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Myelin Water Fraction Estimation from Optimized Steady-State Sequences using Kernel Ridge Regression

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Synopsis

This work introduces a new framework for myelin water fraction (MWF) estimation. We use a novel scan design approach to construct a sequence a fast steady-state sequences and optimize corresponding flip angles and repetition times for precise MWF estimation. We quantify MWF and five other parameters per voxel using a novel method based on kernel ridge regression. We obtain MWF maps in vivo that are comparable to those reported in literature, with possibly shorter overall scan time.

Introduction

Myelin loss is central to the pathogenesis of several neurodegenerative diseases. Myelin quantification is therefore of interest for monitoring the development and progression of WM disorders.

Bulk MR signal arises from multiple water compartments with different relaxation rates, and the fastest-relaxing compartment is due to water trapped between myelin bilayers[1]. "Myelin water fraction" (MWF) denotes the proportion of signal arising from the fast compartment relative to total signal, and is an indirect measure of myelin content.

Multiple spin-echo (MSE) acquisitions[1] and accelerated variations[2] yield MWF estimates in agreement with *in vitro* measurements[3] but are limited by long repetition times TR. Existing short-TR steady-state (SS) sequences are faster, but produce MWF estimates[4,5] that disagree with MSE measurements[6], possibly due to insufficient estimation precision[7].

This work introduces a new SS acquisition for fast, precise MWF estimation. We design the flip angles and repetition times of combinations of spoiled gradient-recalled echo (SPGR) and dual-echo steady-state (DESS) sequences to optimize MWF estimation precision. We estimate MWF and five other parameters using a novel method based on kernel ridge regression[8] (KRR). We obtain MWF maps *in vivo* that are comparable to those reported in MSE literature.

Methods

This section adapts a general method for acquisition design[9] to formulate a cost function that characterizes MWF estimator variance. The method seeks to minimize this cost through a novel greedy optimization procedure.

After image reconstruction, a sequence of scans (e.g., SPGR and DESS) useful for MWF estimation produce at each voxel position a sequence of noisy voxel values $\mathbf{y} \in \mathbb{C}^D$, modeled as

$$\mathbf{y} = \mathbf{s}(\mathbf{x}; \kappa, \alpha, \mathbf{T}_{\mathrm{R}}) + \mathbf{n},$$

where $\mathbf{x} \in \mathbb{R}^L$ denotes L latent parameters; $\kappa \in \mathbb{R}$ denotes (separately acquired and estimated) flip angle variation; $\alpha, \mathbf{T}_{\mathrm{R}} \in \mathbb{R}^D$ denote prescribed flip angles and repetition times; $\mathbf{s} : \mathbb{R}^L \times \mathbb{R} \mapsto \mathbb{C}^D$ models the noiseless signals arising from D datasets; and $\mathbf{n} \in \mathbb{C}^D$ is complex zero-mean Gaussian noise with covariance Σ. We take $\mathbf{s}$ to model two non-exchanging water compartments. Neglecting across-compartment variation in off-resonance effects, this reduces model dependencies to six free latent parameters per voxel: MWF f_{M}; (spin-lattice, spin-spin) relaxation time constants for the myelin water $(T_1^{\mathrm{M}}, T_2^{\mathrm{M}})$ and slow-relaxing $(T_1^{\mathrm{S}}, T_2^{\mathrm{S}})$ compartments; and proportionality constant m_0. We collect these $L \leftarrow 6$ unknowns as $\mathbf{x} \leftarrow [f_{\mathrm{M}}, T_1^{\mathrm{M}}, T_2^{\mathrm{M}}, T_1^{\mathrm{S}}, T_2^{\mathrm{S}}, m_0]^{\mathsf{T}}$.

The Cramer-Rao Bound (CRB) states that the covariance of any unbiased estimator of $\mathbf{x}$ is bounded below by the inverse of the Fisher information matrix

$$\mathbf{F}(\mathbf{x}; \kappa, \alpha, \mathbf{T}_{\mathrm{R}}) := [\nabla_{\mathbf{x}} \mathbf{s}(\mathbf{x}; \kappa, \alpha, \mathbf{T}_{\mathrm{R}})]^{\mathsf{H}} \Sigma^{-1} [\nabla_{\mathbf{x}} \mathbf{s}(\mathbf{x}; \kappa, \alpha, \mathbf{T}_{\mathrm{R}})].$$

For precise MWF estimation, we seek $\alpha, \mathbf{T}_{\mathrm{R}}$ that achieve small (unbiased) MWF estimator variance lower bound $[\mathbf{F}^{-1}(\mathbf{x}; \kappa, \alpha, \mathbf{T}_{\mathrm{R}})]_{(1,1)}$ for a range of typical $\mathbf{x}, \kappa$ values. We seek to (locally) minimize the objective function

$$\Psi(\alpha, \mathbf{T}_{\mathrm{R}}) := \mathbb{E}_{\mathbf{x}, \kappa}([\mathbf{F}^{-1}(\mathbf{x}; \kappa, \alpha, \mathbf{T}_{\mathrm{R}})]_{(1,1)}),$$

where $\mathbb{E}_{\mathbf{x}, \kappa}$ denotes expectation with respect to assumed and measured distributions of $\mathbf{x}$ and κ, respectively.

Since Ψ is nonconvex in $\alpha, \mathbf{T}_{\mathrm{R}}$, local optimizers depend on initialization. Moreover, it is unclear *a priori* how to best allocate scan time amongst initial SPGR/DESS scans, under a given total time constraint. Figure 1 diagrams our approach that greedily constructs a scan combination through a sequence of constrained optimization problems interleaved with SPGR/DESS scan additions. Table 1 lists optimized scan parameters found by our greedy design.

In all experiments, we estimated six parameters per voxel from SPGR/DESS data via non-iterative KRR[8] initialization, followed by iterative local optimization. We evaluate only MWF estimates in the following.

Experimentation and Results

We first show through BrainWeb[10] simulations how greedy scan construction can find desirable scan combinations. Figure 2 and Table 2 demonstrate that for a given total scan time, the proposed acquisition (Table 1) consisting of 4 SPGR and 3 DESS scans with optimized flip angles and repetition times outperforms a sequence of 9 SPGR and 9 DESS scans with fixed minimum TR.

We next estimate MWF *in vivo* using the proposed acquisition. We collected 3D axial SPGR/DESS data from a 32-channel Nova receive head array in a 3T GE scanner using optimized flip angles and repetition times and fixed 4.67ms echo time; $256 \times 256 \times 8$ matrix size; and $24 \times 24 \times 4$ cm^3 field of view. We also collected two Bloch-Siegert (BS) SPGR scans for separate κ estimation[11]. SPGR/DESS and BS acquisitions respectively took totals of 10m8s and 1m40s.

Figure 3 provides representative MWF estimates and compares corresponding sample statistics with WM/GM regions of interest (ROIs). MWF sample means in WM are comparable to those in recent MSE studies[2].

Summary

We introduced a new SS acquisition comprised of fast SPGR/DESS scans optimized for precise MWF estimation. We constructed this acquisition using a novel, greedy design framework and CRB-based optimization[9]. We estimated MWF *in vivo* using a novel method based on KRR[8]. MWF estimates from an optimized SPGR/DESS acquisition are in reasonable agreement with literature MSE measurements, and may afford shorter overall scan times.

Acknowledgements

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Figures
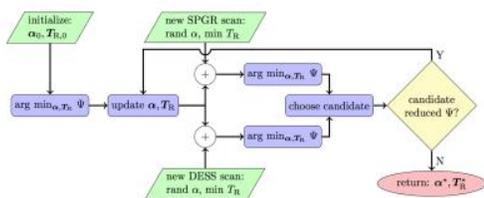
Figure 1: Block diagram of greedy acquisition design. We set an original acquisition consisting of three SPGR and three DESS scans whose flip angles α_0 and repetition times $\mathbf{T}_{R,0}$ are respectively initialized randomly and minimally. We optimize the original acquisition subject to several constraints: $\alpha \in [1, 40]$ deg and $T_R \geq 11.8$ ms for SPGR; $\alpha \in [1, 60]$ deg and $T_R \geq 17.5$ ms for DESS; and $||\mathbf{T}_R||_1 \leq 263.7$ ms. We then seek to improve the acquisition by appending another SPGR or DESS scan and repeating (constrained) optimization. This process iterates until additional scans no longer improve estimation precision.

	$\boldsymbol{\alpha}^*$ (deg)	$\mathbf{T_R^*}$ (ms)
SPGR	$[38.1, 12.9, 9.2, 33.5]^\top$	$[50.2, 32.4, 16.4, 11.8]^\top$
DESS	$[32.0, 40.3, 52.9]^\top$	$[17.5, 98.0, 37.6]^\top$

Table 1: Flip angles α^* and repetition times $\mathbf{T_R^*}$ of SPGR and DESS scans optimized for MWF estimation precision under a total time constraint $||\mathbf{T_R}||_1 \le 263.7$ ms, selected to allow 9 SPGR and 9 DESS scans each at minimal T_R, similar to existing steady-state methods[5]. Remarkably, such scan combinations involving T_R variation can achieve better MWF estimation precision than fixed short-T_R acquisitions (Table 2), even though the latter can utilize more scans for a given time budget.
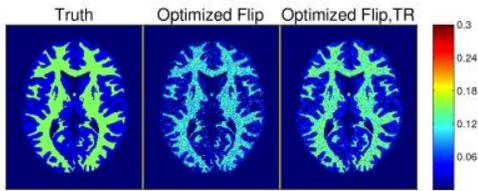
Figure 2: Estimated MWF maps in BrainWeb[10] simulation, compared to (*left*) ground truth. (*Center*) MWF estimates from a scan combination consisting of 9 SPGR and 9 DESS scans with optimized flip angle but fixed short repetition times. (*Right*) MWF estimate from a scan combination consisting of 4 SPGR and 3 DESS scans with optimized flip angles and repetition times (listed in Table 1). Both MWF maps are estimated via the same novel method based on KRR[8]. Voxels outside WM/GM regions are masked out for display. Colorbar range describes a relative signal fraction and is unitless.

	Truth	Optimized Flip	Optimized Flip,TR
WM	0.15	0.1104 ± 0.0294	0.1325 ± 0.0284
GM	0.03	0.0254 ± 0.0339	0.0330 ± 0.0209

Table 2: Sample means $\pm$ sample standard deviations of simulated MWF estimates (Figure 2), computed over 7810 WM-like and 9162 GM-like voxels. Scan combinations with variable repetition times admit MWF estimates with greater WM/GM accuracy and precision over combinations with short, fixed repetition times, even though the latter can use more scans for a given time budget.
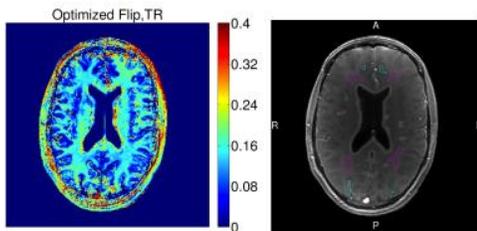
Figure 3: (*Left*) Myelin water fraction map in a healthy volunteer, estimated via a novel method based on kernel ridge regression[8] from fast CRB-optimized SPGR and DESS sequences. Colorbar range describes a relative signal fraction and is unitless. (*Right*) Manually selected WM (magenta) and GM (cyan) ROIs, overlaid on a representative (coil-combined SPGR) image. Within-ROI pooled sample means $\pm$ sample standard deviations are 0.121 ± 0.068 and 0.055 ± 0.094, computed over 725 WM and 176 GM voxels, respectively.