Multivariate Hypothesis Testing for Tissue Clustering and Classification: A DTI Study of Excised Rat Spinal Cord

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ABSTRACT

Tissue clustering and classification are among the most challenging tasks in DT image analysis. While classification identifies the tissue type within a voxel, clustering identifies regions of interest (ROI) in which tissue properties are similar. The aim of this work is to propose and investigate the effectiveness of unsupervised tissue clustering and classification algorithms for DTI data. The former employs four possible models to describe diffusion in each seed voxel; a model selection framework, adapted from Snedecor's *F*-test is used to choose the most parsimonious model. The latter assesses the spatial homogeneity of the distribution of the entire diffusion tensor using the statistical framework of Hext and Snedecor, in which the null hypothesis of diffusion tensors having a similar parameter distribution is determined by an *F*-test. Both numerical phantoms and DWI data obtained from excised rat spinal cord are used to test and validate these tissue clustering and classification approaches.

INTRODUCTION

Diffusion Tensor Magnetic Resonance Imaging (DT-MRI or DTI) provides noninvasive quantitative measurements of the apparent diffusion tensor of water molecules in tissue. The principal diffusivities and principal directions of the tensor within a voxel reflect features of the local tissue structure (e.g., anisotropy or isotropy) and tissue type (e.g., CSF, gray matter, white matter), whereas, their distribution within the imaging volume could help identify different pathways or anatomic structures. Most previous work in DTI clustering is based on thresholding criteria applied to tensor-derived scalar quantities, such as the Trace (*Tr*) or Fractional Anisotropy (*FA*). However, these scalars are subject to bias due to background noise and do not embody all information contained in the 3x3 diffusion tensor. To overcome this problem we perform unsupervised clustering with the entire diffusion tensor using a statistical hypothesis framework adapted from Snedecor [1] and Hext [2]. Prior to clustering, a parsimonious model selection approach is used to classify local tissue structure and type using a series of sequential *F*-tests.

THEORY

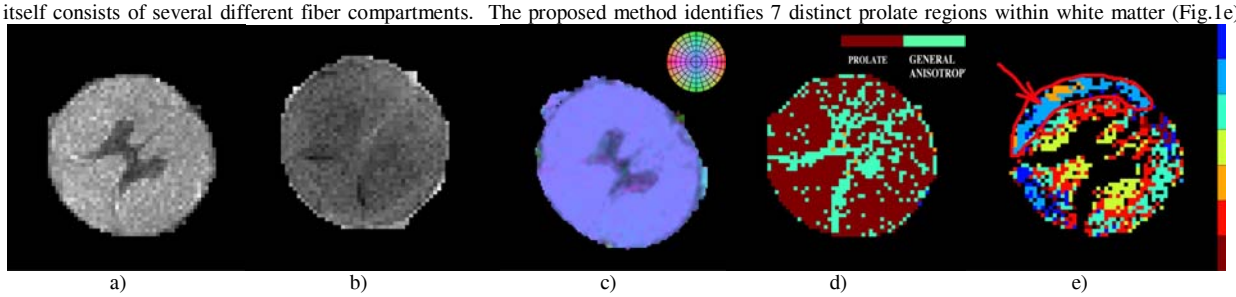
For the *F*-test to be valid the residual sum of squares (*RSS*) errors must be normally distributed and the variance must be uniform within the sample (or set of voxels). In previous works it has been shown that the *RSS* is asymptotically normally distributed at an *SNR* greater than 7. However, the variance in neighboring voxels may not be homogeneous. To overcome this problem, we select a local ROI in which each voxel is described by the same diffusion model (e.g., prolate, oblate, general anisotropic, or isotropic), previously determined by the parsimonious model selection method. Once the optimal model is chosen in each voxel, we use this information to group tissues in ROIs. The null hypothesis assumes that the difference between diffusion tensors for m voxels of the same model type is statistically insignificant. To test this hypothesis, we perform the following steps, adapted from Hext: 1) Combine m sets of acquired signals, S_{CAS}, into an [$n{\cdot}m$ x 1] array, where n is a number of experimental data points in each voxel; 2) Combine m sets of individually estimated signals, S_{CES} ([$n \cdot m$ x 1]); 3) Estimate the average diffusion tensor for m voxels, $\hat{\mathbf{D}}_{Avg}$, by a non-linear least square minimization of the *RSS* for the combined acquired signals, S_{CAS}, and the combined [$n \cdot m$ x 7] design matrix, $\mathbf{B}_C$; 4) Estimate the average signal, S_{Avg}, using $S_{Avg}(\mathbf{G}) = S(0)\cdot e^{-\mathbf{B}_C\hat{\mathbf{D}}_{Avg}}$; 5) Apply Snedecor's *F*-test for testing similarities between voxels: $F_0 = \frac{(RSS_{Avg} - RSS_{CES})/(fp\cdot(m-1))}{(RSS_{CES})/(m\cdot(n-fp))}$ where m is a number of voxels with n experimental data points each, RSS_{Avg} is the residual sum of squares for the estimated averaged (reduced) model from the fit of the averaged diffusion tensor, $\hat{\mathbf{D}}_{Avg}$, and RSS_{CES} is the residual sum of squares for the combined full tensor model ($fp = 7$).

METHOD

Our results are demonstrated on experimental MRI data obtained from an excised rat spinal cord fixed with 4% paraformaldehyde solution. DWIs were obtained using a PGSE DWI sequence with δ (pulse duration) = 2.5 ms, Δ (diffusion time) = 70 ms, repetition time (TR) = 3500 ms, and echo time (TE) = 14.7 ms. Other imaging parameters were: in-plane resolution 200x200μm^2, slice thickness = 2mm, number of averages (NEX): n = 1, bandwidth = 50 kHz. Forty DWIs per slice were acquired during 28 hours of scanning. Thirty-one of these were attenuated by diffusion gradients **G** = (Gx, Gy, Gz) and 9 were not attenuated ($|\mathbf{G}| = 0$). In each direction the approximate b-value was 2000 s/mm^2.

RESULTS

In Monte Carlo simulations regions with a 10° difference in the direction of the axis of symmetry could be resolved at *SNR*≥20 and *FA*≥0.5. By examining the *FA* map (Fig.1a), *Tr* map (Fig.1b), Color map (Fig.1c), and the model map for Prolate and General Anisotropy (Fig.1d), we can only distinguish white from gray matter, although white matter itself consists of several different fiber compartments. The proposed method identifies 7 distinct prolate regions within white matter (Fig.1e). There are two non symmetric regions in Fig. 1e. A closer analysis of the fixed spinal cord revealed fibers in these areas that were compressed during sample preparation.



a) b) c) d) e)

Figure 1. a) *FA* map (bright and dark correspond to white and gray matter, respectively); b) *Tr* map; c) Color (blue through the plane); Model map (prolate and general anisotropy correspond to white and gray matter, respectively); e) 7 ROIs represent areas with different fiber bundles.

DISCUSSION and CONCLUSION

Effective clustering and classification of DTI data is demonstrated using numerical and spinal chord phantoms. Isotropic regions as well as anisotropic regions with subtle differences in diffusion type (oblate, prolate or full anisotropy) and model parameters (e.g., degree of prolateness or oblateness and orientation of axis of symmetry) could be resolved. The sequential *F*-testing framework for both parsimonious model selection and clustering and classification tasks is both efficient and powerful. The current approach is suitable for MR microscopy applications and analysis of fixed samples in which imaging artifacts can be remediated and assumptions of normal residuals and uniform variance for each DWI can be assured. Future work will involve testing on *in vivo* DTI data.

BIBLIOGRAPHY: [1] Snedecor G, Cochran W. Statistical Methods, 1989. [2] Hext GR. 1963; 50:353–357.