Breast ultrasound tomography: Bridging the gap to clinical practice

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ABSTRACT

Conventional sonography, which performs well in dense breast tissue and is comfortable and radiation-free, is not practical for screening because of its operator dependence and the time needed to scan the whole breast. While magnetic resonance imaging (MRI) can significantly improve on these limitations, it is also not practical because it has long been prohibitively expensive for routine use. There is therefore a need for an alternative breast imaging method that obviates the constraints of these standard imaging modalities. The lack of such an alternative is a barrier to dramatically impacting mortality (about 45,000 women in the US per year) and morbidity from breast cancer because, currently, there is a trade-off between the cost effectiveness of mammography and sonography on the one hand and the imaging accuracy of MRI on the other. This paper presents a progress report on our long term goal to eliminate this trade-off and thereby improve breast cancer survival rates and decrease unnecessary biopsies through the introduction of safe, cost-effective, operator-independent sonography that can rival MRI in accuracy.

The objective of the study described in this paper was to design and build an improved ultrasound tomography (UST) scanner in support of our goals. To that end, we report on a design that builds on our current research prototype. The design of the new scanner is based on a comparison of the capabilities of our existing prototype and the performance needed for clinical efficacy. The performance gap was quantified by using clinical studies to establish the baseline performance of the research prototype, and using known MRI capabilities to establish the required performance. Simulation software was used to determine the basic operating characteristics of an improved scanner that would provide the necessary performance. Design elements focused on transducer geometry, which in turn drove the data acquisition system and the image reconstruction engine specifications. The feasibility of UST established by our earlier work and that of other groups, forms the rationale for developing a UST system that has the potential to become a practical, low-cost device for breast cancer screening and diagnosis.

Keywords: Breast imaging, breast masses, image fusion, ultrasound tomography

1. INTRODUCTION

Acoustic tomography (AT) is a technique that uses computed tomography (CT) methods to solve an inverse problem involving sound signals. It is well suited for inferring acoustic properties of a volume of material from measurements made along a surface surrounding the material. Applications can be found in seismology, process flow, industrial non-destructive testing (NDT) and, increasingly in medical imaging where it is more commonly referred to as ultrasound tomography.

The idea of solving acoustic inverse problems in medicine can be traced back to the work of Wilde and Reid [1] and Howry and Bliss [2] in the 1950's. At that time the systems used were crude mechanical scanners utilizing a single transducer that rotates on an arm and collects reflected signals using the pulse-echo technique. The first cross-sectional breast tissue images were made at that time. However, the lack of computational power, combined with the slow rotation made it impossible to apply this technique clinically. These early methods did give birth to what is now known as B-mode clinical ultrasound. However, the tomographic aspect had to wait almost 30 years before the concept of UST was seriously re-visited.

Since then, a number of investigators have developed operator-independent UST scanners, based on the principles of ultrasound tomography [3]-[8]. Clinical examples include the work of Carson et al (U. Michigan),[3] Andre et al (UCSD),[4] Johnson et al (TechniScan Medical Systems),[5] Marmarelis et al (USC),[6] Liu and Waag (U. Rochester),[7], Gemmeke and Ruiter at Karlsruhe, Germany [8] and Duric and Littrup et al (KCI)[9]. More recently, Ruiter *et al*. [10] have reported progress on a true 3-D scanner utilizing a hemispherical array of transducers. The clinical systems developed by these groups employed similar patient positioning systems. Patients were positioned in the prone position on a flat table with the breast suspended through a hole in the table in a water bath lying just below the table surface. The water batch is a requirement that ensures minimal distortion of the breast while allowing strong coupling of acoustic waves to the tissue.

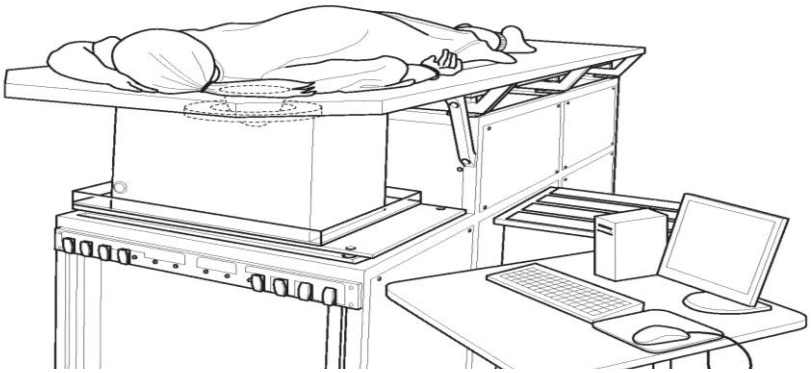

Figure 1: The UST clinical prototype. A patient lies in the prone position such that the breast is suspended inside a water tank that contains the ultrasound sensor. The deformable bed allows access to the chest wall and axillary breast tissue.

In our laboratories, at the Karmanos Cancer Institute (KCI), our group has also focused on the development of ultrasound tomography for breast imaging. To that end we have been developing and testing a clinical prototype in KCI's breast center (Fig 1). The continuing development of the prototype and its associated UST methodology have been guided by clinical feedback from these studies and have led to continuing evolution in imaging performance leading to increasingly greater clinical relevance. This water bath system utilizes a solid state ring array transducer consisting of 256 elements that encircle the breast. It uses a 256-channel data acquisition system that allows single slice acquisitions in about 30 ms leading to whole breast scans of 1 minute or less. Furthermore, it utilizes bent-ray reconstructions for imaging. Although such images have lower spatial resolution compared to wave based approaches they can be run fast, in keeping with the goal of a clinically fast system.

Previously published work [9] describes our research prototype and demonstrates the ability to image the volume of the breast rapidly, without motion artifacts, radiation or breast compression. Furthermore, it demonstrates the feasibility of breast cancer detection with ultrasound tomography, setting the stage for a variety of clinical studies aimed at the life cycle of breast cancer, from risk assessment [11,12] to detection [13-15] to therapy monitoring [16]. The clinical prototype is currently being upgraded into a commercial system, named SoftVue, through the start-up company Delphinus Medical Technologies. The new system will have 2048 active elements and utilize a 512-channel data acquisition system.

The purpose of this paper is to describe the improvements in scanner performance currently being built for commercial and clinical use. We begin with a brief presentation of the performance of the existing research prototype, followed by a description of the commercial scanner and a comparative analysis of the two.

***Research Prototype*.** Our existing research prototype has demonstrated imaging of the whole breast volume. Volumetric imaging has implications for incidental findings and the potential to find multiple cancer foci. We performed a study of 36 patients to first determine whether the scanner could display similar breast structures as MR [15]. The initial focus of the study was to determine how reliably and accurately the breast architecture could be measured. Figure 2 illustrates a comparison of anatomy visualized by the prototype compared to that of MR for four different patients. The MR images (e.g., T1-weighted, fat saturated, gadolinium-enhanced = T1-FS-CE) show the presence of fatty tissue (dark grey), parenchyma (light grey) and fibrous stroma (light bands). The corresponding UST images show fatty tissue (dark grey) parenchyma (light grey) and fibrous stroma (light bands). During the exam, the breast is less distorted by gravity since it is surrounded by water, whereas in MR, the breast is more pendulous within air. This difference accounts for the differences in breast shape notable in Figure 2. Apart from these differences, the study demonstrated that the prototype can accurately map breast anatomy, thereby allowing quality control for artifacts and direct volumetric comparisons to MR. A comparison with MR also validates lesion identification, as shown in Figure 3. A 2 cm cancerous mass, shown in a contrast enhanced MR image is equally visible in a UST image. The UST image verifies the enhancement of SS and AT, as expected for a cancerous mass.

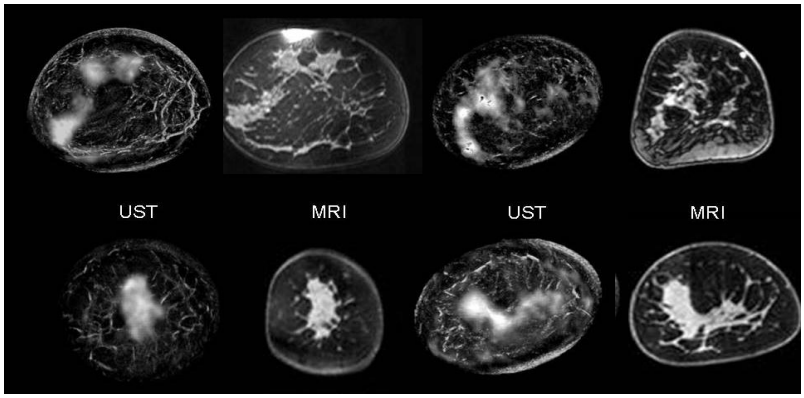

Figure 2. UST fusion image using reflection, SS and AT data shows comparable anatomic distribution of fat, fibro-glandular tissue and fibrous bands as the coronal MRI image (T1 FS CE)

With this initial validation completed we embarked on a study to assess the gap between the current performance of the prototype and the performance needed for a commercial clinical system. The sections below describe the methods used, the results obtained and provide an overview of the commercial system design based on the gap analysis. A discussion of the clinical problem such a system would address is also presented.

2. METHODS

Baseline clinical study: To quantify the ability of UST to detect clinically relevant masses of all sizes, we performed a study of 100 patients with 107 diagnosed masses with either a cyst, fibroadenoma or cancer, ranging in size from 2 mm to over 6 cm. The detection rate was calculated for both the benign and malignant lesions and the performance of the scanner quantified for a continuum of mass sizes.

***Simulations*.** Using the documented performance of the UST prototype as a baseline, we performed simulations to estimate the needed improvements to bridge the performance gap. The simulations were used to (i) generate transducer arrays of varying density and element count, (ii) simulate RF data generated by the arrays and (iii) simulate a variety of signal to noise and dynamic range scenarios for data acquisition systems based on state of the art electronics.

Gap analysis. The baseline performance of the research prototype was compared with the simulation results to initiate a scanner design that would bridge the performance gap.

3. RESULTS

Baseline clinical performance: Table 1 summarizes the research prototype's ability to detect masses of various sizes and types. Despite the current prototype's ability to generate MR-like images, its mass detection performance appears limited for smaller, especially benign masses due to inadequate contrast and beam-width limitations (see below).

***Required improvements in mass sensitivity*.** The initial MR validation of UST, showed that the prototype is sensitive to similar structures as MR and that mass volumes can be quantified, indicating that UST performance has the potential to rival that of MR but at much lower cost. However, these preliminary studies have also identified areas of improvements that are needed in order to bridge the gap between research and clinical use. The performance gap can be quantified by comparing the technical and clinical performance of the current prototype and the desired performance, based on the simulations, as shown in Table 2. The targeted goals are based (i) on the desired ability to consistently detect masses that are routinely biopsied through ultrasound guidance (greater than or equal to 5 mm in size) thus covering almost all invasive cancers and (ii) to be consistent with voxel characteristics of routine MR. The new design minimizes risk by following four simultaneous paths to better mass sensitivity: (i) reducing the image slice thickness, (ii) improving the in-plane resolution (iii) improving image contrast and (iv) suppressing artifacts. The four paths were attained by improving the transducer array density and by utilizing a higher central frequency, as summarized in Table 2.

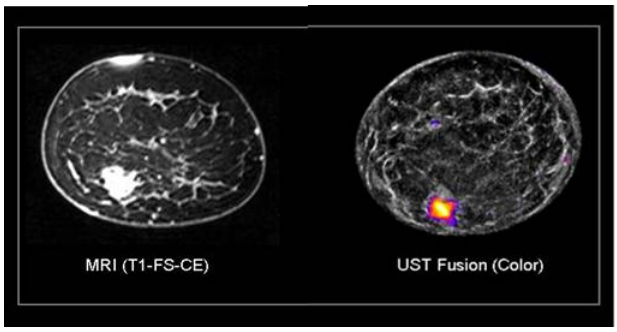

Figure 3. Imaging of a 20mm Invasive Ductal Carcinoma: Coronal T1-FS-CE MR image (left) shows a tumor at 7 o'clock. SS colorized version of the UST image (right) created by a fusion of reflection, SS and ATT images, shows a similar tumor region that is easy to define at a similar coronal level.

Furthermore, the new scanner embodies hardware acceleration of algorithms leading to a clinically relevant image reconstruction time of 15 minutes for a bilateral breast exam.

Table 1: Detection rate for benign masses and cancer

	Tumors		
	Cysts	Fibroadenomas	Cancer
Number included in analysis	19	42	46
Fraction detected by UST (%) [all masses > 5mm]	84%	89%	100%
Desired detection rate by UST (%) [all masses > 5mm]	100%	100%	100%

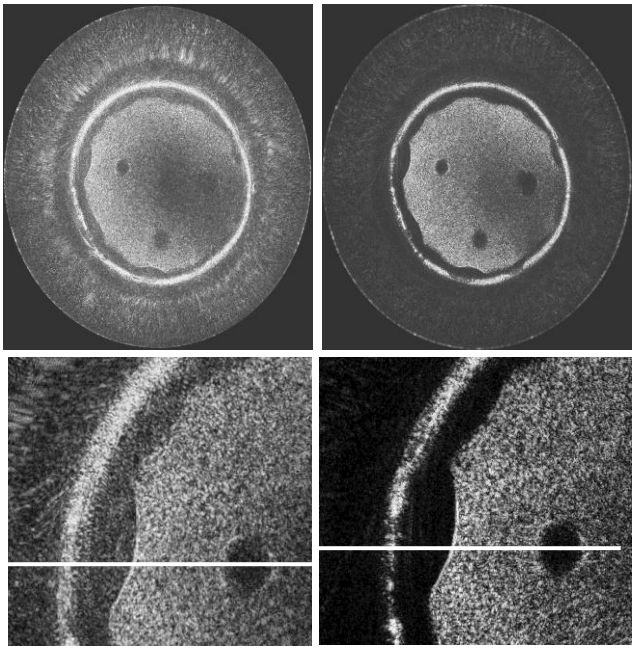

Figure 4. The effect of increasing transducer density. Left column: Original data acquired from 256 transducer elements. Right column: Data combined from 4 rotations of the array. The increase in contrast is evident visually.

Improving Contrast: A greater number of array elements will yield better contrast by virtue of better coverage (reduction of artifacts) and greater number of measurements (greater signal to noise ratio). Furthermore, the flexibility to change the operating frequency provides a path to better spatial resolution. Our focus on better contrast is also motivated by preliminary experimental data.

We have carried out an experiment with the current prototype in which its ring transducer was manually rotated between data acquisitions in order to simulate a higher density array. A calibrated wedge tool was used to produce sub-λ accuracy in rotation. Figures 4 and 5 compare cross-sectional images of a breast phantom using data from a single ring position and combined data from 4 ring positions (i.e. increasing the number of transmit-receive pairs by 4). It is evident that the contrast (signal strength relative to background) is significantly improved and that there is a corresponding reduction in artifacts. The cross-cuts shown in Fig 5 show the direct relationship between the increase in data acquired and the consequent increase in contrast (old value, new value) expressed as a signal-to-noise ratio. Skin: (2.5,7.5); parenchyma relative to fat: (2.5, 10) and cyst (3,7). The new system is designed with 2048 transducer elements, which is 8 times the number of the current prototype. Since the number of transmit-receive pairs scales with the square of the number of elements the new system will yield 64 times the data than is generated by the prototype and 16 times that produced in the experiment above (rotation yields data that scale only linearly with the number of transducer positions). The contrast improvement delivered by the new system should therefore be proportionally greater than the improvement that is shown in Figures 4 and 5, and much greater compared to the current prototype.

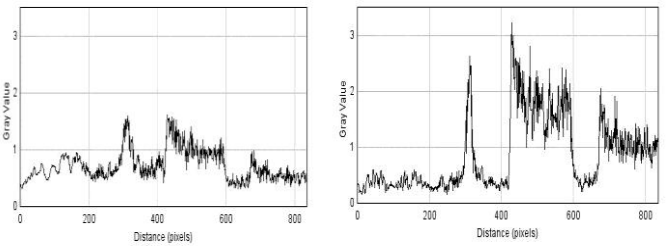

Figure 5. The improvement in contrast is quantified using cross-cuts along the lines shown in Figure 4. The prominent features from left to right are the skin, parenchyma edge and cyst.

Suppressing artifacts: The primary source of artifacts in our current prototype is the wide spacing of the transducer elements (Figure 6). With 256 elements spaced over 20 cm ring, the spacing is about 2λ at 1.5 MHz. With 2048 transducer elements, the spacing is about λ/2 at the new system's central operating frequency of 2.75 MHz. The narrower spacing should greatly reduce the level of artifacts as shown in Figure 6.

Improving In-Plane Resolution: Based on our experience with over 100,000 image reconstructions we have found that bent ray tomography has an inherent resolution limit of ~2λ. In our current prototype this represents ~2mm spatial resolution, corresponding to image pixels of ~1mm. With the increase in frequency from 1.5 MHz to 2.75 MHz the spatial resolution should improve to ~1mm, with image pixels of 0.5 mm.

Reducing slice thickness: The current prototype transducer is characterized by an elevation (*out-of-plane*) beam thickness of 5 mm which also defines the slice thickness of the 2-D cross sectional images generated by the current software. It is defined by the 3 dB fall-off points of an otherwise continuous beam profile. Consequently, the finite beam-width causes volume averaging which limits the contrast of small masses, particularly those whose sizes approach the slice thickness. A study was carried out to determine the effect of mass size showing that the mass detection rate begins to fall off when the mass size approaches the elevation beam width of the transducer, confirming the reason for the underperformance. The dependence of the elevation beamwidth on frequency suggests that the new beamwidth will be ~ 2.5 mm, considerably narrower thereby

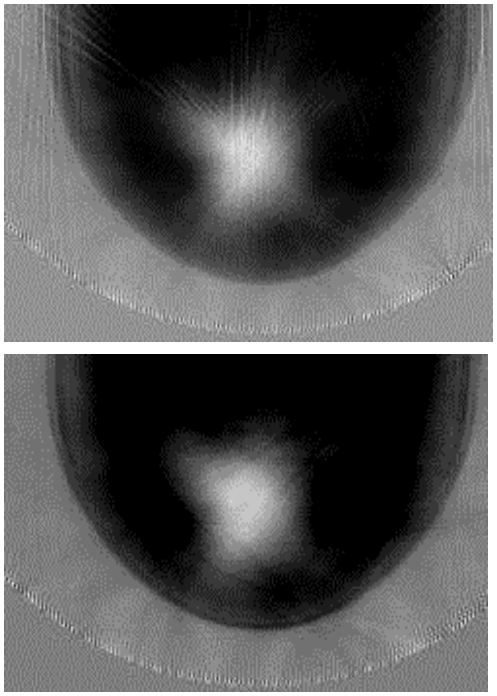

Figure 6. Top: Sound speed image of a simple phantom reconstructed from a numerical simulation using 256 array elements. Note the linear artifacts resulting from under- sampling. Bottom: Reconstruction of the same phantom using a simulation with 512 array elements. Note the suppression of the linear artifacts from just a modest improvement of the spacing interval.

Table 2.		
Parameter	Current Prototype	SoftVue Scanner
Transducer elements	256	2048
Central frequency	1.5 MHz	2.75 MHz
In-Plane pixel size (reflection)	0.4 mm	0.2 mm
In-Plane pixel size (SS and AT)	1.0 mm	0.5 mm
Slice thickness	5 mm	2.5 mm
Relative contrast	1	16
Artifact elimination	No	Yes

potentially improving contrast to small masses.

The data from Table 1, along with the analysis illustrated by Figures 4 and 5, have allowed us to model the needed improvements in contrast and resolution to achieve 100% sensitivity for breast masses 5mm and larger. Based on this modeling we anticipate the imaging improvements as summarized in Table 2. A new scanner, based on these design elements is being constructed by Delphinus Medical Imaging, Inc in Plymouth, MI (USA).

4. DISCUSSION

The aim of the improvements described in this paper is to build a UST scanner that can address important clinical needs relating to breast cancer. We now discuss the possible role of such a device in a clinical setting.

According to SEER statistics, breast cancer incidence varies with the stage of the disease [17]. Approximately, 61% of breast cancers are found to be localized at the time of diagnosis. About 31% are found to be regional. Another 5% are diagnosed with distant metastases while about 3% are unstaged. The five year survival rate varies strongly with stage. The 5-year survival rate for women with localized cancer is 98%. For regional, it drops to 84%. In the case of distant stage, the survival rate drops dramatically to 23%. For unstaged cancers it is about 58%. The survival numbers decline further when periods longer than 5 years are considered [17]. The combination of these trends applied to the population of the United States results in approximately 190,000 new cancer cases diagnosed each year, with a corresponding mortality rate of 40,000/year[20]. There are many reasons why cancers are not detected early but some of the major factors relate to limited participation in breast screening and the performance of screening mammography.

Limited participation in screening. National cancer screening statistics indicate that only 51% of eligible women undergo annual mammograms [18]. That rate is even lower for African American women and/or those of lower socioeconomic groups. Access, fear of radiation and discomfort are some of the factors that contribute to the low participation rate. Greater participation would lead to detection of cancer at an earlier stage leading to a greater survival rate. Increased participation and improved breast cancer detection would have the greatest impact on the nearly 1 in 3 women who are diagnosed each year with later stage (regional or greater) breast cancer, totaling approximately 60,000 women per year in the United States. The net effect would be an increase in survival time and a corresponding decrease in mortality rates, particularly among women at even higher risk for even participating.

Limited performance of mammography. For women with dense breast tissue, who are at the highest risk for developing breast cancer [19-22], the performance of mammography is at its worst [23]. Consequently many cancers are missed at their earliest stages when they are the most treatable. Improved cancer detection for women with denser breasts would decrease the percentage of breast cancer incidence at later stages, which would significantly lower the mortality rate.

Role of Imaging. Although tomosynthesis may improve upon some of the limitations of standard mammography, it is unlikely to create a paradigm shift in performance while still generating ionizing radiation. On the other hand, MR can

significantly improve on these limitations by virtue of its volumetric, radiation-free imaging capability. Studies have shown that MR can impact a large swath of the breast management continuum ranging from risk assessment to diagnosis and treatment monitoring [24-34]. However, MR requires long exam times and the use of contrast agents. Furthermore, MR has long been prohibitively expensive for routine use and there is a need for a low-cost equivalent alternative. Positron emission tomography is also limited by cost. Conventional sonography, which is inexpensive, comfortable and radiation-free, is not a practical alternative because of its operator dependence and the time needed to scan the whole breast and therefore continues to only play an adjunctive role in breast imaging [35]. The lack of such an alternative is a barrier to dramatically impacting mortality and morbidity through improved screening because, currently, there is a trade-off between the cost effectiveness of mammography and the imaging performance of MR.

Our goal is to eliminate this trade-off by combining the low-cost advantage of mammography with the superior imaging performance of MR through the development of the UST scanner described above. An additional advantage of such a system is that it offers comfort, operator independence and low-installation and maintenance costs. These advantages have the potential to support early breast cancer detection and improved participation in breast cancer screening programs.

5. CONCLUSIONS

A new UST scanner has been designed to achieve clinical relevance in the area of breast cancer detection and tissue characterization. The design bridges the gap between research and clinical practice. The resulting scanner has the potential to become a clinically-relevant, operator-independent, non-ionizing imaging modality for cost-effective diagnosis of breast cancer without compression or ionization. In future clinical work, testing on in-vivo data is expected to demonstrate the readiness of the new UST technology for clinical trials in support of product commercialization. The placement of such scanners in a clinical setting will have a *positive societal impact* because the accurate identification of cancer, at relatively low cost, will enable widespread access in clinics, and a reduction in death rates from breast cancer.

Successful implementation of this technology will allow us to challenge existing paradigms. Current clinical practice is based on Mammography screening with diagnostic follow-up and biopsy. The proposed methodology has the potential to streamline this process by combining screening and diagnosis and dramatically reducing the biopsy rate. Such streamlining is made possible by the fact that UST provides whole breast volumetric imaging whose performance is the same regardless of whether it is used for screening or diagnostics. Furthermore, the paradigm of breast compression and use of ionizing radiation is directly averted.

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