Optimization of metabolite basis-sets prior to quantitation: a Quantum Mechanics approach

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Introduction

Nowadays, medical diagnoses are often based on results obtained from HRMAS – High-Resolution Magic Angle Spinning NMR – spectroscopy. This technique enables setting up metabolite profiles of *ex vivo* pathological and healthy tissue, see e.g. [1]. The need to monitor diseases and pharmaceutical follow-up appeals the necessity of automatic quantitation of HRMAS ^{1}H signals [2]. However, the values of chemical shifts of proton groups in several metabolites can slightly differ subject to the microenvironment in the tissue or cells, in particular with its pH [3] which hampers accurate estimation of the metabolite concentrations mainly when using quantitation algorithms based on a metabolite basis-set [2, 4]. The values of corresponding displacements of the spectral peaks can be larger than the peak line-width. A simple method for chemical shift correction was previously presented in [5]. In this work, we propose a more accurate method based on Quantum Mechanics simulations.

Method

The complex-valued time-domain model signal is written as a linear combination of the M weighted metabolite model $\hat{x}^m$ of the basis-set:

$$\hat{x} = \exp(i\phi_0)\sum_{m=1}^{M}\left(c_m \hat{x}_m \exp\left(\left(\Delta\alpha_m + i\Delta\omega_m\right)t + i\phi_m\right)\right) \qquad (1)$$

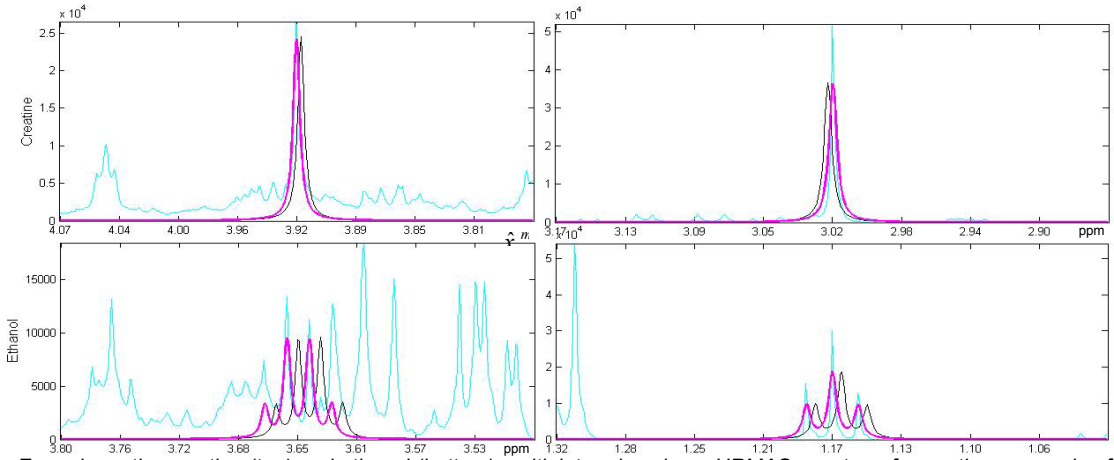
c_m is proportional to the concentration of the metabolite m, $\Delta\alpha_m$, $\Delta\omega_m$, $\Delta\varphi_m$ are small extra damping factors, angular frequency shifts and phase shifts enabling to automatically compensate for distortions due to the magnetic field heterogeneities with respect to the ideal signals of the metabolite basis-set. When a simulated basis-set is used, $\hat{x}^m$ depends directly on the spin parameters (chemical shifts σ_i and coupling constants J_{ij}):

$$\hat{x}_m = f\left(\sigma_i, J_{ij}\right), \quad i, j = 1..N_{spins} \qquad (2)$$

We propose to modify the metabolite basis-set signals $\hat{x}^m$ sensitive to pH changes, before quantitation by maximizing the cross correlation between each of these signals and the investigated one. This means that the chemical shifts σ_i, initially provided to the Quantum Mechanics simulation procedure for each metabolite, will be optimized and $\Delta\sigma_i$ estimated. HRMAS spectra can be simulated with the Quantum Mechanics conventional approach [6]. The cross correlation, chosen as the cost function, avoids signal normalization.

Results

Results are illustrated in the Figure on an HRMAS signal from a tissue sample of a human brain with an oligodendroglioma, acquired at 11.7T. Metabolite signals of the basis-set were automatically optimized prior to the quantitation procedure as mentioned above. In fact, the method allows to move independently the different multiplets of the spectrum, conserving all the strong-coupling effects, in contrary to methods which decompose the signal into multiplets. This enables us to adapt the chemical shifts variations due to pH.



Zoom in on the creatine (top) and ethanol (bottom) multiplet regions in an HRMAS spectrum from a tissue sample of a human brain with an oligodendroglioma, acquired at 11.7T and the basis-set ones (cyan: raw spectrum; black: original basis-set spectra; magenta: optimized basis-set spectra).

Conclusions and discussion

A new method based on Quantum Mechanics to optimize simulated basis-sets prior to quantitation, thus accounting for chemical shift changes related to pH, has been proposed. Despite the fact that the method is time consuming for large spin systems, it offers some avantages: 1) it is the only method which respects the correct fingerprints of metabolites; 2) parameters $\Delta\omega_m$ of the model function (Eq. 1) become redundant after optimization of the chemical shifts, thus reducing the number of free parameters in the quantitation procedure. The proposed method 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 high concentrations.

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