Measuring SPIO and Gd contrast agent magnetization using 3 T MRI

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Traditional methods of measuring magnetization in magnetic fluid samples, such as vibrating sample magnetometry (VSM), are typically limited to maximum field strengths of about 1 T. This work demonstrates the ability of MRI to measure the magnetization associated with two commercial MRI contrast agents at 3 T by comparing analytical solutions to experimental imaging results for the field pattern associated with agents in cylindrical vials. The results of the VSM and fitted MRI data match closely. The method represents an improvement over VSM measurements since results are attainable at imaging field strengths. The agents investigated are Feridex, a superparamagnetic iron oxide suspension used primarily for liver imaging, and Magnevist, a paramagnetic, gadolinium-based compound used for tumors, inflammation and vascular lesions. MR imaging of the agents took place in sealed cylindrical vials in the presence of a surrounding volume of deionized water where the effects of the contrast agents had a measurable effect on the water's magnetization in the vicinity of the compartment of contrast agent. A pair of phase images were used to reconstruct a \( B_0 \) fieldmap. The resultant \( B_0 \) maps in the water region, corrected for shimming and container edge effects, were used to predict the agent's magnetization at 3 T. The results were compared with the results from VSM measurements up to 1.2 T and close correlation was observed. The technique should be of interest to those seeking quantification of the magnetization associated with magnetic suspensions beyond the traditional scope of VSM. The magnetization needs to be sufficiently strong (\( M_r \geq 50\, \text{Am}^2/\text{kg Fe} \) for Feridex and \( x_m \geq 5 \times 10^{-5} \, \text{m}^3/\text{kg Gd} \) for Magnevist) for a measurable dipole field in the surrounding water. For this reason, the technique is mostly suitable for undiluted agents. Copyright © 2009 John Wiley & Sons, Ltd.

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INTRODUCTION

The goal of this work was to demonstrate the ability of MRI to accurately measure the magnetization associated with two commercial MRI contrast agents. These agents were Feridex (AMAG Pharmaceuticals, Cambridge, MA), a superparamagnetic iron oxide suspension used primarily for liver imaging and increasingly for cell-labeling applications (1,2,3,4,5) and Magnevist (Bayer HealthCare AG, Leverkusen, Germany) (6,7,8), a paramagnetic, gadolinium-based (Gd) compound used in a wide variety of tumor and lesion imaging applications.

The investigations used two distinct methods to measure magnetization: vibrating sample magnetometry (VSM) and MRI. VSM measures the sample's magnetization by moving the sample back and forth at high speed, creating a periodically and rapidly changing magnetic field. This changing field is sensed by a set of pick-up coils where the induced coil voltage, as given by Faraday's law of electromagnetic induction, is proportional to the sample's magnetization. While high field VSM platforms exist (e.g., the EV11 system from ADE Magnetics has a 3.1 T maximum field), cost considerations will generally limit VSM use among the MRI community to small samples at fields \( \leq 1 \, \text{T} \), well below fields currently typical in MRI (e.g., 3 T).

This method comes in the wake of measurements of magnetic susceptibility of gadolinium contrast agents and blood susceptibility conducted by Weisskoff (11). Jung (12) also made preliminary measurements of the magnetization associated with both Gd-DPTA (now commercially available as Magnevist) and Ferumoxide suspensions (now commercially available as Feridex). Neither investigation examined magnetization at 3 T or used commercially available agents. Chu et al. (13) has described the theoretical "bulk magnetic susceptibility shift" due to an infinite cylinder of finite wall thickness in two field orientations (parallel and perpendicular to \( B_0 \)). In fact, the "susceptibility shift" refers to the change in the local magnetic field in the region immediately surrounding a paramagnetic species. Bowen et al. (14) have provided a thorough investigation of superparamagnetic iron-oxide loaded cells at 1.89 T by comparing experimental results with the theoretical predictions of Chu (13) for infinitely long cylindrical vessels of magnetic fluid. More recently, focus has switched to the applications in susceptibility weighted imaging in vivo although the technique is broadly similar to that employed here (15,16).

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This work proposes an effective method for predicting the magnetization of Feridex and Magnevist contrast agents using MRI. The experiments are conducted at 3 T but the method could be equally applied at any field strength. The experimental results (both MRI and VSM [vibrating sample magnetometry]) are compared with exact theoretical predictions for infinite length cylinders to correlate the magnetization associated with the samples of Feridex and Magnevist. Close correspondence is observed between the MRI results, results from VSM measurements at 1.2 T and previously published results (11). This technique represents an advancement over prior work in three important respects; (i) it represents the first investigations of commercially available MRI agents, Feridex and Magnevist, (ii) the investigations are the first conducted at 3 T and (iii) the exact rather than an approximate solution (13,14) for infinite length cylinders is employed.

**EXPERIMENTAL**

**VSM measurements**

To examine magnetic saturation effects in a commercial SPIO particle (small iron oxide) contrast agent, 0.0703 cc of Feridex MRI contrast agent was placed in a vibrating sample magnetometer (Model 1660, ADE Magnetics, Westwood, MA) and the magnetic moment was measured. The contrast agents were examined in their undiluted states (i.e., as provided by the manufacturers (2,6)). To account for magnetization effects due to the sample cup, a second VSM measurement was conducted in the absence of the contrast agent with an empty cup and the resulting magnetization was subtracted from the result in the presence of the agent. The contrast agents’ magnetizations are shown in Figure 1(a) where the units of magnetic moment are given as Am²/kg Fe. Feridex is a superparamagnetic agent which saturates at high field. The saturation magnetization of the agent was estimated to be in the region of 82 Am²/kg Fe. Feridex has a nominal density of 11.2 mg Fe/ml and the recommended dosage is 0.56 mg Fe/kg of bodyweight (2). A similar procedure was employed for a 0.07266 cc sample of Magnevist contrast agent. Magnevist is a paramagnetic agent which exhibits a linear magnetic susceptibility up to DC fields of 50 T (9). It consists of a complex chemical formulation, supplied in concentrations containing 469.01 mg gadopentetate dimeglumine per ml Magnevist (6). The recommended dosage is 0.2 ml per kg bodyweight. The mass susceptibility, \( \chi_m \), was estimated by a linear curve fit to be \( 2.06 \times 10^{-6} \) m³/kg Gd from the VSM measurements shown in Figure 1(b). Again, there was no available data beyond 1.2 T. The two VSM measurements took on the order of 1 hour (determined by the iteration step in field strength) to complete without additional postprocessing of the results to determine the magnetic moment per unit volume. Repeated experiments might improve accuracy by adding error bars but this was not attempted.

**MRI measurements**

In order to estimate the magnetization in MRI, \( B_0 \) maps were obtained in a 3 T Siemens Trio MRI. The agent was placed in a long, narrow NMR tube (Bruker Match System NMR Sample Tubes from Norell Inc., Landisville, NJ): 10 cm in length and 3.43 mm inner diameter. The walls of the tube were 0.41 mm thick. The tube was fixed to lie horizontally in a water tank for imaging and positioned so that the \( B_0 \) field lay transverse to the tube’s long axis. The tube’s center slice was imaged in coronal view at 3 T with an imaging resolution of 256 × 256 pixels, a 180mm FOV (field of view), a slice thickness of 7 mm and a repetition time, TR = 100 ms. Using 10 averages, the total scan time was 4.25 minutes. The phase maps and \( B_0 \) maps are shown in Figures 2 and 3 for the Feridex contrast agent, where \( TE = 2.83 \) ms for the phase map and \( \Delta TE = 0.9 \) ms for the \( B_0 \) map. The \( B_0 \) map was corrected for edge effects and shimming.

![Figure 1. Measured magnetization using a VSM for (a) Feridex and (b) Magnevist MRI contrast agents. The units of magnetic moment are (a) Am²/kg Fe for Feridex and (b) Am²/kg Gd for Magnevist.](image)

![Figure 2. The measured phase map is shown for the center coronal slice of a tube of Feridex agent surrounded by water. The phase map only shows the net field component along the x-axis, i.e., \( B_x \). The \( B_0 \) field is left to right (x-directed) and has a value of 3 T.](image)
used in subsequent experiments where the length:inner diameter ratio was 29. For the case of the paramagnetic gadolinium agents, the problem is a two-dimensional, three-region problem where the magnetic susceptibilities of the three regions are $x_1$, $x_2$ and $x_3$. In this work, $x_1$ corresponds to the region of contrast agent (0 < $r < R_1$), $x_2$ is the glass vial ($R_1 < r < R_2$) and $x_3$ is the water region ($r > R_2$), $r$ is the radial displacement from the center of the vial and $R_1$ and $R_2$ are the inner and outer radii of the long glass tube. For the case of the SPIO Feridex agent, the region of the contrast agent (0 < $r < R_1$) is considered to have a spatially-invariant magnetization which is colinear with $B_0$ and has magnitude $M_s$. This case is explored later.

For an infinitely long vial, simplification arises with the consideration of a two-dimensional cylindrical coordinate set $(r, \phi)$ and the definition of a transverse magnetic scalar potential, $\Psi(r, \phi)$, for a non-conducting medium such that $\nabla \times H = 0$ and $H = -\nabla \Psi$. In addition, $\nabla \cdot B = \mu_0 \nabla \cdot (H + M) = 0$. For region 1 ($0 < r < R_1$) in this work, $\nabla \cdot H = 0$ whether (i) $M = \chi H$ where $\chi$ is the spatially-invariant magnetic susceptibility of the gadolinium contrast agent, or (ii) $|M| = M_s$ where $M_s$ is the resulting magnetization of the contrast agent which is a function of and parallel to $H$ as given by the Langevin relation for the SPIO contrast agent at 3 T. In practice, SPIO contrast agents are magnetically saturated at high fields so $M_s$ is virtually independent of $H$ at 3 T. The relation $\nabla \cdot H = 0$ is also true in regions 2 and 3 since these are linearly magnetizable regions with magnetic susceptibilities of $x_2$ and $x_3$ respectively. Under these conditions, $\Psi$ obeys Laplace’s equation, given in (1). $\Psi$ is independent of $z$ for infinitely long cylinders.

$$\nabla^2 \Psi = 0$$ (1)

Eq. (1) has solutions in a cylindrically symmetric geometry as given by Eq. (2) where $C_1, D_1, C_2, D_2, C_3$ and $D_3$ are constants to be evaluated by means of boundary conditions at $r = R_1$ and $R_2$.

$$\Psi(r, \phi) = \begin{cases} 
(1) C_1 r + \frac{D_1}{r} & \text{for } 0 < r < R_1 \\
(2) C_2 r + \frac{D_2}{r} & \text{for } R_1 < r < R_2 \\
(3) C_3 r + \frac{D_3}{r} & \text{for } r > R_2
\end{cases}$$ (2)

The corresponding components of the $B$ field solutions are given by Eq. (4) for a linearly magnetizable region 1.

$$B(r, \phi) = \begin{cases} 
(1) -\mu_0 (1 + x_1) \left( C_1 + \frac{D_1}{r} \right) \cos \phi \phi_i + \mu_0 (1 + x_1) \left( C_1 + \frac{D_1}{r} \right) \sin \phi \phi_i & \text{for } 0 < r < R_1 \\
(2) -\mu_0 (1 + x_2) \left( C_2 + \frac{D_2}{r} \right) \cos \phi \phi_i + \mu_0 (1 + x_2) \left( C_2 + \frac{D_2}{r} \right) \sin \phi \phi_i & \text{for } R_1 < r < R_2 \\
(3) -\mu_0 (1 + x_3) \left( C_3 + \frac{D_3}{r} \right) \cos \phi \phi_i + \mu_0 (1 + x_3) \left( C_3 + \frac{D_3}{r} \right) \sin \phi \phi_i & \text{for } r > R_2
\end{cases}$$ (3)

The constants are solved by considering the boundary conditions as follows:

$$H(r \to 0) = \text{finite}, \Rightarrow D_1 = 0$$
$$B_r(r = R_1) = B_r(r = R_1')$$
$$B_r(r = R_2) = B_r(r = R_2')$$
$$H_r(r = R_1) = H_r(r = R_1')$$
$$H_r(r = R_2) = H_r(r = R_2')$$

$$H(r \to \infty) = \frac{B_0}{\mu_0 (1 + x_3)}$$

Applying these boundary conditions to Eqs. (3) and (4) yields the following solutions for $C_1$ through $D_3$ as given in Table 1(a).
Substitution into (3) and (4) yields the complete solution for the $H$ and $B$ fields. In practice, MRI only measures changes in the local field which are parallel to the large $B_0$ field. Therefore, the imagined change in local magnetic field in the third region ($r > R_2$) is effectively $\Delta B_0$ given by (7) for an $x$-directed $B_0$ field. Defining the main field to be $x$ rather than $z$ is unconventional in MRI region ($0 < r < R_1$) rather than the linear magnetization susceptibility described by $x_1$. In this case, the revised $B$ field for ($0 < r < R_1$) is given by (8) while the $H$ field solution of (3) remains unchanged. The subsequently revised solutions for $C_1$ through $D_3$ are as given by Table 1(b). The theoretical solution of (7) for the SPIO agent, Feridex, is plotted in Figure 4(a).

$$B(r, \phi) = \begin{cases} -\mu_0 \left( C_1 - \frac{3}{2} - M_s \right) \cos \varphi \theta + \mu_0 \left( C_1 + \frac{3}{2} - M_s \right) \sin \varphi \theta & \text{for } 0 < r < R_1 \\ -\mu_0 \left( 1 + x_2 \right) \left( C_2 - \frac{3}{2} \right) \cos \varphi \theta + \mu_0 \left( 1 + x_2 \right) \left( C_2 + \frac{3}{2} \right) \sin \varphi \theta & \text{for } R_1 < r < R_2 \\ -\mu_0 \left( 1 + x_3 \right) \left( C_3 - \frac{3}{2} \right) \cos \varphi \theta + \mu_0 \left( 1 + x_3 \right) \left( C_3 + \frac{3}{2} \right) \sin \varphi \theta & \text{for } r > R_2 \end{cases}$$

(8)

The change in $\Delta B_x$ for $r > R_2$ is again given by (7) but where $D_3$ is now revised as indicated in Table 1(b).

The matching of the simulated theoretical field with the experimental results from the MRI was achieved by manually overlapping of the vial’s outline in each case for the slice at the vial’s axial center. The resultant least-squares fitting was achieved with Matlab (The MathWorks Corp., Natick, MA). Clearly some phase wrapping occurs in the region around the tube as the field varies too rapidly to be captured accurately by the field map. This means that the recorded field immediately surrounding the tube itself is severely distorted from the actual value. However, the dipole fields are closely matched in areas which do not suffer from phase wrapping (e.g., >2 cm from the vial’s axial center).

**RESULTS**

The results of Figure 4 for the Feridex contrast agent were compared for the line of maximum field variation in the coronal plane (indicated by the black solid line). The results are shown in Figure 5 where the blue solid line indicates the measured result for the change in local Larmor frequency in the water region using MRI, the red line represents a least-squares fit of the MRI result assuming $M_s = 80 \text{Am}^2/\text{kg Fe}$ and the black dashed line represents the result based on the VSM measurement of $M_s = 82 \text{Am}^2/\text{kg Fe}$. As usual, the Larmor frequency is related to the local magnetic field by the gyromagnetic ratio with a value of $42.58 \text{MHz/T}$ for the $^1\text{H}$ proton. Since the simulated dipole distribution shown in Figure 4(a) represents the change in the $x$ component of the field.

![Table 1. Table of Coefficients](image)
component of the \( B_0 \) field rather than the magnitude of the magnetic field, the distribution is quadrapolar rather than dipolar as given by Equation 7 for an infinite cylinder in an \( x \)-directed field with finite wall thickness.

Using an identical procedure to that outlined to obtain the results of Figure 4, the \( B_0 \) and phase maps were obtained for the Gd-based contrast agent, Magnevist. The theoretical results from Matlab (using the value for the mass susceptibility estimated
from the VSM results to be $2.06 \times 10^{-3}$ m$^3$/kg Gd and $B_0$ map at 3 T are shown in Figure 6. The results in Figure 6 are compared along the line of maximum field variation in the coronal plane, as was the case for the Feridex results. The results are shown in Figure 7 where the blue solid line indicates the measured result for the change in local Larmor frequency using MRI, the red line represents a least-squares fit of the MRI result assuming $\chi_m = 1.96 \times 10^{-6}$ m$^3$/kg Gd and the black dashed line represents the result from the VSM measurement of $\chi_m = 2.06 \times 10^{-6}$ m$^3$/kg Gd. It should be noted that the mass susceptibility, $\chi_m$ in m$^3$/kg, is related to the absolute susceptibility, $\chi$ (unitless), by the concentration of the magnetic material in the fluid which was 78 kg Gd/m$^3$.

### DISCUSSION

The results for the saturation magnetization of Feridex contrast agent are compared in Table 2 using three different methods. These are (i) the VSM measurements which yielded a result of $82 \text{Am}^2/$kg Fe at 1.2 T, (ii) the fitted MRI measurement which yielded a value of $80 \text{Am}^2/$kg Fe at 3 T and (iii) the published result of Jung et al. who cite a result of $93.6 \text{Am}^2/$kg Fe at 5 T. For the results detailed here, VSM and MRI measurements coincide within 2.5% for Feridex and 5% for Magnevist.

One possible reason for the slight differences between the values of this work and previous result is possible variations in the formulations investigated by earlier workers (11,12) and this current work which uses commercially available solutions. An explanation for the discrepancy between the MRI and VSM results is possible misalignment between the theoretical and experimental phase maps. This would result in an inaccurate fit of the experimental data (for example, if datapoints closer to the vial tend to suffer more from uncompensated edge effects, this is not reflected in the least-squares fit) and a misalignment between the theoretical result and the MRI measurement (meaning that pixels were not exactly matched in space and therefore introducing an error in the predicted value for the saturation magnetization).

The results for the mass susceptibility of Magnevist contrast agent is compared in Table 3. The comments of the previous paragraph are again applicable. A final note on the Magnevist MRI results is regarding the increased noise in the signal of Figure 7 compared to the Feridex MRI result in Figure 5. This perceived increase in noise is only due to the decreased scale of the local Larmor frequency shown in the Magnevist result rather than due to any increase in the noise inherent to the experiment. The SNR might be improved by increasing the slice thickness and the image FOV albeit leading to the inevitable increase in cylinder end-effects and loss in spatial resolution.

While T1 and T2 are the usual parameters most critical to MR image contrast, there are clinical situations where a measure of the absolute magnetization of the contrast agent is desirable. These include susceptibility-weighted imaging (15,16) where the local magnetic field is distorted by the magnetization associated with the contrast agent. While the work outlined here details the in vitro analysis of the magnetization associated with MRI contrast agents, the work might be extended to in vivo studies by examining the flow in long blood vessels where a measurable component of the $B_0$ field lies perpendicular to the vessel.

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### REFERENCES

5. Arbab AS, Yocum GT, Rad AM, Khakoo AY, Fellowes V, Read EJ, Frank JA. Labeling of cells with ferumoxides-protamine sulfate complexes does not inhibit function or differentiation capacity of hematopoietic or mesenchymal stem cells. NMR Biomed. 2005; 18: 553–559.