Progress Report (6 months)

Focused Ultrasound Foundation Research Award for the project entitled
"The development of standards to regulate microbubble cloud formation during histotripsy pulses."

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Overview:

The stochastic nature of microbubble activity makes the development of regulatory standards difficult for cavitation-based ultrasound therapies. We propose to develop *in vitro* and *in silico* models to assess the area, location, and type of microbubble activity and ablation during histotripsy pulses. These data will elucidate a FDA regulatory framework for histotripsy devices, which will profoundly impact the advancement of clinical use of focused ultrasound.

Summary of Progress to Date:

I. Develop a numerical model to predict the spatial area of a microbubble cloud nucleated from a microbubble exposed to a histotripsy pulse.

A hybrid method model is under development to simulate nonlinear propagation of shocked histotripsy pulses. The model employs the Fast Nearfield Method (FNM) to compute the linear nearfield solution. The finite-difference, time-domain (FDTD) method is used to solve the Westervelt equation at the focus, using the FNM solution as the source boundary condition. Computed fields agree with previously reported shocked 2 MHz insonations with peak pressures of 35–63 MPa when the FNM method calculation is set to half the focal distance (**Fig. 1**). This hybrid technique allows reliable calculation of the focal pressure while reducing the FDTD computational domain by a factor of two.

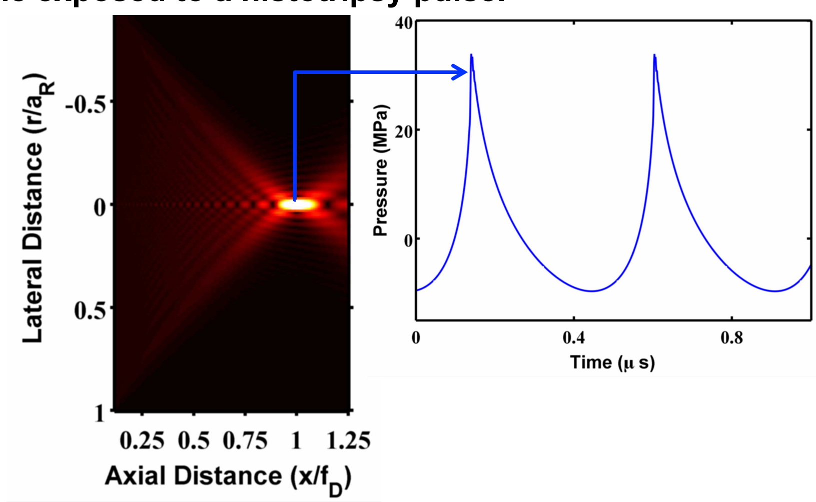

Fig. 1: FDTD computation of field (left) and shocked histotripsy insonation at focus (right) for 2-MHz histotripsy transducer (4 cm aperture, 4 cm focal length).

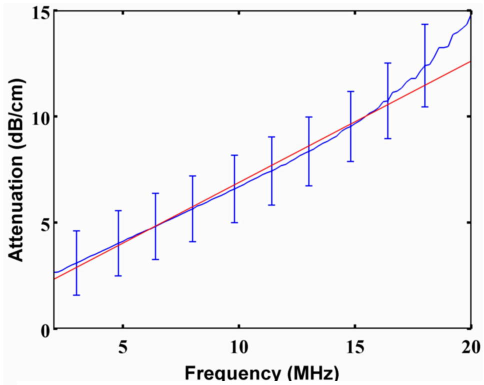

Fig. 2: Frequency-dependent attenuation spectrum of prostate tissue phantom. The red line is a linear fit of the attenuation with frequency.

II. Correlate the parameters of histotripsy insonation with the area and location of microbubble cloud activity and lesion formation in an in vitro tissue phantom.

A. Development of Prostate Tissue Phantom

A prostate tissue phantom was developed with evaporated milk and agar. The attenuation of this tissue phantom was measured between 2 MHz and 20 MHz using a through-transmission technique. The power law dependence of the acoustic attenuation spectra was linear with frequency (R^2 = 0.98) (**Fig. 2**). The attenuation coefficient of the tissue phantom was 0.62 ± 0.02 dB/cm/MHz, which is lower than that reported for *ex vivo* human prostate at 5 MHz. This discrepancy will be addressed in future phantoms by modifying the formulation with an increased concentration of evaporated milk.

These phantoms have been exposed to histotripsy pulses, and lesions have been successfully generated (**Fig. 3**).

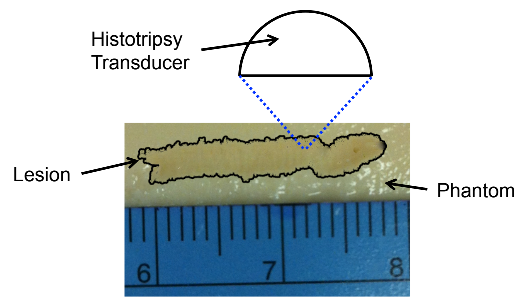

Fig. 3: Lesion generated in prostate tissue phantom. Histotripsy pulses (20 μs pulse duration, 13 MPa peak negative pressure, 200 Hz pulse repetition frequency) were generated 1 cm below the surface of the phantom. The phantom was translated laterally to generate a 1.8 cm long lesion (outlined in black).

B. Histotripsy System Characterization

A custom histotripsy system was designed and built. The system consists of an 8–element, 1-MHz histotripsy transducer (Imasonic, Voray sur l'Ognon, France) driven by a computer-controlled custom class D amplifier with matching network. Acoustic fields generated by the histotripsy system were measured with a needle hydrophone (NP10-3, Dapco Industries, Inc., Ridgefield, CT) affixed to a computer-controlled three-axis positioning system (NF-90, Velmex Inc., Bloomfield, NY). To characterize surface vibrations along the transducer face, the acoustic field was mapped along a nearfield plane, and the surface velocity of the transducer face was calculated using the Rayleigh integral (**Fig. 4**). These surface vibrations will be used to accurately model the transmitted field *in silico*.

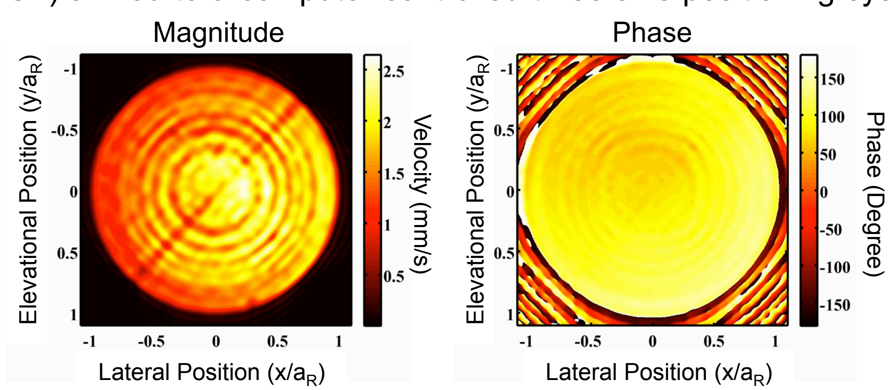

Fig. 4: Magnitude (left) and phase (right) of transducer face velocity computed with Rayleigh integral using a nearfield scan of the field generated by the histotripsy transducer. The lateral (x) and elevational (y) positions denoted on the abscissa and ordinate axes have been normalized by the transducer radius (a_R = 5 cm).

Oral presentations related to the funded project include:

- Michael J. Crowe, Jason L. Raymond, Christy K. Holland, Kenneth B. Bader, "Broadband attenuation measurements of tissue-mimicking phantoms employed for histotripsy," to be presented at the 169th meeting of the Acoustical Society of America (May 2015)
- Kenneth B. Bader, Christy K. Holland, "The development of a hybrid finite difference solution of the Westervelt equation using the Fast Nearfield Solution as a boundary condition for focused sources," to be presented at the 20th International Symposium on Nonlinear Acoustics (June 2015).