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Spatial Shrinkage/Expansion Patterns between Breast Density Measured in Two MRI Scans Evaluated by Non-rigid Registration

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Abstract

Breast MRI acquires many images from the breast, and computer-aided algorithms and display tools are often used to assist radiologist's interpretation. Women with lifetime risk greater than 20% in developing breast cancer are recommended to receive annual screening MRI, but the current breast MRI computer-aided-diagnosis systems do not provide the necessary function for comparison of images acquired at different times. The purpose of this work was to develop registration methods for evaluating the spatial change pattern of fibroglandular tissue between two breast MRI scans of the same woman taken at different times. The registration method is based on rigid alignment followed by non-rigid Demons algorithm. The method was tested in 3 different subjects who had different degree of changes in the fibroglandular tissue, including two patients who showed different spatial shrinkage patterns after receiving neoadjuvant chemotherapy before surgery, and one control case from a normal volunteer. Based on the transformation matrix, the collapse of multiple voxels on the baseline images to one voxel on the follow-up images is used to calculate the shrinkage factor. Conversely, based on the reverse transformation matrix the expansion factor can be calculated. The shrinkage/expansion factor, the deformation magnitude and direction, as well as the Jacobian determinate at each location can be displayed in a 3D rendering view to show the spatial changes between two MRI scans. These different parameters show consistent results, and can be used for quantitative evaluation of the spatial change patterns. The presented registration method can be further developed into a clinical tool for evaluating the therapy-induced changes and for early diagnosis of breast cancer in screening MRI.

1. Introduction

Screening mammography is the standard clinical examination for detecting early breast cancer. The radiologist reviews the mammogram of a woman by comparing to her previous mammogram (typically taken 1 to 2 years ago) side-by-side, so the changes on breast density and/or micro-calcifications can be evaluated for detecting the growth of abnormal lesions. But mammogram does not work well in women with dense breast, and in 2007 the American Cancer Society recommends that women with lifetime risk greater than 20% should receive annual breast MRI for screening (Saslow *et al* 2007). Since MRI acquires 3D

images, more sophisticated image analysis algorithms and display tools are needed. It would be very helpful to develop a co-registration method so that the current MRI can be compared with the previous MRI done one year ago, similar to evaluation of mammograms for cancer detection.

If there is no enhanced lesion that is clearly visible, the changes in fibroglandular tissue (commonly referred as the breast density) may provide useful information to aid in the detection of subtle abnormal changes, so these areas can be followed more closely. However, the distribution of breast density is not uniform, thus the capability to map out local changes within the entire breast is required. The current research in MRI-based density studies has been mainly focused on volumetric measurements of density in the whole breast (Klifa *et al* 2004, Nie *et al* 2008, Wei *et al* 2004). Unfortunately the measurement of the total volume is too coarse and cannot be used for detecting local changes.

The evaluation of the spatial pattern of changes between two MRI's taken at different times may be accomplished by registration. In breast MRI, the enhanced lesion can be best visualized on subtraction images generated by subtracting pre-contrast from post-contrast images. However, due to the minor movement of patient between these two acquisitions, subtraction artifacts are often seen, and the registration techniques are commonly applied to align images acquired before and after contrast injection (Rohlfing and Maurer 2003, Rueckert *et al* 1999). For the small changes between images acquired during the same scan session, the rigid registration using the Affine transformation algorithm is sufficient. For registration of images taken at different scan sessions that has a substantial change, non-rigid registration algorithms are required (Roose *et al* 2008). The method has been applied to co-register breast images acquired at the prone and supine positions, so the lesion detected on breast MRI at the prone position can be better utilized during the operation while the patient is lying at the supine position (Carter *et al* 2006, 2008). These previous studies have been for registration based on the boundary of the whole breast. The registration of the segmented fibroglandular tissue inside the breast has never been reported before.

In this work we developed a method based on non-rigid Demons registration algorithm to register the fibroglandular tissues acquired in two scans from the same woman. Based on the correspondence between two volumes, a metrics indicating the shrinkage/expansion of pixels within the breast was calculated. A 3-dimensional rendering software was developed to display the changes in the breast from different views. The method was tested in 3 different subjects who had different degree of changes in the fibroglandular tissue, including two patients who showed different spatial shrinkage patterns after receiving neoadjuvant chemotherapy before surgery, and one control case from a normal volunteer. This method will provide the basic framework, upon which other algorithms (e.g. the matching of breast boundary) can be further developed and integrated in the future for detection of early cancer.

2. Materials and methods

2.1. Subjects and MR Imaging Protocol

The MRI of two patients (32 and 41 years old) who received neoadjuvant chemotherapy and had a baseline scan and a post-therapy scan after 3 months of treatment were analyzed. One normal volunteer (36 years old) who had 2 scans done one-week apart was analyzed as a control case for comparison. The MRI was performed on a 3T Achieva system (Philips Medical Systems, Best, Netherlands) using a dedicated breast coil. The non-fat-suppressed images acquired before injection of contrast agents were used for segmentation of the breast from the body, and segmentation of the fibroglandular tissue within the breast. The images were acquired using a 3D gradient-echo sequence in axial view to cover bilateral breasts. The parameters were: FOV = 31-36 cm, image-matrix 480×480, TR/TE = 6.2/1.26 ms, flip-

angle = 12 degrees, and SENSE-factor = 2. Therefore, the in-plane resolution was 0.65 to 0.75 mm/pixel, and the slice thickness was 2 mm.

2.2. Breast and Fibroglandular Tissue Segmentation

The detailed procedures have been described in previous publications [Nie *et al* 2008, 2010]. Briefly, a horizontal line was drawn through the posterior boundary of the sternum and all tissues below this line were considered as non-breast tissues and removed. The breast region was extracted using the fuzzy C-means (FCM) based method and the chest wall muscle was identified using the B-spline curve fitting. The inhomogeneity of the signal intensity over the imaging field was corrected using an improved bias field correction algorithm (Lin *et al* 2011) based on combined N3 (Sled *et al* 1998) and FCM (Chen and Giger 2004). Then the FCM algorithm was used to segment the fibroglandular and fatty tissues. The final segmentation results were visually verified by an experienced radiologist. For each subject, the procedure was applied to segment the fibroglandular tissues at the baseline and the follow-up studies independently, and the segmented 3D tissue structures obtained in the two studies were registered to evaluate the differences between them. The segmented fibroglandular tissue volume in the baseline and the follow-up studies, and the percentage change, are summarized in Table 1.

2.3. Image Registration

The overall registration procedures and the evaluation of local change based on deformation are shown in Figure 1. The segmented density in pre-treatment baseline (B/L) and post-therapy follow-up (F/U) were first rigidly aligned based on 6 degrees of freedom, including 3 rotations (r_x, r_y, r_z) and 3 translations (t_x, t_y, t_z), using Eq. (1).

$$T_{rigid}(x, y, z) = \begin{pmatrix} r_x & r_y & r_z \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix} + \begin{pmatrix} t_x \\ t_y \\ t_z \end{pmatrix}. \quad (1)$$

Let F be the fixed image (F/U), M be the moving image (B/L) and $\circ$ be image transformation, the rigid alignment is the iterative process of minimizing the energy function E ,

$$E_{rigid} = \|F - (T_{rigid} \circ M)\|. \quad (2)$$

The optimization of rigid transform was done using the Powell's algorithm (Press *et al* 2002). After the global alignment, Demons algorithm (Kroon and Slump 2009, Thirion 1998) was applied to locally match the density in B/L and F/U. Similar to (2), the energy function of Demons algorithm is provided by

$$E(u) = \|F - M \circ (T + u)\|^2 + \sigma_n^2 \|F - M\|^2 \|u\|^2. \quad (3)$$

where T is the deformation field, u is the update for T in each iteration and σ_n is the image noise ratio coefficient. Let ∇ be the gradient of image and solve u by minimizing E to be 0, the estimated displacement of the original Demons algorithm (Thirion 1998) is given by

$$u = \frac{(M - F) \nabla F}{|\nabla F|^2 + (M - F)^2}. \quad (4)$$

In order to improve the speed of registration convergence and stability, the image edge force of the moving image (Wang *et al* 2005) is introduced to (4). The estimated displacement is now given by

$$u = \frac{(M - F) \nabla F}{|\nabla F|^2 + \alpha^2 (M - F)^2} + \frac{(M - F) \nabla M}{|\nabla M|^2 + \alpha^2 (M - F)^2}. \quad (5)$$

α is a constant which reduces the influence of edges (and noise) and limits the update speed of transformation field. T is often initialized as zero (no displacement) while $\sigma_n = 1/\alpha$ and $\alpha = 0.6$ in our study. The Demons registration was done following these iterative processes:

- a. Given T , update the new estimated displacement u by (5). u is further smoothed by a Gaussian kernel (with $\sigma = 8$) for a fluid-like regulation.
- b. Update T with the newly calculated u by $T + u$. T is further smoothed by a Gaussian kernel for a diffusion-like regulation (with $\sigma = 1$).
- c. Calculate a new cost function E based on the new deformation field.
- d. If the difference of E between two consecutive iterations is less than a pre-set threshold ($t = 0.0001$) or the registration process reaches the maximum iteration number ($n = 200$), the iterative registration process is finished; otherwise, go back to step (a).

We adopted the version developed by Kroon and Slump (2009) that is available at: <http://www.mathworks.com/matlabcentral/fileexchange/21451-multimodality-non-rigid-demon-algorithm-image-registration>.

2.4. Evaluation of Deformation

Based on the deformation matrix T , one can assess the spatial shrinkage pattern by analyzing the convergence of multiple voxels on the source image M into one voxel on the target image F , as illustrated in Figure 1. For example, if 4 voxels (x_1, x_2, x_3 and x_4) in the source image collapse into the same voxel x_0 in the target image after transformation ($x_1 + T_1 \equiv x_2 + T_2 \equiv x_3 + T_3 \equiv x_4 + T_4 \equiv x_0$), that indicates shrinkage. Let $Q(x)$ be the number of overlapping voxels, we have $Q(x_1) = Q(x_2) = Q(x_3) = Q(x_4) = 4$. A higher number of overlapping voxels indicate a greater shrinkage in this area. Expansion is analyzed based on the reverse transformation matrix RT using the same criteria from the target image to the source image. The shrinkage/expansion factor can be calculated by: $O(x) = direction \cdot (Q(x) - 1)$, where $direction = 1$ if shrinkage and $direction = -1$ if expansion. The $O(x)$ map was smoothed by Gaussian kernel and color-coded to illustrate the spatial shrinkage/expansion patterns.

In addition to calculating the number of overlapping voxels, the Jacobian determinant of the deformation matrix was also used to evaluate the shape changes. This is a common approach to assess the volumetric deformation (Qiu *et al* 2008). We adopted the implementation from the Insight Segmentation and Registration Toolkit (ITK, Ibanez *et al* 2005) and Jacobian determinant is given by:

$$|J| = \begin{vmatrix} 1 + 0.5 \cdot \frac{\partial T_x}{\partial x} & 0.5 \cdot \frac{\partial T_x}{\partial y} & 0.5 \cdot \frac{\partial T_x}{\partial z} \\ 0.5 \cdot \frac{\partial T_y}{\partial x} & 1 + 0.5 \cdot \frac{\partial T_y}{\partial y} & 0.5 \cdot \frac{\partial T_y}{\partial z} \\ 0.5 \cdot \frac{\partial T_z}{\partial x} & 0.5 \cdot \frac{\partial T_z}{\partial y} & 1 + 0.5 \cdot \frac{\partial T_z}{\partial z} \end{vmatrix}. \quad (6)$$

$|J| < 1$ indicates inward shrinkage, while $|J| > 1$ indicates outward expansion.

3. Results

The methods are applied to three case examples. Figure 2 shows the younger chemotherapy patient (32 years old) who had extremely dense breasts at baseline and shows severe fibroglandular tissue atrophy after receiving chemotherapy. The total fibroglandular tissue volume was 190 cm^3 before treatment, and decreased to 116 cm^3 at the follow-up scan, showing 39% reduction. The shrinkage of breast density can be easily observed by visual inspection of the MR images, and the most noticeable changes are in the medial and the lateral sides. It can be seen that many voxels in the medial side of the breast show the shrinkage factor of greater than 2 (that is, more than 3 voxels on baseline image collapse into one voxel on follow-up image). The 3D rendering movie of the spatial shrinkage pattern is provided as a supplementary file (Movie 1). Figure 3 illustrates the difference in the breast density between the baseline and follow-up images by overlaying the cone plots from three different views (medial, caudal, and lateral). The cones show the deformation amplitude and direction of pixels at each location on the baseline image to match the follow-up image. Most deformations are pointing inward, indicating shrinkage. The results are consistent with the map of overlapping factors. The 3D rendering movie of the overlay cone plot along the medial-lateral direction is provided as a supplementary file (Movie 2).

Figure 4 shows the results analyzed from the older chemotherapy patient (41 years old) who had a moderate breast density before treatment and showed a milder atrophy compared to the younger patient. She also showed reduced fibroglandular tissue volume from 116 cm^3 at baseline to 110 cm^3 at follow-up, with 5.2% reduction. On the spatial shrinkage map, it can be seen that only a few voxels have overlapping factors greater than 1 (coded by yellow to orange color). Figure 5 shows the change in a healthy volunteer between 2 MRI scans acquired 1 week apart. The fibroglandular tissue volume was 36.6 cm^3 at baseline, and 35.9 cm^3 at follow-up, only showing 1.9% difference. The spatial map of overlapping voxels was mostly coded by green, and the results indicate that there was very little change.

4. Discussion and Future Works

In this work we applied the non-rigid Demons algorithm to coregister breast densities between two scans taken at different times, and Demonstrated that the number of collapsing voxels (noted as the shrinkage factor) at each spatial location during transformation can be used to illustrate the spatial shrinkage pattern. The results were consistent with the quantitative analysis of volumetric reduction and visual inspection findings. In the three selected case examples, the tool reveals the different atrophy patterns caused by chemotherapy, and shows very little change between two scans of a normal volunteer. The results suggest that this registration-based method can be used to provide information on the spatial change in breast density for visual inspection, also provide quantitative parameters using the shrinkage/expansion factor and the Jacobian determinant for further analysis of the degree of changes. For cases that show substantial changes (e.g. subject #1), visual inspection can easily detect these changes. If a quantitative parameter is needed for any purposes (e.g. to correlate the change with patient's future recurrent cancer risk), the coarse volumetric measurement is probably sufficient. However, for cases with little change (e.g. subject #2, #3), these small changes cannot be detected by visual inspection, and the spatial pattern evaluated using the algorithms developed in this work might provide additional information.

The observed difference in the fibroglandular tissue is mainly coming from two sources, the positioning difference of the breast between the two scans, and the intrinsic change of the fibroglandular tissue within the breast. In theory, we can use both the outer boundary of the breast as well as the inner boundary of the fibroglandular tissue for registration, but this is a

much more complicated problem, also it will be difficult to verify obtained results. Therefore, as the initial approach, we selected three cases that show similar shapes of the breast between 2 scans, so we can focus on registration of the fibroglandular tissue within the breast.

Given the highly deformable nature of the soft breast tissues, MR scans of the same breast at different imaging sessions often presents different shapes. In this case, traditional non-rigid registration methods may not be sufficient to recover the large deformations. Carter *et al* (2006, 2008) have successfully combined non-rigid registration together with finite element model (FEM) to overcome the large deformation from two different scanning positions (e.g. between prone and supine). In the future, the FEM-based registration may be applied as the pre-processing step to first match the shape of the breast (Cash *et al* 2005), before the non-rigid registration is applied to co-register the fibroglandular tissue.

In the implementation of the Demons registration, the additive update of transformation field ($T + u$) was applied. Vercauteren *et al* (2009) suggested that the additive Demons algorithm is not fully diffeomorphic and may be incapable of matching objects with large curvature. They proposed a new exponential compositive Demons algorithm with the transformation field updated by $T \circ \exp(u)$ that is fully diffeomorphic and has the potential to coregister objects with irregular boundaries. Whether the registration of the fibroglandular tissue can be further improved by this method needs to be evaluated.

In a recent paper we demonstrated that the normal contralateral breast of patients receiving chemotherapy showed reduction of breast density (Chen *et al* 2010). Since the changes were different between pre-menopausal and post-menopausal patients, the results suggested that the reduction was mediated through the compromised ovarian function. The ability to analyze spatial change patterns may provide quantitative information for evaluating the chemotherapy-induced breast atrophy, as well as how it is related to changes in hormones and patient's future prognosis. In a very recent paper by Cuzick *et al* (2011), the change of breast density was shown as a surrogate marker to predict the efficacy in patients receiving tamoxifen as a chemopreventive drug to reduce the risk of developing breast cancer. Measurement of breast density on mammography is not reliable (Kopans 2008), and the presented method in this work may provide a useful tool and new imaging biomarkers for evaluating efficacy of cancer therapy or chemoprevention.

Another important application of this method is for comparing annual screening MRI in high-risk women to evaluate whether there are any regions showing significant changes in density. If the increase of density is found in a specific region by comparing it to the prior scan, this patient may need a close follow-up to monitor the development of abnormal lesions. For detecting such a small localized change, we need a high precision, and all possible reasons that may cause spatial difference of the breast between two scans (including the positioning) need to be considered. As the next task, we will develop the registration of the breast boundary using finite-element-based method, so the positioning difference can be eliminated, and then we can proceed with the fibroglandular tissue registration according to the method presented in this work.

In summary, we proposed a new method for evaluating the spatial change pattern of fibroglandular tissues between two breast MR scans of the same woman at different times. The deformation analyzed using the combined rigid and non-rigid registration methods can be used to evaluate the collapse of voxels in one volume to match the other, thus indicate the shrinkage; and vice versa for expansion. The Jacobian, as well as the magnitude and direction of the deformation, can be displayed in a 3D rendering view. However, the method was only tested in 3 cases, for proof of feasibility, and further evaluation in more cases is

needed. The presented method in this manuscript will provide the basic framework, upon which other algorithms (e.g. the matching of breast boundary) can be further developed and integrated. These methods can be developed into a clinical tool for evaluating the therapy-induced changes and for early diagnosis of breast cancer in screening MRI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The overall registration procedures and the evaluation of local shrinkage/expansion based on the deformation matrix T . The segmented density in the pre-treatment baseline and post-therapy follow-up studies are first aligned with rigid translation and rotation. Then the non-rigid Demons algorithm is used to register the baseline images (as the source) to match the follow-up images (as the target). The spatial shrinkage pattern is analyzed by calculating the convergence of multiple voxels on the source image into one voxel on the target image. For example, if 4 voxels (x_1 , x_2 , x_3 and x_4) in the source image collapse into the same voxel x_0 in the target image, that indicates shrinkage with a shrinkage factor of 3 voxels. Expansion is analyzed based on the reverse transformation matrix RT from the target image to the source image using the same criteria. Lastly the obtained shrinkage/expansion factor at each voxel location is color-coded and displayed on the baseline image.

Figure 2.

The comparison of fibroglandular tissues before (baseline, B/L) and after chemotherapy (follow-up, F/U) in the younger 32-year-old patient. She has extremely dense breast at baseline and shows a severe atrophy after receiving chemotherapy. The total fibroglandular tissue volume decreases from 190 to 116 cm³. The most noticeable shrinkage is seen in the medial and the lateral sides, as marked by arrows. The map of the overlapping factor shows warm colors (orange to red) in the medial and lateral sides, indicating a large shrinkage in these areas. In addition, the Jacobian determinant of the deformation matrix is used to evaluate the changes. For displaying purposes, the color bar is adjusted to show inward shrinkage ($|J| < 1$) as warm colors and outward expansion ($|J| > 1$) as cold colors. The Jacobian map is consistent with the map of the overlapping factor, also showing shrinkage in the medial and lateral sides.

Figure 3.

The illustration using the cone-plot to indicate the amplitude and the direction of the deformation for voxels on the baseline image to match the follow-up image. The medial, caudal, and lateral views are shown. This is the same case example shown in Figure 2. Most deformations are pointing inward, indicating shrinkage. The results are consistent with the map of overlapping factors. The larger inward cones are seen in the warm color area with a higher shrinkage factor.

Figure 4.

The results analyzed from the older chemotherapy patient (41 years old) who has a moderate breast density before treatment and shows a milder atrophy after chemotherapy compared to the younger patient (from 116 cm³ at baseline to 110 cm³ at follow-up). Only a few voxels have the shrinkage factor greater than 1 that shows yellow to orange color.

Figure 5.

The changes between 2 MRI scans acquired from a healthy volunteer with 1-week apart. The fibroglandular tissue volume is 36.6 cm^3 at baseline, and 35.9 cm^3 at follow-up. The map of overlapping factor is mostly coded by green, indicating very little change.

Table 1

The total fibroglandular tissue volume measured in the baseline and the follow-up MRI studies, and the percentage change.

	Age	Baseline	Follow-up	Percent Change
Subject #1 (Chemotherapy Patient)	32	190 (cm ³)	116 (cm ³)	39 %
Subject #2 (Chemotherapy Patient)	41	116 (cm ³)	110 (cm ³)	5.2 %
Subject #3 (Normal Volunteer)	36	36.6 (cm ³)	35.9 (cm ³)	1.9 %