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Hadamard-Encoded Multi-Pulses for Contrast-Enhanced Ultrasound Imaging

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Abstract

The development of contrast-enhanced ultrasound (CEUS) imaging offers great opportunities for new ultrasound clinical applications such as myocardial perfusion imaging and abdominal lesion characterization. In CEUS imaging, the contrast agents (i.e., microbubbles) are utilized to improve the contrast between blood and tissue based on their high nonlinearity under low ultrasound pressure. In this paper, we propose a new CEUS pulse sequence by combining Hadamard-encoded multi-pulses (HEM) with fundamental frequency bandpass filter (i.e., filter centered on transmit frequency). HEM consecutively emits multi-pulses encoded by a second-order Hadamard matrix in each of the two transmission events (i.e., pulse-echo events), as opposed to conventional CEUS methods which emit individual pulses in two separate transmission events (i.e., pulse inversion, amplitude modulation, and pulse inversion amplitude modulation combined). In HEM imaging, the microbubble responses can be improved by the longer transmit pulse, and the tissue harmonics can be suppressed by the fundamental frequency filter, leading to significantly improved contrast-to-tissue ratio (CTR) and signal-to-noise ratio (SNR). In addition, the fast polarity change between consecutive coded pulse emissions excites strong nonlinear microbubble echoes, further enhancing the CEUS image quality. The spatial resolution of HEM image is compromised as compared to other microbubble imaging methods due to the longer transmit pulses and the lower imaging frequency (i.e., fundamental frequency). However, the resolution loss was shown to be negligible and could be offset by the significantly enhanced CTR, SNR and penetration depth. These properties of HEM can potentially facilitate robust CEUS imaging for a many clinical applications, especially for deep abdominal organs and heart.

Index Terms

Contrast-Enhanced Ultrasound Imaging (CEUS); Nonlinear imaging; Hadamard-encoding; Multi-pulses

I Introduction

The development of contrast-enhanced ultrasound (CEUS) imaging brings great potential 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. This is because the microbubbles can provide strong nonlinear echoes under low mechanical index (MI), whereas the tissue signals are largely linear at low MI . To better detect the nonlinear microbubble echoes, several CEUS imaging sequences are widely used to suppress linear tissue signals, which includes pulse inversion (PI), amplitude modulation (AM), or by combining both (i.e., PIAM) [3-6]. These CEUS imaging techniques generally involve exciting the contrast agents with two transmission events (i.e., pulse-echo events). The emitted pulse in the second transmission event is generated by modifying the pulse polarity (i.e., PI), amplitude (i.e., AM), or both (i.e., PIAM) of the first transmission pulse. Then the backscattered echo radiofrequency (RF) signals from these two transmission events are combined to selectively cancel the linear response from tissue and amplify the nonlinear response from the contrast agents. However, several groups reported that the tissue had significant nonlinear responses which cannot be neglected even under low MI [7, 8], undermining the image contrast of CEUS. Therefore, the tissue signal suppression (both linear and nonlinear) becomes essential in microbubble contrast imaging. Many efforts have been made to remove tissue signals while preserving microbubble responses by manipulating the transmitted pulses [9-11]. Some other approaches focus on the microbubble nonlinear energy within the fundamental transmitting bandwidth to avoid tissue harmonics [7, 12, 13]. These methods reduce the tissue nonlinear response (i.e., mainly 2nd harmonic) by combining themselves with fundamental filters. Accordingly, they suffer less from frequency dependent attenuation as compared to CEUS imaging with second-harmonic frequency band.

Other than residue tissue signals, the detection efficiency of microbubbles is also hindered by electric noise. This is because the low MI in CEUS imaging sometimes results in low signal-to-noise ratio (SNR) for microbubble responses, especially in deeper imaging region [13-15]. Hence, it would be beneficial to improve the SNR of CEUS imaging without increasing MI . The Golay-coded CEUS sequences are considered. However, one disadvantage of Golay codes is the temporal resolution loss, which makes the method more vulnerable to motion artifacts [13-15].

Here we propose a new CEUS imaging pulse sequence that combines Hadamard-encoded multi-pulses (HEM) and the fundamental filter (i.e., a bandpass filter centered on the fundamental transmit frequency). It improves the CTR and SNR of microbubble responses, and also preserves the same frame rate as in other CEUS sequences. The HEM method emits two consecutive pulses encoded by a 2nd-order Hadamard matrix in each of the two transmission events in CEUS imaging. The pulse polarities follow the assigned Hadamard coding factors. The received echo signals undergo a fundamental bandpass filter to eliminate the 2nd-harmonic components from both the tissue and the contrast agents, due to the fact that 2nd-harmonic cannot be Hadamard encoded by pulse inversion [16]. A standard Hadamard decoding is applied to the filtered echo RF signals. The two decoded RF signals corresponding to two pulses are aligned in time by applying a time shift corresponding to one pulse length. The subtraction between the two decoded and re-aligned RF signals cancels the tissue linear responses whereas the contrast agent nonlinear fundamental energy is preserved. The nonlinear energy from HEM can be improved by the longer transmitted pulses as compared to other commonly used microbubble imaging strategies. In addition, the fast polarity change of the coded pulses excites strong nonlinear responses from the

microbubbles. Even though the tissue 2nd-harmonic response is increased due to longer pulse excitation, the implementation of the fundamental filter helps to reduce the tissue nonlinear responses. The combination of these factors leads to enhanced CTR and SNR in HEM-CEUS imaging without increasing MI .

The paper is organized as follows: *Section II* first reviews the concepts of commonly used CEUS pulse sequences: PI, AM, and PIAM; Then the theory behind HEM excitation is explained in detail. The experiment configurations are also introduced. *Section III* shows the result comparison acquired from different CEUS imaging sequences. The CTR, image resolution, SNR, and penetration depth are analyzed. *Section IV* discusses the advantage of HEM over other CEUS strategies. *Section V* presents the conclusion.

II Methods

A. Contrast-Enhanced Ultrasound (CEUS) Imaging with PI, AM, and PIAM

To better detect the nonlinear signals generated by microbubbles, some CEUS imaging strategies have been proposed. The most commonly used approaches include pulse inversion (PI), amplitude modulation (AM), and by combining both (i.e., PIAM) as shown in Fig. 1 [3-6]. A single pulse transmission sequence is also shown as a reference in Fig. 1. Pulse inversion is performed by exciting two transmission events (TX #1 and #2) with opposite pulse polarities. Afterwards, the received echo RF signals are summed to cancel the tissue linear response and increase the microbubble nonlinear response. Instead of changing pulse polarity, the AM method reduces the amplitude of the second pulse to half in TX #2. Upon combination, the echo RF signals from Pulse 1 subtract the doubled echoes from Pulse 2 to extract microbubble nonlinear signals. PIAM changes both amplitude and polarity of the Pulse 2. The echoes from two transmission events also undergo designed combination to cancel linear tissue signals [3-6].

B. Hadamard-Encoded Multi-Pulse (HEM) Design

Fig. 2 shows a Hadamard-encoded multi-pulse (HEM) design example for CEUS imaging. Similar to the sequences shown in Fig. 1, two pulses are involved in the HEM sequence (Pulses 1 and 2). However, the two pulses are emitted continuously in both transmission events rather than individually in separate transmission events. The extended pulse length increases the transmit pulse energy. As a result, the backscattered signal power from both contrast agents and tissue are increased. The two pulses are identical except that in TX #2, the polarity of second pulse is inverted following a 2nd-order Hadamard-encoding matrix (H_2). The fast polarity change between the two pulses in TX #2 excites strong nonlinear signals from microbubbles. This encoding process can be described as

$$H_2 P = M \quad (1)$$

or

$$\begin{bmatrix} 1 & 1 \\ 1 & -1 \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} = \begin{bmatrix} m_1 \\ m_2 \end{bmatrix} \quad (2)$$

where $\mathbf{P} = [p_1, p_2]^T$ is defined as the echo RF signals acquired with single pulse emission (e.g. p_1 is the signal acquired with Pulse 1 excitation and without Pulse 2 excitation) and $\mathbf{M}$ is the received echoes from coded HEM emissions (e.g. m_1 is the combined signals received in TX #1 from Pulses 1 and 2). A bandpass filter centered around the transmit center frequency is applied before Hadamard decoding. This step aims to eliminate the 2nd-harmonic signals that cannot be properly encoded and decoded by Hadamard matrix. As previously reported, the tissue harmonics (mainly the 2nd-harmonic) could be relatively strong even under low MI [7, 8]. Therefore, another role of this fundamental bandpass filter is to facilitate further tissue signal suppression for HEM-CEUS imaging. Then the filtered signal $\mathbf{M}$ undergoes standard Hadamard decoding process by multiplying $\mathbf{M}$ with the inverse of the Hadamard matrix (i.e. $\mathbf{H}_2^{-1}$) to obtain $\mathbf{P}$:

$$\mathbf{P} = \mathbf{H}_2^{-1} \mathbf{M} \quad (3)$$

or

$$\begin{bmatrix} 1 & 1 \\ 1 & -1 \end{bmatrix} \begin{bmatrix} m_1 \\ m_2 \end{bmatrix} = \begin{bmatrix} 2p_1 \\ 2p_2 \end{bmatrix} \quad (4)$$

After Hadamard decoding, $\mathbf{P}$ is equivalent to the signals that would have been obtained by emitting Pulse 1 and Pulse 2 individually in two separate transmission events. The amplitudes, however, are doubled for both pulses as compared to classic CEUS imaging. Now the two HEM pulses have the same amplitude and polarity except for a time delay (t_{pulse}) in Pulse 2 excitation (Fig. 2 (b)). Same as in PI, AM, and PIAM, the linear responses from tissue must be eliminated via specifically designed combination. However, p_1 and p_2 need to be first aligned in time. This can be accomplished by shifting the RF signal p_2 axially along fast time direction by the pulse length (t_{pulse}) as $p_2(t+t_{\text{pulse}})$. Then the tissue linear response can be cancelled by subtracting the time-shifted Pulse 2 from Pulse 1 as $p_1(t) - p_2(t+t_{\text{pulse}})$.

Fig. 3 shows a pair of transmission events of implementing the HEM-CEUS imaging sequence in plane wave coherent compounding [17, 18] at a sample steering angle (i.e., 3°). The [+ , 0, -] in the legend represent the tristate pulses. The [1, -1] labelled in red stand for Hadamard-encoded pulse polarities, following the 2nd-order Hadamard matrix ($\mathbf{H}_2$). In TX #1 and #2, two pulses are emitted continuously with the same angle. Similarly, other transmission angles following the same excitation pattern (i.e., $\mathbf{H}_2$ -coded transmission pairs) can be obtained. The decoding and recombination steps for the echo RF signals from

different steering angles follow the same instructions in Fig. 2, followed by coherent compounding [19]. As in all other microbubble imaging sequences as shown in Fig. 1, the frame rate of HEM is also reduced by a factor of 2 compared to single pulse plane wave compounding.

C. Nonlinear Tissue Signals in HEM Imaging Sequence

The microbubble detection efficiency in CEUS imaging is affected by the residue tissue signals after pulse recombination, including both linear and nonlinear signals. Several groups reported that tissue had significant nonlinear responses even under low MI [7, 8]. The following text will analyze the effect of nonlinear residue tissue signals in HEM imaging.

The tissue nonlinear responses can be modelled using Taylor series expansion [5] as

$$O(p(t)) = a_1 p(t) + a_2 p^2(t) + a_3 p^3(t) + \cdots + a_N p^N(t) \quad (5)$$

Where a_n is the coefficient describing the nonlinear contribution from each term and $p(t)$ is the transmit pulse. Then the tissue echo RF signals from the two HEM transmission events as in Fig. 2 can be described as

$$O[+1, +1] = \begin{bmatrix} a_1, a_1 \\ a_2, a_2 \\ a_3, a_3 \end{bmatrix} \quad (6)$$

and

$$O[+1, -1] = \begin{bmatrix} a_1, -a_1 \\ a_2, a_2 \\ a_3, -a_3 \end{bmatrix} \quad (7)$$

Only the coefficients for fundamental (a_1), 2nd (a_2), and 3rd (a_3) harmonics are shown for simplicity. In Eqs. (6) and (7), each column on the right-hand side describes the tissue responses to a specific coded HEM pulse on the left-hand side. Therefore, for the ‘-1’ HEM pulse as in Eq. (7), the corresponding a_1 and a_3 in the second column of right-hand side are inverted, whereas the sign of a_2 remains positive because the 2nd-harmonic does not change with pulse polarity. The decoding steps are

$$O(2p_1) = \text{Eq. (6)} + \text{Eq. (7)} = \begin{bmatrix} 2a_1, & 0 \\ 2a_2, & 2a_2 \\ 2a_3, & 0 \end{bmatrix} \quad (8)$$

and

$$O(2p_2) = \text{Eq. (6)} - \text{Eq. (7)} = \begin{bmatrix} 0, & 2a_1 \\ 0, & 0 \\ 0, & 2a_3 \end{bmatrix} \quad (9)$$

For proper signal recombination, the decoded $O(2p_2)$ is shifted by a pulse length (t_{pulse}) to be aligned with $O(2p_1)$ in fast time.

$$O(2p_2(t+t_{\text{pulse}})) = \begin{bmatrix} 2a_1, & 0 \\ 0, & 0 \\ 2a_3, & 0 \end{bmatrix} \quad (10)$$

Afterwards, the signal recombination is applied to cancel the linear tissue signals.

$$O(2p_1(t) - 2p_2(t+t_{\text{pulse}})) = \begin{bmatrix} 2a_1, & 0 \\ 2a_2, & 2a_2 \\ 2a_3, & 0 \end{bmatrix} - \begin{bmatrix} 2a_1, & 0 \\ 0, & 0 \\ 2a_3, & 0 \end{bmatrix} = \begin{bmatrix} 0 & 0 \\ 2a_2, & 2a_2 \\ 0 & 0 \end{bmatrix} \quad (11)$$

For HEM tissue responses, both the linear and 3rd-harmonic components can be cancelled as shown in Eq. (11). The 2nd-harmonic frequency, however, remains in the signal with four times of energy as compared to single pulse transmission. This is because the 2nd-harmonic does not follow Hadamard encoding/decoding and thus could not be removed after signal recombination. This effect motivates the implementation of the fundamental bandpass filter in HEM imaging to suppress the tissue residue at the 2nd-harmonic frequency.

D. Phantom Experiment Setup

The proposed HEM-CEUS imaging method was tested with tissue mimicking phantoms following the recipe as described in [20]. Briefly, the phantoms were fabricated from gelatin (6.67% by weight) with a liquid solution of distilled water and evaporated milk (1:1 mixing ratio), cellulose (1% by weight) providing the ultrasound scatterers, and sorbic acid (1% by weight) as preservative. Two phantom configurations were designed for different perspectives as shown in Fig. 4. Phantom 1 had a 1 cm diameter wall-less flow cell that was approximately centered laterally and at 5 cm depth axially (Fig. 4 (a)). This phantom was designed to evaluate the contrast-to-tissue ratio (CTR) of different microbubble imaging sequences. Phantom 2 had a 6 mm diameter wall-less flow channel embedded with an oblique angle to the imaging surface as shown in Fig. 4 (b). This phantom was designed to characterize the penetration depth (i.e., CTR variations along depth) of different imaging sequences. The tilting angle of the flow channel is approximately 45°, ranging from 3 to 6 cm axially. A suspension of microbubble agent (Definity, Lantheus Medical Imaging, N. Billerica, MA, USA) was diluted in saline to a ratio of 0.1:1000 [13]. Controlled by a

syringe pump (KD Scientific Inc. Holliston, MA, USA), the microbubble suspension was steadily flowed through the CEUS cell or channel at an approximate flow speed of 4.7 mm/s to replenish microbubbles for each measurement. All the measurements were completed within 5 min after the suspension preparation.

A Verasonics Vantage system (Verasonics Inc., Kirkland, WA) with a linear array transducer L11-4v (Verasonics Inc.) was used throughout this study. Five pulse sequences (i.e., single pulse, HEM, PI, AM, and PIAM) implemented in coherent plane wave compounding were investigated and compared. The pulse repetition frequency (PRF) was 6.25 kHz. The same four compounding angles (-3° , -1° , 1° , 3°) were used for all imaging sequences. For microbubble imaging sequences, each compounding angle was transmitted twice by their specific designed pulse pairs (Fig. 1 and 2). This led to 780 Hz post-compounding frame rate for all CEUS imaging sequences, and 1560 Hz PRF for the single pulse sequence. All the five pulse sequences were programmed to be executed consecutively, resulting a total acquisition time of 5.8 milliseconds for each phantom. The +1 pulse was a one cycle pulse with a center frequency of 4.5 MHz. The -1 pulse (as in PI or HEM sequences) was transmitted by inverting the pulse polarity of the +1 pulse. The ± 0.5 pulses (as in AM or PIAM) were realized by reducing the duty cycle of the ± 1 pulses to approximately 50%. The duty cycle was fine-tuned around 50% to ensure minimal mismatch between ± 1 pulses and double of ± 0.5 pulses. The hydrophone measurements showed that the amplitude of the emitted AM/PIAM pulse residue after recombination (e.g. $p_1(+1)-2p_2(+0.5)$) dropped by 25 dB as compared to the amplitudes of ± 1 pulses after fine tuning. All acquisitions were obtained with low *MI* (i.e., *MI* 0.1). The data in all pulse sequences were received with full aperture array and sampled at 36 MHz. The sampling frequency was chosen as an integer multiple of the center frequency to simplify the signal recombination in the receive end. This sampling frequency was also sufficiently high for PI imaging at 2nd-harmonic frequency (i.e., 9 MHz). The HEM data received from each pulse pair excitation underwent fundamental frequency bandpass filtering, Hadamard decoding, and recombination, before beam forming as shown in Fig. 2, to cancel the tissue responses. The fundamental frequency bandpass filter was realized by a Hanning window with cutoff frequencies at 3 and 7 MHz, respectively (i.e., Hanning window gets to zero at 3 and 7 MHz). PI, AM, and PIAM signals were also bandpass filtered for optimized image qualities. The same fundamental bandpass filter as in HEM was applied to the AM and PIAM signals, whereas a 2nd-harmonic bandpass filter with a passband of 6-10 MHz was applied to the PI signals.

In the phantom studies, image quality metrics such as contrast-to-tissue ratio (CTR), lateral and axial resolutions, and penetration depth were evaluated and compared for all the pulse sequences. The CTR was calculated as the mean value difference between contrast region and tissue background [15]. The region selections are shown in Fig. 4 (a) and (b). The lateral and axial spatial resolutions were calculated using speckle auto-covariance function in the contrast region [21]. The penetration depth was evaluated by estimating the CTR changes along depth using the flow channel phantom.

III Results

A. Emitted CEUS Pulse Spectra Study

We first measured the emitted spectra for different CEUS pulses as shown in Fig. 5 by a hydrophone placed close to the transducer surface. The ± 1 pulses in Fig. 5 (a) display equivalent spectra whereas the ± 0.5 pulse spectra in Fig. 5 (b) have decreased amplitudes by approximately 6 dB, which is expected. However, reducing the duty cycles to half for the ± 0.5 pulses induced spectra difference as in the fourth peak of the ± 0.5 pulse spectra (pointed by the black arrow in Fig. 5 (b)). Fortunately, such component can be eliminated by the fundamental bandpass filter and the effect is negligible. After HEM encoding as in Fig. 5 (c), the $[+1 +1]$ pulse presents increased pulse energy by 6 dB as compared to the $+1$ pulse in Fig. 5 (a). The bandwidth, however, was reduced due to doubled pulse length. The $[+1 -1]$ HEM pulse introduced complexity in the spectrum due to the fast polarity change between the two coded pulses. After HEM decoding as in Fig. 5 (d), the two decoded pulses (i.e., p_1 and p_2) have similar spectra, both with increased pulse energy by 6 dB and preserved bandwidths as compared to the single $+1$ pulse emission in Fig. 5 (a).

B. Contrast, Resolution, and Filtering Effect Studies

Fig. 6 shows the flow-cell phantom (Fig. 4 (a)) images obtained with (a) single pulse as a reference, (b) HEM, (c) PI, (d) AM, and (e) PIAM, respectively. The microbubble flow cell was almost undetectable under single pulse sequence as in (a) when it was surrounded by strong tissue signals. However, the CEUS imaging sequences could effectively suppress “tissue” signals in the phantom as shown in Fig. 6 (b) to (e). The HEM image provided the best contrast between microbubble and tissue compared to other CEUS sequences, which can be attributed to the higher energy in the longer HEM transmit pulse. The PI, AM, and PIAM images had degraded contrast-to-tissue ratio (CTR) comparing to HEM image. The CTR was lowest for PI because it mainly relied on the 2nd-harmonic component, which has higher attenuation and thus lower SNR in deeper imaging region. The detailed CTR values are given in the titles of sub-images.

The CTR improvement for the HEM sequence can be further demonstrated by the RF power spectra of all the microbubble imaging sequences as shown in Fig. 7. We show the spectra processed without (top row) and with (bottom row) the bandpass filters. The RF power spectra were analyzed from RF data for all imaging sequences (i.e., data after decoding and recombination, but before beamforming and compounding). Two data segments (~ 12 wavelengths at 4.5 MHz) were selected from the microbubble responses and the tissue responses, respectively, at similar depths for all sequences. A fast Fourier transform was applied to the selected RF segments to obtain the power spectra and then the spectra were averaged over 40 receiving channels (i.e., channel 40 - 80) for display.

In the first row, Fig. 7 (a) and (b) show the power spectra of the microbubble and tissue responses without bandpass filtering at a similar depth, respectively. There are large spectra overlaps between the fundamental and 2nd-harmonic, or the 2nd-and 3rd-harmonic bandwidths in both microbubble and tissue responses. This is because of the wide bandwidth of the short pulse emissions as shown in Fig. 1 and 2. Fig. 7 (c) shows the difference

between (a) and (b), indicating the CTR for different CEUS sequences. From Fig. 7 (c), the nonlinear microbubble energies mainly exist in the fundamental bandwidth for HEM, AM, and PIAM whereas PI generates microbubble nonlinear responses mainly at the 2nd-harmonic frequency. The nonlinear energies at the 3rd-harmonic frequency are negligible for all imaging sequences. The reasons may be: 1) large portion of the 3rd-harmonic energy is cancelled after CEUS pulse recombination; 2) they are attenuated due to the high frequency; 3) the L11-4v transducer (centered at 6.25 MHz) provides limited response at the 3rd-harmonic frequency (i.e., 13.5 MHz). In Fig. 7 (c), the highest CTR was achieved by the HEM sequence thanks to both the longer transmit pulse and the fast polarity change between multi-pulses. The CTR in PI at 2nd-harmonic was lower than those in AM and PIAM due to frequency dependent attenuation. Note PI also excited fundamental nonlinear energy of microbubbles (as pointed by the arrow) which agrees with literature [7]. However, such component was negligible for overall image CTR contribution in deep regions as in Fig. 6 (further analysis will be given in later sections).

After corresponding bandpass filtering (Fig. 7, bottom row), the microbubble and tissue responses outside the filter bandwidths were greatly suppressed. However, there may be spectra leakage due to the overlap among different frequency bandwidths as discussed above. After processed by the same fundamental bandpass filter, the bandwidth of the microbubble response (Fig. 7 (d), labelled by red arrows) for the HEM imaging sequence is narrower than those of AM and PIAM. The tissue responses in HEM (Fig. 7 (e)), however, preserved the same bandwidth as AM or PIAM. This may be because in HEM, after Hadamard decoding, most of the tissue responses could be fully decoded to recover tissue signals that would have been obtained with a single pulse emission. Therefore, the tissue signal bandwidth and axial resolution are preserved as in single pulse excitation as used in AM or PIAM. However, the fast pulse polarity change induced complicated responses of microbubbles which may not be fully decoded through Hadamard decoding. This incomplete decoding may result in reduced bandwidth as shown in Fig. 7 (d) due to the longer transmit pulse of HEM. And consequently, the axial resolution of the microbubble region may be degraded as shown in Fig. 6 (b) when comparing to other CEUS imaging modalities. In Fig. 7 (f), the major CTR components for different CEUS sequences remained unaffected by filtering as compared to Fig. 7 (c). The minor CTR components (e.g., PI fundamental nonlinear energy) outside the filter bandwidths were removed. However, this did not degrade overall image CTR quantification. Instead, thanks to the electric noise deduction during filtering, the overall image qualities were enhanced as compared to the ones without filtering (comparison will be shown in later sections).

For further investigation, the lateral and axial resolution inside the flow cell were estimated using the speckle auto-covariance function [21] for different pulse sequences. The values are shown in Table I. HEM, AM, and PIAM have the same lateral resolution, which is lower than that of the single pulse or PI images. This is due to the lower imaging frequency (i.e., fundamental) than the PI (i.e., 2nd-harmonic) or single pulse sequences (i.e., full transmit bandwidth). For axial resolution measurements, PI provided better result compared to other CEUS sequences as for 2nd-harmonic imaging. This value is slightly lower than that in single pulse image. This may be caused by the reduced bandwidth after 2nd-harmonic bandpass filtering. HEM presented comparable but slightly degraded axial resolution as

compared to AM and PIAM. This may be caused by the longer pulse of HEM imaging resulted from incomplete decoding. Nevertheless, the degradation is only about 10% as compared to AM or PIAM and almost negligible as among the images shown in Fig. 6.

C. Signal-to-Noise Ratio and Penetration Depth Studies

Fig. 8 shows the flow-channel phantom images obtained with (a) single pulse as a reference, (b) HEM, (c) PI, (d) AM and (e) PIAM. The CTR in all methods was analyzed as a function of depth which was used as a metric for SNR and penetration depth quantification. This is because the noise level in the RF signals has big impact on the CTR estimation in CEUS imaging. In addition, such SNR is also affected by the frequency dependent attenuation. Therefore, the CTR obtained in deeper imaging region with higher imaging frequency should be lower than that in shallower area with lower frequency. The CTR values acquired with different CEUS sequences are shown in Table II and then plotted in Fig. 9. The CTR values in PI, AM, and PIAM decreased with depth due to reduced SNR levels. The CTR of PI dropped dramatically due to the higher imaging frequency at 2nd-harmonic. HEM sequence provided the highest CTR values at all imaging depths. In addition, such robust CTR values sustained with a larger range of depth than the rest of the CEUS imaging methods thanks to the higher SNR brought by the longer transmit pulse.

IV Discussion

This paper described a new Hadamard-encoded multi-pulse (HEM) sequence for contrast-enhanced ultrasound (CEUS) imaging. HEM doubles the transmitted pulse length with a 2nd-order Hadamard coding matrix. This leads to higher transmit energy which provides higher microbubble signal-to-noise ratio (SNR). In addition, the fast polarity change between the Hadamard-coded pulses excites strong nonlinear responses from microbubbles (further analysis will be shown below). HEM also uses a fundamental frequency bandpass filter to further suppress tissue harmonics. In this study, HEM was demonstrated to provide increased image contrast-to-tissue ratio (CTR) and SNR in the flow-cell and flow-channel phantom studies when comparing to other commonly used microbubble imaging sequences such as PI, AM, and PIAM (Figs. 5-9).

As opposed to PI, HEM images contrast agents with their fundamental nonlinear responses, so that it suffers less from frequency dependent attenuation, especially in deeper imaging regions. The spatial resolution of HEM is degraded as compared to PI due to the lower imaging frequency band (i.e., fundamental frequency) and longer transmit pulse length. However, such resolution loss was balanced by the significantly improved image SNR and CTR as shown in Fig. 6 and 8. As compared to AM and PIAM, HEM achieved better SNR and CTR thanks to the coded transmissions. The improvement was especially significant in the deeper imaging region. HEM provided comparable lateral and axial resolution to AM and PIAM. Higher Hadamard encoding orders (i.e., above 2) could be considered in the future for further improvement. The decreased frame rate and degraded axial resolution due to incomplete decoding for longer pulse length should be carefully investigated in the future.

To verify that the significant microbubble fundamental nonlinear energy in HEM imaging is not solely attributed to the increased pulse length, we performed the following study. In the

study, we compared HEM with classic CEUS sequences on the flow-cell phantom with doubled pulse length (i.e., two-cycle pulses). Hence, all classic CEUS methods emitted the same pulse energy as HEM. The extra CTR enhancement in HEM may demonstrate the benefit from the fast polarity change between the HEM multi-pulses. Fig. 10 below shows the flow-cell images obtained with HEM and classic CEUS sequences with two cycle pulses, respectively. (The flow cell was pressed by the transducer during imaging and resulted in ellipse shapes.) With the same pulse energy between HEM and other sequences, HEM still provided the best CTR (shown in sub-titles) among all methods even though the improvement was not as significant as in Fig. 6 (i.e., classic CEUS with single pulse emissions). This result implies that strong nonlinear energy was excited when microbubbles underwent the fast polarity transitions in HEM imaging. As shown in Table III, doubled pulse length in classic CEUS methods degraded spatial resolutions compared to those of single pulse as shown in Table I.

The fundamental bandpass filter used in HEM imaging suppresses 2nd-harmonics from both tissue and microbubbles, which could not be Hadamard encoded. AM and PIAM data were processed with exactly the same filter as in HEM for optimized image qualities. As a result, AM and PIAM provided similar image qualities in all tests with only fundamental nonlinear components being imaged. As introduced in [5], AM and PIAM could provide both odd and even numbers of microbubble harmonic responses, which makes them more preferable than PI. However, for the imaging depth as in Figs. 6 and 8, most of the 2nd-and higher-order harmonics were attenuated and made no contribution for the reconstructed CEUS images. Fig. 11, top row, shows an example comparison of PIAM data being processed with (a) no filtering, (b) a fundamental, and (c) a 2nd-harmonic frequency filters, respectively. PIAM with fundamental filter provided the best contrast and was chosen for result presentation in this study. In addition, the PI images acquired with (d) no filtering, (e) a fundamental, and (f) a 2nd-harmonic frequency filters are also shown in Fig. 11, bottom row. It can be seen that PI with the 2nd-harmonic filter gave the best result. Therefore, a 2nd-harmonic filter was used with PI throughout this study to compare with other CEUS pulse sequences. Note that one trade-off brought by the bandpass filters is the degraded axial resolutions in classic CEUS images.

In this paper, the ± 0.5 pulses (as in AM or PIAM) were realized by reducing the duty cycle of the ± 1 pulses to approximately 50%. However, modifying the duty cycle can introduce spectra differences in the transmit pulses. Alternatively, for AM/ PIAM plane wave imaging, a checker-board transmission pattern [18] can be used to achieve better performance. For checker-board AM as an example, it usually includes three transmission events: (1) firing all the odd elements; (2) firing all the even elements; (3) firing the entire array. The summation of the returning echoes from the first two transmission events is subtracted from the echoes from the third transmission event to cancel linear tissue signals. Checker-board AM allows better linear signal cancellation and less hardware complexity [22]. However, the post-compounding frame is reduced as compared to AM/PIAM with amplitude modifications because one additional transmission event is needed at every compounding angle. Therefore, for fair comparison, the AM/PIAM with amplitude modifications were adopted in the study, which have the same number of transmission events as HEM or PI, to evaluate different CEUS sequence performances.

The 2nd-order HEM method introduced in this study is expected to achieve the same frame rate as the rest of the CEUS imaging techniques, and therefore may be susceptible to similar motion artifacts. The only extra step in HEM as compared to other sequences is decoding. The computational time for decoding one post-compounded frame (i.e., 3072 temporal sample points for each receiving channel, 128 receiving channels, 4 compounding angles, and 8 transmission events) was 75 milliseconds using Matlab (The MathWorks, Natick, MA, USA). This extra decoding process is highly parallel and only involves simple additions and subtractions. Therefore, computational cost may be negligible for practical HEM implementation. Other than computational load, the HEM sequence requires relatively wide transducer bandwidth to realize the fast polarity transition between coded pulses as shown in Fig. 2. The L11-4v probe used in this study has a fractional bandwidth of about 100%.

Comparing to other microbubble imaging methods, HEM has an equivalent mechanical index (MI), but a higher spatial peak temporal average intensity (I_{SPTA}) due to the longer transmit pulse. Considering the low MI (i.e., $MI < 0.1$) for CEUS imaging, the increased I_{SPTA} may not be a limiting factor for real time imaging.

V Conclusion

In this paper, a new contrast-enhanced ultrasound (CEUS) imaging pulse sequence, Hadamard-encoded multi-pulses (HEM) combined with a fundamental frequency bandpass filter, has been proposed. HEM increases the contrast-to-tissue ratio (CTR) and signal-to-noise ratio (SNR) of microbubble responses from three aspects: (1) transmitting longer coded pulses; (2) exciting strong nonlinear microbubble echoes by fast polarity change between coded pulses; and (3) the implementation of fundamental filter to further suppress tissue 2nd harmonic signals. As compared to other CEUS imaging sequences including pulse inversion (PI), amplitude modulation (AM), and pulse inversion amplitude modulation (PIAM), HEM has slightly degraded spatial resolution. However, the degradation was shown to be negligible and was balanced by the significantly improved CTR and SNR, especially in deeper imaging regions. The results of this study indicate that the proposed HEM imaging method has good potential to enhance CEUS imaging penetration and provide robust microbubble signals from deep tissues.

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References

1. Lindner JR, Villanueva FS, et al. Assessment of resting perfusion with myocardial contrast echocardiography: theoretical and practical considerations. *American Heart Journal*. 2000; 139(2 Pt 1):231–40. [PubMed: 10650295]
2. Burns PN, Wilson SR, Simpson DH. Pulse inversion imaging of liver blood flow - Improved method for characterizing focal masses with microbubble contrast. *Investigative Radiology*. 2000; 35(1):58–71. [PubMed: 10639037]

3. Simpson DH, Burns PN, Averkiou MA. Techniques for perfusion imaging with microbubble contrast agents. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. 2001; 48(6):1483–1494.
4. Simpson DH, Chin CT, Burns PN. Pulse inversion Doppler: a new method for detecting nonlinear echoes from microbubble contrast agents. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. 2002; 46(2):372–82.
5. Eckersley RJ, Chin CT, Burns PN. Optimising phase and amplitude modulation schemes for imaging microbubble contrast agents at low acoustic power. *Ultrasound in Medicine and Biology*. 2005; 31(2):213–219. [PubMed: 15708461]
6. Needles A, et al. Nonlinear Contrast Imaging with an Array-Based Micro-Ultrasound System. *Ultrasound in Medicine and Biology*. 2010; 36(12):2097–2106. [PubMed: 21092832]
7. Li PC, Shen CC, Huang SW. Waveform design for ultrasonic pulse-inversion fundamental Imaging. *Ultrasonic Imaging*. 2006; 28(3):129–143. [PubMed: 17147055]
8. Phillips PJ. Contrast pulse sequences (CPS): imaging nonlinear microbubbles. 2001 IEEE Ultrasonics Symposium Proceedings. 2001; 2:1739–1745.
9. Pasovic M, Danilouchkine M, et al. Broadband reduction of the second harmonic distortion during nonlinear ultrasound wave propagation. *Ultrasound in Medicine and Biology*. 2010; 36(10):1568–80. [PubMed: 20800962]
10. Shen CC, Yeh CK, Chen WS, Wang HW. The effect of third harmonic transmit phasing on contrast agent responses for CTR improvement. *Physics in Medicine and Biology*. 2008; 53(21):6179–94. [PubMed: 18854607]
11. Pasovic M, Danilouchkine M, et al. Second harmonic inversion for ultrasound contrast harmonic imaging. *Physics in Medicine and Biology*. 2011; 56(11):3163–3180. [PubMed: 21540492]
12. Haider B, Chiao RY. Higher order nonlinear ultrasonic imaging. 1999 IEEE Ultrasonics Symposium Proceedings. 1999; 2:1527–1531.
13. Leavens C, Williams R, Foster FS, Burns PN, Sherar MD. Golay Pulse Encoding for Microbubble Contrast Imaging in Ultrasound. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*. 2007; 54(10):2082–2090.
14. Eckersley RJ, Tang MX, Chetty K, Hajnal JV. Microbubble contrast agent detection using binary coded pulses. *Ultrasound in Medicine and Biology*. 2007; 33(11):1787–1795. [PubMed: 17629609]
15. Shen CC, Shi TY. Golay-Encoded Excitation for Dual-Frequency Harmonic Detection of Ultrasonic Contrast Agents. *IEEE Transactions on Ultrasonics Ferroelectrics and Frequency Control*. 2011; 58(2):349–356.
16. Gong P, Song P, Chen S. Delay-encoded Harmonic Imaging (DE-HI) in Multiplane-wave Compounding. *IEEE Transactions on Medical Imaging*. Apr; 2017 36(4):952–959. [PubMed: 27992329]
17. Couture O, Bannouf S, Montaldo G, Aubry JF, Fink M, Tanter M. Ultrafast Imaging of Ultrasound Contrast Agents. *Ultrasound in Medicine and Biology*. 2009; 35(11):1908–1916. [PubMed: 19699026]
18. Couture O, Fink M, Tanter M. Ultrasound Contrast Plane Wave Imaging. *IEEE Transactions on Ultrasonics Ferroelectrics and Frequency Control*. 2012; 59(12):2676–2683.
19. Montaldo G, Tanter M, Bercoff J, Benech N, Fink M. Coherent Plane-Wave Compounding for Very High Frame Rate Ultrasonography and Transient Elastography. *IEEE Transactions on Ultrasonics Ferroelectrics and Frequency Control*. 2009; 56(3):489–506.
20. Farrer AI, et al. Characterization and evaluation of tissue-mimicking gelatin phantoms for use with MRgFUS. *Journal of Therapeutic Ultrasound*. Jun.2016 3:9.
21. Cobbold, RSC. Foundations of biomedical ultrasound. Toronto: Oxford University Press; 2007.
22. Trembaly-Darveau, C. PhD Thesis. Medical Biophysics, University of Toronto; Toronto: Jun. 2016 Contrast-enhanced Doppler Ultrasound Imaging using Plane Waves.

Fig. 1.

Schematic plots of transmission designs for single pulse imaging, PI, AM, and PIAM sequences. These CEUS imaging sequences include two transmission events (i.e., TX#1 and TX#2). All TX#1 events contain the same single pulse as in Pulse 1. TX#2 contains a specifically designed pulse by modifying the pulse polarity, or amplitude, or both (see Pulse 2). The last column shows the combination process designed to cancel tissue signals and extract microbubble harmonics.

Fig. 2.

Hadamard-encoded multi-pulse (HEM) transmission design. The sequence includes two transmission events (i.e., TX#1 and TX#2). Each transmission event contains two pulses emitted continuously (i.e., Pulse 1 and Pulse 2). The sign of Pulse 2 in TX#2 is inverted following a 2nd-order Hadamard matrix. The received signals undergo standard Hadamard decoding. Then Pulse 1 and shifted Pulse 2 (by a pulse length of t_{pulse}) are combined to cancel the tissue responses.

Fig. 3.

A pair of transmission events of HEM-encoded plane wave compounding sequence for CEUS imaging at a 3° steering angle using a tristate pulser.

(a) Phantom 1 **(b) Phantom 2** **Fig. 4.**

Tissue mimicking phantom models. (a) Phantom 1: flow cell phantom; (b) Phantom 2: flow channel phantom. ROIs for microbubble contrast-to-tissue ratio (CTR) calculation are indicated by the solid boxes (contrast) and dashed boxes (background tissue). Note that the ROIs in Phantom 2 moved along the flow channel to calculate the CTR values at different depths.

Fig. 5.

Hydrophone measurements of emitted spectra for CEUS pulses: (a) ± 1 pulses; (b) ± 0.5 pulses; (c) HEM coded pulses; and (d) HEM decoded pulses.

Fig. 6. CEUS images acquired from the flow cell phantom with (a) single pulse, (b) HEM, (c) PI, (d) AM, and (e) PIAM sequences, respectively.

Fig. 7. RF power spectra obtained from microbubbles, tissue, and CTR under CEUS sequences: HEM, PI, AM, and PIAM. The top row shows the spectra processed without filtering whereas the bottom row shows the ones with filtering.

Fig. 8. CEUS images acquired from the flow channel phantom with (a) single pulse, (b) HEM, (c) PI, (d) AM, and (e) PIAM sequences, respectively.

Fig. 9. CTR quantification along depth of the flow-channel phantom images obtained with different pulse sequences.

Fig. 10.

CEUS images acquired from the flow cell phantom with (a) HEM, (b) PI, (c) AM, and (d) PIAM sequences, respectively. Two cycle pulse excitations were used in classic CEUS sequences (PI, AM, and PIAM).

Fig. 11.

PIAM (top row) and PI (bottom row) images processed with (a) no filtering, (b) a fundamental, and (c) a 2nd-harmonic frequency filters, respectively.

Table I

Resolution Quantification of Flow Cell Images in Fig. 6

Resolution (mm)	Single Pulse	HEM	PI	AM	PIAM
Lateral	0.56	0.72	0.49	0.72	0.72
Axial	0.42	0.68	0.46	0.59	0.62

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Table II

CTR Quantification Along Depth of Flow Channel Phantom

Depth (mm)	CTR (dB)			
	Single Pulse	HEM	PI	PIAM
30	9.9	18.0	11.7	15.7
35	8.8	20.4	11.6	19.3
40	8.6	21.7	10.3	16.8
45	10.0	20.2	5.4	16.8
50	10.0	21.6	4.9	16.9
55	6.5	20.8	2.3	12.1
				11.6

Table III
Resolution Quantification of Flow Cell Images in Fig. 10

Resolution (mm)	HEM	PI	AM	PIAM
Lateral	0.73	0.55	0.77	0.77
Axial	0.69	0.60	0.73	0.73

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