Hierarchical Unbiased Group-wise Registration for Atlas Construction and Population Comparison

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ABSTRACT

A novel hierarchical unbiased group-wise registration is developed to robustly transform each individual image towards a common space for atlas based analysis. This hierarchical group-wise registration approach consists of two main components, (1) data clustering to group similar images together and (2) unbiased group-wise registration to generate a mean image for each cluster. The mean images generated in the lower hierarchical level are regarded as the input images for the higher hierarchy. In the higher hierarchical level, these input images will be further clustered and then registered by using the same two components mentioned. This hierarchical bottom-up clustering and within-cluster group-wise registration is repeated until a final mean image for the whole population is formed. This final mean image represents the common space for all the subjects to be warped to in order for the atlas based analysis. Each individual image at the bottom of the constructed hierarchy is transformed towards the root node through concatenating all the intermediate displacement fields. In order to evaluate the performance of the proposed hierarchical registration in atlas based statistical analysis, comparisons were made with the conventional group-wise registration in detecting simulated brain atrophy as well as fractional anisotropy differences between neonates and 1-year-olds. In both cases, the proposed approach demonstrated improved sensitivity (higher t-scores) than the conventional unbiased registration approach.

Keywords: Hierarchical registration, Unbiased registration, Group-wise registration

1. INTRODUCTION

In medical imaging, atlas based statistical inference is designed to increase the statistical power in abstracting functional or structural information from either individuals or populations. One most viable clinical application of this technique is to identify the abnormality within patient population using the atlas from healthy controls.

One critical step in the atlas construction is to transform all individual images towards a common space consistently. This process directly affects the sequential statistical inference. Pair-wise registrations [1-5] towards a chosen template, which can be either a subject in the population or an averaged image obtained from multiple aligned subjects (like MNI template), are widely used for atlas construction. One limitation associated with this approach in atlas construction is that the resulted atlas may be biased towards the predefined template. To overcome this limitation, Joshi et al. have developed an unbiased group-wise registration approach, in which the template (mean) image was gradually formed during the registration procedure [6]. However, this approach ignores the possible inhomogeneous distribution of data within the population, and uses only a single mode to represent all the subjects. There are published works to study the inhomogeneous distribution of data in a population. Blezek and Miller adapted the mean shift theory [7] in combination with a pair-wise mutual information based image distance metric to detect the existence of different modes within a population [8]. Sabuncu et al. proposed an expectation-maximization algorithm to maximize the likelihood of an individual image was generated by a prototype image following a Gaussian process [9]. With affine registration, a 5% improvement in alignment quality was achieved when considering multiple atlases instead of a single one. More recently, this approach in [9] was developed for image clustering. Each individual image was modeled as a weighted summation of a set of template images following Gaussian models. The clustering was performed iteratively with a modified expectation-maximization algorithm.

Currently, most efforts are made to identify the existence of different modes within the population to be analyzed. Since image registration also plays a critical role in atlas construction, we also need to consider multiple modes within a population, in order to increase the overall registration performance and eventually the accuracy of the constructed

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atlases. The number of modes within a population depends on the relative distribution of the internal differences of individual structures or functions. Therefore, the estimation of number of modes should be performed hierarchically during the group-wise registration.

In this paper, we propose a hierarchical unbiased group-wise registration approach to repeatedly cluster and align images within each cluster through unbiased group-wise registration. The repetition stops until all images are aligned onto the same final mean image, which represents the common space, towards which all images will be transformed. The sum of squared differences (SSD) is used as the measure for both image clustering and unbiased group-wise image registration. Image clustering is implemented with a K-Means like iterative algorithm, which updates the cluster center (mean image) dynamically. After memberships of all the individuals are determined, sub-atlas will be built for each cluster. The image clustering and group-wise registration was performed iteratively until the final root mean image of the entire hierarchical structure is reached. Each individual image is transformed towards the template space through concatenating the intermediate displacement fields from the individual subject towards the final template. In our current implementation, image registration is driven with a B-spline model based registration approach similar to [2]. We compared the performances of the proposed hierarchical approach with the conventional unbiased registration in detecting simulated human brain atrophy and fractional anisotropy (FA) changes occurred in early postnatal stage. In both cases, improved statistical power (higher t-scores) were observed with the our approach.

2. METHODS

Different from the conventional group-wise registration which is designed to minimize the variance within the whole population, our hierarchical approach aims to minimize the intra-group variance at each hierarchical level. The proposed algorithm consists of two main steps, image clustering to group similar images together and unbiased group-wise registration to construct the mean image to represent the cluster. The resulted mean images from the clusters in the lower hierarchical level will be used as the input images to the higher hierarchical level. Image clustering and unbiased registration will be performed with these input images again and these two components will be repeated until the final mean image for the whole population is formed. This proposed registration approach was implemented in a B-spline model based registration framework.

2.1 Overview of the Hierarchical Unbiased Group-wise Registration

In this hierarchical registration algorithm, when the image population to be registered at level t is inhomogeneous (consisting of multiple modes), instead of minimizing the variance within whole population as originally proposed in [6], we propose to cluster images into different groups and then minimize the intra-group variance (defined as E_i^t in Eq. (1)) of each cluster (i), so that the total sum of the variances from these clusters is minimized. This is the key feature of the proposed approach.

At hierarchical level t, there are total N^t input images (I_i^t,$i=1\sim N^t$), which are clustered into K^t clusters. Each cluster (i) ($(J_{i,1}^t, J_{i,2}^t, \ldots J_{i,S_1^t}^t)$) has S_i^t elements, and $J_{i,j}^t$ is the *j-th* image within cluster *i*. E_i^t is the variance of cluster i, and $T_{i,j}^t(\vec{x})$ represents the transformation obtained by registering the mean image of the cluster ($\bar{J}_i^t$) to its member, $J_{i,j}^t$. Since each individual image at hierarchical level 0 (the original input image) should have equal weighting in the computation of cluster mean and variance, each cluster member $J_{i,j}^t$'s contributions to E_i^t and $\bar{J}_i^t$ are weighted by $w_{i,j}^t$, which is proportional to the number of original input images $J_{i,j}^t$ represents. After the mean images are formed for all the clusters with group-wise unbiased registration, the resulted mean images are further used as the input images for hierarchical level t+1. The clustering and unbiased registration to minimize intra-group variance is performed iteratively, until the root of the whole hierarchical structure is reached. The resulted root image represents the common space for the whole population, and the intermediate displacement fields are concatenated from the root to each leaf image for the warped image.

$$I_1^t, I_2^t, \ldots I_{N^t}^t \underset{clustering}{\rightarrow} (J_{1,1}^t, J_{1,2}^t, \ldots J_{1,S_1^t}^t), \ldots (J_{K^t,1}^t, J_{K^t,2}^t, \ldots J_{K^t,S_{K^t}^t}^t)$$

$$E_i^t = \sum_{j=1}^{S_i^t} w_{i,j}^t \| J_{i,j}^t (T_{i,j}^t(\vec{x})) - \bar{J}_i^t \|^2 \Big/ \sum_{j=1}^{S_i} w_{i,j}^t$$

$$\bar{J}_i^t = \sum_{j=1}^{S_i} w_{i,j}^t J_{i,j}^t (T_{i,j}^t(\vec{x})) \Big/ \sum_{j=1}^{S_i} w_{i,j}^t \qquad (1)$$

$$(T_{i,1}^t(\vec{x})^*, \ldots T_{i,S_i^t}^t(\vec{x})^*) = argmin(E_i^t)$$

$$\bar{J}_1^t, \bar{J}_2^t, \ldots \bar{J}_{K^t}^t \underset{t->t+1}{\rightarrow} I_1^{t+1}, I_2^{t+1}, \ldots I_{N^{t+1}}^{t+1}$$

2.2 Image Clustering

At each hierarchical level, image clustering is the first important step in order to minimize the total sum of intra-group variance. The membership of each individual image I_i^t at level t can be determined with the image similarities (e.g. SSD or mutual information) or displacement fields obtained by registering image I_i^t to the mean images of all the clusters. Some widely used pair-wise registration methods, such as affine or B-spline model based registrations can be used for the purpose of image clustering. Ideally, an individual image should be clustered towards the cluster center (mean image) with which the registration yields the least displacement and the highest similarity. But as a feasibility study to prove the concept that proper clustering will help to improve the statistical power of the constructed atlas, we only rely on SSD to determine the membership of each individual image. We employed a K-Means like algorithm to determine the membership of an individual image through finding the least SSD after registering the individual image to all the cluster centers. If the membership of any individual image is changed, the cluster center is also updated accordingly with the weighted sum of the current cluster members. The weighting which controls the relative contribution to the mean image from each individual member is determined by the number of input images at the bottom level of the hierarchical structure it represents to ensure the equal contribution from each original input image. This iterative process continues on until the membership function remains unchanged for two consecutive steps.

In order for the above discussed K-Means like procedures to group the images, the number of clusters and the initial cluster centers have to be given as inputs. Since it is usually difficult to determine the exact number of clusters within an image population, we choose to cluster images with a threshold value on SSD to help us determine the number of clusters in the image population and the initial cluster center. If the SSD between two images are less than the threshold, the images will be grouped into one cluster. The choice of the threshold can be dynamic and the threshold value can be gradually increased when traveling up the hierarchy. We first use a conventional group-wise registration method to align every individual image into a common space, so that the SSD between any image pair can be computed directly. Then, the following iterative procedures are performed to determine the number of clusters and initial seed image required for K-mean based image clustering. Afterwards, a final K-means clustering will be performed with the given number of clusters and the initial cluster centers to group the images. The unbiased mean images from each cluster will be used as the input image for the higher hierarchy.

1. choose an SSD threshold value ε based upon the prior knowledge of the data.

2. assume there is only one cluster for all the images (cluster_number = 1), store the mean image of all the images into the cluster seed image array.

3. initialize the index for the current cluster to 1 (current_cluster=1).

4. if current_cluster<=cluster_number, go to step 5. Otherwise, stop the program, and the cluster number and the initial cluster centers have been determined.

5. if the cluster has only one element, increase current_cluster by 1 (current_cluster = current_cluster + 1), store this image as a cluster seed image and go back to step 4.

6. if the cluster has more than one elements, find the image within the cluster (I_max) having the largest SSD from the cluster center (max_SSD).

7. if max_ssd < ε, increase current_cluster by 1, and go back to step 4.

8. if max_ssd >= ε, replace the seed image of the current cluster in the seed image array with two images, I_max and the updated mean image (computed from the rest images within the cluster with I_max removed).

9. after clustering all the images with the current seed images stored in the seed image array, go back to step 3.

It is very difficult to choose the threshold for image clustering (ε) automatically. The choice of the value depends on our prior knowledge of the image data to be analyzed. If it is too small, each image will be determined as one cluster. If it is too large, images having different modes may be clustered together. In our current implementation, we started the clustering with a very low threshold and gradually increase its value to avoid over clustering. The threshold value also has to increase from lower hierarchy to higher hierarchy. The reason is that the input images are more different from each other at a higher hierarchy, and the threshold has to be changed accordingly.

Our current image clustering and image registration are performed with a B-spline model based registration approach. In the clustering step, image registration can be performed with a less flexible registration method such as affine or a less flexible B-spline model based registration to improve speed. In the unbiased registration step to form the mean image for each cluster, a B-spline model with higher flexibility is used to produce a mean image with a higher clarity in brain geometry.

2.3 Unbiased Registration to Combine Clusters

At hierarchical level *t*, following image clustering, unbiased group-wise registration driven by a B-spline model with higher degrees of freedom (compared with the B-spline models used for image clustering) are performed for all the clusters to compute the optimal transformation field ($T_{i,j}{}^{t}(\vec{x})^{*}$) as in Eq. (1). In computing the mean image of each cluster, each cluster member's contribution is weighted by the number of original input images it represents, to ensure that all the individual images at the bottom of the hierarchy have equal contribution to the mean image representing them at level *t*.

The computed mean images of all the clusters at hierarchical level *t* will be used as the input images for hierarchical level *t*+1, so that the two steps of the proposed hierarchical approach (image clustering and unbiased registration to generate the mean image for each cluster) can be performed at hierarchical level *t*+1. These two basic steps will run repeatedly until the program for determining the number of clusters generates the same number of clusters as the input elements. At this stage, a final group-wise unbiased registration is performed to compute the final mean image, which is the root for the whole hierarchical structure. Upon completion of the registration, this final mean image represents the common space for the whole population. Each individual image is warped towards this common space by following the displacement field originated from the root and traveling down the hierarchy until this individual image is reached.

3. RESULTS

To evaluate the performance of the developed hierarchical unbiased registration, we compared the proposed hierarchical unbiased group-wise registration with the conventional group-wise registration in detecting simulated brain atrophy and FA changes in early postnatal stage. The evaluation was performed through comparing the t-scores obtained with these two different approaches to demonstrate that the different registration approach may produce the atlas having different statistical power and prove the concept that improved sensitivity can be achieved with the proposed hierarchical approach compared to the current unbiased registration algorithm.

3.1 Detecting simulated atrophy

As demonstrated in Fig. 1, twelve subjects' original brain images were artificially introduced ~10% atrophy at superior central gyrus [11] (indicated with the red arrows in the first (without atrophy) and second (with atrophy) images of Fig. 1). We compare the proposed registration approach with the conventional unbiased registration in detecting this simulated atrophy. This is a well controlled simulation study with a known ground truth. In our hierarchical approach, a small threshold was used to cluster the images from each individual subject into one cluster. In the bottom of the hierarchy, 12 clusters were formed for 12 subjects. Since the small threshold is unable to enclose any two subjects into one cluster, the 12 clusters were combined with group-wise registration to form the root in the second level of the hierarchy.

For each registration approach, the SPM (Statistical Parametric Mapping, Oxford, UK) software was used for paired t-tests to compare the determinants of Jacobian matrices from the two groups with and without the simulated atrophy. The significant regions with the group difference in local brain volume were marked as the red areas in the third (for conventional unbiased registration) and forth (for the proposed hierarchical approach). The proposed hierarchical approach is able to detect the simulated atrophy with a higher t-score (t-score = 4.63) than the conventional group-wise registration (t-score = 3.42). Thus, the proposed hierarchical clustering/unbiased group-wise registration enhances the sensitivity of the sequential atlas based inference.

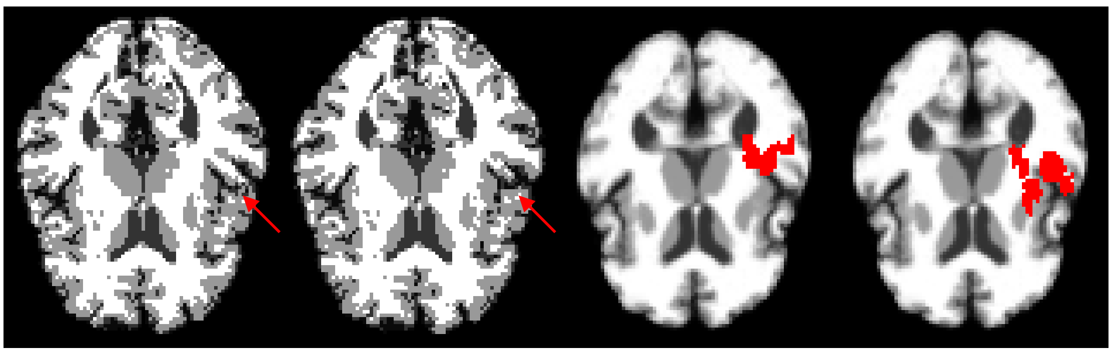

Fig. 1. One representative slice of the same subject's images without (1st image) and with (2nd image) the simulated atrophy and the identified significant regions (labeled in red) with the conventional unbiased group-wise registration (3rd image) and the proposed method (4th image).

3.2 Detecting FA changes in early post-natal stage

The driving project for this work is the investigation of the early brain developmental project in our institution. The most significant change in postnatal stage occurs within the first year of life. In this period, rapid myelination occurs within white matter as observed with diffusion tensor imaging (DTI). DTI is able to non-invasively measure the anisotropy of water diffusion inside brain. Fractional anisotropy (FA) is such a normalized measure which is considered to represent white matter myelination in brain derived from diffusion tensor imaging. Another desired attribute of the FA image is that white matter segmentation can be obtained naturally with this modality due to the low anisotropy diffusion inside gray matter and CSF. Thus, it also provides white matter geometry besides the maturation of myelin. In early postnatal stage, from neonate (Y0) to 1 year old (Y1), extensive FA increases are observed in almost every white matter regions due to the increased white matter myelination. Not only FA, the T1 image also goes through a dramatic change during this period of time and an effective T1 based registration method remains to be established. Ten normal, un-sedated subjects from each group (Y0 and Y1) were scanned (while they were sleeping) after written consents were obtained from their parents. Before registration, each subject's FA images were rescaled to 255 with its 99.5% percentile of the FA values within brain. After registration, the original FA values were utilized to identify the brain regions going through significant changes in FA.

The mean and variance images computed with the proposed hierarchical and the conventional group-wise registrations for the two age groups are both very similar. Only one slice of Y0 and Y1 mean images from the proposed approach in the resulted common space are given in Fig. 2. In the mean image of Y0 group, major white matters are clearly presented, and more fine structures within white matter are developed in the mean image of Y1. The t-scores obtained with the hierarchical approach are slightly higher than the t-scores from the conventional group-wise registration. The three quartiles (25%, 50% and 75%)[1] of t-score's distribution in the identified significant regions are (2.59, 3.26, 4.45) and (2.60, 3.29, 4.54), respectively for conventional group-wise and the proposed hierarchical registrations. This slight increase in t-score suggests the increased sensitivity of the proposed method. T-score maps from four slice locations obtained with these two approaches are given in the two rows of Fig. 3. With visual inspection, there are some areas demonstrating higher t-scores by proposed approach than the conventional approach.

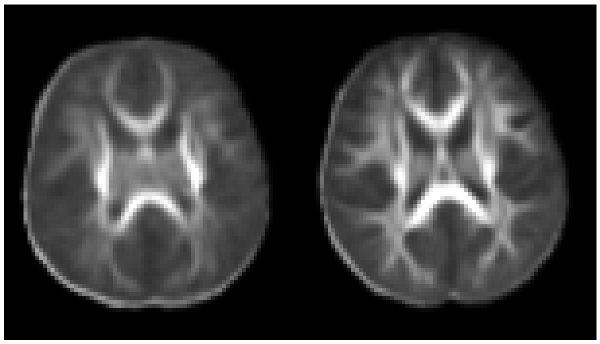

Fig.2. One axial slice of the mean FA images from Y0 (left panel) and Y1 (right panel) groups. More detailed peripheral white matter structures were observed in Y1 group.

Furthermore, this improvement in sensitivity is not achieved with the expense of smoothness of the displacement field. The three quartiles of the distribution of determinants of Jacobian matrices within brain are (0.88, 1.04, 1.31) and (0.94, 1.03, 1.19) for Y0 and Y1 groups obtained with conventional unbiased registration. The same quantities for the proposed hierarchical approaches are (0.92, 1.02, 1.20) and (0.96, 1.01, 1.09) for Y0 and Y1 groups. Since affine registration has been performed for global alignment, all the three quartiles are very close to unity, but all the three quartiles obtained with the proposed approach are closer.

4. DISCUSSIONS

A novel hierarchical image registration method considering the multiple modes within the population is developed. The central of this registration algorithm is that the similar images identified with image clustering should be group-wisely registered first before the registration of more dissimilar images. For subjects with relatively large differences (located in different clusters), the mean images of these two clusters are used for group-wise registration, since each mean image is the typical representative of the individual images within the cluster. Our results demonstrate that this registration route produces an atlas with a better statistical power than the atlas obtained by directly warping every individual image altogether towards the same template at the same time.

There are several limitations associated with the current implementation of the proposed algorithm. The current implementation of image clustering may not be optimal. *First*, in image clustering, using SSD alone for image clustering as in the current form did not consider the valuable information from displacement field obtained from image registration. *Second*, SSD is not a distance metric in strict sense. The pair-wise mutual information based metric used in [8] satisfies the distance requirements, but at the expense of more than doubled computational burden. *Third*, the clustering performance can be designed to be sensitive to certain complex features if machine learning results can be incorporated into the clustering steps. *Last*, a threshold based upon our knowledge of the imaging data to be analyzed has to be chosen by user for data clustering. Techniques to overcome these limitations will be our future work.

[1] The three quartiles (25%,50%,75%) of the distribution of a quantity (e.g., t-scores or determinants of Jacobians) represent the values which are respectively higher than 25%, 50% and 75% of the whole population.

In conclusion, we have demonstrated the advantage of the proposed hierarchical unbiased group-wise registration over the conventional group-wise registration. Our initial experience with this registration approach warrants the future efforts to advance this technique. We expect a greater clinical application of this novel registration technique.

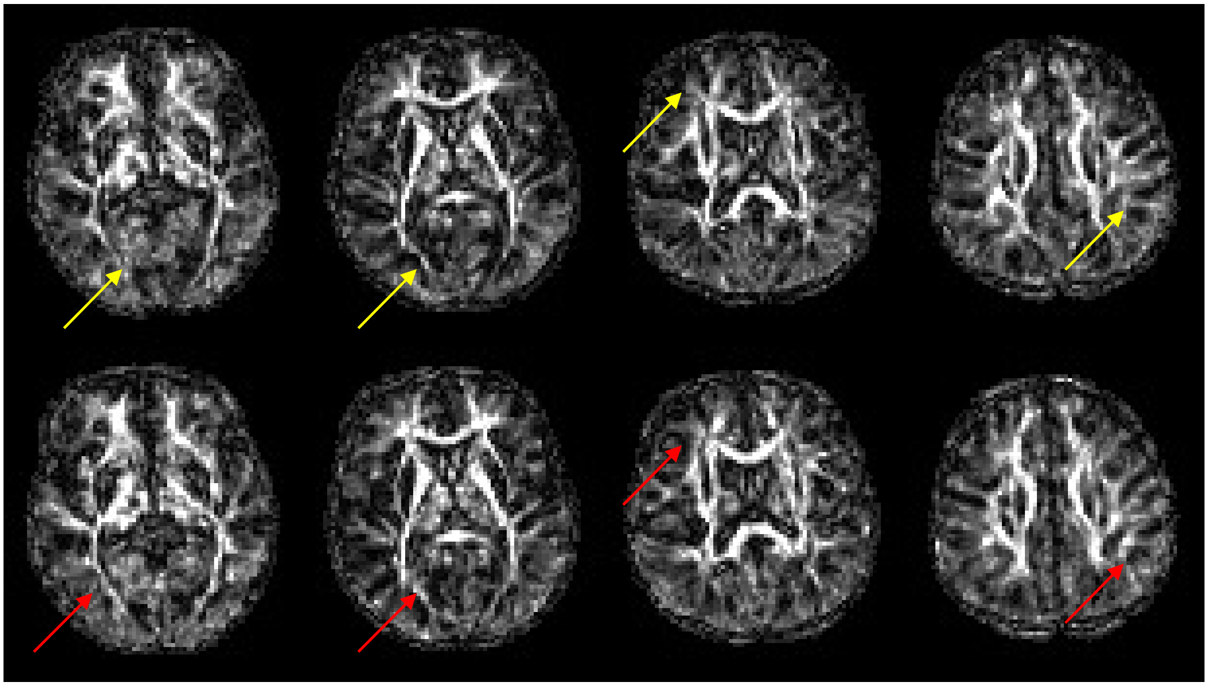

Fig. 3. The gray color encoded t-score maps at four slice locations obtained with the conventional group-wise registration (top row) and the proposed method (bottom row). The regions visually having higher t-scores with the proposed approach are marked with red arrows in bottom row, and the corresponding regions in conventional approach are marked with yellow arrows.

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