Non-regularized multivoxel NNLS is a robust analysis approach to quantitative T_2

T. A. Bjarnason[1], C. R. McCreary[1], J. F. Dunn[1], and J. R. Mitchell[1]
[1]University of Calgary, Calgary, AB, Canada

Introduction: Quantitative T_2 (qT_2) enables scientists to discern tissue microcompartments by measuring multiple T_2 decays using a multiecho acquisition [1]. This technique is sensitive to myelin content [2] and has uncovered previously undetected microcompartments in MS and PKU pathological tissue [3]. We show that traditional qT_2 analysis using a smoothing constraint underestimates the myelin water fraction (MWF) as the signal to noise ration (SNR) decreases. Furthermore, the variance of the measurement cannot be determined for a single ROI analysis using traditional qT_2, so multiple subjects are needed. In order to use qT_2 clinically, however, the variance of a single ROI measurement is required to determine if, and to what degree, the MWF deviates from normal. We present a robust approach to qT_2 that more accurately estimates the MWF with decreasing SNR, provides error bounds on a single ROI, and has confidence intervals on the T_2 distribution.

Methods: Synthetic Decay Data – This portion of the study characterizes how the measured MWF is affected using regularized and non-regularized fitting routines at various SNRs. Simulations are performed using a rat white matter multiexponential model, where MWF = 7 %, using 1000 realizations of Gaussian noise at SNRs 1000, 400, 200, 100, and 50. Gaussian noise is used to ensure no bias is introduced from a Rician noise-floor that can be misinterpreted as a DC offset in the decay data, potentially causing a source of MWF underestimation. These data are analyzed by creating the T_2 distribution with and without a smoothing constraint. The T_2 distributions are generated using a multiexponential basis set with intensities that are determined using NNLS [4]. The smoothing constraint, used for rNNLS, consists of allowing the curvature of the fit to vary such that $1.01\chi_{min}^2 < \chi^2 < 1.015\chi_{min}^2$ [4].

SNR	1000	400	200	100	50
NNLS	7.094 (0.001)	7.25 (0.03)	7.37 (0.05)	7.44 (0.08)	7.4 (0.1)
rNNLS	6.807 (0.008)	6.61 (0.02)	6.16 (0.04)	5.06 (0.07)	4.2 (0.1)

Table 1: MWFs (in %, st-err reported) from 1000 realizations of Gaussian noise at various SNR levels. The true MWF is 7 %. The two cases shown are non-regularized and regularized solutions as NNLS and rNNLS, respectively.

Rat Data – The second portion of this study compares analysis workflows. The traditional analysis workflow, called regularized ROI NNLS (rrNNLS), consists of drawing an ROI, averaging the decay values together within the ROI, creating a T_2 distribution with smoothing, and determining MWF. The proposed workflow consists of determining the T_2 distribution for each voxel, drawing an ROI, averaging T_2 distributions together, and calculating MWFs with variance estimates. The multi-voxel approach can be conducted two ways, with regularization (rmNNLS) [5] or without (nmNNLS). Single slice, 3ms spaced 128 multiecho rat *in vivo* data at 9.4-T data were collected and rrNNLS, rmNNLS, and nmNNLS are performed on data resulting from an ROI drawn in the corpus callosum using AnalyzeNNLS [6]. The resulting MWFs were compared using a 1-factor ANOVA with Student-Newman-Keuls post-hoc testing where $p < 0.05$ is considered significant.

	rrNNLS	rmNNLS	nmNNLS
MWF (%)	4.89 (0.61)	5.08 (0.31)	6.64 (0.40)†

Table 2: MWFs from *in vivo* rat corpus callosum using different analysis techniques. †Indicates significant difference from all other measured values.

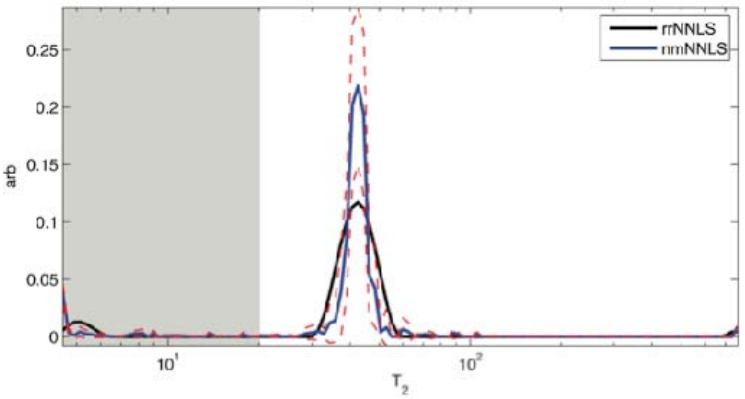

Fig 1: T_2 distributions from rrNNLS and nmNNLS from the same scan. Dashed lines represent the 95 % confidence intervals for the T_2 distribution amplitudes. The gray region represents the T_2 times used to calculate the MWF.

Results: Synthetic Decay Data – NNLS analysis overestimates the true MWF as SNR decreases, while rNNLS underestimates the MWF, as shown in Table 1. However, the magnitude difference from the true MWF is less for NNLS compared to rNNLS at any given SNR.

Rat Data – The nmNNLS workflow provides the largest MWF and is statistically different from rrNNLS and rmNNLS workflows, which are not statistically different from each other, as shown in Table 2. Fig 1 shows the T_2 distributions using rrNNLS and nmNNLS analysis techniques. The 95 % confidence interval is shown with the dashed lines, and the gray region represents the T_2 times used to determine the MWF.

Discussion: The synthetic and rat data both have the highest MWFs when using non-regularized NNLS. A benefit of using the rmNNLS and nmNNLS analysis workflows is that 95% confidence intervals are placed on the T_2 distributions, allowing estimates of variance for MWF using a single ROI, allowing individual time-course studies and comparison with healthy peers. Since rmNNLS is based on rNNLS, which suffers from greater difference from the true value in the synthetic data than NNLS, we suggest that nmNNLS is more robust and should be used for qT_2 analysis.

References: [1] MacKay *et al*. MRI 24: 515-24 (2006). [2] Laule *et al*. MS 12: 747-53 (2006). [3] Laule *et al*. JMRI 26: 1117-21 (2007). [4] Whittall & MacKay JMR 84: 134-52 (1989). [5] Meyers *et al*. ISMRM 16: 3044 (2008). [6] www.imaginginformatics.ca/open-source/analyzennls. We acknowledge financial support from the AHFMR and iCORE.