Simulation of Chemotractant Gradients in Microfluidic Channels to Study Cell Migration Mechanism *in silico*

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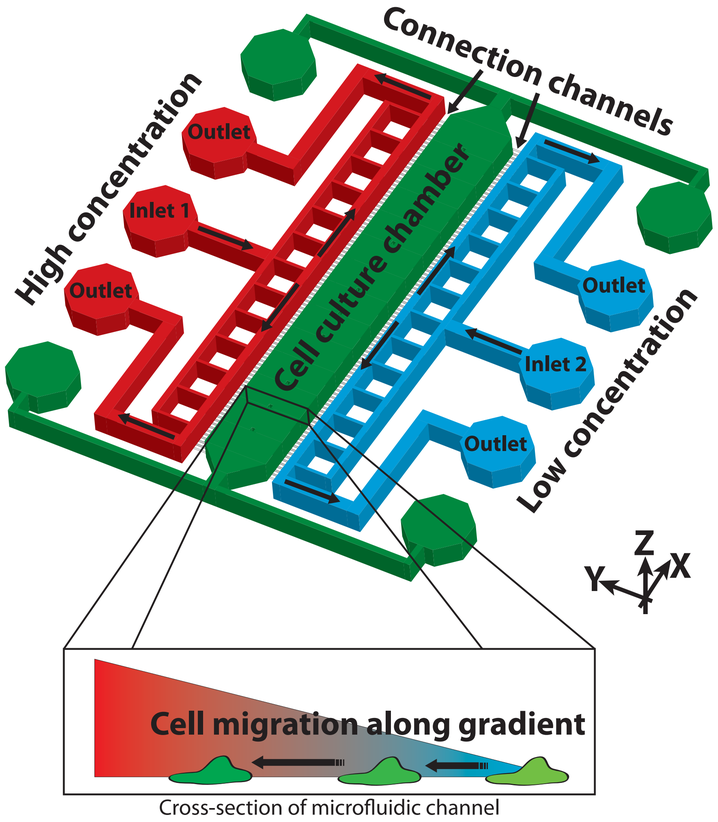
Directed cell migration and Angiogenesis

Directed cell migration along molecular, chemotractant gradients in solution plays an important role in many in vivo processes, from early embryogenesis to wound healing to cancer. One particular process is angiogenesis, during which new blood capillaries are formed to reestablish or improve blood circulation in a certain part of the body in response to e.g. low oxygen levels. To activate and control this process in vitro is a crucial step for tissue engineering larger organ constructs that can be successfully transplanted. Angiogenesis is furthermore a key component in cancer biology, where neovascularization facilitates cancer growth, and will eventually lead to metastases formation.

One very potent migration stimulant for endothelial cells is vascular endothelial growth factor (VEGF) that is recognized by cells via special cell surface receptors. We focus on the binding of VEGF-A to VEGF receptor 2 (VEGFR-2), which is the most interesting interaction for cell migration.



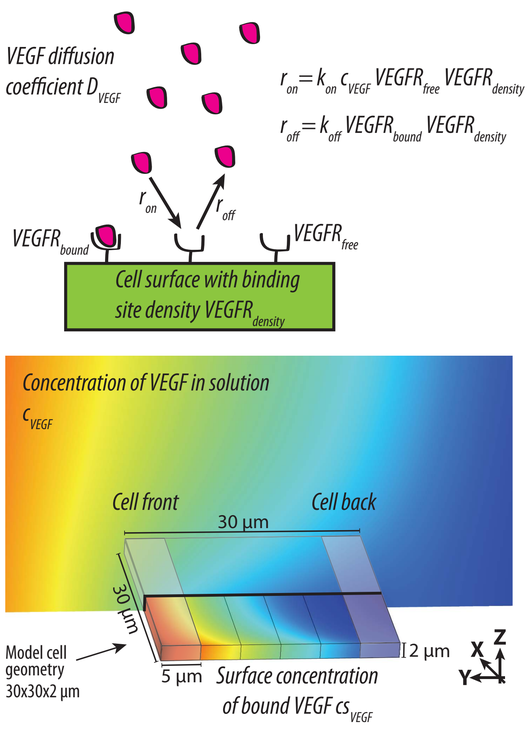
Cross-section of microfluidic channel with cells migrating along the gradient

Cell migration in vitro

The ability to study cell migration in vitro is crucial to understand the underlying cell biological processes in detail and see how they can be influenced. This demands a robust and flexible in vitro cell culture system capable of forming controlled gradients. Microfluidics is a technique capable of forming molecular gradients with high spatial and temporal resolution.

For the work presented here, we used a diffusion based microfluidic gradient generator, because it enables us to form gradients on the cellular length scale without exposing the cells to shear stress. This is especially important when working with endothelial cells since they are very shear stress sensitive.

Computational model



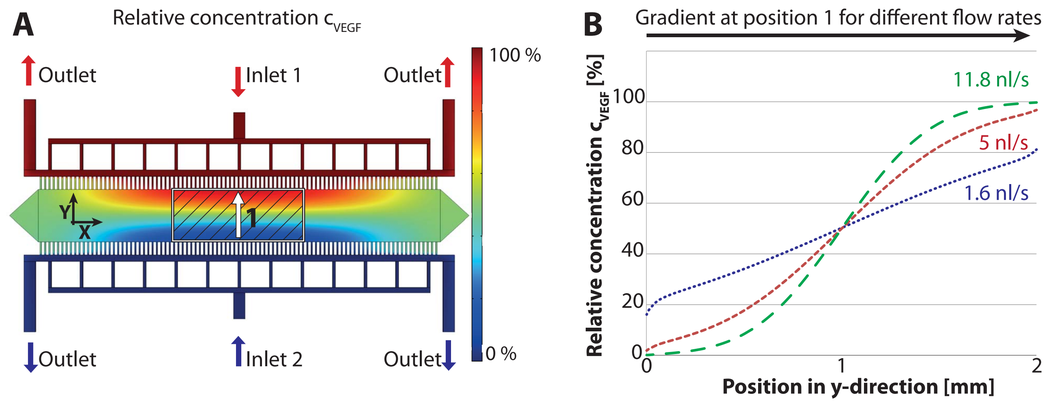
Laminar flow module
--> Fluid velocity field

Transport of diluted species
--> Gradient formation

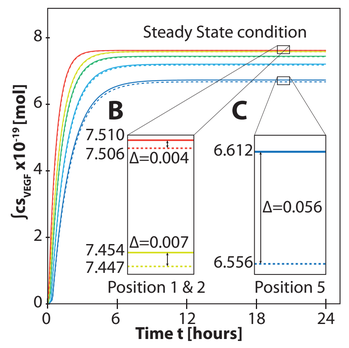
Surface reaction
--> Binding of VEGF to its receptors

Parameter	Value	Unit	Description
c_{VEGF}	calculated	mol/m^3	VEGF concentration in solution
$c_{VEGF\ t=0}$	0	mol/m^3	VEGF concentration in the network at t=0
$c_{VEGF\ inlet\ 1}$	$1.25\cdot10^{-5}$ – $1.25\cdot10^{-8}$	mol/m^3	VEGF concentration at inlet 1 (parametric sweep)
cs_{VEGF}	calculated	mol/m^2	VEGF concentation bound to the surface
$cs_{VEGF\ t=0}$	0	mol/m^2	VEGF concentation bound to the surface at t=0
$VEGFR_{density}$	$3.4\cdot10^{-9}$	mol/m^2	VEGF receptor density [2]
$VEGFR_{free}$	calculated	Ratio 0-1	Ratio of free VEGF receptors
$VEGFR_{bound}$	calculated	Ratio 0-1	Ratio of bound VEGF receptors
u_{inlets}	$6.25\cdot10^{-5}$	m/s	Flow velocity at inlet 1 & 2
D_{VEGF}	$2\cdot10^{-6}$	cm^2/s	VEGF diffusion constant [2]
k_{on}	$3.6\cdot10^{6}$	L/mol·s	Association rate constant VEGF-VEGFR [2]
k_{off}	$2\cdot10^{-6}$	1/s	Dissociation rate constant VEGF-VEGFR [2]
$Cell_{position-y}$	-800 -400 0 400 800	µm (from the center of the channel)	Cell position in y-direction (parametric sweep in study)

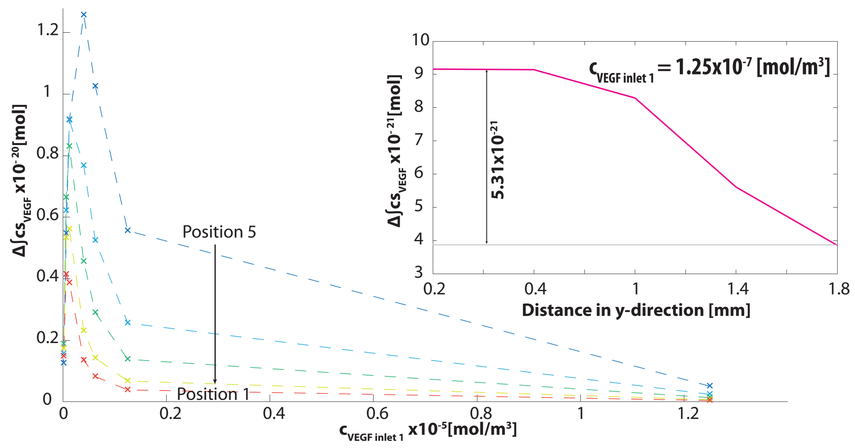
Diffusion based gradient formation



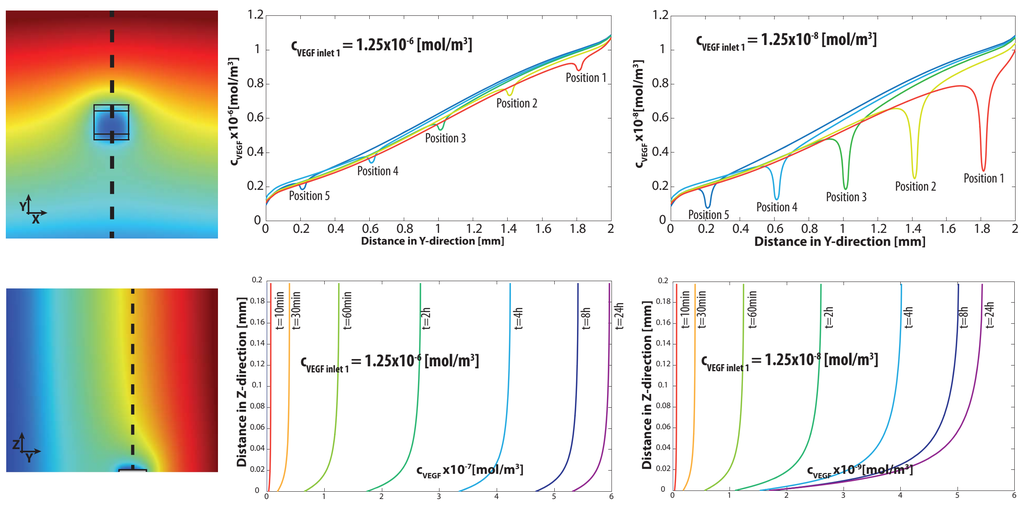
Gradient perception of the cells

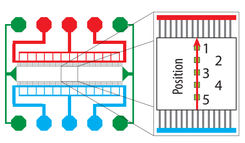


- No direct imprinting of the gradient on the cell surface
- The difference between the front and the back of a cell $\Delta\int cs_{VEGF}$ changes across the channel
- There is a non-linear relation between $\Delta\int cs_{VEGF}$, cell position and inlet concentration



Local depletion above cells





- Local depletion of VEGF above the cells
- The cell is acting as a local VEGF sink
- The effect is pronounced for small inlet concentrations
- Potentially effecting other cells in close proximit

Conclusions

The model developed in this study allowed us to simulate the gradient sensed by a cell in a microfluidic network much better than with previous approaches. There is a clear difference between the gradient in solution and the gradient on the cell surface, which has severe consequences for cell experiments. The difference in receptor-bound signaling molecules between the front and back of a cell varies non-linearly as a function of cell position across the gradient, as well as inlet concentration of signaling molecules. With the model from this study suitable experimental parameters can be predicted with higher certainty and experiments carried out in a more efficient ways.

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