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Spatial–temporal three-dimensional ultrasound plane-by-plane active cavitation mapping for high-intensity focused ultrasound in free field and pulsatile flow

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ABSTRACT

Cavitation plays important roles in almost all high-intensity focused ultrasound (HIFU) applications. However, current two-dimensional (2D) cavitation mapping could only provide cavitation activity in one plane. This study proposed a three-dimensional (3D) ultrasound plane-by-plane active cavitation mapping (3D-UPACM) for HIFU in free field and pulsatile flow. The acquisition of channel-domain raw radio-frequency (RF) data in 3D space was performed by sequential plane-by-plane 2D ultrafast active cavitation mapping. Between two adjacent unit locations, there was a waiting time to make cavitation nuclei distribution of the liquid back to the original state. The 3D cavitation map equivalent to the one detected at one time and over the entire volume could be reconstructed by Marching Cube algorithm. Minimum variance (MV) adaptive beamforming was combined with coherence factor (CF) weighting (MVCF) or compressive sensing (CS) method (MVCS) to process the raw RF data for improved beamforming or more rapid data processing. The feasibility of 3D-UPACM was demonstrated in tap-water and a phantom vessel with pulsatile flow. The time interval between temporal evolutions of cavitation bubble cloud could be several microseconds. MVCF beamformer had a signal-to-noise ratio (SNR) at 14.17 dB higher, lateral and axial resolution at 2.88 times and 1.88 times, respectively, which were compared with those of B-mode active cavitation mapping. MVCS beamformer had only 14.94% time penalty of that of MVCF beamformer. This 3D-UPACM technique employs the linear array of a current ultrasound diagnosis system rather than a 2D array transducer to decrease the cost of the instrument. Moreover, although the application is limited by the requirement for a gassy fluid medium or a constant supply of new cavitation nuclei that allows replenishment of nuclei between HIFU exposures, this technique may exhibit a useful tool in 3D cavitation mapping for HIFU with high speed, precision and resolution, especially in a laboratory environment where more careful analysis may be required under controlled conditions.

1. Introduction

High-intensity focused ultrasound (HIFU) has emerged as a noninvasive technique to selectively and locally produce therapeutic effects in a specific site of the body without affecting the intervening tissue layers [1,2]. It has a promising potential in its applications, such as tumor ablation [3], extracorporeal lithotripsy [4], hemostasis [5], thrombolysis [6] and tissue erosion [7]. As cavitation plays important roles in both of thermal [8,9] and mechanical effects [10,11] which are the two principal mechanisms of HIFU therapy, a better understanding of the spatial–temporal distribution of cavitation bubbles is essential to optimize these applications.

For decades, techniques for detecting and mapping cavitation have been developed, and these techniques are mainly divided into optical and acoustic methods [12,13]. Optical methods, such as high-speed photography (HSP), sonoluminescence (SL) and sonochemiluminescence (SCL), have been employed to image the cavitation field. HSP can capture images of bubble dynamics and distribution when ultrasound exposure is on, and this powerful tool has a sufficiently high frame rate [14,15]. Compared to high-speed photography, SL and SCL can provide more information about the spatial distribution of chemically "active" cavitation

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bubbles [16,17]. In addition to its high cost, HSP, SL and SCL, however, are limited in transparent media, which triggers for seeking alternative methods of cavitation detection.

Acoustic methods take advantage of the acoustical characteristics of bubble activities, such as the sub-harmonic and broadband noise corresponding to the stable and the inertial cavitation, and thus are more suitable for *in situ* studies [18,19]. Passive cavitation detection (PCD) and active cavitation detection (ACD) techniques are two common one-dimensional acoustic detection methods with high sensitivity and spatial specificity [20]. However, they cannot reflect the spatial distribution of cavitation. Recently, PCD and ACD have been adapted to use in cavitation mapping techniques, through employing ultrasound imaging arrays as the cavitation detectors, specifically in passive cavitation mapping (PCM) and active cavitation mapping (ACM). PCM generally uses diagnostic ultrasound scanners with a linear array which receives only to increase spatial coverage [21–24]. The passive images of cavitation field during HIFU exposures can be reconstructed by beamforming the array element signals and time-exposure acoustics (TEA) methods [23–25]. Several groups have approached PCM by performing passive beamforming in the time domain. The cavitation features can also be characterized by transforming cavitation signals from the time domain to the Fourier domain [22]. PCM can be used to monitor cavitation activity during the sonication, providing information about the mode and strength of the oscillations. Arvanitis et al. used a transcranial MRI-guided focused ultrasound (MRgFUS) system to visualize stable and inertial cavitation in the brain transcranially [26,27]. However, in the transcranial cases, PCM cannot reconstruct the bubble cloud without making some correction for field aberrations imposed by the overlying bone.

ACM approaches mainly refer to conventional diagnostic B-mode ultrasound imaging which enables detection and localization of bubble activity [28]. However, strictly simultaneous ACM cannot be achieved by the conventional B-mode imaging, because of its sequential scanning process. Additionally, since the imaging frame rate is limited, conventional B-mode imaging cannot capture the transient behavior of cavitation bubbles. Gateau et al. have proposed an ultrafast active cavitation mapping (UACM) based on plane wave transmission and delay-and-sum (DAS) beamforming, and they combined it with passive detection to detect and locate the cavitation both *in vitro* and *in vivo* [29,30]. A tilted plane wave compounding method was also proposed to improve the signal-to-noise ratio (SNR) and resolution of the bubble images [29,31]. As reported in another study, Hu et al. have developed an UACM with relatively high spatial–temporal resolution, through combining plane wave transmission, minimum variance (MV) beamforming and coherence factor (CF) weighting to monitor the evolution of residual cavitation bubbles in histotripsy [32]. However, as the ultrasound beams are unfocused, lateral resolution of the ultrafast images needs to be improved. In order to develop a standard cavitation mapping similar to the exact acoustic field measurement, we have presented a modified line-by-line scanning ACM to map cavitation bubbles with both high sensitivity and spatial–temporal resolution [33]. Li et al. have proposed a new ACM termed bubble Doppler, which is based on a fusion of the adaptations of three Doppler techniques, i.e., color Doppler, pulse-inversion Doppler, and interleaving Doppler. This technique can both spatially map the presence of transient bubbles and estimate their sizes and the degree of nonlinearity for pulsed HIFU (pHIFU) applications [34].

However, two-dimensional (2D) cavitation mapping could only provide cavitation activity in one plane. In fact, cavitation bubbles are generated in a three-dimensional (3D) volume, which means that the 3D cavitation map is necessary to provide more information of cavitation activity. O'Reilly et al. provided 3D transcranial PCM using a sparse hemispherical array, which was capable of monitoring bubble emissions down to single bubble events through an *ex vivo* human skull [35]. In addition, using noninvasive phase correction and super-resolution image processing, transcranial PCM of brain vascular can be achieved [36]. Collin et al. presented a near-acoustically-transparent, 2D 32-element PVDF array suitable for use as a 3D cavitation mapping sensor, which can be mounted on the therapy transducer of a clinical HIFU device [37]. However, the number of elements and received data for construction of 3D image are greatly increased, which would increase the cost of the instrument and thus restrict the application.

In this study, we proposed a 3D ultrasound plane-by-plane active cavitation mapping (3D-UPACM) based on the linear array of a current ultrasound diagnosis system. The acquisition of channel-domain raw radio-frequency (RF) data in 3D space is performed by sequential plane-by-plane 2D ultrafast active cavitation mapping. Between two adjacent unit locations, there is a waiting time to allow the cavitation nuclei to distribute within the liquid and it can return to its original state. With this spatial series of channel-domain raw RF data, a 3D cavitation map can be reconstructed that encompasses the entire cavitation volume to be detected at one time. MV adaptive beamforming, is combined with CF weighting (MVCF) or compressive sensing (CS) method (MVCS) to process the raw RF data for improved beamforming or more rapid data processing. This 3D-UPACM technique is demonstrated in tap-water and a phantom vessel with the pulsatile flow. Temporal evolutions and spatial distributions of cavitation bubble cloud have been observed. The performance of 3D-UPACM is evaluated in the 2D-UPACM from resolution, SNR level and time penalty. This 3D-UPACM allows 3D visualization of the time evolution of bubble activity, using the linear array of a current ultrasound diagnosis system rather than a 2D array transducer, therefore decreasing the cost of the instrument. Although the application is limited by the requirement for a gassy fluid medium or a constant supply of new cavitation nuclei that allows replenishment of nuclei between HIFU exposures, this technique may exhibit a useful tool in 3D cavitation mapping for HIFU with high speed, precision and resolution, especially in a laboratory environment where more careful analysis may be required under controlled conditions.

2. Materials and methods

2.1. 3D ultrasound plane-by-plane active cavitation mapping

In the 3D-UPACM method, cavitation event is mapped immediately after one HIFU exposure by a linear array of the ultrasound imaging system in plane wave transmitting and receiving mode, and then extended this by sequentially measuring a series of planes. These planes consist of the linear array positioned at different unit locations perpendicular to the axis of the HIFU transducer. Between two adjacent unit locations, there is a waiting time to make cavitation nuclei distribution of the liquid back to the original state. After acquiring the spatial series of channel domain raw radio frequency (RF) data, we can obtain a 3D cavitation map equivalent to the one detected at one time and over the entire volume. The acquisition of the raw RF signals for each unit location is synchronized with HIFU exposure. The duration of HIFU exposure, as well as the delay of the interrogating pulse relative to the moment while HIFU is turned off, can vary from microseconds to seconds.

The 3D-UPACM that we undertake would strictly only be valid when the cavitation distribution is repeatable if all conditions including HIFU output and the physical properties of surrounding medium are same. It has been proved that ultrasound, host media, and nuclei parameters are important in determining cavitation activity *in vitro* [38–40]. In addition, cavitation is highly complex