# In vitro biosensing based on magnetically induced motion of magnetic nanoparticles

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## ABSTRACT

This paper presents a method for in-vitro detection of bioanalyte[1] using conductive microstructures to move magnetic nanoparticles (MAPs) in an integrated microfluidic system. The fundamental idea behind the elaboration of such a biosensing system is that the induced velocity of MAPs in suspension, while imposed to a magnetic field gradient, is inversely proportional to their volume [1-2]. Therefore, the volumetric increase of MAPs due to binding of bioanalyte onto their surface, changes consequently the velocity of the MAPs. The resulting compounds, called loaded MAPs (LMAPs), which consist of the MAPs and the attached bioanalyte, need more time to travel the same distance compared to bare MAPs (smaller). Thus, when a liquid sample is analyzed and a change in the velocity of the MAPs occurs the bioanalyte presence in the liquid under examination is demonstrated.

***Keywords***: biosensors, microfluidics, magnetic particles, velocity change

## 1 INTRODUCTION

On-chip biosensing and bioanalytical devices based on magnetic methods have attracted significant interest in recent years [3-6]. Specifically, by employing magnetism in biomedical applications automation, fine-tuning and miniaturization are enabled. Moreover, such devices have remarkable advantages over laboratory operated methods such as extraordinary decrease in volumes of sample and reagents that need to be used, minimization of human intervention and low cost fabrication. Finally, in comparison to other on-chip biomedical analysis procedures, magnetic methods do not require additional elaborate equipment, but simply a field gradient generated by a permanent magnet or a specially designed electromagnet.

However, one of the greatest challenges in on-chip biosensing utilizing magnetic methods is to develop micro-sized magnetic field generators. They need to produce magnetic field gradients strong enough to move the MAPs, which can be attached to bioanalyte, towards a sensing area and to be integrated to microfluidic systems.

The presented biosensing system addressed this challenge; the motion was achieved through sequentially actuated, conductive microstructures, controlled by a programmable microprocessor. The advantage of these microstructures over an external permanent magnet was that they ensured a better control of the magnetic field gradient hence allowing uniformity regarding the acceleration of the MAPs. In addition to that, the conductive microstructures were integrated in a complete microsystem. In this paper, magnetic field density calculations and numerical simulations by COMSOL Multiphysics are presented. Additionally, the behavior of MAPs with different diameters under the influence of the applied magnetic field gradient was simulated in order to define the optimum geometry of the conductive microstructures. Finally, preliminary experiments for the proof of sequential acceleration of the MAPs are reported.

## 2 CALCULATIONS & SIMULATIONS

The magnetic flux density caused by a rectangular conductor with thickness $t$ = 1 µm and width $w$ = 10 µm, running a current of $I$ = 500 mA was calculated in MATLAB. The same scenario was also simulated with COMSOL Multiphysics 4.3. Then the analytical calculated and the simulated values were compared along two different lines (called cut lines in COMSOL) contiguous to the conductor (see Fig. 1):

- along the y-axis at the center ($x$ = 0) of the conductor (see Fig. 2 , red cut line in Fig. 1)
- along the y-axis at the edge ($x$ = 5 µm) of the conductor (see Fig. 3, black cut line in Fig. 1)

It can be seen that the values retrieved from the analytical calculation and the simulation are identical, which indicates that the simulation with COMSOL is plausible.

The principle design of the biosensing system consisted of a microfluidic measurement channel with one inlet and one outlet, a reference channel with one inlet and one outlet and below them the current carrying microstructures to establish the needed magnetic field gradient. These microstructures consisted of parallel straight rectangular conductors, on which current was sequentially applied controlled by a programmable microprocessor.

[1] The word "bioanalyte„ is used throughout this document as a general definition for biomolecules, cells and viruses and is utilized only in order to facilitate the reader.

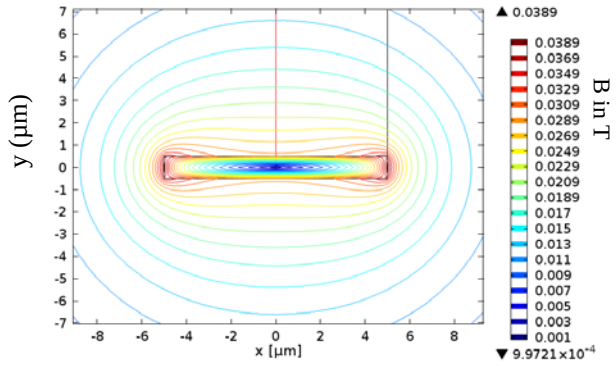


Figure 1: Contour plot of the magnetic flux density caused by a rectangular conductor (1 × 10 µm) running a current of 500 mA, including cut lines (red and black) at which the analytical and simulated values were compared.

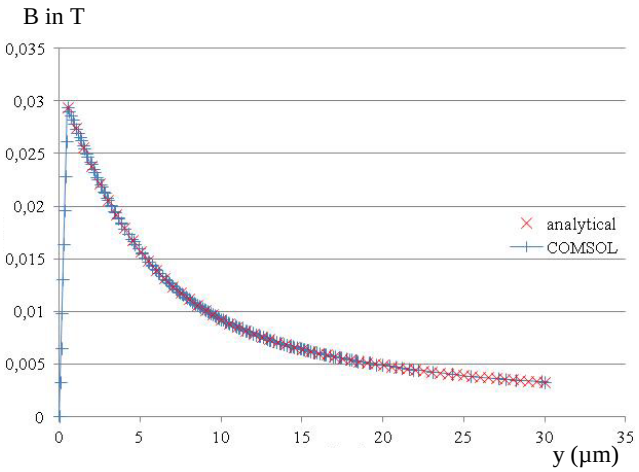


Figure 2: Magnetic flux density calculation (red line) and COMSOL simulation (blue line) along the y-axis at the center of a conductor with dimensions of 1 µm × 10 µm running a current of 500 mA.

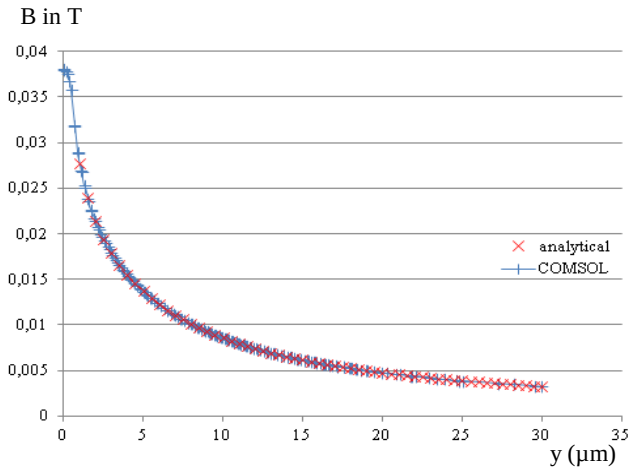


Figure 3: Magnetic flux density calculation (red line) and COMSOL simulation (blue line) along the y-axis at the edge of a conductor with dimensions of 1 µm × 10 µm running a current of 500 mA.

Thus they generated attractive forces on the MAPs and induced their movement along the microfluidic channel from the inlet to the outlet. Several conductor geometries were produced with different conductor widths ($c_w$) and different distances between the conductors (spacing $c_s$). Simulations were carried out with COMSOL, to determine which of these geometries is preferable to use. In terms of the current that can be applied to the conductors the joule heating and therefore the current density is the limiting factor. This leaves the conductor thickness ($c_{th}$) as the last factor that determines the amount of current that can be applied to the different conductor geometries. Two versions were investigated; one with the thickness being 500 nm and the other with the thickness being 1 µm. In a simulation of the joule heating using conductors with a width of 10 µm and a thickness of 1 µm the maximum applicable current was found to be 200 mA, yielding a current density of $J = 2 \cdot 10^{10}$ A/m². Fig. 4 shows the magnetic flux density along the x-axis at a distance of 5 µm from the lower border of a conductor with a width of 10 µm and varying thicknesses (parameter in the plot) and a current density of $J = 2 \cdot 10^{10}$ A/m².

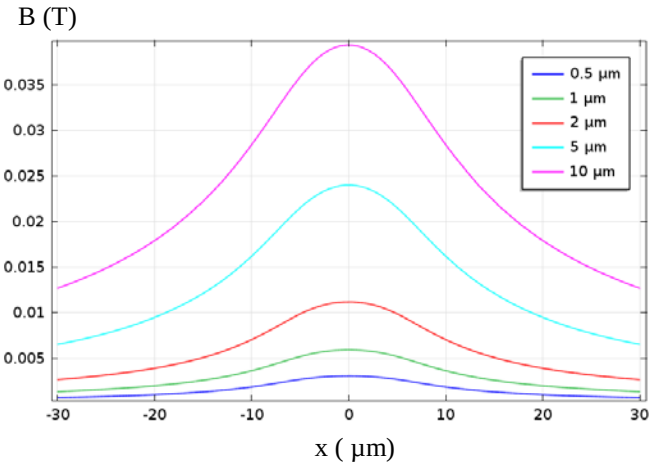


Figure 4: Magnetic flux density along the x-axis at a distance of 5 µm from the lower border of a conductor with a width of 10 µm and varying thicknesses (parameter in the plot) and a current density of $J = 2 \cdot 10^{10}$ A/m².

In practice the maximum achievable conductor thickness is limited by restrictions in the production process; the problem being that the conductors have to be encapsulated in an insulating layer before they can be bonded with the microfluidic channel. Because of the given structure, consisting of parallel conductors separated by predifined distances, the insulating layer does not get an even surface; this effect increases with the conductor thickness. A conductor thickness of 500 nm was found to be the optimum value.

# 3 EXPERIMENTAL

## 3.1 Working Principle

It has been previously reported that the volumetric increase of MAPs, e.g., due to binding of a bioanalyte onto their surface, changes consequently the velocity of the MAPs caused by a magnetic force [1-2]. The resulting compounds, called loaded MAPs (L MAPs), which consist of the MAPs and the attached bioanalyte, need more time to travel the same distance compared to bare MAPs (smaller). Thus, when a liquid sample is analyzed and a change in the velocity of the MAPs occurs the presence of bioanalyte in the liquid is demonstrated. However, the proof of the novel concept was based on acceleration of the MAPs by a NdFeB permanent magnet of 5 × 5 × 1 $mm^3$, which was positioned 2 mm outside the microfluidic device. In order to create a compact and portable device a reliable, integrated solution for the motion of the MAPs is required.

## 3.2 Fabrication Process

First, a photoresist was spin coated, exposed, and developed, for the patterning of the microstructures. Aferwards, 500 nm of silver with a 30 nm adhesion layer of titanium was evaporated on a Si-wafer with a thermally grown oxide. After silver was deposited, the photoresist was stripped using acetone and the remaining debris of the resist was cleaned by oxygen plasma. The silver microstructures consisted of 18 conductors having a 10 μm width and a distance between each of them of 8 μm. An insulating layer of $SiO_2$ with 1 μm thickness was sputtered on top of the conductors and dry etching was employed to free the bonding pads. The usage of $SiO_2$ has an additional benefit. According to [7] a layer of $SiO_2$ produces a negatively charged surface in aqueous buffer, thus producing a repulsive force between negatively charged particles and the solid surface. Thus, particle-solid surface adhesion can be prevented and the MAPs getting stuck at the conductor edges.

Finally, two microfluidic channels were fabricated on top of the conductors; one utilized as a reference channel for the reference sample and the other utilized as the measurement channel. A standard photolithography process and a dry photoresist thin film (Ordyl SY355) of 55 μm thickness (see Fig. 6a,b) was utilized.

## 3.3 Measurement Set-up

The movement of the MAPs was captured by a Samsung VP-HMX20C camcorder mounted on a Carl Zeiss Microscope and a digital image processing method was utilized in order to estimate the velocity of the MAPs (see Fig. 7).

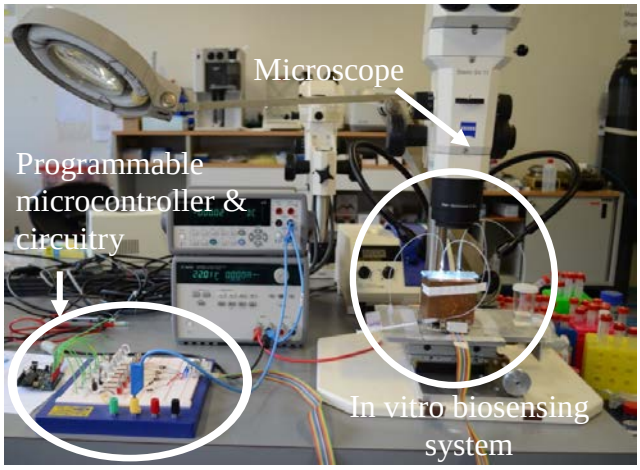


Figure 7: Photograph of the measurement set-up; in vitro biosensing system, programmable microcontroller for the actuation of the conductive microstructures and optical microscope for capturing the movement of the MAPs.

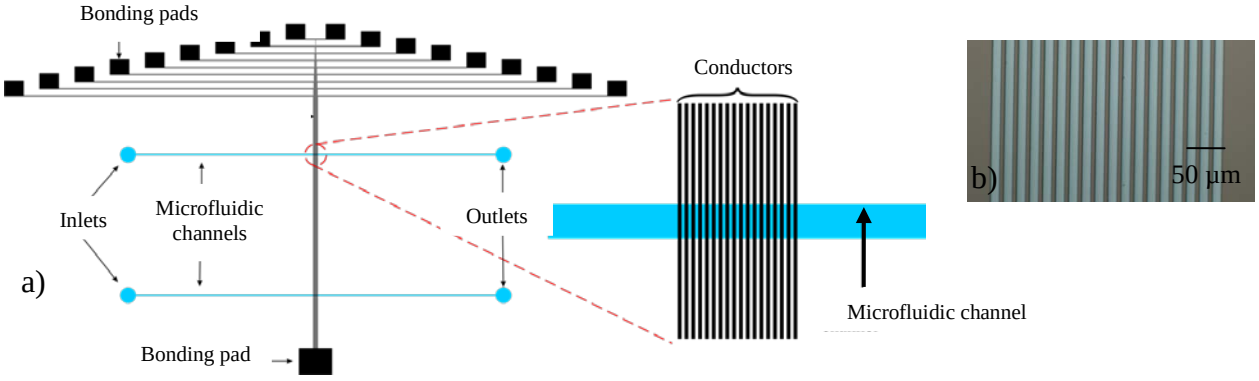


**Figure 6**: a) Schematic of the in vitro biosensing system consisting of the conductive microstructures and the microfluidic channels b) Micrograph of the Ag conductors (10 μm width, 500 nm thickness) fabricated by evaporation on a Si substrate with a top $SiO_2$ protective layer (200 nm thickness).

### 3.4 Results and Discussion

2 µl of MAPs (Micromod) coated with carboxylic acid having different diameters (2 µm - 6 µm) with a diluted concentration of 1 mg/ml were injected to the microfluidic measurement channel. A DC current of 50 mA was applied sequentially to each conductor, controlled by the programmable microprocessor. Forces up to 150 pN were obtained at the surface of the conductors. It was proven that by sequentially applying the current to the different conducting elements, the MAPs were moved from the right to the left conductors (see Fig. 8 for MAPs of 6 µm).

The applied magnetic field causes a magnetic moment in the MAPs. The resulting stray magnetic fields can be detected by GMR sensors [8-9]. By integrating one GMR sensor near the inlet of the microfluidic channel a change in the electrical resistance will occur when the MAPs are introduced in the microchannel. Then the MAPs are moved by the applied magnetic field from the silver conductors and as they exit the microchannel another GMR sensor will register a change in its resistance. The time difference between the detection of the resistance change on the first GMR sensor and the detection of the resistance change on the second GMR sensor can be measured. The velocity of the MAPs within the microfluidic channel can then be calculated.

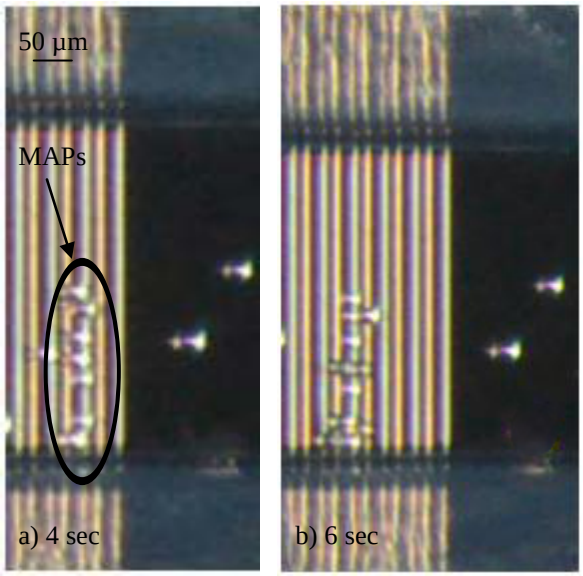


Figure 8: Motion of MAPs with a diameter of 6 µm after sequentially applying current starting from the right conductor towards the left conductors a) 4 seconds and b) 6 seconds.

## 4 CONCLUSIONS

An integrated solution to continuously move magnetic nanoparticles over a certain distance was obtained by sequentially applying electric current to conductive microstructures arranged in parallel. The presented in vitro biosensing system provides a simple, cost effective and reliable detection method which considerably reduces the measurement complexity. The possibility of using GMR sensors to detect the motion of MAPs is currently being investigated to facilitate an integrated device.

## ACKNOWLEDGEMENT

The authors would like to acknowledge the financial support of the Austrian Science Fund (FWF) with Project Nr: P 24372-N19.

## REFERENCES

[1] I. Giouroudi, S. Van den Driesche, J. Kosel, Procedia Engineering, 5, 2010.
[2] I. Giouroudi, S. Van den Driesche, J. Kosel, R. Grössinger, M. Vellekoop, J. Appl. Phys. 109, 07B304, 2011.
[3] M. A. M. Gijs, F. Lacharme, and U. Lehmann, Chem. Rev. 110, 1518–1563, 2010.
[4] I. Giouroudi, J. Kosel, Recent Patents on Nanotechnology, 4, 2, 111-118, 2010.
[5] Y.C. Lim, A.Z. Kouzani, and W. Duan, Microsyst Technol, 16, 1995, 2010.
[6] C. Liu, T. Stakenborg, S. Peeters and L. Lagae, J. Appl. Phy, 105, 102014, 2009.
[7] C. Liu, L. Lagae, R. Wirix-Speetjens, G. Borghs, Journal of Applied Physics, 101, 2, 2007.
[8] G.C. P. Gooneratne, Cai Liang, I. Giouroudi, J. Kosel, Journal of Applied Physics, 111, 07B327, 2012.
[9] G. C. P. Gooneratne, I. Giouroudi, J. Kosel, "Microdevice with Half-Ring Shaped GMR Sensors for Magnetic Bead Manipulation and Detection," Lecture Notes in Electrical Engineering: Advancements in Sensing Technology, Edited by S.C. Mukhopadhyay et al., Springer-Verlag, ISBN 978-3-642-32179-5, 2012.