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3D monitoring and control of microbubble cavitation for gene delivery

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Background, Motivation and Objective

Previous work showed promising results in healing large bone fractures using ultrasound-mediated gene delivery [Bez2017]. However, large bone defects often have an irregular geometry which requires 3D steering of the therapeutic beam. Our goal is to develop the capability to monitor and control cavitation in 3D using passive acoustic mapping (PAM).

Statement of Contribution/Methods

We are developing 2D array transducers to interface with a 1024-channel Vantage system (Verasonics) and assess cavitation activity within a 3D volume. Our goal is to apply a therapeutic ultrasonic pulse at a transmission frequency of ~1.3 MHz and mechanical index (MI) of 0.3 and receive the spectrum through the third harmonic. Challenges in the development of 3D monitoring and control include the acquisition, computation and display of the real-time 3D PAM. We first explored the resolution trade-offs in the design of the 2D array. A real-time implementation of an angular spectrum approach for 3D PAM [Arvanitis2017] on GPU (Geforce GTX 1080 Ti, Nvidia) was then implemented. In proof of concept experiments, the 3D spectrum was simulated and an experimental bone phantom with a cylindrical defect region (15 mm in diameter) was imaged by phased array transducers (P4-1, ATL, Philips). A 2 ml bolus of ~10^7 house made microbubbles was injected into the defect region where the two orthogonal planes were imaged (fig. 1(b)). The defect region was treated by sending long bursts (100 cycles, 1.3 MHz, 325 kPa) using one transducer and the signal was simultaneously received by orthogonally-oriented transducers. B-mode imaging was interleaved with the acquisition of the PAM.

Results/Discussion

For our 2D array geometry, the achievable PAM locus (-3 dB of the maximum intensity) was 0.8×1.7×9.0 mm^3 at a focal depth of 60 mm (fig. 1 (a)). In our proof-of-concept experiments, a volume rate of ~5 Hz was achieved for 3D PAM of an 80×40×60 mm^3 volume (~3×10^7 voxels). The 2nd and 3rd harmonics of the signal were used to create the orthogonal maps (fig. 1 (b)). The PAM locus (-3 dB) was ~2.5 mm in width and ~18.0 mm in length. The ratios between the amplitude of fundamental and harmonics frequencies in the spectrum and between harmonics and ultra-harmonics defined the 'safe' zone of stable cavitation activities (fig. 1 (c)). The acoustic pressure could be modulated based on the PAM to control gene delivery.

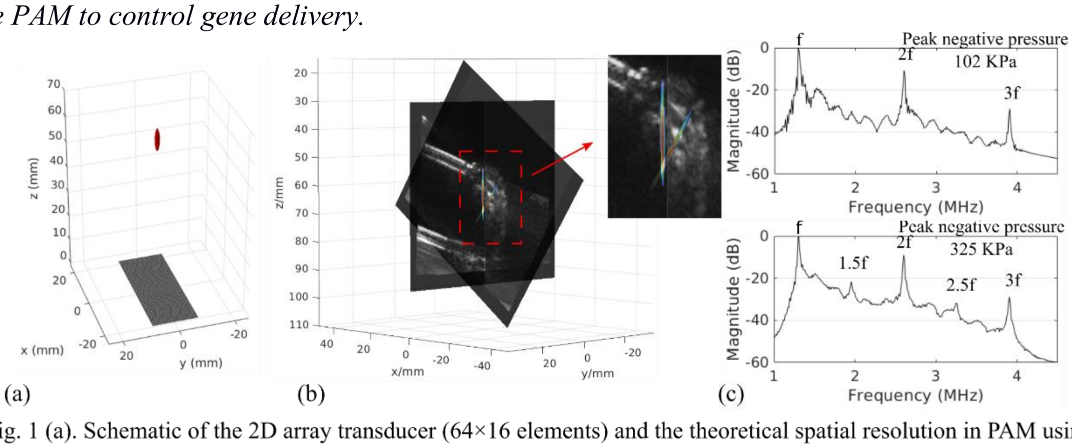

Fig. 1 (a). Schematic of the 2D array transducer (64×16 elements) and the theoretical spatial resolution in PAM using this array. (b) B-mode + PAM images of one longitudinal and transverse section of the defect. (c) Spectrum of the signal received after the treatment. f = 1.3 MHz is the fundamental frequency, 2f and 3f are the harmonics. When the peak negative pressure was increased to 325 KPa, ultra-harmonics (1.5f and 2.5f) were observed.