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Multi-label segmentation of white matter structures: Application to neonatal brains

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ABSTRACT

Accurate and consistent segmentation of brain white matter bundles at neonatal stage plays an important role in understanding brain development and detecting white matter abnormalities for the prediction of psychiatric disorders. Due to the complexity of white matter anatomy and the spatial resolution of diffusion-weighted MR imaging, multiple fiber bundles can pass through one voxel. The goal of this study is to assign one or multiple anatomical labels of white matter bundles to each voxel to reflect complex white matter anatomy of the neonatal brain. For this, we develop a supervised multi-label k-nearest neighbor (ML-kNN) classification algorithm in Riemannian diffusion tensor spaces. Our ML-kNN considers diffusion tensors lying on the Log-Euclidean Riemannian manifold of symmetric positive definite (SPD) matrices and their corresponding vector space as feature space. The ML-kNN utilizes the maximum a posteriori (MAP) principle to make the prediction of white matter labels by reasoning with the labeling information derived from the neighbors without assuming any probabilistic distribution of the features. We show that our approach automatically learns the number of white matter bundles at a location and provides anatomical annotation of the neonatal white matter. In addition, our approach also provides the binary mask for individual white matter bundles to facilitate tract-based statistical analysis in clinical studies. We apply this method to automatically segment 13 white matter bundles of the neonatal brain and examine the segmentation accuracy against semi-manual labels derived from tractography.

Introduction

Diffusion weighted magnetic resonance imaging (DW-MRI) is a unique in vivo imaging technique that allows us to visualize the three-dimensional (3D) architecture of neural fiber pathways in the human brain. Diffusion tensor imaging (DTI) is a simple mathematical model derived from DW-MRI that characterizes the diffusivity profile of water molecules in brain tissue via a single oriented 3D Gaussian probability distribution function (PDF). Detailed labeling of the white matter based on DTI provides insights for understanding white matter development (Huang et al., 2006; Loh et al., 2012; Sadeghi et al., 2013) and detecting white matter abnormalities in disease (Goodlett et al., 2009; Owen et al., 2013; Wang et al., 2011). Nevertheless, it is challenging to obtain anatomical segmentation of the white matter in the neonatal brain since it is undergoing a critical growing process along with forms of cellular maturation, such as myelination and synaptic pruning (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2008). The delineation of white matter structures in the neonatal brain has thus far mainly relied on the fully manual segmentation (e.g., manually drawing regions of interest (Oishi et al., 2011) or semi-manual segmentation with the aid of DTI tractography techniques (Huang et al., 2006). Both are time consuming and require prior anatomical knowledge in order to achieve reasonable reproducibility (Kaur et al., 2014). In addition, Oishi et al. (2011) developed an atlas-based segmentation based on image registration to assign one anatomical label to each white matter voxel. To our best knowledge, no study to date has illustrated automatic segmentation that assigns multiple labels to each voxel in the white matter of the neonatal brain. The multiple labels per voxel can reflect true underlying white matter anatomy as between one and two thirds of the voxels in the human brain white matter are thought to contain multiple fiber bundles (Behrens et al., 2007). The proper white matter annotation is helpful for the interpretation of results derived from voxel-based analysis on DTI parameters, such as fractional anisotropy (FA), axial and radial diffusivity.

Although studies on automatic delineation of the neonatal brain white matter are limited, researchers have spent great efforts on developing tractography-based segmentation techniques for grouping fiber tracts into anatomically meaningful white matter bundles based on DTI data of adult's brain in the last decade (Brun et al., 2004; Clayden et al., 2007; Guevara et al., 2011; Jonasson et al., 2005; Li et al., 2010; Mayer et al., 2011; Ratnarajah et al., 2011). In general, tractography-

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based segmentation methods first employ DTI tractography algorithms to generate fiber tracts, then calculate pairwise distances among fiber tracts, and finally use clustering algorithms, such as hierarchical clustering (Guevara et al., 2011) or spectral clustering (Brun et al., 2004; O'Donnell & Westin, 2007), to group individual tracts into fiber bundles that can potentially characterize anatomically meaningful axonal connections. Even though tractography-based segmentation approaches are attractive and provide promising results, they remain nontrivial to automatically cluster tract trajectories without the involvement of expert anatomical labeling. In addition, fiber tracking reliability can vary with imaging resolution, noise, and patient orientation (Wakana et al., 2007). Moreover, the complexity of axonal connections cannot be fully imaged using DW-MRI with the voxel size at a millimeter scale. Thousands axons connecting different brain regions can pass through one voxel of DW-MRI. Hence, clustering algorithm cannot guarantee that tracts are correctly labeled as one of anatomically meaningful white matter bundles they belong to.

Recently, DTI has been widely used to study structural connectivity of the brain (Ratnarajah et al., 2013; Sporns, 2011; Toga et al., 2012) and hence the white matter can be parcellated based on the cortical regions they connect (Cook et al., 2005; Huang et al., 2005). However, the actual segmentation of the white matter by this connectivity-based method is usually not reported, i.e., the fiber trajectories are not generally visualized (O'Donnell et al., 2013). The tract grouping is highly dependent on the cortical parcellation. Li et al. (2010) recently proposed a hybrid top-down and bottom-up approach for automatic clustering and labeling of white matter tracts, which utilizes both brain parcellation results and similarities between white matter tracts. Again, this hybrid method faces the aforementioned problems in tractography-based segmentation and connectivity-based white matter segmentation.

Lenglet et al. (2005) represented diffusion tensors in a Riemannian manifold of multivariate normal distributions and proposed a variational formulation in the level set framework to estimate the optimal segmentation of the white matter. This work assumed that diffusion tensors exhibit a Gaussian distribution in the different partitions as well as the interfaces exist among the cerebral structures and are detected by the gradient of the diffusion tensor image. By using the theoretically well-founded differential geometrical properties of the Riemannian manifold of multivariate normal distributions, Lenglet et al. (2005) showed possibility to improve the quality of the segmentation results obtained with other dissimilarity measures such as the Euclidean distance or the Kullback–Leibler divergence between tensors. Similarly, Awate et al. (2007) employed the Riemannian structure of diffusion tensors and proposed a nonparametric modeling approach for segmenting the white matter. The authors demonstrated the robustness of the segmentation against imaging artifacts including noise, partial voluming, and inhomogeneity. Unfortunately, these two approaches were only validated in specific white matter bundles, including corpus callosum, corticospinal tract, and cingulum. Moreover, these two approaches cannot assign multiple tract labels to one voxel. Only recently, Bazin et al. (2011) described a Markov random field model to segment the white matter bundles based on features derived from diffusion tensors, including diffusion type that is an attribute of the single tract, overlapping tracts, and isotropic region and local tensor connectivity that characterizes the similarity of two tensor in the neighborhood region. Hence, this approach allows the presence of maximum of two tract labels at one location for the simplicity of the computation, which partially addresses the complexity of the white matter anatomy.

In this study, we take the aforementioned advantage of the Riemannian manifold representation of diffusion tensors and adopt the multi-label k-nearest neighbor (ML-kNN) algorithm (Zhang & Zhou, 2007) in Riemannian diffusion tensor spaces for assigning multiple labels to each location of the white matter. Our ML-kNN considers diffusion tensors lying on the Log-Euclidean Riemannian manifold of symmetric positive definite (SPD) matrices (Arsigny et al., 2005) and their corresponding vector space of symmetric matrices as the feature space of ML-kNN. The ML-kNN utilizes the maximum a posteriori (MAP) principle to make prediction by reasoning with the labeling information derived from the neighbors (Zhang & Zhou, 2007) without assuming any probabilistic distribution of the feature space. Hence, it is robust against noise as compared to tract-based segmentation approaches. The ML-kNN has the advantage by merits of both lazy learning and Bayesian reasoning such as decision boundary can be adaptively adjusted for each test subject voxel and using prior probabilities for each class label reduces the class-imbalance situation (Zhang & Zhou, 2007). Unlike the approach in Bazin et al. (2011) with the maximum of two labels at a location, our approach automatically learns the number of white matter bundles at a location and provides anatomical annotation of the neonatal white matter. In addition, our approach also provides the binary mask for individual white matter bundles to facilitate tract-based statistical analysis in clinical studies. In our experiment, we apply this method to automatically segment 13 white matter bundles of the neonatal brain and examine the segmentation accuracy against manual labels.

Methods

Image acquisition and preprocessing

Neonates scanned for this study were part of a larger ongoing birth cohort study of Growing Up in Singapore Towards Healthy Outcomes (GUSTO) (Soh et al., 2013). At 5 to 17 days of life, neonates underwent (i) fast spin-echo T2-weighted MRI (TR = 3500 ms; TE = 110 ms; FOV = 256 × 256 mm; matrix size = 256 × 256) and (ii) single-shot echo-planar diffusion weighted (DW) MRI (TR = 7000 ms; TE = 56 ms; flip angle = 90°; FOV = 200 mm × 200 mm; matrix size = 256 × 256). For T2-weighted MRI, 50 axial slices with 2 mm thickness were acquired parallel to the anterior–posterior commissure line. For DW-MRI, 40 to 50 axial slices with 3 mm thickness were acquired parallel to the anterior–posterior commissure line. Nineteen diffusion weighted images (DWIs) with $b = 600$ s/mm^2 and 1 baseline with $b = 0$ s/mm^2 were obtained. The images were acquired using a 1.5-Tesla GE scanner at the Department of Diagnostic and Interventional Imaging of the KK Women's and Children's Hospital. The scans were acquired when subjects were sleeping in the scanner. No sedation was used and precautions were taken to reduce exposure to the MRI scanner noise. A neonatologist was present during each scan.

For each subject, diffusion weighted images were first corrected for motion and eddy current distortions using affine transformation to the image without diffusion weighting. To correct geometric distortion of the DW-MRI due to B0-susceptibility differences over the brain, we followed the procedure detailed in (Huang et al., 2008). The T2-weighted image was considered as anatomical reference. Within a subject, the deformation that carried its DWIs to the T2-weighted image characterized the geometric distortion of the DW-MRI. For this, intra-subject registration was first performed using Automated Image Registration (AIR) (Woods et al., 1993) to remove linear transformation (rotation and translation) between the diffusion weighted images and T2-weighted image. Then, the large deformation diffeomorphic metric mapping (LDDMM) image mapping sought the optimal nonlinear transformation that deformed the B0 image to the T2-weighted image (Du et al., 2011). Such diffeomorphic transformation was applied to every diffusion weighted image to correct the nonlinear geometric distortion. Finally, we employed LDDMM DTI mapping (Cao et al., 2006) to align the subject's DW data to the atlas that was created based on the GUSTO sample (Bai et al., 2012). The LDDMM DTI mapping has been well validated for the deep white matter tracts (Cao et al., 2006).

Training set construction

Our automated white matter segmentation method introduced in the subsequent section is built based on the prior information of white matter tracts obtained from a training set. In this study, the training