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On Combination of Hadamard-encoded Multi-pulses and Multiplane Wave Transmission in Contrast-Enhanced Ultrasound Imaging

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Abstract

Contrast-enhanced ultrasound (CEUS) imaging has great potential for use in many new ultrasound clinical applications. We recently proposed a novel CEUS imaging sequence, Hadamard-encoded multi-pulses (HEM), to improve the signal-to-noise (SNR) and contrast-to-tissue ratio (CTR) as compared to other classic CEUS methods. HEM increases microbubble responses by using longer coded transmit pulses and the fast polarity change between coded pulses. In this study, we propose to combine the HEM pulse with multiplane wave (MW) imaging technique to further improve CEUS imaging SNR and CNR. During MW-HEM transmissions, the microbubbles undergo multiple fast pulse polarity changes, leading to significantly improved microbubble nonlinear responses, and thus further enhanced SNR and CTR as compared to HEM alone or other CEUS sequences. This improvement may facilitate more robust CEUS imaging for deep abdominal organs and the heart.

Keywords

Contrast-Enhanced; Ultrasound Imaging (CEUS); Hadamard-encoding; Multiplane wave transmission

I INTRODUCTION

THE development of contrast-enhanced ultrasound (CEUS) imaging brings great opportunities for many clinical applications such as myocardial perfusion imaging [1] and abdominal lesion characterization [2]. The contrast agents are encapsulated microbubbles used to improve the contrast between blood and tissue for their high nonlinearity under low mechanical index (MI). In our previous studies, we proposed a new CEUS pulse sequence, Hadamard-encoded multi-pulses (HEM) [3]. HEM consecutively emits two pulses encoded by a 2nd-order Hadamard matrix in each of the two pulse-echo events. The microbubble responses can thus be improved by the longer transmit pulses. The fast polarity change between consecutive coded pulses can also excite additional nonlinear echoes from microbubbles. In addition, the implementation of a fundamental bandpass filter (i.e., filter

centered on transmit center frequency) in HEM facilitates tissue harmonic signal suppression. Consequently, HEM significantly improves CTR and SNR of microbubble responses in CEUS imaging as compared to other classic methods such as pulse inversion (PI), amplitude modulation (AM), and pulse inversion amplitude modulation (PIAM) [4–7].

Multiplane wave (MW) imaging [8] was recently proposed as a method of increasing the image SNR in conventional coherent plane wave compounding [9]. In our previous work [10], we have described a novel strategy of combining classic CEUS sequences with MW compounding to increase the microbubble responses in plane-wave-based CEUS imaging. In this study, we will extend the combination strategy to HEM and MW transmissions following a similar strategy. The MW-HEM method can further enhance the CTR and SNR in CEUS techniques by using multiple fast polarity changes between consecutive coded pulses. This may facilitate robust CEUS to be applied in many challenging clinical conditions such as endocardial border delineation for patients with larger body mass index, imaging small vessels with weak flow, or characterizing deeply located abdominal tumors [16].

II Methods

A. Combining HEM with Multiplane Wave Compounding

Fig. 1 shows a pulse design example of combining HEM with a two-angle MW compounding. This MW-HEM sequence contains four transmission events (i.e., TX #1–TX #4), each with four tilted plane wave emissions. These four emissions can be further separated into two HEM pulse pairs, each pair containing two consecutive pulses steering at the same angle (i.e., $+1^\circ$ or -1°). The polarity of each emitted pulse follows the 4th-order Hadamard matrix [Eq. (2)][11], which are labeled in red in Fig. 1. A short interleaved time delay, t , is added between adjacent HEM pulse pairs. t needs to be carefully determined for the microbubbles to return to a relatively non-oscillating status after the previous HEM pulse pair excitation for proper decoding. In this study, t value was determined experimentally which will be given in *Section II. C*.

The two-angle MW-HEM transmission process shown in Fig. 1 can be described as

$$H_4 P = M () \quad 1$$

or expanded as:

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \end{bmatrix} \begin{bmatrix} p_{1, +1^\circ} \\ p_{2, +1^\circ} \\ p_{1, -1^\circ} \\ p_{2, -1^\circ} \end{bmatrix} = \begin{bmatrix} m_1 \\ m_2 \\ m_3 \\ m_4 \end{bmatrix} \quad 2$$

Each row in $\mathbf{H}_4$ corresponds to one transmission event, and each column corresponds to the polarity of one emitted pulse in a given transmission event. $\mathbf{P}$ is a column vector with elements p_{1j} or p_{2j} , which correspond to the echo RF signals acquired with Pulse 1 or Pulse 2 individually at steering angle j . For example, $p_{1,+1^\circ}$ in Fig. 1 stands for the signal acquired with Pulse 1 (without Pulse 2) excitation at steering angle $+1^\circ$. $\mathbf{M}$ is a column vector with elements of m_l , which are the received echoes from the l -th MW-HEM transmission event (e.g. m_1 is the received signal from Fig. 1, TX #1).

After MW-HEM transmissions, a bandpass filter centered on the transmit center frequency is applied to the received RF signals to eliminate 2nd harmonic signals as they do not follow Hadamard encoding [12]. Then the filtered signals undergo the decoding steps by multiplying the received echoes (i.e., $\mathbf{M}$) by the inverse of the coding matrix as:

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \end{bmatrix} \begin{bmatrix} m_1 \\ m_2 \\ m_3 \\ m_4 \end{bmatrix} = \begin{bmatrix} 4p_{1,+1^\circ} \\ 4p_{2,+1^\circ} \\ 4p_{1,-1^\circ} \\ 4p_{2,-1^\circ} \end{bmatrix} \quad 3$$

The signals, p_{1j} and p_{2j} , are decoded HEM pulse pair. They are equivalent to those obtained from individually exciting HEM pulses 1 and 2 at steering angle j in separate transmission events, but with higher amplitudes. All decoded signals are then realigned in fast time to compensate for the interleaved time delay t introduced by MW, and the one pulse-length time interval between p_{1j} and p_{2j} introduced by HEM.

Afterwards, the linear tissue signals can be suppressed and the nonlinear microbubble signals can be preserved through the recombination between decoded and realigned HEM pulse pairs as $p_{1j}-p_{2j}$

B. Phantom Experiment Setup

The MW-HEM method was tested on a flow-cell phantom using similar experimental setup as described in [3]. A suspension of microbubbles (Definity, Lantheus Medical Imaging, N. Billerica, MA, USA) was diluted in saline to a ratio of 1:10000 [14]. Controlled by a syringe pump (KD Scientific Inc. Holliston, MA, USA), the microbubble suspension was steadily flowed through the CEUS cell at an approximate flow speed of 5 mm/s to replenish microbubbles for each measurement.

A Verasonics Vantage system with a linear array transducer L11-4v (Verasonics Inc., Kirkland, WA) was used in this study. In addition to MW-HEM, HEM and classic AM implemented with coherent plane wave compounding, and MW-AM [10] images were also obtained as benchmarks. MI was set to 0.1. Classic AM were implemented by reducing the amplitude of the second transmit pulse to half of the first pulse. Four compounding angles ($-3^\circ, -1^\circ, 1^\circ, 3^\circ$) were used which were selected to balance the tradeoffs among resolution, signal-to-noise ratio and post-compounded frame rate. Each steering angle was

emitted twice in HEM (by Pulses 1 and 2) and classic AM (by pulses with full and half amplitudes). This led to eight emitted pulses in total in both CEUS techniques. Therefore, during MW transmissions, an 8th-order Hadamard coding matrix ($\mathbf{H}_8$) was needed for both MW-AM and MW-HEM. The +1 pulse was a one-cycle pulse at 4.5 MHz center frequency. The -1 pulse was transmitted by inverting the pulse polarity of the +1 pulse. The same fundamental bandpass filter as in [3] was applied to all CEUS imaging sequences for optimized image qualities. The short interleaved time delay (τ) in MW transmissions was 1 μ s for MW-AM and 2 μ s for MW-HEM. τ in MW-HEM was doubled to accommodate the longer transmit pulses. The τ values were selected experimentally based on findings that no significant improvement of image quality could be gained with τ above 1 μ s for MW-AM and 2 μ s for MW-HEM.

Image quality metrics CTR and resolution were evaluated and compared for all sequences. In addition, CTR measurement at different imaging depths, different microbubble concentrations, and different flow velocities were studied and compared among all methods.

III Results

Fig. 2 shows the flow-cell phantom images obtained with (a) AM, (b) MW-AM, (c) HEM, and (d) MW-HEM, respectively. HEM provided better CTR between the flow cell and the tissue background (values shown in the titles of sub-images) as compared to classic AM thanks to the increased transmit pulse length and the increased nonlinear microbubble signals as a result of fast polarity change between coded pulses [3]. After combining with MW, both MW-AM and MW-HEM presented significantly improved CTR as compared to the CEUS sequences in standard plane wave compounding. The multiple fast pulse polarity changes during MW-HEM transmissions excite strong nonlinear microbubble echoes, leading to the highest CTR value in MW-HEM among the four sequences.

The lateral and axial resolutions inside the flow cell were estimated using speckle autocovariance function [15] for different CEUS images as summarized in Table I. All sequences had comparable lateral resolutions because they had similar transmit aperture and frequency bandwidth. For axial resolutions, HEM and MW-HEM images had slightly degraded axial resolutions as compared to AM and MW-AM. This may be because the HEM or MW-HEM used two consecutive pulses with fast polarity changes, which induced more complicated microbubble responses. This may lead to incomplete decoding of microbubble echoes, and thus degraded axial resolution.

Fig. 3 shows the CTR quantification as a function of depth in the proposed MW-HEM as well as other studied CEUS methods. MW-HEM preserved the improved CTR values at different imaging depths. This result is in agreement with the flow cell phantom images. In addition, the effect of microbubble concentration among all methods was also investigated as shown in Fig. 4. The microbubble to saline ratio varied from $0.25:10^4$ to $2:10^4$. As the amount of microbubbles added to the solution increased, the CTR was improved for all methods as expected until it reached the plateau. MW-HEM showed consistent improvement in CTR over other CEUS methods throughout the microbubble concentration range tested. Moreover, the CTR enhancement in MW-HEM is more significant at lower microbubble

concentrations (e.g., $0.25 \cdot 10^4$ and $0.5 \cdot 10^4$) which makes the method more attractive for imaging small vessels with weak flow. Fig. 5 shows the influence of flow velocity of the microbubble solution on the MW-HEM performance as compared to other CEUS methods. All sequences showed slight decrease in CTR with increased flow velocity. Such degradation may be because the stationary assumption (e.g., the imaged object remains still between different pulse echo events) was violated. The flow speed had more severe effect in MW-AM and MW-HEM as compared to AM and HEM: the CTR decreased at a faster rate with increased flow velocities. This may be because the MW transmissions contained multiple coded pulses and required more rigorous echo registration for complete decoding. One can consider using smaller Hadamard encoding orders for better performance at high flow rate, at the expenses of compromised CTR improvement.

IV Discussion

This paper described the combination of MW transmission and the recently proposed HEM microbubble sequence. MW-HEM image demonstrated enhanced image CTR as compared to classic AM, HEM, and MW-AM. Note that in both MW-AM and MW-HEM, each transmission event contained the same number of emitted pulses (i.e., eight pulses in this study). Therefore, the higher CTR in MW-HEM as compared to MW-AM may be a result from the stronger nonlinear microbubble response excited by the multiple fast pulse polarity changes during MW-HEM transmissions. Another possible reason for the higher CTR in MW-HEM is that the tissue residue signals in MW-HEM mainly existed at the 2nd-harmonic frequency which could be largely suppressed by the fundamental bandpass filter [3]. For MW-AM, as analyzed in [10], the tissue residue signals contains nonlinear energy within the fundamental bandwidth which could not be removed by the fundamental bandpass filter. Such component increases with Hadamard coding orders, undermining the CTR improvement in MW-AM. Therefore, the Hadamard coding order selection in MW-AM is a tradeoff between microbubble signal improvement and tissue harmonic amplification [10]. In contrast, MW-HEM is more flexible in order selection to improve the CEUS image quality. The CTR enhancement and the flexibility of coding order selection extended the potential of MW-HEM imaging for different applications such as imaging small vessels with weak flow or characterizing deeply located abdominal tumors [16].

The axial resolution in MW-HEM had slight degradation as compared to MW-AM. Another noticeable artifact in MW-HEM image is the longer 'tail' [pointed by the red arrow in Fig. 3 (d)] beyond the microbubble region as compared to other CEUS images. These may be because microbubbles produced complicated responses when they underwent the multiple fast polarity changes during MW-HEM transmissions. This led to incomplete Hadamard decoding of the microbubble echoes, resulting in degraded axial resolution and the tail-shaped artifacts below the microbubble flow cell. MW-HEM preserved the CTR improvement at different imaging depths and different microbubble concentrations as compared to other CEUS methods. However, MW-HEM is more vulnerable to high flow rate as compared to AM or HEM due to incomplete decoding of microbubble echoes. Smaller coding orders can be considered for better echo registration. The MW-HEM method was tested based on Definity contrast microbubbles because it is a FDA-approved agent and widely used in clinical practice. Preliminary evaluation was also performed on Optison (GE

Healthcare Inc., Marlborough, MA) using the same setup as for Definity and similar CTR improvement in MW-HEM was observed as compared to other CEUS methods. Note that the short interleaved time delay between multiple HEM pulses may need to be optimized for different types of microbubbles ($2\text{ }\mu\text{s}$ used in the study which worked for both Definity and Optison). Different microbubbles may also respond differently at various transmit center frequencies. Future studies are needed to systematically investigate and optimize the MW-HEM sequence for different microbubbles.

As previously demonstrated in [10], MW-AM did not introduce extra microbubble disruption or decorrelation as compared to classic AM at low MI . It is expected that MW-HEM would behave similarly as MW-AM in the context of microbubble disruption and decorrelation. These properties make MW-HEM an attractive method for deep and challenging imaging applications which require better penetration and SNR.

V Conclusion

In this paper, the combination of MW and the recently proposed HEM microbubble sequence was described. MW-HEM provided significantly enhanced CTR as compared to HEM, classic AM, and MW-AM. The enhancement offers great potential of facilitating more robust CEUS imaging for deep and challenging tissues as well as the epidemics of obesity.

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Fig. 1.

Transmission pulse design for the two-angle MW-HEM imaging sequence using a tristate pulser. The sequence includes four transmission events (i.e. TX#1–4), each containing four plane wave emissions. The four angled emissions can be grouped into two HEM pulse pairs, each corresponding to one steering angle. A small interleaved time (Δt) was added between adjacent HEM pulse pairs. The red ± 1 labels indicate the pulse polarities at each angle in each transmission event.

Fig. 2.

Flow-cell phantom images acquired with (a) AM, (b) MW-AM, (c) HEM, and (d) MW-HEM sequences. The dotted (tissue) and solid (contrast) boxes at 5 cm depth in (a) indicate the region-of-interest (ROI) selections for CTR quantification. The mean CTR values are shown in the subtitles with standard deviations from four repeated measurements.

Fig. 3. CTR quantification as a function of depth obtained with AM, MW-AM, HEM and MW-HEM. The mean values are plotted with standard deviations shown as error bars from four repeated measurements.

Fig. 4.

CTR quantification as a function of microbubble concentration obtained with AM, MW-AM, HEM and MW-HEM. The mean values are plotted with standard deviations shown as error bars from four repeated measurements.

Fig. 5. CTR quantification as a function of flow velocity of microbubble solution obtained with AM, MW-AM, HEM and MW-HEM. The mean values are plotted with standard deviations shown as error bars from four repeated measurements.

Table I.

LATERAL AND AXIAL RESULTION QUANTIFICATIONS OF FLOW CELL IMAGES IN Fig. 2

	Lateral (mm)	Axial (mm)
(a) AM	0.6	0.5
(b) HEM	0.6	0.6
(c) MW-AM	0.6	0.6
(d) MW-HEM	0.6	0.7

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