Modulatable magnetically mediated thermoacoustic imaging with magnetic nanoparticles

Feng, Xiaohua; Gao, Fei; Zheng, Yuanjin

2015

Feng, X., Gao, F., & Zheng, Y. (2015). Modulatable magnetically mediated thermoacoustic imaging with magnetic nanoparticles. *Applied physics letters*, 106(15), 153702-.

<https://hdl.handle.net/10356/79411>

<https://doi.org/10.1063/1.4918582>

© 2015 AIP Publishing LLC. This paper was published in *Applied Physics Letters* and is made available as an electronic reprint (preprint) with permission of AIP Publishing LLC. The paper can be found at the following official DOI: [<http://dx.doi.org/10.1063/1.4918582>]. One print or electronic copy may be made for personal use only. Systematic or multiple reproduction, distribution to multiple locations via electronic or other means, duplication of any material in this paper for a fee or for commercial purposes, or modification of the content of the paper is prohibited and is subject to penalties under law.

Downloaded on 26 Apr 2023 11:55:22 SGT

Modulatable magnetically mediated thermoacoustic imaging with magnetic nanoparticles

Xiaohua Feng, Fei Gao, and Yuanjin Zheng

Citation: [Applied Physics Letters](#) **106**, 153702 (2015); doi: 10.1063/1.4918582

View online: <http://dx.doi.org/10.1063/1.4918582>

View Table of Contents: <http://scitation.aip.org/content/aip/journal/apl/106/15?ver=pdfcov>

Published by the [AIP Publishing](#)

Articles you may be interested in

[Magnetically mediated thermoacoustic imaging toward deeper penetration](#)

Appl. Phys. Lett. **103**, 083704 (2013); 10.1063/1.4819391

[Spectroscopic thermoacoustic imaging of water and fat composition](#)

Appl. Phys. Lett. **101**, 033705 (2012); 10.1063/1.4737414

[Near-field radiofrequency thermoacoustic tomography with impulse excitation](#)

Med. Phys. **37**, 4602 (2010); 10.1118/1.3467756

[Thermoacoustic molecular tomography with magnetic nanoparticle contrast agents for targeted tumor detection](#)

Med. Phys. **37**, 4193 (2010); 10.1118/1.3466696

[Development of a laser photothermoacoustic frequency-swept system for subsurface imaging: Theory and experiment](#)

J. Acoust. Soc. Am. **116**, 3523 (2004); 10.1121/1.1819393

An advertisement for Oxford Instruments. The background is dark blue. On the left, there is a black mobile phone and a white desktop computer. Text next to them says 'You don't still use this cell phone' and 'or this computer'. In the center, there is a white AFM (Atomic Force Microscope) machine. Text next to it says 'Why are you still using an AFM designed in the 80's?'. On the right, there is more text: 'It is time to upgrade your AFM', 'Minimum \$20,000 trade-in discount for purchases before August 31st', and 'Asylum Research is today's technology leader in AFM'. At the bottom right, there is the Oxford Instruments logo and the tagline 'The Business of Science®'. Below the logo is the email address 'dropmyoldAFM@oxinst.com'.

Modulatable magnetically mediated thermoacoustic imaging with magnetic nanoparticles

Xiaohua Feng, Fei Gao, and Yuanjin Zheng

School of Electrical and Electronic Engineering, Nanyang Technological University, Singapore 639798

(Received 24 July 2014; accepted 7 April 2015; published online 14 April 2015)

Modulatable magnetically mediated thermoacoustic imaging with magnetic nanoparticles is reported here. Under a pulsed radio frequency magnetic field, magnetic nanoparticles absorb energy strongly from the field and then emanate ultrasound signal thermoelastically. The energy absorption and, consequently, generated thermoacoustic signal strength depend sensitively on the magnetization state of magnetic nanoparticles, which can therefore be modulated effectively by a “bias” magnetic field. The magnetic modulation is demonstrated with a static magnet and modulated phantom imaging results are presented. This method offers an alternative modality for mapping magnetic nanoparticles and its unique modulation capability is demonstrated to be useful for contrast enhancement. © 2015 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4918582>]

The thermal utility of magnetic nanoparticles, which stems from their highly localized heating effects under alternating magnetic field (AMF), has pervaded them into myriad of applications in industrial and medical spheres,^{1,2} but seldom to the fast growing field of thermoacoustic (TA) sensing and imaging. Recently, they had been utilized in magneto-motive photoacoustic imaging³ and magnetic-enrichment of photoacoustic imaging.⁴ Yet, rather than thermal effects, it is their mechanical movements under external magnetic field that is exploited. In Ref. 5, magnetic nanoparticles were used as the contrast agent in microwave induced thermoacoustic imaging. However, it relies on the enhanced dielectric absorption of radiation energy instead of magnetic relaxation loss that draws energy from non-radiant magnetic field. This difference matters as most applications resting on thermal utility of magnetic nanoparticles employ the latter approach for heating, including recent reported neuron stimulation.⁶ The thermoacoustic effect of magnetic nanoparticles under alternating magnetic field was initially studied theoretically in Ref. 7, but experimental verifications were lacking. Also, substantial heating of non-magnetic background,⁸ particularly, the shallow tissues that are exposed to larger field, can occur and consequently limit the imaging contrast for rendering nanoparticles labeled region. We report here the thermoacoustic effect of magnetic nanoparticles under AMF experimentally, using magnetically mediated thermoacoustic imaging setup.⁹ Furthermore, it is analyzed theoretically and demonstrated experimentally the magnetic modulation capability of magnetic nanoparticles' TA effect under AMF, which is unique to magnetic nanoparticles and thus useful for contrast enhancement by reducing background via differential imaging. Compared with conventional differential imaging¹⁰ that acquire two images before and after nanoparticles injection, which suffers from the long nanoparticle circulation time in between, the proposed modulation method enables both two images to be formed after nanoparticles injection, with the “before nanoparticles injection image” emulated by the modulation that selectively eliminates TA signals of nanoparticles. This leads to faster differential imaging and thus makes it more robust to physiological movements.

When exposed to an alternating magnetic field, magnetic nanoparticles undergo Neel relaxation and Brown relaxation processes that lead to local heat generation. The volumetric power deposition $S(r)$ at position r is calculated as¹¹

$$S(r) = \frac{\mu_0}{2} H_{ac}^2(r) \chi_0 \frac{\omega^2 \tau}{1 + (\omega \tau)^2}, \quad (1)$$

where μ_0 is the permeability of free space, H_{ac} is the alternating magnetic field amplitude, ω is its radian frequency, χ_0 is the magnetic susceptibility of ferrofluid, and τ is the effective relaxation time. With the magnetic heating being transient or modulated, thermoacoustic waves are then generated⁷

$$\begin{aligned} \nabla^2 p(\vec{r}, t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p(\vec{r}, t) \\ = -\frac{\Gamma}{c^2} \frac{\partial}{\partial t} \{S(r) [U(t) - U(t - \Delta t)]\}, \end{aligned} \quad (2)$$

in which $p(\vec{r}, t)$, c , and Δt represent the thermoacoustic pressure, speed of sound, and heating duration, respectively. Γ signifies the Grueneisen parameter of ferrofluid and $U(t)$ denotes the step function. Under the condition that both stress confinement and thermal confinement are satisfied, the pressure of generated thermoacoustic wave can be estimated¹²

$$P(r) = \Gamma S(r) \Delta t = \Gamma \Delta t \frac{\mu_0}{2} H_{ac}^2(r) \chi_0 \frac{\omega^2 \tau}{1 + (\omega \tau)^2}. \quad (3)$$

The pressure strength is hence proportional to magnetic susceptibility of nanoparticles fluid χ_0 , which is a parameter sensitive to the ferrofluid magnetization state. As a result, the susceptibility χ_0 and therefore generated TA signal can be controlled by varying the magnetization state of magnetic nanoparticles with a DC magnetic field H_0 . The DC magnetic field, 0.5 T, for instance, is generally three orders of magnitude larger than the alternating magnetic field strength (several milli Tesla)⁷ so that the modulation is majorly controlled by the DC field.

Magnetic modulation can be achieved by two different configurations as illustrated in Fig. 1(a). In the first scenario,

the configuration is the same as that in MRI: The DC magnetic field is perpendicular to the alternating magnetic field. Whereas for the second scenario, both the magnetic fields are in the same direction. The first configuration was partially investigated in Ref. 13 in that the effect of DC magnetic field on magnetic heating in MRI environment was investigated. Here, the second scenario is considered and the implications for thermoacoustic imaging in both configurations are studied. Under DC magnetic field H_0 , the magnetic susceptibilities of ferrofluid in both scenarios deviate from χ_0 as DC field H_0 magnetizes the ferrofluid toward saturation, which leaves less headroom for further magnetization. This is equivalent for a reduced magnetic susceptibility. Denoted as χ_{01} and χ_{02} for the first and second scenarios, respectively, the susceptibilities can be calculated as¹³

$$\chi_{01} = \frac{M_0}{H_0} = \frac{M_s}{H_0} \left(\coth(\alpha_0) - \frac{1}{\alpha_0} \right), \quad (4)$$

$$\chi_{02} = \frac{\partial M_0}{\partial H_0} = \frac{M_s}{H_0} \left(-\frac{\alpha_0}{\sinh^2(\alpha_0)} + \frac{1}{\alpha_0} \right), \quad (5)$$

where $\alpha_0 = \frac{M_d V_p \mu_0 H_0}{kT}$ is the Langevin parameter and $M_s = M_d \phi$ is the saturation magnetization of the ferrofluid. M_d represents the single domain magnetization of nanoparticle, $V_p = \frac{4}{3} \pi R^3$ is the nanoparticle volume with R denoting nanoparticle core radius, ϕ is solid volume fraction of the ferrofluid, and T and k are the absolute temperature and Boltzmann constant, respectively. For scenario 2, the volumetric power deposition function can be derived to be slightly different from Eq. (1): $S_2(r) = \frac{\mu_0}{2} H_{ac}^2(r) \chi_{02} \frac{\omega^2 \tau}{(1 + \chi_{02})^2 + (\omega \tau)^2}$. Nonetheless, as χ_{02} is generally much smaller than one¹³ (see below calculation), $S_2(r)$ can still be considered approximately linearly related to χ_{02} . Therefore, in both scenarios, the thermoacoustic signal strength is proportional to the DC magnetic field dependent susceptibility.

The calculated magnetic susceptibility (according to Eqs. (4) and (5)) versus DC magnetic field are plotted in Fig. 1(b) for illustration purpose, with $T = 300$ K, $M_d = 446$ kA/m, $\phi = 0.001$, and $R = 6$ nm. Both configurations yield smaller magnetic susceptibility as the “bias” magnetic field is increased. However, the second configuration shows a sharper decrease, indicating a more efficient modulation. At sufficiently large “bias” field, the susceptibility goes to zero and therefore suppresses the magnetic heating of nanoparticles, which ultimately disables the thermoacoustic process.

FIG. 1. (a) Schematic of two configurations. MAG: magnet and MNP: magnetic nanoparticles. (b) DC magnetic field dependence of susceptibility.

The modulation is unique to magnetic nanoparticles: because the non-magnetic background heating is majorly caused by the Joule heating under AMF,⁹ which is only determined by the alternating magnetic field strength, non-magnetic background heating will be not affected by the DC magnetic field, as verified by the experiments shortly. This will enable specific mapping of magnetic nanoparticles via differential imaging. Also, the differential imaging speed is now determined by the TA imaging time rather than the nanoparticle circulation time in conventional solutions.

A commercial super-paramagnetic iron oxide nanoparticles (SPIONs) product (3327NG, Skyspring Nanomaterials, Inc.) is used in the experiments for demonstration considering it is FDA approved. The SPIONs' average particle size is 10–15 nm in diameter and its specific saturation magnetization is 43.8 emu/g. The effective relaxation time of SPIONs depends on various parameters like the viscosity of ferrofluid, and it is estimated to fall into the order of 1 μ s according to Ref. 11. The experimental setup is illustrated in Fig. 2. A function generator (Tektronix, AFG3252) produces 1 μ s radio frequency (RF) signal at repetition frequency of 1 kHz and feeds the 1 kW RF pulse amplifier (BT01000-AlphaSA-CW, Tomcorf), which drives the coil through a capacitor network. A 2.2 Ω resistor is connected in series with the coil to monitor the current flowing inside. A tube phantom (inner diameter of 3 mm) filled with SPIONs is placed inside the tank with water as ultrasound coupling agent. Using 1 μ s pulse excitation, the highest TA frequency could be generated for a point source is 1 MHz and it will be even lower for finite size objects, a focused ultrasound transducer with center frequency of 1 MHz and focal length of 0.8 in. (Olympus, V303) is hence used for receiving thermoacoustic signal. The transducer is fixed on a linear translation stage to facilitate subsequent TA imaging. Detected TA signal is first amplified by 54 dB with a low noise amplifier (PR5032, Olympus), then digitized and averaged by the oscilloscope (Waverunner 6Zi, Lecroy), and finally transferred to PC for further processing. Cooling of the coil is not needed for thermoacoustic imaging since the duty cycle of the pulsed method is only 0.1%.

To demonstrate thermoacoustic signal generation and to study the dependence of TA signal on nanoparticle concentration and excitation power, a coil containing a ferrite core inside (estimated relative permeability around 6 at 20 MHz, Far-rite, Inc.) is used because the ferrite core can enhance the magnetic field and thus improve the TA signal strength. The coil has 10 turns, a diameter of 10 mm and a resonance frequency of 20.1 MHz when networked with the capacitors (quality factors at resonance around 20). The coil is placed 2 mm beneath the tube phantom. Driven at resonance frequency, the peak current in the coil is about 35 A and the alternating magnetic field intensity is estimated to be 100 kA/m (0.01 T) at the phantom. The received TA signal is averaged 16 000 times and filtered by a 4th order Butterworth bandpass filter (pass band being from 0.2 MHz to 1.5 MHz) in the oscilloscope. With SPIONs at a concentration of 220 mg/ml inside the tube and the transducer being 3.5 cm away, TA signal appears at 24 μ s (Fig. 3(a)) and shifts to 29 μ s (Fig. 3(b)) when the transducer is moved to be 4.3 cm away from the phantom. The measured dependence

FIG. 2. (a) Experimental setup for magnetically mediated thermoacoustics with magnetic nanoparticles, FG: function generator, PA: power amplifier, LNA: low noise amplifier, and TR: transducer. (b) Configuration of the two scenarios in the experiment. MAG: magnet.

of TA signal on the excitation power for 220 mg/ml SPIONs is shown in Fig. 3(c), which reveals a linear relationship between TA signal amplitude and the excitation power (linear fitting coefficient R^2 being 0.995). On the other hand, the TA signal amplitude as a function of the concentration are measured at five concentrations (220 mg/ml, 110 mg/ml, 55 mg/ml, 22.5 mg/ml, and 11.25 mg/ml, respectively) with the excitation power being fixed at 1.6 kW. The result is shown in Fig. 3(d), where the data are fitted by a linear function with R^2 larger than 0.99. This agrees well with general observation that larger concentration gives better magnetic heating and thus stronger TA signal.

Magnetic modulations of TA signal in two configurations are then demonstrated with a static magnet that emanates a surface magnetic field strength of 0.35 T. Since the strong static magnetic field will disable the ferrite core, a second coil without ferrite core is employed. It has a diameter of 10 mm, 24 turns, and a resonance frequency of 20 MHz when networked with capacitors (quality factors at resonance around 20). Under 1.6 kW, the peak current in coil is around 30 A and magnetic field intensity is estimated to be

40 kA/m at the phantom, which is 1 mm above the coil. Due to the reduced magnetic field, SPIONs at 220 mg/ml is used to generate decent TA signal. The configurations of the magnet in two scenarios are illustrated in Fig. 2(b). The magnet is placed 10 mm away from the phantom in both scenarios. TA signals with and without modulation in scenario 1 are shown in Fig. 4(a) and those in scenario 2 are shown in (b). TA signals are significantly abated in both scenarios when the DC magnetic field is introduced, demonstrating the effectiveness of magnetic modulation. Also, scenario 2 achieves roughly 2 times better reduction in terms of peak-to-peak TA signal than scenario 1. Such more efficient modulation of scenario 2 conforms to the theory. Although the TA signals are not fully eliminated in both scenarios due to the relatively smaller magnetic field at the phantom site, the TA signal in scenario 2 is already close to the noise floor. It is thus anticipated that a larger static magnetic field can bring the magnetic susceptibility of SPIONs towards zero, reducing the TA signal below noise floor.

Finally, phantom imaging of SPIONs at 220 mg/ml with the second coil is performed. The image is formed by linearly scanning the phantom with the focused transducer manually and then performing back projection after envelop extraction of each A-line signal. An alumina strip with 2 mm diameter is placed in parallel with the phantom to simulate the non-magnetic background. The resultant TA image is shown in Fig. 5(a), which renders the tube on the left and the metal strip on the right. The tube segments outside the coil (dotted black line) are not as clear as those inside the coil since the magnetic field is weaker there. Modulated image for scenario 2 is formed by introducing the DC magnetic field to suppress TA signals from nanoparticles. The

FIG. 3. TA signals at two different separations between transducer and the phantom, MP: magnetic nanoparticles. (a) 3.5 cm; (b) 4.3 cm; (c) TA signal peak to peak amplitude as a function of excitation power, red square: measured results and black solid line: linear fit result; and (d) TA signal peak-to-peak amplitude at five concentrations; red square: measured values and black solid line: linear fit result.

FIG. 4. (a) Reference (solid line) and modulated TA signal (dotted line) in scenario 1. (b) Reference (solid line) and modulated TA signal (dotted line) in scenario 2.

FIG. 5. (a) Reference thermoacoustic image; (b) modulated image in the scenario 2; (c) coherent differential image between reference image in (a) and modulated image in (b); and (d) TA magnitude along the center line for the reference imaging (virtual blue line) and coherent differential image (solid red line); White dotted line indicates the position of coil beneath the phantom.

modulated image is shown in Fig. 5(b). As expected, no nanoparticles are identified in the modulated image though the metal strip is somewhat blurred. The blurring is caused by some inevitable movements during manual maneuvering of the linear stage. The coherent differential image (subtraction before envelop extraction) between (a) and (b) are presented in (c), which shows a cleaner image of the tube with much weaker background. Such reduction of the non-magnetic background is further illustrated in Fig. 5(d) that depicts the TA magnitudes along the center line of the reference and differential image. Compared with reference image that shows a background magnitude larger than that of the nanoparticles, the differential image presents a much weaker background. The contrast enhancement is calculated to be around 6.2 dB, demonstrating, therefore, the effectiveness of the proposed modulation method for background reduction. The contrast enhancement is limited by the aforementioned movements in forming the modulated image, which results in some non-magnetic background persisting in the differential image. This is similar to physiological movements that restrict the contrast enhancement in conventional differential imaging method.¹⁰ To achieve better background suppression in clinical settings, faster TA imaging, and proper tracking of these physiological movements may be needed.

Currently, the TA method can detect SPIONs at concentration around 11 mg/ml with a ferrite core. Compared with tens kilo-Watts power adopted in microwave induced thermoacoustic imaging^{14,15} (MI-TAI), the 1.6 kW used here is about ten times smaller. Since the TA signal depends linearly on the excitation power, the setup present here can detect SPIONs concentration at least one order of magnitude smaller by using the same power in MI-TAI,^{14,15} enabling

realistic concentrations to be imaged. Moreover, as SPIONs give just a moderate heating under AMF,¹⁶ utilizing ferromagnetic nanoparticles and more efficient nanoparticles under development¹⁷ will improve further the imaging performance presented herein.

In conclusion, modulatable thermoacoustic imaging of magnetic nanoparticles under AMF are demonstrated experimentally with the magnetically mediated setup. Magnetic nanoparticles inside a tube phantom are efficiently mapped by the proposed TA imaging approach, demonstrating its potential for applications that use magnetic nanoparticles like cancer diagnosis. It may also be of interest for other biomedical applications that rely on the magnetic nanoparticles, such as hyperthermia therapy and thermal stimulation, where imaging the nanoparticle distribution is desired prior to applying AMF for efficient therapy or stimulation. Both the two proposed modulation configurations suppress effectively the TA signals of the magnetic nanoparticles and thus “hide” them from the resultant image, with scenario 2 being more efficient than the MRI compatible scenario 1 configuration. Such modulation capability for magnetic nanoparticles is demonstrated to be effective for contrast enhancement via differential imaging, which can potentially be accelerated significantly over traditional differential imaging procedures. *In vivo* animal studies with this approach are the aim of future works.

This research was supported by the Singapore National Research Foundation under its Exploratory/Developmental Grant (No. NMRC/EDG/1062/2012) and administered by the Singapore Ministry of Health’s National Medical Research Council.

- ¹S. M. Morgan and R. H. Victora, *Appl. Phys. Lett.* **97**, 093705 (2010).
- ²S. Bae, S. W. Lee, and Y. Takemura, *Appl. Phys. Lett.* **89**, 252503 (2006).
- ³Y. D. Jin, C. X. Jia, S. W. Huang, M. O’Donnell, and X. H. Gao, *Nat. Commun.* **1**, 1 (2010).
- ⁴E. I. Galanzha, E. V. Shashkov, T. Kelly, J. W. Kim, L. L. Yang, and V. P. Zharov, *Nat. Nanotechnol.* **4**, 855 (2009).
- ⁵H. Qin, S. H. Yang, and D. Xing, *Appl. Phys. Lett.* **100**, 033701 (2012).
- ⁶H. Huang, S. Delikanli, H. Zeng, D. M. Ferkey, and A. Pralle, *Nat. Nanotechnol.* **5**, 602 (2010).
- ⁷D. Q. Piao, R. A. Towner, N. Smith, and W. R. Chen, *Med. Phys.* **40**, 063301 (2013).
- ⁸A. Cervadoro, C. Giverso, R. Pande, S. Sarangi, L. Preziosi, J. Wosik, A. Brazdeikis, and P. Decuzzi, *PLoS One* **8**, e57332 (2013).
- ⁹X. H. Feng, F. Gao, and Y. J. Zheng, *Appl. Phys. Lett.* **103**, 083704 (2013).
- ¹⁰C. G. Hadjipanayis, M. J. Bonder, S. Balakrishnan, X. Wang, H. Mao, and G. C. Hadjipanayis, *Small* **4**, 1925 (2008).
- ¹¹R. E. Rosensweig, *J. Magn. Magn. Mater.* **252**, 370 (2002).
- ¹²M. H. Xu and L. H. V. Wang, *Med. Phys.* **29**, 1661 (2002).
- ¹³P. Cantillon-Murphy, Ph.D. thesis, Massachusetts Institute of Technology, 2008.
- ¹⁴M. Omar, S. Kellnberger, G. Sergiadis, D. Razansky, and V. Ntziachristos, *Med. Phys.* **39**, 4460 (2012).
- ¹⁵D. R. Bauer, X. Wang, J. Vollin, H. Xin, and R. S. Witte, *Appl. Phys. Lett.* **101**, 033705 (2012).
- ¹⁶S. Laurent, S. Dutz, U. O. Hafeli, and M. Mahmoudi, *Adv. Colloid Interface Sci.* **166**, 8 (2011).
- ¹⁷J. H. Lee, J. T. Jang, J. S. Choi, S. H. Moon, S. H. Noh, J. W. Kim, J. G. Kim, I. S. Kim, K. I. Park, and J. Cheon, *Nat. Nanotechnol.* **6**, 418 (2011).