I. Introduction to MRS
Glutamate

GABA

Lactate

NAA
Glutamate + 15 other metabolite “fingerprints”
Many uses of MRS

Proton MRS for metabolic profile

Phosphorus MRS for oxidative phosphorylation

Carbon MRS for TCA cycle dynamics

Deuterium MRS for glucose metabolism


Gordon et al MRM 81(4) 2702-2709

Henk M. De Feyter et al. Sci Adv 2018;4:east7314

1H T2W
Pyruvate
Lactate
Bicarbonate
Visible Neurochemicals

- Water ~10000 times larger
- Lipids – artefactual or pathological

✓ Metabolites with >1 mM concentration
✓ “Macromolecules”: amino acid residues & peptides

✗ Solids, proteins, bound substrates.
✗ Low concentration (<1 mM)
The in vivo spectrum
<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N-acetylaspartate (NAA)</strong></td>
<td>• Present only in neurons (not glia)</td>
</tr>
<tr>
<td></td>
<td>• Biomarker for neuronal integrity</td>
</tr>
<tr>
<td><strong>Lactate (Lac)</strong></td>
<td>• Indicates anaerobic glycolysis</td>
</tr>
<tr>
<td></td>
<td>• Complex, dynamic metabolism.</td>
</tr>
<tr>
<td></td>
<td>• Tricky to monitor by MRS</td>
</tr>
<tr>
<td><strong>Total creatine (tCr: Cr + PCr)</strong></td>
<td>• Energy buffering</td>
</tr>
<tr>
<td></td>
<td>• Often a static reference, except in metabolic disorders</td>
</tr>
<tr>
<td><strong>Myo-inositol (mIns)</strong></td>
<td>• (Disputed) marker for gliosis</td>
</tr>
<tr>
<td></td>
<td>• Varied physiological uses and variations in pathology.</td>
</tr>
<tr>
<td><strong>Total Choline (tCho: PCho + GPC)</strong></td>
<td>• Marker of cellular proliferation, membrane turnover, inflammation.</td>
</tr>
<tr>
<td><strong>Glutamate (Glu) + GABA</strong></td>
<td>• Primary neurotransmitters</td>
</tr>
<tr>
<td></td>
<td>• Glutathione (GSH)</td>
</tr>
<tr>
<td></td>
<td>• Oxidative stress in astrocytes</td>
</tr>
</tbody>
</table>

See
2) De Graaf RA. In Vivo NMR Spectroscopy: Principles and Techniques. Chapter 2
Equipment

- Same scanner
- Same coil hardware

Different sequences
Additional training
Spectroscopy pulse sequences

- $k_x$ and $k_y$
- Time
- Fourier Transform
- Fourier Transform
- Brain images
- Chemical shifts:
  - NAA
  - GABA
  - Ala
  - Lac
  - Cr
  - Glx
  - Tau
  - Asp
Single Voxel Spectroscopy (SVS)

- Single spectrum acquired from one volume
- 2-3 cm isotropic size, ~5 min acquisition
- Examples: PRESS, **STEAM**, Semi-LASER
- Three intersecting slice selective pulses.
MR Spectroscopic Imaging (MRSI)

- Spectra collected from many voxels
- Resolution is 0.5 - 1 cm in-plane
- Long (5-15 min) acquisition
- Examples: CSI, EPSI, CRT
Water suppression

- Water signal >> metabolite signal
- Selective suppression used to remove water
- Reduces baseline distortion

![Graph showing water suppression effect](image)

- Water suppression module placed before SVS sequence
- Distortion from water signal
Outer volume suppression

High concentration lipids present in dura and skull.
Inner volume selection

Use SVS localisation to only excite signal from brain tissue.
Outer volume suppression

Use saturation bands to suppress signal outside brain.
A quick pause for questions

Up next: Pre-processing
FSL-MRS – Tools for Magnetic Resonance Spectroscopy

II. MRS pre-processing
SVS: before pre-processing

Uncombined coils

Un-averaged repeats

Data shape - $N_{\text{Time Points}} \times N_{\text{Averages}} \times N_{\text{Coils}}$
Pre-processing should:

1) Maximise signal-to-noise ratio (SNR)
2) Minimise peak linewidths
3) Reduce baseline and line shape distortion
The water-reference

Very high SNR water signal experiences (almost) the same acquisition conditions.

Use it for:
- coil combination,
- eddy current correction,
- (sometimes) phase and frequency correction,
- (sometimes) motion correction.

Process identically to preserve scaling
Time domain & frequency domain

Conversion between domains via (inverse) Fast Fourier Transform.
Complex MRS Data

MRS data has two channels:
- Stored as complex data,
- Quadrature relationship (90-degree phase offset).
Coil combination

Combine signals with unknown amplitude + phase weighting. Either:

1. Fit water reference to derive complex weights.
2. Explicit rank = 1 problem, use first principal component of stacked multi-coil data.
Combining repeated scans

Combine tens to hundreds of scans for sufficient SNR.

**BUT** hardware drift and physiological motion causes frequency and phase shifts.

Chemical Shift (ppm)
Combining repeated scans: alignment


Small shifts (approx.) corrected by shifting and phasing individual spectra
Combining repeated scans: alignment
Combining repeated scans: outlier removal

Gross motion leads to an incorrectly positioned voxel, severely degraded shim, or both. Exclude!
Combining repeated scans: averaging

Combine by taking the mean to preserve scaling
Eddy currents = time-dependent magnetic field.

- Easily seen in phase of FID.
- Produces anti-symmetric side peaks in spectrum.
- Corrected by subtracting water reference phase
Dealing with global frequency shifts

Fitting relies on ‘fingerprints’ with known frequencies. Therefore, eliminate large global shifts.

ECC or incorrect identification of water frequency on scanner can introduce shifts.
Residual water removal

Large residual water peak can distort baseline.

Data-driven fitting approach used to identify and remove residual peak.

FID formed into Hankel matrix representation.

\[
H = \begin{bmatrix}
    s[1] & \cdots & s[K] \\
    s[2] & \cdots & s[K+1] \\
    \vdots & \vdots & \vdots \\
    s[M-K+1] & \cdots & s[M]
\end{bmatrix}
\]

Then SVD used to identify peak components.

Peaks in water frequency range removed.
Phase correction: $0^{th}$ order

Zero-order phase = uniform phase term $e^{j\phi_0}$

Correct using complex scalar term $e^{j\phi_0}$

Target purely ‘absorption’ real spectrum for:
1) visualisation and 2) fitting initialisation
Phase correction: 1st order

First-order phase - phase term linear with frequency
Correction applies complex vector $e^{2\pi j \omega \phi_1}$
Equivalent to time shift in time domain.
Alignment of edited spectra

Spectral editing dynamically alters spectrum.

Requires alignment of two spectra based on partial similarity.
MRSI Pre-processing

All FSL-MRS pre-processing tools can be applied per voxel.

Planned features:
• Lipid removal
• Phase correction
• Motion correction
MRS Resources

Volume 34, Issue 5
Special Issue: Advanced methodology for in vivo magnetic resonance spectroscopy
May 2021
Issue Edited by: In-Young Choi, Roland Kreis

NMR in Biomedicine
special issue on MRS methods

Robin de Graaf
YouTube channel & book
youtube.com/c/BasicsOfInVivoNMR

MRS online community.
Ask a question in the friendly forums!
Up next: Fitting + FSL-MRS