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Tract Orientation and Angular Dispersion Deviation Indicator (TOADDI): A framework for single-subject analysis in diffusion tensor imaging

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ABSTRACT

The purpose of this work is to develop a framework for single-subject analysis of diffusion tensor imaging (DTI) data. This framework is termed Tract Orientation and Angular Dispersion Deviation Indicator (TOADDI) because it is capable of testing whether an individual tract as represented by the major eigenvector of the diffusion tensor and its corresponding angular dispersion are significantly different from a group of tracts on a voxel-by-voxel basis. This work develops two complementary statistical tests based on the elliptical cone of uncertainty, which is a model of uncertainty or dispersion of the major eigenvector of the diffusion tensor. The orientation deviation test examines whether the major eigenvector from a single subject is within the average elliptical cone of uncertainty formed by a collection of elliptical cones of uncertainty. The shape deviation test is based on the two-tailed Wilcoxon–Mann–Whitney two-sample test between the normalized shape measures (area and circumference) of the elliptical cones of uncertainty of the single subject against a group of controls. The False Discovery Rate (FDR) and False Non-discovery Rate (FNR) were incorporated in the orientation deviation test. The shape deviation test uses FDR only. TOADDI was found to be numerically accurate and statistically effective. Clinical data from two Traumatic Brain Injury (TBI) patients and one non-TBI subject were tested against the data obtained from a group of 45 non-TBI controls to illustrate the application of the proposed framework in single-subject analysis. The frontal portion of the superior longitudinal fasciculus seemed to be implicated in both tests (orientation and shape) as significantly different from that of the control group. The TBI patients and the single non-TBI subject were well separated under the shape deviation test at the chosen FDR level of 0.0005. TOADDI is a simple but novel geometrically based statistical framework for analyzing DTI data. TOADDI may be found useful in single-subject, graph-theoretic and group analyses of DTI data or DTI-based tractography techniques.

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Introduction

Diffusion Tensor Imaging (DTI) (Basser et al., 1994a, b; Pierpaoli et al., 1996) is an important and noninvasive magnetic resonance imaging (MRI) technique used in clinical and research studies of brain white matter architecture. Many aspects of DTI have been studied extensively, from the diffusion tensor model itself (Basser, 2002; Basser et al., 1994b; Basser and Pajevic, 2003; Koay and Özarslan, 2013; Stejskal, 1965) and its higher-order generalizations (Anderson, 2005; Descoteaux et al., 2007, 2011; Jian et al., 2007; Liu et al., 2004; Özarslan and Mareci, 2003), to optimal experimental designs (Cook et al., 2007; Deriche et al., 2009; Dubois et al., 2006; Jones et al., 1999; Koay et al., 2011, 2012) and its inverse problem at various levels of complexity (Andersson, 2008; Basser et al., 1994a; Chang et al., 2005, 2012; Koay et al., 2006; Mangin et al., 2002; Maximov et al., 2011; Veraart et al., 2013; Wang et al., 2004). DTI continues to inspire new analyses, developments, refinements and extensions (Caruyer et al., 2013; Hutchinson et al., 2012; Koay, 2009a, 2009b, 2014; Koay et al., 2009a, 2009b, 2011, 2012; Wu et al., 2004). Uncertainty quantification (Anderson, 2001; Behrens et al., 2003; Beltrachini et al., 2013; Chang et al., 2007; Jeong and Anderson, 2008; Jones, 2003; Jones and Pierpaoli, 2005; Koay et al., 2007, 2008; Lazar and Alexander, 2003, 2005; Lazar et al., 2005; Poonawalla and Zhou, 2004) in DTI is another important area of research with wide-ranging implications to tractography (Barbieri et al., 2011; Basser et al., 2000; Conturo et al., 1999; Mori et al., 1999; Pajevic et al., 2002; Poupon et al., 2000, 2001) and data analyses (longitudinal, single-subject, group or graph-theoretic, e.g., (Rubinov and Sporns, 2010)).

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The purpose of this work is to develop a statistical and computational framework for testing whether an individual principal direction (i.e., major eigenvector of a diffusion tensor) and its corresponding elliptical cone of uncertainty (COU, see Methods for a brief review) (Koay et al., 2007, 2008) are different from a control group of diffusion-tensor-derived major eigenvectors and their corresponding elliptical COUs. Two key motivations behind the work are the pursuit of personalized or precision medicine for individual patients and to address the current inadequacy of group analysis of DTI data in clinical TBI studies.

TBI presents unique challenges to diagnosis due to the heterogeneity of injury source and manifestation across subjects, and mild TBI (mTBI) in particular is challenging due to the subtle imaging findings. Because of the varying degrees of severity of the injuries and the spatial heterogeneity of the affected regions not only in an individual TBI patient but also across TBI patients, there is a clear need to develop diagnostic methods that are effective on an individual basis. Since no two clinical TBI cases are alike, it may not be appropriate to group TBI data for voxel-wise analyses. The key concern is that the averaging effect of the group analysis may smooth out salient anomalies in a single patient and cause them to appear as normal variations within the *averaged* TBI data, i.e., it is very unlikely to build up a statistical group difference at a single voxel if there is rarely a lesion from more than one patient in a voxel.

This framework builds upon as well as extends the capability of our previously proposed uncertainty quantification framework for DTI (Koay et al., 2007, 2008). Our work on an analytical error propagation framework (Koay et al., 2007, 2008) for DTI is a culmination of prior works by others (Anderson, 2001; Jeong and Anderson, 2008; Jeong et al., 2005; Lazar and Alexander, 2003, 2005; Lazar et al., 2005) and our group (Koay and Basser, 2006; Koay et al., 2006). In brief, three independent studies adopted a perturbation-based error analysis (Anderson, 2001; Basser, 1997; Chang et al., 2007) to study uncertainty in fiber orientation and in tensor-derived quantities. These studies developed their respective error analyses from the linear model of the diffusion tensor. Our prior experience with signal and noise characterization in MRI (Koay and Basser, 2006) together with the observations made by Jones et al.(Jones and Basser, 2004) on the effects of noise on tensor-derived quantities led to the adoption of the nonlinear least squares model of the diffusion tensor as the model of choice (Koay et al., 2006) for error propagation (Koay et al., 2007). The most notable difference between the perturbation-based error analysis of Basser (Basser, 1997) or Chang et. al. (Chang et al., 2007) and our error propagation framework is that the former did not incorporate the elliptical COU into the formulation while such a feature is inherent in our framework (Koay et al., 2007). It is important to note that many studies (Basser, 1997; Behrens et al., 2003; Chang et al., 2007; Jones, 2003; Parker et al., 2003; Polders et al., 2011) have adopted the circular COU for modeling the uncertainty in the major eigenvector of the diffusion tensor even though converging and empirical evidence showed that the uncertainty of the major eigenvector is generally elliptical (Jeong et al., 2005; Lazar and Alexander, 2005; Lazar et al., 2005). The key reason for the lack of such an important feature (the elliptical COU) in DTI error analysis in the works of Basser and Chang is due to the absence of the covariance matrix of the major eigenvector in their formulations, which was recently demonstrated to be obtainable from perturbation analysis through a simple reformulation; see (Koay et al., 2008) for the connection between our analytical error propagation framework and the reformulated perturbation-based error analysis.

The covariance matrix of the major eigenvector of the diffusion tensor provides the necessary information to construct the elliptical COU and related scalar measures such as the normalized areal and circumferential measures of the elliptical COU (Koay et al., 2008). While it is relatively easy to visualize or quantify a single elliptical COU within a voxel, it is nontrivial to test whether an individual major eigenvector or the boundary points of its elliptical cone is within the mean elliptical cone of uncertainty formed by a collection of elliptical COUs. This inclusion–exclusion test is a multivariate and geometric problem and is highly relevant to each phase of data analysis, from exploratory investigation to testing of hypotheses. While it is not hard to test the shape characteristics of an individual elliptical COU against those of a collection of elliptical COUs, the main obstacle is in the normalization of a family of elliptical COUs. This problem is solved through a novel utilization of the tensor normalization technique proposed by Zhang et. al. (Zhang et al., 2006). While there are several published approaches to performing voxel-based analysis for DTI (Schwarz et al., 2014; Smith et al., 2006; Zhang et al., 2006), it is not the intent of this work to compare relative merits of these approaches. Challenges of voxel-based analysis have been extensively studied by (Ashburner and Friston, 2000) and one of the key challenges is registration errors, which may cause unnecessary deformations or distortions that do not appear in the original image. One of the ways to minimize the registration errors in statistical inference is through skeletonization as suggested in Tract-Based Spatial Statistics (TBSS) of (Smith et al., 2006) and our approach is to focus only on voxels within the white matter region that satisfy further criteria such as goodness of fit.

To the best of our knowledge, no proposed framework addresses the problems raised above. We propose a novel and conceptually simple statistical and computational pipeline to address these problems. Particular attention is paid to the antipodally symmetric nature of the elliptical cones in order to develop an unbiased orientation of the elliptical COUs. The inverse Gnomonic projection (Coxeter, 1989; Koay et al., 2008) of the elliptical COU onto the unit sphere is used to ensure the tests are well-defined.

The proposed framework, which we termed it as Tract Orientation and Angular Dispersion Deviation Indicator (TOADDI), is capable detecting a statistically and orientationally significant deviation of a principal diffusion direction as compared to those from a group of controls on a voxel-by-voxel basis. It can also detect any statistically significant deviation in the shape characteristics such as the normalized areal measure and the normalized circumferential measure of the elliptical cone as compared to those from the control group. While it is beyond the scope of this paper, which focuses mainly on the proposed methodological framework, to pursue a thorough investigation of all the available clinical TBI cases acquired at the National Intrepid Center of Excellence (NICoE), and in the interest of expediting the process of translational research in clinical TBI studies, we believe it would be beneficial to illustrate the application of the proposed framework on a few clinical TBI cases with complete details of the processing pipeline.

Here, we present two key contributions of the present work. First, this work incorporates the methods of False Discovery Rate (FDR) (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001; Yekutieli and Benjamini, 1999), popularized by Genovese et al. (Genovese et al., 2002) within the context of neuroimaging to control the proportion of false positives in multiple comparison problems, and False Non-discovery Rate (FNR) (Genovese and Wasserman, 2002) within the proposed generalized multivariate test for testing orientation differences. Second, this work shows how differences in shape characteristics – such as area and circumference – of the elliptical cones between a single subject and a control group can be tested using the nonparametric test of Wilcoxon–Mann–Whitney (WMW) (Mann and Whitney, 1947; Wilcoxon, 1945).

Finally, we should mention that the proposed methodology is not a new tissue model at the neuronal level, e.g., (Zhang et al., 2012). While the angular dispersion of the major eigenvector may be affected by the underlying microstructure as well as noise, the geometrical characteristics of the angular dispersion may only be a gross representation of an admixture of the underlying biophysical processes. Further investigation is needed to find out whether the angular dispersion of the major eigenvector corresponds well with the underlying biophysical processes at the neuronal level. A comparison with some of the existing tissue models would be very interesting. This comparative study is being planned but it is beyond the scope of this work.