SP 1 Biomagnetism and medical applications

SP1 - Parallel session 1

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SP1.1.02

Magnetic nanoparticle characterization using thermal noise magnetometry

J. Leliaert, A. Coene, M. Liebl, D. Eberbeck, U. Steinhoff, F. Wiekhorst, L. Dupré, B. Van Waeyenberge

Text Magnetic nanoparticles have appealing properties for many biomedical applications like the emerging cancer treatment magnetic particle hyperthermia. Alternatively, when equipped with a suitable coating, they can be used as drug carriers or disease detectors. The combination of their small sizes and a large magnetic moment also makes them excellent candidates for use in imaging applications. However, for all these applications to work reliably, the nanoparticle properties should be well known and their dynamic behavior should be fully understood.

Typically, magnetic nanoparticles are investigated by measuring their response to externally applied magnetic fields. However, such external excitations affect the aggregation state of the particles via e.g. chain formation, and thus influence the measurement results. We recently demonstrated the feasibility of a new approach[1], in which the noise signal resulting from the thermal switching of the nanoparticles in the absence of any external excitation is measured with the help of SQUIDs in a magnetically shielded environment. Here, we present a magnetic characterization of several magnetic nanoparticle samples based on thermal noise magnetometry, and show the complementarity and similarity to magnetorelaxometry data of the same samples[2].

[1] J. Leliaert, et al., Appl. Phys. Lett., 107, 222401 (2015).
[2] J. Leliaert*, D. Eberbeck*, et al., J. Phys. D: Appl. Phys. 50 (8), 085004 (2017)

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SP1.1.03

A trisymetric magnetic microchip surface for unrestricted two-way directional movement of magnetic microbeads

U. Sajjad, E. Lage, J. McCord

Text The guidance of labelled microcarriers in microfluidic environments is a prerequisite to the development of magnetic pattern assisted lab-on-chip technology. By application of square wave modulations of in-plane applied magnetic fields we enable the forward and backward locomotion of microspheres on discrete hexagonally arranged ferromagnetic structures in flowless microfluidic environments on a single bead level. Using dynamic effects [1], we achieve selective directional transportation and two-way separational motion of different ensembles of superparamagnetic beads across a varying hexagonal stray magnetic field pattern. Multidirectional and independent motion of different bead populations are demonstrated. In consequence, we realize multifunctional patterned magnetic surfaces which enable transport of mixed populations of functionalized microcarriers in an autonomous manner. We show that the characteristics of movement being programmable and not bound to the device allow for adaptive and flexible steering of magnetic microbeads for future lab-on-chip technologies.
The capability of freely routing beads above a symmetrically patterned magnetic surface across two-dimensional areas adds a keystone for the realization of magnetic surface based diagnostic tools. The use of the presented novel approach promises to enable individual handling of differently magnetically labelled cells for efficient lab-on-chip analysis.
[1] U. Sajjad et al 2017 J. Phys. D: Appl. Phys. 50 135003

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SP1 - Parallel session 1

SP1.1.04

Detection of Micron to Submicron Biologic Objects with Giant Magneto-Resistive Sensors

M. Giraud, F. D. Delapierre, G. Jasmin-Lebras, C. Feraudet Tarisse, E. Paul, G. Cannies, S. Simon, C. Fermon

Text Lowering the detection limit of disease biomarkers for early diagnosis with cheap and easy-to-use process is a topic of constant interest. We present a dynamic approach on a chip, combining magnetic detection and antibodies specific recognition. The principle is to incorporate magnetic particles functionalized with the proper specific antibody in a solution containing the biological fluid and biological object of interest and to inject the mixture in a microfluidic channel underneath which sensitive magnetic sensors are placed. A perpendicular magnetic field polarizes the magnetic particles and their stray dipolar field is detected. As the signals of isolated beads or small aggregates and the signals of analytes bound to a large amount of beads are different, the presence of these last ones can be brought out without any other processing of the sample. The chosen analytes are NS1 mouse cancerous cells diluted in phosphate buffer saline solution (PBS). Single cells can be detected. Limitation is today given by false positives due to large aggregates signals. We will discuss approaches to mitigate this limitation.

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SP1 - Parallel session 1

SP1.1.05

Functionalized Iron Nanowires for Chemical and Photothermal Cancer Cell Death Induction

A. Martinez-Banderas, A. Aires, J. E. Perez, M. Quintanilla, T. Ravasi, A. L. Cortajarena, J. Kosel

Text New anticancer therapies attempt to attack the disease using different strategies simultaneously. Iron (Fe) nanowires (NWs) are readily internalized by cells, exhibit a low cytotoxicity, and are a promising nanomaterial for multi-modal cancer treatment. A novel strategy for bimodal cancer cell dead induction was developed combining the chemotherapeutic properties of doxorubicin (DOX) attached to Fe NWs with the NWs photo-thermal properties. Fe NWs were first coated with bovine serum albumin and then functionalized with DOX through a pH sensitive linker. The capability of Fe NWs to convert optical energy from a near infrared laser into heat in physiological conditions was evaluated with a thermal camera reaching an average value of 83±7% transduction efficiency. Cellular internalization of NWs in breast cancer cells was confirmed by confocal reflection microscopy and inductively coupled plasma-mass spectrometry. Upon irradiation of these NW labeled cells, a temperature increase of 20°C was recorded. The ability of the functionalized NWs to induce cancer cell death by combining the selective drug release with photothermal therapy was evaluated by a cell viability assay revealing up to 76% of cell death. The bimodal treatment is more effective than individual therapeutic strategies NWs+DOX (~40%) and NWs+laser (~28%) at the same concentration and comparable to a previously reported bimodal strategy that combined chemotherapy and magneto-mechanical actuation.

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SP1 - Parallel session 1

SP1.1.06

Parametric analysis of magnetic nanostructures for hyperthermia applications

R. Ferrero, A. Manzin, G. Barrera, F. Celegato, M. Coïsson, P. Tiberto

Text Recently, magnetic nanostructures (MNs) have been intensively studied for future application in cancer treatment, thanks to the possibility of inducing cell apoptosis via hyperthermia or cell membrane mechanical stimulation [1]. Focusing on hyperthermia, when an external ac magnetic field is applied to an ensemble of MNs dispersed in a tissue, different physical phenomena can concur to heat generation, e.g. Néel relaxation, Brownian relaxation, hysteresis and eddy current losses, with relative contribution strongly dependent on the size and physical properties of MNs. Here, we present a micromagnetic modelling analysis of permalloy MNs with variable shape (disk, ring, cube, pillar, sphere), for possible application in magnetically mediated hyperthermia. A parametric study is performed by varying aspect ratio and size (up to 1 μm), with the aim of finding the optimal conditions for the maximization of the specific heating capabilities. Hysteresis losses, being the predominant heating contribution for the considered MNs, are calculated by means of a 3D GPU-parallelized micromagnetic code, implementing an FFT approach for the magnetostatic field evaluation and a Cayley transform based scheme for the time integration. The numerical results are validated by comparison to experimental data, obtained for the specific case of permalloy nanodisks (diameter from 200 nm to 650 nm), prepared via polystyrene nanosphere self-assembling.

1) K. Simeonidis et al., Sci. Rep. 6, 38382 (2016).

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SP1 - Parallel session 1

SP1.1.07

Surface Modified Magnetic Nanowires for Inducing Leukemia Cells death

N. Alsharif, Y. Ghosheh, J. Perez, F. Aleisa, J. Merzaban, T. Ravasi, J. Kosel

Text Iron nanowires (NWs) are biocompatible nanoparticles that can be manipulated wirelessly like nano-robots, and they can be functionalized with different biological agents. Previous studies have shown that these NWs can induce death in cancer cells through a magneto-mechanical effect, where the nanowires are vibrated inside of the cells by a magnetic field (MF). In this work, we modified the surface of iron NWs with antibodies against CD44, a cell surface marker that is more highly expressed on leukemia cells compared to normal blood cells. Iron NWs were fabricated by electrochemical deposition into aluminum oxide templates and coated with (3-Aminopropyl) triethoxysilane in order to conjugate them with antibodies. The antigenicity of the antibodies after binding to the NWs was evaluated by Western blot. Moreover, the cell viability effects and the transcriptomic changes of leukemia cells in the presence and absence of a magnetic field were studied. Antibody-coated NWs showed a high level of biocompatibility in the absence of a field and an increase in the targeting efficiency compared to bare NWs. When applying a magnetic field, cell death was induced within a period as short as 10 min. The presence of the magnetic field significantly affected the gene expression profile, where 360 genes were up-regulated. These results indicate the potential for the use of surface-modified iron nanowires for targeted treatment of leukemia cancer.

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SP1.2.02

Local and in-vivo neuronal recordings by micro-sized giant magnetoresistance sensors

J. Torrejon, C. Chopin, V. Trauchessec, T. Wunderle, L. Caruso, J. Trejo-Rosillo, C. M. Lewis, J. Ni, P. Jendritza, C. Fermon, P. Fries, M. Pannetier-Lecoeur

Text Neuronal activity is based on charge transfers, which create electric potentials and ionic currents. These currents generate low frequency (Hz regime) magnetic fields which travel through the tissues without any distortion and very importantly they can shed light on the understanding of the mechanisms of neuronal information transmission. However the observation of these magnetic fields have been mainly limited to magnetoencephalography technique using helium-cooled extracranial SQUID sensors with macroscopic dimensions.
In this work, we present a bio-compatible and local probes for neuronal current imaging based on giant magnetoresistance (GMR) technology [1]. The sensitivity of this type of sensor is almost size independent allowing the miniaturization (µm) and shaping (needle probes) required for in vivo magnetic recordings. The film stack composition and microfabrication (meander shape) have been optimized to obtain sensors with likely linear and non-hysteretic response. The performance of these GMR sensors is determined by GMR ratio (6-8 %) and the noise amplitude. The sensitivity around 10 nT at 10 Hz and below 1 nT in the thermal noise regime above 1 kHz enables to detect the magnetic fields originated inside the neuropil. Here, we will show the firsts experimental in vivo magnetic recordings of neuronal activity performed in mammals and then we will discuss different strategies to increase the sensitivity of the GMR sensors.

[1] Caruso et al, Neuron 95, 1283 (2017).

SP 1 Biomagnetism and medical applications

SP1 - Parallel session 2

SP1.2.03

Separation of excitation and detection coils to locate superparamagnetic iron oxide nanoparticles in vivo

M. M. van de Loosdrecht, S. Waanders, H. J. G. Krooshoop, B. ten Haken

Text Aim
The aim of this study is to develop a novel laparoscopic probe for sentinel node biopsy. The latter is a procedure to analyze the lymph node status of cancer patients [1], enabling personalized patient care.

Methods
Superparamagnetic iron oxide nanoparticles (SPIONs) are used as a tracer to find sentinel nodes in vivo. The principle that we use to locate them is Differential Magnetometry (DiffMag) [2]. In DiffMag, the nonlinear magnetic properties of SPIONs are used, enabling selective detection in the diamagnetic patient.

We propose a set-up with mechanically separated excitation and detection coils. As a result, the size of the excitation coil can be increased and placed outside the body. The detection coil can be made much smaller, and placed inside laparoscopic equipment. However, the main challenge of this set-up is that the detection coils can move with respect to the excitation coils. Therefore, the detector signal is hindered by the excitation field, requiring continuous active compensation.

Results
We implemented active compensation and tested it in a static set-up on three types of SPIONs. It was possible to measure small amounts of SPIONs, the minimum amount tested was 50 µg Fe.

Conclusion
These first results are promising for sentinel node biopsy. Moving the detector is a challenge that we will solve by using faster electronics, allowing real time compensation of the excitation signal.

[1] Giuliano and Gangi, 2015. [2] Waanders et al., 2016.

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SP1 - Parallel session 2

SP1.2.04

AMR sensors made of La0.67Sr0.33MnO3 epitaxial thin films for neuronal activity measurement

O. Rousseau, F. Frantz, S. Flament, B. Guillet, M. Lam Chok Sing, S. Chaludavi, L. Perez, R. Guerrero, P. Perna, L. Mechin

Text We will present our progress in the design of Anisotropic Magneto-Resistive (AMR) sensors patterned in epitaxial La0.7Sr0.3MnO3 (LSMO) oxide thin films within the FET OPEN H2020 ByAxon project [1]. The final goal is to detect neuronal magnetic signals in a frequency range from 20 Hz to 1 kHz, as part of an active bypass based on nanotechnology aiming to neural reconnection directly at the spinal cord level.
A study of the magnetization reversal process using Magneto-optical Kerr microscopy will be presented and related to the measured AMR effects. Thanks to the very low level of 1/f noise measured in LSMO films deposited on SrTiO3 (001) substrates, the measured Magnetic Field Equivalent Noise (MFEN) of our sensors was as low as 200pT/sqrt(Hz) above 20 Hz and at 310 K. As perspectives, it is expected to further decrease this MFEN by tailoring the magnetic anisotropy in particular by growing LSMO on vicinal substrates [2].
Such AMR sensors based on LSMO are very promising competitors to Giant Magneto-Resistive (GMR) sensors so far used in neuronal measurements [3], which have a MFEN of a few hundreds of pT/Sqrt(Hz) but above 1 kHz and requires a careful multilayer deposition of different metallic magnetic layers.
1.www.byaxon-project.eu
2.Perna et al Engineering Large Anisotropic Magnetoresistance in La0.7Sr0.3MnO3 Films at Room Temperature, Adv. Funct. Mater., 2017, 27, 1700664
3.Caruso et al, In vivo magnetic recording of neuronal activity, Neuron 95, 1-9 (2017)

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SP1 - Parallel session 2

SP1.2.05

On-chip detection of Malaria-infected red blood cells

R. Bertacco, M. Giacometti, M. Monticelli, M. Piola, G. B. Fiore, S. Antinori

Text Malaria infected red blood cells (i-RBCs) display a paramagnetic behavior with respect to blood plasma, so that they can be separated from healthy ones. [1] This is because, during the intra-erythrocytic development, the parasite degrades hemoglobin into hemozoin, which crystallizes into paramagnetic nanocrystals.
In this paper we present the concept of a lab-on-chip diagnostic test for malaria based on (i) the magnetophoretic separation and concentration of i-RBC, (ii) the impedimetric detection of i-RBC.
The blood drop is placed on a glass substrate, which is then put in close contact to the surface of a chip with Nickel micropillars (20 micron diameter and height), at a distance defined by an outer ring which defines also the volume of the cell. The chip is placed face-down, so that magnetic attraction towards the nickel pillars, in the macroscopic field gradient produced by external magnets, opposes gravity. In this configuration, only i-RBCs are rapidly attracted towards the micropillars. On top of the micropillars, circular electrodes are fabricated, allowing for the detection of attracted i-RBC via the change of the local impedance. The system has been tested using RBCs from bovine blood, treated with NaNO2 to induce the transformation of hemoglobin into paramagnetic meta-hemoglobin. We estimated a sensitivity high enough to detect a parasitemia of 0.1%, typical of patients infected by Falciparum and Vivax.

[1] C. C. Kim, et al., Malar. J., vol. 17, no. 9, 2010

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SP1 - Parallel session 2

SP1.2.06

Dynamical Magnetic Response of Iron Oxide Nanoparticles inside Live Cells

D. Cabrera, A. Coene, J. Leliaert, E. J. Artés-Ibañez, L. Dupré, N. D. Telling, F. J. Teran

Text Superparamagnetic iron oxide nanoparticles (SPION) exposed to alternating magnetic fields (i.e. 100 kHz) have shown a great potential for acting as magnetic hyperthermia mediators in cancer treatment. However, a dramatic reduction of SPION magnetic losses (ML) has been observed inside cells or tissues. Recent studies suggest the increase of SPION clustering and/or immobilization after interaction with cells alter magnetic relaxation mechanisms resulting in significant ML variations. Although, a quantitative description of this finding is still lacking. Here, we study cell internalization effects on the dynamical magnetic response of SPION of two sizes (11 & 21 nm) for which Néel and Brownian magnetic relaxation processes differently prevail[1]. AC magnetometry and magnetic susceptibility reflect significant differences between magnetic relaxation process of SPION into cells or dispersed in water. Our experimental results and their modeling reveal that the increase of SPION clustering mainly drives the variation of ML inside cells, rather than SPION immobilization. Interestingly, SPION clustering is differently reflected on ML depending on SPION size as being related to the increase of magnetic dipolar interactions and/or hydrodynamic volume. Understanding the intracellular effects on the SPION magnetic response will allow to design magnetic nanostructures whose ML will not be affected by biological environments.[1] Cabrera et al. ACS Nano DOI 10.1021/acsnano.7b08995

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SP1 - Parallel session 2

SP1.2.07

Combined magnetic hyperthermia and drug release by hydrotalcite-coated Fe_3O_4 nanoparticles

K. Simeonidis, R. Xu, P. Rivera-Gil, F. J. Teran, E. Kokkinos, M. Angelakeris, T. Mitropoulos

Text A magnetic nanocomposite, consisting of Fe_3O_4 nanoparticles embedded into a Mg-Al layered double hydroxide (LDH) matrix, was developed for cancer multimodal therapy based on the combination of local magnetic hyperthermia and thermally-triggered drug delivery. The synthesis procedure involves the sequential hydrolysis of iron salts (Fe^{2+}, Fe^{3+}) and Mg^{2+}/Al^{3+} nitrates in a carbonate-rich mild alkaline environment. Magnetite nanoparticles with a diameter around 30 nm, dispersed in water, represent the hyperthermia-active phase able to generate a specific loss power above 400 W/g-Fe in a AC magnetic field of 24 kA/m and 300 kHz. In addition, the LDH structure serves as a host to load anionic anticancer agents that can be released during the heating process on the site of interest. Results from drug adsorption/release tests, AC hysteresis loops, calorimetric determination of the specific loss power under alternating magnetic fields, cell internalization and toxicity assays support the potential of the Fe_3O_4/LDH nanocomposite as a cancer treatment agent with minimum side-effects owed to the exclusive presence of inorganic phases.

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