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Passive Imaging and Measurements of Acoustic Cavitation during Ultrasound Ablation

Student Signature: Vasant Anil Salgaonkar

This work and its defense approved by:

Committee Chair: T. Douglas Mast, PhD

Christy Holland, PhD

Marepalli Rao, PhD
Passive Imaging & Measurements of Acoustic Cavitation during Ultrasound Ablation

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Vasant A. Salgaonkar

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T. Douglas Mast, PhD
Abstract

Cavitation is known to affect therapeutic ultrasound applications such as tissue ablation, where it may complicate heat deposition and make treatment control difficult. In this thesis, acoustic emissions from cavitating bubbles are measured and imaged to serve as indicators of thermal ablation progress. Cavitation acoustic emissions were measured using a 1-MHz transducer during thermal ablation of excised bovine livers with a 32-element linear array (3.1 MHz, 0.8–1.4 MPa pressure amplitude). Broadband, subharmonic and low-frequency emissions consistent with inertial, stable and vaporous cavitation respectively were observed. Broadband ($r = 0.848$) and low-frequency ($r = 0.747$) emissions exhibited statistically significant linear correlations with coagulated tissue volumes. Statistical models based on multinomial logistic regression were implemented to predict tissue temperature based on measured cavitation emission signals.

To perform spatially sensitive measurements of cavitation activity, images were created from beamformed bubble emission signals received by a diagnostic imaging array. This method was called passive cavitation imaging. Analytic models for point spread functions were developed to test this imaging method. It was implemented on a 192-element linear array (7.5 MHz) and separate images of stable and inertial cavitation activity were created in free field and tissue media, with mm-level resolution along the array azimuth. Passive cavitation imaging techniques were used to record emissions during ablation of \textit{ex vivo} bovine liver with 1.1-MHz (1984 W/cm$^2$ focal intensity) focused ultrasound. Spatial correspondence was observed between harmonic emissions and tissue lesioning, along the array azimuth. This was assessed by a statistically significant correlation ($r = 0.684$) and area under a receiver operating characteristics (ROC) curve (AUROC = 0.71).

The present cavitation detection and imaging techniques, implemented in this thesis to monitor ultrasound ablation, can potentially be extended to other therapeutic ultrasound procedures that are significantly influenced by cavitation.
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Chapter 1

Introduction

Thermal ablation is a curative option for treating tumors in soft tissue. During thermal ablation, tumors are subjected to localized heating leading which leads to coagulative necrosis. These treatments use several energy modalities such as radiofrequency waves (Ni 2005), microwave radiation, laser radiation (Izzo 2003) and intense ultrasound (Kennedy 2003). Ultrasound-based methods have potential in minimally invasive or noninvasive ablation, but the bubble activity which results from ultrasound-tissue interaction complicates energy deposition and makes ablation control difficult (Watkin 1996). A better understanding of ultrasound-induced cavitation and possible methods to monitor its effects will make ultrasound ablation more safe and reliable.

During this project, ultrasound arrays were used to passively sense acoustic energy scattered by mechanically active bubbles and provide spatially sensitive information about locally occurring cavitation activity. Conventionally, such cavitation detection schemes employ single-element transducers. These measurements were used to map therapeutic ultrasound beams in tissue and track ablative coagulation. These image-based tools were developed to assist in ultrasound ablation guidance and monitoring.
I. Background

One target application for the imaging methods presented here is image-guided ultrasound ablation of tumors in the liver. To understand the relevance of this technology, some background information about liver cancer treatments, thermal ablation, and the role of cavitation in ultrasound ablation is provided.

A. Liver cancer treatment

Liver cancer is a rapidly growing health problem across the world. Hepatocellular carcinoma (HCC) or primary liver cancer is prevalent in South-East Asia and its incidence in the United States is increasing (El-Serag 2004). In the US, HCC has emerged as the eighth leading cause of cancer related deaths (Wilson 2005). Secondary liver cancer develops when tumor cells originating in other parts of the body migrate to the liver and form metastases or secondary tumors. A large number of patients develop liver metastases due to colorectal cancer (Ruers 2002). Over the last decade, liver cancer mortality rates have increased significantly in the US, particularly in middle-aged males (Perz 2006).

Surgical resection is a viable curative option for some HCC and metastatic tumors (Lagennhoff 2005). Five-year survival rates between 21–50% have been observed for this procedure (Elias 1998). However, several patients have multiple tumor sites, making them ineligible for resection (Mazzaferro 1996). In such cases, orthotopic liver transplantation (OLT) is a treatment option which can ensure tumor removal and low recurrence rates (Bolondi 2003). Unavailability of donor organs severely limits this procedure.

For non-resectable HCC and secondary tumors, alternative non-surgical treatments like chemotherapy or ablation may be used. Local ablation approaches include percutaneous ethanol injection (PEI), cryotherapy and thermal ablation. In cryotherapy, tumors are destroyed through a freeze and thaw process (Ruers 2002). This treatment regime is known to have high complication rates (10–20%) due to hemorrhage or cyroschock (Seifert 1998). PEI,
one of the earliest ablation methods, can deliver highly-selective treatment but exhibits high recurrence rates. In a study conducted by Ishii et al. (1996), a local recurrence rate of 14.2% was observed after 2 years with PEI. Thermal ablation methods have shown potential for treatment of large tumors. As ultrasound ablation falls under this domain, thermal ablation is discussed in detail.

B. Thermal ablation methods

A number of interstitial ablation devices which use radiofrequency waves (Decadt 2004; Ni 2005), microwave or laser (Izzo 2003) are available. Monopolar radiofrequency ablation (RFA) has gained clinical acceptance in treating liver tumors (Kudo 2004), and treatments for HCC have resulted in 5-year survival rates of about 40% (Llovet 2003). A study by Lencioni (2000) reports complete tumor necrosis using RFA in over 80% patients suffering from HCC or secondary liver cancer. RFA was found to produce more complete necrosis than PEI, but with increased treatment complications (Livraghi 1999). Poor tissue selectivity is one of the drawbacks of RFA, and healthy organs on the tumor periphery may get damaged during treatment (Ahmad 2004). Perfusion losses, especially for tumors close to large blood vessels, may reduce the efficacy of these RFA procedures. RFA treatments produce gaseous vapor clouds when tumor tissue is thermally coagulated. These vapor clouds make it difficult to monitor RFA procedures through diagnostic imaging methods (Goldberg 2000).

The use of ultrasound as an energy source for tissue ablation has been explored over the last six or seven decades. Ultrasound energy can be focused at a point inside the tissue to cause an acute temperature rise (Lele 1967). This local temperature increase can induce tissue necrosis. This is called high-intensity focused ultrasound (HIFU) ablation. Such treatment can be potentially delivered in an extracorporeal manner, resulting in a completely noninvasive therapeutic procedure (Kennedy 2003). HIFU shows great potential for treatment of liver cancer (Kennedy 2004), prostate cancer (Gelet 2000a, 2000b), renal
tumors (Häcker 2006) and uterine fibroids (Stewart 2003). HIFU ablation treatments tend to have longer treatment times and multiple exposures may be necessary for removing larger tumors. Bulk ablation, comparable to RFA, may be possible with miniaturized ultrasound arrays delivering unfocused ultrasound energy (Diederich 1999; Chopra 2001; Prat 2002; Makin 2005). This approach can be used laparoscopically or interstitially and may provide an alternative to RFA (Makin 2005, Mast 2005). Precise image-guidance methods will greatly improve the quality of ultrasound-based ablation approaches. Some of these methods are described in the next subsection.

C. Image guidance in thermal ablation

MRI has been successfully implemented for ablation monitoring. MR-based methods have been used in guiding surgical procedures, noninvasive thermometry and post treatment observation.

1. MR-guided ablation

Hynynen et al. (1996) have developed a fully integrated system that uses MRI to guide and monitor ultrasound ablation. In vivo experiments conducted during that study, involved imaging the target with MRI, temperature monitoring based on proton resonance frequency shifts and delineation of necrosed tissue by T2-weighted MR images. A comprehensive review of MR thermometry has been published by Rieke (2008). HIFU ablation with MR guidance has been tested in several other experimental (Chung 1999; Jolesz 2002) and clinical studies (Kennedy 2005). Successful treatments of breast neoplasia (Gianfelice 2003) and uterine fibroids (Stewart 2003), with few complications, have been reported. Recently, an MR-guided HIFU device, developed by Insightec, has received FDA approval for treating uterine fibroids. Preclinical studies have shown the feasibility of MR-guided HIFU ablation of tumors in the brain (McDannold 2003; Pernot 2003). Catheter-based ultrasound devices have been
employed with MR image guidance during treatment of prostate cancer (Diederich 2007). A recent study used T2-weighted and dynamic contrast-enhanced MR imaging for post-operative monitoring of tumor recurrence in the prostate (Rouvière 2009). MR imaging has also been used to guide ablation treatments utilizing energy modalities other than ultrasound. A clinical study was conducted by Puls et al. (2003) where MR images were used to position laser micro-catheters for treating liver tumors. Similarly, MR images have been successfully used in creating thermal maps during RFA treatments (Laumonier 2006). MR thermometry based feedback control has been applied during ultrasound hyperthermia treatments recently (Chopra 2009).

2. Limitations of MR-guidance schemes

MRI-based thermometry is the current gold standard for temperature-mapping during ablation procedures (Wu 2004). Bradley (2009) refers to MR-based thermometry as a “disruptive” technology as it can “overturn” other technologies currently available in the market. However, MR-based temperature measurement yields temperature rise during an ablation procedure and not the absolute temperature value (Lindner 2005). MR-based temperature mapping, performed using proton resonance frequency shifts and T1-weighted images, provides temperature maps with 1–2 °C accuracy. However, these temperature images may be severely affected by subject orientation, geometry and movement (Paliwal 2004). Similarly, any movement of the surgical devices can also cause artifacts in the temperature maps, making this modality unsuitable for minimally invasive ablation procedures that require multiple insertions of the therapy applicator into the tumor (Kinsey 2006). In the context of ultrasound ablation, MR images provide no significant information about acoustic cavitation. Vapor bubbles caused at higher temperatures are known to create substantial artifacts in MR-based temperature images (McDannold 2005). MR-guided HIFU systems sometimes also employ separate cavitation detection methods during ablation procedures (Hynynen
MR-based thermometry is expensive and has measurement equipment with limited portability. Surgical treatments like MR-guided HIFU also require the use of MR-compatible therapy devices. All these specific requirements drive up the cost of such surgical systems. While commercial MRI systems incorporating thermometry are available, the high cost associated with them makes their wide spread clinical use difficult.

3. Ultrasound-guided ablation

Ultrasound-based methods for guidance of ablation are less expensive than their MR-based counterparts. Several published clinical and experimental studies have used conventional ultrasound images to guide percutaneous ethanol ablation (Charboneau 1988), cryoablation (Kane 1993), laser ablation (Pacella 1993), laparoscopic RFA (Rogers 1997) and HIFU (Sanghvi 1996). More recent studies have used bright echogenic regions formed due to vaporization to visualize HIFU ablation (Rabkin 2005, 2006). In one HIFU ablation study, ultrasound contrast agents were released in the tumor to improve image quality (Tung 2006). Doppler ultrasound was used to guide HIFU ablation by tracking the blood flow during breast cancer treatments (Wu 2004, 2005). The system used by Wu et al. (2004, 2005) is commercially available and has HIFU treatment integrated with image guidance.

Elastographic methods to identify tissue coagulation based on ultrasound images have been studied in vitro (Liu 2004). Acoustic radiation force imaging (ARFI) has been successfully implemented with RF ablation. Fahey et al. (2008) implemented ARFI on a B-mode ultrasound scanner to identify the positions of a tumor pre-treatment and then to detect tissue coagulation post-treatment. A similar study was also performed for ultrasound ablation by Lizzi et al. (2003). Radiation force-based methods have also been used in localized harmonic imaging based approaches for ablation guidance in vivo (Curiel 2009). Maleke et al. (2008) employed harmonic motion imaging to detect changes in the mechanical properties of tissue. These methods were used to distinguish between tumors and healthy tissue and also
to monitor ablative coagulation. Recently, Bercoff et al. (2004) introduced a supersonic shear wave imaging (SSI) technique where viscoelastic properties of the tissue could be recorded from ultrasound images. This technique involved generating a supersonic push inside the tissue with a high-energy ultrasound source and then imaging the resulting low-frequency shear waves. Inhomogeneities in the medium could be imaged from the distortions they would introduce in the shear waves. This method was also tested in vivo where viscoelastic properties of breast lesions were mapped successfully (Tanter 2008). These methods could be used in identifying the position of a tumor and also detect ablative coagulation.

Ultrasound-based guidance strategies are difficult to implement in vivo due to tissue motion. Recently, interstitial ultrasound ablation devices with simultaneous image-ablate capabilities have been utilized in experimental studies (Makin 2005; Mast 2005). With these devices, the same ultrasound array delivers therapy and also performs B-mode imaging. These techniques have potential in ultrasound guidance due to the inherent co-registration between the B-mode image and the treated region.

4. Ultrasound-based thermometry

Acoustic scattering recorded by single-element diagnostic ultrasound transducers has been used as a measure of temperature changes by quantifying the change in the frequency content of scattered emissions as a function of temperature (Seip 1995). Sound speed changes due to tissue heating during ablation were utilized by Miller et al. (2004) to estimate tissue temperature. Some ultrasound based methods for detecting hyperthermia, such as echo shifts, attenuation coefficient changes and backscattered energy measurement, have been reviewed by Arthur et al. (2005).

Ebbini et al. (1998) employed a correlation based algorithm to estimate echo displacements, directly related to temperature changes due ultrasonic heating. These echo shifts were estimated in both the time and frequency domains. Similar correlation based methods
were employed by Chiang et al. (2002) to map temperatures between 30–70 °C using B-mode images obtained during RF ablation. Miller et al. (2004) obtained temperature information from images captured by a diagnostic imaging transducer by computing the HIFU-induced echo strain. They were able to identify the HIFU focus position by inducing small temperature increases of 2–5 °C in tissue. Following this initial targeting, temperature increases close to 15 °C were estimated from the echo-strain images. Ebbini (2006) has reported a projection method based on convex sets to estimate a two-dimensional temperature profile from B-mode images. This approach was found to be less sensitive to artifacts caused by medium inhomogeneity and thermoacoustic lensing during thermal ablation. Temperature measurements made from changes in the backscattered energy have also been reported (Anand 2007, 2008). Mast et al. (2008b) computed an echo decorrelation parameter to represent changes in consecutive B-scan frames captured during RF ablation. Echo decorrelation parameter values were used to map both instantaneous temperature and tissue coagulation.

Ultrasound-induced cavitation plays an important role in determining ablation performance. Imaging methods presented above do not capture complete information about cavitation mechanisms. The imaging techniques developed during this project exploit ultrasound-induced bubble activity to monitor ablation. Hence, the role of cavitation in ultrasound-based therapy regimes, including tissue ablation, is explored next.

**D. Cavitation in ultrasound therapy**

Stable and inertial cavitation mechanisms often have a significant impact on therapeutic ultrasound applications. Stable cavitation refers to sustained volumetric shape oscillations of a bubble in an ultrasound field. Some bubbles may grow to more than twice their original size and violently collapse. This implosion is referred to as inertial cavitation (Leighton 1994). Such cavitation activity may be detected actively or passively using single-element transducers (Madanshetty 1991). Bubbles undergoing stable cavitation scatter the incident
ultrasound beam with energy content at half-order harmonics, called subharmonics or ultraharmonics. Stable cavitation can be detected with single-element transducers which listen for acoustic emissions at these frequencies. Inertially cavitating bubbles emit acoustic energy with a broad spectral content. This phenomenon may be detected by a passive cavitation detector from an increase in the broadband noise levels. Passive cavitation detection has been employed in several recent ultrasound ablation studies (Thomas 2005; Rabkin 2006; McLaughlan 2006; Mast 2008a). Conventional passive cavitation detection schemes that employ single-element transducers have limited spatial resolution. Some recent investigations have been focused on developing spatially sensitive passive cavitation detection methods. These studies have employed ultrasound imaging arrays to act as passive cavitation detectors by exploiting synthetic focusing done by ultrasound imaging systems (Farny 2009; Salgaonkar 2009a; Salgaonkar 2009b) and time-exposure acoustics methods (Gyöngy 2009).

Microbubble activity plays an important role in several ultrasound-based therapeutic applications like shockwave lithotripsy, thrombolysis and targeted drug delivery. In shockwave lithotripsy, inertially collapsing bubbles generate shock waves to fragment kidney stones (Crum 1984; Zeman 1990; Cleveland 2007). Thrombolysis may be potentially enhanced due to ultrasound-induced stable and inertial cavitation (Olsson 1994; Everbach 2000; Datta 2006). Ultrasound-induced cavitation also offers the exciting possibility of targeted drug and gene delivery using lipid-coated microbubbles which can encapsulate bioactive materials (Unger 2004; Hynynen 2008; Kopechek 2008).

In tissue ablation, cavitation activity is thought to enhance tissue coagulation. This is attributed to viscous damping from stably cavitating bubbles and enhanced absorption of high-frequency energy content produced by inertially collapsing bubbles (Coussios 2007). However, bubble activity also complicates energy deposition due to acoustic shadowing and distorts ablative lesion shapes (Watkin 1996). There also have been several numerical (Chavrier 2000; Curiel 2004; Mast 2005) and experimental (Watkin 1996; Holt 2001;
Khokhlova 2006, Coussios 2007) studies dealing with the interaction between cavitation and ultrasound-induced heating. Some researchers have recommended using lower sonication intensities with longer treatment times (Hynynen 1991) or the use of overpressure (Bailey 2001; Khokhlova 2006; Karunakaran 2009) to suppress acoustic cavitation. Other studies that promote cavitation activity in order to enhance tissue coagulation are also reported in the literature. During experiments reported by Sokka et al. (2003), cavitation was induced using a short high power pulse and then the ablation was continued at a lower power. The addition of ultrasound contrast agents as cavitation nuclei has also been attempted (McDannold 2005). Liu et al. (2006) used a low frequency transducer to promote cavitation and a high frequency transducer for ablation treatment. Some HIFU experiments where cavitation was either suppressed or promoted are reviewed by ter Haar et al. (2007). During HIFU exposures, vaporization and bubble activity causes thermal lesions to grow away from the HIFU focus, towards the transducer face. Such distorted lesions are sometimes called “tadpole lesions” (Watkin 1996; Coussios 2007).

II. Research Objectives

This project deals with passive cavitation detection during bulk ultrasound and HIFU ablation regimes. Conventionally, such methods employ a single-element transducer that records acoustic emission signals from mechanically active microbubbles (Madanshetty 1991). Here, the use of ultrasound imaging arrays to create images of cavitation activity has been explored. Macroscopic bubbles are often imaged with B-mode ultrasound and sometimes echogenic vapors formed during thermal ablation have been used to monitor the treatment (Rabkin 2005, 2006). In the passive imaging methods developed here, no transmit pulse was initiated and images were created only from the received bubble emissions. Images formed in this way can not only identify the location of cavitating bubbles, but also the underlying cavitation mechanisms responsible for them.
The specific objectives of this research were,

- to measure cavitation activity arising from ultrasound-tissue interaction during bulk ablation with unfocused ultrasound.
- to develop statistical models that will use acoustic emission and tissue echogenicity information to assist in bulk ultrasound ablation monitoring.
- to develop and validate beamforming methods that enable the use of an ultrasound imaging array for spatially sensitive passive cavitation detection in experimental scenarios.
- to image cavitation activity passively during HIFU ablation and utilize the images to monitor treatment progress.

III. Thesis Organization

This document has been organized in 6 chapters, including this Introduction. In Chapter 2, in vitro bulk ablation experiments with a miniaturized linear array are presented. This was a dual-mode array which could deliver intense unfocused ultrasound energy for ablation treatments and also capture B-mode images. Hence, it was possible to record B-mode images at regular intervals during an ablation exposure. The quality of these B-mode images was comparable to a diagnostic ultrasound system. Cavitational acoustic emissions produced due to ultrasound-tissue interaction were measured with an unfocused passive cavitation detector (PCD). A detailed correlation analysis was performed between these measured emissions, tissue temperature and volumetric tissue ablation rates. Chapter 3 presents logistic regression methods which model quantitative relationships between the measurements of temperature and cavitation activity. The data collected during the experiments presented in Chapter 2 was used in this modeling. These models predict tissue temperature during ultrasound bulk ablation, given the cavitational acoustic emission signals.
Single-element PCD measurements reported in Chapters 2 and 3 did not provide sufficient spatial information about the variations in bubble activity inside the ablated tissue volume. Spatially sensitive passive cavitation detection methods were explored by utilizing ultrasound imaging arrays. Chapter 4 details the mathematical framework of such passive cavitation imaging schemes. Analytic expressions are presented for these images. The ability of a conventional imaging array to create two-dimensional maps of localized cavitation activity was tested through simulations. Array beamforming techniques, investigated through simulation in Chapter 4, were implemented in an experimental scenario. Chapter 5 presents methods and results of these experiments related to passive cavitation detection with imaging arrays. Passively acquired cavitation images are used to obtain spatial information about ultrasound-induced bubble activity in free-field and \textit{ex vivo} tissue.

Passive cavitation imaging methods reported in Chapters 4 and 5 were employed to monitor HIFU ablation \textit{in vitro}. Chapter 6 reports on the performance of passive cavitation imaging during \textit{in vitro} HIFU ablation experiments conducted during this project. Passive cavitation images are used to determine the spatial position of HIFU-induced lesions. Chapter 7 summarizes the strengths and limitations of the technology development described here. It also lists future directions, in terms of unmet needs and key research questions along with possible techniques to address them.
Chapter 2

Passive Cavitation Detection during Bulk Ultrasound Ablation

I. Objective

Experiments presented in this chapter were designed to elucidate the effect of cavitation activity on bulk ultrasound (US) ablation, with an overall aim to monitor the treatment through cavitation detection. Several publications have been devoted to understanding cavitation activity and its impact during HIFU ablation (Thomas 2005; Rabkin 2006; Coussios 2006). However bulk ultrasound ablation, performed with unfocused ultrasound beams at relatively lower intensities, may engender substantially different cavitation activity, making it necessary to explore the underlying physical mechanisms further.

In this study, ultrasound ablation was performed in vitro with a miniaturized image-ablate linear array. This device had the ability to deliver unfocused continuous-wave (CW) ultrasound energy at intensities close to 80 W/cm², interleaved with B-mode imaging cycles. The exposure conditions employed in this study were similar to those reported by Mast et al. (2005). Quantitative relations between temperature increase, tissue coagulation, acoustic emissions and tissue echogenicity were investigated for bulk ablation treatments.
II. Materials and Methods

The overall experimental configuration can be seen in Fig. 2.1. The general experimental procedure involved ablating \textit{ex vivo} tissue samples with unfocused ultrasound energy using a miniaturized image-ablate array. During the exposures, acoustic emission signals from the heated tissue volumes were received by a single-element transducer. B-mode images of the treated tissue sample were captured at regular intervals by the image-ablate array. Also, tissue temperature was measured using a needle thermocouple probe for the entire treatment duration. All exposures were performed in a tank of deionized water which had been acclimated to the room temperature and other ambient conditions for more than 12 h. After each exposure, the tissue samples were sliced in order to quantify tissue ablation. Detailed descriptions of the ablation exposures, data collection and data analysis follow next.

A. Image-ablate treatments

A 32-element linear array (THX 3N, Guided Therapy Systems, Mesa, AZ) was used to perform thermal ablation and B-mode imaging. This array was controlled by the Iris 2 system (Ardent Sound, Mesa, AZ) during both ablation and imaging. This imaging system allows users to program ultrasound exposure conditions for ablation therapy and can capture B-mode images comparable to diagnostic ultrasound systems (Barthe 2004; Makin 2005). The image-ablate array had an active surface of $2.3 \times 49$ mm$^2$, with individual element sizes of 2.3 mm in elevation and 1.5 mm in azimuth.

Ablation exposures were performed by using the center 16 elements to deliver ultrasound energy in CW mode at 3.1 MHz. Three distinct acoustic power levels were employed. They were 16.2, 28.8 and 45.0 W. \textit{In situ} acoustic pressure amplitudes were computed for these power levels using the Fresnel approximation (Freedman 1960; Mast 2006). At a distance of 15 mm from the array, the estimated pressure amplitudes for the three aforementioned power levels were 0.83, 1.10 and 1.38 MPa, respectively. This distance of 15 mm was consistent
Figure 2.1: Experimental setup for passive cavitation detection during bulk ablation. The digital photograph at the top contains the tissue sample, needle thermocouple (pink casing visible), THX 3N image-ablate array and 1-MHz PCD. The electronics hardware and the relative positions of the experiment components are indicated on the schematic at the bottom.
Figure 2.2: Representative B-mode image of a tissue sample captured by the THX 3N image-ablate array. The embedded thermocouple probe is visible. Marked on the image is a region-of-interest (ROI) corresponding to the tissue area where maximum heat deposition occurs during an ablation treatment. Changes in tissue echogenicity were monitored by computing the mean grayscale value for this ROI.

with the position of the tissue sample relative to the image-ablate array. The exposures were conducted using pulses with duty cycles of 97–99%. During the quiescent period, the Iris system would switch from therapy to the imaging mode, and capture B-mode images. Details of the exposure conditions are as follows:

- 0.8 MPa sonication amplitude, 20 min. duration, 3.3 s pulse length.
- 1.1 MPa sonication amplitude, 10 min. duration, 1.7 s pulse length.
- 1.4 MPa sonication amplitude, 5 min. duration, 0.9 s pulse length.
The exposure conditions were chosen to ensure definite thermal coagulation. These pressure-duration combinations also maintained a consistent value of the total acoustic energy delivered during the exposures. Six distinct tissue samples were exposed to ultrasound at each of the three sonication amplitudes. This gave a total of 18 experiments.

When the image-ablate array would operate in the pulse-echo imaging mode, beamformed A-line signals were recorded using a 14-bit PC-based A/D card (Compuscope CS 14200, Gage Applied, Montreal, Quebec, Canada). Such A-line signals have energy components in the radio-frequency range. Hence, such ultrasound-related data samples are also called RF data. The RF data acquired during these experiments was sampled at 33.3 MHz. Thirty two A-lines, with 2048 samples each, were stored digitally for every B-scan frame. The size of this image frame was 49 mm along the array azimuth and 47 mm in the depth direction. A representative B-scan can be seen in Fig. 2.2.

B. Tissue handling

During this study, ablation treatments were performed on fresh *ex vivo* beef liver tissue. In order to investigate the effect of cavitation on ablation progress accurately and ensure repeatable measurements, it was necessary to maintain the initial state of all tissue samples consistent in terms of size, temperature and preexisting gas bubbles. To achieve this, whole *ex vivo* bovine livers were procured from a slaughterhouse and used within 12 h *post mortem*. The livers were immersed in a phosphate-buffered saline (PBS) solution and stored on ice close to 0 °C in a thermally insulated box. At the beginning of each exposure, a fresh piece of liver was cut to the dimensions of 7 × 3.5 × 3 cm³. This sample was placed in a latex condom (Probe Guard, Carter Products, New York, NY) with a small amount of PBS solution. This PBS solution was degassed for a minimum of 90 minutes so that the dissolved oxygen content would fall below 36%. The liver capsule was always left intact on one face of the sample (7 × 3.5 cm²), and ultrasound energy was aimed at this face during a thermal
Figure 2.3: Representative digital scan of an ablated tissue section. Tissue samples were sliced (≈ 2 mm thickness) perpendicular to the direction of ultrasound propagation. The dark red region is nominally untreated, the beige region is considered treated, and the brown region is considered overtreated.

Ablation procedure. The liver sample was allowed to equilibrate to the room temperature. Any bubbles entrained in the tissue sample were manually swept away.

After each ablation treatment, the tissue samples were frozen. Frozen tissue samples were sliced into 2-mm thick sections, parallel to the sample face with an intact liver capsule. At this thickness, it was possible to handle the tissue slices consistently in a damage-free manner. Each tissue section was digitally scanned and the ablated areas were computed through manual segmentation of the digital images using ImageJ software (National Institutes of Health, Bethesda, MD). Gross discoloration of tissue samples was used as an indicator of coagulative necrosis and tissue death (Thomsen 1999). The segmentation process is illustrated in Fig. 2.3, where the nominally untreated regions are pink, ablated regions are beige and the overtreated regions are brown. The total volumes of the coagulated tissue samples were calculated from the measured areas of these sections.
C. Passive cavitation detection

A single-element circular transducer (C302, Panametrics, Waltham, MA) was used as a passive cavitation detector (PCD). This detector had a 25-mm diameter, was unfocused and had a broad frequency bandwidth centered at 1 MHz. It was placed perpendicular to the image-ablate array axis and at a distance of $\approx 15$ mm from the opposing tissue surface. A simulated sensitivity pattern of this receiver can be seen along with a simulated pressure profile for the image-ablate array in Fig. 2.4. The therapeutic, unfocused ultrasound beam used for bulk ablation sonicated a large tissue volume and could cause acoustic emissions from a broad spatial region. This necessitated the use of an unfocused PCD to yield a spatially averaged measure of the overall bubble activity (unlike the highly focused detectors used by Thomas (2005), Rabkin (2006), McLaughlan (2006) and Coussios (2006) during studies with HIFU). The acoustic emissions measured by such a PCD also allowed a direct comparison between the overall acoustic emission levels and coagulated tissue volumes.

Signals from the PCD were acquired at a sampling frequency of 10 MHz. During these exposures, B-mode images were captured by turning off the therapy beam for a few milliseconds. A trigger was initiated at the beginning of an imaging cycle. The PCD signals were recorded 100 ms after this trigger event. The 100-ms delay ensured that the therapy cycle had turned on when the PCD data was acquired. The PCD signals were acquired for a time period of 100 ms, resulting in a data set of 1 million points. One such data set was stored following each trigger. The trigger rate was 0.3 Hz for the 0.8-MPa, 0.6 Hz for the 1.1-MPa and 1.1 Hz for the 1.4-MPa sonication amplitudes. PCD signals were digitally sampled by an oscilloscope (WaveRunner 6050A, LeCroy, Chestnut Ridge, NY, USA) after amplification by a low-noise amplifier (SR 560, Stanford Research Systems, Sunnyvale, CA). The pre-amplifier had a cutoff frequency of 1.4 MHz ($-6$ dB/octave slope) and served as a low-pass filter. This reduced contributions to the acoustic emissions from ultrasound beam
Figure 2.4: Simulated beam profile of the 3.1-MHz image-ablate array (axis-elevation plane) is shown in yellow. It depicts spreading of the therapeutic ultrasound beam in the direction of propagation. The simulated sensitivity pattern of the PCD at 1 MHz is shown in blue. The volume interrogated by the PCD corresponds to the region of maximum heat deposition and tissue coagulation during an ablation exposure.

scattering at the 3.1-MHz fundamental frequency.

D. Temperature measurement

Single-point measurements of tissue temperature were made throughout an ablation exposure. A 0.4-mm diameter needle thermocouple (Type B, Ella CS, Hradec, Králové, Czech Republic) was inserted in the tissue sample such that it was parallel to the tissue surface with the intact liver capsule. The thermocouple was embedded at a depth of 8–10 mm from this surface. The position of the thermocouple was estimated from B-scans of the tissue sample. Figure 2.2 contains a representative B-scan indicating thermocouple placement. The thermocouple element was aligned close to the approximate location of maximum tissue heating. The simulations and experimental studies conducted by Mast et al. (2005) revealed that the temperature gradients generated during ex vivo ablation by the THX 3N array were
relatively low. Hence, time-dependent temperature variations at the thermocouple position can be considered roughly proportional to the temperature elevations in other heated regions of the tissue sample.

Temperature from the thermocouple probe was recorded using a digital data logger (Omegaette HH306, Omega Engineering, Stamford, CT) at a sampling rate of 1 Hz. This data collection was performed continuously during the exposure and it was not synchronized with the PCD or B-mode data acquisitions. For data analysis, these recorded temperatures were interpolated to match the time points at which the PCD and B-mode datasets were acquired.

E. Data processing

Power spectra were estimated for acoustic emissions measured by the PCD. An acoustic signal trace, made up of 1 million data points sampled at 10 MHz, was acquired when the ultrasound array was in the imaging mode. Power spectrum density was estimated for such a trace by the periodogram method (Bartlett 1950). For every signal trace, 1000 periodograms were computed. Each periodogram consisted of the squared-magnitude values for a 1000-point discrete Fourier transforms. These 1000 periodograms were averaged to yield an estimate for the power spectrum density with a 10-kHz frequency step size. The energy contained in different frequency bins of these periodograms was integrated to delineate and quantify bubble mechanisms. Stable cavitation causes nonlinear volumetric oscillations of microbubbles and scatters acoustic energy with content at the subharmonic frequency (1/2 of fundamental frequency). To isolate this mechanism, acoustic energy in the 1.55-MHz frequency bin was obtained (Leighton 1994, Yang 2005). Inertial cavitation activity is identified by broadband acoustic emissions due to a sudden collapse of microbubbles. To delineate this phenomenon, acoustic energy contained in the 0.3–1.1-MHz range was integrated (Leighton 1994, Yang 2005). Boiling caused by ultrasound-induced heating during ablation produces
acoustic emission signals at kilohertz frequencies (Osborne 1947; Ying 1973). To quantify this activity, acoustic emission energy in the 10–30 kHz range was integrated. Instantaneous as well as time-averaged values were computed for acoustic emission energy in the three aforementioned frequency bands. These values were expressed in dB, normalized to electronic noise levels measured during sham exposures with a 50 Ω dummy load (see Fig. 2.5).

Changes in tissue echogenicity during an ablation treatment were estimated from the RF echo data recorded by the imaging array. A region-of-interest (ROI) spanning the center 16 image lines (24.5 mm in azimuth) and 8–32 mm in range (distance from the transducer face) was chosen (indicated by a dotted box in Fig. 2.2). This ROI corresponded to the region of maximum heat deposition and was approximately centered on the thermocouple element. A mean grayscale value (MGSV) was computed from the mean-square value of echo data belonging to this ROI. A reference grayscale value was estimated from the B-mode images captured before an exposure began. This reference value was different for each sample (experiment). The instantaneous mean grayscale values were normalized with respect to these initial reference levels.

Correlation analysis was performed on the time-averaged and instantaneous measured
quantities. Volumes of ablated and overtreated tissue were calculated from the segmented
digital scans of the tissue section. Ablation and overtreatment rates were calculated in
ml/min based on the volume measurements. They were correlated with time-averaged emis-
sion levels in the subharmonic, broadband and low-frequency bins. Correlation coefficients
and the associated $p$-values were computed for all 18 experiments and their statistical signif-
icance was assessed. Similarly, measured acoustic emission signals, MGSV and single-point
temperature measurements were cross correlated for all available time points in the 18 exper-
iments ($N = 6179$). This allowed the investigation of any temporal correspondence between
these quantities.

F. Control experiments

Control experiments were conducted to ensure that broadband emission signals measured by
the PCD were indeed related to inertial cavitation. To verify this, an ultrasound contrast
agent Optison (Amersham Health, Amersham, United Kingdom), was destroyed acoustically
using a 3.5 MHz, weakly focused immersion type transducer (Picker 595831A, New York,
NY). The concomitant acoustic emissions had broadband energy content between 0.3–1.1
MHz. Similar detection of inertial cavitation, in frequency ranges lower than the fundamen-
tal, was performed by Giesecke (2003) and Rabkin (2005, 2006). Time-frequency plots for
two exposures are given in Fig. 2.6.

To ensure that the measured acoustic emissions did not result from the tank water,
exposures identical to the tissue treatments were conducted in deionized tank water, with no
tissue sample present. PCD measurements were made during these exposures and acoustic
emission signals were measured in the three cavitation-related frequency bins. These signal
levels were indistinguishable from the background electronic noise, clearly indicating that
the acoustic emissions measured during the tissue experiments originated from the sonicated
samples (see Fig. 2.7).
Figure 2.6: Time-frequency spectrograms for passive cavitation detection experiments, where ultrasound contrast agent Optison was acoustically destroyed with 3.5-MHz ultrasound. The resulting broadband emissions were detected with the 1-MHz PCD, described above.

Some additional exposures were carried out to estimate the impact of thermocouple related cavitation seeding. Two exposures were performed at each of the three sonication levels (0.8, 1.1 and 1.4 MPa) where no thermocouple was inserted in the tissue sample. Acoustic emission levels were comparable to those from the experiments with the thermocouple present (the Results section contains more details). Thermocouple self-heating was determined by conducting exposures with only the thermocouple in saline solution. No tissue sample was used in these experiments. Exposures were conducted at the highest sonication amplitude (1.4 MPa). A small temperature increase, under 3 °C, was recorded.

III. Results

Results from the experiments described above are presented here. Quantitative relationships between time-dependent acoustic emission signals, tissue temperature and tissue echogenicity are explored. Similarly, correlations between time-averaged acoustic emission energy, sonication amplitudes, and ablation volumes are detailed.
Figure 2.7: Detected emission levels at the subharmonic, broadband and low-frequency ranges (top–bottom) for (a) signal levels (reference noise) when the Iris 2.0 system was delivering energy at 0 W nominal power, (b) 1.4-MPa beam sonicating the tank water with no tissue sample.
A. Analysis of time-dependent quantities

Time-frequency plots for the 1.4-MPa exposures are presented in Fig. 2.8. Persistent broadband emission signals were observed during all trials. In 5 out of 6 cases, high energy broadband emissions were observed towards the end of the exposures. High instantaneous broadband emission levels, 20 dB above noise, were observed during all exposures. Low-frequency emission levels stayed low at the beginning of these treatments. A significant increase in low-frequency emissions energy was obtained towards the end of a treatment in 5 out of 6 cases. This is consistent with boiling and vapor formation which can cause low-frequency emission signals. An increase in low-frequency emissions was accompanied with some rise in the broadband emission levels. Subharmonic emissions were observed only sporadically, but were more than 10 dB above noise in some cases. They did not seem to have any temporal correspondence with either broadband or low-frequency emissions.

For the 1.1-MHz sonications (see Fig. 2.9), persistent broadband activity was observed in 4 out of 6 cases. The emission levels were 15–20 dB above noise in those cases. Low-frequency emission levels were below 5 dB in all but one case. Subharmonic levels were again detected sporadically, and sometimes exceeded the noise levels by 30 dB. A persistent subharmonic was observed in 2 of the 6 cases.

For the 0.8-MPa exposures, the time frequency plots shown in Fig. 2.10 revealed relatively low levels of broadband emissions throughout the treatment. Low-frequency emission levels stayed consistently low. At this low sonication amplitude, little vapor formation may have happened leading to reduced low-frequency emissions. A strong persistent subharmonic, similar to observations made in one of the 1.1-MPa exposures, was also observed for one 0.8-MPa exposure.

Representative plots of time-dependent fundamental-frequency emissions, cavitation acoustic emissions, tissue echogenicity and temperature are shown in Fig. 2.11 for each ex-
posure condition. In some cases, a steady drop in temperature was observed towards the end of the 1.4-MPa treatments. This could be associated with shadowing of the thermocouple probe due to boiling and vaporization (Makin 2005). Gaseous vapors due to tissue boiling may act as a barrier to the ultrasound energy and limit thermal deposition to regions proximal to the thermocouple. This may result in reduced thermocouple readings. Acoustic emission in the three frequency bands under consideration can also be seen in Fig. 2.11. As noted above, the subharmonic emissions occurred sporadically. However, for 1.4-MPa exposure a sudden increase in subharmonic emission levels was observed towards the end of the treatment in some cases. This could be a result of stable cavitation nuclei being created due to vaporization and boiling. Broadband emission levels were consistently observed for all three exposure conditions. In most cases, they seemed to increase as the treatments progressed. Low-frequency emissions levels were relatively small, but for the 1.4-MPa treatments they often increased towards the end of an exposure (possibly due to the onset of boiling). Tissue echogenicity, as represented by MGSV, showed a trend similar to low-frequency emissions and its value increased suddenly at the end of the 1.4-MPa treatments for most experiments. This is consistent with the onset of boiling which causes vapors and increased echogenicity (Rabkin 2006). The representative time series shown here, illustrate the temporal correspondence between tissue temperature, MGSV and low-frequency emissions, particularly for the 1.4-MPa exposures.

Scatter plots for time-dependent acoustic emissions and measured tissue temperature are shown in Fig. 2.12. These plots are created by using all temporal data points ($N = 6179$). No significant linear relation was found between subharmonic emissions and tissue temperature. However, a scatter plot of the two quantities [Fig. 2.12(a)] reveals a definite structure. When tissue temperature stayed below 45 °C, the subharmonic emission levels did not exceed 10 dB (one outlier can be seen). For the 0.8-MPa exposures, significant subharmonic emission, above 10 dB, was observed when the tissue temperature stayed between 47–49 °C.
Figure 2.8: Time-frequency plots of the acoustic emission signals measured by the PCD during the 1.4-MPa sonications.
Figure 2.9: Time-frequency plots of the acoustic emission signals measured by the PCD during the 1.1-MPa sonications.
Figure 2.10: Time-frequency plots of the acoustic emission signals measured by the PCD during the 0.8-MPa sonications.
Figure 2.11: Representative plots for time-dependent fundamental energy scattering, broadband emissions, subharmonic emissions, low-frequency emissions, MGSV, and tissue temperature shown for (a) 1.4 MPa, (b) 1.1 MPa, and (c) 0.8 MPa.
For temperature values exceeding 80 °C, an increase in subharmonic emissions was detected for the both the 1.1-MPa and 1.4-MPa exposures. Increases in subharmonic emission activity were observed in some cases for temperature values greater than 50 °C during the 1.1-MPa exposures. For temperatures greater than 80 °C during the 1.4-MPa exposures, increased subharmonic emissions were observed in many cases. A steady rise in broadband emissions can be observed with increasing sonication amplitudes. For most temperature values, broadband emissions stay below 15 dB. However, a sudden increase in broadband emissions was detected at high temperatures during 1.1-MPa and 1.4-MPa exposures. At temperatures below 80 °C, the low-frequency emission levels stayed below 10 dB. As the tissue temperature increased further, a sudden increase in low-frequency emissions would occur. The scattered energy at the fundamental frequency showed some change over the entire temperature range. Linear correlation between the two quantities was found to be statistically significant. Energy scattered at the fundamental frequency would increase with sonication. Similarly, the tissue temperature was found to increase with sonication amplitude. This could explain the positive correlation between scattered energy at the fundamental and tissue temperature. Correspondence of tissue temperature with time-dependent acoustic emissions and tissue echogenicity (MGSV) was quantified by computing correlation coefficients. These values are presented in Table I. These coefficients were computed for \( N = 6179 \) epochs from 18 ablation experiments. Correlations based on temperature-broadband emission, temperature-low-frequency emissions and temperature-MGSV were all statistically significant \( (p < 10^{-25}) \).

<table>
<thead>
<tr>
<th>Fundamental</th>
<th>Subharmonic</th>
<th>Broadband</th>
<th>Low-frequency</th>
<th>MGSV</th>
<th>Temperature</th>
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</tbody>
</table>

Table I: Correlation coefficients for time-dependent temperature vs. acoustic emissions in subharmonic, broadband, and low-frequency ranges, over all measured epochs.

Scatter plots of MGSV vs. scattered energy at the fundamental frequency as well as
Figure 2.12: Scatter plots of time-dependent (a) subharmonic emissions, (b) broadband emissions, (c) low-frequency emissions, (d) MGSV, and (e) scattering of the fundamental vs. temperature are shown ($N = 6179$ or 18 experiments). Data from 1.4-MPa exposures are shown by black circles ($\circ$), 1.1-MPa exposures by brown crosses ($\times$), and 0.8-MPa exposures by green triangles ($\Delta$).
broadband, subharmonic, and low-frequency emissions can be seen in Fig. 2.13 for all 18 experiments. The correlation coefficient between MGSV and low-frequency emissions was statistically significant. This is consistent with tissue boiling which results in vapor formation and may be responsible for the increased echogenicity and low-frequency emissions. Correlation coefficient between the energy scattered at the fundamental frequency and MGSV was statistically significant but its value was very low. Vapor formation which causes an increase in MGSV can also result in increased scattering of the fundamental. Hence, some correlation between the two quantities can be expected. Table II contains correlation coefficients of MGSV vs. cavitational emissions and the scattered fundamental. The statistically significant correlation values are written in bold.

<table>
<thead>
<tr>
<th>Fundamental</th>
<th>Subharmonic</th>
<th>Broadband</th>
<th>Low-frequency</th>
<th>MGSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.066</td>
<td>0.123</td>
<td>2.32 \cdot 10^{-3}</td>
<td>0.219</td>
<td></td>
</tr>
</tbody>
</table>

Table II: Correlation coefficients for time-dependent MGSV vs. scattered fundamental, and acoustic emissions in subharmonic, broadband and low-frequency ranges, over all measured epochs.

B. Analysis of time-averaged emission levels

Figure 2.14 shows emission (mean ± st. dev.) levels in the three frequency bands as a function of sonication amplitude. This plot is created using time-averaged emission levels for all 18 experiments and the emission energy values are expressed in dB. Emissions at the subharmonic frequency show a large variability for different experimental trials. This results in relative large standard deviation values. No consistent linear correlation was seen between subharmonic emissions and sonication pressure levels. Broadband emissions increased with the sonication amplitude. For a given sonication amplitude, broadband emissions exhibited lower variability compared to subharmonic emissions, consistent with lower standard deviations. Low-frequency emission levels were small for 0.8-MPa and 1.1-MPa exposures. For 1.4-MPa exposures, the low-frequency emission levels were larger and showed greater vari-
Figure 2.13: Scatter plots of MGSV vs. (a) scattered fundamental, (b) subharmonic emissions, (c) broadband emissions, and (d) low-frequency emissions for 1.4-MPa (black ◦), 1.1-MPa (brown ×) and 0.8-MPa (green ∆) exposures.

ability. This is consistent with tissue boiling, which is more likely during exposures at the highest sonication amplitude. Mean values of time-averaged acoustic emission levels measured during the control experiments without a thermocouple are also shown in Fig. 2.14. Similar trends between acoustic emission levels and sonication pressure can be seen with or without the thermocouple embedded in the tissue samples.

Correspondence between tissue ablation rate and time-averaged acoustic emission levels was investigated. No clear relationship was observed between subharmonic emissions and
volumetric ablation or overtreatment rates [Fig. 2.15(a), Fig. 2.16(a)]. In Fig. 2.15(b), it is seen that ablation rate and broadband emissions exhibit an approximately linear relationship. Ablation rate would increase with ultrasound intensity due to an increase in heat deposition. The increase in broadband emission levels could happen due to an increase in the number or amplitude of inertial cavitation events. This could explain the linear correspondence between ablation rate and broadband emissions. Similar relation was also observed between overtreatment rates and broadband emissions [Fig. 2.16(b)]. The scatter plot of ablation rate and low-frequency emissions indicates a nonlinear relationship between the two quantities [Fig. 2.15(c)]. For ablation exposures at 0.8, 1.1 MPa nominal pressure amplitudes, the low-frequency emissions were generally low. At the highest amplitude, an increase in the low-frequency emissions was observed along with an increase in the volumetric ablation rates. This is consistent with observations of vaporization and boiling during the 1.4-MPa sonications. However, a linear relationship was observed between overtreatment rates and low-frequency emissions [Fig. 2.16(c)].

Observations made from scatter plots in Fig. 2.15 and Fig. 2.16, further explored through a cross correlation analysis, are shown in Table III. Correlation coefficients were computed for all 18 experiments and the statistically significant values ($p < 10^{-2}$) are indicated in bold. Volumetric ablation rate correlated with broadband and low-frequency emissions. Overtreatment rate showed maximum correlation with low-frequency emissions, consistent with previous observations related to tissue boiling and overtreatment. Correlation coefficients between subharmonic emissions and ablation rate or overtreatment rate were not statistically significant.

<table>
<thead>
<tr>
<th>Subharmonic</th>
<th>Broadband</th>
<th>Low-frequency</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.144</td>
<td>0.848</td>
<td>0.747</td>
<td>Ablation</td>
</tr>
<tr>
<td>0.225</td>
<td>0.682</td>
<td>0.754</td>
<td>Overtreatment</td>
</tr>
</tbody>
</table>

Table III: Correlation coefficients of ablation and overtreatment rates vs. time-averaged subharmonic, broadband and low-frequency emissions, for all 18 experiments.
Figure 2.14: Mean ± standard deviation (○ and error bars) values of the measured (a) subharmonic emissions, (b) broadband emissions, and (c) low-frequency emissions are shown as a function of sonication amplitude ($N = 6$ for each sonication amplitude). Mean acoustic emission levels for the control experiments ($N = 2$ for each sonication amplitude) without embedded thermocouple are shown by crosses ($\times$).

IV. Discussion

This section contains information about strengths and limitations of the experimental approach presented here, and comparison of results from this study with relevant findings in the existing literature.

A. Strengths and limitations

Ultrasound ablation was performed in the experiments reported here with unfocused therapeutic ultrasound beams. The ultrasound-induced tissue heating occurred in a broad region of the tissue sample. Similarly, the PCD utilized here was unfocused and hence interrogated a broad tissue volume for acoustic emission signals. The unfocused nature of the ultrasound source and the PCD mitigates misalignment artifacts. The unfocused PCD provides a spatially integrated measure of the overall bubble activity occurring inside the heated tissue. No information related to spatial variations of bubble activity inside the treated tissue volume can gleaned from these PCD measurements. The received acoustic emission energy may
Figure 2.15: Scatter plots of ablated tissue volume vs. time-averaged (a) subharmonic emissions, (b) broadband emissions, and (c) low-frequency emissions. The 1.4-MPa experiments are represented by black ◦, the 1.1-MPa exposures by brown ×, and the 0.8 exposures by green ∆.

hence result from bubbles cavitating in several tissue regions, subject to different temperature and acoustic pressure conditions. Temperature measurements were made during the experiments with a needle thermocouple, with the thermocouple probe aligned close to the center of the heated tissue volume. The unfocused nature of the ultrasound beam allows for physically relevant comparisons (correlation analysis) between single-point temperature measurements and spatially integrated emission measurements. The broad unfocused ultrasound beams used here do not cause severe temperature gradients in the heated tissue volume (Mast 2005). Hence, the single-point temperature measurement described here may be assumed as an indicator of the overall tissue ablation progress. This tissue temperature estimate can differ from local temperatures at the origin sites of detectable bubble activity. These experiments may be improved by employing cavitation detection schemes with greater spatial resolution, allowing a more accurate investigation of localized temperature values and cavitation behavior. Techniques for such spatially sensitive cavitation detection are addressed in later chapters.

The use of fresh ex vivo tissue is another limitation of this study. Living tissue would
behave differently on account of a lower number of preexisting free gas bubbles and blood perfusion. However as the tissue temperature increases during ablation and the tissue is necrosed \textit{in vivo}, differences between \textit{ex vivo} and \textit{in vivo} tissue in terms of free gas and perfusion characteristics will diminish. After coagulative necrosis, behaviors of \textit{ex vivo} and \textit{in vivo} tissue would be very similar.

\section*{B. Subharmonic emissions}

Subharmonic emissions are caused by stable volumetric oscillations of gas bubbles in an ultrasound field (Leighton 1994). Sustained stable cavitation was seldom detected during the experiments presented here. During the 0.8-MPa exposures, persistent subharmonic emissions were observed when the tissue temperature stayed between 47–49 °C, possibly because the tissue temperature and ultrasound pressure created conditions favorable for stable cavitation. In other circumstances, the continuous-wave ultrasound beams would most likely destroy any preexisting gas bubbles in the tissue and decrease the chances of sustained stable cavitation activity. The short-lived subharmonic emission signals observed
during most experiments were consistent with typical emissions during stable cavitation (Neppiras 1980).

C. Broadband emissions

Broadband emissions observed during these experiments were relatively long-lived and could have resulted from rectified diffusion, which can cause small cavities to grow to sizes optimal for a sudden inertial collapse (Church 1988). The resultingbubble fragments serve as cavitation nuclei that in turn grow in size to provide a self-sustained inertial cavitation activity (Flynn 1964). Based on computations by Church (1988), 0.2–1 μm radii air bubbles in water have a rectified diffusion threshold of 0.7 MPa (peak-negative pressure) for 3-MHz sonication. These thresholds are significantly lower if the bubbles are optimally sized at 1 μm. Hence, the CW exposures used here were likely to produce conditions suitable for rectified diffusion and inertial cavitation. Broadband emissions observed in these experiments were similar to those reported by Neppiras (1980), including the presence of distinct spectral lines unrelated to the source frequency. This signature can be clearly observed in the time-frequency plots (Fig. 2.8–2.10) shown earlier.

Observations of broadband emissions during tissue ablation have been inconsistent over several previous studies. Some HIFU studies report a large increase in broadband emissions at the onset of boiling and vaporization (Bailey 2003, Rabkin 2005, 2006). Conversely, a sudden decrease in broadband emission signals has been observed with the onset of boiling during HIFU ablation of tissue-mimicking phantoms (Farny 2007). Some other studies have observed similar broadband emissions in the absence of boiling (Khokhlova 2006, McLaughlan 2006). Discrepancy in these inertial cavitation observations may be attributed to the strong nonlinear effects of HIFU beams at ablation-relevant intensities (Bailey 2003, Khokhlova 2006).
D. Low-frequency emissions and tissue echogenicity

In the experiments reported here, a near-simultaneous increase in low-frequency emissions and tissue echogenicity was observed for treatments at the highest sonication amplitude. The increase in values of both these quantities occurred at temperatures close to tissue boiling. This is consistent with several other HIFU ablation studies (Khokhlova 2006, MCLaughlan 2006). It may be inferred that both these effects are related to the formation of large bubbles that act as ultrasound reflectors and also undergo low-frequency oscillations. This could explain the reason for the statistically significant correlation of tissue echogenicity with both tissue temperature and low-frequency emissions. Echogenicity was also found to increase steadily during the lowest sonication amplitude exposures (0.8 MPa). Similar observations were made by Khokhlova (2006), when a gradual increase in B-scan brightness was seen as the temperature increased during HIFU ablation of polyacrylamide/gel phantoms.

V. Concluding Remarks

Results from the bulk ablation experiments presented here illustrate relationships between simultaneously measured acoustic emissions, tissue echogenicity and tissue temperature. To exploit these relationships for ablation guidance effectively, further investigation of the effect of ultrasound exposure parameters on cavitation activity, particularly stable cavitation, have to be studied. The following chapter explores a preliminary statistical model for predicting tissue temperature based on the acoustic measurements made here.
Chapter 3

Logistic Regression Models for Temperature Estimation during Bulk Ablation

I. Objective

In the previous chapter, cavitation-related acoustic emissions were measured during bulk ultrasound ablation exposures (Mast 2008a). If tissue temperature could be predicted from these noninvasively measured quantities, it may assist in monitoring ultrasound ablation treatments. Here, statistical input-output models are fitted to the experimental data presented in the previous chapter. Temperature increase during ablation is modeled as a function of the measured acoustic emission signals, tissue echogenicity, sonication amplitude, and exposure time. The models presented here are based on a logistic regression framework.

II. Methods

During the bulk ultrasound ablation experiments reported in the previous chapter, time-dependent quantities like tissue temperature, tissue echogenicity (mean grayscale value or MGSV), and acoustic emissions in subharmonic (1.55 MHz), broadband (0.3–1.1 MHz), and low-frequency (10–30 kHz) ranges were recorded. Bulk ablation exposures were conducted with a 3.1-MHz, unfocused ultrasound beam at nominal pressure levels of 0.8, 1.1, and
1.4 MPa. The temperature was measured at a single point inside the tissue with a needle thermocouple. Acoustic emissions were measured over the entire ablated tissue volume by a single-element, unfocused passive cavitation detector (1 MHz). Scatter plots of tissue sample temperatures vs. acoustically measured quantities are shown in Fig. 3.1. These plots were generated from the same data used in creating Fig. 2.12. The observed relationship between temperature and other measured quantities was highly nonlinear. Hence, a multiple linear regression approach was not sufficient to model this relationship. Instead of using nonlinear curve-fitting, a more convenient multinomial logistic regression model was employed (Hosmer 2004).

A. Logistic regression overview

Logistic regression models are commonly used in studies where the output or response variable is categorical. Particularly, in medical and epidemiologic research, such responses refer to binary outcomes like dead or alive, diseased or normal, cancerous or benign, etc. The outcomes may also be multinomial such as strongly agree, moderately agree, or disagree (sometimes related to the Likert scale used during surveys). Logistic regression models estimate the probability of one of these outcomes, given a certain set of input conditions (Harrell 2001). The “logit” function is the basis for logistic regression. This function is given by

\[
f(z) = \frac{1}{1 + e^{-z}},\tag{3.1}\]

and yields an “s” shaped curve which is asymptotic at values 0 and 1 (see Fig. 3.2).

As mentioned above, the response variable \((Y)\) takes a categorical value, say 1, 2, or 3. The output of a logistic regression model is \(\mathcal{P}[Y = 1], \mathcal{P}[Y = 2], \text{ or } \mathcal{P}[Y = 3]\), where \(\mathcal{P}[.]\) refers to probability. The input variables (say \(X_1\) and \(X_2\)), also called covariates, can be continuous or categorical. Based on the “logit” function described above, the mathematical form of a multinomial logistic regression model for input variables \(X_1\) and \(X_2\) is given by
Figure 3.1: Scatter plots of temperature vs. (a) broadband emissions, (b) subharmonic emissions, (c) low-frequency emissions, and (d) MGSV for all 6179 epochs. Data points from the 1.4 MPa exposures are indicated by black ○, the 1.1 MPa exposure are indicated by brown ×, and the 0.8 MPa exposures are indicated by green Δ.
Figure 3.2: Example of a logit curve

\[ P[Y = 1] = \frac{1}{D}, \]
\[ P[Y = 2] = \frac{\exp(\alpha_0 + \alpha_1 X_1 + \alpha_2 X_2)}{D}, \]
\[ P[Y = 3] = \frac{\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2)}{D}. \]

\[ D = 1 + \exp(\alpha_0 + \alpha_1 X_1 + \alpha_2 X_2) + \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2). \]

Here, \( \alpha \)'s and \( \beta \)'s are the model parameters. The model parameters are estimated for a given data set through a method of maximum likelihood (McCullagh 1995).

Several studies employing logistic regression for image-based medical diagnosis and decision making have been published recently. Stepwise logistic regression models were used by Chou et al. (2001) in computer-aided diagnosis of breast tumors. In that study, tumor contours were mapped on ultrasound images and a logistic regression model was used to classify malignant and benign tumors. Similar breast tumor identification studies using logistic regression models on MR image data have been reported too (McLaren 2009; Nie 2008). Image-based classification of tumors in other soft tissue like thyroid (Savelonas 2009) and prostate (Fujikawa 2001) has also been attempted using logistic regression models. Logistic regression was used to study the impact of peritumoral blood vessels during radiofrequency
ablation of liver tumors by Lu et al. (2003). Uchida et al. (2006) also used logistic regression to evaluate the efficacy of androgen suppression during HIFU ablation of prostate cancer.

During the study presented in this chapter, logistic regression was used to model tissue temperature as a function of the measured cavitationsal emissions occurring during ultrasound ablation. As seen below, the tissue temperature, a continuous quantity, was converted to a categorical response variable by employing threshold values relevant to tissue ablation. This approach allowed a simple and convenient way of modeling the highly nonlinear relationship between temperature and other acoustic quantities (see Fig. 3.1).

**B. Model description**

For the models presented here, the response variable was tissue temperature, which is a continuous quantity. To make this amenable to multinominal logistic regression, it was converted to a ternary variable based on two ablation-relevant temperature thresholds. Coagulative tissue necrosis occurs when the temperature is raised above 60 °C (Mast 2005). Hence, this was chosen as the first temperature threshold to represent irreversible tissue coagulation. Based on the scatter plots in Fig. 3.1, a sudden increase in broadband and low-frequency emissions was observed when the measured temperature exceeded 80 °C. However, these increases were consistent with boiling and vaporization, as seen in Chapter 2 (section II E). It should be noted that the acoustic emission signals were measured in a broad volume, encompassing the heated tissue. Conversely, the temperature was recorded at a single point in the tissue sample. Hence, it was likely that when the temperature at the thermocouple location was 80 °C, the temperature in another part of the heated tissue had exceeded the boiling point. This would result in increased low-frequency emissions and tissue echogenicity. During exposures where the tissue temperature exceeded 80 °C, the ablated regions were brown in color and had a cracked appearance. This occurrence was called “overtreatment” during Chapter 2 (Fig. 2.3). Hence, 80 °C was chosen as the second threshold, indicative of
overtreatment. Based on these thresholds, the temperature ($T$) was converted to a ternary response variable ($Y$):

\begin{align*}
Y = 1 &\equiv T < 60 \degree C \\
Y = 2 &\equiv 60 \degree C \leq T \leq 80 \degree C \\
Y = 3 &\equiv T > 80 \degree C
\end{align*}

(3.3)

Logistic regression models were created for different sets of input variables or covariates. Covariates like acoustic emissions and tissue echogenicity were measured, while covariates like sonication amplitude and time elapsed were known \textit{a priori}. The models developed in this paper use the following covariates:

- \textbf{Model 1}: acoustic emissions and MGSV (quantities measured acoustically)
- \textbf{Model 2}: sonication amplitude and time elapsed during an exposure (quantities known \textit{a priori})
- \textbf{Model 3}: all measured and known quantities

During the experiments presented in the previous chapter, sonications were performed at three distinct levels. As no intermediate sonication levels were employed, sonication amplitude ($P$) was treated as a categorical variable. It was represented using two dummy variables called $P_1$ and $P_2$. When the pressure amplitude was 0.8 MPa, both $P_1$ and $P_2$ were set to 0. When the pressure amplitude was 1.1 MPa, $P_1$ was set 1 and $P_2$ was set to 0. When the pressure amplitude was 1.4 MPa, $P_1$ was set to 0 and $P_2$ was set to 1.

The subharmonic, broadband, and low-frequency emissions were expressed in dB, relative to the measured background noise levels (detailed in the previous chapter, sections II E and II F). The MGSV variable was also expressed in dB, relative to the MGSV before starting
an exposure. The MGSV reference levels were different for different tissue samples. The elapsed treatment times were expressed in minutes.

C. Model implementation

As seen in Chapter 2, 6 exposures were performed at each of the three pressure amplitudes, resulting in a total of 18 experiments ($N = 6179$ epochs for each acoustic emission measurement). To build a model, data from 15 experiments ($\approx 5000$ points), 5 at each pressure amplitude, was used. The model parameters were estimated through a method of maximum likelihood using R-2.9.2 statistical analysis software. Every model was tested on the data used during model building and also on data from the 3 experiments ($\approx 1000$ points), 1 at each pressure amplitude, not used in model building. The estimated outcome with the maximum probability was selected as the model output ($\hat{Y} = 1, 2, \text{ or } 3$). The prediction accuracy of all models was computed (see the next subsection for details). The procedure was repeated for all other distinct combinations of training and testing datasets, giving a total of 216 iterations. Mean and standard error values were calculated for model parameters obtained from these iterations. Mean and standard error values were also computed for prediction accuracy. This process is called cross validation (Hosmer 2004) and was used to assess the goodness-of-fit and robustness of the statistical models presented here.

D. Prediction accuracy

The prediction accuracy for the fitted multinomial logistic regression models was estimated using the following measures:

$$\text{Correct} = \frac{N[Y = \hat{Y}]}{N[Y]} \quad (3.4)$$

$$\text{Below}_{60} = \frac{N[(Y = 1) \& (\hat{Y} = 1)]}{N[(Y = 1)]}$$

$$\text{Above}_{60} = \frac{N[(Y \neq 1) \& (\hat{Y} \neq 1)]}{N[(Y \neq 1)]}$$

63
\[
\begin{align*}
\text{Below}_{80} &= \frac{N[(Y \neq 3) \& (\hat{Y} \neq 3)]}{N[(Y \neq 3)]} \\
\text{Above}_{80} &= \frac{N[(Y = 3) \& (\hat{Y} = 3)]}{N[(Y = 3)]} \\
\text{EOP} &= \frac{N[(Y = 1) \& (\hat{Y} = 3)]}{N[(Y = 3)]}
\end{align*}
\]

Here, \(N[\cdot]\) refers to the number of instances and \& is the logical “AND” operator. Accuracy at the lower temperature threshold indicates the ability to detect irreversible tissue coagulation, while accuracy at the higher threshold value indicates the ability to detect overtreatment. Here, \(\text{EOP}\) stands for extreme over-prediction. It refers to a false positive prediction, where the model indicates overtreatment when the actual temperature is below 60 °C. If this error value is low, the model output may be used as a criterion to stop the exposure and prevent overtreatment.

III. Results and Discussion

This section presents the multinomial logistic regression models implemented for the data acquired during the experiments reported in Chapter 2. Values of the model parameters are interpreted with respect to the physical significance of the corresponding input variable. Accuracy and robustness of these models have also been discussed.

A. Model parameters

Table I contains the values of parameters associated with each covariate for the three models mentioned above. The mean and standard error values were estimated from the cross validation studies described in the Methods section. If the mean ± std. error range for a model parameter does not contain zero, the associated covariate is said to have a significant impact on the model (Kleinbaum 2002). Similarly, a greater numerical difference between zero and this range indicates a greater impact of the associated covariate on the model. For
Table I: Estimates of the parameters of multinomial logistic regression models using (a) acoustically measured variables like acoustic emissions and MGSV, (b) a priori known quantities like sonication amplitude and elapsed time, and (c) all acoustically measured and a priori known quantities as input variables. Mean and standard error values for the model parameters are computed based on the cross validation studies described in the previous section ($N = 216$).

Models 1 and 3, the subharmonic emissions are less impactful based on the above criterion. In Models 2 and 3, it can be seen that the sonication amplitude has a significant impact.

Fig. 3.3 shows the dependence of the output of Model 1 on each model covariate. To create these graphs, one covariate was varied and average values were used for the other covariates. The estimated model parameters were used and the predicted probability of each outcome ($\hat{Y} = 1, 2$ or $3$) was estimated. The graphs are consistent with the observations reported in Chapter 2 (section III A). With an increase in broadband emissions, low-frequency emissions, and MGSV, the probability that the tissue temperature exceeded 80 °C increased and the
probability that the temperature was below 60 °C reduced. The probability of the tissue temperature exceeding 80 °C showed a rapid increase when low-frequency emissions and MGSV increased, consistent with the fact that these two quantities are associated with boiling and vaporization. Fig. 3.4 shows the Model 2 output as a function of elapsed time, for each of the three sonication amplitudes. It can be seen that the probability of the temperature exceeding 80 °C increases with time. The increase occurs earlier in exposures at higher amplitudes.

For Model 1 using the measured variables, the parameters associated with broadband emissions, low-frequency emissions and MGSV were positive for the higher temperature threshold. This was consistent with the experimental observation that these quantities showed an increase when the tissue temperature increased above 80 °C. At higher temperatures, there was an increase in the low-frequency emissions due to boiling and gas vapor formation, which also increased tissue echogenicity (see previous chapter, section IV D). Broadband emission followed a similar trend with respect to tissue temperature. As no clear monotonic relationship was found between subharmonic emissions and tissue temperature (see Fig. 3.1), the covariate associated with the former was not very impactful.

In Model 2, the sonication pressure covariates (categorical variables) dominated. In general, a higher pressure would imply a greater probability of exceeding a temperature threshold. However, the pressure covariate was a categorical variable and the numerical value of sonication pressure was not utilized. This makes it more difficult to interpret the positive value of the parameter associated with pressure. For a given pressure value, the instantaneous tissue temperature depended upon the time elapsed during an exposure. Hence, a combination of the pressure information and the treatment time would help in determining the tissue temperature, and whether it exceeded one of the thresholds.

In Model 3 using all measured and a priori known variables, the parameters associated with the pressure covariate dominated. The time-dependent temperature behavior observed
was significantly different for the three sonication amplitudes. This could explain the high statistical impact of the covariates associated with sonication pressure.

B. Model performance

Performance of a model was first evaluated on the data points used in model building. This was done by computing the number of correct predictions made by a model as seen in Table II (left column). Model 1, which used only the measured variables, showed an overall prediction accuracy of 65%. Model 2, with \textit{a priori} known quantities, showed an overall accuracy of 68%. Model 3, which used all the variables, showed a prediction accuracy of 74%. This is consistent with the increasing input information provided to the individual models. All models showed better accuracy at the higher temperature threshold. This was true in both the training and the test datasets. Reasons for increased accuracy at the higher threshold may be the rapid increase in the values of low-frequency emissions and MGSV in Models 1 and 3, and the rapid increase in the probability of the temperature exceeding 80 °C with time in Models 2 and 3. Similar trends were observed when the models were tested on the test data (see Table III). The accuracy was expectedly lower, but the reduction was less that 5%. This implies that the models are robust and fit the data well.

Model outcome $\hat{Y} = 3$ may be used as a criterion to stop the exposure, as it would indicate overtreatment. The false positive error rate for outcome 3, when the actual tissue temperature is below 60 °C (EOP), should remain low. The extreme right columns of Tables II and III are indicative of this error rate (EOP). Model 1 has the highest EOP, while Model 2 has the lowest. However, it should be noted that EOP for Model 1 was below 17%.

The model coefficients were estimated by optimizing the maximum likelihood function associated with the models. This optimization scheme seeks to maximize the overall prediction accuracy of a model. Hence, the overall prediction accuracy of these models increases with the number of model inputs (increasing information). However, the model parameters
Figure 3.3: Probability of tissue temperature being less than 60 °C, between 60–80 °C, or greater than 80 °C as a function of (a) broadband emissions, (b) subharmonic emissions, (c) low-frequency emissions, and (d) mean grayscale values (MGSV), based on multinomial logistic regression data fitting (Model 1). To create each graph, one covariate (indicated on the horizontal axis) was varied, and the average values were used for the other covariates.
Figure 3.4: Probability of tissue temperature being less than 60°C, between 60–80 °C, or greater than 80°C as a function of the time elapsed during exposures at (a) 1.4 MPa, (b) 1.1 MPa, and (c) 0.8 MPa, based on multinomial logistic regression data fitting (Model 2).
estimated in this manner may not guarantee optimal performance at individual temperature thresholds. Hence, the accuracy of Model 3 can be less than Model 2 at individual threshold levels, as seen in Table II.

The standard errors associated with the prediction accuracy values are indicative of the model robustness. For Model 2, these standard errors are the lowest. Model 2 implemented the pressure covariate as categorical. The tissue temperature behavior for the three amplitudes was sufficiently different. This may have led to a very robust fit for Model 2. In a clinical application, such models may be very useful in the initial planning of a treatment regime.

During a clinical treatment scenario, the sonication amplitude may take several continuous values depending on the targeted tissue or tumor volumes. It may be desired to employ feedback control mechanisms where the sonication amplitude can be varied based on the measured or predicted tissue temperature. Also, the \textit{a priori} known quantities such as sonication pressure may deviate from their nominal values due to changes in the tissue medium, degradation in the performance of the therapeutic devices over time, or other factors. In such cases, a relatively simple model based only on the \textit{a priori} known variables may not suffice. Hence, models which include measured acoustic quantities, such as Models 1 and 3, can be useful.

<table>
<thead>
<tr>
<th>Model</th>
<th>Correct</th>
<th>Below$_{60}$</th>
<th>Above$_{60}$</th>
<th>Below$_{80}$</th>
<th>Above$_{80}$</th>
<th>EOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Mean</td>
<td>0.6459</td>
<td>0.8074</td>
<td>0.6290</td>
<td>0.9027</td>
<td>0.6851</td>
</tr>
<tr>
<td></td>
<td>St. error</td>
<td>0.0240</td>
<td>0.0286</td>
<td>0.0518</td>
<td>0.0174</td>
<td>0.0322</td>
</tr>
<tr>
<td>Model 2</td>
<td>Mean</td>
<td>0.6889</td>
<td>0.8530</td>
<td>0.8057</td>
<td>0.8619</td>
<td>0.8290</td>
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<tr>
<td></td>
<td>St. error</td>
<td>0.0156</td>
<td>0.0168</td>
<td>0.0217</td>
<td>0.0095</td>
<td>0.0265</td>
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<tr>
<td>Model 3</td>
<td>Mean</td>
<td>0.7401</td>
<td>0.8407</td>
<td>0.8093</td>
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<tr>
<td></td>
<td>St. error</td>
<td>0.0202</td>
<td>0.0224</td>
<td>0.0237</td>
<td>0.0163</td>
<td>0.0245</td>
</tr>
</tbody>
</table>

Table II: Performance of the fitted models on data used during model building. The mean and standard error values ($N = 216$) of the performance measures are based on cross validation studies.
Table III: Performance of the fitted models on data not used during model building. The mean and standard error values (N = 216) of the performance measures are based on cross validation studies.

<table>
<thead>
<tr>
<th></th>
<th>Correct</th>
<th>Below&lt;sub&gt;60&lt;/sub&gt;</th>
<th>Above&lt;sub&gt;60&lt;/sub&gt;</th>
<th>Below&lt;sub&gt;80&lt;/sub&gt;</th>
<th>Above&lt;sub&gt;80&lt;/sub&gt;</th>
<th>EOP</th>
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<tr>
<td>Model 1</td>
<td>Mean</td>
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<td>0.7936</td>
<td>0.5877</td>
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<td>St. error</td>
<td>0.1128</td>
<td>0.1682</td>
<td>0.1942</td>
<td>0.0941</td>
<td>0.1722</td>
</tr>
<tr>
<td>Model 2</td>
<td>Mean</td>
<td>0.6121</td>
<td>0.8248</td>
<td>0.7817</td>
<td>0.8536</td>
<td>0.8248</td>
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<tr>
<td></td>
<td>St. error</td>
<td>0.0663</td>
<td>0.1200</td>
<td>0.1087</td>
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<td>Model 3</td>
<td>Mean</td>
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<td>St. error</td>
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<td>0.1511</td>
<td>0.1235</td>
<td>0.0906</td>
<td>0.1678</td>
</tr>
</tbody>
</table>

IV. Concluding remarks

Statistical models may be used to predict tissue temperature during ultrasound ablation, based on the measured acoustic emissions and B-mode images. The nonlinear relationships between tissue temperature and the measured quantities were successfully modeled using a multinomial logistic regression framework. Models which use only the measured information and yield accurate temperature predictions are desired, as they may prove more useful in clinical applications.

The logistic regression models presented here used single-point measures of temperature activity and spatially averaged information about cavitation emissions. If passive cavitation detection schemes can track spatial variations in localized cavitation activity, a better prediction of tissue temperature may be possible based on cavitation measurements. The following three chapters present methods of spatially sensitive passive cavitation detection using ultrasound arrays, with a goal to create two-dimensional images of locally-occurring cavitation activity. Such cavitation detection and statistical data processing, if successfully implemented in real time, may have potential uses in ultrasound ablation monitoring.
Chapter 4

Passive Cavitation Imaging: Theory and Simulations

I. Objective

Single-element transducers have been used as passive cavitation detectors (PCD) in several experimental studies dealing with therapeutic applications of ultrasound. Some recent examples include tissue ablation (McLaughlan 2006; Mast 2008a), thrombolysis (Datta 2006) and targeted drug delivery (Hynynen 2008). Typically, single-element detectors are aligned to interrogate regions in a medium where cavitation activity is most likely. During ultrasound ablation, different locations in a treated tissue volume have different temperatures and physical state, leading to spatial variations in cavitation activity. A single-element PCD is insufficient in capturing such position-dependent changes in cavitation. A multi-element detector like an ultrasound imaging array has the potential to act as a PCD which can provide spatial information about locally occurring bubble activity. Here, an ultrasound array is employed as a PCD and the resulting maps are called passive cavitation images.

Recently, similar passive cavitation imaging techniques have been reported during controlled HIFU experiments with tissue phantoms (Farny 2007, 2009) and ultrasound contrast agents (Gyöngy 2009). Conventional ultrasound imaging systems are not designed to conduct PCD measurements and there is a need to develop array beamforming techniques
customized for passive imaging. Analytic models of passive cavitation images, presented in this chapter, can help in evaluating the effects of imaging array dimensions, beamforming configurations, and frequency bandwidth of cavitation emissions on passive cavitation imaging. This mathematical framework is developed with a goal to assist in optimization of passive imaging parameters for passive cavitation detection with high spatial resolution and quantitative accuracy.

II. Theory

Figure 4.1: Simulated sensitivity patterns of three array subapertures are represented. The white “X” marks the location of a cavitating bubble.

In conventional B-mode imaging, a short ultrasound pulse is transmitted into the medium and images are created from the resulting echoes. Distances of reflectors in the medium are estimated with respect to this initial pulse based on time of flight (Szabo 2004). During passive cavitation imaging as defined here, no transmit pulse is initiated and images are created solely from the received bubble emissions. Spatial sensitivity is obtained in such images through dynamic focusing of the array subapertures at several depths. The spatial position of such a synthetic focus forms a point on the passive cavitation image. Simulated receive-sensitivity patterns for three subapertures focused at distinct locations are seen in
Fig. 4.1. If a bubble is cavitating at location “X” in the medium, the subaperture with sensitivity represented in magenta (extreme left), will be more sensitive to the emissions from this bubble than the other two subapertures. Hence, the point on an image corresponding to the focus of this subaperture (magenta) will have a large brightness (grayscale) value. In this manner, array subapertures are focused at multiple positions to obtain an entire passive cavitation image. Analytic expressions that describe passive cavitation imaging are presented below.

A. Signal received by a rectangular array element

Figure 4.2: Schematic diagram of a rectangular transducer element detecting the acoustic pressure field of a point source. The detector is located in the x–y (elevation–azimuth) plane. Center of this transducer element is considered as the origin. Range direction is along the z-axis.

An expression for bubble emission signal detected by an array element is derived first. To do so, a cavitating bubble is modeled as a point source emitting spherical sound waves. Volume \( Q(t) \) of the fluid flowing out of a sphere with radius \( a \) relates to the particle velocity \( u \) as

\[
Q(t) = 4\pi a^2 \frac{\partial u(a, t)}{\partial r}.
\]

By applying a small-radius limit \((a \to 0)\), the time-varying pressure field at a position \( r \) from the point source (bubble) is given by

\[
p(r, t) = \frac{\rho \dot{Q}(t - r/c)}{4\pi |r|},
\]
where $\rho$ is the medium density, $\dot{Q}$ refers to partial derivative with respect to time and $c$ is the sound speed (Blackstock 2000). The received emission signal $s_n(t)$, for an element $n$ centered at $r_0$ (area $S_0$), due to a bubble at $r_s$ is obtained by integrating the radiated pressure from Eq. (4.2) over the element surface (Pierce 1989). This results in the Rayleigh-Sommerfield integral given by

$$s_n(t) = \rho \dot{Q}(t - |r_0 - r_s|/c) \frac{4\pi}{|r_0 - r_s|} dS_0.$$  

Fig. 4.2 indicates relative positions of the cavitating bubble and the array element. The Rayleigh integral can be expressed in the frequency domain by a Fourier transform operation. The resulting representation is

$$S_n(\omega) = -i\omega \rho \dot{Q}(\omega) \frac{4\pi}{|r_0 - r_s|} e^{i |r_0 - r_s|c/\omega} dS_0,$$  

where $\omega$ denotes radial frequency and $dS_0$ is an area-element on the receiver surface.

An approximate solution for this frequency-domain expression can be obtained using the Fresnel approximation. Simplifications made under this approximation yield

$$|r_0 - r_s| = z_s + \frac{(x_s - x_0)^2}{2z_s} + \frac{(y_s - y_0)^2}{2z_s},$$  

$$\frac{1}{|r_0 - r_s|} = \frac{1}{z_s}.$$  

For an array element with dimensions $2a \times 2b$, focused at depth $F_x$ in elevation and $F_y$ in azimuth, Eq. (4.4) can be written under the Fresnel approximation (Mast 2007) as

$$S_n(\omega) = -i\omega \rho \dot{Q}(\omega) e^{ik z_s^2/2x} \int_{-a}^{a} e^{ikx_0^2/2F_x} e^{ikx_0^2} dx_0 \int_{-b}^{b} e^{iky_0^2/2F_y} e^{iky_0^2} dy_0,$$

$$= -i\omega \rho \dot{Q}(\omega) \Phi(r_s, k) \left( \frac{kx_s + \tilde{k}_x a}{\sqrt{\pi k x_z}} - \frac{kx_s - \tilde{k}_x a}{\sqrt{\pi k x_z}} \right) \left( \frac{ky_s + \tilde{k}_y b}{\sqrt{\pi k y_z}} - \frac{ky_s - \tilde{k}_y b}{\sqrt{\pi k y_z}} \right),$$

$$\times \left( \frac{kx_s + \tilde{k}_x a}{\sqrt{\pi k x_z}} - \frac{kx_s - \tilde{k}_x a}{\sqrt{\pi k x_z}} \right) \left( \frac{ky_s + \tilde{k}_y b}{\sqrt{\pi k y_z}} - \frac{ky_s - \tilde{k}_y b}{\sqrt{\pi k y_z}} \right),$$  

(4.6)
where the wave number \( k = \omega/c \), \( \tilde{k}_x = k \left(1 - \frac{z_s}{\tilde{z}_x}\right) \), and \( \tilde{k}_y = k \left(1 - \frac{z_s}{\tilde{z}_y}\right) \). \( \Phi \) is the complex Fresnel integral which is given by \( \Phi(\zeta) = \int_0^\zeta e^{i\pi u^2} du \). The multiplicative term \( \Phi \) is expressed as \( \Phi(\mathbf{r}_s, k) = \exp(i k \left[z_s^2 + |\mathbf{r}_s|^2 - k(\bar{x}_s^2/\tilde{k}_x + y_s^2/\tilde{k}_y)/(2z_s)\right]) \).

Fresnel integrals may be evaluated numerically using a rational approximation of the Fresnel integral (Abramowitz 1972) to get Eq. 4.6, the basis for the analytic expressions derived in this chapter.

**B. Analytic expression for passive images**

An array subaperture may be modeled as a single, uniform, continuous, rectangular transducer for simplicity. Such a transducer will produce a voltage proportional to the acoustic pressure it senses, based on the principle of acoustic reciprocity (Pierce 1989). As explained above, the brightness value for a passive image point \((Y, Z)\) is defined as the total beam-formed energy from a group of acoustic sources sensed by a subaperture which is focused at that point. The coordinate \(Y\) is defined along the array direction or azimuth and the coordinate \(Z\) is defined along the range direction. Image \((I)\) can be expressed as

\[
I(Y, Z) = \sum_{\forall \omega} |S(\omega, Y, Z)|^2,
\]

where \(\omega\) is the radial frequency of a single radiating frequency component. For stably cavitating bubbles, these frequencies correspond to the subharmonics and ultraharmonics of the sonication frequency. Emissions produced by inertial cavitation are modeled to have broadband frequencies.

To obtain the point-spread function for a passive cavitation image, an expression for the received signal \(S(\omega, Y, Z)\) due to a single source at \((x_s, y_s, z_s)\) is obtained by idealizing the linear array to have small pitch, no edge limits, and continuous receive focusing, so that an N-element subaperture can be represented by a single rectangular transducer of length.
The received signal \( S \) may be expressed as

\[
S(\omega, Y, Z) = \frac{-A_0 i\omega \rho \mathcal{Q}(\omega) \Phi(r_s, k)}{4\sqrt{k_x k_y}} \left( \mathbf{F} \left[ \frac{k x s + k z a}{\sqrt{\pi k x z_s}} \right] - \mathbf{F} \left[ \frac{k x s - k z a}{\sqrt{\pi k x z_s}} \right] \right) \times \left( \mathbf{F} \left[ \frac{k y s - Y + k y b N}{\sqrt{\pi k y z_s}} \right] - \mathbf{F} \left[ \frac{k y s - Y - k y b N}{\sqrt{\pi k y z_s}} \right] \right),
\]

(4.8)

where \( \tilde{k}_y = k \left( 1 - \frac{z_s}{Z} \right) \) and \( \Phi \) is as defined for Eq. 4.6.

C. Passive images by time-delay focusing

In conventional ultrasound arrays, subapertures are focused using time-delay receive beamforming. To derive an expression for a passive cavitation image formed by such beamforming, signals received by individual array elements [Eq. (4.6)] are appropriately delayed and then summed. To focus a subaperture with \( N \) elements on its axis at depth \( Z \), the time delay applied to the \( n \)th element is given by

\[
\tau_n = -Z - \sqrt{(y_n - Y)^2 + Z^2} \frac{c}{c}.
\]

(4.9)

The beamformed emission signal, corresponding to an image brightness value, is then expressed as

\[
I(\omega, Y, Z) = \left| \sum_{\forall\omega} \left( \sum_{\forall n} e^{i\omega \tau_n} S_n(\omega) \right)^2 \right|.
\]

(4.10)

III. Simulations

Expressions derived above were used to simulate passive cavitation images using Matlab 7.1 (Mathworks Inc., Natick, MA). Simulations were performed with the imaging array/system (L7 imaging array and Iris 2 imaging system, Ardent Sound, Mesa, AZ) specifications utilized during experiments reported in the next chapter. This was a 192-element, 7.5 MHz center frequency linear array, with \( 0.195 \times 7.0 \text{ mm}^2 \) element dimensions and \( 0.22 \text{ mm} \) element pitch. The imaging array had a constant focal depth of 25 mm in the elevation direction.
Beamforming configurations with maximum subapertures of 64 elements and 16 distinct focal positions were allowed by the Iris 2 system. Images with a total depth of 101 mm are presented in this section.

A. Simulated passive images of a point source

Images of point sources emitting acoustic signals at frequencies between 5.2–9.36 MHz (in steps of 520 kHz) are simulated. Passive images are simulated for two models by

- idealizing the array subapertures as continuous single-element, focused, rectangular transducers.
- synthetically focusing the received signals for individual array elements by time-delay beamforming methods.

These simulations were designed to evaluate passive cavitation imaging performance in detecting acoustic emissions with energy content at multiple frequencies. The choice of frequency range is also consistent with the experiments described in the next chapter. For the simulated images presented here, single point sources were positioned on the array axis at 20, 55, and 90 mm depths.

Fig. 4.3 has simulated passive cavitation images generated by using 64-element subapertures (14.08 mm). Images in the top row were created using continuous receive focusing, idealized subapertures, without subaperture truncation at the array edges. Eq. (4.6) was numerically evaluated to simulate these images. Images in the bottom row of Fig. 4.3 were created using time delay beamforming, consistent with the specifications of the L7 linear array and Iris 2 imaging system. The subaperture widths were varied between 8–64 elements (1.76–14.08 mm) and 16 distinct focal depths were used. Each focal zone spanned 6.2 mm in the range direction. Subapertures were truncated at the array edges for these simulations. For example, the 32nd A-line on the image was generated by beamforming received signals
from elements 1–64, but the 4th A-line used signals only from elements 1–8.

As shown in Fig. 4.3, the brightness pattern on the passive cavitation image of a point source narrows close to the source location and broadens away from it, both distally and proximally. Receive sensitivity of a subaperture quickly reduces, away from the synthetic foci azimuth. However, in the range direction this sensitivity “roll-off” is more gradual (see Fig. 4.1). Hence, proximally or distally focused subapertures show significant sensitivity to emissions radiating from a given source. This results in an extended brightness pattern in a passive cavitation image along the range direction. Subaperture sensitivity has significant impact on image resolution, as elaborated in the Discussion section.

Simulated images in Fig. 4.4 were created by maintaining a constant ($\approx 7.1$) f-number (ratio between receive-focus depth and subaperture width). All other parameters were the same as in Fig. 4.3. Brightness pattern shapes similar to Fig. 4.3 were observed. However in this case, the patterns narrowed at greater depths than the point sources.

B. Simulated passive images of multiple bubbles

In a clinical or experimental scenario, like HIFU ablation, acoustic energy will be scattered by multiple bubbles or bubble clusters (Coussios 2007). Hence, the ability of passive cavitation imaging to resolve acoustic emissions spatially in such situations was analyzed. A simulated image of 5 acoustic sources with emissions between 6.3–6.7 MHz is shown in Fig. 4.5(a). This passive cavitation imaging configuration is consistent with the experiments presented in the next chapter. It was assumed that the 5 sources radiated acoustic energy continuously. The acoustic emission was assumed to be a stationary process, meaning that the temporal average of the acoustic emission energy always remained constant. The 5 point sources were located at positions (azimuth mm, range mm): (-12, 40), (-10, 40), (0, 10), (0, 40), (0, 70). The source closest to the array, at 10 mm on the array axis, can be clearly seen, but it is
Figure 4.3: Computer simulations for passive images created using 64-element (14.08 mm) subapertures are shown here. The top row contains examples of simulations where an “idealized” array approximation is used for each subaperture, with single point sources at depths (a) 20 mm, (b) 55 mm, and (c) 90 mm. Simulated images in the bottom row were created through time-delay focusing at 16 equally spaced depths (6.2 mm) with single point sources located at (d) 20 mm, (e) 55 mm, and (f) 90 mm. All images are plotted with a 40 dB dynamic range.
Figure 4.4: Computer simulations for passive images created using a constant f-number (7.1) subaperture are shown here. Except for the subaperture sizes, images were created using the same simulation methods, focus positions, and source locations as the corresponding panels in Fig. 4.3.
difficult to locate the two other sources deeper on the array axis. The two off-axis sources, at the same depth, were separated in the azimuth by 2 mm and could be clearly resolved. As seen in Fig. 4.1, azimuthal width of a subaperture focus is smaller than the range width, especially at greater depths. This leads to better spatial resolution along azimuth, compared to the range direction.

The ability of passive cavitation imaging to resolve cavitating bubble clusters spatially was investigated. A simulated image was created for a cluster of 25 sources emitting energy between 6.3–6.7 MHz, randomly placed in the imaging plane between −7 mm to −3 mm azimuth and 31–41 mm range [see Fig. 4.5(b)]. This choice of emission frequency and bubble cluster location is consistent with passive cavitation imaging experiments described in the next chapter. The azimuthal position of the bubble cluster could be determined from this image, but identifying the range position was more difficult. To test the imaging performance quantitatively, image brightness was averaged between 31–41 mm depth across the entire image width, and between −7 mm to −3 mm in azimuth across the entire image depth. Distributions of range and azimuthal positions of the individual point sources were obtained in form of histograms. Averaged image brightness levels and histograms were both scaled between 0–1 and compared [see Fig. 4.5(c), (d)]. The azimuthal brightness distribution and the corresponding histogram of all azimuthal positions showed very good agreement. Due to coarse image resolution in the range direction, less agreement was observed between depth-dependent brightness distribution and the corresponding histogram of source depths.

C. Passive imaging of low-frequency emissions

Monitoring of ultrasound ablation is one of the potential applications of passive cavitation imaging. Low-frequency emissions (kHz-level), consistent with boiling and vaporization, were observed during the experiments presented in Chapter 2. Passive images created from such low-frequency emissions may assist in identifying the onset of boiling activity at specific
Figure 4.5: Point sources represented in this figure were assumed to emit acoustic energy between 6.3–6.7 MHz (64-element subapertures). (a) Simulated image of 5 point sources at (azimuth mm, range mm): (-12, 40), (-10, 40), (0, 10), (0, 40), (0, 70). (b) Simulated image of a cluster of 25 point sources placed randomly in the image plane between –7 mm and –3 mm in azimuth, and 31–41 mm in depth. (c) Comparison between depth-integrated simulated image brightness as a function of azimuth, and the azimuthal distribution of point sources. (d) Comparison between azimuth-integrated simulated image brightness as a function of range, and the range distribution of point sources. Passive cavitation images are plotted with a 40 dB dynamic range.
locations in an ablated tissue volume. During the preceding subsections, simulated passive cavitation images are shown for point sources with acoustic emissions at frequencies greater than 5.2 MHz. Fig. 4.6 shows simulated images created from emissions at relatively low frequencies (idealized 64-element subapertures were employed). For these simulations, the point sources were located at 20 mm in the range direction, 0 in the azimuthal direction, and the emission frequency was varied between 10 kHz and 1 MHz. For the 10 kHz source, the spatial resolution was extremely coarse and the image brightness stayed almost constant throughout the image. For the 100 kHz source, the spatial resolution was very poor. However, the image brightness at the array periphery was less than the image brightness closer to azimuth 0, the source location. For point sources emitting acoustic energy at 500 kHz and 1 MHz, the overall spatial resolution improved. However, the resolution was much poorer than the other high frequency simulations shown earlier.

IV. Discussion

Performance of an imaging modality can be judged in terms of its spatial resolution, quantitative accuracy and contrast. The analytic models described above enable this evaluation.

A. Spatial resolution

Receive-foci sizes depend on the beamforming configuration and have an impact on the image resolution. The $-6$-dB beam width of the receiver sensitivity may be used as a measure of spatial resolution. The $-6$-dB width in the azimuthal direction depends on subaperture size, focal depth, and frequency of the imaged acoustic emissions. For simplicity, a subaperture is approximated as an unapodized line aperture and the $-6$-dB beam width is given by

$$W_{-6\text{-dB}} \approx \frac{F_y \lambda}{2Nb},$$

(4.11)

where $F_y$ is the focal depth, $N$ is the number of subaperture elements, $b$ is azimuthal width of one subaperture element, and $\lambda$ is the wavelength of the measured acoustic emissions.
Figure 4.6: Simulated images of a single point source at 20 mm range position and 0 azimuth position radiating acoustic energy at (a) 10 kHz, (b) 100 kHz, (c) 500 kHz, and (d) 1 MHz. All the images were created using idealized 64-element subapertures and are displayed with a 40 dB dynamic range.
(Szabo 2004). As seen from this equation, spatial resolution becomes finer with an increase in the subaperture size. With an increase in focal depth, the spatial resolution degrades. This can be seen in Fig. 4.3, where 64-element subapertures were used. For constant f-number subapertures, azimuthal width of the receive focus is proportional to depth. Hence, azimuthal resolution stays the same even at greater depths, as seen in Fig. 4.4. Also, acoustic emissions at larger frequencies can be imaged with greater spatial sensitivity. As seen in Fig. 4.6, spatial resolution would be substantially coarse for passive images created from low-frequency emissions, similar to those resulting from vaporization and boiling during ultrasound ablation.

B. Magnitude scaling

For the passive images defined here, image brightness for a given point source is dependent on the source position. To estimate this scale factor, the subaperture can be approximated as an unapodized line aperture (Szabo 2004). Hence, the gain can be expressed as

\[ G_f = \frac{2\sqrt{\lambda N b}}{\sqrt{F_y}}. \] (4.12)

Also, the pressure amplitude detected by the ultrasound array element will depend on its distance from the point source, as given by its Green’s function. The sound field due to the point source is comprised of spherical outgoing waves which cause the pressure amplitude to decrease with distance from the point source as \(1/|r_s|\). Combining this with Eq. (4.12), it can be seen that the focal gain decreases with depth as \(Z^{1.5}\) for constant size subapertures and \(Z^{0.5}\) for constant f-number subapertures. In Fig. 4.3 and Fig. 4.4, the overall image brightness reduces with increasing source depth. When passive imaging is implemented on an ultrasound imaging system, this scaling effect may be corrected using the time gain compensation (TGC) feature, available in most conventional ultrasound scanners.
C. Image contrast

The contrast was evaluated for images of single point sources created using time-delay beamforming. The contrast was computed as a ratio between the image brightness at the point source location and mean brightness value for the entire image. Contrast ratio depends on the shape of the sensitivity pattern for a receive subaperture. This shape is governed by the focal depth. Hence, the contrast ratio (in dB) is represented with respect to image depth in Fig. 4.7. For constant width subapertures, the contrast ratio exhibited a steep rise between 0–8 mm depth and then a rapid decline between 8–20 mm. Beyond 20 mm depth, it increased more gradually, had a broad peak between 30–40 mm, and then decreased monotonically with depth. For constant f-number subapertures, the contrast ratio was low at shallow depths, but increased monotonically. This rise was steeper between 0–40 mm, than the rise at greater depths. In the azimuthal direction, the contrast ratio would change only due to truncation effects.

Figure 4.7: Contrast ratio in simulated passive images of single point-sources, plotted as a function of source depth for (a) 64-element subapertures, (b) constant f-number (≈7.1) subapertures.
V. Concluding Remarks

Analytic expressions of passive cavitation images have been derived. Simulated images of multi-frequency point sources (single point sources and clusters) have been presented. These passive images showed better resolution in array azimuth than depth. The resolution degraded with respect to source depth. Constant width subapertures were employed during several experiments involving passive cavitation imaging, as reported in the next two chapters. It may be inferred that, for constant width subapertures, the best imaging performance would occur at depths between 30–50 mm, where both contrast and resolution were relatively high. Also, images of cavitation sources between −12 mm and 12 mm along the array azimuth would be less sensitive to subaperture truncation at the array edges. This agrees with experimental observations made by Farny (2007), where a region close to the center of the imaging plane was determined as optimal for passive imaging. The next chapter presents preliminary experiments dealing with passive cavitation imaging in phosphate-buffered saline solutions and bovine liver tissue, designed to evaluate this imaging modality for application to ultrasound ablation monitoring.
Chapter 5

Passive Cavitation Imaging: Testing and Validation

I. Objective

Passive cavitation imaging and its theoretical basis were described in the previous chapter. In this chapter, experiments conducted to test this imaging technique are presented. These experiments were designed with the following objectives:

- to test passive cavitation imaging performance in identifying the position of localized acoustic emissions.
- to image ultrasound-induced cavitation activity passively in free field and ex vivo tissue.

A potential application for passive cavitation imaging is in the guidance and control of ultrasound ablation. The tissue experiments reported here explore the possibility of directly mapping therapeutic ultrasound beams in situ. During HIFU exposures, pressure values at the focus may induce localized cavitation activity in vivo. Imaging this bubble activity may assist in identifying the focal position.
II. Materials and Methods

During the experiments described here, media sonicated with continuous-wave (CW) ultrasound were passively imaged using a linear ultrasound array. Passive cavitation imaging was performed in free-field and \textit{ex vivo} bovine liver. The overall experimental setup can be seen in Fig. 5.1. Details of experimental system components, experimental configurations, and data processing methods are presented below.

A. Ultrasound imaging system

A 192-element linear array with 7.5-MHz center frequency, array element dimensions $7 \times 0.195$ mm$^2$ (elevation $\times$ azimuth), and pitch 0.22 mm (L7, Ardent Sound, Mesa, AZ) was used to capture passive cavitation images. The imaging array was focused in elevation (shorter array dimension) with an acoustic lens (focal length = 25 mm), making it less sensitive to out-of-plane acoustic emissions. This array was controlled by the Iris 2 imaging system (Ardent Sound, Mesa, AZ) described in Chapter 2 (section II A). The Iris 2 system was user-programmable, and hence it was possible to operate it in a passive receive mode by switching off the transmit cycle (used in conventional B-mode). It was also possible to
program several beamforming configurations, depending on the imaging system specifications. During the experiments presented here, this array was operated under constant width subaperture (64-elements) and constant f-number subaperture (7.1) beamforming configurations. Beamforming configurations employing 16 receive foci (101 mm image depth or range) were used, where every focal zone spanned 6.2 mm in the imaging or range direction. Images were captured at a frame rate of 28 Hz and the beamformed RF lines were digitally recorded using a PC-based A/D card (Compuscope CS14200, Gage Applied, Montreal, Canada) at a sampling frequency of 33.3 MHz (similar to the description in Chapter 2, section II A).

B. Source transducers

Two CW ultrasound sources were used for sonication. Their specifications were:

- C302, 520 kHz, 1” diameter, unfocused (Panametrics, Waltham, MA),
- IX327, 2.2 MHz, 4 x 15 mm², cylindrically focused at a depth of ≈41 mm (UTX, Holmes, NY).

These transducers were powered with a signal generator (33220A, Agilent, Santa Clara, CA) and a power amplifier (3100L, ENI, Bell Electronics, Kent, WA).

C. Transducer calibration

520-kHz and 2.2-MHz transducer calibration was performed using a scanning hydrophone system, similar to the method described by Porter et al. (2006). The hydrophone calibration system used a motorized 3-axis translation assembly (NF90 series, Velmex Inc., Bloomfield, NY) to move needle hydrophones (0.5 mm diameter; SN 1239, Precision Acoustics Ltd., Dorchester, United Kingdom), with spatial steps of 0.02 mm. The hydrophone signals were captured by a digital oscilloscope (Waverunner DSO, LeCroy Corp., Chestnut Ridge, NY) and the data was transferred to a desktop computer. The hydrophone motion and data
acquisition was controlled by subroutines written in LabVIEW (National Instruments Corp., Austin, TX), residing on the same desktop computer. The measurements were conducted in a tank of degassed water, with dissolved oxygen content below 50%.

The general procedure involved an initial coarse alignment of the hydrophone to locate the focus or Rayleigh distance of the sonicating source. Following this, two-dimensional maps of the acoustic pressure field were measured in the axial and transverse planes with finer spatial steps. At each measurement location, the source was operated in CW mode and 6–8 complete cycles of the sonicating signal were recorded on the oscilloscope. Based on this information, peak-positive and peak-negative values of these signals were stored on the desktop computer. These stored voltage values were converted to pressure using the hydrophone sensitivity graphs provided by the manufacturer. Next, the hydrophone was moved to the Rayleigh distance or source focus position. The electrical input to the source was then increased sequentially and the corresponding pressure output was measured.

D. Experiment configurations

Experiments conducted to test passive cavitation imaging were performed in a tank filled with deionized and degassed ($%O_2 < 35$) water, filtered to keep the particle size less than 0.2 $\mu$m. All the components used in the experiment were mounted on a Velmex 3-axis translation slide assembly. The single-element transducers were aligned using a pulse-echo method. They were driven by an ultrasound analyzer (5052UAX50, Panametrics, Waltham, MA) and a steel target ($\approx 2$ mm diameter disc) was aligned at the source focus or Rayleigh distance. The L7 imaging array was aligned such that the steel target was clearly visible on the B-mode image. The array was translated to set the position of this target in the imaging plane. This same array was used for passive cavitation imaging.

Passive cavitation imaging was tested using three different experimental configurations, as elaborated below.
1. Prediction of acoustic source position

The ability of passive cavitation imaging to map a localized acoustic emission source was tested. To achieve this, passive images were created from 520-kHz ultrasound scattered by a 1-mm steel wire. Due to the focusing lens in the elevation direction, this target served as an approximate point-source and the experiments were more convenient to set up than experiments utilizing a single bubble or a hydrophone-based acoustic radiator (Cleveland 2000). The wire target was moved to 21 known positions in the image plane and source harmonics (5.2–9.36 MHz) scattered by the target were passively imaged. This frequency range was based on the L7 imaging array bandwidth. A constant f-number (7.1) beamforming configuration (as explained in Chapter 4, section III A) was employed.

2. Cavitation imaging in PBS

To test passive cavitation imaging in the presence of confirmed bubble activity, phosphate-buffered saline (PBS) solution was exposed to 520-kHz, CW ultrasound between 0–0.15 MPa (peak-negative pressure). This solution was contained in a 30-mm diameter latex condom, placed perpendicular to the image plane. These sonications nucleated cavitation activity inside the condom, in the form of bubble clusters. Acoustic emissions from such clusters were used to create passive cavitation images.

3. Cavitation imaging in \textit{ex vivo} bovine liver

To assess passive cavitation imaging in sonicated soft tissue, \textit{ex vivo} bovine liver was exposed to 2.2-MHz, CW, focused ultrasound. The source focus was aligned at 20 mm range on the central axis (0 azimuth) of the image plane. The sonication amplitude was varied between 0–1.96 MPa peak-to-peak pressure, corresponding to 0–0.58 MPa peak-negative pressure. These pressures were measured in the free field using the scanning hydrophone system mentioned above.
Four samples of fresh bovine liver, less than 12 hours post mortem, were used. The sample size used was $7 \times 3 \times 3$ cm$^3$, and one side with intact liver capsule ($7 \times 3$ cm$^2$) faced the source transducer. During these experiments, the liver was stored in PBS solution at 0 °C to minimize tissue decay and formation of gas bubbles. Sonication duty cycle was 4 s on and 55 s off, with the sequence repeated for 16 increasing acoustic pressure levels. The initial liver temperature varied between 17–21 ºC. No temperature measurements were made during the exposure. The temperature rise for these exposures, estimated through numerical methods, was 2.93 ºC for one duty cycle at the highest sonication amplitude. The Discussion section (IV A) contains some information about the effect of temperature on cavitation activity and calculations for the estimated temperature rise.

4. Control experiments

To confirm that the passive cavitation imaging methods were indeed sensitive to bubble activity, some initial experiments were conducted where passive imaging was accompanied by simultaneous passive cavitation detection (PCD) with a single-element transducer. This was conducted for experiments in free-field and tissue using PCD transducer with specifications:

- 10-MHz, 0.75” diameter, cylindrically-focused, PVDF hydrophone with focal depth 19 mm (Valpey Fischer 46654, Hopkinton, MA),

Signals received by the detector were digitally recorded using a WaveRunner 6050A oscilloscope (LeCroy Corp., Chestnut Ridge, NY).

E. Power spectrum estimation

RF A-lines that made up the passive cavitation images were beamformed using array sub-apertures focused at multiple depths. On such an image, the focus position corresponds to an image point and is at the center of a focal zone. The brightness value of this image point equals the integrated emission energy in its bounding focal zone. The emission energy
in every focal zone was estimated by computing the power spectra from the beamformed RF A-lines. Energy in frequency bands consistent with inertial and stable cavitation was integrated to form separate images for the two regimes.

Power spectra were estimated over a total of 36 image frames, each consisting of 192 RF lines (total image depth 101 mm). Each RF line was beamformed with 16 equally spaced receive foci, centered at 276-point focal zones. These power spectra calculations yielded passive images having $192 \times 16$ points (number of RF lines per frame $\times$ number of focal zones; azimuth $\times$ range). For each focal zone, the sampled acoustic emission segments from 9 consecutive frames were concatenated to form 2484-point signals, allowing power spectrum estimation with high frequency resolution. No temporal windowing function was applied. Power spectra were estimated by averaging the squared magnitude of the discrete Fourier transform for four of these 2484-point signals.

To obtain a single passive cavitation image (created only with subharmonic or broadband frequencies), 36 image frames (unfiltered images created from RF lines) were utilized. The frame rate for this capture was 28 Hz, so that the total data set required to form a single passive cavitation image was acquired in 1.3 s. The acquisition of each RF line is asynchronous, but the assumed stationarity of cavitation emissions allowed these individual lines to be juxtaposed, forming a meaningful passive cavitation image (see Chapter 4, section III B). Stationarity implies that the temporal average of cavitation emission energy radiating from a specific localized volume, which contains a bubble cluster, remains constant over the total data acquisition time. Hence, it is assumed that while the same bubbles do not necessarily cavitate over the entire acquisition time, the average energy of cavitation acoustic emissions remains constant over the entire acquisition time. Examples of confirmed cavitation activity observed during the experiments were consistent with this assumption, as seen below in the Results section.
1. **Spectral analysis of single-element receiver signals**

Power spectra were computed for acoustic emission signals recorded by the 10-MHz detector by the periodogram method described in Chapter 2 (section II E). Signal traces were recorded at a sampling frequency of 50 MHz. A discrete Fourier transform was computed for each emission signal trace, after applying a 2500-point rectangular window. Squared magnitudes of these Fourier transforms were averaged across all the traces.

**III. Results**

Passive cavitation images captured using the three experimental configurations described above are presented in this section.

**A. Prediction of acoustic source position**

Images formed from the ultrasound energy scattered by a steel wire are shown in Fig. 5.2 (constant f-number subaperture). These images were captured with the wire located at depths of 20, 55 and 90 mm and they are consistent with the simulation results shown in the previous chapter. This wire target was moved to 21 known positions in the imaging plane. Passive images were used to predict the target positions. Azimuthal location of the wire was estimated by averaging image grayscale values in depth direction, for all azimuthal points. The position of maximum magnitude for this averaged value was taken as an estimate of the wire’s azimuthal position. The location of maximum grayscale value in the range direction, at the estimated azimuth of the wire, was taken as an estimate of the wire’s range position. The resulting rms errors in predicting the azimuthal and range locations were 0.9 mm and 17.2 mm, respectively. The target depth was consistently overestimated in the passive images. As seen from the rms error values and based on the simulation results from the previous chapter, the azimuthal resolution was found better than the range resolution.

The wire target employed in these experiments emulated a localized acoustic emission
Figure 5.2: (a) Passive images of 520-kHz ultrasound scattered from a 1-mm steel wire located at 20 mm depth, (b) 55 mm and (c) 90 mm. A constant f-number (7.1) subaperture was employed. Energy in the source harmonics (5.2–9.36 MHz) was integrated. Passive cavitation images are plotted with a 40 dB dynamic range.

source. The L7 imaging array was focused in elevation (smaller dimension of the array) with an acoustic lens. Hence, the array was less sensitive to acoustic scattering from portions of the wire outside the imaging plane. The resulting effective source, although localized in space, was a rough approximation of a single point source. This setup more closely mimicked a localized cluster of acoustic sources, similar to a cavitating bubble cloud, likely to be encountered by passive imaging methods during a scenario such as ultrasound ablation.

The finite dimensions (elevation width and radius) of this effective source could explain the overestimation of the wire’s range position. The target acts as a group of sources and leads to a broader energy pattern along the range direction compared to the energy pattern of individual sources. This discrepancy may cause substantial errors when estimating the range location of spatially-distributed acoustic emission sources. Fig. 5.3 illustrates the variation in passive image magnitude for simulated point sources and acoustic scattering from the wire target along the range direction.
Figure 5.3: Image magnitude along the range direction at azimuth 0, plotted with respect to range, for representative simulation (−−) and experiment (——) cases. The depth location of simulated point-sources and wire target (in experiment) were (a) 20 mm, (b) 55 mm, and (c) 90 mm. The simulations were performed using constant f-number (7.1), time-delay beamforming expressions presented in Chapter 4 (section II C).

B. Cavitation imaging in PBS

To image confirmed cavitation activity, bubbles were nucleated in PBS solution using a 520-kHz source. During some initial experiments, acoustic emissions were recorded using a single-element detector (10 MHz) along with passive imaging. Power spectra were computed for emissions detected by the single-element transducer and the linear array. Broadband emissions consistent with inertial cavitation were observed in the data acquired by both methods (Fig. 5.4). The spectra presented here are normalized to noise levels measured when the CW source was not turned on. These experiments served to verify that the imaging array was indeed detecting cavitation activity. It should be noted that the spatial volume interrogated by the PCD was smaller than the region where the L7 array was sensitive.

During these experiments, echogenic bubbles were seen on B-mode images when the sonication amplitude was increased above 0.13 MPa (peak-negative pressure). These bubbles would appear inside the PBS solution initially (away from the container walls). Due to acoustic radiation force, these bubbles would be pushed towards the distal wall of the container, where they would accumulate [see Fig. 5.5(a)], and cavitate for several minutes, as
Figure 5.4: Acoustic emission spectra from PBS solution sonicated with 520-kHz, CW ultrasound at 0.125 MPa (peak-negative pressure). Power spectra measured in dB relative to the measured noise floors were computed from (a) RF data acquired by the L7 array, (b) acoustic emission signals recorded by the single element (10 MHz) detector.

confirmed from B-scan images. The source pressure was increased from 0–0.15 MPa (peak-negative pressure) and a B-scan was captured at each pressure level, followed by a passive image recorded using 64-element subapertures. Following these two steps, a B-scan was captured again. The initial and final B-scans did not show any significant change in the position or size of the bubble cloud. This also validated the assumption of stationary emission energy, which was central to physically relevant passive cavitation imaging (see Chapter 4, section III B).

Power spectra were estimated in the passive image focal zones, as explained above. For a given focal zone, the energy in the 6.43–6.56 MHz band containing the ultraharmonic frequency at 6.5 MHz (12.5 × 520 kHz), was ascertained. The passive cavitation image point centered in this focal zone was then assigned the estimated energy level. This process was performed at every focal zone position to result in a 192 × 16 point passive cavitation image made from energy in the band centered at 6.5 MHz. Similarly, separate images were formed
from broadband emissions within 6.3–6.7 MHz (energy at the ultraharmonic frequency was not included). Representative images can be seen in Fig. 5.5. In 11 trials, when the sonication pressure exceeded 0.125 MPa (peak negative), half-order \( (n f_0 + f_0/2) \) ultraharmonic energy emissions were detected in one case, while one-third \( (n f_0 + f_0/3) \) and two-third order \( (n f_0 + 2f_0/3) \) ultraharmonics were observed in some runs. These could possibly result from stable cavitation activity (Leighton 1994). Broadband emissions, possibly due to inertial cavitation, were recorded in all 11 trials.

A region-of-interest (ROI) was chosen between the 31–41 mm depth and across all azimuths (entire image width), on both the B-mode and broadband-emissions images. The image brightness was integrated in the range direction to estimate the variation with respect to the azimuthal position in the ROI, for both images. B-mode image magnitudes were obtained from pulse-echo RF data. Broadband-emission image magnitudes were obtained from filtered, passive-RF signals. A representative comparison of azimuthal distributions of depth-integrated image magnitudes can be seen in Fig. 5.5(d). A Pearson correlation coefficient was computed for these two distributions for 11 trials. It was found to be statistically significant for all cases and the correlation coefficient value was always greater than 0.85 \((p < 0.01)\). This confirmed the possibility of predicting the azimuthal location of bubble clusters from passive images. Bubble cluster images obtained during these experiments were consistent with computer simulations in the previous chapter. Here, passively acquired RF signals were filtered to include emission energy in bands corresponding to stable and inertial cavitation (ultraharmonic or broadband frequencies) from mechanically active microbubbles. Conversely, harmonic scattering from larger bubbles could also be imaged by appropriately filtering the passively received RF signals. Such images made from source harmonics are presented in the next chapter.
Figure 5.5: Representative passive cavitation images in saline solution due to 520-kHz CW ultrasound 0–0.15 MPa (peak-negative): (a) B-scan showing a cavitating bubble cloud, (b) co-registered passive cavitation image formed from ultraharmonic emissions (6.5 MHz), (c) co-registered passive cavitation image formed from broadband emissions (6.3–6.7 MHz), (d) Comparison between B-scan and passive image brightness levels integrated between 31–41 mm depth, across all azimuths. Passive cavitation images are plotted with a 30 dB dynamic range.
C. Cavitation imaging in *ex vivo* bovine liver

In a set of experiments, fresh bovine liver was exposed to a 2.2 MHz focused source and passive images were captured with the L7 array. Broadband emission energy was detected and spatially resolved using 64-element subapertures [Fig. 5.6(a)]. The broadband frequency range between 8–10 MHz was sufficiently different from the fundamental frequency of the source transducer. The imaging array has a center frequency of 7.5 MHz and is sensitive up to 10 MHz. The selected frequency range yielded an acceptable signal-to-noise ratio and allowed for consistent detection of broadband emissions, possibly related to inertial cavitation. In case of the 2.2-MHz exposures, the fourth harmonic (8.8 MHz) was filtered out by removing acoustic energy in the 8.63–8.93 MHz band. Fig. 5.6(a) clearly indicates the ability of this imaging modality to obtain spatial information about acoustic emissions from the tissue. Broadband emission energy integrated across the entire image increased monotonically with the sonication amplitude [Fig. 5.6(b)]. This increase in the broadband emission energy could be related to inertial cavitation activity. However, broadband emission levels estimated in this manner may also contain contributions from spectral side lobes of harmonic signals nonlinearly scattered from bubbles in the tissue samples.

Broadband emission images were also employed to ascertain the azimuthal position of the source focus. The source focus was aligned at azimuthal position 0 and 20 mm range in the image plane. The location of the maximum brightness value at 20 mm depth for the 2.2-MHz exposures was assigned the value of source focus azimuth. Source focus azimuths (mean ± st. dev.) for the four samples, based on 16 sonication levels per sample, were $-1.02\pm0.5$ mm, $-1.05\pm0.46$ mm, $-3.69\pm0.46$ mm, and $-1.57\pm0.9$ mm. Peak positions for the broadband emissions distributions were consistent with the known source focus position in 3 out of 4 cases. In case of sample number 3, B-mode images showed accumulation of echogenic gas bubbles at several locations away from the source focus. It was observed
that the largest emissions for sample 3 emanated from these bubbles localized outside the sonication focal region, causing the discrepancy in source focus localization from the passive image. This result could be significant for an application such as HIFU ablation monitoring, where tissue coagulation may also happen away from the source focus (examples presented in the next chapter). Range location of the acoustic emissions could not be determined as reliably as their azimuthal position. The mathematical models described in the previous chapter may provide a means to glean range location of acoustic emission sources, when used in conjunction with the acquired passive images. The discussion section contains a brief and qualitative look at this possibility. The distribution of broadband emission energy with respect to the azimuthal position for different sonication pressures used can be seen in Fig. 5.7. Surface plots are shown for all four tissue samples.

For the 2.2-MHz exposures, broadband emission distribution was compared with the source beam shape, as measured in free field by a scanning hydrophone system. Figures 5.6(c) and 5.6(d) show a comparison between relative magnitudes of source pressure and broadband emission energy with respect to azimuth, both measured for the same spatial region at 20 mm range in the image plane. Azimuthal brightness distribution on the broadband emission image is consistent with the measured beam shape. With an increase in sonication amplitude, the brightness pattern on broadband emission images broadens azimuthally. At lower sonication pressures, broadband emissions occur primarily in the main lobe, resulting in a broadband emission pattern narrower than the source beam pattern [Fig. 5.6(c)]. For higher sonication amplitudes, the emission pattern broadens and is closer in width to the source beam pattern [Fig. 5.6(d)].

IV. Discussion

Passive cavitation imaging is examined here with a future goal of application in real-time guidance and monitoring of ultrasound ablation. Hence, the acoustic emissions detected
Figure 5.6: (a) Representative passive cavitation image using broadband emissions (8-10 MHz) from bovine liver sonicated with 2.2 MHz, CW, focused ultrasound at 0.8 MPa peak-to-peak pressure amplitude (0.38 MPa peak negative pressure). (b) Spatially-integrated emission energy as a function of sonication amplitude, plotted as mean ± st. dev. (c) Comparison of emission amplitude at 20 mm depth with measured beam profile at 0.80 MPa (peak to peak) sonication pressure. (d) Comparison of emission amplitude at 20 mm depth with measured beam profile at 1.44 MPa (peak to peak) sonication pressure. Passive cavitation images are plotted with a 40 dB dynamic range.
Figure 5.7: Azimuthal distributions of broadband emission energy at increasing power levels for (a) sample 1, (b) sample 2, (c) sample 3, (d) sample 4.
from sonicated bovine liver samples are discussed.

A. Tissue emissions and the inertial cavitation threshold

Experimental results presented above indicate a monotonic rise in cumulative broadband emissions energy with increasing sonication amplitudes [Fig. 5.6(b)]. Similar trends have been observed in recent experimental studies with sonicated Optison solutions (Hallow 2006; Tu 2006) and ablated tissue in vitro (Mast 2008). A rise in the number of macroscopic bubbles with increasing sonication has been reported in muscle (ter Haar 1981) and gel phantoms (Daniels 1987). For the prolonged CW exposures employed here, preexisting gas and microbubbles in the tissue samples can grow through rectified diffusion (Eller 1965). During rectified diffusion, gas dissolved in the medium diffuses into bubbles and causes them to grow in size. This process has been observed by other researchers in studies dealing with CW ultrasound exposures (Lewin 1981; ter Haar 1981). Cavities that have grown through rectified diffusion may undergo violent inertial collapse when they attain appropriate sizes (Aymé-Bellegarda 1990). The fragments resulting from such a transient event may produce smaller bubble nuclei, “providing cavitation with a self-enhancing mechanism of positive feedback” (Leighton 1994) due to repeated collapse and coalescence of the bubbles (Church 2001; Gaitan 1992).

Cavitation-related broadband emissions occur above threshold pressure amplitude that depends on factors such as viscoelastic properties of the medium, prevalence of preexisting nuclei and dissolved gas content, among others. The inertial cavitation threshold for an optimally sized bubble and single cycle excitation was calculated by Apfel and Holland (1991), based on the formula

$$\frac{P^{1.67}}{f} = \text{constant},$$

(5.1)

where $P$ is the pressure and $f$ is the frequency. Such peak-negative pressure threshold at 2.2 MHz is 0.47 MPa. This threshold is based on single-cycle exposures. For the CW exposures
employed here a lower inertial cavitation threshold is expected. It is also documented that inertial cavitation thresholds could be 3–40 times higher in tissue than in water (Church 2006). However, for the CW exposure conditions employed here, inertial cavitation may occur at lower pressure values due to the presence of preexisting nuclei and their growth through rectified diffusion. Also, the liver samples used in the experiments contained blood and saline solution around the tissue, with several possible cavitation nucleation sites.

It is estimated through simulations that small (< 3 μm) bubbles may grow through rectified diffusion (Datta 2008). Preexisting nuclei under 3 μm size, subjected to multiple cycle exposures with frequencies between 1–3 MHz, may have a pressure threshold close to 0.09 MPa (peak-negative) [Church 1988; Datta 2008]. Hence, bubbles grown by rectified diffusion may either undergo inertial collapse or cause nonlinear scattering of source harmonics. For the 2.2-MHz exposures, a peak-negative pressure of 0.09 MPa was exceeded in the main lobe of the source beam for most exposure conditions. The pressure values achieved in the first side lobe were about 1/7th of the main lobe. It is likely that pressure in the side lobes was close to this threshold value, especially at higher sonication amplitudes such as 1.44 MPa (peak-to-peak). This could lead to broadband emissions in the side lobes at these pressure levels (see Fig. 5.6).

Temperature changes in the tissue may alter the acoustic pressure threshold values for inertial cavitation or rectified diffusion, due to either the dissolved gas coming out of solution or coagulation of liver samples due to hyperthermia. An estimate of the temperature rise was calculated for the 2.2-MHz exposure conditions employed during the tissue experiments (reported above). This was achieved by solving a simplified Pennes bio-heat transfer equation at the location of the 2.2-MHz source focus and by ignoring acoustic nonlinear propagation, thermal diffusion, and perfusion losses (Mast 2005). The approximate Pennes bio-heat transfer equation is then

$$\rho C \frac{\partial T}{\partial t} \approx Q$$  \hspace{1cm} (5.2)
where $T$ is the temperature elevation, $Q$ is the absorbed ultrasound power, $\rho$ (1060 kg/m$^3$) is the tissue density, and $C$ (3600 J/kg/°C) is the tissue-volume specific heat (Mast 2005). Thermal diffusion and perfusion losses are ignored. $Q$ is the temporal average of the absorbed acoustic power over one duty cycle of 4 s ON and 55 s OFF. The absorbed power $Q$ can be written as:

$$Q = \frac{\alpha \langle |p|^2 \rangle}{\rho c},$$

(5.3)

where $c$ (1540 m/s) is the speed of sound in tissue and $\langle |\cdot| \rangle$ denotes temporal averaging (Nyborg 1981). The maximum temperature rise would occur at the HIFU source focus. As thermal diffusion was ignored, the temperature rise at the HIFU focus would provide an upper bound for the temperature increase in the tissue. The maximum nominal source pressure measured during calibration was 1.96 MPa (peak to peak). Ignoring nonlinear effects, the pressure field inside the tissue is given by $p = \frac{1.96}{2\sqrt{2}} e^{-\alpha z}$ MPa. Here $z$ is the source focus depth inside the tissue and $\alpha$ is the attenuation coefficient (14.836 Np/m) at 2.2 MHz (Mast 2005). In the tissue experiments presented here, the depth of focus inside the tissue sample was approximately 15 mm. Based on these values, the focal pressure was $p = 0.55$ MPa. Substituting these values in equation 5.2, a temperature rise of 2.93 °C was calculated at the HIFU focus for one duty cycle at the maximum sonication level. This temperature value may be treated as a “worst case” estimate. The value of temperature increase was 16.24 °C at the end of 16 sonications of 4 s on/55 s off, where the pressure amplitude was sequentially increased between 0–1.96 MPa (peak-to-peak pressure measured in free-field). The actual temperature rise during the experiments would be less than this estimate, given the conductive heat dissipation. With an initial tissue temperature close to 20 °C, it was likely that the temperature elevation caused by the HIFU source would not result in thermal coagulation (Mast 2005). While no coagulation was observed when the tissue samples were sliced after the exposure, the source ultrasound beam could possibly have caused localized temperature elevations in the tissue. These can result in increased nucleation events and
a reduced inertial cavitation threshold (Church 2006). The relation between cavitation in
tissue, the concomitant emissions, and ultrasound pressure needs further elucidation.

B. Ablation monitoring

The strong dependence of bubble activity on temperature and the physical properties of a
medium make passive cavitation imaging a potential tool for ablation monitoring. Spatially
resolved bubble emissions may enable real-time tracking of cavitation-related phenomena like
“tadpole” lesioning during HIFU ablation (Watkin 1996). The following chapter includes
HIFU ablation experiments with passive imaging where position-dependent cavitation was
tested as a marker for tissue coagulation.

Cavitation activity, as well as vaporization due to boiling, may occur during ultrasound
ablation. Passive imaging may be used for ablation monitoring by tracking both these
phenomena. Experimental evidence suggests that low-frequency emissions arise due to tissue
boiling. Resolution in passive images depends on the emission frequency and images from
such kHz-frequency emissions will probably have low resolution (Chapter 4, III C). However,
tissue boiling may be monitored by imaging the source harmonics scattered by the resulting
vapor bubbles.

Based on the consistent agreement between passive images and HIFU beam shapes, as
presented in the Results section, passive imaging technique may potentially be employed to
align therapeutic ultrasound beams. For example, such imaging methods may be used to
verify the position of a HIFU source focus with respect to a tumor site during a clinical
procedure.

C. Improving cavitation imaging performance

Cavitation imaging performance can be improved if the range location of the acoustic emis-
sions can be ascertained. Although range resolution of passive cavitation images is limited,
spatial correlation between acquired passive images and simulated images may be exploited to estimate source range locations more accurately. As an example, a possible metric \( R \) may be based on the Pearson product-moment correlation coefficient (Rodgers 1988):

\[
R(y_s, z_s) = \frac{\sum \sum (I_a(Y, Z) - \bar{I}_a) (I_a(y_s, z_s, Y, Z) - \bar{I}_s)}{\sqrt{\sum \sum (I_a(Y, Z) - \bar{I}_a)^2} \sqrt{\sum \sum (I_a(y_s, z_s, Y, Z) - \bar{I}_s)^2}}
\]  

(5.4)

where \( I_a \) is the acquired image and \( I_s \) is the simulated image of a point source at \((y_s, z_s)\). The value of \((y_s, z_s)\) that maximizes \( R \) can be used as an estimate of the source location. If this function \( R \) is computed for Fig. 5.6(a) and each of the simulated images in Fig. 4.3(d–f), the value of \( R \) comes out to be 0.54 for point-source location \((0, 20)\), 0.33 for point-source location \((0, 55)\) and 0.37 for point-source location \((0, 90)\). This result is consistent with the location of the HIFU focus, which was aligned to position \((0, 20)\) by the pulse-echo method mentioned above. Development of such algorithms is beyond the scope of this dissertation.

While modeling-based approaches may help in improving cavitation imaging performance, modifications to the ultrasound imaging hardware may potentially achieve better results. In the Iris 2 system described above, the beamformed RF A-lines are acquired sequentially. If multiple A-lines were recorded with parallel channels, it would be possible to receive cavitation emissions synchronously. This would enable the use of cross-correlation based methods (Norton 2006) or inverse source reconstruction techniques (Kim 2004). Such parallel receive hardware would also make it possible to image short-lived cavitation events that occur during procedures like lithotripsy. A lithotripter produces a shock wave which leads to a single transient cavitation event. Passive sensing of such an event with multiple receive channels would potentially provide effective range gating.
V. Concluding Remarks

In this chapter, results of passive imaging implemented on a 192-element ultrasound array were presented. Localized acoustic emission from a wire target was successfully mapped along the array azimuth through passive cavitation imaging. Cavitational emissions from sonicated PBS solution were successfully imaged and separate images of stable and inertial cavitation were created. Passive cavitation imaging was tested in bovine liver tissue for therapeutic HIFU beams. The distribution of azimuthal energy in the broadband emission images of \textit{ex vivo} tissue was compared with the beam shape of the ultrasound source. Consistent agreement between the two indicated a strong possibility of mapping therapeutic ultrasound beams \textit{in situ}, though several quantitative questions dealing with the direct relationships between sonication amplitude, tissue temperature and passive image brightness need to be resolved.
Chapter 6

Passive Cavitation Imaging during HIFU Ablation

I. Objective

Spatially sensitive passive cavitation detection using ultrasound imaging arrays has been described in the previous two chapters. In this chapter, *in vitro* study consisting of passive cavitation imaging during high-intensity focused ultrasound (HIFU) ablation is presented.

Acoustic cavitation, both stable and inertial, is believed to impact tissue coagulation during ablation, as detailed in a review by Coussios et al. (2007). When HIFU fields are utilized, pressure at different points in the medium varies substantially. Similarly, large temperature gradients are observed in the ablated medium. Hence, the concomitant bubble activity shows significant spatial variations. Passive cavitation imaging methods, presented earlier, were utilized in this HIFU ablation study to provide location-specific information about bubble emissions. These spatially-sensitive cavitation measurements were compared with tissue coagulation to investigate spatial correspondence between the two quantities. The ability of passive cavitation images in identifying the spatial positions of ablative lesions is quantitatively evaluated here.
II. Materials and Methods

HIFU ablation exposures were conducted for *ex vivo* bovine liver tissue. During this procedure, cavitation activity was simultaneously monitored using an ultrasound imaging array and a single-element passive cavitation detector (PCD). The overall experimental setup can be seen in Fig. 6.1. Detailed description of the ablation exposures, cavitation measurements, and data processing are presented below.

![Figure 6.1: Schematic diagram of HIFU ablation setup (top view)](image)

Throughout this chapter, the spatial positions will be expressed in relation to the imaging array seen in Fig. 6.1. The longer dimension of the imaging array is called the azimuth. The azimuthal position varied between $-21.02$ mm (extreme left of the array) to $21.02$ mm (extreme right of the array). The direction along the central axis of the array is called the range direction, with $0$ mm range corresponding to the array’s active surface.
A. Ablation procedure

10 samples of ex vivo bovine liver were exposed to 1.1-MHz, focused, continuous-wave (CW) ultrasound at a measured acoustic power of 40 W for a 30-s duration. The power measurements were made using a radiation force balance. The HIFU transducer (H-101, Sonic Concepts, Woodenville, WA) was driven with a signal generator (33220A, Agilent, Santa Clara, CA) and a power amplifier (3100L, ENI, Bell Electronics, Kent, WA), with an impedance matching network (S/N-093, Sonic Concepts, Woodenville, WA) in series. The HIFU source had a radius of 32 mm and was spherically focused at 62.64 mm.

The nominal peak amplitude and peak intensity were computed and their values were 5.8 MPa and 1989.4 W/cm$^2$, respectively. These calculations were performed using the acoustic pressure field expressions developed by Hasegawa et al. (1987) for spherically focused concave transducers. Degassed water was used as a lossless and homogeneous medium for these computations. Nonlinear propagation of the ultrasound energy was ignored. The HIFU focus was aligned approximately 15 mm inside the tissue sample (azimuthal position $\approx$ 6 mm). The alignment with respect to the cavitation detectors is described in the next subsection. Ablation exposures were performed in a tank of deionized, degassed water with dissolved oxygen content below 25%. The tissue temperature was measured before conducting an exposure using a 0.4-mm needle thermocouple (Type B, Ella CS, Hradec, Králové, Czech Republic). The exposure times used here were longer than those typically used in HIFU ablation studies. This was done to ensure that the ablative lesions were large enough for consistent detection by slicing the tissue samples (procedure similar to the description in Chapter 2, section II B and also elaborated later in this section). Similar prolonged exposures have been reported by McLaughlan et al. (2006).
B. Cavitation measurements

The L7 imaging array, controlled by the Iris 2 imaging software (Ardent Sound, Mesa, AZ) was described earlier in Chapter 5 (section II A). This array was used to capture tissue sample B-scans before and after an ablation exposure and passive cavitation images during an ablation exposure. The imaging plane was aligned with the HIFU propagation direction. The HIFU focus was positioned in the image plane at 30–32 mm range and 5–6 mm azimuth. The L7 array had a center frequency of 7.5 MHz. The HIFU source frequency of 1.1 MHz was substantially different from the L7 center frequency. This would improve the ability to detect cavitation acoustic emissions with energy content close to 7.5 MHz, in the presence of a strong signal at the fundamental frequency.

Passive cavitation images were captured using methods similar to those used during the tissue experiments presented in the previous chapter (section II D). Imaging settings different from those mentioned in the previous chapter are detailed. During the experiments presented in this chapter, passive cavitation images contained 9 focal zones and a total image depth of $\approx 56$ mm. Uniform time-gain compensation settings (TGC) were applied across the entire image depth. Beamformed RF data was acquired at a sampling rate of 33.3 MHz using the PC-based data acquisition system, presented in Chapters 2 (section II A) and 5 (section II A). During each acquisition cycle, data from 9 consecutive frames was captured (frame rate $= 28$ Hz). The time interval between two acquisition cycles was limited by the speed with which the acquired data could be transferred from the data acquisition card memory to the PC hard drive. This acquisition time between two consecutive cycles was 3 s. A better temporal resolution could have been achieved with faster computer hardware. During each HIFU exposure, 10 such data sets were captured. To obtain the reference noise level, a single data set was captured before starting a HIFU exposure. Each data set was saved as a separate file with a “.mat” extension. As seen in Chapter 4 (section IV A), passive cavitation
images provided mm-level resolution in the azimuthal direction, but poorer spatial sensitivity along the range direction. Hence, data from only zone number 5, corresponding to the range position of the HIFU focus, was analyzed.

In addition to passive cavitation imaging performed by the L7 array, passive cavitation detection was also performed using a single-element PCD, similar to the description in Chapter 2 (section II C). Acoustic emission signals were recorded using a 1-MHz, unfocused, single-element PCD (C302, Panametrics, Waltham, MA), followed by amplification through a low-noise pre-amplifier (SR 560, Stanford Research Systems, Sunnyvale, CA). These measurements were made simultaneously, but asynchronously, with passive cavitation imaging. 1 million-point signal traces, sampled at 10-MHz, were stored using a WaveRunner 6050A oscilloscope (LeCroy, Chestnut Ridge, NY, USA). 120–130 traces were stored during a 30-s exposure. Each trace was stored as a separate binary file. The PCD was sensitive over a broad volume near the HIFU source focus (see Chapter 2 for the receive-sensitivity pattern). A representative B-scan indicating the PCD and HIFU focus locations can be seen in Fig. 6.2.

C. Tissue handling

Fresh *ex vivo* bovine livers were obtained from a slaughterhouse and used within 4 hours *post mortem*. During this time period, they were immersed in a phosphate-buffered saline (PBS) solution and stored in a thermally insulated container at 0 °C. Before an experiment, a fresh piece (6 × 6 × 10 cm³), with intact capsule on one 6 × 10 cm² surface, was cut. This piece was placed in an acrylic box of the same dimensions. This container had vertical windows, sealed with acoustically transparent Tegaderm (3M, St. Paul, MN) films. A small amount of degassed water from the tank (∼30 ml) was added to the sample to remove any conspicuous air-pockets. In studies dealing with *ex vivo* tissue, the samples are often placed in degassed saline solution. Saline degassing was attempted using a vacuum chamber.
Figure 6.2: Representative B-scan of a tissue sample. Direction of the HIFU beam and the position of the HIFU focus (marked by the yellow “x”) can be seen. The single-element PCD can be seen on the B-mode image as an echogenic horizontal line centered on the image axis, distal to the tissue sample.

However, the dissolved oxygen content could not be decreased below 40% even after several hours of degassing. Hence, degassed water (DO$_2$ < 25%) from the tank was used instead. To minimize damage to the tissue cells from being in a hypotonic solution, it was ensured that the tissue samples stayed in contact with this water for no more than three to four minutes.

The tissue sample was positioned using B-scan images such that the tissue surface with an intact liver capsule was aligned with azimuth 21.02 mm (right edge of the B-scan image in Fig. 6.2). Following an exposure, the ablated tissue samples were frozen in acrylic boxes of the same dimensions (with no windows), to maintain their shapes. The frozen tissue samples were then carefully sliced parallel to the image plane (HIFU propagation direction), yielding
Figure 6.3: Representative scans of ablative lesions in (a) post-focal and focal zones (called “Focal”), (b) focal and prefocal zones (called “Tadpole”), and (c) prefocal zone (called “Prefocal”). Coagulated tissue is discolored as compared to the nominally untreated tissue. The HIFU beam radiated from the right, relative to the tissue scans. The 3-dB beam width of the HIFU source (focal zone) is represented by bold vertical lines.

6 × 6 cm² sections of 1.2–1.5 mm thickness. This thickness allowed consistent, damage-free handling of the tissue sections. These sections were digitally photographed on a conventional flat-bed scanner (CanonScan 8800F, Canon, Lake Success, NY) at a spatial resolution of 1500 dpi (dots per inch). Tissue coagulation was identified through gross tissue discoloration, as described in Chapter 2 (section II B). Typically, the ablative lesion volume spanned 4–6 slices. The slice best corresponding to the image plane was chosen by comparing B-mode images and tissue scans for identifiable structures, like blood vessels. If a clear match was not found, the slice closest to the ablative lesion center was chosen. Ablation area was computed for the chosen slice through manual segmentation of discolored tissue regions. The process employed was similar to the description given by Mast et al. (2008a). Examples of ablative lesion shapes can be seen in Fig. 6.3.

D. Power spectrum analysis

Power spectra were estimated for datasets corresponding to focal zone 5 (192 lines × 276 samples; azimuth × range), which encompassed the HIFU focus. Nine image frames were
collected during a single acquisition cycle. At each azimuth, data points from individual frames were scaled using a Hann window. These windowed datasets were concatenated to form 2484-point signals. These time-domain signals were zero-padded to yield 3333-point power spectra with a frequency step of 10 kHz. Azimuthal distributions of acoustic emission energy were obtained for the following frequency bands:

- fundamental (1.1 MHz)
- harmonics due to nonlinear scattering (6.6, 7.7 and 8.8 MHz)
- ultraharmonics consistent with stable cavitation (6.05, 7.15 MHz)
- broadband noise-floor increases consistent with inertial cavitation (6.6–8.8 MHz)

To compute the broadband noise floor levels, 55-point (0.55 MHz width) sliding windows were moved along a spectrum between 6.6–8.8 MHz. The minimum energy value in the frequency bins contained within a window was assigned to the frequency component corresponding to the window center. The energy distribution obtained from this sliding window operation was integrated over all frequency bins between 6.6–8.8 MHz to provide an estimate of the measured broadband noise level.

An entire data set (10 acquisition cycles) collected during a 30-s exposure yielded azimuthal energy distributions with a spatial resolution of 0.22 mm (array pitch) and a temporal resolution of 3 s (acquisition cycle time period). Power spectra were also computed for the acoustic emission signals recorded by the 1-MHz PCD. The PCD measurements were not synchronized with the passive cavitation image acquisition. Hence, only the traces recorded concurrently with the passive cavitation images were utilized. These concurrent traces were identified by comparing the time stamps of PCD files with the RF data files.
E. Cross correlation analysis

One of the objectives of this study was to predict the positions of HIFU-induced lesions based on the spatial location of cavitation activity. Time-averaged values were computed for azimuthal distributions of the acoustic emission energy in the frequency ranges mentioned above. During the experiments, a sudden transient increase in the overall passive image brightness was observed immediately when the HIFU source was turned on. This could be related to the destruction of some preexisting bubbles. Short 4-s exposures were employed during some initial experiments. No coagulation was observed in those tissue samples. Hence, it was assumed that no significant tissue coagulation happened within the first three seconds and the corresponding RF data was not utilized. Due to the triggering limitations of the Iris 2 system, data acquisition did not always start at RF-line number 1 (azimuth = −21.02 mm). To identify the position of A-line number 1, consecutive A-lines were cross-correlated and the correlation coefficient was plotted as a function of the line position. A sharp decrease in correlation coefficient was observed at the location corresponding to A-line number 1. In most cases, this position could also be estimated by visual inspection. It would correspond to a sharp discontinuity or a relatively dark vertical zone (2–3 elements wide) spanning the entire passive cavitation image depth.

As mentioned above, tissue scans were manually segmented to identify the tissue lesion area and shape. On a segmented tissue scan, the numbers of pixels corresponding to a lesion were summed for all spatial locations coinciding with the L7 array azimuths. These summed values were multiplied by the image resolution to yield an azimuthal distribution of the lesion area. The centroid of this area distribution was taken as the azimuthal position of the lesion. Centroid ($G$) positions were computed using the relation

$$G = \frac{\sum_{i} A_i Y_i}{\sum_{i} A_i},$$

(6.1)

where $A_i$ was the lesion area at azimuth $Y_i$. Acoustic emission signals from zone number
5 on the passive cavitation images (range position of the HIFU focus) were analyzed to identify the energy content at the fundamental, ultraharmonic, harmonic and broadband frequencies. This analysis yielded the acoustic emission energy in these frequency ranges for all 192 array-element azimuthal locations. During each exposure, such distributions were computed for 10 time instances (acquisition time points). Centroid positions were calculated for the time-averaged azimuthal distributions of acoustic energy using Eq. 6.1. This centroid yielded an estimate of the azimuthal position where the time-averaged acoustic energy was concentrated.

The B-scan image of the tissue sample stored before starting an exposure was subtracted from the B-scan stored at the end of the exposure. These images were screen captures of the B-scan images generated by the Iris program. The resulting B-scan subtraction image represented a change in tissue echogenicity during the ablation (Fig. 6.4). Azimuthal variation of this quantity was obtained by averaging the subtraction images between range positions 24.8–43.4 mm (comprising the HIFU focal spot). This was called subtraction image intensity and centroid positions were calculated for the same.

Correspondence between the centroids of ablative lesions, acoustic emission energy and subtraction image intensity distributions were quantified through a cross correlation analysis. A statistically significant correlation coefficient would imply that spatial information about cavitation activity could be used to determine the position of an ablative lesion.

Similarly, centroid locations were also computed for the spatio-temporal variations in azimuthal distribution of the acoustic emission energy. This centroid provided a space-time coordinate representing the spatio-temporal variations in the acoustic emissions measured during an ablation exposure. Second central moments were also computed about the centroid location for space-time variations in the emission signals. This metric was used to quantify the spatio-temporal “spread” of the emission signals. The second central moment \( M \) was
defined as

\[ M = \sqrt{\frac{\sum_{i} A_i (Y_i - G)^2}{\sum_{i} A_i}}, \]

(6.2)

where \( Y_i \) may either be the space or time coordinate (all other notation is the same as Eq. 6.1). These single-point representations of the spatio-temporal variations in the acoustic emission activity were also compared with the positions and shapes of the lesions.

**F. Receiver operating characteristic (ROC) curve analysis**

Time-averaged values for acoustic emission energy provided a metric for the overall cavitation activity during an exposure. If a threshold value for such time-averaged quantities can distinguish between ablated and untreated tissue at all spatial locations, it would be very useful in ablation monitoring. For a given azimuthal distribution, time-averaged acoustic emission signals were calculated for 192 azimuthal points. The lesion-area distribution was interpolated to precisely correspond to these positions (azimuthal locations of the L7 array elements). Data from all the 10 experiments was used to compute such a threshold level. Hence, there were 1920 lesion-area data points and 1920 points for acoustic emissions in a given frequency range.

The ability of developing such a binary classifier, based on the time-averaged azimuthal distributions of acoustic emissions, was tested using receiver operating characteristic (ROC) curves. In order to generate an ROC curve, the discrimination threshold was varied between the lowest and the highest values of the time-averaged emissions. The fraction of true positives (true positive rate) was plotted against the fraction of true negatives (true negative rate) at several threshold values. If the area (AUROC) under the corresponding ROC curve was 0.5, the emission signals would have done no better as classifiers than chance. For an ideal binary classifier, the AUROC value is equal to 1 (Hanley 1982).

Statistical significance of an ROC curve may be determined by calculating the \( p \)-value associated with the null hypothesis, \( H_0: \text{AUROC} = 0.5 \). A \( z \)-statistic, based on the normal
Figure 6.4: Representative example of (a) B-scan before an exposure, (b) B-scan following an exposure, (c) subtraction image, and (d) azimuthal distribution of subtraction image intensity averaged between ranges 24.8–43.4 mm.
distribution, is calculated as
\[ z = \frac{\text{AUROC} - 0.5}{\text{SE}}, \]  
where the standard error (SE) is given by
\[ \text{SE} = \sqrt{\frac{0.25 + (N_p + N_f - 2)0.083}{N_pN_f}}. \]

In the above equation, \( N_p \) is the number of positive outcomes (points where the tissue sample was ablated) and \( N_f \) is the number of negative outcomes (points where the tissue sample was untreated). The \( p \)-value for a two-tailed normal distribution is calculated based on this \( z \)-statistic (Hanley 1982).

### III. Results

Observations made during the experiments described above are presented in this section. Ablative lesioning performance, spatio-temporal variations in the acoustic emission energy, and spatial correspondence of acoustic emissions with tissue coagulation are presented here.

#### A. Ablative lesions

During HIFU exposures, tissue coagulation typically occurs near the source focus to create cigar-shaped, symmetrical lesions. During prolonged exposures, coagulation may be accompanied by boiling and vapor formation. This may lead to irregular-shaped lesions which grow towards the source transducer. Such lesions have larger coagulated volumes, proximal to the source focus and are sometimes called “tadpole” lesions (Watkin 1996). In recent studies, similar lesioning has been observed during HIFU ablation of tissue phantoms (Khokhlova 2006; Farny 2009). Here, lesions were classified based on their shapes into four categories namely,

- **Focal**: small lesions formed in the focal (axial 3-dB width of the HIFU source) zone (5 cases). In some cases, these lesions also extended into the post-focal zone.
• Tadpole: large lesions formed in the focal and prefocal zones, similar to the tadpole lesions reported in literature (2 cases).

• Prefocal: large lesions occurring only in the prefocal zone (2 cases).

• Superficial: small lesion contained in the prefocal zone very close to the tissue surface, with an approximate lesion depth of 3 mm below the tissue surface (1 case).

The Superficial lesion was completely contained in the prefocal zone, but it was not classified under the category Prefocal. The area of this lesion was less than 15 mm$^2$, while the Prefocal lesions had areas exceeding 65 mm$^2$. Excessive cavitation activity at the tissue surface may have resulted in the Superficial lesion.

Examples of the first three lesion types can be seen in Fig. 6.3. The lesion areas obtained in the 10 experiments reported here showed significant variations (Fig. 6.5). Prefocal and Tadpole lesions had larger volumes than Focal lesions.

Cavitation, vaporous gas activity, and preexisting bubbles could have contributed to the irregular lesion shapes observed. The acoustic power and the HIFU transducer focal gain in pressure amplitude ($\approx 39$) were relatively high, which would result in a pressure amplitude of approximately 2.6 MPa (nominal value) \textit{in situ}. The relatively low frequency and long exposure duration would make ultrasound-induced cavitation activity very likely. Structure of the tissue samples, particularly the presence of blood vessels, also influenced the lesion shapes.

B. Acoustic emission spectra

Acoustic emission spectra were computed for the passive cavitation image RF-lines and single-element PCD data. Power spectra, from both the RF and PCD data, had energy content at subharmonic or ultraharmonic frequencies, consistent with stable cavitation, and also showed an increase in the broadband noise levels, consistent with inertial cavitation.
Figure 6.5: Areas of coagulated tissue in the image plane, classified into Focal (black o), Tadpole (green ∆), Prefocal (blue ×), and Superficial (red *).

Figure 6.6 shows power spectra from acquisition cycles at 6 s (black) and 15 s (red) during the experiment that yielded the Prefocal lesion shown in Fig. 6.3(c). Both spectra presented here were normalized to the reference levels (0 dB) obtained before the HIFU beam was turned on. Energy content at the fundamental and its higher harmonics can be seen on both spectra. These higher harmonics could have resulted from medium nonlinearity or nonlinear scattering from bubbles. However, the spectrum in black also contains energy at ultraharmonic frequencies, consistent with stable cavitation. Broadband noise levels, indicative of inertial cavitation, are shown in blue (at 6 s) and green (at 15 s). The noise levels were computed using the procedure described in the Materials and Methods section (II B).
C. Time history of acoustic emissions

Figure 6.7 shows representative grayscale plots for spatio-temporal variations of acoustic emission energy in the frequency ranges corresponding to the scattered fundamental (1.1 MHz), harmonics (6.6, 7.7 and 8.8 MHz), ultraharmonics (6.05 and 7.15 MHz) and broadband noise (6.6–8.8 MHz). Time-dependent acoustic emissions shown in Fig. 6.7 were recorded for the three cases shown in Fig. 6.3.

The space-time centroid locations were computed for acoustic emission time histories for all experiments. These centroids were used as quantitative measures of spatio-temporal variations in acoustic emissions. Figs. 6.8 and 6.9 show the positions of these centroids. The second central moments indicating the spread of acoustic emissions in space and time have been overlaid on the respective figures. Experiments which resulted in Focal lesions
Figure 6.7: Representative spatio-temporal variations in the acoustic emission energy at the fundamental (1.1 MHz), harmonics (6.6, 7.7 & 8.8 MHz), ultraharmonics (6.05 & 7.15 MHz) and broadband noise (6.6–8.8 MHz) are plotted from top–bottom in each column for (a) Focal lesion, (b) Tadpole lesion, and (c) Prefocal lesion. The spatio-temporal centroid positions are shown on each panel as magenta color circles.
are represented in black, Tadpole lesions are represented in green, and Prefocal lesions are represented in blue. The experiment resulting in the Superficial lesion is represented in red. The spatial positions are denoted here in terms of the array azimuth (note that azimuth = 21.02 mm, the extreme right of the images shown in this chapter, corresponds to depth = 0 from the tissue surface facing the HIFU transducer). The centroid positions were analyzed for emissions in the selected frequency ranges and the results are summarized below for each emission frequency range.

1. **Broadband emissions**

   The space-time centroids of broadband emissions were centered in the space-time plane. They had large second moments in both space and time. This implies low spatio-temporal variations in the broadband emission signals. This is consistent with the behavior represented in the space-time plots shown in Fig. 6.7 (bottom row). It must be noted that the broadband emission signal levels stayed low (compared to the harmonic and fundamental signal levels) during all the exposures reported here.

2. **Scattered fundamental**

   The space-time centroids for acoustic scattering at the fundamental frequency were between 1–10 mm azimuth. This was consistent with the HIFU focus azimuthal position of 6 mm, encountered during these experiments. The temporal location of the centroids varied between 13–25 s, indicating that the temporal variations in the emissions at the fundamental frequency were relatively small. Overall, the centroids were centered in the space-time plane. The temporal second moments were comparable to those of broadband emission signals. This implies low temporal variation in the scattered fundamental. However, the signal levels stayed high with respect to the reference noise. The spatial second moment was smaller than the corresponding values for broadband emissions. This is consistent with higher scattering of the fundamental close to the HIFU focus position.
3. **Harmonic emissions**

The space-time centroids of harmonic emissions exhibited some clustering, based on the lesion type. Harmonic emission centroids corresponding to Prefocal lesions had space-time positions close to the tissue surface (21.02 mm azimuth), and early in time, accompanied with relatively small temporal second moments. This was consistent with the observation that large acoustic emission signals were seen early during the exposures when Prefocal lesions were formed. Centroids for the experiments resulting in Focal lesions occurred completely in the post-focal zone, but were spread out over the entire time range. The temporal second moments corresponding to these centroids were larger than those calculated for the experiments resulting in Prefocal lesions. The harmonic emission centroids corresponding to Tadpole lesions were located in the focal zone.

The energy in the harmonics may have some contributions from nonlinear scattering of the fundamental by the tissue structure. However, the space-time centroid plots indicate that emissions at the harmonic frequencies did not result only from nonlinear scattering by the tissue sample structure, as their spatio-temporal variation was much different than that of the emission energy at the fundamental frequency. It is likely that the harmonic frequency emissions mainly resulted from nonlinear scattering of the HIFU beam by bubble clusters.

4. **Ultraharmonic emissions**

The space-time centroids of ultraharmonic emissions exhibited clustering trends similar to the space-time centroids of harmonic emissions, especially for experiments resulting in Prefocal lesions. For experiments resulting in Focal lesions, a greater spatial variation of space-time centroids was observed for ultraharmonic emissions than for harmonic emissions.
Figure 6.8: Centroids of spatio-temporal distribution of acoustic energy emissions at (a) fundamental, (b) harmonic, (c) ultraharmonic, and (d) broadband frequency components. The blue ‘×’ represents Prefocal lesions, the green ‘∆’ represents Tadpole lesions, and the black ‘◦’ represents Focal lesions. The Superficial lesion is represented in red ‘*’. The second central moments indicating the spatial spread of the acoustic emission distributions are overlaid on the centroids with the same color scheme.
Figure 6.9: Spatio-temporal centroids similar to Fig 6.8, with the second central moment indicating the temporal spread of the acoustic emission distributions.
D. Measurements with single-element PCD

Some studies have reported an increase in kHz-range emissions during ablation exposures at the onset of boiling (Anand 2004; McLaughlan 2006; Mast 2008). Passive cavitation images could be potentially generated by beamforming such emissions. However, the L7 array used here was not sensitive in that frequency range. Spatial resolution of passive cavitation imaging, implemented in this project, depends on the frequency of acoustic signals which are beamformed. As seen in the simulation studies reported in Chapter 4 (section III C), passive cavitation images formed by kHz-range emissions have very low spatial resolution, making it difficult to investigate spatial correspondence between these emissions and tissue coagulation. Hence, a single-element passive cavitation detector, similar to Chapter 2, was employed in these experiments.

Acoustic emission measurements made by the single-element PCD were analyzed to identify vaporization. Representative PCD measurements made during the lesion formation are presented in Figs. 6.10–6.12. Based on the results presented previously, harmonic emission images show different behavior for different lesion types (as defined here). Hence, the relation between spatio-temporal variations of harmonic emissions and boiling-related low-frequency emissions (10–30 kHz, similar to Chapter 2, section II C) is further explored.

In both exposures that resulted in Tadpole lesions, increased harmonic emissions were observed in the prefocal regions, late during the exposures. This increase in harmonic emissions correlated in time with increased low-frequency signal levels on the PCD (Fig. 6.10). It also correlated in space with increased tissue echogenicity, estimated from the subtraction images. This correspondence may result from nonlinear scattering of ultrasound by large echogenic bubbles formed due to vaporization and boiling.

During the exposures resulting in Focal lesions, the low-frequency emissions stayed relatively low during the later parts of the exposures (representative case shown Fig. 6.11).
No consistent temporal correspondence was observed between low-frequency emissions and harmonic emissions. Focal lesions were found to be smaller in area than Tadpole lesions, consistent with reduced boiling-related low-frequency emissions during the experiments. Spatial correspondence was seen between tissue echogenicity and large harmonic emissions levels. These emissions could have resulted from bubbles not formed due to vaporization and boiling.

In one experiment leading to a Focal lesion (shown in Fig. 6.3[a]), a short-lived increase in low-frequency emission levels was observed early in the experiment. However, the resulting lesion shape did not show any distortion related to boiling and vaporization. It should be noted that the single-element PCD was also sensitive to acoustic emissions originating outside the image plane. This could have resulted in the observed discrepancy. Similarly, any low-frequency ambient noise could have also contributed to this observation.

During Prefocal lesion formation, no significant increase in low-frequency emissions was detected, but a large increase in harmonic emissions was observed, early into the exposures (see Fig. 6.12). These harmonic emissions may not have occurred due to the presence of vapor bubbles created by tissue boiling. They may be related to preexisting bubbles close to the tissue surface.

E. Cross correlation analysis

Centroid locations computed for time-averaged acoustic emissions in the selected frequency bands, B-scan subtraction images, and ablative lesion area in the image plane are shown in Fig. 6.13.

Correlation coefficients between azimuthal centroids of lesion areas and azimuthal centroids of time-averaged emission energy at fundamental, harmonic, ultraharmonic and broadband frequencies, along with the azimuthal centroids of the subtraction image intensity, are shown in Table I. The correlation coefficient values were greater than 0.5 for all quantities, but statistically significant correlation was observed only between the lesion centroids and
Figure 6.10: Representative (a) space-time plot for harmonic emission energy, (b) time history of low-frequency emissions detected by the PCD, and (c) azimuthal distribution of subtraction image brightness for a Tadpole lesion.
Figure 6.11: Representative (a) space-time plot for harmonic emission energy, (b) time history of low-frequency emissions detected by the PCD, and (c) azimuthal distribution of subtraction image brightness for a Focal lesion.
Figure 6.12: Representative (a) space-time plot for harmonic emission energy, (b) time history of low-frequency emissions detected by the PCD, and (c) azimuthal distribution of subtraction image brightness for a Prefocal lesion.
Table I: Correlation coefficients between centroid positions of lesion areas and centroid positions of time-averaged emission energy at fundamental, harmonic, ultraharmonic, broadband frequencies, and subtraction image intensity. Statistically significant coefficients are written in bold.

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<tr>
<td>Corr. Coef.</td>
<td>0.013</td>
<td><strong>0.684</strong></td>
<td>0.58</td>
<td>0.534</td>
<td>0.546</td>
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<tr>
<td>p-value</td>
<td>0.972</td>
<td><strong>0.029</strong></td>
<td>0.078</td>
<td>0.112</td>
<td>0.103</td>
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Table II: RMS errors in prediction of lesion centroids based on acoustic emissions, subtraction image intensity and known azimuthal position of the HIFU focus.

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<tr>
<td>rms error (mm)</td>
<td>6.348</td>
<td>4.495</td>
<td>5.000</td>
<td>5.623</td>
<td>5.477</td>
<td>6.594</td>
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Relationship between these lesion centroids and centroids of the measured quantities was expressed in terms of a simple linear regression. RMS errors in prediction of the lesion-centroid positions, based on this linear fit, are reported in Table II. If no information regarding the emissions was available, the known position (≈15 mm from the tissue surface, ≈6 mm azimuth) of the HIFU focus could have been used to estimate the lesion position. Based on this, the resulting rms error was 6.594 mm. If a prediction was made based on chance (a random position inside the tissue sample), the rms error would be 20.641 mm. As seen in Table II, prediction based on the measured quantities was more accurate.

The Superficial lesion was completely contained in the prefocal region, but its area was much smaller than the other Prefocal lesions. The area was even smaller than the Tadpole.
Table III: Correlation coefficients, similar to Table I, calculated after removing one outlier experiment (Superficial lesion).

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<tr>
<td>p-value</td>
<td>0.200</td>
<td>0.867</td>
<td>0.769</td>
<td>0.728</td>
<td>0.732</td>
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Table IV: RMS errors in prediction of lesion centroids similar to Table II, with the outlier experiment (Superficial lesion) removed.

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<tr>
<td>5.492</td>
<td>2.817</td>
<td>3.537</td>
<td>4.700</td>
<td>4.468</td>
<td>5.689</td>
<td></td>
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and Focal lesions. This lesion was considered as an outlier and the correlation analysis was repeated after removing this outlier point. The updated scatter plots can be seen in Fig. 6.14 and the correlation coefficients can be seen in Table III. With the outlier removed, the correlation coefficients between the area centroids, acoustic emission centroids and B-scan subtraction image centroids are greater than 0.72 and statistically significant. The correlation coefficient between lesion area centroids and the centroids for scattered fundamental was not statistically significant. The coefficient value was highest for lesion area vs. harmonic emissions, with a corresponding statistical power exceeding 85%. The rms error in prediction of the lesion position by linear regression also decreased. It was lowest (2.817 mm) for harmonic emissions (see Table IV).

F. ROC curve analysis

ROC curves were computed to test the performance of passive cavitation imaging and B-scan subtraction image in classifying ablated and untreated tissue regions. The resulting curves are shown in Fig. 6.15 and they provide a means to estimate the threshold value of the measured quantity for which the classification is optimum. The dashed line on each panel represents AUROC = 0.5. The optimum threshold for a given quantity is defined as the level for which the distance between this line and the ROC curve is the largest.
Figure 6.13: Scatter plots of lesion and acoustic emission energy centroids in (a) fundamental, (b) harmonics, (c) ultraharmonics, (d) broadband noise level, and (e) subtraction image intensity. (f) Scatter plots of centroids of acoustic energy in the harmonic frequency range and centroids of subtraction image intensity. Centroids are calculated as azimuthal positions.
Figure 6.14: Scatter plots of lesion and acoustic emission energy centroids similar to Fig. 6.13, with the outlier experiment (Superficial lesion) removed.
All curves were statistically significant with $p$-values calculated as explained in the Materials and Methods section (II F). B-scan subtraction images and acoustic emissions at the fundamental frequency yielded the highest AUROC values followed by harmonic emissions (see Table V). High AUROC in case of the harmonic emissions was consistent with the high correlation coefficients observed during the centroid analysis. The presence of harmonic emissions may be explained by bubbles in the sound field. There would also be an increased scattering of the fundamental frequency from regions where such bubbles were located. This may have resulted in the high AUROC value in case of the fundamental frequency scattering. The ROC analysis identifies a threshold value. The energy in the fundamental exhibited relatively less spatial variation, but the absolute values of the fundamental scattering were higher in regions corresponding to tissue lesioning. The optimum threshold values associated with the fundamental were much higher than those associated with the other measured quantities (see Table V).

Separate ROC analyses were performed for Focal, Tadpole and Prefocal lesion types. The results can be seen in Figs. 6.16–6.18. The AUROC values for harmonic and ultraharmonic emissions are greater in case of Tadpole and Prefocal lesions than Focal lesions. However, a reversed trend can be observed in case of the AUROC values associated with fundamental scattering. These AUROC values were greater for Focal lesions than the Prefocal and Tadpole lesions. This is consistent with the hypothesis that HIFU-induced cavitation may lead to Prefocal and Tadpole lesions, and also contribute to the emissions at harmonic and ultraharmonic frequencies.

IV. Discussion

Evidence in the literature suggests spatial correspondence between inertial cavitation activity and tissue lesioning (Coussios 2007). In the study presented here, better spatial correspondence was observed for tissue coagulation vs. harmonic emissions, and tissue coagulation
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<tr>
<td>Threshold (dB)</td>
<td>41.72</td>
<td>2.99</td>
<td>2.10</td>
<td>3.01</td>
<td>0.04</td>
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<td>p-value</td>
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<td>$&lt; 10^{-36}$</td>
<td>$&lt; 10^{-24}$</td>
<td>0.04</td>
<td>$&lt; 10^{-52}$</td>
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Table V: AUROC, optimum threshold values, and $p-$values for the ROC curves of acoustic emission energy distributions and B-scan subtraction images, acting as classifiers for detecting tissue coagulation.

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<td>Threshold (dB)</td>
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<td>1.17</td>
<td>4.08</td>
<td>0.04</td>
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<td>p-value</td>
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<td>1</td>
<td>0.60</td>
<td>1</td>
<td>$&lt; 10^{-12}$</td>
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Table VI: AUROC, optimum threshold values, and $p-$values, similar to Table V, generated for experiments that resulted in Focal lesions.

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<td>Threshold (dB)</td>
<td>46.2586</td>
<td>2.8103</td>
<td>1.6137</td>
<td>2.0952</td>
<td>0.06</td>
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<td>p-value</td>
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<td>$&lt; 10^{-8}$</td>
<td>0.13</td>
<td>0.54</td>
<td>$&lt; 10^{-14}$</td>
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Table VII: AUROC, optimum threshold values, and $p-$values, similar to Table V, generated for experiments that resulted in Tadpole lesions.

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<tr>
<td>Threshold (dB)</td>
<td>40.6262</td>
<td>5.5991</td>
<td>2.7416</td>
<td>1.5229</td>
<td>0.03</td>
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<td>p-value</td>
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<td>$&lt; 10^{-15}$</td>
<td>$&lt; 10^{-15}$</td>
<td>0.003</td>
<td>$&lt; 10^{-18}$</td>
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Table VIII: AUROC, optimum threshold values, and $p-$values, similar to Table V, generated for experiments that resulted in Prefocal lesions.
Figure 6.15: ROC curves generated to test classification of tissue lesioning from azimuthal distributions of acoustic emission energy in (a) fundamental, (b) harmonics, (c) ultraharmonics, and (d) broadband noise. (e) ROC curve related to average grayscale value of B-scan subtraction images.
Figure 6.16: ROC curves similar to Fig 6.15 generated for the 5 experiments which resulted in Focal lesions.
Figure 6.17: ROC curves similar to Fig 6.15 generated for the 2 experiments which resulted in Tadpole lesions.
Figure 6.18: ROC curves similar to Fig 6.15 generated for the 2 experiments which resulted in Prefocal lesions.
vs. scattered fundamental, than tissue coagulation vs. broadband emissions (related to inertial cavitation). In this section, the observed relationships between harmonic emissions, fundamental scattering, and tissue coagulation are discussed.

A. Harmonic emissions

Harmonic emissions were observed persistently during the HIFU ablation experiments presented here. Local changes in density associated with acoustic pressure cause the sound waves to travel slightly faster at their spatial peaks as compared to the troughs. This distorts the shape of a sound wave leading to the introduction of higher harmonics. This nonlinear behavior of a medium may be quantified by the $B/A$ parameter (Lencioni 2002). The presence of cavitating microbubbles may also increase the medium nonlinearity and cause increased harmonic emissions. These microbubbles may be pre-existing bubbles below the transient cavitation threshold (Neppiras 1980), pre-existing bubbles close to resonance size (Leighton 1994; Chen 2007), or gaseous vapor bubbles created due to boiling in the tissue medium (Watkin 1996).

Harmonic emissions are absorbed more readily by the tissue, leading to a more efficient conversion from acoustic to thermal energy (Coussios 2007). Simulation studies conducted by Curiel et al. (2004) indicated enhanced tissue lesioning close to the locations of microbubbles. Similar enhancement was observed by Fujishiro et al. (1998) in the presence of ultrasound contrast agents. This could explain the high correlation coefficient value between the ablative lesion centroids and the harmonic emission centroids, observed here. Chavrier et al. (2000) demonstrated through simulation studies that ablative lesions migrate towards the HIFU transducer surface with an increase in the density of bubbles. This may also be attributed to boiling and vaporization (Watkin 1996; Khokhlova 2006). This explains the Tadpole lesions observed during this study and the corresponding harmonic emissions.

The Prefocal lesions may have resulted from a high bubble density near the tissue surface
which increased local ultrasound deposition. These bubbles could have also acted as a shield and restricted the lesioning to the prefocal region. The Prefocal lesions were large and had areas comparable to the Tadpole lesions. Signals from the single-element PCD did not show increases in low-frequency content, indicative of boiling, during the experiments which resulted in Prefocal lesions. The increased harmonic emission during Prefocal lesion formation may be related to preexisting bubbles close to the tissue surface. This observation is consistent with the high AUROC value computed for Tadpole and Prefocal lesions with respect to the harmonic emission signals. AUROC values associated with harmonic emissions were highest in the case of Prefocal lesioning.

Experimental (Khokhlova 2006) and numerical (Chavrier 2000) studies indicate that regular, cigar-shaped Focal lesions are formed when the number of microbubbles in the HIFU beam is reduced. For experiments resulting in Focal lesions here, harmonic emission levels were low except for a short-lived spike early in one exposure. Boiling-related low-frequency emissions measured by the PCD also stayed low in most cases. Hence, for experiments resulting in Focal lesions, most harmonic emission signals may have resulted from nonlinear propagation, rather than from microbubbles. At HIFU intensities, the contribution of medium nonlinearity is relatively less important in lesion formation (Watkin 1996). This observation is consistent with the low AUROC values associated with harmonic emissions (mainly nonlinear propagation related) in the case of Focal lesions.

Based on the results here, harmonic emission images may be used in ablation monitoring, particularly in the detection of shallow lesions. When large lesions were created close to the tissue surface (Prefocal), very strong harmonic emission signals were observed close to the tissue surface and very early in the treatment. Such lesions are undesired during most HIFU treatments. Harmonic emission images may be used as a criterion to abort HIFU treatments where these emissions occur at the beginning of an exposure.
B. Scattered fundamental

The centroid positions for the scattered fundamental were between 1–10 mm azimuthal position, consistent with the HIFU focus which was aligned at azimuth position 6 mm. They did not show a statistically significant correlation with the centroids of ablative lesions. However, statistically significant AUROC values were observed for the scattered fundamental. For Focal lesions, the AUROC value was highest for the scattered fundamental. The corresponding values for bubble-related harmonic, ultraharmonic, or broadband emissions were relatively low. This is consistent with the experimental evidence that uniform cigar-shaped (Focal) lesions result when cavitation activity is reduced (Watkin 1996, Khokhlova 2006). Passive images formed from the scattered fundamental may be used to monitor lesioning in the focal region. They may also be used in identifying the position of the HIFU focus. In a clinical scenario, this may be useful in guiding therapeutic ultrasound beams.

C. Imaging harmonic emissions

In the results shown above, harmonic emission images corresponded spatially with HIFU lesions formed in the presence of microbubbles. Harmonic signals have been used in several other studies to form pulse-echo images with improved contrast. In tissue harmonic imaging, an ultrasound transducer is used to initiate a transmit pulse. The nonlinear propagation of this pulse produces a second harmonic of the transmit frequency, which may be 10–20 dB below the fundamental. The second harmonic signal may be isolated through frequency band filtering or pulse inversion methods to form pulse-echo images which are less sensitive to grating lobes, side lobes, and reverberation artifacts (Hedrick 2005). Tissue lesions may be delineated better with such imaging (Lencioni 2002; Hedrick 2005).

Contrast-specific imaging involves the formation of images by harmonics scattered by stabilized microbubbles (ultrasound contrast agents). Similar to tissue harmonic imaging, a transmit pulse is radiated into the medium and images are created from the second harmonic
generated by the bubbles. This technique may be used to visualize microcirculation in perfused organs or HIFU-induced lesions in the liver (Lencioni 2002).

Vibro-acoustography is another method which generates images from vibrations induced in an object using ultrasound energy. During this method, low frequency vibrations of an object are measured using an ultrasound transducer to identify the mechanical properties of the object (Fatemi 1999). In a similar manner, vibrations from microbubbles may also be used to create images. In these methods, ultrasonic beams of two slightly different frequencies are used to produce vibrations in an object due to the acoustic radiation force. Microbubbles exposed to such fields emit acoustic energy at twice the difference frequency. These harmonics allow imaging of microbubbles with higher contrast than conventional B-mode imaging. This method may be used in perfusion imaging with microbubbles or to study the destruction of microbubbles in ablation procedures (Chen 2007).

Silverman et al. (2006) have published a paper about spectral parameter imaging where harmonics of the transmitted beam were used to form images of HIFU induced tissue lesions. Using this technique, they were able to improve the contrast between the treated tumor boundary and the surrounding tissue by 3 dB, compared to conventional ultrasound imaging.

These methods described above are based on pulse-echo imaging, unlike the passive imaging method presented here. With these harmonic imaging methods, it is easier to obtain range location of microbubbles based on the reference transmit pulse. However, these methods may not be effective when the HIFU beam is turned on due to the interference and imaging artifacts it causes. In case of passive cavitation imaging, the HIFU beam scattered by the bubbles is used to create the image and hence, this method is suited for monitoring cavitation activity during HIFU ablation.
V. Concluding Remarks

Here, passive cavitation imaging methods described in Chapters 4 and 5 were implemented during HIFU ablation of bovine liver. Centroid and ROC curve analyses were used to test correspondence between acoustic emission signals and tissue coagulation. Centroid positions of harmonic emissions correlated with the centroid positions of the ablative lesions significantly. Harmonic emissions were also found to occur close to the tissue surface and early in the exposure when Prefocal lesions were created. The scattered fundamental and harmonic emissions were both effective as binary classifiers for distinguishing between coagulated and nominally untreated tissue.
Chapter 7

Summary and Concluding Remarks

During this project, the effectiveness of passive cavitation detection methods in ultrasound ablation monitoring has been explored. Measurements techniques employing single-element transducers were extended to ultrasound imaging arrays. This enabled spatially sensitive detection of bubble activity and resulted in a method to create passive cavitation images. Power spectrum analysis central to the formation of passive images delineating different cavitation regimes, was done by processing the acquired data. It is desired to obtain such cavitation mechanism-specific images in real time. This would require development of accurate and efficient algorithms that work in conjunction with the data acquisition routines used during this project. It is also necessary to optimize data transfer methods and improve the temporal resolution on these passive cavitation images.

The Iris 2 system used during this project allows only sequential acquisition of RF lines. While this may be acceptable in B-mode imaging, during passive cavitation imaging it puts limitations on the source duty cycle length. For meaningful passive cavitation imaging using the setup presented here, a CW ultrasound source is necessary. Hence, it will not be possible to image short-lived cavitation events, for example cavitation caused during shock-wave lithotripsy. A system with parallel receive channels may be used to image transient cavitation images. For such systems, emission signals received by individual array elements can be accessed over multiple channels. This data can be then beamformed using time-exposure
acoustics (Gyöngy 2009) or cross-correlation analysis (Norton 2006). Such multi-channel data acquisition will also allow short duty cycle exposures typically conducted during HIFU treatments. Investigation of these methods was beyond the scope of this project. Passive cavitation images developed here have low resolution in the range direction. The analytic models developed in Chapter 4 could be employed to develop optimization and deconvolution methods that will allow better identification of bubble locations. A simple example based on Pearson correlation coefficients was presented in Chapter 5.

Passive cavitation imaging methods described here may be used to improve the guidance and control of ultrasound ablation. During the experiments presented in Chapter 6, B-mode images were captured only at the beginning and at the end of the exposures. Interleaved passive and B-mode imaging would provide valuable temporal information and assist in better real time monitoring of the treatment. No temperature measurements were made during the HIFU ablation experiments presented in Chapter 6. Correlations between localized temperature measurements and passive cavitation images would help in better understanding ultrasound-tissue interaction during ablation. The information obtained from the passive cavitation images could be used to form control strategies based on predictive models of tissue temperature (Chapter 3), heuristic rule-based models or more rigorous physical models of tissue ablation. The passive cavitation imaging approach developed here may also be extended to other therapeutic ultrasound applications that utilize the mechanical effects of ultrasound to provide treatment.
Bibliography


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