Quantitative Imaging of Magnetic Nanoparticles

Organizer: Daniel Baumgarten

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Magnetic nanoparticles (MNP) open novel pathways in cancer therapy and non-invasive diagnostics. The quantitative knowledge of a magnetic anoparticle distribution inside a body is essential for the development of these diagnostic and therapeutic approaches, as the MNP distribution essentially determines drug enrichment and heat production in their application. In the last years, different MNP imaging techniques have emerged, among them Magnetic Particle Imaging (MPI), Magnetorelaxometry Imaging (MRXI) and AC susceptibility (ACS) imaging. The latter two, in particular, allow for the quantitative detection of MNP tailored to therapeutic applications in a comparably large field of view. At the same time, excitation fields can be reduced in order to avoid unintentional hyperthermia and neural stimulation during the imaging. This symposium aims at collecting current theoretical and technical developments in the exciting and rapidly expanding field of quantitative nanoparticle imaging for therapeutical and diagnostic applications. It will span a bridge from novel sensor technologies over theoretical modeling and simulations to experimental investigations and in vivo applications. Validating and Evaluating New Methods for Source Analysis

Speakers:

- **Claude Fermon** (CEA - Atomic Energy and Alternative Energies Commission, France)
  "Spin electronics devices for magnetic particle counting and imaging"

  Spin electronics based magnetic sensors may be used for the detection of magnetic nanoparticles for relaxometry or Magnetic Particle Imaging (MPI). Compared to inductive coils, they allow working at very low frequencies, still bringing a rather large sensitivity. In that case, they are coupled to uperconducting or normal flux transformers which push their sensitivity in the range of femtoTeslas. They may also be reduced down to micron size. They are then able to detect single magnetic particles either alone either used for labelling biological objects. In this talk, I shall present the bases of the technology and their use for quantitative particle counting both at large and small scale.

- **Victor Lebedev** (Univ. of Fribourg, Switzerland)
  "MPI and Imaging MRX with Atomic Magnetometers"

  Atomic magnetometers (AMs) are flexible magnetic field sensors featuring femtotesla sensitivity. Their fast frequency response and an atomic scale of sensing element allow developing instruments for dynamic measurement and high resolution spatial mapping of the magnetization of magnetic nanoparticles (MNP). Operation of atomic magnetometers is based on the optical readout of the spin precession of the spin-polarized atoms in the ambient magnetic field. Atomic vapor is localized inside the suitable glass cell, where atoms can be further immobilized by the buffer gas. We report on our progress in application of AMs to two different methods of MNP detection: magnetic particle imaging (MPI) and magnetorelaxation (MRX). Use of AMs opens up a field of the low frequency MPI with access to the first harmonic of the MNP response. Challenge of the AM-based MPI lays in the optimization of the AM performance in vicinity of the millitesla drive and selection fields. AM-based MRX was already successfully deployed for the quantitative detection of the small amounts of MNPs. Our magnetic field camera allows imaging of the MRX of the structured several centimeter large samples with sub-illimeter field mapping resolution.

- **Annelies Coene** (Ghent Univ., Belgium)
  "Comparative study of particle Electron Paramagnetic Resonance and Magnetorelaxometry for quantitative magnetic nanoparticle imaging"

  The imaging of magnetic nanoparticles (MNP) has become an important asset in the biomedical field; it allows to obtain the spatial MNP distribution non-invasively, which in turn aids biomedical applications such as drug targeting and disease detection to function properly. In this study we compare two MNP imaging techniques, namely Magnetorelaxometry (MRX) and particle Electron Paramagnetic Resonance (pEPR). Using sensitive magnetometers such as SQUIDs or Fluxgates, MRX measures the decaying net magnetization of a sample containing MNP after the application of a magnetizing field. In pEPR, a MNP sample is placed in a magnetic field and is then excited by a radio-frequent electromagnetic wave. The latter changes the orientation of the net magnetization, which can then be measured by a pick-up coil. Both measurement techniques require the use of an (illconditioned) inverse problem to relate the measured signal to the spatial MNP distribution. In this contribution, the advantages and disadvantages of both techniques are considered and an outlook is given on how these these techniques can be combined to overcome their weaknesses.

- **Maik Liebl** (Physikalisch-Technische Bundesanstalt, Germany)
  "Feasibility and capability of magnetorelaxometry imaging as a tool for monitoring of magnetic nanoparticle based cancer therapies in humans"

  The development of novel cancer therapy approaches based on magnetic nanoparticles (MNP) requires the quantitative imaging of MNP distribution inside the human body. This is provided by magnetorelaxometry (MRX) measurements mapping the specific MNP response to switched external fields. Up to now MRX has been used for noninvasive imaging of MNP distributions in the context of drug targeting and hyperthermia applications in animal models up to rabbit size. Here, we present a device configuration to extend MRX imaging to human sized objects with the aim to provide a highly sensitive imaging tool to assist the development or control the application of MNP based therapies. Key parameters as spatial resolution (cm3), measurement time (<10 min) and sensitivity (100 µg/cm3) will be addressed by our design together with patient safety considerations. The feasibility of MRX imaging in human sized objects will be demonstrated by means of computer simulations based on measurement data with respect to the above mentioned parameters. In the future, we will evaluate the design as well as its capabilities and limitations by measurements using dedicated realistic body phantoms modeling physiological and physical aspects of selected MNP based therapy scenarios.

- **Sebastian Waanders** (Univ. of Twente, The Netherlands)
  "Numerical modeling and experimental evaluation of magnetic nanoparticle relaxation dynamics in nonstatic magnetic fields using a combined Brownian-Neel relaxation approach"

  With the growing significance of magnetic nanoparticle-based imaging modalities, an accurate and efficient description of the magnetization dynamics governing the behavior of these particles becomes of vital importance. In this contribution, we describe the dynamics of superparamagnetic iron oxide nanoparticles (SPIONs) under varying field conditions using a combination of Brownian and Neel relaxation mechanisms, and show that the steady-state approximation of their respective time constants does not hold under nonstatic field conditions. We numerically evaluate these dynamics based on their respective Fokker-Planck equations, and show how both relaxation mechanisms can be coupled through an effective magnetic anisotropy constant. We verify the results of this method by studying the behavior of several magnetic nanoparticle species in a DiffMag magnetometer. Results indicate that our methodology accurately describes the Particle Response Functions (PRFs) of different SPIONs. Furthermore, for a certain subset of particle sizes where both Brownian and Neel relaxation occurs, a transition occurs from Brownian to Neel-dominated behavior for increasing field strengths.

Finally, we show how this approach can be used to optimize the parameters of specific nanoparticles for specific biomedical applications, illustrating the strong potential of this approach in the fields like nonlinear magnetometry (DiffMag) and Magnetic Particle Imaging.

- **Solomon G. Diamond** (Thayer School of Engineering at Dartmouth, USA)
  "Nonlinear AC Susceptibility of Magnetic Nanoparticle-Cell Interactions"

  Imaging of magnetic nanoparticles (MNPs) is an emerging tool in fundamental and translational medical research. MNP tracers can be used to enhance image contrast due to their size selectivity in biological transport and can also feature surface modifications for selective binding to targeted cell types. The present work examines nonlinear AC susceptibility response characteristics of MNPs that are bound versus unbound to cells. It is demonstrated that this method is capable of determining the quantity of bound and unbound MNPs in 0.5 ml samples of two human cancer cell lines. Testing was performed over a range of five concentrations of MNPs from 0 to 80 µg /ml and five concentrations of cells from 0 to 20 million count per ml. The sensitivity of the presented method to bound MNPs is 3 µg in a 0.5 ml sample. A novel method of exploiting nonlinear AC susceptibility of MNPs to selectively amplify neural magnetic fields is also explored. Experimental results from MNPs bound to a neuronal phantom are used to demonstrate the principles involved. Methods that are capable of selectively showing contrast to cellular-bound MNPs in cancer applications and methods for amplifying neural magnetic fields add unique value to MNP imaging.

- **Oswaldo Baffa** (Universidade de São Paulo, Brasil)
  "Functional Magnetic Nanoparticle Imaging by AC Biosusceptometry"

  In vivo nanoparticles detection and monitoring remains a challenge, opening the possibility for many approaches ranging from simple and low cost to more sophisticated and expensive. The AC Biosusceptometry (ACB) system was extensively employed on monitoring gastrointestinal tract physiological properties with magnetic microparticles and has been recently applied to monitor magnetic nanoparticles (MNPs) in animal models. ACB is based upon a magnetic flux transformer, which allow us to detect and quantify magnetic samples based on the variation in magnetic inductance from an excitation pickup coil to a detection one. The time resolution is high and the spatial resolution is limited by the coils size and sensitivity. Here we describe the first *in vivo* application of the ACB system as an imaging probe for magnetic nanoparticles. A citrate coated, manganese doped, superparamagnetic iron oxide nanoparticles was used due to its good magnetic susceptibility. Five male

  Wistar rats, anesthetized by urethane, were submitted to MNP intravenous injection through their femoral vein while monitored by a single and a multichannel ACB system. After all in vivo procedures, ex vivo measurements of the heart, lungs, liver, spleen and kidneys was done. All these three measurements will allow us to perform a biodistribution analysis.