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Active Fibers: Matching Deformable Tract Templates to Diffusion Tensor Images

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Abstract

Reliable quantitative analysis of white matter connectivity in the brain is an open problem in neuroimaging, with common solutions requiring tools for fiber tracking, tractography segmentation and estimation of intersubject correspondence. This paper proposes a novel, template matching approach to the problem. In the proposed method, a deformable fiber-bundle model is aligned directly with the subject tensor field, skipping the fiber tracking step. Furthermore, the use of a common template eliminates the need for tractography segmentation and defines intersubject shape correspondence. The method is validated using phantom DTI data and applications are presented, including automatic fiber-bundle reconstruction and tract-based morphometry.

Keywords

diffusion tensor imaging; DTI tractography; template matching; deformable curve evolution

1 Introduction

Diffusion tensor magnetic resonance imaging (DT-MRI) is a relatively new technique that measures diffusion of water molecules in tissue [1]. This modality has become particularly important in neuroimaging, since it offers insight into the *in vivo* properties of the white matter (WM) tissue in the brain, and thus can help study connectivity of WM axons in human subjects. The relevance of DT imaging to such studies stems from the fact that, in axons, water molecules diffuse faster along the axonal directions than across their membranes. Thus, modeling water diffusion in each voxel (which is done in DT-MRI using a second-order tensor) provides a certain indication of the local orientation of the neural fibers in that voxel. The problem of tractography consists of inferring the complete shapes of those fibers based on local diffusion measurements [2–5]. In the simplest setting, these measurements are typically reduced to the principal eigenvectors of the diffusion tensors [2,3].

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Still, reliable reconstruction of the neural fibers remains an open problem in neuroimaging. Importantly, accurate inference at the individual axon level is fundamentally infeasible due to the low resolution of today's DT-MR images. In fact, the very notion of accuracy is ill-posed in this context, since precise validation is typically impossible due to the lack of ground truth data for human subjects. As a result, there is no gold standard in tractography algorithms to date. The most commonly used DTI streamline methods [2,3] suffer from several notorious shortcomings, such as the ambiguity of the diffusion tensor model with several fibers crossing a single voxel (partial volume effects) and early termination of fibers, due to low fractional anisotropy (FA) and curvature thresholds. Furthermore, fiber tractography alone, although instrumental for visualization, has only a limited anatomical and analytical applicability. In order to perform quantitative analysis, it is necessary to apply a post-processing step of tractography segmentation that involves filtering, labeling and grouping of the fibers into higher-level bundles that have a clear anatomical interpretation and are found consistently across subjects [6]. Finally, to conduct statistical studies, one needs a way of establishing shape correspondence between bundles in different subjects, which is an open problem as well.

These challenges motivate the use of algorithms that can leverage prior anatomical knowledge. To this end, in this paper we advocate a template matching, "one shot" approach to the reconstruction and subsequent connectivity analysis of fiber tracts of interest. Indeed, multiple WM tracts in the human brain can be identified consistently across subjects, thereby lending themselves to a template representation. Additionally, template matching methods offer several distinct advantages in geometric object reconstruction, and in medical imaging applications in particular (*e.g.*, in brain mapping [7]). Typically, the template serves as a shape prior, modeling the expected geometric and topological (and, sometimes, semantic or anatomical) properties of the reconstructed object, whereas the variability is captured through the fitting process. Furthermore, template matching facilitates object reconstruction at a superior level of detail, as the template is typically represented at a higher resolution. Finally, the resulting mapping between the subject and the template shape provides a "built-in" way to establish a common intersubject coordinate system—a valuable property for statistical shape analysis and morphometric studies. Despite these advantages, template matching approaches in the context of WM tractography remain largely unexplored to date.

The contributions of this paper can be summarized as follows:

- We propose a novel method for automatic matching of fiber tracts to diffusion tensor (DT) images. The method is hybrid in the sense that a geometric template is matched directly to the subject tensor field, skipping the fiber tracking step. Additionally, the use of a common template for all subjects facilitates the subsequent analysis, eliminating the problems of tractography segmentation and fiber correspondence.
- The proposed method can benefit from any available prior knowledge. The use of a shape prior helps avoid some common problems of standard tractography algorithms, *e.g.*, early termination of fibers due partial volume effects, low FA and/or high curvature. Furthermore, tract-specific anatomical constraints, as well as probabilistic priors, can be incorporated into the matching process to improve reliability of the result.
- We present a deformable fiber evolution model cast in the framework of generalized geometric flows, based on our derivation of a discrete curve Laplacian operator. The basic model is then further extended to deformable fiber-bundles that can readily be used in practical scenarios.
- We provide a validation of the method based on a digital DTI phantom. Additionally, we present several practical applications on human brain data, *i.e.*, direct reconstruction of fiber-bundles and tract-based morphometry.

2 Related Work

To date, several knowledge-based approaches to tract-specific reconstruction and quantification have been proposed in the literature. Most commonly, interactive methods are employed, where one selects, from a whole-brain tractography result, a subset of fibers passing through user-defined regions of interest (ROIs). Specialized protocols, *e.g.*, [8,9], have been suggested to dissect tracts of interest in this fashion, and a multi-subject WM atlas was constructed using this technique[10]. However, such interactive selection requires extensive expert knowledge of the 3D fiber tract anatomy. To facilitate the process, automated ROI placement has been suggested, based on affine registration of the structural MRI (T1) subject images to the above atlas [9]. Alternatively, automatic clustering methods [11,12] can be applied to label fibers without the use of ROIs, relying on a previously learned atlas instead. In either case, the problem of intersubject tract shape correspondence remains, although it can be somewhat facilitated with the latter methods by using smaller, very specific clusters. Additionally, the results are still affected by tractography artifacts. To remedy this problem, Hua *et al.* [8] proposed to skip the tractography step altogether and perform the segmentation directly using atlas-aligned tract probability maps. However, they acknowledge that their results are influenced by the atlas-subject registration quality. In fact, the reliance on affine registration of structural MRI for WM correspondence becomes a limitation in all the above methods, as such a registration, even if extended to a deformable solution, can never be guaranteed to correctly align WM tracts. This is due to the fact that fiber orientations can only be inferred from diffusion images. Ziyang *et al.* [13,14] tackle this problem by recovering the pairwise affine transformations between corresponding fiber-bundles and merging the transformation into a global poly-affine deformation. Alas, the affine transformation model for each bundle is still too restricted to capture intersubject variability and is still sensitive to tractography artifacts. We thus propose a fully deformable alignment approach, where geometric tract templates are registered directly to the subject DT field, as explained in the next section.

3 Algorithm

3.1 Problem Formulation

Let us first consider a simpler case of a single-fiber template, modeled as a curve $\mathcal{X}: [0,1] \rightarrow \mathbb{R}^3$. Given a diffusion tensor field $D(x)$, we wish to find the best deformable alignment of the template curve at each point to the tensor orientations, subject to certain smoothness and position constraints. More formally (and ignoring smoothness temporarily), we are looking for a deformation function Φ that satisfies $\Phi(\mathcal{X}) = \mathcal{Y}$, where $\mathcal{Y}$ is a curve *maximizing* the alignment functional (a.k.a. anisotropic Dirichlet energy):

$$E_D(\mathcal{Y}) = \int_0^1 \mathcal{Y}'(t)^T D(\mathcal{Y}(t)) \mathcal{Y}'(t) dt \text{ subject to } \mathcal{Y}(0)=y_0, \mathcal{Y}(1)=y_1, \quad (1)$$

where $\mathcal{Y}'(t)$ denotes the tangent vector to $\mathcal{Y}(t)$. Intuitively, the integrand measures the local alignment of the tangent at a given point to the tensor orientation at that point, using all the information present in the tensor without the need to recover the eigenvectors individually. With this measure, the total energy is mostly influenced by the anisotropic tensors, whereas the isotropic ones are “indifferent” to the local fiber orientation. As a consequence, this global energy is relatively insensitive to local artifacts such as partial volume effects.

Since the energy E_D is unbounded, we must constrain the solution by adding a smoothness term as follows:

$$E_{match}(\mathcal{X}, D) = E_D(\mathcal{X}) - \underbrace{\alpha \int_0^1 |\Delta \mathcal{X}(t)|^2 dt}_{E_B(\mathcal{X})}, \quad (2)$$

where Δ is the Laplace-Beltrami operator for curves (henceforth referred to simply as the Laplacian), and α is the desired smoothness factor. This new term, denoted by $E_B(\mathcal{X})$, corresponds to the *biharmonic energy* of $\mathcal{X}$: while $E_D(\mathcal{X})$ measures the alignment of $\mathcal{X}'_t$ to D , the biharmonic energy serves as a smoothness measure of $\mathcal{X}'_t$.

Note that E_D is conceptually similar to the *path cost* function $\mathcal{Y}'(t)^T D^{-1} \mathcal{Y}'(t)$, where D^{-1} serves as a Riemannian metric tensor that can be used to measure intrinsic distances between two points in the white matter [4,5,15]. Indeed, we can also see the integral of this cost function along the curve as a *misalignment* energy (to be minimized), an option that reduces the dependence regularization. The drawback is potential noise amplification due to the tensor inversion and numerical instabilities in the case of very anisotropic tensors. In practice, the two formulations are almost identical in terms of implementation, and the optimal choice between the two may depend on the nature of the data. In either case, however, since diffusion tensors are never perfectly anisotropic in reality, the DT data is preprocessed with a normalized

sharpening step, as suggested by Fletcher *et al.* [15]. Specifically, $\widehat{D}(x) = |D(x)|^{\frac{1}{3}} \left(\frac{D(x)}{|D(x)|^{\frac{1}{3}}} \right)^\alpha$, with $\alpha = 4$ chosen empirically in our experiments. Throughout this paper, we refer to the sharpened tensor field simply as D .

3.2 Discrete Setup

In practice, the curves are given in a polygonal representation rather than a parametric one, and we will stick to the discrete setting throughout the rest of this paper. Updating the notation to $\mathbf{Y} = \Phi(\mathbf{X})$ with $\mathbf{X} = \{\mathbf{x}_i\}_{i=0..N}$, the integral in (1) becomes a discrete weighted sum:

$$E_D(\mathbf{X}) = \sum_i \frac{\mathbf{e}_i^T \bar{D}_i \mathbf{e}_i}{|\mathbf{e}_i|^2} l_i, \text{ where } \mathbf{e}_i = \mathbf{x}_{i+1} - \mathbf{x}_i, \quad (3)$$

$\bar{D}_i$ is the average value of D over the edge element $\mathbf{e}_i$ and $l_i = |\mathbf{e}_i|$ is the integration weight associated with $\mathbf{e}_i$. This choice of using edges (as opposed to vertices) as basic discrete elements is not accidental: for a polyline edge $\mathbf{e}$, we can directly define a discrete counterpart of the tangent vector at any point $\mathbf{p}$ on $\mathbf{e}$ simply as $\frac{\mathbf{e}}{|\mathbf{e}|}$. Note that this definition converges to the continuous case as the sampling density approaches infinity.

To discretize the biharmonic energy, we first need to define a Laplacian operator for discrete curves. One way to do that is to consider first the discrete curvature at a vertex $x_i \in \mathbf{X}$ which can be defined straightforwardly as

$$\mathbf{K}(x_i) = \frac{1}{m_i} \left(\frac{\mathbf{e}_i}{|\mathbf{e}_i|} - \frac{\mathbf{e}_{i-1}}{|\mathbf{e}_{i-1}|} \right), \quad (4)$$

where $m_i = (l_i + l_{i-1})/2$ is the “discrete mass” of vertex x_i (here, simply the arc length distance between the midpoints of $\mathbf{e}_{i-1}$ and $\mathbf{e}_i$). In fact, $\mathbf{K}(\mathbf{X})$ can be seen as the 1D counterpart of the mean curvature of a surface—this analogy becomes obvious if one regards a curve as a ribbon surface with a fixed infinitesimal width. Thus, we can reuse here a fact known for discrete

surfaces: the matrix $\mathbf{K}$ is nothing but the discrete Laplacian in its *pointwise* formulation [16, 17] which, in turn, is the direct analog of the continuous Δ . (For a detailed discussion of discrete surface Laplacians see, e.g., [17,18].) As a result, we can write the discrete biharmonic energy of $\mathbf{X}$ as $E_B(\mathbf{X}) = \|\mathbf{K}\mathbf{X}\|_{L^2}^2$, where $\|\cdot\|_{L^2}$ denotes the discrete L^2 norm of vector fields in $\mathbb{R}^3$, given by $\|\mathbf{X}\|_{L^2}^2 = \mathbf{X}^T \mathbf{M} \mathbf{X}$ [19]. Here $\mathbf{M}$ denotes the diagonal (or lumped) “mass matrix” associated with $\mathbf{X}$, defined as $M_{ii} = m_i$ (recall Eq. 4). Essentially, the mass matrix is needed to account for irregular sampling of the geometry. We thus obtain:

$$E_B(\mathbf{X}) = (\mathbf{K}\mathbf{X})^T \mathbf{M} (\mathbf{K}\mathbf{X}) = \mathbf{X}^T (\mathbf{K}^T \mathbf{M} \mathbf{K}) \mathbf{X}, \quad (5)$$

with a further simplification of this equation available in Appendix A.

3.3 Optimization Procedure

The optimization algorithm is essentially an iterative evolution of the template curve $\mathbf{X}$ so as to maximize the combined energy E_{match} , using a gradient descent approach. This process is known as discrete gradient flow and is given by:

$$\mathbf{X}_{t+dt} = \mathbf{X}_t + dt \mathbf{M}^{-1} \frac{\partial E_{match}}{\partial \mathbf{X}}(\mathbf{X}_t), \quad (6)$$

with the derivation of $\frac{\partial E_{match}}{\partial \mathbf{X}}$ found in Appendix B.

Deformation Prior—So far, we only used the template fiber $\mathbf{X}$ (with new positions assigned to its endpoints) as the initialization for our optimizer. While such an initialization is helpful to avoid local minima, in reality we also want to ensure that the final curve stays, in some sense, as close as possible to the template. This will minimize the likelihood of fibers straying from their own trajectories due the influence of other nearby tracts. One way to implement this is by adding a *fidelity* term to the total energy, penalizing stretching and bending of the evolving curve with respect to the original. In practice, adding a bending term combined with endpoint constraints will bound the stretching as well. The task is, therefore, to design an energy that measures bending with respect to a *curved* reference shape $\mathbf{X}$. Although this can be done by employing a discrete thin shell model [20], such a strategy would have several drawbacks. First, the resulting energy would be highly nonlinear, leading to slower convergence. Perhaps more importantly, we would like to keep the final mixture of different energies as simple as possible, as it can become increasingly delicate to find a proper balance between them. For these reasons, we opt for a different approach as follows. Consider the *incremental* bending energy of $\mathbf{X}_{t+1}$ w.r.t. $\mathbf{X}_t$ that can be expressed as the total squared change of curvature:

$E_{IB}(t+dt) = \|\mathbf{K}_{t+dt}\mathbf{X}_{t+dt} - \mathbf{K}_t\mathbf{X}_t\|_{L^2}^2$. For a sufficiently small dt , we can assume an approximately isometric deformation, i.e., $\mathbf{K}_t \approx \mathbf{K}_{t+dt}$, leading to

$$\begin{aligned} E_{IB}(t+dt) &\approx \|\mathbf{K}_t(\mathbf{X}_{t+dt} - \mathbf{X}_t)\|_{L^2}^2 \\ &= \|\mathbf{K}_t \mathbf{U}_t\|_{L^2}^2 = \mathbf{U}_t^T (\mathbf{K}^T \mathbf{M} \mathbf{K}) \mathbf{U}_t. \end{aligned} \quad (7)$$

Note that this deformation energy is very similar to the biharmonic energy from Sec. 3.2, with the sole difference that it is defined on a deformation field $\mathbf{U}_t$, as opposed to a shape. Furthermore, it represents a norm in the space of vector fields in $\mathbb{R}^3$, and we can now modify the gradient flow in Eq. 6 to penalize instantaneous bending according to this norm. This is

done using a Sobolev-like deformation prior [19,21,22] of the form $\text{Id} + \lambda \Delta^2$ which can be shown to correspond directly to E_{IB} . Here λ is a parameter assigning a relative cost of the bending deformation component. The resulting discrete flow equation then becomes:

$$\mathbf{X}_{t+dt} = \mathbf{X}_t + dt \mathcal{L}^{-1} \frac{\partial E_{match}}{\partial \mathbf{X}}(\mathbf{X}_t), \quad (8)$$

where $\mathcal{L} = \mathbf{M} + \lambda \mathbf{K}^T \mathbf{M} \mathbf{K}$. This scheme has several key advantages. First, it helps avoid local minima and resist noise, without oversmoothing the final solution. Secondly, the deformation prior does not, in theory, prevent the evolution from reaching the original global optimum¹. The iteration is terminated when convergence becomes sufficiently slow, typically yielding a tradeoff between the objective function and the fidelity criterion. While this is an approximate solution, it performs reasonably well for most our cases, as reported in Sec. 4.1.3.

3.4 Generalization to a Fiber-Bundle Template

So far we have only considered a single-fiber template. In practice, however, we typically seek to reconstruct specific fiber-bundles rather than individual fibers. It is therefore more useful to perform template matching on the bundle level. Thus, we generalize the basic method to fiber-bundle templates in the following simple way. Since a bundle is essentially a set of curves, the naïve approach is to treat each curve independently. However, this may cause a bundle to disintegrate, since there is no “glue” to hold the fibers together as they evolve. We address this problem by extending the deformation prior from the previous section so as to enforce a smooth motion of the *entire bundle*, such that the neighboring fibers move in a coherent fashion. With the deformation prior approach, adding such a global smoothness criterion becomes straightforward when given a Laplacian operator for the underlying shape, *i.e.*, the full bundle, as opposed to a set of “autonomous” curves. Indeed, the matching energy from Eq. 2 readily extends to the bundle case simply by summing up the individual fiber energies. Thus, all we need to do is generalize the deformation prior by defining a *bundle Laplacian*. However, this task involves a challenge. Since the Laplacian operator essentially encodes local spatial relationships, even its simplest discrete-case formulation (a.k.a. the graph Laplacian matrix, see *e.g.* [23]) typically relies on vertex connectivity information, *i.e.*, a finite element mesh is required. A common way to obtain a good-quality mesh is by computing a 3D Delaunay triangulation (*i.e.*, tetrahedralization) of the bundle vertex set. However, we are interested in a mesh whose edges preserve the given curve connectivities, which becomes a constrained Delaunay problem that is much harder to solve in 3D. The brute-force alternative is to establish vertex connectivity simply by finding k nearest neighbors for each for each point. However, this will often produce local meshes of poor numerical quality. Consequently, we establish inter-fiber connectivity using a hybrid of the two methods, in a way similar to the approach proposed in the context of point-based surfaces [24]. A *local* 3D Delaunay triangulation T_i is computed (using CGAL²) around each fiber vertex v_i , based on a candidate set of nearest points from the neighboring fibers and its existing edge neighbors of v_i — see Figure 2 for an illustration. The edges incident on v_i in T_i are then used to establish the local connectivity which is integrated into a global graph Laplacian matrix — an approximation we retain due to its simplicity and robust numerical properties. Specifically, we define the bundle Laplacian $\tilde{\mathbf{L}}$ as follows: $\tilde{\mathbf{L}}_{ij} = \#e_{ij}$ and $\tilde{\mathbf{L}}_{ii} = -\sum_{v_j \in N(v_i)} \tilde{\mathbf{L}}_{ij}$, where $\#e_{ij}$ counts the edges connecting v_i and v_j in both directions. Note that $\tilde{\mathbf{L}}$ is symmetric, which is consistent with the properties of

¹In practice, a very small time step may be required to reach the global optimum with explicit Euler integration.

²CGAL, Computational Geometry Algorithms Library, <http://www.cgal.org>

continuous Laplace-Beltrami operators³. Finally, the updated deformation prior from Eq. 8 becomes:

$$\mathcal{L} = \mathbf{M} + \lambda \mathbf{K}^T \mathbf{M} \mathbf{K} - \mu \tilde{\mathbf{L}}. \quad (9)$$

Here, the second term of the right-hand side still acts on the bundle fibers separately, involving solely intra-fiber connectivity. The new term, however, relies on interfiber connectivity, with μ being the cost of diverging fiber motion. Thus, informally speaking, the fibers can still diverge to reach a global optimum, but only if there is no “cheaper” way. Otherwise, they will tend to move in concert, which also makes the evolution process more robust to noise. Note that the dimension of the system is now given by the total number of vertices in the entire bundle.

4 Applications

4.1 Fiber Tract Reconstruction

4.1.1 Phantom Data Experiments—We first evaluate the single-fiber template approach using a phantom DT image with a known ground truth (Figure 1). The phantom tensor field was simulated based on a fixed-width helical tube. In the shown experiment, the template was purposefully initialized to a helix with much larger radius, with only its endpoints constrained to approximately correct locations. Although this initial shape was a very different one, the algorithm was able to find a correct alignment, as demonstrated in figure 1.

4.1.2 Human Brain Data—As stated in the introduction section, our motivation for using a template for fiber tract reconstruction is to be able to incorporate prior anatomical knowledge in the template matching process. Obviously, this approach hinges on the availability of an adequate template. One viable option is basing such a template on the postmortem WM fiber tract atlas [25] available with the SPM Anatomy Toolbox [26]. This atlas comprises probabilistic maps for ten WM tracts, based on histological staining in several postmortem human brains, and thus reflecting actual ground truth data.

Here we focus without loss of generality on two specific tracts, namely the cingulum and the fornix. For each of these tracts, the geometric fiber template $\mathcal{T}_i$ is initially chosen simply as the curve-skeleton [27] of the corresponding probability map $P(\mathcal{T}_i)$ (see Figure 3 for illustration), providing a compact representation of the tract shape. Now, given a pair of co-registered subject T1 and DT MR images, the task is to match the template to the subject data.

The matching procedure involves two steps as follows. The first step is a purely structural registration: since the atlas is aligned with the T1-weighted MNI reference brain [28], we register the reference brain with the subject T1 image using a non-linear method [29]. The associated deformation field is then applied to each $\mathcal{T}_i$ and $P(\mathcal{T}_i)$, generating their corresponding deformed instances $\mathcal{T}_i'$ and $P(\mathcal{T}_i')$, respectively. Still, structural registration alone, however accurate, is not enough to ensure a correct tract reconstruction. Thus, it is followed by a second step in which $\mathcal{T}_i'$ becomes the initial subject-specific template and is evolved to match the subject tensor data, using the deformable fiber evolution algorithm described in Section 3. Since the use of deformable bundle model, as opposed to individual fibers, improves robustness to noise, the fiber template is first converted to a bundle representation by sampling curves from a fixed-radius tube around each original fiber. This step also includes a moderate Laplacian smoothing applied to the fiber template (using the

³This symmetric property becomes important, e.g., in the definition of the Sobolev norm which makes use of the Laplace-Beltrami operator.

Laplacian operator from Section 3.2), to reduce artifacts and possible overfitting effects specific to Step 1.

Furthermore, the evolution procedure can benefit from having a (deformed) probability map $P(\mathcal{T}_i)'$ to reduce the method's sensitivity to the initial position, as well as its dependence on endpoint constraints. This is done by extending the notion of a template beyond merely a shape prior to also include a probabilistic prior, represented by a new energy term. This energy is based directly on $P(\mathcal{T}_i)'$, simply measuring for each point the probability of *not* having a fiber passing through it, *i.e.*,

$$E_{prior}(\mathcal{X}) = \int_0^1 \bar{p}(\mathcal{X}(t)) dt \approx \sum_i \int_{\omega(\mathbf{x}_i)} \bar{p}(x) dx,$$

where $\bar{p}(x)$ is the probability of no fibers passing through x and $\omega(\mathbf{x}_i)$ is the Voronoi (dual) region of the vertex $\mathbf{x}_i$. One can easily verify that the minimizer of this energy is indeed the most likely curve given $P(\mathcal{T}_i)'$, subject to endpoint constraints. The partial derivatives of E_{prior} are given by

$$\frac{\partial E_{prior}}{\partial \mathbf{x}_i} = \int_{\omega(\mathbf{x}_i)} \nabla \bar{p}(x) dx,$$

where $\nabla \bar{p}(x)$ can be approximated using finite differences.

Likewise, one can now incorporate a segmentation mask (either binary or probabilistic) of the cortico-spinal fluid (CSF) to prevent the fibers from drifting into the ventricles. This is especially useful since CSF-filled regions are characterized by high isotropic diffusion, and E_{match} is in fact sensitive to diffusion tensor magnitude, not just orientation.

4.1.3 Results

Data Processing: HARDI data were acquired from 5 healthy adult subjects (age: 23.9 ± 1.4 SD years) on a 4 Tesla Bruker Medspec MRI scanner using an optimized diffusion tensor sequence [31]. The study was approved by the institutional review boards (IRBs) at the Queensland Institute for Medical Research and at the University of California, Los Angeles; all subjects gave informed consent. 105 images were acquired: 11 baseline (b_0) images with no diffusion sensitization (*i.e.*, T2-weighted images) and 94 diffusion-weighted (DW) images (b -value 1159 s/mm^2) in which gradient directions were evenly distributed on the hemisphere [2]. Imaging parameters were: TR/TE 92.3/8250 ms, $55 \times 2 \text{ mm}$ contiguous slices, FOV = 23 cm. The reconstruction matrix was 128×128 , yielding a $1.8 \times 1.8 \text{ mm}^2$ in-plane resolution. The total scan time was 14.5 minutes. The DT images were obtained from diffusion weighted data using the MedInria tool [32]; skull stripping in T1 MRI images was done in BrainSuite [33].

Reconstruction Results: Figure 4 shows several examples of the atlas-based tract reconstruction procedure described in Section 4.1.2. The superimposed T1 images suggest that the reconstructed bundles appear to follow anatomically valid trajectories, notwithstanding the proximity of *e.g.*, the corpus callosum fibers which were not part of the template. Figure 5 provides an additional quantitative validation, depicting the effect of each of the algorithm's steps, for one of the cases. Note that a relatively moderate deformation of the template shape may lead to a significantly better alignment to the diffusion tensor field, as illustrated by the

corresponding plot of the misalignment energy. Furthermore, the mean energy value along a given pathway can be used as a likelihood measure, a claim supported by Ziyang *et al.* [13], who suggested a similar “Fiber-Tensor Fit” measure in a somewhat different context. Naturally, more conservative measures, such as FA, mean diffusivity (MD), etc., can be computed along the tracts as well.

In addition, Figure 6 provides a comparison of cingulum reconstruction with our method to streamline tractography performed in DTI Studio [30], using a specialized ROI placement protocol [8]. While both methods yielded approximately similar results for the upper part of the cingulum, the ROI-based approach failed to capture the entire C-shaped structure, which is likely to be due to lower FA values in those regions, and/or the high fiber curvature. In contrast, our algorithm does not involve any FA or curvature thresholds, and therefore was not subject to this shortcoming. While it could still be possible to capture the entire cingulum bundle using DTI tractography through a more complex combination of multiple ROIs, this would require even more extensive expert knowledge and manual labor, as opposed to the proposed automatic method. Note also the multiple “straying” fibers in the tractography result, requiring an additional filtering step and complicating intersubject comparisons, whereas the template matching approach avoids these issues by design. Finally, it should be pointed out that the described procedure can be performed using any other probabilistic WM atlas, if available.

4.2 Tract Based Morphometry

The above results are immediately suitable for tract-based morphometric analysis. While the actual analysis is out of the scope of this paper, several possibilities are available. Since each fiber-bundle result has a one-to-one correspondence to the template, the latter becomes a common intersubject “coordinate system”, to which each point of any reconstructed bundle. This property can be used to compute local tract-based maps of scalar measures such as FA, MD, etc., as well as for more complex comparisons of tract shapes and deformation-based morphometry. In fact, the deformable evolution approach makes it straightforward to quantify the deformation of the discrete bundle at each vertex w.r.t. the initial template shape. For instance, one can define the cumulative local deformation as the path integral of the incremental bending energy from Eq. 7 at a given vertex.

5 Discussion and Conclusions

5.1 Potential Clinical Applications

Besides neurological research, white matter connectivity analysis is becoming an important tool in neurosurgical planning. The key distinction in clinical applications is the requirement to correctly analyze pathological cases, *e.g.*, detect WM connectivity in the presence of brain tumors. However, the underlying anisotropic diffusion assumptions can no longer be relied on in the presence of tumor tissue (see, *e.g.* [34]). In fact, to our knowledge, there are no adequate methods to date to reliably reconstruct fiber tract connectivity in demyelinated tissue. Nevertheless, solutions based on basic streamline tractography approaches are increasingly employed in image-guided neurosurgery. While visually useful, such tractography results should be considered with great caution. For instance, if the detected fibers appear to be disrupted by a tumor, that is not yet a sufficient evidence that there are no unobserved fibers going through it, which poses a risk of visual misinterpretation [35]. By contrast, our proposed method does not rely solely on local diffusion measurements, and therefore will always produce a continuous fiber-bundle that may still pass through the tumor region. Then, complementary measures (*e.g.*, FA, MD) could be used to locally assess the certainty of the result. While it is clearly premature to suggest the template-based technique for clinical practice at this point, we believe this approach could ultimately be well suited for this application. Furthermore, the

flexibility to incorporate more sophisticated deformation priors, *e.g.*, based on tumor growth models, suggests potential extensions to specific cases.

5.2 Conclusions

We have presented a novel approach to WM fiber-bundle reconstruction and connectivity analysis, addressing the problem from the template matching point of view. Given an adequate and sufficiently detailed template (or atlas) of the WM fiber tracts, the proposed method has the potential of simultaneously addressing the problems of fiber tracking, fiber-bundle segmentation and anatomical labeling. Reliance on a “good” template, while being a distinctive feature of this method, can also be a limitation. For instance, the reconstruction procedure of the cingulum and fornix bundles in Section 4.1.2 could be made more robust by explicitly incorporating *e.g.*, a corpus callosum template into our prior. Thus, creation of a more complete atlas with built-in tract-specific knowledge becomes a major avenue of future work. Another potential extension of the method is template-based DTI clustering (or segmentation), as the proposed scheme does not attempt to accurately recover the bundle width. Furthermore, since the method is inherently suitable for tract-based morphometric analysis, we intend to extend it for such applications. Finally, incorporating the recent advances in DTI registration [36] into the template matching process is yet another interesting direction.

Obviously, this method has its limitations. Being a template-based approach, it can be useful in the reconstruction of known tracts, but not in the detection of pathways that are not expected *a priori*. Also, while the use of a template can help improve robustness to noise in the DW images, an overconstrained template may not fully capture subject-specific pathologies. Indeed, it is not always clear how the prior knowledge should be weighted in relation to the observed data. Thus, the confidence in the final match should always be assessed using the available measures, *i.e.*, the misalignment energy, FA, MD, etc., with low confidence values indicating that further inspection may be required. A potential way to generalize such a strategy is to incorporate confidence measures in the algorithm directly as weighting criteria, using *e.g.*, a Bayesian filtering framework. Another issue is the sensitivity to the choice of the initial template: while this problem is alleviated by the use of a probabilistic prior (when available), the use of multiple shape priors (*e.g.*, as in [37]) is likely to help better capture subject variability. Finally, we hope that more DTI datasets with expert-delineated tracts will soon become available, which should also allow a more rigorous validation of the proposed method, by “learning” the best set of parameter values.

The “holy grail” of the template matching approach is a combined atlas of both white and grey matter structures, all integrated in a single geometric deformable template. With this goal in mind, we are currently experimenting with the integration of the proposed method with a deformable cortical surface matching framework, similarly based on geometric flows [38].

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Appendix

A Laplacian and biLaplacian Operators for Discrete Curves

Observe that the matrix $\mathbf{K}$ from Eq. 4 can be rewritten as $\mathbf{K} = \mathbf{M}^{-1}\mathbf{L}$, where $\mathbf{M}$ is the discrete mass matrix and

$$\mathbf{L}(\mathbf{x}_i) = \left(\frac{\mathbf{e}_i}{|\mathbf{e}_i|} - \frac{\mathbf{e}_{i-1}}{|\mathbf{e}_{i-1}|} \right) = \left(\frac{1}{|\mathbf{e}_i|} + \frac{1}{|\mathbf{e}_{i-1}|} \right) \mathbf{x}_i - \frac{\mathbf{x}_{i-1}}{|\mathbf{e}_{i-1}|} - \frac{\mathbf{x}_i}{|\mathbf{e}_i|}.$$

This relationship is consistent with what we know about discrete surfaces [16,17], with $\mathbf{L}$ being the corresponding definition of the discrete *vertex-based* Laplacian operator for curves. Consequently, we can simplify Eq. 5 as follows:

$$E_B(\mathbf{X}) = \mathbf{X}^T (\mathbf{K}^T \mathbf{M} \mathbf{K}) \mathbf{X} = \mathbf{X}^T (\mathbf{L}^T \mathbf{M}^{-1} \mathbf{L}) \mathbf{X},$$

where $\mathbf{L}^T \mathbf{M}^{-1} \mathbf{L}$ is, in fact, the discrete biLaplacian operator. The same simplification applies to Eq. 8 and 9.

B Energy Gradient Derivation

From Eq. 2 we know: $E_{match} = E_D - \alpha E_B$. In the discrete case, E_D is given by Eq. 3 and its partial derivatives are as follows:

$$\frac{\partial E_{match}}{\partial \mathbf{x}_i} = \theta_{i-1}(\mathbf{x}_i - \mathbf{x}_{i-1}) - \theta_i(\mathbf{x}_{i+1} - \mathbf{x}_i),$$

$$\text{where } \theta_i = 2 \frac{|\mathbf{e}_i|^2 \bar{D}_i - (\mathbf{e}_i^T \bar{D}_i \mathbf{e}_i) \mathbf{I}_3}{|\mathbf{e}_i|^4}.$$

The discrete biharmonic energy is simply E_B is defined in Appendix A above, and the corresponding partial derivatives can be written simply as $\frac{\partial E_B}{\partial \mathbf{X}} = (\mathbf{L}^T \mathbf{M}^{-1} \mathbf{L}) \mathbf{X}$.

Fig. 1. DTI Phantom Test

A digital DT phantom image was generated from a helical curve (left), with the surface obtained by thresholding the fractional anisotropy. Center: the initial template fiber (in blue) is a helical curve with twice the radius of the original helix, deformed to approximately fit the original helix at the endpoints. Right, the final fiber evolution result: the deformed template is best-aligned to the underlying tensor field.

Fig. 2. Establishing Inter-Fiber Connectivity Within a Bundle

In this example, cortico-spinal fibers (in blue) are linked into a bundle, where the inter-fiber connectivity edges (in red) are obtained through local 3D Delaunay triangulations of the bundle vertices. The resulting connectivity information is then used to define a discrete bundle Laplacian. Notice that only the nearby fibers are connected, *i.e.*, the connectivity is local, as desired.

Fig. 3. Creation of a Fiber-Bundle Template

Left, the canonical fiber template of the cingulum is created based on the corresponding probability map from [25], as the curve-skeleton of its 0.1-isoprobability surface (shown in blue). Once the template fibers are transferred to the subject space, a bundle is generated around each smoothed fiber, as shown on the right. The red edges are generated using local 3D Delaunay triangulations of the bundle vertices and are used to define a discrete *bundle Laplacian*. The resulting subject-specific template is then matched to the corresponding diffusion tensor field.

Fig. 4. Cingulum and Fornix Bundles Reconstruction

Several examples of final reconstruction results for the cingulum (in red) and the fornix (in green). Each row shows several views of a specific subject.

Fig. 5. Deformable Alignment of the Fornix Template

The canonical fiber template of the fornix, left, is transferred to the subject space via a non-linear registration of T1 images, becoming a subject-specific template (center, in purple). The final reconstruction result, in green (for clarity, only one set of curves is shown) is obtained through a deformable evolution process that minimizes the misalignment energy w.r.t. the subject tensor field, as illustrated by the energy plot on the right.

Fig. 6. Comparison to Fiber Tracking with Manual ROIs

Two different cases showing our reconstruction of the cingulum bundle (shown in red), compared to fiber tracking done in DTI Studio [30] (in blue), using a manual ROI delineation protocol [8]. The latter method was able to recover only the upper part of the bundle, whereas the template matching approach captured the full bundle.