Investigations on electromagnetic-acoustics method for biomedical imaging and therapy applications

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2016

Feng, X. (2016). Investigations on electromagnetic-acoustics method for biomedical imaging and therapy applications. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/66722>

<https://doi.org/10.32657/10356/66722>

**INVESTIGATIONS ON ELECTROMAGNETIC-
ACOUSTICS METHOD FOR BIOMEDICAL IMAGING
AND THERAPY APPLICATIONS**

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SCHOOL OF ELECTRICAL AND ELECTRONIC ENGINEERING

A thesis submitted to the Nanyang Technological University

in fulfilment of the requirement for the degree of

Doctor of Philosophy

2015

ACKNOWLEDGMENTS

The fruition of this humble thesis will not be possible without the kind help and support from friends, collaborators, family members and mentors. My first thanks go to my supervisor, Asst. Professor Yuanjin Zheng. He constantly stimulated me to think bolder, to act still finer and challenged me towards a better researcher. His encouragements and advices of wisdom guided me through the journey of research.

Many thanks to our group members: Dr. Fei Gao, Dr. Gaoming Li, Mr. Ganesh, Mr. Rahul, Mr. Supeng Liu, Dr. Yao Zhu, Mr. Lei Qiu, whose companionship and friendship add way more ingredients to my daily life and whose technical insight make the discussions with them inspiring. It is all these great friends that cheer me up during bad times and make the life here more enjoyable. I would also like to thank the technician in the VIRTUS IC design center for their kind assistance, Nanyang Technological University for providing me the scholarship and NMRC for the research funding.

Last, my special thanks go to my parents and my brother, whose love and support are lifelong and unconditional.

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SUMMARY

After several decades of evolution, single-wave imaging modalities, including ultrasound, magnetic resonance and optical imaging etc., have made tremendous success both in clinical diagnostics and in facilitating scientific studies. The inherent physical limits of single-wave imaging modalities, however, restricted their capability for attaining the best overall contrast and resolution. To overcome these limits, the concept of multi-wave imaging had been proposed to combine excellent contrast from one wave and good resolution from the other. Different interactions among various waves have been explored for multi-wave imaging: using electromagnetic waves for generating ultrasonic waves (thermoacoustics, magneto-acoustics), modulating/tagging electromagnetic waves by ultrasonic waves (acousto-optic imaging) and using fast wave to track slow waves (supersonic shear wave imaging), in which the definition of fast and slow waves are relative: any wave that can sample another wave above Nyquist rate could be regarded as the fast wave whereas the waves being sampled is the slow wave. Promising results had been demonstrated and some of these techniques already enjoyed impressive commercial success.

Among these multiwave imaging techniques, using electromagnetic waves for generating ultrasonic waves, generally termed as electromagnetic-acoustics, has attracted tremendous attention owing to its potential in achieving high contrast, fine resolution and good penetration depth. The fusing of electromagnetic waves and ultrasonic waves provides the flexibility in tailoring the parameters in two different worlds, enabling its excellent system scalability for different applications. Yet, there is still a lot of headroom in electromagnetic-acoustic imaging for better imaging performances in terms of deeper penetration and higher contrast. This call for more

research efforts and this thesis is the result of my humble explorations in this exciting field.

After a brief introduction on the background of electromagnetic-acoustic imaging method and prior achievements that significantly advanced the field, this thesis sets out to expound our solution that uses near field low frequency magnetic field for thermoacoustic imaging towards deeper penetration, which is dubbed as *magnetically mediated thermoacoustic imaging (MMTI)*. Various aspects of this method are covered in details. We then move on to elaborate the proposed modulation method for tackling the background issue that limits the contrast in thermoacoustic imaging. Specifically, background-free detection of magnetic nanoparticles by MMTI and thermally modulated photoacoustic imaging for contrast enhancement are demonstrated. Then, we proceed to investigate from application's perspective the potential of using thermoacoustic for temperature monitoring and for guiding subsequent close-loop temperature control in various hyperthermia therapy applications. This includes photoacoustics guided close-loop temperature control of nanoparticle hyperthermia and a self temperature regulated photothermal system based on a single continuous wave laser diode. Last, we present our theoretical and experimental efforts in unifying thermoacoustic wave with magneto-acoustic wave, which encompasses the simultaneous generation of these two waves and of more significance, their nonlinear mixing effects in water. Such mixing effects may open up the possibility of extracting elastic contrast using electromagnetic-acoustic technique.

In summary, this thesis investigates the electromagnetic-acoustic sensing technique for biomedical imaging applications towards deeper penetration and better contrast. Close-loop temperature control empowered by electromagnetic-acoustic sensing are explored for various hyperthermia therapy applications. The concepts,

methods and special techniques involved may be conducive for triggering better ideas to drive future developments inside and beyond this field.

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Chapter 1. INTRODUCTION

Biomedical imaging plays an important role in healthcare. It arms the clinicians and doctors with a powerful "eye" to perceive internal organs for non-invasive diagnosis and almost everyone had some exposure to it. From ultrasound imaging that shows fetus to optical imaging showing microscopic structure of virus and bacteria, from microwave imaging that renders suspicious lesions in the breast to magnetic resonance imaging (MRI) that depicts the fine structure of internal tissues, biomedical imaging is indeed a fertile pond rich in tools and abundant in utility. Despite of its variety, biomedical imaging in general relies on transmitting various kind of waves to interrogate the object to be "seen" and then receiving either the transmitted or reflected wave for image formation. The specific interactions between the transmitted wave and the object determines what kind of contrast to be rendered and more often than not, dictates fundamentally the resolution one could achieve for observing the object.

Single wave imaging matches pretty well with above description: the resolution of most imaging technologies are fundamentally limited by the wavelength of interrogation wave. This include ultrasound imaging, most modalities of optical imaging (like microscope, optical coherence tomography) and microwave imaging. X-ray computed tomography and MRI are fortunate exceptions since their resolution are determined by the sensor rather than wavelength. This may be somewhat inspiring for the emergence of multi-wave imaging. Although single wave imaging like X-rays can penetrate deep and still provide good resolution, the safety concern and imaging sensitivity are other critical factors that drives the research to innovate for a safer and more sensitive imaging method towards better diagnosis. Apart from continual efforts in conventional single wave imaging modalities, an alternative route to the solution

began to emerge in the recent decades - multi-wave imaging, which may transmit one wave whereas receive another wave for image formation and consequently, enabling one to obtain contrast from one wave at a resolution of the other.

1.1 Multi-wave imaging

Mathias Fink et.al summarized nicely in [1] the historical motivations and various multi-wave imaging modalities that had been explored. The principal drive behind multi-wave imaging, as briefly touched earlier, is to beat the fundamental resolution limit imposed by wavelength. Briefly, multi-wave imaging could be achieved by three kinds of wave interactions [1]: **I** - employing wave one for imaging wave two; **II** - utilizing wave one to tag or modulate the other wave and finally, **III** - using one wave to generate the other wave.

1.1.1 Wave one to image wave two

For the first category, the major technology is supersonic shear wave imaging [2]. Under a high intensity focused ultrasound (HIFU) beam, a highly confined shear wave source was induced around the HIFU foci. Subsequent shear wave propagation was then imaged by a ultrafast ultrasound scanner [3] by using the same probe that generates the HIFU beam. Tracking shear wave propagation by ultrasound imaging allows to extract the shear wave speed quantitatively, which is related to shear modulus of the tissue. Therefore supersonic shear wave imaging offers quantitative study of tissue shear modulus distribution, which is reported to be highly sensitive to tissue abnormalities, particularly the malignant tumours [3]. The obtained image resolution is about 1 mm even though the shear wave wavelengths could be several centimetres. It is noted that such shear wave propagation had also been imaged by optical method [4] at high frame rates for superficial tissues. Still, the core principle of

using a fast wave (like ultrasound and light) to image a slow wave (like shear wave) remains the same.

1.1.2 Wave one to tag wave two

When light propagating in the medium encounters ultrasonic waves, the optical frequencies will be slightly shifted, not unlike frequency modulation long used in telecommunications. However, the ultrasound wave could be focused tightly into a small region (sub-millimetre) and therefore limiting the interactions to be within the foci. By selectively detecting the frequency-shifted light component, only the tissue within the foci is essentially imaged by the light. This technology is named as acousto-optical imaging [5] - [7] and it is advantageous because it breaks the light diffusion limit by tagging the light within the foci with different frequencies. It hence combines optical contrast with the high resolution of ultrasonic wave. Besides for biomedical imaging, this technique is also powerful for time-reversed focusing of light into highly scattering object like tissues [8] - [9], which is potential for deep tissue therapy and other applications.

1.1.3 Wave one to generate wave two

The phenomenon of sound wave generation of matter upon light irradiation was discovered in 1880 by Alexander Bell. However, it is now clear that various electromagnetic waves, including low frequency magnetic field, microwaves and light, could cause sound wave generation when irradiating matter. Since the physical process involves energy absorption and subsequent thermal expansion of matter that ultimately produces acoustic waves, it could be generally dubbed as thermoacoustic process. Although photoacoustic technique had been explored for gas sensing long time ago [10], the major thrust to use it for biomedical imaging is relatively recent. Despite of this, it had undergone galvanizing progress in recent decades and its capabilities had

been expanded significantly without any sign of slowing down. In fact, it has attracted up to now the most attention among multi-wave imaging technology.

Another imaging modality falling into this category is magneto-acoustic imaging [11]- [13]. Contrasted from the thermoacoustic mechanism, it relies on the Lorentz force induced acoustic wave generation mechanism for imaging: an alternating magnetic field (AMF) produces first a companion electric field, which induces eddy current inside conductive matter; under a static magnetic field, Lorentz force is exerted on the eddy current and force it to vibrates, leading to acoustic emission. This method is compatible with conventional magnetic resonance imaging and offers electrical contrasts at ultrasonic resolution. However, it suffers from low signal to noise ratio due to the low conductivity of biological tissues and the fact that it depends on the electric field linearly.

1.2 Prior related state of arts in thermoacoustic imaging

Our research work presented in this thesis had gain tremendous inspiration from prior works. Radio frequencies and microwaves had been investigated previously by Kruger [14] and more recently Wang [15] - [18], the Ntziachristos group [19] - [21], Xing Da [22] and others [23] - [24]. In [14], a thermoacoustic imaging scanner was reported, which irradiated 434 MHz microwave energy via helical antenna and received signals by 64 ultrasound transducers arranged inside a hemispherical bowl. A lamb kidney was imaged by this system showing good differentiation of the soft tissues within the kidney. Another microwave induced thermoacoustic imaging (MI-TAI) system that adopted 0.3 us pulsed 3 GHz microwave radiation was presented in [17], where a high contrast phantom image was achieved at resolution of 0.5 mm and penetration depth of 2.5 cm. Only one ultrasound transducer was utilized there and the image was formed by two dimensional mechanical scanning. The state of art

thermoacoustic imaging system that can achieve a resolution down to 100 μm was achieved in [22] by applying an ultra short microwave pulse as narrow as 10 ns for radiation. Such an efficient ultra short microwave pulse generator capable of delivering a peak power up to 40 MW represents an engineering feat that ultimately enables the breakthrough in imaging resolution and conversion efficiency (microwave energy into acoustic energy). An even better resolution was obtained by a near field thermoacoustic imaging method (NRT) [19] - [21] which gives an unprecedented resolution of 45 μm , a value comparable to that of photoacoustic microscopy. In NRT, the object to be imaged is placed in the very proximity (near field) of the antenna so that a much stronger coupling between the antenna and the object is obtained, leading to increased absorption of the electromagnetic energy and thus signal to noise ratio (SNR).

Photoacoustic imaging, which utilized light spanning from infrared to ultraviolet for thermoacoustic imaging, had seen even more exciting developments. As blood offers primary contrast in photoacoustics, it is particularly suited for imaging the vasculature and measuring other physiological parameters [25] (SO_2 , sodium) therein. Moreover, with light being the only electromagnetic wave sensitive to molecular conformation [8], it is versatile in probing anatomical, functional, metabolic, molecular, and genetic contrasts of vasculature, hemodynamics, oxygen metabolism, biomarkers, gene expression [26], etc. The flexibility in tailoring the photonic and ultrasonic parameters allows it to be customized for vastly different applications with scales varying from organelles to organs and penetration depth from superficial layer of several millimetres to an aggressive depth of 7 centimetres [26]. In fact, various embodiments of photoacoustics have been demonstrated. On the small end, a compact functional photoacoustic microscopy (fPAM) system was developed in [25], which obtained an

imaging resolution down to 15 μm and a penetration depth more than 3 mm. In [27], a photoacoustic endoscopic probe was showcased which integrates the ultrasonic transducer and light delivery fiber inside a tube with an out diameter of only 3.8 mm. Further in [28], an even smaller probe that targets for intravascular application is designed with an out diameter of 1.2 mm, which is probably the smallest one to date. On the large end, a photoacoustic tomography system is built in [29], by which the whole brain of a rat is imaged noninvasively in vivo with the skin and skull intact.

Very recently, thermoacoustic/photoacoustic process was found to be highly sensitive on local temperature variations and was hence proposed for tissue temperature monitoring [30]. The reported temperature measurements vary in accuracy and resolution, depending on the applications. In Ref. [31], the temperature in a single cell is measured with accuracy of 0.2 degrees Celsius, and in [32], temperature for cancer therapy is monitored with an accuracy of 0.16 degrees Celsius without accounting the laser energy fluctuations. Even better, [33] reported an improved temperature sensitivity of 0.15 degrees Celsius obtained in a 2 seconds temporal resolution and 0.015 degrees Celsius when temporal resolution is scaled to 200 seconds. Therefore, the measurement accuracy is highly scalable on a desired measurement resolution.

1.3 Motivation

Despite of the impressive achievements of thermoacoustic imaging for various biomedical applications, it still suffers from some limitations that need further research efforts. One limitation is the difficulty of obtaining even larger penetration depth. Generally, light provides penetration of a few centimetres even when near infrared wavelengths were used. Though photoacoustic imaging had been demonstrated to achieve a penetration up to 7 cm by using contrast agent [26], the strong scattering of

light inside biological tissues impose the so called "scattering limit". Deeper penetration could be obtained by using radio frequency or microwave for thermoacoustic imaging [34][34]. Yet, at higher microwave frequencies, water absorption could become excessive that fundamentally limit the penetration depth to a few centimetres. This is particularly true for high water content tissue like muscle.

The second limitation is the lower signal to noise ratio of thermoacoustic imaging when using relatively low power EM sources (laser diodes, radio frequency power amplifiers), which leads to degraded imaging contrast and specifically for thermoacoustic temperature sensing, worsened accuracy. Though these problems could be surmounted theoretically by employing higher peak power EM sources, the safety limit on EM radiation restricts the usable EM doses in a hard way. Innovative methods for improved contrast and temperature measurement accuracy are necessary towards a clinically viable solution.

1.4 Major contribution

This thesis aims to contribute novel solutions for improved penetration depth, better contrast for thermoacoustic imaging and investigates the integration of thermoacoustic temperature measurement into various hyperthermia therapy solutions for tight temperature control. One more contribution is that we predicted and verified the simultaneous generation of thermoacoustic waves and magneto-acoustic waves and further, their nonlinear mixing effects during subsequent propagation.

Deeper penetration: We proposed to employ low frequency magnetic field for thermoacoustic imaging towards deeper penetration considering that human body is non-magnetic and thus is relatively transparent to magnetic field. Conventional radiation method based on antennas is abandoned in favour of magnetic resonance coil

for near field energy delivering. The contrast, penetration, resolution and signal to noise ratio issues of this novel thermoacoustic technique, dubbed as magnetically mediated thermoacoustic imaging (MMTI), are thoroughly explored. Frequency domain MMTI solution for boosting the SNR is put forward, which may ultimately enable a portable system based on low power excitations.

Contrast improvement: Thermoacoustic imaging, being it using light (photoacoustic) or alternating magnetic field (MMTI), could suffer from reduced contrast due to strong backgrounds. Inspired by another multi-wave imaging method that use one wave to tag another wave, a modulation approach that selectively modulate (tag) the desired signal whereas keep the background signals intact is proposed for contrast improvement via differential imaging. Two approaches are investigated: thermally modulated photoacoustic imaging and modulatable MMTI. Both demonstrated effective contrast improvement in phantom studies.

Thermoacoustic powered close-loop temperature control: As both MMTI imaging and some hyperthermia therapy (like magnetic nanoparticle hyperthermia and radio frequency ablation) employ radio frequency or magnetic field for excitation, it is natural to integrate them into a single theranostic system: MMTI could offer imaging guidance and more importantly, it could measure the temperature during therapy in real-time and guide subsequent therapy to prevent over or insufficient heating. Various hyperthermia therapy applications with thermoacoustic based close-loop temperature control are studied extensively, which shows promise of this technique for future seamless integration of thermoacoustic system into hyperthermia systems.

Co-existing and mixing between thermoacoustic and magneto-acoustic waves: Once low frequency magnetic field was utilized for thermoacoustic imaging, it becomes apparent that thermoacoustic wave and magneto-acoustic wave could be generated

simultaneously by adding properly a static magnetic field into the setup of MMTI. The two different waves are superimposed on each other during subsequent propagation and once absorbed or scattered, could lead to mixing effects due to acoustic radiation force induced acoustic emission. Such mixing effects were analyzed theoretically and verified experimentally, which can potentially be used for extracting elasticity contrast of the imaged object. We also discussed other feasible method to utilize the two different waves for potential elasticity imaging.

1.5 Outline

This thesis explores the electromagnetic-acoustic method for innovative biomedical imaging and therapy applications, which involves theoretical investigations as well as experimental studies. Specifically, novel solutions to advance thermoacoustic imaging towards deeper penetration and better contrast are developed. And from application's perspective, the employment of thermoacoustic and photoacoustic temperature sensing is explored for tight close-loop temperature control of various hyperthermia therapy methods like nanoparticle hyperthermia and photothermal therapy.

In Chapter 2, we present our research efforts in developing *magnetically mediated thermoacoustic imaging (MMTI)* for improving the penetration depth of thermoacoustic imaging. Various technical considerations on its system design and performances are expounded in detail. In Chapter 3, our proposed modulation based method for background reduction towards improved imaging contrast is covered. Background-free detection of magnetic nanoparticles by MMTI and thermally modulated photoacoustic imaging for contract enhancement are demonstrated. Chapter 4 elaborates our efforts in using thermoacoustic technique for accurate, non-invasive temperature monitoring during various hyperthermia therapy applications and for their subsequent close-loop temperature control. Analytical model for tissue temperature

behaviour was developed and different embodiments of thermoacoustic powered close-loop temperature control of hyperthermia therapy were illustrated. Enabled by thermoacoustic wave generation using low frequency magnetic field, the seamless fusion of MMTI with magneto-acoustic sensing are explored in Chapter 5. It discusses the simultaneous generation of thermoacoustic wave and magneto-acoustic wave and the nonlinear mixing effects between the two waves in water, which may open up the possibility of elasticity imaging using endogenous acoustic waves. Finally, Chapter 6 summarizes our research efforts and gives a succinct discussion on the challenges ahead and potential methods that may address those issues in the future.

Chapter 2. MAGNETICALLY MEDIATED THERMOACOUSTIC IMAGING

In conventional microwave induced thermoacoustic imaging (MI-TAI), the imaging depth depends on the microwave frequency used for irradiation. For commonly used frequencies such as 434 MHz and 3 GHz, the penetration depths for high water content tissues like skin and muscles are estimated to be 3.2 cm and 1.2 cm respectively [16]. This impedes their applications for imaging deep organs. One way to improve penetration is to use exogenous contrast agents with enhanced microwave absorption for imaging [35] - [36], however, their toxicity for humans is not fully understood yet. Alternatively, deeper penetration can be achieved in principle by using lower frequencies, such as 20 MHz, which offers at least 15 cm penetration. However, antennas for efficient electromagnetic radiation at such frequency is with size comparable to human body and therefore it is difficult to confine the radiation to a specific region [37]. Also, the radiation approach tends to decrease the effectiveness of depositing electric field inside materials with large permittivity. Therefore, given the same conductivity, the large permittivity of tissues in microwave range will sacrifice the effectiveness of thermoacoustic signal generation. Under this context, magnetically mediated thermoacoustic imaging was proposed, whose various aspects are covered in great depth in this chapter.

2.1 Physical principle

As shown in Fig.2.1(a), a compact magnetically resonance solenoid coil networked with capacitors is used as the stimulator. The radio frequency current $I(t)$ flowing in the coil produces alternating magnetic field that penetrates tissue. Since the radius of

the coil R is much smaller than the wavelength λ of the current, i.e., $R \ll \lambda$, the coil shows negligible radiation and the current flowing in the coil is therefore

Figure 2.1. (a) Schematic of magnetically mediated thermoacoustic generation, (b) Illustration on incoherent time domain and coherent frequency domain TA signal.

uniform in phase. Then the magnetic field at location $\vec{r}$ and time t can be computed analytically with the law of Biot and Savart:

$$\vec{B}(\vec{r}, t) = \frac{\mu_0 N I(t)}{4\pi} \int \frac{\vec{e} \times (\vec{r} - \vec{r}')}{|\vec{r} - \vec{r}'|^3} dl', \quad (2.1)$$

where N is the number of turns of the coil, μ_0 is the permeability of tissue, $\vec{r}'$ denotes the position of current element dl' of the coil whose direction is indicated by unit vector $\vec{e}$. According to the Maxwell's equation: $\nabla \times \vec{E} = -\frac{\partial \vec{B}}{\partial t}$, an alternating electric field $\vec{E}$ is thereby generated by the alternating magnetic field, which is:

$$\vec{E}(\vec{r}, t) = \frac{\mu_0 \omega N I(t) \vec{e}}{4\pi} \int \frac{dl'}{|\vec{r} - \vec{r}'|}, \quad (2.2)$$

where ω is the radian frequency of the applied current. Assume tissue conductivity is $\sigma(\vec{r})$, then according to Ohm's law, the electric field will induce conductive current

$\vec{J}(\vec{r},t) = \sigma(\vec{r})\vec{E}(\vec{r},t)$ flowing in the tissue, which causes absorption of incident radio frequency energy through joule heating.

Though the non-magnetic nature of human body implicates that the major source in the magnetically mediated thermoacoustic imaging will be electrical, magnetic sources can arise when foreign objects like steel needle and magnetic nanoparticles are present. In this case, magnetic heating will contribute to the total heating. For general magnetic objects with relative magnetic susceptibility of $\mu(r) = \mu'(r) + j\mu''(r)$, the magnetic heating is $T_M(\vec{r},t) = \omega\mu''|\vec{B}(\vec{r},t)|^2/2\mu_0$. The magnetic losses encompasses that of the magnetic nanoparticles because, for magnetic nanoparticles, the imaginary part of the relative magnetic permeability $\mu''(r)$ equals to the imaginary part of the magnetic susceptibility ($\mu''(r) = \chi''(r)$). Replacing $\mu''(r)$ with $\chi''(r)$ will leads to the same calculation in [38].

The heating function, defined as the absorbed energy per unit time and per unit volume, is therefore calculated as $H(\vec{r},t) = \langle J(\vec{r},t)E(\vec{r},t) \rangle = \langle \sigma |E|^2 \rangle + T_M(\vec{r},t)$, where operator $\langle \rangle$ denotes short time average and $||$ represents absolute value. The absorbed energy disturbs tissues' original thermodynamic equilibrium and rises its temperature slightly, causing thermal expansion that launches acoustic waves:¹⁶

$$\nabla^2 p(\vec{r},t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p(\vec{r},t) = -\frac{\beta}{C_p} \frac{d}{dt} H(\vec{r},t), \quad (2.3)$$

where $p(\vec{r},t)$, c , β , C_p represent the thermoacoustic (TA) pressure, speed of sound, isobaric volume expansion coefficient and specific heat capacity of tissues, respectively. The acoustic signal is received systematically by an ultrasound

transducer to form images. The wave equation can be solved with Green's function method under linear acoustic theory:

$$p(\vec{r}, t) = \frac{\beta}{4\pi C_p} \iiint \frac{d^3}{|\vec{r} - \vec{r}'|} \frac{d \left\langle \sigma(\vec{r}') |\vec{E}(\vec{r}', t')|^2 + \omega \mu'' |\vec{B}(\vec{r}', t')|^2 / 2\mu_0 \right\rangle}{dt'} + \left|_{t'=t-\frac{|\vec{r}-\vec{r}'|}{c}} \right. \quad (2.4)$$

where $\vec{r}'$ indicates points inside tissue while $\vec{r}$ represents the location of receiving transducer.

Note that the thermoacoustic generation is proportional to the square of electric and magnetic field, which means the efficiency in generating electric field is of crucial importance. To make it complete, thermoacoustics in coherent frequency domain is also discussed. Taking the Fourier transform of the wave equation and its solution in time domain, we obtain:

$$\nabla^2 P(\vec{r}, \omega) + k^2 P(\vec{r}, \omega) = -\frac{j\omega\beta}{C_p} H(\vec{r}, \omega), \quad (2.5)$$

$$P(\vec{r}, \omega) = -\frac{j\omega\beta}{4\pi C_p} \int \frac{e^{jk|\vec{r}-\vec{r}'|}}{|\vec{r}-\vec{r}'|} H(\vec{r}, \omega) d^3\vec{r}', \quad (2.6)$$

where k is the acoustic wave number. It is observed that the produced acoustic signals will share the same spectrum with the heating function, which is proved to be the envelop of the carrier signal [39]. Modulating the carrier signal's envelop with chirp signals [40] or other special codes [41] will therefore result in the generation of "coded" TA signal (chirped TA signal for instance), as shown in Fig. 2.1(b), together with incoherent time domain TA signal. Subsequent correlation of the noisy but "coded" TA signal with the known modulation reference renders significant improvement in the signal to noise ratio (SNR). Specifically, consider here a chirp signal sweeping from ω_0 to ω_1 within a time duration T is used to modulate the

envelop of the radio frequency current. The analytical result of the cross-correlation between the modulation reference and the received acoustic signal is:

$$S(t) = \frac{A_0 A_1 T^2}{2\pi m(t-\tau)} \sin \left[\frac{m\pi(t-\tau)}{T} \left(1 - \frac{t-\tau}{T}\right) \right] \cos(\omega_c(t-\tau)), \quad (2.7)$$

where A_0 and A_1 are the amplitude of the reference and received signal respectively,

$\omega_c = (\omega_0 + \omega_1)/2$ represents the center frequency, $m = (\omega_1 - \omega_0)T$ denotes the time-

bandwidth product and $\tau = \frac{|\vec{r} - \vec{r}'|}{c}$ is the propagation delay. With this approach, the

SNR improvement is $\sqrt{m/2\pi}$, which could be over 30 times while still achieving a fast enough repetition rate. For instance, a burst chirp signal sweeping from 0.5 MHz to 1.5 MHz that lasts 1 ms can yield an improvement in SNR by 31 times (30 dB). With a duty cycle of 10% for the burst chirp signal, the repetition rate can be 100 Hz, high enough for real time imaging (50~60 Hz).

To compare with the EM radiation approach, consider a power density of Pd is deposited into a medium. The accompanying electric field generated in the medium

can be proved to be: $E = 2\sqrt{\mu_0/\varepsilon} \times \sqrt{Pd} \propto \frac{1}{\sqrt{\varepsilon}}$, where ε is the permittivity of the

medium. It is seen that the electric field is inversely proportional to the square root of permittivity and thus will be decreased inside tissue compared to that in air since the former has a much larger permittivity. This problem is considerably circumvented in magnetically mediated approach. As seen from Eq. 2.1 and 2.2, only permeability, not the permittivity, affects the generation of magnetic field. As long as magnetic field can penetrate into region of interest, electric field can be generated effectively. The fact that human body shows the same permeability as vacuum and possesses low conductivity ensures the efficacy of generating electric field by the proposed method.

2.2 Imaging characteristics

For effective thermoacoustic imaging, several important issues need be considered, including the energy absorption, signal to noise ratio, and the penetration, which are discussed with details in following subsections.

2.2.1 Energy absorption and signal to noise ratio (SNR)

The generated thermoacoustic signal is determined primarily by energy absorption, which depends on various factors: the utilized power, pulse width, the depth of absorbers and frequency of the field, etc. Under the same power budget, the efficiency of different energy delivering methods in generating electric and magnetic field inside the object is also an important factor. With power limited by safety regulations and pulse width constrained by resolution, the energy absorption is majorly affected by the frequency and imaging depth.

Figure 2.2 (a) Electric field attenuation of the same object at two different frequencies, (b) Corresponding frequency and depth dependent absorption.

2.2.1.1. Frequency and depth dependent energy absorption

Consider first that two electric fields of the same strength E_0 but different frequencies are present at the surface of the object, as shown in Fig. 2.2(a). With the absorbing coefficient for joule heating of the object at frequency f being $\alpha = \sqrt{2\pi f u_0 \sigma}$, the electric field reaching depth l are $E(l) = E_0 \exp(-\alpha l)$. Then at

depth l , the absorbed energy for frequencies of f_1 and f_2 ($f_1 > f_2$) through joule heating within a thickness of dl can be calculated to be respectively

$$\Delta I_1(l) = 2\kappa E_0^2 \exp(-2\alpha_1 l) dl \quad (2.8)$$

$$\Delta I_2(l) = 2\kappa E_0^2 \exp(-2\alpha_2 l) dl \quad (2.9)$$

where κ is a constant. At superficial depths, the energy absorption at higher frequencies is larger due to the bigger absorption coefficient. Exceeding a critical depth, the electric field of high frequencies becomes diminutive whereas that of lower frequency excitation still persists. Thus low frequencies yields larger absorption thereafter even with a smaller absorption coefficient, rendering a deeper penetration. Such frequency and depth dependence are illustrated in Fig. 2.2(b). The critical depth can be derived from the ratio of absorbed energy given by

$$\begin{aligned} S(f, l) &= \frac{\Delta I_1(l)}{\Delta I_2(l)} = \frac{\alpha_1}{\alpha_2} \exp[-2(\alpha_1 - \alpha_2)l] \\ &= \frac{\sqrt{f_1}}{\sqrt{f_2}} \exp[-2(\alpha_1 - \alpha_2)l] \end{aligned} \quad (2.10)$$

which will be useful in signal to noise comparison. Setting it to 1, we get

$$L_{crit} = \frac{\ln(f_1/f_2)}{4(\alpha_1 - \alpha_2)}.$$

2.2.1.2. Efficiency in depositing electric and magnetic field

The efficiency η_α is defined to relate the current magnitude to electric field strength: $E(r) = \eta_\alpha I$. When other parameters are equal, the quadratic dependence on the electric field and magnetic field of energy absorption make the generation efficiency crucial.

Consider without the loss of generality that a one turn circular coil with radius R is used for magnetically mediation method and a one turn magnetic dipole antenna with

radius a is used for conventional radiation approach and both are fed by the same current $I(t)$. The magnetic dipole radius is set to half wavelength of the radio frequency current ($a = \lambda/2$) for efficient radiation. As the antenna near field shows large variations which is not desirable for thermoacoustic imaging, the electric field at the beginning of far field region ($d = \frac{2D^2}{\lambda} = 2\lambda$, where d and D are respectively the distance from the antenna and the dimension of the antenna) is calculated for comparison. In the magnetically mediation method, the field is calculated at a location $2R$ above the coil, which is approximately the penetration limited by coil size, as will be explained later. The calculation geometries for both case is summarized in Fig. 2.3.

Figure 2.3 Electric field calculation geometry for the antenna radiation and magnetically mediation approach.

The electric field generated by the magnetic coil is given in Eq. (2.2) whereas the far field electric field generated by the antenna [42] is

$$E_2(r, t) = -j \frac{\mu_0 \omega I(t) a^2}{4} e^{-jkr} \left(\frac{jk}{r} + \frac{1}{r^2} \right) \sin(\theta) \quad (2.11)$$

where k is the wave number of the electromagnetic wave. Working at the same frequency, the magnitude ratio of electric field at the two defined positions is then

$$\left| \frac{E_1(r,t)}{E_2(r,t)} \right| = \frac{16}{|(j4\pi^2 + \pi)\sin(\theta)|} \int \frac{dl'}{|r-r'|} \quad (2.12)$$

The ratio above is estimated to be $\left| \frac{E_1(r,t)}{E_2(r,t)} \right| = 0.9$ by approximating $|r-r'|$ with the largest distance ($2\sqrt{2}R$) and by setting the angle to 90 degrees that correspond to the largest field direction of the dipole antenna. Therefore, the electric field generated by the two methods are approximately at the same order. If the antenna works at microwave frequencies and the calculation geometry scales with the wavelength accordingly, the electric field of antenna will be increased proportionally with the frequency, according to (2.2). Then it imply that electric field generated by magnetically mediation is an order weaker (0.09) than microwave radiation because its working frequencies are about one order smaller than microwave frequencies. However, the electric field in magnetically mediation method can be augmented by more than 10 times within its working frequency range by adding ferrite core inside the compact coil. Additionally, when taken into account the reflections at the air/object interface in microwave radiation, the field generation efficiency through magnetically mediation (η_{a1}) will be comparable or even superior to antenna radiation (η_{a2}).

2.2.1.3. Signal to noise ratio

Energy absorption (thus signal to noise ratio) under the two energy delivering methods that works at different frequencies can now be calculated. Assuming the excitation current excitation in both method have the same magnitude, we get $\Delta I_1'(L) = (\zeta\eta_{a1})^2 \Delta I_1(L)$ and $\Delta I_2'(L) = (\zeta\eta_{a2})^2 \Delta I_2(L)$, where ζ is a constant relating the electric fields therein to E_0 . The SNRs' ratio in the two method is then

$$\begin{aligned}
\frac{SNR_1}{SNR_2} &= \frac{\frac{\eta_b \Delta I_1'(l)}{N_s}}{\frac{\eta_b \Delta I_2'(l)}{N_s}} = \frac{\Delta I_1'(l)}{\Delta I_2'(l)} \\
&= \left(\frac{\eta_{a1}}{\eta_{a2}} \right)^2 \frac{\Delta I_1(l)}{\Delta I_2(l)} = \left(\frac{\eta_{a1}}{\eta_{a2}} \right)^2 S(f, l)
\end{aligned} \tag{2.13}$$

where η_b is the conversion efficiency from absorbed energy to acoustic wave and N_s is the system noise. Since η_{a1} and η_{a2} are comparable ($\eta_{a1} \approx \eta_{a2}$) as discussed previously, the SNRs will thus show similar characteristics with energy absorption: the conventional microwave induced thermoacoustics prevails before L_{crit} whereas magnetically mediation wins over thereafter.

2.2.2. Penetration and the field of view

Penetration is defined as the depth at which the field amplitude decreases to e^{-1} of the superficial amplitude. For the far field radiation approach, it equals mathematically to the inverse of the absorbing coefficient of the medium: $l = 1/\alpha$. In the magnetically mediated method, the penetration depends on the coil size. For circular coil, the depth at which the magnetic field in the z axis (see Fig. 2.3) falls to e^{-1} of that at the origin can be used as the indicator of penetration. With the magnetic field on the axis $B(z) \propto (R^2 + z^2)^{-3/2}$, where z is the distance to the coil center, the penetration is calculated to be approximately equals to the coil radius R . In practice, the circular coil can be arranged in Helmholtz configuration with a separation of the coil diameter. In this case, the penetration will be equal to the coil diameter. The Helmholtz configuration is preferred because it produces a more homogenous field. The penetration therefore is either absorption limited or coil size limited, whichever is smaller. For the frequency of several tens MHz, the absorption limited penetration is

more than 10 cm, making the penetration ultimately limited by the coil size for most applications.

The field of view is quite similar to the penetration issue. In radiation approach, the illuminated area is determined by the beam size, which is generally on the order of one wavelength. For the magnetically mediated method, the field is confined by the coil size, especially in Helmholtz configuration. Thus, the penetration and field of view can be scaled to image deep laid objects with larger coils and superficial objects could be better covered with smaller coil in the magnetically mediated method.

2.2.3. Resolution

Like conventional microwave induced thermoacoustic imaging, the resolution in magnetically mediated thermoacoustic imaging is determined by the pulse width and the ultrasound transducer center frequency: the pulse width dictates the axial resolution of the applied magnetic field and the ultrasonic transducer determines the lateral resolution. Using the common pulse width of 1 μ s, the achievable resolution is about 1 mm. Further improvement for the resolution is obtainable by using shorter pulse. However, it comes at the cost of degraded signal to noise ratio as less energy will be delivered.

2.3. System design considerations

One important advantage of thermoacoustic imaging is its potential to be integrated with existing ultrasound scanners since they could share the ultrasound probe and signal processing front end. Therefore, there is not much motivation in designing entirely novel receiver for thermoacoustic imaging. However, the transmit part is different: it generally need optimum design in order to achieve best possible performance.

2.3.1. Coil design

Figure 2.4 (a) Circular coil, (b) Figure 8 coil, (c) Double figure 8 coil.

Unlike antennas, the coils used in magnetically mediated method presents its unique design challenges. It affects both field generation and the design of its driving circuits. On one hand, more number of turns is desirable for optimum signal generation as the both electric and magnetic field is linearly related to the number of turns N . On the other hand, the inductance load of the coil will constrain the N to be used in order to make the driving circuits physically achievable. Under such general constraints, various kind of usable coils present different characteristics. Three kind of coils shown in Fig. 2.4 are studied: circular coil, figure 8 coil, and double figure 8 coil. The former two coils' electric field distribution had been covered in [43] for the application of TMS. Yet, the implications for the driving circuit design for these coils are rarely discussed in the literature, which are of significant importance in magnetically mediated system that push the energy delivery part into physically realizable limits. Additionally, unlike TMS, the magnetic field distribution and its optimization are also of considerable interest in magnetically mediated method when magnetic sources are to be imaged like magnetic nanoparticles. Other coils can be evaluated with the same method presented here.

For a given current amplitude and circular coil, the generated thermoacoustic signal by joule heating at any fixed point in the space is derived from (2.2) and (2.8) to be

$$\begin{aligned} S_e &= \eta_b 2\alpha E_0^2 \exp(-2\alpha l) dl \\ &= 2\alpha \eta_b \eta_a^2 I_0^2 \omega^2 \exp(-2\alpha l) dl \end{aligned} \quad (2.14)$$

where I_0 is the current amplitude in the coil. Similarly, from (2.1), the signal generated by magnetic source S_m is found to satisfy $S_m \propto I_0^2 \omega N^2$. With the absorption coefficient $\alpha \propto \sqrt{\omega}$ and the penetration being limited by coil size instead of absorption ($l \propto \alpha^{-1}$), the signal will be stronger at higher frequencies as $\exp(-2\alpha l) \rightarrow 1$. As a result, it is preferred to work in the highest achievable frequencies of the coil. Also, it is noted from the equation that more turns is beneficial to increase the field strength. The number of turns and working frequency tradeoff with each other in the coil design as the coil inductance loading the driving circuit will limit the achievable frequency of the coil, which forms a magnetic resonance tank with the driving circuit. The inductance of a tightly wound N turns circular coil is analytically calculated as

$$L_0 = N^2 R \mu_0 [\ln(8R/a) - 2] \quad (2.15)$$

where R is coil radius and a is the wire radius. The resonance frequency of the coil with the capacitor networks (shown in Fig. 2.1) is

$$f_{res} = 1 / \left(2\pi \sqrt{L(C_1 + C_2)} \right) \quad (2.16)$$

Therefore, for a targeted frequency, large inductance will require extremely small capacitance value that can't be physically realized. Or, with realizable capacitances, the achievable frequencies will be limited by the inductances. Under the constraint of the same number of turns and coil diameter, the coil that can work at the highest

frequency (hence smallest inductance) without degrading the electric or magnetic field is preferred. Hence both the field generation capability of coils and their inductance need be evaluated.

(a) Definition of figure of merit

It is assumed that all the coils have the same diameter and the same number of turns. For figure 8 and double figure 8 coil, this means the sum of the turns in all the wings is the same with that of circular coil and each wing has the diameter of the circular coil. Also, the same capacitances are used in the resonance tank. A figure of merit (FOM) for a coil is then defined to relate its TA signal generation capability to that of circular coil. Because TA signal strength of magnetic sources and electric sources are affected by frequency and field strength in distinct degrees, their relative power will be different.

(1) Magnetic source

Magnetic heating depends on the magnetic field quadratically and is linearly related to the working frequency. Therefore for TA generation, the field strength counters a power of 2 while the frequency counter a power of 1. Then its FOM_m is

$$FOM_m = (f_{res}/f_{res0})(B/B_0)^2 = (B/B_0)^2 / (L/L_0)^{1/2} \quad (2.17)$$

where B , L and f_{res} are the magnetic field strength, inductance and resonance frequency of the coil whereas B_0 , L_0 and f_{res0} are those of the circular coil.

(2) Electric source

Joule heating differs from magnetic heating in that the signal depends approximately on the square of frequency. Hence its FOM is revised to be

$$FOM_e = (f_{res}/f_{res0})(E/E_0)^2 = (E/E_0)^2 / (L/L_0) \quad (2.18)$$

In both the FOMs, the resonance frequency is related to inductance through (2.14). The ratio of inductances in the denominator of *FOM* can be theoretically estimated based on (2.15). For circular coil, it is simply 1. For figure 8 and double figure 8 coil, their inductance can be approximately to a first order accuracy by neglecting the mutual inductance among the wings and then summing the inductance of all the wings. Thus, for figure 8 coil with each wing of $N/2$ turns, its inductance is $L_2 = L_0/2$ and its ratio of inductance is then 0.5. Similarly, double figure 8 coil has an inductance of $L_3 = L_0/4$ and a ratio of inductance of 0.25. The field generation capability of the three coil configurations defies simple analytical comparison and numerical simulations are therefore carried out.

2.3.2. Coil evaluations

The coils are evaluated firstly by numerical methods and then by phantom experiments.

2.3.2.1 Numerical simulations

It is numerically calculated in Matlab[®] the three coils' electric and magnetic field distribution based on (2.1) and (2.2). The number of turns is 4, the radius is 32 mm and the electric field is calculated on the plane of size 256 mm $\times$ 256 mm at height equal to the coil radius (thus the penetration depth) for all coils, whose current directions are given in Fig. 2.4. The results are presented in Fig. 2.5, where the total electric field strength and total magnetic field strength is used since joule and magnetic heating is determined by the total field strength regardless of the field polarizations. The unit used in calculation could be arbitrary as Maxwell's law is scale invariant.

The electric and magnetic field strength distribution across three coils are different, especially for circular coil and the other two coils: figure 8 coil and double figure 8

coil show electric and magnetic fields concentrated around the center of the coil instead of around the coil edge in circular coil. And, the electric and magnetic field strength distribution by the coil are strikingly similar. This is because the electric field is generated by magnetic field and, though the resultant electric field will have different polarizations, they will show similar behaviour when the total field strength is considered. The field polarizations may affect signal generation for heterogeneous matter. The coils' maximum electric and magnetic field and the corresponding FOMs are summarized in Table 2.1, where the numbers are given in arbitrary units. The three coils show roughly the same ability in generating electric field with double figure 8 coil slightly inferior in magnetic generation. Based on the FOM, it is concluded that the double figure 8 coil and figure 8 are superior than circular coil when used for mapping electrical sources whereas they possess no advantages in detecting magnetic sources like magnetic nanoparticles.

TABLE 2.1 MAXIMUM ELECTRIC AND MAGNETIC FIELD STRENGTH FOR THREE COILS

<i>Coil Type</i>	<i>E(V/m)</i>	<i>B(uT)</i>	<i>FOM_e</i>	<i>FOM_m</i>
<i>Circular</i>	3.22	31.96	1	1
<i>Figure 8</i>	3.19	31.75	1.96	1.40
<i>Double Figure 8</i>	3.13	22.56	3.78	1

Figure 2.5 Simulation results of electric and magnetic field distribution for (a) circular coil, (b) figure 8 coil, (c) double figure 8 coil.

2.3.2.2 Experimental verifications

Experimental setup in Fig. 2.6 is used to evaluate different coils and to demonstrate preliminary imaging applications. The coil is configured with a customized matching network commonly used in MRI. Pushed nearly to the limits, the two capacitors C_1 and C_2 are fixed at 11 pF and 22 pF to match all the coils that comes with different inductances. Thus the resonance frequency varies among the coils. A 2.2 ohm resistor

monitors the current flowing in the coil. An arbitrary function generator (Tektronix, AFG3252) produces signal at the resonance frequency of each coil at a repetition frequency of 1 kHz and feeds it into the an RF pulse amplifier (BT00200-AlphaSA-CW, Tomcorf) to drive the coil. The peak power of the amplifier is 250 W and the RF pulse width is set to 1 μ s in all cases, including coil evaluations and imaging. Thermoacoustic signal detected by the transducer is first amplified by a 54 dB low noise amplifier (model 5662, Olympus) and then digitized by the oscilloscope (Waverunner 6Zi, Lecroy). The data in the oscilloscope is averaged first and then lowpass filtered with a four stage Butterworth filter whose a cutoff frequency of 2 MHz to reduce high frequency noise, before being finally transferred to MATLAB 2010b on a PC for offline processing.

Figure 2.6 Experimental setup for coil evaluation and imaging.

Three coils are fabricated (Fig. 2.7(a)), each with 8 turns and a diameter of 2.6 cm. A round metal strip with diameter of 2 mm is used as the phantom for thermoacoustic signal generation. It is erected 2 mm above the coil and placed at the position that shows maximum electric field. Resultant TA signals received by a 1 MHz flat ultrasound transducer (Olympus, V323) are shown in Fig. 2.7(b). Double figure 8 and

figure 8 coil render around 2 and 1.3 times larger signal that that of circular coil. The theoretical improvement of figure 8 and double figure 8 coil can be calculated with (2.18) based on the measured resonance frequencies and currents of three coils (Fig. 2.7(c)). The currents in three coils are compensated in the computation according to (2.14). The result together with the normalized experimental TA signal is given in Fig. 2.7(d). The measurements follows theoretical calculations well. The disparity of double figure 8 coil may be caused by the slight variations in the distance from the coil to the phantom. Another point is that the actual improvements are less than the *FOM* predictions. This is because the inductance calculation in (2.15) assumes perfect coupling among the turns whereas in practice, the coupling is weaker as the coil is arranged in a solenoid manner.

Figure 2.7. (a) Photography of three fabricated coils, (b) Thermoacoustic signal generated by three coils, (c) resonance frequency and currents for three coils, (d) Normalized TA signal amplitude.

2.4 Imaging results

The penetration improvement was firstly demonstrated. In this case, a customized Helmholtz coil separated by 4.5 cm is placed below and above the phantom. Each coil has 5 turns and the diameter of the coil is 4.5 cm. The resonance frequency of the magnetic resonant tank (the coil with capacitor network) is fixed at 12.4 MHz and the measured quality factor is about 20. Driving with a power of 250 W, the peak current flowing in the coil is about 10 A and the magnetic field intensity is estimated to be 2 kA/m. No cooling of the coil is applied thanks to the low duty cycle for both the incoherent time domain method (0.1%) and coherent frequency domain method (5%). However, for the coherent frequency domain method with a long chirp duration and high repetition rate, adequate cooling may be necessary. The phantom (a tapering metal strip with 5 mm width (at the center) and 20 mm length) is immersed in the water tank and placed 2 cm away from the bottom coil. For the coherent frequency domain experiment, a flat transducer (1MHz, Olympus, V323) is used and a chirp signal sweeping from 0.5 MHz to 1.5MHz within 50 μ s is used to modulate the current envelop. Fig. 2.8 presents, from (a) to (d), the time domain signal in coherent frequency domain method for the current, its extracted envelop, received TA signal and the correlation results. TA signal is time-gated to avoid direct electromagnetic coupling, which is applicable here as the chirp modulated current is still in burst mode with low duty cycle (5%) and the chirp duration (50 μ s) is shorter than the propagation delay (70 μ s). Good electromagnetic shielding is necessary to eliminate the direct electromagnetic coupling for longer chirp durations. Correlation is then performed between the extracted envelop signal and received TA signal, which yields a peak at 70 μ s, agreeing with the distance (10.5 cm) between the transducer and the phantom.

The time domain signal shows amplitude variation as the frequency changes due to the limited bandwidth of the transducer.

Figure 2.8 (a) Time domain linear frequency chirp modulated current signal, (b) Extract current envelop (reference chirp signal for correlation), (c) Thermoacoustic signal generated by frequency domain method, (d) Normalized correlation results.

The imaging results for incoherent time domain method and the frequency domain method are shown in Fig. 2.9 (a) and (b) respectively. The images are formed by linearly scanning with the transducer manually and then performing back projection along each A-line signal. The anatomic structure can be clearly identified and agrees well with the optical photography. For the frequency domain image, it shows much less noise than that in time domain, verifying the SNR improvement of the frequency domain method. Even finer image can be got by advanced imaging reconstruction methods [44] - [46].

Figure 2.9. TA image of tapering metal strip reconstructed by (a): incoherent time domain method and (b): coherent frequency domain method.

Then we showcase the scalability of the magnetically mediated thermoacoustic imaging: one with a large circular coil of 5.5 cm diameter and one with a small circular coil of 1 cm diameter. The 5.5 cm coil has 6 turns, a resonance frequency of 15.6 MHz and the peak current flowing in the coil is measured to be about 6 A during imaging. The phantom in this case is a 2 mm radius metal strip, which is placed 1.5 cm above the coil. The signal is averaged by 8192 times and image is formed by linearly scanning with a 1 MHz focused transducer (Olympus, V303) manually and then performing back projection along each A-line signal. The result is shown with the optical photography image in Fig. 2.10 (a). It is noted that a good agreement is obtained.

Next, the small end imaging is carried out. The 1 cm coil has a number of turns of 15 and an RFID ferrite core inside ($\mu' = 20$, Far-rite Inc). Its resonance frequency is 13.6 MHz and the peak current for imaging is about 6 A. The signals are averaged by 4096 times and the image is formed similarly as in the large end imaging. Two thin aluminum strips placed 2 mm above the coil edge is imaged. The strip diameter is 1 mm and the two strips are separated by 9 mm. The TA imaging is given in Fig.

2.10(b). The two strips are clearly rendered and it is observed some part of the two wires are not well imaged because they are placed at the edge of the coil, where large field variation can occur. On the other hand, it indicates the reduced field of view in the small end imaging.

Lastly, a preliminary 3D imaging of the two strips are conducted by attaching the coil and ultrasound transducer to a 2D mechanical scanner. The transducer are facing towards the coil center to be "confocally" aligned. The 3D image formed by zigzag 2D scanning with a step size of 1 mm is shown in Fig. 2.10(c), which clearly identifies the two strips in space.

Figure 2.10 (a) TA imaging of a metal strip with large circular coil, (b) TA imaging of two thin aluminium strips, (c) 3D image of the two strips.

2.5 Summary

Technical issues in magnetically mediation approach, including energy absorption, signal to noise ratio, penetration and coil design are discussed thoroughly in this chapter. The magnetic coil used for energy delivery is found theoretically to have similar field deposition capability with antenna radiation. And, higher working frequencies give larger energy absorption and thus better SNR at shallow places while after the critical depth L_{crit} , low frequencies prevails. Such tradeoff between penetration and SNR is common in other imaging modalities like ultrasound. As

magnetically mediated is a near field approach, the penetration and field of view are roughly of the coil size. Thus, they can be scaled through coil tailoring. The resolution is determined by the pulse width as in other thermoacoustic imaging techniques and better resolution is obtainable by utilizing shorter pulses.

High contrast phantom imaging are demonstrated under different scales: the large end with a big coil and small end with a tiny circular coil. Both imaging results renders clearly the structure of the metal strip phantoms. To image biological tissues, much higher power will be needed. In microwave induced thermoacoustic imaging, several tens kilowatts [24], [47] power are generally employed. Since the magnetic coil is found theoretically to have similar field deposition capability with microwave antenna radiation when enhanced by ferrite cores, it is expected that similar power will suffice for magnetically mediated thermoacoustic imaging. Indeed, it was demonstrated in [48] that thermoacoustic signal was generated in biological tissues under several kilowatts magnetic field excitation. Alternatively, in order to work under low power excitation, coherent frequency domain methods can be adopted so as to increase the signal to noise ratio. The challenge therein is the strong direct electromagnetic interference that can mask the weaker thermoacoustic signal. One potential solution is to apply good electromagnetic shielding. Another is to design a low pass filter before the low noise amplifier to eliminate the high frequency interference because the generated thermoacoustic signal is at the lower frequency end. Considering that the direct interference is much stronger than the TA signal, a high order filter will be needed. Also, contrast agent like magnetic particles can be used when operates with low power. Magnetic particles are attractive as they show excellent heating performance under alternating magnetic field [38] and are long established contrast agents used in magnetic resonance imaging [49].

One challenge in the magnetically mediation method is to improve the resolution by reducing the pulse width, which necessitates much higher power to render comparable SNR. This is particular so when use it for small field of view imaging, where better resolution is generally required to reveal more details. Still, like high resolution microwave induced thermoacoustic imaging had been demonstrated with shorter pulse by pumping high power [22], this issue can be tackled in the same manner for the magnetically mediation method. Future work will target at developing high power system for in-vivo imaging and using magnetic nanoparticles for contrast enhancement to allow low power operation.

Chapter 3. CONTRAST ENHANCEMENT FOR THERMOACOUSTIC IMAGING: A MODULATION APPROACH

Exogenous contrast agents had drawn a lot of attention in both photoacoustic (PA) imaging [26] and thermoacoustic imaging [35] in order to improve the penetration depth or to exploit from their capability of targeted delivery for more sensitive and specific detection. For instance, gold nanoparticles had been used in photoacoustic imaging to probe biological processes at molecular level [50] - [52]. Yet, a difficulty frequently encountered is the strong backgrounds that limit the imaging contrast [53] when using contrast agents for enhanced imaging.

Similar problem could also arise in thermoacoustic imaging when using microwave or magnetic field for mapping contrast agents like magnetic nanoparticles: substantial heating of non-magnetic background [54] in MMTI and non-specific heating of high water content tissues in MI-TAI could occur and consequently limit the imaging contrast for rendering nanoparticles labelled region. Also, the background may be particularly severe for those shallow tissues, which are exposed to larger field.

In order to detect contrast agents with higher contrast, we proposed a modulation based method for suppressing the background in both the photoacoustic imaging and magnetically mediated thermoacoustic imaging. Though the specific modulation methods and their underlying physical principles are different, the core idea of tagging/modulating the desired photoacoustic/thermoacoustic signals whereas keeping the background intact is general.

3.1 Thermally modulated photoacoustic imaging

To ameliorate the background problem in photoacoustic imaging, photoacoustic magneto-motive method [53], [55] and nonlinear PA imaging had been proposed.

However, nonlinear PA imaging utilized either large light fluence [56] or special nanoemulsion bead [57] whereas the magneto-motive method is strictly limited to nanoparticles with magnetic property. The small displacement (on the order of 10 μm) used in magneto-motive method also makes it sensitive to physiological movements. This is more critical for tissues that show large elastic constants like many tumors [58], where the displacements get smaller.

The thermally modulated photoacoustic imaging (TMPI) complements magneto-motive and nonlinear PA method and is applicable to both magnetic and non-magnetic nanoparticles, besides being immune to elastic constants.

3.1.1 Theory

Figure 3.1 Thermally modulated photoacoustic process.

TMPI exploits from the efficient and localized heating of nanoparticles under electromagnetic field and the excellent PA sensitivity on temperature. As illustrated in Fig. 3.1, nanoparticles and background reside on the same temperature level T at thermal equilibrium. The PA pressure generated therein is [31]

$$P = \mu_a \Gamma(T) F = \mu_a F(A + BT) \quad (3.1)$$

where A and B are constants, μ_a is the absorption coefficient, F is optical fluence and Γ is the Grueneisen parameter. In certain cases, due to strong background absorption (like blood) and the limited concentration of nanoparticles, PA signal of background (P_2) is comparable to that of 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. PA pressures at these levels are then modulated by the temperature elevations

$$P_{in} = \mu_a \Gamma(T + \Delta T_i) F = P_i(1 + S_i \Delta T) \quad (3.2)$$

where $i = 1, 2$, $h_i = B \Delta T_i / (A + BT) = S \Delta T_i$ is the modulation coefficient, S is the PA sensitivity on 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 [33]. Therefore, differences in ΔT will yield corresponding different modulation coefficients. Assuming nanoparticles are heated by electromagnetic field more efficiently than background so that ΔT_1 equals, for instance, 3 times ΔT_2 , the modulation coefficient h_1 will then be about 3 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, for at appropriate frequencies, both kinds of nanoparticles can be heated selectively over the background. Magnetic nanoparticles can be heated selectively under alternating magnetic field [59] and non-magnetic single wall carbon nanotubes

[52] can be heated efficiently by low power microwave [60] or radio frequency irradiation [61]. For both nanoparticles, their temperature elevations ΔT can be several times (like more than 4 times in [59]) larger than that of the background. This corresponds to approximately the same difference in their modulation coefficients. Owing to the high sensitivity of PA on temperature [62], only a few degrees temperature elevation is needed to make the modulations detectable: in [63], a temperature variation of 1~2 degrees is used in PA imaging for blood velocity detection, which corresponds to a modulation 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 [33]. Since nanoparticles 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.

3.1.2 Experiments

Consider specifically using SPION in photoacoustic imaging as it is FDA approved and is applicable also to thermoacoustic imaging [64]. The temperature rise caused by Brown and Neel relaxation of the SPIONs under alternating magnetic field satisfies [38]

$$\Delta T \propto \chi_0 H_0^2 \omega^2 \tau / (1 + (\omega \tau)^2) \quad (3.3)$$

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 field, 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 [54],

which is generally weaker than nanoparticles' magnetic heating and will be significantly reduced when low frequency ($<1\text{MHz}$) alternating magnetic field is applied [54].

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 falls on the order of 1 μs according to [38], 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. SP1 is roughly 220 mg/ml and others are consecutively diluted by two times. SP1 has a calculated number concentration of $\sim 4.7 \times 10^{16}/\text{ml}$ and an equilibrium magnetic susceptibility of 9.87×10^{-2} H/m. The SPIONs fluid is poured into a jar of 3 mm diameter and suspended in air 1 mm above a customized 25 turns 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 magnetic susceptibility of SP1 is 8.53×10^{-4} H/m. Since $\omega\tau \ll 1$, the heating is saturated according to Eq. (3.3). The temperature before, during, and after magnetic heating of the fluid is monitored by a K-type thermometer (1 degree accuracy) by inserting its sensor tip inside. 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. Measurement results are given in Fig. 3.2(a) and the extracted heating rates (temperature increase per unit time in the linear region) are shown in Fig. 3.2(b).

Figure 3.2 (a) Temperature rise of S1, S4, S8, and water, (b) SPIONs heating rate.

The temperature increase renders initially a linear behaviour 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 than water with SP1 being 1.5 times larger. The heating rate relates roughly linearly 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 [59], [61], [54], the heating difference between SPIONs and the background water achieved here is weaker. This is also observed in [54] and is caused by the nonspecific heating of background water, which is found to be substantial at frequencies beyond ten MHz (18.4 MHz in this paper). It can be reduced significantly by using frequencies below 1 MHz to enlarge the heating difference between the SPIONs and background water.

placed 2 mm below the phantom. It is not used for PA temperature sensitivity measurement.

Figure 3.4 (a) PA amplitude versus temperature, (b) PA sensitivity on temperature, BI: blue ink.

PA sensitivity on temperature S is measured with SP1, SP2, SP3 and blue ink (simulating absorptive background) by injecting them into the tube. Subsequent procedures follow those of [33]. Briefly, the temperature is varied by pouring hot water into water tank and allowing it to cool down naturally. Then the temperature and PA signals are recorded simultaneously. The results are shown in Fig. 3.4(a) with s extracted in (b) within the temperature range of 42 to 36 degrees. In all cases, PA signals show a linear relationship on temperature (linear fit $R^2 > 0.96$) and the sensitivities are roughly the same: about 2.5%, close to those in [33]. With aforementioned methods to improve the SNR of PA signal, modulations corresponding to only a few degrees of temperature elevation can be detected under the 2.5 % sensitivity.

For TMPI, water of 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. Such high concentrations can be obtained by direct injection or apply magnetic trapping for magnetic nanoparticles travelling in the vasculatures [51]. More generally, proportionally higher power need be used for realistic concentrations. The imaging sequence presented in Fig. 3.3(b) is used. Reference imaging is performed first and upon its termination, the magnetic heating is turned on for 4 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 transducer focal region with the linear translation stage and storing the signals therein. The images are formed with back projection method after envelop extraction of each A-line signal. Coherent difference image is rendered by the 2-D alignment algorithm given in Fig. 3.3(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 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 Fig. 3.5(a) and (b) respectively. In 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, it is 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 Fig. 3.5(c) and (d). Without correction, a widened tube is produced in (c) due to the misalignment whereas the corrected image in (d) is almost identical to (b). Figure 3.5(e) and (f) show respectively the PA amplitudes along the dotted line in image (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. 3.2(a)).

Figure 3.5 (a) Reference image, (b) Difference image, (c) Physiological movements affected difference image, (d) Corrected difference image, (e) Signal along dotted line in (a), (f) Signal along dotted line in (b).

3.1.3 Discussion

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, power amplifier at several hundred watts can heat up SPION of realistic concentrations several degrees within a few seconds [54]. This will shorten the TMPI imaging time

accordingly. Faster and larger heating difference can also be obtained by using more efficient magnetic nanoparticles [65] - [66]. In [66], the MnFe_2O_4 nanoparticle achieved 3 degrees of temperature increase within 5 seconds and a heating rate ratio over background around 7 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 heartbeat. Still, TMPI is more resilient in this respect because, compared to 10 μm order displacement in magneto-motive method, its image resolution around 1 mm (or several hundred μm when using high frequency transducers) can accommodate physiological movements smaller than a resolution cell without affecting much the differential imaging. The small temperature elevation and its transient duration needed in TMPI are expected to induce minimal adverse effects [63] and should therefore be safe in most applications. This approach can also be readily extended to microwave induced thermoacoustic imaging with SPIONs [64] and carbon nanotubes [35] to provide deeper penetration. For other nanoparticles like carbon nanotubes and gold nanoparticles, their toxicity issue may be a hindrance for their applications. Lastly, it is noted that the heating RF field could generate its own thermoacoustic signal as the same series of physical process of thermoacoustic effect will happen under the heating RF field. However, the thermoacoustic signals induced by the heating RF field will generally fall below the noise floor due to the low power (~ 10 W).

For practical applications, it may not be desirable to employ the TMPI method when other safer contrast enhancing methods like magneto-motive photoacoustic imaging could perform well since increasing the temperature of samples is not always convenient, particularly when the sample concentrations are too low. Nevertheless, it

could be a viable solution when physiological movements make magneto-motive PA imaging difficult to perform and nonlinear PA imaging could not be delivered due to its required large laser fluence.

To conclude, 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. Imaging results demonstrated successful discrimination of SPIONs from background ink. Future improvements can potentially enhance the contrast significantly and enable faster TMPI within a few seconds.

3.2 Modulatable magnetically mediated thermoacoustic imaging with magnetic nanoparticles

Magnetic nanoparticles had long been investigated for hyperthermia therapy applications [67] and were used as the contrast agent in microwave induced thermoacoustic imaging [68]. The potential to share the magnetic field in hyperthermia therapy prompts us to investigate the thermoacoustic effect of magnetic nanoparticle under alternating magnetic field: magnetically mediated thermoacoustic detection of magnetic nanoparticles. Though magnetic nanoparticles had been used in microwave induced thermoacoustic imaging, it relies on the enhanced dielectric absorption of radiation energy instead of magnetic relaxation loss that draws energy from non-radiant magnetic field. Thermoacoustic effect of magnetic nanoparticles under alternating magnetic field was initially studied theoretically in [69], but experimental verifications were lacking. Also, as noted earlier, substantial heating of non-magnetic background [54] could occur in MMTI, this could impede the imaging contrast of MMTI in detecting the magnetic nanoparticles.

In this section, we report the magnetically mediated thermoacoustic effect of magnetic nanoparticles experimentally and for improving the imaging contrast, we analyze theoretically and demonstrate experimentally the unique magnetic modulation capability of magnetic nanoparticles in MMTI, which is exploited for background reduction via differential imaging. Compared with conventional differential imaging [70] 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.

3.2.1 Theory

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 as [38]

$$S(r) = \frac{\mu_0}{2} H_{ac}^2(r) \chi_0 \frac{\omega^2 \tau}{1 + (\omega \tau)^2}, \quad (3.4)$$

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 generated [69]

$$\nabla^2 p(\vec{r}, t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p(\vec{r}, t) = -\frac{\Gamma}{c^2} \frac{\partial}{\partial t} \{S(r)[U(t) - U(t - \Delta t)]\}, \quad (3.5)$$

in which $p(\vec{r}, t)$, c , 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 estimated [45]

$$P(r) = \Gamma S(r) \Delta t = \Gamma \Delta t \frac{\mu_0}{2} H_{ac}^2(r) \chi_0 \frac{\omega^2 \tau}{1 + (\omega \tau)^2}. \quad (3.6)$$

The pressure strength is hence proportional to magnetic susceptibility of nanoparticles fluid χ_0 , 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 Tesla 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.

Figure 3.6 (a) Schematic of two configurations. MAG: magnet, MNP: magnetic nanoparticles. (b) DC magnetic field dependence of susceptibility.

Magnetic modulation can be achieved by two different configurations illustrated in Fig. 3.6(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 magnetic fields are in the same direction. The first configuration was partially investigated in [71] 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 scenario respectively, the susceptibilities can be calculated as [71]

$$\chi_{01} = \frac{M_0}{H_0} = \frac{M_s}{H_0} \left(\coth(\alpha_0) - \frac{1}{\alpha_0} \right), \quad (3.7)$$

$$\chi_{02} = \frac{\partial M_0}{\partial H_0} = \frac{M_s}{H_0} \left(-\frac{\alpha_0}{\sinh^2(\alpha_0)} + \frac{1}{\alpha_0} \right). \quad (3.8)$$

where $\alpha_0 = \frac{M_d V_p \mu_0 H_0}{kT}$ is the Langevin parameter, $M_s = M_d \phi$ 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, T and k are the absolute temperature and Boltzmann constant respectively. For scenario two, the volumetric power deposition function can be derived to be slightly different from Eqn. (3.4):

$$S_2(r) = \frac{\mu_0}{2} H_{ac}^2(r) \chi_{02} \frac{\omega^2 \tau}{(1 + \chi_{02})^2 + (\omega \tau)^2}. \text{ Nonetheless, as } \chi_{02} \text{ is generally much}$$

smaller than one [71] (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 Eq. 3.7 and 3.8) versus DC magnetic field are plotted in Fig. 3.6(b) for illustration purpose, with $T = 300 \text{ K}$, $M_d = 446 \text{ kA/m}$, $\phi = 0.001$ and $R = 6 \text{ nm}$. 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. The modulation is unique to magnetic nanoparticles: because the non-magnetic background heating is majorly caused by the Joule heating under AMF [72], 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.

3.2.2 Experiments

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 [38]. The experiment setup is illustrated in Fig. 3.7. A function generator (Tektronix, AFG3252) produces 1 μ s radio frequency 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 ohm 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. Because under 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 inch (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%.

Figure 3.7 (a) Experiment setup for magnetically mediated thermoacoustics with magnetic nanoparticles, FG: function generator, PA: power amplifier, LNA: low noise amplifier, TR: transducer. (b) Configuration of the two scenarios in the experiment. MAG: magnet.

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 Tesla) at the phantom. The received TA signal is averaged 16000 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. 3.8 (a)) and shifts to 29 μ s (Fig. 3.8(b)) when the transducer is moved to be 4.3 cm away from the phantom. The measured dependence

of TA signal on the excitation power for 220 mg/ml SPIONs is shown in Fig. 3.8(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) with the excitation power being fixed at 1.6 kW. The result is shown in Fig. 3.8(d), where the data is 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.

Figure 3.8 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, black solid line: linear fit result; (d) TA signal peak-to-peak amplitude at five concentrations; red square: measured values, black solid line: linear fit result.

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. 3.7(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. 3.9(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.

Figure 3.9 (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.

Lastly, 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. 3.10 (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 two is formed by introducing the DC magnetic field to suppress TA signals from nanoparticles. The modulated image is shown in Fig. 3.10(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 manoeuvring 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. 3.10(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 [70]. To achieve better background suppression in clinical settings, faster TA imaging and proper tracking of these physiological movements may be needed.

Figure 3.10 (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); (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.

3.2.3 Discussion

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[20],[22] (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[20],[22], enabling realistic concentrations to be imaged. Although the testing objects and conditions may differ from those in MI-TAI, the comparison will give an rough estimate on the order of magnitude of what kind of concentrations of SPIONs could be sensed by the proposed MMTI method when utilizing the same power budget. Moreover, as SPIONs give just a moderate heating under AMF [73], utilizing ferromagnetic nanoparticles and more efficient nanoparticles under development [65] 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 the further, in vivo animal studies may be conducted.

3.3 Summary

The modulation based method for improving imaging contrast by background reduction is quite similar to the underpinning spirit of another multi-wave imaging: using wave one to tag wave two. In fact, the thermally modulated photoacoustic imaging could be appreciated in the sense that, the photoacoustic signals from the nanoparticles are tagged by a thermal wave (temperature increase) whereas the background is not. By selectively detect the tagged signals, we can essentially sift out the nanoparticles with higher contrast and better specificity. An even more powerful idea that use thermal wave to tag photoacoustic signal is demonstrated in [63], where the thermal wave propagation inside capillary is dynamically tracked by a fast photoacoustic tomography imaging system. The useful photoacoustic signals for calculating the blood flow speed are only the tagged part of the overall photoacoustic signals.

Similarly, we can understand modulatable magnetically mediated thermoacoustic imaging from the perspective that the thermoacoustic signals from the nanoparticles are tagged/modulated by a "static magnetic wave", and then by retrieving the tagged part of the thermoacoustic signal for image formation, the nanoparticles are rendered with much high contrast since the background is significantly reduced. It should be noted here that, the modulation need not be confined to the nanoparticles. As long as the background and desired region could be differentiated by another wave (thermal, magnetic, ultrasound, etc.), the modulation method could be extended by employing the corresponding wave for contrast enhancement.

Chapter 4. THERMOACOUSTIC POWERED CLOSE-LOOP TEMPERATURE CONTROL OF HYPERTHERMIA THERAPY

After successfully developed magnetically mediated thermoacoustic imaging (MMTI) for both conductive objects and magnetic sources like magnetic nanoparticles, the vision of a integrated theranostic platform that includes hyperthermia therapy and MMTI become closer to reality. MMTI can re-use the radio frequency or alternating magnetic field in hyperthermia therapy by interleaving the sequences between MMTI and hyperthermia therapy. This could lead to a minimal yet more powerful system. Besides imaging guidance of MMTI, a probably more important functionality that could be offered by MMTI is its accurate temperature measurement capability since the thermoacoustic process is found to be highly sensitive to local temperature. We investigate in this chapter using thermoacoustic and photoacoustic technique for non-invasive, accurate temperature measurement at depths and based on it, for further close-loop temperature control of various hyperthermia therapy applications.

4.1 Self temperature monitoring of magnetic nanoparticles by MMTI

There are tremendous interests in applying hyperthermia therapy with magnetic nanoparticles for cancer treatment [74] - [76]. In this method, magnetic nanoparticles are introduced to tumour and then heated under an external alternating magnetic field. Such heating of magnetic nanoparticles raises the temperature of tumour beyond 42 degrees Celsius and causes apoptosis of targeted cancer cells, achieving thus therapeutic effects. However, due to heat diffusion, healthy surrounding tissue could also get damaged under excessive tumour heating during therapy, which can lead to serious complications for patients. To circumvent such side effects, the tumour therapy

temperature needs be tightly controlled. This requires both accurate temperature measurement and subsequent automatic control of hyperthermia heating.

The foremost task is temperature measurement. Although plenty of techniques exist, it is still challenging to achieve accurate temperature measurement at depths economically and non-invasively. Tiny thermometer is accurate [77] - [78] and economical, but its invasiveness limits its practical usages in clinical settings. Ultrasound method, though portable and non-invasive, provides limited accuracy due to its weak temperature sensitivity [79] - [80] or requires sophisticated imaging procedures [81] to boost the accuracy. Magnetic resonance imaging (MRI) can give accurate temperature reading [82], but it is bulky and cost-prohibitive. Optical methods like near infrared spectroscopy (NIRS) [83] - [84] are generally portable and sensitive to temperature. Yet the strong scattering of light inside tissue limits either their achievable penetration depth (e.g. infrared thermometry) or the probing resolution (e.g. NIRS).

Thermoacoustics is an emerging hybrid sensing method that combines the dielectric contrast of materials and excellent resolution of ultrasound. And owing to its large wavelength of excitation waves, it can achieve penetration up to several centimetres while maintaining sub-millimetre resolution. These features, coupled further with its high sensitivity on temperature measurement [32] - [33], make thermoacoustics particularly appealing for non-invasive temperature measurement. Indeed, preliminary deep tissue temperature measurement with sub-degree accuracy had been achieved by photoacoustics [85] and microwave induced thermoacoustics [33].

4.1.1 Theory of thermoacoustic temperature measurement

In magnetically mediated thermoacoustic imaging, magnetic nanoparticles absorb energy from the magnetic field and therefore get heated up. The volumetric power deposition U is calculated to be [38]:

$$U = \frac{\mu_0}{2} H_0^2 \chi_0 \frac{\omega^2 \tau}{1 + (\omega \tau)^2} \quad (4.1)$$

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 produced [34]:

$$\nabla^2 p(\vec{r}, t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p(\vec{r}, t) = -\frac{\beta}{C_p} \frac{d}{dt} H(\vec{r}, t), \quad (4.2)$$

where $p(\vec{r}, t)$, 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:

$$P = kU\Gamma(T) \quad (4.3)$$

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 TA on temperature, defined as TA signal amplitude's change in percentage per degree temperature variation, is about 3~5% for most materials [32]. With a calibrated reference point $P(T_0)$, absolute temperature can be calculated from measurement result P as:

$$T = \frac{P}{P(T_0)} \left(\frac{A}{B} + T_0 \right) - \frac{A}{B} \quad (4.4)$$

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 possesses 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 allows 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 [72], which could provide superior signal to noise ratio without too many time domain averages or using higher power amplifiers. The frequency domain method for accurate temperature

measurement will be presented later that use a low power laser diode for photoacoustic temperature sensing.

4.1.2 Self temperature monitoring experiments

The experimental setup for the self temperature monitoring of magnetic nanoparticle hyperthermia is illustrated in Fig. 4.1. The radio frequency signal is produced by two arbitrary function generators (Tektronix, AFG3252): the first one produce 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 Fig. 4.1(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. 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 cut-off 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.

Figure 4.1 (a) Experiment setup for AMF induced thermoacoustic signal imaging and temperature sensing, (b) Timing sequence for self-monitoring of the temperature during hyperthermia therapy.

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 Fig. 4.2(a) with its

associated spectrum shown in Fig. 4.2(b). The signal to noise ratio of the coil is observed to be around 14 dB, sufficient for image formation but 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 Fig. 4.3(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 4.2 (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

Figure 4.3 (a) TA Tomography of a round metal strip, (b) self-temperature monitoring results of the hyperthermia session, (c) TA temperature measurement versus thermometer measurement.

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 Fig. 4.3(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 Fig. 4.3(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 results [54]. 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.

4.1.3 Discussion

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 kilowatts [19], 1 kW is a relatively small value and in magnetic nanoparticle hyperthermia applications, ferromagnetic nanoparticles that show several or even 10 times heating performances [73] 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.

4.2 Photoacoustic guided close-loop control of nanoparticles hyperthermia

Though MMTI had achieved a sub-degree temperature monitoring for nanoparticle hyperthermia, it is of great interest to see what could be achieved with photoacoustic temperature sensing that comes with inherent better signal to noise ratio owing to the availability of high energy laser sources. Moreover, since the ultimate goal of temperature measurement is temperature regulation, we studied in this section using photoacoustic for close-loop temperature control of nanoparticle hyperthermia. Though magnetic nanoparticles might possess weaker absorption at infrared

wavelengths, strong signal to noise ratio (SNR) and hence good accuracy are still achievable by selecting judiciously the wavelength at the visible range [51]. Also, the engineering of novel magnetic nanoparticles that endows them with good light absorption at desired wavelengths [53], [86] can facilitate further the utilization of photoacoustic technique in magnetic nanoparticle based applications. It is shown in this section that photoacoustic system is well suited to be integrated with magnetic nanoparticle hyperthermia system and can provide accurate temperature measurement. Empowered by this, our proposed pHFC can automatically stabilize the temperature at predetermined values with an accuracy of 0.3 degree Celsius. It thus represents a portable, economical and powerful temperature control solution for nanoparticle hyperthermia therapy.

4.2.1 System model development and controller design

Using photoacoustic for temperature monitoring is not unlike to that in thermoacoustics. At temperature T , the generated PA signal amplitude P is calculated as

$$P = \mu_a \Gamma(T) F \quad (4.5)$$

where F is optical fluence, μ_a and Γ are the absorption coefficient and Grueneisen parameter of the matter, respectively. The temperature measurement is based on the fact that $\Gamma(T)$ is linearly related to absolute temperature and thus with a reference point, absolute temperature can be calculated from measurement result by Eq. 4.4.

The close-loop system for regulating temperature is represented in the block diagram in Fig. 4.4. A function generator (FG) produces signal according to the controller (CON) output and feeds the power amplifier (AMP), which controls the magnetic ferrofluid heating (MFH) process inside tissue. The tissue temperature consequently

changes according to the bio-heating process (BioHeat) and is continuously monitored by photoacoustic system (PAM). The controller monitors the error signal (set point temperature $T_r(t)$ minus actual measured temperature $T(t)$) and yields a corresponding signal for controlling the function generator block to bring the actual temperature $T(t)$ toward $T_r(t)$, achieving therefore tight temperature control inside tissue. From the prospective of the controller (CON), the function generator, power amplifier, MFH process, BioHeat process and photoacoustic measurement form together the plant model.

Figure 4.4 Block diagram for the entire close loop system. FG: signal generator, AMP: power amplifier, MFH: magnetic ferrofluid heating, BioHeat: Biological heating process, PAM: photoacoustic measurement.

(a) System model

As the function generator simply reads the power value specified by the controller and produces correspondingly physical radio frequency signal to feed the power amplifier, it is equivalently a unity gain amplifier in terms of power transfer. Thus it can be combined with the power amplifier into a single block with a power gain of G_1 . The MFH described in Eq. 4.1 states essentially $U \propto H_0^2$ when the magnetic frequency for heating is fixed. Since H_0^2 is proportional to the output power $\psi(t)$ of the amplifier, U can be related to the instantaneous power of the amplifier by

$U(t) = G_2 \psi(t)$ with G_2 as a constant. In Laplace domain, it is: $U(s) = G_2 \psi(s)$, in which the convention of using $F(s)$ to represent the Laplace transform of a general function $F(t)$ is employed and will be used hereafter.

Figure 4.5 Illustration of temperature profile of MNP laden region and surrounding tissue. MNP: magnetic nanoparticles.

The bio-heating process is more complicated. Factoring in nanoparticles heating, heat diffusion and blood convection for *in vivo* scenarios, it can be characterized by the bioheat transfer equation (BHTE) [87]:

$$\rho(r)c(r)\frac{\partial T(r,t)}{\partial t} = \nabla \cdot k(r)\nabla T(r,t) + U(r,t) + c_b w(T_a - T(r,t)) \quad (4.6)$$

where $\rho(r)$, $c(r)$, $k(r)$ are the mass density, specific heat, and thermal conductivity of the nanoparticles laden tissues. c_b, w and T_a are the specific heat, local perfusion rate and temperature of the blood respectively. This differential equation needs to be simplified in order to get an analytical solution for temperature. To this end, the thermal conduction/diffusion between nanoparticles laden region and surrounding tissue is approximated with the lumped system analysis [88]. This translates to a sharp temperature roll-off between nanoparticles laden region and its surrounding tissue as illustrated in Fig. 4.5 (a), though the actual temperature roll-off is much slower like in

(b). This approximation can significantly reduce the BHTE complexity and still model adequately the nanoparticles hyperthermia process, as validated by later experiments.

The BHTE is hence now:

$$\rho c \frac{\partial T(t)}{\partial t} = -R(T(t) - T_a) + U(t) + c_b w (T_a - T(t)) \quad (4.7)$$

where R is the characteristic time constant of the tissue-nanoparticles system for the lumped system analysis. Further reduction gives:

$$\rho c \frac{\partial \Delta T(t)}{\partial t} = -\beta \Delta T(t) + U(t) \quad (4.8)$$

with $\beta = (R + c_b w)$ and $\Delta T(t) = T(t) - T_a$. β is an unknown constant since the local blood perfusion and the characteristic time constant of the tissue-nanoparticles system are not obtainable. The Laplace transfer function of the BHTE is then:

$$\frac{\Delta T(s)}{U(s)} = \frac{1}{s\rho c + \beta} = \frac{1/\rho c}{s + \beta/\rho c} \quad (4.9)$$

Like other temperature sensors such as thermometer, photoacoustic temperature measurement has an inherent time delay (latency). With N times averaging and a laser firing repetition rate of PRF , the latency is $L = N/PRF$. Its transfer function is thus $M(s) = \exp(-sL)$. Generally, the delay is on the order of 1 s. For instance, for measurement with 8 times averaging and a laser with PRF of 10 Hz, the delay is 0.8 s. Compared to tissue temperature response time during nanoparticle hyperthermia that are on the order of several minutes, the delay is negligibly small.

Figure 4.6 (a) Entire system model in Laplace domain. (b) PID implementation with only proportional and integration term. AMP: power amplifier, MFH: magnetic fluid hyperthermia, PAM: photoacoustic measurement, CON: controller.

With each block modelled, the entire system can be compactly represented in Laplace domain as shown in Fig. 4.6(a), with the plant model given as:

$$Q(s) = \frac{G_1 G_2 / \rho c}{s + \beta / \rho c} e^{-sL} \quad (4.10)$$

(b) Controller design

Lots of algorithms are available for the controller design. Here, PID algorithm is chosen owing to its simplicity and robustness. The general form for PID controller is [89]:

$$C(s) = K_p + \frac{1}{t_i s} + t_d \times s, \quad (4.11)$$

where K_p , t_i and t_d are the proportional gain, integration time, and derivative time respectively. To achieve stable, accurate and fast control, the three parameters need be determined based on the theoretical plant model. However, the constant G_2 and β in the plant model are unknown due to unknown local thermal diffusion and blood perfusion. The common solution is tuning, which experimentally measures the plant's step response and then calculates the PID parameters, with necessary iterations to get optimum results.

However, using PA temperature measurement that has negligible latency, the plant model developed above can be approximated to be

$$Q(s) = \frac{G_1 G_2 / \rho c}{s + \beta / \rho c} = \frac{G}{1 + s\tau} \quad (4.12)$$

with $G = G_1 G_2 / \beta$ as the gain of the plant and $\tau = \rho c / \beta$ as the plant time constant. Without the long latency (dead-time) that complicates the traditional tuning, a simpler yet robust PID control design can be achieved. As shown in Fig. 4.6(b), only proportional term K_p and integral t_i term are adopted since the derivative term is inherently sensitive to noise. The output temperature $T(t)$ is related to $T_r(t)$ in Laplace domain as $T(s) = J(s)T_r(s)$, where

$$J(s) = \frac{K_p G s + G/t_i}{\tau s^2 + (K_p G + 1)s + G/t_i} \quad (4.13)$$

is the transfer function. With input being Heaviside step function $T_r(t) = u(t)$, the steady state value output is $T(t \rightarrow \infty) = 1$ regardless the value of G and τ . It thus indicates a tight tracking of $T(t)$ to $T_r(t)$ upon reaching steady state. Under the form of (11), a wide range of values of K_p and t_i are allowed for the controller design without inducing stability issues. Employing only the K_p term ensures unconditional system stability and leads to

$$T(t \rightarrow \infty) = K_p G / (K_p G + 1), \quad (4.14)$$

which prefers larger K_p in order to obtain faster tracking and minimal steady state error. Using only t_i term, one gets

$$T(t \rightarrow \infty) = 1. \quad (4.15)$$

To avoid stability issues, large value of t_i (hence small gain for the integrator) can be used. One attractive aspect of fast PA temperature measurement is that it allows non-optimum PID controller parameters to be used without much knowledge on the plant parameters and still delivers satisfying performance.

(c) FPGA based pHFC controller system implementation

The FPGA based portable hyperthermia feedback controller (pHFC) is shown diagrammatically in Fig. 4.7. It triggers a laser to illuminate the object and receives the generated PA signal from an ultrasound transducer (UST), which directs at the magnetic nanoparticles laden region. PA signal is amplified by 54 dB with a compact amplifier (Model 5662, Olympus) and then sampled by a analog to digital converter (ADC) before entering FPGA (Cyclone II starter board, Altera). The 5 MHz bandwidth for the amplifier also functions as the anti-aliasing filter for the ADC. All

backend processing are realized in the FPGA board. An internal phase lock loop (PLL) generates a 30 MHz system clock (clk) and feeds it into the system (SYS) timer and ADC control block (ADC Ctrl). The timer produces a 10 Hz synchronization signal to trigger laser and initiates the ADC Ctrl module. Upon the rising edge of each sync signal, the laser fires once and ADC Ctrl module commands the ADC to acquire the incoming signal at a sampling rate of 30 MHz for a fixed time interval. The sampling

Figure 4.7 System implementation based on FPGA. MAF: moving average filter, ADC: analog to digital converter, UST: ultrasound transducer, LNA: low noise amplifier, PLL: phase lock loop, FG: function generator, AMP: power amplifier. SYS: system.

eliminate high frequency noises. The "Average" module then performs 8 times averaging of the lowpass filtered signal to improve the signal to noise ratio and feeds the results to the temperature calculation module (T_m Calc), which extracts temperature by detecting the peak to peak value of averaged PA signal and doing conversion according to Eq. (4.4). No laser energy compensation is adopted in current PA temperature measurement since measuring laser energy will need another channel of ADC. The measured temperature is compared with pre-set temperature and generates an error signal that feeds to the PID controller. Since the temperature is updated at the rate of sync signal, the PID controller, which is implemented with a parallel structure, works at this rate as well.

The PID controller output is converted to PWM signal (PWMs) by the pulse width modulation (PWM) core to facilitate hyperthermia power control. Compared with solutions using digital to analog converter that reverts the PID output back to analog domain, PWM that outputs switching values (0 and 1) allows purely digital implementation and therefore more economical and robust control. Denoting the resultant PWM signal as $Y_m(t)$ with a modulation frequency ω_m and duty cycle of D , the temperature increase can be derived from (4.10), which relates the temperature increase to the final controller output (Fig. 4.6(a)), as follows:

$$\Delta T(s) = \frac{G_1 G_2 / \rho c}{s + \beta / \rho c} e^{-sL} Y_m(s) = \frac{G}{1 + s\tau} e^{-sL} Y_m(s), \quad (4.16)$$

with $G = G_1 G_2 / \beta$ and $\tau = \rho c / \beta$. Its corresponding frequency response is:

$$\Delta T(j\omega) = \frac{G}{1 + j\omega\tau} e^{-j\omega L} Y_m(j\omega) \quad (4.17)$$

Expand the PWM signal into Fourier series:

$$Y_m(t) = D + \frac{1}{n\pi} \sum_{n=1}^{\infty} [\sin(n\omega_m t) - \sin(n\omega_m t - 2n\pi D)] \quad (4.18)$$

It is observed that, as long as the PWM frequency ω_m is chosen to be much larger than the cutoff frequency ($1/\tau$) of the plant model ($\omega_m \tau \gg 1$ with τ on the order of seconds), the high frequency components of PWM signal (including the 50 μ s disturbance of PWM heating for EMI issue) will essentially be eliminated and leave only the DC component intact. This renders a linear tuning characteristic with respect to the duty cycle:

$$\Delta T(s) = \frac{DG}{1 + s\tau} e^{-sL} \quad (4.19)$$

4.2.2 Experimental results

Figure 4.8 (a) Experiment setup, (b) photography of the pHFC system, (c) Timing sequence for data collection and imaging. FG: function generator, Amp: power amplifier, UST: transducer.

The experimental setup shown in Fig. 4.8(a) is used to demonstrate the photoacoustic powered pHFC for precise temperature control of nanoparticle hyperthermia. In this proof of concept work, a customized small coil driven at power of 20 W is used for heating the magnetic nanoparticles. The coil has a ferrite core, 10 turns (660 turns/m) and a diameter of 8 mm. It is driven by a power amplifier (ZHL-100W-GAN+, Mini-circuits) at 20.1 MHz, which is produced by a function generator and is the resonance frequency of the coil network. A tube with 3 mm inner diameter is filled with magnetic nanoparticles and immersed inside the water tank as the phantom. The coil is placed directly 2 mm beneath it. The magnetic field strength at the tube is estimated to be 6 kA/m. The 532 nm Q-switched pulsed laser (1.2 ns pulse width, 1 mJ energy) illuminates the phantom with a spot size of 4 mm radius at a repetition rate of 10 Hz. The light fluence is around 2 mJ/cm^2 and the irradiance is smaller than 20 mW/cm^2 , far below the American National Standards Institute safety standards [33]. A 1 MHz flat ultrasound transducer (Olympus, V303) detects the generated PA signal and feeds it to the pHFC system board, which controls the laser firing and data acquisition. The low quality factor 1 MHz transducer is selected here because the absorber phantom (tube with nanoparticles) is at millimetre size and the light is expanded to an almost 1 cm diameter spot, which generates PA signals majorly falling below 1.5 MHz. The detailed timing sequence for the entire close-loop system is given in Fig. 4.8(c). The magnetic heating dose is controlled by the PWM modulation scheme. The pHFC outputs a 10 Hz sync signal to initiate laser firing and PA signal reception of UST, which updates measured temperature at the rate of sync (10 Hz) and since there are 8 times of signal averaging, the latency is 8 sync periods (0.8 s). This speed is fast enough to capture the transient dynamics of hyperthermia

process, as explained previously. With faster laser that can operate at higher repetition rate, the measurement speed will be shortened correspondingly.

(a) Heating of magnetic nanoparticles

A commercial spherical SPION (3327NG, Skyspring Nanomaterials Inc.) is used for nanoparticle hyperthermia considering it is FDA approved. It has an average particle size of 10-15 nm and a specific saturation magnetization of 43.8 emu/g. The effective relaxation time for SPIONs of this size falls on the order of 1 μ s [38], with the exact value depending on various parameters including the viscosity of ferrofluid. Three different concentrations of SPIONs at 100 mg/ml (SP1), 10 mg/ml (SP2), 1 mg/ml (SP3) are tested, with water (conductivity about 0.02 S/m) used as the reference. SP1 has a calculated number concentration of $\sim 2.1 \times 10^{16}$ /ml and an equilibrium magnetic susceptibility of 4.5×10^{-2} H/m. At heating frequency of 20.1 MHz ($\omega\tau \gg 1$), the heating is saturated according to (3). The SPIONs fluid is poured into the 3 mm diameter tube and a K-type thermometer (± 0.1 degree Celsius accuracy) is inserted directly inside it to monitor the temperature. It should be noted that as human body is mostly water based, water inside the tank can account well thermal diffusions of tissues.

Figure 4.9 Temperature rise of SP1 (100 mg/ml), SP2 (10 mg/ml), SP3 (1mg/ml) and water under hyperthermia heating.

The heating experiment of the SPIONs is conducted by disabling the PWM signal so that the heating is continuous. To avoid thermometer malfunction under RF radiation, the heating is turned off by 5 seconds for temperature reading at interval of 35 s. Meanwhile, the photoacoustic signals during heating are continuously recorded. The 5 seconds disturbance for thermometer reading ceases naturally upon termination of the heating. The thermometer reading results are shown in Fig. 4.9. The temperature initially increases asymptotically toward steady state and then decreases monotonically upon termination of heating. All three SPIONs concentrations deliver consistently larger temperature increase than water: SP1, SP2 and SP3 give respectively 1.9, 1.0 and 0.5 degree Celsius larger temperature increase than water. Two factors limit the achieved heating difference between nanoparticles and background water. The first is heat diffusion, which is more efficient for the small tube phantom (3 mm) used in the experiment. The second is that, at several tens megahertz, substantial non-specific heating of water occurs [54]. By using lower frequencies below 1 MHz, non-specific

heating can be largely circumvented. On the other hand, heat diffusion issue is more challenging to deal with and it is proved in the literature [90] that nanoparticle hyperthermia is more effective for larger cancer lesions.

(b) PA temperature measurement

PA temperature measurements, as described above, are conducted in conjunction with SPIONs heating experiment. One representative PA signal trace for 100 mg/ml magnetic nanoparticle (SP1) and its associated spectrum are shown in Fig. 4.10 (a) and (b) respectively, where the achieved signal to noise ratio is at least 42 dB (126). Assuming a sensitivity S of 5% for the magnetic nanoparticles under room temperature, the theoretical temperature measurement accuracy is at least 0.16 degree Celsius. The corresponding PA signals (peak-to-peak value) for SP1, SP2 and SP3

Figure 4.10 (a) Representative time domain signal, (b) Associated spectrum.

during the heating process are given in Fig. 4.11(a), (b) and (c) respectively. The PA readings show similar behaviour with the thermometer measurements in Fig. 4.9, except that there are periodic saw-tooth like signals on PA readings during heating, as indicated in the insets. This is caused by the periodic operation of 5 seconds heating shutdown in order to acquire thermometer readings, as stated previously. The temperature variations during the 5 seconds are not captured by the thermometers, but

are faithfully recorded by the fast PA measurements, which update the temperature readings at 10 Hz rate with a latency of only 0.8 s. The saw-tooth like signals thus demonstrate the real-time capability of PA temperature measurements.

Figure 4.11 (a) PA amplitude during the magnetic heating experiment for SP1, (b) PA amplitude during the magnetic heating experiment for SP2, (c) PA amplitude during the magnetic heating experiment for SP3, (d) PA for temperature measurement for SP1, (e) PA for temperature measurement for SP2, (f) PA for temperature measurement for SP3.

The linear dependence of PA signals on temperature is demonstrated by relating the PA readings to thermometers measurements. To avoid the discrepancies between PA and thermometer readings caused by the saw-tooth signals, the falling edge (upon termination of heating) of thermometer and corresponding PA signals are utilized. Since thermometer reading is only updated every 35 seconds whereas PA signals continuously update at 10 Hz, thermometer readings in Fig. 4.9 are interpolated before being matched to its PA reading counterparts. The results are given in Fig. 4.11 (d) to (f) for SP1, SP2 and SP3 respectively. It is clearly observed that PA signals show

linear dependence on temperature and indeed, linear regression analysis in all three cases gives R^2 larger than 0.98.

It should be noted that, the inherent slow thermometer response to temperature renders less temperature details and hence hampers the matching accuracies between thermometer reading and PA measurements carried out herein. It is thus anticipated that the true accuracy of PA temperature measurement could be better than presented here. The temperature measurement accuracy achieved for three SPIONs samples is characterized by root mean error (RMS) and maximum deviation between measured data and linear fitting. They are shown as insets in Fig. 4.11(d) to (f). Overall, PA temperature measurement accuracy is smaller than 0.5 degree Celsius for maximum deviation and 0.18 degree Celsius for RMS in these experiments, which agrees well with the theoretically estimated value. The accuracy can be further improved by more times of signal averaging at the expense of larger measurement latency.

(c) Close-loop control

Realistic concentration of 1 mg/ml (SP3) is selected for the close loop control experiments. An open loop experiment is conducted first to calibrate the photoacoustic temperature measurement. In practice, such open loop response measurement needs only be done with a small temperature increase in order to avoid safety concerns. Here, for facilitating direct comparison with ensuing close loop temperature control experiments, the open loop measurement is carried out following the same procedures described above at full 20 W power. Since PA depends on temperature linearly and two points define a linear function, the temperature extraction by PA is achieved by relating the maximum PA amplitude to maximum temperature increase and minimum PA amplitude to minimum temperature increase. The measurement results are shown

in Fig. 4.12(a), with PA readings on the left axis and extracted temperature by PA on the right axis. Similar saw-tooth signals are observed in the PA readings, as expected.

Figure 4.12 (a) Open loop hyperthermia experiment results with SP3. left axis: PA amplitude, right axis: extracted temperature by PA. (b) Close loop experiment with the pre-set temperature increase at 3.6 degree, (c) Close loop experiment with the pre-set temperature increase at 5.0 degree, (d) Close loop experiment with the pre-set temperature increase at 5.8 degree, (e) Close loop experiment with the pre-set temperature increase at 5.8 degree and set two PID parameters, (f) Accuracy analysis results for the close loop control.

To verify the developed theoretical plant model $Q(s)$, its theoretical open loop response is fitted in time domain with the measured results. $Q(s)$ is expressed in time domain as $Q(t) = a(1 - \exp(-bt)) + c$, where c is the introduced residual to account for imperfect calibration between PA signals and thermometer readings. The curve fitting result is shown in Fig. 4.12(a), which gives R^2 over 0.97 and a system time constant τ of 2.3 minutes, far larger than the 0.8 s latency. Thus the developed "dead-time" free plant model fits well with the experiment measurements.

TABLE 4.1 PID CONTROLLER PARAMETERS

<i>Parameter</i>	K_P	t_i (s)	t_d (s)
<i>Set One</i>	400	2	0
<i>Set Two</i>	256	2	0

Close-loop experiments are then conducted to demonstrate the effectiveness of designed controller and two sets of PID parameters (listed in Table 4.1) are implemented with FPGA to verify that PID controller is relatively insensitive to plant parameter variations. Using set one parameters and making the set point temperature $T_r(t)$ to be $3.6u(t)$, $5.0u(t)$, $5.8u(t)$ degree Celsius above the baseline temperature, the corresponding close-loop controlled temperature monitored by PA is shown from Fig. 4.12(b) to (d) respectively. Compared with open loop response, the temperature is tightly controlled to follow the set point temperature upon reaching steady state and no significant temperature overshoots are induced.

When set point temperature is fixed at 5.8 degree Celsius and the PID parameters are changed to set two, the close-loop response changes only slightly, as depicted together with close-loop response of set one PID parameters in Fig. 4.12(e). The steady state value is not affected and the major difference is the slightly smaller settling time for PID controller with set two parameters, which features a smaller gain. A plausible reason is that the set two parameters are closer to optimum PID parameters, which not necessarily requires higher gain. Other combinations have also been simulated, which give similar results

The accuracy of temperature control is analyzed for the four close-loop measurements using data set in steady state spanning from 12 minutes to 16 minutes.

The mean value in this interval is the achieved temperature increase and the standard deviation denotes the accuracy. The results are presented in Fig. 4.12(f), where the red error bar is for set two PID parameters whereas the black one for set one parameters. It is observed that the measured temperature increase follows tightly with the pre-set values and the maximum error is about 0.3 degree Celsius, close to the achieved PA temperature measurement accuracy (0.18 degree Celsius in RMS). Since the PID parameters are determined without knowing plant parameters, the PID controller demonstrated here can accommodate plant parameter variations well.

4.2.3 Discussions

Non-invasive PA temperature measurement demonstrated here provides 0.18 degree monitoring accuracy, high update rate at 10 Hz and a latency of only 0.8 s. Such fast measurement enables the approximately dead-time free plant model and consequently, enables general PID controller that features high proportional gain and small integrator gain to be used for satisfying control without much tuning. Further improvements can be made with advanced PID-based algorithms such as self-tuning regulator [91], which can deliver near-optimum performance without knowing the plant model parameters. Meanwhile, with laser that works at higher repetition rate, the measurement can be accelerated further and by using near infrared wavelength, deep penetration could be attained for *in vivo* applications. However, when employing near infrared wavelengths on magnetic nanoparticles, the SNR of generated PA signals and consequent temperature measurement accuracy could be degraded as the absorption at those wavelengths is several times weaker than that at visible wavelengths. For instance, the magnetic nanoparticles absorption is inferred from [51] to be about 10 times smaller at 1064 nm than that at 532 nm, indicating a proportional 10 times decrease of temperature measurement accuracy (1.8 degree Celsius). Fortunately, near

infrared wavelengths allow larger laser exposure and by using faster laser that enables more averaging in time domain, sub-degree measurement accuracy could still be obtained without sacrificing the measurement speed. Even deeper penetration can be achieved by thermoacoustic imaging that uses microwave [17] - [19] or alternating magnetic field [72] for excitation to probe the temperature. The proposed close loop solution could also be applied to different hyperthermia methods such as RF ablation and photothermal therapy that employing other nanoparticles like carbon nanotubes [61] or gold nanoparticles [93] by adapting accordingly the heating methods.

Prior to comparing with other close-loop temperature control results, it is noted here that the final temperature control accuracy is primarily limited by temperature measurement accuracy rather than by properly designed PID controllers (or any other kinds of controllers) used therein. This is because the processing electrical modules in the controllers are generally so accurate that negligible noises/errors are added to the sensed raw signals. In [82], by measuring the temperature with MRI, a close-loop temperature control accuracy about 1 degree Celsius was achieved for ex-vivo experiments and a 1.5 degree accuracy was obtained for in-vivo applications, both corresponds closely to the MRI temperature measurement accuracy. Similarly in [91], the temperature measurement accuracy was around 1 degree Celsius and the resultant close-loop controlled temperature precision was about 1.5 degree Celsius for in-vivo experiments. By using ultrasound thermometry that could provide temperature measurement accuracy around 0.14 degrees, [98] could stabilize the temperature at a preset temperature with a precision about 0.2 degrees in ex-vivo phantoms. However, due to the low signal to noise ratio of ultrasound thermometry and the fact that it relies on sub-wavelength echo-shift for temperature measurement, which makes it sensitive to physiological movements, it is expected that the in-vivo close-loop temperature

control would be worse. In contrast, photoacoustic temperature had routinely achieved sub-degree temperature measurement accuracy for in-vivo applications and thus making it a strong contender for temperature regulation in practical hyperthermia applications.

There are several challenges to be addressed to bring this work toward practical fruition in clinical settings, which require generally three-dimensional (3D) temperature monitoring and controlling. The first challenge is the need of larger number of ultrasound transducers [94] for fast 3D PA imaging. One promising method is to perform 3D temperature mapping using two dimensional (2D) ultrasound arrays and the development of high density 2D transducer arrays using technologies like capacitive machined ultrasound transducer [95] or piezoelectric machined ultrasound transducer [96] could solve this issue in the future. The second, maybe the most challenging one, is to process huge data rate for 3D imaging. For instance, a 64×64 2D array could lead to 1.5 T bit per second data rate under a digital sampling of 30 MHz with 12 bit accuracy for 1 frame (or volume) per second (fps) 3D imaging. To achieve real-time temperature measurement like 10 fps and to scale up the imaging resolution that dictate higher digital sampling frequency (for instance 100 MHz), the resultant data rate is even higher (45 Tbps). Such high data rate would pose significant challenges not only for data transfer but also for signal processing, which will necessitate parallel processors (like FPGA and GPU), a large trunk of memories and tremendous data bus bandwidth. It is expected that the unceasing development of semiconductor industry will gradually catch up with the computing speed and data transfer requirement. On the other hand, compressive sensing techniques could be exploited for relaxing these stringent requirements. The third but not the least challenge is the hardware and algorithm extensions needed in order to control the

temperature of multiple points or even multiple regions. The simplest solution is to identify the critical region, which could be the hottest spot, and then employ proposed solution to control its temperature. For more sophisticated solutions that involve concurrent controlling of the temperature of multiple points or regions, the system need to adopt phase array coils like in conventional RF ablation [97] to dynamically switch the RF heating focus among those points/regions by electronic steering. Making such switching fast enough but with different weights (duty cycle) for each region, simultaneous but varied heating on multiple regions with focused energy is achievable, like in phased array ultrasound hyperthermia [98].

To conclude, a portable and economical hyperthermia feedback controller (pHFC) has been presented in this paper. With accurate photoacoustic temperature measurement, the PID controller implemented on FPGA is able to tightly stabilize the hyperthermia temperature at pre-set values with an accuracy of 0.3 degree Celsius. Such pHFC solution with photoacoustic or thermoacoustic temperature measurement can potentially fulfil the task for non-invasive and deep penetration temperature control in nanoparticle hyperthermia therapy.

4.3 Photoacoustic guided self temperature regulation of photothermal therapy

The obtained photoacoustic guided close-loop temperature control results for nanoparticle hyperthermia are quite promising. But for other hyperthermia therapy technologies that involves much faster temperature variations like high intensity focused ultrasound (HIFU) ablation and photothermal therapy, where the temperature can increase more than 10 degrees within one second, the 0.8 second temporal

resolution achieved in previous section is not sufficiently fast. Considering that the speed is majorly determined by the available laser pulse repetition rate, scaling up the repetition rate is necessary in order to obtain faster temperature measurement. However, there is a limit for using higher repetition rate as it is restricted by safety regulation of laser radiation and also the availability of such laser sources.

An alternative method is to use low power continuous wave laser for photoacoustic temperature sensing. Both Wang [99] and Andreas Mandelis [100] had done comprehensive comparisons of the pulsed photoacoustic technique using high power pulsed laser and frequency domain photoacoustic imaging using low power continuous wave laser. It was well recognized that the lower signal to noise ratio of using low power laser source for photoacoustic imaging could be largely rectified by frequency domain method. Therefore, for some applications, it is appealing to adopt continuous wave laser for photoacoustic imaging and sensing. One such application is to regulate photothermal therapy by a close-loop temperature control technique guided by photoacoustic temperature monitoring. Previous photothermal systems that integrate photoacoustic temperature measurement utilize two different laser sources [32], [101], in which a pulsed laser is employed for temperature monitoring whereas the other continuous laser is used for photothermal heating. Such solution increases the system size, cost and suffers from the slow temperature measurement of pulsed lasers. Also, using a single laser for both heating and photoacoustic temperature sensing appeals in enabling a minimal self-regulated photothermal system once close loop control techniques [102] are incorporated. It may benefit recent innovations that exploit temperature dependence of photoacoustic phenomenon as well like Grueneisen relaxation photoacoustic microscopy [103] and photoacoustic assisted wavefront shaping [104].

4.3.1 System design

Figure 4.13 (a) Illustration on photoacoustic guided self-regulation of photothermal system; (b) Operation timing of the laser diode; (c) Conceived implementation with a AOM. LD: laser diode, OBJ: objective, TR: transducer, LNA: low noise amplifier. FG: function generator, Osc: oscilloscope, AOM: acousto-optic modulator.

The system of a single laser based photothermal system with built-in fast photoacoustic sensing capability is illustrated in Fig. 4.13(a). The laser diode is driven by a customized Howland current source [105], where the current pumping the diode I is made to be related to the control voltage V_{in} by $I = V_{in}$. The laser output power E is related to the pump current by

$$E = \psi V_d (I - I_{th}) \quad (4.20)$$

where η is the electrical-to-optical power conversion efficiency of the laser diode, I_{th} is the laser threshold current and V_d is the operation voltage, which is roughly a constant. With proper air forced cooling, the laser diode is able to work continuously under a DC pump current for photothermal heating without undergoing any self thermal degradation. The driver allows both digital and analog modulation on the input voltage V_{in} at a frequency up to 20 MHz, enabling the laser diode output power to be modulated correspondingly with an efficiency close to 100% according to equation (4.20). This facilitates the incorporation of photoacoustic excitation sequences, as depicted in Fig. 4.13(b). Upon triggering, the DC heating voltage is terminated temporarily and a linear chirp signal is generated instead, which prompts the laser to work in PA temperature measurement mode. As proved in [102], the short disturbances in heating will affect the sample temperature negligibly for most applications. Using the frequency domain photoacoustic method [106], the time domain PA pressure could be related to local temperature T as

$$P_0(t) = \eta\mu_a(A + BT)F_0 \sin(\omega_0 t + \frac{\omega_1 - \omega_0}{2t_c} t^2) \quad (4.21)$$

where A and B are material specific constants, μ_a is the absorption coefficient, F_0 is the optical fluence and η is a constant accounting for the thermal diffusion effects and the conversion efficiency of absorbed energy into heat. t_c is the chirp duration and ω_0 and ω_1 are respectively the start and end frequency of the chirp signal. The cross correlation between the reference chirp signal and detected PA signal is thence

$$S(t) = \frac{k(A + BT)t_c^2}{2\pi m(t - \tau)} \sin\left(\frac{\pi m(t - \tau)}{t_c} \left(1 - \frac{(t - \tau)}{t_c}\right)\right) \times \cos(\omega_a(t - \tau)) \quad (4.22)$$

where k is a constant, $\omega_a = (\omega_0 + \omega_1)/2$ is the center frequency of the chirp signal. $\omega_a = (\omega_1 - \omega_0)t_c$ is the time-bandwidth product and τ is the time delay between the reference signal and detected PA signal. Based on equation (4.22), the peak to peak value of correlation could be calibrated for absolute temperature measurement. The signal to noise ratio (SNR) improvement by this coherent detection method is $\sqrt{m/2\pi}$ and the correlation results are further averaged across N measurements for better accuracy as indicated in Fig. 4.13(b).

Figure 4.14 Software implementation of the control system. GUI: graphical user interface.. BPF: bandpass filter; S-EMI: suppress EMI pulse; Sync: synchronization; GPIO: general purpose input-output.

Self temperature regulation is achieved with a PID controller implemented with a computer software, which is shown in Fig. 4.14. A software approach would facilitate more user friendly interface and enable timely intervention for changing the settings, besides the flexibility of future updates and adding more functionalities. After initialization that establishes connection with the oscilloscope and a customized USB

to GPIO adaptor, the graphical user interface (see a snapshot in Fig. 4.15) is created to enable user interaction and real time results rendering. It allows open loop test to calibrate the thermoacoustic temperature measurement and enables the user to fill in desired temperature for close loop control. The PID coefficients could be dynamically changed during running time to facilitate user intervention. By using the automation interface of the oscilloscope, the acquired signal is streamed into the software, which is then averaged to improve signal to noise ratio. After that, the signal is further filtered by a 4-th order Butterworth bandpass filter to eliminate out of band noise. The TA signal is then retrieved from the filtered signal by correlating with the reference linear chirp signal, which is stored in memory. The temperature calculation module extracts the amplitude of the correlation results and computes the temperature based on open-loop calibration results.

Figure 4.15 A snapshot of the control software. It allows the user to update the PID coefficients and check the results in real time.

The PID controller read the temperature, calculates the error signal and produces correspondingly the control signal for regulating the hyperthermia heating power. The "sync" signal is responsible to initiate one time photoacoustic temperature probing. The "S-EMI" is not necessary but it can be used to turn off the hyperthermia heating for 50 μ s to suppress direct electromagnetic interferences that may contaminate the signal. The pulse width modulation (PWM) module encodes the control signal into a bit stream that enables purely digital implementation. The PWM control mechanism has one extra advantage: it can guarantee that the maxim heating power will not surpass a user specified value. To see this, assume the maximum heating power of the system (restricted by safety standards) is set at W and the PWM duty cycle D could swing from 0 to 100%. Then the linear control of the PWM would only allow the heating power to swing from 0 to W . Other method like amplitude modulation could produce extremely large control values that make the hyperthermia power go beyond W for a while. PWM is simpler to implement as it only involves switching operations. This will be particularly useful when acousto-optic modulator (AOM) is employed to incorporate PA temperature probing into an existing photothermal system that uses CW laser. The conceived design for such a system is shown in Fig. 4.13(c). With laser power being constant, the modulated part of AOM is used for PA temperature measurement whereas the un-modulated part, at the control of a motor, could be directed onto or off the sample for photothermal heating according to the PWM signal.

4.3.2 Experimental results

The major advantage of continuous wave laser solution is that it is capable of performing fast temperature measurement and allows a greater degree of freedom in making tradeoffs between measurement speed and accuracy. Enabled by this, close-

loop temperature control accuracy and speed could also be scaled for different application scenarios.

4.3.2.1 Ultrafast and accurate temperature measurement

The experimental setup in Fig. 4.13(a) was built to characterize the self-temperature regulation performance. of the proposed system. The laser (405nm, maximum power up to 1 W) is focused by a microscope objective lens (NA: 0.4) to illuminate the sample (a black wire with diameter of 2 mm owing to its strong absorption at 405 nm) with a spot size of 1 mm radius. The irradiance in the heating mode is made to be approximately 9600 mW/cm^2 to mimic photothermal treatment of tumour using gold nanoparticles [107]. This irradiance is similar to the irradiances in [107] -[108] that employed CW laser for effective photothermal heating. In PA temperature probing mode, the linear chirp signal sweeps from 0.5 MHz to 1.5 MHz within 40 μs . A flat ultrasound transducer with center frequency of 1 MHz (Olympus, V303) detects the PA waves and the resultant signal is amplified by 54 dB with a low noise amplifier. Then the signal is fed to the oscilloscope (Waverunner 6Zi, Lecroy) and averaged by $N = 64$ times. Consequently, the total SNR improvement is $\sqrt{m/2\pi} = 34\text{dB}$.

Figure 4.16 (a): PA temperature measurement calibration using a thermometer. (b)~(e): PA temperature measurement of various modulated heating functions; (b): top-hat function, (c): square wave, (d): sinusoidal wave, (e): ramp wave.

The PA temperature measurement is calibrated using a K-type thermocouple (0.1 $^{\circ}\text{C}$ accuracy). Briefly, the temperature variation during hot water cooling is recorded by the thermocouple and PA thermometry simultaneously. Through relating the PA amplitudes to thermocouple temperature readings, the PA thermometry is calibrated for absolute temperature measurement by linear extrapolation. The result is shown in Fig. 4.16(a). The PA measurement follows tightly with the thermocouple readings: a

linear fitting analysis reveals a R^2 around 0.91 and the temperature measurement accuracy is 0.75 degree Celsius.

Temperature calibration was not done using photothermal heating because thermocouples with a response time around 1 to 2 seconds is not capable of tracking the fast temperature transients induced by rapid photothermal heating. One advantage of the proposed continuous wave laser solution is the achievable ultrafast temperature measurement. To demonstrate this, the calibrated PA thermometry was used to monitor the fast temperature transients under various photothermal heating excitations: top-hat function, square wave, sinusoidal wave and ramp wave. Except the top-hat function, the other three waves all contain three cycles and have a frequency of 4 Hz. The repetition rate for the PA measurement is set at 4 kHz. Such fast measurement could only be done by making the oscilloscope to work in segment mode. Since the peak irradiance of PA measurement is fixed at 9600 mW/cm^2 , the resultant average irradiances is 1536 mW/cm^2 . The temperature probing results are shown in Fig. 4.16 (b) to (e) respectively, where PA signals are averaged 200 times instead. In all cases, the temperature follows approximately the modulation function and due to heat accumulation, the temperature gets increasingly larger across the three cycles of heating. For top-hat and square wave modulation, the temperature renders a classic exponential characteristic upon the edges. The maximum temperature increase in top-hat function modulation is 43 degrees, which is comparable to that in [108] but smaller than that in photothermal heating using gold nanoparticles [107]. This is because nanoparticles has a much larger absorbing coefficient than the black wire owing to its plasmonic resonance absorption mechanism.

4.3.2.2 Self-regulation photothermal heating

The self-temperature regulation of this system is demonstrated preliminarily using the same black wire since the temperature calibration was done for it. Owing to limited data transfer bandwidth, the achievable PA temperature measurement speed in this case is 20 Hz. Consequently, the PA firing repetition rate is made to be 20 Hz, resulting in an average irradiance of 7.68 mW/cm^2 , satisfying therefore the ANSI safety standards ($<200 \text{ mW/cm}^2$) [33]. For direct comparison, an open loop test is conducted first under photothermal heating with an irradiances of 9600 mW/cm^2 .

Figure 4.17 (a), (b) and (c): self-temperature regulation with closed loop pre-set values at 29, 44, and 56 degree Celsius respectively. Solid black: open loop test temperature results, virtual blue: closed loop results; (d): temperature regulation accuracy analysis result; (e) to (f): closed

loop temperature regulation with sudden change of pre-set values; (e) pre-set value change from 62 to 36 degrees; (f): pre-set value change from 39 to 58 degrees.

Subsequently, close loop tests are conducted at three pre-set temperatures: 29, 44 and 56 degree Celsius. The result is shown in Fig. 4.17(a) to (c), where the open loop result is compared with closed loop results in each figure. It is observed that in open loop test, the temperature increases rapidly upon the initiation of heating and reaches gradually to the steady state value of 68 degrees within 50 seconds. In contrast, for closed loop results, the temperature after reaching the steady state are all stabilized at the pre-set values and no significant temperature overshoots are induced during this process. The accuracy of the temperature regulation is characterized by the steady state temperature variations during the time interval spanning from 55 to 65 seconds. The corresponding mean values, on the other hand, are used to estimate the achieved photothermal temperature inside the probed region. Theoretically, the achievable temperature control precision should be not-better than the obtained temperature measurement accuracy: any error in temperature measurement will lead to an error in controller output for subsequent heating and thus, an error in the final regulated temperature. This is corroborated by the results in Fig. 4.17(d): the temperature regulation precision is 0.9 degree Celsius, worse than the achieved 0.75 degree Celsius temperature measurement accuracy. Therefore, the bottleneck towards a tighter temperature regulation lies in an improved temperature measurement accuracy, which in turn relies on an enhanced SNR of the PA signal.

The capability of the controller to track sudden changes in the pre-set temperature is also tested under two scenarios. In the first scenario, the desired temperature is modified to a larger value after the temperature was stabilized at a previous pre-set temperature; in the second scenario, the target temperature is changed to a smaller

value. The results are shown in Fig. 4.17(e) and (f) for the two cases respectively. In both cases, the steady state temperature was correctly stabilized onto the new pre-set values and no extreme temperature transients are induced in this process. Hence, the temperature regulation allows timely user interventions for changing the parameters if needed.

4.3.2.3 Nonlinear photoacoustic phenomenon

One more interesting aspect of CW ultrafast PA temperature measurement is the capability to achieve nonlinear amplification of PA signals. When conducted at high duty cycles, there will be appreciable heat residue of previous PA measurements, which will amplify subsequent PA signal [103]. To verify this, the chirp duration is extended to 80 μ s with other parameters remaining unchanged. The repetition rate for the PA measurement is set to various frequencies: 100 Hz, 1 kHz, 3 kHz, 6 kHz and 9 kHz, translating to duty cycles (chirp duration $\times$ repetition rate) of 0.8%, 8%, 24%, 48% and 72% respectively.

Figure 4.18 PA amplitude variation at various repetition rate.

Owing to the low duty cycle associated with 100 Hz repetition rate, the resultant PA signals are regarded as free from heat accumulation and hence free from nonlinear amplifications. It then functions as the baseline for comparing with PA measurements

at other repetition rates. The experiments were done by monitoring the PA signal's evolution over time when the repetition rate was firstly set at 100 Hz and then switched to other values. The change of repetition rate is indicated by the virtual line in Fig. 4.18 with the arrows indicating the time instant of switching. It is observed that for duty cycles at 0.8% (100 Hz) and 8% (1 kHz), the nonlinear amplification is negligible since the PA amplitudes therein are almost the same. Yet, after switching the repetition rate from 100 Hz to 9 kHz, the PA signal gets larger over time until reaching steady state, where the PA signal is about 25% higher and thus indicates effective nonlinear amplifications. Further, when repetition rates are switched downwards to 6 kHz and 3 kHz, the nonlinear amplification become correspondingly smaller but still quite obvious because the steady state PA signals at these repetition rates are roughly 14% and 8% larger than those at 100 Hz respectively. Hence, a single laser that performs the ultrafast PA measurement at high duty cycles could enable nonlinear photoacoustic amplification, which is the foundation of several recent innovations like Grueneisen relaxation photoacoustic microscopy [103].

4.3.3 Discussions

Currently, the linear chirp signal lasts only 40 μ s for PA guided self temperature regulation. As a result, it provides a moderate improvement on the SNR. However, the time duration is not a hard limit. The major criteria for selecting the chirp signal duration is two-folds. The first is the capability of using the same laser for photothermal heating. Essentially, the PA temperature measurement mode should only occupy a small duty cycle of laser operation since photothermal heating need much more energy and thus most of the laser operation time. The second is the required temperature monitoring speed and accuracy. With a fixed duty cycle for PA temperature measurement, using longer chirp signal will improve the SNR but reduce

the measurement speed correspondingly. Hence, a tradeoff between temperature measurement speed and accuracy is needed. Also, an important improvement needed for the system is to incorporate two dimensional (2D) measurement of temperature distribution, which is of more practical usage. This could be achieved in the near future either by using linear array probe available in conventional ultrasound imaging platforms or by building customized PA tomography systems.

Ultrafast temperature measurement by using continuous wave laser diode enables ultimately a single laser diode based self-regulated photothermal system. Such fast PA temperature measurement can be beneficial for tracking fast temperature transients in other applications like high intensity focused ultrasound (HIFU) hyperthermia therapy and the temperature regulation method could be adapted to control therapy temperature therein. Also, the nonlinear photoacoustic generation is achieved which can be useful for quite a few recent innovations. One last note is that, the system presented here could be extended easily into a self-regulated nanoparticle hyperthermia therapy and the developed software framework is general in being independent on the specific thermoacoustic temperature measurement method.

4.4 Summary

Thermoacoustic technique, using either light (photoacoustic) or magnetic field (MMTI), is studied thoroughly in this chapter for accurate, non-invasive temperature measurement and for enabling tight close-loop temperature control of various hyperthermia therapy applications. It was found that by proper signal processing, MMTI could achieve sub-degree temperature monitoring for magnetic nanoparticle hyperthermia but for real applications, either higher power need be used in MMTI or frequency domain MMTI solution will be required. Quite differently, pulsed photoacoustics was able to obtain very accurate (0.18 degrees) temperature monitoring

and control (0.3) thanks to its superior signal to noise ratio. Yet, it suffers from relatively slow temperature measurement due to limited repetition rate of pulse laser, which impedes its applications in some applications that involves rapid temperature variations. To its remedy, we further developed a single laser diode based self-regulated photothermal system, where frequency domain photoacoustic solution is adopted for ultrafast and accurate temperature monitoring. This system is not necessarily for photothermal therapy: it could also be utilized for pure temperature probing and as proved in this chapter, for other applications that depends on nonlinear photoacoustic signal generation like Grueneisen relaxation photoacoustic microscopy.

Further challenges to extend the research work into clinical settings lie in firstly calibration free absolute temperature measurement. Though calibrations could be one in ex-vivo, eliminating calibrations will provide better accuracy since tissues may show different behaviours between ex-vivo and in-vivo environments. The second is to achieve real time 3 dimensional temperature imaging, which may be addressed by using 2 dimensional ultrasound transducer array that are currently under development. We expect that 3D temperature mapping will be achieved in the near future.

Chapter 5. THERMOACOUSTIC AND MAGNETO-ACOUSTIC WAVES: UNIFICATION AND NONLINEAR MIXING

The integration of magnetically mediated thermoacoustic imaging (MMTI) with nanoparticle hyperthermia had met preliminary success: in chapter 4, the alternating magnetic field was used both for MMTI and nanoparticle hyperthermia by interleaving these two processes in time domain. Yet, alternating magnetic field had also been utilized in another multi-wave imaging method: magneto-acoustic imaging. The striking similarity of the system setup and physical quantities (AMF, ultrasound wave, conductivity, etc.) should make it natural to consider together magneto-acoustic imaging and MMTI. This chapter is dedicated to this issue and consider in greater depth the implications of unifying these two waves for imaging and sensing applications.

5.1 Magneto-acoustic imaging

One reason that thermoacoustic imaging and magnetoacoustic imaging by magnetic induction (MAT-MI) [11] - [13] are investigated separately is their distinctive physical mechanisms and electrical excitations. MAT-MI employs excitation frequencies at mega Hertz range and the resultant magneto-acoustic waves follow the carrier frequency. On the other hand, MI-TAI uses pulse modulated microwave frequencies and the generated TA waves are roughly determined by the pulse envelop. The microwave frequencies employed in MI-TAI are impossible to be used for MAT-MI because the resultant MA waves at microwave frequencies will decay too rapidly. However, the difference in excitation frequencies is eliminated between MMTI and MAT-MI. To see this, the physical process of MAT-MI need be explained.

MAT-MI maps the conductivity of a object at the resolution of ultrasonography. As shown in Fig. 5.1, by applying a large transient pulsed current (mono-pulse signal) at MHz range in coils, eddy current is induced non-invasively within the conductive object. Under a static magnetic field (B_0), the eddy current endures a dynamic Lorentz force, which vibrate the tissue and ultimately generates ultrasonic waves. The conductivity information of tissue is encoded in eddy current and is thereby sensed via ultrasonic waves.

Figure 5.1 Schematic for MAT-MI. B_0 is the static magnetic field and B_1 is the alternating magnetic field generated by the coil.

Both phantom studies and ex-vivo experiments of MAT-MI have been reported in the literature [11] - [13]. Good conductivity contrast image have been demonstrated and a resolution around 1 mm is achieved. Magneto-acoustic signal will follow the carrier of the excitation signal. A qualitative explanation is that, the acoustic signal will follow the frequency of Lorentz force because it is essentially the result of a forced vibration induced by the latter. Since the Lorentz force is proportional to the generated eddy current that oscillates at the carrier of the excitation signal, the emitted acoustic signal will follow the carrier signal. One point worth noting is that utilizing a burst of quasi-continuous high frequency signals for excitation can provide higher

resolution and enable low power implementation through coded excitation methodology [109]. The employment of quasi-continuous high frequency signals for excitation in magneto-acoustic imaging is important as this will make easier to be integrated with magnetically mediated thermoacoustic imaging.

5.2 Unification of magneto-acoustic wave and thermoacoustic wave

The unification of TA and MA is illustrated in Fig. 5.2(a). The material is subjected to a pulsed low frequency magnetic field irradiation of a coil, which creates an oscillating electric field $\vec{E}(\vec{r}', t)$ inside it, where r' denotes the position inside the material. Assume the material has a conductivity distribution of $\sigma(\vec{r}')$, then according to Ohm's law, a conductive current $\vec{J}(\vec{r}', t) = \sigma(\vec{r}') \vec{E}(\vec{r}', t)$ is induced within the material, which leads to joule heating. The heating function, defined as absorbed energy per unit time and per unit volume, is calculated as $H(\vec{r}', t) = \langle \vec{J}(\vec{r}', t) \vec{E}^*(\vec{r}', t) \rangle = \langle \sigma(\vec{r}') |\vec{E}|^2 \rangle$, where asterisk denotes complex conjugate, operator $\langle \rangle$ and $||$ represent short time average and absolute value respectively. The Joule heating perturbs the thermodynamic equilibrium of the material and leads to TA wave emission

$$\nabla^2 p_t(\vec{r}, t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p_t(\vec{r}, t) = -\frac{\beta}{C_p} \frac{\partial}{\partial t} H(\vec{r}, t), \quad (5.1)$$

where $p_t(\vec{r}, t)$, c , β , C_p represent the TA pressure, the speed of sound of the medium, the isobaric volume expansion coefficient and the specific heat capacity of the material, respectively. In Eq. (5.1), heat diffusion is neglected because the thermal confinement [110] needs be satisfied for efficient TA signal generation, which dictates

the incident excitation signal to be as short as several microseconds so that the heat diffuse negligibly to surrounding matter.

Figure 5.2 (a) Reuse of current generated by MI-TAI for MAI-TI, AMF: alternating magnetic field, US: ultrasound; (b) Simulation on the waveform of superimposed wave of TA and MA (first-order mixing). Above: excitation pulse, below: resultant ultrasound signal.

To integrate the MAT-MI, the conduction current $\overrightarrow{J}(\vec{r}', t) = \sigma(\vec{r}') \overrightarrow{E}(\vec{r}', t)$ is reused by adding a static magnet that emanates a static magnetic field $B_0(\vec{r}')$ perpendicular to it. It is noted that the thermoacoustic process does not rely on the static magnetic field. Whereas for the MAT-MI, static magnetic field is an indispensable ingredient: it is due to the Lorentz force mechanism described as $F_L = qv \times B_0$ in the microscopic level, where q is the electric charge and v is the charge velocity. Hence, in MAT-MI, there is a direct coupling between the magnetic field and the electric charges owing to the Lorentz force mechanism. Macroscopically, the electric charge movements form the conduction current $\overrightarrow{J}(\vec{r}', t) = \rho(\vec{r}')v(t) = \sigma(\vec{r}') \overrightarrow{E}(\vec{r}', t)$, in which $\rho(\vec{r}')$ is the charge density. Consequently, under the static magnetic field, Lorentz force $\overrightarrow{F}(\vec{r}', t) = \sigma(\vec{r}') \overrightarrow{E}(\vec{r}', t) \times B_0(\vec{r}')$ is exerted on the conduction current flowing in the

material, which vibrates the material and consequently emits MA waves. The alternating magnetic field generated by the coil is neglected in Lorentz force calculation because the static magnetic field is about two orders of magnitude stronger than the alternating magnetic field. To account for the complex geometries of both the conduction current and the static magnetic field, the Lorentz force could be written in tensor form as:

$$\overrightarrow{F_i(\vec{r}', t)} = \sigma(\vec{r}') \overrightarrow{E_j(\vec{r}', t)} \times \overrightarrow{B_{0k}(\vec{r}')} \quad (5.2)$$

where subscript i, j, k indicate the three directions (Fig. 5.2(a)) in space. With Lorentz force exerted on the material, both longitudinal wave and shear wave will be generated. For the generated longitudinal MA wave, it is governed by the wave equation:

$$\nabla^2 p_{mi}(\vec{r}, t) - \frac{1}{c^2} \frac{\partial^2}{\partial t^2} p_{mi}(\vec{r}, t) = \nabla \bullet (\sigma(\vec{r}') \overrightarrow{E_j(\vec{r}', t)} \times \overrightarrow{B_{0k}(\vec{r}')}). \quad (5.3)$$

in which, $p_{mi}(\vec{r}, t)$ denotes the MA wave pressure generated by the Lorentz force in the i -th direction. Shear waves have different propagation speeds and differ from longitudinal waves in that their propagation directions are perpendicular to the Lorentz force direction. Thus, the shear wave equation is slightly different from (5.3):

$$\nabla^2 p_{si}(\vec{r}, t) - \frac{1}{c_s^2} \frac{\partial^2}{\partial t^2} p_{si}(\vec{r}, t) = \nabla \bullet (\sigma(\vec{r}') \overrightarrow{E_j(\vec{r}', t)} \times \overrightarrow{B_{0i}(\vec{r}')}). \quad (5.4)$$

where $p_s(\vec{r}, t)$ and c_s represent the generated pressure and sound speed of shear waves in the medium respectively. As will be illustrated shortly, both the longitudinal MA wave and the shear wave will be at the carrier frequency of the incident electromagnetic field, which is normally at mega Hertz frequency range. Such shear wave at MHz frequencies suffers from severe attenuation inside soft biological tissues

and thus will only exist inside a very small volume around the source [2]. Additionally, the far slower propagation speed (<20 m/s) of shear waves implies that they will be truncated when the received signals of transducers are time-gated to certain time period. These two factors dictate that the shear waves will not affect the received longitudinal TA or MA signals. Hence, they will not be considered hereafter. On the other hand, the complex geometry of Lorentz force could be reduced from two aspects for future applications in clinical settings. In the first place, a homogeneous static magnetic field similar to that in MRI system will be applied so that it is predominately in the k-th direction. Secondly, Helmholtz coils could be used to produce a homogenous alternating magnetic field for excitation in the region of interest. By doing so, the Lorentz force is majorly confined to the radial direction that produces longitudinal MA wave efficiently. To simplify the following discussions, the MA waves are approximated by the dominant components in the radial direction:

$$p_m(\vec{r}, t) = \sum_i p_{mi}(\vec{r}, t) \approx p_{mi}(\vec{r}, t) + p_{mj}(\vec{r}, t) \quad (5.5)$$

Therefore, by adding a static magnetic field under the magnetically mediated thermoacoustic setup, both TA and MA waves are generated simultaneously by the same electromagnetic excitation. The resultant acoustic wave is the superimposition of the two waves:

$$p(\vec{r}, t) = p_t(\vec{r}, t) + p_m(\vec{r}, t). \quad (5.6)$$

The temporal characteristic of generated TA and MA waves could be revealed by decomposing incident electric field as $\vec{E}(\vec{r}', t) = \vec{G}(\vec{r}')f(t)$ with $\vec{G}(\vec{r}')$ representing its spatial distribution and $f(t)$ denoting its temporal function. Then, the heating

function is $H(\vec{r}', t) = \sigma(\vec{r}') \left| \overline{G(\vec{r}')} \right|^2 M(t)$, in which $M(t) = \langle |f(t)|^2 \rangle$. It can be proved that $M(t)$ is the envelop of $f(t)$. Solving the wave Eq. 5.1 and 5.3 with Green function's method [4, 7], the TA wave $p_t(\vec{r}, t)$ and MA wave $p_m(\vec{r}, t)$ are derived to be:

$$p_t(\vec{r}, t) = \frac{\beta}{4\pi C_p} \frac{dM(t)}{dt} \iiint \frac{d^3 \vec{r}'}{|\vec{r} - \vec{r}'|} \sigma(\vec{r}') \left| \overline{G(\vec{r}')} \right|^2 \Big|_{t' = t - \frac{|\vec{r} - \vec{r}'|}{c}}, \quad (5.7)$$

$$p_m(\vec{r}, t) = \frac{f(t)}{4\pi} \iiint \frac{\nabla \bullet [\sigma(\vec{r}') B_0(\vec{r}') \overline{G(\vec{r}')}]}{|\vec{r} - \vec{r}'|} d\vec{r}' \Big|_{t' = t - \frac{|\vec{r} - \vec{r}'|}{c}}, \quad (5.8)$$

where $\vec{r}'$ indicates the position inside source and $\vec{r}$ represents the location of receiving transducers. It is noted that TA wave (from Eq. 7) follows approximately the derivative of $M(t)$ whereas MA wave (from Eq. 8) follows the carrier of $f(t)$. Thus, MA is essentially a forced vibration phenomenon. This also holds true for generated shear waves, which have similar wave equation solution with MA waves.

Because TA and MA waves stem from the same conduction current within the material, they overlap inherently in both spatial and time domain. Such linear superposition of TA and MA waves is simulated in MATLAB based on Eq. (5.6) to (5.8) for a point source. The result is then equivalent to the system's spatial impulse response. General sources with complex geometry can be accounted for by two dimensional convolution of the source geometry function with the spatial impulse response. The simulation uses a Gaussian modulated pulse (top of Fig. 5.2(b)) that contains 12 cycles carrier signal. The resultant acoustic signal induced by the pulsed excitation (bottom of Fig. 5.2(b)) shows a high frequency MA signal riding on the low

frequency TA signal, conforming to the theoretical temporal behaviour of TA and MA waves described above.

5.3 Nonlinear mixing of magneto-acoustic wave and thermoacoustic wave

When the superimposed TA and MA waves get absorbed or scattered by objects in the medium during propagation, acoustic radiation force is generated that exert on the absorber or scatterers [111]. For absorbers with an acoustic absorption coefficient of α , the resultant radiation force is: $F_r = \alpha S \langle E \rangle$, where S is the intersection area of the absorber with the ultrasound beam and $\langle E \rangle$ represents the time averaged acoustic energy density. For the superimposed TA and MA waves, the acoustic radiation force is:

$$F_r = \frac{\alpha S}{\rho c^2} \langle p^2 \rangle = \frac{\alpha S}{\rho c^2} \langle (p_t + p_m)^2 \rangle = \frac{\alpha S}{\rho c^2} \langle p_m^2 + p_t^2 + 2p_m p_t \rangle, \quad (5.9)$$

As TA and MA waves falling at distinct frequency bands, the nonlinear square operation in Eq. (5.9) generates not only harmonic frequencies of MA and TA waves but also inter-modulation frequencies between MA and TA waves. To elaborate this, consider that TA and MA signal are $p_t(r, t) = A \cos(\omega_1 t + \theta_t)$ and $p_m(r, t) = B \cos(\omega_2 t + \theta_m)$ respectively, then:

$$\begin{aligned} [p_t(r, t) + p_m(r, t)]^2 &= \frac{A^2}{2} + \frac{A}{2} \cos(2\omega_1 t + 2\theta_t) + \frac{B^2}{2} + \frac{B}{2} \cos(2\omega_2 t + 2\theta_m) \\ &+ AB \cos((\omega_1 - \omega_2)t + \theta_t - \theta_m) + AB \cos((\omega_1 + \omega_2)t + \theta_t + \theta_m). \end{aligned} \quad (5.10)$$

New frequency components created by the square operation are summarized below:

DC term:

$$\frac{A^2}{2} + \frac{B^2}{2};$$

Second harmonics:

$$\frac{A}{2} \cos(2\omega_1 t + 2\theta_1), \frac{B}{2} \cos(2\omega_2 t + 2\theta_2);$$

Mixing frequency components:

$$AB \cos((\omega_1 - \omega_2)t + \theta_1 - \theta_2), AB \cos((\omega_1 + \omega_2)t + \theta_1 + \theta_2);$$

With the time average operator in Eq. (5.9) that filters out high frequency components at second harmonic of the MA waves, the resultant radiation force contains frequency components at the sum frequency $(\omega_1 + \omega_2)$ and difference $(\omega_1 - \omega_2)$ frequency of the TA and MA waves. When the absorber or scatterer is enforced by such a dynamic radiation force F_r at frequency ω_0 (i.e. $\omega_0 = (\omega_1 + \omega_2)$ or $\omega_0 = (\omega_1 - \omega_2)$), it vibrates accordingly and gives rise to acoustic emission at frequency ω_0 . This radiation force induced acoustic emission works in a similar manner as a forced vibrating piston: when a circular piston of radius b was hit by radiation force F_r , the induced acoustic emission is described by Eq. (11), which is given in [111]

$$P_{\omega_0} = -j\omega_0 \rho \frac{\exp(j\omega_0 l / c)}{4\pi l} \times \left\{ \frac{2J_1[(\omega_0 b / c) \sin \theta]}{\omega_0 b / c \times \sin \theta} \times \frac{\cos \theta}{\cos \theta + \beta_B} \right\} (2\pi b^2 F_r / Z), \quad (5.11)$$

where $J_1(\cdot)$ is the first-order Bessel function of the first kind, l is the distance from observation point to the piston, θ is the angle between the line and the piston axis, β_B is the specific acoustic admittance of the boundary surface and Z is the mechanical impedance of the piston. Therefore, the superimposed TA and MA waves generate radiation force that is exerted on the absorber or scatterer at frequencies of $(\omega_1 - \omega_2)$

and $(\omega_1 + \omega_2)$, which then yield corresponding acoustic emissions at the same frequencies. These newly produced acoustic components could be detected by a sensitive ultrasound transducer and show up in the received signal's spectrum as the mixing components of the TA and MA waves.

5.4 Experimental verifications of nonlinear mixing

Figure 5.3 Setup for Mixing of TA and MA. (a) Setup using coil-one; (b) Setup using three set of immersive coils at 2.0 MHz, 3.5 MHz and 5.4 MHz. FG: function generator, PA: power amplifier, TR: transducer, Osc: oscilloscope, LNA: low noise amplifier, MAG: magnet.

The experimental system setup for demonstrating the mixing phenomenon is shown in Fig. 5.3. Water is used as coupling agent as well as absorbing medium here. A function generator (Tektronix, AFG3252) produces radio frequency signals at 100 Hz repetition rate and feeds to the RF pulse amplifier (BT01000-AlphaSA-CW, Tomcorf). The ultrasound transducer detects the ultrasound signal and its output is amplified by a low noise amplifier (Olympus, 5672R) with 54 dB. The signal is then sampled and averaged by a oscilloscope (Waverunner 6Zi, Lecroy), and is finally stored in an mass storage device before being transferred to MATLAB 2010b on a PC for offline processing. Fig. 5.3(a) depicts the setup that uses the coils to excite the phantom from

outside the water tank. The static magnet (30 mm diameter, 2 mm height, 0.3 T magnetic field at the superficial center) is placed directly above the coil and the phantom is immersed in the water tank. The phantom is placed 3 mm above coil and 1 mm above the magnet. The excitation coil is networked with capacitors ($C_1=11$ pF and $C_2=22$ pF) to maximize the current delivered to it and the resonance frequency of the resultant coil networks is 5 MHz.

To validate the concurrent generation of TA and MA waves, a coil denoted as 'coil-one' is driven at 250 W and excites a conductive phantom (an aluminium loop with a diameter of 30 mm) from outside the water tank. This simulates the real applications in which the coil excites conductive matter like human body non-invasively. Coil-one has 11 turns and a diameter of 65 mm. Networked with capacitors, it shows a resonance frequency of 5 MHz and an associated quality factor around 20. The immersed phantom is 3 mm above coil-one and is 1 mm from the magnet. The simultaneously generated TA and MA signals are collected by two ultrasound transducers in order to achieve detection with better signal to noise ratio. First, the MA signals are received by a focused ultrasound transducer placed around 5 cm away from the phantom. The transducer (Doppler, V320, China) has a center frequency of 5 MHz and focal length of 50 mm. Then, a flat ultrasound transducer (Olympus, V303) with center frequency of 1 MHz is used to collect the TA signals. The TA signal is bandpassed in MATLAB by a fourth order Butterworth filter with cutoff frequencies at 0.2 MHz and 2 MHz respectively. Similarly, the MA signal is bandpassed by a fourth order Butterworth filter with cutoff frequencies of 2 MHz and 8 MHz respectively to eliminate out of band noises. The received TA and MA signals are shown in Fig. 5.4(a) and (b) respectively. As the transducers for detecting MA and TA signals are placed at slightly different distances, their arrival times differ a bit. The

associated spectrums of TA and MA signals are presented in Fig. 5.4(c) and (d) respectively, which show a TA signal centered around 280 kHz and a MA signal centered at the 5 MHz carrier frequency of the incident electromagnetic field.

Figure 5.4 (a) Received TA signal from the alumina phantom; (b) MA signal from the alumina phantom; (c) Spectrum of the TA signal in (a); (d) Spectrum of the MA signal in (c); (e), (f), (g) depicts the time domain MA-M signals for 2.0 MHz coil, 3.5 MHz and 5.4 MHz coil respectively.

It should be indicated that when the excitation power is at 250W, the concurrent generation of TA and MA signals is typically observed but the mixing components are relatively weak. To best demonstrate the mixing phenomenon, a second set of experiments are carried out with a 1 kW power amplifier and the pulse duration is extended to 3 μs. Water was used as the absorbing medium for inducing acoustic radiation force in view that most biological tissues show similar acoustic properties with water. Three coils resonating at 2.0 MHz, 3.5 MHz and 5.4 MHz are fabricated to assess the mixing effect at different frequencies. The three immersive coils share the diameter of 4 cm and the 2.0 MHz coil has 10 turns, the 3.5 MHz coil has 6 turns and

5.4 MHz coil has 4 turns. The matching network capacitors are maintained the same for three coils and the values for C_1 and C_2 are 235 pF and 470 pF respectively. For the three immersive coils (2.0 MHz, 3.5 MHz and 5.4 MHz), the setup is modified as shown in Fig. 5.3(b). The static magnet with area of 25×25 mm, height of 20 mm and magnetic field of 0.6 T at the superficial center is used and it is placed 15 mm above the coil. The coils are immersed inside water tank (Fig. 5.3(b)) to generate TA and MA waves directly, which allow to obtain optimum mixing results as the nonlinear mixing process is more salient at large acoustic wave amplitudes.

To rule out nonlinearities of the electrical circuits, the current flowing inside each coil is monitored by the voltage across a serial 2.2 ohm resistor. It is reasoned that the mixing components at sum and difference frequencies of TA and MA waves will be close to MA frequency since the TA frequency (<300 kHz) is much lower than the MA frequency (> 1 MHz). Thus, by selecting ultrasound transducers whose center frequency match the MA frequencies, both the MA signals and the mixing frequency components caused by the acoustic radiation force induced acoustic emission could be effectively detected. For conveniences, the signals so received are denoted as MA-M signals (i.e. MA + mixing signals). Specifically for the 2.0 MHz coil, a transducer with center frequency of 2.25 MHz is used whereas a flat transducer with center frequency 5 MHz is employed for the 3.5 MHz and 5.4 MHz coils. The TA waves generated by the three coils are again detected by the 1 MHz transducer for better signal to noise ratio.

The time domain MA-M signals for the three coils are shown in Fig. 5.4(e), (f) and (g) respectively, where the MA-M waves are all efficiently received. However, no obvious TA signals are observed because the transducer bandwidths are only matched for MA-M waves.

Figure 5.5 (a) Superimposed TA and MA signal from the 2.25 MHz transducer for the 3 turns copper coil; (b), (d) and (f) depict the TA signals for the 2.0 MHz coil, 3.5 MHz and 5.4 MHz coil respectively; (c), (e) and (g) depict the TA signals' spectrums for the 2.0 MHz coil, 3.5 MHz and 5.4 MHz coil respectively; (h), (i) and (j) shows the MA-M signal spectrum for the 2.0 MHz coil, 3.5 MHz and 5.4 MHz coil respectively.

To verify the simulated superimposition of TA and MA waves, a fourth coil (3 turns copper wire with a diameter of 3 cm) is excited at 5 MHz and the generated signals are detected by the 2.25 MHz transducer so that the resultant TA and MA frequencies fall roughly symmetrically around the transducer's center frequency. The received signal is shown in Fig. 5.5(a), where the temporal characteristic agrees well with the simulation result in Fig. 5.2(b). The time domain TA signal received by the 1 MHz transducer for the three coils are shown in Fig. 5.5(b), (d), (f) respectively and their respective

spectrums are depicted in Fig. 5.5(c), (e) and (g). The TA waves' spectrums are consistently centered around 200 kHz. This is expected since TA waves follow the envelopes of the excitation signals, which are the same for all the three coils. The absolute MA wave pressure amplitudes could be estimated from the received MA-M signal magnitudes: with the transducer sensitivity being generally on the order of 1 $\mu\text{V}/\text{Pa}$ and after being amplified by the low noise amplifier with 54 dB, a 20 mV MA-M signal is detected, indicating that the absolute MA wave pressure amplitudes are around 40 Pa. Similarly for the TA waves, the absolute wave pressure amplitude is on the order of 100 Pa after taking account of the frequency response of the 1 MHz transducer. These pressures are all measured from a distance (5~7 cm) from the source. Thus, the absolute wave amplitudes at the source could be several times larger.

The mixing results are revealed in the MA-M signals' spectrums shown in Fig. 5.5 (h), (i) and (j) for the 2.0 MHz, 3.5 MHz and 5.4 MHz coil respectively. In computing these spectrums, the transducers' frequency responses have been compensated across their 80% bandwidth in order to overcome the limited bandwidth effect of the transducers on measuring the mixing components' magnitude. The spectrums of their corresponding excitation currents are also provided for comparison. Distortions of the excitation current caused by the electrical circuits, if any, could be transferred to the generated MA signals (Eq. 5.8) and thus show up in the MA-M signal spectrums. However, the new frequency components existing in the MA-M signals spectrum but not in the current spectrums could then only be caused by the acoustic radiation force mechanism. This is exactly the case for the MA-M signal spectrums in Fig. 5.5. Specifically, the new frequency components pop up at (a): 1.8 MHz and 2.2 MHz for the excitation frequency of 2.0 MHz; (b) 3.3 MHz and 3.7 MHz for the excitation frequency of 3.5 MHz; (c) 5.2 MHz and 5.6 MHz for the excitation frequency of 5.4

MHz, all accurately corresponding to the difference and sum frequency between the MA and TA signals respectively. Additionally, these frequency components do not exist in the current spectrum and are all distinct from the current spectrums' sidebands. Other electrical interferences that may lead to nonlinear effects are also ruled out: the TA and MA signals after 54 dB amplification are smaller than 100 mV in amplitude. This kind of electrical signal is well within the linear range of the transducers and low noise amplifiers. Thus, both the transducers and amplifiers in the receiving electronics cannot cause sufficient nonlinearities to produce noticeable mixing components. Also, because the noises are random across different excitation frequencies (2.0 MHz, 3.5 MHz, 5.4 MHz), the consistent appearances of the mixing frequency components at all the excitation frequencies can only come from the nonlinearity of the radiation force mechanism.

Figure 5.6 (a) (b) and (c) show the mixing frequency components' strength versus the excitation power to the 2.0 MHz, 3.5 MHz and 5.4 MHz coils respectively; (d) mixing frequency components' amplitude versus the MA frequency.

To further corroborate the nonlinearity nature of the mixing effects, the magnitudes of the mixing components (here taking the average of the sum and difference frequency amplitudes) as a function of the excitation power levels are measured and shown in Fig. 5.6(a), (b) and (c) for the three coils respectively. As anticipated, the mixing components' magnitudes at all the three frequencies show obvious nonlinear characteristics with respect to the excitation power levels. Lastly, the mixing components' magnitudes at each excitation frequency are compared in Fig. 5.6(d) to check the frequency dependence of ultrasound absorption of water. Again, the mixing magnitudes show an increasing trend with the excitation frequencies. This conforms to the fact that water absorption of ultrasound waves is larger at higher frequencies, lending more evidence to the acoustic radiation force mechanism that depends on

water absorption in current experiments. It worth pointing out that more significant mixing frequency components are expected to be observed once the excitation power is further increased.

Apart from the acoustic radiation force induced acoustic emission that can yield mixing components, other mechanisms like heating effects and third order elastic constants could also give rise to nonlinear effects in principle. However, the heating effects are responsible for generating TA waves in our method and last only 3 μ s. With the power amplifier working at a repetition rate of 100 Hz in the experiments, the duty cycle of such heating is only 0.03%. In this case, the heating produced during the TA wave generation is dissipated sufficiently and thus will not cause heat accumulation, ruling out the heating effects induced nonlinearity in the experiments. Third order elastic constants, on the other hand, generally require significant mechanical stress on the materials to induce nonlinearity effects. However, the water used here as the absorber is an incompressible fluid and does not suffer from external stresses. Hence, compared with much stronger second order nonlinearity of acoustic radiation force, third order nonlinearities are negligible for water [113].

The concurrent generation and mixing phenomena between endogenous TA and MA waves in water are therefore validated experimentally. The consistently observed mixing frequency components in all sets of excitation frequencies agree well with theoretical prediction similarly as in vibro-acoustography. Though TA and MA signals in the proposed method are generally weaker than externally fired ultrasound, they are generated internally and don't suffer from significant attenuations attributed to the forward propagation from external transducers to internal body. Additionally, TA and MA show excellent contrast in conductivity that is lacking in conventional ultrasound

imaging. These features can be very useful for both medical imaging and non-destructive testing.

To generate detectable TA and MA waves concurrently, the excitation frequency should be lower than 10 MHz to avoid excessive attenuation of MA waves. As the acoustic radiation force depends linearly with the ultrasound absorption coefficient of the medium, media that possess moderate to high absorption coefficients are needed for decent mixing effects to be observed. Fortunately, most biological tissues of human body show good acoustic absorption [114], which allows the mixing effects to be potentially utilized for intrinsic elasticity imaging.

5.5 Discussion

The nonlinear mixing of thermoacoustic and magneto-acoustic wave requires large acoustic amplitudes in order to be notable, as in all other nonlinear acoustic phenomena. Here, the nonlinear mixing is caused by acoustic radiation force induced acoustic emission, which is a established method for performing elasticity imaging. However, this mechanism is not the only way toward elasticity imaging using unified thermoacoustic imaging and magneto-acoustic imaging. It is quite potential to analyze the linear thermoacoustic signal and magneto-acoustic signals systematically so that qualitative elasticity imaging could be achieved without the need of nonlinear mixing, which could be weak and therefore prone to noise and system mechanical instability.

To appreciate this point conceptually, we note that magneto-acoustic wave depend directly on the magnitude of local Lorentz force, which is not unlike acoustic radiation force induced acoustic emission: the acoustic emission strength is also directly dependent on the acoustic radiation force. Since under the same acoustic radiation force, the ultimate acoustic emission is roughly inversely related to the stiffness of the

local tissue, it is reasoned similarly that when exerted by an external Lorentz force, the resultant magneto-acoustic wave will also depend on the local tissue stiffness. In fact, in [115] - [117], the vibration magnitudes of magnetic nanoparticles under alternating magnetic force (Lorentz force at microscopic level) is monitored by ultrasound imaging and used for detecting the local stiffness of the nanoparticles. However, since the Lorentz force also depends on the local conductivity (see Eq. 5.8) in magneto-acoustic imaging, it is impossible for magneto-acoustic imaging alone to extract the stiffness for elasticity imaging. Yet on the other hand, the solution to isolate local the conductivity is exactly thermoacoustic imaging: the local thermoacoustic signal is also proportional to the conductivity but generally minimally affected by local stiffness.

Thus, one simple approach to render both conductivity and stiffness contrast by using the simultaneously generated thermoacoustic and magneto-acoustic wave is to use thermoacoustic signal for render conductivity contrast and to use local thermoacoustic signals for normalizing corresponding magneto-acoustic signals. The normalized magneto-acoustic signal is hence indicative of local stiffness as conductivity's contribution is eliminated by normalization. Of course, there will definitely be more advanced solution to isolate conductivity and stiffness contrast by processing the linear thermoacoustic and magneto-acoustic signals, which is the aim of future work.

5.6 Summary

By choosing proper excitation frequency with sufficient intensity and incorporating static magnetic field appropriately, thermoacoustic and magneto-acoustic are seamlessly integrated for the first time. More importantly, the mixing effect between TA and MA waves owing to acoustic radiation force induced acoustic emissions are predicted theoretically and then observed experimentally. The mixing effects can

potentially be utilized for mimicking vibro-acoustography to provide elasticity contrast without firing external ultrasound, which can find a wide range of applications in medical imaging and non-destructive testing. Combined with conventional conductivity contrast of thermoacoustic and magneto-acoustic imaging, this could enable a new imaging paradigm that provide intrinsically dual contrasts within a single system.

Chapter 6. CONCLUSION AND OUTLOOK

This thesis presented our work in advancing electromagnetic-acoustic method - thermoacoustic imaging specifically, towards deeper penetration, better contrast and for therapy applications, in using thermoacoustic technology for non-invasive close-loop temperature control of various hyperthermia therapy. The unification of two different electromagnetic-acoustic method: magnetically mediated thermoacoustic imaging and magneto-acoustic imaging are also investigated, which lead to the nonlinear mixing of the thermoacoustic wave and magneto-wave that may be potential for elasticity imaging with endogenous ultrasound waves.

6.1 Conclusion

Deeper penetration: Magnetically mediated thermoacoustic imaging (MMTI) that employ low frequency magnetic field for thermoacoustic imaging is demonstrated to provide deeper penetration than other thermoacoustic imaging methods. The contrast, resolution and signal to noise ratio of MMTI compared roughly the same to microwave induced thermoacoustic imaging and the frequency domain MMTI solution is advantageous for a portable system using low power excitations and for seamless integration with nanoparticle hyperthermia therapy applications. The integration of MMTI system with nanoparticles hyperthermia is demonstrated in chapter 4 for self temperature monitoring with sub-degree accuracy of the hyperthermia system by interleaving MMTI sequence and hyperthermia heating.

Contrast improvement: A modulation based method is presented for tackling the background problem in thermoacoustic imaging. The core principle of this method is to selectively modulate (tag) the desired signal whereas keep the background signals intact, allowing differential imaging to reduce background for contrast enhancement.

Two specific approaches are investigated: thermally modulated photoacoustic imaging that and modulatable MMTI. Both demonstrated effective contrast improvement in phantom studies.

Thermoacoustic powered close-loop temperature control: MMTI and photoacoustic temperature sensing were studied in chapter 4 for measuring the temperature and guiding subsequent close-loop temperature control in magnetic nanoparticle hyperthermia and photothermal therapy. It was found that the pulsed photoacoustic technique could achieve 0.18 degree Celsius temperature measurement accuracy and 0.3 degree Celsius accuracy in close-loop temperature control. For using continuous wave laser solution, the frequency domain photoacoustic sensing technique was demonstrated to provide a 0.75 degree Celsius temperature measurement precision at an ultrafast speed up to 4 kHz . The corresponding close-loop control accuracy is 0.9 degree Celsius. Enabled by this, a proof of concept single laser diode based self-regulated photothermal therapy system was obtained.

Co-existing and mixing between thermoacoustic and magneto-acoustic waves: The unifications and nonlinear mixing of magnetically mediated thermoacoustic wave and magneto-acoustic wave in water are predicted and verified experimentally. The mixing effects due to acoustic radiation forced induced acoustic emission can potentially be used for extracting elasticity contrast of the imaged object. Other method besides the nonlinear mixing of the two waves for potential elasticity imaging is probable, which is currently under investigation.

This thesis proposed some interesting concepts and demonstrated experimentally some of their specific applications, which we hope to be beneficial for future research in biomedical imaging and therapy.

6.2 Future work

There are several technical improvements and theoretical advancement need be done in order to bring the work presented in this thesis to higher levels.

Technical improvements: Firstly, the magnetically mediated thermoacoustic imaging (MMTI) need further improvement in imaging speed to enable real time imaging. This could be done by using existing ultrasound imaging array probes, which is also beneficial for integrating MMTI into conventional ultrasound imaging systems. When using existing ultrasound system for MMTI, the lower signal amplitude and strong electromagnetic interference in MMTI may need novel signal processing algorithms and good electromagnetic shielding to be added. Secondly for thermoacoustic powered close-loop temperature control of various hyperthermia therapy application, three dimensional temperature imaging is needed, which requires dense two dimensional ultrasound probes, large data transfer rate and powerful data processing capability for imaging system.

Theoretical advancement: The foremost is to solve either analytically or numerically the exact dependence of thermoacoustic and magneto-acoustic signal on the local stiffness for elasticity imaging. Though it is recognised that thermoacoustic does not depend strongly on the local stiffness, a rigorous analysis or simulation is needed for verification and for understanding the extent to which thermoacoustic signal is affected by tissue stiffness. On the other hand, despite Lorentz force had been used in conjunction with magnetic nanoparticles for probing the tissue stiffness, an accurate link between magneto-acoustic signal and tissue local stiffness is lacking. Once the dependence on tissue local stiffness is sorted out, multi-contrast (conductivity and elasticity) imaging could be achieved with the unified MMTI and magneto-acoustic imaging.

The second theoretical advancement is the calibration-free of non-invasive temperature measurement. This may be extremely challenging since the problem of calibration-free non-invasive temperature measurement is a long standing one and all existing temperature measurement solutions need calibrations. In this regard, a novel physical phenomenon maybe needed to achieve this goal.

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