Limits on measuring axon diameters in vivo using diffusion MRI

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Introduction: This work studies the limits of measuring axon-diameters in vivo using diffusion MRI with current hardware. We construct a simple idealized model of white-matter diffusion and outline a method to find rotationally invariant acquisition schemes that provide the best estimates of the model parameters. The acquisition optimisation extends easily to other models, for example, with distributions of diameters as in [1]. Simulation experiments using these acquisition schemes investigate the accuracy with which we can recover axon diameters. The results provide limits on the axon diameters, and thus diameter distributions, we can expect to measure at various noise-levels and maximum gradient strengths.

Methods: The model for the diffusion-weighted signal from a pulsed-gradient spin-echo sequence is $A(\delta, \Delta, \mathbf{G}) = f\,A_h(\delta, \Delta, \mathbf{G}) + (1\text{-}f)\,A_r(\delta, \Delta, \mathbf{G})$, where $\mathbf{G}$ is the gradient vector, δ and Δ are the gradient pulse length and separation, f is the volume fraction of the extra-cellular space; A_h is the signal from the extra-cellular space and A_r is that from the intra-cellular space. The model is a stripped-down version of the CHARMED model [1]. Axons are cylindrical, impermeable and all have the same radius R and direction $\mathbf{n}$. For A_r, we use Van Gelderen's model [2] for the signal from diffusion within cylinders. For A_h, we assume that displacements in the extra-cellular space are Gaussian with cylindrical symmetry about $\mathbf{n}$ with diffusivity $d_{//}$ in the fibre direction and $d_\perp$ in perpendicular directions. The full set of model parameters is $p_1 = f$, $p_2 = R$, $p_3 = d_{//}$, $p_4 = d_\perp$, and $\mathbf{n}$.

We assume no knowledge of the fibre orientation for in-vivo imaging, so the acquisition scheme should allow us to fit the model for any $\mathbf{n}$. Furthermore, the total acquisition time must be tolerable for live subjects. We limit the number of acquisitions to 120. For orientation independence, we divide the measurements into M combinations of δ, Δ, and $|\mathbf{G}|$ in each of N gradient directions with NM=120. For particular model parameters, we find the M combinations of δ, Δ, and $|\mathbf{G}|$ that minimize $H = \Sigma_a F(\mathbf{n}_a)/a$, where $F(\mathbf{n}) = \Sigma_{i=1\ldots4}\, C_i/p_i^2$ and C_i is the CRLB [3] of p_i for direction $\mathbf{n}$. The CRLB of p_i is the i-th diagonal entry of $\mathbf{J}^{-1}$, where J has ij-th element $\sigma^{-2}\sum_{k=1}^{NM}\left(\partial A/\partial p_i\;\partial A/\partial p_j\right)\left(\delta_k, \Delta_k, \mathbf{G}_k\right)$, and σ is the standard deviation of the signal. The noise level, σ, depends on T_2 and the echo time TE, which we assume is the same for all measurements. We set TE = $\max_k(\delta_k + \Delta_k) + K$, where K is a constant depending on the length of the 90° pulse and readout, and $\sigma \propto \exp(\mathrm{TE}/T_2)$; we take T_2 = 70ms. The CRLB C_i is a minimum bound on the variance of the fitted p_i with the acquisition scheme (δ_k, Δ_k, $\mathbf{G}_k$), k = 1, ..., NM. For orientation independence, we sum $F(\mathbf{n})$ over a set of directions $\mathbf{n}_a$, a=1...A. To construct the set, we select $\mathbf{n}_1$ at random, minimize H, then choose $\mathbf{n}_2$ that has largest $F(\mathbf{n})$ over a large number of sample directions. We iterate until the newly chosen $\mathbf{n}$ is already in the set; A is usually 3 or 4. We minimize H using a customized version of the Matlab genetic-algorithm tool. For the optimization, we set f = 0.3, $d_{//} = 1.7\times10^{-9}$ m^{2}s^{-1}, $d_\perp = 2\times10^{-10}$ m^{2}s^{-1}. We constrain $\Delta_k - \delta_k \geq$ P180 = 5ms, which is the length of the 180° pulse. We optimize separately for each combination of $R \in$ {1, 2, 5, 10, 20} μm and $|\mathbf{G}|_{\max} \in$ {40, 70, 100, 200, 500} mT/m. We take N = 30 and M = 4, which is the combination that usually gives lowest H.

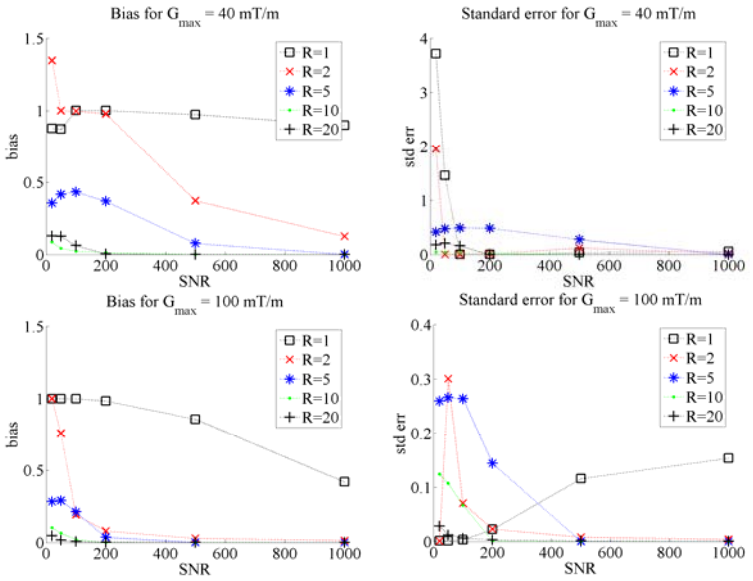

Figure 1. Bias (left) and standard error (right) for each radius, against SNR at $|\mathbf{G}| = 0$, for $|\mathbf{G}|_{\max}$ = 40 (top) and 100 (bottom) mT/m.

Experiments: We synthesize data from the model and add Rician noise. We fit the model using a Levenberg-Marquardt algorithm. We fix $\mathbf{n}$ to the true value and fit the four other parameters, initialized at their true values perturbed by Gaussian noise with standard deviation $p_i/5$. In each trial, we repeat the fitting from ten starting points and pick the result with the smallest residual error. We run 50 trials for each combination of R and $|\mathbf{G}|_{\max}$ and compute the mean R' and standard deviation σ_R of the fitted radius and thus the bias $(R\text{-}R')/R$ and the standard error σ_R/R.

Results: Table 1 lists typical examples of optimized acquisition schemes. Figure 1 plots the bias and standard error against SNR for each R at $|\mathbf{G}|_{\max}$ = 40 and 100 mT/m. Fitting accuracy increases with R, $|\mathbf{G}|_{\max}$ and SNR. With $|\mathbf{G}|_{\max}$ = 40mT/m, R=10μm is the smallest radius we can estimate reliably at achievable SNR=50. With $|\mathbf{G}|_{\max}$ = 100mT/m, we can measure R=5μm at SNR=50 and almost R=2μm; other results show we need $|\mathbf{G}|_{\max}$ close to 500mT/m to measure R=1μm (typical for brain) with this acquisition type.

	$\|\mathbf{G}\|_{\max}$ = 40 mT/m			$\|\mathbf{G}\|_{\max}$ = 100 mT/m		
R=2μm	41.2	46.3	40.0	30.1	40.5	99.9
	15.1	20.1	40.0	10.4	15.4	100
	15.1	20.1	40.0	10.4	15.4	99.9
	36.8	50.6	23.7	28.6	42.1	42.3
R=5μm	49.0	60.8	40.0	26.9	39.9	100
	49.0	60.8	40.0	26.9	39.9	100
	27.7	32.7	40.0	14.0	19.0	100
	45.0	64.8	19.7	08.9	57.9	98.1

Table 1. Optimized four (δ, Δ, $|\mathbf{G}|$) combinations, in (ms, ms, mT/m), for example R and $|\mathbf{G}|_{\max}$ settings.

Discussion: We have outlined a new method for optimizing diffusion MRI acquisition for axon-diameter measurement in vivo. Although not shown here, the optimization improves parameter estimates significantly over naive choices of combinations. Experimental results provide upper bounds on the accuracy, since we tune the acquisitions specifically to measure each R, the model is an idealized extreme and we fix $\mathbf{n}$ during fitting. However, the results give insight into the regions of axon-diameter distributions that we can fit reliably. Reducing P180 may increase accuracy for smaller R, as will incorporating prior knowledge about fibre orientation. Similar optimization can provide acquisitions for fitting diameter distributions, as in [1].

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