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Geometrically Constrained Two-Tensor Model for Crossing Tracts in DWI

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Abstract

MR diffusion tensor imaging (DTI) of the brain and spine provides a unique tool for both visualizing directionality and assessing intactness of white matter fiber tracts in vivo. At the spatial resolution of clinical MRI, much of primate white matter is composed of interdigitating fibers. Analyses based on an assumed single diffusion tensor per voxel yield important information about the average diffusion in the voxel but fail to reveal structure in the presence of crossing tracts. Until today, all clinical scans assume only one tensor, causing potential serious errors in tractography. Since high angular resolution imaging remains, so far, untenable for routine clinical use, a method is proposed whereby the single-tensor field is augmented with additional information gleaned from standard clinical DTI. The method effectively resolves two distinct tract directions within voxels, in which only two tracts are assumed to exist. The underlying constrained two-tensor model is fitted in two stages, utilizing the information present in the single-tensor fit. As a result, the necessary MRI time can be drastically reduced when compared with other approaches, enabling widespread clinical use. Upon evaluation in simulations and application to in vivo human brain DTI data, the method appears to be robust and practical and, if correctly applied, could elucidate tract directions at critical points of uncertainty.

Keywords

White matter; Diffusion tensor; Tractography; Crossing tracts; Anisotropy

1. Introduction

Two of the major uses of diffusion tensor imaging (DTI) in the central nervous system are in tract tracing and quantitative white matter analysis. In white matter tractography, the shape of the anisotropic diffusion tensor is used to delineate fiber tract direction and trace brain connections from voxel to voxel [1-3]. For quantitative analyses of possible white matter anomalies, parameters derived from the diffusion tensor can be associated with tissue microstructure [4,5] and compared between health and disease. The runaway success of DTI (with a single tensor) is in general attributable to the elegance, simplicity and utility of the theory. A variety of diseases, about which white matter injury is known or hypothesized, have been investigated using DTI — including multiple sclerosis, amyotrophic lateral sclerosis,

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epilepsy, Alzheimer's disease, brain tumors, cerebral ischemia and schizophrenia (for recent reviews, see Refs. [6,7]).

From the fitted tensor in each voxel, one usually extracts the principal direction of diffusion, the apparent diffusion constants in three perpendicular directions and the diffusion anisotropy. The diffusion tensor in each voxel can be visualized as an ellipsoid — the three axes of the ellipsoid correspond directly to the three eigenvalues and eigenvectors of the diffusion tensor [8]. The diffusion parallel to the axis of the tracts is usually considered to be approximately free and, thus, adequately described by a single diffusivity. The diffusion perpendicular to the tracts is much lower — thus creating diffusion anisotropy. The lower diffusivity can be hypothesized as due to barriers that either hinder or restrict the diffusion. Diffusion anisotropy is an important parameter in investigations using DTI to assess anatomical connectivity. The anisotropy is assumed to reflect the organization and density of tracts within a voxel. Popular measures of anisotropy include the fractional anisotropy [9], the angular variance of the apparent diffusion constant [10] and geometric measures of anisotropy [11]. The last group is composed of three geometrically intuitive indices derived from the diffusion tensor — linear, planar and spherical — where each index describes the similarity of the diffusion ellipsoid to a line, plane or sphere, respectively. Recognition that a nonlinear tensor shape in white matter probably implies more than one distinct fiber bundle in a voxel is implicit in the latter report.

Upon inspection of histology, much of the white matter in primates is composed of multiple interdigitating fibers. Fig. 1 shows an area of the macaque prefrontal white matter in a silver-stained slice. DTI fits the average diffusion in the voxel, but on the spatial scale of MRI, many voxels will contain more than one main fiber direction. Fitting diffusion data from heterogeneous white matter voxels to a single tensor can lead to errors in both the assessment of white matter tract disruption and the computed tract direction.

High angular resolution diffusion-weighted imaging (DWI) has been proposed as a way of increasing the directional information in order to try to resolve crossing tracts [12]. This approach requires the acquisition of a large number of diffusion-weighted images using gradients in many directions (usually > 100). A number of methods have been proposed for analyzing data acquired at high angular resolution. Both Tuch et al. [13] and Alexander et al. [14] have proposed fitting two tensors to diffusion data, acquired with 126 and 162 gradient directions, respectively. The former study constrained the two tensors by specifying the values of both sets of eigenvalues to be $[1.5, 0.4, 0.4] \mu\text{m}^2/\text{ms}$. The latter study attempted to fit the data to a general two-tensor model but reported that the data did not provide sufficient information for resolving two components.

Diffusion-weighted data can also be analyzed without an underlying model, as in q-ball imaging [15]. Using 252 diffusion directions, considerable neural architecture was revealed using this method. A related model-free analysis method can be applied when a complete 3D Cartesian space of diffusion-weighted gradients is applied, that is, multiple gradient directions and multiple gradient strengths. In this case, there exists a possibility to perform a version of q -space analysis [16-18]. (The most commonly used measure of diffusion weighting is termed b and is approximately given by $b \approx q^2 \Delta$, where Δ is the time between gradient pulses and $q \approx \delta g$, where δ is the duration of each gradient pulse and g is the gradient strength. The exact relationship between b and q depends on the details of the pulse sequence.) q -Space imaging uses the Fourier relation between the spatial displacement of the spins and the MR signal (measured with respect to q) in order to estimate that displacement.

A model of white matter diffusion, combining elements of hindered and restricted diffusion, has recently been proposed by Assaf et al. [19] to explain the apparent non-Gaussian diffusion observed at high b values. Here, as in q -space imaging, diffusion-weighted data are collected

with multiple gradient directions and multiple gradient strengths. This model was shown to allow discrimination of crossing tracts in a phantom from 496 measurements with b values up to 44,000 s/mm².

To summarize the above-described methods for discriminating crossing tracts, it is apparent that crossing tracts can be resolved to some degree when enough gradient directions are applied. However, the duration of the scans is long, as compared with the time available for practical clinical applications; thus, there is a clear need to resolve crossing tract information in clinically acceptable DWI scan times. Model-free methods will always require high angular resolution data acquisition; hence, our approach here has been to simplify the two-tensor model in a geometrically intuitive way. The adherence to the tensor description is utilitarian and rests on the empirically observed Gaussian character of the diffusion at low diffusion weightings ($b \leq 1000$ s/mm²).

We demonstrate that whole-brain DWI data acquired in 6 min are sufficient for effectively resolving two tract directions when no more than two tracts are assumed to populate the voxel. Calculation of the tract directions is achieved by taking into account the geometry associated with two separable fiber bundles within each of the analyzed voxels and by utilizing the information gleaned from single-tensor analysis. The underlying model assumes that two cylindrically symmetric tensors can adequately describe the diffusion in two tracts, with a few additional, physically reasonable constraints. No assumptions are made about compartments, restriction or general diffusive behavior as a function of b or q . The model only requires the geometric assumption of cylindrical symmetry and uses apparent diffusion coefficients. While the single-tensor model will always fail in voxels with complicated tissue architecture, the two-tract model will generally improve the analysis of crossing fibers, although, obviously, it still falls short when three or more tracts run through a single voxel.

From a geometrical viewpoint, the two-tract assumption leads to the conclusion that when the diffusion tensor can be characterized as “planar,” both tracts are in the plane spanned by the first two principal axes of the single-tensor fit; that is, the eigenvector corresponding to the smallest eigenvalue defines the normal vector to this plane. Wiegell et al. [20] used a similar conclusion to identify areas of white matter fiber bundle intersections. In the two-tensor approach, the direction of each tensor is described by one parameter — the angle within this plane. The other parameters of the model are the relative contributions of each tensor to the signal and the magnitude of the largest eigenvalue. Thus, following the single-tensor fit, the model described herein has only 4 free parameters to fit, as compared with 14 parameters in a general two-tensor model (7 parameters for each tensor). Preliminary results for a similar model with five free parameters was presented in Ref. [21].

Note that the model is fundamentally an empirical one, albeit with physical underpinnings — as is the single-tensor description. The aim is to provide a useful tool, not necessarily one that faithfully reflects the intricacies of biological tissue. This technique should significantly improve the ability to track smaller fibers in the brain and to measure subtle changes in white matter fiber tract integrity. This article describes two steps in evaluating the proposed constrained two-tensor model:

1. A computer simulation of the fitting procedure in the constrained two-tensor model. Two tracts were simulated with appropriate noise levels in order to assess the accuracy and precision of the fitting procedure with the following aims: (a) evaluation of the sensitivity of the two-tensor model to the tract configuration, (b) evaluation of the sensitivity of the model to parameters related to data acquisition and (c) recognition of the voxels in which this model is applicable.

2. Application of the method to in vivo whole-brain diffusion-weighted echo planar imaging (DW-EPI) data.

2. Methods

2.1. Theory

The following describes the procedure for fitting the constrained two-tensor model to diffusion-weighted signals. Before fitting the two-tensor model, the single tensor that best describes the diffusion is calculated for each voxel. The signal amplitude, M_0 , corresponding to $b=0$, is extracted from the single-tensor fit. The first two eigenvectors, $\hat{e}_1$ and $\hat{e}_2$, of the single tensor define the plane of the tracts, and the third eigenvector, $\hat{e}_3$ (corresponding to the smallest eigenvalue λ_3), defines the perpendicular to this plane. In the orthonormal coordinate system defined by $[\hat{e}_1, \hat{e}_2, \hat{e}_3]$, given the previously described constraints, two tensors are defined, which have the following forms:

$$\mathbf{D}_\alpha = \begin{pmatrix} d_{\alpha 1} & d_{\alpha 3} & 0 \\ d_{\alpha 3} & d_{\alpha 2} & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix}, \quad \mathbf{D}_\beta = \begin{pmatrix} d_{\beta 1} & d_{\beta 3} & 0 \\ d_{\beta 3} & d_{\beta 2} & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \quad (1)$$

Note that this has now become a 2D problem. The gradient vectors are transformed into this coordinate system: $\mathbf{G} \rightarrow \tilde{\mathbf{G}}$. The signal attenuation equation is given by Eq. (2):

$$S = M_0 \left(f \exp \left(-b \tilde{\mathbf{G}} \mathbf{D}_\alpha \tilde{\mathbf{G}}^T \right) + (1 - f) \exp \left(-b \tilde{\mathbf{G}} \mathbf{D}_\beta \tilde{\mathbf{G}}^T \right) \right), \quad (2)$$

where $b = \gamma^2 \delta^2 (\Delta - \delta/3)$, M_0 is calculated from the single-tensor fit, f is the normalized signal fraction of the first tract and the gradients and diffusion tensors are given in the new coordinate system. The four free parameters of the model that remain after the single-tensor fit are as follows:

- f — the fraction of the first tract $\in [0,1]$,
- φ_α and φ_β — the angles subtended by the principal diffusion directions in the plane and
- λ_1 — the principal diffusivity, which is assumed to be the same in both tracts.

The relation between the components of a 2D diffusion tensor and these parameters is given in Eq. (3):

$$d_1 = \lambda_1 - d_3 \tan \varphi \quad (3)$$

$$d_2 = \lambda_1 - d_3 / \tan \varphi$$

$$d_3 = \frac{\lambda_1 - \lambda_3}{\tan \varphi + 1 / \tan \varphi}$$

Note that λ_3 is calculated from the single tensor.

Eq. (2) can be solved, for example, by using a nonlinear least-squares method with boundary constraints, based on the interior-reflective Newton method [22]. This algorithm has been implemented by Mathworks in Matlab software.

2.2. Simulations

Voxels containing two tract directions were simulated using two tensors with principal axes along unit vectors $\hat{\mathbf{a}}$ and $\hat{\mathbf{b}}$ in the x - y plane (see Fig. 2). The simulated tracts were placed at

angles ψ and $-\psi$ with respect to the x -axis (dashed line). The angle between the tracts (2ψ) was varied from 0° to 90° in increments of 10° . The fraction of the first tensor was varied from 0 to 0.5 in increments of 0.05. Diffusion-weighted signals were generated for a b value of 750 s/mm^2 for each of the following: 15, 31 and 63 diffusion gradient directions, with one baseline non-diffusion-weighted signal for each. These three acquisition configurations were chosen to all be within the scope of a clinical DTI scan. Each configuration had random noise added 50 times, with an SNR of 37.3, 26.4 and 18.7, respectively, for the non-diffusion-weighted images. The SNR of the 31-direction simulation was equal to that of typical in vivo DW-EPI data (see below). The other two SNR values are $26.4 \times \sqrt{2}$ and $26.4 \div \sqrt{2}$, chosen so as to result in theoretically comparable results for each number of gradient directions.

The simulated signals were analyzed using the four-parameter, constrained, two-tensor model. The plane of the tracts and the smallest eigenvalue were estimated from the single-tensor fit as previously described. The two-tensor fitting algorithm was “seeded” with an initial guess in which the relative population fractions were set at [0.35, 0.65] and the angle between the two tracts set to 60° . The simulations had previously been found to be insensitive to the parameters of the initial guess. The eigenvectors corresponding to the largest eigenvalue of the two fitted tensors are denoted $\hat{e}_{\alpha,1}$ and $\hat{e}_{\beta,1}$, respectively, in Fig. 2. These eigenvectors are assumed to indicate the direction of the two tracts. They are not assumed to be in the plane defined by $\hat{\mathbf{a}}$ and $\hat{\mathbf{b}}$. Note that although this type of simulation assumes the model, that is, it assumes that the diffusion can be described by two tensors, it is still useful for testing the fitting procedure and determining parametrical dependencies.

When to apply the model is an essential step in two-tensor analysis. The magnitude of the smallest eigenvector is one indicator of whether a voxel contains no more than two tracts. Although more than two tracts in a voxel could also yield a small value for λ_3 , they would all have to be lying in the same plane. It seems likely that even in this case, two-tract analysis is better than single-tensor analysis, although it is not investigated here. After this initial classification according to λ_3 , the geometric shape of the single-fitted diffusion tensor is determined, specifically the index of planar anisotropy, C_p , where C_p is Westin’s planar anisotropy index² [11] (only planar voxels are amenable to two-tensor fitting).

2.3. In vivo DW-EPI data

This data set was acquired using dual spin-echo DW-EPI with 31 gradient directions and 31 slices (whole-brain coverage) on a 3-T GE scanner. The parameters used were as follows: $b = 750 \text{ s/mm}^2$, $TE = 86.9 \text{ ms}$, $TR = 11.5 \text{ s}$, $FOV = 24 \text{ cm}$, $\text{matrix} = 128 \times 128$, $\text{slice} = 3.5 \text{ mm}$. Total imaging time was 6 min (one average). The SNR in white matter was 26.4 for the T_2 -weighted image. In order to assess the characteristics of diffusion in voxels containing only one tract (for use in the simulations), 134 corpus callosum voxels were chosen close to the midline from three of the slices and the signals were fitted to single tensors. The average of the eigenvalues in these voxels was 2.34 ± 0.31 , 0.56 ± 0.18 and $0.35 \pm 0.19 \text{ ms}/\mu\text{m}^2$ for λ_1 , λ_2 and λ_3 , respectively. The inequality of λ_2 and λ_3 can be accounted for by sorting bias.

3. Results

3.1. Simulations

Unless otherwise noted, the results shown pertain to the simulation using 31 gradient directions. The first step in the method — the single-tensor fit — is critical in determining the success of

²

$$C_p = \frac{2(\lambda_2 - \lambda_3)}{\lambda_1 + \lambda_2 + \lambda_3}$$

the second step. The $b=0$ amplitude [parameter M_0 in Eq. (2)] is quite robustly obtained, but the value of the smallest eigenvalue and the direction of the corresponding eigenvector are more sensitive to noise. The direction of this eigenvector determines the plane to which the two tracts will be constrained. Fig. 3 shows results from the simulation for both of these parameters, for selected tract angles and fractional population. The parameters ψ and the relative fraction, f , are shown in the individual plots. The simulated tracts are placed at angles ψ and $-\psi$ in the x - y plane. Clearly, the larger the angle separation and the more equal the fractional populations, the better the estimation of the tract plane from the single-tensor fit. From these results, the estimation of smallest eigenvalue, λ_3 , does not appear to be sensitive to the tract configuration.

A quantitative evaluation of the two-tensor fits to the simulated data defines the “angle error” in tract directions, $\Delta\varphi$, according to Eq. (4), by choosing the smaller of the mean angular differences between the “true” tracts and the fitted tracts (see notation in Fig. 2):

$$\varphi_1 = \frac{\varphi_{\alpha,a} + \varphi_{\beta,b}}{2} \quad (4)$$

$$\varphi_2 = \frac{\varphi_{\alpha,b} + \varphi_{\beta,a}}{2}$$

$$\Delta\varphi = \min\{\varphi_1, \varphi_2\}$$

Eq. (5) describes the method for calculating the error of the estimated fraction, Δf :

$$\varphi_1 \leq \varphi_2 \Rightarrow \Delta f = |F - f| \quad (5)$$

$$\varphi_1 > \varphi_2 \Rightarrow \Delta f = |F - (1 - f)|,$$

where F is the simulated fractional population and f is the estimated fraction.

Fig. 4 shows some of the results of the simulation. On the whole, as the separation angle grows and the volume fraction of each tract approaches 50%, the accuracy of the estimate improves. The sensitivity to acquisition parameters was determined by comparing simulated data that would have equal acquisition times; that is, if the number of gradient directions is doubled, the SNR is divided by $\sqrt{2}$. It can be concluded from Fig. 4 (and similar data not shown) that using more gradient directions than 31 at the expense of SNR could be detrimental. The single-tensor estimation method that was used in all cases was based on a linear fit to the log of the signal matrix. The data were not investigated using nonlinear fitting, which may mitigate the effect of Rician noise on the low SNR data [23].

Lower values of C_p can be visually correlated with higher errors associated with the two-tensor fit as shown in Fig. 5. Thus, the value of C_p , in each voxel, can provide error assessment input to tractography or a cutoff value for two-tensor analysis dependent on user-determined acceptable error values of angular separation and tract fraction.

3.2. In vivo DW-EPI data

Fig. 6 shows an example of the results of this calculation in vivo. The algorithm was applied to pixels in which $\lambda_3 < 0.6 \text{ ms}/\mu\text{m}^2$ and $C_p > 0.2$, the latter cutoff being determined from Fig. 5. It is clear that there are multiple pixels that exhibit both low values for the smallest eigenvector and high values of planar anisotropy. Fig. 6B, D and F allows visualization of the single-tensor principal eigenvector and the two directions of the two-tensor principal eigenvectors. The data were analyzed on a pixel-by-pixel basis without taking into account neighboring pixels; thus, groups of pixels showing continuity of crossing tracts support the

validity of the analysis. At obvious interfaces between tracts, the crossing tract analysis finds both bordering tract directions.

4. Discussion

The method proposed herein for extracting crossing tracts in human white matter is based on physically reasonable assumptions leading to a constrained two-tensor model. There is no need to acquire additional data over and above what is routinely available from clinical scans to implement this approach. Our analysis shows that the method should be applied selectively to pixels with low values of λ_3 and high values of planar anisotropy C_p , where the limits on these values can be determined from the data set itself.

A simplifying assumption made here is that the apparent diffusion coefficients parallel and perpendicular to the tracts, respectively, are the same for both tracts. This, together with the two-tract assumption, implies that the perpendicular diffusion constants of both tracts in the voxel can be fixed to equal the smallest eigenvalue calculated from the single-tensor fit. The diffusivity in the directions parallel to the tracts, however, is only constrained so as to be equal in both tracts. It is possible that different tracts have different geometric characteristics; how this affects the diffusivities remains an open question that needs further investigation. Future work should address the option of adding one or two additional parameters, which quantify the individual anisotropy of the two tracts, to the model. This is relevant because many studies compare anisotropy indices between regions of interest within a single brain or between subjects, leading to inferences regarding tissue microstructure and even functional connectivity.

The method will not work well if there is significant bending of tracts within the voxel but neither will other existing methods. Evidence from histology indicates that, on the spatial scale of MRI voxels, fibers do not usually change direction abruptly — an exception to this could be at points of insertion into gray matter.

From initial tests of the constrained two-tensor technique on human brain data and in simulations, it shows considerable potential for reforming the way both clinical DTI tractography and anatomical connectivity evaluation are performed. The technique will allow the tensor that corresponds best with the lattice to be used for tractography purposes and for extracting parameters relevant to white matter integrity, such as anisotropy. In the case of crossing fibers, these parameters should more reliably reflect the microstructure of the tract than parameters calculated from the single-tensor estimate, even with the constraints placed on the diffusivities, as outlined above. Unlike other methods for extracting crossing tracts proposed to date, this method can be applied to DTI data acquired in very short, clinically relevant times.

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Fig 1.
Region of prefrontal white matter in macaque brain slice (silver stain; histology was courtesy of V. Berezovskii, Department of Neurobiology, Harvard Medical School).

Fig 2. Schematic showing simulated tract directions ($\hat{\mathbf{a}}$ and $\hat{\mathbf{b}}$) at angles ψ and $-\psi$ relative to the x -axis in the x - y plane, as well as fitted tract directions ($\hat{\mathbf{e}}_{\alpha,1}$ and $\hat{\mathbf{e}}_{\beta,1}$).

Fig 3.

Dots on a sphere indicate eigenvector ($\hat{e}_3$) directions from the single-tensor fit to 50 sets of simulated data for select configurations of relative tract fraction, f , and angle separation, 2ψ .

Fig 4. Mean error in fitted tract parameters as a function of simulated parameters. The two-tensor fitting accuracy is compared between simulations of comparable data acquisition times. Left: error in fractional population as a function of simulated fractional population for simulated angle separation of 80°. Right: error in angle separation as a function of simulated angle separation for a tract population ratio of 0.4:0.6.

Fig 5.

The mean error found in two-tract simulations, with superimposed contours of C_p (white lines), shown as a function of the angle between two tracts, and the fractional populations. These plots can be used to determine the relationship between error values and C_p . Left: error in fitted tract fraction. Right: error in angle separation (in degrees).

Fig 6. Results from in vivo DTL. (A) A region of interest in the brain — enlarged in the rest of the figure. (B) Single-tensor analysis: the direction of the first eigenvector. Vectors with a significant through-plane component are indicated by circles. (C) Single-tensor planar index, C_p . Panels D to F show results from the two-tensor model. (D) First direction. (E) Fraction of smaller tract. (F) Second direction.