LCModel[1] & LCMgui[2] User's Manual

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[1]LCModel Version 5.2-2
[2]LCMgui Version 1.1-0

The latest version of the complete LCModel/LCMgui package and their documentation can be downloaded from the following site:
`http://S-provencher.COM`

Email: `sp@S-provencher.COM`

DISCLAIMERS

LCMgui is not part of the LCModel package. It is being made available without charge for LCModel only, with no warranty, on an "as is" basis.

LCModel is distributed strictly as a research (not a clinical) tool; to the maximum extent permitted by applicable law, in no event shall Stephen W. Provencher or the Max-Planck Society or its organs be liable for any damages whatsoever arising out of the use of or the inability to use LCModel.

Contents

Chapter 1

Preface & Overview

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

1.1 What You Must Read

In order to avoid the proliferation of documents, this is the only manual for the LCModel 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 only to non-users.

The only necessary reading for everyone is Chaps. 1 & 2 (seven pages). 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 will allow you to competently use LCModel.

Chapters 3 & 4 need only be read by the person initially installing LCModel in your laboratory. Chapter 4 describes important input *Control Parameters* specific to your spectra, such as field strength, dwell time, etc. With LCMgui, these are often automatically determined.

Chapter 5 provides useful general guidelines for judging spectra and for recognizing and salvaging problem spectra.

Chapter 6 is a guide on the basics of using LCMgui.

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 library of *in vitro* model metabolite *Basis Spectra* for your laboratory. This is not necessary if your sequence matches one of the libraries that are freely available; check with me first. Otherwise, the LCModel license includes my setting up the Control Parameters and running the program to construct your first library from your model data.

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 LCModel's diagnostic messages and gives general hints for trouble-shooting.

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 LCModel. It is easy to modify the LCModel Control Parameters to make use of the possibilities described in Chaps. 4, 9 & 11.

1.2 Normal Use of LCModel

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 LCModel could also write a simple Pre-Formatting Program or script to automatically format the input data and then run LCModel. 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 LCModel. There is also another LCModel 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

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.ps`. Your home directory is specified by `$HOME/`, although you can usually abbreviate this with a tilde, ~ /.

Further conventions for more advanced users are defined in Sec. 4.1.

1.3.1 Figures

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

FIGURE 2 or FIG. 2 (in all capitals and without a decimal point in the figure number) refers to the Fig. 2 in the `$HOME/.lcmodel/doc/figures.ps` file. You should output this on a printer with PostScript capability, as was done with `$HOME/.lcmodel/doc/manual-letter.ps` or `$HOME/.lcmodel/doc/manual-a4.ps` for this manual. 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 for providing much data during the development of LCModel. The first 10000 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 General Electric Medical Systems (Fremont, CA), Marconi Medical Systems (Highland Heights, OH) and Bruker Medical (Ettlingen, Germany) for contributing model metabolite spectra and much information on their data structures. I thank Else Danielsen (Copenhagen), Thomas Michaelis (Göttingen) and Petra Pouwels (Amsterdam) for providing Siemens 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 (Stockholm), Else R. Danielsen (Copenhagen), Markus Wick (Ettlingen), Jens Frahm (Göttingen) and Ralph Hurd and Napapon Sailasuta (Fremont) for information and suggestions on scaling for absolute concentrations.

LCMgui was written with the free software packages Tcl/Tk (Scriptics Corporation, `http://www.scriptics.com`), Tix (Ioi K. Lam, `http://tix.mne.com/htdocs/tix/index.html`) 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*. Print out `$HOME/.lcmodel/doc/figures.ps`. FIGURE 1 there shows 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 at the entries in the `%SD` column first. These are the estimated standard deviations, expressed in percent of the estimated concentrations. These `%SD` estimates are only lower bounds, 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, and its estimated concentration is not worth looking at. Several metabolites are often undetectable in normal subjects.
- `%SD` $\approx 25\%$ indicates that only changes of about 50% can be detected with high reliability, e.g., the approximate doubling of Gln/Glu in several pathologies. Concentrations with `%SD` $< 20\%$ are in boldface (blue if you have color). This means that all concentrations not in boldface blue are unreliable.
- `%SD` $\approx 10\%$ is very good, and `%SD` $\approx 5\%$ is excellent.
- Of course, means over a group of LCModel analyses of similar spectra can greatly reduce the uncertainties.

The abbreviations of the metabolites are in the 4th column. (Table 8.1 lists these abbreviations.) 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, as described in Sec. 6.3.4 & Chap. 10, are the absolute concentrations meaningful.

NAAG is quite difficult to resolve from NAA, and PCh is practically impossible to resolve from GPC. With lower quality spectra, Glu and Gln are also often difficult to resolve. The last three rows of the table are the sums of these concentration pairs. The sums NAA+NAAG and GPC+PCh are much more accurate than the individual concentrations, as can be clearly seen from their %`SD` values. In this high-quality spectrum, Glu and Gln are well enough resolved so that the %`SD` for Glu+Gln is not smaller than that for Glu.

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 FIG. 1, they look fairly randomly scattered about zero, indicating a fit to within experimental error, with no apparent systematic errors. Chapter 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. 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 FIG. 4, 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. It is obtained from a crude *Preliminary Analysis* using Gaussian-Lorentzian lineshapes and is used only to get starting estimates.

`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 [3, p. 218].

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 data phase corrections, ϕ_0 and ϕ_1, using the conventions in the definition of `DEGPPM` in Sec. 8.5.2.

Section 9.6.5 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 LCModel. 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 with all the tables is printed. It is best to use a printer that prints on both sides of a page; otherwise Sec. 4.3.5 shows how to easily suppress this second page.

The 3rd and 4th lines of this table in FIG. 1 show the simple changes (described in Sec. 9.6.4.1) to get additional plots of the individual contributions of NAA and NAAG to the spectrum. These are shown in FIGS. 2 & 3.

2.6 Optional Further Reading

This is the end of the necessary reading for Normal Users. You should now be able to competently analyze your spectra with LCModel and to interpret the results. If you would like to become a more expert LCModel user, look through the figures accompanying this manual and read Sec. 5.2. Even better would be to read all of Chap. 5. It uses the figures to illustrate guidelines for recognizing and salvaging problem spectra. In most laboratories, such problem spectra occur only rarely (typically at a rate of less than 1%). However, Chap. 5 is still worthwhile, since the remedies are generally very simple and obvious (usually restricting the ppm-range of the Analysis Window or rejecting the spectrum altogether). You can jump directly to Chap. 5 without reading anything in between or after.

Section 4.4 provides useful guidelines for choosing your acquisition protocol; Sec. 4.4 can also be read without reading anything else.

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.

Chapter 3

Installation and Test Runs

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

3.1 PostScript Output

The LCModel documentation and the main results are in PostScript files. You should be able to output these on a printer, preferably one that prints on both sides of a page. In addition to this manual, you should also print out `$HOME/.lcmodel/doc/figures.ps`.

3.2 Test Runs

3.2.1 PostScript Printer

During the LCMgui test run, you are asked to enter the command for printing PostScript files (Fig. 3.1). Before the test run, you can print out this manual and `$HOME/.lcmodel/doc/figures.ps` to test the command. For example, if you were successful with

```
lpr -Pmypr $HOME/.lcmodel/doc/figures.ps
```

then in the green entry field in Fig. 3.1, you enter

```
lpr -Pmypr
```

If

```
lpr $HOME/.lcmodel/doc/figures.ps
```

works, then you leave the green entry field at

```
lpr
```

The test runs will then automatically output the "One-Page Output" (four pages in this case). You compare these with FIGS. 1–3 (in `figures.ps`).

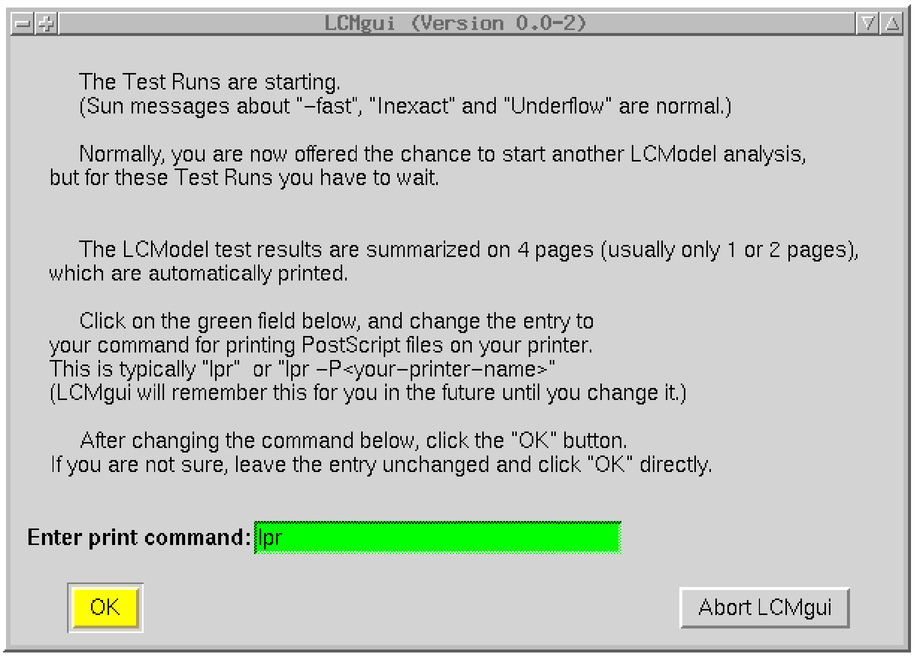

Figure 3.1: Here you enter your command for printing PostScript files.

3.2.2 Display on Your Screen

If you do not have a PostScript printer connected, you can also use a display program. The Aladdin Ghostscript package is freely available from `http://www.cs.wisc.edu/~ghost/index.html`. Versions for Sun are available from `http://sunfreeware.com`. With Ghostscript, if you enter

`ghostview -seascape`

as the print command in LCMgui's green entry field, the One-Page Output will be displayed on your screen.

Other display programs are `gv`, `xv`, `pageview` and `xpsview`.

3.2.3 No Printer or Display

If none of the above is available, enter the harmless command

`touch`

in the green print command field. LCMgui always outputs the test runs results into `$HOME/.lcmodel/tests/output/test.ps`. You can then transfer this file to a computer that can print or display the file. You can also use Ghostscript to print PostScript files on many non-PostScript printers. Ghostscript is easy to install on Microsoft systems.

3.3 Computation Time

The computation time can be considerably reduced if you tell LCModel where to start looking for the phase corrections, as discussed in Secs. 4.3.3 & 4.3.4. This is usually possible if eddy-current correction (ECC) [4] is done. The last two lines of the tables in the test output show how this was simulated with this (old, non-ECC) data, to give you a rough idea of the computation time with ECC data.

The computation time depends on many other factors as well, but, if the computation time for your test runs on your workstation was T_{test}, then we can make the following very rough estimates:

- Marconi/Picker & GE data (which automatically include provision for ECC): $0.8T_{test}$
- Philips, Siemens and Bruker data with ECC: $2T_{test}$
- Without ECC: $4T_{test}$.

Since LCModel does not require interaction, arbitrarily many runs can be put in a queue and processed in background without your presence.

3.4 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 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 "GE 5.x", "GE LX", "Marconi", "Philips" or "Siemens", corresponding to your data. (See Sec. 6.2.1.)
- In Fig 6.1, select your data file. (See also Sec. 6.2.2.)
- LCMgui should automatically convert your data and put the absolute value of the 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.)

3.5 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 $HOME/.lcmodel/gui-defaults
```

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

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

Chapter 4

Essential LCModel Input

If you use LCMgui and GE, Marconi/Picker or Philips single-voxel data or Siemens data, then you can skip this chapter; LCMgui does everything for you, but the basic Control Parameters defined in Sec. 4.3 will interest many of these LCMgui users as well.

Non-graphical programs for preparing single-voxel Bruker binary `fid` files, Marconi/Picker `dump` files, Philips `SDAT` files, Siemens `raw` files, GE Probe raw P-files (Signa 5.x & LX), and GE Signa 5.x spectrum G-files are freely available from me for use with LCModel. Marconi also provides a non-graphical interface to their LCModel users. However, with Bruker files, you will have to add Control Parameters to the file in Sec. 4.3.

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

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

where `my.control` is a `.CONTROL` file (Sec. 4.3) 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 can 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.

4.1 Conventions

4.1.1 File suffixes

LCModel filetypes are denoted by suffixes 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. 4.2. (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. 4.3.

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 suffixes used in this manual are:

`.PS` for a PostScript file that you can directly 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.

4.1.2 Control Parameter Conventions

When a Control Parameter is defined in this manual, its name is followed by its Fortran type in parenthesis. Some example of Fortran type specifications are:

CHARACTER*20 means a string of a maximum of 20 characters enclosed in single quotes, as for `SEQ` in Sec. 4.2.1.

INTEGER(20) means an integer array with up to 20 elements, as for `KEY` in Sec. 4.3. In the `.CONTROL` file, you could specify the first two elements of the `KEY` array as
`KEY = 12345, 23456`
or
`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`

4.2 .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. Truncation effects are automatically accounted for by consistently using un-windowed FFTs with both the Basis Set and the data.

An example is provided by the `.RAW` file with the test data in
`$HOME/.lcmodel/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:

4.2.1 Namelist SEQPAR

The.RAW File begins with the Namelist SEQPAR:

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

Namelists are used throughout LCModel. See your Fortran Manual for their many convenient features. For the generation deprived of Fortran, use the Namelists in your LCModel 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. Almost all 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., HZPPPM $= 42.58 B_0$, with B_0 in Tesla. You should input it with an accuracy of at least three, preferably four, significant figures.

SEQ (CHARACTER*5) must be either PRESS or STEAM, according to the localization method used for this data. Note that the string must be all upper case. In Namelists, strings are case sensitive, but variable names are not. Thus you could also use
seq='STEAM'
but *not* seq='steam'.

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.

4.2.2 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='(8F10.5)'
 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`. The data points are input in order of increasing time, with each point a complex pair (the real part followed by the imaginary part). No default; this 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") This is for Bruker & Philips users only. All Bruker & Philips data must have `BRUKER = T`, which causes all 4 programs in the LCModel package to complex conjugate the data; this is necessary with Bruker & Philips data. (This Control Parameter was named, before I had contact with Philips 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. Section 10 specifies this in detail. In addition, absolute concentrations are more sensitive than concentration ratios to the corrections for relaxation (Sec. 11.1) and partial volume effects (which are all independent of LCModel).

4.3 .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. 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. This is given to you with your license. Together with `OWNER`, it enables you to run LCModel on the workstation for which it was licensed.
- `TITLE` (CHARACTER*120) 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: 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.

4.3.1 Instrument and Acquisition

HZPPPM (REAL) ("Hz per ppm") same as in Sec. 4.2.1. You should input it with an accuracy of at least three, preferably four, significant figures.
Default: `HZPPPM = 84.47` (1.984 T, which you will probably have to change.)

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`

For Bruker users only: Bruker uses another convention for dwell time and bandwidth; you must input twice Bruker's dwell time.

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 rat- and human brain spectra at 1.5 T and 2.0 T, 0.8 s or 1.0 s seems about optimal.

4.3.2 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). For brain, PPMEND should never exceed 1.95.
Default: `PPMEND = 1.0`

PPMST (REAL) ("ppm start") the upper limit of the ppm-range; i.e., the left edge of the Analysis Window. For brain, your PPMST should be at least 3.85 (to include information from Glu & Gln). Default: `PPMST = 4.0`, but at 1.5 T and below or with TE $\geq$ 40 ms, you may need to use `PPMST = 3.85`, as explained below.

Water suppression can attenuate the metabolite signals above 4.0 ppm; so it is usually best not to increase PPMST above 4.0. To avoid distortions around 4.0 ppm, it is best to use a weak to moderate water suppression and restrict its bandwidth, e.g., with GE Signa systems to set `bw_rfsup = 35` or `offset_rfsup = 20`.

Nevertheless, at 1.5 T and below, attenuation above 3.85 ppm is often unavoidable, and `PPMST = 3.85` is better. This is particularly recommended with GE Probe and Marconi/Picker spectra, since their excellent initial phasing can be used as prior knowledge, and the missing Cr peak around 3.93 ppm is not important.

You should also use `PPMST = 3.85` if your TE $\geq$ 40 ms, because of relaxation effects and the easier analyses at long TE.

These two Control Parameters are also the most important ones for salvaging problem spectra. They are probably the only two that the Normal User will also want to occasionally change. This is discussed in Sec. 5.1.

4.3.3 Eddy-Current Correction

Eddy-current correction (ECC) [4] is recommended. This requires also a reference fid from the same voxel with the same sequence, except with no water suppression. This reference is automatically appended to the water-suppressed data in a single GE Probe raw P-file or Marconi/Picker file, and the two required LCModel `.RAW` files (see Sec. 9.3) can be made. In other cases, you have to organize this yourself. You then add `DOECC` & `FILH2O`, as specified in Sec. 9.3 to your `.CONTROL` file.

In addition to improving the baseline and lineshapes, ECC usually greatly reduces the zero-order phase correction. Section 9.4.1 shows how you can experimentally investigate whether this correction is small. If it is, then this prior knowledge can speed up and improve the LCModel analysis, especially of poor quality spectra. 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`.)

For Bruker users only: With Avance data acquired using `ACQP DIGMOD==digital_mode`, you use Bruker's `convdta`. Do not input `SDDEGZ` in this case, since the zero-order phase correction is not small.

In rare cases, particularly if the water suppression is weak and the unsuppressed and water-suppressed pair do not match well enough, 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 by removing `DOECC` and `SDDEGZ` from the `.CONTROL` file for this spectrum only.

4.3.4 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. As specified in Sec. 9.4, 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 (check with me or the manufacturer for the latest info):

- GE Probe data: `SDDEGP = 2.`
- Marconi/Picker STEAM data: `SDDEGP = 2., DEGPPM = 2.5`
- Marconi/Picker PRESS data: `SDDEGP = 2., DEGPPM = 28.`
- Bruker Avance data with `ACQP DIGMOD==digital_mode`: `SDDEGP = 4.`

LCMgui uses the first three above as defaults.

Siemens data unfortunately often have a big ϕ_1. However, this may be quite consistent, i.e., also with a small `SDDEGP`, as with the Marconi/Picker PRESS value of 28 deg/ppm, which they calculated from their precisely known timing. Section 9.4.1 shows how you can experimentally estimate `DEGPPM` and `SDDEGP`.

The test of Sec. 9.4.1 would also be a good idea with Bruker data, since my recommendations for this are based on limited experience. You also may find a small `SDDEGZ` with eddy-current correction.

4.3.5 PostScript Output

Section 9.6.4 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 always change 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.
These are case-sensitive; you must use capital letters.
The default is `PGNORM = '  '` and makes a bad compromise to fit in both page formats.

If 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 send this output to 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);
`IPAGE2 = 1` (the default) to output a second page 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.

4.3.6 Archiving the Results

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 names 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., `'pat_777_77.table'`).

`LTABLE` (INTEGER)
`LTABLE` = 0 (the default) will suppress creation of this file;
`LTABLE` = 7 will make this file.

The `.PS` file contains all the information in the One-Page Output, including the plotted curves. The coordinates for the plots are in a compressed format in the `.PS` file and not so easy to extract; they have also been rescaled to the plot size. If you also want to archive the coordinates of the plots, you can get LCModel to output the `.COORD` file, which also contains all the information for the One-Page Output, but in an easy-to-read and self-explanatory format:

`FILCOO` (CHARACTER*255) ("coordinate file") the name of the `.COORD` file to be output (e.g., `'pat_777_77.COORD'`).

`LCOORD` (INTEGER)
`LCOORD` = 0 (the default) will suppress creation of this file;
`LCOORD` = 9 will make this file.

Thus, three ways to archive your results, in order of increasing information (and storage costs), are:

- Archive the `.TABLE` file (about 2 kbyte);
- Archive the `.PS` file (typically 25 kbyte);
- Archive the `.COORD` file (typically 35 kbyte).

You can also use the `.COORD` file as input to your own plotting program.

4.3.7 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 smoothes them, and this falsifies the statistical tests [5] 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.

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`

In addition, your phantom spectrum must be dominated by at least one of the following: NAA, Cr, Cho, or Lac. Otherwise, you will have to set additional parameters as illustrated in Sec. 11.4. So, it is much simpler if your phantoms always contain significant amounts of at least one of the above 4 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.

4.4 Guidelines for the Acquisition

- **Acquisition protocol:** The field strength, localization sequence (PRESS/STEAM), TE & (for STEAM) TM of your data and the Basis Set must match, as specified in Sec. 8.1.
- GE users only: The standard **Probe** protocol, producing raw "P-files", is highly recommended.

- To fully exploit the capabilities of LCModel, **short echo times** (TE $\leq$ 30 ms, better 20 ms) and long repetition times (TR $\geq$ 5000 ms) reduce differential relaxation effects. The increased signal at long TR can nearly compensate the S/N for the reduced number of scans per unit time.
- **Eddy-current correction** (ECC) [4] is recommended.
- **Avoid all other digital post-processing.** Smoothing is very bad; it destroys information and ruins the statistical tests in LCModel. Other filters, particularly excessive suppression of water or baseline, cannot avoid distorting the spectrum. LCModel wants the truth, not aesthetically pleasing, but distorted, data.
- **Avoid excessive water suppression** in your acquisition protocol, to avoid distortions around 4 ppm. LCModel can account for the residual water signal (as in FIG. 7).

Chapter 5

Tutorial and General Guidelines

5.1 Recognizing and Salvaging Problem Spectra

This section uses the figures in `$HOME/.lcmodel/doc/figures.ps` for a tutorial on judging and possibly salvaging problem spectra. All but FIGS. 5, 15 & 16, use exactly the same data, but often with simulated artifacts added. Thus, you can see the effects of these artifacts by changes in the concentrations from the original unperturbed concentrations in FIG. 1. The concentration ratios tend to be even more robust to artifacts.

The main criteria are provided by the estimated uncertainties in the concentrations and by the Residuals and the Baseline.

5.1.1 Estimated Uncertainties in the Concentrations

The %`SD` is an obvious criterion for judging spectra. If the %`SD` values for even the strongest metabolites exceed 15–20%, then there is not much information in the spectrum. FIGURE 5 illustrates such a borderline case, with a very low S/N in cerebrospinal fluid (CSF), which lacks the usual strong landmarks of NAA, Cr & Cho. LCModel still succeeds in finding Lac and Glc, but the other %`SD` values clearly warn of the large uncertainties.

5.1.2 Residuals

These are the differences between the data and the fit to the data. They are plotted at the top of the One-Page Output. They provide sensitive diagnostics for judging the spectrum.

5.1.2.1 Non-Random Residuals

The Residuals should appear randomly scattered about zero. This is not the case in FIG. 6 (where the choline-containing compounds, GPC & PCh, were removed from the Basis Set). Around 3.2–3.3 ppm, you can see significantly long runs of successive Residuals that all have the same sign. Here the problem occurs well within the Analysis Window and cannot be remedied with `PPMST` or

`PPMEND`. You should reject such a spectrum, because the artifact could very well have corrupted other parts of the spectrum. Another reason to reject it is the following:

5.1.2.2 Outliers

The least-squares criterion in LCModel minimizes the sum of the squares of the Residuals. Residuals several times larger than the rest are called outliers, and they can dominate and distort the analysis. FIGURE 6 has very big outliers between 3.25 and 3.20 ppm.

5.1.3 Baseline

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

- substances not present in the Basis Set;
- substances possibly in the Basis Set, but with abnormally short $T2$ times;
- incomplete water suppression;
- artifacts in the data.

5.1.3.1 Smooth Climbs or Descents can be Handled Well

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 optimal filter in frequency space, as illustrated in FIG. 7. It can handle the residual water signal much better than digital post-processing with more restrictive assumptions and consequent distortions. The concentrations are not seriously perturbed from FIG. 1, although the spectrum is at first disturbing visually. Too strong water suppression inevitably distorts the data around 4.0 ppm. A more typical, less extreme, case is shown in [6, Fig. 4].

5.1.3.2 Sharp Bends are a Problem

The only restriction is that the Baseline cannot bend too sharply (as in FIG. 6). The Baseline in FIG. 8 would have to bend extremely sharply around 4.4 ppm. The key diagnostic that this bend is too much for the Baseline is again in the Residuals; between 4.5 and 4.6 ppm they are much larger and show systematic (non-random) deviations of the fit from the data. Since the problem occurs at the edge of the Analysis Window, the remedy is simply to reduce `PPMST` to the reasonable value of 4.0 in FIG. 1. (Normally, you would never go above `PPMST = 4.0` anyway; `PPMST = 4.6` was used only to provoke this problem.) Residual water seldom causes such sharp bends in the region below 4.0 ppm.

More realistically, such over-sharp Baselines can be caused by susceptibility artifacts [6, Fig. 3] or by sharp macromolecule or lipid peaks. Three such peaks are simulated in FIG. 9. Here the long runs of non-random Residuals clearly show that these lipid peaks are much too sharp to be compensated for by the Baseline.

Again, the problem is at the edge of the Analysis Window, and the remedy is simply to restrict the Analysis Window to be above 1.8, using `PPMEND = 1.8`, as in FIG. 10. (Note that the metabolites Ala, Lac & GABA, which are weakly represented in this Analysis Window, are automatically removed from the analysis; Sec. 9.5.2 specifies how you can control which metabolites are included in the analysis.)

5.1.3.3 Broad Humps can be Handled Well

FIGURE 11 simulates a much more common single broad lipid (or macromolecule) hump plus Lac. There is absolutely no problem separating the lipid and Lac. Only at poor resolution, where the Lac and Ala doublets coalesce are there uniqueness problems, illustrated in [1, Fig. 4].

FIGURE 12 shows a borderline case, with a huge simulated lipid peak. The residuals do not show excessively large systematic deviations around the peak, but such huge peaks can cause difficulties, particularly with referencing. Such peaks occur more often with the small brains of mice, where contributions from outside the brain are more difficult to avoid. If non-random Residuals occur, then you must cut off the lipid with `PPMEND` about 1.9. If referencing problems occur, Sec. 11.2 shows how you can help LCModel with extra information for referencing.

5.1.4 Low-Information Spectra

Restricting to too narrow a ppm-range, i.e., `PPMST` < 3.85 or `PPMEND` > 1.95, greatly reduces the information content and therefore the accuracy of the analysis. FIGURE 13 shows an analysis over a very restricted ppm-range. The estimates are obviously now much more uncertain. (The reasonable NAA estimate shows the remarkable information content of the NAA spectrum, not only at 2.01 ppm.)

Particularly organs other than brain, with less structure in their spectra, could lead to this problem. Sections 9.4 & 11.2 show how you can help LCModel with such extremely low-information spectra by providing phasing or referencing information.

5.1.5 Obvious Failures

FIGURE 14 shows a typical obvious failure, with a wild baseline and obviously wrong referencing. This also illustrates that the error estimates can become meaningless in the presence of huge systematic errors, which invalidate the model (and the error estimates).

One possibility is that the data are hopelessly bad, e.g., due to extreme problems with eddy currents or shimming (particularly with difficult regions, such as the cerebellum or hippocampus). A more common cause is a big mistake in the input to LCModel, as here, where `PPMSHF = 0.4` constrains LCModel to look for the referencing shift in a completely wrong ppm-region. (The NAA peak is around 2.2–2.3 ppm and should be at 2.01 ppm.) Look first for obvious errors, such as using the wrong Basis Set, acquisition protocol, or (as in this example) incorrect constraints.

Another possible cause is that your spectra really do need an unexpectedly large referencing shift, e.g., because your center frequency is far from the water resonance. Section 11.2 shows how you can check this with PlotRaw (or with LCMgui, the "Preview Data" button) and remedy this with `DOREFS, SHIFMN`, or `SHIFMX`.

5.1.6 Sagging Baselines

A Baseline sagging away from the data can be a useful warning that the data are incompatible with the Basis Set, as in FIG. 15, where the data have an echo time of TE = 270 ms and the Basis Set a TE = 20 ms. Here the data are accurate enough to force the Baseline to strongly distort before the incorrect Basis Set could fit them. Wild Baselines are also caused by severe difficulties with shimming, particularly in difficult areas, such as the cerebellum or hippocampus.

Note that the Baseline in [1, Fig. 4] is also far below the data. However, this is normal with low-resolution spectra; the space between the spectrum and the Baseline is filled with the tails of overlapping peaks. The key difference is that in [1, Fig. 4] there is no steep dip in the Baseline away from the data.

FIGURE 16 also has a strong dip in the Baseline but not away from the data. This is obviously due to some artifact in the data itself, not the Basis Set. The Baseline follows the data quite well, but the larger non-random Residuals between 1.1 and 1.0 ppm show that the Baseline cannot quite handle this dip. In any case, such spectra should obviously be rejected, since there is generally no way of knowing to what extent the artifact is present in the rest of the spectrum; the same applies to the succeptibility artifact in [6, Fig. 3].

5.2 Guidelines for Judging Spectra

- **Estimated uncertainties** are the best reliability guides. Always look at %`SD` in the Concentration Table first. A %`SD` > 50% means that the corresponding concentration estimate is not worth looking at.
- Problem spectra are usually clearly indicated by poor fits to the data (most clearly indicated by **non-random Residuals**). If the problems are near the edge of the Analysis Window, restricting `PPMST` or `PPMEND` often provide simple and effective remedies.
- **Low-Information spectra** (e.g., with low S/N or not from brain) can sometimes be salvaged by supplying extra information specified in Secs. 9.4 & 11.2.
- Poor fits **throughout** the Analysis Window usually indicate hopeless artifacts in the data. Reject such spectra.

Chapter 6

Elementary Guide to LCMgui

This chapter gives the basic steps for the Normal User in using LCMgui. Chapter 3 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. 6.2.2).
- Click on "Run LCModel" (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 the "superuser" or root. You can then always start LCMgui with:

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

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

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

or even with simply:

```
lcmgui
```

6.2 Selecting the Data to be Analyzed

6.2.1 Possible Data-File Types

LCMgui automatically handles the following file types (with single-voxel data only, except for Siemens):

Siemens: "raw" files from Vision, Symphony, Sonata (but not from the old SP). With single-voxel data, the analysis proceeds automatically. If the "raw" file contains a CSI data set, then LCMgui prompts you for the voxel number, as explained in Section 7.4.4.1.

GE Probe raw P-files: These are recommended. They are originally in the directory `/usr/g/mrraw/`, with Signa 5.2–5.7 filenames of the form `Pnnnnn` and with Signa LX filenames of the form `Pnnnnn.7`.

GE spectrum G-files: (Signa 5.2–5.7 only, not LX) These are normally 18944 bytes in `/usr/mrspecraw/Gnnnnn.nnn.xxxxxxxxxxxx`. They are not as complete or convenient to use as P-files. You also have to be more careful, since you have the freedom to produce G-files that no longer match your model spectra.

Marconi/Picker: spectroscopy fid "dump" files, obtained by clicking the "dump" button in your Marconi/Picker software.

Philips Gyroscan SDAT files: The corresponding `SPAR` file must be in the same directory. It must have the identical filename as the `SDAT` file, except for `.spar` instead of `.sdat` at the end.

LCModel `.RAW` files: As specified in Sec. 7.4.4, you can always use LCMgui with your own program that converts your data to the standard LCModel `.RAW` file.

6.2.2 File Selector Window

When LCMgui is started, the first window that appears is usually the *File Selector*. An example with GE Signa 5.x data is shown in Fig. 6.1. With data from other manufacturers, the instructions in the left window and the title, "Select your GE Signa 5.x …" will be different. LCMgui remembers the directory where the data file was in the last run, and the File Selector starts there.

If the last LCMgui session did not use GE, Marconi/Picker, Philips or Siemens data, then the window in Fig. 6.3 will appear. You normally then simply click the "Other" button in Fig. 6.3.

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. 3.4) or to install your license (as in Sec. 7.2.5).

As the instructions in the left window in Fig. 6.1 indicate, you first navigate through the directory tree in the right pane by double-clicking on directory names. When you click on a directory, its files are listed in the left 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).

If your Siemens "raw" file contains a CSI data set, LCMgui prompts you for the voxel number, as explained in Section 7.4.4.1.

Only filenames that match the filter shown at the top of the pane of filenames (`P?????  G*` in Fig. 6.1) are

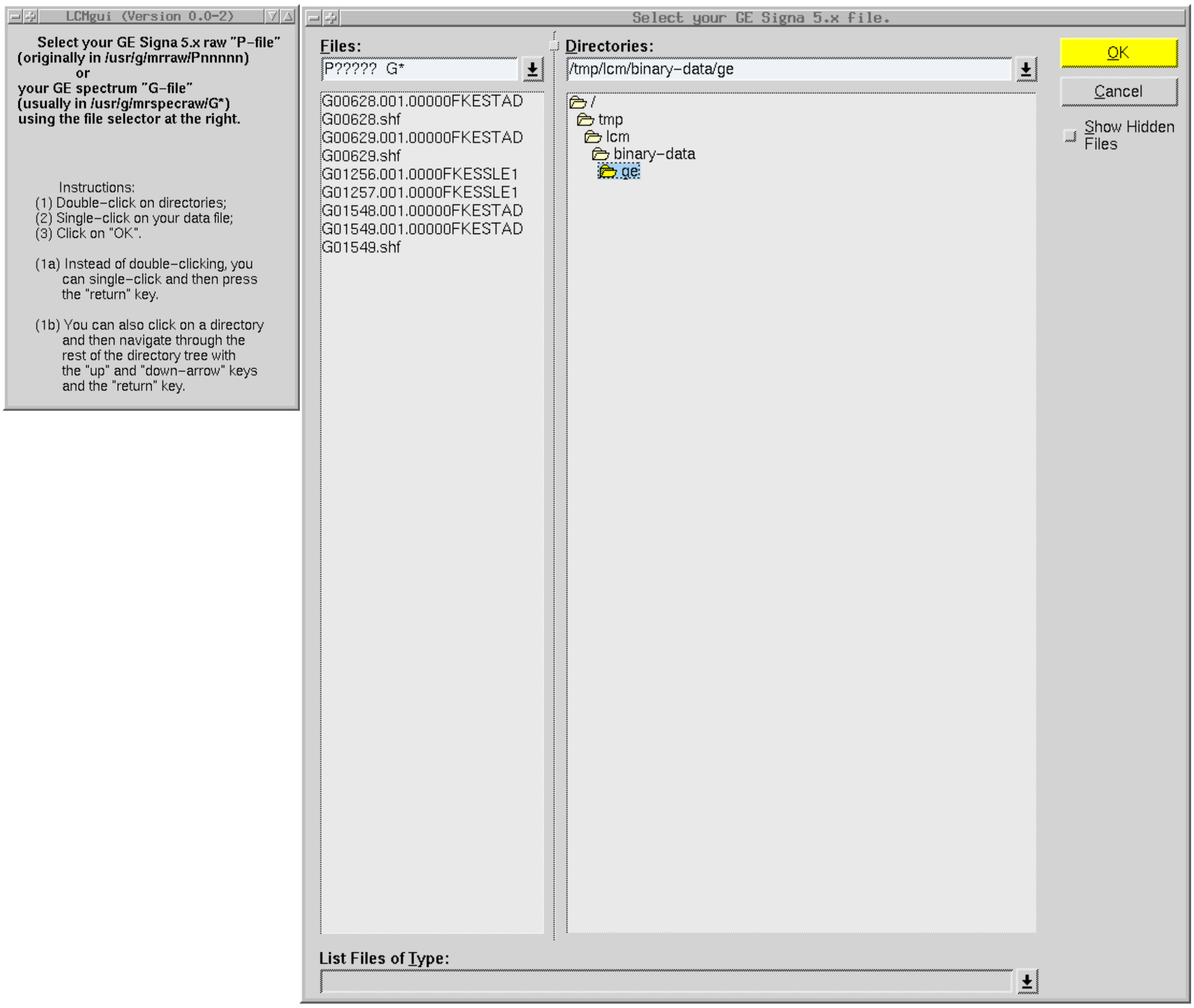

Figure 6.1: The File Selector

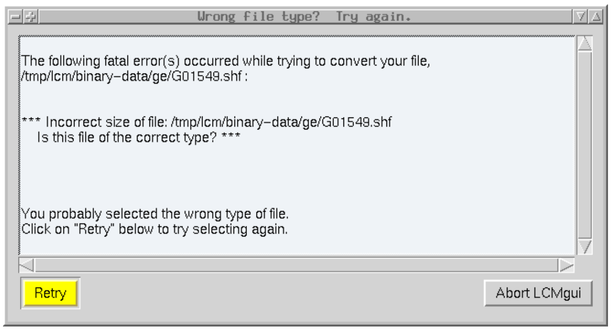

Figure 6.2: You selected a file of the wrong type in the File Selector

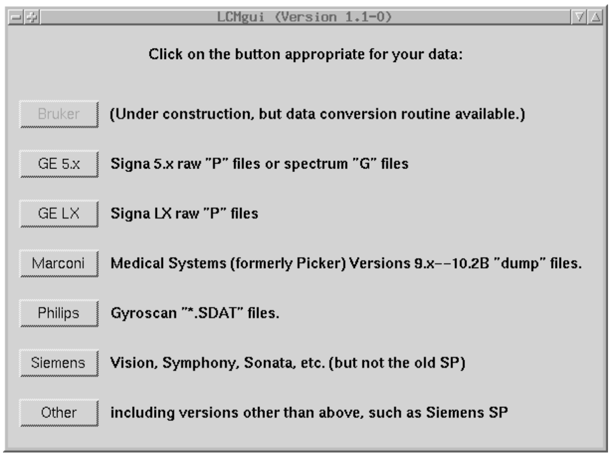

Figure 6.3: Note that GE Signa 5.x & LX have distinct buttons.

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), it will not be listed. You can change the filter by clicking on the field (`P?????  G*`), pressing the "backspace" or "delete" key, entering your new filter (e.g., `*`), and pressing the "Return" key.

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

The filenames in Fig. 6.1 were so long that they were cut off in the original left pane of the window. This left pane was then made wider by holding the the left mouse button down on the small square at the top on the pane boundary (left of "**Directories:**") and dragging the pane boundary to the right.

6.2.2.1 Selecting the wrong file type

LCMgui remembers what type of data was analyzed from this account 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). You should avoid analyzing data of different types from the same username, since you confuse LCMgui's memory of default settings and of the archive directories for the results. The only exception is that you might use one username for both GE Signa 5.x & LX data.
- Select a completely irrelevant file (e.g., an `.shf` header file in Fig. 6.1).

In either case, 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.

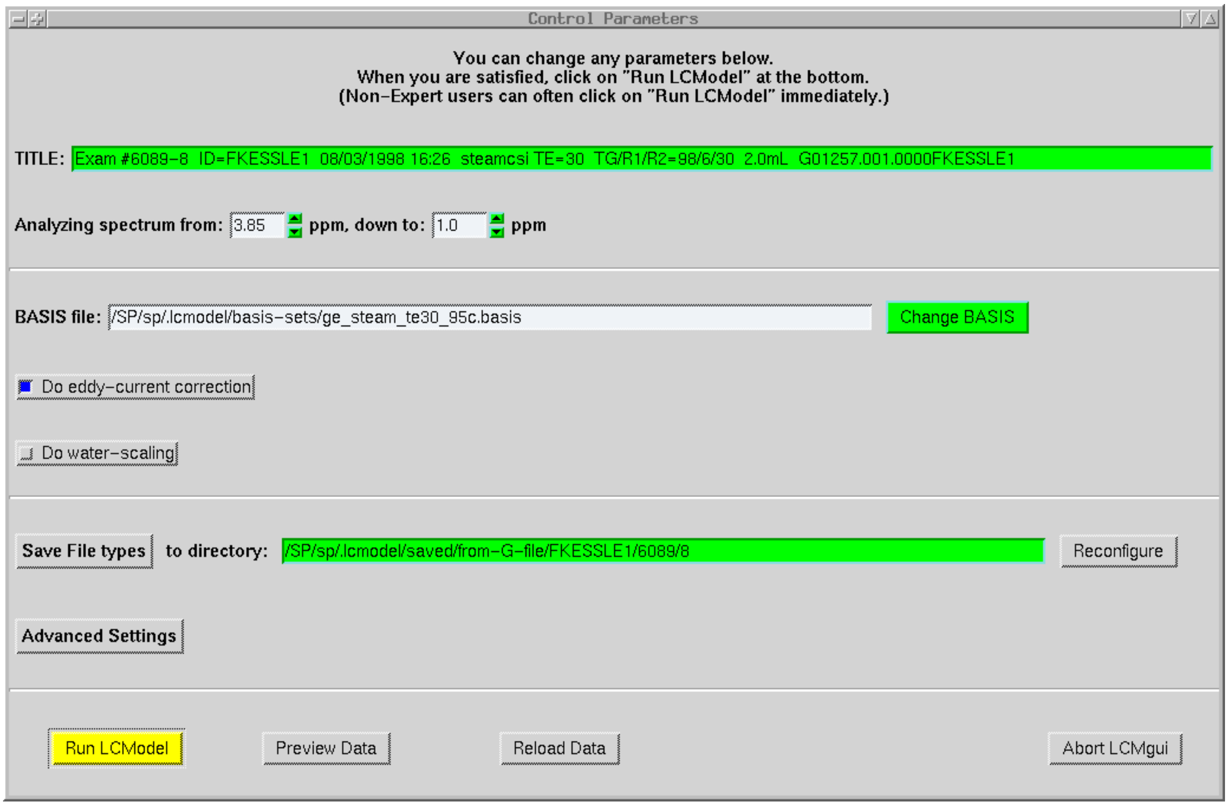

Figure 6.4: The Control Parameters Window

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.)

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 three 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. 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.)

Two reasons why you might want to change these entries are:

(a) As explained in Sec. 4.3.2, `PPMST` (the left entry) should normally be 3.85. You can increase it to 4.0, but normally only if your field strength is at least 2.0 Tesla *and* your TE $<$ 40 ms *and* your water suppression does not attenuate the spectrum in the region 3.85–4.0 ppm.

(b) You may also want to temporarily narrow these limits to salvage a problem spectrum, as illustrated in Chap. 5.

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 LCModel 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 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. 6.2.2.

6.3.3 Do eddy-current correction

Users with Marconi/Picker data or GE Probe P-files can skip this section, 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 eddy-current correction (ECC) between active (blue) and inactive (no ECC). (Blue usually indicates a button that is switched on.)

ECC is recommended, but you then must also have acquired an unsuppressed water reference spectrum from the same voxel immediately before or after acquiring your water-suppressed spectrum. 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 and water-suppressed pair do not match well enough) 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 for this spectrum only.

6.3.4 Do water-scaling

Water-Scaling uses the unsuppressed water reference signal (as used above for ECC) to help estimate absolute concentrations. Section 10.2.2 discusses the significant uncertainties in the corrections needed for this. Chapter 10 also discusses an alternative for GE and Siemens 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 7.3.3 & 7.3.4 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 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 appears at the top of the One-Page Output. It is automatically extracted from the header information in the GE, Marconi/Picker, Philips and Siemens files. You can also 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. 7.5) 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. 7.3.3.

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)

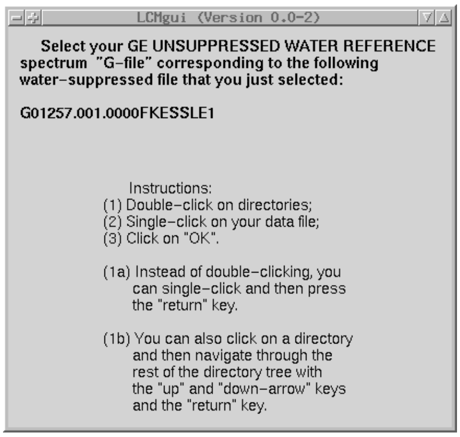

Figure 6.5: The instructions-part of the File Selector for the unsuppressed water reference.

6.3.6 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 yellow 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. 6.2.2.

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. 6.2.2. (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 (`G01256.`··· in this example).

With Philips, Siemens 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.

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 a 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. 7.3.4.

6.5 Where is the Output?

Normally LCMgui automatically prints the One-Page Output with a print command that was specified during installation in Sec. 3.2.1. If you cannot find your printed output, Sec. 7.4.6 specifies how you can check and correct this print 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. 7.3.2, which also specifies how you can change the structure of this archive directory tree.

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 (particularly of GE or Marconi/Picker data) may go so fast 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 (e.g., with Ghostview, by clicking the left mouse button down on the "File" field and releasing your mouse button on "Quit").

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 three buttons:

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

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.

Exit & Forget : LCModel 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.

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. So, occasionally you may have to make emergency escapes from LCMgui, without LCMgui remembering what you have done. If the normal LCMgui exit buttons are not available, you can:

- Enter `Control-C` in the UNIX window from which you started LCMgui.
- In the main pull-down menu of an LCMgui window (usually obtained by clicking in the upper left corner) click on "Kill". If "Kill" is not available, then clicking a menu item like "Exit" or "Close" may do it.

6.8 Avoiding Crashes

If you are using LCMgui over a network, e.g., with TELNET, you can crash LCMgui by trying to iconify its windows. (The icons are tiny anyway.) With Ghostview and other programs, this even happens when you try to change orientation or size (or sometimes even just exiting Ghostview normally).

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 GE, Marconi/Picker, Philips or Siemens files (Sec. 6.2.1). However, it can also be 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 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.

7.1.1 Limitations

Most displays have sufficient resolution for LCMgui. The display must have at least 1024 × 768 pixels (better 1280 × 1024); 800 × 600 pixels are not enough.

With LCMgui, you select a single file, presumably with a single spectrum. There is no provision for viewing or processing a two-dimensional array of spectra. Section 7.4.4.1 discusses modifications to LCMgui that have been made (for Siemens CSI data sets) and could be made to handle CSI and other sets of spectra.

7.2 Installing LCMgui

As mentioned in Chap. 3, downloading from the WWW site on Page 2 and installing (and uninstalling) are very simple. Root privilege is not used. The entire package goes into `$HOME/.lcmodel/` of the user's directory.

7.2.1 How Many Installations?

There can be an unlimited number of users with LCMgui installations. One important constraint is that there should be a separate installation and username for each different type of data (e.g., Bruker and GE). LCMgui has only one file (`$HOME/.lcmodel/gui-defaults`) to store all configuration settings, and this file would likely get inconsistent with two different types of data. The only compatible sharing might be with GE Signa 5.x & LX P-files.

Many sites have dummy usernames with one account for each different type of data, or you might create users `lcmge` and `lcmbrukr`. With only one type of scanner, you might also let each user have their own installation. You can probably better decide on this after reading this chapter and seeing how users share the same LCMgui configuration and the same archive of LCModel output.

You can easily make multiple installations, each with the same configuration, by copying the directory tree `$HOME/.lcmodel` to other user accounts.

7.2.2 Starting LCMgui

To start LCMgui, you normally must enter:

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

7.2.2.1 Simplifying Startup

Enter

```
$HOME/.lcmodel/bin/install-link
```

The script should tell you the link that was installed. As long as you do not delete this link, you should be able to start LCMgui with

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

If `install-link` tells you that it could not install a link, then, with `root` privilege, something like the following might work (and allow other users' copies of `$HOME/.lcmodel/lib/` to be deleted):

```
cd  $HOME/.lcmodel/lib
mv tix4.1  /usr/local/lib/
```

7.2.2.2 Further Simplification

After the preceding step, 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:

Printing: You set the print command in the initial test run (Sec. 3.2.1), and all future results will be automatically printed.
Section 7.4.2 specifies how you can both print and simultaneously display the results on the screen.

Data File Type: In the second test (Sec. 3.4) during installation, you set the data type (e.g., Philips Gyroscan SDAT, Siemens raw, Marconi/Picker dump, or GE Signa LX or 5.x) and test the automatic conversion and input of data to LCModel.
If you do not have the automatically convertible file types specified in Sec. 6.2.1, 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 with the same field strength, localization sequence (PRESS/STEAM), TE & (for STEAM) TM as your data. Bruker, GE and Marconi have contributed LCModel Basis Sets with standard sequences for their users. Basis Sets for standard Siemens sequences (not supplied by Siemens) are freely available to all LCModel users. You can install the GE and Siemens 1.5 T Basis Sets with commands like the following:

```
ftp ftp.S-provencher.COM
  anonymous
  <your e-mail address>
  cd pub/LCModel/siemens
  binary
  get model-spectra.tar
  bye
tar xf model-spectra.tar
./install-model-spectra
```

GE sites can replace “`cd pub/LCModel/siemens`” above with “`cd pub/LCModel/ge`”.

If your firewall prevents you from downloading with FTP, then you can download with your browser from `ftp://ftp.S-provencher.COM`.

It is important that the Basis Sets go into the directory `$HOME/.lcmodel/basis-sets/` and follow the naming conventions in Sec. 7.3.1. Then LCMgui can often automatically select the correct Basis Set as the default. These conditions are fulfilled for the GE & Siemens Basis Sets when you use the above script `install-model-spectra`, which also deletes any outdated Basis Sets. Further information is installed in `$HOME/.lcmodel/basis-sets/README.txt`.

Contact me to see if Basis Sets are available for your other sequences before you acquire your own, using Chap. 8.

7.2.5 Install License

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. When you click “OK”, the File Selector (Sec. 6.2.2) appears, and you are ready to start the first analysis of your data; see Sec. 7.3.

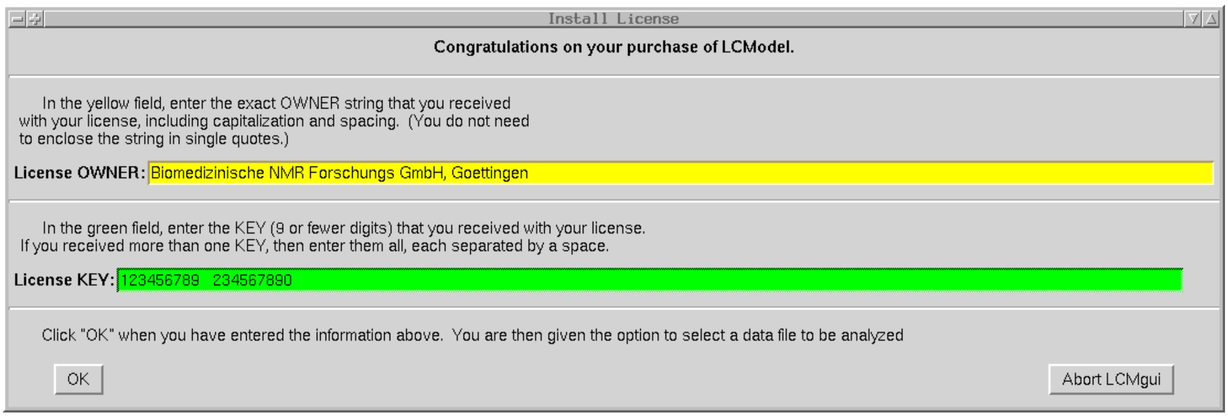

Figure 7.1: The Install License Window

7.2.6 Installing Updates

In contrast to LCModel, which usually lasts years between updates, there will probably be regular LCMgui updates. Updates of any parts of the packages will normally be incorporated in a complete new updated LCModel/LCMgui package (not patches).

You install an update simply by installing the whole package (on top of your present one) as instructed in the WWW site on page 2. However, you will not have to repeat the test run or your license installation. You can 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/.lcmodel` 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.

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) or Water-Scaling (Sec. 6.3.4).

Further important settings are:

7.3.1 `.BASIS` file

If you are using basis sets supplied by me, it is best to follow the instructions in the WWW site listed on Page 2, so that they (and future updates) go into the directory `$HOME/.lcmodel/basis-sets`. Then, with the GE or Siemens Basis Sets, LCMgui normally automatically selects the correct Basis Sets, based on the information in the GE, Marconi/Picker, Philips or Siemens files, and you can skip the rest of Sec. 7.3.1, unless you have GE spectrum G-files. LCMgui cannot extract TE from some older GE spectrum G-files, and you should check the entry next to "BASIS file:" in the "Control Parameters" window and click "Change BASIS" if necessary.

If you will only be using one sequence with one `.BASIS` file, then it is not important where the file is. In the first run, you simply click on the "Change BASIS" button (Sec. 6.3.2) and use the File Selector to select the `.BASIS` file. In the future, LCMgui will search this directory by default, and, if this file is the only one with the extension `.BASIS, .basis` or `.Basis`, then it will be automatically selected.

Otherwise, 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

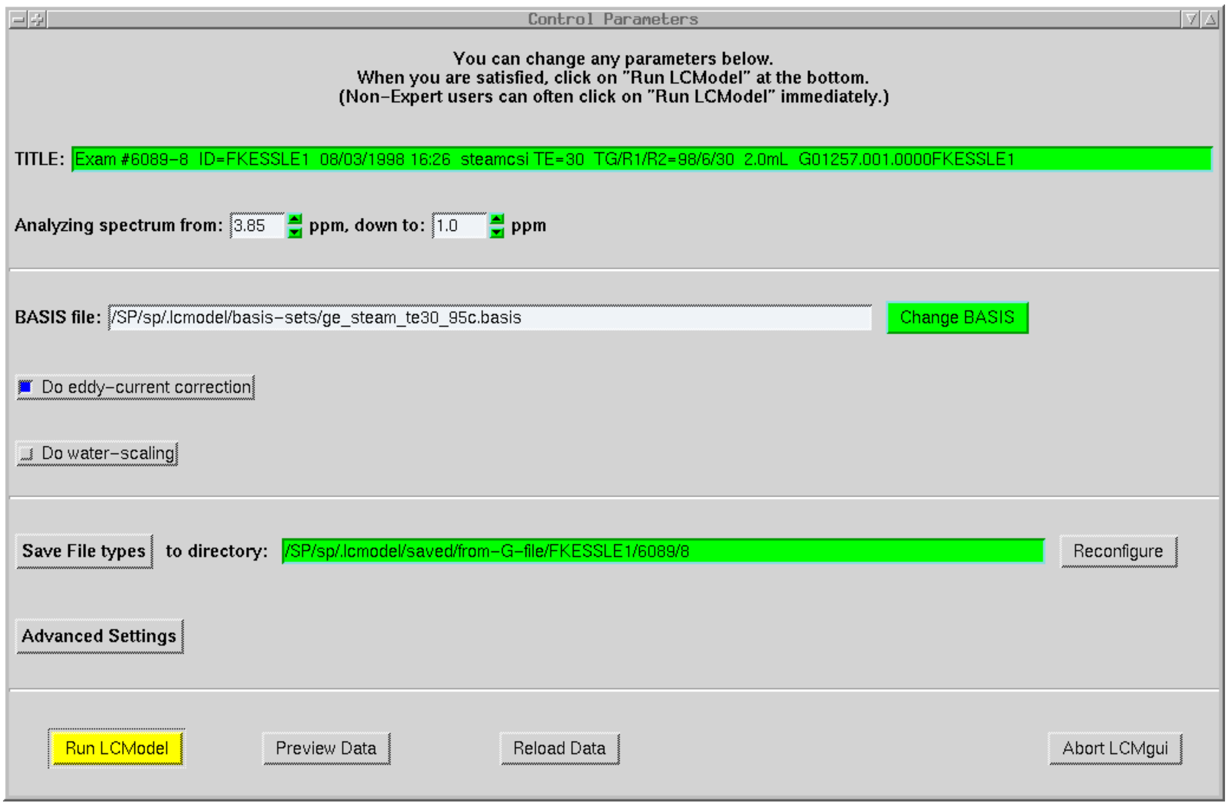

Figure 7.2: The Control Parameters Window

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. Two examples from the GE basis sets are: `ge_steam_te30_95c.basis` and `ge_press_te144_95d.basis`.

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

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

The above rules should be obeyed by all `.BASIS` filenames, including those of any new Basis Sets that you produce using Chap. 8.

7.3.2 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.

7.3.2.1 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

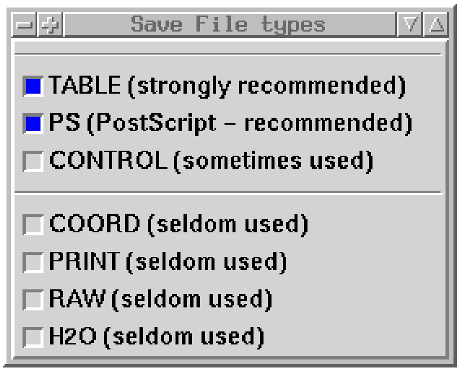

Figure 7.3: You get this menu when you click the "Save File Types" button in Fig. 7.2.

results useful for later statistical and data base 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.

7.3.2.2 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:

GE raw P-files: the standard SAGE data-base hierarchy:
`$HOME/.lcmodel/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.

Marconi/Picker dump files: `$HOME/.lcmodel/saved/`

Philips SDAT files: `$HOME/.lcmodel/saved/examination_name/patient_name/scan_date/`. An alternative script, where `scan_id` is also available is available from me.

Siemens raw files:
`$HOME/.lcmodel/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. 7.3.2.

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

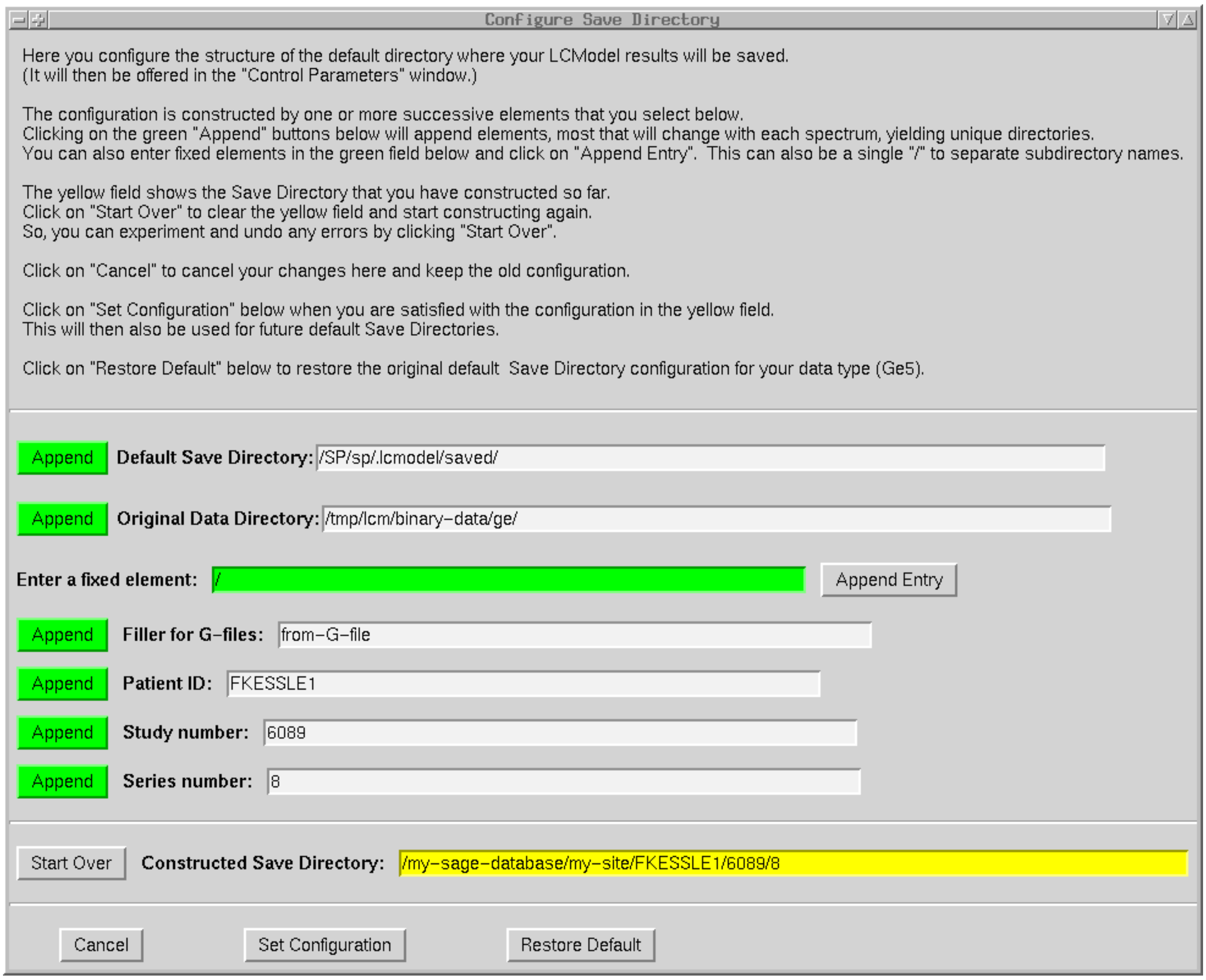

Figure 7.4: The window for permanently reconfiguring the structure of the archive directories.

7.3.2.3 Reconfiguring the Archive Directory Tree

You can permanently change the archive directory tree structure by clicking on the "Reconfigure" button, which produces the window in Fig. 7.4 (with an example from a GE G-file). The instructions in Fig. 7.4 are quite detailed, but the following step-by-step example, may be useful:

Suppose that you wish to use `/my-sage-database/` instead of `$HOME/.lcmodel/saved/` and that you want to put your actual site name (`my-site`) (rather than `from-G-file`) in the directory tree:

(1) Enter `/my-sage-database/my-site/` in the green field next to "Enter a fixed element", and then click the "Append Entry" button to the right.
(2) Click the green "Append" button next to "Patient ID:"
(3) Edit the green "Enter fixed element:" field so that it contains only a "/"; click the "Append Entry" button to the right.
(4) Click the green "Append" button next to "Study number:"
(5) Append another "/" by clicking on the "Append Entry" button, as in Step (3).

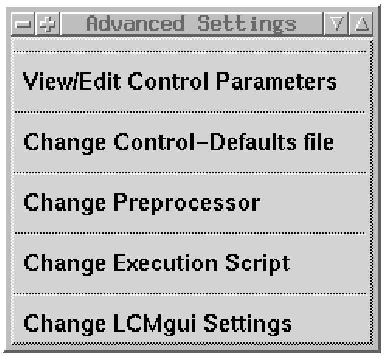

Figure 7.5: You get this menu when you click the "Advanced Settings" button in Fig. 7.2
.

(6) Click the green "Append" button next to "Series number:" This is the stage shown in Fig. 7.4.
(7) If you are satisfied with the structure shown in the yellow field next to "Constructed Save Directory:", then click the "Set Configuration" button.

The necessity of Steps (3) & (5) gives you flexibility in combining header elements, e.g., with the underscore in the default Siemens configuration in Sec. 7.3.2.2.

Note the following:

- You can **experiment**, watching your progress in the yellow 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 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.

You do this by clicking on the "Advanced Settings" button in the "Control Parameters" window (Fig. 7.2). This produces the menu in Fig. 7.5. You then click on "View/Edit Control Parameters" in this menu to obtain the window in Fig. 7.6. This shows the Control Parameters that will be input to LCModel. You can edit or delete these or add new ones. For example, Fig. 7.6 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.)

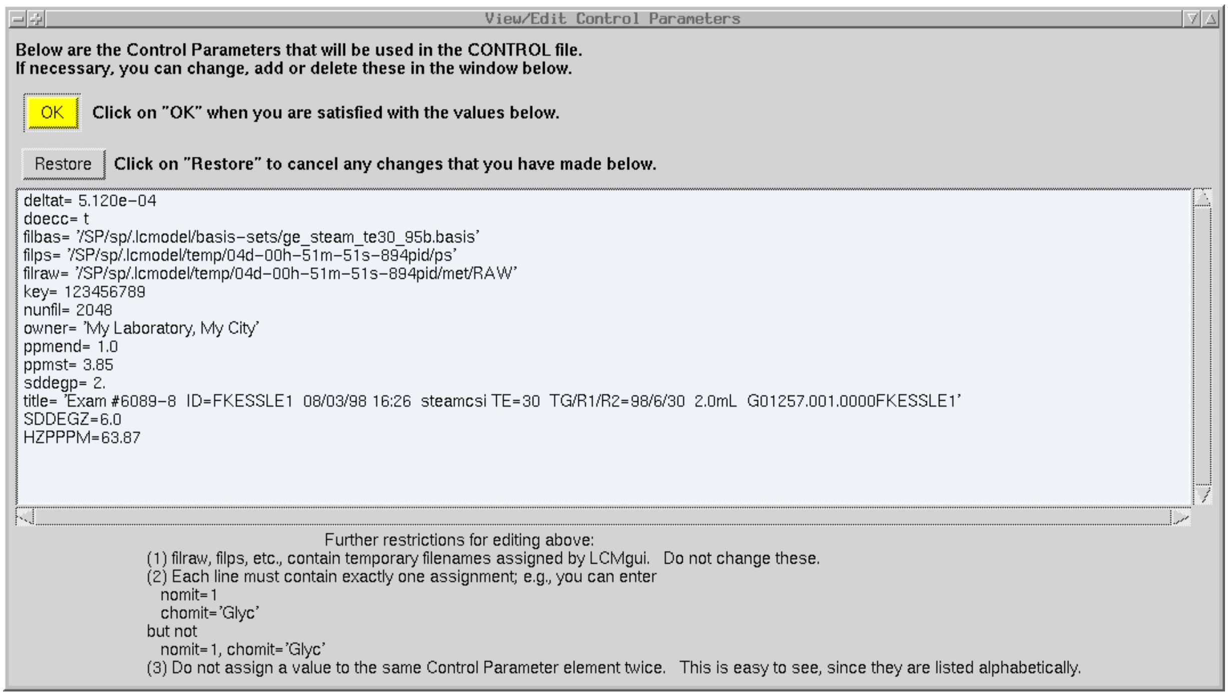

Figure 7.6: You can view, edit, delete or add all Control Parameters here.

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 4.3.3 & 4.3.4 discuss ECC and the settings of `SDDEGZ & SDDEGP`. (However, LCMgui automatically sets the Control Parameter `FILH2O` mentioned in Sec. 4.3.3 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 will not be using duplex printer, then you will also want to enter `IPAGE2=0`.

7.3.4 Saving Your Control Parameters

If you have made any changes to Control Parameters, the window in Fig. 7.7 will appear after you click "Run LCModel". 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. 7.8.

In Fig. 7.8, you enter a name for the file that will store your Control Parameters. This is called a *Control-Defaults File*. In Fig. 7.8, I have entered the name `g-files-ecc`. You are free to choose any descriptive filename. However, if it is identical with one of the filenames listed at the bottom (e.g., `absval`), then your file will overwrite the old file.

All of Control-Defaults Files are in the directory `$HOME/.lcmodel/control-defaults`. You can look at their contents with the usual Unix commands, but do not edit them. You can delete obsolete files, e.g., with
`rm $HOME/.lcmodel/control-defaults/absval`

If you click "Use Next Time" in Fig. 7.8, then this set of Control Parameters will be used as

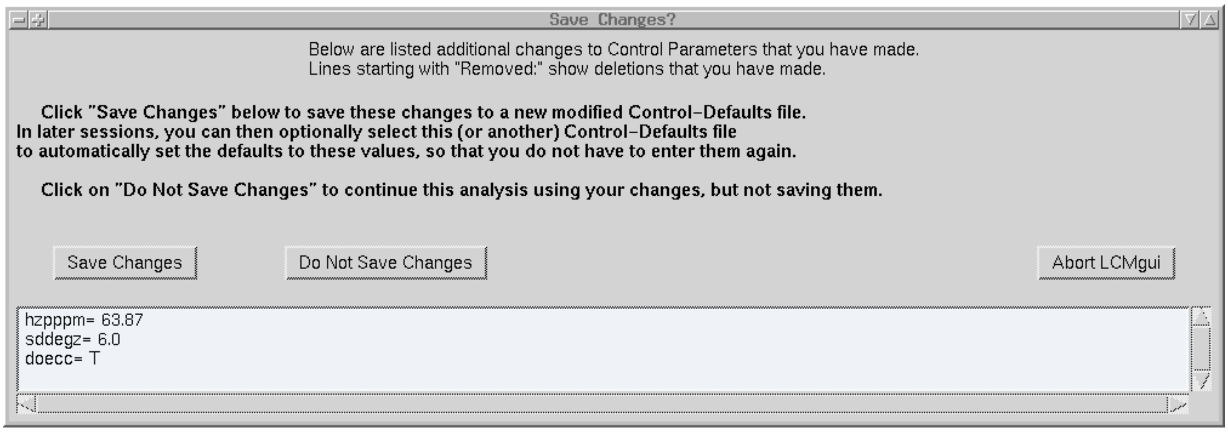

Figure 7.7: You can save all the Control Parameters, including your modifications, for optional use as starting defaults in the future.

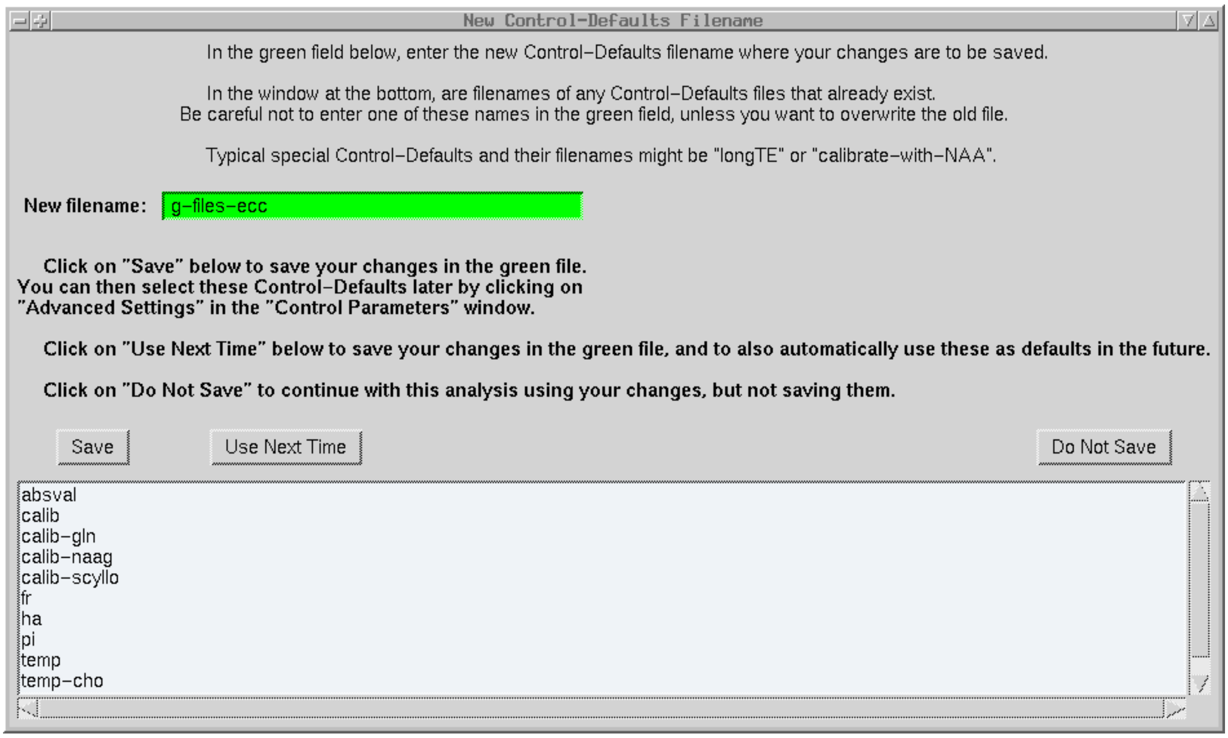

Figure 7.8: Here you enter a name for the file which will store your Control Parameters for optional future use.

defaults for future sessions. (LCMgui will still reset obviously variable Control Parameters, such as `TITLE, FILRAW`, etc.)

If you click "Save", then your Control Parameters will simply be archived in `$HOME/.lcmodel/control-defaults/g-files-ecc`. They will not be used as defaults for next session. The old Control-Defaults File used at the start of this session will again be used.

7.3.5 Changing your Default Control Parameters

How do you know what file in `$HOME/.lcmodel/control-defaults/` is currently being used? And how do you change this to a new set of defaults? You again click on "Advanced Settings" in Fig. 7.2 and then on "Change Control-Defaults File" (Fig. 7.5), producing the window in Fig. 7.9.

If you only wanted to know which file was being used, you can note the name in the green field under "Selected File:" and continue the session by clicking "Use Selected File". In Fig. 7.9, the green field is blank, indicating that no file is being used (i.e., the conversion program called by LCMgui solely determines the starting values of the Control Parameters).

As explained in Fig. 7.9, you can select a new Control-Defaults File by clicking on its name, which then appears in the green field. Then you click "Use Selected File", and LCMgui immediately repeats the conversion of your data and applies these new 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.

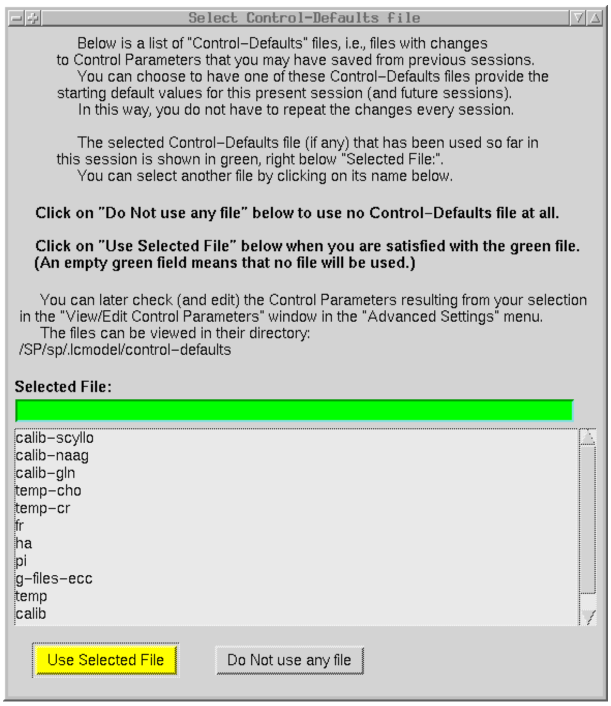

Figure 7.9: Here you select the Control-Defaults file to be used now and in the future.

7.4 Further Useful Settings

7.4.1 Previewing Data

Clicking the "Preview Data" at the bottom of the "Control Parameters" window (Fig. 7.2) produces the window in Fig. 7.10. As explained there, by editing the green field next to "Print the plot with command:" to your command for printing PostScript files and then clicking on "Run Preview", you can print out plots of the data before starting LCModel. This can be useful in checking whether you have selected the correct data file and whether the data are worth analyzing.

It is even faster and more convenient if you edit `ghostview -seascape` in Fig. 7.10 to a command that will display PostScript files directly on your display. Internet sources of these programs are mentioned in Sec. 3.2.2. Note that orientation and magnification should be supplied in the command, since trying to change these in the display program can sometimes crash the display program and LCModel, particularly if you are working over a network. For example, you can use

```
ghostview -seascape -magstep 1
```

to increase the magnification.

You can activate both the "Print the plot" & "Display the plot" buttons to do both.

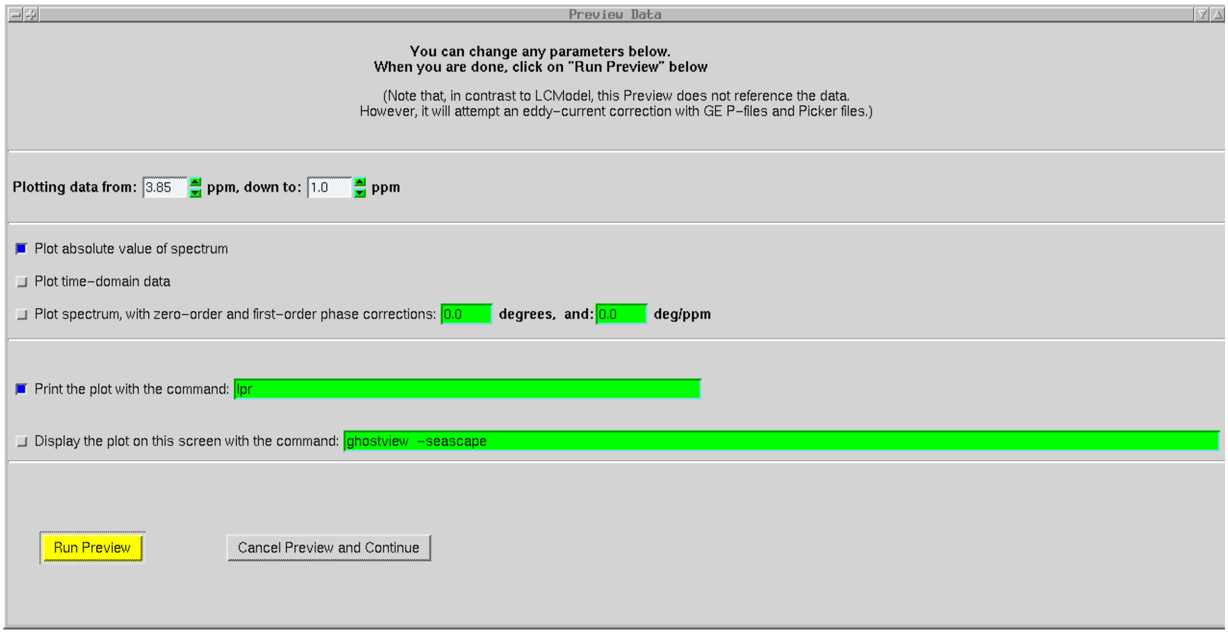

Figure 7.10: Here you can set and execute your commands for printing and/or plotting previews of your data.

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 (particularly of GE or Marconi/Picker data) may go so fast 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 you can change the command for printing your LCModel output to a display command. (Section 7.4.6 shows how to change the print command.) Although you can then usually print from the display program, there is the danger that you forget to print. Therefore, it is better to also modify the Execution Script to automatically print (as specified in Sec. 7.4.3). You then are guaranteed to have both a display (with your "print" command) and a printout (from the execution script).

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, as mentioned in Sec. 6.6.) However, LCModel analyses often go very fast if you can supply prior information on the expected size of phase corrections (Secs. 4.3.3 & 4.3.4).

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/.lcmodel/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 several suggestions on possible changes, including:

nice: Using the Unix `nice` command to reduce the load if your workstation is so slow that you can start several analyses before the first is complete.

Extra output: for example, printing out the One-Page Output, so that you can use the usual LCMgui print command as a display command for interactive processing (as discussed in Sec. 7.4.2).

Postprocessing: for example, modifying the LCModel results before they are output or archived (e.g., for relaxation corrections or the construction of other files for your own data base or statistics).

You should also put your own Execution Scripts into the directory `$HOME/.lcmodel/execution-scripts/`. You can then view the currently active Execution Script or select a new for the future as follows:

- Click on the "Advanced Settings" button in Fig 7.2 to produce the menu in Fig. 7.5.
- Click on "Change Execution Script" to produce the window in Fig. 7.11.
- The currently used script is shown in the green field, under "Selected File". (The original default is `standard`.) If you only wanted to check which script is being used, you can click "Use Selected File" to continue the session (without changing anything).
- If you want to use another Execution Script now (and in the future), click on its name, and its name will also appear in the green field as the "Selected File". (Figure 7.11 shows this stage, after I selected my Execution Script `nice`.) Then click "Use Selected File" and `nice` will be executed from now on, until you change it.

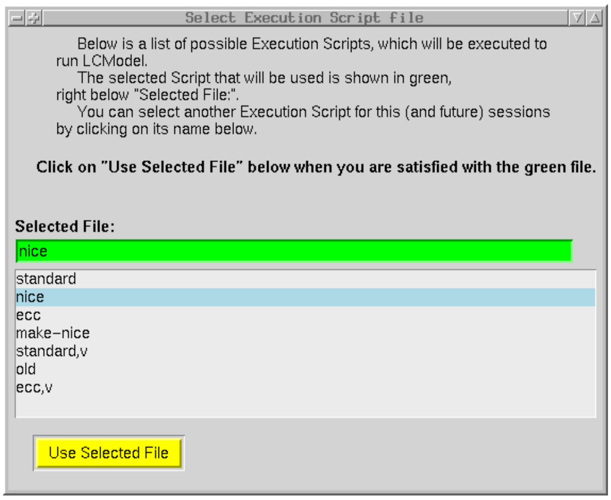

Figure 7.11: Here you can view and/or change the Execution Script that will be started by LCMgui.

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/.lcmodel/???/bin2raw`, where `???  = ge5, gelx, marconi, philips, siemens` 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/.lcmodel/???/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/.lcmodel/other/bin2raw` provided with LCMgui does no data conversion; it simply assumes that your selected file has already been converted to LCModel `.RAW` format. However, this script also specifies 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 `siemens/bin2raw` (Sec. 7.4.4.1) 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.

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 LCModel `.RAW` file.

7.4.4.1 CSI & and Other Sets of Spectra

LCMgui is not designed for multi-dimensional data sets. However, `siemens/bin2raw` does automatically detect and analyze Siemens CSI data, but one voxel at a time. If LCMgui detects a CSI "raw" file, it prompts you to enter the "Voxel Number". You can then preview (Sec. 7.4.1) the spectrum in this voxel. If it does not seem worth analyzing, you can click "Reload Data" and preview another voxel. Or you can start an LCModel analysis of this voxel and then select another voxel for viewing.

A two-dimensional display of all the spectra, as the "Spectral; Grid" in GE's SAGE would be useful in selecting which voxels are worth looking at with LCMgui. Another natural way is to integrate LCModel analysis of CSI data sets into SAGE [7, 8], e.g., using SAGE macros.

The "Voxel Number" that you are prompted to enter by `siemens/bin2raw` simply corresponds to the ordering of the voxel data in the CSI "raw" file. This presumably is simply related to the position in a two-dimensional display that Siemens might provide, perhaps

```
voxel_number = column_number + (row_number - 1) * number_of_columns
```

but I have no information on this. This should be easy for you to determine experimentally.

The script `siemens/bin2raw` does assume that your CSI data has 1024 complex data points per voxel. If this is not the case, then you must modify "`1024`" in one place in the script, as specified in the script.

Because of your input to the prompt from `siemens/bin2raw`, it is necessary that you do not run LCMgui in background with CSI data; e.g., you must start it with a command like

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

There must *not* be an "`&`" at the end.

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 7.12. Here, `??? = ge5, gelx, marconi, philips, siemens`, or `other`, depending on which type of data you selected in Fig. 6.3. Your own Preprocessor scripts must also be in this directory.

The Preprocessor script, `$HOME/.lcmodel/other/water-scale-orig`, is for an obsolete Water-Scaling method (you should use the "Do water-scaling" button in Sec. 6.3.4 instead). However, the script does contain general instructions and can be used as a guide for preparing your own Preprocessor script.

You can check or select the Preprocessor as follows:

- Click on the "Advanced Settings" button in Fig 7.2 to produce the menu in Fig. 7.5.
- Click on "Change Preprocessor" to produce the window in Fig. 7.12. (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 only wanted

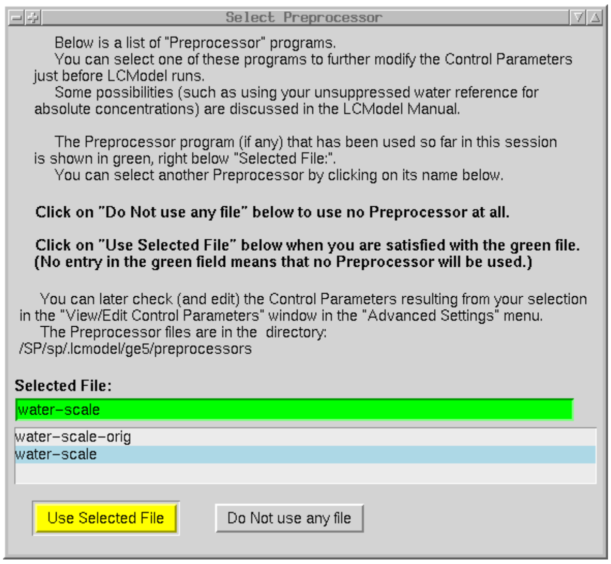

Figure 7.12: Here you can view and/or change the Preprocessor that will be used by LCMgui.

to check which script is being used, then you can click "Use Selected File" to continue the session (without changing anything).

- 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". (Figure 7.12 shows this stage, after I selected my obsolete Preprocessor `water-scale`.) Then click "Use Selected File" and `water-scale` would be executed immediately (and in the future, until you change it).

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. 7.5.
- 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 command that LCMgui is currently using for outputting the LCModel PostScript file.
- 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.

7.5 Fine Points

7.5.1 `gui-defaults` Resource File

LCMgui stores all of your default settings for future sessions in `$HOME/.lcmodel/gui-defaults`. Each line consists of a one-word index (e.g., "i_displayCommand"), whitespace, a value (e.g., "ghostview -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 make the test run, then install the license, and then proceed with data analysis. All your previous defaults will be forgotten (but also your mistakes).

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 BASIS file with model spectra;
- The print and display commands;
- The pathnames of the files with the default Control Parameters, the Preprocessor 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 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.

7.5.1.4 Nice Increment

As explained in `$HOME/.lcmodel/execution-scripts/standard`, the second argument passed to the Execution Script is incremented by 5 (up to a maximum of 19) for each LCModel execution started during the LCMgui session. This can be used with the `nice` command to prevent overloading the workstation (although LCModel execution times are getting shorter with newer workstations). This increment of 5 can be modified in the following line:
`i_niceIncrement 5`

7.5.1.5 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 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, save and display arbitrarily many files with Control-Defaults, Preprocessors and Execution-Scripts. They are saved in
`$HOME/.lcmodel/control-defaults`
`$HOME/.lcmodel/execution-scripts`
`$HOME/.lcmodel/???/preprocessors`
where `???  = ge5, gelx, other, marconi, philips, siemens`. You can always examine these in their directories and delete the obsolete ones.

7.5.2.2 Temporary Files

These are automatically purged, and you normally do not have to bother with them. Each LCModel analysis requires only about 200 kB of temporary disk storage (except for about 8 MB for Siemens CSI data).

They are all in `$HOME/.lcmodel/temp/`. Each time LCMgui prepares data for an LCModel analysis, a unique directory is created, e.g.,
`$HOME/.lcmodel/temp/12d-21h-51m-09s-996pid`
The numbers are, respectively, the day of the month, hour, minute, second and process ID.

When the LCModel analysis is finished, the directory is marked for deletion, and is deleted when the next LCModel analysis is prepared. So, directories only remain for LCModel analyses not completed (including aborts from LCMgui). By default, these remaining directories are deleted if they are more than 604800.0 s (7 days) old. You can modify this value in the following line in `gui-defaults`:
`i_deleteAfterSeconds 604800.0`

Chapter 8

Collecting 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 model spectra compatible with your data are already available.

The LCModel license includes my processing your model-spectra (file types in Sec. 6.2.1) with MakeBasis to produce your first Basis Set. If you do send me your model-spectra files, then you do not have to read Secs. 8.5–8.8, but you must use the Auto-Phasing recipe in Sec. 8.2.4.

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 possibly thousands of spectra. First, review [1, Basis Set of ...].

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 (to within 1%)
- Localization sequence (e.g., STEAM or PRESS)
- TE
- TM (with STEAM)

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

8.2 Model Metabolite Solutions

8.2.1 Choice of Model Metabolites

Table 8.1 shows most of the metabolites and markers that have been used with LCModel. Most experience is with low fields (up to 2.35 T) and short TE (up to 35 ms). In these cases, metabolites in the upper part of the table are recommended. (Note in Sec. 8.2.1.1 that you do not buy Scyllo, which is simulated by shifting the Gly singlet.)

The following alternatives are based on less experience:

long TE : Asp, GABA, Glc, Gln, Glu, GPC (indistinguishable from PCh), NAAG (a shifted NAA can simulate NAAG) & Tau are unnecessary, except that Gln & Glu should be included with fields around 4.7 T [9].

high fields : Considerably more metabolites can be quantitated above 4.7 T, especially at short TE [10].

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. 9.5.1, 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, as you need them.

Whenever possible, use salts rather than acids or bases, 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. Reports of contaminated metabolites will be 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. Only minimum recommended values are given for NAAG and GPC, because they are so expensive.

8.2.1.1 Singlets

No concentration values are given for most metabolites that only have one singlet in the Analysis Window. Normally, you only need to measure 200 mM Gly. Its singlet can then be shifted to 3.35 ppm (using `XTRASH`) to simulate 66.7 mM Scyllo (66.7 mM because the Scyllo singlet has 6 equivalent protons and Gly only 2).

To simulate (less common) singlets below 3.3 ppm, use 200 mM Act.

Do not use Gly as itself in the Basis Set; it cannot be resolved from Ins at 3.56 ppm. Worse, Ins has a different effective number of protons, which would cause unnecessary scatter, even in the sum Gly+Ins.

8.2.1.2 NAAG

NAAG is expensive and one compromise is to use the NAA spectrum 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 (see the test Basis Set or the NAAG curve in [1, Fig. (1)]). This can lead to reduced NAAG/NAA estimates in white matter or a small hump in the Baseline around 2.15 ppm; fortunately, other metabolites and brain regions do not seem to be seriously affected. However, it does illustrate the high information content of proton spectra, when properly analyzed with a good Basis Set.

Table 8.1: Concentrations and Allowed Names of Model Metabolites

Metabolite	Allowed Name(s)	Conc. (mM)	Singlet (ppm)	Vendor	Order #
L-Alanine	Ala	100		Fluka	05129
Aspartate	Asp	40		Sigma	A9256
Creatine	Cr, Cre	50		Fluka	27890
γ-Aminobutyric Acid	GABA	200		Sigma	A2129
Glucose	Glc	200		Fluka	49139
Glutamine	Gln	100		Fluka	49419
Glutamate	Glu	50		Fluka	49449
Glycerophosphocholine	GPC	≥ 25		Sigma	G8005
Glycine	Glyc, Gly	200	3.55	Fluka	50046
myo-Inositol	Ins, mI	200		Fluka	57570
L-Lactate	Lac	100		Fluka	71718
N-Acetylaspartate	NAA	50		Fluka	00920
N-Acetylaspartylglutamate	NAAG	≥ 10		ICN	153036
Phosphocholine	PCh	27		Sigma	P0378
scyllo-Inositol	Scyllo		3.35		
Taurine	Tau	200		Sigma	T0625
Acetone	Acn		2.22		
Acetate	Act	200	1.915		
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			
Glucoronic Acid	Gcr	50			
Glutathione (GSH)		70			
Guanidinoacetate	Gua		3.78		
Isoleucine	ILc	100			
Leucine	Leu	50			
Phenylalanine	PAl	100			
Phosphorylethanolamine		50			
Propylene Glycol	Pgc	100			
Pyruvate	Pyr		2.38		
Succinate	Suc		2.40		
Threonine	Thr	100			
Trimethylphosphate	TMPO	25			
Valine	Val	100			

At fields above 1.5 T, NAAG probably should be used. The concentration should be at least 10 mM.

At long TE, do not use NAAG. A shifted NAA is an excellent 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

It is best to use GPC for the choline-containing compounds. In high-quality spectra, the advantages of GPC over Cho can be seen [Petra Pouwels, personal communication]. You must 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 stock solution 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.

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, 3 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.

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 a huge “stock solution” of

3 mM DSS (TSPS)
72 mM K_2HPO_4
28 mM KH_2PO_4
200 mM Na formate (Sigma S2140, *not* F4166, *not* 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.

Use this standard stock solution as "solvent" for each of your model metabolites. 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 stock solution (due to the phosphate), be sure and dissolve it in 200 mM formate and about 3 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 stock solution, as long as you accurately know the formate concentrations in each.

For several metabolites (particularly NAA, Lac, Glu), you will have to adjust the pH back to 7.2. If you "titrate" carefully with solid 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 very carefully.

Without NaN_3, the solutions can go bad (usually microbiological growth) within a few days. Gln has gone bad especially quickly. The NaN_3 in the stock solution allows you to store them longer (some for months) at low temperature. Let them return to room temperature before measurements.

Normally room temperature seems adequate for acquiring the model spectra. Only with very high-quality spectra (e.g., 9.4 T with excellent shimming [10]) is it worthwhile to increase the phantom temperature closer to 37° C.

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 significicantly higher S/N and resolution than your *in vivo* spectra. Output the file `$HOME/.lcmodel/test/output/basis.ps` with the Basis Spectra from the test run in Chap. 3. You should aim at this high quality.

Although LCModel can handle weaker water suppression *in vivo*, as discussed in Sec. 4.3.2, 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, so that the resolution is nearly the same in each Basis Spectrum and significantly better than *in vivo*.

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 the all 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

Acquiring the Basis spectra with $TR = 6000$ ms seems fine. At least at lower fields, $TR > 6000$ ms does not seem necessary.

As mentioned in Sec. 4.4, you avoid complications with relaxation effects at a small cost in S/N by using long TR *in vivo* (at least 5000 ms; 3000 ms is already critical). In this case, a single Basis Set with a $TR = 6000$ ms should be fine, and there is no need to read the rest of Sec. 8.3.4.

For *in vivo* data with short TR, you might try acquiring a Basis Set with a shorter TR to partially compensate relaxation effects, as follows:

In principle, the optimal TR is one where the $T1$ relaxation effects in the *in vitro* Basis Set match those in the *in vivo* data; then these relaxation effects would be completely eliminated with LCModel. These relaxation effects are approximately $(1 - \exp[-TR/T1])$. Therefore, they would be eliminated if

$$TR_{vitro} = TR_{vivo} \times (T1_{vitro}/T1_{vivo})$$

This implies a somewhat longer TR *in vitro*, since $T1$ is longer *in vitro*.

In practice, $T1_{vitro}/T1_{vivo}$ varies among the metabolites. Perhaps, as a wild guess, you might use $TR_{vitro} = 1.5 \times TR_{vivo}$.

8.4 Eddy-Current Correction

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.) If you send the data to me, include this pair for each metabolite. Otherwise, the rest of Sec. 8.4 specifies how you can do the eddy-current correction (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 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 "`/usr/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 Sec. 7.11 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) Click on “Save Changes” in Fig. 7.7. In Fig. 7.8, enter a new name (e.g., `ecc`) next to “New filename:” and click “Use Next Time”. Then then above changes will automatically be used for ECCs on your other files during this LCMgui session.

(11) 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 (11) 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 (11), 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

Without LCMgui, you can use the program KECC to apply the Klose correction [4], as explained in Section 9.3. 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. 9.3. Section 4.3.1 specifies `NUNFIL`. In case of an abort, a self-explanatory error message is written at the end of the `.ecc` file.

If you are sending your `.RAW` files of model spectra to me for processing with MakeBasis, then you do not have to read the rest of this chapter.

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 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 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/.lcmodel/test/control/plotraw.in` has been supplied to you. You enter:

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

This produces the output file `$HOME/.lcmodel/test/output/plotraw.ps`, which you can send to your PostScript printer. It contains plots of the test data in `$HOME/.lcmodel/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. 4.2;
- `.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. 4.3.1.

`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 (with respect to water), in degrees, e.g., as output by LCModel and Makebasis. (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. 4.3.5.

PPMST Same as in Sec. 4.3.2, 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. 4.3.2, 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:

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 frequency domain, where one Grid Point is 1/(2*NUNFIL*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. 9.6.4.2–9.6.4.4, except `PTOUTP, RHOUTP, RGBLIN,` SUBBAS, and RHVERS.

  WDLINE in PlotRaw has dimensions `WDLINE(6,3)`. `WDLINE(JCURVE,JPLOT)` determines the curve thicknesses as in Sec. 9.6.4.4, 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 `WDLINE(*,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).

8.5.3 PlotRaw Diagnostics

If the run stops before a PlotRaw diagnostic appears on your screen or a `.PS` file is produced, then check the suggestions in Sec. 12.1.

Normally, a standard PlotRaw diagnostic of the form
`Aborting due to error` *Name n.* `Check User's Manual...`
appears on your screen. (It can also 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	1	You must have PPMST > PPMEND.
	2	PAGEWD and PAGEHT must be positive.
	3	NUNFIL must be positive and must not exceed 16384.
	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 < 100.
	8	You must have SDPNTS $\leq$ 60.
	9	This would be my programming error.
PLOT2	1	You must have PTTITL & PTLABL positive and RHTITL & RHLABL at least 1.
	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/.lcmodel/bin/makebasis < makebasis.in
```

where `makebasis.in` (Sec. 8.6.4) contains the changes to Control Parameters. An example is `$HOME/.lcmodel/test/control/makebasis.in` (used for the test run in Chap. 3). 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. 3 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/tests/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 your Basis Spectra are automatically scaled consistently with each other. [All the 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 [4.4,–0.2], but also with [9.0,8.0] and [0.5,–0.5] (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).

The resolution must also be adequate. Auto-Scaling & Auto-Phasing optimize the real part of the formate & DSS peaks over an interval of up to ± 0.15 ppm about the peak maximum. If all formate & DSS peaks have not fully decayed into the Baseline within this interval, then you should repeat the acquisitions.

8.6.3 `.RAW` File

These files have exactly the same format specified in Sec. 4.2 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 (except that it must be positive). 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 (except that it must be positive). A reasonable value is 1.0.

If you do not use Auto-Scaling, then you must be especially careful that the all 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 and Philips users need to input `BRUKER`, and only Bruker users may need to to input `SEQACQ`).

The data following the Namelist are the raw time-domain data 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/.lcmodel/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. 4.2.1; they both include ECHOT & SEQ. However, HZPPPM is not included here (but in NMALL below). In addition, a new Control Parameter is included here:

FWHMBA (REAL) ("FWHM of Basis peaks") the approximate full-width at half-maximum (in ppm) of the singlets in the Basis Set.
Default: FWHMBA = 0.013 (appropriate for the test Basis Set).

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 (2.2, 1.8), (3.2, 2.8) & (3.4, 3.0). You can then estimate the FWHM of these four singlets from the .PS files, and use the mean for FWHMBA. Typical values are 0.02, 0.013, 0.01 for 1.5 T, 2.0 T & 4.7 T, respectively.

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. 4.3.1.

FILBAS (CHARACTER*255) the name of the .BASIS file to be output by MakeBasis.

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. 4.3.5.

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. 9.6.4.2–9.6.4.4, except PTOUTP, RHOUTP, RGBLIN, 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 ± 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 = 9.0 and PPMEND = 8.0. (MakeBasis effectively reduces HWDSCA if possible; so, you should not have to reduce HWDSCA 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 ± 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 = 0.5 and PPMEND = -0.5.

PPMSCA (REAL) See the definition of HWDSCA above. Default: PPMSCA = 8.44.

PPMPHA (REAL) See the definition of HWDPHA above. 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 HWDSCA 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 capitalization; '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.

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 stock solution 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 stock solution could not be used (as with GPC·$CdCl_2$ or the Ca salt of PCh) and a slightly different formate concentration was added.
The units (e.g., mM) must be consistent with all other Basis Spectra.

`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") First plot your the absolute value of your spectrum with PlotRaw. 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, but plot the spectra to be sure.

`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).
`makebasis.in` illustrates shifting the acetate singlet from 1.915 to 3.35 ppm to simulate Scyllo; `XTRASH` = 3.35 – 1.915 = 1.435. 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`
Further examples are `XTRASH = -0.21` to shift Gly (3.56 ppm) to simulate Scyllo (3.35 ppm) and `XTRASH = 0.035` to shift NAA (2.01 ppm) to simulate 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 very large (as with Marconi/Picker PRESS data), i.e., when
$|\texttt{DEGPPM}| > 180/|\texttt{PPMSCA} - \texttt{PPMPHA}|$
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 very large 1st-order phase corrections.
Default: `DEGPAP = 0.0`, which is fine if $|\texttt{DEGPPM}| < 21$.

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` and `DEGPAP` to leave them at their defaults.
- You may omit `CONCSC` when `AUTOSC = F`.

8.6.5 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.

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`, `HWDSCA` 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 Same as `MYDATA 2` in Sec. 12.2.
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 `PPMSCA` and `PPMPHA` must be at least 1.0 ppm apart.
10 When `AUTOPH = F`, you must input `DEGZER` and `DEGPPM`.
11 Same as `PLTRAW 8` in Sec. 8.5.3.
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/2` Grid Points, has been computed.
Hint: Plot the absolute value of the spectrum with PlotRaw; you should see that your values for `PPMAPP` or `PPMPK` are grossly in error.
15 `PPMSCA` is right at the edge of the spectrum. Increase the bandwidth or correct your input of `PPMSCA`.
16 The area of the real part of the formate peak at `PPMSCA` is negative.
Hints: Plot the absolute value of the spectrum with PlotRaw 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 `PPMSCA`.
17 An enormous shift, at least `NUNFIL/2` Grid Points, has been computed with `XTRASH`.
Hint: Plot the absolute value of the spectrum with PlotRaw; 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 `PPMBAS`. Hints: Increase the bandwidth or correct the input of `PPMAPP` or `PPMBAS`. (This diagnostic is now obsolete, since `FLATEN` should no longer be used.)
19 Same as `PLOT2 1` in Sec. 8.5.3.
20 Same as `ONEPAG 4` in Sec. 12.2.
21 Same as `ONEPAG 8` in Sec. 12.2.
22 `PPMSCA` is too close to the edge of the spectral range.
Hint: Increase the bandwidth or correct the input of `PPMSCA`.
23 `PPMPHA` is too close to the edge of the spectral range.
Hint: Increase the bandwidth or correct the input of `PPMPHA`.

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

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

8.6.6 Output .BASIS File

As in the test runs in Chap. 3, 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.

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`. You do not need to supply `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.

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 concentration that comes out of this calibration analysis. You can 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 should then come out 1.0. Then, GPC & PCh are consistently scaled.

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. If the LCModel concentration is in the range 0.85–1.15 (the typical error range with NAAG/NAA calibration), then your NAAG `CONC` probably does not have to be corrected. Otherwise, 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.
- 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 in the window in Fig. 7.6. 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.
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`. Previously, this was achieved with a large `NOMIT` and a long list for `CHOMIT`, omitting all but one.
Default: `NCALIB = 0`; i.e., a normal analysis with all Basis Spectra.

`CHCALI` (CHARACTER(40)*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 have 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 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.

How do you determine if an old .BASIS file was produced with Auto-Scaling? The information is in the Namelist NMUSED. Auto-Scaling was used only if "AUTOSC = T" appears in every Namelist NMUSED. You will then also find CONCSC for each Basis Spectrum in its NMUSED. For example, you will find this information in the Siemens Basis Sets, but not in the GE Basis Sets.

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 a new Basis Spectrum from a metabolite that is in the old set. It should be one of the following (in order of decreasing preference): NAA, PCh, Cho, Cr, Lac. For example, suppose that it is NAA.
(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
With Sun systems, you need
cat old.basis new.basis | sed '100,$s/^ $basis1/ $b1/' > 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'
```
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`] = [9,8], [4.2,-0.2], [0.5,-0.5], to evaluate the resolution and quality, also of the formate and DSS markers. (Sec. 8.6.2)
- Run MakeBasis three times, with [`PPMST,PPMEND`] = [2.2,1.8], [3.2,2.8], [3.4,3.0], to estimate `FWHMBA`, which you now input in Namelist `SEQPAR` in your `makebasis.in`. (Sec. 8.6.4.1)
- Calibrate GPC/PCh and check 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; otherwise they remain at their default values. You should at least scan over the options in this chapter.

9.1 Improvements to LCModel

The following major improvements were made since the submission of [1]:

- A much more elaborate and reliable Preliminary Analysis is performed to initially reference and phase the data.
- [1, Eq. (6)] is no longer used to balance the ratio α_B/α_S. A Bayesian criterion for the most probable *a posteriori* ratio, assuming uniform priors for α_B and α_S, is used.

As mentioned in [1, Appendix], about 1% of the spectra had to be rerun with additional modifications to the Control Parameters, e.g., because of difficulties in referencing CSF spectra. This percentage is now nearly zero. If acceptable results are not obtained with your default Control Parameters, then the data are usually not worth further efforts. Exceptions have been illustrated in Chap. 5.

9.2 Internal Logical Units

(LCMgui users can skip Sec. 9.2.) 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

Table 9.1: Control Parameters for Filenames and Logical Units

Filename	Unit	Default	Alt.	Extension	I/O	Needed when
none	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
FILPRI	LPRINT	0	6	.PRINT	Output	LPRINT > 0
FILTAB	LTABLE	0	7	.TABLE	Output	LTABLE > 0

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.

9.3 Eddy-Current Correction

This was recommended in Sec. 4.3.3. (LCMgui users can skip Sec. 9.3 and instead read Sec. 6.3.3.) ECC requires that a second set of raw time-domain data 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. Details are in [4]. 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 Unsuppressed Data (e.g., 'pat_777_77.h2o'). This file has the same format as the .RAW file.

9.4 Prior Phasing Information

LCModel spends most of its time in an elaborate *Preliminary Analysis* to get good starting values for the phases and referencing shift for the *Final Analysis*. LCModel runs much faster if you have prior information on the approximate phase corrections. More important, this prior information can rescue very low-information spectra, such as in FIGS. 5 and 13, that might otherwise fail.

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 4.3.3 & 4.3.4. Section 9.4.1 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). 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` $\leq$ 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` $\leq$ 22. will increase the speed of the Preliminary Analysis by a factor of 4. This is the most common strength for imposing prior knowledge. If in doubt, it is best to give LCModel a little extra freedom; the main purpose of these priors is to start looking in the correct region in ϕ-space, not to force ϕ values on LCModel. Only with very poor spectra (as in FIGS. 5 and 13), might a more severe restriction, e.g., `SDDEGZ = 5.`, be worthwhile. However, when such a drastic measure is necessary, it is often safest to reject the whole spectrum.

`SDDEGZ` $\leq$ 44. will cause LCModel to start looking for ϕ_0 at `DEGZER`.

`SDDEGZ` $\geq$ 45. will not affect the starting points of the search in parameter space; `DEGZER` is ignored.

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` $\leq$ 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` $\leq$ 7. will increase the speed in the Preliminary Analysis by a factor of 3. This is the most common strength for imposing prior knowledge. If in doubt, it is best to give LCModel a little extra freedom. Only with very poor spectra (as in FIGS. 5 and 13), might a more severe restriction, e.g., `SDDEGP=2.`, be worthwhile. However, when such a drastic measure is necessary, it is safest to reject the whole spectrum.

`SDDEGP` $\leq$ 9. will cause LCModel to start looking for ϕ_1 at `DEGPPM`.

`SDDEGP` $\geq$ 10. will not affect the starting points of the search in parameter space; `DEGPPM` is ignored.

Default: `SDDEGP = 30.`; i.e., only a very weak bias toward reasonably small ϕ_1 values.

`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.) Defaults: `DGPPMN = -30., DGPPMX = 30.`

9.4.1 Estimating Appropriate SDDEGZ, SDDEGP, DEGZER & DEGPPM

The prior phasing information in SDDEG* and DEG* can greatly 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. You can use the means and standard deviations of the LCModel phase corrections (3rd line in the "MISCELLANEOUS OUTPUT" table 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 SDDEGZ $\geq$ 2. and 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.

9.5 Specifying the Basis Spectra for the Analysis

9.5.1 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 Basis Spectra in the .BASIS file that are to be excluded. Default: NOMIT = 0.
- CHOMIT (CHARACTER(100)*6) the first NOMIT elements contain the Metabolite Names of the spectra to be excluded.

For example,

```
NOMIT=2
CHOMIT(1)='Cit'
CHOMIT(2)='Gly'
```

in the .CONTROL file would exclude the Basis Spectra for Cit and Gly from the current analysis.

CHCALI & NCALIB (Sec. 8.7.1) are much more convenient to use when you want to omit all but one or a few of Basis Spectra, e.g., for calibration analyses.

9.5.2 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 & GABA in FIG. 10). You can force some of these to be included as follows:

NKEEP (INTEGER) the number of Basis Spectra in the .BASIS file that are to be kept in the current analysis, regardless of the ppm-range of the Analysis Window.
Default: NKEEP = 0.

CHKEEP (CHARACTER(40)*6) the first NKEEP elements contain the Metabolite Names of the spectra to be kept in the analysis.

9.6 One-Page Output

9.6.1 Concentration Table

9.6.1.1 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 = 10.

CHCOMB (CHARACTER(100)*42) 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 only the first eight characters of CHCOMB are output in the Concentration Table, all Metabolite Names in the sum are needed in CHCOMB.) Default: CHCOMB = 'NAA+NAAG', 'GPC+PCh', 'GPC+Cho', 'Ins+Glyc', 'mI+Glyc', 'Ins+Gly', 'mI+Gly', 'Cr+PCr', 'Cre+PCr', 'Glu+Gln'.

For example, if you want to also output the total GABA+Glu+Gln concentration, then (with the above defaults) you input:

```
NCOMBI=11
CHCOMB(11)='GABA+Glu+Gln'
```

Unlike NAA and NAAG, the main peaks of the Glyc and Ins have different effective numbers of protons [11], 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, do not have a Gly in the Basis Set; it is very poorly resolved from Ins anyway.

At higher fields 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.

9.6.1.2 Concentration Ratios

You can output the concentration ratio relative to any desired metabolite as follows:

`NAMREL` (CHARACTER*42) ("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 8.5, then you would simply input
`CONREL = 8.5`

9.6.2 Boldface & 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 in the following).
Default: `RGBBOL = 0.0, 0.0, 1.0`; i.e., blue.

The three elements of RGBBOL 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 0.99999 instead of 1.0, just in case some Fortran compilers are inaccurate even with the Namelist input of 1.0.)

9.6.3 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 = 1.0, 0.0, 0.0`; i.e., red.

9.6.4 Plot

The Control Variables in this subsection allow you to tailor the plots, e.g, for slides or publications.

9.6.4.1 Individual Metabolite Contributions

You can get separate plots for the contributions of individual metabolites to the data (as in FIGS. 2 & 3). 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(40)*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`.

9.6.4.2 Dimensions

The overall page dimensions for your One-Page Output are usually best set by inputting `PGNORM` as `'US'` or `'A4'` (Sec. 4.3.5). 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 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`

9.6.4.3 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 = 9.`

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 is still only 30 characters long. Inputting a small value, like `PTOUTP=0.001`, will make the tables invisible, e.g, for a slide or figure.
Default: `PTOUTP = 9.`

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.`

9.6.4.4 Curves

The following dimensions are all in cm:

WDLINE (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 `WDLINE(2) = 0.`
(3) data;
(4) Residuals;
(5) axes and frame;
(6) fine grid lines. The vertical grid lines will be suppressed if `WDLINE(6)=0.`, e.g, for a slide or figure.
Defaults: `WDLINE = .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 `WDLINE`.
Default: RGBLIN(1,1) = 1.; 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 nonpositive, 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`

9.6.4.5 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.`

9.6.5 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 $n = \delta n(-\mathtt{Ns}, -\mathtt{Ns}+1, \ldots, \mathtt{Ns}-1, \mathtt{Ns})$. Except for broad lineshapes (or high fields) , $\delta n = 1$ and $\mathtt{Ns} = N_S$.

(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 [12].

Chapter 10

Absolute Metabolite Concentrations

You only need to read this chapter if you want to attempt to get 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. 11.1) and partial volume effects. Concentration ratios are less sensitive to these effects.

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)

+ Well-developed, reliable; successfully used with LCModel for a long time with Siemens [11] and GE data [13].
– An absolute method: Still requires accurate scaling of each spectrum for voxel size and changes in total gain due to coil loading, etc. LCMgui only does this for GE & Siemens data.
• Probably the method of choice for GE & Siemens data.

Water-Scaling: The resonance area of the unsuppressed reference water signal (together with the assumed water concentration) is used [14, 15] (Sec. 10.2).

+ A ratio method: Several sources of error, such as voxel size, total gain and hardware changes are automatically eliminated.
+ 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).

- For data other than GE & Siemens (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

Each data set (`.RAW` file, Sec. 4.2.2) 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.

One method for consistently scaling spectra is to set `TRAMP` equal to the RF transmitter amplitude of a nonselective 90° reference pulse (rectangular and 0.5 ms in duration) [11]. For Siemens data, LCMgui sets `TRAMP` to the "raw" file header element `G19.Acq3.Mr.TransmitterCalibration`.

With GE Signa 5.x systems, LCMgui uses

$$\texttt{TRAMP} = 2^{(6-R1)+(30-R2)} \times 10^{0.005(TG-65)}$$

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, as long as it is consistently used for all `TRAMP`.)

With GE Signa LX data, $R1$ is replaced by $R1/2$:

$$\texttt{TRAMP} = 2^{(6-R1/2)+(30-R2)} \times 10^{0.005(TG-65)}$$

10.1.1.1 Non-GE & Non-Siemens

In these other cases, LCMgui simply sets `TRAMP=1.0`. Therefore, you would have to do one of the following:

- Use Water-Scaling (Sec. 10.2), which does not need consistently scaled data.
- Compute your own `TRAMP`, e.g., using the reference pulse used for Siemens data above. You could do this in a Preprocessor script (Sec. 7.4.5), or do the entire data conversion using the "Other" button (Sec. 7.4.4).

10.1.1.2 Fine Points

To optimally scale spectra with different voxel dimensions, you may have to refine `VOLUME`. The Siemens RF pulse profiles change with slice thickness, and the nominal voxel dimensions in the header are therefore not quite correct. You can calibrate this by measuring the signal change in a phantom as a function of the nominal voxel dimension.

In addition to [11], there are detailed literature references, studies, alternatives and refinements to determining `TRAMP`, e.g., [16, 17, 18, 19]. 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

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 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 powder).

Analyze a spectrum from this phantom with LCModel, 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
```

Let C_{lcm} be the concentration output by LCModel, and let C_{true} be the true concentration in the phantom (e.g., 50 mM). Then, for your future analyses input

$$\texttt{FCALIB} = C_{true}/C_{lcm}$$

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. LCModel 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.

$$Basis_{norm} = Area_{met}/[\texttt{N1HMET} \times Conc_{met} \times \texttt{ATTMET}]$$

where $Area_{met}$ is the observed resonance area of the selected singlet (by default, the Cr CH_3), `N1HMET` is the number of equivalent protons contributing to the selected singlet, $Conc_{met}$ is the model metabolite concentration, and `ATTMET` the attenuation factor.
Similarly,

$$Water_{norm} = Area_{water}/[2 \times \texttt{WCONC} \times \texttt{ATTH2O}]$$

As specified below, `N1HMET` and $Conc_{met}$ are known, the two $Area$ terms are computed by LCModel from the data, but `ATTH2O`, `WCONC` and `ATTMET` must be guessed.

10.2.2 Usage

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 ATTH2O below are difficult to guess correctly. This means that all your concentrations will still be off by an unknown factor. You therefore obtain concentrations in unknown "institutional units", all differing from mM by typically 20% or more (much more with $TE > 30$ ms or $TR < 5000$ 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 concentrations (in your "institutional units") that are useful at detecting trends, pathologies, etc.

WCONC (REAL) the NMR-visible water concentration (mM) in the voxel. This is $55500\beta_{MR}$ in [20], where typical values were 35880 for white matter and (a 21% larger) 43300 for gray matter. Default: WCONC = 35880.0.

ATTH2O (REAL) the attenuation of the NMR-visible water signal due to additional relaxation effects and other effects, such as transmitter amplifier "leakage" [15, p. 337]. ATTH2O 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.* [20] found the major water compartment with $T2 = 80$ ms. This alone would imply ATTH2O=0.7 when $TE = 30$ ms. Longer TE would require even more drastic corrections.
Default: ATTH2O = 0.7.

ATTMET (REAL) the attenuation of the singlet used in the selected Basis Spectrum (specified below with WSMET, etc.) The relaxation effects will be less extreme than for ATTH2O, at least with short TE, since the metabolites *in vitro* usually have longer $T2$ than water *in vivo*. Also, the Siemens Basis Spectra were acquired with $TR = 10$ s and the GE with $TR = 6$ s.
Default: ATTMET = 1.0

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 = 3.03.

N1HMET (INTEGER) the number of equivalent protons contributing to the singlet used for scaling.
Default: N1HMET = 3

NWSST (INTEGER). ("the number of the Water-Scaling starting point") $Area_{water}$ in Sec. 10.2.1 is estimated from the amplitude of an exponential analysis of the early points of the absolute value of the time-domain-data (thanks to suggestions from M. Wick and E. R. Danielsen). The beginning points are not used. NWSST is the subscript of the first point that is used.
Default: NWSST = 10

NWSEND (INTEGER). the subscript of the last time-domain point used for $Area_{water}$. Default: NWSEND = 50

Chapter 11

Fine Points

This chapter contains a collection of further topics and options that could be of interest to you. 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 Relaxation Corrections

The main message of this section is to use short echo times ($TE \leq 30$ ms, better 20 ms) and long repetition times ($TR > 3000$ ms, better 5000 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 concentration ratios to establish norms, provided that you keep TE and TR fixed.

An advantage of LCModel is that it partially accounts for relaxation effects automatically by using actual model spectra attenuated by actual relaxation *in vitro*. For example, you account for $T2$ relaxation by multiplying your LCModel concentrations by

$$f_{TE} = \frac{\exp(-TE/T2_{vitro})}{\exp(-TE/T2_{vivo})} = \exp\left[TE\left(\frac{1}{T2_{vivo}} - \frac{1}{T2_{vitro}}\right)\right]$$

Thus, it is only the *difference* of the $1/T2$ values (relaxation rates) between *in vivo* and *in vitro* that comes into play with LCModel. For concentration ratios, the exponent in the ratio of correction factors contains only the *difference* (between numerator & denominator) of a *difference* (between *in vivo* & *in vitro*), a second-order effect, but it can still be significant with long TE.

In addition, you must also multiply the LCModel concentrations by the correction factor for

TR, which for STEAM is

$$f_{TR} = \frac{[1 - \exp(-RD/T1_{vitro})]}{[1 - \exp(-RD/T1_{vivo})]} \exp\left[TM\left(\frac{1}{T1_{vivo}} - \frac{1}{T1_{vitro}}\right)\right]$$

where $RD = TR - TM - TE/2$. This correction factor usually becomes unimportant with $TR \geq 5000$ ms.

11.2 Prior Referencing Information

Spectra like that of CSF in FIG. 5, without the usual landmark peaks of NAA, Cr & Cho, can be difficult to reference automatically. In case of a referencing failure (which often looks like FIG. 14), you can often salvage the spectrum by helping LCModel with approximate referencing information.

This section can also be useful 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 FIG. 14. If your water suppression is not too extreme, then you can usually remedy this by using `DOREFS(1)=T`, as described in the next paragraph. You may also have to extend the maximum expected shift with `SHIFMN(1)` or `SHIFMX(1)` in Sec. 11.2.1. This could be a universal solution for all your analyses, where you automatically input `DOREFS` and `SHIFMX(1)` or `SHIFMX(1)` in every `.CONTROL` file.

If your water suppression is not too extreme, it is most 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 is only tells LCModel where to start looking. But it cannot have been totally removed, e.g., by some digital filter; there must 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`
(It is not necessary that you read the detailed discussion of `DOREFS` in Sec. 11.2.1.)

Less automatic, but more direct, is to plot the absolute value of the spectrum. With LCMgui, you can use "Preview Data". Otherwise use PlotRaw or input `DOREFS = 2*F` to LCModel, as in FIG. 4. From the plot, estimate the referencing shift. You can then directly impose this starting shift with `PPMSHF`.

`PPMSHF` (REAL) ("shift in ppm") LCModel will start looking for the referencing shift at `PPMSHF` (remember the standard convention that a positive shift shifts the data toward higher ppm). LCModel will start its search only at this one shift; the usual elaborate grid search is suppressed. (Note that the disaster in FIG. 14 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` ≈ 0.2).
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.

11.2.1 Details of Automated Referencing

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 PlotRaw (or "Preview Data" in LCMgui) 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) = 5` (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 in Hz.
Defaults: `PPMREF(1,1) = 4.65` (for water);
`PPMREF(JREF,2) = 1.33, 1.33, 2.01, 3.03, 3.22` (for the Lac doublet, NAA, Cr & Cho); all `HZREF` elements zero, except `HZREF(1,2) = -3.6` and `HZREF(2,2) = 3.6` (for the Lac doublet).
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`.

11.3 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 in the `.BASIS` file that are to be used in the Preliminary Analysis. Default: `NUSE1 = 7`.

`CHUSE1` (CHARACTER(40)*6) the first `NUSE1` elements contain the Metabolite Names of the spectra to be used. Default: `CHUSE1 = 'NAA', 'Cr', 'Cho', 'Lac', 'Ins', 'Glu', 'Glc'`.

If your spectrum is not mainly CSF, then eliminating Glc by setting `NUSE1 = 6` might be better, but this is not critical. With long echo times, `NUSE1 = 4` is better.

11.4 Unusual Phantoms

By default, LCModel assumes that the spectrum being analyzed contains dominating landmark resonances from NAA, Cr, Cho, or Lac. 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. Nevertheless, with such a phantom, you would use the following Control Parameters:

(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, HZREF(1,2)=0.0`
 (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 PlotRaw (or LCMgui’s “Preview Data”), and use `PPMSHF`, as described in Sec. 11.2.
(3) Suppose your unusual phantom only contains metabolites with the Metabolite Names Metab1, Metab2, Metab3. There are two possibilities:
 (3a) `NUSE1=3, CHUSE1='Metab1', 'Metab2', Metab3'`.
 (3b) More accurate and convenient is to use
 `NCALIB=3, CHCALI='Metab1', 'Metab2', 'Metab3'`
 Then, `NUSE1, CHUSE1, VITRO` are automatically set for you.

11.5 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 (and output on the One-Page Output) as follows:

`RFWHM` (REAL) the convolution extends over a range of `RFWHM*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. Usually if the default `RFWHM` is not adequate, then the data are not worth salvaging. However, you can nevertheless rerun with an increased `RFWHM`, say, to 3.0, or more if necessary.

11.6 Prior Probabilities

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:

`EXT2` ("expectation of $1/T2$") Control Parameters with this ending modify γ_ℓ^0 in [1, Eq. (4)]. These Control Parameters specify the increase in $1/T2$ (in s^{-1}) in going from the *in vitro* Basis Spectrum to *in vivo*.

`SDT2` ("SD of $1/T2$") These are for the $\sigma(\gamma_\ell)$; the units are also s^{-1}.

`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*.

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=1.0, DESDSH=0.004`.

`N****` (INTEGER) ("number") the number of quantities that are to be changed from their defaults. Defaults: `NEXT2=0, NSDT2=0, NSDSH=3`.

`CH****` (CHARACTER(40)*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(40) ("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*.

The lineshape parameters can automatically account for increases in $1/T2$ 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.

11.7 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:

(a) The Namelist `LCMODL`, which contains the final values of all the Control Parameters, as described in Sec. 11.8.
(b) A table documenting the Basis Spectra used in the Preliminary Analysis.
(c) Each iteration in the elaborate Preliminary Analysis for starting values for the referencing shift and phase corrections for the data.
(d) A table documenting the Basis Spectra used in the Final Analysis.
(e) Each iteration in the search for optimal regularizors 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*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 four 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)]. These are typically much less smooth than the lineshape itself (which you can see in the plot in the One-Page Output).
(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 –0.5, then you should also output the concentration sum of the pair (Sec. 9.6.1.1). More subtle correlations between 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 order, 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. 7.3.2.1). 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.

11.8 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'
PPMH2O=900.
$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 `PPMH2O` 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 `PPMH2O`, 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=' '`, `PPMH2O=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 (e.g., `PPMH2O`) are so-called *Forbidden Control Parameters*, which are not documented in this manual and should not be changed. These are already set to their optimal values.

11.9 Analyzing Magnitude Spectra

This should only be done if it is impossible for LCModel to phase your spectra. For example, some very fast CSI sequences with long echo times have huge unknown 1st-order phase corrections, and it is necessary to analyze the absolute values of the spectra.

For Bruker users only: With Avance data acquired using `ACQP DIGMOD==digital_mode`, use Bruker's `convdta`. Then the 1st-order phase correction is small and there is *no need* to use `ABSVAL`.

`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. (Don't input absolute values.)
Default: `ABSVAL = F`.

11.10 Old Output Formats

This is only for users who want to have exactly the same output format as Versions 5.1 and earlier (e.g., to avoid changing your postprocessing software).

`YEAR4D` (LOGICAL) ("year with 4 digits") The 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`

Chapter 12

Diagnostics and Trouble-Shooting Hints

LCModel performs extensive checks for abnormal conditions and has about 150 diagnostic messages. 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. Often, one of the most important questions in trouble-shooting is whether the data have been correctly converted or read in. Check this by plotting the input data with PlotRaw (or the "Preview Data" button in LCMgui).

12.1.1 I/O Errors

Input/Output errors are the most common errors, especially during the first few runs. Sun & DEC systems give good diagnostics, often showing exactly where the I/O error occurred.

Unconnected Files: Some systems will simply pause and wait for input from a unit that is not connected. Make sure that you have input all necessary `FIL*` Control Parameters, as specified in Sec. 9.2.

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`.

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.

12.1.2 Arithmetic Exceptions

Underflows: are no problem; they are expected to occur (possibly accompanied by run-time diagnostics) and are replaced by zero. It is normal for Sun workstations to give the warning about underflow, inexact, and compilation with **`-fnonstd`** and **`-fast`**.

Overflows & Zero-Divides: should never occur (and never have). Check whether the format of your `.RAW` data agrees with `FMTDAT`; with the wrong format, huge numbers might be read in that overflow when squared. Plot the data using PlotRaw (or "Preview Data" in LCMgui).

If necessary, rescale your `.RAW` data (e.g., with `TRAMP`) so that the maximum absolute value is, say, below 10^8 and above 10^{-8}.

12.1.3 Other Aborts with no One-Page Output

Maximum Time: LCModel can work very hard to analyze very poor data. Keep this in mind, if you are setting computation-time limits.

Missing One-Page Output: Errors can, in principle, 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, 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 LCModel Diagnostics

These are in the Diagnostics Table in the One-Page and Detailed Output. The 6 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 (but probably will not) affect the final results.

`ERROR`: an error condition has occurred, but corrective action has been taken; the results could be affected.

`CRUDE MODEL`: this is a specialized reminder that the results are based on the Preliminary Analysis with the crude Gaussian-Lorentzian model and that the analysis with the full model has been suppressed by your Control Parameters.

`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.

`Doing Water-Scaling:` this is just an `info` that Water-Scaling has been done.

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 has never occurred in the analyses of the 10000 spectra so far, and it 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 the data may be so poor that LCModel has to work hard.

You can judge from the One-Page Output if your results have been affected. If the fit to the data is reasonable and the other criteria discussed in Sec. 5.2 are satisfied, then there is no reason for doubt.

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.

`BETAIN` evaluates the incomplete beta function, which is used to compute the confidence regions [5] 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)*42); these must satisfy the rules in Sec. 9.6.1.1. The Detailed Output ends with "`Incorrect CHCOMB =`" followed by the first 42 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 100.

2 (`FATAL`) A Metabolite Name in a `CHCOMB` has more than 6 characters.

3 (`FATAL`) A `CHCOMB` has more than 6 Metabolite Names.

`DEMO` only allows analysis of the demo test data, unless you have a license.

1 (`FATAL`) You do not have a license for this data or workstation.
Hints: Check that your input of `OWNER` and `KEY` exactly match what was given to you with your license.

`ERRMES` outputs and counts diagnostics.

1 (`ILLOGICAL`) Meaningless argument in call to `ERRMES`.

2 (`FATAL`) Stopping after `MERMES = 50` 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**, and, if it does, it is probably because all data points are zero.

7 (`warning`) The Baseline required a great deal of freedom and may have a wild shape. **Hints:** This may be due to shimming problems (especially in difficult areas like the cerebellum or hippocampus) 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, you should eliminate this using `PPMST` or `PPMEND`. If the spectrum being analyzed is *in vitro*, try inputting `VITRO = T`. If the problem persists, you should probably reject the spectrum.

8 (`warning`) The magnitude of the first-order phase correction exceeds 40°/ppm.
Hints: If this is not expected with your protocol, then 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.

10 (`warning`) The zero-order phase correction is more than four standard deviations (`SDDEGZ`) from its expectation value (`DEGZER`). The phasing is probably poor, and you will probably 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?

11 (`warning`) The first-order phase correction is more than four standard deviations (`SDDEGP`) from its expectation value (`DEGPPM`). The phasing is probably poor, and you will probably 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`.

`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 Forbidden 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 (`ERROR`) The solution of a nonlinear equation is inaccurate. This could 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:** Your `.RAW` file is probably being read in as all zeroes or extremely small values; check the format of the data in this file.

`GBACKG` ("Get background") computes the B-splines for the Baseline.

1 (`warning`) N_B in [1, Eq. (1)] would be less than 6; it will be set to 6.
Hints: Either the spectrum has extremely poor resolution, or you have set `PPMST` and `PPMEND` to make an unreasonably narrow Analysis Window.

2 (`FATAL`) There is not enough storage for 6 spline knots. **Hints:** This would be my error.

3 (`FATAL`) Your Analysis Window has zero width. **Hints:** This is actually `ILLOGICAL`, since this error should have been caught earlier.

`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 8192 in most versions of LCModel. Rerun to get the Detailed Output; at the end is this diagnostic with `NUNFIL` and its limit. If you need a higher limit, 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 or above 4.65 ppm (water).

4 (`FATAL`) Your `PPMEND` $\geq$ `PPMST`, or the number of data points in your Analysis Window exceeds the allocated storage (normally 2000). **Hints:** 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.

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**.

`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 Forbidden Control Parameters `DEGMAX(1)` or `DEGMAX(2)` is not positive. **Hints:** Leave these at their defaults.

`LOADCH` loads the `Input Changes` table for the One-Page Output.

1 (`ERROR`) You attempted to set the Forbidden Control Parameter `MERMES` to exceed allocated storage. It will be reduced to the maximum allowed value of 50.

`MAKEPS` organizes the production of the PostScript file for the One-Page Output.

1 (`FATAL`) At least one of the Control Parameters `PAGEHT, PAGEWD` is not positive. No One-Page Output can be produced. **Hints:** Correct your input of `PAGEHT, PAGEWD, PGNORM`.

`MYBASI` inputs the Basis Set, selects the Basis Spectra, and scales and shifts them.

1 (`FATAL`) In the Namelist `BASIS1` in your `.BASIS` file, `BADELT` or `NDATAB` is not positive or `NDATAB` > 16384. **Hints:** You must have changed these yourself, since they were checked before MakeBasis output them.

2 `info` The bandwidth (BW) of your data and Basis Set are different; LCModel will convert the Basis BW.
`warning` More than 90% of the Basis BW is needed to cover the Analysis Window. There will probably be distortions at the edges. **Hints:** Use a Basis with a larger BW or narrow the Analysis Window.
`FATAL` The Basis BW is narrower than the Analysis Window. **Hints:** as for the `warning`.

3 No longer used.

4 No longer used.

5 (`FATAL`) The number of Basis Spectra to be used exceeds 40. **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, Cho, Lac, Ins, Glu, Glc, 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 metabolites 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. 11.4.

8 (`info` or `warning`) One (`info`) or more (`warning`) of the `NUSE1` Metabolite Names in the array `CHUSE1` are not in the Basis Set. The Preliminary Analysis will not use all the metabolites named in `CHUSE1`, and this could damage the Preliminary Analysis.
Hints: When `PPMST=3.85`, Glc is automatically omitted, and this `info` is no problem, unless you are trying to analyze CSF.

With `PPMEND` > 1.57, as in FIG. 10 where a huge lipid peak is cut off, Lac & Ala are automatically omitted, and this `warning` is normal.

Otherwise, make sure that your Metabolite Names agree with the Allowed Names in Table 8.1 (see the discussion of `METABO`).

9 (`warning` or `ERROR`) This field strengths in your *in vivo* data and your Basis Set differ by more than 1% (`warning` – barely usable) or more than 2% (`ERROR` – unacceptable). **Hints:** If `HZPPPM` is correct in Namelist `SEQPAR` of your data and of your Basis Set, then you need an appropriate Basis Set.

10 (`ERROR`) The echo times (`ECHOT`) in your *in vivo* data and your Basis Set differ by more than 1 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 was 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.

`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 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 (`FATAL`) Namelist `NMID` in your `.H2O` file contains a different `NUNFIL` from that in your `.RAW` file. The protocols for the `.H2O` and `.RAW` files must be identical, except for water suppression.

`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. 9.6.4.2 & 9.6.4.3 for unreasonable values.

`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 Forbidden Control Parameters:

PMQST, PMQSTL, RSTPMX, RCONVR, RMQDEC, RMQINC, COSMIN, RINCRS, RPMQMN, RSTPMN. **Hints:** Leave them at their defaults.

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 (warning) 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 (warning) Maximum iterations before convergence in the quadratic program; corrective action is taken. **Hints: Working Hard**.

RFALSI ("*regula falsi*") adjusts the overall regularization until the criterion in [5] 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 Forbidden Control Parameters RALIMN or RALINC is less than 1.0. **Hints:** Leave them at their defaults.

3 (FATAL) A critical unregularized least-squares analysis has failed. **Never Happened**, but if it does, 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 regularizor.
Hints: Working Hard.

15 (FATAL) All nonlinear-least-squares analyses in all iterations failed.
Hints: Never Happened.

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 regularizor satisfying the criterion in [5] to within the desired tolerances

could not be found. The regularizor could be inappropriate.
Hints: Working Hard

`SAVBES` saves information on the best solution found so far.

1 (`ILLOGICAL`) Meaningless argument in call to `SAVBES`.

`SETUP` initially sets up regularizors, priors, and starting estimates for the nonlinear-least-squares analyses in [1, Eq. (4)].

1 (`FATAL`) One of the Forbidden Control Parameters `DKNTMN, RBACKG` or `FWHMST` has been set nonpositive. **Hints:** Leave them at their defaults.

2 (`ERROR`) N_B would exceed its maximum allowable value (50). 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 (`ILLOGICAL`) $N_B < 6$, but this should have been caught by `GBACKG 1`.

4 (`FATAL`) an eigenvalue decomposition to get the regularizor 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`) `FWHMBA` ≤ 0, and it must be positive.

8 (`FATAL`) Same as `SETUP 5`.

9 (`warning`) $N_S = 0$. **Hints: Never Happened**. Previous checks should prevent this.

10 (`FATAL`) A starting value is $\alpha_B \leq 0$ or $\alpha_S < 0$.
Hints: This can only occur if you have modified Forbidden Control Parameters, such as `ALPBST, ALPBST` or `DKNTMN`.

11 (`FATAL`) Same as `SETUP 5`.

12 (`FATAL`) Same as `SETUP 5`.

13 (`FATAL`) The Forbidden Control Parameter `FWHMST` ≤ 0 and it must be positive.
Hints: leave it at its default.

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 Forbidden 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 Forbidden Control Parameter `SDMSHF` nonpositive, and it must be positive.

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 Forbidden Parameters has been changed to a nonpositive value: `DFLDMQ, DDGZMQ, DDGPMQ, DSHFMQ, RSHFMQ, DRT2MQ, RRT2MQ, NSIDMN`.
Hints: Leave them at their defaults.

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`.

`SSRANG` ("sum of squares range") finds the range of the first sum in [1, Eq. (4)] corresponding to a given range of confidence levels [5].

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 Forbidden Control Parameter PRMNMX.

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 FIG. 4.

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 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 PlotRaw (or "Preview Data" in LCMgui). 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 FIG. 14 occurs, Sec. 11.2 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 extend SHIFMN or SHIFMX.

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. This could cause a gross referencing error and something like FIG. 14. If this occurs, plot the Absolute-Value Plot of the spectrum with PlotRaw (or "Preview Data" in LCMgui), 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 extend 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, as in FIG. 12). 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 3 δ-functions left (usually the Lac doublet and NAA), and the extreme shift is still being called for by the CCF.
Hints: Either the true referencing shift is extreme (reset SHIFMN or SHIFMX), or your spectrum has very little structure or extreme residual water or lipid peaks. If the referencing looks reasonable, and not like FIG. 14, then LCModel has managed anyway and there is no problem. Otherwise, Sec. 11.2 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 Forbidden Control Parameter) `QUICK = T`, this diagnostic is unavoidable. Otherwise, you can avoid this by increasing `NSHIFT`, but this would increase the computation time, and an `NSHIFT = 8` is usually adequate, despite this diagnostic. If a disastrous referencing error like FIG. 14 occurs, Sec. 11.2 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 Forbidden Control Parameter `NSIDMX` > 20. It will be reduced to 20.

18 (`FATAL`) You have input the Forbidden Control Parameter `NSIDMN` nonpositive or exceeding `NSIDMX` in `STARTV 17`.

19 (`ERROR`) You have input the Forbidden Control Parameter `INCSMX` nonpositive or exceeding 24. It will be changed to the closest of the two limits.

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:** Spectra with such high resolution are good.

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.

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 spectral window or above 4.65 ppm (water).
Hints: Correct these Control Parameters. If they are OK, then you will have to reduce your Analysis Window to fit further within your spectral window. This is most likely to occur when you are analyzing an (unusually broad) unsuppressed water peak to scale for absolute concentrations. In this case, reduce `PPMST` in steps of 0.1. If you are using LCMgui, the comments in `$HOME/.lcmodel/???/preprocessors/water-scale` (where `??? = ge5, gelx, philips` or `siemens`) tell you where to change this.

23 (`ERROR`) The Preliminary Analysis has estimated a lineshape so wide that the convolution in [1, Eq. (1)] would extend beyond the entire spectral window or above 4.65 ppm (water). The convolution range will be reduced. **Hints:** Either your spectrum has very poor resolution or your bandwidth is too narrow.

24 (`info`) 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. 9.6.5, will be made greater than 1 to cover the convolution range in no more than `NSIDMX` steps. **Hints:** This is no problem in itself, and is normal at higher fields.

`TWOREG` (" two regularizors") 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` ≤ 1.0 or `ALPBST` $<$ `ALPBMN` or `ALPBST` $>$ `ALPBMX`. **Hints:** All of these are Forbidden Control Parameters; leave them at their defaults.

3 (`warning`) A less-than-normal extent of lineshape smoothing has been explored. The regularizor might be suboptimal. **Hints:** As for `STARTV 21`.

4 (`FATAL`) A regularized solution within the acceptable range of the confidence region in [5] could not be found. **Hints:** Check for very poor or erroneous data (e.g., that would require an extremely wild Baseline), or check whether you have modified Forbidden Control

Parameters such as PRMNMX.

5 (FATAL) Both PRMNMX(2,1) and PRMNMX(2,3) exceed PRMNMX(1,2). **Hints:** Leave these Forbidden Control Parameters at their defaults.

6 (warning) An important regularized analysis has failed to properly converge. The final results may be affected. **Hints:** As for STARTV 21.

7 (info) A regularized analysis in a refinement step has failed to properly converge. The final results will not be seriously affected. **Hints: Working Hard**.

8 (info) An extra iteration was required in determining the phases.
Hints: This is no problem as long as TWOREG 9 does not occur.

9 (warning) The phase corrections are not very well determined. The plots on the One-Page Output do not correspond to the real parts of the data, so that the fit to the data will look worse than it actually is. However, the concentrations should still be correct.
Hints: This is fairly common with data having low resolution or S/N.

WSCALE ("Water-Scaling") Does Water-Scaling. Errors here simply cause the analysis to proceed without any scaling; the concentration ratios will still be valid.

1 (ERROR) Water-Scaling will be skipped, because one of the following requirements has not been met: NWSST > 0; NWSEND $\leq$ NUNFIL; NWSEND $-$ NWSST ≥ 9.

2 (ERROR) Water-Scaling will be skipped, because 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 (ERROR) Water-Scaling will be skipped, because 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.

4 (ERROR) Water-Scaling will be skipped, because one of the following was not input positive: N1HMET, ATTH2O, WCONC, ATTMET, or because the integral of the unsuppressed water peak is not positive.
Hints: Correct your input of N1HMET, ATTH2O, WCONC, ATTMET, and check for gross errors in the .H2O file, such as all time-domain points zero.

5 (ERROR) Water-Scaling will be skipped, because the integral of the 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.

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Index