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A self-monitored theranostic platform based on nanoparticle hyperthermia therapy and alternating magnetic field induced thermoacoustic imaging

Xiaohua Feng^{*a}, Fei Gao^a, Yuanjin Zheng^a

^aSchool of Electrical and Electronics Engineering, Nanyang Technological University, Singapore 639798;

ABSTRACT

Low frequency alternating magnetic field (AMF) had been advocated for thermoacoustic imaging to exploit their inherent deeper penetrations. AMF induced thermoacoustic imaging of magnetic nanoparticles is particularly appealing since the system setup is inherently compatible with nanoparticle hyperthermia therapy. More importantly, owing to the capacity of thermoacoustics for accurate temperature measurement, the integration of AMF induced thermoacoustic imaging into nanoparticle hyperthermia therapy will potentially enable a theranostic platform with imaging guidance and temperature monitoring capabilities. We present herein the AMF induced thermoacoustic process of magnetic nanoparticles experimentally and then investigate furthermore its utilization in temperature monitoring for the nanoparticle hyperthermia. To demonstrate the concept of an integrated theranostic system with minimal overhead, a single coil is used for both the hyperthermia heating and thermoacoustic imaging by interleaving the two processes in time domain. In thermoacoustic imaging mode, the power is set at the amplifier's maximum value whereas to avoid excess heating of the coil in hyperthermia-mode, the power is switched to a lower value and the coil is further cooled by static water. Phantom imaging results of the magnetic nanoparticles and the self temperature monitoring with sub-degree accuracy during hyperthermia process are demonstrated. These proof-of-concept experiments showcase the potential to integrate thermoacoustic imaging with nanoparticle hyperthermia system.

Keywords: alternating magnetic field, thermoacoustic imaging, magnetic coil, temperature measurement.

1. INTRODUCTION

Thermoacoustic effect refers to the phenomenon of acoustic emission upon pulsed or modulated electromagnetic field irradiation. It could use light¹⁻³, microwaves⁴⁻⁶ and magnetic field⁷ for excitation and then probes ultrasonically the resultant interaction between the electromagnetic field and matter. Since radio frequencies were widely used in medical communities like RF ablation and nanoparticle hyperthermia, using low frequency electromagnetic field in thermoacoustic imaging could not only allow deeper penetration but also potentially enable thermoacoustic imaging to be seamlessly incorporated into existing instruments. One such potential integration instance is to exploit radio frequency magnetic field in nanoparticle hyperthermia system for thermoacoustic imaging, with magnetic nanoparticles as contrast agents. This is appealing because nanoparticle hyperthermia need to know the temperature distribution during therapy while thermoacoustic process is well known to be sensitive to temperature variations. Enabling thermoacoustic imaging capability into nanoparticle hyperthermia could thus lead to both accurate temperature monitoring and ensuing tight temperature control, the latter being critical for minimizing undesirable side effects of hyperthermia therapy.

Here, we use radio frequency magnetic field for thermoacoustic imaging and the magnetic nanoparticles used in hyperthermia therapy as contrast agent. Though some theoretical considerations of AMF induced thermoacoustic signal generation of magnetic nanoparticles had been previously proposed in [8], experimental demonstration is lacking. Further, it is presented here using the AMF induced thermoacoustic effect for temperature monitoring during a proof-of-concept nanoparticle hyperthermia experiment. Uniquely, a single coil is used for both heating and thermoacoustic temperature sensing by interleaving these two processes in time domain, achieving a theranostic prototype with minimal system overhead.

*xfengl@e.ntu.edu.sg; phone +65 81695041;

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2. THEORY

When magnetic nanoparticles are exposed to an alternating magnetic field, due to Brownian and Neel relaxation processes, they will absorb energy from the magnetic field and therefore get heated up. The volumetric power deposition U is calculated to be⁹:

$$U = \frac{\mu_0}{2} H_0^2 \chi_0 \frac{\omega^2 \tau}{1 + (\omega \tau)^2} \quad (1)$$

where ω is the radian frequency of magnetic field, μ_0 is the permeability of free space, H_0 is the magnetic field strength, τ and χ_0 are the effective relaxation time and magnetic susceptibility of the ferrofluid respectively. Under a pulsed magnetic field, the heat function (absorbed energy per unit time and per unit volume) for thermoacoustic signal generation is $H(r, t) = \langle U \rangle$, in which operator $\langle \rangle$ denotes time average within the pulse duration. Consequently under such high power pulsed excitation, thermoacoustic wave is produced¹⁰:

Figure 1. Schematic of AMF induced thermoacoustic generation for magnetic nanoparticles.

$$\nabla^2 p(r, t) - \frac{1}{c^2} \frac{\partial^2 p(r, t)}{\partial t^2} = -\frac{\beta}{C_p} \frac{d}{dt} H(r, t), \quad (2)$$

where $p(r, t)$, c , β , C_p is respectively the thermoacoustic (TA) pressure, speed of sound, isobaric volume expansion coefficient and specific heat capacity of the object. Under the condition that thermal confinement and stress confinement are satisfied during the thermoacoustic process, the generated acoustic pressure could be estimated as:

$$P = kUT(T) \quad (3)$$

where Γ is Grueneisen parameter of the matter and k is a scaling coefficient. The temperature measurement is based on the fact that $\Gamma(T)$ is linearly related to absolute temperature: $\Gamma(T) = A + BT$, where A and B are constants determined by material properties. The sensitivity S of PA on temperature, defined as PA signal amplitude's change in percentage per degree temperature variation, is about 3~5% for most materials¹¹. With a calibrated reference point $P(T_0)$, absolute temperature can be calculated from measurement result P as:

$$T = \frac{P}{P(T_0)} \left(\frac{A}{B} + T_0 \right) - \frac{A}{B}. \quad (4)$$

It is noted that in above equation, the assumption is made that the temperature dependence of absorption coefficient is negligible compared to that of Grueneisen parameter, which is generally satisfied. The accuracy of temperature measurement is determined directly by the signal to noise ratio of the received TA signal, which is affected by system

electronic noise and the power amplifier's stability. Assuming a TA signal to noise ratio of SNR , the temperature measurement accuracy δT could be estimated to be: $\delta T = 1/(S \times SNR)$. Since TA signals generally possess smaller signal amplitude than photoacoustic signals, which implicates inferior signal to noise ratio, more averages in times domain and power amplifier energy compensation will be needed in order to obtain sub-degree temperature measurement accuracy. However, aggressive time domain averaging will give rise to large measurement latency. For instance, with 1000 times time domain averaging and a power amplifier working at 100 Hz repetition rate, the consequent measurement latency is 10 seconds, which is slower than MRI temperature measurement. Fortunately, unlike lasers, most pulsed microwave power amplifiers allow faster repetition rate and by using 1000 Hz repetition rate, the measurement latency could be reduced to 1 second. Another more promising solution is to adopt coherent frequency domain method^{7,12}, which could provide superior signal to noise ratio without too many time domain averages or using higher power amplifiers.

3. EXPERIMENTAL RESULTS AND DISCUSSION

The experimental setup for the proof of concept integrated theranostic platform is illustrated in figure 2. The radio frequency signal is produced by two arbitrary function generators (Tektronix, AFG3252): the first one produces the pulse modulated radio frequency signal at repetition frequency of 1 kHz for thermoacoustic process and the other generates low amplitude continuous radio frequency signal for nanoparticle heating. The two outputs are combined by a T-shape BNC connector. The timing for the input signal of the power amplifier is shown in figure 2(b). During TA signal acquisition, the heating signal is disabled for 70 μ s to avoid any potential electromagnetic interferences. Such short period of disturbances in heating will not affect the temperature elevation of the nanoparticles since the temperature variation is a slow process happening on the order of seconds. An RF pulse amplifier (BT01000-AlphaSA-CW, Tomcorf) with peak power of 1 kW drives the resonance coil. The customized coil has a diameter of 1 cm, 15 turns and a RFID ferrite core is inserted. The coil's resonance frequency is 18.6 MHz and its associated quality factor is approximately 10. With the RF pulse width set to 1 μ s and the carrier frequency fixed at the resonance frequency, the peak current flowing in the coil is measured to be about 20 A, which is monitored by a 2.2 ohm resistor.

Figure 2. (a) Experiment setup for AMF induced thermoacoustic signal imaging and temperature sensing, (b) Timing sequence for self-monitoring of the temperature during hyperthermia therapy.

The generated thermoacoustic signal is first detected by a flat ultrasound transducer (Olympus, V323), amplified by a 94 dB customized low noise amplifier and then digitized by the oscilloscope (Waverunner 6Zi, Lecroy). The data is averaged 1024 times in time domain, lowpass filtered with a cutoff frequency of 1.5 MHz by the oscilloscope, and then transferred to MATLAB 2010b on a PC for offline processing. Imaging is achieved by manually translating the transducer with a linear stage at a step size of 0.5 mm.

A round tube of about 3 mm inner diameter is injected with a commercially available super-paramagnetic iron oxide nanoparticles (3327NG, Skyspring Nanomaterials Inc.) and is placed 1 mm above the coil. The concentration of the super-paramagnetic iron oxide nanoparticles (SPIONs) is made to be 110 mg/dL in order to render decent TA signals since SPIONs generally provide middling heating performances compared to other ferromagnetic nanoparticles used in nanoparticle hyperthermia applications. One representative TA signal generated by the SPIONs is given in figure. 3(a) with its associated spectrum shown in figure. 3 (b). The signal to noise ratio of the coil is observed to be around 14 dB, sufficient for image formation by not high enough for accurate temperature measurement. Therefore, either higher power amplifier is needed or some signal processing technique like coherent frequency domain method could be adopted to enhance the signal to noise ratio when intended to perform TA temperature measurements. The resultant image for the tube with SPIONs is depicted in figure. 4(a). The two edges of the tube are clearly indentified from the background but due to finite bandwidth of the ultrasound transducer, the interior part of the tube is not well rendered.

Figure 3. (a) One representative TA signal trace, (b) Spectrum of the TA signal.

Then, the self temperature monitoring capability of the integrated theranostic platform (hyperthermia and thermoacoustic temperature sensing) is explored. To enhance the signal to noise ratio, a second coil with a number of 10 turns and an RFID ferrite core is made, which has a improved quality factor of 20. The resonance frequency of the coil is now 19.9 MHz. For preventing excessive heating of the coil itself, static water is applied surrounding the coil to provide cooling and the power used for heating is set at 6 W. The nanoparticle hyperthermia session is conducted for 6 minutes and TA temperature measurement is carried out continuously, including temperature measurement after the termination of heating. The temperature variation is indicated by the peak to peak values of the TA signal and the actual temperature is also measured by a 0.1 degree accuracy K type thermometer, which is directly inserted into the tube. It was tested that under 6 W radio frequency magnetic field, the thermometer could still function properly. This may not be the case at much higher power radio frequency field. The self temperature monitoring results by TA during the heating along with the corresponding thermometer readings are shown in figure. 4(b). The TA signals generally increase with the temperature and a linear regression analysis yield a R squared around 0.88 and a root mean squared error being 0.3 degree Celsius. The maximum deviation from the predicted temperature by TA and actual thermometer reading is around 0.8 degree Celsius. With the linear fitting results, the temperature variation during the whole experimental session that involves both heating up and cooling down of the magnetic nanoparticles is then related to the thermometer readings as shown in figure. 4(c). Briefly, the temperature begins to increase upon start of the hyperthermia session and then once the heating is terminated, the temperature decrease sharply back to the equilibrium state. This kind of behaviour is consistent with other reported hyperthermia results¹³. Currently, the measurement results could give rise to maximally around 0.8 degree Celsius temperature error due to limited signal to noise ratio. Nevertheless, a sub-degrees accuracy is still obtained.

To achieve better temperature monitoring results, it is imperative to improve the signal to noise ratio of the TA signal. Also, the magnetic nanoparticle concentration need be reduced to several mg/dL to cater to realistic applications. This complicates further the signal to noise ratio issue. Fortunately, compared to microwave induced thermoacoustic imaging that generally employs several tens kilowatts¹⁷⁻¹⁸, 1 kW is a relatively small value and in magnetic nanoparticle hyperthermia applications, ferromagnetic nanoparticles that show several or even 10 times heating performances¹⁴ are

generally used. These two factors combined could lead to more than one magnitude enhancement to the signal to noise ratio of the TA signal. Consequently, a temperature monitoring accuracy better than 0.5 degree Celsius is obtainable, which is sufficient for most hyperthermia applications.

Figure 4. (a) TA Tomography of a round metal strip, (b) self-temperature monitoring results of the hyperthermia session, (c) TA temperature measurement versus thermometer measurement.

In summary, a proof of concept theranostic platform that integrates seamlessly magnetic nanoparticle hyperthermia and AMF induced thermoacoustic imaging/sensing is presented herein. By using the same coil for hyperthermia heating and thermoacoustic excitation, self temperature monitoring capability is demonstrated with a temperature measurement accuracy around 0.8 degree Celsius in maximum deviation and 0.3 degree Celsius in RMS. With future improvements in the system design that incorporates superior coil cooling and higher power amplifiers, the proof of concept work demonstrated here could be scaled up for pre-clinical studies.

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REFERENCES

- [1] L. H. V. Wang, and S. Hu, "Photoacoustic Tomography: In Vivo Imaging from Organelles to Organs," *Science*, 335(6075), 1458-1462 (2012).
- [2] D. Razansky, M. Distel, C. Vinegoni, R. Ma, N. Perrimon, R. W. Koster, and V. Ntziachristos, "Multispectral opto-acoustic tomography of deep-seated fluorescent proteins in vivo," *Nat. Photon.* 3, 412-417 (2009).
- [3] Z. Yuan, and H. B. Jiang, "Quantitative photoacoustic tomography: Recovery of optical absorption coefficient maps of heterogeneous media," *Appl. Phys. Lett.* **88**, 231101(2006).
- [4] C. G. Lou, S. H. Yang, Z. Ji, Q. Chen, and D. Xing, "Ultrashort Microwave-Induced Thermoacoustic Imaging: A Breakthrough in Excitation Efficiency and Spatial Resolution," *Phys. Rev. Lett.* **109**, 218101 (2012).
- [5] G. Ku, and L. H. V. Wang, "Scanning thermoacoustic tomography in biological tissue," *Med. Phys.* **27**, 1195 (2000).
- [6] F. Gao, Y. J. Zheng, and D. F. Wang, "Microwave-acoustic phasoscopy for tissue characterization," *Appl. Phys. Lett.* **101**, 043702 (2012).
- [7] X. H. Feng, F. Gao, and Y. J. Zheng, "Magnetically mediated thermoacoustic imaging toward deeper penetration," *Appl. Phys. Lett.*, 108, 083704 (2013).
- [8] D. Q. Piao, R. A. Towner, N. Smith, and W. R. Chen, "Magnetothermoacoustics from magnetic nanoparticles by short bursting or frequency chirped alternating magnetic field: A theoretical feasibility analysis," *Med. Phys.* **40**, 063301 (2013).
- [9] R. E. Rosensweig, "Heating magnetic fluid with alternating magnetic field," *J. Magn. Magn. Mater.* **252**, 370 (2002).
- [10] M. H. Xu, and L. H. V. Wang, "Time-domain reconstruction for thermoacoustic tomography in a spherical geometry," *IEEE Trans. Med. Imaging.* **21**, 814 (2002).

- [11] J. Shah, S. Park, S. Aglyamov, T. Larson, L. Ma, K. Sokolov, K. Johnston, T. Milner, and S. Y. Emelianov , “Photoacoustic imaging and temperature measurement for photothermal cancer therapy,” *J. Biomed. Opt.*, **13**, (2008).
- [12] S. Telenkov, A. Mandelis, B. Lashkari, and M. Forcht, “Frequency-domain photothermoacoustics: Alternative imaging modality of biological tissues,” *J. Appl. Phys.* **105**, 102029 (2009).
- [13] X. H. Feng, F. Gao, and Y. J. Zheng, “Thermally modulated photoacoustic imaging with super-paramagnetic iron oxide nanoparticles,” *Opt. Lett.*, **39**, 3414 (2014).
- [14] 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, “Exchange-coupled magnetic nanoparticles for efficient heat induction,” *Nat. Nanotechnol.*, **6**, 418 (2011).