Overview

Thirty leading engineers, physicists and clinicians from 17 organizations convened at the Brain Treatment Envelope & Simulation Workshop in Charlottesville on February 2-3, 2015. They gathered to discuss ways to create accurate simulations to assess the expansion of the brain treatment envelope, facilitate patient selection and to predict and prevent unwanted secondary effects like skull heating.

Focused ultrasound has been successful in treating targets in the center of the brain for movement disorders and neuropathic pain. In order to increase the utility of the technology to treat brain tumors, epilepsy and other disorders, this "treatment envelope" of focused ultrasound needs to be expanded to include targets located more peripherally in the brain.

The empirical approach to achieving this would be trial and error treatments in patients – a potentially risky and costly approach. Alternatively, treatments in these peripheral locations could be modeled with computer simulation to determine which areas can be effectively targeted prior to attempts to treat patients. There are computer models for simulating focused ultrasound treatments in various parts of the body, but none have been validated for the brain.

The Workshop was held to discuss the current status and establish future plans for the development of computer applications that will serve as tools for selecting patients for treatment. These simulations will be based on CT skull characteristics and target locations and predict the required power and duration of ultrasound therapy to treat an individual patient.

The experts created a roadmap of projects leading to computer simulation for expanding the treatment envelope and patient selection and treatment planning.

Projects include:

- Validating the accuracy of the computer simulation by measuring pressures produced by the focused ultrasound transducer using a hydrophone positioned at different locations within human skulls and comparing it with the pressures predicted by the model.
- Determining whether computer simulation can predict treatment effects by comparing real treatment results in patients with the predicted temperature changes from the computer simulation
- Analyzing data from previous clinical treatments to develop an understanding of the relationship between focused ultrasound input power and heating of the targeted tissue.

The net effect of this initiative will be safer, more effective and more rapid treatment of a wide range of brain disorders using focused ultrasound

Presented Topics

The first presentation of the workshop by Nathan Fountain, a neurologist at the University of Virginia, gave an overview of their pilot study for using focused ultrasound to treat 15 essential tremor patients. The remainder of his talk discussed the potential for focused ultrasound in the treatment of epilepsy. Current treatment options for epilepsy are invasive, presenting an opportunity for FUS to meet an unmet clinical need. The problem, however, is that the regions of the brain that cause epileptic seizures are almost always outside of the current treatment envelope. Increasing the treatment envelope for FUS would enable its use for potentially thousands of patients with epilepsy. The group at UVA has designed a pilot study for the treatment of epilepsy in regions inside the current treatment envelope called the Focused Ultrasound Subcortical Epilepsy (FUSE) study. They will enroll 15 patients with subcortical lesions as the cause of medically refractory epilepsy, including hypothalamic hamartoma, periventricular nodular heterotopia, focal cortical dysplasia, and tuberous sclerosis.

Craig Meyer then presented work from his lab to monitor focal spots using real-time 3D thermometry. Current temperature monitoring technology shifts the focal spot if the scanner is not programmed to the proper frequency. Using the spiral scanning technique to read the K space stops this shift from occurring but results in blurring. The spiral in/out method can correct for the blurring and the Kalman filter can be used to accelerate the imaging process.

Wilson Miller presented his work on cranial bone mapping using a dual-echo ultrashort TE (UTE) pulse sequence. The first echo receives the signal from the bone, and the second echo is sent after the bone signal has disappeared. This method had a greater than 85% overlap of pixels with CT scans. With an optimized MR acquisition sequence and an appropriate RF coil, it is entirely feasible to obtain high-quality cranial bone maps of both *ex vivo* and *in vivo* human skulls.

Wayne Kreider presented on the characterization of the intense ultrasound fields created during boiling histotripsy in order to better understand the threshold effects. Holography is used to determine the source's spatial vibration pattern at low amplitudes, and the source's power defines the vibration amplitude. The nonlinear acoustic propagation is modeled by KZK or Westervelt, which can be used to calculate shocks and heating rates, and to account for tissue attenuation.

Brad Treeby has been working on developing a full-wave ultrasound Matlab/C++ simulation for large-scale problems such as: modelling nonlinearity, power law absorption, and elastic waves; spectral collocation methods; large-scale computing (GPGPU and HPC); and bottom-up numerical and experimental validations. Their product is called the k-Wave Toolbox (www.k-wave.org). Errors in their simulation arise from the physical model, discretization, model inputs, and application of model data. There needs to be a balance between increasing the model's complexity and the impact of parameter uncertainty.

Doug Christensen showed results from using their model to simulate the temperatures achieved in 14 transcranial patient treatments at UVA. They then compared the simulated results with the actual temperatures recorded during the treatment. They are using a linear acoustic model with the hybrid angular spectrum method. Half of the simulations were fairly close to the actual result, and the other half generally estimated a lower maximum temperature (max T) with some outliers.

Kim Butts Pauly presented an experimental measure of the "inherent" efficiency of each skull. So if you were to ignore the treatment associated factors in the treatment, each skull still has an inherent efficiency, some are more efficient than others. She came up with a metric for this inherent skull efficiency, the temperature rise at 8,8 seconds after ultrasound was tuned on for the first sonication (with temperature rise significantly above the noise standard deviation) divided by the power for that sonication. At lower powers the temperature rises linearly, but then at higher powers it starts to deviate for unknown reasons. The efficiency is related to full-width half max, average power, energy, and sonication number.

Urvi Vyas presented an acoustic simulation technique that uses the information from subject-specific CT scans to estimate the effect of acoustic wave propagation through the skull. She presented a way of predicting each skull's inherent skull efficiency using the difference in acoustic beam propagation due to the acoustic properties of the skull, while keeping all other parameters constant. Reflection, refraction, scattering and absorption of the acoustic beam through the skull were modelled. The simulated skull efficiency was compared to the experimentally measured skull efficiency in twenty-three patient datasets where the patients were treated with MR-guided focused ultrasound for tremor. The experimental skull efficiency correlated with simulated skull efficiency (r2=0.76).

Henrik Odeen presented his work to evaluate the treatment envelope. He used a gel phantom with a plastic skull and large animal FUS transducer and evaluated the envelope based on efficacy (focal spot heating) and safety (near field heating). Ultimately, this can be used as a way to determine the effects of varying skull anatomy, the efficacy and safety of treatments, and the optimal design of transcranial FUS systems.

Matt Eames then presented Dave Moore work to collect hydrophone measurements of the 220 and 650 kHz InSightec brain transducers. This data will be used to help validate all of the simulations. He will collect the pressure, phase, and waveform data at each point. There will be one 3D data set collected with no skull in place and then 3D data sets collected for at least two different skulls. He will also get a 2D scan at the natural focus of the transducer for single elements with and without a skull.

Esra Neufeld has created a framework called Sim4Life for *in silico* investigation of FUS therapies and transcranial optimization. It can be used to achieve a better understanding of the underlying phenomena and mechanisms of FUS, to create patient-specific treatment planning, and to gain an insight on secondary effects.

Alec Hughes presented on his attempt to use a full-wave model in order to replicate the oblique focus that he and his colleagues have observed during treatments. His work uses a hybrid combination of the finite difference method and the grid method for simulations.

Shy Shoam and his colleagues have developed a model for neuromodulation called the NICE model. Cavitation within neurons causes their membrane to vibrate, creating a time dependent capacitance that stimulates the neuron. They have also found a difference between the excitation of inhibitory and excitatory neurons.

Yun Jing presented on the use of metamaterials, which can be used to eliminate some of the ultrasound reflection due to bone. The metamaterial is capable of effectively cancelling out the aberrating layer. For transcranial applications, two layers would be required – one to cancel out the skull and another for the skin.

Yeruham Shapira gave an insight into what is most important to InSightec at the moment. In 2014 they added eight new sites, doubled the number of treatments performed, and 30% of all treatments were commercial. He also gave a list of things they would like to accomplish and questions they want to answer: predict the hydrophone measurements in the actual configuration, have a skull physical model using CT/MRI/ULS imaging, how hydrophone-level focusing scales to the treatment level, what the non-linear effects are in skull transversal, what the non-linear effects are in the soft tissue response in thermal rise, a better understanding of brain tissue properties, frequency optimization for trans-skull treatments, and to segment skulls to “traversal meaningful” patches.

Matt Meyers from the FDA presented the guidelines that they are creating for producing regulatory-grade simulations. These models would be capable of demonstrating final device performance and could constitute a substantial component of the evidence in regulatory decisions. The context of use for the simulation is critical in determining the level of credibility – or the predictive ability in the reality of interest – required of the computational model. The credibility required is a function of the model risk. High risk constitutes only relying on the model to predict the outcome of a procedure, while low risk would combine the results from the model with other data before making a decision. There will be 16 factors used to assess credibility in the guidelines including an analysis of mesh discretization error and a rigor of output comparison.

Beat Werner gave the final presentation on the use of MR-guided FUS for brain tumors. In his opinion this is the indication that will be able to commercially sustain the field of focused ultrasound. Beat was able to take his experience from treating functional neurological disorders and apply it to the treatment of brain tumors. In the first patient treatment they could only debulk around 10% of the tumor in 3 hours. However, there was no tumor growth at the 6 month checkup and it was well tolerated with the patient leaving the hospital after one day. They had a harder time with the treatment in another patient that had local necrotic tissue, and they had to stop the treatment for a patient with a large solid tumor where heating occurred in multiple spots and the patient complained of vestibular stimulation.

Applications of simulation to transcranial focused ultrasound

- Patient selection
- Treatment planning/prediction
- Optimization of transducer focusing
- Treatment envelope prediction
- Retrospective analysis

Open discussion of simulation and its impact on understanding and improving the treatment envelope

The first discussion topic around improving the treatment envelope was actually defining what the treatment envelope is. There may very well be different envelopes for the different bioeffects of FUS and the safety profile and time expectations need to be kept in mind as well.

In order to create optimal simulations there needs to be a standardization of the data and experimental setup shared among the various sites. The FUS transducer needs to be modelled accurately and there needs to be a better understanding of the tissue material properties. Finally, the existing simulations need to be validated so that their limitations can be known and it can be determined when a particular package is useful and when it is not.

A possible way forward is to create a very simple simulation that is able to calculate the basics of what is needed: what physical phenomena are most important and what are the biggest limitations that make current models inaccurate. Once this is achieved then more complex simulations could be better developed. For example, radiation therapy is only now starting to take bioeffects into account in their simulations.

The current data that is available has registry errors and unknown material properties. It would be beneficial to perform experiments with materials that have known properties and size. It would also be helpful to have the actual shape of the transducer elements and a proper characterization of bone properties as a function of temperature using microCT. Finally, there was also a request for hydrophone data collection for actual treatment energies and pressures, which would require a fiberoptic hydrophone.

Discussion of the non-linearity of power and temperature rise

The phenomena where the efficiency of the treatment decreases as the power is increased throughout the duration of a treatment, and even as an apparent correlation with the cumulative number of sonications during a particular treatment ,was extensively discussed by the group. No one is quite sure of why it occurs though. It was proposed that it could represent hardware issues, but that may not be likely. Other possibilities include skull interaction, something happening at the focal point such as tissue changes or cavitation, or maybe that the focal point simply moves along the axis at higher powers. There has been anecdotal evidence of power fatigue with a plastic skull from the group at Utah as well as in a pig experiment without a skull from Craig Meyer.

Outcomes and Roadmap

The experts created a roadmap of projects leading to a validated computer simulation for expanding the treatment envelope and patient selection and treatment planning.

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Participants:

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Doug Christensen – University of Utah
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