Diffusion-Weighted Signal in White Matter: What Is behind the b-Factor Dependence?

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Diffusion-weighted MRI is believed to probe microscopic cellular structure of living tissue. This potential is used for the fibre tracking, but remains latent in other respects. The main obstacle is an extremely complex connection between the biological structures and the acquired MR signal. The quest for realistic biophysical models of diffusion-weighted water signal leads rapidly to overcomplicated description with too many unknown parameters. In this situation, model free approaches should be given more credit. Such a framework is provided by the cumulant expansion (1, 2 and references therein), which turns into a power series in the b-factor when applied to the dependence of signal, S, on b for a fixed direction of the diffusion sensitising gradient:

$$\ln S = -bD + K(bD)^2/6 + \ldots \quad [1]$$

The message of Eq.[1] is that only integer powers of b enter this expansion ruling out any singularity at b=0. A given tissue is characterised by an infinite set of coefficients the first of which is the apparent diffusion coefficient, D, the second is the apparent kurtosis excess, K, etc. In reality, the noise limits the number of experimentally detectable coefficients to a few first ones. For example, D and K can be found in the brain grey matter using the b-factors up to 2.50 ms/mm^2 (2). The aim of the present study is to find the diffusion parameters entering Eq.[1] in white matter in the same range of b and to discuss the resulted values in terms of the microscopic tissue structure.

Theory. White matter consists of at least two compartments, the myelinated axons (compartment 1) and extra-axonal space (compartment 2), which are well isolated by the myelin sheets. This justifies writing the signal as a sum of two corresponding contributions, $S=w_1S_1+w_2S_2$, where $w_1+w_2=1$ are the weights of compartments and each of the two partial signals, S_1 and S_2, is subjected to expansion [1]. This representation is well known as the bi-exponential model for the case $K_1=K_2=0$. The compartment weights can be estimated as $w_1\approx0.5$ (3,4).

Experimental verification of the two-compartment model is directly related to the number of detectable parameters in Eq.[1] (2). Consider the case in which adjusting D and K in Eq.[1] already provides for a precise description of experimental data. The rest of the series is then below the noise magnitude and cannot be detected. The two-compartment model cannot be verified in this case. It can be brought to the form of Eq.[1] in which only two combinations of the model parameters are fixed by the experiment: $D=w_1D_1+w_2D_2$ and $K=w_1K_1D_1^2/D^2+w_2K_2D_2^2/D^2+3w_1w_2(D1-D2)^2/D^2$. This is the case in the brain grey matter under experimental conditions of Ref.(2). In the opposite limit, description [1] breaks down and the two-compartment model can be given a credit if describes data well. This applies to grey matter voxels with a partial volume of CSF (2). The aim of this study includes an examination of the possibility to detect the histological white matter compartments using the diffusion-weighted signal.

Methods. Data acquisition is described in detail in Ref.(2). In brief, diffusion-weighted MRI was performed on a 3 T whole body clinical scanner for 16 b-factors up to b=2.50 ms/μm^2 in the three orthogonal directions (X, Y and Z) in the scanner reference frame. Five subjects took part in the study. Signal was thresholded to exclude the contamination with noise. Small regions of interest (ROI) were selected in the corpus callosum in areas where the fibres are parallel to the X-direction. The quality of fitting of compared models was evaluated using the F-test.

Results. Both, Eq.[1] and the bi-exponential model resulted in an excellent fitting accuracy (data not shown). The obtained apparent diffusion coefficient, D, (μm^2/ms), kurtosis excess, K, (dimensionless) and the F-value are summarised in the Table (group mean ± group standard deviation (group range)). F is the probability that the bi-exponential model describes data better than Eq.[1] (the corresponding p-value is p=1-F).

	X (parallel)	Y (orthogonal)	Z (orthogonal)
D	2.02 ± 0.13 (1.91 - 2.24)	0.32 ± 0.06 (0.24 - 0.37)	0.33 ± 0.07 (0.26 - 0.42)
K	0.65 ± 0.10 (0.49 - 0.75)	2.68 ± 0.40 (2.21 - 3.12)	2.56 ± 0.32 (2.27 - 3.01)
F	0.44 ± 0.10 (0.33 - 0.59)	0.49 ± 0.06 (0.44 - 0.58)	0.51 ± 0.05 (0.45 - 0.57)

Discussion. The obtained values of ADC agree with literature. The apparent kurtosis excess in the direction parallel to the fibres is comparable with that of grey matter (2). The value of K is much larger in the direction orthogonal to the fibres. This is expectable, since the diffusion in this direction is more hindered and thus deviates more from the Gaussian case. A surprising finding is that the presence of two compartments is not observable as two separable contributions to the signal. This fact constrains the difference in the diffusion parameters in the intra- and extra-axonal compartments as discussed here for the diffusion weighting along the axons. There are several indirect estimations of water ADC inside axons (5-7). The values range from 1.2 to 2.5 μm^2/ms after a correction to 37^{o}C. Since the mean tissue ADC is fixed by the experiment, these limits can be converted to the values of extra-axonal ADC, D_2, which are 2.8 to 1.5 μm^2/ms respectively. Note that the former value approaches the diffusion coefficient in pure water (3.0 μm/ms). The value of K_2 can now be estimated using the above equation for K and a reasonable assumption about K_1. $K_1 = 0$ is expectable as a manifestation of the absence of any restrictions for the diffusion along the axons. In this case, the above limits for D_2 correspond to $K_2= 0.83$ and $K_2=3.9$ respectively. As a function of D_2, K_2 decreases monotonously in the considered interval.

In conclusion, the contributions of the intra- and extra-axonal compartments are not distinguishable up to b=2.50 ms/μm^2. This observation along with literature data constrains the range of currently unknown ADC and the kurtosis excess in extra-axonal space. A low intra-axonal ADC (about 1.2 μm^2/ms) required a high ADC in extra-axonal space with a moderate kurtosis excess. It remain unclear whether such a combination is possible. A high intra-axonal ADC requires a low extra-axonal counterpart with a large kurtosis excess. This corresponds to a restricted diffusion, which appears more realistic and thus gives preference to large values of the intra-axonal ADC. To make a final decision requires more experimental data. Note that different tissue types and compartments have different combinations of two parameters: The ADC and the apparent kurtosis excess. This can be considered as “fingerprints” of specific cell populations.

References: (1) J.H. Jensen, et al. MRM 53(2005)1432; (2) VG Kiselev, KA Il’yasov, MRM 57(2007)464; (3) J Tomasch. Acta Anat 30(1957)902; (4) N Evangelou et al. Ann Neurol 47(2000)391; (5) GJ Stanisz, Israel J Chem 43(2003)33; (6) Kroenke et al. MRM 52(2004)1052; (7) C Beaulieu, PS Allen, MRM 32(1994)579.