Robust optimization of diffusion-weighted MRI protocols used for fiber reconstruction

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Abstract. Diffusion-weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique that employs diffusion-encoding gradients to sensitize the signal to the diffusion of water molecules. DWI allows the noninvasive and quantitative probing of opaque structures such as fibrous soft tissues. Model-based DWI post-processing algorithms, such as diffusion tensor imaging (DTI), solve an inverse problem to estimate from a series of DWI data a set of model parameters representing the diffusion process and the environment of the water molecules. DWI models connect the model parameters (e.g., fiber orientations for fibrous soft tissues) with the experimental parameters (e.g., strengths and directions of the 3-D diffusion-encoding gradients). For spinal cord injuries and skeletal muscle characterization, the fiber orientations within the imaged region can be approximately known a priori using localizer images. Then, we propose and implement a model-based robust optimization framework for two axisymmetric diffusion models, producing robust DWI protocols with respect to the approximate knowledge of the fiber orientations within the images, thereby reducing the uncertainty in the parameter estimates caused by experimental noise. Our goal is to improve the yield of quantitative DWI diagnostics used in clinical and preclinical trials by minimizing the experimental uncertainty.

1. Introduction

1.1. Background

Model-based diffusion-weighted imaging (DWI) methods, such as DTI [1, 2] and QUAQ [3, 4], are a subset of quantitative magnetic resonance imaging (MRI) techniques, which are used to infer important structural information within biological tissues. DWI is based on its sensitivity to the diffusive movement of water molecules [5], which in turn is representative of the molecular environment. The sensitization to diffusion is achieved by applying a pair of pulsed diffusion-encoding gradients [5]. While for standard MRI the imaging is done by collecting points in \( k \)-space, the Fourier reciprocal space of spin locations, DWI protocols involve acquiring a series of DWI images that sample \( q \)-space, the Fourier reciprocal space of spin displacements, by using one different set of diffusion-encoding gradient pulses per image [2, 3]. The 3-D vector \( q \) is related to the diffusion-encoding gradient vector \( g \) via \( q := \gamma \delta g / 2\pi \), where \( \gamma \) is the gyromagnetic ratio (\( \gamma / 2\pi = 42.576 \text{ MHz T}^{-1} \)) and \( \delta \) is the gradient pulse duration. The \( b \)-factor is often used...
instead of the magnitude of $q$ with $b := 4\pi^2(\Delta - \delta/3)||q||^2$, where $\Delta$ is the time between the pulsed gradients, such that the collected signal will depend on the spin displacements occurring during that time. DWI data can be used to compute diffusion metrics that are indicative of the fiber orientation within the tissue and other biophysical information of interest. Also, restricted or hindered diffusion in the direction of diffusion barriers can then be distinguished from unrestricted diffusion [2, 3, 6]. This noninvasive method has been successfully applied for the diagnosis of diseases such as multiple sclerosis [7] and cerebral ischemia [8].

In model-based post-processing approaches, the DWI data is fitted to a diffusion model to extract specific quantitative information. The most often used model, diffusion tensor imaging (DTI [1, 2]), is based on an anisotropic unrestricted diffusion model with six independent parameters, and yields a local “apparent diffusion tensor” (ADT), whose principal eigenvector provides the fiber orientation. The DTI model can be modified by assuming axisymmetric diffusion in the plane transverse to the fibers (ADTI), thereby reducing the number of model parameters to four. A physics-based approach, called QUAQ (quantitative analysis of $q$-space [3]), models fibers as impermeable axisymmetric cylinders, and uses the solution of the diffusion equation inside a cylinder which also contains four parameters.

Studies on DTI have shown that the uncertainty in the model parameter estimation can be reduced by optimizing the experimental parameters, which consists of the $q$-space sampling directions and the $b$-factor. Typically, either several $q$-space sampling schemes have been compared given a performance function, or the directions for the diffusion-encoding gradients have been optimized to be as general as possible using model-independent metrics. Papadakis et al. [9] isolated the effect of gradient directions from the weighting $b$-factor for the ADT estimation. They defined an “index of DTI”, which relates the variance of the measured data to the total variance of the measured tensor components (ADC), and used it as a measure of optimality of the diffusion gradient directions. Skare et al. [10] proposed the condition number as a means of studying the noise propagation, and showed improvements in the estimation of the fractional anisotropy (FA) by minimizing the condition number of the transformation matrix for a given $q$-space sampling scheme. Batchelor et al. [11] showed that noise propagation in DTI is anisotropic and used the standard deviation of FA as a measure of optimality. The variance of FA was also been used by Peng and Arfanakis [12] to compare several $q$-space sampling schemes. Finally, Hasan et al. [13] used several DTI-based or model-independent optimization metrics to be minimized (variance for the ADT components, condition number [10], force [14], Coulomb energy) and compared the resulting $q$-sampling schemes via Monte-Carlo simulations.

1.2. Motivation

One typical application of model-based DWI is to reconstruct the fiber bundle(s) present in each elementary volume element (voxel) in the field-of-view (FOV). Studies of the spinal cord [15–17] and calf muscles [18] have shown promising results for DTI. Ries et al. [15] applied DTI to subjects suffering from a narrowing of the cervical canal and observed substantial differences in diffusion characteristics to detect lesions in the spine. Mottershead et al. [16] demonstrated the existence of a strong correlation between myelin content and axonal density with diffusion anisotropy. Ducreux et al. [17] reconstructed 3D fiber tracts to visualize the deformation of the posterior spinal cord lemniscal and corticospinal tracts. Finally, Sinha et al. [18] performed calf muscle fiber tracking in vivo using DTI in human subjects.

The spinal cord and the calf are regions of the human body with relatively simple structures compared to the brain for example, such that fiber bundles (neuronal and myofibers, respectively) can be assumed to be oriented along a mean direction with some relatively small range. Mathematically, the unit vectors that define each fiber bundle can be assumed to be contained within a cone with a relatively small half-angle (e.g., < 30°), with no specific distribution however. To illustrate this point, T2-weighted and DWI images of a region of the spinal cord,
the corticospinal tract, were acquired using a 3 T GE Signa EXCITE scanner (GE Healthcare, Waukesha, WI) at the Department of Radiology at Michigan State University (MSU). A spin-echo echo-planar imaging sequence was used with an 8-channel head coil with the following parameters: 30 contiguous 3-mm axial slices, TR = 8 000 ms, TE = 76 ms, matrix size =128 × 128, FOV = 22 cm × 22 cm, number of excitation = 2, parallel imaging acceleration factor = 2, \( b = 1 \, 000 \, \text{s mm}^{-2} \), and scan time = 8 min 32 s. The DTI processing of the DWI data was performed using FSL [19] and Matlab (The MathWorks, Natick, MA). The data was collected on a healthy 27-year-old male volunteer, who signed his informed consent approved by the MSU Office of Regulatory Affairs and the MSU Human Research Protection Program.

Figure 1(a) shows the coronal view of the spinal cord section (corticospinal tract) near the brain stem. The underlying image is a T2-weighted MRI image used for demarcation of the axon bundles in the spinal cord. The overlying arrows show the fiber orientation estimated using DTI at each pixel of the image. We observe that the average fiber orientation is at \((\theta_F, \phi_F) = (6.2^\circ, 18^\circ)\). Moreover, the distribution of the deviation angle \(\alpha\) w.r.t. the average orientation of the neuron fibers is plotted in figure 1(b). The majority (85%) of the fiber orientations is contained within a cone of half-angle 35\(^\circ\).

![Figure 1](image)

**Figure 1.** DTI of a human corticospinal tract close to the brain *in vivo*: (a) fiber orientations estimated by DTI superimposed over a T2-weighted image; (b) distribution of the angle between the fiber orientations and the mean fiber orientation.

In this manuscript, a robust optimization framework for model-based DWI is presented, which produces robust \(q\)-space sampling schemes with respect to approximate a priori knowledge of the fiber orientations in the FOV. This problem pertains to skeletal muscle and spinal cord studies, for which localizer images can be used to provide the necessary a priori information and set up the robust DWI protocols on-the-fly.

2. Method

2.1. Robust optimization framework

The proposed robust optimization framework is based on D-optimality and its application for the design of experiments [20, 21]. In model-based DWI, the collected DWI data (\(S(q)\)) is normalized by a T2-weighted image \(S_0\) to obtain the normalized echo attenuation, \(\hat{E}(q) := S(q)/S_0\). Then, \(\hat{E}(q)\) is fitted to a mathematical model \(E(q; \beta)\), where the \(M\) model parameters that need to be estimated are written as a vector \(\beta \in \mathbb{R}^M\) with elements \(\beta_j \ (j \in [1, M] \subset \mathbb{N})\).

Two axisymmetric models, QUAQ and ADTI, are considered here. For QUAQ [3], the fiber radius \(a\) and orientation \((\theta_F, \phi_F)\) of the fibers, and the fluid self-diffusion coefficient \(D\) are estimated, leading to \(M = 4\) and \(\beta = \{D, a, \theta_F, \phi_F\}\). The (long) analytical formula for \(E(q; \beta)\) for QUAQ is available in [3, 22]. The ADTI model is derived from the DTI model: \(E(q; \beta) = \exp[-4\pi^2(\Delta - \delta/3)(q_\parallel^2D_\parallel + q_\perp^2D_\perp)]\), where \(q_\parallel := q \cdot v, v\) is the unit vector along the
fiber direction defined in spherical coordinates \((\theta_F, \phi_F)\), and \(q_1^2 := q^2 - q_2^2\). \(D\parallel\) and \(D\perp\) are the longitudinal and transverse diffusion coefficients w.r.t. the fiber direction, respectively. Then, for ADTI, \(M = 4\) and \(\beta = \{D_\parallel, D_\perp, \theta_F, \phi_F\}\). Unlike most DTI studies (e.g. [9, 14]), we will not linearize the parameter estimation by taking the natural logarithm of \(E(q; \beta)\), which would not work for QUAQ and undermine the noise propagation study of these truly nonlinear models.

As discussed in [20], D-optimality requires the computation of a sensitivity matrix \(X\). The partial derivatives of the model \(E(q; \beta)\) w.r.t. the parameters provide the model sensitivity coefficients \(\eta_j(q; \beta) := \partial E(q; \beta)/\partial \beta_j\) with \(j \in [1, M]\). For \(N\) samples of \(q\)-space, a sequence of \(N\) diffusion-encoded images is collected. The gradient encoding schemes can be defined by \(\Omega := \{q_i; i \in [1, N]\}\) and the sensitivity matrix \(X \in \mathbb{R}^{N \times M}\) is defined as \(X(\Omega; \beta) := (X_{i,j})_{N \times M}\) where \(X_{i,j} := \eta_j(q_i; \beta)\) [23]. For the nonlinear least-squares parameter estimation, by assuming that the experimental noise is additive, independent, normally distributed, with zero mean and variance \(\sigma^2\), the covariance matrix of estimated parameters, \(\Sigma \in \mathbb{R}^{M \times M}\), can be related to the sensitivity matrix \(X(\Omega; \beta)\) and the experimental noise, \(\sigma^2\), as \(\Sigma = \sigma^2(X^T X)^{-1}\). Note that the covariance matrix has to be computed over a large number of measurements [20]. Then,

\[
\text{det } \Sigma = \frac{\sigma^{2M}}{\text{det } (X^T X)}
\]  

(1)

The determinant of the covariance matrix, \(\text{det } \Sigma\), provides a measure of the hypervolume of uncertainty for the parameter estimation. Equation (1) can then be used to assess the performance of the \(q\)-space sampling scheme \((\Omega)\) \textit{a priori} by computing the hypervolume of uncertainty from sensitivity analysis, instead of time-consuming Monte-Carlo simulations [23].

Based on (1), the cost function for our robust optimization framework can be defined as \(f := 1/\text{det } (X^T X)\), where \(X\) is a function of both the model \((\beta)\) and experimental \((\Omega)\) parameters. Thus, by minimizing \(f\) by adjusting \(\Omega\) under certain \textit{a priori} information on \(\beta\), the uncertainty in the parameter estimation will be minimized. When the \textit{a priori} information is in the form of knowing that the fiber orientations in the FOV are within a cone of uncertainty \(\{\theta_F, \phi_F\} \in \Lambda\) with no assumption of the probability distribution of the fiber orientations within that cone, we can take the deterministic and conservative approach of writing the nonconvex robust optimization problem [24–26] as

\[
\Omega_{\text{robust}} := \arg \left[ \min_{\Omega} \left( \max_{\{\theta_F, \phi_F\} \in \Lambda} f := \frac{1}{\text{det } (X^T X)} \right) \right].
\]  

(2)

The interpretation of this “minimax” problem is that we want to find the optimized \(q\)-space sampling scheme \(\Omega\) that is robust with respect to the worst-case scenario of the approximate \textit{a priori} information \(\{\theta_F, \phi_F\} \in \Lambda\) [24, 25]. The “optimization” is done by minimizing \(f\) and varying \(\Omega\), while the “worst-case scenario” is obtained by maximizing \(f\) and varying \(\{\theta_F, \phi_F\} \in \Lambda\).

The noise model in the above case is only approximate since the measured echo attenuation data \(\hat{E}\) is the norm of a complex number where Gaussian, white noise is introduced into the real and imaginary parts individually. The noise in \(\hat{E}\) then follows a Rician distribution [27] with a non-zero mean and non-additive nature. In the case of high signal-to-noise ratio (SNR) in measurement data, the Gaussian assumption holds.

2.2. Robust optimization for axisymmetric models

The \(q\)-space sampling schemes \(\Omega\) considered here are constrained to a single gradient strength (i.e., \(\forall i \in [1, N]\), \(\|q_i\|\) has the same value), such that the optimization consists in finding sampling locations on a sphere, \(\Omega := \{ (\theta_i, \phi_i) ; i \in [1, N]\}\), as in [9–14]. Motivated by section 1.2 and figure 1, the approximate \textit{a priori} knowledge is given in the form of fiber orientations within a cone of axis the \(z\)-axis and half-angle \(\delta\theta\), i.e., \(\Lambda := [0, \delta\theta] \times [0, 2\pi]\). The other model parameters
are fixed to realistic values: \( a = 0.5 \, \mu m, D = D_i = 10^{-3} \, \text{mm}^2 \, \text{s}^{-1}, \) and \( D_\perp = 0.2 \cdot 10^{-3} \, \text{mm}^2 \, \text{s}^{-1}. \) 

Also, the experimental timing parameters are \( \delta = 21 \, \text{ms} \) and \( \Delta = 35 \, \text{ms}. \)

2.2.1. Reduced-order parameterization  For models, such as ADTI and QUAQ, that assume axisymmetry about the fiber orientation, analytical derivations and numerical simulations have shown that when the \textit{a priori} information is given as a single fiber orientation, the optimal \( q \)-space sampling schemes collapse onto axisymmetric rings about the \textit{a priori} fiber direction [23]. This observation led to a reduced-order parameterization for the sampling schemes: \( \Omega := \{\theta_i, N_i, \Delta \phi_i; \ i \in [1, P]\} \), where \( P \) is the number of rings, each located at \( \theta_i \) with \( N_i \) uniformly distributed points and with an offset \( \Delta \phi_{i+1} \) in the \( \phi \)-direction w.r.t. the first ring (see figure 2 and [23]). There are \((P - 1)\) independent values for \( \Delta \phi_i \) (since \( \Delta \phi_1 = 0 \) by construction) and \( N_i \) (since the total number of sampling location is fixed to \( N \)). This parameterization results in considerably shorter computational times by reducing the number of variables used in the optimization from \( 2N \) to \( 3P - 2 \).

2.2.2. Robust optimization algorithm  The robust optimization problem written as (2) is solved for the QUAQ and ADTI models. A preliminary optimization using \( \theta_F = 0^\circ \) (i.e., \( A \) reduces to a singleton) is performed to provide a starting point, \( \Omega_0 := \arg \min_{\Omega} f \), for our robust optimization algorithm. This strategy is preferred to choosing an arbitrary \( q \)-space sampling scheme and results in shorter computational times. To that end, a simulated annealing method, which performs a stochastic exploration of the sampling space controlled by a temperature parameter \( (T) \), is implemented using the full \( 2N \) variables [28]. Solutions satifying the \( T \)-dependent Metropolis criterion [29] are accepted, while others are rejected. The exploration stage is necessary to avoid local optima (the cost function \( f \) is nonconvex), and the step-size for exploration is progressively reduced after a maximum number of rejection steps are reached [23]. Then, the robust optimization problem defined in (2) is solved using our reduced-order parameterization with \( P \) rings. The ring locations, \( \{\theta_i \in [0, \pi/2]; \ i \in [1, P]\} \), and number of points, \( \{N_i \in [1, N - P]; \ i \in [1, P - 1]\} \), are initialized based on the clustering of the \( q \)-space sampling scheme \( \Omega_0 \). These parameters are optimized by iterating on possible values for \( N_i \) and \( P \) and using a deterministic gradient-based “minimax” algorithm [30] for \( \theta_i \).

**Figure 2.** Robust optimization results for the QUAQ model for \( b = 2 \, 500 \, \text{mm}^{-2} \) with \( P = 3 \) rings on a sphere for fiber orientations within a cone of axis the \( z \)-axis and half-angle \( \delta \theta = 20^\circ \): the optimized sampling locations are denoted by \( \Delta \) on a 2-D representation of the sphere with shading and contour lines corresponding to the normalized echo attenuation.

2.2.3. Optimization efficiency  The measure of efficiency or fitness function, \( \chi \), is given by the inverse of the cost function defined in (2): \( \chi := \det (X^T X) \). Since \( X \) is a function of both the model and experimental parameters, so is \( \chi \). For the axisymmetric models considered here, the function \( \chi \) has no dependence on \( \phi_F \), such that the efficiency of a \( q \)-space sampling scheme can be illustrated by a 1-D plot of \( \chi^{\ast} := \chi/\chi_{\text{ref}} \) vs. the deviation angle from the \( z \)-axis, \( \alpha \), where \( \chi_{\text{ref}} \) is a normalizing constant. For instance, figure 3(a) shows the efficiency of \( \Omega_{\text{robust}} \), which is obtained with \( \delta \theta = 20^\circ \) and \( P = 3 \) for QUAQ and depicted in figure 2.
3. Results and discussion

3.1. Efficiency of the robust $q$-space sampling schemes

In figure 3, the variation of $\chi^*$ with the deviation angle $\alpha$ is shown for QUAQ and ADTI with $b = 2,500 \text{ s mm}^{-2}$. In both cases, the 30-point robust $q$-space sampling schemes $\Omega_{\text{robust}}$ are optimized using $\delta \theta = 20^\circ$. The results are compared to the optimized schemes $\Omega_0$ obtained for $\theta_F = 0^\circ$ and to a conventional 30-point “ME30” sampling scheme [31], for which the minimum, mean, and maximum levels of $\chi^*$ are shown. The results are very similar. By construction, $\chi^*$ at $\alpha = 0^\circ$ needs to be larger for $\Omega_0$ than for $\Omega_{\text{robust}}$, and the worst case (i.e., minimum of $\chi^*$) in the interval $\alpha \in [0, \delta \theta]$ has to be worse (i.e., lower $\chi^*$) for $\Omega_0$ than for $\Omega_{\text{robust}}$. Figure 3 reveals that the peak around $\alpha = 0^\circ$ for $\Omega_{\text{robust}}$ is broader and flatter than for $\Omega_0$, which indicates that the uncertainty of the parameter estimation will be improved within a broader region of possible fiber orientations. The performance of our robust optimization is thus validated. In addition, the robust $q$-space sampling schemes for both QUAQ and ADTI are shown to be more efficient than the conventional ME30 until $\alpha = 30^\circ$ from the a priori fiber orientation, which is larger by $10^\circ$ than the design parameter $\delta \theta = 20^\circ$. This illustrates the benefits of using a priori information when it is available instead of using a conventional $q$-space sampling scheme, which should only be used in the absence of a priori knowledge.

![Figure 3](image1.png)

**Figure 3.** Comparison of the efficiency of 30-point sampling schemes ($\Omega_0$, $\Omega_{\text{robust}}$, ME30) with $\delta \theta = 20^\circ$ and $P = 3$ for $b = 2,500 \text{ s mm}^{-2}$: (a) QUAQ and (b) ADTI.

![Figure 4](image2.png)

**Figure 4.** Comparison of the efficiency of 30-point robust sampling schemes $\Omega_{\text{robust}}$ with $\delta \theta = 20^\circ$ and $P = 3$ and $b$ varying from 1,000 to 2,500 s mm$^{-2}$: (a) QUAQ and (b) ADTI.
3.2. Influence of the b-factor

Figure 4 shows the variation of optimization efficiency when the b-factor is varied by changing the diffusion-encoding gradient strength that is common to all $q_i \in \Omega$. Two effects can be observed. First, the relative performance of $\Omega_{\text{robust}}$ decreases with increasing $b$. Second, a secondary peak in the the efficiency appears near $\alpha = 90^\circ$ for lower $b$. These effects are caused by the decrease in sensitivity to fiber orientations as $b$ is decreased [32], such that there is some uncertainty between the longitudinal and transverse orientations w.r.t. the true fiber orientation. This is why, in practice, MRI clinicians typically acquire data at the highest $b$-value for which the SNR is sufficient and why we choose not to include the $b$-value in our optimization framework.

3.3. Influence of the uncertainty in the approximate a priori fiber orientations

The measure of efficiency of 30-point $q$-space robust sampling schemes $\Omega_{\text{robust}}$ is plotted in figure 5 for different sizes ($\delta \theta$) of the cone of uncertainty for the fiber orientations within the FOV. Each $\Omega_{\text{robust}}$ is obtained using $b = 2 500 \text{ s mm}^{-2}$ for the QUAQ model. The number of rings needs to be increased when the a priori information is less precise, so that the reduced-order parameterization does not overly constrain the robust optimization: $P = 3$ for $\delta \theta = 10^\circ$ and $20^\circ$; $P = 5$ for $\delta \theta = 40^\circ$; and $P = 6$ for $\delta \theta = 90^\circ$. The case when $\delta \theta = 90^\circ$ corresponds to when no a priori information is used. Then, the performance of our robust $q$-space sampling scheme outperforms the conventional ME30 for all values of $\alpha$. For $\delta \theta = 10^\circ$ to $40^\circ$, as the region of uncertainty increases, our optimized sampling maintain an efficiency level that is greater than that of ME30 until $\alpha \approx \delta \theta + 10^\circ$.

4. Conclusions

A robust optimization framework for the design of model-based DWI protocols used to estimate fiber orientations in fibrous soft tissues has been proposed. This analytical framework makes use of the approximate a priori fiber orientations that can be obtained from localizer images to optimize the DWI experimental parameters in order to reduce the uncertainty of estimating the model parameters caused by the experimental noise. A region of uncertainty for the a priori fiber orientations is allowed, and defined as a cone with half-angle $\delta \theta$, which is our control parameter. This applies for instance to regions of the human body such as the spinal cord or the calf muscles, for which the neuronal or muscle fibers are oriented within a cone along one direction and a relatively narrow half-angle (e.g., deviations angles $\alpha < 35^\circ$). The optimization strategy consists of optimizing the $q$-space sampling scheme for the worst-case scenario over the entire region of uncertainty by solving a “minimax” problem. This deterministic approach was chosen because only a range of potential fiber orientations $\{\theta_F, \phi_F\} \in \Lambda$ is assumed, as opposed to specifying a probability distribution for $\{\theta_F, \phi_F\}$, which would be much harder to estimate a priori from localizer images.

The optimized sampling schemes obtained within our framework are thus robust with respect to the uncertainty of the a priori information, and yield an improved performance when
compared to a conventional \( q \)-space sampling scheme (ME30). Indeed, we have shown that our robust \( q \)-space sampling schemes outperform the conventional scheme for fiber orientations within a cone of half-angle \( \alpha \approx \delta \theta + 10^\circ \), so that our robust optimization provides a non-negligible safety margin. Since the total uncertainty in clinical and preclinical trials is caused by both the imaging technique and patient variability, such optimized \( q \)-space sampling schemes can reduce the uncertainty due to the DWI technique used for diagnostics, which would facilitate the comparison between patient groups.

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