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A tissue-relaxation-dependent neighboring method for robust mapping of the myelin water fraction

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ABSTRACT

Quantitative assessment of the myelin content in white matter (WM) using MRI has become a useful tool for investigating myelin-related diseases, such as multiple sclerosis (MS). Myelin water fraction (MWF) maps can be estimated pixel-by-pixel by a determination of the T_2 or T_2^* spectrum from signal decay measurements at each individual image pixel. However, detection of parameters from the measured decay curve, assuming a combination of smooth multi-exponential curves, results in a nonlinear and seriously ill-posed problem. In this paper, we propose a new method to obtain a stable MWF map robust to the presence of noise while sustaining sufficient resolution, which uses weighted combinations of measured decay signals in a spatially independent neighborhood to combine tissues with similar relaxation parameters. To determine optimal weighting factors, we define a spatially independent neighborhood for each pixel and a distance with respect to decay rates that effectively includes pixels with similar decay characteristics, and which therefore have similar relaxation parameters. We recover the MWF values by using optimally weighted decay curves. We use numerical simulations and *in vitro* and *in vivo* experimental brain data scanned with a multi-gradient-echo sequence to demonstrate the feasibility of our proposed algorithm and to highlight its advantages compared to the conventional method.

Introduction

A magnetic resonance imaging (MRI) scanner can be used to detect structural abnormalities of the body by measuring the magnetic properties of water molecules in biological tissues. Using the T_2 decay signals in the brain, three different T_2 relaxation components corresponding to the presence of three water pools in the white matter region can be detected (MacKay et al., 1994; Whittall et al., 1997). The fast relaxing T_2 component represents the water pool between the hydrophobic bilayers of the myelin sheath (Laule et al., 2004, 2006; MacKay et al., 2006). Two different relaxing components are assigned to intra/extracellular water and to cerebrospinal fluid. The myelin water fraction (MWF), defined as the ratio of the signal intensity of the shortest T_2 component to the total, shows specificity for myelin content in neurological tissues. Therefore, determination of the MWF can reveal abnormalities in myelin-related disease states, such as multiple sclerosis (MS). Analysis of T_2 relaxation decay curves has been used to investigate different water compartments within heterogeneous tissue (Does and Gore, 2002; Mackay et al., 2006; Valentine et al., 2007; Wachowicz and Snyder, 2002). Similar approaches based on an analysis of T_2^* (rather than T_2) decay curves have also been used to study microscopic components (Bender and Klose, 2009; He and Yablonskiy, 2007; Yablonskiy, 1998) and quantify MWF values in the brain (Du et al., 2007; Hwang et al., 2010; Lenz et al., 2010, 2011).

The determination of the three different T_2 (or T_2^*) relaxation components from measured decay curves is challenging because of the inherent instability of the problem, *i.e.*, the estimation of parameters for the combination of smooth multi-exponential curves may be severely affected by the presence of noise in the measured decay data. To circumvent this ill-posed nature of the MWF estimation problem, various algorithms have been developed to measure the MWF in white matter, such as the non-negative least squares (NNLS) algorithm (Lawson and Hanson, 1974), the regularized non-negative least squares (rNNLS) algorithm (Graham et al., 1996; Whittall and MacKay, 1989), a spatially-regularized nonnegative least squares (srNNLS) algorithm (Hwang and Du, 2009), and rNNLS-after-filtering algorithms (Jones et al., 2003; Oh et al., 2006). These algorithms are mostly based on the continuous distribution of $T_2^{(*)}$ components with different signal strengths. Because there are numerous unknowns to be determined, smoothing constraints are usually incorporated to determine the amplitudes of the relaxation components. Depending on the number of echoes and the algorithms used, different signal-to-noise ratios (SNRs) are recommended for reliable solutions. Generally, a high SNR with a noise standard deviation less than

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1% of the signal strength at the shortest echo time is suggested as a minimum acceptable SNR (Graham et al., 1996; Kolind et al., 2009; Laule et al., 2007). The conventional acquisition method usually requires four averages and takes 26 min of scan time to achieve a reasonable SNR (Jones et al., 2003; Kolind et al., 2009; Laule et al., 2004, 2006, 2007; Whittall et al., 1997). Another type of algorithm used to analyze $T_2^{(*)}$ relaxation decay curves is a three-pool model method, which is based on discrete $T_2^{(*)}$ components where there are only three representative $T_2^{(*)}$ components with three different signal strengths (Andrews et al., 2005; Du et al., 2007; Hwang et al., 2010; Lancaster et al., 2003). In the three-pool model, there are seven unknowns to be estimated, which is substantially less than the number of unknowns in the aforementioned NNLS-based algorithms. However, this problem is still ill-posed, because the three $T_2^{(*)}$ values and the corresponding signal strengths have to be estimated at the same time in the presence of noise. Furthermore, caution should be taken when using this approach for pathologic datasets or other brain regions with additional $T_2^{(*)}$ components, because the three-pool model parameters are optimized for common WM regions, and errors may be introduced in pathologic situations with the presence of additional $T_2^{(*)}$ components. For more practical applications, it is critical to stabilize the ill-posed nature and extract useful information from the noisy measured data.

The purpose of this paper is to present a new method for robust myelin water quantification in the brain using a tissue-relaxation-dependent denoising technique. The proposed method provides a stable MWF map, while sustaining sufficient resolution using a weighted combination of measured decay curves in a spatially independent neighborhood with similar relaxation parameters. In contrast to conventional denoising techniques such as linear filters, median filters, and anisotropic diffusion filters, the proposed method is optimal for MWF estimation in the sense that measurements are processed based on the decay properties of the tissues, rather than on spatial proximity or intensity similarity. To determine optimal weights for the combination of the measured decay curves, we define a new spatially independent metric that measures the decay similarity, $D(\mathbf{r},\mathbf{s})$, between two measured decay curves $S(\mathbf{r},t_n)$ and $S(\mathbf{s},t_n)$, $n=1,\ldots,$ N, at pixels $\mathbf{r}$ and $\mathbf{s}$. The defined distance function has the property $D(\mathbf{r},\mathbf{s})=0$ if and only if two pixels have the same relaxation parameters and MWF values. Considering the defined metric $D(\mathbf{r},\mathbf{s})$, which does not depend on the spatial metric, we determine weighting factors $\omega_{h,\rho}(\mathbf{r},s)$ using the concept of a non-local (NL) means filter, which was originally developed to solve issues related to noise removal in images while maintaining the integrity of the relevant image information (Buades et al., 2005; Freeman et al., 2000; Roth and Black, 2005; Zhu et al., 1998). We determine an optimally denoised decay curve as a weighted combination with $\omega_{h,\rho}(\mathbf{r},s)$, which eliminates dissimilar neighboring pixels that are likely to have dissimilar relaxation parameters and therefore different MWF values.

We use a multi-gradient-echo (MGRE) pulse sequence, which allows for the acquisition of multiple sampling points during the fast decay of the myelin water signal, to verify the proposed method. To demonstrate how the proposed algorithm works, we conducted simulations whereby noise levels were varied and compared to noiseless data. Both *in vitro* and *in vivo* experiments demonstrated that our proposed method considerably reduces noise artifacts and sustains the resolution of MWF maps.

Material and methods

Three-pool relaxation model

The following equation is the three-pool relaxation model we used to measure myelin (*my*), myelinated axon (*ma*), and mixed water (*mx*) pool fraction with seven unknowns:

$$S(\mathbf{r},t)=A_{my}e^{-t/T^*_{2,my}}+A_{ma}e^{-t/T^*_{2,ma}}+A_{mx}e^{-t/T^*_{2,mx}}+A_{bl} \tag{1}$$

where A_{my}, A_{ma}, and A_{mx} denote the amplitudes of the signals arising from the three water pools, respectively, and A_{bl} is any residual baseline signal. Because the measured signal $S(\mathbf{r},t)$ is the summation of three smooth exponential signals at the pixel $\mathbf{r}$, it is difficult to determine $T^*_{2,my}$, $T^*_{2,ma}$, and $T^*_{2,mx}$ stably, in correlation to the coefficients A_{my}, A_{ma}, A_{mx}, and A_{bl}, because small perturbations of the coefficients may result in significant errors when determining all of the parameters.

To simplify the terminologies, we rewrote Eq. (1) in the discretized form

$$S(\mathbf{r},t_n)=a_1e^{-b_1t_n}+a_2e^{-b_2t_n}+a_3e^{-b_3t_n}+A_{bl},\qquad n=1,2,\cdots,N \tag{2}$$

where $a_1=A_{my}$, $a_2=A_{ma}$, $a_3=A_{mx}$, $b_1=\frac{1}{T^*_{2,my}}$, $b_2=\frac{1}{T^*_{2,ma}}$, $b_3=\frac{1}{T^*_{2,mx}}$, and t_n is the n^{th} echo time, respectively.

A conventional optimization problem for Eq. (2) is to find the coefficients a_i and b_i for $i=1,2,3$ and A_{bl} based on minimizing the following least squares problem:

$$\min_{\{a_i\geq 0,b_i\geq 0,A_{bl}\}}\sqrt{\sum_n\left(a_1e^{-b_1t_n}+a_2e^{-b_2t_n}+a_3e^{-b_3t_n}+A_{bl}-S(\mathbf{r},t_n)\right)^2}. \tag{3}$$

Determination of T_2^* components and spectra

To determine the spatially independent neighborhood, we defined a distance function between the measured T_2^* decay signals $S(\mathbf{r},t_n)$ and $S(\mathbf{s},t_n)$:

$$D(\mathbf{r},\mathbf{s}):=\frac{\|S(\mathbf{r})-S(\mathbf{s})\|_1}{h(\mathbf{r})}=\sum_{n=1}^{N}\frac{|S(\mathbf{r},t_n)-S(\mathbf{s},t_n)|}{h(\mathbf{r})} \tag{4}$$

where $h(\mathbf{r})$ is a temporal noise level in the decay signals. In our study, $h(\mathbf{r})$ was approximated by the standard deviation of the fitting residuals with the original decay signals (Hwang et al., 2011; Laule et al., 2008).

The defined distance function $D(\mathbf{r},\mathbf{s})$ is related to the coefficients a_i and b_i for $i=1,2,3$, and A_{bl} in Eq. (2) such that:

$$a_i(\mathbf{r})=a_i(\mathbf{s}),\ \ b_i(\mathbf{r})=b_i(\mathbf{s}),A_{bl}(\mathbf{r})=A_{bl}(\mathbf{s})\quad\Longleftrightarrow\quad D(\mathbf{r},\mathbf{s})=0. \tag{5}$$

Using Eqs. (4)–(5), we can define a spatially independent neighborhood at each pixel $\mathbf{r}$ by introducing a weighting factor ω_ρ with respect to the non-spatial decay-dependent distance $D(\mathbf{r},\mathbf{s})$ as follows:

$$\omega_\rho(\mathbf{r},\mathbf{s}):=\frac{1}{\zeta_r}e^{-D(\mathbf{r},\mathbf{s})}\ \text{ for }\ \mathbf{s}\in B_\rho(\mathbf{r}) \tag{6}$$

where $\zeta_{\mathbf{r}}:=\sum_{s\in B_{\rho(\mathbf{r})}}e^{-D(\mathbf{r},\mathbf{s})}$ is a normalization constant ensuring that $\sum_s\omega_\rho(\mathbf{r},\mathbf{s})=1$, and $B_\rho(\mathbf{r})$ is a disk centered at $\mathbf{r}$ with a radius ρ. The application of the weighted sum of decay signals with ω_ρ results in high SNR decay data, S_{NL}, at location $\mathbf{r}$;

$$S_{NL}(\mathbf{r},t_n):=\sum_{s\in B_\rho(\mathbf{r})}\omega_\rho(\mathbf{r},\mathbf{s})S(s,t_n). \tag{7}$$

Because the weighting factor $\omega_\rho(\mathbf{r},\mathbf{s})$ depends only on the non-spatial decay-dependent distance of the decay signals, the spatial radius ρ of the neighborhood $B_\rho(\mathbf{r})$ can be extended to the whole imaging area, not just the pixels adjacent to pixel $\mathbf{r}$ (*i.e.* spatially independent neighborhood). At the fixed location $\mathbf{r}$, the non-spatial decay-dependent distance $D(\mathbf{r},\mathbf{s})$ implies that the weighting factor $\omega_\rho(\mathbf{r},\mathbf{s})$ is similarly weighted with $\omega_\rho(\mathbf{r},\mathbf{r})$ when the measured T_2^* decay data $S(\mathbf{s},t_n)$ is similar to $S(\mathbf{r},t_n)$. Thus, the weighting factor $\omega_\rho(\mathbf{r},\mathbf{s})$ estimates the T_2^* similarity between $S(\mathbf{r},t_n)$ and $S(\mathbf{s},t_n)$. Therefore, the summation in Eq. (7) can effectively avoid the inclusion of