Diffusion MR Image Analysis with Multiple Fiber Orientations for Clinical Neuroimaging

PhD Thesis Proposal

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A Vision/Introduction

Our proposed research aims to develop, validate, and apply a novel computational framework for the analysis and visualization of diffusion MR imaging datasets. We hypothesize that this will provide generalizable, clinically useful, and theoretically sound methodology in two tasks: model-based image processing and segmentation of anatomical structures. For image processing, we consider statistical estimators of multi-fiber models for interpolation, smoothing, and fusion tasks, which are useful for tractography, and atlas construction. We then develop segmentation algorithms based on probabilistic models of fiber orientation, developing both region and bundle approaches for anatomical localization. Our final contribution consists of two applications to clinical studies of white matter in relation to health and disease. At a high-level, we aim to contribute to both diffusion MR image analysis and clinical neuroscience. This includes the development of novel methodology, comparison to prior work, and experimental evaluation of performance with respect to noise and variability in real-world datasets. Furthermore, our clinical applications will contribute to scientific knowledge of neurobiology as well as provide a basis for the evaluation of our computational methodology and comparison with related work.

B Specific Aims

B.1 Develop methods for performing model-based image processing

This aim develops and evaluates a model-based framework for image processing of orientation data from multi-fiber diffusion MRI datasets. We hypothesize this will provide improvements for tractography and atlas creation by extending existing techniques to support multi-fiber models. A theoretical contribution of this aim is the generalization of the multi-fiber interpolation, smoothing, and fusion tasks with a non-parametric statistical framework, which is analogous to kernel regression in image processing. We'll experimentally evaluate this approach and compare to existing techniques using computational phantoms and clinical human brain data. We'll measure performance with respect to imaging noise, acquisition parameters, and known features of several fiber bundles. Finally, we'll study anatomical structures reconstructed in our atlas and compare them to related work with other diffusion models and tracing studies in non-human primates.

B.2 Develop methods for segmentation of white matter structures

This aim develops and evaluates two segmentation algorithms based on probabilistic models of fiber orientations. We hypothesize this will provide an effective approach for modeling complex white matter fiber bundles that are difficult to reconstruct with existing tools. A theoretical contribution of this aim is a probabilistic mixture model for representing the spatial distribution of fiber orientations, which can be used for segmenting both fiber bundles and regions-of-interest in population studies. We'll experimentally evaluate our approach and compare to existing techniques with computational phantoms, scan-rescan data, and clinical population datasets. We'll measure peformance with reliability of white matter metrics and similarity to manually-delineated "ground truth" fiber bundles. Finally, we'll apply these tools to our population studies and compare our results to arc-length based analysis of bundles as well as other standard skeleton and voxel-based approaches.

B.3 Apply proposed methods to clinical studies of the brain white matter

This aim tests the clinical value of previous aims by applying them to two neuroimaging studies. In the first, we'll examine white matter changes in a normal population, and in the second, we'll look at white matter changes in a pediatric bipolar population. For each dataset, we'll construct a population atlas using the methods of the first aim and localize anatomical group differences using the methods of the second aim. We'll evaluate our results in two ways. First, we'll compare our findings to those obtained with standard diffusion tools and non-diffusion measures, such as voxel-based morphometry and cortical thickness. Second, we'll measure the sensitivity of our results across the various algorithm parameters and use this data for evaluation in the previous two aims.

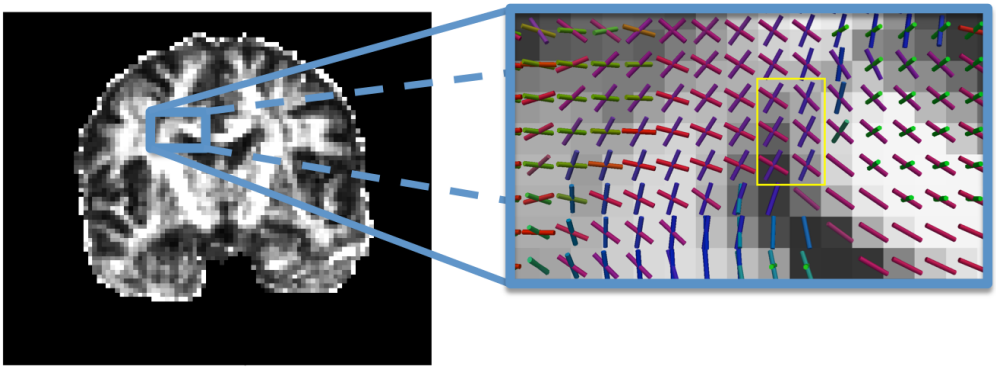


Figure 1: Fiber orientations modeled in the crossing of the corona radiata and corpus callosum

C Significance and Background

Our proposed work has potential to improve public health by advancing the general understanding of human brain white matter structure. This can improve our knowledge of both typical biological development and the anatomical basis of psychiatric and neurological disorders. We focus on Magnetic Resonance Imaging (MRI) as a research tool to provide an in-vivo probe of the macroscopic structure of the brain. MRI provides a rich source of scientific data; however, the quantity and complexity of the data introduces a need for computational tools to aid in image analysis and interpretation [35], particularly for interpolation, registration, and segmentation [62] [101] [88]. Our goal in this thesis is to contribute to this aspect of imaging by providing computational tools that are both clinically useful and theoretically well-grounded.

Our project specifically investigates diffusion MRI (dMRI) and novel computational techniques for making it more useful for scientific research. dMRI is particularly well-suited for imaging brain white matter, as it measures patterns of water molecule diffusion that reflect local anatomical structure of neuronal axons and other supporting structures [7] [90]. While this technique has been shown to be uniquely sensitive to normal and pathological variation in tissue microstructure, its adoption in clinical applications has been slower than other MRI techniques. This is perhaps due to a number of issues that arise specifically in diffusion MR imaging [59]. At a low level, some of the major challenges are Rician noise [46], partial voluming effects [2], and multiple coordinate systems [61] [57]. On a higher level, the diffusion measurement produces image data with a complex geometric structure, which requires extensions to even basic image analysis and visualization tasks [114] [63] [83] [51]. Our work contributes to progress on this high-level computational challenge by expanding diffusion MR imaging methodology for clinical and scientific research.

The innovation of our work comes from a generalization of a number of techniques for processing diffusion fiber orientation data and from an extension to support multiple fibers per voxel in these tasks. Such orientation data arises naturally in dMRI data, as almost all models of diffusion represent the direction of axonal projections in some way [82] [63]. It's especially important to model multiple fibers per voxel when reconstructing white matter pathways, as a large portion of the human brain consists of interwoven crossing fibers [113] [97]. There is a large variety of potential diffusion models available; however, many algorithms are limited to a particular model. This can potentially isolate image analysis techniques based on which model is employed. We propose to work toward bridging that gap by considering methods that deal explicitly with fiber orientations. The hope is for this to accommodate to a number of models but still be generally useful for clinical applications.

Other similar work has considered fiber orientation processing, but the innovation of our work comes from a focus on image analysis with directional statistics and efficient techniques to deal with combinatorial issues that come with multiple fibers per voxel. Results from directional statistics have been applied in diffusion imaging previous for measuring uncertainty [26], filtered tractography [69] [10], and diffusion model fitting [11] [93]. In contrast

to previous work, we explore applications of directional statistics [111] [49] [106] [16] and machine learning [30] [31] to model-based image processing and segmentation.

Next, we examine the significance and background of each of our specific aims and how they relate to our high-level goals.

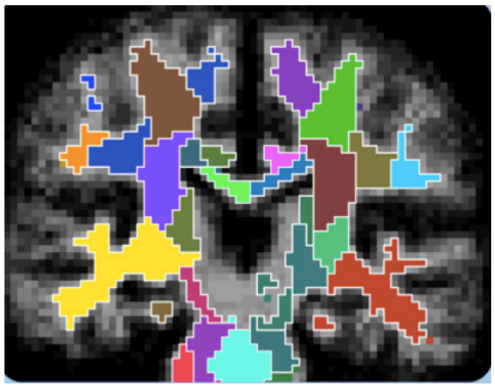
C.1 Model-based image processing

The innovation of our first aim is the ability to construct brain atlases with multiple fibers per voxel and accurately reconstruct complex fiber bundles. This is significant because computational atlases play an important role in population studies [101] [72]. They provide a common frame of reference for comparing individuals in a study, showing statistical results, and identifying population-wide properties. The typical process for creating an anatomical atlas is to iteratively deform each volume to some reference and average the collection of deformed images [47]. Image processing plays a key role, where smoothing is used as a preprocessing step, interpolation is used to resample data when deforming, and fusion is used to combine the deformed images [62]. Our proposed work defines statistical estimators for fiber orientations that can be used for the smoothing, interpolation, and fusion steps in this process.

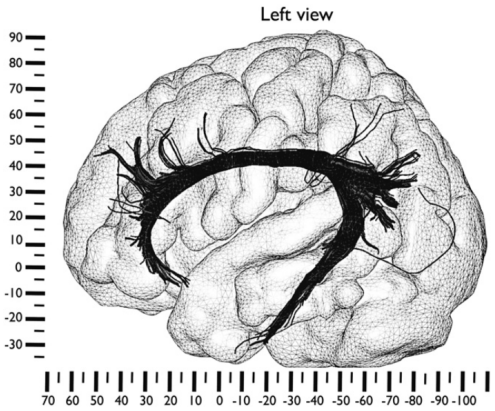
Compared to other approaches, our proposed image processing framework distinguishes itself by supporting fiber orientations from multi-compartment models and by extending a commonly used image processing framework to support orientation data. This kind of technique is sometimes called model-based [63], in contrast to signal-based approaches that process the diffusion-weighted signal directly [118] [76]. The primary benefits of model-based approaches are the incorporation of anatomical knowledge [64] and improved computational efficiency [9]. A variety of model-based approaches have been proposed in the literature, and our work builds on these. A classic example is the diffusion tensor Riemannian framework, which defines fitting, interpolation, and filtering on differential manifolds to ensure positive-definiteness of the model [39] [3] [64]. More recently, manifold techniques have been developed for processing orientation distribution functions (ODFs) [21] [44], which offer a non-parametric representation of the fiber structure in each voxel [105]. Related work has developed estimators for multi-tensor models [104]; however, this approach depends on a high-quality diffusion acquistion that is not always available [98]. We focus instead on fiber orientations, which are more generally available in single shell datasets, either with the ball-and-sticks model [9] or by maxima extraction in ODFs. Some work has explored regularization of fiber orientation fields [36] [91] [87]; however, they have neither explored multi-fiber models, nor generalized to the interpolation and fusion tasks. A related fusion technique has been proposed in prior work [117], but this has not been explored for more general image analysis tasks. We propose to fill these gaps by employing directional statistics [71] and machine learning [103] to develop a multi-fiber orientation processing framework. To accomplish this, we plan to extend a scalar image processing framework [74] that has enjoyed great success in the image processing community but has yet to be applied to model-based analysis of diffusion MR images.

C.2 Segmentation of white matter structures

The innovation of our second aim is the formulation of automated segmentation algorithms with directional statistics that support group-wise analysis. This is significant because most population imaging studies compare specific anatomical structures, which must be delineated in some way. Having an automated approach can be desirable, as manual delineation of structures can be tedious and requires expert training [80]. Compared to manual delineation, automated approaches are potentially more reliable and subject to less intra- and inter-rater variability, as well as less inter-site variability among research groups [77]. In the long term, having such automated and reliable segmentation algorithms may allow for very large population studies to be run and ultimately strengthen our scientific understanding of the brain.



(a) An example of region segmentation from Bloy et al [13] where normalized cuts was applied to voxel-wise orientation distribution functions (ODFs).



(b) An example of bundle segmentation from Catani et al [20] showing a manually delineated cingulum bundle.

Figure 2: Examples of region and bundle segmentation in related works

A segmentation algorithm is often chosen based on the underlying scientific question being considered, and there are numerous methods specific to diffusion MRI, which we'll briefly review. Two of the most common manual methods are region-of-interest (where a volumetric mask is drawn over a structure) and fiber bundling (where individual tractography curves are grouped into larger structures). Automated region segmentation has mostly been applied to segmentation of the corpus callosum and thalamus, including mean-shift, normalized cuts, level-set, and k-means clustering approaches [56] [34] [29] [115] [64]. Two common automated approaches to bundle segmentation are curve clustering and connectivity-based parcellation [80]. Curve clustering algorithms are typically either distance-based or feature-based. The distance functions range from simple Hausdorff measures to more complex integral measures. Given such a curve-to-curve distance function, a number of clustering algorithms can be applied including agglomerative clustering, normalized cuts, or spectral clustering [15] [75] [123] [79]. Feature-based approaches represent curves by their endpoints, centroids, covariance matrices, shape descriptors, or distance fields [24] [27] [42] [66] [67] [108] [109]. Such parameter-oriented representations enable simple algorithms such as k-means or Gaussian mixture modeling to be applied, with varying degrees of anatomical specificity and computational cost. Another technique is connectivity-based parcellation, which identifies pathways that may connect gray matter areas. [107] [48] [17] [110]. The connectivity-based technique typically introduces some prior knowledge about cortical anatomy; however, the actual path taken by fiber bundles is less constrained than for clustering-based approaches.

While the region and bundle selection tasks are typically quite different, our second aim innovates by formulating an approach capable of handling both regional and bundle-based segmentation. Our approach applies probabilistic mixture models to represent the distribution of both spatial and orientation variables in fiber models. This idea is similar to the previously discussed feature-based approaches; however, our work distinguishes itself by including directional statistics to represent orientations and their dispersion in anatomical structures. This extension is significant because probabilisitic models can benefit from theoretical developments that are quite general [12]. We propose that by developing this type of approach further, diffusion MR imaging can benefit from many of the recent results in probabilistic machine learning and statistics. Related works have performed regional segmentation of ODFs using normalized cuts [13], as shown in Figure 2. Related bundle segmentation algorithms have employed probabilistic models of fiber trajectories [109] [94]. Our approach will also produce bundle parameterization which will be compared to other arc-length parameterization methods [81] [79] [25] [67].

C.3 Applications to clinical studies

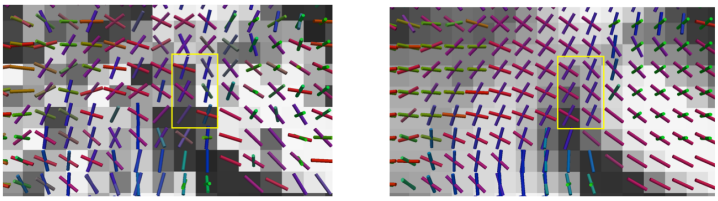
In our third aim, we propose to apply the methodology developed in the first two aims to clinical studies, providing both a practical guide for development and a basis for validation. Defining the practical value of our methodology ensures that our results are not specifically tied to a single small test dataset. Furthermore, by developing with a full study in mind, we can ensure that our methods are reasonably efficient and generalizable, which helps our long-term goal to apply these computational tools in a variety of areas. This aim also provides a basis for validation, where we can compare our approach to other methods for population analysis. We will perform controlled experiments to validate the theoretical claims in the first two aims; however, the application to clinical studies may provide a more important high level understanding of the how valuable our proposed methods will be. This can improve our understanding of the limitations of popularly used tools and what our proposed methods offer. Finally, we propose to study the effect of algorithm parameters on statistical results, which has a practical value for scientific applications.

Our work builds off existing methods in two ways: first, we quantitate white matter integrity with tensor [7] [58] and tractography derived metrics [28], and second, we use deformable registration [101] as a first step in making comparisons between subjects. Clinical studies of white matter typically employ diffusion tensor imaging to measure several indices of white matter integrity, including fractional anisotropy (FA), mean diffusivity (MD) [116] [89], and statistics of tractography [97]. To compare measurements across subjects, some mechanism is needed to establish anatomical correspondence between subjects. This can be done on a voxel-by-voxel basis through deformable registration, an approach similar to Voxel-based Morphometry (VBM) [4]. Misregistration is a common problem and is usually accommodated by spatial smoothing. Tract-based Spatial Statistics (TBSS) [99], a popular alternative to smoothing, computes a white matter skeleton and projects each subject's skeleton to the nearest point on some template skeleton. Another typical approach is to measure FA or MD along atlas-based fiber bundles, which can be found by from surfaces [119] or tractography [24] [79] [25] [67]. Our approach may provide more specific measures for complex fiber bundles that have subtle branching patterns. For example, in the arcuate, there may be several anterior cortical projections that would be grouped together with the standard arclength parameterization techniques.

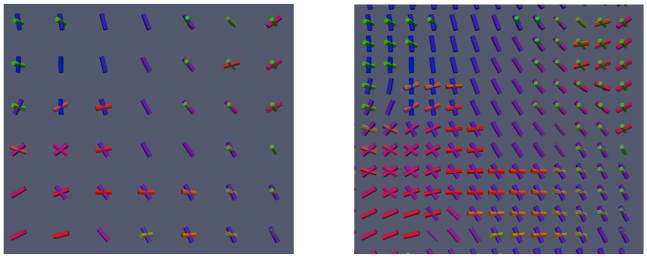
This aim is significant because we will demonstrate the clinical value of the previous aims by producing real insight into scientific problems. Through further experiments, we can also gain insight into the performance of our tools relative to existing approaches, hopefully revealing strengths and weaknesses of each. In relation to the first study, previous work has found a combination of global and local effects with normal aging. Principal component regression of fiber bundle FA has shown global effects, where a single component accounts for a large amount of variation. Studies of more local effects have found a reproducible trend of anterior to posterior decline in FA with age. We plan to explore these two findings with respect to the region- and bundle-based analyses. [60] [45] [43] [73] [86] [70] [23] [95] [8] [85] [68]. For the bipolar study, related works have found frontal-temporal effects with gray matter and functional imaging, as well as cingular and frontal effects in white matter. White matter analyses have mostly performed TBSS with several studies using manually placed regions or voxel-based analysis [1] [65] [40] [6] [32] [33] [84]. We hypothesize that the frontal-temporal effects observed in T1 and fMRI studies will be reflected in our diffusion-based analysis as well. These results will serve as points of comparison of our studies, and we'll consider how our approach fills gaps in the understanding of both normal and pathological anatomical variaion of these populations.

D Preliminary Work

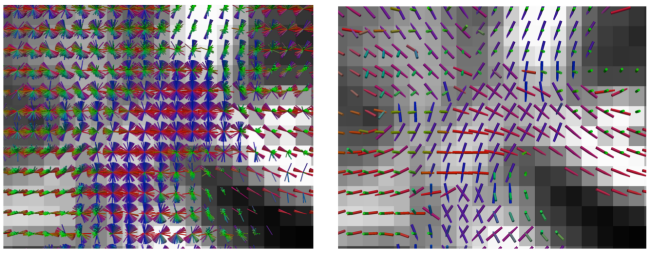
In this section, we discuss preliminary work done towards the specific aims and how to they relate to the proposed work. We also discuss resources related to the project, such as datasets, hardware, and software.



(a) Smoothing, with noisy (left) and gaussian filtered fibers (right)



(b) Interpolation, with source (left) and trilinearly upsampled fibers (right).



(c) Fusion, with a population of fiber models (left) and a composite (right).

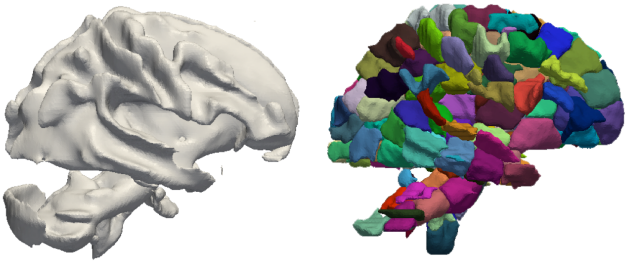
Figure 3: Preliminary work on the model-based processing framework applied to smoothing, interpolation, and fusion tasks. Fibers are colored by orientation. Note fiber volume fractions are also modeled but now shown here.

D.1 Model-based image processing

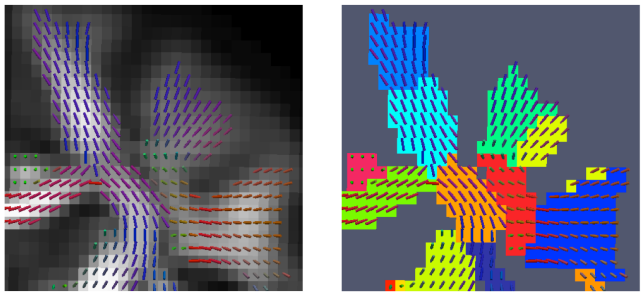
We've conducted preliminary work on the first aim where we explored a clustering approach for performing interpolation, smoothing, and fusion of multi-fiber models. In particular, we found that mixture of Watson clustering could be applied to solve optimization problems for these tasks. Traditional techniques including trilinear interpolation and Gaussian smoothing were extended to multi-fiber models, and a fusion approach allowed a multi-fiber tractography atlas to be constructed. This work was accepted for podium presentation at the 2013 conference for Medical Image Computing and Computer-assisted Intervention (MICCAI) [19] and poster presentation at the 2013 conference for the Organization for Human Brain Mapping (OHBM). Next steps will make the approach more theoretically sound and allow for practical extensions including interpolation with irregular samples and edge-preserving smoothing.

D.2 Segmentation of white matter structures

We've also conducted preliminary work on the second aim by developing tools for performing regional segmentation of white matter. In this work, we derived a clustering algorithm that parcellates white matter voxels similarly to the k-means algorithm, with two notable extensions. First, we include a term that encourages clusters to have coherent fiber orientations, and second we include a regularization term that provides a data-driven way to select the number of clusters [55]. We applied this to a white matter template and found the resulting regions to better match known anatomical boundaries than traditional k-means clustering. This work was accepted for podium presentation at the 2013 MICCAI Workshop on Medical Computer Vision [18] and poster presentation at the 2014 conference for the OHBM. These results demonstrated that this approach is efficient and has potential clinical applications. Further work will generalize this to the full probabilistic mixture model and develop this technique for fiber bundle segmentation. In addition, we'll explore methods for label transfer from the template to the subject volumes to support group analysis of both regions and bundles.



(a) Surface view of the regions, showing the boundary of the white matter (left) and general shapes, sizes, and distribution of regions (right).



(b) Slice view of the regions, showing the input fiber positions and orientations (left) and the extracted regions (right).

Figure 4: Preliminary work on the regional segmentation by hard clustering. Note the regions boundaries coincide with gyral white matter in 4a and corpus callosum/cingulum, corona radiata/superior longitudinal fasciculus interfaces in 4b.

D.3 Clinical Applications

We've conducted preliminary work on the third aim by forming two research collaborations, performing data cleaning, and starting data analysis. Our first collaboration is with Dr. Mark Bastin at University of Edinburgh, which will further the normal population study. Our second collaboration is with Dr. Daniel Dickstein at Brown University, which will further the pediatric bipolar population study.

For the normal population study, all data has been collected, and initial data cleaning and preprocessing have been completed. We've also conducted preliminary data analysis, where we mapped changes in fractional anisotropy using both bundle-based segmentation with lobular regions and bundle-based segmentation using tractography and atlas regions. This work was presented as a poster at the 2013 meeting of the International Society of Magnetic Resonance Imaging in Medicine (ISMRM).

For the pediatric bipolar population, all data has been collected and cleaning and preprocessing have been completed. We've performed a preliminary connectivity study of pilot data, which was presented as a poster at the 2012 meeting of the ISMRM. We have also conducted some preliminary work applying the regional segmentation approach to the full dataset, which has given some positive results. We'll follow up on this work by applying both segmentation approaches and performing statistical analysis across the space of algorithm parameters. In addition, we'll use the multi-fiber processing framework to build population-specific brain templates which can be used for visualization of statistical results and general data exploration. Finally, in the course of these experiments and others, a significant amount of software was developed which will help facilitate further work [14] [96].

D.4 Research Environment

Datasets: Our experiments will be conducted with several datasets. First, we'll use the adult normal dataset collected at University of Edinburgh with Dr. Mark Bastin. This consists of 80 subjects with T1-weighted and diffusion-weighted MRIs along with patient data measuring cognitive, memory, and reaction time performance. In addition, multiple acquisitions of eight subjects are available for measuring test-retest reliability. Second, we'll use the pediatric dataset collected at Brown University and Bradley Hospital by Dr. Daniel Dickstein. This consists of roughly 60 subjects with T1-weighted and diffusion-weighted MRIs, evenly split between patients and typically-developing controls.

Resources: During the project, a significant amount of technical resources will be required. For computation and data management, the Brown CS system will be used. This includes a large filesystem and grid computing

environment. This system already supports a suite of software that will be required, including Freesurfer [38], FSL [100], DTI-TK [122], and 3D Slicer. Finally, much of the proposed work will be custom built on top of our code, which already supports basic functionality, such as data structures, file formats, diffusion model fitting, interactive visualization, and parallel computing.

E Research Plan

In this section, we discuss detailed plans for achieving the contributions of each specific aim. The expected completion date of the dissertation work is the end of Summer 2015 and a detailed timeline of completed and projected milestones are shown in Tables 1 and 2, respectively.

E.1 Multi-fiber processing

To achieve Aim 1, we plan to complete the following steps: derive the model-based image processing framework, implement the system in our codebase, construct synthetic phantoms, conduct experiments testing hypotheses of improved tractography and atlas construction, and prepare written artifacts documenting our findings.

The first step is to derive the framework, which is an extension of the work of Milanfar et al [74] to support fiber orientations. The original framework generalizes interpolation, smoothing, and fusion tasks by considering a class of local least squares estimators, for example, an estimator $\hat{f}$ for an image at a point x in space:

$$\hat{f}(x) = \underset{f}{\operatorname{argmin}} \sum_{(x_n, y_n) \in \mathbf{N}} K\left(\frac{\|x - x_i\|^2}{h^2}\right) \|y_n - f(x_n)\|^2 \tag{1}$$

given a collection of pixel positions x_n and intensities y_n in in some some neighborhood $\mathbf{N}$ of x, a kernel function K, and some space of functions for f. When f is taken to be a constant function, this is known as the Nadaraya-Watson estimator [78, 112]. In this thesis, we extend this idea to multi-fiber diffusion models; in particular, we consider a representation by a set of fiber orientations and associated volume fractions in each voxel, which are key elements for performing tractography. We employ the ball-and-sticks diffusion model [9], which explicitly represents the volume fractions as the proportion of the the voxel occupied by a particular fiber. However, a variety of other diffusion models could be used as well. For example, a single tensor could be represented by the principal diffusion direction and the fractional anisotropy. Similarly, an orientation distribution function could be represented by the peak orientations and their associated probability mass. Given this, we consider the model $M = \{(f_i, v_i)\}_{i=1}^{N}$ of volume fraction and orientation pairs, and propose a fiber model estimator $\hat{M}$ as follows:

$$\hat{M}(x) = \underset{M}{\operatorname{argmin}} \sum_{(x_n, M_n) \in \mathbf{N}} K\left(\frac{\|x - x_i\|^2}{h^2}\right) d_m^2(M, M_n) \tag{2}$$

where the result lies on a manifold of possible fiber models, given some fiber model distance d in place of the standard Euclidean norm. In general, this may be difficult to compute, but in this thesis, we examine a formulation of this problem that is efficient and performs well on common diffusion imaging tasks. Specifically, we propose a model-based distance d_m for multi-fiber models as follows:

$$d_m^2(M, \hat{M}) = \min_{\pi} \sum_{j} f_j d_f^2(v_j, \hat{v}_{\pi(j)}) \tag{3}$$

which is taken over the set of all possible matchings π from fibers in M to fibers in $\hat{M}$. This is derived from a single fiber distance d_f^2:

$$d_f^2(a,b) = 2(1-(a\cdot b)^2) = 2sin^2(\theta) \tag{4}$$

We'll show that the resulting estimator can be efficiently optimized with an Expectation Maximization procedure similar to directional data clustering with a mixtures of Watsons model [19]. We'll also consider an extension to support data-adaptive processing (similar to a bilateral filter). This can be obtained by adding weights accounting for model-to-model distance in addition to the spatial proximity [120]:

$$\hat{M}(x) = \underset{M}{\operatorname{argmin}} \sum_{(x_n,M_n)\in\mathbf{N}} K\left(\frac{d_e^2(x_i,x_0)}{h_p^2}\right) K\left(\frac{d_m^2(M_i,M_0)}{h_m^2}\right) d_m^2(M,M_n) \tag{5}$$

Theoretically, such a data-adaptive estimator should preserve boundaries between structures [50] [5]. To perform multi-fiber tractography, we'll employ a method similar to Extended Streamline Tractography [92].

We'll implement these techniques in our codebase and conduct experiments with synthetic as well as real clinical data. Our synthetic dataset will include two types of computational phantoms: the first will be a simple interface between fiber bundles, and the second will be a more complex set of three bundles that cross and branch. The real clinical data will be from the Edinburgh study, which includes eight participants with three repeated acquisitions and 80 participants with single acquisitions.

Our synthetic data experiments will examine voxelwise measures of performance in the simple phantom and connectivity-based measures in the complex phantom. For this, we'll introduce varying levels of realistic Rician noise to the ground truth phantoms and measure the resulting error, comparing the proposed approach and previously developed approaches. For the voxelwise tests, we'll measure the angular error with a Hausdorff distance, and for the connectivity tests, we'll manually delinete seed regions and expected trajectory masks and measure the Dice overlap coefficient.

Our real data experiments will examine brain white matter fiber bundle reconstruction in both individual subjects and a population atlas. For individual subjects, we'll measure scan-rescan reproducibility of tractography metrics of manually delineated bundles with the coefficient of variation and the intra-class correlation. For population atlas construction, we'll examine frontal-parietal bundles that are not typically found in diffusion atlases due to crossing fibers. We'll compare our reconstructions of these bundles to results from non-human tracing studies and the few dMRI reconstructions done in individual subjects. We'll also compare our multi-fiber atlas with related work on atlas construction with single tensors and ODFs.

E.2 Segmentation of anatomical structures

To achieve Aim 2, we plan to complete the following steps: derive models and algorithms for segmenting white matter, implement them in our codebase, conduct experiments testing our hypotheses about sensitivity, reliability, and agreement with human segmentations, and document our findings.

The first step is to develop a segmentation algorithm for both region and bundle mapping. Our main contribution here is to develop a mixture modeling approach that can be used for both of these tasks. In general, we consider how to statistically represent fiber orientation imaging data and use these models in the segmentation tasks. We propose a simple approach in which the image is represented the following density:

$$p(p,d|\Theta) = \sum_{i=1}^{K} \alpha_i P_N(p|\mu_i,\Sigma_i) P_W(d|\omega_i,\kappa_i) \tag{6}$$

given an input fiber position p, input fiber direction d, parameters Θ that encode the mixing weights α_i, positional means μ_i, positional covariances Σ_i, directional means ω_i, and directional dispersions κ_i. The components are defined by a product of Gaussian P_N and Watson P_W distributions:

$$P_N(p|\mu,\Sigma) = ((2\pi)^n|\Sigma|)^{-\frac{1}{2}} \exp\left(-\frac{1}{2}(p-\mu)^T\Sigma^{-1}(p-\mu)\right) \tag{7}$$

$$P_W(d|\omega,\kappa) = \frac{\Gamma(n/2)}{(2\pi)^{p/2}M(\frac{1}{2},\frac{n}{2},\kappa)} \exp\left(\kappa\left(\omega^T d\right)^2\right) \tag{8}$$

$$\tag{9}$$

This gives a simple representation of the image as a collection of roughly uniform patches of fiber orientations. We hypothesize this is a useful structure for modeling fiber bundles found in white matter. In particular, this allows for components that overlap (to model crossing bundles) and dispersion (to model fanning and branching). We'll show that this model can be fit efficiently with an Expectation Maximization procedure [12] that extends mixture of Watsons clustering to include the spatial Gaussian term [102]. Two issues that will be explored in the course of the thesis are model selection (to choose the number of components in the mixture) and computational efficiency (because parameter estimation in the Watson includes some numerical challenges). Next, we'll discuss how this model provides a basis for both region and bundle segmentation.

For region segmentation, we'll generally work on extracting small homogeneous regions, such as those shown in Fig. 4. These are not intended to capture entire bundle structures, rather, the goal is to break the volume up into a number of areas that tend not to cross known anatomical boundaries. This idea is similar to "superpixel" approaches in the computer vision literature [22]. This can then provide measures of white matter that are useful for testing hypotheses about specific locations of brain anatomy. The mixture model approach is naturally suited for this, as each voxel or fiber can be associated with the mixture component statistically most likely to produce it. This can also be performed across subjects by performing the initital segmentation in an atlas and deforming each individual subject to the atlas before assigning region labels. Of course, noise and mis-alignment are potential problems in the process, so we'll explore spatial regularization with Markov random fields [53] [41].

For bundle segmentation, we'll consider two related tasks. The first is a supervised learning task to select fibers from whole brain tractography that lie in some known bundle. For this, we use the complete mixture model to represent a given bundle. A bundle classifier can then be built that computes the probability that all points along a curve lie in the bundle. This is similar to the Mixture Discriminative Analysis of Hastie et al [52], but uses a density derived from the above mixture model. An issue that will be explored in the thesis work is how to represent "background" fibers that outside the bundle. The second task is to "dissect" a bundle into parts that can be matched across subjects (like prior work that used arc-length parameterization [81]). Given a segmented bundle, the "dissection" step can then be performed similar to the region mapping, where a label is chosed by the most likely component. This can be similarly applied to group analysis through deformable registration.

We'll then implement these techniques and conduct experiments with real clinical data. We'll use test-retest data from the Edinburgh dataset to assess sensitivity and reproducibility. For each region and bundle, we'll compute diffusion indicies including fractional anisotropy, mean diffusivity, and volume fraction. We expect these to be reproducible across acquisitions of the same subject, as well as distinct among subjects. In a statistical sense, this means the within-subject variability should be low and the between-subject variability should be relatively high. To quantify these, we'll measure the coefficient-of-variation within scans of the same subject and the intra-class correlation across acquisitions and subjects. We'll compare these approaches to related voxel-based and skeleton-based methods. We'll also compare the bundle mapping to manual segmentations [54] and existing white matter atlases [77] [20] to assess agreement with human annotations, and compare our bundle parameterization approach to the standard arc-length parameterization approach [81].

E.3 Clinical Applications

Our first application is in collaboration with Dr. Mark Bastin at University of Ediburgh. We plan to study both global and local changes in white matter integrity that occur due to normal variation in age and sex. The dataset used for this study was acquired from an adult population of 80 subjects with patient information, such as age, sex, reaction time, memory, and cognitive performance available as covariates. We'll perform both region-based and bundle-based analyses and compare the results to existing literature on cognitive aging and sexual dimorphism.

Our second application is in collaboration with Dr. Daniel Dickstein at Brown University and Bradley Hospital. We plan to measure anatomical changes associated with pediatric bipolar using the region and bundle analyses. We'll compare our results with the literature across imaging modalities, including dMRI, T1-weighted MRI, and resting-state functional MRI.

To achieve Aim 3, we plan the following steps: apply the techniques of Aims 1 and 2 to both the Edinburgh and bipolar datasets, perform statistical analysis quantifying the relationship of microstructure measures to patient data, evaluate the sensitivity of our results to algorithm parameters, compare to other voxel-based and skeleton-based methods, and prepare manuscripts documenting findings.

In the first step, we'll first construct population templates for each dataset. It is important to do this for each study, as there is a significant difference in ages, i.e. the Edinburgh consists of adult participants aged 25 to 65 and the bipolar study includes participants aged 8 to 17. [121]. We'll first use DTI-TK to compute deformable spatial transformations that coregister the population. We'll then construct volumetric and tractography templates for each population using these spatial transformations and the methods described in Aim 1. This will serve as both a domain for segmentation as well as an anatomical reference for visualizing group differences.

Next, we'll perform both region-based and bundle-based segmentation of each template and propagate the segmentations to each subject. For each region and bundle, we'll compute average tensor indices, including fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity. These will serve as indices of white matter integrity for statistical analysis.

For the Edinburgh study, we'll perform two statistical analyses. First, we'll perform global principal component regression, similar to Penke et al [86]. They found a dominant global pattern for variation that we expect to reproduce. Second we'll perform a more typical regression analysis relating the white matter integrity of each region to the age, memory performance, reaction time, and cognitive performance of each subject. For the bipolar study, we'll perform a regression analysis relating the white matter integrity to the clinical group, sex, and age of each participant. For both studies, we'll perform False Discover Rate control to account for multiple comparisons and assess statistical significance by the resulting q-value.

The results will be visualized by color maps on 3D models of the template brain anatomy, where the user may interactively change the pose of the model, the visibility of anatomical structures, and the parameters of the color mapping. We'll test our hypotheses about improved performance over voxel-based and skeleton-based approaches by directly applying the publicly available pipelines for each and comparing the results. While it's difficult to definitively say which method is better (as no ground truth is available), we can compare the number of statistically significant results found in each method, as well as measures from other modalities, such as cortical thickness [37]. In addition, we will evaluate using error rates obtained from logistic regression classifiers with cross-validation. We'll also perform sensitivity analysis to understand the effect of different algorithm parameters on our results.

Table 1: Milestones already accomplished

Date	*Contribution*
November, 2011	[Aim 3] ISMRM abstract: Preliminary pediatric bipolar connectivity
November, 2012	[Aim 3] ISMRM abstract: Preliminary normal aging connectivity
January, 2013	[Aim 1] OHBM abstract: Multi-fiber fusion
March, 2013	[Aim 1] MICCAI paper: Multi-fiber processing framework
June, 2013	[Aim 2] MCV paper: Region segmentation algorithm
January, 2014	[Aim 2] OHBM abstract: Groupwise region segmentation algorithm
June, 2014	[Aim 1] CDMRI paper: Bilateral filtering algorithm
July, 2014	[Aim 1/3] DTI Challenge paper: Filtering application

Table 2: Milestones for the proposed work

Date	*Contribution*
December, 2014	[Aim 1] Conduct orientation processing experiments
December, 2014	[Aim 1] Submit orientation processing journal paper
January, 2015	[Aim 3] Submit pediatric bipolar journal paper
January, 2015	[Aim 2] Develop segmentation algorithms
February, 2015	[Aim 2] Conduct segmentation experiments
February, 2015	[Aim 2] Conduct Edinburgh experiments
March, 2015	[Aim 2] Submit segmentation paper
April, 2015	[Aim 3] Submit Edinburgh journal paper
July, 2015	Circulate thesis draft to committee
August, 2015	Complete thesis
September, 2015	Defend Thesis

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