New open-source analysis software for advanced magnetic resonance spectroscopy

PIRC Lab Meeting
July 28th, 2021

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Instructor

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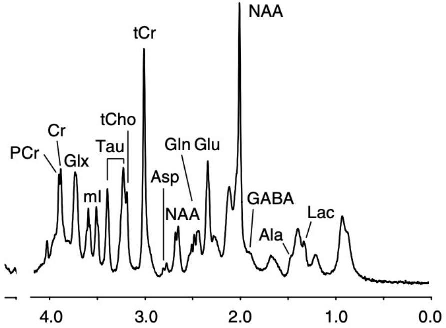
SCHOOL *of* MEDICINE

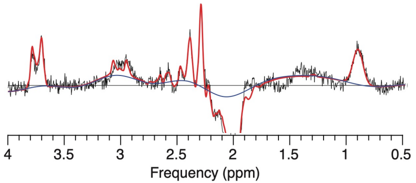
Kennedy Krieger Institute
UNLOCKING POTENTIAL

Outline

- Modern MRS data analysis workflow

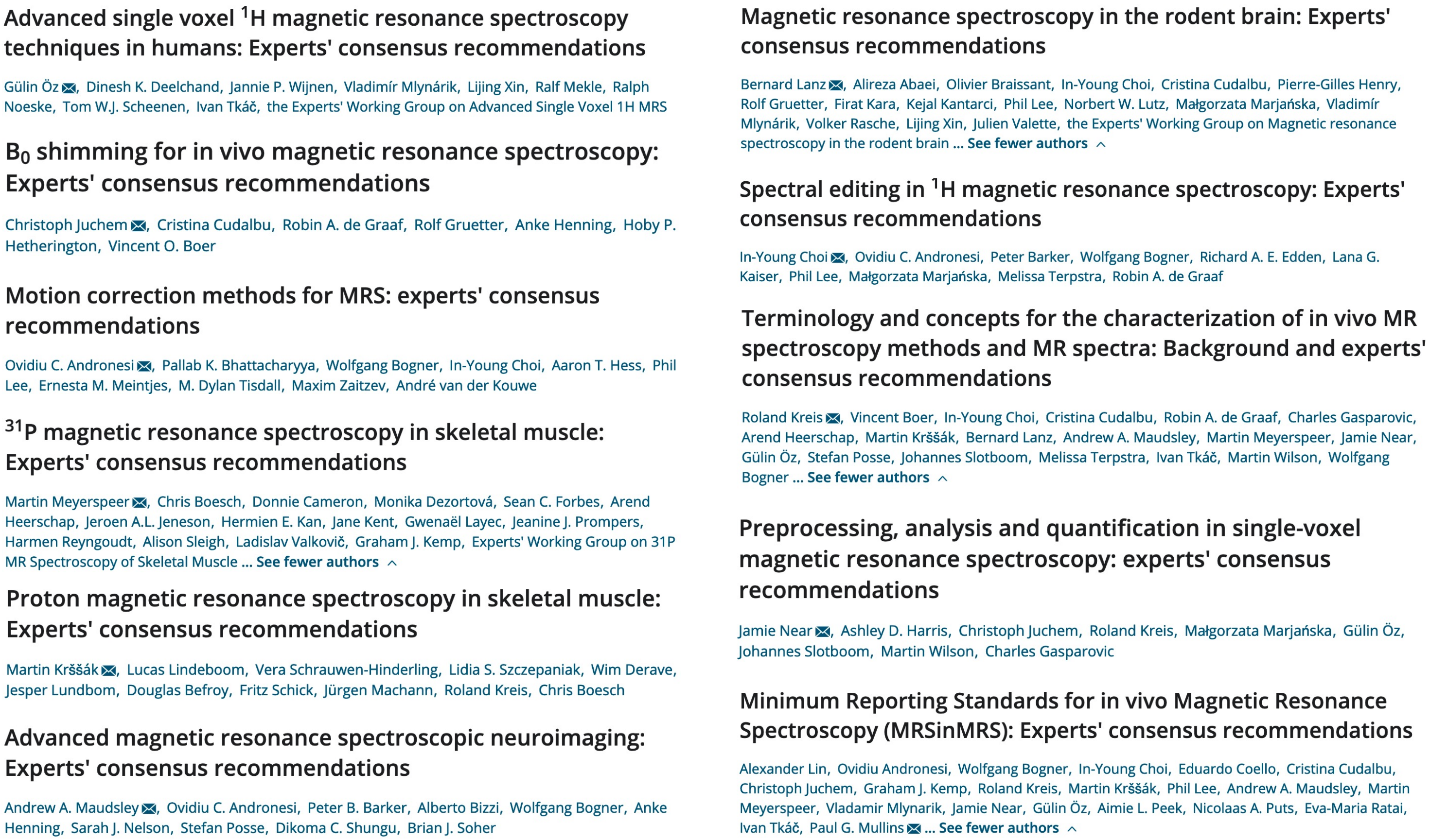
- Open-source MRS analysis software:
  A Quest for Standardization & Reproducibility





MRSHub

2019-2021: Expert consensus efforts



Advanced single voxel ^{1}H magnetic resonance spectroscopy techniques in humans: Experts' consensus recommendations

Gülin Öz ✉, Dinesh K. Deelchand, Jannie P. Wijnen, Vladimír Mlynárik, Lijing Xin, Ralf Mekle, Ralph Noeske, Tom W.J. Scheenen, Ivan Tkáč, the Experts' Working Group on Advanced Single Voxel 1H MRS

B_0 shimming for in vivo magnetic resonance spectroscopy: Experts' consensus recommendations

Christoph Juchem ✉, Cristina Cudalbu, Robin A. de Graaf, Rolf Gruetter, Anke Henning, Hoby P. Hetherington, Vincent O. Boer

Motion correction methods for MRS: experts' consensus recommendations

Ovidiu C. Andronesi ✉, Pallab K. Bhattacharyya, Wolfgang Bogner, In-Young Choi, Aaron T. Hess, Phil Lee, Ernesta M. Meintjes, M. Dylan Tisdall, Maxim Zaitzev, André van der Kouwe

^{31}P magnetic resonance spectroscopy in skeletal muscle: Experts' consensus recommendations

Martin Meyerspeer ✉, Chris Boesch, Donnie Cameron, Monika Dezortová, Sean C. Forbes, Arend Heerschap, Jeroen A.L. Jeneson, Hermien E. Kan, Jane Kent, Gwenaël Layec, Jeanine J. Prompers, Harmen Reyngoudt, Alison Sleigh, Ladislav Valkovič, Graham J. Kemp, Experts' Working Group on 31P MR Spectroscopy of Skeletal Muscle ... See fewer authors ^

Proton magnetic resonance spectroscopy in skeletal muscle: Experts' consensus recommendations

Martin Krššák ✉, Lucas Lindeboom, Vera Schrauwen-Hinderling, Lidia S. Szczepaniak, Wim Derave, Jesper Lundbom, Douglas Befroy, Fritz Schick, Jürgen Machann, Roland Kreis, Chris Boesch

Advanced magnetic resonance spectroscopic neuroimaging: Experts' consensus recommendations

Andrew A. Maudsley ✉, Ovidiu C. Andronesi, Peter B. Barker, Alberto Bizzi, Wolfgang Bogner, Anke Henning, Sarah J. Nelson, Stefan Posse, Dikoma C. Shungu, Brian J. Soher

Magnetic resonance spectroscopy in the rodent brain: Experts' consensus recommendations

Bernard Lanz ✉, Alireza Abaei, Olivier Braissant, In-Young Choi, Cristina Cudalbu, Pierre-Gilles Henry, Rolf Gruetter, Firat Kara, Kejal Kantarci, Phil Lee, Norbert W. Lutz, Małgorzata Marjańska, Vladimír Mlynárik, Volker Rasche, Lijing Xin, Julien Valette, the Experts' Working Group on Magnetic resonance spectroscopy in the rodent brain ... See fewer authors ^

Spectral editing in ^{1}H magnetic resonance spectroscopy: Experts' consensus recommendations

In-Young Choi ✉, Ovidiu C. Andronesi, Peter Barker, Wolfgang Bogner, Richard A. E. Edden, Lana G. Kaiser, Phil Lee, Małgorzata Marjańska, Melissa Terpstra, Robin A. de Graaf

Terminology and concepts for the characterization of in vivo MR spectroscopy methods and MR spectra: Background and experts' consensus recommendations

Roland Kreis ✉, Vincent Boer, In-Young Choi, Cristina Cudalbu, Robin A. de Graaf, Charles Gasparovic, Arend Heerschap, Martin Krššák, Bernard Lanz, Andrew A. Maudsley, Martin Meyerspeer, Jamie Near, Gülin Öz, Stefan Posse, Johannes Slotboom, Melissa Terpstra, Ivan Tkáč, Martin Wilson, Wolfgang Bogner ... See fewer authors ^

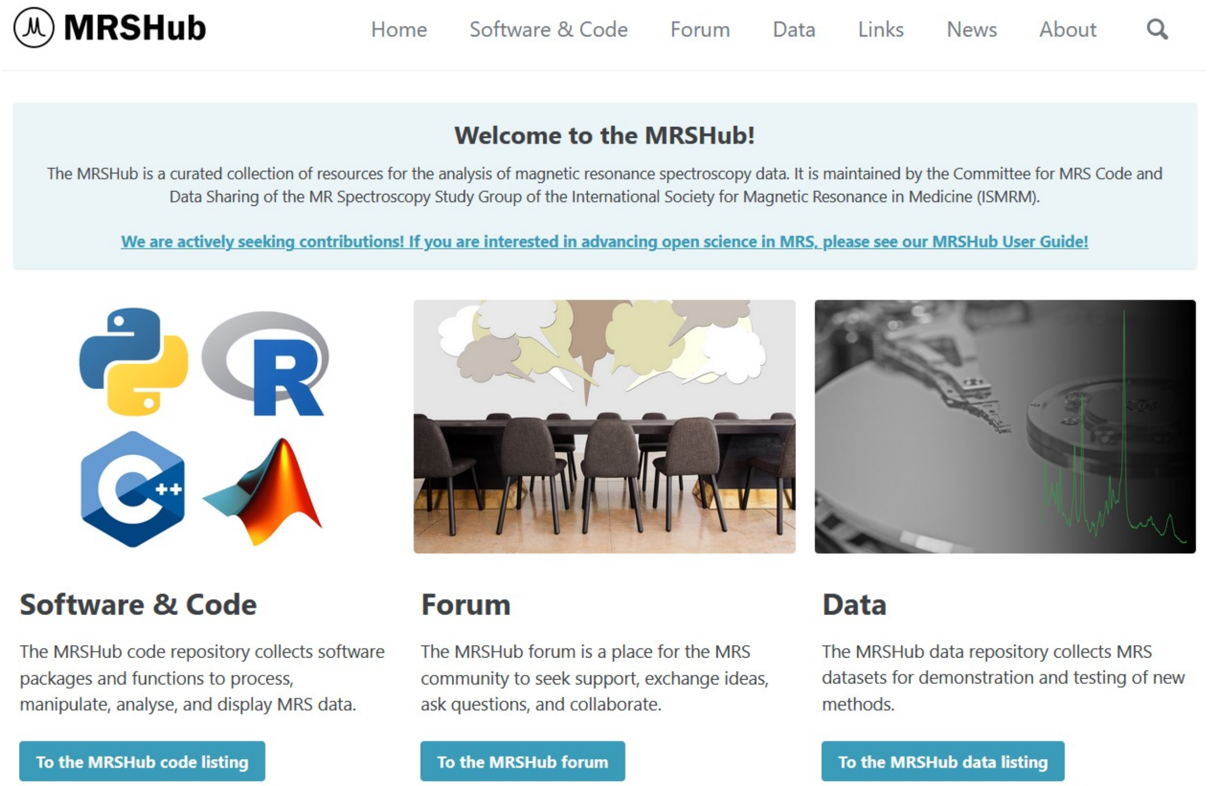
Preprocessing, analysis and quantification in single-voxel magnetic resonance spectroscopy: experts' consensus recommendations

Jamie Near ✉, Ashley D. Harris, Christoph Juchem, Roland Kreis, Małgorzata Marjańska, Gülin Öz, Johannes Slotboom, Martin Wilson, Charles Gasparovic

Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' consensus recommendations

Alexander Lin, Ovidiu Andronesi, Wolfgang Bogner, In-Young Choi, Eduardo Coello, Cristina Cudalbu, Christoph Juchem, Graham J. Kemp, Roland Kreis, Martin Krššák, Phil Lee, Andrew A. Maudsley, Martin Meyerspeer, Vladamir Mlynarik, Jamie Near, Gülin Öz, Aimie L. Peek, Nicolaas A. Puts, Eva-Maria Ratai, Ivan Tkáč, Paul G. Mullins ✉ ... See fewer authors ^

MRSHub – one centralized resource



Welcome to the MRSHub!

The MRSHub is a curated collection of resources for the analysis of magnetic resonance spectroscopy data. It is maintained by the Committee for MRS Code and Data Sharing of the MR Spectroscopy Study Group of the International Society for Magnetic Resonance in Medicine (ISMRM).

We are actively seeking contributions! If you are interested in advancing open science in MRS, please see our MRSHub User Guide!

Software & Code

The MRSHub code repository collects software packages and functions to process, manipulate, analyse, and display MRS data.

Forum

The MRSHub forum is a place for the MRS community to seek support, exchange ideas, ask questions, and collaborate.

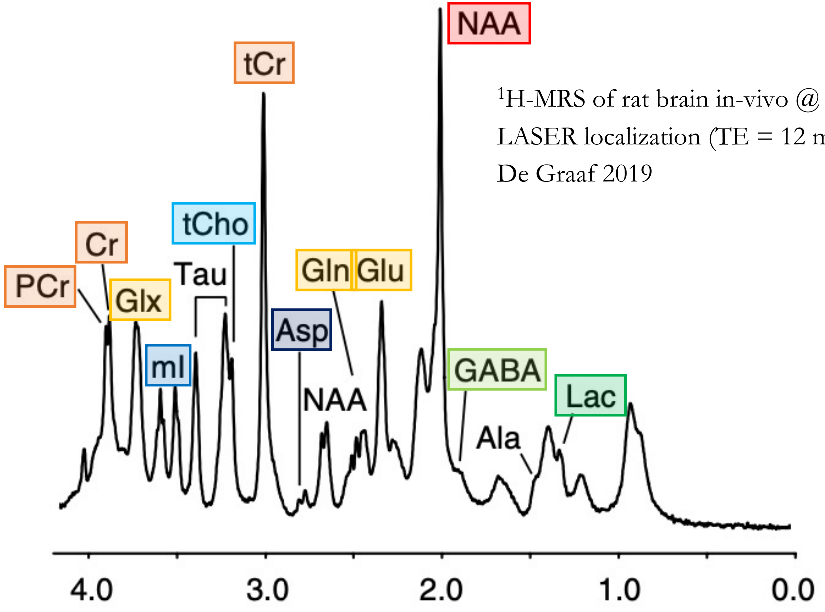
Data

The MRSHub data repository collects MRS datasets for demonstration and testing of new methods.

Modern MRS data analysis workflow

MRS – Looking beyond water

NAA(G)	neuronal integrity; neuromodulator, Glu precursor
Cr,PCr	energy metabolism
Glu	excitatory NT; precursor to GABA/Gln/GSH
Gln	osmotic regulation; GABA/Glu cycle
GABA	inhibitory NT
Lac	oxygen metabolism; marker of anaerobic glycolysis
Cho	cell proliferation; cell membrane component
mI	osmotic regulation; neuroinflammation
Asp	neuromodulation; neurotransmission
GSH,Asc	antioxidants; oxidative stress
2HG,Cyst	tumor mutation markers (IDH, 1p19q codel)



^{1}H-MRS of rat brain in-vivo @ 11.7 T
LASER localization (TE = 12 ms)
De Graaf 2019

- The ^{1}H-MR spectrum contains overlapping molecular signals (1 – 20 millimoles) involved in many different important biochemical processes

From scanner to result

- Raw data export
- Preprocessing
- Modeling
- Quantification
- Quality assessment
- Report

Terminology and concepts for the characterization of in vivo MR spectroscopy methods and MR spectra: Background and experts' consensus recommendations

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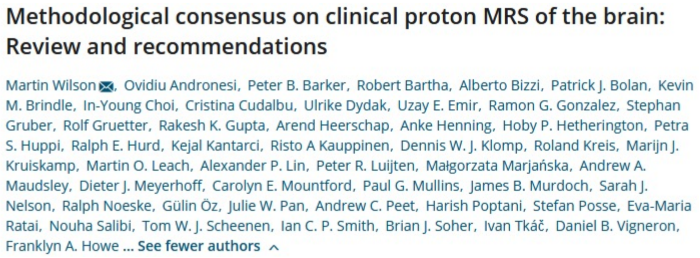
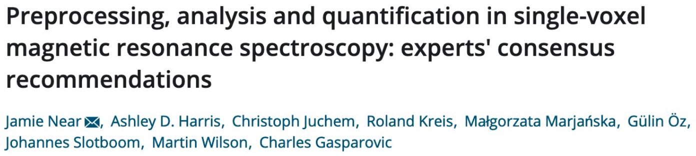


Methodological consensus on clinical proton MRS of the brain: Review and recommendations

Martin Wilson ✉, Ovidiu Andronesi, Peter B. Barker, Robert Bartha, Alberto Bizzi, Patrick J. Bolan, Kevin M. Brindle, In-Young Choi, Cristina Cudalbu, Ulrike Dydak, Uzay E. Emir, Ramon G. Gonzalez, Stephan Gruber, Rolf Gruetter, Rakesh K. Gupta, Arend Heerschap, Anke Henning, Hoby P. Hetherington, Petra S. Huppi, Ralph E. Hurd, Kejal Kantarci, Risto A Kauppinen, Dennis W. J. Klomp, Roland Kreis, Marijn J. Kruiskamp, Martin O. Leach, Alexander P. Lin, Peter R. Luijten, Małgorzata Marjańska, Andrew A. Maudsley, Dieter J. Meyerhoff, Carolyn E. Mountford, Paul G. Mullins, James B. Murdoch, Sarah J. Nelson, Ralph Noeske, Gülin Öz, Julie W. Pan, Andrew C. Peet, Harish Poptani, Stefan Posse, Eva-Maria Ratai, Nouha Salibi, Tom W. J. Scheenen, Ian C. P. Smith, Brian J. Soher, Ivan Tkáč, Daniel B. Vigneron, Franklyn A. Howe ... **See fewer authors ^**



Preprocessing, analysis and quantification in single-voxel magnetic resonance spectroscopy: experts' consensus recommendations

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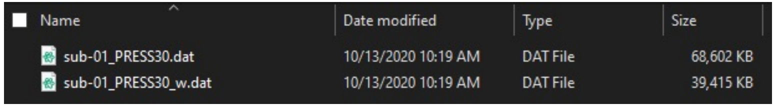
Raw data

Vendor	File extension	Coils combined?	Averaged?	Contains voxel geometry?
Philips	.sdat / .spar	Yes	Depends	Yes
	.data / .list	No	No	No
Siemens	.rda	Yes	Depends	Yes
	.twix	No	No	Yes
GE	.7	Depends	Depends	Yes
DICOM	.dcm (.ima)	Yes	Depends	Yes

- ”Depends”… on sequence developer, software version, exam card settings

Preprocessing

- **Preprocessing:** Preparing raw data into a signal that will be modeled
- Operations depend on the raw data format



Name	Date modified	Type	Size
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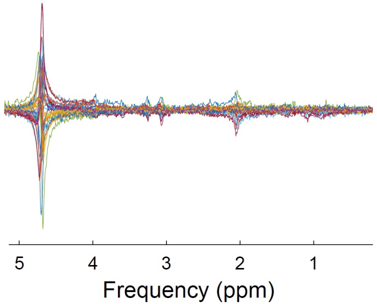
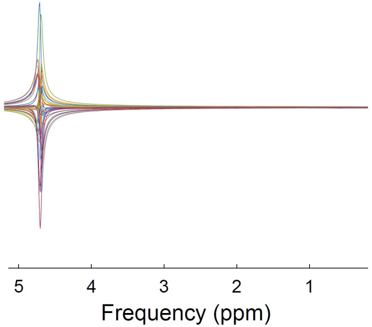
sub-01_PRESS30_w.dat	10/13/2020 10:19 AM	DAT File	39,415 KB

metabolites



water reference



- **Load raw data**
- Coil combination
- Alignment of transients
- Averaging
- Eddy-current correction
- Residual water removal
- Phase correction

Preprocessing

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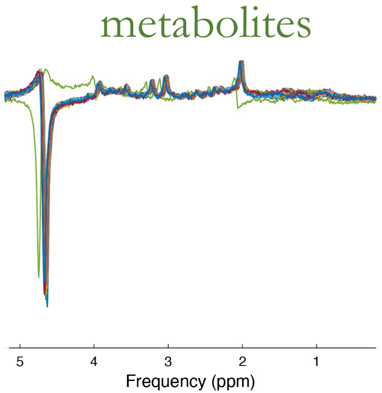

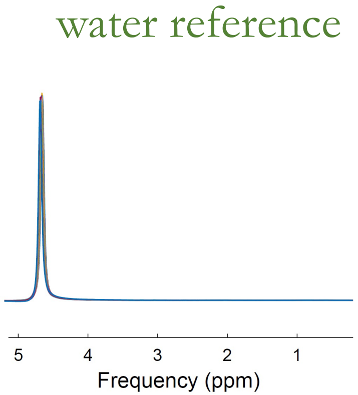

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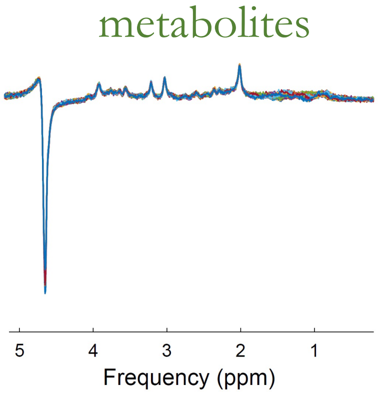
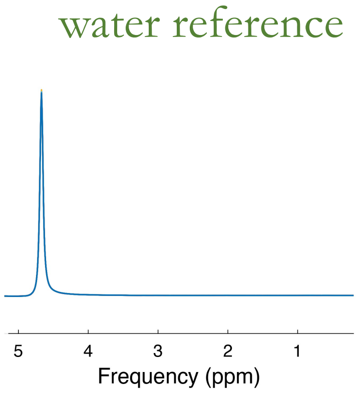


metabolites



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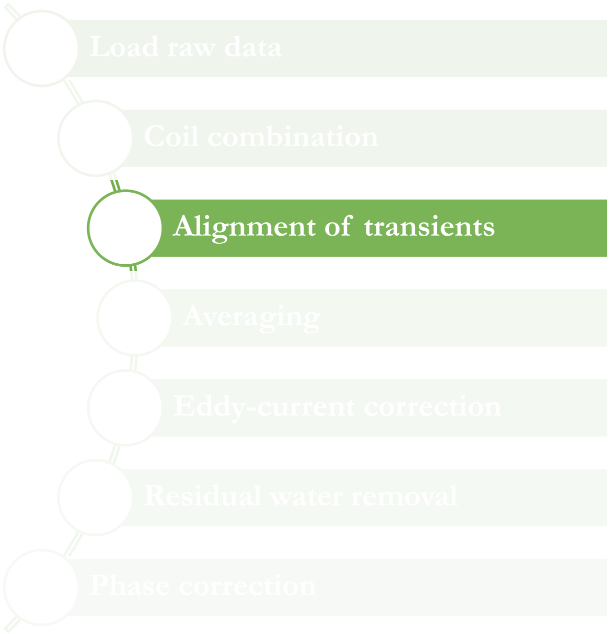

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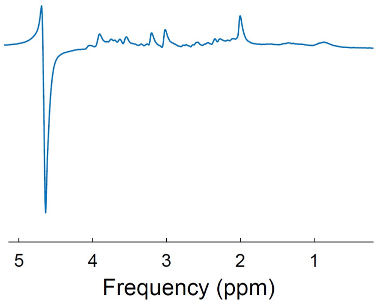

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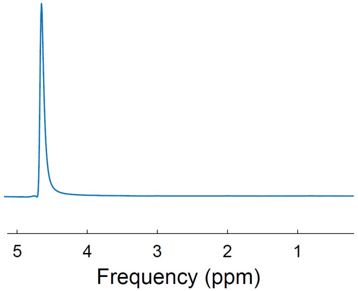
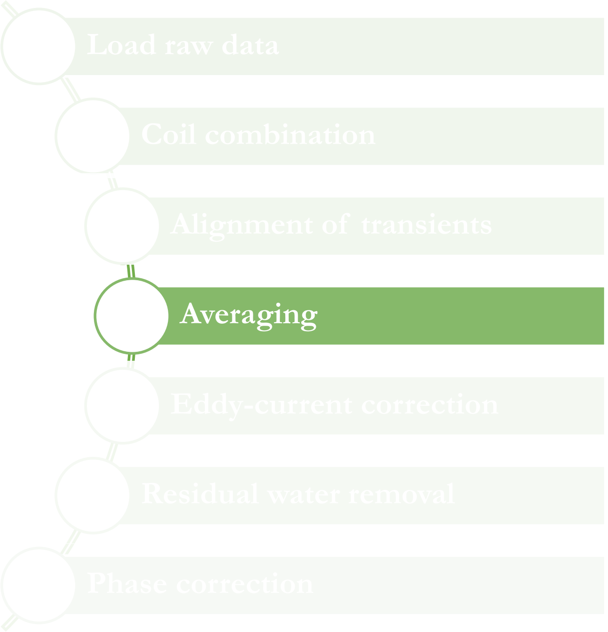


I have added a little bit of eddy-current artefact here…



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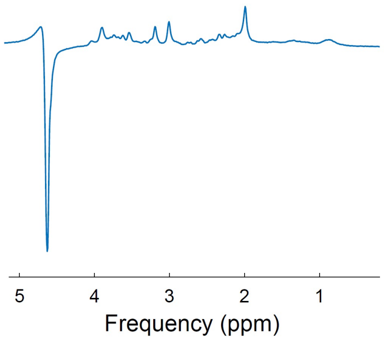

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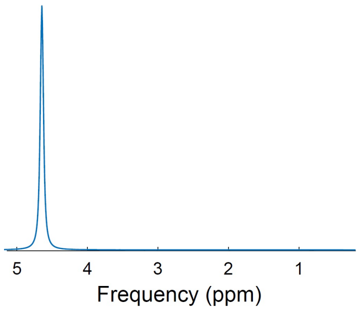
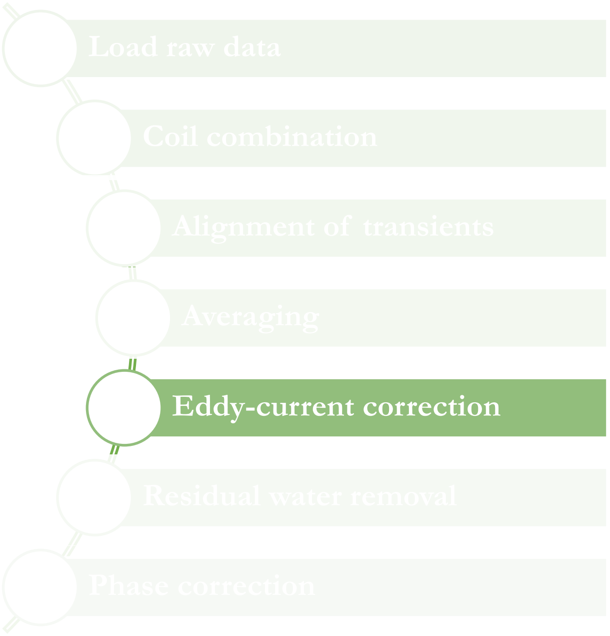


… which the eddy-current correction removes again.



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Preprocessing

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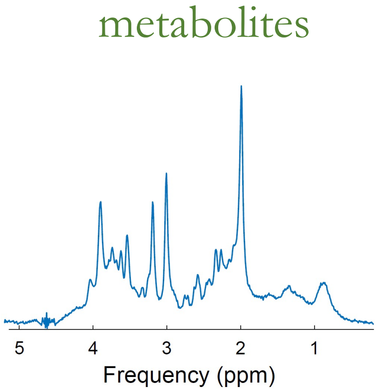
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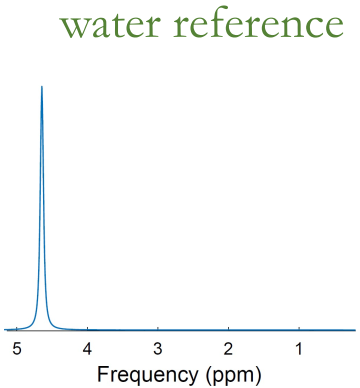
water reference

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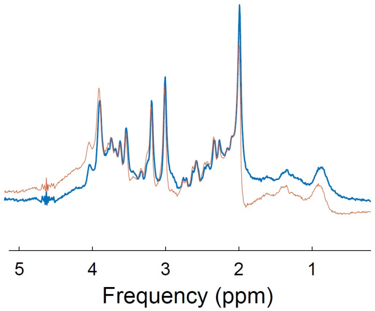

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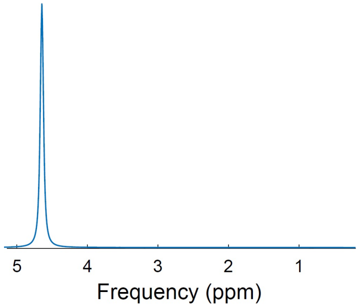
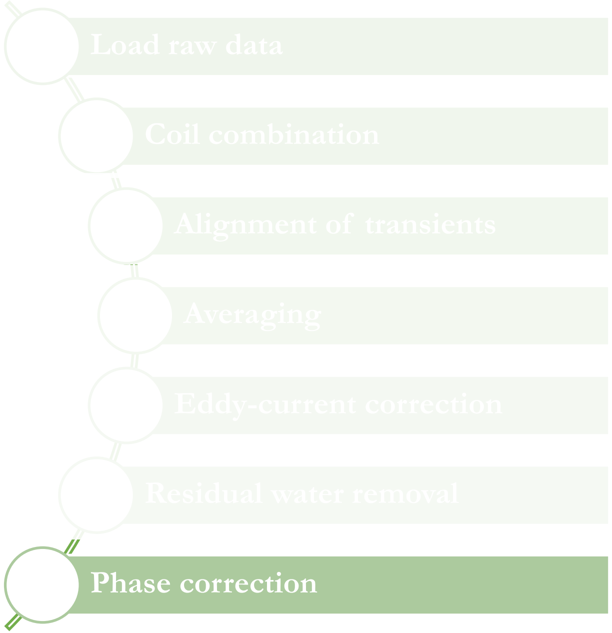


Some additional alignment of frequency and phase happens at this point for spectral editing experiments.



Load raw data

Coil combination

Alignment of transients

Averaging

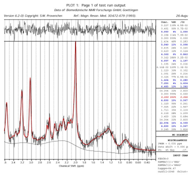
Eddy-current correction

Residual water removal

Phase correction

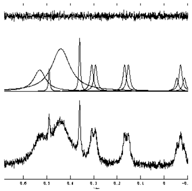
Modeling

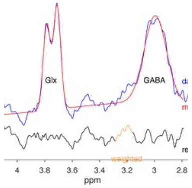
- **Modeling:** Extract quantitative estimates of signal amplitudes from the spectrum



Linear-combination modeling

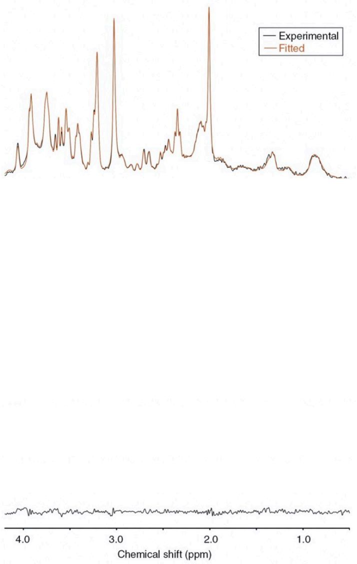
Peak fitting





Peak integration

Linear-combination modeling



Weighted sum of (usually simulated) metabolite basis functions

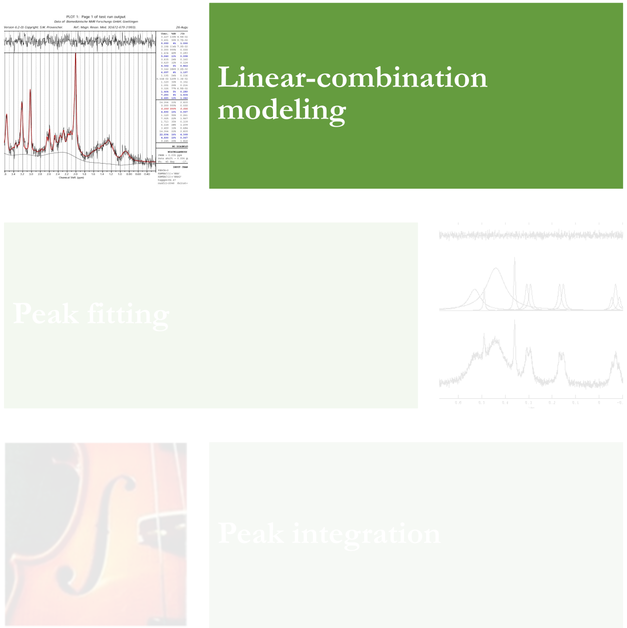
- Model parameters account for…
  - Lineshape (Gauss/Lorentz)
  - frequency and phase shifts

… complicated by:

- Signal overlap
- Broad (short-T_2) macromolecular and lipid signals

LCModel spant TARQUIN INSPECTOR Osprey FSL-MRS jMRUI QUEST AQSES

Recommended for most ^{1}H-MRS brain applications



Linear-combination modeling

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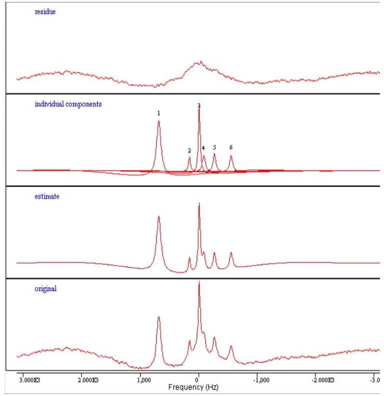


Weighted sum of single peaks

- Prior knowledge (AMARES, VOIGT)
  - Chemical shifts
  - Relative amplitude
  - Phase
  - Lineshape (Gauss/Lorentz/Voigt)

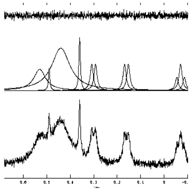
- Baseline terms

jMRUI
SVD
AMARES

Rather suited for sparse data, i.e. little spectral overlap (long TE, spectral editing, ^{31}P, ^{13}C)

Linear-combination modeling

Peak fitting



Peak integration

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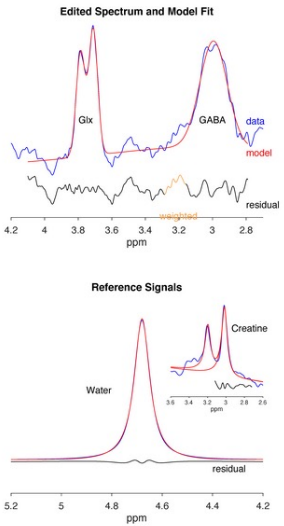
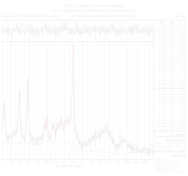


Estimation of area under the curve

- Directly by adding up data points
- Integration of a model to the data

Only recommended for very sparse data, with little spectral overlap or background signal



Linear-combination modeling

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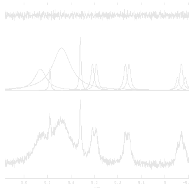
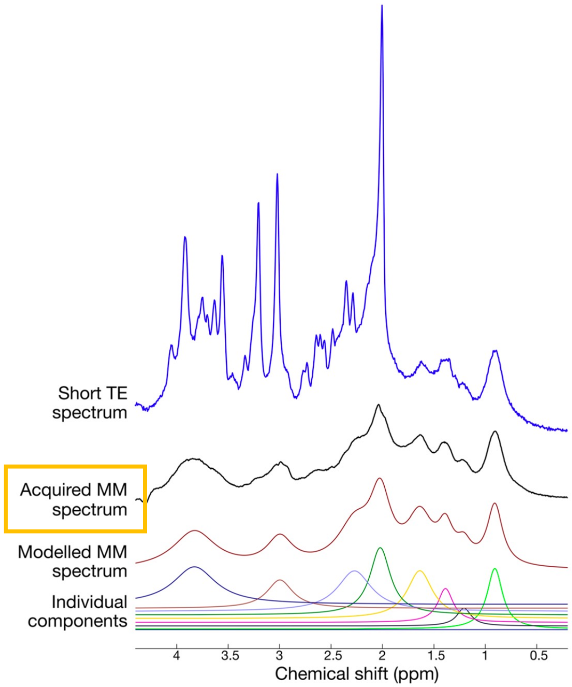


Peak integration

Macromolecules

- MM signals should be included in the model, ideally measured (or parametrized)



Acquired MM

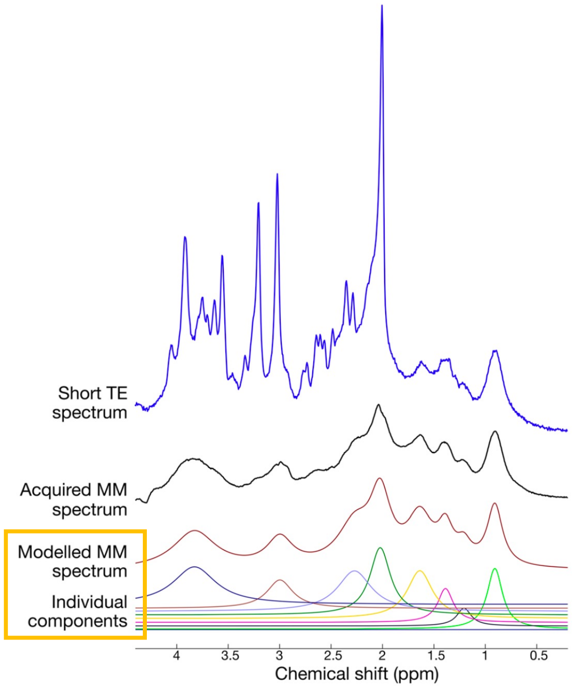
- Should match sequence & TE
- Few MM spectra are publicly available
- Check MRSHub

Modelled MM

- Parametrized components
- Defaults used in some software
- May be inadequate

Macromolecules

- MM signals should be included in the model, ideally measured (or parametrized)



Acquired MM

- Needs to match sequence & TE
- Few MM spectra are publicly available
- Check MRSHub

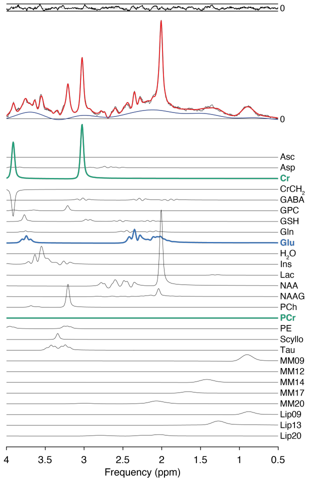
Modelled MM

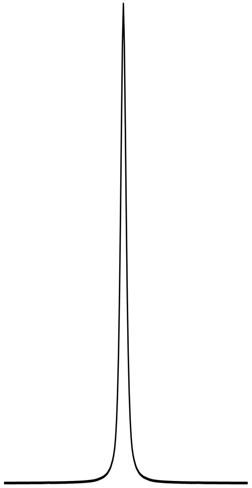
- Parametrized components
- Empirical defaults pre-defined in tools
- May be inadequate

Quantification

- **<u>Quantification:</u>** Converting model parameters into quantitative estimates

Metabolite & water amplitudes





Tissue volume fractions

Parse geometry headers

Create voxel mask

Segmentation

GM

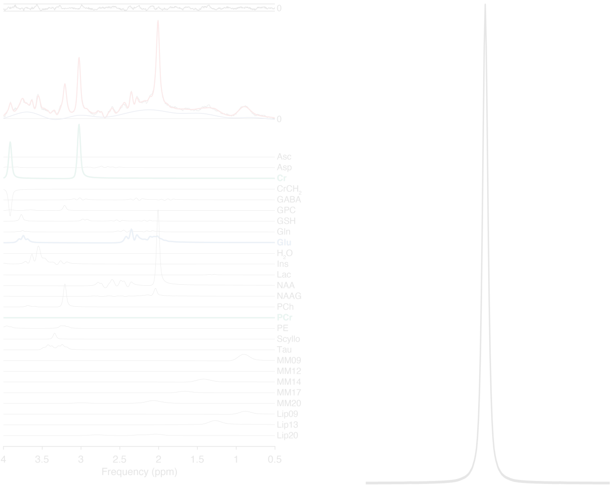
WM

CSF

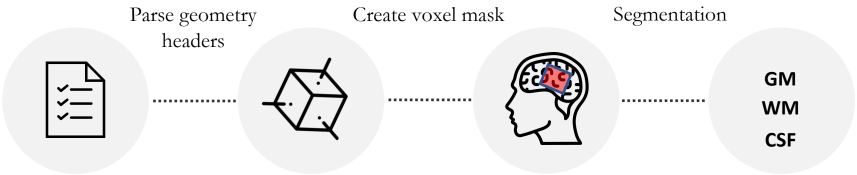
Quantification

- **Quantification:** Converting model parameters into quantitative estimates

Metabolite & water amplitudes



Tissue volume fractions

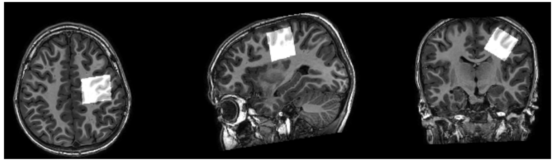


Parse geometry headers

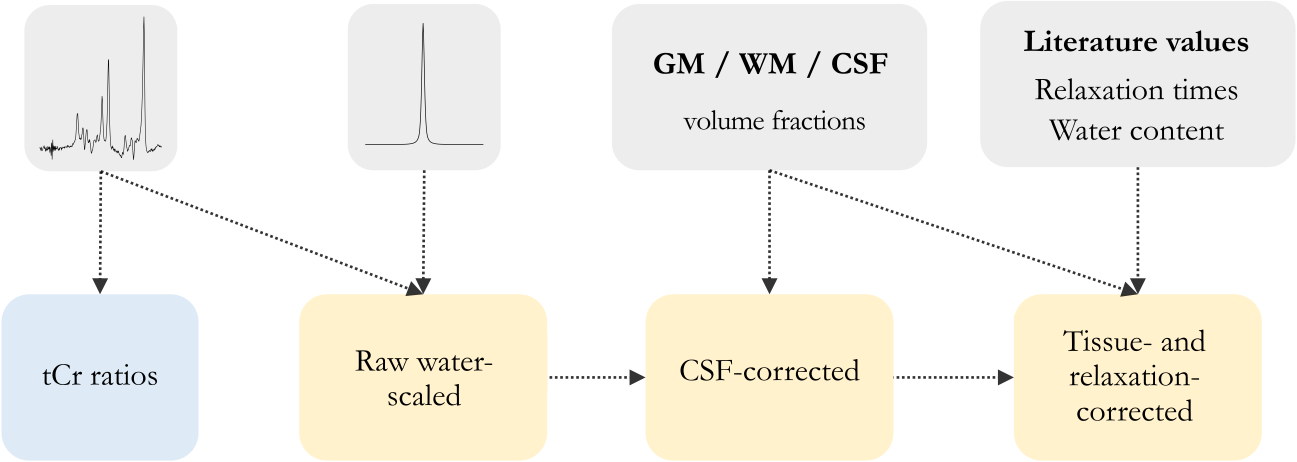
Create voxel mask

Segmentation

GM
WM
CSF



Quantification



GM / WM / CSF

volume fractions

Literature values

Relaxation times

Water content

tCr ratios

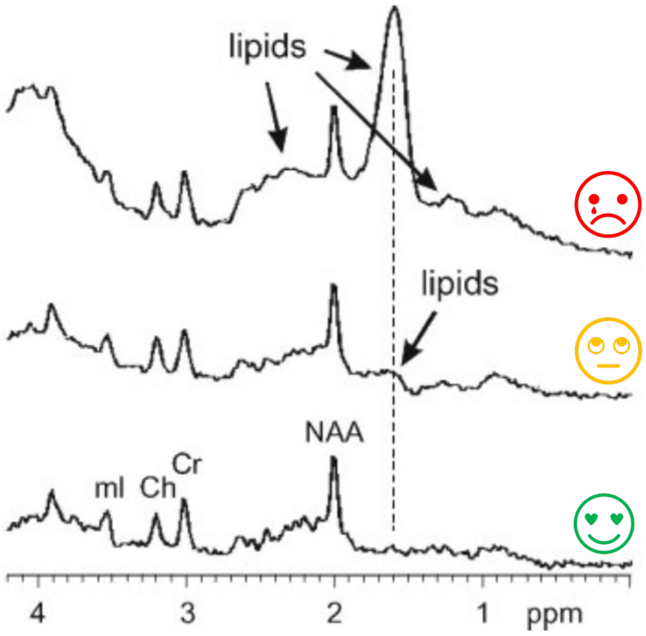
Raw water-scaled

CSF-corrected

Tissue- and relaxation-corrected

- Report tCr ratios <u>**and**</u> tissue-relaxation-corrected metabolite estimates
- Strong effects on metabolite estimates should appear regardless of reference

Quality assessment



Kreis, NMR Biomed **17**:361-381 (2004)

Data quality

Visual inspection
Lipid contamination
“Ghosts”
Residual water

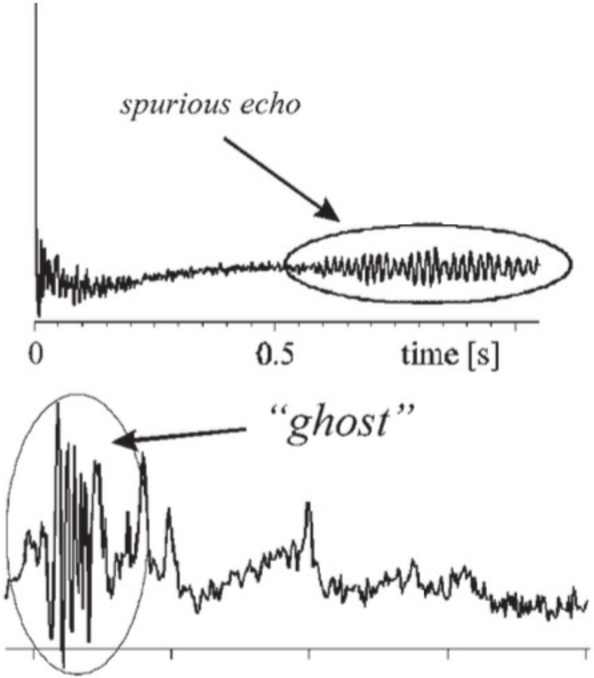
Quality metrics
Signal-to-noise ratio (SNR)
Linewidth (FWHM)

Modeling quality

Visual inspection
Model looks like data
Noise-like residual

Quality metrics
Cramér-Rao lower bounds
Goodness of fit

Quality assessment



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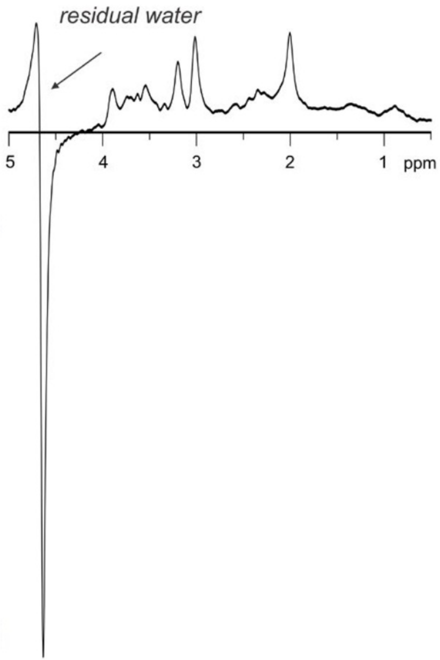

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“Ghosts”
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Signal-to-noise ratio (SNR)
Linewidth (FWHM)

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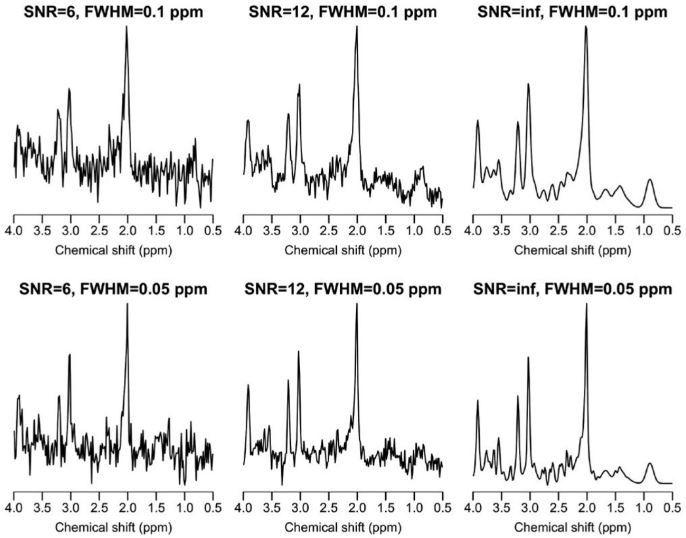
Goodness of fit

Wilson et al, Magn Reson Med **82**:527-550 (2019)

Quality assessment



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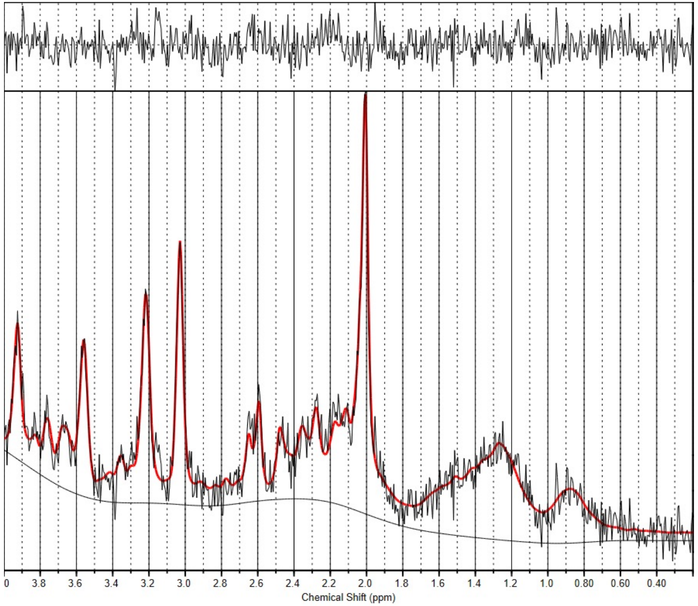

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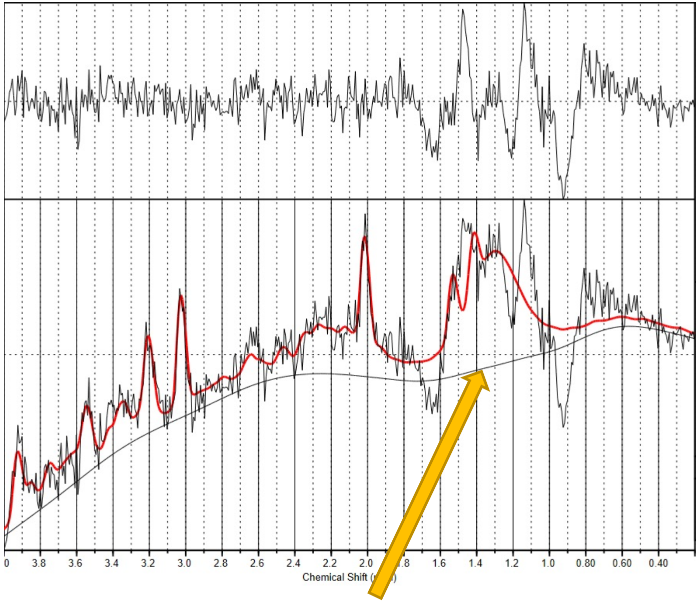
Cramér-Rao lower bounds

Goodness of fit

LCModel manual

Quality assessment



LCModel manual

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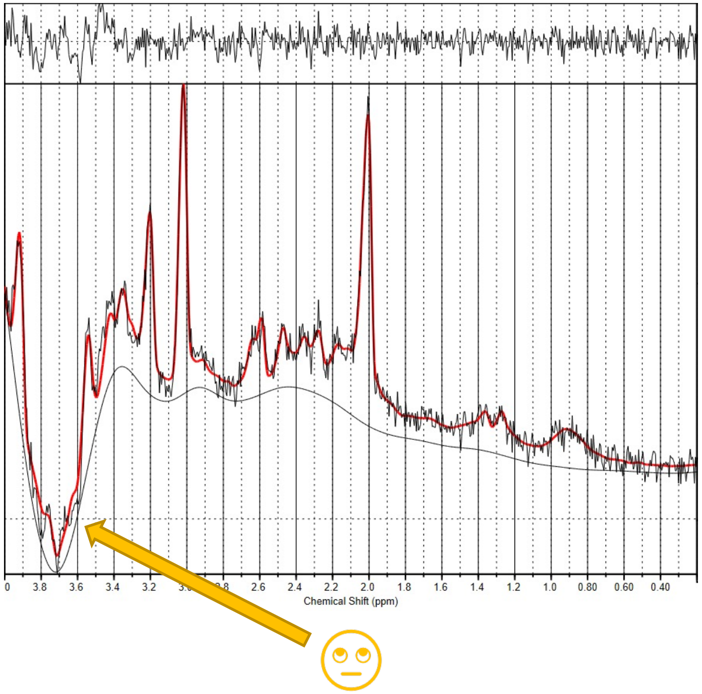

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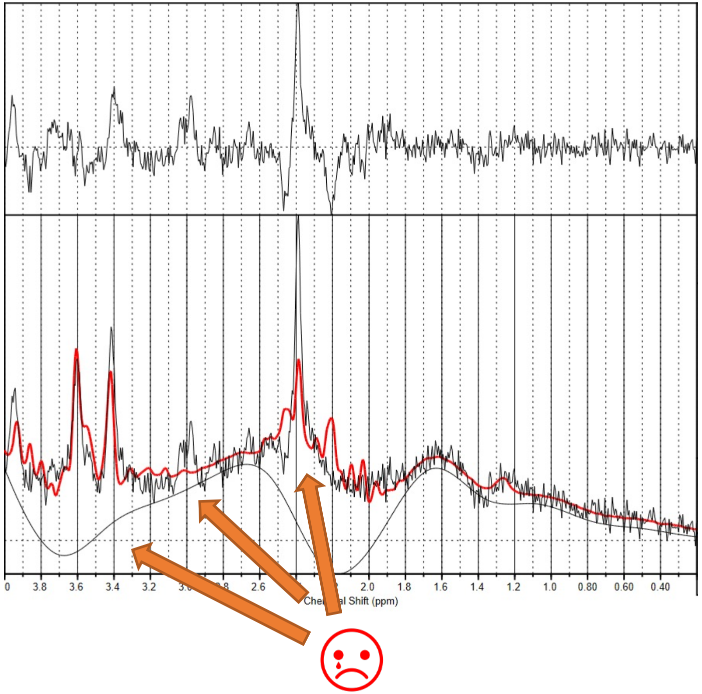

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Noise-like residual

Quality metrics

Cramér-Rao lower bounds

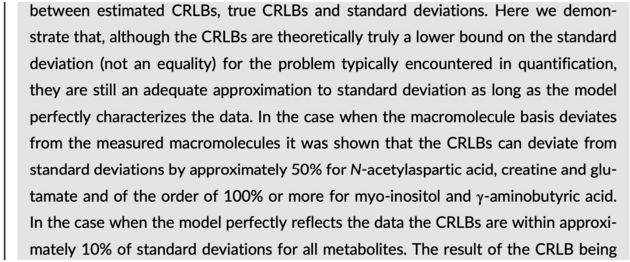
Goodness of fit

LCModel manual

Quality assessment

Cramér-Rao lower bounds (CRLB)

- Estimate of <u>minimal</u> uncertainty in model parameter estimation
- Essentially, they are local derivatives of the model function
- Under ideal conditions, they are identical with the standard deviation
- … but usually, conditions are not identical:



between estimated CRLBs, true CRLBs and standard deviations. Here we demonstrate that, although the CRLBs are theoretically truly a lower bound on the standard deviation (not an equality) for the problem typically encountered in quantification, they are still an adequate approximation to standard deviation as long as the model perfectly characterizes the data. In the case when the macromolecule basis deviates from the measured macromolecules it was shown that the CRLBs can deviate from standard deviations by approximately 50% for *N*-acetylaspartic acid, creatine and glutamate and of the order of 100% or more for myo-inositol and γ-aminobutyric acid. In the case when the model perfectly reflects the data the CRLBs are within approximately 10% of standard deviations for all metabolites. The result of the CRLB being

Data quality

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Noise-like residual

Quality metrics

Cramér-Rao lower bounds

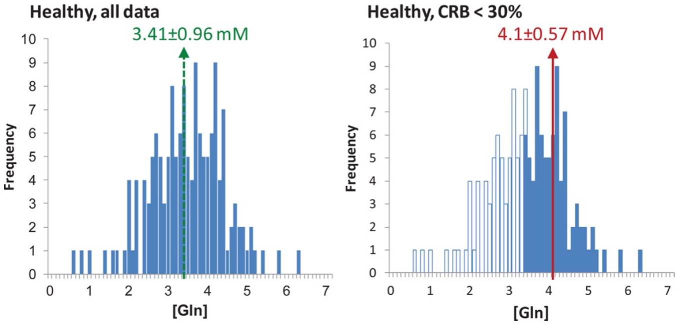
Goodness of fit

Landheer & Juchem, NMR Biomed 2021

Quality assessment

Cramér-Rao lower bounds (CRLB)

- Relative CRLB [%] often used to discard datasets, but that introduces bias against low levels:



- Better practice:
  - Use absolute CRLB
  - Use CRLB as a weighting factor in statistical analysis

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Quality metrics

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Linewidth (FWHM)

Modeling quality

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Noise-like residual

Quality metrics

Cramér-Rao lower bounds

Goodness of fit

Landheer & Juchem, Magn Reson Med 2016

Quality assessment

Goodness of fit

- Not all modeling tools return CRLB
- Other estimates of modeling quality:
  - SD of residual
  - Max/min residual amplitude
  - SD(residual)/SD(noise)

Data quality

Visual inspection

Lipid contamination

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Quality metrics

Signal-to-noise ratio (SNR)

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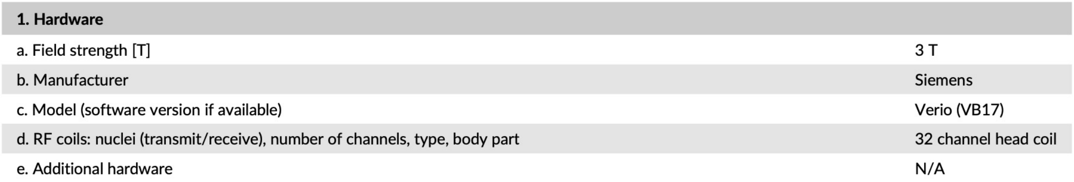
Cramér-Rao lower bounds

Goodness of fit

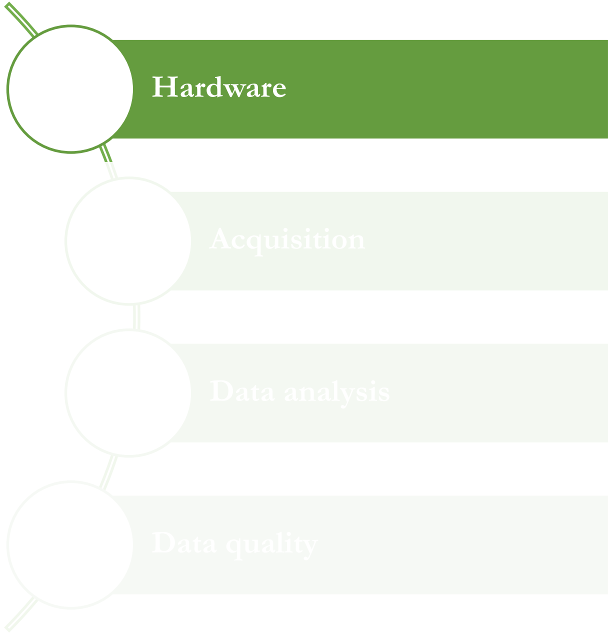
Reporting

Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' consensus recommendations

Alexander Lin, Ovidiu Andronesi, Wolfgang Bogner, In-Young Choi, Eduardo Coello, Cristina Cudalbu, Christoph Juchem, Graham J. Kemp, Roland Kreis, Martin Krššák, Phil Lee, Andrew A. Maudsley, Martin Meyerspeer, Vladamir Mlynarik, Jamie Near, Gülin Öz, Aimie L. Peek, Nicolaas A. Puts, Eva-Maria Ratai, Ivan Tkáč, Paul G. Mullins ✉ ... See fewer authors ^



1. Hardware	
a. Field strength [T]	3 T
b. Manufacturer	Siemens
c. Model (software version if available)	Verio (VB17)
d. RF coils: nuclei (transmit/receive), number of channels, type, body part	32 channel head coil
e. Additional hardware	N/A



Hardware

Acquisition

Data analysis

Data quality

Reporting

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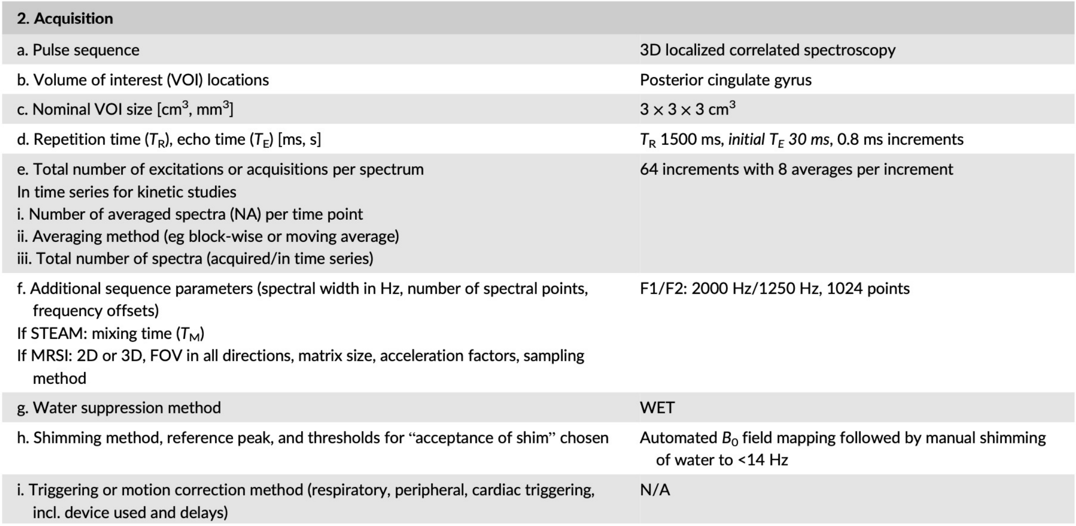
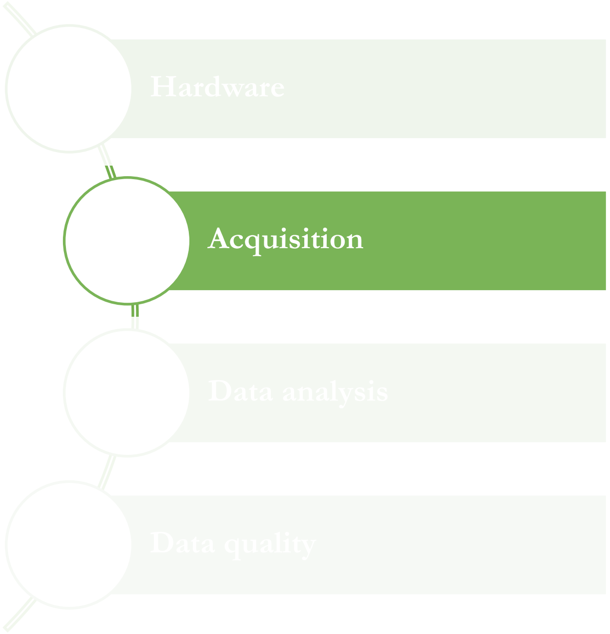


2. Acquisition	
a. Pulse sequence	3D localized correlated spectroscopy
b. Volume of interest (VOI) locations	Posterior cingulate gyrus
c. Nominal VOI size [cm^3, mm^3]	3 × 3 × 3 cm^3
d. Repetition time (T_R), echo time (T_E) [ms, s]	T_R 1500 ms, *initial* T_E *30 ms*, 0.8 ms increments
e. Total number of excitations or acquisitions per spectrum In time series for kinetic studies i. Number of averaged spectra (NA) per time point ii. Averaging method (eg block-wise or moving average) iii. Total number of spectra (acquired/in time series)	64 increments with 8 averages per increment
f. Additional sequence parameters (spectral width in Hz, number of spectral points, frequency offsets) If STEAM: mixing time (T_M) If MRSI: 2D or 3D, FOV in all directions, matrix size, acceleration factors, sampling method	F1/F2: 2000 Hz/1250 Hz, 1024 points
g. Water suppression method	WET
h. Shimming method, reference peak, and thresholds for "acceptance of shim" chosen	Automated B_0 field mapping followed by manual shimming of water to <14 Hz
i. Triggering or motion correction method (respiratory, peripheral, cardiac triggering, incl. device used and delays)	N/A



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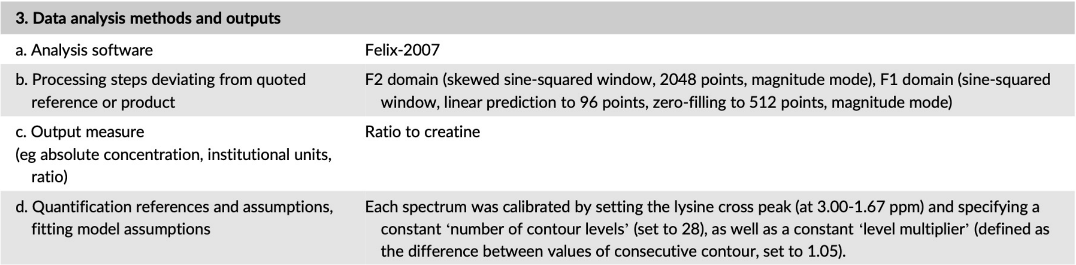
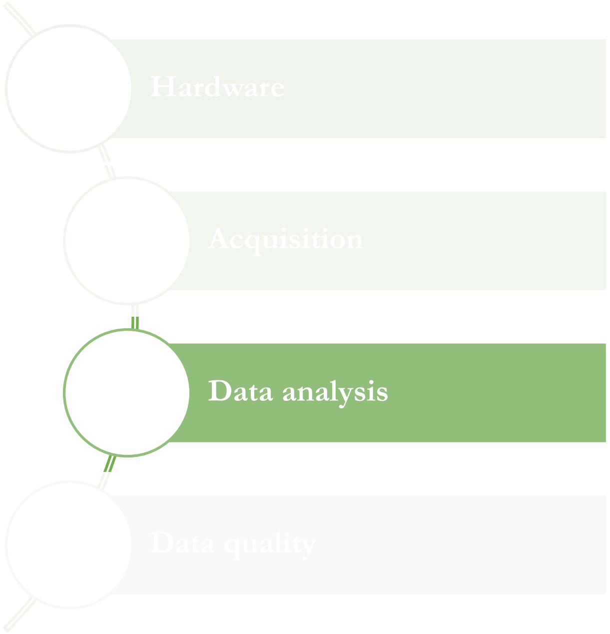


3. Data analysis methods and outputs	
a. Analysis software	Felix-2007
b. Processing steps deviating from quoted reference or product	F2 domain (skewed sine-squared window, 2048 points, magnitude mode), F1 domain (sine-squared window, linear prediction to 96 points, zero-filling to 512 points, magnitude mode)
c. Output measure (eg absolute concentration, institutional units, ratio)	Ratio to creatine
d. Quantification references and assumptions, fitting model assumptions	Each spectrum was calibrated by setting the lysine cross peak (at 3.00-1.67 ppm) and specifying a constant 'number of contour levels' (set to 28), as well as a constant 'level multiplier' (defined as the difference between values of consecutive contour, set to 1.05).



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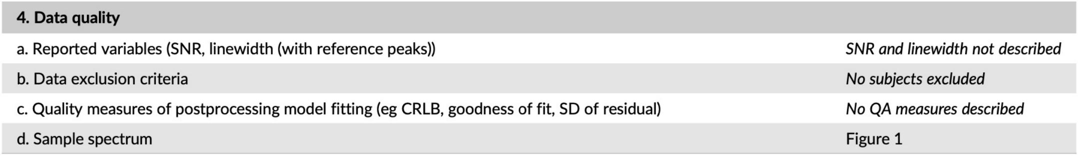


4. Data quality	
a. Reported variables (SNR, linewidth (with reference peaks))	*SNR and linewidth not described*
b. Data exclusion criteria	*No subjects excluded*
c. Quality measures of postprocessing model fitting (eg CRLB, goodness of fit, SD of residual)	*No QA measures described*
d. Sample spectrum	Figure 1

Hardware

Acquisition

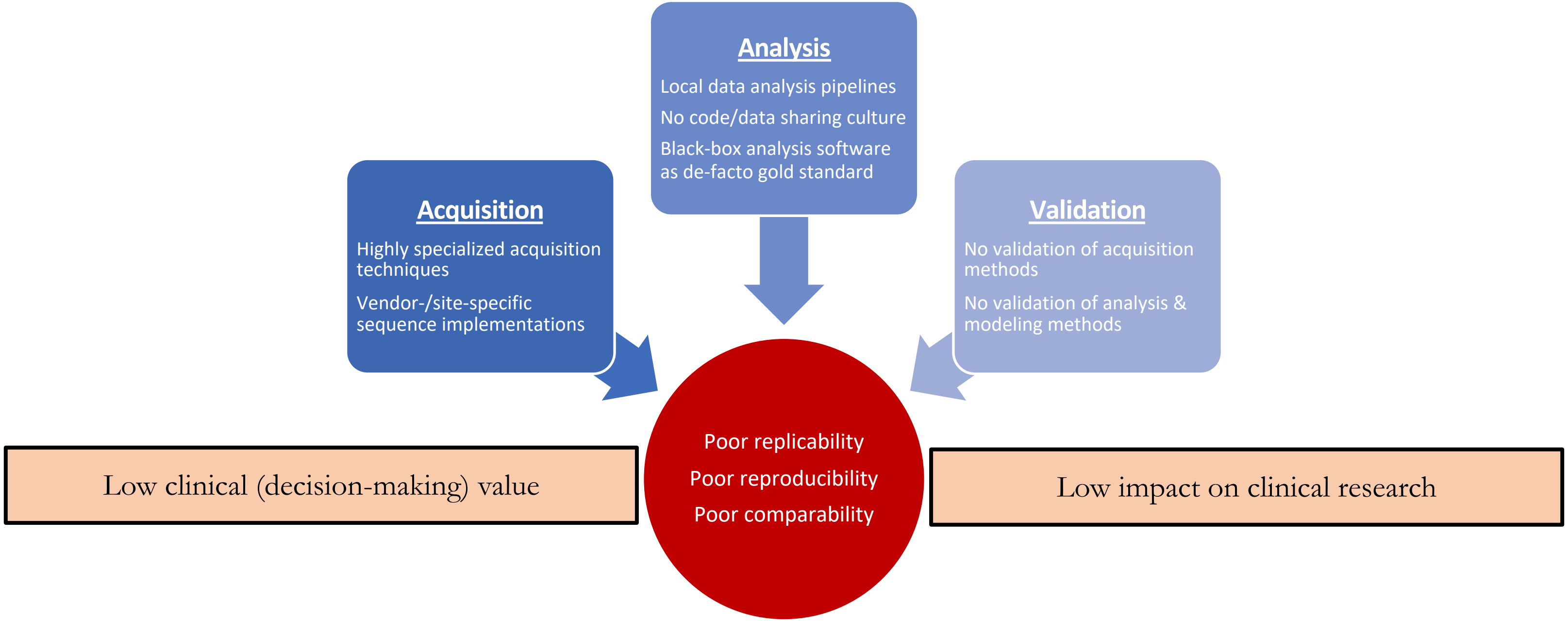
Data analysis

Data quality

Open-source MRS analysis software: A Quest for Standardization and Reproducibility

The wilderness of in-vivo MRS

- MRS was the initial application of the NMR effect (decades before MRI!) – what happened?



Analysis

Local data analysis pipelines

No code/data sharing culture

Black-box analysis software as de-facto gold standard

Acquisition

Highly specialized acquisition techniques

Vendor-/site-specific sequence implementations

Validation

No validation of acquisition methods

No validation of analysis & modeling methods

Poor replicability

Poor reproducibility

Poor comparability

Low clinical (decision-making) value

Low impact on clinical research

Linear-combination modelling in MRS


SPECIAL ISSUE REVIEW ARTICLE

NMR IN BIOMEDICINE WILEY

Preprocessing, analysis and quantification in single-voxel magnetic resonance spectroscopy: experts' consensus recommendations

Jamie Near[1,2] | Ashley D. Harris[3,4,5] | Christoph Juchem[6] | Roland Kreis[7] |
Małgorzata Marjańska[8] | Gülin Öz[8] | Johannes Slotboom[9] |
Martin Wilson[10] | Charles Gasparovic[11]

> “Linear combination model fitting is the most popular method of analysis and is recommended for most in vivo MRS applications.”

> “… three important steps in the workflow of ^{1}H-MRS following data acquisition: *preprocessing*, *spectral analysis*, and *quantification*.”

Lack of standardization

Processing & quantification are lab-specific

Often insufficiently reported

LCModel is the ‘standard’

Black-box (until 02/2021)

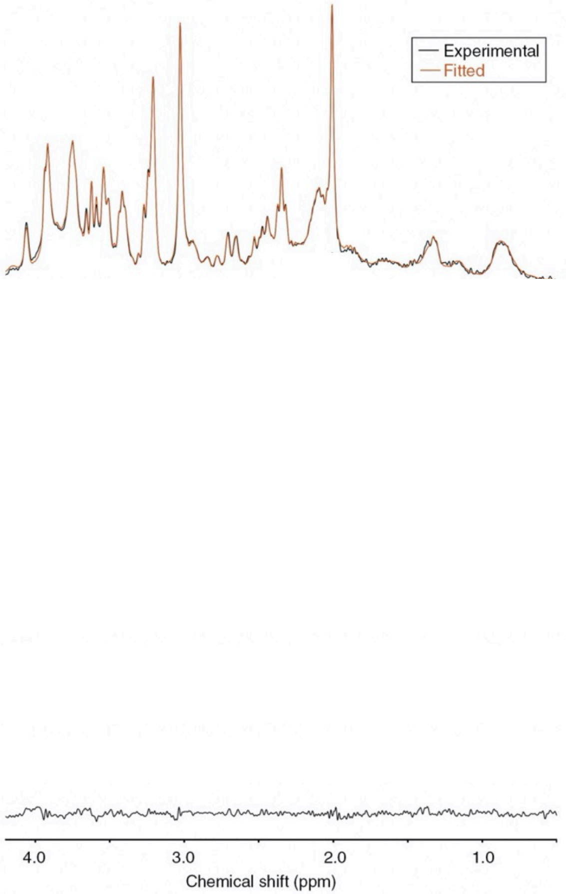
Discontinued development

LCM is poorly understood

Effects of baseline & MM

Algorithmic decisions?

Linear-combination modeling in MRS



Non-linear least-squares optimization

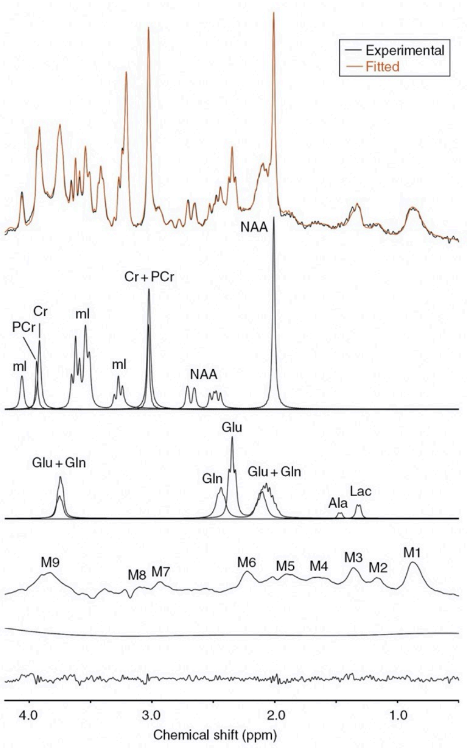
- Weighted sum of metabolite basis functions
- Model parameters account for field homogeneity, small frequency and phase perturbations, etc.

… enormously complicated by:

- Broad (short-T_2) macromolecular signals
- Smooth baseline

This is a really difficult (ill-defined) optimization problem!

Currently available LCM software



Algorithm/software	Cost	Language	Open-source?	Published	Citations
LCModel	**~~$13,300~~** **Free**	**FORTRAN77**	**~~No~~** **Yes**	**1993**	**3710**
QUEST	Free	JAVA	No (jMRUI)	2004	318
AQSES	Free	JAVA	No (jMRUI)	2007	148
Vespa	Free	Python	Yes	No publication	
Tarquin	Free	C++	Yes	2011	287
Osprey	Free	MATLAB	Yes	2020	9
ABfit/spant	Free	R	Yes	2021	2
INSPECTOR	Free	MATLAB	No	2021	6
FSL-MRS	Free	Python	Yes	2021	2

Osprey – a modular open-source workflow

Osprey combines preprocessing, modelling and quantification into one ecosystem

Job

Load

Process

Fit

Coreg

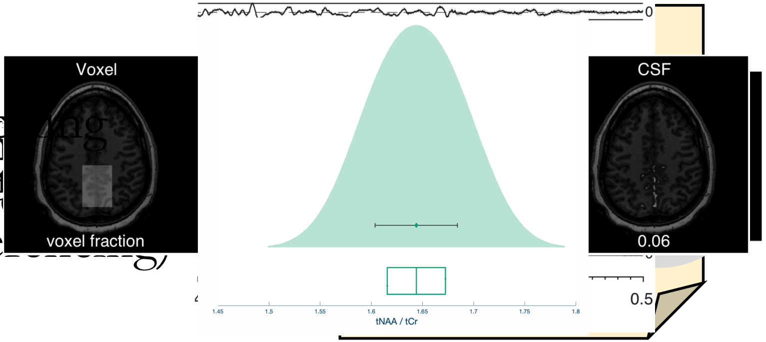
Seg

Quantify

Pre-processing following consensus gu [illegible]

[illegible]

Supports most common vendor-native [illegible] correction; pre-phasing; frequency refe[illegible]



Oeltzschner et al., J Neurosci Methods (2020)

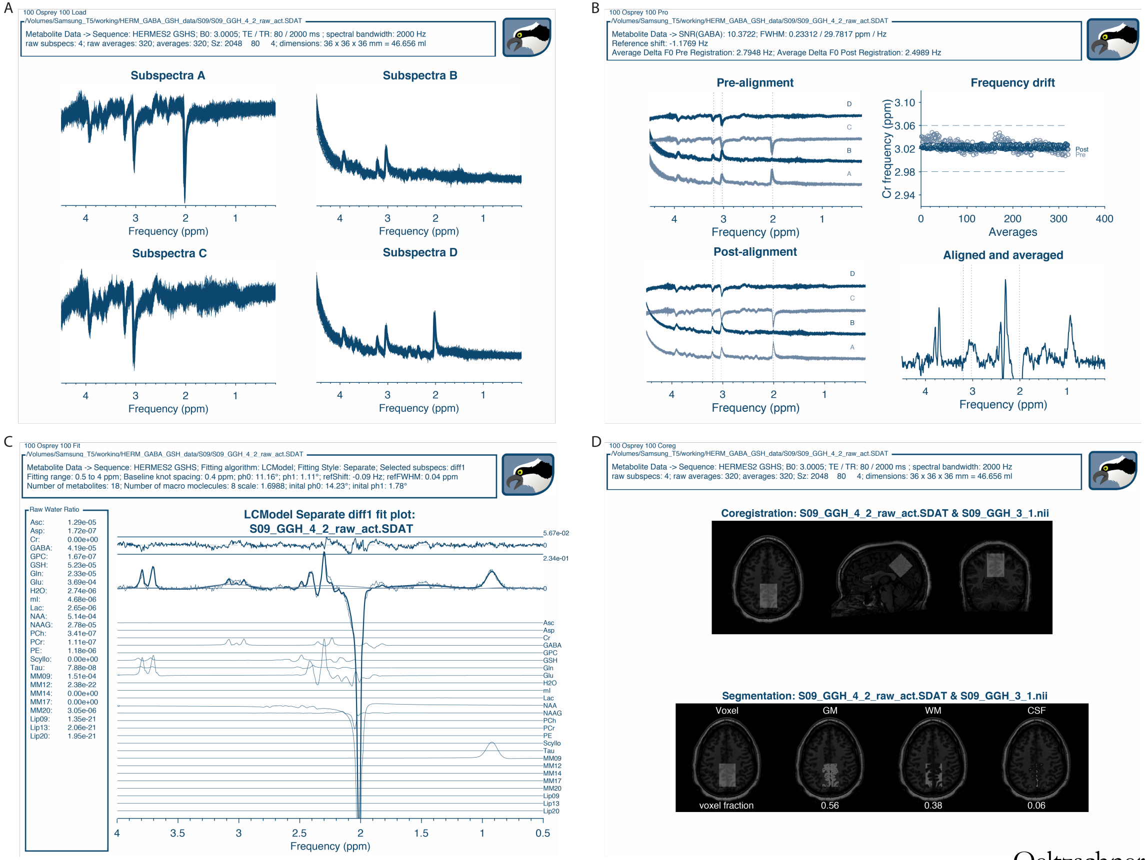
Osprey GUI

Load

Process

Fit

Tissue correction



A

100 Osprey 100 Load

/Volumes/Samsung_T5/working/HERM_GABA_GSH_data/S09/S09_GGH_4_2_raw_act.SDAT

Metabolite Data -> Sequence: HERMES2 GSHS; B0: 3.0005; TE / TR: 80 / 2000 ms ; spectral bandwidth: 2000 Hz
raw subspecs: 4; raw averages: 320; averages: 320; Sz: 2048 80 4; dimensions: 36 x 36 x 36 mm = 46.656 ml

B

100 Osprey 100 Pro

/Volumes/Samsung_T5/working/HERM_GABA_GSH_data/S09/S09_GGH_4_2_raw_act.SDAT

Metabolite Data -> SNR(GABA): 10.3722; FWHM: 0.23312 / 29.7817 ppm / Hz
Reference shift: -1.1769 Hz
Average Delta F0 Pre Registration: 2.7948 Hz; Average Delta F0 Post Registration: 2.4989 Hz

C

100 Osprey 100 Fit

/Volumes/Samsung_T5/working/HERM_GABA_GSH_data/S09/S09_GGH_4_2_raw_act.SDAT

Metabolite Data -> Sequence: HERMES2 GSHS; Fitting algorithm: LCModel; Fitting Style: Separate; Selected subspecs: diff1
Fitting range: 0.5 to 4 ppm; Baseline knot spacing: 0.4 ppm; ph0: 11.16°; ph1: 1.11°; refShift: -0.09 Hz; refFWHM: 0.04 ppm
Number of metabolites: 18; Number of macro moclecules: 8 scale: 1.6988; inital ph0: 14.23°; inital ph1: 1.78°

Raw Water Ratio

Asc:	1.29e-05
Asp:	1.72e-07
Cr:	0.00e+00
GABA:	4.19e-05
GPC:	1.67e-07
GSH:	5.23e-05
Gln:	2.33e-05
Glu:	3.69e-04
H2O:	2.74e-06
mI:	4.68e-06
Lac:	2.65e-06
NAA:	5.14e-04
NAAG:	2.78e-05
PCh:	3.41e-07
PCr:	1.11e-07
PE:	1.18e-06
Scyllo:	0.00e+00
Tau:	7.88e-08
MM09:	1.51e-04
MM12:	2.38e-22
MM14:	0.00e+00
MM17:	0.00e+00
MM20:	3.05e-06
Lip09:	1.35e-21
Lip13:	2.06e-21
Lip20:	1.95e-21

D

100 Osprey 100 Coreg

/Volumes/Samsung_T5/working/HERM_GABA_GSH_data/S09/S09_GGH_4_2_raw_act.SDAT

Metabolite Data -> Sequence: HERMES2 GSHS; B0: 3.0005; TE / TR: 80 / 2000 ms ; spectral bandwidth: 2000 Hz
raw subspecs: 4; raw averages: 320; averages: 320; Sz: 2048 80 4; dimensions: 36 x 36 x 36 mm = 46.656 ml

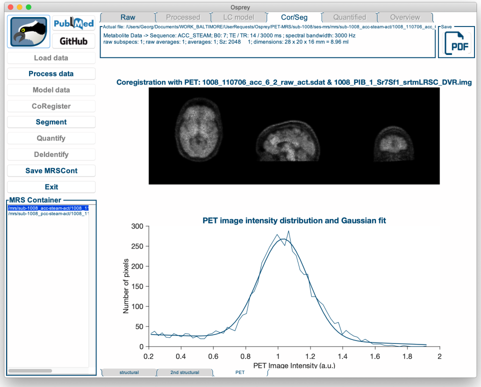
Oeltzschner et al., J Neurosci Methods (2020)

Multimodal datasets with Osprey

Direct interface with all other imaging modalities

- Automated co-registration of single-voxel MRS regions of interest with image inputs (DICOM, NIfTI)
- Histogram-based extraction of various image intensity metrics (separate for GM/WM)

Localized MRS-volume-specific image analysis for multimodal neuroimaging studies:
MRS, MRSI, PET, fMRI, DWI/DTI, CEST/APT…



Actual file: /Users/Georg/Documents/WORK_BALTIMORE/UserRequests/Osprey/PET-MRS/sub-1008/ses-mrs/mrs/sub-1008_acc-steam-act/1008_110706_acc_

Metabolite Data -> Sequence: ACC_STEAM; B0: 7; TE / TR: 14 / 3000 ms ; spectral bandwidth: 3000 Hz
raw subspecs: 1; raw averages: 1; averages: 1; Sz: 2048 1; dimensions: 28 x 20 x 16 mm = 8.96 ml

Coregistration with PET: 1008_110706_acc_6_2_raw_act.sdat & 1008_PIB_1_Sr7Sf1_srtmLRSC_DVR.img

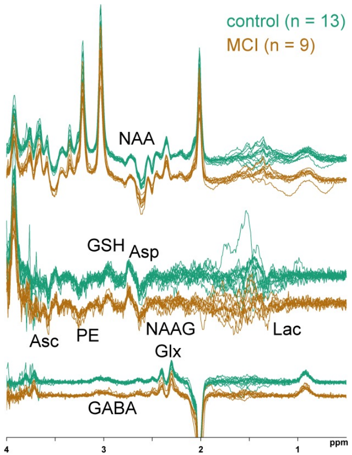
/mrs/sub-1008_acc-steam-act/1008_11
/mrs/sub-1008_pcc-steam-act/1008_11

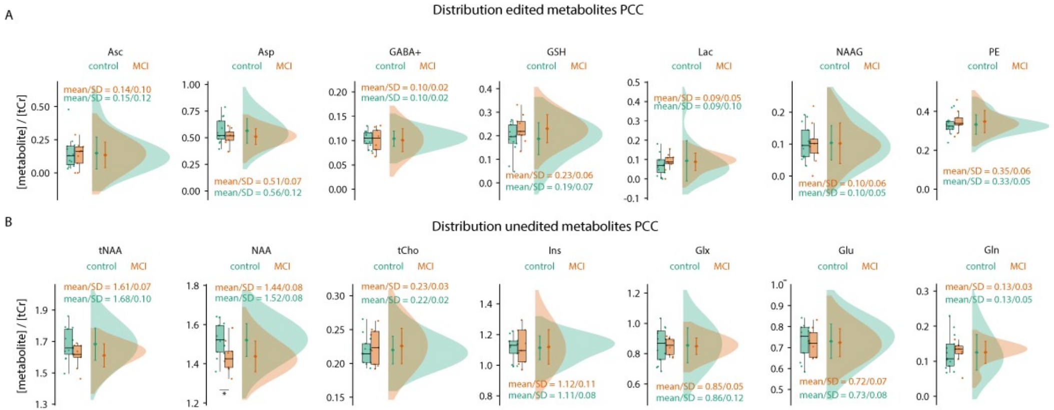
^{11}C PiB (amyloid uptake)

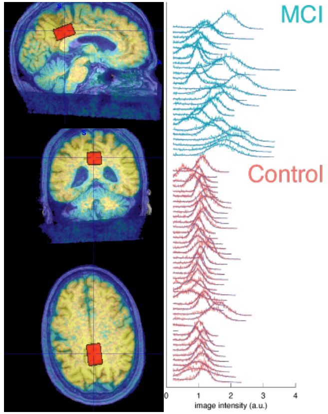
Multimodal datasets with Osprey

3T multi-metabolite-edited MRS (HERCULES) & ^{11}C-PiB & flortaucipir PET

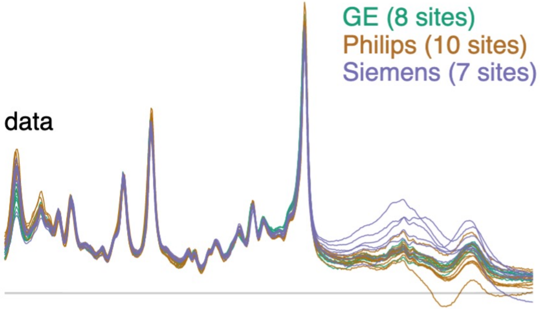
- Preliminary analysis suggests elevated GSH levels in MCI
- Currently analyzing associations with local PET metrics

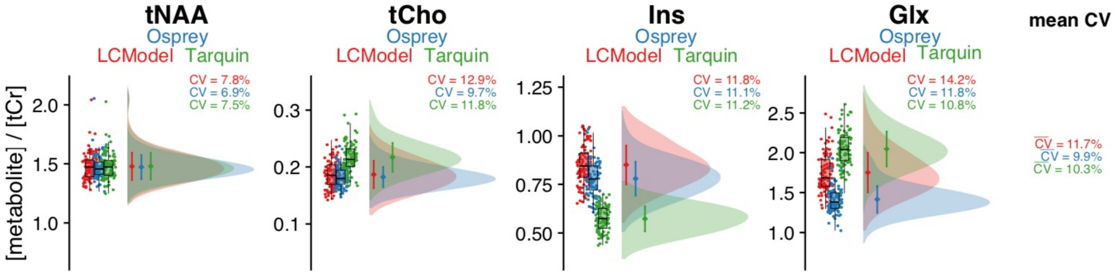


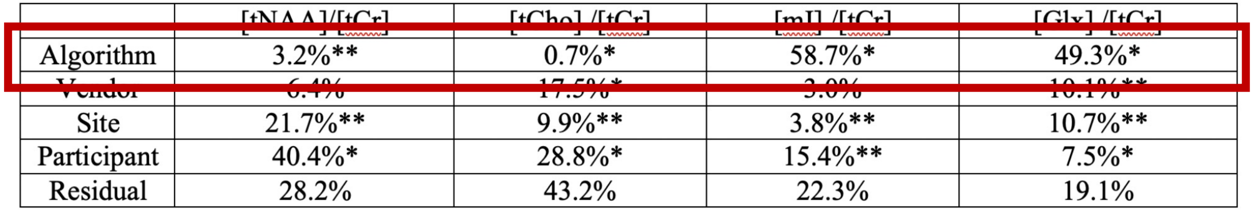




Benchmarking comparison with common tools





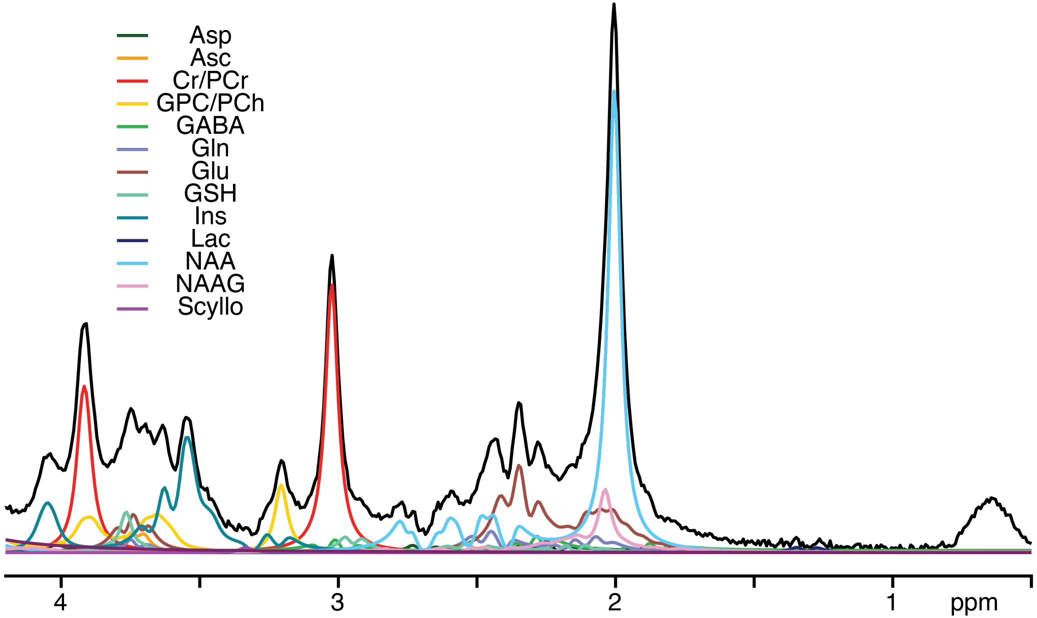


	[tNAA]/[tCr]	[tCho] /[tCr]	[mI] /[tCr]	[Glx] /[tCr]
Algorithm	3.2%**	0.7%*	58.7%*	49.3%*
Vendor	6.4%	17.5%*	3.0%	10.1%**
Site	21.7%**	9.9%**	3.8%**	10.7%**
Participant	40.4%*	28.8%*	15.4%**	7.5%*
Residual	28.2%	43.2%	22.3%	19.1%

- >270 PRESS spectra (TE = 35 ms) analyzed with Osprey, LCModel, Tarquin
- Substantial differences, **poor agreement between tools** for major metabolites
- Choice of tool introduces **substantial variance**

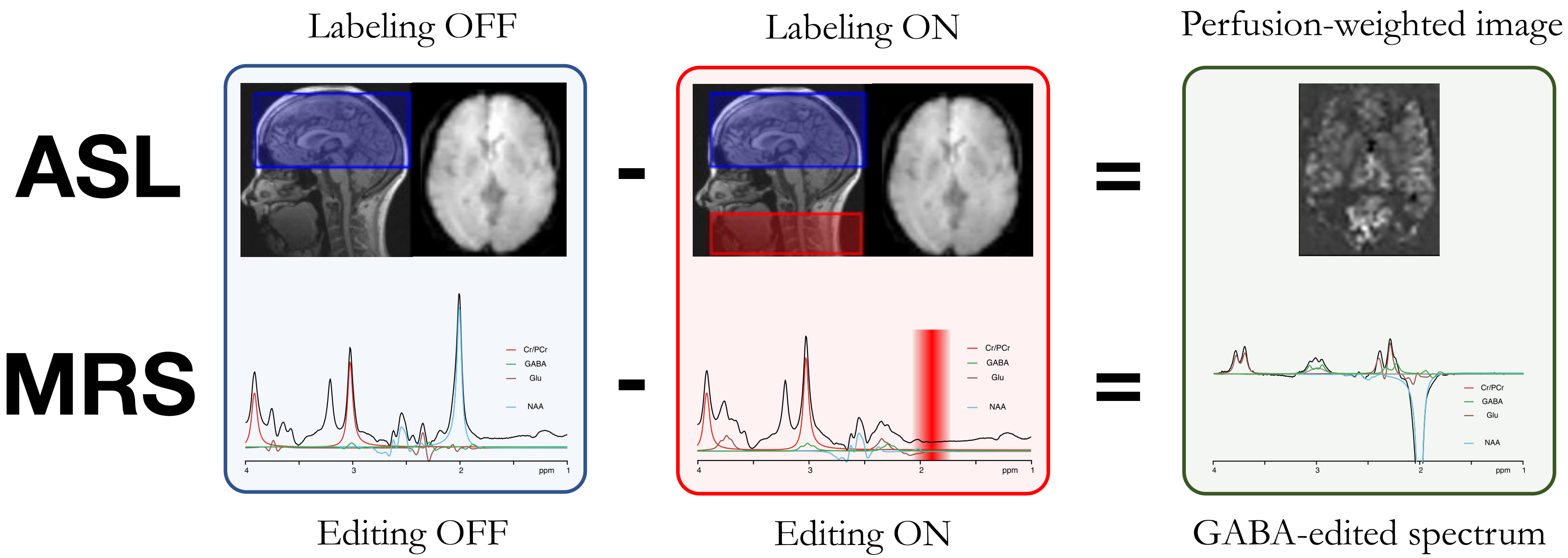
Zöllner et al., NMR Biomed 2021

Spectral overlap at 3T



Even under excellent measurement conditions,
GABA/Glu/Gln/GSH/Asp/Asc/NAAG are very difficult to resolve

Spectral editing resolves overlapping signals



Labeling OFF

Labeling ON

Perfusion-weighted image

ASL

-

=

MRS

-

=

Editing OFF

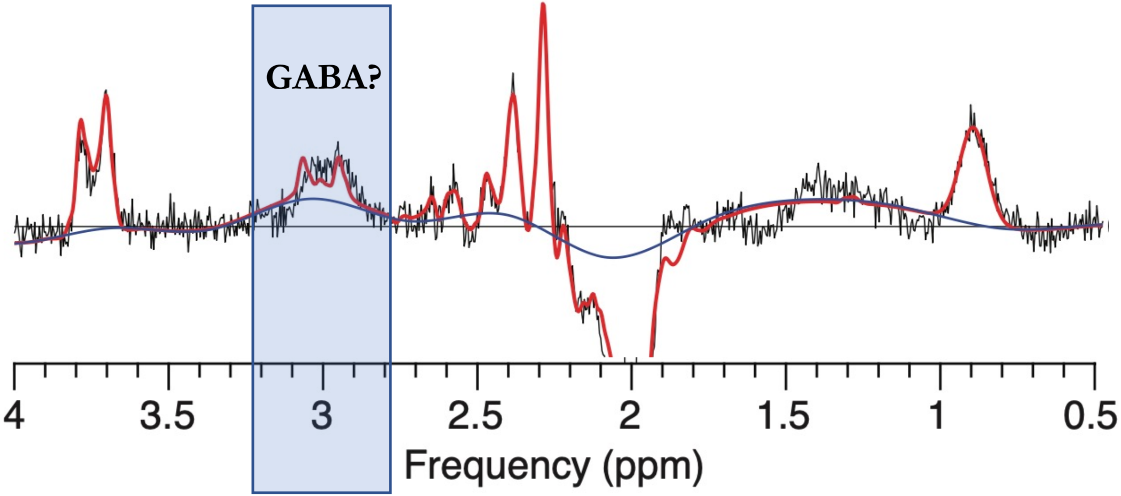
Editing ON

GABA-edited spectrum

- **Spectral editing** selectively manipulates signals of interest with RF “editing pulses”
- Overlapping signals get <u>subtracted out</u> to reveal weak signals

Ferré et al, Diagn Interv Imaging (2013)

Modeling spectral-edited GABA data



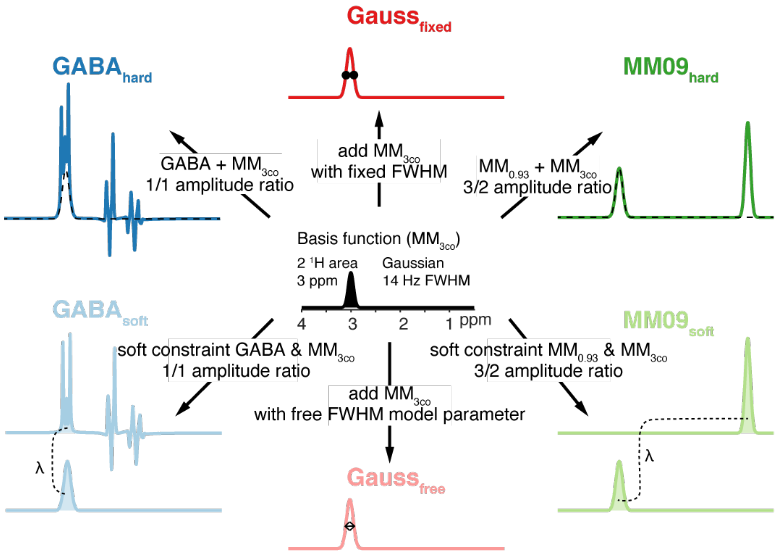
Helge J. Zöllner

Despite consensus recommendation to analyse spectral-edited
MRS data using linear-combination modelling…

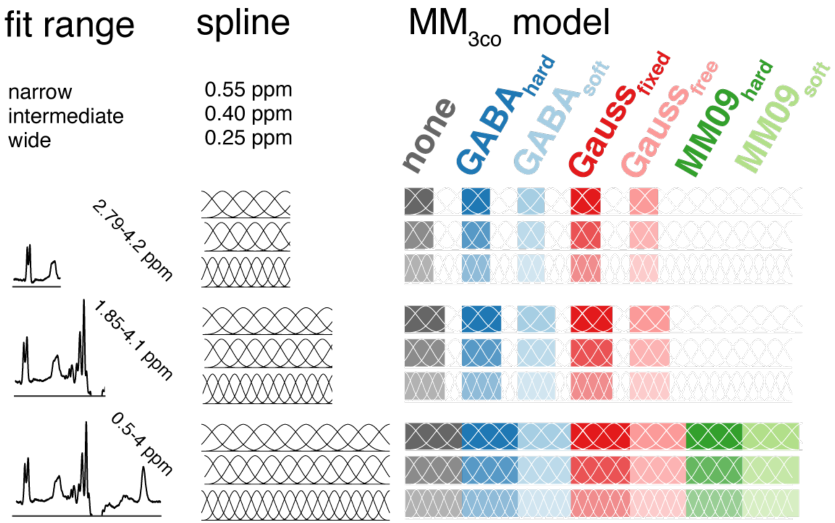
… there is no consensus on **how** this should be done.

Modeling edited GABA (+MM) data

Co-edited MM model implementations



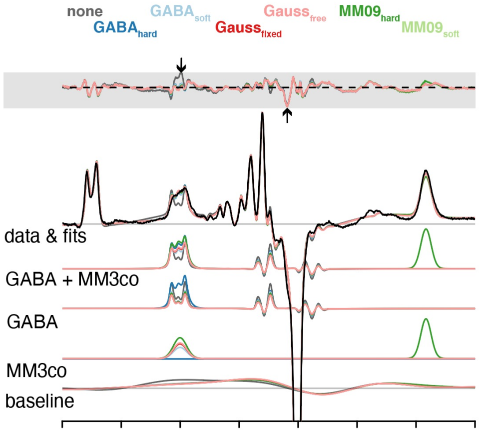
Combination of modelling strategies

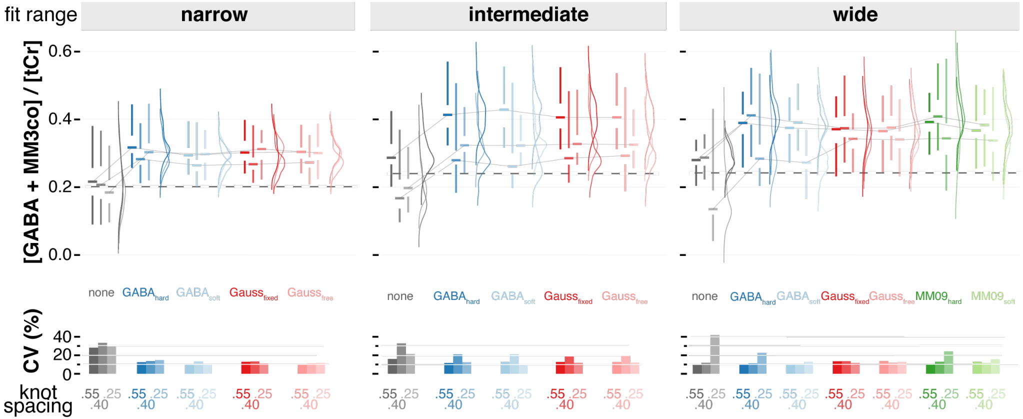


- Testing various strategies to model **co-edited macromolecular signal**
- Investigate effects of **baseline flexibility** and **fit range**

Zöllner et al., NMR Biomed 2021 (in revision)

Modeling edited GABA (+ MM) data





- MM modeling strategies **perform similarly** (improve fit, decrease CV of GABA+)
- **Wide fit range** and **larger knot spacing** (more rigid baseline) are favorable

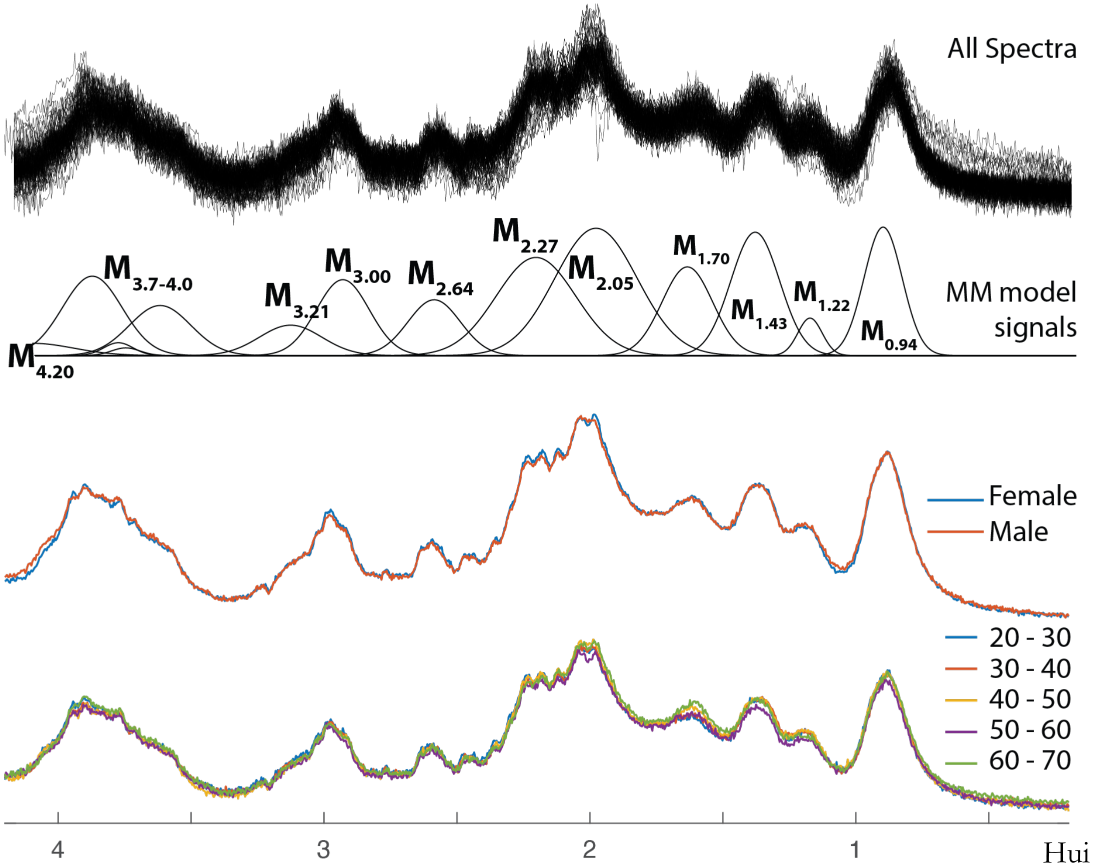
Zöllner et al., NMR Biomed 2021 (in revision)

Characterizing macromolecular background

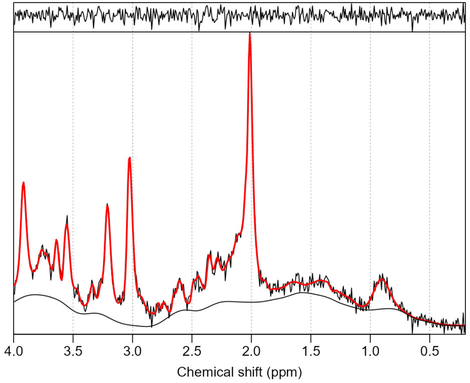
MM signal measured in 100 subjects across the lifespan (10F, 10M per decade of life)

Modeled with Gaussian peaks at literature value frequencies

No apparent sex or age effects on MM signal



Hui et al., in prep.

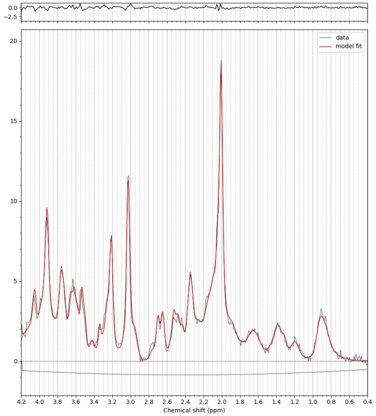


spant

- Modular set of tools to build automated analysis pipelines
- Includes functions for preprocessing, linear-combination modeling, tissue correction, visualization, and simulations

Name	Open source?	Pre-processing	Modeling	Tissue segmentation	OS	Language
LCModel	Yes	Limited	Yes	No	Linux	FORTRAN77
jMRUI	No	Yes (limited)	Yes	No	Win Linux	JAVA
Tarquin	Yes	Yes	Yes	No	Win Linux Mac	C++
Vespa	Yes	Yes	Yes	No	All	Python
FID-A	Yes	Yes	No	No	All	MATLAB
INSPECTOR	No	Yes	Yes	Yes	All	MATLAB
Osprey	Yes	Yes	Yes	Yes	All	MATLAB
spant	Yes	Yes	Yes	Yes	All	R
FSL-MRS	Yes	Yes	Yes	Yes	All	Python

FSL-MRS



FSL-MRS

- Modular set of tools to build automated analysis pipelines
- Includes functions for preprocessing, linear-combination modeling, tissue segmentation, visualization, and simulations
- Interfaces directly with other FSL tools

Name	Open source?	Pre-processing	Modeling	Tissue segmentation	OS	Language
LCModel	Yes	Limited	Yes	No	Linux	FORTRAN77
jMRUI	No	Yes (limited)	Yes	No	Win Linux	JAVA
Tarquin	Yes	Yes	Yes	No	Win Linux Mac	C++
Vespa	Yes	Yes	Yes	No	All	Python
FID-A	Yes	Yes	No	No	All	MATLAB
INSPECTOR	No	Yes	Yes	Yes	All	MATLAB
Osprey	Yes	Yes	Yes	Yes	All	MATLAB
spant	Yes	Yes	Yes	Yes	All	R
FSL-MRS	Yes	Yes	Yes	Yes	All	Python

Committee for MRS Code and Data Sharing

ISMRM ONE COMMUNITY FOR CLINICIANS AND SCIENTISTS

Standing committee

of the

ISMRM Study Group

MR Spectroscopy

Candace Fleischer

Emory University

Georg Oeltzschner

Johns Hopkins University

William T. Clarke

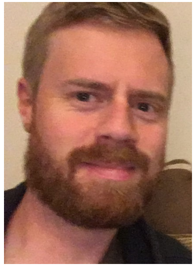
University of Oxford

Kelley M. Swanberg

Columbia University

Alexander P. Lin

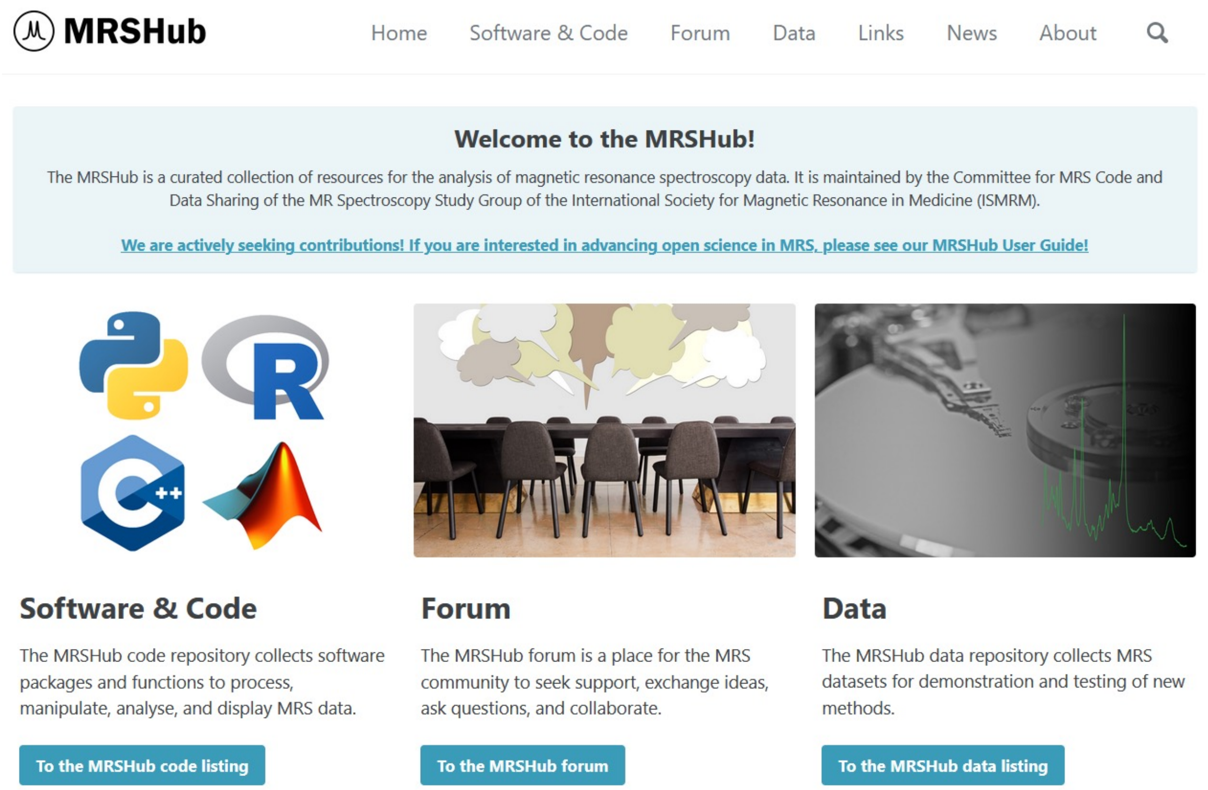
Harvard Medical School



Martin Wilson

University of Birmingham

MRSHub – one centralized resource



Welcome to the MRSHub!

The MRSHub is a curated collection of resources for the analysis of magnetic resonance spectroscopy data. It is maintained by the Committee for MRS Code and Data Sharing of the MR Spectroscopy Study Group of the International Society for Magnetic Resonance in Medicine (ISMRM).

We are actively seeking contributions! If you are interested in advancing open science in MRS, please see our MRSHub User Guide!

Software & Code

The MRSHub code repository collects software packages and functions to process, manipulate, analyse, and display MRS data.

Forum

The MRSHub forum is a place for the MRS community to seek support, exchange ideas, ask questions, and collaborate.

Data

The MRSHub data repository collects MRS datasets for demonstration and testing of new methods.

NIfTI-MRS

Vendor	File extension	Coils combined?	Averaged?	Contains voxel geometry?
Philips	.sdat /.spar	Yes	Depends	Yes
	.data /.list	No	No	No
Siemens	.rda	Yes	Depends	Yes
	.twix	No	No	Yes
GE	.7	Depends	Depends	Yes
DICOM	.dcm (.ima)	Yes	Depends	Yes

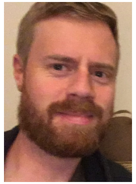
- ”Depends”… on sequence developer, software version, exam card settings
- Software needs to be separately adapted to each individual format/version

NIfTI-MRS

Common storage specification for MRS/MRSI data

Extends on existing NIfTI-2 standard

William T. Clarke
University of Oxford

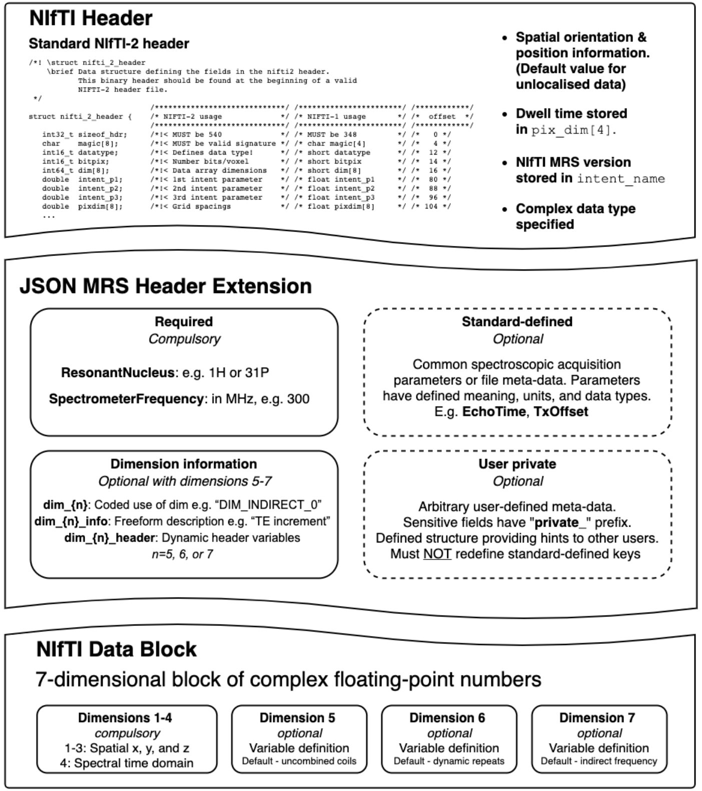


Martin Wilson
University of Birmingham

- Simplified pathway from scanner to final analysis
- Interoperability and modularity of analysis programs
- Easier display and co-interpretation with other modalities
- Format for easy data sharing

Clarke et al., in prep.

NIfTI-MRS



NIfTI Header

Standard NIfTI-2 header

```
/*! \struct nifti_2_header
    \brief Data structure defining the fields in the nifti2 header.
           This binary header should be found at the beginning of a valid
           NIFTI-2 header file.
 */
                           /*****************************/ /**********************/ /************/
struct nifti_2_header {    /* NIFTI-2 usage              */ /* NIFTI-1 usage       */ /*  offset  */
                           /*****************************/ /**********************/ /************/
   int32_t sizeof_hdr;     /*!< MUST be 540              */ /* MUST be 348         */ /*   0 */
   char    magic[8];       /*!< MUST be valid signature */ /* char magic[4]       */ /*   4 */
   int16_t datatype;       /*!< Defines data type!       */ /* short datatype      */ /*  12 */
   int16_t bitpix;         /*!< Number bits/voxel        */ /* short bitpix        */ /*  14 */
   int64_t dim[8];         /*!< Data array dimensions    */ /* short dim[8]        */ /*  16 */
   double  intent_p1;      /*!< 1st intent parameter     */ /* float intent_p1     */ /*  80 */
   double  intent_p2;      /*!< 2nd intent parameter     */ /* float intent_p2     */ /*  88 */
   double  intent_p3;      /*!< 3rd intent parameter     */ /* float intent_p3     */ /*  96 */
   double  pixdim[8];      /*!< Grid spacings            */ /* float pixdim[8]     */ /* 104 */
   ...
```

- **Spatial orientation & position information. (Default value for unlocalised data)**
- **Dwell time stored in `pix_dim[4]`.**
- **NIfTI MRS version stored in `intent_name`**
- **Complex data type specified**

JSON MRS Header Extension

Required
Compulsory

ResonantNucleus: e.g. 1H or 31P

SpectrometerFrequency: in MHz, e.g. 300

Standard-defined
Optional

Common spectroscopic acquisition parameters or file meta-data. Parameters have defined meaning, units, and data types. E.g. **EchoTime**, **TxOffset**

Dimension information
Optional with dimensions 5-7

dim_{n}: Coded use of dim e.g. “DIM_INDIRECT_0”
dim_{n}_info: Freeform description e.g. “TE increment”
dim_{n}_header: Dynamic header variables
n=5, 6, or 7

User private
Optional

Arbitrary user-defined meta-data. Sensitive fields have "**private_**" prefix. Defined structure providing hints to other users. Must NOT redefine standard-defined keys

NIfTI Data Block

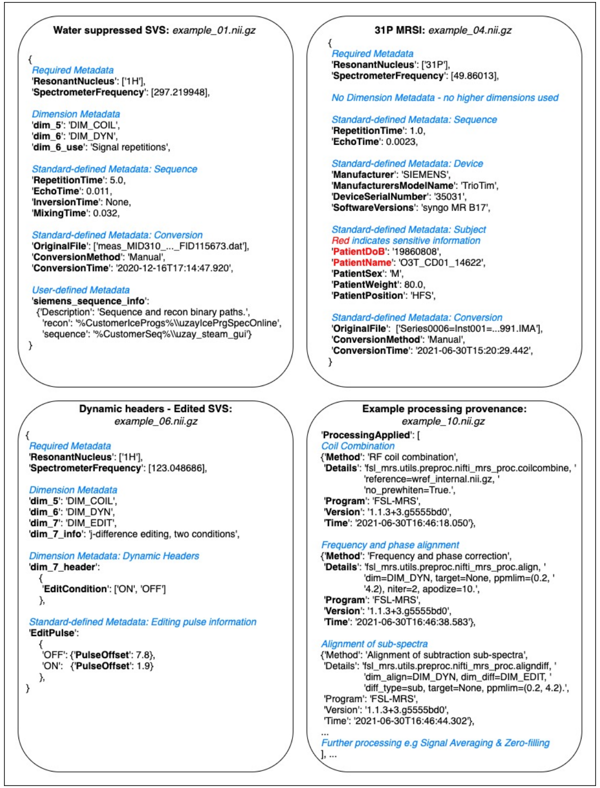
7-dimensional block of complex floating-point numbers

Dimensions 1-4
compulsory
1-3: Spatial x, y, and z
4: Spectral time domain

Dimension 5
optional
Variable definition
Default - uncombined coils

Dimension 6
optional
Variable definition
Default - dynamic repeats

Dimension 7
optional
Variable definition
Default - indirect frequency



Water suppressed SVS: *example_01.nii.gz*

```
{
 Required Metadata
 'ResonantNucleus': ['1H'],
 'SpectrometerFrequency': [297.219948],

 Dimension Metadata
 'dim_5': 'DIM_COIL',
 'dim_6': 'DIM_DYN',
 'dim_6_use': 'Signal repetitions',

 Standard-defined Metadata: Sequence
 'RepetitionTime': 5.0,
 'EchoTime': 0.011,
 'InversionTime': None,
 'MixingTime': 0.032,

 Standard-defined Metadata: Conversion
 'OriginalFile': ['meas_MID310_..._FID115673.dat'],
 'ConversionMethod': 'Manual',
 'ConversionTime': '2020-12-16T17:14:47.920',

 User-defined Metadata
 'siemens_sequence_info':
  {'Description': 'Sequence and recon binary paths.',
    'recon': '%CustomerIceProgs%\\uzayIcePrgSpecOnline',
    'sequence': '%CustomerSeq%\\uzay_steam_gui'}
}
```

31P MRSI: *example_04.nii.gz*

```
{
 Required Metadata
 'ResonantNucleus': ['31P'],
 'SpectrometerFrequency': [49.86013],

 No Dimension Metadata - no higher dimensions used

 Standard-defined Metadata: Sequence
 'RepetitionTime': 1.0,
 'EchoTime': 0.0023,

 Standard-defined Metadata: Device
 'Manufacturer': 'SIEMENS',
 'ManufacturersModelName': 'TrioTim',
 'DeviceSerialNumber': '35031',
 'SoftwareVersions': 'syngo MR B17',

 Standard-defined Metadata: Subject
 Red indicates sensitive information
 'PatientDoB': '19860808',
 'PatientName': 'O3T_CD01_14622',
 'PatientSex': 'M',
 'PatientWeight': 80.0,
 'PatientPosition': 'HFS',

 Standard-defined Metadata: Conversion
 'OriginalFile':  ['Series0006=Inst001=...991.IMA'],
 'ConversionMethod': 'Manual',
 'ConversionTime': '2021-06-30T15:20:29.442',
}
```

Dynamic headers - Edited SVS:
example_06.nii.gz

```
{
 Required Metadata
 'ResonantNucleus': ['1H'],
 'SpectrometerFrequency': [123.048686],

 Dimension Metadata
 'dim_5': 'DIM_COIL',
 'dim_6': 'DIM_DYN',
 'dim_7': 'DIM_EDIT',
 'dim_7_info': 'j-difference editing, two conditions',

 Dimension Metadata: Dynamic Headers
 'dim_7_header':
    {
     'EditCondition': ['ON', 'OFF']
    },

 Standard-defined Metadata: Editing pulse information
 'EditPulse':
    {
     'OFF': {'PulseOffset': 7.8},
     'ON':   {'PulseOffset': 1.9}
    },
}
```

Example processing provenance:
example_10.nii.gz

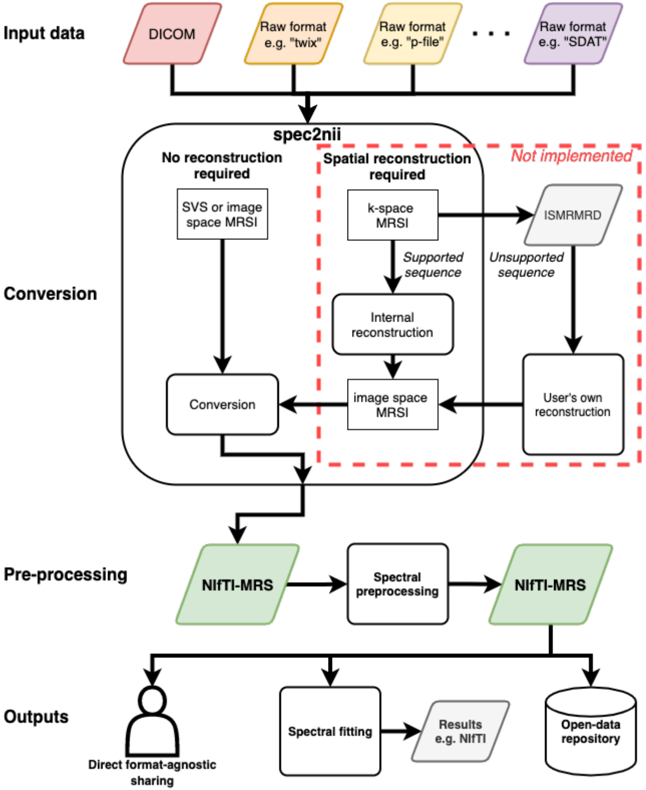
```
'ProcessingApplied': [
Coil Combination
{'Method': 'RF coil combination',
 'Details': 'fsl_mrs.utils.preproc.nifti_mrs_proc.coilcombine, '
            'reference=wref_internal.nii.gz, '
            'no_prewhiten=True.',
 'Program': 'FSL-MRS',
 'Version': '1.1.3+3.g5555bd0',
 'Time': '2021-06-30T16:46:18.050'},

Frequency and phase alignment
{'Method': 'Frequency and phase correction',
 'Details': 'fsl_mrs.utils.preproc.nifti_mrs_proc.align, '
            'dim=DIM_DYN, target=None, ppmlim=(0.2, '
            '4.2), niter=2, apodize=10.',
 'Program': 'FSL-MRS',
 'Version': '1.1.3+3.g5555bd0',
 'Time': '2021-06-30T16:46:38.583'},

Alignment of sub-spectra
{'Method': 'Alignment of subtraction sub-spectra',
 'Details': 'fsl_mrs.utils.preproc.nifti_mrs_proc.aligndiff, '
            'dim_align=DIM_DYN, dim_diff=DIM_EDIT, '
            'diff_type=sub, target=None, ppmlim=(0.2, 4.2).',
 'Program': 'FSL-MRS',
 'Version': '1.1.3+3.g5555bd0',
 'Time': '2021-06-30T16:46:44.302'},
...
Further processing e.g Signal Averaging & Zero-filling
], ...
```

Clarke et al., in prep.

NIfTI-MRS



Input data

DICOM

Raw format e.g. "twix"

Raw format e.g. "p-file"

. . .

Raw format e.g. "SDAT"

Conversion

spec2nii

No reconstruction required

SVS or image space MRSI

Conversion

Spatial reconstruction required

Not implemented

k-space MRSI

ISMRMRD

Supported sequence

Unsupported sequence

Internal reconstruction

image space MRSI

User's own reconstruction

Pre-processing

NIfTI-MRS

Spectral preprocessing

NIfTI-MRS

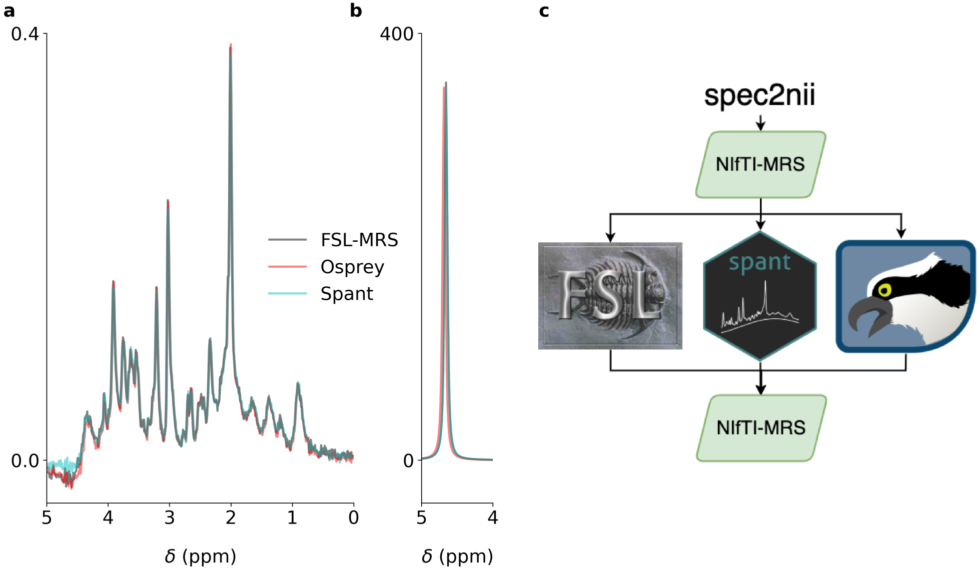
Outputs

Direct format-agnostic sharing

Spectral fitting

Results e.g. NIfTI

Open-data repository



Clarke et al., in prep.

MRSHub vision

Vendor-agnostic acquisition

- Common sequences
- Open-source pulses
- Standardized timing

Clinical workflow integration

- Consensus modeling on scanners
- DICOM integration of quantitative estimates

In-vivo data

- Healthy volunteers across the lifespan
- Incl. relaxometry, MM

MRSHub

ISMRM ONE COMMUNITY FOR CLINICIANS AND SCIENTISTS

Synthetic data

- Arbitrary numbers of artificial spectra including ground truth

Consensus analysis

- Models, basis sets
- Common processing steps
- Tissue/relaxation correction

New analysis methods

- DL-based modeling
- Adaptive LC modeling
- Spatial/spectral recon (MRSI)

Final words

Build relationships with sequence and analysis software developers.

Be aware of new acquisition and analysis methods.

Different analyses will yield different results.

Ask others about their data analysis pipeline.

MRSHub

Acknowledgements

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Tao Gong
Guangbin Wang

Terri Brawner
Kathleen Kahl
Ivana Kusevic
Joe Gillen

Brian J. Soher
William T. Clarke
Candace Fleischer
Kelley M. Swanberg
Cristina R. Cudalbu
Alexander P. Lin
Martin Wilson

NIH / NIMH / NINDS / NIA:
P41 EB015909 (van Zijl/Barker)
R01 EB028259 (Barker)
R21 AG060245 (Edden)
R01 EB016089 (Edden)
R01 EB023963 (Edden)
K99/R00 AG062230 (Oeltzschner)

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