Parameter Values For Metabolite Quantification at 7T

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1 T_1 Values

The T_1 values of metabolites and water are well studied in literature at 7T. The T_1 values used for metabolite quantification at 7T were taken from the following references:

Reference	Acquisition	Notes
Xin, L., Schaller, B., Mlynarik, V., Lu, H., & Gruetter, R. (2013). Proton T1 relaxation times of metabolites in human occipital white and gray matter at 7 T. Magnetic Resonance in Medicine, 69(4), 931–936. https://doi.org/10.1002/mrm.24352	• Semi-adiabatic SPECIAL • Occipital gray matter and white matter	• Main reference used for metabolite T_1 values
Andreychenko, A., Klomp, D. W. J., De Graaf, R. A., Luijten, P. R., & Boer, V. O. (2013). In vivo GABA T2 determination with J-refocused echo time extension at 7 T. NMR in Biomedicine, 26(11), 1596–1601. https://doi.org/10.1002/nbm.2997	• MEGA-sLASER • Occipital lobe	• Main reference used for GABA T_1 value • They did not obtain a separate T_1 value for gray matter and white matter

Rooney, W. D., Johnson, G., Li, X., Cohen, E. R., Kim, S. G., Ugurbil, K., & Springer, C. S. (2007). Magnetic field and tissue dependencies of human brain longitudinal 1H2O relaxation in vivo. Magnetic Resonance in Medicine, 57(2), 308–318. https://doi.org/10.1002/mrm.21122	• Perturbed recovery from inversion (PURR), a modified Look-Locker technique • White matter, gray matter, ventricular CSF	• Main reference used for water T_1 value

1.1 Summary of T_1 Values for Metabolites

The T_1 values of metabolites used for metabolite quantification at 7T are summarized below:

Metabolite	T_1 in GM [sec]	T_2 in WM [sec]	Notes
NAA	1.83	1.90	2.01 ppm singlet only
NAAG	1.21	0.94	
Ala	1.28	1.19	Assumed to be the same as myo-inositol, per Kreis[1]
GABA	1.334	1.334	Authors did not obtain a separate T_1 value for gray matter and white matter. The same value is used for both $T_{1,GM}$ and $T_{1,WM}$.
Asp	1.28	1.19	Assumed to be the same as myo-inositol, per Kreis
Cho	1.51	1.32	
Cre	1.74	1.78	3.03 ppm singlet only
Glc	1.28	1.19	Assumed to be the same as myo-inositol, per Kreis
Glu	1.61	1.75	
Gln	1.64	1.74	
GSH	1.14	1.06	
Gly	1.28	1.19	Assumed to be the same as myo-inositol, per Kreis
Myo	1.28	1.19	
Scy	1.31	1.23	
Lac	1.28	1.19	Assumed to be the same as myo-inositol, per Kreis
Peth	1.31	1.32	
Tau	2.15	2.09	

1.2 Summary of T_1 Values for Water

The T_1 values of water used for metabolite quantification at 7T are summarized below:

	T_1 in GM [sec]	T_1 in WM [sec]	T_1 in CSF [sec]
Water	2.132	1.220	4.425

[1] Kreis, R., Slotboom, J., Hofmann, L., & Boesch, C. (2005). Integrated data acquisition and processing to determine metabolite contents, relaxation times, and macromolecule baseline in single examinations of individual subjects. Magnetic Resonance in Medicine, 54(4), 761–768. https://doi.org/10.1002/mrm.20673

2 T_2 Values

To determine the T_2 values for water and the metabolites, the following references were used:

Reference	Acquisition	Notes
Marjańska, M., Auerbach, E. J., Valabrègue, R., Van de Moortele, P.-F., Adriany, G., & Garwood, M. (2012). Localized 1H NMR spectroscopy in different regions of human brain in vivo at 7 T: T2 relaxation times and concentrations of cerebral metabolites. NMR in Biomedicine, 25(2), 332–339. https://doi.org/10.1002/nbm.1754	• LASER sequence with one AHP pulse and two AFP pulses replaced with a slice-selective 90^0 Hamming-filtered sinc pulse • Measured in the occipital lobe, motor cortex, basal ganglia, and cerebellum	• Used MRS voxel tissue fractions and measured T_2 values in calculation of the tissue-specific T_2 values for water and metabolites
Ryan, K., Wawrzyn, K., Gati, J. S., Chronik, B. A., Wong, D., Duggal, N., & Bartha, R. (2018). 1H MR spectroscopy of the motor cortex immediately following transcranial direct current stimulation at 7 Tesla. PLoS ONE, 13(8), e0198053. https://doi.org/10.1371/journal.pone.0198053	• semi-LASER • motor cortex ($1.6 \times 2.0 \times 1.8$ cm^3)	• Used MRS voxel tissue fractions in calculation of the tissue specific T_2 values of metabolites
Wong, D., Schranz, A. L., & Bartha, R. (2018). Optimized in vivo brain glutamate measurement using long-echo-time semi-LASER at 7 T. NMR in Biomedicine, e4002. https://doi.org/10.1002/nbm.4002	• semi-LASER • motor cortex ($1.6 \times 2.0 \times 1.8$ cm^3)	• Used measured T_2 values in the calculation of the tissue specific T_2 values of metabolites
Andreychenko, A., Klomp, D. W. J., De Graaf, R. A., Luijten, P. R., & Boer, V. O. (2013). In vivo GABA T2 determination with J-refocused echo time extension at 7 T. NMR in Biomedicine, 26(11), 1596–1601. https://doi.org/10.1002/nbm.2997	• MEGA-sLASER • Occipital lobe	• Main reference used for GABA T_2 value • They did not obtain a separate T_2 value for gray matter and white matter

2.1 Estimating the T_2 Value of Water

The T_2 values of water in GM, WM, CSF at 7T has not been well studied. The only reported values are from Bartha *et al*[2]. However, Bartha *et al* used a Carr-Purcell LASER sequence to measure the T_2, whereas a more conventional sequence like PRESS, LASER, semi-LASER is more like a Hahn spin-echo sequence. As a result, the T_2 values reported by Bartha *et al* are longer than what would be observed when using PRESS, LASER, and semi-LASER. Instead, the T_2 value of water in GM, WM, and CSF were estimated using measurements made by Marjańska *et al*.

[2] Bartha, R., Michaeli, S., Merkle, H., Adriany, G., Andersen, P., Chen, W., … Garwood, M. (2002). In vivo 1H2O T2† measurement in the human occipital lobe at 4T and 7T by Carr-Purcell MRI: Detection of microscopic susceptibility contrast. Magnetic Resonance in Medicine, 47(4), 742–750. https://doi.org/10.1002/mrm.10112

Marjańska *et al* measured the T_2 value of water in four different regions of the brain: the occipital lobe, the motor cortex, the basal ganglia, and the cerebellum. The susceptibility effects of increased iron in the basal ganglia relative to other regions of the brain may have affected their measurement, only the occipital cortex, the motor cortex, and the cerebellum are considered.

The fractional tissue composition of their measurements are:

	Occipital Lobe	Motor Cortex	Cerebellum
GM	0.51	0.19	0.72 + (0.02/3)
WM	0.44	0.73	0.19 + (0.02/3)
CSF	0.05	0.08	0.07 + (0.02/3)
			Note that their mean values do not add up to 1.00. The remaining 0.02 was distributed among the three compartments.

Their reported water T_2 values are:

	T_2 in the Occipital Lobe [ms]	T_2 in the Motor Cortex [ms]	T_2 in the Cerebellum [ms]
Water	47	47	48

Their reported T_2 values and fractional tissue compositions may be used to set up a system of equations to estimate the water T_2.

$$\begin{bmatrix} 0.51 & 0.44 & 0.05 \\ 0.19 & 0.73 & 0.08 \\ 0.72 + \frac{0.02}{3} & 0.19 + \frac{0.02}{3} & 0.07 + \frac{0.02}{3} \end{bmatrix} \begin{bmatrix} T_{2,GM} \\ T_{2,WM} \\ T_{2,CSF} \end{bmatrix} = \begin{bmatrix} 47 \\ 47 \\ 48 \end{bmatrix}$$

Solving this equation, the following values are obtained:

	T_2 in GM [ms]	T_2 in WM [ms]	T_2 in CSF [ms]
Water	47	45	66

Note: values are rounded to the nearest millisecond.

2.2 Estimating the T_2 Values of Metabolites

In literature, the T_2 values of metabolites are not typically reported separately for GM and WM. These must be estimated from existing information. To do this, Marjańska *et al*'s measurements in the cerebellum and motor cortex were used. Because the fractional composition of their spectroscopic voxel in the cerebellum is mostly gray matter, and the fractional tissue composition of their spectroscopic voxel in the motor cortex is mostly white matter, there is sufficient information within these measurements about the T_2 values of metabolites in GM and WM.

However Marjańska *et al* used a different acquisition than is typically used at the Centre for Functional and Metabolic Mapping (CFMM) at the Robarts Research Institute. On the CFMM 7T scanner, a semi-LASER sequence is used. Thus, information obtained using this sequence and scanner should be incorporated when estimating T_2 values of metabolites in GM and WM. Using this sequence and scanner, Ryan *et al* obtained spectra in the motor cortex and Wong *et al* used the same voxel placement to measure the T_2 values of metabolites.

The T_2 values were estimated as follows:

2.2.1 Obtain the Fractional Tissue Compositions in the Motor Cortex and Cerebellum

Region	References	Intermediate Values				Final Values	
		GM	WM	CSF	Fudge Factor	GM	WM
Motor Cortex	Marjańska *et al*	0.19	0.73	0.08	0.0	0.28	0.63
	Ryan *et al*	0.37	0.53	0.10			
Cerebellum	Marjańska *et al*	0.72	0.19	0.07	0.0067	0.7267	0.1967

Note: The GM, WM, and CSF tissue fractions in the motor cortex were averaged between Marjańska et al *and Ryan* et al*. The GM, WM, and CSF tissue fractions in the cerebellum were those reported directly by Marjańska* et *al. Because reported averages were used, the sum of the GM, WM, and CSF tissue fractions were not necessarily 1. A fudge factor =* $\frac{1-(GM+WM+CSF)}{3}$ *were added to the GM, WM, and CSF tissue fractions to ensure the sum was 1.*

2.2.2 Gather the T_2 Values of Metabolites in the Motor Cortex and Cerebellum

Region	Metabolites		T_2 Value From:		Final T_2 Value
			Marjańska *et al*	Wong *et al*	
Motor Cortex (MC)	NAA	$^2CH_3$ singlet	168	138	153
	Cr	$N(CH_3)$ singlet	113	120	116.5
	Cho	Entire molecule	139	128	113.5
	Scy		112		112
	Glu		98	72	85
	GSH		97	63	80
	Myo		100	102	101
	Tau		90		90
Cerebellum (CB)	NAA	$^2CH_3$ singlet	191		191
	Cr	$N(CH_3)$ singlet	131		131
	Cho	Entire molecule	200		200
	Scy		130		130
	Glu		139		139
	GSH		80		80
	Myo		160		160
	Tau		120		120

2.2.3 Use the Fractional Tissue Compositions and T_2 Values from the Motor Cortex and Cerebellum to Estimate T_2 of Metabolites in GM and WM

Using the previously obtained fractional tissue compositions and T_2 values of metabolites from the motor cortex and cerebellum, a system of equations for each metabolite may be set up to estimate the T_2 value in GM and WM of that particular metabolite:

$$\begin{bmatrix} 0.28 & 0.63 \\ 0.7267 & 0.1967 \end{bmatrix} \begin{bmatrix} T_{2,GM} \\ T_{2,WM} \end{bmatrix} = \begin{bmatrix} T_{2,MC} \\ T_{2,CB} \end{bmatrix}$$

For metabolites not measured in Wong *et al*, the fractional tissue compositions used were directly from Marjańska *et al*:

$$\begin{bmatrix} 0.19 & 0.73 \\ 0.7267 & 0.1967 \end{bmatrix} \begin{bmatrix} T_{2,GM} \\ T_{2,WM} \end{bmatrix} = \begin{bmatrix} T_{2,MC} \\ T_{2,CB} \end{bmatrix}$$

Solving each system of equation, the following values are obtained:

Metabolite	T_2 in GM [ms]	T_2 in WM [ms]	Notes
NAA	224	143	$^2CH_3$ singlet only
NAAG	224	143	Assumed to be the same as NAA, per Marjańska
Ala	201	71	Assumed to be the same as myo-inositol, per Kreis
GABA	87	87	They did not obtain a separate T_1 value for gray matter and white matter. The same value is used for both $T_{1,GM}$ and $T_{1,WM}$.
Asp	201	71	Assumed to be the same as myo-inositol, per Kreis
Cho	248	102	
Cre	148	119	$N(CH_3)$ singlet only
Glc	201	71	Assumed to be the same as myo-inositol, per Kreis
Glu	176	57	
Gln	176	57	Assumed to be the same as NAA, per Marjańska
GSH	86	89	
Gly	201	71	Assumed to be the same as myo-inositol, per Kreis
Myo	201	71	
Scy	148	115	
Lac	201	71	Assumed to be the same as myo-inositol, per Kreis
Peth	201	71	Assumed to be the same as myo-inositol, per Kreis
Tau	142	86	

2.2.4 Code to Calculate T_2 Values

The following Python code was used for the calculations described above:

```
import numpy.linalg
import numpy as np

print ''
print '==== Calculating T2s for Water ===='
A_water = np.asmatrix([[0.51,0.44,0.05],[0.19,0.73,0.08],[0.72 +
(0.02/3.),0.19+(0.02/3.),0.07+(0.02/3.)]])
b_water = np.array([47,47,48])
print 'A_water', A_water
print 'b_water', b_water
print ''

r_water = np.linalg.solve(A_water, b_water).round()
print '\t', 'T2_GM','\t','T2_WM','\t','T2_CSF'
print 'water', '\t', r_water[0],'\t',r_water[1],'\t',r_water[2]

print ''
print '==== Calculating T2s for Metabolites ===='
t2s = []; names = []
# T2s are: [np.mean([<marjanska, mc>, <wong, mc>]), <marjanska, cerebellum>]]
t2s.append([np.mean([168,138]),191]);       names.append('NAA')
t2s.append([np.mean([113,120]),131]);       names.append('tCr')
t2s.append([np.mean([139,128]),200]);       names.append('tCho')
t2s.append([112,130]);                                  names.append('sIns')
t2s.append([np.mean([98,72]),139]);         names.append('Glu')
t2s.append([np.mean([97,63]),80]);          names.append('GSH')
```

```
t2s.append([np.mean([100,102]),160]);       names.append('mIns')
t2s.append([90,120]);                               names.append('Tau')
print '\t', 'T2_MC', '\t', 'T2_CB'
for i, name in enumerate(names):
       print name, '\t', t2s[i][0], '\t', t2s[i][1]
print ''

f_gm_mc  = np.mean([0.19, 0.37]); f_gm_cb  = 0.72
f_wm_mc  = np.mean([0.73, 0.53]); f_wm_cb  = 0.19
f_csf_mc = np.mean([0.08, 0.10]); f_csf_cb = 0.07

f_fdg_mc = (1 - (f_gm_mc + f_wm_mc + f_csf_mc))/3.
f_fdg_cb = (1 - (f_gm_cb + f_wm_cb + f_csf_cb))/3.

f_gm_mc = f_gm_mc + f_fdg_mc; f_gm_cb = f_gm_cb + f_fdg_cb
f_wm_mc = f_wm_mc + f_fdg_mc; f_wm_cb = f_wm_cb + f_fdg_cb

print '\t', 'f_GM','\t','f_WM','\t','f_CSF'
print '\t', f_gm_mc,'\t', f_wm_mc,'\t', f_csf_mc, '\t', f_fdg_mc
print '\t', f_gm_cb,'\t', f_wm_cb,'\t', f_csf_cb, '\t', f_fdg_cb

A_metab_1 = np.asmatrix([[f_gm_mc, f_wm_mc],[f_gm_cb, f_wm_cb]])
A_metab_2 = A_water[1:3,0:2]
print 'A_metab_1', A_metab_1
print 'A_metab_2', A_metab_2
print ''

print '\t', 'T2_GM','\t','T2_WM','\t','T2_CSF'
for i, name in enumerate(names):
       b_metab = t2s[i]
       if name == 'sIns' or name == 'Tau':
              r_metab = np.linalg.solve(A_metab_2, b_metab).round()
       else:
              r_metab = np.linalg.solve(A_metab_1, b_metab).round()

       print name, '\t', r_metab[0], '\t', r_metab[1], '\t --'

print ''
print '==== Done! ===='
```

3 Number of Protons (^{1}H-MRS Visible Nuclei)

The values for the number of protons are obtained from this reference:

> Govindaraju, V., Young, K., & Maudsley, A. A. (2000). Proton NMR chemical shifts and coupling constants for brain metabolites. NMR in Biomedicine, 13(3), 129–153. https://doi.org/10.1002/1099-1492(200005)13:3<129::AID-NBM619>3.0.CO;2-V

3.1 Summary of Number of Protons Values

The number of protons values used for metabolite quantification at 7T are summarized in the table below:

Metabolite	Number of Protons	Notes
NAA	3	• Using only the NAA_acetyl moiety
NAAG	3	• Using only the NAAG_acetyl moiety
Ala	4	• Using the entire molecule
GABA	6	• Using the entire molecule
Asp	3	• Using the entire molecule
Cho	9	• Using only the $N(CH_3)_3$ group
Cre	3	• Using only the $N(CH_3)$ peak ○ the other peak is affected by water suppression
Glc	6	• Using glucose-alpha ○ glucose-beta is removed by water suppression ○ using only carbons 2-6, 6'
Glu	5	• Using the entire molecule
Gln	5	• Using the entire molecule
GSH	7	• Using only the glycine and glutamate moieties
Gly	2	• Using the entire molecule
Myo	5	• Using carbons 1, 3, 4, 5, 6
Scy	6	• Using the entire molecule
Lac	3	• Using only the $^3CH_3$ group
Peth	4	• Using the entire molecule
Tau	4	• Using the entire molecule

4 Summary of All Parameters

All parameters used for the quantification of metabolites at 7T are summarized in the table below:

Metabolite	Number of Protons	$T_{1,GM}$ [sec]	$T_{2,GM}$ [msec]	$T_{1,WM}$ [sec]	$T_{2,GM}$ [msec]
naa	3	1.83	224	1.9	143
naag	3	1.21	224	0.94	143
ala	4	1.28	201	1.19	71
gaba	6	1.334	87	1.334	87
asp	3	1.28	201	1.19	71
cho	9	1.51	248	1.32	102
cre	3	1.74	148	1.78	119
glc	6	1.28	201	1.19	71
glu	5	1.61	176	1.75	57
gln	5	1.64	176	1.74	57
gsh	7	1.14	86	1.06	89
gly	2	1.28	201	1.19	71
myo	5	1.28	201	1.19	71
scy	6	1.31	148	1.23	115
lac	3	1.28	201	1.19	71
peth	4	1.31	201	1.32	71
tau	4	2.15	142	2.09	86

	Number of Protons	$T_{1,GM}$ [sec]	$T_{2,GM}$ [msec]	$T_{1,WM}$ [sec]	$T_{2,GM}$ [msec]	$T_{1,CSF}$ [sec]	$T_{2,CSF}$ [msec]
water	2	2.132	47	1.22	45	4.425	66