A Two-Compartment Model to Accurately Characterize Extra- and Intra-Cellular Spaces in Neural Tissue with Q-space Imaging

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Introduction

Q-space imaging[1] (QSI) offers potential for indirect assessment of white matter (WM) architecture by exploiting the regularity of molecular diffusion barriers from axon membranes and myelin sheaths[2,3]. The Fourier transform (FT) of the QSI signal decay is known as the displacement profile (DP), and contains axon structure information. However, the DP contains signal from both extra- and intra-cellular spaces (ECS and ICS, respectively). Accurate WM architecture assessment would require separation of both signals. In this work, we fit DPs from WM tracts in mouse spinal cords (SC) with a two-compartment model to characterize ECS and ICS. As the signal decay is a weighted sum of ECS and ICS signals, by linearity, the DP is a weighted sum of the ECS and ICS DPs. ECS and ICS diffusion is expected to be Gaussian and restricted, respectively[4]. Thus, ECS and ICS DPs would be a Gaussian and an autocorrelation of the axon geometry, respectively. QSI simulations were used to determine the exact ICS DP shape. Mean axon diameter (MAD) was estimated from the ICS DP full-width-at-half-maximum (FWHM).

Methods

Five SC sections (C6-C7) were dissected from perfusion-fixated 8-10 month-old female C57 BL/6 mice. Experiments were performed with a custom-built 50T/m z-gradient and solenoidal RF coil set (4-turn, 3*mm* i.d.) interfaced to a 9.4T spectrometer/micro-imaging system (Bruker DMX 400 with Micro2.5 gradients and BAFPA40 amplifiers). A diffusion-weighted stimulated-echo sequence was used: 64×64, SW=25kHz, TR=2s, TE/Δ/δ=17.4/10/0.4*ms*, FOV/THK=4/1*mm*, and an ambient temperature of 19 °C. The diffusion gradient was applied perpendicular to the SC long axis in 64 increments of q (q_{max}=0.82 μm^{-1}). Q-space decay curves were obtained for each pixel and averaged over ROIs (20 pixels after zero-filling image to 256×256) selected within seven WM tracts (Figure 1). The decay curves were reflected about q=0 so that the FT would produce a purely real DP (Δx=0.6μm). Fitting was done with a constrained (non-negative peak amplitudes) nonlinear minimization algorithm (Nelder-Mead) in Matlab[5]. To find the exact ICS DP shape, a 3D finite-difference algorithm previously developed[6] was used to simulate the QSI decay curve based on WM tract histologic images. DPs were simulated with signal only from the intra-axonal space (IAS, excluding myelin). The peak shape that gave the best fit was an exponential decay reflected about the origin (Figure 2a). Experimental DPs were fitted with Gaussian and exponential decay peak shapes (Figure 2b). ICF was computed by normalizing the ICS DP area by the overall fit area (ECS plus ICS). After experiments, SC sections from the MRI slice were stained with toluidine blue and optical images were obtained from all WM tracts. The images were segmented into extra- and intra-axonal, and myelin regions with a custom watershed and profile algorithm. MAD was calculated (excluding myelin) assuming a circular area and ICF was taken to be the area of both the IAS and myelin regions (see Discussion).

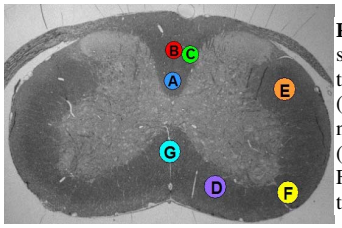

Figure 1. Optical image of SC section showing WM tract locations: A) dorsal corticospinal (dCST), B) gracilis (FG), C) cuneatus (FC), D) rubrospinal (RST), E) spinothalamic (STT), F) reticulospinal (ReST), G) vestibulospinal (VST).

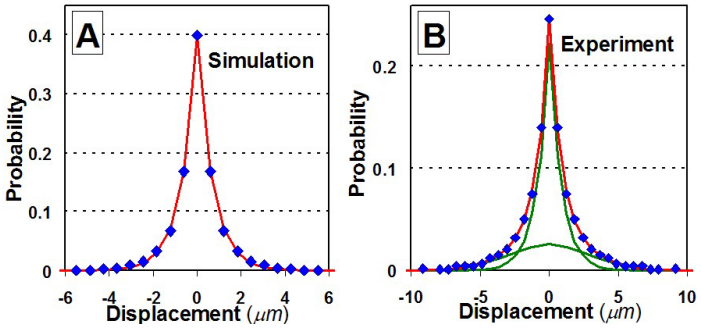

Figure 2. A) Sample simulated DP on histologic image (blue points) with exponential decay peak fit (red line). All fits had R^2>0.99. B) Sample experimental DP (blue points) with overall fit (red line) and ECS and ICS DP fits (green lines). All fits had R^2>0.99.

Results and Discussion

Figure 3 shows a plot of average WM tract MADs calculated from histology versus average experimental ICS DP FWHMs. There is excellent linearity and correlation between histology and experiment. A Bland-Altman plot between the two methods was generated (not shown) and the 95% confidence interval was from –0.07 to 0.03. Also in Figure 3 is the ICF calculated from both histology and experiments averaged over all specimens. A single ICF was calculated for each specimen by averaging the WM tract ICFs, because an ANOVA run on the histologic ICFs showed no significant differences among WM tracts. Both histologic and experimental ICFs fall within the expected range of 60-80%.

Previous work estimated MAD from the DP FWHM without separating ECS and ICS signals[7]. As expected, the measured MADs were larger than histologic MADs by about 20%, although they correlated very well with each other. The QSI results here show a virtual match with histology. Finally, the inclusion and exclusion of myelin in the calculation of ICF and MAD, respectively, necessary for correlation between histology and experiments, may arise from differences in IAS and myelin structure. The ICS DP area should include IAS and myelin water. However, as the myelin barrier spacing is <0.1μm, our DP resolution is not high enough to resolve the myelin structure and the FWHM may primarily reflect IAS.

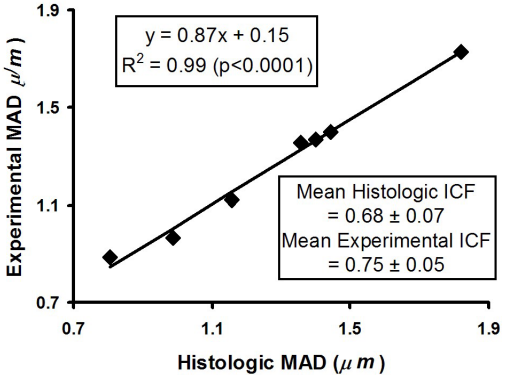

Figure 3. Plot of WM tract histologic vs experimental MADs with equation of line of best fit and mean ICF values.

Conclusion

This work demonstrates the feasibility of this two-compartment model to extract MAD and ICF information with QSI similar to values measured with histology.

References: 1. Callaghan, PT, *Principles of NMR Microscopy*, Oxford University Press (1991). 2. Assaf Y, *et al*, *MRM*, **47**:115-126 (2002). 3. Chin CL, *et al*, *MRM*, **52**:733-740 (2004). 4. Assaf Y, et al, *MRM*, **52**:965-978 (2002). 5. http://www.wam.umd.edu/~toh/spectrum/TOC.html. 6. Hwang S, *et al*, *MRM*, **50**:373-382 (2004). 7. Ong H, *et al*, Proc. ISMRM 15th Scientific Meeting, Berlin, Germany 2007, p. 1533. **Acknowledgements:** NIH grant R21 EB003951