Multi-compartment T2 Relaxometry Using A Spatially Constrained Multi-Gaussian Model

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Target audience: Neurologists and clinicians involved in neurodegenerative and demyelinating diseases; basic scientists interested in quantifying white matter, particularly myelin content in the brain within a clinically feasible acquisition time.

Purpose: To introduce a new post-processing technique for quantifying myelin in the brain, with specific application to the examination of demyelinating disesaes like Multiple Sclerosis [1]. T2 Relaxometry is a popular MRI technique which can separate the contribution of various tissue components in the brain, thereby quantifying the myelin content of brain regions. It works by capturing several MRI scans at different echo times, followed by a numerical fitting procedure to fit multiple components exponentially relaxing at different T2 time constants. Unfortunately, the post-processing required to obtain myelin maps from T2 data is a hard numerical problem due to ill-posedness of the problem [2]. Consequently, the T2 distributions and the resulting myelin water fraction (MWF) maps become very sensitive to noise and are frequently difficult to interpret diagnostically. Hence T2 relaxometry typically necessitates very high SNR T2 scans which can take several hours for whole brain coverage – clearly a clinically unfeasible proposition. Here, we propose a new way of solving the inverse problem in T2 relaxometry by imposing spatial smoothness constraints and by restricting the relaxing T2 distribution to 2 Gaussian-shaped peaks corresponding to myelin water and intra/extra-cellular water. The method greatly improves robustness to noise, reduces spatial variations and definition of white matter fiber bundles in the brain. This allows it to be used on fast but low-SNR spiral acquisitions which take only 10 minutes for whole brain coverage.

Method: Conventional approach [3] models the underlying T2-relaxing tissue compartments by 40 T2 points logarithmically chosen over a range of 5-300 ms. The signal at any echo time TE_k for a single voxel can be given by: $\mathbf{y} = A\mathbf{x} + \boldsymbol{\epsilon}$, with $A_{ki} = \exp(-TE_k/T_2(i))$, where $\mathbf{y}$ is a vector of multi-echo MRI data and $\mathbf{x}$ is a vector of the volume fractions of each T2 pool in the voxel. To impose spatial constraints, we will jointly estimate the T2 distribution over all image voxels, thus we extend the above eqn to: $\bar{\mathbf{y}} = \boldsymbol{A_{ex}}\bar{\mathbf{x}} + \bar{\boldsymbol{\epsilon}}$, by collecting single-voxel quantities $\mathbf{x}$, $\mathbf{y}$, $\boldsymbol{\epsilon}$ into multi-voxel vectors $\bar{\mathbf{y}}, \bar{\mathbf{x}}, \bar{\boldsymbol{\epsilon}}$, and $\boldsymbol{A_{ex}}$ is a large block diagonal matrix. Since there are only 2 distinct T2 pools in the brain – fast relaxing myelin water pool and slower intra/extra-cellular water pool – we model the T2 distribution by a sum of 2 Gaussian peaks, whose parameters (mean location, height and variance) are to be determined. We also add a very long relaxing CSF pool with unknown T2 and strength. We impose a penalty for high norms as well as non-smoothness on the unknown vector $\boldsymbol{\theta_{ex}}$, a collection of multi-voxel Gaussian parameters (8 per voxel) and is related to the resulting T2 distribution by $\bar{\mathbf{x}} = \mathcal{G}(\boldsymbol{\theta_{ex}})$. We then minimize the non-convex function

$$\widehat{\boldsymbol{\theta_{ex}}} = \arg\min_{\boldsymbol{\theta_{ex}}} \|\mathbf{A_{ex}}\mathcal{G}(\boldsymbol{\theta_{ex}}) - \bar{\mathbf{y}}\| + \mu_T\|\boldsymbol{\theta_{ex}}\| + \mu_S\|D_S\boldsymbol{\theta_{ex}}\|$$

Here the 1st term is the usual least squares term, the 2nd term imposes the conventional 2-norm penalty, and the 3rd term is the new proposed spatial penalty term. Matrix D_S is the first difference operator, and the penalty terms are weighted by regularization parameters μ_T, μ_S. Minimizaion was performed by an iterative non-linear least squares solver written in MATLAB. The Jacobian of the objective is calculated in advance and its sparsity is exploited to speed up computations. MWF was defined as the 1st Gaussian strength divided by overall signal.

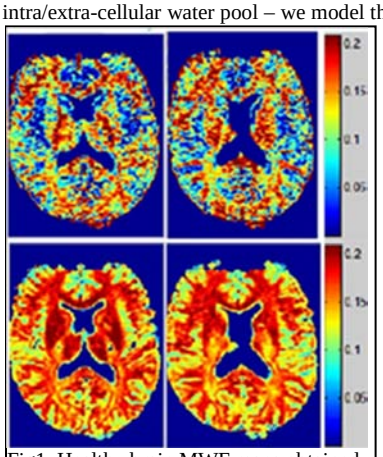

Fig1. Healthy brain MWF maps obtained with conventional (top) and proposed spatial (bottom) algorithms.

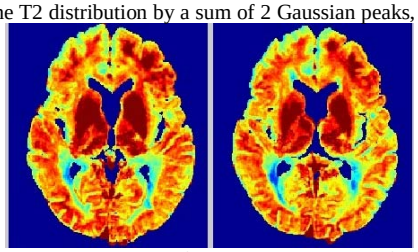

Fig2. 2 axial slices of proposed MWF map of a MS patient. Note the excellent depiction of demyelinating lesions and of normal white

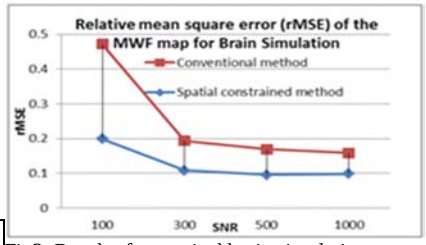

Fig3. Result of numerical brain simulation. Output error was computed for various input SNR values. Proposed method gives around half the error produced by conventional NNLS method.

Table 1	P-value	
	Conventional	Spatial
Patient 1	0.15	0.02
Patient 2	0.04	<0.001
Patient 3	0.07	0.04

Results: Following [4], a custom-designed fast 3D (28 slices, 5 mm thickness) multi-echo T2-prep spiral data was acquired at 3T (GE HDxt 15.0, GE Healthcare) on 3 healthy volunteers and 3 MS patients. We acquired 16 logarithmically spaced echoes between 5 ms to 300 ms, for a total scan time of 10 minutes. Both conventional nonnegative least squares (NNLS) algorithm with regularization [1] as well as the proposed spatial algorithm were used to obtain myelin water fraction (MWF) maps. Healthy axial MWF maps (Fig 1) and MS brain (Fig 2) are shown. Note the improved definition of callosal and peripheral white matter. The MS lesions are depicted very well. The range of MWF values (see color bar) is generally consistent with previous results, but the variability is lower. Spatial maps are extremely detailed and exquisitely depict the white matter bundles. However, our results show much higher values in the deep brain structures, probably due to T2 shortening from iron deposition. Execution time: efficient design reduced computation time to 70 minutes for the whole brain, after 50 iterations.

Next we quantitatively assess these results. First, a numerical brain phantom was constructed with two distinct myelin and axonal pools, whose relative content varied over the brain. By adding various levels of white Gaussian noise and reconstructing MWF maps using above methods, we obtained plots of the output root mean square error – Fig 3. rMSE of proposed method is reduced by around 50% over conventional. On in vivo healthy data, we evaluated the coefficient of variation (COV) over all voxels in 3 subjects to assess the noisiness of MWF maps – Table 2. Proposed method gives several times lower COV than conventional, probably due to the latter's excessive noise. Finally, we assessed how well could each method depict demyelinating lesions in 3 MS patients, based on hand-drawn lesion ROIs guided by their FLAIR images. Table 1 shows the statistical difference of MWF between normal white matter and lesion in terms of p-values. Clearly, the proposed MWFs achieve significance whereas conventional do not.

Table 2	Conventional COV	Spatial COV
Whole brain WM	0.8358	0.1448
Whole brain GM	1.1479	0.2423
Genu of CC	0.4505	0.1122
Splenium of CC	0.4781	0.1503
Internal capsule	0.2775	0.0776

Conclusions: Our results demonstrate that use of spatial constraints along with a 2-Gaussian model of T2 pools allows the reconstruction algorithm to produce stable, noise-free myelin maps compared to conventional method. This is especially important in our application, which uses fast but noisy T2-prep spiral acquisitions. Combined with fast spiral sequences, the proposed algorithm brings T2 relaxometry based myelin imaging into the realm of clinical feasibility.

[1] Laule et al, J Neurol 2004;251(3):284-293 [2] Graham et al, Magn Reson Med 1996;35(3)
[3] Whittall & Mackay, Magn Reson 1989;84:134-152.[4] Nguyen et al, Magn Reson Med. 2012;67(3):614-2