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Selective detection of magnetic nanoparticles in biomedical applications using differential magnetometry

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ABSTRACT

The present study describes a new concept of magnetic detection that can be used for fast, selective measurements on magnetic nanoparticles and which is not influenced by the presence of materials with a linear magnetic susceptibility, like tissue. Using an alternating excitation field ($f \sim 5$ kHz) with a sequence of static offset fields, the magnetometer is selectively sensitive for the nonlinear properties of magnetic nanoparticles in samples. The offset field sequence modulates the measured inductive response of nonlinear magnetic materials, in contrast to linear magnetic materials. We demonstrate a detection limit for superparamagnetic iron oxide nanoparticles in the sub-microgram (iron) range. The mass sensitivity of the procedure increases with offset field amplitude and particle size. Compared to the sensitivity for particles in suspension, the sensitivity reduces for particles accumulated in lymph node tissue or immobilized by drying, which is attributed to a change in Brownian relaxation. The differential magnetometry concept is used as a tool to perform non-destructive analysis of magnetic nanoparticles in clinically relevant tissue samples at room temperature. In addition, the differential magnetometer can be used for fundamental quantitative research of the performance of magnetic nanoparticles in alternating fields. The method is a promising approach for in vivo measurements during clinical interventions, since it suppresses the linear contribution of the surrounding body volume and effectively picks out the nonlinear contribution of magnetic tracer.

1. Introduction

The development of applications with magnetic nanoparticles in biology and medicine arises from their typical magnetic properties that can be used for detection or manipulation [1,2]. In applications like magnetic particle imaging (MPI) and magnetic resonance imaging (MRI), suspensions of superparamagnetic iron oxide (SPIO) nanoparticles are used as a tracer or contrast agent for imaging. The clinical usefulness of a tracer depends on the safety and biocompatible properties, as well as the possibility to provide unique detection in contrast to the environment. The nonlinear magnetization of magnetic nanoparticles differs from the linear diamagnetism of tissue, which makes it suitable for accurate and sensitive detection. MRI contrast agents based on SPIO nanoparticles use the high magnetic susceptibility of the particles to increase proton relaxation [3]. Relaxometry on magnetic nanoparticles with SQUID based systems is used to investigate particle dynamics and interactions with biomolecules, magnetic drug targeting and quantification of particles [4–9]. Since 2005, MPI has been developed as a new imaging modality that uses the typical nonlinear magnetic behavior of superparamagnetic nanoparticles in an alternating excitation field [10]. Furthermore, several studies have been published on intraoperative sentinel lymph node mapping using a magnetic tracer and a handheld probe [11,12]. A handheld magnetic sensor is used to localize sentinel nodes containing magnetic nanoparticles, after a local injection of tracer. The mild safety aspects and physical characteristics of magnetic nanoparticles are an important driving factor behind the development of this new application. Only with excellent performance, the magnetic method may replace the existing and complicated use of radioactive tracers and blue dye that already offer high accuracy in lymph node mapping.

Although magnetic nanoparticles can be very helpful in interventions to determine optimal treatment routes and to localize and evaluate clinically interesting targets, their use in clinical interventions is still scarce. One of the reasons is the magnetic complexity of clinical settings, like an operating theater with all kinds of instrumentation. MRI or SQUID based techniques are difficult to implement in clinical interventions, because of their special requirements regarding magnetic field quality and adequate shielding. MRI and MPI are focusing on whole body imaging with relatively large magnetic fields. Smaller systems and handheld probes that enable local detection of magnetic nanoparticles during interventions with relatively low magnetic fields are not

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well developed. In a previous study the detection and quantification of magnetic tracer in colorectal sentinel lymph nodes was performed using a vibrating sample magnetometer (VSM) [13]. The VSM is a typical laboratory instrument that is not suitable for clinical implementation. Measurements on individual lymph nodes took about 15 min and required high magnetic fields. These factors limit clinical use of the VSM technique. Therefore, development of a clinically suitable magnetometer was proposed, to realize specific and fast analysis of magnetic nanoparticles with relatively low magnetic fields.

Inductive methods based on excitation with alternating magnetic fields are most suitable for detection of magnetic nanoparticles in larger tissue volumes, e.g. during interventions. The technique is fast and can operate with relatively low fields and without a magnetically shielded room. However, in simple alternating field magnetometry the linear magnetism of the body is also contributing to the signal, which prohibits selective detection of small amounts of magnetic tracer. To obtain a system with optimal sensitivity for magnetic particles in tissue, contributions from materials with a linear magnetic susceptibility have to be excluded from the detected signal. Existing techniques, like frequency mixing with alternating fields or MPI based methods, also exploit the nonlinear properties of magnetic nanoparticles with alternating field excitation [14,15]. For larger samples and detection distances in clinical applications, these approaches are complicated, since they require high alternating field amplitudes for excitation and a large dynamic range for detection.

The purpose of the present study is to investigate a new concept of magnetic nanoparticle detection for quick (quantitative) measurements which are not influenced by the presence of large tissue volumes. The aim of the concept is application in clinical interventions with a relatively inexpensive system using standard copper coils, low magnetic field amplitudes and low excitation frequencies.

Specific detection of nonlinear magnetism is achieved by probing the sample with a small alternating field and a sequence of static offset fields. The offset field saturates the magnetization of the nanoparticles and thus the response of the magnetic nanoparticles to the alternating field is modulated. This is expressed in a reduced voltage response in the induction coil. The amplitude of this signal modulation is linearly dependent on the amount of particles in the sample and can therefore be used for quantification. For characterization purposes, the magnetic response of particles to the alternating field can be measured at different offset field amplitudes. This provides information about nonlinear particle characteristics and optimal instrumentation settings for clinical applications.

2. Methods

2.1. Theory

2.1.1. Linear and nonlinear magnetization

The use of superparamagnetic nanoparticles for clinical purposes is driven by the beneficial nonlinear magnetization behavior that contrasts with the linear magnetic behavior of tissue. For materials with a linear magnetic susceptibility, the magnetization M_{lin} [Am^{-1}] is proportional to the applied magnetic field H [Am^{-1}] and can be described by

$$M_{lin} = \chi H. \tag{1}$$

The (volume) susceptibility χ is positive for paramagnetic materials and negative for diamagnetic materials, the latter being more common in biomedical situations.

The susceptibility of superparamagnetic nanoparticles is nonlinear, which can be described by the Langevin function [16]. The average magnetization M_{spm} of an ensemble of superparamagnetic nanoparticles as a function of the external field H is given by

$$M_{spm}(xH) = M_s\left(\coth(xH) - \frac{1}{xH}\right), \tag{2}$$

with M_s is the saturation magnetization and

$$xH = \frac{m\mu_0 H}{k_B T}. \tag{3}$$

The constants μ_0, k_B and parameter T represent vacuum permeability, the Boltzmann constant and absolute temperature, respectively. The particle dependent parameter in the Langevin function is the magnetic moment $m[\mathrm{Am}^2]$. The magnetic moment of a spherical superparamagnetic particle is related to its diameter D [m] by

$$m = \frac{\pi D^3 M_s}{6}. \tag{4}$$

using $\mu_0 M_s = 0.55$ T for Fe_3O_4/Fe_2O_3 [17,18].

Eq. (2) is defined for a single particle size. In practical situations, where samples contain an ensemble of particles with a log-normal size distribution, Eq. (2) should be evaluated according to the actual particle size distribution [18].

2.1.2. Selective measurement of nonlinear magnetization

Alternating magnetic fields are commonly used to measure the magnetic susceptibility of samples. The material's response can simply be measured by a detection coil, according to Faraday's law of induction. Excitation with an alternating field is performed by a sinusoidally alternating excitation field

$$H(t) = H_0 \sin(\omega t), \tag{5}$$

with amplitude H_0 and angular frequency $\omega = 2\pi f$.

The sample's magnetization will change, according to its susceptibility, with the frequency of the alternating excitation field. The induction voltage in the coil is proportional to the time derivative of the magnetization

$$U(t) \propto \frac{dM}{dt}. \tag{6}$$

In a tissue sample that contains superparamagnetic nanoparticles, both linear (M_{lin}) and nonlinear magnetization (M_{spm}) contribute to the measured inductive voltage response.

$$M(t) = M_{lin}(t) + M_{spm}(t). \tag{7}$$

The concept of differential magnetometry, presented in this study, uses first a standard alternating excitation field. If in a next interval an additional offset field $H_{\mathrm{Offset}} \neq 0$ is applied, the measured magnetization response of linear magnetic material does not change. However, for materials with a nonlinear susceptibility, the response to the alternating field will be reduced, since the magnetization moves towards saturation. The differential magnetometry concept is shown in Fig. 1. The contribution from superparamagnetic nanoparticles in the sample can be uniquely determined by calculation of the voltage drop ΔU, here defined as the differential magnetization or the *Diffmag* signal:

$$\Delta U \propto \Delta\frac{dM}{dt} = \left.\frac{dM_{SPM}}{dt}\right|_{H_{\mathrm{Offset}}=0} - \left.\frac{dM_{SPM}}{dt}\right|_{H_{\mathrm{Offset}}\neq 0}. \tag{8}$$

Subtraction of the measured induction voltages for both excitation conditions, provides a selective measure for the amount of magnetic nanoparticles present.

This algorithm can be rapidly executed (<100 ms) and is therefore suitable for implementation in clinical procedures that require real time feedback. Only a few periods of alternating field