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Simultaneous Nerve Displacement Mapping for Human Peripheral Neuromodulation

Stephen A. Lee, *Member, IEEE* Hermes A. S. Kamimura, *Member, IEEE* and Elisa E. Konofagou, *Member, IEEE*

***Abstract*—Focused ultrasound (FUS), being non-invasive and non-ionizing, has been postulated as a possible therapeutic for peripheral nerve modulation. Recently, the ability to use high intensity, short pulse FUS has been demonstrated in rodents. In order to adapt this technology for clinical translation, a technique for real-time imaging and validation of FUS neuromodulation is needed. In this study, we developed a technique to image FUS using a two probes, connected to a single Vantage research ultrasound machine for real-time elastography during FUS delivery without interleaved transmits. Using a custom transmit sequence, we can image displacements around 1 μm. Validation of FUS delivery to the median nerve was performed in humans (n = 5). This technique allows for greater accuracy and confidence in applying neuromodulation to human peripheral nerves.**

***Index Terms*—Ultrasound neuromodulation, simultaneous imaging, elastography, coded excitation.**

I. Introduction

EVIDENCE of effects on electrically excitable tissues such as the brain and nerves using ultrasound has recently been reported [1]–[9]. Recently, we have been able to use high-intensity FUS (3.1 MHz) to stimulate the sciatic nerve in anesthetized mice [10], [11]. FUS application to the nerve generated down-stream muscle activation as recorded through electromyography. We were able to correlate muscle activation to the amount of acoustic radiation force and displacement of the sciatic nerve.

FUS neuromodulation of the human nerve has yet to be fully clinically translated due to many factors. One of which is an accurate targeting method that can be used in the clinic. Since stimulation of the nerve seems to also coincide with acoustic radiation forces exerted in the tissue, current elastographic techniques can be amended to achieve this purpose [12]–[15]. Previously, we developed a technique to monitor FUS and measure displacement of the mouse sciatic nerve as a mechanistic metric for neuromodulation [10], [11]. This technique used cross-correlation to simultaneously image and stimulate the nerve using a function generator, RF amplifier, and a Vantage ultrasound machine. However scaling up to humans introduces various conflicts: 1) the human nerve is much larger than the sciatic nerve, 2) the humans will be awake and are prone to targeting drift and movement, 3) the nerve is much deeper in the forearm and may attenuate higher frequency ultrasound. Current techniques can achieve simultaneous imaging and FUS transmission by interleaving the pulses between the FUS application. However, this limits the effect of the radiation force since the pulses are spaced further apart; for neuromodulation purposes, it has been shown emperically that continuous wave ultrasound has a higher probability of activation. Thus, the focus of this paper was to develop a technique that can simultaneously image and stimulate, without interleaving, the median nerve in humans for clinical feasibility and translation of FUS neuromodulation in human peripheral nerves.

II. Methods and Materials

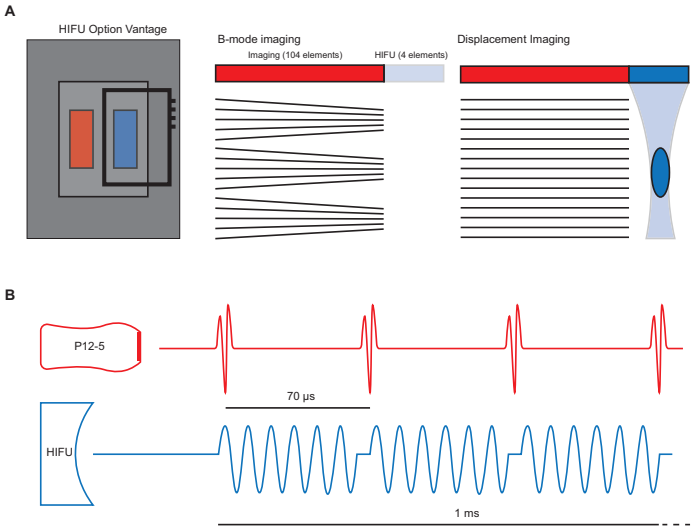

Fig. 1. Customized transmission sequence. (A) HIFU system configuration with imaging channels (RED) and FUS channels (BLUE). B-mode compounded imaging using tilted plane waves were used to first identify the nerve, then displacement imaging using simultaneous imaging and stimulation was used for neuromodulation. (B) cartoon diagram of simultaneous imaging (2 cycle pulses) and extend burst (70 μs) to generate a continuous wave 1 ms pulse

A. Experimental setup

We used a 1.1 MHz, 4-annular array FUS transducer (Sonic-Concepts, Bothell, WA, USA) that can be individually phased to axially steer the beam (1 x 15 mm). The FUS transducer has a central opening, containing the 7.8 MHz imaging transducer (Philips, Amsterdam, Netherlands). Both transducers were connected to a 256 channel research Vantage machine (Verasonics, Kirkland, WA, USA). With one port (64 channels) dedicated to the FUS and the other (104 channels) to the imaging transducer. The vantage was configured with the high intensity focused ultrasound (HIFU) option to drive an extended burst of FUS at the higher intensities required for neuromodulation. A Tesla K40

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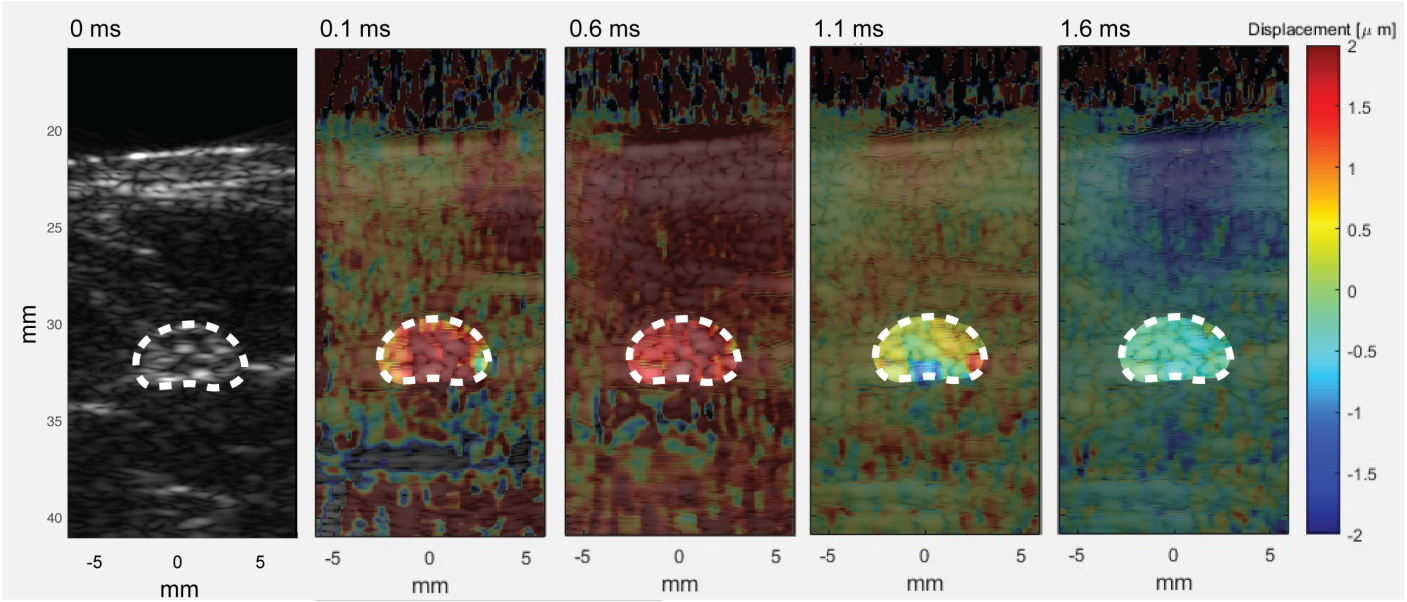

Fig. 2. Frame captures of displacement mapping during the FUS pulse sequence. First B-mode is used to identify and position the median nerve. FUS is applied at the 2nd frame and lasts until the third frame. Positive displacement, away from the transducer, is in red and negative, towards the transducer, is in blue. The median nerve is outlined in white on all frames.

GPU (Nvidia, Santa Clara, CA, USA) was used to beamform and perform 1D cross correlation for real-time operation.

B. Simultaneous customized excitation

Both the imaging transducer and the 4 element FUS transducer were defined as a single transducer in verasonics where 104 channels were devoted to generating a 2 cycle imaging pulse and the other 64 elements were used to drive an extended burst (EB). The total time of the EB was set to the total time-of-flight (TOF) required to generate an image on the imaging transducer. For a scatterer located at a depth of 55 mm, it takes 70 μs to travel there and back. Therefore, the EB time was set to last an integer cycle (1.1 MHz) time equivalent to 70 μs. The channels driving the FUS transducer were programmed to elicit a continuous burst of 70 μs FUS while the other 104 channels transmitted a 2 cycle imaging pulse simultaneously. For a total FUS pulse duration of 1 ms, the sequence was repeated sequentially 14 times to generate a continuous 1 ms burst of ultrasound without interleaving the imaging bursts. The subsequent imaging RF data was beamformed and displacements were tracked in real-time. 95 % overlap and a 10 λ window length was used as cross-correlation parameters to track displacements.

C. Nerve displacement mapping of human peripheral neuromodulation

All human subjects (n = 5) were recruited in accordance with Columbia University's institutional review board (IRB) committee and regulations. Humans were positioned in a reclining chair with the underside of their arm facing up. The FUS transducer system was positioned on the arm by a 6 DOF robotic arm (Kinova, Boisbriand, Canada). The median nerve was located using compounding B-mode imaging using the confocal imaging transducer. An cross-sectional view of the nerve was used due to the echogenicity making it easily identifiable by tilting the transducer at various angles. After identification and position of the nerve at the focus (35 mm relative to the imaging transducer), displacement imaging using a 1 ms burst of ultrasound was performed. Displacement movies were immediately played back to the operator and used for validation of median nerve neuromodulation.

III. Results and Discussion

After beamforming and cross correlation, a displacement map was made for each 1 ms burst of FUS. Figure 2 shows resultant frame captures of FUS delivery to the human median nerve. The median nerve, outlined on the compound B-mode image on the left, is positioned at 30 to 35 mm in depth, where the focus of the FUS transducer is aligned. During modulation, positive displacement, away from the transducer, accumulates at the center of the nerve then propagates outside to other tissues, including muscle. After 1 ms, the FUS terminates and relaxation, negative displacement, is shown on the videos. It is interesting to note, at 1.1 ms after FUS modulation, that while the nerve is moving upwards, the surrounding muscle is still being forced downwards. This may indicate that during FUS modulation, the nerve being compressed may contribute to changes in neural activity, rather than the ultrasound carrier frequency itself. Importantly, when good coupling between the transducer water membrane and the skin was not accomplished, the nerve experienced very little displacement or the software was unable to eliminate FUS interference. This fact alone demonstrates the utility of this technique for clinical translation;

if the nerve was targeted for FUS modulation but was obstructed during travel to the intended target, then it would be completely unknown if the patient received the full therapeutic effect or not.

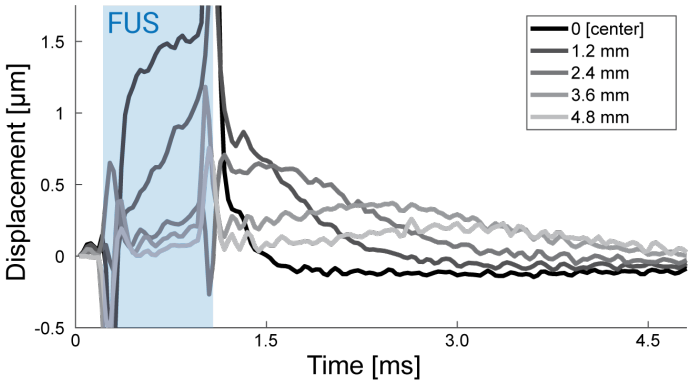

Fig. 3. Displacement traces at ROIs spaced evenly lateral to the center of the nerve (0 mm to 4.8 mm). FUS is delivered during the blue shaded region. Maximum displacement is achieved at the FUS pulse termination.

We further characterized the modulation pulse from this technique by measuring the cumulative displacement estimated at regions of interest at the center and multiples of 1.2 mm away from the center of the nerve. The traces in figure 3 show a drop off of accumulated displacement outside of the nerve (2.4 mm away). The area of displacement is consistent with the lateral size of the full-width half-max (FWHM) FUS focus, however the nerve tissue property itself may also explain the distinction of displacement between the nerve and the surrounding tissue. Future work will be dedicated to understanding how displacement and radiation force plays a role in sensory modulation of human perception.

IV. Conclusion

In the study presented here, we demonstrate a technique to simultaneously image and perform FUS modulation on a single vantage system without interleaving pulses, using a custom transmit sequence. We also demonstrated the validity of the method using *in vivo* human median nerves and created micron displacement maps to characterize individual FUS pulses during modulation. The technique presents an important notion that confirming delivery of FUS can alleviate unknowns in targeting using FUS and gives confidence in results by confirming and validating that FUS is reaching the nerve or any targeted tissue.

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