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Evaluating Kurtosis-based Diffusion MRI Tissue Models for White Matter with Fiber Ball Imaging

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Abstract

In order to quantify well-defined microstructural properties of brain tissue from diffusion MRI (dMRI) data, tissue models are typically employed that relate biological features, such as cell morphology and cell membrane permeability, to the diffusion dynamics. A variety of such models have been proposed for white matter, and their validation is a topic of active interest. In this paper, three different tissue models are tested by comparing their predictions for a specific microstructural parameter to the value measured independently with a recently proposed dMRI method known as fiber ball imaging (FBI). The three tissue models are all constructed with the diffusion and kurtosis tensors, and they are hence compatible with diffusional kurtosis imaging (DKI). Nevertheless, the models differ significantly in their details and predictions. For voxels with fractional anisotropies (FA) exceeding 0.5, all three are reasonably consistent with FBI. However, for lower FA values, one of these, called the white matter tract integrity (WMTI) model, is found to be in much better accord with FBI than the other two, suggesting that the WMTI model has a broader range of applicability.

Keywords

tissue model; kurtosis; diffusion; tensor; fiber ball imaging; white matter; brain; MRI

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INTRODUCTION

Diffusion MRI (dMRI) is notable for its ability to characterize the dynamics of water diffusion in biological tissues through several well-defined metrics, such as the fractional anisotropy (FA) and mean kurtosis (1). These metrics quantify the physics of the diffusion process and have no explicit connection to tissue microstructure, even though water diffusion may be strongly affected by microstructural components such as cell membranes and organelles. In one sense, this is an advantage in that diffusion metrics have unambiguous physical meanings that are independent of the type of tissue. On the other hand, determining their precise biological significance in a specific context is notoriously difficult. This is particularly true for brain due to its highly complex microstructure, comprised of multiple cell types arranged in elaborate geometrical patterns (2).

The bridge between the physics encapsulated by the diffusion metrics and tissue microstructure is a “tissue model,” which is based on assumptions about how the microstructure of a given tissue influences the water diffusion dynamics. For practical reasons, tissue models are typically highly idealized and the validity of the assumptions upon which they rely may be uncertain. From a broad perspective, this is a type of inverse problem wherein one seeks to infer microstructural properties (the cause) from a set of diffusion parameters (the observations). Inverse problems are famous for being ill-conditioned, as there may be multiple possible causes for a given set of observations.

In spite of such obstacles, there has been great interest over the past decade or so in constructing, testing, and applying dMRI tissue models for brain (3–11). This is motivated by the unparalleled sensitivity, among noninvasive imaging modalities, of dMRI to brain microstructure and by the fundamental importance of microstructure to neurological diseases, as well as normal brain function. Although many of the models are similar in their features, they frequently also have important differences that can substantially alter their predications. As a result, many dMRI tissue models are currently rather controversial with considerable uncertainty regarding their relative merits (12). Here we consider three different dMRI tissue models that utilize the diffusion and kurtosis tensors as experimental inputs. These two tensors may be estimated with diffusional kurtosis imaging (DKI) (13–15), and we refer to the models as being “kurtosis-based.”

One kurtosis-based tissue model is the white matter integrity (WMTI) approach, proposed by Fieremans and coworkers (16), which has been applied in a number of prior studies (17–27). It assumes that the diffusion dynamics can be described in terms of two Gaussian compartments, one corresponding to the intra-axonal space and one to the extra-axonal space, with water exchange between these two compartments being neglected. The model is only meant to apply in white matter voxels for which the axons are oriented in similar directions (typically high FA regions). A notable feature of the WMTI model is that the fitting parameters are determined from the diffusion and kurtosis tensors by purely algebraic manipulations.

A flexible tissue modeling framework for DKI has also been developed, known as kurtosis analysis of neural diffusion organization (KANDO) (28), which supports a variety of

specific models. Here the tissue model defines how the free parameters are related to the kurtosis tensor, and the parameters are fit by minimizing the Frobenius norm of the difference between the model and measured kurtosis tensors. In contrast to the WMTI approach, this is generally tantamount to a nonlinear optimization problem with all the attendant challenges, such as local minima, that this implies. The advantage of KANDO is its ability to accommodate diverse models based on different assumptions. To date, three distinct KANDO models have been proposed, one for gray matter and two for white matter. One of the white matter models assumes that axons are unidirectional, while the second allows for the possibility of fiber crossings. We shall refer to these two kurtosis-based models as KANDO 1 and KANDO 2, respectively.

Although these three different tissue models for white matter differ substantially in their associated computational details, the predictions they yield are fairly similar (28). Nonetheless, there are important discrepancies. In particular, the intra-axonal diffusivity (i.e., the diffusivity of intra-axonal water along the axis of the axonal fibers) calculated with the WMTI model tends to be somewhat elevated relative to predictions from the KANDO models. More perplexingly, data from isotropic diffusion encoding experiments yield intra-axonal diffusivity estimates markedly higher than for any of these three models (29). The inherent challenges of properly estimating this parameter from dMRI data have been eloquently described by Jelescu and coworkers (12).

The purpose of this paper is to test the three kurtosis-based tissue models for white matter by comparing their predictions to those of the recently introduced fiber ball imaging (FBI) method (30). The central observation of FBI is that the fiber orientation density function (fODF) for axons can be estimated by taking the inverse Funk transform of high angular resolution imaging (HARDI) data obtained with a sufficiently large diffusion weighting (i.e., b-value). As a byproduct, FBI also provides a value for the quantity

$$\zeta \equiv \frac{f}{\sqrt{D_a}}, \quad [1]$$

where f is the fraction of dMRI-visible water contained within the intra-axonal space and D_a is the intra-axonal diffusivity. Since the kurtosis-based models also give predictions for ζ , these models can be tested by using the FBI value as a quasi-gold standard.

To be sure, FBI is dependent on its own set of assumptions, and its predictions for ζ are therefore not definitive. However, these assumptions are ostensibly milder than those for the three tissue models, as FBI does not posit a specific distribution of axon orientations nor does it stipulate detailed properties for the extra-axonal space. FBI does idealize the axons as thin, impermeable cylindrical tubes, and it assumes that the mobility of the extra-axonal water is sufficiently large so that it makes a negligible contribution to the dMRI signal for high b-values. This picture is plausible in light of the known microstructural features of white matter and has significant experimental support (30–32). Moreover, FBI is independent of DKI in that 1) it uses high ($> 3000 \text{ s/mm}^2$), rather than low ($< 3000 \text{ s/mm}^2$),

b-value dMRI data and 2) it does not involve the calculation of the diffusion or kurtosis tensors. Hence, consistency with FBI may be regarded as supportive evidence for the kurtosis-based tissue models, although this only tests the specific ratio appearing in Eq. [1] rather than f and D_a individually.

In this study, we compare ζ as measured with FBI, WMTI, KANDO 1, and KANDO 2, regarding the FBI value as a benchmark. We employ HARDI data obtained from two human subjects for b-values of 1000, 2000, and 5000 s/mm², with the two lower b-values being used for the kurtosis-based tissue models and the higher b-value being used for the FBI analysis. The results for ζ are evaluated in regions of interest (ROIs) defined as all brain tissue voxels with FA equal to or exceeding a specified minimum, $FA_{\min}$, for $FA_{\min} = 0.3, 0.4, 0.5$, and 0.6 .

METHODS

Kurtosis-based Tissue Models

The detailed assumptions and associated numerical procedures for the three kurtosis-based tissue models are presented in prior publications (16,28). Here we summarize some of the key aspects of each model. All three models regard the diffusion and kurtosis tensors as given, since these can be estimated with DKI. They also employ similar methods of calculating the axonal water fraction, f , in each voxel. For the WMTI model (16), one has

$$f = \frac{K_{\max}}{K_{\max} + 3}, \quad [2]$$

where $K_{\max}$ is the maximum of the diffusional kurtosis over all possible diffusion directions, while for KANDO 1, we utilize

$$f = \frac{K_{\perp, \max}}{K_{\perp, \max} + 3}, \quad [3]$$

where $K_{\perp, \max}$ is the maximum kurtosis over all diffusion directions perpendicular to the principal diffusion tensor eigenvector (28). For KANDO 2, the local maxima of the diffusion orientation distribution function (dODF), as determined with DKI and a radial weighting power of four (33,34), are used to identify a set of fiber directions in each voxel (28). If only a single fiber direction is found, then Equation [3] is again applied except that $K_{\perp, \max}$ is interpreted as the maximum kurtosis over directions perpendicular to this fiber direction rather than to the principal eigenvector. If two or more directions are detected, then the two corresponding to the largest dODF local maxima are chosen, and the axonal water fraction is calculated from

$$f = \frac{K_{\perp}}{K_{\perp} + 3}, \quad [4]$$

with $K_{\perp}$ being the kurtosis in the direction orthogonal to the both of these maxima. Despite these technical distinctions, there are typically only minor differences between the values for f that these three models predict (28).

For the WMTI model, compartmental diffusion tensors are calculated for both the intra-axonal and extra-axonal spaces using only algebraic manipulations. These are based on the assumptions that there is negligible water exchange between the compartments and that the diffusion dynamics within each compartment is Gaussian. This assumption of Gaussianity is most accurate when the axons are aligned in a single direction and becomes less valid when there is significant fanning or crossing of fibers (16). From the diffusion tensor for the intra-axonal space, $\mathbf{D}_a$, the intra-axonal diffusivity is calculated from

$$D_a = \text{tr}(\mathbf{D}_a). \quad [5]$$

Both KANDO 1 and KANDO 2 determine the adjustable model parameters, a_m , by minimizing the cost function

$$C \equiv \sum_{i,j,k,l=1}^3 \left| W_{ijkl}^{\text{mod}}(a_m) - W_{ijkl} \right|^2, \quad [6]$$

where $W_{ijkl}^{\text{mod}}(a_m)$ is a specified function for the model kurtosis tensor and W_{ijkl} is the measured kurtosis tensor (28). The right side of Equation [6] is simply the square of the Frobenius norm for the difference between the model and measured kurtosis tensors. The cost function for KANDO 1 is based on the assumption that all the axons are aligned parallel to the principal diffusion tensor eigenvector, and there is a single adjustable model parameter, $a_1 = D_a/\bar{D}$, with $\bar{D}$ being the measured mean diffusivity. For KANDO 2, the cost function is obtained by assuming that each voxel has either one or two fiber directions, with these being determined from the dODF local maxima, and there are two adjustable parameters for this model. One of these is the same $a_1 = D_a/\bar{D}$ as for KANDO 1, while the other is $a_2 = f_1$, where f_1 is the water fraction associated with the fiber direction corresponding to the largest dODF maximum. In order to ensure that a global minimum of the cost function is found, an exhaustive grid search can be utilized. For this study, we employ 100 grid points for KANDO 1 and 100×100 grid points for KANDO 2. For both models, the search spaces are restricted by constraints needed to guarantee physically viable solutions (e.g., positive compartmental diffusivities). Once the adjustable model parameters have been determined by minimizing C , then all other physical properties for the models are readily calculated.

The WMTI and KANDO 1 models are based on essentially the same physical pictures and differ primarily in their computational schemes; WMTI uses the solution to a set of algebraic equations, while the KANDO 1 model parameters are found by minimizing a cost function. KANDO 2, in contrast, is a fundamentally different model in that it incorporates fiber crossings explicitly.

Fiber Ball Imaging

FBI (30) is closely related to q-ball imaging (35), with the fundamental difference being that q-ball imaging uses the Funk transform of HARDI data to estimate the dODF, while FBI uses the *inverse* Funk transform to estimate the fODF. The distinction between dODF and fODF is that the dODF characterizes the angular dependence of the diffusion dynamics, while the fODF gives the probability density of finding an axon oriented in a given direction. The central formula underlying FBI is

$$F(\mathbf{n}) = \sqrt{\frac{bD_a}{\pi}} T_F^{-1}(S/S_0, \mathbf{n}), \quad [7]$$

where $F(\mathbf{n})$ is the fODF as a function of a unit direction vector $\mathbf{n}$, S is the HARDI signal for a shell in q-space with a b-value of b , S_0 is the signal in the absence of diffusion weighting, and T_F^{-1} indicates the inverse Funk transform. The accuracy of Equation [7] is expected to improve with increasing b-value, and in practice, b-values of 4000 to 6000 s/mm² can be recommended for in vivo brain on clinical scanners (31). In Equation [7], the fODF is normalized so that

$$f = \int d\Omega_{\mathbf{n}} F(\mathbf{n}), \quad [8]$$

with the angular integral being taken over all directions. By combining Equations [1], [7], and [8], we then obtain

$$\zeta = \sqrt{\frac{b}{\pi}} \int d\Omega_{\mathbf{n}} T_F^{-1}(S/S_0, \mathbf{n}). \quad [9]$$

Since the right side of Equation [9] contains only known or measurable quantities, it provides a method of determining ζ . One may simplify Equation [9] to yield

$$\zeta = \frac{1}{2\pi S_0} \sqrt{\frac{b}{\pi}} \int d\Omega_{\mathbf{n}} S(\mathbf{n}). \quad [10]$$

The major conditions for the validity of FBI are that water exchange between the intra-axonal and extra-axonal spaces can be neglected, that intra-axonal water can be idealized as being confined to thin, straight cylindrical tubes, that the extra-axonal water is relatively mobile with a minimum diffusivity of $D_{e,min}$, and that the two inequalities $bD_{e,min} \gg 1$ and $bD_a \gg 1$ both hold. Some ancillary assumptions are given in Ref. 30.

Data Acquisition

MRI scans were acquired for two human volunteers on a 3T Tim Trio system (Siemens Healthcare, Erlangen, Germany) under a protocol approved by the Medical University of South Carolina Institutional Review board.

HARDI data were obtained with a twice-refocused dMRI sequence (36), a 32 channel head coil (adaptive combine mode), and a parallel imaging factor of two. The diffusion-weightings were $b = 1000, 2000$, and 5000 s/mm^2 , and 128 diffusion encoding directions were used for each b-value shell with one excitation for each combination of b-values and directions. The same dMRI sequence was also used to acquire 20 images without diffusion-weighting (b0 images). The other key imaging parameters were $TE = 149 \text{ ms}$, $TR = 7200 \text{ ms}$, field of view = $222 \times 222 \text{ mm}^2$, in-plane resolution = $3 \times 3 \text{ mm}^2$, slice thickness = 3 mm , interslice gap = 0 , number of slices = 40 , and bandwidth = 1351 Hz/pixel . The total scan time was about 49 min.

Data Analysis

All HARDI and b0 images were co-registered with Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London) in order to correct for subject movement. Furthermore, to mitigate the effects of signal noise and Gibbs ringing, all the images were smoothed with a Gaussian kernel having a full width at half maximum of 3.75 mm . The diffusion and kurtosis tensors were calculated with diffusional kurtosis estimator (<http://www.nitrc.org/projects/dke/>, Center for Biomedical Imaging, Medical University of South Carolina) (37) using the b0 images and the HARDI images with $b = 1000$ and 2000 s/mm^2 . This subset of our images constitutes a DKI dataset with standard b-values (15). The diffusional kurtosis estimator algorithm is based on a constrained weighted linear least squares fitting to the full DKI dataset (37). The parametric maps of axonal water fractions and intra-axonal diffusivities for the three kurtosis-based models were calculated as outlined above and described in detail in prior publications (16,28). Maps for the corresponding ζ values were then obtained from Equation [1]. For FBI, the ζ value maps were obtained from the b0 images and the $b = 5000 \text{ s/mm}^2$ HARDI data by simply applying Equation [10], wherein the integral was evaluated from the lowest order term of a spherical harmonic expansion of the dMRI signal (30). Note that except for the b0 images, the DKI and FBI analyses use independent data and distinct computational procedures.

From the diffusion tensors, FA maps were calculated and used to delineate four ROIs for each subject. These were defined to include all brain tissue voxels with $FA \geq FA_{min}$, where $FA_{min} = 0.3, 0.4, 0.5$, and 0.6 . Such moderate to large minimum FA values imply that the vast majority of the ROIs consisted of white matter (38). For Subject 1, the ROIs included 8040, 4660, 2228, and 895 voxels, respectively, while for Subject 2, they included 9124,

4811, 2085, and 795 voxels. The ROIs were defined in terms of FA thresholds, since the kurtosis-based models have often been used with similar types of ROIs.

Three methods were employed to compare the ζ values from the three kurtosis-based models to the FBI results. First, voxel-wise correlations were quantified for each ROI with Pearson's correlation coefficient r . Second, the slopes of linear least squares best fit lines through the origin were calculated for plots, including all the ROI voxels, of the model vs. FBI ζ values. Perfect agreement would yield a slope of one, while a slope of greater than one would indicate a positive bias for the model and a slope of less than one would indicate a negative bias. Third, the mean voxel-wise difference, $\bar{\zeta}$, between the model and FBI ζ values was determined. Although $\bar{\zeta}$ may directly be determined from the model and FBI ζ values averaged over the ROI, it is necessary to do a voxel-by-voxel calculation of the difference in order to obtain the correct standard deviation for $\bar{\zeta}$.

RESULTS

Representative axial slices for the ζ maps obtained with FBI, WMTI, KANDO 1, and KANDO 2 are shown in Figure 1 for both subjects. The ROI for $FA_{\min} = 0.4$ is shown in color, with the gray scale background voxels being taken from the b_0 images. A striking correspondence between the FBI and WMTI maps is apparent. The KANDO maps are also similar, but most of their ζ values are distinctly larger than for the FBI maps.

Figure 2 gives correlation plots for $FA_{\min} = 0.4$, where each data point represents an individual voxel. The correlation coefficients for WMTI exceed $r = 0.8$ for both subjects, while those for the KANDO models are substantially smaller. The correlation coefficients for the other $FA_{\min}$ values are similar, with WMTI having the highest correlation in every case. For a given model, the strongest correlation occurs for $FA_{\min} = 0.4$, except with KANDO 2 for Subject 2 in which case it is for $FA_{\min} = 0.6$ ($r = 0.66$). But all the correlations are statistically significant and similar across the $FA_{\min}$ thresholds for each model. That the highest correlation tends to occur for an intermediate FA threshold is likely due to a compromise between model accuracy and the dynamic range of the ζ values.

Also plotted in Figure 2, are the best fit lines that pass through the origin. The slopes for WMTI from the two subjects are 1.028 ± 0.001 and 1.011 ± 0.001 , indicative of a small positive bias. The slopes for the KANDO models are somewhat larger, ranging from 1.112 ± 0.002 to 1.175 ± 0.002 . One also sees that WMTI tends to overestimate ζ for $\zeta_{FB} < 0.52$ and to underestimate ζ for $\zeta_{FB} > 0.52$, where ζ_{FB} is the ζ value obtained with FBI.

The mean ζ values from FBI and the three models are given by Figure 3 for both subjects and all the ROIs. Also shown in Figure 3 are the mean differences, $\bar{\zeta}$, of the model values relative to the FBI value. For the KANDO models, $\bar{\zeta}$ decreases as the FA threshold is increased and is near zero for $FA_{\min} = 0.6$. This is precisely what one would naively expect, since the requisites for these models are most accurately fulfilled when the axons have a coherent alignment (28), even though KANDO 2 does allow for up to two fiber directions. The mean differences also decrease for the WMTI model, but become negative for $FA_{\min} = 0.5$ and 0.6 . The minimum mean difference magnitude for WMTI occurs at $FA_{\min} = 0.5$ for

Subject 1 and at $FA_{\min} = 0.4$ for Subject 2. Furthermore, the WMTI model has the lowest mean difference magnitude among the three models for all the FA thresholds except $FA_{\min} = 0.6$, which encompasses only a relatively small fraction of the white matter. That WMTI is found to be most accurate for $FA_{\min} = 0.4$ or 0.5 , rather than for $FA_{\min} = 0.6$, could reflect some type of small systematic error.

These same mean differences expressed as percentages are listed in Table 1. For the WMTI model, the differences are less than 10% in all cases. With KANDO 1, the differences are lower than 10% only when $FA_{\min} = 0.6$ for Subject 1 and when $FA_{\min} = 0.5$ and 0.6 for Subject 2. The differences with KANDO 2 are below 10% only when $FA_{\min} = 0.5$ and 0.6 for both subjects. In every case, KANDO 2 has a smaller percent difference than KANDO 1, but WMTI has the least percent difference except when $FA_{\min} = 0.6$. It is also important to note that the standard deviations of the percent differences are substantially smaller for WMTI than for either KANDO 1 or KANDO 2. Overall, the accuracy and precision of WMTI can be judged as superior to that of the KANDO models, based on our FBI benchmark.

Figure 4 shows the model predictions for the mean values of f and D_a . The axonal water fractions are very similar among all three models and increase somewhat with increasing FA threshold. However, the intra-axonal diffusivities are substantially larger for WMTI, which is thus the source of the corresponding ζ value differences. The mean intra-axonal diffusivities for WMTI model are significantly different than those for the KANDO models in all cases (t test, $p < 0.05$).

DISCUSSION

The validation of tissue models for dMRI is challenging, and no single experiment is likely to be definitive. Rather, the ultimate assessment of such models may emerge from a concordance of results derived from multiple investigations. In this study, we have presented data that is relevant to the validation of three kurtosis-based tissue models for white matter.

The predictions from each of the models for the parameter $\zeta \equiv f / \sqrt{D_a}$ have been compared to those derived from FBI, which we regard as a quasi-gold standard. A critical aspect of this comparison is that FBI is independent of DKI, both in terms of postprocessing and data acquisition (except for sharing of the b0 images). This is important, because the diffusion and kurtosis tensors derived with DKI, from which the kurtosis-based models are built, may have associated estimation errors (15,39) that could affect the calculation of ζ .

For $FA_{\min} = 0.5$, all three kurtosis-based models yield ζ values that are within about 10% of the FBI predictions (Table 1), reflecting a reasonable degree of consistency. However, when the FA threshold is lowered, the agreement of KANDO 1 and KANDO 2 with FBI deteriorates markedly. This is not surprising, as the assumptions upon which these two kurtosis-based models rest are expected to hold most accurately when the axons within a given voxel are mainly oriented in a single direction (28). KANDO 2 does incorporate fiber crossings, but only in a highly simplified way, and this is presumably why the deviations for KANDO 2 are generally smaller than for KANDO 1. On the other hand, the KANDO 2 differences also have larger standard deviations than for KANDO 1, and so KANDO 2

provides, at best, a modest improvement over KANDO 1 at the price of a substantially more complex numerical procedure.

What is surprising is the consistency between WMTI and FBI, with the deviations being less than 10% all the way down to $FA_{\min} = 0.3$. This remarkable agreement is also demonstrated by the high correlations for WMTI shown in Figure 2, when $FA_{\min} = 0.4$. Moreover, the standard deviations for the percent differences in Table 1 are also lowest for the WMTI model. Thus the overall performance of WMTI is superior to that of both KANDO 1 and KANDO 2. Although pinning down the exact reasons for this is difficult, it may reflect the WMTI model's use of the assumption that the axons are aligned in a single direction only to justify the intra-axonal space being treated as a Gaussian compartment (16). In contrast, for both KANDO 1 and KANDO 2, the cost functions depend intricately on the assumed details of the axon orientations. It may also be that the more complicated numerical procedures required for KANDO 1 and KANDO 2 increases their sensitivity to signal noise, which would explain their larger standard deviations in Table 1 and in Figure 3.

As can be appreciated from Figure 4, the discrepancies in ζ for the three kurtosis-based models are driven primarily by differences in the intra-axonal diffusivity, D_a , rather than differences in the axonal water fraction, f . The calculations of the axonal water fraction are very similar for all three models, which accordingly leads to very similar predictions for this parameter. In contrast, the intra-axonal diffusivity is substantially higher for the WMTI model. A possible explanation for this is that WMTI is better at accommodating the effects of nonaligned axonal fibers, while the KANDO models tend to underestimate D_a when the fanning or bending of fibers is important.

The broad agreement of all three tissue models with FBI for the larger FA values can be considered as positive evidence for these models being essentially well-founded. Nevertheless, consistency for the ζ values does not guarantee that the other model parameters, such as f and D_a considered separately, are accurately predicted. The difficulties associated with estimating f and D_a from dMRI data have been thoroughly examined by Jelescu and coworkers (12). They give an example of a plausible tissue model for brain in which the accurate estimation of f and D_a is extremely difficult due to a broad minimum in the cost function, a hallmark of an ill-conditioned inverse problem. Numerical evidence suggests that the WMTI and KANDO models are relatively better conditioned, presumably due to their imposing stronger assumptions (28). It should also be noted that the axonal water fraction as estimated with WMTI has recently been shown, in the corpus callosum of mice, to correlate significantly with values obtained from electron microscopy, providing an important validation of this quantity (24).

Interestingly, some alternative methods of determining the intra-axonal diffusivity D_a lead to values substantially higher than those obtained with our three kurtosis-based models (Fig. 4). Dhital and coworkers (29) apply an isotropic diffusion encoding sequence to infer a value of $D_a = 2.6 \pm 0.8 \mu\text{m}^2/\text{ms}$, while Veraart and coworkers (32) utilize methods closely related to FBI to estimate that D_a is in the range of 1.9 to 2.2 $\mu\text{m}^2/\text{ms}$. Measurements in giant squid axon at 20 °C yield $D_a = 1.61 \pm 0.06 \mu\text{m}^2/\text{ms}$ (40). This corresponds approximately to 2.4

$\mu\text{m}^2/\text{ms}$ if extrapolated to 37 °C, although it should be noted that the subcellular structure of giant squid axons differs significantly from that of typical sized axons (41).

Roughly speaking, these alternative D_a estimates are about twice what we find with WMTI. Since WMTI gives fairly accurate values for ζ , such higher D_a values would also imply that WMTI underestimates the axonal water fraction f by a factor of about $\sqrt{2}$, as follows from Eq. [1]. There are at least two reasons why WMTI might lead to systematically low values for D_a and f . First, it neglects the intrinsic diffusional non-Gaussianities of both the intra-axonal and extra-axonal spaces. Second, WMTI is based on the selection of one of two possible solutions to a quadratic equation. Although there is empirical support for this selection (16), the alternative solution would indeed be consistent with a larger D_a (16,29). This alternative solution is closely related to the degeneracy discussed by Jelescu and coworkers (12).

As we have seen, employing FBI as a benchmark suggests that the WMTI model is applicable to white matter over a broader range of FA values than either of the KANDO models, at least with regard to estimating the parameter ζ . This is encouraging given that WMTI has already been applied as a tool to help interpret dMRI data for several prior studies (17–27). However, alternative KANDO models may be possible that match or exceed the performance of WMTI. The two models considered here were, in fact, originally proposed primarily to illustrate the KANDO method rather than as recommended tissue models for practical applications (28).

A limitation of this study is our premise that the FBI value for ζ provides a meaningful reference with which to evaluate the three kurtosis-based tissue models. Since FBI is itself relies on several assumptions, such as idealizing the axons as thin cylindrical tubes, its predictions are not beyond question (30). However, recent work confirming the expected dependence on b-value the direction-averaged dMRI signal provides strong support for the FBI approach (31,32). A second limitation is that our dMRI sequence used a relatively long TE of 149 ms. Therefore, our results could potentially be affected by differences in T2 between the intra-axonal and extra-axonal spaces.

We agree with the overall tenor of the article by Jelescu and coworkers (12) that considerable care and caution ought to be exercised when interpreting microstructural parameters estimated with dMRI tissue models. This study is intended as a contribution toward improving our understanding of three recently proposed models. While providing significant support for their validity, our results are by no means definitive and future investigations on this topic would be of value. This work also demonstrates the potential utility of FBI more generally, as a tool for testing tissue models which may find application elsewhere.

CONCLUSION

In white matter voxels with FA exceeding 0.5, all three kurtosis-based tissue models considered here yield estimates for $\zeta \equiv f / \sqrt{D_a}$ that agree with the FBI values to within about 10%. This provides evidence supporting the accuracy of these models when the axonal

fibers are largely unidirectional. However, when voxels down to an FA threshold of 0.3 are considered, the predictions from the WMTI model deviate considerably less from the FBI estimates than do those for the other two models, indicating that WMTI has a broader range of applicability. The better agreement found for WMTI is primarily due to its yielding larger values for the intra-axonal diffusivity.

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Abbreviations used

DKI	diffusional kurtosis imaging
dMRI	diffusion MRI
dODF	diffusion orientation distribution function
FA	fractional anisotropy
FBI	fiber ball imaging
fODF	fiber orientation density function
HARDI	high angular resolution diffusion imaging
KANDO	kurtosis analysis of neural diffusion organization
WMTI	white matter tract integrity

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FIG. 1.

Comparison of the microstructural parameter ζ , as estimated with FBI and the three kurtosis-based tissue models, for a single axial slice from each subject. Voxels with $FA \geq 0.4$ are shown in color and represent the ζ values, with the scale bar labeled in units of $ms^{1/2}/\mu m$. The colored voxels are overlaid on the corresponding T2-weighted maps obtained with $b = 0$. A remarkable similarity between the FBI and WMTI maps may be appreciated.

FIG. 2.

Correlations between the ζ values obtained with the three kurtosis-based models relative to the FBI values. Each data point indicates an individual imaging voxel, and all brain tissue voxels with $FA_{min} = 0.4$ are included. The symbols ζ_{FB} , ζ_{WMTI} , ζ_{K1} , and ζ_{K2} denote the ζ values for FBI, WMTI, KANDO 1, and KANDO 2, respectively. The lines are best fits through origin so that deviations of the slopes from unity reflect the biases of the kurtosis-based models. The WMTI model (first column) has a higher correlation coefficient (r) and a smaller bias than the two KANDO models (second and third columns).

FIG. 3.

The mean ζ values as obtained from FBI and the three kurtosis-based models for ROIs with $\text{FA}_{\min} = 0.3, 0.4, 0.5$, and 0.6 (first row), and the mean voxel-wise differences, $\Delta\zeta$, of the ζ values for the kurtosis-based models relative to the FBI ζ value (second row). The error bars indicate standard deviations. Note that $\Delta\zeta$ is substantially smaller for the WMTI model when $\text{FA}_{\min} = 0.3, 0.4$, and 0.5 .

FIG. 4.

The mean axonal water fraction, f , (first row) and the mean intra-axonal diffusivity, D_a , (second row) for the three kurtosis-based models with $\text{FA}_{\min} = 0.3, 0.4, 0.5$, and 0.6 . All three models give similar values for f , but WMTI gives a larger value for D_a . Error bars indicate standard deviations.

TABLE 1

F_{Amin}	Subject 1				Subject 2			
	WMTI	KANDO 1	KANDO 2	WMTI	KANDO 1	KANDO 2	WMTI	KANDO 2
0.3	9.5±11.7%	29.1±20.5%	23.4±23.2%	8.0±10.7%	25.6±17.0%	20.5±18.8%		
0.4	3.8±8.9%	18.8±15.9%	15.1±17.5%	2.1±8.5%	15.9±13.2%	12.6±15.0%		
0.5	-0.6±7.5%	10.4±14.1%	8.7±14.8%	-2.9±7.7%	7.1±11.9%	5.3±12.4%		
0.6	-4.9±6.6%	2.6±11.3%	2.0±13.3%	-7.1±6.0%	0.3±9.8%	-0.7±9.8%		

Mean percent differences of ζ for the kurtosis-based models relative to the FBI value. The uncertainties reflect standard deviations.