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Spectroscopic AC susceptibility imaging (sASI) of magnetic nanoparticles

Bradley W. Ficko *, Priyanka M. Nadar, Solomon G. Diamond

Thayer School of Engineering at Dartmouth, 14 Engineering Dr. Hanover, NH 03755, USA

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ABSTRACT

This study demonstrates a method for alternating current (AC) susceptibility imaging (ASI) of magnetic nanoparticles (mNPs) using low cost instrumentation. The ASI method uses AC magnetic susceptibility measurements to create tomographic images using an array of drive coils, compensation coils and fluxgate magnetometers. Using a spectroscopic approach in conjunction with ASI, a series of tomographic images can be created for each frequency measurement set and is termed sASI. The advantage of sASI is that mNPs can be simultaneously characterized and imaged in a biological medium. System calibration was performed by fitting the in-phase and out-of-phase susceptibility measurements of an mNP sample with a hydrodynamic diameter of 100 nm to a Brownian relaxation model ($R^2=0.96$). Samples of mNPs with core diameters of 10 and 40 nm and a sample of 100 nm hydrodynamic diameter were prepared in 0.5 ml tubes. Three mNP samples were arranged in a randomized array and then scanned using sASI with six frequencies between 425 and 925 Hz. The sASI scans showed the location and quantity of the mNP samples ($R^2=0.97$). Biological compatibility of the sASI method was demonstrated by scanning mNPs that were injected into a pork sausage. The mNP response in the biological medium was found to correlate with a calibration sample ($R^2=0.97$, $p<0.001$). These results demonstrate the concept of ASI and advantages of sASI.

1. Introduction

The use of magnetic nanoparticles (mNPs) in medicine is an active area of research with several promising therapies currently under study [1,2]. One of the most promising uses of mNPs in medicine is as an imaging contrast agent. Significant research has resulted in the development of methods such as magnetic particle imaging (MPI) [3–6], magnetic resonance imaging MRI methods such as Sweep Imaging with Fourier Transform (SWIFT) [7,8], magnetic relaxometry (MRX) [9–17] and AC susceptibility detection [18–23]. A particularly relevant study to the present work describes the use of magnetic relaxometry and an array of SQUID sensors and drive coils to spatially localize mNPs using excitation fields in the microtesla range [9]. Magnetic nanoparticles can also be used to detect tumors using either targeted or untargeted mNPs. This approach has been demonstrated in preclinical trials of cancer detection in lymph nodes [24].

Magnetic susceptibility imaging relies on the inherent magnetic susceptibility of mNPs to provide imaging contrast. When a magnetically susceptible material is subjected to an external magnetic field $\mathbf{H}$, the resulting magnetic field will be $\mathbf{B}=\mu_0(\mathbf{H}+\mathbf{M})$, where μ_0 is the magnetic permeability in a vacuum, $\mathbf{B}$ is the magnetic induction or B-field, $\mathbf{H}$ is the externally applied magnetic field strength, and $\mathbf{M}$ is the magnetization field from the magnetic material. The magnetization field arises from the magnetically susceptible material as $\mathbf{M}=\mathbf{H}\chi_v$, where χ_v is the volume magnetic susceptibility. Although the M-field only exists inside of the magnetic material, it gives rise to additional external B-field that contributes to the magnetic field detected by a sensor such as a fluxgate magnetometer. Studying this additional B-field from the magnetically susceptible material requires that it be distinguished from the directly coupled applied magnetic field and from background noise.

We previously introduced a method that we have called susceptibility magnitude imaging (SMI) that achieves mNP imaging with an array of drive coils, fluxgate magnetometers, and compensation coils [25]. SMI scans localize and quantify mNPs with known alternating current (AC) magnetic susceptibility properties within the field of view of the system. If the supplied AC susceptibility properties of the mNPs are incorrect then SMI results will become distorted and inaccurate. The AC susceptibility imaging (ASI) method demonstrated in the present work overcomes this limitation of SMI. This use of susceptibly properties enables a new contrast type for mNP imaging that was previously

* Corresponding author.
E-mail address: Bradley.W.Ficko@Dartmouth.edu (B.W. Ficko).

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not possible with SMI. In addition, using a multi-frequency approach, it is possible to implement sASI to enable yet another contrast type in which it is possible to classify mNPs within the imaging zone.

AC susceptibility has several important applications in biological imaging. It has been shown that the AC susceptibility contrast of mNPs changes between bound and unbound states [20,26–29]. AC susceptibility can be exploited to distinguish multiple mNPs situated inside an imaging region [30] and may allow multiple mNP tracers to be simultaneously imaged inside a tumorous region. In addition, AC susceptibility imaging (ASI) can be optimized to provide maximal contrast for particular mNPs by choosing specific imaging frequencies.

Biological AC susceptibility measurement methods for mNPs have been extensively studied [20,22,31–33]. Many studies have applied Brownian relaxation models for immunoassay applications [11,26,29,34]. AC rotational magnetic fields have been exploited to enhance the measurement of the out-of-phase susceptibility component of mNPs [19,35,36]. A study has looked into simultaneous quantification of multiple mNPs [37] in which the authors were able to accurately quantify three mNPs using mNP saturation harmonics. Another group has attempted to distinguish nanobeads [38,39] where the authors quantified the derivatives of the *n*th order magnetic induction field with respect to the magnetic field in order to create magnetic signatures for different nanobeads. The authors were then able to quantify mixtures of nanobeads. A recent AC susceptibility study [30] distinguished mNPs in a mixture based on their out-of-phase susceptibility components. The authors were also able to detect susceptibility differences based on mNP binding states. These prior studies have not combined methods for distinguishing mNPs with imaging as we undertake in the present study.

Mathematical models for magnetic susceptibility imaging have been developed previously. The magnetic inverse problem has been described in detail [40]. Two-dimensional magnetic susceptibility tomography (MST) methods have been developed for use on samples of uniform thickness [41]. Three-dimensional methods of MST have not been implemented, but the analytical groundwork for the method has been developed [42,43]. Further developments of MST for biological imaging [44], non-destructive evaluation (NDE) [45], diamagnetic and paramagnetic objects [46] and in a non-uniform magnetic field [47] have also been reported. Models including a system of voxels containing magnetically susceptible material, an array of excitation coils, and an array of sensors have been developed for magnetic relaxometry [48] and brain hemodynamics [49]. The susceptibility-imaging model presented in this study relies empirically upon calibration data rather than models of field theory. This empirical approach is necessary for our approach to digital magnetic field compensation and is tolerant of imprecise knowledge of model elements such as coil and sensor geometry. The model presented in this work also incorporates AC susceptibility effects and accounts for the delays that result from electrical components such as inductors and capacitors. By accounting for AC susceptibility and imaging in the same model, the proposed ASI approach simultaneously images and distinguishes mNPs.

In the present study, we introduce a contrast type called ASI and extend the concept to a multi-frequency approach called sASI. We first introduce a model for ASI and then validate the model by performing sASI on three different mNP samples in three voxels using six excitation frequencies. We experimentally show the limitations of MSI and demonstrate how sASI can be used to distinguish different mNP types by exploiting their AC magnetic susceptibility properties. We then show results of a biological demonstration experiment where mNPs were injected into a pork sausage and compare the sASI scans from the mNPs in the biological medium to mNPs in a calibration sample. This new contrast type and its spectroscopic extension enable new possibilities for imaging applications with multiple mNP types or biological interaction with mNPs.

2. Methods

2.1. Hardware

2.1.1. Coil and sensor configuration

In an AC susceptibility method (Fig. 1), a sinusoidal current generates a multiple-frequency applied magnetic field with a drive coil. The applied magnetic field interacts with the magnetically susceptible mNPs. The induced magnetic field is then measured by

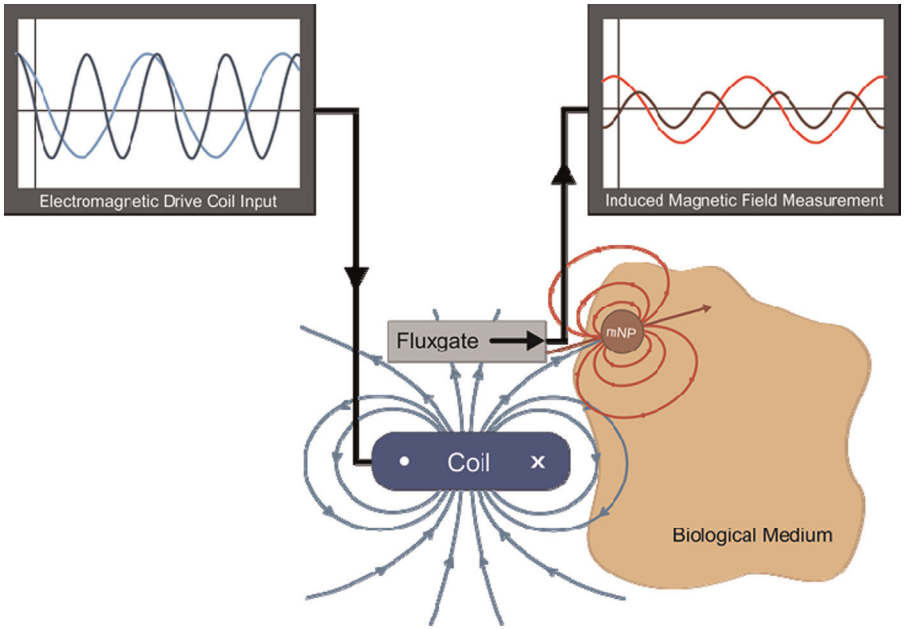

Fig. 1. Conceptual diagram of AC susceptibility measurements. A sinusoidal current produces a magnetic field with a drive coil that interacts with magnetic nanoparticles. The induced magnetic field is detected by a fluxgate magnetometer. The detected magnetic field will have a different amplitude and phase from the applied magnetic field.