Published in final edited form as:

Magn Reson Med. 2020 October ; 84(4): 1977–1990. doi:10.1002/mrm.28259.

Myelin Water Fraction Estimation Using Small-Tip Fast Recovery MRI

Steven T. Whitaker¹, Gopal Nataraj², Jon-Fredrik Nielsen³, Jeffrey A. Fessler¹

¹Department of Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, Michigan, USA

²Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

³Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Purpose: To demonstrate the feasibility of an optimized set of small-tip fast recovery (STFR) MRI scans for rapidly estimating myelin water fraction (MWF) in the brain.

Methods: We optimized a set of STFR scans to minimize the Cramér-Rao Lower Bound (CRLB) of estimates of MWF. We evaluated the RMSE of MWF estimates from the optimized scans in simulation. We compared STFR-based MWF estimates (both modeling exchange and not modeling exchange) to multi-echo spin echo (MESE)-based estimates. We used the optimized scans to acquire in vivo data from which a MWF map was estimated. We computed the STFR-based MWF estimates using PERK, a recently developed kernel regression technique, and the MESE-based MWF estimates using both regularized non-negative least squares (NNLS) and PERK.

Results: In simulation, the optimized STFR scans led to estimates of MWF with low RMSE across a range of tissue parameters and across white matter and gray matter. The STFR-based MWF estimates that modeled exchange compared well to MESE-based MWF estimates in simulation. When the optimized scans were tested in vivo, the MWF map that was estimated using a three-compartment model with exchange was closer to the MESE-based MWF map.

Conclusion: The optimized STFR scans appear to be well-suited for estimating MWF in simulation and in vivo when we model exchange in training. In this case, the STFR-based MWF estimates are close to the MESE-based estimates.

Keywords

myelin water fraction (MWF); small-tip fast recovery (STFR); scan optimization; kernel ridge regression; machine learning

Correspondence: Steven T. Whitaker, 4125 EECS, 1301 Beal Ave, Ann Arbor, MI 48109, stwhit@umich.edu.

Supporting Information

Additional supporting information may be found online in the Supporting Information section.

1 | INTRODUCTION

Quantitative magnetic resonance imaging (QMRI) is the application of MRI to estimate parameters of interest. One QMRI application of growing interest is myelin water imaging, where one seeks quantitative maps of myelin water fraction (MWF) [1, 2]. The MWF is the proportion of MRI signal in a given voxel that originates from water bound within the myelin sheath. MWF maps are desirable for tracking progression of demyelinating diseases [2], e.g., multiple sclerosis [3].

The most widely accepted myelin water imaging techniques use the multi-echo spin echo (MESE) MRI scan (or variants) [3, 4, 5]. MESE is the standard for clinical MWF imaging to which alternative MWF mapping techniques are typically compared. However, MESE traditionally suffers from long scan times, impeding its routine clinical use. On the other hand, a combined gradient and spin echo (GRASE) MRI scan, a variant of MESE, has been shown to enable whole-brain MWF maps in under 8 minutes [6].

An alternative to MESE-based myelin water imaging uses faster, steady-state MRI scans [7] that can acquire whole-brain MWF maps in 7 minutes [6]. Despite evidence showing that this method produces reproducible MWF maps (thus enabling longitudinal studies), there are concerns about overestimating the true MWF [8, 9] and its precision [10]. Other steady-state methods have also been explored for MWF estimation, such as multi-echo gradient echo (GRE) [11, 12, 13] and dual-echo steady-state (DESS). [14, 15, 16].

To our knowledge, most of these myelin water imaging techniques ignore potential differences in the effective magnetic field experienced by myelin-bound water compared to water outside of myelin (an exception being [13]). However, it has been shown that in cerebral white matter, myelin-bound water does in fact experience a different effective magnetic field [17].

In preliminary work [18], we showed that modeling the additional off-resonance experienced by myelin water reduces the Cramér-Rao Lower Bound (CRLB) of estimates of MWF using small-tip fast recovery (STFR) MRI [19]. We showed that the STFR sequence is sensitive to the frequency differences, suggesting that the difference in off-resonance between myelin and non-myelin water is a potentially useful contrast mechanism containing information that can help estimate MWF [18]. Simulations using optimized STFR scan parameters led to MWF estimates with lower errors when there was a fixed, non-zero (but unknown) difference in off-resonance, compared to when there was no (still unknown) frequency difference. To our knowledge, this work was the first to specifically design scans for myelin water imaging that exploit frequency differences. Because the actual frequency difference is unknown and might vary between voxels or disease conditions, the proposed approach treats the difference as an unknown parameter that is estimated alongside other unknown parameters like the T_1 and T_2 values of the various tissue compartments.

One limitation of our previous work was its tissue model. In [18] we assumed a two-compartment, non-exchanging model for simplicity in computing the STFR signal. However, neglecting exchange can lead to biases in MWF estimates [20]. Therefore, the method proposed in this paper uses a three-compartment model. The three compartments are

myelin water, non-myelin water, and a macromolecular pool; myelin water and non-myelin water are in exchange, while myelin water exchanges with the macromolecular pool [21].

We previously estimated MWF from optimized STFR scans using parameter estimation via regression with kernels (PERK), a recently developed learning-based technique for parameter estimation in MRI that uses kernel ridge regression at its core [18, 22]. One alternative method for MWF estimation is non-linear least squares, which requires iterative methods for solving and can get stuck in a local minimum. Another alternative is dictionary search, which requires evaluating the STFR signal model on a discretized grid of the signal model parameters, which is impractical when the number of parameters exceeds three or four. Yet another alternative is to use a neural network. While neural networks can lead to good parameter estimates, they require a lot of training data and long training time. In contrast, PERK trains quickly and avoids the other problems associated with non-linear least squares and dictionary search. Therefore, this work again uses PERK.

This paper substantially builds upon our previous work. First, we re-optimize the STFR scan parameters to model variations of bulk off-resonance and to account for two spoiled gradient-recalled echo (SPGR) scans that are used for separate bulk off-resonance estimation. Next, we compare STFR-based MWF estimates to MESE-based MWF estimates in simulation. In particular, we estimate MWF from the optimized STFR scans with PERK [22] using a three-compartment tissue model with exchange. Finally, we compare our proposed STFR-based MWF estimation method to MESE-based MWF estimation in vivo. Figure 1 illustrates the proposed approach.

The organization of this paper is as follows. Section 1.1 provides background information on the scans used in this work (STFR and MESE), the scan design process, and PERK. Section 2 outlines our experiments, both for the STFR scan design and for MWF estimation in simulation and in vivo. Section 3 reports the experimental results. Section 4 discusses our results. Section 5 gives concluding remarks.

1.1 | Background

1.1.1 | STFR—One repetition of STFR [19] begins with an initial tip-down excitation with flip angle α . Then there is time T_{free} during which free precession occurs, after which there is a tip-up excitation (“fast recovery”) where magnetization is rotated up towards the +z-axis with flip angle β and phase ϕ . Finally there is gradient spoiling for time T_g . For a single compartment, the signal obtained at a given spatial location from a STFR scan is given by [23]

$$s_1(M_0, T_1, T_2, \Delta\omega, \kappa, T_{\text{free}}, T_g, \alpha, \beta, \phi) = \frac{M_0 \sin(\kappa\alpha) \left[e^{-T_g/T_1} (1 - e^{-T_{\text{free}}/T_1}) \cos(\kappa\beta) + (1 - e^{-T_g/T_1}) \right] e^{-T_{\text{free}}/(2T_2)} e^{-i\Delta\omega T_{\text{free}}/2}}{1 - e^{-T_g/T_1} e^{-T_{\text{free}}/T_2} \sin(\kappa\alpha) \sin(\kappa\beta) \cos(\Delta\omega \cdot T_{\text{free}} - \phi) - e^{-T_g/T_1} e^{-T_{\text{free}}/T_1} \cos(\kappa\alpha) \cos(\kappa\beta)}, \quad (1)$$

where M_0 is the equilibrium magnetization, T_1 and T_2 are the spin-lattice and spin-spin time constants, respectively, ω is the off-resonance frequency, and κ is a flip angle scaling constant (to account for differences between the prescribed and actual flip angles). Note that approximating flip angle error as a scale factor is accurate for the small flip angles used in

this work, but typically inaccurate at larger flip angles. STFR with $\beta = 0$ is the same as SPGR with $T_R = T_{\text{free}} + T_g$.

For myelin water imaging, more than one compartment must be modeled. In a two-compartment model, one compartment consists of spins within myelin (myelin water), and the other compartment consists of other spins (non-myelin water). If one neglects exchange, then the STFR signal at a given spatial location is the weighted sum of the single-compartment STFR signals of the individual compartments:

$$\begin{aligned} s_2(M_0, f_f, T_{1,f}, T_{1,s}, T_{2,f}, T_{2,s}, \Delta\omega_f, \Delta\omega, \kappa, T_{\text{free}}, T_g, \alpha, \beta, \phi) = & f_f \\ & \cdot s_1(M_0, T_{1,f}, T_{2,f}, \Delta\omega + \Delta\omega_f, \kappa, T_{\text{free}}, T_g, \alpha, \beta, \phi) + (1 - f_f) \\ & \cdot s_1(M_0, T_{1,s}, T_{2,s}, \Delta\omega, \kappa, T_{\text{free}}, T_g, \alpha, \beta, \phi), \end{aligned} \quad (2)$$

where the weight f_f is the myelin water fraction (MWF), $T_{1,f}$ and $T_{2,f}$ are the T_1 and T_2 time constants for the fast-relaxing, myelin water compartment, $T_{1,s}$ and $T_{2,s}$ are the T_1 and T_2 time constants for the slow-relaxing, non-myelin water compartment, and ω_f is the additional off-resonance that is experienced only by myelin water [17].

Although (2) has a convenient analytical expression, a more accurate tissue model for cerebral white matter consists of three compartments (non-myelin water, myelin water, and a macromolecule water pool) with exchange between the non-myelin and myelin water compartments and from the myelin water compartment to the macromolecule compartment [21]. In this case, the STFR signal is also a function of the macromolecule compartment volume fraction f_m , the macromolecule compartment $T_{1,m}$ and $T_{2,m}$, the residence time for exchange from myelin water to non-myelin water $\tau_{f \rightarrow s}$, and the residence time for exchange from myelin water to the macromolecule compartment $\tau_{f \rightarrow m}$, in addition to the previously mentioned parameters. We assume the myelin water and non-myelin water compartments are in chemical equilibrium, which means that $f_f \tau_{s \rightarrow f} = (1 - f_f - f_m) \tau_{f \rightarrow s}$, and we assume there is no other exchange, i.e., $\tau_{m \rightarrow f} = \tau_{s \rightarrow m} = \tau_{m \rightarrow s} = \infty$ [21]. Because of exchange, the STFR signal no longer has an analytical expression and must be computed using the Bloch-McConnell equation [24].

1.1.2 | MESE—One repetition of MESE [25] consists of an initial excitation with flip angle α_{ex} (typically 90°) followed by a sequence of N_{ref} refocusing excitations with flip angle α_{ref} (typically 180°). The signal is sampled at times $T_E, 2T_E, \dots, N_{\text{ref}}T_E$ after the initial excitation, resulting in N_{ref} images in one MESE scan. The repetition time T_R is typically chosen to be long enough so that the net magnetization of the spins is in equilibrium prior to each repetition. Thus, the MESE signal is a function of α_{ex} , α_{ref} , T_E , and T_R , as well as the same tissue parameters as the STFR signal; but if T_R is sufficiently long there is little dependence on T_1 (of any compartment). Additionally, for myelin water imaging using MESE, normally the acquired MESE signal is modeled as a weighted sum of MESE signals from individual compartments, i.e., ignoring exchange between compartments. When ignoring exchange, we computed the MESE signal using the extended phase graph (EPG) method [26]. When accounting for exchange, we used Bloch-McConnell simulation.

1.1.3 | Scan Design Using the Cramér-Rao Lower Bound—MR image data for a single voxel in a single scan is often modeled as

$$y = f(\mathbf{x}, \mathbf{v}, \mathbf{p}) + \epsilon, \quad (3)$$

where $f(\mathbf{x}, \mathbf{v}, \mathbf{p}) \in \mathbb{C}$ is the MR signal that is a function of unknown parameters $\mathbf{x}$, known parameters $\mathbf{v}$, and scan parameters $\mathbf{p}$; and $\epsilon \sim \mathbb{C}\mathcal{N}(0, \sigma^2)$ is additive complex Gaussian noise. When there are D scans then the data for a single voxel across each scan is collected into a vector:

$$\mathbf{y} = \mathbf{f}(\mathbf{x}, \mathbf{v}, \mathbf{P}) + \boldsymbol{\epsilon}, \quad (4)$$

where $\mathbf{y} \in \mathbb{C}^D$, $\mathbf{f}(\mathbf{x}, \mathbf{v}, \mathbf{P}) = [f_1(\mathbf{x}, \mathbf{v}, \mathbf{p}_1), \dots, f_D(\mathbf{x}, \mathbf{v}, \mathbf{p}_D)]^T$, f_d is the signal given by the d th scan for $d = 1, \dots, D$, $\mathbf{P} = (\mathbf{p}_1, \dots, \mathbf{p}_D)$ denotes the collection of all scan parameters, and the noise vector is $\epsilon \sim \mathbb{C}\mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma})$. We assume that each scan has noise independent of the other scans, and we assume that each scan has the same noise variance σ^2 ; thus $\boldsymbol{\Sigma} = \sigma^2 \mathbf{I}_D$, where $\mathbf{I}_D$ is the $D \times D$ identity matrix.

For simplicity in computing the Fisher information matrix (see below), we further assume that the MR signal model f is real-valued. We also take the magnitude of the received signal y , resulting in a Rician distributed signal [27]; however, we assume sufficiently high SNR so that this magnitude signal is approximately normally distributed with mean $f(\mathbf{x}, \mathbf{v}, \mathbf{p})$ and variance σ^2 .

Under these assumptions, the Fisher information matrix for the magnitude of signal model (4) is [28]

$$\mathbf{I}(\mathbf{x}, \mathbf{v}, \mathbf{P}) = \frac{1}{\sigma^2} (\nabla_{\mathbf{x}} \mathbf{f}(\mathbf{x}, \mathbf{v}, \mathbf{P}))^T (\nabla_{\mathbf{x}} \mathbf{f}(\mathbf{x}, \mathbf{v}, \mathbf{P})), \quad (5)$$

where $\nabla_{\mathbf{x}}$ denotes a row gradient with respect to the unknown parameters $\mathbf{x}$. The inverse Fisher information matrix gives the Cramér-Rao Lower Bound (CRLB) for unbiased estimators [29]. In particular, the variance of an unbiased estimator for the i th unknown parameter x_i has a lower bound given by the i th diagonal element of the inverse Fisher information matrix, i.e., $\text{var}(\hat{x}_i) \geq [(\mathbf{I}(\mathbf{x}, \mathbf{v}, \mathbf{P}))^{-1}]_{i,i}$. This bound on the precision of unbiased estimators is useful for optimizing experimental designs. The CRLB has been used to optimize MR sequence parameters for a variety of pulse sequences and applications, e.g., [22, 30, 31, 32]. In this work, we optimize scan parameters of a set of D STFR scans for MWF estimation by minimizing an expected weighted sum of the CRLB for each unknown parameter [33]:

$$\hat{\mathbf{P}} = \arg \min_{\mathbf{P} \in \mathcal{P}} \mathbb{E}_{\mathbf{x}, \mathbf{v}} [\text{trace}(\mathbf{W}(\mathbf{I}(\mathbf{x}, \mathbf{v}, \mathbf{P}))^{-1})], \quad (6)$$

where $\mathcal{P}$ denotes the scan parameter search space, $\mathbb{E}_{\mathbf{x}, \mathbf{v}}$ denotes an expectation over $\mathbf{x}$ and $\mathbf{v}$, and $\mathbf{W}$ is a diagonal weighting matrix used to indicate the relative importance of precisely estimating the different unknown parameters.

1.1.4 | Parameter Estimation via Regression with Kernels (PERK)—This section describes the PERK method we use to estimate MWF from STFR scans. Suppose a set of scan parameters $\mathbf{P}$ is given, typically the $\hat{\mathbf{P}}$ from the scan design process (6). We seek to estimate unknown parameters $\mathbf{x}$ after acquiring data using the D scans corresponding to these scan parameters. We generate training data by simulating data $\mathbf{y}_n$ via (4) with appropriate signal models $\mathbf{f}$ for various values of unknown and known parameters $\mathbf{x}_n$ and $\mathbf{v}_n$; these N training data points are collected as $(\mathbf{q}_1, \mathbf{x}_1), \dots, (\mathbf{q}_N, \mathbf{x}_N)$, where $\mathbf{q}_n = [|\mathbf{y}_n|^T, \mathbf{v}_n^T]^T$ and $|\cdot|$ denotes element-wise complex modulus. After scanning (with the scan parameters $\mathbf{P}$), we have test data $\mathbf{q}$ for each voxel (where $\mathbf{v}$ collects separately estimated parameters, such as B1+ maps, that are treated as known values), and we want to estimate $\mathbf{x}$. PERK computes estimates via regularized linear regression (ridge regression), after first transforming the feature vectors $\mathbf{q}$ (for both training and testing) via some user-defined feature map (which is never directly used but is indirectly specified through the choice of kernel function). The PERK estimator is [22]

$$\hat{\mathbf{x}}(\mathbf{q}) = \frac{1}{N} \mathbf{X} \mathbf{1}_N + \mathbf{X} \mathbf{M} (\mathbf{M} \mathbf{K} \mathbf{M} + N \rho \mathbf{I}_N)^{-1} \mathbf{k}(\mathbf{q}), \quad (7)$$

where $\mathbf{X} = [\mathbf{x}_1, \dots, \mathbf{x}_N]$ denotes all of the training data, $\mathbf{1}_N \in \mathbb{R}^N$ is a vector of all ones, $\mathbf{M} = \mathbf{I}_N - \frac{1}{N} \mathbf{1}_N \mathbf{1}_N^T$ is a de-meaning operator, ρ is a regularization parameter, the Gram matrix $\mathbf{K} \in \mathbb{R}^{N \times N}$ has entries $K_{ij} = k(\mathbf{q}_i, \mathbf{q}_j)$, where $\mathbf{k}(\mathbf{q}) = [k(\mathbf{q}, \mathbf{q}_1), \dots, k(\mathbf{q}, \mathbf{q}_N)]^T - \frac{1}{N} \mathbf{K} \mathbf{1}_N$, and $k(\mathbf{q}, \mathbf{q}')$ is the user-specified kernel function. In this work, we used the Gaussian kernel

$$k(\mathbf{q}, \mathbf{q}') \triangleq \exp\left(-\frac{1}{2} \mathbf{\Lambda}^{-1} (\mathbf{q} - \mathbf{q}')^2\right), \quad (8)$$

where $\mathbf{\Lambda}$ is a positive definite weighting matrix. PERK with a Gaussian kernel corresponds to first transforming the feature vectors $\mathbf{q}$ via a nonlinear feature map into infinite-dimensional features, and then applying ridge regression on the transformed features. This lifting of features to a higher-dimensional space improves the ability to capture the nonlinear dependence of the signal on the unknown parameters we wish to estimate.

To reduce storage and computational needs, we approximated (7) using random Fourier features [22, 34].

2 | METHODS

This section describes the experiments performed in this work. We first explain the scan design process for optimizing a set of STFR scans for MWF estimation. We then explain simulated MWF estimation experiments that compare our proposed method to MESE-based MWF estimation. Finally, we explain an experiment to test our proposed method in vivo. The code for reproducing the methods and results in this paper is available at <https://github.com/StevenWhitaker/STFR-MWF>.

The raw data is available at <https://doi.org/10.7302/nw6e-1d66>.

2.1 | Scan Design

For the STFR scan design, we computed the CRLB using the two-compartment non-exchanging signal model (2). We chose the weighting matrix $\mathbf{W}$ to place full weight on the CRLB for f_f (i.e., the diagonal entries of $\mathbf{W}$ were all 0 except for a 1 in the location corresponding to f_f). We took the flip angle scaling κ and bulk off-resonance ω to be known, i.e., part of $\mathbf{v}$, and we optimized a set of $D = 11$ STFR scans. Two of these scans were SPGR scans with fixed scan parameters and an echo time shift. We included these scans to enable the option of estimating ω using conventional techniques and then treat ω as known for further parameter estimation.

We fixed $T_g = 2.8$ ms across all 11 scans. We fixed $\alpha = 5^\circ$ and $T_{\text{free}} = 10.3$ ms for the two SPGR scans. The T_E of each STFR scan and the first SPGR scan was 4 ms. The echo time shift between the two SPGR scans was 2.3 ms. For the remaining nine STFR scans, we fixed $T_{\text{free}} = 8$ ms and we constrained $\alpha \in [1, 15]^\circ$, $\beta \in [0, 15]^\circ$, and $\phi \in [-180, 180]^\circ$.

The expectation in (6) requires choices for the probability distributions of the unknown and known parameters. Table 1 shows the distributions we used. To explore the effect that the additional myelin water off-resonance ω_f has on the CRLB of f_f , we performed one scan design (design A) where we took ω_f to be unknown, and another (design B) where we ignored ω_f (i.e., we assumed it was known and equal to 0). To solve the optimization in (6), we used the NLOpt package¹ in the Julia programming language².

2.2 | MWF Estimation

For MWF estimation, we compared several estimation protocols. The proposed method, which we call STFR3-PERK, uses PERK to estimate MWF from the optimized STFR scans, with training data generated using the three-compartment exchanging model. This method assumes bulk off-resonance ω and flip angle scaling κ are known (unless otherwise noted). Another method, STFR2-PERK, is the same as STFR3-PERK, except training data is generated using the two-compartment non-exchanging model. Again, ω and κ are assumed known. The reference method, MESE-NNLS, uses regularized NNLS to estimate MWF from a MESE scan. Following [5], we fit 40 different T_2 components spaced logarithmically from 15 ms to 2000 ms, and computed MWF as the proportion of signal coming from components with $T_2 \leq 40$ ms to the total signal. This method does not assume knowledge of ω or κ , but jointly estimates κ . A fourth method, MESE-PERK, estimates MWF from a MESE scan using PERK, with training data generated using the three-compartment exchanging model. This method was included to determine whether performance differences were due to the estimation method (i.e., NNLS versus PERK), or due to the scans (i.e., MESE versus STFR). MESE-PERK does not assume knowledge of ω or κ . Finally, because the proposed STFR3-PERK assumes ω and κ are known, whereas the reference MESE-NNLS does not, we compared a fifth method, STFR3-PERK-JE, that is the same as STFR3-PERK except ω and κ are assumed unknown. Table 1 shows the training ranges for the methods that use PERK.

¹<https://github.com/JuliaOpt/NLOpt.jl>

²<https://julialang.org/>

The methods that use PERK require specifying the regularization parameter ρ and the positive definite matrix $\mathbf{A}$ in the Gaussian kernel. For the Gaussian kernel, to eliminate dependence on scale we set $\mathbf{A} = \lambda \text{diag}(\mathbf{m}_{|q|})$, where λ is a regularization parameter and $\mathbf{m}_{|q|}$ denotes the sample average across all voxels of the magnitude test data $|q|$, where q collects the magnitude STFR signals $|y|$ and the known parameters $\mathbf{v}$ (see §1.1.4). We chose $\rho = 2^{-60}$ and $\lambda = 2^{3.5}$ for the regularization parameters, which we tuned using a holdout process described in [22, Sect. S.II].

| Numerical Simulation—We compared the two optimized sets of STFR scans to validate the scan design process. We simulated test data using the two-compartment non-exchanging STFR signal model (2) using the range of tissue parameters over which the scans were optimized (to match the scan design assumptions), and we estimated MWF using STFR2-PERK. We measured the root mean square error (RMSE) of the MWF estimates versus the additional myelin water off-resonance ω_f for three cases: first, using design B and training data that ignored ω_f (i.e., all training points had $\omega_f = 0$); second, using design B and training data that accounted for ω_f ; and third, using design A and training data that accounted for ω_f . Section S1 of the Supporting Information describes another experiment where test data was generated using the two-compartment model with fixed white matter and gray matter tissue values (see Table 1).

Next, we investigated the effects of exchange and compared STFR-based MWF estimates to MESE-based estimates. We simulated STFR scans using design A and a MESE scan using $\alpha_{\text{ex}} = 90^\circ$, $\alpha_{\text{ref}} = 180^\circ$, $N_{\text{ref}} = 32$, $T_E = 10$ ms, and $T_R = 1200$ ms. We simulated test data using the three-compartment model with exchange and tissue parameters corresponding to white matter and gray matter (see Table 1). Additionally, we chose bulk off-resonance ω values to vary from -30 to 30 Hz and κ values to vary from 0.8 to 1.2 . We compared MWF estimates from each of the aforementioned methods (STFR3-PERK, STFR2-PERK, MESE-NNLS, MESE-PERK, and STFR3-PERK-JE). For these simulations we added complex Gaussian noise corresponding to a SNR in white matter ranging from 7 – 28 across the STFR scans and from 2 – 122 across the 32 MESE echoes (to match the SNR of the in vivo data), where SNR was calculated by dividing the white matter signal mean by the noise standard deviation.

The proposed method (STFR3-PERK) uses a model that matches the model used to generate the test data in the previous experiment. To investigate the effects of model mismatch, we repeated the previous experiment using a nine-compartment tissue model with exchange for the test data. The nine compartments were created by splitting each of the three compartments in the three-compartment model into three sub-compartments. For example, the myelin water compartment with fraction f_f and relaxation time $T_{2,f}$ was split into three compartments with fractions $0.5f_f$, $0.25f_f$, and $0.25f_f$ and relaxation times $T_{2,f}$, $0.8T_{2,f}$, and $1.2T_{2,f}$. Section S2 of the Supporting Information repeats this experiment for a four-compartment model with exchange and a three-compartment model without exchange.

| In Vivo Experiments—Under an IRB-approved protocol, we scanned a healthy volunteer to compare the proposed STFR-based MWF estimation to MESE-based MWF estimation. We used 3D acquisitions for both the STFR and MESE scans to avoid slice

profile effects. The STFR scans used design A, and the RF pulses had time-bandwidth product of 8 and duration of 1 ms; the two SPGR scans took 58 s and the nine STFR scans took 3 min 36 s for a total scan time of 4 min 34 s. We also acquired a pair of Bloch-Siegert (BS) scans for separate estimation of κ [36]; the excitation RF pulse of these scans had time-bandwidth product of 8 and duration of 1 ms, and used ± 4 kHz off-resonant Fermi pulses between excitation and readout. The total duration of the BS scans was 2 min 40 s. Therefore, our overall STFR-based MWF estimation scan protocol lasted 7 min 14 s. For the MESE scan, we used the same scan parameters as in simulation (described above); the initial excitation RF pulse had time-bandwidth product of 6, duration of 3 ms, and slab thickness of 0.9 cm, and each refocusing pulse had time-bandwidth product of 2, duration of 2 ms, and slab thickness of 2.1 cm. Each refocusing pulse was also flanked with crusher gradients, each of which imparted 14 cycles of phase across the imaging volume. The total duration of the MESE scan was 36 min 11 s. For all scans, we acquired a $22 \times 22 \times 0.99$ cm³ field of view (FOV) with matrix size $200 \times 200 \times 9$ (except the BS scans used matrix size $200 \times 50 \times 9$). We implemented the protocol in TOPPE [37].

We used a GE Discovery™ MR750 3.0T scanner with a 32-channel Nova Medical® head coil. We used conventional inverse FFT reconstruction followed by square-root of sum-of-squares coil combination to make the magnitude images used for MWF estimation. We estimated the SNR in the white matter brain regions (pooling the four white matter regions of interest (ROIs) in Supporting Information Figure S1 for each scan/echo) to vary from 8–17 across the STFR scans and from 6–73 for across MESE echoes.

We analyzed the center slice of the acquired data. We estimated MWF using STFR3-PERK, STFR2-PERK, MESE-NNLS, and MESE-PERK. In this case, for STFR3-PERK and STFR2-PERK we took bulk off-resonance ω_f to be unknown (but still assumed κ to be known).

3 | RESULTS

3.1 | Scan Design

Table 2 reports the two optimized scan design parameters. For design A, the additional myelin water off-resonance ω_f was taken to be unknown and distributed uniformly from 5 to 35 Hz. For design B, ω_f was ignored (i.e., taken to be known and equal to 0).

Figure 2 compares the expected CRLB of the standard deviation of MWF of these two scan designs versus ω_f , where at each data point ω_f is fixed (unlike the other parameters that vary according to the distributions in Table 1) but still unknown, i.e., is contained in $\mathbf{x}$ (see §1.1.3). For these CRLB calculations, we used a noise standard deviation that corresponds to SNR ranging from 9–15 in white matter across the STFR scans to match the SNR of the 1.1 mm isotropic in vivo data. Figure 2 shows that modeling ω_f improves the precision of the optimized scan design, and that MWF becomes easier to estimate as ω_f increases.

3.2 | MWF Estimation

Numerical Simulation—We computed the RMSE of MWF estimates for test data generated using (2) with different values of ω_f and a range of tissue parameters. For design

A, we estimated MWF using training data that was generated with a range of ω_f values. For design B, in one experiment we estimated MWF using training data that was generated with a range of ω_f , and in another experiment the training data included only $\omega_f = 0$. Figure 3 shows the results. The mean MWF value in the test data was 0.17, so the minimum RMSE of 0.045 corresponds to about 26% relative error. Supporting Information Figure S2 reports an analogous experiment using fixed white matter and gray matter tissue values.

Furthermore, we investigated the effects of exchange on MWF estimates. We simulated STFR scans (using design A) and a MESE scan, and we used the three-compartment tissue model with exchange using tissue parameters corresponding to white matter and gray matter. We estimated MWF using STFR2-PERK, STFR3-PERK, MESE-NNLS, MESE-PERK, and STFR3-PERK-JE. Table 3 shows the RMSEs, means, and standard deviations of the MWF estimates. Figure 4 shows the ground truth map and a visual comparison of the estimated MWF maps. Figure 5 shows the results of this experiment when using a nine-compartment exchanging model. Supporting Information Figures S3 and S4 show results when using a four-compartment exchanging model and a three-compartment non-exchanging model, respectively. The anatomy for the simulated data used in these experiments came from BrainWeb [38].

| In Vivo Experiments—We scanned a healthy volunteer using scan design A. Supporting Information Figure S5 shows images of the two SPGR and nine STFR scans of the subject. In the same scan session, we also scanned the volunteer with a MESE scan. Figure 6 shows MWF maps that were computed from the STFR and MESE scans. In this case, we made the STFR-based MWF estimates without using a separately estimated ω map because the MWF estimates made with the separately estimated ω map exhibited spatial variation that mimicked the field map spatial variations, which we do not expect in MWF maps (i.e., we expect myelin content to be independent of ω). Table 4 shows numerical results for the in vivo data for several ROIs.

4 | DISCUSSION

Almost all of the optimized flip angles α and β for both scan designs A and B are equal to (or are very close to) the upper constraint, and there is a wide spread of tip-up phases (see Table 2). This seems to suggest that most of the information needed for estimating MWF lies in the phase accrual that occurs between the tip-down and tip-up excitations, so the flip angles should be chosen to maximize SNR. Interestingly, however, an unreported experiment showed that a scan design with flip angles set to 15° and with an even spread of tip-up phases ϕ resulted in CRLBs that were many orders of magnitude worse than the optimized scans. This result emphasizes the importance of the scan design process in choosing scan parameters, because these optimized parameters are robust across a range of ω_f values (see Figure 2). We also looked at optimized scan parameters when fixing T_{free} to 6 ms. We found that the tip-up phases still covered a spread of values, but the range of phases was slightly smaller, which makes sense because a smaller T_{free} leads to less off-resonance precession.

The expected CRLB for scan design A is better than that of design B when compared across many values of the additional myelin water ω_f (see Figure 2), as expected because the

optimization of design B ignored the presence of ω_f . Figure 2 also illustrates the impact that ω_f has on estimates of MWF; MWF becomes harder to estimate as ω_f approaches 0. These findings appear to be at variance with the findings in [39], where in multi-GRE MWF estimation modeling ω_f led to worse estimates at 3T. However, there is likely more information about ω_f in the STFR scans because of the optimized tip-up phases, which could explain why modeling ω_f in this work improved MWF estimation.

Simulated test data showed that scan design A and scan design B gave similarly good estimates of MWF across many values of ω_f , at least for a range of tissue parameters (see Figure 3). At first glance, one may be surprised that design A performed noticeably better than design B with respect to the expected CRLB, and yet the two designs had similar RMSE values. One may also be surprised that the RMSE values were relatively small (about 25% of the mean MWF value) even though the expected CRLB predicted errors of 100% or more. However, PERK is a Bayesian estimator; thus, the unbiased CRLB does not necessarily predict the precision of MWF estimates computed by PERK. We minimized the unbiased CRLB during scan design because of its simplicity, but recognize that other objective functions for scan optimization may be better suited for MWF estimates from PERK or other Bayesian estimation methods. We investigated the effect of bias in Section S3 of the Supporting Information.

Simulated test data also shows that STFR-based myelin water imaging compares well to MESE-based approaches. Compared to the conventional MESE-NNLS, STFR3-PERK gives more accurate results in simulated white matter voxels, in addition to reducing estimation time by more than an order of magnitude (see Table 3). This result is interesting because the simulated MESE echoes generally had much higher SNR than the STFR scans. Combining MESE with PERK improves upon the NNLS results. However, the MESE scan is longer than the combined time of all the STFR and BS scans. Furthermore, MWF estimation using MESE-PERK takes longer than STFR3-PERK because when simulating the MESE signal one must simulate a collection of spins to account for stimulated echoes, which is not necessary for STFR. This simulated data also shows that ignoring exchange when estimating MWF with STFR scans results in drastically overestimated MWF values (see Figure 4), so it is essential to generate training data that accounts for exchange. These same results hold even when the test data was generated using a nine-compartment exchanging model (see Figure 5). See Section S2 of the Supporting Information for results using a four-compartment exchanging model and a three-compartment non-exchanging model.

The in vivo MWF estimates in Figure 6 further emphasize the importance of modeling exchange. The MWF map given by STFR2-PERK has higher MWF values than the map given by STFR3-PERK. The three-compartment model led to maps that better agreed with the MWF maps estimated from MESE data. Table 4 indicates that in all white matter ROIs the STFR3-PERK estimates are within one standard deviation of the mean MESE-NNLS estimates. In gray matter it is different; however, this difference could be due to how the STFR training data were simulated, as typical values for gray matter $T_{1,f}$ and $T_{1,s}$ are slightly outside of the range of values generated for training. Figure 6 and Table 4 also demonstrate the effect that the estimation method has on MWF estimates: the MESE-PERK estimates have decreased standard deviation compared to the MESE-NNLS estimates.

Furthermore, Table 4 demonstrates that STFR-based MWF estimates have lower standard deviation than MESE-based MWF estimates, despite the MESE scans being 4× longer than the STFR scans.

For the in vivo data, we did not use a separately acquired bulk off-resonance ω map as a known parameter for our proposed STFR-based MWF estimation technique, even though the scan design and simulations assumed that ω was known. When we attempted to use the separately acquired ω map for the in vivo data, the MWF estimates appeared to be more biased in regions with high ω values. Further work is needed to investigate this behavior.

For the in vivo data we acquired a 9 mm slab in about 7 minutes total scan time with 1.1 mm isotropic resolution. Whole brain coverage would require 4 times as much data (with 2 mm slices), so our proposed approach would take about 28 minutes, which is longer than the 8 minutes achieved by the GRASE method. However, in [6] the authors under-sampled the GRASE data by a factor of 4, whereas we acquired fully sampled data. By under-sampling by the same factor the proposed STFR approach would achieve whole-brain coverage in about 7 minutes.

5 | CONCLUSION

This work optimized a set of STFR scans that can be used to estimate MWF. We found that estimates of MWF are more precise for larger values of the frequency difference ω_f between myelin water and non-myelin water. Fortunately, in white matter reported values of ω_f that are far enough away from 0 to aid estimation of MWF [17]. We also found that modeling exchange (i.e., using a more accurate tissue model) greatly impacts the MWF estimates from STFR scans. When modeling exchange, STFR with PERK yields MWF estimates that are comparable to MESE-based MWF estimates.

This is the first work to compare STFR-based MWF estimation to MESE-based MWF estimation. Additionally, to our knowledge, this is the first work to generate MWF estimates from a MESE scan using PERK. While this estimation method was not the main point of this paper, it illustrates another potential method for MWF estimation.

This study was a proof-of-concept study to see if STFR could be applied to estimating MWF. As such, only a single healthy volunteer was scanned. While the initial comparison of STFR to MESE is promising, future studies should compare the two methods across multiple volunteers. Additionally, our proposed MWF estimation method should be validated in pathology to verify that it can detect, e.g., multiple sclerosis lesions. Such verification is especially important because the proposed method assumes a fixed number of tissue compartments, which may or may not inhibit its sensitivity to anomalies.

There are several ways in which the scan design process could be further explored. Our choice to optimize nine STFR scans for scan design was somewhat arbitrary, so one could explore different numbers of scans to see how the CRLB is affected for a given scan time budget. Additionally, one could change the space of scan parameters over which to optimize; especially interesting would be to increase the upper bound on α and β to see if the optimized scans would have a greater variety of flip angles. Another route to explore is to

adjust the weighting matrix $\mathbf{W}$ to optimize STFR scans for estimating other parameters in addition to or instead of MWF. In particular, since the results here suggest that the STFR scans are sensitive to the effects of exchange, it could be interesting to optimize STFR scan design for quantifying exchange parameters. Additionally, future work could explore what parameters to include as known parameters versus unknown parameters, in both the scan design and in PERK.

Finally, to reduce the scan time of the STFR scans, either to allow for more scans or to reduce scan time, one could under-sample the MRI k-space data. The image reconstruction would then be under-determined, thus requiring some sort of regularized reconstruction. Methods that jointly reconstruct all D scans at once would be a natural approach, e.g., [40, 41].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

We thank Scott Swanson for discussions of exchange, and Mingjie Gao for discussions of scan optimization. We also thank Navid Seraji-Bozorgzad for discussion of in vivo results, and the reviewers for comments that improved the paper.

Funding information

Supported in part by NIH Grant R21 AG061839

References

- [1]. Alonso-Ortiz E, Levesque IR, Pike GB. MRI-based myelin water imaging: A technical review. *Mag Res Med* 2015 1;73(1):70–81.
- [2]. West KL, Kelm ND, Carson RP, Gochberg DF, Ess KC, Does MD. Myelin volume fraction imaging with MRI. *Neuroimage* 2018 11;182:511–21. [PubMed: 28025129]
- [3]. Mackay A, Whittall K, Adler J, Li D, Paty D, Graeb D. In vivo visualization of myelin water in brain by magnetic resonance. *Mag Res Med* 1994 6;31(6):673–7.
- [4]. Prasloski T, Rauscher A, MacKay AL, Hodgson M, Vavasour IM, Laule C, et al. Rapid whole cerebrum myelin water imaging using a 3D GRASE sequence. *NeuroImage* 2012 10;63(1):533–9. [PubMed: 22776448]
- [5]. Prasloski T, Mädler B, Xiang QS, MacKay A, Jones C. Applications of stimulated echo correction to multicomponent T2 analysis. *Mag Res Med* 2012 6;67(6):1803–14.
- [6]. Zhang J, Vavasour I, Kolind S, Baumeister B, Rauscher A, MacKay AL. Advanced myelin water imaging techniques for rapid data acquisition and long T2 component measurements. In: *Proc. Intl. Soc. Mag. Res. Med.*; 2015 p. 824 <http://cds.ismrm.org/protected/15MPresentations/abstracts/0824.pdf>.
- [7]. Deoni SCL, Rutt BK, Arun T, Pierpaoli C, Jones DK. Gleaning multicomponent T1 and T2 information from steady-state imaging data. *Mag Res Med* 2008 12;60(6):1372–87.
- [8]. Zhang J, Kolind SH, Laule C, MacKay AL. Comparison of myelin water fraction from multiecho T2 decay curve and steady-state methods. *Mag Res Med* 2015 1;73(1):223–32.
- [9]. West DJ, Teixeira RPAG, Wood TC, Hajnal JV, Tournier JD, Malik SJ. Inherent and unpredictable bias in multi-component DESPOT myelin water fraction estimation. *NeuroImage* 2019 7;195(1):78–88. [PubMed: 30930311]

- [10]. Lankford CL, Does MD. On the inherent precision of mcDESPOT. *Mag Res Med* 2013 1;69(1):127–36.
- [11]. Hwang D, Kim DH, Du YP. In vivo multi-slice mapping of myelin water content using T2* decay. *NeuroImage* 2010 8;52(1):198–204. [PubMed: 20398770]
- [12]. Lenz C, Klarhöfer M, Scheffler K. Feasibility of in vivo myelin water imaging using 3D multigradient-echo pulse sequences. *Magnetic resonance in medicine* 2012 8;68(2):523–8. [PubMed: 22213038]
- [13]. Nam Y, Lee J, Hwang D, Kim DH. Improved estimation of myelin water fraction using complex model fitting. *NeuroImage* 2015 3;116:214–221. [PubMed: 25858448]
- [14]. Nataraj G, Nielsen JF, Fessler JA. Myelin water fraction estimation from optimized steady-state sequences using kernel ridge regression. In: *Proc. Intl. Soc. Mag. Res. Med.*; 2017 p. 5076.
- [15]. Nataraj G, Nielsen JF, Gao M, Fessler JA. Fast, precise myelin water quantification using DESS MRI and kernel learning; 2018.
- [16]. Nataraj G, Gao M, Nielsen JF, Fessler JA. Kernel regression for fast myelin water imaging. In: *ISMRM Workshop on Machine Learning Part 2*; 2018 p. 65.
- [17]. Miller KL, Smith SM, Jezzard P. Asymmetries of the balanced SSFP profile. Part II: White matter. *Mag Res Med* 2010 2;63(2):396–406.
- [18]. Whitaker ST, Nataraj G, Gao M, Nielsen JF, Fessler JA. Myelin water fraction estimation using small-tip fast recovery MRI. In: *Proc. Intl. Soc. Mag. Res. Med.*; 2019 p. 4403 <https://index.mirasmart.com/ISMRM2019/PDFfiles/4403.html>.
- [19]. Nielsen JF, Yoon D, Noll DC. Small-tip fast recovery imaging using non-slice-selective tailored tip-up pulses and radiofrequency-spoiling. *Mag Res Med* 2013 3;69(3):657–66.
- [20]. Harkins KD, Dula AN, Does MD. Effect of intercompartmental water exchange on the apparent myelin water fraction in multiexponential T2 measurements of rat spinal cord. *Mag Res Med* 2012 3;67(3):793–800.
- [21]. Stanisz GJ, Kecojevic A, Bronskill MJ, Henkelman RM. Characterizing white matter with magnetization transfer and T2. *Mag Res Med* 1999 12;42(6):1128–36.
- [22]. Nataraj G, Nielsen JF, Scott CD, Fessler JA. Dictionary-free MRI PERK: Parameter estimation via regression with kernels. *IEEE Trans Med Imag* 2018 9;37(9):2103–14.
- [23]. Sun H, Fessler JA, Noll DC, Nielsen JF. Steady-state functional MRI using spoiled small-tip fast recovery (STFR) imaging. *Mag Res Med* 2015 2;73(2):536–43.
- [24]. McConnell HM. Reaction rates by nuclear magnetic resonance. *J of Chemical Phys* 1958 3;28(3):430–31.
- [25]. Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. *Phys Rev* 1954 5;94(3):630–8.
- [26]. Hennig J Multiecho imaging sequences with low refocusing flip angles. *J Mag Res* 1988 7;88(3):397–407.
- [27]. McGibney G, Smith MR. An unbiased signal-to-noise ratio measure for magnetic resonance images. *Med Phys* 1993 7;20(4):1077–8. [PubMed: 8413015]
- [28]. Nataraj G, Nielsen JF, Fessler JA. Optimizing MR scan design for model-based T1, T2 estimation from steady-state sequences. *IEEE Trans Med Imag* 2017 2;36(2):467–77.
- [29]. Kay SM. *Fundamentals of statistical signal processing: Estimation theory*. New York: Prentice-Hall; 1993.
- [30]. Jones JA, Hodgkinson P, Barker AL, Hore PJ. Optimal sampling strategies for the measurement of spin-spin relaxation times. *J Mag Res B* 1996 10;113(1):25–34.
- [31]. Voigt T, Nehrke K, Doessel O, Katscher U. T1 corrected B1 mapping using multi-TR gradient echo sequences. *Mag Res Med* 2010;64(3):725–33.
- [32]. Asslander J, Lattanzi R, Sodickson DK, Cloos MA. Optimized quantification of spin relaxation times in the hybrid state. *Mag Res Med* 2019;82(4):1385–1397.
- [33]. Nataraj G *Advances in quantitative MRI: acquisition, estimation, and application*. PhD thesis, Univ. of Michigan, Ann Arbor, MI, 48109–2122; 2018.
- [34]. Rahimi A, Recht B. Random features for large-scale kernel machines. In: *NIPS*; 2007 p. 1177–84. <https://papers.nips.cc/paper/3182-random-features-for-large-scale-kernel-machines>.

- [35]. Deoni SCL. Correction of main and transmit magnetic field (B0 and B1) inhomogeneity effects in multicomponent-driven equilibrium single-pulse observation of T1 and T2. *Mag Res Med* 2011 4;65(4):1021–35.
- [36]. Sacolick LI, Wiesinger F, Hancu I, Vogel MW. B1 mapping by Bloch-Siegert shift. *Mag Res Med* 2010 5;63(5):1315–22.
- [37]. Nielsen JF, Noll DC. TOPPE: A framework for rapid prototyping of MR pulse sequences. *Magn Reson Med* 2018 6;79(6):3128–3134. [PubMed: 29096052]
- [38]. Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, et al. Design and construction of a realistic digital brain phantom. *IEEE Trans Med Imag* 1998 6;17(3):463–8.
- [39]. Alonso-Ortiz E, Levesque IR, Pike GB. Impact of magnetic susceptibility anisotropy at 3 T and 7 T on T2*-based myelin water fraction imaging. *NeuroImage* 2018 9;182:370–378. [PubMed: 28958882]
- [40]. Mandava S, Keerthivasan MB, Li Z, Martin DR, Altbach MI, Bilgin A. Accelerated MR parameter mapping with a union of local subspaces constraint. *Mag Res Med* 2018 12;80(6):2744–58.
- [41]. Wang X, Roeloffs V, Klosowski J, Tan Z, Voit D, Uecker M, et al. Model-based T1 mapping with sparsity constraints using single-shot inversion-recovery radial FLASH. *Mag Res Med* 2018 2;79(2):730–40.

Scan Design

Prior distributions
for unknown and
known parameters

Scan parameter
search space $\mathcal{P}$

Weights $\mathbf{W}$

Scan
Design

Optimized scan
parameters $\hat{\mathbf{P}}$

Data Acquisition

Data
Acquisition

Bulk off-resonance

STFR images

$\Delta\omega$ Estimation

$\Delta\omega$

Bloch-Siebert
(BS) images

κ Estimation

κ

Flip angle scaling

Known
parameters

Test
Data

$\mathbf{y}$

$\mathbf{q}$

Parameter Estimation

Generate
Noisy
Training
Data

Training
Data

$(\mathbf{q}_1, \mathbf{x}_1), \dots, (\mathbf{q}_N, \mathbf{x}_N)$

PERK

Prior distributions for
unknown parameters

MWF Estimate

FIGURE 1.

Workflow of the proposed methods. We first optimized a set of STFR scan parameters by minimizing a Cramér-Rao Lower Bound, then acquired data using those scans, as well as Bloch-Siebert (BS) scans. Two of the STFR scans were equivalent to SPGR scans, so were used to estimate ω , and the BS scans were used to estimate κ . These parameters were treated as known values in the MWF estimation step. We then generated noisy training data using an STFR signal model. Finally, we passed the training data, acquired STFR images, and known parameters to PERK to estimate MWF voxel-by-voxel.

Comparison of CRLBs of Scan Designs

FIGURE 2.

The two optimized scans (see Table 2) were evaluated to explore how including the additional myelin water off-resonance ω_f in the design process affects performance. Design A (where ω_f was included in the optimization) has a better expected CRLB for every value of ω_f within the 5–35 Hz range over which design A was optimized. Design B (where ω_f was ignored) understandably has a better expected CRLB for $\omega_f = 0$. For each value of ω_f investigated in this plot, the expected CRLB was computed with that value of ω_f held constant but unknown. Typical values of ω_f in white matter are 5–35 Hz [17]. Although these CRLB values predict estimator standard deviation (for an unbiased estimator) on the order of 100% MWF or more, we are not restricted by these large values because we are using a Bayesian estimator (see Supporting Information Figure S6 for details).

FIGURE 3.

RMSE of MWF estimates from simulated test data for various ways of accounting for the additional myelin water off-resonance ω_f . The diamond-marked green curve was generated using scan design B (where ω_f was ignored) and using PERK training data where $\omega_f = 0$. In other words, ω_f was not considered in any aspect, neither in the scan design nor when training. The square-marked red curve was also generated using scan design B, but the training data included a range of ω_f values. The circle-marked blue curve was generated using design A and a range of values of ω_f . The latter two methods look almost identical, but both have much better RMSE than the first method as ω_f increases.

FIGURE 4.

Right: MWF maps from five methods using simulated test data for a three-compartment tissue model with exchange. Table 3 reports numerical results. The proposed STFR3-PERK estimates are closer to the true MWF value for white matter tissue values than are the MESE-NNLS estimates. *Left:* Bulk off-resonance ω and flip angle scaling κ maps used in this simulation.

FIGURE 5.

MWF maps from five methods using simulated test data for a nine-compartment tissue model with exchange. These results are essentially the same as when using the three-compartment exchanging model (see Figure 4). Thus, even though STFR3-PERK was trained with a three-compartment exchanging model, it still produced good MWF estimates from signal generated using a nine-compartment exchanging model.

FIGURE 6.

MWF maps from in vivo MESE data and STFR data using scan design A. Table 4 shows numerical results for several manually selected regions of interest. The MESE-NNLS MWF map appears noisier than those shown in other works. This is likely due to the lower SNR of our data due to differences in voxel size. To match the STFR resolution, we acquired MESE with 1.1 mm isotropic voxels, whereas often MESE data is collected with slice thickness of 5 mm and 1.6 mm or greater in the phase encode direction. Remarkably, MESE-PERK is much less noisy than MESE-NNLS. This is likely due to PERK being a Bayesian estimator that discourages estimates that are far from the mean MWF training value.

TABLE 1

Unknown and known parameters used in scan design and in simulation. Values were chosen to match literature values for white matter [1, 17, 21, 35]. We used $M_0 = 1$ for the scan designs because it only scales the STFR signal. The line below κ separates parameters used in both the two-compartment and three-compartment models (above) from those used only in the three-compartment exchanging model (below).

Parameter	Design A	Design B	White Matter	Gray Matter	PERK Training Ranges
M_0	1	1	0.77	0.86	$\text{unif}(0, M_0^{\max})^a$
f_i	$\text{unif}(0.03, 0.31)$	$\text{unif}(0.03, 0.31)$	0.15	0.03	$\text{unif}(0.03, 0.31)$
$T_{1,f}$ (ms)	$\mathcal{N}(400, 80^2)$	$\mathcal{N}(400, 80^2)$	400	500	$\text{unif}(320, 480)$
$T_{1,s}$ (ms)	$\mathcal{N}(1000, 200^2)$	$\mathcal{N}(1000, 200^2)$	832	1331	$\text{unif}(800, 1200)$
$T_{2,f}$ (ms)	$\mathcal{N}(20, 4^2)$	$\mathcal{N}(20, 4^2)$	20	20	$\text{unif}(16, 24)$
$T_{2,s}$ (ms)	$\mathcal{N}(80, 16^2)$	$\mathcal{N}(80, 16^2)$	80	80	$\text{unif}(64, 96)$
ω_T (Hz)	$\text{unif}(5, 35)$	0 [*]	15	5	$\text{unif}(0, 35)$
ω (Hz)	$\text{unif}(-50, 50)^*$	$\text{unif}(-50, 50)^*$	Varies	Varies	$\text{unif}(-50, 50)^b$
κ	$\text{unif}(0.8, 1.2)^*$	$\text{unif}(0.8, 1.2)^*$	Varies	Varies	$\text{unif}(0.8, 1.2)^b$
f_m	N/A	N/A	0.1	0.03	$\text{unif}(0.03, 0.31)$
$T_{1,m}$ (ms)	N/A	N/A	1000	1000	$\text{unif}(800, 3000)$
$T_{2,m}$ (ms)	N/A	N/A	0.02	0.02	$\text{unif}(0.01, 0.1)$
$\tau_{f \rightarrow s}$ (ms)	N/A	N/A	100	20	$\text{unif}(80, 150)$
$\tau_{f \rightarrow m}$ (ms)	N/A	N/A	50	10	$\text{unif}(40, 75)$

N/A - Not applicable (scan designs only used two-compartment model).

$\text{unif}(a, b)$ - Uniform distribution on interval $[a, b]$.

$\mathcal{N}(\mu, \sigma^2)$ - Normal distribution with mean μ and variance σ^2 .

^{*} Known parameter.

^a $M_0^{\max}$ given by maximum signal value from data divided by mean signal value from signal model with $M_0 = 1$.

^b Unless parameter is known, in which case training range covers range of values in known map.

TABLE 2

Optimized scan parameters. The first two scans are the STFR (SPGR) scans with fixed parameters; the remaining scans were optimized during the scan design process. All values have units of degrees. For design A, the additional myelin water off-resonance ω_f was taken to be unknown and distributed uniformly from 5 to 35 Hz. For design B, ω_f was ignored (i.e., taken to be known and equal to 0).

	Scan #	1	2	3	4	5	6	7	8	9	10	11
Design A	α	5	5	15.0	15.0	15.0	15.0	15.0	15.0	15.0	11.4	15.0
	β	0	0	15.0	15.0	11.6	15.0	13.3	15.0	14.9	0.3	14.4
	ϕ	0	0	-139.3	-108.1	-66.0	-28.0	25.9	64.4	104.1	146.3	173.0
Design B	α	5	5	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
	β	0	0	15.0	14.5	14.9	14.8	14.8	14.9	0.0	14.5	15.0
	ϕ	0	0	-139.3	-113.3	-63.7	-14.3	14.3	63.7	83.2	113.3	139.3

TABLE 3

Comparison of various methods of MWF estimation. The reported time refers to the entire estimation, combining the time to estimate MWF in white matter voxels and gray matter voxels; it also includes training time for the methods that use PERK. The best value in each column is highlighted. See Figure 4 for a visual comparison of these methods.

	White Matter (MWF = 0.15)			Gray Matter (MWF = 0.03)			Time (s)
	RMSE	Mean	St. Dev.	RMSE	Mean	St. Dev.	
STFR2-PERK	0.215	0.349	0.082	0.185	0.209	0.047	21.9
STFR3-PERK	0.021	0.158	0.020	0.046	0.074	0.015	43.1
STFR3-PERK-JE	0.026	0.145	0.026	0.044	0.069	0.021	41.3
MESE-NNLS	0.063	0.092	0.025	0.029	0.001	0.003	1602.4
MESE-PERK	0.029	0.134	0.025	0.026	0.026	0.025	142.7

TABLE 4

Sample means $\pm$ standard deviations of MWF estimates for four white matter (WM) regions of interest (ROIs) and one gray matter (GM) ROI. Figure 6 shows corresponding MWF maps, and Supporting Information Figure S1 shows the corresponding ROIs.

ROI	STFR2-PERK	STFR3-PERK	MESE-NNLS	MESE-PERK
WM1	0.175 ± 0.021	0.116 ± 0.029	0.096 ± 0.042	0.105 ± 0.030
WM2	0.175 ± 0.009	0.117 ± 0.011	0.089 ± 0.046	0.097 ± 0.023
WM3	0.206 ± 0.010	0.133 ± 0.010	0.108 ± 0.036	0.133 ± 0.014
WM4	0.195 ± 0.008	0.138 ± 0.010	0.121 ± 0.039	0.141 ± 0.014
GM	0.187 ± 0.034	0.110 ± 0.029	0.034 ± 0.035	0.085 ± 0.034