Modeling of Brain Microstructure by Kurtosis Analysis of Neural Diffusion Organization (KANDO)

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PURPOSE: Diffusional kurtosis imaging (DKI) provides estimates for both the diffusion and kurtosis tensors, which constitute a total of 21 independent diffusion parameters.[1] However, these parameters describe the physics of the diffusion dynamics and have no explicit connection to tissue properties. To better understand their biological significance, the parameters can be combined with tissue models that relate them to microstructure. For white matter (WM) with unidirectional axonal fiber bundles, one such model has been previously proposed.[2] Here we present a general modeling framework for DKI, which we call kurtosis analysis of neural diffusion organization (KANDO), that supports a variety of models, including ones that describe WM with crossing fibers and gray matter (GM). In addition to helping to elucidate the biological meaning of diffusion measures obtained with DKI, KANDO also provides specific metrics that may serve as candidate imaging biomarkers.

METHODS: We consider tissue models consisting of $N+1$ multiple Gaussian compartments. The diffusion dynamics of the nth compartment is then characterized by its diffusion tensor $\boldsymbol{D}^{(n)}$ and its water fraction f_n. The components of the model's kurtosis tensor, $\boldsymbol{W}^{\mathbf{mod}}$, are given by $W_{ijkl}^{\mathrm{mod}} = -\left(D_{ij}D_{kl} + D_{ik}D_{jl} + D_{il}D_{jk}\right)/\bar{D}^2 + \sum_{n=0}^{N} f_n\left[D_{ij}^{(n)}D_{kl}^{(n)} + D_{ik}^{(n)}D_{jl}^{(n)} + D_{il}^{(n)}D_{jk}^{(n)}\right]/\bar{D}^2$. Here $D_{ij}^{(n)}$ represents the components of $\boldsymbol{D}^{(n)}$, D_{ij} represents the components of the system's total diffusion tensor $\boldsymbol{D}$ as estimated with DKI, and $\bar{D}$ is the mean diffusivity of the total system. The $n=0$ or "slack" compartment is formally eliminated from the modeling by using the equations $f_0 = 1 - \sum_{n=1}^{N} f_n$ and $\boldsymbol{D}^{(0)} = \left[\boldsymbol{D} - \sum_{n=1}^{N} f_n \boldsymbol{D}^{(n)}\right]/\left(1 - \sum_{n=1}^{N} f_n\right)$. The remaining N compartmental diffusion tensors and N water fractions are then regarded as functions of M model parameters, $a_m, m = 1,2,\ldots,M$. The form of these functions reflects the biophysical assumptions for the specific tissue model being considered. The cost function for the model is $C \equiv \sum_{i,j,k,l=1}^{3}\left[W_{ijkl}^{mod}(a_m) - W_{ijkl}\right]^2$, where W_{ijkl} represents the components of the measured kurtosis tensor $\boldsymbol{W}$ for the total system. The model parameters a_m are found by minimizing C, subject to constraints to ensure that the compartmental diffusion tensors are consistent with the model assumptions (e.g., that they should be semi-positive definite). C is a rotational invariant that corresponds to the square of the Frobenius norm of the difference between the model and measured kurtosis tensors. Note that both the total diffusion and kurtosis tensors are regarded as fixed inputs for KANDO, as they can be independently determined with DKI. Except for the information contained in these two tensors, KANDO is effectively decoupled from the DKI post-processing of the MRI signal.

In order to illustrate KANDO, we consider three specific models. Model I applies to WM with axons aligned in a single direction, Model II applies to white matter with intersecting axons (i.e., fiber crossings), and Model III applies to GM. Model I has two compartments ($N=1$) corresponding to the intra-axonal and extra-axonal spaces. The extra-axonal space is taken as the slack compartment, and the intrinsic intra-axonal diffusivity, D^*, divided by $\bar{D}$ is the single model parameter ($M=1$) found by minimizing C. The axonal water fraction is determined from the measured kurtosis tensor as described in Ref. 2. Using a thin cylinder approximation for axons, the diffusion tensor for intra-axonal space is set so that $D_{ij}^{(1)}(a_m) = \bar{D}a_1 e_i e_j$, where $\mathbf{e}$ is the principal eigenvector of the total diffusion tensor. Model II has three compartments ($N=2$) representing two intersecting fiber bundles and the extra-axonal space, which is again chosen as the slack compartment. There are two free parameters corresponding to $D^*/\bar{D}$, which is the same for both fiber bundles, and the axonal water fraction for the first fiber bundle. The axonal water fraction for the second fiber bundle is inferred from the first by using the measured kurtosis tensor. The diffusion tensors for the two fiber bundles are $D_{ij}^{(1)}(a_m) = \bar{D}a_1 v_i^{(1)} v_j^{(1)}$ and $D_{ij}^{(2)}(a_m) = \bar{D}a_1 v_i^{(2)} v_j^{(2)}$, where $\boldsymbol{v}^{(1)}$and $\boldsymbol{v}^{(2)}$are the fiber directions estimated from the two largest, distinct maxima of the kurtosis diffusion orientation distribution function calculated with a radial weighting factor of four.[3] Model III has a single model parameter equal to the neurite water fraction in GM. The intra-neurite diffusivity (also indicated by D^*) is fixed *a priori* to the value $D^* = 1.0$ μm^2/ms, which is a typical value for neurites.[2] The neurites are isotropically oriented and formally constitute an infinity of individual compartments, while the slack compartment represents the extra-neurite space. Once again invoking the thin cylinder approximation, the neurite diffusion tensor components for a direction with spherical angles (θ,φ) are $D_{ij}^{(\theta,\varphi)}(a_m) = D^* u_i(\theta,\varphi)u_j(\theta,\varphi)$, with $u_i(\theta,\varphi)$ being a component of the direction vector $\boldsymbol{u}(\theta,\varphi) = \hat{\boldsymbol{x}}\sin(\theta)\cos(\varphi) + \hat{\boldsymbol{y}}\sin(\theta)\sin(\varphi) + \hat{\boldsymbol{z}}\cos(\theta)$. For all three models, the cost function was minimized by an exhaustive search strategy to help ensure that a global optimum was found.

These models were applied to DKI data for two healthy volunteers. The data were acquired on a 3T Siemens TIM Trio MRI scanner with a 32-channel transmit/receive head coil. The diffusion sequence used 64 gradient encoding directions, 3 b-values (0, 1000, and 2000 s/mm^2), voxel size = 2.7×2.7×2.7 mm^3, TE = 102 ms, FOV = 222×222 mm^2, and 40 slices for a total acquisition time of 14 min. DKI data was post-processed using Diffusional Kurtosis Estimator[4,5] to yield the total diffusion and kurtosis tensors, as well as associated metrics such as the mean diffusivity, fractional anisotropy, and mean kurtosis. Based on these diffusion metrics, the brain tissue was segmented into three multi-slice regions of interest (ROIs). ROI I was chosen to be mainly WM with aligned axonal fiber bundles, ROI II was chosen to be mainly WM with both aligned and intersecting fiber bundles, and ROI III was chosen to be mainly GM. ROI I was a subset of ROI II. ROIs I, II, and III were utilized for the analysis of Models I, II, and III, respectively. Model II can be applied to voxels with either crossing or aligned fibers, as aligned fibers correspond to a special case of crossing fibers in which one of the axonal water fractions vanishes.

RESULTS: Figure 1 shows maps for one slice of the total neurite (i.e., all axons and dendrites) water fraction f, D^*, and the extra-neurite diffusivity MD$_e$, as obtained with KANDO. For ROI I, average parameter values (±SD) for both subjects were f = 0.52 ± 0.08, D^* = 1.02 ± 0.28 μm^2/ms, and MDe = 1.53 ± 0.21 μm^2/ms, which are comparable to the results of Ref. 2. For ROI II, average parameter values were f = 0.41 ± 0.07, D^* = 0.64 ± 0.30 μm^2/ms, and MDe = 1.36 ± 0.15 μm^2/ms, while for ROI III, average parameter values were f = 0.30 ± 0.07 and MD$_e$ = 1.09 ± 0.32 μm^2/ms (note that D^* is fixed a priori for Model III).

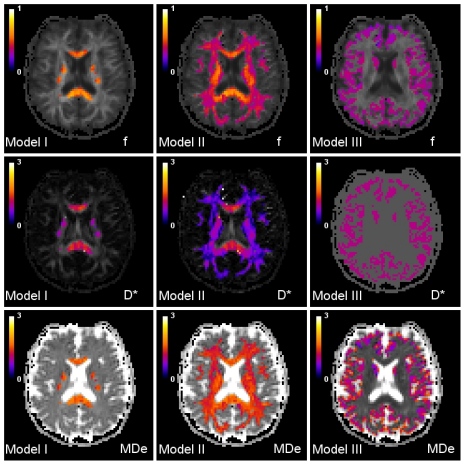

Figure 1. KANDO maps for a single axial slice for Models I, II, and III. The first row shows the total neurite water fraction, the second row shows the intra-neurite diffusivity, and the third row shows the extra-neurite mean diffusivity. Voxels displayed in color indicate the ROIs considered for the respective models. The calibration bars for the diffusivities are in units of μm^2/ms, while the water fractions are dimensionless.

DISCUSSION & CONCLUSION: We have demonstrated KANDO, a new general framework for combining DKI data with models of brain tissue microstructure, which can be applied to help give a clearer biological interpretation of DKI metrics. KANDO supports a variety of models, such as the three simple examples considered here. The validation of such models will be the subject of future investigations.

REFERENCES: 1) Jensen & Helpern. NMR Biomed. 2010;23:698-710. 2) Fieremans et al. Neuroimage. 2011;58:177-88. 3) Jensen et al. NMR Biomed. 2014;27:202-11. 4) Tabesh et al. Magn Reson Med. 2011;65:823-36. 5) Tabesh A. 2012. Diffusional Kurtosis Estimator (nitrc.org/projects/dke).