An MR-compatible preclinical sonication platform for focused ultrasound therapy and monitoring in animal models

A. C. Waspe[1,2], M. O'Reilly[1], J. Zhang[1], Y. Khan[1], A. Chau[1], R. Chopra[1,2], and K. Hynynen[1,2]
[1]Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

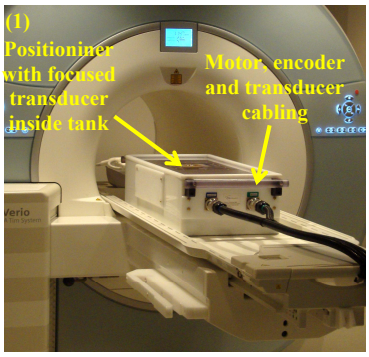
Introduction:
MR-guided focused ultrasound (MRgFUS) is an enabling technology for localized blood-brain barrier disruption (BBBD), targeted delivery of pharmaceuticals, and controlled heating of tissues [1]. Clinical translation of novel MRgFUS therapies require extensive testing in animal models, yet the small size of rodents makes execution of focused ultrasound exposures using clinical MRgFUS systems difficult [2]. Also, many clinical systems are integrated with dedicated MR installations, making it difficult for researchers with existing MR facilities to cost-effectively branch into this rapidly evolving field. To perform these experiments at a resolution suitable for small animals, a dedicated preclinical platform that is capable of delivering ultrasound sonications with a targeting accuracy of approximately 1 mm within a clinical MR scanner has been developed [2,3]. An onboard RF power meter and piezoelectric hydrophone enable the monitoring of acoustic emissions during the sonication process, which provides insight into the ultrasound bioeffects occurring *in vivo* [4]. The objective of this research is to develop a high-precision, MR-compatible, vendor-independent platform for focused-ultrasound therapy and monitoring in animal models, and to evaluate its performance in clinical MR scanners.

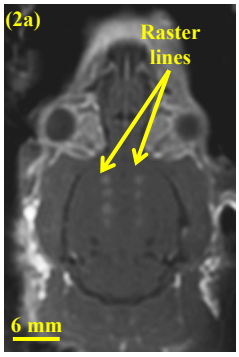
Methods:
A three-axis transducer positioner was developed using non-magnetic hardware, piezoelectric actuators, and sinusoidal-wave linear optical encoders. Precise horizontal motion with a range of 5 cm and a maximum velocity of 50 mm/s is achieved by driving linear piezo actuators along ceramic strips that are mounted to linear slides. A vertical travel of 5 cm with a maximum velocity of 5 mm/s is achieved by driving a leadscrew-based stage with a rotary piezoelectric motor [3]. An MR-compatible single-element spherically-focused transducer is mechanically steered by the positioner while remaining submerged within a closed water tank. The actuator and encoder cables are passed into the magnet room through low-pass filtered connectors on a grounded RF penetration panel. A small RF-receive coil acquires high-resolution images in the vicinity of the target tissue and the subject is placed on top of an acoustic window centered about the RF coil to enable ultrasound transmission from below the body. A photograph of the focused ultrasound system placed on the couch of a 3.0 T Siemens Magnetom Verio MR scanner is shown in Figure 1. For BBBD, successful opening is often achieved by pulsing the ultrasound transducer in short bursts at a single frequency with about a 1% duty cycle following the intravenous injection of a microbubble-based ultrasound contrast agent [1]. A commonly used BBBD protocol involves pulsing the transducer in 10 ms bursts with a 1 Hz pulse repetition frequency (PRF) for a total exposure time of 30-300 s [2]. The rapid horizontal velocity of the positioner enables a rapid raster of the ultrasound focus in order to hit multiple targets within a single cycle of the pulse repetition, increasing the throughput of an *in vivo* experiment. A real-time onboard power meter measures both forward and reflected RF power between the amplifier and transducer, providing information about the amount of acoustic energy emitted by the transducer and the amount of energy reflected back at the transducer due to interaction of the ultrasound beam with the tissue. The power meter has a time resolution of 100 µs, allowing for the power of each individual burst to be resolved. A Polyvinylindene fluoride (PVDF) based hydrophone, which is aligned with the geometric focus of the ultrasound transducer, is calibrated to measure acoustic emissions during sonications. Also, the Fourier spectrum of the hydrophone signal provides information about the harmonic content of the acoustic wave, which displays the harmonics and subharmonics generated by the ultrasound-contrast microbubbles and provides insight into the ultrasound induced bioeffects such as BBBD, cavitation, and tissue damage [4,5].

Results:
Bench top tests have revealed that linear ranges of over 5 cm with a positioning resolution of 0.1 mm were achievable for each axis. The entire system is constructed with MR-compatible components and operation of the positioning system and transducer within the bore of clinical MRI scanners of different manufacturers during image acquisition is feasible [2,3]. Figure 2(a) demonstrates the raster pattern of BBBD produced by sonicating multiple targets in a rat brain at a frequency of 1.503 MHz with 10 ms bursts, a 1Hz PRF and a total exposure time of 120 s. Focal disruption at the individual targets is enhanced by the intravenous injection of a Gadolinium based contrast agent immediately following the ultrasound exposure. Figure 2(b) shows the Fourier transform of the scattered acoustic signal measured at the geometric focus of the transducer with the hydrophone. The acoustic emission signal is measured for the duration of the burst. The Fourier spectrum of the burst is automatically calculated from this data, providing information about the spectral content of the acoustic wave. The generation of harmonics indicate the occurrence of BBBD and stable cavitation, and the generation of subharmonics are an indicator of inertial cavitation and tissue damage [4,5].

Conclusions:
An MR-compatible focused ultrasound platform has been developed that can sonicate anatomical targets in small animals with high precision and can monitor the acoustic emissions during the procedure within the bore of a clinical MR scanner. The positioner has sufficient velocity to raster to multiple targets during a single cycle of the pulse duration and the onboard power meter and hydrophone enable real-time monitoring of acoustic emissions and ultrasound induced bioeffects. This platform enables high throughput ultrasound-enhanced therapy and monitoring involving large numbers of small animals.

References:
[1] K. Hynynen, "Focused ultrasound for blood-brain disruption and delivery of therapeutic molecules into the brain," *Expert Opin. Drug Deliv.* **4**, 27-35 (2007).
[2] R. Chopra, *et al.*, "An MRI-compatible system for focused ultrasound experiments in small animal models," *Med. Phys.* **36**, 1867-74 (2009).
[3] A. Waspe, *et al.*, "An MRI-compatible three-axis focused ultrasound system for performing drug delivery studies in small animal models," *Proc. SPIE* **7629** (2010).
[4] M. O'Reilly and K. Hynynen, "A PVDF receiver for ultrasound monitoring of transcranial focused ultrasound therapy," *IEEE Trans. Bio. Eng.* **57**, 2286-94 (2010).
[5] N. McDannold *et al.*, "Targeted disruption of the blood–brain barrier with focused ultrasound: association with cavitation activity," *PMB* **51**, 793-807 (2010).





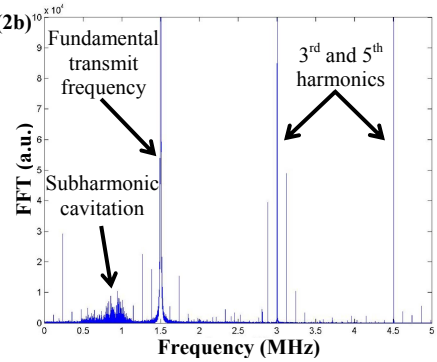


Figure 1: Photograph of the focused ultrasound system installed on the couch of a Siemens 3.0 T Magnetom Verio MR scanner.

Figure 2: (a) Gadolinium-enhanced regions of BBBD produced in a rat brain correspond to multiple targets sonicated along a single raster line. (b) Fourier spectrum of the acoustic pressure at the focus measured with the hydrophone for a 10 ms burst. The subharmonic acoustic emissions indicate inertial cavitation.