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Development and Optimisation of a Microfluidic Device for Magnetic Field Induced Cell Separation

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Motivation

Micro-total-analysis-systems (µTAS) provide new possibilities for cheaper, simpler, faster and more precise ways to analyse biological and medical samples, e.g. cells. These devices aim to integrate all laboratory task, such as tissue organisation, sample selection and analysis on a single microfluidic chip. The movement of cells can be tailored by employing magnetic beads. Since the bead surfaces can be coated biologically, a binding between beads and medical samples can be achieved. Due their magnetic moment the motion of the beads and hence the motion of the entire sample can be controlled by introducing external magnetic field gradients. [2]

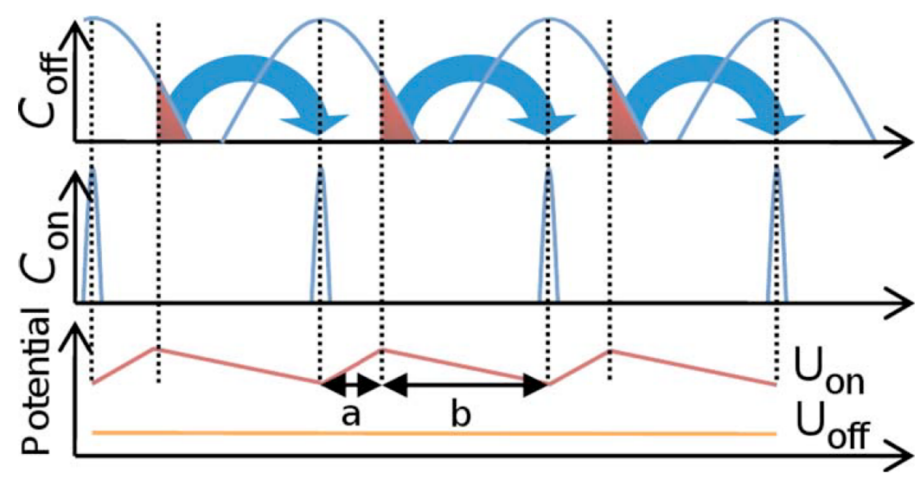
In this work we present a microfluidic device based on a ratchet structure that aims to separate magnetically functionalised cells depending on certain biological properties.

Ratchets

The motion of particles within a ratchet can be described with the following equation of motion [3]:

$$\eta\dot{x}(t) = -U'(x,t) + f(t) + \xi(t)$$

An example for the asymmetric potential U(t) is shown in the figure below (taken from [1]).



While the potential is applied, the particles experience a drag force to the potential minima leading to narrow peaks in the concentration profile. The particles are again able to diffuse freely after the potential is switched off. Starting from the potential minima particles will more likely pass the distance *a* to the next potential well rather than passing the distance *b* due to the asymmetry. This leads to a net current of particles in one direction without applying a net force.

In this work the potential is generated by using inhomogeneous magnetic fields. The force on a particle within a magnetic field and the associated potential are given by the following equation:

$$\vec{F}_{\text{mag}} = \mu_0(\vec{m}\cdot\nabla)\vec{H},\ \ U = -\mu_0\vec{m}\cdot\vec{H}$$

Furthermore we introduced Stokes friction and Brownian motion $\xi(t)$. An additional external field gradient can be taken into account by $f(t)$.

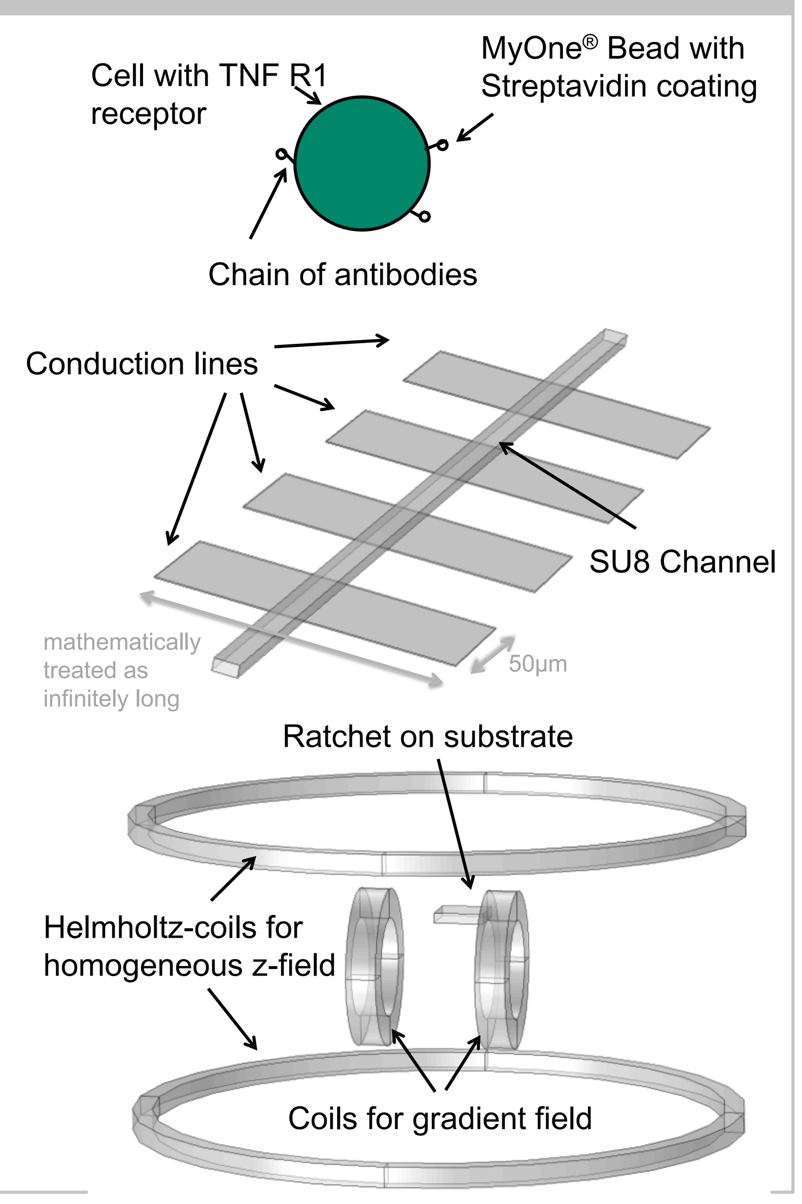
Experimental realisation

Using standard lithography methods, 300 nm high gold conduction lines were prepared into the surface of a silicon wafer as well as a microfluidics channel on top.

A constant current through the conduction lines generates a magnetic field according to Biot-Savart's law. The entire set-up is introduced into a Helmholtz-coil which generates a homogeneous magnetic field perpendicular to the plane of the conduction lines. This field aligns the magnetic moments of the beads parallel which leads to a simplification in the above equation of motion.

For the generation of an additional external field gradient a second pair of water-cooled coils with opposite current directions is implemented.

For first proof-of-principle measurements Human Embryonic Kidney (HEK) cells with commercially available beads were used.



Objectives and mathematical approach

Magnetic fields from conduction lines and coils were calculated using the "Magnetic Fields" module

Particle trajectories were simulated with two different approaches

- continuous ansatz: convection-diffusion-equation from "Classical PDEs" module

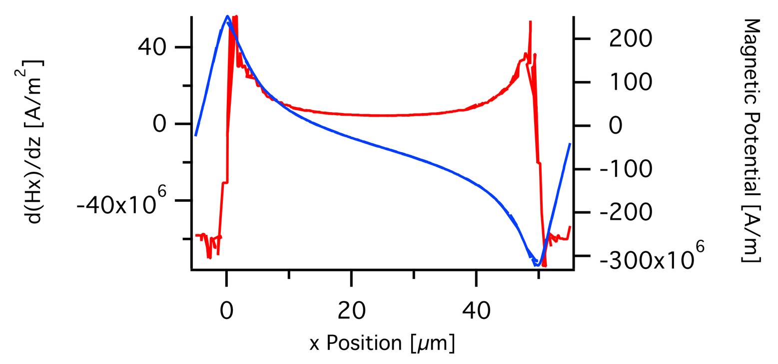
$$\frac{\partial c}{\partial t} + \vec{v}\cdot\nabla c = D\nabla^2 c$$

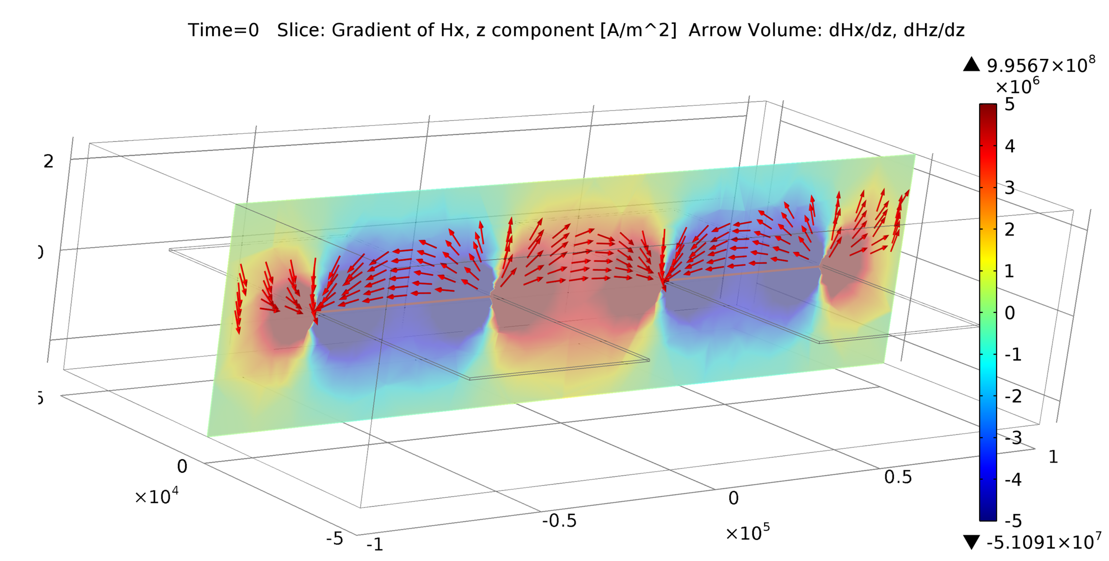
- discrete ansatz: Particle Tracing for Fluid Flow module

$$\tilde{m}\frac{\partial^2}{\partial t^2}\vec{x} = -\mu_0(\vec{m}\cdot\nabla)\vec{H} + 6\pi\eta r\frac{\partial}{\partial t}\vec{x}$$

Simulation results

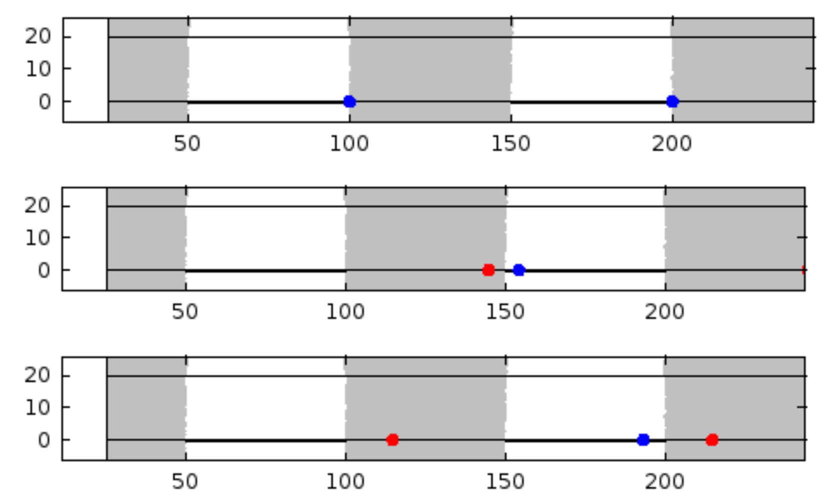
The adjacent figure shows the magnetic field gradient (red) and the magnetic potential (blue) generated from the conduction lines.

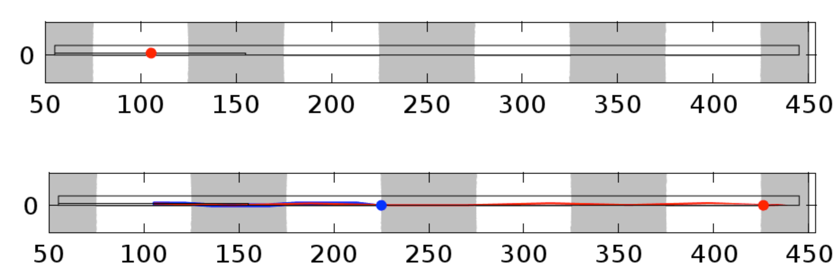




The figure shows a slice plot in a 3D ratchet geometry. Arrows indicate the direction of the forces on the samples. Since the 2nd derivatives of the dependent variables are needed "Coefficient form PDE" modules were added to the model.

The trajectories were calculated starting from a random particle distribution. In the first step all cells are trapped in the potential minima. After swichting off the conduction lines the particles are transported by the external gradient field. The different velocities are due to the different magnetic moment of the sample species. In the last step the samples with lower magnetic moment (depicted in red) are traped within their original potential well whereas the samples with higher moments are transported to a further potential well. Snapshots of the particle positions are shown on the right hand side. Axis units are µm.

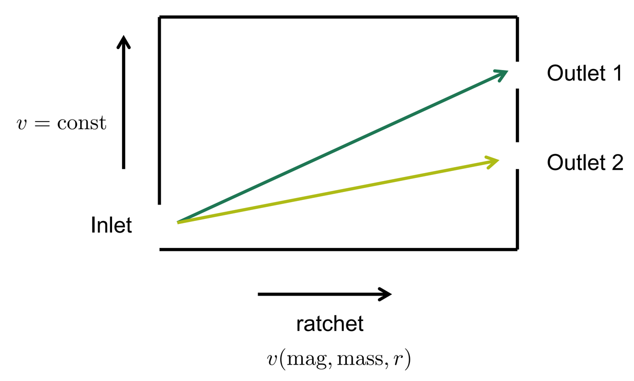


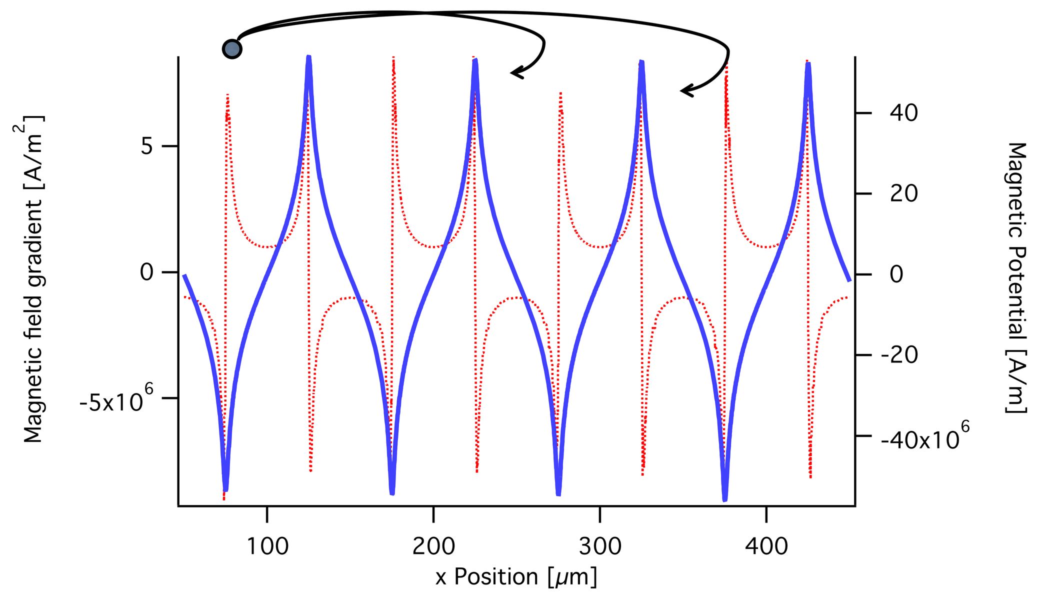


A modification of the external field gradient results in different non-vanishing net velocities for each kind of particle: The external gradient $f(t)$ is chosen to overcome the potential conduction line potential $U(x,t)$ during the first time interval and vice versa during the second time interval:

$$f(\Delta t_1) > U',\ \ f(\Delta t_2) < U'$$

We suggest that a superposition of this effect with a constant flow field will result in an extension to a two-dimensional ratchet for simultaneous separation of various kinds of particles: Each sort of particle will be transported on a different trajectory. A scheme of the separation mechanism and a suitable ratchet-potential landscape are shown below.





References

[1] A. Auge et al., *Magnetic ratchet for biotechnological applications*, Applied Physics Letters 94 18, 2009

[2] B. Eickenberg, L. Helmich et al., *Lab-on-a-Chip Magneto-Immunoassays: How to Ensure Contact Between Superparamagnetic Beads and the Sensor Surface*, Biosensors, accepted

[3] P. Reimann, P. Hänggi, *Introduction to the Physics of Brownian motors*, Applied Physics A 75 2, 2002

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