

# Refinement of cell-based, mathematical models of blood vessel formation: the interaction between the cell and its microenvironment

Roeland M.H. Merks

January 21, 2015

Angiogenesis, the growth of new blood vessels as side branches from existing ones, is a key process in many processes in health and disease. Angiogenesis is responsible for the regeneration of new blood vessels during wound healing. In less fortunate circumstances, growing tumors manage to hijack the growing vasculature such that it delivers nutrients and oxygen to the tumor. A detailed mechanistic understanding of the cellular mechanisms controlling angiogenesis will help us find the means to stimulate or inhibit blood vessel formation with drugs.

The main building blocks of blood vessels are endothelial cells, which together with a series of supporting cell types self-organize into blood-vessel like structures and blood vessel sprouts. A series of previous simulation models by our group and others have used extensions of the Cellular Potts model [1] to derive the rules that endothelial cells follow to form a blood vessel network or side-branch. For example, we have shown that if cells attract one another and have an elongated shape, then they will form network-like structures [2]. A range of alternative mechanisms have the same effect, including a contact-inhibited attractive force [3], and an attractive force towards locally elongated structures [4, 5].

More recently it has become clear that local interactions between the endothelial cells and its direct environment are key to a proper understanding of vascular patterning. Cells are typically surrounded by the extracellular matrix, an umbrella term for the extracellular jelly and fibrous (glyco)proteins that cells produce themselves. In cell cultures, the properties of the substrate to a large extent control the morphology of blood vessel networks. In recent work we [6, 7] (Figure 1) and others [8, 9] have explored both mechanical and chemical interactions between the cells and the extracellular matrix. Although these models have yielded new insights, experiments suggest that via the matrix cells can obtain a much finer control of the cell-cell signaling than in the signaling mechanisms we have hitherto considered in our models. In this project you will explore, by extending our existing mathematical models [10], the types of signaling that cells can make use of in these models and compare the results with published experimental data [11].

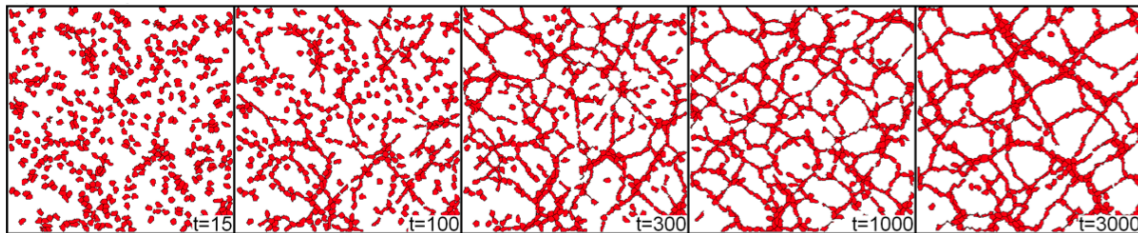


Figure 1: Development of a vascular network via mechanical cell-matrix interaction (modified from Van Oers, Rens et al. [7])

## References

- [1] James A Glazier and F Graner. Simulation of the differential adhesion driven rearrangement of biological cells. *Phys. Rev. E*, 47(3):2128–2154, 1993.
- [2] R M H Merks, Sergey V Brodsky, Michael S Goligorsky, Stuart A Newman, and James A Glazier. Cell elongation is key to in silico replication of in vitro vasculogenesis and subsequent remodeling. *Dev. Biol.*, 289(1):44–54, 2006.
- [3] Roeland M H Merks, Erica D Perryn, Abbas Shirinifard, and James A Glazier. Contact-inhibited chemotaxis in de novo and sprouting blood-vessel growth. *PLoS Comp Biol*, 4(9):e1000163, September 2008.
- [4] Andras Szabó, Elod Mehes, Edina Kosa, and Andras Czirok. Multicellular sprouting in vitro. *Biophys. J.*, 95(6):2702–2710, September 2008.
- [5] Andras Szabó, Erica D Perryn, and Andras Czirok. Network formation of tissue cells via preferential attraction to elongated structures. *Phys. Rev. Lett.*, 98(3):038102, 2007.
- [6] Josephine T Daub and Roeland M H Merks. A cell-based model of extracellular-matrix-guided endothelial cell migration during angiogenesis. *B. Math. Biol.*, 75(8):1377–1399, August 2013.
- [7] René F M van Oers, Elisabeth G Rens, Danielle J LaValley, Cynthia A Reinhart-King, and Roeland M H Merks. Mechanical Cell-Matrix Feedback Explains Pairwise and Collective Endothelial Cell Behavior In Vitro. *PLoS Comput. Biol.*, 10(8):e1003774, August 2014.
- [8] A Köhn-Luque, W de Back, Y Yamaguchi, K Yoshimura, M A Herrero, and T Miura. Dynamics of VEGF matrix-retention in vascular network patterning. *Phys. Biol.*, 10(6):066007, December 2013.

- [9] Alvaro Köhn-Luque, Walter De Back, Jörn Starruß, Andrea Mattiotti, Andreas Deutsch, José María Pérez-Pomares, and Miguel A Herrero. Early embryonic vascular patterning by matrix-mediated paracrine signalling: A mathematical model study. *PLoS ONE*, 6(9):e24175, September 2011.
- [10] Josephine T Daub and Roeland M H Merks. Cell-Based Computational Modeling of Vascular Morphogenesis Using Tissue Simulation Toolkit. In D Ribatti, editor, *link.springer.com*, pages 67–127. Methods in Molecular Biology, New York, NY, October 2014.
- [11] Hesam Parsa, Ranjan Upadhyay, and Samuel K Sia. Uncovering the behaviors of individual cells within a multicellular microvascular community. *P. Natl. Acad. Sci. USA*, 108(12):5133–5138, March 2011.