Thermally modulated photoacoustic imaging with super-paramagnetic iron oxide nanoparticles

Feng, Xiaohua; Gao, Fei; Zheng, Yuanjin

2014

Feng, X., Gao, F., & Zheng, Y. (2014). Thermally modulated photoacoustic imaging with super-paramagnetic iron oxide nanoparticles. *Optics Letters*, 39(12), 3414-3417.

<https://hdl.handle.net/10356/104873>

<https://doi.org/10.1364/OL.39.003414>

© 2014 Optical Society of America. This paper was published in *Optics Letters* and is made available as an electronic reprint (preprint) with permission of Optical Society of America. The paper can be found at the following official DOI:
<http://dx.doi.org/10.1364/OL.39.003414>. 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 23:24:44 SGT

Thermally modulated photoacoustic imaging with super-paramagnetic iron oxide nanoparticles

Xiaohua Feng, Fei Gao, and Yuanjin Zheng*

School of Electrical and Electronic Engineering Nanyang Technological University, 50 Nanyang Avenue, Singapore

*Corresponding author: yjzheng@ntu.edu.sg

Received February 17, 2014; revised April 15, 2014; accepted May 3, 2014;

posted May 5, 2014 (Doc. ID 206560); published June 4, 2014

Thermally modulated photoacoustic imaging (TMPI) is reported here for contrast enhancement when using nanoparticles as contrast agents. Exploiting the excellent sensitivity of the photoacoustic (PA) process on temperature and the highly selective heating capability of nanoparticles under electromagnetic field, the PA signals stemming from the nanoparticles labeled region can be efficiently modulated whereas those from highly light absorptive backgrounds are minimally affected. A coherent difference imaging procedure reduces the background signal and thus improves the imaging contrast. Phantom experiments with super-paramagnetic iron oxide nanoparticles (SPIONs) as contrast agents and alternating magnetic fields for heating are demonstrated. Further improvements toward clinical applications are also discussed. © 2014 Optical Society of America

OCIS codes: (110.5120) Photoacoustic imaging; (060.4080) Modulation; (110.5125) Photoacoustics.

<http://dx.doi.org/10.1364/OL.39.003414>

Photoacoustic (PA) imaging can monitor both static and dynamic biological phenomena with tunable resolution and field of view [1–3]. Exogenous contrast agents further enabled it to probe biological processes at a molecular level [4–6]. Yet, a difficulty frequently encountered is the strong backgrounds that limit the imaging contrast [7] when using these contrast agents for enhanced imaging. To ameliorate it, a photoacoustic magneto-motive method [7,8] and nonlinear PA imaging had been proposed. However, nonlinear PA imaging utilized either large light fluence [9] or special nanoemulsion bead [10], whereas the magneto-motive method is strictly limited to nanoparticles with magnetic properties. The small displacement (on the order of 10 μm) used in the magneto-motive method also makes it sensitive to physiological movements. This is more critical for tissues that show large elastic constants such as many tumors [11], where the displacements get smaller.

An alternative method is proposed here that complements the magneto-motive and nonlinear PA methods, which is applicable to both magnetic and non-magnetic nanoparticles, besides being immune to elastic constants. Specifically, the efficient and localized heating of nanoparticles under an electromagnetic field and the excellent PA sensitivity to temperature are fused to achieve thermally modulated photoacoustic imaging (TMPI). As illustrated in Fig. 1, nanoparticles and background reside on the same temperature level T at thermal equilibrium. The PA pressure generated therein is [12]

$$P = \mu_a \Gamma(T) F = \mu_a F (A + BT), \quad (1)$$

where A and B are constants, μ_a is the absorption coefficient, F is the optical fluence and Γ is the Grueneisen parameter. In certain cases, due to strong background absorption (like blood) and the limited concentration of nanoparticles, the PA signal of background (P_2) is comparable to that of the nanoparticle (P_1), limiting the contrast. In TMPI, an electromagnetic field is introduced to irradiate the nanoparticles and background for a short interval to elevate their temperatures to new levels at $T + \Delta T_1$ and $T + \Delta T_2$, respectively. The PA pressures

at these levels are then modulated by the temperature elevations

$$P_{im} = \mu_a \Gamma(T + \Delta T_i) F = P_i (1 + h_i) = P_i (1 + S_i \Delta T_i), \quad (2)$$

where $i = 1, 2$, $h_i = B \Delta T_i / (A + BT) = S \Delta T_i$ is the modulation coefficient, and S is the PA sensitivity to temperature, which is defined as the percentage of PA signal variation per temperature change. S is around 5% and is only slightly different among various materials [13]. Therefore, differences in ΔT will yield corresponding different modulation coefficients. Assuming nanoparticles are heated by an electromagnetic field more efficiently than background so that ΔT_1 equals, for instance, three times ΔT_2 , the modulation coefficient h_1 will then be about three times h_2 . Based on the disparity in modulation coefficients, nanoparticles can then be discriminated from the background with enhanced contrast.

This approach is potentially applicable to both magnetic and non-magnetic nanoparticles because, at appropriate frequencies, both kinds of nanoparticles can be heated selectively over the background. Magnetic nanoparticles can be heated selectively under alternating magnetic fields [14], and non-magnetic single wall carbon nanotubes [6] can be heated efficiently by low power microwave [15] or radio frequency irradiation [16]. For

Fig. 1. Thermally modulated photoacoustic process.

both nanoparticles, their temperature elevations ΔT can be several times (even more than four times in [14]) larger than that of the background. This corresponds to approximately the same difference in their modulation coefficients. Because of the high sensitivity of PA to temperature [17], only a few degrees temperature elevation are needed to make the modulations detectable. In [18], a temperature variation of 1–2 deg is used in PA imaging for blood velocity detection, which corresponds to a modulation of around 5%–10%. Smaller modulations can be detected by improving the signal-to-noise ratio (SNR) of PA signals through laser energy compensation and more times signal averaging [13]. Since nanoparticle displacements are not utilized, they can be mitigated altogether without using extra tracking to discriminate physiological and magnetic movements. Thus simpler correction is viable, as demonstrated later with a 2D alignment algorithm.

Consider specifically using SPION in photoacoustic imaging as it is FDA approved and is applicable also to thermoacoustic imaging [19]. The temperature rise caused by Brown and Neel's relaxation of the superparamagnetic iron oxide nanoparticles (SPIONs) under alternating magnetic field satisfies [20]

$$\Delta T \propto \chi_0 H_0^2 \omega^2 \tau / (1 + (\omega \tau)^2), \quad (3)$$

where H_0 is the magnetic field magnitude, ω is its radian frequency, τ and χ_0 are the nanoparticles' effective relaxation time and magnetic susceptibility, respectively. Under alternating magnetic fields, the background has negligible magnetic heating because its magnetic susceptibility is six orders of magnitude smaller than that of SPIONs. The major contribution to the background heating is nonspecific heating [21], which is generally weaker than the nanoparticles' magnetic heating and will be significantly reduced when low frequency (<1 MHz) alternating magnetic field is applied [21].

A commercial spherical SPION (3327NG, Skyspring Nanomaterials, Inc.) is used to demonstrate TMPI. Its average particle size is 10–15 nm in diameter and the specific saturation magnetization is 43.8 emu/g. The effective relaxation time for SPIONs of this size is about 1 μ s according to [20], with the exact value depending on various parameters, including the viscosity of ferrofluid that affects the Brownian relaxation. As the heating relates to magnetic susceptibility χ_0 linearly, which is a function of the SPION concentration, eight concentrations designated from SP1 to SP8 and water (conductivity about 0.02 S/m) are measured to study its concentration dependence. The SP1 is roughly 220 mg/ml and the others are consecutively diluted by two times. The SP1 has a calculated number concentration of $\sim 4.7 \times 10^{16}$ /ml and an equilibrium magnetic susceptibility of 9.87×10^{-2} H/m. The fluid from the SPIONs is poured into a jar of 3 mm diameter and suspended in air 1 mm above a customized 25-turn solenoid coil (660 turns/m). The coil has a diameter of 8 mm and is driven by an RF power amplifier (ZHL-100W-GAN+, Mini-circuits) at 18.4 MHz, which is produced by a function generator and is the resonance frequency of the coil network. At this frequency, the imaginary part of the magnetic susceptibility of SP1 is

8.53×10^{-4} H/m. Since $\omega \tau \gg 1$, the heating is saturated according to Eq. (3). The temperature before, during, and after the magnetic heating of the fluid is monitored by a K-type thermometer (1 deg accuracy) by inserting its sensor tip inside. The output power of the amplifier is set at 10 W and the RF field strength is estimated to be about 0.3 kA/m at the sample site. The measurement results are given in Fig. 2(a), and the extracted heating rates (temperature increase per unit time in the linear region) are shown in Fig. 2(b). The temperature increase renders initially a linear behavior with respect to time, then gradually saturates and decreases monotonically upon termination of heating, all dictated by the non-Fourier heat conduction equation of hyperbolic function type. In all cases, SPIONs show consistently superior heating rate to water, with SP1 being 1.5 times larger. The heating rate relates linearly roughly to the concentration with linear curve fitting having R^2 of 0.72. This is consistent with the general observation of better heating at higher concentration. However, compared to hyperthermia experiments using frequencies below 1 MHz [14,16,21], the heating difference between SPIONs and the background water achieved here is weaker. This is also observed in [21] and is caused by the nonspecific heating of background water, which is found to be substantial at frequencies beyond 10 MHz (18.4 MHz in this Letter). It can be reduced significantly by using frequencies below 1 MHz to enlarge the heating difference between the SPIONs and the background water.

The experimental setup illustrated in Fig. 3(a) is used to measure PA sensitivity on temperature S and to demonstrate TMPI with SPIONs, both using immersed tube phantoms. A 532 nm Q-switched pulsed laser (1.2 ns pulse width, 1 mJ energy) is used to illuminate the phantom through a multimode laser fiber with a spot size of 1 mm radius at a repetition rate of 20 Hz. Since achieved coupling efficiency of the fiber is less than 30%, the fluence is smaller than 10 mJ/cm² and the irradiance is smaller than 200 mW/cm², satisfying the American National Standards Institute safety standards [13]. The PA signal is detected by a fixed 1 MHz focused ultrasound transducer (Olympus, V303), amplified by 54 dB with an amplifier and then digitized by the oscilloscope (Waverunner 6Zi, Lecroy). The signal is averaged eight times before being transferred to PC for offline processing. For TMPI, the solenoid coil driven at 10 W is added and placed 2 mm below the phantom. It is not used for PA temperature sensitivity measurement.

The PA sensitivity on temperature S is measured with SP1, SP2, SP3, and blue ink (simulating absorptive background) by injecting them into the tube. Subsequent

Fig. 2. (a) Temperature rise of S1, S4, S8, and water; (b) heating rate of SPIONs.

Fig. 3. (a) Experiment setup, (b) timing sequence for difference imaging, and (c) algorithm for ameliorating physiological movements. FG, function generator; PA, power amplifier; Amp, amplifier; Osc, oscilloscope; TR, transducer.

procedures follow those of [13]. Briefly, the temperature is varied by pouring hot water into a water tank and allowing it to cool down naturally. Then the temperature and PA signals are recorded simultaneously. The results are shown in Fig. 4(a) with S extracted in (b) within the temperature range of 42–36 deg. In all cases, the PA signals show a linear relationship with temperature (linear fit $R^2 > 0.96$) and the sensitivities are roughly the same (about 2.5%), close to those in [13]. With the aforementioned methods to improve the SNR of the PA signal, modulations corresponding to only a few degrees of temperature elevation can be detected under the 2.5% sensitivity.

For TMPI, water at room temperature is used in the tank and another tube phantom containing blue ink at one end, air in between, and SP1 at the other is made. It is fixed on a linear translation stage. SP1 is selected to surpass nonspecific heating at 18.4 MHz in order to achieve good heating over the background. These high concentrations can be obtained by direct injection or application of magnetic trapping for magnetic nanoparticles traveling in the vasculatures [5]. Generally, proportionally higher power needs to be used for realistic concentrations. The imaging sequence presented in Fig. 3(b) is used. Reference imaging is performed first and upon its termination, the magnetic heating is turned on for four minutes before returning to the off state. Immediately after the heating, modulated PA imaging is carried out. Both the reference and modulated imaging are achieved by translating the phantom across the

Fig. 4. (a) PA amplitude versus temperature; (b) PA sensitivity on temperature. BI, blue ink.

transducer focal region with the linear translation stage and storing the signals therein. The images are formed with a back projection method after envelop extraction of each A-line signal. A coherent difference image is rendered by the 2-D alignment algorithm given in Fig. 3(c). The reference and modulated RF A-line signals are first aligned by compensating the inferred displacements between them from a 2-D speckle tracking algorithm and then coherently subtracted and normalized by a reference signal. The resultant signals are envelop extracted to form the final difference image. This algorithm eliminates potential displacements without the need to discriminate their origins as in magneto-motive method.

The reference and difference images of the phantom are shown in Figs. 5(a) and 5(b), respectively. In a difference image, because no PA signals existed in the center part, their normalization results are set to zero. Though the tube is observable in the reference image, nanoparticles SP1 could not be discriminated from blue ink. However, they are readily distinguishable in the different image (b). To demonstrate the effectiveness of the 2D alignment algorithm, another experiment is conducted with physiological movements (e.g., a simple patient movement) mimicked by delaying the received PA signal several microseconds in the axial direction from the phantom. The affected difference image with and without the 2-D alignment correction are given in Figs. 5(c) and 5(d). Without correction, a widened tube is produced in (c) resulting from the misalignment whereas the corrected image in (d) is almost identical to (b). Figures 5(e) and 5(f) show, respectively, the PA amplitudes along the dotted line in images (a) and (b). With thermal modulation, the initially stronger blue ink in (e) is suppressed in (f). The contrast enhancement is estimated to be 4.4 dB (1.65), achieved with the heating difference of 1.5 between SP1 and background [Fig. 2(a)].

Several improvements can lead to better contrast enhancement and faster difference imaging. Using frequencies below 1 MHz, nonspecific heating of the background will be reduced and thereby improves the contrast substantially. Meanwhile, a power amplifier at several hundred watts can heat up SPIONs of realistic concentrations several degrees within a few seconds [21]. This will shorten the TMPI imaging time accordingly. Faster and

Fig. 5. (a) Reference image, (b) difference image, (c) physiological movements affected difference image, (d) corrected difference image, (e) signal along dotted line in (a), and (f) signal along dotted line in (b).

larger heating difference can also be obtained by using more efficient magnetic nanoparticles [22,23]. In [23], the MnFe_2O_4 nanoparticle achieved three degrees of temperature increase within 5 s and a heating rate ratio over background around seven under 100 W operation, indicating a potential contrast enhancement of 17 dB. Simple patient movements happening on the order of seconds can then be corrected. Faster imaging will be needed for mitigating physiological movements induced by a heartbeat. Still, TMPI is more resilient in this respect because, compared to a 10 μm order displacement in the magneto-motive method, its image resolution of about 1 mm (or several hundred μm when using high frequency transducers) can accommodate physiological movements smaller than a resolution cell with little effect on the differential imaging. The small temperature elevation and its transient duration needed in TMPI are expected to induce minimal adverse effects [18] and should therefore be safe in most applications. This approach can also be readily extended to microwave induced thermoacoustic imaging with SPIONs [19] and carbon nanotubes [24] to provide deeper penetration. In terms of other nanoparticles like carbon nanotubes and gold nanoparticles, their toxicity issue may be a hindrance for their applications.

To conclude, the novel TMPI method is proposed for background suppression. It is potentially applicable to both magnetic and non-magnetic nanoparticles and is experimentally demonstrated to have simpler correction schemes for physiological movements. The imaging results demonstrated successful discrimination of SPIONs from background ink. Future improvements are discussed, which can potentially enhance the contrast significantly and enable faster TMPI within a few seconds.

This research is supported by the Singapore National Research Foundation under its Exploratory/Developmental Grant (NMRC/EDG/1062/2012) and administered by the Singapore Ministry of Health's National Medical Research Council.

References

1. L. H. V. Wang and S. Hu, *Science* **335**, 1458 (2012).
2. Z. Yuan and H. B. Jiang, *Appl. Phys. Lett.* **88**, 231101 (2006).
3. D. Razansky, C. Vinegoni, and V. Ntziachristos, *Opt. Lett.* **32**, 2891 (2007).
4. G. Ku and L. H. V. Wang, *Opt. Lett.* **30**, 507 (2005).
5. E. I. Galanzha, E. V. Shashkov, T. Kelly, J. W. Kim, L. L. Yang, and V. P. Zharov, *Nat. Nanotechnol.* **4**, 855 (2009).
6. A. De La Zerda, C. Zavaleta, S. Keren, S. Vaithilingam, S. Bodapati, Z. Liu, J. Levi, B. R. Smith, T. J. Ma, O. Oralkan, Z. Cheng, X. Y. Chen, H. J. Dai, B. T. Khuri-Yakub, and S. S. Gambhir, *Nat. Nanotechnol.* **3**, 557 (2008).
7. Y. D. Jin, C. X. Jia, S. W. Huang, M. O'Donnell, and X. H. Gao, *Nat. Commun.* **1**, 1 (2010).
8. M. Qu, S. Mallidi, M. Mehrmohammadi, R. Truby, K. Homan, P. Joshi, Y. S. Chen, K. Sokolov, and S. Emelianov, *Biomed. Opt. Express* **2**, 385 (2011).
9. V. P. Zharov, *Nat. Photonics* **5**, 110 (2011).
10. C. W. Wei, M. Lombardo, K. Larson-Smith, I. Pelivanov, C. Perez, J. Xia, T. Matula, D. Pozzo, and M. O'Donnell, *Appl. Phys. Lett.* **104**, 033701 (2014).
11. A. Athanasiou, M. Tardivon, B. Tanter, J. Sigal-Zafrani, T. D. Bercoff, J. L. Eux, M. Gennisson, Fink, and S. Neuenschwander, *Radiology* **256**, 297 (2010).
12. L. Gao, L. D. Wang, C. Y. Li, Y. Liu, H. X. Ke, C. Zhang, and L. H. V. Wang, *J. Biomed. Opt.* **18**, 026003 (2013).
13. M. Pramanik and L. V. Wang, *J. Biomed. Opt.* **14**, 054024 (2009).
14. M. Babincova, V. Altanerova, C. Altaner, P. Cicmanec, and P. Babinec, *Med. Phys.* **31**, 2219 (2004).
15. A. Mashal, B. Sitharaman, X. Li, P. K. Avti, A. V. Sahakian, J. H. Booske, and S. C. Hagness, *IEEE Trans. Biomed. Eng.* **57**, 1831 (2010).
16. C. J. Gannon, P. Cherukuri, B. I. Yakobson, L. Cognet, J. S. Kanzius, C. Kittrell, R. B. Weisman, M. Pasquali, H. K. Schmidt, R. E. Smalley, and S. A. Curley, *Cancer* **110**, 2654 (2007).
17. S. H. Wang, C. W. Wei, S. H. Jee, and P. C. Li, *Proc. SPIE* **7177**, 71771S (2009).
18. L. D. Wang, J. Xia, J. J. Yao, K. I. Maslov, and L. H. V. Wang, *Phys. Rev. Lett.* **111**, 204301 (2013).
19. L. M. Nie, Z. M. Ou, S. H. Yang, and D. Xing, *Med. Phys.* **37**, 4193 (2010).
20. R. E. Rosensweig, *J. Magn. Magn. Mater.* **252**, 370 (2002).
21. Cervadoro, C. Giverso, R. Pande, S. Sarangi, L. Preziosi, J. Wosik, A. Brazdeikis, and P. Decuzzi, *PLoS ONE* **8**, e57332 (2013).
22. J. 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).
23. H. Huang, S. Delikanli, H. Zeng, D. M. Ferkey, and A. Pralle, *Nat. Nanotechnol.* **5**, 602 (2010).
24. M. Pramanik, M. Swierczewska, D. Green, B. Sitharaman, and L. V. Wang, *J. Biomed. Opt.* **14**, 034018 (2009).