



Stuart R. Faragher

St. John's College

Supervisor

Prof. Constantin-C. Coussios

Cavitation Methods for Characterising and Testing Clinical High-Intensity Focused Ultrasound Systems

**A thesis submitted for the degree of
Doctor of Philosophy**

Michaelmas 2011

Abstract

High Intensity Focused Ultrasound (HIFU) is rapidly emerging as a viable alternative to more invasive methods for routine treatment of malignant tissue. Key to the success of HIFU therapy is the development of standardised Quality Assessment (QA) procedures, designed to regularly assess the safety and efficacy of clinical HIFU transducers. Current HIFU QA procedures offer either accurate spatial calibration at the expense of impractically long acquisition times, or more rapid characterisation that provides only a spatially averaged measure of performance. Exploitation of acoustically induced inertial cavitation, however, offers the potential for rapid, pre-treatment spatial calibration without the need for time consuming scanning routines.

In this thesis, the concept of cavitation-based HIFU QA is validated for the first time, with various techniques developed to enable its implementation. To begin with, two-dimensional mapping using an array of needle hydrophones establishes that a growing cavitation region may be reconstructed at increasing insonation amplitudes. Extending the study to include a diagnostic linear array provides improved spatial resolution, enabling accurate, two-dimensional field characterisation within a novel, microparticle-seeded test medium that is shown to maximise the magnitude and spatial uniformity of cavitation occurrences. Performing this procedure in multiple focal planes provides a practical means of characterising a clinical HIFU transducer using readily available hardware.

An alternative array geometry is proposed for rapid, three-dimensional field characterisation. To allow accurate placement of a large number of elements within such an array, a novel, multiple-layer Printed Circuit Board (PCB) construction method is adopted. A model is developed to predict the effect of the multiple acoustic layers of the array on its receive sensitivity spectrum and the results contrasted with both a finite element solution and experimental data to inform the eventual array design.

An ideal passive array is thence specified through a combined experimental and computational approach, taking care to optimise the element size, number and distribution. This array configuration has the potential to enable reconstruction of a wide array of sources. The second generation prototype fulfils most of the requirements but has highlighted issues with crosstalk. Nevertheless, the results presented thus far provide a strong foundation for future work into cavitation-based HIFU QA.

Statement of Originality

I hereby declare that this submission is my own work and, to the best of my knowledge, it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the University of Oxford or any other educational institution, except where due acknowledgement is made in the thesis.

Any contribution made to the research by others, with whom I have worked at the University of Oxford or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Stuart Roy Faragher
September 2011

Acknowledgements

Throughout the work of this thesis, there have been many people who have contributed to ensure that my time in the BUBL group has been both enjoyable and rewarding. It has been an honour to work under the supervision of Professor Constantin-C. Coussios, whose enthusiasm and technical expertise has proved invaluable.

I am also grateful for the insight and support provided by academic and industrial partners on the EPSRC funded project titled 'Quality Assessment of Clinical HIFU Systems', of which this thesis forms part. In particular, I would like to thank Dr. Gail ter Haar, Dr. Ian Rivens, Dr. John Civate from the Institute of Cancer Research and Dr. Mark Hodnett and Mr. Adam Shaw from the National Physical Laboratory.

The BUBL group has provided not only a cohort of helpful and knowledgeable co-workers, but also many great friends, to whom I am extremely thankful for their support. Particular thanks go to Dr. Jamie Collin and Dr. Christian Coviello for their help with the transducer modeling work of this thesis, and Dr. Miklós Gyöngy and Dr. Carl Jensen for their guidance when using the diagnostic linear array. Furthermore, the technical skill, friendship and repartee offered by workshop technicians Mr. Jim Fisk and Mr. David Salisbury have helped to ensure that experimental work was a success and moral was maintained.

The latter sections of this thesis would not have been possible without the involvement of two companies in particular. Firstly, for their help with the manufacture and characterisation of the cylindrical array, thanks go to Precision Acoustics Ltd. and, in particular, Dr. Andrew Hurrell. Secondly, acquisition of data from the array would not have followed without the electronics expertise and devotion of Mr. Paul Doust and Mr. Mark Tanner from Det Norske Veritas Ltd..

Finally, and most importantly, none of the work detailed here would have been accomplished without the support of my family. In particular, I am forever indebted to my best friend and considerably better half, Miss Natalie Hockham.

I would also like to gratefully acknowledge the generous support of the Engineering and Physical Sciences Research Council (EP/F01564X/1).

Dissemination

Peer-Reviewed Conference Abstracts

S. Faragher, J. Collin, A. Hurrell, P. Doust, M. Tanner and C-C. Coussios, "In- vitro validation of three-dimensional cavitation-based pressure mapping for quality assessment of clinical high-intensity focused ultrasound devices", J. Acoust. Soc. Am. 129(4), 2405, (2011)

S. Faragher, M. Gyöngy, J. Collin, M. Hodnett, A. Hurrell and C-C. Coussios, "Three-dimensional passive localization of cavitation activity for quality assessment of clinical high-intensity focused ultrasound devices", J. Acoust. Soc. Am., 128(4), 2281, (2010)

C. Coviello, **S. Faragher** and C-C. Coussios, "Robust Capon beamforming for passive cavitation mapping during high-intensity focused ultrasound therapy", J. Acoust. Soc. Am., 128(4), 2280, (2010)

S. Faragher, M. Gyöngy, J. Collin, M. Hodnett, C-C. Coussios, "Design and implementation of a cylindrical array for passive mapping of cavitation fields produced by clinical high-intensity focused ultrasound transducers", J. Acoust. Soc. Am., 127(3), 1865, (2010)

S. Faragher, M. Gyöngy, M. Hodnett, A. Shaw, C.-C. Coussios, "Development of a tomographic cavitation sensor for quality assessment of clinical high-intensity focused ultrasound systems", J. Acoust. Soc. Am., 125(4), 2742, (2009)

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ACRONYMS

HIFU	High Intensity Focused Ultrasound
BBB	Blood-Brain Barrier
CEM	Cumulative Equivalent Minutes
QA	Quality Assessment
MRI	Magnetic Resonance Imaging
PVDF	Polyvinylidene Fluoride
NPL	National Physical Laboratory
NPLCS	National Physical Laboratory Cavitation Sensor
PCD	Passive Cavitation Detector
TMM	Tissue Mimicking Material
DRB	Dynamic Receive Beamforming
CW	Continuous Wave
SNR	Signal-to-Noise Ratio
TEA	Time Exposure Acoustics
PRFP	Peak Rarefactional Focal Pressure
DAQ	Data Acquisition
FFT	Fast Fourier Transform
IFFT	Inverse Fast Fourier Transform
CW	Continuous Wave
IQ	In-phase/Quadrature
PCB	Printed Circuit Board
VNA	Vector Network Analyser
FEA	Finite Element Analysis
ZIF	Zero Insertion Force



INTRODUCTION

The term ‘cancer’ encompasses a number of disorders that share a discerning growth dysregulation, many of which are inherently difficult to cure. Vast levels of funding and research effort are directed to improving understanding of the cause and progression of this disease and thence developing effective treatment options. This chapter summarises these efforts, focusing on the available treatment options and, in particular, on the emergence of High-Intensity Focused Ultrasound (HIFU) as a promising method for non-invasive ablation of malignant tissue. The challenges in developing this technology for frequent clinical application are presented, with particular attention paid to the need for accurate, standardised Quality Assessment (QA) procedures to ensure the safety and efficacy of HIFU therapy.

In 2008, there were 12.7 million newly diagnosed cases of cancer worldwide (Ferlay et al., 2010). Since President Nixon signed the National Cancer Act in 1971, promising \$100 million to fund “the same kind of concentrated effort that split the atom and took man to the moon” to conquer “this dreaded disease”, global cancer research funding has risen dramatically, standing at over £11.5 billion in 2004 (Eckhouse et al., 2008). Despite this vast level of funding, currently one in four people in the UK are expected to die from this disease (ONS, 2009). It is the inherent development of cancer that contributes to its lack of cure, characterised by a form of

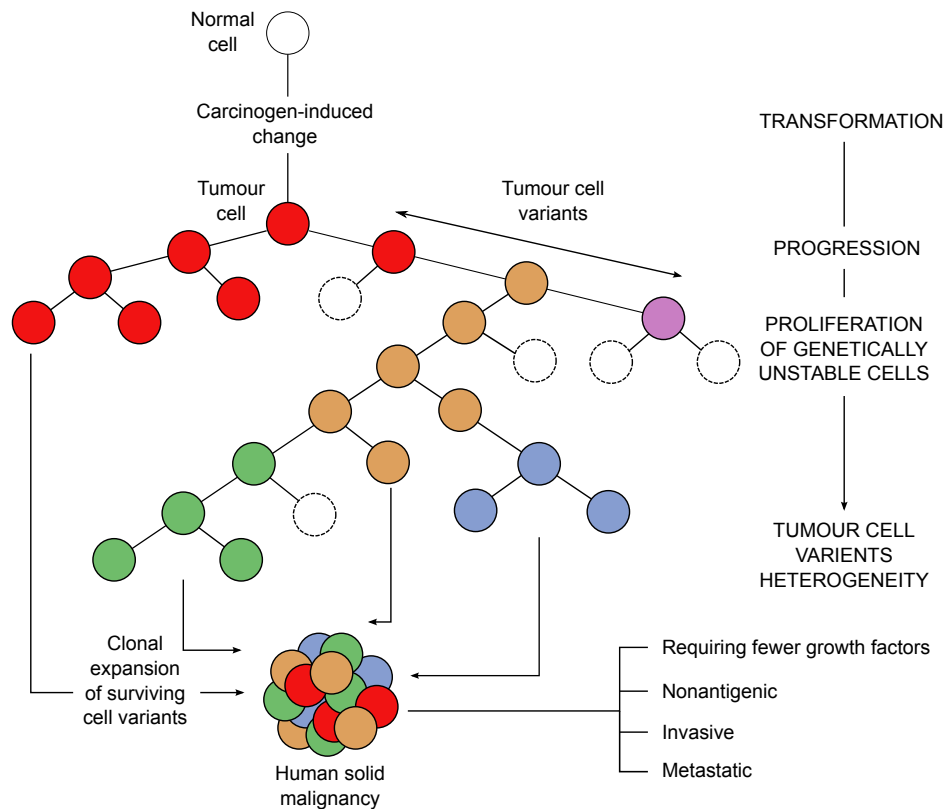


Figure 1.1: Evolution of malignancy showing tumour progression and generation of heterogeneity. Multiple mutations lead to the development of subclones that are adept at evading host defences, forming an aggressive tumour mass. Adapted from Robins and Cotran Pathologic Basis of Disease (Kumar et al., 2010).

Darwinian evolution whereby a succession of genetic changes, each contributing a growth advantage, leads to the progressive conversion of normal cells into cancer cells, as depicted in Figure 1.1.

Once established, cancer cells undergo uncontrolled abnormal mitosis, forming a mass which, when clinically detectable, is termed the *primary tumour*. The primary tumour may then spawn pioneer cells which migrate to adjacent tissues, forming a local metastasis, or to distant sites via lymphatic or hematogenous spread to form a metastatic tumour. Though the exact mechanism for metastatic dissemination is under debate (Klein, 2008), it is clear that metastases are responsible for the majority of cancer deaths, often rendering a patient untreatable and resulting in

multiple organ failure (Sporn, 1996). As such, once malignancy is established, early (preferably pre-metastatic) diagnosis is key to effective treatment of the disease.

1.1 CANCER: DIAGNOSIS AND TREATMENT

Up until the end of the 20th century, cancer diagnosis required exploratory surgery to remove tissue samples for laboratory-based analysis. Such invasive procedures were generally only performed once symptoms manifested themselves. The advent of a variety of screening techniques, designed to detect the pre-symptomatic presence of cancer cells, has had a marked effect on cancer survival rates. Beginning with the introduction of the Pap test for cervical cancer which, since its promotion by the American Cancer Society in the early 1960s, has seen the cervical cancer death rate in the US decline by almost 70%, a number of serological tumour marker and radiological screening methods have gained clinical acceptance and are now widely used (ACS, 2010). Mammography screening has been shown to be a valuable indicator for the presence of breast cancer, with a sensitivity reported in the region of 76% (Houssami et al., 2011), and is currently recommended as a regular screening process for all women in the UK aged 50-70. A host of additional diagnostic tools are currently under investigation, notably faecal occult blood screening for colorectal cancer, which has been the subject of a number of national pilot studies (Bernie et al., 1998). With promising developments in screening techniques, successful treatment of the disease has become much more achievable.

Once diagnosed, modern cancer treatment usually involves a combination of surgical resection, radiation and/or drug-based therapies such as chemotherapy or immunotherapy. This multi-modal approach aims to remove or destroy the malignant mass and, crucially, ensure any remaining cancer cells are eliminated to pre-

vent recurrence of the disease. Although successful in many cases, 5 year survival rates for those diagnosed with the disease currently stand at a disappointingly low 66% (Altekruse et al., 2009), with those surviving often suffering debilitating side effects.

Advances in surgical techniques have informed the progression from mutilating procedures, such as amputation, to more local removal of tumours whereby the primary mass is removed along with a small margin of surrounding healthy tissue. Such invasive intervention, however, is not without risk and complications such as seeding of metastasis or haemorrhaging via visceral or vascular puncture are common (Kennedy, 2005). Radiation therapy limits these risks by using an external, implanted or systemically administered source to direct ionising radiation towards the tumour, forming free radicals which break the double helix of the cell DNA, leading to irreversible loss of a cell's reproductive capacity (Joiner and van der Kogel, 2009). Since cancer cells have a reduced ability to repair this damage they are preferentially destroyed; however, the damage incurred by healthy cells results in a variety of unpleasant side effects for the patient. Similarly, chemotherapy, which aims to limit the proliferation of cancer cells by using cytotoxic drugs to effect DNA synthesis, suffers from a lack of selectivity resulting in toxic effects on other, rapidly dividing, normal cells such as those of the bone marrow, hair follicles and mucus membranes (Skeel, 2007).

There is, therefore, significant demand for less invasive, targeted cancer therapies designed to effectively destroy malignant tissue with minimal adverse side effects. Many technologies designed to satisfy this need are currently under development. One such therapy that shows particular promise is the use of High-Intensity Focused Ultrasound (HIFU) to induce localised hyperthermia within a malignant mass. In contrast with other minimally invasive techniques such as radiofrequency

ablation, laser ablation and cryoablation, HIFU is one of the few truly non-invasive cancer therapies, offering a mechanism for avoiding the aforementioned complications associated with open surgery. Unlike radiotherapy, HIFU uses non-ionising radiation and can be tightly focused to ensure energy deposition is highly localised, causing minimal damage to surrounding tissue. There are, therefore, very few side effects associated with HIFU treatment and, with no upper limit to the number of repeated exposures for a given patient, this treatment offers a promising alternative to current clinical practices. Though HIFU-induced thermal ablation is the primary application of the work of this thesis, it is instructive to consider the range of therapeutic applications of ultrasound that are currently available.

1.2 THERAPEUTIC ULTRASOUND

Ultrasound is no longer merely a diagnostic modality - since the pioneering experimental studies of the late 1930s and early 1940s exploring the use of ultrasound as a medical tool, its possible therapeutic applications have been suggested (Schliephake, 1935; Dussik, 1942). It is not until recently, however, that the potentially beneficial bioeffects of both focused and unfocused ultrasound fields have been explored in depth. The applications of such effects stretch over a wide range of operating regimes, from low-intensity standing wave fields used to structure cells in engineered tissues (Garvin et al., 2009), to high-intensity focused fields designed to induce localised tissue heating, resulting in thermal necrosis of cancerous cells (Leslie and Kennedy, 2007; Haar and Coussios, 2007).

In many of these applications, acoustic cavitation - defined as the oscillation and subsequent collapse of acoustically-formed or pre-existing gas- and vapour-filled nuclei under the action of an acoustic stimulus - is believed to be a mechanism re-

sponsible for the desired therapeutic effect (Leighton, 1994). Perhaps the most common therapeutic application of ultrasound in clinical use today is the treatment of nephrolithiasis via extracorporeal shock wave lithotripsy. First developed in the late 1970s, this non-invasive procedure induces mechanical damage of kidney calculi by focussing shockwaves onto their surface (Chaussy and Schmiedt, 1984). Here it has been observed that the initial fissures created by the shockwave act as nucleation sites for cavitating bubbles, which subsequently fragment the stone following violent collapse (Coleman et al., 1987).

High-intensity, short-duration ultrasound pulses may also be used for localised tissue destruction in a process known as *histotripsy*, whereby small clouds of cavitating bubbles are acoustically driven to induce mechanical damage within tissue. Precise control of the intensity and pulse repetition frequency of the insonating field ensures that tissue heating is minimised, and it is the mechanical damage alone that, in effect, liquifies the tissue within the focal volume (Xu et al., 2005).

Ultrasound also has promising applications for haematology, both in the non-invasive control of internal bleeding by ultrasound-induced vascular occlusion (Vaezy and Zderic, 2007), and in the dissolution of blood clots via enhancement of the thrombolytic effect of recombinant tissue plasminogen activator (rt-PA) (Trübestein et al., 1976; Datta et al., 2006). The former capitalises on both the thermal and mechanical effects of HIFU-induced cavitation to allow cauterisation at the depth of parenchymal tissues, whilst the latter benefits from the effect of cavitation-induced streaming and microjetting to enhance the penetration of thrombolytic drugs into a clot. The addition of microbubbles has been shown to enhance this effect (see Figure 1.2), resulting in a corresponding increase in clot mass loss.

In a similar manner, therapeutic ultrasound may be used to promote the delivery of drugs across the Blood-Brain Barrier (BBB), a specialised structure that limits

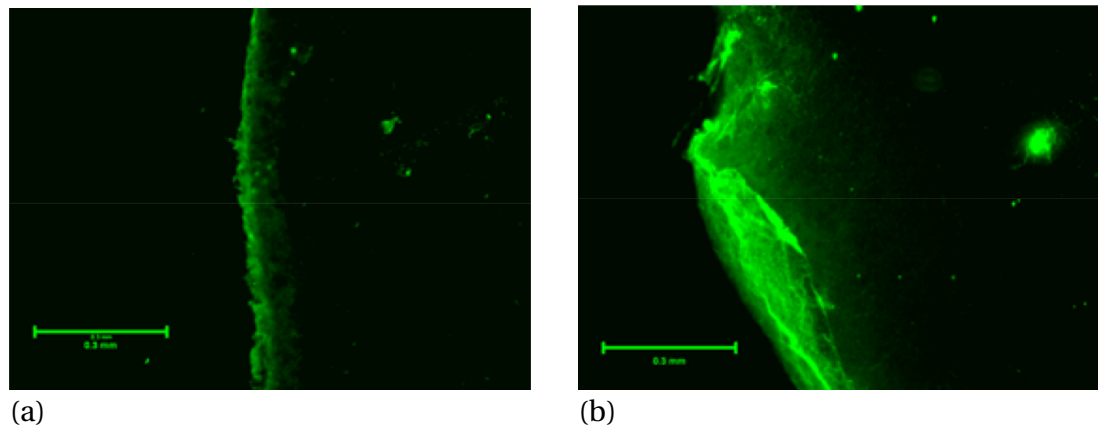


Figure 1.2: Penetration of fluorescent stained rt-PA into an *in-vitro* thrombus model. Thrombus sections are shown for (a) rt-PA and ultrasound alone; and (b) rt-PA, ultrasound and Definity[®] microbubbles (Datta et al., 2008).

transport and diffusion from the vasculature to the central nervous system. Here, the presence of ultrasound contrast agents in conjunction with ultrasound-induced cavitation activity has been shown to promote disruption of the BBB, resulting in a corresponding increase in the delivery of injected MRI contrast agents to the cerebral tissue (McDannold et al., 2006).

Moreover, the therapeutic activity of a pharmaceutical agent may be locally enhanced by exposure to a HIFU field, thereby limiting the characteristic systemic toxicity of traditional chemotherapy treatments. By encapsulating drugs within lipid or polymer spheres, or micelles, they may be activated locally at the intended treatment site by HIFU-induced cavitation (Allen and Cullis, 2004; Coussios and Roy, 2008). Furthermore, the limited extravasation of the typically highly disorganised tumour vasculature can be enhanced by inertial cavitation, a form of violent bubble collapse detailed further in Chapter 2, promoting deeper penetration of cytotoxic drugs (Husseini et al., 2005; Böhmer et al., 2010).

Finally, HIFU has promising applications for non-invasive surgery, facilitating the thermal ablation of cancerous tissue whilst avoiding the risk of metastasis posed



Figure 1.3: Illustration of the Chongqing clinical HIFU device in use at the Churchill Hospital, Oxford. The HIFU transducer is positioned below the central table, on which the patient lies, and is aligned using a computer-controlled, motorised positioning system. Acoustic coupling with the patient is achieved via a pool of degassed and deionised water, whilst treatment monitoring is limited to B-mode hyperecho. Image courtesy of the Oxford HIFU Unit.

by more invasive surgical procedures. The focused nature of the ultrasound beam allows highly localised energy deposition via absorption of the acoustic field, resulting in large temperature rises (on the order of 60°C), the subsequent disruption of secondary and tertiary protein structure, and thermal necrosis of cells within the focal volume.

Currently the subject of a number of clinical trials, it is the use of HIFU for non-invasive ablation of malignant tissue that forms the primary motivation for the work of this thesis. Extracorporeal HIFU devices, such as that depicted in Figure 1.3, have been shown to offer complete tumour ablation, with over 1000 patients in China having received HIFU treatment for a variety of tumour types (liver, breast, kidney, osteosarcoma, pancreas) (Wu et al., 2001, 2004). Within the UK, the Oxford HIFU Unit has been conducting clinical trials for over eight years, with studies indicating

that discrete zones of ablation can be achieved in 100% of hepatic and 67% of renal tumour treatments (Illing et al., 2005; Ritchie et al., 2010).

1.3 HIFU: THERMAL EFFECTS

The mechanical energy carried by therapeutic ultrasound waves can be converted into heat through viscous absorption, and the mechanisms for ultrasound-induced heating are reviewed in greater detail in Section 2.3. Achieving clinically relevant temperature rises during HIFU therapy depends not only on the acoustic energy that is deposited within the tissue, but also on the rate at which heat is removed due to tissue conduction and blood perfusion. It is possible to estimate the acoustically-induced temperature rise using Pennes' bioheat transfer equation (Wissler, 1998):

$$\rho_t C_t \frac{dT_t}{dt} = k_t \nabla^2 T_t - w_b C_b (T_t - T_b) + Q_{ac} + Q_m, \quad (1.1)$$

where ρ_t , C_t , T_t and k_t are the density, heat capacity, temperature and thermal conductivity of the tissue, respectively, w_b , C_b and T_b are the perfusion rate, heat capacity and ambient temperature of the blood, respectively, Q_{ac} is the heat deposition by ultrasound, Q_m is the metabolic heat and t is time. Defining a threshold temperature for thermal necrosis is somewhat arbitrary since it ignores the cumulative effect of elevated temperatures. As Figure 1.4 shows, a whole host of temperature profiles may be used to generate equivalent biological effects, and so a temperature-time based metric of the *thermal dose* administered, known as the "Cumulative Equivalent Minutes" (CEM), is generally adopted. Defined as the amount of time for which tissue would have been held at 43°C to achieve the same effect, the CEM metric reduces the temperature profile to a single dosimetric value, formulated as follows:

$$CEM_{43} = \int R^{43-T(t)} dt, \quad (1.2)$$

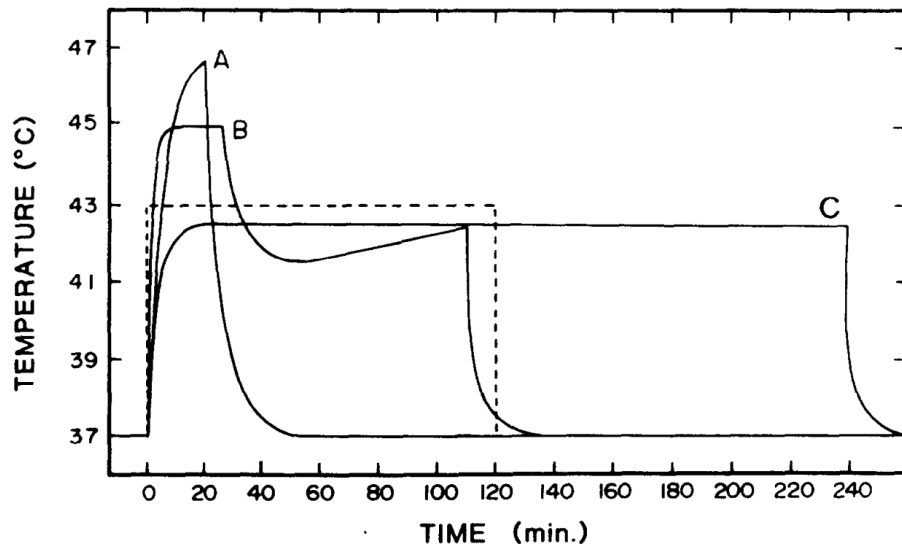


Figure 1.4: Theoretically generated temperature profiles as a function of time. The ideal temperature profile is shown by the dashed line and represents 120 minutes at 43°C. The three additional profiles (A-C) are all equivalent to 120 minutes at 43°C by CEM calculation. Clearly, the areas under each curve are *not* equal (Sapareto and Dewey, 1984).

where R is a temperature-dependent parameter approximated as 0.25 below 43°C and 0.5 above (Sapareto and Dewey, 1984). It is generally accepted that above a CEM value of 240 minutes, sufficient thermal dose has been delivered to achieve thermal ablation, though above 50°C the applicability of this measure becomes uncertain.

Successful thermal ablation of tissue therefore requires high heating rates to be achieved and elevated temperatures to be maintained for sufficient time to deliver an appropriate thermal dose. Acoustic cavitation has been shown to enhance focal heating rates, reducing the time required to achieve a specific CEM metric (Coussios et al., 2007a; Hockham et al., 2010). Furthermore, HIFU-induced cavitation provides a mechanism for real-time treatment monitoring, a key requirement for widespread adoption of the technique (Gyongy and Coussios, 2010).

1.4 HIFU ABLATION: TREATMENT MONITORING

Despite its many advantages, HIFU ablation is yet to be widely adopted as a routine clinical procedure due to several impediments, which researchers are currently attempting to address. One of the major challenges is the required treatment time, which increases with the volume to be ablated, and can stretch to more than 6 hours for a 10cm diameter liver tumour (Kennedy, 2005). Increasing the intensity of insonation increases heating rates and hence reduces lesion formation time; however, this comes at the expense of increased likelihood of pre-focal tissue damage away from the intended treatment site (Watkin et al., 1996).

One of the most restrictive inadequacies of HIFU therapy, however, is the lack of suitable real-time imaging and treatment monitoring techniques. Moreover, regardless of the monitoring modality, successful treatment is reliant upon the ability to generate a highly reproducible pressure field, thus requiring a range of accurate, standardised Quality Assessment (QA) procedures. Though it is the need for HIFU QA procedures that forms the primary motivation for the work of this thesis, it is instructive to first consider the range of HIFU treatment monitoring techniques that are currently available, since the two fields are interrelated. Furthermore, knowledge of the hardware that is currently in use for HIFU treatment monitoring offers a useful starting point for potential QA techniques.

The safe, effective and reliable treatment of a patient using HIFU therapy is reliant upon meticulous monitoring of treatment progress during the procedure. The primary aim of any HIFU monitoring method is, therefore, to accurately determine the region of thermally necrosed tissue without compromising the non-invasive nature of the treatment, preferably in real-time. At present, the most common non-invasive HIFU monitoring modalities in clinical use are Magnetic Resonance Imag-

ing (MRI) and active ultrasound imaging. Each attempts to monitor either the thermal history of the treated region or a change in the mechanical properties of the treated tissue, which may then be used to predict necrosis via calculation of the thermal dose administered. A variety of methods may be used to determine these properties, each approach with its own advantages and disadvantages.

1.4.1 Magnetic Resonance Imaging

Widely used as a medical imaging method for visualisation of soft tissue, MRI offers the ability to distinguish between different tissue types, and is currently the gold standard technique for guidance and follow-up of HIFU-induced thermal ablation (Hynynen and McDannold, 2004). Whilst a comprehensive review of MRI physics is beyond the scope of this work, it is instructive to consider the basic principles of the technique.

The human body consists of primarily fat and water, both of which contain a large proportion of hydrogen atoms. Any spinning hydrogen nucleus has a magnetic field along the direction of its angular momentum. When a patient lies in an MRI scanner, a strong magnetic field is applied in a particular direction and, consequently, the hydrogen nuclei align with the field in either a high or low energy state. By applying an external RF field at the appropriate frequency (the proton resonant frequency or PRF), hydrogen nuclei may be flipped from low to high energy states. When the RF field is removed, the hydrogen nuclei return to their equilibrium orientation and the net magnetic field relaxes to its original state. The time taken to achieve relaxation along the axis of the applied field (T1 or spin-lattice relaxation time) and in the perpendicular plane (T2 or spin-spin relaxation) differs between tissue types, which facilitates the non-invasive imaging of soft tissues.

Post-operatively, HIFU-induced lesions may be accurately identified using T2 weighted images once the tissue has been allowed to cool down (Damianou et al., 2004). During treatment, MR based thermometry techniques may be used to estimate the thermal dose delivered. At lower temperatures ($<50^{\circ}\text{C}$), T1 weighted images have been shown to be highly sensitive to temperature changes (Rivens et al., 2007). However, at the temperatures relevant to HIFU-induced thermal ablation, monitoring the temperature-dependent shift in the PRF has been shown to give more accurate temperature estimations. Using this method, temperature resolutions of $\pm 0.5^{\circ}\text{C}$ may be achieved; however, temporal resolutions are far from real-time (Ishihara et al., 1995). Importantly, this highlights one of the key limitations of MRI-based HIFU treatment monitoring - even the most advanced MRI monitoring systems involve a significant compromise between spatial and temporal resolution: sub-millimetric spatial resolution can be achieved in time steps on the order of seconds, which are comparable to the times required for ablation, whilst faster frame rates result in a spatial resolution that is larger than the typical 1mm diameter of the HIFU focus. Furthermore, MRI equipment is prohibitively expensive and, as a result, not readily available. Concerns have thus been raised regarding the reliability and suitability of this technique for accurately identifying treated tissue (ter Haar, 2009).

1.4.2 Ultrasound Imaging

In contrast to MRI, ultrasound imaging equipment is relatively inexpensive and readily available. Conventional B-mode imaging may be used to observe hyperechogenicity (or ‘bright-ups’) during HIFU therapy, though care is needed to synchronise diagnostic and therapeutic pulses to avoid saturation of the image by the therapeutic pulse (Vaezy et al., 2001). Possibly the simplest and hence most com-

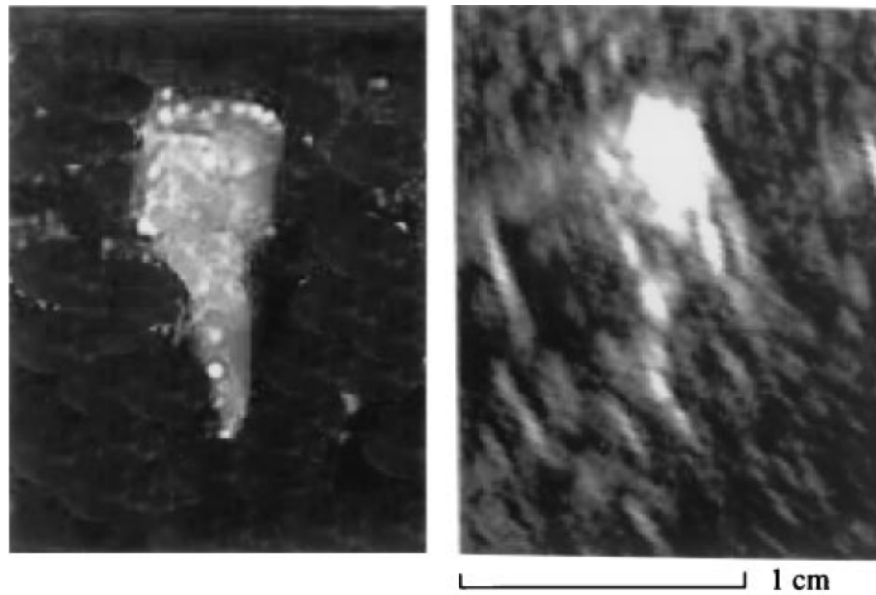


Figure 1.5: Comparison of a HIFU-induced lesion produced at $1750\text{W}/\text{cm}^2$, 0.1MPa overpressure and corresponding B-mode ultrasound image. The hyperechogenicity indicates the presence of boiling bubbles which are the result of over treatment of the target site (Bailey et al., 2001).

monly used method of ultrasound HIFU monitoring, this relies upon the presence of stabilised bubbles, likely due to boiling, which remain in the focal region once the therapeutic pulse has ceased. With a much lower acoustic impedance than the surrounding medium, these bubbles are highly echogenic and so highly visible using conventional B-mode imaging. However, reaching the near-boiling temperatures required to create such bubbles is believed to be unnecessary and may be qualified as overtreatment, since protein denaturation and the associated thermal necrosis of cells can be readily achieved with tissue temperatures on the order of 60°C sustained for a few seconds. Furthermore, several studies have confirmed that hyperechogenicity only becomes significant once a lesion begins to grow in an unpredictable manner (Rabkin et al., 2005, 2006; Bailey et al., 2001), producing undesirable ‘tadpole’ shaped lesions such as those shown in Figure 1.5.

Despite its low cost and ease of access, B-mode hyperecho is, therefore, far from

ideal as a HIFU treatment monitoring tool. The variation of temperature and accompanying denaturation of tissue during HIFU therapy results in changes in a variety of acoustic parameters. This has motivated the experimental investigation of a number of additional ultrasound-based monitoring methods capable of operating at sub-boiling temperatures.

1.4.2.1 Ultrasound Thermometry

Variation of the speed of sound with temperature manifests itself on an ultrasound image as an apparent strain, which can be related to the temperature change provided an accurate relationship between sound speed and temperature is known (Seip et al., 1996). Such relationships exist in non-fatty tissues, where a peak in sound speed is observed around 50°C (Bamber and Hill, 1979). This therefore implies a non-uniqueness in temperature for a given sound speed and so knowledge of the thermal history is required to accurately determine temperature. Furthermore, variations in the lipid content of tissue results in significant differences in temperature dependence, which may be difficult to account for. Finally, once denatured, ablated tissue exhibits an altogether different sound speed due to a dramatic change in stiffness and so attention must be paid to the thermal dose delivered in addition to the temperature attained. The marked increase in stiffness of thermally ablated tissue, believed to result from irreversible protein denaturation and aggregation (Wu et al., 2001), presents further opportunities for HIFU monitoring techniques based on elastography.

1.4.3 Elastography

Both MRI and ultrasound may be used to non-invasively image changes in stiffness that result from HIFU-induced thermal ablation. By mapping the displacement of features pre- and post-application of an external force, estimates of the strain may be calculated to indicate local changes in stiffness. In general, the applied force is either in the form of a simple mechanical load or an ultrasonically-induced radiation force. Ultrasound-based elastographic identification of lesions has been shown to correlate with T1-weighted MRI imaging in *in-vivo* studies of HIFU prostate cancer treatment although, as with B-mode monitoring techniques, interference with the therapeutic signal prevents real-time visualisation (Curiel et al., 2005). Furthermore, care must be taken to account for the temperature-dependent change in sound speed in order to accurately determine tissue displacement. MR elastography is based upon similar principles, using phase contrast MRI techniques to spatially map displacements corresponding to mechanically-induced shear waves (Fatemi et al., 2003; Sinkus et al., 2008). However, long acquisition times (on the order of 20-120s) and high sensitivity to temperature variation mean that this method is more suited to post-treatment follow-up, rather than real-time monitoring.

There is therefore a great need to improve current targeting and monitoring methods for HIFU therapy in order to ensure its overall success as a viable alternative to open surgery and minimally invasive treatments.

1.4.4 Passive Cavitation Monitoring

A particularly promising and novel method of delivering HIFU therapy, which could potentially both reduce treatment times and enable real-time treatment monitoring, lies in the exploitation of HIFU-induced cavitation. By utilising the distinctive

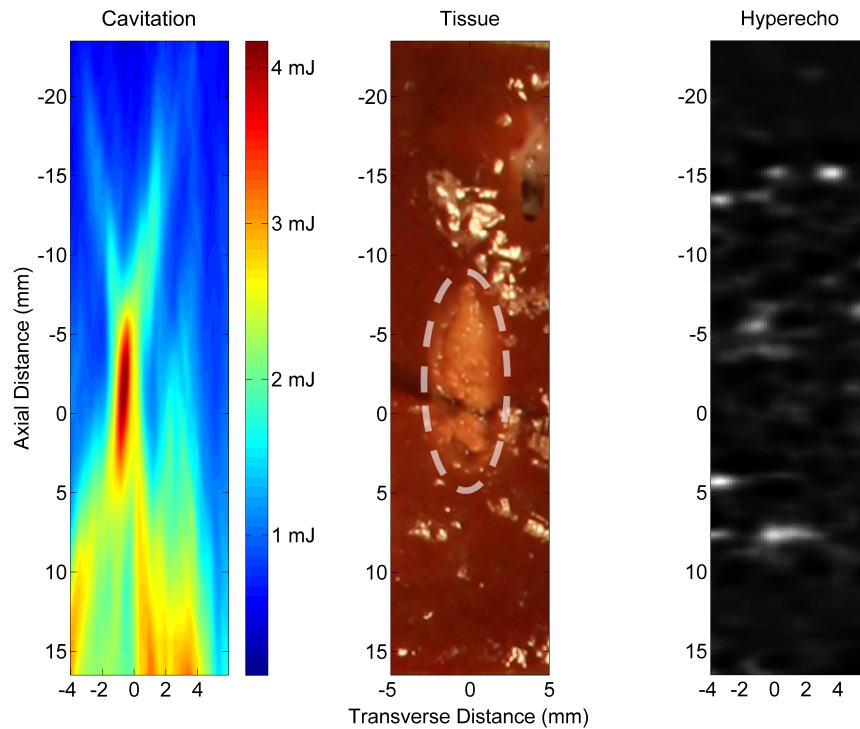


Figure 1.6: Passive cavitation mapping for real-time treatment monitoring. Passive mapping of the spatial extent of the cavitation region correlates well with HIFU lesion size and location, whilst conventional B-mode hyperecho fails to accurately identify the lesion (Jensen et al., 2011).

responses of cavitating microbubbles, which in general shift energy content to frequencies above the fundamental insonation frequency, the type of bubble activity can be ascertained and used to predict the local temperature variation. In one dimension, a focused transducer is used to passively detect these secondary acoustic emissions, whilst two-dimensional mapping is achieved using an array of receiving elements (Holt and Roy, 2001; Coussios et al., 2007a; Gyongy and Coussios, 2010).

As can be seen in Figure 1.6, two-dimensional passive mapping of the spatial extent of the cavitating field has been shown to correlate well with HIFU lesion size and location in excised hepatic bovine tissue, providing a unique opportunity for non-invasive, real-time treatment monitoring and control (Jensen et al., 2011; Hockham et al., 2010). Promising though this phenomenon is, the widespread clin-

ical adoption of cavitation-enhanced HIFU for the regular treatment of deep-seated solid tumours cannot be achieved without detailed knowledge of the conditions for instigation and of the subsequent evolution of bubble clouds under HIFU exposure.

1.5 HIFU ABLATION: QUALITY ASSESSMENT

In general, whether treatment monitoring is to be achieved by B-mode ultrasound, MRI or cavitation monitoring, successful therapy relies on the generation of a highly reproducible pressure field by the HIFU transducer across multiple treatments and multiple patients. Adequate standardised QA procedures are thus required in order to ensure the safety and efficacy of the treatment as a wide range of clinical transducers are used to treat vastly different tissue regions. At present, clinical HIFU systems are assessed on an *ad hoc* basis using a number of different procedures, which are both time-consuming and costly. In general, the peak negative pressure and acoustic intensity are the metrics of most interest for thermal ablation, and it is important to understand the spatial variations of these parameters throughout the HIFU field. Below is a summary of some of the measurement techniques that are currently in use or under investigation.

1.5.1 Hydrophones

Most current QA procedures rely upon the use of a piezo-electric or fibre-optic hydrophone to probe the acoustic field produced by a HIFU transducer. By scanning a hydrophone throughout the HIFU field, accurate maps showing the spatial variation of pressure, such as that shown in Figure 1.7, may be constructed.

For the frequency ranges of interest for medical applications, hydrophones are

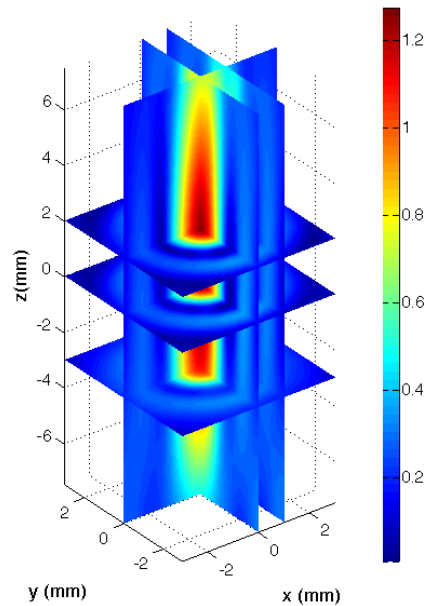


Figure 1.7: Three-dimensional pressure profile of a 1.067MHz HIFU transducer, generated by scanning a $75\mu\text{m}$ needle hydrophone (Precision Acoustics HPM075) throughout the region of interest with 0.25mm spacing in the transverse and elevational directions, and 0.5mm spacing in the axial direction. Scans of this extent typically take around 14 hours to acquire data throughout the entire volume. Values given are peak negative pressures (MPa).

usually in the form of either a membrane, needle or fibre-optic. Membrane hydrophones are considered to be the "gold-standard" of hydrophones due to their smooth, broad frequency response. Consisting of a thin piezo-polymer film that is constructed to be acoustically active in a small area at its centre, a membrane hydrophone can accurately characterise short, broadband pulses, but is less suitable for continuous wave signals which may develop standing waves on the membrane (Dolezal and Kollmann, 2010).

Needle hydrophones, comprising a small (typically in the range $40\text{-}400\mu\text{m}$) piezo-polymer or piezo-ceramic disc supported on the end of a needle-like structure, offer a more robust and less costly solution for HIFU field characterisation. Such devices are, however, particularly susceptible to cavitation and thermal dam-

age around the active element, limiting the intensity and peak negative pressure of the waveform that may be measured.

Several devices have been developed to withstand the high amplitude fields present during HIFU exposure, in particular, reflector style devices and fibre-optic hydrophones (Kaczkowski et al., 2003; Staudenraus and Eisenmenger, 1993). By reflecting the incident HIFU wave off a fused silica optical fibre, and receiving the scattered wave using a number of Polyvinylidene Fluoride (PVDF) receiving elements, Schafer *et al.* were able to monitor focal pressure without exposing the sensitive element to potentially damaging pressure levels (Schafer et al., 2005). Remote sensing of the field does, however, prolong the propagation distance and increase attenuation of the higher frequency components of the field, which must be taken into consideration. Fibre-optic hydrophones are usually based upon either the change in refractive index of water due to ultrasonic pressure, or the acoustically-induced changes in thickness of a film at the tip of the fibre and, since they rely solely upon optical transduction, are effectively immune to electro-magnetic interference (Beard et al., 2000). These devices are usually able to withstand higher amplitude acoustic fields than traditional needle hydrophones and offer the potential for simultaneous temperature and pressure measurement.

Unfortunately, all hydrophones suffer from a common shortcoming: to fully characterise spatial variations within a HIFU field, the hydrophone must be scanned throughout the field, a time-consuming process that can take several hours and is impractical for routine clinical QA of HIFU devices. Additional methods have been developed to assess HIFU field characteristics; however, their accuracy and suitability for clinical application is yet to be demonstrated.

1.5.2 Optical Devices

Using similar principles to fibre-optic hydrophones, a variety of methods have been developed for HIFU field visualisation and measurement that are based upon the acousto-optic effect. Optical interferometry, a process whereby ultrasound-induced oscillations of a membrane are monitored using an optical beam, has been shown to accurately determine acoustic amplitudes in the plane of interest in the 5-15MHz range with a resolution below 0.1mm (Royer et al., 1992). Local changes in the density of the water brought about by the presence of an acoustic field result in perturbations in the localised refractive index which in turn causes changes in the optical path length that may be measured using laser Doppler vibrometry (Harland et al., 2004). Though facilitating the visualisation of the spatial characteristics of the acoustic field, this method is unable to produce quantitative measurements of the acoustic pressure or intensity and is more suited to qualitative evaluation of HIFU field characteristics. Similarly, Schlieren imaging can produce quite beautiful visualisations of HIFU fields, such as that shown in Figure 1.8, but is yet to provide quantitative results (Sasaki et al., 2003; Howard et al., 2003). Furthermore, such optical methods require expensive, cumbersome equipment that is not well-suited to regular clinical use.

1.5.3 Radiation Force Balances

Radiation force balances may also be used to quantify spatially averaged or local acoustic intensities, depending on the size of the target used (Shaw and Hodnett, 2008). When an absorbing target is placed in the path of an acoustic beam, it experiences a force due to the momentum of the beam which can be measured to

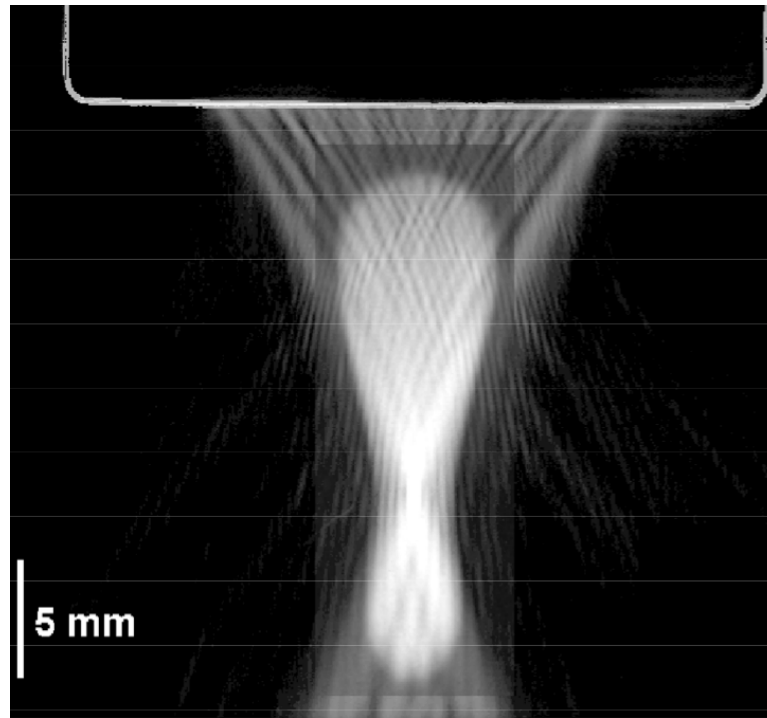


Figure 1.8: Schlieren image of a 4MHz HIFU beam used to visualise the spatial characteristics of a field for evaluation of a tissue mimicking phantom. Superimposed is an image of a lesion obtained in the phantom following 72 seconds of exposure at 10W (Howard et al., 2003).

determine the corresponding acoustic power via Equation 1.3.

$$P = F_m c \frac{2}{1 + \cos \gamma}, \quad (1.3)$$

where P is the acoustic power, F_m is the measured force exerted on the target, c is the speed of sound in the medium and γ is the half angle subtended by the transducer (IEC, 2006). Measurements of the power may then be used to calculate the intensity spatially averaged over the area enclosed by the half-pressure maximum contour in the focal plane, I_{SAL} , a metric originally proposed by Hill et al. and now commonly used as a reference quantity (Hill et al., 1994; Shaw and ter Haar, 2006). Assuming a Gaussian beam, with a -6dB beam diameter, D , determined using a hydrophone, the spatially averaged intensity may be calculated as:

$$I_{SAL} = 0.867 \frac{P}{D^2}, \quad (1.4)$$

where P is the acoustic power determined using a radiation force balance. Though this method has general applicability, the Gaussian approximation ignores contributions to the power from side lobes and so has questionable accuracy.

Commonly used for the calibration of lower intensity therapeutic ultrasound devices, radiation force balances are not well suited to high-intensity focused fields where the near complete absorption that is required within the target to accurately quantify a change in load often leads to significant heating and hence damage of the target. To address this issue, caster oil targets have been developed, whose buoyancy increases as a result of heating during insonation (Shaw, 2006). This method does, however, only provide information about the total power output of a given HIFU transducer, and cannot determine spatial variations in the HIFU field. Furthermore, the radiation force balances used to carry out those measurements are cumbersome and would generally require removal of the transducer from the clinical HIFU device, rendering them poorly suited to frequent clinical use.

1.6 CONTRIBUTIONS OF THE CURRENT WORK

A variety of HIFU QA methods are currently available, each with its own strengths and weaknesses. Hydrophones are the current "gold standard" for HIFU QA; however, in order to fully characterise the region of interest, time-consuming and impractical scanning routines are required. Radiation force and buoyancy methods offer more rapid characterisation, but fail to capture spatial variations in the field. Acousto-optic methods may capture such spatial variations, but cannot provide quantitative measures of the field properties and rely on cumbersome, expensive equipment.

In order to ensure the effective QA of HIFU transducers, it is important that a

device is developed to facilitate rapid, accurate and inexpensive characterisation of HIFU fields in a clinical setting. It has been shown that acoustic cavitation is a prominent phenomenon in a host of therapeutic ultrasound applications. For HIFU ablation, exploitation of the effects of cavitation may offer the ability to overcome some of the shortcomings of the procedure, whilst providing a unique opportunity for rapid spatial characterisation of the field.

With cavitation being primarily a pressure-driven phenomenon, mapping of the extent of the cavitating region under different HIFU pressure amplitudes could effectively enable three-dimensional characterisation of the pressure field produced by a clinical transducer. The primary aim of this work is thus to develop a three-dimensional passive array-based cavitation sensor, capable of quantifying and localising cavitation activity induced by clinical HIFU systems over a range of excitation conditions. In addition to its primary role as a QA tool, this device could also be used to achieve a better understanding of cavitation instigation and cavitation dynamics in Tissue-Mimicking Materials (TMMs) and *ex-vivo* tissue.

Recent work at the National Physical Laboratory (NPL) using a newly developed single cylindrical PVDF element cavitation sensor (the NPLCS) has shown promising results for the characterisation of cavitating fields in ultrasonic cleaning vessels (Hodnett and Zeqiri, 2008). The novel device facilitates quantification of spatially averaged cavitation activity within the cylindrical volume which it encloses and can be scanned throughout a field to map spatial variations. This thesis aims to build upon the design of the NPLCS by developing a multi-element, cylindrical PVDF cavitation sensor that can map cavitation activity in three dimensions without the need for a time-consuming and clinically impractical scanning procedure.

This chapter has described the pathologic basis of cancer, presenting the main treatment options available to patients and introducing the plethora of promising

therapeutic applications of ultrasound. HIFU has been shown to facilitate the non-invasive ablation of malignant tissue, avoiding the complications associated with the traditional treatment options of open surgery, radiation therapy and chemotherapy. The progression of HIFU from laboratory to clinical application does, however, require significant innovation. In particular, accurate, standardised QA procedures must be established, a need which motivates the present work.

The following chapter details the underlying principles of HIFU therapy, exploring the physical mechanisms responsible for HIFU-induced tumour ablation and the role that acoustic cavitation has to play in enhancing focal heating rates and providing a means for remote mapping through observation of acoustic emissions. The principle of the proposed cavitation-based pressure mapping tool is explained in more detail, along with a review of conventional ultrasound imaging and passive mapping techniques. The key aspects of array design are also considered, forming the basis of the work presented in the subsequent chapters.

Chapter 3 first explores the viability of cavitation-based pressure mapping in two dimensions. Initial results demonstrate the proposed technique using an array of needle hydrophones to map a growing cavitation region. Methods are then developed for the use of a medical diagnostic linear array to image cavitation activity in the HIFU focal planes. The measured distribution of activity is correlated with predicted results and a clinically applicable procedure is proposed for rapid, two-dimensional HIFU QA. The results from this chapter eventually inform the design of a cylindrical array intended for three-dimensional reconstruction of a cavitating region, thus enabling more complete characterisation of the insonating field.

Chapter 4 proposes a novel, multiple-layer method of construction of the three-dimensional array to allow accurate placement of the sensor elements in a manner that eliminates sensitivity to acoustic signals along the electrode path. Tech-

niques for characterising the behaviour of piezo-electric devices are considered and an analytic model developed to predict the frequency-dependent sensitivity of the array. This is subsequently compared to finite-element solutions and experimental results.

The design and validation of a prototype cylindrical array is outlined in Chapter 5. Initially, a first-generation sensor supplied by NPL is modelled computationally and evaluated experimentally. This informs the numerical optimisation of a second-generation array which, together with the findings of Chapter 4, yields a functioning multiple-element three-dimensional cavitation sensor. Experimental validation of the second-generation design ensues, offering useful insight into the design of arrays with similar construction and providing a strong foundation for future work into cavitation-based HIFU QA.

On the basis of these results, Chapter 6 suggests a number of applications of the developed cavitation mapping system, along with potential design improvements, and summarises the key findings of the thesis.



THEORY OF ULTRASOUND

The therapeutic applications of ultrasound are widespread; however, in general, each treatment is governed by the basic physics of sound propagation. This chapter considers the fundamental relations describing both linear and non-linear sound propagation, followed by an explanation of the mechanisms by which HIFU insonation results in localised heat deposition. In particular, the role of acoustic cavitation is explored, with attention paid to the distinctive frequency spectra of radiated acoustic emissions. By remotely detecting such emissions, not only is it possible to identify the type of activity that is occurring, but also to localise its source, offering the potential for cavitation-based HIFU QA - a concept which is explained in detail here. Finally, this chapter considers the basic principles of imaging and array design, used to inform subsequent modelling and experimental work.

During HIFU therapy, an extracorporeal or intracorporeal transducer is used to generate a focused ultrasound field centred on the intended treatment site. An alternating voltage applied to the transducer face causes thickness oscillations in the piezoelectric material from which it is made, resulting in pressure perturbations (sound) in the surrounding medium. These pressure perturbations propagate throughout the medium in the form of a longitudinal wave with frequency equal to that of the driving voltage of the transducer. In a way analogous to the focusing of light, the ultrasound waves emanating from each point on the transducer face

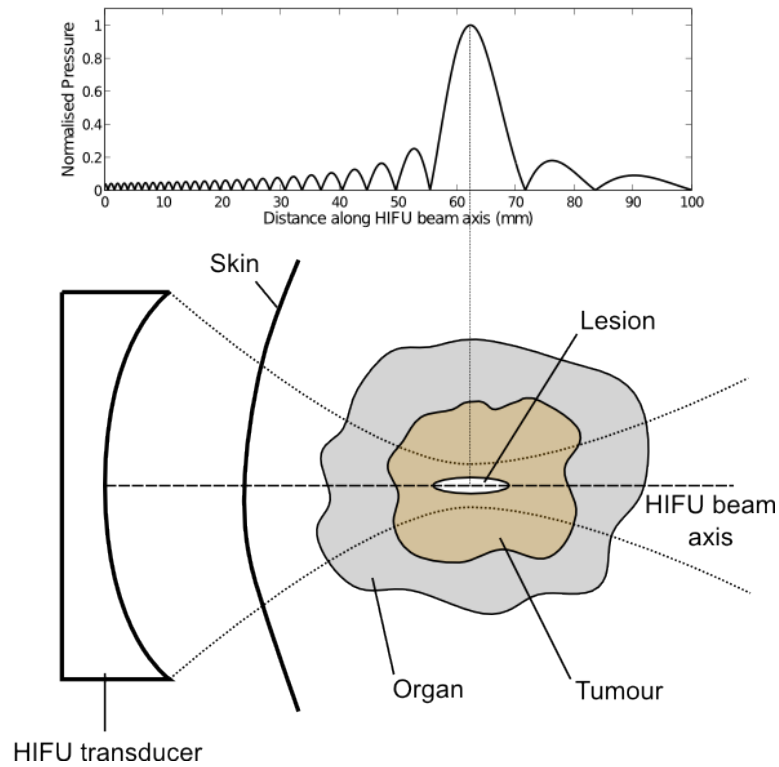


Figure 2.1: Schematic showing the principles of HIFU therapy with typical axial HIFU pressure profile. An extracorporeal HIFU transducer focuses ultrasound radiation deep within the targeted tissue, leading to highly localised heating and resultant cell death via thermal necrosis within the focal region.

are focused to a small volume where constructive interference results in a region of much higher pressure magnitude than elsewhere in the field, as shown in Figure 2.1. These large amplitude pressure fluctuations at the focus of the HIFU field give rise to energy deposition via viscous absorption, resulting in heating of the targeted tissue and cell death via coagulative necrosis (Wu et al., 2001).

This chapter explains in detail the physical principles behind these processes, from simple, linear sound propagation to the more complex effects of HIFU-induced cavitation. The principles of ultrasonic imaging for the purpose of passive acoustic mapping are thence presented, providing the framework for the proposed cavitation-based QA technique.

2.1 LINEAR SOUND PROPAGATION

In essence, sound is a waveform consisting of density variations in an elastic medium, propagating away from a source (Leighton, 1994). Sound therefore represents the transmission of mechanical energy and relies on both the elastic and inertial properties of the medium through which it propagates. Ultrasound refers to sound at frequencies above the upper limit of human hearing (20kHz) and, for HIFU, frequencies in the range 0.8-3.5MHz are typically employed. In the case of small perturbations in pressure and density, the equation of continuity, the momentum equation and the equation of state can be combined to give the linear wave equation

$$\frac{\partial^2 p(\mathbf{r}, t)}{\partial t^2} = c^2 \nabla^2 p(\mathbf{r}, t), \quad (2.1)$$

where p is the pressure perturbation from ambient conditions, $\mathbf{r}$ is the vector position, t is the time and c is the speed of sound in the medium. The speed of sound can be related to the compressibility κ and density ρ of the medium by

$$c^2 = \frac{1}{\kappa \rho}. \quad (2.2)$$

The solution to the linear wave equation in one-dimension is a harmonic plane wave, periodic in both space and time, which propagates with both forwards and backwards travelling components. The pressure variations induced by a harmonic plane wave can be described as

$$p(z, t) = p_0 e^{-i(\omega t \pm k z)}, \quad (2.3)$$

where p_0 is the ambient pressure, ω is the angular frequency of the source, $k = 2\pi f/c$ is the wave number and z is the distance travelled along the axis of propagation. This equation is, however, only valid for small perturbations in pressure and density.

2.2 NON-LINEAR SOUND PROPAGATION

As the excitation amplitude increases, local fluctuations in pressure and density become more significant. For a plane wave, the pressure and particle velocity are in phase, and so the wave travels faster in regions of positive local velocity (compressive regions) and slower in regions of negative local velocity (rarefactive regions). This leads to the gradual steepening of initially sinusoidal waveforms, the effect increasing with amplitude, frequency and propagation distance. In the Fourier domain, this has the effect of increasing the higher harmonic components of the original waveform, as can be seen in Figure 2.2 (Filonenko and Khokhlova, 2001; Khokhlova et al., 2006).

Representing non-linear wave propagation mathematically is not a trivial exercise and, in practice, requires computational solution. For the special case of a directional axisymmetric wave, non-linearities may be described by the Khokhlov-Zabolotskaya-Kuznetsov (KZK) equation

$$\frac{\partial^2 p}{\partial z \partial \tau} = \frac{c}{2} \left(\frac{\partial^2 p}{\partial r^2} + \frac{1}{r} \frac{\partial p}{\partial r} \right) + \frac{\delta}{2c^3} \frac{\partial^3 p}{\partial \tau^3} + \frac{\beta}{2\rho c^3} \frac{\partial^2 p^2}{\partial \tau^2}, \quad (2.4)$$

where r is the radial distance from the centre of the beam, $\tau = t - z/c$ is the retarded time, z is the axial coordinate, ρ is the density of the medium, δ is the sound diffusivity and β the non-linearity coefficient of the medium (Humphrey, 2000). An important material property in relation to HIFU therapy, β describes the non-linearity of the medium, and is calculated as the ratio of the coefficients of the first and second order terms of the Taylor series expansion of the equation of state $P = P(\rho, s)$, where

$$p = A \left(\frac{\rho'}{\rho_0} \right) + \frac{B}{2!} \left(\frac{\rho'}{\rho_0} \right)^2 + \frac{C}{3!} \left(\frac{\rho'}{\rho_0} \right)^3 + \dots, \quad (2.5)$$

and

$$\beta = 1 + \frac{B}{2A}. \quad (2.6)$$

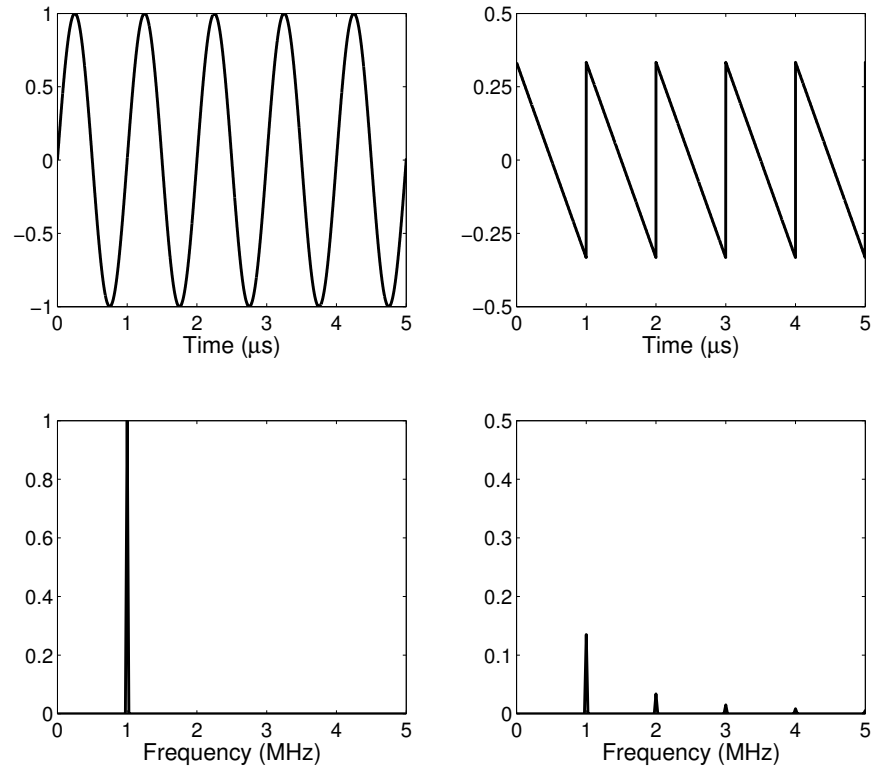


Figure 2.2: Graphical representation of a sinusoidal pressure wave and a resulting shock wave following non-linear propagation with corresponding frequency spectrum. Non-linear effects increase the higher harmonic components of the waveform, which are then more readily attenuated by the medium.

Though water and the majority of tissue-mimicking media have comparatively low coefficients of non-linearity ($\beta \approx 5.0$), biological media, in particular those with high lipid content, generally have much higher values of β (Beyer, 1998). For HIFU therapy, where pressure amplitudes in excess of 1MPa are regularly employed, non-linearity has a significant effect and can lead to undesirable pre-focal heating due to the frequency dependence of attenuation, discussed in greater detail below.

2.3 ATTENUATION, ABSORPTION AND VISCOUS HEATING

As waves propagate through a medium, they experience losses due to *attenuation*. Attenuation encompasses both absorption and scattering components represented by the coefficients α_a and α_s respectively. Absorption describes the conversion of mechanical energy to heat and comprises a variety of mechanisms including molecular relaxation, thermal conductivity and viscous effects, whilst scattering refers to losses experienced as a result of reflections from inhomogeneities in a medium.

The losses experienced by a plane wave propagating through a viscous material can be accounted for as follows:

$$p(z, t) = p_0 e^{-\alpha z} e^{-i(\omega t \pm kz)}, \quad (2.7)$$

where α is the attenuation coefficient ($\alpha = \alpha_a + \alpha_s$). Typically, in a pure viscothermal medium (with no scattering), attenuation, which consists solely of absorption effects, is proportional to the square of the frequency (Hill et al., 2004). In tissue, however, where scattering effects are significant, the frequency dependence of the attenuation coefficient is found to be quasilinear and can be represented by a power law model

$$\alpha(f) = \alpha_0 + \alpha_1 f^n, \quad (2.8)$$

where f is the wave frequency, n is a tissue dependent index (often $n \approx 1.1$) and α_0 and α_1 are constants. Such frequency dependence suggests more pronounced attenuation in non-linear fields, where higher frequency components are present.

In a homogeneous medium, the absorbed sound power density q_s , representing the resultant heat deposition from a plane traveling wave of intensity I , is given by (Nyborg, 1981)

$$q_s = 2\alpha I. \quad (2.9)$$

Attenuation occurs throughout the ultrasound field; however, its heating effect is greatest at the focus where the intensity is at its highest. Immediate thermal toxicity ensues providing temperatures are raised above a threshold of 56°C for more than 1 second, leading to irreversible cell death via coagulative necrosis (Kennedy, 2005). Away from the focus, absorption may lead to tissue damage outside of the intended treatment site. Pre-focal attenuation is a common problem for HIFU surgeons and can result in unpleasant skin burns for the patient (ter Haar, 2009). The likelihood of this occurring can, however, be reduced by harnessing the effects of cavitation-enhanced heating, which facilitates the use of lower insonating frequencies and hence reduces the extent of pre-focal attenuation.

2.4 ACOUSTIC CAVITATION

Ultrasound-induced cavitation initially attracted the attention of researchers concerned by the safety of diagnostic imaging (Miller, 1987; Miller et al., 1996; Holland et al., 1996): observed to induce tissue damage, typically near gaseous interfaces, cavitation was perceived as an undesirable phenomenon that should be minimised to reduce patient risk (Barnett et al., 2000). With the surge of interest in therapeutic ultrasound applications in recent years, the desirability of acoustic cavitation has been re-evaluated, resulting in cavitation being heralded as a possible solution to many of the current shortcomings of HIFU therapy.

2.4.1 Cavitation Nuclei

At sufficiently large rarefaction pressure amplitudes, a propagating ultrasonic wave may generate adequate tension within a medium to form gas and/or vapour filled

cavities, in a process known as acoustically-induced nucleation (Coussios et al., 2007a). In the absence of preferential nucleation sites, this process must overcome the sizeable intermolecular forces that tend to hold the molecules of the medium together, preventing the formation of cavities. In a pure liquid, surface tension is the macroscopic manifestation of these forces, and the net energy W , required to overcome the surface tension σ within a liquid and form a bubble of radius R , is given by

$$W = \frac{4}{3}\pi R^2 \sigma = \frac{16\pi\sigma^3}{3(\Delta p)^2}, \quad (2.10)$$

where Δp is the threshold negative pressure required to form a bubble of size R (Brennen, 1995). To generate the angstrom-sized cavities typically seen in a physiological environment, pressures in the region of 10MPa would thus be required. Cavitation activity has, however, been observed at much lower pressures *in vivo*, inferring the presence of pre-existing, stable nuclei (Coussios et al., 2007a). These nuclei are believed to be stabilised either by micron-sized crevices known as ‘motes’ or organic impurities accumulated on the wall of the bubble, inhibiting their dissolution (Leighton, 1994).

2.4.2 Bubble Behaviour

Once nucleated, the response of bubbles to a time-varying pressure field is termed acoustic cavitation, and can be broadly classified into one of two categories: stable or inertial cavitation (Leighton, 1994). In the case of a spherical bubble subject to a time-varying acoustic pressure, p_{ac} in an incompressible viscous liquid, radial oscillations of the bubble wall may be described by the Rayleigh-Plesset equation

$$R\ddot{R} = -\frac{3}{2}\dot{R}^2 + \frac{p_g + p_v - p_\infty - p_{ac}}{\rho_L} - \frac{2\sigma}{\rho_L R} - \frac{4\nu_L\dot{R}}{R}, \quad (2.11)$$

where R is the bubble radius, p_g and p_v are the gas and vapour pressures of the bubble, p_∞ is the ambient pressure, σ is the surface tension, ν_L is the kinematic viscosity of the liquid and ρ_L is the liquid density (Plesset and Prosperetti, 1977). The assumption of an incompressible medium becomes invalid for large amplitude oscillations and is accounted for in the Keller-Miksis equation (Keller and Miksis, 1980)

$$\left(1 - \frac{\dot{R}}{c}\right)R\ddot{R} + \frac{3}{2}\left(1 - \frac{\dot{R}}{3c}\right)\dot{R}^2 = \left(1 + \frac{\dot{R}}{c}\right)\frac{P}{\rho} + \frac{R}{\rho c} \frac{dP}{dt}, \quad (2.12)$$

where c is the sound speed and

$$P = p_g + p_v - p_\infty - \frac{2\sigma}{R} - \frac{4\nu_L\dot{R}}{R}. \quad (2.13)$$

During stable cavitation, bubble response is dominated by the last three terms on the right hand side of Equation 2.11 and is characterised by repetitive radial oscillation about an equilibrium radius. The extent of such oscillations is governed by the gas compressibility and insonating intensity and frequency, and the equilibrium radius about which they occur may change over time due to gradual dissolution, or growth by a process known as rectified diffusion (Crum and Hansen, 1982). At sufficiently large acoustic amplitudes, the inertial terms ($\dot{R}$) in Equation 2.11 dominate, and bubbles undergo rapid isothermal expansion followed by violent adiabatic collapse driven by the inertia of the in-rushing fluid. Such behaviour is termed inertial cavitation and may result in high temperatures and pressures in addition to microstreaming and, in certain cases, sonoluminescence (Harvey, 1939; Liu and Wu, 2009). The two extremes of these oscillation regimes are illustrated in Figure 2.3.

Despite the distinct differences between each cavitation regime, there actually exists a gradual transition between the two, as illustrated in Figure 2.4. The initial linear pulsations induced by a low amplitude insonating field progress to non-linear, but periodic, oscillations as the driving amplitude is increased. A further in-

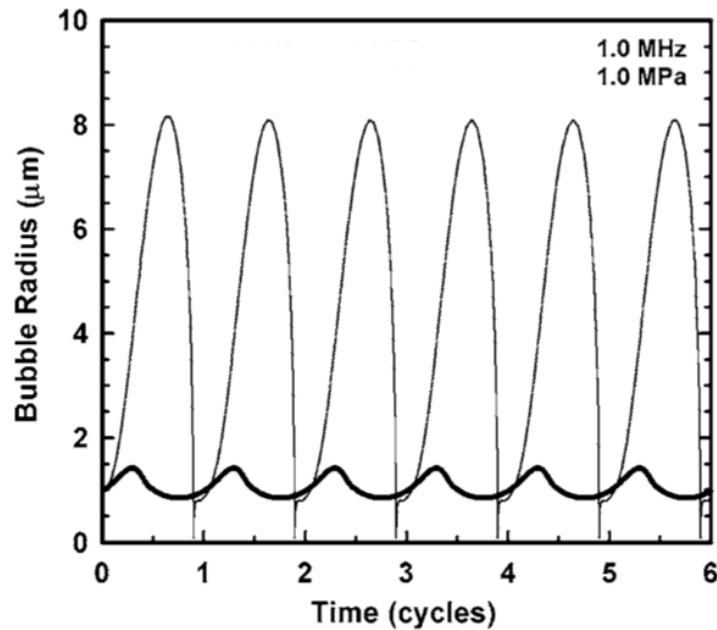


Figure 2.3: A comparison of radial responses for stable (thick line, 0 MPa shear modulus) and inertial (thin line, 1 MPa shear modulus) cavitation behaviour (Yang and Church, 2005).

crease in insonation amplitude leads to a so-called bifurcation zone, where a transition from periodic to non-periodic oscillation takes place by means of a series of period-doubling bifurcations. Increasing the amplitude further still leads to a stochastic zone in which oscillations are chaotic and devoid of periodicity (Ilyichev et al., 1989).

2.4.3 Cavitation Thresholds

It is useful to be able to distinguish between stable and inertial cavitation, since each mechanism yields very different bio-effects. Despite the gradual transition that exists between the two types of behaviour, a number of different criteria have been used to try to pinpoint the pressure at which cavities previously undergoing stable oscillations begin to collapse inertially. This pressure is called the inertial cavitation

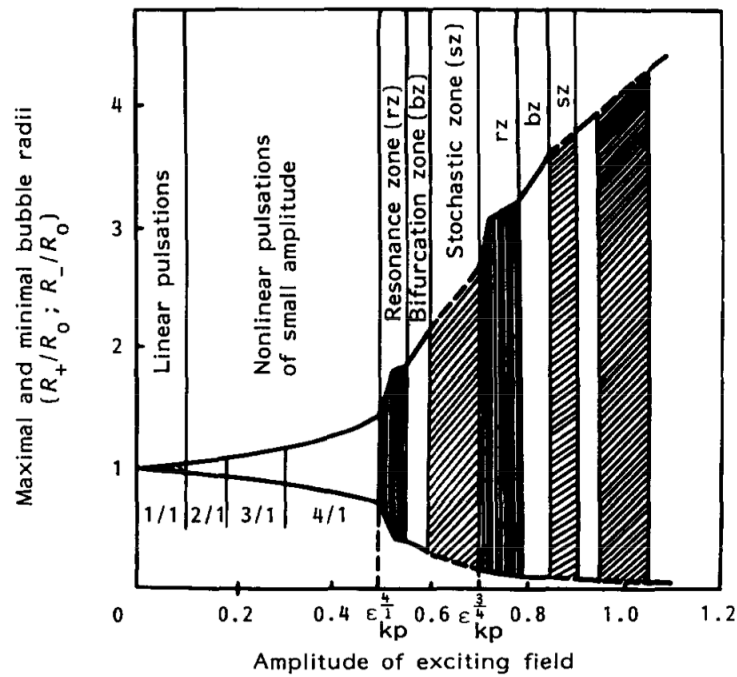


Figure 2.4: Maximal and minimal oscillation radii for a bubble excited with increasing insonation amplitude. Bubbles are excited at $f_0/4$ ($R_0 = 2 \times 10^{-5}\text{m}$, $f = 36\text{kHz}$) and the amplitude given is normalised against the static pressure (Ilyichev et al., 1989).

threshold and the three most common definitions used are:

- When the maximum bubble radius R_{max} is approximately equal to twice the initial radius (Flynn, 1975).
- When the maximum collapse temperature T_{max} of the bubble reaches 5000K (Apfel and Holland, 1991).
- When the bubble wall collapse speed surpasses the speed of sound in air (Church, 2002).

Inevitably, such specific criteria are not broadly applicable and rely upon accurate knowledge of the material properties of the surrounding medium and the number density and size range of pre-existing gas nuclei. Based on the T_{max} threshold

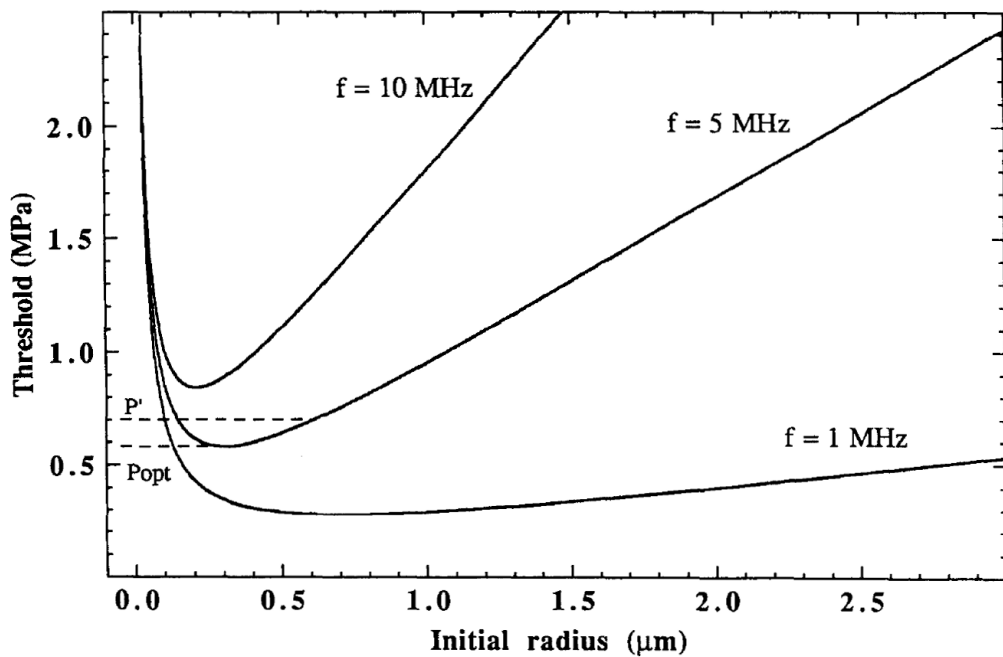


Figure 2.5: Inertial cavitation thresholds for given frequencies in relation to initial bubble radius (Apfel and Holland, 1991). Inertial cavitation occurs above the threshold line at much higher acoustic amplitudes, where the inertia of intruding fluid leads to violent adiabatic collapse, whilst stable cavitation occurs below.

definition, Apfel and Holland were able to obtain expressions for the variation in inertial cavitation threshold with initial bubble size for single-pulse ultrasound in water, assuming all bubble sizes exist *a priori*. As Figure 2.5 illustrates, cavitation thresholds both increase with decreasing initial radius due to surface tension, and increase with increasing radius due to inertial and viscous effects, indicating that there is an optimal bubble radius at which the cavitation threshold is a minimum.

Unfortunately, equivalent relationships do not exist for biological tissue, in which it is believed that a specific subset of bubble sizes are initially present, and the pressures required to instigate inertial cavitation at different frequencies are poorly characterised. Though the criteria outlined above are useful for determining upper and lower bounds on the pressures required to initiate inertial cavitation, experimentally it is the acoustic emissions from cavitating bubbles that provide valuable

information about the particular cavitation regime.

2.4.4 Acoustic Emissions

The acoustic emissions from cavitating bubbles provide not only a means of qualifying cavitation activity, but also the potential to localise its source. It is possible to remotely detect the emissions from a cavitating region by using a Passive Cavitation Detector (PCD), a form of focused transducer usually aligned confocally with the insonating HIFU transducer (Coussios et al., 2007b). By analysing the spectral content of the signal radiated from the cavitating region, it is possible to characterise the nature of the activity that is taking place.

As was mentioned in Section 2.2, non-linear propagation of the incident HIFU wave results in redistribution of energy from the fundamental frequency, f , to higher harmonics, that is to say, integer multiples of the fundamental frequency, nf/m ($n = 2, 3, 4, \dots; m = 1$). Any inhomogeneities in the insonated medium will scatter these signals, resulting in equally spaced peaks in the corresponding frequency spectrum of a PCD. If excessive heating occurs, large vapour-filled boiling bubbles, whose presence is indicative of over treatment, may form. As excellent scatterers of the incident sound wave, these bubbles will act to shield the focal region, resulting in pre-focal heating and significant harmonic content in the radiated signal. As well as scattering the incident wave, the large boiling bubbles may themselves undergo non-linear radial oscillations, re-radiating integer multiples of the driving frequency and further contributing to the harmonic content of the detected signal (Leighton, 1994).

At higher insonation amplitudes, stably cavitating microbubbles can undergo both non-linear radial oscillations and asymmetric shape oscillations. This results

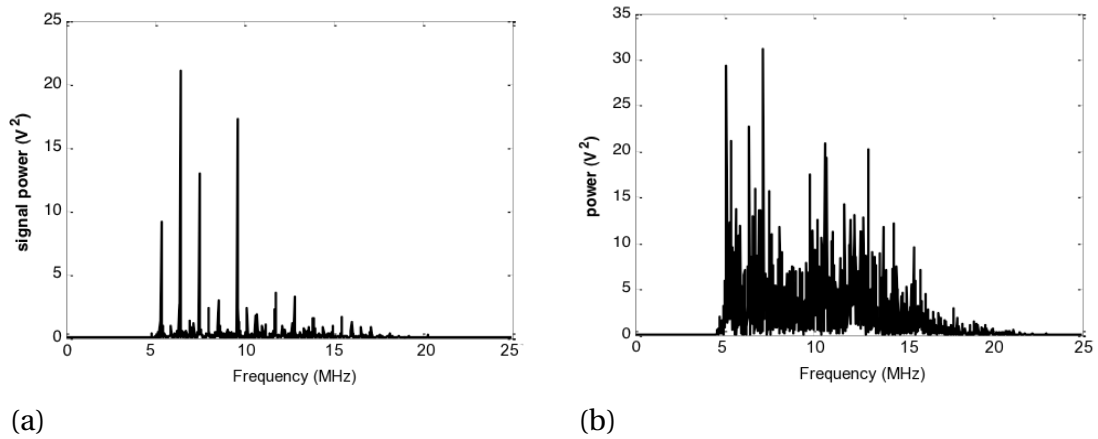


Figure 2.6: Frequency spectra representing acoustic emissions from the focal region of an agar phantom insonated with a 1.067 MHz focussed transducer. Emissions are recorded using a confocally aligned, 15 MHz PCD and are high-pass filtered at 5 MHz. The graph on the left shows the typical spectrum for stable cavitation, showing discrete peaks at the harmonics and ultraharmonics of the driving frequency; the graph on the right is indicative of inertial cavitation, displaying broadband noise throughout the spectrum.

in the generation of harmonic ($n = 2, 3, 4, \dots; m = 1$), subharmonic ($n = 1; m = 2, 3, 4, \dots$) and ultraharmonic ($n = 2, 3, 4, \dots; m = 2, 3, 4, \dots$) emissions. Figure 2.6(a) shows a typical stable cavitation frequency spectrum recorded using a confocally aligned 15 MHz PCD and 1.067 MHz HIFU transducer arrangement. The radiated signal is high-pass filtered at 5 MHz to remove the scattered components at the fundamental frequency and its low order harmonics that tend to saturate the received signal. Clear, discrete peaks are visible at the harmonics and ultraharmonics of the fundamental driving frequency, however, since non-linear scattering from inhomogeneities in the medium and boiling bubbles produces similar results, it is difficult to isolate those emissions solely due to stable cavitation.

The acoustic emissions resulting from inertial cavitation exhibit an altogether different form. The violent collapse driven by the inertia of the in-rushing fluid that is indicative of inertial cavitation is of very short duration, and is therefore associ-

ated with a correspondingly broad spectrum in the frequency domain. When detected remotely using a PCD, this is seen as broadband energy well above the noise floor, as can be seen in Figure 2.6(b).

Cavitation, therefore, has the effect of redistributing the energy content of the insonating fundamental frequency to higher frequencies which, owing to the frequency dependence of the attenuation coefficient α (Equation 2.8), are more readily absorbed by the surrounding medium and converted to heat (Coussios et al., 2007a). When combined with the increase in temperature due to compression of the bubble's contents and viscous heating at the bubble wall, this leads to significant temperature rises and corresponding thermal necrosis of surrounding cells. Furthermore, this potentially enables the use of lower insonating frequencies to achieve sufficient heating at the focus whilst reducing pre-focal tissue damage.

Most relevant to this study, the acoustic emissions from cavitating bubbles provide a means for classification and localisation of cavitation activity. Recent studies have shown that passive imaging techniques can be applied to localise cavitation during HIFU exposure in two-dimensions, providing a viable means for *in vivo* treatment monitoring (Gyongy and Coussios, 2009). Importantly, passive monitoring of the acoustic emissions during HIFU exposure facilitates the precise identification of an inertial cavitation threshold, defined experimentally as the pressure amplitude for which the standard deviation of the broadband content of the recorded signal exceeds six times that of the noise floor. In TMMs of known composition, it has been shown that such methods yield a repeatable peak negative pressure threshold, beyond which broadband emissions of sufficient magnitude are reliably observed. Figure 2.7 shows a typical cavitation threshold plot for a 3% agar TMM using a 1.067 MHz HIFU transducer and the experimental procedure detailed in Section 3.1. In this case, a clear cavitation threshold is seen at 1.52MPa_{PRFP} , be-

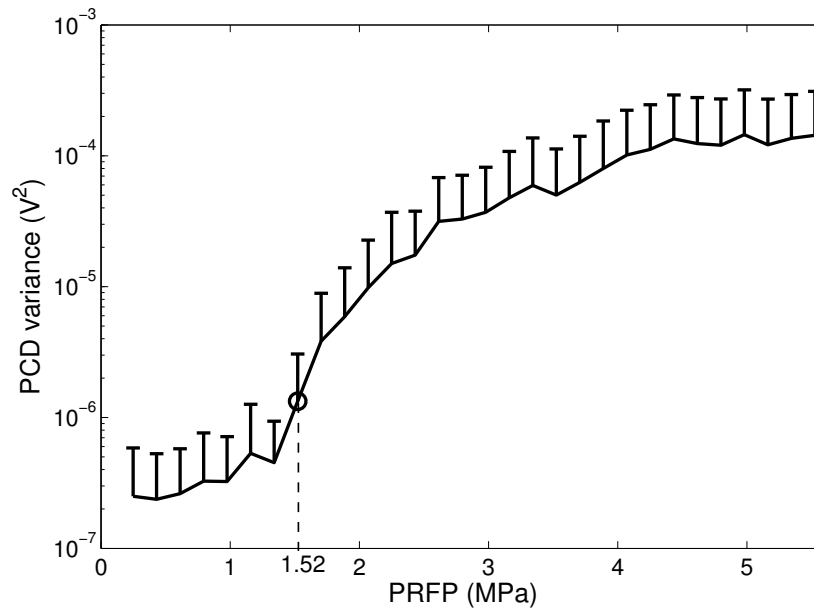


Figure 2.7: Typical cavitation threshold measurement for a 3% agar TMM. Error bars show standard deviations of recorded signal variance at seven spatially discrete locations within a single TMM. In this case, a clear threshold is seen at 1.52 MPa_{PRFP}, beyond which broadband emissions are consistently observed.

yond which the variance of recorded acoustic emissions is of consistently higher magnitude than the noise floor.

2.4.5 Cavitation-Based HIFU QA

Given the potentially beneficial bio-effects of cavitation for HIFU treatment, the need for cavitation-based HIFU QA procedures is evident. The ability to quantify and map cavitating fields in three-dimensions may also provide a clinically applicable means of assessing the acoustic amplitude in a given HIFU field prior to HIFU surgery. Figure 2.8 outlines the principle upon which the proposed HIFU QA procedure is based. For an insonation amplitude below the inertial cavitation threshold of a suitable test medium, no cavitation region will be detected. As the insonation amplitude is increased, the area (or volume in three-dimensions) over which sources

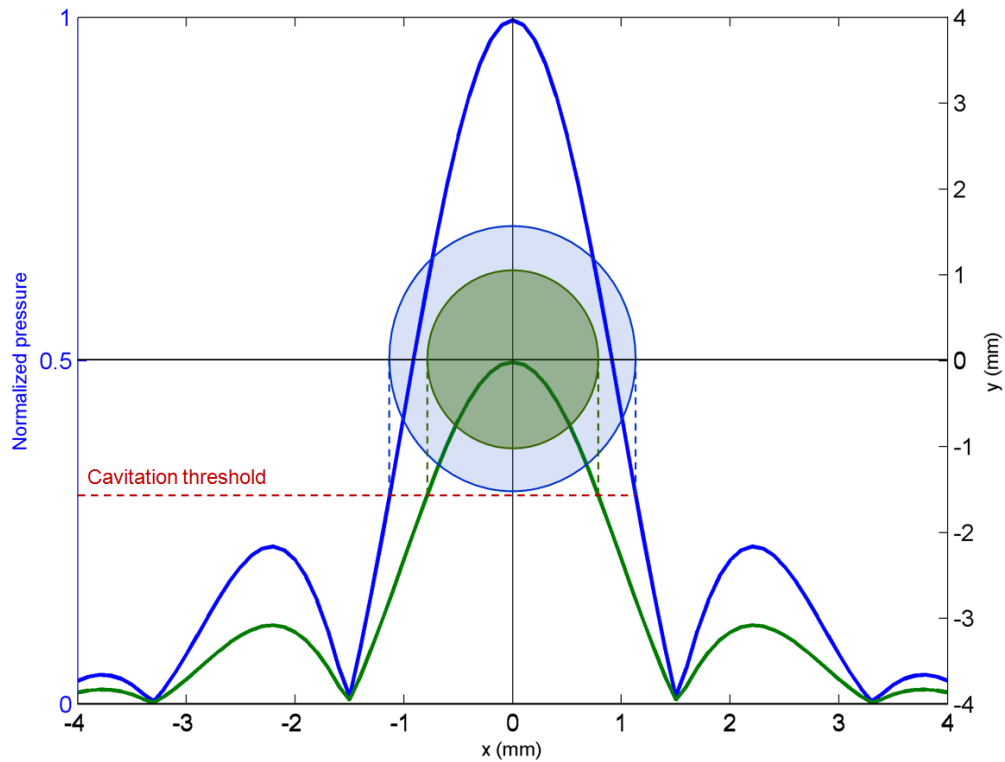


Figure 2.8: Monitoring pressure via mapping of the cavitation field. The size of the cavitation region indicates the area where the acoustic amplitude exceeds the inertial cavitation threshold. For a lower insonating amplitude (shown in green), the region where the pressure exceeds the cavitation threshold is smaller.

of broadband emissions are detected will also increase. At a given insonation amplitude above the inertial cavitation threshold, the size of the corresponding cavitation region is indicative of the region in which this threshold is surpassed. In effect, the resulting cavitation map is an instantaneous ‘pressure snapshot’, highlighting regions where the local peak negative pressure amplitude exceeds the cavitation threshold.

Clearly, rapid deployment of cavitation-based methods for pressure mapping would benefit greatly from the ability to map cavitation activity in two or three dimensions, which requires an array of passive receivers. To understand the concept of a passive array-based cavitation sensor, it is instructive to first consider the prin-

ciples of ultrasonic imaging.

2.5 PRINCIPLES OF ULTRASONIC IMAGING

Conventional two-dimensional ultrasound imaging is generally performed using a B-mode imaging array and a process known as Dynamic Receive Beamforming (DRB) to reconstruct an image from data received on each element of the array. A diagnostic transmit pulse is emitted from a sub-aperture of the array and is reflected by features within the field of interest. The diagnostic pulse can be focused to improve local sensitivity by applying appropriate time delays τ_{nt} to each element, given by Equation 2.14 (for a linear array)

$$\tau_{nt} = \frac{[r - \sqrt{(x_r - x_n)^2 + z_r^2}]}{c} + t_0, \quad (2.14)$$

where r is the distance from the origin to the focal point, $r = \sqrt{x_r^2 + z_r^2}$, x_n is the distance from the origin to the center of an element indexed as “n” ($x_n = np$, where p is the element separation), and t_0 is a constant added to avoid negative delays (Szabo, 2004).

The reflected pulses are received across the sub-aperture of the array and an image is formed using DRB. This process relies upon the depth of focus being relatively close to the region of interest so that the transmitted pulses reach the reflecting surface sufficiently in phase (Macovski, 1979). Received signals are amplitude weighted using an apodization function (a form of windowing which may also be applied on the transmitted pulse), and appropriately delayed and summed for each location in the imaging plane. If a pulse is emitted from a central element (element 0 in Figure 2.9) at time t_0 then the appropriate delay for the n^{th} element is given by the propagation time of the transmitted pulse to the imaged location and back to the

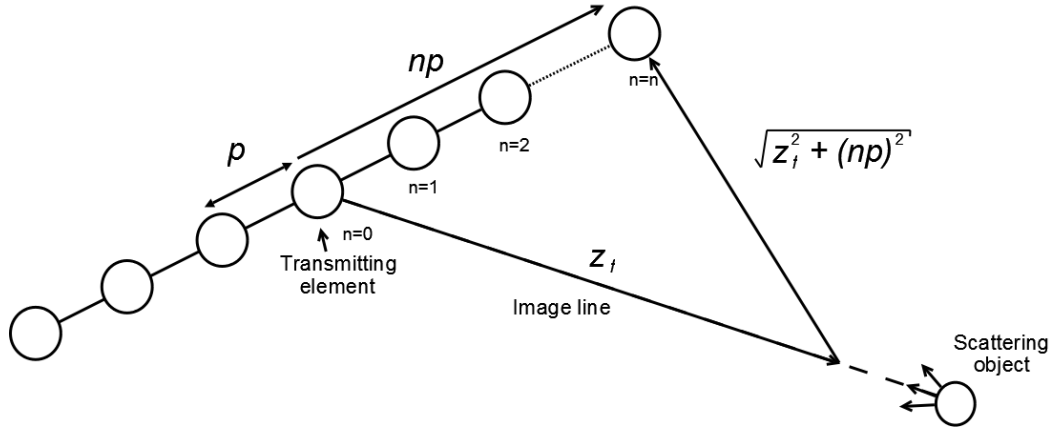


Figure 2.9: Geometry for a linear array with n equally spaced elements. Received signals at each element are amplitude weighted then summed with the appropriate delay to determine the appropriate value for a given image location.

n^{th} element (as shown in Figure 2.9). To image at a distance z_f from the central element of a linear array with inter-elemental spacing p , the corresponding time delay τ_{nr} is given by Equation 2.15.

$$\tau_{nr} = t_0 + \frac{1}{c} \left(z_f + \sqrt{z_f^2 + (np)^2} \right) \approx t_0 + \frac{1}{c} \left(2z_f + \frac{(np)^2}{2z_f} \right). \quad (2.15)$$

The resulting image line $I_r(z_f)$ is then given by

$$I_r(z_f) = \sum a_n y_n \left(t_0 + \frac{1}{c} \left(2z_f + \frac{(nd)^2}{2z_f} \right) \right), \quad (2.16)$$

where a_n is the apodization for the n^{th} element. In this manner, for each transmitted pulse, a number of foci are dynamically generated in reception, resulting in an enhanced uniform resolution throughout the image without sacrificing the system frame rate (Manes et al., 1988). The resulting amplitude along the image line is then calculated by taking the absolute value of the analytic signal (determined using the Hilbert transform) and a two-dimensional image formed by arranging each line in its correct geometrical orientation. This procedure works well for diagnostic imaging, where precise timings of transmitted pulses are known. However, for

the purpose of imaging acoustic emissions produced by collapsing bubbles during Continuous Wave (CW) HIFU excitation, such timings are not available and passive maps obtained using DRB (by setting the transmit pulse amplitude to zero) suffer from high noise levels. Two-dimensional passive cavitation maps with suitable resolution and Signal-to-Noise Ratio (SNR) have, however, been achieved using a linear array and a method originally proposed for seismological studies, known as Time Exposure Acoustics (TEA) (Gyongy et al., 2008; Norton and Won, 2000).

2.6 PASSIVE ACOUSTIC MAPPING

Passive imaging techniques have been in use for a number of years for geophysical and oceanographic applications, using ambient noise as a constant source of illumination to image subterranean or submarine features (Buckingham et al., 1992; Potter, 1994). The use of such methods for biomedical applications, in particular cavitation localisation, is, however, relatively new. TEA is one possible algorithm for implementing passive imaging: new data is incorporated into the image in a recursive fashion, which causes the image background noise to diminish over time (Norton and Won, 2000). During passive cavitation imaging, broadband acoustic emissions resulting from inertial cavitation manifest themselves as spatially correlated signals over a receiving array. The coherent summation of these correlated signals over a number of time steps using an appropriate backpropagation algorithm results in the relatively weak broadband sources growing in strength over time relative to the uncorrelated background noise. As a result, TEA improves upon the low SNR experienced using passive DRB and facilitates accurate mapping of cavitating fields.

Mathematically, the TEA procedure can be explained as follows. If $u(\mathbf{r}_n, t)$ de-

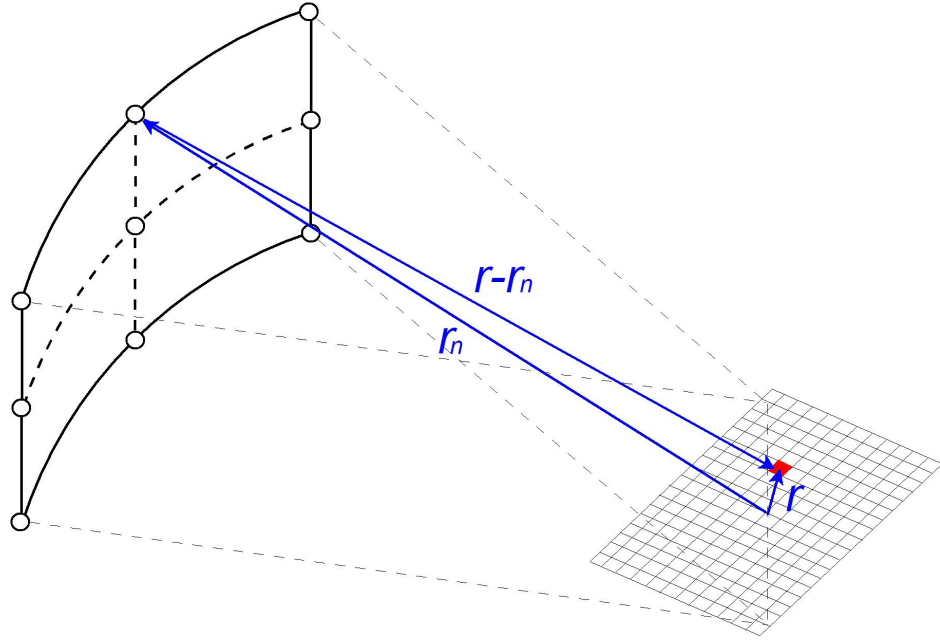


Figure 2.10: Geometry for the implementation of the Time Exposure Acoustics algorithm, where $\mathbf{r}$ is the vector position of the imaging location (or pixel) and $\mathbf{r}_n$ is the location of the n^{th} receiving element.

notes the field recorded at the n^{th} element of a receiving array at position $\mathbf{r}_n$, then an estimate of the signal, $S(\mathbf{r})$ emitted at time, t_0 is given by

$$S(\mathbf{r}) = \sum_{n=1}^N u(\mathbf{r}_n, |\mathbf{r} - \mathbf{r}_n|/c + t_0) |\mathbf{r} - \mathbf{r}_n|, \quad (2.17)$$

where $\mathbf{r}$ is the vector position of the imaging location (or pixel) as shown in Figure 2.10 and the $|\mathbf{r} - \mathbf{r}_n|$ term is included to compensate for signal loss due to spherical spreading. Defining $u_n(\mathbf{r}) = u(\mathbf{r}_n, |\mathbf{r} - \mathbf{r}_n|/c + t_0) |\mathbf{r} - \mathbf{r}_n|$, Equation 2.17 may be written as

$$S(\mathbf{r}) = \sum_{n=1}^N u_n(\mathbf{r}, t). \quad (2.18)$$

Originally intended for imaging subterranean scatterers using ambient noise, the method assumes that the received noise field is a random variable with zero mean. This assumption is equally applicable to passive cavitation imaging and implies that the statistical expectation of the source strength $E\{S(\mathbf{r})\}$ is equal to zero,

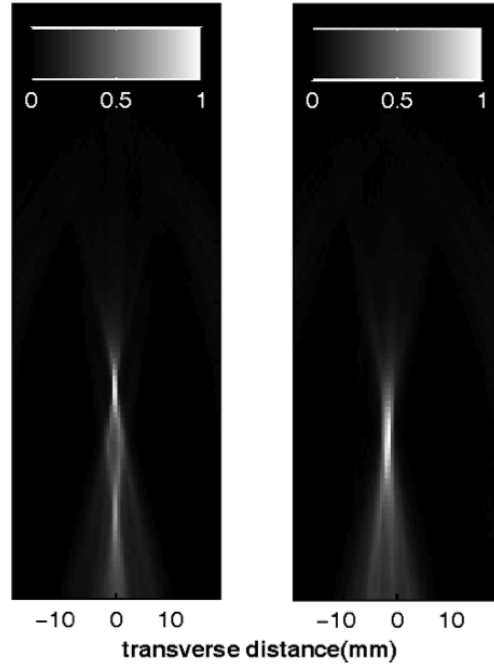


Figure 2.11: Passive acoustic mapping of disjoint (left) and continuous (right) cavitation regions. Continuous regions were created within an agar TMM at 1.67MPa_{PRFP} , whilst disjoint regions were produced by insonating an agar TMM with two talc suspension channels at 0.80MPa_{PRFP} (Gyongy and Coussios, 2010).

precluding the averaging of images on an amplitude basis. As a result, successive realisations of images in the time domain are averaged on an intensity basis (i.e. by averaging $I(\mathbf{r}) = |S(\mathbf{r})|^2$). This does, however, lead to the accumulation of a DC bias over time which may be removed prior to computation of the mean image as follows

$$I^m(\mathbf{r}) = \left| \sum_{n=1}^N u_n^{(m)}(\mathbf{r}) \right|^2 - \sum_{n=1}^N |u_n^{(m)}(\mathbf{r})|^2, \quad (2.19)$$

where $I^m(\mathbf{r})$ is the m^{th} realisation of the intensity image. The average of M images, $\bar{I}_M(\mathbf{r})$ can then be calculated as follows

$$\bar{I}_M(\mathbf{r}) = \frac{1}{M} \sum_{m=1}^M I^m(\mathbf{r}). \quad (2.20)$$

Application of this algorithm to data acquired in an agar TMM using a linear array has been shown to correctly identify both disjoint and continuous cavitation

regions, as depicted in Figure 2.11 (Gyongy and Coussios, 2010). The spatial resolution of the reconstructed source maps is dictated by the Point Spread Function (PSF) of the imaging system, defined as the response of the system to a point source and explained further in the following section.

2.7 ARRAY DESIGN

2.7.1 Point Spread Function

The PSF of an imaging system gives an indication of the spatial resolution that may be achieved with a given combination of reconstruction algorithm and array geometry. For a receive beamformer the PSF is defined for a source radiating with frequency f , located at a focal position $\mathbf{r}_s$, as the ratio of the signal power received from imaging locations $\mathbf{r}$ to the signal power received from the source location $\mathbf{r}_s$.

$$PSF(\mathbf{r}, \mathbf{r}_s, f) = \frac{P(\mathbf{r}, f)}{P(\mathbf{r}_s, f)}. \quad (2.21)$$

In this section, a definition for the PSF of the TEA algorithm is given, following similar derivation steps to several closely related studies (Gyongy, 2010; Mast, 2007). For simple array geometries, such as the linear array used in Chapter 3, analytical expressions may be developed to determine the PSF at a given imaging depth. However, for more complex array geometries, such as those introduced in Chapter 5, numerical simulations may be used to estimate the response of the system to a point source.

In line with the above definition of the TEA algorithm, an estimate of the source strength, $q(\mathbf{r}, t)$, at an imaging location, $\mathbf{r}$, may be reconstructed from N observa-

tions of the received signal voltage, v_n , at receiver locations $\mathbf{r}_n$ as

$$q(\mathbf{r}, t) = \frac{4\pi}{Ns} \sum_{n=1}^N |\mathbf{r} - \mathbf{r}_n| v_n(t + |\mathbf{r} - \mathbf{r}_n|/c), \quad (2.22)$$

where s is a scaling factor that converts received signal voltage to pressure, which here will be set to unity. In the frequency domain, the imaged source strength at a point, $\mathbf{r}$, for a source located at $\mathbf{r}_s$ with strength $Q_s(f)$ may be expressed as

$$Q(\mathbf{r}, f) = \sum_{n=1}^N A_n C(\mathbf{r} - \mathbf{r}_n, f) V_n(f) \exp(jk|\mathbf{r} - \mathbf{r}_n|), \quad (2.23)$$

$$V_n(f) = B(\mathbf{r}_s - \mathbf{r}_n, f) \exp(-jk|\mathbf{r}_s - \mathbf{r}_n|) Q_s(f), \quad (2.24)$$

where A_n is an apodization function that may be used to apply different weights to receiver elements, $B(\mathbf{r}, f)$ is a term which describes spherical spreading, attenuation and scaling of the focal source signal and $C(\mathbf{r}, f)$ is a compensation term, which in the absence of noise may be considered as $1/B(\mathbf{r}, f)$.

Combining Equations 2.23 and 2.24 yields

$$Q(\mathbf{r}, f) = Q_s(f) \sum_{n=1}^N A_i \exp(jk(|\mathbf{r} - \mathbf{r}_n| - |\mathbf{r}_s - \mathbf{r}_n|)). \quad (2.25)$$

The source power, $P(\mathbf{r}, f)$, is then given by (Lighthill, 2005)

$$P(\mathbf{r}, f) = \frac{1}{4\pi\rho_0 c} |Q(\mathbf{r}, f)|^2. \quad (2.26)$$

A general expression for the PSF of the TEA algorithm may then be found by substituting Equations 2.25 and 2.26 into 2.21

$$PSF(\mathbf{r}, \mathbf{r}_s, f) = \left| \sum_{n=1}^N A_i \exp(jk(|\mathbf{r} - \mathbf{r}_n| - |\mathbf{r}_s - \mathbf{r}_n|)) \right|^2. \quad (2.27)$$

For the linear array used in Chapter 3, a number of simplifying assumptions may then be used to provide an analytical expression for the PSF in both the transverse and axial directions. Firstly, it is assumed that the linear array is focussed in the

$(x, 0, z > 0)$ plane, which also contains the source. Secondly, the array is set to lie in the x -plane, implying $\mathbf{r}_n = (x_n, 0, 0)$. Next, a spatially continuous apodization function, $A(l)$, is introduced to make the PSF expression integrable. In the limit of infinite, uniformly weighted, point receivers with aperture, D , and zero element spacing this function becomes

$$A(l) = \frac{1}{D} \Pi(l/D) \quad (2.28)$$

$$\Pi(l/D) = \begin{cases} 1 & \text{for } l/D \leq 1 \\ 0 & \text{otherwise.} \end{cases} \quad (2.29)$$

Finally, the second order binomial expansions of the modulus terms in Equation 2.27 may be used to give

$$PSF(\mathbf{r}, \mathbf{r}_n, f) = \left| \int_{-\infty}^{\infty} A(l) \exp \left(jk \left(\frac{(x-l)^2}{2z} - \frac{(x_s-l)^2}{2z_s} \right) \right) dl \right|^2. \quad (2.30)$$

When considering the transverse resolution with the array correctly focussed in the axial direction ($z = z_s$), the PSF is then given as

$$PSF(\delta x, f) = \left| \int_{-\infty}^{\infty} A(l) \exp \left(-jk \frac{\delta x}{z_s} l \right) dl \right|^2, \quad (2.31)$$

where $\delta x = x - x_s$ and dimensions are considered sufficiently small for their squares to be neglected ($x^2 \approx x_s^2 \approx 0$).

By noting similarities with the Fourier transform, it may be shown that the transverse PSF of a linear array using the TEA algorithm is then given by

$$PSF(\delta x, f) = \left| \text{sinc} \left(\frac{Dk\delta x}{2\pi z_s} \right) \right|^2. \quad (2.32)$$

Similarly, the axial resolution may be determined from Equation 2.30, by considering the focus to be correctly aligned with the source ($x = x_s = 0$), yielding

$$PSF(z, z_s, f) = \left| \int_{-\infty}^{\infty} A(l) \exp \left(jk \frac{1}{2} \left(\frac{1}{z} - \frac{1}{z_s} \right) l^2 \right) dl \right|^2. \quad (2.33)$$

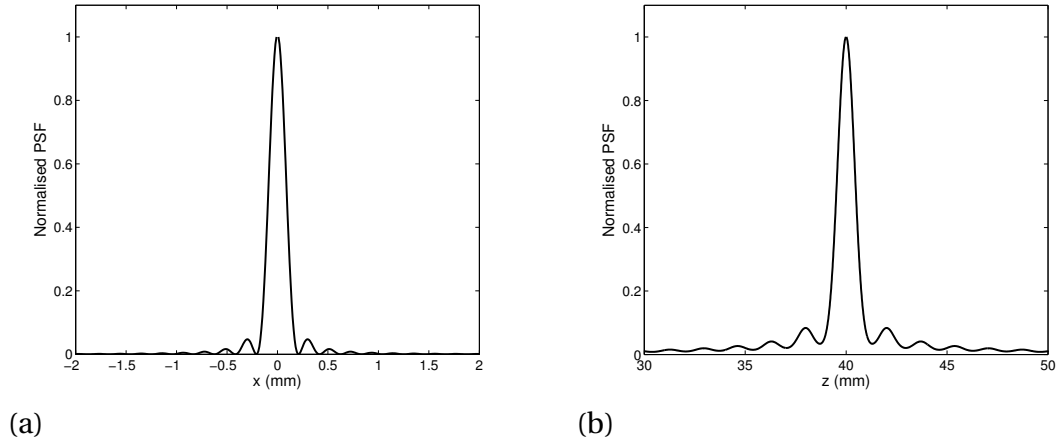


Figure 2.12: Transverse (a) and axial (b) PSF of a 38 mm aperture linear array imaging a source at a depth of 40 mm using the TEA algorithm. At this depth, -3 dB transverse and axial resolutions are estimated as 0.2 mm and 1.1 mm respectively.

If small axial deviations $\delta z = z - z_s$ are considered, then

$$\frac{1}{z} - \frac{1}{z_s} = \frac{z_s - z}{zz_s} \approx -\frac{\delta z}{z_s^2}, \quad (2.34)$$

which may be substituted into Equation 2.33 to give

$$PSF(\delta z, f) = \left| \frac{2}{D} \int_0^{D/2} \exp\left(jk \frac{\delta z}{2z_s} l^2\right) dl \right|^2. \quad (2.35)$$

By using the definition of the Fresnel integral (Mast, 2007)

$$F(\xi) = \int_0^\xi \exp\left(\frac{j\pi l^2}{2}\right) dl, \quad (2.36)$$

solutions may then be found in the form

$$PSF(\delta z, f) = \left| \frac{F\left(\frac{D}{2z_s} \sqrt{\frac{k\delta z}{\pi}}\right)}{\left(\frac{D}{2z_s} \sqrt{\frac{\delta z k}{\pi}}\right)} \right|^2. \quad (2.37)$$

Equations 2.32 and 2.37 therefore provide a means for simulating the transverse and axial PSF of a linear array, which give a useful theoretical prediction of the -3 dB resolution that may be achieved at a given imaging depth. Figure 2.12 shows the

output of these expressions evaluated at a source depth of 40 mm, which is consistent with the configuration used in Chapter 3. At this depth, when imaging a 7.5 MHz source, -3 dB transverse and axial resolutions are estimated as 0.2 mm and 1.1 mm respectively.

For more complex array configurations, such as those considered in Chapter 5, analytical expressions for the PSF cannot be easily formed and numerical simulations of the array response to a point source may be used estimate the imaging resolution. Regardless of geometric complexity, there are, however, several general considerations that should be noted regarding the design of a given array geometry.

2.7.2 Array Geometry

Passive acoustic mapping of cavitating sources is a relatively new concept. As such, the principles of array design for this purpose are presently poorly defined. A wide variety of ultrasonic arrays have, however, been proposed for conventional diagnostic medical imaging and therapeutic ultrasound applications. At present, the majority of diagnostic imaging arrays in clinical use are one-dimensional linear arrays which use a DRB method to image a two-dimensional plane.

Two-dimensional arrays have been developed more recently to facilitate three-dimensional ultrasonic imaging (Light et al., 1998; von Ramm, 2000). For therapeutic applications, concentric ring designs have been proposed to allow variation in depth of focus for hyperthermia therapy, whilst spherical arrays have been designed to steer focal regions significantly far off-axis (Cain and Umemura, 1986; Sokka et al., 2003). Despite the variety of applications, two criteria tend to dominate array design. Firstly, the inter-element spacing should be less than half the wavelength in the propagating medium to avoid constructive interference away from the

intended focus, resulting in unwanted “grating lobes” (Szabo, 2004). Secondly, elements should be small enough so that the emitted ultrasound field covers the entire volume in which focusing, or indeed imaging, is required. Furthermore, each individual application will impose its own constraints upon the array design.

Chapters 4 and 5 explore array design in detail, specifically in the context of cavitation detection in three dimensions during HIFU exposure.

2.8 GAP IN KNOWLEDGE

HIFU therapy offers a promising alternative to the numerous invasive procedures currently used to treat malignant tissue. However, it is clear that standardised QA methods are required before the technique is widely accepted as a viable treatment option. Chapter 3 presents, for the first time, an implementation of passive acoustic mapping for the purpose of HIFU field characterisation. This is achieved with sufficient accuracy in two dimensions using a readily available medical diagnostic linear array, providing a technique suitable for immediate implementation in a clinical setting.

Complete HIFU field characterisation using a linear array requires significant user intervention, as demonstrated in the following chapter. Three-dimensional passive cavitation mapping is a novel concept and, as such, requires an overhaul of preceding array designs. In particular, digression from a linear array requires an inventive approach to sensor construction, informed by novel modelling techniques to determine the resulting frequency response of the array and optimise the array configuration. Chapters 4 and 5 seek to address these issues, providing experimental validation where necessary.

It is intended that the resultant device will form part of a world-leading HIFU characterisation facility located at the Institute of Cancer Research (ICR), and will provide new insight into the dynamics of HIFU-induced cavitation and its role in improving the efficacy of HIFU therapy.



TWO-DIMENSIONAL CAVITATION-BASED PRESSURE MAPPING

This chapter demonstrates how an array of receiving elements may be used to map a distribution of cavitating sources in two dimensions. Preliminary experimentation with a circular array of four needle hydrophones provides a simple proof-of-concept that the observation of broadband emissions facilitates mapping of a growing cavitation region. The subsequent use of a medical diagnostic linear array increases the number of channels available on receive and, therefore, yields images of higher spatial resolution. Furthermore, correlation of the extent of the cavitation region with the HIFU insonation amplitude confirms that cavitation-based pressure mapping is a clinically viable QA procedure.

Inertial cavitation has an important role to play in the progression of HIFU from laboratory to regular clinical use. Key to its success is the development of reliable and practical QA methods. At the very heart of the present work is the fact that, for a TMM of known composition, there exists a well-defined, repeatable threshold Peak Rarefactional Focal Pressure (PRFP) beyond which inertial cavitation is instigated and broadband acoustic emissions are consistently observed. By detecting the radiated broadband emissions across an array of receiving elements, passive imaging

techniques, such as those described in Section 2.6, may be applied to reconstruct the spatial distribution of the cavitation region.

In this chapter, a proof-of-concept experiment is initially presented wherein an array of four needle hydrophones is used to detect the emissions from a cavitating region within an agar TMM. The emissions recorded from exposures of increasing insonation amplitude are then used to map the evolution of the cavitating region and hence show that the concept of cavitation-based pressure mapping is with merit. Following this, the experimental setup is adapted to instead allow passive data acquisition of cavitation emissions across 64 channels of a 128-element medical diagnostic linear array. In doing this, it is possible to reconstruct the extent of the cavitation region with high spatial resolution in the elevation, axial and transverse focal planes. The results are used to monitor both the distribution and evolution of cavitation activity during HIFU exposure, which may then be contrasted with the expected behaviour as derived from hydrophone-based transducer characterisation.

3.1 CIRCULAR HYDROPHONE ARRAY

3.1.1 Experimental Setup

Figure 3.1 shows a schematic of the setup for the initial experiment using a circular hydrophone array. All exposures were carried out in an acrylic tank filled with filtered, deionised and degassed water that is well-matched to the acoustic properties of both tissue and TMMs, making it an ideal transmission medium. Below, each of the components of the experimental setup are described in more detail. Importantly, many of these components are used in the subsequent sections and chapters,

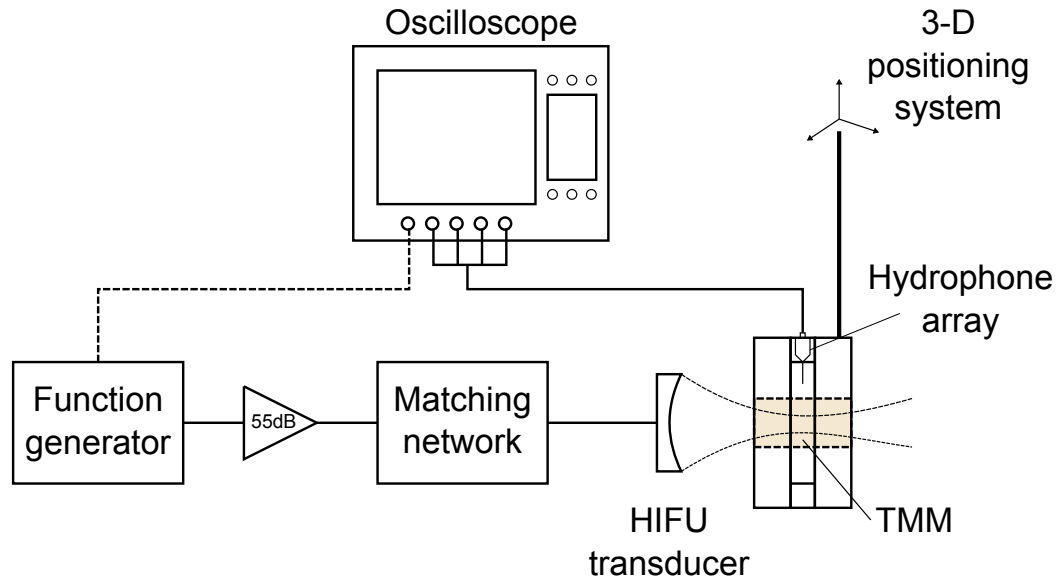


Figure 3.1: Schematic of the setup for the proof of concept experiment. All experiments are carried out in an acrylic tank filled with filtered, deionised and degassed water.

and the reader is invited to refer back where necessary.

3.1.1.1 HIFU Generation

HIFU transducers come in many shapes and forms, each with a specific fundamental frequency of oscillation and a unique beam profile dictated by the transducer geometry and its driving conditions. In the present work, HIFU pulses were generated using a rigidly-supported, single-element, piezo-ceramic HIFU transducer (Sonic Concepts H102), spherically focused (64 mm active diameter, 62.64 mm focal length) to form a narrow focal region that is remote from the source. The transducer (shown in Figure 3.2) was driven at its fundamental frequency by a function generator (Agilent 33220A), the output of which was amplified by a 55 dB fixed-gain broadband amplifier (ENI A-300), and passed through an impedance matching network prior to reaching the transducer.

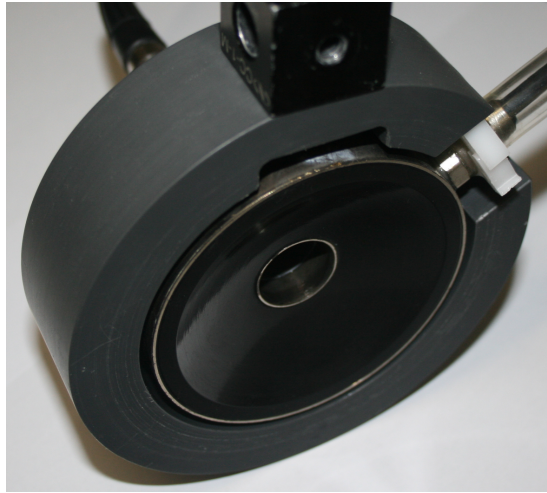


Figure 3.2: Spherically focused HIFU transducer (Sonic Concepts H102) with central cylindrical void for coaxial alignment of a PCD.

In the following experiments, the HIFU transducer was driven at its fundamental frequency of 1.067 MHz to produce 5-cycle, sinusoidal pulses with increasing focal insonation amplitudes, varied from 2.54 MPa_{PRFP} to 5.52 MPa_{PRFP} at 0.36 MPa_{PRFP} intervals. The pulse length (5-cycles) was chosen since it allowed sufficient time for the transducer to ramp to its steady state amplitude whilst remaining short, so as to increase the likelihood of observing a single cavitation event. A calibration procedure was carried out using a needle hydrophone (Onda HNA-0400) aligned at the HIFU focus, in order to deduce the correlation between the electrical signal input and the PRFP. Figure 3.3 depicts this relationship, which is extrapolated beyond the limit of safe operation of the hydrophone to estimate focal pressures at higher input amplitudes.

Additional hydrophone-based characterisation revealed the focal length of the transducer to be 62.64 mm and the -6 dB beam diameter and axial length to be 2.02 mm and 14.55 mm respectively, as illustrated in Figure 3.4.

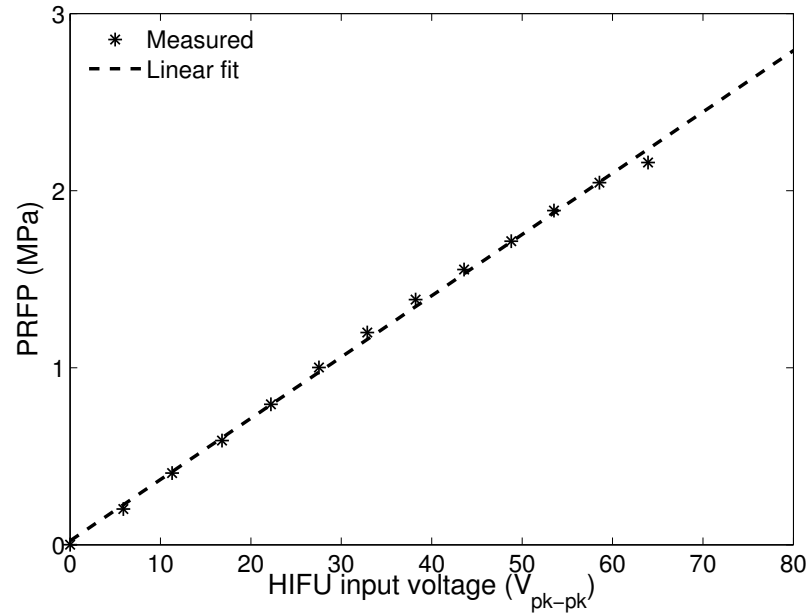


Figure 3.3: Calibration curve for the 1.067 MHz HIFU transducer. Focal pressures were recorded at 5 V_{pk-pk} intervals using a 400 μm needle hydrophone immersed in deionised and degassed water at 21°C. The regression line has been extrapolated to span the full range of safe transducer operation.

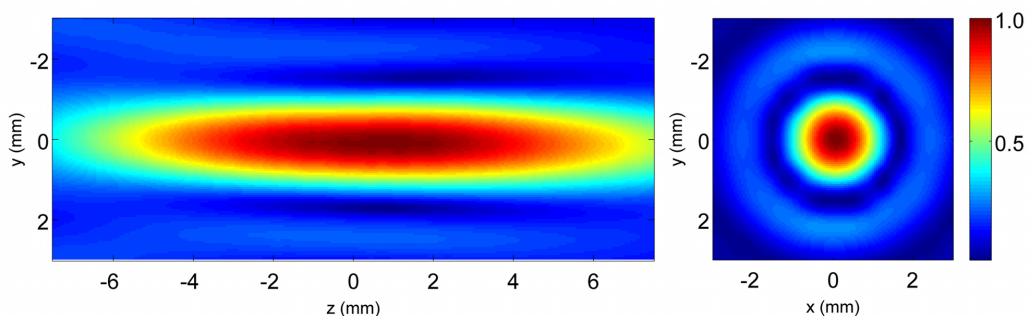


Figure 3.4: Normalised longitudinal and transverse pressure profiles of the HIFU transducer, with both planes intersecting at the focal maximum.

3.1.1.2 Passive Cavitation Detection

The notion of passive cavitation detection was introduced in Section 2.4.4. A PCD is a spherically-focused ultrasound transducer (Olympus Panametrics V309) used to passively detect the broadband emissions emanating from the focal region of a HIFU transducer. In the present work, a 15 MHz PCD with a focal length of 75 mm and active diameter of 13 mm was placed coaxially to, and confocally aligned with, the HIFU transducer. This PCD was chosen due to its centre frequency lying well above that of the HIFU transducer, thus enabling the system to be tuned to detect the broadband acoustic emissions indicative of inertial cavitation. However, some sensitivity remains at lower frequencies, necessitating the use of a 5 MHz high-pass filter prior to amplification of the PCD signal to avoid saturation by the scattered fundamental frequency component and its harmonics.

3.1.1.3 Tissue-Mimicking Material

TMMs are regularly used for laboratory-based HIFU experiments, since they facilitate repeatable, accurate characterisation of the response to HIFU insonation without the expense and time-consuming handling procedures associated with biological tissue. Since the majority of tissue is comprised of water, this might initially be considered an appropriate, simple test medium. However, in contrast to water, tissue exhibits significant elasticity, introduced by the presence of proteins such as elastin in the extracellular matrix. The resulting viscoelastic behaviour of tissue has a notable effect on cavitation dynamics (Yang and Church, 2005) and it is therefore important that this property is also exhibited by a TMM. Furthermore, the viscoelastic nature of the medium prevents movement of cavitating bubbles within the ultrasound field due to acoustic radiation force, facilitating reproducible detection and

Table 3.1: Summary of the acoustic properties of water, agar and tissue. The speed of sound and attenuation of water were taken from (Del Grosso and Mader, 1972; Kaye and Laby, 1995), whilst agar and ox liver properties were measured by JRT Collin and M Gyöngy respectively (Collin, 2009; Gyongy, 2010). All attenuation coefficients correspond to 1.067MHz insonation.

Material	Density (g/ml)	Speed of sound (m/s)	Attenuation (Np/m)
Pure water (20°C)	1.00	1482	0.03
3% Agar (20°C)	1.10	1489	0.11
Soft tissue (ox liver, 37°C)	1.05	1615	7.38

mapping.

In this instance, the TMM was also required to 1) have a repeatable cavitation threshold and 2) have sufficient rigidity to be supported by the array mounting described in Section 3.1.1.5. By referring to previous literature (Burlew et al., 1980), a 3% agar TMM was selected, having adequate viscosity, a high melting point (78°C) and tuneable sound speed. This TMM is also stable under the thermal loads applied during HIFU insonation, and can be easily cast into the desired form. Table 3.1 lists the acoustic properties of the chosen TMM, along with those of water and soft tissue for the purpose of comparison.

The procedure for preparing the agar TMM is outlined below:

- Add 9 g of Invitrogen Ultrapure™ Agarose-1000 to 300 mL of deionized water.

- Mix continuously using a magnetic stirrer and heat to 85°C until all of the agarose powder has dissolved.
- Maintain the temperature of the mixture above 37°C and degas at -0.8 bar for 30 minutes.
- Pour into a suitable mould (a cylindrical PVC mould was used for the experiment detailed here) and refrigerate overnight to allow the agar to set.

It is worth noting that the TMM composition specified above is adapted later in this chapter to improve cavitation levels for the purpose of augmenting the observed SNR for cavitation-based pressure mapping experiments.

3.1.1.4 TMM Cavitation Threshold Characterisation

Accurate knowledge of the threshold PRFP required to initiate inertial cavitation is key to the success of the proposed HIFU QA system. Cavitation thresholds were measured using the experimental configuration shown in Figure 3.5. Labview software was used to remotely control a function generator driving the 1.067 MHz HIFU transducer with 5-cycle, sinusoidal bursts of different PRFP amplitudes at its fundamental frequency, with the HIFU/PCD focus acoustically positioned at a depth of 10 mm within the TMM. The software was also used to control the simultaneous acquisition of data from the 15MHz PCD. Analogue signals from the PCD were high-pass filtered (5 MHz cut-off), amplified using a dedicated 28 dB amplifier (Stanford Research Systems SR445A), and digitised using a 100 MHz, 14-bit Data Acquisition (DAQ) card (National Instruments PCI-5122).

The inertial cavitation threshold was defined as the PRFP beyond which the standard deviation of the detected broadband emissions exceeded six times that of

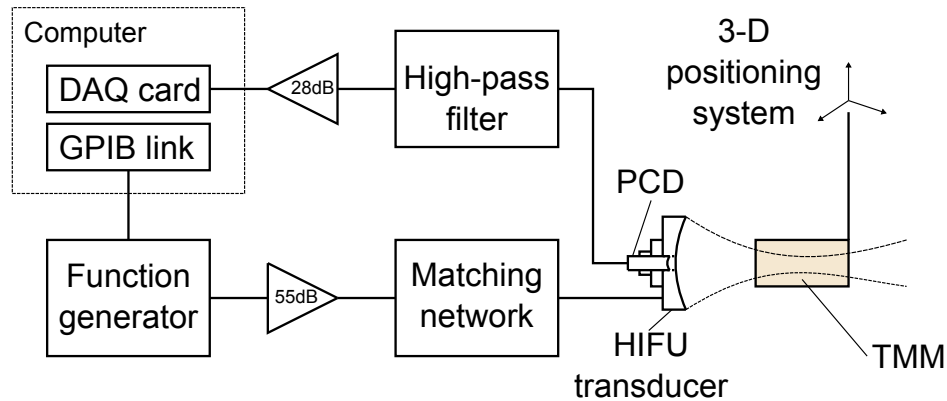


Figure 3.5: Schematic of the experimental setup used for determining TMM cavitation thresholds. A coaxially positioned, confocally aligned PCD is used to passively detect radiated broadband emissions resulting from HIFU-induced inertial cavitation.

the ambient noise (measured from the recorded PCD trace during periods of HIFU off-time). Figure 3.6 shows the resulting plot of the mean and standard deviation of the PCD signal variance versus focal pressure amplitude for a range of threshold measurements acquired at seven spatially distinct locations throughout a 3% agar TMM. As per the above definition, the cavitation threshold is clearly identifiable at 1.52 MPa_{PRFP} .

3.1.1.5 Hydrophone Array

The viability of the proposed HIFU QA system was tested using an array of four needle hydrophones, arranged circumferentially around a cylindrical TMM with 45° angular spacing between each needle. A perspex mount was machined to hold all four hydrophones in place, as well as the TMM, such that each needle extended radially in the transverse mid-plane of the cylindrical TMM (see Figure 3.7). In its mid-plane, the TMM was unsupported and in direct contact with water, providing a 20 mm window to allow any radiated emissions to propagate to the receiving hydrophones without reflection.

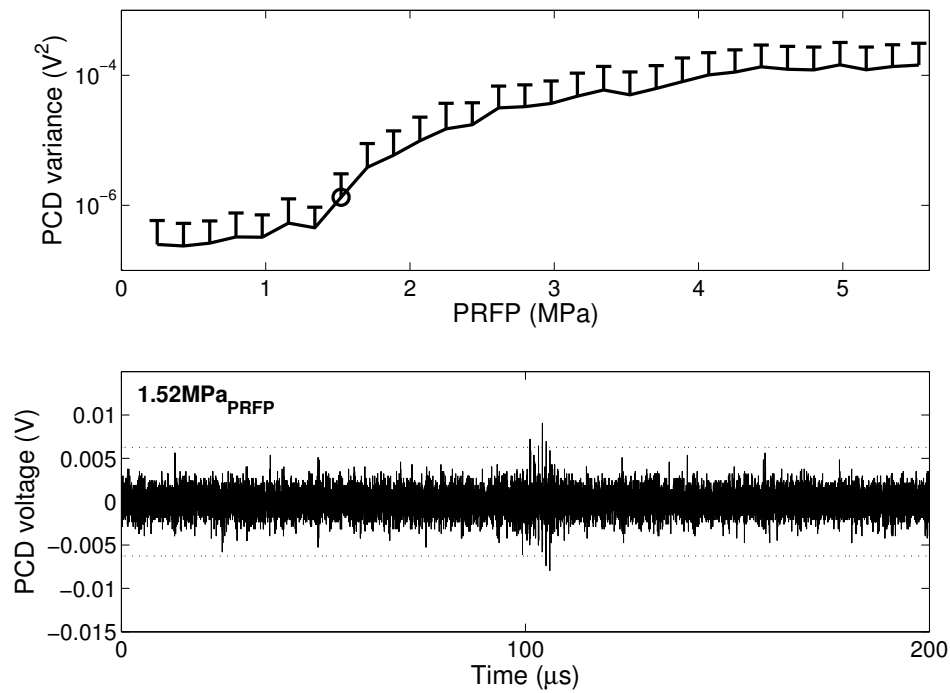
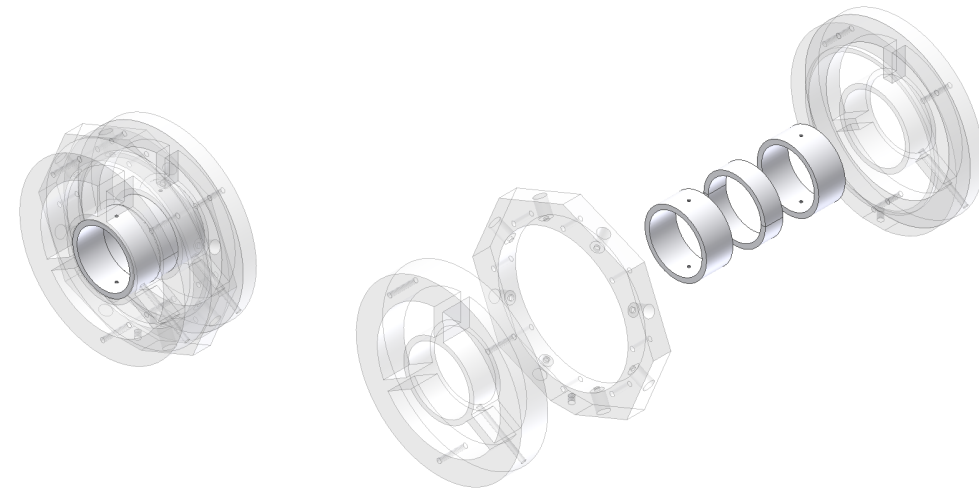


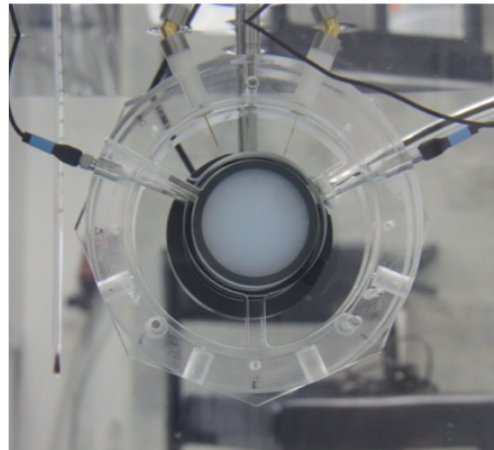
Figure 3.6: Cavitation threshold plot for a 3% agar TMM (above). Error bars show standard deviations of recorded signal variance at seven spatially discrete locations within a single TMM. A clear threshold pressure can be observed at 1.52 MPa_{PRFP}, where the PCD signal variance rises above the noise floor as can be seen in the corresponding PCD time trace (below).

Each of the four hydrophones listed in Table 3.1.1.5 comprises a piezo-polymer disc supported on the end of a needle of unique length. After inserting each hydrophone into the mount, the distance between the tip of the needle and the inner edge of the mount was measured using vernier callipers, allowing accurate localisation of the active element. Prior to testing, the array was acoustically aligned to ensure that the transverse HIFU focal plane was coincident with the imaging plane.

During experimentation, the HIFU transducer was held in a fixed position, whilst the hydrophone/TMM mount was supported by a three-axis motorised positioning system. Alignment of the two was achieved using the PCD, mounted inside the HIFU transducer and driven by a pulser receiver (JSR Ultrasonics DPR300).



(a)



(b)

Figure 3.7: Hydrophone array configuration used for proof-of-concept experiments. The four needle hydrophones were arranged circumferentially around a cylindrical TMM with 45° angular spacing between each needle. Once placed inside the test tank, the HIFU transducer was aligned coaxially with the TMM and the radiated emissions were detected in its mid-plane by the needle hydrophone array.

Table 3.2: Summary of the details of the hydrophones used in the four element array

Manufacturer	Part Number	Element Diameter
Precision Acoustics	HPM05	$500\ \mu\text{m}$
Precision Acoustics	HPM075	$75\ \mu\text{m}$
Onda	HNA-0400	$400\ \mu\text{m}$
Onda	HNA-0400	$400\ \mu\text{m}$

Monitoring of reflections from the surface of the TMM thus enabled accurate positioning of the hydrophone/TMM mount in the axial direction, ensuring that the transverse HIFU focal plane was coincident with the transverse mid-plane of the hydrophone/TMM arrangement. The mount was subsequently scanned in the transverse (x and y) directions to locate its perimeter (characterised by an increase in amplitude of the reflected signal received by the PCD). Once the positions of opposite edges in the x direction had been determined, the device was translated to the midpoint of these x co-ordinates. This procedure was then repeated in the y direction to locate the centre of the hydrophone/TMM arrangement.

All hydrophones were connected via inbuilt pre-amplifiers and DC coupling circuits to an oscilloscope (LeCroy Waverrunner 44Xi) for data acquisition. The oscilloscope was configured to simultaneously acquire 200 μ s of data from each hydrophone at a sample rate of 100MS/s at the start of each HIFU pulse.

3.1.1.6 Signal Processing

Prior to the generation of cavitation maps from the recorded hydrophone emissions, two key signal processing procedures were undertaken. Firstly, variability in the frequency-dependent sensitivity of the hydrophone array elements was accounted for. To do this, data was transformed to the frequency domain using the Fast Fourier Transform (FFT), and the appropriate scaling factor applied as per the frequency-dependent sensitivity calibration supplied by the manufacturer.

Secondly, the data was digitally filtered using a 5 MHz cut-off high-pass filter, as justified in Section 3.1.1.2, prior to conversion back to the time domain using the Inverse FFT (IFFT). The TEA algorithm was then applied to the scaled and filtered data to generate source maps at each insonation amplitude. The following section

presents the results from this analysis.

3.1.2 Cavitation Maps

The results of the proof-of-concept hydrophone array experiment are summarised below. Figure 3.8 shows the reconstructed source maps for exposures of increasing insonation amplitude computed via application of the TEA algorithm to the received broadband emissions on each element of the hydrophone array.

The reconstructed source maps show a clear region of activity near the centre of each image, indicative of a cavitating region. Importantly, as the insonation amplitude increases, so too does the size and amplitude of the mapped cavitation region. In the orientation of Figure 3.8, the four needle hydrophones are located in the bottom half of the image. Towards the top half of each image, and more noticeably at higher insonation amplitudes, there is a region of shadowing, where the limited span of the array reduces our ability to accurately map sources further away from the receiving elements. Clearly, the final array design will need to span the circumference of the focal volume in order to avoid such issues; however, the results presented here demonstrate that, even with a limited number of receiving elements, it is possible to map the evolution of a cavitating region with increasing insonation amplitude. This confirms the potential of the proposed HIFU QA system, which naturally leads to the use of more receiver elements for improved accuracy.

3.2 MEDICAL DIAGNOSTIC LINEAR ARRAY

Ultrasound imaging arrays form part of the basic diagnostic equipment held by almost all hospitals in the developed world. This section builds upon the findings

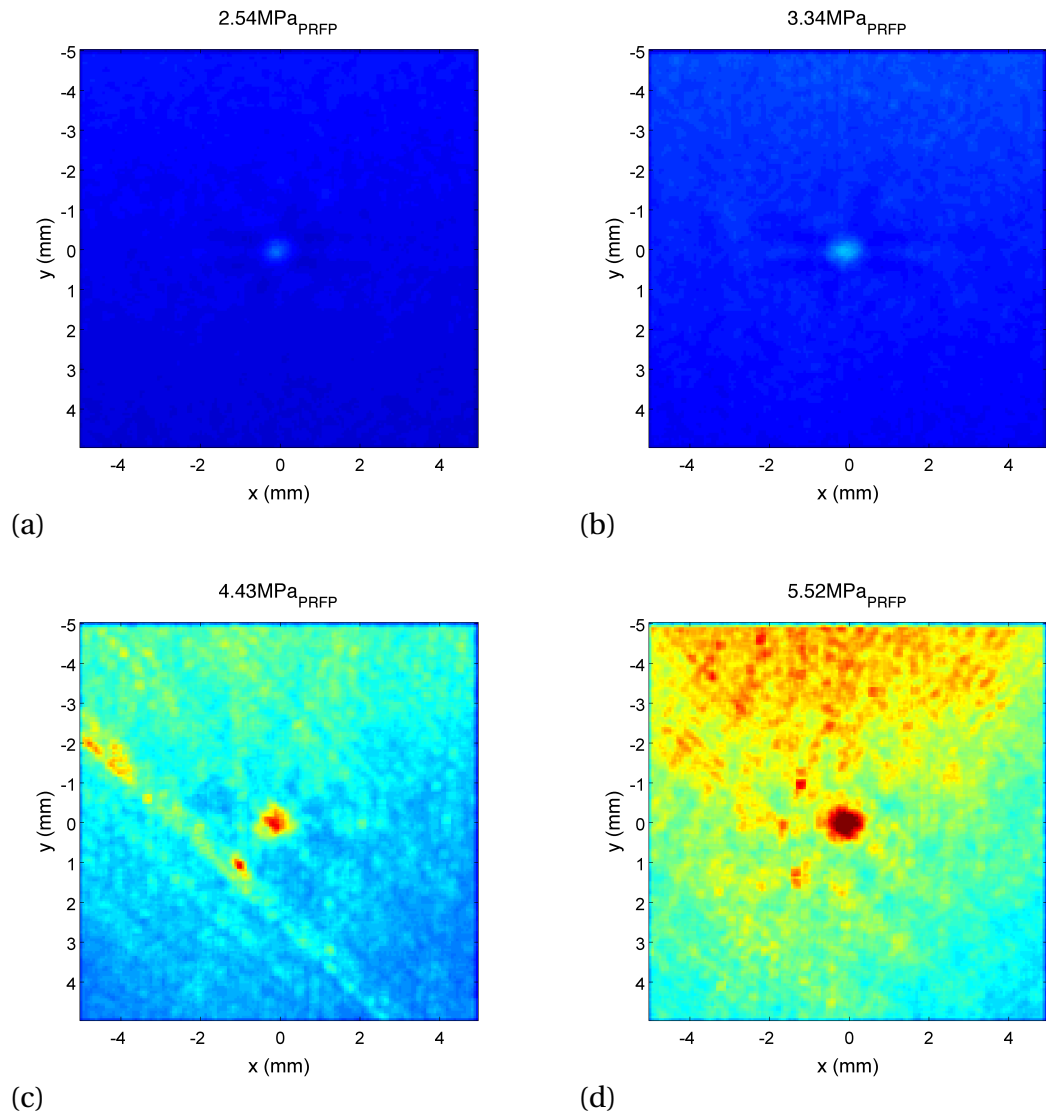


Figure 3.8: Cavitation maps reconstructed from the broadband emissions observed by the hydrophone array during HIFU exposure at 2.54 MPa_{PRFP} (a), 3.34 MPa_{PRFP} (b), 4.43 MPa_{PRFP} (c) and 5.52 MPa_{PRFP} (d). In the orientation shown, the needle hydrophone array spans the bottom half of each image. All cavitation maps are shown on the same colour scale. As the insonation amplitude increases, so too does the size and amplitude of the reconstructed cavitation region.

using the hydrophone array to demonstrate how a relatively inexpensive diagnostic linear array may be used to map cavitation activity within a modified TMM. As well as motivating the work of the following chapters, in which an array is developed to facilitate three-dimensional cavitation mapping, this section presents a viable method for rapid, two-dimensional HIFU QA using readily available hardware with minor software modifications.

For the work described here, 64 elements of a 128-element diagnostic linear array (Zonare L10-5) were used to passively observe the acoustic emissions from a cavitating region within a modified 3% agar TMM. By significantly increasing the channel count from that which was used in the previous section, higher spatial resolution is achieved. Furthermore, adjusting the orientation of the array allows cavitation maps to be reconstructed in the elevation, axial and transverse focal planes, resulting in more complete characterisation of cavitation activity at each insonation amplitude.

3.2.1 Experimental Setup

Figure 3.9 shows a schematic of the setup used for the linear array experiments. Though similar in appearance to the hydrophone array experiment, there are several key differences, each of which are explained in detail below. Most notably, here acoustic emissions were detected by the linear array, arranged in either an axial, transverse or elevation orientation as indicated in Figure 3.10.

3.2.1.1 HIFU Generation

In the experiment described below, the transducer driving electronics were identical to those used in the previous experiment; however, in order to accommodate

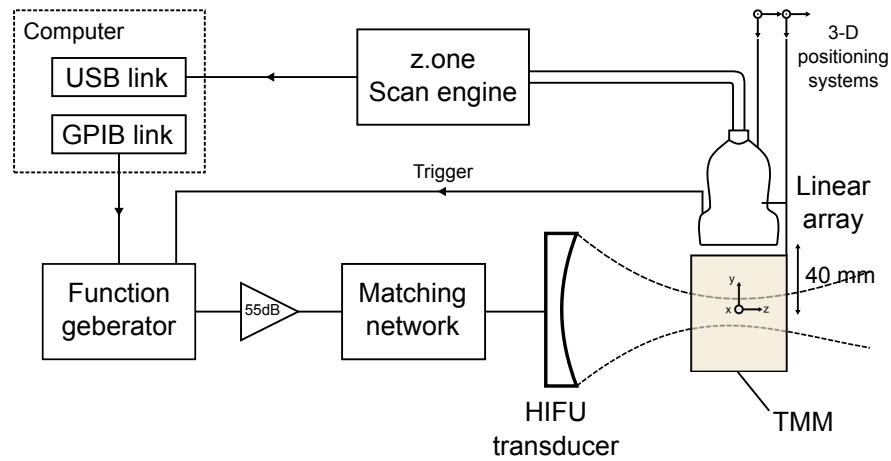


Figure 3.9: Schematic of the experimental setup used for the linear array experiments. Many of the components are similar to those used for the hydrophone array experiment; however, here a linear array is introduced to provide improved spatial resolution and allow imaging in the elevation, axial and transverse focal planes.

the linear array for mapping in the elevational plane an alternative, 1.06 MHz HIFU transducer with a rectangular central opening was used. The transducer, shown in Figure 3.11, was characterised using a needle hydrophone to determine both the absolute relationship between electrical signal input and PRFP, and the spatial distribution of the pressure field.

An absolute calibration was obtained using a 400 μm needle hydrophone (Onda HNA-0400) acoustically aligned at the HIFU focus. The robust design of the hydrophone ensured damage was not incurred at the high focal pressures generated by the transducer; however, data could only be acquired up to 3.02 MPa_{PRFP} , beyond which cavitation was observed and the calibration was blighted by secondary acoustic emissions. The transducer supply voltage, comprising a 1.06 MHz, 5-cycle, sinusoidal burst, was varied from 5 V_{pk-pk} to 130 V_{pk-pk} at 5 V_{pk-pk} intervals, yielding the relationship shown in Figure 3.12. Several acquired waveforms are also displayed, indicating a clear departure from linearity at 93 V_{pk-pk} , beyond which the PRFP is significantly smaller than the observed peak positive pressure. Since it is the

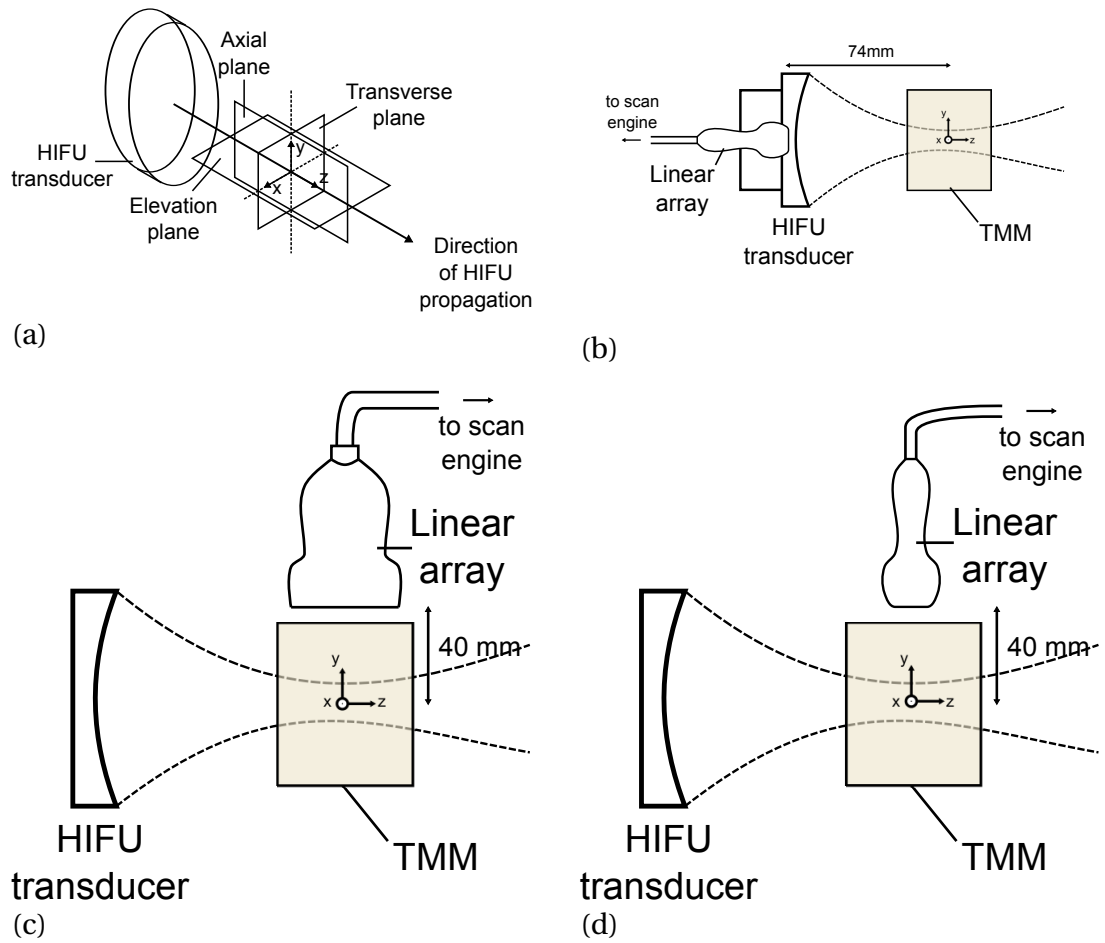


Figure 3.10: Linear array configuration for each of the imaging planes. The geometry of the imaging planes are shown in (a), whilst the orientation of the array for elevation, axial and transverse mapping is shown in (b), (c) and (d) respectively.

PRFP that is believed to dictate the nature of the cavitation activity, accurate knowledge of its dependency on the supply voltage is key to the success of the proposed cavitation-based HIFU QA system. For the range of HIFU input voltages and focal pressures employed in this study, the second order polynomial shown in Figure 3.12 provides a sufficiently accurate fit (coefficient of determination, $R^2=0.9997$), enabling prediction of the PRFP at the highest applied supply voltages.

Spatial calibrations were achieved using a $75\ \mu\text{m}$ needle hydrophone (Precision Acoustics HPM075), scanned throughout the focal volume with 0.25 mm spacing in

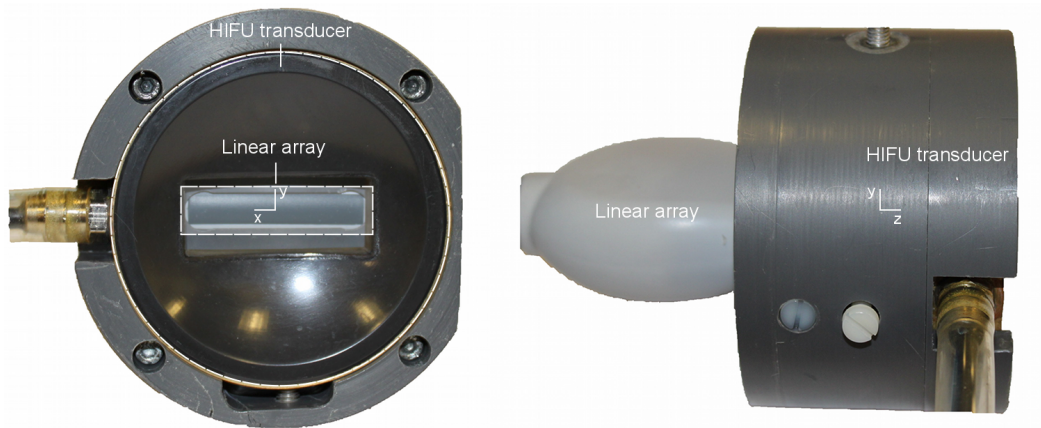


Figure 3.11: Spherically focused, single-element, 1.06 MHz HIFU transducer with rectangular void to accommodate the linear array for imaging in the elevation plane. The rectangular void results in discontinuous side-lobes as that can be seen in the spatial calibration shown in figure Figure 3.13.

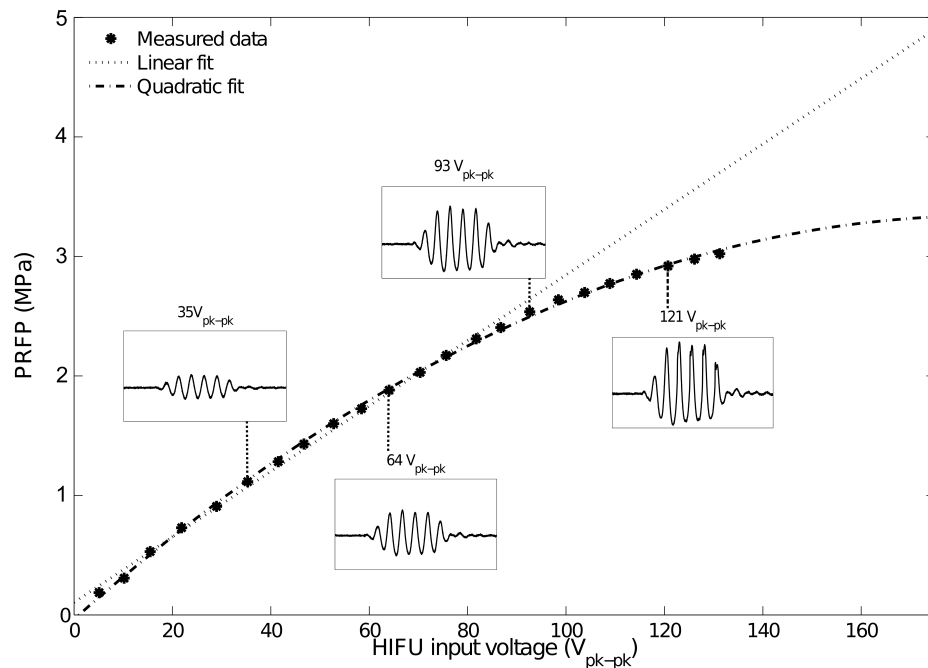


Figure 3.12: Calibration curve for the 1.06 MHz HIFU transducer. Focal pressures were recorded at $5 V_{pk-pk}$ intervals using a $400 \mu\text{m}$ needle hydrophone immersed in deionised and degassed water at 21°C . A departure from linearity becomes obvious around $93 V_{pk-pk}$, beyond which the PRFP is significantly smaller than the observed peak positive pressure.

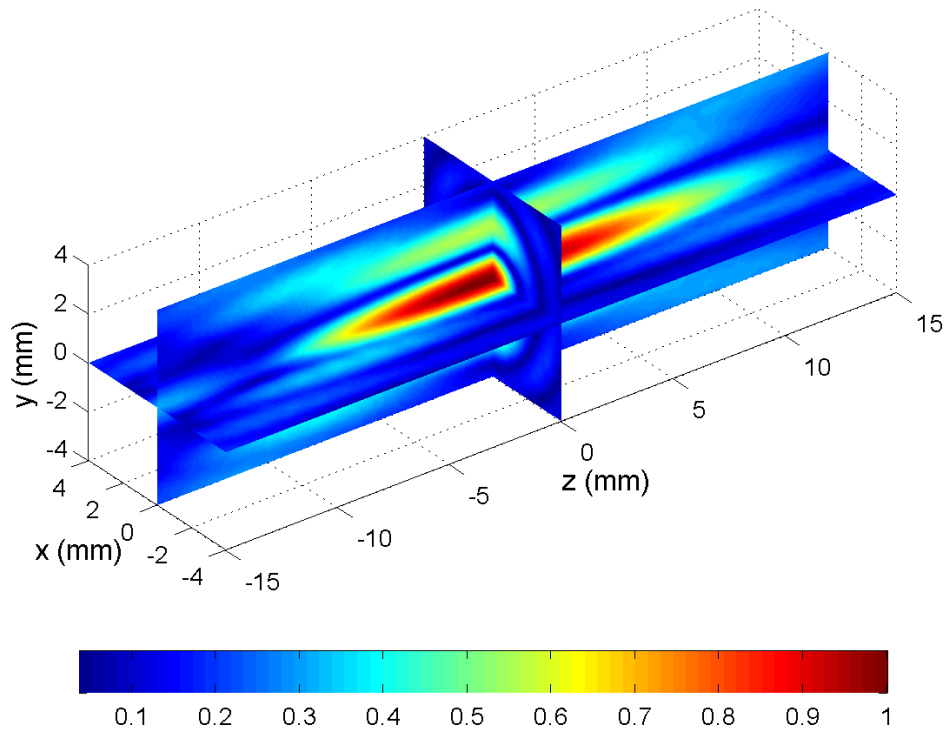


Figure 3.13: Normalised three-dimensional spatial calibration of the 1.06 MHz HIFU transducer. The rectangular void results in discontinuous side-lobes that are clearly visible in the transverse focal plane (see Figure 3.14).

the transverse and elevational directions, and 0.5 mm spacing in the axial direction. The resulting volumetric pressure profile, shown in Figures 3.13 and 3.14, was then used in conjunction with the absolute calibration to determine the size of the region where the PRFP surpassed the cavitation threshold of the TMM, hence facilitating prediction of the spatial distribution of the cavitating field.

When insonating the TMM during cavitation mapping experiments, the HIFU transducer was driven at its fundamental frequency with 5-cycle, sinusoidal pulses varied in amplitude from 1.88 MPa_{PRFP} to 3.33 MPa_{PRFP}. A trigger output from the Zonare array was used to synchronise the acquisition of data and the HIFU driving pulse so that the transducer was turned on at a time, T_{del} , prior to the acquisition of each frame. This ensured acoustic emissions were received near the centre of

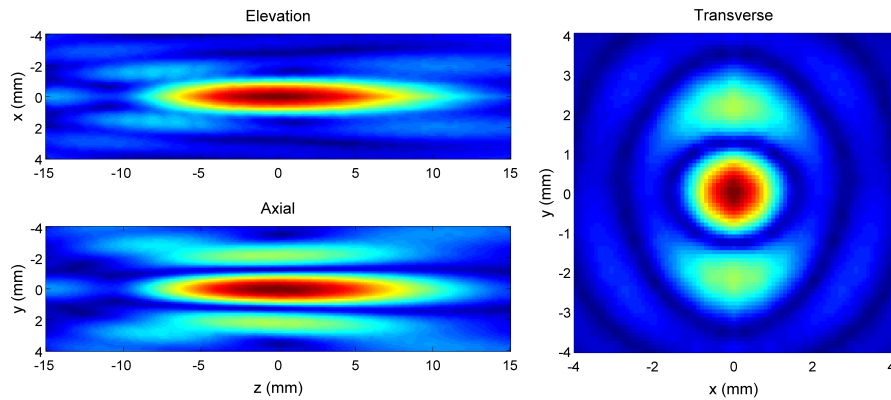


Figure 3.14: Normalised spatial calibration of the 1.06 MHz HIFU transducer in the elevation (above left), axial (below left) and transverse (right) focal planes. The discontinuous side-lobes created by the rectangular central void are clearly visible in the axial and transverse planes.

each acquisition. When the array was positioned within the HIFU transducer for imaging in the elevation plane, the imaging depth was geometrically constrained to ~ 74 mm (see Figure 3.10), necessitating a delay $T_{del}=30 \mu s$. For reconstruction in the transverse and axial planes, however, it was possible to image at a depth of ~ 40 mm and so T_{del} was set to $10 \mu s$.

After each exposure, the TMM was displaced by 5 mm in the transverse plane so that a new region could be insonated thereby avoiding the effect of nuclei depletion within the test medium.

3.2.1.2 Tissue Mimicking Material

Section 3.1.1.3 introduced an agar TMM that may be used to mimic the relevant acoustic properties of tissue for HIFU studies. It was shown that the distribution of cavitation activity within said TMM increased, as expected, with increasing HIFU insonation amplitude. For the following study, the TMM composition was modified by addition of rough, hydrophobic talc microparticles (Johnson & Johnson, $18 \mu m$

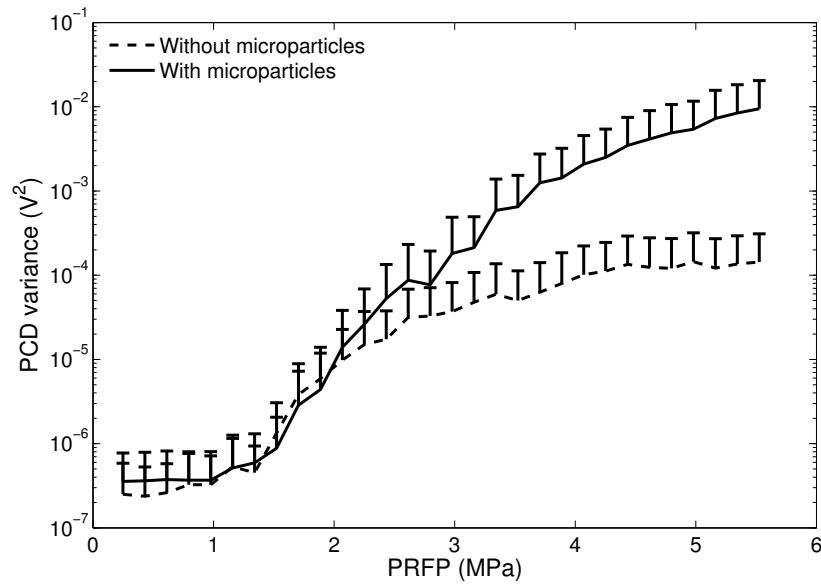


Figure 3.15: Comparison of cavitation thresholds of 3% agar TMMs with and without hydrophobic talc microparticles. Mean and standard deviations are calculated from seven spatially distinct measurements acquired throughout each TMM 24 hours post-preparation. Both TMMs exhibit a clear threshold at 1.52 MPa_{PRFP}, beyond which broadband emissions are repeatedly observed; however, the received signal variance increases more consistently with insonation amplitude and is considerably higher in magnitude (note the log scale) in the TMM that contains microparticles.

mean diameter) in order to increase the number of available cavitation nuclei, and hence encourage cavitation activity throughout the focal volume. As suggested by Arora *et al.* 4.34 g of particles were added per 275 ml of 3% agar TMM, which was prepared using the method described in Section 3.1.1.3 (Arora et al., 2011). Particles were added and thoroughly mixed for 10 minutes prior to degassing of the TMM.

The cavitation threshold of the modified TMM was determined using an identical procedure to that introduced in Section 3.1.1.4, yielding the relationship shown in Figure 3.15. Whilst not noticeably altering the inertial cavitation threshold, the addition of particles significantly increased the level of broadband noise detected, providing consistent increases in detected signal variance with increasing insonation amplitude. This enhanced radiated signal level is likely due to the in-

creased availability of cavitation nuclei, encouraging more cavitation events within the focal region. In addition to improving the SNR of the system, this increases the likelihood of instigating inertial cavitation throughout the region in which the cavitation threshold is surpassed, thence improving the efficacy of the proposed cavitation-based QA procedure.

One further study was conducted to investigate the variability in cavitation threshold of the microparticle TMM. Threshold measurements were carried out at seven different locations throughout a TMM, prepared using the method outlined above. Throughout the work of this thesis, all TMMs were used within 48 hours of initial preparation. Tests were, therefore, conducted both 24 and 48 hours after preparation, providing a measure of the stability of the TMM throughout this time frame. Between tests the phantom was refrigerated in its perspex mould at 4°C. Figure 3.16 displays the resulting probability of cavitation with increasing insonation amplitude.

It can be seen that the cavitation threshold of the TMM is unchanged between 24 and 48 hours post preparation. Whilst in some locations the cavitation threshold is marginally lower than 1.52 MPa_{PRFP} , broadband emissions were observed in all cases, both 24 and 48 hours post preparation, beyond this threshold. The microparticle TMM can, therefore, be considered stable over a 48 hour time period, with a reproducible cavitation threshold of 1.52 MPa_{PRFP} , beyond which broadband emissions are reliably observed.

By combining the three-dimensional pressure profile of the transducer with the measured cavitation threshold, it is possible to predict the extent of the cavitation region within the microparticle TMM at a given insonation amplitude. Figure 3.17 shows the predicted size of the cavitation region in the axial, transverse and elevation planes across the range of insonation amplitudes used in this study. Notably,

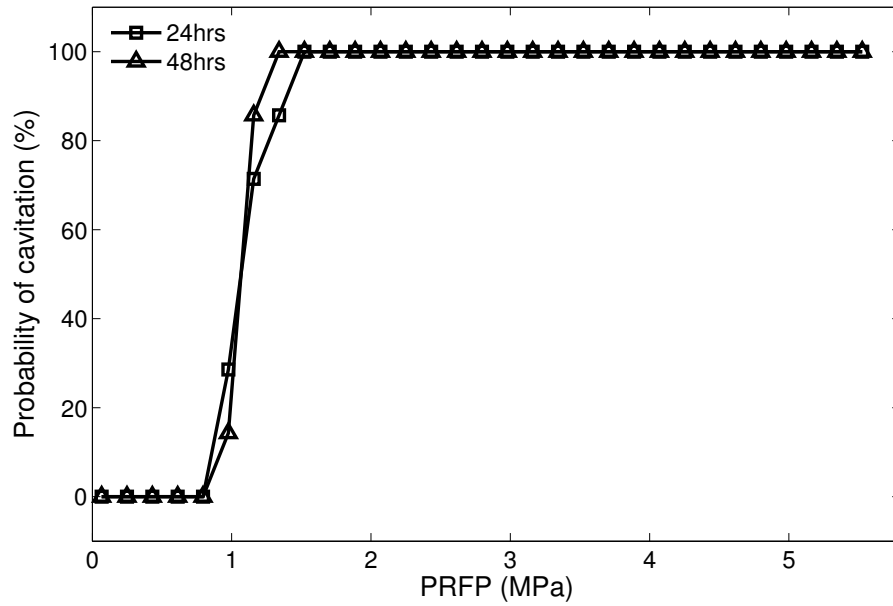


Figure 3.16: Variation in microparticle TMM cavitation threshold both at different sites within a TMM and across different days. The cavitation threshold of the TMM is unchanged between 24 and 48 hours post preparation and in all cases, broadband emissions are consistently observed above 1.52 MPa_{PRFP}

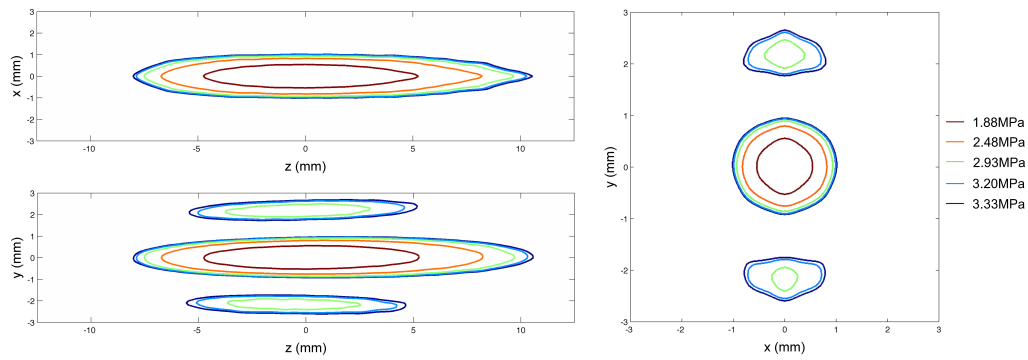


Figure 3.17: Predicted size of cavitation regions in a microparticle TMM in the elevation (above left), axial (below left) and transverse (right) focal planes. Contours indicate the boundary of the region where the cavitation threshold is surpassed and quoted pressures are PRFPs.

the abnormal side-lobe distribution, resulting from the rectangular central void, leads to predicted activity at $y = \pm 2 - 3 \text{ mm}$ that should be observed in the axial and transverse planes, but not the elevation plane.

3.2.1.3 Linear Array

The diagnostic medical imaging array used for the experiment detailed here consists of 128 elements, 64 of which may be triggered to simultaneously acquire data by the controlling scan engine - the z.one Ultrasound System (Zonare, Mountain View, CA). The resolution of the acquired image was maximised by choosing a distribution of 64 elements that spans the 38mm aperture of the 128-element array. Importantly, pulse transmission from the scan engine was disabled during acquisition, so that the array could passively observe acoustic emissions from the HIFU focal region.

At each insonation amplitude, the scan engine was configured to acquire data for 3 s at a frame rate of 50 Hz and with a frame duration of 135 μ s. As outlined in Section 3.2.1.1, the trigger output from the array was used to synchronise data acquisition with the HIFU driving pulse to ensure that acoustic emissions were received near the centre of each 135 μ s frame. HIFU pulses, triggered at the 50 Hz frame rate, were enabled for a total duration of 2 s providing 100 frames of data in which the HIFU transducer was turned on. The acquisition of data across the array was, therefore, arranged to extend 0.5 s pre- and post-HIFU on-time, providing a measure of the baseline noise level. The recording itself was in the form of 5 MHz bandwidth In-phase/Quadrature (IQ) data with configurable centre frequency. Of the frequency bands available, 4.96-9.64 MHz was chosen, thus tailoring the system for observation of cavitation emissions resulting from 1.06 MHz HIFU insonation.

When acquiring data in the transverse and axial orientations, the linear array was positioned so that the HIFU focus was at a depth of 40 mm within the imaging plane. As was shown in Section 2.7 this results in imaging resolutions in the region of 0.2 mm transverse to the array and 1.1 mm along the imaging axis. For accurate characterisation of the extent of the cavitation region, therefore, it is intended that

imaging in the axial orientation will be used to determine axial the length of the region, whilst the imaging in the transverse orientation will indicate its width. In this way, it is possible to exploit the favourable transverse resolution of the linear array.

In the elevation plane, the depth of the HIFU focus was geometrically constrained to be 74 mm from the central element of the linear array. Although resulting in poorer resolution - 0.4 mm transverse and 4.9 mm axial - this configuration mimics current clinical practice, in which a linear array may be placed coaxially with the HIFU transducer for B-mode treatment monitoring. This, therefore, provides a configuration which involves minimal alterations to current procedures.

For each orientation, alignment was achieved using the linear array to acquire B-mode images of a needle hydrophone acoustically positioned at the HIFU focus. The linear array, supported by a three-dimensional manual positioning system, was displaced so that the tip of the needle hydrophone was visible at the desired imaging depth and at the transverse midpoint of the acquired image. Figure 3.18 shows the B-mode alignment images acquired in each orientation. Once the array was correctly aligned, the needle was removed and replaced by a TMM, which was then positioned acoustically so that the HIFU focus lay at a depth of 20 mm within the TMM.

3.2.1.4 Signal Processing

The inherent 4.6-9.6 MHz bandpass filtering of the IQ data acquired using the z.one imaging system means that there is little need for filtering to remove the 1.06 MHz HIFU fundamental frequency from the recorded data. Furthermore, the received RF signals exhibited minimal harmonic content (see Figure 3.19) and so comb filtering

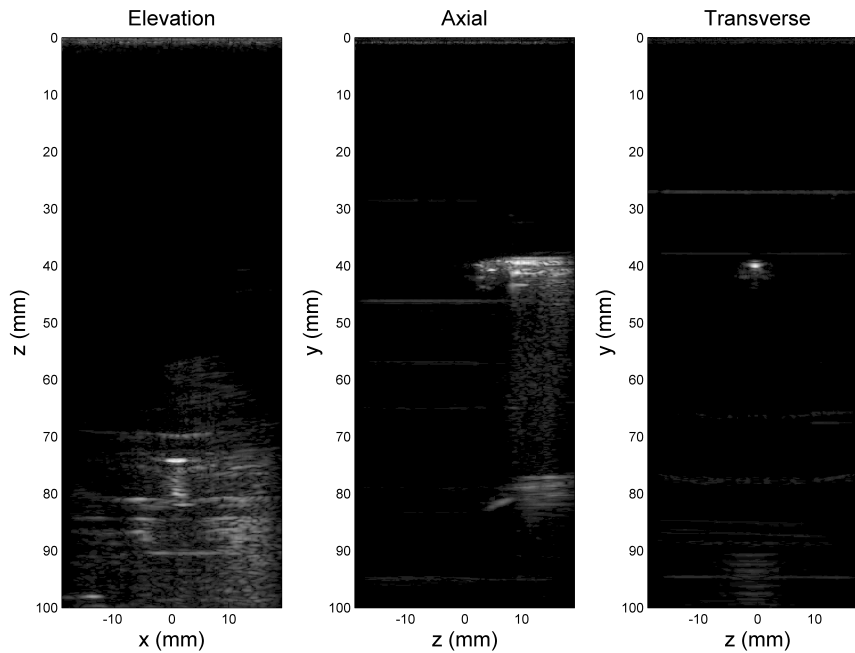


Figure 3.18: B-mode images used to align the linear array in the elevation (left), axial (centre) and transverse (right) orientations. A needle hydrophone, acoustically aligned at the HIFU focus, provides a strong scattering target for B-mode alignment. In each case, the array was manually positioned to ensure the needle tip was at the transverse mid-point of the image and at the correct imaging depth.

to remove these components was deemed unnecessary. The IQ data was, therefore, converted to 64 channels of RF data, which was then reconstructed using the TEA algorithm.

Each $135\ \mu\text{s}$ frame, sampled at 50 MHz, was upsampled using cubic spline interpolation to 200 MHz, thereby limiting quantisation errors when calculating the appropriate delays for the signals received on each element. Integration over time was then computed at the original sample rate to 50 MHz over the first 3000 data points of each frame (corresponding to $60\ \mu\text{s}$ of the $135\ \mu\text{s}$ frame), which was found to produce sufficiently accurate source maps without excessively long processing time. Results were then used to determine the distribution of cavitation activity at each insonation amplitude, as presented in the following section.

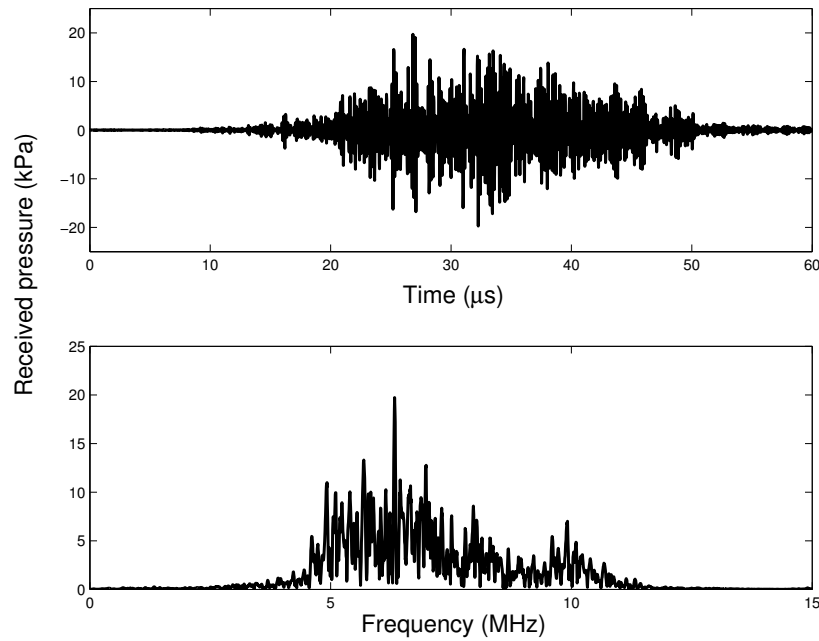


Figure 3.19: Typical RF signal (above) received by the linear array following 3.33 MPa_{PRFP} HIFU insonation with corresponding FFT (below). The received signal consists mostly of broadband noise, with minimal harmonic content. The inherent 4.6-9.6 MHz bandpass filtering of IQ data acquired by the z.one imaging system is also clearly visible. Conveniently this removes any scattered components of the fundamental frequency (1.06 MHz).

3.2.2 Cavitation Maps

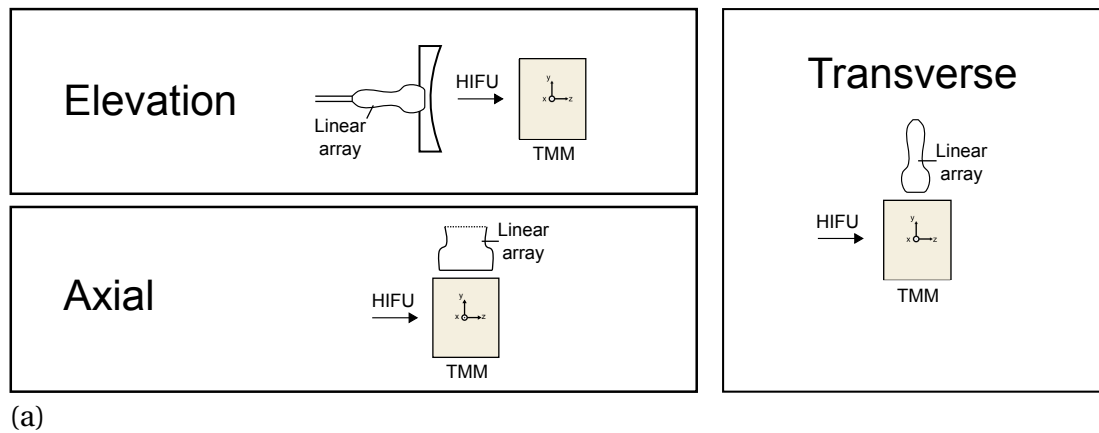
This section summarises the results of the cavitation mapping experiments using the linear array. In order to produce maps which are indicative of the extent of the region over which cavitation occurs during HIFU exposure, each of the displayed images represents the maximum pixel value obtained following reconstruction across all 150 frames of the 3 second acquisition (henceforth referred to as the *maximum pixel image*). Figure 3.20(a) clarifies the arrangement of images that are subsequently presented. In each case, images are reconstructed with 0.1mm resolution, then upsampled and linearly interpolated to 0.02mm resolution.

It is important to note that, since imaging in each plane required re-positioning of the array, the three maps do not correspond to simultaneously acquired data. This highlights a key limitation of the linear array for complete characterisation of the cavitation field, providing motivation for the work of the proceeding chapters. Here, however, similarities in observed cavitation distributions when imaging in each orientation, support the conclusion that the microparticle TMM is a relatively repeatable test medium.

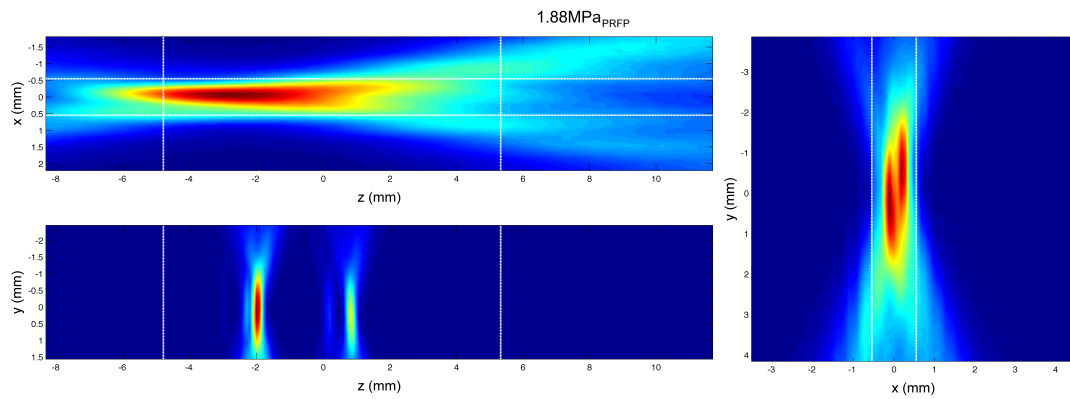
At each insonation amplitude there is a clear cavitation region that is approximately ellipsoidal in shape. As the insonation amplitude increases, so too does the size of the observed region in each of the imaging planes. In the transverse and elevation planes the region appears continuous, although the favourable spatial resolution in the axial orientation allows individual cavitation events to be distinguished. These individual events increase in both number and spatial extent with increasing insonation amplitude. Indicated on each image is the relevant predicted dimension of the cavitation region, which is compared to measured results below.

To provide a quantitative measure of the extent of the imaged cavitation region it is necessary to threshold each acquired image. In the elevation and transverse planes, where a near continuous region is observed, accurate measures of the dimensions of the reconstructed region can be obtained by thresholding the obtained maximum pixel image. Figure 3.22 shows the predicted and measured dimensions of the cavitation region when a threshold of -6 dB of the maximum pixel value is applied to the images acquired in the elevation plane. Predicted dimensions are calculated using a combination of the three-dimensional spatial calibration and the measured cavitation threshold as introduced in Section 3.2.1.2 (see Figure 3.17).

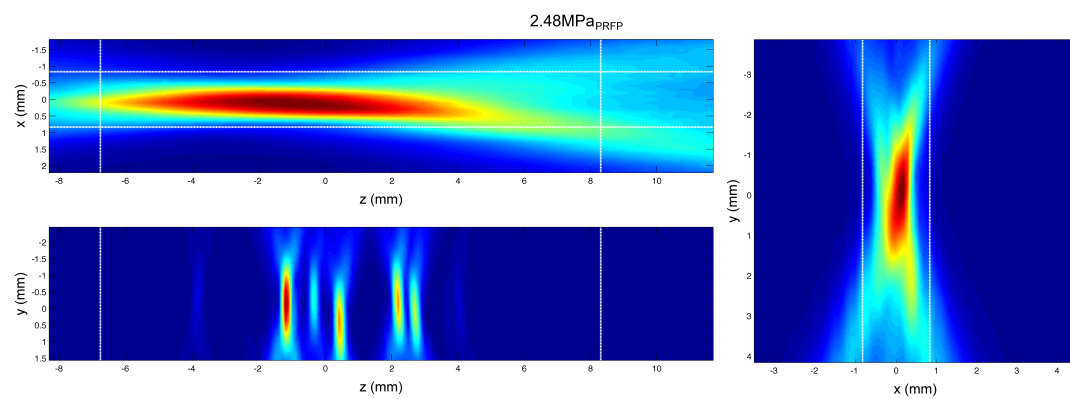
When imaging in the elevation plane, both the length and width of the reconstructed cavitation region are seen to increase with increasing insonation ampli-



(a)



(b)



(c)

Figure 3.20: Configuration of presented images (a) and corresponding cavitation maps following 1.88 MPa_{PRFP} (b) and 2.48 MPa_{PRFP} (c) insonation. Elevation maps are presented above left, axial below left and transverse right. White dashed lines indicate the relevant predicted dimension of the cavitation region.

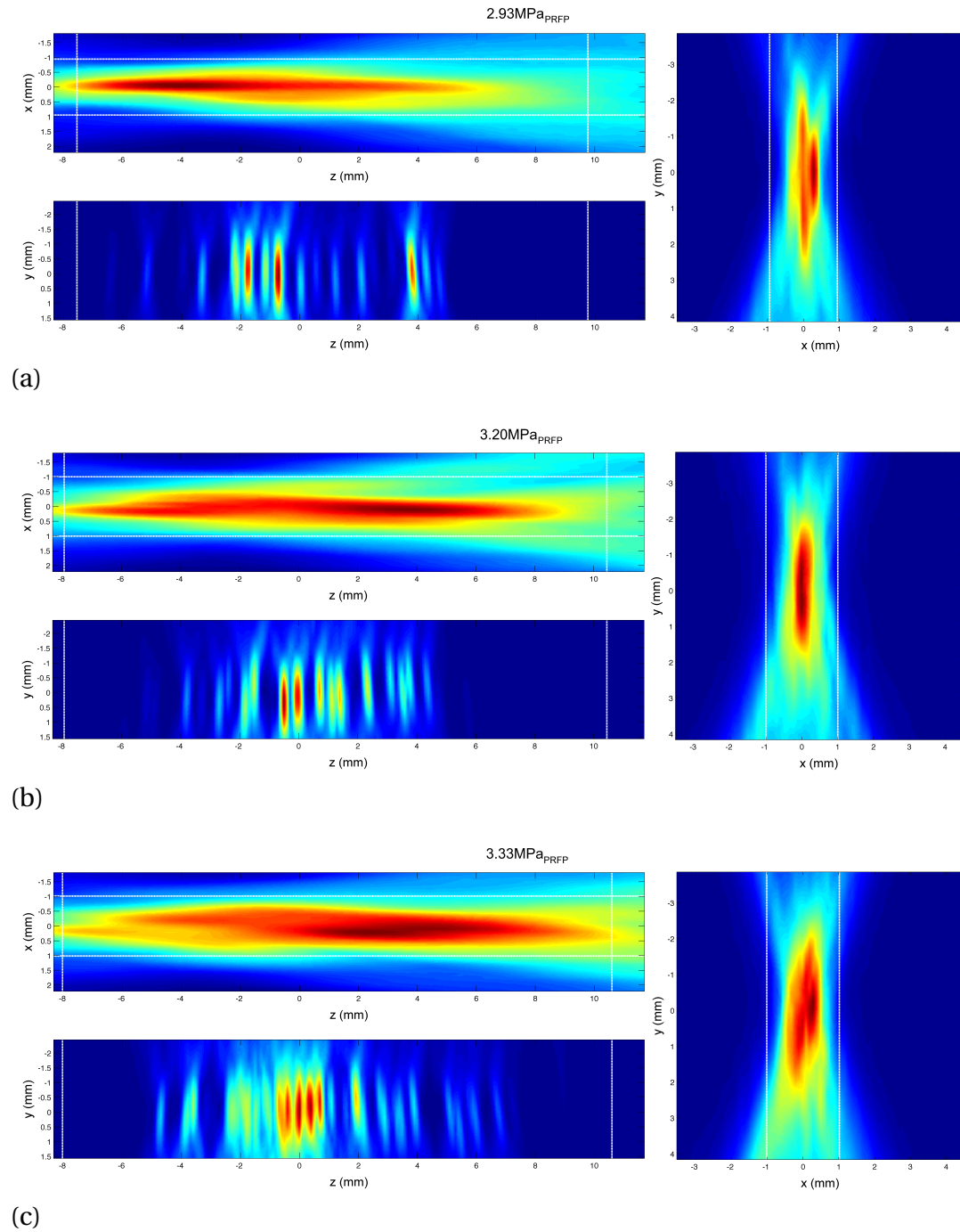


Figure 3.21: Cavitation maps in the elevation, axial and transverse planes following 2.93 MPa_{PRFP} (a), 3.20 MPa_{PRFP} (b) and 3.33 MPa_{PRFP} (c) insonation. White dashed lines indicate the relevant predicted dimension of the cavitation region.

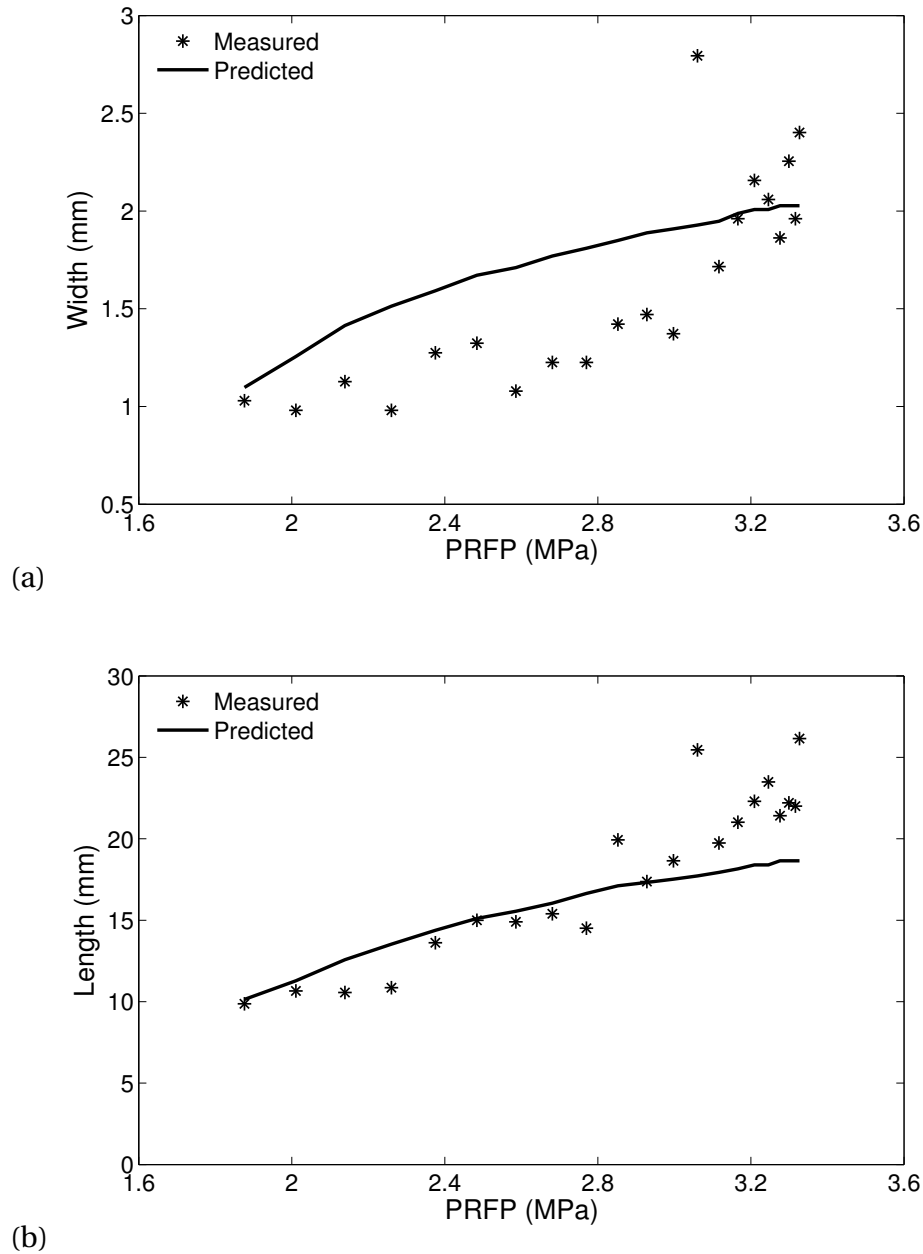


Figure 3.22: Predicted and measured width(a) and length (b) of the cavitation region in the elevation plane. Predicted dimensions indicate the region over which the cavitation threshold of 1.52 MPa_{PRFP} is surpassed. Measured values are determined following thresholding of the images formed by selecting the maximum pixel values observed throughout the 3s acquisition.

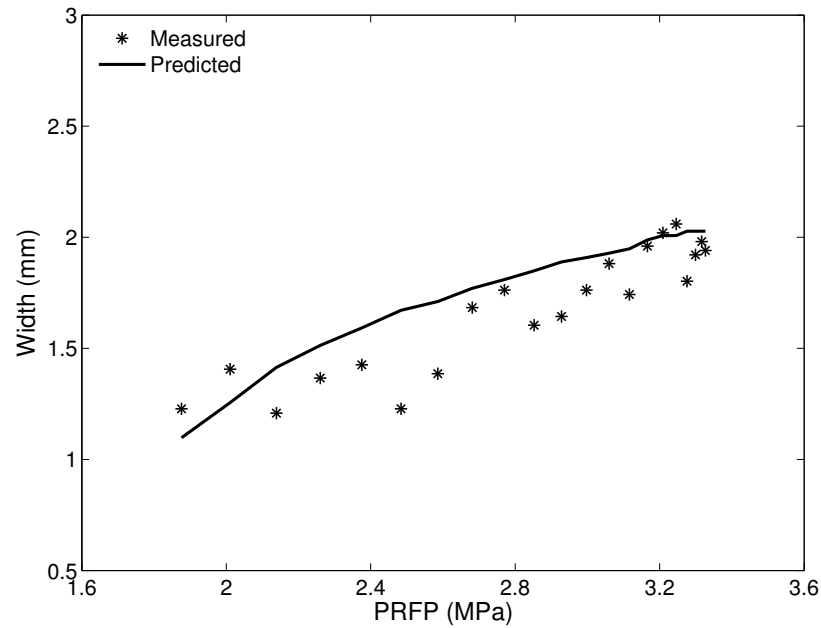


Figure 3.23: Predicted and measured width of the cavitation region in the transverse plane.

tude. It should be noted that the predicted dimensions represent an upper limit of the region over which cavitation would be expected to occur if there existed an endless source of cavitation nuclei. Even with addition of microparticles to seed the focal region with nuclei, the cavitation region was generally observed to be smaller than expected. At higher insonation amplitudes, however, cavitation was observed at, and even beyond its predicted boundary. This fact is exaggerated along the length of the region, where the longer PSF of the array in this configuration leads to the observation of larger cavitation regions than predicted.

Imaging in the transverse plane, at a shallower imaging depth of 40 mm, benefits from a narrower PSF and so favourable imaging resolution. Figure 3.23 depicts the relationship between PRFP and measured width of the cavitation region following thresholding of the maximum pixel images in the transverse plane. Again, there is a clear increase in measured width of the reconstructed cavitation region with in-

creasing insonation amplitude. In this case, measured values are more consistently within the predicted region size, with a maximum deviation above the predicted width of 0.15 mm.

In the axial plane, where the linear array spans the length of the focal region, it becomes possible to resolve individual cavitation events. These individual events are visible in the maximum pixel images displayed above (Figures 3.20 and 3.21); however, simply taking the maximum pixel value observed throughout the acquisition is somewhat misrepresentative of the observed distribution of cavitation activity, since there is considerable bias towards the strongest events observed throughout the 2 second exposure. An alternative processing method is, therefore, adopted whereby for each frame in which cavitation is observed, the image is thresholded at the -6 dB level of the maximum pixel value. Frames are then summed and thresholded again to provide an image which is indicative of the region over which cavitation occurs, regardless of the strength of the individual event. Figures 3.24 and 3.25 illustrate the additional information that appears following application of the thresholding procedure to two typical exposures. Clearly, the frame-by-frame thresholding procedure reveals a distribution which better represents the true spatial extent of the cavitating region, providing a closer match to that which is expected from the hydrophone-based field characterisation.

Once images have been appropriately thresholded, it is then possible to measure the length of the region over which cavitation occurs at each insonation amplitude. Figure 3.26 presents the resulting relationship between PRFP and measured length of the imaged region using both the maximum pixel image (Figure 3.26(a)) and frame-by-frame (Figure 3.26(b)) thresholding techniques. As was observed in the elevation and transverse planes, the measured size of the cavitation region is seen to increase with increasing insonation amplitude. Evidently, thresholding of

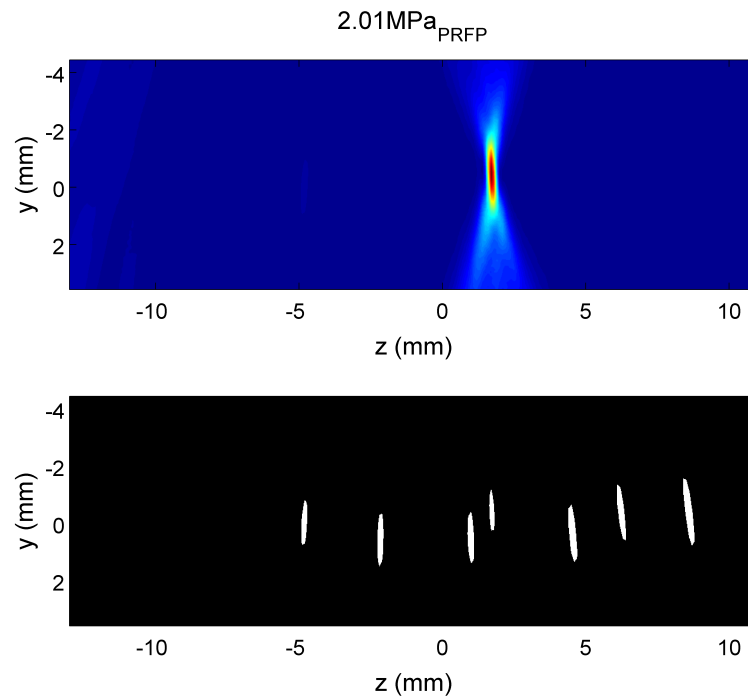


Figure 3.24: Maximum pixel image (above) and frame-by-frame thresholded image (below) for 2.01 MPa_{PRFP} exposure. In this orientation, maximum pixel images are biased towards the strongest cavitation events. By thresholding the image on a frame-by-frame basis, a more accurate representation of the true distribution of the cavitation events becomes apparent.

the maximum pixel images leads to significant underestimation of the length of the cavitation region, since images tend to be dominated by a smaller number of stronger cavitation events. The frame-by-frame thresholding technique, however, captures a distribution of activity that correlates much more convincingly with the predicted length of the cavitation region, deviating less from predictions than the corresponding values in the elevation plane.

Importantly, Figure 3.25 also highlights the ability of the cavitation-based QA method to identify abnormalities in the HIFU field. The thresholded image indicates that, at the higher amplitude of 2.93 MPa_{PRFP}, the discontinuous side-lobes produced by the transducer are of sufficient amplitude to generate cavitation activity at $y = \pm 2-3$ mm, as predicted by the contour plots of Figure 3.17. This observa-

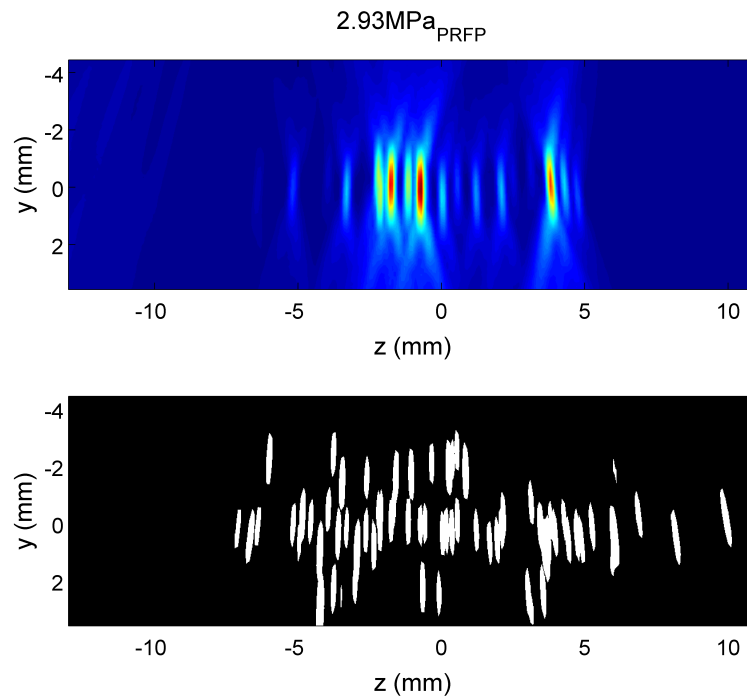


Figure 3.25: Maximum pixel image (above) and frame-by-frame thresholded image (below) for 2.93 MPa_{PRFP} exposure. Thresholding the image on a frame-by-frame basis reveals a much broader distribution of cavitation activity.

tion becomes more evident if the centroid of each of the observed cavitation events is overlaid on a plot of the measured pressure profile of the HIFU transducer. Figures 3.27 and 3.28 illustrate this at a range of insonation amplitudes where, as the PRFP is increased, three distinct bands of activity become visible in the central lobe ($y \approx 0 \text{ mm}$) and two side-lobes ($y \approx \pm 2.2 \text{ mm}$).

Crucially, an equivalent distribution of activity is not observed in the elevation plane, since the discontinuous side-lobes do not extend along the x -axis. This identifies a key feature of the proposed QA method, enabling rapid identification of abnormalities in the HIFU field. In the transverse plane it is also possible to observe activity in the side lobes (Figure 3.21(a) indicates activity at $y \approx \pm 2 \text{ mm}$); however, the narrow cross section of the focal region limits ones ability to resolve individual cavitation events and frames are dominated by stronger events in the central lobe.

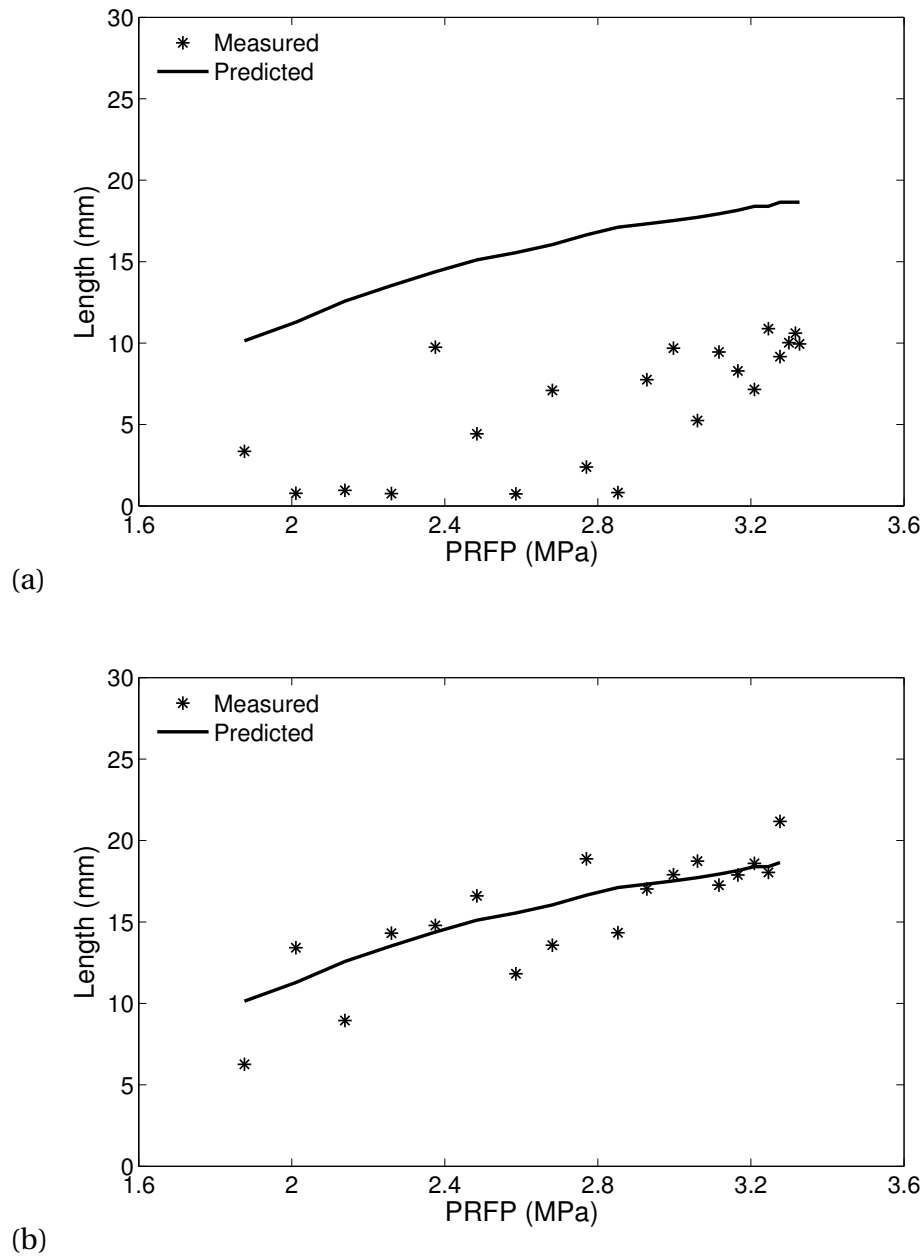


Figure 3.26: Predicted and measured width of the cavitation region in the axial plane following thresholding of the maximum pixel image (a) and frame-by-frame thresholding (b). Thresholding of the maximum pixel images leads to significant underestimation of the length of the cavitation region whilst the frame-by-frame thresholding technique captures a distribution of activity that correlates much more convincingly with predictions.

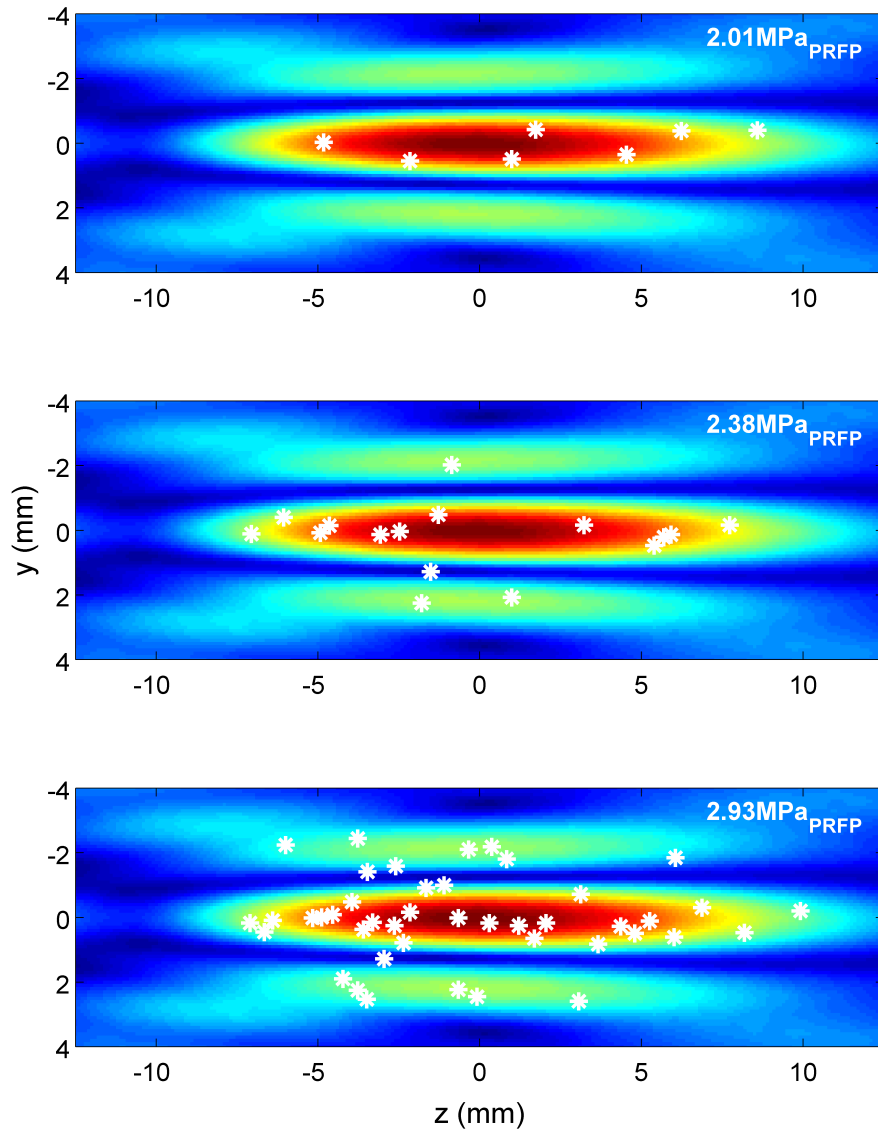


Figure 3.27: Distribution of cavitation activity in the axial plane observed at a range of HIFU insonation amplitudes. Markers indicate the centroid of each cavitation event that is observed and are overlaid on a plot of the transducer pressure profile. At lower amplitudes, cavitation activity is confined to the central lobe. As the insonation amplitude increases, however, three bands of activity become clearly visible, with cavitation events observed in the central lobe ($y \approx 0$ mm) and two side-lobes ($y \approx \pm 2.2$ mm).

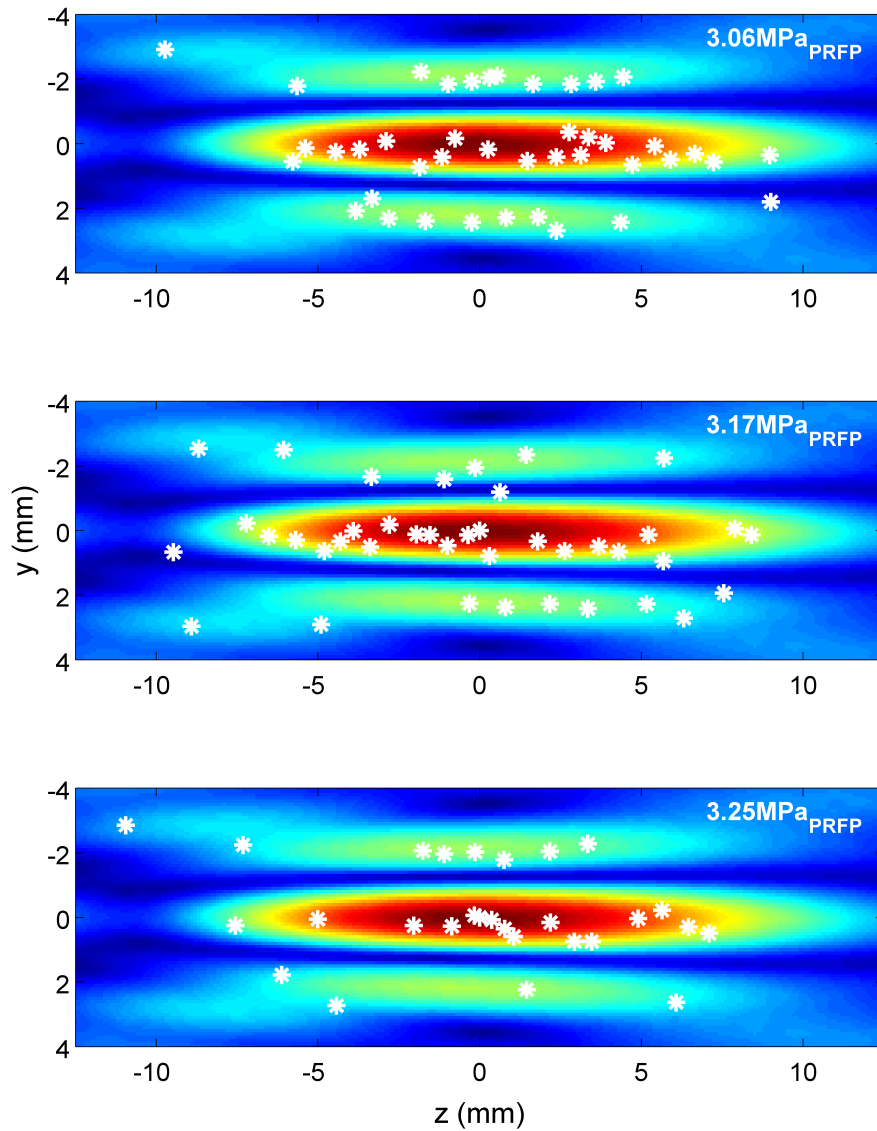


Figure 3.28: Distribution of cavitation activity in the axial plane observed at a range of higher HIFU insonation amplitudes. Markers indicate the centroid of each cavitation event that is observed and are overlaid on a plot of the transducer pressure profile. At these higher amplitudes, three bands of activity are consistently observed, with the side-lobes providing sufficient rarefactional pressure to instigate inertial bubble collapse.

3.3 SUMMARY

Whilst inertial cavitation is an inherently stochastic process, this chapter has shown that the instigation and evolution of cavitation activity behaves as predicted during HIFU exposure. By using a limited array of needle hydrophones to observe the broadband emissions from inertially cavitating bubbles during HIFU exposure, it was possible to apply passive imaging techniques to reconstruct a cavitation region that increased in size with increasing insonation amplitude. These initial results provided qualitative support for the concept of cavitation-based pressure mapping.

Extending the study to a more sophisticated, yet readily available medical diagnostic linear array provided enhanced imaging capabilities, allowing the distribution of cavitation activity to be sampled across three planes within the HIFU focal volume. To improve the efficacy of the proposed technique, an agar TMM was modified to include hydrophobic microparticles, the rough surface of which provides a plentiful supply of cavitation nuclei. Though the addition of particles had little effect on the 1.52 MPa_{PRFP} inertial cavitation threshold of the test medium, it did result in significantly higher amplitude broadband emissions, likely due to the fact that more cavitation events then occur within the focal volume. As well as augmenting the SNR of the system, it is believed that this increases the likelihood of observing cavitation emissions throughout the region in which the cavitation threshold is surpassed, thereby improving the performance of the proposed HIFU QA procedure.

The linear array provided the ability to passively acquire data across 64 channels of the 128-element device. By arranging the array in three orthogonal orientations, cavitation maps have been acquired in the axial, transverse and elevation focal planes, the latter of which provides a readily implementable test configuration

that would require minimal alteration to current clinical practice. Reconstructed source maps from data acquired during insonation at increasing PRFP amplitudes provide valuable information as to the nature of the therapeutic field. In each of the imaging planes, the distribution of cavitation activity is seen to increase with insonation amplitude as predicted. Measured values correlate well with those that are predicted, with results in the axial and transverse planes benefitting from favourable spatial resolution.

Application of multiple insonation pulses increases the likelihood of observing cavitation activity throughout the region in which the cavitation threshold is surpassed. In the elevation and transverse panes, where the cross section of the focal region is much narrower, this results in the observation of an extended cavitation region, the size of which correlates well with predictions following thresholding of the maximum pixel image. Imaging in the axial plane orients the array so as to utilise its favourable resolution along the axis of the cavitating region, allowing identification of individual cavitation events. Importantly, thresholding the reconstructed data on a frame-by-frame basis in this case results in a more accurate representation of the true distribution of cavitation activity throughout HIFU exposure.

By imaging cavitation activity in multiple planes it has been shown that asymmetries in the HIFU field can be accurately identified. Whilst highlighting a key feature of the proposed HIFU QA procedure, that is, rapid identification of any abnormalities in the produced field, this also emphasises an important area for improvement, which will form the basis of the remainder of this thesis. Though diagnostic linear arrays are readily available, and provide a practical method for pre-treatment cavitation-based HIFU QA that would be relatively simple to implement, complete characterisation requires significant operator intervention (re-alignment of the array) and relies on data that is not simultaneously acquired in all orientations. Ide-

ally, transducer characterisation would be achieved with a single device, arranged around the HIFU focal volume, that facilitates three-dimensional cavitation mapping from a single acquisition of data. Reliance on an operator would therefore be minimised, providing a practical solution which requires a simple ramping of the HIFU insonation amplitude and simultaneous data acquisition to achieve complete, three-dimensional characterisation.

It is this goal that forms the motivation for the work presented in the subsequent chapters of this thesis. To begin with, a novel method of array construction is proposed that will allow large numbers of receiving elements to be accurately positioned in the chosen array configuration. Of particular importance for the work of this thesis is the effect of the chosen construction method on the frequency response of the array, which is investigated in detail in Chapter 4. The study then progresses to consider the design and simulation of a prototype array capable of three-dimensional reconstruction of cavitation activity. Experimental validation offers useful insight into the design of arrays with similar construction and provides a strong foundation for future work into cavitation-based HIFU QA.



MODELLING AND CHARACTERISATION OF ARRAY RESPONSE

Understanding the piezoelectric effect is fundamental to the design of ultrasonic arrays. This chapter considers a novel multiple-layer construction method suggested by Precision Acoustics Ltd. for the proposed two-dimensional array designed to enable three-dimensional cavitation mapping. An analytic model is developed to explore the effect of multiple acoustic layers on the receive sensitivity of the proposed design. Key to the success of the model is accurate knowledge of the properties of the piezoelectric material. A method is thence presented for the experimental characterisation of lossy piezo-polymers such as PVDF. The resulting analytic model is compared to finite element simulations and experimental results, with useful implications for the design of similar multiple-layer arrays.

Cavitation-based HIFU QA has been shown to offer promising techniques for rapid, pre-treatment transducer characterisation. Whilst a diagnostic linear array may provide an inexpensive, convenient method for two-dimensional evaluation of the therapeutic field, it is not suitable for complete, three-dimensional field characterisation. The work of this thesis therefore proceeds to consider the design of an array that is capable of mapping cavitation in three dimensions.

It is evident from the work of the previous chapter that imaging performance will

be improved by the use of a relatively large number of receiving elements that are arranged so as to enclose the HIFU focal volume, thereby capturing as much of the radiated broadband energy as possible. Chapter 5 elaborates on the design of the proposed three-dimensional array, specifically in terms of the number and configuration of array elements that will facilitate accurate reconstruction of a cavitation field. Here, however, a novel method of array construction, is considered, which will allow precise placement of the sensor elements in a manner that eliminates sensitivity to stray signals along the electrode path.

Given that the acoustic signature of inertial cavitation is broadband noise, the frequency-dependent sensitivity of the array is of particular importance, which is effected by the addition of multiple acoustic layers to the front and back faces of the central piezoelectric material. In order to investigate this effect, an analytic model is developed to predict the influence of multiple acoustic layers on receive sensitivity. The model is then compared to both finite-element solutions and experimental results. Models are, however, only as reliable as the data upon which they are built. Emphasis is, therefore, initially placed on understanding the piezoelectric effect in order to develop a method for accurately determining the piezoelectric properties of lossy piezo-polymers such as PVDF. Before delving into a mathematical explanation of this phenomena, however, the suggested sensor construction method is considered in more detail. The construction technique itself was proposed and subsequently manufactured by colleagues from Precision Acoustics Ltd.

4.1 SENSOR CONSTRUCTION

In order to satisfy the key requirements of the proposed three-dimensional cavitation sensor - namely precise positioning of a relatively large number of elements in

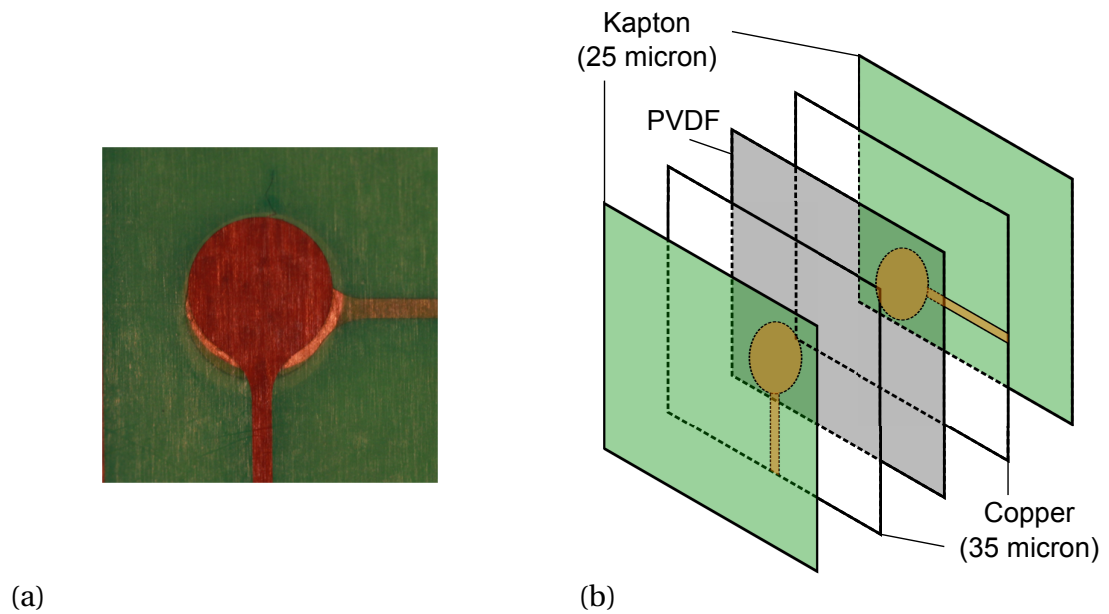


Figure 4.1: Image (a) and schematic (b) of the proposed multiple-layered PCB-PVDF sensor construction. By sandwiching the PVDF layer between two flexible printed circuit boards, sensitivity is precisely constrained to the regions where the copper tracks on the front and back layers overlap.

a configuration that encloses the HIFU focal volume - a novel construction method was suggested whereby a Printed Circuit Board (PCB) forms the electrodes of the piezoelectric device. By etching copper tracks onto a Kapton substrate layer, a flexible PCB can be manufactured and bonded to a layer of piezoelectric material, forming an array of sensitive elements that can be rolled into a shape that encloses the HIFU focal volume. If the backing layer of the sensor is then formed by an additional PCB, the sensitivity of the device can be precisely constrained to the regions in which the copper tracks of the front and back layers overlap, thereby avoiding additional sensitivity along the electrode path that would be encountered with a traditional grounded backing layer. Furthermore, the PCB substrate layer provides electrical isolation from the surrounding water, reducing sensitivity to noise and coupling between elements.

Figure 4.1 illustrates the multiple-layer construction method. For the purpose of the analytic model, the sensor consists of a central, PVDF piezoelectric layer, sandwiched between two 35 μm copper conducting layers forming the electrical ports. Each copper layer is then coated in a 25 μm Kapton polyimide substrate layer, providing structure to the flexible PCB.

4.2 PIEZOELECTRICITY

Piezoelectricity is a property of certain materials that is characterised by the onset of electrical polarisation when the material is subject to mechanical stress (the direct piezoelectric effect) and, conversely, the onset of deformation when the material is subject to an electric field (the inverse piezoelectric effect). First discovered in quartz by the Curie brothers in 1880 (Curie and Curie, 1880), the piezoelectric effect is the result of the reorientation of molecular dipole moments under the action of the applied stress, and it plays a crucial role in the field of medical ultrasonics. In the context of HIFU surgery, this phenomenon governs the basic principles upon which driving transducers and receiving hydrophones are based.

A whole host of natural and synthetically produced materials have been found to exhibit piezoelectricity. Perhaps most commonly used for ultrasonic devices are the piezo-ceramic PZT, composed of lead, zirconium and titanium oxides, and the piezo-polymer PVDF, formed from the $\text{C}_2\text{H}_2\text{F}_2$ monomer. The properties of a given piezoelectric material may be described by a number of material constants which relate the electric field, E and displacement, D to the mechanical strain, S and stress, T via the piezoelectric constitutive relations (Ristic, 1983). In such a system, any two variables may be expressed as a function of the remaining two. Thus, if it is assumed

that $T = T(S, E)$ and $D = D(S, E)$, for small fields the Taylor expansion yields:

$$T = \left(\frac{\partial T}{\partial S} \right)_E S + \left(\frac{\partial T}{\partial E} \right)_S E \quad (4.1)$$

$$D = \left(\frac{\partial D}{\partial S} \right)_E S + \left(\frac{\partial D}{\partial E} \right)_S E. \quad (4.2)$$

In this instance, the material constants are defined as

$$c^E = \left(\frac{\partial T}{\partial S} \right)_E, e^E = \left(\frac{\partial D}{\partial S} \right)_E \quad (4.3)$$

and

$$e^S = \left(\frac{\partial T}{\partial E} \right)_S, \epsilon^S = \left(\frac{\partial D}{\partial E} \right)_S \quad (4.4)$$

measured at either constant electric field or mechanical strain respectively. The constants e^E and e^S represent the direct and inverse piezoelectric effects and may be equated via thermodynamic considerations to give $e^E = -e^S = e$. Thus, Equations 4.1 and 4.2 become:

$$T = c^E S - eE \quad (4.5a)$$

$$D = eS + \epsilon^S E. \quad (4.5b)$$

The constitutive equations may be used to develop analytical expressions for experimentally measurable quantities, such as electrical input impedance, which can be interpreted to determine the relevant piezoelectric material properties for subsequent simulations. Below, an expression is derived for the input impedance of a thin-disk resonator, which is measured experimentally in the subsequent section. Results are used to determine the necessary material properties for a model which predicts the frequency response of the proposed multiple-layer PCB-PVDF array.

4.2.1 Piezoelectric Thin-Disk Resonator

If one considers a longitudinal wave propagating in the positive z direction, Equation 4.5 is given as

$$T_3 = c^E \frac{\partial u_z}{\partial z} - e E_z \quad (4.6a)$$

$$D_z = e \frac{\partial u_z}{\partial z} + \epsilon^S E_z, \quad (4.6b)$$

where u_z is the displacement in the z direction. By using dynamic equilibrium to equate the applied load and particle acceleration as

$$\frac{\partial T_3}{\partial z} = \rho \frac{\partial^2 u_z}{\partial t^2} \quad (4.7)$$

and noting that, given that there is no free charge in a piezoelectric dielectric, Gauss's law implies

$$\frac{\partial D_z}{\partial z} = 0, \quad (4.8)$$

Equations 4.6a and 4.6b, may be combined to give the wave equation in the form

$$\rho \frac{\partial^2 u_z}{\partial t^2} = c^D \frac{\partial^2 u_z}{\partial z^2}, \quad (4.9)$$

where c^D is the piezoelectrically stiffened elastic constant given by

$$c^D = c^E \left(1 + \frac{e^2}{c^E \epsilon^S} \right) = c^E (1 + K^2). \quad (4.10)$$

The factor K^2 , termed the piezoelectric coupling factor, gives an indication of the mechanical oscillation induced when a sinusoidal electric field is applied to the material. In effect, the presence of piezoelectricity stiffens the material, increasing the stiffness constant c^E by K^2 percent. This stiffening results in a corresponding increase in wave speed, thus the stiffened longitudinal wave speed, v_L^D , in a piezoelectric material is given by

$$v_L^D = v_L (1 + K^2)^{1/2}, \quad (4.11)$$

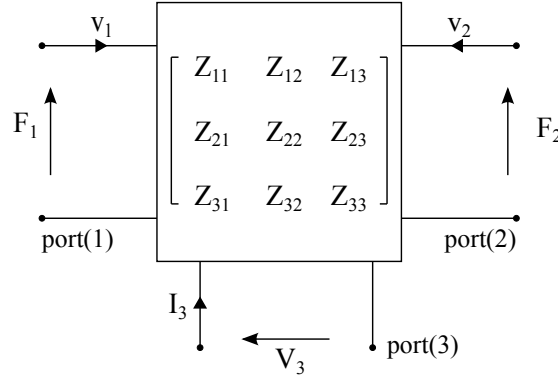


Figure 4.2: Schematic of a thin-disc piezoelectric transducer with acoustic ports (1 and 2) and electric port (3). Reproduced from Ristic, *Principles of Acoustic Devices* (Ristic, 1983).

where v_L is the wave speed in an acoustically equivalent, non-piezoelectric material.

The oscillation of a thin-disc piezoelectric, of cross-sectional area A , where the two lateral dimensions are much larger than the thickness, l , may be represented by a similar, one-dimensional, model. Solutions to Equation 4.9 can be developed to relate the acoustic and electric loads via a transfer matrix, Z , depicted in Figure 4.2. In this case, F_i represents the traction force at port (i), given by $F_i = AT_{(i)}$ where $T_{(1)} = -T_3(0)$ and $T_{(2)} = -T_3(l)$.

Within the piezoelectric layer, the particle velocity, v , can be calculated as the solution to Equation 4.9 and, once the time dependence is suppressed, takes the form

$$v_z(z) = (M' \sin \beta_a z + N' \cos \beta_a z) j\omega, \quad (4.12)$$

where β_a is the wave number, given by $\beta_a = \omega / v_L^D$. The unknowns M' and N' can be determined by analysis of the boundary conditions, where $v_z(0) = v_1$ and $v_z(l) = -v_2$, thus

$$v_1 = j\omega N' \quad (4.13)$$

and

$$-v_2 = j\omega M' \sin \beta_a l + v_1 \cos \beta_a l, \quad (4.14a)$$

hence,

$$j\omega M' = -v_2 \csc \beta_a l - v_1 \cot \beta_a l. \quad (4.14b)$$

The electric field and stress may then be obtained from the constitutive relations given in Equation 4.6 as

$$E_z = \frac{1}{\epsilon^S} \left[D_z - \frac{e}{j\omega} \frac{\partial v_z}{\partial z} \right] \quad (4.15)$$

and

$$T_3(z) = -\frac{e}{\epsilon^S} D_z + \frac{1}{j\omega} \frac{\partial v_z}{\partial z} \left[c^E + \frac{e}{\epsilon^S} \right]. \quad (4.16)$$

Given that the current, I_3 , is found as the product of the displacement current density, $j\omega D_z$, and the cross-sectional area, A , it follows that

$$T_3(z) = \frac{-h I_3}{j\omega A} + \frac{c^D}{j\omega} \frac{\partial v_z}{\partial z} \quad (4.17)$$

where $h = e/\epsilon^S$. This expression may then be used to calculate the stresses at the boundaries of the piezoelectric material as

$$T_3(0) = \frac{-h}{j\omega A} I_3 - \frac{(\rho_m c^D)^{1/2}}{j} [v_2 \csc \beta_a l + v_1 \cot \beta_a l], \quad (4.18a)$$

and

$$T_3(l) = \frac{-h}{j\omega A} I_3 - \frac{(\rho_m c^D)^{1/2}}{j} [v_1 \csc \beta_a l + v_2 \cot \beta_a l]. \quad (4.18b)$$

Furthermore, the voltage, V_3 , across the electric ports is given by integrating the electric field across the thickness of the disk

$$V_3 = \int_0^l E_z dz = \int_0^l \frac{1}{\epsilon^S} \left[\frac{I_3}{j\omega A} - \frac{e}{j} \left(\frac{\rho_m}{c^D} \right)^{1/2} j\omega (M' \cos \beta_a z - N' \sin \beta_a z) \right] dz \quad (4.19)$$

where E_z is given by substitution of Equations 4.12, 4.13 and 4.14b into Equation 4.15, yielding

$$V_3 = \frac{I_3}{j\omega C_0} + \frac{e}{j\omega \epsilon^S} (v_1 + v_2) \quad (4.20)$$

where $C_0 = \epsilon^S A/l$ is the bulk capacitance of the piezoelectric film.

The transfer matrix, Z , of the system shown in Figure 4.2 is then formulated as follows

$$\begin{bmatrix} F_1 \\ F_2 \\ V_3 \end{bmatrix} = -j \begin{bmatrix} \bar{Z}_0 \cot \beta_a l & \bar{Z}_0 \csc \beta_a l & h/\omega \\ \bar{Z}_0 \csc \beta_a l & \bar{Z}_0 \cot \beta_a l & h/\omega \\ h/\omega & h/\omega & 1/\omega C_0 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ I_3 \end{bmatrix} \quad (4.21)$$

where $\bar{Z}_0 = AZ_0 = A\sqrt{\rho_m c^D}$. This generalised expression allows one to model the response of a variety of configurations of thin disk piezoelectric transducers by imposing the appropriate boundary conditions. For a thin-disk resonator, where the acoustic ports are unloaded, $F_1 = F_2 = 0$ and the electrical input impedance is given as

$$Z_3 = \frac{V_3}{I_3} = \frac{1}{j\omega C_0} \left[1 - k_t^2 \frac{\tan(\beta_a l/2)}{\beta_a l/2} \right], \quad (4.22)$$

where k_T is the thickness mode piezoelectric coupling constant, defined as

$$k_T^2 \equiv \frac{K^2}{1 + K^2}. \quad (4.23)$$

Importantly, the electrical input impedance can be easily measured using an impedance network analyser. This, therefore, provides a means to estimate the relevant properties of a given piezoelectric material by fitting the parameters in Equation 4.22 to experimental results. These properties may then be used to simulate the acoustic response of the piezoelectric sensor configuration.

4.3 DETERMINING MATERIAL PROPERTIES

Various methods have been developed to fit analytical expressions for the electrical input impedance of a thin-disk piezoelectric resonator to experimentally measured

results. If Equation 4.22 is re-written as

$$Z_3(f) = \frac{l}{j2\pi f \epsilon^S A} \left[1 - k_T^2 \frac{\tan\left(\pi f l \sqrt{\frac{\rho_m}{c^D}}\right)}{\pi f l \sqrt{\frac{\rho_m}{c^D}}} \right], \quad (4.24)$$

three dominant piezoelectric properties emerge. These properties, defined in the preceding section, are: the clamped dielectric permittivity, ϵ^S , the thickness mode piezoelectric coupling constant, k_T , and the piezoelectrically stiffened elastic constant, c^D . Crucially, these parameters also form the basis of the equivalent circuit models, discussed in Section 4.4.1, that may be used to simulate the acoustic response of the proposed multiple-layer PCB-PVDF array. To account for losses, which are particularly evident in PVDF, the material parameters are treated as complex quantities, denoted as ϵ^{S*} , k_T^* and c^{D*} . These quantities may be written as

$$\epsilon^{S*} = \epsilon^S (1 - j \tan \delta_e) \quad (4.25)$$

$$k_T^* = k_T (1 + j \tan \delta_k) \quad (4.26)$$

$$c^{D*} = c^D (1 + j \tan \delta_m) \quad (4.27)$$

where $\tan \delta_e$, $\tan \delta_k$ and $\tan \delta_m$ are the dielectric, electromechanical coupling factor and elastic loss tangent, respectively.

In the context of the present work, a method based on that described by Kwok *et al.* was used to give an initial estimate of the above parameters by fitting Equation 4.24 to experimentally measured results (Kwok *et al.*, 1997). The fitting procedure is outlined below, though the interested reader is invited to refer to Kwok *et al.* and Brown *et al.* for a more complete description of the method used (Kwok *et al.*, 1997; Brown and Carlson, 1989).

At frequencies far from resonance, Equation 4.24 is dominated by a baseline term, Z_0 , given by

$$Z_0(f) = \frac{l}{j2\pi f \epsilon^S A (1 + j \tan \delta_e)}. \quad (4.28)$$

By solving for the baseline impedance magnitude, $|Z_0|$, and phase, θ_{Z_0} , expressions for the dielectric permittivity and its loss tangent may then be formed:

$$\tan \delta_e = -\frac{1}{\tan \theta_{Z_0}}, \quad (4.29)$$

$$\epsilon^S = \frac{l}{|Z_0|2\pi f \epsilon^S A \sqrt{\tan^2 \delta_e + 1}}. \quad (4.30)$$

Though strictly only applicable at those frequencies far from resonance, these expressions provide a useful first approximation to ϵ^S and $\tan \delta_e$. Using the approximation of $\tan \delta_e$ as a starting point, a non-linear regression procedure (Levenberg-Marquardt method) was applied to fit the measured impedance magnitude to the magnitude of Equation 4.24 to obtain estimates of the remaining material parameters. Estimated values of ϵ^S , k_T , c^D , $\tan \delta_k$ and $\tan \delta_m$ were used to fit the phase of Equation 4.24 to the measured phase, providing a new estimate of $\tan \delta_e$. The procedure was then iterated until convergence was obtained. Estimated parameters, which were assumed to be independent of frequency in the vicinity of the resonance, were then manually adjusted to achieve the best fit to experimental data. Below, the impedance measurement procedure is summarised and experimental results are presented. Estimated parameters are presented in Table 4.1 and the resulting fits to experimental results are displayed in Figure 4.3.

4.3.1 Impedance Measurement

Four samples of 60 μm PVDF film were characterised experimentally using a Vector Network Analyser (VNA) (Hewlett Packard 8712C) to determine both the amplitude and phase of their electrical impedance across the 1-50 MHz range. Square samples were prepared, each with ~ 30 mm side length, and were connected to the VNA via thin wires bonded to copper electrodes held in contact with the sample. Impedance

Table 4.1: Mean and Standard Deviation (SD) of material properties fitted to experimental data

Material property	c^D (GPa)	$\tan \delta_m$	ϵ^S	$\tan \delta_e$	k_T	$\tan \delta_k$
Fitted value	8.6	0.123	5.45	0.250	0.164	0.100
SD	± 0	± 0.0173	± 0.245	± 0.0108	± 0.0131	± 0.0373

measurements were acquired at 60 kHz intervals across the 50 MHz range and transferred to a PC for post processing.

Figure 4.3 shows the average measured impedance spectra of the four 60 μm samples. There is a clear resonance at 18.4 MHz, indicated by a peak in phase and inflection in magnitude of the measured impedance. The procedure outlined above was used to estimate the optimum piezoelectric parameters for fitting Equation 4.24 to the data from each sample. The mean and standard deviation of the parameters themselves are displayed in Table 4.1, demonstrating that there is little variation in fitted parameters between samples.

Overlaid on each plot in Figure 4.3 is the mean predicted measurement calculated by substitution of the estimated parameters into Equation 4.24. Good agreement is achieved between the calculated and measured spectra, particularly at frequencies close to resonance. With confidence in the material properties of the piezo-polymer, models may then be developed to estimate the frequency response of the PCB-PVDF composite array.

4.4 MODELLING FREQUENCY RESPONSE

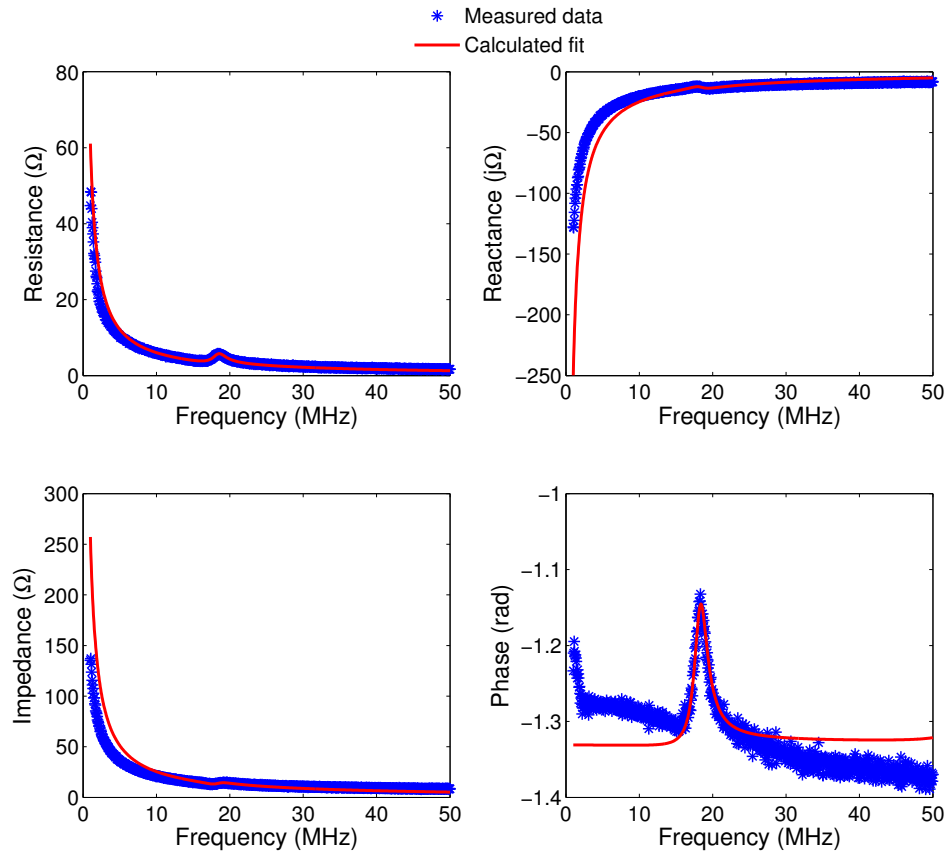


Figure 4.3: Average measured resistance, reactance, impedance magnitude and phase for the four 60 μm PVDF film samples. Data was acquired across the 1-50 MHz range at 60 kHz steps. Overlaid on each plot is the predicted measured value (displayed in red) calculated by substitution of the estimated parameters into Equation 4.24.

4.4.1 Equivalent Circuits

In addition to the matrix representation given in Equation 4.21, the response of a thin-disk piezoelectric may also be characterised by an electrically equivalent circuit, describing its performance in terms of a number of lumped parameters. Several authors have proposed such circuit designs; however, it is the configuration suggested by Krimholtz *et al.*, shown in Figure 4.4, that is most widely used and forms the basis of the work presented here (Krimholtz *et al.*, 1970).

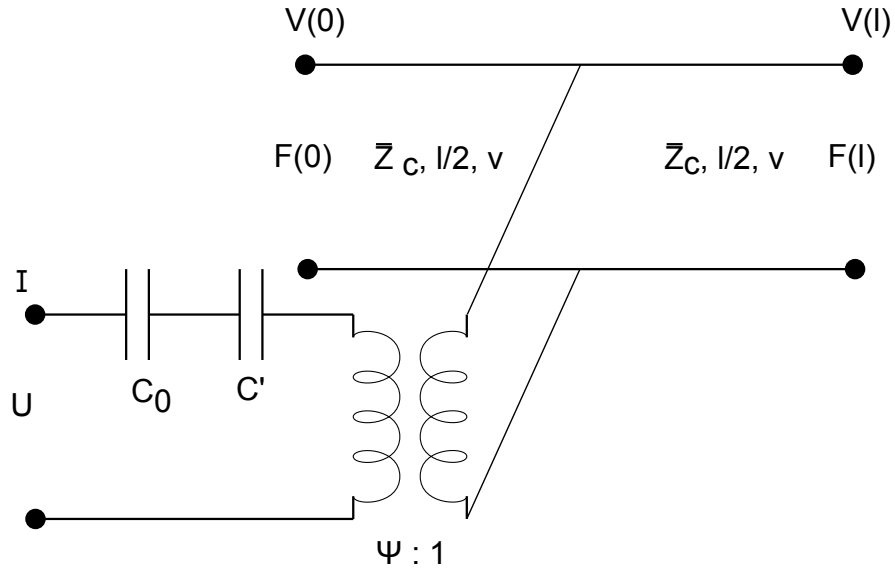


Figure 4.4: Electrical equivalent of a thin-disk piezoelectric transducer as proposed by Krimholtz *et al.* (Krimholtz et al., 1970; van Kervel and Thijssen, 1983).

By representing the piezoelectric disk as an acoustic transmission line of length equal to the thickness of the disk, l , the equivalent circuit, termed the KLM circuit, estimates the response of the piezoelectric using the following, lumped parameters:

$$\psi = k_T^* \sqrt{\frac{\pi}{\omega_0 C_0 Z_C}} \text{sinc}(\omega/2\omega_0)$$

$$C' = -\frac{C_0}{k_T^{*2} \text{sinc}(\omega/\omega_0)}$$

$$\omega_0 = \frac{\pi \nu}{l}$$

$$C_0 = \frac{\epsilon^{S*} A}{l}$$

$$Z_C = A \sqrt{\rho_m c^{D*}}$$

where ψ is the frequency-dependent turns ratio of a transformer through which connection is made to the electrical port, C' is a frequency-dependent reactance, Z_C is the characteristic impedance of the piezoelectric and all other terms are as

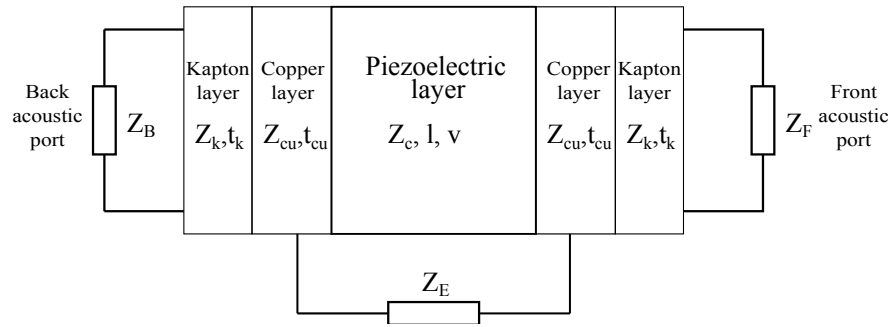


Figure 4.5: Schematic of the multiple-layer PCB-PVDF sensor. The PVDF is sandwiched between two copper conducting layers which form the electrical ports. A kapton PCB substrate covers the copper ports and the transducer radiates into a medium with acoustic impedance Z_F , backed by a medium with impedance Z_B . The piezoelectric is characterised by its impedance Z_c , thickness l , sound velocity v and the piezoelectric parameters determined in Section 4.3.1.

previously defined. It should be noted that the model is only accurate if precise material properties are known, and so it is important to follow the procedure outlined in Section 4.3 in order to provide suitable values for the above expressions.

The KLM circuit may be adapted to include multiple acoustic layers, thereby facilitating the modelling of the response of the proposed multiple-layer cavitation sensor. Figure 4.5 shows a schematic of the complete sensor. The piezoelectric material, PVDF, is sandwiched between two $35\ \mu\text{m}$ copper conducting layers which form the electrical input and output ports. Covering these layers is a $25\ \mu\text{m}$ kapton PCB substrate layer, upon which the copper tracks are printed. The left acoustic port is terminated by a back load, whilst the right a front load.

The transfer function, on both transmit and receive, of the equivalent circuit may be found using a novel extension of the calculation scheme proposed by Kervel and Thijssen to include the effect of multiple backing layers (van Kervel and Thijssen, 1983). In this manner, the response of the overall system may be calculated by considering the transducer as a number of two-port transmission line subunits, shown in Figure 4.6, in which one dimensional waves travel in both the forwards

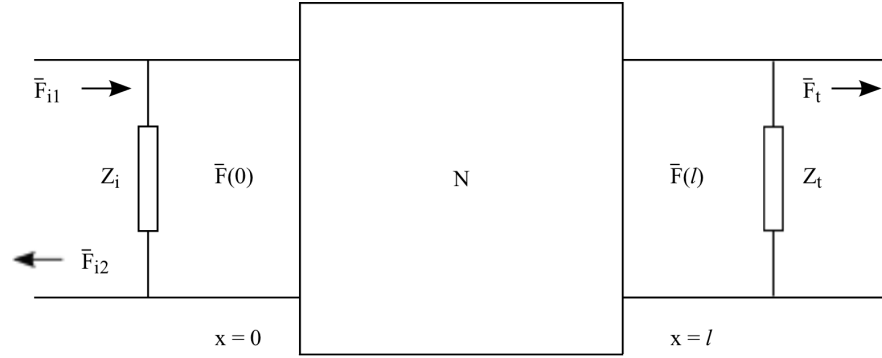


Figure 4.6: A two port scheme as proposed by Kervel and Thijssen with a central transmission line of length l . The generalised voltage $\bar{F}$, and generalised current $\bar{V}$ are both in Laplace form. F_{i1} indicates an incident wave, F_{i2} a reflected wave, and F_t a transmitted wave (van Kervel and Thijssen, 1983).

and backwards directions.

For each subunit, the input and output potential, F , and current, V , are related by the transfer function, N , where:

$$\begin{pmatrix} \bar{F}(l) \\ \bar{V}(l) \end{pmatrix} = N \begin{pmatrix} \bar{F}(0) \\ \bar{V}(0) \end{pmatrix} \quad (4.31)$$

and

$$N = \begin{pmatrix} n_{11} & n_{12} \\ n_{21} & n_{22} \end{pmatrix}. \quad (4.32)$$

The boundary conditions at the input are given by:

$$\begin{aligned} \bar{F}(0) &= \bar{F}_{i1} + \bar{F}_{i2} \\ \bar{V}(0) &= \frac{1}{Z_i}(\bar{F}_{i1} - \bar{F}_{i2}) \end{aligned} \quad (4.33)$$

whilst at the output, the terminating transmission line contains only a positive going wave, hence:

$$\begin{aligned} \bar{F}(l) &= \bar{F}_t \\ \bar{V}(l) &= \frac{1}{Z_t} \bar{F}_t. \end{aligned} \quad (4.34)$$

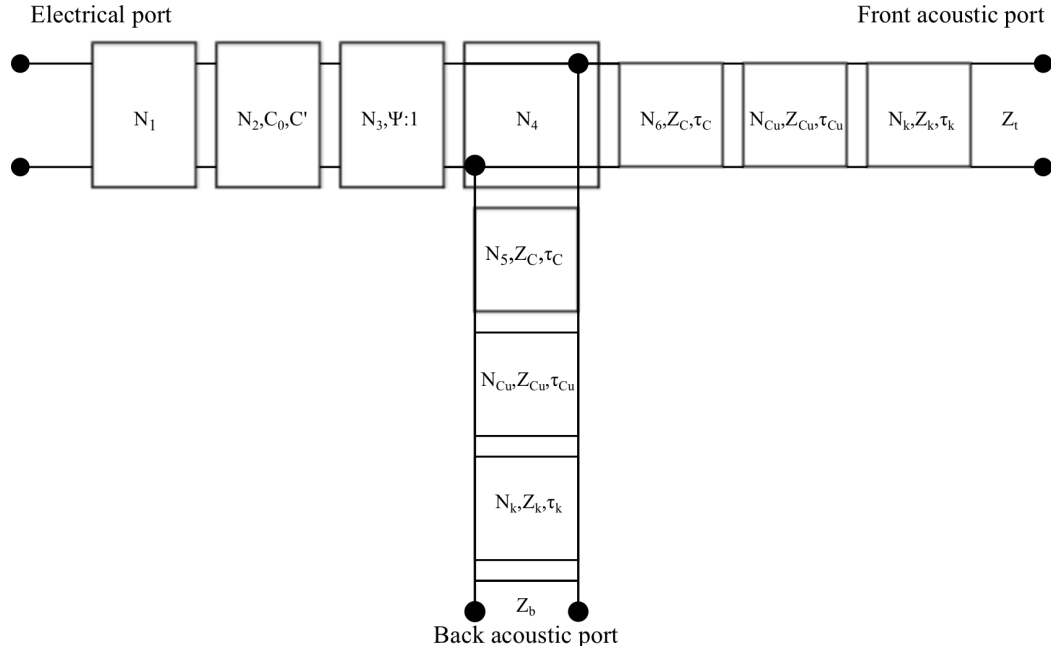


Figure 4.7: Adaptation of the transmission line scheme implementation of the KLM model as proposed by Kervel and Thijssen. Each layer of the PCB, PVDF sensor is represented by a separate subunit. The sensor is divided into three sections: and electrical part, a part representing the backing and left half of the transducer, and a part representing the right half of the transducer and front loading.

By substituting Equations 4.31 and 4.32 into the boundary conditions given in Equations 4.33 and 4.34 and noting that $|N| = 1$, the transfer function from input to output potential can be shown to be:

$$H(p) = \frac{\bar{F}_t}{\bar{F}_{i1}} = \frac{2Z_t}{-Z_i Z_t + Z_i n_{11} + Z_t n_{22} - n_{12}} \quad (4.35)$$

where $p = j\omega$, is the Laplace frequency. Successive subunits may then be combined by multiplying their individual transfer matrices.

The overall scheme splits the transducer into three sections: an electrical part, a part representing the backing and left half of the transducer, and a part representing the right half of the transducer and front loading. The components of the scheme for the transducer in question are shown in Figure 4.7.

The electrical part and back half of the transducer may be combined to give the

electro-mechanical transfer matrix, N_{em} :

$$N_{em} = \begin{pmatrix} \frac{1}{\psi} & -\frac{C_0+C'}{pC_0C'\psi} \\ \frac{1}{\psi Z_{equiv}} & \psi - \frac{C_0+C'}{pC_0C'\psi Z_{equiv}} \end{pmatrix} \quad (4.36)$$

where C_0 and C' represent the capacitive elements of the KLM circuit. Z_{equiv} is the equivalent transformed back loading presented at the centre port, which is calculated by multiplication of the left acoustic layer transfer matrices to give N_{equiv} :

$$N_{equiv} = N_5 N_{Cu} N_k \quad (4.37)$$

where

$$N_i = \begin{pmatrix} \cosh p\tau_i & -Z_i \sinh p\tau_i \\ -\frac{1}{Z_i} \sinh p\tau_i & \cosh p\tau_i \end{pmatrix} \quad (4.38)$$

and τ_i is the transition time for a wave to travel from one surface to the other within the i th layer. The backing impedance may then be transformed through the equivalent left acoustic transfer matrix to give:

$$Z_{equiv} = \frac{-Z_b N_{equiv\ 11} + N_{equiv\ 12}}{-Z_b N_{equiv\ 21} + N_{equiv\ 22}}. \quad (4.39)$$

In a similar manner, the overall front acoustic transfer function for the right half of the transducer, N_f , is given by

$$N_f = N_k N_{Cu} N_6. \quad (4.40)$$

The overall transducer transfer matrix, N_t , may then be found by multiplication of the front face transfer matrix with the electro-mechanical transfer matrix giving $N_t = N_f N_{em}$. For a front acoustic load of Z_t and electrical input impedance Z_e , the transfer function on transmission, as in Equation 4.35, is given by

$$H_t(p) = \frac{2Z_t}{Z_e N_{t11} - N_{t12} - Z_e Z_t N_{t21} + Z_t N_{t22}} \quad (4.41)$$

and the receive transfer function is given by

$$H_r(p) = \frac{2Z_e}{Z_t N_{t11} + N_{t12} + Z_e Z_t N_{t21} + Z_e N_{t22}}. \quad (4.42)$$

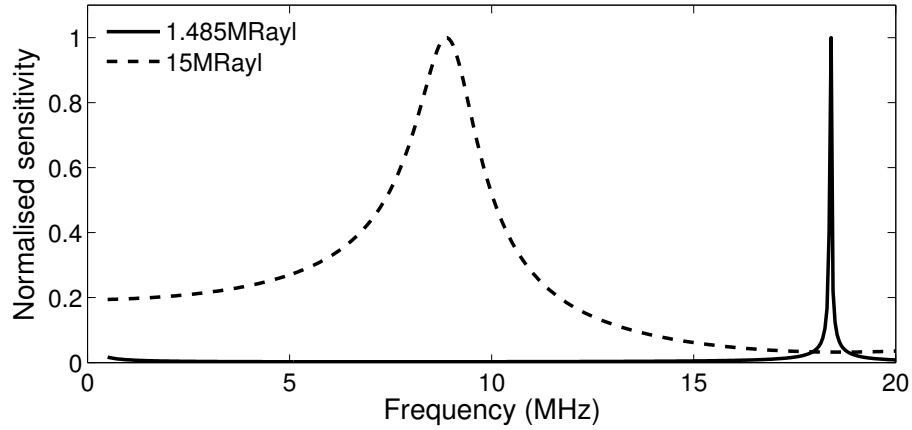


Figure 4.8: Modelled frequency spectrum on receive for a 60 μm layer of PVDF with 1.5 MRayl and 15 MRayl backing impedances and water front loading. The experimentally determined properties of the PVDF are used (see Table 4.1) and a 1 M Ω electrical input impedance is assumed.

The frequency response of the overall configuration is then determined by iterating the calculation scheme over the frequency range of interest. For a 60 μm layer of PVDF loaded with water on its front and back surfaces without the addition of the PCB front and back layers, Equation 4.42 yields a relatively sharp peak in the resulting frequency spectrum, centred at $f = 18.4$ MHz, as shown in Figure 4.8. This is consistent with a half wave resonance, where the resonant frequency may be estimated from the longitudinal wave velocity, v_L , and film thickness, l , as

$$f_0 \approx \frac{v_L}{2 \times l} = \frac{2206}{2 \times 60 \times 10^{-6}} = 18.4 \text{ MHz}. \quad (4.43)$$

Alternatively, if a heavily backed layer of 60 μm PVDF is modelled, again loaded with water on its front surface - a configuration which is closer to that of a typical ultrasound transducer - then Equation 4.42 predicts a more broad frequency spectrum, centred at $f = 8.9$ MHz. As would be expected, this is indicative of a quarter wave resonance, where the impedance mismatch results in a pressure antinode at the more rigid boundary.

If the additional copper and Kapton PCB layers are then introduced to the front

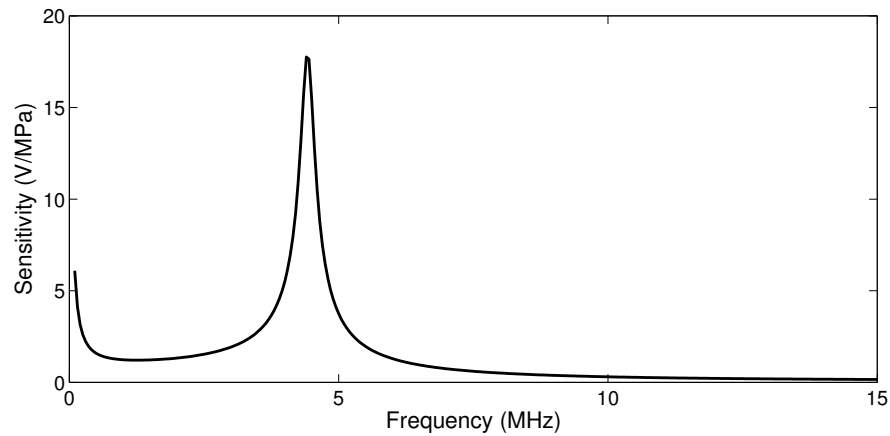


Figure 4.9: Modelled frequency spectrum on receive for a water backed 60 μm PVDF-PCB array. The experimentally determined properties of the PVDF are used (see Table 4.1) and a 1 M Ω electrical input impedance is assumed.

and back face of the PVDF and the backing medium replaced with water, the model predicts a receive frequency spectrum with a narrower bandwidth and a centre frequency that is significantly shifted from that predicted for a single PVDF layer to $f = 4.45$ MHz. Figure 4.9 illustrates the resulting modelled response for a 1 mm radius element, using the measured piezoelectric properties and published values for the mechanical properties of the water, PVDF, copper and Kapton layers all of which are summarised in Table 4.2.

By adjusting the piezoelectric properties used in the model, it is also possible to observe the effect of piezoelectric loss. Figure 4.10 shows the resulting modelled response of the PCB-PVDF composite, both with and without the use of lossy piezoelectric parameters. If the loss tangent components of the measured piezoelectric parameters given in Table 4.1 are omitted, the resulting modelled response shows a much sharper resonance, centred at a frequency of 4.45 MHz. Including the appropriate loss tangents results in a much broader response, with a significantly damped resonant peak that has an amplitude of around 7% of its non-lossy counterpart. Away from the resonance, the modelled effect of piezoelectric loss is less significant

Table 4.2: Summary of material properties used for analytical and FEA sensor simulations

Material	Density ρ (kg/m ²)	Longitudinal velocity v_L (m/s)	Shear velocity v_S (m/s)	Acoustic impedance Z (MRayl)	Thickness l (μ m)
Copper ^a	8930	5010	2270	44.74	35
Kapton ^a	1420	2420	1191	3.44	25
PVDF ^b	1780	2206	-	3.92 [*]	60
Water ^c	1000	1485	-	1.485	-

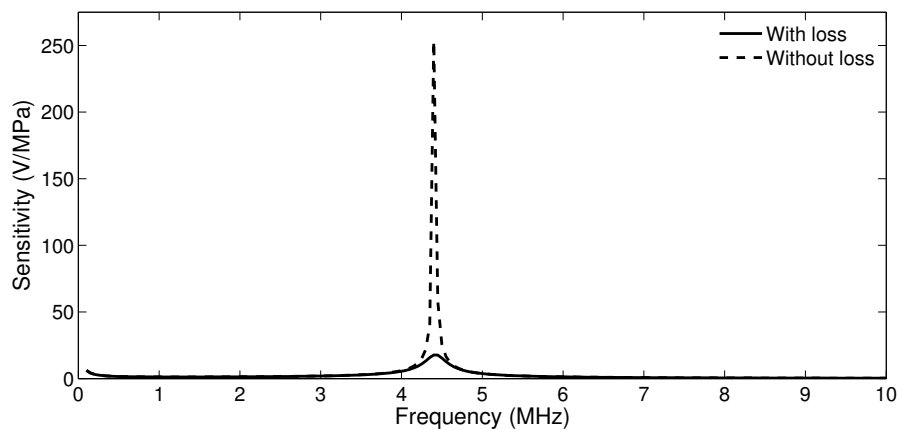
^a (Kino, 1987)^b (Hayward et al., 2000)^c (Kaye and Laby, 1995)^{*} Calculated from measured piezoelectric parameters

Figure 4.10: Effect of piezoelectric loss on the modelled frequency response of the PCB-PVDF composite. Including the appropriate loss tangents results in a much broader response, with a significantly damped resonant peak that has an amplitude of around 7% of its non-lossy counterpart.

with both lossy and non-lossy spectra exhibiting similar magnitudes.

4.4.2 Finite Element Analysis

The electro-mechanical behaviour of a piezoelectric transducer may also be modelled by finite element analysis (FEA). By breaking down the multiple layers of the

sensor configuration into a mesh of two-dimensional elements, approximations of the mechanical stress and strain, and resulting electrical potential and charge may be formed throughout the simulation space. To achieve this, the constitutive equations of Section 4.2 are evaluated at each element node, accounting for the applied boundary and loading conditions throughout the temporal domain.

There are a number of commercially available finite element software packages that may be used to model the frequency response of piezoelectric materials. For the purposes of this study, a time domain, explicit code was written in PZFlex®, a package for modelling multiple-layer piezoelectric materials (Goldberg et al., 1997). The sensor was modelled as a 1 mm radius, axisymmetric composite of 25 μm Kapton polyimide substrate, 35 μm copper, and 60 μm PVDF, with the composite placed in a volume of water. Material properties were identical to those used for the analytic model, though additional parameters (included in Table 4.2) were introduced to account for the two-dimensional response of the composite. Importantly, the FEA software package does not support the use of complex piezoelectric parameters to account for losses and so the real part of the measured parameters was used instead.

A 5 cycle, 1 MPa sinusoidal pressure load was applied propagating normal to the sensor at a distance 3 mm from the front face of the outer Kapton layer as indicated in Figure 4.11. Along the direction of wave propagation the number of mesh elements was dynamically adjusted to ensure that there was always more than 32 elements per wavelength, which was found to produce sufficiently stable results. This did, however, lead to relatively long processing times, particularly at higher frequencies, such that simulation across the entire frequency range took two hours to complete. The receive sensitivity across the 0.1-15 MHz range was simulated at 0.1 MHz intervals, resulting in the frequency response illustrated in Figure 4.12.

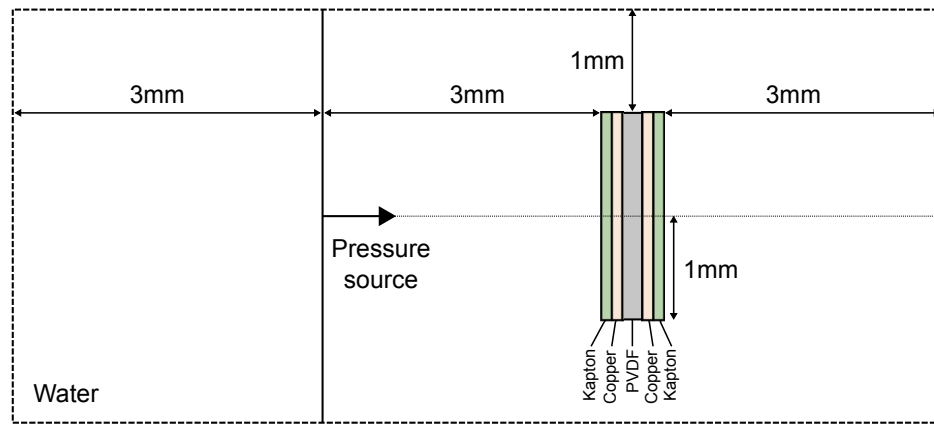


Figure 4.11: Schematic of the finite element simulation of the receive frequency response of the array. A 1 MPa plane pressure load is applied a distance 3mm from the front face of the composite sensor consisting of 25 μm Kapton, 35 μm copper, and 60 μm PVDF layers. The resulting electrical potential is then determined across the 0.1-15 MHz range at 0.1 MHz intervals.

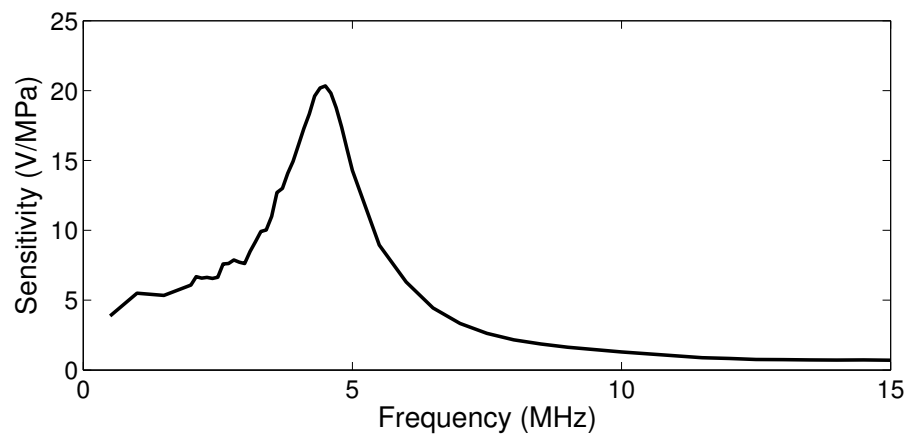


Figure 4.12: Modelled frequency response of the 60 μm PVDF-PCB array resulting from a two-dimensional FEA. In a similar manner to the analytic model, a peak in sensitivity is observed at $f=4.5$ MHz, though the FEA predicts a more broad response and higher absolute sensitivity.

Notably, the FEA model predicts a peak in sensitivity at 4.5 MHz, within 1.2% of the value predicted by the equivalent circuit model. Given that the FEA model does not account for piezoelectric losses, it is not surprising that the magnitude of the predicted response is consistently above that estimated by the analytic model. Interestingly, however, the FEA model predicts a broader resonant peak, with a higher magnitude low-frequency response, which could be introduced by the fact that the two-dimensional FEA model is not confined to the thickness-mode oscillations assumed by the equivalent circuit model. Both the FEA and equivalent circuit models show a drop in sensitivity beyond 7 MHz, limiting the range of detectable frequency components. Comparing predictions to experimental results gives a useful indication of the accuracy of the models presented thus far.

4.5 MEASURED RESPONSE

Simulation of the frequency-dependent sensitivity of a given multiple-layer piezoelectric sensor configuration provides a useful aid for array design. It is important, however, that computational results are experimentally validated. To this end, a prototype array, constructed using the proposed method, was insonated across the frequency range of interest and results were compared with those from a 0.5 mm reference needle hydrophone (Precision Acoustics HPM05) to determine absolute sensitivities.

The experimental setup, shown schematically in Figure 4.13, utilised a number of unfocussed ultrasound sources that were swept across their available frequency range and directed at an axially aligned, 1mm radius receiving element, rigidly clamped around the circumference of the rectangular composite sheet. Table 4.3 summarises the driving conditions for each of the unfocussed sources.

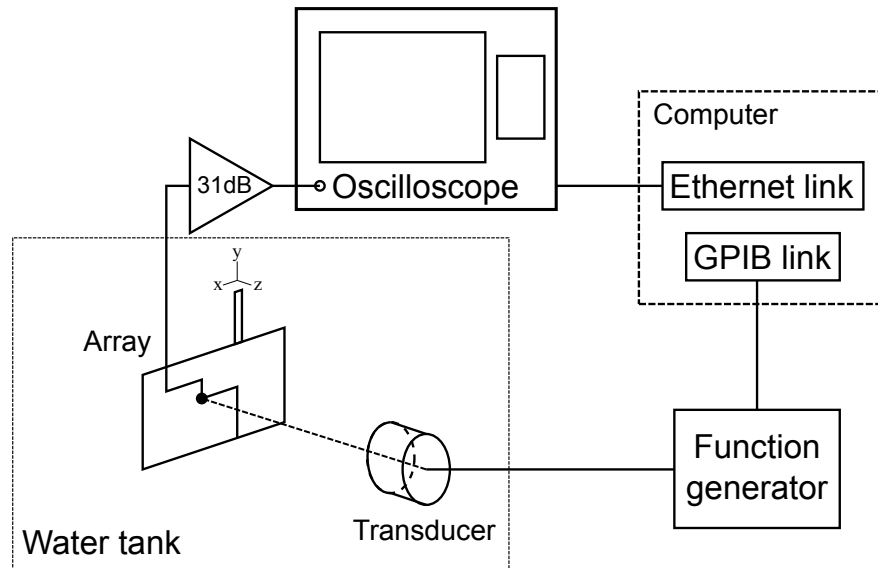


Figure 4.13: Schematic of the experimental setup for validation of frequency response simulations. Each source transducer was driven across the frequency range indicated in Table 4.3 and the resulting waveform detected by a receiving element aligned at the transverse focus.

Table 4.3: Summary of unfocussed transducer driving conditions

Make/ Model	Resonant Frequency (MHz)	Frequency Range (MHz)	Step Size (MHz)
Precision Acoustics	1.0	1.0 - 1.9	0.1
Panametrics V306	2.25	0.95 - 4.55	0.1
Panametrics V320	7.5	3.5 - 11.5	0.25
Panametrics A313S	15	5.0 - 20.0	0.5

A remotely controlled function generator was used to create a $10 V_{pk-pk}$, $20 \mu s$ sinusoidal burst input voltage to drive each of the aforementioned transducers. For each insonation, the receiving element was acoustically aligned at the transverse focus of the source transducer and positioned at a time delay of $160 \mu s$ using a computer controlled three-dimensional positioning system. The driving frequency of each transducer was swept across the range indicated in Table 4.3. At each frequency step, the received signal was acquired on an oscilloscope and transferred to a controlling computer via ethernet link. Each saved waveform was sampled at

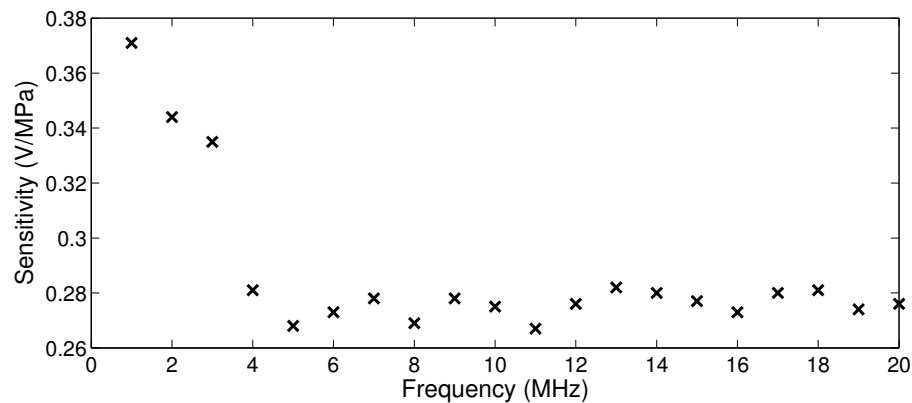


Figure 4.14: Manufacturer's calibration of reference, 0.5 mm active area, needle hydrophone. Values obtained here were used to calculate the absolute sensitivity of the sample element across the 0-20 MHz range.

100MS/s and averaged over 32 acquisitions.

Figure 4.14 shows the manufacturer's sensitivity calibration of the 0.5 mm reference needle hydrophone. Having acquired data across the 1-20 MHz frequency range using the reference hydrophone, values were scaled to provide absolute peak-to-peak pressure magnitudes at each frequency step, yielding the profile shown in Figure 4.15.

To determine the absolute sensitivity of the sample multiple-layer element, the reference pressure values were used to scale the received signal across the 1-20 MHz range. Figure 4.16 shows the resulting peak-to-peak received signal, recorded with the sample element connected to the oscilloscope via a custom made high input impedance, 31 dB broadband pre-amplifier (see Section 5.5 for more details). Values were scaled to account for the pre-amplification and the corresponding sensitivity of the sample element was then determined using the reference pressure values. There is a clear peak in sensitivity of the measured response at 4 MHz, with a relatively sharp decrease beyond this point. Comparison of the measured behaviour with modelled results allows the validity of the modelling techniques to be exam-

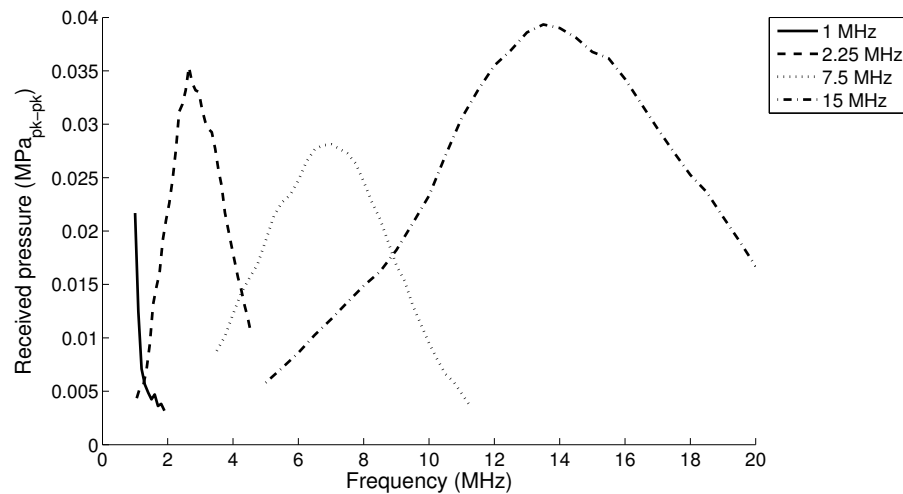


Figure 4.15: Reference peak-to-peak pressure values used to determine the absolute frequency-dependent sensitivity of the sample element. Values are determined using the manufacturer's frequency-dependent sensitivity calibration shown in Figure 4.14. The legend indicates the resonant frequency of the insonating transducer.

ined, providing a useful tool for the design of the proposed array.

4.6 COMPARISON OF RESULTS

Figure 4.17 compares the measured and predicted frequency response of the PCB-PVDF array. Both the equivalent circuit model and the finite element simulation predict a peak in response at a frequency within 12% of that which is experimentally observed. Discrepancies in the predicted and observed location of this peak are likely due to additional damping experienced in each layer as well as marginal differences in the mechanical properties of the copper, Kapton and PVDF layers from the published values that were used. Furthermore, when measuring the frequency response experimentally, the rectangular PCB-PVDF composite was clamped remote from the edges of the element itself, a configuration which may introduce alternative modes of oscillation. Both models do, however, provide a useful estimate

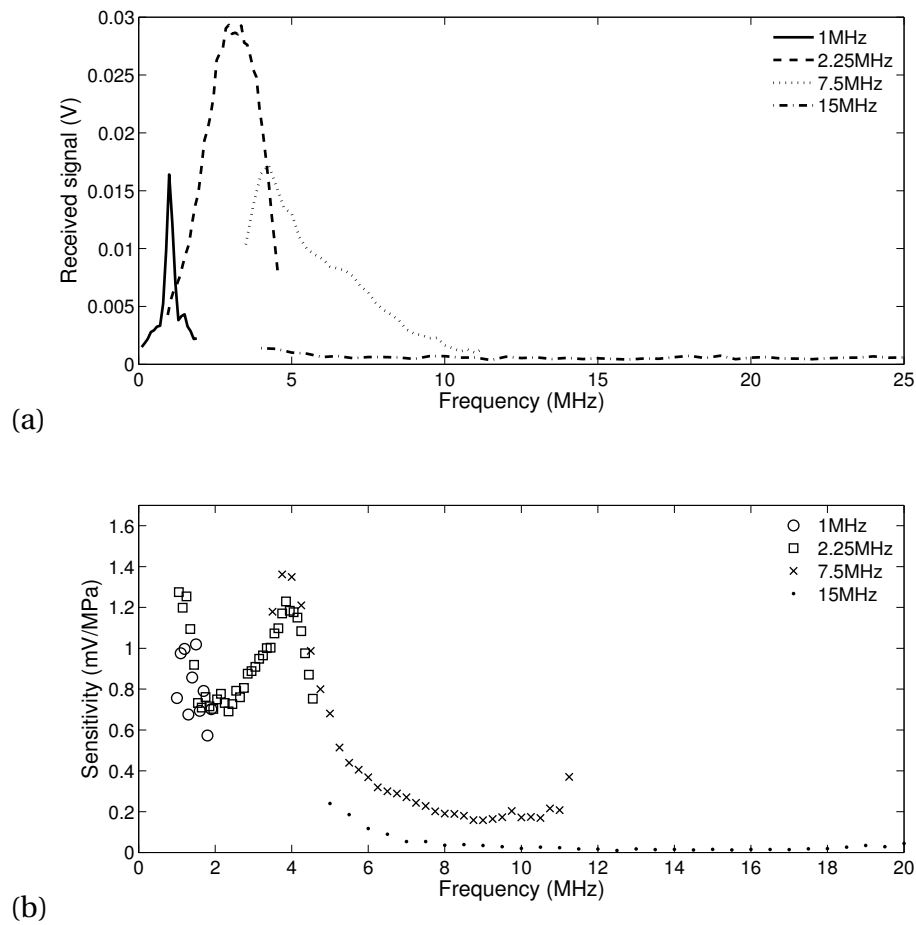


Figure 4.16: Received signal amplitude (a) and corresponding sensitivity (b) of the sample multiple-layer PCB-PVDF element across the 1-15 MHz range. There is a peak in sensitivity at 4 MHz, with a relatively sharp decrease beyond this point, indicating that the element is most sensitive to signals in the 1-7 MHz range.

of the location of the peak in sensitivity of the PCB-PVDF array, which differs significantly from the predicted response of a single PVDF layer. It is important, therefore, that due care is taken to account for the effect of additional acoustic layers when considering the design of PCB-based PVDF sensors.

Both the FEA and equivalent circuit models predict a significantly higher magnitude of response than is experimentally observed. The FEA model has the advantage of extending the simulation to a second dimension, and so is not confined to

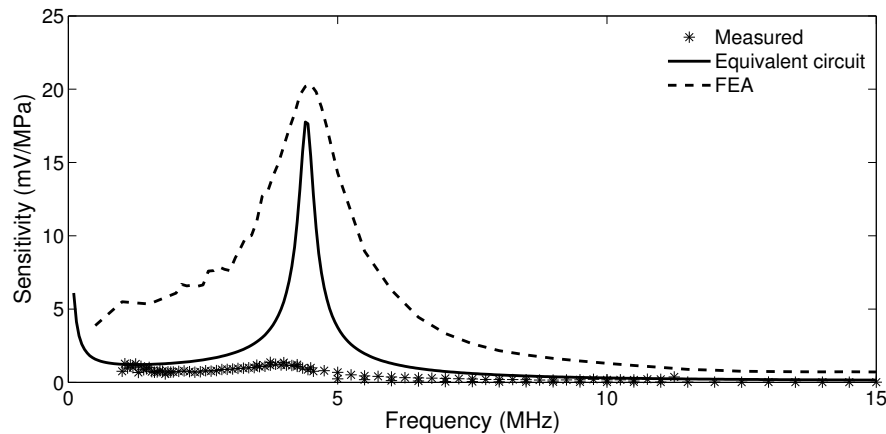


Figure 4.17: Comparison of measured and predicted frequency response of the PVDF-PCB array. Both the equivalent circuit and FEA models predict the location of the peak in frequency response within 12%; however, the magnitude of the response is overestimated in both cases.

the thickness mode oscillations modelled by the equivalent circuit. This could explain the slightly broader response predicted by the FEA model, which more closely resembles the measured spectrum. The FEA software package that was used does not, however, offer the ability to easily include lossy piezoelectric parameters, which are included in the equivalent circuit model. Inclusion of the loss terms has been shown to significantly reduce the magnitude of the resonant peak (see Figure 4.10), and so it is not surprising that the equivalent circuit model offers a better estimate of the absolute sensitivity of the array. Furthermore, the one-dimensional equivalent circuit model is considerably less computationally expensive than its two-dimensional, finite element counterpart, with run-times in the order of 2 seconds rather than 2 hours. As a result, the equivalent circuit model was chosen to inform the design of the proposed array.

Whilst the equivalent circuit model has been shown to provide a useful prediction of the peak in sensitivity of the PCB-PVDF composite, it clearly overestimates the absolute sensitivity of the array and predicts a more narrow response than is ex-

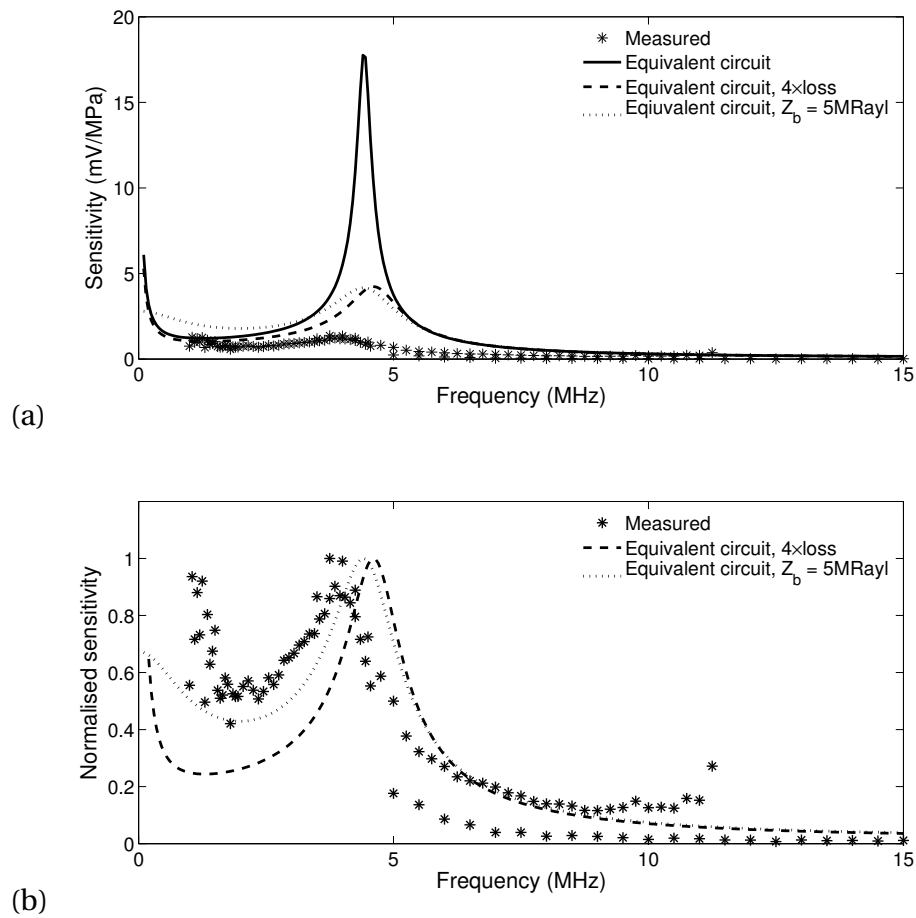


Figure 4.18: Comparison of equivalent circuit model with measured response using a range of input parameters. Both absolute (a) and normalised (b) sensitivities are shown. A more accurate fit to the measured response can be obtained if the level of piezoelectric loss is significantly increased, or a higher, physically unrealistic backing impedance is introduced.

perimentally observed. A closer match to the measured response can be obtained if the magnitude of either the piezoelectric loss tangent or the backing impedance is increased, as shown in Figure 4.18.

Though the modification of these parameters results in a broader response with higher low frequency sensitivity, closer to that which is experimentally measured, the model still over predicts the absolute sensitivity. Possible explanations for this include mechanical losses in the copper and polyimide layers, which are not in-

cluded in the equivalent circuit model, or variations in the thickness of the individual layers introduced during the manufacturing process. Furthermore, the models do not account for the bonding layers used during construction, which were assumed to be sufficiently small to neglect though their exact configuration was not known. Future work will look to develop an understanding of the reason for the improved fit following the introduction of what appear to be physically unrealistic input values for the backing impedance and piezoelectric loss. Here, however, a higher backing impedance is considered (5 MRayl), along with the original water backed model, to provide an estimate of the shape of the array response for a range of PVDF film thicknesses.

In designing the three-dimensional cavitation sensor using the proposed PCB-PVDF construction method, three PVDF film thicknesses were available, namely 25 μm , 60 μm and 110 μm . The equivalent circuit model offers the ability to investigate the effect of each of these film thicknesses. Though the model may not provide an accurate measure of the absolute sensitivity of the array, it does provide a useful indication of the shape of its frequency response. Figure 4.19 displays the receive frequency spectrum for each film thickness used within the PCB-PVDF composite. As would be expected, increasing the thickness of the PVDF layer results in a decrease in the frequency at which peak sensitivity is observed. Furthermore, the sensitivity is generally observed to increase with film thickness.

Given that the majority of clinical HIFU transducers operate in the 0.8-1 MHz range, broadband emissions resulting from HIFU induced inertial cavitation can be expected to be detectable between 2 MHz and 8 MHz, beyond which attenuation is likely to have a significant effect on the signal content. With this in mind, a 60 μm PVDF film thickness was chosen for the multiple-layer PCB-PVDF array, providing sufficiently high absolute sensitivity and a peak in response close to the centre of

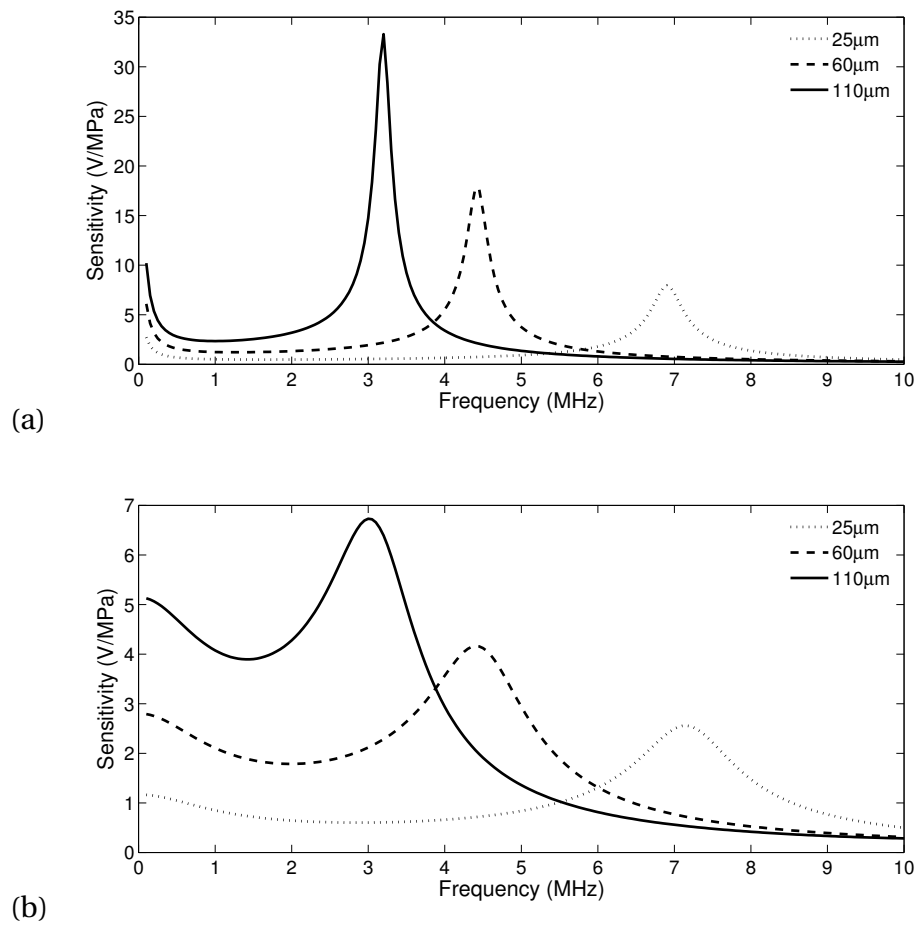


Figure 4.19: Variation in modelled frequency response with PVDF thickness using both the original model (a) and the 5 MRayl backing impedance model (b). Three available thicknesses of PVDF are considered, 25 μm , 60 μm and 110 μm , of which 60 μm provides the best compromise between sensitivity and bandwidth.

the expected cavitation signal spectrum.

4.7 SUMMARY

In this chapter, a novel ultrasonic array construction method was proposed to facilitate precise placement of array elements whilst avoiding sensitivity to stray signals along the electrode path. By sandwiching a central PVDF sheet between two PCB

layers the technique ensures active area is formed only where the copper tracks on the front and back layers overlap. Importantly, however, care must be taken to account for the effect of these additional acoustic layers on the frequency response of the composite array.

To achieve this, it is important to first consider the basic principles of the piezoelectric effect. Characterised by the onset of electrical polarisation when a material is subject to a mechanical stress, this phenomenon can be described by a number of constitutive equations. By considering the appropriate boundary conditions for a thin-disk resonator, these expressions may be developed into an equation for the electrical input impedance of a sample of piezoelectric material, which may, in turn, be measured experimentally. Fitting the various parameters of the impedance expression to experimental results then gives an estimate of the relevant piezoelectric material properties of the sample. Four samples of 60 μm PVDF, a piezo-polymer known to be particularly lossy, were characterised in this manner using a combination of non-linear least squares fitting and manual fine-tuning. The resulting piezoelectric properties gave a predicted impedance that was well matched to the measured response, particularly around resonance, providing accurate parameters for the models developed in subsequent sections.

The equivalent circuit models originally proposed by Krimholtz *et al.*, allow the one dimensional response of a thin-disk piezoelectric to be characterised by an electrically equivalent circuit, described in terms of a number of lumped parameters. To model the effect of the additional layers of the PCB-PVDF array on receive sensitivity a calculation scheme proposed by van Kervel and Thijssen was extended to include multiple acoustic layers on the front and back faces of the central piezo-polymer. The resulting modelled response differed significantly from that which is predicted for a single PVDF layer, shifting the resonant peak to a much lower fre-

quency of 4.45 MHz, and broadening the response. Comparison of the equivalent circuit model with a finite element solution, developed using a time domain, explicit code written in PZFlex®, confirmed this shift in peak sensitivity, providing an estimate of its location which differed by just 1.2%.

Both the equivalent circuit and FEA models have been shown to predict the location of the peak in sensitivity of the composite array to within 12% of the experimentally measured response. Given that this differs significantly from the response of a single PVDF layer, it is important that care is taken to account for the additional PCB layers during the design phase. The methods developed here provide a useful means for estimating the effect of these layers, with the less computationally expensive, one-dimensional equivalent circuit model offering the ability to easily account for piezoelectric loss. This provides a valuable tool for the design of similar multiple-layer arrays, several of which are currently under development for a variety of applications including real-time treatment monitoring of HIFU ablation, and ultrasound-induced, localised release of cytotoxic drugs.

Whilst the peak in response of the PCD-PVDF array is accurately predicted by both models, absolute sensitivities are, however, overestimated, likely due to the fact that they do not account for mechanical damping in each of the composite layers, nor do they account any differences in thicknesses of layers introduced during manufacture. A closer match to experimental results may be obtained by introducing either a larger backing impedance or higher magnitude piezoelectric loss tangent to the equivalent circuit model, though developing a physical explanation for this remains the subject of future work.

To inform the design of the proposed three-dimensional cavitation sensor, the equivalent circuit model was modified to predict the frequency response of the PCB-PVDF composite for a range of PVDF film thicknesses. The results indicate that a 60

μm film will provide a peak in sensitivity closest to the centre of the expected cavitation signal spectrum, with sufficient sensitivity to capture emissions across the 1-7 MHz range. With an appropriate manufacturing technique and PVDF film thickness identified, the following chapter considers the design of the three-dimensional cavitation sensor in more detail. Particular attention is paid to optimisation of the size, number and configuration of elements required to reconstruct an ellipsoidal cavitation region. The optimised design is then evaluated experimentally providing a strong foundation for future studies into three-dimensional cavitation-based HIFU QA.



PROTOTYPE SENSOR DESIGN AND TESTING

This chapter outlines the design and simulation of a three-dimensional cavitation sensor intended for the QA of a range of clinical HIFU devices. An Initial prototype design is discussed along with computational simulations of its performance, which are further complemented by experimental results. The optimisation of a second-generation design is then considered, once again supported by experimental results. Experimental validation of the second-generation design ensues, offering useful insight into the design of arrays with similar construction and providing a strong foundation for future work into cavitation-based HIFU QA.

The present work has shown that cavitation mapping correlates well with HIFU insonation amplitude in the elevation, axial and transverse focal planes of the therapeutic device. However, in order to completely characterise the HIFU field and, in particular, identify any inconsistencies in the acoustic pressure profile, three-dimensional reconstruction is required.

To achieve this, a cylindrical array enclosing the HIFU focal volume is proposed, manufactured using the novel multiple-layer PCB-PVDF construction method introduced in Chapter 4. This chapter delves further into the design of said array. Ini-



Figure 5.1: The National Physical Laboratory Cavitation Sensor (NPLCS). The prototype, three-dimensional cavitation sensor was based upon an extension of this design, incorporating multiple elements to achieve three-dimensional mapping of the cavitating field.

tially, the performance of a pre-existing, multi-element cavitation sensor supplied by NPL is investigated both computationally and experimentally as a simplified, inexpensive precursor to the eventual array design. Subsequent optimisation of the element size, number and geometric configuration for localisation of a discontinuous distribution of broadband sources yields a second-generation array, with supporting electronics and data acquisition hardware, designed and implemented specifically to enable array operation.

5.1 PROTOTYPE DESIGN

A prototype, multi-element cavitation sensor was initially developed as an extension of the technology employed for the cylindrical, single-element NPLCS shown in Figure 5.1. The prototype array consists of ten individual, piezoelectric elements

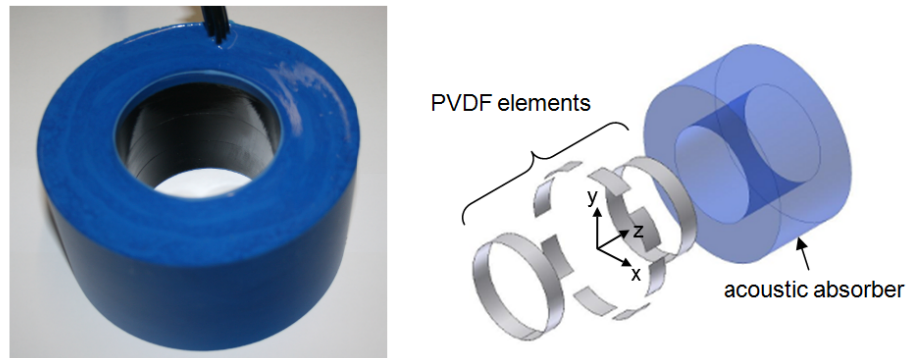


Figure 5.2: Diagram of the prototype, multi-element cavitation sensor. The central ring is divided into eight 45° elements facilitating radial mapping, whilst the outer complete rings facilitate axial mapping.

constructed from $110\ \mu\text{m}$ -thick, silver-inked, PVDF film with nylon bolted electrodes. Elements are arranged in a cylindrical configuration to enclose the ellipsoidal cavitation region generated during HIFU exposure and to capture as much energy of the emitted broadband signal as possible. The physical dimensions of the device are dictated by the range of HIFU transducers intended to be tested and the resulting lesion size from the largest of these devices. To be compatible with existing clinical HIFU transducers, that is to allow focusing at the centre of the sensor, the cylinder diameter and length were fixed at 75 mm and 45 mm respectively. In order to provide sensitivity in the pre-focal, focal and post-focal regions, the sensor is divided into three equal width (15 mm) rings. The central ring is divided into eight equally-sized (45°) elements to facilitate radial mapping in the central transverse plane, whilst the outer rings each consist of a single PVDF strip spanning the circumference of the cylinder (see Figure 5.2), designed to facilitate axial mapping.

For the prototype design, large, individual-element apertures were chosen to conform to the criteria mentioned above. This does, however, lead to a reduction in imaging capability as explained further in Sections 5.1.1 and 5.1.2. The receiving elements are coated in a relatively thick (30mm) layer of acoustic absorbing material

(rho-c polymer) for their protection and support, and to allow adequate space for cable routing such that all cables may exit the device at a single point.

To assess the performance of the prototype device and identify any potential improvements, simulations were conducted and supported by experimental results.

5.1.1 Acoustic Reciprocity

The principle of acoustic reciprocity states that an acoustic response remains the same when the source and receiver are interchanged. In other words, the pressure $p(t)$, received at a position $\mathbf{r}_1$, resulting from an ideal point source $s(t)$, located at $\mathbf{r}_2$, is the same as the pressure received at $\mathbf{r}_2$ when the source is located at $\mathbf{r}_1$. Mathematically, this is illustrated by the symmetry in the Green's Function for the inhomogeneous wave equation:

$$g(\mathbf{r}_1, t_1 | \mathbf{r}_2, t_2) = \frac{1}{\mathbf{r}_1 - \mathbf{r}_2} \delta(|\mathbf{r}_1 - \mathbf{r}_2|/c - (t_1 - t_2)), \quad (5.1)$$

where:

$$s(\mathbf{r}) = \int g(\mathbf{r}, t) p(t) dt. \quad (5.2)$$

As a result, the field produced by a transducer of a given geometry is indicative of the spatial sensitivity of an identically-shaped receiver, where spatial sensitivity refers to the ability of the device to detect a signal emitted from a given location. To examine the spatial sensitivity of the prototype device, therefore, one can model the field produced by an identically-shaped transducer. To achieve this, the transducer is considered as an array of point sources whose summed response is equivalent to that of the complete device. Using a velocity potential approach, as described by O'Neil, the pressure distribution can be calculated as follows (Rayleigh, 1873; O'Neil, 1949). The value of the velocity potential, ψ , at a point $[r, \theta, z]$ due to a cylindrical

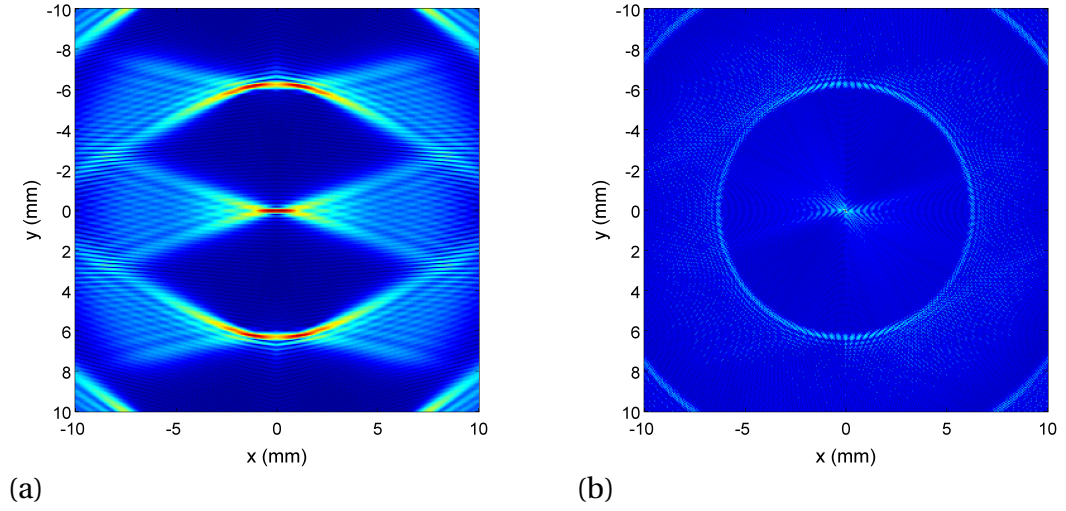


Figure 5.3: Simulated sensitivities of individual (left) and combined (right) 45° elements in a plane transverse to the cylindrical axis. Large, 45° elements are highly sensitive on-axis, resulting in accurate localisation, but cannot accurately localise sources off-axis.

transducer of aperture θ_t , length z_t and radius R_t , can be approximated by:

$$\psi(r, \theta, z) = \int_0^{\theta_t} \int_0^{z_t} \frac{u}{2\pi} s^{-1} e^{-jks} R_t d\theta dz, \quad (5.3)$$

where $k = \omega/c = 2\pi/\lambda$, λ is the wavelength, u is the source velocity, and s is the distance from the source point on the transducer element to the field point at which ψ is to be evaluated. The resulting pressure can then be calculated as:

$$p(r, \theta, z) = \rho \frac{\partial \psi}{\partial t} = j\omega \rho \psi = i k c \rho \psi. \quad (5.4)$$

Using the above method, the spatial sensitivity of the central elements of the prototype design for radial mapping can be assessed. Figure 5.3 shows the simulated spatial sensitivity of both an individual 45° element (spanning a 45° arc of the cylindrical sensor), and the summed response of the eight central 45° elements in a plane transverse to the cylindrical axis.

Clearly, the summed response of the eight central elements is extremely high

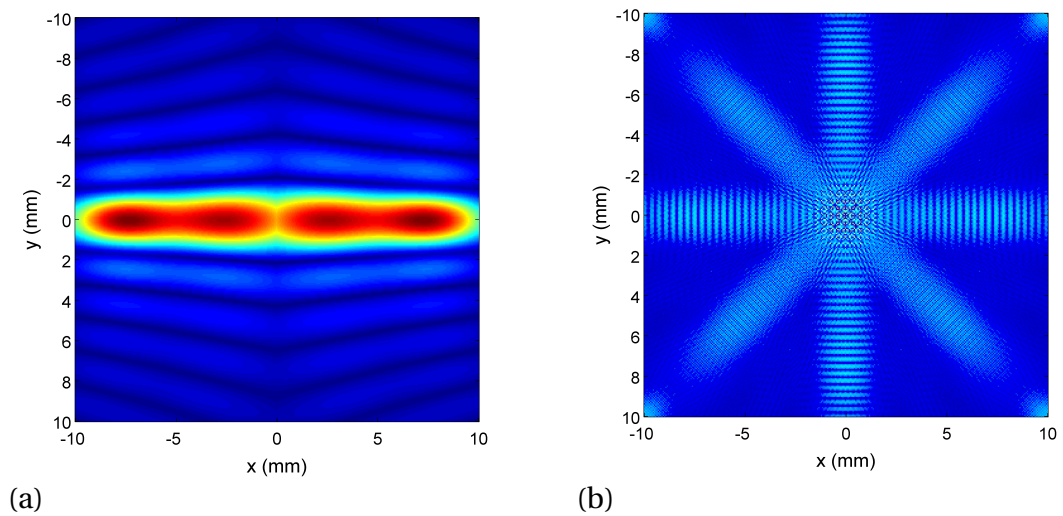


Figure 5.4: Simulated sensitivities of individual (left) and combined (right) 4° elements in a plane transverse to the cylindrical axis of a hypothetical array. Smaller, 4° elements are less tightly focused and so can localise sources much further off axis.

along the cylindrical axis; however, such large aperture elements are highly focused and so exhibit relatively low sensitivity away from this axis. This results in accurate localisation of on-axis sources but poor localisation of any sources that lie off-axis. Given that a typical HIFU lesion cross-sectional diameter is greater than 2 mm and that alignment errors must be accommodated, it is important that the sensor is able to localise sources up to ~5 mm off-axis. Smaller element sizes are less tightly focused and so peak sensitivity is spread over a larger region, as shown in Figure 5.4. It appears, therefore, that smaller elements are required for accurate localisation off-axis. This conclusion is supported by further computational and experimental results, presented in subsequent sections.

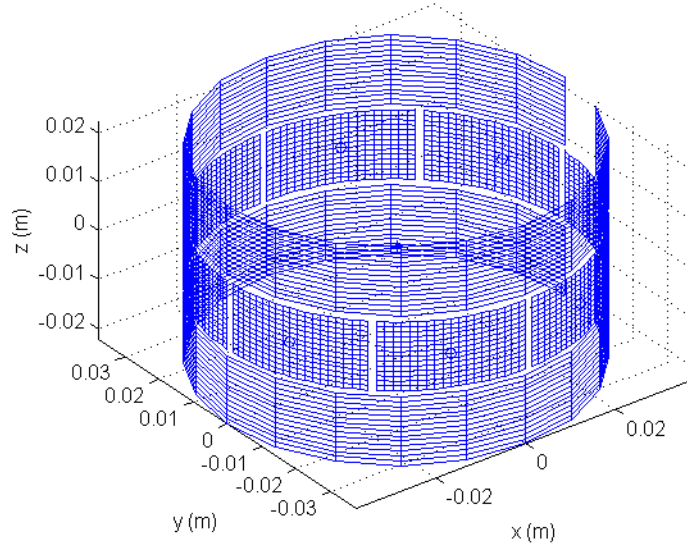


Figure 5.5: Typical mesh used to model the received signal across each element of the prototype design. The source signal is spherically propagated and attenuation is applied, prior to integration over each element area.

5.1.2 Initial Simulations

In order to evaluate the performance of a given sensor geometry for a source at a given location, a model was developed to predict the signals received on each element of the sensor for a source in a particular location. The model takes an ideal point source signal $s(t)$, applies attenuation (based on a centre frequency of 7.5 MHz) and spherical propagation, and integrates the resulting signal over a number of sub-elements across the receiving surface as described by Equation 5.5.

$$p_i(t) = \frac{1}{A_i} \sum_{n=0}^N \frac{1}{4\pi|\mathbf{r}_n - \mathbf{r}_s|} s(|\mathbf{r}_n - \mathbf{r}_s|/c) e^{-\alpha|\mathbf{r}_n - \mathbf{r}_s|} R d\theta dz, \quad (5.5)$$

where $p_i(t)$ is the pressure received over the i^{th} sensor element, A_i is the total area of the i^{th} sensor element, $\mathbf{r}_n$ is the location of the n^{th} sub-element (area $R d\theta dz$), and α is the attenuation coefficient of the medium through which the wave propagates. Figure 5.5 shows a typical mesh used to compute the modelled received signal

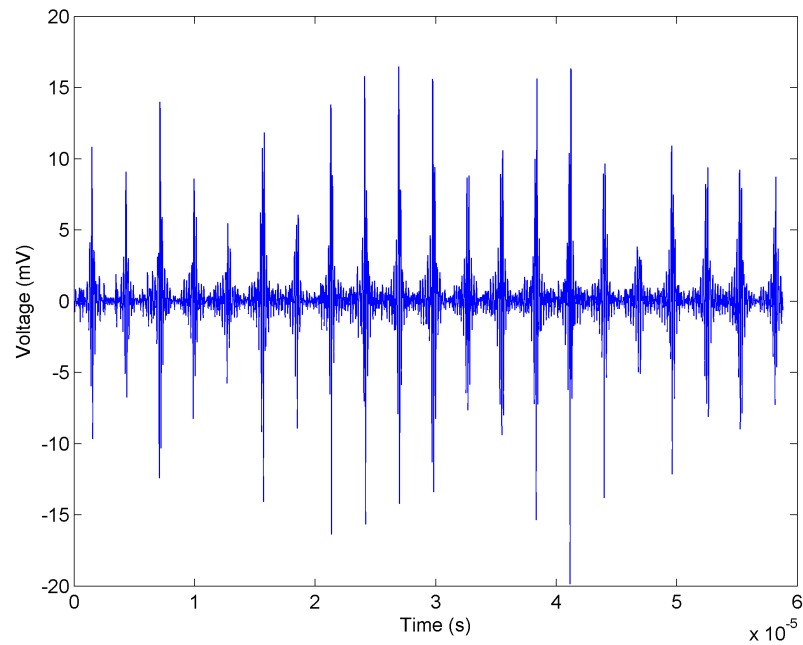


Figure 5.6: Source signal used for modelling received signals across each element of the sensor. A periodic train of acoustic emissions resulting from an oscillating bubble was recorded using a confocally aligned HIFU transducer and PCD arrangement (Gyongy et al., 2008).

across each element of the prototype design.

The source signal used for simulations (shown in Figure 5.6) is an experimentally-gathered, single-bubble emission recorded using a confocally aligned PCD and HIFU transducer arrangement. The modelled recorded signals at each of the sensor elements may then be used to reconstruct the location of the source using the TEA algorithm, as described in Section 2.6. For the initial studies, data from the central ring alone is used to consider two-dimensional mapping in the central transverse plane.

Figure 5.7 shows typical images generated following reconstruction of the modelled received signals over the eight 45° elements of the central ring, for both an on-axis (Figure 5.7(a)) and off-axis source (Figure 5.7(b)) co-ordinates $[1\ 1\ 0]$ mm or

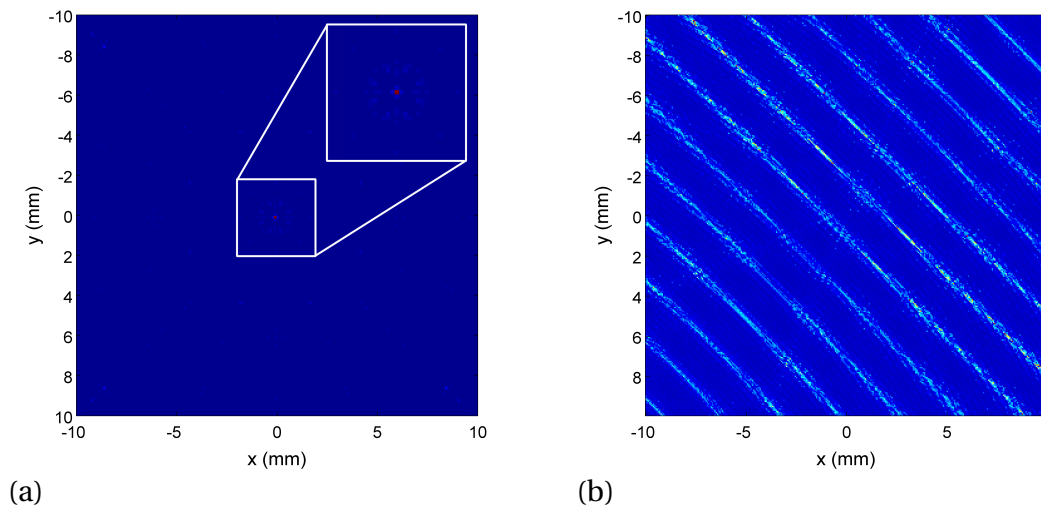


Figure 5.7: Reconstructed source locations using modelled received signals and a single point at the centre of each receiving element for the reconstruction. For an on-axis source (left), accurate localisation is achieved and a small maximum (red) is observed at the centre of the image; however, for an off-axis source (right), significant grating lobe patterns result and localisation is poor.

1.4 mm off-axis). In both cases, the reconstruction algorithm takes the modelled signal received over the entire element and reconstructs from a single point at the centre of each element. For an on-axis source (Figure 5.7(a)), this method works well and the source location is reconstructed to the nearest pixel (0.0625 mm in this case). However, for an off-axis source (Figure 5.7(b)), the method results in an image with significant grating lobe patterns and inadequate source localisation accuracy. To improve upon the quality of image obtained, the reconstruction algorithm may be modified so that, for each receiving element, the signal received across its surface is used to reconstruct the source location from a number of points distributed across the aperture of the element (see Figure 5.8(a)), and the average image is then computed. Figure 5.8(b) shows the resulting reconstructed image using nine points evenly distributed across the receiving element.

It is clear that, despite improving the accuracy of localisation, the reconstructed

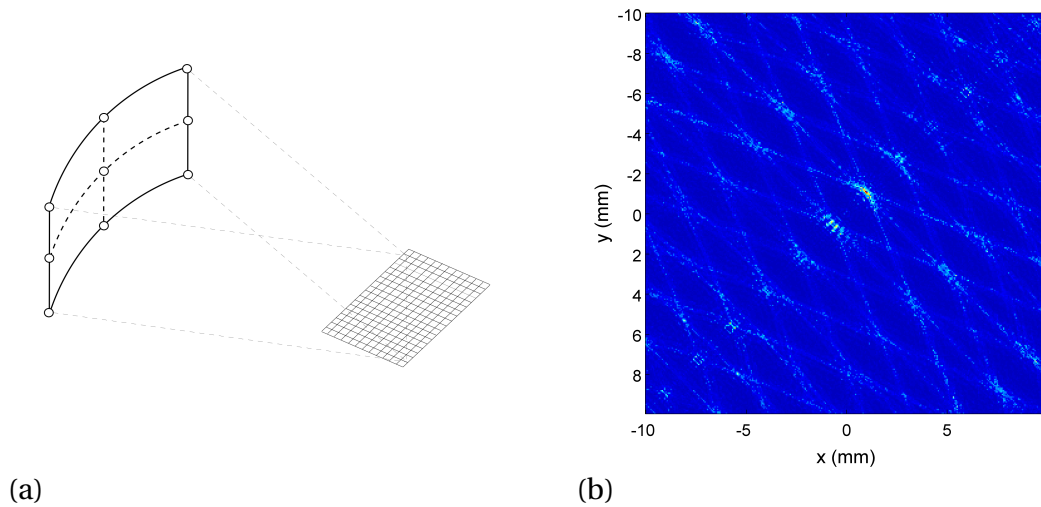


Figure 5.8: Reconstructed source location using modelled received signals and a nine point reconstruction for each element. Sub-figure(a) shows the distribution of points used across each element, whilst Sub-figure(b) shows the resulting improved reconstructed image for a source located at [1 1 0] mm.

image is not ideal, with grating lobes and poor off-axis sensitivity hampering image quality. The experimental results detailed in the following section reinforce these findings and highlight the need for optimisation of the array design prior to construction of a second-generation array.

5.2 EXPERIMENTAL VALIDATION

The initial simulations presented in Section 5.1 indicate that, despite providing high on-axis sensitivity as one would expect from a cylindrical array geometry, the large aperture elements of the prototype sensor are, not surprisingly, inadequate for accurate localisation of off-axis sources, limiting the ability of the device to fully characterise a cavitating field. In this section, this observation is validated experimentally using two sets of experiments. Firstly, a needle hydrophone is used to scatter an incident HIFU pulse to approximate a point source, and the scattered signal

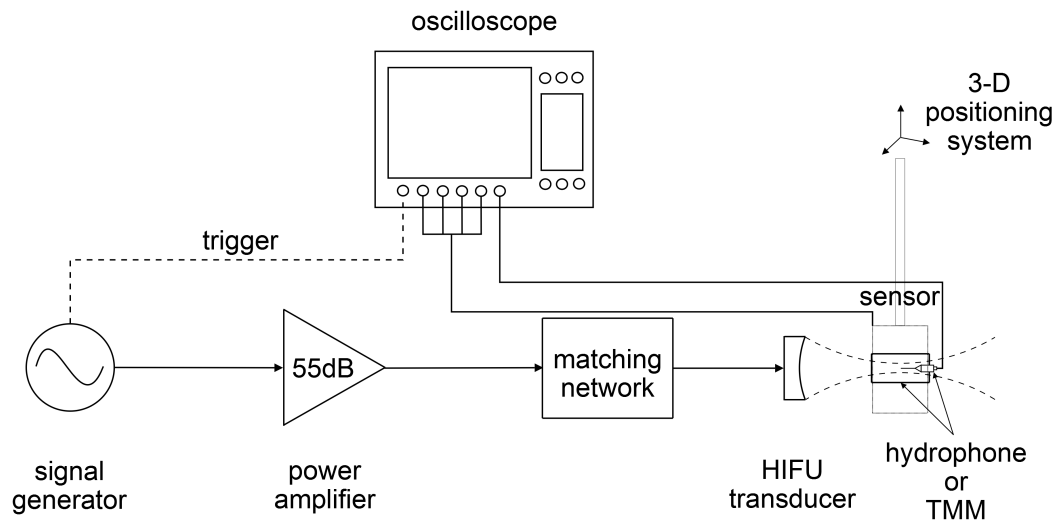


Figure 5.9: Schematic of the experimental setup for the experimental validation of the pre-existing prototype device.

detected using both the prototype array and an array of needle hydrophones for subsequent reconstruction. Secondly, the prototype array is used to map on-axis cavitation activity in a TMM. The experimental apparatus is initially considered, followed by an outline of the procedures adopted. Thereafter, the implications of the experimental results for the design of the next generation sensor are discussed.

5.2.1 Experimental Setup

Figure 5.9 shows a schematic of the setup used for the aforementioned validation experiments. As with all previous experiments, exposures were carried out in a tank of degassed, deionized water. Having already outlined the major components of this setup (see Chapter 3), additional features and procedures are explained in detail below.

5.2.2 Scattering Experiments

In order to validate the point source models detailed in Section 5.1.2 and support the conclusion that smaller elements are required for accurate localisation, two experiments were conducted using a needle hydrophone to scatter a 25-cycle, 1.067 MHz HIFU pulse. By scattering an incident HIFU field from a small object with high acoustic contrast, it is possible to emulate a point source at a known location within an array. The use of a hydrophone as a scattering object also facilitates characterisation of the HIFU field at the scattering point, providing useful information about the scattered waveform for validation. In the following experiments, a 400 μm effective diameter needle hydrophone (Onda Corporation HNA-0400) was used for this very purpose.

5.2.2.1 Prototype Array

In the first scattering experiment, the prototype cavitation sensor was used to record a pulse deflected from the scattering hydrophone. Unfortunately, two of the ten elements of the prototype device were found to have de-laminated during the manufacturing process and so data was recorded from the remaining eight elements. Data was acquired for two exposures using an oscilloscope, triggered by the driving function generator and sampled at 100 MS/s over a 200 μs window. Figure 5.10 shows the arrangement of apparatus for each exposure.

The HIFU transducer was held in a fixed position, whilst the cavitation sensor and scattering hydrophone were supported by a three-dimensional adjustable stage, facilitating precise alignment of each device. The scattering hydrophone was acoustically positioned at the focus of the HIFU transducer then fixed in place for the remainder of the experiment. The prototype cavitation sensor was then posi-

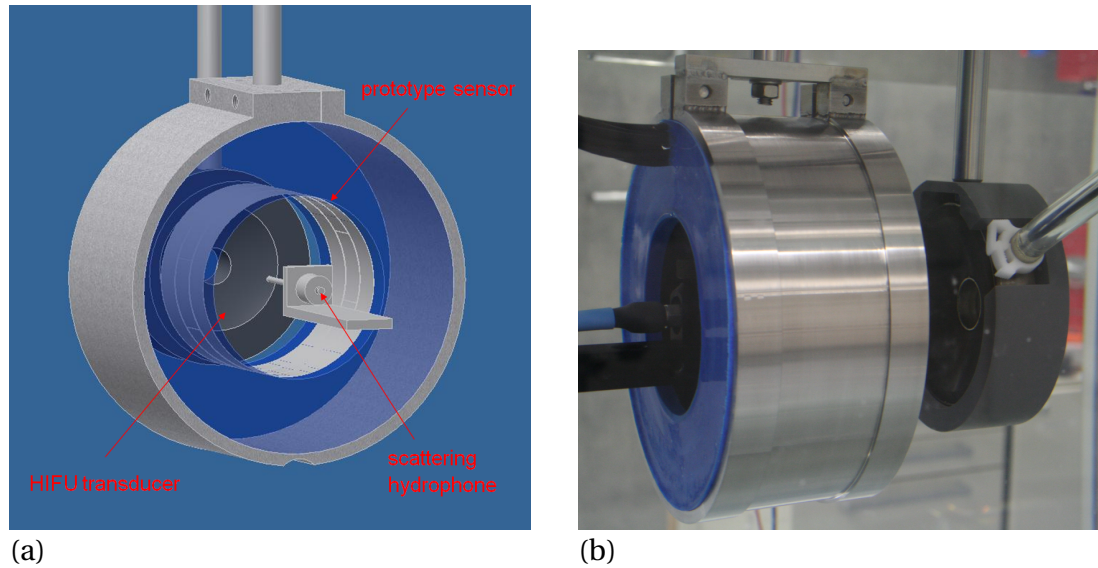


Figure 5.10: Schematic and photograph of the experimental setup for the scattering experiment using the prototype sensor. Data was acquired at a number of locations to investigate the accuracy of localisation both on- and off-axis.

tioned around the scattering hydrophone so that the scatterer lay at the centre of the receiving device. This was achieved by monitoring the delay in received signal on each element of the prototype device. Elements which received the scattered signal with longer delays were moved closer to the scatterer until all delays were approximately equal.

Having acquired data from the seven working elements of the central ring at an on-axis location, the sensor was displaced relative to the scattering hydrophone, thereby shifting the source location. Data was then acquired at the new location to investigate the accuracy of localisation when mapping an off-axis source. Figure 5.11 shows a map of the source location generated by applying the TEA algorithm to data obtained from scattering experiments both on-axis, and 2 mm off-axis. Given that one element of the central ring of the prototype device had delaminated, the data from the remaining seven elements was used for the reconstruction. It is clear that the prototype design is capable of locating on-axis sources; how-

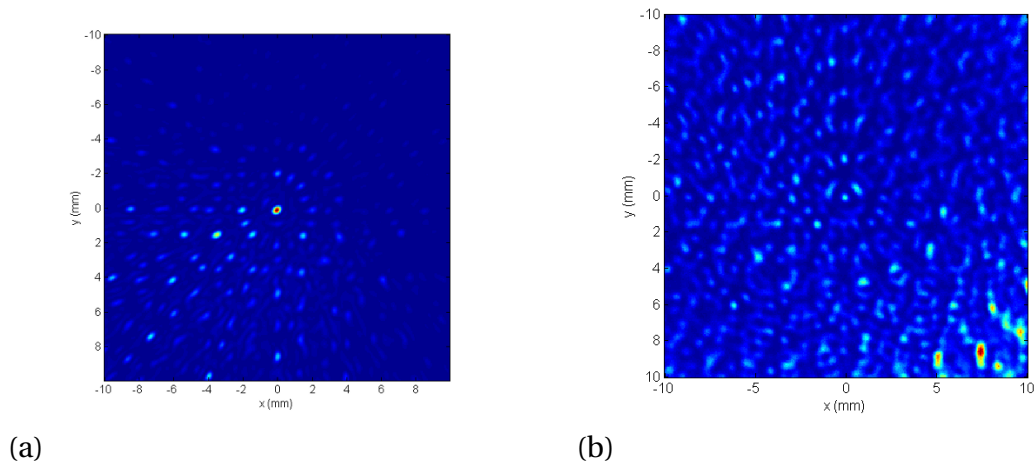


Figure 5.11: Source maps following reconstruction of data gathered on-axis (a) and 2 mm off-axis (b). On-axis localisation is relatively accurate however off-axis, large elements result in low sensitivity and poor source localisation.

ever, when the source is moved a mere 2 mm off-axis, poor off-axis sensitivity of the highly-focused, large-aperture prototype device makes it difficult to determine the true source location. These results reinforce the modelled behaviour of the device detailed in Section 5.1.2.

5.2.2.2 Hydrophone Array

A second scattering experiment was conducted to investigate the effect of reducing the receiving element size. In this experiment, an identical needle hydrophone was used as a receiving element at eight locations distributed circumferentially about the scattering needle, effectively forming an eight element receiving array from a single hydrophone. The output from each needle hydrophone was fed to the high impedance input of an oscilloscope for data acquisition.

Figure 5.12 shows the experimental setup used to record the deflected pulse from the scattering hydrophone. Given the reproducibility of the scattered wave-

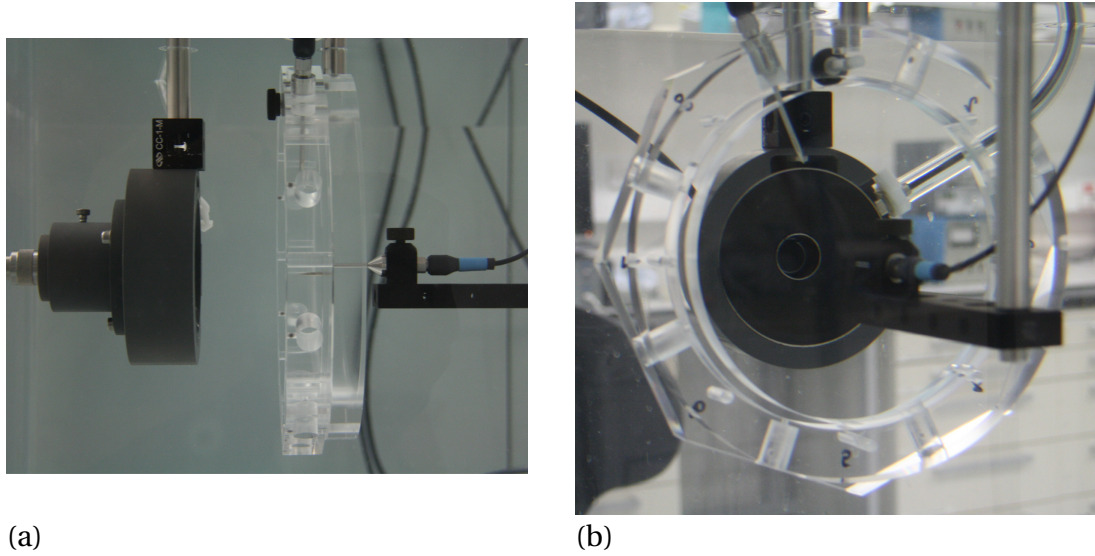


Figure 5.12: Images of the experimental setup for the scattering experiment using the hydrophone array. A needle hydrophone is used to receive the signal scattered from an identical hydrophone at eight fixed locations around the circumference of the scatterer.

form, a single receiving hydrophone was used at eight distinct locations. At each location, the receiving hydrophone was held in place by a perspex mount during insonation and simultaneous data acquisition. After each exposure, the mount, and therefore the receiving hydrophone, was rotated to its new position for further insonation. The HIFU pulse and data acquisition parameters were identical to those used in the previous scattering experiment, as was the alignment procedure for both on- and off-axis exposures.

The reconstructed source location maps for both an on-axis scatterer and a scatterer positioned several millimetres off-axis (co-ordinates [5 -2 0] mm) are shown in Figure 5.13. It appears that the initial alignment procedure was not entirely accurate, resulting in a slightly off-axis ‘central’ source location. However, it is clear that the smaller elements of the hydrophone array facilitate accurate mapping both on-axis and relatively far off-axis. More specifically, the physical displacement between

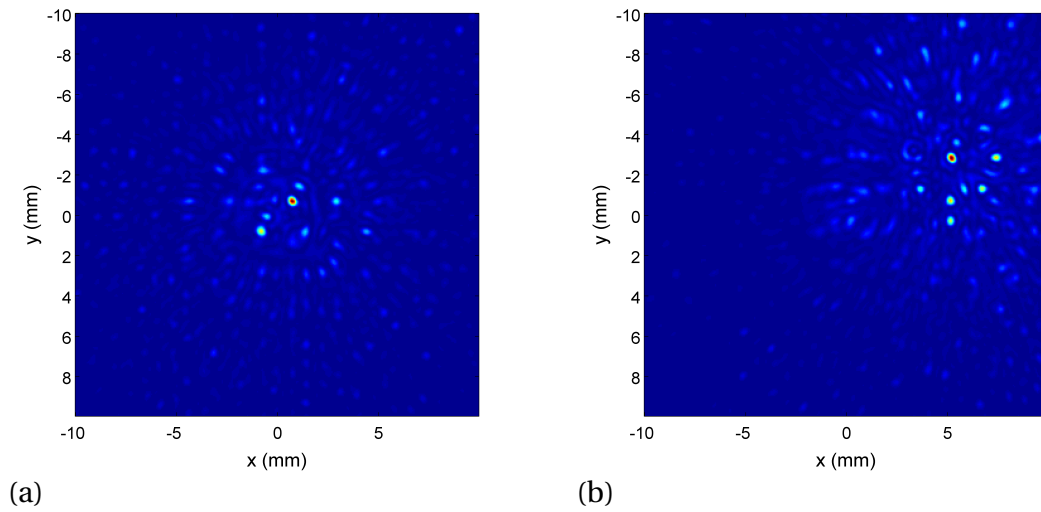


Figure 5.13: Source maps from reconstructed data gathered on-axis (a) and 5.385 mm off-axis (b). The $400\ \mu\text{m}$ receiving elements of the receiving hydrophone facilitate accurate mapping both on- and off-axis.

on- and off-axis exposures was 5.385 mm, whilst the imaged displacement was 5.003 mm, giving a sufficiently small error of 0.382 mm for a source located approximately 5 mm off-axis. Evidently, small active element areas are required to accurately locate off-axis sources, as is explored in more detail in Section 5.3.

5.2.3 Cavitation Experiments

Having experimentally validated the point source models of Section 5.1.2 using a relatively narrowband source, it is important to consider the performance of the prototype cavitation sensing array when detecting broadband signals resulting from HIFU-induced cavitation. A further experiment was therefore conducted using the prototype device to detect broadband emissions from within a 3% agar TMM, cast inside the sensor.

For this experiment an identical setup to that described in Section 5.2.2 was

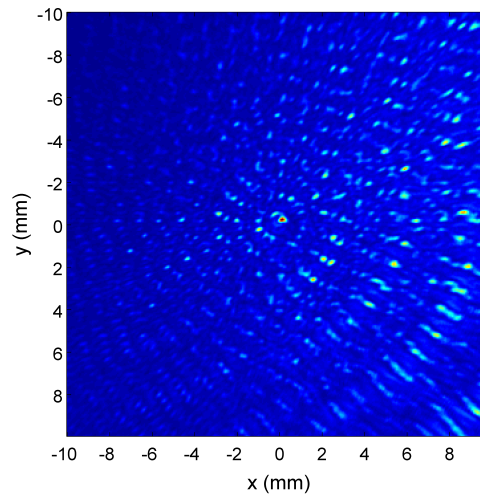


Figure 5.14: Prototype sensor cavitation map for a 3.71 MPa_{PRFP} exposure. The prototype sensor is able to accurately locate on-axis cavitation. However, given its poor sensitivity off-axis, smaller elements are required to fully characterise the cavitating region.

adopted, with a TMM replacing the scattering hydrophone previously used. The insonation amplitude of a 1.067 MHz, 25-cycle pulsed signal was marginally increased for each new exposure, starting at 1.4 MPa_{PRFP}. Data was acquired simultaneously across the central seven working elements of the prototype sensor using two oscilloscopes triggered in parallel and sampling at 100 MS/s over a 200 μ s window. Data was then digitally high-pass filtered to remove the frequency content of the received signal below 5 MHz, whilst retaining any broadband information. Figure 5.14 shows the resulting cavitation map obtained at a pressure amplitude of 3.71 MPa_{PRFP} for an on-axis exposure.

The prototype sensor is therefore able to localise on-axis cavitation activity; however, given its poor off-axis sensitivity, smaller elements are required to fully characterise a HIFU-induced cavitating field. The experimental results presented in this section concur with the findings of the computational modelling section detailed previously. Evidently, a re-design is required to produce an array that is capa-

ble of mapping a distribution of cavitating sources both on- and off-axis in three-dimensions. The following section uses modelled results to optimise the design of a second-generation array.

5.3 SENSOR OPTIMISATION

Based on the preliminary testing of the prototype sensor, both computationally and experimentally, it was decided that the second-generation array would be cylindrically configured, with dimensions equal to that of the prototype device (45 mm length and 75 mm diameter) in order to accommodate a range of lab-based and clinical HIFU transducers. The optimisation procedure detailed here aims to determine the size, number and distribution of elements required to accurately reconstruct the location of a distribution of cavitating sources positioned within the array.

5.3.1 Element Size

It is instructive to first consider the effect of reducing the element size on the accuracy of source localisation. To do this, a single ring of eight sensor elements was modelled with varying element size, receiving emissions from a source located 5 mm off-axis (co-ordinates [3 4 0] mm). Images of the source location in a transverse plane intersecting the centroid of each element were reconstructed using the nine-point TEA algorithm introduced previously. Figure 5.15 shows the variation in localisation error with element aperture. The axial dimension of each element is set equal to its circumferential dimension ($R \times \text{aperture}$) and errors are measured from the true pixel location of the source to the maximum value pixel in the reconstructed

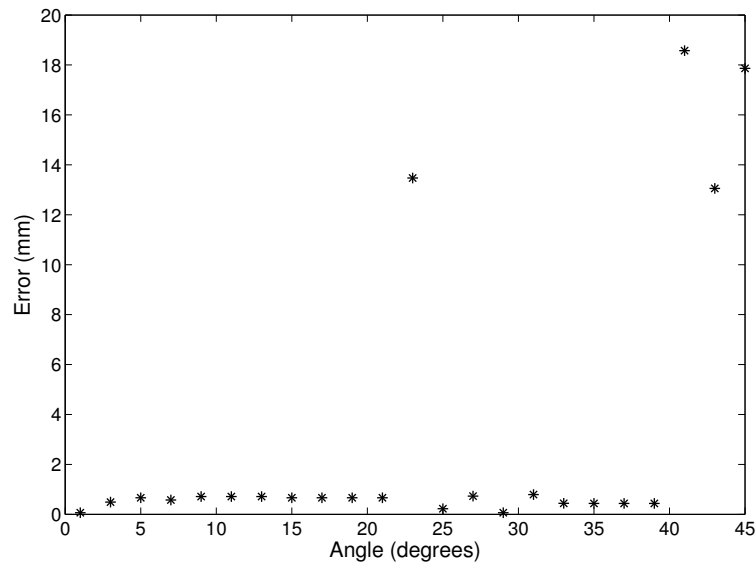


Figure 5.15: Variation of localisation error with element aperture for a source located 5 mm off-axis (co-ordinates [3 4 0] mm). Increasing the size of receiving elements increases the extent of focusing and reduces off-axis sensitivity, limiting the ability to localise off-axis sources.

image.

Evidently, receiving element apertures exceeding 40° result in significantly higher localisation errors for sources relatively far off-axis. Notably, a spurious result is observed at 23.3° , where this particular configuration results in a higher peak observed in a grating lobe and so larger than expected errors. Investigating the effect of element size at the lower end of this scale yields Figure 5.16, where the element aperture has been increased from 0.5° to 4.5° (0.33-2.95 mm) at 0.2° intervals. Below 3.5° , errors in source localisation are limited by the resolution of the reconstructed image and are considered suitably low for accurate localisation. Reducing the element size below 0.5° may well improve the accuracy of modelled localisation; however, in practical terms, this will lead to elements that are difficult to manufacture, require significant pre-amplification and are likely to exhibit poor SNR. An element aperture of 2.7° was therefore chosen for the second-generation array, offering a

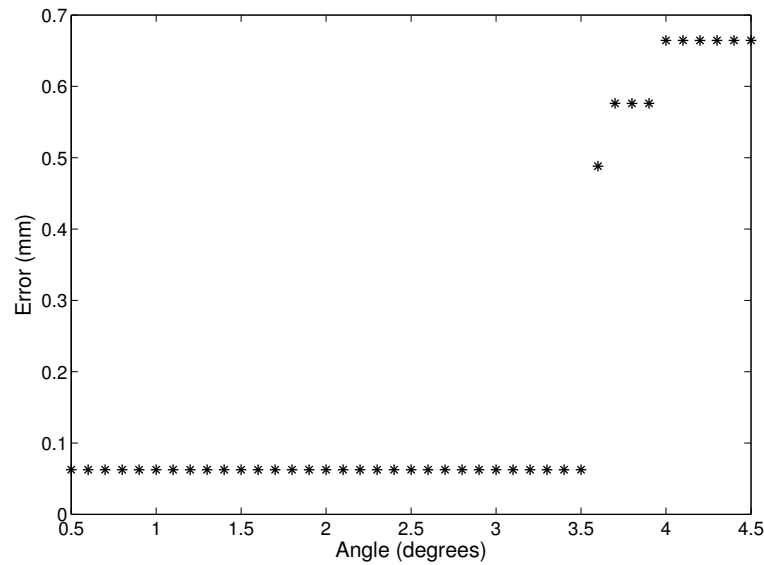


Figure 5.16: Variation of localisation error with element aperture for a source located 5 mm off-axis (co-ordinates [3 4 0] mm) at small subtended angles. Localisation errors increase significantly above an aperture size of 3.5° .

compromise between SNR, ease of manufacture and localisation accuracy. Having investigated element size, the optimal arrangement of elements for localisation of multiple sources, in both the transverse and axial planes, is now considered.

5.3.2 Element Configuration

In the present work, two receiving element configurations are investigated. The first is a regular array, similar to that of the prototype device, consisting of three rings of regularly-spaced elements (shown in Figure 5.17(a)); the second is an array in which elements are randomly distributed around a cylinder with dimensions equal to that of the prototype device (shown in Figure 5.17(b)).

Each configuration was tested using four unique, point sources arranged in the pattern of a cross, so as to represent the typical shape and size of a HIFU-induced

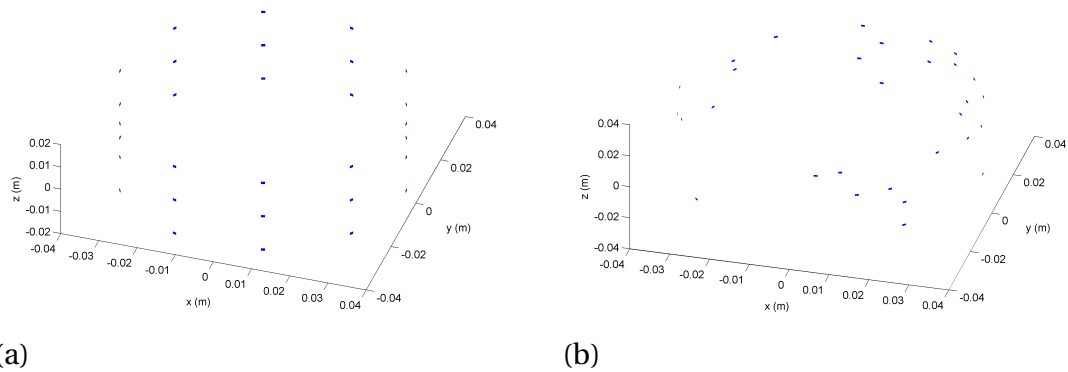


Figure 5.17: Element configurations used for investigating the performance of regular (a) and random (b) arrays.

lesion (20 mm axial length, 2 mm transverse width), as shown in Figure 5.18. The source signals were generated via computational solution of the Keller-Miksis equation, as modified by Yang and Church to include the effect of viscoelasticity, for a variety of modes of oscillation representative of bubble behaviour in HIFU fields (Yang and Church, 2005).

Figure 5.19 shows the source maps generated for increasing numbers of receiving elements in a regular array when detecting signals from the four source locations. The receiving array consists of three rings of equally-spaced elements, with an axial ring separation of 15 mm. It is evident that this configuration suffers from significant grating lobe levels, characterised by regularly-spaced maxima in the corresponding source map, inhibiting its ability to accurately localise multiple sources. As the number of elements in each ring is increased, the distribution of grating lobes is altered, and localisation in the transverse plane improves marginally; however, sufficiently accurate localisation remains unachievable.

To reduce the effect of grating lobes, randomly-distributed element arrays may be implemented, limiting the likelihood of constructive interference at a regular dis-

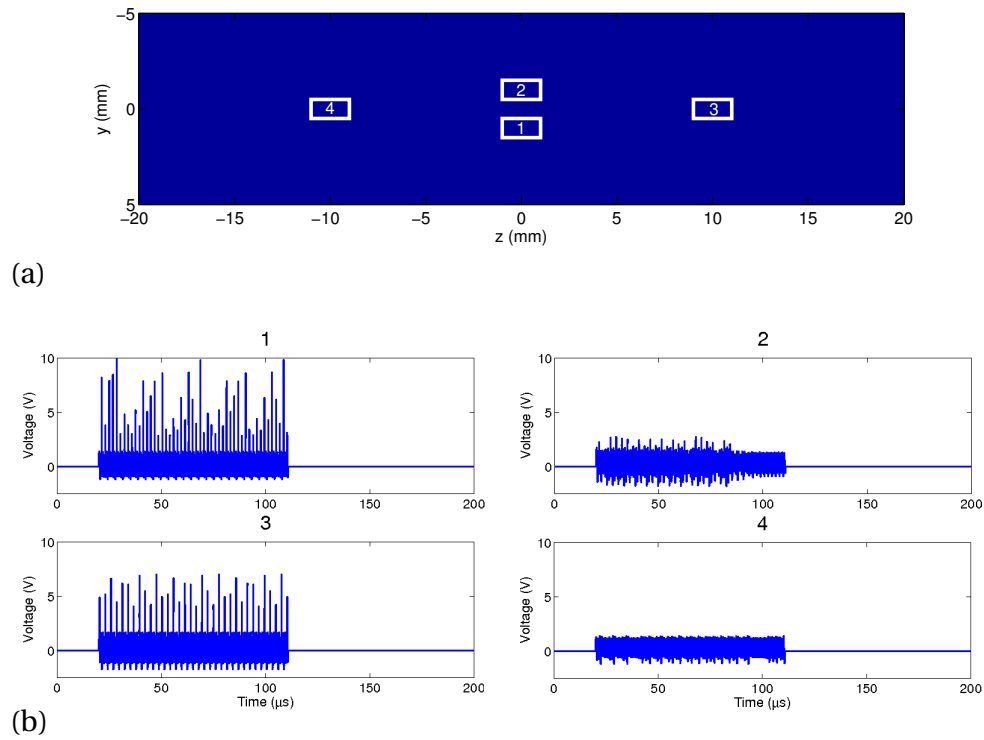


Figure 5.18: Source locations (a) and waveforms (b) used to investigate the performance of random and regular array configurations. The source signals are generated via solution of the Keller-Miksis equation as modified by Yang and Church (Yang and Church, 2005), and sources are arranged so as to represent the typical size and shape of a HIFU lesion (20 mm axial length, 2 mm transverse width).

tribution of points throughout the field of interest. Figure 5.20 shows the source maps generated for increasing numbers of elements distributed randomly about a cylinder of diameter 75 mm and length 45 mm, using computer generated random polar coordinates. Clearly, the effect of grating lobes in random configurations is less significant than in regular arrays, and, for the same number of elements, more accurate localisation of the four point sources is achieved with a random array. Furthermore, as the number of receiving elements is increased, the degree of blurring around each source location is reduced and accuracy of localisation is increased.

In practice, the maximum number of receiving elements is limited by the cost

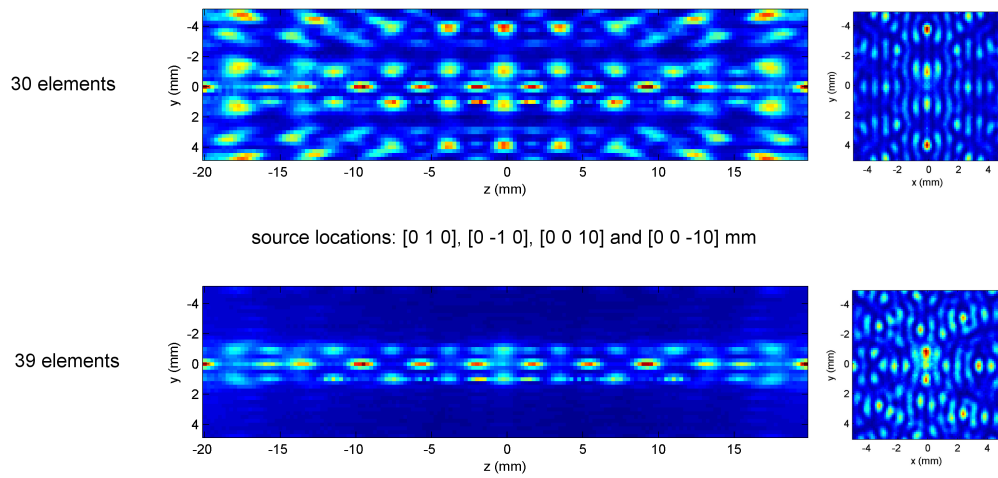


Figure 5.19: Reconstructed source locations for regular arrays of 30 (top) and 39 (bottom) elements in both axial (left) and transverse (right) planes for four point sources arranged in the pattern illustrated in Figure 5.18.

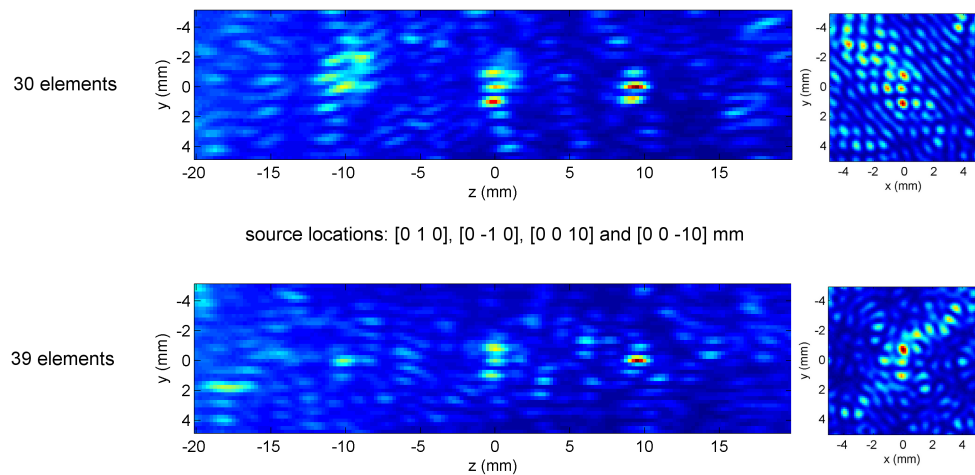


Figure 5.20: Reconstructed source locations for random arrays of 30 (top) and 39 (bottom) elements in both axial (left) and transverse (right) planes for four point sources arranged in the pattern illustrated in Figure 5.18. Elements are randomly distributed about a cylinder of 75 mm diameter and 45 mm length.

of producing the sensor and accompanying electronics. Several configurations of random arrays, with varying numbers of elements, have been investigated to determine the minimum number required for sufficiently accurate localisation of four sources arranged in the cross pattern. It was found that at least 39 elements are required to accurately localise all four sources; however, more elements would be preferable. Having specified the size and configuration of array elements for the second-generation device, the array design was finalised by considering the available manufacturing techniques and, ultimately, the associated cost.

5.4 SECOND GENERATION SENSOR

Thus far, the design and simulation of a prototype, three-dimensional cavitation sensor has been outlined, identifying several limitations which are supported by experimental results. Computational simulations have been implemented to optimise the design of a second-generation sensor for accurate localisation of multiple sources both on- and off-axis in the axial and transverse planes. Consequently, it was proposed that the sensor consist of at least 39, 2.7° aperture elements, randomly distributed about a cylinder of 45 mm axial length and 75 mm diameter.

In order to limit the cost of manufacturing both the new device and its accompanying electronics, the final design was chosen to consist of 50 randomly-distributed elements. The final configuration was chosen based upon qualitative evaluation of best quality reconstruction achieved from simulations of ten different random arrangements. To prevent unwanted edge effects, circular elements were selected, each with 1mm radius and occupying an area equivalent to that of the square-shaped, 2.7° aperture elements originally proposed. Figure 5.21 shows the final element configuration and its corresponding source map, generated by reconstructing

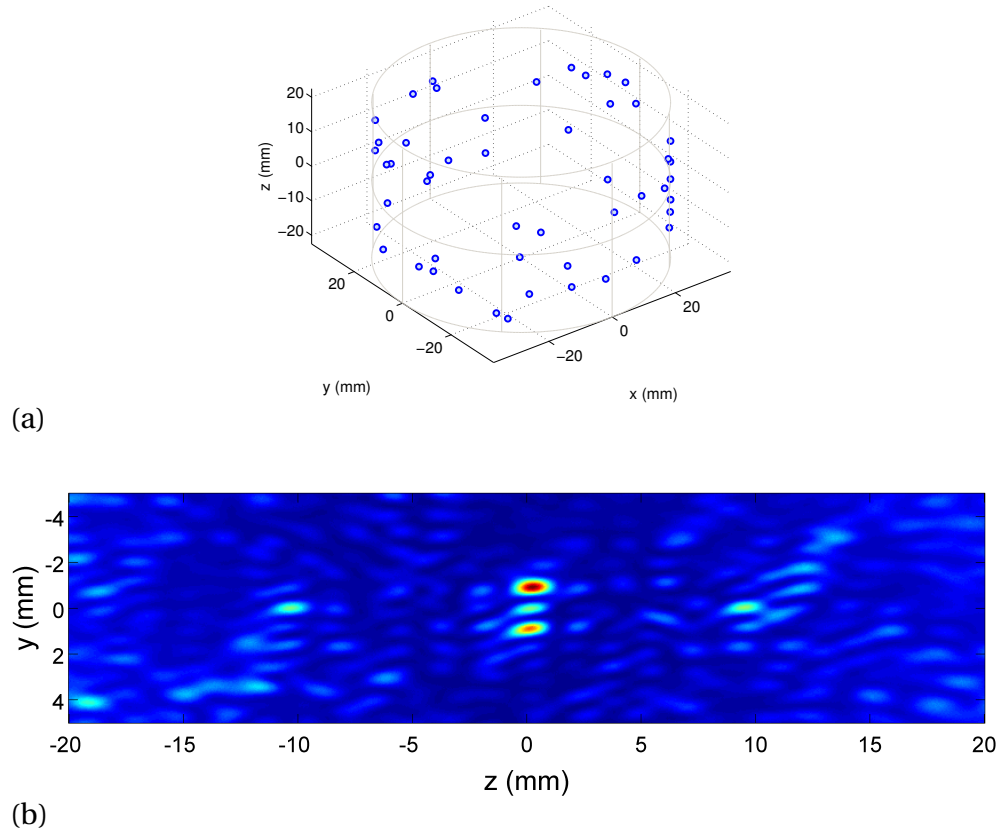


Figure 5.21: (a) Second-generation array configuration and (b) accompanying source map generated by reconstructing the modelled received signals across the array using the four point source distribution previously described.

the modelled received signals across the array using the four point source distribution previously described.

It is clear from Figure 5.21 that the final array design is able to accurately resolve the four simulated sources. To investigate the resolution that may be achieved with the proposed element configuration, however, one further simulation was conducted in which a single broadband source (source 1 from Figure 5.18(b)) was propagated radially from a point at the centre of the array. Following application of the TEA algorithm, the reconstructed source map gives a numerical representation of the PSF of the cylindrical array which, as with the results presented in Chapter 2,

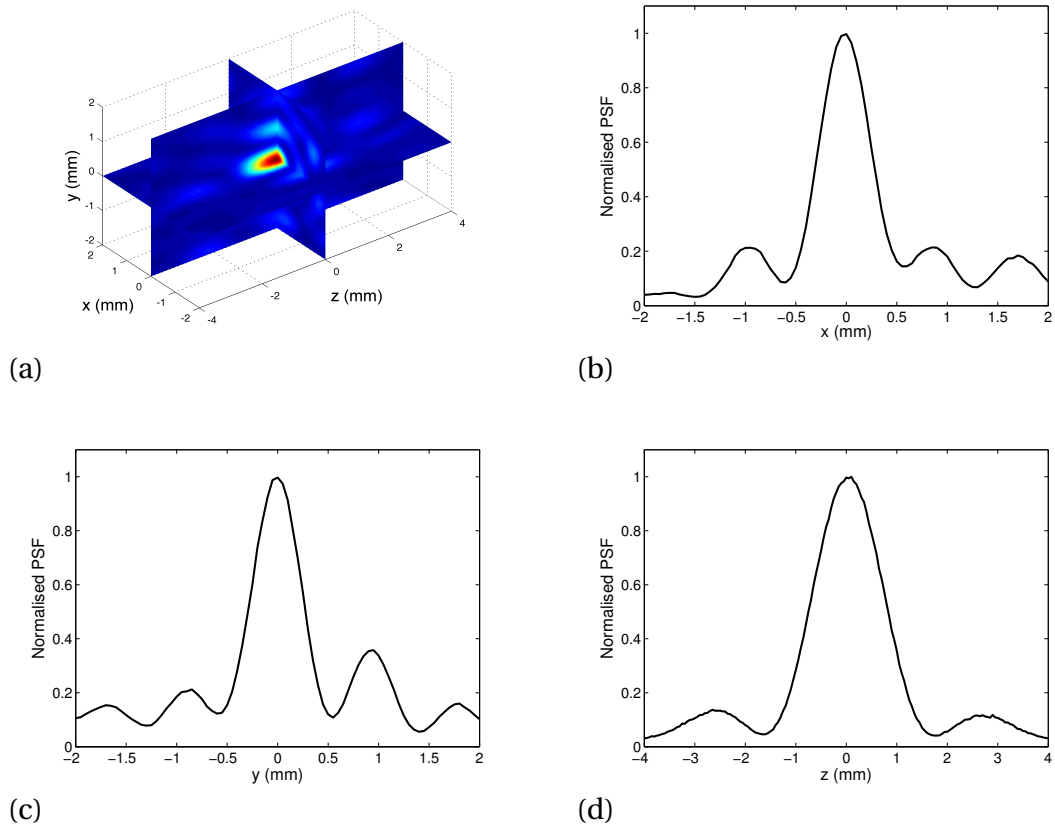


Figure 5.22: Simulated PSF of the final cylindrical array configuration. The volumetric reconstruction (a) indicates that -3 dB resolutions of 0.58 mm, 0.57 mm and 1.58 mm could be achieved in the x -, y - and z -axis respectively.

allows the -3 dB resolutions to be estimated. Figure 5.22 shows the resulting three-dimensional reconstruction of the single broadband source and normalised PSFs along each axis. It is estimated that with the proposed configuration -3 dB resolutions of 0.58 mm, 0.57 mm and 1.58 mm could be achieved in the x -, y - and z -axis respectively, which compare favourably with the corresponding predicted resolution of the diagnostic linear array used in Chapter 3.

Given that relatively small elements were required for accurate source localisation with the array, care was needed to avoid any stray sensitivity introduced by the element tracks themselves. For this reason, the novel manufacturing technique introduced in Chapter 4 was used, whereby a layer of piezo-electric material, PVDF,

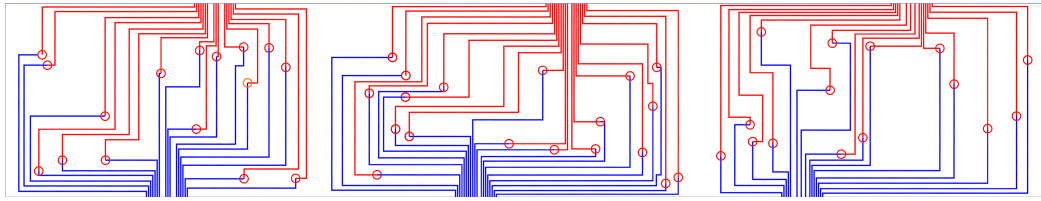


Figure 5.23: Second-generation array plan, showing both rectangular and cylindrical configurations. Red lines indicate tracks on the upper PCB, whilst blue lines indicate those on the lower one.

was sandwiched between two flexible PCBs, providing active area only in the regions where two PCB tracks overlap. Figure 5.23 shows the array design in the rectangular configuration in which it was manufactured, with red and blue lines indicating tracks on the front and back PCBs respectively.

By choosing an appropriate thickness for the central PVDF sheet, the frequency response of the array can be tuned so that peak sensitivity is observed in the range over which broadband emissions are expected. Chapter 4 has shown that, in doing this, care must be taken to account for the contribution of the additional layers of the sensor to the overall frequency response. For the second-generation array, it was decided that a $60\ \mu\text{m}$ PVDF sheet would be used, yielding a peak sensitivity in the 1-7 MHz range. Given that the majority of clinical and lab-based HIFU transducers operate at a fundamental frequency in the 0.8-1 MHz range, this should provide sufficient bandwidth to detect the broadband emissions observed from a cavitating region produced by any one of these devices.

Once manufactured as a rectangular sheet, the array was rolled inside a moulded acoustic absorber to form the required cylindrical configuration. Acquiring data from such a large number of array elements then involved the configuration of several bespoke hardware components.

5.5 DATA ACQUISITION

Prior to the digitisation of analogue signals received by the array it was necessary to pre-amplify the acquired data. This was achieved using custom made, high input impedance, low noise amplification circuitry that was designed to include an analogue high-pass filter stage before amplification. For this purpose, an elliptic filter design was chosen providing a rapid transition between the stopband and passband, thereby eliminating any potentially saturating components of the fundamental frequency. Since the clinical transducers in use at the Churchill Hospital, Oxford, have a fundamental frequency of 0.8 MHz, this was chosen as the high-pass cut off frequency, though it was found that the filter design successfully removed any frequency components below 1.3 MHz. Figure 5.24 presents the frequency-dependent gain of the pre-amplification circuitry, which is seen to provide a consistent gain of 27 dB across the 1.6-25 MHz range. All electronic components were housed in aluminium enclosures to limit susceptibility to electromagnetic interference, which was found to be particularly prevalent in the laboratory environment. Further noise reduction measures involved the introduction of a Faraday cage to the circumference of the array mount, which was found to reduce the level of detected interference.

Pre-amplified and filtered data was digitised using a 64-channel, 12-bit, 50 MHz data acquisition system (National Instruments NI5752). Once configured, the performance of the array and accompanying data acquisition system was evaluated for detection of cavitation emissions.

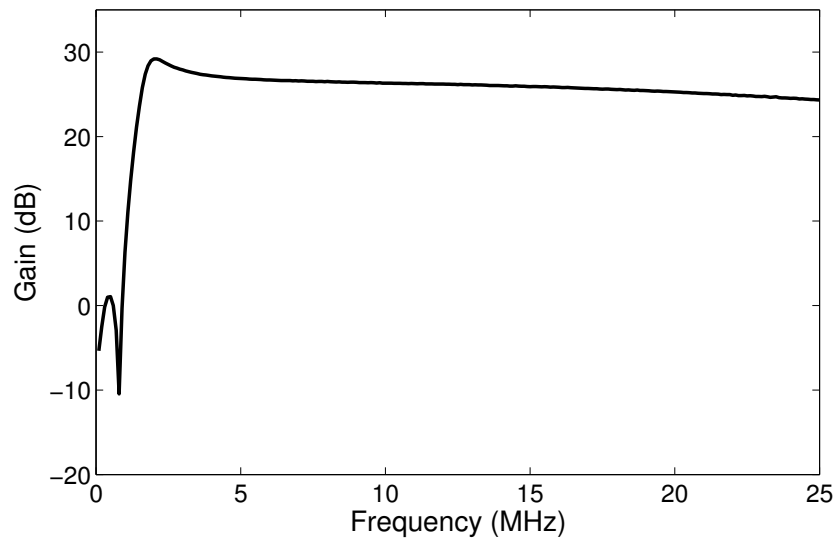


Figure 5.24: Frequency response of the pre-amplification and filtering circuitry. The elliptic filter design ensures that there is a rapid transition between the stopband and passband, removing signals below 1.3 MHz and providing a relatively flat 27 dB gain across the 1.6-25 MHz range.

5.6 SECOND GENERATION SENSOR TESTING

The three-dimensional cylindrical sensor comprises of 50 elements, each of 1 mm radius. Acquisition of data from all sensor elements presents a significant challenge, not only in terms of data handling, but also with regards to the physical configuration of such a large number of connections. For preliminary studies, therefore, a subset of the element distribution was evaluated to assess the performance of the array.

5.6.1 Cavitation Detection

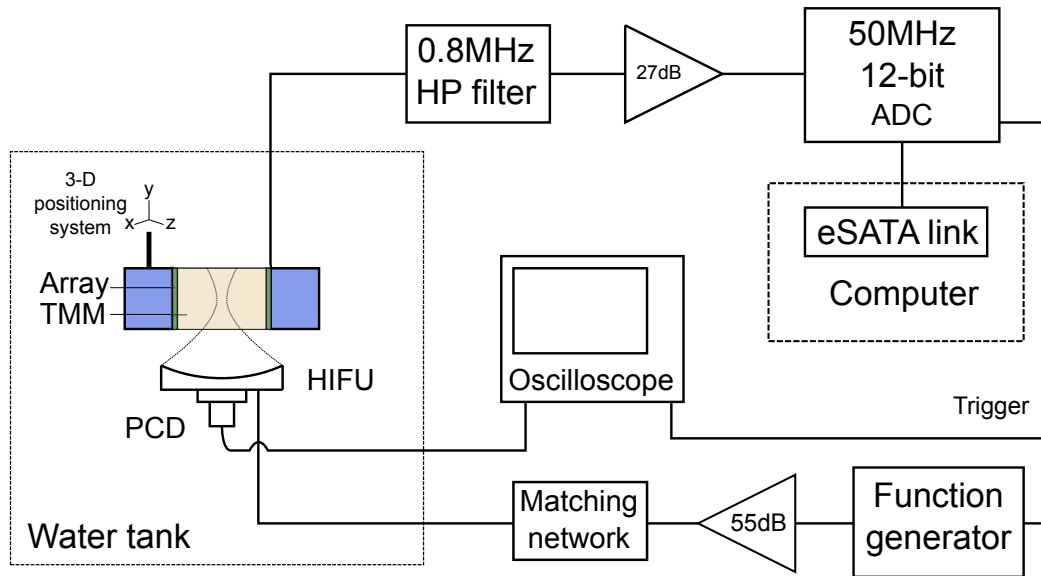


Figure 5.25: Schematic of the experimental setup for cavitation detection with the second generation cylindrical array. Data is acquired simultaneously across the array elements using 64-channel, 12-bit, 50 MHz data acquisition system. Cavitation emissions are also recorded using a confocally aligned PCD via an oscilloscope triggered simultaneously with the data acquisition system.

5.6.1.1 Experimental Setup

Initially, 32 elements of the array were arranged to detect cavitation activity induced within a microparticle-seeded 3% agar TMM, positioned inside the cylindrical sensor. Figure 5.25 presents the experimental setup used to acquire cavitation emissions across the array. With a broadly similar configuration to several of the experiments described throughout the work of this thesis, many of the components of the set-up will now be familiar to the reader. Importantly, this experiment makes use of the cylindrical array and its accompanying data acquisition system (introduced in Section 5.5), along with an alternative, 508 kHz HIFU transducer, both of which are detailed below.

5.6.1.2 HIFU generation

Chapter 4 characterised the frequency response of a typical element of the second-generation cylindrical array, indicating that a peak in sensitivity is observed at a frequency of 4 MHz, beyond which there is a relatively sharp decrease in sensitivity limiting detectable signal to the 1-7 MHz range. To maximise the broadband content of acoustic emissions observed in this range, a 508 kHz HIFU transducer (Sonic Concepts H107) was used rather than the 1.06 MHz transducer used in previous experiments. This had the effect of reducing the frequency of any potentially saturating scattered components of the fundamental and its low-order harmonics, which were then filtered prior to pre-amplification, leaving primarily broadband content in the resulting recorded signal.

The transducer was characterised in an identical manner to those introduced in Chapter 3 (Section 3.1.1), yielding the absolute and spatial calibrations shown in Figures 5.26 and 5.27. With a lower fundamental frequency the transducer has a broader focal region than those previously used, with a -6 dB beam diameter and axial length of 3.9 mm and 25 mm respectively.

Once the transducer was calibrated, cavitation threshold measurements were conducted to determine the PRFP beyond which broadband emissions were reliably observed when insonating a microparticle-seeded 3% agar TMM. Again, an identical procedure and experimental setup was used to that introduced in Chapter 3 (Section 3.1.1); however, in this case broadband emissions were detected using a 3.5 MHz PCD confocally aligned with the HIFU transducer. Any potentially saturating components of the fundamental frequency and its low order harmonics were removed using a 2.5 MHz high-pass filter prior to digitisation. Figure 5.28 presents the probability of cavitation for a given PRFP, calculated following threshold mea-

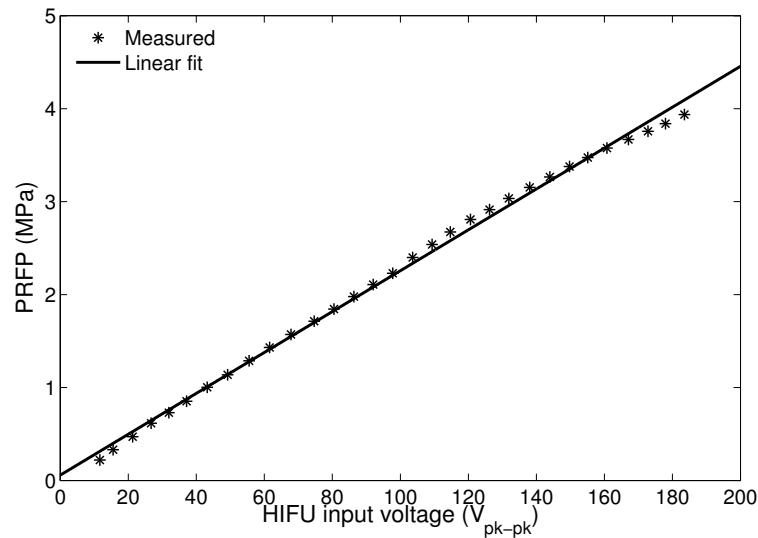


Figure 5.26: Calibration curve for the 508 kHz HIFU transducer. Focal pressures were recorded at $5 V_{pk-pk}$ intervals using a $400 \mu\text{m}$ needle hydrophone immersed in degassed water at 21°C . Over the range of input voltages used in this section, a linear relationship is observed between input voltage and PRFP.

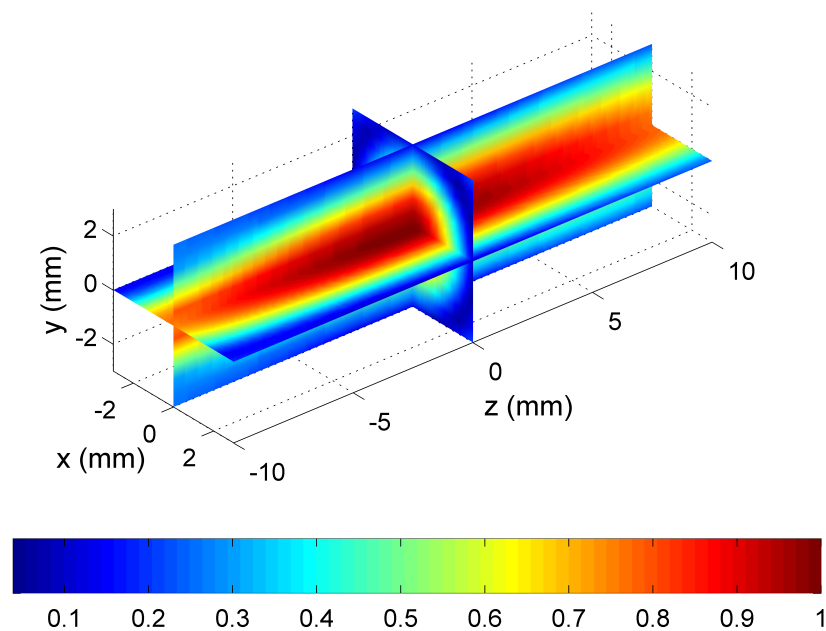


Figure 5.27: Normalised three-dimensional spatial calibration of the 508 kHz HIFU transducer. Pressures were recorded using a $75 \mu\text{m}$ needle hydrophone scanned throughout the focal volume with 0.25 mm spacing in the transverse and elevation directions and 0.5 mm in the axial direction.

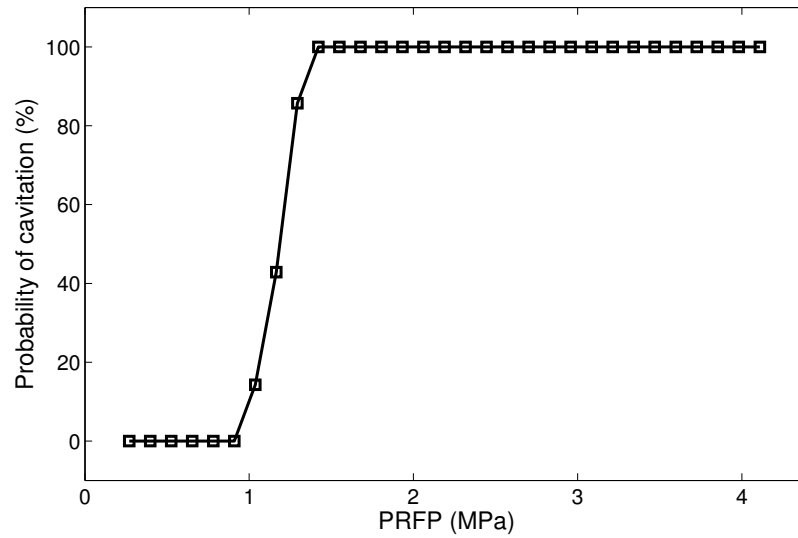


Figure 5.28: Cavitation threshold of the microparticle TMM for 508kHz HIFU insonation. Broadband emissions were detected using a coaxially and confocally aligned 3.5 MHz PCD, digitised using a 100MHz, 14-bit DAQ card following 2.5 MHz high-pass filtering and 28 dB pre-amplification. Cavitation emissions are first detected at 0.91 MPa_{PRFP}, and are reliably observed beyond 1.42 MPa_{PRFP}.

surements at 7 spatially distributed locations throughout the TMM.

It can be seen that the 508 kHz HIFU transducer first instigates cavitation at a similar pressure to the higher frequency device previously used. However, the pressure threshold beyond which cavitation emissions are consistently observed is lower than was seen at 1.067 MHz (1.42 MPa_{PRFP} rather than 1.52 MPa_{PRFP}). This is consistent with the observations of previous authors who have shown that the longer rarefaction phase of lower frequency insonation allows more time for bubble expansion and hence acoustic nucleation (Hynynen, 1991).

When insonating the TMM during cavitation detection experiments, the HIFU transducer was driven at its fundamental frequency with 5-cycle, sinusoidal pulses varied in amplitude from 1.55 MPa_{PRFP} to 4.11 MPa_{PRFP} at 0.13 MPa_{PRFP} intervals. A trigger output from the function generator was used to synchronise the acquisi-

tion of data across the array elements and 3.5 MHz PCD. To ensure acoustic emissions were received within the available acquisition length, a time delay of 20 μs was introduced between the HIFU driving pulse and acquisition trigger.

5.6.1.3 Data Acquisition and Signal Processing

Section 5.5 introduced the bespoke circuitry and data acquisition system configured to acquire data across the cylindrical array. Simultaneous acquisition of data from 32 elements of the array was achieved using the 12-bit, 50 MHz data acquisition system, that was able to acquire 80 μs of data from each element per acquisition. Prior to digitisation, signals were high-pass filtered (1.3MHz cutoff) and pre-amplified using the aforementioned circuitry. Figure 5.29 displays a typical RF signal and corresponding frequency spectrum of a cavitation emission received by the array. Received signals were seen to consist mostly of broadband noise in the 1.4-7 MHz range with minimal harmonic content. A small amount of signal content was observed within the stopband of the analogue filter, possibly due to electrical interference, and so a digital high-pass filter was applied to remove any signal content below 1 MHz.

For the purpose of comparison, data was also acquired by a simultaneously triggered 3.5 MHz PCD using an oscilloscope. The PCD signal was high-pass filtered (2.5 MHz cutoff) and amplified using a 28 dB amplifier, prior to digitisation of 200 μs of data at 100 MS/s. The results of this analysis are presented in the section below.

5.6.1.4 Cavitation Detection Results

Figure 5.30 illustrates the typical cavitation emissions detected by two elements of the cylindrical array and the coaxial PCD following 5-cycle HIFU insonation at 2.31

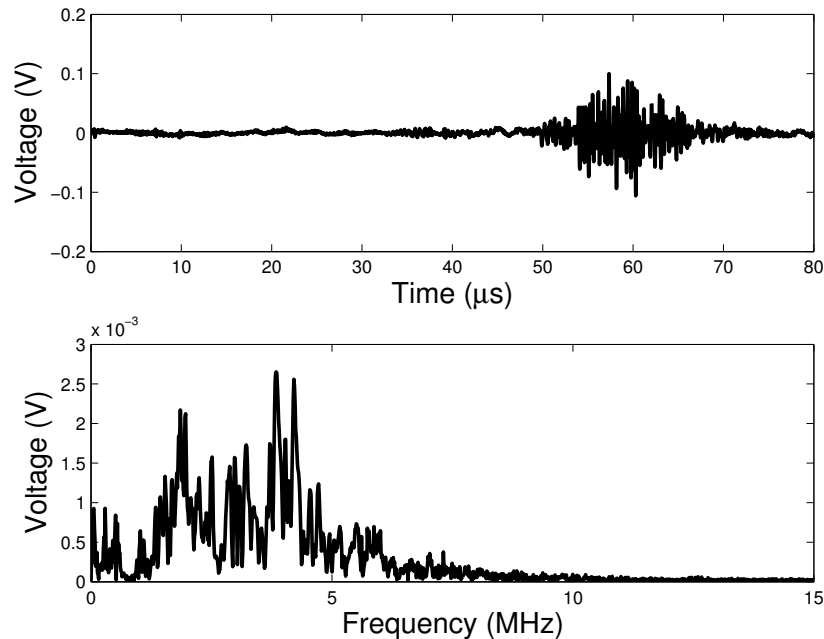


Figure 5.29: Typical time trace (above) and corresponding frequency spectrum (below) of cavitation emissions received using the cylindrical array following 4.11 MPa_{PRFP} insonation. The received signal consists mostly of broadband noise with minimal harmonic content. A small amount of electrical interference results in detection of signal content below the 1.3MHz cutoff of the high-pass filter, necessitating the use of a digital filter to remove signal content below 1 MHz.

MPa_{PRFP}, 3.21 MPa_{PRFP} and 4.11 MPa_{PRFP}.

Clearly the array elements are able to detect acoustic emissions from cavitation events, the presence of which is confirmed by the coaxial PCD. As the insonation amplitude increases, so too does the amplitude of the detected emissions, indicating increased cavitation activity within the focal volume. Promisingly, it is not only the amplitude of emissions that increases with PRFP, but also their duration, implying that cavitation activity occurs over a larger region as the insonation amplitude is increased. Application of the TEA algorithm to the acquired data does not, however, successfully reconstruct a continuous cavitation region.

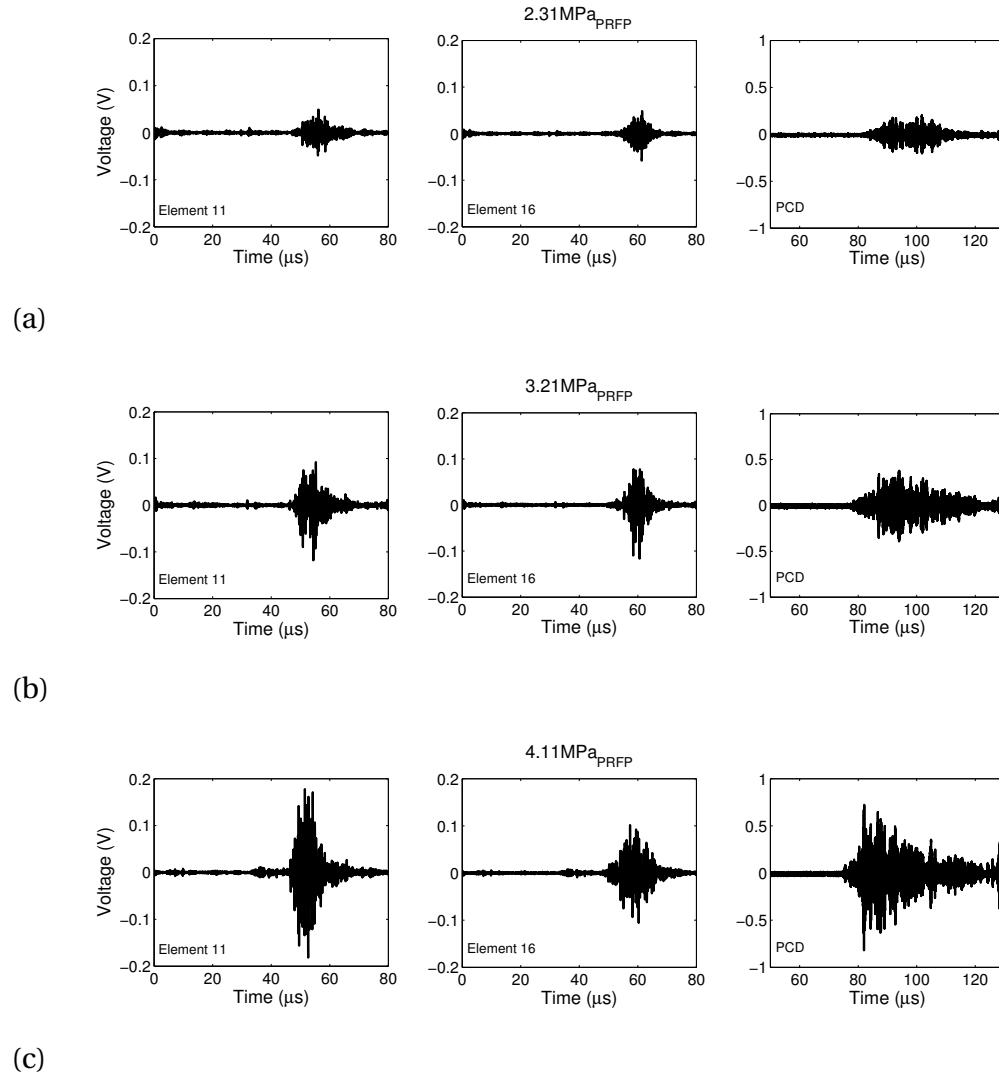


Figure 5.30: Cavitation emissions detected using the 50 element cylindrical array and coaxial PCD following 2.31 MPa_{PRFP} (a), 3.21 MPa_{PRFP} (b) and 4.11 MPa_{PRFP} (c) insonation.

5.6.1.5 Cavitation Mapping Results

It has been shown that the individual elements of the 50 element, cylindrical array are capable of detecting cavitation emissions which show promising trends with increasing insonation amplitude. Unfortunately, however, the recorded emissions fail to produce useful cavitation maps following application of the TEA reconstruction algorithm, the reasons for which are explored in the subsequent section. The post-processed data was reconstructed in an identical manner to that which has been previously presented, with each 80 μ s acquisition upsampled from 50 MHz to 200 MHz to limit quantisation errors when calculating the appropriate delays for each element. Integration over time was then computed at the original sample rate of 50 MHz over the entire 80 μ s frame (4000 data points). Reconstructions were calculated throughout the focal volume, extending ± 5 mm in the transverse directions and ± 10 mm in the axial direction with $0.1 \times 0.1 \times 0.1$ mm voxels. Figure 5.31 displays the resulting reconstructed volumes following application of the TEA algorithm to data acquired during 2.31 MPa_{PRFP} and 4.11 MPa_{PRFP} exposures.

Similar results were obtained following modification of the driving signal and acquisition parameters to allow acquisition of multiple frames of data throughout a 2 second CW exposure. Investigating the cause of these results led to the characterisation of crosstalk throughout the array, which appears to significantly degrade the signal content observed on each element of the sensor.

5.7 CROSSTALK CHARACTERISATION

Crosstalk is a phenomenon whereby a signal observed on one channel of an electrical system, is transmitted to a neighbouring channel, creating an undesirable effect.

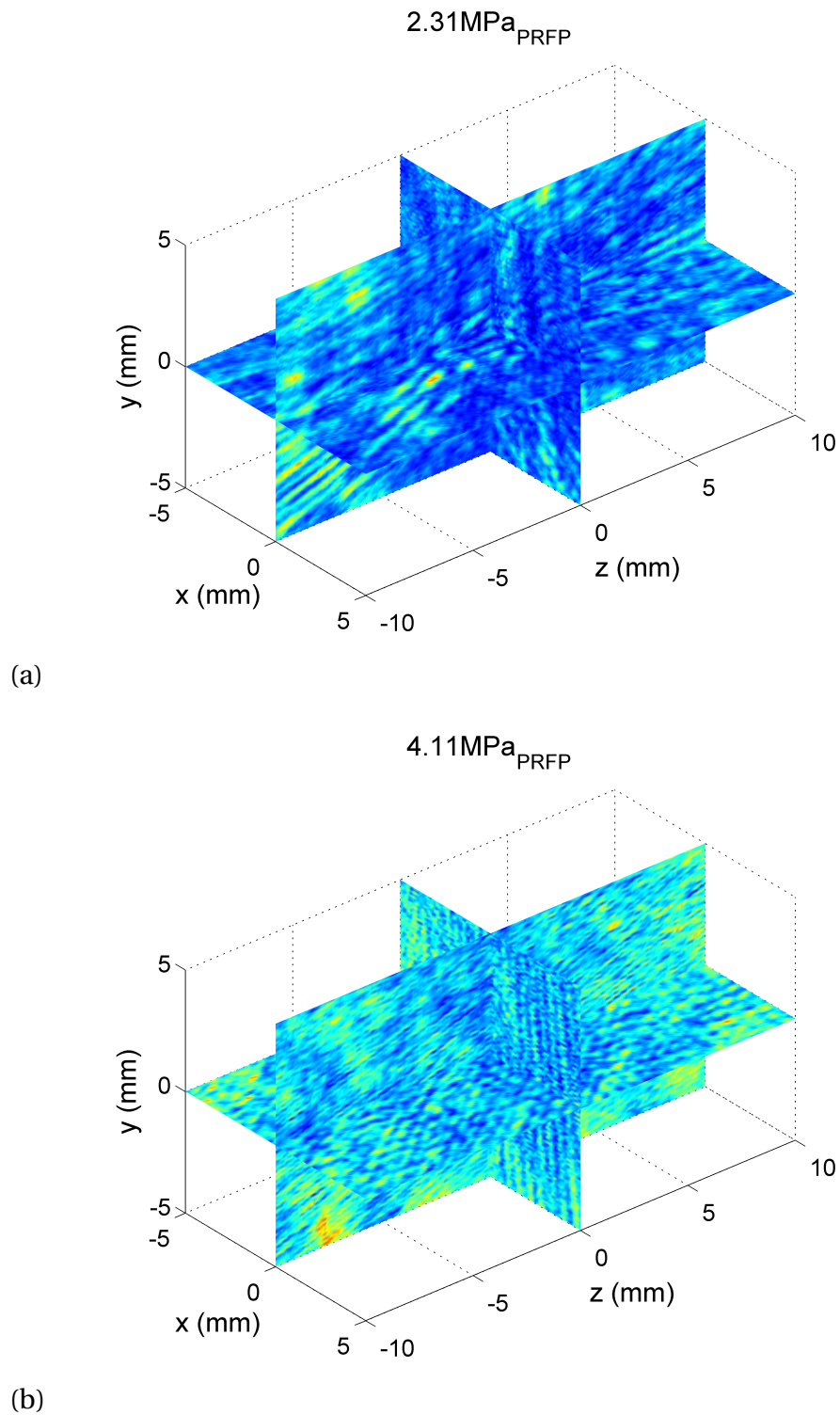


Figure 5.31: Cavitation maps reconstructed from data acquired across 32 elements of the cylindrical array following 5-cycle insonation at 2.31 MPa_{PRFP} (a) and 4.11 MPa_{PRFP} (b).

It is usually caused by capacitive, inductive or conductive coupling from one part of a circuit or cable to another. In the context of the work of this thesis, crosstalk has the potential to cause leakage of signal from one element of the PCB-PVDF array to another, thereby eliminating the spatially discrete nature of individual elements and rendering reconstruction from acquired data extremely difficult.

This section aims to characterise the extent of the crosstalk experienced by elements of the PCB-PVDF array experimentally. By acoustically targeting a single element of the array and observing the signals detected across the remaining elements, it is possible to construct a matrix representation, $\mathbf{X}$, of the experienced crosstalk in the form

$$\mathbf{V} = \mathbf{X}\mathbf{U}, \quad (5.6)$$

where $\mathbf{V}$ is a matrix containing the recorded signal on each element of the array (number of elements - by - length of data), and $\mathbf{U}$ is a matrix of the same size containing the pre-crosstalk signal recorded by each element. Each of the complex elements, $\mathbf{X}_{ij}$, of $\mathbf{X}$ then represents the magnitude and phase of the signal leaked through to element j from element i . For a system in which minimal crosstalk is present, the matrix $\mathbf{X}$ would be close to the identity matrix and it may be possible to mitigate crosstalk by inverting $\mathbf{X}$. For higher levels of crosstalk, $\mathbf{X}$ will be less diagonally dominant and solution of the problem is more likely to require hardware modifications.

5.7.1 Experimental Setup

Figure 5.32 shows a schematic of the experimental setup used to characterise crosstalk throughout the array. Since this involves the alignment of a large number of elements and acquisition of multiple data sets, a subset of the array consist-

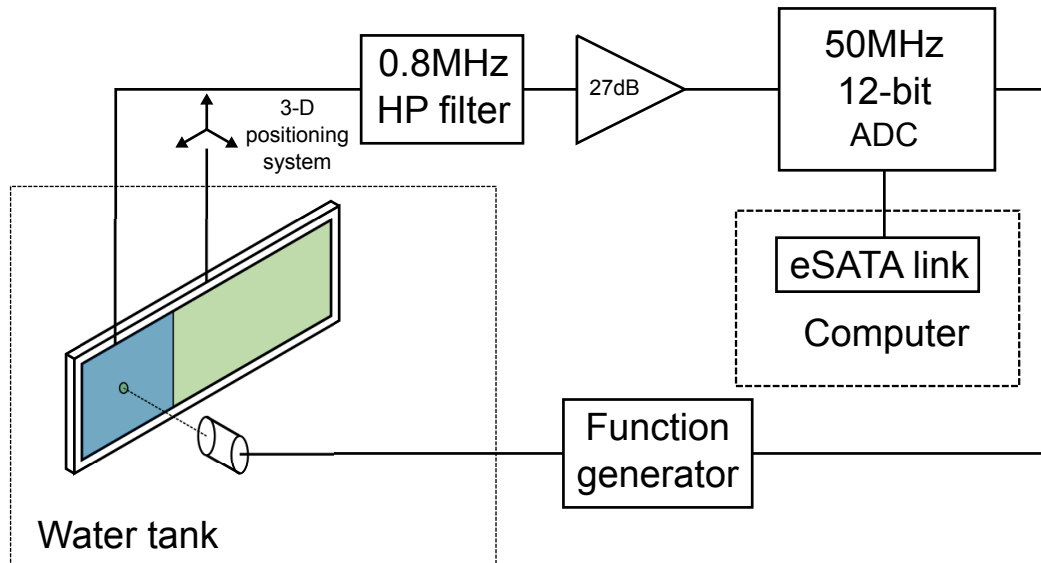


Figure 5.32: Schematic of the experimental setup used to determine the extent of crosstalk throughout the PVDF-PCB array. A machined layer of acoustic absorber (shown in blue) shields non-targeted elements from acoustic signal to allow characterisation of the effect.

ing of 16 neighbouring elements was chosen to characterise the extent of the effect. Crosstalk was evaluated at a single frequency close to the peak in sensitivity of the array using a 3.5 MHz spherically-focused ultrasound transducer (Olympus Panametrics V382-SU) driven with a $10 V_{pk-pk}$, 20-cycle sinusoidal burst.

A 3 mm thick layer of acoustic absorber (Precision Acoustics Aptflex F28) was machined to provide acoustic windows for each element that could be plugged when the element was not targeted. With a transmission loss of 30 dB/cm/MHz, the 42 dB of attenuation offered by the machined layer (illustrated in Figure 5.33) was deemed sufficient to ensure the 3.5 MHz acoustic signal was only experienced by the targeted element, providing confidence that any signal detected on a neighbouring element was likely the result of crosstalk.

Each targeted element was acoustically aligned at the focus of the insonating transducer, after which data was acquired across all 16 channels at 50MHz and av-

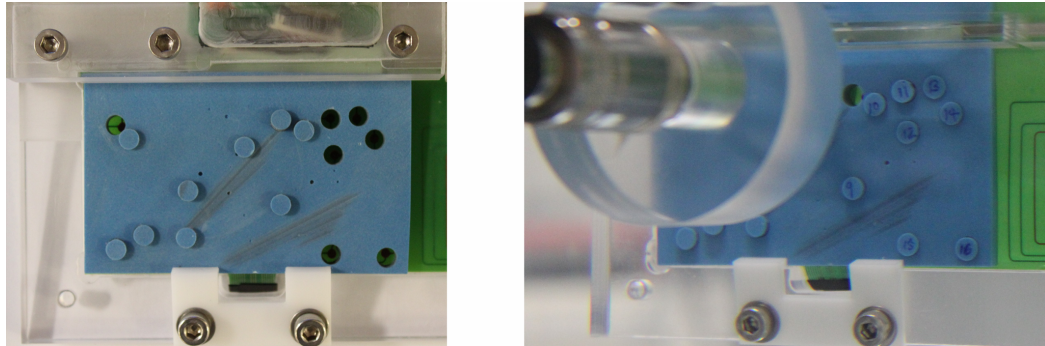


Figure 5.33: Acoustic absorber used to shield non-targeted elements during crosstalk characterisation. The 3 mm thick layer offers 42 dB of attenuation which was deemed sufficient to ensure acoustic signal was only experienced by the targeted element.

eraged over 20 acquisitions. The magnitude and phase of the 3.5 MHz component of the signals acquired on each element was then computed to form the crosstalk matrix, $\mathbf{X}$.

5.7.2 Crosstalk Characterisation Results

The magnitude and phase of the resulting crosstalk matrix is displayed in Figures 5.34, 5.35 and 5.36. Each row index represents the element that was acoustically targeted, whilst column indices indicate the corresponding signals received on each of the neighbouring elements.

Immediately obvious is the fact that the sensitivities of the array elements are not uniform, with elements 8,9,10 and 15 showing significantly higher sensitivity than their neighbours. Whilst this problem could be resolved by appropriate calibration of array elements (provided the SNR is acceptable for lower sensitivity elements), of more concern is the lack of diagonal dominance in the crosstalk matrix. This becomes more apparent when each of the rows of $\mathbf{X}$ is normalised. Clearly, elements 9, 15 and 16 are particularly sensitive and susceptible to crosstalk, picking

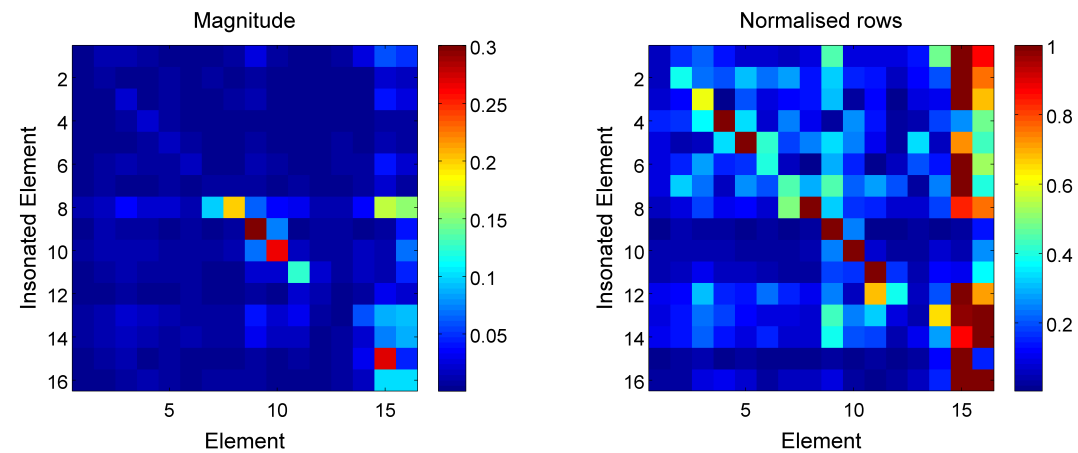


Figure 5.34: Absolute (left) and normalised row (right) magnitude of the experimentally determined crosstalk matrix $\mathbf{X}$.

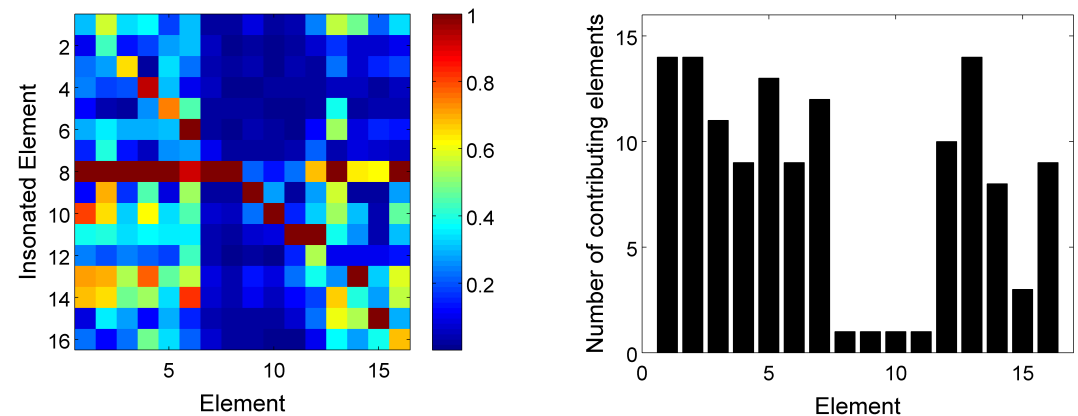


Figure 5.35: Normalised columns of the crosstalk matrix (left) and corresponding number of contributing elements where the magnitude of the observed signal is greater than a third of the targeted element magnitude (right).

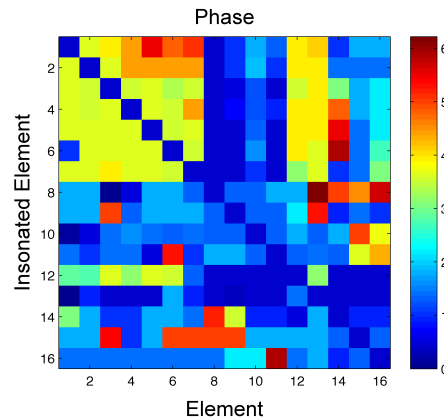


Figure 5.36: Phase of the experimentally determined crosstalk matrix $\mathbf{X}$.

up a large amount of signal that is in phase with that which is acquired on the targeted element. As a result, in 8 of the 16 cases where an element was targeted, a higher magnitude signal was observed on a neighbouring element, resulting from a combination of crosstalk and higher sensitivity of other elements to noise.

Figure 5.35 illustrates the number of elements that contribute to the signal observed by any one element. By normalising the columns of $\mathbf{X}$, it becomes apparent that for any one receiving element, significant signal content is observed when a neighbouring element is targeted. If a conservative noise floor is taken as a third of the magnitude of the signal received when the element is targeted, then it appears that only 4 of the 16 elements act independently, with elements, on average, receiving significant signal content from 8 of their neighbours.

The extent of the observed crosstalk leaves little opportunity for software mitigation, since the signal recorded on any one element is not only a function of the pressure which it experiences, but also a combination of those both geometrically close and those spread further away. This is likely due to the proximity of neighbouring tracks on the PCB-PVDF array, with results suggesting that there is significant electrical coupling between elements. Hardware modifications in which individual

array elements remain electrically isolated are, therefore, suggested to provide the capability for accurate three-dimensional cavitation mapping. Suggestions for such modifications form part of the future work described in Chapter 6.

5.8 SUMMARY

Various methods have been introduced for modelling the performance of a prototype cavitation sensor design, specifically for localisation of cavitation sources both on- and off-axis. Experimental work using two different receiving arrays to localise both narrowband and broadband sources both supported the modelled results and highlighted a number of physical limitations of the proposed system. In particular, it was established that the large elements of the prototype device were unsuitable for characterisation of an extended cavitation source, thereby necessitating the development of a second-generation, cavitation-sensing device.

Optimisation of the various components of the sensor yielded a second-generation design capable of mapping a distribution of cavitation sources. Simulations have shown that the random placement of elements reduces the effect of grating lobes by limiting the likelihood of constructive interference at a regular distribution of points in the field of interest. Furthermore, small elements (below 3.5° aperture or 2.3mm side length) facilitate the mapping of off-axis sources, though may suffer from an inferior SNR in practice.

The optimal array design comprising 50, 1 mm radius, circular elements randomly distributed around a cylindrical shell was manufactured using the novel PCB-PVDF technique introduced in Chapter 4. Numerical simulations have shown this configuration to accurately locate a discontinuous distribution of broadband sources, yielding spatial resolutions of 0.58 mm, 0.57 mm and 1.58 mm in the x -,

y - and z -axis respectively, which compare favourably with the linear array used in Chapter 3. A customised data acquisition system was configured to provide 50 MHz, 12-bit digitisation of data across all channels. Analogue signals were pre-amplified via a high-input impedance, broadband, 27 dB amplifier with an in-built analogue high-pass filter to prevent saturation by the fundamental frequency and its low order harmonics.

Experimental validation of the complete system confirmed that the array was capable of detecting broadband emissions, which increased in both amplitude and temporal extent with increasing insonation amplitude. Unfortunately, reconstruction of emissions acquired across 32 elements of the array during 508 kHz HIFU insonation failed to successfully map cavitation events.

Investigation into the cause of the restricted array performance led to the characterisation of crosstalk between individual elements, which was not predicted during the optimisation procedure of Section 5.3. Experimental evaluation of this phenomenon revealed significant electrical coupling between channels leading to signal leakage between neighbouring elements. Removal of this effect requires an alternative construction technique, which would aim to ensure individual elements remain electrically isolated between the active area and pre-amplification circuitry. The following chapter offers a number of potential design solutions, which form part of the suggested future work. Though three-dimensional cavitation mapping from a single HIFU exposure remains to be achieved, significant progress has been made. Valuable design and validation techniques have been developed and an optimised sensor design proposed, providing a strong foundation for future work into cavitation-based HIFU QA.



CONCLUSIONS AND FUTURE WORK

The work of this thesis addresses the need for rapid, pre-treatment HIFU QA to enable the progression of this promising technique from laboratory to regular clinical use. In this chapter, the techniques developed to enable implementation of a cavitation-based pressure mapping tool are reviewed. Suggestions are made to further the viability of this approach, with the intention of providing a clinically accepted method for cavitation-based HIFU QA.

6.1 CONCLUSIONS

Despite its great promise, clinical approval of HIFU therapy can only be achieved with adequate, standardised QA procedures in place. Current HIFU QA procedures offer either accurate spatial calibration at the expense of impractically long acquisition times, or more rapid characterisation that provides only a spatially averaged measure of performance. Exploitation of acoustically induced inertial cavitation, however, offers the potential for rapid pre-treatment spatial calibration without the need for time consuming scanning routines. The main aim of this thesis has, there-

fore, been to develop a cavitation-based pressure mapping tool for this very purpose.

The concept of cavitation-based characterisation of clinical HIFU fields was validated for the first time in Chapter 3. This was achieved by implementing passive acoustic mapping algorithms, firstly on an array of hydrophones and secondly using a clinical ultrasound imager, to identify the change in size of the cavitating region as the HIFU transducer excitation amplitude is increased. A novel tissue-mimicking material of sufficient consistency for cavitation-based QA was also identified and tested for the first time, consisting of 3% agar seeded with talc particles to maximise the magnitude and spatial uniformity of cavitation occurrences. The phantom provides a highly repeatable cavitation threshold of 1.52 MPa_{PRFP} at 1.06 MHz and 1.42 MPa_{PRFP} at 508 kHz, remaining stable both 24 and 48 hours after preparation.

Passive imaging of cavitation emissions in the three focal planes of the HIFU transducer using a single linear array yields a source distribution which correlates well with the values obtained from hydrophone-based field characterisation. As well as indicating focal pressures, the method clearly identifies abnormalities in the HIFU field. For the 1.06 MHz transducer used in Chapter 3, this is verified by consistent observation of cavitation activity in its discontinuous side-lobes beyond 2.93 MPa_{PRFP} at $y \approx \pm 2.2 \text{ mm}$. Whilst two-dimensional imaging in all three focal planes requires a certain amount of user intervention that would be clinically impractical, the technique adopted offers a viable method for pre-treatment HIFU QA using readily available hardware that requires minor software modifications.

This leads to the notion of a novel, standalone, three-dimensional calibration tool for rapid HIFU QA in a clinical setting, as introduced in Chapter 4. Mapping in three dimensions clearly requires a large number of precisely positioned receiving elements, ideally arranged in a cylindrical configuration so as to enclose the HIFU

focal volume. The search for a cost-effective solution led to the use of a novel manufacturing technique wherein the active piezoelectric material (PVDF) is sandwiched between two PCBs: this has the effect of forming active area only where the conductive tracks on the front and back PCBs overlap, thereby eliminating sensitivity to stray acoustic signals along the electrode path.

An important consideration is the combined effect of the multiple layers of the composite array on its frequency-dependent sensitivity. The properties of the piezopolymer were characterised by fitting an analytic expression for input impedance to experimental data, and used to inform subsequent equivalent circuit and finite-element simulations of the composite response. Extension of the equivalent circuit calculation scheme proposed by Kervel and Thijssen, to include the effect of multiple backing layers, yields a predicted frequency spectrum with a peak location within 1.2% of that predicted by finite element analysis and 12% of the experimentally measured value.

As regards the absolute sensitivity of the composite array, both models overpredict the measured response, although the inclusion of piezoelectric losses in the equivalent circuit model provides a better overall match. Crucially, this frequency response differs significantly from the typical receive sensitivity spectrum of a single PVDF sheet, highlighting the usefulness of the extended equivalent circuit model to account for additional PCB layers in the design of multiple-layer PCB-PVDF arrays. Modification of either the backing impedance or magnitude of loss tangents produces a closer match to the observed response, though developing a physical explanation for this remains the subject of future work. The extended equivalent circuit model was thence used to select a PVDF film thickness for the proposed array. A 60 μm film provides a peak in sensitivity closest to the centre of the expected cavitation signal spectrum, with sufficient sensitivity to capture emissions across the 1-7 MHz

range.

In Chapter 5, the cylindrical array design was finalised by considering the optimal size, number and geometric configuration of receiving elements for accurate localisation of broadband sources. Small elements (less than 3.5° aperture or 2.3 mm side length) were found, by computational and experimental analysis, to offer more accurate localisation of off-axis sources by limiting phase averaging across the active area. Moreover, a random configuration of elements reduces grating lobe levels by limiting the likelihood of constructive interference at a regular distribution of points throughout the field of interest. Higher spatial resolution is achieved using a large number of elements; however, this adds both complexity and expense to the overall system. Consequently, the second-generation array design consists of 50 elements, each 1mm in radius, randomly distributed around a cylindrical shell, and manufactured using the multiple-layer PCB-PVDF technique introduced in Chapter 4.

Experimental evaluation of the final array design using bespoke pre-amplification and data acquisition hardware produced some useful results. The array is capable of detecting broadband emissions, which increase in both amplitude and temporal extent with increasing insonation amplitude. Although reconstruction of the acoustic emissions acquired across 32 elements of the array does not presently generate accurate cavitation maps, the restricted array performance can be attributed to unforeseen complications with electrical isolation.

Investigation into the limited imaging performance led to the characterisation of crosstalk, which has the effect of compromising the spatially discrete nature of individual elements. A 3.5 MHz focused transducer was used to target each array element in turn, confirming the significance of crosstalk: on average, elements were observed to detect signal leakages from 8 of their neighbours. To eliminate this ef-

fect, it is proposed that an alternative construction method is adopted, which aims to maintain electrical isolation between the active area and pre-amplification circuitry. Suggestions for appropriate manufacturing techniques are considered as part of the future work detailed in the following section.

6.2 FUTURE WORK

A number of advancements to the work of this thesis are possible, which would aim to improve its applicability and aid the progression towards regular use in a clinical setting. In the immediate future, the two-dimensional technique using a linear array would benefit from evaluation of its performance with a range of clinical devices, thereby demonstrating its wider applicability. Modelling methods could be improved by including mechanical losses and considering the accuracy of the material properties used, whilst three-dimensional characterisation could be achieved by investigating alternative array construction techniques.

6.2.1 Two-Dimensional Cavitation-Based Pressure Mapping

It has been shown that a medical diagnostic linear array may be used for two-dimensional cavitation-based HIFU QA, which correlates well with hydrophone-based field characterisation and correctly identifies any abnormalities in the HIFU field. Clinical acceptance of this technique would, however, require further investigation into its performance using a range of clinical HIFU transducers. Each transducer is likely to vary in fundamental frequency and achievable focal pressure amplitude. Though typical frequencies and focal pressures have been considered in this work, it may be necessary to tailor the cavitation threshold of the TMM to the

transducer. This could be achieved by offering a range of TMMs, each intended for a subset of PRFPs and frequencies, with varying thresholds adjusted by appropriate preparation (de-gassing) and addition of cavitation nuclei.

Furthermore, in cases where clinics are equipped with a removable diagnostic array that could be positioned in the axial and transverse orientations for more accurate field characterisation, user intervention could be minimised by the manufacture of an array / TMM mount. This would allow alignment of the array in relation to the TMM without the added complexity of positioning stages. Moreover, if multiple probes were available, such a mount could be used to position each array so as to acquire data simultaneously in several imaging planes, in effect offering three-dimensional field characterisation.

Currently, the processing of data acquired using the linear array requires transfer to a PC for reconstruction. With parallel computing techniques, processing times have been limited to several seconds per frame; however, real-time (on the order of 20Hz) reconstruction could be achievable using graphical processing techniques. If this could be implemented on the scan engine itself, truly real-time cavitation-based HIFU QA would become a reality.

6.2.2 Improvements to Models

Whilst the models presented in Chapter 4 provide a useful tool for estimating the shape of the frequency-dependent sensitivity of a given multiple layer PCB-PVDF array, improvements could be made to allow more accurate estimation of absolute values. The piezoelectric properties that were measured experimentally are believed to accurately describe the behaviour of the piezo-polymer; however, the mechanical properties of each material were taken from published results, and so

may not accurately represent the materials used. Measurement of these parameters as well as the inclusion of mechanical losses in the PCB layers would likely improve the accuracy of the model, providing a better fit to measured results.

6.2.3 Three-Dimensional Cavitation-Based Pressure Mapping

The element size, number and configuration required for three-dimensional reconstruction of a distribution of broadband sources was optimised in Chapter 5. Simulation of the -3 dB PSF beam widths of the resultant 50-element design yielded resolutions in the x -, y - and z -axes of 0.58 mm, 0.57 mm and 1.58 mm respectively, which compare favourably with those of the linear array used in Chapter 4. Unfortunately, the performance of the physical array was hampered by high levels of inter-element crosstalk. Efforts to remove this effect would focus on maintaining electrical isolation of individual array elements.

The cylindrical array evaluated in Chapter 5 made use of 0.5 mm pitch Zero Insertion Force (ZIF) connectors to attach the exposed pads of the PCB tracks to a break-out board for connection to pre-amplifiers via coaxial cables. Crosstalk levels may well be reduced by increasing the pitch of these connections, requiring a redesign of the board to allow more spacing between individual tracks. ZIF connectors are, however, limited in pitch to around 2 mm, which may not provide adequate isolation. Further issues may be introduced by the presence of long track lengths on the rear PCB, designed to ensure tracks for each element exit the cylindrical array at one end, for ease of connection and waterproofing. As well as acting as a possible antenna for RF interference, this may increase the potential for signal to leak from one element to another, and so minimising track length could prove useful.

Alternatively, a construction method could be adopted which more closely re-

sembles that of the NPL prototype array validated in Chapter 5. Though the large elements of this device were shown to exhibit poor spatial sensitivity, it is conceivable that a similar construction method, in which coaxial connections to individual elements are formed via nylon bolted electrodes, could be used to arrange multiple, smaller array elements in a cylindrical configuration. Whilst electrical isolation may be maintained with such a method, this comes at the expense of physical size and accuracy of element positioning. The minimum element size would be limited by dependence on mechanical bolted connections, whilst manual positioning of individual elements would not offer the precision afforded by the etching technique used for the PCB-PVDF composite. Inaccuracies in positioning could, however, be overcome by acoustic localisation of element positions post-manufacture, using a scattered signal and multilateration techniques.

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