Whole-brain assessment of microscopic anisotropy using multiple pulse-field gradient (mPFG) diffusion MRI

Alexandru V Avram[1], Joelle E Sarlls[2], and Peter J Basser[1]

[1]*Section on Tissue Biophysics and Biomimetics, NICHD, National Institutes of Health, Bethesda, MD, United States,* [2]*National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, United States*

Introduction: Quantifying microstructural parameters of brain tissues, such as mean axon diameters, could provide valuable neuroanatomical and functional information. Due to its non-invasive character and its ability to image large regions of tissue *in vivo* multiple pulsed-field gradient (mPFG) diffusion MRI has been proposed as an alternative to biopsy-driven histology. Numerous studies have shown that mPFG diffusion MRI (1) can exclusively characterize water trapped in microscopic compartments revealing unique measures of average cell geometry that cannot be obtained with conventional diffusion tensor imaging (DTI) (2). Advances in diffusion encoding strategies (3) and theoretical modeling (4) have recently enabled the clinical translation of this technique (5, 6, 7) and highlighted its potential for quantifying average axon diameters in inter-hemispheric white matter fiber pathways (7). In this study we report our preliminary results of applying quadruple PFG diffusion MRI to obtain a whole-brain quantitative assessment of microscopic anisotropy, and assess the clinical feasibility of this technique.

Methods: The protocol proposed in (7) was used to acquire whole-brain quadruple PFG (qPFG) diffusion MRIs with a 2.75x2.75x2.9 mm^3 resolution and a 3D diffusion encoding scheme. For both correlation times τ_m=0 and τ_m=13.4 ms, the diffusion wave vectors $\mathbf{q_1}$ and $\mathbf{q_2}$ were applied in 9 planes with 4 different angles ψ = 0°, 90°, 180° and 270° relative to each other, using a diffusion gradient pulse width δ=12 ms and maximum gradient amplitude G_{max} = 4.92 G/cm/axis. For three of the nine diffusion encoding planes, gradient pulses were combined on two axes simultaneously to increase the effective gradient amplitude. Thirty two slices were acquired with an imaging matrix size of 80x80 over a 22x22 cm^2 field-of-view (FOV), using parallel imaging with acceleration factor 2, TE/TR = 147/15000 ms and number of excitations (NEX) 2. In the same session, DTI data with the same scan prescription (and resolution) was obtained and all DTIs and qPFG MRIs were registered to an anatomical 1 mm isotropic T_2 weighted scan using TORTOISE (8). The fiber orientations $\hat{\boldsymbol{u}}$ estimated from the measured diffusion tensors were integrated in a numerical model of the qPFG diffusion signal attenuation $E_{\tau_m}(\psi)$ in white matter tissue with parallel impermeable myelinated axons (7): $E_{\tau_m}(\psi) = fE^{ax}_{\tau_m}(\psi, \hat{\boldsymbol{u}}, d, D_{ax}) + (1-f)E^{ex}_{\tau_m}(\psi, D_{ex})$, where $E^{ax}_{\tau_m}$ and $E^{ex}_{\tau_m}$ are the signal attenuations in the axonal (restricted) and extracellular (free) compartments, and d, D_{ax}, f, and D_{ex} are the average axon diameter, axonal water diffusivity, intra-axonal signal fraction and extracellular water diffusivity which were determined using a minimum-least-squared error fit.

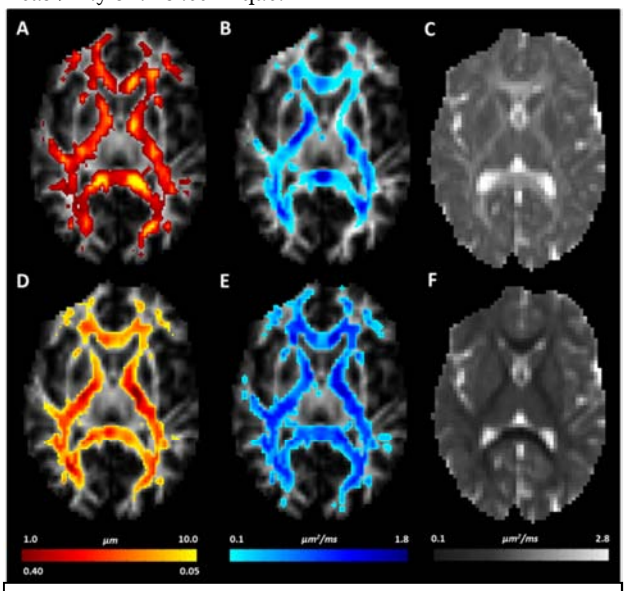

Figure 1: Microscopic anisotropy parameters estimated using qPFG diffusion MRI: average axon diameter d (**A**), intra-axonal water diffusivity D_{ax} (**B**), intra-axonal signal fraction f (**D**), and diffusivity of water in the unrestricted extra-axonal compartment D_{ex} (**E**) provide information complementary to DTI-derived metrics such as the axial (**C**) and radial diffusivity (**F**).

Results and Discussion: Microscopic anisotropy parameters estimated in the major white matter fiber pathways, i.e. with fractional anisotropy FA>0.4 converged to values within the expected physiological ranges (Fig. 1). Coronal views show a smooth variation of d along the cortico-spinal tract (Fig. 2A) while images in the sagittal plane (Fig. 2B) reveal an anterior-posterior organization of the corpus callosum consistent with previous findings (7) – small caliber fibers in the prefrontal and temporal trans-callosal fibers and larger axon diameters in pathways supporting fast integration of visual and sensory-motor functions. Large values of d calculated along the lateral splenium of the corpus callosum (Fig. 2C) correlate with small intra-axonal diffusivity D_{ax} estimates (Fig. 1B), suggesting a potential bias in the estimation, likely due to an broad fiber orientation distribution within the relatively large voxels and/or insufficient sampling of the ($\mathbf{q_1}$, $\mathbf{q_2}$) space. Maps of microscopic anisotropy parameters d, D_{ax}, f, and D_{ex} reveal information complementary to DTI-derived metrics such as axial and radial diffusivities (Fig. 1).

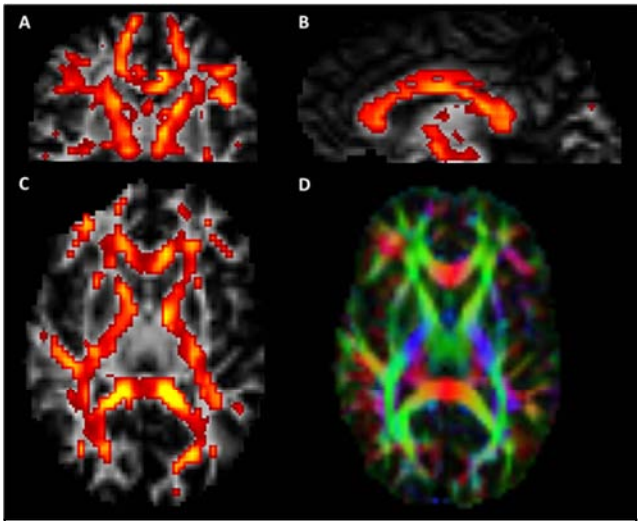

Figure 2: Tri-planar view (**A**-coronal, **B**-sagittal, **C**-axial) of the estimated average axon diameters d (overlay) and DTI-derived direction-encoded color (DEC) FA map (**D**).

Conclusion. Our preliminary results demonstrate that it is possible to acquire qPFG MRIs with whole-brain coverage, and underscore the importance of integrating additional information (i.e., an improved characterization of the fiber orientation distribution) in the model estimation. Upon further technical refinements and clinical validation, mPFG MR could have a broad clinical impact providing specific biomarkers for diagnosing neurodegenerative diseases and monitoring brain maturation, and novel metrics for structural and functional connectivity. Ultimately, mPFG MRI may provide a non-inasive whole-brain histological assessment that can prove transformative to neuropathology and neuroimaging.

References: 1. Özarslan and Basser, JMR 2007;18:285-294; 2. Komlosh et al., JMR 2007;198:38:45; 3. Finsterbusch, JMR 2009;198:174-182; 4. Özarslan and Basser, J Chem Phys 2008;128:154511; 5. Koch and Finsterbusch, MRM 2008;60:90-101; 6. Lawrenz and Finsterbusch, MRM 2012;doi:10.1002/mrm.24347; 7. Avram et al., Neuroimage 2013;64:229-239; 8. Pierpaoli et al., ISMRM 2010;#1597.