How to improve the accuracy of total water content measured using T_2 relaxation

Sandra M. Meyers[1], Shannon H. Kolind[2], and Alex L. MacKay[1,3]
[1]*Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada,* [2]*Medicine, University of British Columbia, Vancouver, BC, Canada,* [3]*Radiology, University of British Columbia, Vancouver, BC, Canada*

INTRODUCTION: Multi-component T_2 relaxation is widely used to measure the myelin water fraction (MWF)[1], a quantity that relates to myelin[2]. This technique has also been applied to measure total water content (TWC)[3], which has recently been validated in phantom measurements[4]. It is important to report TWC alongside MWF because MWF is affected by changes in TWC. TWC can be measured by taking the integral under the T_2 distribution, which gives the intercept at time 0, correcting for T_1 relaxation and B_1 inhomogeneity, and normalizing to a water reference (external water container or cerebrospinal fluid (CSF))[4]. This work is the first to estimate theoretical errors in T_2 based TWC measurement with simulations, and determine the impact of factors including the signal to noise ratio (SNR), flip angle inaccuracies (B_1^+ inhomogeneity), and Rician noise, on the accuracy of TWC estimation.

METHODS: Brain voxels were simulated as a sum of up to 3 different pools of water protons (myelin, intra/extracellular (IE), and CSF). Synthetic signals were created for white matter (WM), grey matter (GM) and water reference voxels (an external standard and CSF). M_o values were multiplied by $(1-\exp(-TR/T_1))$ to reproduce T_1 weighting. T_2 relaxation data was simulated using a modified extended phase graph algorithm, which models stimulated echoes that result from imperfect refocusing pulses[5], matching sequence parameters to a GRASE sequence used previously for TWC mapping [4,6]. Rician or Gaussian noise was added to the decay curves, and T_2 distributions were calculated using NNLS fitting with concurrent correction for B_1^+ inhomogeneity[5]. Simulation parameters were selected based on values observed *in vivo* (see Table 1), and 1000 noise realizations were performed for each set of parameters. Proton density (PD) was calculated by integrating signal in the T_2 distribution and dividing by $(1-\exp(-TR/T_1))$; myelin+IE water and CSF pool peaks in the brain voxel were T_1 corrected separately. TWC was calculated as $PD_{myelin+IEwater}/(PD_{water\_reference} - PD_{CSF})$. TWC accuracy was measured by subtracting actual TWC from simulated TWC (indicating systematic error), and TWC variability was measured by taking the absolute standard deviation (SD) over each set of 1000 noise realizations (indicating random error). A linear model was used to determine the effect of SNR, flip angle and pool fractions on TWC, and a two-tailed Student's t-test was used for all other comparisons.

RESULTS: Unless specified, results are described for Rician noise. TWC was underestimated by 0.8% on average (-3.2%-0.5% error range), which was generally caused by a slight overestimation of signal in myelin+IE peaks and the water standard, and a greater underestimation of the CSF pool signal. The average SD of TWC estimates was 1.6% (0.3-4.6%). Table 2 shows effects of several factors on TWC estimation. Due to increased CSF fraction and T_1 weighting in GM, GM TWC was 0.6% less accurate and 0.3% more variable than that of WM. As SNR increased, the difference between Rician and Gaussian noise TWC values decreased.

Table 1. Simulation parameters

Parameter	Value	
SNR	100, 200, 300	
Refocus flip angle (°)	150, 160, 170, 180	
T_2 analysis	Regularized, non-regularized	
Brain voxel:	**WM**	**GM**
M_o	700	800
Myelin pool fraction	0, 0.05, 0.1, 0.15	0, 0.05
CSF pool fraction (CSFfr)	0	0, 0.05, 0.1
T_1 of myelin and IE (s)	1	1.5
T_1, T_2 of CSF (s)	4.3, 2	4.3, 2
T_2s of myelin, IE, CSF (s)	0.02, 0.08, 2	0.02, 0.08, 2
Water reference voxel:	**External**	**CSF**
M_o	1000	1000
T_1, T_2 (s)	0.65, 0.05	4.3, 2

Table 2. Effect of various factors on accuracy and variability of TWC measurement

Variable	Mean Error TWC (%)		Mean SD TWC (%)	
Noise type	Rician -0.8**	Gaussian -0.3**	Rician 1.6**	Gaussian 0.5**
Standard	External -0.6*	CSF -1.0*	External 1.2**	CSF 1.9**
SNR	↓ as SNR ↑**		↓ as SNR ↑**	
Regularization	Yes -0.8*	No -0.6*	Yes 1.6*	No 1.8*
CSF fraction	↑ as CSFfr ↑**		↑ as CSFfr ↑*	
Myelin fraction	No effect		No effect	
Refocus flip angle	No effect		↓ as flip angle ↑**	

*p<0.05, **p<1E-09

DISCUSSION/CONCLUSION: This work demonstrates that TWC can be measured to a high degree of accuracy (within 3%) using T_2 relaxation, even in the presence of B_1^+ inhomogeneity and Rician noise. Simulations indicate that best results are obtained in voxels with low CSF content and T_1 values, using an external water standard with reduced T_1 and T_2 values, and either regularized or non-regularized T_2 analysis. To improve TWC accuracy further, a correction for Rician noise and the use of T_2 relaxation sequences with SNR>=200 is recommended.

References: 1.MacKay et al. MRM 1994;31:673-7. 2.Laule et al. Mult Scler 2006;12(6):747-53. 3.Whittall et al. MRM 1997;37:34-43.
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