In-vivo ^{1}H-MRS in the Brain: Absolute Metabolite Quantification Using an Internal Water Reference

(BARSTOOL Software Documentation)

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This document describes the concepts and mathematics behind how BARSTOOL software determines absolute metabolite concentrations, and how they are implemented within the code. If you are skimming through the document, look for the boxed equations. Those should tell you everything you need to know at a glance.

Contents

1 Overview

BARSTOOL calculates absolute metabolite concentrations of a metabolite by using an internal water reference. This internal water reference is the unsuppressed water signal collected at the same time as the water-suppressed spectra. Instead of using a ratio of each metabolite signal over the signal of a reference metabolite (e.g. creatine), a ratio over the signal of water is used. This is advantageous because the water signal from brain tissue is consistent between participants, whereas a reference *in vivo* metabolite signal can vary between participants because its concentration varies.

Using an internal reference to determine metabolite concentration is written as follows:

$$\boxed{[M] = \frac{\hat{S}_m}{\hat{S}_W}[W]} \tag{1}$$

where

$$\begin{aligned}
[M] &= \text{concentration of the metabolite} \\
[W] &= \text{concentration of pure water} = 55.14\ \text{M} \\
\hat{S}_W &= \text{corrected water signal} \\
\hat{S}_m &= \text{corrected metabolite signal}
\end{aligned}$$

As Equation (1) shows, BARSTOOL is essentially mapping the measured water signal to the known concentration of pure water, and using that mapping to determine what concentration the measured metabolite signal represents. Note that the measured water and metabolite signals are not used directly; they are first corrected for a variety of factors.[1]

2 Corrections for T_1 and T_2 Relaxation

The most important of these corrections is the correction for T_1 and T_2 relaxation. The objective of the T_1 and T_2 relaxation correction is to determine what the measured signal would be if there was no relaxation. Relaxation of the transverse magnetization is described by the following equation:

$$M_{xy} = M_0 \left(1 - e^{-TR/T_1}\right) \left(e^{-TE/T_2}\right) \tag{2}$$

where M_{xy} is the measured signal, and M_0 is the signal before T_1 and T_2 relaxation begins.

Equation (2) describes relaxation in a single tissue compartment. However, in the context of *in-vivo* brain metabolite quantification, the GM, WM, and CSF compartments must be considered:

$$\begin{aligned}
M_{xy} = {} & M_{0,GM} \left(1 - e^{-TR/T_{1,GM}}\right) \left(e^{-TE/T_{2,GM}}\right) \\
& + M_{0,WM} \left(1 - e^{-TR/T_{1,WM}}\right) \left(e^{-TE/T_{2,WM}}\right) \\
& + M_{0,CSF} \left(1 - e^{-TR/T_{1,CSF}}\right) \left(e^{-TE/T_{2,CSF}}\right)
\end{aligned} \tag{3}$$

$M_{0,GM}$, $M_{0,WM}$, and $M_{0,CSF}$ may be expressed in terms of M_0. Considering only the GM compartment for the moment,

$$M_{0,GM} = f_{GM} \alpha_{GM} M_0$$

[1] Note that BARSTOOL doesn't correct for spectroscopic voxel volume as it is assumed the unsuppressed water signal and the water-suppressed spectra are measured using the same spectroscopic voxel. If this is not the case, voxel volume would have to be considered.

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where f_{GM} is the volume fraction of GM in the spectroscopic voxel, and α_{GM} is the relative proton density in GM.

To explain why $M_{0,GM} = f_{GM}\alpha_{GM}M_0$, it is important to remember that M_0 is proportional to the total number of protons in the spectroscopic voxel. Since proton density is the number of protons in a volume, multiplying the volume fraction by the relative proton density allows us to determine the fraction of the total number of protons contributed by the GM. This fraction can then be used to properly attribute the proportion of M_0 to GM. Using the same reasoning,

$$M_{0,GM} = f_{WM}\alpha_{WM}M_0$$
$$M_{0,CSF} = f_{CSF}\alpha_{CSF}M_0$$

where f_{WM} is the volume fraction of WM in the spectroscopic voxel, f_{CSF} is the volume fraction of CSF in the spectroscopic voxel, α_{WM} is the relative proton density in WM, and α_{CSF} is the relative proton density in CSF.

Thus, Equation (3) may be rewritten as:

$$\begin{aligned} M_{xy} = {} & f_{GM}\alpha_{GM}M_0\left(1-e^{-TR/T_{1,GM}}\right)\left(e^{-TE/T_{2,GM}}\right) \\ & + f_{WM}\alpha_{WM}M_0\left(1-e^{-TR/T_{1,WM}}\right)\left(e^{-TE/T_{2,WM}}\right) \\ & + f_{CSF}\alpha_{CSF}M_0\left(1-e^{-TR/T_{1,CSF}}\right)\left(e^{-TE/T_{2,CSF}}\right) \end{aligned} \tag{4}$$

Since the objective of the T_1 and T_2 relaxation correction is to determine the signal without T_1 or T_2 relaxation, applying a correction for T_1 and T_2 is the same as solving for M_0. Solving (4) for M_0 results in:

$$M_0 = \frac{M_{xy}}{f_{GM}\alpha_{GM}R_{GM} + f_{WM}\alpha_{WM}R_{WM} + f_{CSF}\alpha_{CSF}R_{CSF}} \tag{5}$$

where

$$R_{GM} = \left(1-e^{-TR/T_{1,GM}}\right)\left(e^{-TE/T_{2,GM}}\right)$$
$$R_{WM} = \left(1-e^{-TR/T_{1,WM}}\right)\left(e^{-TE/T_{2,WM}}\right)$$
$$R_{CSF} = \left(1-e^{-TR/T_{1,CSF}}\right)\left(e^{-TE/T_{2,CSF}}\right)$$

2.1 T_1 and T_2 Correction for the Measured Water Signal (S_W)

Equation (5) may be applied directly to correct the measured water signal for T_1 and T_2 relaxation:

$$\boxed{\hat{S}_W = \frac{S_W}{f_{GM}\alpha^W_{GM}R^W_{GM} + f_{WM}\alpha^W_{WM}R^W_{WM} + f_{CSF}\alpha^W_{CSF}R^W_{CSF}}} \tag{6}$$

where

$\alpha^W_{GM} = 0.82 =$ the relative proton density of water in GM as compared to that of pure water
$\alpha^W_{WM} = 0.73 =$ the relative proton density of water in WM as compared to that of pure water
$\alpha^W_{CSF} = 1.00 =$ the relative proton density of water in CSF as compared to that of pure water

and R^W_{GM}, R^W_{WM}, and R^W_{CSF} are the corresponding relaxation terms of Equation (5) using the tissue specific T_1 and T_2 relaxation rates of water. $\boxed{S_W = A_W}$, the amplitude of the fitted water peak.

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2.2 T_1 and T_2 Correction for the Measured Metabolite Signal (S_m)

Unlike the measured water signal, Equation (5) cannot be directly applied to correct the measured metabolite signal because of a couple of reasons. First, it is assumed that the CSF contribution to the metabolite signal is negligible because there are little to no metabolites in the CSF. No part of the metabolite signal should be attributed to the CSF compartment and any metabolite signal should be equally attributed to the WM and GM compartment. Secondly, the relative proton density in GM, WM, and CSF for metabolites are not known. Because of this, α_{GM}, α_{WM}, and α_{CSF} are assumed to be 1.00 for metabolites. The equation to correct the measured metabolite signal for T_1 and T_2 is then:

$$\boxed{\hat{S}_m = \frac{S_m}{\frac{f_{GM}}{f_{GM}+f_{WM}} R^m_{GM} + \frac{f_{WM}}{f_{GM}+f_{WM}} R^m_{WM}}} \tag{7}$$

where R^m_{GM} and R^m_{WM} are the corresponding relaxation terms of Equation (5) using the tissue specific T_1 and T_2 relaxation rates of metabolite m. $\boxed{S_m = \sum_k^K A^m_k}$, the sum of the amplitudes of the metabolite as determined by the fitted prior-knowledge model.

3 Corrections for Number of Averages (N_{avg}), Number of MRS-visible ^1H Nuclei (ρ), and Gain/Scaling Factors (G)

In addition to corrections for T_1 and T_2 relaxation, the following corrections are applied to the measured water and metabolite signals:

1. A correction for the number of averages used to acquire the water signal
2. A correction for the number of MRS-visible ^1H nuclei in the water molecule
3. Corrections for any gain and scaling factors applied by the scanner and during post-processing

These corrections are applied as follows:

$$\boxed{\hat{S}_W = \frac{S_W}{N^W_{\text{avg}}\, \rho^W\, G^W}} \tag{8}$$

$$\boxed{\hat{S}_m = \frac{S_m}{N^m_{\text{avg}}\, \rho^m\, G^m}} \tag{9}$$

4 Summary of Corrections for the Measured Water Signal

Combining Equations (6) and (8), the final equation for the corrected water signal is:

$$\boxed{\hat{S}_W = \frac{A_W}{N^W_{\text{avg}}\, \rho^W\, G^W \left(f_{GM}\alpha^W_{GM}R^W_{GM} + f_{WM}\alpha^W_{WM}R^W_{WM} + f_{CSF}\alpha^W_{CSF}R^W_{CSF}\right)}} \tag{10}$$

5 Summary of Corrections for the Measured Metabolite Signal

Combining Equations (7) and (9), the final equation for the corrected metabolite signal is:

$$\boxed{\hat{S}_m = \frac{\sum_k^K A^m_k}{N^m_{\text{avg}}\, \rho^m\, G^m \left(\frac{f_{GM}}{f_{GM}+f_{WM}} R^m_{GM} + \frac{f_{WM}}{f_{GM}+f_{WM}} R^m_{WM}\right)}} \tag{11}$$

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6 Metabolite Quantification Equations

6.1 Voxel Concentration

The equation to calculate the concentration of a metabolite with respect to the entire of the spectroscopic voxel volume is obtained by substituting Equations (10) and (11) into Equation (1):

$$\begin{aligned}[M]_{\text{voxel}} = &\left(\frac{\sum_k^K A_k^m}{N_{\text{avg}}^m\, \rho^m\, G^m \left(\frac{f_{GM}}{f_{GM}+f_{WM}} R_{GM}^m + \frac{f_{WM}}{f_{GM}+f_{WM}} R_{WM}^m\right)}\right) \\ &\times \left(\frac{A_W}{N_{\text{avg}}^W\, \rho^W\, G^W \left(f_{GM}\alpha_{GM}^W R_{GM}^W + f_{WM}\alpha_{WM}^W R_{WM}^W + f_{CSF}\alpha_{CSF}^W R_{CSF}^W\right)}\right)^{-1} \\ &\times 55.14\ \text{M}\end{aligned} \tag{12}$$

Equation (12) may be simplified into:

$$\begin{aligned}[M]_{\text{voxel}} = &\underbrace{\left(\frac{\sum_k^K A_k^m}{A_W}\right)}_{\substack{\textbf{ratio of}\\ \textbf{measured signals}}} \times \underbrace{\left(\frac{f_{GM}\alpha_{GM}^W R_{GM}^W + f_{WM}\alpha_{WM}^W R_{WM}^W + f_{CSF}\alpha_{CSF}^W R_{CSF}^W}{\frac{f_{GM}}{f_{GM}+f_{WM}} R_{GM}^m + \frac{f_{WM}}{f_{GM}+f_{WM}} R_{WM}^m}\right)}_{\textbf{relaxation correction}} \\ &\times \underbrace{\left(\frac{N_{\text{avg}}^W}{N_{\text{avg}}^m} \times \frac{\rho^W}{\rho^m} \times \frac{G^W}{G^m}\right)}_{\substack{\textbf{correction for number of averages,}\\ \textbf{number of nuclei, and gain}}} \times \underbrace{(55.14\ \text{M})}_{\substack{\textbf{concentration}\\ \textbf{of pure water}}}\end{aligned} \tag{13}$$

6.2 Tissue Concentration

With Equation (13), a metabolite concentration with respect to the entire volume of the spectroscopic voxel was found. To determine the concentration of the metabolite in brain tissue alone, the dilution equation can be applied:

$$\begin{aligned} c_{\text{tissue}} V_{\text{tissue}} &= c_{\text{voxel}} V_{\text{voxel}} \\ c_{\text{tissue}} &= c_{\text{voxel}} \frac{V_{\text{voxel}}}{V_{\text{tissue}}} \\ c_{\text{tissue}} &= c_{\text{voxel}} \frac{1}{f_{GM} + f_{WM}} \end{aligned}$$

Thus, the metabolite concentration in brain tissue is:

$$\begin{aligned}[M]_{\text{tissue}} = &\underbrace{\left(\frac{\sum_k^K A_k^m}{A_W}\right)}_{\substack{\textbf{ratio of}\\ \textbf{measured signals}}} \times \underbrace{\left(\frac{f_{GM}\alpha_{GM}^W R_{GM}^W + f_{WM}\alpha_{WM}^W R_{WM}^W + f_{CSF}\alpha_{CSF}^W R_{CSF}^W}{\frac{f_{GM}}{f_{GM}+f_{WM}} R_{GM}^m + \frac{f_{WM}}{f_{GM}+f_{WM}} R_{WM}^m}\right)}_{\textbf{relaxation correction}} \\ &\times \underbrace{\left(\frac{N_{\text{avg}}^W}{N_{\text{avg}}^m} \times \frac{\rho^W}{\rho^m} \times \frac{G^W}{G^m}\right)}_{\substack{\textbf{correction for number of averages,}\\ \textbf{number of nuclei, and gain}}} \times \underbrace{(55.14\ \text{M})}_{\substack{\textbf{concentration}\\ \textbf{of pure water}}} \times \underbrace{\left(\frac{1}{f_{GM} + f_{WM}}\right)}_{\substack{\textbf{dilution volume}\\ \textbf{correction}}}\end{aligned} \tag{14}$$

Equation (14) can be simplified by multiplying the dilution volume correction through the relaxation cor-

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rection term for the metabolite signal:

$$[M]_{\text{tissue}} = \left(\frac{\sum_k^K A_k^m}{A_W}\right) \times \left(\frac{f_{GM}\alpha_{GM}^W R_{GM}^W + f_{WM}\alpha_{WM}^W R_{WM}^W + f_{CSF}\alpha_{CSF}^W R_{CSF}^W}{f_{GM}R_{GM}^m + f_{WM}R_{WM}^m}\right) \times \left(\frac{N_{\text{avg}}^W}{N_{\text{avg}}^m} \times \frac{\rho^W}{\rho^m} \times \frac{G^W}{G^m}\right) \times (55.14\,\text{M}) \tag{15}$$

7 Implementation in Barstool

To be written ...

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