Impact of the prior knowledge on the quantification of in vivo ^{13}C spectra using two different algorithms: LCModel and AMARES

C. Cudalbu[1], B. Lanz[1], J. M. Duarte[1], N. Kunz[1], and R. Gruetter[1,2]

[1]Laboratory for Functional and Metabolic Imaging (LIFMET), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, [2]Departments of Radiology, Universities of Lausanne and Geneva, Geneva, Switzerland

Introduction:

Measurements at high magnetic fields combined with improvements in localization techniques and with excellent shimming have led to important gains in sensitivity and spectral resolution of ^{13}C in vivo spectra. Consequently, the amount of information that can be obtained from in vivo ^{13}C spectra has considerably increased (i.e. signals from different carbon positions combined with a fine structure arising from ^{13}C-^{13}C J-couplings). In this context, the quantification of in vivo ^{13}C spectra becomes more challenging. Incorporation of prior knowledge has been shown to improve quantification, especially in the presence of overlapping signals. However, fitting the signals arising from different carbon positions with singlets and neglecting the multiplets due to ^{13}C-^{13}C J-couplings might lead to substantial errors in the quantification of the time courses which would consequently lead to errors in the estimated metabolic fluxes. The purpose of the present study was to assess the impact of the prior knowledge on the quantification of in vivo ^{13}C spectra using two different algorithms: LCModel (1, 2) and AMARES (3) and to compare the two algorithms.

Methods:

Experimental: Localized ^{13}C spectra were acquired on Sprague-Dawley rats (n=4, VOI=5x8x8mm^3) fasted overnight and artificially ventilated. The femoral artery and vein were catheterized for monitoring blood gases, blood pressure, glucose concentration, and for infusion of α-chloralose and glucose. An exponentially decaying bolus of 99%-enriched [1,6- ^{13}C$_2$] glucose was administrated over 5 min, followed by a continuous infusion of 70%-enriched glucose for the remaining 6h (4). Glucose was infused at a rate adjustable to the concomitantly measured plasma glucose concentrations to maintain the desired glycaemia levels (around 300 mg/dl). All data were acquired on a 9.4T system (Varian/Magnex Scientific) using: a home-built 10mm (^{13}C)/13mm (^{1}H quad) surface coil as RF transceiver, and the semi-adiabatic DEPT polarization transfer sequence (TR=2.5s, interpulse delay 3.8ms (J$_{CH}$=130Hz), 45° for last ^{1}H pulse to simultaneously measure signals from CH, CH$_2$, CH$_3$ groups) (4). Field homogeneity was adjusted using FASTMAP (5).

Fig.1 : Representative in vivo time courses of Glu C4 and Glu C3 obtained using the 4 approaches. a) 1st approach (blue and red dots) vs 2nd approach (green and yellow dots); b) 3rd approach (dark blue and pink dots) vs 2nd approach (green and yellow); c) 4th approach (light blue and pink dots) vs 2nd approach (green and yellow dots).

Data analysis: In vivo ^{13}C spectra were quantified using four approaches (1st approach based on LCModel and the approaches 2 to 4 based on AMARES):

1) LCModel combined with a basis set generated using Matlab by simulating each isotopomer with the appropriate chemical shift and J-coupling pattern, as previously described by ref (2); (blue and red dots in Fig1a)

2) AMARES combined with improved prior knowledge, which was identical with that used by LCModel in our 1st approach (isotopomers with the same chemical shift and J-coupling pattern). The following constraints were used: linewidths (≤ 8Hz, ^{13}C singlet linewidths typically obtained in our study), relative phases (fixed to zero) and Lorentzian lineshape; (green and yellow dots in Fig.1a,b,c)

3) AMARES combined with minimal prior knowledge: each resonance at a specific carbon position was fitted using a singlet without any information on the J-coupling pattern (for example the multiplet of Glu at the position 4 was fitted using only one singlet). The following constraints were used: linewidths (≤ 8Hz), relative phases (fixed to zero) and Lorentzian lineshape; (dark blue and pink dots in Fig 1b)

4) AMARES with minimal prior knowledge as for the approach 3 with the difference that no constraints on the linewidths were impose; (light blue and pink dots in Fig 1c)

Results:

First we compared the in vivo time courses obtained with LCModel (1st approach, blue and red dots in Fig1a) to those obtained using AMARES with improved prior knowledge (2nd approach, green and yellow dots in Fig.1a). The results of this comparison are plotted in Fig 1a. As can be seen from the in vivo time courses of Glu C4 and C3, the two approaches gave consistent and highly similar results. Therefore, in a second step we compared only the three approaches based on AMARES (Fig 1b and c and Fig 2). In Fig 1b and c we compared the time courses obtained with the 3rd and 4th approach to those obtained with the 2nd approach, respectively. When neglecting the multiplet structure by fitting the resonances of each carbon position by a singlet with constrained linewidth (≤ 8Hz) (3rd approach, dark blue and pink dots in Fig 1b) the time courses for each resonance are underestimated (~40%), due to the limited prior knowledge used in AMARES (Fig 1b and 2). Moreover, when fitting the in vivo data with AMARES with minimal prior knowledge and without constraints on linewidths (4th approach, light blue and pink dots in Fig 1c), a larger variation of the fitted data was noticed together with an underestimation of Glu C4 (~10%) and an overestimation of Glu C3 (~20%) (Fig 1c and 2). The overestimation of Glu C3 when no constraints are imposed on the linewidths (4th approach, light pink dots in Fig.1c) is due to the fitting of a multiplet by a singlet with large linewidth leading to overestimation. It is interesting to note that the quantification of the time courses for the first hour of infusion is similar for all four approaches, however when the structure due to the ^{13}C-^{13}C J-couplings starts to be significant, the fittings of the time courses for the 3rd and 4th approach are not consistent anymore mainly due to the usage of minimal prior knowledge. Indeed, upon the infusion of [1,6-^{13}C$_2$] glucose the probability of ^{13}C isotopes in adjacent positions increases, consequently the splitting of resonances due to homonuclear ^{13}C-^{13}C scalar coupling is more important.

In the present study we assessed the impact of the prior knowledge on the quantification of in vivo ^{13}C spectra using two different algorithms: LCModel and AMARES combined with 4 different approaches to handle the prior knowledge. The results obtained with AMARES were identical with those obtained with LCModel if improved prior knowledge was used. We can conclude that additional prior knowledge used in AMARES leads to a more accurate and reliable quantification of in vivo ^{13}C spectra. In contrary, when limited prior knowledge is used the results obtained with AMARES are over/underestimated.
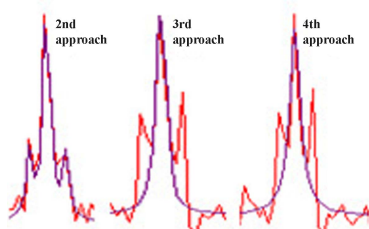

Fig.2 : Representative fit of in vivo Glu C4 (128 averages) with AMARES and the 2nd approach-improved prior knowledge, the 3rd approach-minimal prior knowledge with constraints on linewidths and the 4th approach-minimal prior knowledge with no constraints on linewidths.

References

[1] Provencher SW, Magn Reson Med 1993;30:672. [2] Henry P-G et al., NMR Biomed. 2003;16:400. [3] Vanhamme et. al., J. Magn. Reson. 1997;12:35. [4] Henry P-G et al., Magn Reson Med. 2003;50:684. [5] Gruetter R. Magn Reson Med. 1993;29:804.