Accuracy and precision analysis in spectral fitting - a lesson learned from ProFit

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INTRODUCTION

Reliable and unambiguous detection and quantification of metabolites representing coupled spin systems like glutamate (Glu), glutamine (Gln) or gamma-butyric acid (GABA), which reflect processes such as neurotransmission and are of special importance in basic neuroscience as well as clinical research with regard to neurological and psychiatric diseases is impeded by spectral overlap at 3T. Two dimensional JPRESS spectroscopy showed to significantly reduce signal overlap by spreading the spectral information of coupled spin systems into a second frequency dimension. A software tool called ProFit (V1) [1] was introduced by Schulte et al., which allows two dimensional prior knowledge fitting using fully simulated basis spectra similar to LCModel. Recently a revised version of ProFit (V2) [2] has been developed to overcome shortcomings of ProFit V1 and include consideration of macromolecular baseline, residual baseline distortions and lineshape distortions in the fit model. In addition possibilities for more flexible tuning of the included prior knowledge regarding phase and frequency offsets, line broadening and amplitudes of the resonance lines were provided. **The aim of this work** was a systematic investigation of the accuracy and precision of both 2D JPRESS quantification packages (ProFit V1 versus V2) as well as the influence of regularization, fit constraints and individual T2 correction on quantification results. General recommendations on the performance analysis of spectral fitting packages are derived.

MATERIALS AND METHODS

Simulated test data: A virtual brain data set including 18 metabolites was simulated using the GAMMA [4] library. The starting echo time was set to 24ms while in the indirect dimension 100 steps with 2ms echo time increase was simulated. To mimic realistic line widths approximate relaxation rates were taken from literature [2] where available or otherwise set to similar values as other metabolites. Typical relative concentrations were also defined according to literature values [2]. Subsequently these signals were combined into 20 intra-subject (equal concentrations) and 20 inter-subject (different concentrations) data sets with individual Gaussian random noise that resembles typical in-vivo signal-to-noise (SNR) situations. To emulate inter-subject physiological variability or simple acquisition variations concentration values were varied ±10% from the typical values, zero order phase was distorted in the range of ±5 deg and the spectra were shifted arbitrarily between ±4 Hz in the direct and in the indirect dimension. Realistic inhomogeneous line broadening was achieved by randomly applying the normalized lineshape envelopes extracted from 11 measured water scans to the simulated spectra. Additionally a macromolecular baseline signal was added to each data set. The macromolecular contribution was also randomly sampled from a pool of 10 measured and subsequently smoothed metabolite nulled JPRESS spectra from the visual cortex. *Measured test data:* Additionally ten more 2D JPRESS spectra were acquired from one healthy volunteer on a Philips 3T system using a transmit/receive birdcage coil. The voxel size was set to 25x20x20mm and the VOI was placed in the visual cortex. VAPOR water suppression and interleaved inner volume saturation was used. The minimum achievable echo time was TE=24ms, 100 steps a 2ms were acquired with a of TR=2000ms. *Spectral Fit analysis:* Experimental and simulated data were fitted using the same basis set including the identical measured average macromolecular contribution and the sameconfiguration of fit iterations (ProFit 2) or regularization settings (ProFit 1). *ProFit1* does not consider spline or macromolecular baseline, uses a bi-exponential phase decay to account for eddy currents line shape distortions, applies tight constraints on concentrations and line shape parameters and in addition strong regularization to exponential line broadenings and frequency shifts [1]. *ProFit 2* does only apply non-negativity constraints on metabolite concentrations and bound constraints on frequency shifts and line shape parameters as detailed in [2] and determines a spline line shape model by self-deconvolution in the last fit iteration.

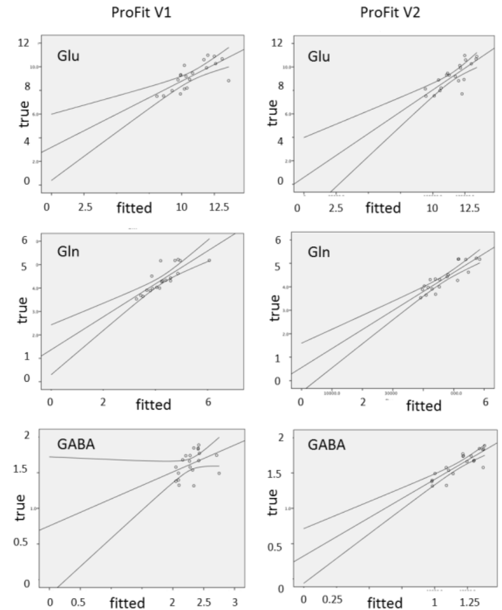

Figure 1: *Accuracy analysis based on 20 simulated 2D JPRESS spectra with in vivo SNR and line shapes of ProFit V1 versus ProFit V2: ProFit V1 overestimates all three metabolites and especially Glu and GABA by a considerable extend, while the concentration estimation by ProFit V2 are much more accurate as indicated by the regression lines going through the 0 point or close by.*

RESULTS AND DISCUSSION

In the accuracy analysis (Figure1) based on simulated data sets with known ground truth the ProFit V2 routine clearly outperforms its predecessor ProFit V1. In case of GABA it is clearly seen that ProFit V1 suppresses the actual variance in metabolite concentration due to strong regularization and most likely the lack of baseline consideration leads to a general overestimation of metabolite levels. In contrast the precision analysis of the experimental intra-subject data resulted in lower coefficients of variance for Gln (15.8 %) and GABA (12.4%) for ProFit V1 in comparison to 17.8% (Gln) and 18.3% (GABA) in ProFit 2. The CVs for Glu were almost identical for both fit packages with 16.16% and 16.03% for ProFit V1 versus V2 respectively. In addition the consideration of individually determined T2 relaxation times (parameter ϑ_e in eq.(2c) of Ref [2]) applied for relaxation correction to fit results reduces CVs in ProFit 2 (Figure 2).

In **CONCLUSION** this work demonstrates that both accuracy and precision are important to evaluate for performance validation of spectral fitting packages as the better accuracy of ProFit 2 is not reflected in a traditional precision (reproducibility) analysis. Strong regularization or tight constraints as implemented in different commercial or freely available spectral fitting routines can lead to small coefficients of variance but strong bias of the quantification results which hinder the detection of naturally occurring variance of metabolite concentrations.

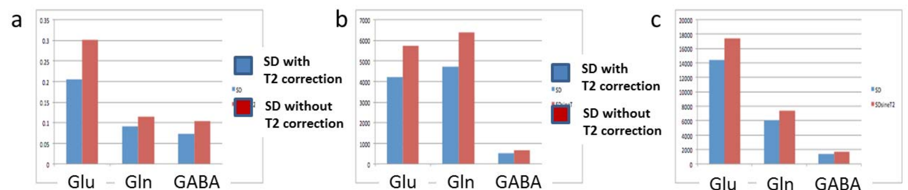

Figure 2: *Precision analysis based on experimental (a)(OCC)(n=10) and simulated (b,c) (n=20 each) 2D JPRESS spectra for ProFit V2: metabolite and volunteer specific T2 corrections consistently decrease the standard deviation (SD) of metabolite concentration estimates for intrasubject (a,b) and intersubject (c)data sets.*

[1] Schulte RF et al, NMR in Biomed 19, 255-263 (2006)
[2] Fuchs A et al MRM Epub 2013