

MR Spectroscopy: The Physical Basis and Acquisition Strategies

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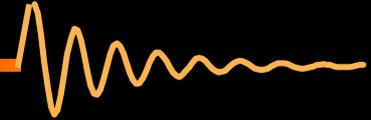


Objectives



- Understand the physical basis of *in vivo* MRS applications
- Appreciate the requirements necessary to obtain high quality *in vivo* MRS data
- Understand the spatial localization strategies commonly used for *in vivo* MRS studies
- Understand common approaches to quantitative interpretation of the measured data
- Understand the dependence of measured parameters on key acquisition parameters

Introduction to Spectroscopy



- Recall the Larmor relation that relates resonant frequency to magnetic field strength:

$$\nu = \gamma B_{\text{nucleus}}$$

where ν is the resonant frequency (MHz), γ is the gyromagnetic ratio (a constant for a given nucleus, *e.g.*, 42.57 MHz/T for protons), and B_{nucleus} is the applied magnetic field strength (T) *at a given nucleus*.

- However, the value of B_{nucleus} depends on the local electronic environment, *i.e.*, it is the value of the applied field, B_0 , modified by the magnetic field due to the chemical environment.

Introduction to Spectroscopy

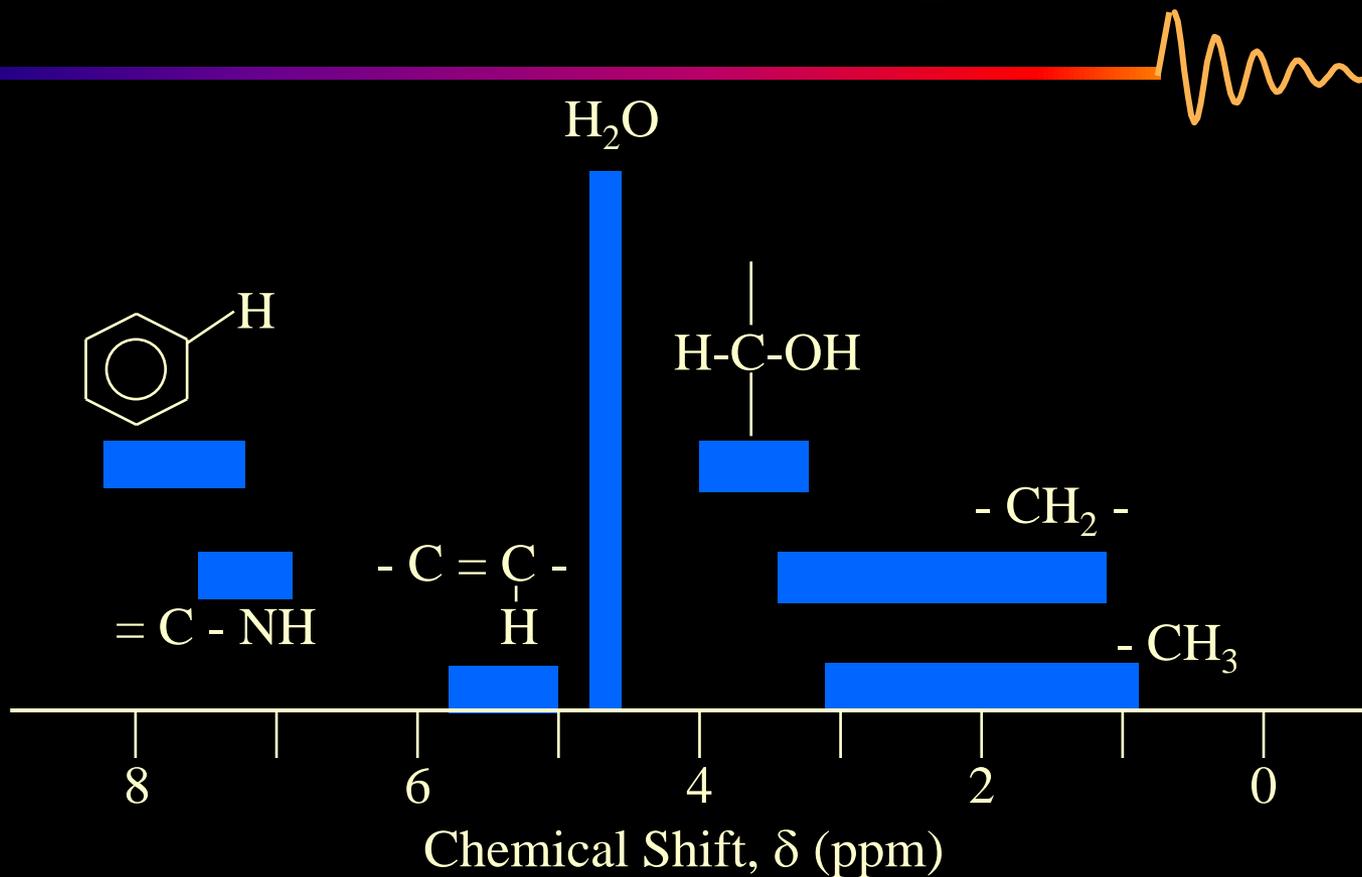


- Therefore, nuclei in different chemical (electronic) environments will have slightly different resonance frequencies depending on the amount of local nuclear shielding, characterized by the screening constant, σ :

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

- It is this local shielding effect that results in spectra with multiple peaks for a given nuclear species, where the peak positions depend on the local chemical environment.

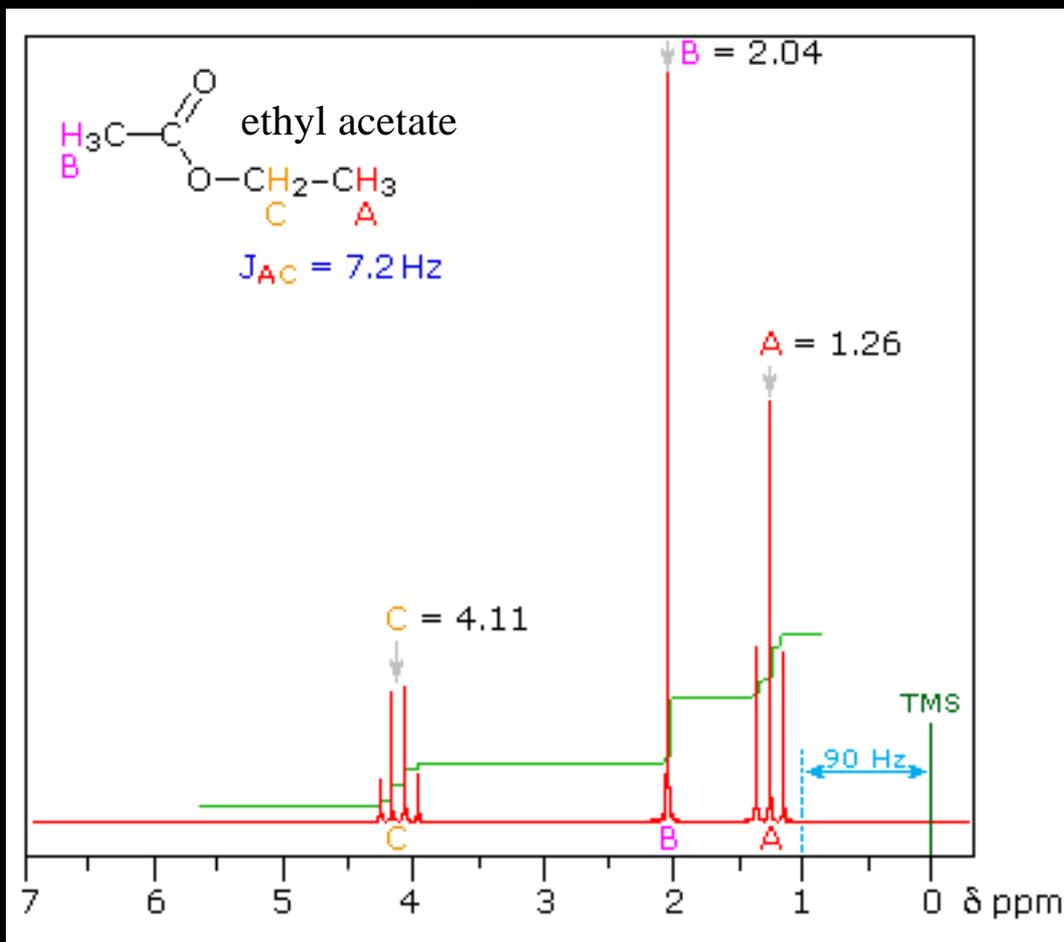
Introduction to Spectroscopy



← Increasing frequency

Increasing shielding →

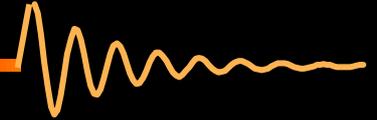
J-Coupled Spectra



“ $n+1$ rule” – a singlet peak is split, by J -coupling, into an $n+1$ multiplet where n is the number of neighboring spin-coupled nuclei.

<http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/Spectrpy/nmr/nmr1.htm>

Introduction to Spectroscopy

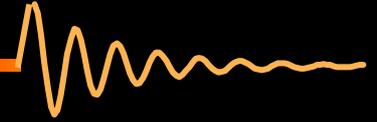


- The position of a given spectral peak is usually given in terms of *chemical shift* with respect to some reference,

$$\delta_x = (\nu_x - \nu_{\text{ref}}) / \nu_{\text{ref}} \times 10^6$$

- It is given in *parts per million* (ppm) to make separations between the peaks independent of applied field strength.
- Note that the separation of the peaks (in Hz) *does* depend on field strength. Therefore, the spectral resolution improves as field strength increases. (So does the SNR.)
- For *in vivo* applications, the reference is usually water for ^1H spectroscopy, and phosphocreatine for ^{31}P studies of tissues such as muscle which have significant amounts of this high energy substrate.

Requirements



The success of an MRS examination depends upon:

- Highly homogeneous magnetic field

The limiting line widths of peaks are inversely proportional to T_2^* , so improved homogeneity results in narrower peaks (improved spectral resolution).

- High quality localization

The volume from which the chemical information (spectrum) is obtained must be accurately known.

- Efficient water suppression (^1H MRS)

This is aided by improved homogeneity as well.

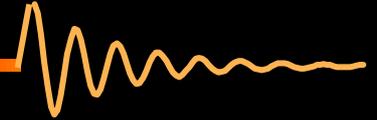
- Spectral quantification

Magnetic Field Homogeneity



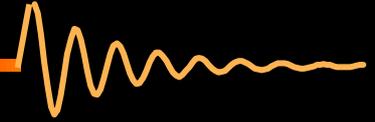
- The requirements for magnetic field homogeneity are stringent if MRS is required, much more stringent than for conventional MRI.
- Good field homogeneity is a prerequisite for good spectral resolution and, for ^1H MRS, effective water suppression.
- All clinical MR systems have automated shimming capabilities which optimize the magnetic field within the chosen volume of interest (VOI). This automatic shimming is usually done as part of the MRS prescan function.

Water Suppression (^1H MRS)



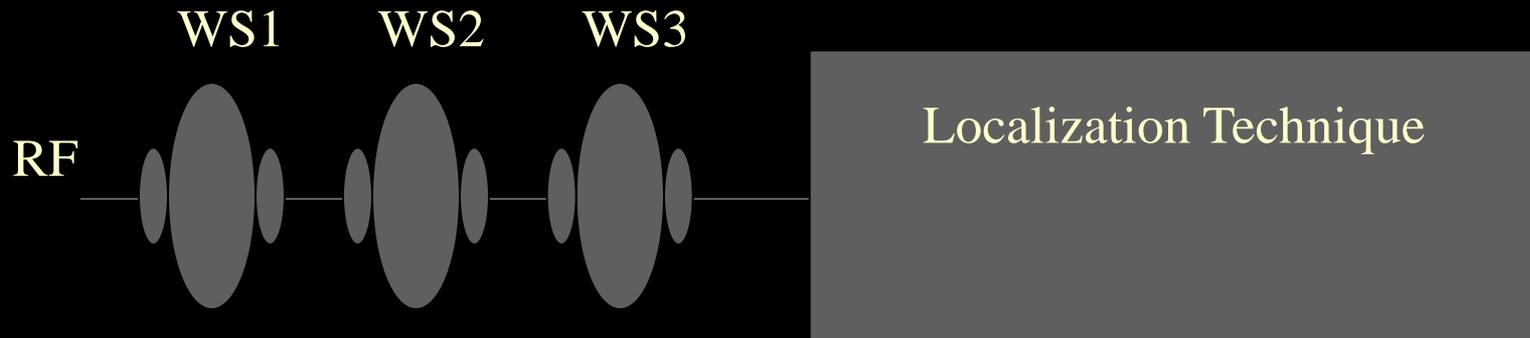
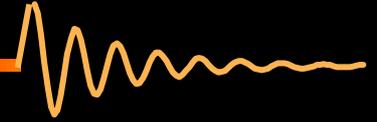
- In ^1H MRS studies, water is seldom the molecule of interest.
- The metabolites of interest are usually about a factor of $\sim 5,000$ less in concentration than water. (Millimolar concentrations vs. ~ 55 M H_2O concentration).
- A very efficient means of suppressing the water resonance (by about 500x) is required to readily detect the metabolite resonances.

Water Suppression (^1H MRS)

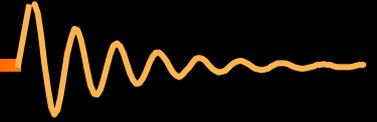


- The most commonly utilized method for water suppression is based on the same principle as “fat sat”. (For MRS sequences, the suppression pulses are commonly referred to as CHESS pulses - *chemically selective saturation*.)
- Typically, multiple (often 3), narrow bandwidth (~ 50 Hz) pulses are applied at the water resonance frequency preceding the localization sequence.
- Multiple pulses are used to improve the degree of water suppression.
- On commercial MR systems, the MRS prescan function includes automated optimization of the suppression pulses.

Water Suppression (^1H MRS)



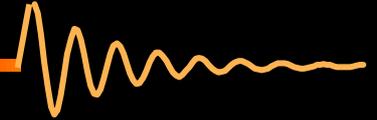
Localization



For a spectrum to have any significance, the region from which it is obtained must be accurately known. There are some basic requirements for the localization technique:

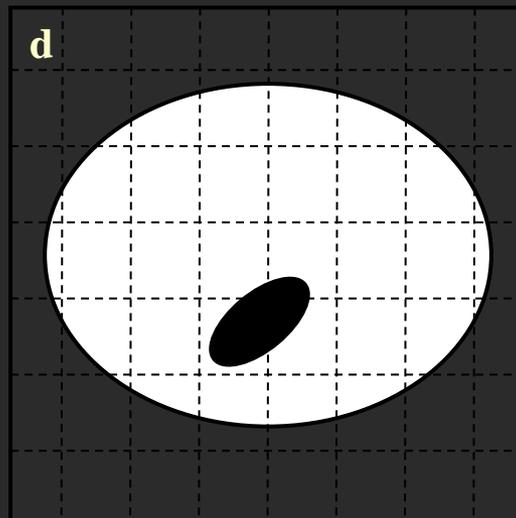
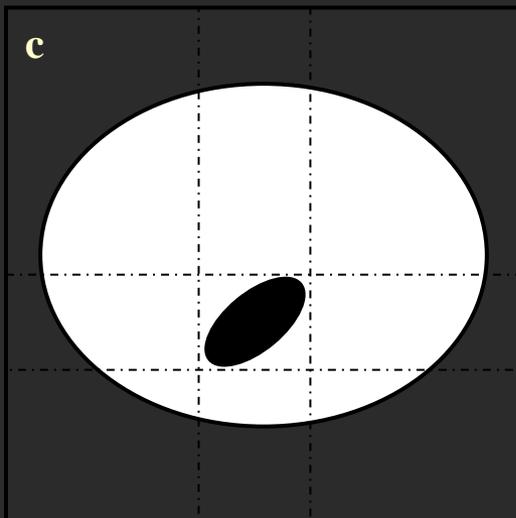
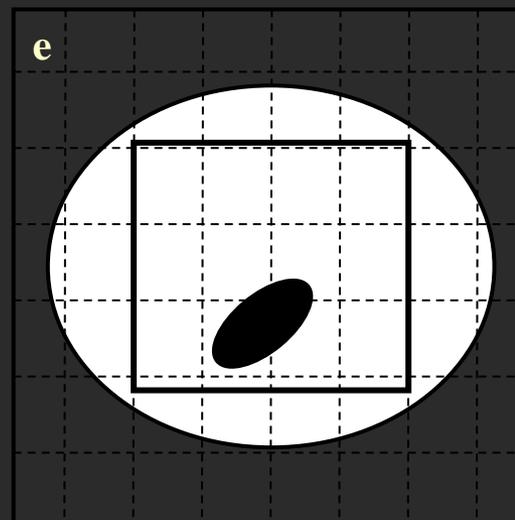
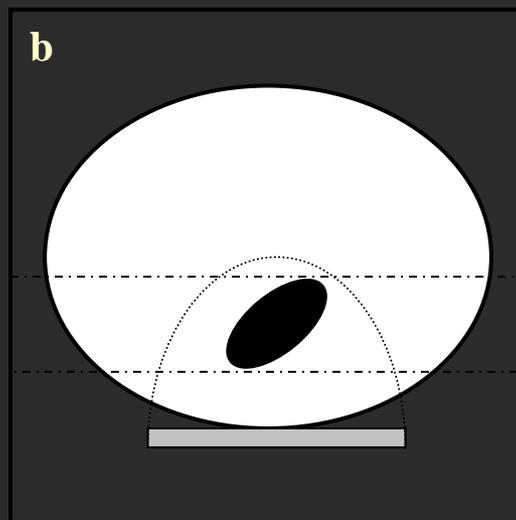
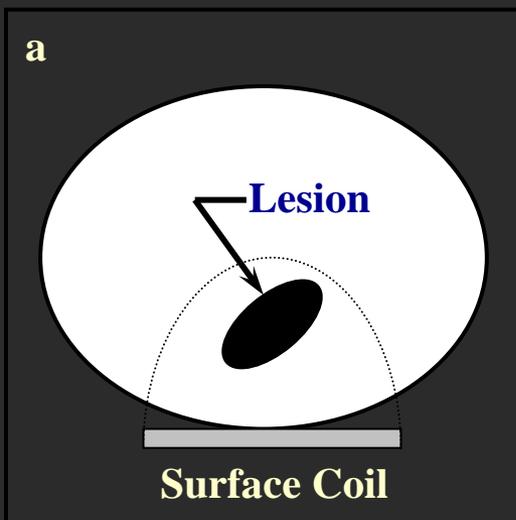
- It should be possible to move the desired volume of interest (VOI) anywhere in the FOV of the image and maintain localization quality,
- It should be possible to obtain the spectrum in a single acquisition in order to shim (manually or auto) on the VOI,
- For ^1H MRS: Water suppression should be efficiently incorporated into the localization sequence.

Localization



- Surface coil localization. Originally used for superficial lesions and/or performing ^{31}P or ^{13}C studies
- Surface coil + single slice selection, *e.g.*, DRESS (*depth resolved surface coil spectroscopy*).
- Single voxel volume localization (SVL): VOI is the intersection of three slice selective gradient/RF pulses. Each slice thickness can be individually varied to define VOI.
- Spectroscopic imaging (SI): Uses phase-encoding for localization.
- Hybrids: Usually a combination of SVL and SI techniques.

Localization



a) Surface coil
localization

b) DRESS

c) SVL

d) SI

e) Hybrid SVL/SI

The resonance frequency for a particular proton spectral peak fundamentally depends on the:

- 20% 1. proton density
- 20% 2. magnetic field homogeneity
- 20% 3. electron configuration surrounding the nucleus of interest
- 20% 4. localization method used to acquire the data
- 20% 5. water suppression efficiency

Ref: Drost DJ, Riddle WR, Clarke GD. Proton magnetic resonance spectroscopy in the brain: Report of AAPM MR Task Group #9, Med Phys 29(9):2177-2197, 2002.

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The spectral resolution of an acquired spectrum depends strongly on the:

- | | |
|-----|---|
| 20% | 1. echo time |
| 20% | 2. magnetic field homogeneity |
| 20% | 3. RF coil used to acquire the data |
| 20% | 4. localization method used to acquire the data |
| 20% | 5. <i>J</i> -coupling constant |

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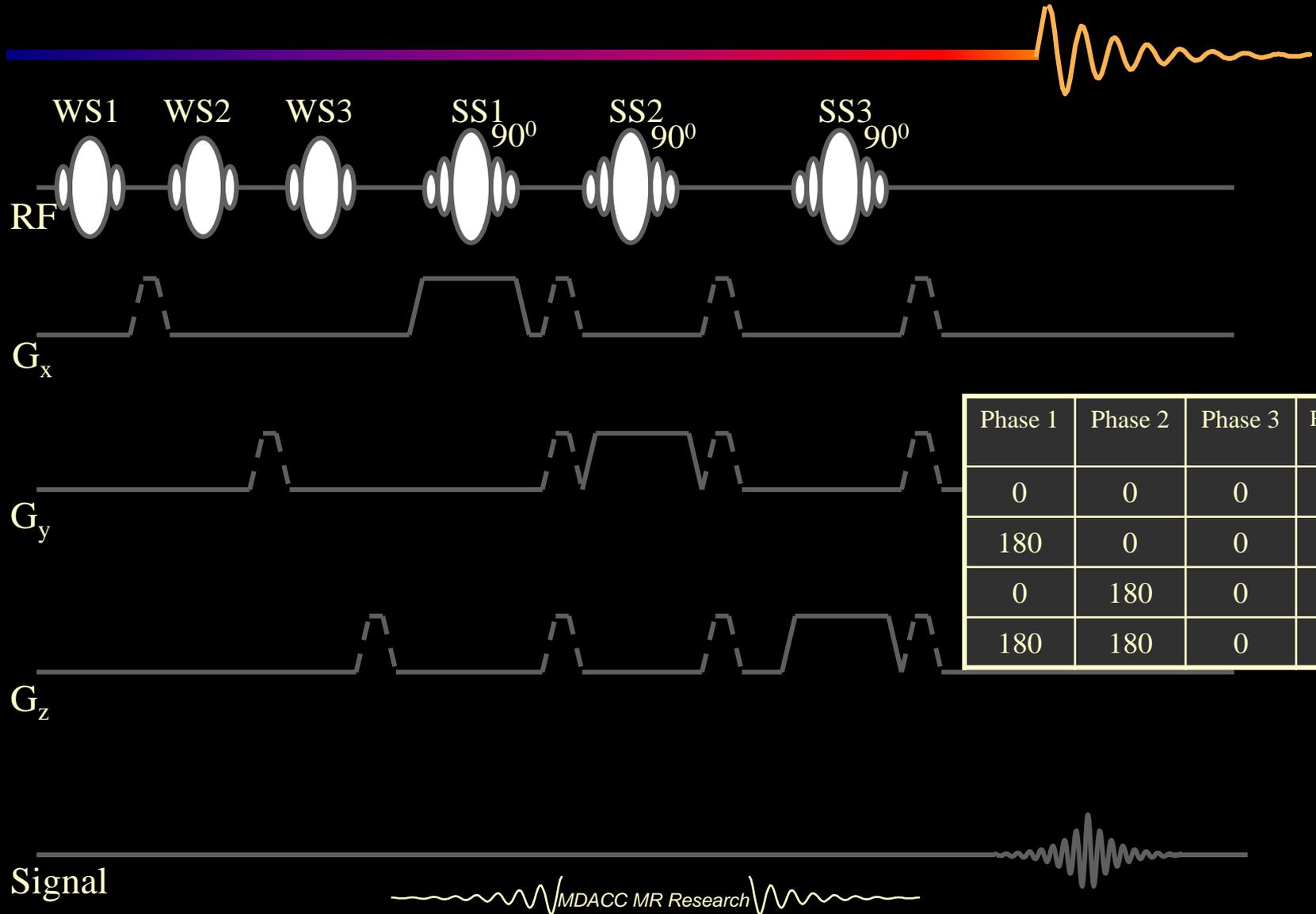
Ref: Drost DJ, Riddle WR, Clarke GD. Proton magnetic resonance spectroscopy in the brain: Report of AAPM MR Task Group #9, Med Phys 29(9):2177-2197, 2002.

Single Voxel Localization (SVL)

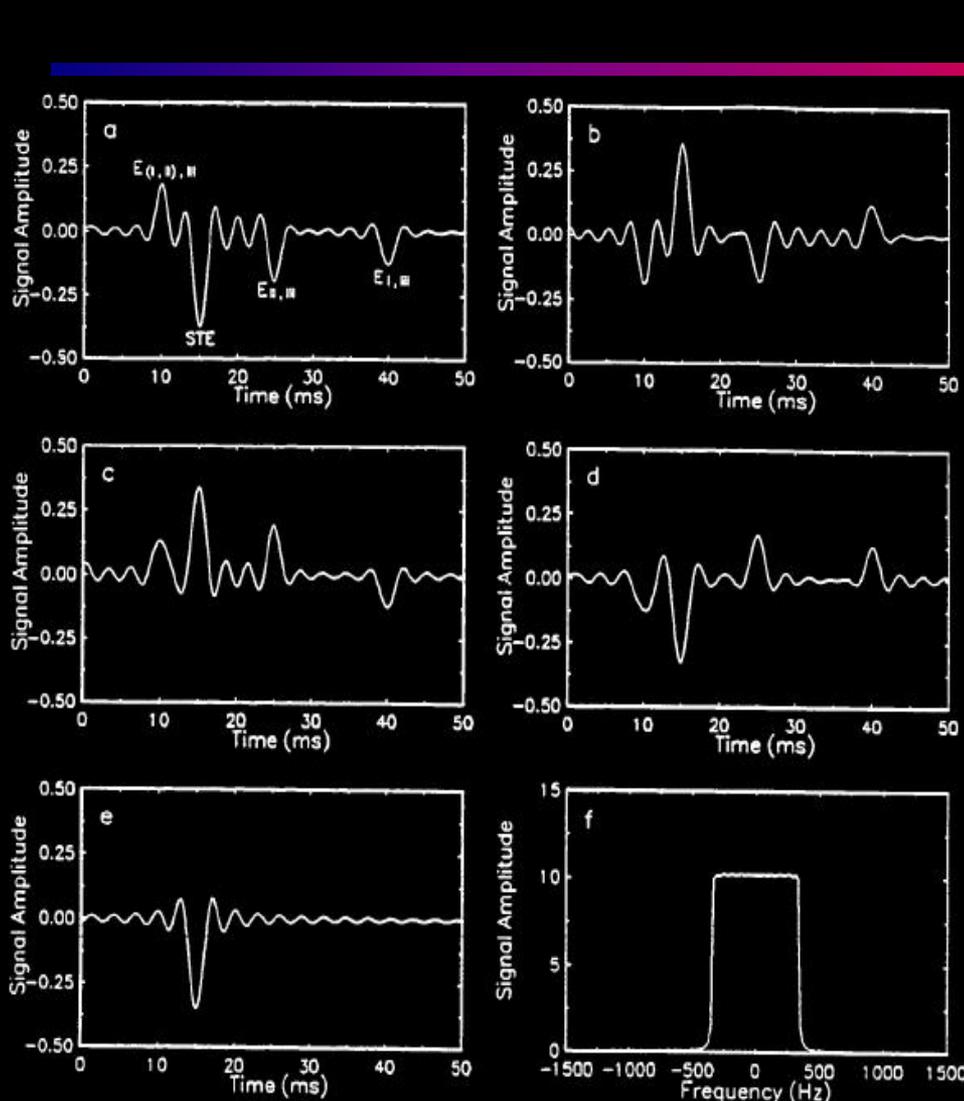


- The most common single voxel localization techniques are those based on the *stimulated echo acquisition mode* (STEAM) and *point resolved spectroscopy* (PRESS) sequences.
 - STEAM: 90° - 90° - 90° -acquire
 - PRESS: 90° - 180° - 180° -acquire
- Advantage of STEAM: shorter minimum echo times
- Advantage of PRESS: 2x SNR compared to STEAM (generally)

STEAM Pulse Sequence



STEAM Phase Cycling



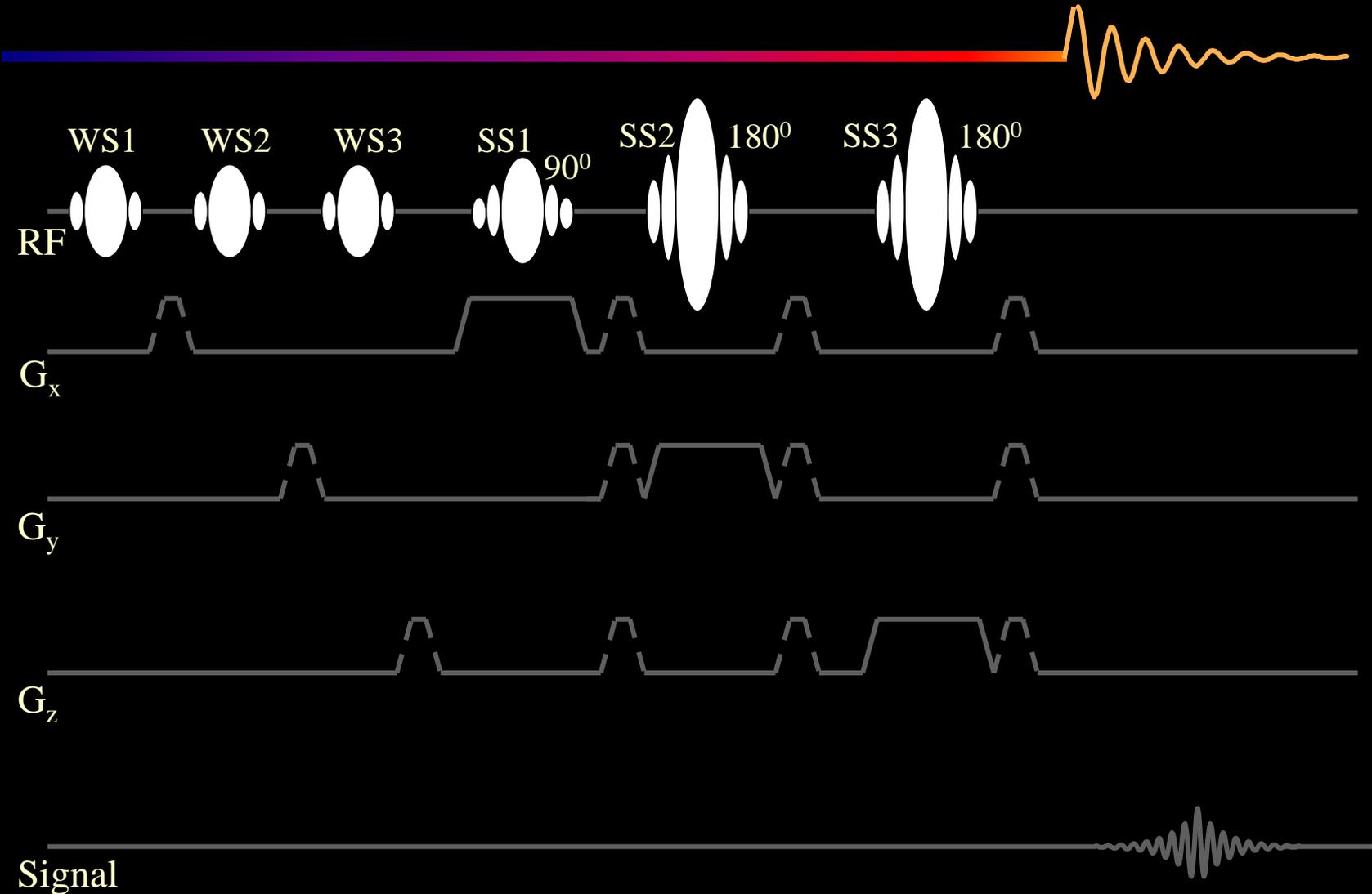
Bloch simulation of echoes generated by each of the four acquisitions outlined on previous slide.

echoes formed after an n -pulse sequence: $(3^{n-1}-1) / 2$

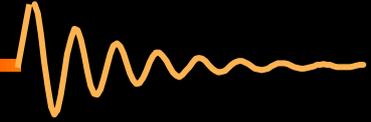
TE / TM = 30 / 25 ms

Frame e is the sum of frames a - d and frame f shows the FT of e .

PRESS Pulse Sequence



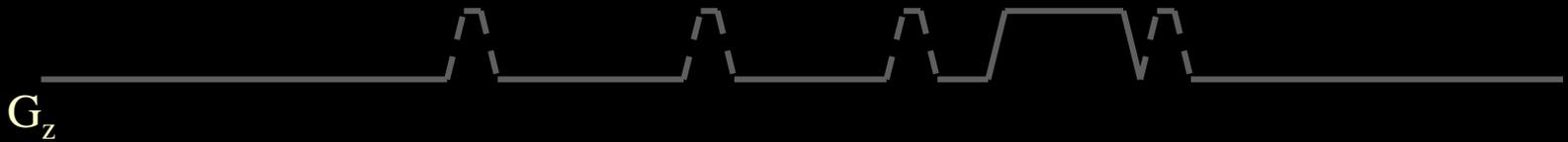
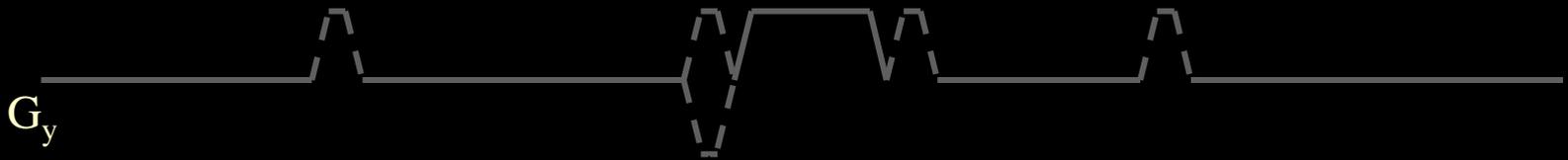
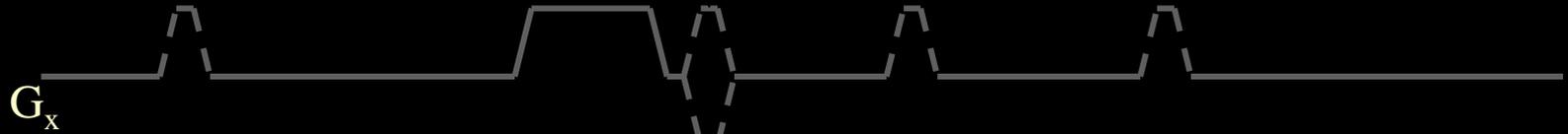
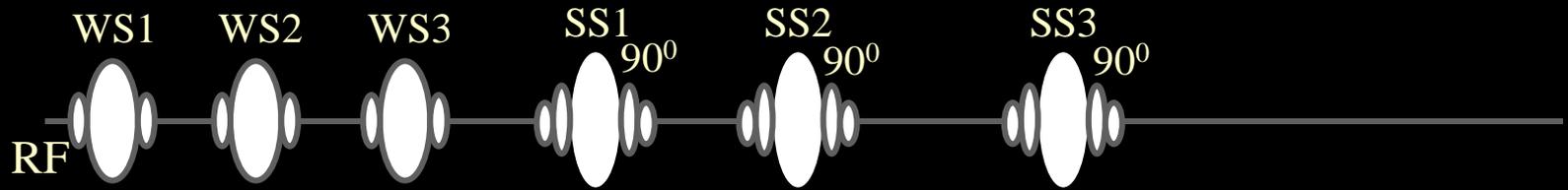
Spectroscopic Imaging (SI)



Instead of relying on the intersection of three planes to define a single VOI, SI techniques use phase-encoding for part of the localization to yield multiple VOIs.

- 1DSI: Uses two slice selection gradient/RF pairs to select a column of interest, and then uses phase-encoding to localize the spectra from the remaining dimension.
- 2DSI: Uses one slice selection gradient/RF pair to define a slice, and then phase-encodes the remaining two dimensions.
- 3DSI: Uses three phase-encoding gradients to define a 3D volume of voxels.

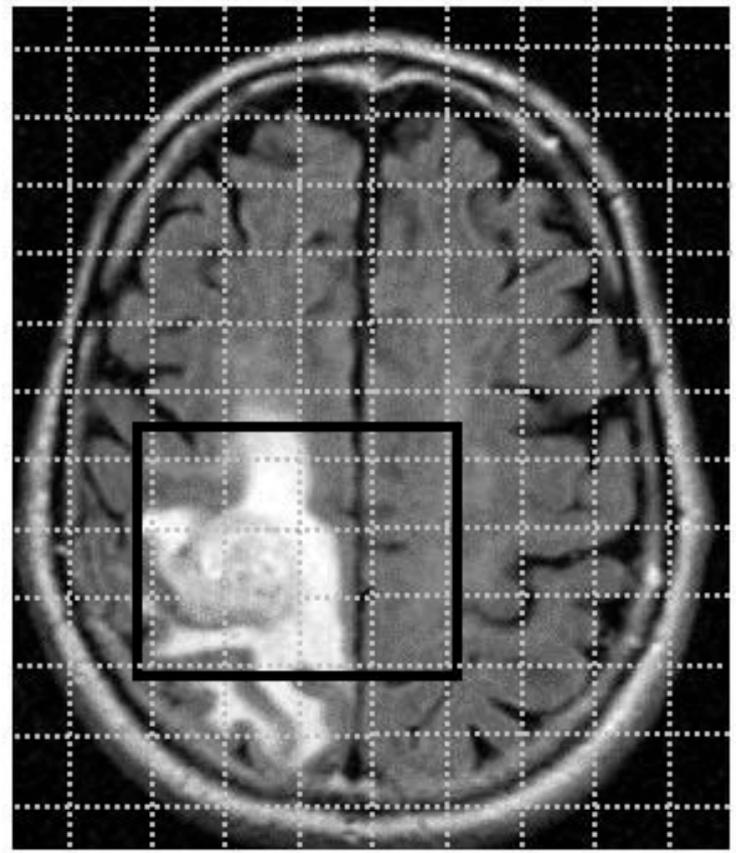
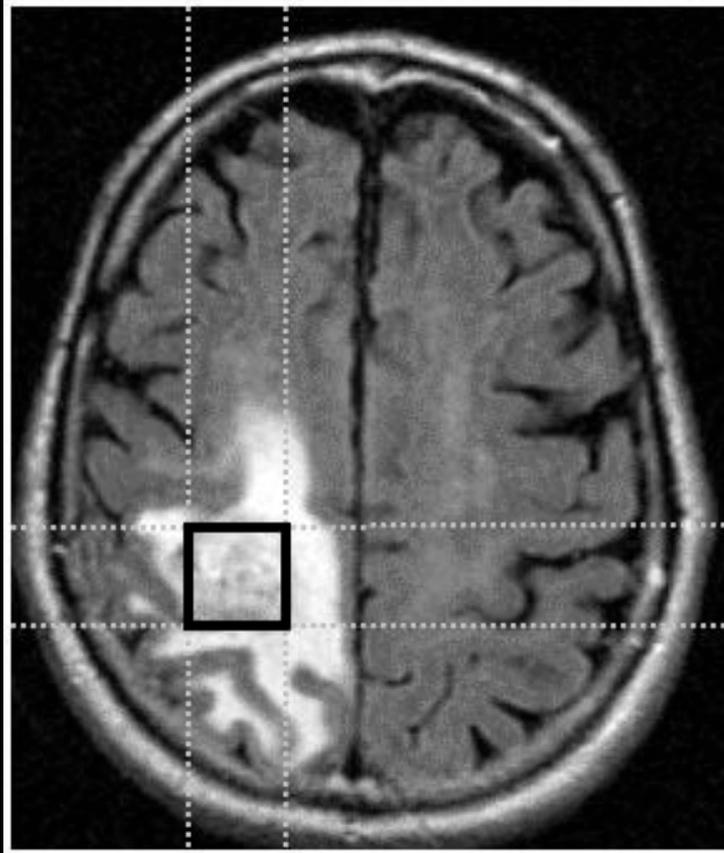
SI Pulse Sequence



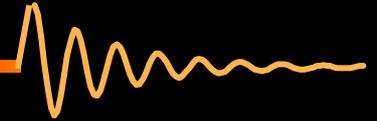
Signal



SVL vs. SI Localization



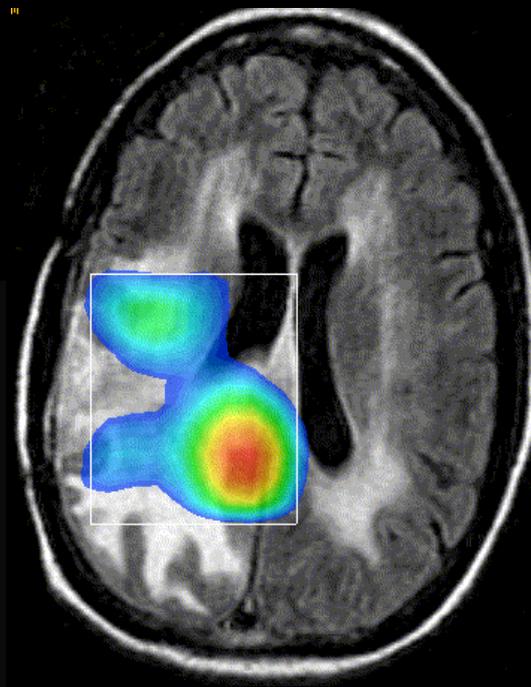
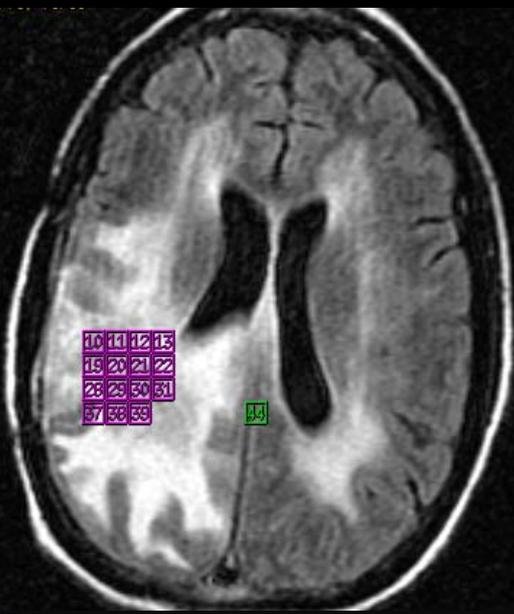
SI Acquisitions



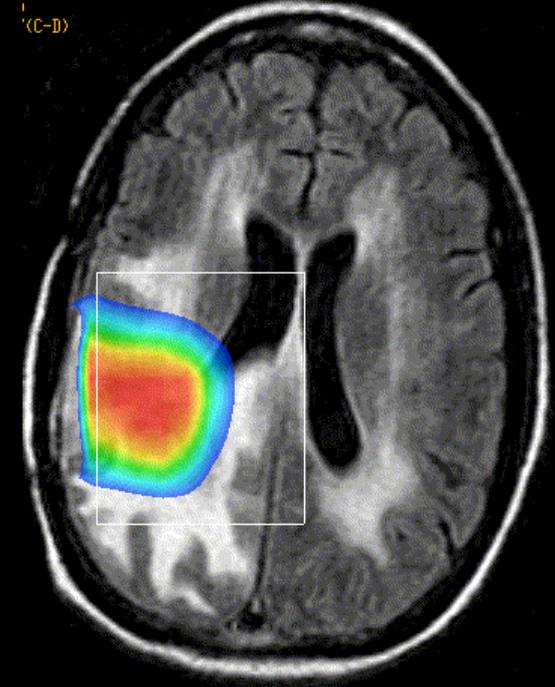
While SVL techniques are faster for obtaining a single localized spectrum, SI techniques have the following advantages:

- Spectra from multiple VOIs can be obtained at one time.
Useful for comparing suspected pathological tissue with normal-appearing contralateral region, or for better assessment of lesion heterogeneity.
- Spectra from smaller VOIs can be obtained compared to SVL techniques.
Less partial volume averaging, better assessment of heterogeneity.
- “Metabolite maps”, in which pixel intensity is proportional to chemical concentration, can be generated.

In Vivo MR Spectroscopy

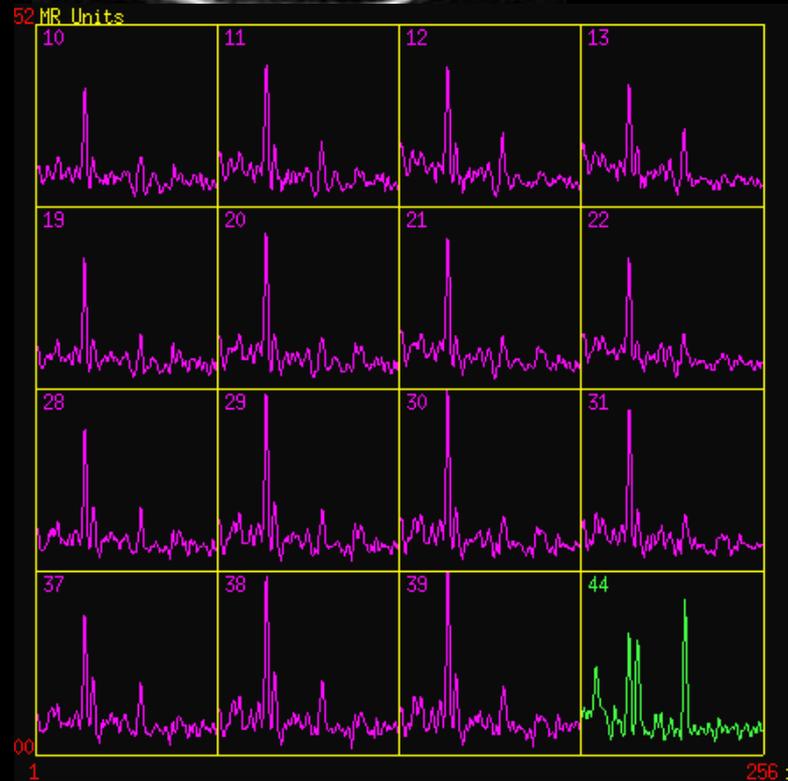


NAA

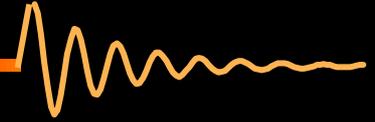


Cho/Cr

Glioblastoma Multiforme



SI Acquisitions



Disadvantages of SI techniques include:

- rather long acquisition times:

$$\text{3DSI:} \quad T_{\text{scan}} = N_{x_{\text{phase}}} \times N_{y_{\text{phase}}} \times N_{z_{\text{phase}}} \times NEX \times TR$$

$$\text{2DSI:} \quad T_{\text{scan}} = N_{x_{\text{phase}}} \times N_{y_{\text{phase}}} \times NEX \times TR$$

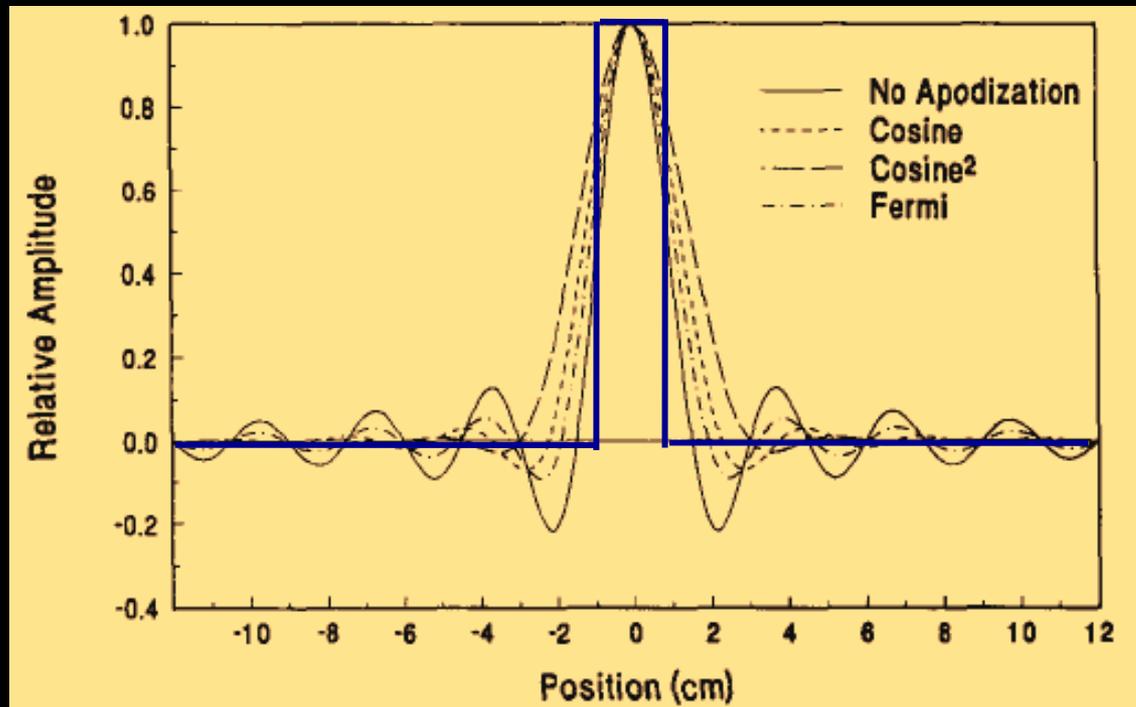
$$\text{1DSI:} \quad T_{\text{scan}} = N_{x_{\text{phase}}} \times NEX \times TR$$

- spatially-dependent water suppression efficiency & spectral quality

much larger volume over which field homogeneity must be optimized -- more difficult to accomplish than with SVL.

- “spectral-bleed” from one voxel to another is possible due to phase-encoding point spread function. (Can be minimized by increasing N_{phases} , but this costs time.)

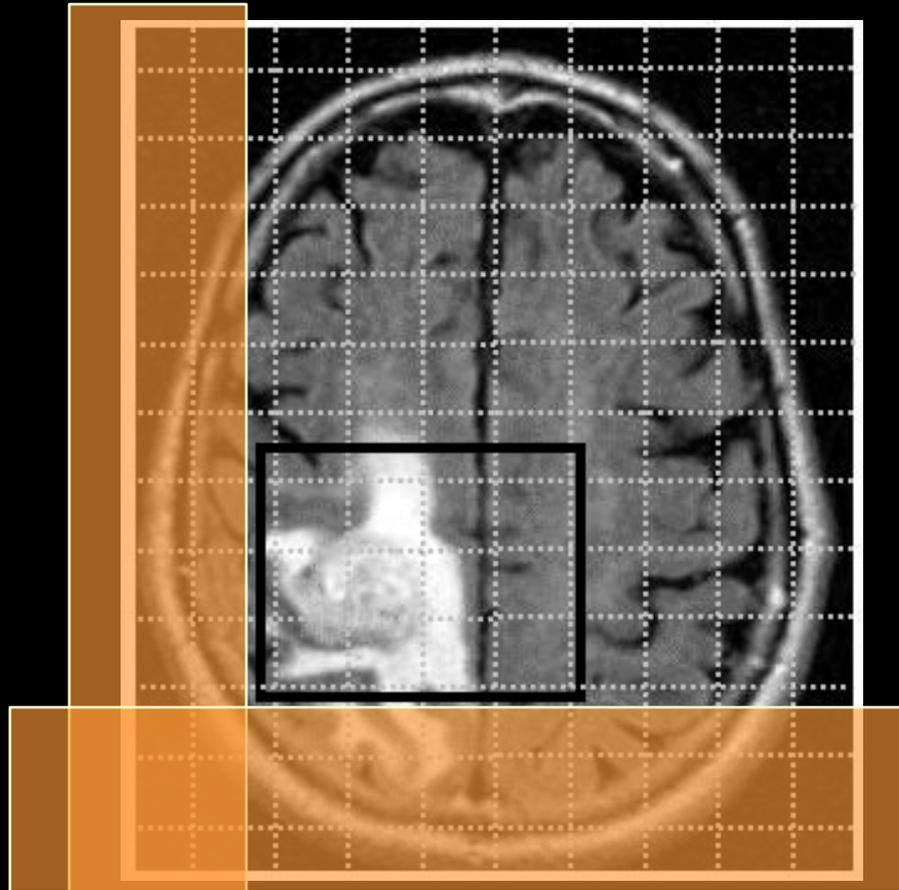
“Spectral Bleed”



Theoretical Voxel Dimension: 1.5 cm

Jackson, et al., *J Magn Reson Imaging* 4:545-551, 1994

Outer Volume Suppression Pulses



PRESS (90°-180°-180°) localization techniques are more commonly used than STEAM (90°-90°-90°) because:

- 20% 1. the echo time can be much shorter
- 20% 2. the repetition time can be much shorter, saving time
- 20% 3. slice selection profiles are sharper for 180° pulses
- 20% 4. only PRESS techniques are compatible with outer volume suppression pulses
- 20% 5. the SNR is superior due to the use of spin-echo detection

Ref: Drost DJ, Riddle WR, Clarke GD. Proton magnetic resonance spectroscopy in the brain: Report of AAPM MR Task Group #9, Med Phys 29(9):2177-2197, 2002.

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Lipid contamination of spectral data acquired with PRESS spectroscopic imaging techniques is typically due to:

- 20% 1. the use of outer volume suppression pulses
- 20% 2. J -coupling of methyl and methylene lipid protons
- 20% 3. insufficient sampling bandwidth
- 20% 4. insufficient number of data samples used to define echo
- 20% 5. limited number of phase-encoding steps

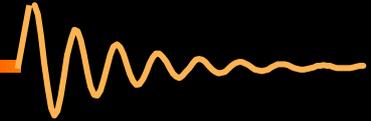
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What is Detected in ^1H -MRS?



In ^1H MRS, the primary peaks are:

- NAA: *N*-acetylaspartate (viable neurons only) 2.0 ppm
- Cr: total creatine (creatine + phosphocreatine) 3.0 ppm
- Cho: choline (phosphotidylcholine, *etc.*) 3.2 ppm
- Lac: lactate 1.4 ppm

(All of the above can be detected at short *and* relatively long TE acquisitions.)

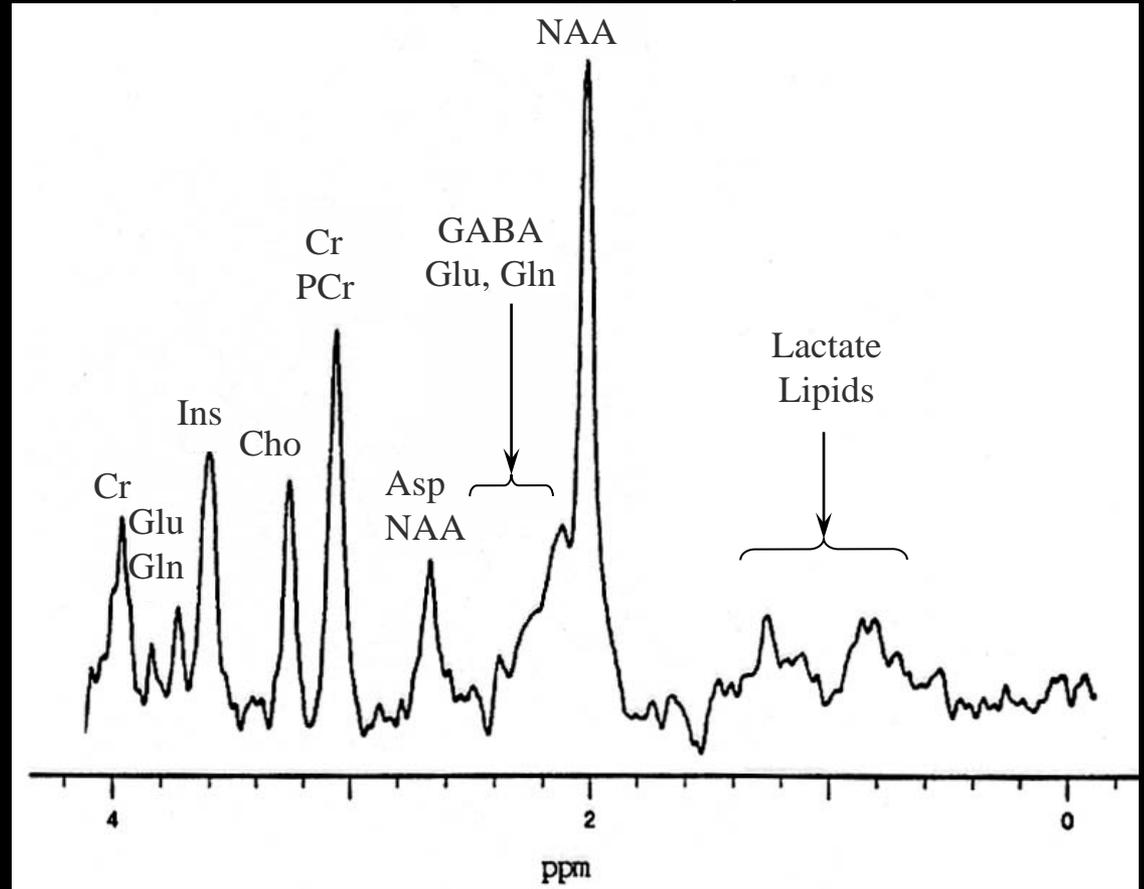
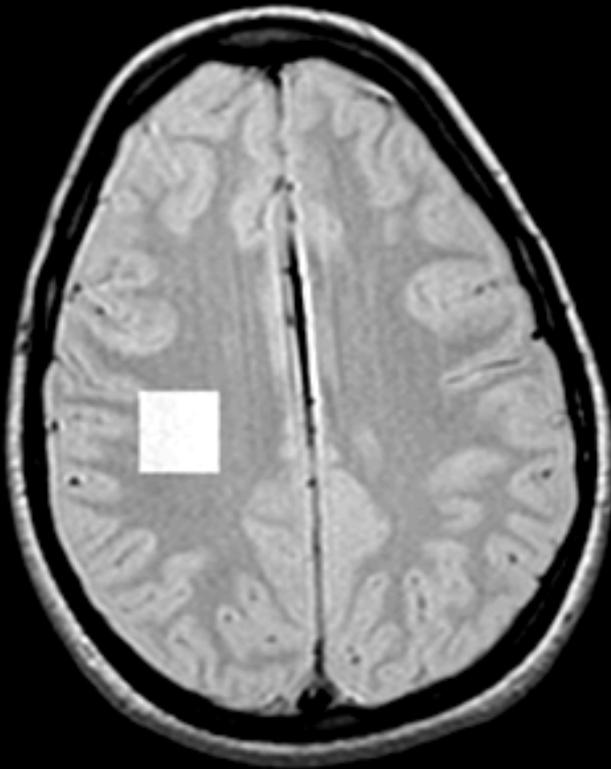
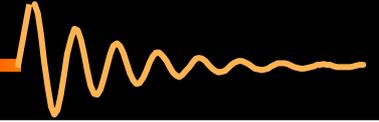
- GABA: γ -aminobutyric acid
- Simple amino acids, *e.g.*, glutamate, glutamine
- NAAG: *N*-acetylaspartylglutamate
- Asp: aspartate
- Citrate

(The above are in the 2.2-2.6 ppm range.)

- Lipids: range of chemical shifts, but dominant is methyl at 1.3 ppm
- Ins: *myo*-inositol 3.6 ppm
- Glucose: 3.5 ppm

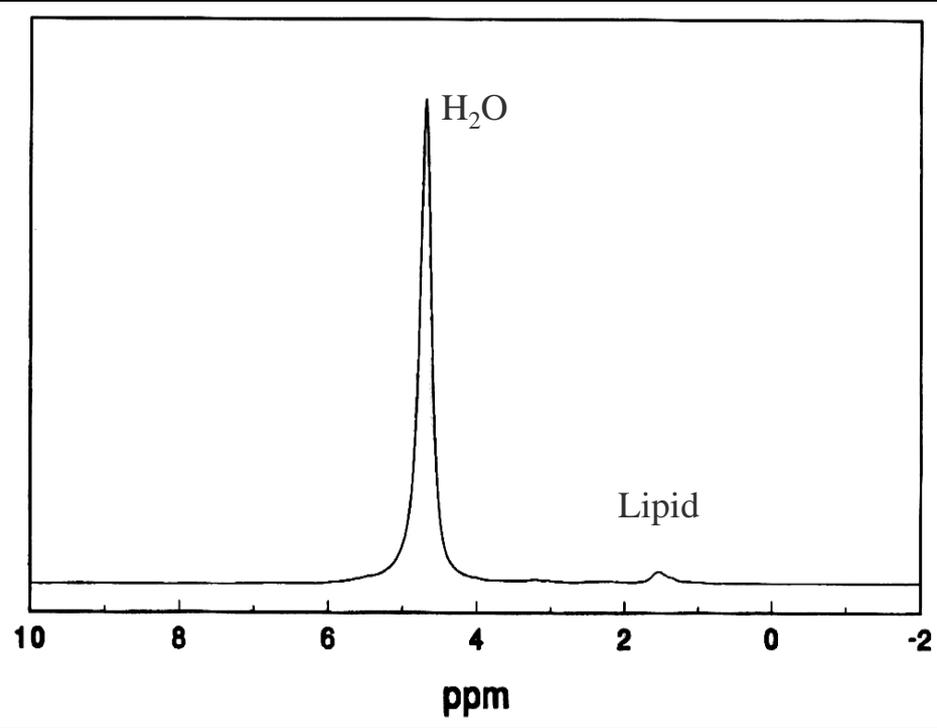
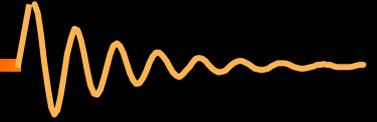
(The above require relatively short TE acquisitions.)

Short TE ^1H MRS

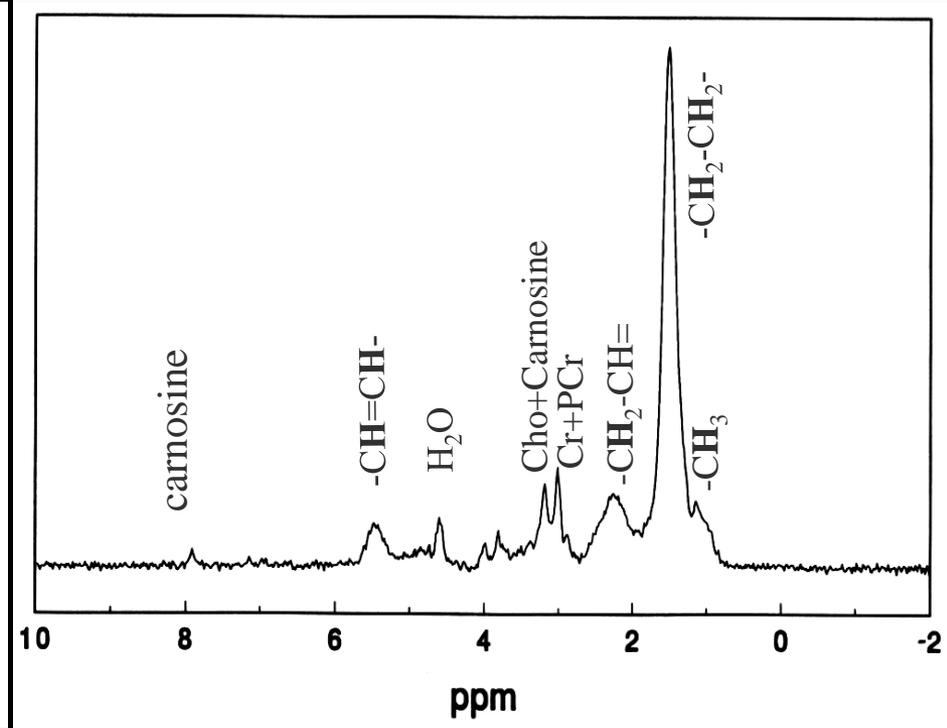


TE=20ms, TM=7.7ms, TR=3000ms - 2x2x2 cm VOI

^1H MRS - Gastrocnemius Muscle

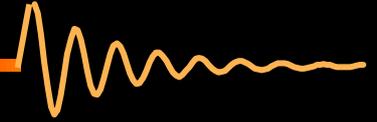


Without H₂O Suppression



With H₂O Suppression

Choice of Echo Times



- Note that the choice of echo times in MRS exams is important.
- As you increase TE, of course, the signal amplitudes from all metabolites decrease due to spin dephasing.
- Short TE: more spectral peaks means more options for lesion characterization or evaluation of therapy. *However*, the examinations are more challenging to obtain reproducibly, mainly due to decreased water suppression efficiency.

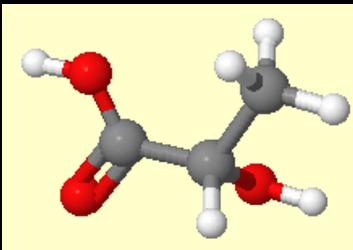
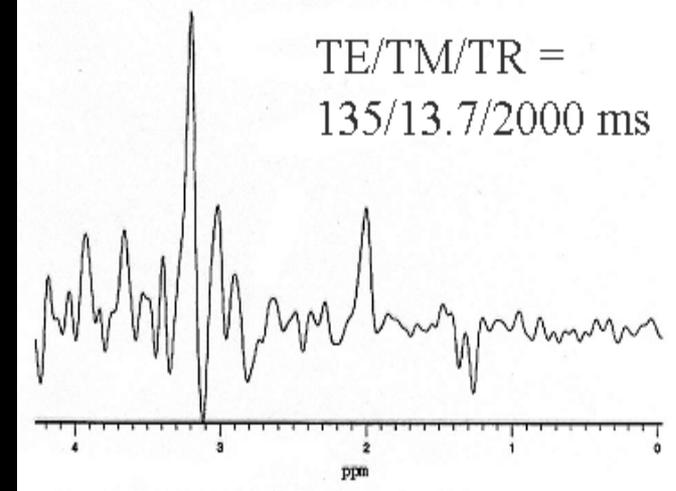
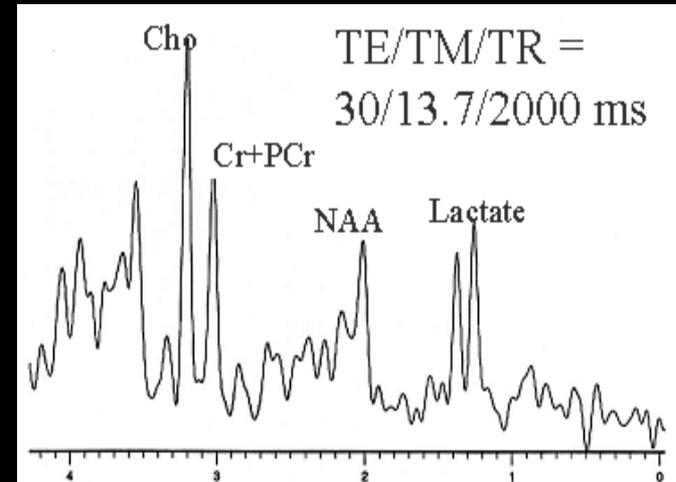
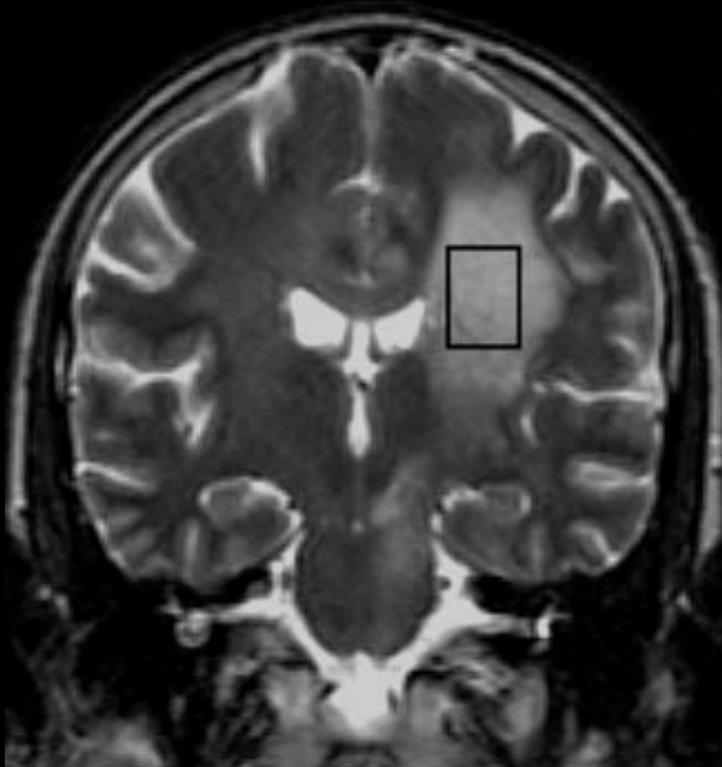
Choice of Echo Times



There are certain choices of echo times that prove very useful in verifying peak assignments. For example, lipid and lactate peaks overlap strongly at 1.5T. To separate them, one can use a TE that takes advantage of the J -coupling that occurs in lactate.

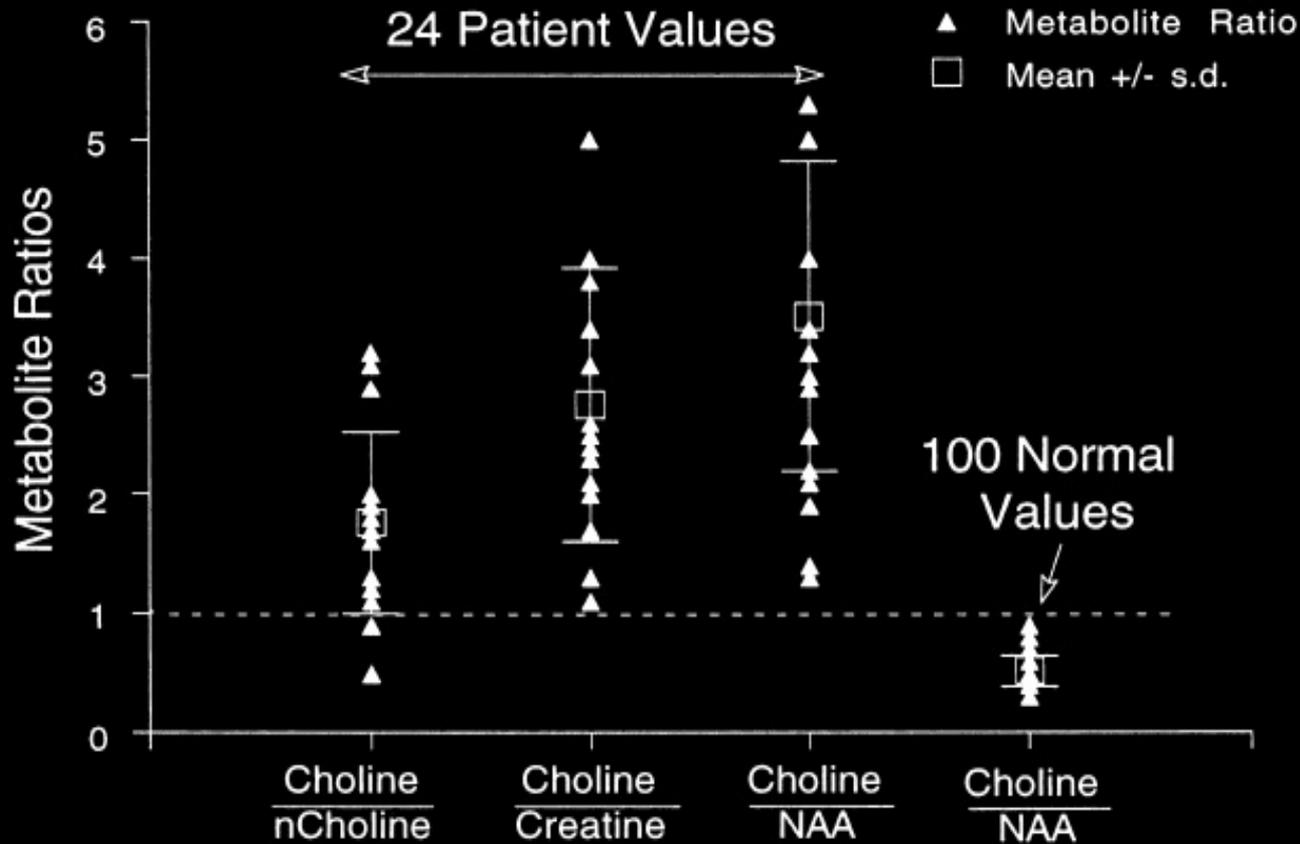
- The use of TE~135ms will result in an inverted lactate peak in phased MR spectra.
- The use of TE~270ms will result in a totally “in-phase” lactate resonance.
- Since lipid protons do not exhibit the coupling, the lipid peaks will be “in-phase” in both cases (no inversion).
- The J -coupling constant (6.93 Hz) is independent of B_0 .

^1H MRS - Glioma



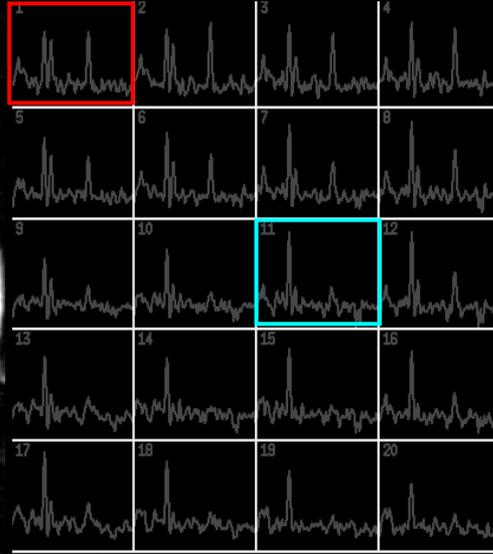
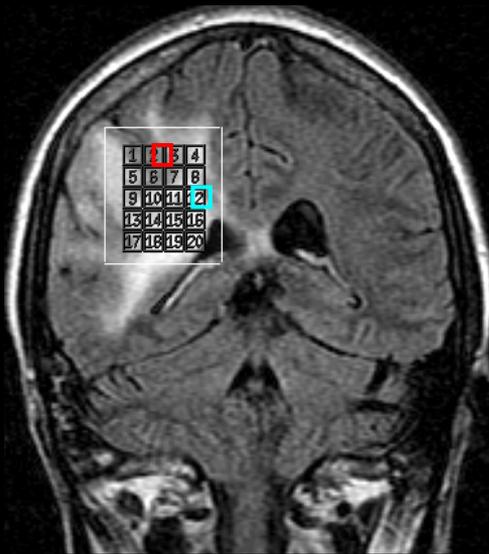
Lactic Acid
 $\text{C}_3\text{H}_6\text{O}_3$

^1H MRS - Glioma

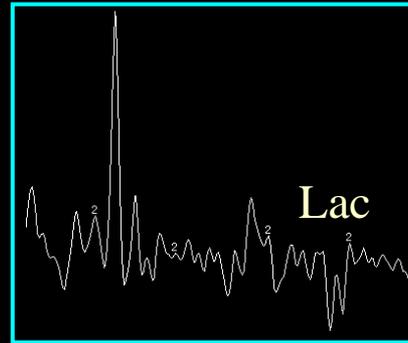
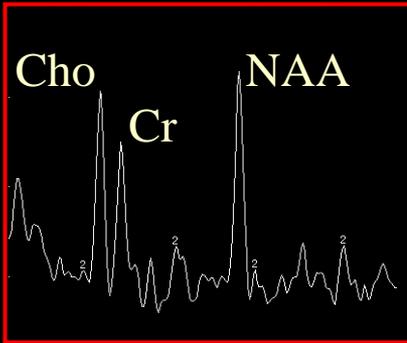


Kurhanewicz, Neoplasia 2:166-189, 2000

In Vivo ^1H MRS



^1H MR Spectroscopic Imaging Applications

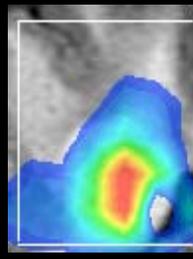
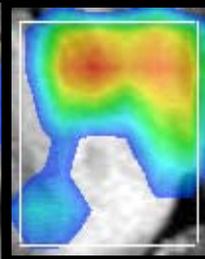
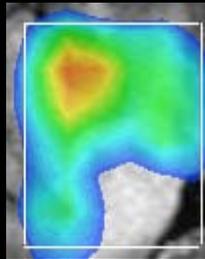
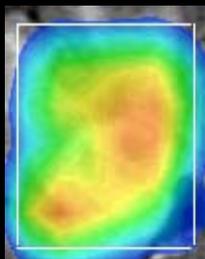


NAA: *N*-acetylaspartate

Cho: Choline compounds

Cr: Creatine/ phosphocreatine

Lac: Lactate



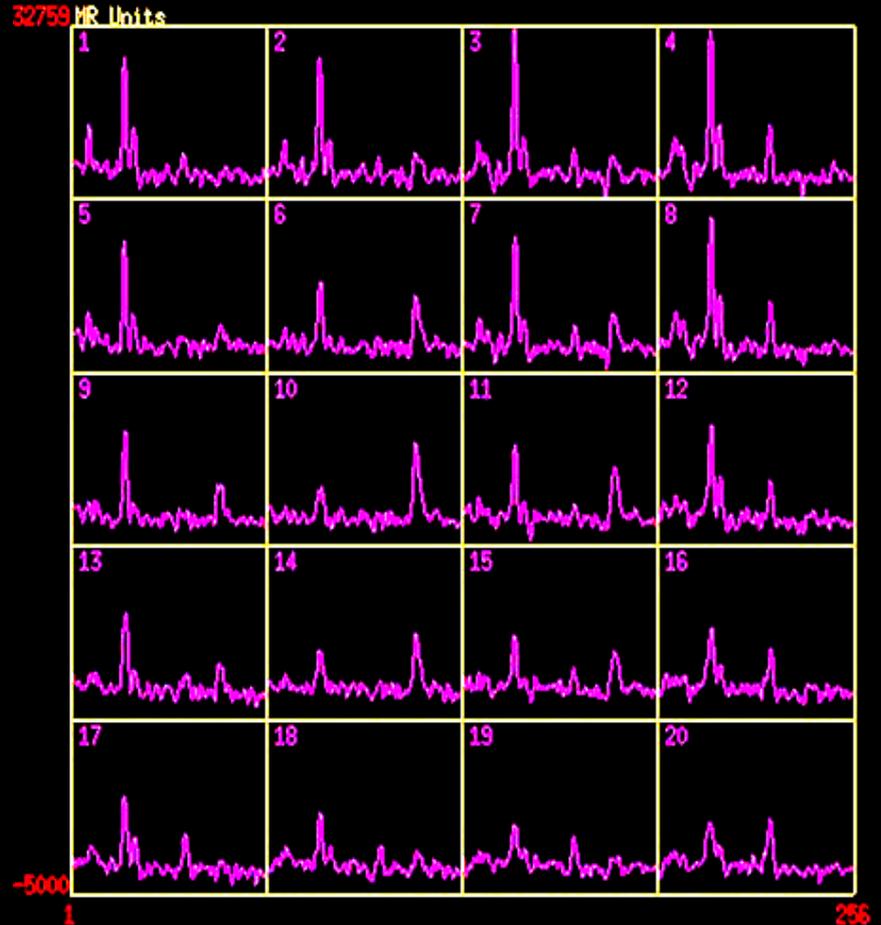
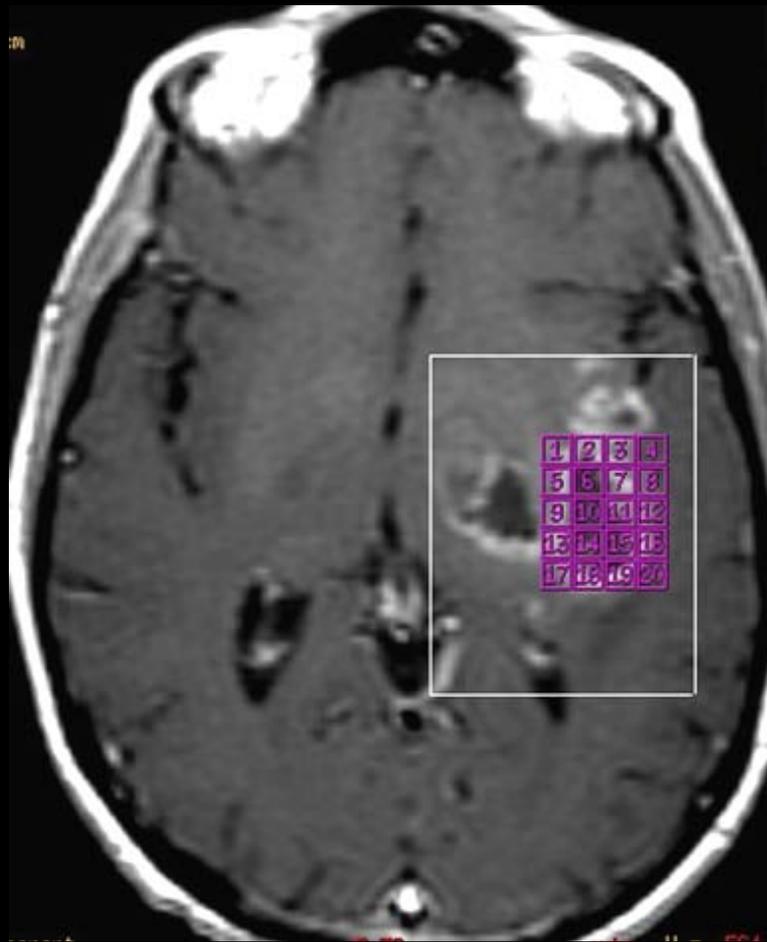
Cho

Cr

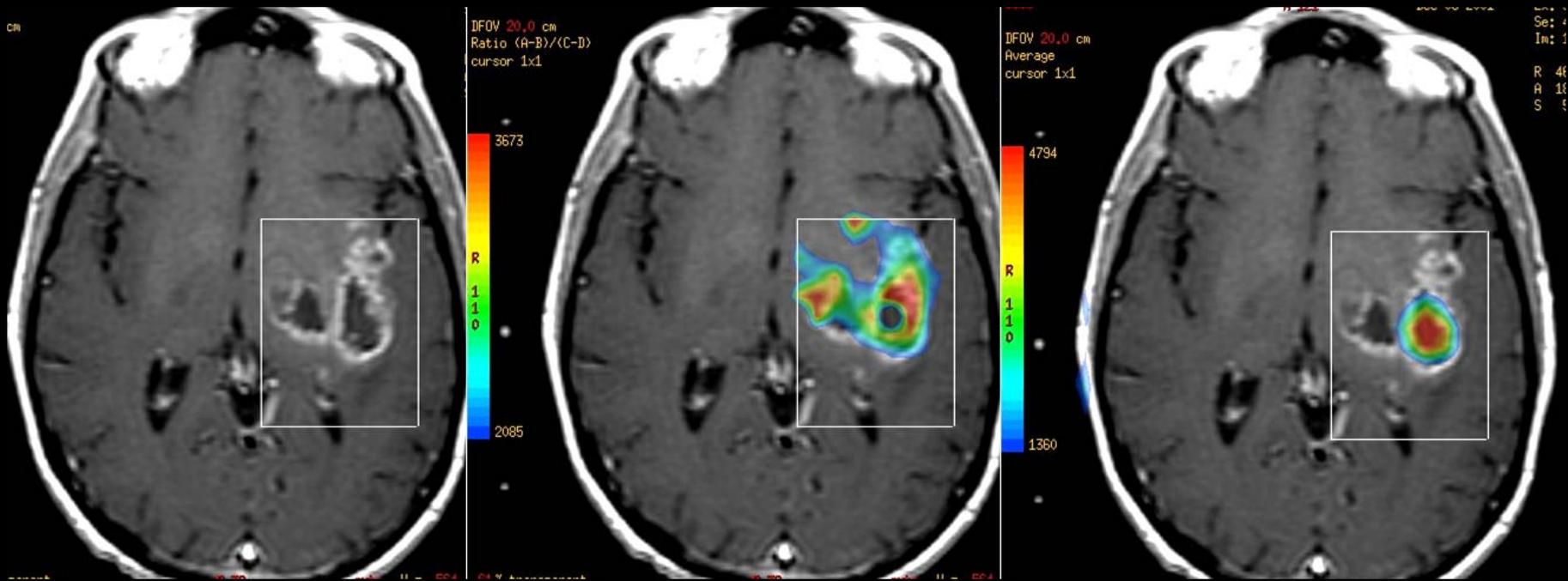
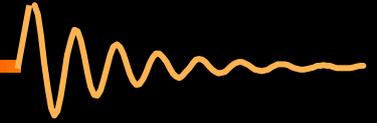
NAA

Cho/Cr

Tumor and Necrosis



Tumor and Necrosis

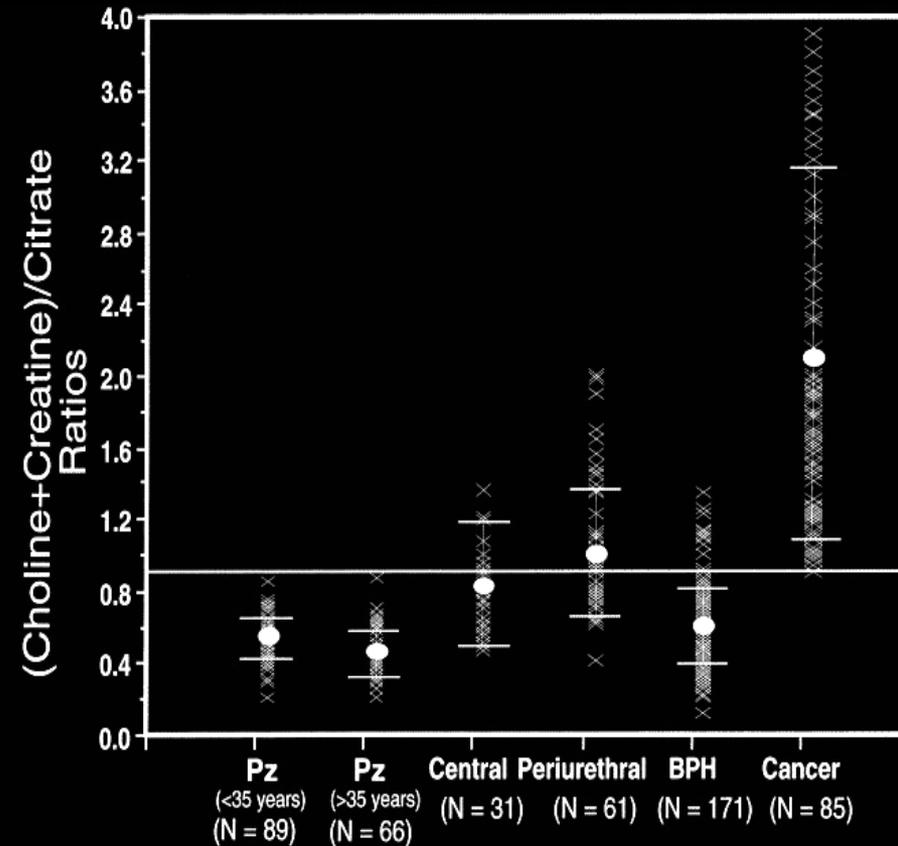
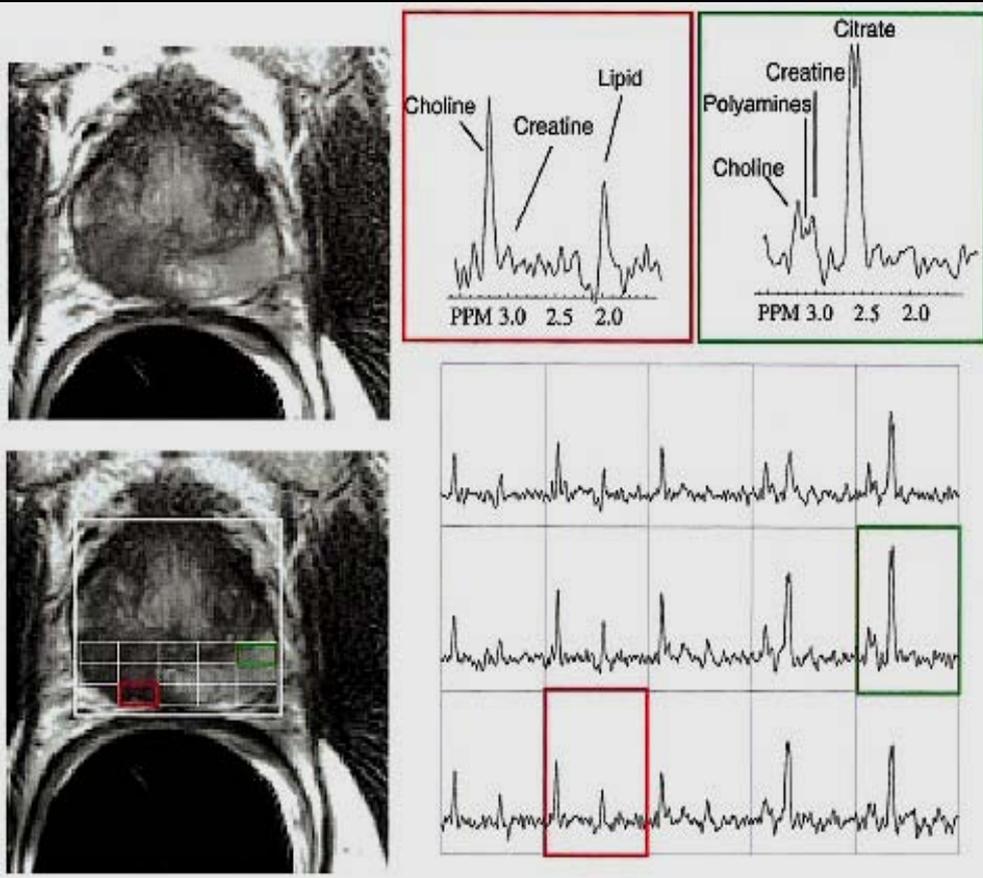


T1+C

Cho/Cr Map

Lipids

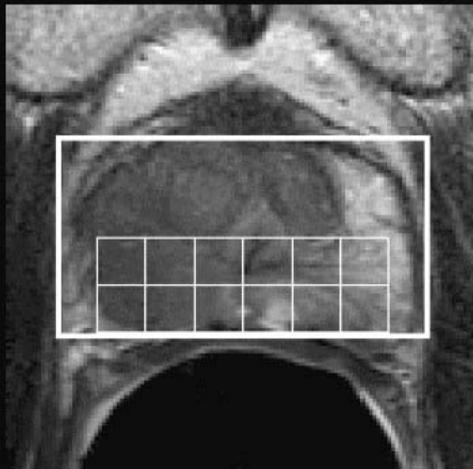
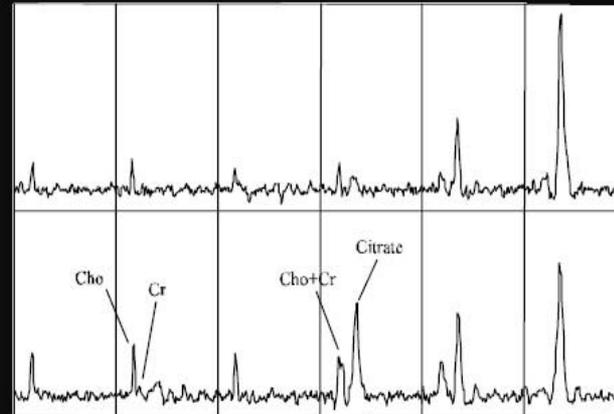
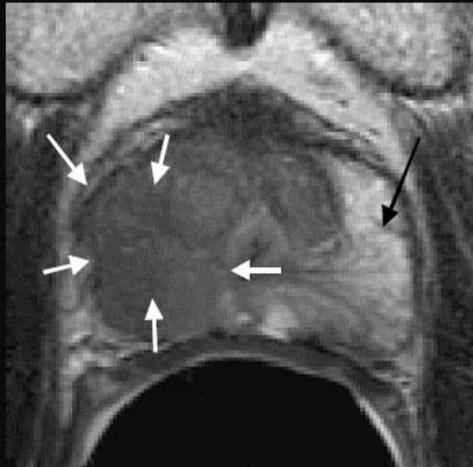
Prostate ^1H MRS



Kurhanewicz et al., *JMRI* 16:451, 2002

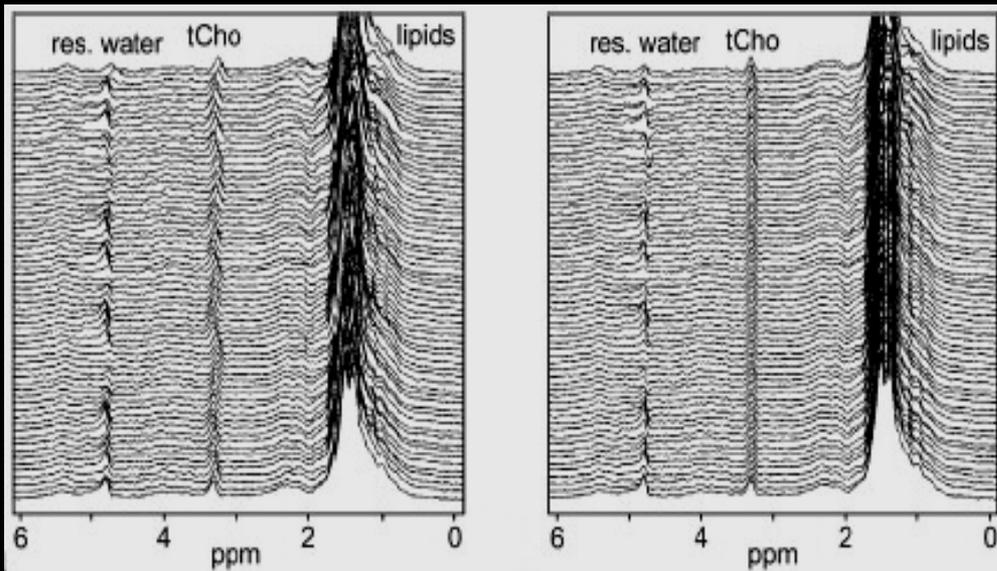
Kurhanewicz, *Neoplasia* 2:166-189, 2000

Prostate ^1H MRS

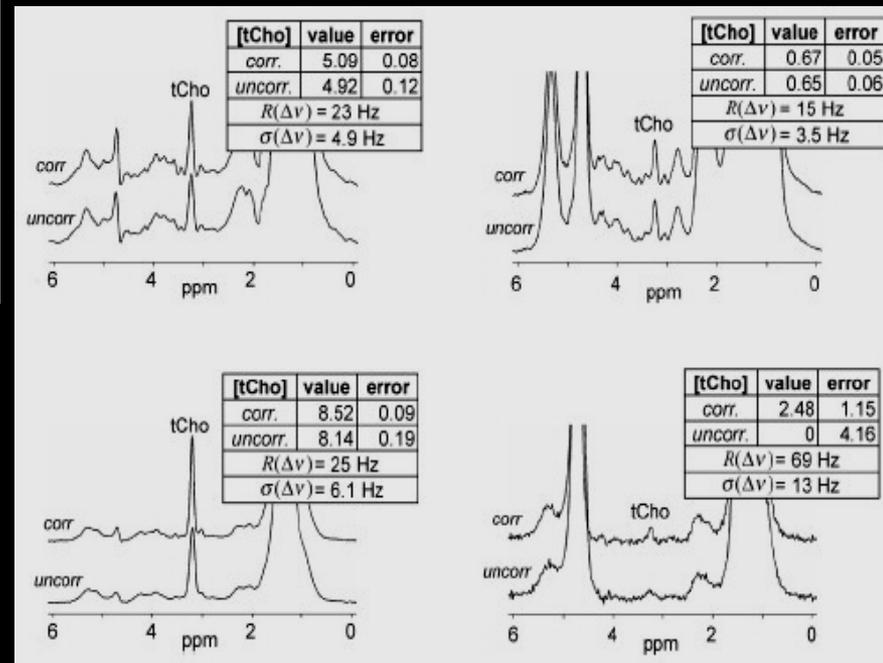


Kurhanewicz, Neoplasia 2:166-189, 2000

Breast ^1H MRS

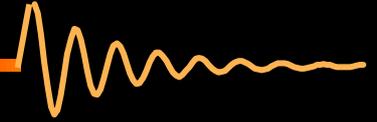


Frequency correction (cross-correlation) to compensate for respiratory motion.



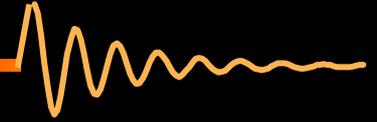
Bolan et al., Magn Reson Med 52:1239, 2004

General ^1H MRS Findings



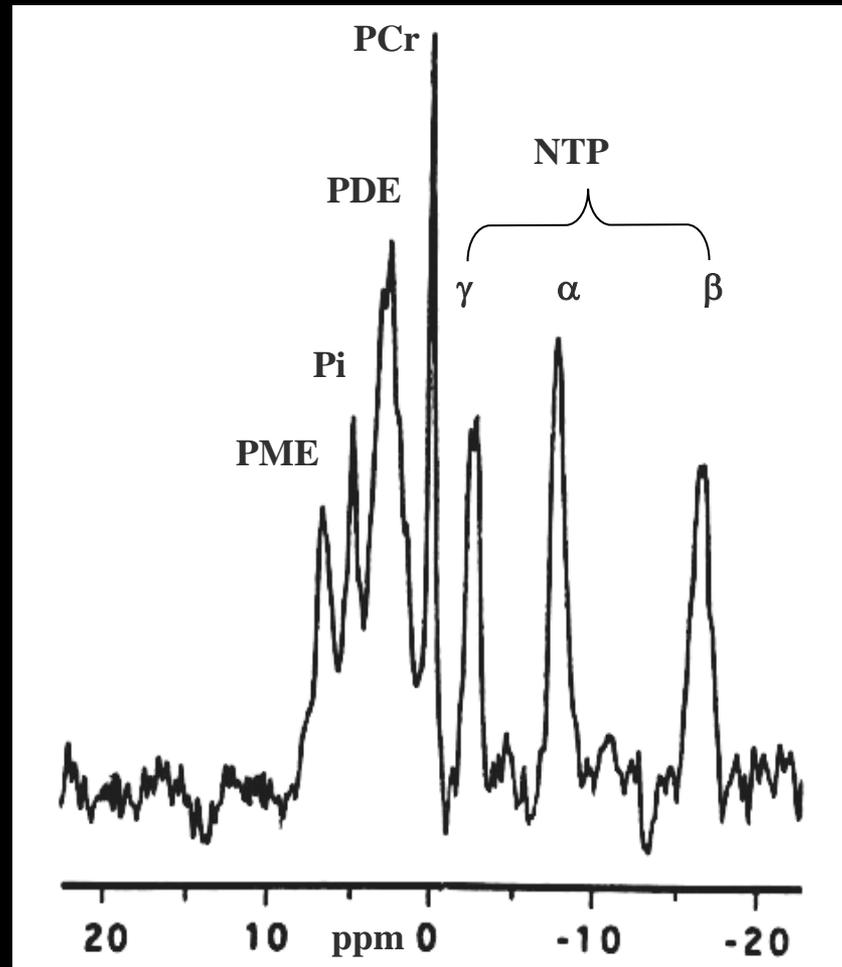
- The most consistent indication of malignant lesions is an elevation in choline (CNS, prostate, breast).
- In brain, the degree of elevation in Cho/NAA and Cho/Cr is, in general, indicative of tumor grade.
- In prostate, malignant lesions demonstrate a decrease in citrate and an increase in choline as compared to normal tissue and benign disease, *e.g.*, BPH.
- Following effective chemotherapy or radiation therapy, the most consistent finding is a decrease in choline.
- In non-enhancing lesions, MRS is a useful tool for biopsy guidance.

What Is Detected (^{31}P MRS)?

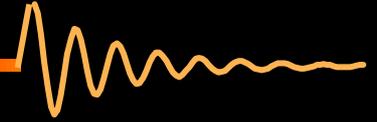


- In ^{31}P MRS the following peaks can be detected:
 - PCr: phosphocreatine 0 ppm
 - Pi: inorganic phosphate ~ -5 ppm
 - ATP:
 - γ : ~ 2 ppm
 - β : ~16 ppm
 - α : ~ 6 ppm
 - PDE: phosphodiester ~ -8 ppm
 - PME: phosphomonoesters ~ -3 ppm
- Also, the chemical shift of the Pi peak relative to the PCr peak provides a means of obtaining intracellular pH noninvasively.

^{31}P MRS (Human Brain)

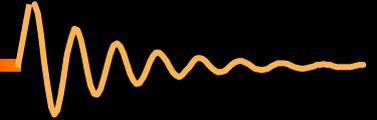


We've Got Peaks, Now What?



- While some information can be gleaned from visual examination of spectral peaks, quantitative assessment is necessary to really put MRS to its fullest use.
- It can be shown that the area under the spectral peak is proportional to the concentration of the corresponding compound.
- Measuring peak heights, while much simpler, is less accurate.

Spectral Quantification



Quantitative analysis comes in two forms:

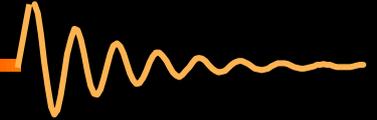
– Relative concentrations

- Most commonly involves taking the ratio of peak areas, *e.g.*, NAA/Cr and Cho/Cr in brain.
- Problem: Changes in ratios can be due to changes in, for example, NAA *or* Cr.

– Absolute concentrations

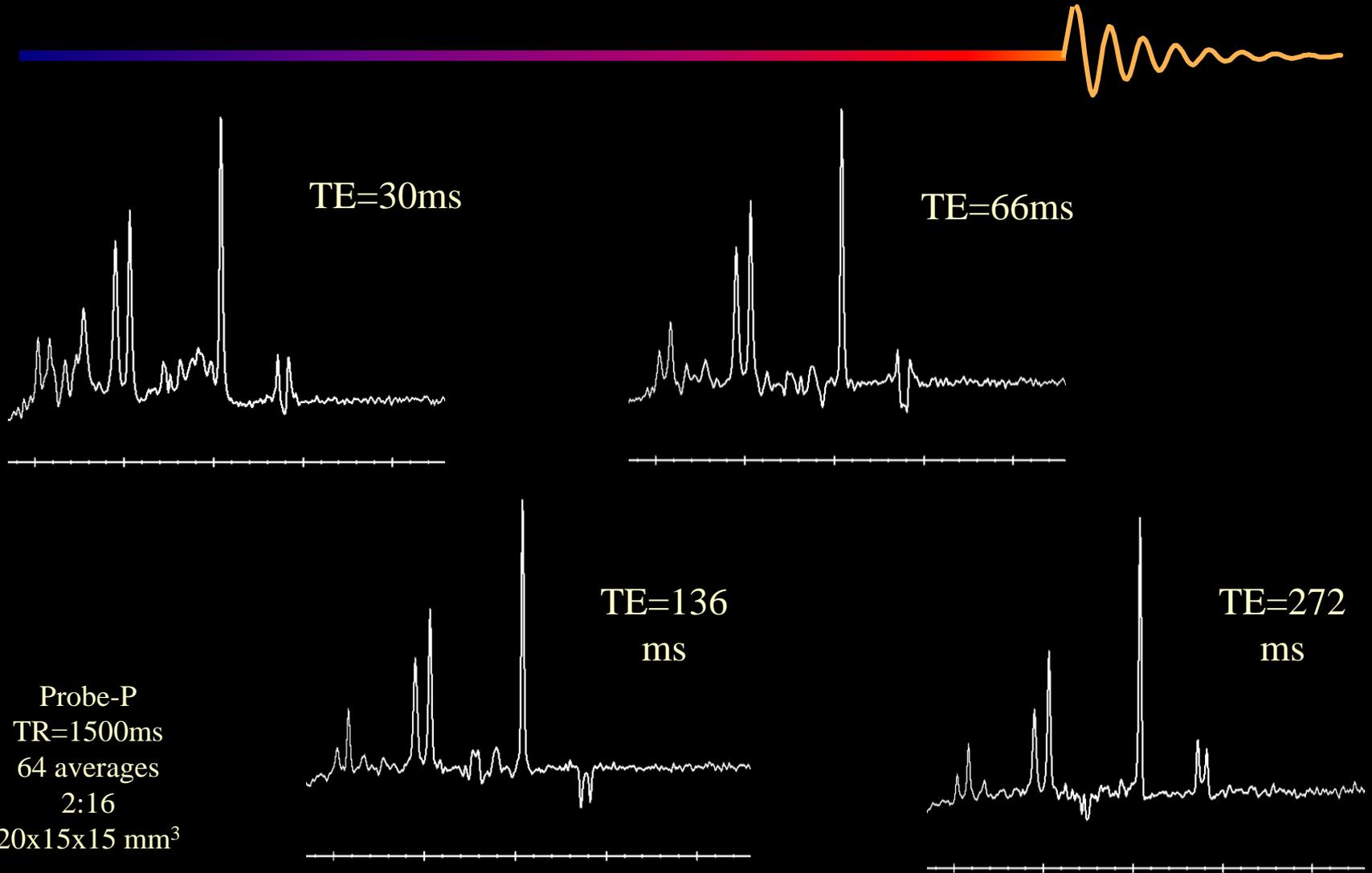
- Much more difficult and requires some form of “standard”.
- External standard: small container of known concentration of reference sample from which reference spectrum is obtained.
- Internal standard: most commonly taken as water.

Chemical Specific T_1 and T_2



- When reviewing MRS data in the literature, and particularly when comparing your data against others, or data acquired from multiple groups, be sure you take the TE and TR times into account.
- Each metabolite has its own T_1 and T_2 relaxation times. Therefore, as you change TE and/or TR, the relative peak areas and heights change.
- If you must compare data acquired at different TE and TR values, you can approximately normalize the data using the equations for T_2 -decay and T_1 -recovery appropriate for the particular localization sequence, and the reported *in vivo* T_1 and T_2 relaxation times for the metabolites of interest.

Effect of Echo Time



The choice of echo time in proton MRS will influence each of the following *except* the:

- 0% 1. ratio of the spectral peak amplitudes
- 0% 2. inherent spectral resolution
- 0% 3. phase of the lactate peak
- 0% 4. degree of observed water suppression
- 0% 5. SNR of the resulting spectra

Ref: Drost DJ, Riddle WR, Clarke GD. Proton magnetic resonance spectroscopy in the brain: Report of AAPM MR Task Group #9, Med Phys 29(9):2177-2197, 2002.

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Hyperpolarized Agents

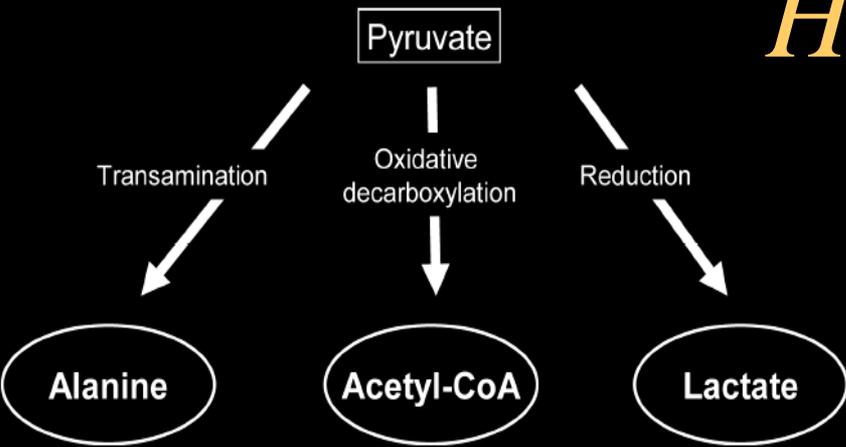
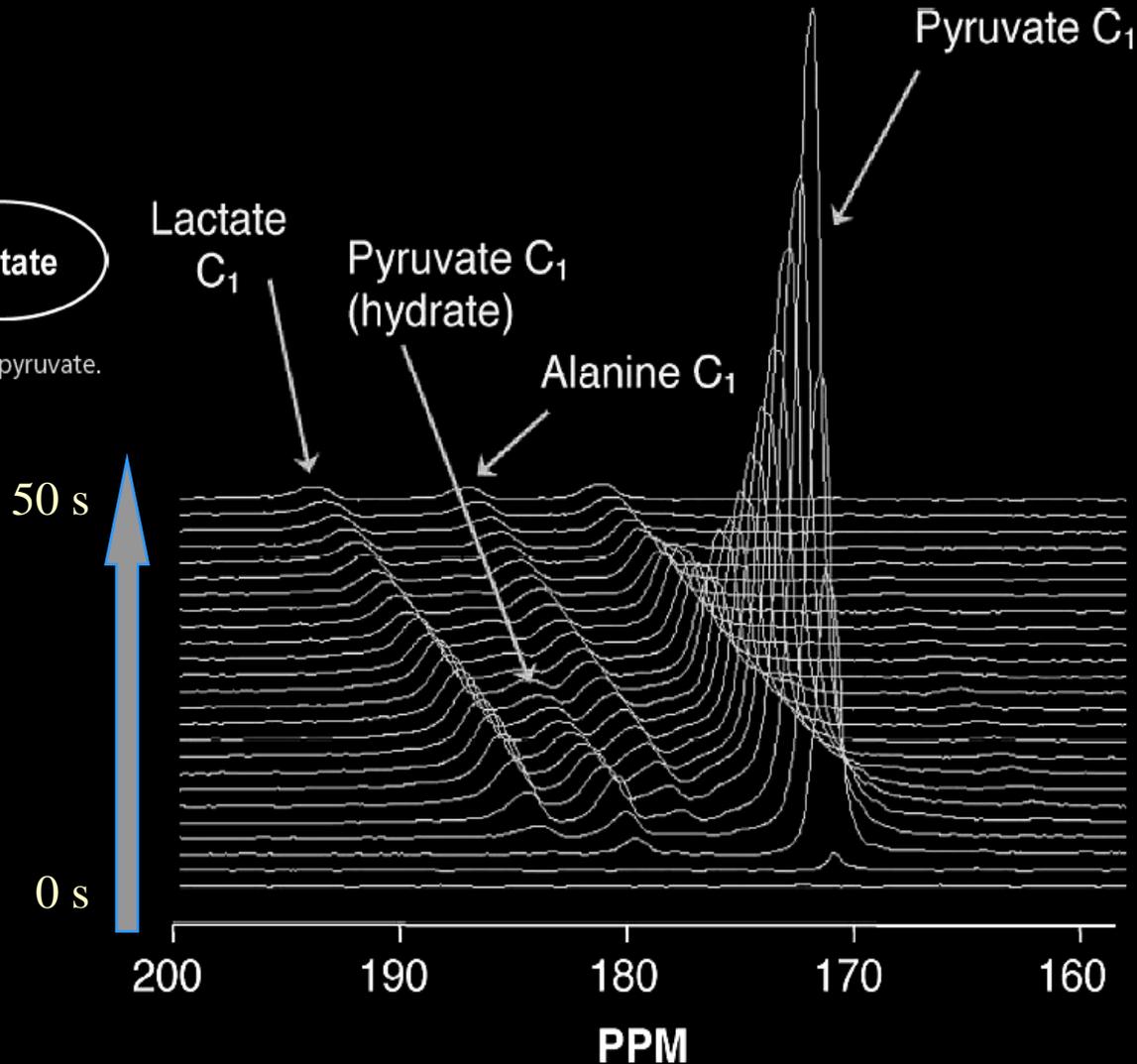


Fig. 1. Simplified overview of the main metabolic pathways of pyruvate.

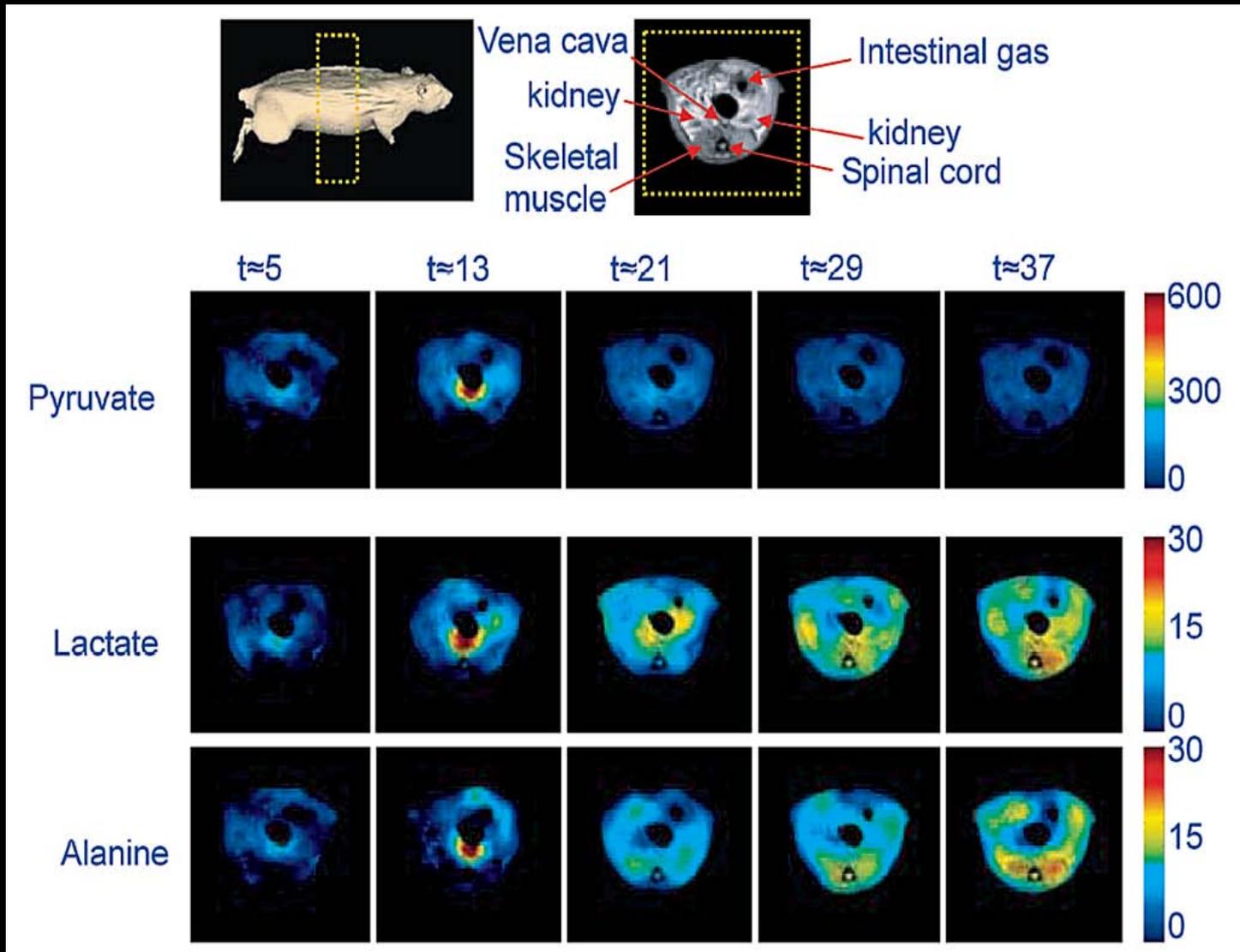
Injection of hyperpolarized $^{13}\text{C}_1$ -pyruvate at time $t = 0$ s.

Data obtained every 3 s following injection from rat muscle.

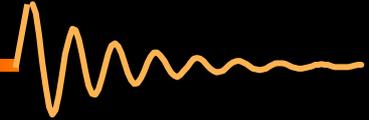


Golman et al., PNAS, 103:11270, 2006

Hyperpolarized Agents



References



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- <http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/Spectrpy/nmr/nmr1.htm>
- Castillo, *Neuroimaging Clinics N Am*, 8(4), 1998. (*Proton MR Spectroscopy of the Brain*)
- Ross and Michaelis, *Magn Reson Q*, 10(4):191-247, 1994. (Mainly ^1H .)
- Bottomley, *Radiology*, 170:1, 1989. (Almost exclusively ^{31}P .)