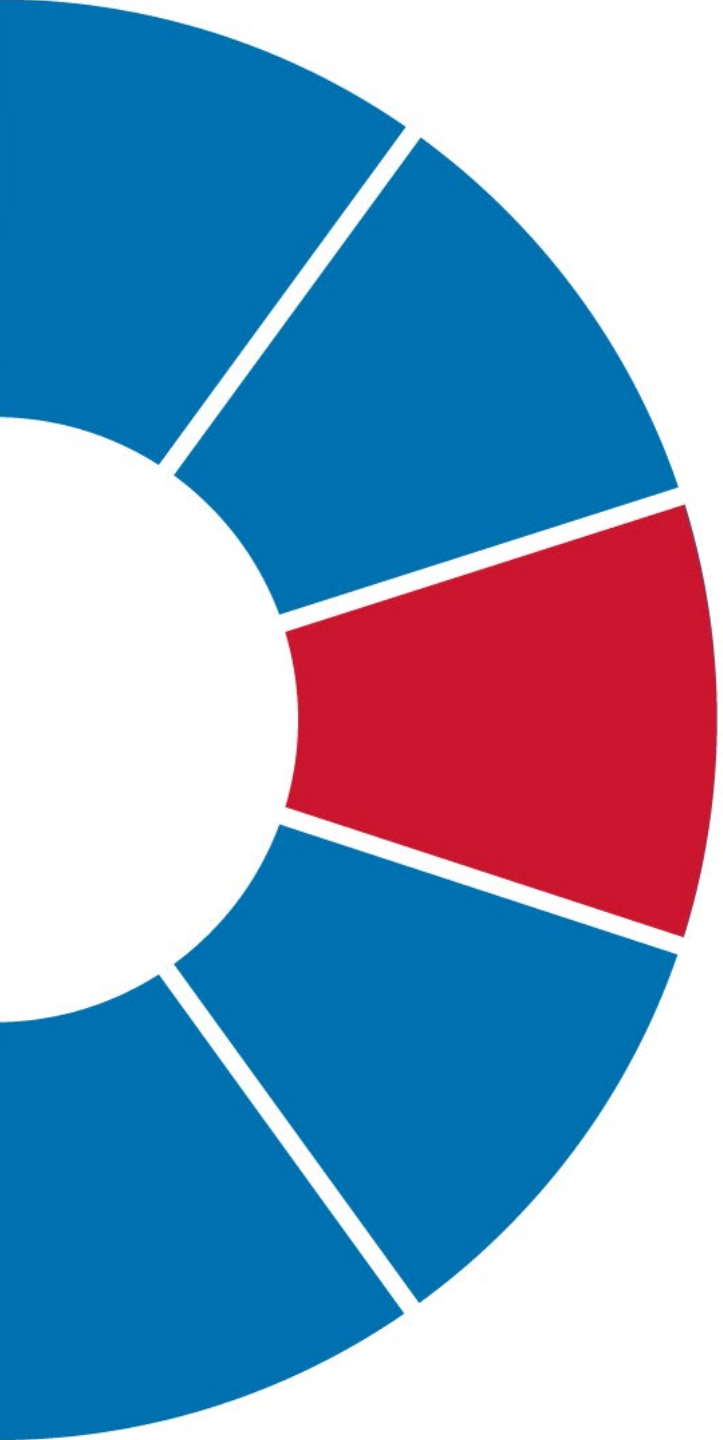
QUANTIFICATION OF MR SPECTRA

Cristina Cudalbu

CIBM MRI EPFL AIT

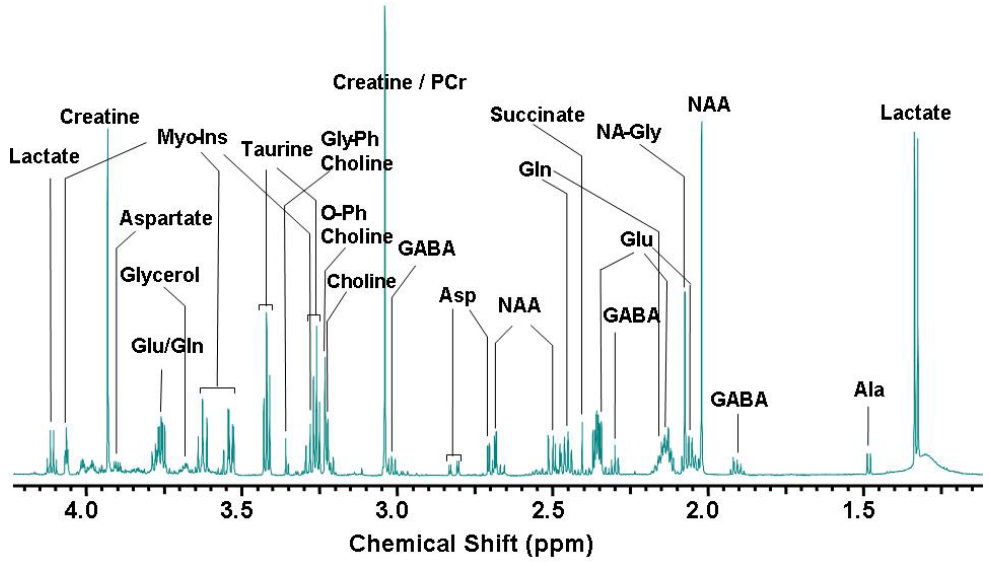
cristina.cudalbu@epfl.ch



QUANTIFICATION

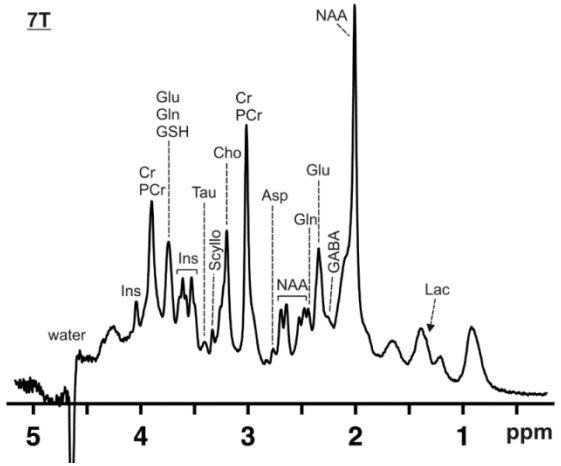
MAGNETIC RESONANCE SPECTROSCOPY

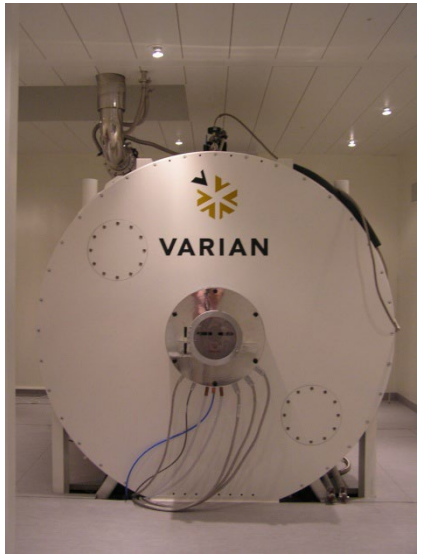
- NMR Spectroscopy



MAGNETIC RESONANCE SPECTROSCOPY

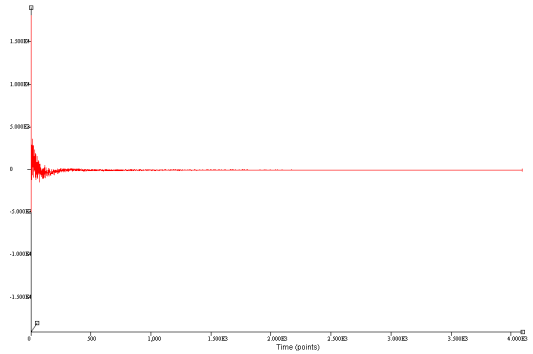
- In Vivo MR spectroscopy (MRS)
  - Measurement of different metabolites- metabolism
  - Different organs
  - Different nuclei: 1H, 13C, 31P, 15N, ..
  - Different magnetic fields
  - Different acquisition parameters



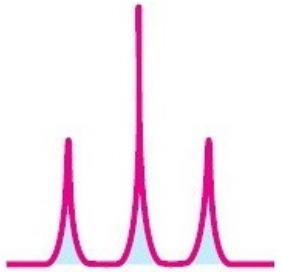


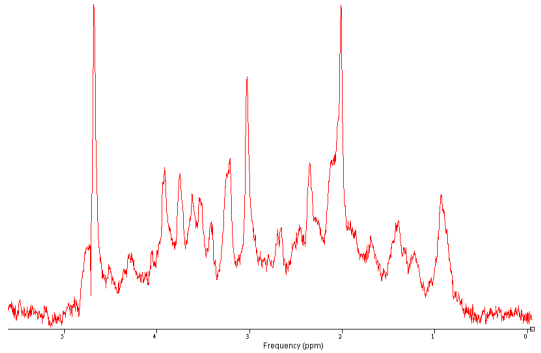
QUANTIFICATION

- MRS – principal goal – quantification of changes in concentration of known metabolites



- Frequencies
- Amplitudes
- Damping factor
- Phase
- Beginning time





- Frequencies
- Surface
- Linewidths
- Zero order phase.
- first order phase

WHY IN VIVO 1H MR SPECTROSCOPY ?

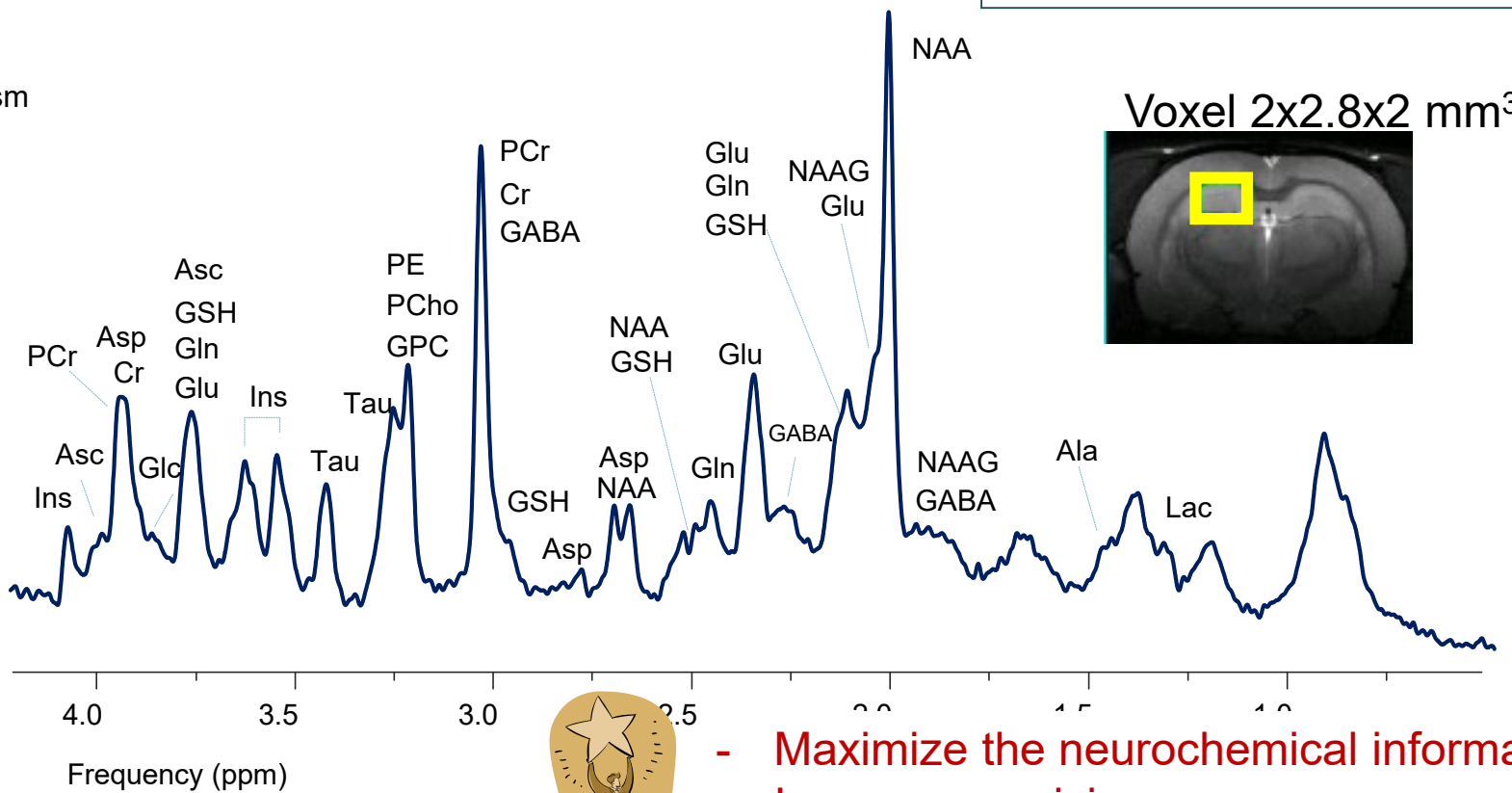
Neurochemical Profile at 9.4T

>18 Markers of :

Myelination/Cell proliferation
Energy metabolism
Osmoregulation
Neurotransmitter metabolism
Antioxidants

- **at high magnetic field (9.4T)**
- **ultra short TE (2.8ms)**

- ***in vivo***
- **non invasively**
- **localized in hippocampus**



Voxel 2x2.8x2 mm^3

- Maximize the neurochemical information
- Increase precision, accuracy – quantification
- Increase the reliability of obtained concentrations

CD Rae et al, Anal Biochem. 2017; CD Rae .Neurochem Res. 2014; V Račkayová et al 2017; JMN Duarte 2012

Received: 10 September 2019 | Revised: 20 May 2020 | Accepted: 21 May 2020

DOI: 10.1002/nbm.4347

SPECIAL ISSUE REVIEW ARTICLE

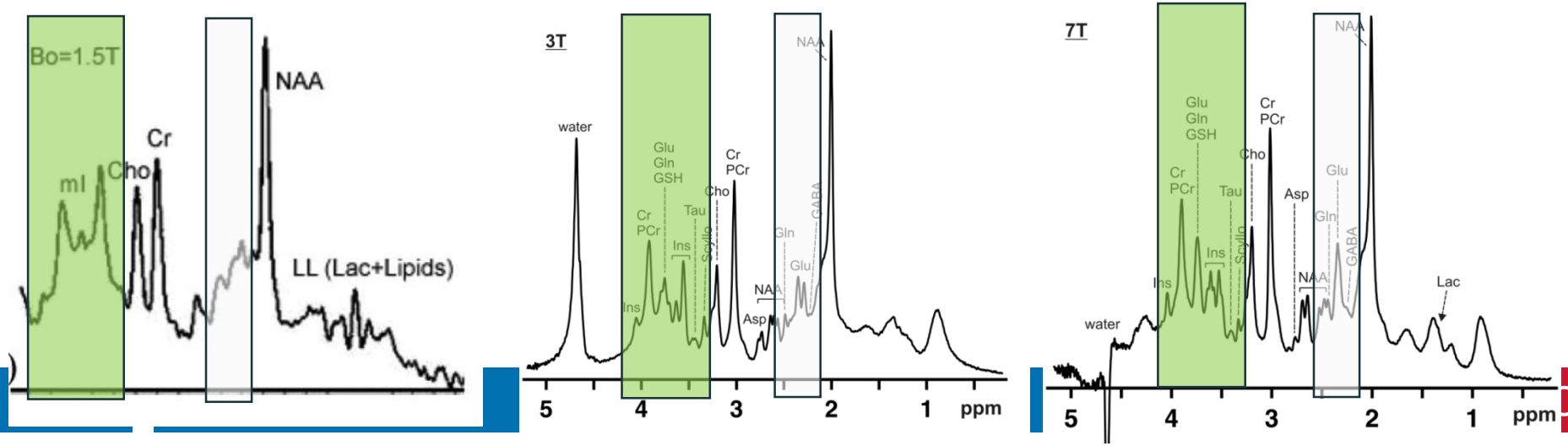
NMR IN BIOMEDICINE WILEY

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

Roland Kreis[1] | Vincent Boer[2] | In-Young Choi[3] | Cristina Cudalbu[4] | Robin A. de Graaf[5] | Charles Gasparovic[6] | Arend Heerschap[7] | Martin Kršňák[8] | Bernard Lanz[9,10] | Andrew A. Maudsley[11] | Martin Meyerspeer[12,13] | Jamie Near[14] | Gülin Öz[15] | Stefan Posse[16] | Johannes Slotboom[17] | Melissa Terpstra[15] | Ivan Tkáč[15] | Martin Wilson[18] | Wolfgang Bogner[19] | Experts' Working Group on Terminology for MR Spectroscopy

WHY HIGH MAGNETIC FIELD ?

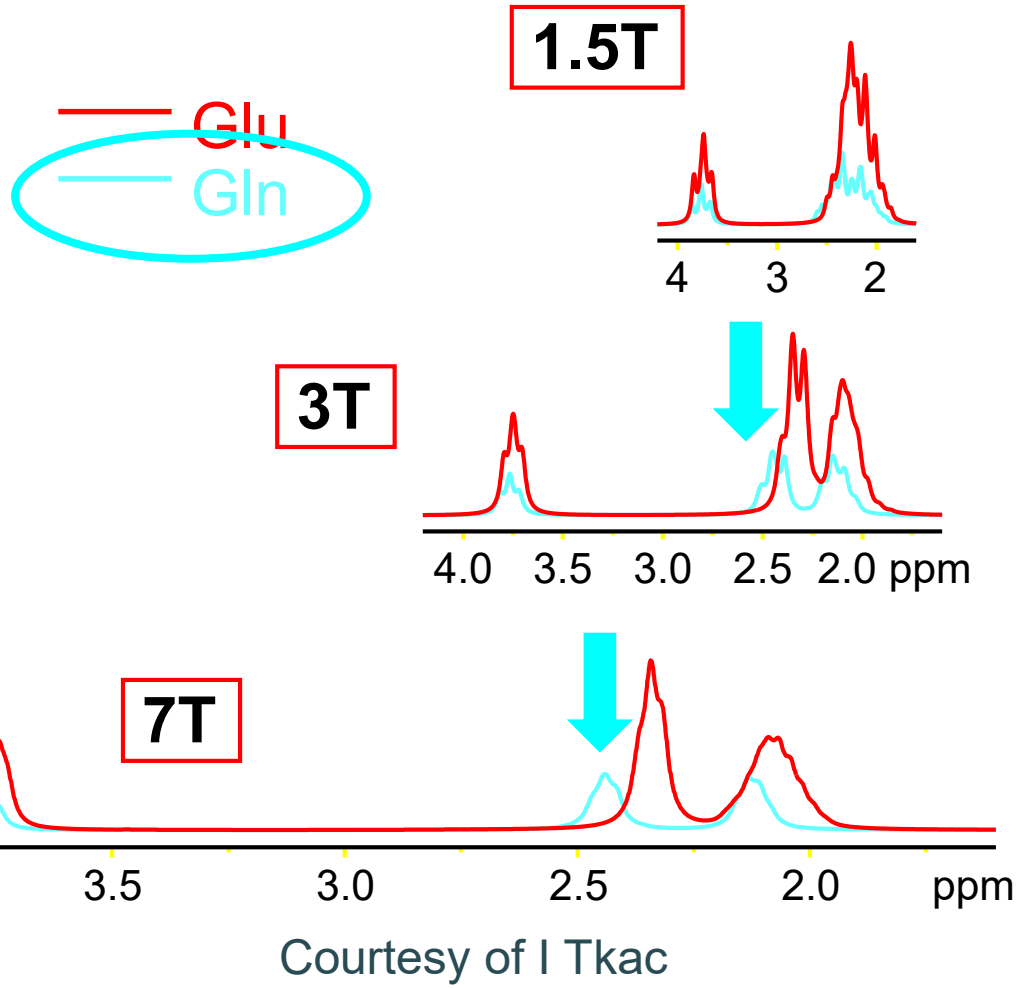
- More signal
- More spectral resolution
- And more sensitivity



Ralf Mekle et al, (2009) MRM 50: 1279

WHY HIGH B_0?

- Enormous progress
  - ↑ SNR
  - ↑ chemical shift dispersion – ↑ resolution
  - decreased strong J-coupling effects
  - Improve quantification precision and accuracy
  - ↓ T_2* - ↑ spectral lw in Hz

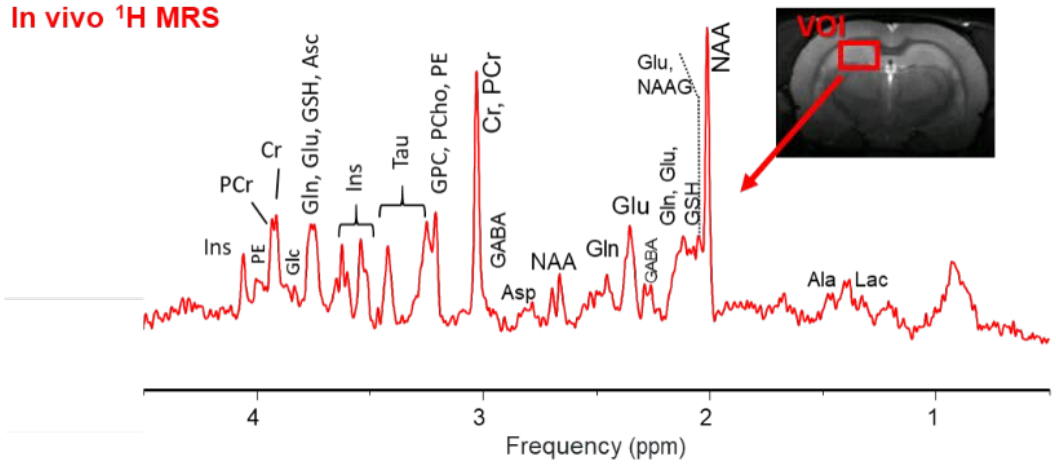


Courtesy of I Tkac

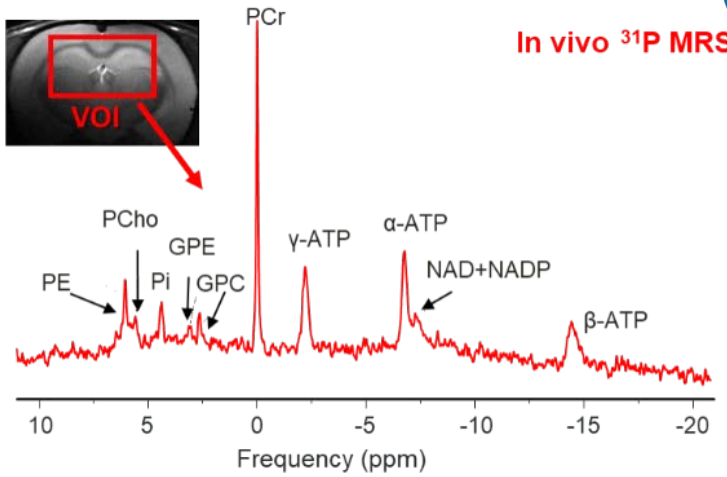
Oz G, et al., Clinical proton MR spectroscopy in central nervous system disorders. Radiology. 2014
Wilson M, et al., Methodological consensus on clinical proton MRS of the brain: Review and recommendations. Magn Reson Med. 2019

X NUCLEI MRS – 9.4T

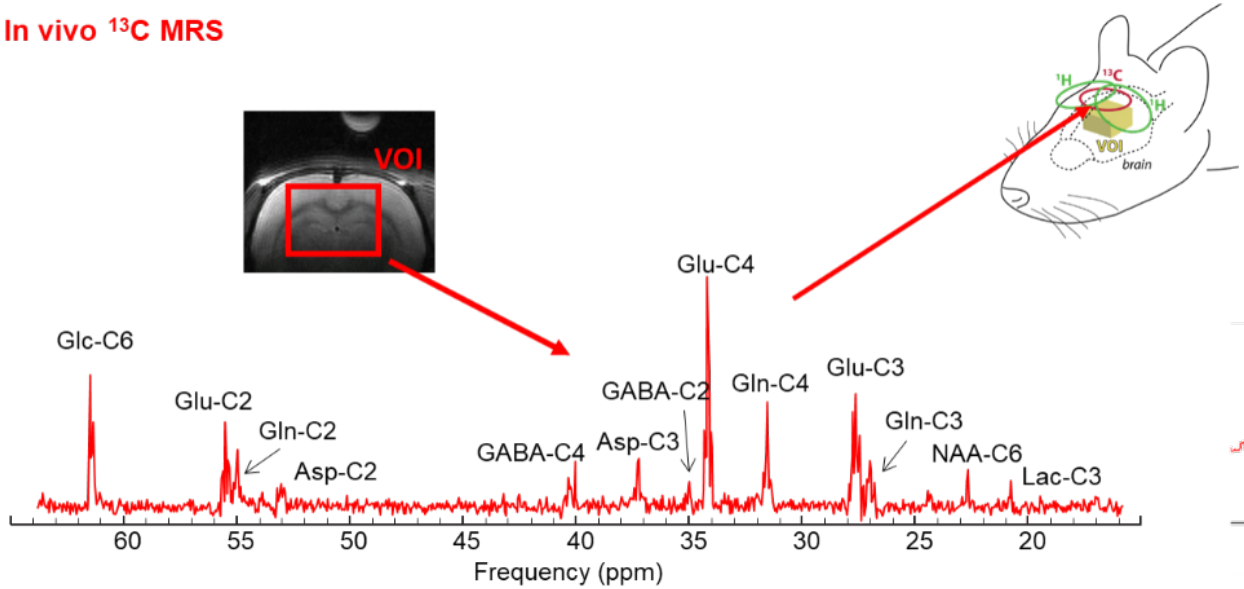
In vivo ^{1}H MRS



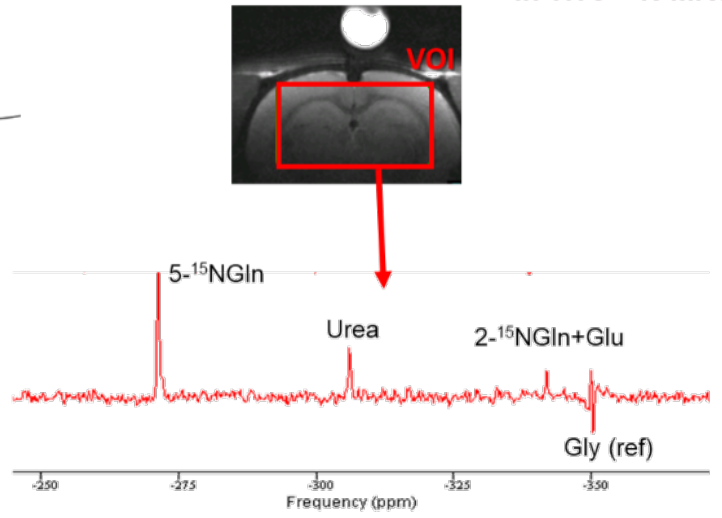
In vivo ^{31}P MRS



In vivo ^{13}C MRS



In vivo ^{15}N MRS



CIBM.CH

Lanz et al, 2017, 2020; Cudalbu et al 2021;

CLINICAL VS PRECLINICAL DATA

	Preclinical	Clinical
Subjects	Animal (rat/mouse) - anesthesia	Human – no anesthesia
Motion	☺	? ☹
Time for scanning	☺ Shim, WS, OVS, …	☹
@scanner	MRS experts	Not necessary MRS experts
Amount of data	+++	+++++++

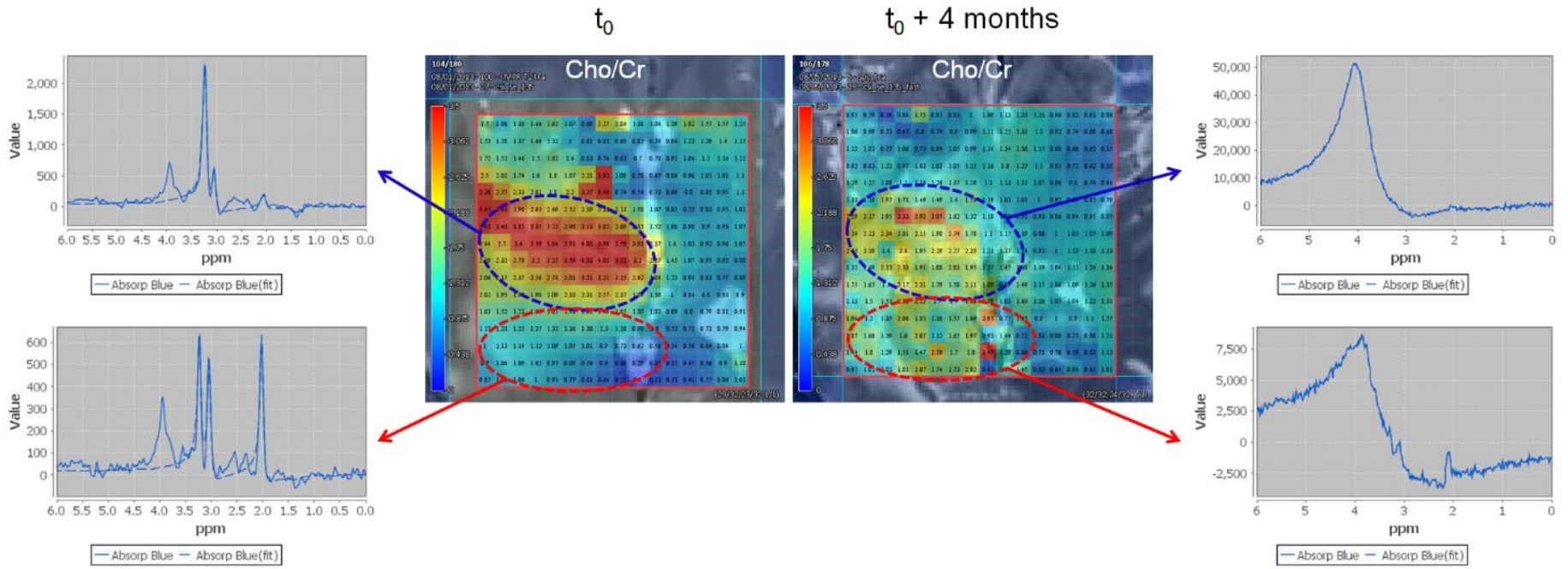
(Lots) Data with sometimes artifacts

- Need to be identified
- Corrected or data discarded
- Preprocessed
- Quantified

Clinicians

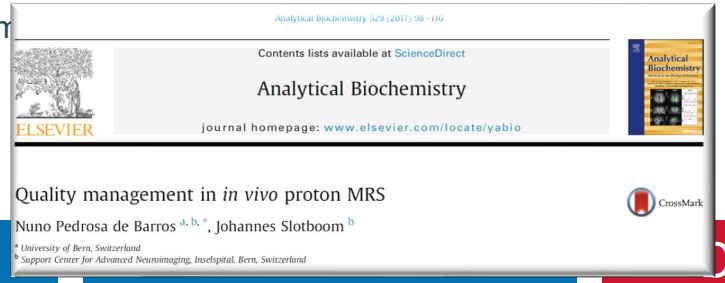
☹ Draw incorrect decisions
☹ Standard quantification software – NO quality check
☹ CRLB …..

CLINICAL VS PRECLINICAL DATA



Example showing two Cho/Cr maps of a Glioma patient acquired 4 months apart.
Siemens Aera 1.5 T, 2D-PRESS, 12x12 interpolated to 32x32, TE/TR 135/1500m

From N Barros et al, Analytical Biochemistry, 2017


Contents lists available at ScienceDirect

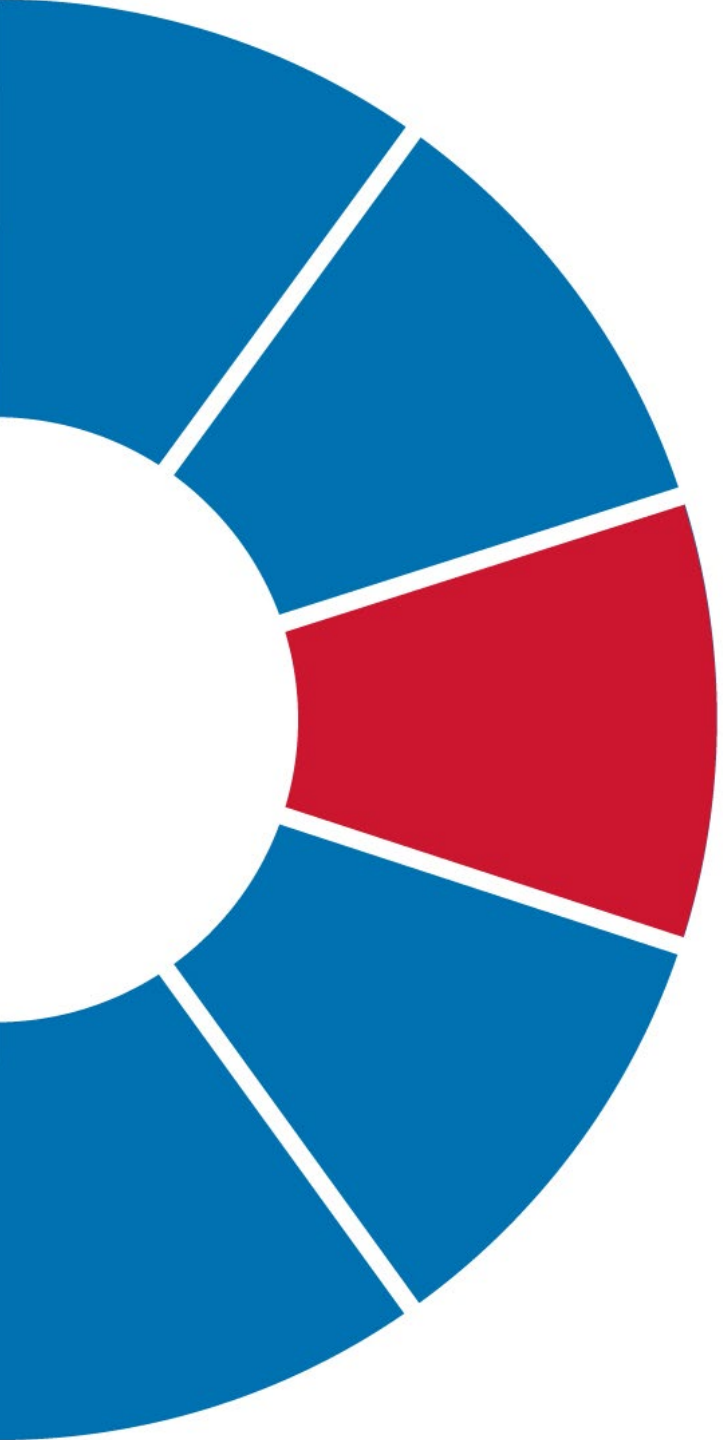
Analytical Biochemistry

journal homepage: www.elsevier.com/locate/yabio

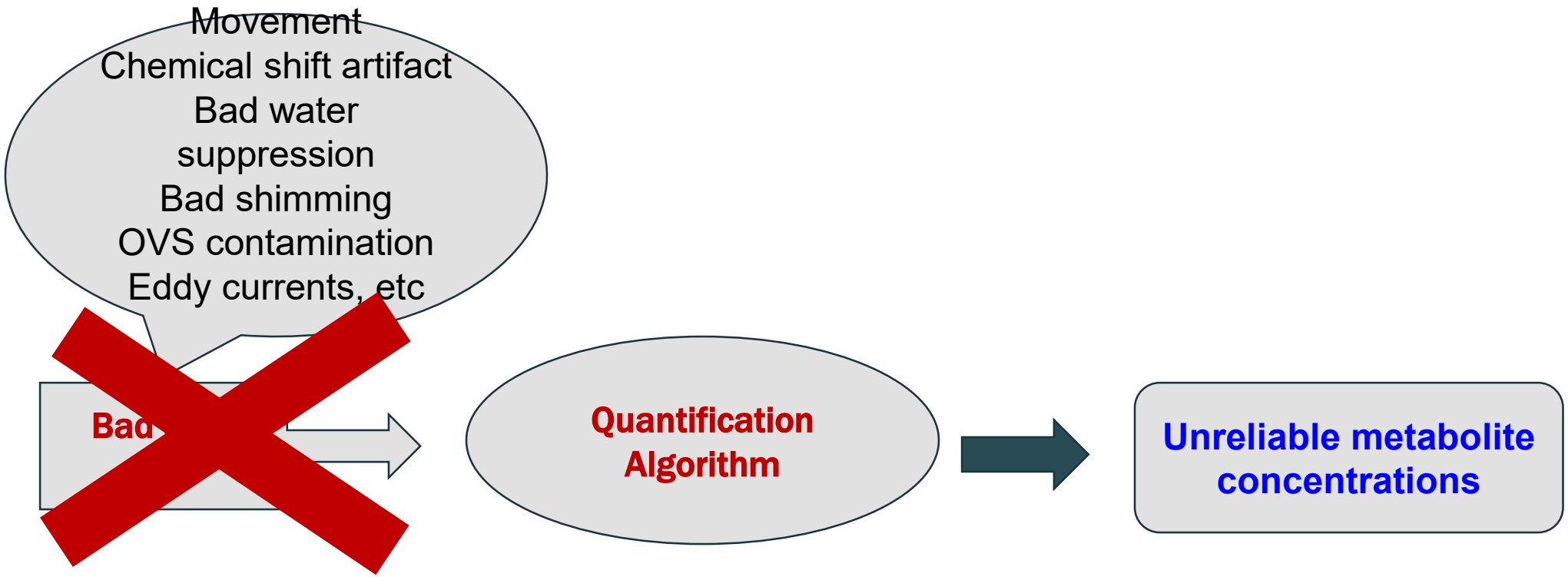
Quality management in *in vivo* proton MRS

Nuno Pedrosa de Barros [a, b, *], Johannes Slotboom [b]

[a] University of Bern, Switzerland
[b] Support Center for Advanced Neuroimaging, Inselspital, Bern, Switzerland

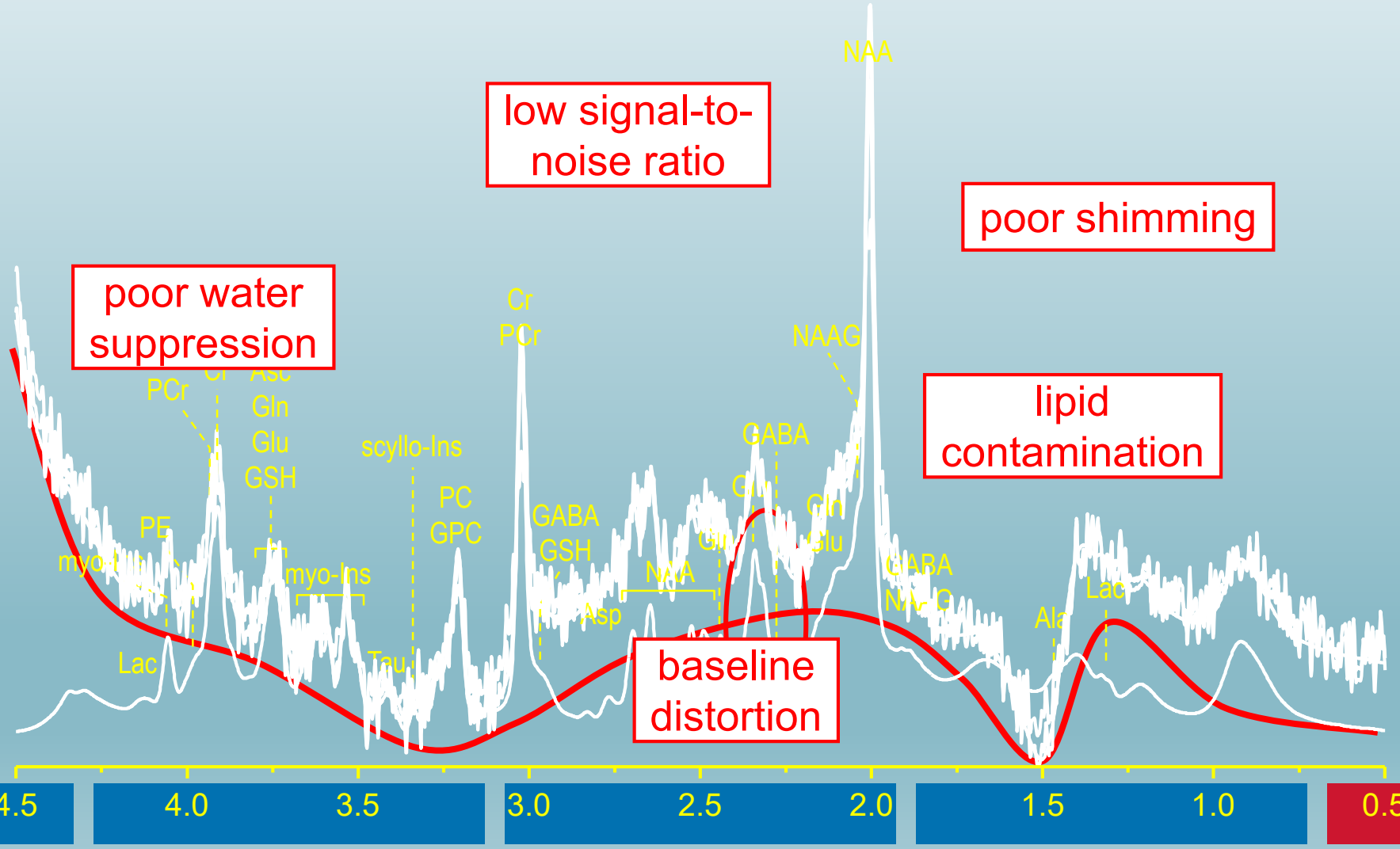


ARTIFACTS IN 1H MRS



ISMRM 2010, Potentials and Challenges at High Field MRS
R Kreis, NMR Biomed 2004, 17:361
Tkáč I, et al, Appl Magn Reson. 2005 29:139.

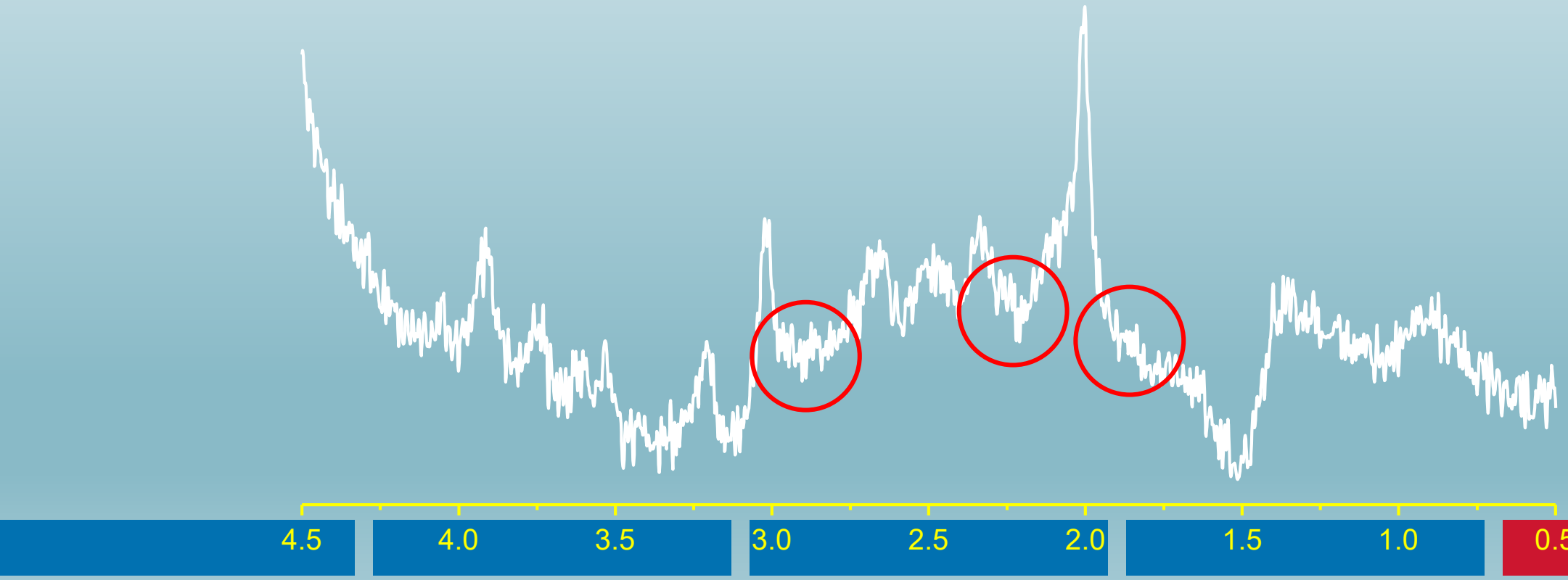
DISTORTIONS OF 1H NMR SPECTRUM OF THE HUMAN BRAIN AT 7T



IS RELIABLE QUANTIFICATION OF GABA AND GLU POSSIBLE?

GLUTAMATE? DIFFICULT, LIMITED PRECISION

GABA? IMPOSSIBLE FROM THIS TYPE OF SPECTRA!!



CIBM.CH

IS RELIABLE QUANTIFICATION OF GABA AND GLU POSSIBLE?

GLUTAMATE?

GABA?

DIFFICULT, LIMITED PRECISION

IMPOSSIBLE FROM THIS TYPE OF SPECTRA!!

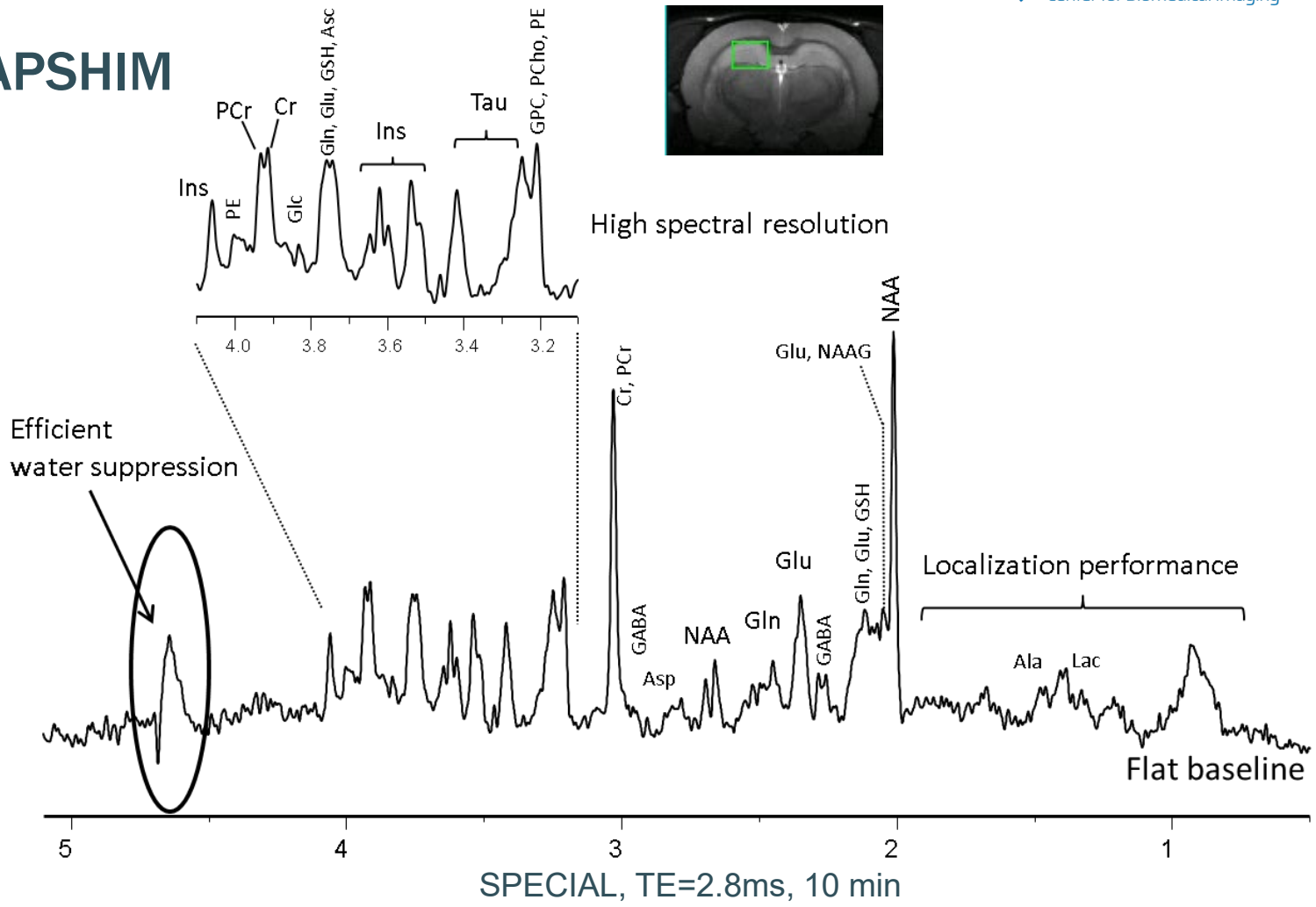
GOOD QUALITY DATA AT SHORT TE

- **Shimming: e.g. FASTMAP, MAPSHIM**
- **Pulse sequence at short TE**

Provide undistorted multiplets and no T_2 weighting

Increased no of metabolites

Improved quantification



R Kreis 2004; C Cudalbu 2013 (450) Quality of MRS/MRSI – YouTube - I Tkac

ACQUISITION SEQUENCES

- Reduced CSDE
- Good localization :
  - double : OVS+Seq or LASER
- Strong crusher gradients
- Good WS

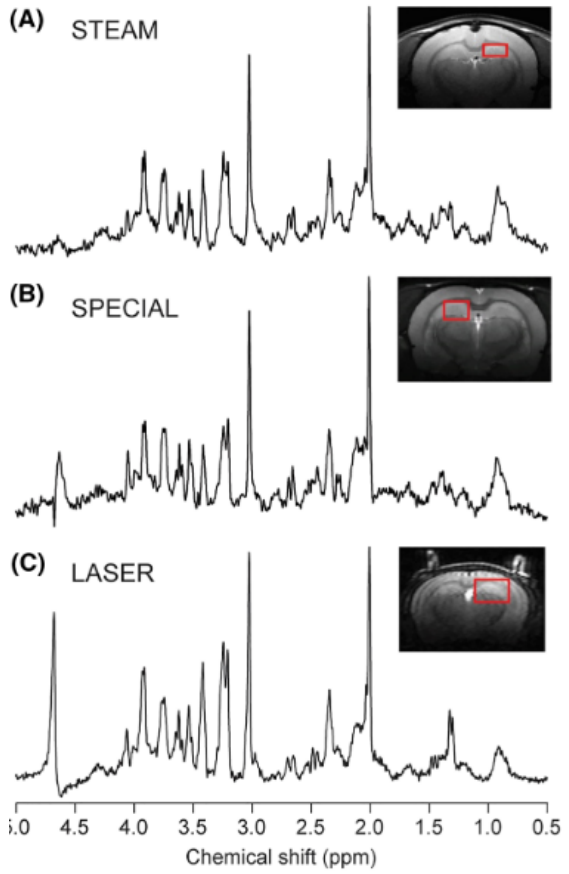
Received: 11 November 2019 | Revised: 29 March 2020 | Accepted: 30 April 2020
DOI: 10.1002/nbm.4325

SPECIAL ISSUE REVIEW ARTICLE

NMR IN BIOMEDICINE WILEY

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

FIGURE 3 Example ^{1}H MR spectra obtained in rodent brains at 9.4 T with STEAM (A), SPECIAL (B) and LASER (C) sequences. A, STEAM spectrum: rat brain, 2.3 × 1.3 × 2.5 mm^3 voxel placed in the hippocampus, TR = 5 s, TE = 2 ms, TM = 20 ms, number of averages = 448. Spectrum is shown with Gaussian factor = 0.15. B, SPECIAL spectrum: rat brain, 2 × 2.8 × 2 mm^3 voxel placed in the hippocampus, TR = 4, TE = 2.8 ms, number of averages = 160. C, LASER spectrum: mouse brain, 1.7 × 2.25 × 2.25 mm^3 voxel placed in hippocampus, TR = 4 s, TE = 27 ms, number of averages = 384. The STEAM spectrum was provided by Ivan Tkáč



Received: 23 March 2020 | Accepted: 23 November 2020
DOI: 10.1002/nbm.4459

SPECIAL ISSUE REVIEW ARTICLE

NMR IN BIOMEDICINE WILEY

Water and lipid suppression techniques for advanced ^{1}H MRS and MRSI of the human brain: Experts' consensus recommendations

Ivan Tkáč[1] | Dinesh Deelchand[1] | Wolfgang Dreher[2] | Hoby Hetherington[3] | Roland Kreis[4] | Chathura Kumaragamage[5] | Michal Považan[6] | Daniel M. Spielman[7] | Bernhard Strasser[8] | Robin A. de Graaf[5]

Received: 15 March 2019 | Revised: 29 October 2019 | Accepted: 7 November 2019
DOI: 10.1002/nbm.4236

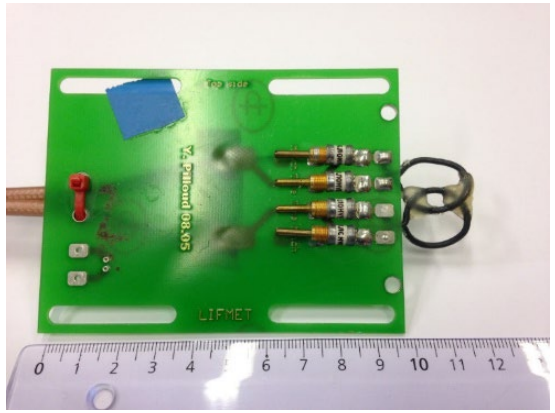
SPECIAL ISSUE REVIEW ARTICLE

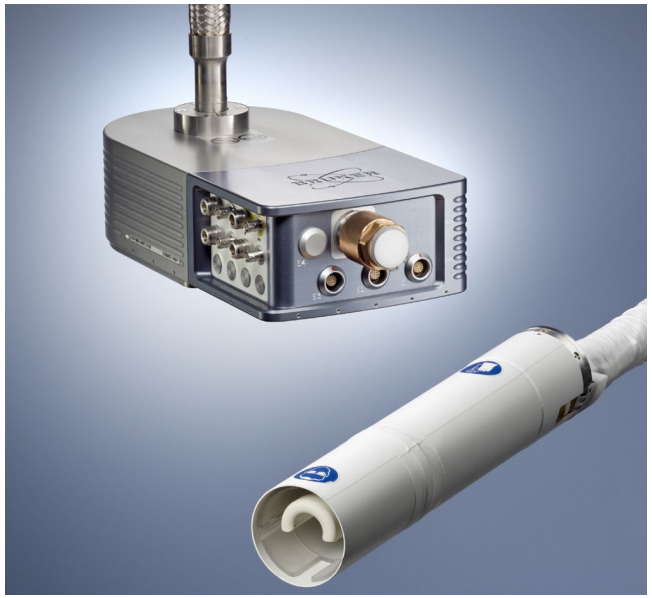
WILEY NMR IN BIOMEDICINE

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

Gülin Öz[1] | Dinesh K. Deelchand[1] | Jannie P. Wijnen[2] | Vladimír Mlynárik[3] | Lijing Xin[4] | Ralf Mekle[5] | Ralph Noeske[6] | Tom W.J. Scheenen[7,8] | Ivan Tkáč[1] | the Experts' Working Group on Advanced Single Voxel ^{1}H MRS

RF COILS





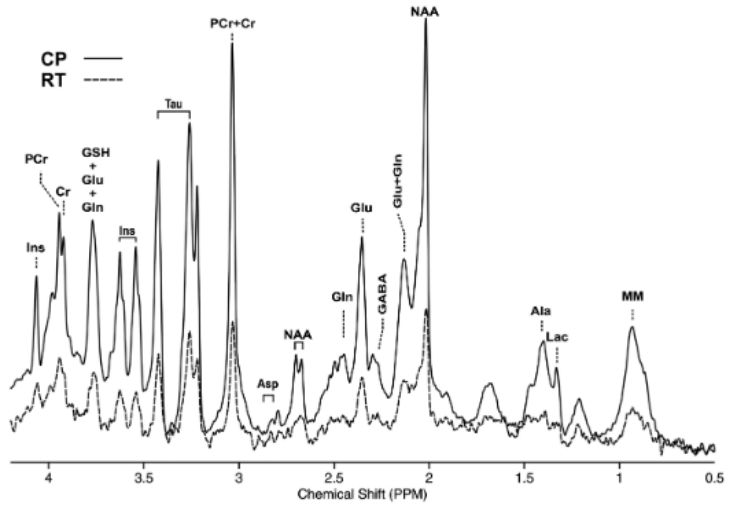


FIGURE 1 Spectra acquired with the STEAM sequence (TR/TE = 5000/3.5 ms, 384 averages) in a 2.0 × 1.1 × 2.0 mm^3 VOI located in the mouse frontal cortex. A cryogenically cooled ^1H two-element phased-array transmit/receive coil was employed for excitation and signal reception (solid line). As a comparison, a 72 mm diameter birdcage quadrature volume resonator was used for excitation and a ^1H receive-only 2 × 2 surface array coil was used for signal reception (dotted line). A 5.2-fold higher SNR was obtained with the cryoprobe (CP) compared with the room-temperature probe (RT)

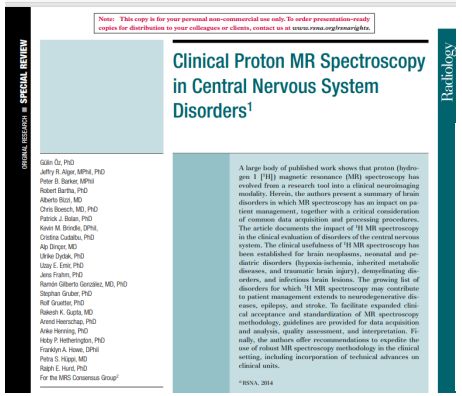
Received: 11 November 2019 | Revised: 29 March 2020 | Accepted: 30 April 2020
DOI: 10.1002/nbm.4325

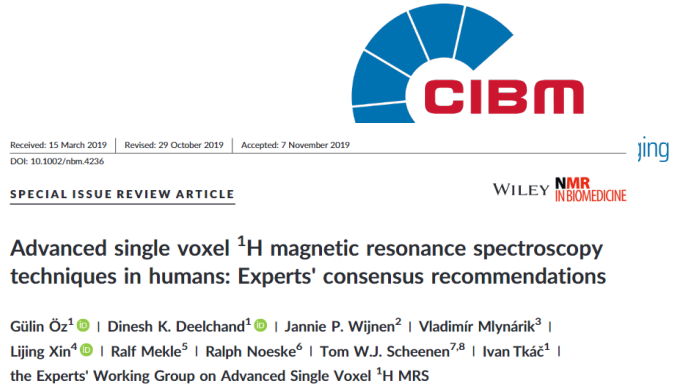
SPECIAL ISSUE REVIEW ARTICLE

NMR IN BIOMEDICINE WILEY

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

MINIMUM QUALITY CRITERIA





Signal

- SNR >3 for major resonances
- Linewidth - shimming
- Lineshape – symmetric
- WS
- No lipid contamination
- No other visible artifacts
  - Not so obvious artifacts (Chemical shift artifact, localization inaccuracies, signal cancellation, etc)

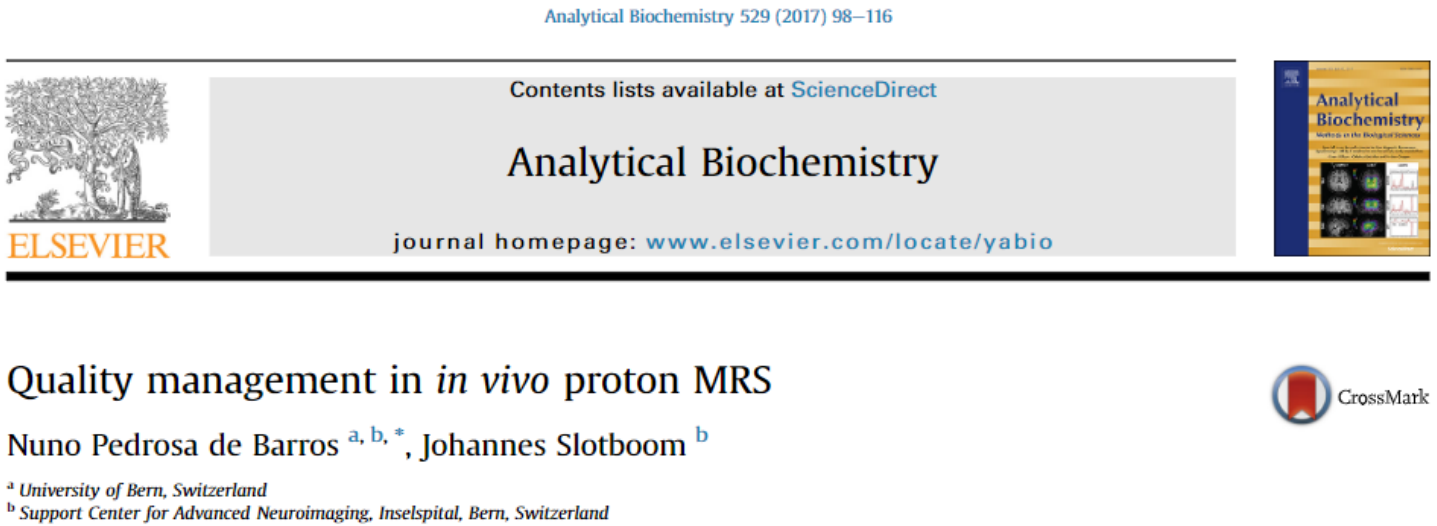
Quantification

- CRBs
- Residuals with unexplained features

ISMRM 2010, Potentials and Challenges at High Field MRS
R Kreis, NMR Biomed 2004, 17:361
Tkáč I, et al, Appl Magn Reson. 2005 29:139.
http://www.ismrm.org/workshops/Spectroscopy16/program.htm
2nd TRANSACT Workshop, University Bern: Quality Issues in Clinical MRS 2014
The MRS Consensus Group. (2014), Radiology, 270(3):658-79.

QUALITY CONTROL

- **Quality Control – detection of artifacts (rejection or correction)**
  - **Signal Quality Control**
  - **Quantification Quality Control**
  - **Automatic (semi-automatic)**



Analytical Biochemistry 529 (2017) 98–116

Contents lists available at ScienceDirect

Analytical Biochemistry

journal homepage: www.elsevier.com/locate/yabio

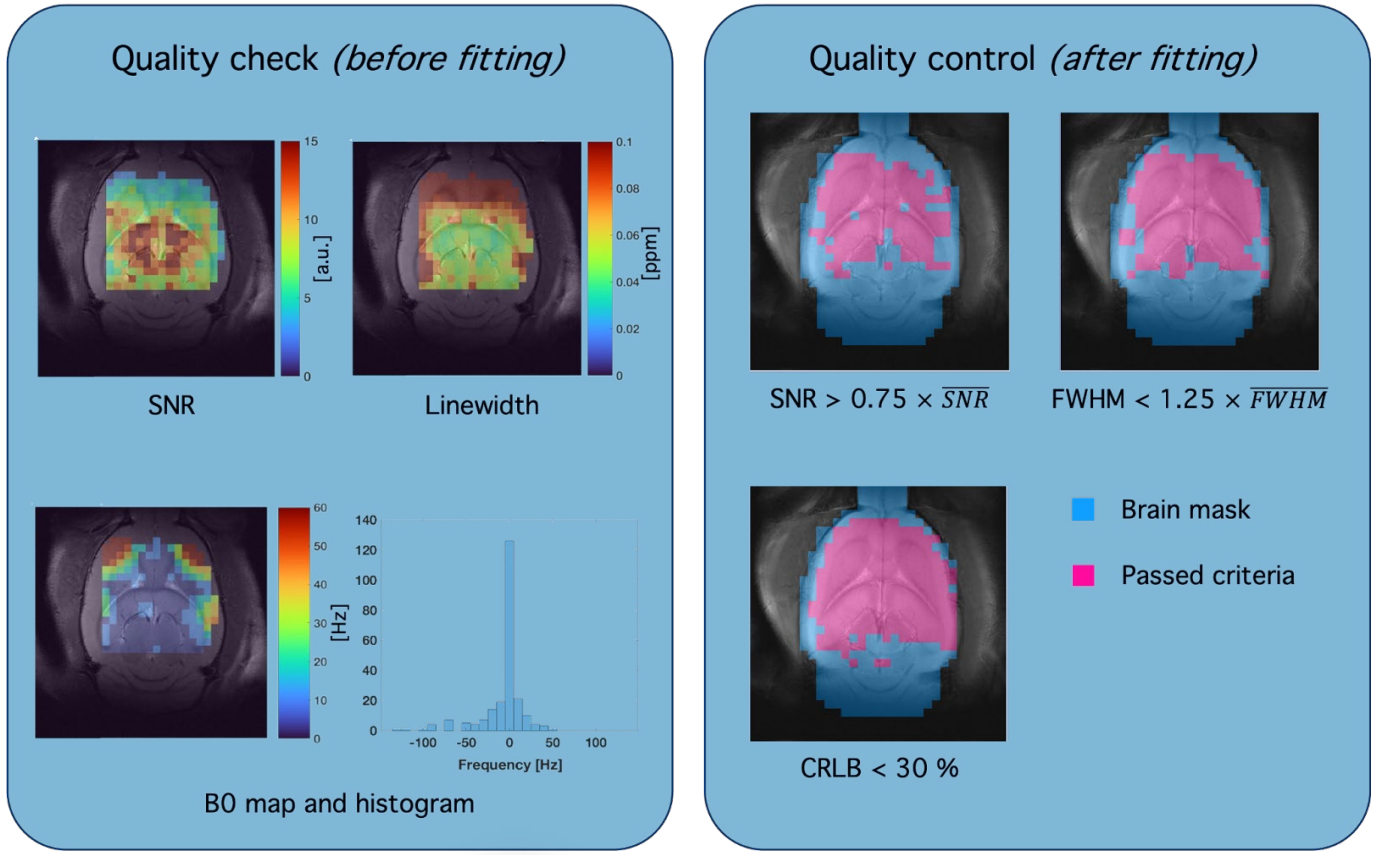
Quality management in *in vivo* proton MRS

Nuno Pedrosa de Barros [a, b, *], Johannes Slotboom [b]

[a] University of Bern, Switzerland
[b] Support Center for Advanced Neuroimaging, Inselspital, Bern, Switzerland

N Barros et al, Analytical Biochemistry, 2017

MRS4BRAIN TOOLBOX : MRSI (QUALITY CONTROL)



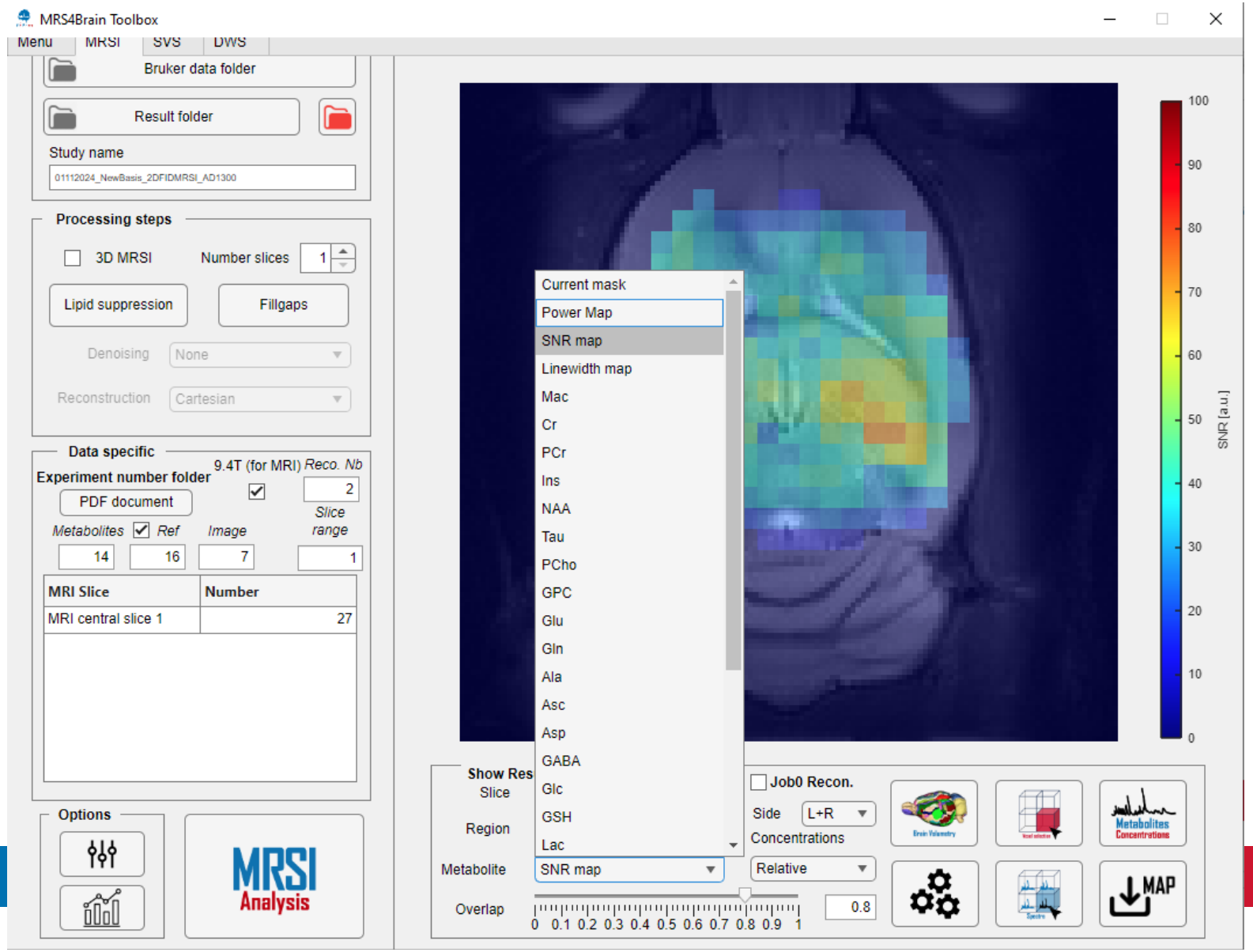
- 4 Quality Metrics reported : Signal-to-noise ratio (SNR), linewidth (lw or FWHM), B_0 shift & Cramer Rao lower bound (CRLB)
- Quality check before fitting (no masking)
- Quality control after fitting (masking of unwanted data)

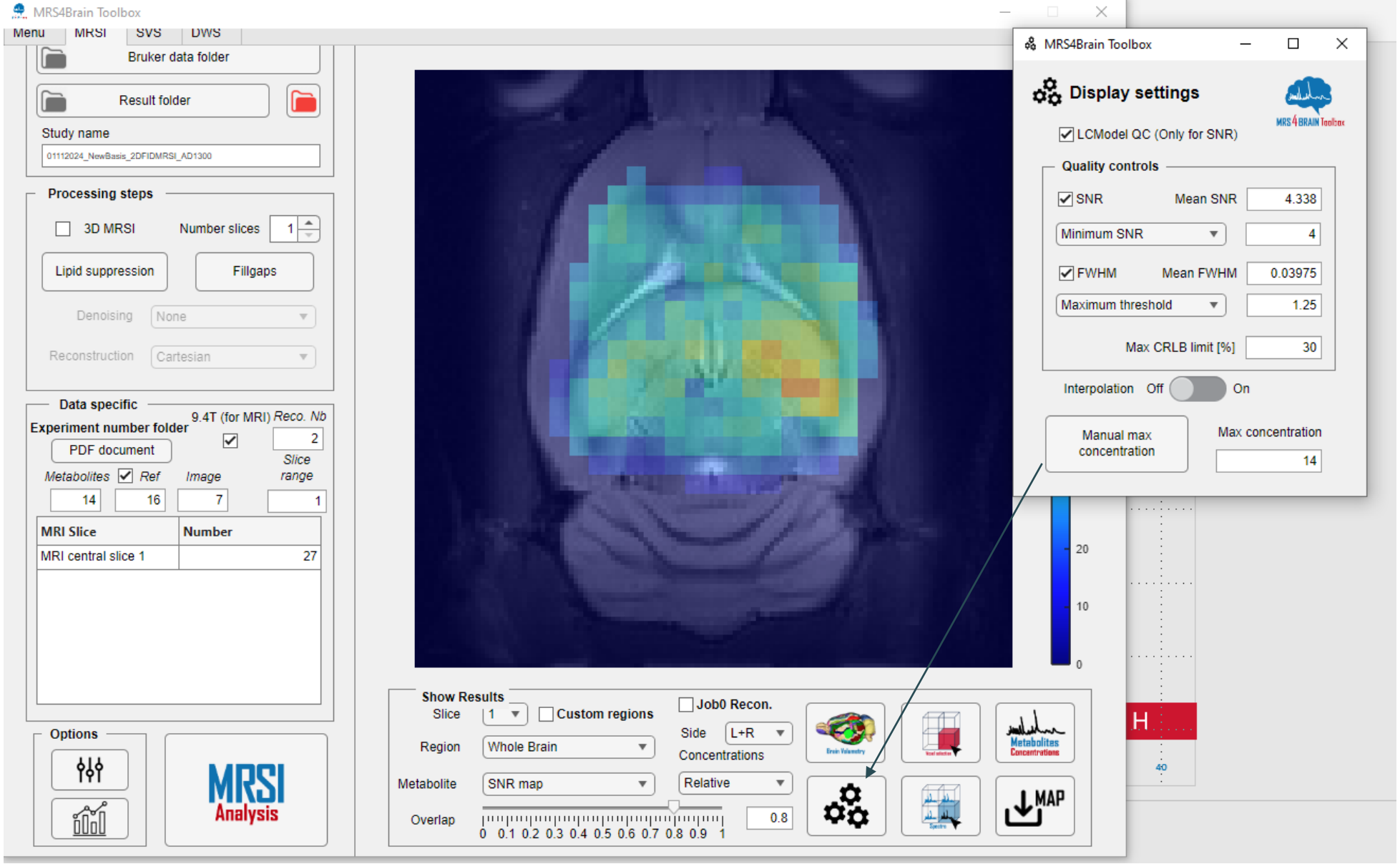
See all video recordings available on gdocs

MRS4BRAIN Toolbox

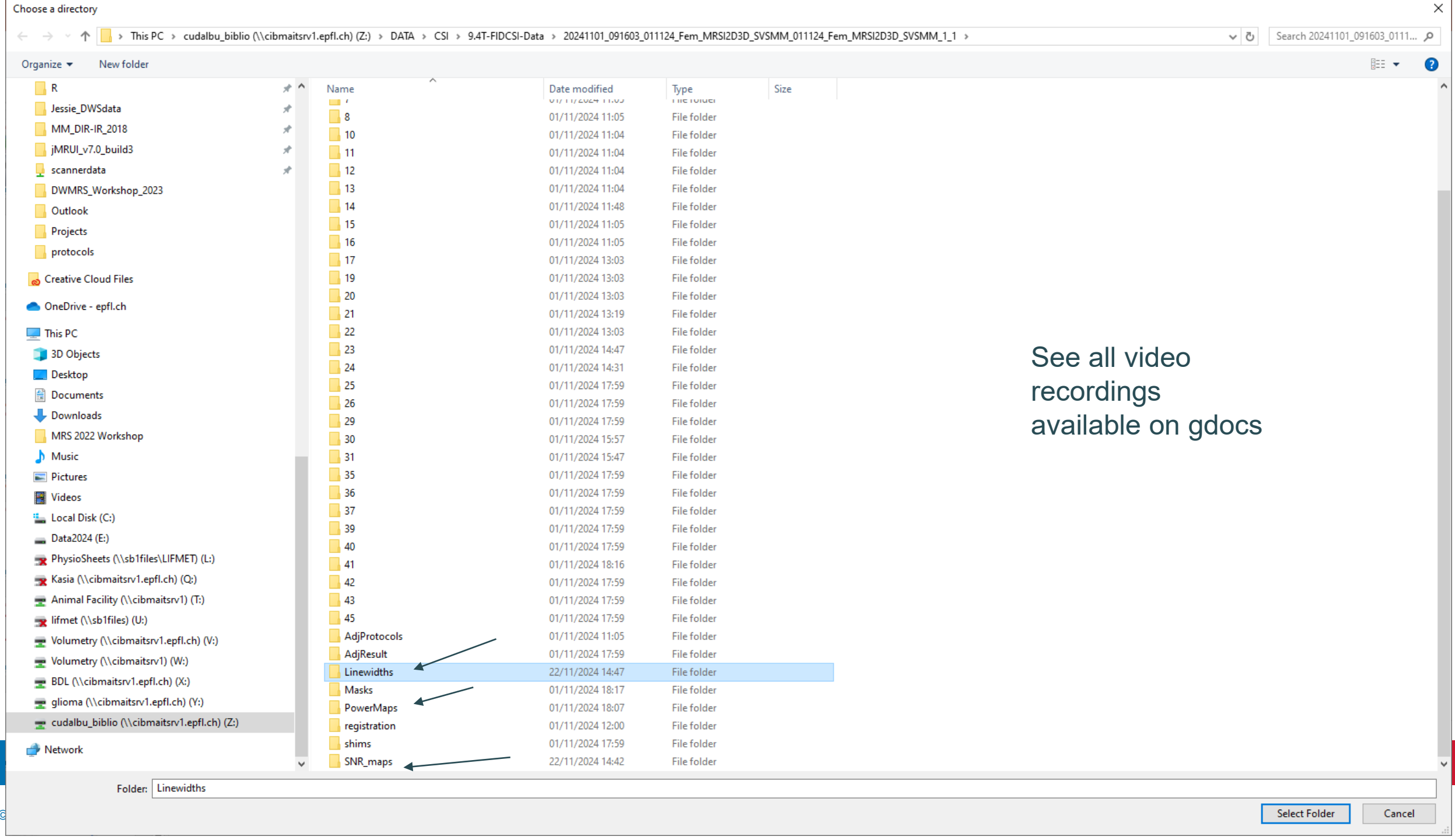
QUALITY CONTROL IN MRS4BRAIN TOOLBOX

See all video recordings available on gdocs





See all video recordings available on gdocs



See all video recordings available on gdocs

PREPROCESSING STEPS

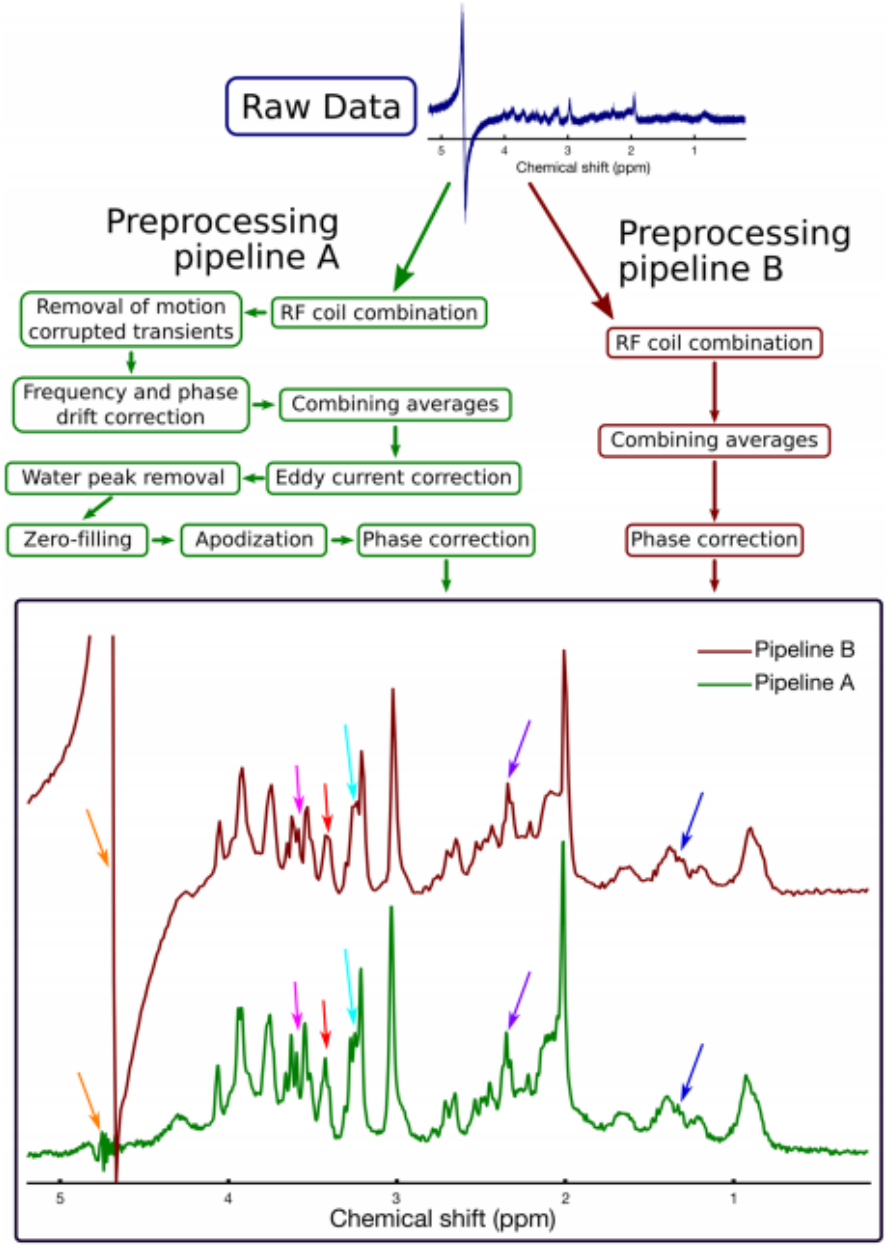
- Phase offsets (0 and 1st order)
- Subject motion
- Scanner drift
- Eddy currents
- Alignment of spectra that need to be added/subtracted
- Water contamination
- …..

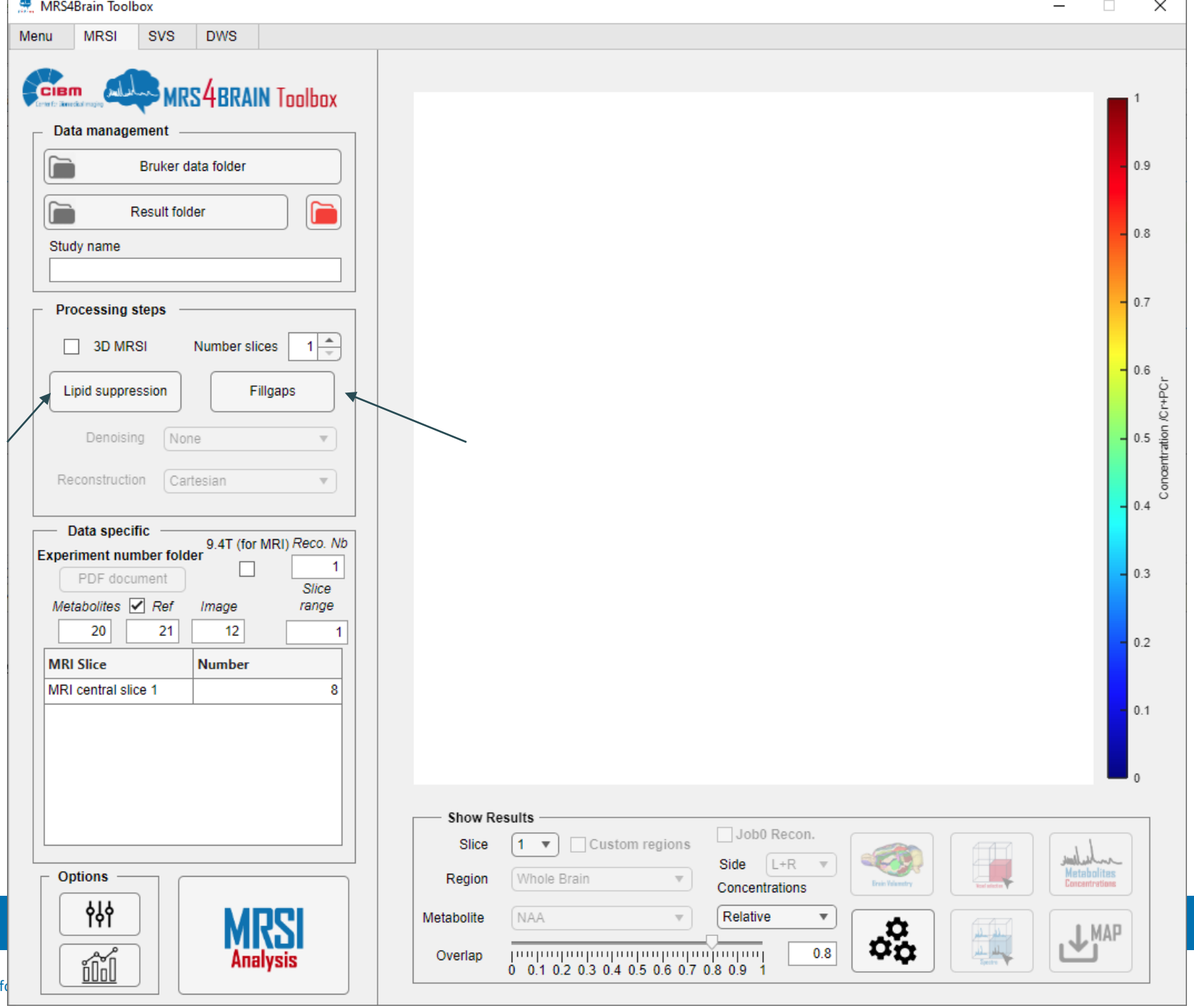
PREPROCESSING STEPS

- Why ?
  - quantification algorithms do not account for all of them
  - Lead to errors in the quantification process

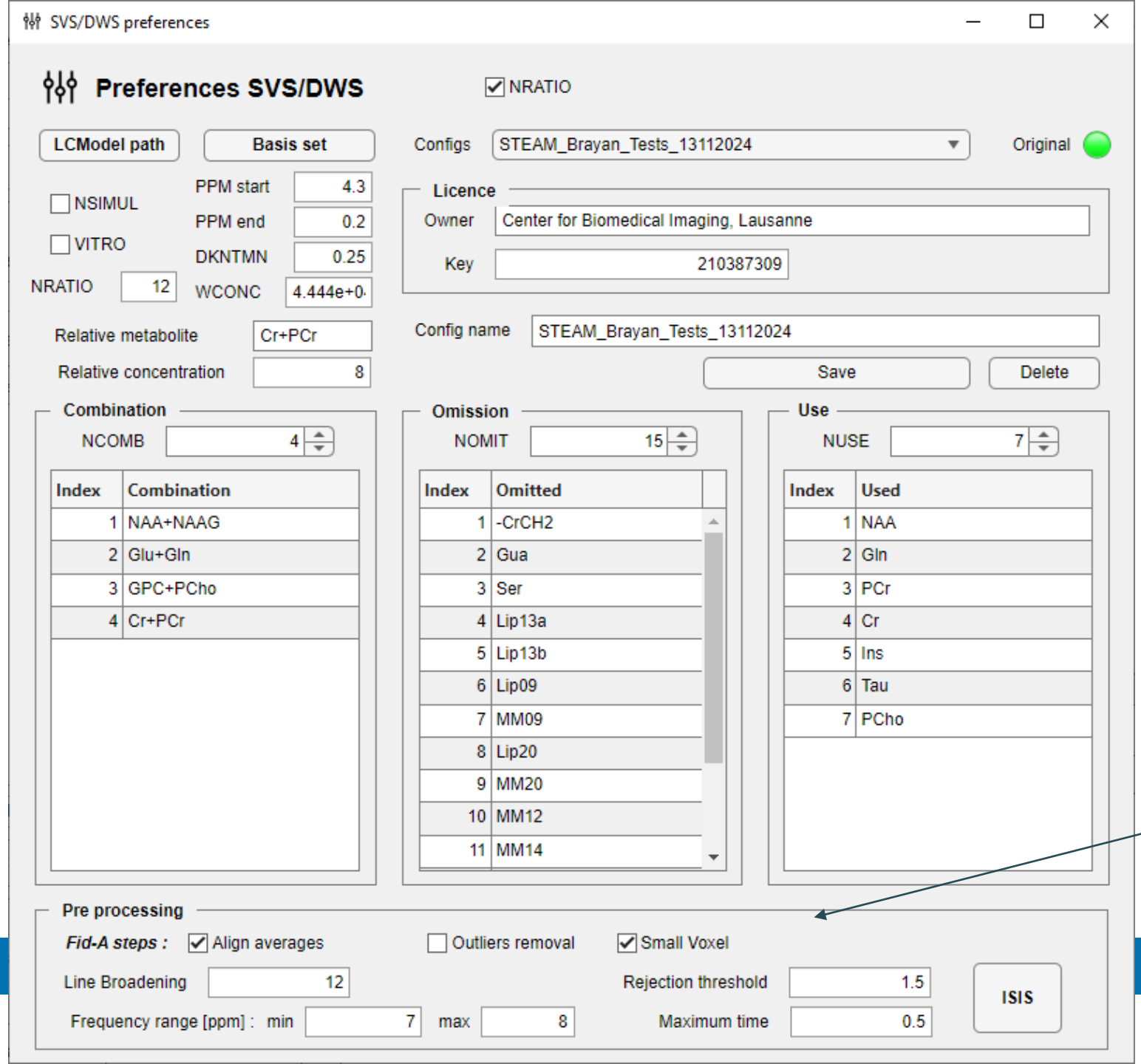
- Requirements:
  - Automated methods
  - Included in the quantification software

FIGURE 4 Illustration of two example processing pipelines, applied to the same raw data. The dataset was obtained from a rat brain using the PRESS sequence at 7 T with T_E = 11 ms. Processing pipeline B (dark red boxes, right-hand side) includes only basic steps to combine the coils and transients (similar to the standard processing pipeline provided by clinical scanner vendors). Processing pipeline A (green boxes, left-hand side) involves additional steps to remove motion-corrupted averages, to retrospectively correct frequency and phase drift, and to remove eddy current artefacts. Pipeline A resulted in several noticeable improvements in spectral quality, including reduced water contamination (orange arrows), and improved visual definition of most spectral peaks, including lactate (1.3 ppm, dark blue arrows), glutamate-H4 (2.3 ppm, purple arrows), tCho (3.2 ppm, light blue arrows), taurine (3.4 ppm, red arrows) and *myo*-inositol (3.5 ppm, pink arrows). These improvements highlight the importance of using an appropriate processing pipeline. Note that, as stated in the recommendation tables, zero-filling and apodization may be used to improve the visual appearance of the spectrum, but should not be performed prior to spectral analysis

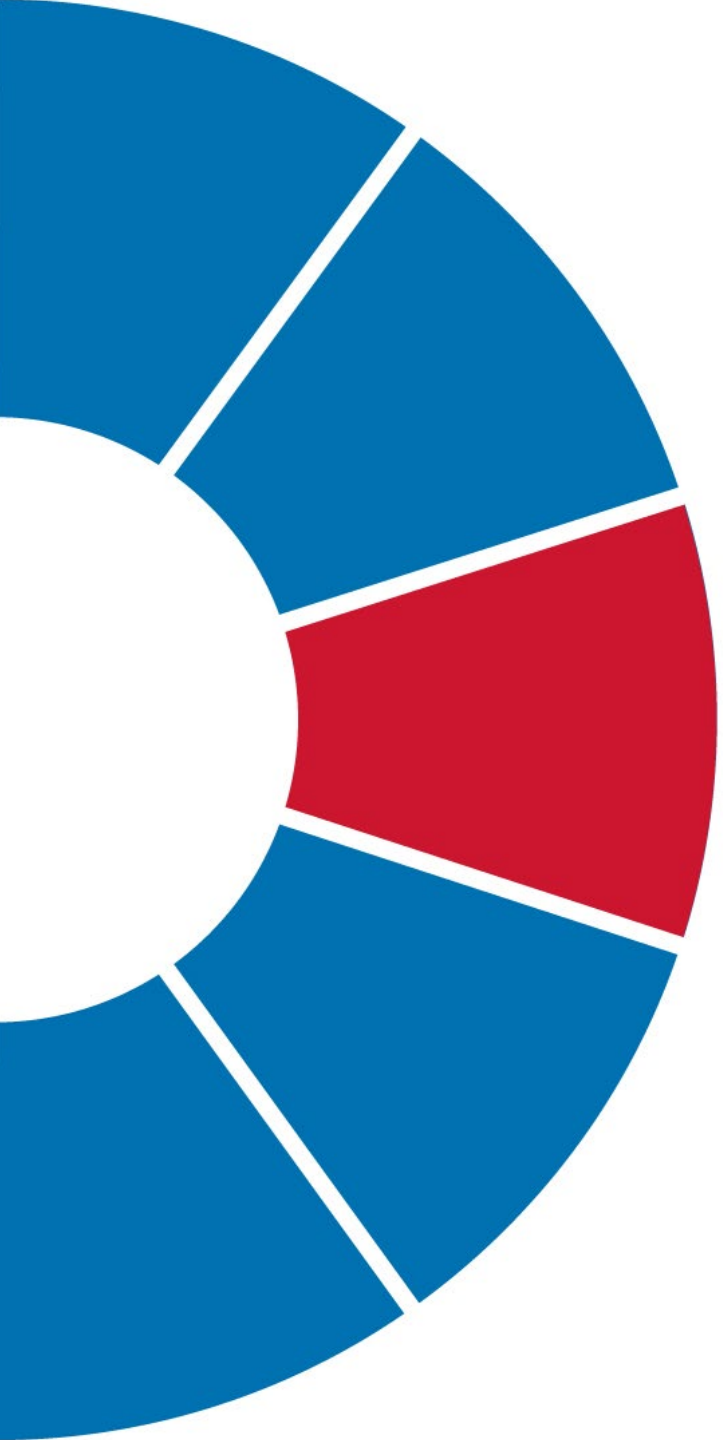




See all video recordings available on gdocs



See all video recordings available on gdocs

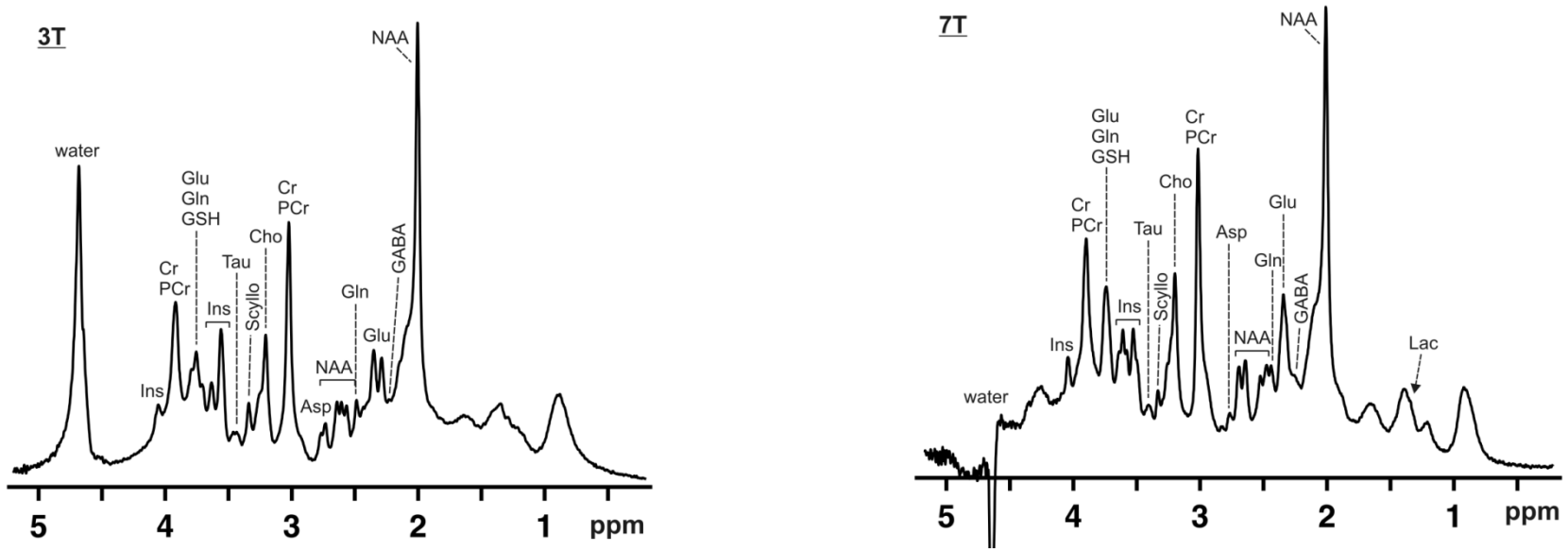


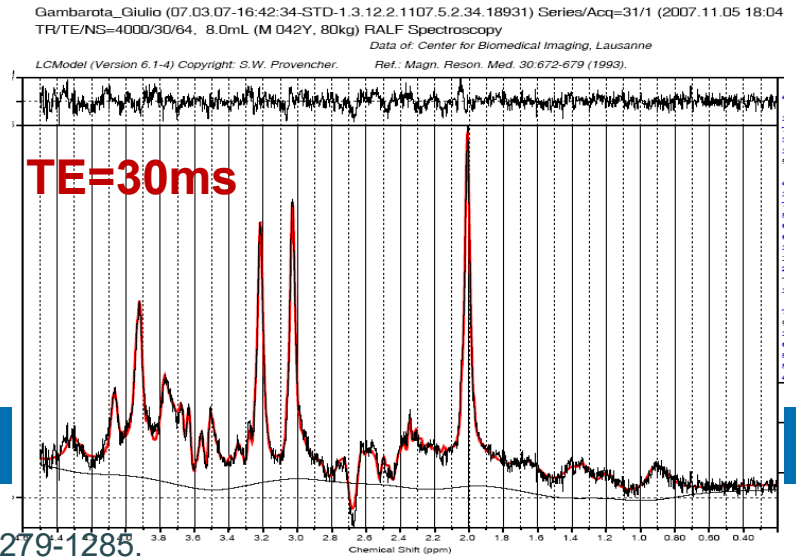
QUANTIFICATION SOFTWARE

QUANTIFICATION

- MRS – principal goal – quantification of changes in concentration of known metabolites
- Accurate and precise quantification:
  - Signal quality
    - Hardware performance
    - Pulse sequence design & adjustment
  - Data (pre)processing (estimate the signal amplitude or peak area)
  - Quantification strategies (→ tissue content)
- Final Goal:
  - Maximize the neurochemical information
  - Increase the precision and accuracy of quantification
  - Maximize the reliability of neurochemical data

QUANTIFICATION





Merkle R, et al. Magn Reson Med 61, 1279-1285.

QUANTIFICATION

Signals are different (acq param, Bo, nucleus, etc)

– quantification is also different

THE ALGORITHMS ARE AUTOMATIC
BUT NOT FULLY PUSH-BUTTON
NEED TO BE ADAPTED

QUANTIFICATION

In vivo spectra - high B_0

- short TE

→ Increased - sensitivity
- spectral resolution

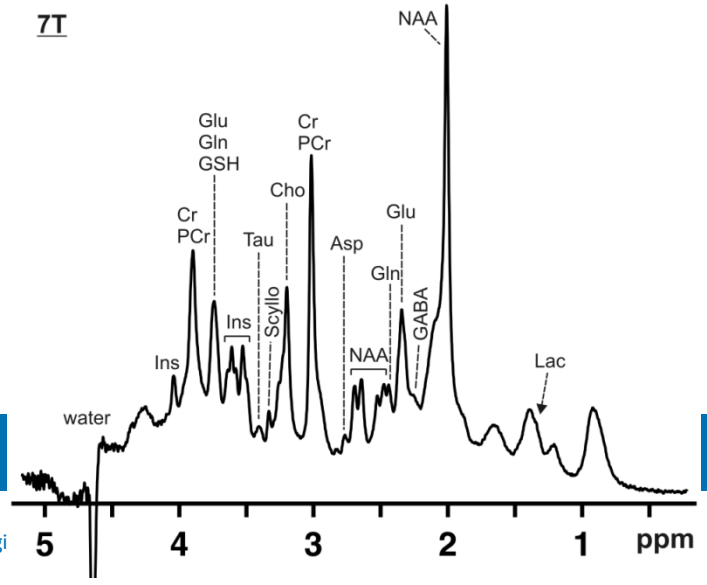
is difficult:

- Complexity of the spectra:
  - many resonances
  - peak overlap
  - contribution of macromolecules and residual water
- Unpredictable lineshape :
  - residual eddy currents
  - field inhomogeneity
- Unpredictable baseline:
  - macromolecules
  - lipid signals
  - partially suppressed water

QUANTIFICATION

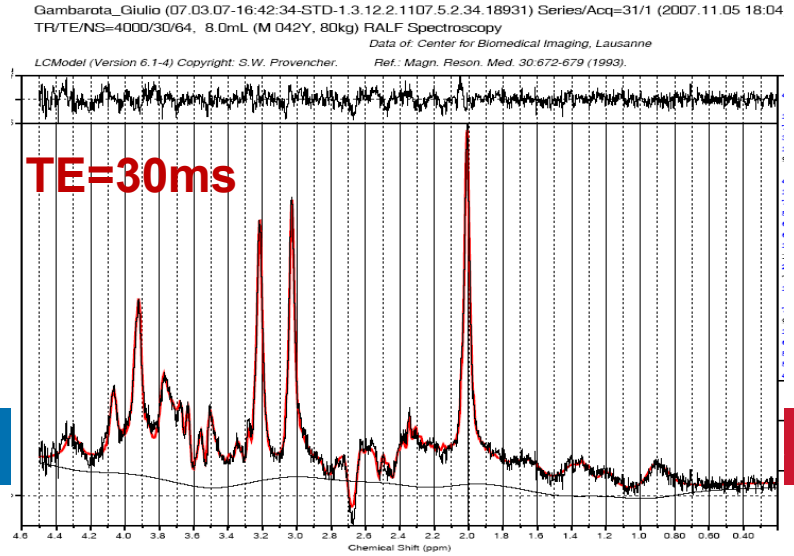
In vivo spectra - high B_0

- short TE



Increased - sensitivity

- spectral resolution



Ralf Mekle & Giulio Gambarota

QUANTIFICATION

☹Vendors software - visualization of spectra

☹Peak fitting - !!!! Overlapping peaks ☹

☺X nuclei

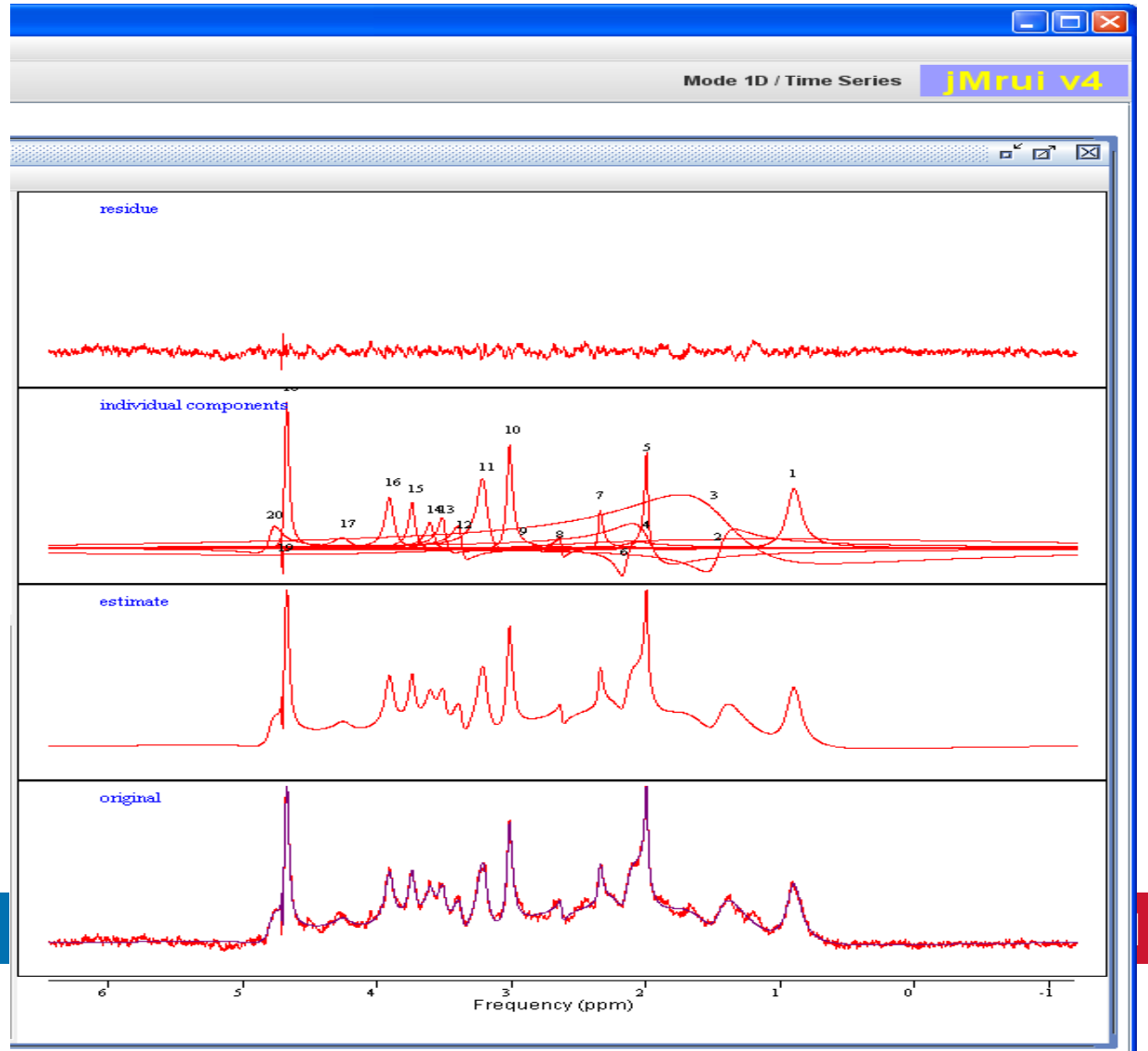
☺"Basis-set" fitting – In vivo MRS spectrum is modelled as a linear combination of individual metabolite basis spectra

- Experimentally
- Simulated
  - User-friendly software packages: NMRScopeB, Vespa, GAMMA, GAVA, ….
- Macromolecules contribution
- Lipids contribution (i.e. malignant brain tumors)

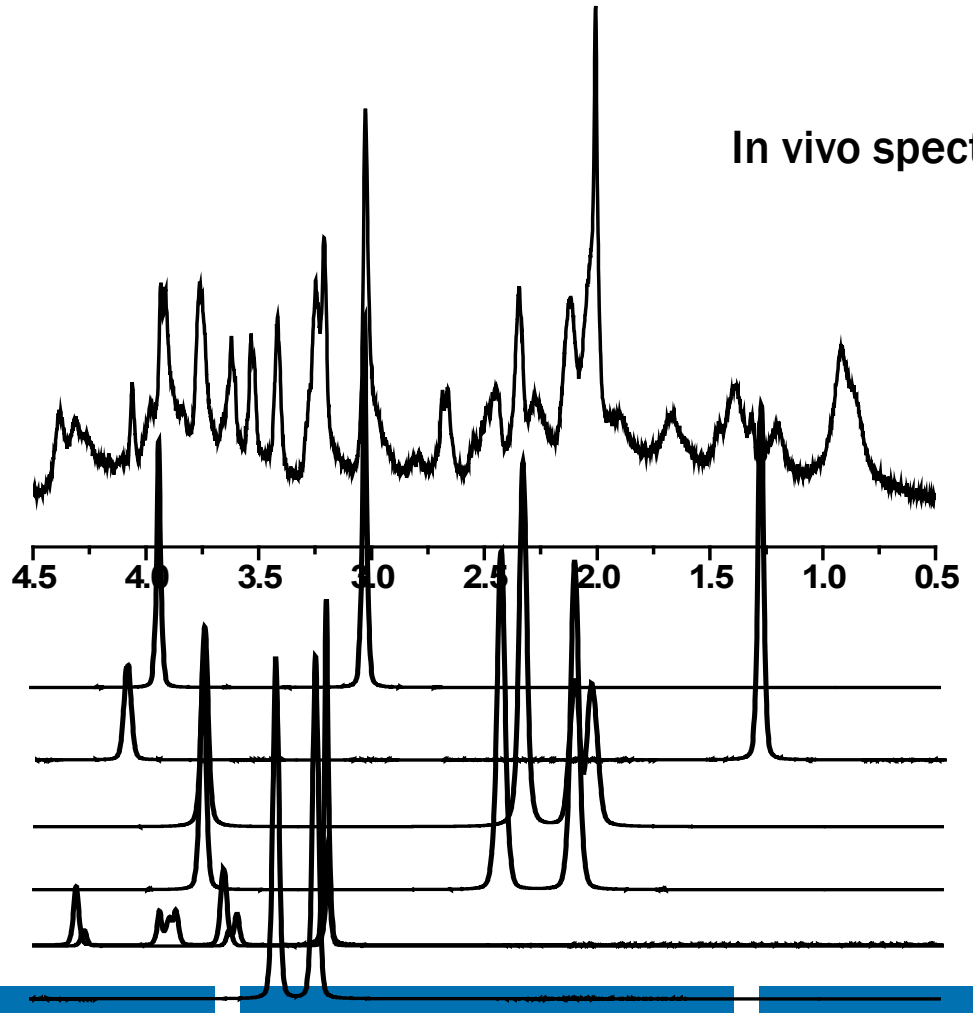
SHORT DESCRIPTION OF THE ALGORITHMS

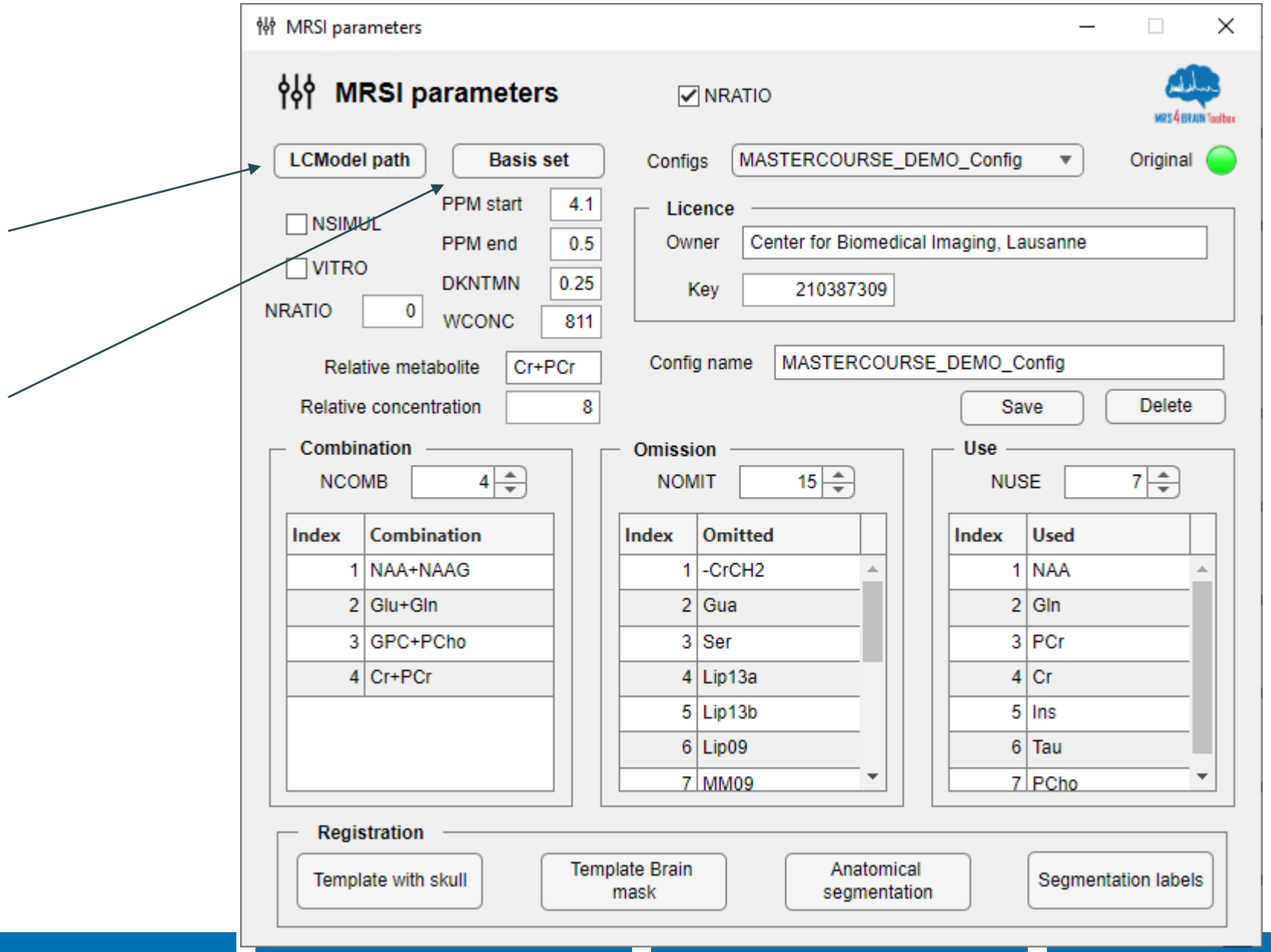
HLSVD quantification

Amplitude	sd. Amp.
666.88	0.2707
676.74	0.1729
333.53	2.40
140.71	0.6707
1.971E4	0.9626
1.111E3	3.45
1.455E3	2.14
479.78	138.56
475.13	34.35
420.84	46.61
551.35	18.94
837.73	11.91
351.08	226.13
1.112E3	0.2797
33.12	0.0265
614.40	0.0191



QUANTIFICATION WITH A BASIS SET



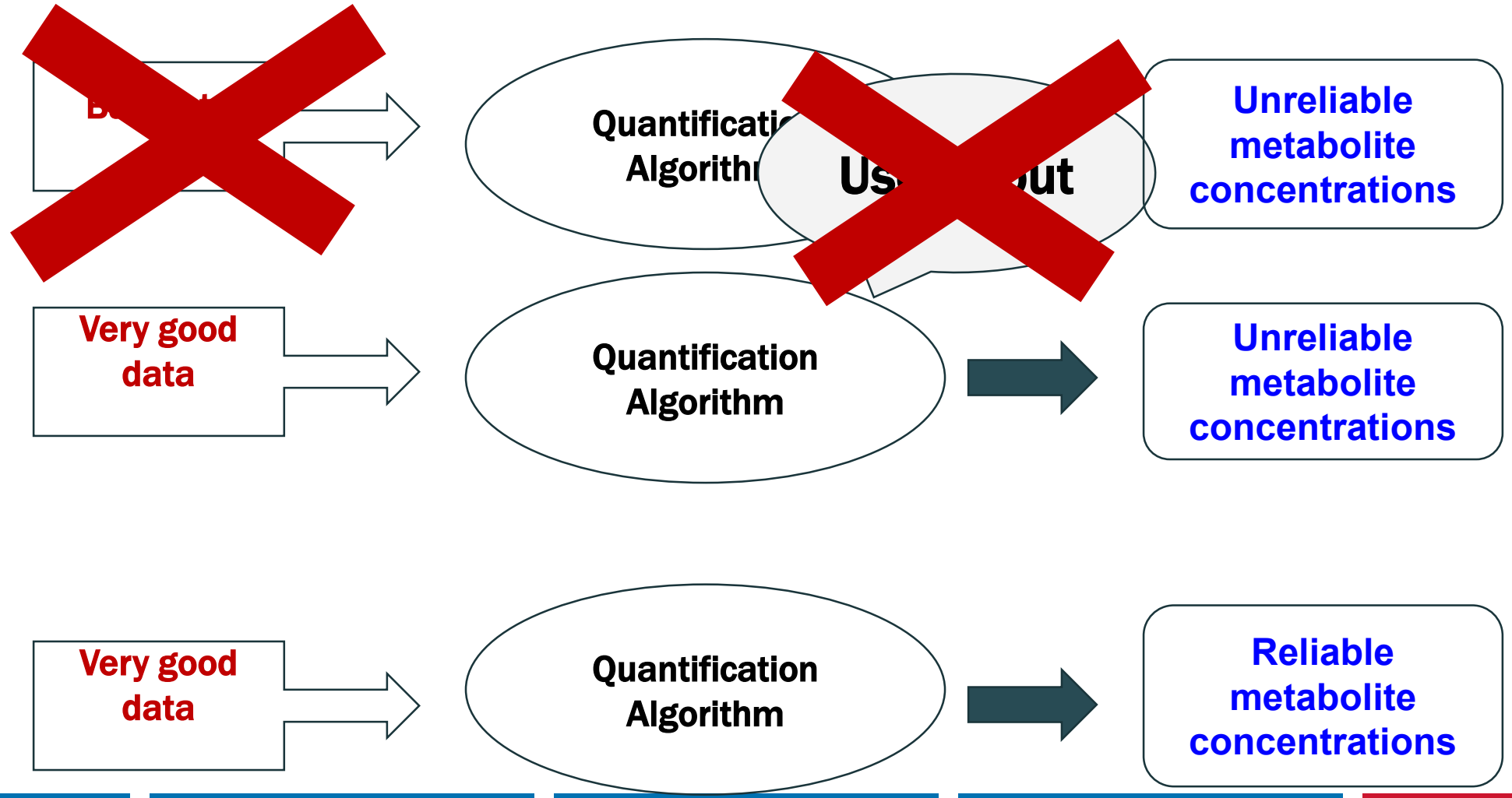


See all video recordings available on gdocs

QUANTIFICATION SOFTWARE

	Cost	Type of data	Preprocessing	Simulations	Lineshape model	MM
Vespa	free	all	yes	yes	yes	yes
TARQUIN	free	all	yes	Yes – basic	Voigt	Baseline –TD Add
jMRUI	free	all	yes	yes	Lorentzian	Add TD
LCModel	Yes	all	yes	No Basis sets	estimated	Splines

Anke Henning. eMagRes, 2016, Vol 5: 981–994. DOI 10.1002/9780470034590.emrstm1472
Dirk van Ormondt, et al, eMagRes, 2015, Vol 4: 651–662. DOI 10.1002/9780470034590.emrstm1427
Jamie Near, Magnetic Resonance Spectrscopy Elsevier 2014
Jamie Near, et al, NMR Biomed, 2020 **https://doi.org/10.1002/nbm.4257**



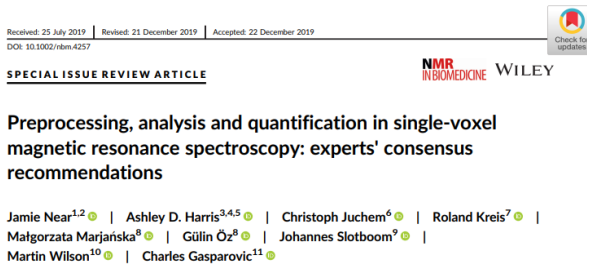
QUANTIFICATION (ABSOLUTE)

Signal amplitudes
Peak area

→

Concentrations
mmol/kg$_{ww}$

- External concentration reference
- Internal concentration reference
  - Ratios to tCr or NAA or Cho - They might change – disease
  - Water internal reference
    - Corrections for T1, T2 and water content
    - Very short TE – T2 correction could be neglected
    - Fully relaxed signals – long TR – T1 neglected
    - MT


Received: 25 July 2019 | Revised: 21 December 2019 | Accepted: 22 December 2019
DOI: 10.1002/nbm.4257
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]

http://www.ismrm.org/workshops/Spectroscopy16/program.htm
2nd TRANSACT Workshop, University Bern: Quality Issues in Clinical MRS 2014
The MRS Consensus Group. (2014), Radiology, 270(3):658-79.

QUANTIFICATION QUALITY CONTROL

- CRLB – theoretical estimation
  - Assumes that the model is perfect
  - R Kreis, MRM 75, 2016 – CRLB % !!! – low conc metabolites
    - CRLB vs mean CRLB in normal cohort

- Fit residuals

QUANTIFICATION: RESULTS DISPLAY

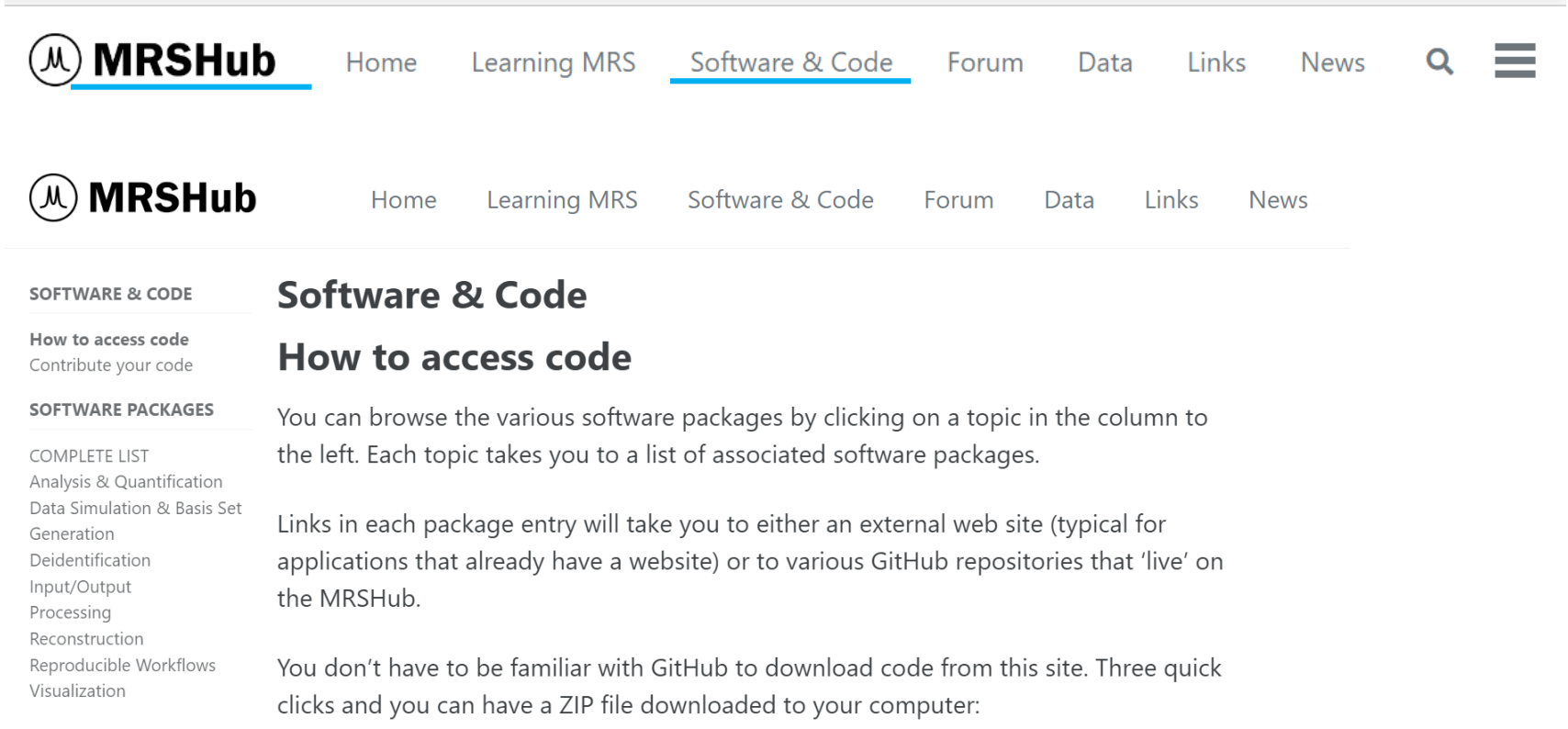
Patient name : anonymous Date of Birth : Patient sex : M Patient ID :	Accession number : 2699671 Study description : Kopf_12_Kanal Study date : 20110630	Series description : svs_se_135_ws Series number : 12 Series time : 155149.015000	Scanner type : Verio Echo time TE : 135000 Repetition time TR : 1500000 Voxel dimension : [15, 15, 15]

Metabolite Name	Concentrations (2 comp) [mmol/kg ww]	Normal (2 comp) [mmol/kg ww]
Choline (Cho)	8.8 ± 0.1	1.5 ± 0.1
Creatine (Cr)	7.7 ± 0.2	5.2 ± 0.1
Glutamate (Glu)	6.6 ± 0.4	3.7 ± 0.2
Glutamine (Gln)	4.4 ± 0.3	2.2 ± 0.1
Lactate (Lac)	1.2 ± 0.2	0.3 ± 0.1
Myo-inositol (m-Ins)	20.7 ± 1.2	7.8 ± 0.4
N-Acetyl Aspartate (NAA)	4.9 ± 0.2	7.5 ± 0.2

For scientific purposes only!
Report created with jMRUI.

Olivier Scheidegger et al, MRM 70:25–32 (2013)

FURTHER READING



SUMMARY & ACKNOWLEDGMENTS

MRS & MRSI is incredibly rich & versatile ☺

Thank you for listening! Questions?

For any question yon might have later on, please write me an email:

cristina.cudalbu@epfl.ch

CIBM
Center for Biomedical Imaging

THANK YOU FOR YOUR ATTENTION

CHUV
UNIL | Université de Lausanne
EPFL
UNIVERSITÉ DE GENÈVE
HUG Hôpitaux Universitaires Genève

CIBM.CH