Academic year 2020/2021
Proposal of an internship subject for Master students, level M2:

Study of embedded acquisition interface for magnetic microsensors for the detection of biological agents

Internship place: Laboratory of Computer Science LIP6, Sorbonne Université
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Context. The detection of a biological entity and the determination of its concentration have become essential in order to anticipate a possible health threat (epidemic as EVD from Ebola or pandemic as COVID-19 from SARS-Cov-2), environmental threat or to fight against other contextual threats (bioterrorism, chemical and biological weapons). In this area, one of the main objectives is to facilitate this detection with a sensitive, reliable and portable system. To achieve this goal, it is then necessary to facilitate this detection by designing a reliable and portable microsystem integrating innovative sensors with high sensitivity.

The use of multilayered planar magnetic sensors coupled with magnetic nanoparticles (MNP) [1-10] makes it possible to obtain a high sensitivity method of detection, particularly promising for immunochemical diagnosis and avoids conventional methods using enzymes, radioisotopes or fluorescent compounds. Thanks to their extractability and sortability, MNP are suitable for the examination of biological samples, serving as markers for biochemical reactions [2, 7-10]. This new magnetic detection technique, which can be miniaturized, involves the specific binding of an antibody to its antigen (Fig. 1) with a magnetic marker. The presence of MNP is then detected by the frequency mixing method which consists of using two distinct frequencies of excitation fields and the reading and quantification of the mixed frequency signals which are indicative of the magnetic non-linearity of the nanoparticles. This technique makes it possible to design a method of rapid detection, requiring very small amount of biological sample, portable and at a lower cost compared with other major detection techniques.

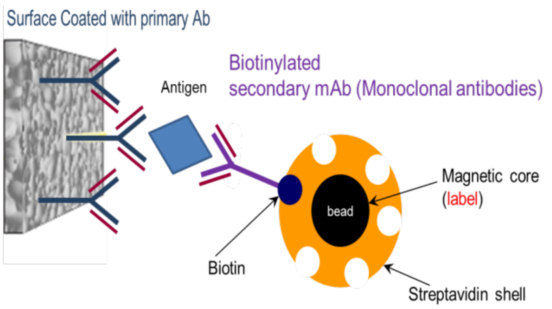

Figure 1: Specific binding of an antibody to its antigen with a magnetic marker.

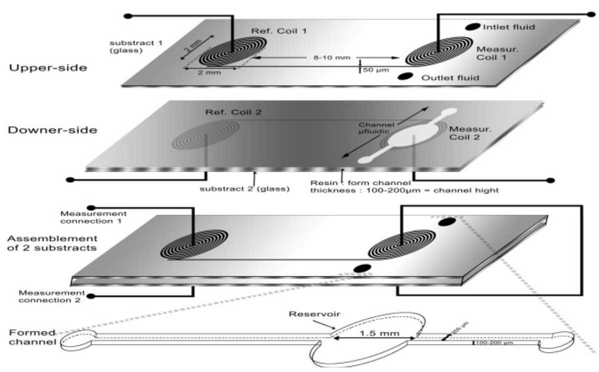

Figure 2: Schematic representation of the integration of magnetic microsensors associated to a microfluidic device.

As part of a multidisciplinary and European collaboration with "Institute of Bioelectronics" in Juelich (Germany), and the preliminary realizations, planar microcoil structures integrated into a multilayered PCB and associated above and below a microfluidic structure have been designed (Fig. 2) and fabricated. An electromagnetic test bench, controlled by LABVIEW, with a frequency mixing technique (Fig. 3) using synchronous detection has been set up and it has been coupled with a microfluidic system.

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Master project objectives.

In presence of magnetic nanoparticles (MNP), the nonlinearity of the magnetization curve (fig. 3a) submitted to an excitation magnetic signal composed of two sinusoids (fig. 3b), leads to non-linear reaction signal of MNP (fig 3.c) and this results in an output with intermodulation harmonics (fig. 3d). The goal of the measurement is to detect the presence or non-presence of these harmonics related to MNP, which serve as marker for the presence of the virus in the sample (fig. 1). Presently, the analysis of the output of the electromagnetic sensor is done with bulky laboratory equipment (network analyzer).

The goal of the project is to propose an embedded architecture of the measurement system able to perform this measurement, the ultimate goal being an implementation of the architecture on an integrated circuit (ASIC).

Master project program. The internship program comprises the following activities.

1. Knowledge of the existing experimental setup using laboratory equipment and understanding of an electrical model of the sensor in a Spice environment.
2. Establishment of electrical specification for the embedded measurement system: functionality, sensitivity, parameters of the signals to be detected
3. In collaboration with the research team working on the project at GeePs laboratory, development of an architecture of the embedded measurement and its system-level (behavioral) modeling in the environment of design of integrated circuits (Cadence, Spice).

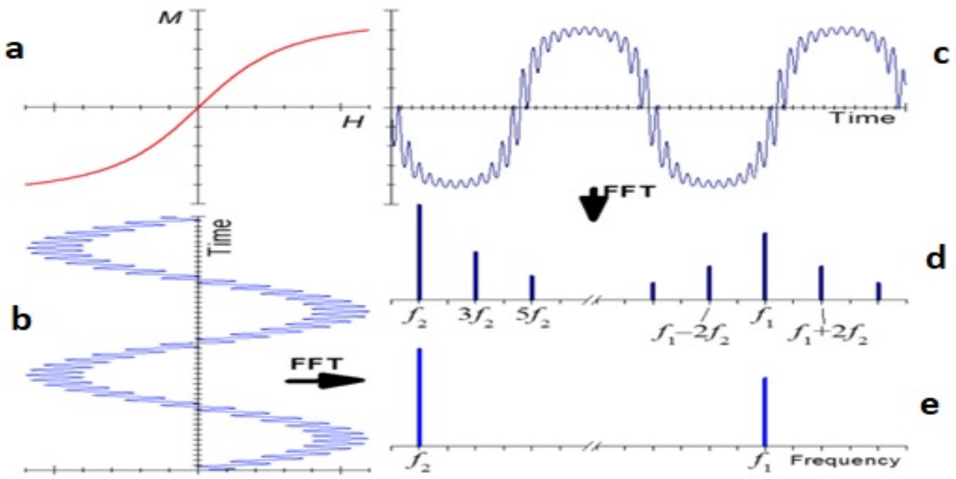

Figure 3: Principle of magnetic nanoparticles detection by "frequency mixing technique" (a) The nonlinear magnetization curve of magnetic nanoparticles, (b) excitation magnetic signal composed of two sinusoids, (c) The resulting time-dependent magnetization curve, (d) Resulting frequency dependent magnetization curve with intermodulation harmonics (fig. 3d). (e) The Fourier transform of magnetization response.

Required skills: With background in electrical engineering, computer science or neighboring disciplines, candidate should have a good knowledge of electrical measurement techniques, of signal processing, and have an experience with electronics CAD tools. A knowledge of sensors and instrumentations, electromagnetism and electrical calculations will be appreciated. **<u>There is the possibility of pursuing a PhD thesis on this subject.</u>**

People to contact with your CV and cover letter:

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Bibliography:

[1] A. Rabehi, B. Garlan, S. Achtsnicht, H.-J. Krause, A. Offenhäusser, K. Ngo, S. Neveu, S. Graff-Dubois and H. Kokabi,"Magnetic Detection Structure for Lab-on-Chip Applications Based on the Frequency Mixing Technique", Sensors, 18, 1747; doi: 10.3390/s18061747, (2018).

[2] S. Achtsnicht, C. Neuendorf, T. Faßbender, G. Nölke, A. Offenhäusser, H.-J. Krause, F. Schröper, "Sensitive and rapid detection of Cholera Toxin subunit B using Magnetic Frequency Mixing Detection", *PLOS ONE* **14**, e0219356 (2019).

[3] A. Rabehi, B. Garlan, F. Shanehsazzadeh, H. Hokabi, K.A. Ngo, H.-J. Krause, "Magnetic detection structure for LOC immunoassays, multiphysics simulations and experimental results", poster id1374, Eurosensors 2017, Paris (Sept. 2017).

[4] H. Kokabi, A. Rabehi, S. Fattoum, N. Yakdi, K.A. Ngo, V. Dupuis, A. Krings, L. Chen, H.-J. Krause, "Magnetic frequency mixing detection of magnetic nanoparticles for immunoquantification in a microfluidic structure", international symposium on biomaterials and smart systems, Cergy-Pontoise, (oct. 2014).

[5] F. Sarreshtedari, H. Kokabi, J. Gamby, K. A. Ngo, H.-J. Krause, M. Fardmanesh, "Aggregation and detection of magnetic nanoparticles in microfluidic channels", Journal of Electrical Engineering, N°63, pp. 27-31, (2012).

[6] H.-J. Krause, N. Wolters, Y. Zhang, A. Offenhäusser, P. Miethe, M.H.F. Meyer, M. Hartmann, M. Keusgen, Magnetic particle detection by frequency mixing for immunoassay applications, *J. Magn. Magn. Mater.* 311, 436-444, (2007).

[7] M.H.F. Meyer, M. Hartmann, H.-J. Krause, G. Blankenstein, B. Müller-Chorus, J. Oster, P. Miethe, M. Keusgen, "CRP determination based on a novel magnetic biosensor", *Biosensors and Bioelectronics*, 22, 973-979 (2007).

[8] M.H.F. Meyer, M. Stehr, S. Bhuju, H.-J. Krause, M. Hartmann, P. Miethe, M. Singh, M. Keusgen, "Magnetic biosensor for the detection of Yersinia pestis", *Journal of Microbiological Methods* 68, 218-224 (2007).

[9] H.-B. Hong, H.-J. Krause, K.-B. Song, C.-J. Choi, M.-A. Chunga, A. Offenhäusser, "Detection of two different Influenza A viruses using an ELIFA system and a magnetic biosensor", *J. Immunol. Meth.* 365, 95-100, (2011).

[10] S. Achtsnicht, J. Tödter, J. Niehues, M. Telöken, A. Offenhäusser, H.-J. Krause, F. Schröper. "3D Printed Modular Immunofiltration Columns for Frequency Mixing-Based Multiplex Magnetic Immunodetection", Sensors 19(1): 148, (2019).