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NEURONAL WHITE MATTER PARCELLATION USING SPATIALLY COHERENT NORMALIZED CUTS

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Abstract

This work presents an automated method for partitioning neuronal white matter (WM) into regions of interest with uniform WM architecture. These regions can then be used to replace atlas-derived regions for any subsequent statistical analysis. The fiber orientation distribution function is used as a model of WM architecture resulting in a voxel similarity function sensitive to both fiber orientations and configurations. The method utilizes the normalized cuts algorithm to partition WM voxels based on this similarity function along with a connected component labeling algorithm to ensure spatial compactness. We illustrate the algorithm's ability to discern regions based on both orientation and complexity through its application to a simulated fiber crossing and an in-vivo dataset.

Index Terms

DW-MRI; FOD; HARDI; Parcellation; Clustering

1. INTRODUCTION

Diffusion weighted MRI (DW-MRI) has become the predominant modality for the non-invasive investigation and characterization of neuronal white matter (WM) architecture and fidelity. It has been successful in demonstrating group WM differences between healthy and diseased populations and for identifying spatial and anatomical regions which are affected [1, 2, 3, 4].

A common approach in studies such as these is to average a WM feature or features of interest within regions derived either from an anatomical atlas [5, 6] or from subject specific fiber tracking [7]. These region of interest (ROI) averages are then used in subsequent statistical analysis to identify group differences as well as for specifying spatial locations where these differences occur. When compared with voxelwise analysis, this approach is more robust to spatial normalization errors, since it includes spatial averaging, and is less susceptible to multiple comparison corrections.

However, because these ROIs are anatomically derived they often extend through a range of diverse WM architectures (orientations, crossings etc). This heterogeneity is problematic, particularly when using robust WM features such as the diffusion tensor or higher order diffusion models, in subsequent analysis. Anatomical ROIs are intended to represent anatomical structures and are therefore often not uniform in the feature space of interest. This nonuniformity causes the representation of the ROIs via their averages to be suspect. This can be seen in figure 2-D which shows a measure of region nonuniformity for the anatomical regions of the EVE [6] atlas. Note that many of the central WM ROIs have a high degree of nonuniformity.

This work seeks to address these issues by applying the superpixel [8] methodology popular in computer vision to medical imaging. We present an automated method to determine white matter ROIs based on their uniformity within the feature space. Beginning with a single WM region or a set of anatomically defined regions, we iteratively partition the ROIs into spatially connected subregions, using a normalized-cut clustering routine and a seed growing algorithm to enforce spatial connectedness. Once the nonuniformity of every ROI falls below a prescribed threshold the process is stopped.

While WM features derived from diffusion tensor imaging (DTI) could be utilized to describe voxel similarity and region uniformity these features suffer from an inability to model complex WM. Since our goal is to define ROIs which will aid in the subsequent statistical analysis of WM architecture as it relates functional and structural connectivity we require the identification of regions based both on WM complexity as well as orientation. A task DTI based features are ill-suited for. For this reason our method utilizes the fiber orientation distribution function (FOD), a popular high angular resolution diffusion imaging data model, to measure the similarity between WM voxels and the regional uniformity. The FOD model is able to capture the orientations and configurations [9, 10] of neuronal fiber bundles yielding the nuanced ROIs which are required by subsequent analysis.

We begin an overview of the proposed method in section 2. The details of the normalized cuts algorithm including the similarity measure used are discussed in section 2.1 and the routine for determining connected subcomponents is described in section 2.2. We apply the method to a simulated dataset of a fiber crossing in section 3.1 and to an in-vivo human dataset in section 3.2. In section 4 and 5, we conclude with a discussion of the method.

2. METHOD OVERVIEW

The proposed method takes an FOD image and a collection of initial regions of interest and partitions these ROIs into spatially connected regions based on the similarity between the FODs making up the output regions.

The FOD image is a collection of FODs fit to each WM voxel in the template space. The FOD model represents the voxel's DW-MRI signal as the spherical convolution of the fiber orientation distribution function (FOD) and the DW signal that would be measured for a single fiber bundle aligned along the z-axis. Information concerning both the orientation and partial volume of any fiber bundles in a voxel is represented via the FOD [9, 10]. In this work each voxel is represented by the real spherical harmonic (RSH) coefficients of its FOD. This representation allows the computation of the difference between two FODs using the L2 norm of the RSH coefficients.

The initial ROIs are supplied as a labeled image, with each label specifying a unique ROI. While these ROIs could take on many forms we will focus on two possibilities. First the labeled image could simply consist of a single ROI specifying every WM voxel allowing the partitioning algorithm to fully delineate the borders of the resultant ROIs. Alternatively, the initial ROIs could be used to impart some anatomical information determined from either fiber tracking or an anatomical atlas. Since these initial ROIs are then subdivided, they provide a means of imparting anatomical context to the output ROIs at the expense of allowing the method to fully determine the boundaries of every ROI. This trade off will be discussed briefly in section 3.2.

The initial step in our algorithm is to parse the initial labeled image in to a collection of regions. Any regions that contain more than one spatially connected component are divided yielding a collection, C , of spatially connected regions derived from the supplied labeled image. From C we choose the region which is most heterogeneous with respect to the FODs

it contains. A region's heterogeneity is represented by the average squared distance (equation 1) between the mean FOD (μ) and the FOD (f_i) of every voxel in the region. This measure is related to the normalized trace of the FOD covariance matrix, thus has an interpretation similar to a variance.

$$\Phi(R) = \frac{1}{n} \sum_{i \in R} \|f_i - \mu\|_{L2}^2 \quad (1)$$

Once the region with the highest nonuniformity ($\Phi(R)$) is determined, it is partitioned using the normalized cuts (N-Cut) algorithm, discussed below in section 2.1. This process is mediated by the chosen form of the similarity function (equation 2). In this work we use the canonical choice of a Gaussian kernel over the FOD domain, with standard deviation σ_f and optionally another Gaussian kernel (standard deviation σ_s) over the spatial locations, to describe the similarity between two WM voxels. The N-Cuts algorithm has no explicit criteria for enforcing spatial connectedness. Therefore the two resultant clusters are further partitioned into spatially connected subcomponents using the seed growing algorithm described in section 2.2. Thus at each iteration the region with the highest nonuniformity is replaced by spatially compact subregions. We repeat the process until every region has a nonuniformity below a predefined threshold ε . Finally these regions are used to generate an output label map.

Algorithm 1

Overview of Proposed Method

Input: Initial ROIS: C

Input: N-CUTS parameters: σ_f, σ_s

Input: Stopping criteria: ε

Output: Final ROIS: C'

$C' \leftarrow C$

while $\max_{R \in C} \Phi(R) \geq \varepsilon$ **do**

Identify the region, C_i , with the maximal degree of nonuniformity.

Remove C_i from collection C' .

Partition C_i using normalized cuts (section 2.1) into C_{i1} and C_{i2} .

Extract all the spatially connected regions (section 2.2) from both C_{i1} and C_{i2} .

Add new spatially connected regions to collection C' .

end while

2.1. Normalized Cuts

The normalized cuts (N-Cut) algorithm [11, 12] is a means of partitioning a set of data points x , in our case a set of white matter voxels, based on a provided similarity measure $k(x, y)$. Using the similarity measure we build an affinity matrix such that $K_{ij} = k(x_i, x_j)$. The affinity matrix describes the weights of a fully connected undirected graph using x as the nodes. The N-cut algorithm labels each node dividing the vertices into 2 sets A and B. The cost $Cut(A, B)$ is the sum of all connections between elements of A and elements of B. The

goal is to find the labeling that minimizes the normalized cut, $Cut(A, B) \left(\frac{1}{Vol(A)} + \frac{1}{Vol(B)} \right)$ where $Vol()$ is the sum of the weights within a set.

The labeling is found via a relaxation to the above problem by finding the second largest eigenvector, $\mathbf{v}$, of the matrix $\mathbf{D}^{-\frac{1}{2}} \mathbf{K} \mathbf{D}^{-\frac{1}{2}}$. Where $\mathbf{D}$ is a diagonal matrix whose i th element is the sum of all elements in the i th row of $\mathbf{K}$. The labels are determined by examining the sign of $\mathbf{v}$. For a complete description please see [11, 12].

Our application of the N-Cut algorithm concerns the ability to label WM voxels based on their FOD. As discussed above we use a Gaussian kernel with standard deviation of σ_f as the basis of our similarity measure. When working without initial anatomic regions our datasets can be on the order of 80,000 elements making storage of the $\mathbf{K}$ matrix unfeasible. In order to increase the sparsity of $\mathbf{K}$ we can optionally include a second Gaussian kernel sensitive to the spatial locations of the voxels yielding the following similarity measure:

$$k(x_i, x_j) = \begin{cases} e^{-\frac{\|f_i - f_j\|_{L^2}^2}{2\sigma_f^2}} & \sigma_s = 0 \\ e^{-\frac{\|f_i - f_j\|_{L^2}^2}{2\sigma_f^2}} e^{-\frac{\|p_i - p_j\|^2}{2\sigma_s^2}} & \sigma_s > 0 \end{cases} \quad (2)$$

where x_i and x_j are WM voxels with f_i, f_j , p_i , and p_j being the corresponding FODs and spatial locations.

Algorithm 2

Seed growing algorithm to extract spatially connected components

Input: List of voxels X

Output: List of labels L

labelValue = 1

labelMembers = $\emptyset$

for all $x \in X$ **do**

if x is not labeled **then**

 add x to labelMembers

repeat

y = next element of labelMembers

$L[y]$ = labelValue

 add all unlabeled neighbors to labelMembers

until all members of labelMembers have been visited

 labelValue = labelValue + 1

 labelMembers = $\emptyset$

end if

end for

Given a collection of WM voxels we compute the affinity matrix $\mathbf{K}$ using the above similarity function. To further increase sparsity any elements of $\mathbf{K}$ that are less than 10^{-2} are set explicitly to 0. We then compute the matrix $\mathbf{D}$ and determine the second largest eigenvector, $\mathbf{v}$, of $\mathbf{D}^{-\frac{1}{2}} \mathbf{K} \mathbf{D}^{-\frac{1}{2}}$ using the SLEPc [13] software package. Two new regions are determined based on the sign of $\mathbf{v}$.

2.2. Spatially Connected Component Extraction

In order to extract all spatially connected subcomponents of a region we use a simple seed growing algorithm. A supplied region consists of a set of voxels that are initially unlabeled. These voxels are then labeled using the seed growing algorithm described in algorithm 2. Each unique label is then used to create a new spatially connected region.

3. EXPERIMENTS

We applied our partitioning method to two example datasets. The first dataset, consisting of a simulated crossing of a straight and semi-circular fiber bundles, was investigated to illustrate the effect that WM orientation and complexity has on the output ROIs. Secondly, we applied the method to a single subject's DW-MRI data fitted with FODs. The method was initialized with both anatomically defined regions as well the entire neuronal WM to illustrate the two main use cases of the method.

3.1. Simulated Fiber Cross

A 64 direction, $B=3000 \frac{s}{mm^2}$, DW-MRI dataset, with Rician noise ($\sigma = 0.05$), was simulated using the Numeric Fibre Generator (NFG) [14]. A fiber crossing between a straight and curved fiber bundle was modeled. Each bundle was segmented into smaller fibers modeled

as a diffusion tensor with fractional anisotropy of 0.8 and mean diffusivity of $0.0009 \frac{mm^2}{s}$. FODs were computed using constrained spherical deconvolution [15] to estimate an order 8 FOD at each voxel and the parcellation method was applied using the following parameters, $\sigma_f = 0.3$, $\sigma_s = 0$ and $\varepsilon = 0.1$. Other parameter sets were used but with negligible effect.

The regions determined by the method can be seen in figure 3.1. A single ROI was determined for the fiber crossing region as well for the remaining portions of the horizontal fiber bundle. The curved fiber bundle is separated into a number of regions containing similarly oriented FODs. For each of these ROIs we would have confidence that the average FOD is a good representation of the region's WM architecture. Contrast this with anatomical ROIs defined by the actual fiber bundles. Since both bundles pass through the crossing region the FODs of the cross would contaminate the averages of both bundles. More problematically the FODs being averaged for the curved fiber bundle have a wide range of orientations obfuscating any directional information. These factors would cause neither fiber bundle to be well represented by its average.

3.2. In-vivo Dataset

A DW-MRI dataset of a healthy human subject was acquired on a Siemens (Siemens Medical Systems, Iselin, NJ) Verio 3T scanner using a spin-echo, echo-planar imaging

sequence, $TE = 106ms$, $TR = 16.9s$, $2mm$ isotropic voxels, $b=3000 \frac{s}{mm^2}$ and 128 gradient directions with 4 images with no diffusion weighting. An FOD image of order 8 was computed using the CSD method. A neuronal WM mask was generated by applying FSL FAST [16] segmentation algorithm to a T1 structural image rigidly registered into the DW-MRI space. Finally, anatomical labels were acquired by registering the John Hopkins EVE atlas [6] to the T1 image using a scalar diffeomorphic demons registration algorithm.

We applied our method to the FOD image using both the anatomical labels as initial regions as well as using the set of all WM voxels as an initial region. In all cases the standard deviation of the feature space Gaussian kernel (σ_f) was 0.3 and we halted the process when every region had a nonuniformity (equation 1) smaller than $\varepsilon = 0.15$. When the EVE ROIs

were used for initialization we performed a parcellation using only the feature kernel ($\sigma_s = 0$) as well as one using both the spatial and feature kernels ($\sigma_s = 6$). When using the entire WM mask as the initial region we only performed a parcellation using $\sigma_s = 6$ which enables the affinity matrix to be stored in the available RAM ($\sim 40Gb$).

Figure 2 shows the initial Eve labels mapped onto the subjects WM (A) and the nonuniformity of these regions (D) followed by the ROIs and regional nonuniformity measures computed via the proposed method initialized with the EVE labels (B,E) and those determined without the anatomical labels (C,F). Maps derived from EVE labels and $\sigma_s = 6$ were not shown due to similarities to both B and C. The number of ROIs, single voxel ROIs and the maximum of the region heterogeneity can be see in figure 3.

A number of interesting observations can be garnered from these results. First all applications of the proposed method produce ROIs of the desired uniformity making them useful for subsequent analysis. Secondly, When initialized with the EVE labels a much larger number of single voxel regions (1073 vs 201) are determined using only the FOD kernel ($\sigma_f = 0.3, \sigma_s = 0$) as opposed to using both kernels ($\sigma_f = 0.3, \sigma_s = 6$), suggesting that the σ_s parameter has the expected effect of producing spatially smoother regions in addition to making the affinity matrix more sparse. Finally, when initializing the method only with the WM mask fewer ROIs and fewer single voxel ROIs are produced than when the method is initialized with only the WM mask. While fewer ROIs is a desired trait it is important to remember that this comes at the expensive of the anatomical information available via the atlas.

4. DISCUSSION

It should be noted that this method is not intended as a segmentation method but instead should be used to determine regions for subsequent analysis. An envisioned application would proceed as follows. Supplied with a population of spatially normalized DW-MRI datasets, a population average FOD image could be computed. This average FOD image would be partitioned using this algorithm to determine ROIs of uniform WM architecture. The resultant ROIs would then be used to perform group-wise statistical analysis on the population or for determining WM features to aid in automated classification.

While the focus of this work was to determine ROIs with uniform WM architecture the methodology employed is quite general. An interesting extension of the methodology would be to utilize structural or functional connectivity to determine the similarity between voxels. While one wouldn't expect that regions of uniform WM architecture would also have uniform connectivity profiles, a comparison of both sets of regions may illuminate interesting structural and functional relationships of WM regions.

5. CONCLUSION

In this work we present a method for the parcellation of neuronal WM using the fiber orientation distribution function to represent WM architecture. Our desire is to create regions which are spatially connected, while also being suitably homogeneous. The proposed framework provides two parameters which affect the smoothness of the ROIs, in the spatial and feature domain, as well as providing a means of imparting anatomical information by supplying an initial set of anatomical ROIs to partition. We show that regions determined by this method are more uniform than those defined using anatomy alone and therefore are better candidates for subsequent region-based analysis.

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Fig. 1.

A) Simulated crossing fiber bundles generated by Numeric Fiber Generator[14], B) Regions with variance below $\varepsilon = 0.1$, generated via the proposed method using a Gaussian kernel ($\sigma_f = 0.3$) to measure FOD similarity. The area containing the fiber crossing is clearly distinguished as are regions with similar orientations.

Fig. 2. Representative slices of regions and regional nonuniformity are shown for the Eve atlas (A,D), resultant regions when initialized with Eve atlas ($\sigma_s = 0$, $\sigma_f = 0.3$) (B,E) and results only initialized with white matter ($\sigma_s = 6$, $\sigma_f = 0.3$) (C,F).

	# ROIs	# SV ROIs	Max $\Phi(R)$	Figure 2 Label
Eve Atlas	275	68	0.56	A, D
Proposed Method using EVE (only FOD kernel)	2971	1073	0.149	B, E
Proposed Method using EVE (Both kernels)	1984	201	0.149	Not Shown
Proposed Method using All WM (both kernels)	1670	115	0.149	C, F

Fig. 3.

Number of ROIs, the number of single voxel (SV) ROIs and max region non uniformity ($\Phi(R)$) are displayed for the EVE atlas, the proposed method ($\sigma_f = 0.3$, $\varepsilon = 0.15$) initialized with the EVE ROIs using different similarity functions, only using FOD kernel ($\sigma_s = 0$), and using both the FOD kernel and the spatial kernel ($\sigma_s = 6$). Finally the proposed method initialized with the WM mask and using both the kernels ($\sigma_s = 6$).