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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**REAL-TIME DIAGNOSIS OF HIFU LESION FORMATION
BY ULTRASOUND ELASTOGRAPHY**

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SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING

2018

**REAL-TIME DIAGNOSIS OF HIFU LESION FORMATION
BY ULTRASOUND ELASTOGRAPHY**

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Summary

Cancer is a serious disease for human beings for centuries. Despite great progress in oncology in the past a few decades there are still significant challenges in this field. Ultrasound elastography is a new imaging modality to detect the relative stiffness of tissue in the diagnosis of cancer in the early stage or calcified tissue or the lesions which have stiffness 3-5 times as the surrounding healthy tissue but much less difference in acoustic impedance ($<10\%$) in forming the conventional B-mode sonography [1]. Ultrasound elastography tracks the movement of acoustic scatterers within the tissue in the sonography with response to quasi-static compression applied to the tissue, and then derives the stiffness distribution. In the last twenty years, conventional axial strain imaging method, shear wave imaging, and other stiffness-detection methods have been well-established. High-intensity focused ultrasound (HIFU) is emerging as a noninvasive and effective ablation approach in the treatment of solid tumors and cancers, such as breast, liver, prostate, kidney, bone cancers and uterine fibroids. The major mechanism of HIFU ablation is to elevate the temperature of tissue in the focal region of HIFU field over 65°C on the order of seconds or ten seconds to form irreversible necrosis. Quantitatively evaluating the shape of lesions and gaps between them, which are much harder than the surrounding tissue, is critical in monitoring the progress and success of HIFU treatment. Although elastography has been tried to detect HIFU- or chemotherapy-induced lesions after the treatment, real-time monitoring and feedback are more important. Especially the thin gap between two vertical aligned lesions must be avoided. Otherwise, cancer cells in

the untreated region have the much high possibility of relapsing. However, there are currently no solutions for detecting the lesion gap in real time.

In this study, a technique was developed and evaluated for this specific problem. We utilized the acoustic radiation force on the lesion area produced by the therapeutic HIFU pulse during ablation to generate high-contrast axial shear strain around the gap region and construct the axial shear strain elastograms (ASSEs). In order to establish the utility of this novel approach, all related fundamental knowledge, such as strain distribution in the tissue induced by the quasi-static compression, displacement of acoustic scatterers using raw radio-frequency (RF) data, reconstruction of elastogram, collection of RF data from an ultrasound research platform, and plane wave imaging for ultrafast sonography, was introduced at first in Chapter 2. Subsequently, numerical simulation was carried out to show the feasibility of using acoustic radiation force from the therapeutic HIFU exposure to illustrate the gap between two vertically aligned lesions in Chapter 3. The effects of lesion size, lesion gap, and acoustic radiation force from HIFU burst on the axial shear strain elastogram were investigated to estimate the feasibility and sensitivity of the proposed method. Overall, the preliminary numerical simulation demonstrated that it is highly feasible to detect the gap between two vertically aligned lesions by axial shear strain (ASS) using acoustic radiation force in real time during HIFU ablation. From the numerical simulation of various conditions, a criterion of ASS ratio was established for detecting the lesion gap. It is found that the threshold is about 0.75. Finally, gel phantom and *ex vivo* tissue (porcine kidney and liver) sample experimental studies

were carried out to further evaluate the performance of our proposed technology. An array of markers were produced in bovine serum albumin (BSA) included polyacrylamide to track the displacement by high-speed photography. Axial strain elastograms (ASEs) under static compression can show the contour of lesions in the gel phantom, but cannot discern whether gap zone exists between two HIFU-induced lesions. However, remote palpation from acoustic radiation force using HIFU exposure can produce axial shear strain elastogram and generate large axial shear strain in the gap zone, which is quite sensitive and reliable in the HIFU monitoring. Because of fast relaxation of gel phantom and *ex vivo* tissue samples, sonography at the high frame rate (about 1000 Hz) using planar wave imaging (PWI) is required. However, the memory size of ultrasound research platform used to collect RF data limits only a few scanlines around the lesions. Experiments in the porcine kidney and liver samples are also very promising. Lesion gap correlates quite well with the presence of large axial shear strain or high ratio of ASS between two lesions to that at the left side of being treated lesion, which provides good compromise for the future animal experiments and clinical trials.

Overall, in this study, we proposed a practical and cost-effective approach of detecting lesion gap during HIFU treatment. Our technology does not need to interrupt the ablation procedure and apply quasi-static compression or ARF to the target using the ultrasound imaging probe. Detection seems to be sensitive and reliable without much intervention and physical background of the operator. It has a high possibility of clinical trials for most of sonography-guided HIFU treatment system with little

modification of configurations and HIFU treatment protocols.

Chapter 1 Introduction

1.1 Cancer and Current Treatment Modalities

Cancer, also known as a malignant tumor, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the human body [2]. It is a major public health problem for both developed and developing countries. There are more than 100 types of cancers, such as breast cancer, skin cancer, kidney cancer and so on [3]. World Cancer Report 2014 showed that there were about 14.1 million new cases of cancer diagnosed worldwide in 2012 [4], which caused about 8.2 million deaths or 14.6% of human total deaths [5]. It was estimated that about \$1.6 trillion was spent on cancer healthcare in 2010 [6]. Cancer therapy demand in the United States is estimated to grow annually by 10%.

Currently, several modalities are available for the cancer treatment, such as surgery, chemotherapy, and radiation therapy. The choice of treatment methods depends on the type and the grade of cancer as well as the health status of patients. Surgery is the fundamental treatment modality of most isolated solid cancers [7]. It attempts to cut malignant tumor from the body. After surgery, further treatment, including chemotherapy and radiation therapy, is often recommended [8]. However, not all cancer patients can undergo surgery. For example, only 20% of pancreatic cancers after being diagnosed can be removed by the surgical method, which takes several hours because of complicated anatomy in the pancreas. Chemotherapy applies one or more kinds of cytotoxic anti-neoplastic drugs to kill cancer cells that divide

rapidly [9]. The side effects of this method are hair loss, fatigue, and vomiting. In addition, only a small portion of chemotherapeutic will be taken by cancer, and some types of tumors are strongly drug resistant. Radiation therapy can damage the DNA of cancer cells using high-energy radiation rays [10]. In order to reduce the effect on the surrounding normal cells, radiation beams in a certain shape are aimed from several directions of exposure to intersect at the tumor. Side effects of radiation therapy include vomiting, diarrhea, fatigue, and inappetence [11]. Therefore, extensive investigations are being done continuously for the new cancer treatment modalities with high efficiency and efficacy.

1.2 HIFU Treatment and Guidance

Ultrasound is a well-established imaging approach widely used in the industry, such as nondestructive evaluation/testing (NDT/NDE). Its technical advantages of easy operation, low cost, mobility and portability, and especially non-ionization make it a good clinical diagnostic candidate for most soft tissues, especially for gynecology and obstetrics. In addition, ultrasound at higher acoustic intensity and energy output has also been involved in the therapeutic field since as early as 1927 to heat the deep-seated tissue [12]. In 1944, focused ultrasound (FUS) was first used for neurosurgery [13]. Fry brothers are credited as the pioneer in the development and application of HIFU to the treatment of Parkinson's disease by destructing deep-seated brain tissue with multiple ultrasound transducers.

High-intensity focused ultrasound (HIFU) is a non-invasive method for the treatment of cancer [14-25]. More than 30,000 clinical trials have been carried out in Asia and Europe since the middle of the 1990s with promising results. This method focuses the ultrasound energy from a concave transducer to a small region inside the body. When the acoustic wave propagates through the tissue, the tissue will absorb the acoustic energy and convert to the thermal energy [26]. As a result, the temperature in the focal region will increase. When the temperature is higher than 65°C within seconds, the denaturalization of protein will lead to the death of cancer cells [27]. Because of the intrinsic energy focusing ability, HIFU produces much less damage to the intervening tissue. The transition distance from the coagulated tissue to the normal one could be as short as 50 μm as shown in Fig. 1-1. Because the size of cancer and solid tumor ($> 1\text{ cm}$) is much larger than the beam size of HIFU (about 1-3 mm $\times$ 10 mm in lateral $\times$ axial dimension, respectively), the focus should be scanned throughout the whole volume of the target. Since HIFU treatment is a non-invasive method, it has much fewer complications and less in-patient stay in comparison to the open surgery and radio- and chemo-therapy. And there is no theoretically upper limit of tissue tolerance to the repeated sessions. Various targets, such as liver, kidney, breast, bone, prostate, pancreas cancer and uterine fibroids, have been tried clinically with the promising results [28-36]. MRI-guided HIFU system (ExAblate 2000, InSightec-Tx Sonics Ltd, Haifa, Israel) has been approved by the Food and Drug Administration (FDA) of the United States for the treatment of uterine fibroids, bone cancer, breast cancer, and essential tremor in 2004, 2012, 2013, and 2016, respectively.

Ultrasound-guided HIFU system (Model-J, Haifu Technology Ltd., Chongqing, China) has been approved by China Food and Drug Administration (CFDA) for the treatment of liver and kidney cancers. In the practice, all HIFU-induced lesions should be overlapped to cover the whole volume of cancer with certain margin (usually 1-2 cm from the diagnosed boundary) without any gaps or untreated regions. Therefore, accurate monitoring of volume and location of HIFU ablated tissue or produced lesions in real time is a critical and preferable issue of improving the efficacy and potential success of HIFU ablation as well as of minimizing the complications. However, the HIFU operators usually perform the ablation empirically despite great variations among patients and diseases. Therefore, the outcome of HIFU therapy using the same treatment protocol and parameters may not be consistent.

Figure 1-1. The schematic diagram of high intensity focused ultrasound (HIFU) beam passing through overlying skin and other tissues without harming them and then being focused to necrose a localized tumor region, which may lie deep within the body. There is a very sharp boundary between dead and live cells at this contour [37].

In the HIFU treatment, guidance is also of importance, including localizing the region-of-interest, monitoring the lesion formation, and detecting the temperature distribution (thermography). Currently, there are two types of guidance approaches in the clinical HIFU system, using sonography [38] and magnetic resonant image (MRI). The high acoustic pressure of HIFU can induce the cavitation effect, forming bubbles within the tissue [39]. Because of the much lower acoustic impedance of the bubbles in comparison to that of soft tissue (i.e., 3 orders difference), a hyperechoic area will appear in the conventional B-mode ultrasound image [40, 41]. The changes in the gray level of sonography may be used in the guidance. However, the presence of bubble may not always relate well to the shape and the location of the HIFU-generated lesions. Small bubbles are short-lived while large ones (i.e., boiling bubbles) last for several seconds. Therefore, this method cannot provide quantitative estimation on various treatment conditions. Meanwhile, MRI is very sensitive to the pathological change with tissue in the combination of contrast agent and has been used for widely detecting cancer and evaluating lesions [42-46]. However, the temporal and spatial resolution of MRI is limited, and its cost is high especially for the real-time monitoring during HIFU ablation, which is usually 2-3 hours dependent on the size of tumors. Furthermore, the exclusion of patients with metal implants, pregnant women, children or large patients, low temporal resolution for the anatomic images, labor-extensive, non-portability, and high operation cost may limit its application in real-time monitoring and efficacy evaluation [35].

Figure 1-2. T1w MRI mammography of a breast cancer (a) 2 days before HIFU ablation without (top) and after (bottom) i.v. contrast, showing a strong tumor, (b) before treatment without i.v. contrast (top) and immediately after HIFU ablation with i.v. contrast (bottom), exhibiting a complete lack of contrast enhancement after HIFU ablation, and (c) T2w MRI treatment planning (top) and MRI thermometry during sonication (bottom) [47].

Integration of ultrasound (US) imaging probe with the HIFU transducer could assess the acoustic condition in the propagation pathway of HIFU burst and real-time monitor the soft tissue. Although the presence of bubble appears as a hyperechoic area in the B-mode sonography [48], it may not relate well with the shape and location of HIFU lesions, and lesions can form without the hyperechoes [41]. The change in blood flow patterns in the three-dimensional contrast-enhanced power Doppler ultrasound (3D-CE-PDU) after therapy can be used to locate and quantify the extent of affected tissue in a good correlation with the histopathology of the specimen (Pearson correlation $r = 0.94$) [49]. However, the outer ring of the macroscopic hemorrhagic necrosis was found 1-2 mm beyond the border of actually dead tissue, and continuous injection of contrast agent (microbubbles) during HIFU therapy is unfeasible. In

comparison to MRI-thermography, the ultrasound technology is more challenging. It is known that the speed of sound (SOS) in the soft tissue changes in the elevated thermal field. Anand et al. proposed a method to measure the change of SOS in the reflected wave to predict the temperature [39]. However, the variations in SOS are very small compared to the changes in the tissue expansion, especially at the higher temperature, which was also confirmed with the other ablation technique, such as radio-frequency ablation (RFA) [50]. Seip and Ebbini et al. suggested that the temperature can be measured by finding the shifts in the backscattering radiofrequency (RF) signals [51]. However, because of the nonlinear relationship between the temperature and SOS (increasing to the critical point of about 50-70°C and then decreasing) [52], the accuracy of this method is limited for moderate hyperthermia applications [53]. In addition, the photoacoustic method is another non-invasive technique to monitor the temperature change within the tissue [54]. When the medium is heated by the optical absorption of pulsed light (i.e., laser), ultrasonic signal will emanate from the inclusion due to the thermal expansion [55]. The amplitude of the ultrasound wave correlates with the temperature, but there is also nonlinear relationship similar to that of SOS [56-58].

Figure 1-3. B-mode ultrasound imaging of HIFU-induced cavitation with bright hyperechoic spots generated by HIFU indicate regions of cavitation [59].

1.3 Ultrasound Elastography

Changes in the tissue elasticity are generally correlated with pathological phenomena. Many cancers have hard nodules as a result of increased stromal density in the breast scirrhous carcinoma. Other diseases associated with fatty and/or collagenous deposits have increased or decreased tissue elasticity. Complicated fluid-filled cysts and cirrhosis of the liver are quite softer than the embedding tissue, but invisible in sonography. However, the small pathological lesion seated deeply in the body makes its detection and evaluation challenging.

Palpation is the process of using one's hands to examine the body, especially

while perceiving/diagnosing a disease or illness. Instruction of manual palpation of the breasts, wounds, bowels, ulcers, uterus, skin and tumors for the tissue elasticity are available as early as in 1500 BC in the ancient Egypt and Greece. In the modern Western world, palpation was considered a respectable method of diagnosis in the 1930s. Since then, the practice of palpation has become widespread as an effective method of detecting tumors and other pathologies by most of practicing clinician. However, manual palpation suffers from several important limitations, such as limited tissues access to the physician's hand, distortion by any intervening tissue, and only qualitative information available.

Elastography, a medical imaging modality that measures the tissue stiffness quantitatively, seeks to address these challenges and has been intensively studied in the past decades [60]. It is known that the denaturing of protein will increase the stiffness of HIFU-induced lesions which is about 3-6 times harder than the surrounding normal tissue [61]. In comparison, the difference in acoustic impedance in forming conventional B-mode sonography is much smaller, i.e., <10% [62]. Therefore, stiffness image can become a quantitative approach to guide and monitor the process of ablation. Currently, several ultrasound elastography approaches, such as quasi-static elastography, acoustic radiation force impulse imaging (ARFI), shear wave elasticity imaging (SWEI), supersonic shear imaging (SSI), and transient elastography, have been studied [63-66]. For example, axial strain elastography (ASE) and axial shear strain elastography (ASSE) could be reconstructed to show the distribution of medium stiffness. Magnetic resonance elastography (MRE) could quantitatively assess the

mechanical stiffness of tissue by examining the propagation of mechanical waves through it [67].

Figure 1-4. Comparison of sonography (left) and elastography (right) of uterine fibroids characterized by their stiffness. Some uterine fibroids can be better visualized using the measured strain distribution, especially if they are significantly stiffer than the adjacent uterus [68].

Ophir et al. firstly introduced the elastography method in 1991 [69]. They applied quasi-static compression to the tissue, obtained RF data by the ultrasound imaging probe before and after the compression, and calculated the displacement and strain map by analyzing the RF data using signal processing methods. The axial strain can reflect the shape and location of lesions, and it is estimated by the following equation

$$\mathcal{E}_{axial-strain} = \left(\frac{\partial v}{\partial y} \right) \quad (1-1)$$

where v is the displacement along the direction of compression, and y is the axial direction. Kallel et al. verified the feasibility of using ASE method to monitor HIFU

therapy in the rabbit livers *in vivo* [70]. Souchon et al. used the similar method to detect HIFU lesions in the human prostate [71]. Lizzi et al. applied acoustic radiation force (ARF) as remote palpation to monitor the growth of HIFU lesions [72]. In their work, they proved that acoustic radiation force impulse (ARFI) imaging didn't have a significant effect on the local temperature. Then they showed that the displacement induced by the acoustic radiation force can estimate the stiffness change in the region of HIFU lesion. However, the crucial problem of this method is that the axial strain depends on the stiffness itself as well as the local stress which is seldom uniform within the whole tissue.

Krouskop et al. proposed sono-elasticity or sono-elastography method which used a low frequency (LF) vibrator to make the tissue vibrate and calculated the stiffness by analyzing the displacement received from the Doppler receiver [21]. Urban et al. used the radiation force to induce vibration instead of an external vibrator and measured the resulting acoustic emission field with a hydrophone [73]. Note that re-emitted signal is sensitive to the temperature and it may magnify the error of stiffness estimation [25].

Catheline and Fink et al. proposed the transient elastography to calculate shear modulus which is nearly one-third of Young's modulus in the soft tissue [74]. They generated that shear wave at a low propagating speed by using an LF vibrator in the near field, measured the axial component of the shear wave by a coaxial ultrasound transducer and analyzed the relationship between received successive A-lines with cross-correlation method. Sandrin et al. extended this method from 1D to 2D [75].

Bercoff et al. measured the stiffness change *in vitro* experiment during HIFU therapy [76]. The challenge of this method is that the ultra-fast ultrasound scanner for the detection of wave propagation is costly (i.e., high-speed data acquisition, DAQ) for the clinical application.

All the methods mentioned above are focusing on the detection of single HIFU lesion. However, because of the large tumor size in comparison to the lesion size (several cm vs. several mm) HIFU focus should be scanned throughout the whole volume of the tumor. Small lesions should be aligned overlapped without the gap to form a large lesion over the target with margin (i.e., 1-2 cm around cancer) in the practice for the successful ablation. During HIFU treatment, it is important to guarantee that there is no untreated missing area within the whole treatment region. Otherwise, the chance of cancer relapse is quite high [77]. Therefore, a real-time technique is required to monitor the gaps between lesions during HIFU ablation. Thittai et al. proposed ASSE method to distinguish benign and malignant tumors [78]. Later, this method was proved to provide the gap information since the gap zone always bears high axial shear strain (ASS) when quasi-static compression is applied to the tissue. Xia et al. obtained ASEs and ASSEs simultaneously in *in vitro* experiment and verified that ASSEs are more robust than ASEs [79]. The limitation of their study is that when the two surrounding lesions are aligned exactly vertical, the untreated gap will be at the normal direction with respect to the axis of compression and will not shear, resulting in no axial shear strain in the ASSEs [80]. Overall, there are few reports of detecting the gap between HIFU lesions in real time [81, 82].

Furthermore, ultrasound elastography was also used to monitor the lesion production with the other thermal or chemical approaches [83, 84]. However, monitoring HIFU-induced lesion production is more challenging because of the interference between two types of acoustic pulses from HIFU and sonography [85, 86]. Although the iso-intensity contour of both the ASE and ASSE can evaluate the area of the enclosed single lesion in canine livers cast in a gelatin block, ASSE is less sensitive to iso-intensity threshold selection (from -2 dB to -6 dB). In addition, ASSE enables high-contrast visualization of a small gap between HIFU-lesions [87]. The feasibility of real-time monitoring during HIFU treatment was also explored. ASSEs can not only improve the lesion visualization and size measurement of a single lesion but also identify the untreated gaps between adjacent lesions with high contrast at certain conditions [79]. However, the opposite polarity axial-shear regions start to cancel at the boundaries when two HIFU lesions aligned exactly vertical are close to each other before the mergence. A gap as thin as 0.1 mm is detectable in the simulation when the axial-shear strain with the same polarity reinforces each other from two lesions vertically offset in an appropriate distance or the gap between two adjacent lesions should be at a non-normal orientation with respect to the axis of compression [88]. Realization of this requisite condition in practice is a problem, and the effect of orientation angle of gap on the contrast is under the investigation. Furthermore, the quasi-static compression of ultrasound imaging probe requires a different acoustic window from that for HIFU exposure in order to avoid the damage to the probe and influence to the propagation of HIFU bursts. However, the available

acoustic window may not be always sufficient in clinical HIFU therapy.

The compression of soft tissue is also possible in a remote way. The generation of acoustic radiation force by the momentum transferred to the tissue due to the acoustic absorption could cause the tissue displacement [89]. Acoustic radiation force impulse (ARFI) imaging can monitor lesion formation and the resulting tissue stiffening in *ex vivo* samples that corresponded to discolored regions in gross pathology [90]. The acoustic intensity of HIFU burst itself is much higher than that of ARFI from the ultrasound imaging probe. Such radiation-force technique can produce detectable motion by a single 5 ms-burst for relative stiffness changes of HIFU lesion but well below the thermal dose of lesion formation [72]. Its use for transient strain imaging, the instantaneous strain immediately following cessation of the radiation force, permits the sensing of variations in the tissue elasticity that is difficult for conventional elastography with high homogeneity in the background and within the inclusions as well as a superior contrast-transfer-efficiency due to greater independence from boundary conditions [91]. Amplitude-modulated (AM) harmonic motion imaging (HMI) for focused ultrasound (HMIFU), utilizing an oscillatory radiation force, could detect the mechanical response of tissue during thermal ablation based on the variation of the HMI displacements [92, 93]. The disturbance created by acoustic radiation force also induces the propagation of a shear wave, travelling sideways through the tissue. Both shear modulus and viscosity of soft tissues can be quantitatively mapped by shear wave elastography (SWE) [94, 95]. However, very high frame rate of RF data acquisition ($> 10,000$ frames/s) is required because of low

speed of shear wave. Overall, there are few reports of detecting the gap between HIFU lesions.

1.4 Objectives

In this thesis, we proposed and evaluated a novel and practical approach to detecting the gap between lesions during HIFU treatment in real time using the confocally and coaxially aligned ultrasound imaging probe. The acoustic radiation force from the therapeutic HIFU bursts themselves during the ablation is utilized to compress the tissue or the being treated lesion locally at its center. Subsequently, the obvious axial shear strain may appear in the gap region between the nearby lesions. With the on-going of HIFU ablation, the lesion size will grow gradually. As a result, the axial shear strain between the lesion gap will decrease, and its disappearance shown in the reconstructed ASSEs may illustrate the information of lesions emergence or overlapping or the disappearance of the gap. The feasibility and performance of the proposed approach were evaluated both numerically and experimentally. In comparison to the currently available monitoring modalities, it may have the advantages of high sensitivity, low cost, easy operation, little changes to HIFU operation and system structure.

The scope of this study is listed as below:

- Quasi-static compression generated ASE and HIFU-induced transient ASSEs could be simulated using the reconstructed sonography by Field II and particle displacement and subsequent strain by finite element method (FEM);

- Acoustic radiation force from the HIFU pulse itself could be used to generate significant displacement of lesion being treated, which is larger than that generated by ARFI;
- Axial shear strain elastogram by HIFU exposure could be reconstructed to compare two lesions without and with a gap between them in real-time;
- Operation parameters (i.e., amplitude of acoustic radiation force, gap width and lesion size) for discerning the lesion gap will be investigated;
- Gel phantom and *ex vivo* experiment will be investigated to confirm the feasibility of detecting lesion gap by axial shear strain from HIFU exposure and evaluate its performance for the future clinical translation.

1.5 Structure of this Thesis

The work presented in this thesis focuses on detecting the lesion gap in the reconstructed axial shear strain elastogram during HIFU treatment. The primary emphasis of this report is to investigate the effect of different operation parameters on the detection reliability and sensitivity and to evaluate the performance for the future *in vivo* experiment and clinical trials. This thesis is organized into five chapters as follows.

Following a brief introduction of cancer disease, cancer treatment modalities currently available and their limitations, emerging HIFU in the noninvasive cancer treatment, and the requirement of complete lesion coverage the whole cancer volume to avoid the late cancer cell proliferation, relapse, and future possible metastasis are

introduced. Two monitoring approaches for the HIFU treatment, ultrasound and magnetic resonant imaging (MRI), are reviewed, especially their technical limitations of real-time monitoring the lesion production and gaps between them. Ultrasound elastography or sonoelastography is reviewed for its clinical application of early-stage cancer diagnosis. However, it has technical limitations in the real-time lesion monitoring.

In Chapter 2, the fundamental knowledge of ultrasound elastography is introduced. Firstly, the acoustic field produced by a typical HIFU transducer could be simulated by a nonlinear acoustic wave propagation model. The acoustic radiation force is calculated from the distribution of acoustic intensity. Then the relationship of stress and strain in the medium, especially the soft tissue is listed. The particle displacement induced by the static compression or localized force applied to the tissue could be simulated using the finite element method (FEM). Sonography of lesions in the soft tissue is simulated using a free software package, Field II, which utilizes the spatial impulse response for arbitrary ultrasound imaging probe and anatomical structure of the testing sample. The signal processing method of radio frequency (RF) data in the estimation of particle displacement by the stress is introduced. Finally, the RF data of soft tissue was collected from an ultrasound research platform to reconstruct the standard B-mode sonography.

In Chapter 3, we firstly describe the calculation of the displacement induced by acoustic radiation force during HIFU exposure from which the axial strain elastogram and axial shear strain elastogram were reconstructed. Further, we discussed the effect

of three important parameters: gap width, lesion size, and magnitude of radiation force on the gap detection. It is found that large axial shear strain presents in the gap zone between two lesions aligned exactly vertical. The detection is quite sensitive and reliable, and its performance is much better than the existing other technologies. Our proposed method has the high possibility of the applications in the clinical trial.

In Chapter 4, we report an extensive series of experiments to measure the axial strain elastogram by static compression and axial shear strain elastogram by remote palpation during HIFU exposure in the gel phantom without and with the gap between two lesions. The elastograms reconstructed using the sonography are found similar to those reconstructed using the photography. The conclusion is same as that in the numerical simulation that large axial shear strain presents in the gap zone between lesions. Then *ex vivo* samples are used to further evaluate the performance of our proposed technology.

Chapter 5 summarizes the novelty of this work. A possible translation to the *in vivo* studies and clinical trials has been presented. Moreover, the future investigation of this innovation is also discussed in this chapter.

Chapter 2 Fundamentals of Ultrasound Elastography

2.1 Introduction

Ultrasound elastography is becoming an emerging diagnostic approach in clinics, which enables differentiating the various types of tissues and organs based on their elasticity or stiffness. The principle of elastography is to detect the deformation of soft tissues according to slight pressure applied to it by the ultrasound imaging probe and then present the reconstructed maps of elasticity in real time with a certain color coding, which is called elastograms. Sonographic system commercially available in the market equipped with sonoelastography option (usually the high-end product) enables more accurate evaluation of the nature of malignant lesions located at the small depth, such as breast, thyroid, testicles, prostate, and some groups of lymph nodes, looking almost identical to a regular sonography examination. Usually, elastogram in a small region-of-interest (ROI) with a color scale is overlaid with the regular grey-scale B-mode sonography for easy analysis of noticed lesion. It is well known that the change in the tissue elasticity due to the pathological or physiological process is much more remarkable than the other physical parameters. Subsequently, the accuracy of ultrasound in diagnosis and the evaluation of the stage of malignant tumors could be increased significantly without the requirement of the biopsy, thus reducing the cost, operation complexity, and time consumption. The chance of detecting lesion early, for example in prostate or breast, could be increased. Sonoelastography was first described by Krouskop et al. in 1987. Now it is one of the

biomedical ultrasound research topics with extensive interests and investigation. Different methods of acquiring elastograms have been developed.

In this chapter, some fundamental knowledge and research methods in the ultrasound elastography, such as the elasticity and strain of soft tissue, the distribution of acoustic intensity of HIFU pulses, the tissue response simulation with response to static compression by the finite element method (FEM), simulation of B-mode sonography in the acoustics before and after the static tissue/phantom compression, and signal processing techniques to calculate the tissue displacement, and reconstruction of the local strain map or elastograms, are introduced and discussed. In addition, the feasibility of collecting echo radio-frequency (RF) data from an ultrasound research platform for the future elastogram reconstruction is also included.

2.2 Elasticity of Soft Tissue

Sonoelastography provides information of internal strains induced in a soft material under an axial stress. According to Hooke's law, there is a linear relationship between the state of stress of every component and the state of strain at the point in many solid materials, the measured strain is proportional to the applied load over a wide range, which is presented as:

$$\sigma_{ij} = C_{ijmn} \epsilon_{ij} \quad (2-1)$$

where C_{ijmn} is a stiffness matrix comprising all elastic constants and σ_{ij} is the stress component in a plane perpendicular to the axis x and parallel to the axis y . The biological tissue behavior in the elastography is assumed to be isotropic, nearly

incompressible, and linearly elastic for small deformations. Therefore, the equation can be expressed by using two independent parameters known as the Lamé's constants λ and μ :

$$\begin{aligned} C_{1122} &= \lambda \\ C_{1111} &= \lambda + 2\mu \\ C_{1212} &= \frac{1}{2}(C_{1111} - C_{1122}) = \mu \end{aligned} \quad (2-2)$$

The constant μ is referred to as the shear modulus. The volume change per unit volume due to the spherical stress is dependent on the bulk compressional modulus K , which is related to the Lamé's constants by:

$$K = \frac{3\lambda + 2\mu}{3} \quad (2-3)$$

Two other parameters are used to represent mechanical properties of the solid medium: Young's modulus, E , and Poisson's ratio, ν . Their relationship with K and μ is given by:

$$K = \frac{E}{3(1 - 2\nu)} \quad (2-4)$$

$$\mu = \frac{E}{2(1 + \nu)} \quad (2-5)$$

However, most tissues are soft and have intermediate properties between solid and fluid media. The mechanical behavior of soft tissues is anisotropic, non-Hookean, viscoelastic, and incompressible. In fact, the linear elastic Hookean behavior can be used for elasticity analysis only for very small static deformations.

2.3 Shear Strain

A strain is a normalized measurement of deformation representing the displacement between particles in the body with respect to a reference length. Both axial strain and shear strain can be used to measure the distribution of relative stiffness in the tissue. Axial strain and shear strain can be computed by the following expressions.

$$\begin{aligned}\varepsilon_x &= \frac{\partial u_x}{\partial x} \\ \varepsilon_y &= \frac{\partial u_y}{\partial y} \\ \gamma_{xy} &= \frac{\partial u_y}{\partial x} \\ \gamma_{yx} &= \frac{\partial u_x}{\partial y} \\ \varepsilon_{xy} &= \frac{1}{2} \left(\frac{\partial u_y}{\partial x} + \frac{\partial u_x}{\partial y} \right)\end{aligned}\tag{2-6}$$

where ε_x , ε_y are normal x -axis and y -axis axial strain, ε_{xy} is the shear strain, and γ_{xy} and γ_{yx} are the axial shear strain and lateral shear strain, respectively, and u_x and u_y are the lateral and axial displacement, respectively. The axial and shear strain are shown in Fig. 2-1.

Figure 2-1. Schematic diagram of the axial and shear strain.

2.4 Simulation Setup

The systematic setup used in the simulation mainly consists of an ultrasound transducer, a tissue-mimicking phantom, and degassed water as shown in Fig. 2-2. An annular concave transducer has an outer and inner radius of 1.7 cm and 4 cm, respectively, the excitation frequency of 2.2 MHz, the focal length of 8.3 cm, and the acoustic power output of 56 W. A diagnostic probe aligned coaxially and confocally with the HIFU transducer has a working frequency of 5 MHz. More details about the imaging probe are described in section 2.5. The tissue-mimicking phantom is placed 5 cm away from the transducer surface in the degassed water. HIFU pulses generated from the ultrasound transducer are used to push the tissue-mimicking phantom and induce the displacement distribution for 0.1 s. The integrated and coaxial diagnostic

ultrasound transducer can capture the raw RF data, from which the displacement will be calculated.

Figure 2-2. The configuration of HIFU ablation in the phantom.

2.5 Acoustic Field and Radiation Force

HIFU simulator (FDA, Silver Spring, MD, USA) was used to determine the acoustic field of the HIFU transducer. It is free Matlab (Mathworks, Natick, MA, USA) toolbox. The nonlinear Khokhlov–Zabolotskaya–Kuznetsov (KZK) evolution equation has been used widely to model high-intensity acoustic beams numerically [96] and was applied to simulate the acoustic field generated by the HIFU transducer,

$$\frac{\partial p}{\partial z} - \frac{\beta}{c_0^3 \rho_0} p \frac{\partial p}{\partial \tau} - \frac{b}{2c_0^3} \frac{\partial^2 p}{\partial \tau^2} = \frac{c_0}{2} \int_{-\infty}^{\tau} \Delta_{\perp} p(\tau') d\tau', \quad (2-7)$$

where p is the acoustic pressure, z is the coordinate along the beam axis, c_0 is the small-signal sound speed, ρ_0 is the ambient density, $\tau = t - z/c_0$ is the retarded time, β is the coefficient of nonlinearity, b is the dissipative parameter, and $\Delta_{\perp}$ is the

Laplacian operator with transverse coordinates $r=(x,y)$. In the frequency-domain schemes, the solution of Eq. (2-7) is represented in the form of a Fourier series expansion,

$$p(z,r,t) = \sum_{n=-\infty}^{\infty} C_n(z,r) \exp(-in\omega_0\tau), \quad (2-8)$$

where ω_0 is the fundamental frequency of the HIFU pulses and C_n is the complex amplitude of the n th harmonic. The acoustic intensity is given by

$$I = \frac{1}{\rho c T} \int_0^T p^2(t) dt, \quad (2-9)$$

where ρ is the medium density, c is the speed of sound of the medium, T is the duration.

The acoustic field of the HIFU transducer is in a shape of the cigar at the acoustic power of 56 W as shown in Fig. 2-3, and its -6 dB beam size is about 1.8 mm×13.4 mm (lateral×axial). The lateral and axial distributions of acoustic intensity at the different location of the focal region are shown in Fig. 2-4. It is found that the acoustic intensity is very sensitive to the location in the acoustic field. Lateral distance of only 1 mm away from the focal point results in a significant decrease by about an order.

Figure 2-3. The distribution of acoustic intensity produced by the HIFU transducer. The side lobes can be seen beside the focal point as shown by the arrows.

Figure 2-4. (a) The lateral (x axis) and (b) axial (z axis) distribution of the acoustic intensity of the HIFU transducer.

Acoustic radiation force (ARF) is a well-defined phenomenon and was first described by Lord Rayleigh on the *Theory of Sound*. It is generated by the interaction between acoustic waves and the obstacle in its propagating path. The mechanisms include: change in the density of energy of the propagating wave due to absorption and scattering, reflection from inclusions or other interfaces, spatial variations in propagation velocity, and spatial variation of energy density in the standing acoustic

waves. When the ultrasound wave is absorbed or reflected by the tissue, the energy carried by the ultrasound waves will be transferred to a body force exerted on the tissue. The magnitude of radiation force is described as:

$$F = \frac{2\alpha I}{c} \quad (2-10)$$

where α in dB/m/MHz is the attenuation coefficient, I in W/m² is the acoustic intensity and c in m/s is the speed of sound in the tissue. The acoustic parameters are listed in Table 2-1.

Table 2-1 The acoustic parameters used in the radiation force simulation

Acoustic parameter	Value	Unit
c	1550	[m/s]
α	0.5	[dB/cm/MHz]

Figure 2-5 shows the acoustic radiation force distribution of the HIFU transducer. Since both c and α are constant and the inherent properties of material, the acoustic radiation force is proportional to the acoustic intensity (so that the shape is same as Figure 2-4). Grating lobes in the pre-focal region can be clearly seen in the figure, especially at $z = 6.2$ cm. Irregular force distribution can be found in the near acoustic field, which is due to the interference of acoustic wave. The acoustic radiation force achieves its maximum value at the focal point and decreases rapidly along the lateral and axial directions. It is noted that no significant scattering or reflection is considered here in the soft tissue, and acoustic absorption seems to dominate in the generation of acoustic radiation force in a small volume element. The acoustic intensity calculated here will be used later to induce the local displacement of tissue or

phantom. By adjusting the output power and geometry of the HIFU transducer for different system configurations and treatment operation, the ARF could be determined correspondingly and easily.

Figure 2-5. The distribution of the acoustic radiation force from the HIFU transducer.

2.6 Finite Element Method Analysis

After calculating the acoustic radiation force, we used the finite element method (FEM) to simulate the induced displacement distribution within the tissue-mimicking phantom using commercial FEM analysis software (ANSYS Inc., Canonsburg, USA). The ANSYS settings are summarized as follows:

(1) Computational model. We used the computational model as shown in Figure 2-6. There are two elliptical identical lesions in the tissue-mimicking phantom, and they are identical in the shape and size and aligned exactly vertical. The size of

phantom and lesion is 40 mm×40 mm and 15 mm×5 mm, respectively. The major axis of the elliptical lesion is parallel to the vertical axis. The gap between two lesions is 1 mm. The Young's modulus of lesions is 6 kPa which is 5 times as that of surrounding tissue [97]. The whole model is assumed linear, incompressible where the Poisson's ratio is set as 0.495.

Figure 2-6. (a) Schematic diagram of two ellipsoidal lesions in the tissue-mimicking gel phantom and (b) mesh setting in the finite element analysis software.

(2) Mesh setting. The triangular grid is adopted to discretize the computational zone. In the lesion zone, the mesh size for the lesion is much smaller than that for the phantom which can achieve the satisfactory computational accuracy and decreased time cost simultaneously. In total, about 23,000 elements and 12,000 nodes are used for the FEM analysis.

(3) Boundary condition and loading. The computational model has fixed boundary at the bottom and free boundary at the other sides, similar to the experimental situation.

Displacement of two lesions in the gel phantom was simulated using the FEM (see Fig. 2-7). 5% normal and quasi-static axial strain was applied to the top of the gel phantom, the produced stress and strain show that the gap between two lesions cannot be easily figured out in the axial strain elastogram (see Fig. 2-7b and Fig. 2-7c) because two hard lesions move together in almost the same magnitude in response to the compression and subsequently, produce the small displacement in the gap. This is an artifact of quasi-static ASE. Stress concentrations become more prominent in the close proximity of two or more masses. In comparison, the large axial shear strains concentrate on the outside corner of lesions with the small ones on the inside corners. Thus, it is also difficult to discern the gap in the quasi-static compression induced ASSE although the shear strain pattern has been used to differentiate between benign and malignant breast masses [98-100].

Figure 2-7. Simulation model of (a) two lesions in the gel phantom with quasi-static planar compression, and the simulated distribution of (b) stress, (c) axial strain, and (d) axial shear strain.

2.7 Ultrasound Simulation

The B-mode sonography of phantom and lesions was simulated using FIELD II, a Matlab acoustic toolbox (<http://server.elektro.dtu.dk/www/jaj/field/>). The Field II program uses the concept of spatial impulse responses [101, 102, 103]. The spatial impulse response provides the emitted ultrasound field at a specific point in space as a function of time when the transducer is excited by a Dirac delta function. The acoustic field for any kind of excitation, both the pulsed and continuous wave case, can then be

found by just convolving the spatial impulse response with the excitation function. The received response from a small oscillating point can be found by acoustic reciprocity, being equal to the spatial impulse response of such point emitting a spherical wave. Thus, the totally received response in pulse-echo is determined by convolving the transducer excitation function with the spatial impulse response of the emitting aperture and the receiving aperture [104, 105]. The system response is assumed to be linear. Thus, the result for the continuous wave case is found by Fourier transforming the spatial impulse response at the given frequency. The simulation program circumvents this problem by dividing the transducer surface into squares and the sum the response of these squares to yield the response. Thereby any transducer geometry and apodization can be simulated. Calculation burden is another major concern in the numerical simulation. Because the square elements consisting of the transducer surface are small, it is appropriate to use a far-field approximation. Furthermore, the sharp discontinuities of the response are accurately tracked and the integrated spatial impulse response is used as an intermediate step in the calculation to prevent the energy lost. Therefore, Field II can have better outcome using the sampling frequency of 100 MHz and approximate calculation than that using the exact analytic expression and GHz sampling. Now this program has been used widely in simulating the sonography.

Firstly, we assume that there are 100,000 scatterers within the tissue-mimicking phantom with a Gaussian distribution of the ability to reflect the acoustic waves along the path. The density of scatterers is similar to the previous studies [106] and should be sufficiently large to fully develop speckles for sonography.

The diagnostic transducer we used here has 192 elements in total and 64 active elements. The element height is 5 mm while the kerf is 0.05 mm. The operation cycle is 2 sine waves. The apodization method was used to eliminate the side lobes. The operation frequency is about 5 MHz and the sampling frequency is about 36 MHz. FIELD II can simulate different kinds of ultrasound imaging probes and compute the corresponding sonography using the concept of the spatial impulse response. Point spread function is the core of the FIELD II package as shown in Fig. 2-8, and raw RF data are available. All the displacement changes are based on the FEM simulation results using the approach mentioned in Section 2.4. It is found that the stiffness is not related to the gray level in the sonography because the HIFU lesion has similar acoustic backscattering ability and acoustic impedances as that of the surrounding soft tissue. After applying the quasi-static compression, the top surface of gel phantom has moved downward, but the B-mode sonography is similar to that before the compression as shown in Fig. 2-11.

Figure 2-8. (a) Distribution of scatterers in the gel phantom and (b) Gaussian distribution of their reflection abilities.

Field II has been used widely in the simulation of sonography. One example of a 3-month-old fetus is shown below. 200,000 scatterers were randomly distributed within the phantom, and their scattering amplitudes have a Gaussian distribution. The phantom was scanned with a 5 MHz 64 element phased array transducer with $\lambda/2$ spacing and Hanning apodization. A single transmit focus 70 mm from the transducer was used, and focusing during reception is at 40 to 140 mm in 10 mm increments. The simulated image consists of 128 lines with 0.7 degrees between lines (as shown in Fig. 2-9). It is noted that the anatomy presented as the different levels of the scatterer map is clearly seen as the same boundary features in the sonography.

Figure 2-9. (a) Map of scatterers in a synthetic fetus and (b) the simulated B-mode sonography [107].

2.8 Displacement Calculation

Figure 2-10. Schematic diagram of calculating the displacement of scatterers by cross-correlating the RF data before and after the compression.

The displacement measurement plays a fundamental and important role in the elastography study. After obtaining the RF data from the ultrasound imaging probe, several methods such as 1-D cross-correlation algorithm, global stretching method, and spectral cross-correlation analysis method, have been used to extract the displacement information [108-110]. Fig. 2-10 illustrates the conventional 1-D conventional cross-correlation method. A window (red waveform) from the post-compression RF data is cross-correlated with the different corresponding windows from the pre-compression in order to determine the most matched one. Calculation of the cross-correlation coefficient is repeated while moving the window, and displacement is defined as the amount of movement when the correlation is at its maximum.

$$R(\delta) = \frac{\int x(z;t)y(z+\delta;t)dt}{\sqrt{\int x^2(z;t)dt \int y^2(z+\delta;t)dt}} \quad (2-11)$$

where $x(z;t)$ and $y(z;t)$ are echo signals before and after compression, respectively,

which are clipped out in the window centered around a depth of z .

Figure 2-11. Comparison of B-mode sonography (a) before and (b) after the compression.

Fig. 2-11 shows the simulated B-mode sonography before and after the compression. In order to accurately calculate the stress and strain in the sample, 1D displacement is not sufficient. Therefore, 2D search strategy is required.

Figure 2-12. Schematic diagram of the matched 2D block pair (black boxes) in calculating the compression-induced displacement.

2-D block matching method was used widely to estimate the tissue motion [111-113]. In this thesis, we adopt it as shown in Fig. 2-12. Every rectangular kernel selected from the pre-compression RF frame is compared with the blocks within the searching region of the post-compression frame. The kernel size is set as 11 axial samples by 9 RF data lines (11×9). The sum-squared difference (SSD) calculation equation is as followed,

$$SSD = \sum_{i=-4}^4 \sum_{j=-5}^5 (r_1(I+i, J+j) - r_2(I+i+u, J+j+v))^2 \quad (2-12)$$

where r_1 and r_2 are the pre- and post-compression RF field; I and J are the axial and lateral coordinate for the point where displacement is measured, respectively; u and v are the axial and lateral searching length, respectively.

Figure 2-13. (a) Schematic diagram of a spherical inclusion in the gel phantom and (b) the error detection and correction in the displacement line [114].

Fig. 2-13 shows a typical error in the displacement estimation. A three-step auto-correlation method was designed to solve this problem. Firstly, a displacement line is cut into three groups. Separation occurs when the difference in the displacement is over 3 samples. Secondly, two non-continuous groups can merge when the difference between two nearest points is smaller than 3 samples. Finally, the group

which consists of more than 70% of all points is recognized as the right one and the remaining points from the other groups are deleted. Then the corrected displacement line is formed by the interpolation of the right ones.

Errors of the displacement calculation may occur due to the decorrelation of RF data. As shown in Fig. 2-13, assume that the phantom (40 mm×40 mm) has a stiff circular lesion ($r = 2.5$ mm) at the center and 5% strain is applied. The maximum axial displacement (on the top of phantom) can be calculated as 2 mm (40mm×5%). The sampling frequency is 72 MHz, which means that its wavelength is about $1500 \text{ m/s}/72 \text{ MHz} = 20.83 \text{ } \mu\text{m}$. So the maximum axial searching range can be 96 samples (2mm/20.83 μm). In addition, the lateral distance also needs to be considered. The Poisson's ratio of the biological tissue is around 0.495 so that the maximum lateral displacement is 0.99 mm (2 mm×0.495). Assume that there are 201 A-lines in the whole echoic field. The distance between two adjacent lines is 0.2 mm (40 mm/200) so that the maximum lateral displacement is about 5 A-lines (0.99 mm/0.2 mm). After computing the both axial and lateral searching range, the displacement of the first row in the echoic field can be determined. To further reduce the calculation time, the displacement of other rows can be guided by the first row. Assume the axial and lateral distances between two adjacent points are 16 samples and 5 A-lines in the displacement. Here 16 samples were selected personally to guarantee the availability of matched groups in the searching range. Too many samples may lead to the beyond searching range while too few may result in longer searching time. The axial and lateral displacement difference should be less than 1 sample (16×5%) and 1 A-line

(5×5%). Therefore, only a 3×3 searching region is enough to cover the exact corresponding block based on the previously estimated displacement.

Figure 2-14. Comparison of the axial displacement using (a) the FEM method and (b) the block matching method.

Fig. 2-14 shows the displacement map reconstructed using the block matching method has good consistency with the simulated one using the FEM method. There is little difference between them, which confirms the feasibility and reliability of block matching method.

2.9 Lesion Elastography

Fig. 2-15 shows the obtained axial strain elastogram (ASE) by compressing the tissue using a quasi-static normal displacement from the top. Although two elliptic HIFU lesions are relatively clear in the ASE, the gap between lesions cannot be detected. In practice, the lesions should be overlapped to make sure all gaps are filled with the whole treatment volume. The HIFU-induced coagulation can block the supply of blood for the solid tumor and cancer cells will lose their viabilities because of lack of the nutrition. If there are some gaps between lesions after HIFU therapy, the cancer cells can grow out of the treated region which leads to the failure of HIFU treatment. The aim of the guided HIFU treatment is to make sure all the tumor volume can be ablated by HIFU doses. In the ASE, the gap region is greatly affected by the lesions aside because the lesions can support most of the compression from the top and the gap region has relatively small axial strain. So the gap cannot clearly be detected because of the lateral lesions.

Figure 2-15. The axial strain elastography of two lesions in the gel phantom.

2.10 Preliminary RF Data Collection

The collection of experimental RF data is the first and critical step for elastography experiment. In this thesis, a simple RF data sample was obtained in order to testify the feasibility for the further research work. Here Ultrasonix Sonix RP system (BK Ultrasound, Peabody, MA, USA) was used for RF data collection. The central frequency of the transducer (L14-5/38) is 14 MHz and bandwidth is 60%. The sampling frequency is about 40 MHz. For the preliminary experiment research, we used this machine to examine the human arm surface and obtain the B-mode image as shown in Fig. 2-16. RF data were saved as binary files. A Matlab code was used to read RF data file, and then Hilbert transform was used to analyze RF data and reconstruct the B-mode image. The Hilbert transformation filter acts like an ideal filter that removes all the negative frequencies and leaves all positive frequencies untouched.

$$F(t) = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{f(x)}{t-x} dx \quad (2-13)$$

Fig. 2-16 shows the B-mode sonography from the RF data analysis. It can be seen that B-mode sonography calculated from RF data is similar to that displayed on the screen of our sonographic system which means that the obtained RF data from the device and our image reconstruction algorithm are correct. The difference between them may be due to the digital image processing used by the sonographic system to enhance the signal-to-noise ratio and contrast which are not available and explicit for the end user. However, this is not a critical issue in the future elastogram reconstruction.

Figure 2-16. Comparison of sonography shown in an ultrasound imaging system (dashed white box in the left) and (b) reconstructed one using the raw RF data (right).

2.11 Plane Wave Imaging (PWI)

Traditional sonography is realized by sweeping the region-of-interest using a series of successive focused or multi-focused beams and then stacking all scanlines. Thus, the reconstruction time of sonography is proportional to the number of scanlines and the maximal depth in the image. Subsequently, the frame rate is about 30-50 Hz.

Ultrafast sonography is an emerging modality in the diagnosis, which provides new perspective and opportunities. Technical advances in the last decades, such as parallel computation [115], high-performance data transfer [116], and high-speed processor [117], allows the production of the sonographic image from a single transmit. In plane wave imaging (PWI), a plane wave is formed and excited from all the elements of ultrasound imaging probe [118]. Diffraction hyperbola that presents the inhomogeneous point spread function for PWI is produced from scatterer as the receiving RF data by all elements simultaneously. In the reconstruction of sonography, all the hyperbolas should be migrated back for coalescence back into their apexes. Theoretically, frame rate up to 15,000 Hz can be attained for a 5-cm imaging depth [119]. This method could also be applied in the transient elastography, ultrafast Doppler imaging, ultrafast vector flow mapping, and functional brain imaging [120, 121, 122].

In the beamforming of plane wave echo RFs in a high image quality, migration method in the frequency-wavenumber (f - k) domain is carried out [123]. This algorithm is adapted from the Stolt migration for seismic imaging [124, 125], which is based on the exploding reflector model (ERM). The ERM is suitable for PWI by a spatial transformation of the hyperbolic traces present in the RF data. In comparison to the conventional delay-and-sum (DAS) approach and Fourier-based method [126-130], the Stolt's f - k migration has comparable or even better contrast-noise ratio and lateral resolution. Multi-angle compounded f - k migration images with a very small number of steering angles are of quality similar to those obtained with a state-of-art dynamic

focusing mode.

Assume $\Psi(x, z, t)$ is a wavefield of the ERM satisfying the linear two-dimensional wave equation and $\Phi(k_x, z, f)$ is the Fourier transform of $\Psi(x, z, t)$ over (x, t) so that

$$\Psi(x, z, t) = \iint \Phi(k_x, z, f) e^{2i\pi(k_x x - ft)} dk_x dt \quad (2-14)$$

where k_x is the spatial wavenumber related to x and f is the temporal frequency. The Fourier transform to the wave equation yields the following Helmholtz equation

$$\frac{\partial^2 \Phi}{\partial t^2} + 4\pi^2 \hat{k}_z^2 \Phi = 0 \quad (2-15)$$

where the wavenumber of k_z is given by

$$\hat{k}_z^2 = \frac{f^2}{c^2} - k_x^2 \quad (2-16)$$

where c is the speed of sound in the medium. The unique boundary condition is $\Phi(k_x, 0, f)$, which is the Fourier transform of $\Psi(x, z=0, t)$. The wave equation can be solved to obtain the migrated wave field

$$\Psi(x, z, 0) = \iint \Phi(k_x, 0, f) e^{2i\pi(k_x x - \hat{k}_z z)} dk_x df \quad (2-17)$$

To benefit from the Fourier transforms, k_z is changed to the following form

$$f(k_z) = \hat{c} \text{sign}(\hat{k}_z) \sqrt{k_x^2 + \hat{k}_z^2} \quad (2-18)$$

Then the Stolt's migration solution is finally derived as

$$\Psi(x, z, 0) = \iint \frac{\hat{c} \hat{k}_z}{\sqrt{k_x^2 + \hat{k}_z^2}} \Phi(k_x, 0, f(\hat{k}_z)) e^{2i\pi(k_x x - \hat{k}_z z)} dk_x d\hat{k}_z \quad (2-19)$$

Then the migrated solution is basically the inverse Fourier transform of

$$\frac{\hat{c} \hat{k}_z}{\sqrt{k_x^2 + \hat{k}_z^2}} \Phi(k_x, 0, f(\hat{k}_z)) \quad (2-20)$$

The f - k migration of PWI-derived RF data is realized in the three-step process for sonography reconstruction as summarized below and shown in Fig. 2-17.

1. The leading zeros of the RF data resulting from the emission delays are removed by calculating the travel time

$$\tau_s(x) = \frac{1}{c} \left[\sin \theta (x_s - x) + \cos \theta z_s + \sqrt{(x_s - x)^2 + z_s^2} \right] \quad (2-21)$$

where θ is the tilting angle of the plane wave from the horizontal direction. This signal trimming could align the hyperbolas of same apical curvature horizontally, but could slightly distort the hyperbolas, especially at large steering angles.

2. The Stolt's migration algorithm described by Eqs. (2.18) and (2.19) is applied using the ERM velocity

$$\begin{cases} \hat{c} = \alpha c \\ \hat{z}_s = \beta z_s \\ \hat{x}_s = x_s + \gamma z_s \end{cases} \quad (2-22)$$

$$\begin{cases} \alpha = 1 / \sqrt{1 + \cos \theta + \sin^2 \theta} \\ \beta = \frac{(1 + \cos \theta)^{3/2}}{1 + \cos \theta + \sin^2 \theta} \\ \gamma = \frac{\sin \theta}{2 - \cos \theta} \end{cases} \quad (2-23)$$

3. Coordinate transformations $(\hat{x}_s, \hat{z}_s) \rightarrow (x_s, z_s)$ are performed to back into the actual position.

These basic 3 steps can be implemented in the Fourier domain to achieve the significant computational speed. Fast Fourier transform (FFT) is applied to the data laid on a regular grid by interpolation or other gridding methods. An algorithm, linear interpolation after extensive zero-padding in the first FFT: $\Psi(x, z=0, t) \rightarrow \Phi(k_x, 0, f)$ is applied for simplicity.

Figure 2-17. Diagram of the Stolt's f - k migration algorithm of the RF signals for plane wave imaging. The parameters k_x and f stand for the spatial wavenumber and the temporal frequency, respectively, and the wavefront angle θ is defined relative to the transducer, with courtesy of [123].

Chapter 3 Axial Shear Strain Elastography

Initially, 5% compression was applied to the top of the gel phantom with two identical lesions as that of axial strain elastography. Note that high axial strain presents in the area adjacent to the upper and lower parts of lesions and it's not easy to judge whether there is a gap zone between lesions in the axial strain elastogram (ASE, see Fig. 2-15). In addition, the quasi-static compression is labor- and time-consuming for real-time monitoring in HIFU ablation.

3.1 Transient Dynamic Analysis

Figure 3-1. Schematic diagram of acoustic radiation force applied to the HIFU lesion.

The distribution of acoustic radiation force calculated in Section 2.5 is applied to the lesion, and the HIFU focus is aligned to the center of the lesion. The acoustic radiation force is proportional to the integration of time so that it increases linearly from zero to the maximum value at $t = 0.1$ s. After that, the HIFU exposure is turned off and the acoustic radiation force decreases to zero in the relaxation process. This dynamic vibration of lesion-embedded gel phantom is calculated by the transient dynamic analysis module of ANSYS software. The phantom is considered as elastic and homogeneous medium. Here the Rayleigh model is used to describe the dynamic process as following:

$$M \frac{d^2 u}{dt^2} + C \frac{du}{dt} + Ku = f \quad (3-1)$$

where u is displacement vector, M is the mass matrix, C is the damping matrix, K is the elasticity matrix, and f is the vector of nodal excitation force. We use the Rayleigh damping model to determine the matrix C expressed by the following equation:

$$[C] = \alpha[M] + \beta[K] \quad (3-2)$$

where α and β are the Rayleigh damping parameters. These two numbers are not fixed for different organs of human. Here we set them as 6.22 and 0.01, respectively [131].

Figure 3-2. Dynamic axial shear strain of lesions in the phantom induced by 0.1 s-HIFU exposure.

The on-going displacement distribution during and after 0.1 s-HIFU exposure in the simulation is shown in Fig. 3-2. The axial shear strain induced by the acoustic radiation force becomes larger as the progress of HIFU exposure. At the time of 0.1 s, the largest axial shear strain can be found in the lesion gap region. Obviously, the gap region presents higher axial shear strain by the transient and local acoustic radiation

force than that by the quasi-static compression (see Fig. 2-7d). Point 1, 2 (center and right end of the being treated lesion, respectively), 3 and 4 (left end and center of the already treated lesion, respectively) as shown in Fig. 3-2 (the interval distance between them is 2.5 mm, 1 mm and 2.5 mm, respectively) are used to monitor the displacement within the tissue (see Fig. 3-3). It is found that the displacement of all observation points increase almost linearly from zero to the maximum values at $t = 0.1$ s (negative value meaning the compression). When the acoustic radiation force is terminated after 0.1 s, all the observation points return to zero exponentially. Such relaxation process is much quicker than the transient compression, which shows the necessity of fast in the RF data acquisition during the relaxation process. The transient responses at different locations are almost in the same way, and the amplitude is determined by the acoustic radiation force applied to it and the distance to the focal point of the HIFU transducer.

Figure 3-3. The temporal change of displacement of 4 points during and after 0.1 s-HIFU exposure.

Figure 3-4. Comparison of the (a) axial- and (b) lateral-shear strain produced by the 0.1 s-HIFU exposure.

Meanwhile, we also calculated the lateral-shear strain at the moment of maximum displacement at the HIFU exposure of 0.1 s (see Fig. 3-4). It is found that much smaller lateral shear strain shows at both bottom and top of the being treated lesion. However, there is no significant increase of the lateral shear strain in the gap zone so

that the measurement of lateral-shear strain may not be sufficiently sensitive for our proposed lesion gap detection. It is well known that the ultrasound detection of the lateral displacement is not as accurate as that of the axial displacement.

3.2 Axial Shear Strain Elastography

In this thesis, we develop a method of using the remote acoustic radiation force of HIFU exposure to detect the lesion gap during HIFU treatment. It may allow the operators to determine the HIFU dose required in the treatment and to enhance the success of ablation. Currently, the operators usually perform the ablation empirically.

Figure 3-5. Elastogram of axial strain (in gray) overlaid with the axial shear strain (in color) of two lesions with the gap of 1 mm between them in the gel phantom.

The acoustic radiation force generated by the HIFU transducer is applied to the tumor with two lesions, and the duration of HIFU pulse is about 0.1 s. Fig. 3-5 shows the axial strain (in gray) overlaid elastograms of axial shear strain (in color). The axial

shear strain is only retained if its value is either higher than 0.015 or lower than -0.015. It is clear that those blue and red regions are located at the both sides of the being treated lesion, and very prominent high red axial shear strain can be found at the gap between the lesions (see the white arrow). This phenomenon is because that the lesions are too hard to distort and the gap zone between them will move together with the adjacent lesions. As a result, the normal soft tissue between two HIFU-induced lesions will produce large axial shear strain. It is noted that although the tissue in the lesion gap zone still has low stiffness, the axial strain is still low because its motion is significantly limited by the surrounding hard lesion-induced small displacement.

Fig. 3-6 shows that the axial shear strain elastogram for the two lesions without a gap between them. It can be seen that high axial shear strain between two lesions disappears which means that these two lesions are already overlapped in comparison to Fig. 3-5. The axial shear strain in the left region of sonication gradually reduces with the distance away from the focus because the tissue there is normal and continuous toward the slip boundary. However, in the right region of the axial shear strain elastogram, the presence of hard lesion will block the continuity of the axial shear strain. Altogether, a strong axial shear strain in the ASSE with low axial strain is a promising hint of the lesion gap zone for monitoring the HIFU ablation and lesion growth.

Figure 3-6. Elastogram of axial strain (in gray) overlaid with axial shear strain (in color) of two lesions without the gap between them in the gel phantom.

3.3 Effect of Parameters on Axial Shear Strain Elastography

In this section, we discuss some important issues and questions for the gap detection using ASSE by the remote and local acoustic radiation force, such as sensitivity and reliability. For example,

- (1) What is the minimum gap width that can be detected?
- (2) What is the minimum lesion size that can be detected?
- (3) What is the minimum acoustic radiation force that can induce enough displacement and axial shear strain for the gap detection?

We intend to evaluate the performance of proposed remote ASSE before carrying out the experiment for further experimental validation.

3.3.1 Lesion growth

At first, a simulation has been carried out to show the growth of a lesion from the size of $6\text{ mm} \times 2\text{ mm}$ to $15\text{ mm} \times 5\text{ mm}$ and the corresponding decrease of gap width from 1.5 mm to 0 mm with the on-going of HIFU ablation (the size of the already treated lesion on the right is $15\text{ mm} \times 5\text{ mm}$) as shown in Fig. 3-7. It is found that the axial shear strain across the center of these two lesions increases with the gap width between them. So the magnitude of axial shear strain can be used to judge whether there is a gap or not and may correlate approximately with the gap size. The corresponding axial shear strains across the lesion centers with decrease the lesion gap width (GW) from 1.5 mm to 0 mm are shown in Fig. 3-8.

Figure 3-7. Comparison of axial shear strain distribution when the left (being-treated) lesion grows to decrease the lesion gap width (GW) from 1.5 mm to 0 mm.

Figure 3-8. Comparison of axial shear strain across the lesion centers with the decrease of the lesion gap width (GW) from 1.5 mm to 0 mm.

3.3.2 Acoustic radiation force

The acoustic radiation force is determined by the acoustic intensity of the HIFU field. Weaker acoustic radiation force can induce less displacement and axial shear strain. We observe the distribution of axial shear strain along a line that crosses the center of lesions. The differences of axial shear strain between the lesions without and with gap zone is found to become less significant with the decrease of acoustic radiation force. Since the sampling frequency is fixed, the minimum detectable displacement is consistent. Greater noise would occur when the force is not large enough to induce the sufficient displacement. In contrast, larger displacement can improve the image quality of our reconstructed elastograms. In Figs. 3-9 and 3-10, it can be inferred that the acoustic radiation force density of 203.3 kN/m^3 can generate the sufficiently large axial shear strain to discern the gap between two lesions. If the acoustic power of actual HIFU treatment is only 56 watts, which is quite low in clinics, the corresponding acoustic radiation force density is 290.4 kN/m^3 . Therefore, the

acoustic radiation force from the HIFU pulse itself is strong enough to generate large enough displacement and to allow accurate measurement using the RF data of sonography.

Figure 3-9. Comparison of two lesions (1.5mmx5mm) with the gap of 1.5 mm (insufficient treated) and no gap (sufficient treated) with response to the acoustic radiation force density of 290.4, 246.8, and 203.3 kN/m³.

Figure 3-10. Comparison of two lesions (12mm×4mm) with the gap of 0.5 mm (insufficient treated) and no gap (sufficient treated) with response to the acoustic radiation force density of 290.4, 246.8, and 203.3 kN/m³.

3.3.3 Gap width

The detectable gap width in the ASSE is affected by the element size of the ultrasound imaging probe. In this thesis, we used a probe with the element width of 0.44 mm and the total width of 15 mm so that there are about 34 raw RF data lines in the B-mode ultrasound image in the experiment. The minimum width between two consecutive data lines is about 0.2 mm which is the threshold of detectable gap. Here two series of simulation have been performed to analyze the minimum gap width. In Figs. 3-11 and 3-12, the lesion size is fixed as 15 mm $\times$ 5 mm and 12 mm $\times$ 4 mm, respectively, but with varied gap width of 1.2 mm, 0.7 mm, 0.3 mm, and 0 mm (no gap). In the first case, the smallest gap width can be detected by the axial shear strain elastography in the ideal simulation is about 0.3 mm. Here, the difference of axial shear strain between two HIFU-generated lesions with and without the gap zone larger than 5% is defined as detectable gap. Overall, the accuracy of gap detection using the proposed approach may be sufficient for monitoring the practical HIFU ablation. It is noted that no noise was included in this FEM simulation.

Figure 3-12. Comparison of two lesions (12 mm × 4 mm) with varied gap width of 0 mm, 0.3 mm, 0.7 mm, and 1.2 mm with response to the acoustic radiation force density of 290.4 kN/m³.

3.3.4 Lesion size

During HIFU treatment, different sizes of lesions can be generated. The size is dependent on the frequency and geometry of the HIFU transducer as well as the accumulated thermal dose. In this thesis, three sizes of elliptical lesions with the same eccentricity, $15\text{ mm} \times 5\text{ mm}$, $12\text{ mm} \times 4\text{ mm}$, and $9\text{ mm} \times 3\text{ mm}$, with the gap width of 1 mm and 0.5 mm between them have been used to investigate the effect of lesion size on the gap detection by the ASSE as shown in Figs. 3-13 and 3-14. So a criterion is used to describe the axial shear strain value. It can be seen that lesions in the size of even $9\text{ mm} \times 3\text{ mm}$ can be detected using the proposed method. The distribution of axial shear strain along the center of two lesions has a peak, whose location is in the gap zone and on the right of the already-treated lesion for insufficiently and sufficiently treatment, respectively. So the peak location could be another hint in detecting the presence of gap zone between HIFU-generated lesions.

Figure 3-13. Comparison of two lesions with the varied size of 15 mm × 5 mm, 12 mm × 4 mm, and 9 mm × 3 mm with the gap width of 1.1 mm (insufficiently treated) and no gap (sufficiently treated) with response to the acoustic radiation force density of 290.40 kN/m³.

Figure 3-14. Comparison of two lesions with varied size of 15 mm × 5 mm, 12 mm × 4 mm, and 9 mm × 3 mm with the gap width of 0.8 mm (insufficiently treated) and no gap (sufficiently treated) with response to the acoustic radiation force density of 290.4 kN/m³.

Plenty of numerical simulations were carried out and shown above. It is critical to propose a criterion to determine whether there is a gap zone between two lesions at various testing conditions. The absolute ratio of axial shear strain in the middle of two lesions to that on the left side of the being treated lesion is found to be a key parameter, such as the acoustic radiation force density, gap width, and lesion size, as shown in Fig. 3-15. All lesions with gaps as small as 0.3 mm have a ASS ratio larger than about 0.75 while those without a gap or sufficiently treated lesions have a small value of ASS ratio.

Figure 3-15. Comparison of the ratios of ASSE at (a) different acoustic radiation force densities, (b) gap width, and (c) lesion size.

3.4 Discussion

In this chapter, we proposed a method to monitor the HIFU procedure and evaluate its performance numerically. During HIFU ablation, some long interval time between the HIFU bursts (i.e., ~ 1 s) could be utilized to detect the displacement and axial shear strain and subsequently, monitor the gap between lesions. In Chapter 2, the FEM simulation results showed that 0.05 s is sufficient to restore the tissue to its initial position. Thus, the interval time of 0.1 s is long enough to obtain the displacement map. Such a time is much shorter than the total HIFU exposure at a single location for lesion formation, which is usually on the order of ten seconds. Therefore, the time spent to ablate the whole tumor would not be elongated significantly.

The accuracy and computation speed of elastography reconstruction is mainly dependent on the calculation of particle displacement. The computation load could be

further reduced by performing the 2D search sparsely [111]. The resolution and accuracy of the lateral displacement are not as high as those of axial one because the lateral sample space is much greater than that in the axial direction. The lateral sampling space is dependent on the interval space between elements in the linear array transducer working in the pulse-echo mode while the axial one is dependent on the sampling frequency of ultrasound acquisition system and the speed of sound in the ROI. For the real-time application, a 2D search region for every certain number of rows will be utilized, and then the next rows of displacement will be estimated using the axial displacement estimation and 1D search, which may reduce the computation load without compromising the accuracy of displacement detection. A more aggressive strategy of the 2D search can be used to only estimate the axial displacement for the first row and then use it to predict the axial displacement of the remaining rows.

Displacement estimation error is critical for us. The large errors usually appear in the first row due to the inherent decorrelation between pre- and post-compression RF data and periodic ambiguities (false-peaks) associated with large search regions. When using the predicted displacement to reduce the size of the searching region, another type of displacement estimation error occurs and accumulates if it is so large that the search region cannot enclose the true displacement. Large and irregular deformation of tissue/phantom may cause local decorrelation in the RF data pair, which tends to accumulate when estimating the displacement near those local regions. In order to reduce such estimation errors, several strategies have been developed. For example, a segmentation method is applied to the displacement estimates for each row

from left to right if the difference between adjacent displacement estimates is larger than 2 samples. Then non-adjacent groups are merged if the difference between two nearest ending points of two groups is smaller than a certain threshold (i.e., 3 samples). Finally, the group with the largest number of displacement estimates is assumed to be correct one while the others as wrong ones. To correct the error, linear interpolation is applied for the displacement values of the wrong groups using the values of the correct group. Such error detection and correction strategy is applied to every a certain number of rows because the small search region prevents large displacement deviations between adjacent rows and the displacement errors gradually accumulate.

Chapter 4 Experimental Validation

4.1 Introduction

In Chapter 3, we have already shown numerically that the remote acoustic radiation force from the HIFU burst during the treatment applied to the being treated lesion could generate large axial shear strain if there is a gap in the region adjacent to the already produced lesion, which would be an effective approach of monitoring the sufficient lesion production. Whether the proposed technology could produce promising results in the experiment is a critical issue for the future clinical translation. In this chapter, we measured the axial shear strain using an ultrasound research platform in the tissue-mimicking phantom and *ex vivo* tissue samples.

4.2 Experimental Setup and Sample Preparation

An annular single-element HIFU transducer (H-172, Sonic Concept) was used in this study, and an ultrasound imaging probe (L14-5/60W) was integrated with the HIFU transducer and aligned coaxially and confocally. The HIFU transducer was driven by the electrical signal generated by a function generator (AF3021B, Tektronics, Beaverton, OR, USA) and amplified by an RF power amplifier (BT1000-AlphaA, Tomco Technologies, Adelaide, Australia). RF data from the imaging probe were acquired with an ultrasound research platform (Sonix-500 RP, Ultrasonix Medical, Richmond, BC, Canada). Both the HIFU transducer and the phantom were immersed in the degassed and deionized water ($O_2 < 4 \text{ mg/L}$, $T = 25^\circ\text{C}$, measured by DO700,

Extech Instrument, Waltham, MA, USA) in a Lucite tank ($L \times W \times H = 50 \text{ cm} \times 35 \text{ cm} \times 25 \text{ cm}$). The integrated transducers were mounted on a 3-D stepper motor system (BiSlide, Bloomfield, Velmex, NY, USA). Sample holder is made from a clear acrylic sheet (Ying Kwang Acrylics Trading, Singapore). The experimental setup is shown in Fig. 4-1.

The motion of an array of markers in the gel phantom was recorded using a high-speed camera (S-PRI plus, AOS Technologies AG, Dättwil, Switzerland), working at 1,000 frames per second in a resolution of 640 by 480 pixels. An optical lens (focal length from 12.5 to 53 mm, $f/1.8D$, Nikon, Tokyo, Japan) and a set of the close-up lens (Nikon) were mounted on the camera to achieve an appropriately magnified view. The camera was triggered by a transistor-transistor logic (TTL) pulse from a digital delay generator (DG535, Stanford Research Systems, Sunnyvale, CA) to synchronize the photography with HIFU exposure, and the recording started 10 ms before the delivery of HIFU pulses. Because of the limited memory in the camera, only one second of HIFU exposure was recorded. A 1,000 W white light (Model H10, Hi-Tech Electronics, Singapore) was used as the illumination source in the photography. The individual frame could be extracted from the captured videos using software (AOS imaging Studio V3, AOS Technologies AG) companied with the high-speed camera.

Figure 4-1. (a) Schematic diagram, (b) and (c) photos of the experimental setup.

The optically transparent polyacrylamide gel with 10% of bovine serum albumin (BSA) which becomes denatured at temperatures over 60-65°C and opaque was prepared to evaluate the HIFU-induced lesion. Briefly, the liquid mixture of polyacrylamide (9%), BSA, and the Tris-Buffer (5%) was degassed for about 1 h in a desiccant chamber (420100000, Scienceware, Pequannock, NJ) by a vacuum pump (VTE8, Thomas, Sheboygan, WI) at a pressure of 150 mbars, then the degassed mixture was poured into a custom mold ($L \times W \times H = 5 \text{ cm} \times 5 \text{ cm} \times 4 \text{ cm}$). The polymerization was then finalized by the addition of a 10% (w/v) ammonium persulfate solution (APS, Sigma-Aldrich, Singapore) and N,N,N',N'-tetra-methylethylenediamine (TEMED, Sigma-Aldrich) in 5 min. The

concentrations of tris-buffer and polyacrylamide are a little lower than the protocol used in most HIFU phantom [97] while the concentration of BSA is higher in order to increase the stiffness ratio of the lesion to the surrounding medium.

Because the phantom is transparent, an array of lesions (12×12) were produced as markers for photography. Low HIFU power (peak-to-peak voltage from the function generator of 230 mV running in the continuous wave mode for about 0.3 s) was used for the lesion production. The interval distance is 2 mm. Lesion size is about 1 mm in diameter, but not consistent. High HIFU power (peak-to-peak voltage from the function generator of 260 mV running in the continuous wave mode for about 10 s) was used to simulate the clinical tumor ablation. That kind of lesion has the size of about $2 \text{ mm} \times 6\text{-}8 \text{ mm}$ (lateral $\times$ axial). No gap and a gap of about 1.5 mm were used for comparison (see Fig. 4-2). Then polyacrylamide gel phantom was embedded inside another semi-transparent gelatin phantom (powder to water ratio of 1:10 for solution). This uniform gelatin phantom did not produce too much speckle noises in the sonography. At the bottom of the gel phantom compound, a piece of rubber absorber was aligned to reduce the acoustic reflection in the B-mode sonography.

Figure 4-2. Photos of phantoms with two embedded HIFU lesions (a) without a gap and (b) with 1.5 mm gap between them. The interval distance of an array of tiny markers is 2 mm.

Fresh porcine kidney and liver samples were purchased from the local grocery store. Samples were immersed in PBS and degassed in a vacuum oven for 30 min before the experiment. The kidney medulla and liver were cut into the size of 2.5 cm×2.5 cm×1 cm and enclosed into the polyacrylamide gel without BSA in the mixture before polymerization. Then the sample was surrounded by gelatin as that for BSA gel phantom.

Figure 4-3. Photos of *ex vivo* porcine liver embedded in the polyacrylamide gel for the experiment.

4.3 Data Acquisition and Processing

In the gel phantom experiment, HIFU exposure is 100 ms at the peak-to-peak voltage of 350 mV from the function generator. Such a short HIFU exposure did not have a significant influence on the lesion size according to our observation. In the *ex vivo* experiment, the lesion was produced in the tissue sample by the continuous wave at the peak-to-peak voltage of 200 mV for 9 s. The gap between two lesions is about 1.5 mm. The HIFU pushing was generated from the function generator at the peak-to-peak voltage of 200–300 mV for 100 ms. The size of produced HIFU lesion is about 8–12 mm and 2.5 mm in the major and minor axis, respectively.

Ultrasound RF data were acquired using Sonic RP system using the ultrasound imaging probe (L14-5/60W) at the central frequency of 9.5 MHz. Using the software development kit (SDK) accompanied with the research platform Sonic DAW (Ultrasonix), the number of scanlines can be changed. As a result, the frame rate is changed correspondingly. The distance between the imaging probe and rubber absorber sheet is about 12 cm so that each scanline is about $160\text{ }\mu\text{s}$ ($12\text{cm}/1500\text{m/s}\times 2$, round trip for acoustic pulse transmission and receiving). The total acquisition time of 12 scanlines is about $160\text{ }\mu\text{s}\times 12 = 1.92\text{ ms}$, which corresponds to about frame rate of 500 Hz. Because of the electromagnetic interference, ultrasound RF acquisition starts about 3 ms after the termination of HIFU exposure. The acquired ultrasonic RF data were transferred to a standard desktop PC (AMD QC-4000 1.3-GHz CPU, 4 GB RAM, Windows 8.1) to process and generate ASSEs offline. B-mode sonography was first produced through the Hilbert transform and log-compression of the RF echo frame. To

minimize the computation overload, the ASSEs were computed and shown only over restricted regions of interest (ROI) containing the HIFU-induced lesions.

In the *ex vivo* experiment, planar wave excitation was used. In order to improve the image quality, planar waves at 4 angles (0° , 0.98° , 1.88° , and 2.87°) were used and then the RF data were summed and averaged. Beamforming was carried out in the frequency-wavenumber (f - k) domain, Stolt's f - k migration, to reconstruct the B-mode sonograph [123]. The diagram and algorithm are shown in Fig. 2-17. Subsequently, the frame rate could be as high as 1 kHz.

4.4 Gel Phantom Experiment

4.4.1 Static ASE in photography

In the first step, static compression of the gel phantom was applied to its top. The photos of gel phantom before and after the quasi-static compression were recorded by a digital camera, the position of each marker was determined by edge detection in digital imaging processing toolbox in the software. Then the axial strain elastogram (ASE) was generated. It is found that two lesions in the gel phantom with and without gap zone between two HIFU-induced cigar lesions and markers move in a similar way. As a result, the calculated ASE in these two cases is very similar (see Figs. 4-4 and 4-5). Because of the limited number of markers produced in the gel phantom, the resolution of ASE is not very high. But it will not affect our conclusion that ASE is not sensitive to the presence of lesion gap as shown in our numerical simulation. In addition, such limitation is not a problem in our ultimate goal using sonography.

Figure 4-4. Photos of the phantom (without a gap) before (a) and after (b) static compression, and (c) the reconstructed axial strain elastogram.

Figure 4-5. Photos of the phantom (with a gap) before (a) and after (b) the quasi-static compression, and (c) the reconstructed axial strain elastogram.

4.4.2 Dynamic ASSE in photography

The motion of gel phantom with markers produced by the HIFU pulse with the duration of 100 ms was recorded by the high-speed photography. Both ASE and ASSE

were calculated and compounded. It is found that if there is no lesion gap the already treated lesion moves together with the being treated one during HIFU exposure. Subsequently, the axial shear strain was found on both sides of the merged lesions, but not in the lesion region (see Fig. 4-6).

Figure 4-6. Photos of the phantom (without a gap) before (a) and after (b) HIFU compression, and (c) the grey axial strain elastogram overlaid with the colorful axial shear strain elastogram.

In comparison, if there is a gap between two lesions (gap width of about 1.5 mm), the being treated lesion moves significantly with response to the acoustic

radiation force during HIFU exposure while the already treated one has much smaller displacement. Subsequently, the large axial shear strain shows up in the calculated ASSE, which indicates the high possibility of the gap detection by our remote ARF palpation.

Figure 4-7. Photos of the phantom (with a gap) before (a) and after (b) HIFU compression, and (c) the colorful axial shear strain elastogram overlaid on the grey axial strain elastogram.

4.4.3 Static ASE in sonography

The experiment was continued, and sonography was used to capture the position of markers and two lesions. In order to clearly display the positions, sonography was reversed in the grey level. However, the cigar-shaped lesions are not clear as those in the photography (see Figs. 4-8 and 4-9).

Similar to the ASEs detected and calculated using the photography, those produced using the sonography for lesions without and with the lesion gap are very similar under the static compression (see Figs. 4-8 and 4-9). It suggests that our sonographic approach and proposed measurement protocols could produce ASE in a good image quality for the practical use.

Figure 4-8. B-mode sonography of the phantom (without a gap) before (a) and after (b) HIFU compression, and (c) the reconstructed axial strain elastogram.

Figure 4-9. B-mode sonography of the phantom (with a gap) before (a) and after (b) HIFU compression, and (c) the reconstructed axial strain elastogram.

4.4.4 Dynamic ASSE in sonography

Figure 4-10. B-mode sonography of the phantom (without a gap) before (a) and after (b) HIFU compression, and (c) the axial strain elastogram in grey overlaid with the axial shear strain elastogram in color.

Figure 4-11. B-mode sonography of the phantom (with a gap) before (a) and after (b) HIFU compression, and (c) the axial strain elastogram in grey overlaid with the axial shear strain elastogram in color.

Furthermore, the sonography was used to reconstruct ASSE by the remote and localized acoustic radiation force by the HIFU pulse during the exposure (see Figs. 4-10 and 4-11). Due to the limitation of memory in the ultrasound research platform, only the central region around the two lesions was used in the planar wave excitation. Because the number of speckles in the sonography is quite large, it has high feasibility of elastogram reconstruction. If lesion gap exists in the gel phantom, high axial shear strain presents in the gap zone.

Figure 4-12. A plot of the axial shear strain across the center of lesions. Red line shows low axial shear strain between two lesions while the blue line shows strong axial shear strain at the untreated gap.

In the lateral line crossing the center of two lesions, the axial shear strain on both the left and right sides of lesion region are very similar in the cases without and with a gap (see Fig. 4-12). However, there is a great difference in the magnitude of axial shear strain in the gap region.

4.5 *Ex Vivo* Experiment

Ex vivo experimental setup was similar to that in the gel phantom study. The sonography of *ex vivo* samples is shown in Fig. 4-13. During our HIFU ablation, no significant large bubbles were produced so that there was no strong echoic region in the sonography, and it is difficult to estimate the location and size of lesions in the conventional B-mode ultrasound image, which has been shown in many clinical HIFU treatments.

Figure 4-13. Comparison of sonography of *ex vivo* porcine kidney with two lesions (a) before and (b) after the static compression.

The axial strain elastogram of *ex vivo* porcine kidney samples embedded with polyacrylamide gel under the static compression was reconstructed using the established protocol that was described in Chapter 3. The kidney sample was cut after the HIFU pushing experiment, the boundary of the produced lesions was determined by the edge detection in digital image processing software (ImageJ, National Institute of Health, Bethesda, MA). Then the lesion boundary was added to the reconstructed axial strain elastogram (see Figs. 4-15 and 4-16). Several findings are found here.

Firstly, the boundaries of the lesion in the histology do not fit well with the boundary of ASEs. Secondly, the regions of low axial strain due to the high stiffness of HIFU-induced lesion are similar to the lesions without and with a 1.5 mm-gap, which is similar to the conclusion from previous studies.

Figure 4-14. Dynamic sonography of *ex vivo* porcine kidney with two lesions inside before and after HIFU exposure.

Figure 4-15. Comparison of (a) two HIFU-induced lesions without a gap between them in the histology of porcine kidney and (b) the axial strain elastogram overlaid with the lesion boundary under static compression on the *ex vivo* sample embedded in the polyacrylamide gel.

Figure 4-16. Comparison of (a) two HIFU-induced lesions with 1.5 mm-gap between them in the histology of porcine kidney and (b) the axial strain elastogram overlaid with the lesion boundary under static compression on the *ex vivo* sample embedded in the polyacrylamide gel.

Furthermore, the protocol of producing the axial shear strain elastogram (ASSE) under HIFU pushing pulse in the *ex vivo* sample is similar to that of the gel phantom. It is clearly seen that large axial shear strain presents in the gap zone between two HIFU lesions (see Fig. 4-17).

Figure 4-17. Comparison of the axial strain elastogram in grey overlaid with the lesion boundary and axial shear strain elastogram in color of *ex vivo* porcine kidney with two lesions (a) without and (b) with a gap between two lesions.

The experiments using porcine liver samples demonstrated the similar performance as those porcine kidney samples (see Fig. 4-18) that only large axial shear strain exits in the gap zone between two HIFU-generated lesions by the acoustic radiation force during HIFU exposure. However, the variations in the shapes and sizes of HIFU-generated lesions in the liver are larger, which may be due to the more inhomogeneities associated with the hypervascular structure. So a larger number of samples ($n = 9$) were used.

Figure 4-18. Comparison of two HIFU-produced lesion (a) without and (b) with a gap in the *ex vivo* porcine liver samples (left column) and transient ASSE in color (right column).

In order to facilitate the gap detection qualitatively and quantitatively, the ratio of axial shear strains on the left edge of the being treated lesion ($ASSE_A$) and that in the gap zone ($ASSE_B$) as shown in Fig. 4-19 is used for comparison

$$Ratio_{ASS} = \left| \frac{ASSE_B}{ASSE_A} \right| \quad (4-1)$$

Figure 4-19. The location of two points used for ASS ratio definition.

Figure 4-20. Comparison of axial shear strain (ASS) ratios of *ex vivo* porcine kidney and liver samples without and with a gap between two HIFU-produced lesions.

Figure 4-21. Statistical comparison of ASS ratios of *ex vivo* samples without and with a gap between two HIFU-induced lesions.

ASS ratios of all *ex vivo* experiments ($n = 4$ and 9 in each kidney and liver groups, respectively, without and with gap zone) are summarized and shown in Fig.

4-20. It is found that there are significant differences of ASS ratios between these two groups ($p < 0.05$, see Fig. 4-21). The sufficiently treated lesions (without a gap) usually has ASS ratio less than 0.5 whereas the insufficiently treated ones (with a gap) has large ASS ratio, > 0.75 , the threshold used in discerning the lesion gap in the simulation.

4.6 Discussion

The axial shear strain elastogram may provide a reliable and easy evaluation modality in HIFU ablation. *Ex vivo* experimental data show apparent differences in ASS ratios in both kidney and liver samples without and with a lesion, which makes discerning the presence of lesion gap easily. Using the acoustic radiation force from the therapeutic HIFU pulses themselves other than the conventional external mechanical compression method provides the possibility of real-time monitoring without interrupting the ablation procedure, such as applying the quasi-static compression. The ASSE using quasi-static compression can only detect lesion gaps which are oriented at an angle to the axis of compression. When two lesions are aligned exactly perpendicular to the compression, the gap region doesn't shear, which means no axial shear strain. Most of the static elastographic methods use the ultrasound imaging probe to compress the tissue mechanically. When thermal damage occurs, tissue stiffness was found to increase up to about 4-fold [132] and strain imaging showed strong shrinkages that blur the temperature information because of the variation of the speed of sound at the different temperatures on the displacement

[50]. We show that axial strain elastograms are not easy to interpret for accurate lesion characterization, but SWI could provide a quantitative mapping of the thermal lesion [94]. Although the quantitative evaluation of ROI using the remote palpation from the acoustic radiation force is challenging because the axial strain in this situation depends on both the medium stiffness and the distribution of stress in the tissue which is difficult to measure *in vivo* due to the tissue inhomogeneity, qualitative information of axial-shear strain is sufficient in evaluating the presence of gaps between HIFU lesions.

The contrast in an elasticity imaging of target under the displacement induced by a global stress is generally poor and influenced by the factors that are irrelevant to the distribution of tissue stiffness [133]. For small strains, a strain image may show contrast that is a good surrogate for (inverse) Young's modulus [134]. The main advantages of using a linear array are that scanning conversion does not need to be performed before the displacement estimation and that the lateral and axial sampling distances are constant as a function of depth. Moreover, the variance of the strain estimation is reduced for high central frequency [135]. Two most important criteria for judging visibility are strain contrast (between the focus, where the acoustic radiation force occurs, and the area away from the focus) and strain noise. As expected, when the size of the strain estimation window was increased, the strain noise became less visible, but the strain contrast also decreased. Acoustic radiation force elastography are less susceptible to artifacts associated with boundary conditions and elastic modulus inhomogeneities compared with surface loading. Furthermore, they possess a reduced

rate of the decay of strain signal-to-noise ratio with depth and demonstrate improved contrast-transfer efficiency (CTE), particularly for inclusions that have negative modulus contrast or that are disconnected from the background by a slip boundary. The contrast-transfer efficiency is defined as the ratio of the observed elastographic strain contrast and the underlying true modulus contrast [136, 137]. The resolution of the strain images obtained using the acoustic radiation force elastography depends on several factors, most of which have been described for the conventional elastography. These include the imaging pulse length and kernel sizes used for the tracking algorithm and strain estimator. In addition, unique to acoustic radiation force elastography, the resolution will also be affected by the number of pushing locations [138]. As for the conventional elastography, the resolution should be almost as good as the B-mode sonography that may be formed from the same RF data. For the acoustic radiation force elastography shown in this paper, the resolution appears to be on the order of 1 mm in all directions as shown in the reconstructed elastograms, but this was degraded compared with what could potentially have been achieved because only a limited number of pushing locations were employed. The use of a focused transducer allows the creation of a force impulse that is highly localized in space and can employ at the low frequencies, outside of the bandwidth desired for the high-resolution imaging transducer, to supply the acoustic radiation force more efficiently to the deeper-lying tissues. However, in our proposed approach the pushing pulse is from the therapeutic HIFU burst so that the acoustic radiation force is applied to the being treated lesion only, not the other region.

This kind of transient imaging proposed here is passive elastography and could reduce the operational complexity. It does not need the use of pushing pulse as in ARFI and HMIFU and not intentionally change the treatment plan. ARFI needs to push a large ROI using several pulses which need several relaxation times of the tissue or gel phantom. Therefore, the total time required for one ARFI frame is dependent on the number of pushing pulses. In addition, the acoustic intensity produced by the ultrasound imaging probe is several orders less than that of the therapeutic HIFU transducer. Although smaller displacement reduces the possibility of decorrelation in the measurement of ARF-induced displacement, it also produces the less sensitivity in differentiating the stiffness distribution. During HIFU ablation, the inter-pulse delay between the HIFU bursts which are usually not in continuous mode could be utilized to detect the displacement and subsequently monitor the gap between lesions. The simulation results show that 0.05 s in the relaxation is sufficient to restore the tissue to its initial position and to obtain the displacement map. Such a time is much shorter than the total HIFU ablation at a single location, which is usually several minutes. In addition, the temperature change due to the thermal diffusion in such a short time is negligible so that the effect of the variation of the speed of sound at the different temperatures on the displacement estimation could be ignored.

Bubble cavitation is an important phenomenon in the acoustic field, especially at the high acoustic intensity. The presence of ultrasound-induced bubbles could enhance the absorption of delivered acoustic energy and scatter the incoming acoustic pulses toward the transducer. As a result, the produced lesion becomes larger, but

changes its symmetric shape of a cigar to an asymmetric tadpole with the large head gradually growing and moving away from the focus [139]. ASEs and ASSEs using quasi-static compression provide accurate size of lesion produced at the low-power setting. However, the presence of the cavitation bubbles produced at the high-power setting was found to affect the lesion appearance in the elastography and have more influence in ASEs than in ASSEs [79]. ASEs contrast the lesion core from the surrounding tissue whereas contrast in ASSEs shows at the lesion boundary. Thus, cavitation bubbles inside the lesion may not have a strong influence on the ROI in ASSEs. However, if many bubbles distribute in a large region during HIFU ablation with the presence of multiple lesions, their effect on ASSEs is still unknown. Hyperechoes from the markers and HIFU-induced lesions in the homogeneous gel phantom are found in the B-mode sonography, which suggests the presence of cavitation bubbles. They would enhance the SNR of sonography because of effective and strong acoustic scatterers from those bubbles and, therefore, be beneficial to tracking the displacement of speckles for the better quality of reconstructed ASSEs. The transient ASSEs using the remote palpation from the HIFU pulses shows the satisfactory ability of detecting the lesion gap and seems to have little influence from those bubbles. In comparison, more speckles appear in the sonography of tissue samples because of their inhomogeneity. Large boiling bubble will be produced when water changes its state from liquid to vapor at the high temperature, such as in the boiling histotripsy. Such a large bubble will block the propagation of acoustic wave and cause the shadowing in the sonography. However, high temperature $>80^{\circ}\text{C}$ is

usually avoided during HIFU ablation to minimize the unintended injury to the intervening tissues.

Sonography is conventionally realized by sweeping the ROI using a series of focused or multi-focused beams and then stacking all scanlines. Thus, the reconstruction time is proportional to the number of scanlines and the maximal depth of ROI. Subsequently, the frame rate is limited to about 30-50 Hz, which is not fast enough for transient elastography. Ultrafast sonography from a single transmit using PWI provides new perspective and opportunities in the diagnosis without compromising the contrast-noise ratio and lateral resolution [91, 120]. Although limited sonography width was applied in this study due to the tradeoff between the required frame rate and sonography reconstruction speed, it is sufficient to detect the gap between the being treated lesion and those already treated ones. If no gaps are found at all previously treatment spots, such a small window (but larger than the width of two typical lesions) will not affect the reliability and sensitivity of monitoring. With the advances in the parallel computing [115], high-performance data transfer [116], and high-speed processor [117], a wide monitoring window is technically possible.

The minimum detectable gap width is affected by the element size of the ultrasound imaging probe or the distance between two consecutive data line. In this paper, a probe with the whole width of 15 mm and the element width of 0.44 mm was used, and there were around 34 raw RF data lines in the B-mode ultrasound image.

The accuracy and computation speed of elastography reconstruction is mainly dependent on the calculation of particle displacement, which could be reduced using

the 2D sparse search. Searching the lateral displacement is not required to be as densely as that of axial one because of larger sample space. For real-time application, a 2D search region for every a certain number of rows will be utilized, and then the displacement of the next rows will be estimated using the lateral displacement and 1D search. A more aggressive strategy is to only estimate the lateral displacement for the first row and then use it in the prediction for the remaining rows. The large displacement errors usually appear in the first row due to the inherent decorrelation between pre- and post-compression RF data and periodic ambiguities (false-peaks) associated with large search regions. When using predicted displacement to reduce the size of searching region, another type of displacement estimation error occurs and accumulates if the search region cannot enclose the true displacement. Large and irregular deformation of tissue/phantom may cause local decorrelation. In order to reduce such estimation errors, a certain strategy of error detection and correction was applied for every a certain number of rows. A segmentation method was used to the estimated displacement for each row from left to right if the displacement difference between adjacent positions is larger than 2 sample intervals. Then non-adjacent groups were merged if the difference between nearest end points of two groups is smaller than a certain threshold (i.e., 3 sample intervals). Finally, the group with the largest number of displacement estimates was assumed to be correct one. The remaining displacement values of the wrong groups were estimated using those of the correct group by linear interpolation. Here only a 3×3 searching region is found enough to cover the exact corresponding block based on the previous estimated displacement.

Chapter 5 Summary and future work

This chapter summarizes the entire work carried out for detecting lesion gap in real time during HIFU treatment. The future work based on this research has also been recommended.

5.1 Conclusions

In this thesis, we propose and evaluate a new method to detect lesion gaps during HIFU treatment using the localized acoustic radiation force with little interference on the current system configurations and treatment protocol. The axial shear strain elastogram produced by the HIFU pulse may provide a reliable and easy monitoring modality in HIFU ablation. Using the acoustic radiation force from the HIFU pulses themselves other than the conventional external mechanical quasi-static compression method provides the possibility of real-time monitoring without interrupting the ablation procedure, such as applying the quasi-static compression. In addition, the orientation of lesions is not critical for gap detection using our approach, but a serious problem for the conventional one using the static compression which can only be available with lesion not aligned perfectly vertical and the detection sensitivity and accuracy is dependent on the angle of compression with respect to the lesions.

The conventional axial strain elastogram can only provide the approximate region of HIFU lesions, but it fails to describe the information of the gap. Furthermore, whether the lesion boundary agrees with the threshold contour in the conventional axial strain elastogram needs further investigation. However, according to our

experience, careful selection of such threshold and contour reconstruction is highly required. In practice, HIFU gap detection greatly depends on the operator's experience other than the diagnostic result. The conventional axial shear strain elastography using quasi-static compression can detect lesion gaps when they are oriented at an angle to the axis of compression. However, when two lesions are aligned exactly perpendicular to the compression, the gap region doesn't shear. It means the axial shear strain elastography fails to detect the gap in this situation. Most of the conventional methods use the ultrasound imaging probe to compress the tissue mechanically. The efficiency of mechanical compression can be much lower than that of acoustic radiation force.

Our gel phantom and *ex vivo* tissue sample experiments show that ASSE reconstructed using our proposed technology can illustrate the gap zone between two almost identical lesions clearly and quite sensitively. In HIFU monitoring, the quantitative determination of axial shear strain in the region-of-interest is not very important. Qualitative information is sufficient and easy for HIFU operator without the solid background of acoustics and other physics. Our experimental results are promising for the future clinical translation.

The conclusions of our work are summarized and listed below:

- High-intensity focused ultrasound (HIFU) bursts with the pulse duration on the order of 100 ms at the clinical power output could produce significant and localized stress applied to the lesion being treated;
- The induced acoustic radiation force could generate large axial shear strain in the gap zone between two lesions, but not in the region with two merged lesions. The

sensitivity of lesion gap detection is reliable for various experimental settings, such as the size of lesions, acoustic radiation force, and the size of gap, in the numerical simulation;

- Both gel phantom and *ex vivo* tissue sample experiments validate the performance of our proposed approach and large axial shear strain appears in the gap zone between two lesions and the reconstructed axial shear strain elastogram is similar to that using high-speed photography and from the numerical simulation.

5.2 Recommendations for future work

This work conducted in the thesis has great scope in the qualitative and quantitative of lesion gap detection. The possible future work would include but not limit to the following items.

1. Extending the current 2D model to 3D model

In this thesis, planar strain assumption is applied for the displacement calculation. Lesions are elliptic and the relative position between them is 2D. In fact, both lesions and normal tissue is 3D model. The relative position between two lesions can be much complicated than the 2D case. Moreover, the acoustic radiation force has 3D distribution which is always simplified to the 2D distribution in most papers. The simulation using the 3D model can provide more accurate results than that using the 2D model. The effect of such dimension extension on the accuracy and reliability of lesion gap detection needs further investigation. In the practical HIFU ablation, the imaging plane of sonography may not always be perfect through the center of lesion

centers and not exactly confocally and coaxially with the HIFU transducer. Therefore, such investigation has great value in the clinical application.

2. Operation parameters for gap detection

The axial shear strain within the gap region can be influenced by several aspects: lesion size, stiffness contrast between lesion and normal tissue, gap width and so on. This thesis provides a preliminary method of gap detection both numerically and experimentally. However, plenty of gel phantom or *ex vivo* experiments should be carried out to obtain more reliable parameter values for the gap detection. More convincing evidences are required for the future *in vivo* animal experiments and clinical trials.

3. Prediction method for HIFU treatment

Generally, it takes dozens of seconds to produce a lesion by the HIFU transducer. During this process, several axial shear strain elastograms can be produced as a reference to the operator. All the images and detected gap width at different time could be used to predict the remaining time for complete lesion formation, which would help the operators to automatically and accurately adjust the HIFU treatment dose in practice due to the large variations between patients. In our experiment, only one HIFU pushing pulse was used to generate the axial shear strain elastogram. Actually, the progressive production of lesions during HIFU exposure is required to continuously reconstruct the ASSEs and monitor the lesion gap. However, the number of experiments is very large, and it is very time consuming to complete all sets of experiments.

4. More robust strain estimation method

Currently, the conventional 2D block matching method is applied to measure the displacement within the tissue. However, this method shows certain problems sometimes. Especially, a former de-correlation error always induces the subsequent displacement estimation. Although plenty of research work has been done to solve this problem, the solution is still not fully settled. The major reason is due to much larger acoustic radiation force and subsequently larger displacement produced by HIFU exposure in comparison to the pushing pulses in ARFI. High-performance data transfer, parallel computation, and the use of graphic processing unit (GPU) have already been applied to increase the frame rate of conventional sonography. These approaches could also be applied to our proposed technology using the established protocols. However, we believe that further work and modification of ASSE reconstruction algorithms and real-time lesion gap detection protocols should be carried out according to the characteristics of RF data, especially in clinical environment.

5. Validation

The simulation results have already shown the ability of axial shear strain image in monitoring the HIFU treatment. Good graphic user interface (GUI) will be developed for the easy operation. We need apply this method to the real applications, especially the animal experiment and clinical trials. For example, the blood vessel may transfer the heat and affect HIFU ablation. The inhomogeneous and multiple layers of tissues can alter the axial shear strain elastogram. A lot of work need be completed

before applying this technique to the real applications. Animal experiments and clinical trials need great and plenty paperwork before being approved, which may be more challenging than the technical development.

6. Real-time system

In order to display axial shear strain images in real time, several time-consuming procedures should be accelerated. The first one is the displacement measurement. In this thesis, we use the 2D block matching method to match signal segment pairs in calculating the displacement. Displacement measurement of each point only depends on the former point in the same RF data so that all the displacement tasks can separate into several sub-tasks. Graphic processing unit (GPU) technique or parallel method can greatly speed up the efficiency of measuring the displacement. The second time-consuming procedure is to calculate the axial shear strain based on a differential technique. The strain calculation of one specific point is only decided by the points around it. This task as the first procedure can be separated into sub-tasks. In addition, GPU technique and parallel method can accelerate the procedure. A real-time monitor system can greatly benefit the HIFU operator during the ablation.

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