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Lock-in thermography as a rapid and reproducible thermal characterization method for magnetic nanoparticles

Philipp Lemal[a,1], Christoph Geers[a,1], Christophe A. Monnier[a], Federica Crippa[a], Leopold Daum[a], Dominic A. Urban[a], Barbara Rothen-Rutishauser[a], Mathias Bonmarin[b,*], Alke Petri-Fink[a,c,**], Thomas L. Moore[a,*]

[a] *Adolphe Merkle Institute, University of Fribourg, Chemin des Verdiers 4, CH-1700 Fribourg, Switzerland*
[b] *Institute of Computational Physics, Zurich University of Applied Sciences, Technikumstrasse 9, 8400 Winterthur, Switzerland*
[c] *Chemistry Department, University of Fribourg, Chemin du Museé 9, CH-1700 Fribourg, Switzerland*

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ABSTRACT

Lock-in thermography (LIT) is a sensitive imaging technique generally used in engineering and materials science (*e.g.* detecting defects in composite materials). However, it has recently been expanded for investigating the heating power of nanomaterials, such as superparamagnetic iron oxide nanoparticles (SPIONs). Here we implement LIT as a rapid and reproducible method that can evaluate the heating potential of various sizes of SPIONs under an alternating magnetic field (AMF), as well as the limits of detection for each particle size. SPIONs were synthesized *via* thermal decomposition and stabilized in water *via* a ligand transfer process. Thermographic measurements of SPIONs were made by stimulating particles of varying sizes and increasing concentrations under an AMF. Furthermore, a commercially available SPION sample was included as an external reference. While the size dependent heating efficiency of SPIONs has been previously described, our objective was to probe the sensitivity limits of LIT. For certain size regimes it was possible to detect signals at concentrations as low as 0.1 mg Fe/mL. Measuring at different concentrations enabled a linear regression analysis and extrapolation of the limit of detection for different size nanoparticles.

1. Introduction

Superparamagnetic iron oxide nanoparticles (SPIONs) are fascinating materials for biomedical applications due to their biocompatibility [1–4] and capabilities of generating heat when exposed to an alternating magnetic field (AMF) [5]. These features, in combination with their nanoscale size and versatility, render them particularly intriguing over a wide range of disciplines, including drug delivery, magnetic resonance imaging (MRI) and hyperthermia treatment [6], the latter having been recently approved in Europe for the treatment of glioblastoma multiforme [7]. The success of these SPION-mediated hyperthermia treatments relies strongly on the local concentration of SPIONs within the tumor and their heating potential in the region of interest. In turn, the latter factor is dictated by the specific material properties (*e.g.*, size shape, crystallinity *etc.*) and external parameters, such as magnetic field strength and frequency [5,8–14]. While field strength and frequency can be easily controlled, a myriad of variables affect the physico-chemical makeup of SPIONs and consequently their overall ability to generate heat. As an example, it has been reported that significant variations in the heating power also occur in SPIONs produced on an industrial scale [15]. As a result, experimentally assessing heating power in every synthetic batch is highly recommended as a means of quality control. This work presents a comparative screening of the thermal SPION characteristics *via* LIT as an extension to Monnier et al. [16]. The lower detection limit of the LIT system as a function of different particle diameters was investigated by measuring thermal properties at decreasing concentrations.

There are numerous ways to measure and quantify the heating potential of a respective SPION sample. Standard calorimetric methods are arguably the most common ones, which rely on monitoring the transient temperature change (*e.g. via* fiber optic cables) of the sample over time after exposure to an AMF [6,17]. The heating slope (ΔTemperature/Δtime) within the initial seconds of exposure can then be deduced [6,8,18]. However, inconsistencies in sample measurement

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[*] Corresponding authors.
[**] Corresponding author at: Adolphe Merkle Institute, University of Fribourg, Chemin des Verdiers 4, CH-1700 Fribourg, Switzerland.
E-mail addresses: mathias.bonmarin@zhaw.ch (M. Bonmarin), alke.fink@unifr.ch (A. Petri-Fink), thomaslee.moore@unifr.ch (T.L. Moore).
[1] These authors contributed equally to this manuscript.

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and difficulty interpreting these data are becoming increasingly recognized, and call into question how reliable these approaches are and to what extent the results can be reproduced [17,18]. A very promising contactless alternative method is lock-in thermography (LIT). Pioneered in 1984 [19], this method assumes that the stimulus (*i.e.*, the AMF), and consequently the heat dissipating from the excited material (*i.e.*, the magnetic nanoparticles) are periodically modulated [20]. In this particular case, the result of LIT demodulation would be an amplitude image showing within the AMF the heating signature which originates from only the magnetic nanoparticles (MNPs).

Here, MNP batches of different sizes prepared within the same research group were synthesized by thermal decomposition, coated with citric acid and transferred to an aqueous environment. The MNP in the measurements were varied only by size and concentration. A multi-sample holder enabled screening and comparison of multiple samples/parameters simultaneously. A colloidal suspension of commercially available nanoparticles was also included in each experiment to act both as a guide value within the measurement series (*i.e.*, to assure that values or conditions did not vary between them) and as an overall reference standard independent of the research group.

2. Experimental section

2.1. Synthesis of SPIONs and ligand exchange

All chemicals were used as received without any further purification. Each aqueous solution was prepared with deionized water received from a Milli-Q system (resistivity=18.2 MΩ cm, Millipore AG). The SPIONs used in this work were prepared *via* thermal decomposition of an iron oleate complex in the presence of oleic acid [21,22]. The desired nanoparticle sizes could be varied by changes in the defined heating ramps and by minor changes to the iron (III) chloride hexahydrate to sodium oleate ratio, and iron oleate complex proportion to oleic acid. To stabilize the SPIONs in aqueous solutions a ligand exchange with citric acid (CA) was performed [23].

2.2. Transmission electron microscopy

Transmission electron microscopy (TEM) was used to determine size, dispersity and morphology of the synthesized SPIONs. Sample preparation was performed by following a method described by Michen and Geers, et al. [24]. TEM experiments were carried out on a FEI Tecnai Spirit operating at a voltage of 120 kV and equipped with a side-mounted Veleta camera. Particle size analysis was performed using ImageJ (v1.46r) particle sizing software ($n > 1500$ nanoparticles).

2.3. Dynamic light scattering

Dynamic light scattering (DLS) measurements were performed at 25 °C using a commercial goniometer instrument (3D LS Spectrometer, LS Instruments AG, Switzerland). Three measurements were made at a scatterings angle 90° and autocorrelation functions were analyzed with a customized script in Mathematica (Version 10.1, Wolfram Research Inc).

2.4. Iron quantification by ICP-OES

Iron quantification of SPIONs was achieved through Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES, PerkinElmer Optima 7000 DV). A triplet of each nanoparticle suspension (10 µL) was dissolved in aqua regia (HNO_3:HCl with a volume ratio of 1:3, 500 µL per tube), transferred to 15 mL Falcon tubes (BD Biosciences, Switzerland) and diluted to 10 mL with Milli-Q water. Additionally a standard curve of aqueous iron solution was prepared and all samples were measured by ICP-OES at a wavelength of 238.2 nm for iron.

2.5. Vibrating sample magnetometer

Magnetic properties of the citric acid coated SPIONs were determined by a vibrating sample magnetometer (VSM, Model 3900, Princeton Measurements Corporation). Nanoparticle suspensions were deposited onto hydrophobic cotton pellets and dried overnight. The samples were attached to the sample holder with grease and hysteresis loop measurements were performed at room temperature using a measurement averaging time of 300 ms, and a constant field increment. The resulting magnetization curves were normalized by the dried sample mass of iron.

2.6. Thermal measurements

All thermal measurements were performed with a previously described lock-in thermal imaging setup [16]. SPIONs were exposed to an alternating magnetic field generated by a commercial coil system (Magnetherm™ V1.5, nanoTherics Ltd) consisting of a water cooled coil, a laboratory power supply (EA-PS 3032-20B, EA Elektro Automatic) and a function generator (SFG-2004, GW Instek). The apparatus was set to run at 524.5 kHz and 18.5 mT. The heating rates were determined using an infrared camera (Onca-MWIR-InSb-320, XenICs) mounted on a standard microscope stand (Leica Microsystems), and recorded infrared images with a full frame rate of 250 Hz. Data were transferred to a personal computer and processed in real time. The modulation frequency was set to 1 Hz for all measurements. LIT measurements were performed in 4 chambers of a nine-well plate. It was verified that the magnetic field was comparable in the 4 positions used for measurement, and characterization of the magnetic field is included in a forthcoming manuscript [25].

3. Results and discussion

A typical LIT setup is composed of three main components (Fig. 1A): an infrared camera to record the thermal emission of the

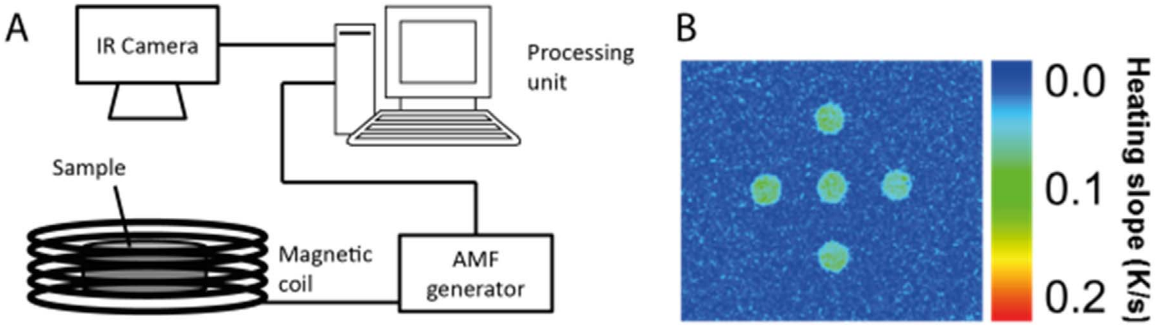

Fig. 1. A simplified scheme of the lock-in thermography system (A) consisting of the sample, a magnetic coil, a thermal imaging device and processing unit. Under implementation of a customized lock-in demodulation algorithm, the output is a two-dimensional image in which every pixel can be related to the initial heating slope values (B).