Advanced MRI in the Clinic: MR Spectroscopy

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Declaration of Financial Interests or Relationships

- I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.
Disclaimers

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2. References to any commercial product are only for information and do not constitute an endorsement or recommendation.

Objectives

• Understand the physical basis of MR spectroscopy (MRS)
• Recognize the prerequisites to obtaining high quality MRS data in vivo
• Become familiar with clinically-available MRS pulse sequences and their optimization
• Understand common MRS analysis approaches in the clinic
• Recognize common MRS artifacts
• Become familiar with the clinical applications of MRS
• Become familiar with the current best practices for MRS QA
Information Encoding

Larmor equation

\[ \omega = \gamma B \]

Extrinsic factors
- \( B_0 \)
- Magnetic field gradients
- Magnetic field inhomogeneity

Intrinsic factors
- Electron shielding
- J-coupling

Magnetic information encoded in frequency, \( ^{13}\text{C} \), etc.

Information Encoding

Larmor equation

\[ \omega = \gamma B \]

Electron shielding

\[ \delta = B_0 - B, \]
\[ B = B_0 (1 - \sigma) \]
\[ \omega = \gamma B_0 (1 - \sigma) \]

Scalar spin-spin interaction (J-coupling)

Interaction between spins mediated through chemical bonds

Slide courtesy of Ivan Tkáč.
Chemical Shift

\[ \omega_i = \gamma B_0 (1 - \sigma_i) \]

\[ \nu_i = \gamma B_0 (1 - \sigma_i)/2\pi \]

\[ \delta_i = (\nu_i - \nu_{\text{ref}})/\nu_0 \]

Chemical shift reference
Tetramethylsilane (TMS)

- independent of \( B_0 \)
- units: ppm

increased proton shielding

Courtesy of Ivan Tkáč.

J-coupling evolution

180° RF pulse does NOT re-phase evolution due to J-coupling.

**J-coupling evolution**

Choice of TE affects spectral peak appearance of coupled nuclei.

![Diagram of J-coupling evolution](De_Graaf,_Robin_A._In_vivo_NMR_spectroscopy:_principles_and_techniques._John_Wiley&_Sons,_2007.)

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**4 Requirements for Successful MRS**

1. Incredibly homogeneous magnetic field
2. Effective water/fat suppression
3. High-quality localization
4. Robust analysis
Magnetic Field Homogeneity

- MRI requires a homogenous magnetic field. MRS requires an incredibly homogenous field.
- FWHM $\propto 1/T_2^*$ so better homogeneity $\rightarrow$ narrower peaks (i.e. better spectral resolution).
- Narrow peaks are also required for good water suppression.
- Good shimming is critical
  - Figure out which technique works best on your scanner.
  - Repeat the shim and/or re-position the patient if necessary.
  - Use a system with at least 2\(^{nd}\)-order shims.

![Magnetic Field Homogeneity](image)
Water suppression

- Water signal (55M) must be suppressed to accurately visualize metabolite signals (0.5-10mM), even with high-quality digital ADCs.
- Our goal is to suppress the water signal by >98%.
- Relaxation-based methods (e.g. IR prep) are problematic so most clinical techniques use chemically-selective saturation (i.e. FatSat tuned to water).
- CHESS is the most common in the clinic.
- As a general rule, the longer and stronger (i.e. more time and/or SAR), the better the water suppression.

Courtesy of Allen D. Elster, MRIquestions.com

Water suppression

- Fat suppression
  - Fat signal is also often greater than metabolite signals.
  - Fat outside the region of interest can be suppressed with outer volume suppression (OVS).
  - Fat within the tissue of interest can be suppressed with usual methods (IR, FatSat).
Localization

- For a spectrum to aid clinical diagnosis, the location from which it was obtained must be known accurately.
- Surface coil localization was originally used for superficial lesions and cardiac studies, but is no longer common.
- Single voxel spectroscopy (SVS) and multi-voxel spectroscopy (MVS, a.k.a. spectroscopic imaging [SI]) are currently used in the clinic.

Single voxel spectroscopy (SVS)

- Most common technique.
- Simple to acquire and interpret.
- Excellent SNR efficiency.
- Single, localized voxel allows for excellent shimming and, therefore, high-quality spectra.
- Many sequences clinically available.

Courtesy of R. Jason Stafford
**Image Selected In Vivo Spectroscopy (ISIS)**

![Diagram of ISIS pulse sequence](image)

**PROS**
- TE can be made VERY short allowing the detection of metabolites with very short $T_2$ values.

**CONS**
- Many

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**ISIS**

**PROS**
- TE can be made VERY short allowing the detection of metabolites with very short $T_2$ values.

**CONS**
- Many

Stimulated Echo Acquisition Mode (STEAM)

STEAM

Courtesy of Allen D. Elster, MR_questions.com
STEAM

**PROS**
- TE can be made quite short allowing the detection of metabolites with short $T_2$.
- 90° pulses
  - Sharper slice profiles lead to sharper voxel edges
  - Higher bandwidth minimizes chemical shift displacement (discussed later)
  - Lower SAR

**CONS**
- Multiple coherence pathways
  - Result in the need for crushers, which reduce the SNR by an approximate factor of two compared to spin-echoes.
  - Induce polarization transfer effects that can affect J-coupling.

STEAM


Point Resolved Spectroscopy (PRESS)

Courtesy of Allen D. Elster, MRTquestions.com
PRESS

PROS
• Easy to implement and very reliable.
• ~2x the SNR compared to STEAM.

CONS
• Difficult to achieve short TEs (minimum is ~30 ms).
• Refocusing pulses have narrow bandwidths that result in:
  • Less-sharp edges
  • Displacement error
  • Altered amplitudes and phases of J-coupled resonances

Localization by Adiabatic Selective Refocusing (LASER)

**PROS**
- Insensitive to $B_1$ inhomogeneities.
- Minimal chemical shift displacement.
- Excellent SNR and well-defined voxels.

**CONS**
- Difficult to achieve short TEs.
- Very high SAR.
semi-LASER

Mitigates most of the problems with LASER, while keeping most of the benefits of using adiabatic pulses.
**Sequence Recommendation**

For routine clinical use:

1. Try semi-LASER if you have it.
2. If not available, try PRESS (3 T and lower) or STEAM (7 T).


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**Multi-Voxel Spectroscopy (MVS)**

- A larger total coverage area takes the guesswork out of SVS voxel placement and permits “mapping” of metabolite distribution.
- Smaller individual voxels are possible, which leads to higher spatial resolution, but lower SNR and potential spectral contamination from adjacent voxels.
- Acquisition times are usually long, though acceleration techniques are clinically available.
- Difficulties obtaining a good shim/water suppression over the entire region often results in reduced quality.
- MVS sequences are usually just SVS sequences with phase encoding.
**Multi-Voxel Spectroscopy (MVS)**

- Goal is to quantify different metabolites and several software packages are available.
- Spectra are processed (baseline correction, phase correction, apodization, Fourier transform, etc.) and then quantified.
- Some software programs are significantly more advanced than others.

![Diagram of MVS sequence]

*Courtesy of Allen D. Elster, MRIquestions.com*
# MRS Analysis Software

<table>
<thead>
<tr>
<th>Vendor Basic</th>
<th>Vendor Agnostic</th>
<th>Vendor Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comes with the vendor MRS package.</td>
<td>e.g. LCModel, Tarquin</td>
<td>e.g. Syngo, IntelliSpace, READYView</td>
</tr>
<tr>
<td>Often automatic.</td>
<td>Very advanced software with sophisticated fitting algorithms.</td>
<td>Best of both worlds.</td>
</tr>
<tr>
<td>Very simple peak height or integral quantification.</td>
<td>Fully customizable (basis sets, metabolites, processing, etc.).</td>
<td>Rapidly approaching vendor agnostic software in terms advanced features.</td>
</tr>
<tr>
<td>Only a few metabolites can be quantified.</td>
<td>Provide estimates of quantification errors and metrics of spectral quality.</td>
<td>Allows for sophisticated processing, custom metabolites, error estimation, etc.</td>
</tr>
</tbody>
</table>

**Not FDA approved.**

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## A note of caution

![Metabolite Spectra](image)

Are you calculating signal intensity or metabolite concentration?

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Another note of caution

Ionic GBCAs can decrease the choline signal by 0-50%.

MRS Artifacts

- Artifacts in MRS appear very different from artifacts in MRI and are often less conspicuous.
Holes/Spikes in MVS

- Caused by failure of the analysis software's automatic peak assignment.
- More common in lower-quality spectra.
- Sometimes re-processing can correct this.

Peak mis-assignment

- Caused by failure of the analysis software's automatic peak assignment.
- More common in lower-quality spectra.
- Sometimes re-processing can correct this.
Motion artifact

Unusual Peaks
Susceptibility Artifact

- Poor shimming results in wide, short (low SNR), and poorly-separated peaks.
- Strong susceptibility artifacts may arise from air-tissue interfaces, blood products, etc.
- The presence of strong susceptibility gradients may prevent a good shim and, therefore, the acquisition of high-quality spectra.

Poor Water Suppression

- Poor water suppression is usually evidenced by non-linear baselines and low peak SNR, especially above 3.5 ppm.
- Often due to poor shim and more common in MVS (where getting a good shim over the entire volume is challenging).
**Signal Bleed**

- Typically evidenced by the phase difference and broadness of the peak.
- This particular voxel was located very near the skull and sequence/pulse imperfections (and, possibly, patient motion) acquired some signal from the scalp.
- OVS is important.

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**Crusher Failure/Spurious Echoes**

- This ringing was due to failure of the crusher gradients, which resulted in unwanted additional echoes in the FID.
- During processing, these echoes become high-frequency ringing artifacts.
- These artifacts are more common in oblique voxels, but can be suppressed by signal processing (e.g. apodization).
Clinical Applications of MRS

- MR spectroscopy (MRS) is rapidly expanding in the clinic where it is primarily used to quantify metabolites in vivo.
- This metabolic information may enable better diagnoses, personalized treatments, and rapid assessment of treatment response.
- Primary application is oncology and the most consistent indication of malignancy is elevation of choline.

CNS

- MRS is indicated for a variety of neurological conditions
- The most common uses include:
  - Primary diagnosis of brain lesions.
  - Distinguishing recurrent brain tumor from radiation necrosis.
  - Diagnosis of inborn errors of metabolism affecting the CNS.


<table>
<thead>
<tr>
<th>INDICATIONS</th>
</tr>
</thead>
</table>
**CNS**

- **Primary peaks:**
  - Total NAA (2.0 ppm)
    - N-acetylaspartate and N-acetylaspartylglutamate
    - Neuronal marker
  - Total Cr (3.0 ppm)
    - Creatine and phosphocreatine
    - Energy buffer
  - Total Ch (3.2 ppm)
    - Choline, glycerophosphorylcholine and phosphorylcholine
    - Membrane turnover

**CNS**

- **Other peaks:**
  - Glx (glutamine, glutamate)
  - γ-Aminobutyric acid
  - Lactate
  - Lipids
  - Myo- and scyllo-inositol
  - Citrate
  - (D)-2-hydroxyglutarate (2HG)
  - Taurine
  - Glucose
  - Ethanol
  - Mannitol
  - Acetate and succinate
  - Branched-chain amino acids

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Breast

- Breast MRS has 2 primary clinical applications:
  - As a supplement to breast MRI to improve specificity in differentiating benign from malignant lesions
  - Monitoring/predicting treatment response in patients undergoing neoadjuvant chemotherapy
- Choline is usually the metabolite of interest, with elevated levels of choline indicative of active tumor.


Prostate

- Primary peaks:
  - Citrate (2.6 ppm)
    - Accumulates in non-malignant cells
  - Total Cr (3.0 ppm)
    - Energy buffer
  - Polyamines (3.1 ppm)
    - Synthesized by prostate epithelial cells
  - Total Ch (3.2 ppm)
    - Choline, glycerophosphorylcholine and phosphorylcholine
    - Membrane turnover

Non-proton MRS

- Non-proton MRS is still in clinical trials with $^{13}\text{C}$ and $^{31}\text{P}$ closest to routine clinical use.
- $^{13}\text{C}$ and $^{31}\text{P}$ are primarily used for metabolic imaging.
- There is now a clinical hyperpolarizer available for $^{13}\text{C}$ that boosts the signal by 10,000x.

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>Natural abundance (%)</th>
<th>Gyromagnetic ratio (MHz/T)</th>
<th>Relative Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1\text{H}$</td>
<td>99.98</td>
<td>42.58</td>
<td>100.00</td>
</tr>
<tr>
<td>$^{13}\text{C}$</td>
<td>1.11</td>
<td>10.71</td>
<td>1.59</td>
</tr>
<tr>
<td>$^{31}\text{P}$</td>
<td>100.00</td>
<td>40.05</td>
<td>83.30</td>
</tr>
<tr>
<td>$^{23}\text{Na}$</td>
<td>100.00</td>
<td>11.26</td>
<td>9.25</td>
</tr>
<tr>
<td>$^{31}\text{P}$</td>
<td>100.00</td>
<td>17.23</td>
<td>6.63</td>
</tr>
<tr>
<td>$^{39}\text{K}$</td>
<td>93.10</td>
<td>1.99</td>
<td>0.05</td>
</tr>
</tbody>
</table>

31P-MRS

- Changes in myocardial energy metabolism have been implicated in several cardiac disease.
- $^{31}\text{P}$-MRS is a great tool to study in vivo cardiac energetics.
- Specific $^{31}\text{P}$-MRS applications include measuring ATP/ATP flux and CK flux.

13C-MRS

- Currently in clinical trials for prostate imaging.
- Hyperpolarized 13C-pyruvate is injected and its conversion to 13C-lactate is imaged and quantified.

Courtesy of GE Healthcare

MRS QA

- AAPM Report 100 (2010) details recommended MRS acceptance testing using a phantom.
- I personally argue that phantom-based MRS QA alone is insufficient since the phantom poorly emulates both the biochemical milieu and electromagnetic environment found in vivo.


MRS QA

- I would argue that every spectrum from every scan from every patient be verified for quality before being sent to a radiologist.
- This process can be semi-automated and also used for longitudinal monitoring of scanner performance.


- SNR > 3 for major resonances such as high tCho and low tNAA in tumors; SNR > 2 for detection only of important indicator metabolites such as lactate
- Spectral resolution: FWHM of metabolites < 0.1 ppm
- Line shape: symmetric
- Water suppression > 98%
- No lipid contamination from the scalp
- Artifacts (chemical shift artifact, ghosting, patient motion, eddy currents, volume averaging) are absent or minor

Thank you!