

Cumulative Phase Delay Imaging - a new contrast enhanced ultrasound modality

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Cumulative Phase Delay Imaging - a new contrast enhanced ultrasound modality

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Abstract. Recently, a new acoustic marker for ultrasound contrast agents (UCAs) has been introduced. A cumulative phase delay (CPD) between the second harmonic and fundamental pressure wave field components is in fact observable for ultrasound propagating through UCAs. This phenomenon is absent in the case of tissue nonlinearity and is dependent on insonating pressure and frequency, UCA concentration, and propagation path length through UCAs. In this paper, ultrasound images based on this marker are presented. The ULA-OP research platform, in combination with a LA332 linear array probe (Esaote, Firenze Italy), were used to image a gelatin phantom containing a PVC plate (used as a reflector) and a cylindrical cavity measuring 7 mm in diameter (placed in between the observation point and the PVC plate). The cavity contained a 240 $\mu\text{L/L}$ SonoVue[®] UCA concentration. Two insonating frequencies (3 MHz and 2.5 MHz) were used to scan the gelatine phantom. A mechanical index $\text{MI} = 0.07$, measured in water at the cavity location with a HGL-0400 hydrophone (Onda, Sunnyvale, CA), was utilized. Processing the ultrasound signals backscattered from the plate, ultrasound images were generated in a tomographic fashion using the filtered back-projection method. As already observed in previous studies, significantly higher CPD values are measured when imaging at a frequency of 2.5 MHz, as compared to imaging at 3 MHz. In conclusion, these results confirm the applicability of the discussed CPD as a marker for contrast imaging. Comparison with standard contrast-enhanced ultrasound imaging modalities will be the focus of future work.

INTRODUCTION

Several dynamic contrast enhanced ultrasound (DCE-US) imaging methods detects and estimates ultrasound contrast agent (UCA) concentration based on the amplitude of the harmonic components generated during ultrasound (US) propagation through UCAs. However, harmonic generation is not specific to UCAs, as it also occurs for US propagating through tissue. Moreover, nonlinear artifacts affect standard DCE-US imaging causing possible tissue misclassification, misinterpretation of UCA concentrations, and further contrast to tissue ratio (CTR) reduction [1]. Also when considering US tomography, no contrast-specific modality exists, and in particular speed of sound changes due to UCAs are well within those caused by different tissue types [2]. Recently, a new marker for UCAs has been introduced [3]. A cumulative phase delay (CPD) between the second harmonic (2H) and fundamental (F0) component is in fact observable for US propagating through UCAs, and is absent in tissue. In fact, tissue nonlinearity and consequent harmonic formation are a result of the pressure dependency of the speed of sound producing a deformation of the wave-form (wave-form steepening) which cumulates with depth. Figure 1 illustrates this type of deformation by means of numerical results as obtained with the INCS method [4, 5]. An example of a transmitted ultrasound gaussian pulse given at the source location (a) and the related deformed pulse after propagation through tissue (b), together with the corresponding frequency spectrum (c) and fundamental and second harmonic time profile (d), are shown. In particular, it is interesting to notice that the peak of the second harmonic pulse anticipates the peak of the fundamental pulse in time, as effect of the waveform steepening. This ultimately results in a negative time delay between the second harmonic and fundamental pulse. Conversely, this does not occur for harmonics formed due to ultrasound propagation through UCAs, where the harmonic content is in fact produced as a consequence of bubble oscillations after insonification. Here, the peak related to the second harmonic pulse appears with a certain (positive) time delay with respect to the peak of the fundamental pulse [3]. Hence, contrast-enhanced ultrasound tomographic images based on this new marker can be obtained. The process for data acquisition and image formation is discussed in the Methodology Section. Tomographic cumulative phase delay images (CPDI) as obtained at different insonating frequencies are

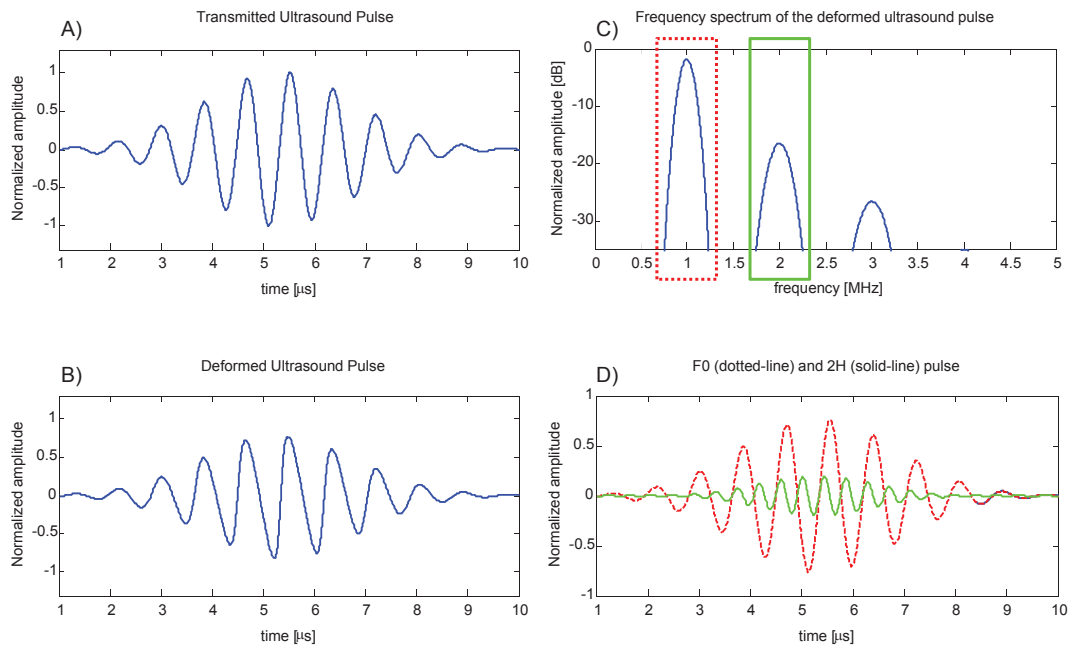


FIGURE 1. Example of transmitted ultrasound gaussian pulse as obtained at source location (a) and related deformed pulse after propagation through tissue (b) together with the corresponding frequency spectrum (c) and band-pass filtered fundamental (dotted-line) and second harmonic (solid-line) time profile (d).

presented in the Results Section. Finally, the paper ends with a discussion on possible clinical applications of these results.

METHODOLOGY

The ULA-OP research platform [6], in combination with a LA332 linear array probe (Esaote, Firenze Italy), were used to image a gelatin phantom containing a PVC plate (used as a reflector) and a cylindrical cavity with a diameter of 7 mm (placed in between the observation point and the PVC plate), see Figure 2. The cavity contained a 240 $\mu\text{L/L}$ SonoVue[®]. UCA concentration. An insonating frequency of $f_0 = 2.5$ MHz and $f_0 = 3$ MHz, and a mechanical index $MI = 0.07$, measured in water at the cavity location with a HGL-0400 hydrophone (Onda, Sunnyvale, CA), were used for imaging. An ultrasound data-set consisting of twenty consecutive frames was acquired for each configuration. Next, the echoes obtained from the PVC plate were processed as described in [3] in order to obtain, for each line imaged, a measure of the time delay (D) between the second harmonic and the fundamental component. Exploiting the employed linear array, D can be estimated as a function of space in the lateral direction. The axis of the cylindrical cavity was positioned at $(z,x)=(80 \text{ mm}, 0 \text{ mm})$, with z and x being the axial and lateral direction, respectively, and with the center of the linear array aperture coinciding with the center of the coordinate system.

For this particular *in-vitro* configuration, we can exploit the symmetry of the target and assume consecutive frames as if acquired from different observation angles. Consequently, a sinogram can be constructed, and an ultrasound image generated in a tomographic fashion using the filtered back-projection method [7].

RESULTS

Figure 3 shows, for $f_0 = 2.5$ MHz, the normalized pressure field reflected from the PVC plate (top), as obtained from a single frame, and corresponding delay values (bottom) measured as a function of x . The mean values (solid line), \pm the standard deviation (error-bars) measured over twenty consecutive frames are shown. When observing the reflected

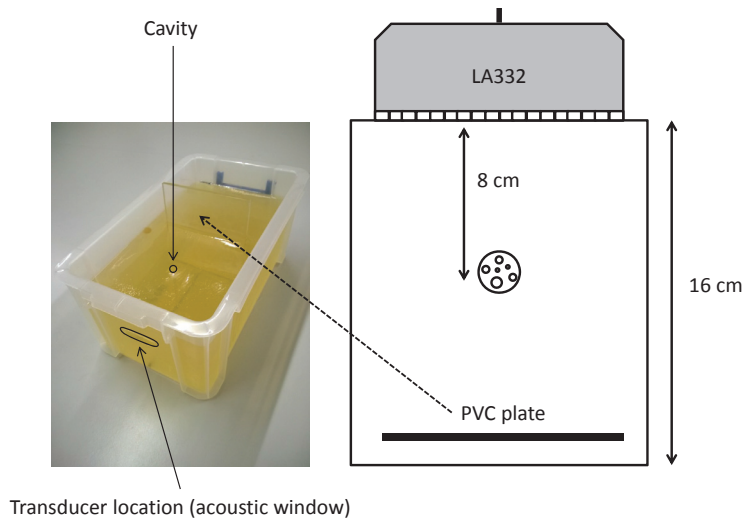


FIGURE 2. Picture (left) and schematic representation (right) of the utilized phantom.

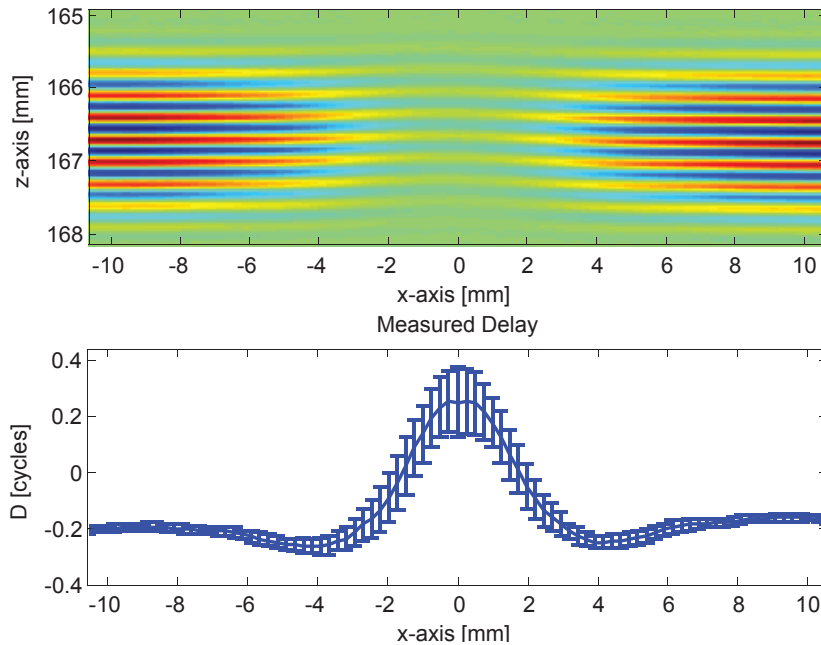


FIGURE 3. Normalized pressure field reflected from the PVC plate (top), as obtained from a single frame, and corresponding delay values (bottom) measured as a function of the x -axis. The mean values (solid line), \pm the standard deviation (error-bars) measured over twenty consecutive frames are shown.

pressure field, higher attenuation in correspondence to the cavity location, from x equal to -3.5 mm to 3.5 mm, is clearly visible. Analyzing the measured delay, this appears negative (-0.2 cycles) and relatively constant for tissue. Conversely, when entering the area corresponding to the propagation paths through the cavity, the delay increases to a max value of approximately 0.4 cycles, which is obtained in correspondence to the largest propagation path length through UCAs. It is also interesting to notice increased variability of D with increasing propagation path length through UCAs. This most likely relates to local variations in UCA concentrations over time. Figure 4 shows CPDI results as obtained with a transmitted frequency equal to 2.5 MHz (left) and 3 MHz (right), respectively. Image values

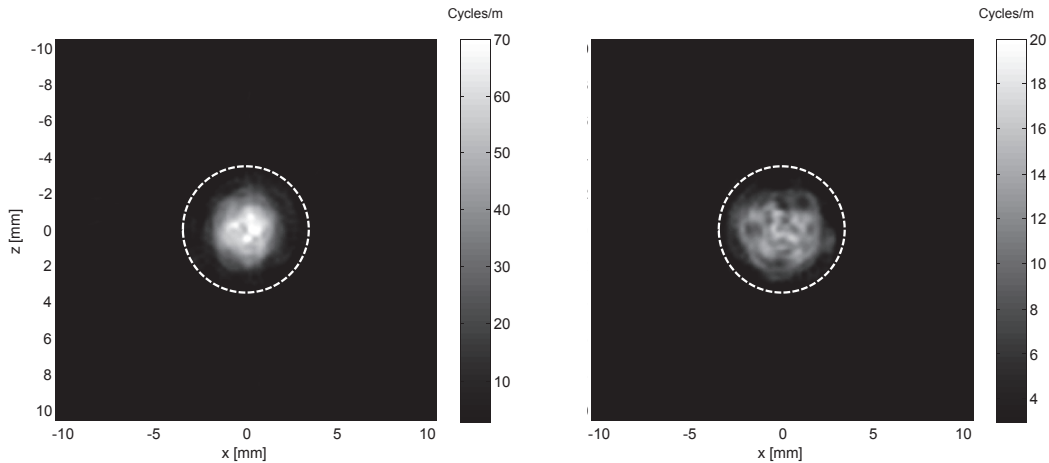


FIGURE 4. CPDI results as obtained with a transmitted frequency of 2.5 (left), and 3 MHz (right), respectively. The dashed circle indicates the cavity.

relate to the measured delay and are expressed in cycles/m. Values above 3 cycles/m are displayed, as this represents a suitable threshold for discriminating contrast from tissue. As already observed in [3], significantly higher CPD values are measured when imaging at a frequency of 2.5 MHz, as compared to imaging at 3 MHz.

CONCLUSION

Although a simple set-up was adopted, where the symmetry of the imaged target facilitated the image formation, these results confirm the applicability of CPD as a marker for contrast specific ultrasound imaging. These results may find relevant application in the development of contrast enhanced ultrasound tomography of the breast aimed at angiogenesis imaging for cancer detection and localization. Comparison with standard contrast-enhanced ultrasound imaging modalities will be the focus of future work.

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