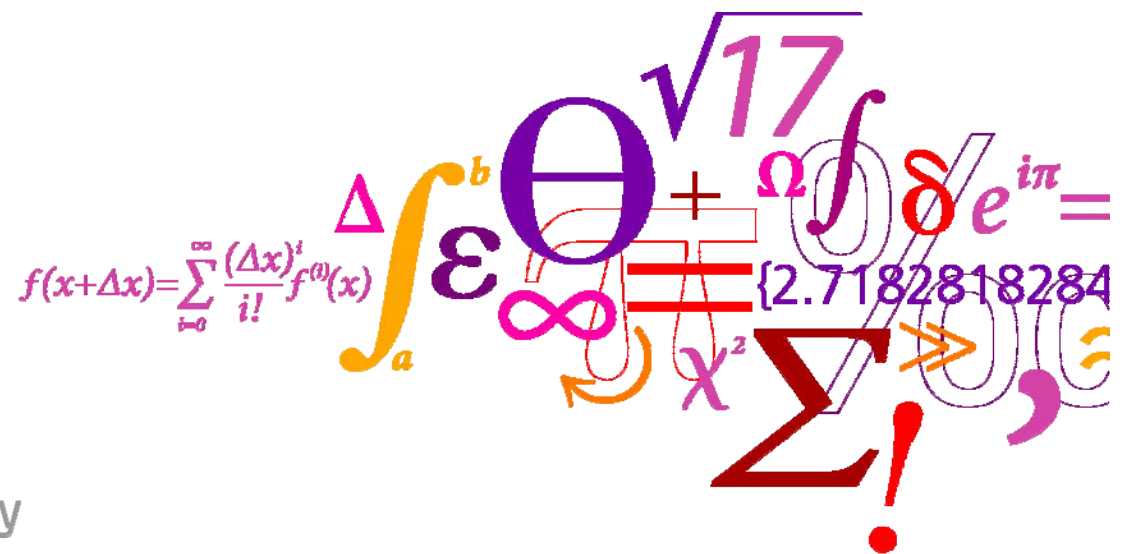# Comsol Multiphysics Simulations of Microfluidic Systems for Biomedical Applications

Maria Dimaki, Jacob Moresco Lange, Patricia Vazquez, Pranjul Shah, Fridolin Okkels and Winnie Edith Svendsen

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DTU Nanotech
Department of Micro- and Nanotechnology

Overview

- Background
- Use of Comsol
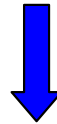- Models and Simulations
- Summary and outlook

The NaBIS group at DTU Nanotech

- Led by Associate Professor Winnie Edith Svendsen, created in 2005
- An experimental group currently concentrating on three projects
  - Microfluidic systems for cell culturing and sorting, for chromosome manipulation and analysis
  - Assembly, manipulation and applications of peptide nanotubes
  - Fabrication of 3D nanoelectrodes for cell electrical measurements

Gold microelectrodes

2.0µm

Peptide nanotube immobilized using dielectrophoresis
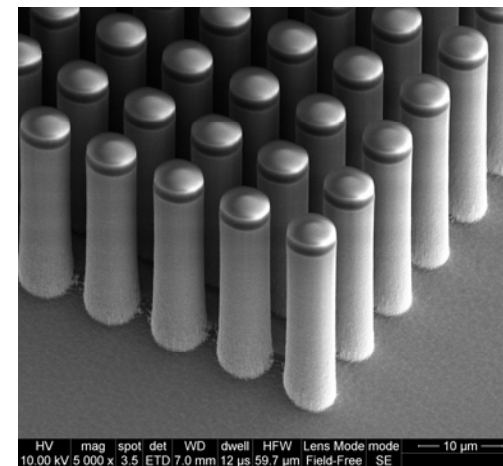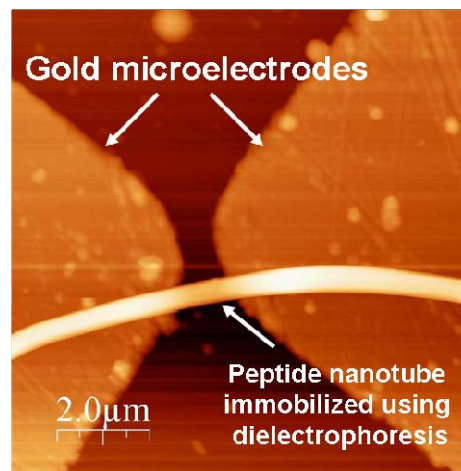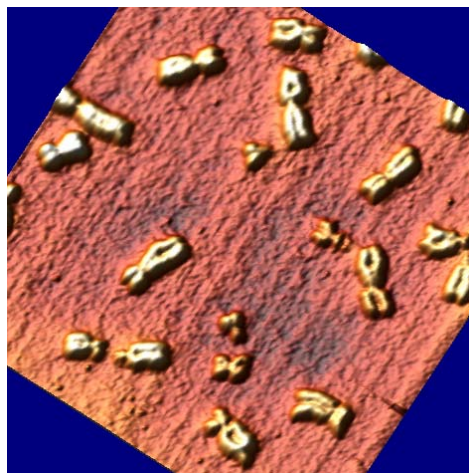
Why use Comsol?

- 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

Models and simulations

- Cell culture chamber
- Tissue culture chamber
- Herringbone mixer
- Cell sorter (pinched flow fractionation)
- Electrical fields
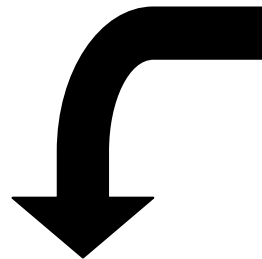
Cell culture chamber (1)

- A two level structure fabricated in PDMS
  - Bottom level: cell chamber, cells are constantly loaded and unloaded
  - Upper level: perfusion of cells with media, instant start of perfusion
- Culture area (orange): 2x2 mm
- Cells not in contact with perfusion stream → All mass transport towards and away from the cell is diffusion limited
  - Metabolic tolerance: point where consumption of nutrients is matched by the diffusion feeding
  - In close proximity to the cells the concentration of cellular products (growth factors and cytocines) is increased
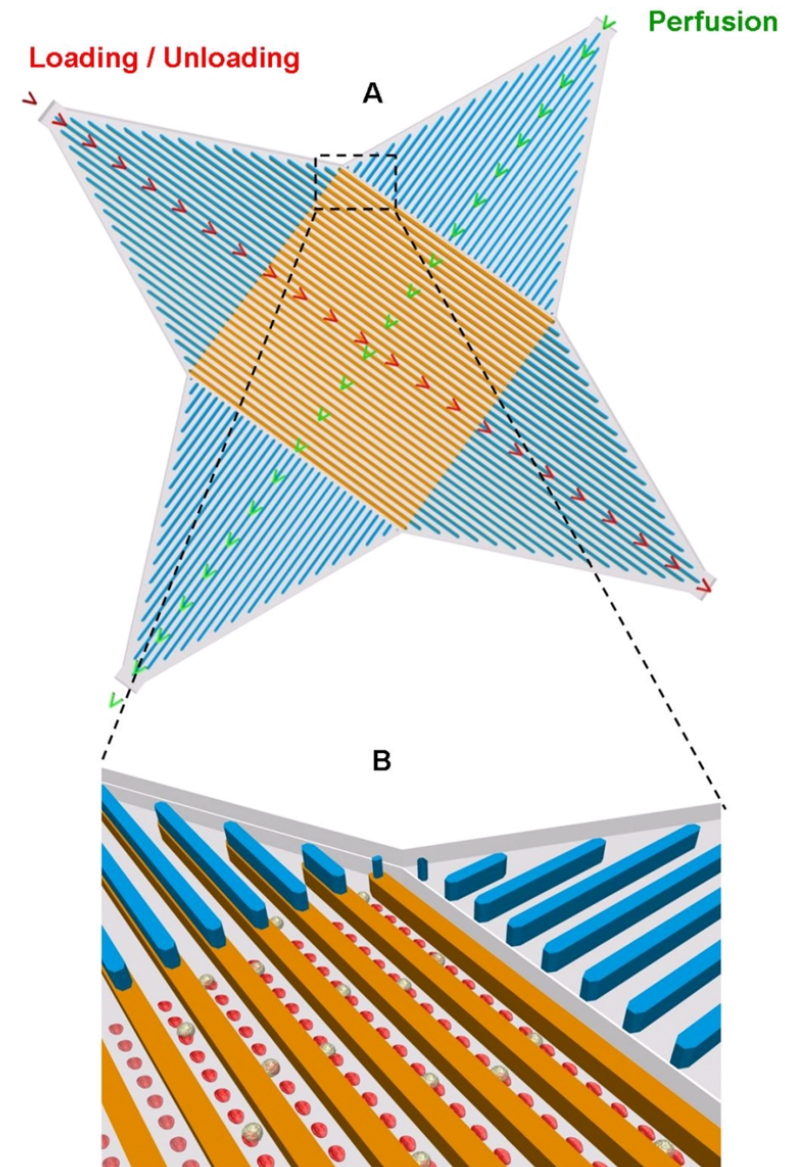

Design and simulations by Jacob Moresco Lange

Cell culture chamber (2)

- Simulations:
  - 2D simulation of the flow (and shear stress) in the grooves
  - Simulation of concentration of nutrients (oxygen and glucose) and concentration of extreted interleukin-2
  - Coupled Incompressible Navier Stokes with Convection and Diffusion for the three chemical species
  - Fluid properties (density, viscosity, permittivity) are taken to be that of water
 - Inlet velocity of 1 mm/sec

Lack of convective transport in the grooves → possible malnutrition of the cells inside the grooves

Surface: Velocity field [m/s] Streamline: Velocity field   Max: 1.512e-3
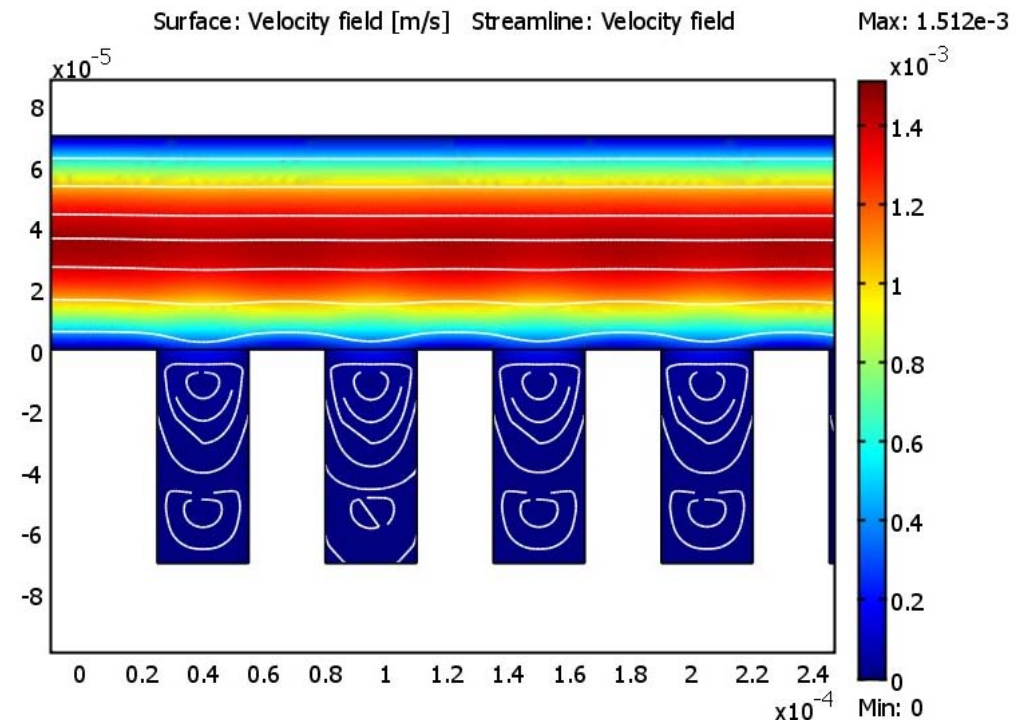
Cell culture chamber (3)

- Each groove is a subdomain consuming (for oxygen and glucose, negative reaction rate) or producing (interleukin-2, positive reaction rate) nutrients or proteins respectively
  - Values used for diffusion coefficients and consumption/production of compounds are averages of vastly differing values and are therefore to be taken as guidelines only

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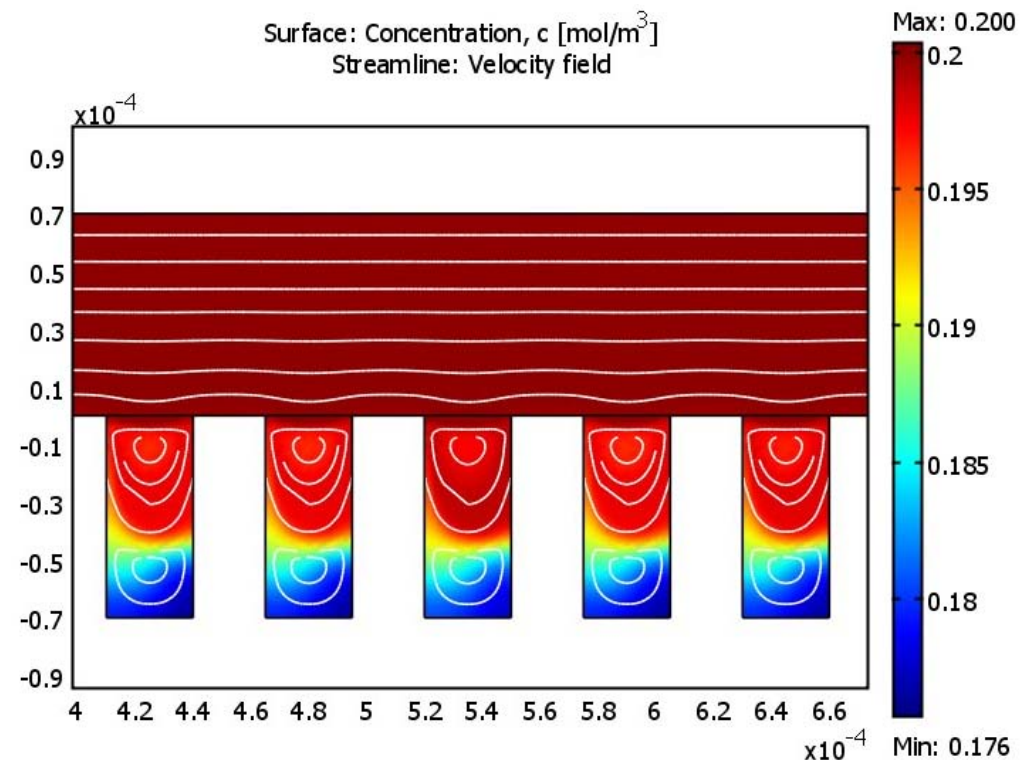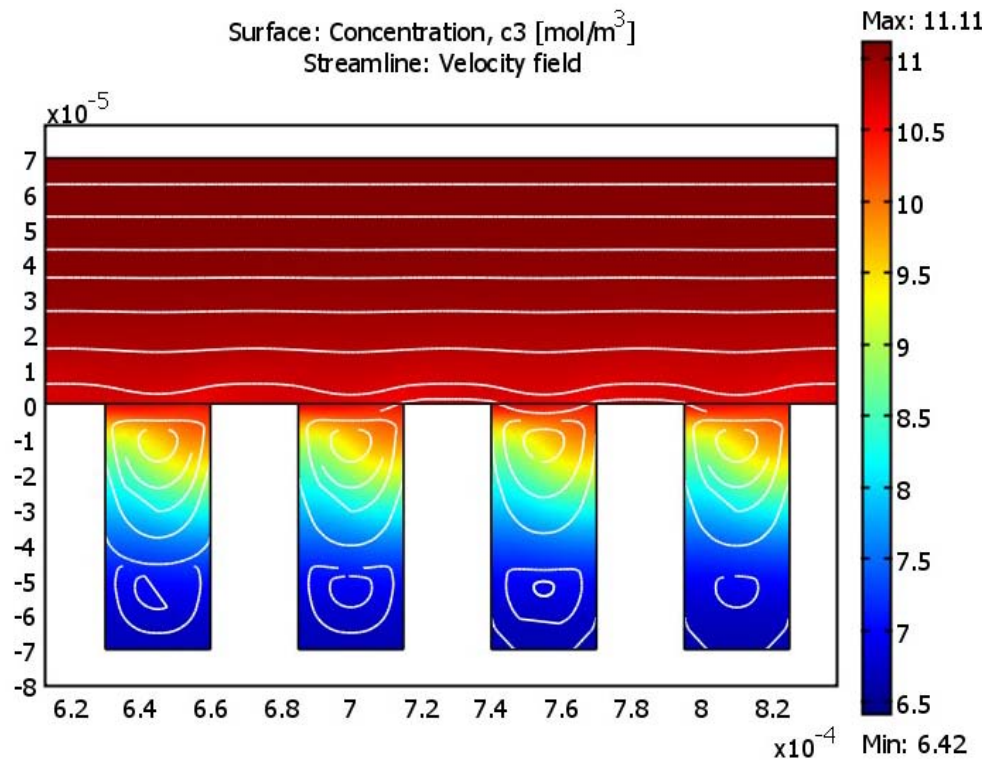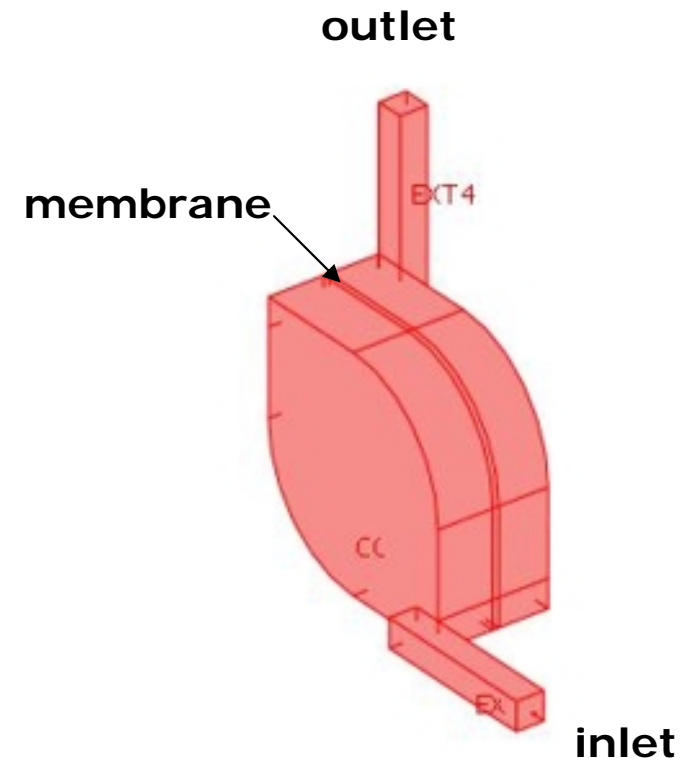
Tissue culture chamber (1)

- Membrane simulated as a subdomain with a volume force on the fluid $\mathbf{F}=-\alpha\mathbf{u}$
- α is a constant calculated by the Darcy number (dimensionless group for flow in porous media) (units $kgm^{-3}s$) = (Darcy permeability)$^{-1}$

$$Da = \frac{K}{L^2}$$

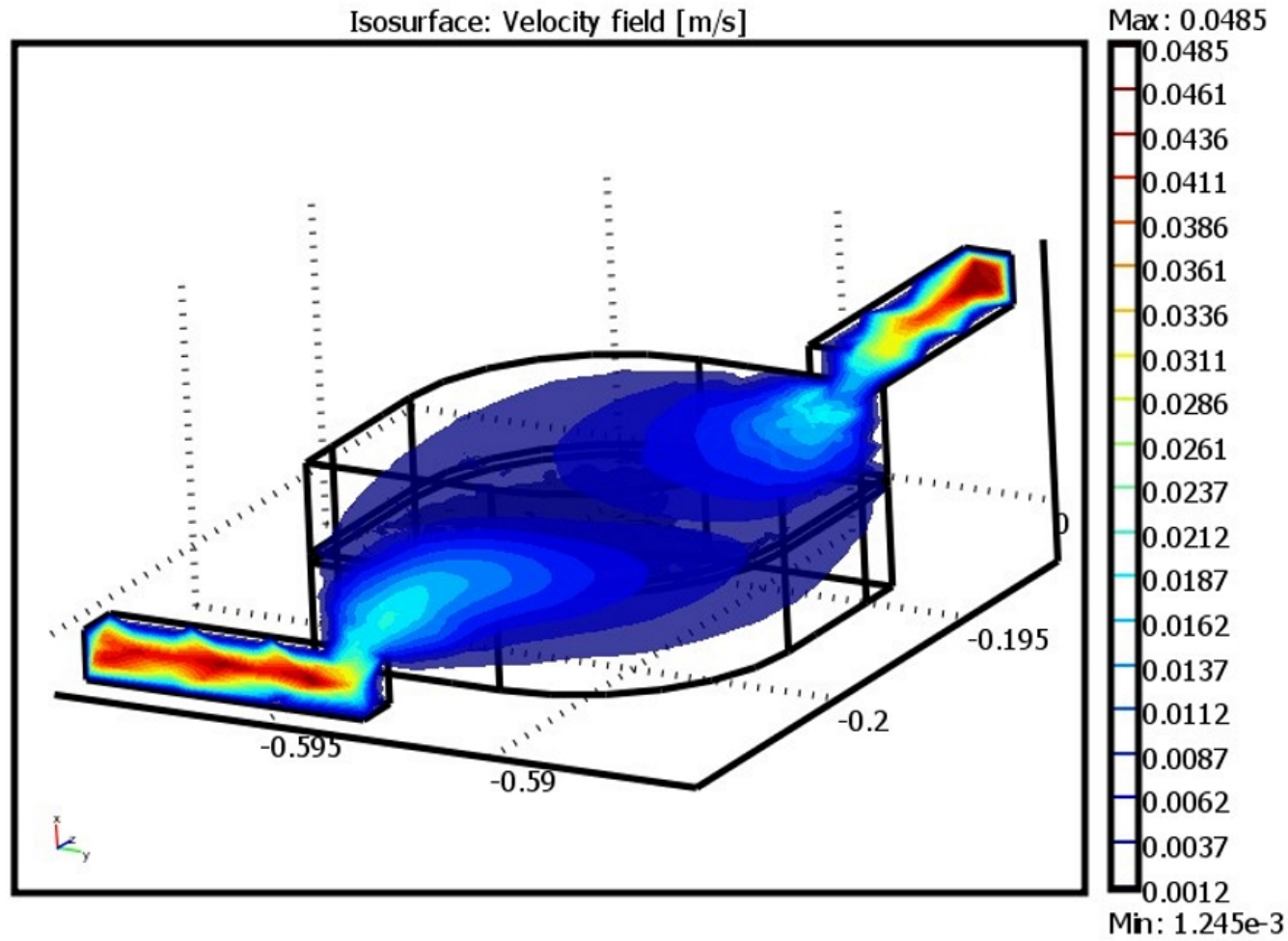$$\Longrightarrow \quad \alpha = \frac{\eta}{Da \cdot L^2}$$

$$K = \frac{\eta}{\alpha}$$

For our system α=6.25 10^5

- Rounded corners as flow is pressure driven
- Inlet and outlet in opposite corners to even out the path for the fluid marked by pressure drop

outlet

membrane

EXT4

CC

inlet

Patricia Vazquez, Fridolin Okkels

Tissue culture chamber (2)

Herringbone lyser (1)

- Based on the work by Stroock et al (2002) and Yang et al (2006)
  - Channel with grooves to improve mixing by forcing the fluid in and out the grooves in a periodic pattern
- Modified design to achieve better mixing and also investigated the effect of grooves and ridges
- The lyser is used to mix blood with water → WBC can withstand exposure to water for longer time → RBC lyse faster. Fast mixing needed to avoid damage of the WBC
- 3D simulation using Incompressible Navier Stokes coupled to Convection and Diffusion application mode
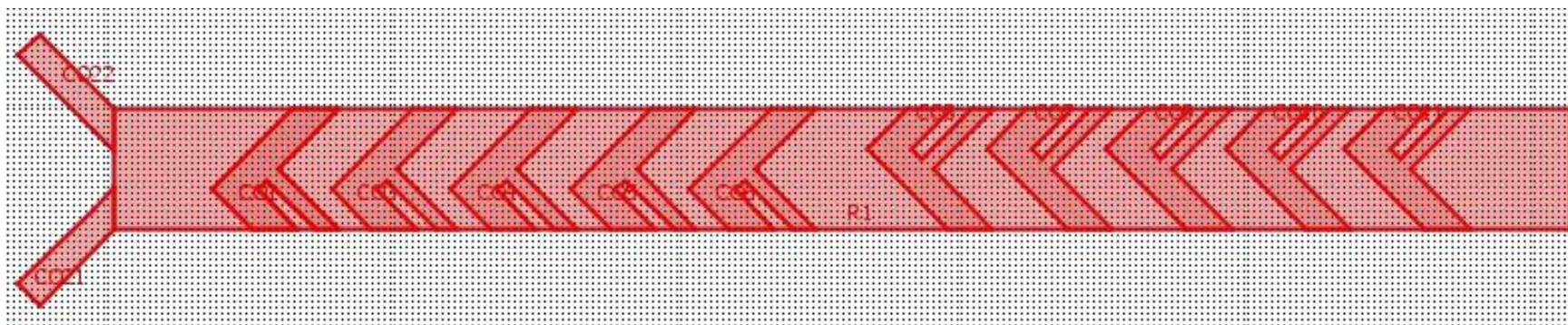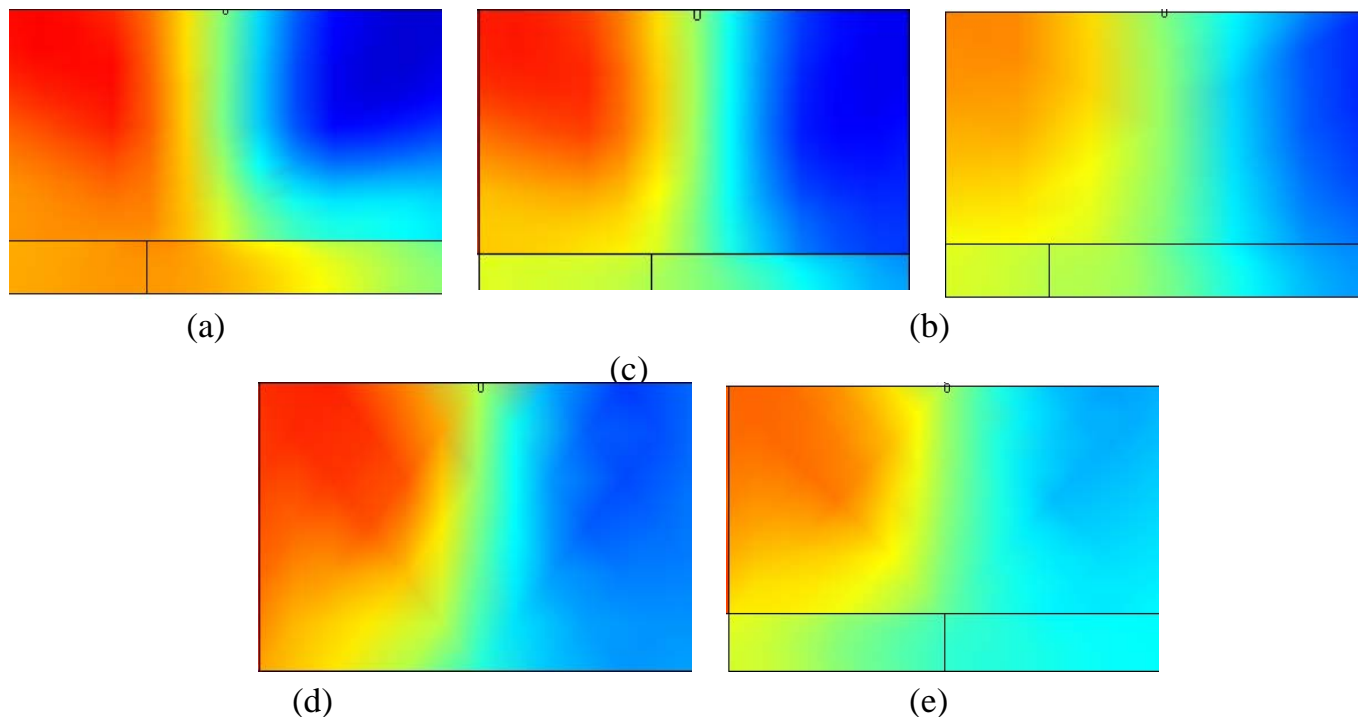

Design by Pranjul Shah

Herringbone lyser (2)

Flow direction

Grooves

Flow direction

Ridges
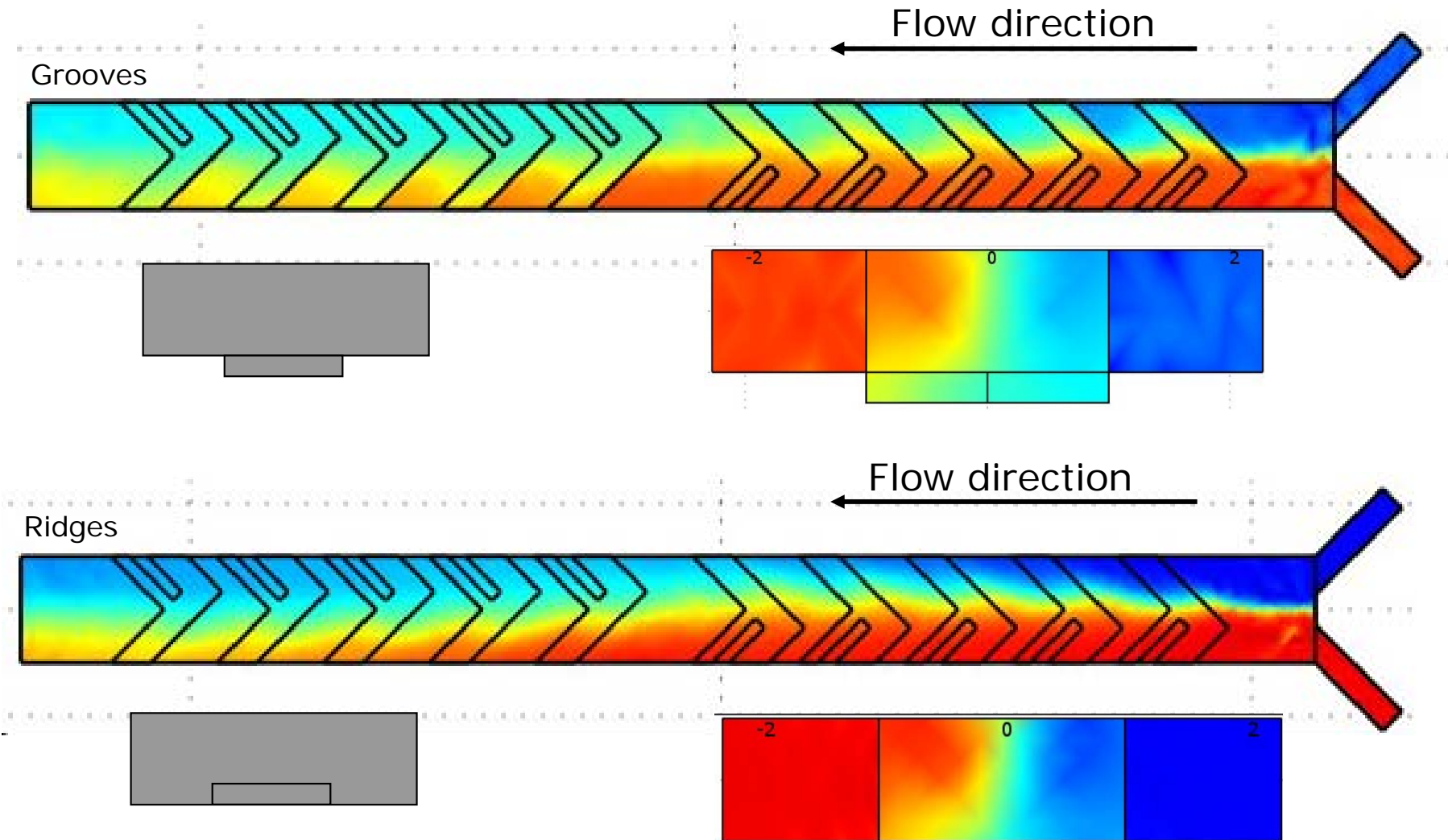
Herringbone lyser (3)

- Comparison between the best design of the Yang et all paper and a new design
  - The new design further improves the mixing. This has also been shown experimentally

(a)

(b)

(c)

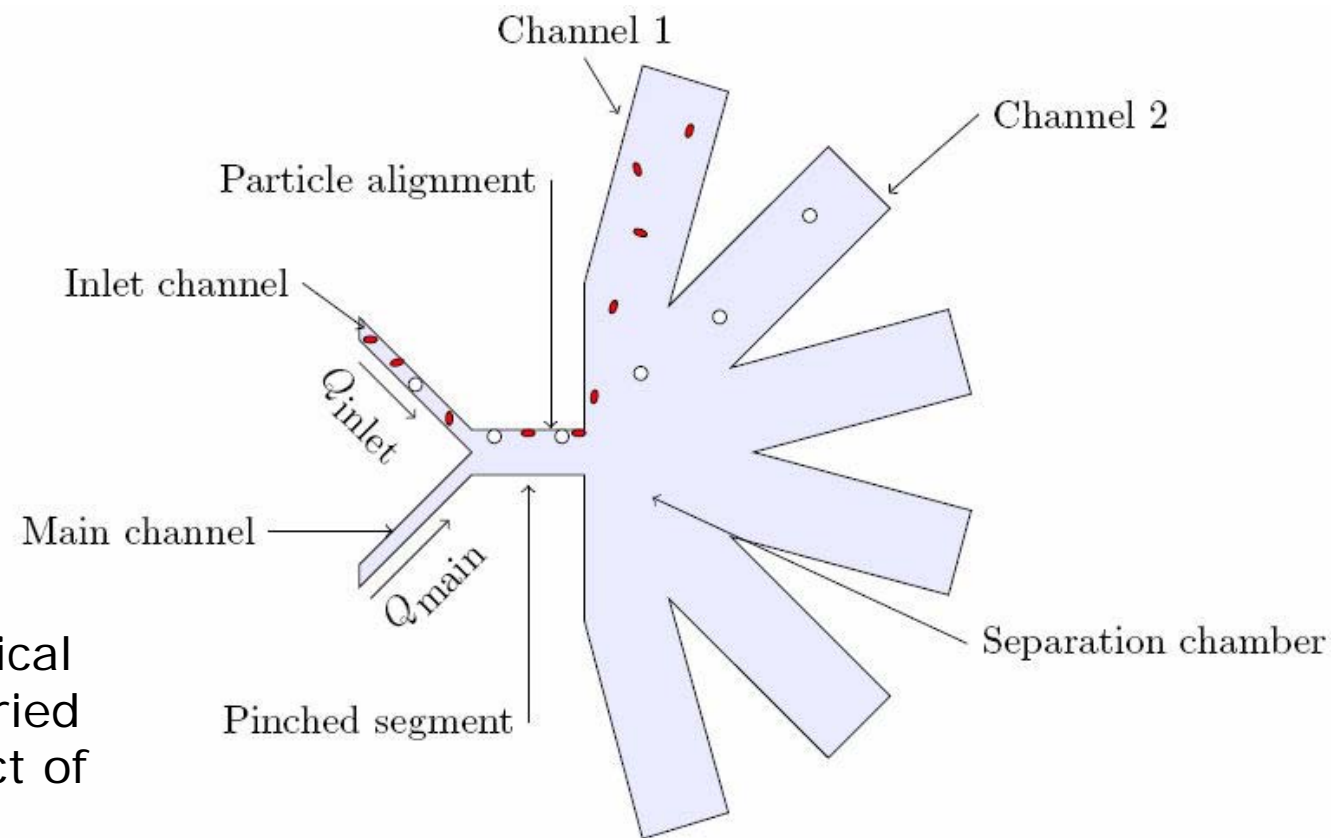(d)

(e)

Pinched flow fractionation (PFF)

- Based on the work of Yamada et al

Critical parameters

1. Inlet flow rate ratio

2. Width of pinched segment

3. Hydraulic resistance of outlet channels

Both analytical and numerical simulations have been carried out to investigate the effect of these parameters on the separation

PFF (2)

- Quasi 3D method for reducing mesh size
    - For channels of stable height h a damping term can be added to the Navier Stokes equation $\alpha(h)\mathbf{v}$. where $\alpha(h) = -12\eta/h^2$, where η is the viscosity of the fluid ($kg\ m^{-1}\ s^{-1}$)
    - Damping factor calculated by equating the flow rates from a 3D model to those of the quasi 3D (2D where Navier Stokes has the extra term)
    - The pinched segment length is set to 100 μm for the simulations
- Particles are introduced into the channels as a concentration profile. Diffusion coefficient is sent to 10^{-13} m^2/s, which covers particles with radius above 0.2 μm
- The flow rate ratio, the width of the pinched segment for a desired alignment of a particle with radius r and even the number and hydraulic resistances of the outlet channels needed can be calculated when a certain separation is desired

Theoretical modelling by Karsten Brandt Andersen, Simon Levinsen and Fridolin Okkels

PFF (3)

- By Comsol simulations the following relation between flow rate ratio and intersection width ratio has been found
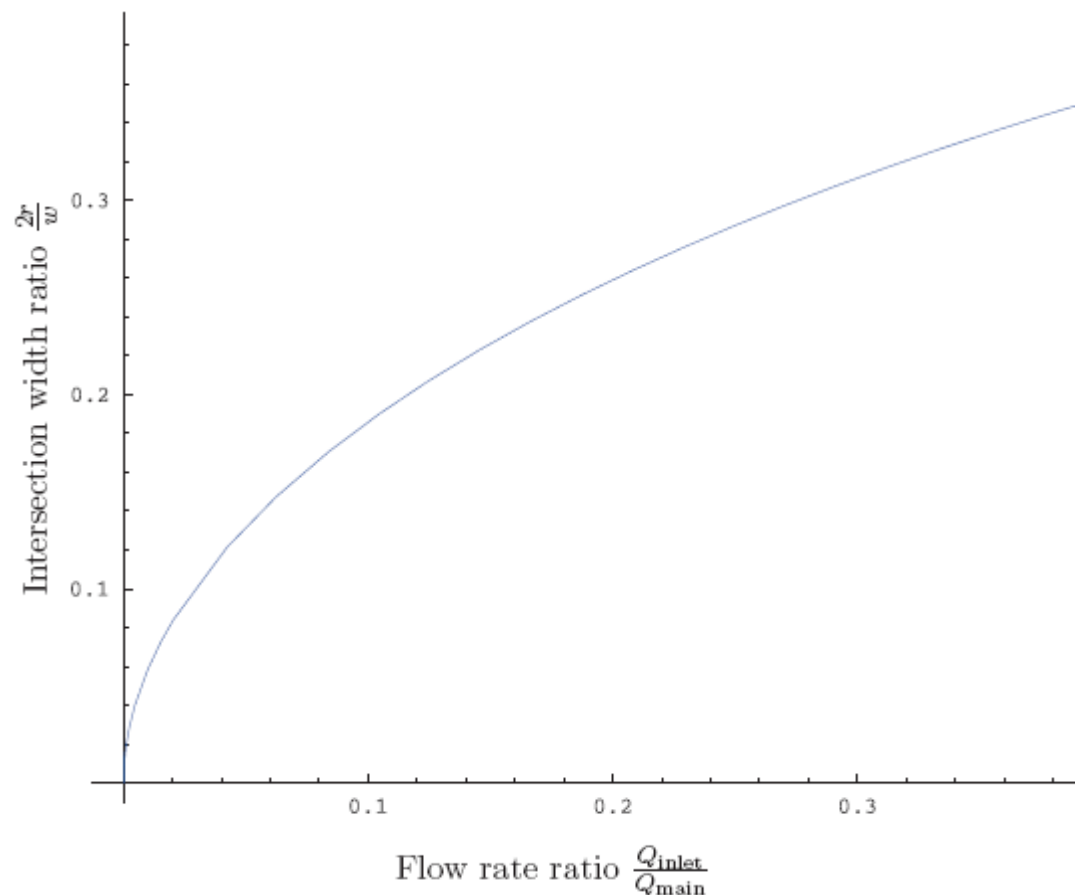
Flow rate ratios under 0.02 should not be used
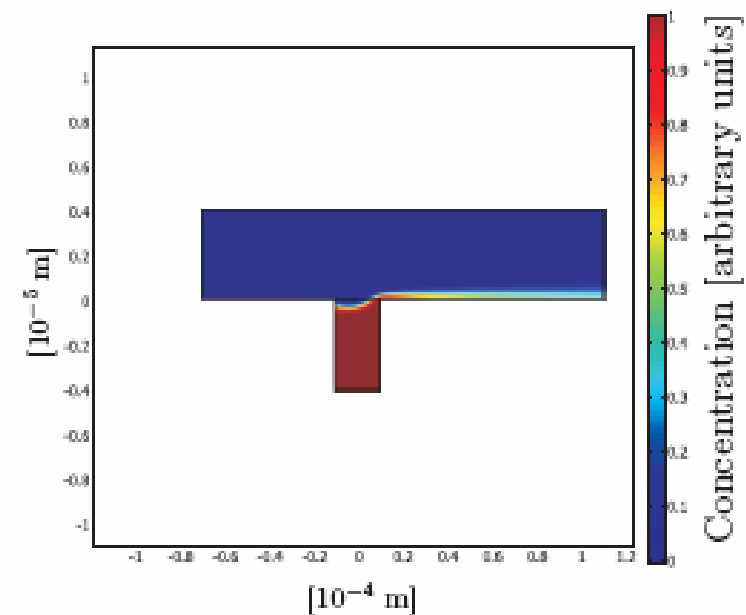
Model is also capable of controlling number of outlet channels and length ratios for desirable separation position

PFF example

- Separation of red ($r_{aver}=3.6\,\mu m$) and white ($r_{aver}=5\,\mu m$) blood cells

▶ Pinched segment width: 40 μm

▶ Flow rate ratio: 0.1

▶ 6 outlet channels

▶ $R_{hyd,\,1} = 7 \times R_{hyd,other}$

▶ Pinched segment width: 30 μm

▶ Flow rate ratio: 0.15

▶ 3 outlet channels

▶ $R_{hyd,\,2} = \frac{1}{1.1} \times R_{hyd,\,1}$

▶ $R_{hyd,\,3} = \frac{1}{16.7} \times R_{hyd,\,1}$
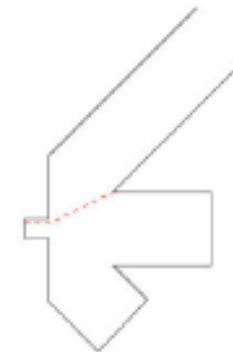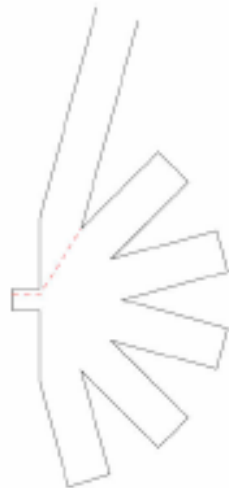
Electrical fields

- The electrostatics application mode is used for the calculation of the electric field and electric field gradient (~ DEP force) generated by microelectrodes in liquid in 3D
- Electrodes are 2D objects embedded in a subdomain
- In all boundaries we assume a normal electric field of 0. The electrodes are given the voltage boundary condition
- Subdomains are treated as water with a relative permittivity of 80.
- We are interested in the homogeneity of the electric field → gradient
  - Optimise electrode geometries for obtaining a large dielectrophoretic force
  - Find domains where the field can be said to be homogeneous, even though the electrodes are 2D in a 3D space
  - Get an idea of the temperature rise in the liquid due to the voltage
    - By means of intergrating the electric energy density in the subdomain
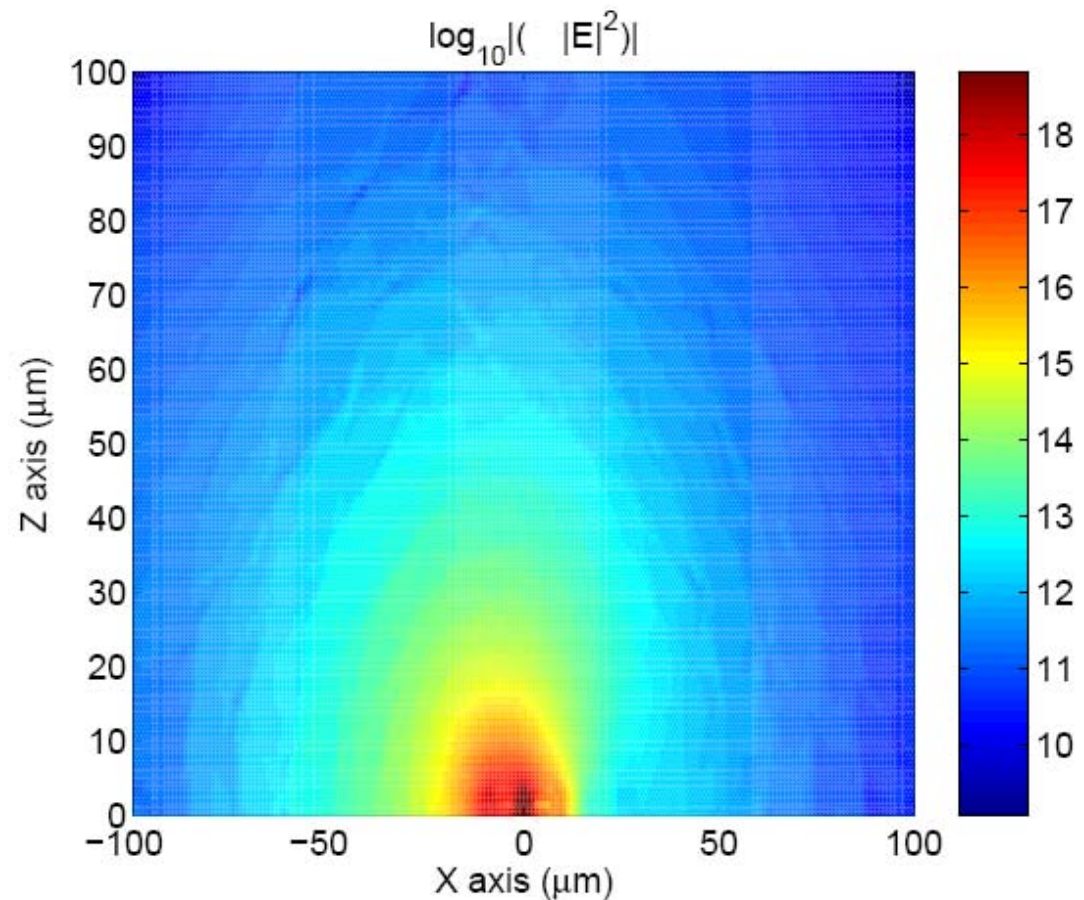
Example 1: Homogeneity of electric field

- We would like to use electrodes at the bottom of a channel to create a relatively homogeneous field in order to measure the electrophoretic mobility of chromosomes.

Slice: log10(sqrt(diff(normE_dc^2,x)^2+diff(normE_dc^2,y)^2+diff(normE_dc^2,z)^2))
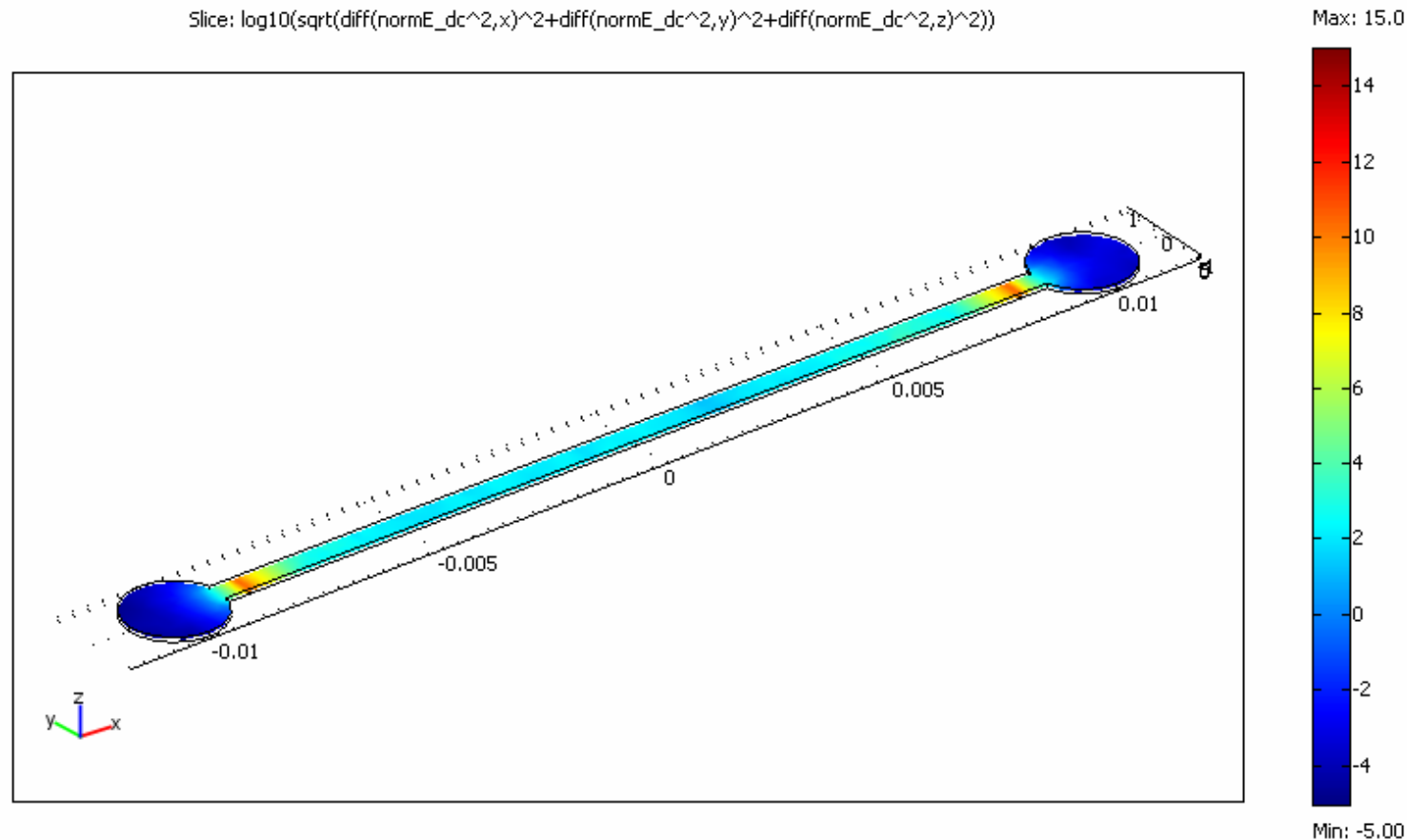
# Example 2: Inhomogeneity of electric field

- Here we would like a large electric field gradient in order to catch peptide nanotubes with dielectrophoretic forces
  - As a first approximation we ignore the effect of the nanotubes on the electric field

$\log_{10}|(\ |E|^2)|$

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Other work

- Bumper arrays: separation of particles of different sizes. Comsol is used to calculate the velocity field and matlab is used to calculate the particle movement
  - Assume that particles don't disturb the flow
  - Only round particles are treated

- Temperature rise and resulting fluid flow due to heating
  - Relevant for DEP simulations when a larger voltage is used
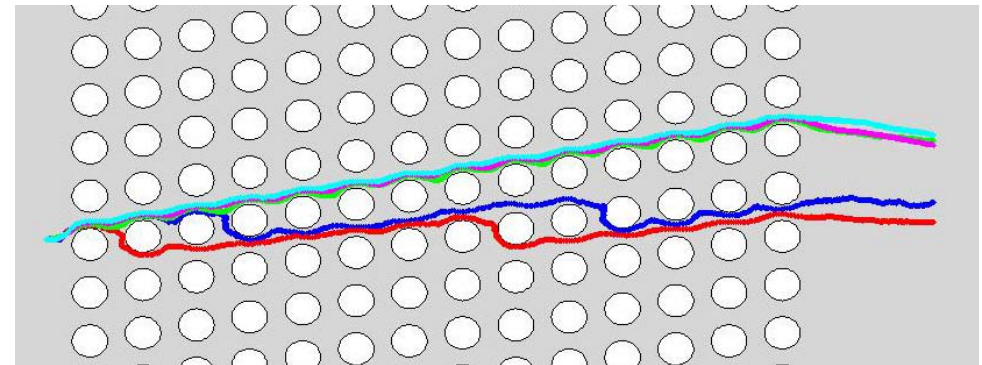
Summary and outlook

- Comsol as a tool for design and optimisation
- Several models presented dealing with applications in microfluidics and particle separation
- Several issues still remain:
  - Heating in liquids
  - Incorporation of particles in the simulations
  - Tissue oxygen consumption and perfusion for the tissue cell chamber
  - Experimental validation of the PFF simulations

Thank you for your attention

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