Introduction. Multi-tensor models are of great interest for clinical applications because they enable the assessment of the white matter microstructure of individual fiber bundles and brain connectivity. In this work we propose a novel acquisition scheme and a novel optimization algorithm for estimating the parameters of a multi-compartment model with two tensors and free water diffusion. In conjunction with our acquisition scheme, which requires only short duration scans that are compatible with routine clinical use, our optimization algorithm ensures we estimate positive definite tensors, and incorporates a novel spatial regularization, thus enabling the characterization of complex white matter microstructure. Our acquisition scheme combines spherical and cubic sampling. It incorporates multiple non-zero b-values, necessary to fully estimate two-tensor models [1]. It enables high b-values to be acquired with low TE, while achieving the same TE as a single-shell HARDI scheme, thus providing identical geometrical and intensity distortion for each DWI image. We evaluate our CUSP-MFM (CUbe+SPhere Multi-Fiber Model) on both synthetic and clinical data. We demonstrate the ability of CUSP-MFM to characterize complex fiber structures from short duration acquisitions.

Material and methods.

Novel optimization for multi-fiber model (MFM). We consider in each voxel two anisotropic compartments representing two fiber bundles and one isotropic compartment modeling the diffusion of free water. We ensure the positive definite property of each tensor by parameterizing them in the log-Euclidean framework. We simultaneously estimate and regularize the multi-compartment model via a variational formulation, by minimizing:

$$\left(\hat{\mathbf{L}}, \hat{\mathbf{f}}\right) = \arg\min_{\mathbf{L},\mathbf{f}} \int_{\mathbf{x}\in\Omega} \sum_{k=1}^{N_g} \left[S_0\big(f_0(\mathbf{x})e^{-b_k D_{iso}} + f_1(\mathbf{x})e^{-b_k \mathbf{g}_k^T e^{\mathbf{L}_1(\mathbf{x})}\mathbf{g}_k} + f_2(\mathbf{x})e^{-b_k \mathbf{g}_k^T e^{\mathbf{L}_2(\mathbf{x})}\mathbf{g}_k}\big) - \mathbf{y}_k(\mathbf{x})\right]^2 + \alpha \sum_{j=1}^{2} \phi\Big(\Big[\sum_{m=1}^{3} ||\partial_{j,m}\mathbf{L}(\mathbf{x})||_{LE}^2\Big]^{\frac{1}{2}}\Big)\, d\mathbf{x}$$

L_j: tensor parameterized in the log-Euclidean framework; f_j: fraction of occupancy of each compartment; Ω: image domain; N_g: number of gradient directions; S_0: signal with no diffusion applied; D_{iso}: diffusivity of free water; g_k: gradient direction k; b_k: b-value for the gradient k,; y_k: measured signal for the gradient direction k; α: regularization weight (α=2); Φ: functional accounting for anisotropic regularization.

The partial derivatives $\partial_{j,m}$ are approximated with a finite difference scheme. We relate neighboring tensors which are part of the same fiber bundle by considering $\vartheta_{j,m}\mathbf{L}(\mathbf{x}) \approx \Big(\arg\min_{L_q}||\mathbf{L}_q(\mathbf{x}+\mathbf{x}_m) - \mathbf{L}_j(\mathbf{x})||_{LE} - 2\mathbf{L}_j(\mathbf{x}) + \arg\min_{L_q}||\mathbf{L}_q(\mathbf{x}-\mathbf{x}_m) - \mathbf{L}_j(\mathbf{x})||_{LE}\Big)/(2||\mathbf{x}_m||)$. The minimization is performed using the BOBYQA algorithm, a recent iterative derivative-free bound-constrained optimization technique. It converges quickly and allows the introduction of bound constraints for the fractions. Experimentally, we found it to be less sensitive to local minima than a conjugate gradient descent scheme.

Novel acquisition scheme: CUSP. As analytically demonstrated in [1] two-tensor models require multiple non-zero b-values for their full estimation. Multi-shell HARDI acquisitions have been employed but impose the minimum TE achievable for the largest b-value. It increases the TE leading to a longer imaging time, increased intensity and geometric distortion and a suboptimal signal-to-noise ratio for the lower b-value measurements. We propose instead to combine a single-shell HARDI with the hexa- and tetrahedral gradients lying on the enclosed cube [2]. Because the diffusion sensitivity is dependent on the square of the gradient norm, the six √2-norm hexahedral gradients double the nominal b-value. The four tetrahedral gradients are √3-norm gradients and triple the nominal b-value. The strength of this technique is to integrate *multiple* b-values *higher than the nominal b-value* while utilizing the same minimum TE as a single-shell HARDI. Our CUSP (cube+sphere) acquisition scheme consequently enables 1) to fully estimate two-tensor models and 2) to introduce high b-values which are known to better characterize multi-compartment models. The TE is not increased, leading to identical geometric and intensity artifacts as a single-shell HARDI.

Results. We focused on short duration acquisitions which are of great practical interest for clinical applications. We considered CUSP35 (5xb=0, one shell 16direction, 1xhexaedral, 2xtetrahedral) and compared it to a both a single-shell HARDI35 (5xb=0, one shell 30d.) and a HARDI256. Fig1 shows the mean and variance of the tALED (tensor average log-Euclidean distance) and fAAD (fraction average absolute difference) quality metrics over one hundred synthetic tensors crossing with various angles in different configurations. The quality metrics demonstrate that employing a large number of directions does not dramatically improve the results, whereas introducing multiple non-zero b-values does (CUSP35 has best performance). Fig2 shows that CUSP35-MFM provides 1) a better tensor uniformity and better crossing fibers (area 1) and 2) a better alignment of the two tensors in the single fiber region of the corpus callosum (area 2). Fig3 shows the benefits of employing a multi-fiber model rather than a one-tensor (1T) model (HARDI35-1T) for tractography. It also demonstrates better tractography results when using CUSP35-MFM instead of HARDI35-MFM. CUSP35-MFM leads to 1) a smaller amount of fibers outside of the CC and 2) a higher density of fibers in the frontal and occipital parts.
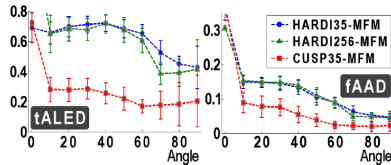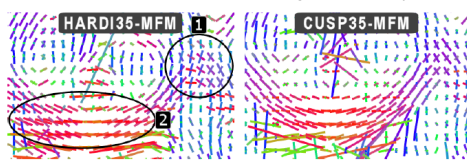

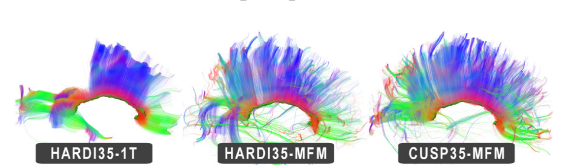**Fig1. Synthetic data evaluation**   **Fig2. Clinical data** (Siemens 3T Trio, 1.8x1.8x2.4mm³)   **Fig3. Corpus Callosum mono-/multi-fiber tractography**

Conclusion. We have proposed a novel optimization algorithm for a multi-fiber model (MFM) which utilizes both a novel multi-tensor fitting procedure and a novel acquisition scheme (CUSP). Our fitting procedure ensures spatially smooth and consistent positive definite tensors. CUSP satisfies the need of multiple non-zero b-values without increasing the TE. It leads to comparable imaging time, geometric and intensity distortion as a single-shell HARDI scheme while it incorporates high b-values (2000s/mm², 3000s/mm²) which enable better characterization of complex fiber structure. We show the ability of CUSP-MFM to recover complex brain fiber structure from short duration acquisitions. CUSP-MFM may enable new investigations of white matter microstructure in research and in clinical practice.

References.
[1] B Scherrer and S K Warfield, "Why multiple b-values are required for multi-tensor models: evaluation with a constrained log-Euclidean model," in ISBI 2010: from nano to Macro, Rotterdam, Netherlands, 2010, pp. 1389–1392, IEEE Press.   [2] S Peled, S Whalen, F A Jolesz, and A J Golby, "High b-value apparent diffusion-weighted images from curve-ball DTI" J Magn Reson Imaging, vol. 30, no. 1, pp. 243–248, Jul 2009.