Application of Diffusional Kurtosis to Modeling of the Cerebral Microenvironment

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Purpose: The biophysical interpretation of bulk diffusion MRI (dMRI) metrics remains challenging due to the complexity of neural tissue. One approach is to exploit the links between cytoarchitecture and the non-Gaussianity of water diffusion, which may be estimated with diffusional kurtosis imaging (DKI)[1]. In this work, a previously proposed method[2] is generalized so that specific microstructural properties of the entire brain parenchyma may be obtained with DKI. This method is termed cerebral microenvironment modeling (CMM).

Methods: Theory CMM idealizes neural tissue as consisting of two non-exchanging compartments, a non-Gaussian confined- (CC) and Gaussian open- (OC) compartment. The CC represents water confined within neurites that are idealized as infinitely long, narrow cylinders. The OC represents all other water that yields a detectable signal and is fully characterized by its diffusion tensor, $\mathbf{D}^{OC}$. The non-Gaussianity of the CC stems from a probability distribution of neurite orientations, denoted by $F(\mathbf{n})$ for neurite aligned along a direction $\mathbf{n}$. The diffusion tensor (DT) for CC is $\mathbf{D}^{CC} = \int \mathrm{d}\Omega_{\mathbf{n}} F(\mathbf{n})\mathbf{D}^*(\mathbf{n})$, where $\mathbf{D}^*(\mathbf{n}) \equiv \mathbf{R}_x(\mathbf{n}) \cdot \mathbf{\Lambda}^* \cdot \mathbf{R}_x^T(\mathbf{n})$ is the subcomponent DT of a neurite, $\mathbf{R}_x(\mathbf{n})$ is a rotation matrix, and $\mathbf{\Lambda}^*$ is defined as $\Lambda_{11}^* = \lambda_{||}^*$ (intrinsic neurite diffusivity) and zero otherwise. The DT for the full system (OC+CC) is $\mathbf{D} = f\mathbf{D}^{CC} + (1-f)\mathbf{D}^{OC}$, where f is the CC water proton fraction, and its associated directional diffusivity in direction $\mathbf{m}$ is $D(\mathbf{m}) = \mathbf{m} \cdot \mathbf{D} \cdot \mathbf{m}$. The kurtosis for CC is approximated by a directionally averaged value that should satisfy the explicit formula: $K_{CC} = [12(\lambda_1^{CC}\lambda_2^{CC} + \lambda_1^{CC}\lambda_3^{CC} + \lambda_2^{CC}\lambda_3^{CC})] / \left[D_{CC}{}^2 + 2\sum_{i=1}^3 \left(\lambda_i^{CC}\right)^2\right]$ (1), with λ_i^{CC} being the eigenvalues of $\mathbf{D}^{CC}$ and $D_{CC} = \mathrm{Tr}(\mathbf{D}^{CC})$. Notice that $K_{CC} = 2.4$ for isotropic distribution of neurites, and $K_{CC} = 0$ for perfectly aligned neurites. Using $D(\mathbf{m})$ and the corresponding directional $K(\mathbf{m})$ to solve for $D^{CC}(\mathbf{m})$ yields

$$D^{CC}(\mathbf{m}) = \frac{D(\mathbf{m})}{1+(1-f)K_{CC}/3}\left[1 - \sqrt{\frac{1-f}{3f}}\sqrt{K(\mathbf{m}) - fK_{CC} + \frac{(1-f)K(\mathbf{m})K_{CC}}{3}}\right]. \quad (2)$$

Algorithm $D^{CC}(\mathbf{m})$ can then be calculated from $D(\mathbf{m})$, $K(\mathbf{m})$, K_{CC} and f. Since $D(\mathbf{m})$ and $K(\mathbf{m})$ can be measured with DKI[3], a set of viable solution candidates that depend on f and K_{CC} can then be generated. These must satisfy the bounds $K_{\max}/(3+K_{\max}) \leq f \leq 1$ and $0 \leq K_{CC} \leq 2.4$, respectively, where $K_{\max}$ is the maximum of $K(\mathbf{m})$ over all possible directions. A subset of viable solution candidates can be selected that minimizes $C_1 \equiv \left|K_{CC} - [12(\lambda_1^{CC}\lambda_2^{CC} + \lambda_1^{CC}\lambda_3^{CC} + \lambda_2^{CC}\lambda_3^{CC})] / \left[D_{CC}{}^2 + 2\sum_{i=1}^3 \left(\lambda_i^{CC}\right)^2\right]\right|$ so that Eq. (1) is satisfied as well as possible. From the C_1-minimzed subset of solutions, a single best solution is chosen that minimizes $C_2 \equiv \sum_{j=1}^N \left|S_{\exp}(\mathbf{g}_j)/S_{\exp}(0) - S_{CMM}(\mathbf{g}_j)\right|/N$, where $S_{\exp}(\mathbf{g}_j)$ is the measured dMRI signal for a diffusion gradient encoding vector $\mathbf{g}_j$ and $S_{CMM}(\mathbf{g}_j) = f\exp\left[-\mathbf{g}_j^T\mathbf{D}^{CC}\mathbf{g}_j + \left(\mathbf{g}_j^T\mathbf{D}^{CC}\mathbf{g}_j\right)^2 K_{cc}/6\right] + (1-f)\exp\left[-\mathbf{g}_j^T\mathbf{D}^{OC}\mathbf{g}_j\right]$ is the predicted signal for the model.

Experiment and post-processing A healthy normal adult volunteer was scanned on a 3T Siemens TIM Trio scanner. DW images (DWIs) were acquired with 4 b-values (1000, 2000, 3000, 4000 s/mm^2) along 64 directions using TR/TE = 6300/125 ms, matrix = 82x82, resolution of 3x3x3 mm^3, BW/pixel = 1351 Hz. Diffusion and kurtosis tensors were calculated from DWIs up to a b-value of 2000 s/mm^2 using DKE[3]. CMM parameters were computed using C and MATLAB programs.

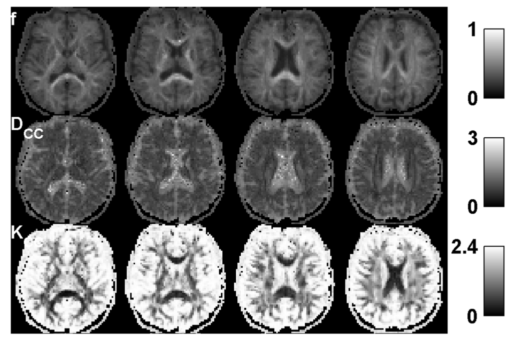

Fig. 1 Maps of CMM parameters: neurite density (f), intra-neurite diffusivity (D_{CC}) and intra-neurite diffusional kurtosis (K_{CC}).

Table 1. Measurement of CMM parameters

	f	D_{CC}	K_{CC}
WM	0.46 ± 0.11	1.03 ± 0.33	0.86 ± 0.36
GM	0.27 ± 0.11	0.97 ± 0.40	1.50 ± 0.59

Results and Discussion: Fig.1 shows the maps of f, D_{CC} and K_{CC}. White (WM) and gray (GM) matter measurements of the CMM parameters are tabulated in Table 1. Pixels with FA > 0.3 and mean kurtosis > 1.0 were considered as WM, and GM otherwise after removing CSF with MD < 2.0. In human brain, axons occupy about 44% of WM volume[4], which is similar to the neurite density of 0.46 estimated by CMM. On the other hand, 60% of GM is composed of axons and dendrites in equal proportion[5]. As dendrites are expected to have longer exchange times due to their size, the f in GM may be mainly attributable to the water confined in dendrites. **Fig.2** illustrates the fidelity of CMM prediction as compared to $S_{\exp}$ for various b-values. The slope (m) and correlation coefficient (r) of linear regression at the corresponding b-value are also shown. We note the robustness of the CMM predictions in view of the fact that its parameters were estimated from $S_{\exp}$ only up to b-value of 2000 s/mm^2. In conclusion, we have proposed a new method which allows specific microstructural properties of the entire brain to be obtained.

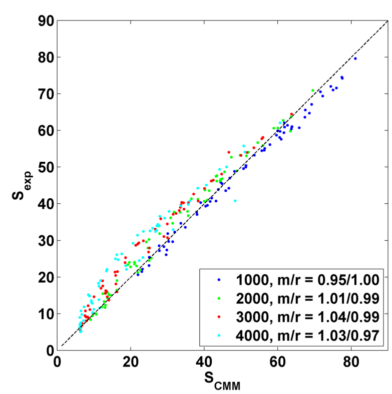

Fig. 2 CMM (S_{CMM}) prediction versus measured dMRI ($S_{\exp}$) for various b-values. m and r are the slope and correlation coefficient of linear regression, respectively at the corresponding b-value.

References 1. Jensen and Helpern. *NMR in Biomedicine.* 2010;23:698-710. **2.** Fieremans et al. *NeuroImage.* 2011;58:177-188. **3.** Tabesh et *MRM.* 2011;65:823-836. **4.** Beiu et al. In: Schmid et al, eds. Vol 20: Springer Berlin Heidelberg; 2009:231-241. **5.** Laughlin and Sejnowski. *Science.* 2003;301(5641):1870-1874.

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