Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

RTD Fluxgate performance for application in magnetic label-based bioassay: preliminary results

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Abstract — **Magnetic bioassay is becoming of great interest in several application including magnetic separation, drug delivery, hyperthermia treatments, magnetic resonance imaging (MRI) and magnetic labelling. The latter can be used to localize bio-entities (e.g. cancer tissues) by using magnetic markers and high sensitive detectors. To this aim SQUIDs can be adopted, however this result in a quite sophisticated and complex method involving high cost and complex set-up. In this paper, the possibility to adopt RTD Fluxgate magnetometers as alternative low cost solution to perform magnetic bio-sensing is investigated. Some experimental results are shown that encourage to pursue this approach in order to obtain simple devices that can detect a certain number of magnetic particles accumulated onto a small surface such to be useful for diagnosis purposes.**

I. INTRODUCTION

Magnetic bioassay is becoming of great interest due to advances in magnetic materials and in high sensitive detection techniques [1]. The main idea behind these techniques is the possibility of labelling target bio-entities with magnetic particles performing direct or indirect tasks.

A large ensemble of magnetic particles is available which differs in magnetic properties, sizes and biocompatibility properties. Particles with sizes ranging from a few nanometres up to tens of nanometres are available, which make them comparable to the biological entity of interest like a cell (10–100 μm), a virus (20–450 nm), a protein (5–50 nm) or a gene (2 nm wide and 10–100 nm long). For larger size target cells both magnetic nanoparticles and larger particles can be used. To this end microspheres (agglomerations of sub-micron sized magnetic particles) represents a convenient solution [2].

Labelling is made possible usually through coating the magnetic particles surface with biocompatible molecules providing a link between the particle and the target site on a cell or molecule. A large number of coatings are commercially available.

Target cells are usually targeted by antibodies or other biological macromolecules binding to their matching antigen. For example, magnetic particles coated with immunospecific agents have been successfully bound to red blood cells [3, 4], lung cancer cells [5], bacteria [6] and other target entities [7-8].

Actually, several applications in the field of magnetic bioassay have been identified of which magnetic separation, drug delivery, hyperthermia treatments, magnetic resonance imaging (MRI) and magnetic labelling are a limited number of examples.

In separation task the magnetically labelled material is separated from its native solution by applying a magnetic force conveying the target entities into the inspection site.

Aims of drug delivery are the reduction of side effects caused by the systemic distribution of traditional pharmacological therapy and dosage reduction by a specific drug localization. As an example, in cancer therapy, usually a cytotoxic drug is conveyed to the target site by a biocompatible ferrofluid carrier.

Concerning hyperthermia treatments the use of magnetic labelling allows to fix the unsustainable heating of healthy tissue of traditional techniques.

Magnetic particles as contrast agent in MRI are used for the localization of brain and cardiac infarcts, liver lesions or cancers. There are several commercially available magnetic contrast agents such as dextran coated supermagnetic iron oxide which are biocompatible and are excreted via the liver after the treatment. The particles used are magnetically saturated in the normal range of magnetic field strengths used in MRI scanners, thereby establishing a substantial locally perturbing dipolar field.

Magnetic biosensing techniques can be used to localize target entities. In this case, after labelling the target entities a remote sensing approach must be adopted. The most common techniques are AC susceptometry or SQUID magnetometry [9-10]. Although these schemes allow high

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sensitive, main drawbacks are related to expensive cryogenics and instrumentation.

Alternative solutions use giant magnetoresistance sensor (GMR) which presents a resistance varying with the applied magnetic field [11]. Although these device are nominally less sensitive than SQUID magnetometers, the extreme proximity of the sensor to the inspected entities tagged by magnetic beads could dramatically boost its performance.

Fluxgate magnetometers represent another solution to sense weak magnetic field or field perturbation. Recently, Residence Times Difference (RTD) Fluxgate have been proposed as competitive devices to the traditional second harmonic architectures [12]. Low cost, small dimensions, high sensitivity, low power consumption and an intrinsic digital form of the output signal are the main advantages given by the innovative readout strategy.

In this paper, preliminary results concerning the use of RTD-Fluxgate as candidate for magnetic beads detection in bioassay application are given.

II. THE RTD-FLUXGATE: BASIC PRINCIPLE AND TECHNOLOGICAL ISSUES

A RTD Fluxgate is based on the two-coils structure (a primary coil and a secondary coil) shown in Figure 1a. Coils are wound around a suitable ferromagnetic core showing a sharp hysteretic input-output characteristic which allows to infer that switching between the two stable states of the magnetization occurs instantaneously when the applied magnetic field exceeds the coercive field level Hc.

A periodic driving current, Ie, is forced in the primary coil and generates a periodic magnetic field, He parallel to the geometry of the core. This geometry is adopted to guarantee uniformity of magnetic field along the ferromagnetic core. A target field Hx is applied in the same direction of He; the secondary coil is used as pick-up coil and the output voltage Vout, shown in Figure 1b, carries information on the target magnetic field.

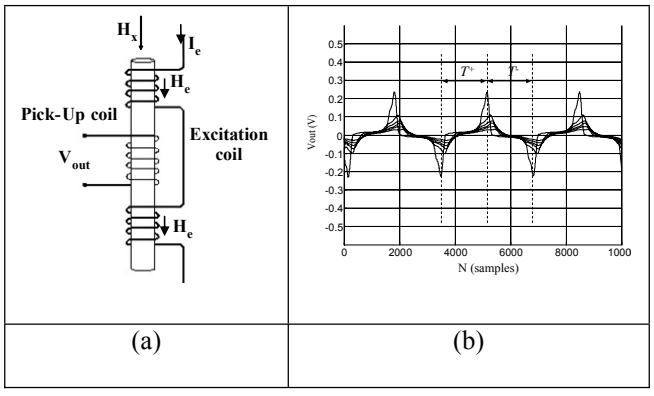

Figure 1. (a) RTD Fluxgate sensor structure; (b) Typical pick-up coil output signal.

The principle of RTD Fluxgate is to exploit the information carried by the time position of spikes in the Vout signal. Time intervals, T+ and T-, defined by two successive peaks represent times spent by the core magnetization in the two steady states. These time intervals are called Residence Times.

In the case of a time-periodic excitation having amplitude large enough to cause switching between the steady states and in the absence of any target field, the hysteresis loop is symmetric and two identical Residence Times are obtained. The presence of a target dc signal, Hx, leads to a skewing of the hysteretic loop with a direct effect on the Residence Times, which are no longer the same. The difference between two Residence Times is directly correlated to the target field Hx.

Operatively, it can be affirmed that the device operates almost like a static hysteretic nonlinearity and the Residence Times Difference can be computed from spikes in the pickup coil output voltage Vout, as shown in Figure 1b. A detailed treatment of RTD Fluxgate can be found in [13, 14].

The RTD-Fluxgate adopted in the experimental set-up for magnetic beads detection is realized in PCB technology. The Magnetic Alloy 2714 As Cast (Cobalt based), by Metglas® has been chosen for the magnetic core layer due to its suitable hysteretic characteristic which encourages the use of a readout strategy based on the estimation of the RTD. In the process a patterned Metglas foil (wet etching is adopted for Metglas patterning) is embedded between two FR4 PCB layers. A simplified process description can be summarized by the following steps:

- the patterned Metglas is aligned respect the two RF4 layers;
- the patterned metal layers are aligned to the sensor structure according to layout design;
- the whole layers are pressed, while heating the whole system up to 200 °C.
- Finally the vias formation between the lower and upper layer let to complete the windings for the coils.

Figure 2 shows a set of RTD-Fluxgate developed in PCB technology with an embedded foil of Metglass. Details on the technology adopted and the characterization of devices with different shapes and dimensions of the Metglass core are given in [15-16].

Table 1 summarizes typical figure of merit of the RTD Fluxgate magnetometer adopted.

TABLE I. MAIN FIGURE OF MERIT OF RTD-FLUXGATE

Sensitivity	0.2 μs/nT
Noise level peak-peak	5 μs
Power Consumption (Absorbed current peak-peak)	40 mApp

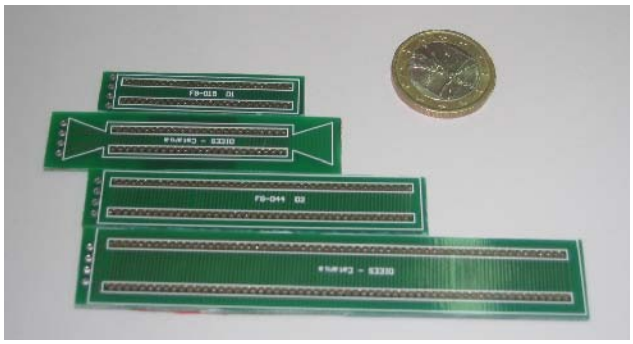

Figure 2. Image of a set of PCB integrated Fluxgate sensors.

III. THE EXPERIMENTAL SET-UP FOR MAGNETIC BEADS DETECTION

The task to be accomplished within this experiment is the detection of micrometer magnetic particles. In particular, magnetic beads **CM-10-10** from Spherotech have been adopted which are commonly used for several applications as cell separation, affinity purification, DNA probe assays and magnetic bioassay [17]. Particles (spherical in shape, uniform in size and paramagnetic) are prepared by coating a layer of magnetite and polystyrene onto monodispersed polystyrene core. They become non-magnetic when removed from a magnetic field, and do not retain any detectable magnetism even after repeated exposure to strong magnetic field.

The experimental set-up is shown in Figure 3. It consists of a RTD-Fluxgate magnetometer, operated with a sinusoidal bias @80Hz, a permanent magnet used to polarize the magnetic particles and a glass tube containing the solution given by Spherotech with a know concentration of magnetic beads.

The experiments have been conduced by measuring the changes in the Fluxgate output with and without the presence of the magnetic particles. Two parameters have been varied: the distance between the beads and the magnetometer and the concentration of the magnetic solution. The whole experiment has been conducted inside a shield for DC magnetic fields in order to reduce environmental spurious effects on the measurement results.

Actually, the inspected target distance ranges between 1 cm and 4 cm, while the beads number has been varied from 10^4 to 10^{10}. Given the beads diameter (1 μm), the magnetic particles concentrations considered here roughly correspond to an estimated target surface ranging from fractions of mm^2 to few cm^2 respectively. The latter value is probably too large for actual use of the proposed sensor, however the goal of this paper is simply to show the suitability of the approach to contribute to a field where a simple and low cost sensor for targeting magnetic label can be of great interest. The sensor has still a significant margin for improvements that will give certainly a better spatial resolution.

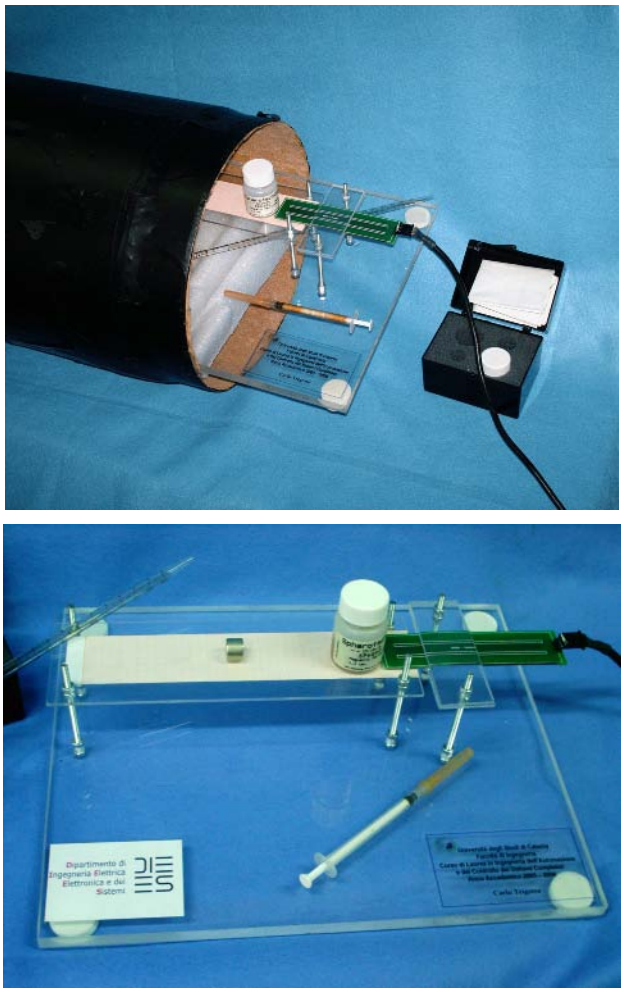

Figure 3. The experimental set-up for magnetic beads detection.

IV. RESULTS AND CONCLUSION

RTD estimated through the experimental set-up are given in Figures 4. In particular, the evolution of the RTD for two different values of the number of beads is reported. Each plot reproduces the alteration of the RTD when the magnetic sample is positioned or removed in front of the fluxgate. A complete characterization of the system in terms of RTD variation (DRTD) is given in Fig.5 and Fig.6.

It must be observed that to test efficiency and limits of the experiment conduced, for each target distance the lowest detectable beads number has been estimated taking into account limitation given by the intrinsic noise floor in the readout signature. During the experiment a noise level of 5 μs was recorded which, as an example, in the case of 1 cm target distance set the lowest detectable number of beads to 108. Turning on magnetic bioassay tasks, this experiment demonstrates the possibility of using RTD-Fluxgate magnetometers to estimate target entity sizing 1 cm by 1 cm, under the hypothesis of one-to-one bonding between magnetic beads and target bio-particles. Of course, this

represents a lower bound which can be reduced by optimizing the operating condition of the readout strategy.

Results presented evidences the possibility to adopt RTD-Fluxgate magnetometers as a suitable readout strategy in magnetic biosensing, when low cost and ease-to-use features become dominant as respect to extreme resolution in the localization of target bio-entities.

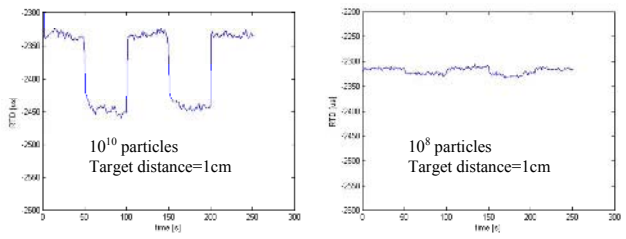

Figure 4. The RTD as a function of the magnetic beads number.

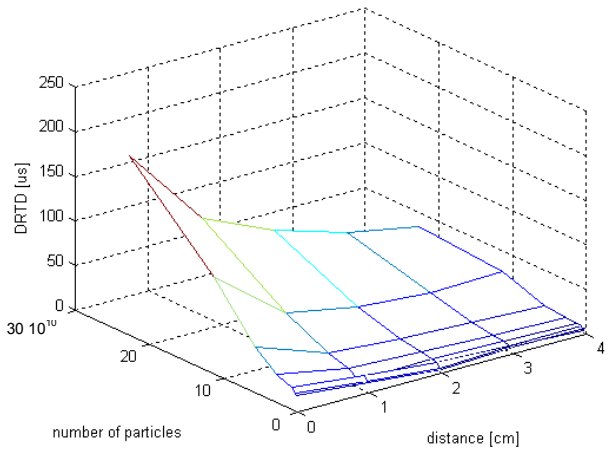

Figure 5. RTD variation (DRTD) as a function of the target distance and beads number.

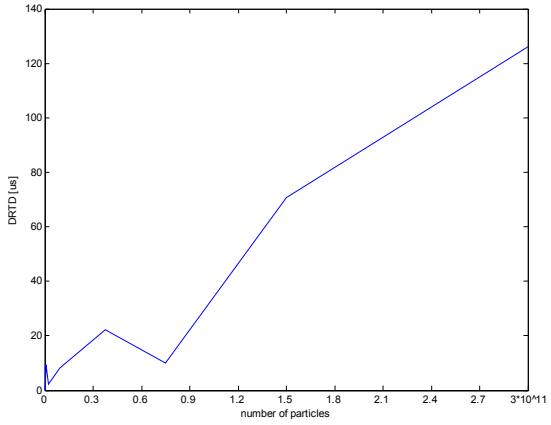

Figure 6. RTD variation (DRTD) as a function of the beads number with the sensor placed .

V. REFERENCES

[1] Q A Pankhurst1, J Connolly2, S K Jones3 and J Dobson, Applications of magnetic nanoparticles in biomedicine, J. Phys. D: Appl. Phys. 36 (2003) R167–R181, IOP Journ. Phys. D: Appl. Physics.

[2] Ugelstad J, Prestvik W S, Stenstad P, Kilaas L and Kvalheim G 1998 Selective cell separation with monosized magnetizable polymer beads *Magnetism in Medicine* ed H Nowak (Berlin: Wiley-VCH) pp 471–88

[3] Molday R S and MacKenzie D 1982 Immunospecific ferromagnetic iron–dextran reagents for the labeling and magnetic separation of cells *J. Immunol. Methods* 52 353–67

[4] Tibbe A, de Grooth B, Greve J, Liberti P, Dolan G and Terstappen L 1999 Optical tracking and detection of immunomagnetically selected and aligned cells *Nature Biotechnol.* 17 1210–13

[5] Kularatne B Y, Lorigan P, Browne S, Suvarna S K, Smith M O and Lawry J 2002 Monitoring tumour cells in the peripheral blood of small cell lung cancer patients *Cytometry* 50 160–7

[6] Morisada S, Miyata N and Iwahori K 2002 Immunomagnetic separation of scum-forming bacteria using polyclonal antibody that recognizes mycolic acids *J. Microbiol. Methods* 51 141–8

[7] Zigeuner R E, Riesenberg R, Pohla H, Hofstetter A and Oberneder R 2003 Isolation of circulating cancer cells from whole blood by immunomagnetic cell enrichment and unenriched immunocytochemistry *in vitro J. Urol.* 169 701–5

[8] Mura C V, Becker M I, Orellana A and Wolff D 2002 Immunopuri.cation of Golgi vesicles by magnetic sorting *J. Immunol. Methods* 260 263–71

[9] C.B. Kriz, K. Radevik, D. Kriz, Anal. Chem. 68, 1996

[10] R. Kotiz, H. Matz, L. Trahms et al., IEEE Trans. Appl. Supercond., 7, 3678, 1997

[11] M.M. Miller, P.E. Sheehan, R.L. Edelstein, C.R. Tamanaha, L. Zhong, S. Bounnak, L.J. Whitman, R.J. Colton, A DNA array sensor utilizing magnetic microbeads and magnetoelectronic detection, Journ. of Magnetism and Magnetic Materials, 225, 138-144, 2001

[12] B. Andò, S. Baglio, A. Bulsara, V. Sacco. Theoretical and experimental investigations on residence times difference Fluxgate Magnetometers, *Measurements (Elsevier)* 38 (2) (2005). p. 89-112.

[13] B. Andò, S. Baglio, A. Bulsara, V. Sacco. "Residence Times Difference" Fluxgate Magnetometers, *Sensors Journal, IEEE* 5 (5) (2005). p. 895-904.

[14] B. Ando, S. Baglio, A. Bulsara, V. Sacco: Effects of driving mode and optimal material selection on RTD-Fluxgate. IEEE Transaction on Instrumentation and Measurement, Vol. 54, issue 4, pp. 1366-1373 (2005).

[15] B. Andò, S. Baglio, V. Caruso, V. Sacco, A. Bulsara, Multilayer based technology to build rtd fluxgate magnetometer, IFSA, Sensors & Transducers Magazine, March 2006.

[16] B. Andò, S. Baglio, V. Caruso, V. Sacco, Investigate the optimal geometry to minimize the demagnetizing effect in RTD-Fluxgate, IEEE IMTC 2006.

[17] http://www.spherotech.com/tech.htm