Experimentally estimated non-Gaussian water diffusion at a large range of b-values

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Introduction: With the growing clinical applications of diffusion weighted MRI, and advances in hardware performance allowing for increasing b-values, the importance of carefully choosing a suitable model for diffusion data analysis has never been more topical. Here we present experimental data suggesting that the diffusion kurtosis imaging (DKI) model is the most accurate model to describe the attenuation of the diffusion weighted MR signal compared to the more commonly employed diffusion tensor imaging (DTI) model, even for b-values generally deemed suitable for DTI data analysis. With the recent report of a fast method for estimation of the mean kurtosis by Hansen et al.[1], the present study, indicating a non-Gaussian displacement probability distribution function (pdf) for water diffusion in brain tissue at low b-values, as well as the reported sensitivity of mean kurtosis towards tissue pathology, we suggest that diffusion kurtosis is a convincing alternative to DTI, indeed also for routine diffusion MRI.

Theory: The MR diffusion signal can be regarded as a function of b-value; one can consider the Taylor series: $\ln(S(b)) = \ln S_0 - bD_{app} + O(b^2)$, where D_{app} is the apparent diffusion coefficient and $S_0 = S(b=0)$. In DTI, the diffusion tensor, $D(n) = \Sigma\,(n_i n_j D_{ij})$, which has six degrees of freedom is computed by probing the tissue in at least six directions at two or more b-values. If b-values are kept sufficiently small so that the $O(b^2)$ term is negligible, we have the approximation for the signal equation:

$$\ln(S(b)) = \ln(S(0)) - bD \quad (1)$$

In DKI, the non-Gaussian water diffusion is estimated based on the cumulant expansion of the diffusion signal[2]: $\ln(S(b)) = \ln(S0) - bD_{app} + 1/6b^2D_{app}^2\,K + O(b^3)$. The kurtosis tensor, $K(n) = D_{app}^2/D(n)^2 \Sigma n_i n_j W_{ijkl}$, where W_{ijkl} has 15 independent degrees of freedom, is can be computed and the DKI extension of signal equation is:

$$\ln(S(b)) = \ln(S(0)) - bD + 1/6b^2D^2K, \quad (2)$$

for b-values sufficiently small so that the $O(b^3)$ term is negligible; as for DTI, this is sample dependent. If the maximum b-value is too large, there will be a systematic error in the estimates because the $O(b^2)$ or $O(b^3)$ has been neglected in the DTI or DKI model fit, respectively. If the maximum b-value is too small, then the variation of the signal intensity will be small and as a consequence sensitive to noise for the DTI model. For the DKI model, the $O(b^2)$ term is included in the cumulant expansion, and $O(b^3)$ should indeed be negligible in the approximation of the signal equation. Assuming a monotonically decreasing $S(b)$ as b increases, the upper bound of the signal equation can be derived: $b < 3/DK$. In brain $D \approx 1\mu m^2/ms$ and $K \approx 1$, which imply $b < 3000$ s/mm^2 as an upper bound. Commonly, DTI and DKI models have been supposed accurate when keeping the maximum b-value below 1000 s/mm^2 and 2000 s/mm^2, respectively, for in vivo brain imaging.

Methods: An adult male Wistar rat was exsanguinated during intraaortic perfusion with saline containing heparin followed by perfusion-fixation using 4% PFA in PBS. The dissected hemisphere was then immersion fixed until 48 hours prior to scanning, when it was washed in PBS (48 h) and then imaged at 16.4 T (Bruker Biospin); a standard spin echo diffusion-weighted sequence was used to acquire 15 diffusion directions chosen from a 15 point spherical 3-design each at 24 linearly spaced b-values ranging from 0 to 4600 s/mm^2. The remaining diffusion and imaging parameters were as follows: TR = 2.5 s, TE = 14.38 ms, acquisition matrix =68x68, field of view =4.4mm x 4.4mm, slice thickness = 0.250 mm, Δ/δ = 8/2ms, and five averages were acquired. The experiments were acquired at 18°C. Imaging in a human volunteer was performed on a Siemens Trio using a 32-channel head coil. A standard diffusion weighted EPI sequence was used to acquire a total of 30 diffusion directions each at 16 b-values linearly ranging from 0 to 4500 s/mm^2, in-plane resolution was1.8 mm x 1.8 mm, slice thickness 2 mm and two averages were acquired.

Results: To compare the accuracy of the DKI and DTI models to describe the diffusion MR signal attenuation as a function of b-values, sub-datasets were created that included an increasing maximum b-value. To each sub-dataset both models (equation 1 and 2) were fitted using non-linear least squares (Matlab ®), and the model outcome was tested using an F-test (p<0.5 %). Voxels for which the DKI model described the data significantly better than the DTI model is shown in figure 1 for in the rat (left) and the human (right) brain as white. Figure 2 summarizes this result in addition to results for fractional anisotropy based segmented gray matter (GM), white matter (WM) and corpus callosum (CC) of the human brain (right), as well as for manually drawn region of interests (ROIs) of the hippocampus (Hip), and corpus callosum (CC) in the rat brain (left). Interestingly, for both the human and fixated rat brain, a linear trend is noted up to b-values of 2500 s/mm; and at a maximum b-value of around 1000 s/mm^2, commonly used for DTI, up to one third of the voxels are described significantly better by the DKI model. Surprisingly, this linear trend as well as its slope is similar for GM and WM. In addition, figure 1 shows the percentage of voxels for which the DKI fit the data best as a function of maximum b-value times the average diffusion coefficient (D_{rat} = 0.2 μm^2/ms and D_{human} = 0.8 μm^2/ms), top x-axes. The DKI model fit the data better for 50 % of all voxels in the fixated rat brain when the bD-value is 0.4 and for human brain the corresponding bD value is 1.3. This indicates that the fixation process restricts diffusion, probably by decreasing the water permeability of cells, in contrast to previous study[3].

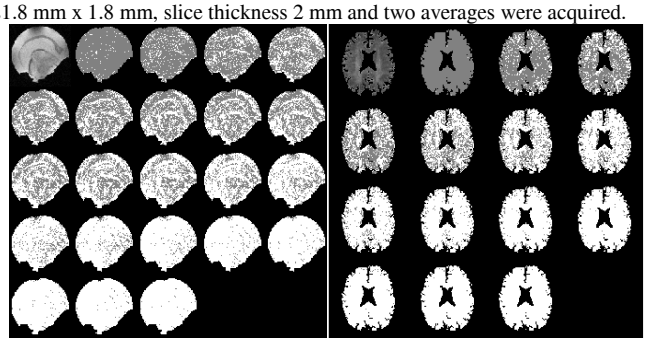
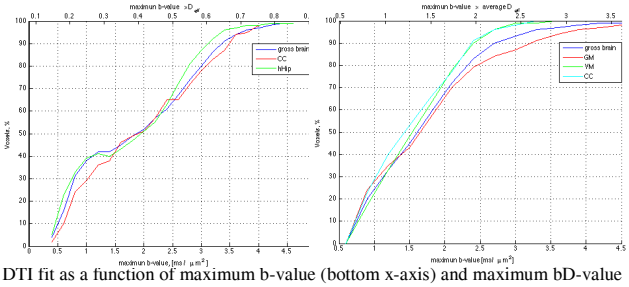


Figure 1 Left (rat) and right (human) figures: from upper left corner to bottom right: S(0) image, followed by statistical maps from model fits including an increasing maximum b-value from 400 to 4600 (left subfigure) or from 600 to 4500 s/mm2 (right subfigure). White voxels indicate that the DKI model fit data significantly better than the DTI model.



DTI fit as a function of maximum b-value (bottom x-axis) and maximum bD-value (maximum b-value times the diffusion coefficient) for all voxels (gross brain) hippocampus (hip), corpus callosum (CC) for fixated rat brain (left) and white matter (WM) and gray matter (GM) for in vivo human brain (right)

Conclusions: These results contests the assumption of Gaussian water displacement pdf approximated in DTI even at b-values below 1000 s/mm for a substantial amount of voxels, and indicates that the conventional maximum b-value of 1000 s/mm^2 for DTI should be lowered, as well as the DKI model should be considered for b-values smaller than commonly applied. Since a substantial amount of voxels can be better described by the DKI model, also at low b-values, and because a fast method for estimation of DKI have been reported[1], it can be concluded that DKI is a strong alternative to DTI even for routine diffusion MR at b-values below 2000 s/mm^2. In addition, we have shown that the aldehyde fixation process does indeed increase restriction in nervous tissue. Such insight into the biophysical change of nervous tissue microstructure is important when extrapolating fixative-based data to in vivo studies.

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References: [1] Hansen, B., et al., Magn. Reson. Med., 2013, **69**; [2] Jensen J.H., et al., Magn. Reson. Med., 2005, **53**; [3] Shepherd T.M., et al. Magn. Reson. Med. 2009, **62**.