

Cell Motility and Capillary Network Formation

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The focus of our research is on capillary networks induced by chemical signals from tumors, a process known as angiogenesis. This process marks the critical transition from diffusion limited solid tumor growth to vascular growth. When angiogenesis occurs inside a tumor, the newly acquired vasculature provides an abundant source of nutrients to the tumor and increases the tumor's capacity to export waste products, thereby allowing the tumor to sustain continued growth unattainable by avascular tumors. Tumor vascularization has been closely linked to metastasis, a progressive stage of cancer that is difficult to treat and often indicative of a poor prognosis.

To ensure its sustained growth, a tumor secretes tumor angiogenic factors (TAF), chemical compounds which cause nearby capillaries to form sprouts which migrate towards the tumor. One such chemical compound, which has been found to be critical to tumor angiogenesis, is a protein called vascular endothelial growth factor (VEGF). Endothelial cells (EC), which form the lining of neighboring blood vessels, respond to this chemotactic stimulus by degrading the blood vessel membrane, proliferating and migrating towards the chemical source. In order to travel towards the chemical source, endothelial cells must migrate through the extracellular matrix (ECM), a complex cellular support system made up of fibrous proteins, collagen and elastin, specialized proteins, such as fibronectin and laminin, and chains of complex sugars. To overcome the ECM barrier, the endothelial cells secrete proteases which degrade the ECM, allowing the endothelial cells to migrate towards the tumor.

Although the sequential steps involved in angiogenesis are well known, the interplay between the biochemical and biomechanical mechanisms (including cell-cell interactions, cell-matrix in-

teractions, and intracellular signaling pathways) that make angiogenesis possible is a complex and largely unresolved matter. Experimental evidence has established that the ECM plays a central role in cellular migration, cell shape and orientation, and hence in the control of capillary network formation. Despite the large body of research and the importance of the ECM in capillary network formation, previous mathematical investigations have largely ignored the interactions between endothelial cells and the extracellular matrix. We have developed a multiscale mathematical model to examine the effects of EC / ECM interactions on cellular migration and the development of capillary networks. A reliable model of these processes will provide a tool for addressing questions of how cells interact with each other and their environment in order to ensure successful angiogenesis and tumor progression. This type of modeling can help investigate the chemical pathways that lead to increased endothelial cell survival, enhanced angiogenesis, and accelerated tumor growth. On a larger scale, it can help us understand how vascular architecture and blood supply influence tumor growth and metastasis.

Our model is a hybrid of discrete and continuum models. Endothelial cell proliferation and migration are modeled using a discrete model based on the cellular Potts model. This lattice Monte Carlo model partitions the domain into cells and extracellular matrix. Each cell has a unique ID number and occupies all the lattice sites within the cell domain. Under this framework, each cell has a finite volume and a deformable shape. Cells directly interact with each other through surface adhesion and competition for space. The intercellular interactions are characterized by an equation for total energy that incorporates intercellular surface adhesion, cellular elasticity, cell volume constraint, and chemotaxis.

$$E = \sum_{sites} J_{\tau,\tau'}(1 - \delta_{\sigma,\sigma'}) + \sum_{cells} \gamma(v - V^T)^2 + \sum_{sites} \mu u$$

We also incorporate the effects of VEGF on EC survival and proliferation. The cellular model evolves by a standard Monte Carlo procedure and is designed to minimize total energy. The host ECM is treated as a semi-rigid elastic meshwork,

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which interacts with the endothelial cells mechanically and biochemically. Endothelial cells adhere strongly to the ECM. Haptotaxis, which is directed movement up an adhesive gradient, is a natural result of the cellular adhesion to ECM through the cell adhesion term in the equation for total energy. At the EC sprout tip, the enzymes endothelial cells produce degrade the ECM. As endothelial cells migrate through the ECM, they also synthesize and secrete cellular fibronectin, which produces new ECM. High local ECM density will result in strong adhesion with cells and hence low cell motility. The mechanical forces exerted on ECM by endothelial cells will also be a natural result of the rigidity and elasticity of ECM. Cells also interact with their microenvironment, which is characterized by local chemical concentrations of tumor angiogenic factors. At the extracellular level, the chemical dynamics of VEGF are represented by a partial differential equation describing the diffusion of VEGF through the domain, the binding of VEGF to endothelial cell surface receptors and the natural decay of VEGF.

$$\frac{\partial u}{\partial t} = D\nabla^2 u - A(x,y) - \lambda u + f(x,y,t)$$

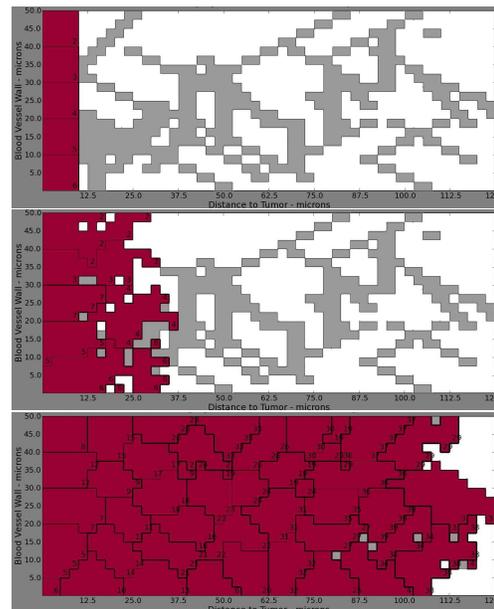
where

$$A(x,y) = \begin{cases} \alpha, & \text{if } (x,y) \in \text{EC}; \\ 0, & \text{otherwise,} \end{cases}$$

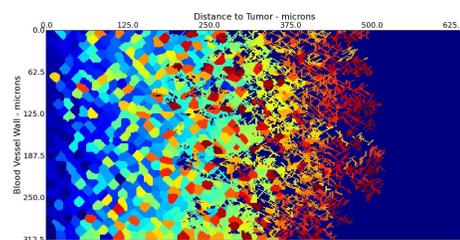
D , λ and α are positive constants, and $f(x,y,t)$ is tumor secreted VEGF. Using this model, we will investigate the chemical and mechanical interactions between endothelial cells and the ECM of host tissue. Specifically, we will investigate the following questions:

- What is the role of ECM in endothelial cell migration?
- Can chemotaxis or cell-matrix adhesion alone explain the vascular structure?
- What is the relative importance of chemotaxis and mechanical forces, such as cell-matrix adhesion, in endothelial cell migration?

Preliminary results show ECs moving along the ECM fibers and angiogenesis occurring on timescales consistent with those observed experimentally. 2-D simulations are shown below. Further model refinements are still necessary, as well as 3-D implementation and analysis.



Numerical simulation showing the growth and migration of EC (red) while interacting with ECM (gray).



Same numerical simulation but on a proportionally larger domain/time scale. Captures the overall capillary network formation and patterning.

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