Published in final edited form as:

Mach Learn Med Imaging. 2016 October ; 10019: 69–76. doi:10.1007/978-3-319-47157-0_9.

Dual-Layer Groupwise Registration for Consistent Labeling of Longitudinal Brain Images

Minjeong Kim, Guorong Wu, Isrem Rekik, and Dinggang Shen

Department of Radiology and BRIC, University of North Carolina at Chapel Hill, Chapel Hill, USA

Abstract

The growing collection of longitudinal images for brain disease diagnosis necessitates the development of advanced longitudinal registration and anatomical labeling methods that can respect temporal consistency between images. However, the characteristics of such longitudinal images and how they lodge into the image manifold are often neglected in existing labeling methods. Indeed, most of them independently align atlases to each target time-point image for propagating the pre-defined atlas labels to the subject domain. In this paper, we present a *dual-layer groupwise registration method* to consistently label anatomical regions of interest in brain images across different time-points using a multi-atlases-based labeling framework. Our framework can best enhance the labeling of longitudinal images through: **(1)** using the group mean of the longitudinal images of each subject (i.e., subject-mean) as a bridge between atlases and the longitudinal subject scans to align atlases to all time-point images jointly; and **(2)** using inter-atlas relationship in their nesting manifold to better register each atlas image to the subject-mean. These steps yield to a more consistent (from the joint alignment of atlases with all time-point images) and more accurate (from the manifold-guided registration between each atlases and the subject-mean image) registration, thereby eventually improving the consistency and accuracy for the subsequent labeling step. We have tested our dual-layer groupwise registration method to label two challenging longitudinal brain datasets (i.e., healthy infants and Alzheimer's disease subjects). Our experimental results have showed that our method achieves higher labeling accuracy while keeping the labeling consistency over time, when compared to the traditional registration scheme (without our proposed contributions). Moreover, the proposed framework can flexibly integrate with the existing label fusion methods, such as sparse-patch based methods, to improve the labeling accuracy of longitudinal datasets.

1 Introduction

Automatic and accurate region-of-interest (ROI) labeling has drawn significant attention in numerous medical image analysis studies, since it grounds the quantitative measurement of morphological structures related to brain disease or development across individuals or between groups. However, inter-subject anatomical variation in a population of brain images constitutes a key hurdle in achieving highly accurate ROI labeling. To partly overcome this difficulty, multi-atlas-based labeling approaches became more popular with the use of multiple atlases (with pre-defined labels) to propagate their labels to a target subject, then

fusing them to obtain the final subject-specific labels. However, since the registration errors often occurs when registering multiple atlases to a subject image before the label fusion step, patch-based label fusion approaches have been proposed to reduce effects from these registration errors [1, 2]. These approaches can nicely incorporate neighboring information and also establish correspondences between a subject patch and atlas patches based on a patchwise similarity metric.

The potential registration errors may get more inflated when handling longitudinal brain data (and not only time-specific data). Hence, there is a need to develop advanced techniques to produce a longitudinally consistent registration and labeling that can accurately quantify subtle structural changes, which may be caused by brain development, aging or diseases. Notably, to devise a robust framework for consistent registration/labeling in the temporal domain, two key challenges must be overcome: **(1)** consecutive subject-specific registrations between different time-points would generate temporal registration errors (e.g., from brain atrophy or development across time), and **(2)** atlas-to-subject registration would engender spatial registration errors (from anatomical variations between subject and atlases). Therefore, to consistently label the ROIs in the longitudinal images, the atlas images with pre-labeled ROIs need to be warped in a temporally-constrained fashion to all time points of longitudinal images. However, the existing methods generally just register an atlas to each time-point image independently, or register different time-point images of the longitudinal scans to a pre-selected image at a certain time-point (used as a reference). This independence of registration may generate incoherent longitudinally registered images. Additionally, the existing methods only deployed pairwise registration to warp atlases to a target subject image. This strategy would also create a biased registration result due to the considerable anatomical difference between the atlases and the longitudinal subject images, which may cause inconsistent measurement of the small brain structure with longitudinal subtle changes (e.g., hippocampus).

To address these challenges, we propose a novel *dual-layer groupwise registration method*, which comprises two layers: **(1)** *Time-serial groupwise registration* to first register longitudinal images of the same subject. This estimates a subject-mean image as a common space to jointly align all different time-point images; and **(2)** *Manifold-guided registration* to label each time-point image by propagating the pre-defined ROIs from each of the multiple atlases, through the subject-mean image and with the help of neighboring atlases in the manifold. Then, subject-specific ROI labels, propagated from the aligned atlases, are fused using any label fusion method (e.g., sparse patch-based label fusion method [3]).

We tested our registration-labeling framework on two challenging longitudinal datasets from Alzheimer's disease (AD) patients and healthy infants, respectively. These two datasets present different challenges: AD subjects suffer from subtle but continuous anatomical changes, such as atrophy in hippocampal area, while structural brain images from infants show drastic changes both in shape and appearance especially in the first two years of postnatal development. Our dual-layer groupwise registration method showed a better labeling accuracy of the hippocampus in both datasets, compared to the traditional registration scheme, using the same multi-atlas-based label fusion method.

2 Method

Standard pairwise registration between the atlas to the target image is often used for labeling a single image with a single atlas. Intuitively, one could employ this standard pairwise registration in a serial fashion to label ROIs in a target longitudinal image sequence with multiple atlases. In other words, one can perform a series of pairwise registrations between N atlases $\mathbf{A} = \{A_i | i = 1, \dots, N\}$ and each of all T time-point subject images $I^t (t = 1, \dots, T)$. Thus, the dense deformation field $F_t = \{f_t(x) | f_t(x) = x + u_{A_i \rightarrow I^t}(x), x \in \Omega_{A_i}\}$ for each pair of A_i and I^t can be estimated through this framework, where $u_{A_i \rightarrow I^t}(x)$ denotes the displacement of a point x in the atlas domain Ω_{A_i} to the image I^t in the longitudinal sequence.

However, as we pointed out before, this simple extension may generate both registration and labeling errors. To address this issue, we include the following two steps in our method for consistent labeling of a longitudinal image sequence: **(1)** the incorporation of a group mean of the target longitudinal images, called a subject-mean image I^M , as a bridge between atlases and the longitudinal images to align atlas images to all time-point images jointly; **(2)** the use of inter-atlas relationship between atlases in a manifold to better register each atlas image to the subject-mean. Thus, we can expect to achieve good temporal coherence between registered longitudinal images from the joint alignment of all time-point images with atlases (Step 1) as well as better spatial registration accuracy between the subject-mean image and atlases from the manifold guidance (Step 2).

Specifically, in the Step 1, we use a groupwise registration method to jointly register all time-point images I^t onto a common space, i.e., a subject-mean embedding space. In turn, this simultaneously generates the subject-mean image I^M and the intermediate deformation fields $F_{I^M \rightarrow I^t} = \{f_{I^M \rightarrow I^t}(x) | f_{I^M \rightarrow I^t}(x) = x + u_{I^M \rightarrow I^t}(x), x \in \Omega_{I^M}\}$ of all I^t towards the common space. In the Step 2, we propose a manifold-guided registration method to estimate the deformation fields from the best atlas images $\mathbf{B} = \{B_i | i = 1, \dots, P, P < N\}$ (i.e., $\mathbf{B} \subset \mathbf{A}$) to the subject-mean image I^M , denoted as $F_{B_i \rightarrow I^M} = \{f_{B_i \rightarrow I^M}(x) | f_{B_i \rightarrow I^M}(x) = x + u_{B_i \rightarrow I^M}(x), x \in \Omega_{B_i}\}$. Finally, the deformation field F_t from B_i to each time-point image I^t in the longitudinal sequence is estimated by composing the deformation fields $F_{I^M \rightarrow I^t}$ and $F_{B_i \rightarrow I^M}$, i.e., $F_t = F_{I^M \rightarrow I^t} \circ F_{B_i \rightarrow I^M}$.

Figure 1 illustrates the overall idea of the proposed method, by comparison with the traditional scheme. The traditional registration scheme (Fig. 1(a)), independently aligns the atlases with each time-point image, which neglects the appealing properties of data distribution among atlases and the similarity of different time-point images of subject longitudinal sequence. In contrast, in our proposed framework (Fig. 1(b)), the registration between the atlases and different time-point images always goes through the subject-mean. Moreover, the manifold of atlases determines the deformation pathways from each atlas to the subject-mean by finding the best cost-efficient routes linking neighboring atlases in a graph hierarchy. Also, similarity of different time-point images is used in estimating subject-mean, and longitudinal consistency is further respected.

2.1 Groupwise Time-Serial Image Registration

The goal of groupwise registration is to register all time-point images I^t to a common space by jointly estimating the deformation field $F_{I^M \rightarrow I^t}$ and the subject-mean image I^M . Specifically, we implement the groupwise registration method for longitudinal image sequence with implicit template [4]. First, all time-point images of the same subject are initially registered using groupwise affine registration, and then the initial subject-mean image can be built by averaging those affine-aligned images. Next, the consistent registration of longitudinal images to the subject-mean image and the updating of subject-mean image are performed by iterating the following two steps: (1) register each time-point image to the current subject-mean image by a pairwise registration algorithm; and (2) estimate the subject-mean image based on the current registration results of all time-point images. Specifically, at the $(k-1)^{th}$ iteration, each subject image I is deformed into I_{k-1}^t via its current estimated deformation field $F_{I^M \rightarrow I^t}^{k-1}$, where $I_{k-1}^t(x) = I_{k-1}(F_{I^M \rightarrow I^t}^{k-1}(x))$. Similarly, at the k^{th} iteration, the mean image $I^{M_k}(x) = \frac{1}{T} \sum_{t=1}^T I_{k-1}^t(x)$ can be updated. Next, each time-point image I is registered to I^{M_k} using standard pairwise registration, thus obtaining its updated deformation field $F_{I^M \rightarrow I^t}^k$ for the $(k+1)^{th}$ iteration. In the end of groupwise registration, the subject-mean image I^M in the common space can be obtained, as well as the deformation field $F_{I^M \rightarrow I^t}$ of each time-point image I^t .

2.2 Manifold-Guided Registration of Atlases and Subject Image Sequence

We use a manifold-guided registration algorithm to rapidly and more accurately register all atlases to the subject-mean image I^M , with the help of other atlases by exploring their distribution on the atlas manifold. Specifically, the image graph is first built by computing the distance between all pairs of atlas images as weights of the graph edges that connect image nodes (atlases). Note that atlas images with high structural similarity are adjacently located in the graph; therefore, we use the built graph to progressively register each atlas to the subject-mean image by traversing the intermediate neighboring atlases one-by-one using the shortest path in the graph. In this way, the registration accuracy between each atlas and the subject-mean can be highly and incrementally improved by only estimating small deformations between similar atlases in the graph, thereby ascertaining a better propagation of the multi-atlas labels to the target different time-point images.

Specifically, we first use affinity propagation (AP) [5] to cluster all atlas images into several groups based on the distance matrix $D = [d_{ij}]_{N \times N}$, where each entry $d_{ij} = d(A_i, A_j)$ denotes the distance (i.e., image similarity) between the atlas $A_i (i = 1, \dots, N)$ and the atlas $A_j (j = 1, \dots, N)$. For each group, we build a graph to represent the interior image distribution by connecting only similar atlas images in the graph. Given a well-defined graph, we only calculate the deformation fields for the atlas images directly connected in the graph. This helps overcome the difficulty of directly registering atlas images with significant shape difference.

Given a target subject-mean image I^M , to which the atlases will be warped, we look for the most similar atlas image A_{i_0} among a group of atlases $A = \{A_i | i = 1, \dots, N\}$ in the manifold.

It is worth noting that the atlases in the same group of A_{i_0} are considered as the best atlases $B = \{B_i | i = 1, \dots, P, P < N\}$. This can provide a straightforward solution on how to select atlases for the label fusion step, which highly influences the final labeling accuracy.

Next, we use deformable image registration to estimate the deformation F_{B_i, B_j} for the directly connected best atlases $B_i (i = 1, \dots, P)$ and $B_j (j = 1, \dots, P)$ in the graph. The goal of image registration is then to estimate the deformation field that warps B_j to the space of A_{i_0} using these directly connected atlases in the graph. In a traditional registration approach, the optimization of the deformation pathway could be very complex and prone to local minima, since the shape and appearance differences between A_{i_0} and B_j are typically large in the aging/developing brains. However, the graph structure built in the atlas manifold can provide an easier way to estimate the deformation pathway between B_j and A_{i_0} by concatenating intermediate deformations on the shortest route linking them. To locate the shortest route from an atlas image B_j to A_{i_0} , we apply Yen's algorithm, which explores multiple shortest paths between them. Finally, we can obtain the total deformation pathway $F_{A_{i_0} \rightarrow B_j}$ by sequentially composing the small deformations of all graph edges along the shortest route. Ultimately, we further refine the deformation between A_{i_0} and I^M using a pairwise registration method with reasonable performance [6]. These steps are applied to all pairs of those selected atlas images and the subject-mean. After we get the warped atlases in the subject-mean space, we use patch-based label fusion to determine the final labels for each voxel in the subject-mean image as described next.

2.3 Consistent ROI Labeling of Longitudinal Image Sequence

The limitation of patch-based label fusion methods [1, 2] stems from that the atlas patches with low patch similarity to the target patch can still contribute to label fusion, thus leading to possibly inaccurate labeling. Instead, sparse patch-based label fusion methods [3] have been applied to solve this issue. Specifically, the low-similar atlas patches are automatically excluded for label fusion, by employing a sparsity constraint to reconstruct each target patch only from a small number of atlas patches. Thus, the estimated sparse reconstruction coefficients (with zeros for many low-similar atlas patches) can be used for effective label fusion.

Using the deformation $F_t = F_{I^M \rightarrow I^t} \circ F_{B_j \rightarrow I^M}$, a set of P warped best atlas images

$B' = \{B'_i | i = 1, \dots, P\}$ and their corresponding label maps $L' = \{L'_i | i = 1, \dots, P\}$ are obtained for propagating the labels from the warped atlases to each time-point image I^t . At each target point $x (x \in I^t)$ of each time-point image I^t , we can compute the patchwise similarities between all atlas patches within a certain search neighborhood $n(x)$, denoted as

$\vec{\beta}_{i,y} (\vec{\beta}_{i,y} \subset B'_i, y \in n(x))$, and the image patch $\vec{\alpha}_{I^t, x} (\vec{\alpha}_{I^t, x} \subset I^t)$ of I^t . Then, we can get the respective weighting vector $\vec{w} = [w_{i,y}]_{i=1, \dots, P, y \in n(x)}$ to integrate the atlas labels for estimating a label for the target point x . We can further adopt the sparse representation to reconstruct the local patch at target point x of each time-point image I^t (represented by column vector $\vec{\alpha}_{I^t, x}$) from the adjacent atlas patches centered at nearby voxels y in all atlases, which are also represented by column vectors and organized into a matrix C . Therefore, the sparse

representation can be formulated as $\vec{w} = \arg \min_{\vec{w}} \|\vec{\alpha}_{I^t, x} - C\vec{w}\|^2 + \lambda \|\vec{w}\|_1$, s.t. $\vec{w} > 0$,

where λ controls the strength of sparsity. With this estimated weight vector $\vec{w}_i$, we can also estimate a label for the target point x , as similarly done in the above.

3 Experimental Results

We evaluated our dual-layer registration framework in terms of both labeling consistency and labeling accuracy. Two longitudinal datasets, i.e., Alzheimer's disease (AD) patients from ADNI database and infant brain scans, were used in the following experiments. For AD dataset, 88 subjects with 3 time-point longitudinal scans, each with manual hippocampus labels, were first selected from ADNI database. 20 subjects among 88 subjects were used as the testing dataset (to-be-labeled) while the rest (i.e., 68 subjects) were considered as atlases. For infant dataset, we used 10 longitudinal infant brains with 5 time-points, acquired at birth to less than 2-years-old, with manual hippocampus labels delineated by an expert. Due to the small sample size, labeling was performed in a leave-one-out (LOO) fashion. To better take the advantage of manifold-guided registration by including more samples in the graph hierarchy, 20 infant subjects without hippocampus labels were also included in the construction of atlas manifold to provide more efficient routes between atlases and subject-mean image.

3.1 Evaluation of Longitudinal Labeling Consistency

We evaluated the consistency of longitudinal labeling by quantifying the trend of longitudinal hippocampus volumes, segmented using our proposed framework and the traditional registration scheme (i.e., pairwise registration between atlases and each time-point image in the longitudinal subject images) followed by sparse patch-based label fusion [3]. Figures 2 and 3 show the longitudinal hippocampal volumes measured by our framework (right panel) and the conventional method (left panel) averaged across 20 AD subjects and 10 infant subjects, respectively. One can see that the longitudinal hippocampal volume decreases more consistently due to disease progress (for AD subjects) or increases due to brain growth/development (for infant subjects), thus showing the effectiveness of consistent labeling enhanced by our dual-layer groupwise registration framework.

3.2 Evaluation of Longitudinal Labeling Accuracy

The overall hippocampus labeling accuracy of longitudinal brain sequences using our dual-layer registration method, followed by using several label fusion methods such as standard majority voting (MV), locally-weighted voting (LWV), non-local mean (NLM) [5] methods, and more advanced sparse patch-based label fusion (SPBL) [3], was evaluated in the comparison with the conventional registration framework. Table 1 compares the averaged Dice overlap ratios between manually-delineated hippocampus labels and the automatic labeling results by two methods, respectively. It shows that our dual-layer groupwise registration consistently helps achieve higher labeling accuracy for all four label fusion algorithms incorporated in our framework, compared to the traditional registration scheme, on both AD and infant datasets. This indicates that our proposed registration-labeling framework can integrate existing label fusion algorithms to immediately boost the final labeling accuracy.

4 Conclusion

We have proposed a dual-layer groupwise registration method for longitudinal brain labeling. Our method is anchored in two fundamental contributions. First, time-serial groupwise registration is applied to register longitudinal images of the same subject to estimate a subject-mean image as a common space to jointly align all different time-point images. Second, manifold-guided registration is proposed to label all subject time-point images by more accurately and rapidly propagating the pre-defined ROIs from each of the multiple atlases. Intensive evaluations were conducted using two compelling longitudinal AD and infant subjects that challenge our method with an opposing spectrum of image variability, from atrophy to drastic shape growth and dramatic appearance changes. Our experiments showed that our framework led to better labeling consistency and higher labeling accuracy of hippocampus for both datasets when compared to the traditional registration scheme. It is worth noting that the applications of our method are not limited to labeling hippocampus, but can be tested on various anatomical structures with time-serial scans. In future works, we will explore more high-order manifold neighborhoods for best atlas incremental selection and incorporate more advanced label fusion methods, e.g., group-sparsity based label fusion, in our dual-layer registration-labeling framework.

References

1. Coupé P, et al. Patch-based segmentation using expert priors: application to hippocampus and ventricle segmentation. *NeuroImage*. 2011; 54:940–954. [PubMed: 20851199]
2. Rousseau F, et al. A supervised patch-based approach for human brain labeling. *IEEE Trans. Med. Imaging*. 2011; 30:1852–1862. [PubMed: 21606021]
3. Zhang, D., Guo, Q., Wu, G., Shen, D. Sparse patch-based label fusion for multi-atlas segmentation. In: Yap, P-T, Liu, T, Shen, D, Westin, C-F, Shen, L., editors. *MBIA 2012*. LNCS. Vol. 7509. Heidelberg: Springer; 2012. p. 94–102.
4. Wu G, et al. Registration of longitudinal brain image sequences with implicit template and spatial-temporal heuristics. *NeuroImage*. 2012; 59:404–421. [PubMed: 21820065]
5. Frey BJ, Dueck D. Clustering by passing messages between data points. *Science*. 2007; 315:972–976. [PubMed: 17218491]
6. Vercauteren T, et al. Diffeomorphic demons: efficient non-parametric image registration. *NeuroImage*. 2009; 45:S61–S72. [PubMed: 19041946]

Fig. 1. Schematic illustration of the proposed registration framework (b) in comparison with the traditional registration framework (a).

Fig. 2. Longitudinal hippocampal volumes segmented by our dual-layer registration framework (right) in comparison with those by the traditional registration scheme (left) for 20 AD subjects.

Fig. 3. Longitudinal hippocampal volumes segmented by our dual-layer registration framework (right) in comparison with those by the traditional registration scheme (left) for 10 infant subjects.

Quantitative comparisons between conventional method and our dual-layer groupwise registration framework for measuring longitudinal hippocampus in 20 AD subjects and 10 infant subjects. (unit: %)

Table 1

	Conventional registration scheme				Our dual-layer registration framework			
	MV	LMV	NLM	SPBL	MV	LMV	NLM	SPBL
AD subjects	68.91	79.43	84.52	86.24	70.28	81.51	85.35	87.02
Infant subjects	60.24	62.56	58.13	62.98	62.52	63.70	59.98	65.07