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Fast Myelin Water Fraction Estimation Using 2D Multi-Slice CPMG

Alireza Akhondi-Asl¹, Onur Afacan¹, Mukund Balasubramanian¹, Robert V. Mulkern¹, and Simon K. Warfield¹

¹Computational Radiology Laboratory, Department of Radiology, Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, USA

Abstract

Purpose— T_2 relaxometry based on multi-exponential fitting to a single slice multi-echo sequence has been the most common MRI technique for myelin water fraction (MWF) mapping, where the short T_2 is associated with myelin water. However, very long acquisition times and physically unrealistic models for T_2 distribution are limitations of this approach. We present a novel framework for myelin imaging which substantially increases the imaging speed and MWF estimation accuracy.

Method—We used the 2D multi-slice CPMG sequence to increase the volume coverage. To compensate for non-ideal slice profiles, we numerically solved the Bloch equations for a range of T_2 and B_1 inhomogeneity scales to construct the bases for the estimation of the T_2 distribution. We used a finite mixture of continuous parametric distributions to describe the complete T_2 spectrum and used the constrained variable projection optimization algorithm to estimate MWF. To validate our model, synthetic, phantom, and in-vivo brain experiments were conducted.

Results—Using the Bloch equations we can model the slice profile and construct the forward model of the T_2 curve. Our method estimated MWF with smaller error than the non-negative least squares (NNLS) algorithm.

Conclusions—The proposed framework can be used for reliable whole brain myelin imaging with a resolution of $2 \times 2 \times 4 \text{ mm}^3$ in ≈ 17 minutes.

Keywords

Myelin Imaging; T_2 Relaxometry; CPMG; Bloch Equations; Variable Projection

Introduction

Quantitative MRI assessment of myelin has been studied for over twenty years (1) and advances in imaging speed and spatial resolution have led to the emergence of multi-echo T_2 mapping as an important tool for studying neurological disorders including multiple sclerosis and schizophrenia (2–4). Since the brain is inhomogeneous and each imaged voxel

contains a population of spins with different T_2 relaxation rates, the observed MR signal from a given voxel has a spectrum with multiple components. The fastest decaying component is generally attributed to myelin associated water with a T_2 below 40 ms with a peak around 10 – 20 ms, whereas the intra-cellular and extracellular water of the brain have T_2 values in the range of about 80 – 120 ms, and cerebrospinal fluid (CSF) with T_2 values over 1000 ms (5, 6). Therefore, by measuring the MR signal at multiple echo times and forming an estimate of the distribution of relaxation rates at each voxel, the fraction of water molecules characterized by each component, including the fast decay component can be estimated.

The classical Hahn spin echo pulse sequence is the most straightforward MRI sequence that can be used for T_2 relaxometry (7). However, in practice it is not feasible to use this sequence as it is very slow. While the long acquisition time of this sequence can be partially overcome by using multiple spin echoes to sample the signal decay curve, as in the Carr-Purcell-Meiboom-Gill (CPMG) sequence, these sequences suffer from imperfect refocusing due to B_1 inhomogeneities (6, 8, 9). The imperfect refocusing in these sequences leads to image artifacts such as stimulated echoes which generate undesired spurious signals that can significantly decrease the accuracy of T_2 estimation (10). To overcome this problem different approaches have been proposed (11, 12). One possibility is to use crusher gradients to decrease the sensitivity of the observed echoes to B_1 inhomogeneities (11). While this approach can eliminate stimulated echoes, the need for large crushers and lower SNR of the observed echoes are the main drawbacks of this strategy (12). The Extended Phase Graph (EPG) algorithm or Bloch simulations can also be used for the calculation of observed echoes as a function of flip-angle, T_1 , T_2 , and echo time (13–16).

It is generally accepted that myelin water fraction (MWF) provides the most specific measure of myelination in the central nervous system (CNS) (17). It has been shown that single slice multi-echo CPMG with 180 degree hard RF pulses produces MWF values that are highly correlated with histology results in MS patients (1). While this sequence has been used by several groups for MWF estimation (18), unfortunately, the acquisition time for a single slice is more than 6 minutes for a 192×192 matrix size, with $TR = 2s$ necessary to allow longitudinal magnetization to recover between shots to reduce T_1 weighting (19). This long acquisition time and low volume coverage reduce the impact of this sequence in clinical practice. In order to achieve clinically feasible scan times, it was suggested to use 3D

GRASE sequence (20). While the scan time can be reduced to $\frac{1}{3}$, reduced SNR and T_2^* related artifacts are the main drawbacks of this approach.

The single-slice CPMG sequence can be extended to a multi-slice CPMG sequence by changing the 180 degree hard RF pulses to slice-selective RF pulses. Multi-slice CPMG acquires several slices per repetition time, yielding good volume coverage (21). This slightly increases the minimum echo time, but enables full brain MWF mapping. Multi-slice CPMG has an increased susceptibility to magnetization transfer that reduces the SNR of the acquisition. In addition, the slice profile is not rectangular even if there is no B_1 inhomogeneity. To improve the homogeneity of the slice profile it is possible to broaden the refocusing pulse (21). However, this limits the slice number and spacing, making it

impractical for the whole brain myelin imaging (22). Because of these issues, multi-slice CPMG thus far has been disregarded for myelin imaging.

Here, we propose a framework to overcome the aforementioned challenges of 2D multi-slice CPMG, leading to a substantial reduction in the acquisition time. We address the low SNR per unit time using a superior fitting algorithm that better exploits the acquired data. We also consider the exact slice profile of each one of the echoes in our model which addresses the slice profile issue. These improvements enable faster myelin imaging with greater accuracy than current methods.

A few other groups have attempted to model the slice profile imperfections in the slice-selective 2D CPMG sequence (22, 23). In these approaches, the distribution of the flip angles is estimated by sampling the slice profile at limited number of points. The slice profile is generated either using the frequency response of the RF pulse obtained from its Fourier transform (23) or the forward Shinnar-Le-Roux transform (22). These approaches make a small tip angle (STA) approximation that allows for a simple scaling of flip angles based on the B_1 inhomogeneity scaling factor. However, this assumption is invalid and must be reconsidered to achieve accurate modeling of the signal decay curve (22).

To overcome these limitations, we precisely model the impact of imperfect slice profiles and B_1 inhomogeneity on the signal decay curve. In general, the impact of the slice profile and B_1 inhomogeneity cannot be represented with a parametric model for the 2D multi-slice CPMG sequence. Therefore, we numerically solve the Bloch equations for a range of possible T_2 values and B_1 inhomogeneity scales for the known acquisition parameters of the excitation and refocusing RF pulses, crushers, gradients, and echo times (16). In this way, for a range of T_2 values and B_1 inhomogeneity scales, the signal decay curves with the required number of echoes are generated and utilized to estimate the T_2 spectrum of each voxel.

Non-negative least squares (NNLS) analysis is a well-known technique for estimating MWF (1, 24, 25). In this approach, it is assumed that the entire $R_2 = \frac{1}{T_2}$ spectrum can be modeled as the sum of a small number of impulse functions at predetermined relaxation rates with unknown amplitudes. Each one of the impulse functions represents a single relaxation rate. The CPMG images are analyzed voxelwise using a NNLS algorithm to estimate the amplitude of each impulse function; the fraction of components with short relaxation times represents the myelin water fraction. However, this method has some limitations. The discretization of the T_2 range is physically unrealistic and determination of the magnitude of occupancy of each T_2 value leads to a large number of parameters to estimate, which is numerically unstable (9, 26).

We have developed an alternative representation in which we use a finite mixture of continuous distributions to describe the complete T_2 spectrum (27). The fraction of the myelin-bound water is the area under the fast component curve divided by the total area of the component curves. This representation has the specific advantage that the number of parameters that must be estimated to characterize the transverse relaxation rate spectrum at

each voxel from the data is small. We use a mixture of three inverse Gaussian (IG) distributions with unknown mixture weights, mean and shape parameters to represent the distribution of myelin-bound water, tissue water, and cerebrospinal fluid. This distribution is very similar to the Gaussian distribution but with positive support, making it a good candidate for the representation of transverse relaxation rate distributions. Finally, we simultaneously estimate the parameters of the T_2 spectrum and B_1 inhomogeneity scale by solving the inverse model using the constrained variable projection method as a substantial number of unknown parameters are linear.

We show how our model can be used for MWF estimation using the 2D multi-slice CPMG sequence which uses slice-selective refocusing pulses. This approach is novel and enables accurate and fast quantitative assessment of the T_2 spectrum, MWF, and B_1 inhomogeneity scale.

Theory

Problem Definition

The signal decay curve at a voxel can be represented as the sum of the signals from a population of spins with each spin contributing to the observed signal as a function of its

relaxation rates $R_1 = \frac{1}{T_1}$ and $R_2 = \frac{1}{T_2}$. For long enough repetition times, the impact of R_1 on the observed signal is negligible. Therefore, the observed signal, S_M can be represented as:

$$S_M = S_0 \int_0^\infty f(R_2) GEC(SP, R_2, B_1, TE, M) dR_2 \quad [1]$$

where $f(R_2)$ is the density function of the relaxation rates, S_0 is a constant, and generalized echo curve (GEC) is a function that describes the observed echoes from a spin with a given R_2 value. This function depends on the sequence parameters SP , echo spacing TE , echo number M , B_1 field inhomogeneity scale, and R_2 . Since the sequence parameters are known for a given acquisition, for simplicity we use $GEC(R_2, B_1, TE, M)$ through the rest of the text. For the Hahn spin echo sequence and 2D single-slice CPMG sequence, parametric forms of this function are available. In fact, for the Hahn spin echo sequence $GEC(R_2, B_1, TE, M) = \exp(-MTER_2)$ and for the 2D single-slice CPMG sequence $GEC(R_2, B_1, TE, M) = EPG(R_2, B_1, TE, M)$ where EPG is the extended phase graph function. However, for the 2D multi-slice CPMG sequence, the function GEC does not have a parametric form and should be solved numerically using the Bloch equations as described in the Methods section where we generate a signal decay curve pool.

Without loss of generality, we can assume that the density function $f(R_2)$ can be expressed as a mixture of distributions of n components:

$$f(R_2) = \sum_{j=1}^n a_j f_j(R_2) \quad [2]$$

where $f_j(R_2)$ is the density function of the j -th component and $a_j \leftarrow S_0 a_j$ for simplicity. The generally accepted model is that the spectrum of relaxation rates has $n - 3$ Gaussian-like components representing myelin-bound water, intra-cellular and extra-cellular water, and CSF (1). There are a variety of distributions with positive support which can be used to model the distribution of the components such as the truncated Gaussian, log-normal, and generalized inverse Gaussian (GIG) distributions. Since the pdf should satisfy $f(R_2 = 0) = 0$, the truncated Gaussian is not an appropriate distribution in the general case. In addition, the log-normal distribution is heavy-tailed which makes it inappropriate for modeling the R_2 spectrum. Therefore, to model $f_j(R_2)$, we use the GIG distribution which has positive support, is not heavy-tailed, and satisfies $f(R_2 = 0) = 0$. The GIG distribution belongs to a three-parameter family of distributions which covers a large pool of distributions. In this paper, we focus on the IG distribution as a specific case of the GIG distribution, which is a two-parameter family of continuous probability distributions with positive support (28):

$$f_j(R_2) = \left(\frac{\lambda_j}{2\pi R_2^3} \right)^{\frac{1}{2}} \exp \left(\frac{-\lambda_j}{2\mu_j^2 R_2} (R_2 - \mu_j)^2 \right) R_2 > 0 \quad [3]$$

where $\mu_j > 0$ and $\lambda_j > 0$ are the mean and shape parameter of the distribution, respectively,

and $\frac{\mu_j^3}{\lambda_j}$ is the variance of the distribution.

The IG distribution has several properties similar to the Gaussian distribution. In fact, when

$\frac{\lambda_j}{\mu_j} \rightarrow \infty$, the distribution is asymptotically normal with mean μ_j and variance $\frac{\mu_j^3}{\lambda_j}$ (Figure 1) (29). In addition, the multi-exponential model is a special case of our formulation where each IG distribution tends to an impulse function (See Appendix).

Optimization

We are interested in estimating the parameters of each component and the B_1 inhomogeneity scales using the observed y_M , a noisy version of the signal S_M , at several echo times. Since the SNR is higher than 40dB, we assume that the noise is zero mean, additive white Gaussian (25,30). Let $\{\Phi(\mathbf{a})\}_{M,j} = \phi_j(\mu_j, \lambda_j, B_1; t_M)$ be a matrix of size $m \times n$ where

$$\phi_j(\mu_j, \lambda_j, B_1; t_M) = \int_0^\infty \left(\frac{\lambda_j}{2\pi R_2^3} \right)^{\frac{1}{2}} \exp \left(\frac{-\lambda_j}{2\mu_j^2 R_2} (R_2 - \mu_j)^2 \right) GEC(R_2, B_1, TE, M) dR_2 \quad [4]$$

and $\mathbf{a} = (\mu_1, \lambda_1, \dots, \mu_n, \lambda_n, B_1) \in \mathcal{R}^{2n+1}$ be the vector of parameters of n distributions and the B_1 inhomogeneity scale.

We need to minimize the following functional to find $\hat{\mathbf{a}} = (\hat{a}_1, \dots, \hat{a}_n)$ and $\hat{\mathbf{a}} = (\hat{\mu}_1, \hat{\lambda}_1, \dots, \hat{\mu}_n, \hat{\lambda}_n, \hat{B}_1)$, the estimated parameters of the model:

$$r(\mathbf{a}, \boldsymbol{\alpha}) = \|\mathbf{y} - \Phi(\boldsymbol{\alpha})\mathbf{a}\|^2 = \sum_{M=1}^m \left(y_M - \sum_{j=1}^n a_j \phi_j(\mu_j, \lambda_j, B_1; t_M) \right)^2 \quad [5]$$

where $\mathbf{a} = (a_1, \dots, a_n) \in \mathcal{R}^n$, $\mathbf{y} = (y_1, \dots, y_m) \in \mathcal{R}^m$, and $M = 1, \dots, m = 3n + 1$ are the vectors of mixture weights, noisy observations, and time indices, respectively.

We use the constrained variable projection optimization algorithm to estimate the model parameters (31). We first estimate the nonlinear parameters of each component by eliminating the linear parameters and then use the estimated non-linear parameters to estimate the linear ones using the minimal least square solution. This approach has been shown to be very effective in cases where the number of linear parameters is substantial (27). To improve the performance of the optimization, we use analytical derivatives to estimate nonlinear parameters (See Appendix). The maximum number of iterations of 400 and the termination tolerance on parameters of $10e-6$ were used as the convergence criteria. In addition, we use an extra optimization stage using an exhaustive search over a range of B_1 inhomogeneity scales to estimate its optimal value, as there is no closed-form derivative with respect to B_1 (25). We have implemented the algorithm using MATLAB (Mathworks, Natick, MA). The optimization run time for a voxel was $\approx 11s$ when calculations were performed on a 64-bit Intel® Xeon® CPU E5530 running at 2.4 GHz.

In summary, we use a finite mixture of inverse Gaussian (MOIG) distributions to model the complete T_2 spectrum and constrained variable projection optimization algorithm to estimate the T_2 spectrum parameters. This framework enables robust and accurate estimate of MWF as shown below, using a combination of synthetic, phantom, and in-vivo MRI data.

Methods

Generation of a Signal Decay Curve Pool

Using sequence parameters such as the shape of the refocussing RF pulse and the gradients, it is possible to accurately calculate the signal decay curve for an arbitrary T_2 spectrum and B_1 inhomogeneity scale. Therefore, we propose to numerically solve the Bloch equations for given sequence parameters and a range of possible B_1 inhomogeneity scales and T_2 values and use the generated curves to solve the inverse problem, simultaneously estimating the T_2 distribution and B_1 inhomogeneity scale from an observed noisy T_2 curve.

Similar to the multi-slice T_2 mapping approach proposed in (16), we use Siemens' sequence simulator tool (POET) to obtain 2D multi-slice CPMG sequence parameters including the shape of RF and gradient pulses and a Bloch equation simulator toolkit to numerically solve the Bloch equations (<http://www-mrsrl.stanford.edu/brian/blochsims/>). Using this framework, the shape of the slice profile for each one of the echoes as well as the signal decay curve for any given T_2 value and B_1 inhomogeneity scale can be calculated. We solve the Bloch equations numerically for 1000 T_2 values equally spaced between 0.001 – 2000ms and 71 B_1 inhomogeneity scales equally spaced between 0.5 – 1.2 to generate a pool of $1000 \times 71 = 71000$ T_2 curves. This pool covers the whole T_2 spectrum of interest and also

practical B_1 inhomogeneity scales. It is possible to enrich the pool by sampling the T_2 values and B_1 inhomogeneity scales with a higher rate; however, our experiments indicate that the improvement in MWF estimation accuracy is negligible and the optimization process is computationally more expensive.

Synthetic Data

Experiment 1—To show the limitation of the STA approximation, we investigated its impact on the accuracy of the slice profile and signal decay curve estimation. Two spins with $T_2 = 75\text{ms}$ and $T_2 = 20\text{ms}$, and two scaling factors of $B_1 = 1$ and $B_1 = 0.8$ were used for the experiment. We also tested the impact of the STA approximation on the accuracy of MWF estimation. A T_2 spectrum with two impulse functions at $T_2 = 20\text{ms}$ with fraction of 0.2 and $T_2 = 75\text{ms}$ with fraction 0.8, i.e., $MWF = 0.2$, was used for this experiment.

Experiment 2—We also used synthetic data with known distributions to compare the performance of our method, MOIG, with NNLS, an established method in the literature. While we used the IG distribution to model the R_2 distribution in our model, to have a fair comparison with the NNLS method, we used the Gamma distribution as an alternative continuous distribution to generate the ground truth. We also adapted the NNLS algorithm to work with slice selective RF pulses where the *EPG* model was replaced with the Bloch simulation based *GEC* function. For the NNLS algorithm the two-step optimization approach in (25) was used to estimate the B_1 inhomogeneity scale. To represent the distribution, we used 40 impulse functions, logarithmically spaced between 15ms and 2000ms . A mixture of three Gamma distributions was considered as the ground truth with the peaks at 50s^{-1} , 10s^{-1} , and 1s^{-1} and standard deviations of 10s^{-1} , 2s^{-1} , 0.4s^{-1} , respectively. The fraction of the components was 0.2, 0.75, and 0.05, respectively. We used constraints on the mean and shape parameters of each component in MOIG. We assumed that the mean of the components are in the range of $15 - 25\text{ms}$, $60 - 120\text{ms}$, $200 - 2000\text{ms}$ and the shape parameters are between $0.2 - 2000\text{s}^{-1}$. These are reasonable ranges without any strong assumption about the T_2 spectrum (6). We added zero mean white Gaussian noise to the echoes and repeated the experiment 500 times for all combinations of 5 equally spaced SNRs between 32dB and 48dB and 7 equally spaced B_1 inhomogeneity scales between 0.75 and 1.05. We initialized our method with three IG distributions with the means at 40s^{-1} , 8s^{-1} , and 1s^{-1} and with shape parameters of 300s^{-1} . For both approaches, we considered any component with the T_2 shorter than 40ms as the myelin related component to estimate the MWF.

We also calculated Cramer-Rao lower bound (CRLB) of estimated MWF using MOIG where we normalized the CRLB by the true MWF value. We computed CRLB for all combinations of 5 equally spaced SNRs between 32dB and 48dB and 80 equally spaced B_1 inhomogeneity scales between 0.75 and 1.05.

Phantom Experiment

Experiment 3—To investigate the impact of slice-selective RF pulses and B_1 inhomogeneity on the slice profile, experimental slice profiles were obtained by modifying the CPMG sequence to play the readout imaging gradients along the slice-select direction

(e.g., see (32)). A cylindrical phantom containing a mixture of NiSO_4 solution and saline ($T_2 \approx 75\text{ms}$) was scanned with the axis of the cylinder, the slice-select gradient and the readout gradient all aligned with the direction of the main magnetic field. Similar pulse-sequence parameters were used for this acquisition and the other CPMG data presented in this manuscript (i.e., slice thickness= 5mm , FOV= $21 \times 21\text{cm}$, matrix= 192×192 , $TR = 2\text{s}$, $TE = 9\text{ms}$, $N_{TE} = 32$, $BW = 230\text{Hz/px}$). The B_1 scaling factor was varied in this experiment by manually adjusting the RF transmit voltage.

Experiment 4—For validation purposes, the T_2 spectrum fitting methods were also tested on a two chamber phantom. The chambers were filled with different levels of gadolinium

doped water solutions. While gadolinium doped water solutions compartments have $\frac{T_1}{T_2}$ values that are not typical for brain tissue, they are frequently used in the literature for the evaluation of T_2 relaxometry methods. For this experiment, 6mM Gd-DPTA (Magnevist) doped solution was used for the inner chamber such that the inner chamber had $T_2 \approx 30\text{ms}$. Using a similar strategy the outer chamber was set to have $T_2 \approx 100\text{ms}$. T_2 relaxation measurements were performed on a 3T Siemens TRIO scanner with a 2D multi-slice CPMG sequence (4mm thick). Thirty-two echoes were acquired with a minimum echo time of 9ms. A 21cm FOV was used with a matrix size of 192×192 (in plane resolution of 1.1mm). We compared the MWF estimation accuracy of MOIG and NNLS for 630 ROI's. Each ROI had three voxels from the chamber with longer T_2 and one voxel from the chamber with the short T_2 . The ROI's were selected to have B_1 inhomogeneity scales very close to 1, based on the estimated B_1 map. The average of the signals in each one of these ROI's was used for the estimation of the fraction of the short component, representative of myelin, which is

expected to be $\frac{1}{1+3} = 0.25$. The estimation procedure was similar to that used in the synthetic data experiments.

In-vivo MRI Data Acquisition

Experiment 5—MOIG and the NNLS algorithm were tested on 5 healthy volunteers (age range 22–36, 2 male). T_2 measurements were performed on a 3T Siemens TRIO scanner with a 2D multi-slice CPMG sequence ($TR = 2000\text{ms}$, $TE = 9\text{ms}$, $N_{TE} = 32$, matrix size= 192×192 , FOV= $210 \times 210\text{mm}^2$, slice thickness= 5mm , refocusing/excitation slice-thickness factor= 1.2 , number of averages= 1 , $BW_{acq} = 230\text{Hz/px}$). The scans were performed with a 32-channel head and neck coil and the total scan time was 6 minutes and 34 seconds for the acquisition of 6 slices.

In order to compare the estimated MWF values of our method with the reported values in the literature, we also segmented four white matter structures: genu of the corpus callosum, forceps major, forceps minor, and splenium of the corpus callosum of the 5 healthy volunteers and calculated the average and standard deviation of the MWF in these regions and compared them with the reported numbers in the literature (33).

Experiment 6—To test if it is practical to acquire whole brain myelin maps, in clinically feasible scan times, we have also acquired data on one of the subjects by repeating the

imaging 5 times with different slice positions. A 20cm FOV was used with a matrix size of 128×96 (phase resolution of 75%) and total scan time of 17 minutes and 10 seconds for the acquisition of $5 \times 6 = 30$ slices with 4mm thickness. For the same subject, we also repeated the acquisition to analyze the test-retest variability of both NNLS and MOIG (34). Pearson correlation analysis was used for the quantitative comparison of the repeatability of the two methods. We initialized our method with three IG distributions with the same parameters as in the simulation experiment.

Results

Synthetic Data

Experiment 1—In Figure 2.a, we show the slice profile of the first and second echoes arising from a spin with $T_2 = 75ms$ for a $B_1 = 1$ scaling factor. It can be seen that the shape of the slice profile varies with echo number and the magnitude of the second echo (i.e., area under the curve) is bigger than the first echo. In Figure 2.b, we show the slice profile of the first echo for $T_2 = 75ms$ and $B_1 = 0.8$ and also the slice profile calculated using the STA approximation approach (22, 23). It can be seen that the impact of B_1 inhomogeneity scale cannot be modeled accurately by scaling the flip angle distribution. The magnitude of the first echo in the scaling based approximation is smaller than the correct value calculated by numerically solving the Bloch equations. This limitation of the scaling based approach has been discussed by Petrovic et al. (22). In Figure 2.c and d, we show the impact of non-ideal slice selective RF pulses on the signal decay curve when $T_2 = 75ms$ and $T_2 = 20ms$, respectively. It can be seen that with $B_1 = 1$ for both hard and non-ideal slice-selective RF pulses, non-ideal slice-selective RF pulses generate strong flip angle deviations, causing significant reduction in the magnitude of several echoes, especially the first echo. It can also be seen that the STA approximation is not sufficient to calculate the signal decay curve accurately, especially for the short echoes.

Also, for the T_2 spectrum with two impulse functions at $T_2 = 20ms$ with fraction of 0.2 and $T_2 = 75ms$ with fraction 0.8, the estimated MWF using the numerical solutions of Bloch equations and STA approximation are 0.199 and 0.056, respectively, when no noise is added to the observed signal curve. This indicates that the estimated MWF using the STA approximation is significantly smaller than the true value of 0.20.

These results demonstrate that the shape of the slice profile has a nonlinear relation with the B_1 inhomogeneity scale which cannot be modeled correctly using the STA approximation.

Experiment 2—Figure 3.a shows the normalized Cramer-Rao lower bound (CRLB) of MWF estimated using MOIG where we normalized the CRLB by the true MWF value. This figure indicates that MWF can be estimated with very high accuracy in a clinical imaging scenario with SNR=40 – 50dB, estimated using "Difference method" (35), and B_1 inhomogeneity scales larger than 0.85. Next, we evaluate MOIG and NNLS for the same range of SNRs and B_1 inhomogeneity scales. Figure 3.b shows the relative mean absolute error (MAE) of MOIG and NNLS at different SNRs and B_1 inhomogeneity scales. As can be seen, for practical B_1 inhomogeneity scales and SNRs, MOIG estimates the MWF with very small error as compared to the NNLS algorithm.

Phantom Experiment

Experiment 3—In Figure 4.(a), experimental slice profiles of the first and second echoes are shown. The slice profiles of the first echo for $B_1 = 0.8$ as well as the slice profile calculated from $B_1 = 1.0$ using the STA approximation are shown in Figure 4.(b). Figure 4.(c) shows the observed echoes by integrating over the calculated slice profiles and the estimated echoes. These observations are consistent with the synthetic data experiment, which indicate that the STA approximation is not sufficient to calculate the signal decay curve accurately.

Experiment 4—Figure 5.a shows the observed echo of the two chamber phantom at 90ms. The results in Figure 5.b indicate that the variance of the estimated fraction is smaller in MOIG which indicates that our approach is more robust as compared to the NNLS algorithm. Moreover, normalized MAE of MOIG and NNLS were 0.08 and 0.12, respectively. Figure 5.c and d show the Box and scatter plots of estimated fraction of the shortest component using MOIG versus NNLS, respectively. It can be seen that the NNLS approach is biased and tends to underestimate the MWF (36). In fact, the average fraction of the shortest component of MOIG and NNLS are 0.258 and 0.226, respectively. These results demonstrate that our method can estimate the fraction of the first component more accurately as compared to the NNLS approach.

In-vivo MRI Data Acquisition

Experiment 5—Figure 6.a shows the observed echoes from a voxel inside genu of corpus callosum of one of the subjects and estimated echoes using our proposed framework and NNLS. In addition, figure 6.b shows the estimated T_2 spectrum using MOIG and NNLS for the same voxel. The estimated MWF using MOIG and NNLS are 0.18 and 0.16, respectively.

Figure 7.a–d show the MWF mapping of two slices of the same subject using MOIG and NNLS. For both models the components with T_2 shorter than 40ms are used to estimate the MWF. The results show that our approach generates MWF maps that are smoother and less noisy in the regions such as corpus callosum and optic radiation. Figure 7.e–h show the estimated B_1 inhomogeneity scale maps using MOIG and NNLS, with no meaningful difference apparent between the two approaches. In addition, as expected, the estimated B_1 inhomogeneity scales are close to one at the center and substantially smaller than one at the front of the brain.

Table I shows the average MWF estimated for the 5 subjects in Experiment 5 using the proposed method in comparison with the values from the literature (5, 9, 20, 25, 33, 37–42). The results indicate that our estimated values are in the range of reported values for all of the white matter structures.

Experiment 6—Figure 8 shows MWF maps from twelve sample slices generated via MOIG for whole brain myelin imaging. The images show plausible definition at structure borders and tissue interfaces. These results indicate that our proposed method can be used for whole brain myelin imaging in clinically feasible scan times. Also, Figure 9.a and b

show the scatter plots of test-retest analysis of both NNLS and MOIG, respectively. Pearson correlation coefficient of MOIG and NNLS was 0.89 and 0.84, respectively, indicating that our method has lower test-retest variability than NNLS.

Discussion and Conclusions

In this paper, we have introduced a novel framework for T_2 -based myelin imaging that enables the use of the 2D multi-slice CPMG sequence for this purpose, giving us the ability to acquire multiple slices per repetition time and thereby attaining good volume coverage. In our framework, we have acquired 6 slices per repetition time which makes the acquisition 6 times faster than the 2D single-slice CPMG sequence often used for MWF mapping. This increased acquisition speed gives us the opportunity to acquire more slices in clinically practical acquisition times, making it practical to use this method to study myelin-related diseases.

Non-ideal slice profiles pose a major challenge in 2D multi-slice CPMG based T_2 relaxometry. Unfortunately, creating an ideal slice profile is not practical. Hence, to avoid systematic errors in MWF estimation, one needs to precisely model the impact of the slice profile on the signal decay curve. Several groups have attempted to do so, estimating the distribution of the flip angles for a single inhomogeneity scale using the STA approximation. In addition, to consider B_1 inhomogeneity, the slice profile was only scaled by an overall scaling factor (22, 23). However, the B_1 inhomogeneity scale has a non-linear impact on the slice profile that cannot be adequately modeled with the STA approximation (22). We have addressed this problem by solving the Bloch equations numerically to obtain the exact slice profile for the given imaging sequence parameters (16).

In addition, we have proposed a more natural model for the representation of the T_2 spectrum which makes it possible to estimate the MWF with a precision higher than the NNLS algorithm. It can be seen in Figure 6 that while the MOIG and NNLS algorithms have estimated the signal decay curve similarly, the estimated MWF of these methods are different and the NNLS algorithm underestimates the MWF. The reason is that in a 32-echo imaging sequence, only 32 samples are acquired for each voxel which is not enough for the estimation of the 41 unknowns in NNLS model. Therefore, a regularization is used that leads to a smoothing of the spectrum and underestimation of MWF. This limitation of NNLS has been discussed in the literature (36). Furthermore, NNLS is sensitive to the location of the impulse functions. However, in our model, there are only 10 unknown parameters, three parameters for each one of three components and one B_1 inhomogeneity scaling factor, which can be estimated using the 32 observations. This we believe increases the reliability of the quantitative analysis of the myelin imaging and should increase sensitivity to myelin changes over time.

We have also used an optimization algorithm which deals with linear sums of nonlinear functions. In this optimization approach, we separate linear and non-linear parameters and estimate the nonlinear parameters independently. This significantly increases the optimization speed and decreases sensitivity to the initialization of the parameters, leading to higher parameter estimation accuracy. Currently, the optimization run time for a voxel is $\approx$

11s. Decreasing the optimization run time is a point for future improvement. It is worth noting that MWF estimation accuracy is more sensitive to SNR than B_1 inhomogeneity, as can be seen in Figure 3 where the B_1 scaling factor has smaller impact on the MWF estimation accuracy (43, 44).

There is a compromise to be made between the impact of magnetization transfer, T_1 weighting, and imaging time. With $TR = 2s$, $TE = 9ms$, and 32 echoes, up to six slices per TR can be acquired. In this way, while the TR is long enough to reduce T_1 weighting significantly, magnetization transfer effect is minimized. It is possible to increase the number of acquired slices; however the impact of magnetization transfer could then be severe, a consideration that should be studied more carefully in further studies. To be able to cover the whole brain with smaller number of slices, we have used 4 and 5 mm thick slices for the in-vivo experiments. This might impact the results as the thicker slices have higher SNR. The impact of using thinner slices should be studied more carefully in the future studies.

In order to quantify MWF, it has also been suggested to use the T_2^* decay curve with a multi-echo Gradient recalled echo (meGRE) sequence (45, 46). Although meGRE is much faster compared to CPMG and does not have the stimulated echo problem, the reported MWF values calculated from meGRE are much lower than from CPMG (47). Also, using a combination of a set of GRE and steady state free precision (SSFP) sequences with multiple acquisitions with varying flip angle, MCDESPOT method calculates slow and fast (myelin) T_2 components (48). MCDESPOT requires a more complex fitting procedure than ours and requires many assumptions about the distributions (47).

In summary, we have used synthetic, phantom, and in-vivo MRI for the validation of our method. In addition, we have compared our method with the NNLS algorithm and showed the advantages of our method. The proposed framework is fast and should facilitate studies of myelin-related diseases. That being said, the inherent difficulty in fitting even noise free, or high SNR, decay curves with an unknown number of components with unknown distribution widths makes validations performed on the basis of comparisons between synthetic data and in vivo results somewhat problematic and, though useful for demonstrating consistency, cannot prove ultimate veracity.

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Appendix

Relation to Multi-Exponential Model

For an ideal spin echo sequence and using the Laplace transform of the IG distribution, it can be seen that (29):

$$\int_0^\infty f_j(R_2) \exp(-t_M R_2) dR_2 = \exp\left(\frac{\lambda_j}{\mu_j} \left(1 - \sqrt{1 + \frac{2t_M \mu_j^2}{\lambda_j}}\right)\right) \quad [6]$$

where t_M is the time of the M -th echo. Therefore, we can rewrite Eq. [1] as:

$$S_M = \sum_j a_j \exp\left(\frac{\lambda_j}{\mu_j} \left(1 - \sqrt{1 + \frac{2t_M \mu_j^2}{\lambda_j}}\right)\right) \quad [7]$$

As $\lambda_j \rightarrow \infty$, variance of the distribution tends to zero and the IG distribution becomes more

like an impulse function. In fact, when λ_j tends to infinity, $\sqrt{1 + \frac{2t_M \mu_j^2}{\lambda_j}} \rightarrow 1 + \frac{t_M \mu_j^2}{\lambda_j}$ and Eq. [7] simplifies to:

$$S_M = \sum_j a_j \exp(-t_M \mu_j) \quad [8]$$

This is the sum of multi-exponential form utilized in (6) where $T_j = \frac{1}{\mu_j}$ is the relaxation time of the j -th impulse function.

Jacobinan Matrix

The jk -th element of Jacobian matrix is:

$$\frac{\partial \phi_j(\mu_j, \lambda_j, B_1; t_M)}{\partial \alpha_k} = \begin{cases} \int_0^\infty \left(\frac{\lambda_j}{2\pi R_2^3}\right)^{\frac{1}{2}} \exp\left(\frac{-\lambda_j(R_2 - \mu_j)^2}{2\mu_j^2 R_2}\right) \frac{\lambda_j R_2(R_2 - \mu_j)}{\mu_j^3 R_2} GEC(R_2, B_1, TE, M) dR_2 & k=2j-1 \\ \int_0^\infty \exp\left(\frac{-\lambda_j(R_2 - \mu_j)^2}{2\mu_j^2 R_2}\right) \frac{1 - \frac{\lambda_j(R_2 - \mu_j)^2}{\mu_j^2 R_2}}{2(\lambda_j 2\pi R_2^3)^{\frac{1}{2}}} GEC(R_2, B_1, TE, M) dR_2 & k=2j \end{cases}$$

[9]

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

(a)

(b)

(c)

(d)

Figure 5.

Figure 6.

Figure 7.

Figure 8.

Figure 9.

TABLE I

Estimated MWF using the proposed method and other methods in the literature (5, 9, 20, 25, 33, 37–42). The results indicate that the estimated MWF values using our method are in the range of reported values in the literature.

White Matter ROI	Literature	MOIG
Forceps Major	0.07 – 0.13	0.12 ± 0.02
Forceps Minor	0.04 – 0.16	0.11 ± 0.03
Genu of Corpus Callosum	0.09 – 0.18	0.14 ± 0.05
Splenium of Corpus Callosum	0.13 – 0.18	0.14 ± 0.04