Analysis of the cumulant expansion terms of the diffusion-weighted MRI signal in the human brain

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Target audience. This work is devoted to the study of the cumulant expansion of the diffusion-weighted (DW) MRI signal in the human brain. It is of great importance for researchers working in the field of non-Gaussian water diffusion, in particular in Diffusion Kurtosis Imaging (DKI) [1,2].

Purpose. Water diffusion in biological tissue deviates from the Gaussian profile observed in bulk free water due to constraints imposed by the complex cellular microstructure. Deviations of the DW signal from the mono-exponential behaviour become significant at *b*-values (b) exceeding the range used in conventional human brain DTI (b < 1.0 ms μm^{-2}). The DKI technique was proposed as a model-free approach to quantify these deviations [1,2]. It is based on the cumulant expansion of the DW signal, truncated at second order in *b*. Thus, the maximum *b*-value for a DKI analysis must be such that the third and higher expansion orders are still negligible. The maximum *b*-value in DKI analyses found in the literature falls in the typical range of (2.0 – 3.0) ms μm^{-2} [3-7]. Although some optimization schemes for *b*-values and gradient directions have been proposed [8], the influence of the *b*-value fitting range on the cumulant expansion terms of the DW signal has not been yet fully investigated. The aim of this work is to study the dependence of the cumulant expansion terms of the DW MRI signal expanded up to third order in *b*. This information is relevant for setting the validity of fitting *b*-value range in DKI. The analysis is done for both numerical simulations and *in vivo* experiments.

Methods. *Simulations.* Synthetic data were simulated using the biexponential model [3,9] as the "ground truth". In this model the DW signal is given by $S_{\mathrm{biexp}}(b) = f_{\mathrm{f}}\exp(-bD_{\mathrm{f}}) + (1-f_{\mathrm{f}})\exp(-bD_{\mathrm{s}})$, were D_{f} and D_{s} denote the diffusivity of the "fast" and "slow" pools, respectively, and f_{f} is the fraction of the "fast" pool. This model was previously shown to fit the DW signal in the human brain with high accuracy [3,9]. The value of f_{f} was fixed to 0.65, corresponding to the peak of its distribution in the human brain [3]. Rician noise was added to S_{biexp} according to: $S(b) = \sqrt{\left(S_{\mathrm{biexp}}(b) + N(0,\sigma)\right)^2 + N(0,\sigma)^2}$ where $N(0,\sigma)$ is the normal distribution with mean zero and standard deviation σ. Three values of $SNR \equiv 1/\sigma$ were considered: 20, 60 and 100. The range of *b*-values was 0 - 10.0 ms μm^{-2}.
Experiments. MRI experiments were performed in a whole-body 3T Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) on a healthy volunteer who gave prior written informed consent. A twice-refocused spin-echo EPI sequence with bipolar diffusion gradients was applied using *b*-values in the range 0 – 5.0 ms μm^{-2}, 6 field gradient directions and voxel-size 2×2×2 mm^3.
Data analysis. The cumulant expansion up to n^{th} order can be expressed as $S_n(b) = S_0\exp(\sum_{i=1}^{n} a_i(b))$, where $a_1(b) = -bD_{\mathrm{app}}$, $a_2(b) = \left(bD_{\mathrm{app}}\right)^2 K_{\mathrm{app}}/6$ and $a_3(b) = -b^3 C_{\mathrm{app}}$ with $C_{\mathrm{app}} > 0$ [2,9]. Thus, the n^{th} order expansion is valid whenever the condition $|a_{n+1}/a_n| \ll 1$ holds true. In particular, the 1$^{\mathrm{st}}$ order expansion (DTI) is valid provided that $|a_2/a_1| \ll 1$. Similarly, the 2$^{\mathrm{nd}}$ order expansion (DKI) is valid provided that $|a_3/a_2| \ll 1$. In order to evaluate these two ratios, the n^{th} (n = 1, 2, 3) order expansions were fitted to the simulated as well as the experimental DW signals (S) by minimizing the following objective function: $f_N = \sum_{i=1}^{N}\left(S_i - \sqrt{S_n(b)^2 + \sigma^2}\right)^2$, where N refers to the index of the maximum *b*-value considered in a given fitting range. Thus, N was between 4 (minimum number of fitting *b*-values for n = 3) and N_{tot}, with N_{tot} being the total number of *b*-values.

Results. Figures 1a and 1b show the ratios $|a_2/a_1|$ evaluated from the 2$^{\mathrm{nd}}$ order expansion and $|a_3/a_2|$ from the 3$^{\mathrm{rd}}$ order expansion in the simulated data for different SNR values. Simulations from two pairs of (D_{app}, K_{app}) are shown: (1.0, 0.5) (solid lines) and (1.0,1.0) (dashed lines). For the *in vivo* experiments, the histograms of $|a_2/a_1|$ (c) and $|a_3/a_2|$ (d) were evaluated over the four slices for each fitting *b*-value range and put together into the 3-dimensional surface plot (c,d). Solid and dashed lines show the mean of the corresponding ratio over white matter (WM) and grey matter (GM), respectively. One can see from Figure 1a that the curves of $|a_2/a_1|$ show minima at approximately $b \approx 1.0$ ms μm^{-2}. The same feature, although less pronounced, is observed in the *in vivo* case. Similarly, the ratio $|a_3/a_2|$ shows minima at approximately $b \approx 3.0$ ms μm^{-2}, in both simulations and experiments.

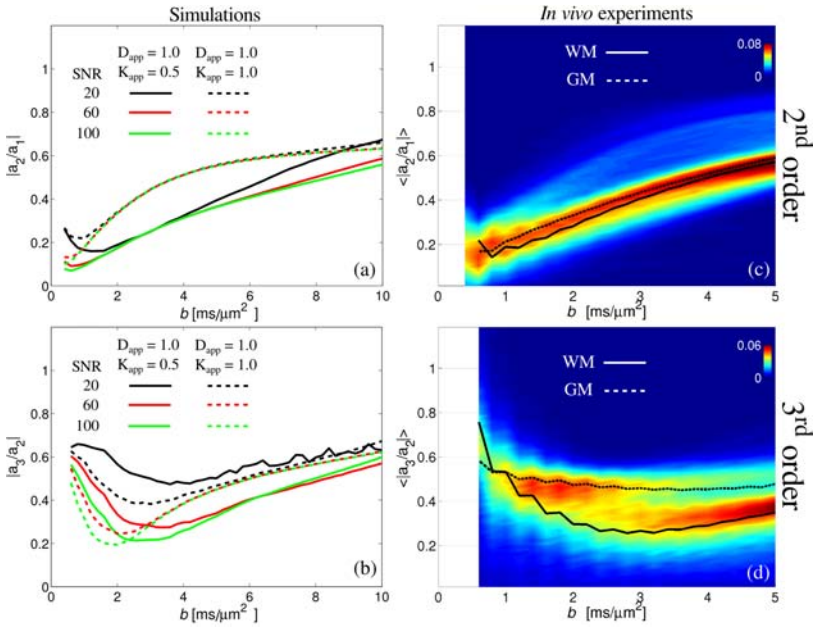

Figure 1. The ratios $|a_2/a_1|$ (a,c) and $|a_3/a_2|$ (b,d) for the simulated (a,b) and the experimental datasets (c,d) as functions of the fitting *b*-value range. WM and GM separation was based on a fractional anisotropy map from conventional DTI [3].

Discussion. The observed minima of $|a_2/a_1|$ at around $b \approx 1.0$ ms μm^{-2} suggest that the expansion up to 1$^{\mathrm{st}}$ order (DTI) is valid in the range 0 – 1.0 ms μm^{-2}. For $b > 1.0$ ms μm^{-2} the term a_2 starts being significant compared to a_1, and therefore the 2$^{\mathrm{nd}}$ order expansion (DKI) needs to be used to describe the signal. Following the same reasoning, the minima of $|a_3/a_2|$ at roughly $b \approx 3.0$ ms μm^{-2} set the limit for the validity of the 2$^{\mathrm{nd}}$ order expansion. For $b > 3.0$ ms μm^{-2} the term a_3 starts increasing and therefore the 3$^{\mathrm{rd}}$ order expansion term needs to be considered in the analysis. In the case of WM, the minimum is very pronounced, while in GM it is less pronounced and shifted towards larger *b*-values. In terms of SNR one can see that for lower SNRs the minima are shifted towards larger *b*-values.

Conclusions. In this study, we have carried out a simple but eloquent analysis of the cumulant expansion terms of the DW MRI signal with the range of fitting *b*-values. We have proposed an approach to set the limit for the maximum *b*-value allowed in DKI, in terms of the negligibility of the 3$^{\mathrm{rd}}$ order cumulant expansion term. The *b*-value ranges estimated through this analysis is approximately in agreement with other reports in the literature [8,9]. Our analyses have shown the differences regarding WM and GM. Further quantitative analysis of the expansion terms is currently being carried out in our group.

References. [1] Jensen J, et al. Magn Reson Med 2005; 53:1432-1440; [2] Jensen J, et al. NMR Biomed 2010; 23:698-710; [3] Grinberg F. et al. Neuroimage 2011; 57:1087-1102; [4] Grinberg F, et al. NMR Biomed. 2012; 25:1295-1304; [5] Jensen J, et al. NMR Biomed. 2011; 24:452-457; [6] Zhuo J., et al. Neuroimage 2012; 59:467-477; [7] Falangola M, et al. J Magn Reson Imaging 2008; 28:1345-1350; [8] Poot D, et al. IEEE T Med Imaging 2010; 29:819-829; [9] Kiselev V, et al. Magn Reson Med 2007; 57:464-469.