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Image Registration for Microwave Tomography of the Breast Using Priors From Nonsimultaneous Previous Magnetic Resonance Images

Gregory Boverman,

GE Global Research Center, 1 Research Circle, Niskayuna, NY, 12309 USA

Cynthia E.L. Davis,

GE Global Research Center, 1 Research Circle, Niskayuna, NY, 12309 USA

Shireen D. Geimer, and

Thayer School of Engineering, Dartmouth College, 14 Engineering Drive, Hanover, NH 03755 USA

Paul M. Meaney [Senior Member, IEEE]

Thayer School of Engineering, Dartmouth College, 14 Engineering Drive, Hanover, NH 03755 USA

Abstract

Microwave imaging is a low-cost imaging method that has shown promise for breast imaging and, in particular, neoadjuvant chemotherapy monitoring. The early studies of microwave imaging in the therapy monitoring setting are encouraging. For the neoadjuvant therapy application, it would be desirable to achieve the most accurate possible characterization of the tissue properties. One method to achieve increased resolution and specificity in microwave imaging reconstruction is the use of a soft prior regularization. The objective of this study is to develop a method to use magnetic resonance (MR) images, taken in a different imaging configuration, as this soft prior. To enable the use of the MR images as a soft prior, it is necessary to register the MR images to the microwave imaging space. Registration fiducials were placed around the breast that are visible in both the MRI and with an optical scanner integrated into the microwave system. Utilizing these common registration locations, numerical algorithms have been developed to warp the original breast MR images into a geometry closely resembling that in which the breast is pendant in the microwave system.

Keywords

breast cancer; image reconstruction; image registration; magnetic resonance; microwave tomography; neoadjuvant chemotherapy

I. INTRODUCTION

EOADJUVANT chemotherapy for locally advanced breast cancer is rapidly becoming one of the more effective means for treating larger tumors. The first cases utilizing neoadjuvant therapy were reported in the late 1970's [1],[2] and large-scale trials were conducted as part of the National Surgical Adjuvant Breast and Bowel Project [3],[4]. In general, it can provide a means for reducing lesion size and positive nodes prior to surgery which results in a reduction in the number of mastectomies needed [5]. In addition, it can provide prognostic information about the future response of systemic tumors after surgery [6]–[9].

It is critical that the patient's progress throughout the therapy is monitored carefully to ensure the most positive result [10]. In fact, recent studies have demonstrated that for clinical cases where the therapy was monitored and feedback provided to clinicians, final outcomes were substantially improved compared to those where women were not monitored[11]. Currently, physical examination supplemented with mammography, contrast-enhanced MR or FDG-PET imaging are used for monitoring treatment [12]–[16]. However, both MR and PET are expensive and many patients do not have routine access to these systems. Furthermore, contrast MR has been shown to be less sensitive during neoadjuvant chemotherapy [17]. Therefore, it is difficult to justify more than one exam during the lengthy treatment period which typically lasts upwards of 6 months. A monitoring method that is low cost, fast and that can be utilized in the chemotherapy clinic is needed to further maximize the effectiveness of neoadjuvant chemotherapy.

A. Microwave imaging

Microwave tomography holds the promise of being a low cost and easy to use imaging modality. It has been evolving over the past two decades as a means of imaging breast cancer [18],[19],[20]. The Dartmouth College microwave imaging group has advanced their concept to the clinic and has published several in vivo reports on normal breast tissue properties [21],[22], diagnosis of tumors from benign lesions and normal tissue [23], and more recently for the application to neoadjuvant chemotherapy monitoring [23],[24].

The breast microwave imaging system developed at our institution uses frequency-domain measurements of modulated radiofrequency waves as they interact with the breast to noninvasively reconstruct the breast's internal distribution of conductivity and relative permittivity [18]–[24]. Typically, measurements are made at a set of frequencies from approximately 300 MHz to 2 GHz. In our system, the woman lies prone and the breast is pendant below the table with discrete source and detector antenna positions arranged in a ring configuration surrounding the breast. The system utilizes a low-contrast matching fluid for the purposes of improving electromagnetic coupling with the breast [25]. This fluid is comprised of a glycerin and water mixture, with the exact composition optimized on a case-by-case basis as described in [25].

B. The Use of a Soft Prior Algorithm

For the neoadjuvant chemotherapy application, small changes in the conductivity early in the treatment can be indicative of a therapy response [24]. Therefore, obtaining the most

accurate measurement of conductivity and permittivity is highly desirable for this application. One method of improving the accuracy of the microwave measurements of conductivity and permittivity is the use of prior structural information from a complementary imaging modality, for example, a MR image [26].

The “soft prior” regularization procedure combines structural information of the constituent tissue zones with the normal image reconstruction to provide more refined and accurate property maps [27]. Microwave images suffer from the inherent property smoothing associated with the necessary regularization during the reconstruction process [28]. In contrast to other microwave reconstruction methods which require actual estimates of the properties within these zones [29], the regularization method utilized herein only requires data regarding the location, shapes and sizes of the internal features [30].

This soft prior technique utilizes the same minimization criteria as the non-prior algorithm but adds a specialized penalty term for regularization. It consists essentially of a weighting matrix which multiplies a difference vector between the current image and the initial solution – in this case the distribution for the homogeneous bath [26]. The weights in the regularization matrix consist of elements $L_{i,j}$, corresponding to the i th and j th nodes in the reconstruction mesh. Utilizing the spatial information from the MR image, the mesh is segmented into subzones associated with the different tissue types – such as the adipose tissue, fibroglandular tissue, skin and tumor. When i and j reside in the same zone, $L_{i,j}$ is set to $-1/N_s$, where N_s is the number of nodes in the common subzone, while when they don't, $L_{i,j}$ is set to zero. $L_{i,i}$ is always set to 1. Depending on the strength of the associated regularization parameter, the final distribution within each subzone is nearly homogeneous with steep gradients between the different zones.

Studies in both 2D and 3D setting have demonstrated that the soft prior algorithm recovers more accurate measures of the properties within each zone. [26][27][31] With the use of the 3D spatial prior the permittivity and conductivity errors were ~5 times and 2 times smaller, respectively, versus without the spatial prior[31].

Ideally, the soft prior would be obtained from a MR exam performed at the same time and in the exact same positioning as the microwave imaging. While the Dartmouth team has pioneered the use of microwave imaging simultaneously with MR [32], as alluded to above, it is impractical to perform a MR exam at multiple times during the chemotherapy regimen. In the standard workflow for neoadjuvant chemotherapy at our institution, only a single MR exam is expected to be performed at the start of the treatment. Furthermore, to minimize complexity for the actual workflow, the MR and microwave exams will be performed at separate times and in slightly different configurations. The MR examination will be performed in a prone position with the breast relatively free, within the constraints of the MR breast coil. For our microwave imaging, as was described above, the patient will be in a prone position as well, however a glycerin and water bath will be utilized. The glycerin water bath has a higher density than water and standard breast tissue (50/50 fat/dense) has a density of less than water. Therefore, depending upon the composition of the breast tissues a buoyancy issue arises leading to a deformation of the breast especially away from the chest wall. A similar buoyancy issue in pure water exists for prone tomographic ultrasound

imaging as well as MR guided focused ultrasound. In some cases, it has been addressed via mechanical means [33].

In our procedure, we have chosen to address this buoyancy issue with a deformable registration. Breast deformation methods have been studied extensively [33]–[35]. Due to the method of our soft prior, we will not have knowledge of the internal structure of the breast from the microwave imaging. Therefore, registration based upon internal structures is not possible and only external landmarks can be used.

To visualize external landmarks, a 3D-camera imaging system that simultaneously acquires an image of the exterior of the breast while pendant in the microwave imaging system liquid bath has been developed and tested [36]. The scanner is a unique combination of laser lines illuminating the breast surface while a digital camera records the lines from which accurate 3D renderings can be produced. The algorithm is designed to account for the parallax associated with different indices of refraction for air, the imaging tank material Plexiglass, and the glycerin-water coupling fluid. The whole configuration rotates about the breast in under 1 minute and recovers surface positions that are essentially continuous in the vertical direction and at every 1° surrounding the breast as is shown in Fig. 1. Previous studies indicated that the position accuracy was within 0.5 mm or less [36].

To facilitate the registration, registration fiducials, visible in both the MR and optically scanned images, will be placed on the breast. These fiducials will be placed at the end of the MR acquisitions as part of a normal clinical workflow and an additional MR acquisition will be taken for high resolution fat-water separation. These fiducials will remain on the breast and the microwave and then optical scan images will be acquired in quick succession, to minimize the chance for patient motion. The MR images will be segmented and the fiducials located in both the MR and optical images. Using the corresponding fiducial positions, the MR image will be registered to the microwave imaging geometry. Finally, we will generate a “warped” MR volume corresponding to the microwave imaging configuration. From this MR volume, a mesh will be generated for the soft prior algorithm with the dense and fatty voxels discriminated. This mesh then serves as the initialization for the microwave soft prior reconstruction. For subsequent microwave imaging, the fiducials will be placed on the patient and the MR volume will be registered to the new optical scan.

In a sensitivity analysis of the 3D soft prior, shifts in size and location from the true data were tested [31] and it was found that a location shift of 87% of the radius of an object resulted in a shift of 4% of the permittivity and 15% of the conductivity. For our current application, in an average breast, this corresponds to less than 1 cm. For our chemotherapy monitoring studies, thus far, we have found in pathological complete responding patients the permittivity shows a greater than 30% decrease and the conductivity demonstrates an early decrease of more than 50% and by the end of therapy of ~80% decrease [24]. In the case of non-responders, the permittivity as well as the conductivity do not change or in some cases may increase. While these studies were performed on 8 patients, we estimate that a shift of 1 cm or less in the spatial prior location will not introduce a change in permittivity or conductivity to negate the gains from the prior nor to change a response profile.

In this paper, we describe a study of the deformation caused by the breast buoyancy in the glycerin-water coupling fluid as well as registration methods to align air-acquired MR images to the coupling fluid acquired configuration. Section II describes the MR images, the registration techniques and the MR warping strategies. Section III presents representative individual warping experiments along with a summary of data for two patients. Finally, Section IV discusses these results and presents the associated conclusions.

II. METHODS AND PROCEDURES

We collected two MR data sets for each of two volunteers: In one data set the volunteers were prone with one breast pendant, in a tank with the water-glycerin fluid, and the second data set had the volunteers prone with the breast pendant, in air. MR visible fiducial markers were attached to the breast in a predefined configuration. The MR images in the fluid represents the microwave configuration and are used as a surrogate for the optical images. However, as the internal structures are visualized it is possible to choose a set of features within the breast to assess the alignment error for several registration algorithms. We used this artificial test method to determine if an accurate registration could be obtained for those cases where the deformation was large.

A. MR images

Under an Institutional Review Board (IRB) approved protocol at the Advanced Imaging Center at Dartmouth Hitchcock Medical Center, we collected isotropic fat-suppressed volumetric MR images of both breasts for two normal subjects with the subject in the prone position. The first was acquired in air and the second in the glycerin-water bath to simulate the microwave acquisition configuration. The MR data was acquired using a Philips Achieva (Philips Medical Systems, Eindhoven, The Netherlands) system. The THRIVE, ultrafast, spoiled, gradient, echo, sequence was used with an isotropic 1.5 mm voxel size. The MR Sense Flex Medium coil (Philips Medical Systems, Eindhoven, The Netherlands) was placed around the fluid tank. See Fig. 2.

In order to repeatedly use the fiducial locations, markings for the center of the fiducials were placed on the breast with a ruler and marker with the angles being determined by eye. The fiducials were placed over the marks. The fiducials were placed at 45 degree increments, at 12 o'clock, 1:30, 3 o'clock etc. with 3 or 4 cm spacing. A total of 13 fiducial markers were placed on each breast. The locations of the markers are represented in Fig. 3. By utilizing the nipple and the standard clock positioning familiar to breast imaging, it should be possible to reproduce the location of the markers for subsequent imaging. For cosmetic reasons, it is highly desirable to not permanently mark the patient. Thus, the marker used can be removed after the microwave imaging and only serves to allow for replacement during transition from the MR to the microwave imaging system or, as in the case here, from transition from air to fluid based imaging.

Representative planes from the volumes, visualized with the open-source 3D Slicer [37] visualization and image processing application, are shown in Fig. 4 with the top row of the figure showing the breast in air and the bottom row showing the breast in the matching fluid. There is significant deformation between the sets of images and, as expected, the breast is

elongated in the coronal direction (center column) for the scan in air due to gravity. The buoyancy of the breast in the liquid serves to flatten the breast. A denser breast is shown in Fig. 5. in which the flattening of the breast due to the buoyancy is reduced.

In both sets of images, the breasts have been manually segmented from the background. An automated segmentation of the in-air breast images is possible. However, due to the artifacts from the fluid and similarity of MR contrast between the breast tissue and the fluid, a manual segmentation was deemed more effective for this limited test set.

The images were volume-rendered to most accurately determine the positions of the fiducial markers as is shown in Fig. 6. The fiducials and nipple were located manually with the aid of an initial window/level adjustment to highlight the markers which were of higher density (whiter) than the breast tissue. A more automated method will be leveraged in the future. However, for this experiment automated methods could not be used due to the artifacts caused by the fluid.

B. Registration Approaches

We used several registration approaches, comparing the results for a set of manually selected landmark features. The features were selected to be clearly identifiable in both sets of images and covering as much of the breast volume as possible. We also compared registrations generated using the entire image data with registrations generated using only the positions of the fiducial markers in both volumes. Although the full image-based registration is not practical given that the in-fluid MR imaging will not be performed in the standard patient workflow, this serves as a baseline for the best possible performance for a given approach using a full image-based information set. Specifically, we employed the following image-registration approaches; affine registration, B-spline deformable registration and thin-plate spline deformable registration. Since the thin-plate spline approach was specifically designed for registration of images by means of fiducials, its performance was not evaluated in the case of image-based information.

1) Affine Registration—In affine registration, the two images are related by a linear transformation: $\mathbf{y} = \mathbf{P}\mathbf{x}$ where $\mathbf{y}$ is the transformed pixel position, $\mathbf{P}$ is a projection matrix, and $\mathbf{x}$ is the original pixel position. The matrix $\mathbf{P}$ has 12 free parameters to be estimated and can be decomposed as follows:

$$\begin{bmatrix} R_{1,1} & R_{1,2} & R_{1,3} & T_1 \\ R_{2,1} & R_{2,2} & R_{2,3} & T_2 \\ R_{3,1} & R_{3,2} & R_{3,3} & T_3 \\ 0 & 0 & 0 & 1 \end{bmatrix} \quad (1)$$

where the matrix $\mathbf{R}$ is a linear transformation that is further decomposed into scaling, rotation, and skew components, and where the vector $\mathbf{T}$ describes the translation between the two volumes.

In three dimensions, it theoretically is possible to uniquely estimate $\mathbf{P}$ using the positions of four fiducial markers, but it is preferable to use as many marker positions as possible. In the case of image data, a transform is estimated using various image-based metrics such as normalized cross-correlation or mutual information as described in [38]. In the case of fiducial data, we write the following linear relationship between the marker position coordinates:

$$\mathbf{u} = \mathbf{M}\mathbf{v} \quad (2)$$

where

$$\mathbf{u} = \begin{bmatrix} y_{1,1} \\ y_{1,2} \\ y_{1,3} \\ y_{2,1} \\ y_{2,2} \\ y_{2,3} \\ y_{3,1} \\ y_{3,2} \\ y_{3,3} \end{bmatrix} \quad (3)$$

$$\mathbf{M} = \begin{bmatrix} x_1 & 0 & 0 \\ 0 & x_1 & 0 \\ 0 & 0 & x_1 \\ x_2 & 0 & 0 \\ 0 & x_2 & 0 \\ 0 & 0 & x_2 \\ x_3 & 0 & 0 \\ 0 & x_3 & 0 \\ 0 & 0 & x_3 \end{bmatrix} \quad (4)$$

$$\text{and } \mathbf{v} = \begin{bmatrix} R_{1,1} \\ R_{1,2} \\ R_{1,3} \\ T_1 \\ R_{2,1} \\ R_{2,3} \\ R_{3,3} \\ T_2 \\ \dots \end{bmatrix} \quad (5)$$

We then determine the elements of $\mathbf{v}$, the parameters of the affine transformation matrix, by solving these equations using the method of least-squares.

2) Deformable registration approaches—There are multiple variations of deformable registration algorithms which primarily use parametric and nonparametric methods to model the deformation vector field mapping of the two images. Two popular approaches are to model the deformation field using cubic B-splines [39] and thin-plate splines [40]. The cubic B-spline approach is often used in cases where we have image data sampled on a regular grid and where the control points are placed on a regular grid. The cubic spline basis ensures that the deformation vector field is smooth and differentiable. Thin-plate splines are often used for modeling deformation fields not defined on a regular grid and are often used to model the deformation field between a set of landmark positions. We implemented these registration algorithms using the Insight Software Toolkit (ITK) [41].

III. RESULTS

We have computed registration errors for a set of manually selected landmark positions for internal features present in both the air and fluid MR images. Specifically, we considered the following cases:

- No alignment of the two volumes
- Affine-based alignment of the two volumes using the entire images
- Affine-based alignment of the two volumes using the fiducials only
- B-spline deformable registration of the two volumes using the entire images
- Thin-plate-spline deformable registration of the two volumes using fiducials only

The results for the breast shown in Fig. 4 are quantified in Table I with all distances given in units of millimeters. Prior to registration, the mean alignment error was 11.6 mm and it could be reduced to 6.5 mm using an affine transformation and the position information for the 13 fiducials. A deformable thin-plate spline registration further reduced the mean alignment error to 4.6 mm.

The left breast of this subject experienced a rotation and translation as is seen in Fig. 4b. In this case the affine marker based registration had a mean error of 10 ± 5 mm. This illustrates that consistent and straight positioning of the patient is important.

To determine the error in the fiducial detection, two of the authors (G.B. and C.D.) separately located the fiducials for one of the data sets. The average difference for the locations of the fiducials was 2.8 ± 1.2 mm which is on the order of 1 voxel.

In practical use of the system, utilizing multiple imaging markers is not feasible due to the time required to place the markers. In addition, since the MR registration will be needed for image reconstructions over a span of 6 months, a reproducible method of marker location will be required. A test was performed to determine the sensitivity of the registration error to the number of markers on the skin. For the less dense breast in Fig. 4, the registration error for an affine registration could be reduced by 30% from the unregistered images using only four markers and the nipple. The markers were selected at locations furthest from each other and the nipple. This may prove sufficient and reproducible in clinical use.

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As shown in Fig. 5 the denser breast experienced little deformation in the fluid. The average difference in marker location after registration with only the nipple location was less than 2 mm. As this is less than our measured accuracy of marker location placement, it is not surprising that the additional use of the marker locations did not improve the registration accuracy.

In our final implementation, the fiducial locations are acquired from the optical images as is shown in Fig. 8. The MR images in air are registered to the optical images (microwave image space) and from the deformed MR images a mesh is generated with the dense and fatty regions segmented as is shown in Fig. 9. This fatty/dense mesh is then used in our soft prior regularization.

IV. CONCLUSION

For our simulated microwave experiment, we could obtain registration of the MR images in air to MR images in our microwave coupling fluid to the accuracy required by the soft prior algorithm. A good registration in our test simulation indicates that we can meet the needed registration accuracy of less than 1 cm in clinical practice.

The buoyancy with the glycerin-water mixture is an issue for less dense breasts (nominally BI-RADS density A and B categories). Due to the increased density with the addition of the

glycerin, the deformation is larger than for water alone. For these patients, coverage with the fiducials of the full breast in a reproducible manner is important. For dense breasts (BIRADS C, D) this buoyancy and deformation may be less of an issue and proper registration can be made with fewer fiducials.

One limitation for this work is that it does not address the accuracy over time for the placement of the fiducials and the potential loss of accuracy. The use of tattoos or internally placed metal markers such as those used for radiation therapy are not acceptable for this application. Hence, further analysis of both the longitudinal shift of marker accuracy as well as the impact on the soft prior accuracy will be the subject of further investigation.

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Author P. M. Meaney is a co-owner of Microwave Imaging System Technologies, Inc., Hanover, NH, USA. He is an inventor on several U.S. patents related to microwave tomography for medical applications. Authors G. Boverman and C. Davis are employees of General Electric Corporation. They each hold several U.S. patents on medical imaging. The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Health or the prime recipient Dartmouth College.

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Biographies

Gregory Boverman receive the B.S. degree in computer and systems engineering from Rensselaer Polytechnic Institute, Troy, NY USA in 1995 and the Ph.D. degree in electrical engineering from Northeastern University, Boston, MA USA in 2007.

Since 2012 he has been a biomedical engineer at GE Global Research, Niskayuna, NY. His areas of research include image reconstruction, electrical impedance tomography, image processing, reliability modeling and machine learning.

Cynthia E. L. Davis received the B.S. degree in physics in 1989, the master’s degree in Physics in 1991 and the Ph.D. in physics in 1995 from Rensselaer Polytechnic Institute, Troy, NY, USA.

Since 1995 she has been a research scientist at GE Global Research, Niskayuna, NY. She is currently a principal scientist in the imaging organization at GE Research. Her areas of research include in x-ray, mammography and breast imaging in general. Currently she is working on new ways to leverage machine learning and image analysis to improve workflow in breast cancer screening and diagnosis.

Shireen D. Geimer received the B.S. degree in physics from Purdue University, Fort Wayne, IN, USA, in 1991, and the M.S. degree in engineering (with a specialization in space physics) from the Dartmouth College, Hanover, NH, USA, in 1995. Since 1994, she has been a Research Engineer with the Numerical Methods Laboratory, Thayer School of Engineering, Dartmouth College. Her current research interests include mesh generation in two and three dimensions for remote sensing and biomedical applications, and execution of simulations and processing of modeling solutions.

Paul M. Meaney (M'91–SM'11) received the AB degree in electrical engineering and computer science from Brown University, Providence, RI, USA, in 1982, the master's degree in microwave engineering from the University of Massachusetts, Amherst, MA, USA, in 1985, and the Ph.D. degree from Dartmouth College, Hanover, NH, USA, in 1995.

He was involved in the millimeter-wave industry with Millitech Corporation, South Deerfield, MA, USA, and Alpha Industries, Woburn, MA. He spent two years as a Post-Doctoral Fellow, including one year at the Royal Marsden Hospital, Sutton, U.K. He has been a Professor with Dartmouth College since 1997 and is also the President of Microwave Imaging System Technologies, Inc., Hanover, which he co-founded with Dr. K. D. Paulsen in 1995. He is also a Professor with the Signals and Systems Division, Chalmers University of Technology, Gothenburg, Sweden. The Dartmouth group has authored several clinical studies in various settings including breast cancer diagnosis, breast cancer chemotherapy monitoring, bone density imaging, and temperature monitoring during thermal therapy. He has also explored various commercial spin-off concepts, such as detecting explosive liquids and noninvasively testing whether a bottle of wine has gone bad. He has co-authored over 70 peer-reviewed journal papers, co-written 1 textbook and presented numerous invited papers related to microwave imaging, and holds 12 patents. His current research interests include microwave tomography, which exploits the many facets of dielectric properties in tissue and other media, and also include breast cancer imaging, where his group was the first to translate an actual system into the clinic.

Fig. 1. Optical imaging of a breast phantom in the microwave imaging system. The components of the system are; A) microwave antennas B) camera C) camera rotational system D) lasers E) glycerin-water coupling. The tank has a diameter of 30cm and a depth of 20cm.

Fig. 2.

The MR imaging configuration used. The microwave imaging tank (top) is 30cm in diameter and 8cm tall. It is placed inside of the MR magnet and the body flex coil is placed around the tank. The subject lies on top of the tank for both the air and fluid imaging (bottom)

Fig. 3.

Fiducial marker placement map. The nipple is the center of the diagram. Fiducials were placed at 45 degree increments with spacing of 3 cm (marked a) or 4 cm (marked b). A total of 13 fiducial markers were placed on each breast.

Fig. 4.

Visualizations of the same tissue for the right (a) and left (b) breast in air (top row) and the breast in matching fluid (bottom row). The location of the one of the markers is marked with F1 (in air) and F2 (in fluid)

Fig. 5. Visualizations of the same tissue for the breast in air (top row) and the breast in matching fluid (bottom row) in the bottom row for a second volunteer breast. This small dense breast did not deform in the matching fluid and the slice location is not shifted between air and fluid data sets.

Fig. 6.
Volume rendered breast with fiducial labels

Fig. 7.
Demonstration of the marker based affine transformation. The top images are of the breast in fluid and the bottom of the air image registered to the fluid image.

Fig. 8.
Optical Point Cloud rendered with MeshLab [42]

Fig. 9. Mesh for soft prior initialization. Mesh is generated from the MR image deformed for the microwave fluid orientation.

IMAGE REGISTRATION RESULTS FOR THE SELECTED REGISTRATION METHODS

TABLE I

Landmark	No Alignment (mm)	Affine Image (mm)	Affine marker (mm)	B- Spline (mm)	Thin plate spline (mm)
1	13.7	4.4	6.9	3	6.1
2	13.6	4.7	8.9	1.7	6.0
3	13.6	5.6	9.1	0	1.3
4	8.2	5.7	4.2	3.2	4.4
5	8.7	5.4	3.3	5.6	5.1
Mean	11.6	5.2	6.5	5.1	4.6
Std. Dev.	2.8	0.6	2.7	2.1	2.0