Comsol Multiphysics Simulations of Microfluidic Systems for Biomedical Applications

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Abstract: The need of fast, easy and cost-effective analysis of blood samples as well as our understanding of the functionality of cells in general and neurons in particular are two rather pressing issues in the modern world. Both of these can be addressed by functional lab-on-a-chip systems, which have been designed and optimized for specific analyses. This paper deals with the design of several different systems for cell growth (cell culture chambers), cell sorting (mainly by pinched flow fractionation and bumper arrays) and cell lysing (either by mixing or by electric field), as well as systems for the manipulation of human chromosomes by electrical forces (dielectrophoresis and electrophoresis). We have used COMSOL Multiphysics in order to simulate fluid flow and electrical fields inside various structures and used the results to optimize their design.

Keywords: microfluidics, dielectrophoresis, pinched flow fractionation, bumper arrays

1. Introduction

A good design is imperative when producing and testing lab-on-a-chip systems for blood or genetic analyses, as it assists the quick transfer from the design board to production. Comsol Multiphysics simulations offer a great way to optimize the performance of a structure before it is produced, thus significantly reducing the time between testing and production.

The Nano-Bio Integrated Systems group (NaBIS) at the Department of Micro- and Nanotechnology at the Technical University of Denmark is developing lab-on-a-chip systems for biomedical applications. There are two main focus areas: 1) Handling of blood samples with the goal of the analysis of chromosomal translocations on chip and 2) Monitoring the activity of neurons, both electrically and chemically, either in brain slices or as individual cells. For both applications there is a need for a functional culture chamber, optimized for the particular purpose. For the blood handling activities the chamber should be capable of easy unloading of the cells so that other devices for cell trapping, lysing, sorting etc can use the cells. For the neurons and brain slices, that need to stay in culture for extended periods of time, it is important to design the chamber so that the dead volume is minimized, for the long term survival of the slices.

For genetic testing only the white blood cells containing chromosomes are needed, and therefore they need to be separated from the other cells in the blood. For this purpose we have simulated a pinched flow fractionation system based on work by [1] as well as a rapid and selective cell lysing system based on herringbone structures, as was also presented in the work of [2].

Finally we use Comsol to simulate the electric fields produced by microelectrodes for the purposes of electrophoresis and dielectrophoresis of chromosomes, fibers, nanotubes and cells.

2. Description of the various systems

In this section the various designs are going to be presented together with the simulation parameters.

2.1 Cell culture chambers

Two micro cell culture chambers (μCCC) have been designed and simulated. The first is a design targeted at blood cells and is shown in figure 1. The chamber is on two levels, where both levels are used for entrance and extraction of cells while the top level is used for perfusion of the cells with nutrients. There are two important issues with this design. First, it is important that the perfusion flow will not disturb

the cells settled on the bottom level. This gives some restrictions for the depth and width of the grooves where the cells are situated. Secondly, the cells at the bottom need nutrients to survive, so it is important that the rate of nutrient consumption of the cells at the bottom of the chamber is at least as big as the rate of nutrient diffusion to the cells. We have for the simulation purposes only looked at glucose and oxygen consumption.

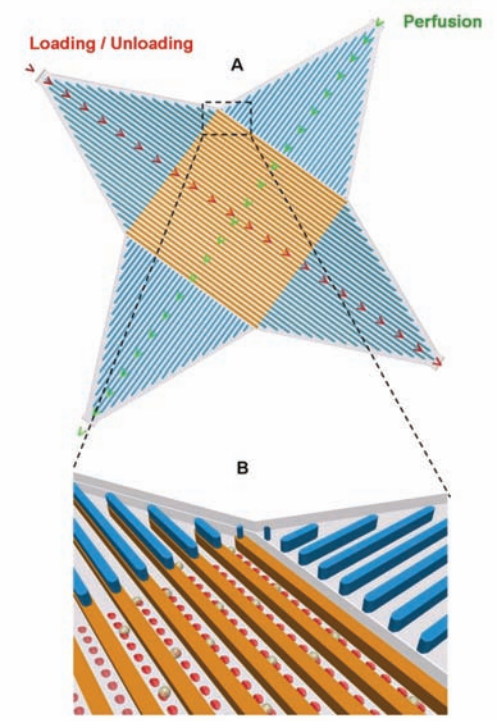

Figure 1. Illustration of the working principle. A) The chip has a central culture area (orange) in which the cells can be loaded (red arrows). The culture area can then be perfused perpendicular to the grooves (green arrows), thereby keeping the cells in the groove. B) Close up showing how the inlet for perfusion is kept above the grooves.

The second cell culture chamber is targeted towards brain slices and consists of a large chamber with a membrane of 200 μm thickness with pore size of 0.45 μm placed in the middle. The brain slice is placed on top of the membrane and the media enters the chamber from the bottom, moves through the membrane and exits from the top outlet (figure 2). In this design it is important to see that there is no dead volume and that the membrane does not affect the flow through the chamber. The subdomain representing the membrane has been simulated using the Darcy law for convection in porous media. Thus a term of a volume force on the liquid given by $\vec{F} = -\alpha \cdot \vec{u}$ has been added, where $\vec{u}$ is the velocity of the fluid and α is a constant that can be roughly calculated using the Darcy number. This is given by $Da = \frac{\eta}{\alpha \cdot L^2}$, where η is the viscosity of the fluid and L is the characteristic length scale of the system. By assuming a value for the Darcy number equal to 10^{-4} and the typical length scale of our system to be 4 mm, we can calculate that $\alpha = 6.25 \cdot 10^5$ kg m^{-2} s^{-2}.

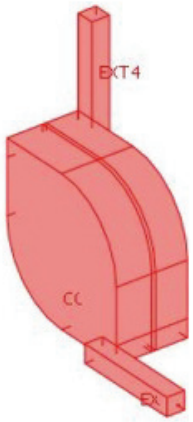

Figure 2. An image of the chamber for tissue culture The fluid enters from the bottom inlet and exits from the top outlet. The thin membrane in the middle is where the tissue is placed.

The basic idea behind the design is to place both the inlet and the outlet in opposite corners, so that the path for the fluid marked by the pressure drop is evened out in the whole chamber. Since the flow is driven by the derivative of the pressure, which cancels out in sharp corners, we have chosen to design the chamber with round corners, in order to minimize the dead volume.

2.2 Cell lysing

Herringbone mixers have been reported by Stroock et al. to mix fluids in microfluidic

systems with laminar flow profiles [2]. Yang et. al. suggested modifications to the Stroock design which showed considerable improvement in the mixing efficiencies [3]. Considering the complex processes involved in fabricating these structures, simulations were the key to finding the optimal mixing pattern. We simulated various herringbone designs (e.g. figure 3), either made with grooves or ridges, in order to compare the achieved mixing and to study the principles of herringbone mixers. The simulations were conducted using the Multiphysics Incompressible Navier Stokes mode coupled with the conduction and diffusion application mode. To evaluate the results we used plots of the concentration as well as the vorticity of the subdomain.

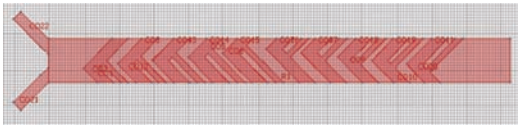

Figure 3. One example of a herringbone lyser.

2.3 Cell sorting

The pinched flow fractionation method for cell sorting was treated theoretically both analytically and numerically with Comsol. The concept behind this method has been described in [1]. Briefly, two inlet channels, one containing the cells and the other the buffer, meet in a narrow segment called the pinch and the cells are forced towards the wall of the segment by the fluid flow in the second inlet channel. Depending on the position of the center of the cell at the edge of the pinch, the cell will follow a particular streamline away from the pinch into a broad channel before entering an outlet channel. Clever design of the pinched segment and outlet channels and the choice of inlet velocities determine the dimensions of the cells able to be sorted.

We have used a quasi 3D method to reduce the number of mesh elements by simulating the finite height h of the channels as an artificial damping force. In this way, a 3D model can be solved in 2D by adding an extra term in the Navier-Stokes equation:

$$\rho\left(\partial_t \mathbf{v} + (\mathbf{v}\cdot\nabla)\mathbf{v}\right) = -\nabla p + \eta\nabla^2\mathbf{v} + \alpha(h)\mathbf{v} \qquad (1)$$

where $\alpha(h)$ is the damping factor. It can be shown that this factor is given by $\alpha(h) = -\frac{12\eta}{h^2}$. A simplified geometry shown in figure 4 has been used in order to investigate the effect of different parameters on the sorting efficiency both analytically and numerically.

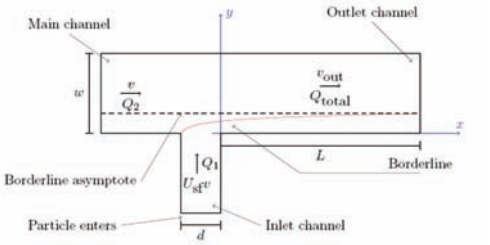

Figure 4. The simplified design for the pinch flow simulations, conducted both analytically and numerically.

The cells in the numerical simulations are treated as a concentration entering from the inlet channel in figure 4. The diffusion coefficient is set as $D = 1\times10^{-13}$ m^2/s, which covers particles with a minimum radius of 0.2 μm.

2.4 Electrical fields

Several designs of electrodes in microfluidic channels have been simulated for various purposes. We are mainly interested either in producing large field gradients for the purposes of dielectrophoretic motion or in having homogeneous fields in order to investigate the electrophoretic motion of biological particles. In both cases the Electrostatics application mode has been used, as we assume that the liquid in the channels is not conducting.

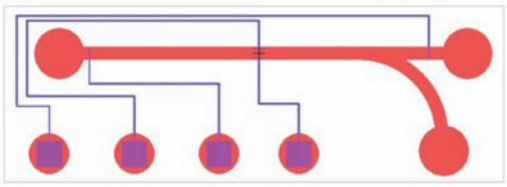

Figure 5. Top view of channel with incorporated electrodes for electrophoretic manipulation.

Figure 5 shows one such geometry used to check the homogeneity and strength of the produced electric field. The electrodes are simulated as embedded surfaces on the bottom surface of the channel. All other boundaries are set as zero charge boundaries.

3. Results

In this section some of the obtained simulation results will be shown.

3.1. Cell culture chambers

The velocity field in a small part of the two level cell culture chamber is plotted in figure 6 top, while the concentration of glucose in the grooves is shown in figure 6 bottom.

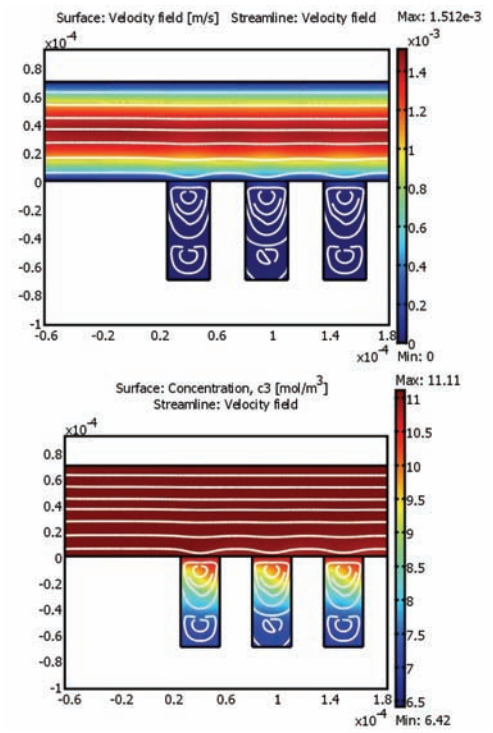

Figure 6. Top: the velocity profile in the chamber down the grooves. Bottom: concentration of glucose in the grooves.

Here it can be seen that the flow is not entering the grooves and thus any transport of nutrients to the cells in the grooves will be by diffusion. By making assumptions about the rate of oxygen and glucose consumption per cell we can set the reaction rate for each nutrient in the grooves subdomain, as the cells take up most of the groove space and it can thus be assumed that the entire groove is consuming nutrients.

Figure 7 shows the velocity field in the neuron chamber. Cross-sectional plots of the flow reveal that the velocity field through the membrane is at a minimum, exactly as it is expected. These results have also been verified experimentally.

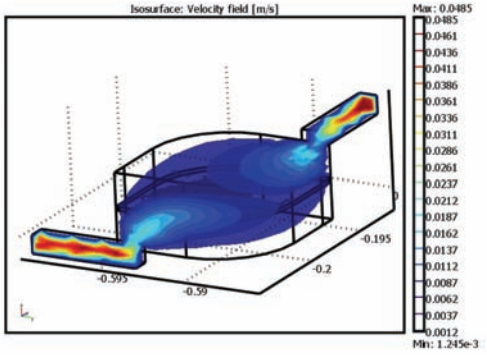

Figure 7. Isosurface plots of the velocity field in the neuron chamber. The velocity through the membrane is reduced in relation to the velocity under and on top of the membrane.

3.2 Cell lysing

Three designs were simulated: the original design from [2] as well as two more designs aimed towards faster mixing. The mixing of two fluids in terms of concentration was simulated. The vorticity of the flow in lysers with a grooved configuration is shown in figure 8.

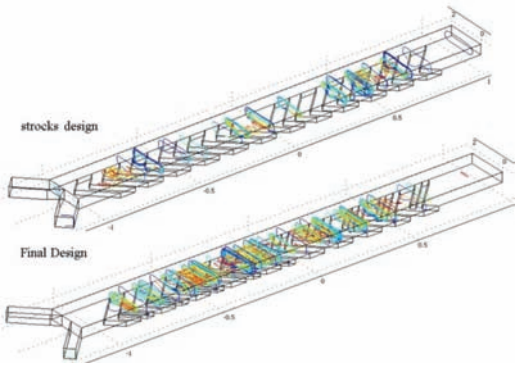

Figure 8. Vorticity in the design of reference [2] and the design of figure 3.

The vorticity is the rotation of the velocity and as such gives an idea of how the fluid is moving inside the channels. In the modified designs the vorticity is moving continuously thus improving the mixing. The results were verified by mixing of two liquids died with different colours. The modified design shown in figure 3 was able to totally mix the two liquids faster than the design of reference [2].

3.3 Cell sorting

Comsol simulations involved solving the Navier-Stokes equation in quasi 3D, as described in section 2.3, coupled with the convection and diffusion application mode in order to backtrace streamlines at edges of outlet channels and thus find the separation distances possible with the various designs. Many simulations were done and compared with analytical results and thus optimal parameters were found. Figure 9 shows the results achieved analytically on the structure of figure 4 and validated numerically with Comsol for a number of configurations.

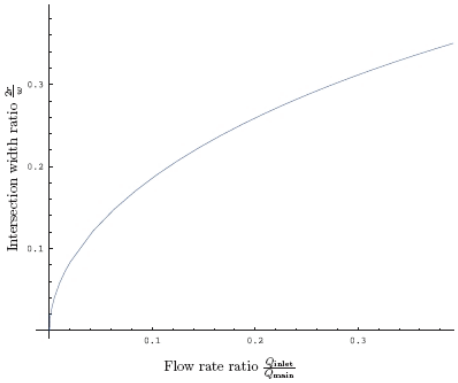

Figure 9. This figure is used to determine the flow rate ratios between the inlet- and main flow rate, that will insure the alignment of particles with radius r in a pinched segment of width w.

3.4 Electrical fields

Depending on the purpose of the structures we are interested in generating either a large field gradient or a very homogeneous electric field. In the case of a simple channel with electrodes at the bottom surface at the inlet and outlet, we are interested that the field in the middle is homogeneous. Plotting the field and the gradient of the square field $\nabla \mathbf{E}^2$, which is proportional to the dielectrophoretic force, we can get a good idea about the homogeneity of the field. In figure 10 it can be seen that the field is quite homogeneous in the center of the channel but rather inhomogeneous close to the electrodes. This is expected, as the electrodes are planar and not as high as the channel, but there is also a significantly large region between the electrodes where the gradient is minimal and therefore no dielectrophoretic motion is to be expected.

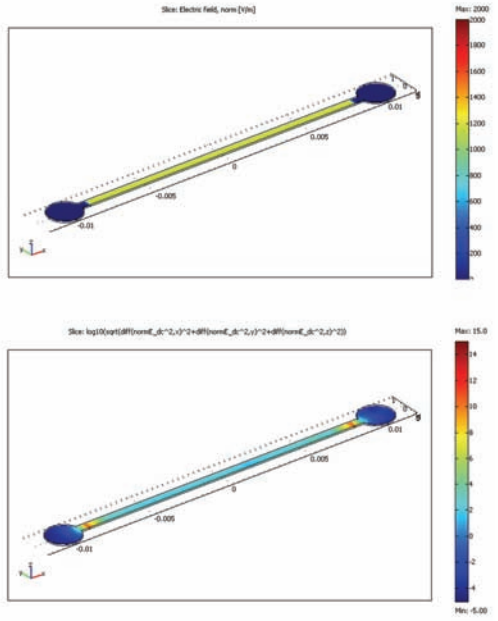

Figure 10. The electric field (top) and the logarithm of the electric field square gradient (bottom) for a simple straight channel with electrodes after the inlet and before the outlet. The field is homogeneous and therefore the structure is suitable for electrophoretic mobility experiments.

4. Discussion

In the above a number of models for microfluidic systems aimed towards biological applications have been presented. We have used Comsol Multiphysics mainly for validation of designs to be produced for experiments, like in the case of the cell culture chambers, but also as a design tool itself, for deciding the best parameters for a certain structure, e.g. the pinched flow fractionation system or the electric field simulations, e.g. when deciding on optimal

electrode shape for achieving large field gradients.

Experiments were conducted with the herringbone lysers and the various electric field structures. These validated the Comsol results of a fast mixing process for the modified design of figure 3, as well as the electrophoretic motion of charged species achieved by the structures of figure 10. Moreover, experiments with electrodes of various shapes validated Comsol results of larger field gradients for sharper electrodes.

In the future we plan to validate the Comsol simulations for the blood cell culture chamber and the pinched flow fractionation system.

5. Conclusions

Comsol Multiphysics is a valuable and powerful tool when designing non trivial lab-on-a-chip structures, as it helps identify key parameters for the performance of the device and optimize them. A few examples demonstrating this functionality were presented above.

6. References

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