Non-invasive Diagnostic Breast Imaging using a Hand-held Optical Imager

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ABSTRACT

Hand-held based optical imaging devices are currently developed as a noninvasive method for breast cancer diagnosis. However, the devices developed to date have not performed 3D tomography since they are unable to perform coregistration. In our Optical Imaging Laboratory we have developed a hand-held optical imager with automated coregistration facilities to enable 3D tomography of breast cancer. Herein, coregistered imaging and 3D tomography are demonstrated *in vitro*, and preliminary *in vivo* studies are performed to demonstrate 2D surface mapping and coregistered imaging in breast tissue of normal human subjects. The results demonstrate potential toward clinical translation of a portable and patient-comfortable method for breast cancer diagnosis.

Keywords: Diffuse Optical Imaging, Fluorescence, Near-infrared, Breast Cancer, 3D Tomography, Hand-held Device, Coregistration

1. INTRODUCTION

Breast cancer is the second leading cause of death of women in the U.S. and one in eight are at risk of developing the disease within their lifetime. X-ray mammography is currently the gold standard for breast cancer detection. However, it has several limitations: (i) the use of harmful ionizing radiation, (ii) the compression of breast tissue which can be uncomfortable and even painful for the patient, and (iii) a 10% false negative rate (that increases with denser breast tissue) which means that many cancers go undetected. Optical imaging using near-infrared (NIR) light is an emerging non-invasive and non-ionizing technique that is currently developed toward in vivo deep tissue imaging, including breast cancer. Many of the optical imaging systems developed to date have bulky instrumentation and some require compression of the breast tissue which can be uncomfortable for the patient.

Several research groups have developed hand-held based optical imaging devices which are portable and patient comfortable [1]. However, the NIR devices developed to date have been used primarily towards spectroscopic measurements from a few points and have not attempted three dimensional (3D) tomography since they are unable to coregister the image to the tissue geometry. In our Optical Imaging Laboratory we have developed a hand-held optical imager which has the following unique features: (i) flexible probe face to contour to different tissue curvatures for maximum contact and patient comfort, (ii) ability to rapidly image a large tissue area, and (iii) automated coregistration facilities to enable 3D tomography of breast cancer [2-3]. Herein, coregistered imaging and 3D tomography are demonstrated *in vitro*, and preliminary *in vivo* studies are performed to demonstrate 2D surface mapping and coregistered imaging in breast tissue of normal human subjects.

2. MATERIALS AND METHODS

2.1 Instrumentation

The hand-held based optical imaging system (shown in Fig. 1) is composed of three major sections: the hand-held probe, the laser diode source, and the intensified charge coupled device (ICCD) based detector [2].

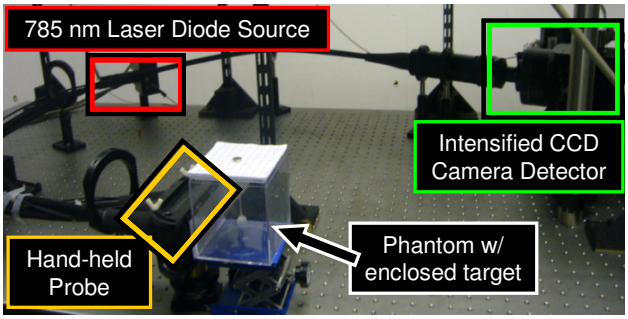

Fig. 1 Hand-held based optical imaging system. The three major components are the hand-held probe, the laser diode source, and the ICCD camera based detector.

The laser signal is carried to and collected from the probe head via optical fibers. The probe head contains six illumination points and 165 detection points which illuminate and collect the signal simultaneously for rapid data acquisition. The probe head is flexible to contour different tissue curvatures as illustrated in Fig. 2.

The instrumentation for the hand-held optical imager is capable of performing both continuous wave (CW) and frequency-domain (FD) based measurements. For the different studies described here, FD measurements (100 MHz) are used for 3D tomography since they provide more information while requiring a longer imaging time. CW measurements are used to perform fast 2D imaging toward rapid target (or tumor) detection.

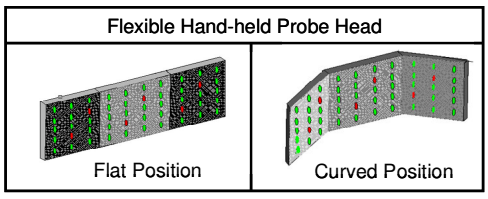

Fig. 2 Schematic of the flexible probe head.

2.2 Automated Coregistration

Coregistered imaging is required in order to perform 3D tomography since the 2D image must be located in the exact position of the hand-held probe on the tissue surface. In coregistered imaging, the position and orientation of the probe is tracked with respect to the tissue or phantom surface being imaged. This tracked 3D positional information is then used to accurately position the acquired optical images onto the tissue geometry.

Coregistration was carried out as a three-step process (Fig. 3) using MATLAB/LabVIEW software developed in house [3]: (1) real-time tracking was used to find the probe location with respect to the tissue; (2) a real-time 2-D surface contour image was acquired at the probe location; (3) the probe location and image were coregistered onto a discretized phantom mesh. The 3-step process is automated to enable fast 2D coregistered imaging (~35 seconds per image).

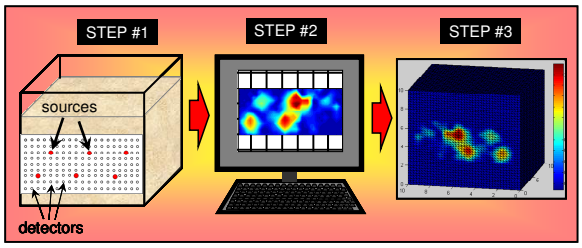

Fig. 3 The 3-step coregistered imaging process. Step 1: The probe location is tracked in real-time. Step 2: A 2D contour map of optical measurements is acquired. Step 3: The probe location and image are coregistered onto a discretized phantom mesh.

2.3 Experimental Studies

Experiments were performed *in vitro* to demonstrate 3D tomography and validate the coregistered imaging process. Parallely, 2D imaging was performed *in vivo* with healthy female volunteers. Additionally, preliminary studies were performed to validate the coregistered imaging process on human tissue and demonstrate core

2.3.1 2D imaging and 3D tomography *in vitro*: Experiments were performed using *in vitro* phantoms, which were composed of minced chicken breast combined with 1% Liposyn solution, in order to introduce a non-uniform optical property distribution in the background. The *in vitro* mixture of minced chicken breast (480 ml) and 1% Liposyn (260 ml) was placed inside a 10×10×10 cm^3 acrylic cube. The probe was placed in full contact with the phantom surface and 2D images of fluorescence intensity were collected using the FD measurement technique. A 0.45 cm^3 target filled with indocyanine green (fluorescent contrast agent) was placed at different depths between 1-2.5 cm. A subtraction-based post-processing technique was used in all cases to eliminate excitation leakage. The FD images of fluorescence intensity were used to perform 3D tomography studies. An approximate extended Kalman filter (AEKF) based algorithm [2] was used to reconstruct the 3D location and volume of the target. The discretized mesh of the phantom was generated using Gambit software and the 2D image was manually coregistered at the appropriate location.

2.3.2 Coregistration validation *in vitro*: In order to quantitatively determine the accuracy of the tracked location in comparison to the true location of the probe on the *in vitro* phantom, the probe was placed at five different positions of known [x,y,z] coordinates and the tracking position was recorded (5 repetitions at each location). The average and standard deviation of the tracked location, and its total distance-off from the true location at each position number were measured. The average total distance off is ~0.19 cm. For these measurements, the probe was held in place with a lab jack and the error in measurements is primarily due to error in the tracking system and possibly some movement of the phantom during positioning of the probe. Currently work is carried out to improve the accuracy of the tracking system.

2.3.3 Coregistered imaging *in vitro*: Coregistration was initially demonstrated *in vitro* on simple cubical geometries, prior to *in vivo* on human subjects with curved tissue geometries. *In vitro* experiments were performed using the heterogeneous (i.e. non-uniform optical property distribution in background) phantoms as described in section 2.3.1. Fast 2D coregistered images of fluorescence intensity were acquired under different experimental conditions using 0.23-0.45 cm^3 fluorescent targets under perfect and imperfect (T:B=100:1) uptake conditions. The target was placed at different depths between 1.5-4.0 cm within the *in-vitro* phantom. Multiple images (CW measurements of fluorescent intensity) were collected from a single side of the phantom for each case at different probe positions moving the probe in the vertical direction in 0.5 cm increments. The images were coregistered to the discretized phantom geometry (generated using MATLAB software developed in house).

2.3.4 *In vivo* studies: Experimental studies were performed *in vivo* with healthy female volunteers (above age 21). All human subject studies were approved by the Florida International University Institutional Review Board. Initial experiments were designed to demonstrate near-real time imaging (~5 seconds per image) of fluorescent targets through actual human breast tissue. The experimental set-up for the *in vivo* studies is shown in Fig. 4 (with mannequin shown for demonstration only). Fluorescent targets of 0.23-0.45 cm^3 were placed noninvasively underneath the breast tissue and imaged through the tissue using the probe in both the flat and curved position (as shown in Fig. 2 above). In the flat position, gentle compression is applied to enable full contact of the probe with the tissue. In the curved position, the probe contoured to the curvature of the breast and no compression was required. A subtraction-based post-processing technique was used to eliminate excitation leakage.

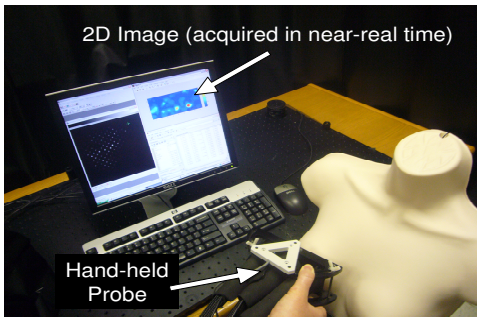

Fig. 4 Experimental set-up for *in vivo* studies with human subjects (mannequin shown for demonstration only).

2.3.5 Coregistered imaging *in vivo*: Preliminary studies were performed to demonstrate coregistered imaging in human subjects. The discretized geometry of the breast tissue is acquired using a commercially available 3D scanner and MATLAB software developed in house to generate the discretized mesh for the 3D-scanned geometry. The coregistered imaging process was validated *in vivo* (as described in section 2.3.2 for the *in vitro* case) for different probe positions using known reference points generated in the discretized geometry and marked on the tissue. The average total distance off was ~1 cm, which can be attributed to instrumentation error such as fluctuation in the tracked position of the probe, and human error such as hand movement of the operator. Currently, efforts are made to overcome these limitations and improve the accuracy of the tracking system. A study was performed with a normal human subject to demonstrate coregistered imaging on actual human tissue. In order to perform coregistered imaging, a 0.45 cm^3 spherical target was placed underneath the flap of the breast tissue in the center. The location of the probe was tracked with respect to the tissue and a 2D image was collected and coregistered at the appropriate position.

3. RESULTS AND DISCUSSION

3.1 *In vitro* studies

The results for 2D imaging and 3D tomography *in vitro* are shown in Fig. 5A and 5B, respectively, for the case of a 0.45 cm^3 target located 2.5 cm deep under perfect uptake conditions.

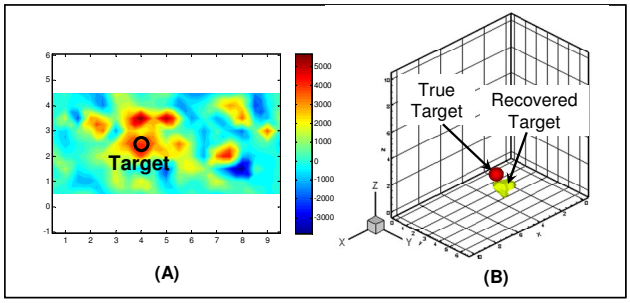

Fig. 5 (A) 2D image of FD fluorescence intensity data from a 0.45 cm^3 target located 2.5 cm deep from the imaging surface of the *in vitro* phantom under perfect uptake conditions. (B) 3D iso-surface contour plot showing the 3D reconstruction of the target.

Fig. 5B shows that the target was recovered close to the true location. This case represents the greatest depth at which a target was recovered using a single FD image. Targets located at greater depth or under imperfect uptake (100:1) conditions (deeper than 1.5 cm) were not recovered.

Fig. 6A shows images of 2D contour plots of fluorescence intensity (CW measurements) coregistered to the discretized phantom mesh at four probe positions.

The images represent the case of a 0.45 cm^3 located 2.0 cm deep *in vitro* under imperfect (T:B=100:1) uptake conditions. It can be seen from the images that the target was not detected in a single scan (2D coregistered image) at a depth of 2.0 cm. However, it was observed that upon summation of the four scans (shown in Fig. 6B) the target was clearly detected. This is due to the random nature of the noise signal which appears in different locations for each image. The signal from the target remains in the same location in each image and hence becomes intensified upon summation whereas the random signals tend to diminish.

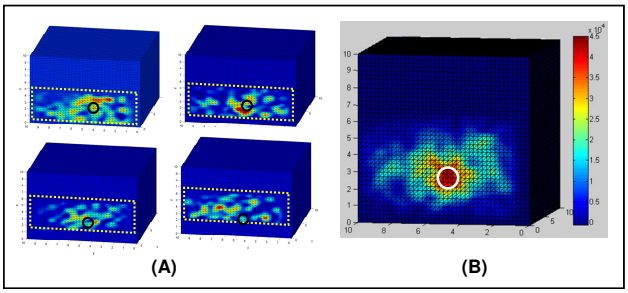

Fig. 6 (A) Multiple coregistered images collected from four probe positions using a 0.45 cm^3 located 2.0 cm deep *in vitro* under imperfect (T:B=100:1) uptake conditions. (B) Summation of the multiple coregistered images.

The multiple-scan summation approach was applied *in vitro* under perfect and imperfect uptake conditions to determine the improvement in detection limits over single-scan images. Under perfect uptake conditions, a 0.45 cm^3 target was detected at a depth of 3.5 cm and under imperfect (T:B=100:1) uptake conditions the target was detected at a depth of 2.5 cm. The summated images can be used to perform 3D reconstructions to determine if the method can improve the depth at which a target can be recovered by 3D tomography (future work).

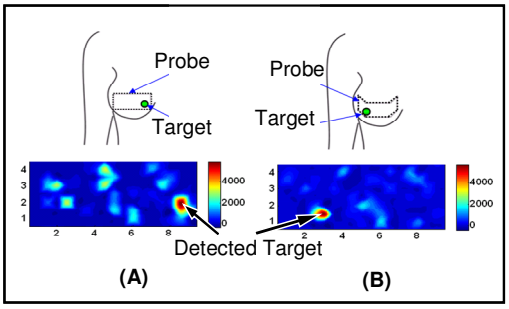

Fig. 7 2D images of fluorescence targets through human breast tissue. (A) A 0.23 cm^3 target placed at the four o'clock location imaged with the probe in the flat position. (B) A 0.45 cm^3 target placed at the eight o'clock location imaged with the probe in the maximum curved position.

3.2 *In vivo* studies

Fig. 7 shows 2D images (CW measurements) of fluorescent targets placed underneath the breast tissue in a healthy human subject. In the first experiment (Fig. 7A), a 0.23 cm^3 target was placed at the four o'clock location and imaged with the probe in the flat position.

In the second experiment (Fig. 7B), a 0.45 cm^3 target was placed at the eight o'clock location and imaged with the probe in the maximum curved position (45 degrees on each side). The results show that in both cases the target was detected, which demonstrates the ability of the device to detect a fluorescent target ~2.5 cm deep through actual human breast tissue.

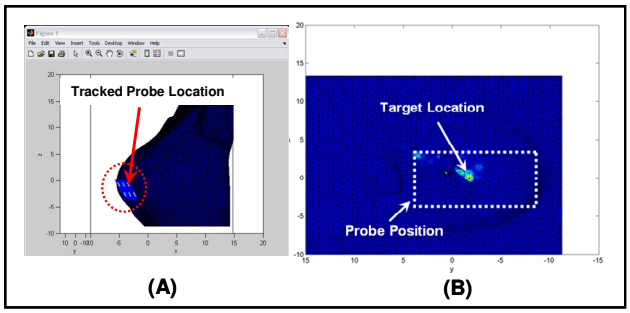

Fig. 8 (A) Image showing tracked probe location with respect to the discretized breast geometry as the probe approaches the breast tissue. (B) Coregistered image of a 0.45 cm^3 target placed underneath the tissue.

Fig. 8A shows the 3D discretized breast geometry acquired from a healthy human subject. The image of the probe is tracked in real-time as it approached the tissue surface. Once the probe was placed in full contact with the tissue an image was collected and coregistered at the probe location. The coregistered image is shown in Fig. 8B where it can be seen that the target was detected and coregistered at its position within the breast tissue geometry. These results demonstrate the ability of the device to detect a target and coregister the image at its appropriate location within arbitrary curved geometries of human breast tissue.

4. CONCLUSION

A hand-held optical imager has been developed with unique features of flexibility to contour to different tissue curvatures, ability to rapidly image a large tissue area, and coregistration capabilities towards 3D tomography. Studies were performed *in vitro* to demonstrate 2D imaging and 3D tomography of a target within a non-uniform background. Coregistered imaging was demonstrated *in vitro* and a multiple-scan summation technique was applied to enable deeper target detection. Preliminary *in vivo* studies demonstrate the ability of the hand-held device to detect a target and perform automated coregistered imaging in human breast tissues with complex geometries. These results demonstrate potential for clinical translation of the device for 3D tomographic analysis of breast cancer.

5. REFERENCES

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