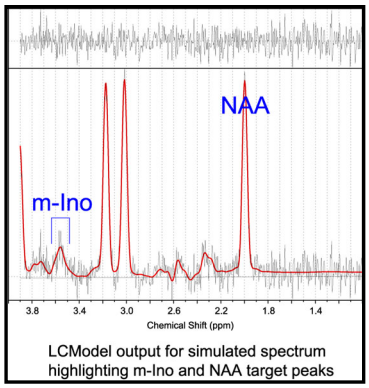
Prospective design of in vivo MRS experiments: Simulation approach to allow the correlation of group size with concentration changes required for significance.

C. C. Hanstock[1], P. Seres[1]

[1]Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada

Introduction : The design of MRS experiments to assess our ability to observe significant changes in brain metabolite concentrations that result from disease states, has to date relied on empirical measurement. While these measurements have used a prior knowledge of disease-related physiological changes, the magnitude of such a change to be statistically significant could only be determined post hoc. This abstract introduces an approach which is prospective in nature which requires linking the following three aspects. First, numerical simulation of proton MR spectra containing a full complement of metabolites, and with sequence timings tuned to allow selective observation of target peaks. Then, to allow these model data to exhibit similar properties to those seen in-vivo, by including variations in metabolite concentrations (both within and between study groups), incorporation of noise to mimic metabolite S/N for typical voxel sizes and number of averages acquired, and to add line-broadening to reflect magnetic field inhomogeneities. Finally, the simulated data sets be suitable for spectral fitting analysis (LCModel (1)), such that the fitted data output can be tested for statistical significance between two study groups. As an example, we describe the analysis of the normalized signals for control (C_{signal}) and diseased (D_{signal}) brain from N-acetylaspartate (NAA) [C_{NAA} = 1.0; D_{NAA} = 1.0], compared to those from myo-inositol (m-Ino) for both normal and for a range of abnormal brain [$C_{m\text{-}Ino}$ = 0.500; $D_{m\text{-}Ino}$ = 0.526 to 0.601], that would be acquired using the STEAM sequence tuned for the optimal observation of m-Ino (TE,TM = 160,40 ms) at 3 Tesla, that we have described previously (2).

Methods : A numerical engine was used for the simulation of the spectral line-shapes of a full range of human brain metabolites (3). These simulations take into account both real RF and gradient pulses, as well as field strength. The input parameters for the simulations were adjusted to yield a series of time domain data for the target metabolites NAA and m-Ino (together with equivalent data for NAAG, Cr, Cho, Glu, Gln, GABA, Asp, Tau, Lac, and Ala) that would result from applying a STEAM sequence (4) with TE, TM = 160, 40 ms, spectral width = 2500 Hz, number of samples = 2048 points. A weighting function was applied to each metabolites FID prior to their summation. The weighting function for the m-Ino was varied in each group to simulate intra-group variations, and then increased through four 5% increments. This was done to assess the precision of the fitting program and also our ability to discriminate between two groups. In addition to the weighting function, the summed data was multiplied by a 6Hz exponential to yield line-widths that were equivalent to those in-vivo, and to each summed data set was added random noise equivalent to that observed in typical brain data sets. A different array of random noise, but of the same amplitude, was added to each summed FID. Thirty FIDs were simulated for each m-Ino group, yielding 150 spectra for analysis by LCModel (1). The simulated time domain data for each of the metabolites listed above, and identical to those used for the preparation of the test data, were used as basis spectra for the fitting program. A typical simulated spectrum is illustrated in the figure and highlights the peaks from m-Ino and NAA that were the focus of this study. Statistical analyses of the peak area outputs from LCModel (1) were performed using a Students t-test, and deemed significant with $p < 0.05$.



LCModel output for simulated spectrum highlighting m-Ino and NAA target peaks

Results and Discussion : The results of our analysis are illustrated in the Table below. The mean and SD's were obtained for 30 spectra in each group. These simulated data represent our "best case" in-vivo expectations, with no distortions from either residual water or macromolecules. The initial analysis showed that there was a systematically higher peak area estimate from the LCModel (1) fit compared to that prepared by simulation (3-4% increase for the NAA, 9-11% for m-Ino). We believe that the larger increase for m-Ino as compared to NAA reflects the lower S/N for m-Ino.

Metabolite	***(1) Control***	***(2) m-Ino + 5%***	***(3) m-Ino + 10%***	***(4) m-Ino + 15%***	***(5) m-Ino + 20%***
Simulated NAA	1.000	1.000	1.000	1.000	1.000
LCModel NAA	1.035 +/- 0.029	1.037 +/- 0.026	1.042 +/- 0.021	1.038 +/- 0.024	1.033 +/- 0.023
Simulated m-Ino	0.500 +/- 0.007	0.526 +/- 0.007	0.550 +/- 0.007	0.575 +/- 0.006	0.601 +/- 0.007
LCModel m-Ino	0.556 +/- 0.047	0.604 +/- 0.042	0.616 +/- 0.032	0.626 +/- 0.038	0.654 +/- 0.059
	For n = 30	$p_{1,2}$ = 0.121	$p_{1,3}$ < 0.001	$p_{1,4}$ < 0.001	$p_{1,5}$ < 0.001
	For $p_{1,x} < 0.05$	n > 30	n ~ 8	n ~ 6	n ~ 5

The Students t-test analyses for each series of increased m-Ino content compared to the control, showed that an increase of 5 - 10% is required to enable us to discriminate between groups of 30, while smaller group sizes would be required for >10% increases in m-Ino. For an in-vivo investigation one would expect a greater increase in m-Ino might be required to attain significance, perhaps in the 15 – 20% range, bearing in mind the greater variations in the observed S/N and line-width.

In summary, we present a method by which MRS studies can be planned prospectively. While we have used only a single variable metabolite (m-Ino) as an example here, it would be reasonable to repeat an analysis for several metabolites each with variable concentration, and incorporate more challenges to the fitting program by the application of a non-linear baseline (eg. residual macromolecule signal), and by adjusting line-width and noise levels to simulate variations in in-vivo conditions.

References: 1. Provencher, Magn.Reson.Med. 30:672 (1993). 2. Kim et al, Magn.Reson.Med. in press (2004). 3. Thompson et al, Magn.Reson.Med. 45: 955 (2001). 4. Frahm et al, J.Magn.Reson. 72: 502 (1987).