

# Quantitation of Edited GABA Signals in Magnetic Resonance Spectroscopy

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**Abstract**— $\gamma$ -Amino butyric acid (GABA) is an inhibitory neurotransmitter that plays an important role in several brain disorders. Reliable detection of GABA *in vivo*, using <sup>1</sup>H Magnetic Resonance Spectroscopy is difficult and faces various challenges. Spectral-Editing sequences based on multiple quantum filtering techniques enable removing overlapping signals. However, advanced signal processing accommodating sequence-dependence of the edited signals are needed for quantitation of GABA. We propose to optimally exploit Quantum Mechanics and the time-domain QUEST quantitation algorithm. Quantitation with QUEST of <sup>1</sup>H *in vitro* double-quantum signals at 300 MHz of a ‘phantom’ containing a solution of metabolites with concentrations of a normal brain is demonstrated.

**Keywords**—Magnetic Resonance Spectroscopy (MRS), Signal Processing, GABA Spectral-Editing, Double Quantum Filtering, Quantitation.

## I. INTRODUCTION

$\gamma$ -Amino butyric acid (GABA) is an inhibitory neurotransmitter that plays an important role in several brain disorders such as epilepsy, schizophrenia [1], alcoholism [2] and in cocaine dependence [3, 4]. Reliable detection of GABA *in vivo*, using <sup>1</sup>H Magnetic Resonance Spectroscopy (MRS), is difficult and faces various challenges [5–16], 1) GABA has a low concentration; 2) there are strong overlaps with many metabolite resonances of higher intensity, such as N-Acetylaspartate (NAA), creatine (Cr), glutamate (Glu) and glutamine (Gln) in the brain spectra and GABA cannot be directly observed at 1.5T. Advanced ‘spectral editing’ – *i.e.*, data acquisition with quantum-mechanical filtering – and adapted signal processing algorithms – *i.e.*, using maximal *a priori* knowledge – are therefore essential to its measurement and quantitation. Note that in MRS, signal processing and quantitation are considered synonyms. Among the spectral-editing methods, one can distin-

guish, 1) spin-echo-based difference techniques [6, 17]; 2) ‘single-shot’ techniques using multiple quantum filters (MQF) [5, 7–9, 11]. Multiple quantum techniques are generally preferred because they have better performance with regards to singlet suppression and difference techniques are limited by subtraction errors.

We propose, 1) To use a single-voxel PRESS sequence including a double-quantum (DQ) filter [18] to edit/measure the GABA signal. DQ filtering is an excellent tool to effectively suppress the intense singlet resonances of Cr, Cho and NAA overlapping the GABA spectrum; 2) To simulate by Quantum Mechanics with the NMR-SCOPE program [19] or measure the DQ GABA signal and use it as prior knowledge in the QUEST quantitation algorithm [20–23]; 3) To refine available spin Hamiltonian parameters of GABA with both the Quantum-Chemistry software package Gaussian [24] and NMR-SCOPE, 4) To quantitate the edited DQ GABA signal with QUEST. The method is tested on a phantom solution of cerebral metabolites with concentrations corresponding to a normal human brain. The GABA signal was perfectly edited. Finally, we apply QUEST successfully to quantitate the corresponding signal.

## II. MATERIAL AND METHODS

### A. Spin Hamiltonian parameters of GABA

GABA –  $\text{NH}_2\text{-}^4\text{CH}_2\text{-}^3\text{CH}_2\text{-}^2\text{CH}_2\text{-}^1\text{COOH}$  – is an  $A_2M_2X_2$  spin system with three  $\text{CH}_2$  groups; see Fig. 1 displaying the 3D structure of the molecule. We optimized this lowest-energy geometrical structure using Quantum Chemical calculations based on a DFT/B3LYP approach with basis sets 6-311+G(2d,p) with the Gaussian software package. The normal spectrum of GABA exhibits a quintet (GABA-3) at 1.88 ppm, a triplet (GABA-2) at 2.28 ppm and a multiplet resembling a

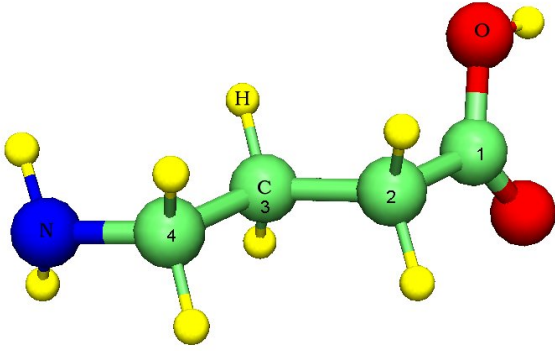


Fig. 1. Optimized 3D structure of the GABA molecule obtained using Quantum-Chemical calculations with Gaussian. Carbon atoms are in green, hydrogen atoms in yellow, oxygen atoms in red and nitrogen atoms in blue.

triplet (GABA-4) at 2.99 ppm, see Fig. 2c. The Hamiltonian spin parameters given in Govindaraju *et al.* [25] were refined with NMR-SCOPE and Gaussian and the J coupling constants were found to be  $J_{2-3} = J_{2-3'} = J_{2'-3} = J_{2'-3'} = 7.35$  Hz;  $J_{4-3} = J_{4'-3} = 7.5$  Hz;  $J_{4-3'} = J_{4'-3'} = 6.8$  Hz. A strong coupling effect is found between the protons on C<sub>2</sub> and C<sub>3</sub> at 1.5 T.

Our objective was to quantitate the edited GABA triplets at 2.28 ppm and 2.99 ppm.

### B. PRESS sequence with a Double-Quantum Filter

We used a PRESS-DQF sequence based on [11]. The conventional single voxel PRESS sequence with a fixed echo time of 68 ms ( $1/2J$  where  $J = 7.35$  Hz) was modified by adding a double quantum filter midway between the two  $180^\circ$  slice-selective pulses. Double quantum coherences were created by the first three pulses ( $90^\circ - 180^\circ - 90^\circ$ ). The delay  $\tau$  between these pulses was fixed to 17 ms ( $1/8 J$ ). Then, after a mixing period  $TM$ , these coherences were converted into observable quantum coherences by a Gaussian frequency selective  $270^\circ$  pulse, tuned to the GABA-3 resonance at 1.88 ppm. Gradients were used to crush magnetization that did not originate from a double-quantum coherence.

The theoretical analysis (not reported in this study) of this PRESS-DQF sequence was done by Quantum Mechanics using the product-operator formalism [18, 19] in order to tune the sequence parameters  $\tau$  and  $TM$ . This analysis enables to predict the amplitudes and phases of the edited spectral components. As such, it is very useful for MR sequence design. We also simulate by Quantum Mechanics with NMR-SCOPE the expected double-quantum spectrum of GABA. NMR-SCOPE, based on

the product-operator formalism, can handle various NMR pulse sequences such as PRESS-DQF. It directly provides the corresponding time-domain signals; see also Sec. II-C.1.

### C. Quantitation

The QUEST quantitation algorithm [20, 26–28] was used to quantitate the edited double-quantum signals as it can easily take into account the MR editing-sequence dependence of the signal and cope with low SNR. QUEST is a time-domain method which fits a combination of weighted whole-metabolite signals (quantum-mechanically simulated or *in vitro* measured) directly to the (*in vivo*) data at hand.

An *in vivo* MRS signal, contaminated by a nondescript background signal, can be modelled by

$$x = \hat{x}_{\text{Met}}(p) + b(\theta) + e \quad (1)$$

where  $\hat{x}_{\text{Met}}$  is the metabolite part whose model function is known,  $b$  the background signal whose model function is often only partially known, and  $e$  Gaussian-distributed noise.

For optimal fitting of Eq. (1) to (contaminated) MRS data, QUEST needs

1. A time-domain basis set of ‘whole-metabolite’ signals.
2. Time-domain semi-parametric estimation of metabolite and macromolecule parameters,  $p$  and  $\theta$ .

QUEST is in fact based on a semi-parametric approach sequentially using untangling of the background from the metabolite signal, and separate modelling and a parametric nonlinear least-squares fitting of the untangled metabolite signal knowing the background.

#### C.1 Whole-Metabolite Basis Set

In order to invoke optimum *a priori* knowledge, the basis set must comprise the double quantum signals of edited metabolites. Ideally, only the double quantum signal of GABA is needed. The latter can be either simulated by NMR-SCOPE or measured *in vitro*. If necessary, the signals of the basis set can be multiplied by an appropriate function – *e.g.*, determined from the signal of a reference molecule – such that they better approximate the actual *in vivo* metabolite signal-shape. Alternatively, one can use the signal of a reference molecule or a singlet to correct the actual *in vivo* metabolite signal-shape with the time-domain procedure QUALITY [29].

## C.2 QUEST Parametric nonlinear least-squares fitting

In absence of – or after removal of – the nonparametric part, a Levenberg-Marquardt algorithm is used in QUEST to minimize the distance between the raw signal  $x$  and the model function  $\hat{x}$

$$\|x - \hat{x}\|^2 \longrightarrow \min \quad (2)$$

The complex-valued time-domain model samples,  $\hat{x}_n, n = 1, 2, \dots, N$  where  $N$  is the number of data-points, is written as a linear combination of the  $M$  – either quantum-mechanically simulated or *in vitro* measured – weighted metabolite model samples  $\hat{x}_n^m, m = 1, 2, \dots, M, n = 1, 2, \dots, N$  of the basis set

$$\hat{x}_n = \exp(i\phi_0) \times \sum_{m=1}^M a_m \hat{x}_n^m \exp[(\Delta\alpha_m + i\Delta\omega_m)t_n + i\Delta\phi_m], \quad (3)$$

where

- $\hat{x}^m$ ,  $m$  being a superscript, can be modelled first as a sum of exponentially damped sinusoids or used as a whole.
- $a_m$  are  $M$  amplitudes to be estimated. Note that these amplitudes represent the relative proportions of the  $M$  metabolite signals  $\hat{x}^m$  in the signal  $x$ .
- $\Delta\alpha_m, \Delta\omega_m, \Delta\phi_m$  represent small changes of the exponential part of the damping factors, angular frequencies, and phase shifts respectively. These changes – relative to the initial values in the metabolite basis set – are included in the estimation procedure to automatically compensate for the effect of magnetic field inhomogeneities. Soft constraints on  $\Delta\alpha_m$  and  $\Delta\omega_m$  have been used in the minimization procedure;
- $t_n = nt_s + t_0, n = 1, 2, \dots, N$ , are the sampling times, in which  $t_0$  is the dead-time of the receiver – included in the estimation – and  $t_s$  the sampling interval,
- $\phi_0$  is an overall phase, included in the estimation,
- $i^2 = -1$ .

The vector  $p$  of the metabolite parameters to be estimated is then  $p = ((a_m, \Delta\alpha_m, \Delta\omega_m, \Delta\phi_m), m = 1, 2, \dots, M; \phi_0, t_0)^T$  where the superscript  $T$  denotes transposition. Note that the number of parameters is only  $4M + 2$ .

## C.3 QUEST Semi-parametric approach

In the case of *in vivo* signals, one needs to handle a perturbing background originating mainly from macromolecules plus lipids. This can be achieved with the

procedure Subtract-QUEST [22]. The background signal is first estimated in a preprocessing step based on signal truncation and subsequently subtracted from the raw data before the QUEST quantitation step. This procedure will be useful for disentangling the overlapping residual macromolecule signal at 2.99 ppm from the double quantum triplet signal of GABA-4.

## III. RESULTS

The experiments were performed *in vitro* on a 300 Mhz Bruker spectrometer. The PRESS-DQF sequence was implemented. The delay  $\tau$  was chosen equal to 17 ms corresponding to  $1/8 J$ , the mixing time TM was optimized and found equal to 10 ms, and we used a Gaussian frequency selective  $270^\circ$  pulse of 13 ms.

Two phantoms were used, a phantom containing a solution of 1.5 mM GABA and eleven metabolites whose known concentrations correspond to a normal adult human brain [25] in  $D_2O$ , see Table I, and a phantom containing only a solution of 1.5 mM GABA in  $D_2O$ . The

TABLE I  
METABOLITE CONCENTRATIONS CORRESPONDING TO A NORMAL ADULT HUMAN BRAIN USED IN THE PHANTOM SOLUTION

Metabolite	Concentration mM
N-Acetylaspartate (NAA)	13.0
Creatine (Cr)	8.0
Phosphocreatine (PCr)	4.0
Myo-Inositol (mI)	5.5
Glutamate (Glu)	9.5
Glutamine (Gln)	4.0
Aspartate (Asp)	1.2
$\gamma$ -Amino butyric acid (GABA)	1.5
Lactate (Lac)	0.6
Glucose (Glc)	1.0
Taurine (Tau)	1.2
Choline (Cho)	2.0

proton signals of both phantom solutions were measured with the conventional one pulse sequence and the mentioned PRESS-DQF sequence. GABA was well edited, see Figs. 2b and d and 'doublets' are observed at 2.99 ppm and 2.28 ppm. The intense NAA, Cho, Cr singlets are perfectly suppressed as well as most of the metabolite coupled spectral components. The additional peaks between 2.2 ppm and 2.5 ppm are DQ peaks of Glu and Gln. They are due to the imperfect selectivity of the Gaussian

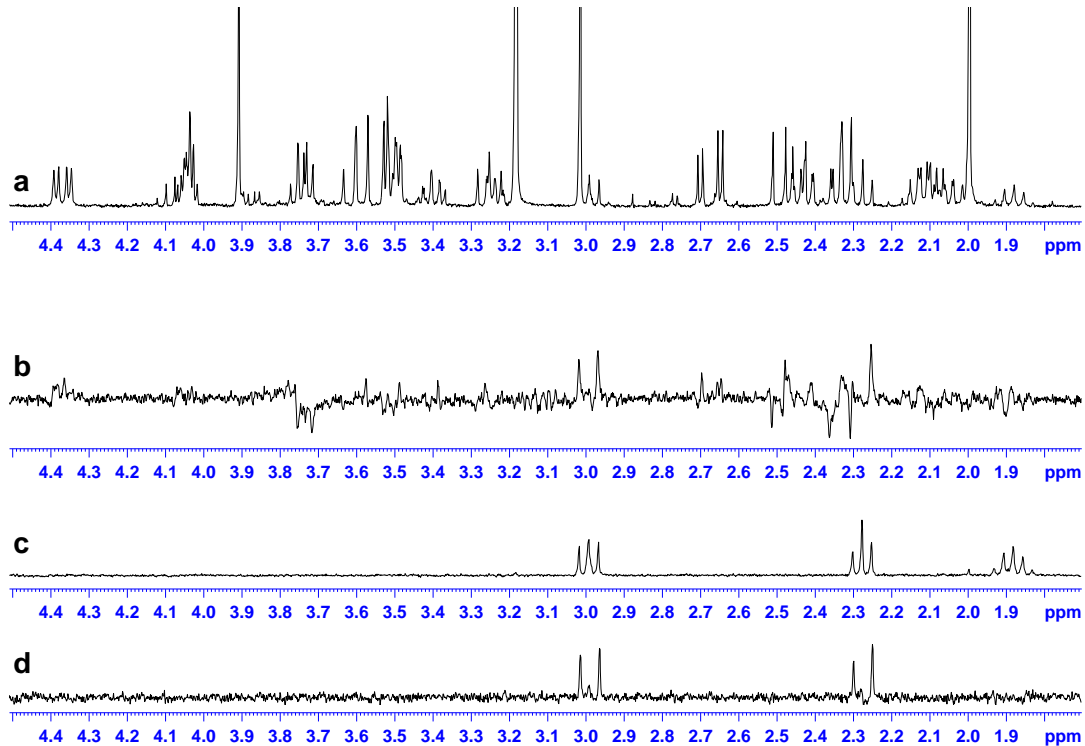


Fig. 2. Spectra of phantoms containing metabolite solutions obtained at 300 MHz with a PRESS-DQF and a one pulse sequences respectively. a) Zoom in of normal spectrum of the solution containing GABA and eleven metabolites with concentrations corresponding to a normal adult human brain; b) Edited double quantum spectrum of this solution, note that the intense singlets of NAA, Cr and Cho have been well suppressed and that mainly GABA spectrum is edited; c) Normal spectrum of GABA; and d) Double quantum spectrum of GABA used in the QUEST metabolite basis set.

frequency selective pulse.

For quantitation, we used the jMRUI software package [30, 31]. After water removal with ER-Filter [32], the edited double quantum signal of the solution containing all metabolites (see Fig. 2b) and exhibiting mainly GABA was quantitated with QUEST. The basis set was made only of the DQ GABA signal measured *in vitro* from the GABA solution. Consequently, only this signal was included in the QUEST fit. Quantitation results are given in Fig. 3. The DQ spectrum of GABA was perfectly estimated. The observed residue is mainly due to the DQ spectra of Glu and Gln. For better quantitation of *in vivo* signals, the basis set should also include the DQ signals of Glu and Gln.

Different gains of the receptor were used when acquiring the edited metabolite and GABA signals. After correction of the gain differences, the estimated proportion of GABA signal in the phantom with respect to the metabolite basis set was  $1 \pm 5\%$  a.u which is to be compared with the true value of 1. a.u. provided that the error on

concentration was negligible. Quantitation results are in good agreement with the true GABA concentration in the phantom solution of metabolites.

#### IV. CONCLUSIONS

1. We successfully edited the GABA signal from a solution containing GABA and eleven metabolites with concentrations corresponding to a normal adult human brain using a PRESS-DQF sequence.
2. We demonstrated that QUEST is well-suited to accommodating sequence-dependence of the edited signals.
3. GABA in edited PRESS-DQF *in vitro* signals of metabolites was automatically and reliably quantitated with QUEST.

Our method will be applied to automatic quantitation of  $^1\text{H}$  *in vivo* MRS signals.

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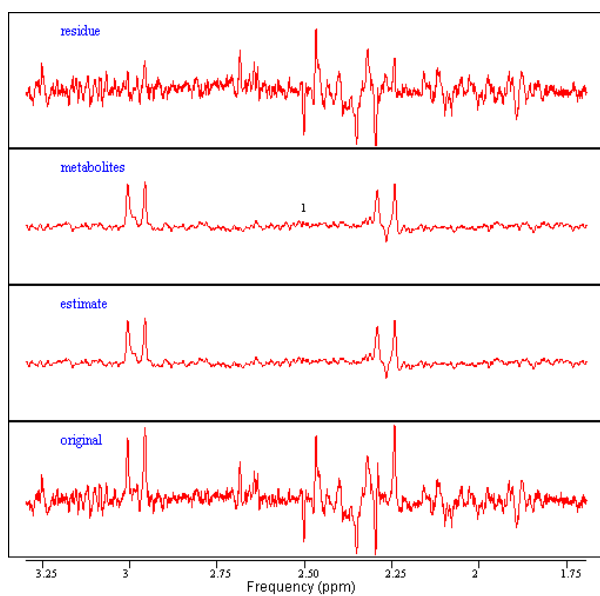


Fig. 3. Edited double quantum spectra of a solution containing GABA and eleven metabolites with concentrations corresponding to a normal adult human brain, quantitated with QUEST. From bottom to top, raw edited DQ spectrum, estimated spectrum, individual DQ spectrum of GABA and the residue.

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## REFERENCES

- [1] F.M. Sherif and S.S. Ahmed, "Basic aspects of GABA-transaminase in neuropsychiatric disorders," *Clin. Biochem.*, vol. 28, pp. 145–154, 1995.
- [2] K. Kuriyama, T. Ueha, M. Hirouchi, T. Hashimoto, and S. Ohkuma, "Functional alterations in GABA A receptor complex induced by ethanol," *Alcohol Suppl.*, vol. 2, pp. 321–325, 1993.
- [3] Y. Ke, C. Streeter, L. Nassar, O. Sarid-Segal, J. Hennen, D. Yurgelun-Todd, M. Rendall, S. Gruber, S. Blank, A. Nason, M. Mudrick, C. Knapp, D. Ciraulo, and P.F. Renshaw, "Brain GABA levels in cocaine dependent subjects increased after the treatment for cocaine dependence," Kyoto, Japan, May 2004, Int. Soc. Magnetic Resonance in Medicine, 12th Scientific Meeting and Exhibition, p. 111.
- [4] Y. Ke, C. Streeter, L. Nassar, O. Sarid-Segal, J. Hennen, D. Yurgelun-Todd, L.A. Awad, M. Rendall, S. Gruber, A. Nason, M. Mudrick, S. Blank, A.A. Meyer, C. Knapp, D. Ciraulo, and P.F. Renshaw, "Frontal lobe GABA levels in cocaine dependence : a two-dimensional, J-resolved magnetic resonance spectroscopy study," *Psychiatry Research Neuroimaging*, vol. 130, no. 3, pp. 283–293, 2004.
- [5] A.H. Wilman and P.S. Allen, "Yield enhancement of a double-quantum filter sequence designed for the edited detection of GABA," *J. Magn. Reson. B*, vol. 109, pp. 169–174, 1995.
- [6] J.R. Keltner, L.L. Wald, J.D. Christensen, L.C. Maas, C.M. Moore, B.M. Cohen, and P.F. Renshaw, "A technique for detecting GABA in the human brain with PRESS localization and optimized refocusing spectral editing pulses," *Magn. Reson. Med.*, vol. 36, pp. 458–461, 1996.
- [7] J.R. Keltner, L.L. Wald, B.B. Frederick, and P.F. Renshaw, "In vivo detection of GABA in human brain using a localized double-quantum filter technique," *Magn. Reson. Med.*, vol. 37, pp. 366–371, 1997.
- [8] J. Shen, D.C. Shungu, and D.L. Rothman, "In vivo chemical shift imaging of  $\gamma$ -aminobutyric acid in the human brain," *Magn. Reson. Med.*, vol. 41, pp. 35–42, 1999.
- [9] H. Lei and J. Peeling, "Simultaneous spectral editing for  $\gamma$ -aminobutyric acid and taurine using double quantum coherence transfer," *J. Magn. Reson.*, vol. 143, pp. 95–100, 2000.
- [10] C.C. Hanstock, N.J. Coupland, and P.S. Allen, "GABA X2 multiplet measured Pre- and Post- administration of vigabatrin in human brain," *Magn. Reson. Med.*, vol. 48, pp. 617–623, 2002.
- [11] M.A. McLean, A.L. Busza, L.L. Wald, R.J. Simister, G.J. Barker, and S.R. Williams, "In vivo GABA+ measurements at 1.5T using a PRESS-localized double quantum filter," *Magn. Reson. Med.*, vol. 48, pp. 233–241, 2002.
- [12] A.H. Trabesinger, D. Meier, and P. Boesiger, "In vivo 1H NMR spectroscopy of individual human brain metabolites at moderate field strengths," *Magn. Reson. Im.*, vol. 21, pp. 1295–1302, 2003.
- [13] I.Y. Choi, S.P. Lee, and J. Shen, "Single-shot 3D localized multiple quantum spectroscopy of GABA in the human brain in vivo with two double-band pulses for enhanced selectivity," Kyoto, Japan, May 2004, Int. Soc. Magnetic Resonance in Medicine, 12th Scientific Meeting and Exhibition, p. 685.
- [14] I.Y. Choi, S.P. Lee, H. Merkle, and J. Shen, "Simultaneous detection of multiple quantum filtered GABA and single quantum creatine in the human brain in vivo using a single shot, two-echo acquisition scheme.," Kyoto, Japan, May 2004, Int. Soc. Magnetic Resonance in Medicine, 12th Scientific Meeting and Exhibition, p. 308.
- [15] M. Wylezinska and P. Jezard, "Simultaneous detection of GABA, glutamate and NAA using MEGA editing and PRESS localization," Kyoto, Japan, May 2004, Int. Soc. Magnetic Resonance in Medicine, 12th Scientific Meeting and Exhibition, p. 2427.
- [16] K. Lymer, K. Haga, I. Marshall, and J. Wardlaw, "Reproducibility of in vitro GABA measurements using 2D J-resolved MRS," Kyoto, Japan, May 2004, Int. Soc. Magnetic Resonance in Medicine, 12th Scientific Meeting and Exhibition, p. 686.
- [17] H.P. Hetherington, B.R. Newcomer, and J.W. Pan, "Measurements of human cerebral GABA at 4.1 T using numerically optimized editing pulses," *Magn. Reson. Med.*, vol. 39, pp. 6–10, 1998.
- [18] O.W. Sorensen, G.W. Eich, M.H. Levitt, G. Bodenhausen, and R.R. Ernst, "Product operator formalism for the description of NMR pulse experiments," *Prog. in NMR Spect.*, vol. 16, pp. 163–192, 1983.
- [19] D. Graveron-Demilly, A. Diop, A. Briguet, and B. Fenet, "Product-operator algebra for strongly coupled spin systems," *Journal of Magnetic Resonance*, vol. A101, pp. 233–239, 1993.
- [20] H. Ratiney, F. Mitri, Y. Coenradie, S. Cavassila, D. van Ormondt, and D. Graveron-Demilly, "Time-Domain Quantitation based on a Metabolite Basis Set in Magnetic Resonance Spectroscopy," in *ProRISC, IEEE Benelux*, Veldhoven, The Netherlands, November 2002, pp. 432–437.
- [21] H. Ratiney, Y. Coenradie, S. Cavassila, D. van Ormondt, and D. Graveron-Demilly, "Semiparametric Estimation for

- Metabolomics,” in *ProRISC, IEEE Benelux*, Veldhoven, The Netherlands, November 2003, pp. 418–426.
- [22] H. Ratiney, Y. Coenradie, S. Cavassila, D. van Ormondt, and D. Graveron-Demilly, “Time-Domain Quantitation of  $^1\text{H}$  Short Echo-Time Signals: Background Accommodation,” *MAGMA*, vol. 16, pp. 284–296, 2004.
- [23] H. Ratiney, M. Sdika, Y. Coenradie, S. Cavassila, D. van Ormondt, and D. Graveron-Demilly, “Time-Domain semi-parametric estimation based on a metabolite basis set,” *NMR Biomed.*, vol. 17, pp. 1–13, 2004.
- [24] “<http://www.gaussian.com/>,” .
- [25] V. Govindaraju, K. Young, and A.A. Maudsley, “Proton NMR chemical shifts and coupling constants for brain metabolites,” *NMR in Biomedicine*, vol. 13, pp. 129–153, 2000.
- [26] D. Graveron-Demilly, “Spectroscopy Beyond NAA, Time Domain processing,” Honolulu, Hawaii, USA, May 18-24 2002, Int. Soc. Magnetic Resonance in Medicine, 10th Scientific Meeting and Exhibition.
- [27] H. Ratiney, F. Mitri, Y. Coenradie, S. Cavassila, D. van Ormondt, and D. Graveron-Demilly, “QUEST: Time-Domain Quantitation with Advanced Prior Knowledge,” in *MAGMA*, 2002, vol. 15, p. 373.
- [28] H. Ratiney, Y. Coenradie, S. Cavassila, D. van Ormondt, and D. Graveron-Demilly, “Time-domain quantitation with a metabolite basis set,” Toronto, Canada, May 2003, Int. Soc. Magnetic Resonance in Medicine, 11th Scientific Meeting and Exhibition, p. 1161.
- [29] A.A. de Graaf, J.E. van Dijk, and W.M.M.J. Bovée, “Quantification improvement by converting lineshapes to the Lorentzian type.,” *Magnetic Resonance in Medicine*, vol. 13, pp. 343–357, 1990.
- [30] A. Naressi, C. Couturier, J.M. Devos, M. Janssen, C. Mangeat, R. de Beer, and D. Graveron-Demilly, “Java-based Graphical User Interface for the MRUI Quantitation Package,” *MAGMA*, vol. 12, pp. 141–152, 2001.
- [31] A. Naressi, C. Couturier, J.M. Devos, M. Janssen, C. Mangeat, R. de Beer, and D. Graveron-Demilly, “Java-based Graphical User Interface for the MRUI Quantitation Package,” *Computers in Biology and Medicine*, vol. 31, pp. 269–286, 2001.
- [32] S. Cavassila, B. Fenet, A. Van Den Boogaart, C. Remy, A. Briguet, and D. Graveron-Demilly, “ER-Filter : preprocessing technique for frequency-selective time-domain analysis,” *J. Magn. Reson Analysis*, vol. 3, pp. 87–92, 1997.