PERFORMANCE BOUNDS FOR DIFFUSION MRI MODELS OF TISSUE MICROSTRUCTURE

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TARGET AUDIENCE Researchers with an interest in inferring tissue microstructure from diffusion weighted MRI

PURPOSE Model based image analysis of Diffusion Weighted Magnetic Resonance Imaging (DWI) promises the identification of morphological parameters of brain microstructure, leading to the possibility of identifying changes over time and an ability to track neurodegenerative disorders [1]. The objective of this work is to analyse published methods for Axon Diameter Distribution or mean axon diameter estimation, using a Cramer-Rao Lower Bound (CRLB) analysis. The CLRB [2], computed for a given parametric model, determines the theoretical lower bound on the variance of an estimator of that model. That is, the CRLB provides an indication of the best possible performance of an estimator applied in ideal conditions. The diffusion models considered are the bi-exponential model [3], CHARMED [4], AxCaliber [5], MMWMD [6] and Generalised 1D (G.1D) [7]. High CRLBs for any of these models will demonstrate that, even in the ideal case of the model being a completely accurate representation of the data (and therefore zero bias error), no parameter estimator of that model can perform well enough to provide robust and accurate values. This work is critically important for improved understanding in research concerned with inferring microstructure from DWI.

METHODS Our analysis is of single-gradient direction DWI acquisitions in the ideal case in which the imaging plane and gradient direction are chosen perpendicular to a bundle of collinear axons. Let θ denote the parameters of each diffusion model, and $\hat{\theta}$ an unbiased estimator of that model. The CRLB, computed from the Fisher Information matrix, was calculated to provide $\sigma_{min}(\hat{\theta})$, the minimum standard deviation of estimator $\hat{\theta}$. Observation noise was considered to be additive white, Gaussian noise, with SNR of 10. The CRLB for an estimator is inversely proportional to the observation noise variance, and thus there is an inverse relationship between $\sigma^2_{min}(\hat{\theta})$ and SNR. In order to provide a single figure of merit, we computed the relative error ratio (RER) for estimator $\hat{\theta}$ as: $RER(\hat{\theta}) = \sigma_{min}(\hat{\theta})/\theta$. It was assumed the normalised signal, $x(q,\Delta)$, is a two-compartment model, with hindered, $x_h(q,\Delta)$, and restricted, $x_r(q,\Delta)$, compartments, $x(q,\Delta) = (1-f)x_h(q,\Delta) + f x_r(q,\Delta)$, where f is the volume fraction and Δ is the diffusion time. The hindered signal is modelled by Gaussian diffusion: $x_h(q,\Delta) = e^{-4\pi^2 q^2 D_h(\Delta-\delta/3)}$, where D_h is the diffusivity for the hindered part and δ is the gradient field pulse width. As we are analysing the best-case performance, we simplify the models to consider only a single (mean) axon radius (Table 1). The CRLB depends on both acquisition and tissue parameters; the parameter space that was combinatorially explored for each model is presented in Table 2. The average RER is quantified across the full range of tissue parameters.

Bi-exp.	$x_r(q,\Delta) = e^{-4\pi^2 q^2 D_r(\Delta-\delta/3)}$
CHARMED	$x_r(q,\Delta) = e^{-(\frac{4\pi^2 q^2 R^4}{D_r\Delta})(\frac{7}{96})(2-\frac{99}{112}\frac{R^2}{D_r\Delta})}$
Single-radius AxCaliber	$x_r(q,\Delta) = \sum_k 4e^{-\beta^2_{0k} D_r\Delta/R^2}\left(\frac{(2\pi qR)J'_0(2\pi qR)}{(2\pi qR)^2-\beta^2_{0k}}\right)^2 + \sum_{nk} 8e^{-\beta^2_{nk} D_r\Delta/R^2} \times \frac{\beta^2_{nk}}{\beta^2_{nk}-n^2} \times \left(\frac{(2\pi qR)J'_n(2\pi qR)}{(2\pi qR)^2-\beta^2_{nk}}\right)^2$
MMWMD	$x_r(q,\Delta) = e^{-4\pi^2 q^2 R^2}$
Single radius G.1D	$x_r(q,\Delta) = \mathrm{sinc}^2(2Rq)$

Table 1. Restricted diffusion models, $x_r(q,\Delta)$.

Parameter [unit]	Min	Max	# Steps
G_{max} [mT/m]	47	986	21
No. of q values	6	20	8
Δ [ms]	20	100	5
δ [ms]	5	5	1
D_h [μm^2/ms]	0.1	2.9	15
D_r [μm^2/ms]	0.05	2	6
f	0.1	0.9	9
R [μm]	0.5	4	8

Table 2. Acquisition (top) and tissue (bottom) parameter ranges.

RESULTS A reasonable uncertainty level would be 0.1 for the total average RER, which represents minimum 10% estimation error. i.e. under the best possible situations, the estimations will have at least 10% uncertainty. The results in Table 3 indicate that none of the diffusion models give rise to estimators with reasonable uncertainty levels under practical measurement setup. Theoretically, the RERs can be reduced to acceptable levels by drastically increasing the SNR or number of measurements; however, this would lead to impractical acquisition times.

	Bi-exp.	CHARMED	AxCaliber	MMWMD	G.1D
Min. Total Avg. RER	632.55	15.17	0.63	0.66	0.62
Avg. RER (D_h)	27.97	0.32	0.36	0.32	0.35
Avg. RER (D_r)	34.25	-	-	-	-
Avg. RER (f)	570.33	0.05	0.11	0.17	0.12
Avg. RER (R)	-	14.80	0.16	0.18	0.16

Table 3. Relative Error Ratios (RER) computed from CRLB analysis

CONCLUSIONS The CRLB analysis of two-compartment hindered/restricted diffusion models clearly demonstrates that all models suffer from high Cramer-Rao lower bounds, which call into question the ability of any of the methods to robustly estimate parameters relating to axon diameter distributions or mean axon radii. Our analysis represents strictly best-case scenarios in which DWI data is derived directly from the model and the tissue is comprised of axons of only a single diameter. As practical application of the models is far removed from these best-case scenarios, the performance of the estimators applied to experimental datasets can only be worse than the error rates presented here. This will show up in estimation algorithms that are extremely sensitive to parameter initial conditions, for example. Our analysis sheds a new light on methods that aim to infer microstructure from DWI data, and provides a method by which to assess the practicality of proposed techniques in the future.

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