

# IMAGE REGISTRATION AND SEGMENTATION IN LONGITUDINAL MRI USING TEMPORAL APPEARANCE MODELING

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## ABSTRACT

With increasing use of subject-specific longitudinal imaging for assessment of development, degeneration and disease progression, there is a clear need for image analysis segmentation/registration tools dedicated to 4D image time series. Previous work has mostly focused on temporal modeling of geometric deformations and shape changes, assuming that image intensity changes can be normalized. However, in studies of early infant development or aging, e.g., we encounter low contrast and appearance alterations due to tissue property changes which pose challenges to temporal registration and 4D segmentation. The two problems are linked since registration can be solved if appearance changes are accounted for, and 4D segmentation requires registration of image time series. In this paper, we propose to integrate a temporal appearance change model into diffeomorphic registration thus accounting for such variations, where voxel-wise intensity model parameters are calculated from temporal image coregistration. Moreover, we demonstrate a novel 4D segmentation of co-registered images that uses local intensity change rather than intensity itself for Gaussian mixture model. Both methods can be seen as two stages of an integrated registration/segmentation framework for 4D time-discrete image data making use of the same underlying model of longitudinal appearance changes. We demonstrate feasibility of the new approach with validation on longitudinal, multimodal pediatric MRI of infants in the age range neonates to 24 months.

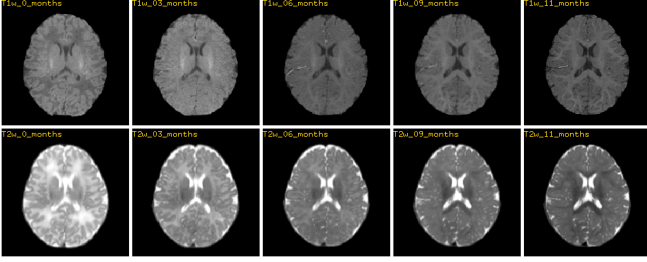
**Index Terms**— Temporal appearance modeling, 4D segmentation

## 1. INTRODUCTION

Longitudinal image analysis of MR images plays an important role in studying the trajectory of normal brain development, degeneration patterns of aging brains, and monitoring disease progression and therapeutic intervention. Accurate and consistent tools for longitudinal segmentation and registration are necessary requirements for many clinical applications. Current methodologies do not fully solve the significant challenges related to temporal variations in image appearance

due to differences in scanner calibrations, global or local tissue changes related to development or aging, and appearance variations related to disease.

Previous work reflects a variety of approaches to address these difficulties. Xue et al. [1] propose image-adaptive clustering, spatiotemporal smoothness constraints, and image warping to jointly segment single subject serial MRI to achieve consistent longitudinal alignment and segmentation. The clustering objective function treats the spatially and temporally adaptive smoothness constraints in a similar manner despite significant differences across space and time. Shi et al. [2] take advantage of the fact that MRI presents improved tissue contrast at older ages and proposed the use of a subject-specific tissue probability atlas to guide segmentation at earlier time points along with iterative bias correction. Niethammer et al. [3] propose a geometric metamorphosis formulation to explain changes in image appearance by a composition of a global deformation and a deformation of a geometric model. Csapo et al. [4] model longitudinal intensity changes explicitly and propose a model-based image similarity measure for longitudinal image registration in the presence of spatially non-uniform intensity changes. Reuter et al. [5] introduce a longitudinal analysis framework based on unbiased within-subject template creation to avoid processing bias, over-regularization and build workflow on FreeSurfer to get the capacity of producing a large variety of reliable imaging statistics. Prastawa et al. [6] present a framework for construction of subject-specific longitudinal anatomical models including joint segmentation, registration, and personalized atlas building, with individual Gaussian mixture model per time point to account for temporal contrast differences. Regularization over time is achieved via kernel smoothing of the longitudinal subject-specific tissue probability atlas. Kim et al. [7] focus on brain maturation and related contrast changes and developed a spatial intensity growth map (IGM), which was computed as the coefficient of a voxel-wise linear regression model, to compensate for white matter intensity inhomogeneity. Gao et al. [8] work on temporal intensity change modeling via voxel-wise intensity Gaussian smoothing based on aligned image series and



**Fig. 1.** Clinical pediatric scans at ages 0, 3, 6, 9, and 11 months (from left to right) after affine alignment. Axial slices are shown for T1W (top row) and T2W (bottom row) images.

provide a joint 4D segmentation and appearance modeling.

Most of the previously reported work relies on geometric deformation modeling which suffers difficulties related to low contrast common in longitudinal pediatric MRI (Fig. 1). We propose a novel joint temporal appearance and deformation model to account for intensity changes due to tissue property alterations and geometric deformations resulting from brain growth. We also demonstrate that the temporal appearance model can be used for 4D image segmentation, a task which is difficult for infant MRI at ages where contrast vanishes (mark in Fig. 2 with a black ellipse).

## 2. METHOD

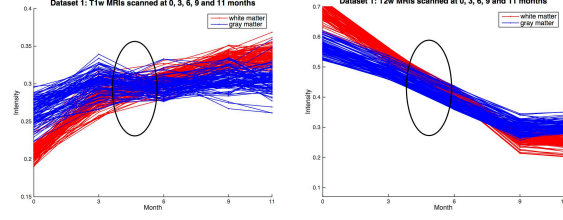
Let us consider a longitudinal MRI sequence of a single subject acquired at multiple time points. There may be large variation among the image series, so we firstly eliminate bias artifacts associated with MRI acquisition for each image, then apply affine transformations to co-register the image series. For temporal consistency, we adjust all images in a time series to be at the same intensity level. The central ventricular CSF area shows image intensity stability over time, so we choose the average value within this region for a reference to apply temporal intensity normalization. Finally, we have a pre-processed sequence of MRI images:  $I^t = \{I^t(x) : x \in \mathbb{R}^3\}$ , where  $t \in \{1, \dots, T\}$ .

### 2.1. Temporal appearance model

The choice of temporal appearance model should depend upon the application. Fig. 2 shows typical intensity change over time for pediatric MRI of infants and it suggests that a linear model would be a good candidate for this application. In this section, we assume images are co-registered, for each voxel  $x$ , the intensity model with respect to time  $t$  is as follows:

$$f(t, x) = w(x)t + b(x) , \quad (1)$$

where  $w(x)$  is the slope and  $b(x)$  is the intercept in linear intensity model for voxel located at  $x$ .



**Fig. 2.** Voxel-wise intensity changes over time in gray and white matter regions of interest shown for T1w and T2w images after registration.

### 2.2. Diffeomorphic temporal registration

In this section, for notation simplicity, we omit parameter  $x$  in the temporal intensity model and notate  $f(t, x)$  as  $f^t$ . Our goal is that after successful image registration, the intensity model parameters would provide a closer fit to the images at each time point. Via the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework [9], given a sequence of images,  $I^t \in L^2(\Omega, \mathbb{R})$  where  $t \in \{1, \dots, T\}$ , we define the following energy function:

$$E(\phi^t) = \sum_{t=1}^T \frac{1}{2\sigma^2} \|f^t \circ (\phi^t)^{-1} - I^t\|^2 + (Lv_0^t, v_0^t) . \quad (2)$$

Here  $\sigma^2$  represents noise variance, and the  $v_0^t \in L^2([0, 1], V)$  is the initial velocity field (for time point  $t$ ) in reproducing kernel Hilbert space  $V$  equipped with metric  $L : V \rightarrow V^*$ , a positive-definite, self-adjoint and differential operator, which maps  $V$  to its dual space  $V^*$ . The notation  $(m, v)$  denotes the pairing of a momentum vector  $m \in V^*$  with a tangent vector  $v \in V$ . The deformation  $\phi^t$  is defined as the integral flow of  $v^t$ . To clarify our notation, subscript  $t$  is used for the time variable in the time-varying velocity field, for example,  $v_t : [0, 1] \rightarrow V$ , however, superscript  $t$  is used for the index of discrete time point in sequence MR images. The geodesics that minimize the energy function Eq. 2 are characterized by the following EPDiff equation:

$$\frac{\partial v}{\partial t} = -K \text{ad}_v^* m = -K[(Dv)^T m + Dm v + m \text{div} v] , \quad (3)$$

where  $D$  denotes the Jacobian matrix, operator  $\text{ad}^*$  is the dual of the negative Lie bracket of vector fields, and  $\text{ad}_v w = [v, w] = Dvw - Dwv$ .

### 2.3. Joint estimation of model parameters

Integrating the temporal appearance model (Eq. 1) with diffeomorphic temporal registration (Eq. 2), the objective function for registration with temporal appearance model is defined as follows:

$$\mathcal{F} = \sum_t \frac{1}{2\sigma^2} \|(wt + b) \circ (\phi^t)^{-1} - I^t\|^2 + (Lv_0^t, v_0^t) . \quad (4)$$

Minimizing this objective function (Eq. 4), by taking derivative and applying the chain rule (e.g.  $\frac{\partial \mathcal{F}}{\partial f^t} \frac{\partial f^t}{\partial w}$ ), gives closed-form solutions for  $w$  and  $b$  with respect to  $\phi^t$  as follows:

$$w = \frac{YP - XQ}{Y^2 - XZ}, \quad b = \frac{YQ - ZP}{Y^2 - XZ} \quad (5)$$

where

$$X = \sum_t |D\phi^t|, \quad Y = \sum_t t|D\phi^t|, \quad Z = \sum_t t^2|D\phi^t|,$$

$$P = \sum_t I^t \circ \phi^t |D\phi^t|, \quad \text{and} \quad Q = \sum_t tI^t \circ \phi^t |D\phi^t|.$$

Please note that in this novel framework, the voxel-wise intensity change model's parameters  $w$  and  $b$  are estimated together with the deformation fields  $\phi^t$  from the diffeomorphic registration framework.

#### 2.4. 4D Segmentation

After registration with temporal appearance model, images are co-registered across time and each voxel's intensity is a function over time, then we can use these model parameters, which represents the set of longitudinal images, for tissue segmentation. In the case of linear intensity model (Eq. 1), these are slope and intercept parameters. For the segmentation based on the intensity model's parameters, we model each class  $c \in \{1, \dots, C\}$  by a normal distribution with parameters  $\Theta_c = \{\mu_c, \Sigma_c\}$ , where  $\mu_c$  is the mean and  $\Sigma_c$  is the covariance. The joint probability of the intensity model's parameters  $\{w(x), b(x)\}$  attributed to class  $c$  is  $p(\{w(x), b(x)\} | \Gamma_x = c; \Theta_c) = \mathcal{N}(\{w(x), b(x)\}; \Theta_c)$ , where  $\mathcal{N}$  is the normal density function.

Given the prior probability of the voxel  $x$  belongs to class  $c$  via atlas, i.e.  $p(\Gamma_x = c) = A_c(x)$ , by the law of total probability:  $p(\{w(x), b(x)\}; \Theta) = \sum_c A_c(x) \mathcal{N}(\{w(x), b(x)\}; \Theta_c)$ , which is a mixture of normal distributions, and  $\Theta$  represents all parameters of normal distributions.

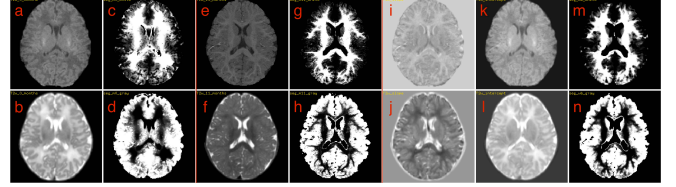
Assuming the slope  $w(x)$  and intercept  $b(x)$  from the temporal intensity model of a longitudinal image sequence are statistically independent over space, the likelihood function is given by the mixture of normal models

$$\begin{aligned} \mathcal{L}(\Theta) &= p(w, b; \Theta) = \prod_x p(\{w(x), b(x)\}; \Theta) \\ &= \prod_x \sum_c A_c(x) \mathcal{N}(\{w(x), b(x)\}; \Theta_c). \end{aligned} \quad (6)$$

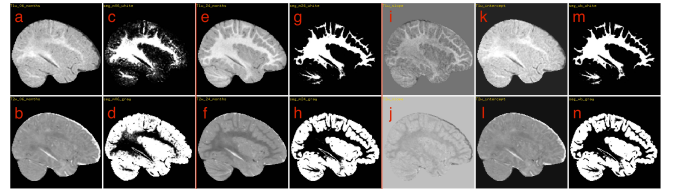
### 3. RESULTS AND DISCUSSION

We use two datasets to evaluate our model: both of them are multimodal (T1w and T2w) pediatric brain MRI of infants. Dataset 1 contains scans from 0, 3, 6, 9 and 11 months and Dataset 2 contains scans from 6, 12 and 24 months. Axial

sections from Dataset 1 are shown in Fig. 1. For the temporal appearance model, we apply the linear model (Eq. 1). For the registration, we use diffeomorphic registration (Eq. 2). Due to the inherent challenge for experts to label such complex, multimodal data, instead of comparing with ground truth, we use well-accepted EM segmentation for Gaussian mixtures with atlas priors [10] as the baseline to compare with our results.



**Fig. 3.** Dataset 1 in axial view: a, b are T1w and T2w MRI from 0 month, c, d are the baseline white and gray tissue segmentations based on a, b; e, f are T1w and T2w MRI from 11 months, g, h are the baseline white and gray tissue segmentations based on e, f; i, j are estimated voxel-wise slope parameters based on T1w and T2w longitudinal images; k, l are estimated voxel-wise intercept parameters based on T1w and T2w longitudinal images; m, n are the white and gray tissue segmentations based on i, j, k, l.



**Fig. 4.** Dataset 2 in sagittal view: a, b are T1w and T2w MRI from 6 month, c, d are the baseline white and gray tissue segmentations based on a, b; e, f are T1w and T2w MRI from 24 months, g, h are the baseline white and gray tissue segmentations based on e, f; i, j are estimated voxel-wise slope parameters based on T1w and T2w longitudinal images; k, l are estimated voxel-wise intercept parameters based on T1w and T2w longitudinal images; m, n are the white and gray tissue segmentations based on i, j, k, l.

In Fig. 3 and Fig. 4, the slope images (i, j) show clear boundaries between brain tissue, which implies different intensity change speed over time. The intercept images (k, l) represent the temporal intensity model at time  $t = 0$ . The segmentation results (c, d), by using only the first time point (a, b), show that without proposed 4D segmentation, the neonate MRIs are difficult to be segmented. We clearly observe that our proposed longitudinal 4D segmentations (m, n) using temporal intensity models provide tissue segmentations, which are qualitatively very close to the EM segmentations (g, h) of the final time point, whereas they are significantly better than the single time point segmentations (c, d) before

the final time point. These results are interesting since we do not use image intensities but solely intensity change profiles to differentiate the different tissue classes.

#### 4. CONCLUSIONS

This paper presents work towards a new framework for joint registration/segmentation of longitudinal time series, with a particular focus on image data where we observe intensity changes over time. Unlike most tissue segmentation methods that assume a clear separation of intensity distributions per class, we explore the potential to classify tissue types via their differences in temporal intensity change patterns, i.e. to use the parameters of temporal functions of intensity rather than the intensities themselves for classification. Such an approach requires accurate registration of serial images, which itself is challenging in the presence of appearance changes. In the spirit similar to Csapo et al. [4], but instead of iterative optimization for elastic deformation, we integrate local intensity change modeling into the image match function of group-wise LDDMM image registration and give a closed-form solutions of intensity model. Registration and segmentation use the same temporal intensity models, but are presented as separate processing steps. Calibration of intensities of the original MRI data is a necessary preprocessing step, so far performed using fatty tissue in T1w and fluid in T2w MRI. We currently explore automatic calibration across time following the proposed temporal intensity modeling scheme. Although the new 4D segmentations provide promising results, we will investigate higher-order models which may better fit expected appearance changes. This work is clearly motivated by the analysis of longitudinal infant neuroimage data where we encounter the well-known tissue contrast reversal and even disappearance over time, demonstrating that conventional 3D single time point segmentation is not feasible for some of the time points. The proposed 4D registration and segmentation concept results in a series of segmented datasets by applying the inverse mapping of segmentations into the original coordinate spaces, even including consistent mapping of brain parcellation templates. Beyond tissue segmentation, we also see the potential to analyze local patterns of the intensity model parameters to provide measurements on maturation speed patterns, quantitative information which is of great interest in pediatrics.

#### 5. REFERENCES

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