Simulation of Chemotractant Gradients in Microfluidic Channels to Study Cell Migration

Patric Wallin[1], Elin Bernson[1], Julie Gold[1]

[1]Chalmers University of Technology, Applied Physics, Biological Physics, Gothenburg, Sweden

Abstract

Angiogenesis is a process in which new blood capillaries are formed to re-establish or improve blood circulation in a tissue. During angiogenesis, endothelial cells migrate from existing capillaries along a chemotractant gradient of vascular endothelial growth factor (VEGF), originating from a tissue section with low oxygen levels; in successive steps new blood capillaries are formed. Angiogenesis is a key player in cancer and VEGF is being targeted to limit neovascularization of tumors. On the other hand, the controlled formation of new blood capillaries is essential for successful tissue engineering. Overall a better understanding of the underlying processes of angiogenesis is needed and microfluidics offer a unique experimental way to mimic cellular microenvironments in vitro. In combination with multiphysics simulations, the value of such experimental tools can even be further enhanced. In this study, COMSOL 4.2 is used to model a microfluidic diffusion based gradient generator and study how cells sense this gradient in a three dimensional environment (Figure 1). Due to the small dimensions in the micrometer regime, the flow within the channels can be modeled as laminar. In order to simulate gradients of bioactive molecules, the calculated velocity field is coupled to the transport of diluted species module as convective transport. The binding of VEGF to cell receptors is modeled as a surface reaction and two probes are used to calculate the difference in binding between the front area and the back area of the cell. Biological properties like kon/koff, binding site density and diffusion constants are taken from experimental data to model the interaction of endothelial cells with the chemotractant VEGF as closely as possible. The results show that it is possible to form gradients of bioactive molecules with the designed microfluidic network (Figure 2A). The gradient steepness for a given molecule, like VEGF, can be adjusted by changing the flow rate in the inlets (Figure 2B), which was confirmed with experimental results. The results for the surface binding reaction show that it is possible to model VEGF binding to the cell receptors (Figure 3) and detect a difference between the two sides of a cell. More in-depth parameter analysis will follow to obtain results at different positions in the channel and under varying conditions. Overall, this study demonstrates the ability to model cell microenvironments and their interactions with great detail, by coupling fluid dynamics with the transport of a chemotractant molecule that interacts with a modeled cell surface. Previous approaches have modeled either the gradient formation [1] or the cell-molecule interaction [2]. By combining the two into a single model it is possible to study for example effects of flow velocity and local depletion on a single cell level, while still modeling the whole microfluidic network. The model developed in this study will greatly improve the ability to find suitable parameters for experiments and help to understand processes that cannot be visualized in cell experiments.

Reference

[1] Amir Shamloo et al., Endothelial cell polarization and chemotaxis in a microfluidic device, Lab on a chip,8,1292-1299, 2008.
[2] Feilim Mac Gabhann et al., Monte Carlo simulations of VEGF binding to cell surface receptors in vitro, Biochimica et biophysica acta, 1746, 95-107, 2005.

Figures used in the abstract

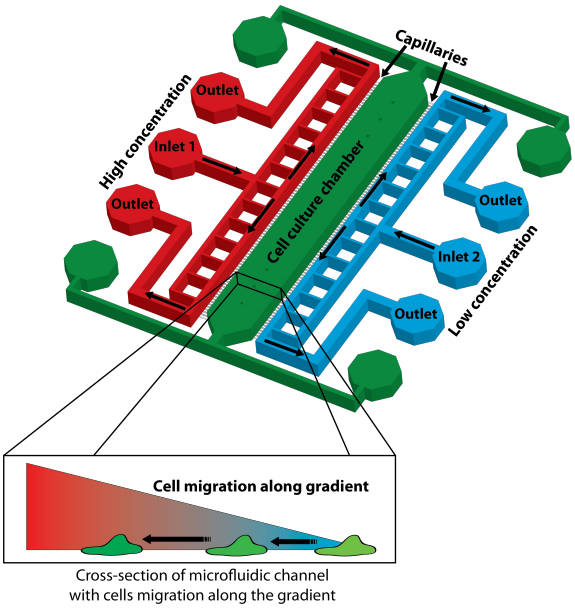

Figure 1: Schematic of the experimental setup with a microfluidic chip capable of producing chemottractant gradients that cells migrate along.

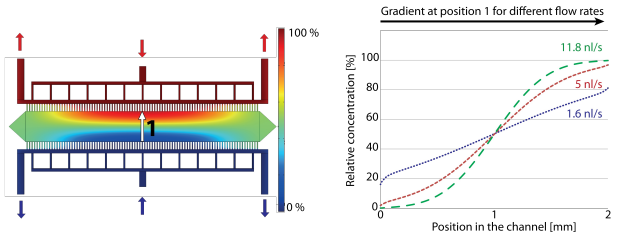

Figure 2: Comsol simulation data of the microfluidic network showing the concentration of chemottractant throughout the channel and along the center for different flow rates.

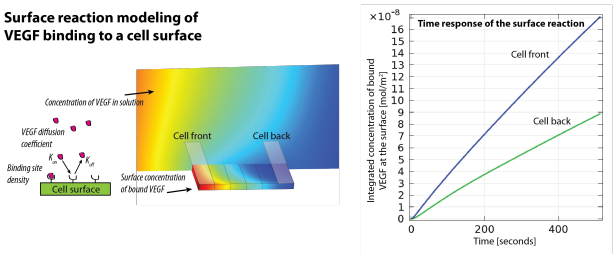

Figure 3: Surface reaction modeling of VEGF binding to the cell surface.