In this paper we present a variational probabilistic approach to the registration of brain white matter tractographies extracted from DT-MRI scans. Initially, the fibers are projected into a D-dimensional feature space based on the sequence of their spatial coordinates. The alignment of two fiber-sets is considered a probability density estimation problem, where one point-set represents Gaussian Mixture Model (GMM) centroids, and the other represents the data points. The transformation parameters are represented as spatially-dependent coefficients of the same invertible affine transformation model. The alignment term of the energy-function is minimized by maximizing the likelihood of correspondence between the data-sets while the smoothness term penalizes spatial changes in the coefficient functions. The energy-function, composed of the alignment and smoothness terms, is minimized using gradient descent optimization. Results of preliminary experiments on inter-subject full-brain data show improvement over global linear (affine) registration schemes.

Index Terms— DTI, Fibers, Registration, Gaussian mixture model, Variational methods

1. INTRODUCTION

Diffusion Tensor Magnetic Resonance Imaging (DT-MRI or DTI) is a relatively new but rather fast developing MR imaging modality, aiming to measure the diffusivity of water in tissue [1]. DT images are becoming widely used to investigate in vivo white matter (WM) microstructure and its changes in brain, including normal brain development, aging and pathological damages [2].

Based on the DTI tensor data, tractography algorithms allow reconstruction of the axonal tracts in the central nervous system (CNS) [3]. Presently it is the only approach available to noninvasively study the 3D architecture of white matter tracts. The increasing popularity of DT-MRI among brain researchers and clinicians has created the need for robust registration methods for white matter tractographies that allow for longitudinal (intra-subject) and population (inter-subjects) studies.

In previous works, registration was performed prior to the tractography, based on the scalar [4] or tensorial [5] level. Recently, a third approach was proposed in which registration is performed directly at the tractographic fibers level [6,7]. This approach has two main advantages: 1. the reconstructed WM fiber naturally inherits the directional information entailed in the diffusion tensors along its trajectory, 2. the voxels connectivity information augments the information available from the data-set. The extended connectivity information can increase robustness to noise.

In this work we propose a fiber-based piecewise-smooth affine registration method which improves on previous global affine methods, by providing the flexibility required to accommodate local inhomogeneities, while preserving a fixed and invertible transformation model. The registration task is presented as an energy minimization problem, balancing an alignment term with a smoothness term, within a variational framework.

The fibers are initially projected into a D-dimensional feature space based on the sequence of their 3D coordinates, so that each fiber is represented by a D-dimensional point. The alignment of two point-sets is considered a probability density estimation problem [8], where one point-set represents Gaussian Mixture Model (GMM) centroids, and the other point-set represents the data points. The alignment term is minimized by maximizing the likelihood of correspondence between the two fiber-sets.

The transformation parameters at each voxel are represented by different coefficients of the same transformation model, affine in our case. Such an over-parameterized representation has the advantage that the smoothness term may now penalize deviations from the transformation model instead of directly penalizing the changes in displacement vectors [9]. For example, in an affine model, if the transformation in a region can be accurately represented by an affine model, then in this region there will be no regularization penalty. While the alignment term measures the likelihood of correspondence between D-dimensional point-sets, the smoothing term measures changes of the transformation parameters in 3D.

The rest of the paper is organized as follows: In section 2 we describe the theory & implementation of the proposed algorithm. In section 3 we perform validation on inter-
subject registration, and give both visual and quantitative results. We conclude with a discussion in section 4.

2. METHODS

2.1. Over-Parameterization Model

Based on [9], we represent the transformed spatial coordinates by the general over-parameterized model:

\[ \begin{align*}
\hat{x}(x, y, z) &= \sum_{i=1}^{n} \phi_i(x, y, z)\theta_i, \\
\hat{y}(x, y, z) &= \sum_{i=1}^{n} \phi_i(x, y, z)\eta_i, \\
\hat{z}(x, y, z) &= \sum_{i=1}^{n} \phi_i(x, y, z)\mu_i,
\end{align*} \tag{1} \]

where \( \phi_i, \eta_i \) and \( \mu_i \) are basis functions of the transformation scheme, and \( A_i \) are varying coefficients of the model. The basis functions are fixed and selected a-priori. The coefficients are the unknown functions we solve for in the registration process. Appropriate basis functions are selected such that the true spatial transformation could be described by piecewise constant coefficients, so that most of the local changes of the transformation are induced by changes in the basis functions and not by variations of the coefficients. This way, regularization applied to the coefficients becomes meaningful since major parts in the transformation variations can be described without changes of the coefficients.

The affine model is a good approximation of the transformation in large regions in many scenarios. We therefore use it for our method, where each voxel has “its own” independent affine model parameters. For the 3D affine model, we choose the following basis functions:

\[ \begin{align*}
\phi_i &= x, \quad \phi_i = y, \quad \phi_i = z, \quad \phi_i = 1, \quad \phi_i = 0, \quad i \neq 1..4, \\
\eta_i &= x, \quad \eta_i = y, \quad \eta_i = z, \quad \eta_i = 1, \quad \eta_i = 0, \quad i \neq 5..8, \\
\mu_i &= x, \quad \mu_i = y, \quad \mu_i = z, \quad \mu_i = 1, \quad \mu_i = 0, \quad i \neq 9..12.
\end{align*} \tag{2} \]

This leads to the following representation of the transformed coordinates:

\[ \begin{bmatrix} \hat{x} \\ \hat{y} \\ \hat{z} \end{bmatrix} = \begin{bmatrix} \phi_1(k) & \phi_2(k) & \phi_3(k) & \phi_4(k) \\ \eta_1(k) & \eta_2(k) & \eta_3(k) & \eta_4(k) \\ \mu_1(k) & \mu_2(k) & \mu_3(k) & \mu_4(k) \end{bmatrix} \begin{bmatrix} x \\ y \\ z \\ 1 \end{bmatrix}. \tag{3} \]

Where \( k \) denotes the spatial coordinates \((x, y, z)\).

Our effort will focus on estimating the parameters values across the volume, using a data similarity (alignment) measure and a regularization (or smoothness) measure that quantifies the smoothness of the parameters field. An energy function composed of both measures will be presented later and minimized to achieve our goal.

2.2. Alignment Term

The alignment of two point-sets is considered a probability density estimation problem [8], where one point-set represents Gaussian Mixture Model (GMM) centroids, and the other point-set represents the data points. The alignment term is minimized by maximizing the likelihood of correspondence between the data-sets. Throughout this section we use the following notations:

- \( D \) – dimension of the point sets
- \( N_T, N_M \) – number of points in the point sets
- \( M_{N_T, D} = (m_{1}, m_{2}, \ldots, m_{N_T}) \) – the 1st point set (the GMM centroids)
- \( T_{N_M, D} = (t_1, t_2, \ldots, t_{N_M}) \) – 2nd point set (the data points)
- \( A \) – 3D field, where each voxel represents a set of 12 affine transformation parameters.
- \( \Gamma(A) \) – Transformation \( \Gamma \) applied to \( A \), where \( A \) is a set of the transformation parameters
- \( M_0 \) – initial locations of the GMM centroids

Consider the points in \( M \) as the GMM centroids, and the points in \( T \) as the data points generated by the GMM. The probability density function of a D-dimensional point \( t_i \) is:

\[ p(t_i) = \sum_{j=1}^{N_M} P(m_{j}) p(t_i | m_{j}) \tag{4} \]

where all GMMs are considered to have equal probability \( p(m_{j}) = 1/N_M \). Also, since \( m_{j} = \Gamma(m_{j}; A) \), we can express Eq. 4 as:

\[ p(t_i; A) = \sum_{j=1}^{N_M} P(m_{j}) p(t_i | m_{j}; A) \tag{5} \]

where:

\[ p(t_i | m_{j}; A) = \frac{1}{(2\pi\sigma^2)^{D/2}} \exp \left( -\frac{\| t_i - \Gamma(m_{j}; A) \|^2}{2\sigma^2} \right) \tag{6} \]

for \( j=1,2,\ldots,N_M \) and we assume equal isotropic variances \( \sigma^2 \). We also add to the mixture-model an additional uniform distribution to account for noise and outliers:

\[ p(m_{N_M+1}) = w, \quad p(t_i | m_{N_M+1}) = \frac{1}{C} \tag{7} \]

where \( w \) (0.1 in our experiments) denotes the probability of outliers or noise, and \( C \) denotes the volume of the hyperspace encompassing all possible values of the D-dimensional points.

The likelihood of a scene given a set of estimated transformation parameters \( A \) is given by:

\[ L(A, \sigma^2) = \prod_{i=1}^{N_T} \sum_{j=1}^{N_M+1} P(m_{j}) p(t_i | m_{j}; A) \tag{8} \]

That is equivalent to matching (in the ML sense) of \( N_T \) Gaussians to \( N_T \) points. Here, \( A \) parameterizes the GMM centroids new position in the D-dimensional space. Maximizing the likelihood function is equivalent to minimizing the negative log-likelihood function:

\[ E(A, \sigma^2) = -\sum_{i=1}^{N_T} \log \left( \sum_{j=1}^{N_M+1} P(m_{j}) p(t_i | m_{j}; A) \right) \tag{9} \]
Since our D-dimensional points-sets are actually a concatenation of three-dimensional spatial coordinates, D/3 in length, we can obtain the alignment term in the form of a volumetric integral:

\[
E_D = -\sum_{j=1}^{N} \log \frac{(1-w)}{N} \cdot \left( \frac{1}{2\pi\sigma^2} \right)^{\frac{D}{2}} \cdot \sum_{k} \exp \left( -\frac{1}{2\sigma^2} \sum_{l=1}^{D/3} \left[ \left( x_l^j - \Gamma(m_l^j, A(k)) \right)^2 \right] \right) \delta(k - m_l^j(d)) \cdot d_k
\]  

(10)

where \( k \) represents spatial coordinates \((x,y,z)\) and \( m_l^j(d) \) is the coordinates of point \( d \) along the trajectory of fiber \( m_l^j \). Minimizing \( E_D \) will achieve maximum data-sets alignment.

2.3. Smoothness Term

The proposed smoothness measure [9] penalizes changes in the coefficient functions, measured by a volume integral:

\[
E_s = \int \psi \left( \sum_{l=1}^{D/3} \left| \nabla A_{lq} \cdot (k) \right|^2 \right) \cdot d_k
\]  

(11)

where:

\[
\psi(s^2) = \sqrt{s^2 + \epsilon^2}
\]  

(12)

Maximum spatial parameters smoothness is achieved by minimizing \( E_s \).

2.4. Variational Solution

The solution to the registration problem should minimize the (weighted) sum of the alignment and smoothness measures:

\[
E = E_D + \alpha E_s
\]  

(13)

at every spatial location \((x,y,z)\) and for every transformation parameter \( A_{lq} \). The Euler-Lagrange equation for the alignment-term is:

\[
\frac{\partial E_D}{\partial A_{lq}}(k) = \sum_{j=1}^{N} \left( \frac{1}{N\sigma^2} \sum_{i=1}^{D/3} \rho(t_l) \cdot p(t_l | m_j) \cdot \sum_{d=1}^{D/3} \left[ m_l^j(d) - \Gamma(m_l^j(d), A(k)) \right] \cdot \delta(k - m_l^j(d)) \right)
\]  

(14)

where the notation \( l=1,2,3 \) at the fiber descriptors stands for the spatial coordinates \( x,y,z \) respectively, and for rows 1,2,3 at the local affine matrix \( A(k) \). For \( q=4 \) we drop the \( m_l^j(d)_q \) term.

The Euler-Lagrange equation for the smoothness-term is:

\[
\frac{\partial E_s}{\partial A_{lq}}(k) = -\text{div} \left( \psi \left( \sum_{i=1}^{D/3} \left| \nabla A_{lq} \cdot (k) \right|^2 \right) \cdot \nabla A_{lq} \right)
\]  

(15)

2.5. Preprocessing

The fibers generated by a tractography software are represented by variable length sequences of 3D coordinates. Each fiber is therefore re-sampled at 20 equally spaced points along its trajectory, creating a constant length representation. The number of sampling points is an empirical compromise between dimensionality and fidelity to the original representation [6]. The concatenation of the resulting \((x,y,z)\) samples generates a 60x1 feature vector. Fibers shorter than 10mm are removed since most of them correspond to artifacts located outside the brain.

2.6. Algorithm Steps

The algorithm has 5 main stages, which are repeated in a loop for a fixed number of iterations:

1. Calculate the probability function \( p(t_l | m_j) \) for every target fiber \( i \) and model fiber \( j \). Probabilities which are below a certain threshold are ignored to reduce computation time.
2. Calculate the Euler-Lagrange functions for the alignment & smoothing terms.
3. Find better estimation of the \( A \) parameters using gradient-descent optimization:

\[
A_{lq}(k)_{t+1} = A_{lq}(k)_t - \Delta \cdot \frac{\partial E}{\partial A_{lq}}(k)
\]  

(16)

Where \( t \) is the iteration number and \( \Delta \) is a fixed small step size used to control the rate of divergence.

4. Transform the model point-set according to the latest \( A \) parameters.
5. Decrement \( \sigma^2 \) by a small factor.

3. EXPERIMENTS & RESULTS

We present initial results for inter-subject DTI data. Real brain DTI data of 15 normal subjects was downloaded from Johns Hopkins Medical MRI Laboratory website [10]. Each brain is represented by 50-55 axial slices with a voxel size of 1x1x2.6 mm in the \( x,y \), and \( z \) directions, respectively. Full brain tractographies were generated using DTIstudio [11]. An average count of 100K fibers per brain was measured after pre-processing. To reduce computation complexity, each fiber-set was down-sampled by a ratio of 50. Furthermore, the 3D voxel space was divided by a factor of \( 10^3 \), increasing the granularity of the piecewise model.

The experiment included matching brains 1-3 to brains 4-15 (total of 36 experiments). Initially, the model data-set was registered to the target using ICF – the global fiber-based method described in [6]. The warped model data-set was used as starting point for our method. The algorithm’s performance is evaluated both by calculating the mean square error (MSE) between the warped model and the target fiber sets and by visual inspection of the results. To evaluate the improvement over global registration, we calculated Residual MSE (RMSE):

\[
RMSE(t) = 100 \times \frac{\text{local method MSE at iteration } t}{\text{global method final MSE}}
\]  

(17)
Fig. 1 presents RMSE averaged over all the experiments as a function of iteration number. Two examples, demonstrating full brain inter-subject fiber-set registration using our algorithm, are shown in Fig. 2.

![Fig. 1. RMSE (see Eq. 17) as a function of iteration number.](image)

![Fig. 2. The two columns shows examples of registering same model brain (blue) to two different target brains (red), shown in sagittal view. Top to bottom: before registration, after global registration, after registration using our method. Colored rectangles mark regions where the local method shows visually significant improvements.](image)

4. CONCLUSIONS & DISCUSSION

This paper proposes a method for direct non-linear yet invertible registration of brain WM fiber-sets. The main advantage of performing registration at the fibers level rather than at voxels or tensors level is the connectivity information entailed in the fiber representation.

The proposed piecewise-affine registration method improves on previous global affine methods by providing the flexibility to accommodate local inhomogeneities, and yet adheres to a fixed and invertible transformation model. The registration task, solved as an energy minimization problem within a variational framework, allows a fine balance between the point-sets alignment weight relative to the parameters smoothness weight.

Our algorithm was tested on inter-subject real-brain data, demonstrating an average of ~17% accuracy improvement over a global affine method. In future work we plan to optimize the algorithm parameters, investigate their influence on registration results, and investigate possible contribution to the task of automatic brain fiber-tracts segmentation, both for healthy and non-healthy subjects.

5. REFERENCES


