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Detection of superparamagnetic nanoparticles for immunoassays

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Abstract – We 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. We successfully tested this device with different concentrations of nanoparticles and determine the limit of detection of the prototype. These results are promising and are a step toward the creation of a portable pathogen sensing device.

Keywords: Lab-on-chip, magnetic detection, pathogen sensing, superparamagnetic nanoparticles, in vitro diagnostic device, microfluidics

I. INTRODUCTION

Ever-increasing number of people traveling on airplanes leads to the rapid spread of diseases worldwide and enhanced risks of pandemics. So there is a need for a rapid, sensitive, reliable, low-cost, and portable system for nomadic applications of pathogen detection. Moreover, the detection of a biological agent or entity and the determination of its concentration can be crucial for anticipating possible health threats, whether epidemic or pandemic, environmental threats, or to combat other contextual threats, including bioterrorism, or chemical and biological weapons. To achieve this objective, designing and generating embedded microsystems composed of innovative sensors is necessary [1-2]. Many attempts have been made to develop LoC systems. Among them, electrochemical and optical based methods dominate; however, they often suffer from drawbacks such as a nonlinear detection range, a lack of sensitivity, non-specific detection, and complexity of integration [3-5]. Other methods include mechanical [6-7] and magnetic detection approaches. The latter holds promise due to their miniaturization possibility [8-11].

The LoC system we designed is based on the development of a simple, cost effective system using magnetic detection, taking advantage of the nonlinearity of superparamagnetic nanoparticles (SPN). Biological analysis with high sensitivity magnetic measurements is a new type of immunochemical diagnosis using SPN as markers instead of conventional enzymes, radioisotopes or fluorescent compounds [12-13]. This novel method of analysis, which can be miniaturized, involves the covalent ligation of biomarker-specific

monoclonal antibodies to SPN. The presence of SPN is then detected by the frequency mixing method (Figure 1) which consists in the use of two distinct excitation frequencies and the reading and quantification of the mixed frequency signals indicative of the magnetic non-linearity of the superparamagnetic nanoparticles [14-16]. This technique makes it possible to envisage a rapid, portable and cheap pathogen detection method [17].

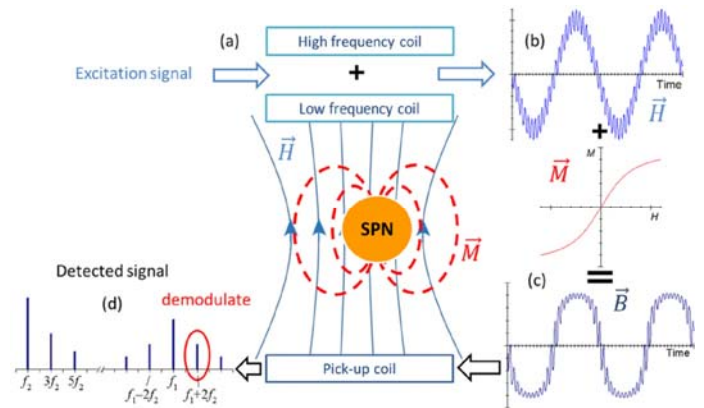


Figure 1. (a) Principle of detection of the proposed structure. (b) Magnetic excitation field with low and high frequencies. (c) Resulting magnetic flux density. (d) Fourier transform of the detected signal. In red, the selected mixing term for the detection of SPNs is marked.

II. DEVICE PROTOTYPE FOR SPN DETECTION

A. Device architecture

A PCB/microfluidic prototype was developed. The structure is composed of 4 copper multilayer coils: three coils emit the electromagnetic field, two for low frequency and the other for high frequency, the fourth one is the detection coil. These coils are contained in two PCB structures ($100 \times 40 \times 1.55 \text{ mm}^3$) surrounding above and under the serpentine like microfluidic channel ($12 \times 12 \text{ mm}^2$) which can contain $14 \mu\text{L}$ of magnetic nanoparticles solution. Each coil is composed of four layers; the tracks are $100 \mu\text{m}$ wide with an inter-distance of $100 \mu\text{m}$. Each layer of track has a thickness of $35 \mu\text{m}$. The emitting coils have a radius of 13 mm (60 turns/layer) and the detection coil has a radius of 10 mm (46 turns/layer). Because both the excitation and pick-up coils are made in the same PCB, we had to balance the above mentioned criteria for proper

magnetization and detection. In the case of this validation process, the distance between the PCBs is 4 mm and the distance between the detection coil (lower PCB) and the microfluidic chamber is 1 mm. Two sets of PCB/microfluidic are used, one for the measurement and the other one for reference. They are linked in order to subtract the signal detected with the sample and the signal detected with the reference to get a precise gradiometric measurement of the difference (Figure 2).

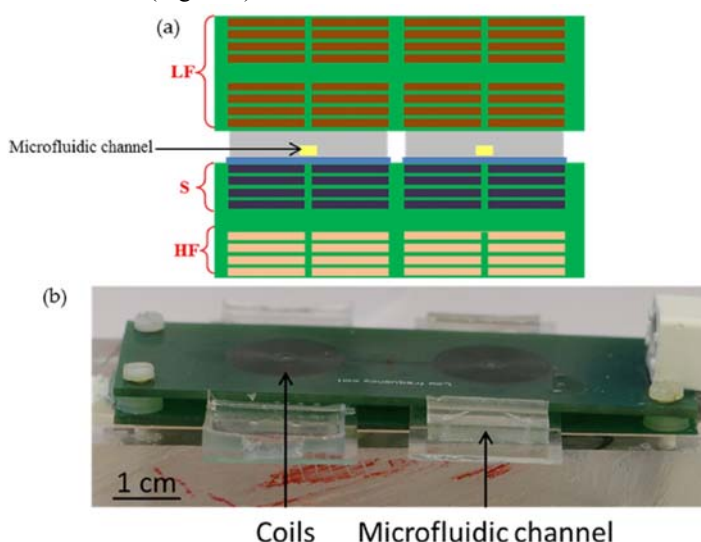


Figure 2. (a) Schematic description of the layers (front view): the two green blocks represent the two PCBs containing the coils (LF: Low Frequency, S: Sensor and HF: High Frequency), the grey part represents the PDMS layers which contains the microfluidic channel (the yellow part) and which is bonded to a glass slide (in blue). (b) Picture of the PCB/ microfluidic first prototype detection structure.

B. Detection of superparamagnetic nanoparticles

The sensitivity response of the structure was tested with respect to the concentration of the SPNs. For these experiments the low frequency is 80 Hz with a coil voltage of 14 V and the high frequency is 40 kHz with a voltage of 15 V. The response signal of the detection coil is amplified by a factor of 500 using a standard lock-in amplifier. Different concentrations of iron oxide nanoparticles (Fe_2O_3) suspensions were used to validate the detection technique and determine the limit of detection (LoD) of the structure. The core of the SPNs is 20 nm in mean diameter. The magnetic response as a function of the mass concentration of iron oxide nanoparticles is shown in Figure 3. The amplitude of the detected signal is linear with the concentrations of the nanoparticles for a linear range of 2 orders of magnitude. Furthermore, the tests were repeated at day's interval and proved to be very reproducible. With an accepted error of less than 15 %, the limit of detection is about $15 \text{ ng}/\mu\text{L}$.

Furthermore, other types and sizes of nanoparticles were successfully detected using this device. Different microfluidic chambers were also tried to optimize the voltage response.

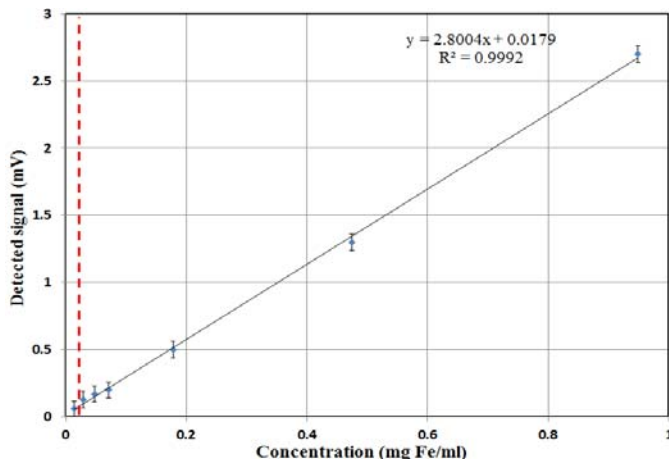


Figure 3. Magnetic response as a function of the mass concentration of 20 nm Fe_2O_3 nanoparticles. The red dotted line indicates the calculated limit of detection.

III. CONCLUSION AND PERSPECTIVES

These results are very promising and validate the magnetic detection of SPNs within the developed first prototype device. Experiments to validate the magnetic detection of biological entities with the PCB structure are in progress. We hope to achieve rapid LoC magnetic immunoassays for healthcare or environmental purposes in a close future.

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