A CLOSED-FORM METHOD FOR IMPROVING INTER-SUBJECT COHERENCE IN DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING

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ABSTRACT

A simple method is presented to reduce within-group inter-subject scatter in diffusion tensor magnetic resonance imaging (DT-MRI). By "borrowing strength" across co-registered subjects to accommodate indirect effects of unmeasured machine and physiological noise, the method reduces voxel-specific tensor variance across subjects. The technique may aid in fiber bundle atlas construction, in testing differences between groups of subjects, and in automated outlier detection. While the technique does not in itself address DT-MRI signal artifact issues directly, it may serve to lessen the effects of these artifacts when their sources have not been measured. An example application to DT-MRI of twelve healthy male volunteers at the splenium of the corpus callosum slightly right of midline demonstrates the possible utility of the method.

1. INTRODUCTION

At every voxel $\mathbf{s}$ in DT-MRI of a volume $\mathbf{S}$ of human brain tissue sits a 3×3 symmetric tensor

$$\mathbf{D}_\mathbf{s} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}_\mathbf{s}, \qquad \mathbf{s} \in \mathbf{S},\ \#(\mathbf{S}) = v.$$

Estimation of tensor fields helps to determine the principal directions of anisotropic diffusion of water protons in brain tissue and thus to track major fiber bundles (white matter tracks, fasciculi). DT-MRI echo data are obtained by application of multiple diffusion gradients in at least six mutually non-redundant directions through the tissue.

Writing

$$\mathbf{d}_\mathbf{s} = (D_{xx}\ D_{xy}\ D_{xz}\ D_{yy}\ D_{yz}\ D_{zz})^\mathsf{T}_\mathbf{s}$$

as the vector of non-redundant elements of $\mathbf{D}_\mathbf{s}$, each tensor is most often estimated as the weighted least squares solution to

$$I = I_0 \exp(-TE / T_2) \exp(-\mathbf{b}\mathbf{d}_\mathbf{s}),$$

where I_0 is the intrinsic signal, *TE* is the echo time, T_2 is the transverse relaxation time, and

$$\mathbf{b} = (b_{xx}\ 2b_{xy}\ 2b_{xz}\ b_{yy}\ 2b_{yz}\ b_{zz})$$

is a minimal form of an operator-specified design matrix of diffusion sensitivities, the *b*-matrix [1].

Many rotation invariant functionals of tensor fields are used to produce summary images of various aspects of anisotropic and isotropic diffusion. These include versions of the apparent diffusion coefficient (ADC), the principal diffusivities (eigenvalues of the estimated tensors), the mean diffusivity defined as $trace(\mathbf{D}_\mathbf{s})/3$, and various anisotropy indices (fractional anisotropy, relative anisotropy, lattice index) that quantify differences between eigenvalues and their eigenvectors [2]. Subject motion, eddy currents, magnetic susceptibility artifacts, RF noise, hardware issues, cardiac pulsation and other physiological noise all affect the estimated tensor field in deleterious ways [2,3].

The preceding artifacts affect the numerical stability, bias, variance and covariance of the tensor field. For instance, baseline noise biases the tensor eigenvalues and their rankings and hence can inflate anisotropy indices [4]. Although recent advances in the spatial normalization of DT-MRI images enable registration of homologous brain regions across multiple subjects, these artifacts continue to distort within- and between-group analyses when using current methods. Better statistical methods are needed to improve tensor field estimation and interpretation.

The purpose of this paper is to develop a simple closed-form method for multiple-subject, grouped DT-MRI that may improve aggregated tensor field estimation and inference, and to provide an example application of the technique.

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2. A CLOSED-FORM VARIANCE COMPONENTS METHOD FOR MULTIPLE SUBJECT DT-MRI

The central idea of this paper is to take the following simple data analytic steps: 1) use weighted least squares to produce an initial estimate of the tensor field; 2) "shrink" each subject-specific tensor toward the mean field by "borrowing strength" across subjects to improve inter-subject coherence and an estimated mean field with lower variance; and 3) apply standard tensor functionals to produce summary DT-MRI images with greater statistical power.

Denote by $\mathbf{D}_{i,\mathbf{s}}$ the weighted least squares estimate of the diffusion tensor at voxel $\mathbf{s} \in \mathbf{S}$ for $i = 1,...,n$ co-registered subjects. Let

$$\mathbf{y}_{i,\mathbf{s}} = (D_{xx;i,\mathbf{s}}\ D_{xy;i,\mathbf{s}}\ D_{xz;i,\mathbf{s}}\ D_{yy;i,\mathbf{s}}\ D_{yz;i,\mathbf{s}}\ D_{zz;i,\mathbf{s}})^{\mathsf{T}}$$

and define $\mathbf{y}_i = (\mathbf{y}_{i,\mathbf{s}_1} \cdots \mathbf{y}_{i,\mathbf{s}_u})^{\mathsf{T}}$. Consider a linear mixed effects model for each subject's contribution defined as

$$\mathbf{y}_i = \boldsymbol{\mu} + \mathbf{1}_v \otimes \boldsymbol{\delta}_i + \boldsymbol{\varepsilon}_i, \qquad (1)$$

$i = 1,...,n$. In (1), $\boldsymbol{\mu}$ is the mean tensor field over $\mathbf{S}$, a fixed and unknown parameter to be estimated, and is composed of vectors

$$\boldsymbol{\mu}_{\mathbf{s}} = (\mu_{xx}\ \mu_{xy}\ \mu_{xz}\ \mu_{yy}\ \mu_{yz}\ \mu_{zz})^{\mathsf{T}}_{\mathbf{s}}, \mathbf{s} \in \mathbf{S}$$

that are assumed to be shared across subjects. Mean field $\boldsymbol{\mu}$ is estimated by an aggregation of models (1) across all subjects at each voxel. $\mathbf{1}_v$ is a vector of 1's of length equal to the number of voxels v, and $\otimes$ is Kronecker's product. Independent subject-specific effects $\boldsymbol{\delta}_i$ are random offsets to $\boldsymbol{\mu}$ that attempt to adjust for unmeasured subject effects arising from a variety of unspecified sources. These random effects are defined as

$$\boldsymbol{\delta}_i = [\delta_{xx;i}\ \delta_{xy,i}\ \delta_{xz,i}\ \delta_{yy,i}\ \delta_{yz,i}\ \delta_{zz,i}]^{\mathsf{T}},$$

where $E(\boldsymbol{\delta}_i) = \mathbf{0}$ and $\operatorname{cov}(\boldsymbol{\delta}_i) = \boldsymbol{\Sigma}_\delta$. $\boldsymbol{\Sigma}_\delta$ may be any patterned variance-covariance matrix having an explicit inverse. The error term $\boldsymbol{\varepsilon}_i$ in (1) is also assumed to be multivariate Gaussian with expectation $\mathbf{0}$ and variance-covariance matrix $\boldsymbol{\Sigma}_\varepsilon$ independent of $\boldsymbol{\Sigma}_\delta$. $\boldsymbol{\Sigma}_\varepsilon$ is shared by all subjects and accommodates spatially auto-correlated noise. Only through registered replicates across multiple subjects can one estimate the subject-specific random effects and their variance-covariance matrix, a separate variance component from the error variance, thus to shrink them towards $\boldsymbol{\mu}$ to increase inter-subject, voxel-specific coherence and hence to reduce $\hat{\operatorname{var}}(\hat{\boldsymbol{\mu}})$.

2.1 Spatial auto-covariance functions

Since an unstructured $\boldsymbol{\Sigma}_\varepsilon$ has a potentially large number of free parameters, with maximum $6v(v+1)/2$, a simple low dimensional parameterization can improve both statistical and computational efficiency. One such choice, found to be useful in Fourier analyses of functional MRI time series [10], is to specify a set of mutually independent and isotropic auto-covariance functions (ACFs) defined over $\mathbf{S}$, one independent ACF for each of the six components of $\mathbf{y}_{i,\mathbf{s}}$. Modeling residual errors in this fashion appears sensible, and especially so if indeed the mean function parameters $\boldsymbol{\mu}$ and $\{\boldsymbol{\delta}_i\}$ capture much of the systematic inter-dependence and anisotropy as intended.

Let $h = |\mathbf{s} - \mathbf{s}'|$ denote a spatial lag measured in voxels. Of course, anisotropic ACFs would utilize more complicated functions of the vector difference that preserve directional information in addition to the simple distance from the origin used here. Two choices of parametric auto-covariance models are the mono-exponential and Gaussian forms

$$\sigma_{\mathbf{s},\mathbf{s}'}(\alpha_j) = \sigma_{\mathbf{s},\mathbf{s}} \exp(-\alpha_j h)$$

and

$$\sigma_{\mathbf{s},\mathbf{s}'}(\alpha_j) = \sigma_{\mathbf{s},\mathbf{s}} \exp(-\alpha_j h^2),$$

respectively, for $j = 1,...6$. Denote by $\Delta_{\varepsilon,j}$ the six symmetric matrices of spatial auto-covariances (either mono-exponential or Gaussian or both) whose off-diagonal elements decrease in h, and define $\boldsymbol{\Sigma}_{\boldsymbol{\varepsilon}} = \sum_{j=1}^{6} \Delta_{\varepsilon,j}$. The total variance covariance matrix for $\mathbf{y}_i$ is thus

$$\boldsymbol{\Sigma}_i = \mathbf{1}_{v\times v} \otimes [\boldsymbol{\Sigma}_\delta + \boldsymbol{\Sigma}_{\boldsymbol{\varepsilon}}].$$

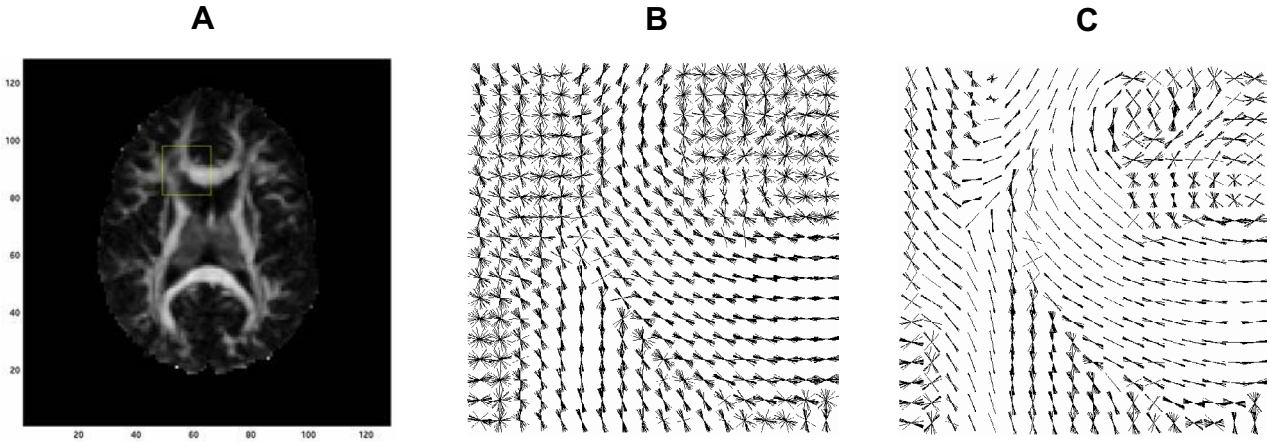
2.2 Grouped analyses

Aggregation of models (1) across subjects by concatenation of the $\mathbf{y} = (\mathbf{y}_1^{\mathsf{T}} \cdots \mathbf{y}_n^{\mathsf{T}})^{\mathsf{T}}$ yields the full mixed effects model

$$\mathbf{y} = \mathbf{X}\boldsymbol{\mu} + \mathbf{1} \otimes \boldsymbol{\delta} + \boldsymbol{\varepsilon},$$

where $\mathbf{X}$ is a conformable matrix of subject specific covariates, $\boldsymbol{\delta} = (\boldsymbol{\delta}_1 \cdots \boldsymbol{\delta}_n)^{\mathsf{T}}, \boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_1 \cdots \boldsymbol{\varepsilon}_n)^{\mathsf{T}}$. $\mathbf{1}_{n\cdot v}$ is a vector of 1's of length $n \cdot v$, and $\boldsymbol{\Sigma} = \boldsymbol{\Sigma}_1 \otimes \cdots \otimes \boldsymbol{\Sigma}_n$.

Figure 1. Bow-tie plot comparison of the inter-subject alignment of principal eigenvectors in 12 healthy male volunteers. A. Fractional anisotropy map of a selected voxel patch in the splenium of the corpus callosum slightly right of midline (radiological convention); B. Jones et al., 2002; C. The method proposed in this paper.



Since co-registered DT-MRI data are balanced and complete (all subjects measured at the same brain locations and no missing data) estimates of all parameters in (1) and (3) exist in closed-form [6].

3. EXAMPLE APPLICATION

As described by Jones et al. [7], the DT-MRI data we employ were acquired from 12 healthy male volunteers (one more than reported therein). Isotropic resolution (2.5 mm) DT-MRI data were collected on a GE Signa 1.5 T LX system using a sequence fully optimized for DT-MRI of white matter [8]. Following correction for distortions induced by eddy currents, the tensor was estimated in each voxel for each subject using linear regression [1]. The DT-MRI volume from each subject was elastically normalized to a standard anatomical reference space, being the MNI EPI template supplied as part of SPM (The Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK), by employing a procedure similar to that outlined in [7], yet with elastic registration [9] and preservation of principal directions [10] algorithms without the affine transformation used previously in [7].

Once each subject's tensor volume had been estimated, the principal eigenvector, being the eigenvector associated with the largest eigenvalue, was determined in each voxel and its 2-D projection onto the (x, y) plane is represented by a small bar of unit length. The orientation plots thus obtained from each of the twelve subjects were then overlaid. This visualization method is termed a 'bow-tie plot' due to its appearance at voxels where the principal eigenvectors from the twelve subjects are modestly well aligned [7].

Figure 1 is a bow-tie plot comparison of the method in the present paper to that of Jones et al. within the splenium of the corpus callosum. Figure 1A is a fraction anisotropy map [2]. In Figure 1B, a high degree of coherence of principal eigenvectors is seen (tight bow-ties), while there is less coherence in regions of gray matter and CSF (the bow-ties become star-shaped). The difference in coherence could be attributable to two different phenomena. First, high within-voxel orientational coherence may be the result of good spatial normalization of truly homologous regions across subjects, whereas those voxels showing lower orientational coherence may be those for which spatial normalization has performed poorly. However, there is uncertainty associated with every estimate of an eigenvector and it has been shown that the orientational uncertainty in a DT-MRI data set is non-uniform throughout the brain, even with data collected in the same experiment. Regions with high diffusion anisotropy have lower orientational uncertainty than regions with lower diffusion anisotropy [11]. The anatomical variation in inter-subject orientational coherence, seen in Figure 1B, could therefore reflect difference in the quality of spatial normalization, differences in intra-subject eigenvector uncertainty, or a combination of these effects.

Figure 1C is a bow-tie plot of the application of the proposed new method (1) to these same data. No spatial autocovariance functions were computed. It appears that the shrinkage operation has increased inter-subject orientational coherence in all voxels. In regions where the intra-subject uncertainty in the principal eigenvectors is intrinsically high, namely in regions of apparent low anisotropy, it is not clear that improving the inter-subject orientational coherence (such as is seen in Figure 1C) is desirable since this would imply a consistent orientation

across subjects. Yet perhaps this issue may not be of much practical importance. If the region is one exhibiting truly isotropic diffusion, incoherent subject contributions at each voxel are shrunken to either one or the other "principal direction" at random, changing a '$*$' into an approximate '$\times$', which may be acceptable in such a case. Further study of the preceding issues is warranted, especially as they relate to the proposed procedure used here.

4. DISCUSSION

Fiber tracking or tractography is currently one of the hottest topics in DT-MRI research. In this technique, discrete (voxel-based) estimates of the eigenvector field are used to infer continuous white matter trajectories. Tractography maps that summarize a population by combining information from a number of subjects have been created in two ways: 1) tracking on the average tensor field computed from a set of spatially normalized tensor fields [7], and 2) tracking on individual DT-MRI data sets and then overlaying the individual tractography results [12]. In the former approach, since it appears that the shrinkage operation proposed here does not introduce any bias in the mean orientation (concurring with theory), there is little advantage conferred in applying the technique when one wants only to study the mean tensor and not its variance. With DT-MRI data, the estimated mean field in unaffected by changes in the assumed variance field. Such decoupling of mean and variance is a theoretical property shared by balanced and complete repeated measures data under Gaussian conditions. Yet of course one cannot ignore the variance field when inferring properties of the mean field. However, with the latter approach, one expects intuitively that tracts launched from the same voxel will follow similar courses and hence the degree of overlap of the individual trajectories will be increased. This should allow more confidence to be assigned to the tracking result.

Another exciting potential application of the proposed method is also in the automated detection of outlier data sets. Just as the method itself requires no iteration, so too do empirical influence functions exist in closed form [13]. This means that one need not delete each subject in turn and re-compute to obtain leave-one-out results. Instead, it is easy to explicitly 'down-sample' the original result that included all subjects to obtain the same results.

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