A PVDF Receiver for Ultrasound Monitoring of Transcranial Focused Ultrasound Therapy

Meaghan A. O'Reilly and Kullervo Hynynen*

Abstract-Focused ultrasound (FUS) shows great promise for use in the area of transcranial therapy. Currently dependent on MRI for monitoring, transcranial FUS would benefit from a realtime technique to monitor acoustic emissions during therapy. A polyvinylidene fluoride receiver with an active area of 17.8 mm² and a film thickness of 110 μ m was constructed. A compact preamplifier was designed to fit within the receiver to improve the receiver SNR and allow the long transmission line needed to remove the receiver electronics outside of the MRI room. The receiver was compared with a 0.5 mm commercial needle hydrophone and focused and unfocused piezoceramics. The receiver was found to have a higher sensitivity than the needle hydrophone, a more wideband response than the piezoceramic, and sufficient threshold for detection of microbubble emissions. Sonication of microbubbles directly and through a fragment of human skull demonstrated the ability of the receiver to detect harmonic bubble emissions, and showed potential for use in a larger scale array. Monitoring of disruption of the blood-brain barrier in rats showed functionality in vivo and the ability to detect subharmonic, harmonic, and wideband emissions during therapy. The receiver shows potential for monitoring acoustic emissions during treatments and providing additional parameters to assist treatment planning. Future work will focus on developing a multi-element array for transcranial treatment monitoring.

Index Terms—Blood-brain barrier (BBB), focused ultrasound (FUS), polyvinylidene fluoride (PVDF) hydrophone, transcranial therapy.

I. INTRODUCTION

OCUSED ultrasound (FUS) shows promise in transcranial applications, including tissue ablation [1]–[6] and disruption of the blood–brain barrier (BBB) [7]–[12]. The complex geometry of the skull and the high attenuation of sound through bone create unique challenges for transcranial therapy. Several methods have been used, with success, to overcome the high levels of attenuation and aberration through the skull and produce a sharp transcranial focus. These include low-frequency focused

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M. A. O'Reilly is with the Department of Imaging Research, Sunny-brook Health Sciences Centre, Toronto, ON, M4N3M5, Canada (e-mail: moreilly@sri.utoronto.ca).

*K. Hynynen is with the Department of Imaging Research and the Centre for Research in Image-Guided Therapeutics, Sunnybrook Health Sciences Centre, Toronto, ON, M4N3M5, Canada, and also the Department of Medical Biophysics, University of Toronto, Toronto, ON M4N3M5, Canada (e-mail: khynynen@sri.utoronto.ca).

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transducers [1], shear wave transmission [13]–[15], and phased arrays [1], [2], [4], [5], [16].

Transcranial FUS currently relies on MRI to monitor therapy, which only provides information on the temperature elevation and the effect of the therapy (such as tissue coagulation and BBB disruption (BBBD) after the exposure) and does not provide feedback on the generated sound field itself. Although MRI-monitored thermal effects are of importance, equally important are the indicators of nonthermal effects, such as the interaction of contrast agent microbubbles with the generated sound field in BBBD [8]. The addition of diagnostic capabilities to a transcranial therapy transducer would not only allow for non-thermal treatment effects to be monitored, but could also provide important information regarding the generated sound field

Cavitation detection, both active [17] and passive [18], [19], is a well-established field of study. Cavitation has been investigated as a means to monitor different ultrasound therapy procedures [20]–[23]. In BBBD, the appearance of harmonic signal components has been shown to correlate with disruption [8]. This could eventually lead to BBB therapy conducted independently of MRI. In that study, a narrow band receiver was used and low-frequency noise made detection of subharmonics impossible. A sufficiently wideband receiver would allow for acquisition of signals with more complete spectral information, without receiver-induced limitations. Further, in thermal applications where inertial cavitation is of interest, or of concern, the receivers would allow monitoring of the bubble activity, which could be correlated with the tissue-heating information gained from MRI.

Polyvinylindene fluoride (PVDF) is a piezoelectric polymer that has been extensively used in medical ultrasound [24]. Although PVDF has been used in high-frequency imaging transducers [25], the acoustic power output from PVDF transducers is much less than from piezoceramic transducers [26], thus making PVDF transducers unsuitable for therapeutic purposes. However, PVDF's high sensitivity, broadband response, and close acoustic match to water make it an excellent material choice for ultrasound receivers, and it has been widely used in needle and membrane hydrophones [24], [27]–[30]. PVDF has previously been used to monitor acoustic cavitation [31], and we hypothesize that PVDF receivers may be used in combination with piezoceramic therapy elements to create a therapeutic transcranial array with monitoring capabilities.

The 1372-element phased array presented by Song and Hynynen [16] consists of laterally coupled piezoceramic ring elements operating in extension mode and set within a hemispherical dome of 30 cm diameter. PVDF receivers placed

in the middle of the rings and aligned with the acoustic axes of the individual elements would allow the individual hybrid elements to act in a transmit-receive mode, and would make use of the available space within the ring elements. Multiple receivers would allow microbubble harmonic emissions or broadband inertial cavitation emissions to be detected and localized using passive beam-forming techniques [32]–[34] and possibly used to control the exposure [8]. Unfortunately, commercially available hydrophones are expensive, not MRI compatible, and often too large to be used for this purpose with arrays that have a large number of elements. Therefore, alternatives are required in order to be able to harness the control potential of the acoustic emissions from the oscillating microbubbles in the brain vasculature. The goal of the current research is to create a lowcost, MR-compatible wideband receiver with high sensitivity and a flat response over the frequency range of approximately 100 kHz-1.5 MHz, corresponding to clinically relevant frequencies in transcranial therapy. Further, the receiver must be designed so as to be contained within and function in combination with one of the previously described cylindrical transmit elements to form a dual-purpose pair.

In this paper, a low cost, MRI-compatible, and miniature PVDF receiver is presented and directly compared with a commercial needle hydrophone. The ability of the PVDF receiver to function in combination with a ceramic transmit element is demonstrated. Microbubbles were sonicated through a fragment of human skull, establishing the proposed receiver's ability to detect transcranial harmonic emissions. Finally, the receiver was implemented to monitor BBBD in rats and to demonstrate its ability to detect differences between signals emitted during sonications producing different biological effects. Preliminary results from this study have been reported [35].

II. MATERIALS AND METHODS

A. Receiver Construction

Hundred and ten micrometer thick metalized PVDF film (Measurement Specialties, Inc., Hampton, VA, USA), with NiCu electrodes (700 Å Cu, 100 Å Ni) and an active area of approximately 17.8 mm², was stretched across brass tubing having a diameter of 4.76 mm. A thin electrically insulating layer (Glad Press'n Seal wrap) was applied around the tubing, leaving the face of the tube exposed. A second length of brass tubing, which had been worked to create a rim at the top edge, was used to clamp the PVDF film. Fig. 1 shows the PVDF film resting between the uninsulated face of the inner tube and the worked rim of the outer tube, with these two surfaces forming the electrode connections. The tubes were held together using a nylon-set screw. Signal and ground connections were made to the internal and external brass tubes, respectively, as shown in Fig. 1.

A small preamplifier with 20 dB of gain was constructed and enclosed within the brass tubing to improve the receiver SNR and to drive the long coaxial cables required to reach outside the MRI. The tubing was sealed to provide air backing, and the receiver was mounted through a piece of cork-backed acrylic inside a PZT-4 cylinder element ($h=6\,\mathrm{mm}$; internal

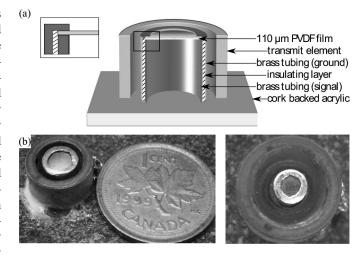


Fig. 1. (Top) Cut section showing receiver construction. The PVDF film is clamped between two brass tubes. (Bottom left) Large receiver and transmit element pair. (Bottom right) Small receiver and transmit element pair.

diameter = 7 mm; external diameter = 10 mm; and length mode resonance frequency $f=306~\mathrm{kHz}$), similar to the ones used in an existing 1372-element transcranial array [16] [see Fig. 1(b)]. In air-backing the receiver, some bandwidth was sacrificed in order to be able to enclose the preamplifier entirely within the receiver. Parylene coating was applied to electrically insulate the device and to prevent corrosion. A second smaller receiver with a diameter of 2.4 mm was constructed using the same method in order to examine the feasibility of reducing the receiver's active area to improve the field of view.

B. Preamplifier Design and Characterization

To minimize the electrical noise introduced to the system, the preamplifier had to be contained within the grounded brass tubing, limiting the circuit-board dimensions. Additionally, an op-amp with a large bandwidth was desired to avoid narrowing the bandwidth of the receiver beyond the range of interest. The selected op-amp (FHP3131, Fairchild Semiconductor Corporation, California, USA) has a unity gain bandwidth of 70 MHz and component dimensions of $1.45 \times 1.00 \times 0.55$ mm (6 Lead MicroPak). The circuit, shown in Fig. 2, provides 20 dB of gain. The resulting single-sided circuit board was constructed in-house and had board dimensions of 7.1×1.8 mm.

The response of the preamplifier circuit over a range of frequencies (0.1–5 MHz), rail voltages, and coaxial cable lengths was examined, both with and independent of the PVDF receiver.

C. MRI Compatibility

The receiver was imaged in an 1.5 T MRI (Signa 1.5 T, General Electric, Fairfield, Connecticut, USA) to determine the level of interference, if any, with the MRI. A sonication was performed during MR image acquisition to demonstrate functionality of the device in the MRI.

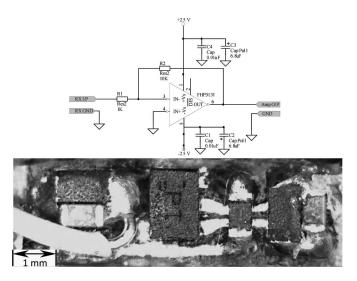


Fig. 2. (Top) Preamplifier circuit diagram. (Bottom) Populated circuit board.

D. Receiver Characterization

The receiver sensitivity was measured at the fundamental frequency and third harmonic of the transmit element using a characterized element and was compared with both a 0.5 mm commercial needle hydrophone (Precision Acoustics Ltd., Dorset, U.K.) and a PZT-4 element of the same size and shape as the receiver. The sensitivity of the receiver was further measured at four frequencies ranging from 649 kHz to 4.589 MHz using an existing, in-house constructed, calibrated transducer. Both the transmit element and calibrated transducer were calibrated using a scanning laser vibrometer (PSV-400 Scanning Vibrometer, Polytec, Waldbronn, Germany) to measure the particle velocity of a membrane placed normal to the acoustic axis and at a fixed distance from the transducer [36]. The peak pressures resulting from different excitation voltages were then calculated. The SNR of the receiver and the hydrophone were compared when each device was used in receive mode only, by placing the receiver and hydrophone in the field, and when acting in a transmit/receive pair. For this comparison, the needle hydrophone was mounted through the center of the transmit element in the same configuration, as the constructed receiver. A function generator (AFG3102, Tektronix, TX, USA) was used to send a pulse train to a power amplifier (KAA2030, AR, Washington, USA), and then to the transmit element. The receiver signal was received using a signal amplifier (DA1820 A, LeCroy, Chestnut Ridge, NY, USA) and digital oscilloscope (TDS3014B, Tektronix). The signals were transferred from the oscilloscope to the computer using a general purpose interface bus (GPIB) interface and LABVIEW software (National Instruments, TX, USA). Data analysis was performed in MATLAB (Mathworks, MA, USA).

The thresholds for detection of various microbubble emissions were established by sonicating a solution of Definity contrast agent (Lantheus Medical Imaging, MA, USA) in a thin-walled tube (0.0152–0.0203 mm double-wall thickness, 2 mm diameter medical balloon; Advanced Polymers, Inc., NH, USA) using a 0.548 MHz spherically focused therapy trans-

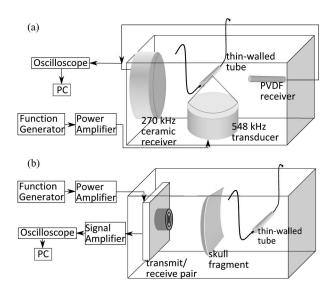


Fig. 3. (a) Experimental setup, receiver characterization. (b) Transcranial bubble excitation setup.

ducer (5 cm aperture, f-number = 1), as shown in Fig. 3(a). A focused passive transducer (5 cm aperture, f-number = 2) with a center frequency of 0.270 MHz was cofocused with the therapy transducer at the tubing. Focusing was achieved using a 0.10 μ m planar fiber-optic hydrophone (Precision Acoustics Ltd.). The PVDF receiver was then aligned with the tubing opposite the passive receiver. Ten millsecond bursts were delivered with increasing focal pressure until wideband emission was detected. Waveforms from each burst were captured using a LeCroy WavePro 715Zi oscilloscope (LeCroy) and transferred to computer for analysis in MATLAB.

The directivity of the receiver was measured using a ring transmit element that was mounted at the end of a rotational arm and was used to sonicate the receiver at the center of rotation. The signal strength was measured for 180° of incidence in 5° steps. This was performed for the fundamental frequency (306 kHz) and the third harmonic of the transmit element (830 kHz). The measured results were compared with the theoretical values obtained using the normalized far-field directivity function for a circular piston [37]

$$D(\theta) = \frac{2J_1 \left[(2\pi a/\lambda) \sin \theta \right]}{(2\pi a/\lambda) \sin \theta}$$
 (1)

where J_1 is the first-order Bessel function of the first kind, a is the radius of the receiver, and λ is the wavelength.

E. Transcranial Bubble Excitation

The transmit/receive pair was used to excite a solution of Definity contrast agent in a thin-walled tube (0.0152–0.0203 mm double-wall thickness, 2 mm diameter medical balloon) both directly and in the presence of a fragment of human skull. The experimental setup is illustrated in Fig. 3(b). The thin-walled tube was mounted in a tank filled with degassed, deionized water. Rubber (Neoprene 70 durometer, Global Rubber Products Ltd., Toronto, ON, Canada), with approximately 4.5% reflected intensity at 1 MHz based on tests conducted in this laboratory,

was used as an absorber to reduce unwanted reflections from the tank walls and bottom. To further reduce the impact of reflections, short bursts were used. All sonications consisted of ten cycle bursts at 10 ms intervals. The transmit/receive pair was mounted on a three-axis stage and was aligned with the thinwalled tube by maximizing the reflection from the tube when it was filled with air. After alignment, the tube was filled with degassed water and a reference sonication was performed. The captured reference waveform was subtracted from subsequent sonications to remove the reflections from the tubing, tubing mount, and other parts of the tank, as well as reduce the effects of coupling with the transmit element. Attempts were made to repeat the experiment with the commercial hydrophone; however, alignment of the hydrophone with the tubing was impossible, as the reflected signal was completely lost in the electrical coupling with the transmit element.

The acoustic pressure at the tubing was measured using the 0.5 mm needle hydrophone. The waveforms captured using the needle hydrophone were analyzed to confirm that no harmonic signals were present in the outgoing therapy pulse. The hydrophone was then removed and 25:1 and 100:1 solutions of Definity contrast agent were injected into the tubing, which was then sonicated using the transmit element. Reflected waveforms detected with the PVDF receiver for each solution were recorded. Pulse inversion techniques [38] were used to amplify the harmonic components of the reflected waveform. A fragment of human skull was placed between the transmit/receive pair and the tubing, and the alignment, hydrophone pressure measurements, and reference waveform acquisition procedures were repeated. Sonications were performed for 100:1, 25:1, and 10:1 Definity solutions. A second transmit element was used to increase the pressure at the tubing and sonications were repeated. Measurement of the acoustic pressure at the tubing using the needle hydrophone was performed to ensure that the addition of the second transmit element had increased the local acoustic pressure rather than causing phase cancellations.

F. In Vivo Monitoring of BBBD

The receiver was used to monitor disruption of the BBB in rats to examine its effectiveness in monitoring transcranial therapy, given more realistic concentrations of microbubbles and realistic therapeutic pressures. Disruption of the BBB was performed in six rats using a 558 kHz spherically focused transducer (10 cm diameter and 78 mm focal length), and the three-axis positioning system described by Chopra et al. [39]. To avoid introducing harmonic components to the transmitted pulse, the therapy transducer was matched to 50 Ω at 558 kHz using an external matching circuit, and the power input to the RF power amplifier was kept far below the saturation point of the amplifier, as measured with a 50 Ω load. Ten millisecond ultrasound bursts were delivered at a repetition frequency of 1 Hz for 2 min. The applied electrical power was kept constant during the bursts of each sonication, but it was varied from sonication to sonication between 0.24 and 1.17 W, at an efficiency of approximately 76%, which corresponds to an applied acoustic power range of 0.18– 0.88 W. The corresponding peak-negative pressure amplitudes

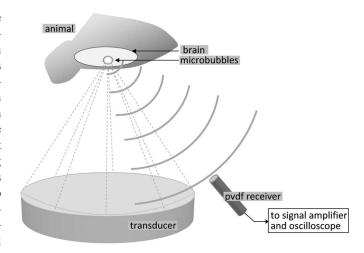


Fig. 4. Positioning system arm with transducer and PVDF receiver.

in situ were estimated to be 0.14–0.33 MPa taking the attenuation in the brain to be approximately 5 (Np·m⁻¹)/MHz [40] and assuming the transmission through rat skull to be approximately 73%, based on previous measurements taken in this laboratory. The peak-negative acoustic pressure amplitude was calibrated using a scanning laser vibrometer (PSV-400 Scanning Vibrometer, Polytec) and the acoustic power output using a radiation force measurement system with an absorbing target [41]. The PVDF receiver was mounted on the positioning arm, directed toward the focus, as illustrated in Fig. 4. The signal was amplified using a 35 dB gain MITEQ preamplifier (AU 1583, MITEQ, New York, USA), in addition to the built-in 20 dB gain preamplifier, and captured using a LeCroy WavePro 715Zi oscilloscope (LeCroy). Waveforms were captured and stored approximately every 3 s for the duration of the sonications.

Six animals (Wistar; 303-380 g) were anesthetized using a mixture of ketamine (40-50 mg/kg) and xylazine (10 mg/kg) injected intraperitoneally. Their heads were shaved and depilated to remove hair from the ultrasound path. The animals were placed supine on the positioning system table with their heads over the transducer, in contact with the water. Single-point sonications were performed at four separate locations in each rat. Sonication locations were selected from T2-weighted MR images taken in a 1.5-T MRI (Signa 1.5 T, General Electric). A bolus of Definity contrast agent (0.02 mL/kg) was injected, via a tail vein catheter, immediately before the start of sonication. A minimum delay of 4 min was allowed between sonications to allow the contrast agent to clear from the system. Opening was confirmed via contrast-enhanced (OmniScan, 0.2 mL/kg) T1weighted MRI images, and T2-weighted images were used to check for edema (see Table I). In two rats, sonication of the first location was performed at low power, and when BBBD was not observed, the same locations were sonicated a second time using a higher power. A total of 26 sonications were performed at 24 separate locations. Waveforms were analyzed using MATLAB and results were compared with the captured MR images.

Thorough reviews of acoustic emissions during cavitation exist [42], [43] and will therefore not be covered in depth in this paper. During analysis, the presence of harmonics,

TABLE I
MR PARAMETERS

Scan Type	T1-weighted	T2-weighted
Sequence	FSE	FSE
TE	10 ms	60.6 ms
TR	500 ms	2000 ms
ETL	4	4
FOV	6 cm x 6 cm	6 cm x 6 cm
Slice Thickness	1 mm	1 mm
Matrix	128 x 128	128 x 128

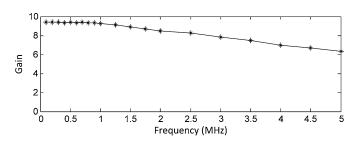


Fig. 5. Frequency response of the preamplifier.

subharmonics, and ultraharmonics were considered to mark microbubble presence and stable cavitation, whereas inertial cavitation was identified by a sharp rise in broadband emissions. To account for harmonics arising from the nonlinearity of the tissue and water, harmonic signal strengths were considered relative to the waveform acquired at time t=0 s, when contrast agent would not be present.

III. RESULTS

The preamplifier produced high gain over a reasonable frequency range. The -3 dB point of the gain occurred around 4 MHz, with roll-off beginning around 1 MHz (see Fig. 5).

Supplied rail voltages and load had little effect on the gain of the amplifier, which was able to drive loads across coaxial cable lengths of 8.5 m without loss of signal strength (81 mV peak-to-peak for a 1.5-m cable; 82 mV peak-to-peak for a 8.5-m cable), sufficient to drive the signal outside the MRI.

Imaging of the device revealed small artifacts near solder points (see Fig. 6). The artifacts did not extend far from the surface of the device and would therefore not interfere with imaging of the brain during therapy. Waveforms captured while in or near the MRI bore while the MRI was not imaging showed little or no distortion (see Fig. 6). Acquiring MR images while simultaneously operating the device in pulse—echo mode added some distortion to the ultrasound signal (see Fig. 6). However, the frequency content of the signal was not substantially altered, and even at low amplitudes the reflected waveforms were still discernable.

The sensitivity of the PVDF receiver (1.62 ± 0.09 V/MPa at 306 kHz and 1.38 ± 0.16 V/MPa at 830 kHz) was 6.8 times and 4.1 times that of the 0.5 mm commercial hydrophone (0.24 ± 0.01 V/MPa at 306 kHz and 0.34 ± 0.03 V/MPa at 830 kHz) at 306 and 830 kHz, respectively. By comparison, the smaller

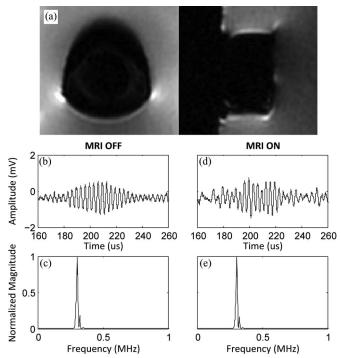


Fig. 6. (a) MR images of receive/transmit pair in water. (b) Pulse echo while in MRI bore with MRI off. (c) Frequency spectrum from 0 to 1 MHz while in MRI bore with MRI off. (d) Pulse echo while in MRI bore while acquiring MRI. (e) Frequency spectrum from 0 to 1 MHz while in MRI bore while acquiring MRI.

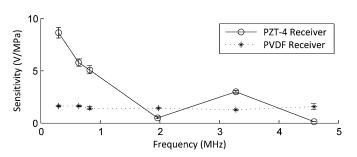


Fig. 7. Sensitivity of the PVDF receiver corrected for the preamplifier characteristics and sensitivity of a PZT-4 reciever with the same effective area. Error bars indicate one standard deviation.

receiver sensitivities were 0.88 ± 0.03 V/MPa at 306 kHz and 1.12 ± 0.09 V/MPa at 830 kHz. As expected, the PZT-4 had a much higher sensitivity than the PVDF (see Fig. 7); however, it also had a greater variation in sensitivity over the range examined. At higher frequencies, the receiver displayed a similar frequency response to the preamplifier, rolling-off around 1 MHz. Correcting for the response of the preamplifier, a flat trend was obtained (see Fig. 7). The sensitivity variations in the corrected response are consistent with the variations at low frequency observed in needle-type polymer hydrophones [44], [45], although the expected periodic nature of these fluctuations due to finite-aperture effects and reflections along the brass tubing may be not be completely visible, given only a few data points. Since frequencies above 1.5 MHz are not expected to be detected through the human skull due to the large attenuation

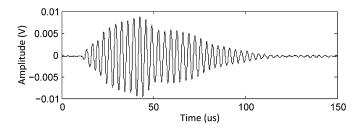


Fig. 8. Response of the receiver during sonication into free field.

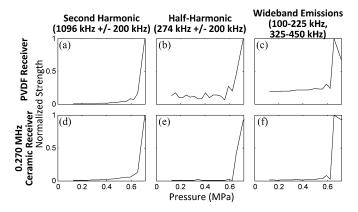


Fig. 9. Area under the fast Fourier transform (FFT) curve from the PVDF receiver with increasing pressure for (a) second harmonic 1096 kHz \pm 200 Hz, (b) half-harmonic 274 kHz \pm 200 Hz, and (c) wideband emissions (100–225 kHz and 325–450 kHz). Area under the FFT curve from the ceramic receiver with increasing pressure for (a) second harmonic 1096 kHz \pm 200 Hz, (b) half-harmonic 274 kHz \pm 200 Hz, and (c) wideband emissions (100–225 kHz and 325–450 kHz).

through the skull associated with higher frequencies [46], the response of the receiver was accepted.

Both devices demonstrated a high SNR when used in receive-only mode. The SNR of the PVDF receiver was 61.1 ± 4.9 , while that of the commercial hydrophone was 90.8 ± 6.2 . However, when used in the transmit/receive configuration, the commercial hydrophone was more susceptible to electrical coupling with the transmit element. In this instance, the SNR of the hydrophone decreased to 0.41, compared with an SNR of 16.43 for the PVDF receiver. A single waveform was used for this comparison, as it proved too difficult to repeatedly capture the reflected waveform with the needle hydrophone.

When placed inside the transmit element, the receiver was also subject to acoustic coupling with the transmit element (see Fig. 8). This signal component was removable through filtering of the fundamental frequency during post-processing. In the intended application of monitoring therapy, this would leave the signal components of interest, namely the microbubble harmonic emissions and any wideband emissions.

The PVDF receiver was able to detect different types of microbubble emissions at the same time as the 5 cm aperture passive detector (see Fig. 9). The focused detector with a center frequency near the transmit subharmonic and harmonics near the transmit ultraharmonic frequencies had stronger sub- and ultraharmonic signal components than the PVDF. However, the transmit harmonic frequencies detected by the PVDF receiver

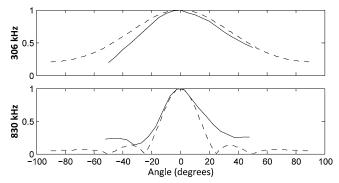


Fig. 10. Measured and theoretical directivity of the receiver at (top) 306 kHz and (bottom) 830 kHz. Calculated theoretical values are shown with a dashed line.

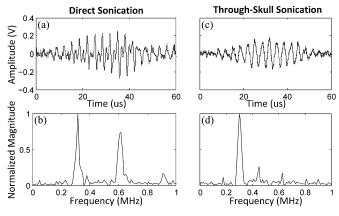


Fig. 11. (a) Waveform and (b) frequency spectrum for direct sonication of a 25:1 solution of Definity contrast agent. (c) Waveform and (d) frequency spectrum for through-skull sonication of a 10:1 solution of Definity contrast agent. The timing shown in (a) and (c) are to show scale, and time t=0 marks the start of the waveform capture.

were an order of magnitude stronger than those detected by the focused detector.

The measured directivity of the receiver was a close match to the calculated theoretical values for the first and third harmonics of the transmit element (see Fig. 10). At a distance of 15 cm, the fundamental frequency can be detected to approximately ± 7 cm from the acoustic axis (3 dB point). However, this range decreases to approximately ± 2.6 cm at 830 kHz.

When directly sonicating the thin-walled tubing, a peak pressure of approximately 46 kPa was measured using the needle hydrophone. The reflected waveforms for both the 25:1 and 100:1 solutions of Definity showed an increase in signal amplitude over the reference sonication, and the presence of harmonic components indicated the detection of the microbubbles (see Fig. 11).

After the addition of the skull fragment, the pressure at the tubing decreased to 22 kPa. An increase in received waveform amplitude was seen for Definity concentrations of 10:1 and 25:1; however, harmonic signal components were not detected (see Fig. 11). The peak received pressures were approximately 1.1 kPa (5%) and 0.6 kPa (2.5%) for the 10:1 and 25:1 solutions, respectively. At a concentration of 100:1, no distinct difference from the reference waveform was visible.

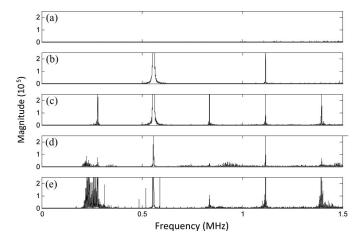


Fig. 12. FFTs showing different signal types received. (a) Receive baseline noise level. (b) Fundamental frequency and second harmonic. (c) Harmonics and sub/ultraharmonics. (d) Harmonics and broadband noise. (e) Harmonics, sub/ultraharmonics and broadband noise.

After the addition of a second transmit element, a small second-harmonic component was detected for a concentration of 25:1.

In vivo, opening of the BBB was observed for 23 of 26 sonications. Harmonic signal components were detected for all sonications. Sub- and ultraharmonics were detected for 12 locations, all of which showed edema in the T2-weighted images. Only one sonication produced edema without the detection of subharmonics. Additionally, no subharmonics or ultraharmonics were detected at locations where edema had not occurred. Inertial cavitation was detected at five locations, which had been sonicated at high power (four locations at 0.27 MPa peak-negative pressure and one location at 0.33 MPa peak-negative pressure), all of which experienced notable edema. Fig. 12 shows sample spectra from the in vivo work displaying the different types of signal components observed: baseline noise, harmonics, suband ultraharmonics, and wideband emissions. Fig. 13 shows T1 and T2 images of a rat brain sonicated in four locations with increasing pressure applied at each location. The ultrasound frequency spectra for the four locations are shown in Fig. 13(e) and (f). Opening of the BBB at three locations can be seen on the T1-weighted image, of which edema is visible in two locations in the corresponding T2-weighted image. Spurious peaks were seen on the frequency spectra from some sonications. These seem to be an artifact of the MRI and may be dependent on the receiver position within the field.

IV. DISCUSSION

The presented receiver shows great potential for use in ultrasound monitoring of transcranial therapy. Positive results were achieved in bench-top work and *in vivo*, and comparison with a commercial hydrophone demonstrated the performance advantage of the constructed receiver. In addition, the MRI compatibility and low-cost of the receiver make it suitable for the proposed application in a large-scale, MRI-guided array. The manufacturing cost of the PVDF receiver was less than \$15 (CAD) in parts. This is a small fraction of the cost of commercial needle

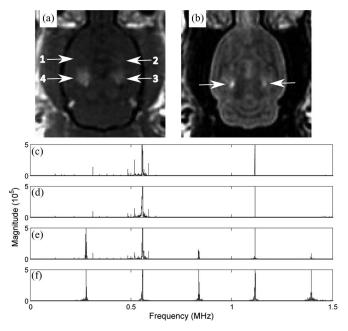


Fig. 13. (a) Contrast-enhanced T1-weighted image showing enhancements at sonication locations 2, 3, and 4. (b) Corresponding T2-weighted image showing edema at locations 3 and 4. Frequency spectra from 0 to 1.7 MHz for (c) location 1 (0.15 MPa), (d) location 2 (0.18 MPa peak-negative pressure), (e) location 3 (0.22 MPa peak-negative pressure), and (f) location 4 (0.27 MPa peak-negative pressure).

hydrophones, and would make construction of a large receiver array more economically feasible than if commercial hydrophones were used.

Due to the nature of therapeutic ultrasound and, more specifically, transcranial therapy, there is a greater interactions between transmit and receive components than in diagnostic ultrasound. The ability to receive while transmitting is necessary to allow for real-time monitoring. For transcranial therapy, lower frequencies are also desired as the attenuation and phase aberration through the skull increases greatly with increasing frequency [1]. It should be noted that while low frequencies can give rise to complications, such as standing waves in the skull cavity, their use is a necessary compromise to ensure ultrasound transmission transcranially while minimizing focal distortion. The resulting long outgoing pulses may interact both electrically and acoustically with the receiver, and some degree of interaction between transmit and receive sides may be present when the reflected waveform is detected. If isolation of the device is poor, the reflected waveforms may be indiscernible from the coupling contributions. Gating the therapy pulses to reduce the interference between transmit and receive elements may be possible. However, investigation of the effects of a reduced duty cycle on BBBD would be required to ensure that this did not influence treatment efficacy. The proposed use of the receivers in a hemispherical array would add the additional complication of signals emanating from facing transmit elements in the array and from multiple reflections caused by the skull. In the proposed application, filtering of the fundamental frequency would eliminate these, leaving only the generated harmonics and wideband emissions. While reflections of the microbubble

emissions within the skull, as well as harmonics generated by the nonlinearities of tissue and water, must be still considered, elimination of the transmit frequency substantially simplifies the signal analysis.

The PVDF receiver was able to reject electrical coupling with the transmit element better than the commercial hydrophone. Although less sensitive than PZT-4 of equivalent size, the broadband response of PVDF is desirable, and comparison with a highly sensitive passive transducer demonstrated that the PVDF receiver is sufficiently sensitive for the proposed application. Its success in transcranially sonicating and detecting microbubbles, both on the bench-top and in vivo, shows promise for use in a large-scale array. The superior sensitivity of the PVDF is also important, as in practice, reflected pressures can be less than 1% of the transmitted-signal strength [15]. While the reflected signal strength was low for the bubble excitation experiments, the experiments utilized only a single element, and therefore, the excitation pressure was low. The absence of harmonic signal components in the single-element through-skull sonications suggests either linear bubble oscillations, in which case the peak pressure at the contrast agent was insufficient to cause nonlinear behavior, or the attenuation of the harmonic components through the skull, as above 600 kHz the attenuation of sound through adult skull bone begins to increase [46]. Nonlinear effects were restored with the addition of a second transmit element, which implies feasibility for use within a multielement array. The concentrations of contrast agent used in this study were high relative to those used in vivo. Thus, the in vivo experiments served not only to confirm the ability of the receiver to detect realistic microbubble concentrations while transmitting the therapy pulse, but also showed that the sensitivity of the receiver was sufficient to detect differences in the waveforms at different powers and given different biological effects.

One fall back of the current design is the directivity of the receiver. The transcranial dome presented by Song and Hynynen has an effective beam steering range of ± 50 mm in the lateral direction and ± 30 mm in the depth direction. At 306 kHz, with the large receiver, the entire beam steering range is within -3 dB of the maximum receiver signal strength. However, at 830 kHz, only signals originating ± 26 mm from the geometric focus can be detected without significant signal loss, and at 918 kHz, the approximate third harmonic generated by the microbubbles, this range is even further reduced. The smaller receiver that was successfully constructed without sacrificing signal strength and that has a PVDF film diameter of 2.4 mm will be able to detect the third harmonic over the whole beam steering range.

Having demonstrated the feasibility of using the PVDF receiver in combination with a therapy array element, and *in vivo*, future work will focus on expanding to a multielement array, as well as identifying the control parameters necessary to realize real-time monitoring of therapy.

V. CONCLUSION

A compact, MRI-compatible PVDF receiver for use in combination with a transcranial array element has been presented. The low-cost receiver has been demonstrated to be more suitable

for the proposed application than a commercial hydrophone, with greater sensitivity and rejection of electrical coupling. The receiver was able to function in combination with a transmit element to sonicate a transcranial target and detect the resulting low-pressure microbubble oscillations. Preliminary *in vivo* work further demonstrated the functionality of the receiver and demonstrated the possibility of correlating ultrasound signals with biological effects of treatment. Future work will focus on developing a multielement receiver array and its acquisition system, and their testing for brain treatment monitoring.

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Meaghan A. O'Reilly received the B.Sc. degree in mechanical engineering from Queen's University, Kingston, ON, Canada, in 2007, and the M.Sc. degree in biomedical engineering from the University of Oxford, Oxford, U.K., in 2008.

Since 2009, she has been a Research Engineer in the Focused Ultrasound Laboratory, Sunnybrook Health Sciences Centre, Toronto, ON.



Kullervo Hynynen received the Ph.D. degree from the University of Aberdeen, Aberdeen, U.K.

In 1984, after completing his postdoctoral training in biomedical ultrasound, also at the University of Aberdeen, he accepted a faculty position at the University of Arizona, Tucson. In 1993, he joined the faculty at the Harvard Medical School and Brigham and Women's Hospital, Boston, MA. There he reached the rank of Full Professor, and founded and directed the Focused Ultrasound Laboratory, Brigham and Women's Hospital. Since 2006, he has been at the

University of Toronto, Toronto, ON, Canada. He is currently a Professor in the Department of Medical Biophysics at the University of Toronto, and is the Director of Imaging Research and the Centre for Research in Image-Guided Therapeutics at the Sunnybrook Health Sciences Centre.

Dr. Hynynen is the Tier 1 Canada Research Chair in imaging systems and image-guided therapy awarded by the Government of Canada.