Detection of curvature and microscopic anisotropy of neurites at short length scales

Jonathan Scharff Nielsen[1], Tim B Dyrby[1], and Henrik Lundell[1]
[1]*Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark*

PURPOSE: Interpretation of fractional anisotropy is ambiguous in voxels with randomly oriented neurites as measured with conventional diffusion tensor imaging. This has recently been addressed in a number of studies using double diffusion encoding (DDE) or other novel diffusion encoding schemes [1-5]. As an additional effect, the observed anisotropy in curvilinear fibers, as undulating axons or dendrites in gray matter, decrease when the mean square displacement is approaching the fiber's radius of curvature [6,7]. The purpose of this work is to explore the feasibility for using circularly polarized oscillating gradient spin echo (CP-OGSE) [8] as a method for achieving microscopic anisotropy measurements, as done with DDE, at the short length scales probed with OGSE [9].

THEORY: A CP-OGSE gradient design can be realized as proposed earlier using two orthogonal apodized cosine modulated oscillating gradient trains [8]. To allow investigation of the transition between linear and circular polarization the gradient amplitudes were scaled to produce the following phase space trajectory **k**(t) and **B**-matrix:

$$\mathbf{k}(t) = \cos(\psi)\cos(\omega t)\hat{\mathbf{x}} + \sin(\psi)\sin(\omega t)\hat{\mathbf{y}}, \quad \mathbf{B} = \int_0^{TE} \mathbf{k}(t)'\mathbf{k}(t)dt$$

Where omega is the oscillation frequency, **x/y** are unit vectors, TE is the echo time and the parameter ψ controls the polarization, from linear encoding as in conventional OGSE for $\psi = 0°$ and $\psi = 90°$ along the x- and y-axes respectively, to circular encoding in the xy-plane for $\psi = 45°$. The diffusion weighting, i.e. the trace of the diffusion weighting **B**-matrix, is constant for all ψ. The signal attenuation from isotropic, but not anisotropic, Gaussian domains will thus be independent of polarization.

METHODS: *Monte Carlo simulation:* 50000 walkers were run for 1D random walk along infinite straight lines randomly oriented in 3D, as well as along sinusoidal segments along the same axes with amplitude and period respectively 1 µm and 4 µm. These substrates are by construction macroscopically isotropic, but microscopically anisotropic. Schematic illustration of the substrates are shown in figure 1A. Time step size was 4.2 µs and spatial step size was 0.22 µm. The length of the diffusion experiment was 40 ms. Maximum gradient strength was 0.19 T/m, but adjusted for each frequency to give a **B**-matrix with a constant trace of 500 s/mm^2. Simulation was done for 40 equidistant values of ψ between 0° and 90° with oscillation frequencies 50 and 150 Hz. *Tissue preparation:* A perfusion fixated excised brain from a 3.5 year old Vervet monkey was used for imaging in a setup optimized for ex vivo DWI experiments [10]. The animal was handled and cared for according to a protocol approved by the local ethics committee. *Ex vivo DWI*: Experiments where performed on a 4.7T Agilent MRI scanner with a quadrature RF-coil. The following imaging parameters where used; TE/TR: 58/2500 ms. voxel size: 0.25x0.25x1.0 mm^3, coronal slice orientation. Maximum gradient strength was 0.49 T/m, gradient oscillation frequency 100 Hz with 2 full oscillation periods on each side of the inversion pulse. ψ was incremented from 0° to 90° in steps of 5°. The trace of the **B**-matrix was 860 s/mm^2. The signal was averaged over one slice in gray and white matter masks defined by thresholding the b=0 image. This was done to mimic a uniform fiber orientation distribution and for enhancing SNR.

RESULTS: In Monte Carlo simulations we find a ψ -dependence in the diffusion weighted signal with higher attenuation for circular polarization (ψ *=45°*), as expected for non-anisotropic diffusion encoding schemes [1-5], see figure 1B. This modulation is decreased for undulating fibers. Signal attenuation is constant over frequency for straight fibers, but increase with frequency for undulating fibers. In the results from the DWI experiment, the effect of polarization is visible in regions with macroscopically anisotropic fiber bundles and show opposite contrasts for linear polarizations (ψ = *0°, 90°,* 1 and 3 in figure 1C) in e.g. the corpus callosum and the corticospinal tract (red and blue arrows in figure 1C), but is more flat with circular polarization (ψ = *90°*, 2 in figure 1C). The mean normalized signal attenuation calculated over whole volume gray and white matter masks showed in figure 1D show similar behavior as in simulated data.

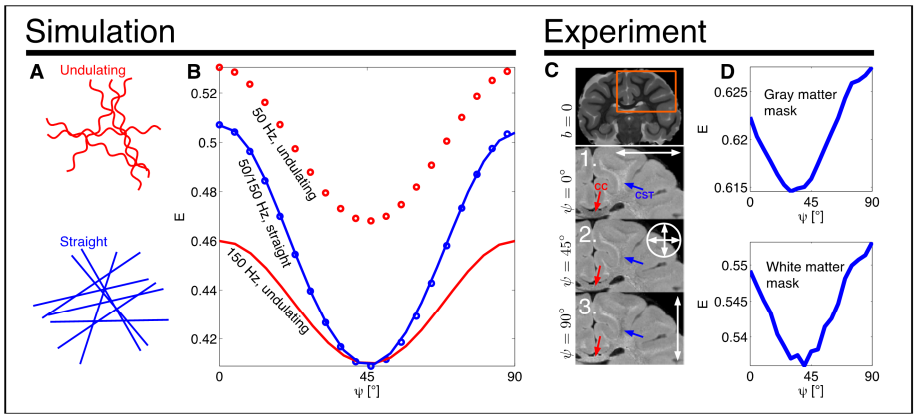

Figure 1: A) Schematic illustration of substrates for Monte Carlo simulations, constructed as uniformly oriented undulating (top, red) and straight (bottom, blue) 1D pathways. B) Simulated signals for 50 Hz (circles) and 150 Hz (solid line) for the substrate with straight (blue) and undulating (red) fibers. C) Mid-coronal slice from MRI experiment with b = 0 (top) and zoomed in versions of normalized DWI images for three different ψ at 100 Hz oscillation frequency. The polarization of the diffusion encoding is illustrated by the white arrows. The corpus callosum (CC) and the corticospinal tract (CST) are marked with red and blue arrows. D) Mean normalized signal attenuation for gray matter (top) and white matter (bottom).

DISCUSSION: We demonstrate that the polarization dependent signal modulation in OGSE can be used to detect anisotropy in randomly oriented Gaussian domains. Moreover, the frequency contains information about fiber curvature. Curvature and anisotropy could in particular be of interest for studies of dendrite structure in gray matter. We acknowledge the fact that the diffusion time dependent signal from conventional PGSE may resolve similar information regarding multiple Gaussian domains [11], but the experimental requirements may be hard to meet with limited gradient strength. Further work will be needed for evaluating the additional effects of isotropic compartments and finite fiber radii, and for formalizing the analysis for rotationally invariant acquisitions and robust quantification.

REFERENCES: 1. Komlosh et al, 2007, JMR, 189:38-45, **2.** Koch and Finsterbuch, 2008, MRM, 60:90-101, **3.** Shemesh and Cohen, 2011, MRM, 65:1216-1227, **4.** Jespersen et al, 2013, NMR in Biomed, 26:1647-1662, **5.** Lasic et al, 2014, Front. Phys. 2,11, **6.** Jespersen and Buhl, 2011, JMR, 208:34-43, **7.** Nilsson et al, 2012, NMR in Biomed., 25(5):795-805, **8.** Lundell et al, 2014, MRM, in press, **9.** Gore et al, 2010, NMR in Biomed, 23:745-756 **10.** Dyrby et al, 2010, HBM, 32:544-563, **11.** Jespersen et al 2012,, NMR in Biomed, 25:813-818.