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Microfluidic Systems for Cell Growth and Cell Migration Studies

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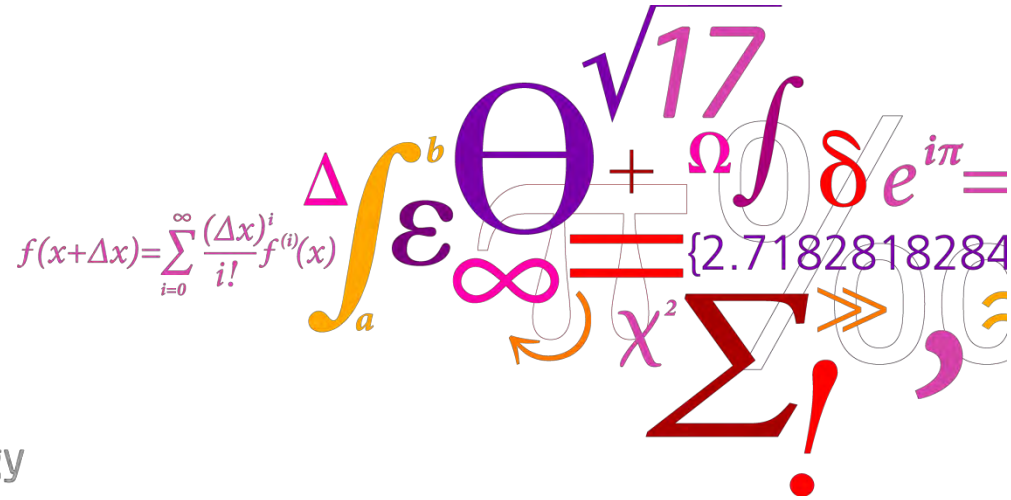
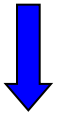


DTU Nanotech
Department of Micro- and Nanotechnology

Use of Comsol

- Expensive and/or time consuming fabrication processes → Need to minimize repeated fabrication runs and test cycles
- Competitive field → Design to product time should be minimized



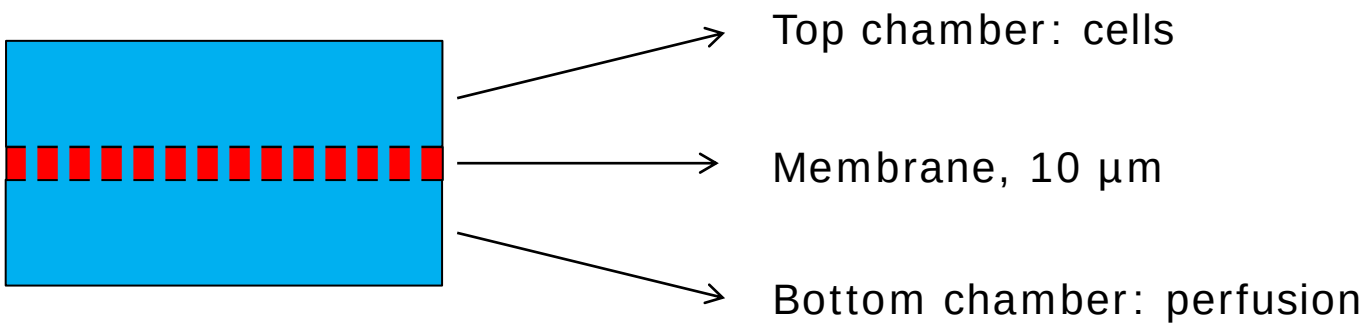
- Comsol contribution:
  - Optimise the performance of existing designs by calculating experimental parameters
  - Design and simulate the performance of new structures
  - Explain the experimental results

Overview

- Geometry and Physics
- Cell culture chambers
  - Design 1
  - Design 2
  - Results
- Cell migration chamber
  - Design
  - Results
- Conclusion and outlook

Geometry and Physics

- Common for all systems:



- **Incompressible Navier Stokes** coupled with **Convection and Diffusion**
- Flow solved in steady state and solution stored and used to solve for the concentration with time-dependent solver
- Membrane treated as a separate subdomain controlled by Darcy's law for porous flow

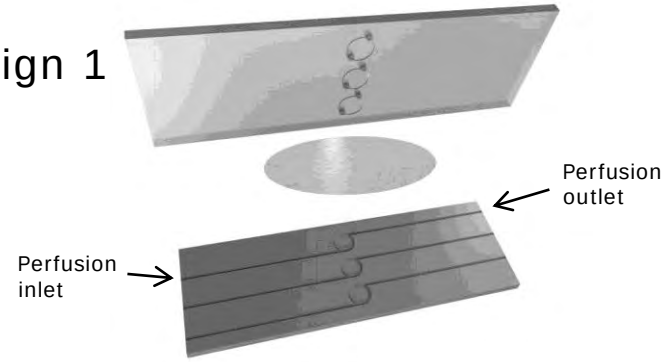
The membrane

- 10 µm thick, 5 µm pore size, porosity of 0.14
- In the subdomain settings for the Incompressible Navier Stokes a body force on the liquid was added, given by $\vec{F} = -\alpha \cdot \vec{u}$
- α is a constant calculated from the Darcy number (Da) as $\alpha = \frac{\eta}{Da \cdot L^2}$

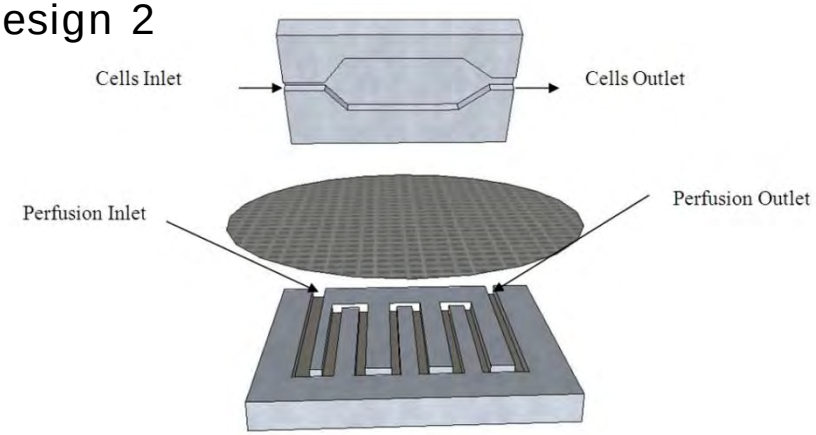
- For the 10 µm thick porous membrane this gives $\alpha = 10^{11}$ kg/(m^{3}s) for a Darcy number of 10^{-4} and a viscosity equal to that of water (0.001 Pa·s)
- Diffusion coefficient for various species was corrected with the membrane porosity
- The validity of the Darcy approximation was tested in a 2D simulation where a geometric approximation of the membrane was designed and simulated

Cell culture chamber

Design 1



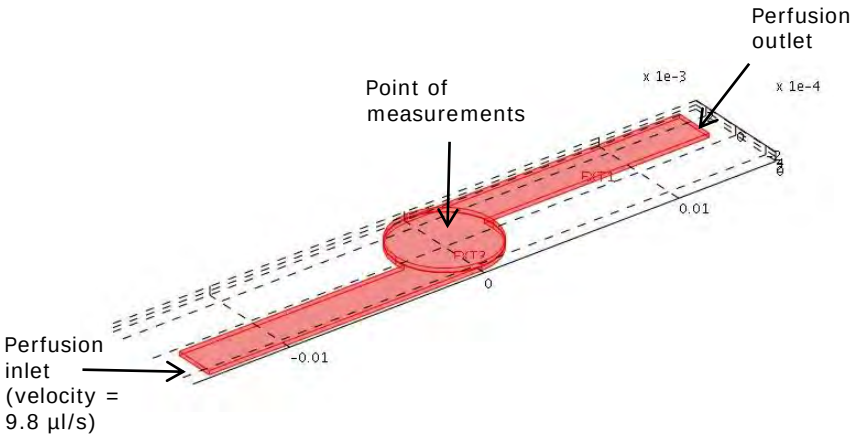
Design 2

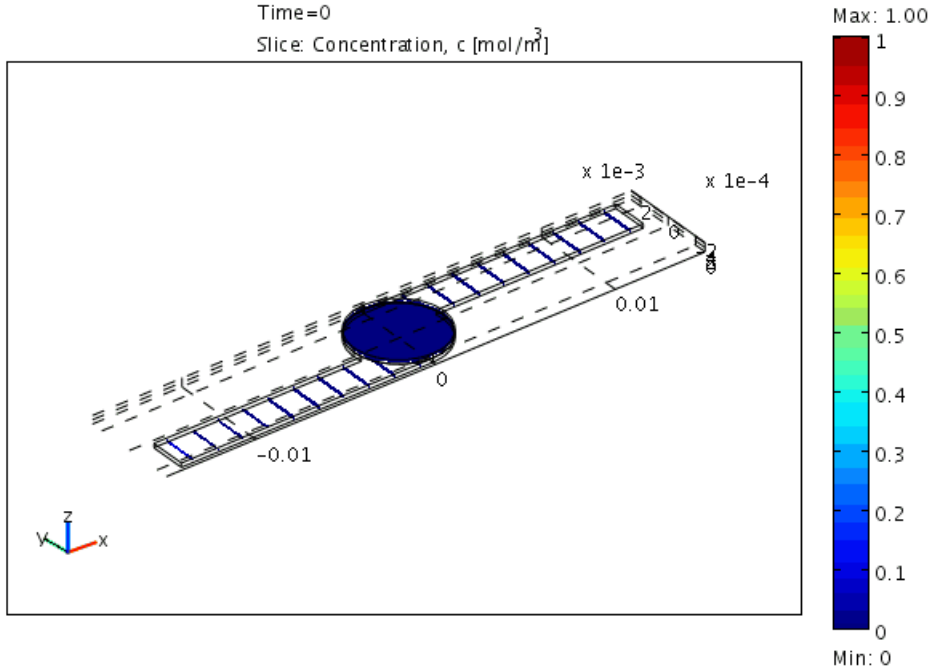


- The two systems function essentially in the same way with some small differences:
  - Loading and unloading of cells by pipette (design 1) as opposed to flow (design 2)
  - Diffusion through large 5 mm circular opening as opposed to a meandering channel 500 µm wide
  - Depth of bottom chamber: 200 µm (design 1), 300 µm (design 2)
  - Depth of top chamber: 200 µm (design 1), 250 µm (design 2)
  - Perfusion inlet velocity: 9.8 µl/min (design 1), 2.5 µl/min (design 2)

Design 1

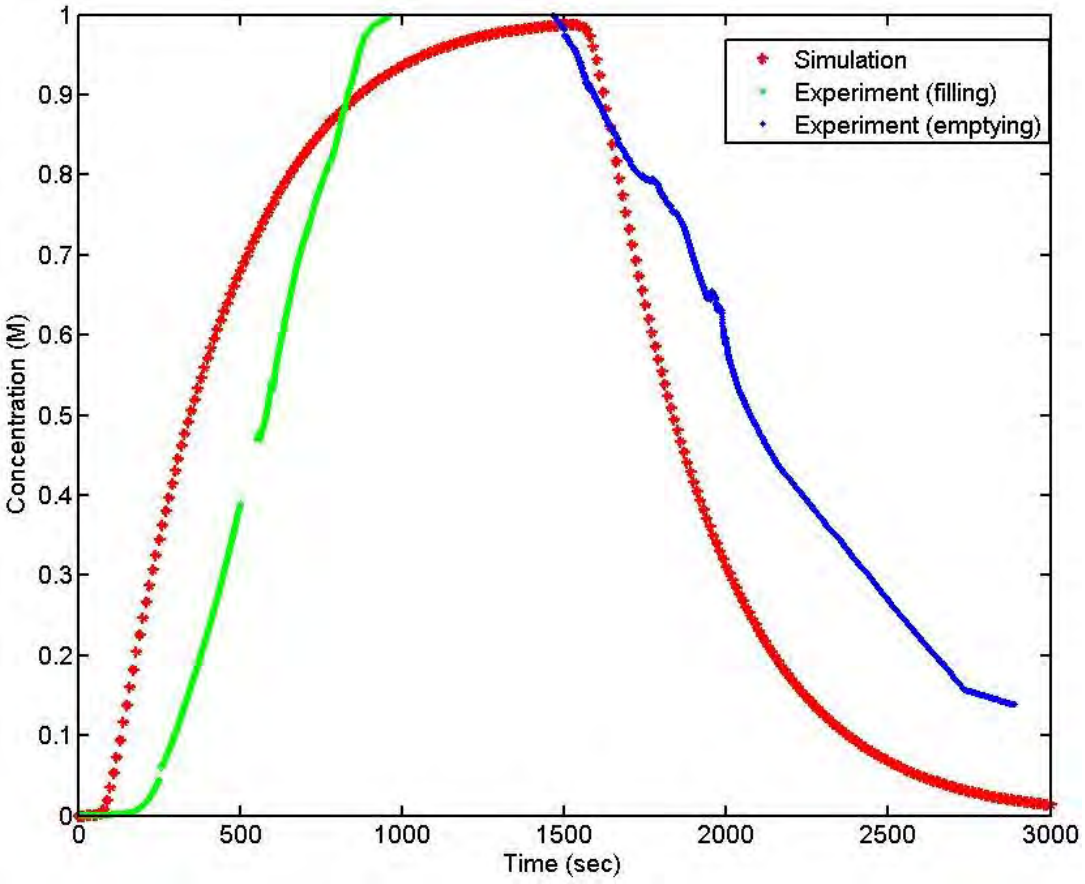
- Simulating the filling and emptying of the top chamber with a solution of streptavidin (D = 130 $\mu m^2/s$). Boundary condition at perfusion inlet was set to (t<1500), i.e. 1 M for t<1500 sec and 0 M for t>1500 sec.
- Only part of the inlet and outlet channels were simulated
- Chamber practically at max concentration after 1000 sec and almost empty 1000 sec after solution switch

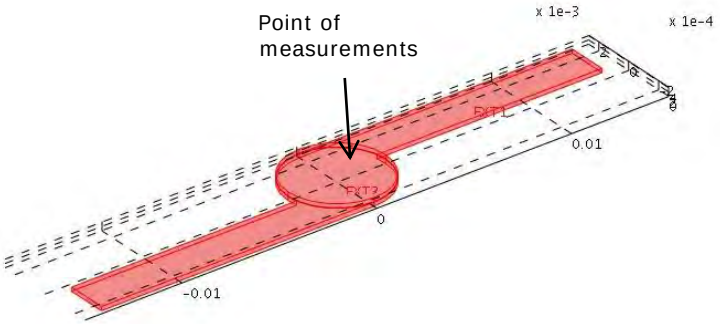




Results

- Concentration roughly at experimental measurement point (average of simulated concentrations in a volume of 25000 µm^3 just below the top surface of the chamber towards the outlet)





A few discrepancies

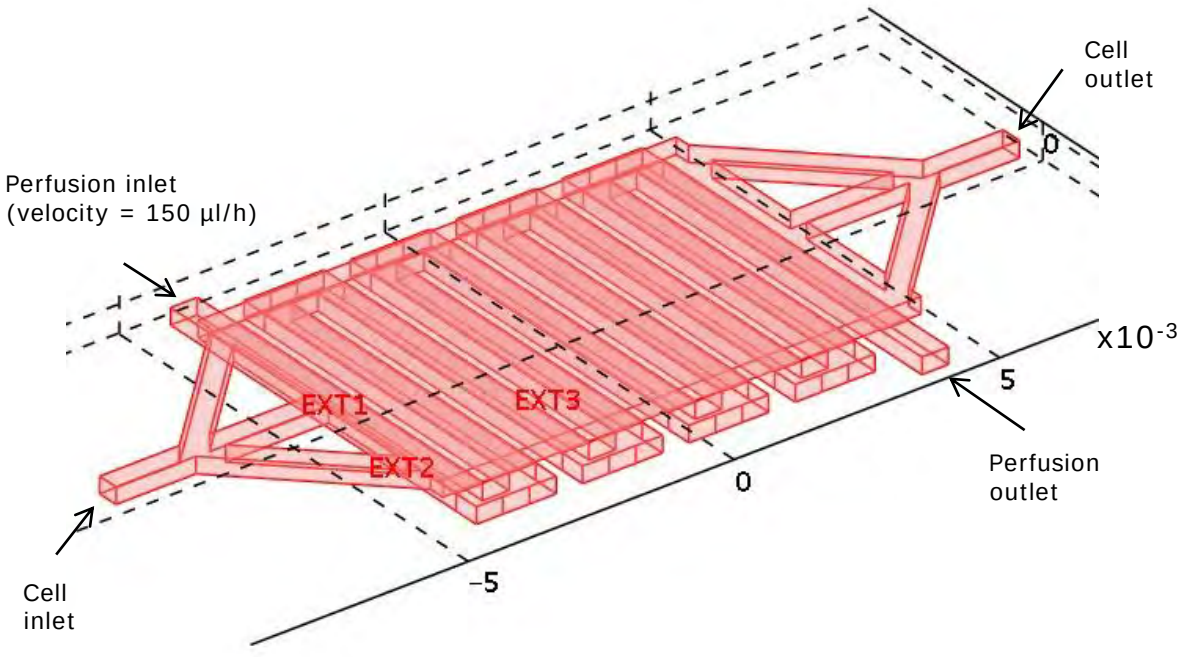
-Fluorescence signal first detectable after a certain concentration has been reached

- Unspecific binding on channel walls

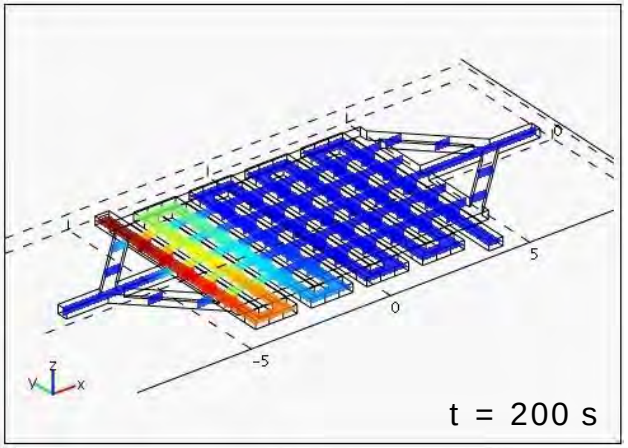
-Uncertainty regarding exact measurement point

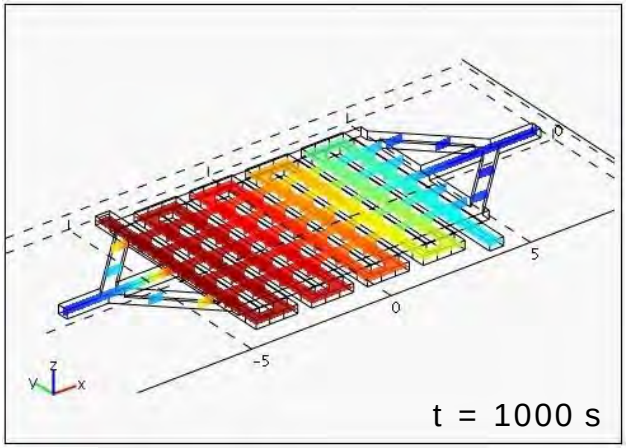
Design 2

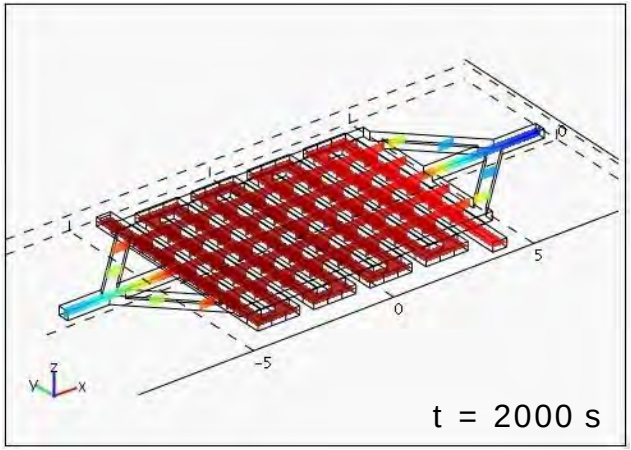
- Simulating the filling of the top chamber with a solution of KCl (D = 2000 $\mu m^2/s$) as part of the cell treatment protocol for cytogenetic analysis

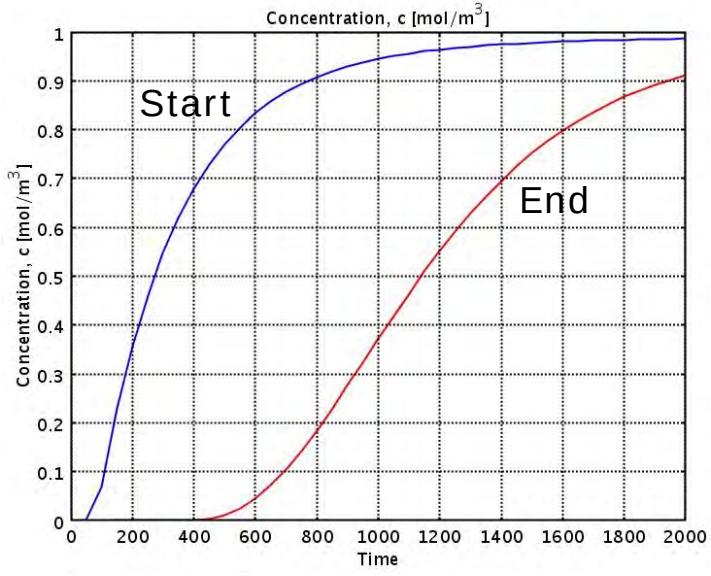


Results



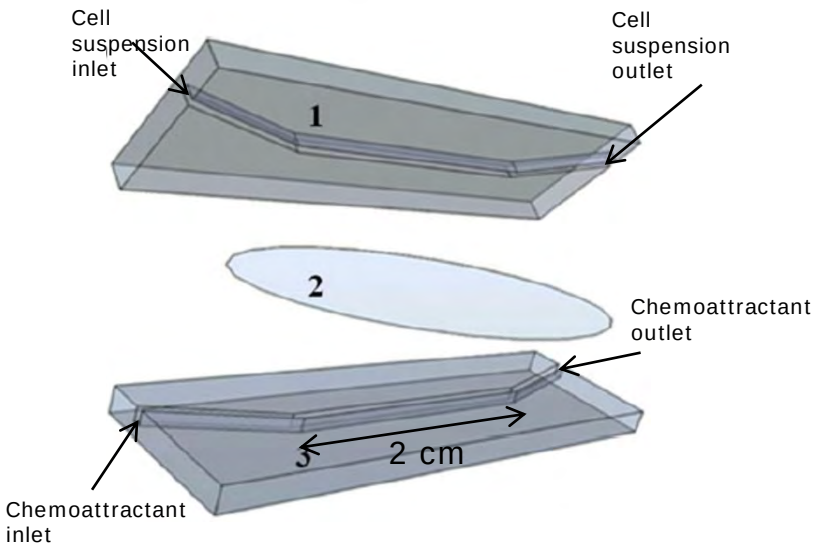




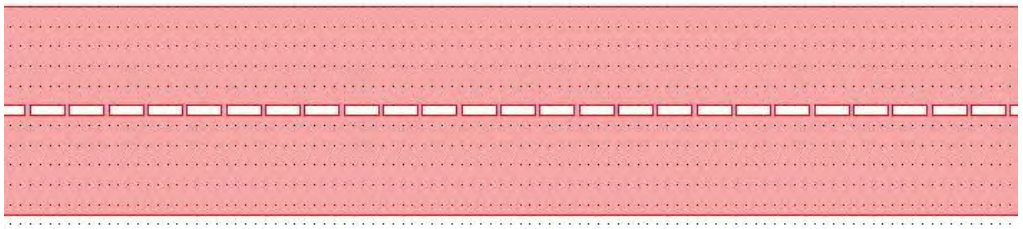


Experimentally 25 min (1500 s) were used for filling the chamber with good results

Cell migration chamber

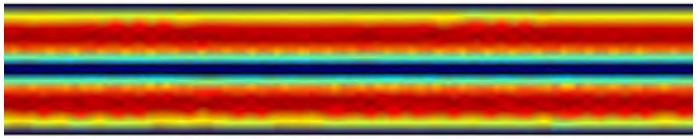


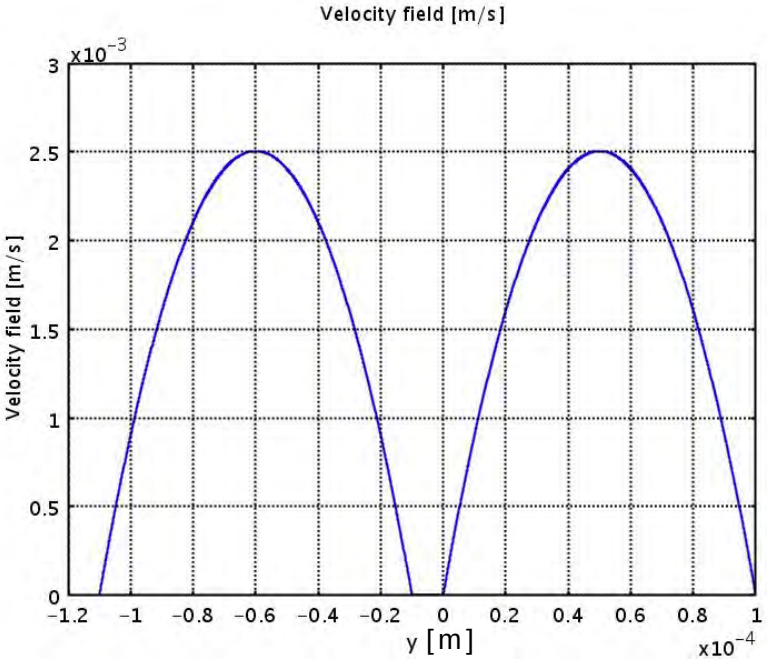
- Parallel flow in the two channels. Inlet velocity at 1.67 x 10^{-3} m/s
- Diffusion coefficient of chemoattractant calculated to be 1.76 x 10^{-10} m^2/s
- Simulation conducted in 2D
  - By treating the membrane as a subdomain with a volume force on the liquid
  - By physically designing a 10 µm thick membrane with a large number of 5 µm wide holes to achieve a porosity of 0.14 over the 2 cm channel



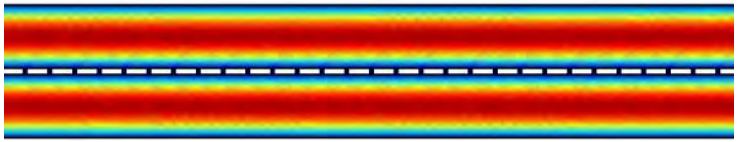
Results – velocity field

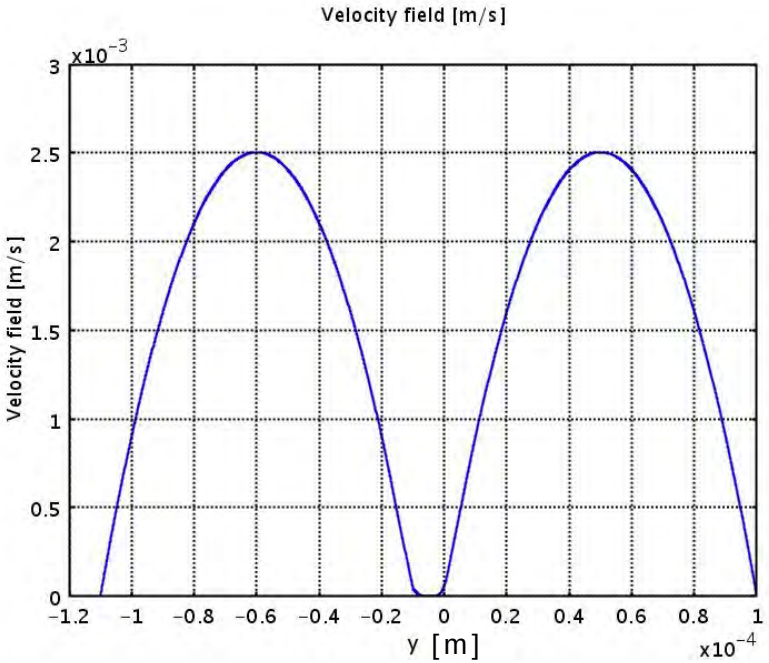
Darcy representation





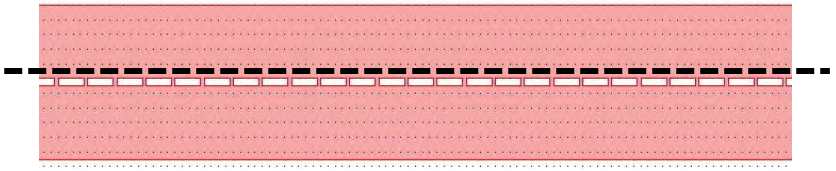
Geometrical representation



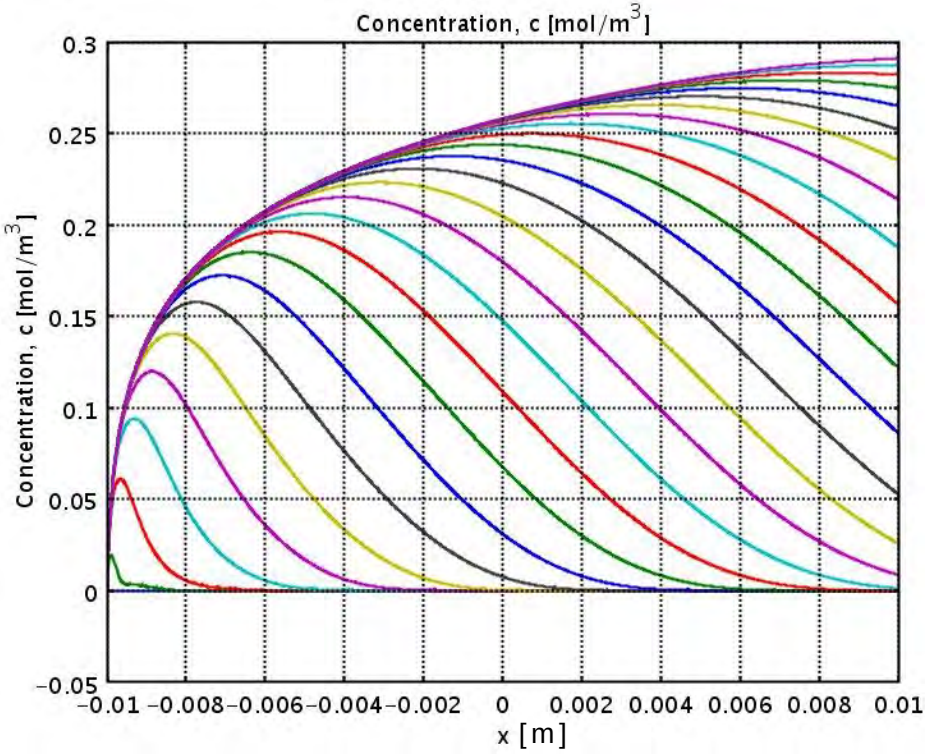


Results - concentration

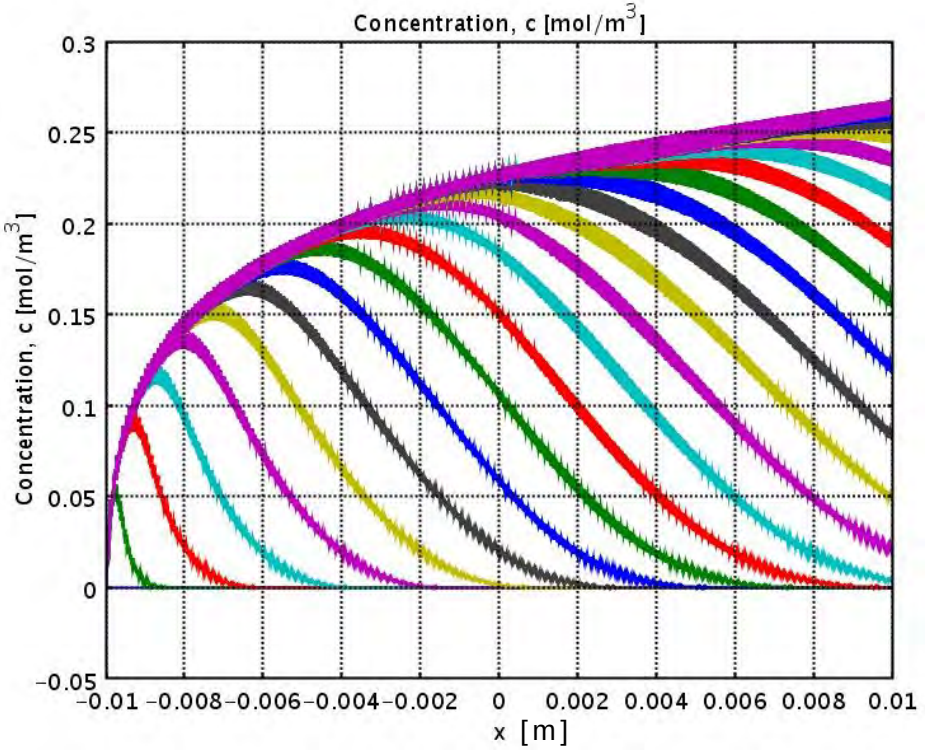
5 µm above membrane



Darcy representation

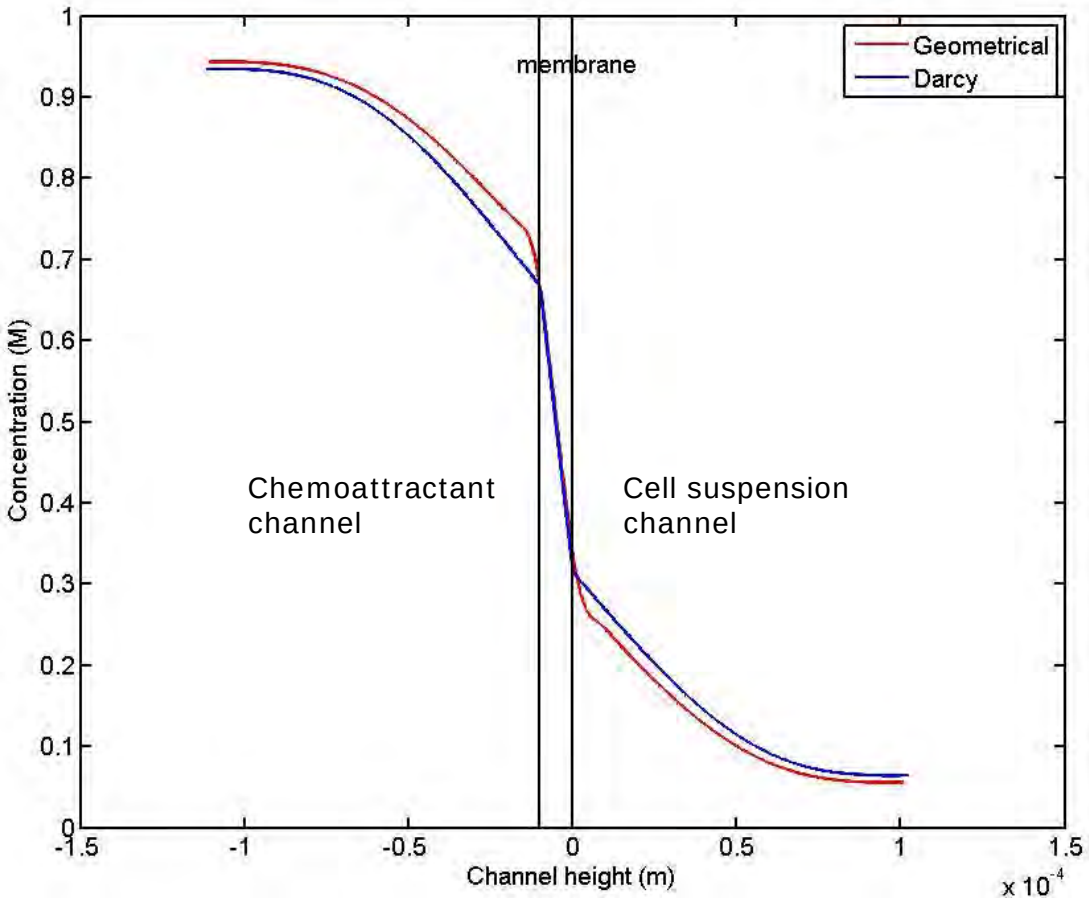


Geometrical representation



Results - concentration

- Concentration gradient at the end of the channel at steady state (t = 25 s)



! The geometrical plot is taken at the middle of the last membrane opening (2 cm from inlet)

! Experimental data confirm that cells only migrate through the membrane close to the channel outlet, where the concentration is the highest

Conclusion and outlook

- Darcy modelling of the membrane gives similar results to those achieved with the geometrical representation of the membrane → Greatly reduces computational needs and geometric complexity
- Experimental results fit mostly with the theoretically predicted ones for all presented systems. Discrepancies can be due to:
  - Uncertainties for various simulation parameters such as diffusion coefficient and viscosity
  - Fabrication accuracy of the experimental device as opposed to the simulated one (micromilling error can be up to ± 5-10 µm)
- The effect of the structural uncertainties needs to be quantified in the future

Thank you for your attention