Assessment of mcDESPOT Precision Using Constrained Estimation

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Target Audience: This work is intended for scientists developing imaging protocols and estimation techniques for quantitative relaxometry of myelin and white matter.

Introduction: Multi-component Driven Equilibrium Single-Pulse Observation of T1 and T2 (mcDESPOT) [1] is recently proposed technique to perform multi-component relaxometry and estimate myelin water fraction (MWF) values from steady-state imaging data, overcoming imaging time and resolution limitations of conventional spin-echo based techniques. The technique has been applied in a number of studies (e.g. neurotypical infant development [2], multiple sclerosis [3], animal models of dysmyelination [4]) and shown to provide biologically plausible myelin-specific estimates of MWF with reasonable precision. However, the mcDESPOT 2-pool model may be difficult to estimate, as the parameter space contains up to 7 free parameters and multiple local minima. To overcome these difficulties, fitting is typically performed using a global optimization method called Gaussian contraction (GC) [5], a constrained estimation technique known to be sensitive to both initial conditions and contraction step size [6]. Recent theoretical work has also called into question the reliability of estimates, using the Cramér–Rao lower bound (CRLB) to evaluate the theoretical precision of the model [6]. In order to investigate the observed discrepancy between experimental results and theoretical predictions on the precision of mcDESPOT, we demonstrate an extended CRLB framework that includes not only the inherent precision of the model but also the effect of GC constrained estimation and biased estimators.

Theory and Methods: CRLB: Consider a model g(x,θ), where x is a vector of user-selectable parameters (e.g. flip angle, TR, etc) and θ is a vector of model parameters. In an MR experiment, a series of noisy observations are fitted to this model to derive an estimate of θ, $\hat{\theta}$. CRLB sets a bound on the variance of these parameters given an input noise level. Specifically, the minimum achievable variance
$$\sigma_{\theta_j} = \sqrt{EJ^\top \sigma^{-1} JE^\top}$$
where $J = \dfrac{\partial g_i}{\partial \theta_j}$ is the Jacobian matrix and $E = \dfrac{\partial E[\hat{\theta}]}{\partial \theta}$ is the gradient estimator matrix, and $E[\hat{\theta}]$ is the expectation value operation. Previous work [6] assumed the value of E to be identity, as is the case for an unbiased estimate.

mcDESPOT: A digital phantom was created by generating signals from the mcDESPOT model with added noise such that the SNR was 500, relative to the proton density of SPGR. For this phantom, prototypical values in white matter were chosen. T1/T2 myelin = 465/26 ms, T1/T2 intracelluar = 1070/117 ms, MWF = 0.00→0.25, and Tau = 180 ms. Scan parameters were TR$_{SPGR}$ = 6.5ms, TR$_{bSSFP}$ = 5.0 ms, α$_{SPGR}$ = [3 4 5 6 7 9 13 18]°, α$_{bSSFP}$ = [12 16 21 27 33 40 51 68]°, and bSSFP phase cycling φ = [0 180]°. Off-resonance ω = 40 Hz, but was set as a fixed parameter in fitting (assuming external calibration) for a total of 6 model parameters. B1 was assumed to homogenous, as it is corrected externally in our protocol. To estimate both Monte Carlo noise performance as well as the gradient estimator matrix E, 2000 realizations of the digital phantom were generated (noiseless in the case of E) and fit to the mcDESPOT model using the Gaussian contraction approach.

Results & Conclusion: Fig. 1 shows the results of Monte Carlo simulation for the digital phantom. Fig. 2 shows the precision (standard deviation) of mcDESPOT predicted by CRLB superimposed over the precision observed using Monte Carlo. The CRLB for unbiased estimates is computed taking only the model into account, indicating an unusable lack of precision (red line). By numerically computing the gradient estimator matrix E from the GC constrained estimation and incorporating it into CRLB, theoretical precision increased by an order of magnitude without the need for explicitly fixing model parameters (blue line).

References: [1] Deoni, S.C.L. et al. MRM 2008; [2] Deoni S.C.L. et al. JNEUROSCI 2011; [3] Kitzler H.H. et al. Neuroimage 2012 [4] Hurley S.A. et al. ISMRM 2012 #88; [5] Personal communication, S. Deoni (Brown University) & Tobias Wood (King's College London); [6] Lankford C.L. et al. MRM 2013
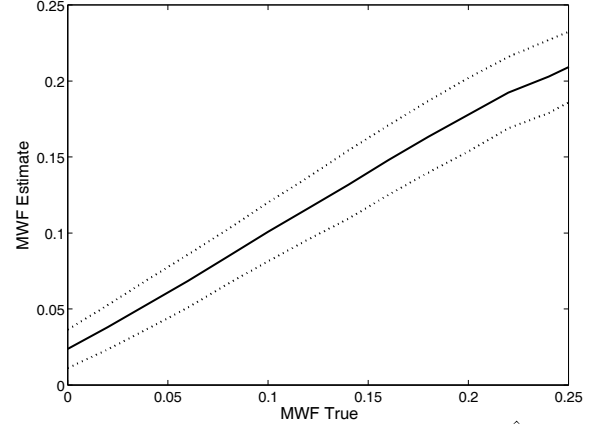
Fig 1. Monte Carlo results showing θ_{MWF} vs. $\hat{\theta}_{MWF}$ Solid line indicates mean, dotted ± σ$_{MC}$. MWF is observed to be nearly linear and monotonically increasing, with slight underestimation for MWF < 0.10 and slight overestimation above.
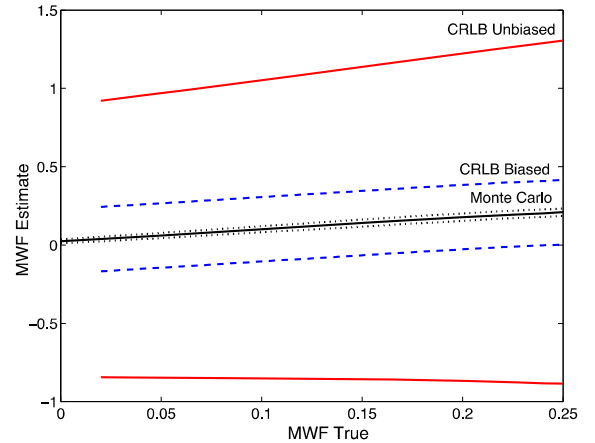
Fig 2. Results of CRLB simulation superimposed over Monte Carlo. Note extended y-scale. Solid line (red) indicates ± σ$_{CRLB}$ (unbiased), and dash lines indicate ± σ$_{CRLB-Biased}$ (biased), taking the effect of GC estimation into account. Note that CRLB biased is evaluated at MWF=20. Biased estimation results in an order of magnitude improvement in CRLB theoretical precision, yet fails to completely account for observed precision using mcDESPOT fitting.
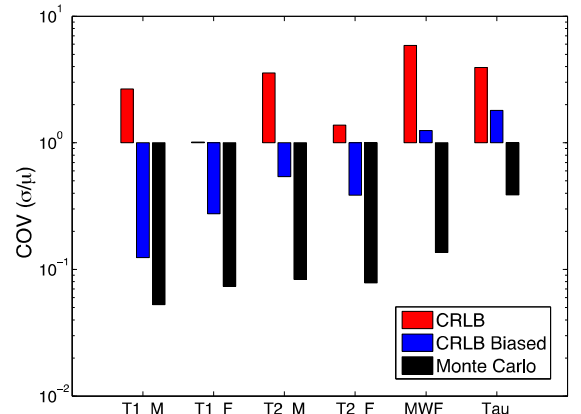
Fig 3. Coefficient of variation (stdev/mean) of all mcDESPOT parameters for the model system at MWF=0.20. Results from left to right show CRLB unbiased (red), CRLB biased (blue), and MC (black).