NeuroImage 83 (2013) 1031–1040

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

On the use of Cramér–Rao minimum variance bounds for the design of magnetic resonance spectroscopy experiments

Christine S. Bolliger [a,b,c], Chris Boesch [a,b], Roland Kreis [a,b,*]

[a] Institute of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[b] Department of Clinical Research, University of Bern, Bern, Switzerland
[c] Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland

ARTICLE INFO

Article history:
Accepted 23 July 2013
Available online 8 August 2013

Keywords:
Magnetic resonance spectroscopy
Cramér–Rao minimum variance bounds
Quantification
Experiment optimization
GABA
Bootstrapping

ABSTRACT

Localized Magnetic Resonance Spectroscopy (MRS) is in widespread use for clinical brain research. Standard acquisition sequences to obtain one-dimensional spectra suffer from substantial overlap of spectral contributions from many metabolites. Therefore, specially tuned editing sequences or two-dimensional acquisition schemes are applied to extend the information content. Tuning specific acquisition parameters allows to make the sequences more efficient or more specific for certain target metabolites. Cramér–Rao bounds have been used in other fields for optimization of experiments and are now shown to be very useful as design criteria for localized MRS sequence optimization. The principle is illustrated for one- and two-dimensional MRS, in particular the 2D separation experiment, where the usual restriction to equidistant echo time spacings and equal acquisition times per echo time can be abolished. Particular emphasis is placed on optimizing experiments for quantification of GABA and glutamate. The basic principles are verified by Monte Carlo simulations and in vivo for repeated acquisitions of generalized two-dimensional separation brain spectra obtained from healthy subjects and expanded by bootstrapping for better definition of the quantification uncertainties.

Introduction

In vivo magnetic resonance spectroscopy (MRS) allows for the in vivo and in situ quantitation of tissue metabolite contents. Different MRS techniques are available and the best suited technique in a particular situation depends on the target metabolites, the organ studied, the (patho-)physiological circumstances, as well as the experimental situation (in particular the B_0 field strength available). Given that metabolite signals in a proton MR spectrum usually have considerable overlap that makes the quantification difficult, generally, one of the three different approaches is taken: 1) use of a single non-specific one-dimensional spectrum (e.g. a localized short echo time (TE) spectrum) followed by linear combination model fitting based on prior knowledge about the constituent metabolites and spectral parameters (Provencher, 1993; Ratiney et al., 2005; Slotboom et al., 1998; Wilson et al., 2011), or 2) use of a dedicated (so-called editing) one-dimensional experiment optimized for exclusive or selective sensitivity for a single metabolite of interest, usually followed by simple model peak fitting or signal integration (Allen et al., 1997), or 3) use of a standard localized two-dimensional MR spectrum followed by peak integration (Thomas et al., 1996, 2001) or prior knowledge fitting (Chong et al., 2011; Gonenc et al., 2010; Kiefer et al., 1998; Kreis et al., 2005; Schulte and Boesiger, 2006; Thomas et al., 2008; van Ormondt et al., 1990; Vanhamme et al., 1999). In cases 1 and 3, the choice of experimental parameters like TE and repetition time (TR) is most often based on general considerations about maximum signal for given relaxation times, insensitivity to changes in relaxation times or arguments about minimization of macromolecular baseline contributions, while in case 2 the signal yield of wanted and unwanted metabolites and their relative overlap is modeled based on quantum mechanical simulations or solution measurements.

An alternative route to arrive at optimal parameters for a particular experimental setting is to calculate the expected lower bound of the achievable precision for a range of potential experimental situations and select the experiment with best precision for the targeted metabolites. The so-called Cramér–Rao minimum variance bounds (CRBs) (Cavassila et al., 2001) are an ideal measure for such an approach. 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. In addition, they can be estimated without actually acquiring spectra, but purely based on a parameterized model function and the expected

Abbreviations: 2DJ, 2DJ separation; CRBs, Cramér–Rao minimum variance bounds; FT, Fourier transformation; Gln, glutamine; GSH, glutathione; HES, half echo sampling; MRS, magnetic resonance spectroscopy; PRESS, Point RESolved Spectroscopy; TR, repetition time; Cr, creatine; FiTAID, Fitting Tool for Arrays of Interrelated Datasets; GABA, γ-aminobutyric acid; Glu, glutamate; GW, Gaussian width; MES, maximum echo sampling; NAA, N-acetylaspartate; TE, echo time.

* Corresponding author at: University of Bern, Inselspital, P.O. Box 35, CH-3010 Bern, Switzerland. Fax: +41 31 632 0580.
E-mail addresses: christine.bolliger@insel.ch (C.S. Bolliger), chris.boesch@insel.ch (C. Boesch), roland.kreis@insel.ch (R. Kreis).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.07.062

signal-to-noise ratio (SNR). This method of experiment optimization has been used in different fields (Anastasiou and Hall, 2004; Brihuega-Moreno et al., 2003; Ober et al., 2002) but only preliminary results of its use for in vivo MRS have been reported (Bolliger et al., 2012; Chong et al., 2007; Snyder and Lange, 2012).

To demonstrate the principle, we investigated the optimization of localized one- and two-dimensional spin echo experiments of human brain. The one-dimensional case corresponds to the clinically most frequently used localization sequence, PRESS (Point RESolved Spectroscopy (Bottomley and General Electric Company, 1984)), with the echo time as an optimizable parameter and with a linear combination model of basis sets as evaluation tool. Simultaneous evaluation of multiple spectra with differing echo times corresponds to 2DJ-separation spectroscopy (2DJ MRS or J-PRESS) (Aue et al., 1976; Kreis and Boesch, 1994; Thomas et al., 1996, 2003), where a series of PRESS scans is acquired with TE incremented by a fixed step size, thus obtaining a two-dimensional dataset, which is usually Fourier transformed in both dimensions before evaluation. 2DJ-MRS has been recommended (Roussel et al., 2010; Schulte et al., 2006) for simultaneous quantification of brain metabolites, and it has been claimed previously (Gonenc et al., 2010) that in particular the quantification of coupled metabolites is improved with 2DJ compared to 1D experiments. The benefit of acquiring multiple echo data in single shots and Monte Carlo parameter optimization in view of a compromise between spectral resolution and added information from multiple echoes was described in Ref. Kiefer et al. (1998).

Here, 2DJ experiments are considered where no Fourier transformation (FT) is applied in the second dimension and which can be evaluated with a linear combination model with prior knowledge relations like in the 1D case using FiTAID (Fitting Tool for Arrays of Interrelated Datasets) (Chong et al., 2011). This provides the freedom to combine scans of arbitrary echo times (i.e. not equally-spaced timings) and arbitrary number of scans per TE. This so-called *generalized 2DJ experiment* was thus optimized with CRBs criteria for optimal precision for a targeted set of metabolites.

Acquiring a series of PRESS scans with varying TEs has two main advantages over single short TE experiments: First, it allows for the fitting of transverse relaxation times and second, J-coupled spins undergo J-evolution, which leads to specific spectral patterns as function of TE (or cross-peaks in 2D spectra after double FT) and therefore better discrimination between metabolites. Short TE scans have the advantage of a higher signal-to-noise ratio, but this comes at the expense of large underlying macromolecular signals. Due to their short transverse relaxation time compared to metabolites, it is possible to eliminate macromolecular signals by using long enough TE while maintaining metabolite signals — though they are evidently reduced by relaxation and phase dispersion through J-evolution, as well. Therefore, sampling short as well as long echo times in one experiment may possibly improve the discrimination of macromolecules and metabolites.

Here, we propose the principle of using CRBs for MRS experiment design and illustrate it by determining whether short TE spectra, conventional, or generalized 2DJ scans are the best for the quantitation of specific brain metabolites. Additionally, the question was addressed which TE to use in 1D MRS and which maximum TE and TE spacing are best suited in conventional 2DJ scans for the quantitation of the metabolites of interest. Exemplary interest was placed on γ-aminobutyric acid (GABA), glutamate (Glu), glutamine (Gln) and glutathione (GSH). Model simulations were used to identify general characteristics, while in vivo spectra were recorded to demonstrate the general validity of this design approach. In order to document small improvements in quantification precision in vivo, a large number of repeated measurements in human subjects are needed. However, the scan time that can be tolerated by individual subjects is limited. Therefore the number of repeated measurements was extended artificially by bootstrapping (Efron, 1979), which has turned out to be a very useful technique to estimate probability distributions and has previously been used in in vivo MRS in order to estimate errors of fitting parameters (Bolan et al., 2004) based on resampled subsets of individually stored single MRS acquisitions.

Material and methods

Estimation of CRBs

CRBs provide a lower bound of the standard deviation ρ_{pl} for the parameters p_l of a model function ξ fitted to experimental data by minimizing χ^2, provided that the parameter estimator is unbiased and the SNR is above a certain threshold (Vallisneri, 2008). For the estimator to be unbiased and thus for the CRBs to yield valid bounds for the physical variables described by the fitting parameters, the model has to be correct and the minimization procedure has to provide the global minimum. Besides, the model has to be fully parameterized. The CRBs are obtained using the Fisher information matrix F, by extracting the roots of the corresponding diagonal elements of its inverse:

$$\rho_{p_l} \geq CRB_{p_l} = \sqrt{\left(F^{-1}\right)_{ll}}. \tag{1}$$

As described in Ref. Cavassila et al. (2001), F can be calculated by taking the real part of a complex-valued matrix product:

$$F = \Re\left(D^H D\right), \tag{2}$$

where H denotes Hermitian conjugation. The columns of the matrix D are partial derivatives of the discretized model function ξ_n (where n denotes the data point index of the measured data, possibly a multi-dimensional index) with respect to the fitted parameters

$$D_{nj} = \frac{1}{\sigma_n} \cdot \frac{\partial \xi_n}{\partial p_j}, \tag{3}$$

where σ_n is the standard deviation of the noise at the respective data point. Here, we assume equal standard deviations at all data points, i.e. $\sigma_n = \sigma$, thus the CRBs depend linearly on σ.

In order to obtain the matrix[1] D, the partial derivatives should be evaluated at the true parameter values. In practice, however, these values are unknown and D is estimated with fitted parameter values.

In addition, the information matrix is invariant under FT of the data since the FT preserves the inner product. Therefore, CRBs can be calculated in either time or frequency domain. This applies to both, the directly measured dimension and the indirect (second) dimension.

In the context of trying to understand which particular subsets of 2DJ data are most relevant for generalized 2DJ experiments, it is worthwhile to note that the inverse of the diagonal elements of the Fisher matrix provides a lower bound to the respective CRB, since for any positive definite matrix it can be shown that $(F_{kk})^{-1} \leq (F^{-1})_{kk}$. (The proof is presented in the inline supplement P.1.)

Furthermore, in the case of a complete model, decreasing the number of data points by selecting a limited data range in any dimension cannot decrease the CRBs (inline supplement P.2 contains the proof for the equivalent statement that extending the data range from a selected region leads to decreased or at least invariant CRBs).

[1] Typically, in a valid model, the rows of D are linearly independent and hence the corresponding Fisher information matrix is positive definite and the inverse exists. However, under certain circumstances it is possible that the Fisher matrix becomes singular (or nearly singular, i.e. ill-conditioned), in which case F^{-1} in Eq. (1) can be replaced by the Moore–Penrose pseudoinverse $F^{\dagger}$ of F (Vallisneri, 2008). This is usually a sign that prior knowledge should be applied to the parameters that cause the singularity.