

LCModel¹ & LCMgui User's Manual

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February 4, 2021

¹LCModel Version 6.3-1R

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The latest version of the complete LCModel/LCMgui package and the documentation can be downloaded from the following site:

<http://lcmodel.ca>

DISCLAIMER

Please also read the License Agreement for LCModel/LCMgui, which is on <http://lcmodel.ca/lcm-license.shtml>.

The sole task of LCModel is quantitation of proton MRS data, input in the standard LCModel format. To help users, most of the LCModel manual now covers areas far beyond this task. For example:

- Information on data acquisition, conversion and scaling for the numerous data and hardware types is based on information kindly provided by others. It may not be up to date, accurate or complete. Consult the manufacturer of your hardware.
- Much additional information on possible applications is based on research, still in progress, and subject to error and revision.

The LCModel manual (*LCModel & LCMgui User's Manual*) is available free of charge, on the understanding that neither the author, nor LCMODEL Inc nor any contributors of information to the LCModel manual shall be held liable for possible errors or omissions in the LCModel manual or the consequences thereof.

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Chapter 1

Preface & Overview

The LCMModel package is for the automatic quantitation of *in vivo* proton MR spectra [1]. LCMgui is a graphical user interface for running LCMModel with more convenience and less knowledge of this manual. LCMgui is provided without charge for use with LCMModel only.

1.1 What You Must Read

In order to avoid the proliferation of documents, this is the only manual for the LCMModel package and LCMgui. It is a detailed reference manual. However, as outlined below, most of you can use this as a shorter users guide, consisting of only a few of the chapters here. In addition, some parts are clearly noted to be only of interest to users of LCMgui and many parts only to non-users.

The only necessary reading for everyone is the Disclaimer on page 2 and Chaps. 1–3. LCMgui users will also find Chapter 6 useful. It is also assumed throughout this manual that you are familiar with Ref. [1] (but not necessarily its Appendix). This is sufficient for most users (referred to here as *Normal Users*); it should allow you to competently use LCMModel.

Chapters 4 & 5 need only be read by the person initially installing LCMModel in your laboratory. Chapter 5 describes important input *Control Parameters* specific to your spectra, such as field strength, dwell time, etc. With LCMgui, these are often automatically determined.

Chapter 6 is a guide on the basics of using LCMgui. It is highly recommended for LCMgui users.

Chapter 7 is a detailed reference manual on LCMgui. It can help you fully exploit the flexibility of LCMgui and optimally install and configure it for your site and your Normal Users.

Chapter 8 need only be read by the person constructing the *Basis Set* of *in vitro* model metabolite *Basis Spectra* for your laboratory. This is not necessary if your sequence matches one of the Basis Sets that are freely available; check with me first.

Chapter 9 describes further useful Control Parameters.

Chapter 10 need only be read if you want to estimate absolute metabolite concentrations; it is not necessary for concentration ratios.

Chapter 11 discusses fine points and further Control Parameters that will be useful for some users.

Chapter 12 explains all of LCMModel's diagnostic messages and gives general hints for troubleshooting.

Even as a lowly Normal User, you may still want to at least look at the Table of Contents at the front of this manual to get an overview of all the possibilities of LCMModel. It is easy to modify the LCMModel Control Parameters to make use of the possibilities described in Chaps. 5, 9 & 11.

LCMgui users may also want to learn about a Control Parameter or other term that is usually set automatically for them. You can often look up such a term using the Index at the end of this manual.

1.2 Normal Use of LCMModel

With LCMgui, you generally only have to click on a few choices, such as the name of the file containing the data to be analyzed.

Instead of using LCMgui, the person installing LCMModel could also write a simple Pre-Formatting Program or script to automatically format the input data and then run LCMModel. Then the Normal User only has to input the name of the raw time-domain data to be analyzed.

It is not even necessary to view the data before analysis; phasing, referencing, and quantitation are done automatically by LCMModel. There is also another LCMModel output file archiving the results, which are then available for computing means, standard deviations, trends, etc., in the metabolite concentrations in a series of measurements. Since there is no user interaction, the results are user-independent, thus improving objectivity and exchangeability of the results within and between laboratories.

1.3 Conventions & Notation

Metabolite abbreviations are used throughout and are defined in Table 8.1.

As already used above, [1] means reference [1] in the Bibliography at the end of this manual.

Special terms, such as Normal User, are italicized the first time that they appear and capitalized thereafter. Less obvious special terms are in the Index at the end of this manual, and are therefore not cross-referenced when they appear in the text.

File names and LCModel input/output are written in the teletype style, as `figures.pdf`. Your home directory is specified by `$HOME/`, although you can usually abbreviate this with a tilde, `~/`.

Unix means Sun, SGI or Compaq/DEC, in the few cases where they behave differently from the Linux version.

Concentrations should be labeled “mmol per Kg wet weight”. We use the shorter (incorrect) abbreviation mM. The actual mM is the mmol per Kg wet weight multiplied by the specific gravity of the tissue, typically 1.04 in brain.

We use the term “directory” and not “folder”.

Further conventions for more advanced users are defined in Sec 5.1.

1.3.1 Figures

Figure 6.2 or Fig 6.2 refers to Fig 6.2 in Chap 6 of this manual.

PLOT 6 (PLOT rather than Figure and no decimal point in the number) is not in this manual; it is in the file `$HOME/.lcmodel/doc/figures.pdf`. You should output this on a printer with PostScript capability, as was done with this manual (which is in the same directory) . It is convenient to have these figures bound separately from this manual, so that the two can be read side-by-side.

[1, Fig 2] means Fig 2 in Ref. [1].

1.4 Acknowledgments

I thank the Biomedizinische NMR Group in Göttingen, especially Wolfgang Hänicke, for providing much data during the development of LCModel. The first 10,000 spectra were processed with LCModel by them [2]. I thank Jens Frahm for permission to use the test data in this manual.

I am very grateful to many other users of LCModel for helpful comments, which have significantly contributed to the development of LCModel.

I thank the groups at GE Medical Systems, Toshiba Medical Systems, Marconi, Bruker Medical, Varian, Philips and Siemens Medical Solutions for providing much information on their data structures. I am especially grateful to Rolf Schulte (Munich) for guidance and GAMMA routines for simulating model metabolite spectra, to Jim Murdoch (Cleveland) for detailed information on Picker and Philips data conversion and to JBob Brown (Fremont), Timo Schirmer (Munich) and Ralph Noeske (Berlin) for essential information on GE data conversion.

I thank the GE, Marconi, and Bruker groups and Else Danielsen (Copenhagen), Thomas Michaelis (Göttingen) and Petra Pouwels (Amsterdam), Jan Weis (Uppsala), Noriaki Hattori (Osaka), and R. Mark Wellard (Brisbane) for providing model spectra, and Xiangling Mao (Göttingen) for information on Siemens data. Section 8.2 is mainly based on the results of Thomas Michaelis and Petra Pouwels.

The code generating the PostScript output files is based on advice and routines kindly provided by Christian Labadie, Dept. of Chemistry, SUNY Stony Brook.

I am grateful to Gunther Helms (Tübingen), Else R. Danielsen (Copenhagen), Markus Wick (Ettlingen), Uwe Seeger (Tübingen) and Jens Frahm (Göttingen) for information and suggestions on scaling for absolute concentrations. I thank Uwe Seeger also for making [3] available before publication and for helpful discussions on including lipids and macromolecules in the analysis. I thank Brad Beyenhof for advice on forwarding X windows. I thank Philipp Böhm-Sturm (Berlin) for much information and advice on Bruker data.

LCMgui was written with the free software packages

Tcl/Tk, <http://www.tcl.tk>,

Tix (Ioi K. Lam, <http://tixlibrary.sourceforge.net>) and

Plus Patches (Jan Nijtmans, <http://members1.chello.nl/~j.nijtmans/plus.html>).

Chapter 2

One-Page Output

The results of an LCModel analysis are summarized on the so-called *One-Page Output* (now usually two pages), contained in a PostScript file. Print out `$HOME/.lcmmodel/doc/figures.pdf`. PLOTS 1 & 2 there show the One-Page Output from an analysis of the test data supplied with your LCModel package.

At the top is the title. Normally LCMgui or another Pre-Formatting Program automatically supplies this by copying identification information from a header in the original data file.

2.1 Concentration Table

These are the results of main interest to you. The most important message of this chapter is that, before looking at the concentrations themselves, you should always look first at the entries in the %SD column. These are the estimated standard deviations (Cramér-Rao lower bounds) expressed in percent of the estimated concentrations. These %SD estimates are only lower bounds (Sec 11.1), but they are still the most useful reliability indicators. As usual, you must multiply them by 2.0 to get rough 95% confidence intervals; i.e., the range that would contain the true value about 95% of the time. Thus:

- %SD > 50% indicates that the metabolite concentration could well range from zero to twice the estimated concentration. Thus, the metabolite is practically undetectable with this data. Several metabolites are often undetectable in normal subjects.
- %SD \approx 20% indicates that only changes of about 40% can be detected with reliability, e.g., the approximate doubling of Gln/Glu in several pathologies. A %SD < 20% has been used by many as a very rough criterion for estimates of acceptable reliability. However, it is only a subjective indication, not a rigorous limit.
- %SD < 15% are in boldface blue.
- Of course, averages over a group of LCModel analyses of similar spectra can significantly reduce the uncertainties. Section 11.1.1 specifies how to compute these average concentrations.

The abbreviations of the metabolites are in the 4th column. (Table 8.1 defines most of these *Metabolite Names*.) The corresponding absolute concentrations are in the 1st column. Usually the units of the absolute concentrations are unknown, and only concentration ratios are meaningful. These ratios are given in the 3rd column, whose heading (/Cr) indicates that the ratio is relative to creatine (plus phosphocreatine). Only when the Basis Spectra and your input data are consistently scaled with each other, are the absolute concentrations meaningful; for example, you can use Water-Scaling (Sec 6.3.4 & Chap 10).

2.1.1 Upper Part

The Concentration Table usually is split into two parts by a horizontal line. The upper part contains the usual low molecular weight metabolites of interest.

NAAG is quite difficult to resolve from NAA, and PCh is very difficult to resolve from GPC, as is PCr from Cr. With lower quality spectra (or long TE), Glu and Gln are also often difficult to resolve. The last rows of the upper part of the table are the sums of these concentration pairs. The sum GPC+PCh is much more accurate than the individual concentrations, as can be clearly seen from the much lower %SD of GPC+PCh than of GPC and PCh. So, in a series of spectra, if the %SD of a concentration sum is usually lower than those of the components, you ignore the values of the components and consider only the sum. This is almost always the case with GPC+PCh and Cr+PCr, usually with NAA+NAAG and sometimes with Glu+Gln.

-CrCH₂ is a correction term, rather than a metabolite. It is a simulated negative creatine CH₂ singlet around 3.94 ppm. This corrects for attenuation of the Cr CH₂ singlet due to water suppression and differential relaxation effects at longer TE.

With old basis sets, Gua was a simulated singlet to account for occasional significant signals at 3.78 ppm, especially in tumors. The Gua stood for guanidinoacetate [4], but, in nearly all cases, this assignment is probably wrong, and Gua was only an empirical fit to the signal at 3.78 ppm (which may be partly due to GSH).

2.1.2 Lower Part

The lower part of the Concentration Table contains simulated lipid (Lip) and macromolecule (MM) components. As with -CrCH₂, they are often considered nuisance correction parameters, but they may also be of interest, e.g., in classifying tumors [5].

Section 11.7 defines the Metabolite Names in this lower part. It also explains how to specify your own simulated components. The numbers after MM (for “macromolecules”) and Lip (for “lipids”) indicate the approximate chemical shift in ppm of the peaks; e.g., MM14 for the macromolecule peak near 1.4 ppm (which may also contain lipid contributions).

If Water-Scaling (Sec 6.3.4) is used to estimate the concentrations in the upper part in mM; then all of the MM* & Lip* will be in mM of CH₂ groups, except for Lip09

& MM09, which will be in mM of CH₃ groups. Otherwise, the (unknown) scaling of the simulated metabolites will be inconsistent with the (unknown) scaling of the metabolites in the Basis Set.

2.1.3 Prior Ratio Probabilities

Section 11.8 shows how prior probabilities (so-called “soft constraints”) are imposed on ratios of some poorly determined concentrations to more accurate concentrations. An example is Lip09/Lip13a+Lip13b, the ratio of the lipids near 0.9 ppm to those near 1.3 ppm. In PLOT 1 in `$HOME/.lcmode1/doc/figures.pdf`, the line with Lip09 is bold-italic red and the name Lip09 is preceded by a minus sign. This means that the Lip09 concentration is significantly lower than expected. (A plus would mean significantly higher.) This is common with the highly variable lipids and macromolecules.

There are similar (very weak) constraints on the weak normal metabolites Asp, GABA, Glc, Scyllo and Tau. If one of these is output in red italic, then consider whether this may be a real effect due to a pathology. If so, then use Sec 11.8.1 to omit this constraint.

2.2 Plot

The real part of the frequency-domain data (spectrum; i.e., the phased and referenced FFT of your raw input data with *no* smoothing) is plotted as a thin curve. The thick red curve is the LCModel fit to this data. Also plotted as a thin curve is the so-called *Baseline*. We will call the ppm-range of the plot the *Analysis Window* (i.e., the range over which the data are analyzed).

At the top are plotted the *Residuals*, i.e., the data minus the fit to the data. The Residuals are a sensitive diagnostic of the analysis. In PLOT 1 in `$HOME/.lcmode1/doc/figures.pdf`, they look fairly randomly scattered about zero, indicating a fit to within experimental error, with no apparent systematic errors. Section 3.5 gives a series of examples and guidelines on the diagnostic use of the Residuals and Baseline.

2.3 Diagnostics

The table below the Concentration Table summarizes all the diagnostic messages from LCModel during this analysis. Always look at this table. The 5 types of diagnostics, in increasing order of severity, are: **info**, **warning** (boldface blue), and (all in boldface red) **ERROR**, **FATAL** and **ILLOGICAL**. Chapter 12 lists and explains each diagnostic and suggests possible remedies. You should consult Chap 12 if **ERROR** or **warning** occurs. The type **info** is generally harmless.

When **FATAL** or **ILLOGICAL** occurs, the run aborts, and you must consult Chap 12. If the run aborts, whatever is available is plotted —

- the usual fit to the data (usually not available), or
- the absolute value of the frequency-domain data (the *Absolute-Value Plot*), or
- no plots, only the tables of diagnostics and input changes (if the raw data have not yet been read in).

The Absolute-Value Plot (of the test data) is illustrated in PLOT 5 in `$HOME/.lcmmodel/doc/figures.pdf`, where the FATAL was caused by inputting unreasonable values for a Control Parameter (DOREFS). The most common causes of a FATAL are input errors (which are usually obvious from the diagnostics) or hopelessly bad data (which is often immediately apparent from the Absolute-Value Plot).

2.4 Miscellaneous Output

The lines in this table are:

- (1) **FWHM** (full width at half-maximum) is a *rough* estimate of the linewidth in the *in vivo* spectrum.

S/N is defined here as the ratio of the maximum in the spectrum-minus-Baseline over the Analysis Window to twice the rms Residuals. This seems to be widely used [6, p. 218], but some may use twice this value. This S/N is also rough, because it depends on offsets in the model spectra and Baseline.

Neither of these single numbers can unambiguously characterize the quality of your data. They are only rough guides. Only the %SD values in the Concentration Table simultaneously account for both resolution and noise level (as well as many other things) to give the most useful guides to the reliability of the estimates.

- (2) **Data shift**: the referencing shift performed on the data spectrum.
- (3) **Ph**: the zero-order and first-order data phase corrections, ϕ_0 and ϕ_1 , using the conventions in the definition of DEGPPM in Sec 8.5.2.

Section 9.9.4 explains optional additional output that you can easily get in this table.

2.5 Input Changes

This last table lists all input that was made to change default Control Parameters in LCMModel. These are usually automatically supplied by LCMgui or the Pre-Formatting Program to set Control Parameters characteristic of your instrument. If the list is too long to fit on the front page, then, by default, a second page (PLOT 2 in `$HOME/.lcmmodel/doc/figures.pdf`) with all the tables is printed. It is best to use a printer that prints on both sides of a page; otherwise Sec 5.3.6 shows how to easily suppress this second page (but then the documentation will be incomplete).

The first three lines of this table in show the simple changes (described in Sec 9.9.3.1) to get additional plots of the individual contributions of NAA and NAAG to the spectrum. These are shown in PLOTS 3 & 4.

Chapter 3

Essential Guide

This chapter briefly lists important guidelines and special cases. It refers you to other chapters for details.

Print out `$HOME/.lcmmodel/doc/figures.pdf`. Remember, figures located only in `figures.pdf` are denoted by PLOT, e.g., PLOT 6. Figures located in this manual are denoted by Figure or Fig, e.g., Fig 6.2.

3.1 Special Spectra

LCModel attempts to automatically handle a wide variety of spectra with no special input from you, especially if you use LCMgui. However, there are some special cases where you should input extra information to LCModel.

You input this information with *Control Parameters* (Sec 5.1.2). With LCMgui, these are simply entered in the “Control Parameters” window (Fig 7.7). Without LCMgui, they are input in *Namelists* (Sec 5.2.1). Many Control Parameters have default values, but you override these defaults when you input values yourself.

The Control Parameter **SPTYPE** (Sec 9.1) informs LCModel of special types of spectra (remember that PLOTS are in `$HOME/.lcmmodel/doc/figures.pdf`):

- **Weak NAA, Tumors, Lesions:** Input **SPTYPE** = 'tumor' when you suspect that the NAA singlet around 2.0 ppm could be weak compared to the cholines (around 3.2 ppm) or the creatines or the lipid or macromolecule signals around 1.3 or 0.9 ppm. So, this is not only for tumors. See PLOTS 6 & 7 in `$HOME/.lcmmodel/doc/figures.pdf` for examples and Sec 9.1 for instructions.
- **Muscle:** Input **SPTYPE** = 'muscle-5' for muscle spectra. See PLOT 8 for an example and Sec 9.2 for important limitations and instructions.
- **Lipids, Breast, Liver, etc.:** For spectra with mainly lipids (and water) and possibly choline. Examples are in PLOTS 9–11. To use these, you must read Sec 9.3.

- **MEGA-PRESS:** Input SPTYPE = 'mega-press-3' for quantifying GABA [7] using MEGA-PRESS. To use this, you must read Sec 9.4.
- **CSF; NAA, cholines & Cr all weak:** Input SPTYPE = 'csf' in the (unusual) case that you have mainly cerebrospinal fluid (CSF), with the three usual landmarks (NAA, cholines and creatines) weaker than Lac & Glc. PLOT 13 shows an example.

3.2 Chemical Shift Imaging

For GE CSI data sets, use the Research Version of SAGE, which now has Mary McLean's LCModel interface [9]. For this SAGE/LCModel interface, you must use Sec 11.4.1.

Most other single-channel 2D & 3D CSI data sets can be handled by LCMgui. (See Secs. 3.7 & 11.4.) PLOT 14 in `$HOME/.lcmodel/doc/figures.pdf` shows an LCMgui absolute-value display of a full slice with 8×8 voxels. (A laser printer can usually give useful plots of up to 32×32 voxels.) LCMgui does not handle data that is both multi-voxel and multi-channel.

With LCMgui, you can then select and display a rectangular subset of the voxels in this slice and have LCModel analyze this subset (or the whole slice) in one multi-voxel run. An advantage of this is that LCModel first analyzes a central voxel of the subset and then works outwards, using Bayesian learning to get starting estimates and "soft constraints" for the first-order phase correction and the referencing shift from the preceding (often better) central voxels for the (often poorer) outer voxels. This speeds up and improves the analyses.

LCModel outputs concentrations from all voxels in the subset to a file that can be imported into spreadsheet programs (Sec 11.4.4).

You should still be selective with your subset. It is a waste of time to include outer rows or columns with only poor spectra. Analyses of poor quality voxels can take several times longer than normal voxels.

3.3 Acquisition Parameters

- **Apodization:** Never apodize the spectral data; smoothing ruins the statistical tests in LCModel and usually destroys information. (See Sec 3.6.4.)
- **AQ, the acquisition time for one scan** should be long enough so that the data always decay into the noise. At 1.5T use $AQ \geq 800$ ms. At higher fields, it is usually shorter. Consistently use the same AQ for all data with a given sequence.
- **Bandwidth** should be at least 1000 Hz at 1.5T, 2000 Hz at 3T and proportional to these at other field strengths.

3.4 Analysis Window

Two of the most important Control Parameters define the *Analysis Window* (the window of frequency-domain data that will be analyzed). The left edge of the window is PPMST ppm (4.0 by default). The right edge is PPMEND ppm (normally, 0.2 by default).

3.4.1 PPMEND

Normally, you should leave PPMEND at its default of 0.2. However, there are two important cases when this default should be changed:

- (1) **long echo times:** When LCMgui or LCModel detects $TE > 100$ ms, it resets the default to PPMEND = 1.0, because the macromolecule signal around 0.9 ppm is usually too attenuated to be useful at such long TE . You can override this default by inputting your own PPMEND.
- (2) **CSI data with lipid artifacts:** Strong lipid signals often occur in voxels near the edge of the slice. This is no problem if the lipid signals are where they should be, around 1.3 & 0.9 ppm, as in PLOT 6 in [\\$HOME/.lcmmodel/doc/figures.pdf](#). The problem is that some of these signals can originate from outside the voxel and can be significantly shifted or out of phase. These artifacts distort the analysis in PLOT 15. With such artifacts, there is no hope of estimating Lac, Ala or anything else below 1.8 ppm. PLOT 16 is the analysis of the same voxel with PPMEND = 1.8. In this particular case the concentration ratios do not change drastically, but they can be unreliable in cases like PLOT 15. In these cases, you should input

PPMEND = 1.8

For brain, never set PPMEND < 0.1. The model metabolite spectra usually have a DSS marker around 0.0 ppm that must be kept out of the analysis.

For brain, PPMEND should never exceed 1.9.

3.4.2 PPMST

PPMST = 4.0 seldom has to be changed. Only when the noise is much higher in the region near 4.0 ppm, would a lower PPMST be called for. If this would require a PPMST < 3.85, then reject the spectrum or try omitting eddy-current correction.

LCModel attempts to find the smoothest Baseline that is still consistent with the data. No other restrictive assumptions are made. In this sense, it is an efficient filter in frequency space. It can handle the tail of the residual water signal better than digital post-processing with more restrictive assumptions and consequent distortions.

Do not use too strong water suppression, which can attenuate metabolite signals below 4 ppm. Even with moderate water suppression, it is usually best to leave PPMST = 4.0, at least at fields below 4.7T.

3.5 Criteria for Rejecting Analyses

3.5.1 Non-Random Residuals

The residuals are the data values minus the fit values. They are plotted at the top of the plot in the One-Page Output. They should appear randomly scattered about zero, as in PLOT 1 in `$HOME/.lcmode1/doc/figures.pdf`.

Reject an analysis with strongly non-random residuals, as in PLOT 15, with systematic peaks and valleys below 1.8 ppm, indicating an inadequate model or artifacts in the data.

3.5.2 Wild Baseline

The Baseline must be flexible enough to account for a wide variety of unpredictable complications, including:

- (1) artifacts in the data.
- (2) substances not present in the Basis Set of model metabolite spectra;
- (3) substances possibly in the Basis Set, but with abnormally short T_2 times;
- (4) inaccuracies in the simulated models for the highly variable lipid and macro-molecule signals;
- (5) incomplete water suppression;

Item (1) often leads to failure, as in PLOT 15 in `$HOME/.lcmode1/doc/figures.pdf`, where wild Baseline oscillations are not enough to fit the artifacts.

PLOT 17 is an analysis of the data from PLOT 1. It was forced to fail by inputting a grossly incorrect constraint on the referencing shift. The Baseline has huge dips and huge Glu & Ins concentrations trying to fit peaks of other metabolites displaced by the huge referencing error. Here the model is wrong (with Glu trying to fit NAA, etc), and the small %SD values for Glu & Ins are therefore also wrong.

Reject analyses with wild Baselines. Huge dips down, away from the data (as in PLOT 17), are particularly bad, with huge concentrations being assigned to metabolites trying to fit the data with the wrong model.

Smaller dips and humps in the Baseline are normal, particularly compensating for item (4) around 2.0–2.3 ppm and below 1.8 ppm. Weak examples of this are in PLOTS 1 & 7.

Similarly, the Baseline in PLOT 18 handles the huge artifact dip fairly well. The Baseline dip follows the data; it does not sag down away from the data. However, the results still should be rejected; the baseline is still too wild.

3.6 Causes & Remedies for Failures

3.6.1 Artifacts

If the artifacts seem to be confined to an edge of the Analysis Window, then the obvious remedy is cut them off by restricting PPMEND or PPMST, as discussed in Sec 3.4. With CSI, this is often done by inputting PPMEND = 1.8 (PLOT 16 in \$HOME/.lcmmodel/doc/figures.pdf). Improved sequences might also eliminate the artifacts.

3.6.2 Referencing

The three major landmarks for initial referencing are at 3.22 ppm (cholines), 3.03 ppm (Cr) & 2.01 ppm (NAA). Tumors are particularly difficult, because Cr & NAA are often both weak.

Referencing errors are usually easy to recognize and correct, by inputting extra information. Section 11.3 explains how to do this.

If the central frequency of your spectrum is more than about 0.1 ppm from the water resonance (4.65 ppm), then referencing may fail, and you may have to input PPMCEN, as specified in Sec 11.3.1.

3.6.3 Phasing

Phasing errors are quite obvious and also rare. They are most likely to occur in spectra with few well-defined peaks, as in tumors or outer CSI voxels. Prior knowledge on the expected value of phase corrections can greatly improve analyses of difficult spectra, as well as speed up the analyses. LCModel attempts to build up this information during a multi-voxel analysis of CSI data.

For single-voxel data, LCMgui already inputs this prior knowledge (that only small phase corrections are needed) with GE Probe P-files. However, other scanners usually each have their own narrow distribution of first-order phase corrections. Section 5.3.5 explains how to make good use of this.

3.6.4 Smoothing

Don't do it. Smoothing ruins the statistical tests in LCModel and usually destroys information. Other digital filters, particularly excessive suppression of water or Baseline, cannot avoid imposing assumptions and distorting the spectrum. Do not zero-fill. Spatial apodization of CSI data is OK, but not spectral apodization.

3.7 Vendor-Specific Guidelines

To be certain, you can test the conversion of your data files with LCMgui and the reading of these by LCModel. Chapter 4 shows how to do this, even without a license.

3.7.1 Bruker

- Normally, you have the files `fid`, `acqp` and `method` in one directory, and LCMgui handles these automatically (Sec 7.3.1). However, with ParaVision 6 and CSI data, instead of `fid`, you select the file `ser` in Fig 6.1.
- Do not switch on zero-filling or exponential filtering.
- Turn on Eddy-Current Correction (ECC) in ParaVision (only with single-voxel data). Normally, the ECC-corrected file is then `fid`, which you select. Do not do ECC again with LCMgui.
- For Water Scaling, you should be able to use the file `fid.refscan` as your unsuppressed water reference file. It is in the same directory as your water-suppressed file `fid`. Only if `fid.refscan` is absent: use `fid.ref`, but only if it has the same size as `fid`. A reference scan fid file is absent in PV6.0; use PV6.0.1 (or higher) instead.
- If you use LCMgui, see Sec 7.3.1.
- If you do not use LCMgui, you will probably have to first use Bruker's `convdta` to correct `fid` for Bruker's digital filter.

3.7.2 GE

- Probe raw P-files are highly recommended. They are originally in the directory `/usr/g/mrraw/`, with Signa 5.2–5.7 filenames of the form `Pnnnnnn` and with Signa LX (and higher) filenames of the form `Pnnnnnn.7`. Single-voxel processing with LCMgui is then pretty much automatic, including phased-array data.
- AMRSP files can reportedly be converted to P-files using the GE utility `recon2011`.
- LCMgui can also handle some spectrum G-files (Signa 5.x) and old “spectro” raw P-files (LX and higher), but these are not as complete as Probe raw P-files.
- LCMgui only handles single-voxel GE files. For CSI data sets, use the Research Version of SAGE, which now has Mary McLean's LCModel interface [9]. To use this SAGE/LCModel interface, you must read Secs 11.4.1 & 7.2.5.3.
- It is best to have a separate user account and installation for each vendor. GE Probe data require very little phase correction, and the Control Parameters `SDDEGP` & `SDDEGZ` are automatically set to exploit this. Saving these as defaults and using them with data of other vendors can result in

disastrous phasing errors. With other data, check Fig 7.7, and delete them if necessary.

3.7.3 Hitachi

- LCMModel is part of the Hitachi system. There is nothing that you need to do.

3.7.4 Marconi/Picker

- LCMgui handles single-voxel spectroscopy fid “dump” files, obtained by clicking the “dump” button in your Marconi/Picker software.
- If you are using PRESS, then see Sec 7.3.1 (using LCMgui) or Sec 5.3.5 (not using LCMgui).

3.7.5 Bruker, Philips, Siemens, Canon/Toshiba, Varian, Microsoft

Do not use spaces in filenames or directory names.

Transfer your data files directly to a Linux or Unix system. With FTP, transfer with “binary mode” (not “text” and not “ASCII” mode). Avoid file manipulations on Microsoft & Apple systems as much as possible. They can introduce non-printing characters that make the files unreadable on other systems. MATLAB & IDL have reportedly done this as well.

3.7.6 Philips

- LCMgui handles single-voxel and CSI DICOM and SDAT files containing the time-domain data. LCMgui does not accept XSDAT files.
- DICOM files: If you get an abort with the error message that the file is not a complete spectroscopy file, you must set the Philips output (export) configuration to “Enhanced MR,” not “Classic MR.”

You only have to select the DICOM file. By default, eddy-current correction (ECC) has already been done; do not do it again; i.e., do not activate the “Do eddy-current correction” button in Fig 6.4. You can activate the “Do water-scaling” button there (Sec 6.3.4).

- SDAT files: must have the extension `.SDAT` or `.sdat`. The corresponding SPAR file must be in the same directory with the identical filename, except with the extension `.SPAR` or `.spar`, respectively.
- With single-voxel SDAT files: If you want to do ECC: In the Philips “post proc” page, set “Spectral correction” to “yes”. Then ECC is automatically done, and you only have to input the file whose name ends in `_raw_act.SDAT`. Do not do ECC again in LCMModel; i.e., do not activate the “Do eddy-current correction” button in Fig 6.4. If you activate the “Do

water-scaling” button in Fig 6.4, when asked for your unsuppressed water reference, select the file whose name ends in `_raw_ref.SDAT`.

- With SDAT CSI files: Do not do ECC. (Your menus will now be different.)
 - Prior to acquisition, be sure to change the echo acquisition mode to "Half Echo" (from "Maximum").
 - You must use the "Delayed Reconstruction" option on the raw data (on a system equipped with reconstruction hardware, such as the scanner itself).
 - Set "Spectral correction" & "Ringing filter" to "yes".
 - Export your data as `.SDAT` & `.SPAR` files.
 - Select the `.SDAT` file with LCMgui. In Fig 6.4 switch off "Do eddy-current correction".

3.7.7 Siemens

Quite a variety of files (single-voxel and 2D & 3D CSI) are automatically recognized and handled by LCMgui.

With the "syngo" PC platform, you must transfer the files to your Linux or Unix workstation. With FTP, transfer with "binary mode" (not "text" and not "ASCII" mode).

- Use the syngo `.rda` files. They are generated in the spectroscopy card via `'options -> export raw data'`.
- Some syngo DICOM `.ima` files (of course, with time data, not image data) can also be used. They are generated by the command `'transfer-> export to off-line'` in the patient browser. Future DICOM files may not work.
- LCMgui can also handle syngo raw binary files with no header, but the above `.rda` and `.ima` types are much more complete and convenient to use.
- Vision single-voxel `.raw` files from the Sun Unix platform are also handled automatically with LCMgui.
- With single-voxel spectra, you should acquire an unsuppressed water reference spectrum from the same voxel. You then select "Do eddy-current correction" in LCMgui (Sec 6.3.3). You will then be prompted to select the unsuppressed water reference file.
- Estimates of absolute concentrations using calibration phantoms (Sec 10.1) is only convenient with Vision `.raw` files and only when the transmit coil is also the receive coil. In other cases, a more elaborate calibration is necessary [23]. Water-Scaling (Secs. 6.3.4 & 10.2) is a convenient alternative for all cases.

3.7.8 Canon/Toshiba

- LCMgui handles **rawData** files (V4.10–V6.30) for both 2D CSI & single-voxel data.
- LCMgui handles DICOM files (V7.xx and later) for both 2D CSI & single-voxel data. With CSI data, the unsuppressed water reference must have the same number of voxels as the water-suppressed scan; i.e., you must set **ref_mode** to 1, not 11. LCMgui only accepts CSI single-channel (not CSI multi-channel) files.
- With single-voxel spectra, you should select “Do eddy-current correction” in LCMgui (Sec 6.3.3).

3.7.9 Varian/Agilent

- LCMgui handles single-channel **fid** files (CSI & single-voxel). It handles multi-channel single-voxel (but not CSI) **fid** files. The corresponding file **procpa**r must be in the same directory with **fid**.
- With single-voxel data or multi-channel data, you should select “Do eddy-current correction” in LCMgui. You will then be prompted to select the unsuppressed water reference **fid** file corresponding to your selected data file. With multi-channel data, you must input **IAVERG=1** (Sec. 11.9.2).
- With single-voxel, single-channel spectra, you can increase the speed of the analysis by using only the first 2^N complex data points, where N is the largest possible integer. You only have to input this as **NUNFIL** (Sec 5.3.1); you do not have to change your file **fid**.

3.7.10 Other Vendors

You can convert other types of data for LCModel. Until a few years ago, there was no LCMgui, and everyone converted their own data to the simple LCModel format specified in Chap 5. The analysis is then performed by a single Unix command of the form

```
$HOME/.lcmodel/bin/lcmodel < my.control
```

as specified in Chap 5.

LCMgui also has an “Other” button that allows you to use your own conversion script within LCMgui (see Sec 7.4.4).

Chapter 4

Installation and Test Runs

The complete LCMModel/LCMgui package can be downloaded from the WWW site on Page 2. The simple instructions for installing (and uninstalling) the package and making the test runs are also on this site.

You install as a normal user (not `root`) with no special privileges using the commands:

```
tar xf lcm-??tar
./install-lcmmodel
```

where ?? is 32 or 64.

Please note: If you are using a remote computer and get a message about not being able to open or connect to a display, see the suggestions on <http://lcmmodel.ca/lcm-test-x.shtml>.

Section 7.2 gives further options for installing LCMgui (e.g., for a group of users).

4.1 PostScript Output

The summary of each LCMModel analysis (the One-Page Output) is in a PostScript file. You may want to print this out. However, for routine analyses on a large scale, you will instead probably want to display these files (in color) on the monitor and archive them for easier future access (than piles of paper). LCMgui facilitates archiving these files. You can usually print the file from your display program anyway.

4.2 Test Runs Using LCMgui

4.2.1 Display on Your Screen

Try just clicking the “Continue” button in Fig 4.1 to use the default `evince`, which is usually installed. If it is not, LCMgui will give you a chance to enter another display command (e.g., `gv` or `okular`) in the green field. You can later download and install

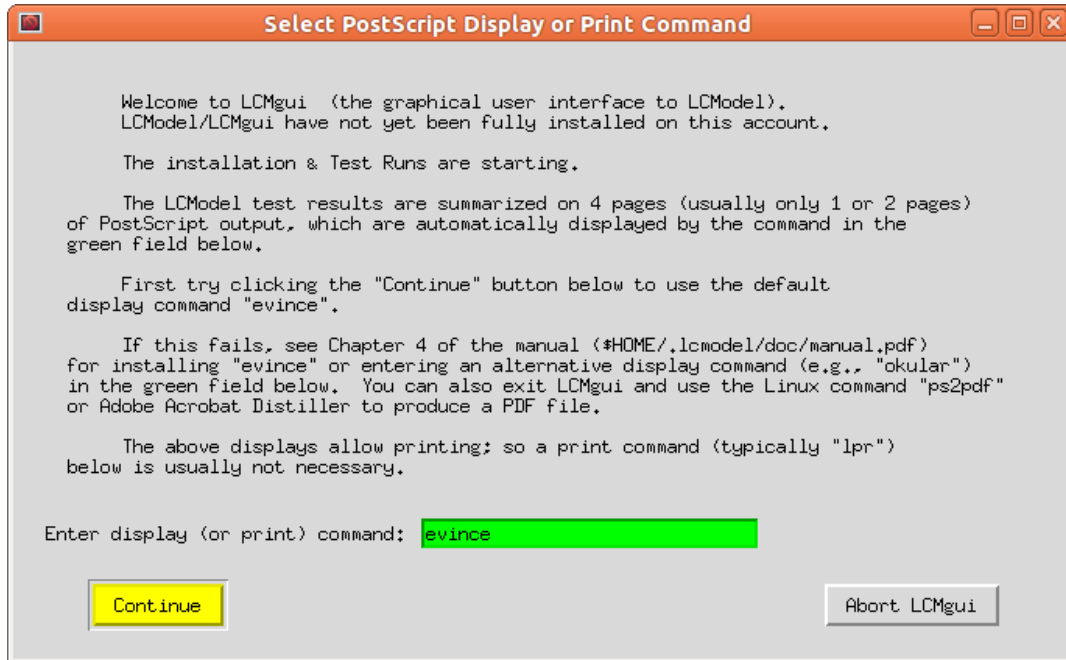


Figure 4.1: Here you enter your command for displaying or printing PostScript files.

`gv` or `evince` from your Linux distributor’s repository. `gv` (written by one person more than 20 years ago) is better than `evince` for PostScript files; `evince` is better for PDF files. It is easy to install `gv` from the Ubuntu repository. With `evince`, you can put an icon on the toolbar for rotating the plot left. Instead, you can click “Edit” in the toolbar and “Rotate Left”; then click “Edit” and “Save Current Settings as Default”.

Some Linux distributions (e.g., Ubuntu) have missing fonts or files that cause warnings with `evince` and the others. Usually, these do not affect the output and can be ignored. However, LCMgui will ask for a corrected display command. If the display or printing was successful, you can click “Use Old Command”. You can later suppress these warnings by using Sec 7.4.6 to change the display command, e.g., to

```
evince 2>/dev/null
```

The test runs will automatically output the “One-Page Output” (four pages in this case). These should approximately agree with PLOTs 1–4 in `$HOME/.lcmmodel/doc/figures.pdf`.

4.2.2 PostScript Printer

You can instead output to a printer. Most printers can print PostScript files. If your default printer can, you would probably enter

```
lpr
```

in the green entry field in Fig 4.1. For another printer (e.g., called `mypr`), you would enter a command like

```
lpr -Pmypr
```

4.2.3 No Printer or Display

If neither printing nor display is possible, then enter the harmless command

```
touch
```

in the green field in Fig 4.1. LCMgui outputs the test run results into `$HOME/.lcmmodel/test/output/test.ps`. You can then transfer this file to a computer that can print or display the file. You could also convert the PostScript files to PDF files, using Adobe Acrobat Distiller, `okular` or `ps2pdf`, present in some Linux distributions.

If you later find a display or print command that works, you can build this into LCMgui using Sec 7.4.6.

4.2.4 Further Tests

Without a license and without the test data, LCModel will stop with an error message, but a plot of the absolute value of the spectrum (without a referencing shift correction) will still be output. Therefore, this plot will indicate whether your data have been correctly converted and read by LCModel.

You can continue with your first session, or you can exit and start LCMgui again with the following commands:

```
cd $HOME/.lcmmodel
./lcmgui
```

You can test the automatic conversion of your data as follows:

- Click on the “Further tests” button when the run with the LCMgui test data is finished, or click on “Test My Data” when you restart LCMgui later.
- In Fig 6.3, click on the data type corresponding to your data. (See Sec 3.7.)
- In Fig 6.1, select your data file. (See also Sec 6.2.1.)
- LCMgui should automatically convert your data and plot the absolute value of the (unreferenced) spectrum in the LCModel One-Page Output. (Keep in mind that the absolute value of a spectrum has much poorer resolution than the real part.)
- *For CSI data sets:* only one voxel near the center will be selected. Section 4.2.5 allows you to display whole slices from 2D & 3D data sets.

4.2.5 More Complete Test of LCMgui with a False License

You can test all facilities of LCMgui by installing a *false license*.

- First make a false basis file with the commands:

```
mkdir -p $HOME/.lcmmodel/basis-sets
```

```
touch $HOME/.lcmodel/basis-sets/dummy.basis
```

- With Linux, simply enter

```
touch $HOME/.lcmodel/license
```


With Sun, SGI or DEC/Compaq, install the license (Sec 7.2.5), by entering any name next to “License OWNER:” and an integer 1–9 digits long next to “License KEY:”.
- You can then select one of your data files. You can then use the full LCMgui with the numerous possibilities documented in Chaps. 6 & 7. You can try setting everything up for possible future routine analyses and archival.
- When you click “Run LCModel” in Fig 6.4, you may (or may not) be asked to select a Basis Set. Select any file, e.g.,

```
$HOME/.lcmodel/basis-sets/dummy.basis
```

; LCModel will exit before it is used.
- LCModel will still only output the absolute value plot with the licensing message, but the files will now also be archived, as specified in Sec 7.3.3. You can set up and test the archival system and the rest of the configuration that you would use with a valid license.

4.2.6 Starting Over

LCMgui remembers what you have done so far. You can make as many test conversions of your data as you wish, but, if for some reason you want to start again from the very beginning, i.e., from the test run, you can clear LCMgui’s memory by entering:

```
rm -fr $HOME/.lcmodel/profiles
```

You can then start again as though you had just downloaded and unpacked the whole package by entering:

```
$HOME/.lcmodel/lcmgui
```

Then click the “Repeat Test Run” button.

4.3 Test Runs without LCMgui

Until a few years ago, there was no LCMgui. You can still use LCModel directly, without LCMgui. It is easiest to do the usual installation with the two commands at the beginning of this chapter. If the test runs are not done (e.g., because X windows is not running), everything that you need will still be installed (mainly in `$HOME/.lcmodel/bin/`).

You can do the test runs without LCMgui with the commands

```
cd
$HOME/.lcmodel/bin/testrun
```

The One-Page Output is then in the PostScript file

```
$HOME/.lcmodel/test/output/test.ps
```

On Linux systems, run-time messages about “Skipping namelist . . .: Seeking namelist . . .” are normal and harmless.

Chapter 5 specifies how to prepare and analyze your data either directly with LCModel or by using the “Other” button (Sec 7.4.4) with LCMgui.

4.4 Benchmark Timings

To compare several computers, you can execute the following command on each:

```
$HOME/.lcmodel/bin/time-testrun
```

The test run will be executed and then the time will be output on the screen.

On a Linux platform, no other computationally intensive process should be running, since the elapsed time is measured. With Unix (Sun, DEC/Compaq or SGI), this is less critical, since the LCModel CPU time is usually measured. Unix computers typically take about 150 seconds. Recent Linux PCs typically take about 5 seconds.

Chapter 5

Running LCModel without LCMgui – Basic Input

Although all users would benefit by becoming familiar with the Control Parameters in this chapter, LCMgui users with GE, Marconi/Picker, Philips, Siemens, Canon/Toshiba & Varian data can usually skip this chapter; LCMgui usually does all this for you. Mainly LCMgui users with other data types (e.g., using the LCMgui “Other” button) need this chapter.

Instead of using LCMgui, you can run LCModel directly with a command like

```
$HOME/.lcmmodel/bin/lcmodel < my.control
```

where `my.control` is a `.CONTROL` file (Sec 5.3) containing changes to the Control Parameters.

This chapter specifies the necessary Control Parameters that you may have to set for the conditions in your laboratory. It also outlines how you would write a simple Pre-Formatting Program or script to automatically do this and to connect files to LCModel. The Normal User then only needs to input one name identifying the data.

5.1 Conventions

5.1.1 File extensions

LCModel filetypes are denoted by extensions below. (For clarity, this manual uses upper case; LCMgui generally uses lower case, except for `RAW`; you do not have to follow either of these conventions.)

LCModel needs three input files:

- `.RAW` for the LCModel `.RAW` file with *time-domain* data, defined in Sec 5.2. (GE & Siemens “raw” files will be referred to in lower case.)

.BASIS for a file containing the *Basis Set* of model metabolite Basis Spectra, defined in Chap 8.

.CONTROL for the file with the changes to the Control Parameters input to LCModel, defined in Sec 5.3.

For a given acquisition protocol and field strength, the **.BASIS** file is generally the same, whereas the **.RAW** and **.CONTROL** files must be prepared for each spectrum.

Some other extensions used in this manual are:

.PS for a PostScript file that you can display or send to your PostScript printer;

.IN for a file with analogs to Control Parameters input to the MakeBasis, PlotRaw or KECC programs in the LCModel package.

5.1.2 Control Parameter Conventions

When a Control Parameter is defined in this manual, its name (6 or fewer characters) is followed by its Fortran type in parenthesis. Some examples of Fortran type specifications are:

CHARACTER*56 means a string of a maximum of 56 characters enclosed in single quotes, as

```
NAMREL = 'Cr'
```

Note that the string **'Cr'** is case sensitive, but the Namelist name **NAMREL** is not. Thus you could also use

```
namrel='Cr'
```

but *not* **NAMREL = 'cr'**.

INTEGER(20) means an integer array with up to 20 elements, as for **KEY** in Sec 5.3. In the **.CONTROL** file, you could specify the first two elements of the **KEY** array as

```
KEY(1)=12345 KEY(2)=23456
```

LOGICAL can be assigned the value **.TRUE.** or **.FALSE.**, However, you can also use **T** or **t** instead of **.TRUE.** and **F** or **f** instead of **.FALSE.** LCMgui and this manual use **T** and **F**; e.g.,

```
BRUKER = T
```

5.2 .RAW File

“RAW” is used to stress that the raw data should *never* be smoothed or windowed. Smoothing destroys information and ruins the statistical tests in LCModel.

An example is provided by the **.RAW** file with the test data in

\$HOME/.lcmmodel/test/raw/test.RAW. A **.RAW** file consists of two *Namelist* headers preceding the time-domain data itself, as specified in the rest of this section:

5.2.1 Namelist SEQPAR

The Namelist **SEQPAR** is optional, but very useful. If it is included, its data will be compared with that in Namelist **SEQPAR** of the **.BASIS** file to be used. Diagnostics will then warn of inconsistencies between your *in vivo* data and your model spectra.

The **.RAW** File begins with the Namelist **SEQPAR**:

```
$SEQPAR
ECHOT = 20.
HZPPPM=84.47
SEQ = 'STEAM'
$END
```

Namelists are used throughout LCMModel. See your Fortran Manual for their many convenient features, or use the Namelists in your LCMModel package as guides; Namelists are very easy to use. The one critical pitfall: the **first column** of Namelist input is always ignored; so *each line must start with one space*. The start of the Namelist is specified by a \$ (which must be in column 2) followed by the Namelist name (e.g., **\$SEQPAR** above). The end is specified by **\$END**.

Most convenient is that the Namelist can be very long, but only the variables explicitly input in the Namelist are changed; the rest keep their original (default) values. Most Control Variables have default values, and these are specified in this manual. If you agree with the default of a Control Parameter, then you do not have to input anything for it. (Exceptionally, none of the Control Variables in Namelist **SEQPAR** has a default value.)

The above Control Parameters are:

ECHOT (REAL) (“echo time”) the echo time (in ms) used for this data.

HZPPPM (REAL) (“Hz per ppm”) the field strength, in terms of the proton resonance frequency in MHz, i.e., $\text{HZPPPM} = 42.58B_0$, with B_0 in Tesla. You should input it with an accuracy of at least four significant figures.

SEQ (CHARACTER*5) must be either **PRESS** or **STEAM**, according to the localization method used for this data.

5.2.2 Namelist NMID

The second Namelist in the **.RAW** file is **NMID**, and it is always required. An example is:

```
$NMID
ID='pat_777_77'
FMTDAT='(2E15.6)'
VOLUME=18.0,
TRAMP=89.6,
$END
```

The above Control Parameters are:

- ID** (CHARACTER*20) a string that you can use to identify the data. It appears in the so-called *Detailed Output* and in the plot of the data with the program **PlotRaw**. It is useful for documentation, but it is optional; if you leave it out of the Namelist input, then a blank ID is output.
- FMTDAT** (CHARACTER*80) the Fortran FORMAT specification for your raw time-domain data, which must immediately follow Namelist NMID. (See also Sec 5.2.3 below.) This has no default; it must be input.
- VOLUME** (REAL) the voxel size (always in the same units, e.g., mL).
Default: **VOLUME** = 1.0
- TRAMP** (REAL) The data are multiplied by the factor **TRAMP/VOLUME** to scale the data consistently with the Basis Set, as discussed in Sec 10.1.1. **VOLUME** and **TRAMP** do not affect the concentration ratios; they only need to be input for absolute concentrations. Default: **TRAMP** = 1.0.
- BRUKER** (LOGICAL) (“Bruker data”) Bruker, Philips & Canon/Toshiba data must have **BRUKER** = T, which causes all 4 programs in the LCModel package to complex conjugate the data, which is necessary with these data types. (This Control Parameter was named before I had contact with Philips or Toshiba data.)
Default: **BRUKER** = F
- SEQACQ** (LOGICAL) (“sequential acquisition”) This is for Bruker users only. You do not need to input this in the normal case of simultaneous acquisition, where the real and imaginary parts of the complex pair of time-domain data are acquired simultaneously. If you do not input it, then it will be left at its default value of **SEQACQ** = F. Only for Bruker sequential acquisition mode (default on some Bruker systems prior to the AVANCE series), where the imaginary part of the complex pair is acquired one sample time after the real part, must you input **SEQACQ** = T; in this case, you input the uncorrected data (as the usual complex pairs), and all 4 programs in the LCModel package automatically correct the data for you.

So, the only necessary input in this Namelist required from everyone is **FMTDAT**, if you are only interested in concentration ratios.

For absolute concentrations, LCModel needs a **TRAMP** that scales the *in vivo* data consistently with the Basis Spectra. **VOLUME** then accounts for the voxel size. Chapter 10 specifies this in detail. In addition, absolute concentrations are more sensitive than concentration ratios to the corrections for relaxation (Sec 11.2) and partial-volume effects (which are all independent of LCModel).

5.2.3 Time-Domain Data

These must start on the line immediately after the **\$END** of Namelist NMID. These data points must be in order of increasing time, with each point a complex pair (real, imaginary, real, imaginary, ...).

5.2.3.1 CSI data sets

The time-domain data for one voxel must be immediately concatenated to the preceding time data, with no blank positions between (therefore, a FMTDAT with only one complex pair per line is safest, e.g., '(2E15.6)'). There are also no Namelists SEQPAR or NMID for voxels after the first, only the time data.

This is already the structure of the the time-domain data in Bruker, Philips, Siemens, Canon/Toshiba & Varian files in Sec 3.7, which are automatically handled by LCMgui.

5.3 .CONTROL File

An example from the test runs is the file `test.control`. The `.CONTROL` file consists solely of the the Namelist LCMODL. A simple example is:

```
$LCMODL
OWNER='Biomedizinische NMR Forschungs GmbH'
KEY=123456789
TITLE='pat_777_77 (41Y, M) 18.0ml, gm, PMP'
FILBAS='/home/lcm/basis-sets/te20_2c.basis'
FILRAW='pat_777_77.raw'
FILPS='pat_777_77.ps'
$END
```

The above Control Parameters are:

OWNER (CHARACTER*120) the name of the license holder. (With Linux, this is not used, but the Linux license file must be in `$HOME/.lcmodel/license`.) This string is given to you with your license. You must input it exactly, i.e., with the same capitalization and spacing, all on one line.

KEY (INTEGER(20)) your license key. (With Linux, this is not used, but the Linux license file must be in `$HOME/.lcmodel/license`.) This is given to you with your license. Together with **OWNER**, it enables you to run LCModel on the licensed Unix workstation.

TITLE (CHARACTER*244) the title that you want to appear at the top of the One-Page Output (and elsewhere).

FILBAS (CHARACTER*255) the pathname of the `.BASIS` file to be input.

Note: On most platforms, you *cannot* use symbols like `~` or `$HOME` to denote your home directory with any Control Parameters.

FILRAW (CHARACTER*255) the pathname of the `.RAW` file to be input.

FILPS (CHARACTER*255) the pathname of the `.PS` file that will contain the PostScript One-Page Output.

You will have to add more changes to your `.CONTROL` file. These are specified in this chapter. However, these changes are usually always the same; the only Control Parameters in the `.CONTROL` file that are normally changed with every data set are

TITLE, FILRAW, and FILPS. You should be able to write a simple Pre-Formatting Program so that the Normal User only has to input one name, e.g., `pat_777_77`. The Pre-Formatting Program then

- finds the corresponding raw time-domain data and formats it as the `.RAW` file;
- makes the `.CONTROL` file by extracting TITLE from a header in your original data file and by inserting `pat_777_77` into FILRAW and FILPS;
- runs LCModel and prints or displays the One-Page Output in the `.PS` file.

In the following, I specify the additional (generally data-set-independent) changes that your Pre-Formatting Program adds to the `.CONTROL` file to change the default Control Parameters to those appropriate for your instrument and protocol. Note that the ordering in a Namelist is not important, except that a Control Parameter input several times will take on the value closest to the end of the Namelist. It is therefore best to add changes to the bottom of the list (just above `$END`). The table **Input Changes** in the One-Page Output prints your `.CONTROL` file from the bottom up, so that the most recent changes (at the bottom of the file) are at the top of the table.

5.3.1 Instrument and Acquisition

HZPPPM (REAL) (“Hz per ppm”) the field strength, in terms of the proton resonance frequency in MHz, i.e., $\text{HZPPPM} = 42.58B_0$, with B_0 in Tesla. You should input it with an accuracy of at least four significant figures.

Default: `HZPPPM = 84.47` (1.984 T; so, you will almost certainly have to input your own value.)

NUNFIL (INTEGER) (“N unfilled”) the number of complex pairs of data points in one scan, without zero-filling. Default: `NUNFIL = 2048`

DELTAT (REAL) (“ δt ”) the time (in s) between two consecutive real points (or two consecutive imaginary points). This is just the sample time or “dwell time” or the reciprocal of the “bandwidth.” Default: `DELTAT = 0.0005`

The acquisition time for one scan, `DELTAT*NUNFIL`, should be long enough so that the *in vivo* time-domain data decay into the noise. For brain spectra at 1.5 T, this is typically 0.8 s or 1.0 s. At higher fields it is usually shorter.

5.3.2 Multi-Voxel Data Sets

One voxel’s data is immediately concatenated to the preceding one’s. We use the DICOM standard that the voxels in the file start at the top left and are ordered as in three nested loops, with the columns in the inner loop, the rows in the middle loop, and the slices in the outer loop; i.e., the voxels are row-after-row, then slice-after-slice. Thus, the second voxel’s data in the file is said to come from Column 2 of Row 1 of Slice 1 (assuming that there is more than one column). Scanner displays are not always consistent with this (Sec 11.4.3.2).

You specify the CSI data set dimensions of the .RAW file with the following Control Parameters:

NDCOLS (INTEGER) (“Number of data columns”) The number of columns in the CSI data set.

Default: **NDCOLS** = 1

NDROWS (INTEGER) (“Number of data rows”) The number of rows in the CSI data set.

Default: **NDROWS** = 1

NDSLIC (INTEGER) (“Number of data slices”) The number of slices in the CSI data set.

Default: **NDSLIC** = 1

You specify the range (rectangular subset) of voxels to be analyzed by LCModel with:

ICOLST & ICOLEN (INTEGER). Voxels in columns **ICOLST** through **ICOLEN** will be analyzed.

Default: **ICOLST** = **ICOLEN** = 1

IROWST & IROWEN (INTEGER). Voxels in rows **IROWST** through **IROWEN** will be analyzed.

Default: **IROWST** = **IROWEN** = 1

ISLICE (INTEGER). Voxels in slice **ISLICE** will be analyzed.

Default: **ISLICE** = 1

There will now be a set of output files for each voxel, and these are uniquely identified as follows: the **Slice#** (only for 3D sets) and **Row# & Col#** are inserted at the beginning of each **TITLE** (as in PLOT 15 in `$HOME/.lcmodel/doc/figures.pdf`). The output filenames are extended as in the following example: if you input **FILPS** = ‘filename.ps’, then the Slice#1, Row#2, Col#3 file will be `filename_sl1_2-3.ps`. Section 11.4.3 lists other cases and also specifies how to change the format of these identifiers.

Section 11.4 specifies how to combine .PS files into a single file, and how skip over a voxel in the rare case that it causes an abort, breaking off the multi-voxel analysis.

5.3.3 Analysis Window

You select the Analysis Window (the window of frequency-domain data that will be analyzed) as follows:

PPMEND (REAL) (“ppm end”) the lower limit of the ppm-range; i.e., the right edge of the Analysis Window (with the usual convention of the ppm-axis decreasing toward the right).

Defaults: See Sec 3.4.1.

PPMST (REAL) (“ppm start”) the upper limit of the ppm-range; i.e., the left edge of the Analysis Window.

Default: **PPMST** = 4.0

These two Control Parameters are the most important ones for salvaging problem spectra. They are probably the only two that the Normal User will also want to occasionally change. See Sec 3.4 for guidelines.

5.3.4 Eddy-Current Correction

Philips users can skip Sec 5.3.4; you should have Philips do the eddy-current correction (ECC) as specified in Sec 3.7.6.

With single-voxel brain data, eddy-current correction [10] is recommended. This requires also a reference fid from the same voxel with the same sequence, except with no water suppression. With a CSI data set, all of the voxels in the unsuppressed reference data set must be the same as those in the suppressed data set. However, ECC is often ineffective with CSI data and is seldom done.

These reference data are automatically included with the water-suppressed data in a single-voxel GE Probe raw P-file or Marconi/Picker file, and the two required LCMModel .RAW files (see Sec 9.6) can be made. In other cases, you have to organize this yourself: You put the unsuppressed reference data in a separate file (FILH20). You then add DOECC & FILH20, as specified in Sec 9.6 to your .CONTROL file.

In addition to improving the Baseline and lineshapes, ECC usually greatly reduces the zero-order phase correction. Section 9.7.1 shows how you can experimentally investigate whether this correction is small. If it is, then this prior knowledge can speed up and improve the LCMModel analysis, especially of poor quality spectra. With single-voxel data, add the following Control Parameter to your .CONTROL file to impose this prior information:

SDDEGZ = 6.

(The Index at the end of this manual tells you where to find the discussion of other Control Parameters, such as **SDDEGZ**.)

With CSI data, ECC may be less effective and the phases highly variable. Do not input **SDDEGZ**; let the Bayesian learning in LCMModel set **SDDEGZ**.

For Bruker users only: In ParaVision, choose the option to have ECC done. Do not do ECC again in LCMModel. Without LCMgui, you first correct these for Bruker's digital filter using Bruker's **convdta**. Do not input **SDDEGZ**, since the zero-order phase correction is often not small.

In rare cases, particularly if the water suppression is weak and the unsuppressed water reference not very good, you may see that ECC obviously amplifies the noise in the high-ppm part of the spectrum. If this amplified noise extends into the Analysis Window, then you should switch off ECC by removing **DOECC** and **SDDEGZ** from the .CONTROL file, for this spectrum only.

5.3.5 First-Order Phase Correction

The first-order phase correction (ϕ_1) is often small, and prior knowledge of this can be used to speed up and improve analyses. At least two well-separated landmark peaks are needed to determine the zero-order and first-order phase corrections. Therefore prior knowledge of phases is very important with spectra lacking two strong landmarks, as in PLOT 6 in `$HOME/.lcmode1/doc/figures.pdf` (although this case also worked without specifying `SDDEGP` or `SDDEGP`).

As specified in Sec 9.7, the Control Parameter `SDDEGP` tells LCMODEL the standard deviation of the expectation value, `DEGPPM`, of the first-order phase correction. The following seem to work well for single-voxel data:

- GE Probe data: `SDDEGP = 1.`
- Marconi/Picker data with STEAM and current PRESS sequences:
`SDDEGP = 2., DEGPPM = 2.5`
- Marconi/Picker data with very old PRESS sequences:
`SDDEGP = 2., DEGPPM = 28.`
If you are not sure whether your PRESS sequence is “older” or “newer,” then try both 28 and 2.5 for `DEGPPM`; they are very different, and the wrong one should give very poor phasing. If you are in doubt, send me two or three “dump” files with high-quality PRESS spectra.

Siemens data often have a big ϕ_1 . However, this is usually quite consistent, i.e., also with a small `SDDEGP`, as with the Marconi/Picker values, which were calculated from their precisely known timing. Section 9.7.1 shows how you can experimentally estimate `DEGPPM` and `SDDEGP`.

5.3.6 PostScript Output

Section 9.9.3 gives many possibilities to tailor the format of the One-Page Output to your wishes, even for preparing slides or figures for publication. In any case, you should input the following Control Parameter:

`PGNORM` (CHARACTER*2) (“page norm”) ‘US’ sets the page dimensions of the One-Page Output to 8.5×11.0 inches;
‘A4’ or ‘EU’ sets the dimensions to 21.0×29.7 cm.
The default is `PGNORM = ' '` and makes a compromise to fit in both page formats.

Usually there is not enough room for the complete tables to the right of the plots in the “One-Page Output”. Then, by default, a second page with the complete tables (and no plot) is produced. Therefore, you should use a duplex printer, if possible, so that both pages are on one sheet.

`IPAGE2` (INTEGER)
`IPAGE2 = 0` to suppress printing the second page (e.g., if you do not have a duplex printer), thereby losing information;
`IPAGE2 = 1` (the default) to output a second page (PLOT 2 in

`$HOME/.lcmmodel/doc/figures.pdf`) with the complete tables, if there is not enough room on the first page;
`IPAGE2 = 2` to always output a second page with the tables.

5.3.7 Archiving the Results

The `.PS` and `.TABLE` files contain the essential graphic and numeric information from the analysis. The `.CSV` file contains the concentrations and can be imported to spreadsheet programs. With LCMgui, you can select any of these to be output using Fig 7.3.

5.3.7.1 .TABLE File

The `.TABLE` file contains all the information in the tables of the One-Page Output as a self-documented text (ASCII) file. You can archive these files (particularly if you have assigned them unique pathnames with `FILTAB`) into a database (e.g., for computing means or other statistics over a group of spectra). For this, you must input the following:

`FILTAB` (CHARACTER*255) (“table file”) the pathname of the `.TABLE` file to be output. (e.g., `’/home/user1/.lcmmodel/saved/pat_777_77/table’`).

`LTABLE` (INTEGER)

`LTABLE = 0` (the default) will suppress creation of this file;

`LTABLE = 7` will make this file.

5.3.7.2 .CSV Spreadsheet File

The `.CSV` file for spreadsheets is convenient for multi-voxel analyses (Sec 11.4.4). (For single-voxel analyses, it consists of only two very wide rows of concentration data.)

`FILCSV` (CHARACTER*255) the name of the `.CSV` file to be output (e.g., `’/home/user1/.lcmmodel/saved/pat_777_77/spreadsheet.csv’`). A file with the extension `.csv` (but not a file simply with the name `csv`) is automatically imported as a “comma-separated-value” file by spreadsheet programs.

`LCSV` (INTEGER)

`LCSV = 0` (the default) will suppress creation of this file;

`LCSV = 11` will make this file.

5.3.7.3 .PS PostScript File

The `.PS` file is output automatically. It contains all the information in the One-Page Output, including the plotted curves. You could archive this in the same directory as the `.TABLE` file. You can then view it with a PostScript viewer (Sec 4.2.1). You can also archive it on paper using a (duplex) PostScript printer.

5.3.7.4 .COORD Coordinate File

If you want to make your own plots, the .COORD file contains the coordinates of all curves on the One-Page Output (in an easy-to-read and self-explanatory text file):

FILCOO (CHARACTER*255) (“coordinate file”) the name of the .COORD file to be output (e.g., '/home/user1/.lcmode1/saved/pat.777_77/coord').

LCOORD (INTEGER)

LCOORD = 0 (the default) will suppress creation of this file;

LCOORD = 9 will make this file.

5.3.8 Phantoms

Tests with *in vitro* data from model solutions are unrealistic and not always useful. The accuracy and spectral resolution in the Basis Set must be higher than that in the data, and this is often not the case here. Broadening the *in vitro* test data also smooths them, and this falsifies the statistical tests [11] in LCModel. Even without smoothing or broadening, the systematic errors in such data often exceed the normal scatter due to the noise, and this falsifies the model itself.

Your phantom data at room temperature will be inconsistent with simulated basis sets using data from 37° C.

If you are analyzing *in vitro* data, then use

VITRO (LOGICAL) .TRUE. if the spectrum is an *in vitro* spectrum; this will override some statistical tests that could otherwise be falsified with such data.

Default: VITRO = F

If necessary, increase AQ, the acquisition time for one scan, so that the time data have decayed into the noise.

In addition, your phantom spectrum must be dominated by at least one of the following: NAA, Cr or Cho. Otherwise, you will have to set additional parameters as illustrated in Sec 11.6. So, it is much simpler if your phantoms always contain significant amounts of at least one of the above 3 landmark metabolites.

Even simpler is when you are doing standard calibrations either of the scanner (Sec 10.1.2) or of the Basis Spectra (Sec 8.7.1). Then, VITRO=T (and several other Control Parameters) are automatically set.

Chapter 6

Elementary Guide to LCMgui

This chapter gives the basic steps for the Normal User in using LCMgui, with references to Chap 7 for details. Chapter 4 gives the simple steps for downloading and installing LCMgui. Chapter 7 is a detailed reference, allowing you to make full use of the flexibility of LCMgui and to optimally configure LCMgui for the Normal User.

LCMgui remembers many of the settings from the previous run. If an expert user has already made runs from your account, then you may not have to change any settings, and the following three simple steps may be sufficient:

- Start LCMgui (Sec 6.1).
- Select the file containing the data to be analyzed (Fig 6.1 in Sec 6.2.1).
- Click on “Run LCMModel” (Fig 6.4 in Sec 6.4).

Parts in this fine print are seldom necessary reading, but they can help you make better use of LCMgui. If you are one of the first to run LCMgui from this account, then you should check the points in fine print.

6.1 Starting LCMgui

LCMgui is installed under one or more usernames. You must log on using one of these usernames. Log in normally, as the user, not as `root`. You can then always start LCMgui with:

```
$HOME/.lcmmodel/lcmgui
```

LCMgui may have been installed so that you can also start it with simply:

```
lcmgui
```

6.2 Selecting the Data to be Analyzed

See Sec 3.7 for a list of the types of data files automatically handled by LCMgui and for important guidelines.

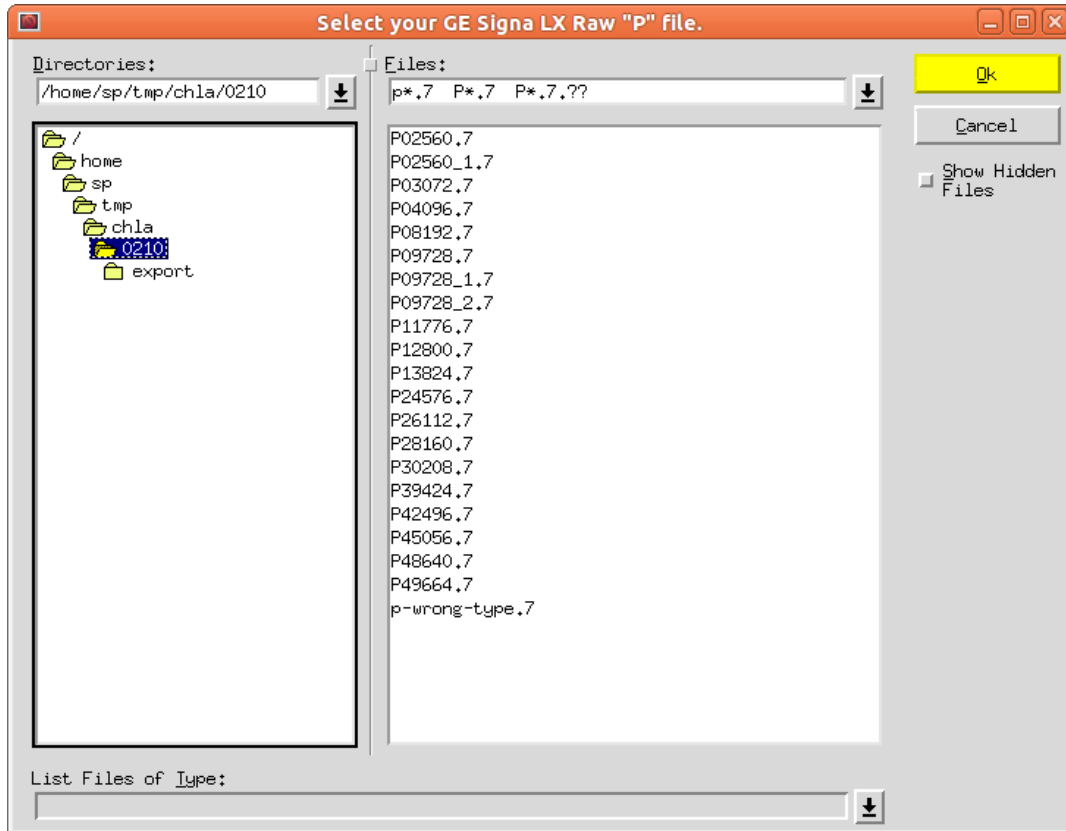


Figure 6.1: The File Selector, shown here for GE LX files

6.2.1 File Selector Window

When LCMgui is started, the first window that appears is usually the *File Selector*. An example with GE Signa LX data is shown in Fig 6.1. With data from other manufacturers, the title, “Select your GE Signa LX ...” will be different. LCMgui remembers the directory where the data file was in the last run, and the File Selector starts there.

If you have several *User Profiles*, then the window in Fig 7.12 will appear first. Normally, you immediately click on “Use Selected Profile” to continue using your present User Profile.

If the last LCMgui session did not use Bruker, GE, Marconi/Picker, Philips, Siemens, Canon/Toshiba or Varian data, then the window in Fig 6.3 will appear first. You normally then click the “Other” button in Fig 6.3, as you did in the previous session.

If no license has been installed, a window will first appear offering you the chance to test the conversion of your data (as in Sec 4.2.4).

You first navigate through the directory tree. When you click on a directory, its files are listed in the right pane (the stage shown in Fig 6.1). You then click on the filename that you want to use and click the yellow “OK” button at the right (or simply double-click on the filename).

Only filenames that match the filter shown at the top of the pane of filenames (p*.7, P*.7 or P*.7.??) in Fig 6.1) are displayed. If your filename differs from this standard (e.g., if you analyzed GE Signa 5.x data last time and LX data this time), then it will not be listed. You can change

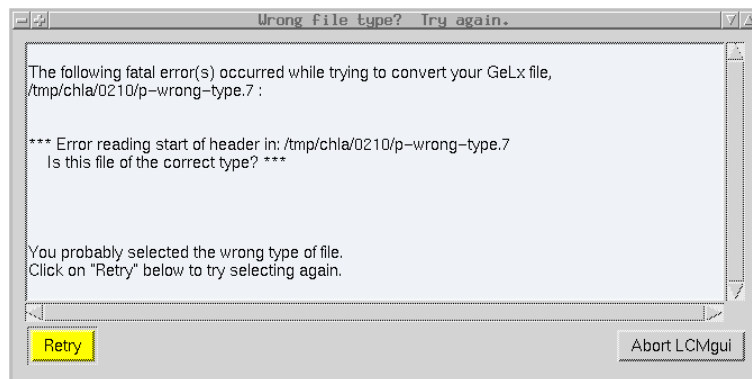


Figure 6.2: You selected a file of the wrong type in the File Selector

the filter by clicking on the field (`p*.7 P*.7 P*.7.??`), pressing the “backspace” or “delete” key, entering your new filter (e.g., `*`), and pressing the “Enter” key.

If you want to also see files or directories that start with a dot (e.g., `.lcmode1/`), then click on the “Show Hidden Files” button on the right to make it yellow.

If the filenames or directories in Fig 6.1 are so long that they are cut off, then the width of the panes can be adjusted by holding the left mouse button down on the small square at the top on the pane boundary (between “**Directories:**” and “**Files:**”) and dragging the pane boundary. (You can also simply use the scroll bar that appears at the bottom of the pane when names are too long.)

6.2.1.1 Selecting the wrong file type

LCMgui remembers what type of data was analyzed from this account and User Profile the last time, and it expects the same type this time. You therefore get a window like Fig 6.2 if in the File Selector you:

- Select a file of another type (e.g., a Siemens “raw” file after GE Signa LX last time). If you have data of different types (e.g., GE and Siemens), then you should use a different User Profile (Sec 7.3.7) for each. This way, the default settings for each data type are preserved and kept separate.
- Select a completely irrelevant file (e.g., `p-wrong-type.7` in Fig 6.1 to produce Fig 6.2).

If you selected the wrong User Profile at the start of session, then you can click the “Abort LCMgui” button, and then restart and select the correct User Profile.

Otherwise, click the yellow “Retry” button in Fig 6.2. A window like Fig 6.3 appears. Here you click on the appropriate type of data. The File Selector then returns, giving you another chance to select your data file.

6.3 Control Parameters Window

After you click the “OK” button in the File Selector, the second of the two most important windows, the “Control Parameters” window (Fig 6.4), appears. LCMgui remembers most of the settings from the previous session. Thus, Normal Users often can simply click the yellow “Run LCModel” button at the bottom to start the LCModel analysis. (Yellow is generally used to show you the usual path to take.)

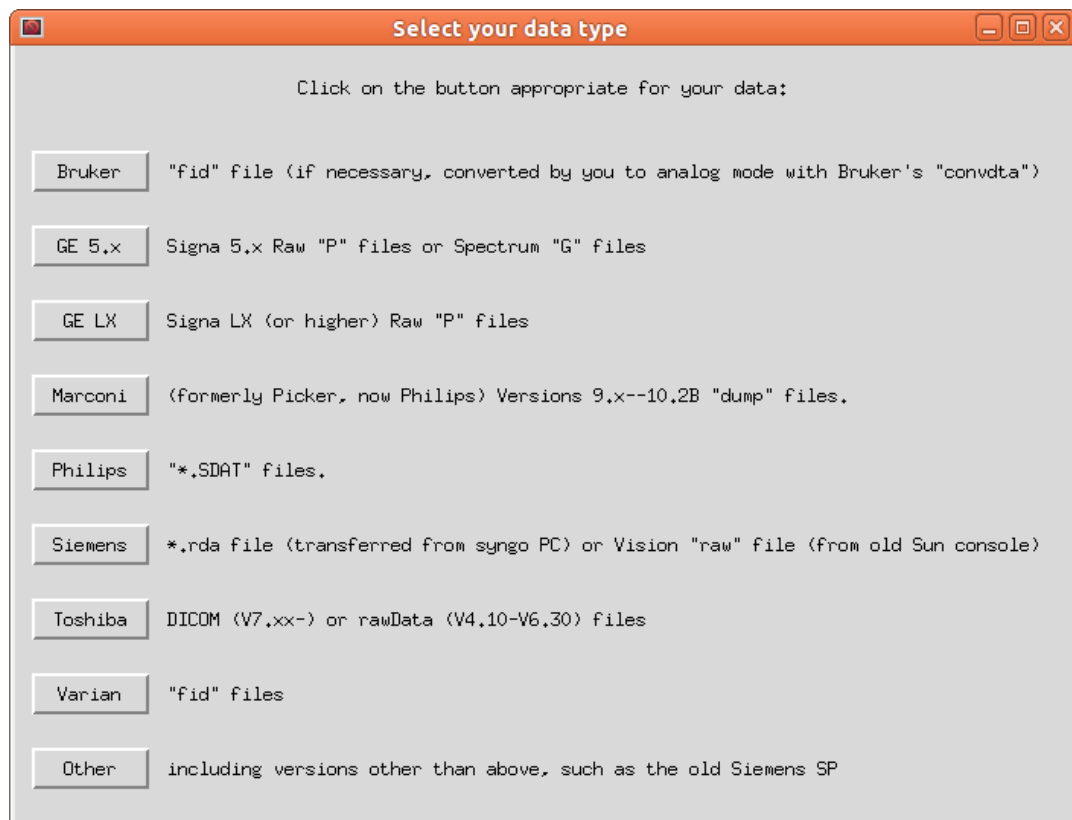


Figure 6.3: Note that GE Signa 5.x and LX (or higher) have distinct buttons.

However, you should check the following in your “Control Parameters” window, at least during your first runs. (Most of the fields have balloon help messages that pop up if the cursor remains over a field for 3 seconds.)

6.3.1 Analyzing spectrum from:

In the second row in Fig 6.4, the entries next to “**Analyzing spectrum from:**” define the Analysis Window, the ppm-range over which the spectrum will be analyzed (Sec 3.4). You can change this range by clicking on the green up or down arrow next to the value. (Green usually indicates fields that you can click on or edit to make changes.)

You may want to change these values to cut off artifacts (Sec 3.6.1).

6.3.2 BASIS file:

In the third row in Fig 6.4, the entry next to **BASIS file:** shows the pathname of the .BASIS file containing the model spectra that will be used to analyze your data. If the .BASIS files are installed as specified in Sec 7.2.4, then LCMgui should automatically select the proper one, if it exists. Also LCMModel normally produces diagnostics if the .BASIS file does not match your data.

For the first runs, you should nevertheless check whether the entry is correct. (STEAM or PRESS and TE should be visible in the filename.) If it is wrong, you cannot edit the white field (only green

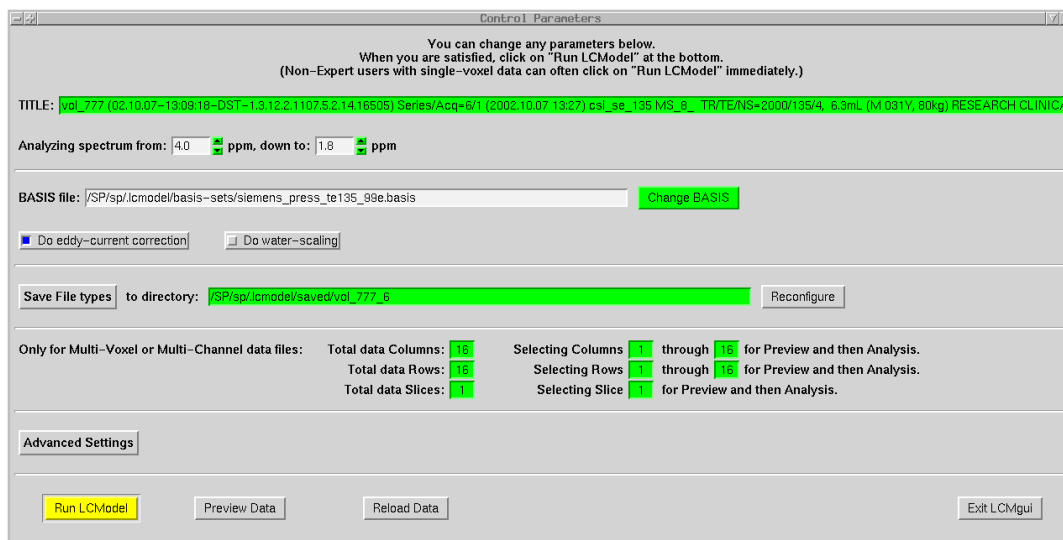


Figure 6.4: The Control Parameters Window

fields). Instead you click on the green “Change BASIS” button, and you get a File Selector for your .BASIS file, which you select just as in Sec 6.2.1.

6.3.3 Do eddy-current correction

Philips users can skip Sec 6.3.3; you should have Philips do the eddy-current correction (ECC) as specified in Sec 3.7.6.

Users with Canon/Toshiba, Marconi/Picker data or GE Probe P-files can skip Sec 6.3.3 since eddy-current correction (ECC) is done automatically. Other users only have to set this as default the first time for future analyses. In the fourth row in Fig 6.4, a mouse-click switches the button for ECC between active (blue) and inactive (no ECC). (Blue usually indicates a button that is switched on.)

ECC is recommended for single-voxel data (but not for CSI, where it is usually ineffective). You then must also have acquired an unsuppressed water reference spectrum from the same voxel immediately before or after acquiring your water-suppressed spectrum. With a CSI data set, all of the voxels in the unsuppressed reference data set must be the same as those in the suppressed data set. If you have this reference data file, be sure to make the ECC button blue.

In rare cases, particularly if the water suppression is weak and the unsuppressed water reference not very good, you may see that ECC obviously amplifies the noise in the high-ppm part of the spectrum. If this amplified noise extends into the Analysis Window, you should switch off ECC for this spectrum only.

6.3.4 Do water-scaling

Water-Scaling uses the unsuppressed water reference signal (as used above for ECC) to estimate absolute concentrations. Section 10.2.2 discusses the significant uncertainties in the corrections needed for this. Chapter 10 also discusses an alternative for Siemens Vision and 1.5T GE data, using Calibration Phantoms.

You activate Water-Scaling simply by making the “Do water-scaling” button blue. However, Sec 10.2.2 specifies important additional Control Parameters that you may have to change from their default values. Sections 7.3.4 & 7.3.5 specify how to change Control Parameters and save these changes for future use.

Concentration ratios are not affected by Water-Scaling and are less sensitive to relaxation and partial-volume effects.

6.3.5 Only for Multi-Voxel data files:

If you only have single-voxel data, then you can skip this section and this part of the “Control Parameters” window. LCMgui does not handle data that is both multi-voxel and multi-channel.

The balloon that pops up over this part gives step-by-step instructions on previewing a whole slice and then selecting a rectangular subset to be analyzed. It also gives troubleshooting hints.

Some headers do not have complete information on the total numbers of slices, rows & columns in the data file, even though LCMgui still correctly converts the file. So, you should first check and (if necessary) correct these values (which usually default to 1).

The “Preview Data” button at the bottom of the “Control Parameters” window is especially important with CSI data sets. Details and troubleshooting hints are given in Sec 7.4.1.

6.3.5.1 Multi-Voxel output

You get one PostScript output file for each voxel. If your default display/print command is a display command, then you will get a series of displays that each have to be closed before you view the next. It is usually more convenient to suppress the display/print command by deleting it using Sec 7.4.6. You can then use Sec 11.4.5 to combine all the files into one for convenient viewing.

6.3.6 The Rest of the Control Parameters Window

The rest are briefly listed here, with references to more detailed descriptions. They make LCMgui very flexible.

TITLE: This field at the top of Fig 6.4 will also appear at the top of the One-Page Output. You can edit this field, e.g., to insert comments on location or pathology.

Save File Types See Sec 6.5.

Advanced Settings Clicking this button produces a menu (Fig 7.6) offering several new windows. In this menu, the “View/Edit Control Parameters” window allows you to view, change, delete or add Control Parameters. For example, if the ECC button in Sec 6.3.3 was off and you turned it on (blue), then you should check the Control Parameter **SDDEGZ**, as specified in Sec 7.3.4.

Preview Data This allows you to first view your data (in the time- and/or frequency-domain, on your screen or printer), e.g., to make sure that you have the correct data and that it is worth analyzing. (Sec 7.4.1)

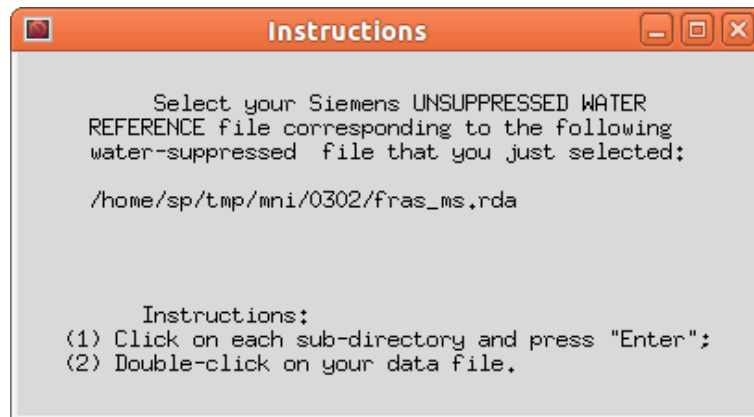


Figure 6.5: The instructions-part of the File Selector for the unsuppressed water reference.

6.3.7 Reload Data

The **TITLE:** line or “Preview Data” may cause you to wonder whether you selected the correct data file. You can further check this by moving the mouse (without clicking it) to the “Reload Data” button at the bottom. A balloon message will appear showing the filename that you selected. If this file is incorrect, you can click on the “Reload Data” button; the File Selector window will appear, and you can start over selecting a new data file; i.e., you start again at Sec 6.2.1.

6.4 Run LCModel

Once you are satisfied with the settings in the “Control Parameters” window, you click the yellow “Run LCModel” button at the bottom. Normally, the analysis is immediately started (as a background process), and a new window appears offering you the chance to start another analysis by selecting a new data file and proceeding again from Sec 6.2.1. (You can start a new analysis before previous analyses have finished; as each analysis finishes, its results are automatically output.) However, four windows may appear before the analysis can start:

Select unsuppressed water reference file If the “Do eddy-current correction” button is active (blue), the File Selector window appears (unless you have Marconi/Picker files or GE Probe P-files, which already contain the water reference). It is exactly as in Fig 6.1, except for the window of instructions at the upper left (Fig 6.5). As you can see from Fig 6.5, the filename of your currently selected water-suppressed data is shown, and you must select the corresponding unsuppressed data file.

With Philips, Siemens, Canon/Toshiba and GE spectrum G-files, if the voxel locations of the two files do not coincide, then a window appears with an error message and with options for continuing or starting over. LCMgui cannot always extract accurate voxel positions from Siemens syngo files, and this warning is sometimes a false alarm; if you are sure that the voxels

match, then you can simply click the button “Do Wrong Water” to continue with the analysis.

Missing data If LCMgui is not able to extract all necessary information from the data files, new windows will prompt you for these values.

Overwrite archive files? LCMgui automatically archives the output in an *Archive Directory* that is usually unique for each data file. However, if you want to analyze a data file for a second time, a window will appear warning you that the old output is about to be overwritten. You are given the opportunity of aborting, changing the output directory or overwriting it.

Save changes? If you have changed any Control Parameters (e.g., activated the “Do water-scaling” button), a window offering you the chance to save these changes for possible future use as defaults appears. This can be very useful in saving you from having to remember and enter these changes in the future. This is described in Sec 7.3.5.

6.5 Where is the Output?

Normally LCMgui automatically outputs the One-Page Output with a print or display command that was specified during installation in Sec 4.2.2. If you cannot find your output, Sec 7.4.6 specifies how you can check and correct this print or display command.

There are several other useful files that can be output and archived by LCModel. Clicking on “Save File types” in Fig 6.4 produces a menu where you can select which types of output files will be archived. In addition to the .PS file (with the One-Page Output), the .TABLE file (with tables summarizing the results) should be selected.

The green field following “Save File types to directory:” (which you can edit) shows the directory where they will be archived. See Sec 7.3.3, which also specifies how you can change the structure of this Archive Directory tree.

By default, the filename is simply the type of output, e.g., **ps** is the .PS file and **table** is the .TABLE file. By default, for multi-voxel (CSI) data sets, they are made unique as in the following example: The **Slice#2, Row#3, Column#4** .PS filename is **sl2_3-4.ps**.

The “INPUT CHANGES” table in your One-Page Output also has information on file locations:

SAVDIR (“Save-Directory”) shows the directory where the output was archived.

SRCRAW (“Source of RAW file”) gives the full pathname of the data file that you chose with the File Selector.

SRCH2O (“Source of H2O file”) gives the full pathname of the unsuppressed water reference file (if you chose one).

6.6 Interactive Processing with LCMgui

Normally, you use LCMgui to start a series of analyses, without waiting for one to end before starting the next. However, your analyses may go fast enough that you would want to run “interactively”, viewing the LCModel results of one analysis on your terminal before starting the next.

Section 7.4.2 specifies how to do this. If this has been implemented, then you should wait for the results to be displayed on your screen. To continue with LCMgui, you must then exit the display program yourself.



Figure 6.6: Here you decide how to save the settings from this session.

6.7 Getting out of LCMgui

LCMgui usually has an “Exit LCMgui” or an “Abort LCMgui” button. When you click this, you are usually given the choice of four buttons (Fig 6.6):

Exit & Save : This is the normal exit. LCMgui exits and saves the changes that you have made to LCMgui settings (such as the locations of your Basis and data files). When the next LCMgui session is started, these will then be offered as defaults.

Do Not exit : to cancel the exit and continue with LCMgui;

Exit & Forget : LCMgui exits, but does not save any settings that you made during this session. When the next LCMgui session is started, you will be offered the same defaults that you were offered at the start of this session. This can be helpful if you have made some big mistakes during this session, or if you used some unusual settings that you do not want to have saved as defaults for the future.

New Profile : allows you to save your settings to a new User Profile, using the window in Fig 7.12. You should use different profiles for different types of data (e.g., GE & Philips or 1.5T & 3T).

If the normal LCMgui exit buttons are not available, then enter **Control-C** or **Control-Z** in the Linux/Unix window from which you started LCMgui.

Chapter 7

LCMgui Reference Manual

This chapter will allow you to fully exploit the flexibility of LCMgui. It will also allow you to optimally install & configure LCMgui for less experienced Normal Users.

You must be familiar with Chap 6.

7.1 LCMgui Structure

The main steps executed by LCMgui are:

- (1) **File Selector.** You select the file containing your (binary scanner) data to be analyzed with the window in Fig 6.1.
- (2) **Data Conversion.** A program is executed to produce the LCModel `.RAW` file and any available Control Parameters (e.g., `NUNFIL`, `DELTAT`) from the file selected in Step (1). You can specify this program to be the standard LCMgui program for the standard Bruker, GE, Marconi/Picker, Philips, Siemens, Canon/Toshiba or Varian files (Sec 3.7). However, there is also an “Other” button to use a script supplied by you for another type of file.
- (3) **Preprocessor.** Even if you specify one of the standard programs for Step (2), you can still supply your own script in this step to modify the `.RAW` file or Control Parameters from Step (2). (The original default, when LCMgui is installed, is to use no Preprocessor.)
- (4) **Control Parameters Window.** This window (Fig 7.2) allows you to make many checks of the data and modifications of the Control Parameters and the LCMgui configuration before starting LCModel. You can also configure LCMgui so that the Normal User usually only has to click “Run LCModel” at the bottom of the window, without much knowledge of the rest.
- (5) **Run LCModel.** When you click the “Run LCModel” button, LCMgui makes many checks and then starts an Execution Script in background. The default script starts LCModel and archives the results. However, this script is available to you as a template, and you can modify it for your own

purposes.

The possibility of supplying your own scripts in Steps (2), (3) & (5) makes LCMgui very flexible. At the same time, LCMgui remembers most settings from the previous run; so, if you make the first analyses after installation, Normal Users with limited knowledge can often analyze their data with your configuration. You can even prevent Normal Users from permanently changing your most important settings (using Sec 7.5.1.2).

7.1.1 Limitations

Unlike LCModel (which was written by one person and is quite self-sufficient), LCMgui combines free software from several sources and depends on your particular window manager and system. With Linux, some window managers (especially old ones) may on rare occasions require that you manually move and resize some windows. Sometimes, you get a tiny window (smaller than an icon), which you have to find (usually toward the upper left), click on and then resize; it is best to then exit and start LCMgui again.

Most displays have sufficient resolution for LCMgui. The display must have at least 1024×768 pixels (better 1600×1200 or 1280×1024); 800×600 pixels are not enough. If the LCMgui windows are only slightly too large, then you can try reducing the font size (Sec 7.5.1.4).

7.2 Installing LCMgui

As specified in Chap 4, downloading from the WWW site on Page 2 and installing (and uninstalling) are very simple. Do **not** work as **root**; for example, this could set file access privileges so that LCModel updates by the user do not work properly. The entire package goes into `$HOME/.lcmodel/` of the user's directory.

However, you can avoid continually entering the dot and everywhere use `lcmodel` instead of `.lcmodel` by entering:

```
cd
ln -s .lcmodel lcmodel
```

7.2.1 Multi-User Installations

One license allows an unlimited number of users to have LCMgui and LCModel installations. An unlimited number of users can simultaneously run LCMgui and LCModel on the licensed computer. You could install into a new account and have all users use this installation. This would make installing upgrades simpler. However, it is better if each user has their own installation (as with a browser), so that their settings and archive of results are not overwritten by others. This also allows them to decide if or when to upgrade. (Upgrades are free.)

7.2.2 Starting LCMgui

You start LCMgui with the command

```
$HOME/.lcmodel/lcmgui
```

If you set your PATH environment variable to include `$HOME/.lcmodel`, then you should be able to start LCMgui simply with:

```
lcmgui
```

7.2.3 First Test Runs

LCMgui uses most of the settings from the previous run as defaults for the current run. So, your first runs are most important, since the Normal User can then later successfully use LCMgui often simply by selecting the data file and clicking “Run LCModel”.

The most important initial settings at this stage are:

Output: You set the print (or display) command in the initial test run (Sec 4.2.2), and all future results will be automatically output in this way.

Section 7.4.2 specifies how you can both print and simultaneously display the results on your monitor.

You can also completely avoid printing, by displaying only and using the archived .PS and .TABLE files for later reference. (Most display programs allow you to print anyway.)

Data File Type: In the second test (Sec 4.2.4) during installation, you select the data type in Fig 6.3 and test the automatic conversion and input of data to LCModel.

If you do not have the automatically convertible file types specified in Sec 3.7, then Sec 7.4.4 specifies how you use your own data conversion script with the “Other” button in Fig 6.3.

7.2.4 Install Model Spectra

You need a Basis Set of model metabolite spectra compatible with your data, as specified in Sec 8.1. We have a large collection of basis sets (especially for PRESS) freely available for use with LCModel. Be sure to contact me first before acquiring your own using Chap 8.

To install the basis sets, first unzip them (e.g., with `gunzip`) and then be sure to `mv` them to the directory `$HOME/.lcmodel/basis-sets/`.

7.2.4.1 Multiple Field Strengths

You can skip this unless you have data acquired at more than one field strength. LCMgui does not use field strength to select default Basis Sets. Here is a detailed

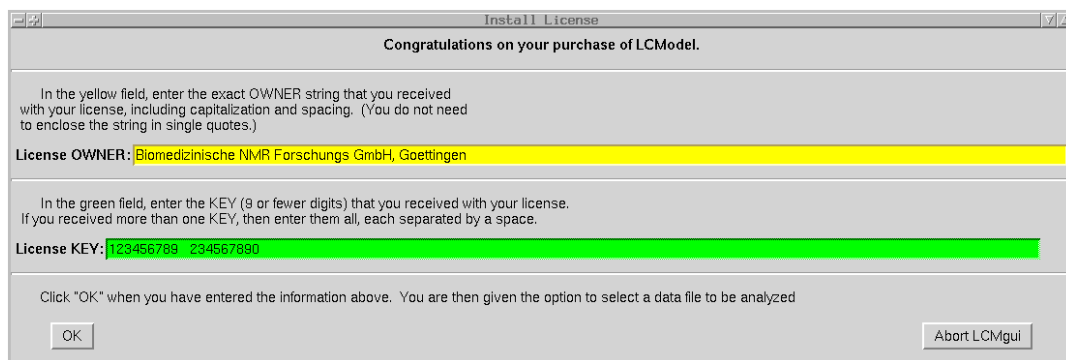


Figure 7.1: The Install License Window (with Sun, SGI or DEC/Compaq)

example of how you can separate field strengths:

Suppose that you have 1.5T & 3T data.

- mv your 1.5T Basis Sets into the directory `$HOME/.lcmmodel/basis-sets/`
- For your 3T Basis Sets:
`mkdir $HOME/.lcmmodel/basis-sets/3t`
 and mv the 3T .BASIS files into this directory.
- The first time that you analyze 3T data, click the “Change BASIS” button in Fig 7.2 and then select the appropriate 3T basis file from the `3t/` directory.
- When you exit from this first 3T session, click “New Profile” in Fig 6.6, enter “3T” in Fig 7.11, and then click “Save”.
- At the start of future LCMgui sessions, Fig 7.12 allows you to select “1” (for your 1.5T User Profile) or “3T” (for your 3T User Profile). This way, you keep your 1.5T and 3T Basis Sets, archives of results, default settings, etc., separate.
- When you exit from LCMgui sessions after the first 3T session, you can exit normally by simply clicking “Exit & Save” in Fig 6.6.

7.2.5 Install License

7.2.5.1 Linux

You receive your `license` file attached to an email. You install it simply with the command:

```
mv license $HOME/.lcmmodel/
```

If your email comes through some other system, it might rename the file `license.dat` or `license.bin`. Be sure that the file is correctly renamed back to `license`. be sure to transfer `license` to your Linux computer using “binary” mode (not “ascii” and not “text” mode).

7.2.5.2 Sun, SGI or DEC/Compaq

After you have completed the test runs, a window appears with an “Install License” button. Clicking this produces the window in Fig 7.1. You enter the information that you received with your license. After clicking “OK” and accepting the License Agreement from the website

on page 2, the File Selector (Sec 6.2.1) appears, and you are ready to start the first analysis of your data; see Sec 7.3.

be sure to exit normally from LCMgui, with the “Exit & Save” button in Fig 6.6, so that your license information is saved.

7.2.5.3 GE SAGE/LCModel interface

With Linux, set the following in your `.sagerc` file:

```
setenv LCM_OWNER 'dummy'
setenv LCM_RUNKEY 123
```

(They are not used by the Linux version.) With Sun, SGI or DEC/Compaq, replace `dummy` above with the `OWNER` string provided with your license, and replace `123` above with the value for `KEY` provided.

When you run the SAGE/LCModel interface, the window titled “LCModel Analysis” appears.

Be sure to make the following changes *in every session*:

```
SDDEGZ: 999.0 (only for CSI)
SDDEGZ: 3.0 (only for single-voxel data)
SDDEGP: 1.0
Start PPM: 4.0
End PPM: 0.2
```

Section 3.4.1 discusses cases where you might want to use other values for `End PPM: (PPMEND)`. There is reportedly a configuration file, where you can set these values once, for all future analyses.

Missing from the Concentration Table in the output are the important Concentration Sums NAA+NAAG and probably Cr+PCr and the sum of all choline-containing compounds GPC, PCh & Cho (Sec 2.1.1). You will have to compute these sums yourself. It is important to use only these sums (e.g., NAA+NAAG) and not the much less accurate individual estimates (e.g., NAA and NAAG). Similarly, if PCr is estimated, compute the concentration ratios to Cr+PCr instead of the ratio to only Cr.

7.2.6 Installing Updates & Upgrades

(“Updates” and “upgrades” are used here interchangeably.) Updates to any parts of the package will normally be incorporated into a complete new updated LCModel/LCMgui package (not patches).

If you also wish to save your old LCModel package (e.g., for perfect compatibility in longitudinal studies) before updating, you can enter:

```
cp -a $HOME/.lcmodel $HOME/.lcmodel-old
```

Then in the future (after updating) you can switch to the old version with:

```
mv $HOME/.lcmodel $HOME/.lcmodel-new
mv $HOME/.lcmodel-old $HOME/.lcmodel
```

(You can also use symbolic links.)

Do not delete your old `$HOME/.lcmodel`; instead install your update “on top of” your old installation. You install an update simply by downloading from

<http://lcmodel.ca/lcm-test.shtml> and installing with the two commands:

```
tar xf lcm-?? .tar
./install-lcmodel
```

where ?? is 32 or 64.

The test run will automatically be done, but you can then continue as before, since only files that have changed in the update will be modified. Your license and other configuration settings will not be changed. Any files that you have added or archived in the `$HOME/.lcmode1` directory tree will also be preserved.

The only exception is that you should not manually modify any of the files originally delivered with LCMgui, since these are overwritten by an update. However, this is normally never done and is never recommended in this manual.

Be sure to exit normally from LCMgui, with the “Exit & Save” button in Fig 6.6, so that all of your update information is saved.

7.3 Basic Settings and Usage

The first runs are the most important, since LCMgui uses your previous settings as defaults for the future. This section shows the most important settings, which can often allow you and inexperienced Normal Users to make future analyses with only a few mouse clicks.

For the first run, you should follow Chap 6, including all the fine print. Particularly important are your settings in the “Control Parameters” window (Fig 7.2) for the Analysis Window (Sec 6.3.1) and deciding whether to use eddy-current correction (Sec 6.3.3) and/or Water-Scaling (Sec 6.3.4).

See Sec 3.7 for important guidelines and for a list of the types of data files automatically handled by LCMgui. Also note the following:

7.3.1 Vendor-Specific Guidelines

Bruker, Marconi, Canon/Toshiba, Varian: To avoid writing outside of `$HOME/.lcmode1/` during testing, the initial default Archive Directory is `$HOME/.lcmode1/saved/`. Section 7.3.3.3 specifies how to archive in a more convenient place (near your original data).

Bruker: With single voxel data, the files `acqp` and `method` must be in the same directory as your data file `fid`. However, with ParaVision 6 and CSI data, instead of `fid`, you select the file `ser` in Fig 6.1.

If the file `method` is missing, you have a very old ParaVision version. The instructions at the beginning of the (text) file `$HOME/.lcmode1/bruker/bin2raw` show you how to proceed.

GE: Section 7.4.5.1 describes Preprocessors that are important in the following special cases:

- when you are not using automated Probe and your data require large phase corrections;
- when you want to select frames to salvage a spectrum damaged by patient motion during part of the acquisition;
- when you are not using the standard 5000 Hz bandwidth with 3T data.

Marconi/Picker: *Only if you are using PRESS:* You will probably have to select the Preprocessor `new-press` (Sec 7.4.5). Prior phase information is very accurate, and LCMgui uses this. However, older and newer PRESS sequences have very different values. For backwards compatibility, the older values are used by default. Try a few analyses with and without the Preprocessor `new-press`. The wrong choice should yield very poor phasing. If in doubt, send me two or three “dump” files

with high-quality spectra.

Philips: Be sure to use Sec 3.7.6.

Siemens: Since a wide variety of Siemens files are accepted, you may select totally irrelevant files (e.g., with 2^N bytes), and they may be accepted. This can be checked with “Preview Data” (Sec 7.4.1), but it is also usually apparent from errors in the **TITLE:** line in Fig 7.2. You can then click “Reload Data” in Fig 7.2.

Further important settings are in the following sections:

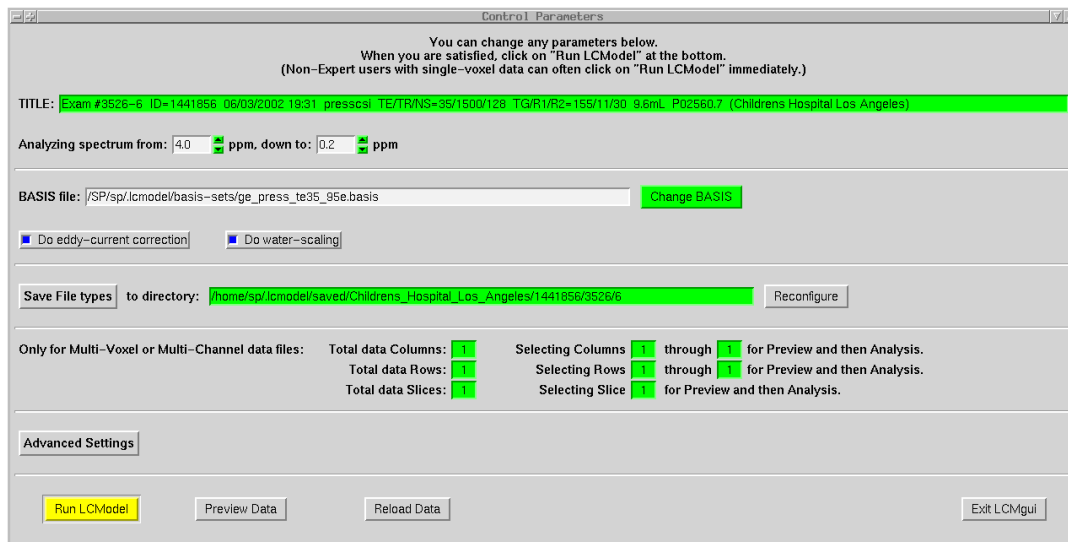


Figure 7.2: The Control Parameters Window

7.3.2 .BASIS file

Your .BASIS files should go into the directory `$HOME/.lcmodel/basis-sets/`. Then, LCMgui normally automatically selects the correct Basis Set, based on the information in the scanner data files. In some cases, information is missing (e.g., TE in older GE spectrum G-files), and you should check the entry next to “BASIS file:” in the “Control Parameters” window (Fig 7.2) and click the “Change BASIS” button if necessary. If you are using only .BASIS files supplied by me, then you can skip the rest of Sec 7.3.2.

LCMgui attempts to automatically select the correct .BASIS file from the default Basis directory (the Basis directory from the last session). It first attempts to extract TE and the localization sequence (STEAM/PRESS) from your data headers. It then attempts to find the corresponding .BASIS file, whose filename must satisfy the following rules:

TE: The filename must contain the string `_teNNN_` (including underscores at each end), where NNN is the integer value of TE in ms. An example is:
`gamma_press_te8_300mhz_070.basis`

steam/press: The appropriate string must be in the filename.

File Extension: This must be `.basis`, `.BASIS` or `.Basis`.

7.3.3 Archiving the LCModel Results

You can specify which type of output will be archived by LCMgui and where it will be archived. It is obviously best to organize this data base as soon as possible.

7.3.3.1 Which File Types will be Archived?

Clicking on the “Save File types” in the “Control Parameters” window (Fig 7.2) produces the menu in Fig 7.3. You click on a filetype to make its button blue to have LCMgui archive it in this (and each future) session. By default, the .TABLE file (a compact tabular summary of the results useful for later statistical and data base

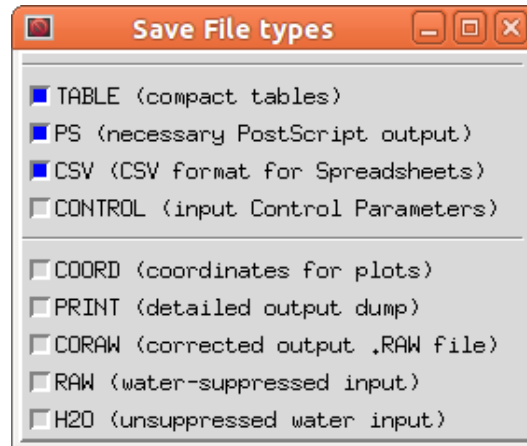


Figure 7.3: You get this menu when you click the “Save File Types” button in Fig 7.2.

analyses) and the .PS file (with the One-Page Output) are archived. See the Index at the end of this manual for the other filetypes in Fig 7.3.

7.3.3.2 In which Directory will they be Archived?

The directory where these files will be saved is shown in the green field. The following are the default structures:

Bruker, Marconi/Picker, Canon/Toshiba, Varian: \$HOME/.lcmmodel/saved/
(see Sec 7.3.3.3 for a good alternative)

GE raw P-files: the standard SAGE data-base hierarchy:
\$HOME/.lcmmodel/saved/Site/PatientID/Study/Series/

GE spectrum G-files: As with P-files, except that your Site is replaced with from-G-file, since LCMgui cannot recover the Site from G-files.

Philips: \$HOME/.lcmmodel/saved/examination_name/patient_name/scan_date/.
An alternative script, where scan_id is also available is available from me.

Siemens: \$HOME/.lcmmodel/saved/<PatientName>_<the part of the DataSetId following ‘/’>

Here, Site/PatientID/Study/Series, examination_name/patient_name/scan_date, PatientName & DataSetId are all taken from header information, which can vary with each spectrum. Therefore, the directories are often unique for each spectrum.

If you are satisfied with these defaults, then you can skip the rest of Sec 7.3.3.

You can edit the green field next to “to directory:”, but this new directory will only be used during this one analysis.

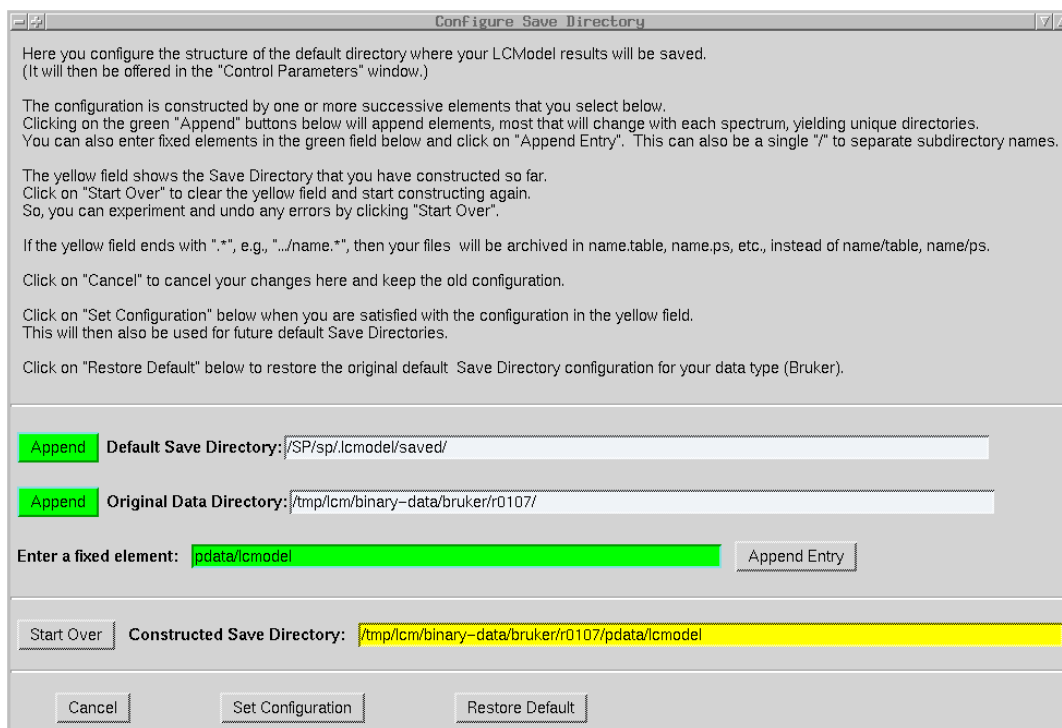


Figure 7.4: The window for permanently reconfiguring the structure of (Bruker) Archive Directories.

7.3.3.3 Reconfiguring the Archive Directory Tree

You can permanently change the Archive Directory tree structure by clicking on the “Reconfigure” button in Fig 7.2, which produces a window like Fig 7.4 for Bruker, Marconi, Canon/Toshiba & Varian data. For these four data types, a good alternative to their original default Archive Directory (`$HOME/.lcmodel/saved/`) is in the same directory as the original scanner data. (This is not the default for safety reasons only — all original default output of LCMModel/LCMgui is confined to `$HOME/.lcmodel/`.)

The instructions in Fig 7.4 are quite detailed, but the following step-by-step example, may be useful:

- (1) Click the green “Append” button next to “Original Data Directory”.
- (2) Enter `pdata/lcmodel` in the green field next to “Enter a fixed element”, and then click the “Append Entry” button to the right. This is the stage shown in Fig 7.4.
- (3) If you are satisfied with the structure shown in the field next to “Constructed Save Directory:”, then click the “Set Configuration” button.

For example, the LCMModel output .PS file will be
`/tmp/lcm/binary-data/bruker/r0107/pdata/lcmodel/ps`

For Marconi, Canon/Toshiba & Varian data, you might enter `lcmodel` rather than `pdata/lcmodel` in Step (2).

Note the following:

- You can **experiment**, watching your progress in the field next to “Constructed Save Directory”, and undoing mistakes by clicking the “Start Over” button.
- You can **cancel** everything that you have done in the present “Configure Save Directory” window by clicking the “Cancel” button.
- Your changes only **take effect** when you click the “Set Configuration” button.
- Even after “Setting Configuration”, you can always click on “Change Configuration” to further modify or **correct** the configuration.
- You can **restore** the original LCMgui default Save Directory configuration by clicking on “Change Configuration” and then on “Restore Default”.
- No matter how badly you have messed things up, you can always **start over** completely, as specified in Sec 7.5.1.1.
- You can **protect** your configuration from being accidentally permanently changed, as specified in Sec 7.5.1.2.

7.3.3.4 Reconfiguring for File Extensions

Normally, the .PS file is a file called **ps** in the Archive Directory. The following Siemens example using Fig 7.5 shows how to archive them as extensions to filenames.

- (1) Click the green “Append” button next to “Default Save Directory”.
- (2) Click the green “Append” button next to “PatientName:”
- (3) Enter _ (underscore) in the green field next to “Enter a fixed element”, and then click the “Append Entry” button to the right.
- (4) Click the green “Append” button next to “Tail of Data SetId:”.
- (5) In the green field next to “Enter a fixed element”, delete the underscore and enter .* (period then asterisk), and then click the “Append Entry” button to the right. This is the stage shown in Fig 7.5.
- (6) If you are satisfied with the structure shown in the field next to “Constructed Save Directory:”, then click the “Set Configuration” button.

This special dot-star (.*) combination at the end of the Archive Directory causes LCMgui to make a file extension. In this example, the .PS file will be /SP/sp/.lcmmodel/saved/vol_2401_148.ps. Without the dot-star at the end, the file would be /SP/sp/.lcmmodel/saved/vol_2401_148/ps; i.e., a slash would replace the dot, and the extension would become a file.

7.3.4 View/Edit Control Parameters

LCMgui gives you the full capability of comfortably setting all Control Parameters in this manual. You can also save these settings for optional use as defaults later.

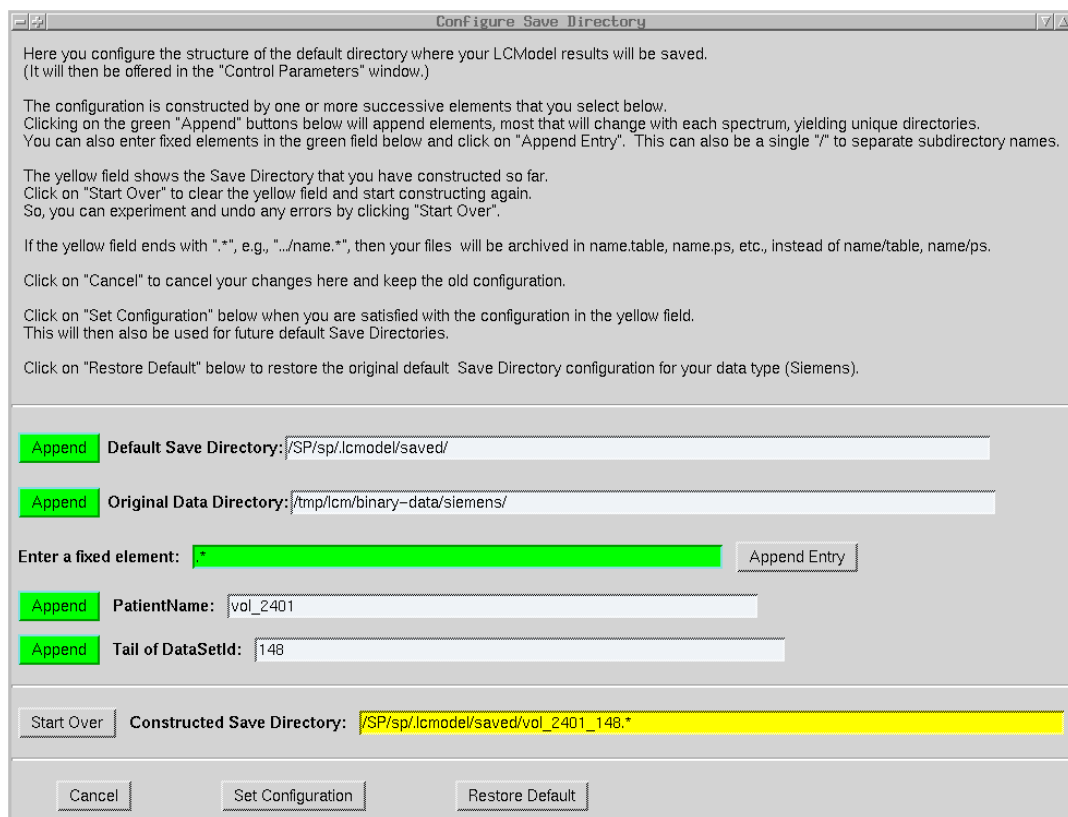


Figure 7.5: The window for permanently reconfiguring the structure of (Siemens) Archive Directories.

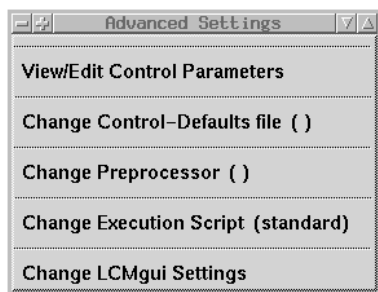


Figure 7.6: You get this menu when you click the "Advanced Settings" button in Fig 7.2.

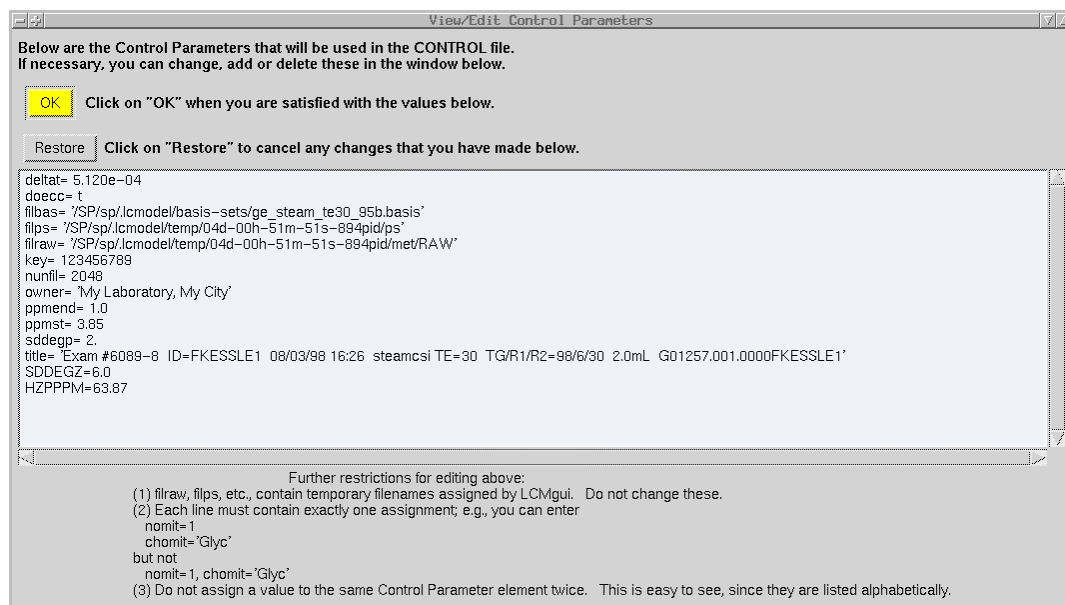


Figure 7.7: You can view, edit, delete or add all Control Parameters here.

You do this by clicking on the “Advanced Settings” button in the “Control Parameters” window (Fig 7.2). This produces the menu in Fig 7.6. You then click on “View/Edit Control Parameters” in this menu to obtain the window in Fig 7.7. This shows the Control Parameters that will be input to LCMModel. You can edit or delete these or add new ones. For example, Fig 7.7 shows where I have added **SDDEGZ** & **HZPPPM** at the bottom. (Case is not important for the names of Control Parameters; only strings within single quotes are case-sensitive.)

With GE Probe raw P-files and Marconi/Picker data, eddy-current correction (ECC) is automatically done by LCMgui. Otherwise, during your first runs, you should decide whether you can do ECC. Sections 9.6 & 9.7 discuss ECC and the settings of **SDDEGZ** & **SDDEGP**. (However, LCMgui automatically sets the Control Parameter **FILH20** mentioned in Sec 5.3.4 for you.)

During one of your first runs you should also enter **PGNORM** in this window. (See the Index at the end of this manual for terms like **PGNORM**.) If you print, then you should use a duplex printer; otherwise you will also want to enter **IPAGE2=0**.

7.3.5 Saving Your Control Parameters

If you have made any changes to Control Parameters, the window in Fig 7.8 will appear after you click “Run LCMModel”. Only the modified Control Parameters are shown, but you are offered the chance of saving all the Control Parameters for optional use in the future. You can click the “Save Changes” button. This produces the window in Fig 7.9.

In Fig 7.9, you enter a name for the file that will store your Control Parameters. This is called a *Control-Defaults File*. In Fig 7.9, I have entered the name **g-files-ecc**.

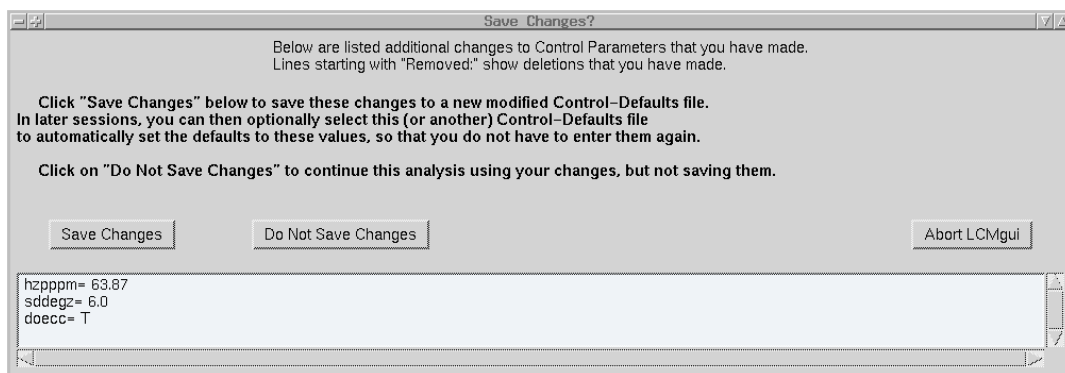


Figure 7.8: You can save all the Control Parameters, including your modifications, for optional use as starting defaults in the future.

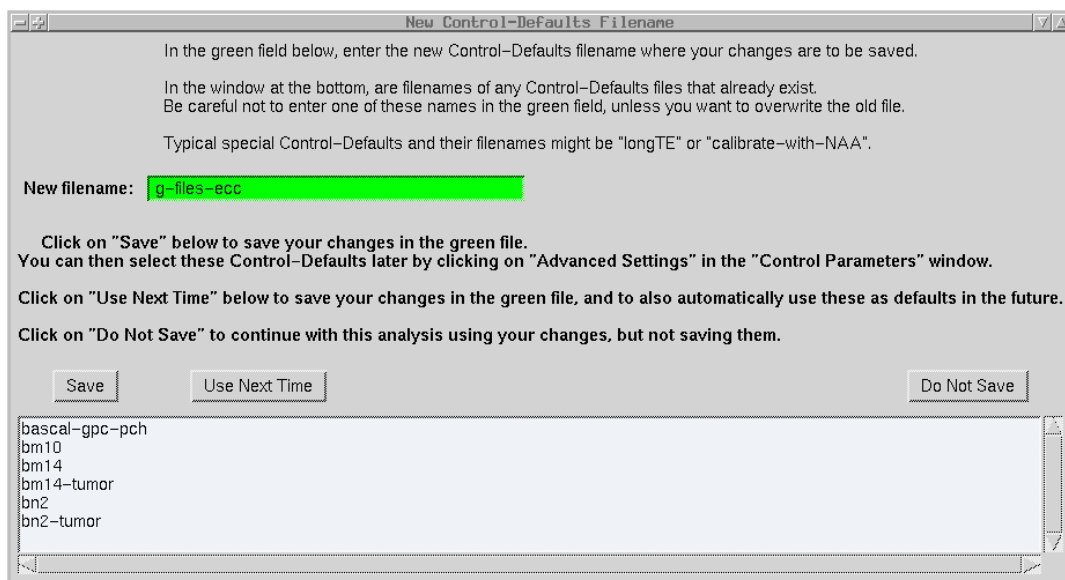


Figure 7.9: Here you enter a name for the file which will store your Control Parameters for optional future use.

You are free to choose any descriptive filename. However, if it is identical with one of the filenames listed at the bottom (e.g., `bm10`), then your file will overwrite the old file.

If you click “Use Next Time” in Fig 7.9, then this set of Control Parameters will be used as defaults for future sessions. LCMgui will still reset obviously variable Control Parameters, such as `TITLE`, `FILRAW`, etc.

In addition, LCMgui may reset some Control Parameters (e.g., `SDDEGZ` & `SDDEGP`) to their commonly used values. The only way to avoid having to manually set them back to their desired values every time is to use a Preprocessor (Sec 7.4.5).

If you click “Save”, then your Control Parameters will simply be archived for optional use later. They will not be used as defaults for the next session. The old Control-

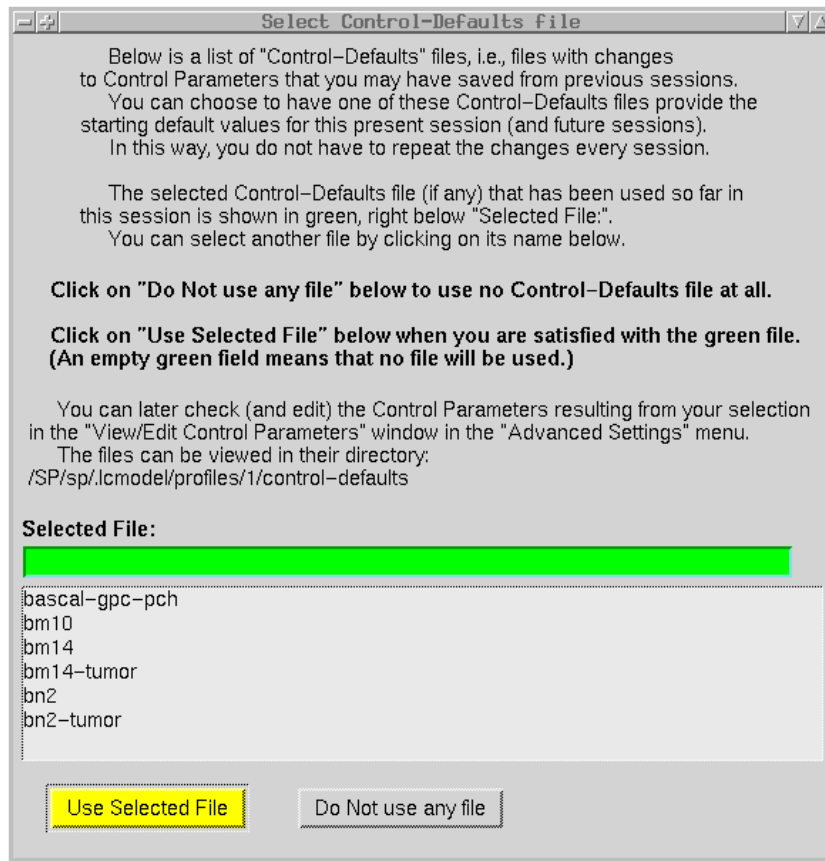


Figure 7.10: Here you select the Control-Defaults file to be used now and in the future.

Defaults File used at the start of this session will again be used.

7.3.6 Changing your Default Control Parameters

How do you know what file Control-Defaults file is currently being used? You again click on "Advanced Settings" in Fig 7.2. The Control-Defaults file currently being used is in parentheses next to "Change Control-Defaults file". In Fig 7.6, there is nothing between the parentheses, indicating that no file is being used (i.e., the conversion program called by LCMgui solely determines the starting values of the Control Parameters).

You can change the Control-Defaults file currently being used as follows:

- Click on the "Advanced Settings" button in Fig 7.2 to produce the menu in Fig 7.6.
- Click on "Change Control-Defaults File" to produce the window in Fig 7.10. (If there is no Control-Defaults file in your directory, then you will be told this and given the chance to continue.)
- The currently used file is shown in the green field, under "Selected File".

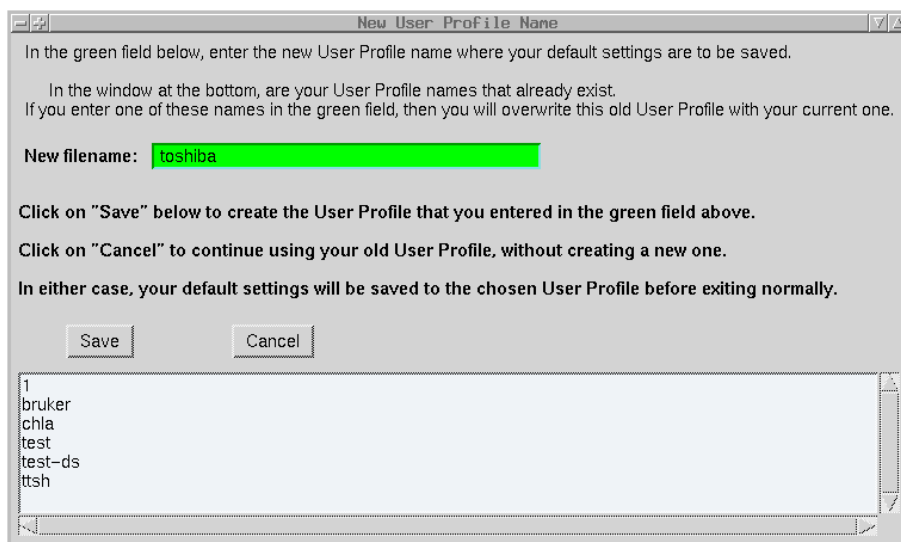


Figure 7.11: At the end of a session, you can select a new User Profile where all of your settings from the session will be saved.

(The original default is no Control-Defaults File; the green field would then be blank.)

- As explained in Fig 7.10, you can select a new Control-Defaults File by clicking on its name, which then appears in the green field.
- Click “Use Selected File”, and LCMgui immediately repeats the conversion of your data and applies these new Control Defaults. This newly selected Control-Defaults File will also be used in the future (until you change it again).

Note that the Control-Defaults File only provides you with starting defaults. You can then modify these values as you wish in the “Control Parameters” window.

7.3.7 User Profiles

There are two sets of default settings, one for LCModel and one for LCMgui. The Control-Defaults file (Sec 7.3.5) contains default Control Parameters for LCModel. The `gui-defaults` file contains default settings for LCMgui, including the Control-Defaults file path, directories for archiving results and finding Basis Sets, etc. Both of these sets of defaults are saved in your User Profile.

If you have different types of data that require different LCMgui settings (e.g., different Archive Directories), then you should have a User Profile for each. This would always be the case with data from different scanner types (e.g., GE and Siemens). Different users sharing the same account could also have different User Profiles.

You create a new User Profile by clicking on “New Profile” in Fig 6.6, which appears as you exit LCMgui. The window in Fig 7.11 appears, and you enter the name of the User Profile. In Fig 7.11, I have entered `toshiba`. You may choose any descriptive

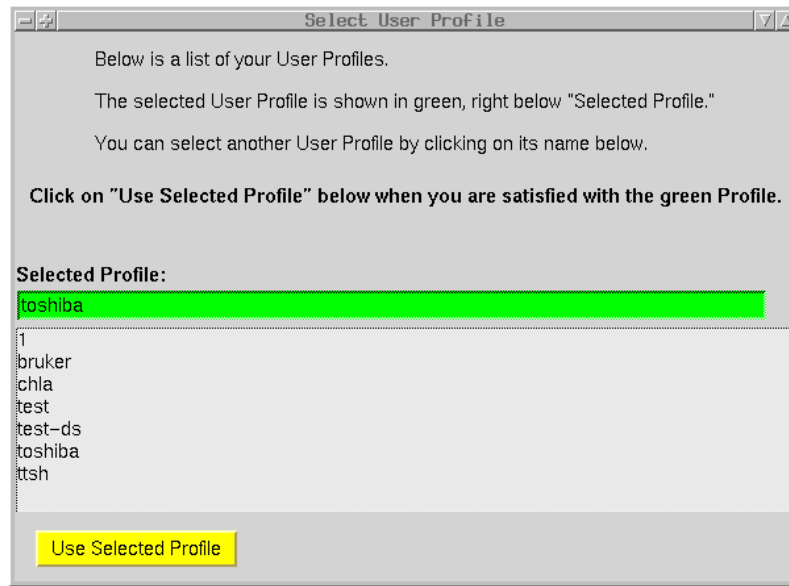


Figure 7.12: At the start of a session, you select the User Profile to be used.

directory name. However, if it is identical with one of the names listed at the bottom (e.g., 1), then your default files will overwrite the old files.

If you enter `toshiba` as your User Profile, then your `gui-defaults` will be in `$HOME/.lcmode/profiles/toshiba/gui-defaults` and all Control-Defaults files that you save from this User Profile will be in the directory `$HOME/.lcmode/profiles/toshiba/control-defaults/`. You can look at their contents with the usual Unix commands, but do not edit them. You can delete obsolete Control-Defaults files, e.g., with

```
rm $HOME/.lcmode/profiles/toshiba/control-defaults/bm10
```

Your initial User Profile is 1. You can rename this (or any of your others) by a command like

```
mv $HOME/.lcmode/profiles/1 $HOME/.lcmode/profiles/siemens
```

When you start LCMgui, Fig 7.12 allows you to select any one of your User Profiles for that session (if you have more than one User Profile from previous sessions).

7.4 Further Useful Settings

7.4.1 Previewing Data

Clicking “Preview Data” at the bottom of the “Control Parameters” window (Fig 7.2) produces the window in Fig 7.13. As explained there, by editing the green field next to “Print the plot with command:” to your command for displaying or printing PostScript files and then clicking on “Run Preview”, you can display or print plots of the data before starting LCMModel. This can be useful in checking whether you have selected the correct data file and whether the data are worth analyzing.

You can activate both the “Display or print...” & “Second display...” buttons to both print and display.

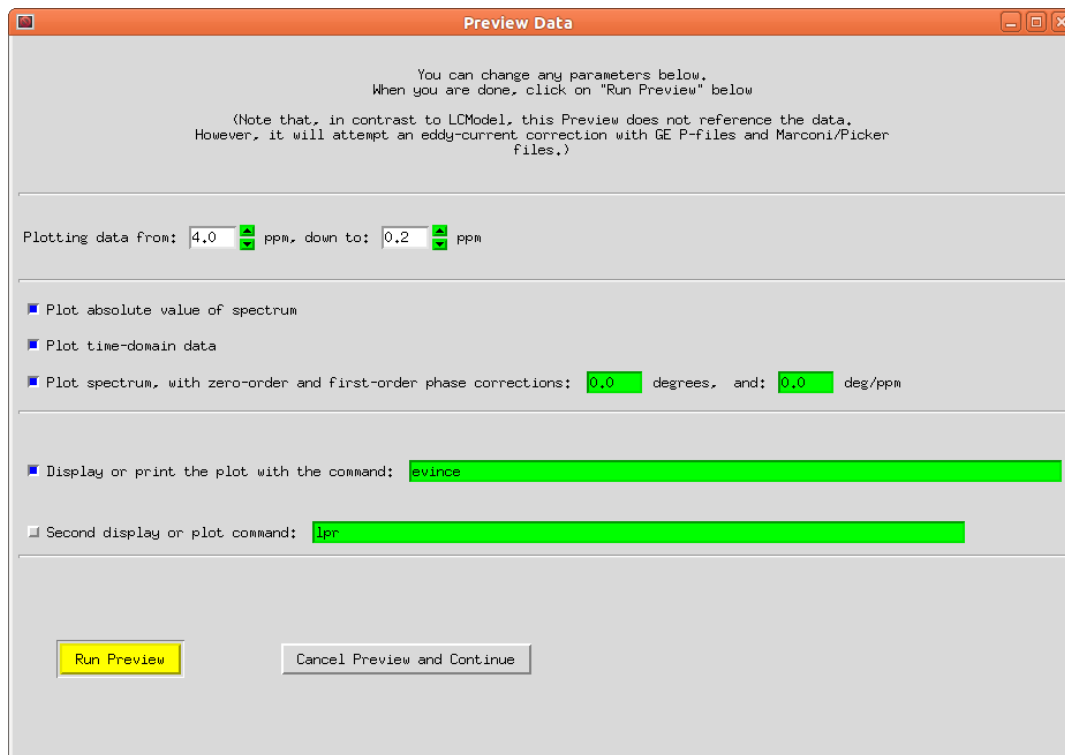


Figure 7.13: Here you can set and execute your commands for printing and/or plotting previews of your data.

If possible, orientation and magnification should be supplied in the display command, since trying to change these in the display program can sometimes crash the display program and LCMgui, particularly if you are working over a slow network. For example, you might use `gv -orientation=seascape`.

With multi-voxel data sets, you can select a complete 2D slice with Fig 7.2, or a rectangular subset. If your selection contains more than one voxel, then Fig 7.13 will indicate this voxel range, and will only offer a plot of the absolute value spectra (in a 2D array, as in PLOT 14 in `$HOME/.lcmmodel/doc/figures.pdf`). This display (following the DICOM standard) may not always be consistent with the scanner's display (Sec 11.4.3.2).

If you want to save the plots, they are in a file with a name of the form

`$HOME/.lcmmodel/temp/12d-21h-51m-09s-996pid/plotraw.PS`

where the numbers will be different, as explained in Sec 7.5.2.2. Copy this to a safe place, since the above directory will be deleted with the next analysis.

If no plot is produced, check your plot and display command. If a diagnostic message, `‘Aborting due to error ... Check User's Manual’`, appears in your Unix window, then check Sec 8.5.3. Check that your selected data file is correct. Finally, you could start LCMModel, which has extensive diagnostics.

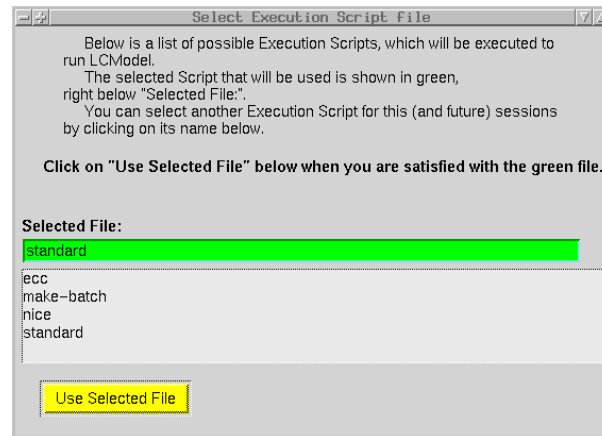


Figure 7.14: Here you can select the Execution Script that will be started by LCMgui.

7.4.2 Interactive Processing

Normally you use LCMgui to start LCModel analyses in background, without waiting for one to end before starting the next. However, your analyses may go so quickly that you would want to run “interactively”, viewing the LCModel results of one analysis on your terminal before starting the next.

If you can display PostScript files on your terminal (as discussed in Sec 7.4.1), then Sec 7.4.6 shows how to change the command for printing your LCModel output to a display command. The one limitation of this interactive mode is that you should wait for one analysis to end before starting the next (to avoid multiple displays popping up).

7.4.3 Execution Scripts

As outlined in Sec 7.1, the final step of LCMgui is to start an *Execution Script* in background. By default, this script is `$HOME/.lcmmodel/execution-scripts/standard`. You should not edit this script. However, you can copy it and use it as a template for your own customized scripts. It contains suggestions on possible changes.

You must also put any Execution Scripts that you make into the directory `$HOME/.lcmmodel/execution-scripts/`.

The currently active Execution Script is shown in parentheses next to “Change Execution Script” in Fig 7.6. If you click “Change Execution Script”, the window in Fig 7.14 shows you how to select another Execution Script for now (and for the future).

7.4.3.1 Batch Processing

Normally you use LCMgui to start LCModel analyses in background, without waiting for one to end before starting the next. However, if your workstation is slower

processing analyses than you are in starting them, you may want to avoid overloading it with many simultaneous jobs.

The Execution Script `nice` helps by reducing the priorities of the LCModel analyses, but a much more effective way is to use the Execution Script `make-batch`, as follows:

- Select the Execution Script `make-batch` in Fig 7.14.
- Prepare and start your analyses as usual, clicking “Run LCModel”, one after another.
- Exit LCMgui and enter
`$HOME/.lcmmodel/bin/run-batch`
 Only then will the analyses be started, one after another, one at a time.
- The start and finish times, as well as any run-time error messages appear on your screen. All run-time messages (including harmless ones) go into
`$HOME/.lcmmodel/temp/batch-messages`.

7.4.4 Processing Non-Standard Data Files

LCMgui’s first computation step [Step (2) in Sec 7.1] is to produce LCModel input files from the data file that you selected in Step (1) in Sec 7.1. LCMgui does this by executing

`$HOME/.lcmmodel/???/bin2raw`, where `???` = `bruker`, `ge5`, `gelx`, `marconi`, `philips`, `siemens`, `toshiba`, `varian` or `other`, depending on the type of data file that you specified in the menu in Fig 6.3.

Actually, LCMgui first attempts to execute `$HOME/.lcmmodel/???/my-bin2raw`. If `my-bin2raw` does not exist, then it executes `bin2raw`. This gives you the opportunity of copying `bin2raw` to `my-bin2raw` and modifying `my-bin2raw` to your special purposes. Your `my-bin2raw` will be preserved, since only `bin2raw` is overwritten during LCMgui updates.

Normally, you would produce `other/my-bin2raw`, and use the “Other” button in Fig 6.3 for your special-purpose processing. `$HOME/.lcmmodel/other/bin2raw` provided with LCMgui does no data conversion; it simply assumes that your selected file has already been converted to LCModel `.RAW` format (Sec 5.2). However, the comments in this script also specify what you must do to prepare your particular type of data files.

After you make your special `other/my-bin2raw`, then, in your next LCMgui session, select your non-standard file with the File Selector. Your previous LCMgui session probably did not use the file type “Other”, and you will then get the error window in Fig 6.2. Click “Retry” and then select “Other” in the window in Fig 6.3 to use your customized script in `other/my-bin2raw`.

The scripts `bruker/bin2raw` and `philips/bin2raw` provide further examples and specifications on preparing your own `my-bin2raw` script or executable program. Particularly `philips/bin2raw` contains arbitrary assumptions (e.g., on filenames) which you can easily modify to your needs.

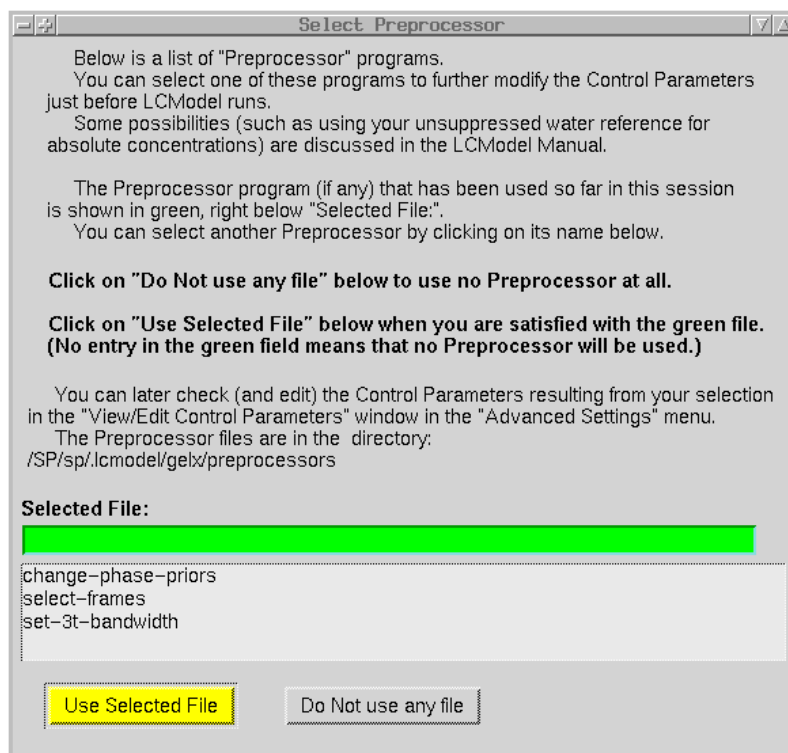


Figure 7.15: Here you can view and/or change the Preprocessor that will be used by LCMgui.

Even after you make **other/my-bin2raw** to handle your file types, the instructions in the File Selector will still (incorrectly) tell you that you must select an LCMModel **.RAW** file.

7.4.5 Optional Preprocessor

This is Step (3) in Sec 7.1. It gives you the opportunity of modifying the Control Parameters or the **.RAW** file computed from your standard data conversion in Step (2).

Only files in the directory `$HOME/.lcmodel/???/preprocessors/` will be available as Preprocessors in Figure 7.15. Here, `???` = **bruker**, **ge5**, **gelx**, **marconi**, **philips**, **siemens**, **toshiba**, **varian**, or **other**, depending on which type of data you selected in Fig 6.3.

Your own Preprocessor scripts must also be in this directory.
`$HOME/.lcmodel/doc/preprocessors/README.txt` explains how to make your own Preprocessor.

You can check the Preprocessor currently being used by clicking "Advanced Settings" in Fig 7.2. The current Preprocessor is in parentheses next to "Change Preprocessor". In Fig 7.6, there is no Preprocessor is being used.

You can then change the Preprocessor as follows:

- Click on “Change Preprocessor” to produce the window in Fig 7.15. (If there is no Preprocessor script in the directory, then you will be told this and given the chance to continue.)
- The currently used script is shown in the green field, under “Selected File”. (The original default is no Preprocessor step; the green field would then be blank.)
- If you want to use another Preprocessor now (and in the future), then click on its name, and its name will also appear in the green field as the “Selected File”. Then click “Use Selected File” and the selected Preprocessor would be executed immediately (and in the future, until you change it).

7.4.5.1 GE Preprocessors

The following Preprocessors are available for GE data:

change-phase-priors : GE automated Probe spectra usually need only very small phase corrections, and this prior information is used by default. However, this can cause huge phasing errors, if you have non-standard data requiring large phase corrections. If analyses of non-standard data show poor phasing, then you should first edit the file `$HOME/.lcmmodel/???/preprocessors/change-phase-priors` as explained in the file (where `??? = ge5 or gelx`). Then select this Preprocessor in Fig 7.15.

select-frames : can salvage a spectrum that has been damaged by patient motion. You can select a subset of frames that excludes the period where there was motion (or other damage). Full instructions are in the comments in `$HOME/.lcmmodel/gelx/preprocessors/select-frames`. Note that LCMgui must not be running in background; i.e., it must not have been started with a “&” at the end of your command. **select-frames** is not available for 5.x data or for multi-channel data.

set-3t-bandwidth : LCMgui assumes that the bandwidth of 3T data is 5000Hz. If this is not the case with your 3T data, then edit the file `$HOME/.lcmmodel/gelx/preprocessors/set-3t-bandwidth` as instructed in the comments there. Then select this Preprocessor in Fig 7.15.

use-unsuppressed : (Cannot be used with multi-channel (phased array) data.) It will cause the unsuppressed water reference frames to be analyzed instead of the usual water-suppressed frames. You acquire many water reference frames and only a small number of water-suppressed frames (there still must be at least one, although it is not used). This is used instead of Water-Scaling to get a direct and unified analysis of a single spectrum including the water signal, for example for bone marrow. (Sec 9.3).

7.4.6 Changing the License & the Print Command

These settings were made during installation. You can change them as follows:

- In the main “Control Parameters” window, click on “Advanced Settings” to get the menu in Fig 7.6.
- Click on “Change LCMgui Settings”. This produces a window with entries containing the current **OWNER** and **KEY** license settings (as in Fig 7.1) and the print (or display) command that LCMgui is currently using for outputting the LCMModel PostScript file. (With Linux, there are no **OWNER** and **KEY** entries.)
- Edit any of these entries that you want to change and click on “OK”, or click “Cancel Changes” to cancel your changes and leave everything as it was.

One common change is to delete the entire print command, leaving the entry blank (which is not accepted during installation). This suppresses printing and display, but not the archiving of the plots in the .PS files. This can be useful if you are processing many spectra (e.g., a multi-voxel data set) and want to view the results later from the archive. You can later collect all of the .PS files into one file for convenient viewing using Sec 11.4.5.

7.5 Fine Points

7.5.1 gui-defaults Resource File

LCMgui stores all of your default settings for future sessions in `$HOME/.lcmmodel/profiles/???/gui-defaults`, where `???` is your currently selected User Profile (1 by default). Each line consists of a one-word index (e.g., `i_displayCommand`), whitespace, a value (e.g., `gv --orientation=seascape`), and nothing else on the line. In exceptional cases listed below, you may wish to edit this file. You should only edit the value and only as specified below.

7.5.1.1 Starting Over

If you hopelessly corrupt `gui-defaults`, you can always recover by deleting `gui-defaults`. When you start LCMgui the next time, it will be as with a new installation. You first click “Repeat Test Run”, then install the license (unnecessary with Linux), and then proceed with data analysis. All of your previous defaults (and mistakes) will be forgotten.

7.5.1.2 Protecting your Settings

You can make the initial LCMgui runs and optimize the default settings for Normal Users. During any future LCMgui session, the user can modify any of your settings. Normally, LCMgui will store these new settings in `gui-defaults` for use as defaults for the next session. However, you can prevent LCMgui from storing changes to critical settings by changing the value of `i_preserveConfiguration` in `gui-defaults`

from “0” to “1”:

```
i_preserveConfiguration 1
```

Some of the critical defaults that are protected by the above setting are:

- The structure of the Archive Directory for LCModel results and which types of output files will be saved there;
- The default .BASIS file;
- The print and display commands;
- The pathnames of the files with the default Control Parameters, the Pre-processor and the Execution Script;
- The license data.

In this way users have full freedom to change everything for their present session, but they and others are protected from the most critical of their changes in future sessions.

7.5.1.3 Data Filename Filters

The File Selector window in Fig 6.1 will only display filenames that match the filter, which is specified by the values `i_fileType*`, where `*` = `Bruker`, `Ge5`, `GeLx`, `Marconi`, `Other`, `Philips`, `Siemens`, `Toshiba` or `Varian`. You can temporarily enter a new filter in the entry below “Files:” in Fig 6.1. However, you can permanently change this in `gui-defaults`. For example, you can specialize

```
i_fileTypeSiemens *
to
i_fileTypeSiemens *.rda
```

7.5.1.4 Window & Font Size

You may find the LCMgui windows too big. The best way to reduce them is to increase the resolution of your display. Otherwise, you can slightly reduce the windows by reducing 10 in

```
i_fontPoints 10
```

Missing fonts in your Linux/Unix distribution may cause the characters to be poorly displayed. Changing `i_fontPoints 10` above may help, although the best collection of fonts is often 10-point.

7.5.1.5 Help Balloon Delay

Particularly in the “Control Parameters” window, balloons with help messages pop up after the cursor has been over a field for

```
i_balloonWait 3000
```

ms. A smaller value may be useful to beginners, but irritating to experienced users.

7.5.1.6 Colors

The five colors specified in `gui-defaults` all have (self-explanatory) indices beginning with `i_color`. For example,

```
i_colorFollowMe yellow
```

specifies that the normal path to take is denoted by yellow buttons. You can change these values to symbolic names (e.g., `red`) or by hexadecimal numbers preceded by a `#` (e.g., `#ff0000`) with the RGB value. Your X-Windows system must be able to assign the color. (This manual will then no longer be correct in its color references to buttons and fields.)

7.5.2 Cleaning up the File System

7.5.2.1 Obsolete User-Defined Files

You can produce and save arbitrarily many files with Control-Defaults, Preprocessors and Execution-Scripts. They are saved in

```
$HOME/.lcmmodel/profiles/***/control-defaults/
$HOME/.lcmmodel/execution-scripts
$HOME/.lcmmodel/???/preprocessors
```

where `***` is your User Profile and `??? = bruker, ge5, gelx, other, marconi, philips, siemens, toshiba or varian`. You can always examine these in their directories and delete the obsolete ones.

You can also (be careful with `rm -fr`) delete a whole User Profile with a command like

```
rm -fr $HOME/.lcmmodel/profiles/my-profile
```

7.5.2.2 Temporary Files

These are automatically purged, and you normally do not have to bother with them. Each LCMModel analysis typically requires only about 200 kB of temporary disk storage (more with CSI data).

They are all in `$HOME/.lcmmodel/temp/`. Each time LCMgui prepares data for an LCMModel analysis, a unique temporary directory is created, e.g.,

```
$HOME/.lcmmodel/temp/12d-21h-51m-09s-996pid
```

The numbers are, respectively, the day of the month, hour, minute, second and process ID.

When the LCMModel analysis is finished, the directory is marked for deletion, and is deleted when the next LCMModel analysis is prepared. So, directories only remain for LCMModel analyses not completed (including aborts from LCMgui). By default, these remaining directories are deleted if they are more than 86400.0 s (1 day) old. You can modify this value in the following line in `gui-defaults`:

```
i_deleteAfterSeconds 86400.0
```

Chapter 8

Making the Basis Set

It is only necessary to read this chapter if you must collect your own Basis Set of *in vitro* model metabolite spectra. Your *in vivo* data must be compatible with the Basis Set, as specified in Sec 8.1. If you have been supplied with a Basis Set, and your data will always satisfy the compatibility requirements in Sec 8.1, then you do not need to read the rest of this chapter. **Before acquiring model spectra, check with me to see if a basis set compatible with your data is already available.** We have a large collection freely available for use with LCModel.

Your *in vivo* spectra are analyzed as a linear combination of these Basis Spectra. Your efforts in getting a good Basis Set are well invested, since this will be the basis of the analyses of probably thousands of spectra. This is *not* a nice little project for a student. It requires great care and expertise.

An alternative is simulating the basis spectra [12]–[15].

8.1 Compatibility Requirements

The following conditions in your *in vivo* data must be the same as those in the Basis Set:

- B_0 field strength (only to within a few %)
- Localization sequence (e.g., STEAM or PRESS)
- TE (to within a few ms)
- TM (with STEAM) (to within about 5–10 ms)

The following do *not* have to match: TR , the spectral bandwidth or the acquisition time per scan.

8.2 Model Metabolite Solutions

8.2.1 Choice of Model Metabolites

Table 8.1 shows most of the metabolites that have been used with LCModel. At low fields (up to 2.35 T) and moderate TE (up to 80 ms), all metabolites in the upper part of the table are recommended. Note that you do not buy Glyc (or any other metabolite with only a singlet in the Analysis Window); you simulate Glyc simply by inputting into LCModel (Sec 11.7):

NSIMUL = 14

Under the following other conditions:

long TE: Asp, GABA, Glc, GPC (indistinguishable from PCh) & NAAG (a shifted NAA can simulate NAAG) are unnecessary.

high fields: Considerably more metabolites can be quantified above 4.7 T, especially at short TE [16].

The metabolites in the bottom part of Table 8.1 occur in pathologies and some may be necessary for your studies.

It is better to measure too many than too few metabolites. You should include all metabolites that you will conceivably ever want to use. With Control Parameters in Sec 9.8.1, you can easily exclude irrelevant Basis Spectra from an analysis, and for consistency it is best to acquire all Basis Spectra in one session, rather than adding new ones later.

Whenever possible, use salts rather than acids, in the interests of better pH control.

The order numbers in the table were kindly supplied by users who obtained spectra with no apparent contamination. They are the latest that I have, but most are outdated. Reports of contaminated metabolites are listed below. For example, it seems important to use L-Lactic acid and L-Alanine; D/L mixtures of Lac from several sources were contaminated.

The Basis Spectra must have both higher accuracy and resolution than the *in vivo* spectra. Higher concentrations are useful in achieving this. The recommended concentrations are in column 3. NAAG and GPC are expensive, but do not go below their minimum concentrations in Table 8.1.

8.2.1.1 Singlets; Glycine

No concentration values are given for metabolites that only have one singlet in the Analysis Window. You simulate these using Sec 11.7, where simulating Scyllo is illustrated.

Inputting NSIMUL=14 to LCModel will simulate Glyc (Sec 11.7). Normally, you do not use Glyc; it is poorly resolved from Ins at 3.56 ppm. Worse, Ins has a different effective number of protons [17], which would cause unnecessary scatter, even in the sum Ins+Glyc (about 15%, if Glyc is mistaken as Ins or *vice versa*). As an exception,

when Glyc is pathologically high (e.g., in some tumors), you might want to replace Ins with a simulated Glyc (Sec 9.8.1), especially at long TE, where Ins is weak. In these pathologies, even at short TE, you might as an exception use both Ins and a simulated Glyc.

If you do use both Ins & Glyc, you could input PPMST = 4.2, if the baseline has no sharp increase or decrease above 4.0 ppm. The Ins signal around 4.06 ppm should then help to resolve the two.

8.2.1.2 NAAG

NAAG is expensive and one compromise is to use the NAA spectrum shifted, with the main peak shifted to 2.045 ppm from 2.01 ppm. This is a good approximation to NAAG, except that a small NAAG peak near 2.15 ppm is missing. (Compare PLOTs 3 & 4 in `$HOME/.lcmodel/doc/figures.pdf`.) This can lead to reduced NAAG/NAA estimates in white matter.

For human brain, NAAG should be used. The concentration must be at least 20 mM. For rodent brain, NAAG is often omitted.

At long TE, do not use NAAG. A shifted NAA is a good approximation. Furthermore, inconsistencies in concentration or signal strength between NAA & NAAG are then fully excluded.

If you do use NAAG, you should check the NAAG concentration by analyzing it as NAA, as specified in Sec 8.7.1.

Do not use Sigma NAAG; it is often contaminated.

8.2.1.3 Choline-Containing Compounds

Use GPC for the choline-containing compounds. In high-quality spectra, the advantages of GPC over Cho can be seen [Petra Pouwels, personal communication], [18]. You should also use PCh in addition to GPC.

Unfortunately the usual forms of GPC (CdCl_2 adduct) and PCh (Ca salt) cannot be used in the phosphate “Standard Solvent” in Sec 8.2.4, but be sure to use the formate and DSS markers with these two solutions, as specified in Sec 8.2.4. The Cd also makes pH adjustment with NaOH impossible. It would be better to find GPC without Cd (but also without alcohols).

8.2.2 Reference Markers

Consistent referencing is essential. Thus, it is best to use the same referencing marker for all model spectra. It should have no significant resonances in the Analysis Window. T. Michaelis uses 3-(trimethylsilyl)-1-propane-sulfonic acid (DSS, also called TSPS) (Fluka no. 92754) at a concentration (say, 1 mM) high enough to precisely locate the singlet at 0.0 ppm, but still dilute enough so that its weak resonances in the Analysis Window are in the noise.

Table 8.1: Concentrations and Allowed Names of Model Metabolites

Metabolite	Allowed Name(s)	Conc. (mM)	Singlet (ppm)	# protons	Vendor	Order #
L-Alanine	Ala	100			Fluka	05129
Aspartate	Asp	40			Sigma	A9256
Creatine	Cr, Cre	50			Fluka	27890
Phosphocreatine	PCr	50				
γ -Aminobutyric Acid	GABA	200			Sigma	A2129
Glucose	Glc	200			Fluka	49139
Glutamine	Gln	100			Fluka	49419
Glutamate	Glu	50			Fluka	49449
Glutathione (GSH)	GSH	70				
Glycerophosphocholine	GPC	≥ 25			(Sigma	G8005)
Phosphocholine	PCh	27			Sigma	P0378
<i>myo</i> -Inositol	Ins, mI	200			Fluka	57570
L-Lactate	Lac	100			Fluka	71718
N-Acetylaspartate	NAA	50			Fluka	00920
N-Acetylaspartylglutamate	NAAG	≥ 20			ICN	153036
<i>scyllo</i> -Inositol	Scyllo		3.35	6		
Taurine	Tau	200			Sigma	T0625
Acetone	Acn		2.22	6		
Acetate	Act		1.915	3		
Betaine	Bet	100				
β -hydroxybutyrate	bHb	100				
Carnitine	Car	50				
Choline	Cho	100				
Citrate	Cit	200				
Cysteic Acid	Cys	50				
Ethanol	Eth	200				
Fucose	Fuc	20				
Glucone	Gcn	100				
Glucuronic Acid	Gcr	50				
Glycine	Glyc		3.55	2		
Guanidinoacetate	Gua		3.78	2		
Isoleucine	ILc	100				
Leucine	Leu	50				
Phenylalanine	PAI	100				
Phosphorylethanolamine	PE	50				
Propylene Glycol	Pgc	100				
Pyruvate	Pyr		2.38	3		
Succinate	Suc		2.40	4		
Threonine	Thr	100				
Valine	Val	100				

8.2.3 Phantom

Use a spherical phantom of plastic or glass with about 300 mL volume (smaller for animal scanners). A simple way is to use normal spherical flasks (with no flat bottom) and cut or grind the neck off. The phantom should be full and without air bubbles.

8.2.4 Solutions

MakeBasis can automatically phase and scale your spectra consistently with each other. To make use of this, use the following protocol: Make one single huge “Standard Solvent” of

- 1 mM DSS (TSPS)
- 72 mM K_2HPO_4
- 28 mM KH_2PO_4
- 200 mM Na formate (*not* Sigma F4166 or F6502)
- 1 g/L NaN_3

At fields of 4T and above, you may have to reduce the ionic strength by reducing the phosphate concentrations. At fields of 9.4T and above, reduce DSS to 0.5 mM. Handle NaN_3 with care; it is hazardous, especially when mixed with strong acid.

Dissolve each of your model metabolites in this Standard Solvent. In this way, the formate concentration is exactly the same in all phantoms, and MakeBasis can use the resonance area of the formate singlet around 8.44 ppm to scale the spectra consistently with each other, which is absolutely essential. The formate and DSS singlets are also used by MakeBasis for automatic phasing.

If a metabolite (such as the CdCl_2 adduct of GPC or the Ca salt of PCh) cannot be dissolved in the Standard Solvent (due to the phosphate), be sure to dissolve it in 200 mM formate and about 2 mM DSS, so that the Auto-Scaling and Auto-Phasing can still be done. The formate concentration need not be exactly the same as in the Standard Solvent, as long as you accurately know the formate concentrations in each.

pH control is essential, particularly for NAA & Glu; otherwise, some of their resonances shift significantly, and the entire LCModel analysis can be ruined. For several metabolites (particularly NAA, Lac, Glu), you will have to adjust the pH back to 7.2. If you titrate carefully with concentrated NaOH (or possibly with concentrated HCl), the dilution will not be serious. Otherwise, you can simply correct each formate and metabolite concentration for the dilution. At high fields, if you had to reduce the phosphate concentrations, then the reduced buffering capacity will require that you titrate especially carefully.

Without NaN_3 , the solutions can go bad (decomposition or microbiological growth) within a few days. Gln must be measured the same day as preparation (even with NaN_3). The NaN_3 in the Standard Solvent allows you to store them longer (some, but not all, for weeks) at low temperature. Let them return to room temperature before measurements.

To minimize oxidation, GSH should also be measured quickly.

Room temperature is often adequate for acquiring the model spectra below 3T. With high-resolution spectra (e.g., 9.4 T [16]) it is best to increase the phantom temperature closer to 37° C. At 3T and above, this should be done at least with Cr & PCr.

Obviously, it is essential that the metabolite concentrations be accurately known. The only exception is that the concentration of Sigma GPC is very uncertain (because of the Cd complex). Section 8.7.1 specifies how you can estimate the GPC concentration by analyzing its singlet as PCh (whose concentration you accurately know).

8.3 Acquiring the Basis Spectra

8.3.1 Quality

The Basis Spectra should have a significantly higher S/N and resolution than your *in vivo* spectra. Output the file `$HOME/.lcmmodel/test/output/basis.ps` with the Basis Spectra from the test run in Chap 4. You should aim at this high quality (higher quality at 9.4T and above).

Although LCModel can handle weaker water suppression *in vivo*, as discussed in Sec 3.4, your water suppression *in vitro* must be good enough so that the formate and DSS singlets have nearly flat Baselines (in order for Auto-Scaling and Auto-Phasing to be reliable).

The high concentrations in Table 8.1 can help the S/N. You can also do more scans, but only as long as the resolution loss due to frequency drifts is certain to be negligible. Similarly, do not use an excessively large voxel. It is important to use the same voxel size for each Basis Spectrum and to **shim before every model spectrum**. The **resolution** must be better than you will ever achieve *in vivo* (at low fields, singlet linewidth FWHM less than 0.03 ppm). The resolution must also be **consistent** (FWHMs within about 0.005 ppm of each other) among the Basis Spectra. Check this by plotting the phased spectra (or by running MakeBasis). Repeat some acquisitions, if necessary.

8.3.2 Consistency

It is essential that the Basis Spectra are scaled consistently with each other; otherwise even the concentration ratios will be incorrect. The Auto-Scaling capability of MakeBasis should greatly facilitate this.

If you do not use Auto-Scaling, then you must be especially careful that all the spectra for a Basis Set are acquired under identical conditions (including coil loading), so that the effective gain is the same for all. Otherwise, you must scale them as specified in Sec 10.1.1.

However, the spectra should still be acquired under the same conditions — voxel in the center of the phantom, phantom position in the magnet, etc., as well as the more

obvious conditions in the protocol. It is therefore best if all spectra are acquired in the same time period.

If you nevertheless later want to add some new Basis Spectra to an old Basis Set then:

- If both old and new were acquired with formate and DSS markers as in Sec 8.2.4, then you can simply process them all together using Auto-Scaling with MakeBasis. You need only specify the different concentrations of the formate with `CONCSC`.
- Otherwise, you must also acquire one new spectrum of a metabolite that is also in the old Basis Set, and scale these two together, as specified in Sec 8.7.2.

8.3.3 Acquisition Time and Bandwidth

These parameters must be the same for each spectrum in the Basis Set. However, they do not have to be the same as in your *in vivo* data.

The acquisition time for one scan must be long enough so that the time-domain data decay into the noise. Otherwise, oscillations due to truncation effects in the DSS and formate markers can hurt the automatic scaling and phasing. Particularly at higher fields, you may need to use a longer acquisition time for your Basis Spectra than you normally use for your *in vivo* spectra.

The bandwidth must be high enough (i.e., the dwell time `DELTAT` small enough) so that the formate and DSS peaks are not near the edge of the spectrum. Otherwise, these can be so distorted by your scanner's anti-aliasing filter that the Auto-Phasing fails. If the center frequency is at water, the bandwidth must be at least 16 ppm. At 1.5 T, this corresponds to 1000 Hz (`DELTAT`=0.001 s). A bandwidth of 12 ppm causes Auto-Phasing to fail; you would have to phase the spectra yourself manually.

8.3.4 Repetition Time

Acquire all Basis Sets with $TR = 10000$ ms. The basis spectra are then fully relaxed, and you only have to correct for the T_1 relaxation *in vivo*. You can (and should) avoid these T_1 relaxation effects *in vivo* at a small cost in S/N by using long TR *in vivo* (at least 4000 ms).

8.4 Eddy-Current Correction

Eddy-current correction (ECC) is automatically done by Philips if you set "spectral correction" to "yes" on the "post proc" page; you can then skip Sec 8.4.

For each spectrum, you should acquire an unsuppressed water reference from the same voxel. (This is automatically done for you with GE Probe P-files and all Marconi/Picker files.) The rest of Sec 8.4 specifies how you can do the ECC with or without LCMgui.

8.4.1 ECC with LCMgui

During one LCMgui session, you will probably do a series of ECCs, one for each Basis Spectrum. The first time that you do an ECC, you have to change settings in LCMgui to execute the program KECC rather than LCModel. (After you have done all your ECCs, you exit LCMgui with “Exit & Forget”, and all these strange settings are forgotten, and you have your usual default settings for LCModel in the next session.)

- (1) Select the file with your water-suppressed data.
- (2) In the “Control Parameters” window, change the two values next to “Analyzing spectrum from:” to 4.0 ppm and -0.5 ppm. (This only determines the range of the plots of the data.)
- (3) If necessary, click the “Do eddy-current correction” button to make it blue.
- (4) In the “Save File Types” menu in Fig 7.3, select only the TABLE to be saved.

No .TABLE file will be produced, and you will get an error message in your Unix window. However, it is necessary that something be selected for saving, so that the Save Directory is made available for output of the ECC data.
- (5) To specify a directory to receive your ECC data, click on “Reconfigure” to produce the window in Fig 7.4. For example, you could enter “/home/myname/press25/” in the field next to “Enter a fixed element”. (Put a slash at the end.) Then click “Append Entry” and then “Set Configuration”.
- (6) This is now shown in the green field next to “Save File types to directory”. Append a unique name for the metabolite in your data (e.g., `naa` to make /usr/myname/press25/naa). Then your ECC data will go into the file /usr/myname/press25/naa/ecc.
- (7) Click on “Change Execution Script” in the “Advanced Settings” menu, select `ecc` in the window in Fig 7.14 and then click “Use Selected File”.
- (8) By default, your LCMgui print command will output plots of your ECC data.

`$HOME/.lcmodel/execution-scripts/ecc` shows you how to change which plots will be output and how to suppress all plots (although plots of the absolute value of the spectrum are recommended). You can also suppress all plots by clicking on “Change LCMgui Settings” in the “Advanced Settings” menu, and then changing the Print Command to “`touch`”.
- (9) Now you can click “Run LCModel”. Unless you have Marconi/Picker data or GE Probe P-files, you will then be instructed to select the corresponding unsuppressed water reference file.
- (10) You may be asked to select a .BASIS file. You can select any file; it will not be used.
- (11) Click on “Save Changes” in Fig 7.8. In Fig 7.9, enter a new name (e.g., `ecc`) next to “New filename:” and click “Use Next Time”. Then the above changes will automatically be used for ECCs on your other files during this

LCMgui session.

(12) Click on “Next Analysis” to prepare an ECC of your next data file.

For further ECCs during this LCMgui session, do the following:

- Step (1) above (Select your water-suppressed data).
- Step (6) above. (Enter a unique metabolite name.) In this way, your ECC data (in the format of `.RAW` files for direct input to MakeBasis) go into the files
`/usr/myname/press25/???/ecc`, where the `???` are your names for the metabolites (e.g., `naa`, `gaba`, etc.).
- Step (9) above. (Click “Run LCModel”)
- Step (12) above. (Click “Next Analysis”). If you have no more ECCs to do, click “Exit LCMgui”. Then click “Exit & Forget”; all of the strange settings above will be forgotten, and your next LCMgui session will offer the usual defaults for an LCModel analysis.

If you click “Exit & Save” by mistake in Step (12), you can quite easily undo the above changes in the next LCMgui session. To undo Step (4), you usually save `TABLE` and `PS` files. To undo Step (5), you usually simply click on “Change Configuration” and then on “Restore Defaults”.

8.4.2 ECC without LCMgui

If you convert your data to LCModel `.RAW` files (Sec 5.2), you can use the program `KECC` to apply the Klose correction [10], as explained in Sec 9.6. An example is:

```
$HOME/.lcmodel/bin/kecc <gaba.keccin
```

The output file `gaba.ecc` contains the eddy-current-corrected time-domain data in the format of a `.RAW` file. You input the `.ecc` file (without any changes) in place of the `.RAW` file in Sec 8.6.3.

The input file `gaba.keccin` is the Namelist:

```
$NMKECC
FILRAW='gaba.RAW'
FILH2O='gaba.h2o'
FILOUT='gaba.ecc'
NUNFIL=????
$END
```

where `gaba.RAW` and `gaba.h2o` are LCModel `.RAW` files with the time-domain data for the metabolite with the normal protocol and with the Unsuppressed Data, respectively. These data files for KECC have exactly the same meanings and formats as those specified in Sec 9.6. Section 5.3.1 specifies `NUNFIL`. In case of an abort, a self-explanatory error message is written at the end of the `.ecc` file.

8.5 Plotting .RAW Files with PlotRaw

The program PlotRaw can plot the time-domain or frequency-domain data directly from a .RAW file. It is useful for choosing input parameters for MakeBasis, as well as for looking at suspect *in vivo* data in detail. (You could also skip Sec 8.5 and use the plots of the spectra output by MakeBasis. The only advantage of PlotRaw is that you can also plot the time-domain data and absolute-value spectra.) You should first plot the absolute value of your model metabolite spectra with PlotRaw. (All plots are properly scaled by your factor TRAMP/VOLUME.)

PlotRaw is also implemented in LCMgui. You simply click on “Preview Data” in the main “Control Parameters” window in Fig 7.2. If you want to plot a .RAW file, select the .RAW file, click “Retry” in Fig 6.2, click “Other” in Fig 6.3, and then select your .RAW file again. LCMgui users can skip the rest of Sec 8.5.

8.5.1 Test Run of PlotRaw

For this test, the file \$HOME/.lcmmodel/test/control/plotraw.in has been supplied to you. You enter:

```
cd
.lcmmodel/bin/plotraw <.lcmmodel/test/control/plotraw.in
```

This produces the output file \$HOME/.lcmmodel/test/output/plotraw.ps, which you can send to your PostScript printer. It contains plots of the test data in \$HOME/.lcmmodel/test/raw/test.RAW on three pages — the time-domain data, the frequency-domain data, and the absolute value of the frequency-domain data.

8.5.2 PlotRaw .IN File

PlotRaw needs two input files,

- .RAW file, the identical file with the raw time-domain data that all the other programs use; it is specified in Sec 5.2;
- .IN file, the file with the changes to the default parameters that control the plot.

As you can see from the example plotraw.in, the .IN file consists of only the Namelist PLTRAW. You must input the following in Namelist PLTRAW:

HZPPPM, NUNFIL, DELTAT Same as in Sec 5.3.1.

FILRAW (CHARACTER*255) the name of the .RAW file containing the data to be plotted.

FILPS (CHARACTER*255) the name of the PostScript output file that will contain the plots.

You will want to input values for the following (unless you want the default values to be used):

PLTIME (LOGICAL) **.TRUE.** to plot the real and imaginary parts of the time-domain data (on one page). Default: **PLTIME = T**.

PLFREQ (LOGICAL) **.TRUE.** to plot the real and imaginary parts of the frequency-domain data (on one page). Default: **PLFREQ = T**.

PLABSV (LOGICAL) **.TRUE.** to plot the absolute value of the frequency-domain data (on one page). Default: **PLABSV = T**.

DEGZER (REAL) ϕ_0 , your zero-order phase correction in degrees, e.g., as output by LCModel and MakeBasis. This is with respect to water; see the following definition of **DEGPPM**. If **PLFREQ=F**, then you do not need to input **DEGZER** or **DEGPPM**.

Default: **DEGZER = 0**.

DEGPPM (REAL) ϕ_1 , your first-order phase correction, in degrees/ppm, e.g., as output by LCModel and MakeBasis. Thus, the FFT of the data in the **.RAW** file will be multiplied by

$$\exp\{i[\phi_0 + (\delta - 4.65)\phi_1]\pi/180\},$$

where δ is the chemical shift in ppm. You can quickly see from the plots of the phased spectra from PlotRaw whether our conventions for ϕ_0 and ϕ_1 agree.

For Bruker users:

DEGZER = **PHC1/2 + PHC0**

DEGPPM = **-PHC1/(bandwidth, in ppm)**,

where **PHC0** and **PHC1** are output by the Bruker routine **pk**.

Default: **DEGPPM = 0**.

PGNORM Same as in Sec 5.3.6.

PPMST Same as in Sec 5.3.3, except that it sets the left edge of the plotting window, i.e., the ppm-range over which the frequency-domain data will be plotted. (The time-domain data are always plotted over the full time range.)

Default: **PPMST = 999.**; i.e., the ppm-axis will extend up to the maximum ppm value of the data. (The axis will only extend far enough to plot the data, and not to this excessive value.)

PPMEND Same as in Sec 5.3.3, except that it sets the right edge of the plotting window. Default: **PPMEND = -999.**; i.e., the ppm-axis will extend to the minimum ppm value of the data.

You probably will not have to input values for the following:

GLOSCA (LOGICAL) (“global scaling”) This affects only multi-voxel plots.
.TRUE. for all spectra in the plot to have the same vertical scaling.
.FALSE. for each spectrum to be scaled individually, to fill the whole frame of its subplot. Weak spectra are therefore expanded.
 Default: **GLOSCA = T**

SDPNTS (REAL) (“standard deviation in points”) LCModel analyzes the *unsmoothed* data. However, to more reliably locate the referencing peak in the Basis Spectrum, MakeBasis *temporarily* convolutes the spectrum with a smoothing Gaussian with a standard deviation of **SDPNTS Grid Points** in the fre-

quency domain, where one Grid Point is $1/(2*\text{NUNFIL}*\text{DELTAT})$ Hz. The default value for SDPNTS is 1.0 in MakeBasis and 0.0 (no smoothing) in PlotRaw. If you want to plot smoothed spectra (e.g., to see what MakeBasis sees when it looks for the referencing peak) then you can input a positive SDPNTS.

- You can customize the plots (e.g., for slides or figures) by inputting values for any of the Control Variables in Secs. 9.9.3.2–9.9.3.4, except PTOUTP, RHOUTP, RGBLIN, SUBBAS, and RHVERS.

WDLIN in PlotRaw has dimensions WDLIN(6,3). WDLIN(JCURVE,JPLOT) determines the curve thicknesses as in Sec 9.9.3.4, where JPLOT=1 for the plot of the time-domain data, JPLOT=2 for the plot of the frequency-domain data, and JPLOT=3 for the plot of the absolute value of the frequency-domain data; only JCURVE=3, 5, 6 are relevant in PlotRaw.

NAIM (INTEGER(3)) the number of numerical labels on the abscissa will be roughly NAIM(JPLOT), where JPLOT has the same meaning as for WDLIN(*,JPLOT) immediately above.

Default: NAIM = 8, 18, 18

XLABEL, YLABEL (CHARACTER(3)*80, CHARACTER(2,3)*80) label the abscissas and ordinates. You can deduce their usage by outputting Namelist PLTRAW using LPRINT below.

LPRINT (INTEGER) You can output the Namelist PLTRAW to see all default values by inputting LPRINT = 6.

Default: LPRINT = 0; i.e., no file will be created.

FILPRI (CHARACTER*255) the name of the file that will contain the output Namelist PLTRAW (only needed if LPRINT > 0).

For CSI .RAW files only: NDSLIC, NDCOLS, NDROWS, ISLICE, IROWST, IROWEN, ICOLST, ICOLEN have the same usage and defaults as with LCModel (Sec 5.3.2).

8.5.3 PlotRaw Diagnostics

If the run stops before a PlotRaw diagnostic appears on your screen and no .PS file is produced, then check the suggestions in Sec 12.1.1.

Normally, a standard PlotRaw diagnostic of the form

Aborting due to error *Name n*. Check User's Manual...

appears on your screen. (If not, it can always be found at the end of the .PS file, if some or all of the plots are not produced.)

The following lists all the *Name n*, possibly with suggested remedies, if they are not obvious.

- | | |
|--------|---|
| PLTRAW | <ol style="list-style-type: none"> 1 You must have PPMST > PPMEND. 2 PAGEWD and PAGEHT must be positive. 3 NUNFIL must be positive and must not exceed 65536. 4 Same as INITIA 1 in Sec 12.2. 5 Same as MYDATA 1 in Sec 12.2. 6 Same as MYDATA 2 in Sec 12.2. 7 You must have DEGPPM < 9999.0. |
|--------|---|

- 8 You must have `SDPNTS` ≤ 60 .
 - 9 This would be my programming error.
 - 10 There is an error in your Namelist `PLTRAW`. See Sec 12.1.1 on Namelist Errors.
 - 11 End-of-File reading your Namelist `PLTRAW`. See Sec 12.1.1.
 - 12 There is an error in `FMTDAT` in your Namelist `NMID` in your `.RAW` file, or the format of your time-domain data in your `.RAW` file does not match `FMTDAT`. See Sec 12.1.1 on Namelist Errors.
 - 13 End-of-File reading your `.RAW` file. See Sec 12.1.1.
 - 14 You must have `PTTITL` & `PTLABL` positive and `RHTITL` & `RHLABL` at least 1.0.
 - 15 Same as `ZEROVX` 4.
-
- `PLOT2`
- 1 Same as `PLTRAW` 14.
 - 2 Same as `ONEPAG` 4 in Sec 12.2.
 - 3 Same as `ONEPAG` 8 in Sec 12.2.
-
- `AXRND1`
- 1 One curve to be plotted consists of only one point. Are `PPMST` and `PPMEND` very close to each other?
 - 2 All 3 elements of `NAIM` must exceed 1.
 - 3 One curve to be plotted consists of at most two points. Are `PPMST` and `PPMEND` very close to each other?

8.6 Running MakeBasis

You run `MakeBasis` with a command like

```
$HOME/.lcmode/bin/makebasis < makebasis.in
```

where `makebasis.in` (Sec 8.6.4) contains the changes to Control Parameters. An example is `$HOME/.lcmode/test/control/makebasis.in` (used for the test run in Chap 4). In addition, a `.RAW` file is needed for each metabolite in the Basis Set.

All of the Control Parameters for these two types of files are specified in Secs. 8.6.3 & 8.6.4. However, we will first discuss the general features and usage of `MakeBasis` with examples, often mentioning Control Parameters that are not defined in detail until later, in Secs. 8.6.3 & 8.6.4.

`MakeBasis` does the following:

- optionally phases your Basis Spectra (*Auto-Phasing*);
- references your Basis Spectra;
- optionally consistently scales your Basis Spectra with each other (*Auto-Scaling*);
- outputs the `.BASIS` file that will be used by `LCModel`.

To do this, `MakeBasis` requires the `formate` standard (for *Auto-Phasing* and *Auto-Scaling*) and the `DSS` marker (for *Auto-Phasing* and referencing), as specified in Sec 8.2.4.

Each spectrum is scaled (multiplied) by the Control Parameter `TRAMP` in its `.RAW` file. The metabolite spectra used for the test run in Chap 4 were acquired before *Auto-Scaling* was available and have no `formate` standard. *Auto-Scaling* and *Auto-Phasing*

therefore had to be suppressed (by setting `AUTOSC = AUTOPH = F` in `makebasis.in`). Thus the phase corrections and the `TRAMP` scale factors had to be carefully determined beforehand and input.

8.6.1 Auto-Scaling

Auto-Scaling and Auto-Phasing are illustrated with a small set of test data provided with your package. Enter

```
cd
.lcmodel/bin/makebasis <.lcmodel/test/control/makebasis-auto.in
```

This produces the `test-auto.basis` file and a PostScript file (`basis-auto.ps`) (both in the directory `$HOME/.lcmodel/test/output`). Output `basis-auto.ps` on a PostScript printer. There is one plot for each metabolite (with this test data, only three). The top line of each plot contains the metabolite name, the phase corrections (if `AUTOPH=T`), and the *Scale Factor* (if `AUTOSC=T`). MakeBasis multiplies `TRAMP` by this Scale Factor in `test-auto.basis`, so that all of your Basis Spectra are automatically scaled consistently with each other. [All Basis Spectra are scaled to match the formate standard of the first metabolite in the `.IN` file (Cho in this example); thus its Scale Factor is identically 1.]

8.6.2 Judging the Basis Spectra

You should always carefully check the plots in the `.PS` file output by MakeBasis. The phasing and referencing should look reasonable, and the quality should be comparable to that of the test runs (in `basis.ps` and `basis-auto.ps` in the directory `$HOME/.lcmodel/test/output`).

If you use Auto-Scaling or Auto-Phasing, you should run MakeBasis 3 times — with the default `[PPMST, PPMEND]` of `[4.2,-0.2]`, but also with `[8.54,8.34]` and `[0.1,-0.1]` (to zoom in on the formate and DSS peaks). The formate and DSS peaks should be at least as well defined and phased as in the test run `basis-auto.ps` (where only 100 mM formate and 1 mM DSS were used).

8.6.3 .RAW File

These files have exactly the same format specified in Sec 5.2 for the `.RAW` files for *in vivo* data. However, Namelist `SEQPAR` is not used, and the values of the following Control Parameters in Namelist `NMID` are more important with the Basis Spectra:

ID You should give a unique name to each Basis Spectrum, at least if your filenames are not unique (e.g., if you call all NAA data files simply `naa.RAW`). However, it is much better to also use unique filenames.

VOLUME is not important if you are using Auto-Scaling. Otherwise, it should equal the voxel size (say, in mL), so that the Basis Set will be consistently scaled, even if you use different voxel sizes (although a fixed voxel size for the Basis Set is recommended).

TRAMP is not important if you are using Auto-Scaling. A reasonable value is 1.0.

If you do not use Auto-Scaling, then you must be especially careful that all the spectra for a Basis Set are acquired under identical conditions (including coil loading), so that the effective gain is the same for all; in this case a **TRAMP** = 1.0 could also be used. Otherwise, you must set **TRAMP** according to the methods mentioned in Sec 10.1.1.

For MakeBasis, you must explicitly input the complete Namelist **NMID** (except that only Bruker, Philips & Canon/Toshiba users need to input **BRUKER**, and only Bruker users *may* need to input **SEQACQ**).

Immediately following this Namelist are the raw time-domain data (see Sec 5.2.3). They are for the metabolite Basis Spectrum, possibly corrected for eddy-current effects as in Sec 8.4. Phase corrections will be applied later by MakeBasis.

8.6.4 MakeBasis .IN File

As you can see from `$HOME/.lcmode1/test/control/makebasis.in`, it consists of:

- Namelist **SEQPAR**, once at the beginning
- Namelist **NMALL**, once at the beginning;
- For each Basis Spectrum, a Namelist **NMEACH**.

8.6.4.1 Namelist SEQPAR

This is nearly the same as **SEQPAR** in Sec 5.2.1; they both include **ECHOT** & **SEQ**. However, **HZPPPM** is not included here (but in **NMALL** below). In addition, a new Control Parameter is needed here:

FWHMBA (REAL) (“FWHM of Basis peaks”) the approximate full-width at half-maximum (in ppm) of the singlets in the Basis Set. However, if the singlets are Lorentzian, you should set **FWHMBA** = **4*FWHM**, to account for the long tails. (None of the basis sets that we distribute is Lorentzian.)
Default: **FWHMBA** = 0.013

You can initially omit **FWHMBA** and use your first runs of MakeBasis to determine **FWHMBA** by zooming in on NAA, Cr & GPC/PCh, respectively, inputting **PPMST**, **PPMEND** in Namelist **NMALL** below as (2.1, 1.9), (3.1, 2.9) & (3.3, 3.1). You can then estimate the FWHM of these four singlets from plots of the .PS files, and use the mean for **FWHMBA**. Typical maximum values are 0.02, 0.013, 0.01 for 1.5 T, 2.0 T & 4.7 T (and higher), respectively. A **FWHMBA** \geq 0.025 is unacceptable; it is too close to possible *in vivo* resolution.

FWHMBA is used to estimate the total FWHM for the One-Page Output and the final lineshape and the smoothness of the lineshape.

8.6.4.2 Namelist NMALL

This sets parameters universally for all Basis Spectra in the run. You must input the following in Namelist NMALL:

HZPPPM, NUNFIL, DELTAT Same as in Sec 5.3.1.

FILBAS (CHARACTER*255) the name of the .BASIS file to be output by MakeBasis. If you are going to use LCMgui, then follow the naming rules in Sec 7.3.2.

FILPS (CHARACTER*255) the name of the PostScript file to be output for plotting the real and imaginary parts of the Basis Spectra, e.g., 'basis.ps'. (The spectra are properly scaled by your factor TRAMP/VOLUME.) You can leave out FILPS only if you have suppressed the plots with PPMST and PPMEND below.

AUTOSC (LOGICAL) ("Auto-Scaling") .TRUE. to do Auto-Scaling; the formate standard must then be in all Basis Spectra. See the definition of TRAMP above in Sec 8.6.3 for the requirements when AUTOSC = F.

AUTOPH (LOGICAL) ("Auto-Phasing") .TRUE. to do Auto-Phasing; in this case, the formate and DSS standards must then be in all Basis Spectra, and you must also input
AUTOSC = T.

You will want to input values for the following (unless you want the default values to be used):

IDBASI (CHARACTER*80) an optional name for uniquely identifying this Basis Set. This will be output in the .BASIS file and by LCModel.
Default: IDBASI=' '.

PGNORM Same as in Sec 5.3.6.

PPMST Same as in Sec 8.5.2, except that the default is PPMST = 4.2. PPMST and PPMEND only affect the plots in the .PS file; they do not affect the Basis Spectra in the .BASIS file at all.

PPMEND Same as in Sec 8.5.2, except that the default is PPMEND = -0.2 (to see the DSS marker). Note that if you input PPMST < PPMEND, then no plots will be made.

You probably will not have to input values for the following:

FMTBAS (CHARACTER*80) ("format, Basis") the Fortran FORMAT specification for the Basis Spectra output in the .BASIS file. Default: '(6E13.5)'.

- You can customize the plots (e.g., for slides or figures) by inputting values for any of the Control Variables in Secs. 9.9.3.2–9.9.3.4, except PTOUTP, RHOUTP, RGLIN, SUBBAS, and RHVERS.

NAIM (INTEGER) Same as in Sec 8.5.2, except that there is only one element in NAIM, not three, since MakeBasis only plots the frequency-domain data.
Default: NAIM = 18

HWDSCA (REAL) ("half-width for scaling") When AUTOSC=T, the real part of standard formate peak will be integrated over an interval up to \pm HWDSCA ppm about the peak maximum. The default is HWDSCA = 0.15. If any of your formate peaks are so broad that they have not decayed into the Baseline within this interval, then you should repeat your acquisitions.

You can check this by running with `PPMST = 8.6` and `PPMEND = 8.3`. (MakeBasis effectively reduces `HWDSKA` if possible; so, you should not have to reduce `HWDSKA` or `HWDPHA`.)

HWDPHA (REAL) (“half-width for phasing”) When `AUTOPH=T`, the phase of the real part of the DSS peak will be optimized over an interval up to \pm `HWDPHA` ppm about the peak maximum. The default is `HWDPHA = 0.15`. If any of your DSS peaks are so broad that they have not decayed into the Baseline within this interval, then you should repeat your acquisitions. You can check this by running with `PPMST = 0.15` and `PPMEND = -0.15`.

PPMSCA (REAL) The chemical shift (accurate to within `HWDSKA` ppm) of your reference peak for scaling.
Default: `PPMSCA = 8.44`.

PPMPHA (REAL) The chemical shift (accurate to within `HWDPHA` ppm) of your reference peak for phasing.
Default: `PPMPHA = 0.0`.

PPMBAS (REAL) (“ppm Baseline”) The Baseline in the integration of the formate peak is estimated from two intervals `PPMBAS` ppm wide on each side of the integration interval (specified in the definition of `HWDSKA` above).
Default: `PPMBAS = 0.1`.

SDPNTS Defined in Sec 8.5.2.

8.6.4.3 Namelist NMEACH

There is one of these for each Basis Spectrum to be included in the Basis Set. It sets parameters for the particular Basis Spectrum being processed.

FILRAW (CHARACTER*255) the name of the `.RAW` file containing the (ECC) time-domain data for the Basis Spectrum to be processed.

METABO (CHARACTER*6) the abbreviation of the metabolite. In this manual, it is called the *Metabolite Name*. This is used throughout LCMODEL for identification. *You must use the Metabolite Names in the “Allowed Name” column of Table 8.1.* If two Metabolite Names are given in Table 8.1 for a metabolite, then you can use either. If you introduce a new metabolite, then use a Metabolite Name that is not in the table. You must be consistent, even with case; `'LAC'` will not be recognized as `'Lac'`. Input without blanks, i.e., `'Lac'` and not `' Lac'`.

DEGZER Same as in Sec 8.5.2. This is only needed when `AUTOPH = F`.

DEGPPM Same as in Sec 8.5.2. This is only needed when `AUTOPH = F`. You must have `DEGPPM < 200`, but it should be much less; shift the time-domain data if necessary.

CONC (REAL) the concentration of the metabolite in the model solution. The units (e.g., mM) must be consistent with all other Basis Spectra.

CONCSC (REAL) the concentration of the formate concentration standard in the model metabolite solution. This is only needed when `AUTOSC = T`. Normally, it is the same, since the same Standard Solvent was used as “solvent” for all metabolites, as specified in Sec 8.2.4. However, it can vary when

- (i) a metabolite solution was diluted by titration,
- (ii) combining Basis Spectra from different times or laboratories, or
- (iii) when the phosphate Standard Solvent could not be used (as with GPC·CdCl₂ or the Ca salt of PCh) and a slightly different formate con-

centration was added.

The units (e.g., mM) must be consistent with all other Basis Spectra.

NOSHIF (LOGICAL) (“no shift”) **.TRUE.** to suppress referencing. This can be useful with simulated basis spectra that are already referenced. You still have to input sensible values for **PPMAPP**, although they will not be used. Default: **NOSHIF = F.**

PPMPK (REAL) (“ppm peak”) the chemical shift (in ppm) of the resonance that will be used for referencing. Default: **PPMPK = PPMPHA**; i.e., usually 0.0 for DSS.

PPMAPP (REAL(2)) (“ppm apparent”) You may want to first plot the absolute value of your spectrum with PlotRaw (Sec 8.5) or with LCMgui’s “Preview Data” (Sec 7.4.1). From this plot, you must specify with **PPMAPP** the interval on this apparent (unreferenced) ppm-axis that contains your referencing peak. The program **MakeBasis** will find the maximum on this interval and compute the shift that will translate this maximum to (the correct) **PPMPK**. Note that **PPMPK**, **PPMSCA**, **PPMPHA**, **PPMST** and **PPMEND** are all true ppm values, after any necessary referencing; only **PPMAPP** refers to apparent unreferenced values.

PPMAPP(1) is the high-ppm end of the interval.

PPMAPP(2) is the low-ppm end of the interval.

If DSS is the marker for the metabolite, then **PPMAPP = 0.1, -0.4** is typically sufficient to bracket the peak.

XTRASH (REAL) (“extra shift”) is used to shift a complete spectrum along the ppm-axis to simulate another spectrum. **XTRASH** = $\delta_{new} - \delta_{old}$ (in ppm).

Note that **PPMSCA**, **PPMPHA**, **PPMAPP**, etc., are not affected by **XTRASH**; scaling, phasing, and referencing are correctly done before the extra shift, although the plots in the .PS file will show your formate and DSS peaks shifted away from **PPMSCA** and **PPMPHA**.

makebasis-auto.in illustrates the case where you shift Cho (main peak at 3.19) to approximate GPC or PCh (main peaks at 3.22), using
XTRASH = 3.22 - 3.19 = 0.03

Another example is **XTRASH = 0.035** to shift NAA (2.01 ppm) to approximate NAAG (2.045 ppm).

Default: **XTRASH = 0.0.**

DEGPAP (REAL) (“DEGPPM, approximately”) is only needed when **AUTOPH=T** and only when the 1st-order phase correction is large (as with old Marconi/Picker PRESS data), i.e., when

$$|\text{DEGPPM}| > 180/|\text{PPMSCA} - \text{PPMPHA}|$$

This is ± 21 deg/ppm when formate & DSS markers are used. It must then be a rough approximation (e.g., to within 21 deg/ppm) of **DEGPPM** to resolve the ambiguity in large 1st-order phase corrections.

You must have **DEGPAP** < 200, but it should be much less; shift the time-domain data if necessary.

Default: **DEGPAP = 0.0**, which is fine if **|DEGPPM|** is less than about 15. Otherwise, input **DEGPAP** equal to your approximate value of **DEGPPM**.

PPMOFF (REAL(2)) (“ppm range for offset correction”). This does not affect the

LCModel results; it is only for aesthetics. If a Basis Spectrum has a constant offset, then the LCModel Baseline will compensate this with the same offset. This can look strange if the Baseline has to move higher (cutting through metabolite peaks) or move way below the data spectrum; it would also falsify the output S/N (Sec 2.4).

MakeBasis will adjust the offset so that the average offset over the ppm-range $\text{PPMOFF}(1) > \text{PPMOFF}(2)$ is zero. So, you set this range where there is only Baseline in the Basis Spectrum. It should also be in the Analysis Window. For example, for NAA, you might use the range [3.8, 3.2] or [1.6, 1.0].

Default: $\text{PPMOFF} = -999., -999.;$ i.e., meaningless values, so that PPMOFF is not used.

You must explicitly input all of the above Control Parameters in each Namelist NMEACH, except that:

- You must omit DEGZER and DEGPPM when AUTOPH = T.
- You may omit PPMPK, XTRASH, DEGPAP, NOSHIF and PPMOFF to leave them at their defaults.
- You may omit CONCSC when AUTOSC = F.

8.6.5 MEGA-PRESS

Because of the limited accuracy of MEGA-PRESS (and probably most other difference spectra), you can use a shifted NAA to approximate NAAG with XTRASH (Sec 8.6.4.3). If you simulate the basis set, you can skip the rest of this section.

You must make a basis set from the difference spectra, but the usual landmark singlets of formate & DSS are practically absent. So, you use the unedited “off” spectra for phasing, referencing and scaling:

- (1) Make a basis set from your unedited “off” spectra. Use $\text{AUTOSC}=\text{T}$, $\text{AUTOPH}=\text{T}$.
- (2) Make your final basis set from your difference spectra using the same Control Parameters as in (1), except:
 - (2a) $\text{AUTOSC}=\text{F}$, $\text{AUTOPH}=\text{F}$, $\text{NOSHIF}=\text{T}$ in each namelist NMEACH, and:
 - (2b) Use the values from the basis file from (1) for: DEGZER, DEGPPM in each namelist NMEACH.
- (3) Edit your basis file from (2) to the values from the basis file from (1) for: FWHMBA in namelist SEQPAR; all 6 values in each namelist BASIS (one for each metabolite). You use the resultant basis file.

8.6.6 MakeBasis Diagnostics

If the run stops before a MakeBasis diagnostic appears on your screen or a .BASIS file is produced, then check the suggestions in Sec 12.1.1.

Normally, a standard MakeBasis diagnostic of the form

Aborting due to error *Name nn*. Check User's Manual...

appears on your screen. (It can also be found at the end of the .BASIS file, if the .BASIS file is incomplete or if some or all of the expected plots are not produced.)

The following lists all the *Name nn*, possibly with suggested remedies, if they are not obvious.

- MAKEBA
- 1 Same as PLTRAW 2 in Sec 8.5.3.
 - 2 Same as PLTRAW 3 in Sec 8.5.3.
 - 3 You forgot to input DELTAT, NUNFIL, or HZPPPM in Namelist NMALL, or you input a non-positive value for one of them.
 - 4 When you use AUTOSC = T, HWDSKA must correspond to at least 2 Grid Points and PPMBAS to at least 4 Grid Points.
 - 5 You forgot to input CONC, METABO or FILRAW in Namelist NMEACH, or you input CONC non-positive.
 - 6 You forgot to input CONCSC in Namelist NMEACH, or you input it non-positive.
 - 7 Same as MYDATA 1 in Sec 12.2.
 - 8 You input a non-positive TRAMP or VOLUME in Namelist NMID in one of your .RAW files.
 - 9 When AUTOPH = T, you must input AUTOSC = T; HWDPHA must correspond to at least 2 Grid Points; you must not input DEGZER or DEGPPM; and PPMSKA and PPMPHA must be at least 1.0 ppm apart.
 - 10 When AUTOPH = F, you must input DEGZER and DEGPPM.
 - 11 You must have SDPNTS ≤ 60 .
 - 12 You forgot to input PPMAPP or you input $PPMAPP(1) \leq PPMAPP(2)$ or a PPMAPP is so extreme that it comes too close to the edge of the ppm-range of the data to also allow proper smoothing.
Hints: If your reference peak is really near the edge, increase the bandwidth. Otherwise, correct your input of PPMAPP.
 - 13 In the entire window between PPMAPP(1) and PPMAPP(2), either
(a) the real part of the spectrum is negative (where it should actually have the referencing peak). Hint: This might be just a negative offset that could be remedied by adding a positive number to the first time-domain data point. or
(b) the absolute value of the spectrum is zero. Hint: Check for gross errors in your .RAW file that could cause the data to be all identically zero.
 - 14 An enormous shift, at least NUNFIL Grid Points, has been computed.
Hint: Plot the absolute value of the spectrum with PlotRaw (Sec 8.5) or with LCMgui's "Preview Data" (Sec 7.4.1); you should see that your values for PPMAPP or PPMPK are grossly in error.
 - 15 PPMSKA is right at the edge of the spectrum. Increase the bandwidth or correct your input of PPMSKA.
 - 16 The area of the real part of the (formate) peak at PPMSKA is negative.
Hints: Plot the absolute value of the spectrum with PlotRaw (Sec 8.5) or with LCMgui's "Preview Data" (Sec 7.4.1) to see if there is a well-defined formate peak in the spectrum. Another possibility is that a big referencing error due to too weak a DSS referencing peak shifted the formate peak away from PPMSKA.
 - 17 An enormous shift, at least NUNFIL Grid Points, has been computed with XTRASH.
Hint: Plot the absolute value of the spectrum with PlotRaw (Sec 8.5) or with LCMgui's "Preview Data" (Sec 7.4.1). You should see that your values for XTRASH or perhaps PPMAPP or PPMPK are grossly in error.
 - 18 PPMAPP is right at the edge of the spectrum, or you forgot to input a positive PPMFLA.
Hints: Increase the bandwidth or correct the input of PPMAPP or PPMFLA. (FLATEN & PPMFLA are obsolete and should no longer be used.)
 - 19 You must have PTTITL & PTLABL positive and RHTITL & RHLABL at least 1.0.
 - 20 Same as ONEPAG 4 in Sec 12.2.
 - 21 Same as ONEPAG 8 in Sec 12.2.
 - 22 PPMSKA is too close to the edge of the spectral range.
Hint: Increase the bandwidth or correct the input of PPMSKA.
 - 23 PPMPHA is too close to the edge of the spectral range.
Hint: Increase the bandwidth or correct the input of PPMPHA.

- 24 You must have $\text{PPMOFF}(1) > \text{PPMOFF}(2)$, and the difference must be sufficient to include at least 5 Grid Points.

GETPHA 1 PMPHA is right at the edge of the spectrum.
Hints: Increase the bandwidth or correct your input of PMPHA.

AXRND1 1,2,3 Same as AXRND1 1,2,3 in Sec 8.5.3.

8.6.7 Output .BASIS File

As in the test runs in Chap 4, this output file can be input directly without change to LCModel, and there is normally no need to read this subsection.

The .BASIS file has the following general structure:

- Namelists SEQPAR & BASIS1 (only once at the beginning), then for each Basis Spectrum:
 - Namelist NMUSED (used only to document your input to MakeBasis);
 - Namelist BASIS used by LCModel;
 - the real and imaginary parts of the Basis Spectrum obtained after phasing and zero-filling, ordered as (real, imaginary, real, imaginary, ...).

The only new names in Namelist BASIS1 are:

BADELT (REAL) (“Basis δt ”) equals DELTAT input in Namelist NMALL in the .IN file.

NDATAB (INTEGER) (“no. of zero-filled data points in Basis”) equals 2*NUNFIL input in Namelist NMALL in the .IN file.

The only new name in Namelist BASIS is the referencing shift:

ISHIFT (INTEGER) the number of Grid Points that the Basis Spectrum will be shifted for correct referencing. A positive ISHIFT shifts the spectrum toward higher ppm values.

8.7 Calibrating Basis Spectra

8.7.1 Calibrating GPC/PCh & NAA/NAAG

Auto-Scaling cannot detect or fix errors in CONC, your concentration values. Such errors are directly propagated to the LCModel concentrations. However, they are at least reproducible, so that you can still see changes or trends. A worse situation is when two very similar metabolites (whose sum is usually studied, such as GPC+PCh or NAA+NAAG) are inconsistent. Then the (normally much more reliable) sum will have increased scatter.

It is therefore important to calibrate members of such pairs with each other. The concentration of the Cd-complex of GPC from Sigma is particularly unreliable.

To calibrate GPC with PCh, input the following Control Parameters (which are defined below):

```
BASCAL=T
CHBCAL='GPC'
NCALIB=1
CHCALI(1)='PCh'
```

PPMST=3.45

You must also supply the usual HZPPPM, NUNFIL, DELTAT, FILBAS, FILPS, FILRAW. You can supply the name of any valid .RAW file for FILRAW (since the “data” will be the GPC Basis Spectrum). PPMST cuts off the resonances above 3.45 ppm, which are different in GPC & PCh.

Normally, one singlet of each of the two metabolites is used for calibration. PPMSHF (Sec 11.3.3) might be needed in cases where the CHBCAL singlet must be greatly shifted to the CHCALI singlet.

When BASCAL=T, the “data” Basis Spectrum is divided by its CONC. Thus, when the number of protons contributing to the peak is the same for CHBCAL and CHCALI(1) (as here), the LCModel concentration will be 1.0 if the two are consistently scaled. Therefore, you correct the GPC CONC in your makebasis.in file by multiplying it by the LCModel CONC that comes out of this calibration analysis. Check this by running MakeBasis with this corrected makebasis.in and then running the LCModel calibration analysis with this new Basis Set. The LCModel concentration that comes out of the calibration analysis should now be 1.0. Then, GPC & PCh are consistently scaled.

What happens if the numbers of protons contributing to the singlets are different? Suppose CHBCAL='GPC' (9 protons) and CHCALI(1)='Cr' (3 protons in the CH₃ group). Then you multiply the GPC concentration by 3/9 times the LCModel CONC that comes out of the calibration analysis. With this corrected GPC concentration, the calibration analysis should now yield 3.0 (9/3).

To calibrate NAAG with NAA, use the above input, except with CHBCAL=NAAG', CHCALI(1)='NAA' and no input for PPMST. This is not as accurate, because of the differing signals above 2.1 ppm. However, PPMST=2.1 often cuts too close to the base of the main peak and produces worse results. So, it is probably best to leave PPMST at its default of 3.85 or 4.0. Correct the NAAG CONC by multiplication, as for GPC above.

LCMgui users can do the following:

- With the File Selector in Fig 6.1, select an incorrect file type.
- Click on “Retry” in Fig 6.2.
- Click on “Other” in Fig 6.3.
- Again select any (reasonably small) file with the File Selector in Fig 6.1.
- In the main “Control Parameters” window (Fig 6.4), if necessary, click on “Change BASIS” and select the Basis Set to be calibrated.
- Also in the “Control Parameters” window, click on “Advanced Settings”, then on “View/Edit Control Parameters”, and enter the above Control Parameters (including HZPPPM, etc., listed above) in the window in Fig 7.7. Click “OK” and then “Run LCModel”.
- If you wish, you can save these changes (e.g., in bascal-gpc) for possible future use.
- When you exit LCMgui, you can click on “Exit & Forget”. This will cause your “Other” file type to be forgotten, and your next LCMgui session will start as your present one did, expecting the usual file type.

Finally, the definitions of the above Control Parameters are:

- BASCAL** (LOGICAL) (“Basis calibration”) **.TRUE.** to analyze one spectrum of the Basis Set with another spectrum of the Basis Set. (Note: only spectra in the Basis Set can be used, not spectra simulated with **NSIMUL**, which is set to zero.)
Default: **BASCAL = F.**
- CHBCAL** (CHARACTER*6) is the Metabolite Name of the Basis Spectrum that will be analyzed as “data” when **BASCAL=T.**
- NCALIB** (INTEGER) **NCALIB > 0** specifies that only **NCALIB** Basis Spectra from the Basis Set will be used for the analysis.
The normal use is **NCALIB=1.**
Default: **NCALIB = 0**, which will cause **FATAL MYBASI 12** when **BASCAL = T**; i.e., you must input **NCALIB** when **BASCAL = T.**
- CHCALI** (CHARACTER(60)*6) The first **NCALIB** elements contain the Metabolite Names of the Basis Spectra that will be used in the analysis.
In addition, these Basis Spectra will automatically be used in the Preliminary Analysis and **VITRO=T** is set.
Furthermore, when all **CHCALI** are members of the (usual) set [Lac, NAA, Cr (or Cre), GPC, PCh, Cho], then the Control Parameters **NREFPK**, **PPMREF** & **HZREF** are automatically set. Then, the only extra Control Parameters for calibration that you need to input are **NCALIB** & **CHCALI** and (if you want to calibrate a Basis Spectrum) **BASCAL** & **CHBCAL.**

8.7.2 Adding New Basis Spectra

This section specifies how you can add new Basis Spectra to an old Basis Set. As mentioned in Sec 8.3.2, if all Basis Spectra were processed using Auto-Scaling and Auto-Phasing with formate and DSS, then you simply run them all together with one **makebasis.in** file. They are all scaled together using their **CONCSC** values for the respective formate concentrations. Of course, the sequence parameters must always match, including **HZPPPM**, **DELTAT** & **NUNFIL**. The linewidth of your new spectra must match the old one (given, in ppm, by **FWHMBA** near the beginning of the **.BASIS** file).

How do you determine if an old **.BASIS** file was produced with Auto-Scaling & Auto-Phasing? The information is in the Namelist **NMUSED**. Auto-Scaling was used only if “**AUTOSC = T**” & “**AUTOPH = T**” appear in every Namelist **NMUSED**. You will then also find **CONCSC** for each Basis Spectrum in its **NMUSED**.

The rest of Sec 8.7.2 specifies how you can add new Basis Spectra to an old Basis Set that was *not* Auto-Scaled. The steps are:

- (1) Also acquire one new Basis Spectrum from a metabolite (NAA or Cr) that is in the old set. For example, suppose that it is NAA. (If you do use NAA, be sure to bring the pH up to 7.2 by titration with concentrated NaOH.)
- (2) Make a new Basis Set from your new Basis Spectra. Give your NAA a new name, e.g., in **makebasis-new.in**, set
METABO='NAA2'

As with all Basis Sets, the new Basis Spectra must be consistently scaled with

each other. Suppose that the new Basis Set is called `new.basis`.

- (3) Suppose your old Basis Set is called `old.basis`. Combine them with

```
cat old.basis new.basis > combined.basis
```
- (4) Run LCModel (as in Sec 8.7.1) with the following extra Control Parameters:

```
BASCAL=T
CHBCAL='NAA2'
NCALIB=1
CHCALI(1)='NAA'
```

(You must also input NUNFIL, DELTAT & HZPPPM equal to those of the basis set.) Call the concentration output by this analysis $CONC_{bascal}$.
- (5) Modify your `makebasis-new.in` by multiplying CONC for each metabolite by $CONC_{bascal}$. Then run MakeBasis to produce your modified `new.basis`.
- (6) Repeat Steps (3) & (4). The concentration output by LCModel should now be 1.0.
- (7) Modify your `makebasis-new.in` by removing the complete Namelist NMEACH for NAA2. (You can also simply change the NAA “\$NMEACH”, e.g., to “\$NM”.) Run MakeBasis to get this final `new.basis` (without the superfluous NAA2).
- (8) Step (3) now produces your final `combined.basis`.

8.8 Summary

The main steps in processing your Model Spectra are:

- Eddy-Current correction (Sec 8.4).
- Run MakeBasis three times, with $[PPMST, PPMEND] = [8.54, 8.34], [4.2, -0.2], [0.1, -0.1]$, to evaluate the resolution and quality, also of the formate and DSS markers. (Sec 8.6.2)
- Run MakeBasis three times, with $[PPMST, PPMEND] = [2.1, 1.9], [3.1, 2.9], [3.3, 3.1]$, to estimate FWHMBA, which you now input in Namelist SEQPAR in your `makebasis.in`. (Sec 8.6.4.1)
- Calibrate GPC/PCh and NAAG/NAA (Sec 8.7.1). In your `makebasis.in`, correct CONC for GPC and (if necessary) for NAAG. Run MakeBasis and repeat the calibration runs. The GPC and NAAG concentrations output by LCModel should now be 1.0. Then, your Basis Set should be ready for use.

Chapter 9

Further Useful Options and Information

This chapter specifies useful Control Parameters that you can input in the `.CONTROL` file (or, with LCMgui, Fig 7.7); otherwise they remain at their default values. You should at least scan over the options in this chapter.

9.1 Special Types of Spectra

LCModel uses the choline, creatine & NAA landmarks at 3.22, 3.03 & 2.01 ppm for initial referencing. You can inform LCModel of missing landmarks or of special types of spectra (remember that PLOTs are in `$HOME/.lcmodel/doc/figures.pdf`):

`SPTYPE (CHARACTER*16)` (“special type”)

`SPTYPE = 'muscle-5'` for muscle spectra (PLOT 8). To use this, you must read Sec 9.2.

`SPTYPE = 'lipid-8'` for spectra with only lipid (and water) signals. PLOT 9 shows a vertebral spectrum. To use this, you must read Sec 9.3.

`SPTYPE = 'breast-8'` for spectra with only lipid (and water) and possibly choline signals. PLOT 10 shows a breast spectrum, but this is not only for breast. To use this, you must read Sec 9.3.

`SPTYPE = 'only-cho-2'` for spectra where you only want to estimate choline, e.g., with breast, where fat suppression has distorted the lipid signals around 1.3 ppm. To use this, you must read Sec 9.3.

`SPTYPE = 'liver-11'` for spectra with only lipid (and water), choline signals and glycogen. PLOT 11 shows a liver spectrum. To use this, you must read Sec 9.3.

`SPTYPE = 'mega-press-3'` for estimating GABA using MEGA-PRESS. To use this, you must read Sec 9.4. PLOT 12 shows an example.

`SPTYPE = 'csf'` when you expect mainly cerebrospinal fluid (CSF), with all three

landmarks (NAA, cholines and creatines) weaker than Lac & Glc (PLOT 13).

SPTYPE = 'version5' is for consistency with very old versions (Sec 11.17).

SPTYPE = 'tumor' when the NAA singlet may be weak compared to choline or creatine or the lipid or macromolecule signals around 1.3 or 0.9 ppm. So, this is not only for tumors. (PLOTS 6 & 7). The following (except (2)) are automatically set:

- (1) Since there is often only one useful landmark (at 3.22 ppm) SHIFMN(2) = -0.07 and SHIFMX(2) = 0.07, to prevent Cr from being shifted to 3.22. If your referencing shift exceeds ± 0.07 ppm, you may have to adjust SHIFM*(2) to bracket this shift or input PPMSHF. (See the Index to find definitions of the Control Parameters SHIFMN, etc.)
- (2) In pathologies where Glyc is high (e.g., some tumors), you may want to add Glyc to the analysis. This is discussed in Sec 8.2.1.1.
- (3) Referencing landmarks PPMREF(*,2) are 3.03, 3.22, 1.28 & 0.90 ppm; i.e., lipids replace NAA.
- (4) Because of the unpredictable spectra, the Preliminary Analysis uses all metabolites (rather than the usual NUSE1 ones).
- (5) NRATIO = 13; i.e., a "soft constraint" on NAAG/NAA is added.
- (6) NAMREL = 'GPC'; i.e., the ratios to total cholines (rather than to Cr) will be output.

The above settings are only initial defaults. You can overwrite them by inputting your own Control Parameters. For example, if you input

```
NAMREL = 'Cr'
SPTYPE = 'tumor'
```

you overrule Setting (6) above.

9.2 Muscle Spectra

9.2.1 Standard Input

LCModel will not work with apodized spectra (Sec 3.6.4). Spatial apodization with CSI is acceptable, but not frequency (spectral) apodization.

Normally, you use water suppression.

LCMgui users input the Control Parameters below using Fig 7.7 in Sec 7.3.4. For muscle spectra it is essential that you input the following extra Control Parameters:

```
SPTYPE = 'muscle-5'
PPMEND = -1.0
PPMST = 3.8
```

If your spectrum does not go down to -1.0 ppm (i.e., you get the diagnostic "FATAL INITIA 3"), increase PPMEND to be about 0.3 ppm inside the end of the spectral range. However, to fully include the main lipid peaks and some adjacent

baseline, keep `PPMEND` < 0 . In future measurements, be sure to increase the spectral bandwidth so that you can go down to -1.0 ppm. At 2.9T, you need a bandwidth greater than 1200 Hz; you need at least 1800 Hz.

If you want to estimate E55 & I53 (the lipid components around 5.5 and 5.3 ppm) you could input `PPMST=8.0`. Your residual water peak should not strongly overlap with I53.

9.2.2 Additional Input

9.2.2.1 Dummy .BASIS file

LCMgui users can select any valid file name for the .BASIS file in Fig 6.4; it is not used. All basis spectra are automatically simulated inside LCMModel. For example, you could click “Change BASIS” in Fig 6.4, activate “Show Hidden Files” in the upper right of the .BASIS file selector (similar to Fig 6.1). Then select `$HOME/.lcmmodel/test/output/test.basis`. This only needs to be set once.

9.2.2.2 *Ex Vivo* spectra

If your VOI is at room temperature, input

`ROOMT = T`

9.2.2.3 Eddy-current correction

Normally, you do not do eddy-current correction (ECC). ECC assumes a pure water reference signal. Large lipid signals invalidate this assumption and can cause artifacts. LCMModel automatically switches off ECC for muscle and lipid spectra (even if you have selected ECC). You can force ECC by inputting `FORECC = T`.

With Philips data, in the “post proc” page, setting “Spectral correction” to “no” will switch off ECC.

9.2.2.4 Water-Scaling

For Water Scaling, you must also acquire an unsuppressed water reference spectrum from the same voxel immediately before or after the water-suppressed spectrum. LCMgui users can activate the “Do water-scaling” button in Fig 6.4 (Sec 6.3.4). Otherwise you could input

`DOWS = T`

Bruker users must use Sec 10.2.2.1. Users with all other scanners must also use Sec 10.2.2.1 if the total gains in the suppressed and unsuppressed spectra are different. However, in the correction factor, use only the *Gain* ratio, not the *NS* ratio, which is only needed with Bruker. You can set `ATTH20` to this correction factor (without the 0.7 factor, since the default value of `ATTH20` is 1.0 with `muscle-5`).

Section 9.3.2.1 specifies how to convert from resonance areas to (less convenient) concentrations.

9.2.2.5 Referencing

You only need to read Sec 9.2.2.5 if the LCModel output spectrum is shifted to an incorrect referencing shift.

LCModel uses the Cr peak for referencing. If the Cr peak at 3.03 ppm is not clearly dominant in this region, you could instead try referencing to the residual water peak, provided it is within about 0.05 ppm of 4.65 ppm. You then input

```
DOREFS(1) = T
DOREFS(2) = F
```

If the water peak cannot be used and the Cho peak around 3.2 ppm is higher than the Cr peak at 3.03 ppm, you could try referencing to Cho by not inputting DOREFS and instead inputting:

```
PPMREF(1,2) = 3.2
```

Instead of the above, you could reference to the maximum over the whole range of 3.8 ppm to -1.0 ppm. This is often EMCL at 1.52 ppm. You then input

```
PPMREF(1,2) = 1.52
```

Instead of the above, you can specify the referencing shift with PPMShf (Sec 11.3.3).

9.2.2.6 Phasing

Phasing can also be difficult without a strong Cr peak. If you have prior phasing information you should definitely use it (Sec 9.7) with SDDEGP. (This is all automatically done with single-voxel GE, Picker & Canon/Toshiba data.)

9.2.3 Output

See PLOT 8 in \$HOME/.lcmodel/doc/figures.pdf.

With Water-Scaling, the **Conc.** column of the Concentration Table has the ratio of the metabolite resonance area to the unsuppressed water resonance area. (The term “resonance area” is used instead of “peak area,” since LCModel attempts to resolve overlapping signals, even when they form only one combined peak.)

Without Water-Scaling, only resonance area ratios, such as IMCL13/Cr, are meaningful.

The resonance areas of the following signals are in the Concentration Table:

IMCL13 : the IMCL CH₂ signal around 1.3 ppm

EMCL15 : the EMCL CH₂ signal around 1.5 ppm

- Cr** : the Cr CH₃ signal around 3.03 ppm. However, some of the (orientation-dependent) Tau signal may also contribute to this signal [29]. Similarly, some Cr CH₃ signal may be spread to around 2.8–2.95 ppm (roughly estimated by **cr28**) and to around 3.1–3.2 ppm, where it overlaps with the signal from cholines (total roughly estimated by **cho**).
- I09** : IMCL CH₃ signal around 0.9 ppm.
- E11** : EMCL CH₃ signal around 1.1 ppm.
- Water** : water signal; this value is useless in the usual case of water suppression. In addition, a residual suppressed water signal is sometimes so distorted that the models cannot fit it well.
- I53** : IMCL signal around 5.3 ppm.
- E55** : EMCL signal around 5.5 ppm.
- I21** : total signals similar to IMCL3 and IMCL4 in [30, Fig 2] in the region 1–3 ppm, mainly visible as a broad hump around 2.0–2.5 ppm. These are important to avoid overestimating EMCL15 & IMCL13, as simple peak integration would do.
- E23** : total signals similar to EMCL3 and EMCL4 in [30, Fig 2] in the region 1–3 ppm, mainly visible as a broad hump around 2.0–2.5 ppm. These are important to avoid overestimating EMCL15 & IMCL13, as simple peak integration would do.
- tau** : total signal (possibly Tau) in the region 3.3–3.6 ppm.
- cr39** Cr CH₂ signal around 3.93 ppm, but this is often strongly distorted, and there are often other poorly defined signals in this region.

Please also note the following:

- As with all peak-fitting methods (in contrast to LCModel analyses of brain), restricted empirical models are used, and the %SD values are much more strongly underestimated (Sec 11.1). Therefore, only %SD values below 5% are output in boldface
- Some analyses can take much longer, because of the search for optimal phase corrections. The diagnostic ‘‘**info TWOREG 12**’’ signals a very detailed search.

9.3 Lipid Spectra (Liver, Breast, Bone, etc.)

The four SPTYPES, **lipid-8**, **liver-11**, **breast-8** & **only-cho-2**, are similar and are specified together here. They are summarized in Sec 9.1. It is essential that you read Sec 9.3.2 on output and carefully follow Sec 9.3.1 on input. Additional instructions for **only-cho-2** (to estimate choline only) are in Sec 9.3.3.

LCModel will not work with apodized spectra (Sec 3.6.4). Spatial apodization with CSI is acceptable, but not frequency (spectral) apodization.

9.3.1 Input

LCMgui users can select any valid file name for the .BASIS file in Fig 6.4; it is not used. All metabolites are automatically simulated inside LCModel. Section 9.2.2.1 gives a suggestion.

LCMgui users input the Control Parameters below using Fig 7.7 in Sec 7.3.4.

You must always input the following:

```
SPTYPE = ??  
PPMST = ??  
PPMEND = -1.0
```

If your spectrum does not go down to -1.0 ppm (i.e., you get the diagnostic “FATAL INITIA 3”), increase PPMEND to be about 0.3 ppm inside the end of the spectral range. However, to fully include the main lipid peaks and some adjacent baseline, keep PPMEND < 0. In future measurements, be sure to increase the spectral bandwidth so that you can go down to -1.0 ppm. At 2.9T, you need a bandwidth greater than 1200 Hz; you need at least 1800 Hz.

Input SPTYPE='lipid-8' or SPTYPE='liver-11' or SPTYPE='breast-8' or
SPTYPE='only-cho-2'

PPMST is very important. It is specified in Secs. 9.3.1.2 & 9.3.1.1.

Often you want to estimate ratios of metabolite resonance areas to water. You then need a spectrum without water suppression, and there are two possibilities:

9.3.1.1 Two spectra: Separate water-reference spectrum

You acquire a water-suppressed spectrum and an additional unsuppressed water reference spectrum from the same voxel immediately before or after the water-suppressed spectrum (GE Probe, Picker and Canon/Toshiba do this automatically.)

- (1) Normally, you input:

```
PPMST = 3.6 when SPTYPE='lipid-8' or  
PPMST = 3.8 when SPTYPE='breast-8' or  
PPMST = 4.0 when SPTYPE='liver-11'
```

If you also want to estimate the lipids around 5.3 ppm, you instead input:

```
PPMST = 8.0
```

(For SPTYPE='only-cho-2' see Sec 9.3.3.)

- (2) Do Water-Scaling using Sec 9.2.2.4.
- (3) Eddy-current correction is automatically suppressed (Sec 9.2.2.3).
- (4) If you have prior knowledge about the phase corrections, be sure to input this with SDDEGZ, SDDEGP, DEGZER, DEGPPM (Sec 9.7). (This is automatically done with GE Probe and Picker data.)

If you cannot do Water-Scaling [Step (2) above], you must use ratios of the metabolites (Sec 9.3.2).

9.3.1.2 One spectrum: Single spectrum with no water suppression

The Two-Spectra Method is usually preferable. In principle, this One-Spectrum Method is attractive because the additional water peak allows better phasing, referencing and consistent resonance area ratios to water. However, it should only be used if the lipid peak around 1.3 ppm is usually at least 25% the height of the water peak. Otherwise, the water signal can dominate the analysis at the expense of the accuracy of the other metabolites, especially the weaker ones.

You acquire a single spectrum without water suppression (with as many scans as you usually use for water-suppressed spectra).

Alternatively, with GE Probe data, you can use Sec 7.4.5.1 to analyze only the (many) unsuppressed data frames using the Preprocessor `use-unsuppressed`, documented in `$HOME/.lcmode/gelx/preprocessors/use-unsuppressed`.

For consistency in a study, it is important to always use exclusively the One-Spectrum Method of this section or the Two-Spectra Method of Sec 9.3.1.1, not both.

With the One-Spectrum Method, you also must input

PPMST = 8.0

If your spectrum does not go up to 8.0 ppm (i.e., you get the diagnostic “FATAL INITIA 3”), decrease PPMST to be about 0.3 ppm inside the spectral range. However, keep $\text{PPMST} \geq 7.0$ to fully include the water peak and enough adjacent baseline.

9.3.1.3 Excising residual water

If you also want to estimate Lip53+Lip52 (Sec 9.3.2), you should use the Two-Spectra Method (i.e., with water suppression). For several of your representative spectra, use the “Preview Data” button in Fig 7.2 (Sec 7.4.1) to display the absolute-value spectrum between 7 ppm and 1 ppm. If the residual water peak is strongly distorted (e.g., with an extra peak or shoulder), then use `DOWATR=F` below. Otherwise, it is best to let LCMODE fit the residual water peak, since it will tend to handle its overlap with Lip53+Lip52 better than if this water peak is cut out using `DOWATR=F`. Consistently use the same value for `DOWATR` for an entire study.

`DOWATR` (LOGICAL) `DOWATR=F` will not analyze the data between 5.0 ppm and 3.6 ppm (4.0 ppm when `SPTYPE='liver-11'`).
Default: `DOWATR = T`.

9.3.1.4 Measurements at room temperature

`ROOMT` (LOGICAL) Set `ROOMT=T` if your VOI is around room temperature (e.g., *ex vivo*).
Default: `ROOMT = F`

9.3.2 Output

See PLOT 11 in `$HOME/.lcmode1/doc/figures.pdf`.

The main output is in the (top-right) Concentration Table. All concentrations are measured as resonance areas of the metabolite. (The term “resonance area” is used instead of “peak area,” since LCMODEL attempts to resolve overlapping signals, even when they form only one combined peak.) The main differences between the four SPTYPE are which metabolites are present in the analysis:

Lip13 : lipid signal around 1.3 ppm.

Lip09 : lipid signal around 0.9 ppm; usually difficult to resolve from Lip13.

Lip16 : lipid signal around 1.6 ppm. At most resolutions, this is considered part of Lip13. Thus for “fat” you would probably use Lip16+Lip13 or L16+L09+L13 in the output table.

Lip21 : lipid signal around 2.02 ppm.

Lip23 : lipid signal around 2.23 ppm; this often cannot be resolved from Lip21.

Lip28 : lipid signal around 2.75 ppm.

Lip41 : lipid signal around 4.1 ppm.

Lip43 : lipid signal around 4.3 ppm. Lip41 & Lip43 are weak and only seen with high resolution and signal/noise.

Water : around 4.65 ppm, if PPMST = 8.0. This value is only meaningful when the spectrum is unsuppressed (i.e., with the One-Spectrum Method).

Lip53 : lipid signal around 5.3 ppm.

Lip52 : lipid signal around 5.2 ppm. This can almost never be resolved from Lip53, and only the sum Lip53+Lip52 should be used.

Cho : signal from choline-containing compounds around 3.2 ppm (omitted when SPTYPE='lipid-8'). PLOT 10 in `$HOME/.lcmode1/doc/figures.pdf` is from breast.

Glycg : (formerly called Glyu) (only with SPTYPE='liver-11'): signals in the region 3.5–3.9 ppm. Part of these may be due to glycogen.

Clearly the sums, like Lip16+Lip13, are used in the output, because they are more accurate than the parts, Lip16 and Lip13.

In the Concentration Table, the meanings of **Conc.** (1st column) and the resonance area ratios (3rd column) depend on your input of PPMST and DOWS=T (Water-Scaling):

With Water-Scaling, the **Conc.** column has the ratio of the metabolite resonance area to the unsuppressed water resonance area. The 3rd column has the heading /L16+L0 (for ratios to the total resonance area of Lip16+Lip09+Lip13); you can change to other ratios using Sec 9.9.1.2.

Without Water-Scaling, the **Conc.** column has the resonance areas, generally, in unknown (useless) units. If PPMST < 5.0, the 3rd column has the heading /L16+L0 (for ratios to Lip16+Lip09+Lip13). If PPMST ≥ 5.0, the 3rd column may instead

have the heading `/Water`; this is only meaningful if you are using the One-Spectrum Method with no water suppression.

Obviously PPMST around 5.0 is never used; it is either at least 7.0 to fully include the water signal or not exceeding 4.0 to exclude the water signal.

Please also note the following:

- As with all peak-fitting methods (in contrast to LCModel analyses of brain), restricted empirical models are used, and the %SD values are much more strongly underestimated (Sec 11.1). Therefore, only %SD values below 5% are output in boldface.
- Some analyses can take much longer, because of the search for optimal phase corrections. The diagnostic “`info TWOREG 12`” signals a very detailed search.
- These analyses require more work than brain, and `info` diagnostics about `Working Hard` (Sec 12.2) are common (as in PLOT 9).

9.3.2.1 Resonance areas vs. concentrations

Two of the three cases above give you $Ratio_{area}$, the ratio of the metabolite resonance area to the unsuppressed water resonance area. If you want to convert this to $Conc_{met}$, the concentration of the metabolite groups, in mM, for example:

$$Conc_{met} = Ratio_{area} \times (2/N1H_{met}) \times (ATTH20/att_{met}) \times WCONC$$

$N1H_{met}$ is the number of equivalent protons contributing to the resonance, e.g., $N1H_{met} = 2$ for mM of CH_2 groups (not mM of lipid molecules). This becomes meaningless for `Lip16+Lip09+Lip13`, which has CH_3 (`Lip09`) and CH_2 (`Lip13` & `Lip16`) groups; therefore resonance areas are more convenient.

$ATTH20$ & att_{met} are the factors (< 1) by which the water and metabolite resonance areas are attenuated by relaxation. With Case (2) above, $ATTH20$ might also have to correct for the decreased total gain of the unsuppressed water-reference spectrum compared to the water-suppressed spectrum (see Sec 9.2.2.4).

$WCONC$ is the water concentration (in mM) in the voxel, and this is usually difficult to guess.

9.3.3 Estimating only choline

Particularly in breast, fat suppression can distort the lipid signals around 1.3 ppm (and possibly 2.0 ppm as well), making their quantitation meaningless. Usually water suppression is also necessary. The only interesting undistorted signal is then Cho around 3.2 ppm.

You can then estimate the Cho by following Sec 9.3.1.1, except Step (1), where you input the following:

```
SPTYPE = 'only-cho-2'
PPMST = 3.8
PPMEND = 2.7
```

PPMST and PPMEND are also very important.

9.3.3.1 Referencing

There is one prerequisite: water suppression must be balanced as follows: It must be strong enough so that the baseline around 3.8 ppm does not climb or fall towards the residual water signal. It must be weak enough so that the residual water peak is not significantly shifted from the original; i.e., the maximum must still be within about 0.05 ppm of 4.65 ppm. This is necessary, because the water peak is used for preliminary referencing; Cho cannot be used, since it can be undetectable (e.g., in healthy tissue).

However, if the water suppression is too strong and the water peak is too distorted, you could try referencing with Cho by inputting:

```
DOREFS(1) = F
DOREFS(2) = T
SHIFMN(2) =  $\overline{shift} - 0.2$ 
SHIFMX(2) =  $\overline{shift} + 0.2$ 
```

where \overline{shift} is the expected value of the referencing shift (often zero). Extend the above two by 0.2 if the possible range (Sec 11.3.5) is greater than 0.2 ppm, but keep them as small as your prior knowledge allows.

A more direct way is to specify the referencing shift with PPMSHF (Sec 11.3.3).

9.3.3.2 Rejection criterion

Even when Cho is absent, you will often get a (small) peak (fitting noise). This is also normal with weak metabolites in brain spectra. The difference is that, with this empirical fit to a single peak, the %SD value is underestimated (Sec 9.3.2) and cannot be used as a rejection criterion (Sec 2.1). Instead, you might consider a (signal/noise) $S/N < 2$ to indicate that Cho is undetectable. S/N is output in the “MISCELLANEOUS OUTPUT” table (Sec 2.4).

9.4 MEGA-PRESS for GABA

This is for the MEGA-PRESS specified in [7]. PLOT 12 in `$HOME/.lcmmodel/doc/figures.pdf` shows an example.

9.4.1 Input

9.4.1.1 Necessary input

You select the final difference spectrum.

Your input is simply:

```
SPTYPE = 'mega-press-3'
PPMST = 4.2
```

PPMEND = 1.95

(LCMgui users use Fig 7.7 in Sec 7.3.4.)

The above PPMEND cuts off dangerous artifacts that usually occur between 1.95 and 1.2 ppm. Only if they are nearly absent, as in PLOT 12, can you use PPMEND=0.2. With PPMEND=1.95, part of the NAA peak is truncated. However, LCModel uses the complete spectra, not peak integration, and the incomplete NAA peak can still provide an accurate estimate.

If you also want to quantify the macromolecule peak around 0.9 ppm (MM09), e.g., to get a rough idea of the contribution of macromolecules to the peak around 3 ppm: You can cut out most artifacts by inputting (Sec 11.11):

PPMEND = 0.2

PPMGAP(1,1) = 1.95

PPMGAP(2,1) = 1.2

9.4.1.2 Additional necessary input with Philips files

With Philips MEGA-PRESS files be sure to also input:

IAVERG = 34

or (for earlier versions):

IAVERG = 3

since the data set is usually a series of alternating “on” and “off” spectra that are summed using IAVERG=3 or subtracted using IAVERG=34. If you are unsure which to use, try both; only one will give reasonable results. (Sec 11.9.2).

With IAVERG=34 an LCMgui window starting with “Do you really want to ...” appears. Click “Yes”. SDAT files are preferred.

If you switch from MEGA-PRESS to other data, be sure to delete IAVERG in Fig 7.7.

If you are doing Water Scaling be sure to input

ATTH20 = 0.86

as explained in Sec 9.4.1.4.

SDAT users can usually skip this paragraph. The MEGA-PRESS data set is stored as a CSI data set. The total number of spectra (say, 40) in the data set is given in the “Only for multi-voxel ...” panel in Fig 6.4. With SDAT files, this is usually the “Total data columns:”, and nothing has to be done. However, with DICOM files, this is usually “Total data Slices:”, and you must instead enter this number as “Total data columns:” and change “Total data Slices:” to 1, since LCModel only analyzes 1 CSI “slice” at a time. (Of course, you must also set 40 in “Selecting Columns 1 through 40”.)

You can preview the data set by clicking the “Preview Data” button. You can get a squarer preview by first changing the rows and columns in the panel in Fig 6.4 from 1×40 to 5×8 . The analysis is not affected by this.

You can also do a separate analysis of the “off” spectra with a standard PRESS basis set. You input either:

`IAVERG = 32`

to sum only the even spectra (i.e, when the first spectrum is “on”) or

`IAVERG = 31`

to sum only the odd spectra (i.e, when the first spectrum is “off”). If in doubt preview the data. You can also try both; the wrong choice will show almost no NAA.

9.4.1.3 Analyses of “off” spectra

You can also do a standard PRESS analysis of an “off” spectrum. However, the scaling of the MEGA-PRESS and “off” concentrations will be different, since the basis sets are different. Therefore to take even a concentration ratio of one metabolite from a MEGA-PRESS spectrum to one from an “off” spectrum (e.g., GABA/Cr), you must do Water Scaling (Sec 9.4.1.4) in both analyses.

9.4.1.4 Water-Scaling

For this you need in addition an unsuppressed water reference spectrum acquired from the same voxel immediately before or after the water-suppressed spectrum. It must be an “off” spectrum, not a difference spectrum. You input

`DOWS = T`

(With LCMgui, you use Sec 6.3.4.) Except for Philips, you select the difference water-suppressed spectrum to be analyzed and then, as water reference, the “off” unsuppressed spectrum. With Philips, you select the suppressed and unsuppressed SDAT files. In all cases, the 2 files must have identical format. With Philips files, they must have the same number of spectra.

The unsuppressed water relaxation attenuation is automatically accounted for by ‘mega-press-3’ internally with the factor (Secs. 10.2.2 & 11.2)

$$\text{ATTH20} = \exp(-\text{TE}/\text{T2}) = \exp(-68/80) = 0.43$$

(For TE = 80 ms you could input ATTH20 = 0.37)

With Philips files and `IAVERG=34` or `IAVERG=3`, you must double this and input `ATTH20 = 0.86`, because two spectra (“on” and “off”) are used to compute the water-suppressed difference spectra, whereas full water peaks are present in all the unsuppressed water spectra. (With a standard PRESS analysis of the “off” spectra (using `IAVERG=31` or `IAVERG=32`), only half the spectra in both the suppressed and unsuppressed are used, and you do not double `ATTH20`.)

The T1 relaxation times of water and the metabolites are similar and would therefore approximately cancel (Sec 10.2.1); so, corrections are often neglected. In principle, you still would have to correct the absolute concentrations for the significant T2 relaxation of the metabolites. In view of all of these uncertain relaxation corrections, it is best to consistently use the same sequence and corrections. Then, even if you skip some corrections, you should hopefully still be able to see increases or decreases (e.g., with pathologies), even if your concentrations are in your “institutional units” instead of mM.

9.4.1.5 Basis set

Your basis set should contain GABA, Gln, Glu, GSH, NAA & NAAG. You can acquire phantom data (not recommended) or simulate them. Sec 8.6.5 specifies how to do both.

9.4.2 Output

Without Water-Scaling, only the concentration ratios (e.g., GABA/NAA+NAAG) are meaningful, unless the sequence, voxel size and total gain are assumed constant over the study. Even then, the units of the macromolecule estimate (if you use $PPMEND \leq 0.6$) are different from those of the metabolites in the upper part of the table.

The signal around 3 ppm has a significant contribution from macromolecules as well as GABA. This apparent GABA concentration is often called GABA+ [8].

Because of the simplified models, the %SD values are underestimated more than usual. Therefore, only %SD values below 5% are output in boldface.

9.5 Internal Logical Units

(LCMgui users can skip Sec 9.5.) Table 9.1 summarizes the files used by LCModel. They are defined in more detail in other parts of this manual.

The pathnames are specified by Control Parameters beginning with FIL, listed in the column headed “Filename”. You must always input the Control Parameters for the names of all files that you will use. If you forget this input, then no Fortran OPEN will be executed.

These files have internal Fortran unit numbers given by Control Parameters beginning with the letter L (in the “Unit” column of Table 9.1). The only allowed input values of these Control Parameters are in the column headed “Alt”, i.e., to enable output (with a positive number) or disable output (with zero) of a file. It is essential that two files do not have the same positive unit number.

The entries in the column headed “Extension” are only the conventions used in this manual; you are free to use others.

9.6 Eddy-Current Correction

Eddy-current correction (ECC) is automatically done by Philips if you set “spectral correction” to “yes” on the “post proc” page; you can then skip Sec 9.6.

This is recommended for single-voxel (not CSI) data. (LCMgui users can skip Sec 9.6 and instead read Sec 6.3.3.) ECC requires that a second set of raw time-domain data

Table 9.1: Control Parameters for Filenames and Logical Units

Filename	Unit	Default	Alt.	Extension	I/O	Needed when
<i>none</i>	LCONTR	5		.CONTROL	Input	Always
FILBAS	LBASIS	3		.BASIS	Input	Always
FILRAW	LRAW	1		.RAW	Input	Always
FILH2O	LH2O	2		.H2O	Input	DOECC=T or DOWS=T
FILPS	LPS	8	0	.PS	Output	LPS > 0
FILCOO	LCOORD	0	9	.COORD	Output	LCOORD > 0
FILCOR	LCORAW	0	10	.CORAW	Output	LCORAW > 0
FILPRI	LPRINT	0	6	.PRINT	Output	LPRINT > 0
FILTAB	LTABLE	0	7	.TABLE	Output	LTABLE > 0
FILCSV	LCSV	0	11	.CSV	Output	LCSV > 0

be acquired with each set of *in vivo* data. This second set (called the *Unsuppressed Data*) is acquired with exactly the same protocol, but without water suppression. It must be acquired from the same voxel, immediately before or after the water-suppressed acquisition. Details are in [10]. You can have LCModel do ECC as follows:

DOECC (LOGICAL) (“do eddy-current correction”) .TRUE. to do the eddy-current correction in LCModel. Default: DOECC = F.

FILH2O (CHARACTER*255) the name of the file containing the time-domain Un-suppressed Data (e.g., ‘pat_777_77.h2o’). This file has the same format as the .RAW file.

9.7 Prior Phasing Information

LCMgui users with GE Probe data can skip Sec 9.7; the settings are done for you. GE Probe users using the SAGE/LCModel interface must make the entries specified in Sec 7.2.5.3.

LCModel spends much of its time in an elaborate *Preliminary Analysis* to get good starting values for the phases and referencing shift for the *Final Analysis*, where the final concentration estimates are made. LCModel runs faster if you have prior information on the approximate phase corrections. More importantly, this prior information can rescue spectra with weak NAA, creatine & choline landmarks, such as in PLOTs 6 & 13 in \$HOME/.lcmmodel/doc/figures.pdf, that might otherwise fail (although these particular cases also worked without this prior information).

As specified below, you impose this prior information as an expectation value and its standard deviation. Recommendations for several types of scanners were given in Sections 5.3.4 & 5.3.5. Section 9.7.1 suggests how you can experimentally estimate the next four values:

DEGZER (REAL) your expected value for the zero-order phase correction, ϕ_0 (using the definition of **DEGZER** in Sec 8.5.2) in the range 0.0–360.0.
Default: **DEGZER** = 0.

SDDEGZ (REAL) the standard deviation (i.e., the uncertainty) in your expectation value **DEGZER** (in degrees). A normal (Gaussian) prior probability distribution is used; so ϕ_0 can wander about three standard deviations from its expectation value, **DEGZER**, if the data demand this. The four degrees of strength with which you can impose this prior information are (in decreasing order of strength):

SDDEGZ ≤ 1 . fixes ϕ_0 to **DEGZER** (with a standard deviation of 0.0, not 1.0). This is not recommended; a little freedom is better:

SDDEGZ ≤ 22 . will increase the speed of the Preliminary Analysis by a factor of 4. This is the most common strength for imposing prior knowledge.

SDDEGZ < 45 . will cause LCModel to start looking for ϕ_0 at **DEGZER**.

SDDEGZ ≥ 45 . will not affect the starting points of the search in parameter space.

Default: **SDDEGZ** = 999.; i.e., effectively no prior information.

DEGPPM (REAL) your expected value for the first-order phase correction, ϕ_1 (using the definition of **DEGPPM** in Sec 8.5.2). Default: **DEGPPM** = 0.

SDDEGP (REAL) the standard deviation in your expectation value of **DEGPPM** (in degrees/ppm). See the discussion of **SDDEGZ** above. The 4 levels of strength with which you can impose this prior information (in decreasing order) are:

SDDEGP ≤ 0.4 fixes ϕ_1 to **DEGPPM** (with a standard deviation of 0.0, not 0.4). This is not recommended; a little freedom is better:

SDDEGP ≤ 7 . will increase the speed in the Preliminary Analysis by a factor of 3. This is the most common strength for imposing prior knowledge.

SDDEGP < 10 . will cause LCModel to start looking for ϕ_1 at **DEGPPM**.

SDDEGP ≥ 10 . will not affect the starting points of the search in parameter space.

Default: **SDDEGP** = 20.; i.e., only a weak bias toward reasonably small ϕ_1 values. Do not use **SDDEGP** > 20 ; it can destabilize the analysis.

DGPPMN, **DGPPMX** (REAL) These define the lower and upper limits (in degrees/ppm) of the range over which LCModel will start looking for ϕ_1 . (**SDDEGP** may, of course, further restrict this range.) If **DEGPPM** above is non-zero, input

$$\text{DGPPMN} = \text{DEGPPM} - 30.0$$

$$\text{DGPPMX} = \text{DEGPPM} + 30.0$$

$$\text{SDDEGP} = 30.0/1.5$$

Increase 30.0 above if the possible range (Sec 9.7) is greater than ± 30.0 .

Defaults: **DGPPMN** = -30., **DGPPMX** = 30.

9.7.1 Estimating Appropriate **SDDEGZ**, **SDDEGP**, **DEGZER** & **DEGPPM**

The prior phasing information in **SDDEG*** and **DEG*** can speed up and improve your analyses.

You can estimate appropriate values for these by doing a series of LCModel analyses on a large number of your best *in vivo* spectra. Do not use any prior phasing information. Compute the means and standard deviations of the LCModel phase corrections (3rd line in the “MISCELLANEOUS OUTPUT” table, and use these means & SDs for DEGZER, DEGPPM and SDDEGZ, SDDEGP. The SDDEG* will tend to be too large, because of the extra scatter due to the noise in your data; that is the reason to use your best spectra.

Always use $\text{SDDEGZ} \geq 2$. and $\text{SDDEGP} \geq 1$.

If LCModel strongly disagrees with your constraints in future analyses, then you will get warning FINOUT 10 or FINOUT 11. Follow the suggestions for these diagnostics in Sec 12.2.

9.8 Specifying the Basis Spectra for the Analysis

9.8.1 Omitting Basis Spectra from the Analysis

Normally all Basis Spectra in the .BASIS file are used by LCModel. If some of these are very unlikely to be detectable in your spectrum, then you should exclude these from this analysis, as follows:

NOMIT (INTEGER) the number of metabolites to be excluded. You can exclude Basis Spectra in the .BASIS file, as well as simulated spectra.
Default: NOMIT = 0.

CHOMIT (CHARACTER(100)*6) the first NOMIT elements contain the Metabolite Names of the spectra to be excluded.

For example, some pathologies have Glyc much stronger than Ins, at least at long *TE* (Sec 8.2.1.1). You add a simulated Gly by inputting (Sec 11.7):

```
NSIMUL = 14
```

and you may want to omit Ins (Sec 8.2.1.1) with:

```
NOMIT=1  
CHOMIT(1)='Ins'
```

CHCALI & NCALIB (Sec 8.7.1) are much more convenient to use when you want to omit all but one or a few of the Basis Spectra, e.g., for calibration analyses.

9.8.2 Keeping Basis Spectra in the Analysis

When PPMST or PPMEND restricts the Analysis Window, LCModel automatically omits from the analysis metabolites that are weakly represented in the Analysis Window (e.g., Lac & Ala in PLOT 16 in [\\$HOME/.lcmmodel/doc/figures.pdf](#)). You can force some of these to be included as follows:

NKEEP (INTEGER) the number of metabolites that are to be kept in the current analysis, regardless of the ppm-range of the Analysis Window. You can include Basis Spectra in the .BASIS file, as well as simulated spectra.
Default: NKEEP = 0.

CHKEEP (CHARACTER(300)*6) the first NKEEP elements contain the Metabolite Names of the spectra to be kept in the analysis.

For example,

```
NKEEP=1
CHKEEP(1)='Lac'
```

in the .CONTROL file would keep Lac in the current analysis, even if PPMEND > 1.41 (not recommended).

9.9 One-Page Output

9.9.1 Concentration Table

9.9.1.1 Concentration Sums

It is important to have separate Basis Spectra for all metabolites that have a chance of being resolved, even if they are poorly resolved, e.g., NAA and NAAG. However, the sum of the concentrations of metabolites with similar spectra can be much more accurately determined than the individual concentrations, and it is important to also output these sums, together with their %SD values, in the concentration table.

NCOMBI (INTEGER) (“no. of combinations”) the number of sums that you want output in the Concentration Table. Default: NCOMBI = 16.

CHCOMB (CHARACTER(100)*56) the first NCOMBI elements specify the metabolite concentrations to be summed, as a string with the Metabolite Names separated by '+' with no spaces. There can be up to six Metabolite Names in the sum. (Although long CHCOMB may be truncated in the Concentration Table, the full sums will be used.)
Default: CHCOMB = 'GPC+PCh', 'GPC+Cho', 'PCh+Cho', 'Cho+GPC+PCh', 'NAA+NAAG', 'Ins+Glyc', 'mI+Glyc', 'Ins+Gly', 'mI+Gly', 'Cr+PCr',

```
'Cre+PCr', 'Glu+Gln', 'Lip13a+Lip13b', 'MM14+Lip13a+Lip13b+MM12',
'MM09+Lip09', 'MM20+Lip20'
```

For example, Thr & Lac are very strongly correlated. If you want to also output the total Thr+Lac concentration, then (with the above defaults) you input:

```
NCOMBI=17
CHCOMB(17)='Thr+Lac'
```

Unlike NAA and NAAG, the main peaks of the Glyc and Ins have different effective numbers of protons [17], which means that the Concentration Sum could have up to about a 15% error if Glyc is mistaken as Ins or *vice versa*. So, for consistency, you normally do not have Glyc in the Basis Set (Sec 8.2.1.1); it is poorly resolved from Ins anyway.

The same goes even more so for GABA and Glu+Gln. The GABA signal is much weaker. So, you should not consider the sum GABA+Glu+Gln; it can fluctuate strongly, because of the unreliable GABA concentration estimate.

At higher fields (3T and above) and resolution, Glu & Gln are well resolved, and the sum Glu+Gln is unnecessary (but it does no harm). If the %SD for the sum Glu+Gln is lower than that of both Glu and Gln, then Glu and Gln are strongly enough correlated that the sum Glu+Gln is useful.

9.9.1.2 Concentration Ratios

You can output the concentration ratio relative to any desired metabolite as follows:

NAMREL (CHARACTER*56) (“name for relative concentration”) the Metabolite Name corresponding to the concentration in the denominator of the ratio. It can also be one of the Concentration Sums in **CHCOMB**. Default: **NAMREL** = **'Cr'**.

CONREL (REAL) The third column in the Concentration Table is actually the ratio multiplied by **CONREL**, but the default is **CONREL** = 1.0. If you want to output absolute concentrations in the third column assuming that, say, the total creatine concentration was 6.5, then you would simply input **CONREL** = 6.5

LCModel attempts to automatically make reasonable extensions to your **NAMREL**. For example, **NAMREL** = **'Cho'** will be replaced with a Concentration Sum of all that are present of Cho, PCh, GPC. Similarly, the creatines will be extended to include all of Cr, Cre, PCr.

9.9.1.3 Fonts & Colors

ISDBOL (INTEGER) (“Integer SD for boldface”) A line in the Concentration Table will be in boldface if its %SD (rounded to the nearest integer) is less than **ISDBOL**.

Default: `ISDBOL = 20`

RGBBOL (REAL(3)) (“RGB for boldface”) The boldface line defined by `ISDBOL` will be in the color defined by `RGBBOL` (as explained below).

Default: `RGBBOL = 0.0, 0.0, 0.999`; i.e., blue.

RATIPM (REAL) If a ratio with a Concentration Ratio Prior (Sec 11.8) is more than `RATIPM` standard deviations from its expectation value, then a + or a - is inserted before the Metabolite Name in the table (+ if higher, - if lower). The line in the table is bold red italic. This is common with the highly variable lipid & macromolecule components.

Default: `RATIPM = 2.0`

RGBRAT (REAL(3)) (“RGB for ratio priors”) The bold italic line defined by `RATIPM` will be in the color defined by `RGBRAT` (as explained below).

Default: `RGBRAT = 0.999, 0.0, 0.0`; i.e., red.

The three elements of `RGBBOL` & `RGBRAT` specify the fractions of red, green & blue, respectively. For example,

1.0, 0.0, 0.0 is red.

0.0, 0.0, 1.0 is blue.

0.0, 0.0, 0.0 is black (*not* 1,1,1).

These fractions must always be in the range 0.0–1.0. (I input 0.999 instead of 1.0, since Namelist input can have slight rounding errors.)

9.9.2 Diagnostics Table

Diagnostics of type **warning** are output in boldface in the color specified by `RGBBOL`.

RGBERR (REAL(3)) (“RGB for errors”) RGB specification for the color of diagnostics of severity **ERROR** and higher.

Default: `RGBERR = 0.999, 0.0, 0.0`; i.e., red.

9.9.3 Plot

The Control Variables in this subsection allow you to tailor the plots, e.g, for slides or publications.

9.9.3.1 Individual Metabolite Contributions

You can get separate plots for the contributions of individual metabolites to the data (as in PLOTs 3 & 4 in `$HOME/.lcmmodel/doc/figures.pdf`). This can be useful for a detailed evaluation, e.g., of the compatibility of your data with the Basis Spectra.

NEACH (INTEGER) the number of metabolites for which individual plots are to be made.
Default: **NEACH** = 0.

NAMEAC (CHARACTER(60)*6) the first **NEACH** elements contain the Metabolite Names for the individual plots. If **NEACH** \geq (the total number of Basis Spectra in the analysis), then individual plots are made for all metabolites, and you do not need to input anything for **NAMEAC**.

9.9.3.2 Dimensions

The overall page dimensions for your One-Page Output are usually best set by inputting **PGNORM** as 'US' or 'A4' (Sec 5.3.6). Only if you leave **PGNORM** = ' ' are the following two Control Parameters used (e.g., for specifying non-standard page dimensions):

PAGEHT (REAL) the height of your page in cm. Default: **PAGEHT** = 27.9, i.e., 11 inches.

PAGEWD (REAL) the width of your page in cm. Default: **PAGEWD** = 21.0.

LANDSC (LOGICAL) ("Landscape") .TRUE. if the ppm-axis is determined by the page height. Default: **LANDSC** = T; this is almost always correct; i.e., if you think of the ppm-axis as horizontal, then you can think of the page being rotated 90°, and **PAGEHT** now defining the width.

XLEFT, **XRIGHT** (REAL) the margins (in cm) on the left and right of the page; i.e., the ppm-axis will be shortened by these amounts. Defaults: **XLEFT** = 1.3, **XRIGHT** = 1.3

YTOP, **YBOTT** (REAL) the margins (in cm) at the top and bottom of the page.
Defaults: **YTOP** = 1.5, **YBOTT** = 1.3

9.9.3.3 Lettering

Lettering dimensions are specified in points (about 1/72 inch):

PTTITL (REAL) the size of the title at the top of the page; Default: **PTTITL** = 11.

PTLABL (REAL) the size of the axis labels; Default: **PTLABL** = 7.8

PTOUTP (REAL) the size of the lettering in the tables. Reducing **PTOUTP** will increase the space for the ppm-axis; each line in the tables still has the same number of characters. Inputting a small value, like **PTOUTP**=0.001, will make the tables invisible, e.g, for a slide or figure.
Default: **PTOUTP** = 7.8

The vertical space from one line of lettering to the next is given by the following factors multiplying the lettering size; e.g., a factor of 1.0 is a little closer than single spacing; a factor of 2.0 is almost double spacing:

RHTITL (REAL) title spacing; Default: **RHTITL** = 1.5

RHLABL (REAL) axis-label spacing; Default: **RHLABL** = 1.2

RHOUTP (REAL) table spacing; Default: **RHOUTP** = 1.3

RHVERS (REAL) spacing of the lines with your laboratory name and the version number of LCModel at the top of the page. Default: **RHVERS** = 2.

9.9.3.4 Curves

The following dimensions are all in cm:

WDLIN (REAL(6)) these six elements give the curve thicknesses for the:

- (1) fit to the data;
- (2) Baseline; the plot of the Baseline can be suppressed (e.g., for figures) with **WDLIN(2)** = 0.
- (3) data;
- (4) Residuals;
- (5) axes and frame;
- (6) fine grid lines. The vertical grid lines will be suppressed if **WDLIN(6)**=0., e.g., for a slide or figure.

Defaults: **WDLIN** = .06, .01, .005, .01, .04, .005

RGBLIN (REAL(3,6)) **RGBLIN(J,K)** (J=1,2,3) is the RGB color specification for the curves of Type K, using the Type numbering of **WDLIN**.

Default: **RGBLIN(1,1)** = 0.999; all other elements are 0.0. Thus line Type 1 (the fit to the data) is red, and all the others are black.

DSHPAT (REAL(2,2)) **DSHPAT(JDASH, JCURVE)** specifies the dashed pattern for the fine grid lines when **JCURVE** = 1 and for the data when **JCURVE** = 2. The length of the dashes is given by

DSHPAT(1, JCURVE), and the space between the dashes by **DSHPAT(2, JCURVE)**. If either of the lengths is non-positive, then a solid curve is drawn.

Defaults: **DSHPAT** = .05, .1, 2*0.

SUBBAS (LOGICAL) ("subtract Baseline") **SUBBAS** = T subtracts the Baseline from the data and the fit before plotting them. This can help visualizing the fit if the water suppression is very weak and the Baseline is much larger than the metabolite peaks. Default: **SUBBAS** = F

9.9.3.5 ppm-Axis

XSTEP (REAL) the positive increment between the numbers on the ppm-axis.

Default: **XSTEP** = 0.2.

NSUBTK (INTEGER) the number of fine grid lines in going from one number to the next on the ppm-axis. Default: **NSUBTK** = 2.

9.9.4 Miscellaneous Output Table

More information can be output in this table. I used this during development and testing.

IETCOU (INTEGER) maximum number of lines that will be output in this table.

Default: **IETCOU** = 3

The first three lines have already been described in Sec 2.4. The further lines in this table are:

- (4) **alphaB,S**: α_B and α_S in [1, Eq (4)].
- (5) **spline knots**: N_B in [1, Eq (1)];
Ns: The number in parentheses is δn , the increment in n in the sum in [1, Eq (1)].
The sum runs over $n = \delta n(-Ns, -Ns + 1, \dots, Ns - 1, Ns)$. Except for broad line-shapes (or excessively long acquisition times per scan), $\delta n = 1$ and $Ns = N_S$.
- (6) **infls**: the number of inflection points in a typical lineshape;
extrs.: the number of extrema in this lineshape;
Numbers in parentheses are the corresponding values at an initial stage. The concentrations are determined by an integral over the lineshape, and this is a well-determined quantity, even if the lineshape itself has several extrema [19].

Chapter 10

Absolute Metabolite Concentrations

You only need to read this chapter if you want to estimate absolute concentrations. Concentration ratios are not affected by any of the settings in this chapter.

Note that, in addition to the scaling correction discussed in this chapter, you must also correct for relaxation (Sec 11.2) and partial volume effects (Sec 10.2.2.3). Concentration ratios are less sensitive to these effects; you should consider ratios at least as supplemental data.

The LCModel concentrations estimate how much of each Basis Spectrum is in the *in vivo* data. Since the Basis Set and the *in vivo* data are generally not acquired under identical conditions (scanner, coil loading, etc.), their scaling is different, and the LCModel concentrations will all be off (e.g., from mM) by an unknown *Scale Factor*. Therefore, for meaningful absolute concentrations, the *in vivo* data must be first scaled by this factor, so that they are consistent with the Basis Spectra.

To determine this Scale Factor, LCModel/LCMgui provides help with two different strategies:

Calibration Phantoms: Data from a phantom of (say) NAA with a known concentration is analyzed periodically. The Scale Factor is simply the factor necessary to make the LCModel NAA concentration come out correctly. (Sec 10.1)

- Generally, can only be used with Siemens Vision [17] and 1.5 T GE data [20] (but not phased-array data).
- An absolute method: Still requires accurate absolute scaling of each spectrum for voxel size and changes in total gain due to coil loading, etc. LCMgui only does this for Siemens Vision & GE data — and even here, on the assumption that methods in Sec 10.1.1 are exact.

Water-Scaling: The resonance area of the unsuppressed reference water signal (together with the assumed water concentration) is used [21, 22] (Sec 10.2).

- + A ratio method: Several sources of error, such as voxel size and hardware changes are automatically eliminated. Relaxation effects (especially T_1 effects) are reduced.
- + Very convenient: just click the “Do water-scaling” button (but also check Control Parameter settings in Sec 10.2.2).
- + No calibrations with phantoms.
- Requires large uncertain corrections for water concentration and relaxation, possible instrumental attenuation of the unsuppressed water signal, etc. (Sec 10.2.2).
- Automatically done by LCMgui with GE single-voxel phased-array data.
- For data other than Siemens Vision or 1.5T GE (unless you can do your own scaling for instrumental effects, as in Sec 10.1.1).
- For data where voxel size is uncertain.
- For convenience and simplicity.

10.1 Calibration Phantoms

The Scale Factor, for scaling data consistently with each other, actually has two factors:

intra-hardware: to account for differences in acquisition conditions (e.g., coil loading) with the same hardware that change the total effective gain (Sec 10.1.1).

inter-hardware: to scale the data with the Basis Set, to account for hardware changes or different hardware (Sec 10.1.2).

10.1.1 Data Scaling (intra-hardware)

Each data set (.RAW file, Sec 5.2.2) is scaled by the factor `TRAMP/VOLUME`. LCMgui computes `VOLUME` as the VOI volume (in mL) from the GE, Marconi/Picker, Philips & Siemens headers.

`TRAMP` must then be inversely proportional to the total gain, accounting for varying acquisition conditions, so that a given number of protons always produces the same resonance area in each spectrum.

10.1.1.1 Siemens Data

The following only works with Siemens Vision data: `TRAMP` is set equal to the RF transmitter amplitude of a non-selective 90° reference pulse (rectangular and 0.5 ms

in duration) [17]. For Siemens Vision data, LCMgui sets **TRAMP** to the “raw” file header element **G19.Acq3.Mr.TransmitterCalibration**.

You cannot use this with other Siemens data. The above **TRAMP** is meaningless in the usual case that the transmit and receive coils are not the same. For non-Vision files, **TRAMP** is simply set to 1.0. Also, **VOLUME** is not correctly obtained for multi-voxel DICOM files (use **.rda** files). And, of course, headerless **.raw** files have no such information. So, you would have to use Water-Scaling or a more elaborate calibration procedure [23].

10.1.1.2 GE data

The following formulas are used for all GE data, but they reportedly do not accurately describe the behavior with *TG* at 3T. So, Calibration Phantoms should only be used at 1.5T. With 3T data (and all phased-array data), you would have to use Water-Scaling (Sec 10.2).

With GE Signa 5.x systems, LCMgui uses

$$\text{TRAMP} = 2^{(6-R1)+(30-R2)} \times 10^{0.005(TG-65)}$$

where I have arbitrarily chosen $R1 = 6$, $R2 = 30$ and $TG = 65$ to be the reference point where **TRAMP** = 1.0. (This reference point is unimportant, since it is consistently used for all **TRAMP**.)

With GE Signa LX data, $R1$ is replaced by $R1/2$:

$$\text{TRAMP} = 2^{(6-R1/2)+(30-R2)} \times 10^{0.005(TG-65)}$$

10.1.1.3 Data Other than Siemens Vision or 1.5 T GE

Except for Siemens and GE data, LCMgui simply sets **TRAMP**=1.0. Therefore, you would have to do one of the following:

- Use Water-Scaling (Sec 10.2).
- Compute your own **TRAMP**, e.g., using a more elaborate calibration procedure [23].

10.1.1.4 Fine Points

In addition to [17], there are detailed literature references, studies, alternatives and refinements to determining **TRAMP**, e.g., [24, 25, 26, 27]. You could incorporate most of these into LCMgui, either with a Preprocessor (Sec 7.4.5) or with your own **my-bin2raw** (Sec 7.4.4).

10.1.2 Scanner Calibration (inter-hardware)

Even if your Basis Spectra were scaled as in Sec 10.1.1, there will still be a second unknown calibration factor, if they were acquired on another scanner. Furthermore, the properties of your scanner may change with time, and you must periodically redetermine the factor scaling your Basis Set to data acquired on your scanner.

By using the simple method below, you can compute the following calibration factor:

FCALIB (REAL) (“factor for calibration”) This will multiply your data being analyzed to correct for scaling differences between your Basis Set and your data.

Default: **FCALIB** = 1.0

(This could also be done by multiplying **TRAMP** in the .RAW file by this factor, but **FCALIB** is more convenient, and it is documented in your One-Page Output.)

Make a calibration phantom with 50 mM NAA in the solution in Sec 8.2.4 (except that DSS and formate are unnecessary). Don’t forget NaN_3 , if you want to store the phantom (at low temperature). You will also have to bring the pH up to 7.2 (e.g., with NaOH).

Analyze a spectrum from this phantom with LCMModel, using the following Control Parameters (in addition to the usual HZPPPM, NUNFIL, DELTAT, FIL*, etc, which are usually automatically set by LCMgui):

```
NCALIB=1
CHCALI(1)='NAA'
FCALIB=1.0
NSIMUL=0
```

Let C_{lcm} be the concentration output by LCMModel, and let C_{true} be the true concentration in the phantom (e.g., 50 mM). Then, for your future analyses input

$$\text{FCALIB} = C_{true}/C_{lcm}$$

Repeat this calibration every few months at the beginning to see how rapidly it changes with time.

This **FCALIB** is not only restricted to this Basis Set, but also to the bandwidth and acquisition time per scan of the calibration phantom acquisition. LCMModel can automatically adapt the Basis Set to changes in these, but the scaling also changes. So, if (for some reason) you are using more than one bandwidth in time or frequency, then you need an **FCALIB** for each.

10.2 Water-Scaling

10.2.1 Method

With Water-Scaling, LCModel multiplies the data by f_{scale} to scale the data consistently with the Basis Set (i.e., so that the signal strength per proton resonance is the same in both). This is the ratio of the normalized signal strength in the Basis Set to the normalized unsuppressed water signal in the data:

$$f_{scale} = Basis_{norm}/Water_{norm}$$

A normalized signal is the measured resonance area divided by the concentration of protons and by the factor (< 1.0) by which the measured signal is attenuated through relaxation, etc.

$$Basis_{norm} = Area_{met}/[N1HMET \times Conc_{met} \times ATTMET]$$

where $Area_{met}$ is the observed resonance area of the selected singlet in the basis set (by default, the Cr CH₃), $N1HMET$ is the number of equivalent protons contributing to the selected singlet, $Conc_{met}$ is the model metabolite concentration in the basis set, and $ATTMET$ the attenuation factor of the singlet used in the (*in vitro*) basis set.

Similarly,

$$Water_{norm} = Area_{water}/[2 \times WCONC \times ATTH20]$$

As specified below, $N1HMET$ and $Conc_{met}$ are known, the two $Area$ terms are computed by LCModel from the data, but $ATTH20$ and $WCONC$ must be guessed.

10.2.2 Usage

With LCMgui, You activate Water-Scaling by activating the “Do water-scaling” button in Fig 7.2, which sets `DOWS=.TRUE.:`

DOWS (LOGICAL) (“Do Water-Scaling”) `DOWS = T` to activate Water-Scaling. You definitely know whether or not Water-Scaling has been done by the presence or absence of the “Doing Water-Scaling” message in the **DIAGNOSTICS** table in the LCModel output.

Default: `DOWS = F`.

Note that `DOWS` is automatically switched off (overriding any input of `DOWS`) if any of the following conditions exists:

No unsuppressed water reference is available;

`NCALIB > 0` or `BASCAL = .TRUE.` (indicating an internal basis calibration run);

`FCALIB` \neq 1.0 (indicating that the Calibration Phantom method of Sec 10.1 is being used).

`WCONC` and `ATTH20` below are difficult to guess correctly. This means that all of your concentrations will still be off by an unknown factor (even if you also use Sec 11.2 to correct for metabolite relaxation). You therefore obtain concentrations in unknown “institutional units”, all differing from mM by typically 20% or more (much more with $TE > 35$ ms or $TR < 3000$ ms). However, if relaxation times and acquisition parameters do not change much during a study, then this factor may not change much either, and you may still get reasonably consistent measures of absolute con-

centrations (in your “institutional units”) that are useful at detecting, e.g., increases or decreases in pathologies.

WCONC (REAL) the NMR-visible water concentration (mM) in the voxel. This is $55556\beta_{MR}$ in [28], where typical values were 35880 for white matter and (a 21% larger) 43300 for gray matter. Default: **WCONC** = 35880.0.

There is no reason to measure phantoms, but, if you did, you would obviously use
WCONC = 55556.

ATTH20 (REAL) the attenuation of the NMR-visible water signal due to additional relaxation effects and other effects, such as transmitter amplifier “leakage” [22, p. 337] or the extra attenuation in the Gain of the unsuppressed water spectrum. In this last case, you must include the factor

$$Gain_{unsuppressed}/Gain_{suppressed}$$

in **ATTH20**. The default value of **ATTH20** is 0.7; so, for example, if the above gain ratio were 0.5, you would input **ATTH20** = 0.35. Thus, **ATTH20** must contain all corrections that affect the unsuppressed water reference, but not the water-suppressed signal.

(Equal effects in both unsuppressed and suppressed signals cancel out, because the unsuppressed signal is in the denominator of f_{scale} in Sec 10.2.1, and f_{scale} multiplies the suppressed signal.)

However, there are probably big relaxation corrections, since Ernst *et al.* [28] found the major water compartment with $T2 \approx 80$ ms. This alone would imply **ATTH20**=0.7 when $TE = 30$ ms, since $\exp(-TE/T2) = \exp(-30/80) \approx 0.7$

This is partially compensated by your multiplying each concentration output by LCMModel by $\exp(TE/T2)$, where $T2$ is now that of the metabolite, but this is often ignored when $TE \leq 35$ ms (Sec 11.2).

You can probably ignore $T1$ relaxation, at least for $TR \geq 4000$ ms, since $T1$ is approximately the same for water and the metabolites, and the two corrections then partially cancel.

Default: **ATTH20** = 0.7.

There is no reason to measure phantoms, but, if you did, you should input **ATTH20** = 1.0, because of the long $T2$ of water *in vitro* [28].

ATTMET (REAL) the attenuation of the singlet used in the selected Basis Spectrum (specified below with **WSMET**, etc.) The relaxation effects will be smaller than for **ATTH20**, at least with short TE , since the metabolites *in vitro* usually have longer $T2$ than water *in vivo*. Also, the Basis Spectra should have been acquired with $TR \geq 6000$ ms; so, you can usually use the:

Default: **ATTMET** = 1.0

PPMH20 (REAL) the position (in ppm) of the unsuppressed water peak. This is only needed if Water-Scaling fails, usually with the diagnostic “**WSCALE** 1”. Without LCMgui, plot the unsuppressed water spectrum in **FILH20**. With LCMgui, (if necessary, click “Reload Data” in Fig 7.2), select the unsuppressed water file, click “Preview Data”, and display the absolute-value spectrum from 99 ppm down to -99 ppm (range automatically shrinks). If the water peak is more than 1 ppm from 4.65 ppm, input **PPMH20**.

Default: **PPMH20** = 4.65

You probably will not want to change the following:

- WSMET** (CHARACTER*6) (“Water-Scaling metabolite”) the name of the metabolite whose singlet in the Basis Set will be used for scaling. Default: **WSMET** = ‘Cr’.
- WSPPM** (REAL) the chemical shift (in ppm) of the singlet used for scaling. Default: **WSPPM** = 3.027.
- N1HMET** (INTEGER) the number of equivalent protons contributing to the singlet used for scaling. Default: **N1HMET** = 3

10.2.2.1 Bruker ParaVision 6 Data

PV6.0 is missing information for Water Scaling; use PV6.0.1 (or higher). LCMgui does not divide the Bruker data by the total gain, *Gain*. With Water-Scaling, you must multiply the LCModel concentrations by the factor

$$(Gain_{unsuppressed}/Gain_{suppressed})$$

Most convenient is to include this correction in LCModel, by inputting **ATTH20** multiplied by this factor. Then the output concentrations are already multiplied by this factor. The default value of **ATTH20** is 0.7; so, for example, if the above factor were 0.2, you would input **ATTH20** = 0.14.

In the file **acqp**: Do not use **RG**, as in older PV versions. Instead:
Gain_{suppressed} = the 5th value in the line following **ACQ-jobs** = ...

In the file **method**:

$$Gain_{unsuppressed} = PVM_RefScanRG$$

This is usually missing with CSI data; you may be able to use **PVM_NavRg**, but this reportedly sometimes produces obviously incorrect scaling of the absolute concentration estimates.

10.2.2.2 Bruker ParaVision 5 Data (and lower)

LCMgui does not divide the Bruker data by the number of scans, *NS*, or by the total gain, *Gain*. With Water-Scaling, you must multiply the LCModel concentrations by the factor

$$(NS_{unsuppressed}/NS_{suppressed}) \times (Gain_{unsuppressed}/Gain_{suppressed})$$

More convenient is to include this correction factor in LCModel, by inputting **ATTH20** multiplied by this factor, as above in Sec 10.2.2.1.

With PV5, you should be able to do the following: Set the parameter **PVM_RefScanYN** to **Yes**. The unsuppressed water reference is then in the file **fid.refscan**. In the file **method**:

$$PVM_RefScanNA = NS_{unsuppressed}$$

$$PVM_RefScanRG = Gain_{unsuppressed}$$

In the file **acqp**:

$$NA = NS_{suppressed}$$

$$RG = Gain_{suppressed}$$

10.2.2.3 Partial-Volume Correction

Many do not bother with this. The partial-volume correction is often small, and the segmentation of the VOI into classes is seldom accurately known. You may at least want to consistently assume the same segmentation, unless you have clear knowledge of a different segmentation.

Suppose you segment into 3 classes: f_{gm} , f_{wm} and f_{csf} , with $f_{gm} + f_{wm} + f_{csf} = 1$, where f_{csf} is the volume fraction of the VOI with a nearly pure water signal. Then, instead of WCONC suggested in Sec 10.2.2, you would input

$$\text{WCONC} = \frac{43300f_{gm} + 35880f_{wm} + 55556f_{csf}}{1 - f_{csf}}$$

The numerator is simply the total water concentration in the VOI. The additional factor $1/(1 - f_{csf})$ is not part of the water concentration; it is the partial-volume correction. It corrects for the fact that the metabolites are practically all concentrated in the gray matter and white matter. You can see from the equations in Sec 10.2.1 that WCONC multiplies f_{scale} , and therefore the absolute concentrations output will then already have the partial-volume correction.

Chapter 11

Fine Points

This chapter contains a collection of further topics and options. Scan the section headings. Topics that are of more restricted interest or that have been included mainly for completeness are in smaller print.

11.1 Error Estimates & Reproducibility

The standard error estimates, %SD (Sec 2.1) are also called Cramér-Rao lower bounds (from the Cramér-Rao inequality). In practice, the most important limitation of these lower bounds is not the nonlinearity of the model or the finite amount of data mentioned in the textbooks that makes them “lower bounds.” A far bigger problem is that these lower bounds (and most statistical tests) assume that the *model is correct* (or at least *sufficiently parameterized* to describe the data), and this is seldom true in biological systems.

Methods that fit, say, a linear baseline plus a Lorentzian to each “peak” give too optimistic lower bounds, because the models are wrong (over-simplified). There are usually more complicated lineshapes & baselines, and each “peak” is generally a mixture of several metabolite signals. And regardless of the quantitation method, there are numerous possible systematic errors, such as relaxation and partial-volume effects. So, although these %SD are useful guides, all of these limitations and additional sources of error must be kept in mind.

Reproducibility can also be misleading. For example, the LCModel baseline can automatically account very well for a missing or incorrect macromolecule model, with good data [16]. With poorer data, the baseline becomes flatter (because there is no longer sufficient information to determine the baseline detail), and the concentration estimates systematically get worse. Methods always using flat baselines can yield more reproducible (consistently wrong) results, with deceptively low coefficients of variation. Flexible baselines are needed to compensate for the inevitable variability,

particularly of macromolecule and lipid signals. The (higher) coefficient of variation using (the more realistic) LCModel should yield more realistic statistical tests.

11.1.1 Averaging Concentrations over a Series of Analyses

In computing an average concentration of a metabolite from a series of analyses, you should include all values (even those with higher %SD). You could do a weighted average over the series of analyses [31]:

$$\bar{C} = \sum w_j C_j / \sum w_j, \quad w_j = 1/\sigma_j^2, \quad \sigma_j = (\%SD)_j \times C_j / 100$$

with an estimated standard deviation

$$\sigma(\bar{C}) = 1/\sqrt{\sum w_j}$$

The C_j are constrained to be nonnegative; their minimum allowed value is zero. When a $C_j = 0$, SD cannot be easily estimated [11], and %SD is arbitrarily output as 999. You might take an unweighted average in this case. The \bar{C} of a metabolite that has zeroes will probably have a large relative uncertainty and not be useful anyway.

11.2 Relaxation Corrections

The main message of this section is to use short echo times ($TE \leq 30$ ms) and long repetition times ($TR \geq 4000$ ms). This avoids (or at least reduces) the complications below.

In practice, the corrections below are often ignored anyway, because of the uncertainties in the relaxation times, particularly *in vivo* and especially in pathologies. You can still attempt to use uncorrected concentrations to establish norms, provided that you keep TE and TR fixed. If the relaxation times do not change much during a study, then you may still get consistent measures of absolute concentrations in “institutional units,” all deviating from mM by the same (unknown) factor. These can then be useful at detecting increases or decreases in pathologies, etc. Concentration ratios are less sensitive than absolute concentrations to relaxation effects.

With acquired basis sets, you would also have to include the *in vitro* relaxation. For example, you account for T_2 relaxation by multiplying your LCModel concentrations by

$$f_{TE} = \frac{\exp(-TE/T_{2_{vitro}})}{\exp(-TE/T_{2_{vivo}})} = \exp \left[TE \left(\frac{1}{T_{2_{vivo}}} - \frac{1}{T_{2_{vitro}}} \right) \right]$$

Simulations usually have effective *in vitro* $T_2 = \infty$ and $T_1 = 0$, so that only the *in vivo* relaxation must be accounted for. Concentration ratios have the advantage that

the exponents contain only differences of relaxation times between the two metabolites.

If you use Water-Scaling (Sec 10.2) you can probably ignore the TR correction below (and in ATTH20 in Sec 10.2.2), since the two corrections approximately cancel. Otherwise, you must also multiply the LCModel concentrations by the correction factor for TR , which for STEAM is

$$f_{TR} = \frac{[1 - \exp(-RD_{vitro}/T1_{vitro})]}{[1 - \exp(-RD_{vivo}/T1_{vivo})]} \exp \left[TM \left(\frac{1}{T1_{vivo}} - \frac{1}{T1_{vitro}} \right) \right]$$

where $RD = TR - TM - TE/2$, or to good approximation for both PRESS & STEAM:

$$f_{TR} = \frac{1}{1 - \exp(-TR_{vivo}/T1_{vivo})}$$

since we require $TR_{vitro} \gg T1_{vitro}$ for the basis set. This correction factor usually becomes unimportant with $TR_{vivo} \geq 5000$ ms.

11.3 Prior Referencing Information

Spectra without the usual landmark peaks of NAA, Cr & Cho, can be difficult to reference automatically. The settings in Sec 9.1 can often help. If not, in case of a referencing failure (which often looks like PLOT 17 in `$HOME/.lcmmodel/doc/figures.pdf`), you can often salvage the spectrum by helping LCModel with more specific referencing information. Try the following, in the order listed:

11.3.1 Off-Resonance Spectra

If the center frequency of your spectra is further away from the water resonance than expected by default (about 0.1 or 0.2 ppm), and you sometimes get results like PLOT 17 in `$HOME/.lcmmodel/doc/figures.pdf`, use:

PPMCEN (REAL) is the ppm value at the center of the spectrum (to within about 0.1 ppm).

Default: PPMCEN = 4.65

It may be absolutely necessary to input PPMCEN if your spectral bandwidth is so narrow (and the frequency offset so large) that the Analysis Window would otherwise appear to be at the edge of your spectrum.

Note that if you do eddy-current correction (Sec 6.3.3 or 9.6), you normally must not use PPMCEN; the referencing shift is usually corrected by ECC. This assumes that the unsuppressed water-reference spectrum has about the same shift as the water-suppressed spectrum. If the water-reference spectrum is not shifted, then you cannot use PPMCEN; you can only use PPMShf (Sec 11.3.3).

11.3.2 Referencing to Water

If your water suppression is not too extreme, it is convenient to use the huge water peak as an approximate referencing landmark. You can check this by plotting several of your spectra with PlotRaw (LCMgui users, see Sec 7.4.1) to see if there is a reasonable water peak around 4.65 ppm. The water peak need not be exactly at 4.65 ppm, and it can be distorted, since it only tells LCMModel where to start looking. But it cannot have been totally removed, e.g., by some digital filter; there must always be a clear maximum in the correct region. If a reasonable water peak is present, then you can use this (at least in problem cases) for referencing by setting the Control Parameter

`DOREFS(1) = T`

You may also have to extend the maximum expected shift with `SHIFMN(1)` or `SHIFMX(1)` in Sec 11.3.5. This could be a universal solution for all of your analyses, where you automatically input `DOREFS(1)` and `SHIFMN(1)` or `SHIFMX(1)` in every `.CONTROL` file.

11.3.3 Inputting a Starting Shift

Less automatic, but more direct, is to plot the absolute value of the spectrum. With LCMgui, you can use “Preview Data” (Sec 7.4.1). Otherwise input `DOREFS=2*F` to LCMModel, as in PLOT 5 in `$HOME/.lcmmodel/doc/figures.pdf`. From the plot, estimate the referencing shift. You can then directly impose this starting shift with `PPMSHF`.

`PPMSHF (REAL)` (“shift in ppm”) LCMModel will start looking for the referencing shift at `PPMSHF` (remember the LCMModel convention that a positive shift shifts the data toward higher ppm). LCMModel will start its search only at this one shift; the usual elaborate grid search is suppressed. (Note that the disaster in PLOT 17 was provoked by using a grossly incorrect `PPMSHF`).

Before you go to the trouble of plotting the absolute value, you might simply try `PPMSHF=0.`; this is often close enough (except for phantoms at room temperature, which usually need a `PPMSHF` \approx 0.18).

If the magnitude of `PPMSHF` exceeds the total ppm-range of your Analysis Window (obviously a senseless value), then `PPMSHF` is not used, and the usual grid search is performed.

Default: `PPMSHF = 1.E37`; i.e., `PPMSHF` is not used.

An example: Suppose the Cho peak, which should be at 3.2 ppm is fit as Cr at 3.03 ppm. We need to shift Cho from 3.03 to 3.2; i.e., by +0.17. However, suppose the table MISCELLANEOUS OUTPUT shows `Data shift = -0.050`; i.e., the observed spectrum has already been shifted by -0.050. Therefore the total shift of the original spectrum must be `PPMSHF=0.17-0.05=0.12`.

11.3.4 Fixing the Shift

The very first estimate of the starting shift is from the cross-correlation function (CCF) described in Sec 11.3.5. The Preliminary Analysis then refines this. If the spectrum is poor (e.g., with the usual landmarks very weak), the Preliminary Analysis may wander away and find a bad shift. You can override the Preliminary Analysis and fix the shift to that from the initial CCF:

FIXSHF (LOGICAL) **.TRUE.** to fix the shift to be that from the CCF.

Default: **FIXSHF** = F, except for **FIXSHF** = T with **SPTYPE** = 'muscle-5', since muscle is especially difficult to automatically reference.

The most drastic measure is if **PPMSHF** is also input with **FIXSHF**=T; then even the CCF is overridden, and the shift is fixed at the input **PPMSHF**. You must then be much more accurate with your input **PPMSHF** than when **FIXSHF**=F.

11.3.5 Details of Automated Referencing

If you have to adjust the above settings from one analysis to the next, then you might find a universal solution with the following settings.

LCModel determines the grid over which it will search for the referencing shift using the cross-correlation function (CCF) with δ -functions described in [1, Appendix]. Two CCFs can be computed, the first using the water peak (even though it may be distorted due to water suppression), and the second using the typical metabolite landmarks.

DOREFS (LOGICAL(2)) **DOREFS(JCCF)** = F will exclude CCF JCCF.

If your residual water peaks are often strongly distorted or poorly defined (e.g., as sometimes with digital water suppression or in diffusion experiments) and if your spectra usually have well-defined landmarks (e.g., NAA, Cr, Cho, etc.), then you should avoid using the water peak by leaving **DOREFS(1)** = F.

On the other hand, if you are using weak water suppression, with a well-defined water peak, then it is best to set **DOREFS(1)** = T; if, in addition, the climb toward the residual water peak is strong enough so that the Baseline at 4.0 ppm is comparable to the Cr, Cho & NAA peaks, then you should also set **DOREFS(2)**=F. Plotting the absolute value of a few spectra with "Preview Data" in LCMgui (Sec 7.4.1) can help you make this decision.

Default: **DOREFS** = F, T; i.e., water is not used, and the usual metabolite landmarks are used.

NREFPK (INTEGER(2)) **NREFPK(JCCF)** is the number of δ -functions (reference peaks) for CCF JCCF. It cannot exceed 10. Default: **NREFPK(1)** = 1 (for water) and **NREFPK(2)** = 3 (for the usual landmarks, listed below).

PPMREF, **HZREF** (REAL(10,2)) the position of δ -function JREF for CCF JCCF is

PPMREF(JREF,JCCF) + **HZREF(JREF,JCCF)**,
where **PPMREF** is in ppm and **HZREF** is input in Hz.

Defaults: **PPMREF(1,1)** = 4.65 (for water);

PPMREF(JREF,2) = 2.01, 3.03, 3.22 (for NAA, Cr & Cho);

all **HZREF** elements zero.

To use the Lac doublet, input two `PPMREF = 1.33` and the corresponding two `HZREF = 3.6 & -3.6`. However, lipid signals can be mistaken as Lac and distort the referencing.

The elements of `PPMREF(JREF,2)` should increase with `JREF`, since `NREFPK(2)` is automatically decremented if problems at high ppm due to incomplete water suppression are detected.

`SHIFMN (REAL(2)) SHIFMN(JCCF)` is the minimum (in ppm) allowed endpoint for the referencing-shift grid obtained from CCF `JCCF`. Default: `SHIFMN = -0.2, -0.1`.

`SHIFMX (REAL(2)) SHIFMX(JCCF)` is the maximum (in ppm) allowed endpoint for the referencing-shift grid obtained from CCF `JCCF`. Default: `SHIFMX = 0.3, 0.3`.

`NSHIFT (INTEGER)` the maximum number of different starting points from the referencing-shift grid. (The referencing-shift grid itself is much finer.) Each new starting point is the grid point farthest from all preceding parameter trajectories. You must have `NSHIFT ≤ 25`.

Default: `NSHIFT = 8`.

11.4 Multi-Voxel Data Sets

11.4.1 GE CSI data

For GE CSI data sets, use the Research Version of SAGE, which now has Mary McLean's LCModel interface [9]. When using this SAGE/LCModel interface, a window titled "LCModel Analysis" appears. See Sec 7.2.5.3 for important necessary settings and discussion.

Section 3.4.1 discusses cases where you might want to set other values for "End PPM" (`PPMEND`).

11.4.2 Non-GE CSI data

Most other 2D & 3D CSI data sets can be handled by LCMgui. See Sec 3.7 for details. For other types of CSI data, you can make your own LCModel `.RAW` file, as specified in Sec 5.2.3.1.

With LCMgui or PlotRaw, you can select and display a rectangular subset of a slice and have LCModel analyze this subset (or the whole slice) in one multi-voxel run. An advantage of this is that LCModel first analyzes a central voxel of the subset and then works outwards, learning starting estimates and "soft constraints" for first-order phase corrections and referencing shifts from the preceding (often better) central voxels for the (often poorer) outer voxels. This can speed up and improve the analyses. You should still be selective with your subset; analyses of poor quality voxels can take several times longer than usual.

Without LCMgui, the Control Parameters in Sec 5.3.2 specify the dimensions of the CSI data set and of the rectangular subset.

11.4.3 Multi-Voxel Filenames

You input a single TITLE and single output filenames, but there will be one for each voxel. These are made unique as follows:

The `Slice#` (only for 3D sets) and `Row#` & `Col#` are inserted at the beginning of each TITLE.

A voxel identifier is inserted into every output filename. For `Slice#2`, `Row#3` & `Column#4`, the default identifier is `s12_3-4`, as used by Alger *et al.* [32]. The Postscript output file is then `s12_3-4.ps`.

11.4.3.1 Customizing Output Filenames

The placement of the identifier depends on the form of your input pathname. For example, FILPS normally ends with `ps`. There are three allowed cases:

```
dir/ps (default for LCMgui): dir/s12_3-4.ps
dir/filename.ps : dir/filename_s12_3-4.ps
dir/filename (neither of the above): dir/filename_s12_3-4
```

So, the identifier is of the general form

`CHSLIC#CHROW#CHCOL#`

where the `#` are slice number, row number & column number, respectively. You specify the identifier as follows:

```
CHSLIC (CHARACTER*9) Default: CHSLIC = 's1'
CHROW (CHARACTER*9) Default: CHROW = '_' (underscore).
CHCOL (CHARACTER*9) Default: CHCOL = '-' (minus sign).
```

11.4.3.2 Inconsistencies between LCModel and Scanner Labeling & Displays

LCModel strictly follows the DICOM standard: The order of voxels in a slice is from left to right, top to bottom. Thus, the upper left voxel (labeled 1,1) is followed by (1,2) and the rest of row 1, followed by the left voxel of row 2 (labeled 2,1) and so on.

With Siemens data, the LCModel voxels will be those of the CSI slice. They will also be those of the Siemens reference image, provided that the CSI slice has not been rotated with respect to the reference image.

Sometimes scanner displays are transposed; i.e., the rows and columns are interchanged. Sometimes the labeling is also changed from (row, column) to (column, row).

In some early scanner versions, the number of rows and columns is interchanged (in violation of DICOM), and it is necessary to also interchange the total number of rows and columns in Fig 6.4 (or, if LCMgui is not used, Sec 5.3.2) before starting LCModel.

11.4.4 Output for spreadsheets

As specified in Sec 11.4.3, each voxel has its own set of files. Only the `.CSV` file combines the concentration data from all voxels into a single file, which can be imported to spreadsheet programs.

With LCMgui, this file is produced automatically in your output directory. It has the extension `.csv`, and is usually named `spreadsheet.csv`. Without LCMgui, you specify it using Sec 5.3.7.2.

Often spreadsheet programs recognize the `.csv` extension and import it automatically. Each (wide) row contains all of the concentration estimates for one voxel. The first two columns contain the row and column numbers of the original multi-voxel grid. With Excel, OpenOffice.org & LibreOffice, you can easily sort these in ascending order. You can also select the table and then use the Format—Column—Autofit Selection (or Optimal Width) option to improve the column widths. In the Data menu, you can use Pivot Table (Excel) or Data Pilot to easily produce the 2D grid of, e.g., NAA+NAAG values.

11.4.5 Combining Multi-Voxel .PS files

You can combine all the files with names ending with `.ps` in a directory (e.g., `my-dir`) into a single file with the following commands:

```
cd my-dir
$HOME/.lcmodel/bin/cat-paged-ps
```

This produces the PostScript file `my-dir/cat-paged.ps`, which you can comfortably page through with your PostScript viewer (although the ordering may not be optimal with large subsets, e.g., with Row 10 coming before Row 2). You may want to set `IPAGE2 = 0` to get only one page per analysis. Use a PostScript viewer like `gv` or `evince`.

11.4.6 Skipping bad voxels

With LCMgui and LCModel version 6.3-0D and above, LCModel automatically skips to the next voxel when a voxel causes an abort in a multi-voxel analysis. It will do this up to `MAX_BAD=16` times before stopping. If necessary, you can change `MAX_BAD` in the Execution Scripts `standard` or `nice`. However, if there is an abort with the very first voxel, LCModel stops, so that you can check your input for gross errors. The settings below are no longer needed with version 6.3-0D and above.

You can skip over voxels as follows:

`NVOXSK` (INTEGER) the number of voxels to be skipped. Default: `NVOXSK = 0`
`ICOLSK` (INTEGER(64)) `ICOLSK(J)` specifies the column of the J'th voxel to be skipped.
`IROWSK` (INTEGER(64)) `IROWSK(J)` specifies the row of the J'th voxel to be skipped.

11.5 Basis Spectra in the Preliminary Analysis

The Preliminary Analysis for initial referencing and phasing uses a reduced set of Basis Spectra that are meant to contain only the major landmarks in the spectrum being analyzed. (Since crude Gaussian-Lorentzian lineshapes are used in this Preliminary Analysis, weak metabolites cannot be estimated anyway.) The Basis Spectra used for this Preliminary Analysis are specified as follows:

NUSE1 (INTEGER) the number of Basis Spectra that are to be used in the Preliminary Analysis.

Default: **NUSE1** = 5.

CHUSE1 (CHARACTER(300)*6) the first **NUSE1** elements contain the Metabolite Names of the spectra to be used. Default: **CHUSE1** = 'NAA', 'Cr', 'GPC', 'Glu', 'Ins'.

ECHOT (REAL) The echo time (in ms). If $\text{ECHOT} \geq 100.0$, then the default becomes **NUSE1** = 4, because of the weak Ins at long *TE*. However, you can override this by simply inputting your own value for **NUSE1**.

11.6 Unusual Phantoms

By default, LCModel assumes that the spectrum being analyzed contains dominating landmark resonances from NAA, Cr or Cho. These are used to get a starting point for referencing. A “unusual phantom” is one that has none of these landmarks dominating. You would never use such a phantom for calibration. With such a phantom, you must use the Control Parameters in the following three steps:

- (1) **VITRO=T**
- (2) You must also help with the referencing. There are two possibilities:
 - (2a) Suppose your phantom spectrum has a strong isolated resonance (say, at 3.33 ppm) that can be used for referencing. You then input the Control Parameters **NREFPK=1**, **PPMREF(1,2)=3.33**
 - (2b) Method (2a) could not be used if your phantom only had metabolites like Asp, GABA, Glc, Gln, Glu, or Tau. In this case, you must plot the spectrum with LCMgui’s “Preview Data” (Sec 7.4.1), and use **PPMSHF**, as described in Sec 11.3.3.
- (3) Suppose your unusual phantom contains metabolites with the Metabolite Names **Metab1**, **Metab2**, **Metab3**. There are two possibilities:
 - (3a) **NUSE1=3**, **CHUSE1(1)='Metab1'**, **CHUSE1(2)='Metab2'**, **CHUSE1(3)='Metab3'**.
 - (3b) More accurate and convenient is to use **NCALIB=3**, **CHCALI(1)='Metab1'**, **CHCALI(2)='Metab2'**, **CHCALI(3)='Metab3'** and **NSIMUL=0**. Then, **NUSE1**, **CHUSE1**, **VITRO** are automatically set for you.

11.7 Simulating Basis Spectra

By default, LCModel simulates (mainly lipid & macromolecule) Basis Spectra that are also included in the LCModel analysis. You can change these with the following:

NSIMUL (INTEGER) is the number of Basis Spectra that you will simulate.

Default: NSIMUL = 13.

CHSIMU (CHARACTER(60)*528) specifies the simulation parameters.

Defaults:

```
CHSIMU(1) = 'Lip13a @ 1.28 +- .01 FWHM= .15 < .2 +- .035 AMP= 2.'
```

```
CHSIMU(2) = 'Lip13b @ 1.28 +- .01 FWHM= .089 < .09 +- .035 AMP= 2.'
```

```
CHSIMU(3) = 'Lip13c @ 1.30 +- .01 FWHM= .089 < .09 +- .035 AMP= 2.'
```

```
CHSIMU(4) = 'Lip13d @ 1.26 +- .01 FWHM= .089 < .09 +- .035 AMP= 2.'
```

```
CHSIMU(5) = 'Lip09 @ .89 +- .02 FWHM= .14 < .19 +- .035 AMP= 3.'
```

```
CHSIMU(6) = 'MM09 @ .91 +- .02 FWHM= .14 < .17 +- .015 AMP= 3.'
```

```
CHSIMU(7) = 'Lip20 @ 2.04 +- .005 FWHM=.15 < .2 +- .025 AMP=1.33
```

```
           @ 2.25 FWHM=.15 AMP=.67
```

```
           @ 2.8 FWHM=.2 AMP=.87'
```

```
CHSIMU(8) = 'MM20 @ 2.08 +- .005 FWHM=.15 < .18 +- .01 AMP=1.33
```

```
           @ 2.25 FWHM=.2 AMP=.33
```

```
           @1.95 FWHM=.15 AMP=.33
```

```
           @ 3. FWHM=.2 AMP=.4'
```

```
CHSIMU(9) = 'MM12 @ 1.21 +- .01 FWHM= .15 < .2 +- .02 AMP= 2.'
```

```
CHSIMU(10) = 'MM14 @ 1.43 +- .02 FWHM= .17 < .2 +- .02 AMP= 2.'
```

```
CHSIMU(11) = 'MM17 @ 1.67 +- .03 FWHM= .15 < .17 +- .02 AMP= 2.'
```

```
CHSIMU(12) = '-CrCH2 @ 3.93 +- 0. FWHM= -9. < 0. +- 0. AMP= -2.'
```

```
CHSIMU(13) = 'Gua @ 3.78 +- 0. FWHM=-9.<0. +- 0. AMP=2.'
```

```
CHSIMU(14) = 'Glyc @ 3.55 +- 0. FWHM=-9.<0. +- 0. AMP=2.'
```

These are of the form

```
metabo @ ppm1 +- sdppm FWHM= fwmin1 < fwex +- sdfw AMP= amp1
```

```
@ ppm2 FWHM= fwmin2 AMP= amp2
```

```
...
```

metabo = the simulated Metabolite Name

*ppm** = the expectation ppm-value of peak *. There can be up to 20 peaks.

sdppm = the (positive) standard deviation of the shift in the simulated spectrum.

*fwmin** = the minimum (Gaussian) FWHM of peak *

fwex = the expectation FWHM of peak 1, which is exponentially (Lorentzian) broadened. All peaks in this Basis Spectrum get equal exponential broadening. You must input *fwmin1* < *fwex*.

sdfw = the (positive) standard deviation of the expectation *fwex*

*amp** = the effective number of protons contributing to peak *. The amplitudes are scaled consistently with the spectra in the .BASIS file using WSMET, WSPPM & N1HMET as in Sec 10.2.2. So, if the spectra in the .BASIS file are scaled to yield mM, then AMP = 2.0 would yield mM of CH₂ groups (not necessarily mM of molecules).

fwmin1 < 0 simulates (a sum of) singlets with the same FWHMBA as the Basis Spectra in the .BASIS file and with same (restricted) broadening (as with -CrCH₂ & Glyc above). In this case, only the input *metabo*, *ppm** & *amp** are used.

- The tokens @ +- FWHM= AMP= must be exactly as above, with only spaces between the entries; i.e., each CHSIMU must be in one line, with no new line, despite the incorrect multi-line printing of CHSIMU(7) & CHSIMU(8) above.

Notes:

- The numbers after Lip & MM above indicate the approximate ppm value of the main peak.
- The most important signals of Lip20 & MM20 are considered to be around

2 ppm. The respective AMP values in this region sum to 2.0, to estimate mM of CH₂ groups. The minor peaks at 2.8 & 3 ppm are counted separately.

- The easiest way to omit some of the above simulated Basis Spectra from the analysis is to use CHOMIT & NOMIT.
- At short *TE*, you should have PPMEND = 0.2 to include MM* as well as the lipids. If PPMEND > 0.6, most MMs and lipids are omitted. This can be overridden using Sec 9.8.2.
- If you acquire your own basis set, do not acquire any singlet spectra; simulate them. For example, for Scyllo input:
 NSIMUL=14
 CHSIMU(14) = 'Scyllo @ 3.35 +- 0. FWHM= -9.<0. +- 0. AMP= 6.'

NNOT2 (INTEGER) is the number of metabolites to be omitted from the Final Analysis; i.e., they are only used in the Preliminary Analysis.
 Default: NNOT2 = 3

CHNOT2 (CHARACTER(300)*6): the first NNOT2 elements contain the Metabolite Names of the Basis Spectra to be excluded from the Final Analysis.
 Default: CHNOT2(1)='Lip13c' CHNOT2(2)='Lip13d' CHNOT2(3)='Lip13e'.
 These are only needed to give more flexibility to the Preliminary Analysis, which uses more primitive models than the Final Analysis.

HIFMM (REAL) ("High-field MM"): When HZPPPM > HIFMM, sharper CHSIMU for the MM & lipids are used (with FWHM about 1/3 those of above).
 Default: HIFMM = 190.

11.7.1 Method

Lipid and macromolecule (MM) signals are highly variable, and it is therefore difficult to specify accurate Basis Spectra for them, in contrast to the usual low molecular weight metabolites in the .BASIS file.

When there is uncertainty in the model, constrained regularization [11], which is nearly model-free, can be useful. Figure 4 in [16] shows how the regularized LCModel Baseline can automatically account well for a strong MM signal in high-quality data, with no prior knowledge of (or biasing assumptions about) the MM signal. However, with lower resolution and S/N, the information is not sufficient to determine such sharp high-amplitude bends in the Baseline, which occur in high-resolution spectra.

Three approaches have been useful with LCModel:

- (1) Add an extra typical MM spectrum (obtained from metabolite nulling) to the Basis Set [16, 18]. Even if this MM Basis Spectrum does not perfectly match each *in vivo* spectrum, the Baseline now only needs to make smaller corrections, which are easier than fitting the full MM profile, especially with lower-quality data.
- (2) A metabolite-nulled spectrum can be acquired for each *in vivo* spectrum and subtracted from it [33]. This reduces the S/N, but, as in (1), any errors in subtraction, e.g., due to changes during acquisition of the two spectra, would often require smaller corrections by the Baseline than without subtraction.
- (3) Additional simulated lipid and/or MM spectra can be added as Basis Spectra [5, 3].

Approach (3) is used here. It requires a difficult delicate balance between over-parameter-

ization and over-simplification. Regularization provides this balance for the Baseline & lineshape, but the concentrations themselves are normally not regularized, and there are now far too many concentrations to estimate without some type of stabilization. The Concentration Ratio Priors below attempt to do this. LCModel uses the following:

Parsimony: In [5, 3], the simulated components were parsimoniously chosen, so as not to over-parameterize the analysis. Similarly, MM20 combines three components around 2.25 & 2.0 ppm and also includes a weak component near 3.0 ppm. Allowing these four components to be independent produced flat Baselines, but great scatter (and unrealistic values) in concentrations in test sets of control spectra. Similarly, Lip20 is a combination.

Lineshape: Concentration estimates depend critically on the lineshape model. Normally, all the resonances in the Analysis Window are simultaneously used to determine the nearly model-free regularized lineshape function, which accounts for field inhomogeneity, etc. However, the lipid or MM peaks can have highly variable deviant lineshapes that have nothing to do with the normal metabolite lineshapes. These stronger lipids & MMs would dominate the determination of the lineshape function. The normal metabolites would then have this incorrect lineshape, causing significant errors in their concentration estimates.

Therefore, the lineshape function is not used for the simulated lipids and MMs. Their lineshape is adjusted as a crude Gaussian-Lorentzian model. The two major signals near 1.3 & 0.9 ppm are given more flexibility (six parameters) by the two Lip13a & Lip13b and by MM09 & Lip09, respectively.

Concentration Ratio Priors: Even with the above two steps, the analysis is still seriously over-parameterized. It is also necessary to impose “soft” (nonlinear) constraints on the ratios of lipid components to Lip13a+Lip13b and of the MM components to MM09. They stabilize the analysis considerably, and they help to separate Lip09 from MM09 and Lip20 from MM20, by the chains of constraints from (the more accurate) Lip13a+Lip13b to Lip09, etc., and from MM09 to MM20, etc. They are specified in Sec 11.8.

Flexible Baseline: The Baseline has been given the necessary extra flexibility to correct for the inevitable inaccuracies, particularly in the crude lipid & MM lineshape models.

11.8 Concentration Ratio Priors

You can specify prior probabilities (“soft constraints”) on concentration ratios as follows:

NRATIO (INTEGER) is the number of soft constraints on concentration ratios that are specified.

Default: NRATIO = 12; i.e., CHRATO(13) below is not used.

CHRATO (CHARACTER(60)*264) specifies the soft constraints. Defaults:

```
CHRATO(1) = 'Lip09/Lip13* = 0.267 +- 0.1 +WT= MM12'
CHRATO(2) = 'Lip20/Lip13* = 0.15 +- 0.07 +WT= MM12'
CHRATO(3) = 'MM20/MM09* = 1.5 +- 0.375 +WT= Lip09*'
CHRATO(4) = 'MM12/MM09* = 0.3 +- 0.1 +WT= Lip09*'
CHRATO(5) = 'MM14/MM09* = 0.75 +- 0.45 +WT= Lip09*'
CHRATO(6) = 'MM17/MM09* = 0.375 +- 0.3 +WT= Lip09*'
CHRATO(7) = '-CrCH2/totCr = 0.1 +- 0.15'
```

```

CHRATO(8) = 'Asp/Big3 = 0.05 +- 0.05'
CHRATO(9) = 'GABA/Big3 = 0.04 +- 0.04'
CHRATO(10) = 'Glc/Big3 = 0.05 +- 0.075'
CHRATO(11) = 'Scyllo/Big3 = 0.02 +- 0.02'
CHRATO(12) = 'Tau/Big3 = 0.04 +- 0.06'
CHRATO(13) = 'NAAG/NAA = 0.15 +- 0.15'

```

These are of the form

metnum/metdenom = *expect* +- *stddev* +WT= *metwt*

metnum = the numerator of the ratio; it must be a single Metabolite Name, not a Concentration Sum.

metdenom = the denominator. The more accurate concentration in the ratio should be in the denominator. It can also be a Concentration Sum. There are also the following special symbols:

A wildcard * at the end will match any string of zero or more characters. With the default Metabolite Names in Sec 11.7, Lip13* in CHRATO(1) becomes Lip13a+Lip13b, and MM09* in CHRATO(3) becomes MM09.

totCr in CHRATO(7) will sum all that are present of Cr, Cre & PCr.

totCho will sum all that are present of Cho, GPC & PCh.

totNAA will sum all that are present of NAA & NAAG.

Big3 in CHRATO(8) is a special symbol for

totNAA+totCr+totCho+totCho+totCho. To make Big3 more invariant, totCho is added three times, because it is often present when the totNAA & Cr are weak (as in tumors). (totCho also has three times as many protons per molecule contributing to its main peak.)

expect = the expectation value of the ratio.

stddev = the standard deviation of *expect*.

metwt is optional. It will be included in the initial estimate of the weighting of the (nonlinear) ratio constraint. It should include metabolites that could be mistaken for *metdenom*.

- The tokens / = +- +WT= totCho totCr totNAA Big3 must be exactly as above, with each CHRATO on one line. There must be no space on either side of /.

The necessity of the Concentration Ratio Priors for the lipid & MM components is explained in Sec 11.7.1. The prior for -CrCH2/totCr reflects typical attenuations of the Cr CH₂ signal by relaxation and water-suppression. By default, CHRATO(13) is only used when SPTYPE='tumor' or 'csf'.

The priors for the other ratios are extremely weak, with *stddev* typically 100% of *expect*. The Asp GABA Glc Scyllo & Tau signals are often so weak, that it is tempting to omit them from the analysis. The weak priors allow for the variability of these, but still help to avoid unrealistic concentrations in low-information spectra. This still introduces a weak bias, but not as strong as omitting them (which fixes them to zero). Weak bias toward their *expect* values should yield more accurate overall analyses than setting them to zero or giving them complete freedom to assume huge values.

If (e.g., in a pathology) one of these metabolites is unexpectedly well-determined and strongly deviates from *expect* by more than four times *stddev*, then the line for *metnum* in the One-Page Output is in bold red italic, with a plus (or minus) preceding the Metabolite Name (Sec 9.9.1.3). If this deviation seems plausible, then you should relax or remove this prior, as specified in Sec 11.8.1. For example, with rodents, Tau is often high, and you should probably eliminate its prior, as illustrated in Sec 11.8.1.

In a restricted study, with more accurate *expect* from controls, you might be able to strengthen some constraints. However, do not make *stddev/expect* too small. Their main purpose is to bring stability (not self-deceptive bias). Very small values would also increase the difficulty in the constrained nonlinear optimization algorithm in LCModel.

11.8.1 Omitting Ratio Priors

If you want to eliminate a few Concentration Ratio Priors, then the following are usually more convenient than rearranging the **CHRATO** array:

NNORAT (INTEGER) is the number of Metabolite Names whose Concentration Ratio Priors will be omitted.

Default: **NNORAT** = 0.

NORATO (CHARACTER(60)*6). The first **NNORAT** elements contain the Metabolite Names of the priors to be omitted. All priors with *metnum* (Sec 11.8) equal to one of these Metabolite Names will be omitted.

For example, with rodents, you should input

```
NNORAT = 1
```

```
NORATO(1) = 'Tau'
```

since they have higher Tau than humans. At 4.7T and above, this is automatically done, and the above input is unnecessary.

11.9 Coherent Data Averaging

This section specifies how you can combine multiple (replicate) spectra into one spectrum with an increased signal/noise and then analyze this. (Siemens users should use the Siemens utility for combining Siemens phased-array data and skip Sec 11.9.) There are three cases:

11.9.1 GE & Canon/Toshiba Phased-Array Single-Voxel Data

LCMgui recognizes GE & Canon/Toshiba single-voxel phased-array data. It causes LCModel to do a weighted coherent average over the channels and analyze the resultant spectrum. So, there is nothing that you need to do; this is done automatically.

You may notice an extra Control Parameter, **IAVERG=1**. Do not change this. It tells LCModel that this is a set of phased-array spectra to be coherently averaged (and not a multi-voxel set to be analyzed individually). Water-Scaling is needed for statistical weighting. If, for some reason, you do not want to do Water-Scaling, you could change to **IAVERG=3** (Sec 11.9.2), but Water-Scaling does no harm, since it does not change the concentration ratios.

11.9.2 Other Spectra with Identical Phases & Referencing Shift

Use Sec 11.9.1 for GE & Canon/Toshiba data. Use the Siemens utility to combine their multi-channel data. For others, this is usually multi-channel data from a phased array or a Philips MEGA-PRESS file (see Sec 9.4.1.2). Rarely, it is just a (time) series of spectra with identical phases and referencing.

With phased-array data, in order to coherently sum each channel, you must do eddy-current correction (Sec 6.3.3). For this, you must have a reference data set from the same voxel with no water suppression. You then use **IAVERG=1** (defined below).

You must put the data sets in the format of CSI data sets (specified in Sec 5.2.3.1). With phased array data, Varian automatically does this for you. Philips does this for you, producing a file as a series of spectra, usually in a row (e.g., in a series of scans of the same voxel). For Philips MEGA-PRESS see Sec 9.4.1.2. You then simply select this file with LCMgui, with phased array data activate eddy-current correction and input one of the following values for **IAVERG**:

IAVERG (INTEGER)

IAVERG = 1 to analyze a weighted average of the spectra. Use this if you also have a corresponding set of unsuppressed water reference spectra from the same voxel. This is required for the statistical weighting and must be in the same CSI format. You must also activate Water-Scaling by inputting **DOWS=T**.

IAVERG = 3 to analyze an unweighted average of the spectra; i.e., the spectra are simply summed (and divided by the number of spectra). This is not too bad if the scalings and noise levels in the spectra are not extremely different.

IAVERG = 34 is the same as **IAVERG=3**, except that the even spectra are subtracted rather than added [as for Philips MEGA-PRESS (Sec 9.4.1.2)].

IAVERG = 31 to do an unweighted average of only the odd spectra, e.g., for Philips MEGA-PRESS (Sec 9.4.1.2).

IAVERG = 32 to do an unweighted average of only the even spectra, e.g., for Philips MEGA-PRESS (Sec 9.4.1.2).

Philips often sets the number of rows, columns & slices in the SPAR file automatically. Check the multi-voxel panel in Fig 6.4 and set them to correspond to the number of spectra, if necessary. You can also view the spectra with the “Preview Data” button in Fig 6.4. You can get a squarer preview by setting the number of rows and columns approximately equal (e.g., going from 1×40 to 5×8). This adjustment does not affect the analysis.

11.9.3 Varying Phases or Referencing Shifts

Even in a series of scans of the same voxel, motion (especially in the pelvic region) can cause the phases to vary. These motion (or other) artifacts can sometimes be reduced by partitioning subsets of scans into separate files, phasing and referencing each with LCMModel, averaging, and analyzing the average with LCMModel. You can do this with the following (labor-intensive) steps:

You analyze each file separately. The Control Parameters below (or the “CORAW” button in Fig 7.3) will then use the phases and referencing shift from this LCMModel analysis to

phase and reference the data and output this into FILCOR (in the format of a .RAW file). The simple text format of the .RAW and .CORAW files is specified in Sec 5.2. You can then take a (weighted) average over the series of .CORAW files (using your own script or program) to produce an averaged .RAW file for the final optimal analysis using the default “Other” button in Fig 6.3 (Sec 7.4.4).

The Namelist NMID has correctly set TRAMP=VOLUME=1.0, since the data there have already been scaled. Similarly, any LCModel corrections called for by DOECC, DOWS, BRUKER, SEQACQ or FCALIB are in FILCOR. So, you should be able to directly sum the .CORAW files. The only scaling necessary would be for statistical weighting, if the original data files have different accuracies or scaling. Use the Namelist NMID from a .CORAW file for your averaged .RAW file.

Note that the individual separate input files must be of sufficient quality to yield meaningful LCModel analyses. Single scans may not be good enough.

FILCOR (CHARACTER*255) (“corrected .RAW file”) the name of the .CORAW file to be output (e.g., '/home/user1/.lcmodel/saved/pat_777_77/coraw'). LCMgui will automatically output the file coraw in the directory that you specify in Fig 7.2.

LCORAW (INTEGER)

LCORAW = 0 (the default) will suppress creation of this file;

LCORAW = 10 will make this file. With LCMgui, you only need to select CORAW in Fig 7.3.

11.10 Analyzing a (Time) Series of Spectra

You can analyze any series of spectra if you input them in the format of a CSI data set, specified in Sec 5.2.3.1. LCModel will treat it as a CSI data set, analyzing one spectrum after the other.

Often Philips series are automatically of this form, with 1 row and N columns. Check Fig 6.4; if necessary, enter N in “Total data Columns” and right of “through”. As with a CSI data set, the analysis of spectrum j will be output in `s11_1-j.ps`.

If you want to use the “Preview Data” in Fig 6.4 to view a series of 64 spectra, you can (temporarily) set the limits in the multi-voxel panel for an 8×8 array for better viewing.

As with CSI data, you can select a subset (e.g., spectra 7–31) to be analyzed.

11.11 Analyzing Data Left & Right of the Water Signal

If you want to analyze data both to the left and right of the residual water peak, you can have LCModel insert a gap in the ppm-axis being analyzed. In this way you can cut out the huge meaningless residual water signal from the analysis, without having to try to remove it with filters (which inevitably cause distortions).

PPMGAP (REAL(2,10)) specifies that the J 'th gap in the analysis is from PPMGAP(1, J) down to PPMGAP(2, J). The gaps must not overlap and must be in strictly decreasing

order. Typically, $\text{PPMGAP}(1,1) = 5.1$ and $\text{PPMGAP}(2,1) = 4.2$
 Default: $\text{PPMGAP} = 20 * 1.E37$, i.e., no gaps.

For better labeling of the wide ppm-axis (Sec 9.9.3.5), you might input:

```
NSUBTK = 5
XSTEP = 0.5
```

This could be useful for Glc quantitation at 4.7T and above [16, Fig 9]. At lower fields, water suppression would probably also suppress the Glc signal at 5.23 ppm. It could also be useful for metabonomics of body fluids at high resolution, where there are many signals above 5 ppm.

Quantitation of phenylalanine in brain at lower fields is probably hopeless, because of its extremely weak signal and overlap around 7.4 ppm with homocarnosine and a relatively strong poorly defined macromolecule signal. Also, NAA has a signal around 7.8 ppm at 37° C.

11.12 Multimodal Lineshapes

The finite convolution in the last sum in [1, Eq (1)] is a very flexible model-free correction for lineshape. The convolution should extend over a wide enough range to cover the linewidth, but not so far that it wastes computer time and reduces numerical stability. This extent is determined by the **FWHM** of the lineshape estimated in the Preliminary Analysis as follows:

RFWHM (REAL) the convolution extends over a range of $\text{RFWHM} * \text{FWHM} / 2$ in both directions.
 Default: **RFWHM** = 1.8.

The **FWHM** estimate from the crude Preliminary Analysis can be too low if the real lineshape has several peaks, as with the extreme eddy-current effects in [1, Fig 3b]. This is obvious from the poor fit to the side peaks and the non-random residuals. You should discard such a spectrum. However, you can nevertheless rerun with an increased **RFWHM**, say, to 3.0, or more if necessary.

11.13 Relaxation & Shift Priors

The last sum in [1, Eq (4)] imposes normal prior probability distributions for the broadening parameters, γ_ℓ and the shifting parameters, ϵ_ℓ , in [1, Eq (3)]. These priors are mainly to stabilize the nonlinear-least-squares analysis when it is far from the optimum or when a metabolite has nearly zero concentration. Normally you should not change these Control Parameters. Only if your metabolites have very unusual differences between their *in vivo* and *in vitro* spectra, would it be worthwhile to adjust these Control Parameters.

The priors for each metabolite in [1, Eq (4)] are defined by three quantities. The last four characters of the Control Parameter names tell which of these three quantities are being modified:

- SDSH (“SD of shift”) These are for the ϵ_ℓ . They specify the uncertainty in the referencing (in ppm) between *in vitro* and *in vivo*.
- EXT2 (“expectation of $1/T_2$ ”) Control Parameters with this ending modify γ_ℓ^0 in [1, Eq (4)]. These Control Parameters specify the increase in $1/T_2$ (in s^{-1}) in going from the *in vitro* Basis Spectrum to *in vivo*.
- SDT2 (“SD of $1/T_2$ ”) These are for the $\sigma(\gamma_\ell)$; the units are also s^{-1} . The SDT2 & EXT2 Control Parameters are scaled by the factor $\sqrt{\text{HZPPPM}/85.15}$ to roughly account for the decrease in T_2 with field strength.

For each of the above three quantities, there are four types of Control Parameters. These four are listed below, where **** can be EXT2, SDT2, or SDSH:

- DE**** (REAL) (“default”) these specify the defaults for the three quantities for all metabolites. They will be used unless they are changed by the Control Parameters below. Defaults: DEEXT2=2.0, DESDT2=0.4, DESDSH=0.004.
- N**** (INTEGER) (“number”) the number of quantities that are to be changed from their defaults. Defaults: NEX2=0, NSDT2=0, NSDSH=3.
- CH**** (CHARACTER(60)*6) (“character”) the first N**** elements contain the Metabolite Names corresponding to the quantities to be changed. Defaults: CHSDSH(1)='NAA', CHSDSH(2)='NAAG', CHSDSH(3)='Cho'.
- AL**** (REAL(60)) (“alternate”) the first N**** elements contain the changes to the quantities. Defaults: ALSDSH(1)=0.002, ALSDSH(2)=0.002, ALSDSH(3)=0.008.

As explained in [1, Appendix], the uncertainties in the referencing of NAA and NAAG are reduced to prevent them from strongly overlapping. The uncertainty in the referencing of Cho is increased because the Cho chemical shift does not agree with those of the choline-containing compounds *in vivo*. It is better to use GPC & PCh instead of Cho.

The lineshape parameters can automatically account for increases in $1/T_2$ from *in vitro* to *in vivo*. The parameters in the priors are needed to account for only *differences* in these increases from one metabolite to the next. These differences are often negligible compared to the larger broadening of the lineshape due to field inhomogeneity, etc.

11.14 Detailed Output

This output (with up to 132 characters per line and typically 2000 lines) is a full documentation of the analysis. I used this during testing and development. You may be interested in some of its contents, which are briefly summarized as follows:

- The Namelist LCMODL, which contains the final values of all the Control Parameters, as described in Sec 11.15.
- A table documenting the Basis Spectra used in the Preliminary Analysis.
- Each iteration in the elaborate Preliminary Analysis for starting values for the referencing shift and phase corrections for the data.
- A table documenting the Basis Spectra used in the Final Analysis.
- Each iteration in the search for optimal regularizers in the Final Analysis. After each final iteration, are the values of the parameters; the last set in the Detailed Output are generally the final values. These values for $1000 \cdot \text{Shift}$ (in ppm/1000) for ϵ_k in [1,

Eq (4)] are useful for checking the compatibility of the Basis Set with the data. The shift parameters for the different Basis Spectra are listed in the same order as in the Basis-Spectra table in (d). Any shift that is more than $4\sigma(\epsilon_\ell)$ in [1, Eq (4)], i.e., more than 6 standard deviations in the prior, is straining the prior, and this Basis Spectrum is probably incompatible with the data.

- (f) A line-printer plot of the lineshape coefficients, S_n in [1, Eq (1)] convoluted with a Gaussian with a FWHM of FWHMBA. This gives a rough idea of the final lineshape of singlets.
- (g) The triangular table of correlation coefficients between the metabolite concentrations. This table is useful for seeing strong pairwise correlations (e.g., between NAA and NAAG). If the correlation between a pair is consistently more negative than -0.3 , then you should also output the Concentration Sum of the pair (Sec 9.9.1.1). More complicated correlations among groups of three or more metabolites are not so clear; the best reliability indicator is still the %SD (in the One-Page Output), which accounts for correlations of all orders, and many other things as well.

To get this output with LCMgui, you simply activate the button next to “PRINT” in Fig 7.3 (Sec 7.3.3.1). Otherwise, you can use the following:

FILPRI (CHARACTER*255) the name of the text (ASCII) file that will get the Detailed Output, e.g., 'pat-777-77.print'.

LPRINT (INTEGER)

LPRINT = 0 (the default) will suppress creation of this file;

LPRINT = 6 will make this file.

11.15 Default Control Parameters

Most of the default values for the Control Parameters have been listed in this manual. In case you want to check these defaults, you can do the following: First, make a file, say, `dump.control`:

```
$LCMODL
LPS=0
LPRINT=6
FILPRI='dump.print'
PPMCEN=999.
$END
```

Run LCModel:

```
$HOME/.lcmodel/bin/lcmodel <dump.control
```

The changes to LPRINT and FILPRI produce `dump.print`, the Detailed-Output file. The unreasonable value for PPMCEN produces a FATAL diagnostic and abort almost immediately, but not before the complete Namelist LCMODL has been written in `dump.print`.

All Control Parameters are in Namelist LCMODL, and can therefore be modified by the Namelist input in the `.CONTROL` file input to LCModel. Since `dump.control` only modified LPS, LPRINT, FILPRI, and PPMCEN, all other values output in `dump.print` are the original default

values. The original defaults for the modified four are: LPS=8, LPRINT=0, FILPRI=' ', PPMCN=4.65. This Namelist output is ordered in four groups, according to Fortran type — CHARACTER, INTEGER, LOGICAL & REAL, with alphabetical ordering within each group.

Most of these Control Parameters need not be changed (or even checked). Many are so-called *Hidden Control Parameters*, which are not documented in this manual and should not be changed. These are already set to their optimal values.

11.16 Analyzing Magnitude Spectra

This should only be done if it is impossible for LCModel to phase your spectra. For example, some CSI sequences have huge unknown 1st-order phase corrections, and it is necessary to analyze the absolute values of the spectra.

Otherwise, do not do this. The resolution suffers, and, much worse, this nonlinear transformation introduces errors — the absolute value of a sum is not the sum of the absolute values. Information is destroyed and artifacts introduced by taking absolute values of overlapping signals.

For Bruker users only: There is no need to use magnitude spectra. You correct the shift caused by Bruker's digital filter with Bruker's `convdta` or automatically with LCMgui (Sec 7.3.1). The 1st-order phase correction is then moderate.

ABSVAL (LOGICAL) .TRUE. to analyze the absolute value of the data. You input the usual complex .RAW and .BASIS files, and LCModel does the conversions. (Do not input absolute values.)
Default: ABSVAL = F.

11.17 Consistency with Old Versions

This is only for users who want consistency with Versions 5.x, e.g., of concentration estimates in longitudinal studies or of output format for your own post-processing programs.

SPTYPE = 'version5' sets the following:

NRATIO = 0

NSIMUL = 0

PPMEND = 1.0

PPMST = 3.85

The results will then be closer (but not identical) to Version 5.x results. Contrary to the other SPTYPE settings, it is not possible to overwrite these Control Parameters. If you want to change only some of the four above Control Parameters, then input them and do not input SPTYPE.

Other settings for backward consistency are:

NTITLE (INTEGER). Input NTITLE = 1 for the old one-line TITLE of Version 5.x.

Default: NTITLE = 2 (Any value other than 1 will allow the TITLE to range over

a maximum of two lines.)

YEAR4D (LOGICAL) (“year with 4 digits”) The Sun, SGI & DEC versions now have a 4-digit year at the top of the One-Page Output. Use **.FALSE.** to keep the old 2-digit year.
Default: **YEAR4D** = T

CONC3F LOGICAL (“concentration to 3 figures”). When the concentrations in the One-Page Output are in exponential (“E”) format, they now have 3 significant figures. Use **.FALSE.** to keep the old 2 significant figures.
Default: **CONC3F** = T

11.18 Nuclei Other than ^1H

LCModel was designed from the beginning for proton MRS and is restricted to this. Pierre-Gilles Henry [34], using many special LCModel settings, has managed to analyze ^{13}C spectra quite successfully. However, there are no plans to extend or support LCModel analysis of any nucleus other than ^1H .

Chapter 12

Diagnostics and Troubleshooting Hints

LCModel performs extensive checks for abnormal conditions and has about 300 diagnostic messages that go into the diagnostics table in the One-Page Output. These standard LCModel diagnostics are fully covered in Sec 12.2. Sometimes there is an abort before there is a chance for a standard diagnostic, particularly with input errors. These are discussed in Sec 12.1.

12.1 Non-Standard Diagnostics

These often involve an abort with no One-Page Output, and therefore no plot of the data. However, there is usually an error message in your Unix/Linux window, often with a Standard Diagnostic (Sec 12.2).

Often, one of the most important questions in troubleshooting is whether the data have been correctly converted or read in. Check this by plotting the input data with the “Preview Data” button in LCMgui (Sec 7.4.1).

With LCMgui, all run-time messages, including error messages, are logged in the file `runtime-messages` in the temporary directory for this analysis (Sec 7.5.2.2). Without LCMgui, they appear in the Linux/Unix window. (Linux messages about “Skipping namelist ...” are normal.)

12.1.1 I/O Errors

This is mainly for non-LCMgui users. Input/Output errors are the most common errors, especially during the first few runs. Some systems give good diagnostics in

`runtime-messages`, often showing exactly where the I/O error occurred.

End-of-File during Read: The most common cause is a missing or incorrect Namelist name. The system reads the file until it finds the Namelist or an end-of-file. Violating the Namelist rules for spaces in the first column or “\$” characters in the second column can cause the system to miss your Namelist.

If this occurs with a `.RAW` file, also check that the format of your time-domain data agrees with `FMTDAT` in Namelist `$NMID` and that there are at least `NUNFIL` complex pairs in the `.RAW` file.

Namelist Errors: These usually involve simple rule violations, or confusion of variable types, such as omitting a single quote for `CHARACTER` variables, or misspelling a variable name. (Linux messages about “Skipping namelist . . .” are normal.)

12.1.2 Arithmetic Exceptions

Overflows & Zero-Divides: should never occur. Check whether the format of your `.RAW` data agrees with `FMTDAT`; with the wrong format, huge numbers might be read that overflow when squared. Plot the data using the “Preview Data” button in `LCMgui` (Sec 7.4.1).

If necessary, rescale your `.RAW` data (e.g., with `TRAMP`) so that the maximum absolute value is below 10^8 and above 10^{-8} .

12.1.3 Other Aborts with no One-Page Output

Missing One-Page Output: Errors can occur during the production of the One-Page Output and suppress it. If the run ends without producing a `.PS` file, although it should have, check for an error message in your Linux/Unix window. If no message can be found, rerun getting the Detailed Output. One of the Standard Diagnostics listed in the summary of diagnostics at the end of the Detailed Output will tell you why the One-Page Output could not be produced.

12.2 Standard LCMModel Diagnostics

These are in the Diagnostics Table in the One-Page and Detailed Output. The 5 types, in increasing order of severity, are:

info: information of a non-standard condition that might be of interest you, but generally does not endanger the analysis.

warning: something has happened that could affect the final results.

ERROR: an error condition has occurred, but corrective action has been taken; the results could be affected.

FATAL: an error that cannot be corrected has occurred; the run is aborted.

ILLOGICAL: these diagnostics were used during development and testing to detect programming errors; they should never occur.

There are also the following special **info** messages:

Doing Water-Scaling: Water-Scaling has been done.

CRUDE MODEL: The results are based on the Preliminary Analysis with the crude Gaussian-Lorentzian model, and the analysis with the full model has been suppressed by your Control Parameters.

In the following, all LCModel diagnostics are listed alphabetically and explained. The diagnostic name also identifies the subprogram, and the general purpose of this subprogram and general hints are sometimes given. (Read this before going to the diagnostic number.) Then the individual diagnostics are listed by number. Possible remedies and suggestions are given after the word “**Hints:**”. There are no **Hints** with the **ILLOGICAL** type or when the remedy is obvious. There are standard **Hints** with the following meanings:

Never Happened This diagnostic is unlikely to occur. Therefore, further hints are usually not given.

Working Hard LCModel performs many independent analyses (typically about 100) from different starting points, and usually recovers completely from difficulties in one of these analyses. This diagnostic has occurred in one of these many analyses, and will probably not affect the final results. However, these diagnostics are useful signals that that LCModel is working hard on difficult data.

You can judge from the One-Page Output if your results have been affected. Check that the fit to the data is reasonable and the other criteria discussed in Sec 3.5 are satisfied.

Control Parameters and other terms are usually not cross-referenced. The Index at the end of this manual tells you where you can locate their definitions.

AREABA computes the resonance area of the reference Basis Set singlet (specified by **WSMET**) for Water Scaling. Errors here simply cause the analysis to proceed without any scaling. Only the concentration ratios of the metabolites in the **.BASIS** file will be valid. If you are simulating Basis Spectra inside LCModel (Sec 11.7), then the concentrations of all these simulated metabolites would have to be multiplied by an (unknown) scale factor to be consistent with the concentrations of the **.BASIS** metabolites. All **AREABA** diagnostics are of type **ERROR**.

1 The integration range for the Basis Set singlet (Cr at 3.03 ppm, by default) used for scaling is not completely in the Analysis Window.

Hints: Extend your Analysis Window with **PPMST** or **PPMEND**, or choose

another singlet with WSMET, etc.

- 2 One of the following was not input positive: N1HMET, ATTMET.
- 3 The integral of the reference Basis Set singlet is not positive.

Hints: Maybe you are integrating where there is no peak; check your input of WSMET, WSPPM or your .BASIS file.

AREAWA manages the computation of the resonance area of the unsuppressed water signal. Errors here cause the analysis to proceed without any scaling. If you are attempting Water-Scaling (DOWS=T), then only the concentration ratios of the metabolites in the .BASIS file will be valid. If you are simulating metabolite Basis Spectra, then the concentrations of all of the simulated metabolites would have to be multiplied by an (unknown) scale factor to be consistent with the concentrations of the .BASIS metabolites.

If you are analyzing GE phased-array data, then the analysis will abort with **FATAL AVERAG 5**.

All **AREAWA** diagnostics are of type **ERROR**.

- 1 One of the following requirements has not been met: $NWSST > 0$; $NWSEND \leq NUNFIL$; $NWSEND - NWSST \geq 9$.
- 2 The least-squares analysis to estimate the water signal was too unstable.
Hints: Never Happened, but if it does, try increasing **NWSEND**, or check for gross errors in the .H2O file, such as all time-domain points zero.
- 3 Same as **AREAWA 2**.
- 4 The absolute value of one of the first **NWSEND** values in the .H2O file is zero.
Hint: Check for an error in **FMTDAT** of Namelist **NMID** of the .H2O file that would cause zero values to be read.

AREAW2 Computes the resonance area of the unsuppressed water signal for Water-Scaling.

- 1 (**FATAL**) The water peak is outside the range of your spectrum.
Hint: Check your input of **PPMCEN**. If it is correct, then the water peak at 4.65 ppm may really be outside the range of your spectrum. In this case, you could try inputting (the undocumented) **IAREAW=1**, which does Water-Scaling without the water peak.
- 2 (**FATAL**) Same as **AVERAG 3**.

AVERAG combines phased-array spectra or spectra to be averaged.

- 1 (**FATAL**) Same as **INITIA 1**.
- 2 (**FATAL**) You input invalid values for the Hidden Control Parameter **NBACK**. Do not input it.
- 3 (**FATAL**) Unable to find or read the file with your unsuppressed water reference data. (Should never happen with GE Probe P-files, unless you prevent water reference scans.)
- 4 (**FATAL**) You have eliminated all channels of your phased-array data, using the parameters in Sec 5.3.2 or Sec 11.4.6. Do not eliminate any; let **LCModel** (statistically) average all channels.
- 5 (**FATAL**) Water reference signal could not be integrated; the phased-array data cannot be combined.
- 6 (**FATAL**) Noise analysis of a channel failed. **Hints: Never Happened**
- 7 (**FATAL**) Same as **AVERAG 6**.
- 8 (**WARNING**) You have eliminated some channels of your phased-array data or spectra from your Philips MEGA-PRESS data set, using the parameters in Sec 5.3.2 or Sec 11.4.6. It is usually better to let **LCModel** (statistically) average all channels or spectra.
- 9 (**FATAL**) Same as **AVERAG 6**.
- 10 (**FATAL**) Same as **AVERAG 6**.

- 11 (FATAL) All channels or spectra to be averaged have been eliminated from the analysis.

Hint: Check your input of NDCOLS, ICOLST, ICOLEN, NDROWS, IROWST, IROWEN, NDSLIC, ISLICE, NVOXSK, ICOLSK or IROWSK.

BETAIn evaluates the incomplete beta function, which is used to compute the confidence regions [11] for α_B and α_S in [1, Eq (4)].

- 1 (FATAL) meaningless arguments in call to BETAIn, probably caused by more than 40 000 data points. **Hints: Never Happened.**
- 2 (ERROR) A series expansion has failed to converge; α_S and α_B could be poorly chosen. **Hints: Never Happened.**

COMBIS processes the CHCOMB Control Parameters (CHARACTER(100)*210); these must satisfy the rules in Sec 9.9.1.1. The Detailed Output ends with “Incorrect CHCOMB =” followed by the first 112 characters of the CHCOMB.

Hints: Namelist errors are the most common cause, e.g., forgetting a single quote for a CHARACTER Control Parameter somewhere in the Namelist.

- 1 (FATAL) NCOMBI exceeds 200.
- 2 (FATAL) A Metabolite Name in a CHCOMB has more than 6 characters.
- 3 (FATAL) A CHCOMB has more than 50 Metabolite Names.

CONCPR computes the initial approximations for the priors for the concentration ratios. See Sec 11.8 for the symbols and tokens used below.

- 1 (FATAL) NRATIO must not exceed 100.
- 2 (FATAL) In one of the CHRATO, the / is missing in *metnum/metdenom*. The illegal ratio part of the CHRATO is also at the end of the Detailed Output.
- 3 (FATAL) In one of the CHRATO, the *metnum* is missing in *metnum/metdenom*. The illegal ratio part of the CHRATO is also at the end of the Detailed Output.
- 4 (FATAL) In one of the CHRATO, *expect* is negative or *stddev* not positive.
- 5 (FATAL) You input the Hidden Control Parameter FCSUM non-positive. Do not input it.
- 6 (warning) All concentrations in an analysis were zero. A constraint is going to be skipped.

Hints: There is probably a big problem with the data, and a later FATAL diagnostic is likely.

DEMO only allows analysis of the demo test data, unless you have a license.

- 1 (FATAL) You do not have a license for this Sun, SGI or DEC/Compaq workstation, or your system date is wrong.
Hints: Check that you are using the licensed workstation. Check that your input of OWNER and KEY exactly match what was given to you with your license. Correct your system date setting.
- > 1 (FATAL) With Linux, there are numerous diagnostic numbers (11, meaning unreadable license, is the most common).
Hints: (a) If you have a license, then make sure that it is called \$HOME/.lcmode/license (and not license.dat or license.bin).
(b) Send me the file \$HOME/.lcmode/data-for-licensing (if it was produced) and the .PS file produced.

ECC Performs eddy-current correction.

- 1 (FATAL) Same as INITIA 1.
- 2 (FATAL) Unreasonable values of NUNFIL, PPMCEN or the Hidden Control Parameters PPM_TRUNCATE_MAX or PPM_TRUNCATE_MIN.

ERRMES outputs and counts diagnostics.

- 1 (ILLOGICAL) Meaningless argument in call to ERRMES.
- 2 (FATAL) Stopping after MERMES = 2000 diagnostics.

FINOUT does the computations and error analyses for the output at the end of the analysis.

- 1 (ERROR) An analysis to rephase the data for plotting failed. The plot will not be of the real part of the data. The concentrations are not affected. **Hints: Never Happened.**
- 2 (ERROR) Giving up after maximum iterations in trying to rephase the data for plotting. The results are as in FINOUT 1.
Hints: This is a sure sign that your data are so poor that the phase corrections are very uncertain; you should probably reject the data.
- 3 (FATAL) An analysis to get error estimates failed. **Hints: Never Happened**, but if it does, then your data should be rejected anyway.
- 4 (FATAL) Same as FINOUT 3.
- 5 (FATAL) Same as FINOUT 3.
- 6 (warning) The fit to the data was perfect and the S/N therefore cannot be calculated and is being set to -1.0. **Hints: Never Happened**, but, if it does, it is probably because all data points are zero.
- 7 (info) The Baseline required a great deal of freedom and may have a wild shape.
Hints: This may be due to shimming problems or to susceptibility (or other) artifacts, or to very sharp residual water or lipid peaks. If the problem is near the edge of the spectrum, then you should eliminate this using PPMST or PPMEND. If the spectrum being analyzed is *in vitro*, then try inputting VITRO = T. If the problem persists, then you should probably reject the spectrum.
- 8 (warning) The first-order phase correction is below DGPPMN - SDDEGP or above DGPPMX + SDDEGP.
Hints: If you are expecting such extreme first-order phase corrections, then adjust DGPPMN, DGPPMX, DEGPPM, SDDEGP accordingly. Otherwise, the hints of FINOUT 2 apply.
- 9 (info) The lineshape is not very smooth.
Hints: These lineshapes occur more often at low resolution or long echo times, where there are relatively few peaks in the spectrum. This generally does not seriously affect the concentrations, since they are obtained by effectively integrating over the lineshapes, and the oscillations tend to cancel out. However, the FWHM listed in the One-Page Output (but not used for anything else) may be wrong.
- 10 (warning) The zero-order phase correction is more than 4 standard deviations (SDDEGZ) from its expectation value (DEGZER). The phasing may be poor, and you may have to reject this analysis.
Hints: Large artifacts or errors in the data can in rare cases cause this.

Much more common is that the prior information that you are imposing is wrong. Check for a wrong value of DEGZER (default is 0.0.) or too small an SDDEGZ. This prior information often assumes that an eddy-current correction was done. Did you forget this or did you use the wrong water reference file?

With CSI data, do not input DEGZER or SDDEGZ. Let the Bayesian learning in LCModel set these; SDDEGZ is usually very large with CSI anyway. (Occasional occurrences of this diagnostic are then normal.)

- 11 (warning) The first-order phase correction is more than 6 standard deviations (SDDEGP) from its expectation value (DEGPPM). The phasing may be poor, and you may have to reject this analysis.
Hints: Large artifacts or errors in the data can in rare cases cause this.

Much more common is that the prior information that you are imposing

is wrong. Check for a wrong value of DEGPPM (default is 0.0.) or too small an SDDEGP.

With CSI data, do not input DEGPPM or SDDEGP. Let the Bayesian learning in LCModel set these. (Occasional occurrences of this diagnostic are then normal.)

12 (ILLOGICAL) Programming error with the priors for concentration ratios.

FISHNI evaluates the Fisher F-distribution, used for determining the regularization parameters α_B and α_S in [1, Eq (4)].

- 1 (FATAL) The number of free parameters in [1, Eq (1)] is either zero or greater than the number of data points in the Analysis Window. **Hints: Never Happened**, but if it does, check PPMST and PPMEND for an unreasonably narrow Analysis Window.

FSHSSQ computes the quality of the fit (sum of squared deviations) to the data corresponding to a given confidence level; for choosing the regularization parameters α_B and α_S in [1, Eq (4)]. For all of the FSHSSQ diagnostics, **Hints: Never Happened** applies.

- 1 (FATAL) A meaningless argument has been passed to FSHSSQ. This could be the Hidden Control Parameter PRMNMX, which you should not change. It could also be caused by a perfect fit to the data or less than one effective free parameter in the full model in [1, Eq (1)], for which the hint of FINOUT 6 applies. It could also be caused by more free parameters than data points in the Analysis Window, for which the Hints of FISHNI 1 apply.
- 2 (ERROR) There are less than two free parameters in the full model in [1, Eq (1)], and the approximation for the sum of squares could be poor. This could lead to bad regularization parameters.
- 3 (FATAL) The sum of squares would be so large that it would cause an arithmetic overflow. **Hints:** See the discussion of overflows in Sec 12.1.2.
- 4 (warning) The solution of a nonlinear equation is inaccurate. This could in rare cases cause bad regularization parameters.
- 5 (ERROR) Same as FSHSSQ 4.
- 6 (ERROR) Same as FSHSSQ 4.

FTDATA Fourier-transforms the time-domain data and shifts the spectrum.

- 1 (FATAL) The sum of the absolute values of all the points in the Analysis Window is zero.
Hint: (a) Your .RAW file is probably being read in as all zeroes or extremely small values; check the format of the data in this file.
(b) This will also occur if you are using BASCAL=T and your CHBCAL specifies a Metabolite Name that is not in the Basis Set.

GBACKG (“Get background”) computes the B-spline basis set for the Baseline.

- 1 Not used.
- 2 (FATAL) There is not enough storage for NBCKMN spline knots.
Hints: Do not input the hidden Control Parameter NBCKMN.
- 3 (FATAL) Your Analysis Window has zero width.
Hints: This is actually ILLOGICAL, since this error should have been caught earlier.
- 4 (ILLOGICAL) There are less than 6 knots for the Baseline. This error should have been caught earlier.

GETPHA (“Get phases”) Phase the unsuppressed water peak.

- 1 (FATAL) Part of the unsuppressed water peak is at the edge of the spectrum.
Hint: Increase your bandwidth.

GFIELD parses individual elements of the strings in CHSIMU & CHRATO.

- 1 (ILLOGICAL) Programming error.
- 2 (ILLOGICAL) Programming error.

HEX converts to hexadecimal format for the .PS file.

- 1 (ILLOGICAL) Programming error in this conversion. No One-Page Output can be produced.

ICYCLE computes subscripts in arrays from (circular) FFTs.

- 1 (FATAL) A non-positive subscript has been computed, probably due to my programming error. **Hints: Never Happened.**

INITIA does initial computations of basic quantities.

Hints: Errors here are almost always due to your input of unreasonable Control Parameters.

- 1 (FATAL) At least one of the following Control Parameters is not positive: DELTAT, NUNFIL, HZPPPM.
- 2 (FATAL) At least one of the Control Parameters in INITIA 1 is unreasonably large.

Hints: This is most likely NUNFIL, which cannot exceed 65536 in most versions of LCModel. Rerun to get the Detailed Output; at the end is this diagnostic with NUNFIL and its limit. If you really need a higher limit, then I can send another version.

- 3 (FATAL) Your PPMST or PPMEND or one of the Control Parameters in INITIA 1 is so unreasonable that your Analysis Window extends outside your entire spectral window.

Hints: Increase your bandwidth or correct your input of PPMST or PPMEND.

- 4 (FATAL) Your PPMEND \geq PPMST; or one of the following is unrealistically small: DELTAT, NUNFIL, HZPPPM; or the number of data points in your Analysis Window exceeds the allocated storage (normally 12000).

Hints: First check the above five Control Parameters. If they are correct, then I can send a version with even more allocated storage, but this would only occur with unusually large fields, Analysis Windows, or acquisition times for one scan. You probably should truncate your time data; see STARTV 24.

- 5 (ILLOGICAL) My computation of the machine precision shows more than 100 significant figures for DOUBLE PRECISION.

- 6 (warning) There are less than 12 significant figures in your DOUBLE PRECISION arithmetic. **Hints: Never Happened.**

- 7 (FATAL) There are less than 7 significant figures in your DOUBLE PRECISION arithmetic. **Hints: Never Happened.**

- 8 (ERROR) There are less than 64 points in the Analysis Window.

Hints: Check for PPMST too close to PPMEND, or too large gaps using PPMGAP.

- 9 (FATAL) Gap boundaries must be strictly decreasing and not overlap; i.e., $\text{PPMGAP}(J,K) > \text{PPMGAP}(L,K+1)$ when $L \geq J$

LDEGMX checks whether the curves to be plotted on the One-Page Output have been phased well enough to correspond to the real part of the spectrum.

- 1 (ILLOGICAL) Meaningless arguments for LDEGMX.
- 2 (FATAL) One of the Hidden Control Parameters DEGMAX(1) or DEGMAX(2) is not positive. **Hints:** Do not input these.

LESSMO Checks if the Preliminary Analysis has found concentrations of the metabolites named in **CHLESS** that are unexpectedly large compared to the metabolite named in **CHMORE**. If so, the Preliminary Analysis is then repeated with the **CHLESS** metabolites omitted. For the first three diagnostics, the Hint is: **CHLESS** & **CHMORE** are Hidden Control Parameters and should not be input.

- 1 (FATAL) There is an unreasonable number of metabolites named in **CHLESS**.
- 2 (ERROR) One of the metabolite names in **CHLESS** equals that in **CHMORE**. **LESSMO** will be skipped.
- 3 (ERROR) Same as **LESSMO** 1. **LESSMO** will be skipped.
- 4 (info) **LESSMO** will repeat the Preliminary Analysis with the **CHLESS** metabolites omitted.

LOADCH loads the **Input Changes** table for the One-Page Output.

- 1 (ERROR) You attempted to set the Hidden Control Parameter **MERMES** to exceed allocated storage. It will be reduced to the maximum allowed value of 600.
- 2 (FATAL) Error trying to re-read Namelist **LCMODL** in your **.CONTROL** file.
Hints: System error in rewinding file? Other errors should have already been caught with **MYCONT** 1 or **MYCONT** 2.

MAIN is the main program.

- 1 (FATAL). Input or output error with the internal file **filcsi_sav_1** or **filcsi_sav_2**.
Hints: Correct your changes to the Execution Script **standard** or **nice**. Do not input the hidden Control Parameters **filcsi_sav_1**, **filcsi_sav_2**, **lcsi_sav_1** or **lcsi_sav_2**.
- 2 (FATAL) Error trying to open **FILCSV**. **Hints:** Check permissions.
- 3 (FATAL) Error trying to read **FILCSV**. **Hints:** Check permissions.

MAKEPS organizes the production of the PostScript file for the One-Page Output.

- 1 (FATAL) At least one of the Control Parameters **PAGEHT** or **PAGEWD** is not positive. No One-Page Output can be produced.
Hints: Correct your input of **PAGEHT** or **PAGEWD**.
- 2 (FATAL) Error trying to open **FILPS**. No One-Page Output can be produced.
Hints: Check permissions.

MERGLF (“Merge left”) merges Baseline segments to be continuous across gaps.

- 1 (ILLOGICAL). Programming error.

MERGRT (“Merge right”) merges Baseline segments to be continuous across gaps.

- 1 (ILLOGICAL). Programming error.

MYBAS1 inputs the Basis Spectra from the **.BASIS** file and simulates additional Basis Spectra.

- 1 (FATAL) You are using a basis set that requires **LCModel** version 6.3-1 or higher.
Hints: Update to the latest **LCModel** (Sec 7.2.6).
- 2 (warning) More than 90% of the Basis bandwidth (BW) is needed to cover the Analysis Window. There will probably be distortions at the edges.
(FATAL) The Basis BW is narrower than the Analysis Window.
Hints: Use a Basis with a larger BW or narrow the Analysis Window.
- 3 No longer used.
- 4 No longer used.
- 5 (FATAL) The number of Basis Spectra to be used exceeds 60. **Hints:** If you really want to use more, then I can send a new version.

- 6 (FATAL) At least one of the following input variables in a Namelist BASIS in your .BASIS file is not positive: TRAMP, VOLUME, CONC. The last line in the table of Basis Spectra in the Detailed Output gives the Metabolite Name corresponding to the Basis Spectrum involved.
- 7 (FATAL) All of the metabolites in your Basis Set have been omitted from the analysis; there are none left.
Hints: (a) This may be due to your .BASIS file having (almost) no metabolites.
 (b) These could also have been omitted by your input of NOMIT and CHOMIT or of BASCAL and CHBCAL or of NCALIB and CHCALI.
 (c) They could have been automatically omitted if your PPMST and PPMEND produce a very narrow Analysis Window.
 (d) The Preliminary Analysis uses only the metabolites named in CHUSE1: (NAA, Cr (or Cre) GPC (or PCh or Cho), Glu, Ins, by default). So at least one of these must be in the analysis. However, in order for the Preliminary Analysis to work properly, all of the major landmarks in the spectrum being analyzed should be included; i.e., you need at the very least NAA, Cr, Cho, and (at short TE) Ins, except possibly with a phantom. If you are analyzing a phantom that contains none of these metabolites, see Sec 11.6.
- 8 (warning) One or more of the NUSE1 Metabolite Names in the array CHUSE1 is not in the Basis Set. The Preliminary Analysis will not use all the metabolites named in CHUSE1, and this could weaken the Preliminary Analysis.
Hints: See Hints in MYBASI 7.
 Also make sure that your Metabolite Names agree with the Allowed Names in Table 8.1 (see the discussion of METABO).
- 9 The field strengths in your *in vivo* data and your Basis Set differ by more than 20% (FATAL) or 5–20% (warning). LCModel will try to correct by bandwidth conversions, but warning may mean poor modeling of coupled resonances.
Hints: If HZPPPM is correct in your input and in your Namelist SEQPAR of your Basis Set, then you need to get an appropriate Basis Set.
- 10 (ERROR) The echo times (ECHOT) in your *in vivo* data and your Basis Set differ by more than 3 ms.
Hints: If ECHOT is correct in Namelist SEQPAR of your data and of your Basis Set, then you should use an appropriate Basis Set.
- 11 (ERROR) Your *in vivo* data were acquired with STEAM and your Basis Set with PRESS (or *vice versa*).
Hints: If SEQ is correct in Namelist SEQPAR of your data and of your Basis Set, then you need an appropriate Basis Set.
- 12 (FATAL) You have BASCAL=T, and at least one of the following requirements was not met: NCALIB ≥ 1 ; CHCALI must be defined in your input.
- 13 (FATAL) You have BASCAL=T, and have input the same Metabolite Name for CHBCAL and one of the CHCALI. Thus, you would be calibrating a Basis Spectrum with itself.
- 14 Not used.
- 15 Not used.
- 16 (FATAL) When the simulated Basis Spectra are added, the total number of Basis Spectra to be used exceeds 100. **Hints:** Check and reduce NSIMUL. If you really want to use so many, then I can send a new version.
- 17 (FATAL) A CHSIMU cannot have more than 20 simulated peaks (i.e., 20 ppm* in Sec 11.7).
- 18 (FATAL) The elements of all CHSIMU (Sec 11.7) must satisfy $f_{min} < f_{wex}$ and $sdfw > 0$.
- 19 (warning) The elements f_{min} & f_{wex} of a CHSIMU (Sec 11.7) are too close

- together. To avoid numerical problems, *fwex* will be slightly increased.
- 20 (warning) The element *sdfw* of a CHSIMU (Sec 11.7) is too small. To avoid numerical problems, *sdfw* will be slightly increased.
- 21 (warning) The element *sdppm* of a CHSIMU (Sec 11.7) is too small. To avoid numerical problems, it will be increased slightly.
(FATAL) *sdppm* ≤ 0 .
- 22 (FATAL) The elements of all CHSIMU (Sec 11.7) must satisfy *amp** $\neq 0$ and $|ppm *| \leq 998$.
Hints: Check the format of your CHSIMU for erroneous or blank entries.
- 23 Not used.
- 24 (FATAL) The elements *fwmin** of all CHSIMU (Sec 11.7) must satisfy *fwmin** > 0 .
- 25 Same as MYBASI 16
- 26 (FATAL) Incorrect values for the Hidden Control Parameters RINCSH, SDSHMN or SDSHMX. Do not input these.
- 27 (FATAL) When using only simulated basis spectra (as with most values of SPTYPE), you cannot have BASCAL=T, NCALIB > 0 or NSIMUL ≤ 0 .
- 28 (FATAL) Error trying to open FILBAS.
Hints: Check for non-existent file or permissions.
- 29 (FATAL) Error trying to read Namelist BASIS1 in FILBAS.
Hints: See Sec 12.1.1.
- 30 (FATAL) Error trying to read Namelist BASIS in FILBAS.
Hints: See Sec 12.1.1.
- 31 (FATAL) Error trying to read a Basis Spectrum in FILBAS.
Hints: In FILBAS, check that the Basis Spectrum data correspond to FMTBAS.
- 32 Not used.
- 33 (FATAL) You have not input anything for FILBAS, or you input LBASIS < 0 .
- 34 (ERROR) It was not possible to scale the simulated peaks. They will all differ from the concentrations of the metabolites in the .BASIS file by an unknown factor.
Hints: By default the Cr from the .BASIS is used for scaling. Does your .BASIS file have creatine with the Metabolite Name Cr? For example, if it is instead Cre, then you must input WSMET = 'Cre'. If you use something other than the Cr CH₃ singlet for scaling then you will also have to input WSPPM & N1HMET.
- 35 (FATAL) There is not enough storage to convert the basis set to the bandwidth of your data.
Hints: Contact me about a modified basis set or data or about a larger version of LCModel.
- 36 (FATAL) With SPTYPE='lipid-8', 'breast-8' or 'liver-11', you must have the Hidden Control Parameter NOBASI=T, and CHSIMU must have a special (undocumented) structure.
Hints: Do not use CHSIMU or NOBASI with these SPTYPE.
- 37 (FATAL) When using an SPTYPE in Sec 9.2 or 9.3, you must not use *fwmin1* < 0 (Sec 11.7) to simulate spectra in a basis set, since there is no input basis set.
- 38 (FATAL) When using SPTYPE='lipid-8', 'breast-8' or 'liver-11', all concentrations in the Preliminary Analysis were estimated to be zero.
Hints: Check for very poor data.
- 39 (FATAL) Invalid values for Hidden Control Parameter NPOWER.
- 40 (FATAL) You cannot simulate additional model spectra when SPTYPE = 'muscle-5', 'lipid-8', 'breast-8' or 'liver-11'.
- 41 (warning) With short TE, you should have PPMEND ≤ 0.6 to include all the macromolecule and lipid models, such as MM09, which is used to impose

important soft constraints on the other concentrations. If your $TE \geq 100$ ms, you can ignore this diagnostic.

MYCONT reads the Control Parameters and does preliminary checks.

- 1 (FATAL) An end-of-file was encountered before your Namelist LCMODL in the .CONTROL file could be read completely. No One-Page Output will be produced.
Hints: See Sec 12.1.1.
- 2 (FATAL) An error was encountered in your Namelist LCMODL in the .CONTROL file. No One-Page Output will be produced.
Hints: See Sec 12.1.1.
- 3 (FATAL) You have not input anything for FILPS, although you set $LPS > 0$. No One-Page Output will be produced.
- 4 (FATAL) You have not input anything for FILCOO, although you set $LCOORD > 0$.
- 5 (FATAL) You have not input anything for FILTAB, although you set $LTABLE > 0$.
- 6 (FATAL) You have not input anything for FILRAW, or you input $LRAW \leq 0$.
- 7 (FATAL) You have not input anything for FILH2O, or you input $LH2O \leq 0$, although $DOWS = T$ or $DOECC = T$ or $IAVERG = 1$ or 4 or $UNSUPR=T$.
- 8 (FATAL) Your input for SPTYPE contains an invalid string.
Hints: Correct your input of SPTYPE (or do not input it).
- 9 (FATAL) You input one of the following non-positive:
NDCOLS, NDROWS, NDSLIC, ICOLST, ICOLEN, IROWST, IROWEN, ISLICE
Hints: (1) You must explicitly set these in LCMgui, when LCMgui cannot determine these values (e.g., from CSI data in Siemens Vision or .ima files).
(2) This error can also be caused by incorrectly transferring files (see Sec 3.7.5).
- 10 (FATAL) Your input violates one of the following requirements:
 $ISLICE \leq NDSLIC$; $ICOLEN \leq NDCOLS$; $IROWEN \leq NDROWS$.
- 11 (FATAL) You have not input anything for FILCOR, although you set $LCORAW > 0$.
- 12 (FATAL) $NUNFIL < 64$, an unreasonably small value.
- 13 (FATAL) You must have $0 \leq IAVERG \leq 4$ or $IAVERG = 31$ or $IAVERG = 32$.
- 14 (FATAL) You must have $1 \leq IROWSK(J) \leq NDROWS$ and $1 \leq ICOLSK(J) \leq NDCOLS$ for $1 \leq J \leq NVOXSK$.
- 15 (FATAL) You have not input anything for FILCSV, although you set $LCSV > 0$.
- 16 Not used.
- 17 (warning) With SPTYPE = 'muscle-5', 'lipid-8', 'breast-8' or 'liver-11', you should have $PPMEND \leq -1.0$, to give sufficient baseline to the right of the lipid signals around 1.3 & 0.9 ppm.
- 18 (warning) With SPTYPE = 'lipid-8', 'breast-8' or 'liver-11' and $PPMST \geq 5.0$, you should have $PPMST \geq 8.0$, to give sufficient baseline to the left of the water signal.
- 19 (warning) With SPTYPE = 'liver-11' and $PPMST < 5.0$, you should have $PPMST = 4.0$, to give sufficient baseline to the left of Glycg, but to avoid the tail of the residual water signal.
- 20 (warning) With SPTYPE = 'breast-8' and $PPMST < 5.0$, you should have $PPMST$ between 3.8 and 4.0, to give sufficient baseline to the left of Cho, but to avoid coming too close to the tail of the residual water signal.
- 21 (warning) With SPTYPE = 'lipid-8' and $PPMST < 5.0$, you should have $PPMST$ between 3.4 and 4.0, to give sufficient baseline to the left of the lipid signals, but to avoid coming too close to the tail of the residual water signal.
- 22 (warning) With SPTYPE = 'only-cho-2', you should have $PPMST$ between

3.8 and 4.0 and PPMEND between 2.6 and 2.8, to give sufficient baseline to the left and right of Cho, but to avoid coming too close to the tail of the residual water signal or the lipid signals.

- 23 (FATAL) With SPTYPE='lipid-8', 'breast-8' or 'liver-11', the Hidden Control Parameter IPOWRG must be 1 or 2.

Hints: Do not input IPOWRG.

- 24 (FATAL) You must have the Hidden Control Parameter NBCKMN ≥ 4 .

Hints: Do not input NBCKMN.

- 25 (FATAL) You must have the Hidden Control Parameter DKNTMN(1) or DKNTMN(2) > 0 .

Hints: Do not input DKNTMN.

MYDATA reads and scales the data in the .RAW and .H2O files.

- 1 (FATAL) Namelist NMID in your .RAW file contains no (or a blank) FMTDAT format specification. The data cannot be read.

- 2 (FATAL) At least one of the following input variables in Namelist NMID in your .RAW file is not input positive: TRAMP, VOLUME or your Control Parameter FCALIB is not positive.

- 3 (FATAL) Namelist NMID in your .H2O file contains no (or a blank) FMTDAT format specification. The data cannot be read.

- 4 (warning) HZPPPM in the .CONTROL file differs from that in the .RAW file by more than 5%. The HZPPPM from the .CONTROL file will be used. This could mean poor modeling of coupled resonances if it is wrong.

Hints: Check the values in both files.

- 5 (ERROR) No .H2O file could be read, although DOWS = T or DOECC = T. Water-Scaling and eddy-current correction will not be done.

- 6 Not used.

- 7 (FATAL) Error trying to read Namelist NMID in FILRAW.

Hints: See Sec 12.1.1.

- 8 (FATAL) Error trying to read time data in FILRAW.

Hints: In FILRAW, check that the time data correspond to FMTDAT. Does the file size correspond to your input NUNFIL, or (with multi-voxel data) with NDSLIC, NDROWS, NDCOLS?

- 9 (FATAL) Error trying to read Namelist NMID in FILH2O.

Hints: See Sec 12.1.1.

- 10 (FATAL) Error trying to read time data in FILH2O.

Hints: In FILH2O, check that the time data correspond to FMTDAT. Be sure that FILH2O corresponds exactly to FILRAW, except for water suppression, especially for multi-voxel data sets.

- 11 (warning) At least one of the following input variables in Namelist NMID in your .H2O file is not input positive: TRAMP, VOLUME. The values from your .RAW file will be used. If these values are not the same for .H2O & .RAW, then this would cause an error in your Water-Scaling and therefore the absolute concentrations.

- 12 (FATAL) No .H2O file could be read, although UNSUPR=T says to analyze the .H2O file as data.

ONEPAG produces the One-Page Output. Aborts in ONEPAG will suppress the One-Page Output.

- 1 (ILLOGICAL) Meaningless argument in call to ONEPAG.

- 2 (FATAL) At least one of the following Control Parameters is not positive: PTLABL, PTTITL, PTOUTP, or at least one of the following is less than 1.0: RHLABL, RHTITL, RHOUTP, RHVERS.

- 3 (ILLOGICAL) As ONEPAG 1.

- 4 (FATAL) You have allocated so much space for margins, titles and labels that there is no room left for the plot, or you have input negative values for XLEFT or YBOTT.
- 5 (ERROR) You have input a non-positive value for XSTEP. It will be set to 0.20.
- 6 (FATAL) The ppm-axis consists of at most two Grid Points.
Hints: Are PPMST and PPMEND very close together?
- 7 (ERROR) You have input a non-positive value for NSUBTK. It will be set to 1.
- 8 (FATAL) All the curves to be plotted have exactly one single value. **Hints:** **Never Happened**, but if it did, this single value would probably be zero, indicating gross input errors.
- 9 (FATAL) Same as ONEPAG 8.
- 10 (ERROR) All of the Residuals to be plotted have exactly the same value.
Hints: **Never Happened**, but if it did the value would probably be zero, and the hints for PLINLS 3 or ONEPAG 8 would apply.
- 11 (FATAL) Same as ONEPAG 8.
- 12 (ERROR) There is not enough vertical space for even the Concentration Table.
Hints: Check the Control Parameters in Secs. 9.9.3.2 & 9.9.3.3; if they are reasonable, then input IPAGE2 = 1.

OPENOU Opens and checks output files, giving them unique names with multi-voxel data sets.

- 1 (FATAL) One of your output pathnames would be more than 255 characters long. This probably happened inserting a unique identifier for multi-voxel data. **Hints:** Shorten the pathname.
- 2 (FATAL) Error trying to open FILPRI. **Hints:** Check permissions.
- 3 (FATAL) Error trying to open FILCOO. **Hints:** Check permissions.
- 4 (FATAL) Error trying to open FILTAB. **Hints:** Check permissions.
- 5 (FATAL) Error trying to open FILCOR. **Hints:** Check permissions.

PARSIM Parses the string in CHSIMU(JSIMU). Except for error number 0 below, the error number is JSIMU + 100 × IERR, which are listed below. For example, if you get FATAL PARSIM 709, then your CHSIMU(9) caused the diagnostic labeled 7nn below. All PARSIM errors are FATAL.

Hints: See Sec 11.7 for the symbols below. The tokens and rules in Sec 11.7 must be followed exactly. The errors here refer to wrong tokens or format. The actual values are checked elsewhere. The number of spaces between elements should not be important, but only spaces (not tabs, etc.) are allowed.

- 0 The end of CHSIMU could not be found. Are there more than 20 peaks, i.e., more than 20 ppm*? Is CHSIMU more than 528 characters? It must end with a number preceded by AMP=
- nn Error reading *metabo* @.
- 1nn Error reading *ppm1* +-
- 2nn Error reading *sdppm* FWHM=
- 3nn Error reading *fwmn1* <
- 4nn Error reading *fwex* +-
- 5nn Error reading *sdfw* AMP=
- 6nn Error reading *amp1* @ (or end of CHSIMU instead of @)
- 7nn Error reading *ppm** FWHM= (where * > 1)
- 8nn Error reading *fwmn** AMP= (where * > 1)
- 9nn Error reading *amp** @ (or end of CHSIMU instead of @) where * > 1.

PARSUM parses the Concentration Sums *metdenom* & *metwt* in Sec 11.8. At least part of the illegal string is output at the end of the Detailed Output. All PARSUM diagnostics are FATAL.

- 1 A *metdenom* or *metwt* has more than 211 characters. There is probably an error in the **CHRATO** string.
- 2 One of the Metabolite Names in the Concentration Sum has more than 6 characters.
- 3 A Concentration Sum has more than 30 Metabolite Names.

PHALIP Phases lipid spectra.

- 1 The Hidden Control Parameter $\text{PPMST_PHALIP} \leq \text{PPMEND_PHALIP}$. Do not input these parameters.

PHASTA Gets starting estimates for the phase corrections.

- 1 (**ERROR**) Your input **DEGPPM** is not between **DGPPMN** and **DGPPMX**. It will be changed to the closest of these two.
Hint: Correct your input of **DEGPPM**, **DGPPMN** or **DGPPMX**

PLINLS (“Partially linear least-squares”) organizes the nonlinear-least-squares analyses. There are many independent analyses, and diagnostics here often only mean that LCMODEL is working hard, but that the final results are not affected.

- 1 (**ILLOGICAL**) Meaningless argument in call to **PLINLS**.
- 2 (**FATAL**) Meaningless value for at least one of the following Hidden Control Parameters: **PMQST**, **PMQSTL**, **RSTPMX**, **RCONVR**, **RMQDEC**, **RMQINC**, **COSMIN**, **RINCRS**, **RPMQMN**, **RSTPMN**. **Hints:** Do not input these.
- 3 (**warning**) Somehow, a perfect fit has been achieved. **Hints: Never Happened**, but if it did, it would probably be due to inputting data that were all zero or equal to a Basis Spectrum.
- 4 (**info**) Numerical instabilities have caused a normally nonnegative dot product to become negative; corrective action is taken. **Hints: Working Hard.**
- 5 (**warning**) Somehow, the magnitude of the step or the gradient of the objective function has become zero; corrective action is taken. **Hints:** This can happen when the Marquardt parameter gets very large; **Working Hard.**
- 6 (**ERROR**) Somehow, the denominator of a formula computing step size has become zero; corrective action is taken. **Hints: Never Happened.**
- 7 (**info**) Maximum iterations before complete convergence in one analysis. **Hints: Working Hard.**

PNNLS (“partial nonnegative least squares”) does a quadratic-programming analysis at each iteration in the nonlinear-least-squares analysis.

- 1 (**info**) Maximum iterations before convergence in the quadratic program; corrective action is taken.
Hints: Working Hard. This is common when there is only one dominant peak, as often with lipid-dominated spectra, such as muscle or liver. It is especially critical when prior phasing information has not been input using **SDDEGZ** or **SDDEGP**. It can occur many times in one analysis. With prostate or lipid-dominated spectra, it does not seem to be a problem.

PPRIOR parses the **CHRATO** for the Concentration Ratio Priors. The error number is $\text{JPRIOR} + 100 \times \text{IERR}$, which are listed below. For example, if you get **FATAL** **PPRIOR** 213, then your **CHRATO**(13) caused the diagnostic labeled **2nn** below. All **PPRIOR** errors are **FATAL**.

Hints: See Sec 11.8 for the symbols below. The tokens and rules in Sec 11.8 must be followed exactly. The errors here refer to wrong tokens or format. The actual values are checked elsewhere. The number of spaces between elements should not be important, but only spaces (not tabs, etc.) are allowed.

nn **CHRATO**(**nn**) is an empty string, or the token = is missing, or

metnum/metdenom is missing.

1nn *expect* is missing or non-numeric, or the token *+-* is missing.

2nn *stddev* is missing or non-numeric, or the token *+WT=* is missing, or an unexpected character instead of the end of the string was encountered.

3nn *metwt* is missing or non-numeric, or an unexpected character instead of the end of the string was encountered.

RBASOL (“Ratio of baseline to solution”) If the distance traveled by the baseline is large compared to the maximum peak in the solution, a more detailed search for phase corrections is made.

1 (**FATAL**) A critical optimization has failed to converge.

Hint: Check for poor quality data.

2 (**FATAL**) Same as **RBASOL** 1.

3 (**warning**) All concentrations are zero at an intermediate stage in the analysis. This probably means that the data are very poor.

RFALSI (“*regula falsi*”) adjusts the overall regularization until the criterion in [11] for choosing α_B and α_S in [1, Eq (4)] is satisfied. Problems here are often restricted to one of many independent analyses and do not necessarily affect the final results.

1 (**ILLOGICAL**) Meaningless arguments in call to **RFALSI**.

2 (**FATAL**) At least one of the Hidden Control Parameters **RALIMN** or **RALINC** is less than 1.0. **Hints:** Do not input these.

3 (**FATAL**) A critical unregularized least-squares analysis has failed.

Hints: Check for very poor or erroneous data.

4 (**info**) α_B has reached its maximum allowable value.

Hints: This is normal with very smooth Baselines or with very noisy data.

5 (**info**) α_B has reached its minimum allowable value. **Hints: Working Hard.**

6 (**info**) α_S has reached its maximum allowable value.

Hints: This is common with very noisy data or very smooth lineshapes.

7 (**warning**) α_S has reached its minimum allowable value. **Hints:** This can happen with very narrow lineshapes, e.g., narrower than the Basis Spectra, as often *in vitro*.

8 (**info**) α_B and α_S have both reached their maximum allowable values.

Hints: This is common with very noisy data or very smooth lineshapes and Baselines.

9 (**warning**) α_B and α_S have both reached their minimum allowable values.

Hints: Working Hard.

10 (**ERROR**) A nonlinear-least-squares analysis has failed; corrective action will be attempted. **Hints: Never Happened.**

11 (**info**) A local minimum in the objective function has been detected and corrected.

Hints: Working Hard.

12 (**info**) A local minimum in the objective function in an unregularized analysis has been detected and corrected. **Hints: Working Hard.**

13 (**info**) Numerical instabilities have caused the objective function to increase; corrective action is taken. **Hints: Working Hard.**

14 (**warning**) Maximum iterations in looking for an acceptable regularizer.

Hints: Working Hard.

15 (**FATAL**) All nonlinear-least-squares analyses in all iterations failed.

Hints: Never Happened, but, if it does, check for very poor or erroneous data.

16 (**ERROR**) Somehow, the objective function or the number of free parameters has gone to zero. Corrective action will be attempted. **Hints: Never**

Happened.

- 17 (**warning**) A regularizer satisfying the criterion in [11] to within the desired tolerances could not be found. The regularizer could be inappropriate.

Hints: Working Hard

- 18 (**info**) α_S has reached its maximum allowed value.

Hints: Common with lipid spectra.

SAVBES saves information on the best solution found so far.

- 1 (**ILLOGICAL**) Meaningless argument in call to **SAVBES**.

SETUP initially sets up regularizers, priors, and starting estimates for the nonlinear-least-squares analyses in [1, Eq (4)].

- 1 (**FATAL**) One of the Hidden Control Parameters **DKNTMN**, **RBACKG** or **FWHMST** has been set nonpositive. **Hints:** Do not input these.

- 2 (**ERROR**) N_B would exceed its maximum allowable value (80). It is being reduced to this value.

Hints: This should cause no problems, but it could only occur with unusual values of the Control Parameters in **SETUP 1** or a very wide Analysis Window.

- 3 Not used.

- 4 (**FATAL**) an eigenvalue decomposition to get the regularizer R_B failed.

Hints: Never Happened.

- 5 (**FATAL**) The number of parameters exceeds the available storage. Actually this is an **ILLOGICAL**, since these limits should have already been checked.

Hints: Never Happened.

- 6 (**FATAL**) Same as **SETUP 5**.

- 7 (**FATAL**) $\text{FWHMBA} \leq 0$, and it must be positive.

- 8 (**FATAL**) Same as **SETUP 5**.

- 9 Not used.

- 10 (**FATAL**) A starting value is $\alpha_B \leq 0$ or $\alpha_S < 0$.

Hints: This can only occur if you have modified Hidden Control Parameters, such as **ALPBST**, **ALPSST** or **DKNTMN**.

- 11 (**FATAL**) Same as **SETUP 5**.

- 12 (**FATAL**) Same as **SETUP 5**.

- 13 (**FATAL**) The Hidden Control Parameter $\text{FWHMST} \leq 0$ and it must be positive.

Hints: Do not input this.

- 14 (**FATAL**) A starting value for a γ_ℓ is not positive, and they must be.

Hints: Check that your Control Parameters **DEEXT2**, **ALEXT2** are positive; leave the Hidden Control Parameter **FWHMST** at its default.

- 15 (**FATAL**) Same as **SETUP 5**.

SOLVE sets up and solves the quadratic programming problem at each iteration of the nonlinear-least-squares analysis of [1, Eq (4)].

- 1 (**ILLOGICAL**) Meaningless arguments in call to **SOLVE**.

- 2 (**FATAL**) One of the $\sigma(\epsilon_\ell) \leq 0$, and they must be positive.

Hints: These values are given in the table of Basis Spectra in the Detailed Output. Check that your Control Parameters **DESDSH**, **ALSDSH** are positive.

- 3 (**FATAL**) You have set the Hidden Control Parameter **SDMSHF** nonpositive, and it must be positive. Do not input it.

- 4 (**FATAL**) Same as **SOLVE 2**.

- 5 (**FATAL**) One of the $\sigma(\gamma_\ell) \leq 0$, and they must be positive.

Hints: These values are given in the table of Basis Spectra in the Detailed Output. Check that your Control Parameters **DESDT2**, **ALSDT2** are positive.

- 6 (**FATAL**) Same as **RFALSI 3**.

- 7 (**FATAL**) One of the following Hidden Control Parameters has been changed to

a nonpositive value: DFLDMQ, DDGZMQ, DDGPMQ, RSHFMQ, RPOWMQ, RSDSMQ, RRT2MQ, NSIDMN. Do not input these.

- 8 (ERROR) Somehow there are as many free parameters as data points, or the fit to the data is perfect. **Hints:** As for FISHNI 1.
- 9 (FATAL) The Hidden Control Parameter FRACT_POWER_SD must be positive.

SSRANG (“sum of squares range”) finds the range of the first sum in [1, Eq (4)] corresponding to a given range of confidence levels [11].

- 1 (ILLOGICAL) Meaningless arguments in call to SSRANG.
- 2 (FATAL) the computed upper limit in the range is smaller than the lower limit.
Hints: This is only conceivable if you have modified the Hidden Control Parameter PRNMNMX. Do not input it.

STARTV (“starting values”) manages the elaborate Preliminary Analysis to get starting estimates for the Final Analysis.

- 1 (FATAL) Both DOREFS(1) and DOREFS(2) are .FALSE.. Thus, no referencing can be done.

Hints: This is a simple way to force an abort early in the run to get the Absolute-Value Plot of the raw data on the One-Page Output, as in PLOT 5 in \$HOME/.lcmode1/doc/figures.pdf.

- 2 (FATAL) SHIFMN(JREFS) > SHIFMX(JREFS) for JREFS = 1 or 2.
- 3 (FATAL) NREFPK(JREFS) is nonpositive or exceeds 10 for JREFS = 1 or 2.
Hints: NREFPK(2) will be automatically decremented for each δ -function that is not within the Analysis Window. If you drastically restricted the Analysis Window with PPMST or PPMEND, then you may have to change PPMREF(*,2) and HZREF(*,2) so that at least one δ -function is in the Analysis Window. Alternatively, you can use PPMSHF, which avoids using NREFPK.
- 4 (warning) The CCF with the first set of δ -functions, specified by PPMREF(*,1) (the water peak), would cause an extreme shift of SHIFMN(1) or SHIFMX(1). Thus, the residual water peak after water suppression is very far from 4.65 ppm.

Hints: This is often caused by a very distorted or weak residual water peak. If this diagnostic consistently occurs, plot the absolute value of the spectrum, including the water peak, with “Preview Data” in LCMgui (Sec 7.4.1). If your water peaks are consistently very weak and distorted, then do not input DOREFS(1) = T; leave it at its default of .FALSE.. However, except for wasted computer time, this diagnostic should imply no problems, unless the landmarks specified by the second set of δ -functions are also very weak. If a disaster like PLOT 17 in \$HOME/.lcmode1/doc/figures.pdf occurs, Sec 11.3 can help.

A second possibility is that this extreme shift really is necessary. You can also see this from the Absolute-Value Plot. If this is so, then input PPMCN or adjust SHIFMN(1) or SHIFMX(1).

- 5 (warning) The CCF with the second set of δ -functions, specified by PPMREF(*,2), would cause an extreme shift of SHIFMX(2).

Hints: This is usually caused by a spectrum with little structure or with a huge lipid peak. This could cause a gross referencing error and something like PLOT 17 in \$HOME/.lcmode1/doc/figures.pdf. If this occurs, try SPTYPE='tumor' (only with brain) or plot the Absolute-Value Plot of the spectrum with “Preview Data” in LCMgui (Sec 7.4.1) and use PPMSHF.

A second possibility is that this extreme shift really is necessary. You can also see this from the Absolute-Value Plot. If this is so, then input PPMCN or SHIFMN(2) or SHIFMX(2).

- 6 (**info**) The CCF with the second set of δ -functions, specified by `PPMREF(*,2)`, would cause an extreme shift of `SHIFMN(2)`.
Hints: This is often caused by the spectrum climbing steeply towards the incompletely suppressed water peak (or possibly a strong lipid peak). A new CCF will be computed with `NREFPK(2)` reduced by one (to eliminate the δ -function closest to water).
- 7 (**warning**) The action in `STARTV 6` has been repeated until there are only 2 δ -functions left (usually NAA and Cr), and the extreme shift is still being called for by the CCF.
Hints: Either the true referencing shift is extreme (reset `PPMCEN`, `SHIFMN` or `SHIFMX`), or your spectrum has very little structure or extreme residual water or lipid peaks (more common with CSI). If the referencing looks reasonable, and not like `PLOT 17` in `$HOME/.lcmode1/doc/figures.pdf`, then LCModel has managed anyway and there is no problem. Otherwise, Sec 11.3 can help.
- 8 (**warning**) The FWHM of a CCF extends to the right beyond the whole spectral window. **Hints:** As in `STARTV 5`.
- 9 (**warning**) The FWHM of a CCF extends to the left beyond the whole spectral window. **Hints:** As in `STARTV 5`, or the residual water peak is very strong.
- 10 (**ERROR**) You input an `NSHIFT > 25`. It will be reduced to 25 (still a very large value).
- 11 (**FATAL**) You have input `DGPPMN \geq DGPPMX`.
- 12 (**FATAL**) Same as `SETUP 13`, which should have already caught this.
- 13 (**info**) The Preliminary Analysis did not search the whole grid for the referencing shift as finely as it normally does.
Hints: When (the Hidden Control Parameter) `QUICK = T`, this diagnostic is unavoidable. Otherwise, you can avoid this by increasing `NSHIFT`, but this would increase the computation time, and the default `NSHIFT = 8` is usually adequate, despite this diagnostic. If a disastrous referencing error like `PLOT 17` in `$HOME/.lcmode1/doc/figures.pdf` occurs, Sec 11.3 can help.
- 14 (**FATAL**) All nonlinear-least-squares analyses in the Preliminary Analysis failed.
Hints: As in `RFALSI 3`.
- 15 (**FATAL**) An essential nonlinear-least-squares analysis at the end of the Preliminary Analysis failed. **Hints:** As in `RFALSI 3`.
- 16 (**warning**) All nonlinear-least-squares analyses in the Preliminary Analysis failed to fully converge to optima. **Hints:** As in `RFALSI 3`.
- 17 (**ERROR**) You have input the Hidden Control Parameter `NSIDMX > 20`. It will be reduced to 20.
- 18 (**FATAL**) You have input the Hidden Control Parameter `NSIDMN` nonpositive or exceeding `NSIDMX` in `STARTV 17`.
- 19 (**ERROR**) You have input the Hidden Control Parameter `INCSMX` nonpositive or exceeding 20. It will be increased to 1 or decreased to 20.
- 20 (**info**) The Preliminary Analysis has estimated a lineshape so narrow that N_S in [1, Eq (1)] would be less than `NSIDMN=5`; N_S will be increased to `NSIDMN`.
Hints: Be sure that AQ, your acquisition time for one scan, is not so short that the spacing between spectral points is too large to sample your peaks finely enough. If this diagnostic occurs often, then you should increase (e.g., double) AQ. You must then do this for all your acquisitions; all your data must have the same AQ. If it occurs only seldom, then you have only occasional high-resolution spectra, and nothing needs to be done.
- 21 (**ERROR**) The Preliminary Analysis has estimated a lineshape so wide that an N_S in [1, Eq (1)] would effectively exceed `NSIDMX*INCSMX` ($11 \times 15 = 165$) Grid Points. This is being reduced to `NSIDMX*INCSMX` (in increments of

INCSMX).

Hints: Check for very poor data or spectral resolution. If the data quality is acceptable, then follow the Hints for **STARTV** 24.

- 22 (FATAL) Your PPMST or PPMEND or one of the Control Parameters in INITIA 1 is so unreasonable that your Analysis Window (extended by the finite convolution in [1, Eq (1)]) extends outside your entire spectrum.

Hints: Check these Control Parameters. If they are OK, then you will have to reduce your Analysis Window to fit further within your spectrum or acquire your data with a larger bandwidth.

- 23 (ERROR) The Preliminary Analysis has estimated a lineshape so wide that the convolution in [1, Eq (1)] would extend beyond the entire spectrum ppm-range. The convolution range will be reduced.

Hints: Either your spectrum has very poor resolution or your bandwidth is too small.

- 24 There seem to be a large number of spectral data points per peak. That is, the Preliminary Analysis has estimated a lineshape so wide that an N_S in [1, Eq (1)] would effectively exceed $NSIDMX = 11$ Grid Points. The increment, δn in Sec 9.9.4, will be made 2, 3 or 4 (**info**) or greater (**warning**) to cover the convolution range in no more than $NSIDMX$ steps.

Hints: With a **warning** only:

The following can only be used for single-voxel data, not CSI or multi-channel data: If the data quality and resolution are acceptable and *you consistently get this warning for all your spectra*, then display your time data with LCMgui's "Preview Data" (Sec 7.4.1). If these time data have completely decayed into the noise in the first half or quarter of the time range, then truncate the remainder that is mainly noise. You simply input an $NUNFIL$ 1/2 or 1/4 the original $NUNFIL$; there is no need to change the .RAW file. Bruker and Varian users can use the Preprocessor (Sec 7.4.5) **truncate** to automatically reduce $NUNFIL$. You must consistently do this for all your data; all your spectra must have the same acquisition time for one scan.

- 25 (**warning**) The Preliminary Analysis has estimated an excessively broad lineshape.

Hints: Check for very poor data or spectral resolution.

- 26 (FATAL) Your spectrum does not extend far enough on the ppm-axis to make your input PPMSHF possible.

Hints: Adjust PPMST, PPMEND, PPMSHF or your bandwidth.

TWOREG ("two regularizers") Manages the Final Analysis, finding the solution with the best pair of regularization parameters, α_B and α_S in [1, Eq (4)].

- 1 (FATAL) An essential unregularized nonlinear-least-squares analysis has failed.

Hints: As in RFALSI 3.

- 2 (FATAL) $RDALPB \leq 1.0$ or $ALPBST < ALPBMN$ or $ALPBST > ALPBMX$.

Hints: All of these are Hidden Control Parameters; do not input them..

- 3 (**warning**) A less-than-normal extent of lineshape smoothing has been explored. The regularizer might be suboptimal.

Hints: Check for very poor data or spectral resolution.

- 4 (FATAL) A regularized solution within the acceptable range of the confidence region in [11] could not be found.

Hints: Check for very poor or erroneous data (e.g., that would require a wild Baseline). Do not modify Hidden Control Parameters such as PRMNMX.

- 5 (FATAL) Both $PRMNMX(2,1)$ and $PRMNMX(2,3)$ exceed $PRMNMX(1,2)$.

Hints: Do not input these Hidden Control Parameters.

- 6 (**warning**) An important regularized analysis has failed to properly converge. The final results may be affected.

Hints: Check for very poor data or spectral resolution.

- 7 (**info**) A regularized analysis in a refinement step has failed to properly converge. The final results should not be seriously affected.

Hints: Working Hard.

- 8 (**info**) An extra iteration was required in determining the phases.

Hints: Working Hard

- 9 (**info**) Extra iterations were required in determining the phases.

Hint: This is common in spectra dominated by lipids, as muscle, liver, bone marrow, etc. Imposing prior knowledge about phase corrections (Sec 9.7) can help greatly.

- 10 (**warning**) A regularized solution within the specified confidence region could not be found at some stage. The closest solution will be used.

Hint: This is fairly common in spectra dominated by lipids, as muscle, liver, bone marrow, etc. If it does not occur in the final stage, the solution will hardly be affected.

- 11 Not used.

- 12 (**info**) A more detailed search for phase corrections will be made. This can increase the computation time considerably.

Hint: This is common in spectra dominated by lipids, as muscle, liver, bone marrow, etc.

- 13 (**FATAL**) DDEGP3 is non-positive, or $MDEGP3 \leq 2$.

Hint: Do not input these Hidden Control Parameters.

- 14 (**warning**) Too many extra searches from a grid of first-order phase corrections are needed. The grid will be made coarser.

Hints: An extreme first-order phase correction may be needed. If so, you should input DEGPPM, DGPPMN and DGPPMX to specify its range. If you have already input a wide range with DGPPMN & DGPPMX, then there is nothing further to do.

- 15 Not used.

- 16 (**info**) The usual solution found a first-order phase correction outside the range of DGPPMN and DGPPMX. A further search for better phase corrections will be made.

- 17 (**info**) An additional search was made for phase corrections, but the original solution was found to be best.

UPDPRI (“Update priors”) Updates prior probabilities for phases & shift during a multi-voxel analysis.

- 1 (**FATAL**) Same as MAIN 1.

WSCALE (“Water-Scaling”) Does Water-Scaling. Errors here mean that if you are attempting Water-Scaling (DOWS=T), then only the concentration ratios of the metabolites in the .BASIS file will be valid. If you are simulating metabolite Basis Spectra, then the concentrations of all of the simulated metabolites would have to be multiplied by an (unknown) scale factor to be consistent with the concentrations of the .BASIS metabolites. All WSCALE diagnostics are of type ERROR.

- 1 The integral of the unsuppressed water reference signal is not positive or could not be computed because of AREAWA 1-4.

Hints: Your water-reference must be without water suppression. Check and/or display this data (in FILH20). See PPMH20 in Sec 10.2.2.

- 2 One of the following was not input positive: ATTH20, WCONC.

ZEROVX (“Zero voxels”) Opens and checks the `.RAW` file. In multi-voxel analyses, it skips over voxels whose data are all zeros (which can occur in Philips SDAT files if you do not follow the steps in Sec 3.7.6).

1 (**FATAL**) Namelist `NMID` in your `.RAW` file contains no (or a blank) `FMTDAT` format specification. The data cannot be read.

2 (**FATAL**) There are more than 65536 voxels in your `.RAW` file.

3 (**FATAL**) Error trying to open `FILRAW`.

Hints: Check for non-existent file or permissions.

4 (**FATAL**) Error trying to read Namelist `NMID` in `FILRAW`.

Hints: See Sec 12.1.1.

5 (**FATAL**) Error trying to read time data in `FILRAW`.

Hints: In `FILRAW`, check that the time data correspond to `FMTDAT`. Does the file size correspond to your input `NUNFIL`, or (with multi-voxel data) with `NDSLIC`, `NDROWS`, `NDCOLS`?

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