Presented at the COMSOL Conference 2009 Milan

Design and Simulation of a Microscale Magnetophoretic Device for the Separation of Nucleated Fetal Red Blood Cells from Maternal Blood

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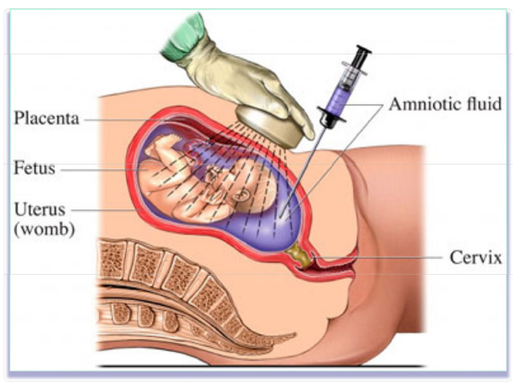
Abstract

This work focuses on the separation of fetal nucleated red blood cells from the maternal circulation based on their intrinsic magnetic properties. The design and simulation of a magnetophoretic separator is described, as it will be one of the stages of a lab-on-chip for non-invasive prenatal diagnosis (NIPD).

Motivation

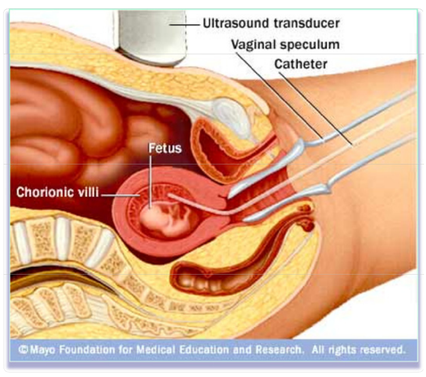
Conventional (invasive) techniques associated with 0.5% to 2% fetal miscarriage rate.

Amniocentesis



www.rocg.org.uk

Chorionic Villus sampling



www.revolutionhealth.com

Fetal erythroblasts in maternal circulation (2÷6 per ml against ~10^6 per ml adult blood cells)
They can be used as a DNA source for genetic testing,
but their rarity in maternal circulation requires minimization of cell loss during processing.

Microscale techniques are the answer
FACS is expensive and requires expressly trained personnel,
MACS requires tagging through beads.
A reliable and inexpensive technique is sought to build new devices for NIPD.

Principle

In magnetophoresis cells are separated based on their native magnetic properties, different in deoxygenated red blood cells (deoxyRBCs) and white blood cells (WBCs). Both cell types are diamagnetic, but the former exhibits significant variation of the susceptibility according to the oxygenation state of the haemoglobin molecules, as experimentally shown in [1], with numerical values [2]:

$$\chi_{deoxy,rbc} = -3.9 \cdot 10^{-6} \quad \chi_{wbc} = -9.2 \cdot 10^{-6}$$

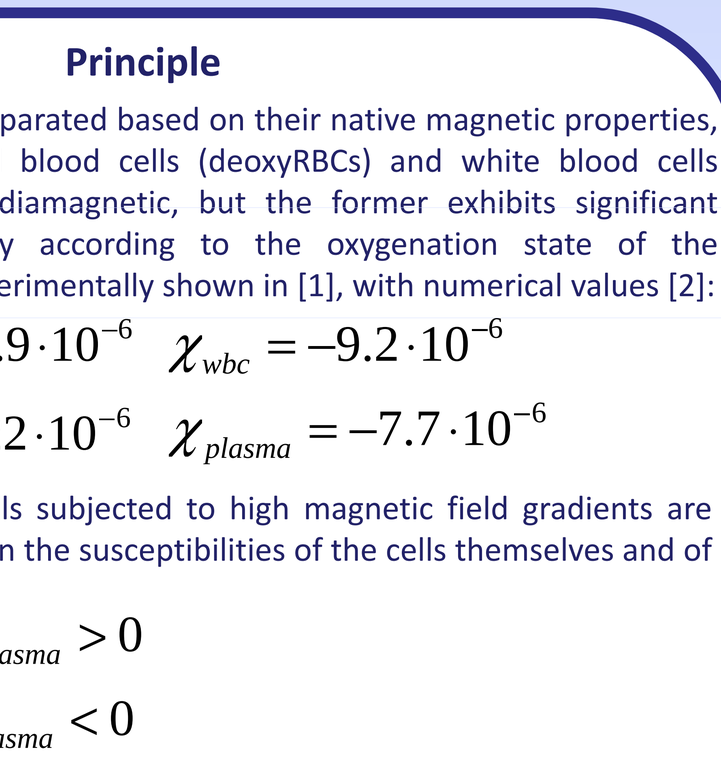
$$\chi_{oxy,rbc} = -9.22 \cdot 10^{-6} \quad \chi_{plasma} = -7.7 \cdot 10^{-6}$$

Magnetic forces arising on cells subjected to high magnetic field gradients are proportional to the difference in the susceptibilities of the cells themselves and of the medium they flow in [3]:

$$\chi_{deoxy,rbc} - \chi_{plasma} > 0$$

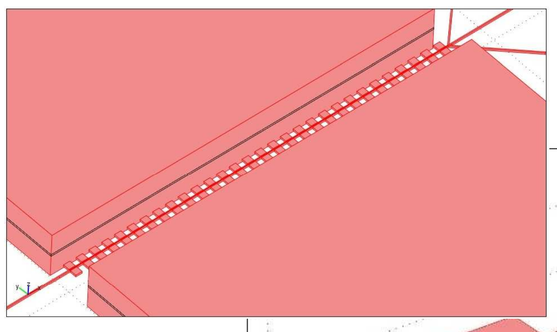
$$\chi_{wbc} - \chi_{plasma} < 0$$

Therefore a magnetophoretic device can be designed in order to properly couple the magnetic and microfluidic forces and achieve separation between deoxygenated red blood cells and other cells. Among the former there will be fetal erythroblasts, which have the same magnetic behaviour as adult RBCs, but they are nucleated. A lab-on-chip can thus be thought as a double stage device as shown in the side scheme.

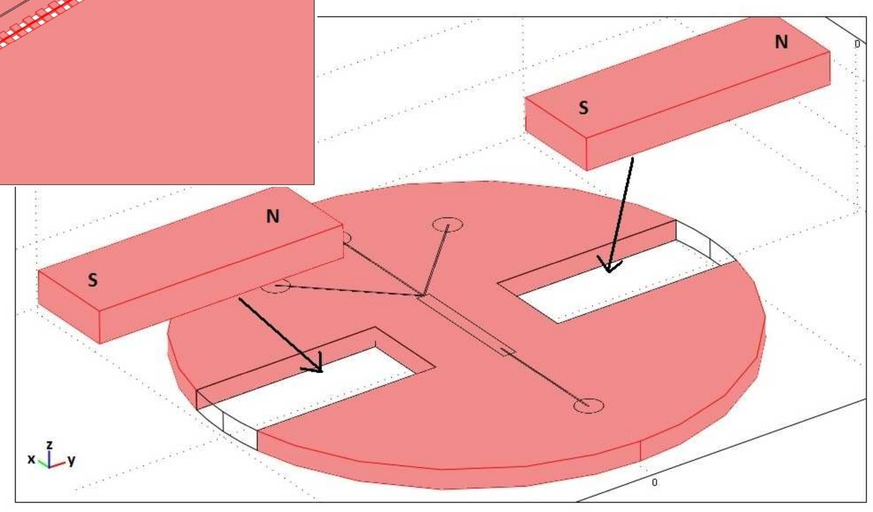


Device

A microfluidic continuous flow device has been designed in a two stage continuous flow lab on chip system. The first separation stage of the device should filter deoxygenated whole blood allowing fetal nucleated red blood cells (NRBCs) and adult RBCs to flow together to the second stage, while discarding all other particles.

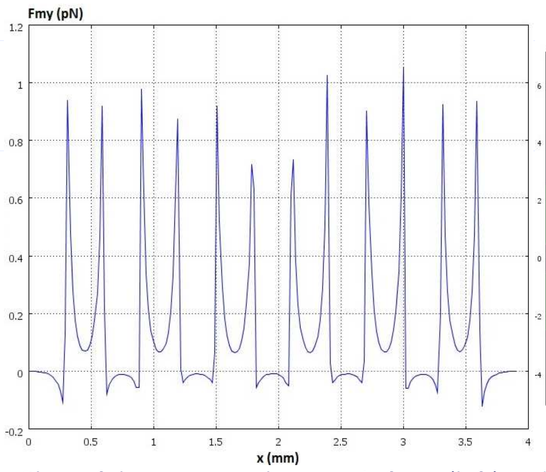


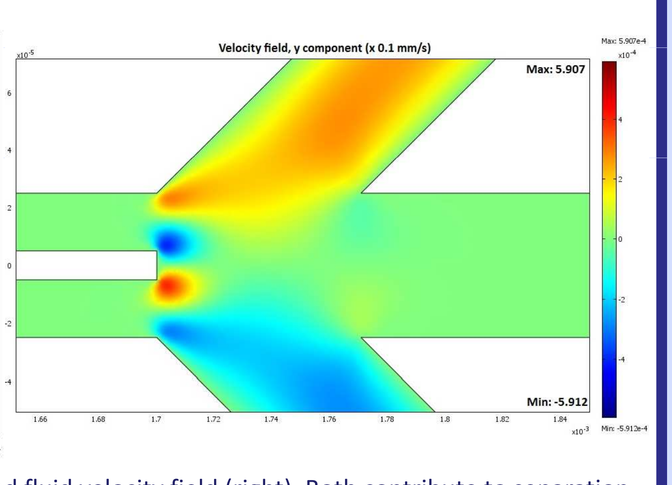
Schematic for the placement of the magnets, with detail on the microchannel region with electrodeposits on either sides.



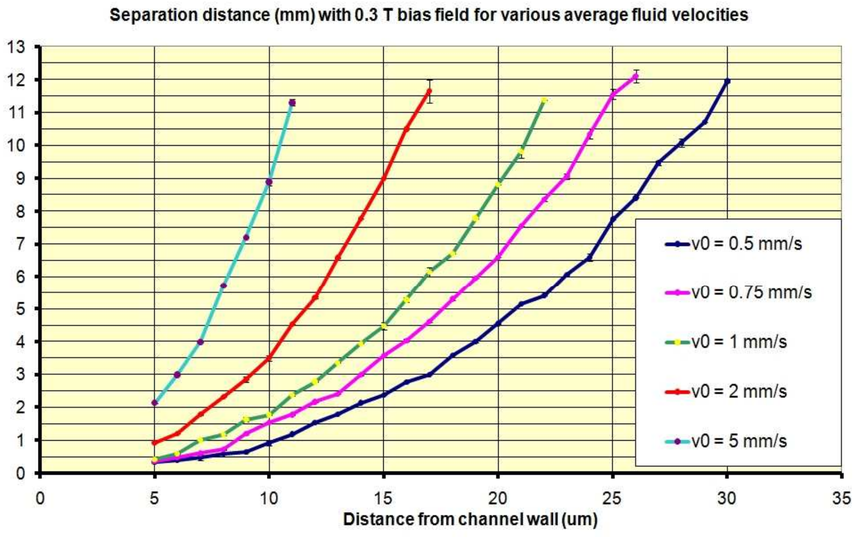
Simulations

Comsol Multiphysics was used to compute the magnetic field distribution in the device, as the superimposition of a bias field provided by permanent magnets and the magnetization response of the magnetic electrodeposits. The fluid velocity field was then computed in the microchannel. Expressions for the fluidic drag force and the magnetophoretic force were set as subdomain expressions and used as force inputs in the particle tracing postprocessing application.
The device was sized for various values of the bias magnetic field and of the inlet pressure, in order to achieve efficient and reliable separation for any cell entering the microdevice.





Plots of the transversal magnetic force (left) and fluid velocity field (right). Both contribute to separation.



The particle tracing application solves the equation of motion for cells injected in the device. Plots of the length of the separation path as a function of the starting width and for various values of the input fluid velocity and bias field are provided to help sizing the length of the device.

Fabrication and testing in progress…

References

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[3] T. P. Jones, Electromechanics of Particles. Cambridge University Press, Cambridge, UK, (1995)