Is the diffusion biexponential in brain grey matter?

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Numerous studies, indicate that the diffusion weighted signal from the brain can be described as a weighted sum of two exponential functions which is commonly referred to as the biexponential diffusion. This models provides a very good fitting accuracy on the cost of unrealistic weights of the fast and slow compartments. In this study, we resolve this paradox by analysing whether experimental data require the biexponential description on a statistically significant level. Beyond the statistical tests, we propose and apply a non-statistical indicator for the validity of model testing.

Theory. The present analysis is based on a model independent description of the magnitude of the diffusion weighted signal as a power series in the b-factor, the cumulant expansion (1-4). The usefulness of this expansion depends crucially on its convergence which is regulated by the convergence radius, b_c (5). The series converges for $b<b_c$. In this range, the series can be terminated to provides a model for the signal, in this study $\ln S = \ln S_0 - bD + K(bD)^2/6$, (Ref. 3), which is the simplest function describing the non-monoexponential decay. Here S is the diffusion weighted signal, S_0 is its magnitude for b=0, D and K are the apparent diffusion coefficient (ADC) and the apparent curtosity excess respectively. The biexponential model can be cast in this form by the Taylor expansion. A successful fitting of the above equation to experimental data fixes S_0, D and K which are combinations of the four original parameters, while the rest of the series cannot be determined from noisy data. Thus, a good agreement with data for $b<b_c$ does not prove the biexponential model. For $b>b_c$, the cumulant expansion is useless being divergent. The biexponential model cannot be simplified and a high fit accuracy gives a credit to the model.

Methods. All measurements were performed on a 3 T whole body clinical scanner (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany). Imaging was performed with a diffusion-weighted single-shot Eddy current compensated double-refocused spin-echo echo-planar sequence (6) with 75% partial Fourier in the phase encoding direction (in-plane resolution 2*2 mm^2, slice thickness 3 mm interslice gap 9 mm, TE= 112 ms, TR=4000 ms, isotropic weighting, four repetitions). Images were obtained for 16 b-factors up to b_{max}=2.50 ms/μm^2. Five subjects took part in the study. Images were masked by the condition $S_0 > 6S_{out}$, where S_{out} is the mean signal outside the head and the ghost areas. The range of b-factors processed was restricted by the condition $S>2S_{out}$. The quality of fitting was evaluated using the run test (7) to detect systematic in the fit residual and the F-test (7,8) to compare the two models. The confidence level for both tests was set to 0.9.

Results. The results were similar in all subjects. A scatter plot of all processed voxels in the plane D, K in a single subject is shown in Fig 1 in agreement with Ref. (3). A novel finding is a very good correspondence of the four regions shown in the figure to the grey matter (I), white matter(II), the interface between the brain and CSF (III) and CSF respectively (IV) (data not shown). Both models fitted the averaged signal in each region with a comparable accuracy in grey matter and CSF. The cumulant expansion failed to describe data in region III. This correlated with a short convergence radius of the biexponential model (b_{max}/b_c=1.8±0.2, group averaging). A more detailed analysis was guided by the value of the diffusion coefficient. The total range of observed D was subdivided in a number of small bins, including regions I, III and IV. The signal in each bin was averaged and fitted with the both models. The result in a single subject is presented in Fig. 2. Fig. 3 shows the zoomed grey matter region. The solid red and blue lines represent the χ^2 values for both the cumulant expansion (red line) and the biexponential model (blue line). The black dashed line is the number of points in each bin. Circles around the data points indicate a systematic deviation in the fit residual (run test). Blue crosses on the red data points indicate a significantly better fitting with the biexponential model (F-test).

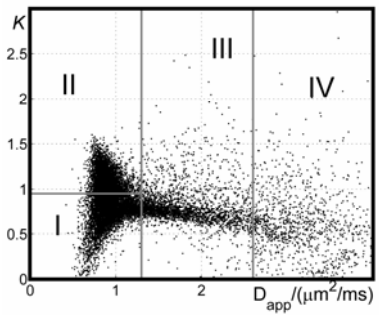

Fig. 1

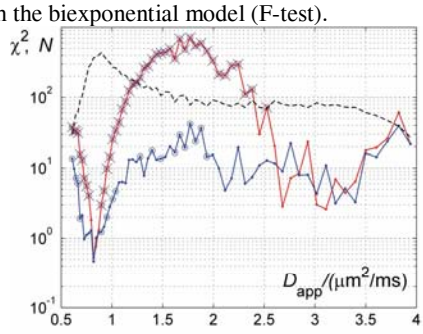

Fig. 2

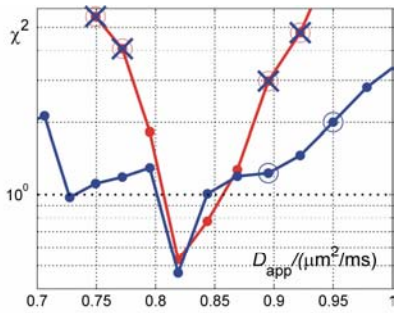

Fig.3

Discussion. The main finding of this study is an abundant population of grey matter voxels (20 – 41% of analysed grey matter, group range) in which the cumulant expansion describes data equally well with fewer parameters. This population is provides for the minimum of χ^2 in Figs. 2, 3 coinciding with the maximum in the distribution of the ADC. These voxels form an apparently random pattern in the anatomical images. We treat these voxels as those which are by chance entirely in grey matter taking into account that the image resolution is very close to the cortical thickness. An admixture of CSF increases the mead diffusivity in a voxel causing a shift to the right in Figs. 2,3 which correlates with a rapid decrease in the accuracy of the cumulant expansion. The minimum near D=3 μm^2/ms corresponds to pure CSF. The biexponential model is adequate in voxels with a partial volume of CSF which explains its success. However, it is superfluous in grey matter voxels where it can be reduced to a simpler cumulant expansion without compromising the accuracy. This conclusion depends crucially on the range of b-factors probed. It is important to test the biexponential model beyond its convergence radius which is 3.0±0.3 ms/μm^2 in this study. The invisibility of individual contributions from the intra and extracellular compartments in grey matter suggests the regime of fast exchange between them, although realistic theoretical models are currently not available.

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