Intensity-Based Volumetric Registration of Contrast-Enhanced MR Breast Images

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Abstract. In this paper, we propose a fast intensity-based registration algorithm for the analysis of contrast-enhanced breast MR images. Motion between pre-contrast and post-contrast images has been modeled by a combination of rigid transformation and free-form deformation. By modeling the conditional probability function to be Gaussian and considering the normalized mutual information (NMI) criterion, we create a pair of auxiliary images to speed up the registration process. The auxiliary images are registered to the actual images by optimizing the simple sum of squared difference (SSD) criterion. The overall registration is achieved by linearly combining the deformation observed in the auxiliary images. One well-known problem of non-rigid registration of contrast enhanced images is the contraction of enhanced lesion volume. We address this problem by rejecting the intensity outliers from registration. Results have shown that our method could achieve accurate registration of the data while successfully prevent the contraction of the contrast enhanced lesion volume.

1 Introduction

Contrast-enhanced magnetic resonance mammography (CEMRM) uses magnetic resonance imaging (MRI) to obtain 3-D tomography of the human breast. An intravenously-injected, paramagnetic contrast agent (Gd-DTPA) enhances vascular structures, including hypervascular lesions such as breast cancers. When several images are obtained in a time sequence, malignancy may be distinguished by the enhancement curve of each voxel. However such analysis cannot always be directly applied since patient motion due to breathing and discomfort is present. The breast is also soft and deformable and will not move in a uniform fashion. To analyze these images, we need to register them. Breast image registration has been studied by several research groups. Some previous attempts at registering CEMRM images used mutual information (MI) or normalized mutual information (NMI) as a similarity measure [1, 2, 3]. MI and NMI measures the statistical dependency between pair of images and therefore they are insensitive to intensity changes. To model the motion, it has already been shown

that free-form deformation is a viable tool to effectively reduce the motion artifacts that exist in CEMRM images as shown by Rueckert *et al.* in [3]. They used a combination of global affine and local free-form transformation to model the image deformation. A known problem of CEMRM image registration is the artificial reduction of the volume of contrast enhanced lesions due to intensity changes [2]. This is definitely undesirable since breast tissue is known to be incompressible.

The determination of MI and NMI is a very computation-intensive task. It requires the formation of the joint histogram of corresponding voxel pairs. The optimization of the transformation parameters often requires computation of the gradient of the MI or NMI based cost function with respect to the transformation parameters. With appropriate interpolation of the histogram, an analytic expression could be computed for MI derivatives. Maes *et al.* used partial volume interpolation on the histogram and derived analytic derivatives of MI to allow exact computation of the gradient [4]. Thévenaz *et al.* proposed to use Parzen windowing to form the histogram and derived an analytic form for the MI gradient [5]. Another way of computing the gradient is through numerical approximation. Wells *et al.* used stochastic approximation for the MI gradient [6]. Rohlfing *et al.* used finite-difference approximation to find the gradients of NMI [7]. Stochastic approaches only make use of limited samples from the data, not all information from the data has been utilized. Other approaches involving all samples are very computationally intensive. During optimization of the transformation, the gradient of the cost function is often required to be computed many times. Therefore, it is desirable to design fast methods to approximate the gradients.

In this paper, we propose a simplified way to register CEMRM images. The sum of squared difference (SSD) is a robust and fast when intensity is assumed constant [8,9]. If we can correct for the intensity changes in CEMRM, SSD can be used as the similarity measure. Motivated by this observation, we show that if the conditional probability function is parameterized as Gaussian, NMI can be reduced to a combination of SSD terms. Thus, we divide the overall registration problem into two subproblems. Each of the subproblem involves the registration of an auxiliary image to the original image using SSD. With the final solution obtained from the solutions to the subproblems. To further enhance the robustness of our method, we identify intensity outliers and exclude them from non-rigid registration. This is simply done by thresholding the intensity difference when computing SSD, and the effect of outliers is then reduced significantly.

2 Method

We perform registration in two stages, i.e., rigid registration followed by non-rigid registration. Spline basis functions are used in nonrigid registration. In each stage of registration, the problem is divided into the subproblems of registering auxiliary images to the original images. Overall registration is achieved by combining them. In the nonrigid registration phase, we reject the outliers in order to prevent erroneous local deformation.

2.1 Problem Formulation

We denote the pre-contrast image to be U and the post-contrast image to be V . Defining some similarity measure $S(\cdot)$ that is either minimized or maximized when the images are aligned, we could formulate the overall registration as

$$T = \arg \max_T [S(u(\mathbf{p}), v(T(\mathbf{p})))] \quad (1)$$

$T(\cdot)$ is some geometrical transformation that models the motion between images, and $\mathbf{p}$ the coordinates of a voxel in the reference image. The optimal transformations will be represented by a T that gives a similarity measure S at its optimal point. S could be any similarity measure that gauges the registration quality. The simplest will be the SSD criterion, which is attractive because of its low complexity.

$$\text{SSD}(u, v) = \frac{1}{N} \sum_{\mathbf{p}} [u(\mathbf{p}) - v(T(\mathbf{p}))]^2 \quad (2)$$

where N is the total number of voxels. Another option which does not require intensity conservation is NMI.

$$\text{NMI}(u, v) = \frac{H(u(\mathbf{p})) + H(v(T(\mathbf{p})))}{H(u(\mathbf{p}), v(T(\mathbf{p})))} \quad (3)$$

where $H(\cdot)$ denotes the marginal entropy and $H(\cdot, \cdot)$ the joint entropy. In the following subsection, we describe how NMI may be simplified to SSD so as to achieve fast registration.

2.2 Dividing Registration Task into Subproblems

It has been shown that the joint probability density function (joint PDF) of the image voxel pairs can be modeled as a Gaussian mixture [10]. It is difficult to estimate the Gaussian mixture due to the large number of parameters need to be determined. Instead of modeling the joint probability function, we model the conditional probability density function (conditional PDF) between image voxel pairs.

The conditional PDF is given using the standard Gaussian density function, $p(u|v) = \frac{1}{\sqrt{2\pi}\sigma_v} \exp\{-\frac{(u-m_v)^2}{2\sigma_v^2}\}$, where a pair of volumes are denoted by $u(\mathbf{p})$ and $v(T(\mathbf{p}))$, we have omitted the coordinate $\mathbf{p}$ for simplicity. m_v and σ_v^2 denote the conditional mean and variance respectively. By considering the conditional entropy of $u(\mathbf{p})$ and $v(T(\mathbf{p}))$, it follows that

$$H(u|v) = \frac{1}{2} \log(2\pi) + \sum_v p(v) \log(\sigma_v) + \text{SSD}(\hat{u}, \hat{v}) \quad (4)$$

where $\text{SSD}(\cdot)$ denotes the sum of squared difference as defined in (2) and we have introduced a pair of normalized signals $\hat{u}(\mathbf{p}) = \frac{u(\mathbf{p})}{\sqrt{2}\sigma_v}$ and $\hat{v}(\mathbf{p}) = \frac{m_v}{\sqrt{2}\sigma_v}$. In (4), the first term is constant. If we can assume the second term involving σ_v to be

constant, we can greatly simplify the computation of the derivative. σ_v turns out to be approximately constant during nonrigid registration because the extent of local motion is extremely small. Similarly, we can derive another expression for $H(v(T(\mathbf{p}))|u(\mathbf{p}))$ and the corresponding pair of approximated signals $\tilde{u}(\mathbf{p})$ and $\tilde{v}(T(\mathbf{p}))$. It follows that an approximation of the NMI gradient with respect to a transformation variable ϕ is given by

$$\frac{\partial \text{NMI}(u, v)}{\partial \phi} = \frac{1}{H^2(u, v)} [-\text{MI}(u, v) \frac{\partial}{\partial \phi} \text{SSD}(\tilde{u}, \tilde{v}) - H(u, v) \frac{\partial}{\partial \phi} \text{SSD}(\hat{u}, \hat{v})] \quad (5)$$

where $\text{MI}(u, v) = H(u) + H(v) - H(u, v)$ denotes the mutual information of the two images. $\hat{u}(\mathbf{p})$ and $\hat{v}(T(\mathbf{p}))$ can be interpreted as the normalized images with respect to the pre-contrast image. The contrast enhanced structures in $v(\mathbf{p})$ would be replaced by non-enhanced structures expected to be found in the pre-contrast image. On the other hand, $\tilde{u}(\mathbf{p})$ and $\tilde{v}(T(\mathbf{p}))$ could be regarded as normalized images with respect to the post-contrast image. These images are regarded as auxiliary images which will aid us in registration. From (5), we can see that the two SSD terms involved are weighted by MI and JE (*joint entropy*) respectively. At the initial stage of registration, JE will be large and MI will be small because the two images are not well aligned. Therefore, the value of the gradient will be dominated by the second SSD term. With better alignment, we expect JE to decrease and MI to increase. The contribution of the two SSD terms will be weighted accordingly. When computing SSD, we consider the effect of intensity outliers which are not removed by the normalization. SSD is computed as,

$$\text{SSD}(u, v) = \frac{1}{N} \sum_{\mathbf{p}} \min[|u(\mathbf{p}) - v(T(\mathbf{p}))|, \xi]^2 \quad (6)$$

where N is the number of voxels and ξ is a threshold used to suppress the effect of outliers. Experimentally, we found that a threshold value of 100 gives satisfactory results.

It is interesting to note that each of the SSD terms is in fact equivalent to the computation of correlation ratio (CR), introduced by Roche *et al.* [11]. The existence of equivalence provides new insights to the different similarity measures used. Although our starting point is NMI, the derived expression of NMI (5) combines MI, JE and CR in an elegant manner.

3 Experiments

3.1 Data

We used a total of 17 normal patient datasets and 10 lesion datasets. Image acquisition was done using a GE Sigma 1.5 Tesla coil MRI scanner with 3-D fast-spoiled gradient echo and no spectral fat suppression (TR = 25.6ms, TE=3ms, fractional echo, Flip angle = 30°, FOV = 32 to 40cm). The contrast agent

used was MagneVist Gd-DTPA of concentration 0.2mmol/kg. A typical dataset has 5 scans ($256 \times 256 \times 24$ voxels) of voxel size $1.05\text{mm} \times 1.05\text{mm} \times 5.45\text{mm}$. Slice direction used is axial. Variations to this protocol are mainly in the number of slices, which can vary from 16 to 56 depending on the volume size to be acquired. The contrast agent is injected after the first scan, and post-contrast scans will follow in the next 5 to 20 minutes. Each 3-D scan requires 30-60 seconds of acquisition time, depending on the number of slices.

3.2 Implementation

We have implemented the registration algorithm based on the Insight Toolkit [12]. A rectangular region of interest (ROI) around each breast is manually selected and ROI registration is performed. Rigid registration is implemented using gradient descent optimization with a single resolution. Optimization is terminated when the change in cost function is smaller than a predefined threshold value. We have found that a threshold between 10^{-2} to 10^{-4} could achieve good registration. Nonrigid registration also employs gradient descent technique with four different image resolution used. The terminating condition for nonrigid registration will also depend on the value of the cost function. If the change in value of the cost function is smaller than a threshold, we stop the optimization process. Currently, the running time is about 10 to 15 minutes. However, we expect this time to further decrease with code optimization.

3.3 Registration Quality

It is difficult to provide a numerical test of registration quality. We have identified sum of squared difference (SSD) (2), normalized mutual information (NMI) (3) and normalized correlation coefficient ($NCC(u, v) = \frac{\sum_{\mathbf{p}} (u(\mathbf{p}) \cdot v(T(\mathbf{p})))}{\sqrt{\sum_{\mathbf{p}} u(\mathbf{p})^2 \cdot \sum_{\mathbf{p}} v(T(\mathbf{p}))^2}}$) as similarity measures to gauge how well the two images match one another. Since our NMSSD method does not optimize these three similarity measures directly, the value of these measures could give us an indication of the objective registration quality. Across the board, rigid registration is able to gain in terms of similarity measures compared to no registration for both NMSSD method and SSD method. Similarly, nonrigid registration further improves registration for both methods. As shown in Table 1 and Table 2, the NMSSD method generally offers greater gain over traditional SSD method for all the similarity measures. We have separated the lesion breasts from the normal breasts in our tests. Results have shown that NMSSD performs consistently better than SSD for both normal cases and lesion cases.

The gain of NMSSD over SSD could be attributed to the use of auxiliary images, which accounts for the intensity changes induced by the contrast agent. This will reduce the chance of the optimization being trapped in a local minima. The chances of having erroneous registration is reduced too since we corrected the intensity difference.

Table 1. Registration results of NMSSD method. The average value and the variance of SSD, NMI and NCC is presented separately for a) before registration; b) after rigid registration; c) after nonrigid registration.

	Normal Cases			Lesion Cases		
	Before	Rigid	Nonrigid	Before	Rigid	Nonrigid
SSD (Average)	51.896	39.496	33.508	47.681	39.713	34.177
(Variance)	62.304	54.875	56.173	31.453	28.545	26.459
NMI (Average)	1.2699	1.2849	1.2934	1.2459	1.2625	1.2698
(Variance)	0.0797	0.0751	0.0762	0.0450	0.0426	0.0425
NCC (Average)	0.9803	0.9832	0.9841	0.9916	0.9933	0.9941
(Variance)	0.0413	0.0379	0.0380	0.0057	0.0047	0.0045

Table 2. Registration results of traditional SSD method. The average value and the variance of SSD, NMI and NCC is presented separately for a) before registration; b) after rigid registration; c) after nonrigid registration.

	Normal Cases			Lesion Cases		
	Before	Rigid	Nonrigid	Before	Rigid	Nonrigid
SSD (Average)	51.896	41.838	31.355	47.681	42.197	34.867
(Variance)	62.304	55.991	44.844	31.453	30.636	27.431
NMI (Average)	1.2699	1.2798	1.2917	1.2459	1.2577	1.2684
(Variance)	0.0797	0.0759	0.0794	0.0450	0.0437	0.0427
NCC (Average)	0.9803	0.9825	0.9841	0.9916	0.9929	0.9940
(Variance)	0.0413	0.0387	0.0373	0.0057	0.0051	0.0047

3.4 Effect on Lesion Volume Reduction

To calculate the volume of the lesion, we create a binary mask of the breast lesion after rigid registration. The lesion is identified using the 3TP method [13]. The volume of the lesion is determined from the total number of voxels in the mask that are labelled as lesion. To see whether there are any changes in the lesion volume, we apply the final transformation obtained from the optimization process to the mask, and compute the lesion volume in terms of number of lesion voxels after transformation. The change in volume could then be calculated as

$$\Delta V = \frac{V_{after} - V_{before}}{V_{before}} \times 100\% \quad (7)$$

where ΔV denotes the change in volume, V_{after} and V_{before} are the number of lesion voxels before and after nonrigid registration. We measure the volume change for the case where outlier rejection is performed and compare it with the case where outliers are included. The effect of lesion reduction is only evident if the size of the lesion is not too small. In our experiments, we pick from the lesion datasets a few examples that contains big lesions and tested the effect of volume reduction.

Table 3. Effect of lesion volume reduction in terms of number of lesion voxels before and after nonrigid registration

Case ID	Outliers Included			Outliers Rejected		
	Before	After	Reduction	Before	After	Reduction
1	1816	1464	-19.4%	1816	1799	-0.936%
2	383	348	-9.14%	383	371	-3.13%
3	1173	1099	-6.31%	1173	1140	-2.81%
4	2561	1754	-31.5%	2561	2223	-4.80%
5	276	257	-6.88%	276	263	-4.71%

Fig. 1. Lesion volume test Case 1. From left to right: Maximum intensity projection (MIP) of the subtraction image without registration; MIP of subtraction image after rigid registration; MIP of subtraction image after nonrigid registration without lesion segmentation, the volume shrank by 19.38%; MIP of subtraction image after nonrigid registration with lesion segmentation, volume shrinkage is reduced to 0.936%. **Fig. 2.** Lesion volume test Case 4. From left to right: Maximum intensity projection (MIP) of the subtraction image without registration; MIP of subtraction image after rigid registration; MIP of subtraction image after nonrigid registration without lesion segmentation, the volume shrank by 31.51%; MIP of subtraction image after nonrigid registration with lesion segmentation, volume shrinkage is reduced to 4.802%.

The results are presented in Table 3. By excluding the lesions from optimization, it is possible to preserve the lesion volume. There is no significant volume reduction observed. However, due to the registration of surrounding regions, slight contraction of the volume in the order of less than 5% of the original volume is observed. The contraction is extremely small, and hence it can be considered negligible.

4 Conclusion

We have developed a nonrigid registration algorithm for CEMRM images in this paper. By the use of auxiliary images constructed from conditional probability

distribution of image pairs, we showed that the problem could be divided into subproblems of registering the auxiliary images to original images using SSD. Our algorithm is able to take into account of the non-uniform intensity changes induced by the administration of contrast agents, thus reducing the chances of misregistration. Experiments have confirmed the effectiveness of our algorithm. Our algorithm could consistently outperform traditional sum of squared difference. By excluding outliers from nonrigid registration, we prevent artificial lesion volume reduction. Experiments have shown that this method is simple yet effective. We can restrict the change of lesion volume to within 5% of its original volume.

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