Simultaneous Multiple Image Registration Method for T_1 Estimation in Breast MRI Images

Jonathan Lok-Chuen Lo¹, Michael Brady¹, and Niall Moore²

¹ Wolfson Medical Vision Laboratory, University of Oxford, Oxford, UK
{jlo, jmb}@robots.ox.ac.uk

² MRI unit, John Radcliffe Hospital, Oxford, UK

Abstract. The estimation and subsequent use of tissue $T_1(\mathbf{x})$ parameters at each image location $\mathbf{x}$ can potentially lead to a more reliable classification of breast tissues. T_1 values can be estimated using multiple (typically 3) MRI images of different flip angles. However, breathing and other slight movements can render the highly non-linear estimation procedure error-prone. In this paper, a simultaneous multiple image registration method is proposed to solve this problem. The registration method is built upon the idea of conserving inverse consistency and transitivity among the multiple image transformations. The algorithm is applied to both simulated data and real breast MRI images. The performance is compared with existing pairwise image registration method. The results clearly indicate that the simultaneous multiple image registration algorithm leads to much more accurate T_1 estimation.

1 Introduction

Contrast-enhanced magnetic resonance imaging (CE-MRI) has gained considerable attention over recent years for early detection of breast cancers, and is increasingly used for cancer staging and treatment planning. This imaging modality is particularly useful for younger women, for whom the dense radiographic density of glandular tissues often render X-ray mammography ineffective.

Due to the frequent lack of contrast difference between abnormalities and normal tissues in conventional breast MRI, contrast agents such as gadolinium diethylene triamine pentaacetic acid (Gd-DTPA) are widely used to enable the detection and characterization of tumours, because they highlight areas with increased vascular density, which correlate with the presence of tumours. Temporal scans of the breast (approximately every one minute) are made before, during and after the administration of the contrast agent. The dynamic MRI image sequences are often fitted using a pharmacokinetic model to provide a physiologically relevant characterization of the underlying tissues [1]. Such curves/parameters have been applied clinically to identify and characterize tumours into malignant or benign classes, although the success has been variable with generally very good sensitivity ($> 95\%$) but often poor specificity [2].

A major reason for the poor specificity stems from the erroneous assumption that intensity enhancement is linearly proportional to contrast agent concentration. In [3], the authors suggested that the relationship is both non-linear and

Fig. 1. Estimated T_1 mapping for breast MRI images, with (a) no registration and (b) pairwise nonrigid registration. The near white pixel indicates $T_1 > 2500$ ms, which is unrealistically large for breast tissues.

highly dependent on the intrinsic tissue T_1 values, and that contrast agent concentration is to a good approximation linear proportional to the change in T_1 . It follows that accurate estimation of T_1 at each voxel is a necessary prerequisite for more reliable tissue classification using the uptake curves of the pharmacokinetic model. T_1 values may, for example, be estimated from images resulting from using the fast spoiled gradient echo (FSPGR) pulse sequence. The MRI signal then takes the form [4]:

$$S(t) = g\rho \exp(-T_E/T_2(t)) \sin \alpha \frac{1 - \exp(-T_R/T_1(t))}{1 - \cos \alpha \exp(-T_R/T_1(t))}, \quad (1)$$

where S is the measured MR signal, g is the scanner system gain, ρ is the proton density, T_E is the echo time and T_R is the repetition time and α is the flip angle. A series of n volumes, each with a different flip angle α_n , are acquired. The model in (1) is fitted to $S_n(t)$ vs α_n data at each voxel to obtain the unknown parameters $T_{10} = T_1(0)$ and k , where $k = g\rho \exp(-T_E/T_2(t))$.

Armitage et al. [3] used Monte Carlo simulation to calculate the optimal number of flip angles required for measuring the ranges of T_1 found in the breast. They concluded that the use of three flip angles ($\{3^\circ, 10^\circ, 17^\circ\}$ were suggested) provides the best compromise between acquisition time and the accuracy of the resulting T_1 estimation.

In practice, however, breathing and other slight positional movements result in large errors in the T_1 estimation. For example, in Figure 1(a), the effect of this misalignment is shown. It can be seen that unrealistically large T_1 values (> 2500 ms) are estimated around the edge of the breast, shown as white pixels in the image. To address this problem, we first used the non-rigid registration algorithm, on a pairwise image basis, described in [5], i.e. two separate registrations are performed on two pairs of images. However, we found that the results are unpromising (see Figure 1(b)).

In this paper, we propose a new method to simultaneously register three MRI images of different flip angles, based on the idea of constraining the inverse consistency and transitivity among the transformations, as proposed in [6]. Following

Rueckert, B-splines are used as the underlying non-rigid transformations, with mutual information as the similarity measure. Though alternative non-rigid registration algorithms could have been used, this provided a more direct test of the added value of the consistency and transitivity constraint. Simulated data, as well as real MRI breast images, are tested using our proposed technique. The results show that the method significantly improves the accuracy of the estimated T_1 values.

2 Method

Christensen and Johnson suggested the idea of constraining inverse consistency and transitivity for multiple images registration [6]. A pair of transformations from image I_1 to I_2 and I_2 to I_1 are said to be inverse consistent if the composition of the two transformations is the identity mapping. A set of transformations is said to be transitive if the composition of transformations from I_1 to I_2 and I_2 to I_3 equals to the transformation from I_1 to I_3 . In [6], the registration is based on the idea of fluid flow, where the smoothness of the transformation is guaranteed by using a linear-elastic regularization model. However, the complexity of the transformation requires large magnitude nonlinear kinematics, and significant computation time is needed. Furthermore, gray levels are used to drive the similarity measure, which is not suitable in our application where intensities are vastly different among images with different flip angles.

Based on the above ideas, Geng et al. [7] had proposed a contour/surface-based method, where three manifolds were registered at the same time, and the results seem encouraging. Closest point distance was used as the cost function for minimization. However, in our application, the tissue boundaries are not always clearly defined, especially for images with low flip angle where signal contrast between tissue types tends to be fairly low, and therefore contours cannot be found accurately. Our new method is proposed in the following sections.

2.1 Multiple Image Registration

Assume that all images are of size $X \times Y = N$, and let us denote the discrete position of the pixels as $\mathbf{r}(i) \in \Omega_d$, where $\Omega_d = \{(x, y) : x = 1, 2, \dots, X; y = 1, 2, \dots, Y\}$ and $i \in \{1, 2, \dots, N\}$. A set of transformations is defined as $\mathcal{T} = \{\mathbf{T}_{ab} : 1 \leq a, b \leq 3, a \neq b\}$, where $\mathbf{T}_{ab}$ indicates the transformation mapping any point in image I_a to the corresponding point in image I_b , i.e. $\mathbf{T}_{ab} : (x_a, y_a) \mapsto (x_b, y_b)$. The goal of registration is to find the transformation set $\mathcal{T}$ such that the following cost function is minimized:

$$C(\mathcal{T}) = \alpha C_{\text{similarity}} + \beta C_{\text{smooth}} + \gamma C_{\text{invertibility}} + \nu C_{\text{transitivity}}, \quad (2)$$

where $C_{\text{similarity}}$ is the image similarity cost function, C_{smooth} defines the constraint of the transformation smoothness, $C_{\text{invertibility}}$ and $C_{\text{transitivity}}$ are the penalty terms for the inverse consistency and transitivity respectively.

Tensor products of B-splines [5] are used to represent the transformation, with $\Phi = \{(\mu, \nu) : \mu = 1, 2, \dots, n_x; \nu = 1, 2, \dots, n_y\}$ denoting the underlying $n_x \times n_y$

mesh of control points. The 2-D transformation can be written as the tensor product of cubic splines:

$$\mathbf{T}(x, y) = \sum_{m=0}^3 \sum_{n=0}^3 B_m(u) B_n(v) \phi_{i+m, j+n}, \quad (3)$$

where $i = \lfloor x/n_x \rfloor - 1$, $j = \lfloor y/n_y \rfloor - 1$, $u = x/n_x - i - 1$, $v = y/n_y - j - 1$ and B_l represents the l th basis function of the B-spline. Registration becomes the problem of finding the set of control points Φ which minimizes the cost function in (2).

Similarity Cost Function. As the difference in contrast between the three MRI images with different flip angles is quite pronounced, direct comparison of image intensities is not appropriate. Mutual information is chosen to be the similarity measure. The cost function is defined as:

$$C_{\text{similarity}} = \sum_{a=1}^3 \sum_{\substack{b=1 \\ b \neq a}}^3 \left[H(I_a) + H(\mathbf{T}_{ba}(I_b)) - H(I_a, \mathbf{T}_{ba}(I_b)) \right], \quad (4)$$

where $H(I_i)$ denotes the marginal entropy of image i and $H(I_i, I_j)$ is the joint entropy of image i and j .

Smoothness Constraint. The deformation of the breast tissues is assumed to be smooth, and this can be enforced on the B-spline transformation by including a penalty term which associates the curvature of the splines:

$$C_{\text{smooth}} = \sum_{a=1}^3 \sum_{\substack{b=1 \\ b \neq a}}^3 \sum_{i=1}^N \left[\left(\frac{\partial^2 \mathbf{T}_{ab}(\mathbf{r}(i))}{\partial x^2} \right)^2 + \left(\frac{\partial^2 \mathbf{T}_{ab}(\mathbf{r}(i))}{\partial y^2} \right)^2 + 2 \left(\frac{\partial^2 \mathbf{T}_{ab}(\mathbf{r}(i))}{\partial x \partial y} \right)^2 \right]. \quad (5)$$

This term corresponds to the bending energy of a thin-plate, which acts as a constraint on the smoothness of the transformation.

Inverse Consistency Constraint. To ensure that two transformations are inverse consistent, we want the combined transformation, $\mathbf{T}_{ab} \circ \mathbf{T}_{ba}$, as close to identity transformation as possible. Therefore, the inverse consistency constraint is defined as the following:

$$C_{\text{invertibility}} = \sum_{a=1}^3 \sum_{\substack{b=1 \\ b \neq a}}^3 \sum_{i=1}^N \|\mathbf{r}(i) - \mathbf{T}_{ab} \circ \mathbf{T}_{ba}(\mathbf{r}(i))\|^2. \quad (6)$$

Transitivity Constraint. Similarly, transitivity describes how close the combined transformation, $\mathbf{T}_{ab} \circ \mathbf{T}_{bc}$, is compared to the direct transformation $\mathbf{T}_{ac}$. We define the transitivity constraint to be:

$$C_{\text{transitivity}} = \sum_{a=1}^3 \sum_{\substack{b=1 \\ b \neq a}}^3 \sum_{\substack{c=1 \\ c \neq a \\ c \neq b}}^3 \sum_{i=1}^N \|\mathbf{T}_{ac}(\mathbf{r}(i)) - \mathbf{T}_{ab} \circ \mathbf{T}_{bc}(\mathbf{r}(i))\|^2. \quad (7)$$

2.2 Implementation

The registration method is implemented using ITK[8]. In order to provide an efficient registration method, a gradient-based optimization technique is used, and hence the gradient vector of the cost function, i.e. $\nabla C = \partial C(\Phi)/\partial \Phi$, is required.

The gradient of the inverse consistency constraints with respect to each transformation parameters is:

$$\frac{\partial C_{\text{invertibility}}}{\partial \phi_{\mu,\nu}} = -2 \sum_{a=1}^3 \sum_{\substack{b=1 \\ b \neq a}}^3 \sum_{i=1}^N \left[\|\mathbf{r}(i) - \mathbf{T}_{ab} \circ \mathbf{T}_{ba}(\mathbf{r}(i))\| \cdot \left\| \frac{\partial \mathbf{r}'(i)}{\partial \phi_{\mu,\nu}} \right\| \right], \quad (8)$$

where

$$\mathbf{r}'(i) = \begin{cases} \mathbf{T}_{ba}(\mathbf{r}(i)) & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{ba} \\ \mathbf{T}_{ab} \circ \mathbf{T}_{ba}(\mathbf{r}(i)) & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{ab}. \end{cases} \quad (9)$$

Similarly, the gradient of the transitivity constraint is:

$$\frac{\partial C_{\text{transitivity}}}{\partial \phi_{\mu,\nu}} = -2k \sum_{a=1}^3 \sum_{\substack{b=1 \\ b \neq a}}^3 \sum_{\substack{c=1 \\ c \neq a \\ c \neq b}}^3 \sum_{i=1}^N \left[\|\mathbf{T}_{ac}(\mathbf{r}(i)) - \mathbf{T}_{ab} \circ \mathbf{T}_{bc}(\mathbf{r}(i))\| \cdot \left\| \frac{\partial \mathbf{r}'(i)}{\partial \phi_{\mu,\nu}} \right\| \right], \quad (10)$$

where

$$\mathbf{r}'(i) = \begin{cases} \mathbf{T}_{bc}(\mathbf{r}(i)) & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{bc} \\ \mathbf{T}_{ab} \circ \mathbf{T}_{bc}(\mathbf{r}(i)) & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{ab} \\ \mathbf{T}_{ac}(\mathbf{r}(i)) & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{ac} \end{cases} \quad (11)$$

$$k = \begin{cases} 1 & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{bc} \text{ or } \mathbf{T}_{ab} \\ -1 & \text{if } \phi_{\mu,\nu} \text{ in } \mathbf{T}_{ac}. \end{cases} \quad (12)$$

3 Results

Our proposed registration method was tested by using both simulated data and real clinical MRI images. Simulated MRI images of flip angles $\{3^\circ, 10^\circ, 17^\circ\}$ were generated from a phantom T_1 image. The simulated images were then distorted by using randomly generated B-spline deformation field places upon the images,

Fig. 2. Box plots for the 100 simulated images for (a) 0%, (b) 3% and (c) 5% noise are shown. The symbol N, P and M represent the results for: No registration, Pairwise registration and Multiple image registration. The boxes shown stretch from the 25th percentile (bottom) to the 75th percentile (top), and the median is shown as the line across the box.

with Gaussian noise being added to the final images. A hundred sets of such images were generated with 0%, 3% and 5% noise level. The images were then registered using pairwise non-rigid registration and our proposed simultaneous multiple image registration method, with control points spacing $\delta = 10$ pixels. The pairwise registration uses the same cost function in (2), but with both γ and ν set to zero. Due to the intrinsic smoothness properties of B-splines, the choice of λ is not critical for our application, and $\lambda = 0.01$ is chosen.

T_1 values were then estimated and compared to the known values of the phantom image. The average errors in the estimated T_1 per pixel are plotted in Figure 2. Our multiple image registration has definitely improved the T_1 estimation from images without any registration. Our method also outperforms the normal pairwise registration, and more importantly, the error ranges are greatly reduced.

Tests have also been carried out on clinical breast MRI images. Data from eight patients were used. All volumes were acquired on General Electric Medical Systems (Genesis Signa) 1.5 T clinical scanner using a T1-weighted 3D fast spoiled gradient echo (FSPGR) pulse sequence ($TE = 4.2$ ms, $TR = 8.9$ ms). Three image volumes were acquired with flip angles set to $\{3^\circ, 10^\circ, 17^\circ\}$. Each image volume contains between 60-80 images. The slice is coronal orientation, with 3 mm spacing between slices.

Table 1. The average residual errors in the T_1 estimation for the eight sets of breast MRI images

Example number	No registration	Pairwise registration	Multiple image registration
1	12.3132	8.0006	5.5265
2	9.7924	5.0489	3.9482
3	7.5746	3.8106	2.0601
4	18.3493	7.8637	6.0015
5	15.9211	9.3463	7.1164

Fig. 3. Some examples of estimated T_1 using (a)-(e) no registration, (f)-(j) pairwise registration and (k)-(o) multiple image registration. The color scheme is similar to that in Figure 1, with near white pixel representing high T_1 values, i.e. > 2500 ms.

Similarly, these image sets were registered using both the pairwise registration and our multiple image registration. The registered images were used to estimate the T_1 values. Because, in this case we do not have the ground truth T_1 values, the residual error in our T_1 values estimation were recorded. Some examples of the estimated T_1 mapping are shown in Figure 3, and their average residual errors are shown in Table 1.

As can be seen from the estimated T_1 mapping for images without registration, regions of high estimated T_1 values (> 2500 ms, as indicated by near white pixels in the images) are mainly concentrated in the breast boundaries, as expected. Both registration techniques improve the results, but it clearly shows that our multiple image registration method performs better. The unrealistic high T_1 values are almost completely removed. With the simultaneous multiple image registration, we have shown that better estimation of T_1 values is achieved.

4 Discussion

In this paper, we have proposed a simultaneous multiple image registration technique for aligning multiple MRI images taken at different flip angles. The aim of the registration is to enable a better estimation of the pre-injection T_1 . The initial testing on clinical data shows that the registration has indeed improved the T_1 estimation. Furthermore, our proposed multiple image registration has also outperformed the normal pairwise registration method.

The ultimate goal of our research, however, is to show that with improved T_1 estimation, we can achieve a more reliable classification of breast tissues from CE-MRI images. Further work is currently underway for such study.

References

1. Tofts, P.S.: Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *Journal of Magnetic Resonance Imaging* **7** (1997) 91–101
2. Rankin, S.: Mri of the breast. *British Journal of Radiology* **73** (2000) 806818
3. Armitage, P., Behrenbruch, C., Brady, M., Moore, N.: Extracting and visualizing physiological parameters using dynamic contrast-enhanced magnetic resonance imaging of the breast. *Medical Image Analysis* **9** (2005) 315–329
4. Christen, K.A., Grant, D.M., Schulman, E.M., Walling, C.: Optimal determination of relaxation-times of Fourier-transform nuclear magnetic-resonance. *Journal of Physical Chemistry* **78** (1974) 1971–1977
5. Rueckert, D., Sonoda, L.I., Hayes, C., Hill, D.L.G., Leach, M.O., Hawkes, D.J.: Non-rigid registration using free-form deformations: Application to breast MR images. *IEEE Transactions on Medical Imaging* **18** (1999) 712–721
6. Christensen, G.E., Johnson, H.J.: Consistent image registration. *IEEE Transactions on Medical Imaging* **20** (2001) 568–582
7. Geng, X.J., Kumar, D., Christensen, G.E.: Transitive inverse-consistent manifold registration. In: *Information Processing in Medical Imaging, Proceedings*. Volume 3565 of *Lecture Notes in Computer Science*. (2005) 468–479
8. Insight Toolkit, ITK: <http://www.itk.org>. (2005)