Fast and robust measurement of microstructural dimensions using temporal diffusion spectroscopy

Hua Li[1], John C. Gore[1], and Junzhong Xu[1]
[1]*Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States*

Targeted audience: Investigators interested in characterizing tissue microstructure using diffusion MRI

Background and Purpose: Mapping axon sizes non-invasively may have significant clinical potential because nerve conduction velocity is directly dependent on axon size (1). Current approaches to measuring axon sizes using diffusion-weighted MRI, including q-space imaging with pulsed gradient spin echo (PGSE) (2-3) or double-PGSE methods (4), usually require very long scanning times and high q-values to detect small axons (diameter $d < 2$ μm), which are limited by the long diffusion times used and the significantly reduced sensitivity to small scales. The oscillating gradient spin echo (OGSE) has been shown to be able to achieve much shorter diffusion times and hence may be able to detect smaller axon sizes with high sensitivity (5). In the current study, OGSE experiments were performed to estimate the inner diameters of hollow microcapillaries with a range of sizes (~1.5-19.3 μm) that mimic axons in the human central nervous system. The accuracy of fitting cylinder diameters and intrinsic diffusion coefficients using OGSE was analyzed, and a possible fast method of mapping axon sizes non-invasively is proposed.

Methods: *Theory*: Under the Gaussian phase approximation, the apparent diffusion coefficient (ADC) perpendicular to a cylinder main axis measured by the cosine-modulated OGSE method can be expressed as

$$\mathrm{ADC}(f,D,d) = 8\pi^2 \sum_k \frac{B_k a_k^2 D^2 f^2}{\delta(a_k^2 D^2 + 4\pi^2 f^2)^2} \left\{ \frac{(a_k^2 D^2 + 4\pi^2 f^2)\delta}{2a_k D} - 1 + exp(-a_k D\delta) + exp\left(-\frac{1}{2} a_k D \cdot TE\right)(1 - cosh(a_k D\delta)) \right\} \quad [1]$$

where f is the oscillation frequency, δ is the gradient duration, TE is the echo time, and a_k, B_k are structure dependent parameters (6).

Experiments: All NMR diffusion experiments were performed on a Varian 7T scanner with a 12mm Doty micro-gradient coil. Hollow microcapillaries with nominal inner diameters of 1.5-1.6, 4.3-4.5, 9.5-9.7, 14.9-15.0, 19.0-19.3 μm (lower bound–upper bound provided by the manufacturer) and the same outer diameter around 150 μm (Polymicro Technologies, USA) were used as well-characterized diffusion phantoms. The diffusion gradients were applied perpendicular to the microcapillary main axis with a duration of 20 ms on either side of a refocusing pulse. Temporal diffusion spectra (7) were acquired at 12 oscillating frequencies ranging evenly from 50 Hz to 600 Hz. At each frequency, the ADC was calculated with b = 0 and b = 700 s/mm^2, except higher b-values from 700 to 50000 s/mm^2 were used for the smallest (1.5-1.6 μm) microcapillaries. The measured ADC spectra were fit to Eq. [1] with two unknown variables D and d. To explore the sensitivity of the ADC spectra to the cylinder diameter with a limited range of low frequencies, the ADC spectra were also fit with only a subset of frequencies (ranging from 2 to 12).

Results and Discussion: Fig. 1 shows the measured ADC spectra (markers) and fitted spectra (lines) of all five types of microcapillaries. The fitted results are summarized in Table 1. The fitted inner diameters are in good agreement with the known values, especially for the small sizes, which are usually overestimated using other methods (8). All fitted intrinsic diffusion coefficients are consistent with the measured diffusion coefficient of free water (1.82 μm^2/ms) except that of the 1.5-1.6 μm microcapillaries. This is because the applied gradient frequencies for such a small size are not high enough to probe intrinsic diffusion adequately so that the ADC spectra in this low frequency range are still dominated by boundary effects, i.e. are sensitive to distance of restriction barriers. Figure 2 shows the results of fitting with only the first N frequencies. All fitted sizes were consistent with real values regardless of the number of frequencies used. The results suggest that even two ADC values with different relatively low frequencies (50 and 100Hz in this study) may be sufficient to extract the compartment sizes as small as 1.5 μm accurately. This suggests that OGSE may serve as a fast and robust measurement method for mapping axon sizes non-invasively.

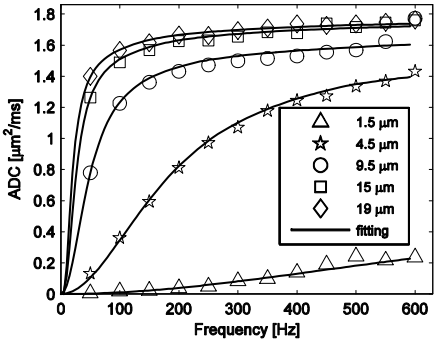

Fig. 1 The measured diffusion spectra and fitted spectra.

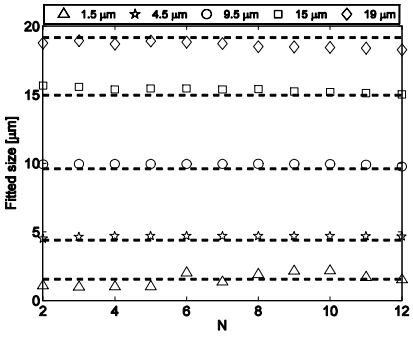

Fig. 2 The fitted sizes using the first N frequencies.

References:
(1) Ritchie Proc R Soc Lond B Biol Sci 1982.
(2) Cory MRM 1990. (3) Ong NIMG 2010.
(4) Shemesh JMR 2009. (5) Does MRM 2003.
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(8) Siow JMR 2010.

Real size [μm]	Fitted size [μm]	Fitted D [μm^2/ms]
1.5-1.6	1.51±0.17	0.80±0.61
4.3-4.5	4.67±0.08	1.80±0.04
9.5-9.7	9.76±0.87	1.79±0.06
14.9-15.0	15.01±0.88	1.85±0.02
19.0-19.3	18.28±0.87	1.85±0.01

Table. 1 Summary of the fitting results using Eq. [1].