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Research articles

Excitation frequency dependence of temperature resolution in magnetic nanoparticle temperature imaging with a scanning magnetic particle spectrometer

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A B S T R A C T

This paper investigates the dependence of temperature resolution in magnetic nanoparticle (MNP) temperature imaging on the frequency of an applied ac magnetic field with a custom-built scanning magnetic particle spectrometer (SMPS). The fundamental f_0 and $3f_0$ harmonics are measured with the SMPS while the amplitude ratio of the $3f_0$ to f_0 harmonics is used to determine the spatial distribution of temperatures. Experiments on a three-line phantom filled with a MNP sample are performed in different-frequency ac magnetic fields with a constant strength of 8 mT. The standard deviation of measured temperatures is used to characterize the temperature resolution. Experimental results show that the temperature resolution improves from 0.9 K to 0.2 K with increasing the excitation frequency from 600 Hz to 5 kHz, which is mainly caused by a higher signal-to-noise ratio due to Faraday's law and by a higher temperature sensitivity of the $3f_0$ to f_0 harmonic ratio.

1. Introduction

Non-invasive and *in-vivo* temperature imaging is of great significance and interest to biomedical applications, such as magnetic hyperthermia for cancer treatment [1,2] and thermally-controlled drug delivery [3,4]. Magnetic nanoparticle (MNP) thermometry employs the temperature sensitivity of the induced magnetization in ac and/or dc magnetic field for temperature determination [5–8]. For instance, MNP spectroscopy induced in an ac magnetic field has been reported to determine the integral and average temperature of a MNP sample [7–10]. Generally, two harmonics, e.g. the fundamental f_0 and $3f_0$ harmonics, or the $3f_0$ and $5f_0$ harmonics, were measured to determine temperature independent of the MNP concentration [7,9,10]. MNP thermometry is a remote, non-invasive and robust method of temperature determination, which has great potential for in-vivo temperature determination with applications in biomedicine.

To date, multi-dimensional temperature imaging with MNPs is still challenging. Magnetic particle imaging (MPI) has shown great promise in the determination of the spatial distribution of MNP concentration [11–13] while the color-MPI approach has been reported to demonstrate the feasibility of temperature imaging [14]. However, the temperature dependent MNP properties in a gradient and a homogeneous magnetic field have not yet well investigated, as well as the temperature imaging with the MPI approach. Recently, a custom-built scanning magnetic particle spectrometer (SMPS) was built to measure the spatial distributions of magnetic nanoparticle (MNP) harmonics for temperature imaging, extending MNP thermometry from 0-dimensional to 2-dimensional temperature imaging [15]. The spatial distribution of the amplitude ratio of the $3f_0$ harmonic to fundamental f_0 harmonic, which is independent of MNP concentration but dependent on MNP temperature, is used to determine temperature image. In principle, the approach for temperature imaging with the SMPS does not have any depth limitation due to the penetration of magnetic fields, which is an intrinsic advantage compared to optical approaches, such as thermal camera. Thus, the approach can be used for *in-vivo* temperature imaging for some disease diagnostics and therapy, such as breast cancer. However, the spatial resolution is limited by the depth, meaning that a larger depth allows for a worse spatial resolution. In addition, a large depth decreases the strength of the magnetic signal of the MNPs measured by a detection system, which will worsen the resolution of the temperature resolution as well. To compensate the decrease in the magnetic signal strength, a high-frequency ac magnetic field can be used for the excitation of the MNPs. While the temperature dependent MNP magnetic response in static or low-frequency ac magnetic fields can be described by the static Langevin function, in an ac magnetic field with a sufficiently high frequency, MNP relaxation significantly affects the MNP harmonics, as well as temperature sensitivity and resolution. Therefore, the excitation frequency of the applied ac magnetic field is a

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key influence factor affecting the temperature sensitivity and resolution of the MNP thermometry for temperature determination and imaging. Study on the dependence of the temperature resolution on the excitation frequency is of great interest and significance to improve the temperature resolution.

This paper investigates the temperature resolution in MNP temperature imaging in different-frequency ac magnetic fields with a custom-built SMPS. Specifically, the dependence of the temperature resolution on the excitation frequency, as well as the underlying mechanism, is studied. The standard deviation of the measured temperatures with the 3rd to 1st harmonic ratio, defining the *i*th harmonic at $i{\cdot}f_0$ frequency, is used to characterize the temperature resolution. Experiments on a three-line phantom are performed at different-frequency ac magnetic fields with constant amplitude of 8 mT. Experimental results of temperature resolution in different-frequency ac magnetic fields are presented. In addition, the underlying mechanisms – The excitation frequency dependence of temperature resolution, including the signal-to-noise ratio (SNR) and the temperature sensitivity – Are discussed.

2. Results and discussion

2.1. Experimental description

A three-line phantom with a distance of 3 mm between two adjacent lines is filled with a MNP suspension for phantom experiments. Fig. 1a shows the three-line phantom filled with MNPs while Fig. 1b shows the schematic of the MNP concentration versus *y* curve. Each line in the phantom has a length of 8 mm, a width of 2 mm and a depth of 1.5 mm. The experimental sample is SHP-30, purchased from Ocean NanoTech. Ltd. Corp. (San Diego, USA), which consists of Fe_3O_4 single-core nanoparticles with an average core diameter of 30 nm, a coating of monolayer oleic acid and monolayer amphilic polymer, and concentration of 5 mg/ml (Fe).

A custom-built SMPS is used to measure the spatial distributions of the 1st and 3rd harmonics of the MNP sample in different-frequency ac magnetic fields. The excitation frequency is varied from 600 Hz to 5 kHz whereas the excitation magnetic field amplitude is kept constant at 8 mT. A Helmholtz coil in the SMPS is used to generate the ac magnetic fields whereas a gradiometric pickup coil is designed to measure the MNP magnetization. The gradiometric pickup coil has a diameter of about 2.5 mm and a length of 3 mm, which can locally measure the MNP magnetization. The pickup coil is placed about 2–3 mm above the MNP sample (the distance in *z*-direction/the depth), allowing for a spatial resolution of about 2–3 mm. A mechanical scanner moves the MNP sample, which allows the measurements of the spatial distribution of the MNP harmonics. The SMPS moves the sample far away from the pickup coil for blank measurement to allow the

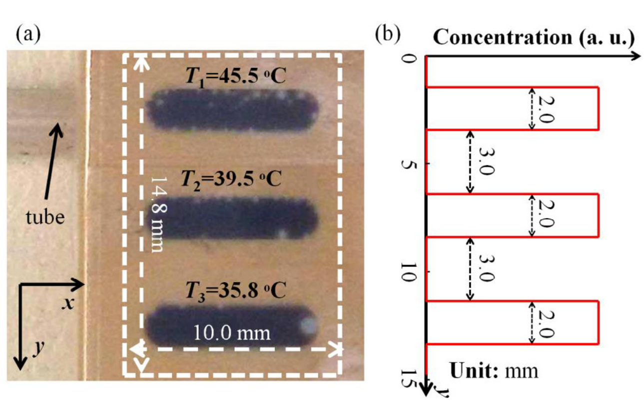

Fig. 1. (a) Photo of the three-line phantom. (b) Schematic of the MNP concentration versus *y* curve.

measurement of the fundamental harmonic. In the SMPS, the measured *i*th harmonic amplitude $u_i(x,y)$ can be described by $u_i(x, y) = i\omega{\cdot}s(x, y)*h_i(x, y)$, where $s(x,y)$ is the point spread function [15,16], defined by the sensitivity profile of the pickup coil, ω is the angular frequency of the excitation magnetic field, $h_i(x,y)$ is the *i*th harmonic amplitude generated by the local MNPs at a position (x,y). The details of the SMPS design have been presented in [15]. Note that the amplitude of the measured *i*th harmonic $u_i(x,y)$, in this study, is multiplied with the excitation frequency due to a detection coil based measurement system and the Faraday's law.

A water – Tube with temperature-controlled water, cycled by a pump, is placed under the top-line MNP suspension to heat the MNP sample, as shown in Fig. 1a. The water inside the tube is controlled by a water bath, which allows a stable temperature distribution during the measurements. Thus, the top-line MNP suspension has the highest temperature compared to the other two-line MNP suspensions. A thermal camera was used to measure the temperatures of the centre of the individual line of the phantom, as shown in Fig. 1a. With the same temperature profile of the phantom, the measurements of the MNP harmonics for temperature imaging are performed in different-frequency ac magnetic fields. The scanning field-of-view is 10.0 mm × 14.8 mm in *x*- and *y*-direction, respectively.

2.2. Results and discussion

The 1st and 3rd harmonics are measured with the custom-built SMPS for simultaneous imaging of MNP concentration and temperature. Each MNP harmonic is sensitive to MNP concentration and temperature whereas the harmonic ratio, e.g. the 3rd to the 1st harmonic ratio, is independent of MNP concentration but only dependent on MNP temperature. Thus, either the 1st or the 3rd harmonic allows for the measurements of the spatial distribution of MNP concentration whereas the 3rd to 1st harmonic ratio is used to determine the spatial distribution of MNP temperature. During the mechanical scanning of the SMPS, the 1st and 3rd harmonics are measured with a digital lock-in amplifier, realized in LabVIEW, in different-frequency ac magnetic fields.

Fig. 2a and b show the spatial distributions of the measured 1st and the 3rd harmonics at a 2004 Hz ac magnetic field, respectively. Both of the images of the 1st and 3rd harmonics show three blurred lines, corresponding to the experimental phantom in Fig. 1a. It indicates that either harmonic image can be used for MNP concentration imaging. Fig. 2c shows the 1st (left axis) and 3rd (right axis) harmonics versus *y* curve located at the red dashed lines in Fig. 2a and b whereas Fig. 2d shows the corresponding harmonic ratio M_3/M_1 versus *y* curve. Note that temperature imaging with a SMPS can only be realized at a specific position where there are enough MNPs. Thus, a threshold δ is applied on $M_1(x,y)$ for the measurements of 2D temperature distribution. At a specific position where $M_1(x,y) < \delta \cdot M_{1,\max}(x,y)$, the harmonic ratio is set to be 0.208 (measured at room temperature = 296 K) while at the specific position where $M_1(x,y) > \delta \cdot M_{1,\max}(x,y)$, the harmonic ratio is calculated from the measured 1st and 3rd harmonics. Herein, δ is set to be 0.75 to avoid any artefacts on the measured temperature at the edge of the line-phantom. $M_{1,\max}(x,y)$ is the maximum value of the 1st harmonic in the whole-image. Fig. 2c shows that the M_3-*y* curve is slightly different from the M_1-*y* curve regarding the curve shape, which is caused by the difference in temperature dependent 1st and 3rd harmonics. Fig. 2d shows that the harmonic ratio M_3/M_1 decreases with temperature decreasing due to the heat dissipation by the hot-water tube located at about *y* = 2.0 mm. This phenomenon is opposite to what is expected from the static Langevin function [7]. The decrease of the harmonic ratio M_3/M_1 with decreasing temperature is caused by the temperature dependent dynamics, i.e., by a faster relaxation at a higher temperature.

The measured temperatures in the centres of the individual lines of the multi-line phantom and the measured harmonic ratio M_3/M_1 are