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IDENTIFYING AND MONITORING THE ROLES OF CAVITATION IN HEATING FROM HIGH-INTENSITY FOCUSED ULTRASOUND

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IDENTIFYING AND MONITORING THE ROLES
OF CAVITATION IN HEATING FROM
HIGH-INTENSITY FOCUSED ULTRASOUND

by

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IDENTIFYING AND MONITORING THE ROLES OF CAVITATION IN HEATING FROM HIGH-INTENSITY FOCUSED ULTRASOUND

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ABSTRACT

For high-intensity focused ultrasound (HIFU) to continue to gain acceptance for cancer treatment it is necessary to understand how the applied ultrasound interacts with gas trapped in the tissue. The presence of bubbles in the target location have been thought to be responsible for shielding the incoming pressure and increasing local heat deposition due to the bubble dynamics. We lack adequate tools for monitoring the cavitation process, due to both limited visualization methods and understanding of the underlying physics. The goal of this project was to elucidate the role of inertial cavitation in HIFU exposures in the hope of applying noise diagnostics to monitor cavitation activity and control HIFU-induced cavitation in a beneficial manner.

A number of approaches were taken to understand the relationship between inertial cavitation signals, bubble heating, and bubble shielding in agar-graphite tissue phantoms. Passive cavitation detection (PCD) techniques were employed to detect inertial bubble collapses while the temperature was monitored with an embedded
thermocouple. Results indicate that the broadband noise amplitude is correlated to bubble-enhanced heating. Monitoring inertial cavitation at multiple positions throughout the focal region demonstrated that bubble activity increased prefocally as it diminished near the focus. Lowering the HIFU duty cycle had the effect of maintaining a more or less constant cavitation signal, suggesting the shielding effect diminished when the bubbles had a chance to dissolve during the HIFU off-time. Modeling the effect of increasing the ambient temperature showed that bubbles do not collapse as violently at higher temperatures due to increased vapor pressure inside the bubble. Our conclusion is that inertial cavitation heating is less effective at higher temperatures and bubble shielding is involved in shifting energy deposition at the focus.

The use of a diagnostic ultrasound imaging system as a PCD array was explored. Filtering out the scattered harmonics from the received RF signals resulted in a spatially-resolved inertial cavitation signal, while the amplitude of the harmonics showed a correlation with temperatures approaching the onset of boiling. The result is a new tool for detecting a broader spectrum of bubble activity and thus enhancing HIFU treatment visualization and feedback.
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Chapter 1

INTRODUCTION

1.1 Background

1.1.1 Early Years

Ultrasound has many important commercial applications in the industrial and biomedical markets. Short wavelengths from the high-frequency waves provide fine spatial resolution for pulse-echo imaging, used in non-destructive testing and medical imaging. The mechanical effects of ultrasound are also used in cleaning applications and to generate low-amplitude heating used in physical therapy. One of the earliest investigations of ultrasound was its application at high intensities (Wood 1927), where it was discovered that absorption from ultrasound caused significant heat deposition and disruption in frog tissue. Following discovery of this effect, high-intensity focused ultrasound (HIFU) was investigated as a therapy for killing tumors (Lynn 1942; Lynn 1944). Cancer is a difficult disease to treat and often surgery is the only option. HIFU is an attractive alternative to surgery and other damaging treatments, as it is a non-ionizing and minimally-invasive method for delivering energy to the tumor. However, despite its initial promise as a therapy, the treatment has remained in development and only recently found clinical acceptance.

Much of the early development of HIFU was driven by the desire to thermally treat brain tumors and apply the mechanical effects of ultrasound to the central nervous system to treat Parkinson’s disease. The field was pioneered by Francis Fry (Fry 1950; Fry 1951; Wall 1953; Fry 1954; Fry 1970) but both these applications were faced with
significant challenges. Tumor therapy in the brain was hindered by the need to remove a portion of the skull to allow the sound to propagate to the targeted location. Competing therapies, such as L-dopa, hindered early enthusiasm for HIFU as a therapy for Parkinson’s disease (Haar 2004). Evaluating success rate was difficult since imaging techniques were inadequate. It should be noted that while HIFU has been used for a number of other therapeutic applications (such as lithotripsy, thrombolysis, acoustic hemostasis, tissue erosion), the work presented in this Thesis is focused on the application of HIFU as a thermal therapy for tumor necrosis.

One of the reasons why HIFU has had a long history of development as a treatment is the number of difficult barriers regarding its successful application. HIFU treatment of cancer relies on a thermal effect to necrose and/or mechanical effects (shearing stresses, cavitation) to ablate the targeted tissue region. The approach is based on focusing sound either via a lens, spherically-curved transducer, or phased array, creating significantly higher pressures at the focus than along the intervening path. In the case of thermal therapy, energy is absorbed by the tissue and converted into heat, and energy deposition from the sonication is applied until the target region experiences tissue death. Entire tumors are necrosed by systematically overlapping multiple small lesions created at the HIFU focus, as depicted in Fig 1.1.

Many of the challenges faced by HIFU are related to its non-invasive nature, as both targeting the beam and visualizing the relevant physical effects (heating, ablation, necrosis) in vivo is a difficult task. Tissue heterogeneity, the presence of bones and lung, and other uncontrollable environmental factors such as respiration and cooling from
blood flow make it difficult to know exactly how the sound will propagate and how much actual heating will occur. Indeed, in the case of physiological processes such as cooling through blood flow and perfusion, variability is not just present from patient to patient, but also within a given patient during the course of treatment. The basic concerns are whether the target volume is adequately treated and whether nearby healthy tissue is affected. The latter is a particular concern in the near-field portion of the HIFU beam, where overlapping treatment “shots” can lead to accumulated energy deposition in otherwise healthy tissue (see Fig. 1.1).

Figure 1.1: Cartoon depicting how one goes about treating a clinically relevant volume using a HIFU source. For many HIFU systems, the size and shape of the lesion is on the order of a grain of rice, necessitating a lengthy treatment protocol. Note that the HIFU beam in the near field is not as narrow, and thus tissue between the source and target volume experience multiple overlapping exposures that can result in deleterious heating effects. (Image courtesy of Gail ter Haar, Institute for Cancer Research, Sutton, Surrey, UK.)
Two main driving factors for the increasing success rate for HIFU therapy have been improvements in investigative tools and monitoring techniques. Given that the effect is primarily thermal, it was important that a method be developed through which the temperature as a function of time could be compared between multiple exposures. Thorough testing of cellular survival rates established that many biological systems, both in vitro and in vivo, exhibited an exponential relationship between exposure temperature and time required to reach a desired isoeffect (i.e., 10% cellular survival) (Dewey 1977). The relationship is biphasic, in that there is a clear transition point or ‘break point’ in the biological effect that occurs at a threshold temperature. In human cells this temperature threshold is about 43 °C. To achieve a given isoeffect, the treatment time is cut in half for every degree increase above 43 °C, but to achieve the same effect below 43 °C the treatment time increases by a factor of 3 – 4 for every degree decrease below 43 °C. For example, Dewey et al. (Dewey 1977) found that in Chinese hamster ovary cells, 10% of the cells survived when heated for 7 min at 44.5 °C but it took 41 min to achieve the same effect at 42.5 °C. The break point temperature is thought to be related to thermotolerance effects based on protein breakdown in the tissue, and so the break point temperature can shift depending on the biological system (Sapareto 1984).

By analyzing these results, Sapareto and Dewey (Sapareto 1984) developed a thermal dose model, whereby the “thermal dose” resulting from exposure of a given duration and temperature is expressed in terms of an equivalent time at an arbitrary temperature (43 °C, chosen from the break point temperature). For example, consider an exposure of duration $\Delta t$ at some average temperature $\bar{T}$. The concept of equivalent
thermal dose says that one can duplicate the same level of cell death by exposing the
tissue to a equivalent temperature of, say, 43°C for an equivalent time period of $t_{43}$. The
strength of the concept resides in the fact that the thermal dose is cumulative: the longer
the equivalent time of exposure, the greater the biological effect. Thus, treatment
progress is continuously updated based on the exposure history. The model is described
in Eq. (1.1),

$$t_{43} = \sum_{t=0}^{t_{\text{final}}} R^{43-T} \Delta t$$  \hspace{1cm} (1.1)

where $t_{43}$ is the equivalent time at 43 °C and $\bar{T}$ is the average temperature of actual
exposure over $\Delta t$. $R$ is a compensation factor that accounts for tissue response to
temperature change and is determined by the activation energy $\Delta H$ and the temperature $T$
through the relationship $R = e^{-\Delta H(2T(T+1))}$. There is some variation, but for most tissues
$R = 0.5$ for $T > 43$ °C and $R = 0.25$ for $T < 42$ °C. This model is often used to report
treatment results for studies in biological media.

Perhaps due in part to the results upon which the thermal dose is based, the
heating effect of HIFU was investigated more carefully in the 1970’s than previous
efforts (Kremkau 1979; Corry 1984). Since then, success rates (i.e., total tumor necrosis)
in clinical trials have gradually improved. Corry et al. (Corry 1984) treated 142 patients
suffering from miscellaneous tumor types, all in advanced stages, with 0.5 – 3 MHz
focused ultrasound alone or in combination with either chemotherapy or radiation.
Temperature in the tumor and surrounding tissue was monitored with an array of
thermocouples. Treatment with ultrasound alone resulted in 45% complete or partial
(50% tumor size decrease) response, while ultrasound combined with chemotherapy had negligible success and ultrasound combined with radiation resulted in 66% complete or partial response. Side effects such as skin blisters, edema and moderate pain during the procedure ranged from 27 – 45%. The authors were encouraged by the efficacy of the therapy but stressed that a lack of thermometry feedback was a fundamental problem.

1.1.2 HIFU Visualization and Image Guidance

A number of techniques have been developed to improve visualization and monitoring of the HIFU treatment. Hynnen et al. (Hynnen, Darkazanli et al. 1993) used magnetic resonance (MR) imaging to monitor changes in tissue structure after HIFU treatment of in vivo dog thigh muscle. The group showed it was possible to image the lesion shape, as the water proton relaxation times from which the MR images are constructed depend on the water-macromolecule structure. In addition they found it was possible to sonicate inside the magnet, expediting feedback of damage created by the ultrasound. Water proton resonance frequency measured using MR techniques is also related to temperature change, as demonstrated by Ishihara et al. (Ishihara, Calderon et al. 1995) who used MR data to measure temperature rise from laser energy deposition in tissue. MR thermometry is currently the gold standard for noninvasively measuring temperature rise (Wu 2004; McDannold 2005) and also provides excellent spatial resolution of tissue structure. However, the presence of vapor bubbles produced at high temperatures can introduce artifacts in the image (McDannold 2005). Widespread adoption of MR thermometry is also prevented in part by its cost and lack of portability, as well as compatibility issues regarding the materials employed in the treatment hardware. Finally, as is the case with
many non-invasive modalities, images acquired with MR are affected by target movement due to respiration and patient movement.

Diagnostic ultrasound is also used to visualize HIFU effects. B-mode images from diagnostic ultrasound systems have been known to indicate HIFU-induced changes in tissue since the 1970’s (Fry 1970) and have been widely used to monitor HIFU treatment (ter Haar 1989; Sanghvi, Fry et al. 1996; Wu 2004). The images show an appearance of a bright or echogenic region near the HIFU focus following treatment, and the image intensity of the “bright-up” gradually decreases over time after the HIFU is turned off. The bright region has been attributed to the generation of large vapor bubbles (similar to boiling) created as the tissue heats up, as vapor bubbles will scatter the interrogation pulse from the diagnostic transducer and create a hyperechoic region apparent in the B-mode image. The effect has also been replicated in tissue phantoms, indicating that it is not necessarily a biological effect.

One limitation of the use of diagnostic ultrasound for monitoring HIFU treatment is a lack of temperature information. Sibille et al. (Sibille, Prat et al. 1993) found no correlation between the presence of the bright region and rate of tumor destruction, although many researchers have found the bright region to indicate necrosis. Another drawback to this technique is that it cannot be used during CW sonication. The high intensities employed by the therapeutic ultrasound transducer obscure reflection of the transmit signals from the diagnostic transducer, effectively reducing the sensitivity of the imaging system. This problem has been overcome to some degree recently (Vaezy 2001; Owen, Bailey et al. 2006) by operating the therapeutic transducer in pulse mode and
interleaving synchronized HIFU and imaging pulses so that the imaging transducer operates during the periods when the HIFU signal is off.

Diagnostic ultrasound has shown some indication that temperature changes can be estimated via acoustic scattering. Seip and Ebbini (Seip and Ebbini 1995) used a 1.44-MHz focused ultrasound therapy transducer to generate a low temperature rise (5 – 10 °C) in rubber tissue phantoms, chicken liver and dog thigh. Two diagnostic ultrasound transducers (5 and 3.5 MHz) were driven by a pulser-receiver and the RF signals from the backscattered signal were acquired. At the diagnostic frequencies employed, biological tissue and media can be considered as discrete scatterers, and the spacing in between the scatterers changes as a function of temperature due to thermal expansion in tissue. The power spectrum of the backscattered signal demonstrated that the harmonic frequencies corresponded to the average spacing between scatterers. By monitoring the shift in the harmonic frequencies during heating, the temperature change could be determined, and was found to agree well with the measured temperature change. This technique shows great promise but has not been successfully demonstrated clinically (Bailey 2003).

Miller et al. (Miller, Bamber et al. 2004) take a different approach to ultrasound thermometry, in which they compare subsequent B-Mode ultrasound images and measure the apparent translation of scattered returns from tissue structure. The assumption is, as the tissue heats up, the sound speed increases, and this results in a reduction in the time-of-flight to/from a scattering site. Since the commercial scanner assumes a constant speed of sound, the net effect is an apparent translation of the image feature towards the transducer. By measuring the changes in the position of image features, one can estimate
the change in sound speed and thus the temperature rise. Although the technique shows promise, it has not been extensively tested in vivo. Moreover, the presence of cavitation in the focal region compromises both of the aforementioned acoustic techniques (due to strong scattering), as does any form of target movement.

With the development of MR and diagnostic ultrasound visualization techniques the success rate of HIFU clinical trials has improved. Gianfelice et al. (Gianfelice 2003) used MR-guided HIFU ablation to treat breast carcinoma in a 12-patient study. Two ultrasound ablation systems (Mark 1, Mark 2, Insightec-TxSonics) of varying sophistication (regarding the control of the transducer) were employed. In comparison to the single-element transducer Mark 1 system, the Mark 2 transducer, which employs a phased array, was capable of treating deeper regions. The results showed a strong dependence on the system used for treatment. The Mark 1 system was successful in

Figure 1.2: A photo of the Chongqing Haifu Corp HIFU therapy system. The HIFU transducer projects a beam vertically up through the hole in the table. (Image courtesy of Gail ter Haar, Institute for Cancer Research, Sutton, Surrey, UK.)
targeting 47% of the tumor volume and 43% of the tumor was necrosed. The Mark 2 system had a 96% success rate for targeting the tumor volume and 88% of the tumor was necrosed. 66% of the patients reported moderate pain and 17% suffered second-degree skin burns. Follow-up tests suggested that residual cancer was due to poor targeting. The group reported that the main difficulty in the treatment was patient discomfort caused by the long treatment time, which ranged from 38 – 133 min.

Wu et al. (Wu 2005) conducted a clinical study of HIFU treatment of breast cancer in 22 patients. The treatments used the Chongqing Haifu system shown in Fig. 1.2. This system employs color Doppler ultrasound for guidance during the procedure (Wu 2004). The patients were monitored over a five-year period following treatment. Following this period, 95% of the patients were free of disease and 89% had no recurrence of the cancer. Earlier studies conducted by the group (Wu 2004) indicated that skin burns were encountered following treatments but there was no evidence of skin burn, bleeding or infection in any of the patients from the later study. Changes in the gray-scale B-mode image within the treated lesion were reported for 15 patients and color Doppler ultrasound showed reduced blood flow to the tumor in 19 patients. The group stressed that successful treatment was due in part to follow-up treatment with other modalities such as chemotherapy, radiation and endocrine therapy and that multi-modality approaches for treatment should be pursued.

Improvement in targeting and guidance techniques has clearly helped increase success rates in clinical trials. The trials have demonstrated that treatment feedback still needs to be improved and that treatment times need to be reduced. The time required to
create a single lesion is relatively short (~5 – 10 sec) but treatment times are lengthened by the time required for intervening healthy tissue along the ultrasound path to cool in between individual sonications, a problem that is compounded by the fact that heating clinically relevant lesions involves overlapping beams in the pre-focal region, as was shown in Fig. 1.1. An additional problem is an incomplete understanding of the underlying physics governing the interaction of high-intensity sound and tissue. In particular, the formation and acoustically driven oscillation of bubbles in the sound field, a process referred to as acoustic cavitation, leads to a host of complex mechanical, thermal and even chemical effects during HIFU application. A complete review of cavitation effects in therapeutic ultrasound is beyond the scope of this discussion. We choose to focus on those aspects of cavitation behavior that are thermal in nature. Indeed, it has been widely noted (Lele 1985; Hynynen 1991; ter Haar 1995; Holt 2001) that cavitation is an important factor in heat generation when ultrasound is operated at high intensities. This effect is addressed in the next Section.

1.2 Acoustic Cavitation

1.2.1 Cavitation Taxonomy

When bubbles are driven acoustically, they respond by undergoing primarily volumetric pulsations that are highly nonlinear in nature (Leighton 1994). At low forcing pressures, the response is linear and described by the standard second-order equation for a spring-mass oscillator. Here, the compressibility of the gas is the spring and a shell of surrounding fluid provides mass. Such a bubble will respond preferentially at a well-
defined resonance frequency. To get some idea of the relevant scales, bubbles with radii of order 1 mm bubbles resonate at frequencies of order 3 kHz, and micron bubbles resonate at frequencies of order 3 MHz. It is the latter that are more relevant to HIFU processes, as most HIFU systems operate in the MHz frequency range.

As the forcing pressure is increased, things get interesting. Depending on the bubble equilibrium size (i.e. the size the bubble would have with no sound present), it can undergo repetitive, nonlinear radial pulsations characterized by the presence of a sub-harmonic response as well as harmonic and ultra-harmonic resonances (Neppiras 1968; Eller 1969). This class of behavior is loosely termed stable cavitation, and the dynamics of these bubbles are controlled by the compressibility of the gas.

A third general category of bubble motion occurs when subresonant-size bubbles are driven at high acoustic pressures. Inertial cavitation is distinguished by near-isothermal bubble growth to several times the bubble equilibrium radius, at which point it becomes essentially a vapor cavity and subsequently collapses violently and adiabatically, much like a Rayleigh cavity (Rayleigh 1917; Leighton 1994). The sudden collapse generates theoretical internal temperatures in excess of 5000 K and emits a nonlinear pressure wave. The collapse is dominated by inertia from the inrushing liquid and often results in destruction of the bubble (Yang 2004). For a given equilibrium bubble size and set of acoustical and environmental conditions, there is a well-delineated pressure threshold for the onset of inertial cavitation. Because the collapsing cavity emits a highly nonlinear acoustic emission, the onset of inertial cavitation is often characterized by the sudden appearance of broadband noise emanating from the HIFU focal region.
In order for a bubble to undergo unstable growth, the forcing pressure must be large enough to overcome the retarding effect of surface tension, which can be significant for very small bubbles. The forcing pressure amplitude must exceed the so-called Blake pressure for a given bubble equilibrium size (Blake 1949; Leighton 1994). Blake considered stability conditions for a bubble in static equilibrium exposed to a drop in ambient pressure. In order for a bubble to go “inertial”, the forcing pressure must first exceed the Blake pressure, which scales as the inverse of the bubble equilibrium radius. This effectively establishes a lower bound for bubble sizes that can respond inertially at a given acoustic pressure amplitude.

1.2.2 Cavitation Detection

Several methods exist for the detection of cavitation activity. The method used depends on several factors, such as sensitivity, time response, operational constraints, media type, and the type of cavitation activity expected. In the context of therapeutic ultrasound, two of the more popular approaches involve sound scattering and noise generation: active (Roy, Madanshetty et al. 1990) and passive (Atchley 1988) cavitation detection. Passive and active cavitation detection take advantage of the acoustical characteristics of inertial and stable cavitation and are commonly-used techniques to monitor and classify cavitation activity. Both techniques typically employ a single-element focused transducer to improve spatial resolution, although unfocused transducers have been used for passive cavitation detection (Madanshetty 1991; Zeqiri 2003). Active cavitation detection uses a pulse-echo method to detect the presence of bubbles. A short, low-amplitude burst is transmitted from the transducer and if bubbles are present along the
path the pulse will reflect off the bubbles back to the transducer. The received signal can provide information about the position of the bubbles, based on the time of the reflected signal, and is particularly helpful for monitoring individual cavitation events. Many schemes for active bubble detection have employed imaging arrays as well, such as B-mode ultrasound scanners, as mentioned above. The detection of HIFU “bright-ups” using clinical diagnostic scanners is a form of active cavitation detection.

Passive cavitation detection uses a transducer operated solely in receive mode, where the transducer is referred to as a passive cavitation detector (PCD). By operating in receive mode the PCD has an advantage of constantly monitoring the signals transmitted by and/or reflected off any bubbles present in its path. The tradeoff is that the position of the bubbles cannot be determined since the time origin of the received signal is unknown. The focus is positioned in a region where cavitation is most likely to occur, such as the HIFU focus. PCDs can be designed to be maximally sensitive to different forms of cavitation activity. For example, by tuning the sensor to the sub-harmonic of the HIFU drive, acoustic emissions from stable cavitation are singled out. By tuning the sensor to detect broad band emissions above the HIFU drive frequency, inertial cavitation noise is targeted. It is of practical interest to note that large-amplitude HIFU signals often contain harmonics that generate sound power at large frequencies. This can occur irrespective of the presence of inertial cavitation activity.

Two methods have been employed to separate broadband cavitation signals from the scattered HIFU signal. One method is to digitally sample the waveform from the PCD and post-process, where cavitation emissions are determined by examining the
spectral content of the signal (Rabkin 2005). The problem with this technique is that the signal can only be monitored intermittently due to the time required to acquire the signal. An alternate method of detecting inertial cavitation is to use a transducer with a sufficiently-high center frequency relative to the HIFU frequency and apply a high-pass filter to remove the lower-frequency HIFU energy from the signal (Edson 2001). The result is a signal comprised largely of the broadband noise energy. This method provides constant signal monitoring and can be easily processed in the time domain by determining the root mean squared (RMS) value of the RF signal or by peak-detecting the PCD RF voltage. Both the RMS and peak signals can then be digitized and displayed in real time.

One of the main drawbacks to active and passive cavitation detection is the limited sensing volume resulting from the use of tightly focused transducers. For this reason, these techniques are often restricted to laboratory use. (A notable exception is the use of B-mode ultrasound to detect HIFU bright-ups in the clinic) As mentioned later in this Chapter, cavitation is often noted as playing a central role in shifting the HIFU pressure field, and monitoring such a dynamic environment requires a tool which possesses greater spatial coverage.

1.2.3 Observations of Cavitation

The first in vivo observation of cavitation was made by Lehmann and Herrich in 1953 (Lehman 1953), by observing the presence of hemorrhage produced by a 1 MHz focused source and varying the overpressure. Hemorrhage was observed with 1 atmosphere of overpressure but not when the overpressure was increased to 7 atmospheres; the
difference was attributed to the fact that cavitation is suppressed at the higher ambient pressure.

Watkin et al. (Watkin 1996) measured lesion sizes in ox liver and porcine bladder in vitro at suggested clinical intensities (~1500 W/cm²). The group found that lesions grew back towards the transducer over time, producing a tadpole shape, in contrast to the expected cigar shape predicted from the focal geometry. In addition, employing longer and/or higher intensities did not increase the maximal lesion depth. Their explanation for the distorted shape was that bubbles from cavitation or tissue boiling shielded the incoming ultrasound. Their recommendation that cavitation be avoided in exchange for longer sonication times at lower intensities has been mirrored throughout most of the HIFU community (Fry, Kossoff et al. 1970; Lele 1985; Hynynen 1991; Sibille, Prat et al. 1993).

Bailey et al. (Bailey 2001) investigated the effect of cavitation and boiling on lesion shape by applying an overpressure to suppress cavitation and elevate the boiling temperature in excised beef liver. The study employed two different overpressures and two different HIFU transducers. The first measurement used a 0.7 MPa overpressure, and the acquisition from a diagnostic ultrasound imaging array was interleaved with the output from a 3.5 MHz HIFU transducer to obtain evidence of hyperchogenicity (i.e. bright-ups) during sonication. The group found that large distorted lesions grew back towards the therapy transducer whenever hyperechogenic regions were formed in the B-mode image, yielding the same tadpole shape reported by Watkin et al. The second measurement employed a 1 MHz HIFU transducer and an overpressure of 5.6 MPa but
no B-mode imaging. Using the same intensity of 1750 W/cm² and exposure time of 30 s, a lesion was formed in the expected cigar shape, demonstrating that either cavitation or vapor bubbles created from boiling were responsible for lesion distortion. Khokhlova et al. (Khokhlova, Bailey et al. 2006) applied a similar overpressure technique to study formation of tadpole shape lesions in low-attenuation transparent acrylamide gels containing bovine serum albumin (BSA). BSA provides a visible thermal indicator as the protein denatures and turns white when heated above 65 °C. The group found that lesion distortion developed only when boiling occurred in the gels.

It has been established, however, that cavitation has an effect not just on the ultrasound propagation but also on the local heat generation. Lele (Lele 1985) studied the effects of temperature rise in fresh calf liver using a 2.7 MHz HIFU source operated over a range of different intensities. Temperature and acoustic emissions were both measured during sonication. At low intensities temperature rise was modest and there was no indication of acoustic emission. Stable cavitation was detected at slightly higher intensities via the presence of sub-harmonic emission and, at these intensities, the temperature rise was slightly higher than expected. However, at yet higher intensities, both stable and inertial cavitation were detected and the temperature rose dramatically. Lele theorized that the high heating rates were due to inertial cavitation bubbles.

Hynynen (Hynynen 1991) measured temperature rise and broadband noise during in vivo dog thigh sonication as a function of HIFU frequency (0.246 – 1.68 MHz), and intensity. The intensity threshold for onset of stable cavitation was found to increase with frequency. The cavitation threshold also demonstrated a hysteresis effect depending
on whether the intensity was steadily increased or decreased for multiple exposures at the same position. He found that measured temperature rise had a linear dependence on intensity at lower intensities, as expected, but temperature rise was greatly increased at higher intensities when broadband noise and sub-harmonic emissions were present.

Holt and Roy (Holt 2001) used a 1 MHz HIFU source for 0.5 – 10 sec continuous wave exposures in agar-graphite phantoms at multiple pressures. Temperature was measured with thermocouples embedded at multiple positions adjacent to the HIFU focus. The temperature rise at low pressures corresponded to heating from classical thermoviscous absorption from the 1 MHz ultrasound but above a threshold pressure of approximately 1.5 MPa the temperature rise was significantly higher than that predicted by the classical model, which did not include bubble phenomena. This effect was attributed to cavitation as the onset of the elevated temperature rise was corroborated by needle hydrophone measurements that indicated elevated sub-harmonic and broadband signals near and above the threshold pressure. The authors recognized that cavitation plays a role in lesion distortion but also argued that if controlled properly, the enhanced heating caused by cavitation could provide a benefit to HIFU treatment.

In Holt and Roy (Holt 2001) and ensuing investigations by Hilgenfeldt et al. (Hilgenfeldt 2000), Edson (Edson 2001), and Yang (Yang 2003; Yang 2004), modeling of the bubble dynamics showed that two mechanisms can explain the additional heating: viscous damping from the radial motion of stable cavities, and local absorption of the acoustic emissions from inertial bubble collapses. Both mechanisms produce similar enhanced heating effects, but in different viscosity and equilibrium bubble radius
regimes. In addition, Edson demonstrated that a relatively low number of bubbles (~10 – 35) were capable of producing the enhanced heating measured in the experiments. Edson followed up the results of Holt and Roy by using a nearly identical measurement setup with an addition of a 15 MHz PCD transducer followed by a 2 MHz high pass filter to selectively detect broadband emissions from inertial cavitation. His results clearly showed that the onset of enhanced heating corresponded with the onset of inertial cavitation noise emissions. Edson concluded that based on this coincidence, local absorption of the broadband collapse emissions was most likely the dominant mechanism in bubble-enhanced heating.

Sokka et al. (Sokka 2003) investigated bubble-enhanced heating in in vivo rabbit thigh using two different therapeutic ultrasound arrays operating at 1.1 and 1.7 MHz. Cavitation was monitored with a 0.6 MHz focused array assembled in a ring shape around the therapeutic array and the signal from the ring transducer was sampled every 4 sec at 5 MHz. The spectrum of the signal was analyzed for the presence of stable cavitation via appearance of the sub-harmonic signal and inertial cavitation via appearance of a broadband signal. A MRI system was used to monitor the temperature change every 4 sec and the lesion shape 15-30 min after sonication. Two treatment protocols were used to determine the heating efficacy of cavitation. In the first protocol, the thigh was subjected to a 0.5 sec high-power burst followed by a much lower intensity for 19.5 sec. The second control protocol sonicated the thigh for 20 sec at a constant intensity of the same time-averaged power as the first protocol. In all of the measurements where cavitation was detected the temperature rise was significantly
higher than in the control protocol, where cavitation was not detected in any of the measurements. The elevated temperature rise continued past the initial high-power burst and in some cases the heating was enhanced for the duration of the entire exposure, indicating that cavitation was responsible for the enhanced heating. The group also noticed that lesions that contained cavitation were more rounded than the elongated lesions produced from the control measurements.

Melodelima et al. (Melodelima 2004) used a similar protocol to examine heating from cavitation in ex vivo pig liver. A 5.16 MHz planar therapy transducer was used to generate lesions using a control sonication of 28 W/cm² for 20 sec, and comparing results with a “cavitation generation” sonication at 60 W/cm² for 0.5 sec followed by a sustained lower intensity exposure 14 W/cm² for 20 sec. Temperature was measured at the end of the sonication at four positions along the therapy transducer axis and cavitation was detected by the appearance of hyperechogenic regions (attributed to cavitation bubbles) using a 12 MHz diagnostic imaging array. The group found that lesions created using the control protocol were nearly half the height of the lesions created using the cavitation sonication.

These studies have demonstrated a clear relationship between cavitation and accelerated heating. Such a relationship suggests the intriguing possibility that cavitation can be detected and controlled, in a manner that can improve HIFU treatment. The introduction of cavitation into the HIFU target region will accelerate heating rates, thereby reducing treatment time. The fact that this enhancement is limited to the cavitating region (Holt 2001) will serve to localize lesion formation and reduce pre-focal
heating effects. The presence of bubbles will help to target the lesion via active scattering (i.e. bright-ups in B-mode imaging). Non-invasive noise diagnostics provide a means for monitoring the onset and nature of the bubble activity and thus could be a vehicle for feedback control. Finally, in addition to thermal effects, bubble activity also yields mechanical bioeffects that could also serve to destroy diseased tissue. Phenomena such as acoustic streaming and collapse microjets (Leighton 1994) can disrupt cells and ablate entire regions of tissue. The key, however, is control – and therein lies the problem.

In order to safely utilize acoustic cavitation in, say, tumor therapy, one needs to be able to safely initiate and control the cavitation process. Most tissues have nucleation thresholds that far exceed the inertial cavitation threshold for a pre-existing bubble of 0.1 – 1 µm-radius size. The former is on the order of 5-7 MPa for most non gas-bearing tissues and organs (Hynynen 1991; Rabkin 2005), whereas the latter is of order 1 MPa @ 1 MHz for a so-called optimal bubble size of 0.7 µm (Apfel 1991). Thus, in order to initiate cavitation in tissue, one must employ pressure amplitudes so great that once the bubbles are formed, it is extremely difficult to control them. They form a rapidly growing cavitation cloud that serves to shield the focus and tends to propagate towards the transducer, resulting in deformed lesions. This process continues until the tissue reaches boiling temperatures and large, bulbous vapor cavities form, which serves to further distort the lesion. Sometimes, when the exposure intensities are extremely high say, 6000 W/cm², this process can take place so quickly – order 10’s of milliseconds - that one is hardly aware that cavitation has occurred (Khokhlova, Bailey et al. 2006).
such a case, controlling the cavitation cloud is virtually impossible without pulsed, low-duty cycle HIFU. For CW HIFU, what is required is a means for safely nucleating bubbles prior to HIFU treatment, or otherwise reducing the nucleation threshold of the tissue during treatment. The former approach motivated the “cavitation producing” pulse studies by Sokka (Sokka 2003) and Melodelima (Melodelima 2004). The latter could be achieved by the addition of cavitation nuclei such as ultrasound contrast agents (Miller 1995; Miller 1996; Umemura, Kawabata et al. 2005; McDannold, Vykhodtseva et al. 2006; Yu, Xiong et al. 2006) or even laser activated gold nano-particles (Farny 2005; Roy 2005; Wu 2006).

Once the bubble field is initiated at modest HIFU intensities, that presents the possibility of using active scattering and/or passive noise diagnostics to monitor the bubble field and effect feedback control through adjustment of HIFU drive parameters such as intensity and exposure duration. If operating in pulse mode, one can also vary the pulse duration and duty cycle. To develop such a controller, we require an improved understanding of the nature of bubble-enhanced heating and how it relates to cavitation noise. We also need improved tools for sensing bubble noise in both space and time. Both of these issues will be addressed in the Chapters that follow.

1.3 Thesis Overview

Three major difficulties faced by HIFU as a tumor treatment modality are tumor targeting, treatment feedback, and length of treatment. Improvement in targeting and feedback will likely reduce treatment time since less time will be required to heat up
diseased tissue and allow healthy tissue to cool. It is clear that inertial cavitation plays a contributing role in these problems, as its presence can disrupt treatment but can also potentially expedite it via enhanced heating (thus from here on, unless otherwise indicated, ‘cavitation’ will refer to inertial cavitation). In this work we have sought to further explore the correlation between enhanced heating and detection of cavitation demonstrated by Edson and Yang. If the cavitation signal is to be used to as a feedback indicator for controlling sonication it is important to understand the nature of the signal and how it changes during sonication. Thus inspired, three main questions were addressed in this work:

1.) If inertial cavitation signals detected experimentally are related to a viable heating mechanism, can the measured signals then be used to as an indicator of both the presence and magnitude of accelerated heating within the targeted region?
2.) How is inertial cavitation affected by changing environmental conditions such as local temperature and changing HIFU drive parameters?
3.) Is it possible to improve cavitation noise diagnostics by implementing multiple-sensor PCD configurations?

As suggested above, noise emissions could serve as a noninvasive descriptor of bubble heating and ultimately drive a feedback loop for real-time treatment monitoring and control. From a control standpoint, it is important to understand how and why the cavitation characteristics may change over the course of sonication. Finally, measurement of cavitation via a PCD uses an established and well-characterized technique but is limited by its localized detection volume, as described previously. The third question seeks to address this limitation and extend the utility of the passive noise monitoring technique to a greater range of application.
This Thesis begins with a discussion of the theory and modeling behind absorption from the HIFU field and the bubble dynamics relevant to tissue heating and noise diagnostics; see Chapter 2. A study of the effect of ambient temperature on the bubble dynamics and, in particular, on the bubble heating mechanisms is also presented. The first half of Chapter 3 describes the HIFU drive instrumentation, the characterization of the HIFU source, and the thermocouples, tissue phantoms and PCD systems employed in the experiments. The remainder of the Chapter presents results from four separate experiments designed to addressed the first two questions listed above. To explore the impact of HIFU drive parameters on cavitation noise, the influence of sonication duty cycle on noise emission level was investigated, the cavitation signal was measured as a function of position throughout the prefocal region to evaluate the extent to which pre-focal shielding influenced noise and heating in the focus, and certain subtle details of the pressure-amplitude-dependent bubble dynamics were studied. Finally, the cavitation emission signal was compared to measured bubble-assisted heating rates rise to examine whether the key correlation posed in the first question in fact existed. Chapter 4 addresses the last question. A linear array from a diagnostic ultrasound imaging system was used to passively monitor inertial cavitation noise in both space and time and to \textit{passively} sense the onset of boiling. The result was an enhanced ability to interpret bubble noise as well as a greatly expanded PCD sensing volume. Chapter 5 applies the measurement techniques described in Chapter 4 and knowledge gained from Chapter 3 to measurements in excised beef liver to evaluate how our methods and results translate to a
biological system. In conclusion, a brief summary of results and conclusions from Chapters 2 – 5 are presented in Chapter 6.
Chapter 2

THEORY

Overview

This Chapter will describe the theory which was used in this research. No new theory was developed here; rather this Chapter primarily represents modeling efforts to inform experimental results and to gain intuition from the bubble dynamics. Much of this work is dedicated to understanding the impact of ultrasound and bubble activity on creating heat, and modeling the necessary physics behind the ultrasound and bubble interaction with the medium allows us to isolate these two relationships in a manner that is otherwise difficult to accomplish experimentally. Thus it is important to quantify the energy output of the HIFU source and the heating that results from its interaction with the medium. Ideally we would adopt the same treatment for the bubble heating but there are a number of unknown parameters that make anything but an estimate based on these parameters’ boundary limits impossible; such an approach has been taken before (Edson 2001; Yang 2003) and further refinement in this area is beyond the scope of this work. Instead we are interested in a qualitative assessment of the role of the bubbles, to explore how environmental conditions such as temperature affect bubble dynamics.

The success of the modeling here is based on our confidence in the knowledge of our experimental system, which we have specifically chosen to be as ideal as possible (see Chapter 3); with the exception of a comparison study with in vitro tissue presented in Chapter 5, we work primarily with homogeneous tissue phantoms which have been well-
characterized, giving us assurance that we can apply modeling results to those from the experiments.

2.1 HIFU Pressure

The pressure from the HIFU source was modeled for two reasons: to compensate for the medium properties in order to determine the focal pressure to properly compare exposures, and to determine a time-averaged, spatially-dependent ultrasound power deposition from the HIFU source from which the heating could be calculated. Here we model sound propagation using a similar approach to previous work in this area (Hallaj 1999; Edson 2001; Huang 2002; Yang 2003), in which we employ the Westervelt Eqn. (Westervelt 1963; Hamilton 1998), shown in Eq. (2.1).

\[
\nabla^2 p - \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} + \frac{\delta}{c^2} \frac{\partial^3 p}{\partial t^3} + \frac{\beta}{\rho c^4} \frac{\partial^2 p^2}{\partial t^2} = 0 \tag{2.1}
\]

Here, \( p \) is the acoustic pressure, \( c \) is the sound speed, \( t \) is the time, \( \delta \) is the local acoustic diffusivity, \( \beta \) is the nonlinearity coefficient and \( \rho \) is the density. The acoustic absorption \( \alpha \), is related to the acoustic diffusivity by \( \alpha = \frac{\delta \omega^2}{2c^3} \), where \( \omega \) is the angular frequency.

The Westervelt equation describes wave propagation through a weakly nonlinear thermoviscous fluid and accounts for losses from thermal conduction and viscosity in the third term and nonlinear distortion in the fourth term. The formula approximates the nonlinearity by taking into account the effects that accumulate with distance but not the smaller local effects, which can be neglected for focused sound sources (Hamilton 1998). The material-dependent parameters that are required by the model, such as the
absorption, sound speed, nonlinearity coefficient and density, were determined from an independent characterization of the medium described in Ch. 3. Equation (2.1) requires a numerical solution to determine the pressure field; for this we implemented a finite-difference time-domain (FDTD) solver, which will be described in Section 2.3.

One of the drawbacks to solving Eq. (2.1) in the time domain is an error associated with properly accounting for frequency-dependent absorption. Most tissues correspond to a weak power law with frequency, $\alpha = \alpha_0 f^y$, where $\alpha_0$ is the attenuation coefficient, $f$ is the frequency and the power law coefficient, $y$, is typically ~1.1 in most tissues. However, the model instead assumes a classical thermoviscous medium in which $y = 2$. The problem lies in the fact that the model is solved in the time domain, so the frequency is assumed to be monochromatic. By using a measured attenuation at 1.1 MHz we can be confident that the pressure solved for in the model is correct for sufficiently-low pressures, but the attenuation will be misrepresented at higher pressures, where nonlinear effects will become more important.

### 2.2 Temperature

In this work we investigate how HIFU deposits energy in a small region for the purpose of generating localized heating. Thus it is important that we understand the process behind which ultrasound is converted to heat. A number of models exist to describe the energy balance from which the temperature in the ultrasound pressure field can be determined. Here we will refer the reader to reviews by Edson (Edson 2001) and Yang (Yang 2003), where early models of varying complexity by Fry and Fry (Fry 1954) and
Parker (Parker 1983; Parker 1985) are described. Briefly, Fry and Fry placed a thermocouple junction in a sound field with the intent of determining acoustic absorption coefficients from the absolute intensity. The absorption was determined by comparing short-term temperature rise with a linear rate of heating model. Short heating exposures were used to exploit the relatively long thermal diffusion timescale so that conduction could be neglected. In a 1-D and a later 2-D formulation, Parker improved on the Fry’s methods with a different approach to compare experimental exposures with an energy balance to determine absorption, using a Gaussian approximation for the ultrasound beam pattern. The contribution here was to provide an analytical solution to account for radial and axial conduction of the heat.

Parker’s model, however, is limited by the assumption of a Gaussian shape for the temperature distribution and the inability to account for complex material and source geometries, particularly when strongly-focused sources are employed. Instead we chose to model the temperature with the Pennes bioheat transfer equation (Pennes 1948). The Pennes model provides more flexibility since it does not assume a Gaussian temperature distribution. Also, additional heat sources and sinks such as metabolic heat generation and blood perfusion can be included, and the material geometry can be more accurately modeled. The Pennes model is essentially a 3-D thermal diffusion equation with source and sink terms added:

$$\rho_i C_i \frac{\partial T}{\partial t} - K \nabla^2 T = -W_i C_s (T - T_a) + q_m. \quad (2.2)$$

The left hand side of Eq. (2.2) is the standard thermal diffusion equation, in which the rate of heating is proportional to the spatial gradients of the temperature field. Here, $\rho_i$,
$C_t$ and $K_t$ are the density, heat capacity, and thermal conductivity of the medium, respectively. An important heat loss effect in tissue, perfusive blood cooling, is represented by the first term on the right hand side of Eq. (2.2), where $W_b$ is the blood perfusion coefficient of the tissue (to account for micro-vascularity) and $C_b$ and $T_a$ are the heat capacity and ambient temperature in the blood, respectively. Living organisms also generate heat via metabolic processes, and the resulting heating is represented by the source term on the right hand side of Eq. (2.2). The metabolic heat generation is given by the quantity $q_m$, expressed as a power density. Note that we have not yet incorporated source terms due to ultrasound absorption into the thermal model.

A strength of the Pennes model is its adoption by a diverse community (Wissler 1998), allowing for direct comparison of model results. In particular, the Pennes model has been widely used in the HIFU community (ter Haar 2004). A numerical method, described in Section 2.3, was employed to solve for the temperature. Solving the model numerically makes the model more accurate and flexible in its ability to account for focused sound beams and the geometry of the experimental setup when compared to the Fry and Parker models. The drawback is that it is more computationally intensive and takes a longer amount of time.

As indicated previously, we chose to work with non-perfused tissue phantoms and excised tissues rather than living biological tissue. Our heat source derives from the thermoviscous absorption of HIFU energy directly along with sound energy converted to heat by inertial cavitation effects and viscous damping from the bubble oscillation. It is important to recognize that living biological systems are far more complex, and other
heat sources (such as metabolic processes) and sinks (such as perfusion (Huang 2002)) can have a large impact on the energy balance and must be accounted for. However, this same complexity can lead to uncertainty that can compromise the unambiguous interpretation of experimental results – thus our desire to work in more or less idealized tissue-mimicking phantoms. In our system we need not consider perfusion or metabolic effects, but we do need to incorporate an additional source term that accounts for the thermal power density from the aforementioned acoustic effects, resulting in:

\[ \rho C_t \frac{\partial T}{\partial t} = K_t \nabla^2 T + q_a \]  
(2.3)

Here we broadly describe our heat generation as coming solely from acoustic processes, whereas in actuality there are three separate mechanisms for acoustic heat generation in our HIFU experiments. The first is heating from absorption of the HIFU pressure field due to thermal conductivity and viscous dissipation. The process of thermoviscous absorption in Newtonian media is well understood and described in Section 10.2 in Pierce (Pierce 1989). We will refer to \( q_a \) as the primary field absorption. The HIFU pressure field was determined from Eq. (2.1), from which we may compute the spatially-dependent deposited power density, \( q_{HIFU} \), using the following expression for the acoustic power dissipated per unit volume in a thermoviscous fluid (Pierce 1989),

\[ q_{HIFU} \approx \frac{2\alpha}{\rho c \omega^2} \left( \frac{\partial p}{\partial t} \right)^2. \]  
(2.4)

Again, \( \alpha \) is the absorption, \( \rho \) is the density, \( \omega \) is the driving frequency and \( p \) is the acoustic pressure. For the purposes of determining the temperature rise from the primary
field absorption, \( q_{HIFU} \) represents the acoustic heat generation term in Eq. (2.3), and thus the heat transfer equation appears as

\[
\rho_i C_v \frac{dT}{dt} = K_i \nabla^2 T + \frac{2\alpha}{\rho c \omega^2} \left( \frac{\partial p}{\partial t} \right)^2,
\]

where the pressure is obtained from the solution of Eq. (2.1).

The second and third acoustic heat generation mechanisms come from viscous damping at the bubble wall and absorption of the pressure wave emitted from inertial cavity collapses. Thermal damping of pulsating bubbles can play a role as well but not at the high frequencies (order 1 MHz) and small bubble sizes (order 1 \( \mu \)m) under consideration (Devin 1959). These effects will be described in more detail in Section 2.4.4.

2.3 The Method of Solution

The pressure and temperature models were solved using a FDTD method. A FDTD approach allows a differential equation to be solved using discrete time steps over a discrete spatial grid, resulting in a spatial distribution of the solution over time. This method provides flexibility in regards to the grid space geometry (i.e., sound source and target geometry) and material properties, with the drawback that it is computationally-intensive. All FDTD simulations performed for this work were executed on the Boston University Supercomputing network using a Fortran v.90 compiler. The FDTD codes employed here were adapted from Hallaj (Hallaj 1999) and Edson (Edson 2001).
**Solution Space**

Since FDTD modeling is solved through discrete temporal and spatial increments it is important to consider the impact of the grid space resolution that is chosen in the solution to ensure stability. FDTD modeling has its roots in electromagnetic applications, where the solution space is generally on the order of a few wavelengths. For acoustic modeling it is necessary to choose 10 – 12 grid steps per wavelength, and since we are primarily interested in resolving the effects of a 1 MHz HIFU wave we have chosen 100 µm for the grid step. The time step, which is dependent on the sound speed and spatial grid step, was chosen to be 10 ns. To conserve grid size the models were solved using an axi-symmetric approximation, by taking advantage of the spherical source geometry and the homogeneity of the cylindrical phantom, and in this manner the grid consisted of half of the physical space. Figure 2.1 shows a graphical layout of the geometry employed.

![Figure 2.1: The grid geometry for the FDTD pressure and temperature solutions. The curve represents the front face of the HIFU transducer, the shaded region represents the phantom and the rest of the region represents water. The pressure solution utilizes the entire grid, whereas the temperature solution uses only the dashed region that surrounds the phantom.](image149x153to498x352)
for the pressure and temperature solutions; the curve depicts the front face of the transducer (which is centered at (0, 0) and has a hole in the middle), the shaded region depicts the phantom and the rest of the grid represents water. Thus a cylindrical coordinate system was chosen and the models were solved as a function of axial and radial position, where the source axis was the edge of the grid (radial distance = 0). The pressure grid size was 5 x 10 cm. All of the experiments conducted employed a constant source pressure amplitude, so in our ultimate goal of determining the temperature we only need the steady-state solution for the pressure field. Thus the pressure code was solved for the time necessary for 100 cycles to propagate throughout the grid, at which point the pressure was deemed to be in steady state.

The temperature code was solved over the duration that the phantom was heated in the experiment (~5 sec) plus three seconds to monitor cooling. However, the temporal resolution was not required to be as high due to the much slower temperature diffusion timescale, so to reduce computation time we chose 1 ms for the time step employed in the temperature codes, with the same 100 µm spatial grid resolution. As indicated by the shaded box that represents the phantom in Fig. 2.1, the temperature code was solved over a smaller grid than the pressure code since we are interested only in the temperature change inside the phantom; relative to the pressure grid, the temperature grid typically extended from 3 – 9 cm in the axial direction and 0 – 1.5 cm in the radial direction, resulting in a 1.5 x 6 cm grid and fewer points to compute.
2.3.1 Discretized Equations

Pressure

When expressed in cylindrical coordinates the Westervelt equation is

\[
\frac{\partial^2 p}{\partial r^2} + \frac{1}{r} \frac{\partial p}{\partial r} + \frac{\partial^2 p}{\partial z^2} + \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} + \frac{2\alpha}{\rho c^2} \frac{\partial^3 p}{\partial t^2} + \frac{\beta}{\rho c^4} \frac{\partial^5 p^2}{\partial t^2} = 0, \tag{2.6}
\]

where \(r\) and \(z\) are the radial and axial coordinates, respectively. Equation (2.6) is solved by calculating pressure over discrete spatial and temporal steps, where the mapping from location \((i, j)\) at time \(n\) to the next corresponding point is related by

\[
z_i = z_0 + (i - 1)\delta_z, \tag{2.7}
\]

\[
r_i = r_0 + (j - 1)\delta_r, \tag{2.8}
\]

\[
t_n = t_0 + (n - 1)\delta_t. \tag{2.9}
\]

Here, \(\delta_z\), \(\delta_r\) and \(\delta_t\) are the axial and radial spatial and temporal grid steps, respectively.

The terms in Eq. (2.6) are solved to second order accuracy (Hallaj 1999) by employing the relations

\[
\frac{\partial p}{\partial r} = \frac{1}{2\delta_r} (p_{i,j+1}^n - p_{i,j-1}^n), \tag{2.10}
\]

\[
\frac{\partial^2 p}{\partial r^2} = \frac{1}{\delta_r^2} (p_{i,j+1}^n - 2p_{i,j}^n + p_{i,j-1}^n), \tag{2.11}
\]

\[
\frac{\partial^2 p}{\partial z^2} = \frac{1}{\delta_z^2} (p_{i+1,j}^n - 2p_{i,j}^n + p_{i-1,j}^n), \tag{2.12}
\]

\[
\frac{\partial p}{\partial t} = \frac{1}{2\delta_t} (3p_{i,j}^{n-1} - 4p_{i,j}^{n-2} + p_{i,j}^{n-3}), \tag{2.13}
\]

\[
\frac{\partial^2 p}{\partial t^2} = \frac{1}{\delta_t^2} (2p_{i,j}^n - 5p_{i,j}^{n-1} + 4p_{i,j}^{n-2} - p_{i,j}^{n-3}). \tag{2.14}
\]
\[
\frac{\partial^3 p}{\partial t^3} = \frac{1}{3\delta_i^3} \left( 6p_{i,j}^n - 23p_{i,j}^{n-1} + 34p_{i,j}^{n-2} - 24p_{i,j}^{n-3} - 8p_{i,j}^{n-4} - p_{i,j}^{n-5} \right).
\] (2.15)

Hallaj notes that there are two formulations for the second time derivative. The time derivative can either be solved in the same ‘centered’ manner as the spatial derivatives in Eqs. (2.10-12), where the ‘forward’ step is necessary for the solution, or it can be solved in the ‘right-sided’ formulation as shown (and implemented) in Eq. (2.14). The ‘right-sided’ formulation was chosen in order to conform to causality. The power density \(q_{\text{HIFU}}\) was calculated as the average power density over the last ten cycles using Eq. (2.4).

**Temperature**

The Pennes heat transfer equation expressed in cylindrical coordinates is

\[
\frac{\partial^2 T}{\partial r^2} + \frac{1}{r} \frac{\partial T}{\partial r} + \frac{\partial^2 T}{\partial z^2} - \frac{D_i C_i}{k_i} \frac{\partial T}{\partial t} + q_{\text{HIFU}}(r, z) = 0.
\] (2.16)

where \(q_{\text{HIFU}}(r, z)\) was determined from the output of the pressure code. The partial differential terms are solved in the same manner as Eqs. (2.10-13), with the exception that temperature is now the independent variable.

**Initial and Boundary Conditions**

For each new source pressure amplitude and phantom geometry employed, the initial conditions for the entire grid were set to zero for the acoustic pressure and to 22 °C (average water temperature in our measurement tank) for the temperature. With the exception of the transducer axis (corresponding to the 0 cm radial position in Fig. 2.1) the acoustic pressure at the grid boundary positions was determined using an ‘absorbing boundary condition’ (ABC), for the purpose of minimizing reflections due to a false boundary \(i.e.,\) the grid boundaries were not representative of the experimental boundary.
conditions, due to computational constraints). By employing an ABC the energy that is incident at the boundary is effectively absorbed, rather than reflected in a manner that would be incongruent with our experimental arrangement. Here we have employed the Mur ABC (Mur 1981):

\[
\frac{\partial p}{\partial r} - \frac{1}{c} \frac{\partial p}{\partial t} = 0; \quad \text{(2.17)}
\]

\[
\frac{\partial p}{\partial z} - \frac{1}{c} \frac{\partial p}{\partial t} = 0; \quad \text{(2.18)}
\]

\[
\frac{\partial p}{\partial r} = 0, \text{ at } r = 0. \quad \text{(2.19)}
\]

In addition to the ABCs it was necessary to specify the pressure at the source, from which the wave was launched. This was done by simply setting the pressure at the transducer face to the specified source pressure; the process for determining this source pressure will be described in the next section. With the exception of the transducer axis \((r = 0)\), the temperature at the boundaries was set to the water temperature.

*Source Pressure Calibration*

To ensure that the simulation results are relevant and comparable to the experimental results it was important that the pressure ‘output’ from the simulation source matched that of the actual HIFU source. As mentioned above, pressure is determined by specifying the pressure at the boundary of the source and letting the wave propagate from the source boundary throughout the field. In actuality the HIFU transducer is excited by a voltage which is converted to a pressure by the transducer, but we are unable to measure this source boundary pressure directly. However, for the range of pressures
considered in this study, the input voltage to the source has a linear relationship with the focal pressure, both of which are easily measured. In addition, the source pressure is linearly proportional to the focal pressure (for linear sound fields), so by measuring the input voltage and focal pressure in water we can determine the necessary source pressure in the code to match the measured focal pressure and in this manner can determine a ‘calibration’ for the input voltage relationship to the source pressure.

This calibration was performed by measuring the input voltage from the matching network to the HIFU transducer using a high-impedance attenuating voltage probe and measuring the focal pressure in water with a calibrated fiber optic probe hydrophone, as described in Section 3.1. Following the method used by Edson (Edson 2001), the excitation and pressures correspond to

\[ P_f^{pk-} = k_1 V_{input}^{pk-} \]  \hspace{1cm} (2.20)

\[ P_s^{pk-} = k_2 P_s^{pk-} \]  \hspace{1cm} (2.21)

allowing the input voltage \( V_{input}^{pk-} \) and source pressure \( P_s^{pk-} \) to be related by

\[ P_s^{pk-} = \frac{k_1}{k_2} V_{input}^{pk-} \]  \hspace{1cm} (2.22)

\( P_f^{pk-} \) is the focal pressure and \( k_1 \) and \( k_2 \) represent the proportionality constants. The calibration resulted in \( k_1 = 0.0979 \text{ MPa/V}, k_2 = 43.05 \), resulting in \( P_s^{pk-} = 0.00227 V_{input}^{pk-} \).

### 2.4 Bubble Dynamics

The main phenomena that we are interested in examining is the impact that bubbles have on the acoustic pressure and heat deposition in a medium exposed to HIFU. As
mentioned in Chapter 1, the presence of bubbles is thought to have a negative impact due to scattering and shielding effects but have a positive effect by acting as local heat sources. All of these effects are due to the complex manner in which the bubbles oscillate relative to the sound field and surrounding material. Bubbles are filled with a combination of gas and vapor, thereby creating a large acoustic impedance mismatch when surrounded by tissue. This impedance mismatch, despite the relatively small size scale, results in a reflection at the bubble wall boundary. The situation is complicated further by the generally-spherical bubble geometry, so the reflection now becomes a scattering problem off a sphere. Another major complicating aspect is the inherent compressibility of the bubble, which responds like a spring-mass oscillator when subjected to a fluctuating pressure. Here the gas provides the spring and the mass derives from the surrounding medium. For low amplitude forcing, the response is linear and described by the standard equation for a damped 2nd-order system. At large forcing amplitudes the radial response is highly nonlinear and results in a host of physical, thermal, and even chemical effects. Acoustically-driven bubble phenomena are generally referred to as acoustic cavitation. For a complete review of acoustic cavitation and related effects, the reader is directed to the excellent review by Leighton (Leighton 1994).

The study of bubble dynamics has resulted in an evolving suite of models with increasing levels of complexity customized for a number of different applications. Here we are interested in describing the nonlinear motion of a single air bubble in a Newtonian viscous fluid under conditions of high-frequency, high-amplitude driving pressures and no streaming effects (i.e., no fluid flow). The absence of fluid flow around the bubble is
justified by the fact that our experiments are carried out in non-perfused gels. While we model the bubble dynamics as an air bubble in a water medium, we recognize that our phantoms are not fluids; modeling the nonlinear radial response of cavitation bubble in a non-Newtonian medium is well beyond the scope of this work (see Allen and Roy (Allen 2000) for a detailed treatment of the problem).

In this work we are also cognizant of effects such as rectified diffusion and bubble wall instability but do not take these into account in the modeling at this time. For a full treatment of these effects, including the impact that boiling bubbles have on sound propagation, see Yang (Yang 2003) and Wu (Wu 2006). Our goal lies in assessing how the evolving cavitation field impacts the changing temperature field, how one can employ noise diagnostics to assess thermally-relevant bubble behavior, how one might achieve sustained bubble-enhanced heating through modification of the sound field, and how the ambient temperature of the medium affects the radial dynamics of the bubble, the nature of bubble heating and our ability to monitor cavitation activity through noise diagnostics and acoustic scattering.

To investigate the bubble dynamics we used the Keller-Miksis model (Keller 1980). In order to understand the Keller-Miksis model we must consider its root, the Rayleigh-Plesset equation.

2.4.1 Rayleigh-Plesset (‘RPNNP’) Model

The Rayleigh-Plesset model as it is known today is a result of collective theoretical work by Rayleigh (Rayleigh 1917), Plesset (Plesset 1949), Noltingk and Neppiras (Noltingk 1950; Neppiras 1951), and Poritsky (Poritsky 1952), giving the final result the alternate
title of the RPNNP model. This model builds upon the original early work by Lord Rayleigh, who pioneered investigation of bubble motion by considering the collapse of an empty cavity in water. Rayleigh’s model provided the very basic framework for describing the motion since it assumes a constant external pressure, an absence of gas or vapor inside the bubble, that the bubble remains spherical during the collapse and that the water is incompressible. Surface tension and viscosity effects were neglected, as was the history of the cavity before the collapse. By considering the kinetic energy in the liquid during the collapse, Rayleigh described the motion using the following force balance equation:

\[ \frac{3}{2} \ddot{R}^2 + R \dddot{R} = p_0 \rho, \]  

(2.23)

where \( R, \dot{R}, \ddot{R} \) are the cavity radius, velocity and acceleration, respectively, \( p_0 \) is the external pressure and \( \rho \) is the surrounding liquid density.

Rayleigh’s model was used as a basis for describing the motion of a vapor-filled bubble for most of the early 20th century. The more complete version commonly used today is derived by considering the kinetic energy in the work done by the liquid pressure, \( p_l \), and the ambient pressure, \( p_a \), resulting in

\[ \frac{3}{2} \ddot{R}^2 + R \dddot{R} = \frac{p_l - p_a}{\rho}. \]  

(2.24)

The liquid pressure is determined by first considering a bubble in equilibrium, where the gas pressure in the bubble, \( p_{g,eq} \), is

\[ p_{g,eq} = p_0 + \frac{2\sigma}{R_0} - p_v. \]  

(2.25)
Here, $p_0$ is hydrostatic pressure, $\sigma$ is surface tension, $R_0$ is equilibrium radius and $p_v$ is vapor pressure. The surface tension acts in opposition to the internal bubble pressure and helps preserve the curvature of the bubble wall. When the external pressure changes from $p_0$ to $p_L$, the pressure in the liquid, the radius changes from $R_0$ to $R$. Assuming the gas corresponds to a polytropic law, the change in gas pressure inside the bubble is

$$p_g = p_{g,eq} \left( \frac{R_0}{R} \right)^{3\eta}$$

(2.26)

where $\eta$ is the polytropic exponent. Here $\eta$ can take on values between 1 for isothermal behavior and the ratio of specific heats, $\gamma = C_P/C_V$, for adiabatic behavior. The liquid pressure just outside the bubble wall is then

$$p_L = \left( p_0 + \frac{2\sigma}{R_0} - p_v \right) \left( \frac{R_0}{R} \right)^{3\eta} + p_v - \frac{2\sigma}{R}.$$  

(2.27)

Plugging the liquid pressure into Eq. (2.24) and substituting $p_\infty$ for the hydrostatic and applied time-harmonic pressure $P(t)$,

$$\frac{3}{2} \ddot{R}^2 + R\dddot{R} = \frac{1}{\rho} \left\{ \left( p_0 + \frac{2\sigma}{R_0} - p_v \right) \left( \frac{R_0}{R} \right)^{3\eta} + p_v - \frac{2\sigma}{R} - p_0 - P(t) \right\}. $$

(2.28)

Viscous effects were first included by Poritsky (Poritsky 1952) (these effects are explained in greater detail in Section 2.4.4), giving the final expression for the RPNPP equation:

$$\frac{3}{2} \ddot{R}^2 + R\dddot{R} = \frac{1}{\rho} \left\{ \left( p_0 + \frac{2\sigma}{R_0} - p_v \right) \left( \frac{R_0}{R} \right)^{3\eta} + p_v - \frac{2\sigma}{R} - 4\mu \frac{\dot{R}}{R} - p_0 - P(t) \right\}, \quad (2.29)$$

where $\mu$ is the liquid viscosity.
2.4.2 Keller-Miksis Model

In an effort to better understand the origin and behavior of the harmonics of the bubble resonances, Lauterborn (Lauterborn 1976) used the Rayleigh-Plesset model to investigate bubble dynamics for 0.1, 1 and 10-µm radius bubbles driven at a range of pressures, including pressures above the Blake pressure. As described in Chapter 1, the Blake pressure represents the pressure threshold below which a bubble is no longer confined by the surface tension and liquid pressure (Blake 1949; Leighton 1994). A phenomenon which Lauterborn encountered was that some of the resonances of the 10-µm radius bubble featured expansion amplitudes significantly higher than those for the rest of the curves and some resonances were not found to have a stationary solution. Keller and Miksis (Keller 1980) later showed that some of these phenomena were the result of the incompressibility assumption for the fluid surrounding the bubble. The incompressibility assumption stipulates that the Mach number \( \mathcal{M} = \frac{|u|}{c} \ll 1 \), where \( u \) is the bubble wall velocity and \( c \) is the fluid sound speed; this relationship is violated at high forcing pressures, and thus, at higher expansion ratios and collapse velocities. By allowing the fluid medium to be compressible Keller and Miksis found that resonance curves for the 10-µm radius bubble always gave periodic solutions of expected amplitude (in addition to agreement with the curves from the smaller bubble sizes). The Keller-Miksis equation, as formulated by Parlitz et al. (Parlitz 1990), is

\[
\left(1 - \frac{\dot{R}}{c}\right)\ddot{R} + \frac{3}{2} \left(1 - \frac{\dot{R}}{3c}\right)\dot{R}^2 = \left(1 + \frac{\dot{R}}{c}\right) \frac{P(\dot{R}, R, t)}{\rho} - \frac{R}{\rho c} \frac{\partial P(\dot{R}, R, t)}{\partial t},
\]  

(2.28)

where
The dots denote the time derivative, \( p_a \) is the ambient pressure, and the time-harmonic driving acoustic pressure \( p_s(t) = p_a \sin(\omega t) \) has amplitude \( p_a \). Equations (2.28-29) assume that the pressure and temperature inside the bubble are spatially uniform and the fluid motion is spherically symmetric.

### 2.4.3 Bubble Internal Pressure

The internal bubble pressure and temperature is highly dependent on the timescale of the bubble motion. A slow change in size will allow the internal temperature to respond isothermally, while relatively fast changes will yield an adiabatic response. The easiest way to model the thermal response is to assign a single value for the polytropic index when relating radius to pressure, as shown in Eq. (2.26). However, a single value for \( \eta \) is unrealistic for micron-sized inertial cavitation bubbles, since the radial response is generally isothermal during the “slow” growth phase and adiabatic during the rapid inertial collapse (Moss, Clarke et al. 1997). Prosperetti et al. (Prosperetti 1988) relaxed this assumption by solving for a nonuniform temperature distribution inside the bubble and including the heat transport effects of convection and conduction. The internal bubble pressure can be found from

\[
\dot{p}_{\text{int}} = \frac{3}{R} \left[ (\eta - 1)K \frac{\partial T}{\partial r} \bigg|_R - \gamma p_{\text{int}} \dot{R} \right],
\]  

(2.30)

where \( K \) is the thermal conductivity of the gas and \( \gamma \) is the ratio of specific heat of the gas. The temperature distribution \( T(r,t) \) in the gas is described by
\[
\frac{\gamma - 1}{\gamma} \frac{p_{\text{int}}}{T} \left( \frac{\partial T}{\partial t} + \nu \frac{\partial T}{\partial r} \right) = p_{\text{int}} + \frac{1}{r^2} \frac{\partial}{\partial r} \left( Kr^2 \frac{\partial T}{\partial r} \right),
\]

(2.31)

where the radial velocity \( \nu \) in the gas is given by

\[
\nu = \frac{1}{\gamma p_{\text{int}}} \left[ (\gamma - 1) \frac{\partial T}{\partial r} - r \dot{p}_{\text{int}} \right].
\]

(2.32)

The formulation assumes that the temperature at the bubble wall is equal to the ambient temperature. We solved the Keller-Miksis model with the Prosperetti polytropic index correction using numerical methods described by Kamath and Prosperetti (Kamath 1989). The numerical integration makes use of the Galerkin spectral method and shifted Chebyshev polynomials to solve the temperature terms; further detail can be found in Kamath and Prosperetti (Kamath 1989). This model was used in Section 3.8.

2.4.4 Bubble Heating Mechanisms

This work does not seek to theoretically quantify the heat contributed by the bubbles, but nonetheless it is important to understand the underlying mechanisms and the implications that accompany them. There are three mechanisms by which an individual acoustically-driven bubble can convert acoustical energy into heat energy (Devin 1959; Prosperetti 1977): thermal damping, viscous damping, and absorption of the radiated pressure wave from an inertial collapse.

Thermal damping refers to the process by which there is a net flow of heat from an oscillating bubble to the surrounding liquid via conduction. A hysteresis effect caused by a phase lag between the increase in pressure per unit original pressure and the decrease in volume per unit initial volume results in greater work done by the fluid to compress the bubble than is performed by the gas on the liquid upon expansion. Devin
shows, however, that dissipation due to heat conduction vanishes for the cases of adiabatic, isothermal, and/or very small bubbles. We assume most of our bubble population to be comprised of inertially-cavitating bubbles, which undergo largely isothermal expansion and adiabatic collapses, and are likely sub-resonant in equilibrium size. Prosperetti’s more detailed evaluation shows that thermal damping is low compared to viscous and acoustic processes at high frequencies, due to the small net variation in internal energy. Therefore the contribution of thermal damping to the bubble heat generation is likely to be quite small and we will neglect its contribution.

Viscous damping is related to the transfer of momentum from the bubble to the liquid. The fluid is assumed to be viscous and incompressible, or very nearly so, so while it can be shown that there are no net viscous forces acting in the bulk of the fluid, there are viscous stresses in the fluid boundary layer that act on the bubble surface. When the bubble expands, the fluid shell around the bubble decreases in thickness and the lateral shell surface area increases, while compression causes the fluid shell to increase in thickness and decrease laterally. Since the distortion of the fluid shell cannot be caused by fluid compressibility, it must be due to shearing flows. The associated viscous stress is dissipative, which results in a net energy loss per cycle of oscillation. The energy loss is realized as a subsequent conversion into heat. The stress from viscous damping is approximated as

\[ p_{vis} = \frac{4\mu \dot{R}}{R}. \] (2.33)
The rate of work done on the boundary layer is equal to the viscous stress that acts over the surface area (a force) times the velocity of the interface (strain rate). The resulting expression for the cycle-averaged power (denoted by \( \langle \cdot \rangle_t \)) deposited into the liquid is

\[
D_{\text{vis}} = 16\pi \mu \langle \dot{R}^2 R \rangle_t. \tag{2.34}
\]

Heat generation from absorption of the pressure wave emitted upon bubble collapse is perhaps the most intuitive mechanism to understand since it is the most-readily observed. When a bubble is made to grow explosively and collapse inertially, the manifest acceleration present upon rebound results in the launching of a broadband acoustic wave that is readily observed experimentally. This wave is viscothermally absorbed as it propagates, in much the same way that the HIFU wave is absorbed. The relative importance of this mechanism becomes greater in highly-attenuating media, such as tissue. Moreover, the power law dependence of attenuation on frequency suggests that the broadband emissions associated with inertial collapses are very likely to be converted to heat.

Here we assume the bulk of the energy deposition occurs in the far-field \((kr >> 1)\), and that the bubble collapses spherically, such that the radiated pressure is

\[
p_{\text{rad}} = \frac{\rho \dot{R}}{r} \left(2\ddot{R}^2 + R \dddot{R} \right), \tag{2.35}
\]

where \( r \) is the distance from the bubble. The energy from the sound emission is obtained by first determining the time-averaged intensity, which for a plane wave sound emission is...
\[ I_{\text{rad}}(r) = \left( \frac{P_{\text{rad}}^2(r,t)}{\rho c} \right) \]  

The maximum radiated power available for absorption is then found by multiplying over the radiated area:

\[ D_{\text{rad}}^{\text{max}} = 4\pi r^2 \times I_{\text{rad}} \]  

The actual power deposited will depend on the pathlength over which the acoustic emission is attenuated, so the final expression for the power deposition within a volume subtended by \( r \) is

\[ D_{\text{rad}}(r) = D_{\text{rad}}^{\text{max}} - 4\pi r^2 \left( p_{\text{rad}}^2 e^{-2\alpha(f)r} \right) \]  

where the loss due to attenuation has been included. The power density over the volume is

\[ q_{\text{rad}}(r) = \frac{D_{\text{rad}}(r)}{\frac{4}{3}\pi r^3} \]  

While it is helpful to be aware of the bubble heating mechanisms, an attempt to quantify the actual heat contribution is hindered by our lack of knowledge regarding three physical parameters: the fluid viscosity at megahertz frequencies, the equilibrium size of the bubbles and the number of bubbles per unit volume. Edson (Edson 2001) and Yang (Yang 2003) used the Keller-Miksis model and (without and with the Prosperetti polytropic index correction, respectively) to run a parameter study to evaluate what types of bubbles would be affected by the viscous damping and radiation absorption mechanisms. The fluid viscosity was made to vary from 0.001 (water) to 0.1 Pa.sec and the bubble equilibrium radius was varied from 0.1 to 49.77 \( \mu \)m. The pertinent results are
shown in Yang et al. (Yang 2004). Both mechanisms demonstrated sufficient heating to match experimental predictions for bubble-enhanced heating given a reasonable number of bubbles in the focal region (order 10), but for considerably different viscosity and size regimes. In general, smaller bubbles and lower viscosities resulted in greater heating from radiation absorption, while viscous dissipation was relevant mostly for larger bubbles and higher viscosities. Edson concluded that since detection of inertial collapses was coincident with the enhanced heating, the radiation absorption mechanism was most likely the dominant bubble heating mechanism, and therefore, the bubbles which contributed to the enhanced heating were mostly likely sub-micron-sized and the viscosity was likely similar to water or blood. Moreover, Yang showed that for low viscosity media ($\mu < 0.01$ Pa.sec) the maximum permissible size that a bubble could attain was limited by instabilities on the bubble surface that lead to breakup. Both investigators concluded that, for the phantom experiments performed, enhanced heating effects were most likely due to the absorption of reradiated sound from inertially collapsing, sub-resonance-size bubbles. The work of Edson and Yang is summarized in Holt and Roy (Holt 2005), and their parameter regimes were used to guide the choice of bubble sizes and fluid viscosities considered in this work.

### 2.5 Impact of Ambient Temperature

To examine the effect of ambient fluid temperature on the dynamics of a single bubble it was necessary to incorporate the temperature dependence of the physical parameters into the model. Here we assumed the bubble was filled with vapor and air and the fluid was
water. The temperature dependence of the water sound speed (Del Grosso 1972), density (Lide 2000), vapor pressure (Lide 2000), viscosity (Kestin 1978) and surface tension (Maroto 2004) was fed into the numerical code in the form of either an empirical fit or a look-up table. The model was used to evaluate radius-vs.-time curves to determine the maximum radiated acoustic power and the power deposited from viscous dissipation from an air bubble in water. The model was evaluated over a 20 – 100 °C range in 10 °C steps and the bubble was driven by a 6-cycle acoustic burst at 3 MPa pressure amplitude and 1 MHz center frequency. It should be made clear that ‘maximum radiated power’ refers to the result obtained from Eq. (2.37) and assumes that all the radiated acoustic energy is ultimately absorbed and converted to heat. We are interested in the qualitative bubble dynamics and not a quantifiable heat generation since attenuation and path lengths can vary.

A constant initial bubble radius of 50 nm was used for all temperatures. The bubble radii in the experiments are unknown and will most likely be determined by the radius which corresponds to the instability threshold. The scenario is complicated further by the possibility that the instability threshold may change with temperature (Wu 2006). However, the use of a constant initial radius with temperature can be justified since in the regime of inertially-cavitating bubbles (i.e., $R_0 < 1 \mu m$) $R_{max}$ changes very little relative to $R_0$ for radii greater than the Blake radius (Holt 2002) and smaller than the instability boundary.
Assumptions

The internal bubble pressure and temperature is highly dependent on the timescale of the bubble motion. A slow change in size will allow the internal temperature to respond isothermally, while relatively fast changes will yield an adiabatic response. The easiest way to model the thermal response is to assign a single value for the polytropic index when relating radius to pressure, \[ \frac{P_{\text{int}}}{P_0} = \left( \frac{R_0}{R} \right)^\eta \], where again \( \eta \) is the polytropic index.

However, a single value for \( \eta \) is unrealistic for micron-sized inertial cavitation bubbles, since the radial response is generally isothermal during the “slow” growth phase and adiabatic during the rapid inertial collapse. Prosperetti et al. (Prosperetti 1988) relaxed this assumption by solving for a nonuniform temperature distribution inside the bubble and including the heat transport effects of convection and conduction (see Section 2.4.3).

Unfortunately, the Prosperetti model does not specifically account for the vapor pressure, which has a strong dependence on temperature. So although the Prosperetti model is more accurate for modeling the bubble thermodynamics, the Keller-Miksis model was used to evaluate the effect of ambient temperature on the bubble response. The polytropic index was set to 1.3, corresponding to adiabatic conditions, since we are most interested in the collapse dynamics.

Another drawback to using the Keller-Miksis model is that evaporation and condensation effects are not accounted for. In order to include these effects the energy equation in the liquid and the gas-vapor diffusion equation in the bubble must be considered. The bubble wall boundary conditions would also have to be modified to
account for the heat flux from the bubble. Accounting for these effects is beyond the scope of this thesis and will therefore be neglected.

Results

The viscous and radiated power and maximum radius as a function of temperature are shown in Fig. 2.2. Based on Edson and Yang’s results and the low viscosity investigated here it is not surprising that the viscous power is much lower than the radiated power. The radiated power decreases slightly from 20 – 70 °C and more steeply at the higher temperatures, resulting in a decrease of 43% over the entire range. The viscous power decrease over the temperature range is more pronounced, exhibiting a decrease of approximately 80%. The maximum radius, however, steadily increases as water temperature is increased. Similar trends exist for higher viscosities, such as that of blood ($\mu = 0.005$ Pa.sec), although the temperature dependence was not known for these viscosities.

Ambient temperature clearly has an effect on the bubble dynamics. The trends shown in Fig. 2.2 are best understood by considering how some of the physical parameters change with temperature. Both surface tension and viscosity decrease as temperature increases. Surface tension acts to confine the bubble, so a decrease in surface tension will allow the bubble expansion to increase. Viscosity also acts to damp the bubble motion, further allowing increased expansion at higher temperatures. Both these effects are apparent in Fig. 2.2(b), as the maximum radius increases for elevated temperatures. The temperature dependence of viscosity ($\mu$ is lower at higher temperatures) will also have a direct impact on viscous power, as Eq. (2.31) shows that
Figure 2.2: The a) maximum radiated power and viscous power absorbed and b) maximum bubble radius as a function of ambient water temperature from a single air bubble over 6 cycles of acoustic forcing at a pressure amplitude of 3 MPa and a frequency of 1 MHz. The initial bubble size was 50 nm and the viscosity was that of water. The temperature dependence of sound speed, vapor pressure, surface tension, viscosity and density were incorporated into the model. Both the radiated and viscous power decreases as the temperature increases.

viscosity is proportional to viscous power, contributing to the trend observed in Fig. 2.2. Of all the parameters, the greatest impact of temperature change is provided by the vapor pressure: at $T_w = 20$ °C the vapor pressure is 2.3 kPa, relatively low compared to the 101-kPa atmospheric pressure, but at $T_w = 50$ °C the vapor pressure is 12.3 kPa, and is comparable to atmospheric pressure at $T_w = 100$ °C. At higher temperatures the elevated vapor pressure acts to cushion the bubble collapse, particularly in the last stages, by providing increased resistance against the inertia from the surrounding medium. The result is decreased bubble wall velocity and acceleration, both of which figure strongly
into the viscous and radiated power. Vapor pressure may play a competing role in the expansion phase, as an elevated internal pressure will cause the bubble to expand.

The impact of vapor pressure was investigated by modeling the bubble response when vapor pressure was held constant over the temperature range, such that \( P_v(T) = P_v(T = 20 \, ^\circ \text{C}) \), while the other temperature-dependent properties of water (surface tension, viscosity, density, sound speed) were allowed to change with temperature. The result is displayed in Fig. 2.3. In this scenario \( D_{\text{rad}}^{\text{max}} \) remained more or less constant from

![Graph](image)

**Figure 2.3:** The a) maximum radiated power and b) maximum bubble radius as a function of ambient water temperature from a single air bubble over 6 cycles of acoustic forcing. All of the physical and acoustical parameters are the same as in Fig. 2.2, with the exception of a constant vapor pressure of 2.3 kPa, the pressure at \( T = 20 \, ^\circ \text{C} \). In contrast to the trend exhibited in Fig. 2.2(a), the radiated power increases slightly as temperature increases. The increase in the maximum bubble radius with temperature is not as great as in Fig. 2.2(b).
20 - 70 °C and increased slightly at the higher temperatures, by about 3% at 100 °C. The viscous power is not plotted due to its negligible amplitude but featured a trend similar to that displayed in Fig. 2.2(a), likely due to the change in viscosity. The maximum radius increased with temperature, although to a slightly lesser degree when compared to the trend seen in Fig. 2.2(a), suggesting that increasing vapor pressure assists in bubble expansion. All else being equal, a larger $R_{\text{max}}$ should increase the potential energy of the bubble before the collapse, thereby increasing the radiated pressure upon collapse. When this effect is considered, it is clear that vapor pressure plays a dominant role in decreasing the thermal effects of inertial cavitation at high temperatures.

In light of the view that bubbles can assist HIFU heating, the implications of these results are simple but important. From an efficiency standpoint, dynamic energy conversion from bubbles due to boundary layer heating and absorbed acoustic emissions will not aid the HIFU heating process at higher temperatures as greatly as at lower temperatures. (Note that there may still be some enhancement due to multiple scattering from vapor bubbles.) From a cavitation monitoring and control standpoint, the temperature effect on radiated pressure should be taken into account if noise diagnostics are used to monitor the bubble activity and provide feedback control to the HIFU driver, since the results imply that hot bubbles are relatively quiet.

2.6 Summary

The first part of this Chapter described the theory and methods by which a pressure and temperature distribution in the phantoms can be obtained. The Westervelt equation was
used to determine the pressure from the HIFU source and the heat conduction was
determined from an adaptation of the Pennes heat transfer equation. FDTD methods for
the solution of these equations were explained. Results from the Westervelt equation
were used to determine the focal pressure in the experimental results of Chapters 3-5 and
the Pennes heat transfer equation was used to account for the temperature rise from the
primary field absorption, allowing us to determine the temperature rise from the bubbles
in Chapter 3. The rest of the Chapter was devoted to bubble dynamics theory, based on
the Rayleigh-Plesset and Keller-Miksis bubble dynamics models. A study of the effect of
liquid water temperature on a single air bubble was presented. It was found that as water
temperature increases, power generation from the bubble decreases, largely due to an
increase in vapor pressure during this process. These results will be helpful in
interpreting the experimental results that will be presented in Chapter 3.
Chapter 3
EXPERIMENTAL SETUP AND RESULTS FROM PCD CAVITATION MEASUREMENTS

Overview
This Chapter is organized into two main sections. The first half describes the experimental arrangement and those procedures for instrument characterization for experiments involving cavitation and temperature monitoring in tissue phantoms exposed to HIFU. The second half follows with a specific experimental description and results for each of the investigations that were performed using a single-element PCD to monitor cavitation activity. Three experiments are described in this Chapter: multiple duty cycles were employed for the HIFU driving pressure to look at bubble shielding effects; a dual-PCD setup was used to monitor multiple positions in the focal region in order to examine how cavitation activity changed as a function of time and position; and the cavitation noise power was compared with the temperature rise from the bubbles to evaluate whether the inertial emissions are indicative of bubble heating. A discussion and summary of these investigations follows at the end of the Chapter.

3.1 HIFU Characterization
A single-element spherically-focused piezoceramic HIFU transducer (H102-6, Sonic Concepts, Woodinville, WA) was used for all of the experimental work. The transducer has a 20 mm-diameter hole in the center (for either flow accommodation or in-line
positioning of a second, smaller-diameter transducer, neither of which were employed here), with a 70 mm aperture and 62.4 mm focal length in water. A custom matching network (Sonic Concepts) was used to drive the transducer at its nominal 1.1-MHz center frequency. For all of the cavitation measurements performed here the transducer was driven using a function generator (33120A, Agilent Corp., Santa Clara, CA), a 25-dB passive in-line attenuator (JFW Ind., Indianapolis, IN) and a 60-dB power amplifier (A-500, ENI Corp., Rochester, NY), as shown in Fig. 3.1. (Note that the power amplifier employed in the HIFU signal generation did not always provide repeatable amplification of the input signal, resulting in a ±100 kPa deviation of the focal pressure from run to run.) For the experiments, the voltage supplied to the transducer from the matching network was monitored using a high impedance attenuating (-20 dB) probe connected to a RMS-DC converter (AD637, Analog Devices, Norwood, MA). The output of the converter was sampled via an 8-channel breakout box (TBX-1328, National Instruments, Austin, TX) connected to a SCXI analog signal conditioner (SCXI-1120, National Instruments), which provided optional 4 Hz or 10 kHz low-pass filter and on-board pre-amplifiers; the 10 kHz low-pass filter was used with no supplemental amplification. The

![Figure 3.1: Experimental arrangement for HIFU signal generation.](image-url)
SCXI output was digitized by a data acquisition board (AT-MIO-16E-1, 12-bit resolution, National Instruments) at 2 kHz and stored in computer memory. Software control of both the function generator output (via GPIB) and the signal acquisition process was performed using Matlab. The HIFU transducer and test sample were submerged in a Lucite tank (45 x 45 x 58 cm) filled with water which had been degassed, deionized and filtered (0.2-µm particulate filter, Fin-L-Filter). The temperature of the water (22 ± 2 °C) was monitored with an alcohol thermometer daily and the sound speed of the water (employed in simulations) was adjusted accordingly.

Two calibrations of the HIFU transducer were performed. At low drive pressures, a membrane hydrophone (1502-031, 0.2 mm element, Precision Acoustics, Surrey, UK) was first used to map the pressure distribution along the axial direction to determine the length of the focal region and in the radial direction in the focal plane, yielding both a focal pressure calibration and radiated beam patterns for relatively low-amplitude (i.e. no cavitation) pressure fields. The scan step size employed was 0.17 mm. We restricted

Figure 3.2: Experimental arrangement for HIFU source calibration using the membrane hydrophone.

ourselves to a low-pressure calibration in clean degassed water to avoid damaging the membrane hydrophone through cavitation on its surface. The setup for the membrane
hydrophone pressure calibration is shown in Fig 3.2. The HIFU transducer was driven with a 10-cycle sine burst and the hydrophone signal was averaged on the oscilloscope (LT342, LeCroy Corp., Chestnut Ridge, NY) and acquired via GPIB into Matlab. The transducer driving voltage was monitored on the oscilloscope. The function generator voltage was increased and the pressure at the focus was measured by the hydrophone.

![Normalized pressure along the HIFU axis measured with the membrane hydrophone. The negative direction is towards the HIFU source.](image)

Figure 3.3: Normalized pressure along the HIFU axis measured with the membrane hydrophone. The negative direction is towards the HIFU source.

![2-D HIFU pressure plot measured in the focal plane.](image)

Figure 3.4: 2-D HIFU pressure plot measured in the focal plane.

The profiles along the transducer axis and radially in the focal plane are shown in Figs. 3.3 and 3.4 – 3.5, respectively. The focal length (full-width half-max pressure) in water
is 11.4 mm and the focal width is 1.8 mm. The spherical symmetry of the transducer is demonstrated in a scan of the radial plane at the focus, shown in Figs. 3.4 and 3.5. The resulting calibration curves for the peak negative ($P_f^- = 0.0928V_{\text{HIFU}}$) and peak positive pressures ($P_f^+ = 0.103V_{\text{HIFU}}$) using the membrane hydrophone are displayed in Fig. 3.6.

Figure 3.5: Normalized pressure as a function of radial distance from the HIFU axis measured in the focal plane.

Figure 3.6: (a) Negative and (b) positive focal pressure as a function of the HIFU source driving voltage, as measured with the membrane hydrophone.
The HIFU transducer pressure output was also calibrated with a fiber optic probe hydrophone (0.1 mm diameter, FOPH 500, Universitat Stuttgart). The FOPH has the advantage of being able to withstand higher pressure amplitudes, but is subject to a higher noise floor than the membrane hydrophone. A similar procedure to the membrane hydrophone was used; the experimental arrangement is shown in Fig. 3.7. The FOPH calibration results are shown in Fig. 3.8. The calibration was within 2% of the membrane hydrophone calibration for the lower pressures but the trend over the entire range (5 – 80 V) corresponded to a quadratic dependence rather than a linear dependence at the higher pressures. The calibration for the peak negative pressure was
\[ P_f^- = -0.0002 \, V_{HIFU}^2 + 0.1 \, V_{HIFU} \]
and the peak positive pressure corresponded to
\[ P_f^+ = 0.0002 \, V_{HIFU}^2 + 0.114 \, V_{HIFU} \]
This relationship was used in the calibration of the source pressure for the FDTD pressure model described in Chapter 2 (see Section 2.3.1 for the details behind this calibration).

Figure 3.7: Experimental arrangement for HIFU source calibration using the fiber optic probe hydrophone.

3.2 Phantom

Working with the appropriate material for HIFU and cavitation research is a surprisingly complicated issue and may have significant implications for the results and conclusions
that are drawn from them. The bottom line is that HIFU must be effective in tissue, but
as mentioned in Chapter 2, tissue is not an ideal medium to work with. Variability due to
the presence of blood vessels, musculature, bone, lungs, and other heterogeneities in
tissue can disrupt the ultrasound propagation, making it difficult to study the basic effects
of cavitation. Tissue phantoms offer an alternative to studying HIFU and cavitation
effects but a number of tradeoffs exist. Phantoms are attractive since they can be easily
molded to custom shapes, they do not suffer the same aging and deterioration effects as
tissue, they can be homogeneous and thus can provide repeatable results so that
comparison with models and between multiple measurements is possible. Some
important physical effects present in tissue are not easily duplicated, however. Perfusion
is difficult to mimic and most importantly, the development of a single phantom that
matches the thermal, acoustic and lesioning characteristics of tissue has been elusive.
Most of the work presented here, including all of the work in this Chapter, employed an agar-graphite recipe. Agar-graphite phantoms offer thermal and acoustic properties that are not only nearly identical to tissue but can be varied to match different tissue types. These phantoms suffer from the fact that preparation of the phantom requires it be heated above 80 °C, and so it is difficult to add protein to provide the irreversible lesioning characteristics of cooked tissue without denaturing the protein in the process.

3.2.1 Agar-Graphite Phantoms

The recipe for the agar-graphite phantoms used in the experiments is shown in Table 3.1.

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (g)</td>
<td>600</td>
</tr>
<tr>
<td>Graphite (g)</td>
<td>24</td>
</tr>
<tr>
<td>Agar (g)</td>
<td>18</td>
</tr>
<tr>
<td>n-Propanol (ml)</td>
<td>16</td>
</tr>
<tr>
<td>Methyl paraben (g)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Table 3.1: Agar-graphite phantom recipe.

The agar (Sigma-Aldrich Corp., St. Louis, MO) and water (0.2 µm filtered, de-ionized, Barnstead Int., Dubuque, IA) combined to make a solid matrix to bind the phantom together. The graphite (325 mesh, Mallinkdrodt, Phillipsburg, NJ) provided the scattering sites needed to enhance attenuation and to duplicate the volumetric scattering properties of some tissues. The addition of propanol (Fisher Scientific, Hampton, NH) increased the sound speed and the methyl paraben (Sigma-Aldrich) acted as a preservative. The phantom was made by using a hot plate and magnetic stirrer (Cole-Parmer Instrument Co., Chicago, IL) and a vacuum pump (Cole-Parmer) to first degas and heat the water. Once the water was above 80 °C agar was mixed in and dissolved, followed by the methyl paraben, graphite and propanol. The mixture was transferred to a
vacuum flask and set back on the hot plate and stirrer to keep warm and prevent the graphite particles from settling. The mixture was degassed until vacuum pressure of -730 Torr could be maintained for approximately one minute; this process generally took 20 – 30 min for the ~200 mL phantom mixtures typically used. Finally, the degassed phantom was poured into a mold and allowed to cool until set. Unless otherwise specified, cylindrical film canisters (~31 mm diameter x 47 mm long) were used as molds for the agar-graphite phantoms.

The properties of human tissue (Duck 1990) are compared with those of the agar-graphite phantom at room temperature (Huang 2002) in Table 3.2. The specific heat was measured using adiabatic calorimetry (Bowman 1975) and the thermal conductivity was measured a steady-state longitudinal heat flow method (Vendrik 1957; Bowman 1975). A detailed description of the materials and methods used for these measurements are given by Huang (Huang 2002).

In order to assess how the acoustic properties in the agar-graphite phantom might change due to HIFU heating, we measured the acoustic properties as a function of

<table>
<thead>
<tr>
<th>Property</th>
<th>Tissue</th>
<th>Agar-graphite phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (kg/m$^3$)</td>
<td>1000-1100</td>
<td>1003</td>
</tr>
<tr>
<td>Sound speed (m/s)</td>
<td>1450-1600</td>
<td>1520</td>
</tr>
<tr>
<td>Attenuation (Np/m/MHz)</td>
<td>5.6-17</td>
<td>5.0</td>
</tr>
<tr>
<td>Thermal diffusivity (mm$^2$/s)</td>
<td>0.105</td>
<td>0.158</td>
</tr>
<tr>
<td>Specific heat (J/kg. °C)</td>
<td>3600-3900</td>
<td>3710</td>
</tr>
</tbody>
</table>

Table 3.2: Acoustic and thermal property values for tissue and the agar-graphite phantom.
ambient temperature using a through-transmission setup shown in Fig. 3.9. Two 1.9-cm diameter, 2.25 MHz, unfocused piston transducers (V305-SU, Panametrics-NDT Corp.) were flush mounted in two stainless steel baffle plates (0.6 x 10.15 x 11.4 cm) which were in turn oriented directly opposite each other on adjustable sliders. The source and receive transducers shared a common acoustic axis and the sliders allowed precise

![Figure 3.9: Experimental arrangement for the measurement of tissue phantom attenuation and sound speed as a function of temperature.](image)

adjustment of the distance between the plates. The phantom was then sandwiched between the two plates and the entire arrangement was submerged in a water-filled constant temperature bath and allowed to reach thermal equilibrium with the surroundings.

A 15-cycle burst from a function generator (33120A, Agilent) drove one transducer and the signal was received by the other transducer, digitized and averaged by an oscilloscope (LT342L, LeCroy) and sent to Matlab via GPIB. In the course of the experiments, the temperature of the water bath (PSP-DX6, Cole-Parmer) was increased in 5 °C steps from 25 – 50 °C. We had hoped to characterize the properties over the entire temperature range experienced in the HIFU measurements (20 – 100 °C) but were limited by the maximum operating temperature of the transducers. The relevant acoustical
properties (sound speed and attenuation) were measured for tone burst center frequencies ranging from 1.0 – 3.5 MHz in 0.5 MHz steps.

The attenuation and sound speed were determined by measuring the signal loss and time-of-flight difference, respectively, between the reference and received signal in phantoms of two different thicknesses. Five phantoms were made in a rectangular mold (2.5 x 2.5 x 7.5 cm) and were measured along the longitudinal and lateral axes. One of the phantoms contained an embedded thermocouple to monitor the temperature of the phantoms. The temperature bath was set to the desired temperature and once the phantom temperature equilibrated to the target temperature, an additional two minutes passed before the sound speed and attenuation of the remaining four phantoms was measured, using the following procedure.

**Attenuation**

The signal $V$ from the receiving transducer for the phantom path lengths of thickness $l_1$ and $l_2$ (i.e., along the length and width) can be described by

$$V_{l_1} = V_0 D_1 e^{-\alpha l_1}, \quad (3.1)$$

$$V_{l_2} = V_0 D_2 e^{-\alpha l_2}, \quad (3.2)$$

where $D$ is a diffraction correction and $\alpha$ is the attenuation coefficient. The attenuation can then be solved using

$$\alpha = \frac{\ln \left( \frac{V_{l_2} D_2}{V_{l_1} D_1} \right)}{l_2 - l_1}. \quad (3.3)$$
The diffraction correction is dependent on sound speed, frequency, and distance from the surface of the transducer. Liauh and Lin [Liauh & Lin] show that by normalizing the axial propagation distance by the Rayleigh distance \( X = 0.5ka^2 \), where \( k \) is the wave number and \( a \) is the aperture, the near-field diffraction patterns in two different arbitrary media, when expressed as a function of the normalized propagation distance, are in fact the same. This result is demonstrated in Fig. 3.10, which shows the axial diffraction pattern measured for two different materials possessing the indicated sound speeds. Note normalized pressure is plotted versus normalized distance, the patterns line up nicely.

The baseline diffraction pattern for our apparatus was obtained that, when the baseline pressure was normalized by the pressure at the source (0 cm) and the range dependent signal level was measured in water. Since attenuation in water is negligible, range dependent changes in the received signal level should be due to diffraction alone. Therefore, we can say that:
\[
\frac{D_1}{D_2} = \frac{V_l}{V_l_{\text{water}}}, \quad (3.4)
\]

where the signals were measured at the same distances as the two phantom measurements. The difference in the Rayleigh distance in water and in the phantom was accounted for by dividing \( l_2 \) and \( l_1 \) by \( X_p/X_w \), where \( X_p \) is the Rayleigh distance in the phantom. In our setup, where the same transducers and frequencies were used for the phantom and water measurements, the ratio of the Rayleigh distances simplifies to the ratio of their sound speeds, \( c_w/c_p \), so the attenuation was obtained by substituting this ratio and Eq. (3.4) into Eq. (3.3).

**Sound speed**

Huang measured the sound speed using a simple time-of-flight method, where

\[
c = \frac{d_2 - d_1}{t_2 - t_1}, \quad (3.5)
\]

\( d \) is the thickness of the phantom, and \( t \) is the time of flight of the pulse train measured from the first zero crossing of the digitized waveform. This method relies on an accurate measurement of the arrival time of the pulse train, which is compromised when the signal-to-noise ratio is poor. An alternate method of measuring sound speed which does not require manual determination of \( t \) from the digitized pulse is by using a cross correlation technique on the received signals from the two thickness measurements (Hein 1993). The two received pulses will differ only in arrival time and amplitude, so cross correlating the pulses will reveal the number of samples one needs to shift one data train relative to the other in order to achieve maximum correlation. The time difference between the two pulses can then be determined by multiplying the sampling period by the
index of maximum correlation. Comparing sound speeds measured with the cross correlation and time-of-flight techniques over multiple observations yielded similar mean values, but cross correlation proved to be more precise as it yielded a lower standard deviation.

The frequency and temperature-dependent attenuation and sound speed from four agar-graphite phantoms were averaged and the standard deviation was determined. The result is shown in Fig. 3.11. The sound speed showed little dispersion and increased with temperature as expected, due to the high water content and its dependence on temperature (Del Grosso 1972). The sound speed near physiological conditions agreed well with

![Graphs showing sound speed and attenuation](image-url)

Figure 3.11: Measurement of the (a) sound speed and (b) attenuation in the agar-graphite phantom as a function of temperature at 1 – 3.5 MHz in 0.5 MHz steps. (c) The normalized attenuation as a function of temperature, where attenuation was normalized by the attenuation at \( T = 25 \degree C \). The error bars represent the standard deviation of the measurement for the four phantoms.
reported *in vivo* sound speeds \((c(T=37 \, ^\circ C) \approx 1540 \, \text{m/s})\). The attenuation displayed the expected weak power law with frequency and also increased with temperature, with a peak at about 35 – 40 °C, before decreasing slightly. The effect at 1 MHz shows a 25% increase at 35 °C over the 25 °C baseline value while the measurement at 3.5 MHz increased to almost twice the baseline attenuation at 40 °C. Somewhat surprisingly, the attenuation frequency dependence was not constant with temperature, as highlighted in Fig. 3.11(c), where all the temperature dependent attenuation curves are normalized by the attenuation at baseline. Indeed, the role of temperature in modifying attenuation in the phantoms is more pronounced the higher the frequency.

As pertains to HIFU and cavitation, attenuation has two main effects, heat generation and loss of signal amplitude. The role of increased attenuation with temperature at the HIFU operating frequency (1 MHz) is mild, but the elevated values at the higher frequencies could have a significant impact on the absorption of higher harmonics from the HIFU signal and the broadband inertial cavitation signals. The temperature gradients surrounding the HIFU focus are high, ensuring that a relatively short portion of the PCD signal path length will experience elevated temperatures. Regardless, it is possible that the elevated attenuation could play a small role in decreasing the cavitation signal amplitude. These results will have an impact on the experimental results reported later in the Chapter.

Attenuation in tissue and most phantoms obey a weak power law with frequency, where \(\alpha = \alpha_0 f^\gamma\), where \(\alpha_0\) is the attenuation coefficient at 1 MHz, \(f\) is the frequency in MHz, and \(\gamma\) is a power law coefficient which ranges between 1.1 – 1.4 for tissue. The
temperature dependence of attenuation was investigated by applying the Allegra and Hawley (Allegra 1971) theory of scattering and absorption in a suspension of particles to a distribution of graphite particles in water. By including the temperature dependence of the physical parameters required by the model, the theoretical attenuation was found to be in qualitative agreement with the experimental results (see Fig. 3.12) despite the fact that the phantom consists of an agar gel and not water. Indeed, the temperature dependence shows a remarkable similarity.

3.3 Temperature Sensing

Temperature was measured using a bare-wire thermocouple (125 µm tip diameter, Type E, Omega, Stamford, CT), which was cast into the phantom during the phantom construction process. The thermocouple was placed approximately 15 mm from the phantom edge proximal to the HIFU transducer. One of the issues that accompanies thermocouple measurements is viscous heating, where the movement of the thermocouple relative to the medium due to the incident sound contributes additional heating (Fry 1954; Fry 1954). This phenomenon is viewed as artifactual heating, as it is
not representative of the temperature in the tissue when the thermocouple is not present. When the sound field is first applied the temperature rise caused from the thermocouple artifact is relatively high compared to the temperature rise from thermoviscous absorption and cavitation effects, if present. Over time, the heat deposition in the medium from HIFU and cavitation will eventually surpass heat generated from the viscous artifact and the error in the measurement due to the viscous artifact will decrease. To reduce the viscous heating artifact, the thermocouple was always aligned parallel to the HIFU axis and positioned 0.5 mm lateral to the focus, unless specified otherwise (see Section 3.7). Another concern regarding the presence of the thermocouple is possible distortion of the ultrasound pressure field. Hynynen and Edwards (Hynynen and Edwards 1989) showed that thermocouple tip diameters greater than $\lambda^{1/2}/5$ cause scattering and shadowing; the thermocouples employed here were safely below this criterion, allowing us to neglect the impact of the thermocouple on the propagation of the ultrasound.

A diagram of the temperature measurement setup is shown in Fig. 3.13.

Thermocouple signals are generally low in amplitude and can be affected by electrical noise. To reduce the noise the thermocouple signal was sampled by the same 8-channel TBX-1328 breakout box and SCXI-1120 signal-conditioning unit used for the HIFU signal. A 4 Hz low-pass filter and a 60 dB pre-amplifier was used to reduce the noise.
and increase the amplitude. Since the measurements generally used CW insonation, the data was acquired in batch mode asynchronously from the ultrasound signal; a common time base between the temperature and cavitation measurements was later established by comparison the temperature-versus-time profile with the on/off times of the HIFU driving voltage signal, whose measurement is described in Section 3.1. We employed a NIST Type E thermocouple calibration with a cold junction compensator built into the breakout box. The noise was quantified by measuring the steady-state temperature in the phantom when placed in a large water reservoir, where the temperature was expected to be constant over short durations. The input range on the data acquisition board was set to 0 to 10 V to accommodate temperatures approaching 100 °C. The signal is shown in Fig. 3.14. Given the range on the digitizer, the noise fluctuations were on the order of ±1-2 least significant bit, which amounts to an absolute precision of ±0.04 °C and a relative precision of ±0.04% of the full scale output. The low noise amplitude allowed us to measure the temperature without any additional filtering.

![Figure 3.14: Measurement of the baseline temperature in the agar-graphite phantom when the HIFU source is off.](image_url)
3.4 Cavitation Noise Diagnostics

3.4.1 Passive Cavitation Detection

We now consider candidate processing methods to be applied to a passive cavitation detector output in order to ‘quantify’ the cavitation activity. Ideally, the entire time sequence corresponding to emission from an inertial bubble collapse would be measured, and in such a case, a determination of the amount of energy from the collapses is made possible. A number of factors make this difficult, however, mostly owing to the fact that the signal of interest is so broadband. Moreover, the energy from the primary HIFU signal, which includes the high-amplitude fundamental and harmonics that are generated from nonlinear effects, is scattered by the medium (both graphite and bubbles) and superimposed on the radiated broadband inertial cavitation signals. It may be possible to filter out parts of the HIFU signals but it is impossible to completely isolate the underlying inertial signal without compromising its integrity. Another problem is that any detector employed will have a band-limited response and will be insensitive to some frequencies and overly sensitive to others. Finally, not all of the radiated bubble signal will reach the receiver, due to scattering and absorption effects, a factor that becomes ever more pronounced as the bubble field grows in size and density.

One method for circumventing these difficulties is to generate a FFT with enough frequency resolution to allow us to isolate a portion of the noise spectrum nestled between harmonics (Chen 2003). A second approach is to detect with a broadband receiver possessing a higher center frequency, high-pass filter out the HIFU fundamental and 2-3 of the lower harmonics, and monitor either the peak-detected RF signal or root
mean square (RMS) signal amplitude in a fixed time window (Edson 2001). The first method assures that only the broadband signal is detected but requires considerable dynamic range due to the large amplitude difference between the scattered HIFU signal and the broadband noise emissions. Moreover it does not support real-time processing and usually involves the use of a transient-capture digitizer or an oscilloscope; both of which are subject to rather large sensing dead time. The second method can be performed in real-time and can achieve superior signal-amplitude resolution, but may also capture some of the higher harmonics in the signal particularly at very high HIFU drive amplitudes.

It is important to keep in mind that the agar-graphite phantoms exhibit low cavitation threshold pressures (on order 1.4 MPa, as will be seen). That fact, when combined with our desire to work at or slightly above threshold conditions, led us to employ HIFU fields with pressure amplitudes significantly lower that commonly employed in clinical systems. As such, there was relatively little shock formation in our HIFU waveforms and high-pass filtering should be sufficient for eliminating the scattered HIFU signal and isolating at least a significant portion of the noise emission spectrum.

Thus inspired, we chose to employ the latter method in our work. A real-time signal was desired in order to obtain fine time resolution, and by choosing a sufficiently-high center frequency for the PCD and applying proper filtering we were confident that we were indeed sensitive only to the broadband emissions – particularly given the relatively low HIFU drive levels employed in this study. In addition to real-time response, it was important to have good spatial sensitivity so we could be certain of the
region where the cavitation signal is coming from. Thus, all of the cavitation noise sensing performed in this chapter used a single-element focused transducer (V313, Panametrics-NDT Corp., Waltham, MA) as a passive cavitation detector (PCD). The transducer had a 12-19 MHz bandwidth (–6 dB), a 19-mm focal length and a 6.35-mm aperture. The PCD was oriented so its beam was perpendicular to the HIFU beam and unless noted otherwise (see Section 3.6), positioned confocally with the HIFU transducer. In this arrangement, the sensing volume of the PCD was determined by the PCD focal zone and the HIFU focal zone. The focal width of the PCD was determined by positioning a 3.18-mm diameter brass sphere at the focus and exciting the transducer’s impulse response with a voltage “spike” from a pulser-receiver (5052UA, Panametrics-NDT Corp.). The echo from the sphere was received by the pulser-receiver and the sphere target was moved laterally across the focus in 10-µm increments. The output from the pulser-receiver was digitized by an oscilloscope and acquired by Matlab via GPIB. The focal width (–6 dB) was 285 µm, as shown in Fig. 3.15. The measured width was in good agreement with the theoretical focal width (Olympus-NDT Corp. 2006),

$$BD(-6dB) = \frac{1.02Fc}{fD},$$

(3.6)

where $BD$ is the beam diameter, $F$ is the focal length, $c$ is the sound speed, $f$ is the frequency and $D$ is the element diameter. The focal width computed from Eq. (3.6) is 300 µm. In addition to having a tight focus the transducer possessed negligible side lobes, so the signals that were detected most likely originated from the small PCD focus.
The length of the PCD focal region was measured in a similar manner. The target was positioned at the focus and moved in 200-µm increments along the PCD axis in 8 mm spanning the focus. The length of the focal zone was 7.5 mm, compared with the theoretical focal zone length of 7.2 mm (Olympus-NDT Corp. 2006).

3.4.2 Conditioning the PCD Signal

The setup used for the PCD signal conditioning is shown in Fig. 3.16. First the signal was filtered with a passive 5 MHz high-pass filter (60 dB/octave, F5081-FP0-B, Allen Avionics, Mineola, NY), effectively removing the HIFU fundamental signal and the initial higher harmonics. Next, the signal was amplified through a combination of passive attenuators (-15 dB, JFW Ind.) and a 60-dB preamp (W40D, TronTech). With the exception of the experiments in described in Section 3.1.4, an analog RMS-DC converter chip (AD8361, Analog Devices, Norwood, MA) was used to obtain a measure.
of the power in the time-varying cavitation signal. The integration time of the converter was set to 300 µsec. Therefore, at any instant in time, the output voltage of the converter yielded the RMS value of the radiated sound power from inertial bubble activity averaged over the previous 300 µsec of HIFU insonation; the measurement dead time was negligible. The output from the converter was passed on to the same 8-channel TBX-1328 breakout box and SCXI-1120 signal-conditioning unit used to acquire the HIFU voltage and the thermocouple signal. The 10 kHz low-pass filter was applied to the slowly varying (on acoustic timescales) PCD signal, with no additional amplification required.

The AD8361 was chosen due to its large bandwidth (DC – 2.5 GHz) and was used in its evaluation board arrangement, so that conforming the signal processing on the chip to our measurement conditions was not difficult. The chip has an averaging filter that poses a tradeoff between integration time and bandwidth. The averaging filter is separate from a high-pass input filter, both of which were modified. The high-pass input filter ships with a 8-MHz corner frequency, so the coupling capacitance was increased by 1 nF to reduce the corner frequency to 800 kHz. The averaging time is determined in part by the filter capacitor. The chip's internal resistance changes based on the signal input voltage (2 kΩ for higher-amplitude signals, 500 Ω for lower-range signals), so in order to increase the averaging time from the nominal 20 µs, the filter capacitance was increased to about 100 nF, for an averaging time of about 300 µs.

The AD8361 board has a conversion gain which depends on the frequency, signal
amplitude and input impedance. Since we are interested only in the signals above 5 MHz, the chip response was measured from 5–20 MHz at the signal amplitude expected from the PCD. A function generator (8116A, Hewlett-Packard) output a continuous wave (CW) signal into the board and the input signal was monitored on an oscilloscope with an attenuating high-impedance probe. The error of the chip output relative to the input RMS voltage with respect to frequency is shown in Fig. 3.17. Two chips were used in the dual PCD experiments, and there was less than 3% deviation from the input signal RMS over the frequency range for both chips. Additionally, the amplitude response at 5, 10, 15 and 20 MHz was investigated. The deviation over the 20 – 1100 mV$_{input, pp}$ range was less than 3% as well; a representative plot at 10 MHz is shown in Fig. 3.18. The conversion gain for the chip used for the prefocal PCD was $V_{rms} = 8.55V_{in}$ and the gain for the chip used for the focal PCD was $V_{rms} = 8.45V_{in}$. The input voltage range on the data acquisition board was 0 – 5 V and once the RMS conversion was performed, the noise amplitude, with the power amplifier and positioning motors turned off, was approximately 21.4 mV and the voltage resolution was 0.29 mV.

![Figure 3.17: Frequency response of the AD8361 RMS-DC chip employed for the focal PCD transducer.](image)
3.4.3 Frequency Selectivity and the PCD

We now have a convenient means for sensing the RMS signal due to inertial cavitation noise, a quantity that corresponds to the square root of the radiated sound power. However, this signal could also include harmonic and super-harmonic components of the scattered HIFU field that may not be filtered out by the 5 MHz high-pass filter. It was important to establish that the band-limited PCD transducer response and high-pass filter frequency were sufficient to yield a signal that was dominated by the broadband emissions from inertial cavitation, and not the HIFU harmonics. Using the setup in Fig. 3.19 two PCDs were aligned confocally at the HIFU focus, and thus were sensing the
same region. An agar-graphite phantom was used as a target and the HIFU source was driven continuously for 1 sec for discrete driving pressure amplitudes ranging from just below the cavitation threshold to approximately 3.5 MPa. The exposures at each pressure were separated by 120 sec to allow the phantom to cool. The output from one PCD was processed by the RMS-DC chip, as described above. The signal from the other PCD was filtered and amplified in a similar manner but was then digitized at 50 MSample/sec by a 14-bit high speed digitizing card (CompuScope 14100, Gage Corp.) so that repeated 5-kSample waveforms (100 µsec data streams) were obtained at a rate of about 10 waveforms per second.

In order to determine the amplitude of the broadband signal without the harmonics present we applied a custom comb-type filter to remove the energy at the harmonic and super-harmonic frequencies \((nf, nf/2, \pm nf/3, \text{where } f \text{ is the fundamental frequency and } n = 1, 2, ..., 10)\); however, inertial cavitation energy also subtended the HIFU harmonics so we did not want to remove the entire signal at these frequency bands. To obtain the spectrum of the broadband signal, an FFT was performed for each waveform and the data within the harmonic/super-harmonic frequency bands were set equal to the average broadband signal amplitude in the frequency band above each respective harmonic frequency. In this manner the spectrum was filtered such that it contained only the broadband energy in the frequencies where the HIFU and inertial cavitation signals did not coincide and the frequency bands where the broadband signal did overlap with the HIFU signal now contained a representative amplitude for the broadband energy. The filter was applied by identifying a \(\pm 150 \text{ kHz} \) band around each
harmonic and ±50 kHz band around each sub- and super-harmonic. The frequency range between each particular frequency band of interest and the next-highest frequency band was windowed and the signals in the indices corresponding to this broadband window were randomly assigned (using the Matlab ‘randint’ function) to the indices that corresponded to the harmonic frequency band. This filtering process will be described in greater detail in Section 4.2.

Figure 3.20 shows representative data from one of the measurements, where $P_{foc} = 2.7$ MPa. The $V_{rms}$ from the first PCD acquisition, as measured using the RMS-DC converter, is shown on top, and some of the raw magnitude spectra from the second PCD, as captured on the digital oscilloscope, are shown in Fig. 3.20 (b-e). The spectra shows that the signal is largely broadband, with little signal at the lower frequencies due to the 5 MHz high-pass filter and a decreasing signal at the higher frequencies due in part to attenuation. Multiple traces are shown to demonstrate that, aside from the overall amplitude, the frequency response is fairly characteristic with time (i.e., broadband, with low energy at the harmonics).

Following comb filtering, an inverse FFT was performed and the RMS level of the broadband component of the PCD signal was determined. The RMS level of the raw, unfiltered signal was also determined, and by comparing the filtered and unfiltered amplitudes the relative error incurred by assuming that the unfiltered signal contained only broadband energy could be determined:

$$\%\text{error} = \frac{V_{rms,unfil} - V_{rms,fil}}{V_{rms,unfil}},$$ (3.7)
Figure 3.20: Typical PCD measurement in an agar-graphite phantom, where $P_{\text{foc}} = 2.7$ MPa. (a) The $V_{\text{rms}}$ signal following the 5-MHz highpass filter. (b-e) Magnitude spectra following the 5-MHz highpass filter at $t = 0.27, 0.39, 0.56, 0.69$ sec.

Figure 3.21: Relative error in the RMS voltage from the PCD that results from assuming that the detected signal in the agar-graphite phantom is due solely to broadband inertial cavitation noise and not from harmonics and ultraharmonics of the HIFU drive that scatter into the detector aperture. The error bars represent the standard deviation of the error for the number of waveforms acquired over the 1 sec measurement.
The mean relative error at each pressure was determined and four such pressure ramps were performed; results are plotted in Fig. 3.21 as a function of focal pressure. The mean error is fairly low, between 3 – 4%, and in many instances is less than the observed fluctuations. This result demonstrates that, at these HIFU pressures in agar-graphite phantoms, sound power from the scattered HIFU signal contributes minimally to the PCD signal in the presence of cavitation; the resulting bias error is on the order of +5%. Thus we can feel confident that our approach for measuring inertial cavitation noise is appropriate for the frequency, pressure and phantom parameters defined thus far.

### 3.4.4 Alignment

The PCD was positioned such that its axis was perpendicular to the HIFU axis. The two transducers were then confocally aligned in water using a multi-step process. First, we located the focus of the PCD by positioning a target (brass sphere, 3.18-mm diameter) at the position of maximum backscatter return, where the PCD was driven in pulse-echo mode by a pulser-receiver (5052UA, Panametrics-NDT Corp.). The target was translated towards the PCD by a distance equal to its radius, such that the center of the sphere was at the PCD focus. Next the HIFU source was driven in pulse-echo mode using the same pulser-receiver and moved such that the center of the fixed target was at the HIFU focus. Finally, the target was removed and replaced by the test sample. From this point on, both transducers remained fixed and all subsequent targeting adjustments were done by moving the phantom. The thermocouple in the phantom was aligned at the focus by two concurrent methods: the HIFU was operated at a low pressure and low duty cycle and the phantom (and by extension, the thermocouple) were moved to the position of maximum
temperature; the PCD was driven again by the pulser-receiver to confirm the alignment by detecting the echo off the embedded thermocouple tip.

3.4.5 The Cavitation Threshold

As this work is concerned with the heating effects associated with inertial cavitation, it is useful to assess what range of HIFU pressures are required to induce inertial cavitation in our phantoms. We call this the inertial cavitation threshold pressure. Strictly speaking, it is not clear whether the onset of bubble activity in the phantom is the result of satisfying a pressure threshold criterion for bubble nucleation or for inducing inertial response from a preexisting bubble. However, such a distinction is not important in the context of this study. What is important is that we recognize that the PCD is selectively sensitive to inertial cavitation noise, thus any threshold we measure will be indicative of the onset of detectable inertial cavitation.

The inertial cavitation threshold was measured using an arrangement similar to that shown in Fig. 3.19 and a protocol similar to that used for the broadband error measurement above. The phantom was insonified with a constant pressure-amplitude HIFU burst for 0.9 sec, followed by no ultrasound insonation for 120 sec for cooling, and after each burst the pressure was increased, ultimately covering a range of 0.8 – 2 MPa in 0.07 MPa steps. Temperature was monitored with a thermocouple placed 0.5 mm lateral to the HIFU focus. We defined the inertial cavitation threshold as the lowest pressure at which the mean amplitude of the broadband noise between 6 – 6.5 MHz (sufficiently above the filter cutoff frequency and below the sixth harmonic) was greater than three standard deviations above the mean broadband noise measured between 6 – 6.5 MHz.
when the sound field was turned off. The broadband noise was monitored by both the spectra obtained from the PCD signal sampled by the digital oscilloscope and the RMS voltage obtained from the PCD signal that was processed by the RMS-DC chip. The threshold was determined to be about 1.4 MPa, similar to the threshold measured by Holt and Roy (Holt 2001) and slightly lower than the 1.7-MPa threshold measured by Edson (Edson 2001).

The magnitude spectra, PCD RMS signal level, and temperature at 1.33 MPa (just below the threshold) and 1.4 MPa (slightly above the threshold) are compared in Fig. 3.22. The spectra amplitude was low at 1.33 MPa. When the pressure was increased to 1.4 MPa there was a sudden and obvious onset of broadband noise, indicating the onset

![Figure 3.22](image_url)

Figure 3.22: Temperature and cavitation noise diagnostics obtained in the agar-graphite phantoms exposed to 0.9-sec HIFU insonation just below and just above the inertial cavitation threshold pressure. The sound field was turned on at approximately 0.2 sec and turned off at 1.1 sec. (a) Magnitude spectra at $P_{foc} = 1.33$ MPa. (b) Magnitude spectra at $P_{foc} = 1.4$ MPa. (c) PCD $V_{rms}$ signal at 1.33 and 1.4 MPa. (d) Temperature rise measured near the focus at 1.33 and 1.4 MPa.
of inertial cavitation. This effect is nicely represented in the plots of the PCD RMS signal level for both cases as well as in the measured temperature rises. Note the enhanced heating rate in the presence of cavitation activity. The observed 300% increase in peak temperature rise above ambient (23 °C) is far greater than one would expect from the primary absorption on the HIFU field alone. For small pressure increases, the latter scales with the pressure squared, yielding a predicted increase of only 10%.

3.5 Duty Cycle Experiments

The duty cycle experiments were designed to monitor how the cavitation signals changed depending on the HIFU pulse length and pulse repetition frequency (PRF). The objective was to evaluate two hypotheses: 1) at high CW pressures the cavitation signals detected by the PCD would decrease over time due to prefocal bubbles shielding the signal; 2) pulsing the HIFU at an optimum combination of pulse length and PRF would provide time for the bubbles to dissolve during the HIFU off-time and thus avoid bubble shielding, allowing the HIFU beam to reach the focus such that the cavitation bubbles could be driven steadily over time. We were motivated to investigate the effects of a variable duty cycle since pulsed ultrasound has been shown to enhance a number of cavitation-related bioeffects, such as lung hemorrhage (Child 1990) and tissue erosion (Xu 2004). Flynn and Church (Flynn 1984) showed that optimal duty cycles exist for producing a maximum effect from cavitation by monitoring the percent iodine release in sodium iodide solution, a cavitation-mediated effect.
Consideration of the HIFU on-time and on-off time in the context of cavitation is important, since bubble equilibrium size, which plays a significant role in determining thermal and shielding effects, is affected by a number of time-related factors. Rectified diffusion will cause a gradual increase in equilibrium radius during the time the HIFU source is turned on. Another factor to consider, for low viscosity media, is surface instability, which will cause the bubble to break up and generate multiple smaller nuclei, which can then be made to grow by rectified diffusion. Both these processes occur when the bubble field is driven and both can result in a cavitation zone substantial enough to shield the focus from the incident HIFU. In a degassed medium, HIFU off-time will have the opposite effect of rectified diffusion: the concentration gradient between the gas in the bubble and the low dissolved gas content in the medium will cause gas to diffuse out of the bubble, decreasing the equilibrium radius. Surface tension effects will accelerate this effect in very small (order 1 µm) bubbles, causing them to dissolve completely (ignoring stabilization mechanisms for nuclei). If the HIFU is turned off too long all the bubbles will dissolve and the process of establishing the bubble field will have to be repeated. Thus, we believe there exists an optimum balance between bubble generation/growth during the HIFU-on phase and bubble dissolution during the HIFU-off phase such that one can sustain cavitation activity without shielding. Indeed, we believe that PCD based noise diagnostics may be an ideal way to monitor the bubble field in real time, and thus provide a means for feedback control of key HIFU insonation parameters such as pressure and duty cycle.
The first hypothesis was evaluated by monitoring the PCD output over time as a function of HIFU focal pressure. The phantom was continuously sonicated for 5 sec at a constant pressure in a previously unexposed region for each measurement, from 0.5 – 3.9 MPa in ~0.15 MPa steps. The PCD signal was found to decrease over time at higher pressures; detailed results will be shown below. Based on this finding, we considered the second hypothesis by insonating the phantom at a pressure known to produce such a signal decrease and then manipulated the pulse length and PRF while keeping the pulse amplitude constant. Pulse lengths of 100, 200 and 1000 cycles were employed in conjunction with PRFs chosen to yield duty cycles (DC, not to be confused with “direct current”) from 10 – 90%. The duty cycle is the percentage of time the sound field is turned on and is related to pulse length and PRF by DC = pulse length * PRF * 100%, so a 100 cycle burst at 2.2 kHz yielded a 20% duty cycle.

The experimental arrangement is shown in Fig. 3.23. The HIFU transducer was

![Figure 3.23: Experimental arrangement for the cavitation control via duty cycle experiments.](image)
driven at its resonant frequency (1.1 MHz) by a tone burst generated by a function
generator (“HIFU function generator”) and amplified as described in Section 3.1; we
refer to this burst as the HIFU “pulse” and its duration can be precisely varied, or made
constant. A second function generator (“trigger signal generator”) was employed to
control the repetition rate of the HIFU pulses, by externally triggering the HIFU function
generator. The trigger signal generator output a square wave at a frequency determined
by the desired PRF; the trigger frequency would therefore determine the PRF of the
HIFU signal in burst mode. The phantom was positioned such that the HIFU focus was
approximately 15 mm in from the edge of the phantom.

The PCD was positioned confocally with the HIFU transducer. The PCD signal
was amplified and high-pass filtered as described above, but instead of acquiring the
RMS signal, the signal was sampled using a gated peak detector (5607, Panametrics-NDT
Corp.) armed with an internally-generated, 20-µs long gate window. (The reason for this
was simple: at the time these experiments were run, we had not yet constructed the RMS
detection circuitry described previously.) The peak detector was triggered by the square
wave output by the trigger signal generator. The detector’s internal delay circuit was set
so that the detection gate window corresponded with the arrival of the cavitation noise
signal to the PCD. The output from the peak detector was digitized and saved to PC via
the signal conditioning unit and data acquisition board described above. The voltage into
the HIFU transducer was measured with a high-impedance probe digitized by the
oscilloscope to determine the focal pressure.
When employing CW insonation, the recorded PCD signals exhibited three distinct trends, depending on the HIFU pressure amplitude. At focal pressures between 1.4 – 1.6 MPa, the cavitation steadily increased over the insonation time. For focal pressures between 1.6 – 1.8 MPa the cavitation signal remained more or less constant, and above 1.8 MPa the cavitation signal had an increasingly negative slope. The 2.6-MPa result is shown in the curve labeled “CW” in Fig. 3.24(a), and serves as evidence of diminishing cavitation levels associated with bubble shielding effects; i.e., the first hypothesis.

Once we determined a pressure regime where the cavitation signal (and, by assumption, inertial-cavitation-enhanced heating) decreased over time, we varied the pulse length and PRF for 5 sec sonications using a 2.6-MPa focal pressure. The duty cycles with 1000- and 200-cycle pulse lengths generally produced cavitation signals that either decreased over time or were erratic, with no consistent trend. The results using a 100-cycle pulse length were repeatable. The PRF for the 100-cycle pulse length was varied in 1.1 kHz steps from 1.1 – 9.9 kHz. Although the higher duty cycles continued to produce a steady decrease in cavitation signal over time, the 20 – 30% duty cycle exposures yielded PCD emissions that were more or less constant over time. Following this result, the 20% duty cycle (100-cycle burst, 2.2-kHz PRF) was tested for longer periods and was found to be constant for sonications up to 60 sec. The reliability of the 20% duty cycle for a 10-sec exposure is compared to the CW case in Fig. 3.24(a).
Next, the use of pulsed HIFU to subsequently stabilize cavitation following CW insonation was investigated. The HIFU source was excited with a 2.6-MPa focal pressure continuously for 5 sec, after which the sound was pulsed for an additional 60 sec using 100-cycle bursts at a 2.2-kHz PRF (20% duty cycle). The result is shown in Fig. 3.24(b), where it is evident that the CW regime produced the expected decreasing signal. Upon switching to the pulsed regime, the cavitation signal initially jumped ~70 mV (~18%), where it increased steadily to the initial signal amplitude of ~580 mV over a 25-sec time period. The signal then remained relatively constant for the remainder of the insonation period. The fact that the cavitation activity not only reversed its negative slope but increased to its initial amplitude is an indication that the shielding effect associated with the decreasing signal was effectively stabilized by pulsing the HIFU with 100 cycle bursts at a 20% duty cycle. We expect the heating rate due to direct absorption
of the HIFU beam to be reduced at the lower duty cycle, but it appears here that the bubbles can be driven to produce a constant level of cavitation over time.

3.6 Dual PCD Experiments

The dual PCD experiments built upon the results of the duty cycle experiments by using the pressure regimes that indicated shielding conditions. The duty cycle experiments revealed that the cavitation signals decreased over time at high pressures for CW insonation, suggesting that bubbles nucleated prefocally along the HIFU propagation path were shielding the HIFU from the focus. Here we hypothesized that if prefocal bubble activity was causing shielding then the cavitation signals in the prefocal region should increase until such time that the prefocal region of interest was affected by shielding as well. It has been our experience (Thomas 2005) that when tadpole-shaped lesions form they are only developed in the regions where the pressure is above the cavitation threshold. This means that, depending on the pressure and the cavitation threshold, the tadpole shape is still contained within the ‘cavitation region’, the region where the pressure exceeds the cavitation threshold, and the underlying problem has more to do with the difficulty of delivering energy to the entire target region rather than lesion formation in the truly prefocal path. Thus, for the context of the dual PCD experiments, ‘prefocal’ will refer to the positions that are proximal relative to the HIFU transducer.

Prefocal cavitation activity was investigated by positioning the focus of a second PCD (“prefocal PCD”) along the HIFU transducer axis and monitoring the cavitation signal amplitude over time at discrete positions, all the while monitoring the signal from
the fixed, focal PCD. In this manner, the cavitation activity was measured over a range of discrete locations extending from the focus to 5 mm towards the HIFU transducer, in 1-mm increments, for 6-sec CW sonications. Fresh phantoms were used for each measurement, and the experiment was completed using 2.6 and 3 MPa focal pressure amplitudes.

The dual PCD setup is shown in Fig. 3.25, and differed only slightly from the duty cycle setup. The HIFU was operated in CW mode, so the signal generation was internally triggered. The prefocal PCD was set in an articulated holder, such that its focus could be positioned along the HIFU axis in the prefocal region. Both PCDs employed identical post-processing, as described in Section 3.4.

Results obtained for the two pressures are displayed in Figs. 3.26 ($P_{foc} = 2.6$ MPa) and 3.27 ($P_{foc} = 3$ MPa) and had similar trends. For the 3 MPa measurement set, the PCD signal at the focus, -1 and -2 mm (prefocal) decreased rapidly over the first second of
ultrasound exposure. The signals obtained from the focus through -2 mm exhibited a steady decrease over the first 2.5 – 3 sec before leveling off. Both the -3 mm and -4 mm signals decreased slightly over the first ~1.5 sec, followed by an increase in signal from approximately 2 – 3.5 sec. The measurement at -5 mm was flat until about 4 sec when it jumped suddenly and remained relatively constant. Based on the HIFU source calibration, the pressure throughout the region exceeded the cavitation threshold,

![Image](image1.png)

Figure 3.26: Inertial cavitation noise emissions as a function of position (relative to the HIFU focus) and time, where $P_{foc} = 2.6$ MPa. The negative orientation on the y-axis refers to the axial position proximal to the HIFU transducer.

![Image](image2.png)

Figure 3.27: Inertial cavitation noise emissions as a function of position relative to the HIFU focus and time, where $P_{foc} = 3$ MPa.
assuming no bubbles present. It should be noted, however, that the pressure -5 mm prefocal was only slightly above the threshold; the initial PCD signal here corroborates this fact, given its low amplitude. The focal signals decreased similarly for the 2.6-MPa results, while the cavitation signal increased over time at 4 mm. Note that, at 2.6 MPa focal pressure, no signal was present -5 mm prefocal, for at that point the pressure was in fact below the cavitation threshold.

For $P_{foc} = 3$ MPa (Fig. 3.27) the PCD signals obtained at -4 and -5 mm are particularly illustrative, as the jump in cavitation at -5 mm occurred coincidentally with the decrease at -4 mm. This type of trend, where the cavitation signals closer to the transducer increased as the cavitation activity closer to the focus decreased, supports the hypothesis that prefocal bubble clouds are shielding the focal energy deposition. These prefocal bubble clouds will increase the prefocal temperature in a manner that is similar to tadpole shape lesion development.

### 3.7 Heating From Inertial Cavitation

#### 3.7.1 Theoretical Basis For Heating From Bubbles

One of the chief observations surrounding the presence of inertial cavitation has been the elevated heating which accompanies it. This connection was the main focus of Edson’s dissertation, shown clearly in Fig 3.22. When the pressure is increased by less than one atmosphere, the difference in temperature rise is dramatic and cannot be solely attributed to heating from the primary field absorption. Edson, who obtained a similar result, concluded that the absorption from the collapse emissions was the most likely reason for
the elevated heating and that depending on the pressure, a small population of 10 to 35 sub-micron-sized bubbles could theoretically produce the necessary heating.

One of the goals in this work was to build off of Edson’s results and conclusions by trying to better understand the cavitation signals and what they can tell us about the pressure and temperature – to develop an ability to *diagnose* cavitation noise. If the elevated heating is caused by absorption of the cavitation emissions, is the transmitted signal detected by the PCD therefore directly indicative of bubble enhanced heating? Treatment feedback during HIFU application would greatly benefit if the inertial cavitation signal could provide information about the heating that is caused by bubble activity. The relationship between the pressure wave from the collapse and absorbed power density $q_{rad}$ was given in Eq. (2.39), and is manifested as an additional source term in the bioheat transfer equation:

$$\rho C \frac{dT(r,t)}{dt} = K \nabla^2 T(r,t) + q_{HIFU}(r) + q_{rad}(r,t)$$  \hspace{1cm} (3.8)

Here we must consider the drawbacks to cavitation detection highlighted in Section 3.4. It is not possible to measure the entire pressure wave, as the PCD has only a limited bandwidth and detection region, and the scattered HIFU pressure is present in the measured signal as well. The limited detection region is especially important when the second term of Eq. (3.8), the heat conduction, is considered. By only measuring a portion of the inertial cavitation signals it is not possible to account for conduction of heat away from the focal region or, possibly, heat into the PCD focal region from nearby undetected regions where inertial cavitation is occurring. Thus, a single-region measurement of the inertial cavitation cannot give an absolute temperature. However, if $q_{rad}$ is considered
over short durations where the conduction effects are small, the cavitation signal may still describe the instantaneous heating rate. Since we are only interested in the relationship between the bubble signal and the bubble heating, the primary field absorption can be accounted for by modeling the temperature field using the HIFU pressure field as an input, as described in Chapter 2, and subtracting that computed (bubble-free) temperature at the position of the thermocouple from the measured temperature over the duration of the experiment.

We assume a time \( \delta t \) that is short enough for us to ignore conduction and a sensing volume that is small enough so that the bubble enhanced absorbed power density can be considered uniform. The heat transfer equation describing the bubble-enhanced temperature field reduces to

\[
\rho C_t \frac{\partial T_b}{\partial t} = q_{\text{rad}}(r_{TC}, t), \tag{3.9}
\]

where

\[
T_b(t) = T_{TC}(t) - T_{HIFU}(t, x_{foc}, r_{TC}), \tag{3.10}
\]

\( T_{TC} \) is the measured thermocouple temperature, and \( T_{HIFU} \) is the temperature obtained from the FDTD solution to the bubble-free heat transfer equation at a position \( r_{TC} \), the position of the thermocouple. As mentioned in Section 3.3, the thermocouple was positioned 0.5 mm lateral to the HIFU focus for all the measurements in this thesis. The square of the RMS voltage from the PCD should give a signal that is proportional to radiated power incident on the receiver, which in turn is proportional to the radiated
power at the source, which in turn is proportional to the absorbed power density within
the PCD sensing volume. These relationships allowed Eq. (3.9) to be simplified to

\[
\frac{\partial T_b}{\partial t} \bigg|_{\text{P}} = A \cdot V_{\text{rms}}^2 \bigg|_{\text{P}} ,
\]

(3.11)

where \( A \) is a proportionality constant that includes a number of fixed parameters, such as \( \rho C_t \) and the unknown PCD calibration of the \( V_{\text{rms}} \) to the cavitation emission pressure, the absorption coefficient in the medium, the dimensions of the sensing volume, and so on.

The model assumption is simple; the thermal power that is deposited in the
sensing volume of the detector should be proportional to the mean square voltage at the
PCD. The question remains, is this proportionality consistent with experimental
observations? If so, then it might be possible to use noise diagnostics as a way to assess
in real time the rate of accelerated heating from cavitation, provided the PCD is suitably
calibrated (i.e. the \( A \) term in Eq. (3.11) is determined by measurement). While it does not
have the proper dimensions to be termed a power, the right side of Eq. (3.11) will be
referred to as the cavitation power for the sake of notational convenience.

By simply subtracting out primary absorption heating from HIFU we are
assuming that the HIFU pressure and heating effects remain constant over the course of
the experiment, and this is not necessarily the case. The phantom attenuation and sound
speed both change with temperature and will affect both the pressure and temperature.
However, these effects can be neglected since the attenuation dependence on temperature
at 1 MHz is small. Another potential complication is bubble shielding which may
develop over the course of sonication, as discussed in Sections 3.5 – 6. The development
of bubble shielding brings about the possibility that not only is the ultrasound energy not reaching the focus and post-focal region, but that the pre-focal pressure is higher due to the impedance mismatch from the changing effective medium. Without a calibrated pressure sensor in place it is not possible to compensate for a changing focal pressure in this situation, so we cannot necessarily know whether this is a critical factor.

One way to understand the impact of the bubble field on the focal pressure is by monitoring the HIFU driving pressure. Thomas et al. (Thomas CR 2005) noticed that the HIFU driving voltage fluctuated periodically about its initial voltage when bubbles appeared and a bubble front developed in the direction of the HIFU transducer in acrylamide phantoms. The fluctuation period correlated well with the velocity of the bubble field movement obtained from video analysis, suggesting that the voltage change was due to a changing impedance load on the transducer brought on by the presence of bubbles in the HIFU focus. While it is not as periodic, the HIFU voltage in the agar-graphite phantoms fluctuates as well; see Fig. 3.28 for plots of the time-dependent RMS level of the HIFU voltage observed in the presence of cavitation in the agar-graphite and acrylamide phantoms.

These fluctuations do not necessarily mirror the pressure change at the focus due to shielding, but they do describe the influence of the bubbles on the pressure output from the transducer. The impact of these source pressure fluctuations on primary absorption heating was investigated by factoring in the measured fluctuations into the HIFU power source term in the FDTD temperature simulation. The HIFU source term in Eq. (2.4) was multiplied by the square of the measured fluctuation about the mean voltage in time and
Figure 3.28: The HIFU CW driving voltage (converted from the measured RMS voltage) as a function of time for (a) an acrylamide and (b) agar-graphite phantom. The frequency in both cases was 1.1 MHz and the focal pressure amplitude was 6.86 MPa and 3.47 MPa for plots (a) and (b) respectively.

in this manner the simulated temperature field with and without the fluctuation was compared, as shown in Fig. 3.29. The impact is minimal, owing most likely to the fast timescale of the fluctuation, and can be neglected.

Figure 3.29: Computed temperature in an agar-graphite phantom (via the FDTD simulation) as a function of time for a constant source pressure and fluctuating source pressure. The constant focal pressure employed in this simulation was 3.47 MPa, and the exposure frequency was 1.1 MHz CW.
It is also important to consider the signal that the PCD is measuring and how it relates to the phenomena that we are trying to observe, especially in regards to the three main roles that attenuation plays here. When the bubble collapses and a pressure wave is emitted, part of the pressure will be absorbed and be converted to heat, and part of the pressure will propagate to the PCD and converted to the measured signal. Thus, the PCD signal does not directly indicate how much of the signal is absorbed, but rather the portion that is not absorbed. However, by working in a static, homogeneous medium we can assume that the detected pressure is related to the absorbed pressure, and thus can act as a proxy to detecting the enhanced heating.

A second complication in the measurement is the attenuation – frequency relationship, which carries two consequences. Not only are the higher frequencies that are measured by the PCD transducer more heavily attenuated than the lower frequencies, disproportionately reducing the signal with distance, but the energy in the higher frequencies is responsible for more heat production near the bubble. The loss of signal with frequency is not compensated by our real-time signal processing, as the RMS chip gives a relatively flat response with frequency. For a situation where the RMS signal is expected to describe the heating it may make more sense to design a PCD receiver that compensates for the change of attenuation with frequency; such a method would correlate more closely with energy deposition. Such a real-time solution that would require a stand-alone programmable signal processing chip equipped with FIR filters and a bandwidth extending to at least 20 MHz. Lastly, the attenuation has been shown to
depend on the temperature, in tissue as well as the phantoms used here. The impact of this factor will be discussed below.

3.7.2 Experimental Arrangement

To reiterate, we seek to establish that the PCD can be used as a non-invasive sensor of bubble-enhanced heating. The experimental arrangement is shown in Fig. 3.30. The procedure consisted of a 5.5-sec, 1.1 MHz CW exposure in the agar-graphite phantom in which the PCD $V_{rms}$, thermocouple voltage and HIFU $V_{rms}$ were simultaneously sampled at 2 kSamples/sec. The tip of the thermocouple was in the focal plane and displaced 0.5-mm off axis. A total of 41 experiments were performed for six focal pressure amplitudes (2, 2.5, 2.8, 3.3, 3.5, 4.2 MPa) in order to evaluate whether the cavitation heating efficacy changed with pressure. A fresh phantom was used for each measurement. A representative measurement of the PCD $V_{rms}$ and measured temperature is shown in Fig. 3.31, where $P_{foc} = 2.6$ MPa. The melting temperature of the phantom, 80 °C, and FDTD-simulated (no bubbles) temperature at the location of the thermocouple for the 2.6-MPa focal pressure are plotted as well. The measured temperature was much higher than that
Figure 3.31: Measurement of cavitation noise and temperature rise in the agar-graphite phantom at $P_{foc} = 2.6$ MPa. (a) Inertial cavitation signal recorded over the course of the measurement. (b) Temperature measured by the thermocouple and determined from the FDTD simulation. The dotted line in (b) indicates the approximate melting temperature of the phantom.

predicted from primary field absorption alone, and the phantom was heated to above the melting point in about 2.1 sec. The cavitation noise signal shows the familiar decreasing trend seen in Sections 3.5 – 6 but there is a sudden increase in cavitation activity at 1.5 sec after which the cavitation decreased again. The burst in cavitation activity is coincident with a sudden increase in temperature, yielding a much higher heating rate than any other point during the measurement. This sudden increase in cavitation and heating rate was a characteristic feature of our measurements in agar-graphite phantoms when a thermocouple was present. When a thermocouple was not present the cavitation noise and heating profiles remained relatively smooth, with no characteristic jumps. We suspect that this feature is the result of cavitation occurring directly on the tip of the thermocouple, as the thermocouple may act as a nucleation site.

To investigate further, we positioned a second PCD such that it was 2.5 mm post-focal, perpendicular to the HIFU axis. The thermocouple was positioned in the same
manner as before, coaxial with the HIFU beam and 0.5 mm lateral to the HIFU focus (see Fig. 3.30 for the thermocouple orientation). By positioning the second PCD 2.5 mm post-focal, the thermocouple sheath was present in the focal region of the second PCD. Figure 3.33 shows that the cavitation noise and temperature bursts occurred coincidently at the focus, but a noise burst followed later at the post-focal position. Next the thermocouple tip was drawn back away from the focus and its tip positioned 2.5 mm post-focally; at this point there is no thermocouple present in the HIFU focus. In this case, the post-focal PCD measurement showed a noise burst that was coincident with a transient increase in heating, however, there was no noise burst emanating from the HIFU focus.

The timing suggests that, in both experiments, a spurious burst of cavitation occurred at the thermocouple tip and this resulted in a concurrent increase in heating. However, in the first experiment, the bubble cloud appears to have “propagated” along the thermocouple sheath, utilizing the ready supply of nucleation sites either present on the imperfectly wetted surface of the thermocouple teflon sheath, or emanating from trapped gas emitted from the open end of the sheath. Indeed, video measurements of thermocouples embedded in acrylamide phantoms have clearly showed air trapped in the thermocouple sheath and that cavitation originated from these air pockets. It is also possible that the cavitation cloud could have migrated along the sheath in the second experiment, but in that case there was no “downstream” PCD positioned to sense the delayed noise burst.
The cavitation power (the RHS of Eq. 3.11) was compared to the rate of temperature rise (the LHS of Eq. 3.11) by first subtracting the predicted temperature from the primary field absorption from the measured temperature. The rate of temperature rise from the bubbles was then calculated over time steps of $\delta t = 20$ ms, during which we assume that the conduction effects are appreciably small. The timescale over which conduction effects become important will be discussed below. The cavitation power was determined by squaring the PCD RMS voltage and computing the average of the mean square voltage over each 20 ms step. In general we noticed that the features similar to the cavitation and temperature measurements, such as the nucleation burst on the thermocouple tip, occurred slightly earlier in the cavitation signal (~100 - 200 ms), suggesting that the temperature rise from the absorption of the cavitation emission takes time. For this reason the $V_{rms}^2$ and $dT_b/dt$ measurements were shifted by 100 ms when the fit was compared. The possible cause of this time difference will be discussed below.

Our hypothesis is that the cavitation power is proportional to the bubble temperature rise, as shown in Eq. (3.11). The unknown proportionality constant, $A$, was obtained via a least-squared error (LSE) linear fit between the cavitation power and the rate of temperature rise. $A$ is assumed to be constant over the course of the measurement but three factors will limit the region where the cavitation noise and bubble heating relationship can be expected to remain valid. First, our assumption of negligible conduction sets the timescale over which conduction losses to cooler regions are small. This limit is the thermal diffusion time, given by $t_\alpha = L_\alpha^2/\alpha$, where $L_\alpha$ is the relevant length over which the temperature gradient will cause significant heat loss and $\alpha$ is the
thermal diffusivity in the phantom. For situations where the primary absorption is the chief heat source $L_α$ should be the -6 dB focal radius. In our case where inertial cavitation is the chief heat source, $L_α$ is the ‘cavitation-zone radius’, the radial distance from the HIFU axis at the focus to the position which corresponds to the cavitation threshold, beyond which bubble-assisted heating is not a factor. Table 3.3 shows the lengths and diffusion times for the pressures used here; our 20 ms processing time-step falls well within these times.

<table>
<thead>
<tr>
<th>$P_{foc}$ (MPa)</th>
<th>2</th>
<th>2.5</th>
<th>2.8</th>
<th>3.3</th>
<th>3.5</th>
<th>4.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_α$ (mm)</td>
<td>0.52</td>
<td>0.75</td>
<td>0.84</td>
<td>0.93</td>
<td>0.97</td>
<td>1.04</td>
</tr>
<tr>
<td>$t_α$ (s)</td>
<td>1.71</td>
<td>3.56</td>
<td>4.47</td>
<td>5.47</td>
<td>5.89</td>
<td>6.87</td>
</tr>
</tbody>
</table>

Table 3.3: Parameters involved in the thermal diffusion time.

The second limiting factor is the time that the temperature at the focus reaches the melting temperature $T = 80^\circ$C in the phantom. Not only is the melted region poised to boil, the physical properties have likely changed and bulk movement is possible, leading to possible contributions from convective heat transfer. The third limit is the time that the thermocouple nucleation event occurs (if it occurs at all). Figure 3.32 shows that the thermocouple is more sensitive to the nucleation event than the PCD, so while there will be a general agreement between cavitation power and rate of temperature rise, the relationship will break down when the nucleation event occurs.

Another factor to consider in the proportionality of cavitation power and rate of temperature rise is the uncertainty of the bubble cloud position relative to both the thermocouple tip and PCD focus. The thermocouple tip is always positioned 0.5 mm lateral to the HIFU focus, which means that it is located in the PCD prefocal region.
If the bubble cloud is generated in the PCD postfocal region, the temperature rise will be lower than if the bubble cloud were located next to the thermocouple. The difference in attenuation over the distances considered in this scenario will be minimal, so the cavitation power is not likely to be appreciably reduced from this effect, although the thermocouple could shield bubble emissions originating from the distal side of the thermocouple relative to the PCD. The location of the bubble cloud relative to the thermocouple could also explain the 100 – 200 ms time delay between cavitation power and rate of temperature rise described above. Thermal diffusion over this time corresponds to a distance of 125 – 178 µm, which is in the ballpark for the distance from the edge of a bubble cloud centered at the focus to the thermocouple.

In light of these concerns, the proportionality constant $A$ was initially obtained from each experimental run using 2 different protocols. Firstly, we considered the worst-
case scenario by assuming Eq. (3.11) held for the duration of the exposure. The resulting value for \( A_1 \) was thus based on an LSE fit to the entire data stream. For the second scenario we fit only the data corresponding to the time interval starting with \( t(T=40 \, ^\circ C) \) and leading up to the lowest limiting time based on the three aforementioned criteria: diffusion time; melting time; thermocouple tip nucleation time. The constant \( A_2 \) was extracted from the LSE fit taken over this interval. The basis of comparing the fit for \( A_2 \) starting at \( t(T=40 \, ^\circ C) \) will be described below.

Three examples of the cavitation power and bubble temperature rise are shown in Figs. 3.33-35 for \( P_{\text{foc}} = 2, 2.6 \) and 3.3 MPa, respectively. The fit used in the comparison plots (c) in each figure corresponds to \( A_1 = 299 \), which is the average of \( A_1 \) from all 41 experiments run. The two vertical arrows in each comparison plot indicates the times over which \( A_2 \) was analyzed. The cavitation power shows general agreement with the

![Figure 3.33](image)

Figure 3.33: Comparison of heating rates and cavitation powers in an agar-graphite phantom for 5.5 sec CW exposures at 1.1 MHz and \( P_{\text{foc}} = 2 \) MPa. (a) Inertial cavitation noise measured by the PCD. (b) Measured and predicted (no bubbles) temperature rise 0.5 mm lateral to the focus. (c) Bubble-generated heating rate and cavitation power.
Figure 3.34: Comparison of heating rates and cavitation powers in an agar-graphite phantom for 5.5 sec CW exposures at 1.1 MHz and $P_{foc} = 2.6$ MPa. (a) Inertial cavitation noise measured by the PCD. (b) Measured and predicted (no bubbles) temperature rise 0.5 mm lateral to the focus. (c) Bubble-generated heating rate and cavitation power.

Figure 3.35: Comparison of heating rates and cavitation powers in an agar-graphite phantom for 5.5 sec CW exposures at 1.1 MHz and $P_{foc} = 3.3$ MPa. (a) Inertial cavitation noise measured by the PCD. (b) Measured and predicted (no bubbles) temperature rise 0.5 mm lateral to the focus. (c) Bubble-generated heating rate and cavitation power.
temperature rise for the portion that lies between $T_{TC} \sim 40$ °C and the onset of the “thermocouple cavitation” burst (which did not occur in the 2-MPa measurement). In all of the measurements where the thermocouple nucleation occurred, the temperature rise during the cavitation burst was always higher than the corresponding cavitation power, which further suggests that it is a very localized phenomenon and not necessarily representative of the heating that is occurring in the general region. The temperature rise during the cavitation burst also appeared to have the greatest amplitude when it occurred at lower temperatures, which corroborates with the modeling results of Section 2.5; a higher ambient temperature will suppress the collapse and ensuing heating effects.

The agreement universally suffers at the lower temperatures ($T_{amb} < T < 40$ °C), which also happens to be the startup portion of the measurement, lasting approximately 0.5 sec. Note that in all the data sets, the initial rate of temperature increase was less than expected given the initial level of cavitation power (undershoot). This was then followed by a brief period where the heating rate exceeded that predicted by the cavitation power (overshoot). A number of effects that are unique to this temperature range and time period could explain the disagreement. The phantom characterization revealed that the attenuation is strongly affected by temperature, especially at the higher frequencies that were investigated. The attenuation is lower at the start of the measurement, resulting in less heating to go along with a relatively-high amplitude cavitation signal – leading to undershoot. Attenuation increases with temperature, thus increasing the heating and reducing the detected emissions – resulting in overshoot.
Another factor to consider is the viscous heating artifact on the thermocouple tip, a prompt effect that will elevate the measured temperature by a fixed amount depending on the pressure amplitude. We had hoped to characterize the viscous heating artifact in the phantoms by suppressing cavitation via a pressure chamber and comparing the measured temperature to the model-predicted temperature; however equipment and time restraints prevented this measurement from getting realized. This supplemental heating could explain the over-prediction of the heating rate in the overshoot region, but it is completely inconsistent with the observed undershoot. Realistically, the viscous heating artifact has generally resulted in temperature elevations on the order of a few degrees, so its overall impact relative to the rate of temperature rise is likely to be small. In addition, the artifact is reduced when the thermocouple is positioned parallel to the sound field axis and slightly off the focus, such as we have in our setup.

A third effect is the evolution of the equilibrium bubble size and number of bubbles, also a transient effect. Yang et al. (Yang 2004) showed that 1-MHz CW sound can drive the evolution of the bubble field to a relatively mono-disperse size over a short timescale (~10 ms), where micron-sized bubbles in a low-viscosity medium (~0.001 – 0.01 Pa.sec) are bounded by the instability threshold. Evolution of the ensemble equilibrium size is a transient effect that will impact the relationship between the cavitation signals which are detected and rate of temperature rise over this period. Formation of a bubble cloud will increase multiple bubble scattering and will act to shield the emissions that radiate out to the PCD. Re-radiated sound in the cloud will also increase the heat generation, as more of the sound is locally absorbed, rather than radiated.
out of the sensing area of the thermocouple. Over the evolution period, the combination of these effects will result in increased heating and reduced cavitation power, leading to an overshoot. However, the timescale for this process is too fast to fully explain the disagreement observed in the data, which ranges between 300 – 500 ms.

The disagreement in the comparison between cavitation power and rate of temperature rise in the initial period of the measurement is not fully explained by these three effects and it is likely that they all contribute to some degree. In light of these three effects and the initial disagreement in the curves, the analysis for \( A_2 \) was chosen to start at \( t(T=40 \ ^\circ C) \), the region where we can expect to avoid such effects.

While the cavitation power generally agrees with the rate of temperature rise when an ensemble average of \( A_1 \) is used, Fig. 3.36 shows that \( A_1 \), when plotted against the focal pressure for each individual measurement, varies considerably (note that the voltage output of the power amplifier in response to the function generator voltage was not always repeatable from run-to-run, so the same driving pressure was not always

![Figure 3.36](image)

**Figure 3.36:** The cavitation power proportionality constant \( A_1 \) (\( R^2 = 0.11 \)) determined from the least-squared error fit for each of the data runs, plotted as a function of focal pressure.
obtained, hence the deviation in pressure). The proportionality relationship is particularly scattered at 3.5 MPa, and to a lesser degree at 3.3 MPa, where there appears to be a bifurcation in the value of \( A_1 \). Overall, \( A_1 \) appears to decrease at higher focal pressures, suggesting that inertial cavitation is not as effective at higher pressures.

Figure 3.37 shows \( A_1 \) and \( A_2 \) when the data is binned (±100 kPa) about the six pressures and the average constant at the binned pressures is used to generate a fit of \( A_n \) with pressure. The fits corresponded to \( A_1 = -90.5 \times P_{foc} + 608 \) and \( A_2 = -57.9 \times P_{foc} + 470 \). Analysis of the rate of temperature rise and cavitation power over the shorter, restricted duration results in a lower overall amplitude for the fit, mostly due to the absence of the thermocouple nucleation effects in the data, and with the exception of the data at 3.3 MPa, the data agree more closely with an overall linear decreasing trend with
pressure. The data are not strictly linear with pressure, so while it may not be valid to hold the proportionality relationship to such a fit, the trend is nonetheless present.

The overall validity of $A_1$ and $A_2$ was evaluated by comparing the error in the difference of the fit, defined as

$$E_n(t) = \left. \frac{dT_b}{dt} \right| - A_n \cdot V_{\text{rms}}^2(t).$$

(3.12)

The total errors were evaluated for three cases for $A_n$: the $A_n$ for each individual measurement, the mean $A_n$ across all of the measurements, and the $A_n$ from the pressure-weighted fit. The total error for each measurement was averaged to determine both the mean difference, such that $E_{\text{avg},n} = <E_n(t)>_t$, and the mean absolute difference, such that $E_{\text{avg},n} = <|E_n(t)|>_t$. Finally, the average error for each measurement was binned for the six focal pressures. The error for $A_1$ and $A_2$ from the pressure-weighted fit is shown in Fig. 3.38. The mean difference was generally negative, suggesting that the cavitation power overestimated the temperature rise. The agreement is better at the lower pressures for both comparison timescales and is generally within $\sim 5$ °C/sec. The absolute difference is included to demonstrate that while the mean difference for $A_1$ appears to be better at some pressures than for $A_2$, the mean difference can be misleading due to fluctuation in the actual difference and that the overall error is lower in the partial measurement comparison case $A_2$. When the error is compared to that of the individual and mean fits, the pressure-weighted fit is slightly better than the mean fit, as expected, while the individual fit error is understandably the best, particularly at 4.2 MPa.
Figure 3.38: Mean and absolute difference in the bubble-generated temperature rise and cavitation power as a function of focal pressure for (a) $A_1$ and (b) $A_2$, both of which were derived from the pressure weighted fits, Fig. 3.37. The vertical error bars represent the standard deviation for the differences at each particular pressure. The horizontal error bars represent the standard deviation of the focal pressures.

A number of measurements exhibited errors due to periodic fluctuations in the agreement between cavitation power and rate of temperature rise. One such example is shown in Fig. 3.39, where the focal pressure was 3.56 MPa. From 0.5–1.2 sec, the rate of temperature change fluctuates, rather than changing smoothly as seen in Figs. 3.33–35. The cavitation power shows similar fluctuation around 0.7 sec but nonetheless does not agree perfectly. Here it is possible that the bubble field is located very close to the thermocouple so that cavitation is occurring on the thermocouple tip, and the thermocouple shields some of the cavitation signals. Aside from uncertainty in the location of the bubble field relative to the thermocouple tip, other sources of error include conduction loss, the temperature dependence of attenuation, the alignment of the PCD
Figure 3.39: Comparison of heating rates and cavitation powers in an agar-graphite phantom for 5.5 sec CW exposures at 1.1 MHz and $P_{foc} = 3.56$ MPa. (a) Inertial cavitation noise measured by the PCD. (b) Measured and predicted (no bubbles) temperature rise. (c) Bubble-generated heating rate and cavitation power. Note the large fluctuation in the heating rate about 1.2 sec into the exposure.

and thermocouple relative to the HIFU source as well as each other, and differences in the phantom properties between different batches.

The cavitation power cannot account for all of the heating that occurs during HIFU application, especially when effects from conduction, or perfusion, if present, are particularly strong, and nor can it predict the absolute temperature in the sensing region. (Keep in mind that neither conduction nor perfusion is present in Eq. (3.9).) However, it does appear to be proportional to the rate of temperature rise when the HIFU heating is accounted for and when nonlinear effects are small, as appears to be the case for the pressures employed in the agar-graphite phantoms. Most of the errors shown in Fig. 3.38 are negative, suggesting that the cavitation power over-predicts the rate of temperature rise.
3.8 Dynamic Dip

In the process of performing the cavitation-assisted heating experiments an interesting trend was observed. We expected that the cavitation signal levels and heating rates would increase as the focal pressure increased but instead the cavitation noise amplitude and the temperature both exhibited decreased amplitude at 3.5 MPa, before subsequently increasing in amplitude at 4.2 MPa. The trend was exhibited through the first second of the insonation, as shown in Fig. 3.40, where the PCD $V_{rms}$ and bubble temperature rise at 1 sec are plotted against the driving pressure. The local ‘dip’ in amplitude is weak, but the effect has been observed in numerous other experiments and was previously documented by Holt and Roy (Holt 2001) in experiments employing similar phantoms (see Fig. 3.41).
The cause of this curious phenomenon was investigated further by modeling the effect of pressure on the dynamics of an air bubble in a Newtonian compressible fluid using the Prosperetti models detailed in Section 2.4.3. The driving pressure was increased for a range of equilibrium bubble sizes and medium viscosities and the power deposition from viscous damping and the maximum radiated power was evaluated. The driving frequency was 1 MHz and the driving pressure was incremented in 0.2 MPa steps from 1.5 – 5.1 MPa. All of the properties of the fluid were that of water at $T = 20 \, ^\circ\text{C}$ ($c = 1482.3$ m/s; $\rho = 998$ kg/m$^3$; $\sigma = 0.073$ N/m), with the exception of viscosity, which was

![Figure 3.41: Published cavitation enhanced heating data from Holt and Roy (Holt 2001) as a function of pressure in an agar-graphite phantom similar to the one employed in this thesis. This is the total measured temperature rise; no attempt was made to subtract out the contribution of thermoviscous absorption of the primary HIFU field. TCA and TCB are the temperatures at the given distance from the acoustic axis. (a) Temperature rise for a 0.7 sec insonation. (b) Temperature rise for a 1.2 sec insonation.](image)
varied from 0.001 – 0.01 Pa.sec. The result at $\mu = 0.002$ Pa.sec is shown in Fig. 3.42.

Two distinguishing features are evident in the plots. First, a trend similar to the experimental results was inherent in the small viscosity range that spans that of water and blood (0.001 and 0.005 Pa.sec, respectively). Both the viscous power deposition and the radiated sound power initially increased with pressure, experienced a dip and continued to increase thereafter. The location of the dip shifted to higher pressures as the bubble size decreased. In particular, the trend for the 300-nm bubble is most similar to the experimental trend. The second feature is the difference in amplitude between the two power mechanisms. The radiated power is several times greater than that of the viscous damping as expected, due to the low viscosity. However, the dip is not evident

Figure 3.42: (a) Viscous and (b) maximum radiated power as a function of pressure generated from a single air bubble in a Newtonian viscous fluid, where $\mu = 0.002$ Pa.sec. The equilibrium radius ranged from 100 – 900 nm in 200 nm increments. The results for the 300 nm bubble, shown by the arrow, mirror most closely our experimental results.
for the same range of pressures at larger viscosities and bubble sizes where the viscous damping power is dominant.

Examination of the bubble motion indicates that nonlinear effects and the bubble growth time play a major role in the trend. Figures 3.43–44 shows the curves for the 300-nm-radius bubble as well as the radiated pressure at a range of 1 mm for some of the driving pressures used in the measurements. As the driving pressure is increased, the expansion ratio increases, causing the growth time to increase and the start-time for the collapse to be retarded later and later into the acoustic cycle. If this retardation is long enough, then the sound field enters its rarefaction phase before the bubble has had a chance to fully collapse and serves to arrest the inward motion, reducing maximum collapse velocity and acceleration. This effect is most pronounced at 3.5 MPa, the location of the dip in Figs. 3.40 and 3.42. It is also evident in computed radiated pressure amplitude (Fig. 3.44), which is clearly diminished for the bubble driven at 3.5 MPa. The

Figure 3.43: Normalized radius ($R_{\text{max}}/R_0$) for a 300-nm radius air bubble in a Newtonian viscous fluid at (a) 2, (b) 2.8, (c) 3.5 and (d) 4.2 MPa. The physical parameters were the same as those employed in Fig. 3.42.
decreased emission level and heating at 3.5 MPa is not apparent by $t = 2$ sec in the measurements, which may explain why the same effect is not apparent in the pressure

dependence of the cavitation power and bubble temperature rise in Figs. 3.36 – 37.

The trend exhibited in Fig. 3.42 is clearly dependent on the equilibrium size of the bubble and suggests that many of the bubbles present at the 1 sec point of the 3.5 MPa exposures possessed equilibrium sizes on the order of 300 nm. It is unrealistic to assume that the in vitro bubble population will maintain a constant equilibrium size but an upper bound on the bubble size distribution is plausible owing to surface instabilities that set in at a critical equilibrium radius and cause bubbles to break up (Wu 2006). Add to this the fact the lower limit in size is set by the Blake radius, and the net effect is a narrowing of the bubble size distribution during and immediately after HIFU exposure.

It is interesting to note that the pressure effect demonstrated in Fig. 3.41 provides further evidence the enhanced heating effects are due to inertial cavitation, since the dip

![Figure 3.44: Radiated pressure at a range of 1 mm from the bubble for a 300-nm radius air bubble in a Newtonian viscous fluid forced at (a) 2, (b) 2.8, (c) 3.5 and (d) 4.2 MPa. The parameters employed in the simulation are the same as those employed in Fig. 3.43.](image)
in the response evident at 3.5 MPa is predicted by the bubble dynamics governing small bubbles and low viscosities (*i.e.* inertial cavitation) but not for large bubbles and high viscosities. Most likely, the absorption of broadband radiated pressure is the dominant heating mechanism in our phantoms and the bubbles generating the effect are likely sub-micron in size and behave as if the gel medium possessed a viscosity similar to water or blood.

### 3.9 Summary

Sections 3.1 to 3.4 described the setup and characterization of the HIFU source, PCD system, temperature sensing setup and the phantoms. The suite of experiments presented in this Chapter were intended to better understand the relationship between cavitation noise emissions and bubble-assisted heating and the factors that impact the generation and interpretation of cavitation signals. In general, the cavitation signal decreases over time, due in part to prefocal bubble shielding as well as the temperature effects described in Chapter 2. Pulsing the HIFU resulted in a steady cavitation signal over time, suggesting that adequate time between sound bursts allows shielding conditions to subside. The cavitation signals were found to correlate to the bubble-assisted heating rates, providing the possibility of monitoring HIFU heating rates non-invasively through cavitation noise diagnostics. Finally, the pressure dependence of the cavitation signal and bubble temperature rise corresponds to trends in the bubble dynamics indicating that the radiated pressure from inertially-collapsing submicron bubbles is the dominant heating mechanism.
Chapter 4
PASSIVE DETECTION OF BUBBLE ACTIVITY WITH A DIAGNOSTIC ULTRASOUND SYSTEM

Overview

As mentioned in Chapter 1, one of the limitations of passive cavitation detection is the small detection volume as the technique typically employs a tightly focused single-element transducer. Section 3.6 reported on the use of two transducers to detect cavitation at multiple positions throughout the HIFU focal region. This approach shed light on bubble shielding effects but the setup only provided discrete monitoring regions and would be cumbersome to implement clinically. In order to improve inertial cavitation and boiling detection to provide better visualization for bubble dynamics, we sought to develop a tool that combined the spatial coverage of a diagnostic ultrasound scanning system with a PCD’s ability to sense stable and inertial cavitation through passive noise diagnostics.

Most diagnostic ultrasound systems achieve real-time feedback by only providing an extensively processed, compressed grey scale video output of the B-mode image, resulting in a loss of the raw radiofrequency (RF) signal from which the image was generated. Without the RF signal, frequency analysis cannot be performed to definitively determine the presence and dynamics of cavitation. The Terason 2000 Ultrasound System (Teratech Corp., Burlington, MA), however, does enable acquisition of the beamformed RF signals from which the B-mode images are generated. This Chapter details our attempt at using the RF output from a Terason 2000 system to provide a
spatially and temporally resolved post-treatment (i.e. off line) detector of inertial and
stable cavitation over a large region of tissue phantom material.

This Chapter was originally written as a stand alone manuscript for publication
and has been adapted for the thesis. It is organized into four main sections. The Terason
system is characterized in the first section, particularly with regards to evaluating how the
Terason system signal processing affects the RF signals. The second section describes
the signal processing techniques used to isolate inertial and stable cavitation signals.
Results from the application of these techniques to measurements of agar-graphite
phantoms are shown in Section 3 and a discussion follows in Section 4.

4.1 Terason System Characterization

Measurements described in this chapter were performed using the experimental
arrangement shown in Fig. 4.1. The setup is similar to that used in Section 3.7 with the

Figure 4.1: Experimental arrangement used in the Terason cavitation noise imaging experiments.
The PCD signal was passed through a 50-Ohm power splitter (ZSC 2-2B, Mini-Circuits Lab., NY). One output was directed through a variable attenuator, amplified and filtered by a passive 5 MHz high-pass filter in order to remove the main HIFU energy from the signal, as described in Chapter 3. The signal was sent to a broadband RMS-DC converter and acquired with the signal conditioning unit and data acquisition board also described in Chapter 3. This signal provided a measurement of the broadband inertial cavitation signal from the HIFU focus along with any higher harmonics from the scattered HIFU field as well as ultra-harmonics from stable cavitation; the broadband noise dominates this signal. The other output from the RF power splitter was passed through an analog 1.1-MHz band-reject filter (Allen Avionics) to remove the fundamental HIFU signal. The signal was sampled with a 14-bit oscilloscope board (CompuScope 14100, Gage Corp., Lockport, IN) at 25 MSamples/sec and 5 kSamples per acquisition. The analysis and results from the PCD waveforms will be presented in Chapter 5 for comparison of agar-graphite phantom and beef liver measurements.

The Terason was operated using their 10L5 broad band linear array transducer (128 elements, 38 mm aperture) and the Terason system software. The linear transducer array was aligned parallel to the HIFU transducer axis such that the center element of the array was positioned above the HIFU focus using the same brass target employed for the PCD alignment. The system employs a 64-channel beamformer and the resulting image frame consisted of 128 lines. The number of data points in an given RF line is
determined by the depth of field that is set for the imager and the sound speed. The system assumes a single sound speed for the entire imaging field, the settings of which will be discussed below. The depth of field and transmit center frequency depend on the ‘T-shirt’ setting in the acquisition software. Here, the ‘middle T-shirt’ setting was employed to provide an 8 cm depth of field, resulting in a center frequency of 5.8 MHz for the transmit frequency. The transducer has an optional ECG connection that offers the possibility of obtaining a trigger from the system. We did not possess the necessary hardware to obtain the ECG signal so an absolute timebase for the data acquisition relative to the thermocouple data was not possible. A relative timebase was established by monitoring the presence of the HIFU signal present in the Terason RF signal and B-mode image, since all HIFU sonications were 5.1 sec in duration and the Terason signal clearly showed when the sonication started and ended. RF signals were obtained following sonication by converting the proprietary signal data format to a Matlab format using the Ult2matlab_Bmode software package provided by the manufacturer.

A number of changes to the default image acquisition setup were necessitated in order to obtain the bubble noise signals. Many of these changes were made possible through use of an Advanced Tools software package obtained from the manufacturer, providing greater control over system operation. Specifically, it allowed changes to the transmit/receive modes, assumed sound speed, frame rate and acquisition buffer, focal number, system noise subtraction, absolute time gain compensation (TGC) levels, and apodization window type. These changes will be detailed below. It should be noted that not all of the functions in the Advanced Tools software were operational. Further, the
Terason system is a proprietary system, making it difficult to know exactly how the signals were processed in the software.

Several of the changes that we employed to the Terason software were unique to our measurement and differed from the normal mode of operation for a diagnostic ultrasound system. In particular, we were interested in only listening to the bubble signals, to emulate passive cavitation detection and not active cavitation detection. The software allows for the transmit capability of the array to be disabled, such that the transmit voltage was 0 V. It was not possible to simply reduce the transmit signal voltage, unless it was turned off altogether. By disabling the transmit signal the array was essentially a passive receiver, thus increasing the sensitivity of the array to the bubble signals. All measurements during sonication were conducted with the transmit signal disabled. Following sonication, the transmit signal was enabled and a B-mode image was acquired to detect the hyperechogenic region. Sound speed was set to that of the tank water, adjusted for temperature. The frame rate was set to 15 Hz and the acquisition duration was set to 6.5 sec. While the maximum possible frame rate was 48 Hz, it was found that resulting file sizes for the acquisition duration employed using rates higher than 15 Hz were difficult to process in Matlab. The receive focal number was set to 1.

Separate from the transmit signals, the Terason system itself is a source of electrical noise which fluctuates slightly over time, and would appear in the B-mode image were it not accounted for. This is achieved via an automated reference frame subtraction process. In this process, the transmit signal is turned off and the resulting
signal acquired in receive mode is used as a measurement of the electrical noise; the image resulting from this noise signal is referred to as the reference frame. Fluctuation in the noise is compensated for by obtaining a new reference frame every minute, resulting in a single ‘dropped’ frame in the B-mode image every time the reference frame is acquired. The impact of noise on the image is apparent when the reference frame subtraction setting is turned off and when no other high-frequency noise sources are present in the measurement setup. Figure 4.2 shows an example of a reference frame,

![Figure 4.2: A typical Terason “reference frame,” which is a B-mode image of the Terason system noise obtained when the transmit signal level is set to zero.](image)

where the transmit signal was turned off and TGC levels were constant with depth. Although the concept of noise subtraction is certainly useful when trying to detect small levels of broad band cavitation noise, the fact that the Terason updated the reference frame every minute proved to be quite problematic. This is because there was no way to know when the new reference frame was acquired and sometimes the Terason sought to
update the reference frame while the bubble noise was present. In subsequent frames, the Terason would be subtracting the very noise we sought to image! This problem was circumvented by turning the reference frame subtraction mode off and acquiring a reference frame before each experiment, at which point the HIFU source was off (i.e., the system electrical noise was present in all measurements). The system noise was subsequently removed from the data in post-processing by subtracting the reference frame RF signals from the RF signals in each measured frame.

The receive frequency response of the system was determined by operating the system in pulse-echo mode and reflecting the transmit signal off a water-air interface separated by a thin plastic membrane (CVS plastic wrap) in the HIFU water tank. A calibrated capsule hydrophone (HGL-0200, Onda Corp., Sunnyvale, CA) was placed in front of the Terason transducer to measure the transmit waveform, which was digitized by an 8-bit digital oscilloscope (LT264, LeCroy, Chestnut Ridge, NY) and transferred to a PC via GPIB. The Terason RF echo signal and the hydrophone signal were windowed using a Hanning window and a FFT was performed to obtain the magnitude spectra of the transmit pulse (hydrophone) and the transmit/receive pulse (Terason). The hydrophone signal was corrected for its own frequency response, which changed slightly over the frequency range. The magnitude transforms of the Terason echo and hydrophone spectra are shown in Fig. 4.3. The transmit spectra measured by the hydrophone indicates that the transmit energy is centered around 5.8 MHz, while the backscattered signal measured by the Terason peaks at 5.2 MHz. This shift is attributed to the receive characteristics of the Terason system, which include transducer response and beamforming effects.
Figure 4.3: a) The magnitude spectrum of the received echo from an air-water interface generated using the Terason 10L5 transducer. b) The magnitude spectrum of the transmit signal from the Terason 10L5 transducer, as measured by an Onda hydrophone. Note that the signal is centered around 5.8 MHz, whereas the signal in (a) is centered around 5.2 MHz.

The Terason amplitude response on receive was subsequently obtained by dividing the Terason spectrum by the hydrophone spectrum and normalizing the result, as depicted in Fig. 4.4. Here we employed a Wiener filter to prevent false singularities from appearing at off-resonance nulls (Oppenheim 1978). The value of $\epsilon$ for the filter was based on the noise amplitude in the hydrophone signal and was increased until the singularities were reduced. The process was guided by maintaining the relative change of
the 5.2 MHz peak amplitude to the -6-dB bandwidth and the amplitude at the nulls, at 3.2
and 7.8 MHz, to ensure the characteristics of the main response peak at 5.8 MHz were
preserved. The receive response shows peak sensitivity at 5.2 MHz but also indicates
sensitivity to signals centered around 1 and 2.3 MHz.

By operating in passive mode and positioning the Terason transducer array
parallel to the HIFU axis we generate 2-D images such that the HIFU axis resides in the
image plane in a constant distance from the imaging scan head. Therefore, the HIFU
acoustic axis occupies a line in space corresponding to a straight “horizontal” line in the
images to follow. We expected the Terason transducer would be sensitive to three types
of signals. The first signal comes from the HIFU fundamental frequency and harmonics
that are scattered by graphite particles in the phantom and stable cavitation and boiling
vapor bubbles formed during sonication, particularly at elevated temperatures.
Reverberation off of other structures present in the tank as well as direct propagation of
the HIFU signal are also likely to be detected. The second signal comes from sub- and
super-harmonic emissions generated from stable cavitation (although the sensitivity of
the array at the HIFU sub-harmonic frequency was quite low). The third signal will come
from broad band acoustic emissions generated by inertial bubble collapses. Inertial
cavitation is most likely to occur along the HIFU axis where the pressure is highest in
amplitude. The -6-dB focal radius of the HIFU source is 1.8 mm, so the radial extent of
cavitation relative to the HIFU axis is likely to be relatively low, depending on the source
pressure, compared to the Terason imaging depth. Thus, inertial cavitation noise is most
likely to be produced along a fairly narrow line which is a constant distance from the scan head. For this reason, the TGC levels were set to be constant for the entire depth of field. It was not possible to disable all of the signal processing utilized by the Terason software, so it was important to understand how the Terason system affected the inertial cavitation signals in regards to apodization, receive focusing, beamforming effects, and signal sensitivity with respect to lateral position. To investigate these effects a needle hydrophone (Dapco, Ridgefield, CT) was used to simulate a point source, similar to the radiated signal from inertially-collapsing bubbles. The hydrophone was positioned opposite of the Terason transducer, in line and 6 cm from the center element, and was driven continuously at 3 MHz by a function generator (33120A, Agilent Technologies) with the Terason array set in receive mode. The Terason Advanced Tools menu offers a number of apodization options (see Section 7.5 in Szabo (Szabo 2004) for differences in image clarity based on apodization). The Hanning, Hann and Rectangular window settings were compared based on apparent signal width. The B-mode images are compared in Fig. 4.5; the Hann window image is not shown due to similarity to the Hanning window image. The main differences were that the Hanning and Hann windows resulted in a slightly longer region of constant signal amplitude, while the Rectangular window resulted in the narrowest beamwidth. In order to improve lateral resolution we decided to use the flat weighting that the Rectangular window provided.

To examine the effects of receive focusing, the hydrophone was positioned opposite of the center array element and was moved in 0.5-cm increments towards the Terason array over a distance of 7 – 1 cm from the array. The signal measured by the
Figure 4.5: B-mode image of the 3 MHz CW needle hydrophone signal using the a) Hanning and b) Rectangular window settings for the apodization in passive mode.

Terason was acquired at each position. The peak amplitude of the center element RF line acquired for each position was multiplied by the respective distance from the array to account for signal spreading. The result is plotted as a function of distance in Fig. 4.6.

Figure 4.6: Peak amplitude of the received Terason RF signal from the needle hydrophone (3 MHz CW) as a function of distance, accounting for spherical spreading from the source.
The signal amplitude increased as the hydrophone was positioned further from the array, until about 4.5 cm, where the signal amplitude leveled off. There is some variation in signal amplitude from 4.5 – 7 cm but the variation is less than 3% and may be due to fluctuation in signal output from the needle hydrophone. The increase in amplitude with distance is most likely due to a dependence of focal gain on distance. Focal gain in arrays typically increases with distance, as the number of elements used to receive the signals increases for signals originating further from the array, increasing the size of the aperture (Szabo 2004). Beyond a certain distance all of the elements will be utilized and gain will no longer increase with distance. Thus, the setup was aligned such that the Terason array was positioned 6 cm from HIFU axis in order to avoid the region where the gain decreased and to ensure that the Terason transducer did not interfere with the HIFU pressure field and phantom.

Next we investigated the impact of beamforming effects on the RF signals. The hydrophone was positioned 6 cm from the Terason transducer and moved in 1-mm increments parallel to the Terason transducer array to investigate how the signal changed with respect to lateral position. Again, the hydrophone was driven continuously at 3 MHz at a constant signal amplitude and the array was operated in passive mode. Here we were interested in examining two aspects of the received signal. First, even though the hydrophone signal was located at a constant position and the array was operated in receive mode, the receive signal amplitude was not constant over time, an effect attributed to beamforming processing. It was therefore important to determine the extent of the signal amplitude that was constant in time to avoid changes in signal amplitude due
to beamforming effects and not actual signal fluctuations. Second, it was expected that the beamforming would employ fewer elements near the outer edges of the element array, causing a decrease in signal amplitude. We identified the regions over which these two effects were apparent by first determining the maximum signal amplitude for the RF line that corresponded to each lateral position. The signal was inspected for the region over which the amplitude was within 10% of the maximum amplitude, thus determining a region where the signal was more or less constant. It was found that the signal amplitude was relatively constant from 56.6 to 73 mm from the Terason transducer and from -13 to +12 mm relative to the center element (0 mm) for the lateral position. The cavitation signals were analyzed over this region.

The effect of TGC gain on the integrity of the received signals was evaluated in order to avoid clipping the signal with too much gain or compressing the dynamic range of the detector by utilizing too little gain. It was found that a TGC gain of 20 dB maximized signal dynamic range while avoiding clipping. This value was determined by observing the signal scattered by a 3.18-mm diameter brass sphere exposed to HIFU insonation at levels required to generate scattered signals with amplitudes comparable to inertial cavitation noise emissions.

4.2 Signal Processing

The Terason data were analyzed for two types of signals as a function of position and time. The first signal which we sought to measure was the broadband emissions from inertial cavitation. Based on the trends seen in cavitation measurements in Chapter 3 the
broadband energy was expected to decrease as the tissue phantom heats up. The second was the signal generated by stable cavitation bubbles (sub-harmonic and ultra-harmonics) and scattering of harmonics of the HIFU field off of stable cavitation bubbles and larger vapor bubbles from boiling. This signal will be referred to as the harmonic signal for notational convenience. At a sufficiently-high temperature it was expected that boiling would commence and that large vapor bubbles created in the process would scatter the HIFU signal, such that the amplitude of the scattered HIFU harmonics would increase over time.

4.2.1 Filtering For Inertial Cavitation Detection

To obtain the broadband signal an FFT was performed on each RF line over the space and time window described above, where the signal consisted of energy from the scattered HIFU (fundamental and nonlinear harmonics), stable cavitation (sub- and super-harmonics), and radiated pressure from inertial bubble collapses (broadband). In order to isolate the contribution from inertial cavitation it was necessary to remove the HIFU and stable cavitation signals through filtering. One simple method to remove these signals would be to apply a comb filter around each of the harmonic and super-harmonic frequencies, resulting in signal energy only in the unfiltered frequency gaps between the filtered sub/super/harmonic peaks. However, the raw signal in the filtered frequency bands possessed energy from inertial cavitation as well; such an approach would underestimate the contribution from inertial cavitation, reduce the signal-to-noise ratio, and limit our ability to correlate integrated broadband noise with heating rates (see Chapter 3). Instead a variation on the standard comb filter was used that set the level of
the spectrum in each of the filtered frequency bands equal to the average level of unfiltered spectrum levels just above and below a given filtered band. The assumption is that the frequency dependence of the broadband cavitation noise does not vary appreciably as one traverses a given filtered band. In this manner, the HIFU harmonics and stable cavitation signals were removed from the signal while preserving energy from inertial cavitation emissions.

The filter was applied by taking a ±150 kHz band around each harmonic \((nf, \text{ for } n = 1, 2, \ldots, 12 \text{ and } f \text{ is the fundamental frequency})\) and a ±50 kHz band around each sub- and super-harmonic (where the \(n/2, ±n/3\) super-harmonics were considered, for \(n = 1, 2, \ldots, 12\)), across the entire frequency range. The frequency range between each particular frequency band and the next-highest frequency band, where the signal contained only broadband energy, was windowed and signals in the indices corresponding to this broadband window were randomly assigned (using the Matlab ‘randint’ function) to the indices that corresponded to the harmonic frequency band. It was necessary to randomly select the indices in the broadband window to avoid aliasing effects upon taking the inverse FFT. Figure 4.7 illustrates a typical detected magnitude spectra before and after application of the broadband comb filter. Note the reduction in signal level at the sub/ultra-harmonic frequencies following the application of the filter (note the change in scale of the plots). After the data were filtered an inverse FFT was performed and the RMS signal level of each RF line was calculated to obtain an RMS level for inertial cavitation as a function of position and time.
Figure 4.7: Terason signal a) before and b) after the broadband comb filter was applied. The dotted lines indicate the frequencies that corresponded to the harmonics that were filtered. The data was obtained in an agar-graphite phantom exposed to 5.1 sec of CW 1.1 MHz at a pressure amplitude of 2.5 MPa.

4.2.1 Filtering For Stable Cavitation Detection

As mentioned above, stable cavitation (including boiling) is characterized not by broadband emissions but rather by a combination of sub- and ultra-harmonics emissions and scattering of the HIFU fundamental and its harmonics. The stable cavitation signal amplitude was thus obtained by subtracting the broadband spectrum (as described above) from the measured signal spectrum in order to remove the inertial cavitation signals. The inverse FFT was taken and the data were high-pass filtered above 1.5 MHz using a six-stage Butterworth digital filter in Matlab to remove the HIFU fundamental signal. The RMS signal level of each RF line was then determined to obtain the amplitude as a function of position and time.
4.3 Results

The results shown here were taken from the same data set and were characteristic of previous measurements in the agar-graphite phantom performed with similar focal pressures. Figure 4.8 shows the measurement of the high-pass-filtered RMS PCD signal and temperature measured 0.5 mm lateral to the HIFU focus in an agar-graphite phantom. The HIFU transducer was operated at a 3.5-MPa focal pressure continuously for 5.1 sec. and the temperature measured near the focus. The 3.5-MPa focal pressure employed here was sufficiently high so that the onset of inertial cavitation was more or less immediate. The PCD signal decreased over time, in a similar fashion to the measurements performed in Chapter 3. Also present in the PCD signal is an increase in cavitation activity at 2.4 sec, most likely due to the nucleation event described in Section 3.7. The temperature increased until approximately midway through sonication, at which point the thermocouple measured a rapid period of heating before leveling off near the boiling point at about 3.1 sec.

The broadband RMS signal detected by the Terason, following post-processing, is shown in Fig. 4.9. The plot qualitatively agrees with the PCD RMS signal, as elevated
broadband signals were present at the focus and steadily decreased with time. These elevated signals are indicative of inertial cavitation, and the signal amplitude decreased further from the focus, where the pressure is lower. Over time, inertial cavitation decreased at the focus and increased closer to the HIFU transducer such that the entire inertial cavitation region shifted in the prefocal direction. This trend agrees with the results of Section 3.6 regarding the change in inertial cavitation over time with respect to position in the prefocal region.

Figure 4.10 shows the RMS signal of the harmonic frequencies over time throughout the focal region. Again, when the HIFU source is turned on, the signal amplitude is highest around the HIFU focus and is most likely due to scattering of the nonlinear harmonics by the graphite particles. The amplitude stays relatively constant until about 2.4 sec, at which point there is a dramatic increase in the harmonic signal. The elevated signal eventually extends both in the pre- and post-focal directions. The
high-amplitude signal at 2.4 sec coincides with the rapid increase in temperature near the focus to 80 °C and higher. Having surpassed the melting temperature of the phantom (80 °C), the high vapor pressure present in the hot molten region promoted the generation of stable cavitation and eventually led to boiling conditions – note the large amplitude signals observed in the focal region towards the end of the insonation.

It is interesting to speculate on the origin of the acoustic emission observed at the 2.4 sec point in Fig. 4.8. We had argued previously that this was due to a burst of inertial cavitation near the thermocouple tip (when observing the PCD signal which included both broadband and harmonic signals above 5 MHz). However, examination of Fig. 4.9 reveals no clear increase in broad-band noise at this time. Rather, we see much more compelling evidence of this transient emission in Fig. 4.10. Could it be that the spurious signals formerly attributed to inertial cavitation could in fact be due to vapor cavities in the hot medium? (Keep in mind that the high pass filter employed in the PCD did not eliminate harmonic energy from the scattering of the HIFU field off of stable cavitation...
bubbles and boiling bubbles above 5 MHz.) The fact that these large amplitude spurious emissions tended to occur further on into the insonation is consistent with this point of view.

The appearance of a hyperechogenic region often followed sonication, when the array was operated in pulse-echo mode. The B-mode image of the phantom acquired from a different data set where $P_{\text{foc}} = 3.4 \text{ MPa}$ is depicted in Fig. 4.11. The harmonic

**Figure 4.11:** Comparison of the extent of the boiling region as measured by (a) the scattered harmonic signal during sonication and (b) the hyperechogenic region measured in pulse-echo mode after sonication. The two arrows denote the extent of the appearance of vapor bubbles in the two images.
signal from the Terason measurement during sonication is plotted as well. The extent of
the bright region correlated well with the extent of the region where the high-amplitude
harmonic signals appeared. The agreement seen here provides further evidence that the
bright region corresponds to stable cavitation bubbles and large vapor bubbles created at
boiling temperatures.

4.4 Discussion
The results demonstrate that a commercial diagnostic imaging system can be used to
apply standard cavitation detection techniques to expand the detection region for both
inertial cavitation and boiling. Inertial cavitation and boiling are loosely-connected
phenomena which have both been identified as important mechanisms in HIFU energy
deposition.

The application of passive cavitation detection techniques in an imaging array is a
natural extension of a single-element PCD, given the option to acquire the RF signals,
and the result is an improved method for observing cavitation dynamics. There are
several limitations to this approach, however. Currently, this technique cannot be used
for real-time imaging and the current setup only allows a relative timebase to be
established, in the absence of a trigger. In addition, the processing time inherent in the
multi-beam imaging system makes it difficult to measure cavitation dynamics in the
presence of a lower duty cycle or situations where cavitation is sporadic and higher
acquisition rates are required. However, the frame acquisition rate is similar to typical
ACD and PCD setups where the waveform is acquired on an oscilloscope and uploaded to a computer.

The signal from stable cavitation and the HIFU source scattered in the phantom overlaps with the broadband signals from inertial cavitation. The broadband comb filter assumes that the broadband energy which is used to replace the harmonic signals is representative of the broadband energy that would be present in the absence of the harmonic signals. The bandwidths that were chosen for the filter were related to the bandwidth of the HIFU source and were based on experimental observation of the bandwidth of the harmonic signals. The entire spectrum was filtered to obtain the inertial cavitation signal as opposed to detection of the broadband signal over a narrow band between two harmonics (Chen 2003) in order to increase the signal-to-noise ratio and get an indication of broadband noise emissions that is better correlated with accelerated heating rates (although the latter was not assessed in the study presented in this Chapter).

Two dynamics of opposing direction were observed here. First, inertial cavitation decreased over time as the temperature near the focus increased and the distribution of inertial cavitation along the HIFU axis shifted towards the HIFU transducer. The decrease was investigated in Chapters 2 – 3 and was explained by elevated bubble vapor pressure which cushions the bubble collapse, and to a lesser extent, prefocal bubble shielding. Indeed, visualization of inertial cavitation with this technique reveals a rather small prefocal shift in inertial cavitation, indicating that temperature effects on bubble dynamics play a greater role than prefocal bubble shielding in decreasing inertial cavitation in the PCD signals observed in our experiments. Interestingly, the filtered
Terason data (Fig. 4.9) also fails to show an increase in broad band noise emissions at times when a spurious increase was observed in the single-element PCD detector, presumably do to cavitation on the thermocouple (see Fig. 4.8). The Terason “harmonic signal” however, did show correlation with the spurious emissions evident in the PCD data.

In contrast with the broad-band noise signal, the Terason harmonic signal increased as the temperature (measured 0.5 mm lateral to the focus) reached approximately 80 °C. Given a constant driving pressure in a non-perfused and homogeneous medium there are two main explanations for the increase in the harmonic frequency amplitudes. In a nuclei-rich and gassy medium, bubbles will grow over time via rectified diffusion, where gas from the surrounding region of the bubble is diffused into the bubble, causing it to grow (Eller 1965). This process will be governed largely by bubble size, medium viscosity and driving pressure, and a consistent expansion in the bubble size should be observed over time. Eventually, surface instabilities will cause the bubble to break up, but in a region that likely contains many bubbles this process should result in an averaged ensemble effect where evolution of bubble size over time (Yang 2004) will increasingly scatter the HIFU signal. Another explanation for increased harmonic scattering is bubbles that scatter more effectively because they are larger in comparison to small inertial cavitation bubbles, oscillate with a low expansion ratio relative to the driving pressure and do not collapse and break up over time. This scenario could be realized by an increase in vapor pressure, a process driven by an increase in temperature; a rapid increase in temperature would suggest that this effect would behave
in a threshold fashion, as observed in the results. These bubbles will also oscillate nonlinerly, resulting in the generation of sub-harmonic and super-harmonic frequencies, both of which will contribute to the amplitude of the harmonic signal shown in Fig. 4.10. Finally, as the medium gets really hot, the phantom melts and boiling ensues. These vapor cavities will be very effective at scattering the harmonics of the HIFU drive. Moreover, the development of large vapor bubbles is believed to be the reason why hyperechogenic regions often appear during sonication and persist for several seconds (even minutes) afterwards. While the observation of increased harmonic scattering could be due to growth by rectified diffusion, correlation of the increase in scattering with the high temperatures measured in the phantom indicates that high vapor pressures and boiling are the main causes. Further evidence that hyperechogenic regions are caused by boiling conditions is bolstered by the correlation of the hyperechogenic region to the harmonic scattering region.

The signal processing techniques described here were necessary for detection of inertial cavitation. Boiling detection, however, was only moderately enhanced by the application of the comb filter. Given the Terason transducer frequency response, the strongest harmonic signals that were detected, aside from the 1.1-MHz signal, were the signals from the second, fourth and fifth harmonics, and generally a plot of the RMS signal level following the 1.5-MHz digital high-pass filter revealed emergence of the boiling signature without the aid of the broadband signal subtraction (although the signal-to-noise ratio benefited from the subtraction of the broadband noise). Monitoring the real-time, unfiltered B-mode image showed a very noisy signal, but there was a defined
bright signal region from the focus which visibly narrowed when temperatures reached 80 – 90 °C. Thus, implementation of an in-line analog (or digital) high-pass filter could provide real-time boiling detection. Many diagnostic ultrasound systems possess in-line filtering (Szabo 2004), so the technique is feasible. In addition, diagnostic ultrasound systems offer a relatively-common platform by which this method could be applied clinically.
Chapter 5

CAVITATION AND HEATING IN BOVINE LIVER

5.1 Overview

The primary results of this thesis work were presented in Chapters 2 – 4, where the role of inertial cavitation in energy deposition was studied and a new technique was developed to monitor the spatial distribution of inertial cavitation and high temperature stable cavitation/boiling conditions. All of the experimental results thus far have been based on experiments in a single medium, namely agar-graphite gels. These phantoms represent a medium that was developed to mimic tissue properties but nonetheless possess different physical characteristics than tissue. In particular, it is important to understand how the characteristics of cavitation and heating in agar-graphite phantoms compare to biological media. In addition it would be helpful to evaluate whether the bubble detection techniques developed in Chapter 4 translate to other media as well.

Although the best choice would be an in vivo tissue sample, we do not have the facilities within the department to carry out live animal experiments. Therefore, excised beef liver was chosen to conduct a brief study in which temperature, PCD and Terason signals were simultaneously measured during sonication with HIFU. Liver was chosen due to the large body of literature regarding its acoustical properties (Goss, Johnston et al. 1978; Bush, Rivens et al. 1993; Sibille, Prat et al. 1993; Clarke 2003; Zderic 2004). These measurements are then compared to similar measurements in agar-graphite phantoms.
5.2 Bovine liver study

5.2.1 Objectives and Experimental Arrangement

The study was conducted using a single beef liver (< 6 hrs of slaughter, Blood Farm, Groton, MA). The liver was sliced into rectangular sections (~10 x 10 x 7 cm) and an effort was made to avoid large vessels in the samples. Measurements were performed over the course of three days, and with the exception of the samples measured on the first day, the tissue was kept frozen until used and thawed overnight before sonication on the following day. Attenuation and sound speed in liver and other tissue types have been demonstrated to be insensitive to freezing and thawing (van der Steen, Cuypers et al. 1991; Sasaki, Saijo et al. 1996).

The experimental arrangement was similar to that used in the experiments in Chapter 4, shown in Fig. 4.1. The PCD was positioned and aligned in the same manner as the measurements in Chapters 3 and 4. When temperature measurements were performed, the thermocouple was inserted by first housing the thermocouple in a disposable needle tip (18G1½, Becton-Dickinson). The needle tip and thermocouple were inserted into the tissue sample under diagnostic ultrasound guidance and the needle tip was carefully removed while the thermocouple was kept in place.

Due to limited time and samples for these experiments a thorough study of the liver was not possible. Instead, three basic questions were posed:

1.) Is inertial cavitation a factor in the heating? Many studies mention cavitation as a possibility for enhanced heating and/or macroscopic mechanical damage but very few show direct acoustic measurements of bubble activity.
2.) Are the Terason signal processing techniques for inertial cavitation and boiling detection applicable in tissue?

3.) How is the cavitation activity affected by degassing time?

The first two questions were strongly influenced by the third question, so the results are best presented in the context of the degassing time employed for the samples measured in this Chapter. Three degassing times of 0, 30, and 60 min were employed. The non-degassed sample was measured on the day the tissue was obtained from the slaughterhouse. The samples were degassed by submerging the tissue in a water bath placed inside a vacuum chamber and degassed for the specified time at a vacuum of -730 Torr. The cavitation threshold was measured using the same procedure described in Section 3.4. The lowest pressure amplitudes required to induce broadband emissions were 2.9 MPa (non-degassed), 5.8 MPa (30 min) and 6.8 MPa (60 min). The focal pressures reported were obtained assuming an attenuation of 9.1 Np/m at 1 MHz (Goss, Johnston et al. 1978) in the FDTD pressure code. Temperature and Terason measurements were not performed for the non-degassed samples. The sonication time was 5.1 sec and the water temperature was 22 ± 2 °C for all the measurements discussed here.

Here we were also interested in determining whether the PCD signal could be used to detect boiling in the same manner as the boiling detection technique described for the Terason signals in Section 4.2. Recall that filtering out the fundamental and broadband signals to isolate the harmonic signals provided an indicator of boiling and high-temperature stable cavitation, so we expected that the same indication could be obtained using the PCD signal by monitoring a single harmonic frequency. This analysis
employed the data obtained from the PCD signal which had been filtered with the 1.1-MHz band-reject filter and acquired by the oscilloscope board (see Fig. 4.1). The hypothesis was evaluated by taking a FFT of the PCD waveform and the amplitude of each of the higher harmonics \( n_f \), where \( n = 2, 3, \ldots, 8 \) in the frequency domain was evaluated as a function of time and temperature.

5.2.2 Results Using Non-degassed Liver Samples

The same focal pressure, \( P_{foc} = 6.5 \) MPa, was used for the non-degassed and 30-min degassed samples to compare the cavitation activity. The measurements of the PCD RMS signal, PCD magnitude spectra and amplitude of the third harmonic are displayed in Fig. 5.1. The vertical axes of plots (b, c) have been purposefully scaled in order to highlight the low-amplitude signals. Plots (a-c) show that the first half of the insonation had significantly more inertial cavitation activity than the second half. It is intriguing that the broadband noise, while decreasing in amplitude from \( t \sim 1.2 \) to \( 2 \) sec, seems to stop abruptly at \( t \sim 2.6 \) sec. The rest of the measurement featured distinct harmonic and super-harmonic signals amidst very low-amplitude broadband noise. The sudden change suggests that the inertial cavitation process stopped, possibly due to a sudden change in temperature or rapid development of prefocal shielding. Without temperature and Terason data it is difficult to determine if temperature or prefocal shielding were factors behind the change in the cavitation signal. However, Fig. 5.1(d) shows a strong increase in the amplitude of the third harmonic at \( t = 1.5 \) sec. Based on the trends shown in the Terason measurements of the phantoms it is likely that the temperature reached 80 °C or
Figure 5.1: PCD measurements in non-degassed *ex vivo* beef liver, where $P_{foc} = 6.5$ MPa. (a) Highpass-filtered $V_{rms}$ as a function of time. The arrows denote the acquisition times of the data in (b) and (c). (b) The magnitude spectra after filtering with a 1.1-MHz band reject filter, acquired at approximately $t = 0.55$ sec. The image is purposefully clipped to enhance the resolution of the low-amplitude signals. The broadband noise had a high amplitude and decreased with frequency partly due to attenuation. The second, third, fourth and fifth harmonics are present as well. (c) The magnitude spectra acquired in a similar fashion at approximately $t = 3.4$ sec. The broadband noise is very low in comparison to the earlier signal. (d) The amplitude of the 3rd harmonic peak in the PCD spectra as a function of exposure time.

higher at this time, and that the temperature was most likely much higher by the time the inertial cavitation signal detected by the PCD ceased. The inertial cavitation signal decreased after 1.5 sec, as expected from the bubble dynamics at high temperatures, but the signal did not drop significantly until approximately 1.2 sec later, however, so prefocal shielding is the more likely cause of the abrupt change in inertial cavitation emanating from the PCD sensing volume.
5.2.3 Results Using Liver Samples Degassed For 30 Minutes

The PCD measurements for the 30-min degassed sample are displayed in Fig. 5.2, where again, the vertical axes have been scaled in plots (b, c) to enhance the lower-amplitude signals. The results are similar to the non-degassed sample but the timescale for the progression of events was slightly different. Figure 5.2(a) shows that the highpass-filtered signal quickly decreased to approximately the amplitude of the background electrical noise. The rapid decline was mostly due to the change in broadband signal amplitude. Figure 5.2(b) shows the presence of inertial cavitation along with the harmonic and super-harmonic signals at $t = 0.12$ sec, but by $t = 0.5$ sec the broadband

![Figure 5.2: PCD measurements in beef liver degassed for 30 min, where $P_{foc} = 6.5$ MPa. (a) Highpass-filtered RMS signal as a function of time. The arrows denote the acquisition times of the data in (b) and (c). (b) The magnitude spectrum after filtering with a 1.1-MHz band reject filter, acquired at approximately $t = 0.1$ sec. The vertical axes were scaled to enhance the resolution of the low-amplitude signals. The signal contains mainly super-harmonics scattered into the PCD and a low-amplitude broadband signal. (c) The spectra acquired in a similar fashion at approximately $t = 0.55$ sec. The broadband noise present in the earlier signal is no longer present.]
noise amplitude is negligible, as shown in plot (c). While the change in inertial cavitation is not as abrupt as for the non-degassed sample, inertial cavitation only occurs over a short time before ceasing altogether. The amplitude of the harmonic signals was quite high at the beginning of the measurement, especially when compared to the measurement in the non-degassed sample. The high-amplitude harmonic signals are attributed to a large bubble or cluster of bubbles located near the focus that were not removed in the degassing process.

The nature of the change in the inertial cavitation signal is illuminated somewhat when the temperature data and the amplitude of the third and fifth harmonics over time are compared, shown in Fig. 5.3. The temperature increased 52 °C by the time the

![Diagram](image.png)

Figure 5.3: (a) The highpass-filtered RMS signal and measured temperature as a function of time in beef liver degassed for 30 min, where $P_{fo}$ = 6.5 MPa. The temperature rise was greatest for the first 200 ms and reached 100 °C at 2.5 sec. (b - c) The amplitude of the third and fifth harmonics, respectively, scattered into the PCD as a function of time. Note that the amplitudes are highest when the temperature measured near the focus approached boiling.
inertial cavitation signal decreased to the amplitude of the background noise. Thereafter, the temperature rise slowed significantly and peaked above 100 °C around $t = 2.5$ sec. The presence of the inertial cavitation signals strongly correlated with the initial rapid heating, while the temperature rise slowed once inertial cavitation stopped. The timing of the increase in harmonic signal correlated with the onset of boiling, as the amplitude increased once the temperature increased above 90 °C and peaked once the temperature increased above 100 °C. The second and fourth harmonics (not shown) also increased near the same temperatures and decreased shortly afterwards. There is also good correlation between the transient increases in the harmonics signals (c, d) and transient increases in the high-pass filtered PCD signal. This is consistent with the results of Chapter 4, where we theorized that the noise bursts evident as the tissue phantom heated up (Fig. 4.8) were due to ultra-harmonic noise generation and harmonic scattering from larger stable cavities and/or vapor bubbles (see Fig. 4.10), and not from bursts of inertial cavitation as originally thought.

The change in harmonic signal amplitude as measured by the Terason is shown in Fig. 5.4. The timing for the onset of the elevated harmonic signals agrees well with the timing of the high temperatures displayed in Fig. 5.3(a). The harmonic signal shows strong evidence of prefocal lesion migration, as the boiling started around the focus and the boiling region increased to -5 mm by the end of the measurement. The broadband signals detected with the Terason showed evidence of inertial cavitation at the beginning of the sonication, in agreement with the PCD RMS signal over the first 500 ms, but the
signal amplitude was fairly low and decreased to the amplitude of the background noise after approximately 400 ms.

![Figure 5.4](image)

Figure 5.4: The amplitude of the harmonic signals from the measured by the Terason array as a function of time and position relative to the HIFU focus in the 30-min degassed liver sample. The broadband signal and HIFU fundamental frequency have been filtered out. The dark regions correspond to low signal amplitude and the white regions correspond to high signal amplitude. The signal appears near the focus at approximately \( t = 0.7 \) sec and progresses back towards the HIFU transducer over time.

5.2.4 Results Using Liver Samples Degassed For 60 Minutes

Figure 5.5 shows the PCD measurements from the sample that had been degassed for 60 min and sonicated with a focal pressure of 7.4 MPa. The PCD results in Fig. 5.5 show similarity to the 30-min degassing time results with the exception of the inertial cavitation signals. Instead, plot (b) shows little evidence of inertial cavitation activity, while scattering of the harmonic frequencies was present throughout the measurement. The former is due to a lack of nuclei in the degassed tissue sample and the latter is due to the nonlinear HIFU beam scattering from microstructure in the tissue. The signal in plot (a) remained low until \( t \sim 3.3 \) sec, at which point it jumped erratically for the remainder
Figure 5.5: PCD measurements in beef liver degassed for 60 min, where \( P_{\text{foc}} = 7.4 \) MPa. (a) Highpass-filtered RMS signal as a function of time. The arrows denote the acquisition times of the traces in (b) and (c). (b) The magnitude spectra after filtering with a 1.1-MHz band reject filter, acquired at approximately \( t = 0.1 \) sec. The signal contains mainly HIFU harmonics scattered into the PCD by microstructure in the tissue. The broadband signal amplitude is similar to that of the background noise. (c) The magnitude spectra acquired in a similar fashion at approximately \( t = 4 \) sec. The vertical axes were scaled to enhance the resolution of the low-amplitude signals. Despite the signal detected in (a) the broadband signal amplitude was low, while the amplitude of the harmonic signals was quite high, probably due to noise and scattering from stable cavitation bubbles.

of the measurement, presumably because the temperature elevation served to lower the level of dissolved gas under-saturation to the point where bubbles nucleated. At this point, the formation of stable cavities in the heated phantom further enhanced harmonic noise generation due to radiation and scattering. Plot (b) illustrates that the increase in RMS signal level at this time was due to an increase in amplitude of the harmonic and super-harmonic frequencies. Note that the level of broadband noise remained low.
throughout. By the time bubbles nucleated, the tissue was already too hot to support inertial bubble collapses.

Figure 5.6 compares the temperature measurement with the PCD RMS signal, the amplitude of the second, third and fourth harmonic frequencies measured with the PCD,

![Figure 5.6](image)

Figure 5.6: (a) The highpass-filtered RMS signal and temperature measured near the focus as a function of time in the 60-min degassed liver sample. The temperature rise was low compared to the previous measurements in beef and reached 80 °C by \( t = 3.2 \) sec. The error bars represent the uncertainty of the temperature based on a ±0.2 mm uncertainty in the position of the thermocouple. (b) The amplitude of the second, third and fourth harmonics scattered into the PCD as a function of time. Note that the amplitude is low until the temperature near the focus reached 80°C, after which point stable cavitation ensues. (c) The amplitude of the harmonic signals measured by the Terason array as a function of time and position relative to the HIFU focus. The broadband signal and HIFU fundamental frequency have been filtered out. The dark regions correspond to low signal amplitude and the white regions correspond to high signal amplitude. Note that the amplitude of the harmonic signals increases near the focus once the measured temperature reaches 80°C. This is due to the sudden onset of cavitation activity at the 3.4 sec mark. The signals show rapid progression of the bubble front towards the HIFU transducer. Also note that the heating rates observed in the first 3 seconds (where there is no cavitation of any kind) are significantly less then those observed in the initial stages of Fig. 5.3 (where inertial cavitation is present).
and the harmonic amplitude measured with the Terason. It is evident that the temperature increase was much lower compared to the initial rapid increase measured in Fig. 5.3 where the degassing time was lower. The second, third and fourth harmonics, along with the Terason-detected harmonics, all demonstrate a sudden increase in amplitude when the temperature reached 80 °C. Plot (c) shows that the cavitating region quickly progressed towards the HIFU source, in a similar fashion as the signals displayed in Fig. 5.4. The broadband signals detected by the Terason did not change significantly over the course of the temperature rise.

It is curious that the measured temperature levels out at 80 °C while the Terason data indicates that boiling commences at approximately 3.2 sec. This discrepancy could be explained by a misalignment of the thermocouple, so that the thermocouple is further than 0.5 mm from the focus. The placement and alignment of the thermocouple in the beef liver is more difficult than in the phantoms, so we estimate a ±0.2 mm uncertainty in the thermocouple position. Since the measurement in Fig. 5.5 did not have inertial cavitation present, we can assume the heating comes entirely from thermoviscous absorption of the HIFU energy. By inserting the acoustical and thermal properties\(^1\) of bovine liver into the FDTD pressure and temperature simulations, an estimate of the uncertainty in the temperature, based on the ±0.2 mm position uncertainty (\(i.e., 0.3 - 0.7\) mm lateral to the focus), can be obtained. This uncertainty is shown in the error bars in Fig. 5.6(a). The error bars show that a relatively small misalignment can result in a

\[^1\] \(c = 1540 \text{ m/s} \); \(\alpha = 9.1 \text{ Np/m} \); \(\rho = 1003 \text{ kg/m}^3 \); \(\beta = 4.4 \); \(C = 3710 \text{ J/kg.°C} \); \(k = 0.158 \text{ mm}^2/\text{s} \).
relatively large difference in the temperature—enough to show that the temperature is very likely high enough for boiling to occur near the focus.

The temperatures and broadband signals measured in Fig. 5.3 and conspicuously absent in Figs. 5.5 and 5.6 clearly demonstrate that inertial cavitation greatly enhances heating rates in beef tissue. Indeed, the heating rates in Fig. 5.3 are significantly greater than those observed in the absence of inertial cavitation (Fig. 5.5), despite the fact that the intensity in the latter is approximately 30% greater and the waveform is likely more shocked.

5.2.5 Comparison With Agar-Graphite Phantom Measurements

The same approach of monitoring the harmonics measured with the PCD was applied to the agar-graphite phantom measurements. Figure 5.7 shows results from the same data set displayed in Figs. 4.10 – 12, where $P_{foc} = 2.5$ MPa and the amplitude of the third harmonic is displayed in Fig. 5.7(b). The second harmonic signal did not change significantly over the course of the measurement but the third harmonic signal increased when the temperature approached the onset of boiling. The harmonic signals are not as sensitive to the onset of stable cavitation and/or boiling in agar-graphite phantoms as in the liver measurements. This is due to the fact that the nucleation threshold pressures in the liver samples were much greater and thus the HIFU pressures in the beef liver experiments were larger by about a factor or 2 or 3, which is a significant increase. These higher-pressure waveforms were more susceptible to nonlinear distortion, thus there was more harmonic energy in the incident HIFU beam available to scatter from stable cavitation and boiling bubbles once they were formed.
Figure 5.7: (a) The highpass-filtered RMS signal and temperature measured near the focus as a function of time in an agar-graphite phantom. The focal pressure was 2.5 MPa. The cavitation signal steadily decreases until about 2 sec, after which it remains more or less constant. The temperature reaches 80 °C by approximately 2.5 sec and approaches 100 °C by about 3 sec. (b) The amplitude of the third harmonic scattered into the PCD over the measurement. The amplitude is highest at approximately 2.8 sec, when the temperature approaches boiling. (c) The amplitude of the harmonic signals measured by the Terason array as a function of time and position relative to the HIFU focus.

5.3 Discussion

The results from the measurements in bovine liver demonstrated some similar characteristics of inertial cavitation when compared to similar measurements in agar-graphite phantoms. As in the agar-graphite measurements, the heating rate was highest when inertial cavitation was detected, indicating that bubble-enhanced heating is an important factor in tissue as well as in the phantoms. Unlike the agar-graphite phantoms, the cavitation threshold in the liver strongly depended on the degassing period, and the
nucleation threshold was significantly higher even when the liver was not degassed. This may be due to the fact that in agar-graphite phantoms, the high concentration of graphite particles provides a large population of bubble nuclei, whereas liver does not possess such a large population of nuclei from which inertial cavitation can be generated.

While their acoustic and thermal properties are ideal for studying the effect of ultrasound heating in tissue, agar-graphite phantoms are also an ideal medium for studying and isolating inertial cavitation effects. Figure 3.21 showed that above 5 MHz and at temperatures below ~80 °C, the PCD signal consisted mostly of the broadband noise (indicative of inertial cavitation), with very little of the signal coming from the scattered HIFU signal and stable cavitation. It is likely that these signals are present but their amplitude is low compared to that from inertial cavitation. This is not necessarily the case in all media, as demonstrated in the liver measurements. It is important to note the change in the PCD RMS signal with respect to the broadband and harmonic signals in Fig. 5.2. Unlike the signal in agar-graphite phantoms, where the scattered harmonic signals above 5 MHz are indistinct from the broadband noise, the highpass filter does not remove all of the scattered HIFU energy and ultra-harmonics from stable cavitation, thus undermining the assumption that the RMS signal is representative of inertial cavitation alone. This is not surprising, since development of shocks is to be expected at the high pressures employed here. The RMS signal in Fig. 5.2(a) is fairly low from 0.7 – 2 sec but nonetheless is greater than the amplitude of the electrical noise (~30 mV rms). The effect is especially apparent after \( t = 2.3 \) sec, as the scattering of the nonlinear HIFU signal is particularly strong due to boiling.
The process of monitoring the change in amplitude at the harmonic frequencies was successful in detecting the onset of stable cavitation and boiling in both media not only when applied to the Terason data but for the PCD data as well. In particular, the third harmonic showed agreement between the media in regards to its correlation with the onset of stable cavitation and boiling. Monitoring a single frequency for boiling detection would be simpler and easier to implement when compared to the filtering process used for the Terason data.

The measurements presented in this chapter were intended to highlight differences in cavitation and heating in different media and to test the techniques developed in Chapter 4 for detection of bubble activity in tissue. It is clear that agar-graphite phantoms represent an ideal medium for observing effects from inertial cavitation and that not all media have a readily-available population of nuclei from which bubble-assisted heating can be obtained. Indeed, very high pressures were required to induce inertial cavitation in the liver samples and when it occurred, the heating rate was so high that it is difficult to imagine that inertial cavitation signals could be used as an effective feedback mechanism, as proposed in Section 1.3 and explored in Chapter 3. At 6 or 7 MPa, by the time you get cavitation the tissue is either (1) too hot to support inertial collapses or (2) the cavitation field evolves so rapidly that you lose control. However, it maybe possible to add nuclei to tissues in vivo and thereby promote inertial cavitation at lower HIFU pressure amplitudes. As mentioned in Chapter 1, research is underway on lowering cavitation thresholds by introducing external nuclei into tissue, giving rise to the
hope that heating from inertial cavitation can someday be harnessed more easily and safely.

It is important to take the role of the bubbles and the signals which can be detected from them into context. Inertial cavitation may not always be present during sonication but the results of Chapters 3 – 5 clearly show that the heating rate is greatly enhanced when it is present. In light of this approach, the correlation between inertial cavitation signals and bubble-enhanced heating are a viable method for informing HIFU treatment. Regardless of the presence of inertial cavitation, if the tissue gets sufficiently hot then vapor bubbles will form and stable cavitation will occur. The harmonics that are detected from HIFU scattering and nonlinear oscillation of stable cavitation provide an indicator of temperature, adding a powerful method of detecting the temperature in the tissue. By applying these noise diagnostics – detection of broadband noise (inertial cavitation) and sub/super/harmonic frequencies (boiling, stable cavitation) – to a single sensor (PCD or diagnostic ultrasound system), we can truly enhance treatment feedback during HIFU sonication.
Chapter 6

SUMMARY AND CONCLUSIONS

6.1 Summary and Discussion of Results

The main results of the experimental and numerical simulation results are summarized in the following list. A discussion of the findings and conclusions drawn from these results will follow below. Suggestions for future work based on these results will be presented in Section 6.2.

1. In agar-graphite phantoms (degassed for 20 – 30 minutes at a vacuum pressure of -730 Torr gauge) sonicated over a pressure range of 1.4 – 3.5 MPa, the signal detected by the PCD above 5 MHz consisted almost entirely of broadband noise. Less than 5% of the signal was attributed to nonlinear distortion and/or stable cavitation, signifying that the PCD was mainly sensitive to inertial cavitation signals in agar-graphite phantoms.

2. For CW sonications of sufficient focal pressure and duration, the broadband signal from inertial cavitation steadily decreased in amplitude until a baseline level was reached. This pressure was determined to be 1.8 MPa (0.4 MPa above the cavitation threshold) for our degassed agar-graphite phantoms.

3. By employing pulse durations of 100 cycles and a 2.2 kHz PRF, corresponding to a duty cycle of 20%, the amplitude of the inertial cavitation signal could be maintained over time periods as long as 60 seconds. Following CW sonication for periods up to 5 sec, where the inertial cavitation signal amplitude decreased over time, reducing the exposure to a 20% duty cycle induced an increase in broadband signal level back to the initial amplitude, after which point the signal remained constant for periods of up to 60 sec.

4. When the physical properties of water were allowed to change with temperature (sound speed, vapor pressure, viscosity, surface tension, density) in our simulation of bubble-assisted heating, the maximum radiated power and viscous power deposition from a 50-nm air bubble driven at 1 MHz and 3 MPa decreased as the temperature increased from 20 – 100 °C, while the expansion ratio increased over the same temperature range. For the same conditions but with vapor pressure held constant ($p_v = p_v(T = 20 \degree C)$), both the expansion ratio and maximum radiated power increased at higher temperatures.
5. At a distance of 4 and 5 mm (proximal to the HIFU focal plane and measured along the HIFU axis) at 2.6 and 3 MPa, respectively, the cavitation signal increased over time, while the cavitation signal nearer the focus decreased over time.

6. For 1-sec exposure durations and five out of the six focal pressures employed in the measurements employing degassed agar-graphite phantoms (2, 2.5, 2.8, 3.3, and 4.2 MPa), the amplitude of the cavitation signal and the change in temperature increased monotonically with focal pressure. Alternatively, the cavitation signal amplitude and temperature exhibited a dip at 3.5 MPa relative to the results obtained at 3.3 and 4.2 MPa.

7. The same effect was observed in the computed total radiated and absorbed viscous power for a 300-nm radius bubble in a fluid with viscosity 0.002 Pa.sec driven over the same pressure range at 1 MHz. The relative decrease in radiated and viscous power was not observed at viscosities above 0.008 Pa.sec for the same range of pressures and bubble sizes.

8. The broadband cavitation noise power measured with the PCD and rate of temperature rise from enhanced heating were proportional over a 5-sec sonication. The proportionality constant decreased at higher HIFU pressures.

9. A diagnostic ultrasound system was adapted to enhance our ability to perform noise diagnostics over a larger sensing volume. The unit recorded and saved RF data streams for post processing in the frequency domain. Specifically, time and space-dependent broadband, harmonic, and super-harmonic signals levels were extracted from the received RF signal trains. The broadband signals were indicative of inertial cavitation and the harmonic/super-harmonic signals were indicative of stable cavitation at elevated temperatures as well as the onset of boiling.

Note: For purposes of the discussion to follow, the term “cavitational boiling” will be used to refer to the onset of stable gas/vapor cavity formation or, in the extreme case, vapor filled boiling bubbles. This phenomenon occurs in both the phantom and the beef liver at elevated temperatures that may or may not reach the boiling temperature. The result is manifested as an increase in super-harmonic noise levels due to the nonlinear oscillations of the stable cavities, and (principally) an increase in harmonic noise levels due to scattering of the shocked up HIFU beam from stable cavitation and/or boiling bubbles.

10. The spatial extent and position of the cavitational boiling region detected with a diagnostic ultrasound system correlated very closely with the extent and position
of the hyperechogenic region (imaged immediately after HIFU exposure) in agar-graphite phantoms.

11. High pressures were necessary for the onset of inertial cavitation in ex vivo beef liver. The threshold pressure was highly dependent on the degassing time and ranged from 2.9 to 6.8 MPa. The signals detected with a PCD above 5 MHz contained significantly greater energy at the harmonic frequencies than that attributed to broadband noise emissions. The harmonic signals measured with a diagnostic ultrasound system and a PCD were indicative of cavitational boiling in beef liver, as well as in agar-graphite phantoms.

12. We observed in both the agar-graphite phantoms and the excised beef liver that local heating rates measured in the presence of inertial cavitation noise emissions were significantly greater than those measured in the absence of inertial cavitation, or in the presence of cavitational boiling at elevated temperatures.

The studies of inertial cavitation and bubble-enhanced heating reported in this thesis were motivated primarily by a desire to understand elevated heating rates reported in biological and gel-based media during HIFU sonication. A secondary goal was to understand the role that inertial and stable cavitation bubbles play in prefocal lesion migration and to determine if monitoring cavitation noise yielded a means for non-invasive sensing of HIFU-relevant processes (accelerated heating, shielding, etc.). Given the high intensities employed in many clinical applications of HIFU, bubbles undergoing inertial collapses are most likely present in the focal region and perhaps in the pre-focal region as well. It has been well established that inertial cavitation bubbles are capable of producing the reported elevated heating rates and that the onset of enhanced heating coincides with detection of inertial cavitation, so it follows that inertial cavitation signals are indicative of the heating caused by their presence.

While recognizing the known correlation between the onset of detected broadband signals and elevated heating rates, it is important to stress that the measurement of
broadband noise had not yet been demonstrated to provide a quantitative assessment of bubble heating effects. A thorough understanding of the relationship between cavitation noise and bubble enhanced heating is necessary in order to utilize said noise as a source signal for feedback control of sonication parameters. In addition, current detection techniques for inertial cavitation require significant acoustical access, utilize small sensing volumes, and are thus limited for clinical use. Improvements in sensing technology and the addition of noise-based feedback and visualization of heating during HIFU sonication could significantly enhance the utility, effectiveness, and safety of clinical HIFU for a range of applications.

Thus motivated, we sought to first understand how inertial cavitation signals are influenced by some of the environmental factors that affect bubble activity in agar-graphite phantoms. The main trend observed for CW sonication was that inertial cavitation decreased over time at pressures above 1.8 MPa. This trend was influenced by three factors. Modeling the bubble dynamics demonstrated that an increase in temperature decreased the velocity and acceleration of the inertial bubble collapse, reducing the radiated power and effectively “shutting down” the inertial cavitation field. As a result, the amplitude of the detected broadband emissions and concomitant bubble-assisted heating will decrease when the medium heats up. This effect was due to an increase in vapor pressure at higher temperatures and had the influence of cushioning the bubble collapse.

Another potentially important effect is temperature dependent acoustic attenuation. In agar-graphite phantoms, this was found to increase from 25 – 35°C but
decreased from 40 – 50°C. Increased attenuation will increase heating from the bubbles while at the same time decreasing the amplitude of the detected signals. The two processes are still correlated, but the functional relationship will change slightly as the temperature changes. The slope of the attenuation increase with temperature was higher for higher frequencies, so this effect will have a greater influence on radiation and heating from broadband, harmonic, and super-harmonic emissions than it will on the 1.1-MHz component of the HIFU sound field.

Inertial cavitation from a fixed volume was influenced by bubble shielding effects. In the agar-graphite phantom exposed to CW ultrasound, cavitation noise emanating from the focus decreased over time while broadband signals from the pre-focal region tended to increase. Lowering the HIFU duty cycle resulted in an inertial cavitation signal of constant amplitude over time. The combination of these two results suggests that the number and/or size of the bubbles in the pre-focal region increase with time, blocking the HIFU beam from reaching the focus. If the bubbles in the pre-focal region are periodically allowed to dissolve, then their influence on HIFU sound propagation will be reduced.

Finally, the nature of the bubble dynamics were also influenced by the driving pressure. Inertial cavities experience a relatively slow growth phase initiated in the tensile phase of the sound cycle, followed by a rapid collapse during the ensuing acoustic compression cycle. As bubbles are driven harder in a medium of fixed temperature, one would expect their expansion ratio to increase, followed by an ever more violent collapse. In general this is the case, but the time required for growth will increase as well and the
start of the collapse will shift in time so that the bubble does not collapse fully before the next tensile cycle sets in. When this occurs, the tensile acoustic stress serves to arrest the collapse, which in turn reduces the radiated sound power and associated heating effects. Thus, for a specific equilibrium bubble size, there exists ranges of driving pressures over which the collapse energy and radiated power are reduced. The actual influence of this effect on experimentally-observed bubble heating is small for real cavitating systems, which usually possess a range of equilibrium bubble sizes. Nevertheless, it was observed experimentally and its existence is important, since it offers further evidence that the enhanced heating attributed to bubbles is due to small inertially-collapsing bubbles, not large bubbles undergoing stable cavitation.

Armed with an understanding of why inertial cavitation changes over time, we were better equipped to understand how the detected cavitation signals were related to the measured rate of temperature rise. Since our experimental arrangement did not allow for measurement of cavitation or temperature at multiple positions we were unable to account for conduction effects – thus the cavitation signal could only measure rate of temperature rise and not the absolute temperature at any point in time.

The relationship between cavitation power and rate of temperature rise was based on the Pennes bioheat model and a number of assumptions regarding the detected signals and heating effects. We assumed conduction effects were small for the short periods over which the temperature change was analyzed and that the absorbed power density in the sensing volume of the PCD was uniform. Following these assumptions, the model was simplified so that the absorbed power density from the bubble collapse was proportional
to the rate of temperature rise from the bubble activity. The rate of temperature rise was defined as the change in measured temperature minus the change in simulated temperature assuming only thermoviscous absorption over a 20 ms time period. The PCD cannot detect the power that is absorbed, but rather the power that is radiated to the PCD. Thus, we assumed that the radiated power detected by the PCD is proportional to the radiated power density from the bubbles collapsing in the sensing volume, which in turn is proportional to the absorbed power density in the sensing volume. (This assumption clearly breaks down if the local attenuation is dramatically altered due to temperature effects or bubble shielding.) We also assumed that the proportionality between cavitation power and rate of temperature rise was constant over the period of heating.

In spite of these rather broad assumptions, we found that in the agar-graphite phantom the cavitation power was indeed linearly proportional to the rate of heating for pressures ranging from 2 to 4.2 MPa. Agreement suffered over the initial 300 – 500 ms of sonication, for reasons that may be related to the temperature dependence of attenuation in the phantom, viscous heating on the thermocouple tip, and evolution of the bubble field.

We computed the average difference between the predicted heating rate based on the measured cavitation noise power and rate of temperature rise measured with the thermocouple, evaluated over the duration of each measurement. This value was then averaged over the number of measurements at each pressure and found to vary between +1°C/sec and -6°C/sec, depending on the HIFU pressure amplitude. The standard error
of these population means were typically on the order of ±2.5°C/sec, but in some cases were as great as ±10°C/sec. Large standard errors in an ensemble of repeated cavitation measurements are not unusual given the statistical nature of cavitation nucleation and bubble cloud formation. For example, changes in the spatial location of the bubble cloud relative to the PCD sensing volume and thermocouple tip will lead to differences in the proportionality constant from measurement to measurement, and likely contributed significantly to the fluctuations in the error. In truth, we were quite surprised to find the results to be as repeatable as they were, and the fact that a single proportionality constant was able to capture the functional relationship between inertial cavitation noise and heating rates over the entire temperature range of the exposure (approaching 100°C in some cases) was remarkable.

The results demonstrated that detection of inertial cavitation can provide an approximate measurement of the rate of temperature rise from bubble activity in agar-graphite phantoms. The PCD signal conditioning provided real-time detection, so the signal could potentially measure the rate of temperature rise during the course of sonication. There are several caveats to this method, however. Here we have employed perfusion-free phantoms, so heat loss from blood flow and heat generation from metabolic effects did not have to be taken into account. (Thus is true for any model that seeks to describe externally induced heating in tissue, be it by microwaves, lasers, ultrasound, or cavitation.) The rate of temperature rise is highly dependent on knowledge of heat generation in the phantom from the direct absorption of the HIFU beam and assumes sonication at relatively low pressures such that the HIFU beam is not
significantly shocked and inertial cavitation noise dominates the PCD signal at high
frequencies. The beef liver measurements demonstrated that *ex vivo* tissue cavitation
thresholds were considerably higher than the threshold in agar-graphite phantoms. Such
high pressures resulted in significant shock formation at the focus, and as a result the
PCD signal was no longer sensitive only to inertial cavitation. It is possible, however,
that the high cavitation thresholds observed in tissue can be artificially lowered, by
‘seeding’ or introducing cavitation nuclei into the tissue that will cavitate at lower
pressures. This concept has been investigated through the use of gas-filled contrast
agents coated with a spherical shell (Miller 1995; Miller 1996) and gold nano-particles
(Farny 2005; Roy 2005; Wu 2006) in conjunction with laser heating.

Another drawback to this method is that the PCD only provides information for a
small volume in the phantom. This was addressed by the use of the Terason imaging
array to detect inertial cavitation. The techniques described in Chapter 4 give a spatial
and temporal measurement of cavitation noise. One of the strengths of this technique is
that it takes advantage of a diagnostic ultrasound system, a platform that is often
employed in clinical HIFU treatments. Active B-mode imaging gives effective
visualization of the area over which HIFU energy has been deposited, but is only
applicable after the therapeutic sound field has been turned off and therefore cannot
provide a history of the treatment. By operating the Terason in a passive mode and
filtering the RF signals, a time history of the bubble activity during sonication can be
obtained. Furthermore, this signal could be analyzed in the frequency domain to
determine if the noise is due to broadband emissions from inertial cavities or the
detection of generated super-harmonics and scattered harmonics from cavitation boiling at elevated temperatures.

For example, the onset of cavitation boiling was detected by monitoring the amplitude of the harmonic components of the PCD time domain signals. The harmonic signals increased in a threshold fashion for temperatures between 80 – 95 °C, due to emissions from stable cavitation and increased scattering of the HIFU pressure off of large vapor bubbles formed at these temperatures. The onset for the increase in harmonic signals could also provide a valuable feedback signal for HIFU treatment, for it signals the onset of elevated temperatures (lesioning?) in the sensing volume and the progression to boiling conditions within the lesion. The spatial extent of the cavitation boiling region detected passively during sonication agreed well with the extent of the hyperechogenic region detected in pulse-echo mode immediately following sonication.

To conclude, using a well-characterized phantom we have demonstrated that inertial cavitation noise emissions can be monitored to provide a spatially-resolved, real-time assessment of the rate of temperature rise. The cavitation activity can be controlled to some degree by changing the HIFU duty cycle. These two results suggest that inertial cavitation signals can be used as feedback signals by which the heating during HIFU application can be controlled, provided the HIFU drive pressures are not too high – a fact that may necessitate the introduction of supplemental cavitation nuclei in vivo, or the use of large-amplitude, short-duration HIFU pulses to “pre-populate” the tissue with free bubble nuclei prior to exposure. A diagnostic ultrasound system was demonstrated to be sensitive to inertial cavitation and what we term “cavitational boiling”, the latter of which
describes a state of elevated temperature in which the sensor picks up super-harmonic noise emissions from non-linearly oscillating gas-vapor cavities and/or scattering of harmonics of the HIFU drive by stable cavitation bubbles or boiling vapor bubbles. Correlation of the harmonic signal amplitude with boiling temperatures demonstrates that the bubble signals can not only provide a measurement of the rate of temperature rise (by monitoring inertial cavitation) but also an indication of the temperature, albeit for a limited range (above 70 – 80 °C).

6.2 Suggestions For Future Study

There are a number of directions which can be pursued based on the results reported in this Thesis. The focus of the investigation was mainly on understanding the cavitation signals, and some aspects of the work begs further study. Firstly, the duty cycle measurements did not employ temperature monitoring, so we do not know how the heating is affected for lower duty cycles. We expect that decreasing the duty cycle results in an increase in overall time required to heat the medium at the focus. The question is: how much of a reduction in heating is caused by sonications at a low duty cycle, and does the overall efficiency of focal heating relative to HIFU on-time change? It would be helpful to better understand the relationship between duty cycle and bubble-enhanced heating, and the pulse lengths and PRFs which were employed only covered a small range of possible combinations relevant to clinical HIFU.

With regards to understanding how to control cavitation it may be helpful to understand how different pulse lengths and PRFs affect the evolution of the bubble field.
and associated heating rates. A natural extension of this Thesis is to implement the measurement of cavitation power as a feedback signal into a control loop, to demonstrate control of inertial cavitation during sonication. To do this, it would be necessary to have a background in control theory and an understanding of how cavitation power could be used as a feedback signal. A possible outcome could be the ability to generate lesions in less time, or to produce lesions in a fixed time but using lower time-average HIFU intensity. Both of these outcomes would enhance safety and patient comfort by minimizing prefocal heating.

The second area which could be pursued more fully is the application of the Terason system (or an equivalent imaging system capable of being driven in a passive receive mode) for bubble activity detection. The Terason system was not investigated until after the bubble heating measurements in Section 3.7 were conducted. The data collected with the Terason system during these measurements could have provided insight regarding the axial position of the bubble cloud relative to the thermocouple and PCD sensing volume, thus informing the error analysis regarding variability of the proportionality constant. The inertial cavitation signal from the Terason system could have also been analyzed for a measurement of cavitation power to evaluate how it correlated with the PCD and thermocouple data.

In general we found that the amplitude of the harmonic frequencies detected by the Terason system correlated with temperatures above 80 °C, but the thermocouple was positioned 0.5 mm outside of the focus. The temperature at the focus, where the Terason array was centered, was most likely higher than the thermocouple temperature, so the
temperature that correlated to the increase in harmonic signal amplitude was most likely higher than 80 °C, and should be measured.

The success of these techniques at detecting inertial cavitation and cavitational boiling during sonication in tissue phantoms and \textit{ex vivo} tissue samples indicates that not only would our methods translate well into a clinical setup, but that the information provided by these methods could be valuable for treatment guidance. However, the approach employed clearly benefited from our particular system setup. Working in a homogeneous phantom allowed us to instrument and position the HIFU and array transducers for optimal noise detection, so that the change in the bubble noise along the HIFU axis was monitored. This particular arrangement was chosen in order to monitor the possible development of bubble shielding conditions. Using a homogeneous phantom presents an idealized scenario, as all sides of the phantom offer acoustical access, and thus the cavitation noise and sound scattering may be more easily detected in the phantom than in a clinical setting. Quite often it is difficult to find even a single acoustical window for the therapy transducer in a clinical setting, so the arrangement employed in this Thesis will not transfer well to all possible clinical scenarios. Typically, diagnostic ultrasound feedback is performed coaxially with the therapy transducer (such as the Chongqing Haifu therapy system), and so it is important to consider how our approach for bubble noise detection will be affected by such an arrangement.

A coaxial configuration for the diagnostic and therapeutic transducers would provide bubble noise detection along the lateral direction, rather than the longitudinal axis. Pre-focal shielding conditions tend to shift the region of energy deposition towards
the therapy transducer, so a coaxial alignment would make it difficult to track such a shift. Tadpole lesions often grow wider over time, as they progress towards the front of the lesion so it is possible that the development of a tadpole shape could instead be determined by monitoring the width of the cavitation and/or boiling region over time. A coaxial alignment would still provide an indication of when cavitation and/or cavitational boiling commences, although it would be difficult to determine where along the HIFU axis the bubble signals occur in an coaxial alignment.

Another important aspect of adapting a diagnostic ultrasound scanner to a clinical setting is to properly account for the frequency of the HIFU transducer and the harmonics and super-harmonics that may be generated. The current analysis was based on the 1.1 MHz HIFU transducer, which we employed for all of our experiments, but a different transducer with a different frequency would make it necessary to adjust the frequencies of the software filters. The analysis was performed in software, which provides a flexible platform by which the frequency for the analysis could be changed.

An experiment that was not conducted due to equipment issues was a measurement of the thermocouple heating artifact. One way to determine the thermocouple heating artifact is to compare the measured temperature rise with the temperature rise predicted by the FDTD simulation. This method is only valid in the absence of cavitation, however, since we cannot account for the heating from bubble activity in the FDTD simulation. To get around this problem, we had hoped to suppress cavitation by applying an overpressure to the phantom and measure the temperature rise when the phantom was heated by HIFU inside the overpressure chamber. In this manner,
the difference between the measured and simulated temperature rise should be due to viscous heating on the thermocouple tip, and by measuring the temperature rise at multiple pressures, a type of calibration for the viscous heating artifact could be determined. This was not done due to equipment problems, but it could be factored into future studies.
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