Advanced MRI in the Clinic: MR Spectroscopy

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WellSpan York Hospital

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

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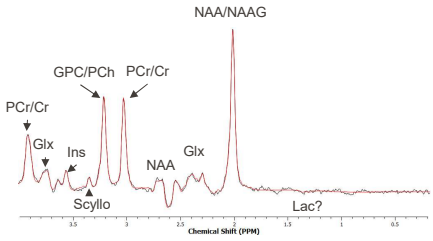
Objectives

- 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



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Information Encoding

Larmor equation

$$\omega = \gamma B$$

Magnetic information encoded in frequency

Fixed for a specific nucleus (^{1}H, ^{13}C, etc.)

Extrinsic factors

- B_0
- Magnetic field gradients
- Magnetic field inhomogeneity

Intrinsic factors

- Electron shielding
- J-coupling

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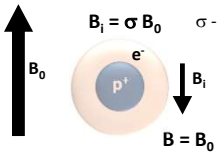
Information Encoding

Larmor frequency $\omega = \gamma B$

Electron shielding

$B_i = \sigma B_0$ σ - shielding constant



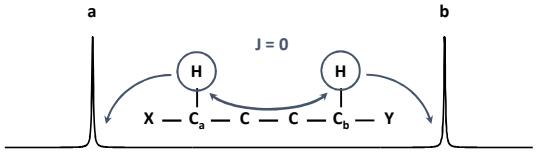
$B = B_0 - B_i$

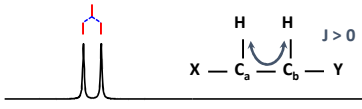
$B = B_0 (1 - \sigma)$

$\omega = \gamma B_0 (1 - \sigma)$

Scalar spin-spin interaction (J-coupling)

Interaction between spins mediated through chemical bonds





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Slide courtesy of Ivan Tkáč.

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Chemical Shift

$\omega_i = \gamma B_0 (1 - \sigma_i)$

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

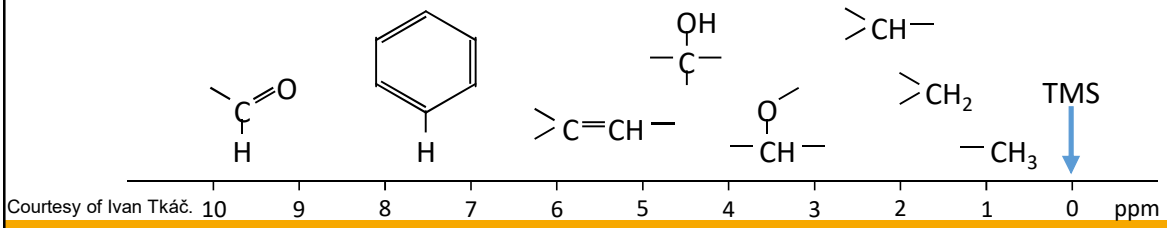
$\delta_i = (\nu_i - \nu_{ref})/\nu_0$

Chemical shift reference

Tetramethylsilane (TMS)

- **independent of B_0**
- **units: ppm**

increased proton shielding



Courtesy of Ivan Tkáč.

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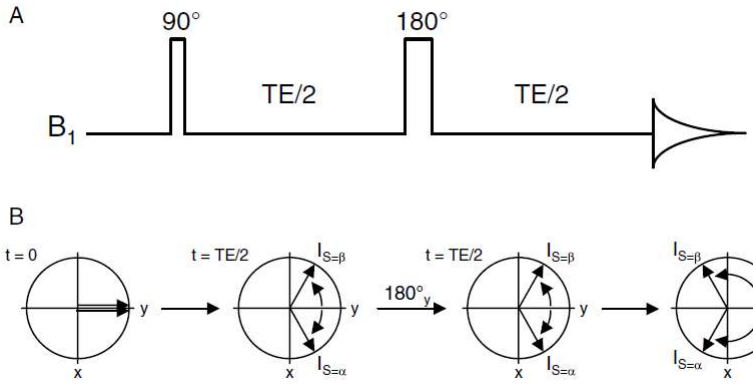
J-coupling evolution



De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.

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

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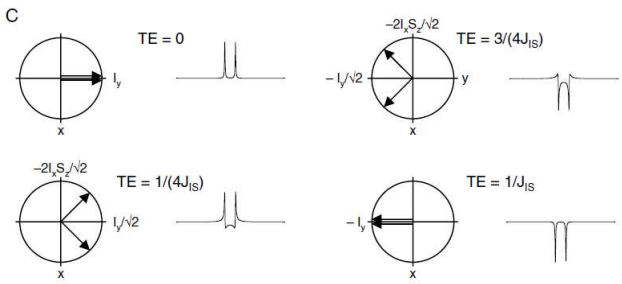
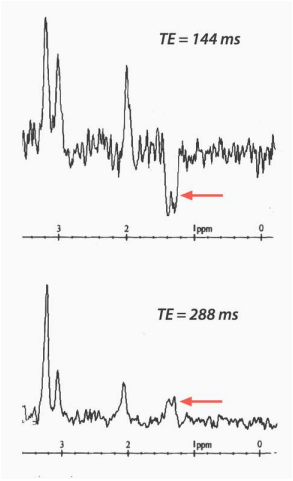
J-coupling evolution



De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.



Courtesy of Allen D. Elster, MRIquestions.com

Choice of TE affects spectral peak appearance of coupled nuclei.

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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

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Magnetic Field Homogeneity

- MRI requires a homogenous magnetic field. MRS requires an incredibly homogenous field.
- FWHM $\propto 1/T_2^*$ so better homogeneity → 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 2nd-order shims.

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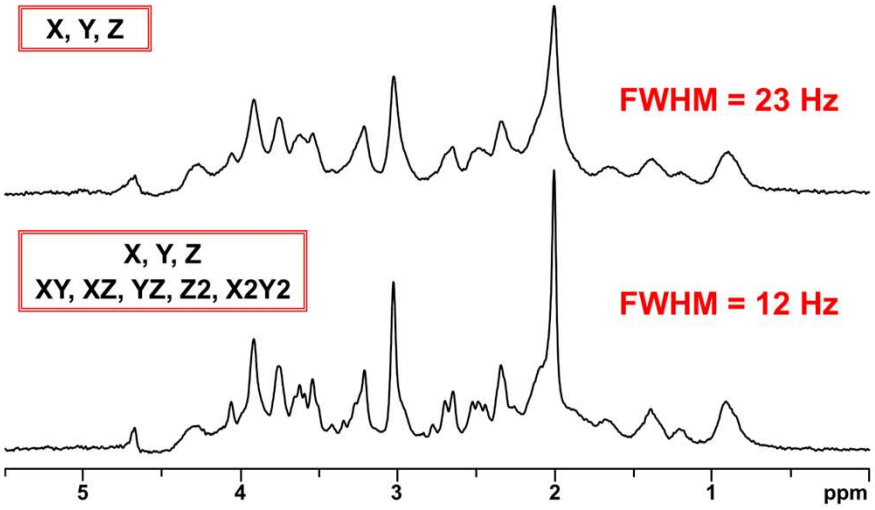
Magnetic Field Homogeneity



Courtesy of Ivan Tkáč.

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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.

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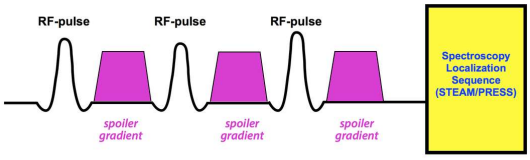
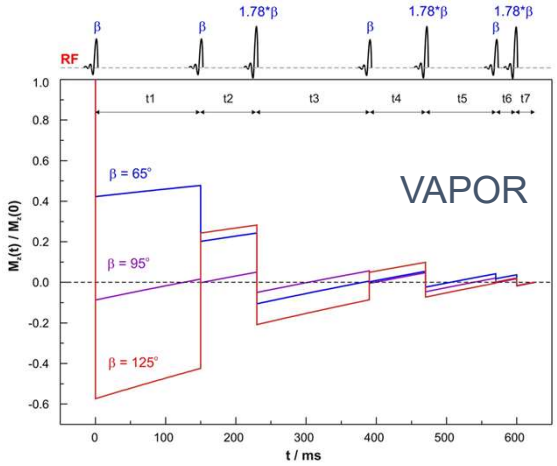
Water suppression

3x CHESS



Courtesy of Allen D. Elster, MRIquestions.com



Tkáč, Ivan, et al. "In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time." *Magnetic Resonance in Medicine* 41.4 (1999): 649-656.

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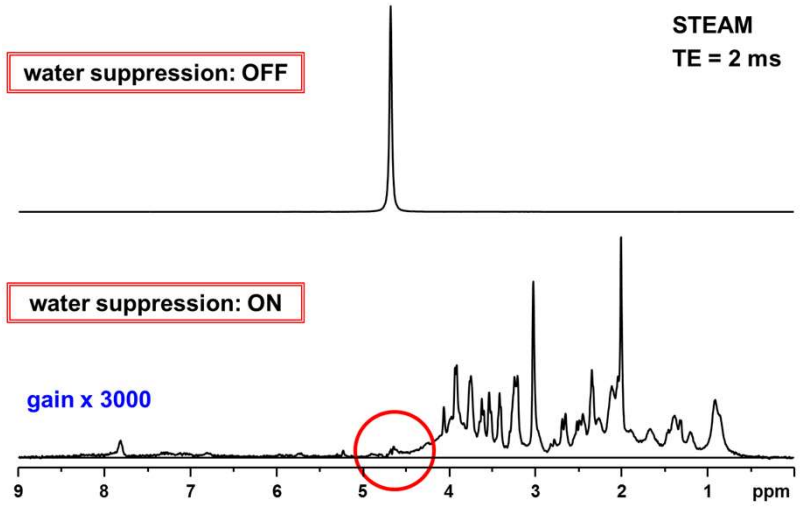
Water suppression



Courtesy of Ivan Tkáč

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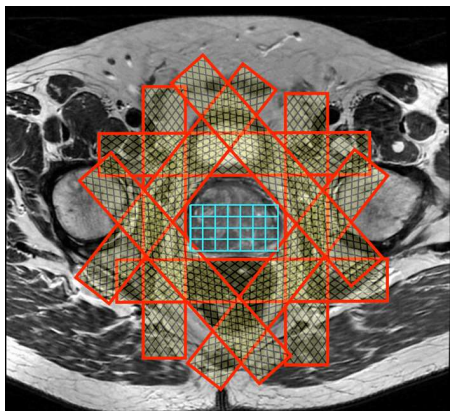
Fat suppression

- 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).



Courtesy of Allen D. Elster, MRIquestions.com

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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.

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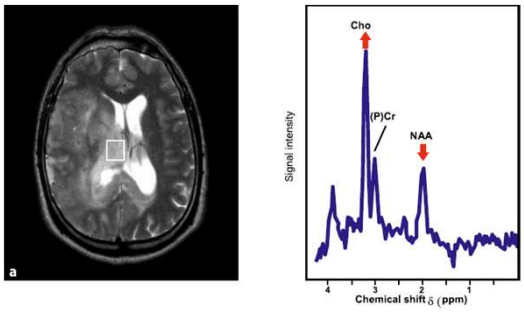
Single voxel spectroscopy (SVS)

- 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

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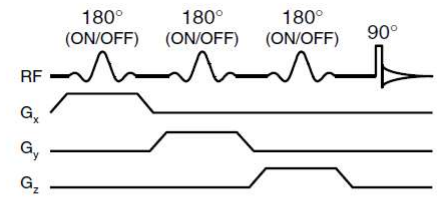
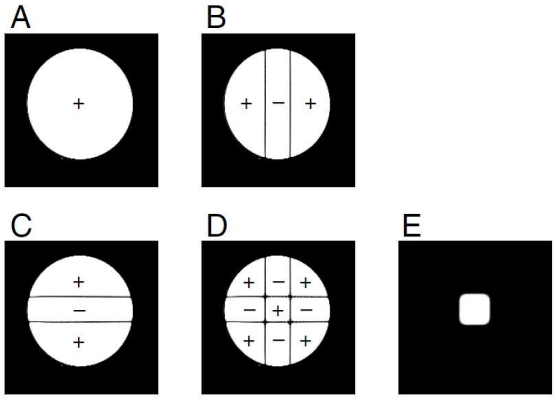
Image Selected In Vivo Spectroscopy (ISIS)



Exp 1	OFF	OFF	OFF	+
Exp 2	OFF	OFF	ON	–
Exp 3	OFF	ON	OFF	–
Exp 4	ON	OFF	OFF	–
Exp 5	OFF	ON	ON	+
Exp 6	ON	OFF	ON	+
Exp 7	ON	ON	OFF	+
Exp 8	ON	ON	ON	–



De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.

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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

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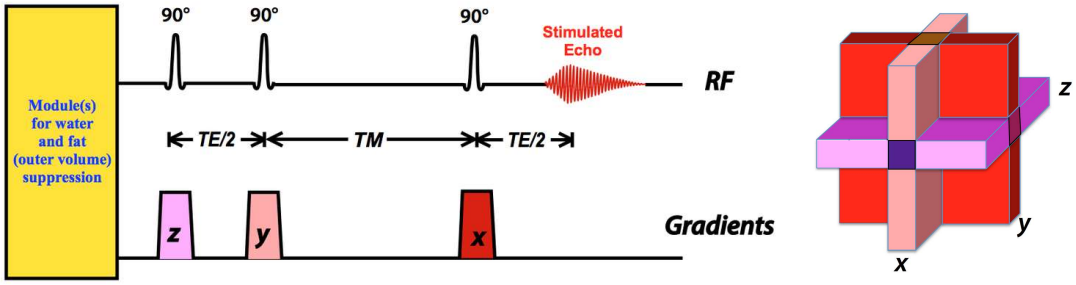
Stimulated Echo Acquisition Mode (STEAM)



Courtesy of Allen D. Elster, MRIquestions.com

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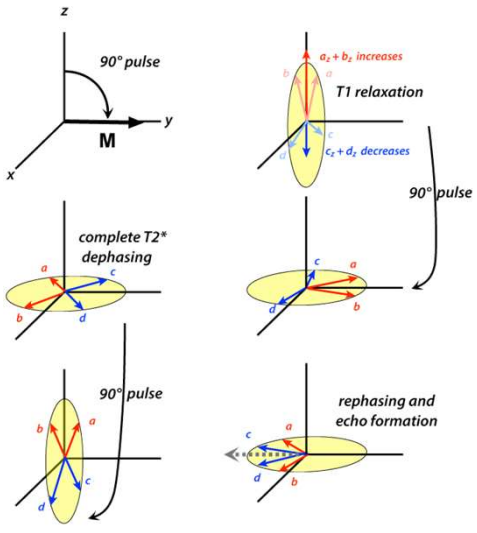
STEAM



Courtesy of Allen D. Elster, MRIquestions.com

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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.

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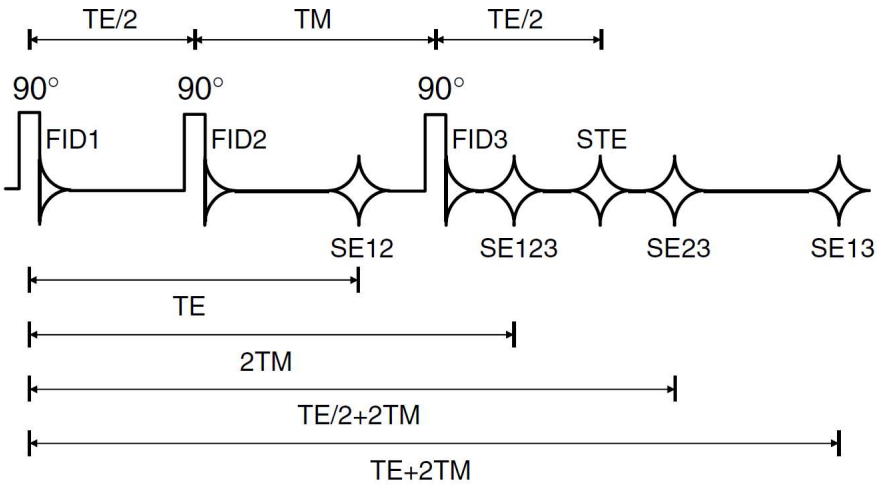
STEAM



De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.

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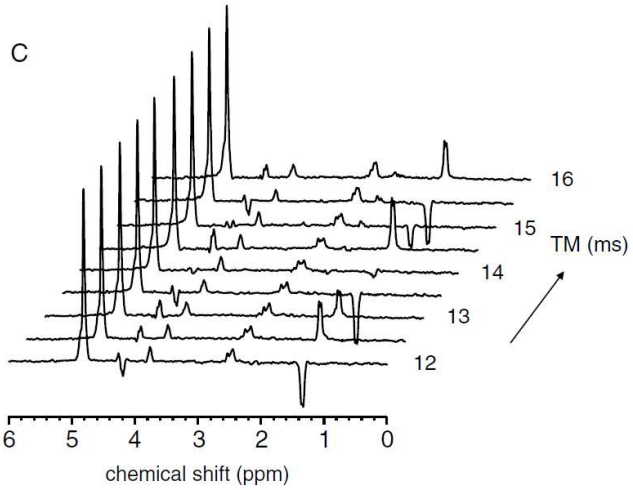
STEAM



De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.

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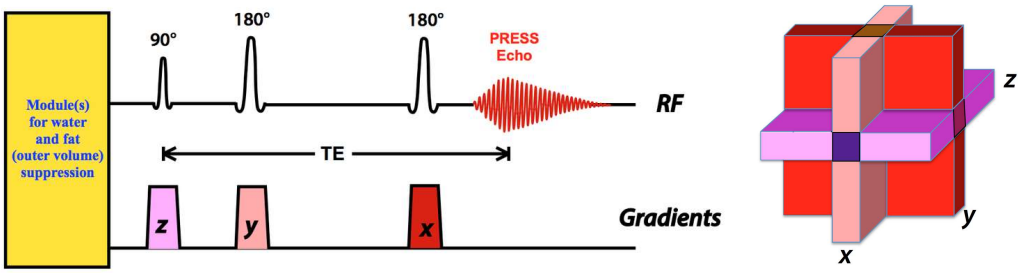
Point Resolved Spectroscopy (PRESS)



Courtesy of Allen D. Elster, MRIquestions.com

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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

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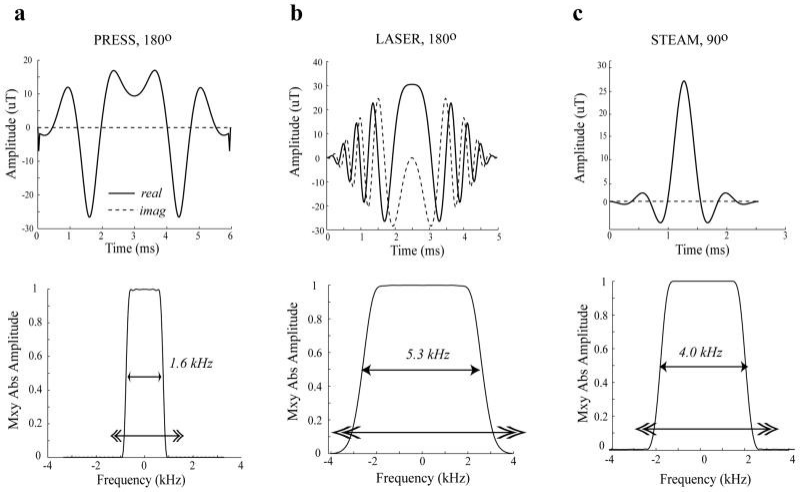
PRESS



Kaiser, Lana G., Karl Young, and Gerald B. Matson. "Numerical simulations of localized high field 1H MR spectroscopy." Journal of magnetic resonance 195.1 (2008): 67-75.

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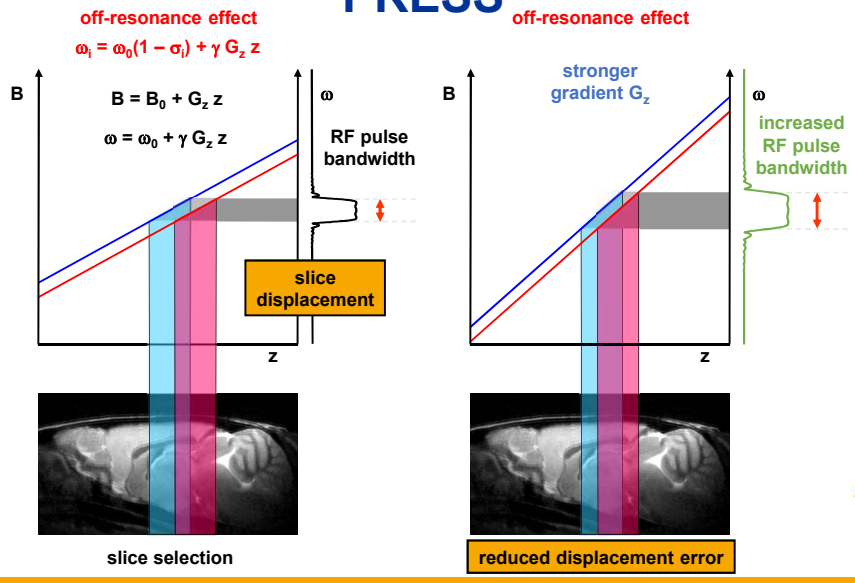
PRESS



Courtesy of Ivan Tkáč

slice selection

reduced displacement error

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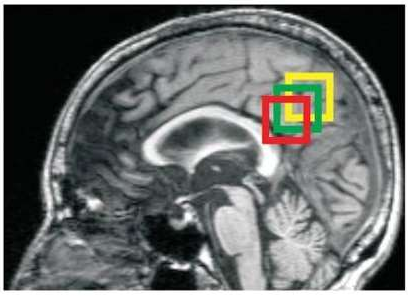
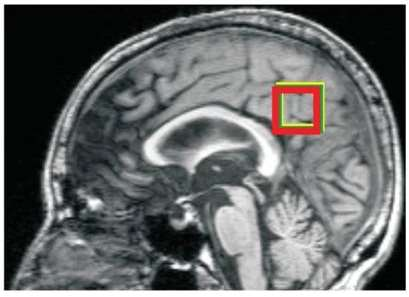
PRESS

CSDE with conventional (PRESS) sequence



CSDE with advanced (sLASER) sequence



Deelchand, Dinesh K., Kejal Kantarci, and Gülin Öz. "Improved localization, spectral quality, and repeatability with advanced MRS methodology in the clinical setting." Magnetic resonance in medicine 79.3 (2018): 1241-1250.

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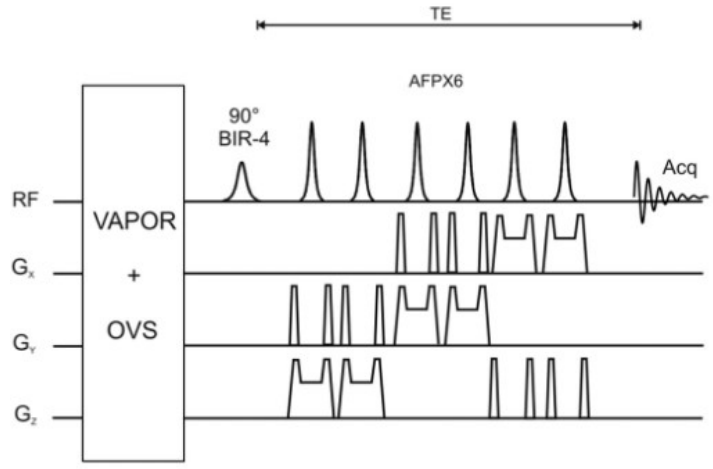
Localization by Adiabatic Selective Refocusing (LASER)



Stagg, Charlotte, and Douglas L. Rothman, eds. *Magnetic resonance spectroscopy: tools for neuroscience research and emerging clinical applications*. Academic Press, 2013.

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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.

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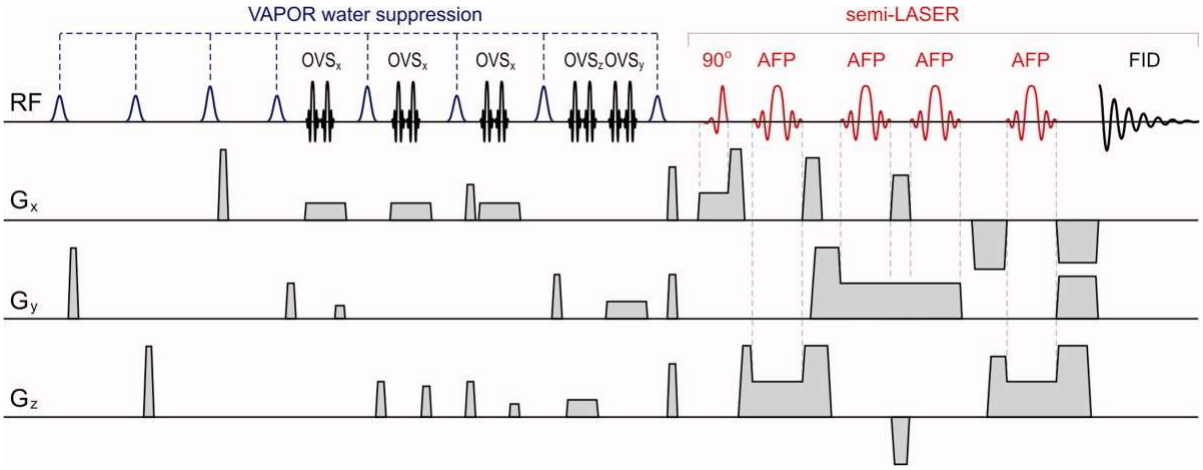
semi-LASER



Öz, Gülin, and Ivan Tkáč. "Short-echo, single-shot, full-intensity proton magnetic resonance spectroscopy for neurochemical profiling at 4 T: validation in the cerebellum and brainstem." Magnetic resonance in medicine 65.4 (2011): 901-910.

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semi-LASER

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

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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).

Wilson, Martin, et al. "Methodological consensus on clinical proton MRS of the brain: Review and recommendations." Magnetic resonance in medicine 82.2 (2019): 527-550.

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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.

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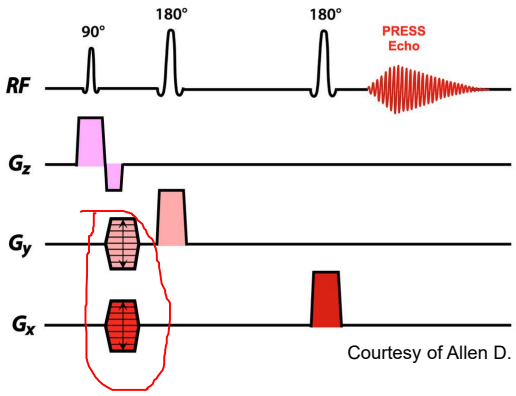
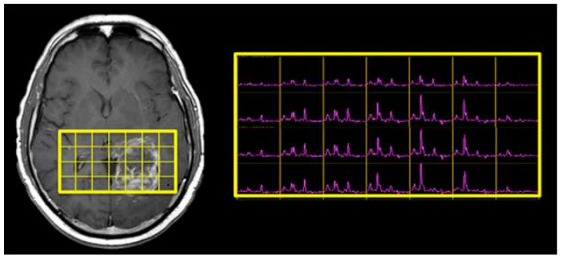
Multi-Voxel Spectroscopy (MVS)





Courtesy of Allen D. Elster, MRIquestions.com

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MRS Analysis

- 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.

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MRS Analysis Software

Vendor Basic	Vendor Agnostic	Vendor Advanced
Comes with the vendor MRS package.	e.g. LCModel, Tarquin	e.g. Syngo, IntelliSpace, READYView
Often automatic.	Very advanced software with sophisticated fitting algorithms.	Best of both worlds.
Very simple peak height or integral quantification.	Fully customizable (basis sets, metabolites, processing, etc.).	Rapidly approaching vendor agnostic software in terms advanced features.
Only a few metabolites can be quantified.	Provide estimates of quantification errors and metrics of spectral quality.	Allows for sophisticated processing, custom metabolites, error estimation, etc.
	Not FDA approved.	

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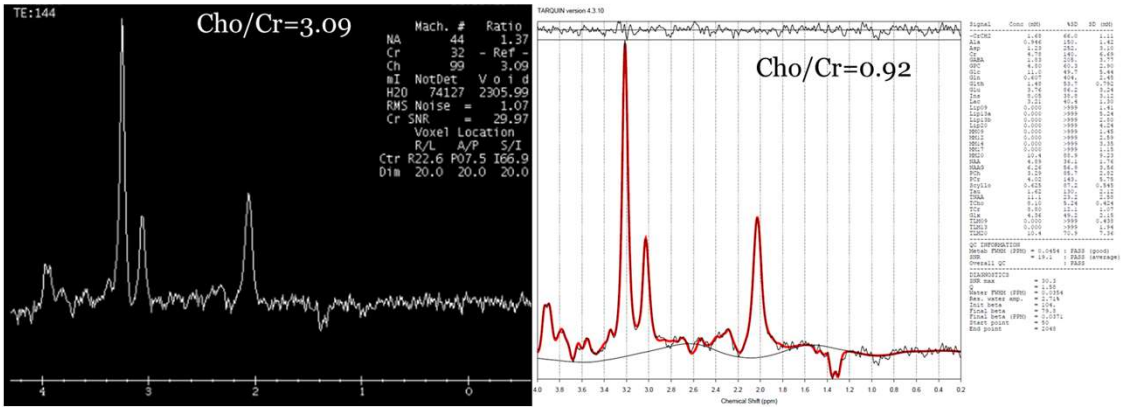
A note of caution



Einstein SA, Johnson JM, and Stafford RJ. "Potential Pitfalls of MR Spectroscopy." RSNA (2018).

Are you calculating signal intensity or metabolite concentration?

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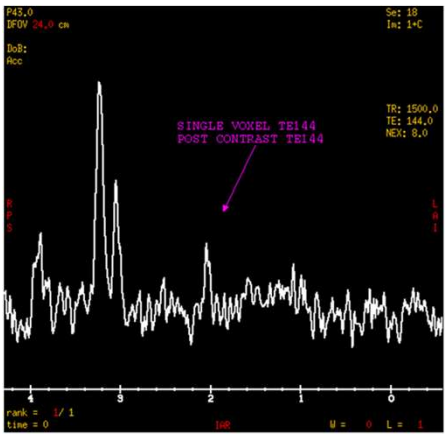
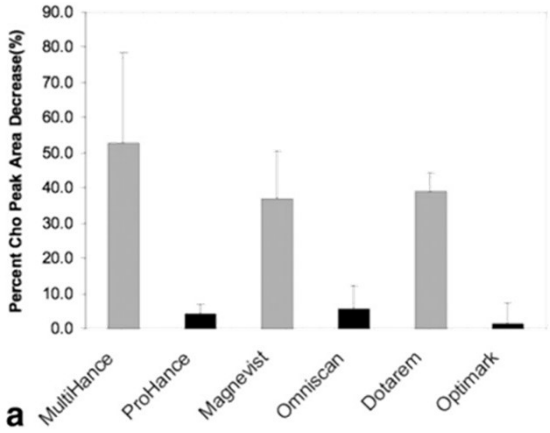
Another note of caution





Lenkinski, Robert E., et al. "Interaction of gadolinium-based MR contrast agents with choline: Implications for MR spectroscopy (MRS) of the breast." MRM: 61.6 (2009).

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

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MRS Artifacts

- Artifacts in MRS appear very different from artifacts in MRI and are often less conspicuous.
- Kreis, Roland. "Issues of spectral quality in clinical 1H-magnetic resonance spectroscopy and a gallery of artifacts." NMR in Biomedicine 17.6 (2004): 361-381.

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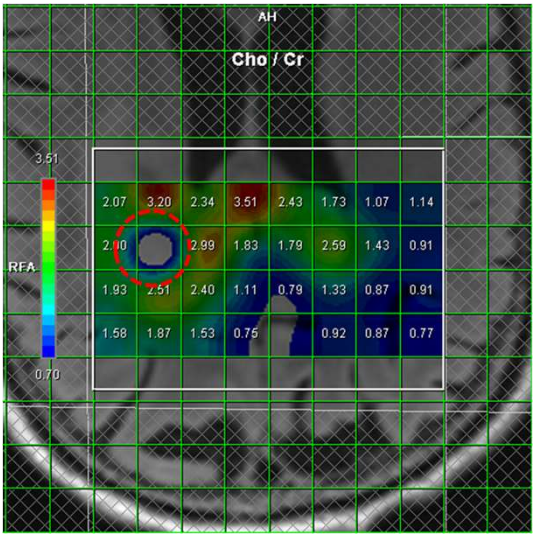
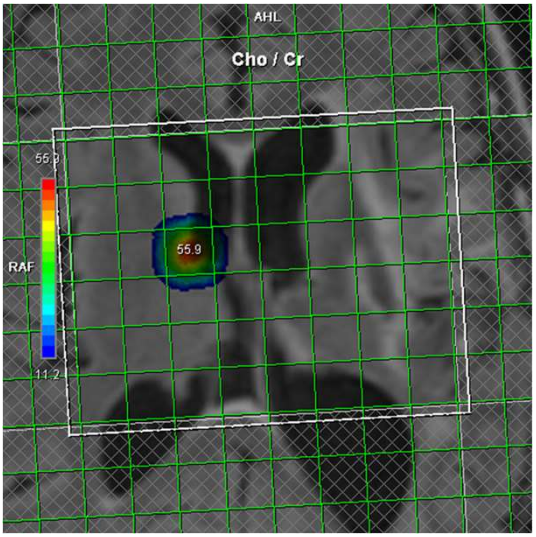
Holes/Spikes in MVS





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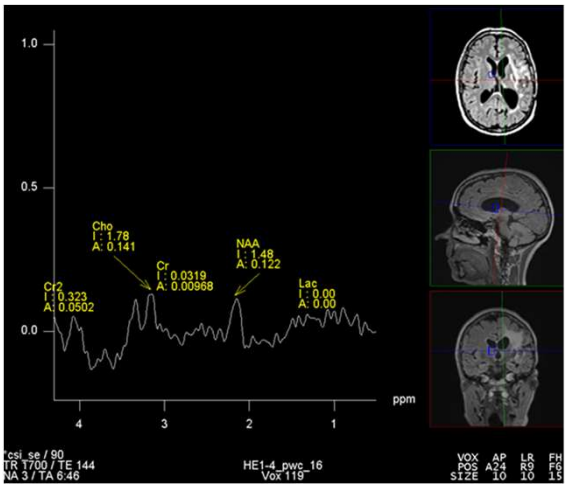
Peak mis-assignment

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



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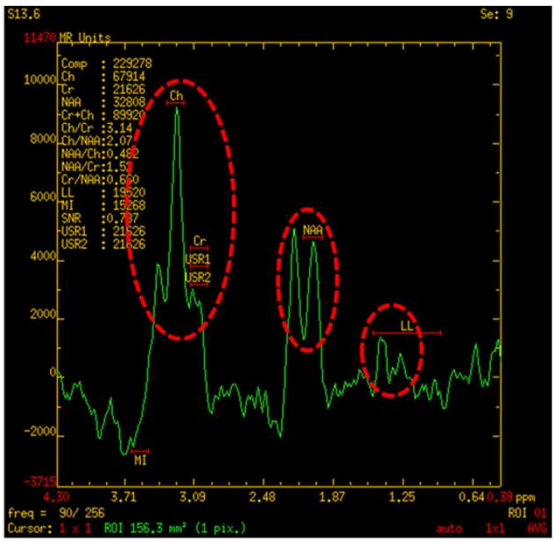
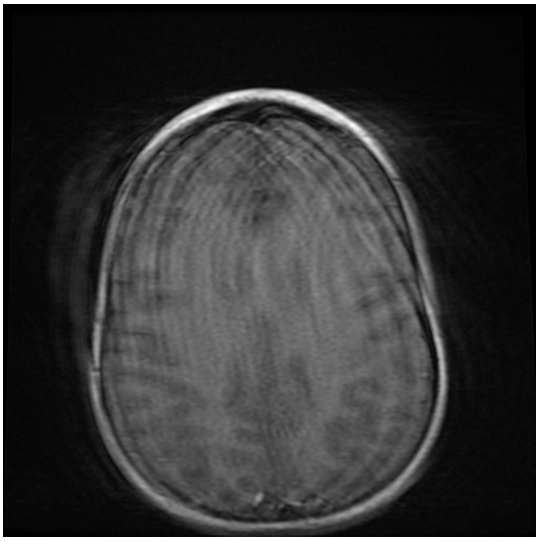
Motion artifact





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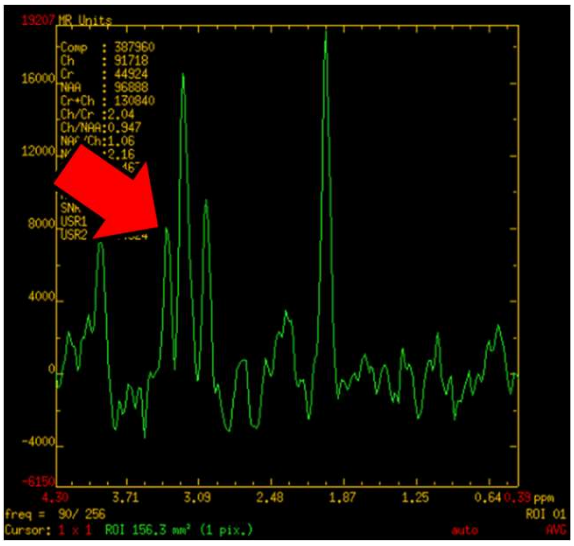
Unusual Peaks



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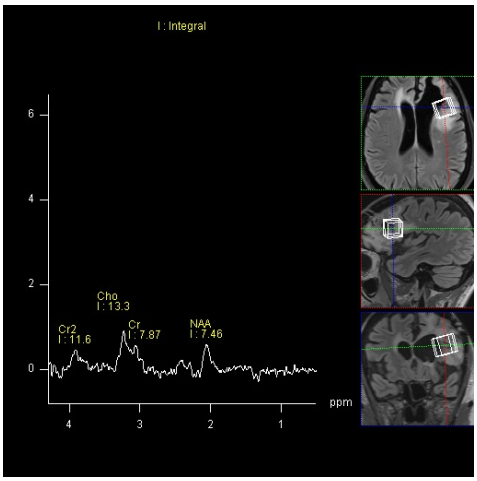
Susceptibility Artifact

- 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.



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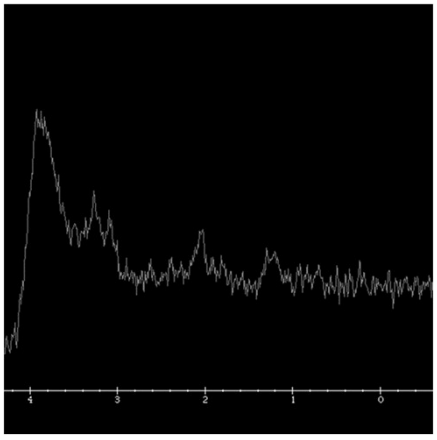
Poor Water Suppression

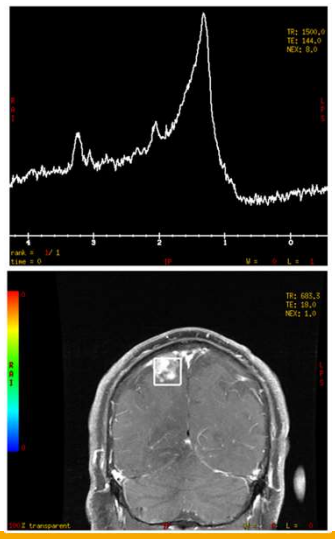
- Poor water suppression is usually evidenced by non-linear baselines and low peak SNR, especially above 3.5 ppm.
- Often due to poor shim and more common in MVS (where getting a good shim over the entire volume is challenging).



48

Signal Bleed

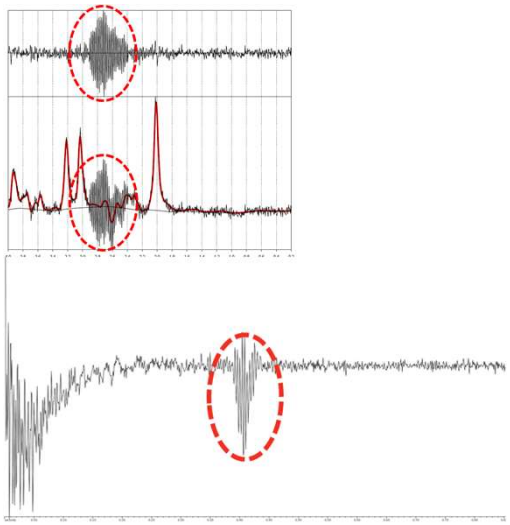
- Typically evidenced by the phase difference and broadness of the peak.
- This particular voxel was located very near the skull and sequence/pulse imperfections (and, possibly, patient motion) acquired some signal from the scalp.
- OVS is important.



49

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).



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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.

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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.

ACR–ASNR–SPR Practice Parameter for the Performance and Interpretation of Magnetic Resonance Spectroscopy of the Central Nervous System (2019).

II. INDICATIONS

When conventional imaging by magnetic resonance imaging (MRI) or computed tomography (CT) provides limited information regarding specific clinical questions, indications for MRS in adults and children include, but are not limited to, the following:

1. Evidence or suspicion of primary or secondary neoplasm (pretreatment and posttreatment)
2. Grading of primary glial neoplasm, particularly high-grade versus low-grade glioma [5,6]
3. Evidence or suspicion of brain infection, especially cerebral abscess (pretreatment and posttreatment) and HIV-related infections
4. Seizures, especially temporal lobe epilepsy
5. Evidence or suspicion of neurodegenerative disease, especially Alzheimer's disease, Parkinson's disease, and Huntington's disease [7-9]
6. Evidence or suspicion of subclinical or clinical hepatic encephalopathy
7. Evidence or suspicion of an inherited metabolic disorder, such as Canavan disease, mitochondrial encephalopathies, and other leukodystrophies [10,11]
8. Suspicion of acute brain ischemia or infarction, including birth asphyxia [12]
9. Evidence or suspicion of a demyelination or dysmyelination disorder [13-16]
10. Evidence or suspicion of traumatic brain injury
11. Evidence or suspicion of brain developmental abnormality and cerebral palsy
12. Evidence or suspicion of other neurodegenerative diseases, such as amyotrophic lateral sclerosis
13. Evidence or suspicion of chronic pain syndromes
14. Evidence or suspicion of chromosomal and inherited neurocutaneous disorders, such as neurofibromatosis and tuberous sclerosis
15. Evidence or suspicion of neurotoxicity, such as misuse of medications, and exposure to environmental hazards, such as carbon monoxide and inhalants
16. Evidence or suspicion of hypoxic ischemic encephalopathy
17. Evidence or suspicion of spinal cord disorders, such as tumors, demyelination, infection, and trauma
18. Evidence of neuropsychiatric disorders, such as depression, posttraumatic stress syndrome, and schizophrenia [17-26]
19. Differentiation between recurrent tumor and treatment-related changes or radiation injury
20. Differentiation of cystic lesions (eg, abscess versus cystic metastasis or cystic primary neoplasm)
21. Evidence or suspicion of cerebral vasculitis, systemic lupus erythematosus (SLE), and neuropsychiatric systemic lupus erythematosus (NPSLE)
22. Evaluation of response to treatment of neurological disorders (eg, tumor evaluation)
23. Detection of 2-hydroxyglutarate (2-HG) in suspected IDH1 mutant gliomas
24. Developmental delay
25. Evaluation of response to treatment of metabolic disorders

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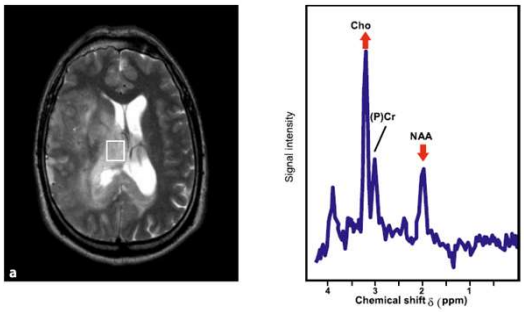
CNS

- 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



Courtesy of R. Jason Stafford

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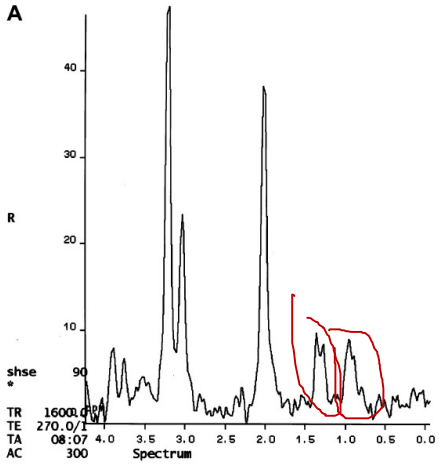
CNS

- 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



Jan, Wajanat, et al. "MR diffusion imaging and MR spectroscopy of maple syrup urine disease during acute metabolic decompensation." Neuroradiology 45.6 (2003): 393-399.

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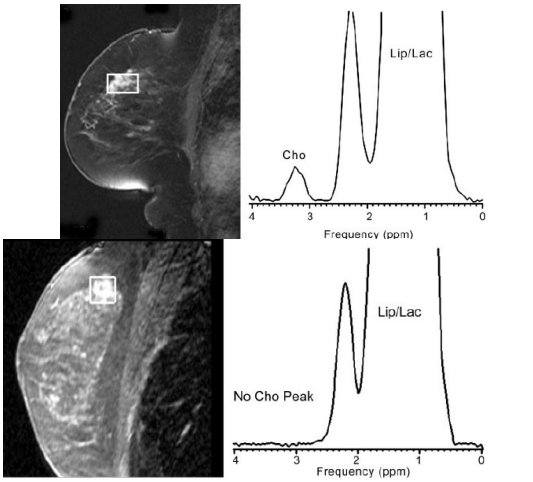
Breast

- 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.

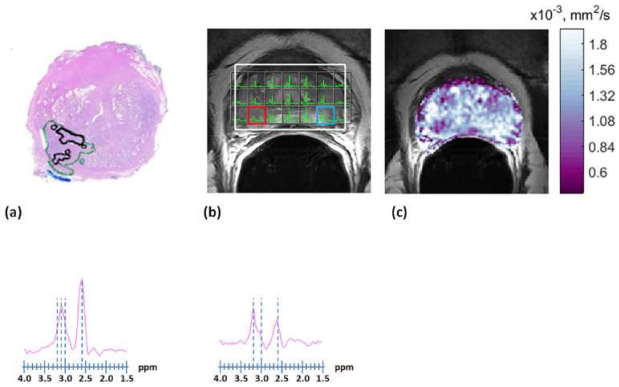


Bartella, Lia, et al. "Enhancing nonmass lesions in the breast: evaluation with proton (1 H) MR spectroscopy." Radiology 245.1 (2007): 80-87.

55

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



Mazaheri, Yousef, et al. "Characterization of prostate cancer with MR spectroscopic imaging and diffusion-weighted imaging at 3 Tesla." Magnetic resonance imaging 55 (2019): 93-102.

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Non-proton MRS

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

Nucleus	Natural abundance (%)	Gyromagnetic ratio (MHz/T)	Relative Sensitivity
^{1}H	99.98	42.58	100.00
^{13}C	1.11	10.71	1.59
^{19}F	100.00	40.05	83.30
^{23}Na	100.00	11.26	9.25
^{31}P	100.00	17.23	6.63
^{39}K	93.10	1.99	0.05

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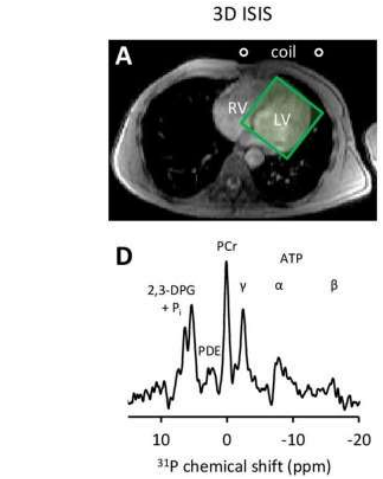
^{31}P-MRS

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



Bakermans, Adrianus J., et al. "Human cardiac 31P-MR spectroscopy at 3 tesla cannot detect failing myocardial energy homeostasis during exercise." Frontiers in physiology 8 (2017): 939.

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^{13}C-MRS

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

Courtesy of GE Healthcare

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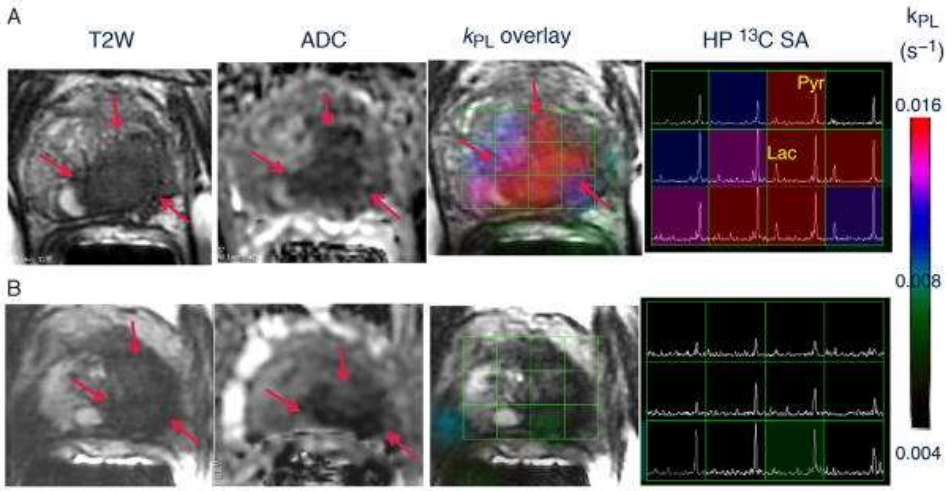
^{13}C-MRS



Aggarwal, Rahul, Daniel B. Vigneron, and John Kurhanewicz. "Hyperpolarized 1-[13C]-pyruvate magnetic resonance imaging detects an early metabolic response to androgen ablation therapy in prostate cancer." European urology 72.6 (2017): 1028.

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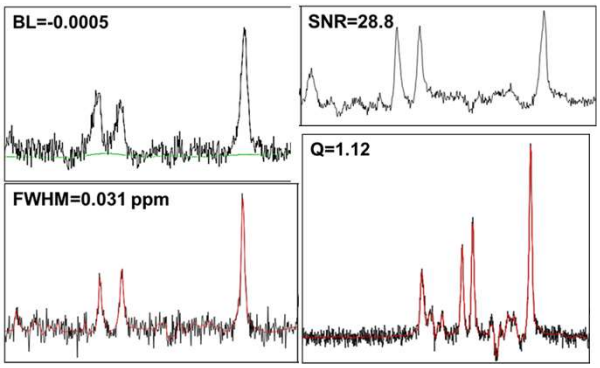
MRS QA

- AAPM Report 78 (2002) details recommended MRS QA based on a simple phantom.
- 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.



Einstein, S. A., et al. "QC of Patient MR Spectroscopy Can Identify Sub-Optimal Data and System Malfunctions." AAPM (2018).

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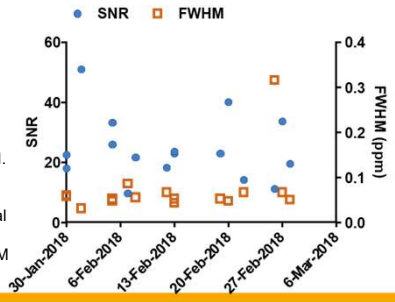
MRS QA

- 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.



Einstein, S. A., et al. "QC of Patient MR Spectroscopy Can Identify Sub-Optimal Data and System Malfunctions." AAPM (2018).

✓ 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

Öz, Gülin, et al. "Clinical proton MR spectroscopy in central nervous system disorders." Radiology 270.3 (2014): 658-679.

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Thank you!

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