

Conditional least squares estimation of diffusion MRI parameters

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Introduction: In the field of diffusion magnetic resonance imaging (dMRI), several diffusion models were proposed to quantitatively describe the diffusion of water molecules in biological tissue. Most of the diffusion models require the acquisition of many highly diffusion-weighted MR images (DWIs), which suffer from low signal-to-noise ratio (SNR), severe geometric eddy current distortions, and subject motion. It has already been shown that diffusion parameter estimation might be inaccurate when not accounting for the Rice distribution of magnitude DW data [1]. Several groups proposed methods to remove the so-called Rician bias in dMRI studies [2]. We would like to point out that those estimators might still be biased in dMRI studies, despite their apparent favorable theoretical properties. DW data namely suffers from potential motion artifacts as well as severe geometrical eddy current distortions. Prior to diffusion model fitting, those distortions should be corrected by aligning all DWIs to a less distorted non-DW reference image. Afterwards, the b-matrix needs to be rotated to preserve the orientation information of the DW data, and, although often overlooked, the DW signal intensities need to be modulated to compensate for voxel volume changes that occur when reversing the stretch or compressing induced by the eddy currents [3]. Both resampling the DWIs into the reference image, as well as the intensity scaling will alter the Rician data distribution. To the authors' knowledge, the previously proposed estimators do not incorporate such a DW data distribution modification. In this work, we propose an estimator, using the linearity property of the expectation value operator, to obtain more accurate, in well-defined cases even unbiased, diffusion parameter estimates if the Rician distributed diffusion weighted images are scaled or resampled prior to diffusion model fitting. **Material and methods:** We propose a **conditional least squares estimator (CLS)** based on the minimization of a sum of squared deviations about the conditional expectation of a Rice distributed DW signal. Given a set of DW measurements, \mathbf{S} , we estimate the diffusion model parameters, θ , by minimizing the conditional sum of squares:

$$\hat{\theta} = \arg \min_{\theta} \left\| \mathbf{S} - \sigma \sqrt{\frac{\pi}{2}} L_{1/2} \left(-\frac{\hat{\mathbf{S}}(\theta)}{2\sigma^2} \right) \right\|_2^2$$

with $L_{1/2}$ a Laguerre polynomial, σ the Gaussian noise level and $\hat{\mathbf{S}}(\theta)$ the reconstructed DW signal. If the error term is normally distributed, the CLS method renders a maximum likelihood (ML) equivalent and achieves consistency and asymptotic normality, under some mild regularity condition [4]. In theory, weight should be applied to account for the signal dependency of the variance of a Rice distribution. Those weights are however not discussed in this abstract. **Head motion and eddy current correction:** Both resampling the DWIs into the reference image, as well as the intensity scaling will alter the data distribution. Nevertheless, two important properties should be considered. Firstly, the Rice distribution is scale invariant, i.e., if the random variable m follows a Rice distribution with underlying intensity v and noise level σ then λm is also Rice distributed with parameters λv and $\lambda \sigma$. Note, however, that the scaled DW data can no longer be assumed to be homoscedastic. Secondly, the Central Limit Theorem states that the (weighted, with weights w_i , met $i=1..n$) average of large set of samples, drawn from an arbitrarily distributed, follows a normal distribution. Thus, interpolation between Rician distributed samples, causes the Rician PDF to change towards a Gaussian PDF. The mean of the original distribution, however, does not alter in some well-defined circumstances, favorising the CLS. The CLS, unlike the ML, might still be unbiased after interpolating the DW images. The accuracy of the CLS however depends on the regions, which are considered. The CLS can only be unbiased if:

$$\Sigma \left(\sum_{i=1}^n w_i m_i \mid \sigma \right) = \sigma \sqrt{\frac{\pi}{2}} L_{1/2} \left(-\frac{\left(\sum_{i=1}^n w_i v_i \right)^2}{2\sigma^2} \right)$$

a premises which only holds in high SNR or homogeneous regions. In border regions, neither of the evaluated estimators will be (asymptotically) unbiased.

Results and discussion: For each corner of an unit cube, Rician distributed data (with varying SNR) was simulated using the DTI model, given a diffusion tensor, \mathbf{D} , with FA = 0.85 and MD = 10^{-3} mm²/s. The b-value was set to 1200 s/mm², 60 isotropically distributed directions were selected. In addition, 5 non DW signals were simulated for each corner. Next, the DW signals were interpolated at arbitrarily chosen points within the unit cube. We accounted for the heteroscedasticity arising from the different interpolation weights [5]. Finally, MD was estimated by fitting the DTI model to the interpolated DW data. We compared the accuracy of the CLS to the performance of 3 other estimators: (i) ML based on a Rician PDF [2], (ii) bias reducing nonlinear LS, based on an approximation of the expectation of a Rice distribution (brNLS) [1],

and (iii) an ordinary nonlinear LS (NLS). In Fig 1., it is shown

that the CLS outperforms all other estimators in terms of accuracy. This conclusion will be more expressed with decreasing SNR or the use of higher b-values such as in Diffusion Kurtosis Imaging (DKI). The MLE suffers from a significant bias if the noise level was not known a priori (Fig 1a). If the noise level is known, the MLE appears more robust to the modification of the PDF due to the interpolation (Fig 1b). In a whole brain simulation, the diffusion tensors, obtained by fitting the DKI model to normal human brain DW data, were used to reconstruct DW data. For the reconstruction, 2x60 gradient directions and a b-value of 1000s/mm² were chosen. In addition, 5 non-DW images were simulated. After adding Rician noise (median SNR of non DW image = 15) to the data, we simulated motion and eddy current correction by a subpixel shift of the data. All DW were kept aligned by shifting all DW volumes equally. It can be seen from Fig. 2 that the CLS is unbiased in most of the human brain regions. Regions around strong edges will however inherently suffer from a bias (see identical positioned red arrows). **Conclusion:** Although only few simulation results were shown, we demonstrated that some favorable theoretical properties, such as asymptotical consistency, of previously proposed estimators (e.g. MLE), does not apply for dMRI in which data correction or smoothing prior to model fitting is a customary step. Nevertheless, the MLE appears rather robust to data correction (including interpolation and scaling of the data) if the noise level was known a priori. We here proposed the CLS estimator, which is from a theoretical point of view an equivalent for the MLE. The CLS is, however, in well-defined cases robust to the data correction as it can rely on the linearity of the expectation operator in high SNR and homogeneous regions. We only showed DTI results, but the approach can also be used for other diffusion models, such as DKI and constraint spherical deconvolution. **References:** [1] Jones, D.K. et al., (2004). *MRM*, 52(5), pp.979-93. [2] Sijbers, J. et al., (1998). *IEEE TMI*, 17(3), pp.357-61. [3] Leemans, A. et al., (2009). *MRM* 61(6), pp.1336-1349. [4] Klimko, A. et al., (1978). *Ann Statist*, 6(3), pp.629-642. [5] Rohde, G.K. et al., (2005). *NeuroImage*, 26(3), pp.673-684. [6] Gudbjartsson, H. et al., (1995). *MRM*, 34(6), pp.910-914.

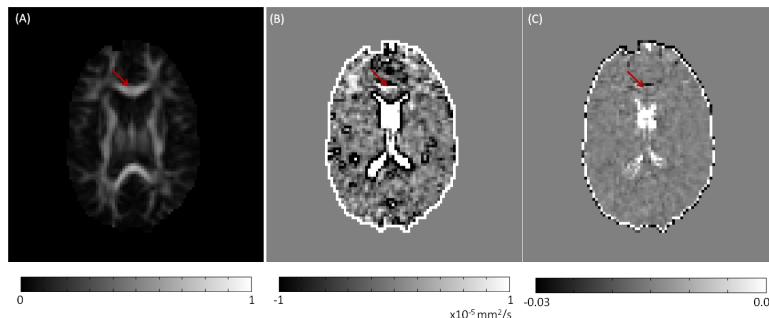


Fig. 2: (A) FA map for anatomical reference, (B) bias on MD, and (C) bias on FA