Theoretical study of the free water elimination model

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Target audience: Researchers using diffusion MRI

Purpose: In diffusion MRI, multiple brain structures exist with sizes of the same order of magnitude as the voxel size, which typically range from 2 mm to 3 mm. This makes that partial volume (PV) effects are an important issue in diffusion MRI. This is especially true for brain structures close to cerebrospinal fluid (CSF) regions because the diffusivity of water in CSF can easily be up to 3 times larger than the water diffusivity in white matter brain tissue. This often leads to large biases in the estimation of the diffusion parameters. One way to account for CSF effects is to incorporate a free water component in the diffusion model. The 'Free Water Elimination' (FWE) model proposed by Pasternak et al. [1] is one of the most widely applied models. Despite being used in multiple studies, a thorough theoretical analysis of the FWE model is yet to be performed. In this work, we address this issue by studying the Cramér-Rao lower bound (CRLB) and using it to determine the optimal experimental design and justify the need for regularization.

Methods: The FWE model describes the diffusion weighted (DW) signal S_i with a bi-exponential function consisting of a tissue compartment and a 'free water' compartment linked by a relative volume fraction f [1,2]: $S_i = S_0\left[(1-f)e^{-b\boldsymbol{g}^T\boldsymbol{D}\boldsymbol{g}} + fe^{-bd}\right]$, with S_0 the signal without diffusion weighting, $\boldsymbol{g}$ the diffusion weighting unit gradient, $\boldsymbol{D}$ the diffusion tensor as known from the DTI model, and $d = 3\times10^{-3}\ mm^2/s$ the diffusivity of free water at body temperature. Studying the CRLB of the FWE model provides insights in the highest attainable precision with which the FWE model parameters can be estimated unbiasedly. Additionally, the optimal diffusion weighting gradient directions and strengths in terms of maximal precision of an unbiased estimator of the parameters of interest can be determined by minimizing the trace of the CRLB in function of the experimental design [3]. The CRLB is calculated by taking the inverse of the so-called Fisher Information Matrix (FIM) $I(\boldsymbol{\theta})$ [4]: $I(\boldsymbol{\theta}) = -E\left[\frac{\partial^2}{\partial\boldsymbol{\theta}^2}\log p(X;\boldsymbol{\theta})\middle|\boldsymbol{\theta}\right]$, with $p(X;\boldsymbol{\theta})$ the Rician probability density function of the observations X given the model parameters $\boldsymbol{\theta} = [S_0, D_{xx}, D_{xy}, D_{xz}, D_{yy}, D_{yz}, D_{zz}, f]$. The CRLB was minimized for a diffusion tensor with mean diffusivity of $1{,}2\times10^{-3}$ mm^2/s and variable FA and CSF fractions. Initialization was done using the multi-shell optimized FWE acquisition scheme proposed by Pasternak et al. [5], having the following number of directions per respective b-value shell [s/mm^2]: 1 × b=0, 3 × b=50, 6 × b=200, 10 × b=500, 30 × b=900 and 16 × b=1400. The optimized gradient set was restricted to the same maximum b-value and number of measurements. Monte Carlo simulations were performed for all combinations of FA and CSF fraction. Rician noise was imposed with a signal-to-noise ratio of 20 on the non-diffusion weighted images and 1000 noise realizations per voxel. An FWE fit was also performed on a real data set of a healthy volunteer. The acquisition scheme was: 6 × b=0, 25 × b=600 and 45 × b=1200.

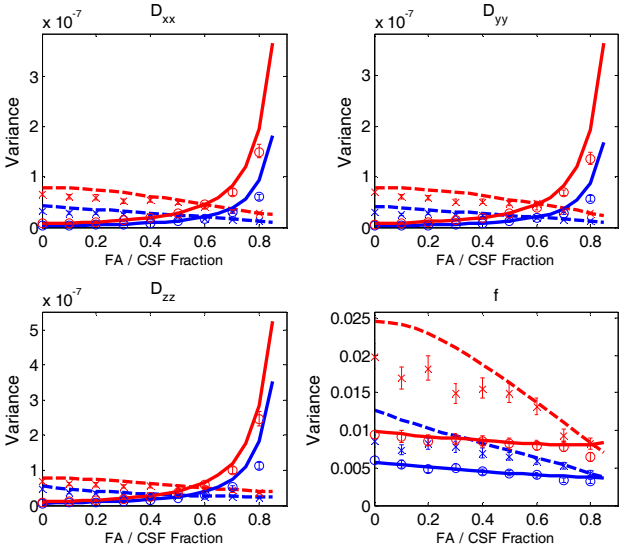

Figure 1: The CRLB in function of the CSF fraction (full line, FA fixed on 0.8) and FA (dashed line, f fixed on 0.5) with their respective simulation results (CSF: o; FA: x) of the three diagonal DT elements (D_{xx}, D_{yy}, D_{zz}) and the estimated CSF fraction (f). The initial and optimized acquisition schemes are shown in red and blue, respectively. Errorbars indicate the 95% confidence interval.

Mask	S_0	D_{xx}	D_{xy}	D_{xz}	D_{yy}	D_{yz}	D_{zz}	f
Low FA (%)	0.00	5.81	2.54	1.80	6.32	2.59	5.81	1.52
High FA (%)	0.00	0.23	1.24	0.40	0.17	0.23	0.06	0.11

Table 1: Percentage of voxels in a mask from a real data set where the estimation of a model parameter exceeds a predetermined threshold.

Results and discussion: Minimization of the trace of the CRLB matrix resulted in an acquisition protocol with 4 distinct b-value shells (s/mm^2): 3 × b=0, 15 × b=422, 10 × b=592, 38 × b=1400. This result appears independent of the initial acquisition scheme. When looking at the diagonal CRLB elements and corresponding simulation results in figure 1, it is clear that a significant gain in terms of attainable precision can be obtained with the optimized acquisition scheme. However, we see that in voxels with a high CSF fraction, the variance of the distribution of the estimated diffusion parameters becomes increasingly larger. Similarly, the precision of the estimation of f will decrease significantly for voxels with tissues with low FA. Due to the absence of a ground truth in the real data set, we tried to quantify the need for regularization by counting the number of times an estimated parameter exceeds a certain threshold, beyond which it could be considered incorrect and regularization is thus needed. This threshold was defined as the median of each parameter over all voxels ± 10 times the median absolute deviation of the parameter distributions. Two masks of the data set were studied separately based on their FA (from a DTI estimation): 1) low FA mask: 0.05 < FA < 0.2, and 2) 'high' FA mask 0.3 < FA < 0.9. The low FA mask will also encompass voxels with high CSF fractions since these voxels typically have very low FA values. The results are presented in table 1. We note that in the low FA mask, considerably more voxels exhibit erroneous parameter estimates when compared to the high FA mask. These findings confirm our theoretical and simulation results.

Conclusion: From the results we can conclude that using the optimized acquisition protocol enables the user to achieve a significantly higher precision when estimating the diffusion parameters. Furthermore, in voxels containing a large CSF fraction or a low FA value, the FWE model becomes ill-conditioned and additional regularization and/or constraints become necessary. These theoretical findings are confirmed by both simulation and real data experiments.

References:**[1]** Pasternak et al.,MRM 62, 717-30, 2009; **[2]** Pierpaoli et al., Proc. ISMRM, 2004:1215; **[3]** Poot et al., TMI 29, 819-29, 2010; **[4]** van den Bos, Wiley, 51-53, 2007; **[5]** Pasternak et al.,MICCAI 15, 305-12, 2012