The variation of *in vivo* ^{31}P brain MRS measurements due to analysis technique

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Introduction: An important application of ^{31}P MR spectroscopy is the measurement of intracellular pH of tissue. This is achieved by measuring the chemical shift of inorganic phosphate (Pi) relative to phosphocreatine (PCr). It does not require complex modelling as is required when determining peak areas. However, accurate measurement of the chemical shift is required as small changes in the pH are significant. To investigate the most robust method of measuring the pH from spectra acquired *in vivo*, three different techniques were used to determine the chemical shift from which the pH was then calculated.

Methods: ^{31}P MR spectra were obtained using a 1.5T Eclipse scanner (Philips Medical Systems, Cleveland, OH). Four brain spectra were each obtained from eight healthy volunteers using a birdcage transmit/receive coil, dual tuned for ^{31}P/^{1}H operation. The ^{31}P MR spectra were localized on a volume of interest in the centre of the brain using an ISIS sequence with voxel size 70×70×70mm, TR 10,000 ms and 64 signal averages. A typical *in vivo* ^{31}P MR spectrum from the brain is shown in Figure 1. The peaks are assigned to phosphomonoesters (PME), Pi, phosphodiesters (PDE), PCr and γ, α and β nucleotide triphosphates (NTP).

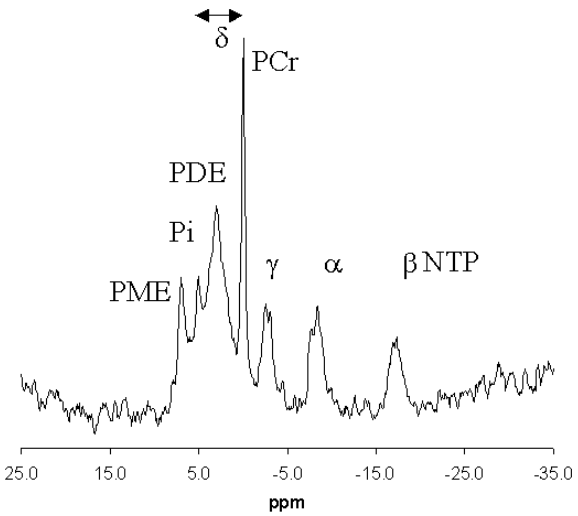

Figure 1: An *in vivo* ^{31}P MR spectrum of the brain.

Analysis: A single observer blinded to all details other than the spectral data carried out the pH calculations in this study. There were three different techniques used to calculate the chemical shift: 1) careful *manual measurement* using the manufacturer's proprietary spectroscopy package, 2) Fitting the data in the frequency domain to inverse polynomials using NMR1 (New Methods Research, Syracuse, NY), 3) Using the values produced by quantification of the ^{31}P signals carried out in the time domain by the AMARES algorithm (1), included in MRUI software (2). A full description of fitting techniques 2) and 3) are described in ref 3. In all methods, the pH was calculated using:

$$pH = 6.77 + \log \{(\delta - 3.29) / (5.68 - \delta)\}$$

where δ was the chemical shift between Pi and PCr (4). The coefficient of variation of the pH in each of the subjects was calculated to allow comparison of the pH values. A paired t-Test was used to compare the pH values produced by the different methods. Reproducibility of results was assessed using the coefficient of variation.

Results: Table 1 shows the mean pH and the mean coefficient of variation of the pH found from the chemical shift as measured by each of the methods. The mean pH values for each of the volunteers produced by MRUI and manual measurement were significantly different ($p < 0.001$), as were the values produced by NMR1 and manual measurement ($p < 0.001$). There was no significant difference between the pH values calculated by the MRUI and NMR1 analyses. Further, it is noticeable that the coefficient of variation of the pH is smaller in the manual measurement compared to that of the other two analysis methods.

Conclusion: The lower variability of the pH values produced by manual measurement makes this the preferable method to calculate pH. It may be that the process of fitting a full multi-parameter model, such as with NMR1 or MRUI, introduces variability in the single parameter of interest here. Further, systematic differences could potentially be introduced when the complex shaped Pi and PCr peaks are fitted by simple line shapes models. Even though NMR1 modelled the peaks with asymmetric line shapes, it still produced similar values to MRUI. Interestingly, MRUI performed similarly to NMR1 when calculating the pH despite having been shown to be far more successful than NMR1 when used to quantify the peak areas of *in vivo* ^{31}P MR spectra (3).

Finally, the differences in pH values produced by the different methods may explain the wide variation of pH values in literature, as noted by Sijens *et al* (5), though Sijens *et al* found the fitting method did not make a difference to the pH. This study suggests that the fitting method is a significant factor.

Method	Mean pH	Mean Coeff. of Var.(%)
Manual Measurement	6.980	0.277
MRUI	7.036	0.606
NMR1	7.042	0.501

Table 1: The pH as calculated using the chemical shifts measured manually, by MRUI and by NMR1.

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