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Fat-based Registration of Breast Dynamic Contrast Enhanced Water Images

Subashini Srinivasan¹, Brian A. Hargreaves¹, and Bruce L. Daniel¹

¹Department of Radiology, Stanford University, Stanford, California, USA

Abstract

Purpose: In this study, a three-dimensional fat-based deformable registration algorithm was developed for registering dynamic-contrast-enhanced breast images.

Methods: The mutual information (MI) similarity measure with free-form deformation motion correction in rapidly enhancing lesions can introduce motion. However, in Dixon-based fat-water separated acquisitions, the non-enhancing fat signal can directly be used to estimate deformable motion, which can be later used to deform the water images. Qualitative comparison of the fat-based registration method to a water-based registration method, and to the unregistered images was performed by two experienced readers. Quantitative analysis of the registration was evaluated by estimating the MSSD on the fat images.

Results: Using a scale of 0 (no motion) to 2 (> 4 voxels of motion), the average image quality score of the fat-based registered images was 0.5 ± 0.6 , water-based registration was 0.8 ± 0.8 , and the unregistered dataset was 1.6 ± 0.6 . The MSSD metric on the fat images was significantly lower for fat-based registered images compared to both water-based registered and unregistered images.

Conclusion: Fat-based registration of breast DCE images is a promising technique for performing deformable motion correction of breast without introducing new motion.

Keywords

fat-based registration; breast deformable motion

INTRODUCTION

Four-dimensional dynamic-contrast-enhanced (DCE) breast MRI, which is used to characterize breast lesions, takes about five to ten minutes to acquire (1). Within this acquisition duration, breast motion is a common problem and may require motion correction before performing post-processing analysis such as wash-out slope, time-to-peak enhancement (2) or quantitative pharmacokinetic modeling (3,4).

The three-dimensional breast images may undergo deformable and/or bulk motion during the DCE acquisition. Iterative three-dimensional motion correction algorithms consist of a transformation model, similarity measure, and an optimizer to vary the transformation

parameters to maximize the similarity measure (5). Bulk motion is usually corrected using an affine transformation model. This is followed by deformable motion correction using a free-form deformable transformation model based on b-splines (6,7), and finite element models (8). Intensity-based deformable registration using demons algorithm (9) has also been used for registering time-series images without varying signal intensity. Landmark or feature-based deformable registration has also been performed by choosing identical features in the 3D breast datasets and performing deformable motion correction on these feature points or surfaces (10). Feature-based registration, however, can be time consuming for high-resolution four-dimensional datasets, and several spatial features may not be available in all the time points.

Motion correction between images of similar signal intensity can be performed by using squared-signal-difference as the similarity measure. As the DCE image signals change with contrast enhancement, the motion correction is performed with normalized mutual information as the similarity metric (6,11). This metric accurately corrects rigid transformation motion between images acquired using differing image modalities. However, the mutual information similarity metric may introduce motion when applied with a deformable transformation on images with contrast enhancing lesions (12).

Several methods have been proposed to reduce the errors in deformable motion correction using a mutual information metric. For example, the DCE images are de-enhanced by modeling the spatially varying intensities before performing deformable motion correction (13,14). A local volume preservation constraint (15) is used with a deformable motion model or the enhancing lesions are assumed to be rigid during motion correction (14).

The fat signal in breast DCE images appears bright due to short T_1 and can obscure small enhancing lesions. Hence the fat signal in breast images is often suppressed using spectrally-selective inversion or saturation pulses (16). However, due to increased B_0 and B_1 inhomogeneities at higher field strength, fat suppression may be non-uniform and may also result in inadvertent water suppression. Post-contrast images can also be subtracted from the pre-contrast images to suppress fat, but any motion between the acquisitions could result in erroneous enhancements and non-uniform fat suppression. Dixon-based fat-water separation (17) is robust to B_0 and B_1 inhomogeneities and provides both fat and water images that are acquired simultaneously and are co-registered, at a cost of more scan time. Additionally, the SNR gain from averaging over 2 echoes allows greater acceleration factors that can mostly compensate for increased scan time (18,19). The fat signal does not enhance with contrast (20), and hence could be used for deformable motion estimation mitigating the errors introduced by the previous methods. Moreover, the fat is interspersed throughout the breast in nearly all patients, providing high signal and features for motion correction. The deformable motion from the fat images can then be used to correct the water images, and hence may reduce the likelihood of change in enhancing tumor volumes.

The objectives of the study were to: (i) develop a fat-based deformable motion correction technique; and (ii) compare the technique qualitatively and quantitatively with water-based deformable motion correction.

METHODS

The intertwined effects of tissue motion and contrast-enhancement on fat and water signal are illustrated in Supporting Fig. S1. The Gadolinium contrast agent leaks through the blood vessels into the extravascular space causing signal changes over time in the water image, such as the rapid signal enhancement in a fibroadenoma, that is near the magenta and orange voxels. These voxels in the water image (Supporting Fig. S1b) show washout signal characteristics due to both contrast uptake as well as motion (Supporting Fig. S1d - dashed line), but when motion is corrected the uptake is persistent – an important distinction for diagnosis (Supporting Fig. S1d - dashed line). The corresponding voxels in fat-image show signal variations in time due to motion alone (Supporting Fig. S1c - dashed line), as the fat-signal does not enhance (20). Hence the three-dimensional image displacements can be estimated from the temporal fat signal variations when fat-water separated images are available. These fat-based image displacements can later be used to deform the water images. The green and blue voxels that are in the uniformly enhancing or non-enhancing regions respectively did not exhibit temporal fat-signal variations (Supporting Fig. S1c - dashed lines). Hence the temporal dynamics of the corresponding voxels in the water signal were also unaltered after motion correction (Supporting Fig. S1d - dashed vs. solid lines). Supporting video S1 shows the motion in the acquired fat and water images leading to errors in time curves.

Fat-based Motion Correction

The three-dimensional fat-based motion correction algorithm was implemented in the Insight Segmentation and Registration Toolkit (ITK) (21), and the corresponding code is provided as Supporting material. The 3D fat image acquired at three minutes post contrast injection was considered as the reference image for motion correction. All of the other post-contrast and pre-contrast images were motion corrected to match this reference frame. The images were affine transformed with Mattes mutual information (MMI) (22,23) as the metric and conjugate gradient as the optimizer. The MMI metric in ITK computes the negative of the mutual information. Hence a lower MMI metric means greater mutual information between the two images. The number of iterations of the optimizer was set to 200 with minimum convergence value of 10^{-7} . This was followed by b-spline transformation with the same metric, and Limited memory Broyden Fletcher Goldfarb Shannon minimization with simple bounds optimizer (LBFGSB) (24). The number of iterations of the optimizer was set to 500 and cost-function convergence factor was 10^9 . The motion correction was performed in a 3D volume of a single breast with a b-spline grid with five control points along each dimension. The combined affine and b-spline transformation of the fat images was then applied to the water images. The individual steps of the fat-based registration method implemented in ITK are detailed in Fig. 1.

As a standard registration method for comparison, the water-based registration was performed with MMI similarity metric with identical transformations and optimizers as fat-based registration. The fat images were also then warped using the deformation of water images for further quantitative analysis.

In Vivo Imaging

The quantitative and qualitative image quality of the original unregistered image series and images from both fat- and water-based registration methods were evaluated in 14 patients (2 bilateral) with known lesions (age= 24 to 70 years). Our Institutional Review Board approved the protocol, and informed consent was obtained from the patients. The 14 patients had 24 lesions with 15 malignant lesions (10 invasive ductal carcinoma and 5 ductal carcinoma in situ) and 9 benign lesions (3 fibroadenoma, 2 adenosis, 1 radial scar, 1 papilloma with usual ductal hyperplasia, 1 atypical lobular hyperplasia and 1 florid usual ductal hyperplasia). The largest dimension of the malignant lesions varied from 10.6 cm to 0.8 cm, and the largest dimension of the benign lesions varied from 1.8 cm to 0.8 cm. Three-dimensional RF-spoiled gradient echo fat-water separated DCE images were acquired using Differential Subsampling with Cartesian Ordering (DISCO) (25), a pseudorandom k_y - k_z sampling scheme enabling a favorable tradeoff between temporal and spatial resolution, on a 3T scanner (GE Healthcare, Waukesha, WI). The imaging parameters were: field-of-view (FOV)=300×360 mm, receiver bandwidth=325 Hz/pixel, echo times (TE_1/TE_2)=2.2/3.3 ms, repetition time (TR)=6.2 ms, flip angle=12°, number of slices=188, parallel imaging reduction factor (26) of 2.5×2.0, partial echo factor=0.8 along readout direction, number of acquired DISCO “B regions”=4, and percentage of k-space included in the innermost DISCO “A region” was 16%. One pre-contrast and four post-contrast images were acquired with high spatial resolution of 0.5×0.6×1.0 mm³ and low temporal resolution of 2 min. Fourteen images were acquired during the wash-in period with a high temporal resolution of 13s and lower spatial resolution of 0.5×1.2×2.0 mm³. All of the images were reconstructed to identical spatial resolution before performing fat- and water-based registration. Fat-water separation was performed using a two-point Dixon reconstruction with single peak fat model and a region-growing algorithm for estimation of field inhomogeneities (17).

Qualitative Analysis

The image quality of the original, water- and fat-based registration methods was reviewed by two experienced readers. The dicom images were displayed in the 4D viewer of Osirix software (27). The three datasets were presented in three adjacent columns in random order. The images were initially viewed in axial plane and later reformatted to sagittal and coronal planes. The images were scored in a scale of 0 to 2 based on all the three viewing planes. A score of 0 was given to images with minimal motion of less than 2 voxels in each direction, over the entire breast. Similarly, a score of 1 was given to residual motion of 2 to 4 voxels, and score of 2 for motion greater than 4 voxels. The readers also ranked the datasets from best (rank 1) to worst (rank 3) based on the overall motion in the 4D dataset. The statistical analysis was performed in MATLAB 2015a (Mathworks, Natick, MA, USA). The statistical differences in score and rank of the three groups were determined using Friedman test with $p < 0.05$. The pairwise significance between the groups was performed using a Tukey – Kramer method with $p < 0.05$.

Quantitative Analysis

The image registration quality was measured by calculating the average mean-squared-signal-difference (MSSD) metric between the three-dimensional reference image and each

of the 3D temporal phases of the fat images in the original, fat- and water-based registration methods. The statistical differences between the original and the new registration methods were measured using a repeated measures ANOVA test with $p < 0.05$. Pairwise statistical differences between original, water- and fat-based registration methods was determined using Tukey – Kramer method with $p < 0.05$.

RESULTS

Supporting Figure S2 shows a single reformatted sagittal slice of the seventh temporal phase of the fat images (Supporting Fig. S2 a-c), difference between the fat image in seventh temporal phase and reference phase (Supporting Fig. S2 d-f), water image (Supporting Fig. S2 g-i), and difference between the water image and the reference phase water image (Supporting Fig. S2 j-l). The bright and dark regions (arrows) in the original subtracted images (Supporting Fig. S2 d,j) indicate the motion in the slice. Both water-based (Supporting Fig. S2 e,k) and fat-based (Supporting Fig. S2 f,l) registration methods have reduced bright and dark regions in the difference images indicating motion correction. The mean qualitative scores on these images show that both water- and fat-based registration methods reduced the motion (score=1.0) compared to the original images (score=2.0). The temporal motion in the water and subtracted fat images for all of the methods can be better visualized in supporting video S2.

Figure 2 compares the fat images (a-c), water images (d-f), and the difference in fat images with respect to the reference phase (g-i) of an example dense breast with minimal motion (arrows). Figure 2h shows that the water-based registration method introduces new motion (arrows) compared to the original images (Fig. 2g), and the fat-based registration (Fig. 2i) reduces the original motion without introducing new motion. The mean qualitative score of the original image was 1.5, water-based was 2.0 and fat-based registration was 0.5. The MSSD metric (Fig. 2j) shows that in a few phases the water-based registration method (red) has a higher metric (new motion) compared to the original images. The fat-based registration method had a lower metric for all of the temporal phases compared to the original images, even in this example of dense breast with relatively less fat tissue. This quantitative metric also compares well with the qualitative scores. Supporting video S3 shows the temporal motion in fat images, water images and difference in fat images for the original, water- and fat-based registration methods.

Figure 3 shows another example comparison of original unregistered images (a,d,g), water-based (b,e,h) and fat-based (c,f,i) registered images of a dense breast. In this example, the water-based registration has introduced new motion (yellow arrows) compared to both original and fat-based registration. The fat images in the supporting video S4 of the individual temporal phases for each method show that the cardiac flow artifacts (red arrows) are reduced in water-based registration compared to both original and fat-based registration. These flow artifacts could be introducing new motion in the water-based registration method. The MSSD metric (Fig. 3k) is lowest for the fat-based registration compared to original and water-based registration, even though it does not capture the introduction of the new motion by the water-based method compared to the original images.

The average image quality scores of the acquired unregistered images, water-based and fat-based registration methods are tabulated in Table 1a. A Friedman test showed significant ($p<0.01$) differences between the three categories. The pairwise comparison of the three categories showed that the water- ($p<0.01$) and fat-based ($p<0.01$) registered images received a significantly lower score than the original images. Three water-based registered datasets received an average score of 2 that was equal to or higher than the original images due to insufficient motion compensation or introduction of new motion. The fat-based registered images received a score lower than the original images for all the datasets. The average fat-based registered image score for 15/16 breasts was lower than or equal to that of the water-based registered images. One dataset received an average score of 1 for fat-based registration, 0.5 for water-based registration and 2 for the unregistered dataset. There was no significant difference between the water- and fat-based registered image score ($p=0.45$).

Table 1b shows the rank of the original, water- and fat-based registered images. The water- ($p=0.01$) and fat-based ($p<0.01$) registered images received a significantly better rank compared to the original images. There was no significant difference in the rank between the water- and fat-based registered images ($p=0.06$).

The MSSD metric on the fat images (Fig. 4a) showed that both fat-based ($p<0.01$) and water-based ($p=0.01$) registration methods had a significantly lower metric compared to the unregistered original images. In addition, the fat-based registration had a significantly lower metric ($p<0.01$) than the water-based registration method as well. The Bland-Altman plot for fat- and water-based MSSD metrics for the 16 datasets (Fig. 4b) show that the fat-based registration metric is reduced in all the breast images compared to the water-based registration, with a mean bias of -366.2 . The ratio of the mean bias to the average of the MSSD metric for fat-based registration is -0.09 .

DISCUSSION

Breast deformable registration is performed using mutual information similarity metric on images with varying signal due to contrast injection, and is susceptible to the introduction of new motion. The fat signal on DCE breast images, on the other hand, is a potentially useful reference for motion registration, both because it provides bright signal and because the signal does not enhance with contrast injection. The deformation transformation from the fat images can then be applied to corresponding water images provided that they were acquired simultaneously, for example using Dixon-based techniques. This fat-based registration method corrected the motion observed in the original images and did not introduce new motion when compared to water-based registration method. Even in patients with dense breasts, the subcutaneous fat surrounding the central cone of fibroglandular tissue was sufficient for estimation of the deformable motion as shown in Figs. 2 and 3. Future work is required to evaluate the fat-based registration method in patients with extremely dense breasts such as in lactating women (28).

The quantitative analyses were performed by analyzing the MSSD metric on the fat images for the acquired, water- and fat-based registered images. As the fat signal does not enhance with contrast, any difference in the mean-squared signal of the fat indicates residual motion

(in both fat and water images). The fat signal however, is relatively lower in tumor regions and the MSSD metric may not be able to uniformly capture the motion in the tumor region and the surrounding fat due to their inherent signal differences. Due to the enhancement differences in the water images, the motion in the water images was analyzed qualitatively.

During warping, the 3D images were interpolated and potentially introduced minimal blurring in patients with motion greater than 4 voxels regardless of the choice of registration methods. The image quality including blurriness will be further evaluated in more patients with significant motion. The estimation of pharmacokinetic parameters is affected by motion (4). The effect of fat-based registration on estimation of pharmacokinetic parameters needs to be evaluated in a greater number of patients and compared to the conventional water-based registration technique.

The fat-based registration algorithm is based on the assumption that all signal intensity differences in the images are due to the motion. However, if the fat-water separation is incomplete with inconsistent fat-water swaps in the temporal image series, the fat-based registration may fail. In our study population of 14 patients, the fat and water separated images did not have any regional swaps. Furthermore, Dixon-based methods continue to improve in robustness by acquiring multiple echoes (29), so the use of fat-based registration remains promising for such studies.

CONCLUSION

Fat-based registration of breast DCE images is a promising technique for deformable registration. The fat-based registered images were qualitatively scored better than the unregistered images for all the cases and did not introduce new motion. The quantitative residual motion captured by the MSSD metric was significantly lower in fat-based registration compared to both water-based registration and the original unregistered images.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

The steps of the fat-based registration of a single three-dimensional breast dataset to the post-contrast image acquired at 3 min post injection. The iterative registration algorithm used Mattes mutual information as the similarity metric, and images were first affine transformed followed by b-spline based deformable transformation. The parameters were updated, after each iteration, using conjugate gradient descent algorithm for the affine transformation and LBFGSB optimizer for b-spline registration. The transformation from the fat images was later applied to the corresponding water images.

Figure 2:

An example dense breast fat image (a-c) of the 12th temporal phase, water images (d-f) and difference between the fat image (fat₁₂) and reference phase (fat₁₆) (g-i) with minimal motion (arrows) in the original subtracted fat images (g). The water-based registration method (h) introduces new motion (arrows) compared to the original images, and the fat-based registration (i) reduces the original motion without introducing new motion. The MSSD metric (j) calculated over the entire volume of single breast fat images shows that few phases of water-based registration method (red) have a higher metric (new motion) compared to the original images. The dots represent the metric for the 12th phase. The mean qualitative scores on these images are also shown.

Figure 3:

A sagittal reformatted example of dense breast fat images (a-c), water images (d-f) and difference in fat between the 17th phase (fat₁₇) and reference image (fat₁₆) (g-i) from the reference fat image. The water-based registration method (h) introduces new motion (yellow arrows) compared to the original images (g), and the fat-based registration (i). The cardiac flow artifacts are similar in both original and fat-based registered images, but are reduced in the water-based registered images (red arrows). The MSSD (j) metric calculated over the entire volume of single breast fat images for all the three methods, show that both water-based (red) or fat-based (black) registration method have a better metric compared to the original (blue) images. The mean qualitative scores on these images are also shown.

Figure 4:

Box-whisker plot (a) of the average MSSD metric on the fat images showed that the fat-based registration method had a significantly lower metric compared to both the original and water-based registration methods. Bland-Altman plots (b) MSSD metric show that the fat-based MSSD metric is lower than the water-based metric for all the breasts with a mean bias of -366.2

Table 1a:

Qualitative study – score of the original, water- and fat-based registered images

Score		Original	Water-based*	Fat-based*
Mean $\pm$ standard deviation [Range]	Reader 1	1.6 $\pm$ 0.6 [0 to 2]	0.9 $\pm$ 0.8 [0 to 2]	0.6 $\pm$ 0.7 [0 to 2]
	Reader 2	1.5 $\pm$ 0.5 [1,2]	0.8 $\pm$ 0.8 [0 to 2]	0.4 $\pm$ 0.5 [0,1]

Table 1b:

Qualitative study – rank of the original, water- and fat-based registered images

Rank		Original	Water-based*	Fat-based*
Mean $\pm$ standard deviation [Range]	Reader 1	2.8 $\pm$ 0.5 [2,3]	2.0 $\pm$ 0.7 [1 to 3]	1.3 $\pm$ 0.5 [1,2]
	Reader 2	2.9 $\pm$ 0.3 [2,3]	1.9 $\pm$ 0.6 [1 to 3]	1.2 $\pm$ 0.4 [1,2]

* indicates significant difference between the original, and water/fat-based registration method.