Modeling MEGA-PRESS macromolecules for a better grasp of GABA

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Introduction: GABA (γ-aminobutyric acid) is a primary inhibitory neurotransmitter in the human brain and the object of many a spectroscopic quest. A MEGA-PRESS sequence [1] with TE=68 ms and interleaved selective inversion at 1.9 ppm and 7.5 ppm has been shown to be a useful technique for measuring GABA at 3T, and LCModel [2] can then be used to analyze the resulting difference spectra. A complication, however, is the presence of a co-edited macromolecular peak at 3.0 ppm ("MM30") which overlaps the most prominent feature of the GABA difference lineshape.

LCModel in general fits spectra as a sum of metabolites plus macromolecule *(and lipid)* lineshapes plus a baseline. However, LCModel's default set of macromolecule ("MM") lineshapes was not designed for difference spectra. Some MM's are indeed co-edited with GABA in a MEGA-PRESS sequence, yielding peaks in the difference spectrum – notably at 0.9 ppm and 3.0 ppm. Non-edited MM's far from the inversion notch at 1.9 ppm are canceled in the difference spectrum, whereas MM's near 1.9 ppm are nulled on alternate scans and should thus appear as negative peaks in the difference spectrum (as does the CH_3 peak of NAA). One way to generate more appropriate macromolecular curves is to acquire metabolite-nulled spectra [3-6], then fit these to create a new set of MM functions for LCModel [6]. Unfortunately, acquiring such spectra is a drain on scan time. Moreover, it's difficult to obtain a spectrum with all metabolites nulled properly, due in part to the inherent variation in their T_1 values. We propose instead to obtain a better estimate for MEGA-PRESS MM's by deconstructing the spectra themselves: (1) LCModel fits spectra as a sum of metabolite functions + MM functions + baseline. (2) Subtract the fitted metabolites from a set of spectra to yield "everything else," and average the results. (3) Fit this averaged remainder as a sum of peaks + baseline to generate a new set of MM functions. (4) Use the new (and presumably improved) MM's for more refined LCModeling.

Methods: We used LCModel to analyze TE 68 MEGA-PRESS spectra from the thalamus and adjacent basal ganglia of ten Mn-exposed smelters from a factory in China plus ten age-matched controls [7]. Metabolite basis set spectra were simulated using published chemical shift and J-coupling values [8], with an exact treatment of spin evolution during the selective "MEGA" inversion pulses. We then experimented with four different techniques to model the sum of GABA + MM30:
Method 1: Do nothing special and instead rely on the LCModel baseline function to fill in the MM30 contribution *(likely overestimates GABA)*
Method 2: Add a new MM30 peak to the LCModel recipe with no constraints *(likely underestimates GABA)*
Method 3*:* To control the amplitude of the MM30 peak relative to the non-overlapped macromolecule peak at 0.9 ppm (MM09), replace the separate MM30 and MM09 components with a new combined peak with an MM30/MM09 amplitude ratio of 2/3 *(a value obtained after some trial and error)*
Method 4*:* Apply a soft constraint on MM30 [6]: MM30/MM09 = 0.667 ± 0.1

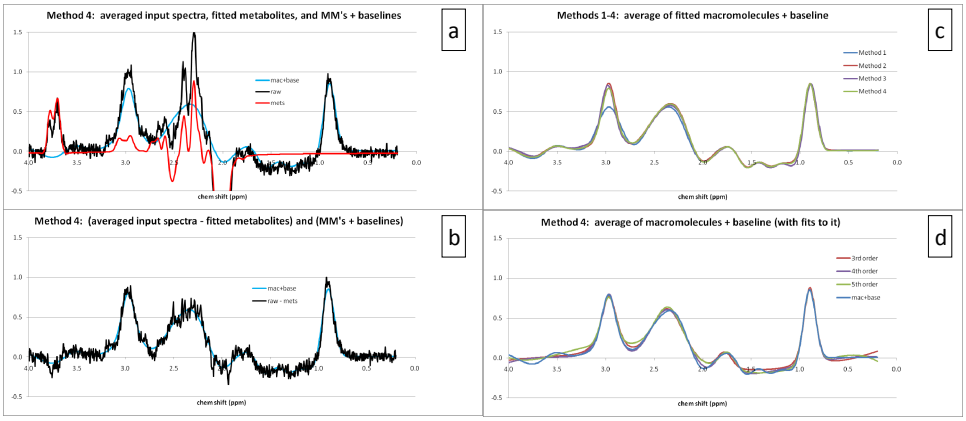
Other than the addition of MM30, these four initial fitting variants all used the default set of LCModel MM functions. To better model macromolecules, we used these results and followed the steps outlined above to obtain synthetically "nulled" spectra averaged over all 20 subjects for each method. We next fit these MM + baseline functions as a sum of *new* MM peaks plus a simplified baseline. In particular, we chose the following set of parameters: (1) four peaks initially centered at 3.0 ppm, 2.33 ppm, 1.74 ppm, and 0.9 ppm (MM30, MM23, MM18, and MM09), each with a variable height, width, position, and Gaussian vs. Lorentzian fraction. (2) a baseline of Legendre polynomials from 0-order up to Nth order, with N = 3-5 *(i.e., 4-6 baseline terms)*

Results: Averaged spectra obtained with Method 4 are displayed below in Figs. 1a and 1b. Average macromolecule + baseline curves (i.e., "everything else") for all four methods appear in Fig. 1c – note how similar the results are for Methods 2-4. Fits of the Method 4 curve using four peaks and 4-6 baseline Legendre functions appear in Fig. 1d. Finally, results for GABA/tCr for Methods 1-4 and a fit using the new set of MM functions ("Method 5") appear in Table 1.

Discussion: By subtracting simulated metabolites from MEGA-PRESS difference spectra, we have obtained "metabolite-nulled" spectra without the need to actually acquire them. For four different LCModel fitting methods, we averaged these nulled spectra and then fit the result as a sum of four peaks plus a set of Legendre polynomials. We thereby obtained a new set of LCModel macromolecule functions: three new ones (MM30, MM23, MM18) plus one holdover (MM09). These new MM functions were then used to fit the 20 input spectra again. Resulting LCModel baselines were flatter, but group GABA/Cr values did not change appreciably nor did the Student two-tailed t-test "p" value for the smelter vs. control group difference. (The difference remained significant at p = 0.025.) Despite the lack of fitting fireworks thus far, an improved set of MM functions for MEGA-PRESS spectra *should* yield better estimates of metabolite concentrations in future experiments. Moreover, this analysis technique can be applied to other types of difference spectra.

References: [1] Mescher et al, *NMR Biomed* 1998; 11:266-272. [2] Provencher, *Magn Reson Med* 1993; 30:672-679. [3] Behar et al, *Magn Reson Med* 1994; 32**:** 294–302. [4] Seeger et al, *Magn Reson Med* 2003; 49: 19–28. [5] Gottschalk et al, *NMR Biomed* 2008; 21**:** 507–517. [6] Bhagwagar et al, *Biol Psychiatry* 2007; 61:806-812. [7] Dydak et al, *Environ Health Perspect* 2010; doi:10.1289/ehp.1002192. [8] Govindaraju et al, *NMR Biomed* 2000; 13**:** 129–153.

Figure 1



Method:	1	2	3	4	5
smelters	.219	.103	.120	.151	.124
controls	.150	.057	.076	.102	.083
all	.184	.080	.098	.126	.104
t-test p	.028	.014	.024	.011	.025

Table 1: GABA/tCr values and group-difference p's between smelters and controls for Methods 1-5. (Method 1 and 2 results appear in Ref. [7])