Original article

A quantum mechanics-based approach for optimization of metabolite basis-sets. Application to quantitation of HRMAS-NMR signals

Optimisation des bases de métabolites fondée sur une approche par mécanique quantique. Application à la quantification de signaux RMN-HRMAS

A. Lazariev [a], A.-R. Allouche [b], M. Aubert-Frécon [b], F. Fauvelle [c], M. Piotto [d,e], K. Elbayed [e], I.-J. Namer [f], D. van Ormondt [g], D. Graveron-Demilly [a,*]

[a] Inserm U1044, CNRS UMR 5220, laboratoire creatis, université Claude Bernard Lyon 1, 69616 Villeurbanne, France
[b] LASIM, université Claude Bernard Lyon 1, 69622 Villeurbanne, France
[c] CRSSA/BCM, 38702 La Tronche, France
[d] Bruker BioSpin, 67166 Wissembourg, France
[e] Institut de chimie, 67000 Strasbourg, France
[f] Department of Biophysics and Nuclear Medicine, University Hospitals of Strasbourg, 67098 Strasbourg, France
[g] Applied Physics; Delft University of Technology, Delft, Netherlands

Abstract

High-resolution magic angle spinning (HRMAS) Nuclear magnetic resonance (NMR) 1H spectroscopy is playing an increasingly important role for diagnosis. This technique enables setting up metabolite profiles of ex vivo pathological and healthy tissue. Automatic quantitation of HRMAS signals provides reliable reference profiles useful to monitor diseases and pharmaceutical follow-up. However for several metabolites, the values of chemical shifts of proton groups may slightly differ according to the microenvironment in the tissue or cells, in particular to its pH. This hampers accurate estimation of the metabolite concentrations mainly when using quantitation algorithms based on a metabolite basis-set: the metabolite fingerprints are not correct anymore. In this work, we propose an accurate method based on quantum mechanical (QM) simulations. The proposed algorithm automatically corrects mismatches between the signal under analysis and the signals of the simulated basis-set by modifying the basis-set signals. In the optimization procedure, the basis-set signals are simulated again by varying the chemical shifts of metabolites in the QM procedure. Cross-correlation was used as cost function to measure how well the signals match each other. The proposed method, QM-QUEST, provides more robust fitting while limiting user involvement and respects the correct fingerprints of metabolites. Its efficiency is demonstrated by accurately quantitating signals from tissue samples of human brains with oligodendroglioma.

Résumé

La Spectroscopie de résonance magnétique nucléaire (RMN) Haute résolution à l'angle magique (HRMAS) joue un rôle de plus en plus prépondérant pour le diagnostic médical. Cette technique permet d'établir les signatures ex vivo de tissus sains et pathologiques. Cependant, pour certains métabolites, les valeurs des déplacements chimiques des groupes de protons peuvent légèrement varier en fonction de l'environnement des tissus particulièrement son pH. Cet effet gêne l'estimation correcte des concentrations des métabolites lorsqu'on utilise des algorithmes de quantification fondés sur une base de données de métabolites: les signatures des métabolites ne sont plus respectées. Dans ce travail, nous proposons une méthode fondée sur les simulations des signaux par mécanique quantique (MQ) pour pallier ce problème. L'algorithme corrige automatiquement les différences entre le signal expérimental et les signaux simulés de la base de métabolites en modifiant ces derniers en variant les déplacements chimiques des noyaux des métabolites. La corrélation croisée permet dans la procédure d'optimisation de maximiser l'adéquation entre le signal

* Corresponding author.
 E-mail address: danielle.graveron@univ-lyon1.fr (D. Graveron-Demilly).

à quantifier et ceux de la base de métabolites. Cette méthode, QM-QUEST, est plus robuste tout en limitant l'implication de l'utilisateur et respecte les signatures des métabolites. Son efficacité est démontrée en quantifiant de façon précise des signaux d'échantillons du cerveau humain présentant des oligodendrogliomes.

1. Introduction

High-resolution magic angle spinning (HRMAS) Nuclear magnetic resonance (NMR) is playing an increasingly important role for diagnosis. This technique enables setting up metabolite profiles of ex vivo pathological and healthy tissue, i.e. biopsies [1]. Automatic quantitation of HRMAS signals [2] will provide reliable reference profiles useful to monitor diseases and pharmaceutical follow-up.

For many metabolites, the values of chemical shifts of proton groups may slightly differ according to the microenvironment in the tissue or cells, see e.g. [3]. These changes of chemical shift values hamper accurate estimation of the metabolite concentrations mainly when using quantitation algorithms based on a metabolite basis-set [4,5]: the metabolite fingerprints are not correct anymore.

For HRMAS spectroscopy, this increases the error of quantitation to tens of percents for certain metabolites (e.g. creatine, lactate). Several methods were proposed to circumvent this problem. Splitting of the basis-set signals of given metabolites into basis sub-components according to chemical groups and adding appropriate constraints (prior knowledge) to the parameters of the groups was proposed, see e.g. [6]. To limit user involvement, a simple method for chemical shift correction based on signal processing and stretching/shrinking of the metabolite basis-set signals, was reported in [7]. Warping methods were recently given in [8], see references herein. Also, in in vivo MR Spectroscopy, chemical shift recalibration based on linear interpolation was proposed [9]. In the present work, we propose a more accurate method based on quantum mechanical (QM)-simulations, thus respecting the correct fingerprints of metabolites [10,11].

2. Method

In magnetic resonance spectroscopy, quantitation based on a metabolite basis-set has become very popular in the last ten years. In the present work, we used the method QUEST [5].

In QUEST, the complex-valued time-domain model signal modeling the investigated signal x is written as a linear combination of the M weighted metabolite model signals $\hat{x}^m$ – either quantum –mechanically simulated or in vitro measured–of the basis-set.

The samples of the model signal $\hat{x}_n$, $n = 1, 2 \ldots N$ where N is the number of data-points, can be written as:

$$\hat{x}_n = \exp\left(i\varphi_0\right) \sum_{m=1}^{M} \left(c_m x_n^m \exp\left(\Delta\alpha_m t_n + i\Delta\omega_m t_n\right) \exp\left(i\Delta\varphi_m\right)\right)$$

where c_m is proportional to the concentration of the metabolite m; $\Delta\alpha_m$, $\Delta\omega_m$, $\Delta\phi_m$ are small extra damping factors, angular
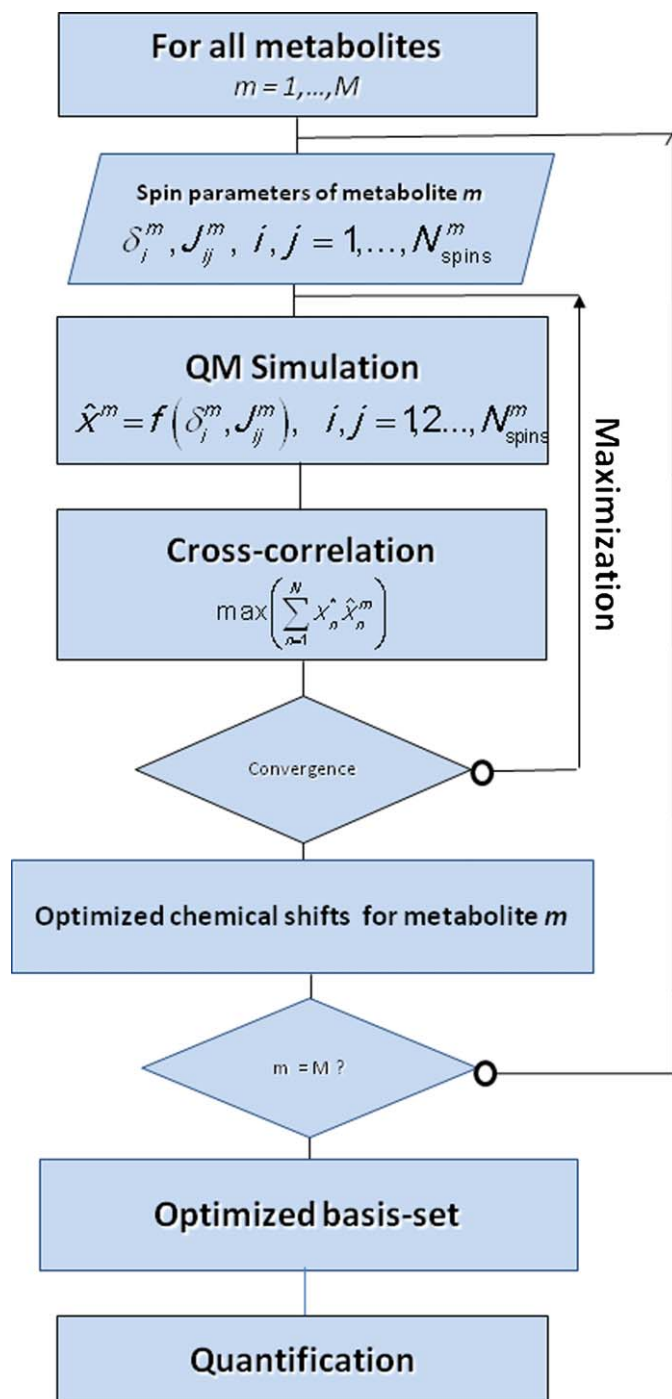

Fig. 1. Scheme of the optimization algorithm based on quantum mechanical simulations. The model signals $\hat{x}^m$ are adjusted to the high-resolution signal x.
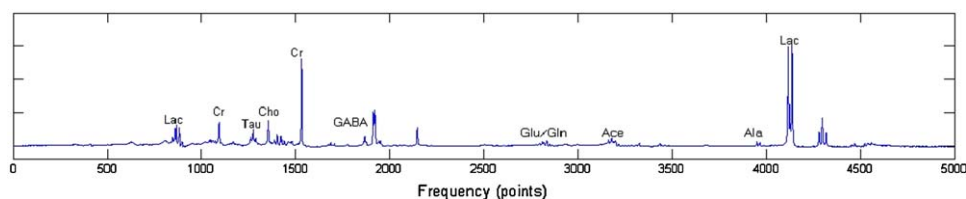
Fig. 2. Region of interest of an HRMAS spectrum from a tissue sample of a human brain with an oligodendroglioma, acquired at 11.7 T. Ace: acetate; Ala: alanine; Cr: creatine; Cho: choline; GABA: γ-amino-butyric acid; Glu: glutamate; Gln: glutamine; Lac: lactate; Myo: myo-inositol; NAA: N-acetylaspartate; Tau: taurine; Eth: ethanol as a trace of biopsy procedure are shown.

frequency shifts and phase shifts enabling to automatically compensate for distortions due to the magnetic field heterogeneities with respect to the ideal signals of the metabolite basis-set. $\hat{x}_n^m$, $n = 1, 2, \ldots, N$; $m = 1, 2, \ldots M$ are the metabolite model samples. Metabolite parameters c_m, $\Delta\alpha_m$, $\Delta\omega_m$, $\Delta\phi_m$ are estimated in the quantitation procedure [5]. The parameters c_m are proportional to the metabolite concentrations.

QM simulators were used to simulate the basis-set signals $\hat{x}^m$. The latter depend directly on the spin parameters (chemical shifts δ_i^m and coupling constants J_{ij}^m, i, $j = 1, \ldots N_{\text{spins}}^m$) of the metabolites [12]. N_{spins}^m represents the number of spins/nuclei of the metabolite m. We propose to adjust the metabolite basis-set signals $\hat{x}^m$, sensitive to pH and/or temperature changes, prior to quantitation to better match the data. For this, $\hat{x}^m$ are simulated again by QM [13] in an optimization procedure by varying the chemical shift values of metabolite nuclei. In the optimization, cross-correlation between $\hat{x}^m$ and the investigated HRMAS signal x was used as cost function [10,11]. Cross-correlation, avoids signal normalization. To speed up and simplify the procedure, the optimization was done for one metabolite at a time. The chemical shifts δ_i^m, initially provided to the QM simulation procedure for metabolites subject to pH and/or temperature changes, are then optimized.

The full procedure is schematized in Fig. 1. Note that the QM simulation algorithm is inside the maximization procedure of the cost function. The optimization, based on a gradient descent method, was done in Matlab (©MathWorks) using a conventional QM algorithm in C. Constraints were set on chemical shift values. Quantitation was performed with the jMRUI software package [13].

3. Results

A series of thirty-three spectra (sampling interval: 0.143 ms, number of data-points N = 16384), acquired at 11.7 T, from

tissue samples of human brains with oligodendroglioma, were quantitated, see one of them in Fig. 2. For each HRMAS signal to be quantitated, the metabolite basis-set signals were automatically optimized prior to the quantitation procedure as mentioned above.

The proposed method enables to move independently the different multiplets of the spectrum, while conserving all the strong-coupling effects. That is not the case for methods based on subdividing the basis-set signals into basis sub-components according to chemical groups, in the quantitation procedure. This enabled us to adapt the chemical shift variations due to pH and/or temperature. One can easily see in Fig. 3 for an oligodendroglioma spectrum of the series that the mismatches between the lactate basis-set and the HRMAS spectra have been reduced.

The optimized chemical shifts for creatine and lactate for all thirty-three spectra are shown in Fig. 4. The left plot represents the chemical shifts of two spin groups (rhombs). The dots correspond to the starting values provided to the optimization procedure. In absence of pH-dependence, a straight line (corresponding to a global spectrum shift) would be expected as represented by the dashed-line for creatine. The "cloud points" represent independent changes of the chemical shifts of the different multiplets due to the microenvironment conditions. On the right, the series of optimized chemical shift differences are plotted as a function of the experiment number. Again, it can be easily seen that independent chemical shift corrections are needed to adapt the distance between the lactate multiplets. To establish possible correlation between the obtained variations in chemical shifts across different metabolites and among the thirty-three investigated biopsies, the differences between chemical shifts of two proton groups of various metabolites were analyzed leading to the conclusion that chemical shift mismatches are not only due to pH and/or temperature changes but also have a statistical nature [10,11].
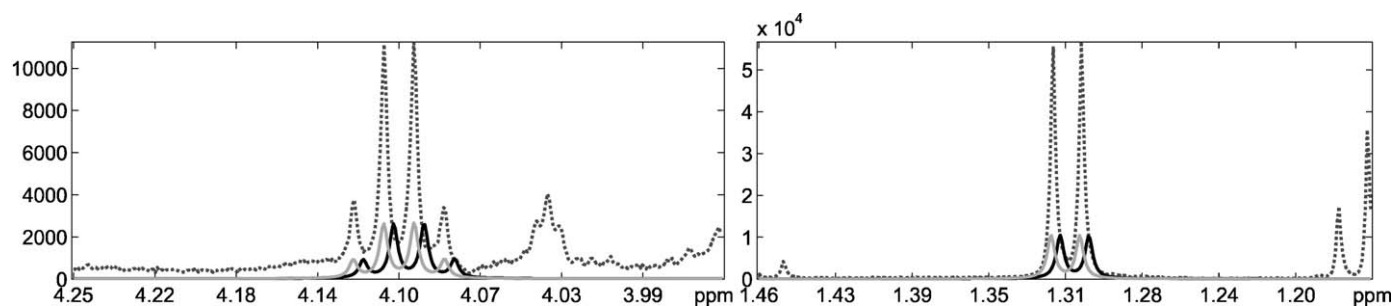

Fig. 3. Zoom in on the lactate multiplet regions in an HRMAS spectrum from a tissue sample of a human brain with an oligodendroglioma, acquired at 11.7 T and on the corresponding basis-set regions (dotted lines: raw spectrum; black: original basis-set spectrum; gray: optimized basis-set spectrum).
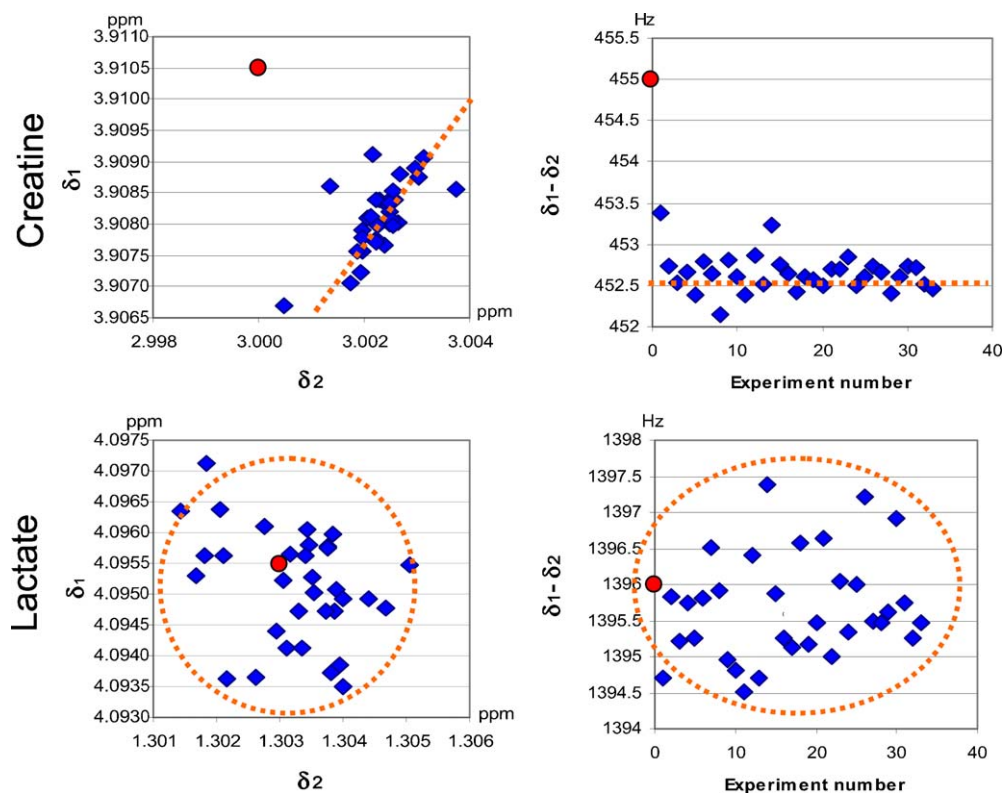
Fig. 4. Optimized chemical shift values (rhombs) of creatine and lactate for thirty-three spectra from tissue samples of human brains with oligodendroglioma, acquired at 11.7 T. Left: chemical shifts δ_1 and δ_2 of the two proton groups; right: differences $\delta_1 - \delta_2$. The dots represent the starting values provided to the optimization procedure. For creatine, the straight dashed-lines correspond to the fits of the optimized values. Cloud points are obtained for lactate.

Results (not reported here) show an improvement of quantitation quality when using the optimized basis-set. As quality criterion of the method, we chose the estimated standard deviations (estimated from the Cramér-Rao lower bounds) on the amplitudes provided by QUEST for metabolites subject to pH and/or temperature changes. Comparing these values obtained using the initial and optimized basis-sets respectively, one finds decreases of as much as 30–40% [11].

4. Discussion and conclusion

A novel method based on QM simulations was proposed that provides an automatic approach for accurate quantitation of the metabolite concentrations in high-resolution spectra from biopsies. Despite the fact that the method is time consuming for large spin systems, it offers significant advantages:

- it is the only method which respects the correct fingerprints of metabolites;
- it limits user involvement;
- parameters $\Delta\omega_m$ of the model become redundant after optimization of the chemical shifts, thus reducing the number of free parameters in the quantitation procedure.

The proposed method QM-QUEST, is well suited to improve quantitation of metabolites with well resolved spectra (lactate, creatine, aspartate, inositol, ethanol as a trace of the biopsy procedure, etc.). For more complicated spin systems like glutamate and glutamine, the method works well if these metabolites have sufficient concentrations.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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