White Matter Integrity Measured by Fractional Anisotropy Correlates Poorly with Actual Individual Fiber Anisotropy

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ABSTRACT

Fractional anisotropy (FA), a very widely used measure of fiber integrity based on diffusion tensor imaging (DTI), is a problematic concept as it is influenced by several quantities including the number of dominant fiber directions within each voxel, each fiber's anisotropy, and partial volume effects from neighboring gray matter. High-angular resolution diffusion imaging (HARDI) can resolve more complex diffusion geometries than standard DTI, including fibers crossing or mixing. The tensor distribution function (TDF) can be used to reconstruct multiple underlying fibers per voxel, representing the diffusion profile as a probabilistic mixture of tensors. Here we found that DTI-derived mean diffusivity (MD) correlates well with actual individual fiber MD, but DTI-derived FA correlates poorly with actual individual fiber anisotropy, and may be sub-optimal when used to detect disease processes that affect myelination. Analysis of the TDFs revealed that almost 40% of voxels in the white matter had more than one dominant fiber present. To more accurately assess fiber integrity in these cases, we here propose the differential diffusivity (DD), which measures the average anisotropy based on all dominant directions in each voxel.

Index Terms— High-Angular Resolution Diffusion Imaging, Diffusion tensor imaging, Fractional Anisotropy.

1. INTRODUCTION

Diffusion-weighted MRI is a powerful tool to study water diffusion in tissue, providing vital information on white matter microstructure, such as fiber connectivity and integrity in the healthy and diseased brain. To date, most clinical studies still employ the *diffusion tensor imaging* (DTI) model [1], which describes the anisotropy of water diffusion in tissues by estimating, from a set of *K* diffusion-sensitized images, the 3x3 *diffusion tensor* (the covariance matrix of a 3-dimensional Gaussian distribution). Seven independent gradients are mathematically sufficient to determine the diffusion tensor, but MRI protocols with higher angular and radial resolutions, such as the high angular resolution diffusion imaging (HARDI) or diffusion spectrum imaging techniques [3,10], have been proposed to resolve more complex diffusion geometries, such as fiber crossings and intermixing of tracts. These geometries are incorrectly captured by a single-tensor model, as employed in standard DTI.

Among several recent advances in HARDI, the Q-ball imaging technique has been proposed to reconstruct fiber orientation density functions (ODFs) from the raw HARDI signal [2]. Deconvolution methods [3,4] can also yield mathematically rich models of fiber geometries using probabilistic mixtures of tensors [5], fields of von Mises-Fisher mixtures [6], or higher-order tensors (i.e., 3x3x…x3 tensors) [7,8]. Recent work on stochastic tractography [9, 10] also exploits the increased angular detail in HARDI. In most deconvolution-based methods, however, prior assumptions on fibers are usually imposed, e.g., all fiber tracts are forced to have the same anisotropy profile. Leow et al. recently proposed a more flexible approach, the Tensor Distribution Function (TDF) [11] to model fiber crossing in HARDI. Using the calculus of variations, the TDF approach can separate different dominant fiber directions in each voxel and compute their individual eigenvalues.

Much progress has been made in modeling more complex diffusion geometries that a single tensor fails to model, but most clinical studies still rely on simple DTI-derived scalar measures. Some of these, such as the trace of the covariance matrix or mean diffusivity (MD) can adequately describe isotropic water diffusion, but this only occurs in the cerebrospinal fluid spaces in the brain. In the white matter, myelinated fibers resist water diffusion orthogonal to the local dominant fiber orientation, and diffusion occurs preferentially along local fiber tracts. In clinical research, white matter fiber integrity is commonly assessed by determining how strongly diffusion is directionally constrained. One common scalar measure of directional diffusion, the fractional anisotropy (FA), is computed from the diffusion tensor's eigenvalues, and quantifies the magnitude of this directional preference. Clinical studies now routinely use FA as an index of white matter integrity, sensitive to white matter deterioration in aging and neurodegenerative diseases [12].

Even so, FA does not truly reflect the multidimensional complexity of the water diffusion profile. Regions with complex fiber-crossing tend to have lower FA values than predominantly unidirectional white matter structures (such as the midline corpus callosum; see **Figure 3**). However, it

is unlikely that each of these crossing fibers in these regions has a true decrease in its integrity when compared to, say, corpus callosum fibers. In this paper, we argue that "white matter integrity", as measured by FA, is somewhat vague and imprecise, and may be greatly improved by using the full diffusion gradient information in HARDI. Factors that influence FA values may include the number of dominant fiber directions in each voxel, the eigenvalues of each of these fibers, partial volume effects from neighboring gray matter, and the non-Gaussianity of water diffusion. By using the TDF approach, which can separate crossing fibers, we examine where FA fails to reflect the underlying diffusion anisotropy.

2. METHOD

An individual young adult subject was scanned using a diffusion-sensitized MRI protocol on a Bruker Medspec 4 Tesla MRI scanner, with a transverse electromagnetic (TEM) headcoil. The timing and angular sampling of the diffusion sequence was optimized for SNR [13]. The protocol used 94 diffusion-sensitized gradient directions, and 11 baseline scans with no diffusion sensitization (b-value: 1159 s/mm^2; TE/TR: 92.3/8250 ms; FOV=230x230; in-plane resolution: 1.8mmx1.8mm; 55 x 2mm contiguous slices; acquisition time: 14.5 minutes).

Firstly, a positive definite diffusion tensor was estimated from the raw HARDI signal using the MedINRIA software (http://www-sop.inria.fr/asclepios/software/MedINRIA), which projects the tensor manifold to its tangent plane at the origin to avoid negative or zero eigenvalues. Based on the diffusion tensor eigenvalues (λ_1, λ_2, and λ_3), the FA (defined in this paper as FA^{DTI} to avoid confusion) and MD (MD^{DTI}) may be calculated using Eq. 1:

$$\begin{cases} FA^{DTI} = \sqrt{\frac{3}{2}\left(\frac{(\lambda_1-<\lambda>)^2+(\lambda_2-<\lambda>)^2+(\lambda_3-<\lambda>)^2}{\lambda_1^2+\lambda_2^2+\lambda_3^2}\right)} \\ MD^{DTI} =<\lambda>=\frac{\lambda_1+\lambda_2+\lambda_3}{3} \end{cases} \quad (1)$$

Values of FA^{DTI} range from 0 (no directional dependence of diffusion) to 1 (diffusion along a single direction). In addition to modeling the HARDI signal with a single tensor, we also applied the TDF framework [13] to compute a probabilistic ensemble of 3D Gaussian diffusion processes at each voxel that best describes the observed signal. This ensemble is denoted by a *pdf* P defined on the space of symmetric positive definite 3-by-3 matrices. In the TDF framework, all fibers are assumed to be cylindrical, and planar-shaped tensors are excluded. Thus, $\lambda_1 \geq \lambda_2 = \lambda_3$ for each tensor in the tensor space $\bar{\mathcal{D}}$.

Given any TDF *P*, the number of dominant fibers may be estimated from the local maxima of the tensor orientation distribution: $TOD(\theta) = \int_\lambda P\big(D(\lambda,\theta)\big)d\lambda$. The eigenvalues of each fiber can be calculated by computing their expected values. In this paper, we investigate two sets of eigenvalues: those of the 1st dominant fiber $(\lambda_1^1, \lambda_2^1)$ (Eq. 2) and the voxelwise TDF-averaged eigenvalues $(\overline{\lambda_1}, \overline{\lambda_2})$ (Eq. 3).

$$\begin{cases} \lambda_i^1 = \frac{\int P(D(\theta^*,\lambda))\lambda_i d\lambda}{\int P\left(D(\theta^*,\lambda)\right)d\lambda} \quad (i=1,2) \\ \theta^* = argmax(TOD(\theta)) \end{cases} \quad (2)$$

$$\overline{\lambda_i} = \int_{D\in\mathbb{D}} P(D)\lambda_i dD \quad (i=1,2) \quad (3)$$

To assess the overall diffusion anisotropy in each voxel using the TDF framework, we propose the differential diffusivity (DD; Eq. 4). To compare TDF-derived measures to those from standard DTI, we can also compute the 1st dominant fiber's FA, defined as FA^1, and the TDF-averaged FA, defined as FA^{TDF} (MD^1 and $\overline{MD}$ are defined similarly).

$$DD \triangleq \frac{\overline{\lambda_1}-\overline{\lambda_2}}{\overline{\lambda_1}+\overline{\lambda_2}} \quad (4)$$

$$\begin{cases} FA^1 = \sqrt{\frac{3}{2}\left(\frac{\left(\lambda_1^1-<\lambda^1>\right)^2+\left(\lambda_2^1-<\lambda^1>\right)^2+\left(\lambda_2^1-<\lambda^1>\right)^2}{{\lambda_1^1}^2+{\lambda_2^1}^2+{\lambda_2^1}^2}\right)} \\ \mathrm{MD}^1 =<\lambda^1>=\frac{\lambda_1^1+\lambda_2^1+\lambda_2^1}{3} \\ FA^{TDF} = \sqrt{\frac{3}{2}\left(\frac{(\overline{\lambda_1}-<\bar{\lambda}>)^2+(\overline{\lambda_2}-<\bar{\lambda}>)^2+(\overline{\lambda_2}-<\bar{\lambda}>)^2}{\overline{\lambda_1}^2+\overline{\lambda_2}^2+\overline{\lambda_2}^2}\right)} \\ \overline{MD} =<\bar{\lambda}>=\frac{\overline{\lambda_1}+\overline{\lambda_2}+\overline{\lambda_2}}{3} \end{cases} \quad (5)$$

3. RESULTS AND DISCUSSION

We first assessed whether FA derived from standard DTI (FA^{DTI}) is an accurate measure of fiber anisotropy. Even though FA^{DTI} is usually intended to measure *white matter integrity*, it in fact measures the compound effect of several factors, including the FA of individual fibers, the number of dominant fiber directions and partial volume effect from gray matter. Many of these will vary when the integrity of the fibers is not impaired, confounding its interpretation. Since any disease process that affects white matter myelination will most likely affect individual fiber anisotropy, we here restrict ourselves to investigating how well FA measures the anisotropy of individual fibers. As the TDF approach can separate multiple dominant fibers in one voxel and can determine their respective eigenvalues, we may answer the above question by investigating how well FA^{DTI} correlates with the FA values of the underlying dominant white matter fibers. As more than one fiber direction may be present, we examined how well FA^{DTI} correlates with either FA^1 or the overall FA^{TDF}. **Table 1** shows the results of these correlations. Only moderate correlations are found (0.431 for FA^{DTI} vs. FA^{TDF}, 0.252 for FA^{DTI} vs. FA^1) when both gray and white matter are included. Correlations are much weaker (0.206 and 0.294. respectively) when we only consider the white matter (operationally defined by a threshold of FA^{DTI} at 0.2), which is the tissue type FA was originally designed to investigate

(FA^{TDF} correlates well with FA^{1}). By contrast, correlations are better between DTI- and TDF-derived MD measures (**Table 2**) than for FA. These results support our hypothesis that in the white matter, FA^{DTI} correlates very poorly with the actual individual fiber anisotropy, and thus (1) may be suboptimal for detecting subtle disease processes that affect myelination, and (2) may even be misleading, as low FA values may simply reflect the presence of multiple fibers.

Table 1 Correlations among FA^{DTI}, FA^{1} and FA^{TDF} for the whole brain and for voxels with FA^{DTI} >0.2 (thus mainly white matter voxels). FA^{DTI} correlates poorly with actual individual fiber anisotropy computed from the TDF.

Correlations	Whole brain	Voxels with FA^{DTI} >0.2
FA^{DTI} *vs.* FA^{1}	0.252	0.206
FA^{DTI} *vs.* FA^{TDF}	0.431	0.294
FA^{TDF} *vs.* FA^{1}	0.893	0.835

Table 2 Correlations among MD^{DTI}, MD^{1} and MD^{TDF} for the whole brain and for voxels with FA^{DTI} >0.2. Compared to FA, MD^{DTI} correlates better with actual individual MD.

Correlations	Whole brain	Voxels with FA^{DTI} >0.2
MD^{DTI} *vs.* MD^{1}	0.591	0.410
MD^{DTI} *vs.* MD^{TDF}	0.623	0.500
MD^{TDF} *vs.* MD^{1}	0.826	0.793

Table 3 Correlations between MD^{DTI} and MD^{TDF} for different numbers of dominant fibers.

Correlations	Whole brain	Voxels with FA^{DTI} >0.2
Number=0	0.656	0.566
Number=1	0.503	0.414
Number=2	0.390	0.340
Number≥3	0.345	0.319

To visualize these correlations, we plotted FA^{DTI} against FA^{TDF} in **Figure 1**. There is an overall trend of positive correlation between these two measures, but a closer look suggests that FA^{DTI} is highly variable in the white matter. To understand this, we notice that a high FA^{DTI} value always indicates white matter, but some white matter voxels have medium-to-low FA^{DTI} values (e.g., due to multiple fibers crossing). This can be observed in **Figure 1:** when FA^{DTI} takes a higher value (indicating white matter), FA^{TDF} almost always takes a high value. For voxels with FA^{DTI} values higher than 0.8, mean FA^{TDF} is 0.776 (with a standard deviation of 0.144). However, the converse is not true (i.e., some white matter voxels may have low-to-medium DTI-FA values). Indeed, for voxels with FA^{TDF} values higher than 0.8 (indicating that at least one dominant fiber is present), the mean FA^{DTI} is 0.444 with a standard deviation of 0.19.

FA measurements have a higher variability in the white matter when they are derived from the simple DTI model versus computing them from the full TDF model; this is important for clinical applications where groups are often compared using a two-sample *t* test, or the general linear model. In these studies, the larger standard deviation of FA^{DTI} inevitably lowers the statistical power of a test with a fixed *N* (requiring more subjects to detect subtle changes).

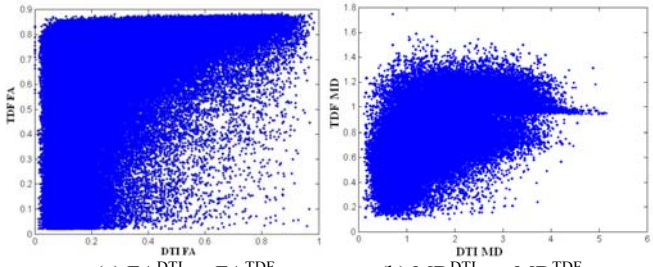
We next further explored the relation between DTI derived measures and the number of dominant fibers (derived from the TOD at thresholds of 0.15 and 0.1). As DTI is a single-tensor model, one would assume that the correlations with individual fiber measures would decrease (be less accurate) as the number of dominant fibers increases. This is indeed the case for MD (**Table 3**). However, the same trend is not present for FA (results not shown). To understand this, we plotted FA^{DTI} against the number of dominant fibers (**Figure 2**), which shows a more complex picture. Here, the number of dominant fibers first shows an increase when FA^{DTI} increases, followed by a decrease for voxels with the highest FA^{DTI} values. We hypothesize that the highest FA^{DTI} values usually correspond to predominantly uni-directional white matter structures (e.g., corpus callosum), which have fewer dominant fiber directions compared to white matter voxels with fiber-crossing (thus lower FA^{DTI} values). However, at low FA^{DTI} values, we have to consider at least two opposing factors, both of which tend to cause a decrease in FA^{DTI} (but have opposite effects on the number of fiber directions): the partial volume effect from gray matter (causing a *decrease* in the number of dominant fibers as the volume ratio of gray matter increases), and the fiber-crossing effect (causing an *increase* in number of dominant fibers as more fibers cross one another). These factors may combine to explain the overall positive correlation for low-to-medium FA^{DTI}.

To summarize, these results indicate that FA is a complex measure, and is relatively difficult to interpret. Our results are consistent with those in [14], where FA was positively correlated with fiber density index (which measures how many fibers go through a given voxel) in patients with glioblastoma. Lastly, we found that the TDF-derived differential diffusivity, unlike FA^{DTI}, does not suffer much from a drop in values in voxels with fiber-crossing (**Figure 3**).

4. CONCLUSION

In this paper, we showed that white matter integrity, measured using the fractional anisotropy (FA) derived from standard DTI, is imprecise as it is dependent upon several quantities. When compared with TDF-derived anisotropy measures, the FA obtained from standard DTI does not correlate well with the anisotropy of the individual component fibers, and may be sub-optimal in detecting subtle disease processes that affect white matter myelination (in contrast, DTI-derived MD appears to correlate better with those of individual fibers). Clinical studies often interpret lower FA^{DTI} values as a sign of compromised fiber integrity, but this may be misleading. Future imaging studies of white matter integrity may benefit from assessing the number of dominant fiber directions in each voxel, and their corresponding eigenvalues and anisotropy. The TDF

framework and its related measures provide more accurate reconstruction of the full diffusion profile, using more of the information in the diffusion images, and may empower future clinical studies.



(a) FA^{DTI} vs FA^{TDF} (b) MD^{DTI} vs. MD^{TDF}

Figure 1. Correlation between DTI-derived and TDF–derived measures of FA and MD. Here the plots are for the whole brain using the control subject described in the methods section. When compared to MD, FA derived from DTI is less well correlated with its TDF–derived analog (see text for more details).

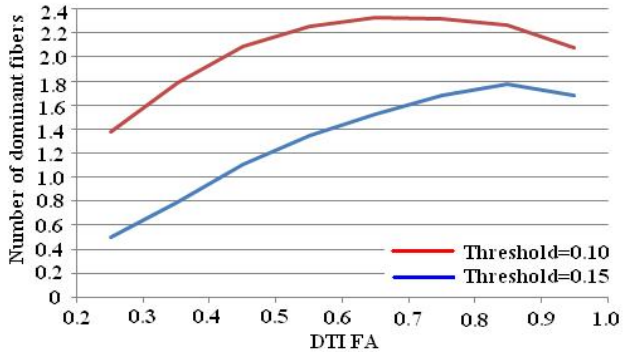
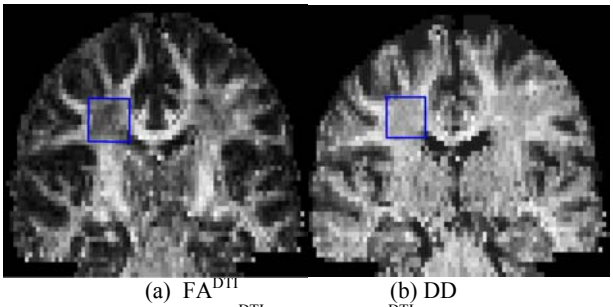


Figure 2. DTI FA vs. Estimated number of dominant fibers

Here FA^{DTI} values are related to the number of dominant fiber directions, determined by thresholding the corresponding TOD at two different values (0.15 and 0.1) and counting the number of local maxima (e.g., at a threshold of 0.15, 61.2% of white matter voxels have one dominant fiber direction, 31.6% have two, and 7.2% have three or more). The mean number of dominant fiber directions for different ranges of FA^{DTI} is calculated by averaging the number of fiber directions within that range (e.g., when FA^{DTI} is within 0.6 and 0.7, the mean number of dominant fiber directions is 1.529). Both curves showed a non-linear relationship - with an initial increase for the number of fiber directions, followed by a decrease as FA^{DTI} increases.



(a) FA^{DTI} (b) DD

Figure 3. Comparing FA^{DTI} and DD. FA^{DTI} is incorrectly depleted in regions with extensive fiber crossing (*blue box, inset*). By contrast, the differential diffusivity (DD) separates the dominant fiber directions and their corresponding anisotropy measures. Fibers from corpus callosum and *corona radiata* cross in the highlighted region. Here FA^{DTI} values are artifactually lowered relative to those of neighboring white matter, because the best single-tensor fit is more spherical than for the surrounding fibers that enter these voxels. Here, FA^{DTI} poorly reflects the fiber content of the voxel. For DD, the signal is more consistent with that of the fibers entering the highlighted region.

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