Quantitative conversion of multiple MR measurements into predictions of non-MR parameters illustrated by the evaluation of 1H-MRS changes in the postmortem brain

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Introduction: Quantitative MRI and MRS attempt to connect changes of MR measurements such as metabolite concentrations, relaxation times, diffusion, magnetization transfer etc. with non-MR parameters, e.g. grades or progress of diseases, effects of drugs, etc. [1]. The final goal of such studies is the non-invasive, MR-based, and quantitative determination of the non-MR parameter such as the brain development in children or the progression of plaques in Multiple Sclerosis. Typically, the MR measurements are calibrated in a cohort of patients or volunteers where the non-MR parameter is determined by a gold standard, e.g. biopsy or clinical outcome. These experiments define a functional relation between MR measurement and non-MR parameter. In order to predict the non-MR parameter (in the following indicated by $X_{estimated}$) from the MR measurement, it is necessary to calculate the inverse functional relation. As long as only one MR parameter is concerned, this inversion may be trivial, however, in many cases MR provides multiple parameters, e.g. different metabolite concentrations obtained from a single spectrum. This study proposes a strategy to combine multiple MR findings quantitatively and tests the robustness and accuracy of this procedure on the example of spectral changes recorded by ^{1}H-MRS of brain in situ that are used to calculate postmortem intervals (PMI).

Material & Methods: Experimental data has been described earlier in detail [2] and is only briefly recapitulated here. *Animal model*: In situ brain spectra from 8 sheep heads were acquired regularly up to 18 days postmortem. *Spectroscopy:* Single voxel ^{1}H-MRS was performed at 1.5 T (GE SIGNA) using a short echo time PRESS sequence (TR=3s, TE=20ms) with water and outer volume suppression. ROI's were placed in the frontal lobe and the parieto-occipital region. The spectra were quantified using the fully relaxed water signal as internal concentration standard [3] and fitted with LC Model. *Mathematical analysis and test for robustness:* MRS changes were measured and the time course of each metabolite concentration was parameterized with an appropriate function. The calculation of the inverse functions included a statistical estimation of the error. Final estimations for the value $X_{estimated}$ were based on a combination of the predicted $X_{individual}$ from each of the metabolites. The contribution of each $X_{individual}$ to $X_{estimated}$ was weighted by the inverse of their respective variance (Eq.1). The variance of the weighted prediction ($X_{estimated}$) and its square root (standard deviation) were calculated according to Eq.2. Finally, the correlation between the true values and the estimated values for different combinations of MR parameters were calculated. While the method is generally applicable, $X_{estimated}$ in this very example is the PMI calculated on the basis of 2-5 metabolites out of acetate (ACE), alanine (ALA), butyrate (BUT), free trimethylammonium (fTMA) and propionate (PROP).

(Eq.1) $$X_{estimated} = \frac{\sum_i X^i_{individual} / \mathrm{var}_i}{\sum_i 1/\mathrm{var}_i}$$ i = parameters used

(Eq.2) $$\mathrm{var}(X_{estimated}) = \frac{1}{\sum_i 1/\mathrm{var}_i}$$ i = parameters used

Results: Overall a good correlation is achieved between true and predicted PMI (correlation coefficient 0.87-0.97, mean 0.92), surprisingly irrespective of the number and choice of the metabolites (Fig.1). In contrast, the average variance increases from 107 to 922 [h^2]if the number of metabolites included in Eq.1 is reduced. Fig.2 shows two examples of correlations based on all 5 metabolites (Fig.2a) and 2 metabolites only (Fig.2b). While the agreement between true and predicted times in both examples is very good for PMI < 250h, average variance and error bars are smaller with more metabolites included.

Discussion & Conclusion: The correct quantitative interpretation and combination of multiple MR findings is a frequent problem. If changes from several parameters have to be accounted for, a method with a remarkable robustness in the realistic example of PMIs is proposed here. Postmortem intervals calculated from metabolite concentrations in the brain show surprisingly good correlations between true and predicted times, almost independent of the combination of metabolites. While it is obvious that a larger number of MR parameters leads to smaller variances, the robustness of the method in our example is nevertheless convincing for the application of this procedure to many other examples in MRI and MRS.

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References: [1] Tofts P. Quantitative MRI of the Brain. Wiley Chichester, 2003 [2] Scheurer E et al., Proc. ISMRM 11:568, 2003 [3] Ith M et al., MRM 48: 915, 2002

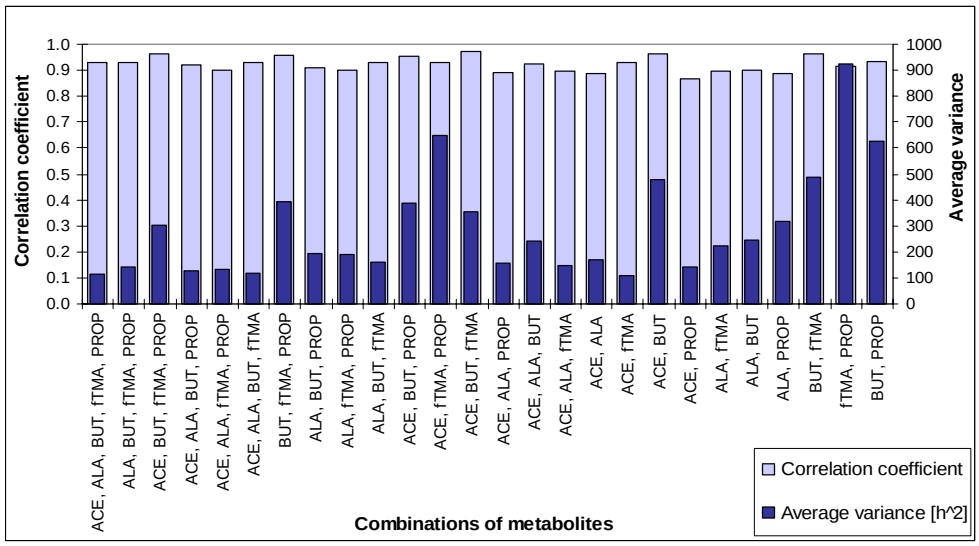

Fig.1: Correlation coefficients and average variances of different combinations of metabolites

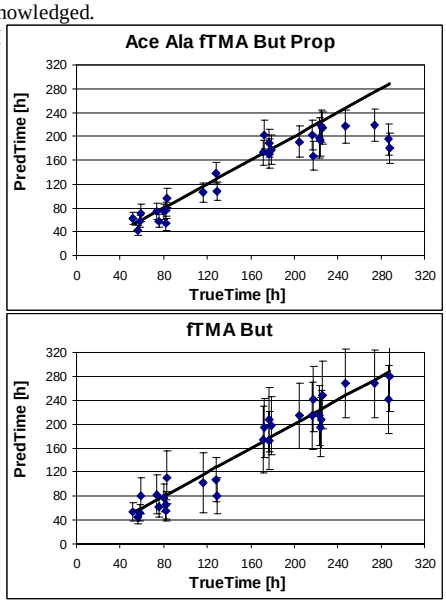

Fig.2a & b: Correlation of true with predicted times for 2 metabolite combinations (straight line: unity)