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► **To cite this version:**

Amine Rabehi, Benjamin Garlan, Hamid Kokabi, Kieu An Ngo, Hans-Joachim Krause. Electromagnetic Immunoassays using Magnetic Nanoparticles in a Microfluidic Structure. Journées d'Etude sur la TélÉSANTé, 6ème édition, Pôle Capteurs, Université d'Orléans, May 2017, Bourges, France. hal-01692437

HAL Id: hal-01692437

<https://hal.science/hal-01692437>

Submitted on 25 Jan 2018

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Electromagnetic Immunoassays using Magnetic Nanoparticles in a Microfluidic Structure

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Abstract – *Magnetic nanoparticles are commonly used in numerous applications such as magnetic resonance imaging (MRI), local hyperthermia treatment, magnetic separation, information storage, and medical diagnostics using magnetic immunoassays. The latter field has become increasingly popular in the last years because of the favorable properties of magnetic particles. In fact, the particles can be used both for magnetic actuation as well as for magnetic detection of biomolecules. In the case of immunoassays, the magnetic beads are bound to the biological target substance using the highly specific antibody-antigen interaction. The most common assay format is the sandwich immunoassay in which the analyte is captured by an immobilized primary antibody and the streptavidin-coated magnetic particles are bound to the analyte by a biotinylated secondary antibody. This article reports the conception and realization of a magnetic detection system that encompasses a microfluidic structure along with multilayer designed set of planar coils in a printed circuit board (PCB). The challenge is to measure the magnetic marker particles with high accuracy and with high selectivity using a small quantity of biological sample. The magnetic frequency mixing technique is very well suited for this purpose of immunoquantification. For this concept, analytical calculations along with Comsol Multiphysics simulations have been achieved to optimize the dimensions of the coils and the microfluidic reservoir.*

Keywords: *Lab-on-chip; magnetic detection; pathogen sensing; multiphysics simulations.*

I. INTRODUCTION

Due to the effect of spread diseases and pandemics caused by the amount of people that travel every day, a need of rapid, low cost and sensitive pathogen sensing systems is urgent. Many approaches try to develop a Lab-On-Chip (LOC) system. Among them, electrochemical and optical based methods are dominant. However, some suffer from few drawbacks like nonlinear detection range, lack of sensitivity, non-specific detection and complexity of integration [1-3]. Other methods include mechanical and magnetic based methods. The magnetic based ones 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]. Main drawbacks include magnetic nanoparticles residues due to sticking effect in the edge of the magnetic material area and hysteresis effects. A good LOC pathogen sensing system should be sensitive with a low limit of detection, cost effective, selective, and simple to use and with a large dynamic range. Having low cost and very sensitive detection system is rather challenging. Commercial products find a compromise between these criteria, and the majority of them are not magnetic based.

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). We use frequency mixing method with two magnetic excitation signals at distinct frequencies (f_1 , f_2) and we measure the amplitude of the signal response at a specific frequency ($f_1 + 2f_2$) that allows detecting and quantifying the amount of SPN [7].

For sensitive magnetic field detection, we optimize the detection system taking into account the pick-up and excitation coils optimization for sensitive detection and efficient magnetization. Furthermore, we must consider practical aspects like heating effects that can cause substantial damage to the biological samples and endanger the detection. Heating can also cause both a decrease and fluctuation in the detected signal since the magnetization of the SPN is inversely proportional to the temperature. Consequently, compromises should be made in order to have a sensitive miniaturized detection system.

II. PCB STRUCTURE

To design the PCB structure for the planar coils, an analytical program that includes the calculation of axial magnetic field along with sensor sensitivity and magnetic field noise has been developed. Both the magnetic excitation field and induced sensitivity formulas depend on a geometrical function that represents the dimensions of the studied coil. Fig.1 (a, b) show the dependence of the coil sensitivity and magnetic noise on the frequency and outer radius of the coil. A compromise should be made between sensitivity and magnetic noise minimal value. We can also conclude from Fig.1a that the magnetic field noise is mainly dependent on the thermal noise, thus minimal values of the coil resistance are required.

Finally, excitation coils are optimized according to the produced magnetic field, heat dissipation and total impedance value. Along with the mathematical calculations, we performed a set of Multiphysics simulations. First, a coupled 2D axisymmetric magnetic and heat transfer simulation (Fig.1d) allows for rapid testing and evaluation of the distribution and intensity of the excitation field. The heat transfer simulations (Fig.1d) were performed in order to study the heating effects due to excitation coils in the vicinity of the sample reservoir. This later simulation is used to define a limit in heat dissipation power, thus total impedance value to be used in the analytical calculations.

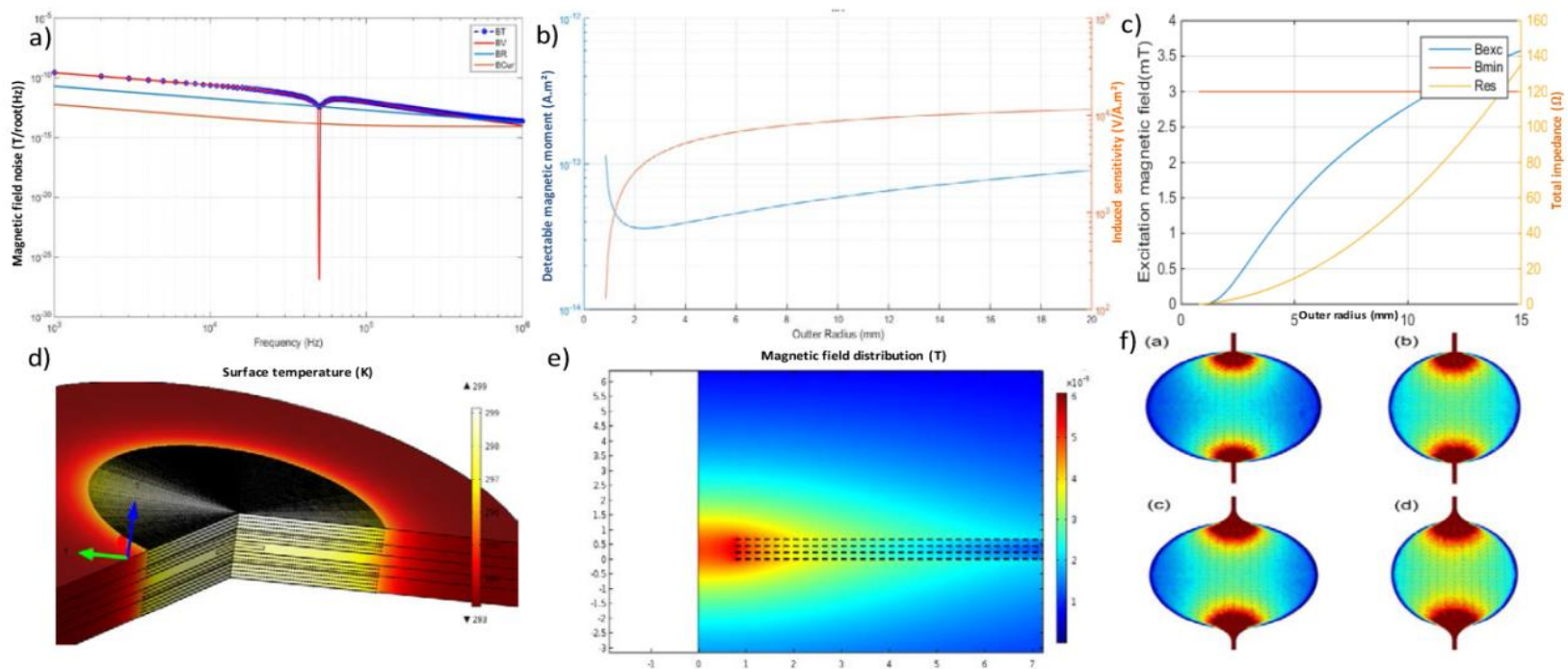


Fig. 1. (a) Magnetic field noise components: B_T , B_V , B_R and B_{Cur} are respectively total field noise, voltage noise, resistance noise and current noise for an AD745 preamplifier; (b) Detectable magnetic moment and induced sensitivity with respect to the outer radius of pick-up coil; (c) Magnetic excitation field (B_{exc}) and total impedance (Res) with respect to outer radius; (d) Heat transfer simulation; (e) magnetic field distribution; (f) fluidic flow with respect to reservoir shape.

III. MICROFLUIDIC STRUCTURE

Based on the multiphysics optimization of the microfluidic reservoir and coils dimensions, we designed and realized the whole structure. Because of the compromise between high number of turns and vicinity of excitation coils to sample reservoir, we chose to use a 8-layer for the realization of the excitation and pick-up coils. Four 4 layers are assigned to each coil and the appropriate number of turns were chosen from the analytical and multiphysics simulations. The PCB structure allows accurate gradiometric detection, with one reference side and one detection side, the measuring coil must then be wounded in opposition.

Besides, a PDMS based microfluidic reservoir was made in accordance to the microfluidic simulations. Fabrication steps include mask design, mold fabrication, PDMS replica structure fabrication and plasma bonding to a glass substrate.

IV. CONCLUSIONS

In this work, a first miniaturized system with planar excitation and detection coils for magnetic frequency mixing SPN detecting system was designed and fabricated. Both analytical and multiphysics simulation tools have been developed in order to optimize and miniaturize the system. Consequently, microfluidic reservoirs along with a multilayer printed circuit board have been realized in accordance. Further work includes the testing with different sizes of superparamagnetic nanoparticles (SPN) in order to investigate the sensitivity of the realized device. 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 to identify and keep track of infections and diseases that cause inflammation.

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