Optimizing 2DJ experiments using Cramer Rao Minimum Variance Bounds

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Introduction For the simultaneous quantification of brain metabolites, 2DJ-spectroscopy has been recommended[1], where a series of PRESS scans is acquired with the echo time (TE) incremented by a fixed step size. We call an analogous experiment *generalized 2DJ* when arbitrary TEs and arbitrary number of scans per TE are used. Generalized 2DJ data is fitted as a 2D-array without Fourier transformation (FT) along TE. It has been shown previously[2,3] that especially the quantification of coupled metabolites improves with (conventional) 2DJ compared to 1D experiments. In addition, 2DJ experiments benefit from maximum-echo sampling (signal acquisition starting right after the last RF pulse rather than at the echo maximum)[1].
Here, we investigated how conventional and generalized 2DJ scans can be optimized for a set of metabolites (GABA, glutamate (Glu), glutamine (Gln) and glutathione (GSH)), by searching acquisition parameters that yield minimal Cramer Rao Minimum Variance Bounds (CRBs)[4], as suggested previously[5,6]. CRBs provide a lower bound for the variance of fitted parameters and thus can be used as a measure for the maximum precision attainable by a specific experiment if the model for the data is complete and correct. CRBs can be estimated without actually acquiring spectra, but based on simulated metabolite spectra, a parameterized experimental macromolecular baseline (MMBL), literature values for concentrations and T_2s and an assumed noise level.

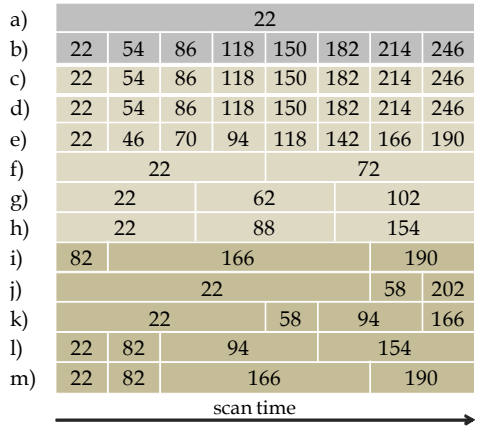

Fig. 1: Optimized experiments from the table. Bars refer to scan time dedicated to a specific TE (in ms).

Methods The data was assumed to be fitted as a 2D-array without FT along TE using linear combinations of model functions and prior knowledge in both dimensions[7]. Basis spectra for 18 metabolites were simulated for 3T in GAVA[8] using chemical shifts and J-couplings from Ref. 9. Parameters obtained from fitting of experimental 2DJ datasets (human gray matter) were used to apply Voigt lines on the metabolites and to add a MMBL (modeled as equally spaced Voigt lines with common line widths and T_2). Metabolite concentrations from the literature[10] were used. CRBs were calculated in frequency domain (0 to 4.2ppm).
In a first step, only conventional 2DJ experiments were considered, with TEs sampled from 22 to 322ms on a grid with 2ms spacing. In a second step, the 2DJ experiment that was found to be optimal for GABA quantification was used as basis for further optimization into generalized 2DJ. This search covered all generalized 2DJ experiments with 8 PRESS scans and TEs from 22ms to 202ms, in steps of 12ms (allowing repetitions of the same TE). Experiments yielding minimal CRBs for GABA, Glu, Gln and GSH were identified as well as an experiment dedicated to GABA and Glu quantification, where the experiment with minimal CRB for Glu was selected from all experiments with a GABA CRB that was at most 1% larger than the GABA optimum.

Results Some optimal sampling strategies are presented in the Table and Fig. 1. Maximum-echo sampling improves CRBs for the selected metabolite concentrations by ~ 30%. CRB based 2DJ parameter optimization found the largest potential for improvement for Glu, with 20% CRB improvement, corresponding to a 36% saving in scan time. Conversely, optimal conventional 2DJ experiments can lower CRBs for GABA by only a few percent, and a further small improvement can be achieved with generalized 2DJ experiments. If mostly interested in the neurotransmitters GABA and Glu, experiment m) may be considered to be best as it is virtually optimal for GABA and almost without penalty for Glu.

	Experiment	Opt. for	T_2 fitted	Half / Max. echo sampl.	CRB [%] GABA	Glu	Gln	GSH
a)	1D	×	×	M	128	68	90	95
b)	2DJ	×	×	M	97	78	98	92
c)	2DJ	×	✓	H	133	123	130	130
d)	2DJ	×	✓	M	**100**	**100**	**100**	**100**
e)	2DJ	GABA	✓	M	**96**	97	95	97
f)	2DJ	Glu	✓	M	113	**84**	92	102
g)	2DJ	Gln	✓	M	106	90	**87**	101
h)	2DJ	GSH	✓	M	100	95	90	**95**
i)	gen. 2DJ	GABA	✓	M	**92**	115	101	100
j)	gen. 2DJ	Glu	✓	M	121	**80**	90	101
k)	gen. 2DJ	Gln	✓	M	106	86	**87**	98
l)	gen. 2DJ	GSH	✓	M	96	105	93	**94**
m)	gen. 2DJ	GABA,Glu	✓	M	**93**	**101**	96	97

Table: CRBs for selected experiments with equal scan time. Values given relative to the default experiment d). a)-b) T_2 not fitted. c) Default conventional 2DJ with half-echo sampling. d)-h) Default and optimized conventional 2DJ with maximum-echo sampling. i)-m) Generalized 2DJ experiments, optimized for individual metabolites and GABA+Glu (cf. text).

Discussion CRBs provide well suited criteria to select optimal sampling strategies for clinical 2DJ MRS. Optima depend on which metabolites are prioritized, but also on experimental circumstances, like shim quality, or on whether or not the MMBL or metabolite T_2s are expected to change or can be assumed to be constant. If T_2s or the MMBL are not fitted, optimal experiments tend to feature shorter TEs. Maxiumum-echo sampling was proven to provide a large benefit for all metabolites and careful selection of TEs can further lower the CRBs substantially.
It should be stressed that above results are strictly only valid for the specific circumstances considered (e.g. field strength, ideal RF pulses, linewidth, metabolite set) and the case of a complete model where the treatment of the baseline is crucial. It may be argued that the spectra should be analyzed after 2nd FT. However, CRBs are the same if calculated in frequency or time domain since the Leibnitz integral rule applies for the model function and FT preserves the inner product. Therefore, the presented CRBs are also valid for 2D spectra after 2D FT. Restriction of χ^2 calculation to off diagonal areas doesn't help in the case of a complete model - on the contrary.
Final proof for the validity of the suggested concepts can only be obtained from reproducibility studies with optimized sequences.

References 1. Schulte RF et al. NMR Biomed 19:264 **2.** Roussel T et al. Proc. ISMRM 2010:904 **3.** Gonenc A et al. MRM 64:623-628 **4.** Cavassila S et al. NMR Biomed 14:278 **5.** Anand CK et al. J.Magn.Res. 197:63 **6.** Bolliger CS et al. Proc. ESMRMB 2011:243 **7.** Chong DG et al. Magn.Reson.Mater.Phy. 24:147 **8.** Soher BJ et al. J.Magn.Reson 185:291 **9.** Govindaraju V et al. NMR Biomed 3:129 **10.** Mekle R et al. MRM 61:1279

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