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Characterization of magnetic nanoparticles as contrast agents in magnetic resonance imaging using high- T_c superconducting quantum interference devices in microtesla magnetic fields

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Abstract

In this paper, we characterize the spin–lattice relaxation T_1 , spin–spin relaxation T_2 , and effective relaxation rate Γ_{MF} of magnetic fluids for magnetic resonance imaging using a high- T_c superconducting quantum interference device (SQUID) in microtesla magnetic fields. When the magnetic susceptibility of the magnetic fluid was increased, a broadening of proton nuclear magnetic resonance spectra and a growing spin–lattice relaxation T_1 as well as spin–spin relaxation T_2 were observed. The effective relaxation rate Γ_{MF} increased monotonically from 0 to 13 s^{-1} when the magnetic susceptibility of the magnetic fluids, relative to tap water, was increased from 0 to 0.0015 emu g^{-1} . We demonstrate the magnetic fluid as an image contrast via a high- T_c SQUID in microtesla magnetic fields.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Magnetic nanoparticles are of great interest to those developing new techniques for nuclear magnetic resonance (NMR) [1], magnetic resonance imaging (MRI) [2], magnetically labeled immunoassays [3], magnetic hyperthermia treatments of cancer, cancer diagnostic, therapeutic purposes [4, 5], etc. In these technologies, magnetic nanoparticles are introduced to a specific anatomical or functional region being imaged. This is done in order to allow specialists to differentiate between normal and abnormal tissues. In MRI at high field it offers an improved signal-to-noise ratio (SNR). In the cases of NMR/MRI, the discrimination of the tissues on the basis of the spin–lattice relaxation time is superior

at low magnetic fields. To better understand the effects of spin–lattice and spin–spin relaxation times on NMR/MRI, we study the relaxation times using a sensitive superconducting quantum interference (SQUID) spectrometer. Dextran-coated magnetic nanoparticles, which dispersed uniformly in water, were used as phantoms to study the spin–lattice and spin–spin relaxation times. We observed that the proton NMR spectra broadened and relaxation rates increased with increasing magnetic susceptibility χ . Additionally we obtained an effective relaxation rate Γ_{MF} due to χ of the magnetic fluids.

2. Experiments

The NMR of protons based on the free precession effect of the proton nucleus spin is known to have a gyromagnetic factor

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Figure 1. Schematic of a high- T_c SQUID-based NMR/MRI detection system.

of $42.58 \text{ kHz mT}^{-1}$. In figure 1, we show a schematic in which the proton precession spin is inductively coupled to the SQUID magnetometer. Coupling is accomplished through a resonance circuit with both the SQUID and input coupling coil set up in a superconducting $\text{Bi}_2\text{Sr}_2\text{Ca}_2\text{Cu}_3\text{O}_y$ vessel. The superconducting $\text{Bi}_2\text{Sr}_2\text{Ca}_2\text{Cu}_3\text{O}_y$ vessel allows avoidance of environmental noises and sets the SQUID in a stable operation. The resonance circuit, which consists of a Helmholtz coil with an inductance L and capacitor C , is tuned to the resonance frequency 4.3 kHz in a measuring magnetic field of $101 \mu\text{T}$. When we conducted our study using this schematic setup, the direct-coupled high- T_c SQUID magnetometer had a magnetic field resolution of $280 \text{ fT Hz}^{-1/2}$ at 4.3 kHz .

The sample was placed in a pre-polarization coil which can produce a magnetic field of 45 mT . The uniformity of the magnetic field was better than 0.01 per cent in a central region of 216 cm^3 . The high- T_c SQUID-based NMR spectrometer was set up in a magnetically shielded room. Then to produce a uniform magnetic field, we employed a planar coil system consisting of three coil pairs [6]. The first coil pair consisted of one turn with a radius of 1.6 cm , the second coil pair was four turns with a radius of 9.6 cm , and the third coil pair was 140 turns with a radius of 38.9 cm . The three coil pairs were connected in series to produce a field with a uniformity of 1 in 10^4 within a measuring volume of 64 cm^3 . The bandwidth of the NMR spectra was expected to be 0.4 Hz at $101 \mu\text{T}$.

Figure 2 shows the wave sequences used in the NMR measurements. In our study, a static field B_0 of $101 \mu\text{T}$ was active along the z -axis, which was parallel to the plane of the high- T_c SQUID magnetometer. A pre-polarization field, B_p , of 45 mT was applied along the y -axis, which was also parallel to the plane of the SQUID magnetometer. Since the strength of the pre-polarization field was much higher than that of the measuring static field, the direction of nuclear spin magnetization of water was almost aligned along the y -axis of the pre-polarization field. After applying a pre-polarization field for a duration of T_{Bp} , the pre-polarization

Figure 2. Sequences used in the NMR detection for (a) the measuring field B_0 , (b) the pre-polarization field with a duration time t_{Bp} , (c) $M(t)$ as a function of time during pre-polarization and free induction decay, and (d) the FID signal as a function of time.

field was quenched after 3 ms . The precession of the nuclear magnetization was along the direction of B_0 . The free induction decay (FID) signal of the proton spin was detected by a pick-up coil. The normal of the pick-up coil was along the z -axis direction and coupled to the high- T_c SQUID that was shielded within the superconducting vessel. NMR signals of the FID were filtered through band-pass filters. Then, through a fast Fourier transformation (FFT) we obtained the NMR spectra.

3. Experimental results and discussion

Figure 3(a) depicts the NMR intensity of water, and figures 3(b), (c), (d), (e), and (f) depict the NMR intensity of magnetic fluids as a function of magnetic susceptibilities of 0.0003 , 0.0006 , 0.0009 , 0.0012 , and 0.0015 in units of emu g^{-1} , respectively. The magnetic fluids consisted of

Figure 3. The NMR intensity for (a) water, and the NMR intensity magnetic fluids with different χ values: (b) 0.0003, (c) 0.0006, (d) 0.0009, (e) 0.0012, and (f) 0.0015 emu g⁻¹, respectively. The dependence of the linewidth on the magnetic susceptibility is displayed in (g).

dextran-coated magnetic nanoparticles dispersed uniformly in water [7]. The size of the magnetic nanoparticles was 30 nm in diameter. The linewidth of the NMR spectrum was 1 Hz, with a signal-to-noise ratio of 45 in a single shot. The intensity of the proton NMR signal decreased as the magnetic susceptibility (χ) of the magnetic fluids increased. The magnetic susceptibility χ reduced the intensity of the NMR signal and caused the linewidth to broaden. Figure 3(g) depicts the linewidth of the NMR spectra and the intensity as a function of the concentration of the magnetic fluid. The magnetic susceptibility of the magnetic fluids deteriorates the homogeneity of the field which causes the dephasing of the proton nuclear spin, and the domination of the spin–spin and spin–lattice relaxation. Therefore, a broadening of the proton NMR spectra and growing relaxation rate were observed when the χ value of the magnetic fluids was increased.

Figure 4(a) shows the transverse spin–spin relaxation time, T_2^* , as a function of χ in units of emu ml⁻¹. T_2^* is determined from the equation

$$M(t) = M_o \exp(-t/T_2^*), \quad (1)$$

Figure 4. (a) T_2^* and (b) Γ_{MF} of the magnetic fluids as a function of χ in units of emu g⁻¹.

where $M(t)$ is magnetization of samples at the instant of time t , $M_o = M(t = 0)$, and T_2^* is the total relaxation time. The relationship between M and χ is given by $M = \chi H$, where H is the applied magnetic field. T_2^* is related to the inhomogeneity parameter $\Gamma_{\text{inhomogeneity}}$ of the magnetic fields by the following equation:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \Gamma_{\text{inhomogeneity}}, \quad (2)$$

where $\Gamma_{\text{inhomogeneity}}$ is the effective relaxation rate, which is caused by the inhomogeneity of the measuring magnetic field. T_2^* decreased from 0.43 to 0.07 s when the magnetic susceptibility χ of the magnetic fluids increased from 0 (pure water) to 0.0015 emu g⁻¹. The magnetic fluids affect the relaxation time T_2^* through the equation

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \Gamma_{\text{inhomogeneity}} + \Gamma_{MF} \quad (3)$$

where Γ_{MF} is the relaxation rate due to the magnetic susceptibility χ caused by the magnetic fluid. Equation (2) represents the effects of the inhomogeneity of the magnetic field on the relaxation time T_2 . In addition to the effect of the field homogeneity, equation (3) shows that the magnetic susceptibility will introduce additional effects to the relaxation time T_2 . In NMR measurements, the field B_o was kept at 101 μ T; hence, $\Gamma_{\text{inhomogeneity}}$ remained the same value. From

Figure 5. (a) The top view and (b) the side view of a cylinder containing water with a capillary filled with magnetic fluid inserted into the center of the cylinder, and (c) the MRI image. (d) Fourier transform for the image shown in (c).

equations (1)–(3), we can derive Γ_{MF} as a function of magnetic susceptibility χ from the measured T_2^* . Figure 4(b) shows the derived values of $\Gamma_{MF} = 1/T_{MF}$ as a function of the magnetic susceptibility χ in units of emu g^{-1} , where T_{MF} is the effective relaxation time (in seconds) of the magnetic fluids. It was observed that Γ_{MF} increased from 0 to 13.5 s^{-1} when the magnetic susceptibility, relative to water, increased from 0 to $0.0015 \text{ emu g}^{-1}$. Both the magnetic susceptibility and the inhomogeneity of the fields caused the proton nuclear spin to dephase and reduced the spin–spin relaxation time.

The longitudinal relaxation time T_1 was investigated [8], and T_1 was estimated to be $(2.11 \pm 0.04) \text{ s}$ at 24°C in a measuring field of $95 \mu\text{T}$ via the equation

$$M(t) = S_o(1 - e^{-t_{Bp}/T_1}), \quad (4)$$

where S_o is the NMR intensity at saturation and t_{Bp} is the pre-polarization time in NMR measurements. By using the same method, we measured the NMR signal as a function of T_{Bp} and derived $T_1 = 140 \text{ ms}$ for magnetic fluids with $\chi = 0.0006 \text{ emu g}^{-1}$. We found that T_1 decreased significantly as the value of χ of the magnetic fluids was increased from 0 to $0.0006 \text{ emu g}^{-1}$. The decreased T_1 can be attributed to magnetic dipole–dipole interaction. A sufficient impact of the thermal noise due to random collisions between the ferromagnetic grains and the molecules of the carrier liquids induces fluctuations. There have to be fluctuations of magnetization of nanoparticles and these are most likely the main reason for the relaxation time T_1 being short. For a study of fluctuations of magnetic fluids, for instance ferrofluids as a thermal ratchet, readers may refer to [9, 10].

Figures 5(a) and (b) show the top view and the side view of a cylinder containing 6.3 ml of water as well as a capillary filled with magnetic fluid (0.3 emu g^{-1}) placed at the axis of the cylinder. The capillary has an inner diameter of 0.25 mm and

Figure 6. (a) A photograph of a cut portion of celery, (b) magnetic resonance image after injecting 0.2 ml of magnetic fluid with $\chi = 0.3 \text{ emu g}^{-1}$.

an outer diameter of 0.36 mm. Figures 5(c) and (d) show the MRI image and its Fourier transform respectively. An image contrast was observed in the MRI image at the location of the capillary where it was filled with the magnetic fluid. The bright image shows an SNR of 20 while the central region shows an SNR of 16. The Fourier transform shows a dip at the resonating frequency and the 50% dip corresponds to a spatial resolution of about 1 mm.

Figures 6(a) and (b) are photographs showing a portion of cut celery and its corresponding MRI obtained after 50 averages, respectively. Figures 6(c) and (d) are photographs of a portion of celery injected with magnetic fluid and the corresponding MRI image after injecting 0.2 ml (0.3 emu g^{-1}) of magnetic fluids, respectively. Without the magnetic fluid we cannot observe any image contrast. On the other hand, the image contrast is clearly enhanced at the location where magnetic fluid was injected. The MRI contrast in the central region is due to the effects of the magnetic susceptibility. The dephasing of the proton nuclear spin reduces the NMR intensity in that region.

The feasibility of using SQUIDS in conjunction with NMR and MRI technologies has been actively studied [11–18]. A review of NMR was given in [19]. Sensitive high- T_c and low- T_c spectrometers for J-spectroscopy [11, 15] have been reported. There is much less reporting of studies on the basis of the spin–lattice relaxation time, which is superior at low magnetic field [20]. In this work a high sensitivity and high resolution SQUID spectrometer was set up to study the effects of magnetic susceptibility on the spin–spin relaxation time and the spin–lattices relaxation time at microtesla levels. A broadening of the proton NMR spectra and a growth in the transverse relaxation rate were observed when χ of magnetic fluids increased. The T_1 of water decreases from 2.11 s to 140 ms rapidly at 24°C when the value of χ is increased from 0 to $0.0006 \text{ emu g}^{-1}$. We obtained the effective relaxation rate Γ_{MF} due to the magnetic susceptibility of the magnetic

fluids, and Γ_{MF} increased from 0 to 13.5 s^{-1} when the magnetic susceptibility, relative to water, increased from 0 to $0.0015 \text{ emu g}^{-1}$. Previously, there were no reports on using magnetic fluids as a contrast agent in magnetic fields as low as microteslas. In this work we have demonstrated the feasibility of using a magnetic fluid as a contrast agent for MRI in the microtesla range. Using low magnetic field NMR/MRI, we suggest a feasibility study of magnetic nanoparticles coated with bio-probes to associate with bio-targets (such as cancer cells), which will be of great interest. Indeed magnetic nanoparticles coated with bio-probes that associate with bio-targets, such as vascular cell adhesion molecules to locate plaque, have been demonstrated [21].

4. Conclusion

We have characterized magnetic nanoparticles in magnetic fluids as contrast agents for MRI using a high- T_c SQUID-based NMR spectrometer. The magnetic susceptibility of the magnetic fluid caused a dephasing of the proton nuclear spin, and a domination of the spin–spin and spin–lattice relaxation. Therefore, a broadening of the proton NMR spectra and increasing relaxation rate were observed when the χ value of the magnetic fluid was increased. We obtained an effective relaxation rate Γ_{MF} due to the magnetic susceptibility of the magnetic fluid. We have demonstrated magnetic fluids as image contrast agents using a high- T_c SQUID at the microtesla level for the first time.

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