Breast lesion detection using diffuse optical imaging
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Automated 3D whole-breast ultrasound imaging: results of a clinical pilot study

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Abstract

We present the first clinical results of a novel fully automated 3D breast ultrasound system, the CUPidUS. This system was designed to match a Philips diffuse optical mammography system to enable straightforward co-registration of optical and ultrasound images. During a measurement, three 3D transducers scan the breast at 4 different views. The resulting 12 datasets are registered together into a single volume using spatial compounding.

In a pilot study, benign and malignant masses could be identified in the 3D images, however lesion visibility is less compared to conventional breast ultrasound. Clear breast shape visualization suggests that ultrasound could support the reconstruction and interpretation of diffuse optical tomography images.
Introduction

Early-stage breast cancer detection is still a challenge, especially in dense breast. The current gold standard for breast imaging, X-ray mammography, is widely used for screening and diagnostics examinations. Ultrasound imaging is as well extensively used in breast screening as an adjunct to mammography and helps differentiating solid from cystic mass. Studies showed that in dense fibroglandular breast tissue, ultrasonography detected masses that were invisible in the mammogram [3-10]. Thus, there might be a role for ultrasound screening of young women with dense breast.

X-ray mammography has the disadvantages of using harmful ionizing radiation for both the patients and the radiologist, applying painful compression to the breast and having a high number of false positives resulting in a large number of unnecessary biopsies. As a future possible solution, Diffuse Optical Tomography (DOT) is a non-invasive and harmless method for breast imaging. It uses near-infrared light to assess the optical properties inside the breast. Maps of concentration of water, lipid, hemoglobin and deoxy-hemoglobin can then be derived from these optical properties. These functional breast images can be used to discriminate different tissue and thus detect breast cancer at localized area where high contrast of hemoglobin and oxygenation compared to surrounding tissue is found. However, DOT has low spatial resolution and similarly to mammography has low sensitivity in dense breast tissue. Ultrasound imaging, with good spatial resolution and with potential to image lesions in dense breast, could thus help DOT to achieve high sensitivity screening of breast. One of the main drawbacks of the current ultrasound examination is the use of hand held probes which gives operator-specific outcomes and a success rate depending on the skills of the operator.

To replace harmful and painful mammography by DOT and to take advantage of rather good detection of ultrasound in dense tissue, we developed an automated 3D whole-breast ultrasound imaging system, designed to match the Philips diffuse optical mammography system, the fDOT system described in chapter 2 of this thesis and [1]. Our prototype uses three 3D transducers in a fixed geometry to image the whole breast: no more interaction with the operator is then required. Combination of ultrasound and optical imaging can be achieved at different levels. First, to compensate for low spatial resolution of Diffuse Optical Tomography (DOT), ultrasonic data can be used to construct co-registered images of anatomical structure and optical absorption. Furthermore, ultrasonic data can support DOT by incorporating the anatomical information from ultrasound as prior constraints into the DOT reconstruction algorithm.

In this paper, we investigate the clinical feasibility of automated (operator-independent) whole-breast ultrasound and discuss the added value of combining ultrasound imaging with diffuse optical tomography (DOT).
Automated 3D whole-breast ultrasound imaging system

The aim was to develop a 3D whole-breast ultrasound imaging system that could be combined with the Philips optical whole-mammography system, the fDOT system described in chapter 2 and [1], see Figure 1 (a). To compensate for low spatial resolution of Diffuse Optical Tomography (DOT), ultrasonic data can be used to construct co-registered images of ultrasonic anatomical structure and optical absorption. A typical optical image is shown in Figure 2: the nipple (dotted arrow) and the lesion (solid arrow) are visible in the images. However, it is difficult to know their exact localization due to the non-visibility of the breast surface, and their exact shape and size, due to the low spatial resolution. This missing information could be obtained with ultrasound imaging. Furthermore, ultrasonic data can support DOT by incorporating the anatomical information from ultrasound as prior constraints into the DOT reconstruction algorithm. In previous work, it has been shown that the use of a correct breast shape estimation to initialize the reconstruction of the DOT images significantly improves the reconstruction [1].

Figure 1. (a) Photograph of the Philips diffuse optical tomography system for breast cancer imaging, the fDOT system. (b) Photograph of the ultrasound prototype

Figure 2. Optical absorption at 780 nm image of an 81 years old patient. (a) Ipsilateral breast. The solid arrow points to the 29*22*28 mm^3 malignant lesion. (b) Healthy breast. The dotted arrow points to the nipples. The measurement cup wall is shown by the white dashed line. The breast shape is not visible in this optical image and the spatial resolution of the lesion is low. Anatomical information from ultrasound imaging would be useful for the interpretation of the optical images.
The prototype ultrasound scanner has thus been designed similarly as the optical scanner: a bed where the patient can lie down in a prone position with one breast hanging in a cup, in combination with a standard Philips iU22 ultrasound system, Figure 1 (b). Three standard transducers 3D9-3v, see Figure 3 (a), are mounted in the cup wall, Figure 3 (b), which is covered with a lining to minimize acoustic reflections. The lining is a FDA compliant Vinyl/Buna-N rubber sheet of 1/32 inch thickness. The 3D curved array transducers have been chosen for several reasons. First they must image deep in order to see as close as possible to the chest wall: the frequency of the transducers has then been set at 3.5 MHz. Conventional 2D breast ultrasound probes image on the contrary at high frequency, varying from 9 to 12 MHz. Secondly, the 3D9-3v transducers were chosen because they have a relatively small cross-section. The integration of the ultrasound transducers in the optical measurement cup must indeed as little as possible perturb the original geometry and the optical scanning. Figure 3 (b) shows the placement of the transducers in the cup: they are localized at the lower part of the cup where the breast is expected to touch the cup wall the least, but not fully at the bottom to be able to image the breast surface with minimized angle and to reduce shadowing artifacts from the nipple. Incidentally, to image the breast surface, the scanning area of the transducer is located at the surface of the cup. It is not intended to get the probes closer to the breast. The transducers have an electrical scanning field of view of 130° in the azimuth plane, i.e. B-scan plane, and a mechanical scanning field of view of 85° in the elevation plane, i.e. plane normal to the B-scan plane. Furthermore, each transducer can be rotated around its axis by an electromotor which is controlled by a PC. Automated operation of the prototype was realized by running the iU22 in diagnostic mode with WinRunner software to simulate normal user interactions. During a scan the iU22 communicates with the PC to enable synchronization of the image acquisition and the rotation of the transducers. When the patient is lying on the bed with one breast in the cup, the space between the breast and the cup wall is filled with an ultrasound matching liquid consisting of a mixture of purified water, glycerin and polysorbate 20. The cup is filled and emptied using a fluidic system inside the bed.

Figure 3. (a) Transducer 3D9-3v. (b) Measurement cup with the 3 transducers 3D9-3v.
Spatial compound imaging

In normal ultrasound B-mode scan, the object is imaged along a single direction which is perpendicular to the surface of the transducer. Spatial compound imaging is an improved technique to obtain better image quality: the object is imaged under different views and the resulting images from the different views are then combined together. We decided to proceed in 2 levels, explained as follows, to perform spatial compound imaging with the images of our prototype. During a measurement, each of the 3 transducers successively acquires a partial volume of the breast at 4 different views. For the first volume the transducer array is in the vertical plane. For each subsequent volume the transducer is rotated over 45 degrees clockwise (looking top down to the cup). A set of 12 3D images can thus be collected and processed into a single volume. The first level of compound imaging consists of combining the 4 volumes for each transducer, resulting in a set of three 3D images, one image per transducer. Then, the second level of compound imaging would consist of combining these 3 resulting volumes together. A mask can be applied to this final single image to remove artefact outside the measurement cup caused by residual cup wall reflections.

Figure 4 shows an ultrasound image of a phantom, without and with compounding of the 4 views seen by a single transducer. This shows some of the advantages of compound sonography over standard B-mode sonography: reduced speckle, increased resolution (especially lateral resolution), increased field of view, reduced echoes from air-bubbles and particles in fluid and symmetric point spread function (PSF).

In our study, spatial compound of the 3 transducers was achieved successfully in phantoms, as seen in Figure 4. In patients, due to variations in speed of sound and to less overlap of tissue for registration, the image quality of spatial compound of the 3 transducers was reduced. Therefore the patient’s and volunteer’s scans were processed in 3 volumes; one volume per transducer. To be able to register the 3 different volumes from the 3 transducers with patient data, an algorithm with elastic transformation will need to be developed and the issue of limited overlapping tissue available for the registration will need to be solved.
Clinical trial

The clinical feasibility of automated whole-breast ultrasound imaging with our prototype has been investigated by assessing the mass visibility in the images of our prototype, helped by the images from the conventional ultrasound probe.

A first pilot study with 23 patients (mean age 46, range 20 to 74) was performed at Leiden University Medical Center. The study protocol was approved by local IRB (Institutional Review Board), and written informed consent was obtained from all patients. The inclusion criteria for this study were patients with visible mass in the conventional 2D ultrasound image, with breast size similar or smaller than cup, and who could bear prone position. This study included 29 masses visible with the 2D handheld ultrasound probe. Of these 29 masses, 10 were confirmed as malignant (8 adenocarcinomas, 1 papillar carcinomas, 1 ductal carcinoma in situ (DCIS)) by histopathology and 19 as benign masses (10 cysts, 8 fibroadenomas, and 1 old hematoma). Breasts of patients were imaged with both conventional ultrasound and automated whole-breast 3D ultrasound. With the prior knowledge of the mass positions and dimensions from the 2D ultrasound, the masses were identified in the 3D images of our prototype, i.e. in each compound image from a single transducer, and were assessed as visible, maybe visible or non visible. The result of this visibility study presented here is thus the number of masses visible in a compound image from at least one of the 3 probes. Lesion visibility was assessed for both imaging modalities in collaboration with an ultrasound radiologist.

Results - Clinical feasibility of automated whole-breast ultrasound

Table 1: Results of the visibility study

<table>
<thead>
<tr>
<th>Mass</th>
<th>histopathology</th>
<th># visible lesion</th>
<th># maybe visible lesion</th>
<th># non visible lesion</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign mass</td>
<td>hematoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cyst</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>fibroadenoma</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Malignant mass</td>
<td>adenocarcinoma</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>papillar carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>DCIS</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The result of the visibility study is shown in Table 1. Among the benign masses, 5 out of 8 fibroadenomas were visible and 1 maybe visible, 7 out of 10 cysts were visible and 1 maybe visible, the old hematoma was maybe visible. Among the malignant masses, the
Figure 5. Cyst visible with the automated 3D whole-breast ultrasound prototype. Dimension of 11.5*12.6*10.6 mm³ and location at 10 mm from nipple assessed in the 2D image. (a) Conventional 2D ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype

Figure 6. Fibroadenoma visible with the automated 3D whole-breast ultrasound prototype. Dimension of 27*17*20 mm³ assessed in the 2D image. (a) Conventional 2D ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype

Figure 7. Adenocarcinoma visible with the automated 3D whole-breast ultrasound prototype. Dimension of 14*11*12 mm³ and location at 50 mm from nipple assessed in the 2D image. (a) Conventional handheld ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype
papillar carcinoma was maybe visible, 2 out of 8 adenocarcinomas were visible, and the DCIS was maybe visible. The detected lesions were located at less than 50 mm from the nipple and had a minimum volume of 0.4 cm$^3$. The mean size of malignancies based on conventional handheld ultrasound was 2.2 cm$^3$, and the mean size of benign lesions was 3.8 cm$^3$. The mean distance nipple-mass of malignancies was 38 mm, and the mean distance of benign lesions was 26 mm.

Figures 5 to 9 show the images obtained with the conventional handheld ultrasound and with the automated 3D ultrasound scanner for respectively a cyst, a fibroadenoma, an adenocarcinoma, a papillcarcinoma and a DCIS.

(a) Conventional 2D ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype

Figure 8. Papillar carcinoma maybe visible with the automated 3D whole-breast ultrasound prototype. Dimension of 26*17*20 mm$^3$ and location at 50 mm from nipple assessed in the 2D image. (a) Conventional 2D ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype

(a) Conventional 2D ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype

Figure 9. DCIS maybe visible with the automated 3D whole-breast ultrasound prototype. Dimension of 16*9*1 mm$^3$ and location at 40 mm from nipple assessed in 2D image. (a) Conventional 2D ultrasound image. (b) Image from the automated 3D whole-breast ultrasound prototype
Discussion

An automated (operator-independent) whole-breast 3D ultrasound system has been described: three 3D transducers in a cup scan the breast at 4 different views. The 4 volumes from a single transducer are registered together and spatial compound imaging can be performed on the volumes from the three transducers in order to obtain one final high quality image.

In our study, spatial compound of the 3 transducers was achieved successfully in phantoms. In patients, the image quality of spatial compound of the 3 transducers was reduced. The spatial compound imaging of breast needs to be done with a very accurate registration, based on non-rigid anatomical transformation algorithm [6]. Indeed, the resolution of structures depends on the scanning direction; scanning perpendicular to an object will result in high resolution and scanning almost parallel to the object will result in very low resolution. Besides, elastic transformation based on various speed of sounds of the different types of breast tissue must be included in the registration algorithm. At last, the issue of limited overlapping tissue available for the registration needs to be solved in case of breast data. Therefore the patient’s scans were processed in 3 volumes; one volume per transducer.

The feasibility of 3D ultrasound has been investigated with our system in a clinical pilot study. Automated 3D whole-breast ultrasound images have been obtained in patients. The lesion visibility study of the images shows that 63% of the benign masses and 20% of the malignant masses were visible. The detected lesions were located at less than 50 mm from the nipple and had a minimum volume of 0.4 cm$^3$. The malignant lesions are clearly less visible than the benign lesions. This is probably due to the difficult echo pattern of the malignancies and by the fact that in this study group the malignant lesions were on average smaller in size and deeper in the breast than the benign lesions. Indeed the mean size of malignancies based on conventional handheld ultrasound was 2.2 cm$^3$, while the mean size of benign lesions was 3.8 cm$^3$. The mean distance nipple-mass of malignancies was 38 mm, while the mean distance of benign lesions was 26 mm. For use in lesion detection, our prototype needs a higher sensitivity and higher penetration depth. The quality of the compound images from a single transducer was less than the quality of the images from a conventional handheld ultrasound probe. It has nevertheless been shown in literature that compounding increases image quality [5]. Here, the system design and the hardware of the prototype are limiting the image quality. Indeed, while in the conventional ultrasound the handheld probe is pushed inside the breast to get close to the masses, with the automated 3D system the probes are at a fixed position in the cup. Besides, as mentioned in the description of the system, the transducers are imaging at 3.5 MHz to achieve sufficient penetration depth, which is lower than the frequency of the conventional handheld breast ultrasound probe, usually varying from 9 to 12 MHz. This difference in frequency results in a loss of axial resolution of about a factor 3 for the automated 3D scanner. The design of the system compensates this issue by using three 3D transducers and combining these images from 3 different views together resulting in higher image quality with better spatial and contrast resolution. However,
as explained earlier, this compound imaging was not yet performed on our images of patients.

The breast surface and the nipple are clearly visible in the 3D ultrasound images. Because spatial compound imaging of the 3 transducers has not been performed on patient’s data, breast surfaces are not uniformly sharp. Nevertheless, the quality of the images is already sufficient so that DOT imaging could in principle benefit from it. In previous work, it has been shown that the use of a correct breast shape estimation to initialize the reconstruction of the DOT images significantly improves the reconstruction [1]. Figure 10 (a) shows an example of the cross-section of an ultrasound image from a volunteer: the skin and nipple are visible. The breast shape used in the reconstruction of the optical images for the same volunteer is shown Figure 10 (b). Comparing the ultrasound and optical images of the same breast in the same view, it is clear that the optical image is not representative of the real breast shape. These results suggest that ultrasound has the potential to significantly improve DOT by either co-registering both images to help interpretation or including the ultrasound anatomical data as prior information in the reconstruction.

![Figure 10](a) Axial view of the ultrasound compound image of a single transducer from a volunteer. The imaging transducer is located at the left top of this image. (b) Axial view of the breast shape estimation from the optical scan of the same volunteer.

Currently, the registration of the ultrasound and optical images would not be trivial to perform because of the positioning of the breast in the cup. Indeed, even though an assistant person guides the patient to lie on the bed and place her breast in the cup, the positioning of the breast inside the cup is hardly repeatable. For an effective registration, the ultrasound part should be integrated in the optical scanner. The measurement cup of the optical scanner has not been designed originally for this type of combination: 512 fibers are mounted on its surface. Half of the fibers are used to illuminate the breast sequentially from all side and the other half are used for parallel probing of the light emanating from the breast surface. The transducers have been therefore chosen partly for their small cross section; it minimizes the number of optical fibers that would have been removed for the integration of the probe. However, the ideal situation would be to keep all optical fibers and to integrate the ultrasound probes between them. This could be achieved with for instance a 2D matrix transducer, see Figure 11. This solution has the advantage of an increased numerical aperture, resulting in an increased resolution: a lower frequency can thus be used to achieve deeper imaging. Furthermore, in both optical and ultrasound modalities, the
space between the breast and the cup needs to be filled with a fluid. For the optical scanner, a scattering fluid matching the average optical properties of the breast is used to ensure good optical contact between the breast and the fibers. For the ultrasound scanner, a fluid with a speed of sound of 1610 m/s is used for good penetration of the sound in the breast and for minimizing the skin reflection. Combining ultrasound and optical imaging implies designing a matching fluid capable of working with both modalities.

![Figure 11. A 2D matrix transducer is implemented between the optical fibers in the optical measurement cup](image)

These above results on lesion detection and breast surface visibility show the added-value of combining ultrasound imaging with diffuse optical tomography with our systems. We expect that compound imaging would enable better lesion detection and easier breast surface extraction to be used as support information for optical imaging. Optimization of the design and hardware, for instance on the transducers, geometry of the transducer or use of contrast ultrasound fluid, are also considerable but not the first priority for further study.

**Conclusion and future work**

The first, to our knowledge, automated 3D whole-breast ultrasound scanner using 3D transducers has been presented. The objective of this study was to investigate the clinical feasibility of automated (operator-independent) whole-breast ultrasound and discuss the added value of combining ultrasound imaging with diffuse optical tomography (DOT). A prototype ultrasound scanner has been developed with three 3D transducers in a cup. During a measurement each transducer scans the breast at 4 different views, enabling spatial compound imaging. The shape of the cup matches the fDOT system to enable straightforward co-registration of optical and ultrasound images. Indeed, ultrasound has a clear potential to improve DOT by either co-registering both images to support interpretation or by including the ultrasound anatomical data as prior information in the reconstruction.

Spatial registration of the 4 images from single transducers has been achieved. Spatial compound imaging of the 3 transducers was performed in phantoms shown in this paper and not yet in patients. A pilot study with 23 patients has been performed: breasts of patients were imaged with both automated 3D ultrasound and with
conventional ultrasound. Lesion visibility was assessed for both imaging modalities in collaboration with an ultrasound radiologist. Automated 3D whole-breast ultrasound images have been obtained. The study of these images has validated the potential performance of lesion detection of the prototype: individual benign and malignant masses could be visualized in images from patients. Besides, breast surfaces were clearly visualized in the ultrasound images. These results show the added value that our automated 3D ultrasound system would have in combination with DOT. Lesion visibility and image quality were less compared to conventional breast ultrasound.

A major next step is the optimization of the spatial compound imaging. In this study, spatial compound imaging has been performed on single transducer by rotating it around its own axis. A second level of compound imaging can be performed by combining together the 3 compound volumes from the 3 transducers. This needs to be done with a very accurate registration, based on non-rigid anatomical transformation algorithm. It is expected that spatial compound imaging of the 3 transducers will provide high quality compound images enabling better lesion detection and easier breast surface extraction.

In conclusion, this paper presented the first validation of our 3D whole-breast ultrasound scanner using 3D transducers. Automated 3D whole-breast ultrasound images have been obtained in patients. An improved spatial compound imaging needs to be performed for further studies.

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References


