A Hybrid Model of Sprouting Angiogenesis

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Sprouting Angiogenesis:
Tumor induced sprouting angiogenesis is the process of new capillary growth from an existing vasculature, induced by tumor cells that have the "angiogenic switch" turned on. Vascular endothelial growth factors(VEGF) released by tumor cells diffuse through the extracellular Matrix and stimulate endothelial cells lining existing vessels in the proximity of the tumor to form sprouts. As the newly formed sprout tips migrate through the ECM, defining the morphology of the developing tumor vasculature, fibrous structures in the ECM, cell-cell adhesion and growth factor gradients determine their migration paths.

A 3D Model of Sprouting Angiogenesis:
The present model quantifies several biological assumptions and their dynamic interactions, thus enabling the identification of critical factors in the process of angiogenesis and paving the way for future integration of experimental data.

Model Assumptions:

Vascular Endothelial Growth Factors(VEGF):
VEGF is implicated as a key regulator of pathological, tumor induced angiogenesis. In the presented model, we consider three functionally distinct forms of VEGF:

sVEGF diffuses through the computational domain, and establishes a constant chemotactic gradient:

$$\frac{\partial[\mathrm{sVEGF}]}{\partial t} = k_V \nabla^2[\mathrm{sVEGF}] - v_V \rho - d_V[\mathrm{sVEGF}]$$

bVEGF is bound to the ECM. It can become soluble upon cleaving from the ECM by MMPs:

$$\frac{\partial[\mathrm{bVEGF}]}{\partial t} = -v_{bV}[\mathrm{MMP}][\mathrm{bVEGF}]$$

cVEGF is the cleaved form of bound VEGF

$$\frac{\partial[\mathrm{cVEGF}]}{\partial t} = k_V \nabla^2[\mathrm{cVEGF}] + v_{bV}[\mathrm{MMP}][\mathrm{bVEGF}] - v_V \rho - d_V[\mathrm{cVEGF}]$$

Matrix Metalloproteinases (MMPs):
MMPs are proteases, which are primarily involved in the degradation of certain ECM proteins, and the processing of a number of bioactive molecules.

MMPs are released by the endothelial sprout tip cells, and diffuse through the ECM. Upon contact with matrix-bound VEGF, they cleave the VEGF and transform it into a soluble form (cVEGF):

$$\frac{\partial[\mathrm{MMP}]}{\partial t} = k_M \nabla^2[\mathrm{MMP}] + \gamma_M[\mathrm{MMP}][\mathrm{EC}] - d_M$$

Fibronectin (FIB):

FIB is released by endothelial sprout tip cells and binds to the ECM, establishing a gradient which the EC's move up to, accounting for haptotaxis.

Extracellular Matrix (ECM):

The ECM consist of fibrous collagen bundles providing guiding structures for migrating endothelial cells.

Migration Cues (MC):

The Migration cues for the endothelial tip cells are given by a combination of chemotaxis, haptotaxis and the structure of the ECM.

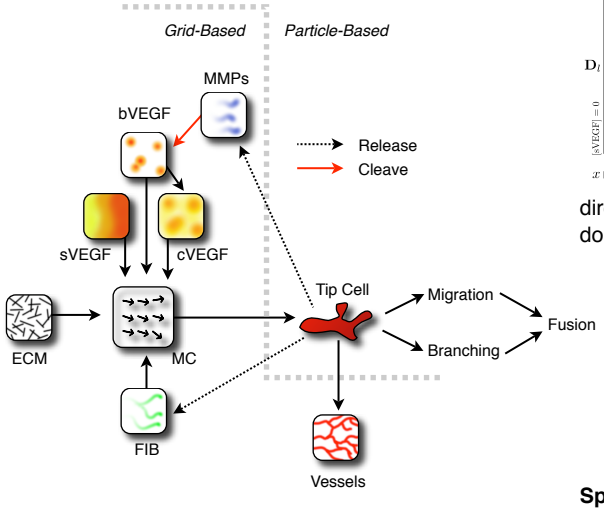
Endothelial Tip Cells (EC):

Endothelial tip cells are guided by migration cues as they define the morphology of the capillary network

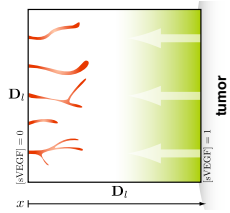
Vessels:

Vessels are represented by the endothelial cell density ρ. The density is given by the track of the tip cells

Model Outline:



Computational Domain:
Five sprout tips are initially placed on the y-z plane lower end of the domain in x direction, a tumor source of soluble VEGF is modeled at the upper end in x direction outside the computational domain.



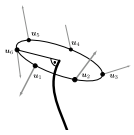
Sprout Tip Migration:
Sprout tips are modeled by particles that are advected according to the migration cues given by the acceleration:

$$\boldsymbol{a} = [\mathrm{ECM}]\underline{\boldsymbol{T}}\left(\mathcal{W}\left([\mathrm{VEGF}]\right)\nabla[\mathrm{VEGF}] + w_F \nabla[\mathrm{bFIB}]\right)$$

Particle positions are then updated according to:

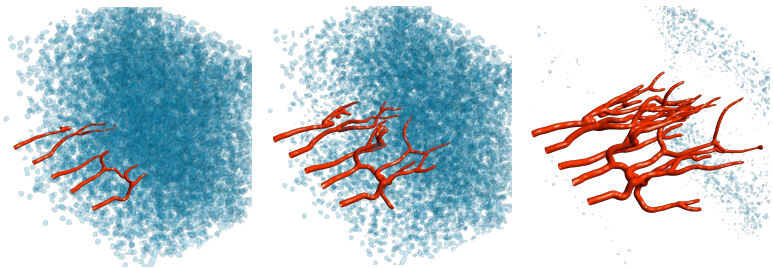
$$\frac{\boldsymbol{x}_p}{\partial t} = \boldsymbol{u}_p, \quad \frac{\boldsymbol{u}_p}{\partial t} = \boldsymbol{a}_p - \lambda \boldsymbol{u}_p$$

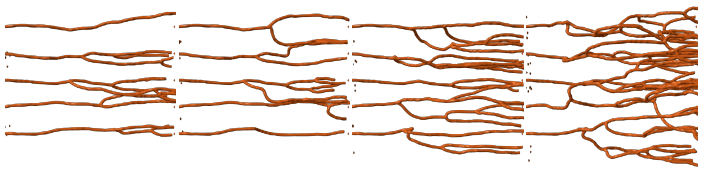
Sprout Branching:
We model sprout tip filopodia by satellite particles distributed radially around the sprout tips. If migration cues at satellite locations diverge sufficiently and the sprout age exceeds a predefined threshold age, a new tip cell particle is initialized and branching occurs.



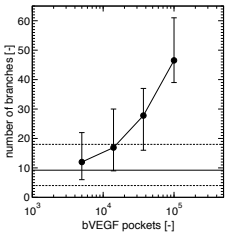
Simulations:

Sprouting angiogenesis in the presence of bound VEGF.

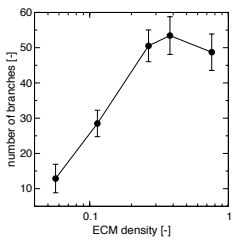




Sprouting angiogenesis for increasing number of bound VEGF pockets.



Statistics for number of branches. Left: with respect to the number of distributed VEGF pockets. Right: with respect to the Matrix fiber density



F. Milde, M. Bergdorf and P. Koumoutsakos. A Hybrid Model of Sprouting Angiogenesis. *Biophys. J., 95, 3146–3160, 2008.*
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