, and grows up to a maximum size that is limited by the amount of nutrients it can absorb through its surface. Then some of the cells of an avascular tumor produce and release TAFs. These substances trigger a cascade of events which lead to vascular growth towards the tumor. Once this occurs the tumor enters the vascular stage. In this stage, the tumor has access to virtually unlimited resources, so it can grow beyond its limited "avascular" size!!

Thus, avascular phase tumors are basically harmless, but once they become vascular they are potentially fatal.

2 The Model

The model is built on three levels: the vascular level, the cellular level, and the intracellular level. The vascular level is modeled by laying out a hexagonal grid of vessels as in Figure 2. Blood flow along each segment is calculated by Krichoff's laws, and then this is used to determine other hydronic variables including oxygen transport. The cross-sectional radius of each segment is updated according to (1). (1) accounts for the change in radius due to wall shear stress, t_w , VEGF, k_m , and shrinking, k_s . No geometric modifications to the vasculature occur, only the radius of each segment is

modified.

$$\begin{aligned}
 R_i(\mu, \nu; t + \Delta t) = & R_i(\mu, \nu; t) + R_i(\mu, \nu; t) \Delta t \left(\log \left(\frac{\tau_{wi}(\mu, \nu; t)}{\tau(P_i(\mu, \nu; t))} \right) \right. \\
 & \left. + k_m (V_i(\mu, \nu; t)) \log \left(\frac{\dot{Q}_{ref}}{\dot{Q}_i(\nu, \mu; t) H_i(\nu, \mu; t)} + 1 \right) - k_s \right) \quad (1)
 \end{aligned}$$

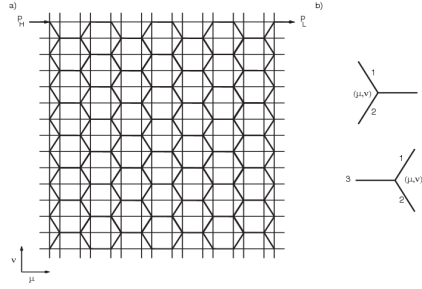


Figure 1: Vasculature and labeling at a vertex

Cells are placed on a lattice like that in Figure 2. Each lattice site or pixel is labeled by two integers, and has a state in $\mathbb{Z}^2 \times \mathbb{R}^{11}$. The first integer state tells us whether the pixel is a normal cell, a cancer cell, a blood vessel, or empty. The second keeps track of how many times that cell has divided. The real states keep track of concentrations such as oxygen, VEGF, and the internal biochemical state of each cell. The vasculature vertices are mapped onto the cellular grid and then connected by straight lines.

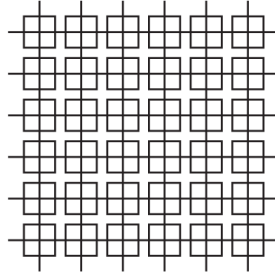


Figure 2: Lattice for cells

For oxygen and VEGF we need to solve two boundary problems. The boundary value problem (BVP) for oxygen is:

$$D_P \nabla^2 P - k_P(r) P = 0 \quad (2)$$

$$-D_P \mathbf{n}_w \cdot \nabla P = \mathcal{P}(P_b - P) \quad (3)$$

where

$$k_P(r) = \begin{cases} k_N^P & \text{if there is a normal cell at } r \\ K_C^P & \text{if there is a cancer cell at } r \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

This assumes that the leakage rate of oxygen is equal to its diffusion rate. No flux boundary conditions are also enforced.

The BVP for VEGF is:

$$D_Q \nabla^2 Q + k_Q(r)Q = 0 \quad (5)$$

where

$$k_P(r) = \begin{cases} k_N^P & \text{if there is a normal hypoxic cell at } r \\ K_C^P & \text{if there is a cancerous hypoxic cell at } r \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

A cell looks at its neighbors and if it have more of the same type around it then the apoptosis threshold for p53 is set higher than if it has a different type of cells around it. An example is Figure 2

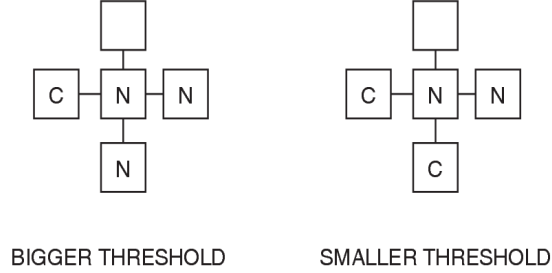


Figure 3: Two examples of how the p53 threshold is determined.

The following equations model the cell division cycle.

$$\frac{dx(\mathbf{r})}{dt} = \frac{(k'_3 + k''_3 u(\mathbf{r}))(1 - x(\mathbf{r}))}{J_3 + 1 - x(\mathbf{r})} - \frac{k_4 m(\mathbf{r}) y(\mathbf{r}) x(\mathbf{r})}{J_4 + x(\mathbf{r})}, \quad (7)$$

$$\frac{dy(\mathbf{r})}{dt} = k_1 - (k'_2 + k''_2 x(\mathbf{r}) + k'''_2 z(\mathbf{r})) y(\mathbf{r}), \quad (8)$$

$$\frac{dm(\mathbf{r})}{dt} = \mu \left(\frac{y(\mathbf{r})}{y(\mathbf{r}) + y_0} \right) m(\mathbf{r}) \left(1 - \frac{m(\mathbf{r})}{m_*} \right) \quad (9)$$

$$\frac{dz(\mathbf{r})}{dt} = \chi(m, \mathbf{r}) - k'_5 \frac{P(\mathbf{r})}{B + P(\mathbf{r})} z(\mathbf{r}) \quad (10)$$

$$\frac{du(\mathbf{r})}{dt} = k'_6 - (k'_6 + k_6 y(\mathbf{r})) u(\mathbf{r}) \quad (11)$$

$$v = 1 - u \quad (12)$$

The dependence on \mathbf{r} tells us these are local interactions.

Cancer cells react differently than normal cells to hypoxia. In normal cells hypoxia leads to production of VEGF and p53, but p53 inhibits VEGF and leads to apoptosis. In cancer cells p53 upregulates VEGF production. This leads to the following set of equations:

$$\frac{dp(\mathbf{r})}{dt} = k_7 - k'_7 \frac{P(\mathbf{r})}{C + P(\mathbf{r})} p(\mathbf{r}) \quad (13)$$

$$\frac{dq(\mathbf{r})}{dt} = \xi(p, q, \mathbf{r}) - k'_8 \frac{P(\mathbf{r})}{D + P(\mathbf{r})} q(\mathbf{r}) \quad (14)$$

where p is the concentration of p53 in a cell, and q is the concentration of VEGF. ξ differs if a cell is normal or cancerous, in normal cells it negative and in cancer cells it is positive.

We put all this together as demonstrated by Figure 2.

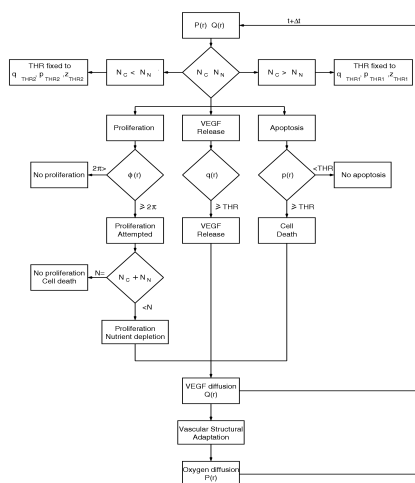


Figure 4: Flow chart of the algorithm for the model.

3 Results

Look at three types of conditions for a single type of cell:

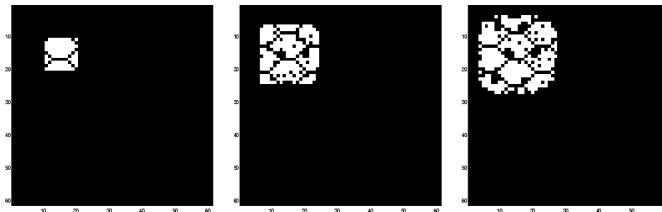
1. Constant oxygen.
2. Oxygen is determined by vasculature that doesn't change.
3. Vasculature reacts to VEGF and increases capacity to modify the oxygen supply.

Then look at different types of interactions between normal and cancer cells.

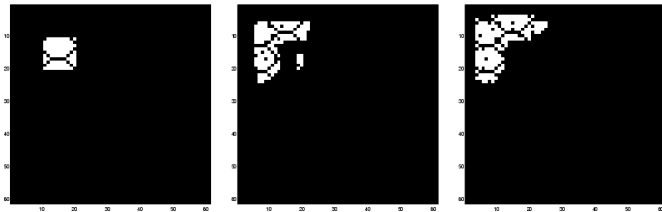
1. Equally intermixed cancer cells and normal cells
2. Invasion by cancerous cells.

3.1 Single type of Cells

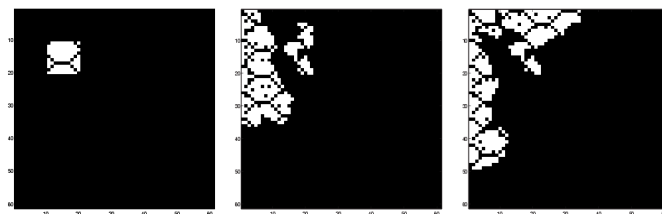
1. If we have a constant oxygen level, cells expand in a circular fashion.



2. If we have the vasculature uncoupled from the tissue cells grow where there is nutrient.

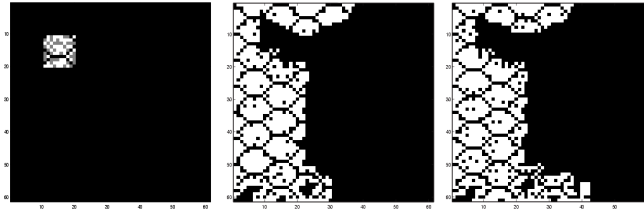


3. If we couple vasculature to the tissue cells grow where there is nutrient and where they convince nutrient to come to.

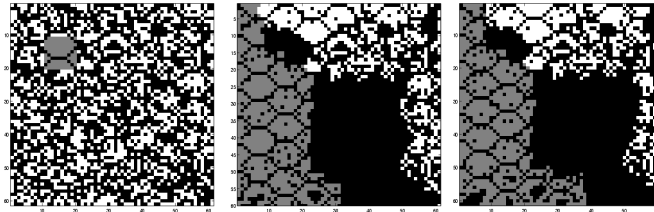


3.2 Two Types of Cells

- If cancer cells are mixed evenly with cancer cells, cancer cells out compete normal cells.



- If we have cancer cells invade a tissue of normal cells, cancer cells out compete normal cells where there are cancer cells, but cancer cells don't fill the entire domain.



3.3 Growth Curves

It was found that normal cells obey the Gompertz law. $N_G(t) = K \exp(-\lambda e^{-\frac{rt}{\ln K}})$, where the growth rate is proportional to population size and the decay rate depends exponentially on the population. Cancer cells start off growing exponentially ($C_1 e^{-rt}$) and then obey a power law ($C_2 t^\delta$) and then reaches a carrying capacity (C_3). Cancer cells still obey these forms in tissue with normal cells, though with different constants.

4 Improvements

Several improvements could be made to the model. These include:

- Improve vasculature to support entire simulation region and to modify geometry of the vasculature.
- Improve the realism of p53 and VEGF dynamics.
- Extend to three dimensions.
- Multipixelated cells along the lines of the Cellular Potts model.

Reference:

T. Alarcon and H. M. Byrne and P. K. Maini, A Multiple Scale Model for Tumor Growth, SIAM, 2005, Multiscale Modeling & Simulation, Vol 3,2, 440-475