Effect of diamagnetic contribution of water on harmonics distribution in a dilute solution of iron oxide nanoparticles measured using high-$T_c$ SQUID magnetometer

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1. Introduction

Magnetic nanoparticles have been utilized in medical imaging as contrast agents and tracers [1]. In addition, the use of such nanoparticles in bio-immunoassay, magnetic nanoparticle imaging, and magnetic drug targeting has been studied owing to their promising results in these applications. The inherent magnetic properties of these particles can be determined by measuring their magnetic susceptibility [2–4], relaxation [5–7], and remanence [8,9]. Lately, some researchers have reported the development of sensitive measurement systems that are capable of measuring the magnetic relaxation and remanence of magnetic nanoparticles in solution [7,10,11]. Although the magnetic responses of magnetic nanoparticles in solutions of different concentrations have been widely studied by observing magnetic relaxation, remanence, and AC susceptibility, the behavior of a low-concentration solution of magnetic nanoparticles in wide magnetic field regions still remains unclear. This might be because conventional magnetometers such as low-sensitivity magnetic sensors have certain limitations and the magnetic properties are often measured using concentrated and/or powdered samples. Furthermore, the magnetic response of the nanoparticles is assumed to be similar in solutions of different concentrations and the effect of the diamagnetic carrier liquid is neglected even in diluted solutions. This requires clarification, as most biomedical applications involve measurements of magnetic nanoparticles in low-concentration solutions, wherein the diamagnetic background signal from the carrier liquid may be comparable to the magnetic responses of the nanoparticles. Therefore, development of highly sensitive magnetometers is critical in order to detect small amounts of magnetic nanoparticles in low concentration solutions. Furthermore, magnetic susceptibility must be measured in the presence of an excitation magnetic field, in contrast to the measurement of magnetic relaxation and remanence. Interferences from the excitation magnetic field may limit the sensitivity of measurement systems, particularly in the case of AC susceptometer systems [12–14]. Such interferences from the excitation magnetic fields during dynamic magnetization measurements have been reduced by employing harmonics generated from the nonlinear magnetization characteristics of MNPs [15–17]. These harmonics are used to quantify MNPs with fast measurements and improve their sensitivity by isolating the frequency component of excitation magnetic fields. In addition, large amplitudes of excitation magnetic fields can further lead to enhancement in the generation of harmonics, as they tend

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to cover the wider regions of the nonlinear characteristics.

In this study, we have developed a highly sensitive AC–DC magnetometer using a high-critical-temperature superconducting quantum interference device (high-$T_c$ SQUID) on the basis of our previously developed system \[18,19\]. This flux transformer-based high-$T_c$ SQUID exhibited high sensitivity with less interference from the excitation magnetic fields. Using the developed system, we measured the static magnetizations and harmonics distribution of low-concentration solutions of iron oxide nanoparticles and investigated their magnetic responses in solutions of different concentrations. As a preliminary analysis to investigate the relationship between the concentration and the harmonics generation of diluted iron oxide nanoparticles during the application of DC and AC magnetic fields, we simulated the generation of harmonics on the basis of measurement results of the static magnetization. The static magnetization curves indicate the contribution of the diamagnetism of water as a function of concentration. Detection of low-concentration magnetic nanoparticles with high sensitivity has been demonstrated using second harmonics.

2. Material and method

2.1. Iron oxide nanoparticles

Iron oxide nanoparticles analyzed in this study were nanomag®-D-spio (Micromod Partikeltechnologie GmbH, Rostock-Warnemuende, Germany). In the typical experiment, a pre-determined quantity of iron oxide nanoparticles was suspended in water such that the concentration of iron in the resulting solution is 2.4 mg/ml. The iron oxide nanoparticles used in this study have an overall diameter of 100 nm, and consist of dextran iron oxide composites. Subsequently, low-concentration solutions were prepared by further diluting the suspension in purified water to obtain iron concentrations of 24 μg/ml, 48 μg/ml, 72 μg/ml, and 96 μg/ml. The diluted iron oxide solutions thus obtained were stored in 3-ml acrylic cases for further analysis.

2.2. AC–DC High-$T_c$ SQUID magnetometer for evaluating magnetic nanoparticles in solution

Fig.1 illustrates the overview of the high-$T_c$ SQUID magnetometer developed in this study and the coil arrangements used for static and dynamic magnetization measurements. The flux transformer consists of first-order planar and axial differential coils as the pickup coils for static and dynamic magnetization measurements, respectively, to reduce the environmental noise being transferred to the high-$T_c$ SQUID. Both types of coils were constructed by connecting two identical elliptical coils in a series opposing configuration. A ramp-edge-type Josephson junction was fabricated on an MgO substrate by a multilayer fabrication technique \[20\]. The sensitivity of the magnetic susceptibility of the developed system was $1 \times 10^{-8}$ emu (dimensionless). Details of the measurement system have been reported elsewhere \[18,19\].

For static magnetization measurements, the sample was exposed to a DC magnetic field generated by an electromagnet and perpendicularly vibrated to the axis of the DC magnetic field using an actuator having amplitude 5 mm and vibration frequency 2.82 Hz. The sensitive axis of the planar differential coil was maintained parallel to the axis of the DC magnetic field, as shown in Fig. 1(a). The induced signals were transferred to the inductively coupled SQUID and the output was detected by a lock-in amplifier. The motion of the actuator that was detected by a laser position sensor was used as a reference signal for the lock-in amplifier. The magnetization curve of the diluted solutions was determined in the range from 260 to 260 mT with a complete cycle of magnetization loop.

The characteristics and the concentration of the iron oxide nanoparticles in the solution could be quantitatively determined from the static magnetization curve; however, this is a time consuming process. Some biomedical applications such as bio-immunoassay require simultaneous measurements of multiple samples. For such applications, harmonics detection \[15,21\] can provide fast information on the magnetic response of magnetic nanoparticles by covering wide magnetic field regions in one-shot measurements. In this technique, the distribution of the induced harmonics of magnetic nanoparticles is related to the applied AC and DC magnetic field bias and the magnetization curve. For an AC magnetic field with amplitude larger than saturation magnetic field $H_s$, the magnetic response consists of harmonic components in the region below $H_s$, whereas in the region above $H_s$, the magnetic response is suppressed because of moment saturation. However, the introduction of the DC magnetic field will result in the magnetic response of the magnetic nanoparticles following the magnetization curve and production of a distorted waveform of the magnetic field with odd and even numbers of harmonic components \[16,17\]. Cutting the fundamental frequency component with a filter and measuring the harmonic components of the magnetic response will result in a high signal-to-noise ratio. In our measurement system, the sensitive axis of the axial differential

![Fig. 1. Schematic diagram of the developed AC–DC magnetometer with coil arrangements of (a) first-order planar differential coil for static magnetization measurement and (b) first-order axial differential coil for dynamic magnetization measurement.](image-url)
coil was placed perpendicular to the excitation magnetic field so as to reduce the interference of the excitation magnetic field. As shown in Fig. 1(b), the sample was placed at the center of the axial differential coil to which an AC magnetic field of frequency 5 Hz superimposed with a DC magnetic field was applied. The high-\(T_c\) SQUID output was detected by a lock-in amplifier using a reference signal at a function generator. The excitation magnetic fields were determined by a Hall sensor. Second and third harmonics were measured with different AC amplitudes and DC biases of magnetic fields to investigate their distributions and the effect of low concentration on magnetic response.

3. Theoretical model

3.1. Static magnetization model

The magnetization curves of the magnetic nanoparticles can be described by the Langevin function under the assumption that they are not affected by interparticle interactions and that they have isotropic spin governed by thermal fluctuations and the magnetization field [16,22]. This model is applicable to the iron oxide nanoparticles analyzed in this study as they were well dispersed in the diluted suspensions. Although the size of the iron oxide nanoparticles was distributed to some extent, which could be represented by the so-called log-normal spread [23], to avoid complexity during the fitting procedure, a mean diameter was assumed for the iron oxide nanoparticles. Moreover, since the iron concentration in the solution was low, the diamagnetic signal from the carrier liquid might be significant enough to decrease the magnetization curve in high magnetic field regions. This effect was corrected by introducing the parameter \(C\). Accordingly, the magnetization curve of the diluted iron oxide nanoparticles can be expressed as

\[
M(\mu_0 H) = M_S L\left(\frac{m\mu_0 H}{k_B T}\right) - C\mu_0 H
\]

where \(L(m\mu_0 H/k_B T)\) is the Langevin function, \(m\) is the magnetic moment of iron oxide nanoparticles, and \(k_B\) is the Boltzmann constant. Furthermore, \(M_S = \phi M_0\) is the saturation magnetization, which is the product of the volume concentration \(\phi\) of the suspended magnetic nanoparticles and their spontaneous magnetization \(M_0\). In this model, we treated \(M_S\), \(C\) and \(m\) as functions of concentration in order to fit the static magnetization data by Mathematica (Wolfram Research, Champaign, IL, USA) using the least-squares fitting method.

3.2. Harmonics generation

In a diluted solution, the addition of the diamagnetic signal of the carrier liquid due to the deformation of the magnetization curve might affect harmonics generation. For a low frequency of the AC magnetic field, the time varying magnetization can be assumed to follow the magnetization curve. Magnetization \(M(t)\) resulting from the excitation of magnetic field \(B_{\text{excitation}}(t) = B_{\text{amp}}\sin(\omega t) + B_{\text{DC}}\) can be expressed as

\[
M(t) = M(B_{\text{excitation}}(t)) = M_0 + M_1 \cos(\omega t + \theta_1) + M_2 \cos(2\omega t + \theta_2) + \ldots + M_n \cos(n\omega t + \theta_n)
\]

where \(M_n\) is the amplitude coefficient and \(\theta_n\) is the phase angle at angular frequency \(n\omega\). The signal response detected by a normal conductive coil can be calculated by the time derivative of \(M(t)\). In addition, we performed Fast Fourier Transform (FFT) analysis to extract harmonic components. The fundamental, second, and third harmonics were analyzed, as the higher harmonic components rapidly decrease with increasing harmonic number.

4. Magnetization curve of iron oxide nanoparticles solution

Fig. 2 shows the measured magnetization curves of the iron oxide nanoparticles in different dilute solutions after subtraction of the signal from the acrylic cases. The magnetization curve of purified water used in this study was included as a reference. The magnetization curves show superparamagnetic characteristics with \(H_c\) of approximately \(\mu_0 H_c = 40\) mT, whereas \(C\) rapidly decreases with concentration. This suggests that the diamagnetic signal of the carrier liquid in a dilute solution of magnetic nanoparticles should not be completely ignored, because the diamagnetism of the solution might exist as a function of concentration. As the concentration of iron oxide nanoparticles increases in high concentration solutions, the diamagnetic signal of water can be predicted to linearly decrease with decreasing volume percentage of water. However, the substantial decrease in \(C\) with increasing concentration could be attributed to the increasing number of small as well as large particles at higher concentrations. The large particles saturate and increase the saturation magnetization at higher concentrations. However, the small particles do not saturate even in a high magnetic field [24], thus canceling out the diamagnetic signal of water. Therefore, the diamagnetic effect rapidly disappeared at higher concentrations. The values of \(m\) were similar for solutions of different concentrations in the range from 3.3 to 3.4 \(\times 10^{-17}\) Am\(^2\). This value indicates that the size distribution of the iron oxide nanoparticles was similar at all concentrations. Further studies using fine particles could improve our understanding from this viewpoint. Nonetheless, the results show that the diamagnetic contribution of the carrier liquid has an effect on magnetization curves, when the magnetic moments of iron oxide nanoparticles and water are compared. This behavior could be beneficial in harmonics detection.
concentration of the iron oxide nanoparticles.

6. Harmonics signal of iron oxide nanoparticles solution

In an attempt to compensate for circumference noise, the signals detected from the lock-in amplifier with and without the samples were subtracted during harmonics measurements.
were consistent with the simulation results. The response of the second harmonics revealed less noise compared with that of the third harmonics, suggesting an additional advantage of using second harmonics in our measurement system. Fig. 7 shows the second and third harmonics corresponding to the DC magnetic field at 20 and 0 mT, respectively, during the excitation of the AC magnetic field with an amplitude of 30 mT with respect to the concentration. The second and third harmonics linearly responded to increasing concentrations, consistent with simulated results shown in the superimposed graphs in Fig. 4. This proves the existence of a linear relation between detected harmonics and concentration, despite the dependence of diamagnetic effect on the concentration. However, as the fundamental component was completely buried in the residual magnetic field, the effect of the diamagnetic contribution of water on the ratio of the harmonics could not be directly assessed.

7. Conclusion

In this study, we developed a high-$T_c$ SQUID magnetometer and utilized it to investigate the magnetization curve and harmonics distributions of low-concentration solutions of iron oxide nanoparticles. The static magnetization results of the low-concentration solutions showed that the diamagnetic signal from the carrier liquid deformed the magnetization curve and the diamagnetism of the solutions existed as a function of concentration. This suggests that the diamagnetic effect in the high magnetic field region could not be ignored while measuring a diluted solution of magnetic nanoparticles, for instance in biomedical applications. To facilitate fast analysis of magnetic nanoparticles, we simulated the generation of harmonics on the basis of measurement results of the static magnetization. The simulation results reveal that, at an appropriate bias of the DC magnetic field, the harmonic components linearly increase with increasing concentration, in the existence of diamagnetism of carrier liquid. Furthermore, the diamagnetic effect of the carrier liquid was beneficial for the harmonics detection technique from the perspective that the ratio of the harmonics to fundamental components had considerably improved. In the harmonics measurement, a linear relation between harmonics and concentration was obtained at an appropriate bias of the DC magnetic field. The harmonics distributions were similar to the simulated data. The use of second harmonics with an appropriate bias of the DC magnetic field showed that a high signal-to-noise ratio of measurement could be obtained when measuring dilute solutions of magnetic nanoparticles in the large interference of the excitation magnetic field.

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References