Modeling and Measuring the Myelin g-ratio

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Introduction: In myelinated axons, the ratio between the axon caliber (diameter) and the total caliber of the axon plus its myelin sheath (i.e., the fiber caliber) is relatively constant and is observed to be near the theoretically optimal value of 0.6 [1]. Recently, variations in this axon-to-fiber ratio (the "g-ratio") have been proposed to be associated with differences in brain development [2]. Here we describe a method to estimate the g-ratio in-vivo by combining diffusion imaging and bound pool fraction (BPF) mapping; BPF mapping is a quantitative magnetization transfer technique that estimates the proportion of exchanging protons bound to macromolecules such as those comprising myelin. The methods described here form a novel MR contrast mechanism that may be useful for quantifying the development of white matter and the deterioration of white matter in demyelinating diseases.

Methods: We developed a quantitative tissue model to incorporate BPF and diffusion measures of white matter brain regions with high fiber direction coherence, such as the corpus callosum. Using a numerical diffusion simulation method [3,4], we computed the predicted diffusion anisotropy for a biologically plausible range of fiber caliber distributions derived from published postmortem measurements in human corpus callosum [5]. We found a simple relationship between anisotropy and the fiber volume fraction (FVF), the fraction of a voxel occupied by neural fibers. Measurements of BPF provide an estimate of the myelin volume fraction (MVF), which is the fraction of a voxel occupied by myelin sheaths. To estimate the MVF, we used cross-relaxation imaging [6] to measure BPF, which has been shown to be linearly related to the MVF with a proportionality constant of 2.5 [7]. The MVF is related to the FVF with the following model that we derived from the simple geometry of concentric cylinders: MVF = FVF*(1-g^2). Thus, we can estimate the axon-to-fiber ratio (g) given FVF and MVF: $g = \sqrt{(1 - MVF/FVF)}$. To test our model, whole-brain DTI and BPF measurements were acquired in five healthy human volunteers (1.5T GE Signa MRI scanner, 8-channel head receive-only coil, 2 mm^3 resolution). The DTI data were used to predict the FVF according to the diffusion simulation, and the BPF data were used to predict the MVF. We then used the FVF and MVF estimates to calculate the g-ratio in five manually-defined segments of the corpus callosum.

Results: The left panel of Figure 1 shows that higher fiber counts are associated with higher fractional anisotropy (FA) for all five fiber caliber distributions. These same simulation data are plotted in the right panel, but with FA shown as a function of the FVF rather than the fiber count. The smooth quadratic curve summarizes the relationship between FVF and FA for all fiber caliber distributions combined. Figure 2 shows the mean FA (top), the mean BPF (middle) and the estimated myelin g-ratios (bottom) for each of five measured callosal segments. The g-ratios are remarkably close to the theoretically optimal value of 0.6 (light gray line). In Figure 3, we combine our estimates of FVF, MVF and the g-ratio (averaged across subjects) with the published fiber caliber distributions [7] to produce simulated tissue cross-sections for five segments of the corpus callosum.

Conclusion: The tissue model and simulations provide a one-to-one correspondence between FA and the FVF in regions of high fiber direction coherence, making it possible to infer the FVF in-vivo from diffusion measurements. The MVF can be estimated from in-vivo measurements of the BPF. By combining these estimates of FVF and MVF we can compute the g-ratio in white matter. The g-ratios that we estimate are in excellent agreement with those published in literature [1]. Paus and Toro hypothesize that individual differences in the g-ratio underlie observed variations in myelin density (measured using MTR) between girls and boys [2]. However, individual differences in the FVF would also produce variations in myelin density. As we show, integrating diffusion and myelin measures provides a method to directly measure variations in g-ratio across individuals. These methods also may prove useful in detecting subtle changes in myelin sheath thickness due to demyelinating diseases.

References: [1] Rushton, W., J Physiol, 115(1): 101-122 (1951) [2] Paus and Toro, Front Neuroanat 14(3): 1-7 (2009) [3] Szafer et al., Magn Reson Med 33(5):697-712 (1995) [4] Ford and Hackney, Magn Reson Med 37(3): 387-394 (1997) [5] Aboitiz, F. Brain Res 598: 143-153 (1992) [6] Yarnykh and Yuan, Neuroimage, 23(1): 409-424 (2004) [7] Dula et al., Magn Reson Med, 63(4): 902-909 (2010) [8] Stikov et al. Neuroimage (in press)

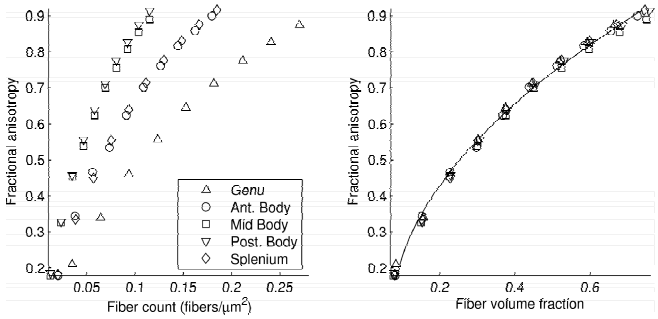

Figure 1: *Diffusion anisotropy from the diffusion simulation plotted as a function of fiber count (left) and fiber volume fraction (right) for five fiber caliber distributions corresponding to five regions of the corpus callosum.*

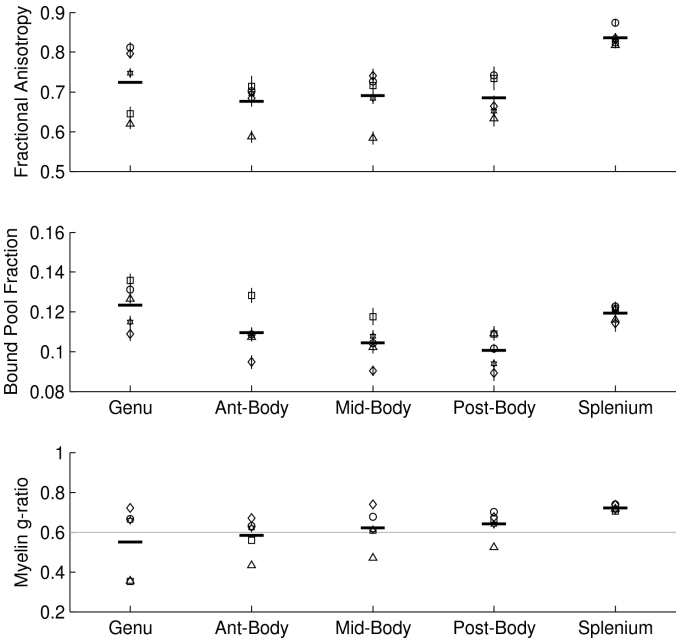

Figure 2: *Mean FA (top), mean BPF (middle) and estimated g-ratio in five regions of the corpus callosum for five subjects (represented by five different symbols). The error bars in the FA and BPF plots indicate the standard error of the mean across all the voxels in a subject's callosal segment. The thick horizontal bar indicates the group mean.*

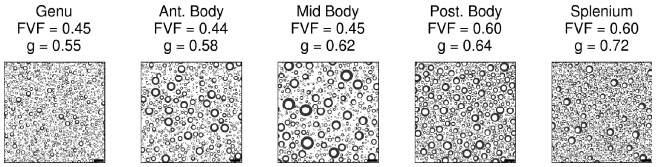

Figure 3: *Simulated tissue cross-sections of five callosal regions derived from our estimated MVF values and published caliber distributions. The scale bar indicates 10 μm.*