Chemical shifts and coupling constants of the GABA spin system

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Introduction. Quantitative analysis of *in-vivo* magnetic resonance spectroscopy data often requires prior knowledge of the unique spectral signature, or basis spectrum, for individual metabolites. LCModel analysis [1], in particular, relies on such prior knowledge, and inaccurate basis spectra will inevitably lead to inaccurate concentration estimates. Metabolite basis spectra are commonly generated using quantum mechanical simulations based on the chemical shifts (δ_i) and scalar coupling constants (J_{ij}) of the spin-system in question, as well as the pulse sequence used. When such simulations are performed, the accuracy of the resulting basis spectrum depends heavily on the accuracy of the estimates of δ_i and J_{ij}, which are generally estimated using high-resolution NMR studies. In the case of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), several different values for δ_i and J_{ij} have been previously published [2,3], each of which, when simulated, produces a slightly different GABA spectrum. The purpose of this study is to estimate robust values of δ_i and J_{ij} for the GABA spin system, to compare the estimated values to previously published values, and to suggest the most accurate values of δ_i and J_{ij} for *in-vivo* MRS detection of GABA.

Methods. High-resolution ^{1}H-NMR experiments were carried out at 500 MHz on a Bruker DRX NMR spectrometer. Two samples were prepared to a final volume of 0.50 mL in a 5 mm NMR tube (Norell) with 100 mM GABA and 2mM DSS (as a chemical shift reference) in 100% D_2O and 90% H_2O + 10% D_2O respectively. The pH of the phantom was adjusted to 7.0 using HCl/DCl or NaOH/NaOD, as necessary. During the experiment, the sample was incubated and maintained at a constant temperature of 37 degrees C. A pulse-acquire experiment was acquired with 32768 spectral points and a spectral width of 6009.6 Hz. The chemical shifts and coupling constants of the GABA spin system were then estimated using PERCH Automated Consistency Analysis (ACA) software (PERCH Solutions Ltd. Kuopio, Finland). This software estimates the δ_i and J_{ij} by finding the parameters that produce the best fit to the data through quantum mechanical simulation, while ensuring theoretical consistency between the known molecular structure and the resulting 1H NMR spectrum. The estimated values of δ_i and J_{ij} along with two previously published set of values [2,3], were evaluated by generating simulated GABA spectra for all three sets of [δ_i and J_{ij}] values and comparing the resulting simulations to the acquired 500 MHz data. In this abstract, only data from the spectrum in H_2O + D_2O is considered for analysis.

Results and Discussion. Results. PERCH ACA was successful in finding estimates for δ_i and J_{ij} from the acquired NMR data. The estimated values of δ_i and J_{ij}, as well as the two previously published sets of values to be investigated, are shown in Table 1. Figure 1 shows the experimental spectrum, as well as the simulated spectra from all three sets of δ_i and J_{ij} values. Sim 1 corresponds to the values estimated in this study using PERCH, Sim 2 corresponds to the values published by Kaiser et al, and Sim 3 corresponds to the values published by Govindaraju et al. Also shown in Figure 1 are the differences between simulated and experimental spectra (dotted lines). Figure 2 shows the total RMS error between simulated and experimental GABA spectra for each of the three simulations. The δ_i and J_{ij} values estimated by PERCH produced the smallest RMS error of approximately 6.7%, while the values of Kaiser and Govindaraju produced RMS errors of 10.3% and 21.1% respectively. Discussion. The newly estimated values of δ_i and J_{ij} presented here seem to provide an improved definition of the GABA spin system for the purposes of spectral simulation. This is suggested by the reduced RMS error between experimental and simulated data, but it is also somewhat evident through qualitative inspection of the peak shapes in Figure 1. Specifically, there are marked differences in the shape of the C4 multiplet (3.02 ppm) between the three simulations, with the values of Govindaraju producing a triplet of doublets, the values of Kaiser producing a triplet with an overly broad central peak, and the values of this study producing a triplet that much more closely resembles the experimental data. In summary, a new set of δ_i and J_{ij} values has been proposed which may yield more accurate GABA simulations compared to previously published values.

Param	Current study	Kaiser et al.	Govindaraju et al.
δ_2	2.284	2.284	2.284
δ_3	1.888	1.888	1.889
δ_4	3.013	3.012	3.0128
$J_{2\text{-}2'}$	-15.938	0	0
$J_{2\text{-}3}$	7.678	7.352	7.755
$J_{2\text{-}3'}$	6.980	7.352	6.173
$J_{2'\text{-}3}$	6.980	7.352	7.432
$J_{2'\text{-}3'}$	7.678	7.352	7.933
$J_{3\text{-}3'}$	-15.000	0	0
$J_{3\text{-}4}$	8.510	6.377	5.372
$J_{3\text{-}4'}$	6.503	7.960	10.578
$J_{3'\text{-}4}$	6.503	8.139	7.127
$J_{3'\text{-}4'}$	8.510	7.495	6.982
$J_{4\text{-}4'}$	-14.062	0	0

Table 1. δ_i and J_{ij} Values.

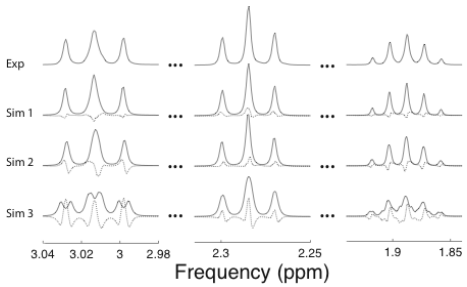

Figure 1. Simulated vs. Experimental GABA spectra. Sim 1: Current study. Sim 2: Kaiser et al. Sim 3: Govindaraju et al.

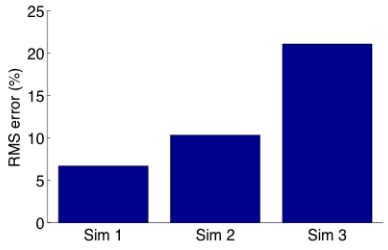

Figure 2. Total RMS error between simulated and experimental data.

References. [1] Provencher SW. Magn Reson Med (1993); 30:672. [2] Kaiser LG et al. NMR Biomed (2008);21:22. [3] Govindaraju V et al. NMR Biomed (2000); 13:129.