ANGIOGENESIS COMPULCELL3D VS MORPHEUS

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Contact-Inhibited Chemotaxis in De Novo and Sprouting Blood-Vessel Growth

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Abstract

Blood vessels form either when dispersed *endothelial* cells (the cells lining the inner walls of fully formed blood vessels) organize into a vessel network (*vasculogenesis*), or by sprouting or splitting of existing blood vessels (*angiogenesis*). Although they are closely related biologically, no current model explains both phenomena with a single biophysical mechanism. Most computational models describe sprouting at the level of the blood vessel, ignoring how cell behavior drives branch splitting during sprouting. We present a cell-based, Glazier–Graner–Hogeweg model (also called Cellular Potts Model) simulation of the initial patterning before the vascular cords form lumens, based on plausible behaviors of endothelial cells. The endothelial cells secrete a chemoattractant, which attracts other endothelial cells. As in the classic Keller–Segel model, chemotaxis by itself causes cells to aggregate into isolated clusters. However, including experimentally observed VE-cadherin–mediated contact inhibition of chemotaxis in the simulation causes randomly distributed cells to organize into networks and cell aggregates to sprout, reproducing aspects of both de novo and sprouting blood-vessel growth. We discuss two branching instabilities responsible for our results. Cells at the surfaces of cell clusters attempting to migrate to the centers of the clusters produce a buckling instability. In a model variant that eliminates the surface–normal force, a dissipative mechanism drives sprouting, with the secreted chemical acting both as a chemoattractant and as an inhibitor of pseudopod extension. Both mechanisms would also apply if force transmission through the extracellular matrix rather than chemical signaling mediated cell–cell interactions. The branching instabilities responsible for our results, which result from contact inhibition of chemotaxis, are both generic developmental mechanisms and interesting examples of unusual patterning instabilities.

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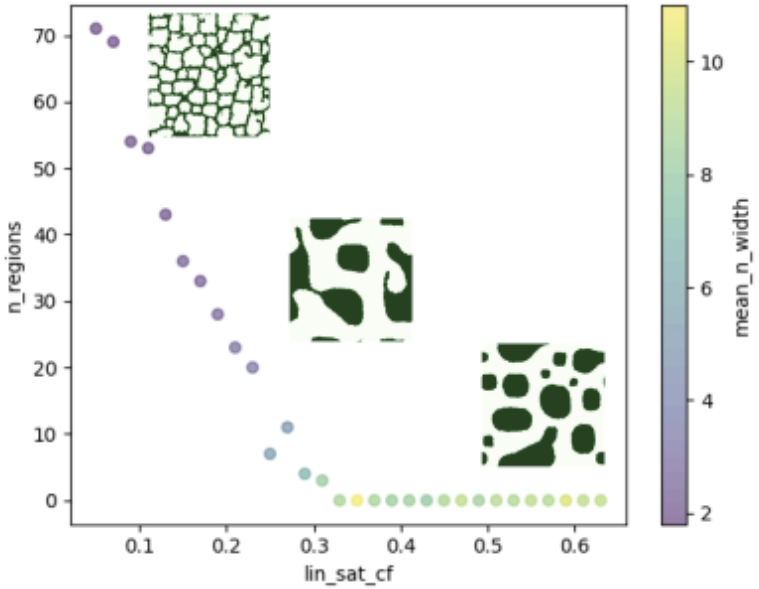
Idea of Model

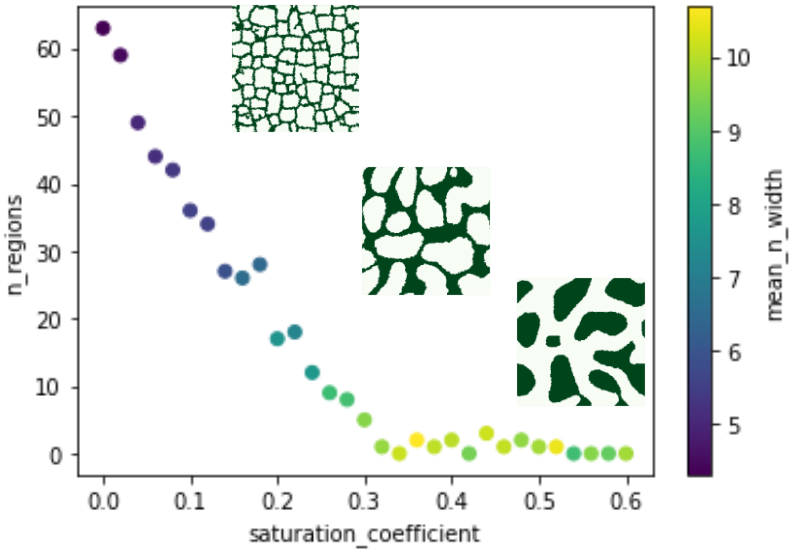
- Cells secrete morphogen (VEGF) that diffuses and is degraded outside the cells
- Cells move towards the morphogen gradient
- Contact inhibition: only chemotactic movement in direction of the medium

Saturation Coefficient

$$\Delta H_{\text{chemotaxis}} = -\mu\left(\frac{c(\vec{x}')}{1+sc(\vec{x}')} - \frac{c(\vec{x})}{1+sc(\vec{x})}\right)$$



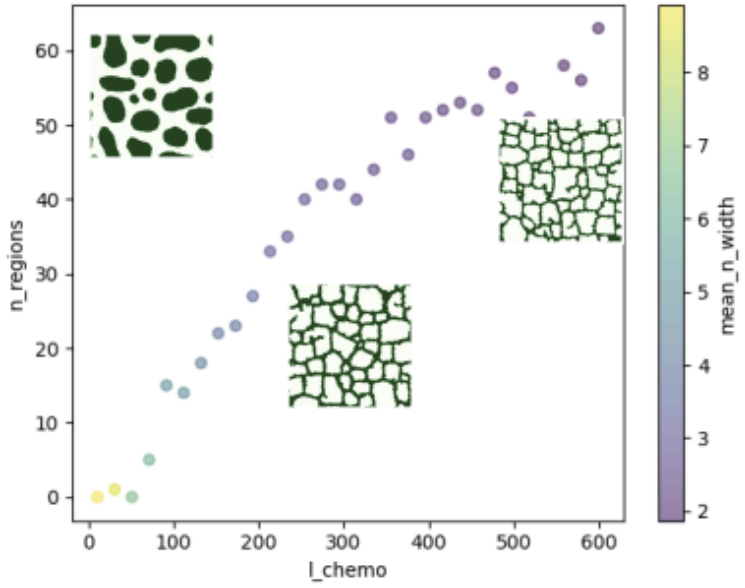
CompuCell3d



Morpheus

Chemotaxis strength

$$\Delta H_{\text{chemotaxis}} = -\mu\left(\frac{c(\vec{x}')}{1+sc(\vec{x}')} - \frac{c(\vec{x})}{1+sc(\vec{x})}\right)$$



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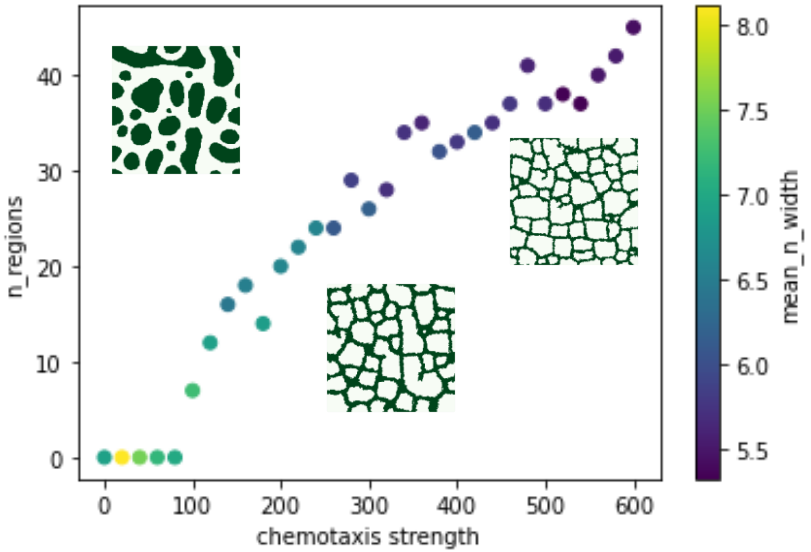

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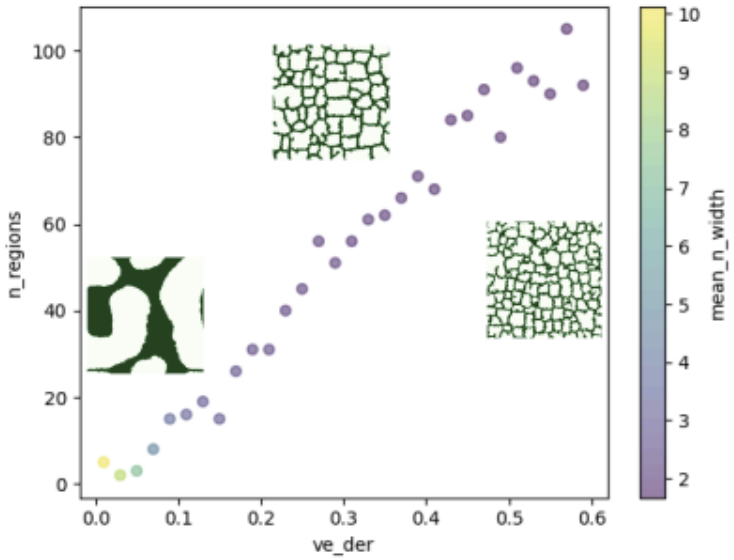
VEGF Degradation

$$\frac{\partial c}{\partial t} = \alpha(1-\delta(\sigma(\vec{x}),0)) - \varepsilon\delta(\sigma(\vec{x}),0)c + D\nabla^2 c$$



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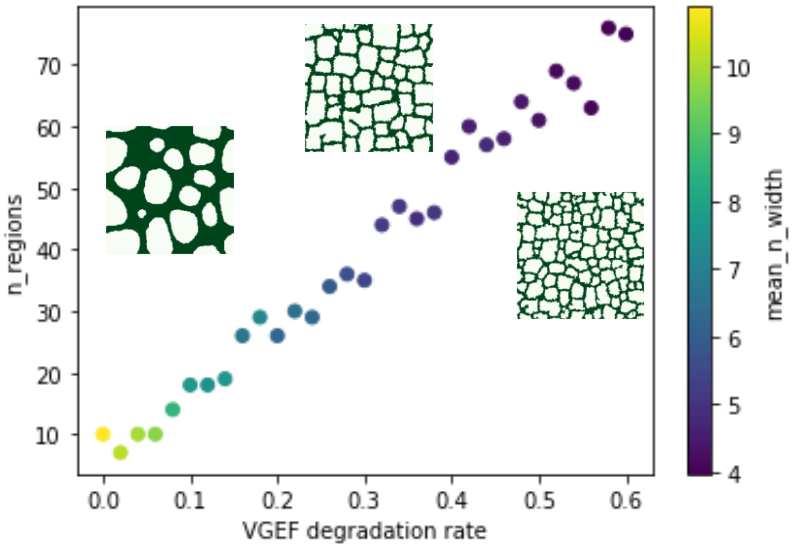

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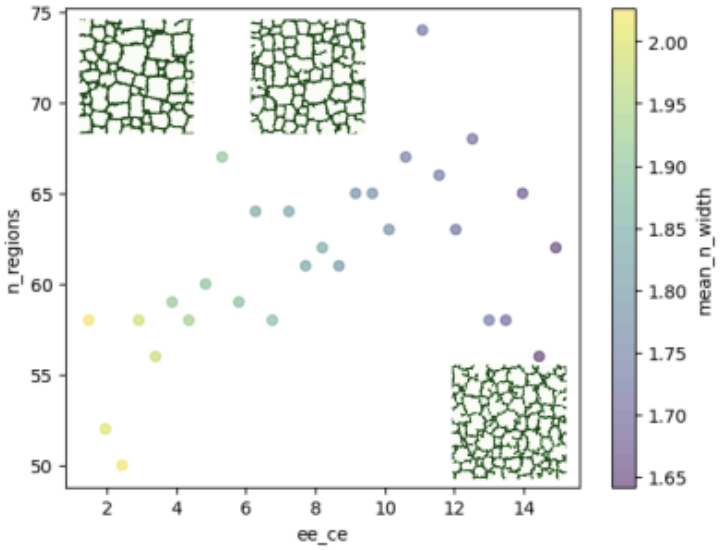
Cell-Cell Adhesion



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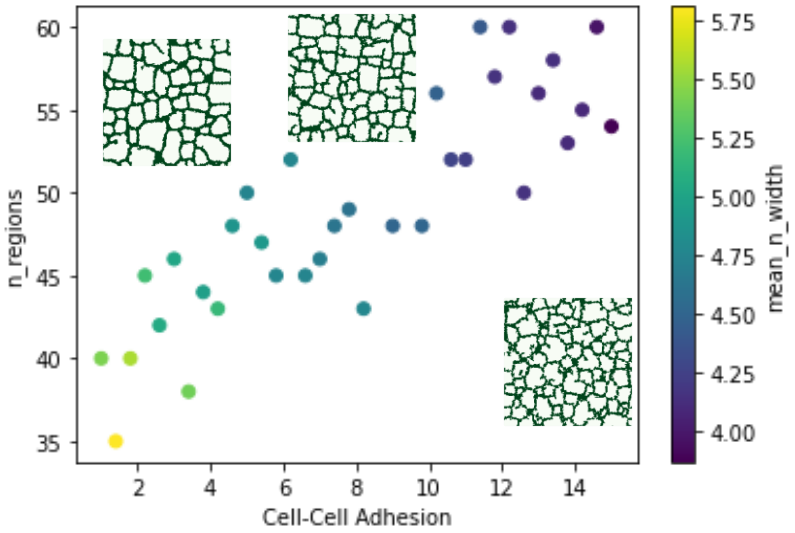

Morpheus

Thank you!