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We introduce a method to improve the detection sensitivity for the magnetization M of superparamagnetic nanoparticles (MNP). The M response of MNP to an applied magnetic field H (M–H characteristics) could be divided into a linear region and a saturation region, which are separated at a transition point H_k. When applying an excitation magnetic field (H_{ac}) with a frequency ω_0 and an additional dc bias field $H_{dc} = H_k$, the second harmonic of M reaches the maximum due to the nonlinearity of the M–H characteristics. It is stronger than any other harmonics and responsible for small H_{ac} without a threshold. The second harmonic selected as the readout criterion for M response of MNP is systematically analyzed and experimentally proven. © *2013 AIP Publishing LLC.*
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I. INTRODUCTION

Magnetic particle imaging (MPI) introduced by Gleich and Weizenecker[1] is based on utilizing the nonlinear magnetic response M for detection of superparamagnetic iron oxide nanoparticles (MNP). The excited M contains not only the fundamental excitation frequency ω_0 but also its harmonics when applying an ac excitation magnetic field $H_{ac} = H_0\sin(\omega_0 t)$. A number of magnetic readout methods have been developed to determine the MNP volume (or mass)[2,3] for different application purposes, for example, immunoassay.[4] In the MNP detection and the MPI technique, the most commonly employed method is the detection of the odd harmonics of the M response.[5–8]

In this paper, we analyze and utilize the second harmonic of the M response as readout criteria to enhance the MNP detection sensitivity, when applying a properly additional dc magnetic field H_{dc}. Here, the M response for an excitation magnetic field H_{ac} looks like a half-wave rectified sine wave with only even harmonics. The experimental results demonstrate that the second harmonic of M response is stronger than any other harmonics.

II. ANALYSES

A. Two typical waves and their frequency spectra

We first analyze the frequency spectra of two typical time varying waves, namely, a square wave (SW) and a half-wave rectified sine wave (HRSW), with the same amplitude of 2A. The expressions of their harmonics are described as

$$SW = \frac{4A}{\pi} \sum_{n=3,5,7...}^{\infty} \frac{1}{n} \sin(n\omega_0 t) \qquad (1)$$

and

$$HRSW = \frac{4A}{\pi} \sum_{n=2,4,6...}^{\infty} \frac{1}{(n^2-1)} \cos(n\omega_0 t), \qquad (2)$$

whereby ω_0 and n denote the fundamental frequency and the harmonic number, respectively.

The harmonics of SW in (1) include only the odd numbers, while HRSW only the even numbers (2). The third harmonic of SW and the second harmonic of HRSW reach the same amplitude of $4A/3\pi$, greater than those of the higher harmonics. The two typical wave-shapes and their spectra are frequently referenced below.

B. *M–H* characteristics at two different bias points

The M response of MNP for the ac excitation field $H_{ac}(t)$ is nonlinear. Our detection is just based on this nonlinearity. In order to understand the M response, M–H characteristics can be simply divided into two parts; the linear region (I) and the saturation region (II) (see Fig. 1(a)). The transition point of separating these two regions is called the "knee point" in this paper. Its corresponding field H and magnetization M are denoted as H_k and M_k, respectively. In order to generate the harmonics of M, in the case of $H_{dc} = 0$ (i.e., the (modulation) bias point is set at the origin of M–H characteristics), the sinusoidal excitation field amplitude H_0 should be larger than the knee point H_k, so that the M response is reached in the saturation region (II) and limited to $\pm M_k$. Therefore, the symmetrical M response consists of two components; a sine wave in region (I) and a square wave (SW) in region (II) (see Fig. 1(b)). Note that only the SW component contributes to the odd harmonics, which is the most popular criterion for MNP detection.

Our method is to set the bias point at the knee-point of the M–H characteristics of MNP (see Fig. 1(a)) with an additional $H_{dc} = H_k$. Here, the M response exhibits two different behaviors depending on the sign of the excitation field $H_0\sin(\omega_0 t)$: In the negative half wave of H_{ac}, M traces the sine-shape wave in the region (I). In the positive half, however, M remains M_k in the region (II) (M = constant). The total M response is thus like a HRSW (see Fig. 1(c)), which contains only the

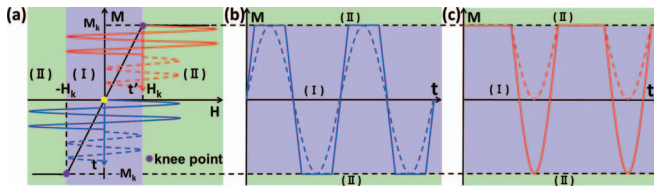a)Electronic mail: tanakas@ens.tut.ac.jp

FIG. 1. (a) The M–H characteristics contain two regions: the linear region (I) and the saturation region (II). The positive and negative knee-points are marked. The M responses for the excitation field of $H_{ac} = 2H_k \sin(\omega_0 t)$ (solid line) and $H_k \sin(\omega_0 t)$ (dashed line) at bias points of $H_{dc} = 0$ (b) and $H_{dc} = H_k$ (c) are schematically indicated.

even harmonics (see Eq. (2)). In other words, the bias point shift (H_{dc} from zero to H_k) acts like a rectifier diode on the M response.

Indeed, the components of the sample M response with odd or even numbers depend on H_{dc} bias points, which typically set at $H_{dc} = 0$ or $H_{dc} = H_k$, when applying an excitation magnetic field $H_{ac} = H_0 \sin(\omega_0 t)$.

III. EXPERIMENTS

A. Samples and arrangement

In order to prove our analyses above, we performed experiments using two high-concentration MNP samples under different H_{ac} and H_{dc}. The information on the samples, which are mostly used in applications, is listed in Table I. For the detection of the sample M responses, three solenoid coils were employed: coil L_{dc} was used to generate the static field H_{dc}, L_{ac} to generate the excitation field H_{ac} and L_d to detect the M responses of MNP sample. L_d consisted of two coils arranged oppositely as a gradient pickup coil which reduced the influence of fundamental frequency ω_0, thus increasing the amplifier dynamic range. One of the two coils surrounded the sample to detect its M response. The three coils, L_d, L_{ac}, and L_{dc}, were arranged coaxially. The parameters of the three coils are listed in Table II.

Fig. 2(a) shows the measurement arrangement. The sample volume was about 70 μl in a cylindrical form with 5 mm in diameter and located inside of the detection (pickup) coil. The M response signal of the sample was detected with the pickup coil connecting to the input of the dynamic signal analyzer (Agilent 35670A) to obtain its frequency spectrum.

In our experiments, the amplitude of the excitation field $\mu_0 H_{ac}$ could be varied up to ± 5.1 mT generated by applying a 165 V_{PP} sine wave signal with $\omega_0/2\pi = 20\,020$ Hz across the L_{ac}. This maximal excitation field of 10.2 mT$_{PP}$ is larger

TABLE I. Sample information.

Sample	#1	#2
Name	Resovist	Feridex
Composition	Ferucarbotran	Ferumoxides
Fe (mg/ml)	27.8	11.2
Diameter (nm)	60	120–180
$\mu_0 H_k{}^a$ (mT)	±3.3	±6.9

^{a}The measured value, where the second harmonic reaches a maximum.

TABLE II. Data of the three coils.

Type	L_{dc}	L_{ac}	L_d
Turn (number)	1040	541	240 + 240
Layer (number)	10	2	5
Wire diameter (mm)	0.9	0.4	0.2
dc resistance (Ω)	6.5	4.2	4.8 + 4.8
Impedance (Ω)@20 kHz	...	88.7	50 + 50
$\mu_0 H_{dc}/\text{I}^a$ (mT/A)	10.6	5.5	...

^{a}Magnetic field $\mu_0 H_{dc}$ generated by 1 A of current.

than $2\mu_0 H_k = 6.6$ mT of sample #1, but less than $2\mu_0 H_k = 13.8$ mT of sample #2. The static field $\mu_0 H_{dc}$ generated by L_{dc} reached values up to ± 26.5 mT.

B. Measurements and results

In our experiments, the influence of the Earth's field can be neglected because all applied magnetic fields are in the mT range.

To demonstrate the different properties between the two bias points, $H_{dc} = 0$ and $H_{dc} = H_k$, we should observe the M
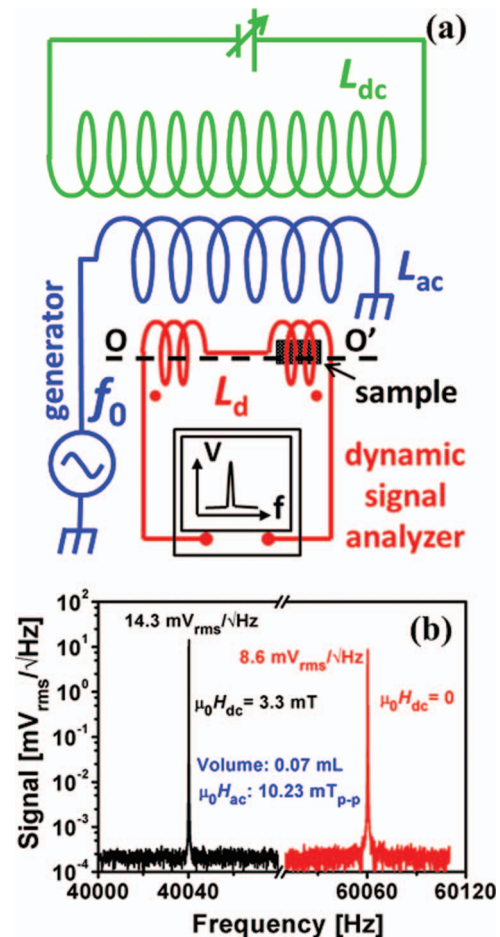

FIG. 2. (a) Schematic of the measurement arrangement. Here, three coaxial coils with o-o' axis are coupled to the sample. (b) The recorded spectra of sample #1, whose M response frequencies appear at $\omega_0/\pi = 40\,040$ Hz (second harmonics, $H_{dc} = H_k$) or $3\omega_0/2\pi = 60\,060$ Hz (third harmonics, $H_{dc} = 0$).

response for the excitation field H_{ac} with two typical amplitudes of $2H_k$ and H_k, respectively.

(1) Applying the excitation field $H_{ac} = 2H_k\sin(\omega_0 t)$, the M response at $H_{dc} = 0$ is schematically, indicated in Fig. 1(b). Here, the amplitude of M response is cut at $\pm M_k$ due to the saturation effect. Using Fast Fourier Transform (FFT), its frequency spectrum was simulated (not shown here). The largest amplitude of third harmonics reaches $0.14\,M_k$, which is about 33% of the theoretically achievable value of $4M_k/3\pi$ according to Eq. (1). Only when the excitation field amplitude $H_0 \gg 2H_k$ is fulfilled, the M response is close to SW. In this extreme case, the third harmonics of M approaches the value of $4M_k/3\pi$.

In contrast, setting the bias point at $H_{dc} = H_k$, the M response should be an ideal HRSW shown in Fig. 1(c) with a spectrum described in Eq. (2). Here, the second harmonics of sample M response reaches the theoretical value of $4M_k/3\pi$, when applying the same excitation field $H_{ac} = 2H_k\sin(\omega_0 t)$.

(2) When the excitation field H_{ac} is reduced to half of the above value, i.e., $H_{ac} = H_k\sin(\omega_0 t)$, the whole M response at $H_{dc} = 0$ is located in linear range (I) and traces the excitation field H_{ac} (see dashed lines in Fig. 1(b)). Thus, no harmonics of M are present. In other words, H_k is a threshold for the detection of the odd harmonics.

When setting the bias point at $H_{dc} = H_k$, the performance of the M response should retain the shape of a HRSW, while the amplitude of the second harmonics of M is divided in half, i.e., $2M_k/3\pi$ (dashed lines in Fig. 1(c)). In this case, there is no threshold of M response for an ideal M–H characteristic of MNP.

According to the above discussion, the bias point set at $H_{dc} = H_k$ is useful to enhance the harmonic M response. Furthermore, a sufficient M response without a threshold is possible even for a very small excitation field H_{ac}. In actual operation, it is very helpful to reduce the excitation field H_{ac} because the generation of a large H_{ac} is not easy. For example, a power supply with an output voltage of 180 V_{PP} and an output current 100 A is required to generate a $\mu_0 H_{ac}$ of 30 mT_{PP}[9] with a frequency of 20 kHz (here, μ_0 denotes the vacuum permeability). In contrast, the condition of $H_{dc} = H_k$ is easily fulfilled.

In real M–H characteristics of some samples, there is no clear "knee point" for separating the linear region (I) and the saturation region (II) described in Fig. 1(a). In other words, the two regions are not clearly arranged. The value of H_k at "knee point" listed in Table I was obtained experimentally, where the second harmonic of the sample M response reached the maximum with varying H_{dc} and a constant H_{ac}.

To demonstrate the effect of the "knee point," Fig. 2(b) records the frequency spectra with the third harmonics of M response at $\mu_0 H_{dc} = 0$ or the second harmonics at $\mu_0 H_{dc} = \mu_0 H_k = 3.3$ mT. Indeed, the M response frequency depends on H_{dc}, as discussed above in Eqs. (1) and (2).

Fig. 3(a) shows the M responses of the sample #1 vs. the H_{ac} variation in the two cases of $H_{dc} = H_k$ and $H_{dc} = 0$. The second and the third harmonics increased with increasing H_{ac}.
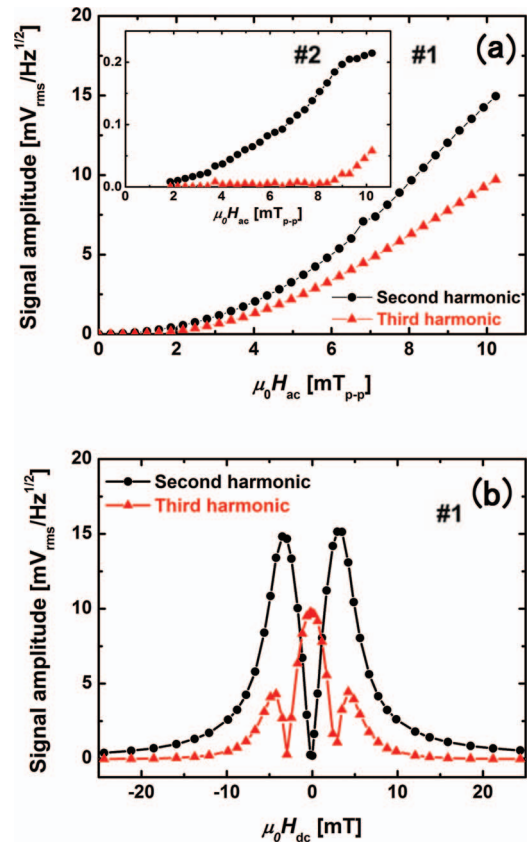

FIG. 3. (a) The dependence of M harmonics on varying H_{ac} excitation field, measured with sample #1 and #2 (inset). (b) The dependence of M harmonics of sample #1 on varying H_{dc}.

No clear threshold effect of the third harmonic appeared in small H_{ac} region at $H_{dc} = 0$. It reflected a strongly rounded M–H characteristics of the sample #1, because no clear linear region (I) in the sample M–H characteristic existed. However, the second harmonic ($2\omega_0/2\pi = 40\,040$ Hz) of the M response at the bias point of $\mu_0 H_k = \pm 3.3$ mT was always stronger than the third harmonic ($3\omega_0/2\pi = 60\,060$ Hz) at $H_{dc} = 0$. At the maximal excitation field $\mu_0 H_{ac} = 10.2$ mT$_{PP}$, 15 mV$_{rms}$/$\sqrt{Hz}$ at the second harmonic and 10 mV$_{rms}$/$\sqrt{Hz}$ at the third harmonic were recorded in frequency spectrum, respectively. According to the Faraday's principle, the induced voltage signal across the pick-up coil is proportional to the signal frequency. Therefore, the M response ratio of second harmonic/third harmonic should be close to 3, as discussed above.

The $\mu_0 H_k = \pm 6.9$ mT of sample #2 is about twice as large as that of sample #1. The experimentally observed harmonics of sample #2 in response to H_{ac} are shown in the inset of Fig. 3(a). Taking the bias point at $H_{dc} = 0$, the measured data showed that no third harmonics of M could be recorded in the range of $\mu_0 H_{ac} < 8.5$ mT$_{pp}$. In other words, a threshold effect was clearly observed. Over 8.5 mT$_{PP}$, the signal amplitude increased with $\mu_0 H_{ac}$. When setting the bias point at $H_{dc} = H_k$, in contrast, no threshold of the second harmonic appeared for $\mu_0 H_{ac} < 8.5$ mT$_{PP}$. The second harmonic monotonically increased with increasing H_{ac} and reached 220 μV$_{rms}$/$\sqrt{Hz}$ at $\mu_0 H_{ac}$ of 10.2 mT$_{PP}$. In this case, this response was about four times stronger than the measured third harmonic of 60 μV$_{rms}$/$\sqrt{Hz}$ under the same H_{ac}. The

measurement of sample #2 explicitly demonstrated the key benefits of setting the bias point at H_k.

The measured M responses exhibited a large difference between sample #1 and sample #2. It should depend on the properties of MNP, e.g., their diameters (see Table I).

Keeping the ac excitation field constant at $\mu_0 H_{ac} = 10.2$ mT$_{PP}$, the M response harmonics of sample #1 vs. the $\mu_0 H_{dc}$ variation between ± 25 mT were recorded in Fig. 3(b). In other words, the bias point was scanned in the range of $\mu_0 H_{dc} \approx \pm 25$ mT. As expected, the M maxima of second harmonic appeared at $\mu_0 H_{dc} = \pm \mu_0 H_k = \pm 3.3$ mT, while the third harmonic reached a maximum at $\mu_0 H_{dc} = 0$. The half-widths of the maximums were estimated to be about 4.7 mT. No significant difference of the half-widths between the second harmonic and the third harmonic was observed. The half-width with a gradient field decides the imaging resolution of x-space in MPI technique.[1]

For the third harmonic response, two symmetrical peaks with the half value of the maximum at $\mu_0 H_{dc} \approx \pm 5$ mT were exhibited. However, the two peaks were blinded by the second harmonic detection. We believe that there are two additional (symmetrical) steps at $\mu_0 H_{dc} \approx \pm 5$ mT in real M–H characteristics of sample #1. The steps generated SW components, thus leading the peaks. But, it did not affect the HRSW response, i.e., the second harmonic of M.

Such M steps were not observed with sample #2, i.e., the characteristics of the third harmonics vs. H_{dc} exhibited only one maximum at $H_{dc} = 0$ (not shown here).

IV. CONCLUSION

In conclusion, the magnetization M of the MNP was analyzed with two typical components, a square wave and a half-wave rectified sine wave, under a time varying excitation field H_{ac}. Setting the bias point at the knee-point of M–H characteristics, two important advantages arise: (1) The second harmonic of M is stronger than any other harmonics. (2) M responds to a small H_{ac} without a threshold. Therefore, the second harmonic of M response could be selected as the readout criterion to enhance the sensitivity of MNP detection.

Indeed, all imaging methods developed in MPI technique, e.g., moving FFP (field-free point),[1] can be modified for second harmonic detection of M. Furthermore, the second harmonics can be simply read out with a lock-in amplifier in order to reduce the environment disturbances and the video bandwidth in MPI technique.

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