Creating Large Scale Population Atlases Using Diffusion Tensor Images

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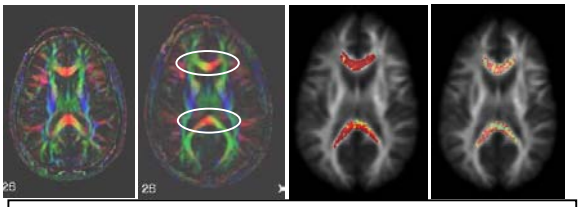
Abstract: We propose a novel framework for the statistical analysis of diffusion tensor images (DTI) applicable to large population studies, which addresses the challenging problems of tensor averaging, smoothing and statistics on tensors, unaddressable by commonly used linear statistical methods, due to the inherent non-linearity of tensors. We perform multivariate statistical analysis on tensors by identifying the underlying manifold of the set of tensors under consideration using the Isomap manifold learning technique and defining geodesic distances between tensors along the manifold. Application on human brains with simulated pathology and average population atlasing, show that the proposed statistical analysis method properly captures statistical relationships among tensor image data, while identifying group differences.

INTRODUCTION: DTI [1] has enabled the investigation of anatomical connectivity in vivo, particularly in the brain. The need for population atlases of the brain has led to the growing demand for group-based statistical analysis that quantifies normal variability, and also provides signatures of brain disorders and diseases. However developing statistical methods for DT-MRI is very challenging because tensors are restricted to lie on a submanifold of the space in which they are defined, R^6, imposed by the mathematical properties of positive definiteness and symmetry and the tissue properties of anisotropy. Therefore, statistics of tensors need to be performed along the manifold using geodesic distances between tensors, contrary to Euclidean distances as linear statistics assume. In order to circumvent the lack of statistical methods for tensorial data, current day studies perform statistical analyses on scalar (fractional anisotropy and diffusivity [1]) and vector (orientation of tensor [2]) measures, computed from the tensor data. This in turn requires the prior knowledge as to which of these measures is affected by disease, limiting their general applicability. Our proposed methodology for statistical analysis of tensor data is applied directly to the diffusion tensor, without requiring a priori assumptions on effect on scalar quantities to be extracted or the underlying shape of the statistical distribution of the tensor measurements. The key challenge here is, given a number of tensor measurements obtained from a number of individuals for a particular voxel (or its neighborhood), to determine the structure and dimensionality of this underlying manifold and define geodesic distances on it.

METHOD: A dataset consisting of tensor values which need to be statistically analyzed may, for example, represent measurements at a given voxel from a group of individuals whose statistics are to be determined or measurements from two groups to be compared. Isomap [3] is used to identify the underlying manifold structure of the data and determine its dimension in the following way:

1. *Construction of a tensor neighborhood graph*: This determines neighbors from the tensor dataset, using a tensor-based metric and creates a graph with the tensors as nodes.
2. *Defining the geodesic distance and creation of Distance Matrix*: The geodesic distance between two faraway tensors on the graph is determined as the graph based shortest distance between nodes, which is computed using the Floyd-Warshall algorithm [4] and is used to create the *distance matrix* relating all tensors.
3. *Fitting the manifold*: Multidimensional scaling (MDS) [5] is used to extract the manifold fitted to the tensors. The dimension d of the underlying manifold is equal to the rank of the centered distance matrix. The top d eigen vectors are then chosen to obtain the representation of these tensors in the d - dimensional space. The residual variance is captured by the ratio of d eigen values of the distance matrix to all the eigen values, and provides a measure of the information captured by the data.

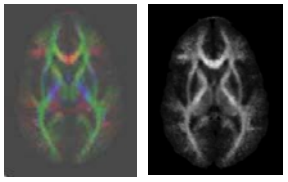


(a) (b) (c) (d)

Fig. 2: Identifying voxels with significant pathological changes, slice from colormap of (a) original normal tensor data (red is horizontal, green is vertical, and blue is perpendicular to viewing plane). (b) tensor data modified in the corpus callossum. (c) Color coded p values of Hotelling T^2-test differences between data in (a) and (b) represented on a manifold using Isomaps with red indicating $p < 0.001$ and yellow indicating $0.001 < p < .05$. Blue depicts voxels with insignificant change. (d) Same as (c) where the tensors are treated as elements of R^6 and no manifold structure is identified. The p values are overlayed on an FA map.

RESULTS: ***Group Average***: 10 DTI datasets of size 256 x 256 x 50 (Philips 1.5T), are spatially normalized to one of the scans chosen as a template [6]. We grouped tensors at each voxel across all the spatially normalized scans and created a tensor dataset of 10 tensors each. We then used isomaps to fit a manifold to these tensors. The average was determined using manifold geodesics on a voxel-by-voxel basis. Fig. 1(a) shows the average colormap and 1(b) the average fractional anisotropy map. Spatial smoothing is achieved by using neighborhood information while fitting manifolds.

Simulated Pathology We applied the tensor isomap technique to these datasets after simulated pathological change was introduced in them in the form of a region of interest (ROI) on the corpus callossum in which tensors had been randomly rotated (such reorientational changes often happen in the vicinity of tumors, albeit in more systematic ways). In Fig. 2, we show the color maps of (a) a representative healthy subject and (b) a slice in which tensors have been modified to simulate pathology (in the region enclosed by the ellipses). It may be noted that such reorientation changes do not affect any scalar anisotropy or diffusivity measure. We therefore had 20 tensors associated with each voxel, 10 of simulated patients and 10 of healthy controls. We performed the pairwise *Hotelling T^2-test* on each voxel and identified the points of significance, in which the means were significantly different. In Fig. 2(c,d), we color code significant voxels. In order to compare our approach to standard voxel-wise statistical analysis, we applied this test to tensors represented as elements in six dimensional Euclidean space and found lesser voxels to be identified as significantly different (Fig. 2(d)).



(a) (b)

Fig. 1: Average (a) colormap (b) fractional anisotropy map

DISCUSSION: We have presented a methodology for statistical analysis of tensorial image data, by estimating the structure of the nonlinear manifold on which these data lie, thereby enabling the proper definition of statistical measures via geodesic distances. In particular, it can be used to analyze pathological differences in disease, localize regions of maximum effect and to investigate new avenues in probabilistic atlasing of brains, as statistical measures defined along the manifold provide a biologically and mathematically consistent way to summarize anatomical variability within groups of patients or research subjects. Promising experimental results on data for which the ground truth is known, shows that the proposed methodology addresses the challenging problem of computation of tensor statistics and consolidates the information obtained from the statistical analysis of the individual scalar maps of anisotropy and vector maps of orientation.

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