Cumulative phase delay imaging for contrast-enhanced ultrasound tomography

Citation for published version (APA):

DOI:
10.1088/0031-9155/60/21/L23

Document status and date:
Published: 07/11/2015

Document Version:
Publisher’s PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.
Cumulative phase delay imaging for contrast-enhanced ultrasound tomography

This content has been downloaded from IOPscience. Please scroll down to see the full text.
(http://iopscience.iop.org/0031-9155/60/21/L23)

View the table of contents for this issue, or go to the journal homepage for more

Download details:

IP Address: 131.155.151.137
This content was downloaded on 04/12/2015 at 11:36

Please note that terms and conditions apply.
Cumulative phase delay imaging for contrast-enhanced ultrasound tomography

Libertario Demi\textsuperscript{1}, Ruud J G van Sloun\textsuperscript{1}, Hessel Wijkstra\textsuperscript{1,2} and Massimo Mischi\textsuperscript{1}

\textsuperscript{1} Laboratory of Biomedical Diagnostics, Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands
\textsuperscript{2} Academic Medical Center Amsterdam, 1105 AZ Amsterdam Zuid-Oost, The Netherlands

E-mail: l.demi@tue.nl

Received 6 August 2015, revised 7 September 2015
Accepted for publication 18 September 2015
Published 13 October 2015

Abstract

Standard dynamic-contrast enhanced ultrasound (DCE-US) imaging detects and estimates ultrasound-contrast-agent (UCA) concentration based on the amplitude of the nonlinear (harmonic) components generated during ultrasound (US) propagation through UCAs. However, harmonic components generation is not specific to UCAs, as it also occurs for US propagating through tissue. Moreover, nonlinear artifacts affect standard DCE-US imaging, causing contrast to tissue ratio reduction, and resulting in possible misclassification of tissue and misinterpretation of UCA concentration. Furthermore, no contrast-specific modality exists for DCE-US tomography; in particular speed-of-sound changes due to UCAs are well within those caused by different tissue types. Recently, a new marker for UCAs has been introduced. A cumulative phase delay (CPD) between the second harmonic and fundamental component is in fact observable for US propagating through UCAs, and is absent in tissue. In this paper, tomographic US images based on CPD are for the first time presented and compared to speed-of-sound US tomography. Results show the applicability of this marker for contrast specific US imaging, with cumulative phase delay imaging (CPDI) showing superior capabilities in detecting and localizing UCA, as compared to speed-of-sound US tomography. Cavities (filled with UCA) which were down to 1 mm in diameter were clearly detectable. Moreover, CPDI is free of the above mentioned nonlinear artifacts. These results open important possibilities to DCE-US tomography, with potential applications to breast imaging for cancer localization.
Keywords: ultrasound contrast agents, ultrasound tomography, contrast enhanced ultrasound imaging

(Some figures may appear in colour only in the online journal)

1. Introduction

Dynamic-contrast enhanced ultrasound (DCE-US) is an imaging modality that finds wide application in medical diagnostics. With DCE-US, diagnostic ultrasound (US) is used in combination with intravascular contrast agents, which are typically gas-filled micro-bubbles encapsulated in a lipid shell. It was first reported in 1968 that gas-bubbles could be exploited as contrast enhancers for US imaging, allowing better visualization of the aortic root wall (Gramiak and Shah 1968). Later, the development of stable trans-pulmonary ultrasound contrast agents (UCAs) made DCE-US imaging also applicable for left-ventricular endocardial border enhancement (Feinstein et al 1990). Nowadays, DCE-US imaging is also used to quantify perfusion (Elie et al 2007) and UCA dispersion (Mischi et al 2012), permitting the characterization of the vasculature architecture, and ultimately being applicable for cancer detection and localization. For these applications in particular, accurate localization and quantification of UCA concentration is crucial.

Standard DCE-US imaging (i.e. harmonic imaging, pulse inversion, and amplitude modulation) detects UCA concentration based on the amplitude of the harmonic components (de Jong et al 2000), that is, emerging frequency content centered at multiples of the transmitted center frequency. However, harmonics generation is not specific to UCA. In particular, due to a nonlinear distortion of the wave-form caused by the pressure dependency of the speed of sound, harmonics are generated also during US propagation through tissue (Averkiou et al 1997, Demi and Verweij 2014). This phenomenon is responsible for deteriorating the contrast to tissue ratio (CTR). Moreover, nonlinear artifacts affect DCE-US imaging causing further CTR reduction, misclassification of tissue, and misinterpretation of UCA concentration (Tang and Eckersley 2006). Differently than standard DCE-US imaging, sub-harmonic imaging exploits the formation of sub-harmonic components (frequency content centered at half the fundamental frequency) to detect and localize UCA. Sub-harmonic imaging results in higher CTRs (Shankar et al 1998, Shi et al 1999). However, the relatively low signal to noise ratio (Maikusa et al 2007) in combination with the complex generation process of sub-harmonic content (Faez 2012) affects the performances of a sub-harmonic based imaging modality.

Overall, these facts limit the applicability of DCE-US. In the search of solutions to these limitations, several research groups have proposed alternative imaging strategies (Krishnan et al 1998, Bouakaz et al 2002, Shen and Hsieh 2008, Olivier et al 2008, Pasovic et al 2010, 2011). The two most recent approaches are reported in Renaud et al (2012) and (Yildiz et al 2015). The first is based on the interaction of counter propagating waves and proposes the use of a pulse sequence with two transmission phases during which a low center frequency pulse, and a copy of it together with a pulse at a higher center frequency, are respectively transmitted. Emitting the low frequency pulse alone during the first transmission phase provides a reference, and comparison of the echoes received in the two phases allows UCA localization. The limitations of this modality are the relatively low sensitivity as compared to standard imaging modalities, and the requirement of a wide-band transmitter (3–9 MHz). The second approach proposes a post-processing algorithm to cancel the effect of tissue nonlinearity by subtracting an estimated tissue contribution from the final image. This approach does not require particular transmission schemes and can be easily applied with standard hardware. The limitations
of this approach are the computational load required by the iterative algorithm necessary for the optimization, and the fact that only artifacts due to tissue nonlinearity are addressed. Moreover, when extending the analysis outside echo-mode US imaging and focusing on US tomography (typically implemented based on speed of sound variations), no contrast-specific modality exists and, in particular, speed-of-sound changes due to UCAs are well within those caused by different tissue types (Hibbs et al 2009). Potentially, harmonic and sub-harmonic amplitude variations may be used in a tomographic fashion for contrast specific US imaging; however, ambiguities due to attenuation phenomena may complicate the applicability of this approach.

Recently, addressing the differences in the physical phenomena behind harmonics formation in tissue and UCAs, respectively, a new marker for UCAs was discovered (Demi et al 2014). A cumulative phase delay (CPD) between the second harmonic (2H) and fundamental (F0) component can in fact be observed for US propagating through UCA. This delay is dependent on agent concentration, propagation path length through UCA, pressure field amplitude, and insonified frequency. Most importantly, this delay is absent in tissue, and clearly observable at frequencies (2.5 MHz) and pressure regimes (0.05 < MI < 0.2) of interest for DCE-US imaging.

In this paper, we investigated the possibility of exploiting this marker to generate contrast enhanced US images. Tomographic in-vitro US images based on CPD are for the first time presented and compared to standard US tomography. Results show the applicability of this marker for contrast specific US imaging, with cumulative phase delay imaging (CPDI) showing superior capabilities in detecting and localizing UCA, as compared to speed-of-sound US tomography. Cavities (filled with UCA) which were down to 1 mm in diameter were clearly detectable. Moreover, CPDI is free of the above mentioned nonlinear artifacts. These results open important possibilities to implement DCE-US tomography, with potential applications to breast imaging for cancer localization. Section 2 introduces the materials and methods utilized to obtain and process the US data. Results are presented in section 3. Discussion and conclusions are reported in section 4.

2. Materials and methods

2.1. Principle

While harmonics generation is not specific to UCAs, the way these harmonics are formed is fundamentally different from those originating from nonlinear propagation through 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. Most importantly, when decomposing the deformed pressure wave into its different frequency components, i.e. fundamental and harmonic components, the peaks of the harmonic components anticipate in time the peak of the fundamental component, as effect of the waveform steepening. This ultimately results in a negative time delay between the harmonic and fundamental components. Conversely, this does not occur for harmonics formed due to ultrasound propagation through UCAs, where the harmonic content is produced as a consequence of bubble oscillations after insonification. Specifically, in this case a positive cumulative phase delay (CPD) can be observed for the second harmonic (2H) with respect to the fundamental component (F0) (Demi et al 2014).

The total delay $D$ between 2H and F0, as measured from a point $A$ to $B$ may thus be modeled as:
\[ D_{\text{AB}} = \int_A^B \text{CPD}(z) \, dz + \int_A^B \Delta c_{\text{tissue}}(z) \, dz, \]  

where \( z \) represents depth, \( \text{CPD}(z) \) is expressed in \( \text{s m}^{-1} \) and accounts for the space dependent apparent velocity difference between \( 2H \) and \( F_0 \) due to propagation through UCAs, and \( \Delta c_{\text{tissue}}(z) \) is expressed in \( \text{m s}^{-1} \) and accounts for the combined effect of wave-form steepening and frequency dispersion.

The effects of tissue nonlinearity and frequency dispersion on the total delay \( D \) have been clustered into a single term as they both result in a negative time delay between \( 2H \) and \( F_0 \). In fact, in line with the Kramers-Kronig relationship between absorption and phase velocity (O’Donnell \textit{et al} 1981), increasing absorption of tissue with respect to frequency relates to an increase in phase velocity against frequency. Conversely, the above described CPD has opposite sign, i.e. positive.

In conclusion, it was hypothesized that variations in the total delay \( D \) can be exploited to detect and image UCAs.

2.2. In-vitro set-up and imaging system

Two types of tissue-mimicking phantoms were used for the \textit{in-vitro} experiment. Phantom 1 is a gelatin phantom containing a single cylindrical cavity with a diameter of 7 mm. Phantom 2 is a gelatin phantom containing three cavities with diameters of 1 mm, 3 mm, and 5 mm, respectively. The cavities were separated by a distance of 4 mm. For both phantoms, the cavities were filled with a 240 \( \mu \text{L L}^{-1} \) SonoVue® UCA concentration. An overview of the \textit{in-vitro} set-up is shown in figures 1(A) and (B).

To reconstruct two-dimensional CPD images, we adopted a transmission CT scanning approach. By including a polyvinyl-chloride (PVC) plate reflector, only one linear array probe is required, serving as transmitter as well as receiver, see figure 1(C). To this end, the ULA-OP research scanner (Boni \textit{et al} 2012) and a LA332 192 elements linear array probe (Esaote, Firenze Italy) were used. The PVC plate was placed at a distance of 160 mm from the transducer. For insonification, we used a 10-cycle pulse with a center frequency of 2.5 MHz, of which the amplitude was modulated by a Hamming envelope. The adopted mechanical index (MI) was 0.07. A sub-aperture of 64 elements was used both in transmit and receive, and linearly shifted over the array to create 129 radiofrequency (RF) lines to form one image (frame) (Thijssen and Mischi 2014). A sampling frequency of 50 MHz was used. A total of 20 frames was consecutively acquired per phantom. In total, three separate data sets (each consisting of 20 frames) were obtained for each phantom.

2.3. Signal processing

First, the echoes backscattered from the gelatin-PVC interface were selected by time windowing in each frame. Next, for each RF line the fundamental and second harmonic components were extracted by bandpass filtering around 2.5 MHz and 5 MHz, respectively. For both \( F_0 \) and \( 2H \) the –12 dB bandwidth was extracted. Next, their envelopes were determined by the Hilbert transform. Finally, the delay between the two components was measured from the maxima of the envelopes. The above described steps are exemplified in figure 2. This process results in the estimation of the total delay \( D \) as a function of the lateral direction \( x \) (see figure 3), representing a projection of the volume imaged. Using the projection data from a set of 20 frames, and exploiting the symmetry of the cavities, a sinogram of the time delays was
constructed. Finally, the filtered back-projection algorithm (Natterer 1986) was used to create a 2D-CPD image.

2.4. Performance evaluation

The obtained CPD US tomographic images were compared to conventional speed-of-sound US tomography. As a performance metric, we evaluated the contrast to tissue ratio (CTR) with respect to the gelatin background. The CTR for a parameter $\xi$, was defined as:

$$\text{CTR}(\xi) = 20 \log_{10} \left( \frac{\sum_{(x,y) \in \Omega} \xi(x,y)}{\sum_{(x,y) \in \Omega} \xi_{bg}(x,y)} \right)$$

where $S$ and $N$ represent the surface and the amount of pixels describing a region. Subscripts $c$ and $bg$ relate to the cavity and gelatine background, respectively.

3. Results

Figure 4 shows the results from phantom 1. CPD images obtained with the cavity filled with (A) only saline, and (B) a 240 $\mu$L L$^{-1}$ UCA concentration, are shown together with a (C) speed-of-sound tomographic image obtained for the same intra-cavity UCA dilution. The circles indicate the cavity (dashed red lines) and gelatine background regions (magenta solid and white dash-dotted lines) used to estimate the CTRs. CPD image values relate to the measured delay, which is here expressed in cycles m$^{-1}$. From figure 4(A) it can be noticed that, in the absence of UCAs, the delay values are all negative. Here, the
total delay values depend only on the second term on the right hand side of equation (1). Figure 4(B) shows enhancement of the cavity, where positive total delay values are measured in the presence of UCA. Figure 4(C) shows that imaging speed of sound variations has a low sensitivity to UCA, considering realistic values in tissue. For example, benign breast tissue shows mean sound speed and standard deviation equal to \(1514 \pm 34\) m s\(^{-1}\) (Li et al 2009). Here, values of speed of sound between 1430 and 1584 m s\(^{-1}\) are shown, corresponding to fat and blood, respectively (Demi and Verweij 2014). The estimated CTRs are reported in table 1. Two types of region have been considered for the gelatine background. Figure 5 shows the histograms obtained from the CPD ((A), (B)) and speed-of-sound ((C), (D)) tomographic images, as obtained when considering the surrounding ((B), (D)) and adjacent ((A), (C)) regions. In figure 5(B), although a clear separation is visible between gelatin and UCA, a significant percentage (41\%) of positive delay values can be observed for gelatine. This percentage reduces to 0\% when considering the adjacent region. The total delay (positive) values observed in the surrounding gelatine region are however very low (\(\leq 8\) cycles m\(^{-1}\)).
Figure 3. (A) Schematic representation of the data set, arranged with respect to axial direction (z), lateral direction (x) and frame number, and (B) measured total delay $D$ from phantom 1. Mean values (solid line) over 20 frames ± standard deviation (error bars) are shown. Increasing total delay is visible for increasing propagation path length through UCA.

Figure 4. CPD images as obtained from phantom 1 with (A) only saline and (B) a 240 μL L$^{-1}$ UCA concentration present inside the cavity. (C) Speed-of-sound tomographic image as obtained for the same intra-cavity UCA dilution. The circles indicate the cavity (dashed red lines) and gelatine background regions, surrounding (solid magenta lines) and adjacent (dash-dotted white lines), used to estimate the CTRs.

Table 1. Contrast to tissue ratio’s (CTR) for cumulative phase delay (CPD) and speed-of-sound (c) US tomography.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Surrounding region</th>
<th>Adjacent region</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPD</td>
<td>10.823</td>
<td>--$^{a}$</td>
</tr>
<tr>
<td>c</td>
<td>0.017</td>
<td>0.024</td>
</tr>
</tbody>
</table>

$^{a}$ Note that, for the adjacent region, no CTR could be obtained for CPDI as the total delay values measured in the gelatin region were all negative, thus allowing perfect classification of that area as tissue.
Figure 6 shows the CPD images as obtained from phantom 1 and 2. The dashed circles indicate the location of the different cavities. For all cavities, a small overestimation of the cavity diameter can be observed.

Figure 7 shows the binary CPD images as obtained after thresholding. White indicates total delay values higher than 15 cycles m$^{-1}$. The dashed circles indicate the location of the different cavities. The line plot shows mean ± standard deviation, calculated over six different data-sets, of the obtained diameter estimation after thresholding with different threshold values. Diameter estimation was performed along the line $z = 0$.

4. Discussion

The applicability of CPDI (in tomographic mode) to the detection and localization of UCAs was investigated and its performances compared to speed-of-sound US tomography. Two different phantoms were used as targets. In total, four cavities with different diameters, ranging from 1 to 7 mm, were filled with a 240 $\mu$L L$^{-1}$ UCA concentration and used as test targets. Results show the capability of CPDI to detect and localize all the cavities. When compared to speed-of-sound tomography, CPDI showed superior capabilities at discriminating UCA from tissue-mimicking material. CTR values equal to 10.823 and 0.017 were respectively obtained for CPDI and speed-of-sound US tomography, when considering a gelatine region which is
surrounding the cavity. For the adjacent region, no CTR could be obtained for CPDI as the total delay values measured in the gelatin region were all negative, thus allowing perfect classification of that area as tissue. Results also showed an overestimation of the cavity size, which is most likely due to the lateral width of the transmitted beam producing an enlargement of the target in the final image. This also explains the occurrence of positive total delay values in the surrounding gelatin region.

Contrary to many contrast-enhanced imaging techniques (counter propagation imaging, pulse inversion and amplitude modulation), CPDI does not require multiple transmission-phases to obtain the necessary information to form the image. This is positively affecting the attainable temporal resolution with this imaging modality.

In this paper, only static measurements were performed. Although the dependency of the phase delay on UCA concentration has already been reported (Demi et al. 2014), no final conclusion can be drawn with respect to the ability of CPDI to quantify variations of UCA concentration.
concentration based on the given results. To this end, and to evaluate CPDI performance with respect to UCA kinetics estimation, experiments with flow-mimicking phantoms can be considered.

The assessment of the phase delay between the fundamental and second harmonic component was performed by estimation of the delay between the maxima of the corresponding envelopes. In more noisy environments this simplistic approach to delay estimation may not be sufficiently accurate. To this end, more advanced techniques can be tested and compared.

In this paper we only reported results obtained with SonoVue®, which is a poly-disperse contrast agent, as to verify whether this technique would be directly applicable to commercially available and clinically approved agents. However, the size distribution of the contrast agent is expected to influence the phase delay between the fundamental and second harmonic. Moreover, the utilized pulses and band-pass filters properties, mainly the bandwidths, are expected to influence significantly the estimation of the phase delay, also in combination with the size distribution of the agent. The influence of these parameters will be investigated, numerically and experimentally, in future work.

5. Conclusion

Although a relatively simple in-vitro set-up was adopted, where the symmetry of the targets imaged facilitated the image formation, this study confirms the applicability of CPD as a marker for contrast specific ultrasound imaging. These results may find relevant application to the development of contrast enhanced ultrasound tomography of the breast aimed at angiogenesis imaging for cancer detection and localization. To this end, investigating the performances of CPDI in estimating UCA flow dynamics and imaging more complex and heterogeneous targets will be the focus of future work.

Acknowledgments

This work was supported by the European Research Council Starting Grant (#280209) and by the Dutch Technology Foundation (STW) VIDI Grant (#10769).

References

Faez T 2012 Subharmonic Venture PhD Thesis Erasmus MC, University Medical Center Rotterdam
Shen C C and Hsieh Y C 2008 Optimal transmit phasing on tissue background suppresion in contrast harmonic imaging Ultrasound Med. Biol. 34 1820–31