

## SBC2009-206621

### SIMULATING THE EFFECTS OF ANGIOGENESIS ON TUMORIGENESIS THROUGH COMPUTATIONAL MODELING

Michele D. Cooper (1), Martin L. Tanaka (2), Ishwar K. Puri (1)

(1) Department of Engineering Science & Mechanics  
 Virginia Tech  
 Blacksburg, VA

(2) Department of Orthopaedic Surgery  
 Wake Forest University School of Medicine  
 Winston-Salem, NC

#### INTRODUCTION

Angiogenesis is a physiological process in which new blood vessels are formed from pre-existing vessels. It is one of the hallmarks of cancer and contributes greatly to the sustained growth of a tumor. Without the nutrient influx provided by newly formed capillaries, tumors growth is curtailed due to a lack of oxygen diffusion into the central region of the tumor body. Angiogenesis substantially increases the risk of developing cancer and as a result, anti-angiogenic therapies are being developed for cancer treatment.

Previous researchers have investigated tumors by modeling the different systems related to cancer as individual contributors, i.e. avascular tumor, angiogenesis, cellular migration, etc. Recently, research has shifted toward coupled models that integrate multiple aspects of a tumor simultaneously to create a more complete representation of a cancerous tumor. Some models exist for angiogenic tumors; however, we have not come across a model that has addressed the effects of angiogenesis on tumor growth and development.

The goal of this research is to improve our understanding of the functionality of angiogenesis and its effects on tumorigenesis in order to aid in the further development of the anti-angiogenic therapies. The model is a continuous analytical model that simultaneously integrates the growth of the tumor body through cell proliferation and new blood vessel formation. Preliminary results for tumor growth simulations are also presented.

#### THEORY

Our integrated model was inspired by a tumorigenesis model [1] and an angiogenesis model [2]. Specific modifications made to the previous models include the following: (1) a multifaceted view of tumor growth was taken, (2) angiogenesis has been reduced to a continuous system enabling simulation of the tumor throughout all

phases of growth, and (3) rather than using endothelial cells as a measure of angiogenesis capillary length density and sprout tip density were employed.

Symbol	Variable Name
n	Tumor Cell Count
c	AGF Concentration
f	Fibronectin Concentration
s	Sprout Density
$\phi$	Capillary Length Density

Table 1: Variables

The first component of the model simulates tumorigenesis. Briefly, the cell count for live,  $N_B$ , and dead,  $N_D$ , proliferative,  $N_P$ , and necrotic,  $N_N$ , cells are determined with

$$\frac{dN_B}{dt} = \omega_P N_P - \omega_A N_B - \omega_N N_N - \omega_T N_P \quad (1)$$

$$\frac{dN_D}{dt} = \omega_N N_N - \omega_{Deg} N_D \quad (2)$$

The tumor radius,  $R_T$ , is found using the previously calculated cell counts

$$R_T = R_C (N_B + N_D)^{1/3} \quad (3)$$

where  $R_C$  is the cell radius. Fickian diffusion solved for spherical coordinates with an added nutrient uptake term is used to determine the avascular and vascular nutrient concentration.

Total nutrient concentrations at a given radius are found by adding avascular and vascular nutrient concentrations. The volume

fractions needed to find the tumor volumes are calculated using Table 2. The values used in the conditions are the thresholds for the hypoxic and necrotic regions, 0.75 and 0.5nmol/mm<sup>3</sup> respectively.

Case	Conditions (nmol/mm <sup>3</sup> )	Volume Region	Method of Calculation
1	$c_n \geq 0.75$	Proliferative, $V_p$	1
		Hypoxic, $V_H$	0
		Necrotic, $V_N$	0
2	$0.75 > c_n \geq 0.5$	$V_p$	$\pi R_p^2 \phi$
		$V_H$	$1 - V_p$
		$V_N$	0
3	$c_n < 0.5$	$V_p$	$\pi R_p^2 \phi$
		$V_H$	$\pi R_H^2 \phi - V_p$
		$V_N$	$1 - V_p - V_H$

**Table 2: Solving for Volume Fractions**

The number of cells from the proliferating, hypoxic, and necrotic regions can be calculated from volume fractions of the tumor body. The volume fractions are the portion of the total tumor volume at each level of oxygenation, representing the local environment for each cell. The local environment is divided into three distinct regions,  $V_p$ ,  $V_H$ ,  $V_N$ , indicating the proliferative, hypoxic, and necrotic volumes, respectively.

Angiogenesis is initiated upon the development of the hypoxic core. First, the AGF and fibronectin concentrations are found, respectively

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \omega_u s \quad (4)$$

$$\frac{\partial f}{\partial t} = D_f \nabla^2 f + \omega_f s - \mu_f s f \quad (5)$$

where  $D_c$  is the diffusivity of AGF,  $c$  is the AGF concentration,  $\omega_u$  is the uptake rate of  $s$ , the sprout tip density,  $f$  is the fibronectin concentration,  $D_f$  is the diffusivity of fibronectin,  $\omega_f$  is the production rate of fibronectin, and  $\mu_f$  is the uptake rate for fibronectin. With these equations the sprout tip density and capillary length density, derived from [3], can be determined

$$\frac{\partial s}{\partial t} = D_n \nabla^2 s - \nabla \cdot (\chi_0 s \nabla c) - \nabla \cdot (\rho_0 s \nabla f) \quad (6)$$

$$\frac{\partial \phi}{\partial t} = D_n \nabla^2 s - \chi_0 s \nabla c - \rho_0 s \nabla f \quad (7)$$

$$\left. \frac{\partial s}{\partial t} \right|_{r=R_t} = \alpha c \quad (8)$$

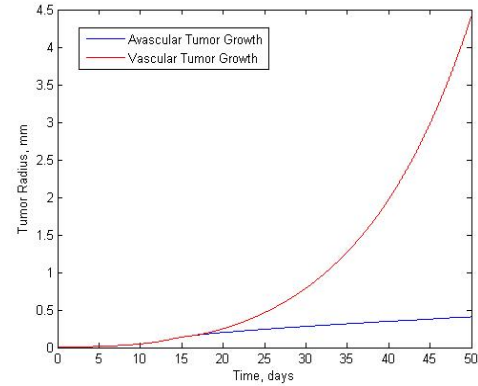
where  $D_n$  is the diffusivity of endothelial cells,  $\chi_0$  and  $\rho_0$  are constants.

## RESULTS & CONCLUSION

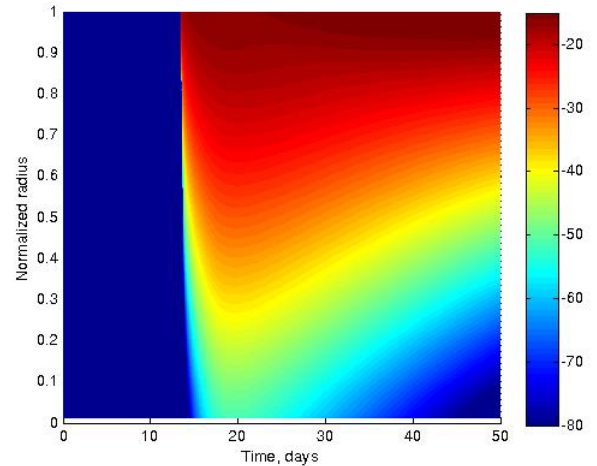
These equations were solved over a time period of fifty days with a time step of 0.01 days. A difference between the avascular and vascular tumor was seen after 18 days (Figure 1). Both the avascular and vascular tumor growth rates were the same until the generation of hypoxic cells which initiated angiogenesis. Upon initiation of angiogenesis, vascular tumor growth continues to progress at an exponential rate, whereas the avascular tumor growth rate begins to plateau due to the lack of nutrient penetration.

The sprout tip density (Figure 2) is the number of active sprout tips per mm<sup>3</sup>, these sprout tips later form capillaries and serve as another indicator of angiogenesis progression. The sprout tip density is displayed as the color variation in this figure and is shown as a log

scale (i.e.  $-20 = 10e^{-20}$ ). Capillaries form at 14 days and continue to advance inward from the periphery ( $r=1$ ) toward the core ( $r=0$ ). Initially, the capillary density increases towards the center of the tumor with time. However by 20 days, the tumor body growth rate exceeds the angiogenic penetration rate and the normalized penetration depth begins to decrease. This model demonstrates that even with angiogenesis, a hypoxic and necrotic core can form in a tumor.



**Figure 1: Avascular and Vascular Tumor Growth**



**Figure 2: Sprout Tip Density**

Numerical values of the results are different than those reported previously [1,2] due to differences in the parameter values used. However, the general trends are the same which adds to our confidence in the validity of model. In the future, we plan to obtain appropriate clinical data in order to calibrate the model parameters and verify the model's performance. We plan to use this predictive tumor growth model as a tool to better understand the effects of angiogenesis on tumorigenesis and to simulate the effects of new anti-angiogenic therapies.

## REFERENCES

1. Tanaka ML, Debinski W, Puri IK, "Hybrid Mathematical Model of Glioma Progression," Cell Proliferation, in press.
2. Anderson, ARA, Chaplain, MAJ, 1998, "Continuous and Discrete Mathematical Models of Tumor-induced Angiogenesis," Bulletin of Mathematical Biology 60, 857-900.
3. Mantzaris, NV, Webb S, Othmer HG, 2004, "Mathematical modeling of tumor-induced angiogenesis," Journal of Mathematical Biology 49, 111-187.