3-D Deformable Registration of Medical Images Using a Statistical Atlas

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Abstract

Registration between voxel images of human anatomy enables cross-patient diagnosis and post-treatment analysis. However, innate variations in the shape, size, and density of non-pathological anatomical structures between individuals make accurate registration difficult. Characterization of such normal but inherent variations provides guidance for registration.We extracted the pattern of normal variations in the appearances of brain structures from the T1-weighted magnetic resonance imaging (MRI) volumes of 105 subjects. This knowledge serves as a domain-relevant constraint which increases the accuracy of deformable registration.

We represent domain knowledge in the form of voxel statistics, and embed these statistics into a 3-D digital brain atlas which we use as the reference. The knowledge acquisition process involves registering a training set of MRI volumes with the atlas. The method employed is a previously developed 3-D hierarchical deformable registration algorithm. This associates each voxel in the reference atlas with distributions of normal variations of intensity and 3-D positions of the training set. We evaluate statistical properties of these distributions for each atlas voxel to build a statistical atlas which contains the anatomical information of the population. When we register this atlas to a particular subject, the embodied statistics function as domain-relevant constraints. The deformation process tolerates non-pathological variations between subjects. When applied to 40 test cases, this knowledge-constrained registration method achieved a correct voxel classification rate above 95% for 36 cases; this is a 24% improvement over the performance of the algorithm without knowledge constraints.

To overcome imprecisions in unconstrained registration that affect the rigorousness of the statistical atlas, we propose to build an initial statistical model of a small but accurately registered training set, then bootstrap it into a more reliable model. Besides guiding deformable registration, our knowledge representation also enables quantitative investigation of possible anatomical divergences between populations.

Table of Contents

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Abstract

Registration between 3-D images of people's anatomy enables cross-patient diagnosis. However, innate variations in the appearance of non-pathological anatomical structures between individuals make accurate registration difficult. Characterization of such normal variations provides domain-specific guidance for registration.

We extracted the pattern of normal variations in the appearance of brain structures, and embed it into a 3-D digital brain atlas to build a statistical atlas. The 3-D deformable registration procedure uses the statistics embedded in the atlas to accurately register brain images from different individuals, despite the substantial anatomical variations between them. Compared to a registration method without knowledge guidance, our algorithm reduced the registration error by 30%.

1. Motivation

Registration between voxel images of human anatomy enables cross-subject diagnosis and post-treatment analysis. However, due to genetic and life-style factors, there are innate variations in the appearance and location of non-pathological anatomical structures between individuals. Figure 1 displays cross-sections of two healthy brains' T1-weighted magnetic resonance imaging (MRI) volumes. The example structure, corpus callosum, has different intensity, shape, size, and locations in these two brains. For registration algorithms that only use intensity or shape information to achieve correspondence, these inherent variations make accurate inter-subject registration difficult.

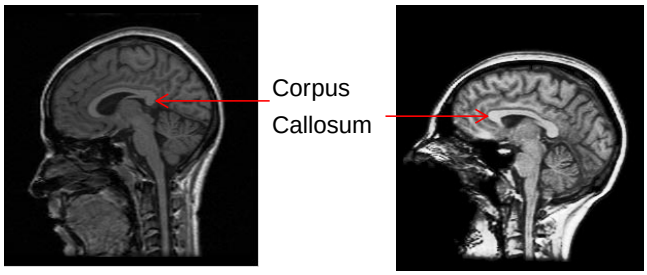

Figure 1. Innate variations between individuals.

Currently there exists many intensity correspondence based registration algorithms [(1), (3), (5), (12)]. Figure 2 shows a registration result using one such method. One cross-section of a subject's brain MRI is overlaid with computed segmentations of several anatomical structures. The segmentation was computed by registering this subject's MRI with a pre-segmented MRI. Note that there exists misalignment because the registration method does not have the knowledge to tolerate variations between individuals.

Figure 2. A cross-section of a subject's brain MRI overlaid with computed segmentation from an intensity correspondence based registration method.

Embedding the knowledge of anatomical variations in the registration process provides domain-specific guidance to improve accuracy. Characterization of such *normal* variations also facilitates anomaly detection. Experienced neuroradiologists glean this knowledge of normal, non-pathological, variations through experiences of comparing numerous subjects' brain images, and gradually build up their own *models* of anatomical variations. These *models* help them to distinguish and relate apparently dissimilar anatomical features in different subjects, and to detect abnormalities. We extract such domain knowledge and apply it systematically to improve registration accuracy.

2. Problem definition

We extract anatomical variations between individuals, compile it into a statistical model, and apply this model to automatically provide domain-specific guidance to registration.

Radiologists learn anatomical variations through *registering* subjects' images so as to compare the corresponding features. Similarly, we register different voxel images to a reference image using an automatic algorithm that was pre-

viously developed [12].

Our reference image is a 3-D digital atlas, which consists of 123 T1-weighted MRI slices of a non-pathological brain. A medical professional spent 8 months classifying and labelling 144 anatomical structures in the voxel image. Figure 3 displays one cross-section of the voxel image, and the corresponding color-coded classification of anatomical features.

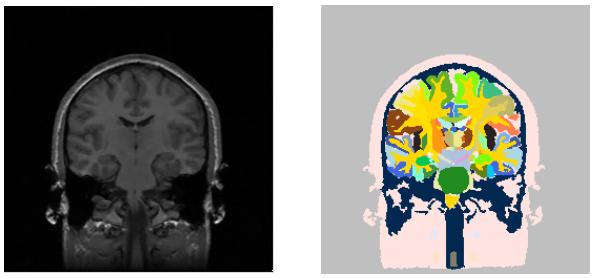

Figure 3. The atlas voxel image (left), and the corresponding color-coded classification of anatomical structures (right).

The training set for knowledge extraction is composed of T1-weighted MRI volumes of 105 non-pathological brains. There are not only intrinsic variations between these voxel images, but also extrinsic variations from the different image acquisition processes. As illustrated in Figure 4, the extrinsic variations are differences in orientation, overall scale, and intensity distributions. These differences need to be eliminated to enable extraction of intrinsic anatomical variations.

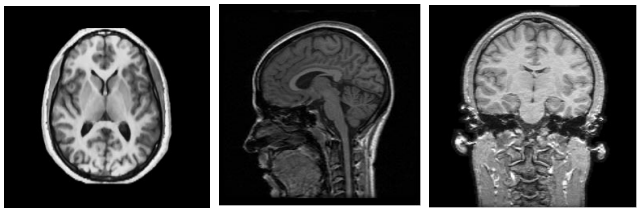

Figure 4. Examples from the training set. There exist differences in orientation, scale, and intensity distribution.

We use a previously developed 3-D hierarchical deformable registration algorithm [12] to compensate for extrinsic variations, and to register corresponding anatomical structures to the reference atlas. Once the training set is registered with the atlas, we can examine intrinsic variations to build statistical models. The reference atlas is then augmented into a statistical atlas to automatically provide domain-specific guidance to the registration process.

3. Knowledge Extraction Algorithm

In order to glean knowledge of intrinsic variations, we first compensate for the extrinsic variations. We extract and model intrinsic variations as statistical distributions, and embed the models into the atlas.

3.1. Adjusting Extrinsic Geometric Variations

The 3-D hierarchical deformable registration algorithm[12] addresses the extrinsic geometric variations between different MRIs via 3-D rotation, scaling, and translation. This brings the training set to have the same orientation, size, and location as the atlas. Figure 5 shows the middle training sample in Figure 4 rotated and aligned with the atlas after the adjustment of extrinsic differences.

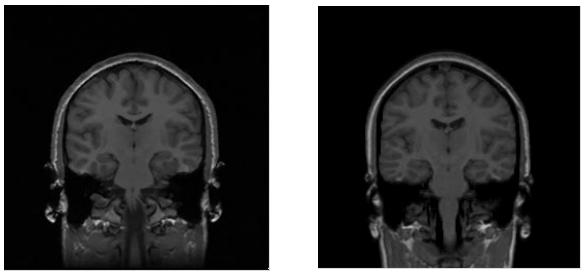

Figure 5. The atlas (left), and a training sample after the compensation of extrinsic variations (right).

3.2. Capturing Anatomical Variations

After the compensation for extrinsic variations, intrinsic variations are responsible for the remaining misalignment of anatomical structures between the training set and the atlas. We capture this information by aligning the training set with the atlas through 3-D deformation, and store the 3-D displacement of each voxel. Multi-level intensity equalization is interwoven with the deformation hierarchy so as to adjust the extrinsic intensity discrepancy resulting from different image acquisition processes. Each atlas voxel is associated with two important distributions: one is a distribution of intensities of corresponding voxels in the training set, the other is a distribution of the 3-D deformation vectors between the atlas voxel and the corresponding voxels in the training set. The former contains density variations of anatomical structures over a population, while the latter embodies geometrical variations of anatomical features, e.g. shape, size, and location discrepancies.

3.3. Modeling Anatomical Variations

The two distributions associated with each atlas voxel contain rich information about anatomical variations. We model both distributions as Gaussian distributions. For each atlas voxel, the intensity distribution $P(Intensity)$ is a 1-D Gaussian distribution of the intensity difference between the corresponding voxels in the training set and the atlas voxel:

$$P(Intensity) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{(I_S - I_A - \mu)^2}{2\sigma^2}} \qquad (1)$$

I_S and I_A are corresponding voxel intensities in the subject and the atlas. μ is the average intensity difference between the training set and the atlas at this voxel; σ is the variance of the intensity difference distribution.

The geometric distribution $P(Geometry)$ is a 3-D Gaussian distribution of the 3-D displacement vectors between the atlas voxel and its counterparts in the training set:

$$P(Geometry) = \frac{1}{\sqrt{(2\pi)^3|\Sigma|}} e^{-\frac{(V_S - V_A - \nu)^T \Sigma^{-1} (V_S - V_A - \nu)}{2}} \quad (2)$$

ν is the average 3-D displacement vector at this voxel; Σ is the 3x3 covariance matrix of the geometric distribution; V_S and V_A are 3-D position vectors of the corresponding voxels in the subject and the atlas. Note that V_S is transformed from the subject's coordinate frame to the atlas' coordinate frame to adjust for extrinsic geometrical variations.

In this way, the non-pathological variations in geometry and intensity are expressed in the form of voxel statistics. A more comprehensive model would consider the dependency of the 3-D deformation of neighboring voxels. This involves a trade-off between complexity and efficiency. We choose the more efficient approach.

3.4. A Statistical Atlas

We augment the reference atlas into a statistical atlas to embody the knowledge of anatomical variations of a population. In the statistical atlas, each voxel is associated with a position vector that contains the information of the mean of its geometrical variation distribution, and an intensity value that is modified by the mean of its intensity variation distribution:

$$V_{Stat} = V_A + \upsilon \quad (3)$$

$$I_{Stat} = I_A + \mu \quad (4)$$

V_{Stat} is a 3-D voxel position vector in the statistical atlas, and I_{Stat} is the intensity at voxel V_{Stat}. Also attached to each voxel in the statistical atlas are the variances σ and Σ of the intensity and geometric distributions.

4. Applying Knowledge to Registration

The statistical atlas embodies non-pathological anatomical variations. It helps the deformable registration to tolerate anatomical variation while retaining discrimination between different structures. When we deform the atlas to register with a particular subject's voxel image of the same modality, we evaluate the 3-D deformation at each voxel D by how likely it is according to the intensity and geometric distributions embedded in the statistical atlas:

$$P(D) = P(Intensity) \cdot P(Geometry) \quad (5)$$

To find the deformation that best registers the statistical atlas to a subject, we maximize the logarithm of the measurement in (5) for each voxel:

$$\log P(D) = \log P(Intensity) + \log P(Geometry)$$

Ignoring the constants, this is equivalent to minimizing:

$$\frac{(I_{Stat} - I_S)^2}{2\sigma^2} + \frac{(V_{Stat} - V_S)^T \Sigma^{-1} (V_{Stat} - V_S)}{2} \quad (6)$$

One method to find the deformation that minimizes the above criterion is gradient descent. The 3-D gradient ∇ at each step of the descent is given by the first order derivative of (6):

$$\nabla = \frac{I_{Stat} - I_S}{\sigma^2} \nabla Stat + \Sigma^{-1} (V_{Stat} - V_S) \quad (7)$$

$\nabla Stat$ is the 3-D image gradient at the voxel in the statistical atlas. It is a function of the voxel's position. Since σ and Σ can have small values, we add a stabilizing factor to σ and to the diagonal elements of Σ to regularize the gradient. The empirical value we use is $|\nabla Stat| + 1$. The 3-D shift δD of the voxel is then:

$$\delta D = -\lambda \nabla \quad (8)$$

λ is a step size constant. In this way, each atlas voxel is guided to search for a counterpart in the subject so their differences in intensity and position are most probable according to the statistics gathered from a population. We apply 3-D Gaussian smoothing to the voxels' 3-D displacements after each iteration to smooth the deformation. This compensates for the fact that we ignored the dependence between the deformation of neighboring voxels.

This algorithm differs from the previously developed 3-D hierarchical deformable registration algorithm [12] in the measurement of the goodness of the voxel deformation flow. In this method we maximize the likelihood of the current deformation with respect to domain-specific statistics, whereas in the previous algorithm we minimize the intensity difference between spatially corresponding voxels in the atlas and the subject. Before undergoing voxel flow deformation, both algorithms globally align the two 3-D images to eliminate extrinsic variations, and use a 3-D spline-based deformation to roughly adjust for the intrinsic variations between the individuals. The algorithms are automated by using a randomized initialization for the global alignment.

5. Experiments and Evaluation

We evaluate the effectiveness of our model of anatomical variations by comparing registration guided by domain-specific statistics, and registration without knowledge guidance.

5.1. Evaluation metric

We assess the quality of registration by estimating classification accuracy. Since each voxel in the atlas is labelled with the class of the anatomical structure that contains it, when we register the atlas with a subject, we can then label each voxel from the subject with its anatomical structure. This creates a customized atlas which contains classifications of the subject's anatomical features. Figure 6 illustrates this process. Given the *ground-truth* classification of the subject's anatomical structures given by human experts, we can evaluate the quality of the registration by assessing the voxel classification accuracy.

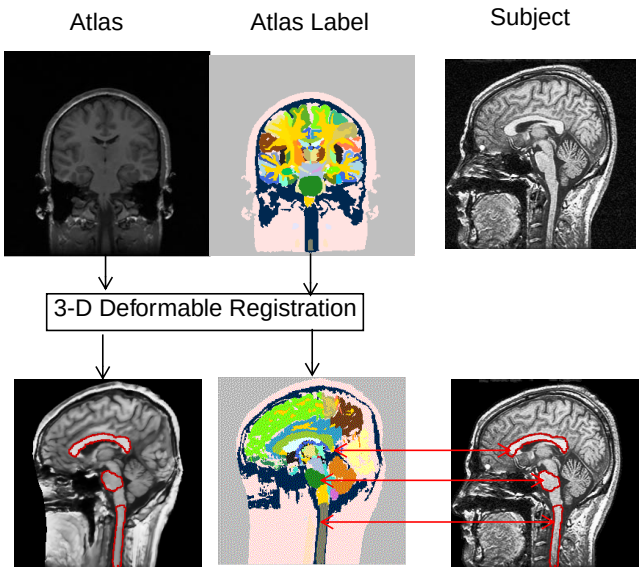

Figure 6. Illustration of classifying a subject's anatomical structures through registration with the atlas.

Currently we have 40 subjects' brain MRIs that come with expert classification of one structure, the corpus callosum, in one plane, the mid-sagittal plane (Figure 7). We use these images as the test set, and the number of mislabelled voxels relative to the size of the corpus callosum in the expert-segmentation to quantify the classification accuracy. Mislabelled voxels include those labelled as corpus callosum by the deformed atlas but not in the expert-segmentation and vice versa. We use the ratio of mislabelled voxels as the error metric to evaluate the registration performance.

5.2. Registration Guided by the Statistical Atlas

We evaluate the effectiveness of our statistical models

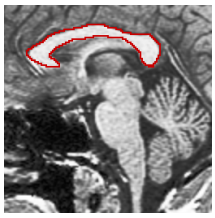

Figure 7. Expert classification of corpus callosum in the mid-sagittal plane of a brain MRI.

by comparing registration guided by the statistical atlas, with the previous registration algorithm that has no domain-specific guidance. We apply both methods to our test set, and computed the ratio of mislabelled voxels for all samples. Our statistics guided registration method has an overall mislabelled voxel ratio of 3.42%, versus 4.88% for the algorithm with no knowledge guidance, a 30% improvement. Figure 8 compares the distribution of classification results for all test cases. The horizontal axis is the ratio of mislabelled voxels, and the vertical axis is the number of sample cases. Note that the algorithm with statistical guidance achieved more cases with small ratio of mislabelled voxels, and eliminated cases with more than 10% error.

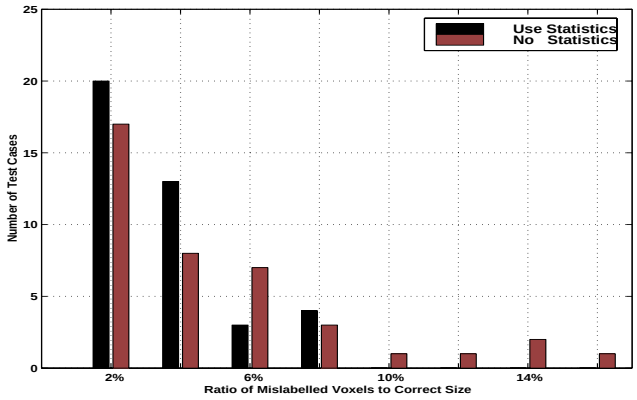

Figure 8. Comparison of performance between the original algorithm and registration using the statistical atlas.

5.3. Experiments

To better understand the roles of the intensity and geometric statistics, we conduct experiments to evaluate their independent contributions in the registration process.

5.3.1. Contribution of the Intensity Statistics

In this experiment, we assess the 3-D deformation at each voxel by how likely it is according to the intensity distribution embedded in the statistical atlas. To find the deformation that best registers the atlas to the subject, we maximize $P(intensity)$ using gradient descent technique (Section 4). The 3-D gradient at each step is the first term in

equation (7):

$$\nabla = \frac{I_{Stat} - I_S}{\sigma^2} \nabla Stat$$

We apply this method to our test set, and computed the ratio of mislabelled voxels for all samples. It has an overall mislabelled voxel ratio of 4.03%, which is a 17.4% error reduction over the algorithm with no knowledge guidance.

5.3.2. Contribution of the Geometric Knowledge

In this experiment, we assess the 3-D deformation at each voxel by how likely it is according to the geometric distribution embedded in the statistical atlas. We use gradient descent to maximize $P(geometry)$ to find the deformation that best registers the atlas to the subject (Section 4). The 3-D gradient at each step is the second term in equation (7):

$$\nabla = \Sigma^{-1}(V_{Stat} - V_S)$$

We apply this method to our test set, and computed the ratio of mislabelled voxels for all samples. It has an overall mislabelled voxel ratio of 4.1%, which is a 16% error reduction over the algorithm with no knowledge guidance.

These experiments tell us that the intensity statistics plays a slightly more significant role in guiding the deformable registration. The best registration result is given when the intensity and geometric statistics are combined to provide domain-specific guidance.

6. Related Work

Many researchers have been exploring the characterization of anatomical variations. Bookstein analyzed the underlying statistical and geometric models of morphometrics[7], and applied landmark-based morphometrics to biomedical shape comparison[8]. Martin et. al. characterized neuropathological shape deformations using finite element modeling and statistical analysis[9]. Szekely et. al. studied flexible parametric shape models by combining the mean contour with a set of eigenmodes of the parameters to characterize shape variations[6]. Guimond et. al. developed an automatic method to build average intensity and shape models of the human brain[10]. Wang and Staib incorporated statistical shape models into elastic model based 2-D non-rigid registration[11]. Effort has also begun to combine the strength of physically-based models and statistical models.

7. Conclusion and Future Work

We extracted the pattern of non-pathological variations in the appearances of brain structures from the T1-weighted magnetic resonance imaging (MRI) volumes of 105 subjects. We represent domain knowledge in the form of voxel statistics, and embed these statistics into a 3-D digital brain atlas which we use as the reference. The knowledge acquisition process involves registering a training set of MRI volumes with the atlas. The method employed is a previously developed 3-D hierarchical deformable registration algorithm. This associates each voxel in the reference atlas with distributions of normal variations of intensity and 3-D positions of the training set. We evaluate statistical properties of these distributions for each atlas voxel to build a statistical atlas which contains the anatomical information of the population. When we register this atlas to a particular subject, the embodied statistics function as domain-specific guidance. Intuitively, each atlas voxel is guided to search for a counterpart in the subject so their differences in intensity and position are most probable according to the statistics gathered from a population. The deformation process can tolerate non-pathological variations between subjects. When applied to 40 test cases, this knowledge-guided registration method reduced the voxel mis-classification rate by 30% compared to the algorithm without knowledge guidance.

The statistical atlas is built from registration done without domain knowledge. This can affect the accuracy of the statistical atlas, and thus the registration done with it. In future work we will investigate methods of overcoming this problem, such as bootstrap. We can build an initial statistical model from a small but accurately registered training set, then bootstrap it into a more reliable model.

In the future we also plan to use our method for representing variations in brain structure to quantitatively study anatomical differences between populations.

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References

[1] Christensen et al., "Individualizing Neuroanatomical Atlases Using A Massively Parallel Computer", IEEE Computer, pp. 32-38, January 1996.

[2] Evans et al., "Warping of Computerized 3D Atlas to Match Brain Image Volumes for Quantitative Neuroanatomical and Functional Analysis. Proceedings of SPIE Medical Imaging, Vol. 1445, pp. 236-246.

[3] Vemuri et al., "An Efficient Motion Estimator with Applications to Medical Image Registration", Medical Image Analysis.

[4] Bajcsy and Kovacic, "Multiresolution Elastic Matching", Computer Vision, Graphics, and Image Processing, Vol. 46, pp 1-21, 1989.

[5] Jean-Philippe Thirion, "Fast Non-Rigid Matching of 3D Medical Images", INRIA, Technical Report No. 2547, May, 1995.

[6] Szekely et. al., "Segmentation of 2-D and 3-D objects from MRI volume data using constrained elastic deformations of flexible Fourier contour and surface models", Medical Image

Analysis, vol. 1, No. 1, pp. 19-34.
[7] Bookstein, “Shape and the information in Medical Images: A decade of the Morphometric Synthesis”, Computer Vision And Image Understanding, vol. 66, No. 2, pp. 97-118, 1997.
[8] Bookstein, “Landmark methods for forms without landmarks: morphometrics of group differences in outline shape”, Medical Image Analysis, Vol. 1, No. 3, pp. 225-243.
[9] martin et. al., “Characterization of Neuropathological Shape Deformations”, IEEE Transactions on Pattern Analysis and Machine Intelligence, Vol. 20, No. 2, 1998.
[10] Guimond et. al., “Automatic Computation of Average Brain Models”, Proceedings of the First International Conference on Medical Image Computing and Computer-Assisted Intervention, pp. 631-640, 1998.
[11] Wang and Staib, “Elastic Model Based Non-rigid Registration Incorporating Statistical Shape Information”, Proceedings of the First International Conference on Medical Image Computing and Computer-Assisted Intervention, pp. 1162-1173, 1998.
[12] Mei Chen et. al., “Anomaly Detection through Registration”, Proceedings of IEEE Computer Society Conference on Computer Vision and Pattern Recognition, pp 304-310, June, 1998.