Introducation: A quantitative measurement of the myelin content of white matter (WM) can be used as a significant predictor of the prognoses of the clinically isolated syndrome and for earlier diagnosis of WM diseases such as multiple sclerosis (MS). One approach developed to provide valuable information on myelin content is to measure myelin water fraction (MWF) by analyzing $T_2$ decay curves using a nonnegative least square (NNLS) algorithm [1, 2]. This technique has successfully demonstrated the merit of quantitative measurement of MWF in the study of MS. The NNLS algorithm is commonly used with a regularization in the $T_2$ spectral domain, which will be referred to as rNNLS hereafter. The rNNLS algorithm showed an improved performance, but it is still prone to the noise in the measurements [3].

The purpose of our current study is to develop a new analysis approach, referred to as a spatially regularized NNLS (srNNLS) algorithm, for robust MWF estimation with a reduced sensitivity to the noise. In the srNNLS algorithm, the regularization is expanded into the spatial domain in addition to the $T_2$ spectral domain.

Method: A postmortem MS brain with several focal lesions was scanned with a multi-gradient-echo (MGRE) sequence [4] to acquire free-induction-decay (FID) signals on a 3T MRI scanner (General Electric, Waukesha, WI). The image matrix was 256 x 256, TR = 2 s, FOV = 20 cm, slice thickness = 3 mm, the first echo time = 2.1 ms, and echo spacing = 1.1 ms. The $T_2^*$ spectra were estimated from the acquired FID signals for the individual pixels using the rNNLS and the srNNLS algorithm, respectively. MWF maps were obtained from the estimated spectra and their contrast-to-noise ratios (CNR) over small lesions were compared. The srNNLS algorithm was implemented by minimizing $||\mathbf{As} - \mathbf{y}||^2 + \mu||\mathbf{H}\mathbf{s}||_2^2$, subject to $\geq 0$, where $\mathbf{A}$ is the system matrix, $\mathbf{s}$ is the $T_2^*$ spectrum, $\mathbf{y}$ is the $T_2^*$ decay measurements, $\mu$ is the regularization parameter, $H$ is the weighting matrix, and $p$ is the a priori spectrum. $\mu$ was estimated from the spectra obtained by the rNNLS algorithm. Simulations with synthetic data were also performed to assess the variability of MWF estimation and the visibility of small lesions due to the measurement noise. The synthetic data were produced with different noise (SNR=70, 100, 150) and contrast levels (C=7.5, 12, 15).

Results: Figure 1 shows the results of simulation studies. In all three cases (a~c), CNR was substantially improved with the use of the srNNLS algorithm. Figure 2 shows the results of the postmortem MS brain studies. The MWF map estimated by the srNNLS algorithm, referred to as MWF$_{srNNLS}$ (b), contained high spatial noise (“hole”-type noise [3]) and the visibility of small lesions (indicated by arrows in $T_2$-Flair image (a)) was significantly degraded. In contrast, this hole-type noise was substantially reduced in MWF$_{srNNLS}$ (c) with an improved visibility of small lesions. Figure 3 shows CNRs for 7 lesions. CNR was improved by a factor of two with the use of srNNLS algorithm. Figure 4 and 5 shows the effect of regularization strength ($\mu$) on the estimation of MWF maps. The optimal $\mu$ was found at $\mu=15$.

Discussion: The results of this study demonstrate the effectiveness of the srNNLS algorithm for robust MWF estimation. A substantial decrease in the MWF variability was observed in both simulations and the analysis of in vitro MGRE data. The visibility of small MS lesions was substantially improved. In contrast to the regular low-pass filters which reduced the noise with a penalty of reduced spatial resolution, the srNNLS algorithm effectively preserved the boundaries with substantial noise reduction.