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Combining time of flight and diffraction tomography for high resolution breast imaging: Initial *in vivo* results (L)

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Ultrasound tomography (UST) is being developed to address the limitations of mammography in breast cancer detection. Central to the success of UST is the possibility of obtaining high-resolution images of tissue mechanical properties across the whole breast. A recent paper [Huthwaite and Simonetti, J. Acoust. Soc. Am. **130,** 1721–1734 (2011)] made use of a numerical phantom to demonstrate that sufficient image resolution can be obtained by simply treating refraction and diffraction effects in consecutive steps through the combination of ray-based time of flight and diffraction tomography. This letter presents the first experimental demonstration of the method using phantom and *in vivo* data from a cancer patient. © *2012 Acoustical Society of America*. [http://dx.doi.org/10.1121/1.4742697]

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Over the past decade significant progress has been made in the field of ultrasound tomography (UST) for breast cancer detection. A major attraction of this approach is the possibility of mapping tissue mechanical properties such as speed of sound throughout the volume of the breast. Regions of high sound speed have been shown to correlate well with the presence of cancer owing to the higher stiffness of a cancerous mass compared to the surrounding healthy tissue. Importantly, the sensitivity of UST to sound speed contrast becomes critical in dense breasts where x-ray mammography, which is the current gold standard, fails to detect as many as 50% of cancer masses and also results in a very high false-positive rate approaching 80% as shown by Kolb *et al*.[1] The problem of dense breasts is an acute one because it precludes the possibility of early detection in young women who tend to have denser breasts but most importantly because women with dense breasts are also at the highest risk of developing cancer. For this reason the radiology community is driving the development of alternative imaging technologies that could address the limitations of mammography. In this context, UST is a strong candidate with clinical prototypes currently being developed by Delphinus Medical Technologies,[2] Techniscan,[3] and the Karlsruhe Institute of Technology.[4] The main differences between these systems lie in the architecture of the ultrasonic arrays used to measure signals transmitted through the breast and in the imaging methods used to interpret the signals and produce sound speed maps.

The main challenge in the development of UST technology is the integration of the array architecture with the imaging method. From an imaging perspective it would be ideal to surround the breast with transducers distributed over a spherical aperture to interrogate it with a wave incident from any possible solid angle and to measure the transmitted field in any direction. However, such an approach would require a vast number of transducers and ultrasonic channels that are beyond the capabilities of current hardware technology. As a result, the technical solutions implemented in the current prototype systems use sparse arrays combined with mechanical scans that attempt to achieve omnidirectional insonification and detection. The system developed by Delphinus uses a toroidal ring array that encircles the breast and is scanned from the chest wall to the nipple region to sweep the entire volume of the pendulous breast immersed in a water bath. The array contains a single line of transducers arranged along the interior wall of the torus.[2] The system developed by Techniscan uses instead a plane wave source and a two-dimensional planar array of detectors placed on opposite

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sides of the breast. The two arrays are mechanically rotated around the breast and translated vertically to achieve full breast coverage.[3] Finally, the Karlsruhe system uses transducers distributed over a semi-ellipsoidal aperture that contains the breast. Due to the array sparsity the array is rotated and lifted at incremental steps to improve coverage.[4]

Even after mechanical scanning, array measurements contain a significant level of spatial undersampling which, together with the presence of unavoidable experimental noise, are known to introduce errors in the images due to the ill-posedness of the inverse problem. Imaging artifacts tend to be the most severe with those imaging methods that attempt to reconstruct high resolution images. Therefore, the success of UST for breast cancer detection is strongly dependent on the possibility of striking the optimal compromise between a practical array architecture design and a robust imaging algorithm that can achieve sufficient resolution.

Time of flight tomography (TFT), which is based on the ray theory of geometrical optics, provides a robust approach to image formation from sparse array data and for this reason it has been widely employed since the beginning of breast UST research in the early 1970s.[5] Initially, TFT was based on the straight ray propagation model of high energy photons used in x-ray CT resulting in the use of the Radon transform. Now, thanks to advances in computer power, TFT algorithms can account for beam refraction due to sound speed contrast variations inside the breast and have led to what is referred to as bent ray tomography (BRT) which generally yields more accurate reconstructions than straight ray tomography.[6]

Another imaging technique that has been applied to breast imaging is diffraction tomography (DT) which, in contrast to TFT, accounts for diffraction effects and can achieve a higher resolution than TFT.[7–9] However, standard DT suffers from two main drawbacks: (1) It is more sensitive to undersampling and (2) the phase delay accumulated by the incident field as it travels within the breast must be less than π. The latter condition is due to the single scattering approximation[10] implicit in DT and poses a limit to the overall size of the breasts that can be imaged as well as restricting the level of sound speed contrast inside the breast. A large contrast is known to lead to the acoustic equivalent of optical aberrations.

A recent study[11] has shown that the robustness of BRT and the high resolution of DT can be integrated in a single imaging algorithm to reconstruct sound speed maps across a complex three-dimensional (3D) numerical breast phantom. The method named the *hybrid algorithm for robust breast ultrasound tomography,* or HARBUT, uses the BRT image to compensate for the acoustic aberration. In contrast with nonlinear inversion techniques such as those used in Ref. 3, HARBUT does not attempt to minimize a cost function and therefore is not susceptible to local minima and other convergence problems. The image is obtained by applying beamforming (BF) to the transmission measurements (backscattered signals encode little sound speed information) and using focal laws that account for phase distortions through an inhomogeneous sound speed field.[11] In the first instance the focal laws are calculated using the sound speed map provided by BRT. Once the aberration corrected BF image is calculated the sound speed map is obtained by applying a DT filter (a detailed description of the method can be found in Ref. 11). As shown in Ref. 11 HARBUT leads to a drastic resolution improvement over BRT and is intrinsically stable due to the robustness of BRT and BF which underpin it.

To validate the performance and robustness of HARBUT, this letter applies the algorithm to experimental data. The data was obtained with an early prototype system developed by Karmanos Cancer Institute[2] (technology now being developed by Delphinus in collaboration with KCI) using a toroidal array consisting of 256 transducers evenly spaced along the circumference of a 200 mm diameter toroidal array. The transducers were 12 mm tall, 0.5 mm wide, and had a center frequency of 1.5 MHz with 100% bandwidth. The sampling frequency was 6.25 MHz, and pre-BF data was obtained by firing sequentially each of the 256 transducers. For each transmission, the scattered field was recorded with all 256 transducers thus leading to 256×256 waveforms in total. The prototype was used to scan a breast phantom and a cancer patient who had a heterogeneously dense breast containing an invasive, ductal adenocarcinoma of approximately 25×30 mm in size. The presence of the cancer mass and its size were diagnosed by mammography and conventional B-mode ultrasound that showed a poorly differentiated and irregularly shaped hypoechoic mass with associated shadowing; further details can be found in Ref. 9.

The software implementation of HARBUT was the same as that used to process the data from the numerical phantom in Ref. 11. However, different data pre-processing had to be applied to the experimental signals to extract travel times and the Fourier components that are the inputs of BRT and DT, respectively.

The arrival times were obtained with the automatic arrival time picker outlined in Ref. 12. After gating the initial part of each signal preceding the main arrival, the signals were Fourier transformed to provide all the frequency components of the signal spectrum in the 700 to 800 kHz range. This frequency range was below the transducer center frequency and was selected to reduce the effect of transducer undersampling.

For calibration purposes it is desirable to collect one reference dataset before immersing the breast in the water bath to obtain what is known as the incident field. Measurements performed with the breast are referred to as the total field instead. Both BRT and HARBUT use the perturbation induced by the presence of the breast to the incident field to reconstruct sound speed maps. In particular, BRT employs the difference between the arrival times measured with and without the breast while the form of DT implemented in HARBUT uses both the phase and amplitude of the spectral components of the total field.

The arrival time, phase, and amplitude of each measured signal are dependent on the characteristic of the sources which therefore need to be calibrated. For the case studied in

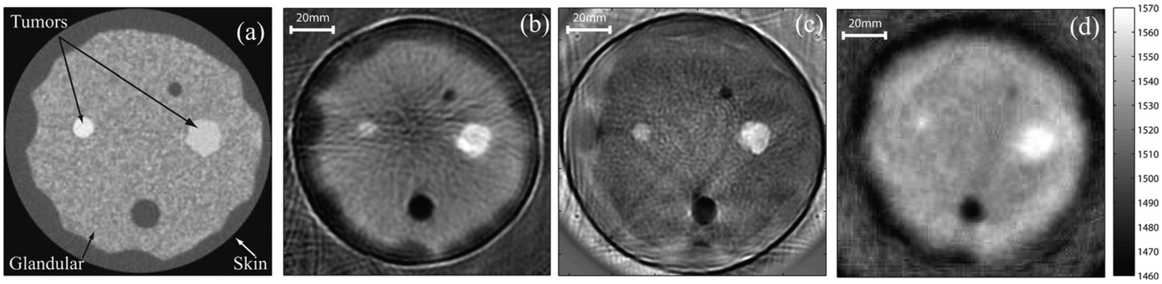

FIG. 1. Experimental images of a 3D breast phantom: (a) X-ray CT image; (b) HARBUT; (c) DT; (d) BRT. HARBUT provides a more accurate reconstruction of the subcutaneous fat layer compared to DT and a higher resolution than BRT.

this letter the incident field measured without the breast was not available, therefore calibration was based on the transmit-receive pairs whose line-of-sight did not intersect the breast. From these signals it was possible to estimate the time when the signals were launched and therefore predict the arrival times of the incident field for the transmit-receive pairs intersecting the breast. To calibrate for phase and amplitude, it is observed that the HARBUT algorithm assumes that each transducer source acts as an ideal point source, $G = -i/4H_0^{(1)}(kr)$ where $H_0^{(1)}$ is the Hankel function of the first kind of order zero, k is the wavenumber in water, and r is the distance from the source. Clearly, the actual transducers are directional and with arbitrary phase and amplitude. Here, the directivity was neglected and it was assumed that the ultrasonic field radiated from the sources, ψ_0, was proportional to G through a complex constant A, i.e., $\psi_0 = AG$. The constant A was determined as the average of the ratio ψ_0/G evaluated for the transmit-receive pairs that did not intersect the breast. Since the scattering model is linear, it was then sufficient to divide the total field measurements by A to obtain measurements consistent with the HARBUT model. Finally, additional calibration was performed to reduce uncertainties on the actual water sound speed and array element position (due to manufacture the elements tend to have a random offset relative to the nominal radius) using the nonlinear method outlined in Ref. 13.

A CT image of the phantom used in the first set of experiments is shown in Fig. 1(a). The phantom consists of several materials mimicking a bulk glandular region embedded in an irregular fat layer covered by skin. Inside the phantom there are four inclusions representing cancer (bright) and fat (dark) masses; more details can be found in Ref. 2. Next, Fig. 1(b) shows the HARBUT reconstruction which provides a very accurate representation of all the features observed in the CT image. The HARBUT image retains the same level of resolution as DT [Fig. 1(c)] and leads to a much more accurate reconstruction of the subcutaneous fat layer where the contrast is too high for DT. Both HARBUT and DT lead to a substantial improvement over the BRT image shown in Fig. 1(d).

Figure 2(a) shows the HARBUT reconstruction of the breast along a plane parallel to the chest wall. The bulk of the breast has a low sound speed compared to the water background that is at 1500 m/s. Most importantly, the image shows an area inside the breast with a higher sound speed which corresponds to the cancer mass. A complex network of filament-like structures is visible throughout the breast with some of the filaments radiating from the cancer mass. The structures could be associated with the complex anatomy of the breast that includes milk ducts and fibrous structures such as Cooper's ligaments as well as the vascularity of the cancer mass. Next, Fig. 2(b) shows the image obtained without compensating for acoustic aberration using standard DT. The image has a comparable level of resolution to HARBUT; however, due to the combination of large contrast and breast size, DT fails to reveal the higher sound speed inside the cancer mass. Many of the structures seen in the DT image are also visible in the HARBUT reconstruction. Figure 2(c) is the BRT image used in HARBUT to compensate for the acoustic aberration. BRT clearly shows the presence of the mass; however, it appears to have a lower resolution than HARBUT. Based on the clinical evidence available for the case considered in this letter it is not possible to assess whether the fine structures observed in Fig. 2(a) are real. From the B-mode image of the same cancer mass it is known that the mass was 25×30 mm^2 in size;[9] this compares to a size of 20×18 mm^2 provided by HARBUT and 16×13 mm^2 from BRT. Although it is likely that the shape of the mass was altered by the pressure required to perform the B-mode exam it appears that

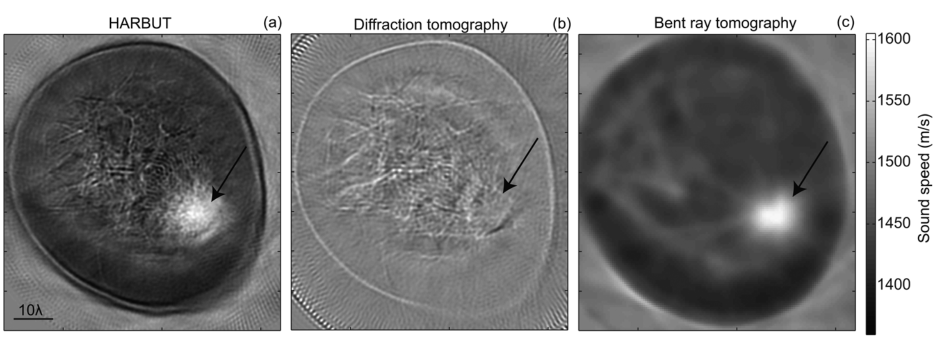

FIG. 2. *In vivo* sound speed maps along a plane parallel to the chest wall obtained with: (a) HARBUT; (b) DT; (c) BRT. The arrows indicate the position of a cancer mass. HARBUT and BRT show an increase in sound speed in correspondence of the mass which is not seen in the DT image. HARBUT and DT show a network of filament-like structures which are not visible in the BRT image. The 10λ scale shown corresponds to 20 mm at the middle of the frequency range used, 750 kHz.

HARBUT leads to more accurate sizing than BRT, thus suggesting that HARBUT achieves a higher resolution than BRT. This result would be consistent with the resolution gain demonstrated with the phantom images in Fig. 1.

While the nature of the detailed structures in Fig. 2(a) remains uncertain, the experimental results presented in this letter clearly demonstrate that the HARBUT approach is robust, providing a reconstruction that yields at least the same information contained in BRT. Moreover, the features observed in the HARBUT image suggest that it may enhance image resolution significantly; a hypothesis consistent with the numerical evidence presented in Ref. 11 and the phantom experiments shown in Fig. 1. Finally, it is demonstrated that HARBUT overcomes the limitations of the single scattering approximation, retrieving a relatively large sound speed contrast corresponding to the cancer mass, which is not visible in the standard DT image.

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