A novel biophysical model that characterizes the distribution of anisotropic micro-structural environments with DWI (DIAMOND)

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PURPOSE. To develop a novel biophysical model to characterize the distribution of three-dimensional (3D) microstructural environments in each voxel with diffusion-weighted imaging (DWI). This enables characterization of isotropic diffusion and of *each* fascicle in *each* voxel.

MATERIAL AND METHOD. We propose a novel biophysical model of the diffusion signal. Inspired by the ADC approach of Yablonskiy [1], we consider measurements of the signal arising from a large number of individual homogeneous spin packets within a voxel. In contrast to the 1D model of [1], we consider that each spin packet undergoes 3-D Gaussian diffusion described by a diffusion tensor $\mathbf{D}$. This enables characterization of the 3-D geometry of diffusion barriers to diffusion for each spin packet. We consider in each voxel the presence of various large scale microstructural environments (LSME) such as environments with freely diffusing, hindered or restricted water molecules. These give rise to N_p heterogeneous populations of 3D spin packets in the voxel. Each population is described by the estimation of a peak-shaped distribution of 3D spin packets, enabling the characterization of the underlying microstructure: the distribution expectation describes the average diffusivity of the population while the concentration of the peak described its heterogeneity. Specifically, a distribution with a broad peak indicates a highly heterogeneous population of spin packets. The signal is modeled as the continuous sum of the contribution of all the 3D Gaussian spin packets (see left-side of (1)). We parameterize each distribution of spin packet by a matrix-variate Gamma distribution $P_{\kappa_j,\mathbf{\Sigma}_j}(\mathbf{D})$ [shape parameter: κ_j; scale parameter: $\mathbf{\Sigma}_j$; expectation $\mathbf{D}_0^j = \kappa_j \mathbf{\Sigma}_j$]. With this choice, the mathematical integration over the space of symmetric positive definite matrices (SPD) has an analytical solution[2], leading to:

$$S_k = S_0 \sum_{j=0}^{N_p} f_j \int_{\mathbf{D}\in\mathcal{S}_3^+} P_{\kappa_j,\mathbf{\Sigma}_j}(\mathbf{D}) \exp\left(-b_k \mathbf{g}_k^T \mathbf{D} \mathbf{g}_k\right) d\mathbf{D} \quad = \quad S_0 \sum_{j=0}^{N_p} f_j \left(1 + \frac{b_k \mathbf{g}_k^T \mathbf{D}_0^j \mathbf{g}_k}{\kappa_j}\right)^{-\kappa_j} = S_0 \sum_{j=0}^{N_p} \mathcal{D}(\mathbf{D}_0^j, \kappa_j, f_j) \quad (1)$$

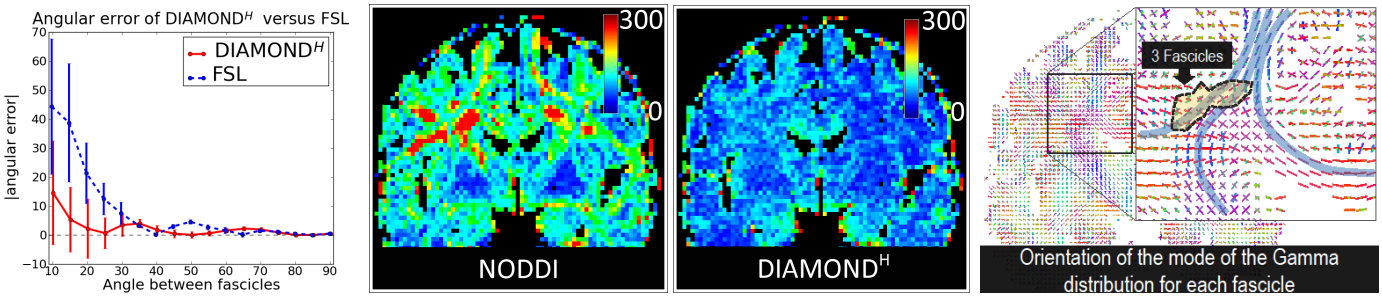
$\mathcal{S}_3^+$: set of 3×3 SPD matrices; $f_j \in [0,1]$: fractions of occupancy; b_k: b-value k; g_k: gradient k; S0: non-DW signal ; $\mathcal{D}(\mathbf{D}_0^j, \kappa_j, f_j) = f_j \left(1 + \frac{b_k \mathbf{g}_k^T \mathbf{D}_0^j \mathbf{g}_k}{\kappa_j}\right)^{-\kappa_j}$

Equation (1) provides the general expression of the diffusion signal arising from heterogeneous populations of 3-D spin-packets in each voxel. It describes the DIstribution of Anisotropic MicrOstructural eNvironments from DWI (DIAMOND). One may consider introducing a prior information that depicts our knowledge of the presence of specific microstructural environments in voxels. Particularly, for *each* fascicle, water molecules restricted to the intra-axonal space and the surrounded hindered water molecules can *each* be represented by a distribution with anisotropic cylindrical modes and identical eigen-vectors. The free water diffusion can be modeled with a distribution with isotropic mode. This leads to the following DIAMOND^H model that accounts for hindered diffusion:

$$S_k = \mathcal{D}(\mathbf{D}_0^{\mathrm{iso,u}}, \kappa_{\mathrm{iso,u}}, f_{\mathrm{iso,u}}) + \sum_{j=1}^{N_f} \left[\mathcal{D}(\mathbf{D}_0^{j,\mathrm{iax}}, \kappa_{j,\mathrm{iax}}, f_{j,\mathrm{iax}}) + \mathcal{D}(\mathbf{D}_0^{j,\mathrm{hin}}, \kappa_{j,\mathrm{hin}}, f_{j,\mathrm{hin}})\right] \quad (2).$$

N_f is the number of fascicles and is estimated at each voxel by minimizing the generalization error [3]. Following [4], we impose the spin packets inside and around axons to have the same parallel diffusivity ($\lambda_{\parallel}(\mathbf{D}_0^{j,\mathrm{iax}}) = \lambda_{\parallel}(\mathbf{D}_0^{j,\mathrm{hin}})$). The hindered radial diffusivity is determined using a simple tortuosity model [5] ($\lambda_{\perp}(\mathbf{D}_0^{j,\mathrm{hin}}) = \lambda_{\perp}(\mathbf{D}_0^{j,\mathrm{iax}})(1 - f_{j,\mathrm{iax}}/(f_{j,\mathrm{iax}} + f_{j,\mathrm{hin}}))$). This corresponds to a DIAMOND^H model with a total of $9N_f+1$ free parameters. The numerical optimization was achieved with BOBYQA with a least-square criteria. We simulated the signal arising from two crossing fascicles (represented by a tensor, FA=0.9, rician noise corruption=30dB) with varying angles. We compared DIAMOND^H to the ball and stick model (FSL) by assessing the angular reconstruction error. We also compared DIAMOND^H to NODDI on in-vivo data by assessment of the generalization error[6]. This was achieved by acquiring a CUSP65 acquisition (FOV=240mm, matrix-size=128x128, 68 slices, resolution=1.8x1.8x2mm3, TE=78ms, TR=10.1s, ~12min acquisition time) which provides a large number of different b-values between 1000s/mm2 and 3000s/mm2 with low TE and high SNR.

RESULTS. Fig.a shows that the angular accuracy of DIAMOND^H favorably compares to the ball-and-stick model. Fig.b and Fig.c shows that DIAMOND better predicts the diffusion signal compared to NODDI. In NODDI, a number of parameters are fixed (intra-axonal diffusion, no radial diffusivity) and only a single fascicle per voxel is modeled. In contrast, Fig.b/c show that estimation of populations of 3-D spin packets in each voxel better captures the underlying biophysical phenomena. Fig.d reports the orientation of the mode of the gamma distributions for each fascicle and shows that that it matches the known anatomy, capturing three fascicles in the corona radiata.



a **b** **c** **d**

CONCLUSION. We proposed a novel biophysical model of the diffusion signal that characterizes the distribution of microstructural environments in each voxel. DIAMOND^H enables characterization of isotropic diffusion and of the hindered and restricted diffusion arising from each fascicle in each voxel. It better predicts the diffusion signal compared to NODDI and has a low angular reconstruction error. DIAMOND^H may lead to novel biomarkers and novel investigations of the white-matter microstructure, in both normal development and in disease and injury.

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