# Anatomically induced regularization of Myelin Water Estimation by DW-MRI

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***Introduction*** Reliable quantitative estimation of myelin content within neuronal tracts can substantially advance our understanding of neuro-degenerative diseases. Low signal-to-noise ratio (SNR) of such imaging methods, in particular T2 relaxometry (T2R), makes signal regularization unavoidable[1-3]. With newly developed 3D T2prep stacks-of-spiral GRE (SPIRAL) sequence for T2R, capable of a whole brain scan in the clinically acceptable time (<*20*mins) at the expense of SNR [4], the importance of adequate spatial regularization is increased even more.

Over time, various spatial regularization methods have been proposed[2-3]. The best existing method seems to be the *anisotropic diffusion filter* (ADF) [2-3] which, despite its similar name, is not to be confused with our work -ADF is an edge preserving filter that operates only on T2R data.

While manual tuning of the parameters in ADF and other spatial filters can result in visually plausible myelin maps, these methods operate solely on data from a single MRI modality and mostly ignore underlaying brain anatomy, exibiting patch-like artifacts[3] and/or the danger of over-smoothing the data[2]. This is particularly troublesome for small lesions and deceases such as multiple sclerosis.

We propose a spatially adaptive filter, based on the Diffusion-Weighted (DW) MRI, that regularizes data with respect to neuronal direction, information otherwise unavailable in myelin imaging. We present the method on T2R, but similar approaches can be used with other myelin content estimation techniques.

***Methods*** T2R is a series of T2-weighted images at different echo times. At each voxel, signals $y_k$ are measured at echo times $TE_k$ and a set of $N$ exponential decay curves are hypothesized to exist, each having a known T2 time $T_2(i)$ $i=1,..,N$ and an unknown volume fraction $x_j$ representing different brain compartments. Assuming a slow exchange regime, the signal equations can be written as $y = Ax+\varepsilon$, with $A_{ki}=exp(-TE_k/T_2(i))$, ε is the noise. This system is under-determined and ill-posed and Tikhonov regularization is used to partially overcome this problem[1] by *regularized Non-Negative Least Squares* (rNNLS) fitting: $\hat{x} = \arg\min_x ||Ax - y||^2 + \mu||x||^2$ where μ is determined by $\chi^2$ fitting. Following [1], *80* $T_2(i)$*'s* were logarithmically spaced between *5*ms and *2*s and the *myelin water content* (MWC) corresponds to T1-corrected fraction of $\hat{x}$ between *0* to *40*ms.

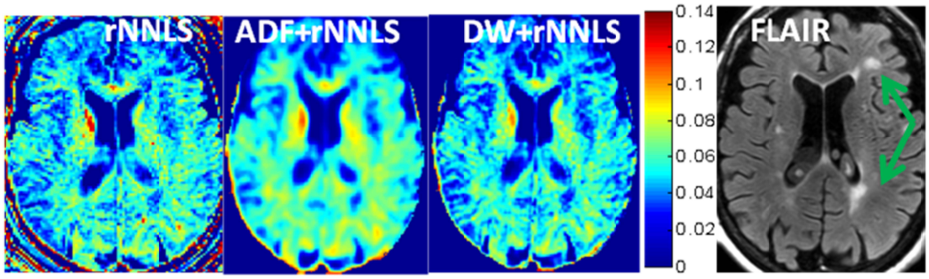


**Figure 1:** MWC maps with different regulatization. Note the lesions.

We propose filtering the signal vectors $y$ before *rNNLS,* with data from neighoboring voxels: $y^{new}=y^{old}+\frac{1}{4}Wy^{old}$ This is similar to ADF, but a 3D difference kernel $W$ has location of non-zero entries determined by neuronal orientation within the voxel and values of the non-zero entries $f_j$ are given by the neuronal fibers volume fraction coming from the DW-MRI multi-tensor diffusion model[5]: $\frac{S_i}{S0} = f_0 \exp(-b_i d) + \sum_{j=1}^{N} f_j \exp\left(-b_i d\left(n_i^T R_j\right)P\left(R_j^T n_i\right)\right)$ Here, $S_0$ is the non-gradient weighted signal, $S_i$ are gradient signals, $d$ is the diffusivity, $b_i$ and $n_i$ are the i-th $b$-value and gradient direction, $R_j$ is the rotation aligning the gradient with $j$-th fiber and P is a projection matrix. $f_0$ is the signal contribution from the isotropic component and $f_j$ , $j>0$ is the fraction coming from the $j$-th fiber. The value of the $W$ entry corresponding to the filtered voxel is $-2\sum_{j=1}^{N} f_j$, accounting for the two voxels in the neighbourhood of $y$ on the same direction. Factor 1/4 was chosen so that in the (theoretical) case of $\sum_{j=1}^{N} f_j = 1$, voxel retains half of its original signal. Other values are possible, modulating the level of smoothing.

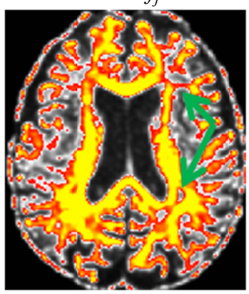

**Figure 2:** $\sum_{j=1}^{N} f_j$ heat map. Note the lesions.

MS lesions exhibit isotropic DW signal[6]. This results in smaller values of $f_j$, $j>0$, so lesion voxels are not over-smoothed by surrounding voxels. See figure 2. In order to merge data from T2R and DW-MRI, T2R data is co-registered[7] to the low b-value ("$b_0$") DW-MRI volume and all the calculations are performed in the DW-MRI images'space, so that vector information is preserved.

*Data acquisition*. MS patients' data was acquired on a 3T GE Excite HDst scanner. DW-MRI had 33 diffusion-encoding directions at $b=1000s/mm^2$, voxel size $2x2x2mm^3$, scan time <*10* mins. T2R by SPIRAL sequence: TR=*2.5*s, *21* TEs at *5*ms, *10-90*ms (*10*ms step), *110-310*ms (*20*ms step); flip angle $10^o$, matrix *192x192*; slice=*5*mm; number of slices *28*; spiral TR=*5.6*ms; number of spiral leaves per segment *128*; scan time *10* mins[4].

***Results*** We compared our method to MWC estimation by rNNLS and ADF+rNNLS as proposed in (2) on five MS patients (4 female, 1 male). The results on representative brain regions for one of the female patients are in table 1. Lesion regions were detected manually on the FLAIR images, standard deviations are calculated over the voxels in the region. The proposed DW+rNNLS regularization maintained the MWC averages of the rNNLS, with smaller variance. ADF+rNNLS had the smallest variance, but also higher MWC in the lesions. Figure 1 illustrates the whole brain MWC maps. Other patients presented the same tendencies.

**Table 1:** Comparison of MWC on the same patient

| Structure | Myelin Water Content (MWC) ± std dev | | |
|---|---|---|---|
| | rNNLS | ADF+rNNLS | DW+rNNLS |
| lesions | 3.0% ± 1% | 3.5% ± 0.5% | 3.0% ± 0.9% |
| genu | 7.0% ± 1.1% | 6.7% ± 0.7% | 7.0% ± 0.8% |
| splenium | 7.4% ± 0.6% | 6.9% ± 0.5% | 7.3% ± 0.6% |

We note that motion correction of T2R data, by linear coregistration over different echo times, is possible and desirable. It can enable analysis on the scans that are otherwise unusable (1 case). Although visual inspection of the coregistration is necessary and it is difficult to estimate precision, tested data sets showed no visible discrepancies.

***Conclusion*** With experimental scanners with diffusion gradients already reaching echo times under *20*ms, we are confident that directional myelin content estimation will eventually become possible. While the proposed merge of DW-MRI with existing myelin estimation techniques has downsides (T2R related issues, need for careful coregistration, etc.), it offers a clinically viable alternative to more precise myelin estimation at the present time.

***References*** [1]Whittall K *et al. MRM* 1997,37:34-43. [2] Jones K. *et. al. MRM* 2003,50:206-209.[3] Hwang D. *et. al.JMRI* 2011,34:189-195. [4]Nguyen T. *et. al. ISMRM 2011* 19:4078. [5] Behrens T. *et. al. NeuroImage.*2007,34:144-55. [6]Werring, D. *et.al. Neurology 1999;* 52:*1626-1633.*[7]Avants B *et.al.MIA* 2008,12: 26-41.