



Magnetic Detection Structure for LOC Immunoassays, Multiphysics Simulations and Experimental Results [†]

Amine Rabehi ¹, Benjamin Garlan ^{1,*}, Faezeh Shanehsazzadeh ², Hamid Kokabi ¹, Kieu Ngo ³ and Hans-Joachim Krause ⁴

¹ Sorbonne Universités, UR2, L2E (Laboratoire d'Electronique et Electromagnétisme), Paris, France; amine.rabehi@upmc.fr (A.R.); hamid.kokabi@upmc.fr (H.K.)

² Superconductive Electronics Research Lab, Sharif University of Technology, Tehran, Iran; f_shanehsaz@yahoo.ca

³ Sorbonne Universités, UPMC, UMR 8235, LISE (Laboratoire d'Interfaces et Systèmes Electrochimiques), Paris, France; kieu.ngo@upmc.fr

⁴ Institute of Bioelectronics, Peter Grünberg Institute (PGI-8), Forschungszentrum Jülich (FZJ), Jülich, Germany; h.-j.krause@fz-juelich.de

* Correspondence: benjamin.garlan@gmail.com; Tel.: +33-668-893-923

[†] Presented at the EuroSensors 2017 Conference, Paris, France, 3–6 September 2017.

Published: 18 August 2017

Abstract: The aim of this work is to develop a completely integrated Lab-On-Chip (LOC) for easy, rapid and cost-effective immunoassays. The pathogen sensing system is composed of a microfluidic channel surrounded by planar microcoils which are responsible for the emission and the detection of magnetic fields. The system allows the detection and quantification of superparamagnetic beads used for immunoassays in a “sandwich” antigen-antibody configuration. Multiphysics simulations have been achieved and preliminary experimental results have allowed to validate the structure.

Keywords: Lab-on-chip; magnetic detection; pathogen sensing; multiphysics simulations; diagnostic in vitro device; microfluidics.

1. Introduction

The need of a rapid, low cost and sensitive pathogen sensing systems is urgent because of the increase of spreading diseases and epidemics. This is due to the increasing movement of goods and people especially by flight. There are many approaches to develop such in vitro diagnosis systems specially Lab-On-Chip (LOC) one. Most of these approaches use electrochemical and optical methods. However, they have several drawbacks like nonlinear detection range, lack of sensitivity, non-specific detection and complexity of integration [1–3]. The other approaches use mechanical and magnetic based methods. The systems based on magnetic approaches hold promising perspectives due to their miniaturization possibility [4,5]. Some attempts have been made in order to embed magnetic sensors such as GMR, TMR, and planar Hall Effect sensors [6]. The LOC pathogen sensing system should be sensitive with a low limit of detection, cost effective, size selective, simple to use and with a large dynamic range. Having low cost and very sensitive detection system is rather challenging.

The miniaturized system that we aim to develop tends to overcome these challenges. In our case, we take advantage of the nonlinearity of superparamagnetic nanoparticles (SPN). Because of their biocompatibility, SPN are particularly well suited for the biomedical domain. They are commonly used in numerous applications such as magnetic resonance imaging (MRI), information storage, and medical diagnostics using magnetic immunoassays. In fact, the particles can be used both for magnetic actuation and detection of biomolecules. In the case of immunoassays, the SPN can become

markers by bounding them to the biological target substance using the highly specific antibody-antigen interaction [7]. The challenge is to detect the magnetic marker particles with high accuracy and selectivity. These particles are described by two characteristics: magnetization curve and frequency-dependent relaxation effects. The magnetization curve is nonlinear, non-hysteretic and it saturates at high fields [8]. To exploit this nonlinearity, we use the frequency mixing method in order to detect the presence of particles in a microfluidic channel. In this method, two magnetic excitation signals are applied to the sample reservoir at distinct frequencies (f_1 , f_2) and the amplitude of the response signal is measured at a specific frequency ($f_1 + 2f_2$) that allows detecting and quantifying the amount of SPN [9]. The magnetic frequency mixing technique is very well suited for this purpose, thus allowing its use for immunoquantification.

The development of SPN detection techniques in a microfluidic platform has been investigated. To achieve this, a magnetic micro-detection unit is combined with a microfluidic structure for the first time. The microfluidic allows us to use small quantities of analyte and reagents, and will enable also quick analysis. The goal is to develop a simple and portable analysis platform for magnetic immunoquantification which may be applied for diagnosis of illnesses, prevention of pandemics, food monitoring, environmental protection, etc.

2. Multiphysics Simulations and Analytical Calculation

In the scope of the design and realization of a microstructure aimed for multipathogen immunoassays using superparamagnetic beads, we have achieved multiphysics simulations in order to get a good compromise between the various important parameters. These simulations allow to optimize the microstructure, a proper magnetization of the nanoparticles, the detection sensitivity, minimize the heat transfer effects, and thus the viability of the biological samples. Also, we should consider the diffusion in the microfluidic structure.

In a first step towards using the magnetic frequency mixing technique in microfluidic structures, planar coils have to be designed and simulated. COMSOL electrical and magnetic simulations along with an analytical calculation have been used in order to optimize the dimensions, shape, and positions of the coils so that a proper distribution and density of magnetic flux can be obtained at the sample area.

Actually, the most important goal using multiphysics simulations is finding the best parameters that ensure an uniform distribution of the sample flow, sufficiently low temperatures in the microfluidic reservoir (below 37 °C), a homogeneous magnetic field distribution and optimum coil sensitivity. These entities are sensitive to heat resulting from the bias current of the coils. The variation of the voltage and magnetic flux as a function of the relative magnetic permeability of the sample is presented in Figure 1. Besides, heat transfer and microfluidic simulations (Figure 2a,b) have been achieved to optimize the microstructures for their usage with biological entities.

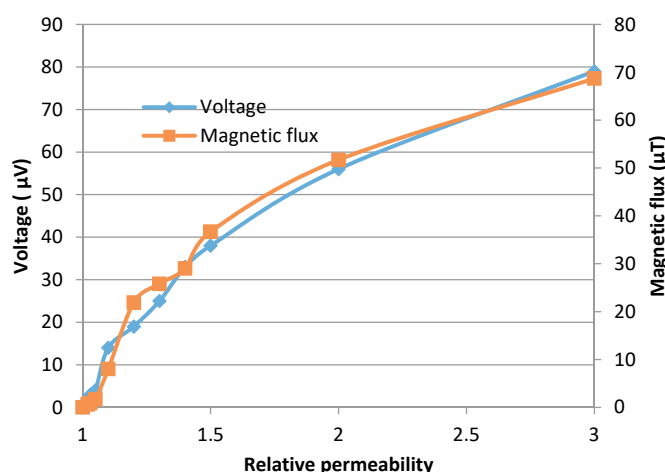


Figure 1. COMSOL Multiphysics simulation results for the variation of the voltage and magnetic flux as a function of the relative magnetic permeability of the sample.

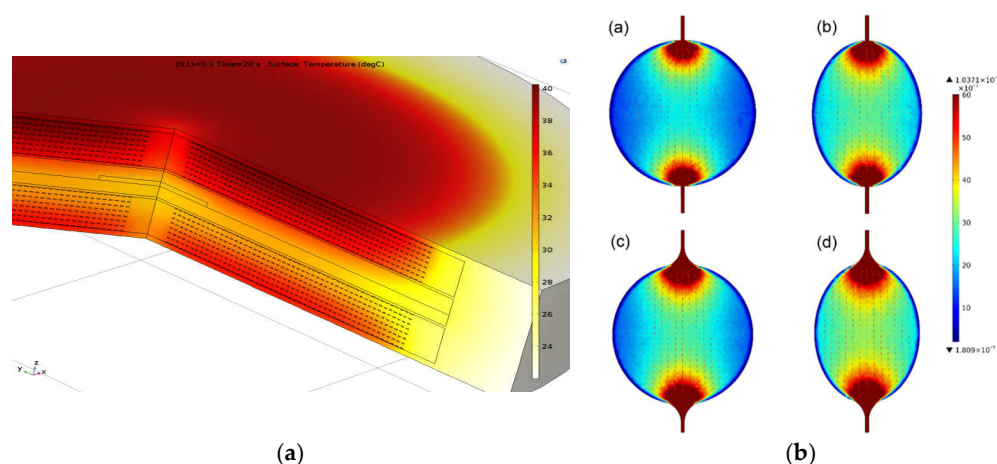


Figure 2. Simulations for heat transfer showing the contribution of the set of coils to the rising temperature of the microfluidic reservoir after 20 s (a); the fluid flow homogeneity relative to the reservoir shape (b).

3. Experimental Structure and Preliminary Results

The miniaturized experimental structure is composed of planar copper coils as excitation and detection coils. For the detection coil, defining the inner and outer radius by choosing a good compromise between sensitivity and minimum detectable moment is important (Figure 3). These coils surround the microfluidic channel, optimized with the shape of meander (Figure 4), which can contain 14 μL of SPN solution, equivalent to a droplet of blood.

The magnetic response curve for different concentrations of SNP in the microfluidic channel is shown in Figure 5.

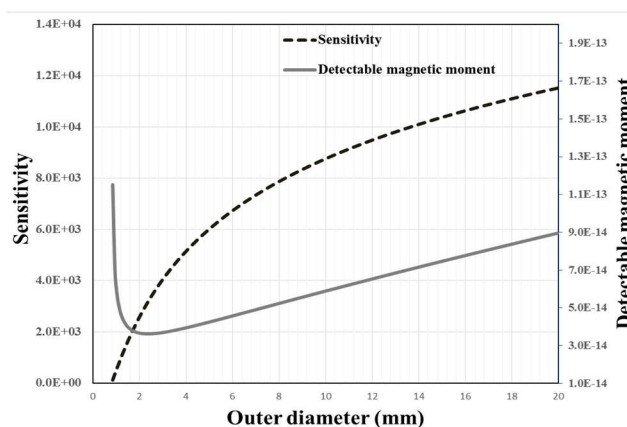


Figure 3. Pick-up coil optimization with sensitivity and minimum detectable moment versus coil outer radius. Internal radius fixed at 0.8 mm.

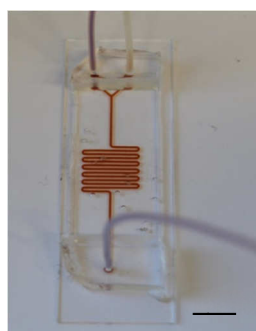


Figure 4. Meander shape microfluidic reservoir fabricated with PDMS.

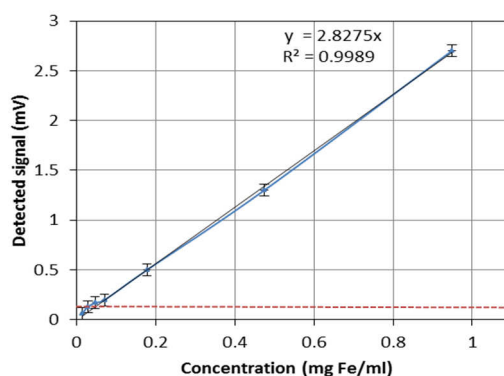


Figure 5. Magnetic response as a function of the mass concentration of iron nanoparticles. The red dotted line indicates the approximate limit of detection.

A very good linearity of detected signal versus SNP concentration has been observed for 3 orders of magnitude. Furthermore, the test was repeated in day's intervals and proved to be very reproducible. With an accepted error of less than 15%, our limit of detection is about 15 ng/ μ L for 20 nm core sized SPN which is very promising preliminary result for a LOC (Figure 5). A small quantity of solution sample was used which is very convenient for future cost effective biological tests. These preliminary results validate the magnetic detection of nanoparticles and further improvements are expected regarding the limit of detection, especially with noise reduction. With our magnetic detection system validated, this structure will be used for implementing immunoassays for testing C-reactive protein samples with different concentrations.

4. Conclusions

In this work, a miniaturized system with planar excitation and detection coils was designed and fabricated to achieve magnetic immunoassay using superparamagnetic nanoparticles (SPN) with frequency mixing technique. Both analytical and multiphysics simulation tools have been done in order to optimize different electrical and geometrical parameters of the system. Consequently, PDMS microfluidic structures along with planar coils have been realized in accordance. The variation of the voltage and magnetic flux versus relative magnetic permeability of the sample has been calculated analytically. Heat transfer and microfluidic simulations allowed to optimize the microstructures for their usage with biological entities. The meander shape of the optimized microfluidic reservoir can contain 14 μ L of SPN solution, equivalent to a droplet of blood. Based on the preliminary experimental results, our limit of detection is about 15 ng/ μ L for 20 nm core sized SPN which is very promising for a LOC. The simulations have been also in correlation with the experiments. Moreover, the device should be validated for the detection of biological substances such as C-reactive protein which indicates the general level of inflammation in the body and allows identifying and keeping track of infections and diseases that cause inflammation.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Wu, J.; Gu, M. Microfluidic sensing: State of the art fabrication and detection techniques. *J. Biomed. Opt.* **2011**, *16*, 080901.
2. Mairhofer, J.; Roppert, K.; Ertl, P. Microfluidic systems for pathogen sensing: A review. *Sensors* **2009**, *9*, 4804–4823.
3. Ng, A.H.; Uddayasankar, U.; Wheeler, A.R. Immunoassays in microfluidic systems. *Anal. Bioanal. Chem.* **2010**, *397*, 991–1007.
4. Koh, I.; Josephson, L. Magnetic nanoparticle sensors. *Sensors* **2009**, *9*, 110.
5. Haun, J.B.; Yoon, T.J.; Lee, H.; Weissleder, R. Magnetic nanoparticle biosensors. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2010**, *2*, 291–304.

6. Tamanaha, C.; Mulvaney, S.; Rife, J.; Whitman, L. Magnetic labeling, detection, and system integration. *Biosens. Bioelectron.* **2008**, *24*, 1–13.
7. Kriz, K.; Gehrke, J.; Kriz, D. Advancement toward magneto immunoassays. *Biosens. Bioelectron.* **1998**, *13*, 817.
8. Kötz, R.; Fannin, P.C.; Trahms, L. Time domain study of Brownian and Néel relaxation in ferrofluids. *J. Magn. Magn. Mater.* **1995**, *149*, 42–46.
9. Krause, H.-J.; Wolters, N.; Zhang, Y.; Offenhausser, A.; Miethe, P.; Meyer, M.H.; Hartmann, M.; Keusgen, M. Magnetic particle detection by frequency mixing for immunoassay applications. *J. Magn. Magn. Mater.* **2007**, *311*, 436–444.



© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).