Modeling and validation of particle and cell manipulation in Lab-On-a-Chip devices

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Theses of the PhD Dissertation

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1. Introduction and aims

The rapid development of biomedical diagnostics enabled new methods and tests, which could not be performed before due to their high cost and time requirement. Point of Care (POC) tests offer short turn-around times and often require minimal volume of specimen. Manipulating this small amount of fluids is a challenging task. The field of microfluidics is focusing on fluid manipulation in the microchannels to overcome difficulties such as mixing or separation of particles. The process of scaling down transport channels leads to the change of surface to volume ratio, thus surface forces become dominant over the volume forces. The aim of microfluidics research is to understand and exploit the emergent hydrodynamic effects in the microchannels.

Numerical modeling aids the design and optimization of Lab-on-a-Chip (LOC) devices. **The aim of my research was to understand complex hydrodynamic effects emerging from the microchannel geometries and external fields focusing on the transport of particles in these systems.** Integrability of microfluidic units into complex bioanalytical systems is a key issue. Sample preparation units are one of the most important parts of these LOC microsystems, the complexity of the task is well demonstrated by the fact that commercial microanalytical systems often require off-chip sample preparation carried out in large laboratory equipment. Present work focuses on the design and analysis of microfluidic systems integrating basic sample preparation functions. ***Behavior of formed elements in micromixers and microseparators*** was studied with respect to their optimal geometry and operating parameters.

The herringbone ***micromixer*** was integrated as a sample preparation unit into a photonic biosensor. The aim of the design process was to find an optimal width and arrangement of the herringbones resulting in satisfactory mixing of particles and molecules on the given transport path leading to the biosensor.

Zweifach-Fung bifurcation based microchannels aim to separate blood plasma from the formed elements of blood. Introducing geometric singularities and cascaded arrangement of daughter channels to the microsystem the aim was to improve its efficiency by creating and rebuilding cell-free layers along the channel walls exploiting the effect of lateral migration. The resulting plasma may serve as input sample for a nanopore-based analytical system.

Plasma separation in autonomous microfluidic chips is a challenging task. In cooperation with the MTA-ELTE Immunology Research Group an AB0 blood type analyzing system was designed which incorporates sample preparation steps on-chip. The aim of my work was to be able to ***mimic immobilized red blood cells on the channel surface*** introducing randomly arranged obstacles and to study the behavior of free-flowing cells in the vicinity of these obstacles with varying surface coverage values.

Separation of the particles from the fluid can be carried out by trapping and releasing. A Microfluidic Magnetic Separation (MMS) system was designed to ***trap magnetic microparticles in the microchannel***. The aim of the study was to be able to create a multidomain model of the system calculating particle trajectories considering the magnetic field created by a neodymium permanent magnet and the fluid dynamics as well. The device is intended to be a part of a possible microfluidic aptamer selection (M-SELEX) system. The optimal

operating flow rate regime of the devices is also to be found ensuring continuous washing of the beads without loss of selection.

Separation of particles by their size is a key sample preparation step often required for biomedical tests. Our microseparator design aimed to separate pollens by their size for a possible air pollution monitoring system application. Separation method was ***based solely on hydrodynamic effects***, utilizing Pinched Flow Fractionation (PFF) and lateral migration created by geometric singularities. The system was studied with respect to possible operational flow rate regimes. The usability of the microchannel for separation of particulate elements of blood was also studied taking shear rate values in consideration.

2. Methods

COMSOL Multiphysics finite element modeling (FEM) software was used for the ***modeling of microchannels***. Stationary laminar flow field and transport of diluted species were considered in case of the micromixers. Convergence study was carried out on one mixer unit due to the possibility of false, numeric diffusion using periodic boundary condition on the concentration field. Time dependent model of particle tracing was calculated based on stationary flow field modeling result. Postprocessing of exported data – mixing efficiencies, phase portrait and Lyapunov exponent – were calculated with MATLAB software. Microfluidic chips were realized using multilayered soft lithography in polydimethylsiloxane (PDMS). Qualitative and quantitative verification of the diffusion model was made using dye and fluorescent human serum albumin (HSA), respectively. Trajectory based model result were verified using yeast cells under dark field microscopy imaging. Experimental data was obtained and postprocessed with ImageJ software.

In case of the passive hydrodynamic separators a stationary laminar flow was considered, and a time dependent particle tracing problem was solved. Postprocessing of the model results of the ***Zweifach-Fung bifurcation based cascaded blood plasma separator*** was done in MATLAB software calculating the width of cell-free regions along the channel. Dark field microscopy and yeast cells were used for the experiments. Intensity data was recorded by ImageJ software.

The ***microchannel separating particles by their size*** was modeled similar to the Zweifach-Fung bifurcation based chip. Two different particle diameters with uniform distribution were set at the channel inlet. Distribution of the two particle

populations and overlap values were calculated with MATLAB during the postprocessing. A mixed solution of two particle populations with different fluorescent labels was introduced to the microchannel and a multichannel image was created using two fluorescent filter sets. Intensity data of the particles was also recorded with ImageJ software and compared to the model results.

Random geometries of ***immobilized red blood cells*** were generated with MATLAB and then stationary laminar flow and time dependent particle tracing were calculated in COMSOL Multiphysics. Postprocessing of the particle trajectory data was made in MATLAB calculating the cumulated lateral movements of the red blood cells (RBC).

In case of the ***active microfluidic magnetic separation*** (MMS) device the stationary magnetic field of the neodymium permanent magnet was calculated first. Stationary laminar flow and time dependent particle tracing were calculated afterwards hierarchically, inheriting the results. Distribution of particles over the permalloy grid was calculated with MATLAB. Experimental validation was carried out using paramagnetic microparticles and their intensity on the grid was recorded with ImageJ.

3. Novel scientific results

I. I have created concentration and trajectory based finite element models which are able to describe chaotic micromixers, to quantify their efficiency and to optimize their geometry. I have validated the modeling result with experimental setups.

I.a. I have compared the concentration and the trajectory-based modeling approach with respect to their performance and computational resource requirements. I have demonstrated that numerical diffusion can be avoided using trajectory-based modeling which requires lower mesh resolutions to obtain an equally adequate result. I was able to get the same accuracy of the model results having lower computational cost and the calculation time was shortened by nearly an order of magnitude. [F4, K9]

The effect of numerical diffusion demands higher mesh resolutions in concentration-based modeling. Low mesh resolution results in false mixing and information loss. This effect, however, can be avoided by trajectory-based modeling, and obtain the same approximate results at a lower computational cost (Figure 3.1.). Mesh convergency study was carried out on one mixing unit using periodic boundary condition for the concentration, so that higher mesh resolution (with 7 500 000 elements) could be set for the subset without the need for creating the fine mesh for the whole channel. Calculation time was 3796 s for the mesh accepted (with 0.5% error) for concentration-based modeling, however the trajectory-based model required only 411 s to converge. Running time hence was shortened by nearly an order of magnitude maintaining the same quality of results. While concentration-based models cannot differentiate between

molecule populations, the trajectory model defined by me is able to label and follow each particle individually along the channel.

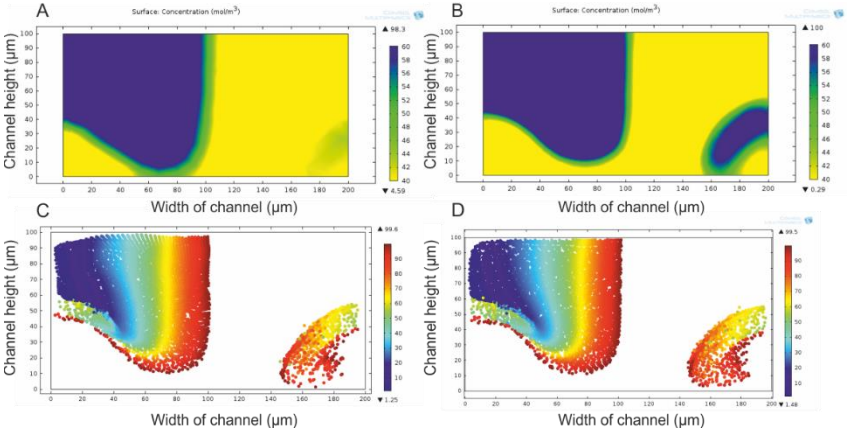

Figure 3.1. – Concentration distribution and Poincaré map at the outlet in case of the lowest (A, C) and the highest (B, D) computational mesh resolutions. Concentration modeling with low mesh resolution results in significant information loss, trajectory model however is less sensitive to the mesh resolution (13% deviation in the case of the best and the worst resolutions). [F4]

I.b. I have optimized the geometry of asymmetric herringbone chaotic micromixer to achieve more efficient mixing. I have shown that mixing efficiency is dependent on the width and number of herringbones by mixing units and demonstrated that efficiency can be doubled even with less mixing cycles over the studied parameter sets. [F1-F4, K1-K9]

Preliminary studies of the herringbone micromixer parameters were not focusing on optimal herringbone width and their optimal number by mixing cycles. I have created six different mixer geometries to study these parameters with three different herringbone widths. Mixing efficiency was evaluated by two different

quantitative measure – particle distribution ratio in the two channel halves (Table 3.1.) and the Lyapunov exponent. I have created an outline of Poincaré sections to get a qualitative comparable picture about particle distribution at the outlet (Figure 3.2.). Best mixing was achieved with the 40/5/4 geometry with 0.4526 efficiency index consisting of 40 µm width herringbones, 5 herringbones per mixing unit and 4 mixing cycles. Based on the results I have stated that using wider and more herringbones by mixing units mixing can be improved even with less mixing cycles. The improvement was twofold in the case of the worst and the best mixing efficiency.

Table 3.1. – Mixing efficiency in case of different herringbone parameters.

Name	30/4/6	30/6/4	35/4/5	35/5/4	40/4/5	40/5/4
Efficiency	0.1984	0.2105	0.2998	0.3655	0.4513	0.4526

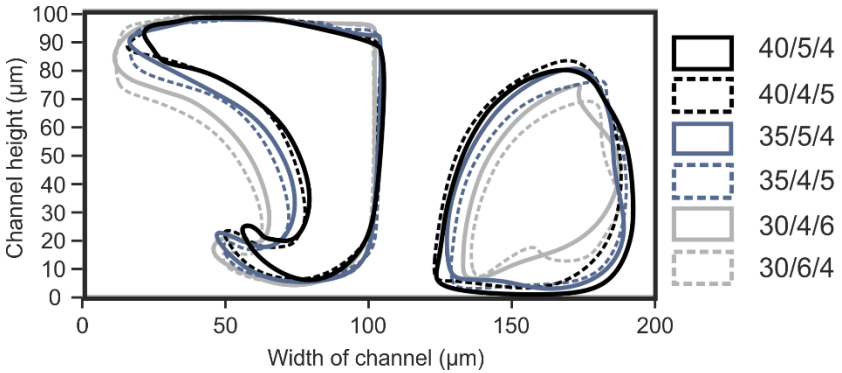

Figure 3.2. – Comparison of different herringbone parameters. Outline of the particle populations on the left and the right channel sides demonstrates the mixing results. The area on the left side is shrinking and the right side is growing with the increasing mixing efficiency. [F4]

I.c. I have validated simulation results by molecular diffusion and particle mixing experiments in microchannels realized by multilayered soft lithography in polydimethylsiloxane. I have stated that the trajectory model is able to describe microfluidic systems quantitatively with less computational cost. [F1-F4, K1-K9]

I have designed experiments to validate diffusion-based and trajectory-based simulation results. Diffusion-based model results were compared to experimental results qualitatively and quantitatively, using dye and HAS, respectively. I have recorded the intensity distribution of the fluorescent labeled molecule and compared it to modeled concentration distributions at the channel outlet. (Figure 3.3.). Modeled and measured results agreed well. To verify trajectory-based model results I have used a solution of yeast cells with dark field microscopy imaging. Intensity values at the channel outlet were recorded and compared to the modeled particle distribution (Figure 3.4). Intensity distribution at the outlet differed slightly from the modeled particle distribution. The lack of the expected peak intensity, however, can be explained by nonlinear dependence of the dark field intensity on the quantity of yeast. A dip is caused by less scattered light getting into the aperture due to the increased amount of yeast which could be expected considering the model results.

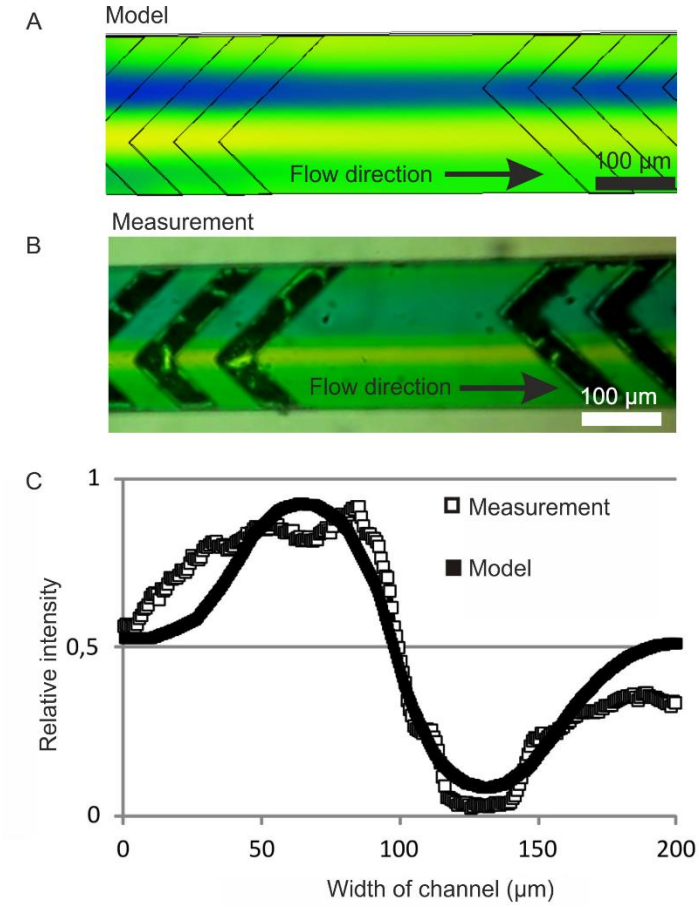

Figure 3.3. – Qualitative and quantitative comparison of modeled (A) and measured (B) molecule distributions. Comparing recorded relative intensities to the modeled concentration values the results are in a good agreement.

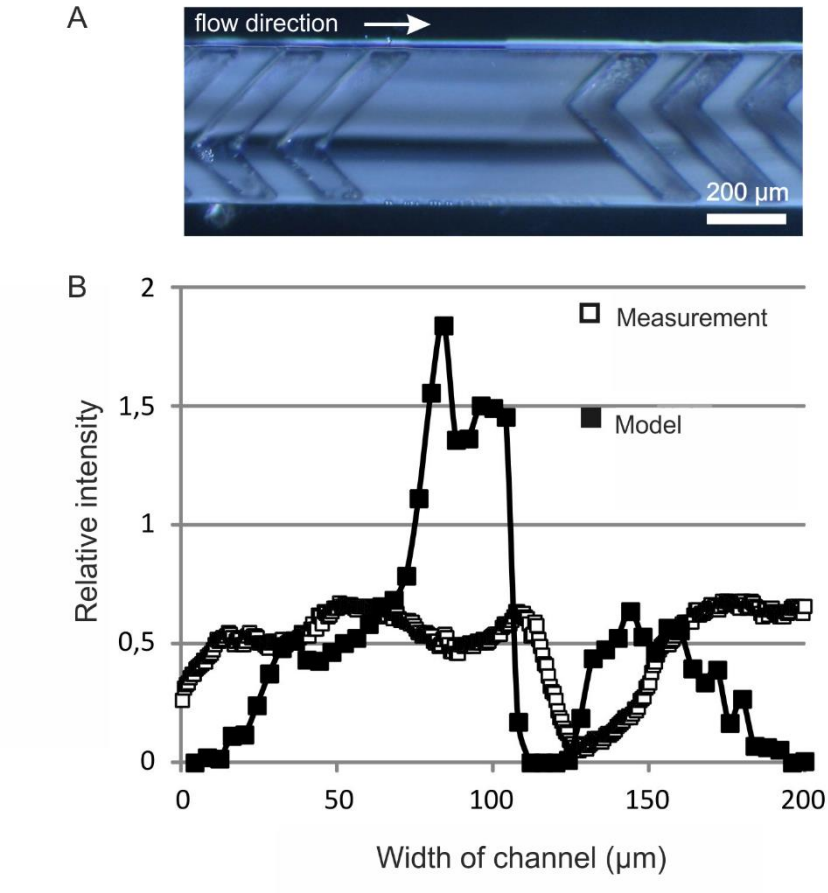

Figure 3.4. – Validation of the trajectory model with yeast using dark field microscopy (A). Recorded intensities (B) are in a good agreement with the thinning of yeast, however peak intensity is missing due to light scattering properties of the microscopy. [F4]

II. I have studied the parameter dependence of complex microfluidic separation systems using trajectory-based modeling. Based on the modeling and the experimental results I have proposed an optimal structure of the application-oriented devices.

II.a. I have demonstrated that by introducing cascaded geometric singularities into the Zweifach-Fung effect-based microfluidic separation channel efficiency of blood plasma separation can be improved without lowering the purity. Based on the calculations and experimental results I have demonstrated that the proposed geometry is able to create and maintain a cell-free layer at the channel wall. [F5, K10, K11]

I have assessed six microchannel geometries in order to study their complex hydrodynamic behavior –focusing particularly on vortex generation – and to study their possible blood plasma efficiency (Table 3.2.). Particle tracing was used to study the dependence of the width of cell-free layer on the inlet flow rate. I have found that optimal separation occurs in low flow rate regimes (0.5-2 µl/s) (Figure 3.5.). With the experiments I confirmed, that different flow rate regimes lead to different vortex generation scenarios in the singularities (Figure 3.6.). All geometries were able to create cell-free layers during the experiments, the model, however underestimated its width in case of the 2^{nd} and the 4^{th} geometries. Difference between model and measurement results can be explained by blocked daughter channels. Experiments confirmed the existence of the optimal flow rate regime (Figure 3.7.)

Table 3.2. – Effect of geometry on the plasma yield

	1st geometry	2nd geometry	3rd geometry	4th geometry	5th geometry	6th geometry
Geometry						
Yield	0.4 %	1 %	1.1 %	1.1 %	1.4 %	2.3 %

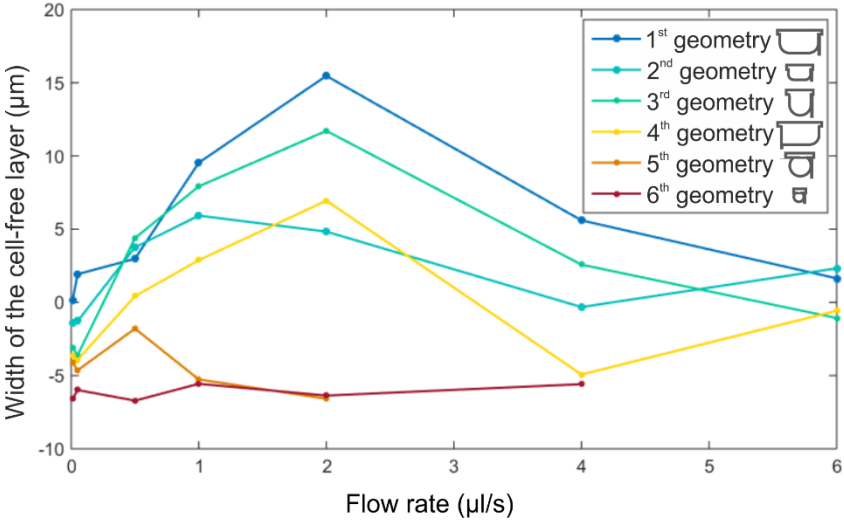

Figure 3.5. – Dependence of the width of cell-free layer width on the flow rate. Separation is optimal in the 0.5-4 µl/s flow rate regime.

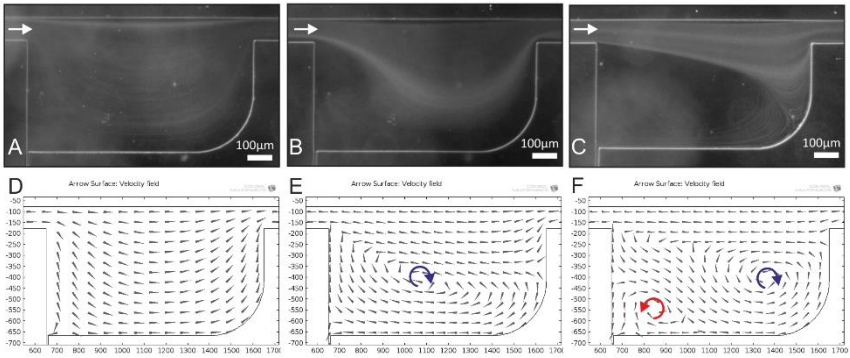

Figure 3.6. – Measured (A-C) and modeled (D-F) flow fields at the broadening of the channel with different flow rate values. Development of vortices is demonstrated and confirmed by experiments. [F5]

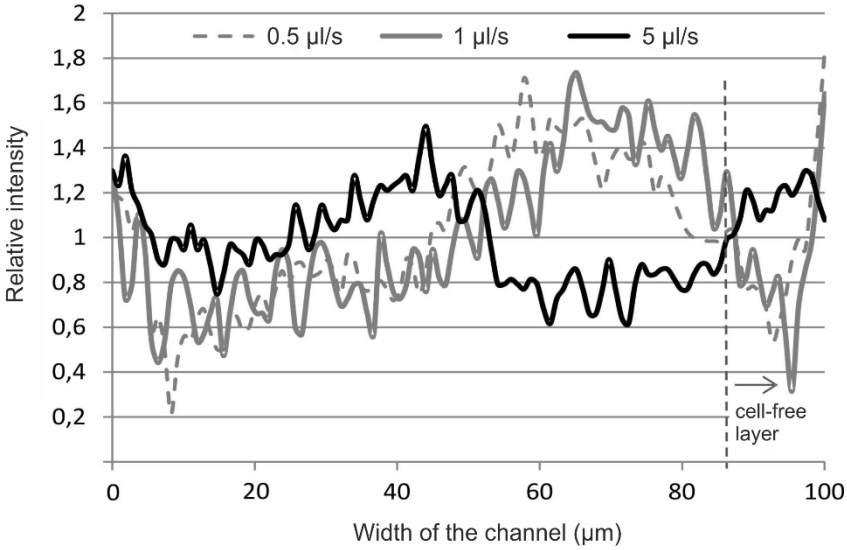

Figure 3.7. – Cell-free layer at the outlet of the microchannel with varying flow rates. At 5 µl/s flow rate value a cell-free layer has not developed. [F5]

II.b. I have created an active time dependent three-dimensional model of a microfluidic magnetic separation (MMS) device, where transport of magnetic particles can be controlled actively by magnetophoresis. The model contains the properties of the magnetic materials and deals with different size ranges and physical principles hierarchically. I have demonstrated the principle and operation of magnetic particle separation with experiments. [F6, K12, K13]

The aim of this work was to trap magnetic particles in a given section of the microchannel. Magnetic field created by neodymium permanent magnet was locally enhanced by Fe-Ni structures deposited at the bottom of the channel. Particle trajectories were calculated with respect to magnetic field and fluid dynamics. I have studied the effect of the Fe-Ni grid on magnetic particle distribution with respect to the flow rate. I have found that in the 0-4 μl/s flow rate regime trapping of the particles were complete, in the 4-20 μl/s flow rate regime 51-91% of particles were trapped (Table 3.3.). Based on the experimental results I have reported successful trapping and releasing of the particles (Figure 3.8.). In higher flow rate regimes, the particles lined up with the horizontal lines of the grid when leaving the separation area which was predicted well by the model.

Table 3.3. – Ratio of trapped particles with varying flow rate values

Flow rate (μl/s)	4	6	8	10	12	14	16	18	20
Ratio of trapped particles on the grid	96%	83%	75%	68%	62%	59%	55%	52%	49%
Ratio of trapped particles in the microchannel	100%	91%	80%	71%	65%	62%	58%	56%	51%

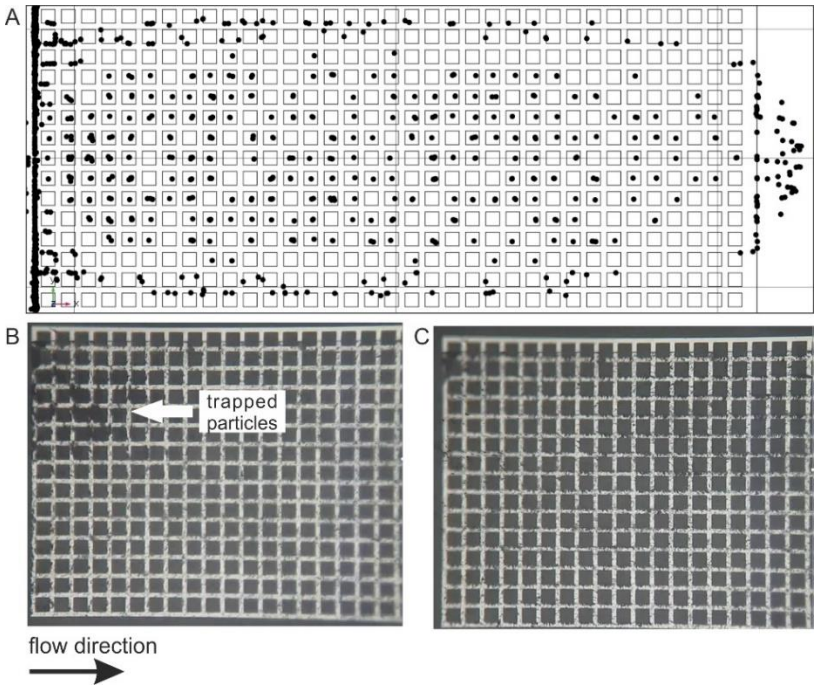

Figure 3.8. – Trapping of the magnetic particles in the numerical simulation in the case of 3.5 μl/s flow rate (A). The effect is stronger neard the leading edge of the Fe-Ni grid, particles with higher velocities are distributed along the channel length. Microscopic image of trapping and releasing of particles (B).

III. I have demonstrated the applicability of trajectory models for designing LOC systems.

III.a. I have created a model of immobilized red blood cells to study their hydrodynamic effect on free-flowing red blood cells. I have shown the modified velocity field created by the obstacles and their ability to retain free-flowing cells leading to blood plasma separation. I have proposed an optimal channel height value which is near the double of the height of the immobilized cells. [F7]

I have created a MATLAB script which generates randomly distributed obstacles in the microchannel representing the immobilized red blood cells (RBCs). I have described hydrodynamic effect of these obstacles by calculating cumulated lateral movements of the particles. I have compared the cumulated lateral movements of particles released from 2-6 μm height in the 7 μm high microchannel and proposed the parameter of 5 μm channel height and 2 μm release height. Using these parameters, I have studied the velocity fields above the obstacles, and I have found that they hydrodynamic effect is present even 2 μms above them (Figure 3.9.). Cumulated lateral movements of the particles were calculated in case of 0-40% surface coverages and an optimal coverage at 30% was found (Table 3.4.). Modeling results were compared to experimental results and a significant dependence of cumulated side movements on surface coverage was found (Figure 3.10.). Modeled and measured results agreed well, blood plasma separation caused by the immobilized cells were confirmed in the microchannel.

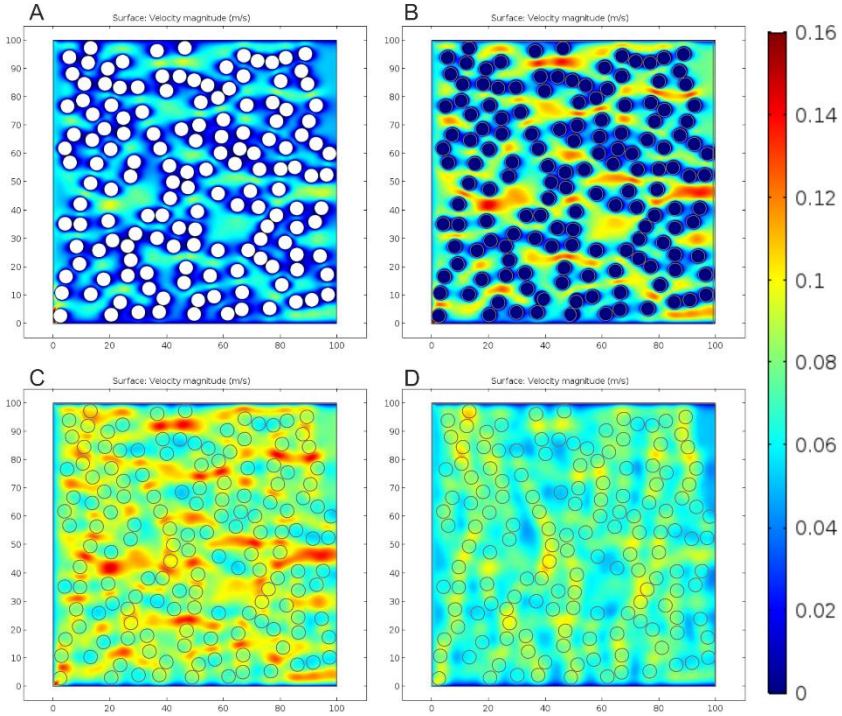

Figure 3.9. – xy planes of velocity magnitudes in the case of 5 µm channel height at 1 µm (A), 2 µm (B), 3 µm (C) and 4 µm (D). The hydrodynamic effect of the attached cells is notable even at 2 µm height over the 2 µm high obstacles.

Table 3.4.– Cumulated lateral movements of RBCs with different surface coverages

Surface coverage	0%	10%	20%	30%	40%
Cumulated lateral movement	2.93 µm	15.94 µm	24.33 µm	41.52 µm	20.28 µm

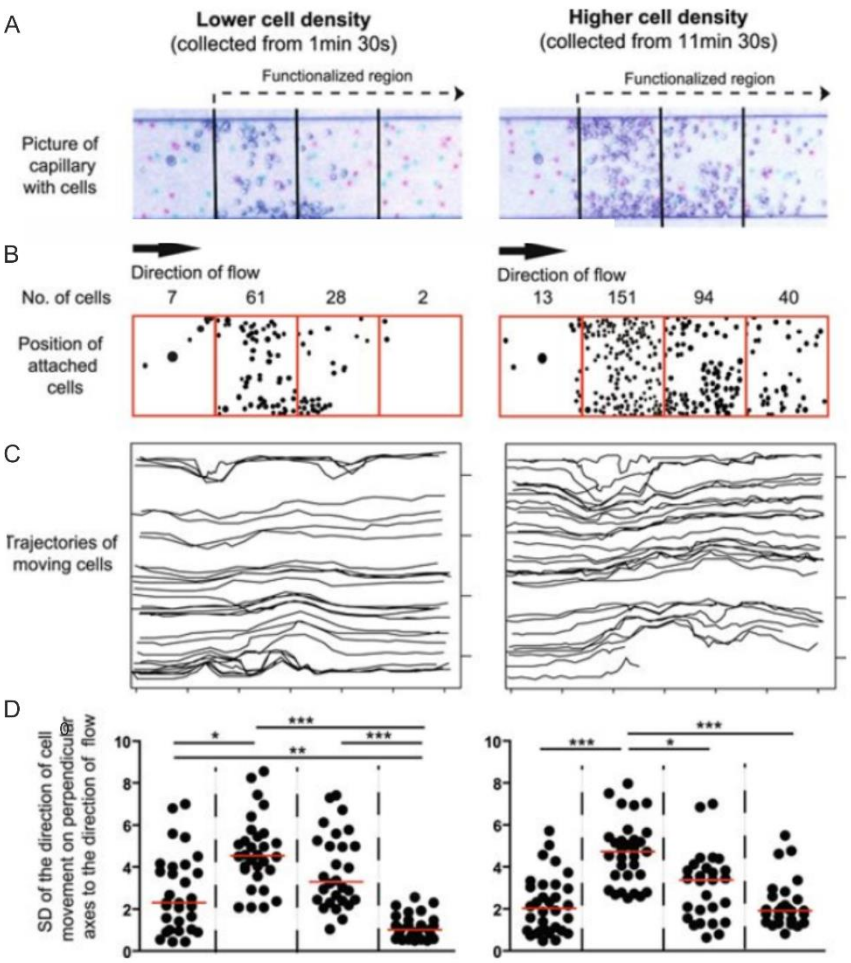

Figure 3.10. – Attached cells in the trapping region perturb the motion of moving cells and force them into perpendicular directions to the flow. [F7]

III.b. I have investigated the dependence of particle transport on the flow rate and particle size in sequential microfluidic systems by numerical modeling and experiments. I have demonstrated the effect of shear rate created by the narrow region of the microchannel on size dependent separation of particles. I have stated that separation efficiency can be improved by increasing the number of units of wider and narrower channel regions. [F8, K14-K16]

I have studied pressure distribution and shear rate values in the microchannel containing separation chambers. I have found that pressure drops mainly at the narrow regions of the channel and the shear rate is also significant there. I have demonstrated the effect of shear rate on the particle trajectories as the particle changed streamlines along the high shear rate region (Figure 3.11.). By modeling two particle populations with different diameters I have shown that particle separation takes place at the narrow regions (Figure 3.12). I have defined the overlap of the two particle population distributions as a quantitative parameter. I have studied the dependency of this parameter on the inlet flow ratios (Figure 3.13.). I have investigated the separation efficiency of varying second particle diameters using two flow rate ratio setups: 0.1:5 μl/s, and 1:5 μl/s. I have found that separation efficiency improves significantly with the increasing of the particle size difference, however, the improvement is more remarkable in the case of larger flow ratio difference. I have shown that separation efficiency may be improved by increasing the number of chambers. This improvement, however, was only significant if the separation was observable before, and the overlap value was under 90%. Multichannel images of measurement results and their intensity analysis confirmed the separation of 10 μm and 16 μm diameter particles (Figure 3.14.). Overlap of the two particle populations was only 27%

in case of 5:10 µl/s flow rate ratio. I have confirmed experimentally the flow rate dependency of separation efficiency also.

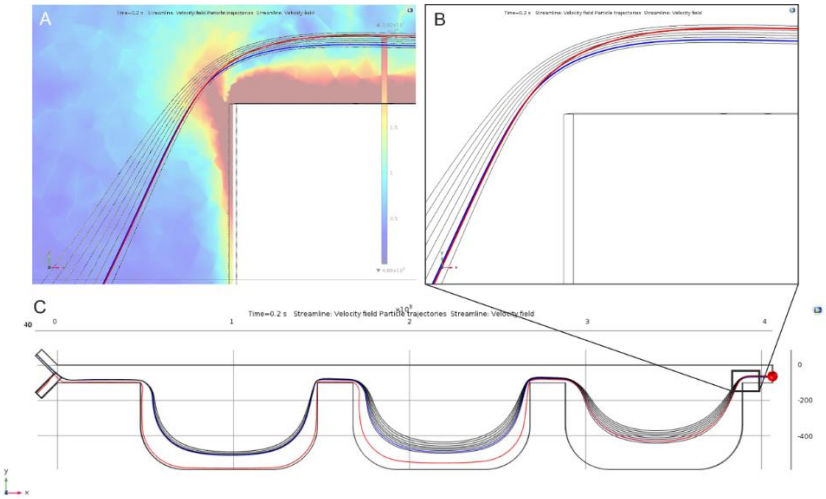

Figure 3.11. – Separation of particle trajectory (red) from the streamline (blue). The particle changes streamlines at the high shear rate zone (A).

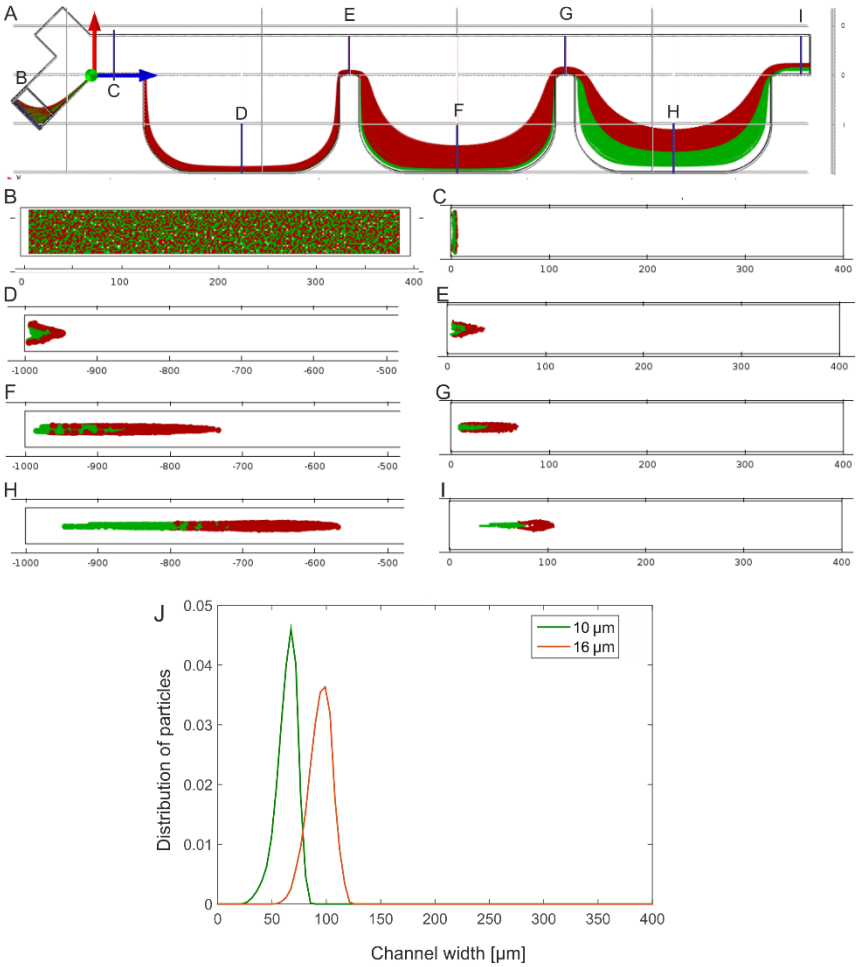

Figure 3.12. – Poincaré sections along the channel. At the inlet the particles are well mixed (B), sheet fluid squeezes the particles to the channel side (C), then particle trajectories are stretched in the first chamber (D). At the narrow region the two particle populations (10 µm diameter – green, 16 µm diameter – red) are starting to separate from each other (E). At the outlet (I) the two populations are well separated, overlap of their distributions is minimal (J).

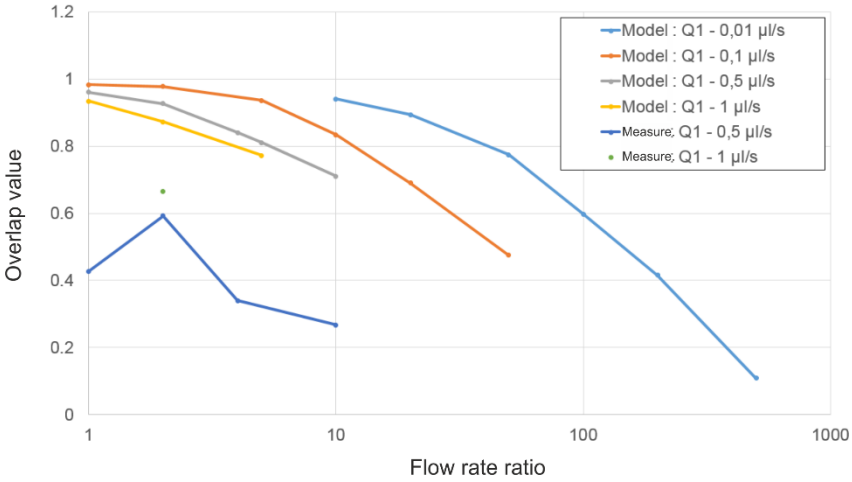

Figure 3.13. – Effect of flow rate ratios on the separation efficiency. Larger flow rate ratios result in better separation of particles.

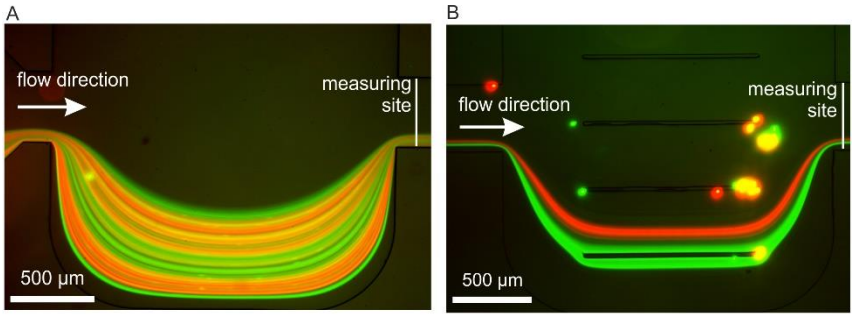

Figure 3.14. – Multichannel representation of measurement results at the inlet (A) and at the channel outlet (B). Separation of 10 µm diameter (green) and 16 µm diameter (red) particles is well captured.

4. Possible applications

Microfluidic systems use fine-tuned sample preparation units which are specially designed for the current application. The previously demonstrated microfluidic channels were also designed for these kind of systems which were the subject of international collaboration between research groups in European Union funded projects.

Herringbone micromixers were designed for the P3SENS: Polymer Photonic multiparametric biochemical SENSor for Point of care diagnostics European Union project as a proposed sample preparation unit. The task of the unit is to ensure that analytes are mixed thoroughly when they reach the sensing area of the photonic biosensor. Numeric modeling aided the design process by proposing optimal mixer parameters taking pressure drop and transport length in consideration ensuring adequate mixing of the sample.

Zweifach-Fung bifurcation based separation device and the MMS device were part of the CAJAL4EU: Chip Architectures by Joint Associated Labs for European diagnostics European Union project. The separation device was a proposed sample preparation unit for a nanopore based diagnostic device. Broadening the spectrum of possible detectable biomarkers was also the aim of the project which included aptamer selection as well. MMS device was proposed as a possible candidate for the separation unit of a microfluidic SELEX device. During the SELEX method aptamers bound to the magnetic beads needs to be separated from the rest of the candidates while enduring continuous washing. Based on the modeling and experimental results our microchannel is a good candidate for the task.

Separation of particles by their size was a task in the PAMIAQ: Particle Matter Sensors for Indoor Air Quality European Union project in cooperation with Technoorg Linda. The first design of the microfluidic transport system was proposed and tested with a suspension of artificial particles. We have confirmed separation ability of the device required for the project. A possible application of the microchannel for the separation of the particulate elements of blood was also proposed.

Study of the effect of immobilized RBCs was also carried out in cooperation with MTA-ELTE Immunology Research group. Results and proposed parameters were applied in an autonomous microfluidic device for AB0 blood type examination. The device requires no off-chip sample preparation. The blood sample is divided into two channels with anti-A and anti-B functionalization. A and B type RBCs are becoming immobilized in the channels during flow, respectively. Immobilized cells lead to the retention of other cells from the blood plasma and the separation is observable. In case of blood type A separation takes place in the anti-A channel, blood type B gives separation in the anti-B channel. Blood type AB leads to separation in both channels type 0 has no observable separation.

5. Publications

5.1. Publications related to the theses

5.1.1. Journal papers

[F1] Z. Fekete, E. G. Holczer, E. Tóth, K. Iván, and P. Fürjes, "Stochastic mixing in microfluidics integrable in bioanalytical systems," ***PROCEDIA ENGINEERING***, vol. 25, pp. 1229–1232, 2011.

[F2] P. Fürjes, Z. Fekete, E. G. Holczer, E. Tóth, K. Iván, and I. Bársony, "Particle Mixing by Chaotic Advection in Polymer Based Microfluidic Systems," ***PROCEDIA ENGINEERING***, vol. 47, pp. 454–457, 2012.

[F3] P. Fürjes, E. G. Holczer, E. Tóth, K. Iván, Z. Fekete, D. Bernier, F. Dortu and D. Giannone, „PDMS microfluidics developed for polymer based photonic biosensors", ***MICROSYSTEM TECHNOLOGIES***, apr. 2014.

[F4] E. L. Tóth, E. G. Holczer, K. Iván, and P. Fürjes, „Optimized Simulation and Validation of Particle Advection in Asymmetric Staggered Herringbone Type Micromixers", ***MICROMACHINES***, vol. 6, pp. 136–150, dec. 2014.

[F5] E. L. Tóth, E. Holczer, K. Iván, and P. Fürjes, „Effect of Geometric Singularities on Plasma Separation Performance in Cascade Zweifach-Fung Bifurcations", ***PROCEDIA ENGINEERING***, vol. 120, pp. 1083–1086, 2015.

[F6] E. L. Tóth, E. Holczer, P. Földesy, K. Iván, and P. Fürjes, „Simulation and experimental validation of particle trapping in microfluidic magnetic separation (MMS) system", ***PROCEDIA ENGINEERING***, vol. 168, pp. 1458–1461, 2016.

[F7] É. Sautner, K. Papp, E. Holczer, E. L. Tóth, R. Ungai-Salánki, B. Szabó, P. Fürjes, J. Prechl „Detection of red blood cell surface antigens by probe-triggered cell collision and flow retardation in an autonomous microfluidic system", ***SCIENTIFIC REPORTS***, vol. 7, pp. 1008, 2017.

[F8] E. L. Tóth, E. Holczer, P. Földesy, K. Iván, and P. Fürjes, „Microfluidic Particle Sorting System for Environmental Pollution Monitoring Applications", ***PROCEDIA ENGINEERING***, vol. 168, pp. 1462–1465, 2016.

5.1.2. Conference proceedings

[K1] Z. Fekete, E. G. Holczer, E. Tóth, K. Iván, P. Fürjes, Design and Realisation Microfluidic Stochastic Mixers Integrable in Bioanalytical Systems, ***MME 2011***, Tonsberg, Norway, 2011

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5.2. Other publications

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