LISA: LONGITUDINAL IMAGE REGISTRATION VIA SPATIO-TEMPORAL ATLASES

Ahmed Serag[a], Paul Aljabar[a], Serena Counsell[b], James Boardman[b,c], Jo V. Hajnal[d] and Daniel Rueckert[a]

[a] Biomedical Image Analysis Group, Department of Computing, Imperial College London, UK
[b] Centre for the Developing Brain, Imperial College London and MRC Clinical Sciences Centre, UK
[c] Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, UK
[d] Imaging Sciences Department, MRC Clinical Sciences Centre, Imperial College London, UK

ABSTRACT

We propose a novel framework for longitudinal registration which can handle large intra-subject anatomical variations. The framework exploits freely available spatio-temporal atlases, which can aid the longitudinal registration process as it provides prior information about the missing anatomical evolution between two scans taken over large time-interval. The spatio-temporal atlas is used to develop an approach to carry out longitudinal registrations via atlas propagation. We carried out evaluation experiments using 50 neonatal subjects with two scans taken at different time-intervals. We used different metrics, including intensity similarity and segmentation overlap, to assess the registration performance. The proposed registration framework outperforms direct registration by providing an accurate and consistent registration, particularly when the time-interval between scans increases. We refer to our approach as a framework for Longitudinal Image registration via Spatio-temporal Atlases (LISA).

Index Terms— Longitudinal registration, intra-subject, spatio-temporal atlas, neonatal, brain, MRI

1 Introduction

Magnetic resonance imaging (MRI) studies designed to compare anatomical variability within or across populations often require the transformation of large numbers of images into a common space with the aim to align images acquired from different subjects. However, registration of longitudinal images (images acquired from the same subject at different time points) also have an increasingly important role in medical image analysis because this approach is valuable for assessing the brain in early development, normal aging, and neurodegenerative diseases such as dementia. For instance, in early development, before birth and during the first few months, the brain undergoes significant changes in size, shape and structure than at any other time in life [1]. Therefore, registering two scans of the same subject taken during early brain development is challenging due to large shape and appearance differences.

Several approaches have been proposed to overcome the problem of medical image registration when there is large anatomical variation. The framework of the Large Deformation Diffeomorphic Metric Mapping (LDDMM) [2] is one of these registration techniques: It can represent large deformations through time-varying velocity fields that describe geodesics between images, i.e., the shortest path between the image according to a selected metric. LDDMM approaches have provided a mathematically elegant solution to the problem of large deformations and in particular the LDDMM registration framework finds geodesics within the space of diffeomorphisms. However, the space of diffeomorphisms is still a very large, unconstrained space. As a result a geodesic path in this space can easily lie outside the space of *anatomically plausible deformations*. Recently, Hamm et al. [3] proposed a registration framework to cope with such a problem by approximating analytical geodesic paths through the anatomical manifold with finite sequences of small deformations observed in the actual anatomies in the populations. Although this method can handle large deformations, it is difficult to apply because the study population has to be very large.

In the context of longitudinal image registration, Liao et al. [4] recently proposed a framework to construct longitudinal atlases that takes both the subject-specific longitudinal changes and the population shape variation information into account. However, this method is limited by requiring several scans per subject with relatively small variation. More recently, Holland et al. [5] presented a nonlinear registration method that enables precise quantification of large whole brain deformations, cortical surface shrinkage and subtle subcortical changes in small ROIs, based on serial MRI scans of an individual. The method relies on the assumption that tissue intensity signatures do not change over time. Therefore, application of the method to quantify structural development in neonatal brains, or to progression of diseases, will require modelling of the associated MRI contrast changes [6].

In this paper, we propose a novel framework for longitudinal registration, which can accommodate large intra-subject anatomical variations. The framework exploits spatio-temporal atlases with anatomical snapshots at different time-points that aid the longitudinal registration process. The

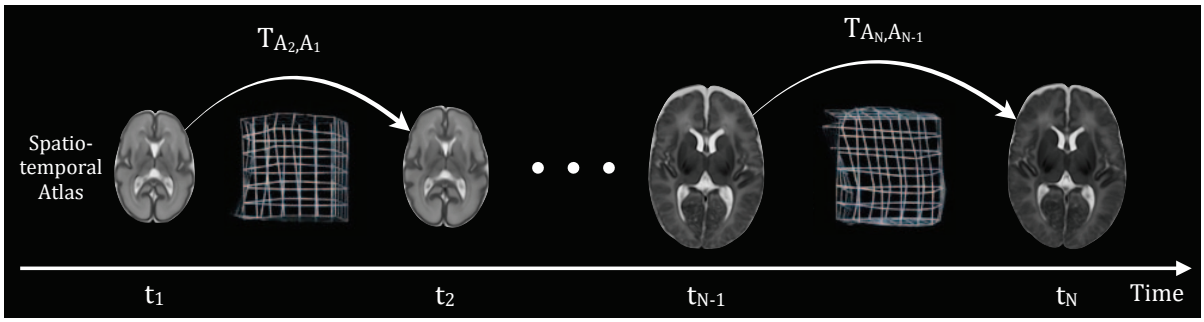


Fig. 1: Temporal registration between atlas successive templates.

assumption is that spatio-temporal atlases can provide prior information about the missing anatomical evolution between two scans taken over large time-intervals. We carried out an evaluation using 50 neonatal subjects with intra-subject scans at different time-intervals. We used information from different evaluation metrics to assess the quality of the proposed registration framework.

2 Methods

2.1 Subjects and Image Acquisition

The study group comprised 50 premature infants; two scans were available for each subject. The mean age at birth was 28.77 ± 2.77, range $24.57 - 35.29$ weeks postmenstrual age (PMA). The age range at the time of scan was 27.14 to 44.29 weeks PMA, with mean and standard deviation of 36.33 ± 5.64 weeks. The mean length of time to the second scan was 10.33 weeks later (range = 3.71 to 15.98 weeks).

All images were acquired on 3T Philips Intera system with the following parameters: T2-weighted fast spin-echo (FSE): TR = 8700 ms, TE = 160 ms, flip angle = 90 degrees, acquisition plane = axial, voxel size = 1.15 x 1.18 x 2 mm, FOV = 220 mm and acquired matrix = 192 x 186.

2.2 Preprocessing

A first step in the proposed framework is the masking of non-brain tissues in all images in the database. The Brain Extraction Tool (BET) is used [7] to remove all non-brain tissue in each image. Then, images were corrected for intensity inhomogeneity using the N4 algorithm [8].

2.3 Image Registration

For a given pair of images, image registration is carried out in two steps: first, a global transformation is estimated using affine registration; second, a non-rigid registration step is carried out using the result of the affine registration as the initial transformation. After registration, the obtained transformation maps locations in the target image to locations in the source image. The non-rigid deformations are obtained using the free-form deformation (FFD) model proposed by Rueckert et al. [9] with normalized mutual information as the similarity metric.

2.4 Spatio-temporal Atlases

Spatio-temporal atlases with anatomical snapshots at close time-points can aid the longitudinal registration process because they provide information about the missing anatomical evolution between two scans taken over large time-interval. Recently, we constructed a spatio-temporal atlas [1] of the developing brain from 204 neonatal subjects aged $26 - 44$ weeks PMA at time of scan [10]. This spatio-temporal atlas has greater anatomical definition than currently available atlases created using various affine and non-rigid registration approaches. Furthermore, the atlas has a dense temporal sampling of evolution as it provides average anatomical templates at every week between 28 and 44 weeks of PMA. As the variation between a template at a specific time-point and its temporal neighboring template tends to be small, this allows more precise registrations between the average template at any given time and its temporal neighbors (see Fig. 1). Therefore, the atlas can be used to develop an approach to carry out longitudinal registrations via atlas propagation as described in the next subsection.

2.5 Longitudinal Registration Framework

The longitudinal registration of intra-subject images requires the registration of 3D volumes of of the same subject taken at different time points. Given a pair of images ($\mathcal{S}_1$) ($\mathcal{S}_2$) which show the anatomy for subject $\mathcal{S}$ at two different time-points, we aim to find a transformation $\mathbf{T}_{S_2,S_1}$ which maps every location in $\mathcal{S}_2$ to $\mathcal{S}_1$. As both images may have been acquired over a large period of time (on average the time period between scans is 10.33 weeks) for the cohort studied, direct registration between $\mathcal{S}_1$ and $\mathcal{S}_2$ is very difficult and often leads to poor registration results. This is because the anatomical variation between both scans is large (due to the rapid evolution of brain in the neonatal period [1]), and it is difficult for the registration algorithm to capture it. We propose to solve this longitudinal registration problem using algorithm 1.

Algorithm 1 starts by estimating a mean deformation field to register $\mathcal{S}_1$ to $\mathcal{S}_2$. This is performed by mapping the subject's image at earlier time-point ($\mathcal{S}_1$) to the atlas coordinates,

[1] http://www.brain-development.org

Algorithm 1: The LISA Algorithm

Input : Two intra-subject images $\mathcal{S}_1$ and $\mathcal{S}_2$.
Output: A transformation $\mathbf{T}_{\mathcal{S}_2,\mathcal{S}_1}$ which maps $\mathcal{S}_2$ (target) to $\mathcal{S}_1$ (source).

begin
Let $\mathcal{A}_1$ and $\mathcal{A}_N$ to represent the closest atlas templates to $\mathcal{S}_1$ and $\mathcal{S}_2$, respectively.
Compute the composed transformation from $\mathcal{A}_1$ to $\mathcal{A}_N$ via the spatio-temporal atlas growth model,
$\mathbf{T}_{\mathcal{A}_N,\mathcal{A}_1} = \mathbf{T}_{\mathcal{A}_N,\mathcal{A}_{N-1}} \circ \cdots \circ \mathbf{T}_{\mathcal{A}_2,\mathcal{A}_1}$.
Transform $\mathcal{S}_1$ to the atlas coordinates, deform it with the atlas mean growth model, and transform it back to $\mathcal{S}_2$ coordinates,
$\tilde{\mathbf{T}}_{\mathcal{S}_2,\mathcal{S}_1} = \mathbf{T}_{\mathcal{S}_2,\mathcal{A}_N} \circ \mathbf{T}_{\mathcal{A}_N,\mathcal{A}_1} \circ \mathbf{T}_{\mathcal{A}_1,\mathcal{S}_1}$.
Register $\mathcal{S}_1$ to $\mathcal{S}_2$ using $\tilde{\mathbf{T}}_{\mathcal{S}_2,\mathcal{S}_1}$ to drive the registration process.
end

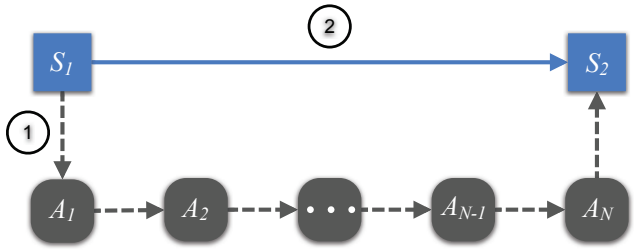


Fig. 2: The proposed framework for longitudinal image registration using spatio-temporal atlases, aka LISA.

transform it to the later time-point using the atlas 4D deformation model, and then map it back to the subject's coordinates at the later time-point ($\mathcal{S}_2$) as seen in Fig. 2. Then, the composed transformation from the previous step is used to initialize the registration between the intra-subject images $\mathcal{S}_1$ and $\mathcal{S}_2$.

3 Results

Figure 3 shows the result of registering $\mathcal{S}_1$ to $\mathcal{S}_2$. The figure shows different subjects with different time-intervals between the two scans. The direct registration between $\mathcal{S}_1$ and $\mathcal{S}_2$ works well when the time-interval is quite small (< 6 weeks), however the direct registration peforms poorly when the time-interval increases. On the other hand, registering $\mathcal{S}_1$ and $\mathcal{S}_2$ using LISA yields a better result as shown in the fourth column of the figure.

Since the assessment of the quality of any registration approach is a challenging problem, no metric alone is sufficient to evaluate the performance of a registration approach. However, using information from different metrics will provide a good indication of the registration performance. Therefore, we have included the following metrics: (1) intensity similarity measures and (2) segmentation overlap.

3.1 Intensity-based Evaluation

We have carried out this experiment using the 50 subjects with intra-subject scans over different time-intervals. $\mathcal{S}_1$ was registered separately to $\mathcal{S}_2$ using direct registration and LISA.

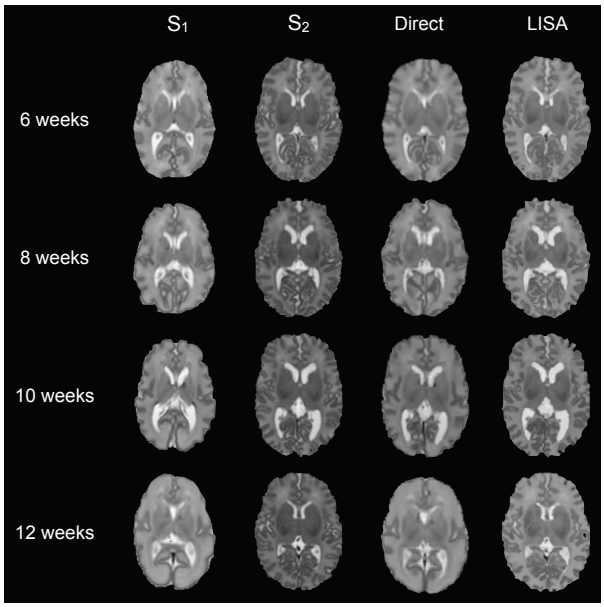


Fig. 3: Visual comparison of the results from direct registration versus the results from LISA. Exemplary slices from different subjects with different time-intervals are shown.

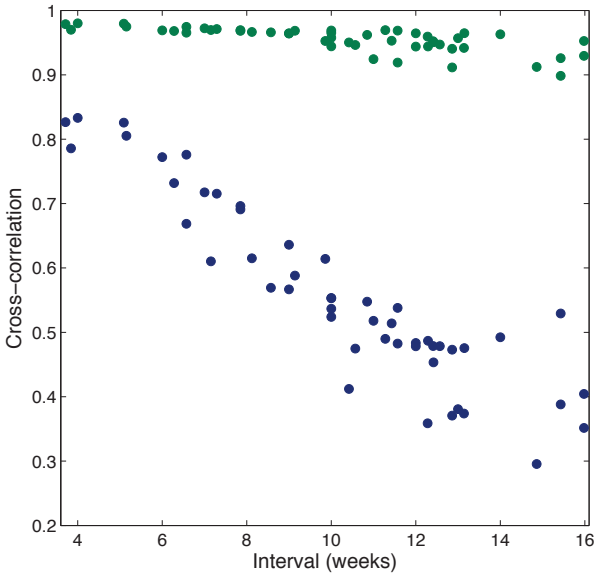


Fig. 4: Time-interval is plotted against cross-correlation measure between registered $\mathcal{S}_1$ and $\mathcal{S}_2$ images using LISA in green and direct registration in blue.

Cross-correlation was then used to quantify the degree of similarity between the two registered images.

Using LISA, registered $\mathcal{S}_1$ and $\mathcal{S}_2$ share high similarity regardless of the time-interval between both images. In contrast, directly registered $\mathcal{S}_1$ and $\mathcal{S}_2$ share lower similarity and it is affected strongly by the time-interval increase between the two scans. This is shown in Fig. 4 where the time-interval

is plotted against cross-correlation.

3.2 Segmentation-based Evaluation

The alignment of the regions of interest (ROIs) is also a good indicator of how well two images are registered. The Dice overlap coefficient is a measure of how well two corresponding segmented regions agree with each other. The Dice overlap coefficient is defined as

$$D(X,Y) = \frac{2|X \cap Y|}{|X|+|Y|}$$

where X and Y are two corresponding segmentations. In our case, X corresponds to a segmentation transformed from image $\mathcal{S}_1$ to $\mathcal{S}_2$ compared to the corresponding segmentation Y defined in image $\mathcal{S}_2$.

The registered $\mathcal{S}_1$ and $\mathcal{S}_2$ images of 50 subjects were segmented using probabilistic atlas priors [11] into five different brain structures: white matter (WM), cortex, brainstem, cerebellum, and deep gray matter (DGM). Table 1 shows the Dice coefficient (averaged over all subjects) for different segmented brain structures after registration using direct registration and LISA, separately. The Dice coefficient is lower when using direct registration than the Dice coefficient when the registration is performed using LISA. This is true for all segmented brain structures, however, the difference is more pronounced for complex structures such as cortex.

Table 1: Dice overlaps for segmentations.

	WM	Cortex	Brainstem	Cerebellum	DGM
Direct	0.77±0.07	0.71±0.10	0.91±0.02	0.92±0.01	0.93±0.01
LISA	**0.86±0.04**	**0.83±0.05**	**0.94±0.01**	**0.94±0.01**	**0.95±0.01**

4 Discussion

We have presented a novel framework for longitudinal registration which can accommodate large intra-subject anatomical variations, and is therefore useful for studying the brain in early development. An advantage of our framework is that is uses spatio-temporal atlases that are freely available [*www.brain-development.org*]. In contrast to this, the method proposed in Hamm et al. [3] requires very large study population.

LISA outperforms direct registration by providing an accurate and consistent registration, particularly when the time-interval between scans increases. The quantitative assessment showed that LISA provides registered images which share a high degree of similarity and better overlap when compared with direct registration, regardless of the time-interval between images.

In conclusion, the longitudinal image registration via spatio-temporal atlases method, which has not been used previously for registration of MR images, appears appropriate for use in intra-subject analysis of brain MR images, particularly when the intra-subject scans are acquired over a large time-interval.

5 References

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