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Automatic quantitation of localized *in vivo* ^{1}H spectra with LCModel

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ABSTRACT: The LCModel method analyzes an *in vivo* spectrum as a Linear Combination of Model *in vitro* spectra from individual metabolite solutions. Complete model spectra, rather than individual resonances, are used in order to incorporate maximum prior information into the analysis. A nearly model-free constrained regularization method automatically accounts for the baseline and lineshape *in vivo* without imposing a restrictive parameterized form on them. LCModel is automatic (non-interactive) with no subjective input. Approximately maximum-likelihood estimates of the metabolite concentrations and their uncertainties (Cramér-Rao lower bounds) are obtained. LCModel analyses of spectra from users with fields from 1.5 to 9.4 T and a wide range of sequences, particularly with short *TE*, are used here to illustrate the capabilities and limitations of LCModel and proton MRS. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: magnetic resonance spectroscopy; proton MRS; quantitation; LCModel; brain; *in vivo*

INTRODUCTION

Proton spectra can provide much information on metabolites *in vivo*. However, their quantitation is difficult because of two types of problems: (i) *complexity* of the spectra, with their many resonances; and (ii) *unpredictable forms* of the lineshape and baseline.

The complexity problem is aggravated by the increased overlap of peaks that are broadened, for example, by field inhomogeneity. Since the amount of peak overlap depends on variable factors like shimming, peak areas as measures of metabolite concentrations can be inconsistent, as well as erroneous. The LCModel method[1] analyzes an *in vivo* spectrum as a Linear Combination of Model *in vitro* spectra from individual metabolite solutions. By using a model of complete spectra, rather than individual peaks, the complexities of the metabolite spectra now become an advantage, since two metabolites with nearly identical spectra in one frequency region can still be resolved if they have different signals in other parts of the spectrum. By using the same sequence for the library of model *in vitro* spectra as that used for the *in vivo* spectra, complications such as multiplet structures due to coupling are automatically accounted for and full prior knowledge is incorporated.

More difficult are the unpredictable forms of the lineshape and baseline. The basic form of the lineshape can vary greatly, depending upon residual eddy currents and field inhomogeneities. Similarly, particularly with the more informative short-echo-time spectra, macromolecule and lipid resonances (as well as the non-causal signal from partially suppressed water) produce a baseline that is also difficult to parameterize. Models with too few parameters introduce bias through the incorrect model. Too many parameters produce instabilities and artifacts through over-fitting. Both situations increase errors in the concentration estimates. LCModel uses a nearly model-free constrained regularization method[2] that attempts to achieve the best compromise between these two situations by finding the smoothest lineshape and baseline consistent with the data. The aim of this regularization method is that only complexity *demanded* by the data (on the basis of statistical tests) is allowed into the lineshape or baseline. Thus, the model adapts itself to the data; no subjective fixed parameterized model is required. This permits flexibility but at the same time attempts to prevent concentration errors due to over- or under-parameterization.

MATERIALS AND METHODS

The LCModel algorithm is specified in detail elsewhere,[1] and will only be briefly outlined here. To account for the

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Abbreviations used: Ala, alanine; Asp, aspartate; Cr, creatine; GABA, γ-aminobutyric acid; Glc, glucose; Gln, glutamine; Glu, glutamate; GPC, glycerophosphocholine; GSH, glutathione; Ins, *myo*-inositol; Lac, lactate; NAA, *N*-acetylaspartate; NAAG, *N*-acetyl aspartylglutamate; PC, phosphocholine; PCr, phosphocreatine; PE, phosphoethanolamine; Scyllo, *scyllo*-inositol; S/N, signal-to-noise ratio; Tau, taurine.

extra line broadening in the *in vivo* spectrum being analyzed, the *in vitro* model spectra are convoluted with an effectively model-free lineshape function, which is determined by constrained regularization. In addition, each model metabolite spectrum is allowed its own small shift (to account for possible referencing errors) and its own extra broadening (to account for the shorter T_2 *in vivo* than *in vitro*).

In addition to the lineshape and baseline functions, parameters for the zero-order and first-order phase corrections and the overall (possibly large) referencing shift are included in the model. All the data in the analysis range (typically 4.0–1.0 ppm) are simultaneously used in a constrained least squares analysis to obtain (approximately maximum-likelihood) estimates of all the model parameters (metabolite concentrations, phases, referencing shift, lineshape, baseline, etc.) and the uncertainties in the concentrations (Cramér–Rao lower bounds). The analysis is automatic (non-interactive), and no subjective input, phasing, referencing or starting estimates are required. There is one version of LCModel for all field strengths and sequences; only the appropriate model spectra must be selected.

The fully relaxed model metabolite spectra are normally acquired once at each laboratory for each sequence (e.g. STEAM/PRESS, TE, TM). However, manufacturers (General Electric Medical Systems, Fremont, CA, USA; Bruker Medizintechnik, Ettlingen, Germany; Picker International, Highland Heights, OH, USA) have contributed LCModel libraries of model spectra for some of their standard sequences. These seem to be very portable among sites. This improves the objective comparison of results, since each site will obtain exactly the same LCModel results with the same *in vivo* data.

LCModel was originally developed and tested with 4000 human-brain and rat-brain spectra at 2.0 and 2.35 T from the group of J. Frahm. In the meantime LCModel has been used elsewhere at fields ranging from 1.5 to 9.4 T with a wide range of sequences. Some of these results (from human and animal brain) will be used here to illustrate the capabilities and limitations of LCModel and proton MRS.

RESULTS AND DISCUSSION

Validation

The basic algorithm was validated with Monte Carlo simulations and analyses of phantom data,[1,3] but exact validation of concentration estimates is not possible *in vivo*. However, during glucose (Glc) infusion experiments, the LCModel Glc concentration in gray matter followed the smooth rise and fall of the plasma Glc concentration (with a slight delay),[4] although Glc is considered very difficult to quantify. Similarly, during dynamic studies of ischemia[5] and functional MRS,[6] the time courses of Glc and lactate (Lac) could be clearly followed. In all of these studies the concentrations of the other metabolites remained constant with time to within experimental error, as would be expected. Detailed studies[3,7,8] of intra-assay and inter-assay reproducibility with LCModel are discussed below.

Baseline

The flexibility of the regularization method allows the baseline to automatically account for large unexpected distortions, such as residual water signal, susceptibility artifacts[9] and macromolecule[7,10] or lipid signals.[11] Even in spectra with no water suppression the strong climb towards the water resonance is handled by the baseline.[12] Further capabilities and limitations are illustrated elsewhere.[7,11]

Lineshape

Similarly, the regularized lineshape can automatically account for unexpected lineshapes, e.g. extreme eddy-current distortions.[1] However, this flexibility is also important for lineshapes that appear reasonable; e.g. excellent shimming can result in nearly Lorentzian shapes, whereas less perfect shimming can lead to very different lineshapes.

Spectra with high information content

Figure 1, from the group of R. Gruetter, illustrates the large amount of information available with proton MRS and excellent shimming. The intra-assay reproducibility was tested with a series of 32 three-minute acquisitions[7] (each with 1/16 the scans of Fig. 1). The coefficient of variation for the LCModel concentrations was still below 5% for glutamate (Glu), *myo*-inositol (Ins), *N*-acetyl aspartate (NAA), taurine (Tau), phosphocreatine (PCr) and creatine (Cr) (1.8% for total Cr + PCr). It was below 12% for cholines (total glycerophosphocholine plus phosphocholine; GPC + PC), glutamine (Gln), glutathione (GSH), Lac, phosphoethanolamine (PE) and Glc. It was between 27% and 57% for alanine (Ala), aspartate (Asp), γ-aminobutyric acid (GABA), *scyllo*-inositol (Scyllo), and *N*-acetylaspartylglutamate (NAAG), indicating that these metabolites are too weakly represented to be reliably estimated (although in other cases Ala, Scyllo and NAAG are strong enough to be reliably estimated). The excellent reproducibility for Tau, Glu, NAA and Ins is not surprising, since some of their detailed characteristic patterns in the *in vitro* model spectra can even be recognized by visual inspection of the *in vivo* data. However, even when this is not the case, the

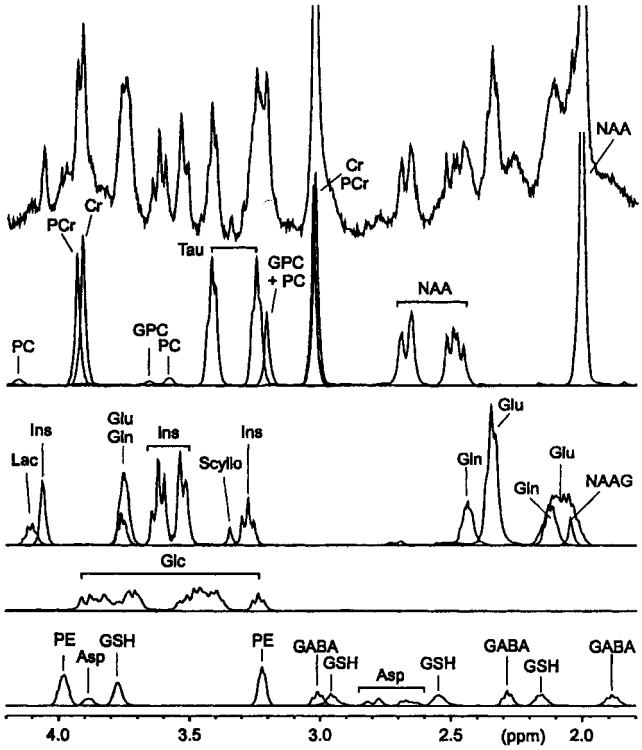

Figure 1. LCModel analysis of a high-quality *in vivo* spectrum (of rat brain at 9.4 T with STEAM, *TE/TM/TR* = 2/20/6000 ms, 512 scans and 63 μL volume). The top panel shows the segment of the data (unsmoothed spectrum) in the crowded region above 1.8 ppm. The lower panels show the contributions of the individual *in vitro* model metabolite spectra determined by the LCModel analysis. Eighteen metabolites can be estimated, including reliable resolution of PCr from Cr and complete separation of Glu from Gln. Reprinted with permission from Ref. 7

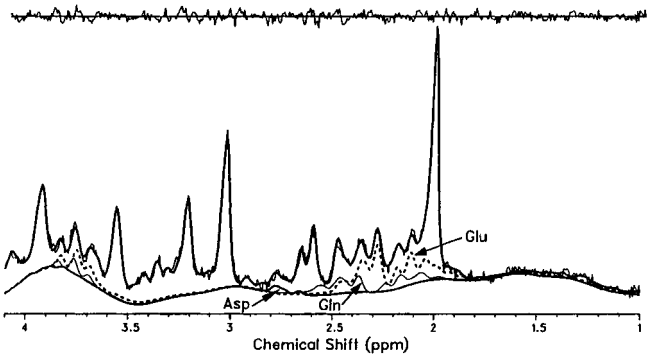

Figure 2. LCModel analysis (thick curve) of a high-quality (linewidth about 0.04 ppm) *in vivo* spectrum (thin curve) at 2.0 T. The differences (residuals) between these data and the fit are plotted at the top. The contribution of the baseline (plotted at the bottom) has been included in the plotted contributions of the Glu, Gln and Asp model spectra to the analysis. Glu and Gln can be reliably resolved. Reprinted with permission from Ref. 1

complicated (i.e. information-rich) patterns of complete model spectra can still make a reliable analysis possible, as with Glc and GSH.

Figure 2 shows a relatively high-quality spectrum from normal human gray matter (at 2.0 T with STEAM, *TE/TM/TR* = 20/30/3000 ms, 128 scans and 18 mL volume). Even at lower resolution, the reproducibilities of LCModel estimates at 2.0 T[1,4] and 1.5 T[3,8] indicate that a considerable number of metabolites can be reliably estimated.

Spectra with low information content

Figure 3 shows an unusually low-resolution spectrum (from abnormal human gray matter *in vivo* at 2.0 T with STEAM, *TE/TM/TR* = 20/30/3000. ms, 128 scans and volume 18 mL). There is obviously more ambiguity than in Fig. 2. For example, when the doublets of Lac and Ala are resolved, there is no problem in distinguishing them from lipids or macromolecules,[7,11] which often have broad signals around 1.4 ppm, but in Fig. 3 this is not at all clear. On the other hand, generally total NAA + NAAG, Cr + PCr and cholines (and often Ins and Glu or total Glu + Gln) are reliably estimated from such spectra. The Cramér–Rao lower bounds provide useful estimates of reliability.

Spectral resolution and S/N are both important determinants of information content. For example, spectra mainly of cerebrospinal fluid *in vivo* often have high resolution, and good estimates of Glc and Lac can be obtained despite very low S/N and the lack of all other strong metabolite landmark signals.[9]

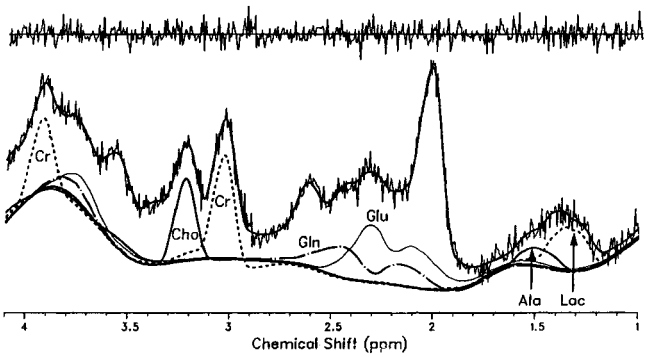

Figure 3. LCModel analysis of a low-resolution spectrum (linewidth about 0.11 ppm). Conventions are as in Fig. 2. The contribution of the basis spectra of Cr plus PCr is labeled Cr. Note that the wide space (compared to Fig. 2) between the fit and, for example, the Glu curve is entirely filled by other overlapping model metabolites, since the baseline has already been added to the Glu curve. Despite this strong overlap and poorly defined peaks, Cramér–Rao lower bounds of 10% or less for NAA + NAAG, Cr + PCr and total cholines are obtained. Reprinted with permission from Ref. 1

Echo times

At long *TE* the regularized baseline is much flatter, and good estimates can be obtained at resolutions and S/N unacceptable at short *TE*.[9] Of course, with long *TE* (and low fields) coupling greatly reduces the signal of many metabolites. However, at 4.7 T (and higher), weaker coupling effects and higher resolution allow, e.g. Glu, Tau and elevated Gln to be quantitated with LCModel at long echo times.[13]

A major argument for short *TE* (and $TR \geq 6000$ ms) is to avoid relaxation effects. Absolute concentrations are routinely estimated with LCModel from single-voxel spectra[7,8,14,15] and chemical shift imaging.[16] With LCModel, the relaxation corrections to absolute concentrations are only differential, since the relaxation *in vitro* is automatically included in the model spectra. The T_2 relaxation corrections involve the difference between 1/T_2 *in vivo* and *in vitro*, but they can still be significant with long *TE*. LCModel concentration ratios tend to be less sensitive, since T_2 correction factors are greater than unity and therefore partially cancel in the ratio.

Applications

With chemical shift imaging, LCModel has been applied with short and long *TE* at 1.5 T to obtain maps of metabolites,[17] including Ins and Glu with automated processing.[16]

Precise concentration estimates of human brain metabolites have allowed single-voxel studies of regional variations (also of NAAG)[18] and of age dependence.[19] Smaller, precisely localized volumes permit studies of absolute concentrations and relaxation of metabolites in difficult regions such as the hippocampus.[20]

LCModel has been applied at 1.5 and 2.0 T to studies of epilepsy,[15,17,21,22] multiple sclerosis,[23–25] tumors,[26–28] Alzheimer's disease[29] and other pathologies,[30–35] including the identification and quantitation of unusual metabolites.[36,37] Many other applications of LCModel to childhood disorders can be found in a review article.[14]

Additional material

LCModel is available as a commercial package. It can be downloaded, installed and tested from http://s-provencher.com. The user's manual, with figures illustrating capabilities and limitations, is also available there.

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