Statistical strategy to overcome estimation bias in CRLB threshold approach for LCModel analysis of MRS

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INTRODUCTION

Noninvasive study of changes in neurochemicals is beneficial to characterization of the disease progression and diagnosis of disease in early stages, which can be accessed through use of *in vivo* ^{1}H MRS, particularly at high magnetic fields. Although LCModel analysis of ^{1}H MRS has been the subject of intense activity [1-2], the way to exhibit valid metabolite concentrations in statistics is still inconclusive. In addition to investigation of the effect of threshold values on the averaged metabolite concentrations, in this study we implement weighted analysis of the simulated and *in vivo* ^{1}H MR spectra in rat brains to demonstrate alternative exhibition of the concentration averages for the neurochemical profiles.

METHODS

The procedure of implementing Sprague-Dawley rats expressing experimentally induced type-1 diabetes in the MRS measures in the regions of the rat cortex and hippocampus, with a voxel dimension of 6×3×5 mm^3 defined in images, was described in our previous study [3]. In the present work *in vivo* baseline ^{1}H MR spectra acquired in the brains of 25 rats before streptozotocin (STZ) injection were collected for LCModel analysis. Brain metabolite concentrations resulting from the LCModel analysis were averaged as an empirical reference. Upon using a set of experimental metabolite basis spectra, there were 25 simulated ^{1}H MR spectra generated containing the same metabolite concentrations as the reference but varying with signal-to-noise ratios in a range of 28 – 51. The simulated spectra were then fit using LCModel to obtain the metabolite concentrations and their corresponding uncertainties, representing the standard error estimates (%SDs) determined by Cramér–Rao lower bound (CRLB) [1]. Several statistical analyses of the metabolite concentrations in the simulated spectra were performed for comparison – the arithmetic means of the estimated metabolite concentrations with corresponding %SDs below given thresholds; the weighted means of the estimated metabolite concentrations with weighting factors derived from the corresponding %SDs. The same statistical approaches were also applied in the 25 experimental spectra to evaluate their stability and reliability.

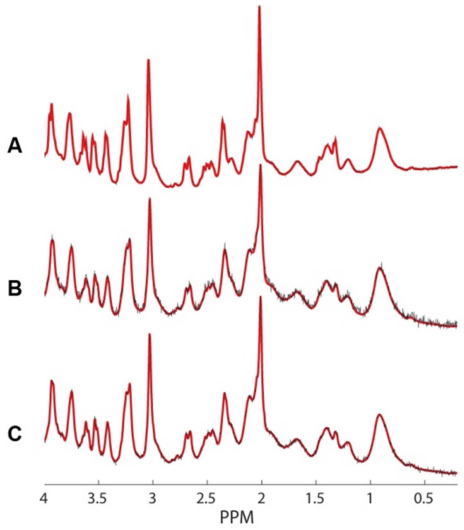
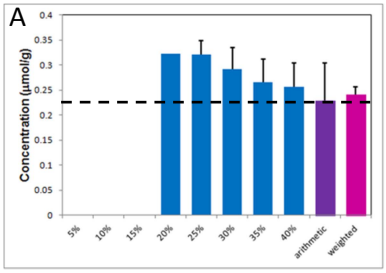


Figure 1. Resultant outcome exhibits the ^{1}H MR spectra (black trace) and the fitting curves (red trace) in (A) the *in vivo* spectrum;(B) the stimulated spectrum of SNR = 28; and (C) the stimulated spectrum of SNR = 51. Several peaks including Asp, bHB, GABA, GSH and NAA are selected for further analysis.

RESULTS AND DISCUSSION

Figure 1 exhibits an *in vivo* MR spectrum acquired in the regions of rat cortex and hippocampus and two simulated ^{1}H MR spectra. To demonstrate how signal-to-noise ratio (SNR) and linewidth impact the result of LCModel analysis, different levels of random noise and line broadening factors were added into the stimulated time-domain MR signals so that, for example, the spectra of SNR = 28 (Fig. 1B) and 51 (Fig. 1C) in frequency domain were generated, respectively. For each of the selected metabolites, the fitting outcomes of the LCModel analysis of the stimulated spectra were averaged under different approaches (Fig. 2). In each panel of Fig. 2, the arithmetic means of the fitting outcomes with corresponding %SD values lower than the threshold, in a range of 5 – 40% with an increment of 5%, were exhibited from left to right in the bar graph, respectively, compared with the arithmetic means of all the fittings (n = 25) and the weighted means of the fittings using weighting factors derived from the %SD values. It is obvious that the arithmetic means was disturbed by the threshold value, particularly for the metabolites with lower concentrations. In the arithmetic means analysis, for example in Fig. 2A, none of the estimated bHB concentrations from the stimulated spectra were included as the threshold value below 20% and only one of the estimated bHB concentrations was selected as the threshold = 20%. In contrast, the weighted means are closer to the arithmetic means calculated using all the estimated concentrations than the arithmetic means using thresholds are. Additionally, the weighted means performed much smaller standard deviations in all the metabolites selected. Similarly, once the threshold was applied prior to the average analysis, disturbance in the arithmetic means of the metabolite concentrations, resulting from LCModel analysis of the experimental spectra, was more notable in metabolites with lower concentrations, e.g. bHB (Fig. 3A), than in metabolites with higher concentrations. e.g. GSH, GABA (data not shown), and NAA (Figs. 3B). These observations indicate that spectral fittings resulting from LCModel analysis were affected by SNR and line broadening factors and, therefore, choosing a threshold to exclude data points from statistical analysis is crucial, particularly for low concentration metabolites. In summary, localized ^{1}H MRS provides a capability of detecting subtle changes in metabolite concentrations. However, selection of statistical analysis is essential because they may alter conclusions even only a threshold changes. Weighted means provides a capability of precisely presenting metabolite concentrations, particularly for those with low concentration *in vivo*.



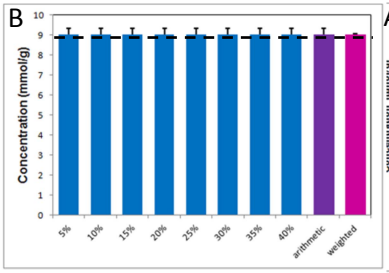
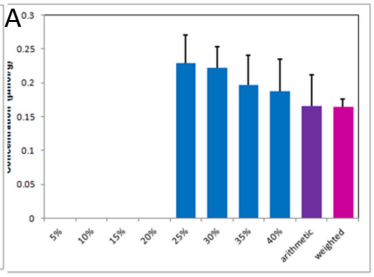


Figure 2. The bar graphs represent the concentration averages of (A) bHB, and (B) NAA using a threshold value of %5 through 40% with an increment of 5%, without a threshold and weighted analysis, respectively, in the stimulated ^{1}H MR spectra. Numbers of spectra passing the thresholds for analysis are 0 (for 5%), 0 (for 10%), 0 (for 15%), 1 (for 20%), 4 (for 25%), 8 (for 30%), 16 (for 35%) and 19 (for 40%), respectively in (A), and numbers are all 25 for all the thresholds in (B). Dashed lines represent the inputs of desired concentrations prior to simulation.



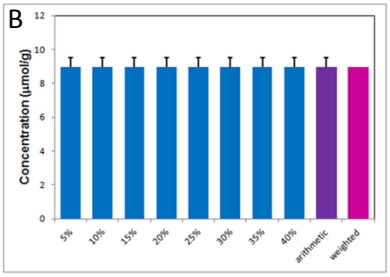


Figure 3. The bar graphs represent the concentration averages of (A) bHB and (B) NAA using a threshold value of %5 through 40% with an increment of 5%, without a threshold and weighted analysis, respectively, in the *in vivo* ^{1}H MR spectra in rat brains. Numbers of spectra passing the thresholds for analysis are 0 (for 5%), 0 (for 10%), 0 (for 15%), 0 (for 20%), 4 (for 25%), 7 (for 30%), 13 (for 35%) and 15 (for 40%), respectively in (A), and numbers are all 25 for all the thresholds in (B).

REFERENCES

1. Provencher, Magn Reson Med 30, 672 (1993). 2. Tkac et al., Magn Reson Med 41, 649 (1999). 3. Choi et al. ISMRM (2012).