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Non-rigid registration of serial dedicated breast CT, longitudinal dedicated breast CT and PET/CT images using the diffeomorphic demons method

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Abstract

Rationale and Objectives—Dedicated breast CT and PET/CT scanners provide detailed 3D anatomical and functional imaging datasets and are currently being investigated for applications in breast cancer management such as diagnosis, monitoring response to therapy and radiation therapy planning. Our objective was to evaluate the performance of the diffeomorphic demons (DD) non-rigid image registration method to spatially align 3D serial (pre- and post-contrast) dedicated breast computed tomography (CT), and longitudinally-acquired dedicated 3D breast CT and positron emission tomography (PET)/CT images.

Methods—The algorithmic parameters of the DD method were optimized for the alignment of dedicated breast CT images using training data and fixed. The performance of the method for image alignment was quantitatively evaluated using three separate data sets; (1) serial breast CT pre- and post-contrast images of 20 women, (2) breast CT images of 20 women acquired before and after repositioning the subject on the scanner, and (3) dedicated breast PET/CT images of 7 women undergoing neoadjuvant chemotherapy acquired pre-treatment and after 1 cycle of therapy.

Results—The DD registration method outperformed no registration ($p<0.001$) and conventional affine registration ($p\leq 0.002$) for serial and longitudinal breast CT and PET/CT image alignment. In spite of the large size of the imaging data, the computational cost of the DD method was found to be reasonable (3–5 min).

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Conclusions—Co-registration of dedicated breast CT and PET/CT images can be performed rapidly and reliably using the DD method. This is the first study evaluating the DD registration method for the alignment of dedicated breast CT and PET/CT images.

Keywords

dedicated breast CT; breast PET/CT; non-rigid registration; diffeomorphic demons

1. INTRODUCTION

Dedicated breast computed tomography (bCT) is being actively investigated for early detection of breast cancer [1–3], with recent data showing that such imaging with contrast-enhancement (CE) may improve conspicuity of malignant breast lesions, especially in dense breasts, compared to mammography [4]. To further the utility of bCT for local staging of breast cancer and for monitoring of response to therapy, such as neo-adjuvant chemotherapy (NAC), dedicated bCT systems have been combined with dedicated positron emission tomography (PET) [5] or single photon emission computed tomography (SPECT) [6] breast scanners. Methods for high-resolution image-guided radiation therapy (RT) using the bCT platform are also being explored [7].

Detailed quantitative analysis of lesion enhancement in CE-bCT may allow improved detection and diagnosis of breast cancer [4] and optimized RT planning [8]. Such analysis is aided by spatial normalization of serial (pre-contrast and post-contrast) CT images via software-based image registration tools and performing a voxel-by-voxel analysis, such as subtraction or tumor volumetrics. The need for such tools arises because inter-scan patient motion or repositioning may lead to different orientations of the inherently non-rigid breast tissue in the field of view of the scanner. Image registration may also play an important role for dedicated breast PET/CT and SPECT/CT, where early monitoring of response to NAC is the clinical goal [9–11]. In this case software-based alignment of the anatomical images from the bCT component in a longitudinal setting may enable rapid region-of-interest (ROI)-based comparisons for the PET or SPECT images. Registration of longitudinal bCT images with cross-sectional magnetic resonance (MR) images may also aid in radiotherapy (RT) planning.

In this paper we evaluate the performance of the diffeomorphic demons (DD) method [12] for the non-rigid 3D alignment of large (~512×512×512 voxels): (1) serial pre- and post-contrast bCT images, (2) bCT images before and after patient repositioning on the scanner, but at the same time point, and (3) dedicated breast PET/CT (bPET/CT) images at two time-points (baseline and after one cycle of NAC) in patients with established breast cancer. The performance of deformable image registration methods including the DD method have been reported for alignment of anatomical images in other areas of the human body [13–16]. To the best of our knowledge, however, there has been no report of the use of the DD method for registration of bCT or dedicated breast PET/CT images. bCT images possess different noise and contrast properties compared to images from conventional CT [17] motivating the need for the analysis presented.

2. MATERIALS AND METHODS

2.1. Study subjects and imaging data

This retrospective HIPAA-compliant study had approval from our university's Institutional Review Board prior to initiation (approval date: February 16, 2012). The bCT images were from scans conducted on women suspected of having breast cancer, lying prone on the scanner tabletop with a single pendant breast hanging through a hole in the tabletop [17]. In each scanning session, the patient was first positioned for a pre-contrast contralateral (i.e, unaffected) breast scan. The patient was then repositioned to obtain a pre-contrast ipsilateral (i.e., affected) breast scan. A 100 ml intravenous injection of iodixanol (Visipaque™, GE Healthcare, Little Chalfont, UK) was administered at a rate of 3–4 ml/s depending on patient weight in either the left or right arm. A post-contrast ipsilateral scan was obtained starting at either 70 s or 90 s after the completion of the injection, depending on injection speed (4 mL/s or 3 mL/s, respectively), with the patient asked to maintain her position. Finally, the patient was repositioned to obtain a contralateral breast scan.

To evaluate the DD method, we randomly chose pre- and post-contrast scans of the ipsilateral breast in 20 subjects out of over 200 scans conducted on the bCT system, for our first study. In this case, the patient was expected to maintain position on the scanner and minimize movement. For our second study, we randomly chose 20 pre- and post-contrast scans of the contralateral breast of a separate population that were acquired at least 4 min apart, resulting in minimal contrast-enhancement. Between these scans, the patient was completely repositioned on the scanner bed. For our third study, we used bPET/CT scans of a different set of 7 patients undergoing NAC. In this case, the bPET scan with injected doses of ^{18}F-fluorodeoxyglucose ranging between 133.2–203.5 MBq and uptake time ranging between 85and 95 min of the ipsilateral breast was conducted immediately before the pre-contrast bCT scan of that breast.

The reconstructed CT image matrix has dimensions $512 \times 512 \times n$, with n set to contain the given breast length (450–512 slices) [4]. The voxel dimensions ranged from 0.36 mm transaxially and from 0.2–0.3 mm axially for our study. The PET images were reconstructed using the maximum a posterori (MAP) method [5] with a voxel size of $1.1 \times 1.1 \times 3.3\text{mm}^3$.

2.2. Registration scheme

All CT images were pre-processed by segmenting the breasts using intensity-based thresholding and connected-component analysis to remove artifacts outside the breast, such as those introduced by the scanner's cone-beam geometry. Images were registered in two steps. First, affine 3D registration based on the minimization of the mean-squared error between the template and target images was carried out to minimize gross translational and rotational errors. Our implementation was based on that from the publicly available Insight Toolkit (ITK) [18]. The resulting warped image provided an initialization for the subsequent non-rigid registration using the DD algorithm. The cost function for the DD method was based on the minimization of mean-squared error between the intensity images [12]. The optimal parameters were chosen for both the affine and the DD method based on 10 consecutive registration runs on a test dataset consisting of 3 separate pre- and post-contrast breast images and 3 separate breast images before and after repositioning, corresponding to the least mean-squared error. The sensitivity of the following registration parameters required by the DD method was analyzed – the number of multi-resolution levels to obtain the mapping, the number of demons iterations per level, the smoothing sigma for the deformation field at each iteration, the smoothing sigma for the update field at each iteration, and the type of gradient used for computing the demons force. For our bCT images the parameters converged to a 4-level pyramid multi-resolution scheme with 100 iterations at each level for the affine registration and a 4-level pyramid scheme with 10 iterations at the highest level and 100 iterations at levels 2–4, a smoothing factor for the displacement field of 1.5 and a maximum step length of 0.5 for the DD method. The sinus cardinal (sinc) interpolation method was used. These parameters were then unchanged throughout the study. Computation was performed on an AMD Phenom II X6 3.2 GHz CPU with 16 GB of system memory running Windows 7.

2.3. Image Analysis, registration accuracy assessment and statistical analysis

For the first study, the post-contrast image (template) was warped to the pre-contrast image (target). For the second study, the CT of the breast after repositioning (template) was warped to the scan of that breast before repositioning (target). For the longitudinal study, the follow-up CT image (template) was registered to the CT image from baseline (target). For demonstration in a representative case (Fig. 3), the 3D warping field thus obtained was applied to the corresponding PET image.

To assess the performance of the registration method, we used a well-validated image similarity metric, symmetric uncertainty coefficient [19] given as $SUC = (2M(X, Y))/(H(X) + H(Y))$ where M denotes the mutual information between the warped template (X) and target (Y), and H(.) denotes the marginal entropy for the individual images. For images that are perfectly registered the SUC metric is close to 1, whereas for images that have no commonality, the SUC metric is 0. This metric therefore offers a way to quantitatively evaluate registration accuracy. We computed this metric between the unregistered target and template, the target and warped template after affine registration, and the target and warped template after applying the DD method. The SUC metric was chosen as a metric for the evaluation of registration because the minimization of our similarity metric (mean-squared intensity difference) does not guarantee an optimization of this metric. Another metric that we considered for validation of the registration method was the Hausdorff distance, but two considerations prevented us from using it: (1) our goal was to have good registration of the internal tissues of the breast, as well as the breast outline. The Hausdorff distance was not sensitive to the registration of internal structures of the breast; and (2) the CT field of view may not the same in each scan of the same subject, especially after patient repositioning. The Hausdorff distance based on pointsets derived from breast outlines alone was expected to be too sensitive to the end planes (edges of the field of view).

We performed a paired t-test with a 95% confidence interval between SUC obtained from the unregistered images and that from the two methods. Our null hypothesis was that there was no statistically significant difference in SUC between the groups.

3. RESULTS

3.1. Pre- and post-contrast bCT registration

A statistically significant increase in SUC was measured consistently in every data set for DD method compared to no registration or affine registration (Table 1). The raw SUC values are provided in Table 2. Difference images post-registration showed a decrease in overall error unambiguously for the breast outline as well as for internal fibroglandular tissue for the DD method compared to no registration and affine registration (Figure 1). The resulting difference image showed improved contrast for the tumor unavailable using the affine registration method.

3.2. bCT registration before and after repositioning

The mean SUC for breast data with no registration was significantly lower ($p=0.005$) than the corresponding values for the serial pre- and post-contrast scans as expected and was attributed to patient repositioning on the scanner (raw SUC values are in Table 2). Affine registration showed statistically significant improvement over unregistered images but produced large errors in several areas of the breast (Table 1, Figure 2). The DD method consistently performed better than the affine registration method in spite of the relatively large movement induced by the repositioning process.

3.3. PET/CT registration

In patients undergoing NAC, two changes in the breast images were expected. The first were attributed to technical factors such as patient repositioning and scan-specific parameters. The second were anatomical changes in the glandularity of breast tissue induced by therapy and/or changes in the phase in the patient’s menstrual cycle. The DD method allowed for improved spatial normalization of bCT and may enable rapid ROI analysis from PET compared to affine registration for this task (Figure 3). A higher residual error even after DD registration was measured compared to the results from the repositioning study ($p<0.005$) and was attributed to the change component associated with biological variability.

3.4. Computation time

The time required for computation of the 3D warping transform were in the range of 25–40 s for the affine registration method and 3–5 min for the DD method depending on the magnitude of deformation. For comparison, the computational time for a conventional B-spline based non-rigid method for the same dataset was found to be ~10–15 min to obtain a similar level of accuracy.

4. DISCUSSION

The DD method has the following desirable properties that make it useful for bCT and bPET/CT registration. First, the impenetrability of matter is ensured, i.e., the computed transformations are smooth one-to-one mappings, thus avoiding unnatural folding of tissue in the registered images. This is an advantage over conventional non-rigid registration methods where the invertibility of the warping transform is not assured. Second, the calculated transformation fields may be made consistent with the tissue properties, such as elasticity. Although not exploited in this work, this is an important consideration when registering soft tissue non-rigid organs like the breast. Third, relatively fast image registration (less than 5 min) becomes possible. Such rapid analyses of data may facilitate applications such as RT planning based on bCT. Fourth, the technique is compatible with advanced multithreaded or parallel computing.

Our study had limitations. For the quantitative assessment of the quality of image registration, the SUC metric was reported in our paper. The maximization of this metric was not guaranteed by our similarity metric (mean-squared intensity difference). We however believe that the SUC is good metric for validation of the registration, because if the registration quality is improved, then in practice, this measure is optimized. The SUC metric was objectively derived for this paper. Assessment of deformable registration quality is challenging in general [14] and a future study utilizing fiducial markers, such as expert annotated features [13], will be undertaken to provide further assessment of the DD method. Another limitation of our study is that we have not performed detailed comparisons of the DD method with other non-rigid registration methods. It has however been shown by others that the DD method is indeed faster [20] and has improved convergence properties [15] compared to rigid and other non-rigid registration methods.

5. CONCLUSION

The DD method has the potential to enable fast registration of large bCT or bPET/CT datasets and to allow for a detailed analysis of breast tumor characteristics. The method was found to be flexible and may be useful for a number of applications such as monitoring of therapeutic response and for RT planning in breast cancer. This study, albeit conducted using a small number of subjects, showed that statistically significant improvement in image alignment is achieved for the DD method compared to other methods. A future direction will be the extension of the method to MR-MR and MR-CT registration.

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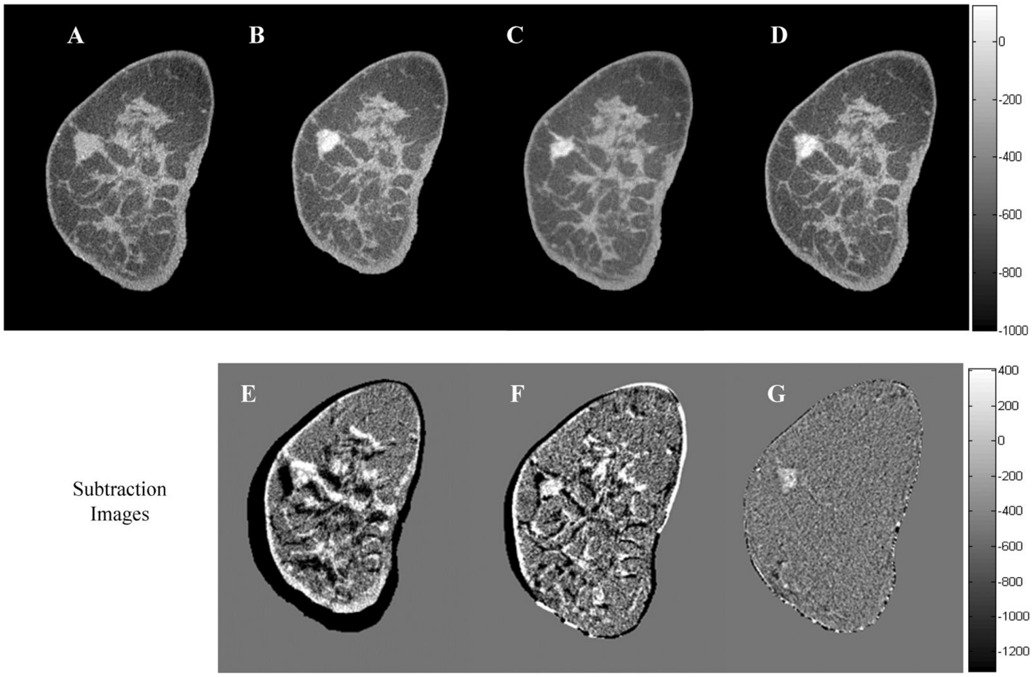

Figure 1.

Breast CT (bCT) registration using affine and the DD method in a breast cancer patient pre- and post-contrast enhancement; Top row: Raw representative image from (A) the pre-contrast CT (target), (B) post-contrast CT without registration (template), (C) post-contrast CT after registration with an affine transform, and (D) using the DD method. Bottom row: subtraction images showing the difference between (E) the pre- and post-contrast imaging data sets with no registration and after registration using the (F) affine, and (G) DD methods respectively. The top colorbar is in Hounsfield Units.

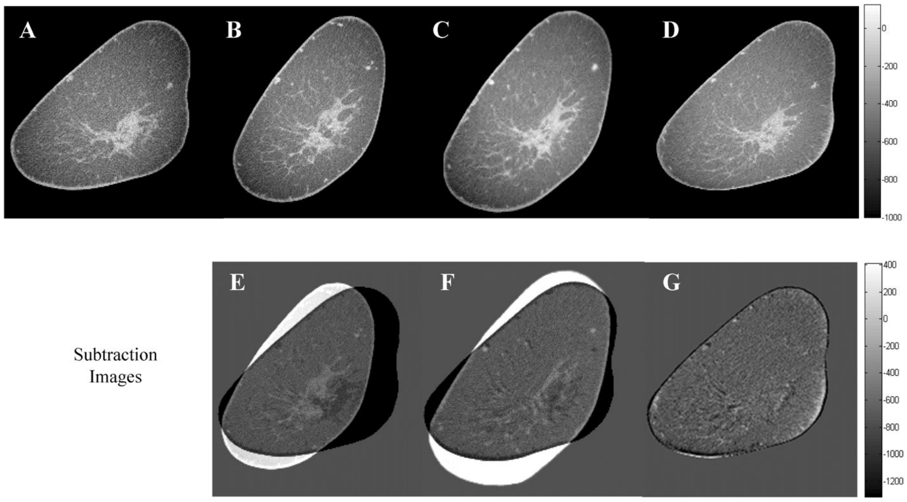

Figure 2.

bCT registration using affine and the DD method after repositioning of the patient on the scanner bed; Top row: Raw representative image from (A) CT dataset (target) before repositioning, (B) the corresponding CT slice after repositioning without registration (template), and after repositioning following registration with (C) affine and (D) DD methods; Bottom row: subtraction images showing the difference between (E) the pre- and post-repositioning imaging data sets with no registration and after registration using the (F) affine and (G) DD methods respectively. The top colorbar is in Hounsfield Units. DD achieved superior alignment with regards to the internal structure of the breast, with reasonable accuracy for the skin.

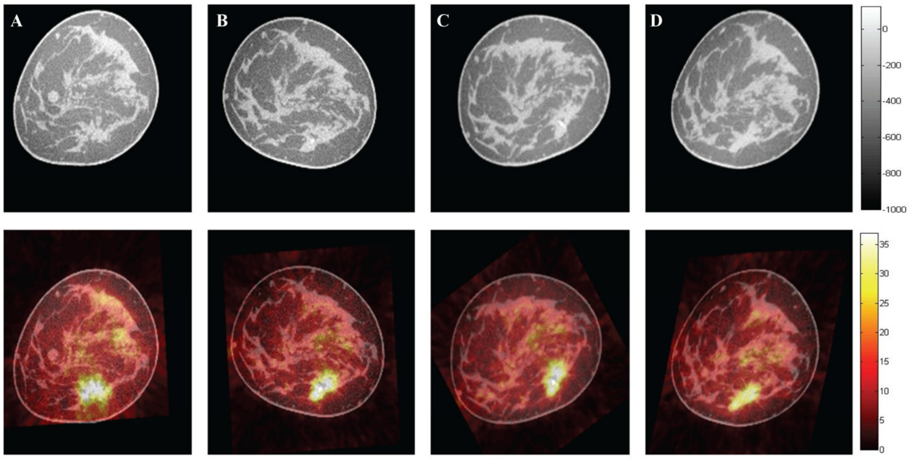

Figure 3.

Monitoring of early response to NAC in breast cancer using dedicated breast PET/CT in a representative case; Top row: Representative CT sections. Bottom row: Corresponding fused PET/CT sections showing the lesion (hot spot); (A) scan at baseline (column 1), (B) scan after one therapy cycle (column 2), (C) follow-up scan registered to the baseline scan using affine registration (column 3), (D) follow-up scan registered to baseline scan using the DD method (column 4). The colorbars for PET are on a relative scale. This patient was found to be a partial responder based on pathology, consistent with these images.

Table 1

p-values* for serial pre- and post-contrast images, breast registration after repositioning, and NAC study

Dataset	**NR & Affine**	**NR & DD**	**Affine & DD**
Pre- & post-contrast	1.87×10^{-3}	1.36×10^{-7}	1.49×10^{-7}
Repositioning	3.75×10^{-6}	2.50×10^{-8}	1.50×10^{-6}
NAC	1.20×10^{-3}	1.99×10^{-4}	2.81×10^{-3}

*p-values calculated based on a paired t-test for the results between no registration (NR), affine and DD-based registration methods.

Table 2

SUC values for the three studies undertaken in the paper

Serial pre- and post-contrast breast image registration analysis			
Set	**Pre-registration**	**Affine**	**Demons**
1	0.9650	0.9681	0.9893
2	0.9670	0.9678	0.9931
3	0.9694	0.9697	0.9943
4	0.9564	0.9572	0.9898
5	0.9589	0.9658	0.9966
6	0.9350	0.9407	0.9997
7	0.9494	0.9498	0.9119
8	0.9195	0.9247	0.9978
9	0.9280	0.9373	0.9999
10	0.9370	0.9413	0.9999
11	0.9410	0.9425	0.9947
12	0.9503	0.9484	0.9999
13	0.9350	0.9440	0.9880
14	0.9443	0.9445	0.9999
15	0.9277	0.9287	0.9947
16	0.8972	0.9023	0.9771
17	0.9137	0.9137	0.9765
18	0.9021	0.9094	0.9968
19	0.8962	0.8995	0.9826
20	0.9615	0.9556	0.9948
Repositioning study image registration analysis			
Set	Pre-registration	Affine	Demons
1	0.9463	0.9463	0.9570
2	0.9520	0.9567	0.9642
3	0.9632	0.9678	0.9713
4	0.9292	0.9413	0.9535
5	0.9157	0.9463	0.9570
6	0.9290	0.9414	0.9494
7	0.9314	0.9493	0.9550
8	0.9271	0.9356	0.9439
9	0.9193	0.9425	0.9521
10	0.9071	0.9228	0.9362
11	0.9296	0.9381	0.9409
12	0.9083	0.9237	0.9400
13	0.9467	0.9528	0.9566
14	0.9275	0.9380	0.9458

<table>
<tr><th colspan="4">Serial pre- and post-contrast breast image registration analysis</th></tr>
<tr><th>Set</th><th>Pre-registration</th><th>Affine</th><th>Demons</th></tr>
<tr><td>15</td><td>0.8726</td><td>0.9162</td><td>0.9296</td></tr>
<tr><td>16</td><td>0.8968</td><td>0.9136</td><td>0.9315</td></tr>
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<tr><td>20</td><td>0.8290</td><td>0.8340</td><td>0.8662</td></tr>
<tr><th colspan="4">NAC study image registration analysis</th></tr>
<tr><td>SET</td><td>Pre-registration</td><td>Affine</td><td>Demons</td></tr>
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