

1. Basics of MR Spectroscopy

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M219: Introduction to Magnetic Resonance Imaging/03/04/24





Basics of MRI and MRS Physics

Single-voxel localized MRS

Selected Applications



1. Basics of MR Imaging (MRI) and MR Spectroscopy (MRS)

Historical Perspective

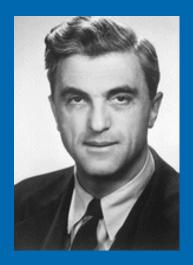


≻ 1940's

- Radio (RADAR) technology developed during WWII lead to a new approach to measuring the proton spin
 - Protons have an electric charge
 - Protons have spin
 - Therefore it could be possible to measure the spin by placing the protons in a magnetic field and then measuring radio frequency emissions or absorptions
- Edward Purcell (Harvard/MIT) and Felix Bloch (Stanford) were awarded the Nobel Prize in Physics in 1952 for independently detecting nuclear magnetic resonance signals for the first time using this methodology

Magnetic Resonance

Nobel Prize in Physics 1952



Felix Bloch Ph.D.



Edward Purcell Ph.D.



Historical Perspective

≻ 1950-1970's

- NMR became a much used technique for study of molecular structure
 - Chemistry
 - Molecular Biology
 - Materials Science
- Prof. Richard Ernst developed a highly efficient technique based on the Fourier Transform for the detection and quantification of the NMR signal
 - 1991 Nobel Prize in Chemistry
 - Fourier transform technique also proved to be the most efficient approach for MRI



Historical Perspective

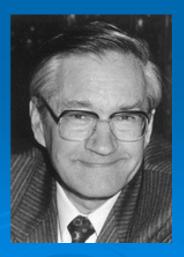
≻ 1970's

- Prof. Raymond Damadian (SUNY-Downstate Medical Center) proposed that cancer tissue had abnormal relaxation time and built the first human MRI scanner
- Prof. Paul Lauterbur[†] (SUNY-Stony Brook) demonstrated how to make images from NMR signals using magnetic field gradients in conjunction with a 'back projection' technique used in CT imaging
 - Awarded the 2003 Nobel Prize in Medicine or Physiology with Mansfield
- Prof. Peter Mansfield (Nottingham) developed a more efficient 'echo planar imaging' technique and did fundamental studies involving MRI of solids
 - Awarded the 2003 Nobel Prize in Medicine or Physiology with Lauterbur

Nobel Laureates in *Magnetic Resonance*



Felix BlochEdward Mills PurcellNobel Prize in Physics1952



Richard R. Ernst Nobel Prize in Chemistry in 1991



Paul C. Lauterbur Sir Peter Mansfield Nobel Prize - Medicine 2003



Historical Perspective

≻ 1980's

- First commercial MRI scanners based on the Fourier imaging technique
- First commercial superconducting MRI magnets

≻ 1990's

 Development of medical and basic science applications

> 2000's

Hardware and software engineering sophistication



Nuclear Magnetic Resonance

Nuclear spin moment

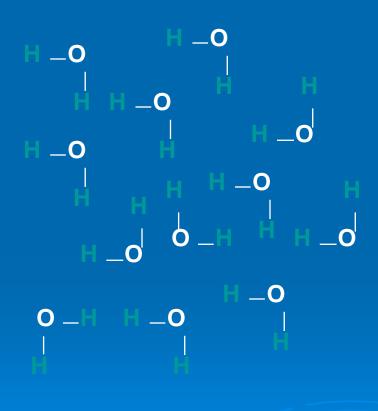
μ = γħ I
μ - magnetic moment
γ - gyromagnetic ratio
I - spin quantum number
ħ - Planck's constant

I is a property of the nucleus		
Mass #	Atomic #	Ι
Odd	Even or odd	1/2, 3/2, 5/2,
Even	Even	0
Even	Odd	1, 2, 3





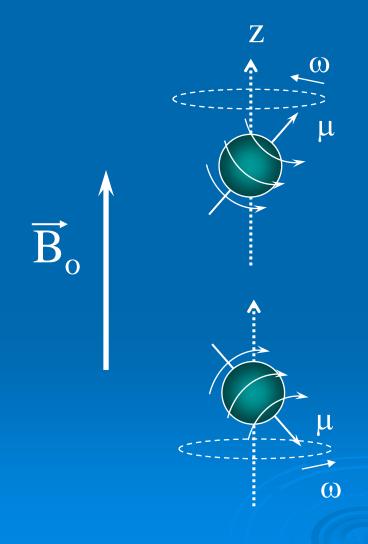
Water Molecule



Apply an external magnetic field



(i.e., put your sample in the magnet)

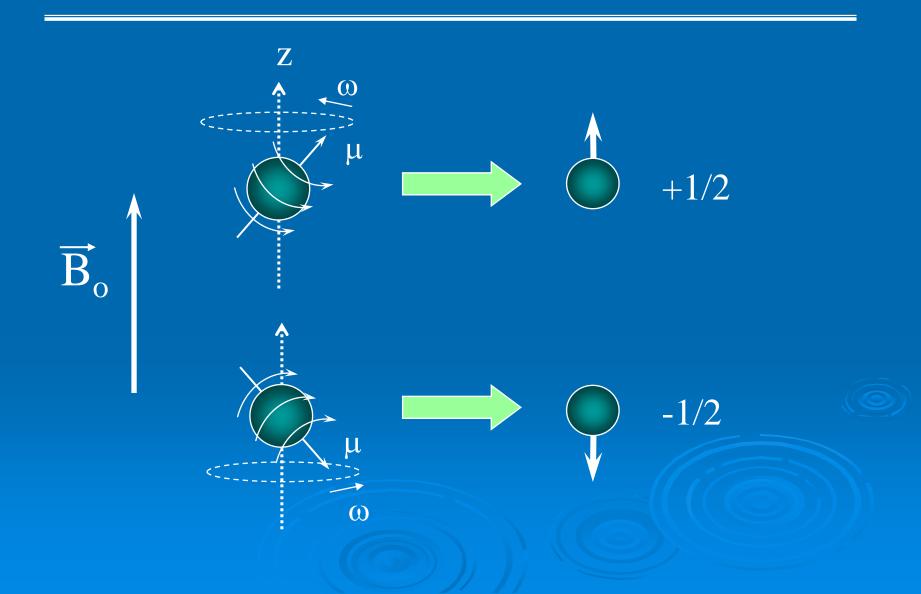


 $\omega = \gamma B_o = \nu/2\pi$

 ω - resonance frequency in radians per second, also called Larmor frequency v - resonance frequency in cycles per second, Hz γ - gyromagnetic ratio B_o - external magnetic field (the magnet) Spin 1/2 nuclei will have two orientations in a magnetic field

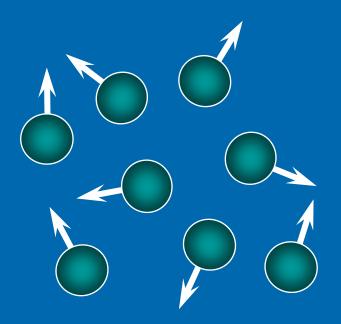
+1/2 and -1/2.

Net magnetic moment





Ensemble of Nuclear Spins



$\overrightarrow{B}_{o} = 0$ Randomly oriented



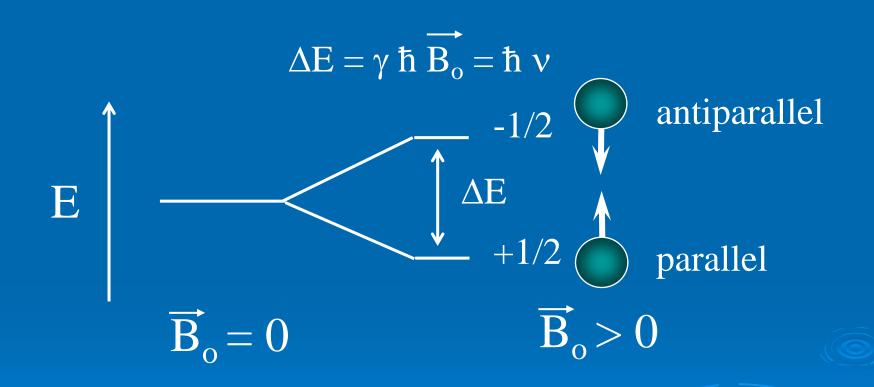
Each nucleus behaves like a bar magnet.

 $\vec{B}_{o} > 0$

Highly oriented



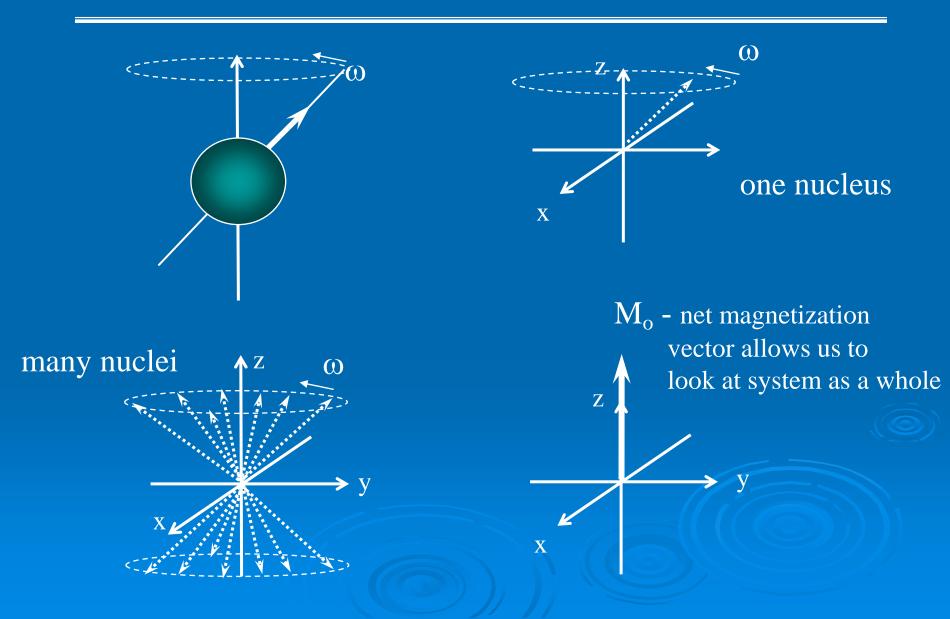
Allowed Energy States for a Spin 1/2 System



Therefore, the nuclei will absorb light with energy ΔE resulting in a change of the spin states.

The net magnetization vector

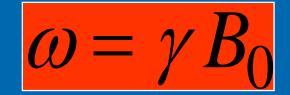






MR Imaging

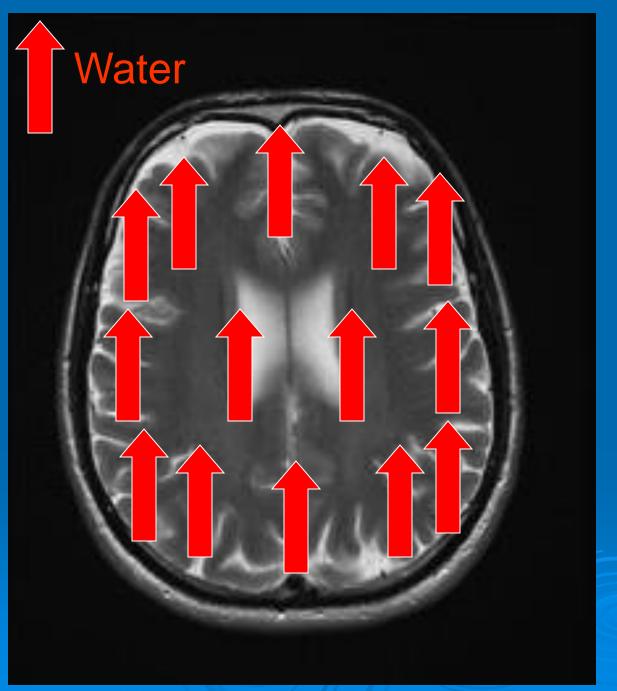
Larmor Equation:



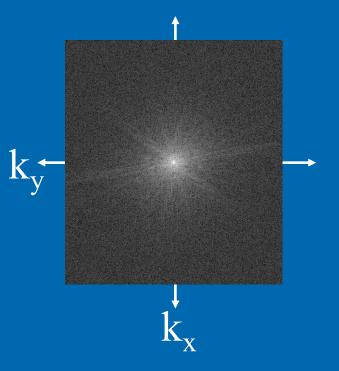
Larmor Frequency

constant

gyromagnetic Apply spatially varying frequency and phase encoding magnetic field gradients

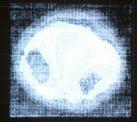




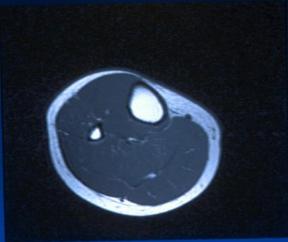




MRI: Day one









Magnetic Resonance Imaging (MRI)

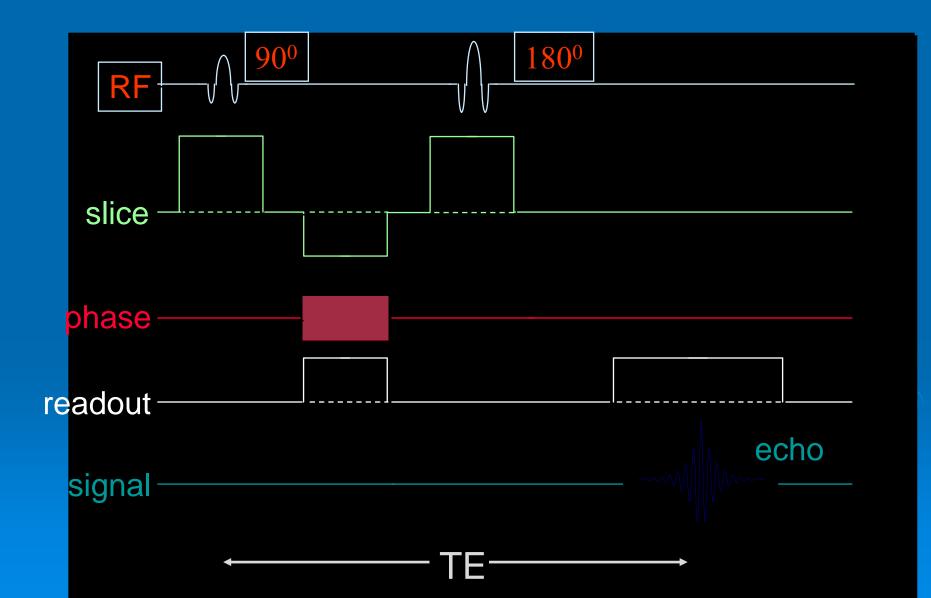
- MRI exploits Nuclear Magnetic Resonance (NMR) to produce water-based images
 - Signal from ¹H in water
 - Gray scale caused by T1/T2 relaxation and ¹H density within a voxel
- MRI resolution
 - 512x512 voxels in a slice
 - Sub-millimeter voxel volume
- Structural differences cause
 T1/T2 relaxation variation
 among voxels
 - No biochemical information

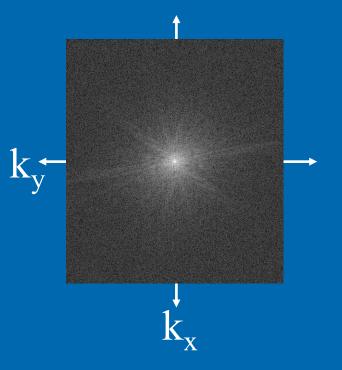


Magnetic Resonance Imaging

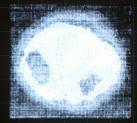
> provides anatomical images T1 and T2 Weighted MRI Contrast enhanced MRI > MR Angiography (MRA) Interventional MRI (iMR) > functional MRI (fMRI) Perfusion MRI Magnetization transfer (MT) MRI and Spinlocking Diffusion-weighted MRI (DWI) and DTI

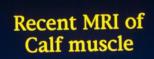
Spin Echo MRI pulse timing

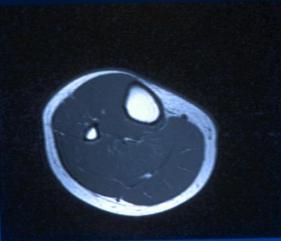




MRI: Day one







Problems with Anatomical Imaging

- Despite its superb soft tissue contrast and multiplanar capability, anatomical MRI is largely limited to depicting morphological abnormality.
- Anatomical MRI suffers from nonspecificity. Different disease processes can appear similar upon anatomic imaging, and in turn a single disease entity may have varied imaging findings.

The underlying metabolic or functional integrity of brain cannot be adequately evaluated based on anatomical MRI alone. To that end, several physiology-based MRI methods have been developed to improve tumor characterization.

Functional Imaging

- Four physiology-based MRI methods have been developed to improve tissue characterization:
- Diffusion Weighted (DW) MRI: In addition to early diagnosis of cerebral ischemia, DW MRI is extremely sensitive in detecting other intracranial disease processes, including cerebral abscess, traumatic shearing injury, etc.
- Perfusion Imaging: Dynamic susceptibilityweighted contrast-enhanced (DSC) perfusion MRI of the brain provides hemodynamic information.
- CEST/Para-CEST/APT: Recently developed new class of MR contrast agents
- MR Spectroscopy

In Vivo NMR Spectroscopy

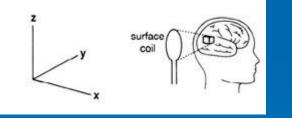
1987, The British Journal of Radiology, 60, 367-373

April 1987

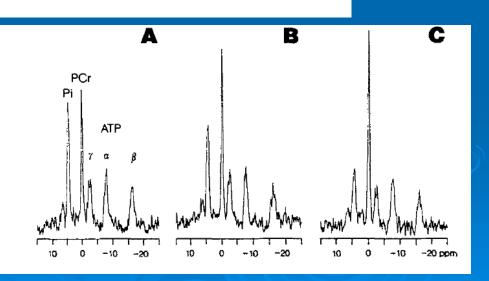
The study of human organs by phosphorus-31 topical magnetic resonance spectroscopy

By Rolf D. Oberhaensli, M.D., Graham J. Galloway, Ph.D., David Hilton-Jones, M.R.C.P., Peter J. Bore, F.R.C.S., Peter Styles, D.Phil., Bheeshma Rajagopalan, M.R.C.P., D.Phil., Doris J. Taylor, D.Phil. and George K. Radda, D.Phil., F.R.S.

MRC Clinical Magnetic Resonance Facility, John Radcliffe Hospital, Headington, Oxford OX3 9DU

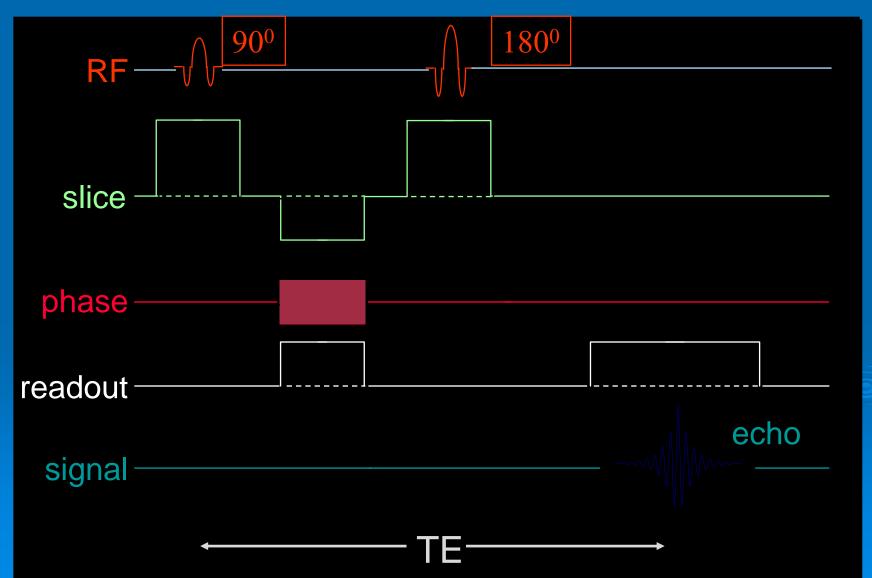


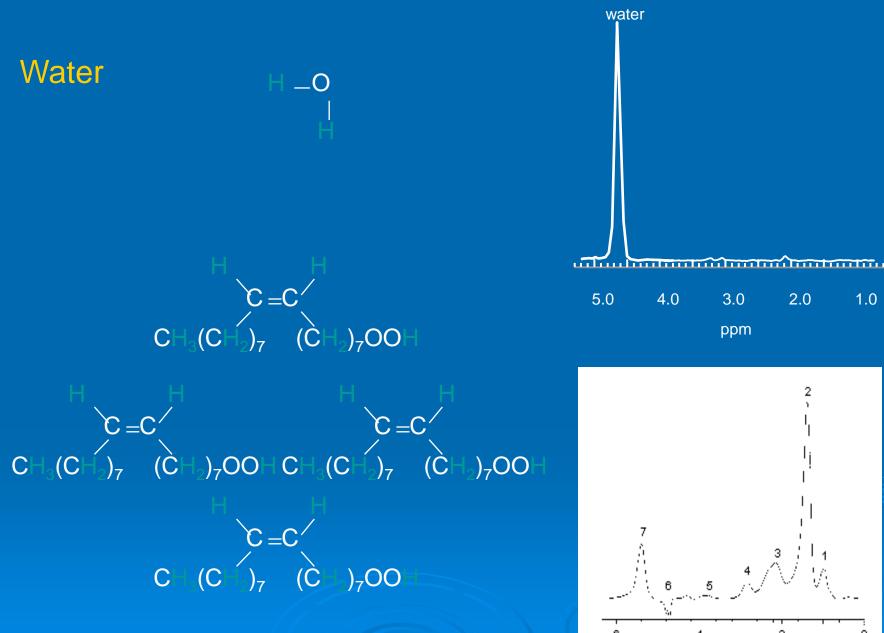
Typical 10-second spectra (2 FIDs) obtained from a single subject at the end of exercise (A) and at 15 (B) and 35 seconds (C} into the recovery period (different levels of work :2-18; 10 + 3.6) and reached different end-exercise force levels (64-599 J/min; 274 -+ 125).



Lodi et al MAGMA 1997

Spin Echo MR Spectroscopy pulse timing





(a)

Oleic Acid (Corn Oil)

2

ppm

MR Spectroscopy

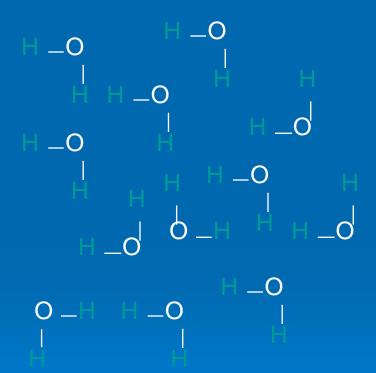
Larmor Equation:

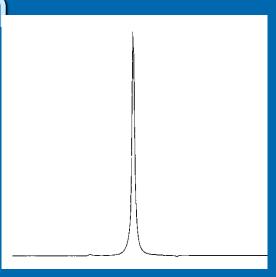


Larmor Frequency

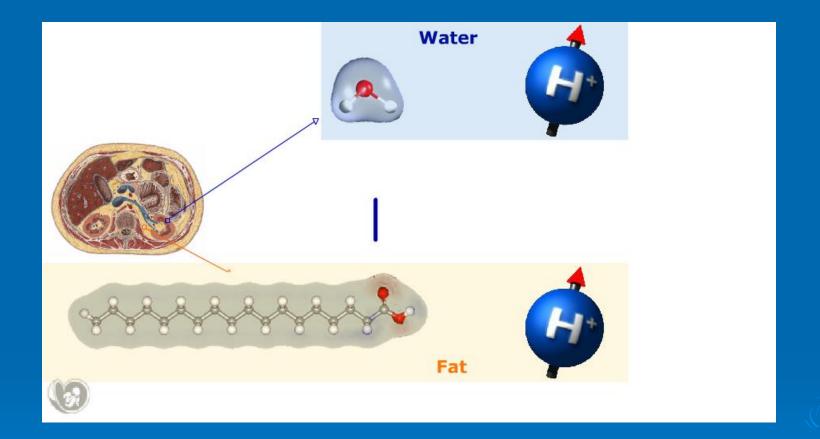
gyromagneticConstant appliedconstantexternal magnetic field

MR Spectrum

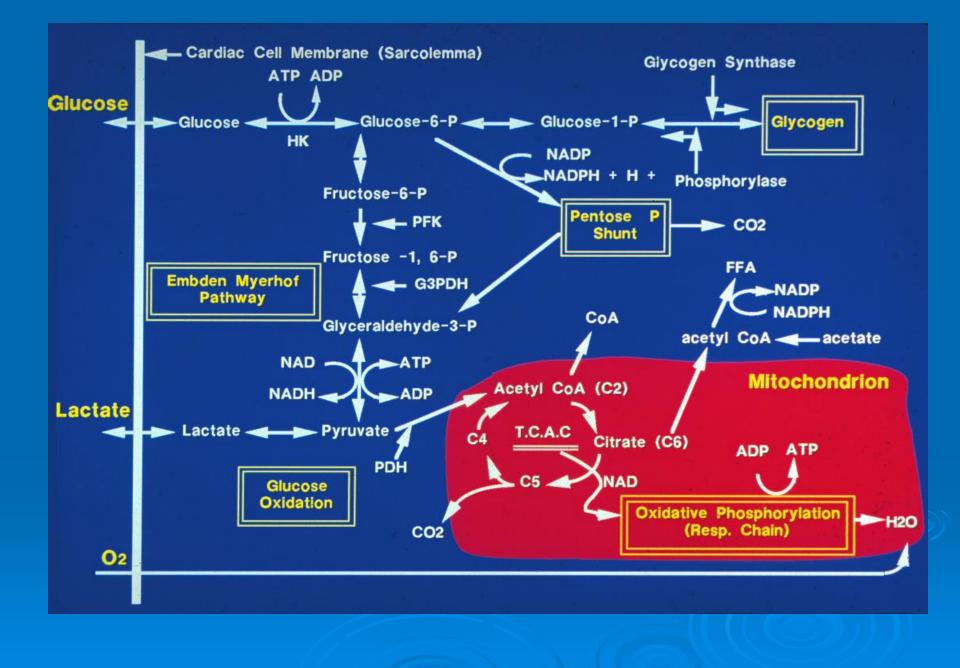


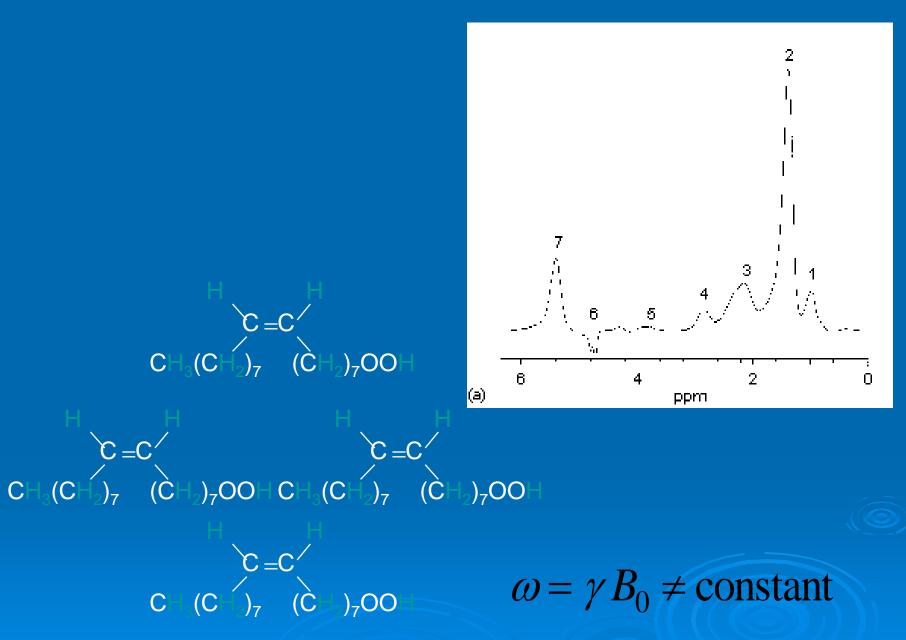


Area α # of spins FWHM α 1/T₂* $\omega = \gamma B_0 = \text{constant}$

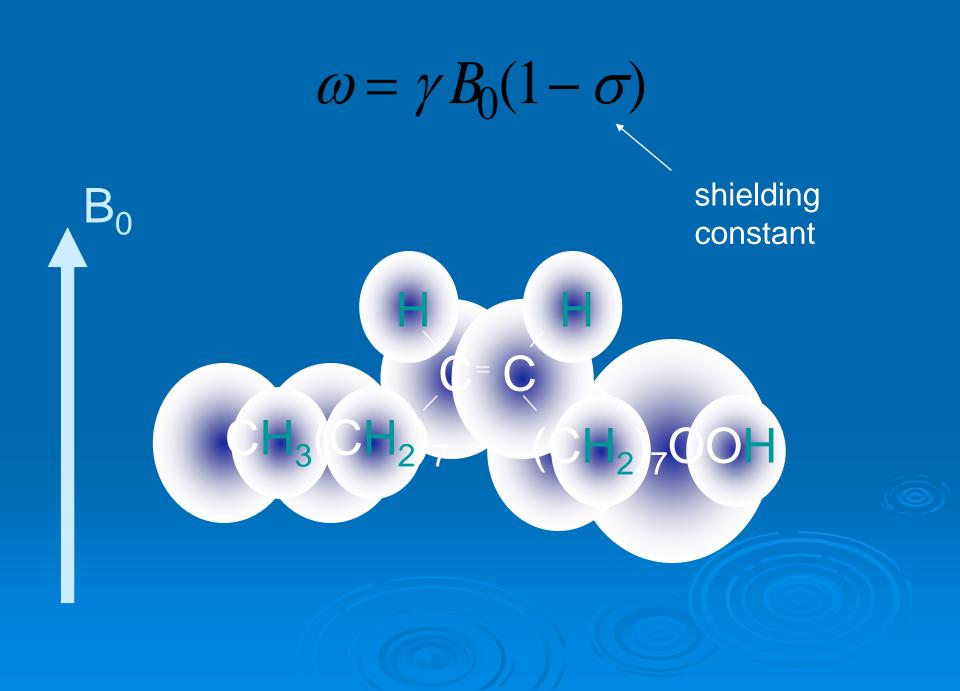


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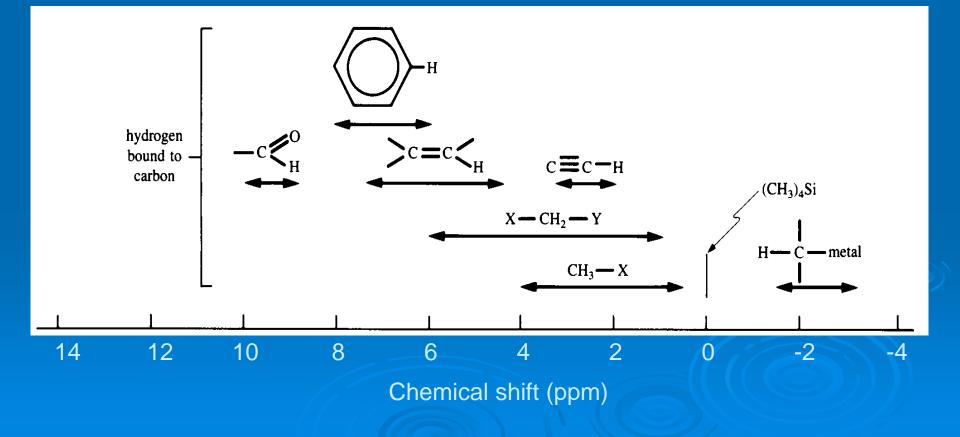




Oleic Acid (Corn Oil)



Chemical shifts of H bound to C



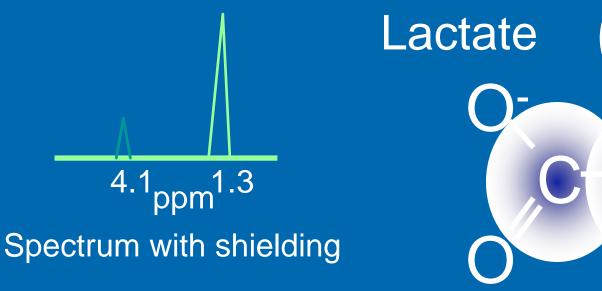
Chemical Shift

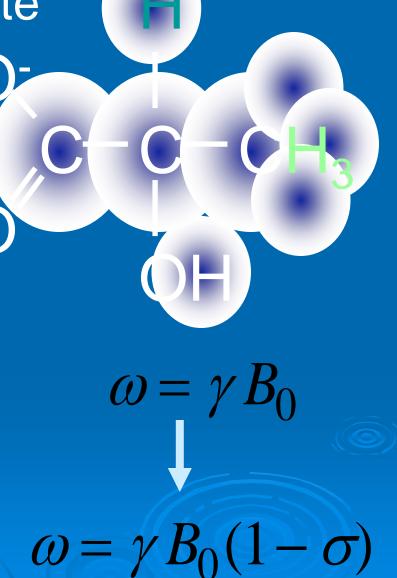
The frequency shift increases with field strength. For example, shift difference between water and fat

 $\begin{array}{ll} (\omega_{water} - \omega_{fat}) & at 1.5 \, \text{T is } 255 \, \text{Hz} & at 3.0 \, \text{T is } 510 \, \text{Hz} \\ & \delta = (\omega_{water} - \omega_{fat}) \, 10^6 / \gamma \text{Bo, in ppm units} \\ & \delta_{water-fat} \, \text{is } 3.5 \, \text{ppm independent of field strength} \end{array}$

- \succ By convention
 - o Signals of weakly shielded nuclei with higher frequency are on the left
 - o Signals of more heavily shielded nuclei with lower frequency are on the right

Chemical shift of water is set to 4.7 ppm at body temperature





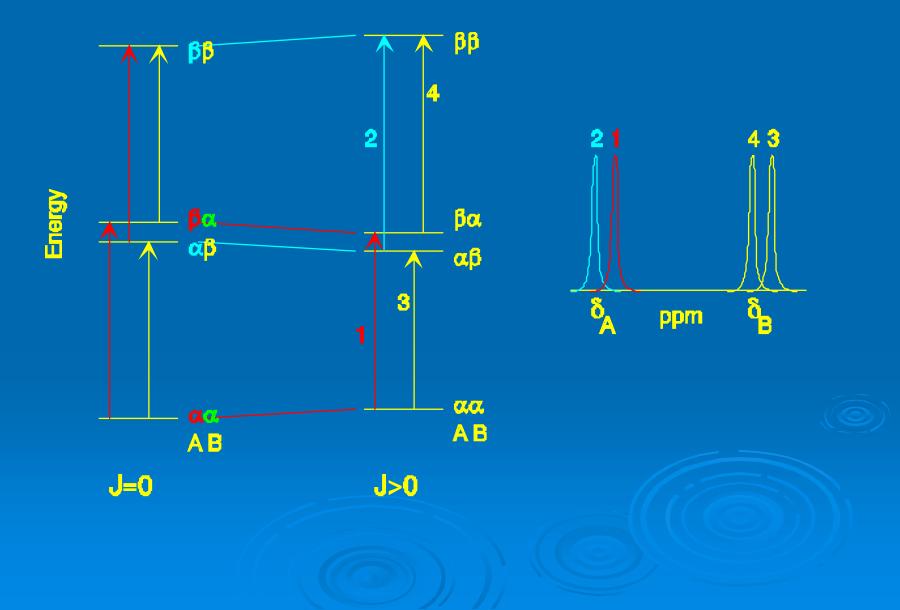
Indirect Spin-Spin Coupling (J-coupling)

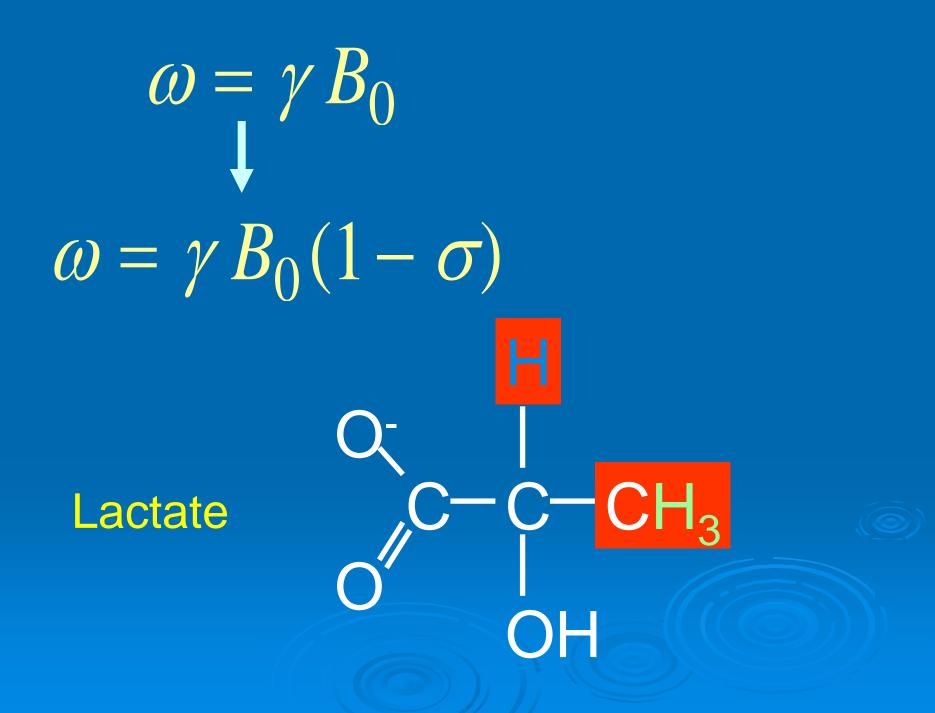


 $\omega = \gamma B_0(1 - \sigma)$

 $\omega = \gamma B_0(1 - \sigma) + f(J)$

Stationary Energy States



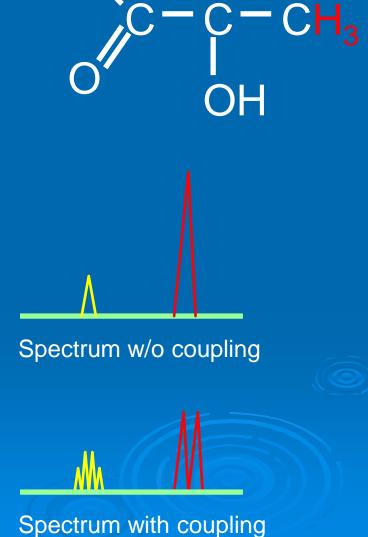


Spin-spin coupling actate

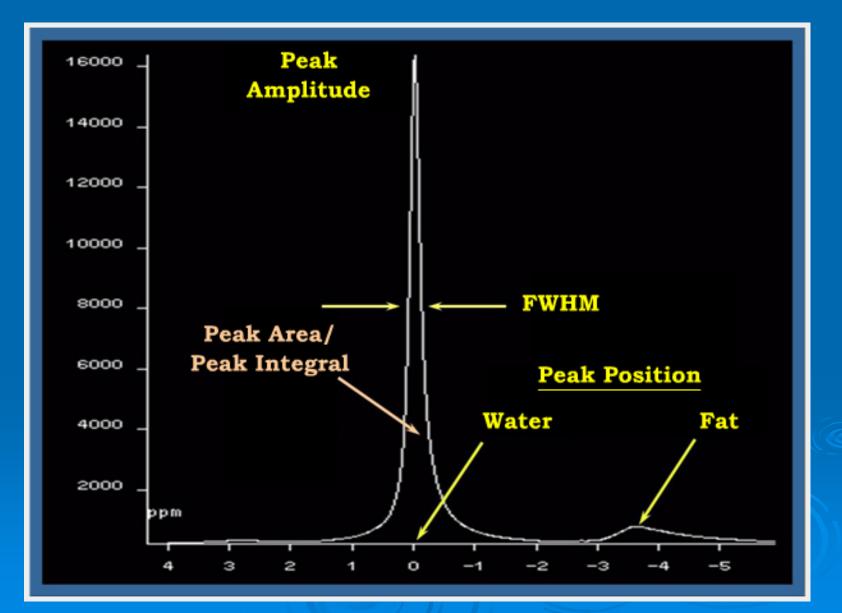
 H_3 has n=1 neighbor H which is in n+1=2 states : α , 1 β 1

H has n=3 neighbors H₃ which are in n+1=4 states :

ααα, 1
ααβ, αβα, βαα, 3
αββ,ββα, βαβ, 3
βββ 1



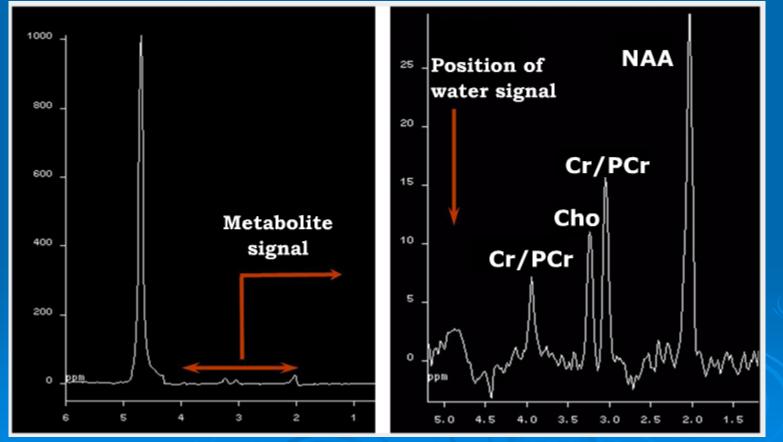
MR Spectrum: Peak Characteristics



¹H MR Spectrum from Brain

Water Signal

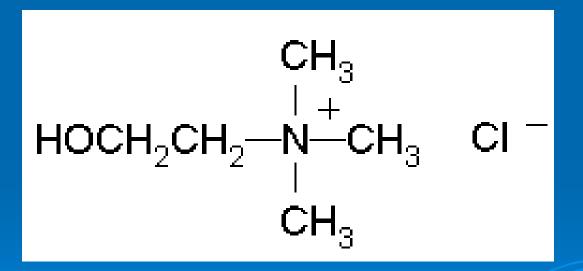
Metabolite Signals



Cerebral metabolites

N-acetyl aspartate Neuronal marker	Glutamate Excitatory neurotransmitter
Creatine/Phosphocreatine	Glutamine
Supplier of phosphate to convert ADP to ATP	Product of reaction of Glu with ammonia.
Choline	Glucose
Total cerebral choline including neuro-	Energy source.
transmitter acetylcholine, phospho- choline, and phosphotidylcholine	
	Lactate



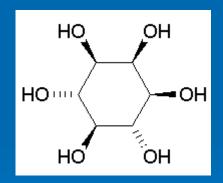




$$\begin{array}{ccc} \mathsf{NH} & \mathsf{O} \\ \mathsf{H}_2\mathsf{N}-\mathsf{C}-\mathsf{N}-\mathsf{CH}_2 & -\mathsf{C}-\mathsf{OH} \\ \mathsf{H}_3 \\ \mathsf{CH}_3 \end{array}$$

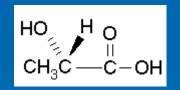




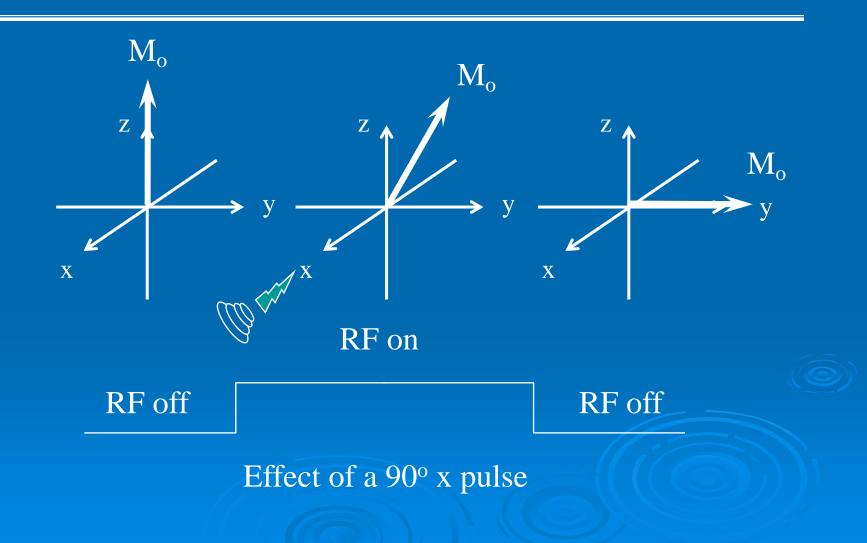








Nuclear Spin Dynamics





When a nucleus is in B₀ the initial population of energy levels are determined by thermodynamics as described by the Boltzmann distribution

• Lower energy levels will contain slightly more nuclei than the higher level

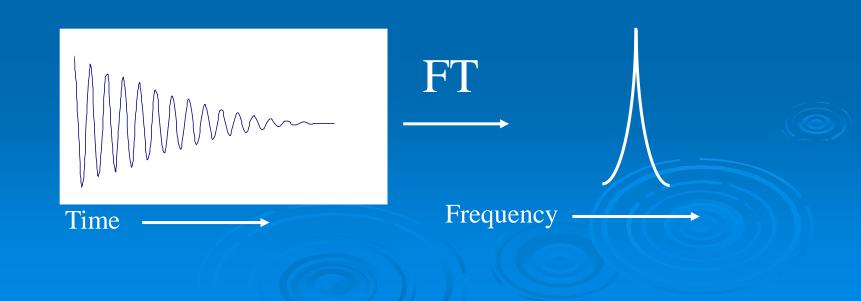
- Nuclear magnetization can only be observed by rotating the net longitudinal magnetization towards or onto the transverse plane
 - This can be accomplished by applying a second magnetic field in the transverse plane oscillating at the Larmor frequency

Free Induction Decay

The signals decay away due to interactions with the surroundings.

A free induction decay, FID, is the result.

Fourier transformation, FT, of this time domain signal produces a frequency domain signal.



Signal detection

In principle, Signal intensity generated by a class of nuclei is linearly proportional to the number of nuclei in the sample

In NMR peaks may be broadened by T2* losses, which is caused by spin-spin coupling and B₀ inhomogeneities

Signal detection

Spectral Resolution

Spectral Re solution = $\frac{1}{(\# complex \ point \ s)^* \Delta t}$

> MRI

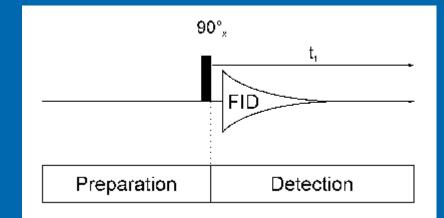
- 64,128 or 256 complex points, short acquisition time
- Low spectral resolution (~350 Hz)
 - Limited to water and lipid concentration

> MRS

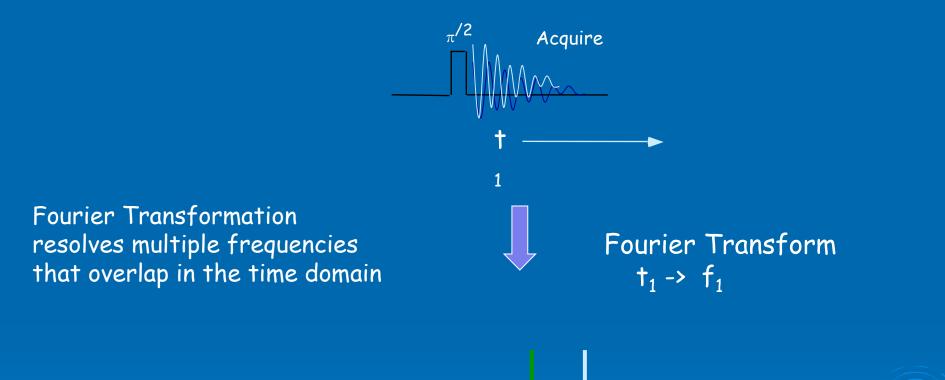
- 256-2048 complex points
- Much high spectral resolution (8-25 Hz)

1D NMR

Pulse Sequence



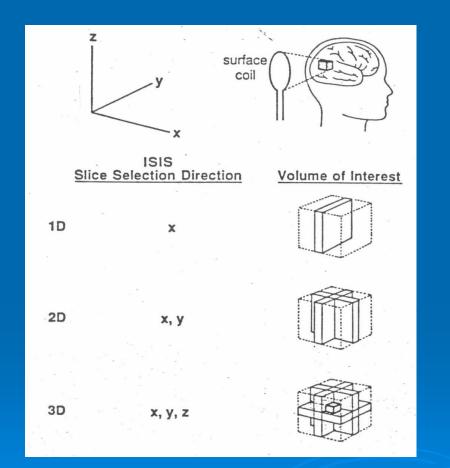
General One Dimensional Experiment

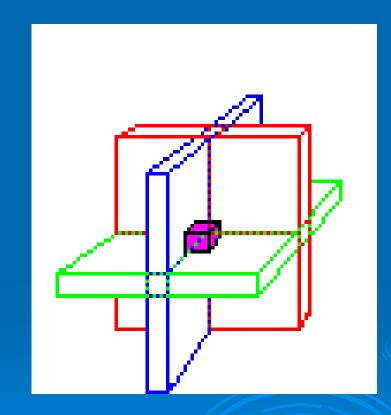


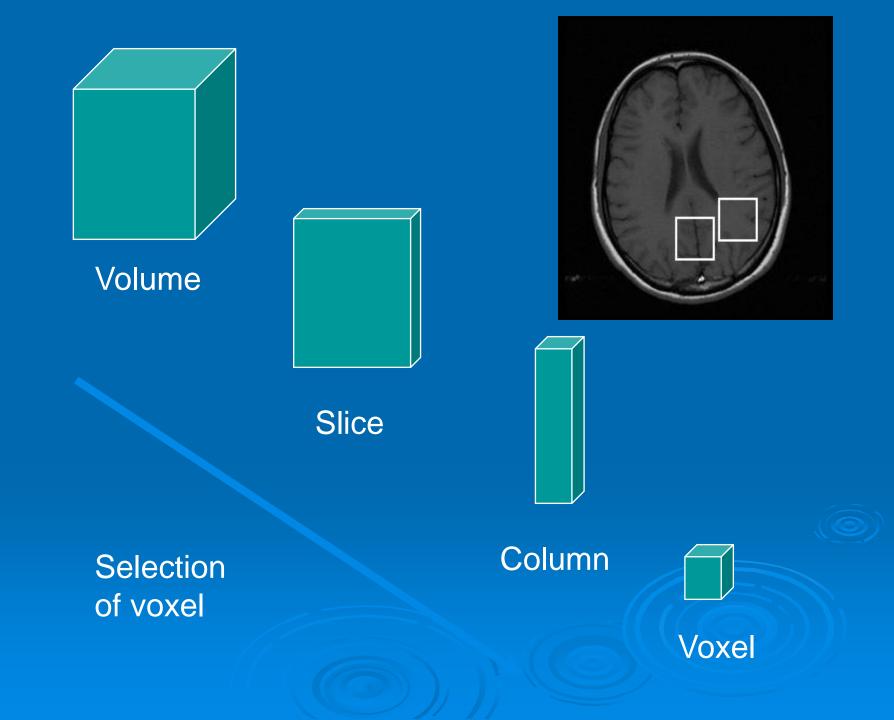


2. Single-Voxel MR Spectroscopy (MRS)

Localization



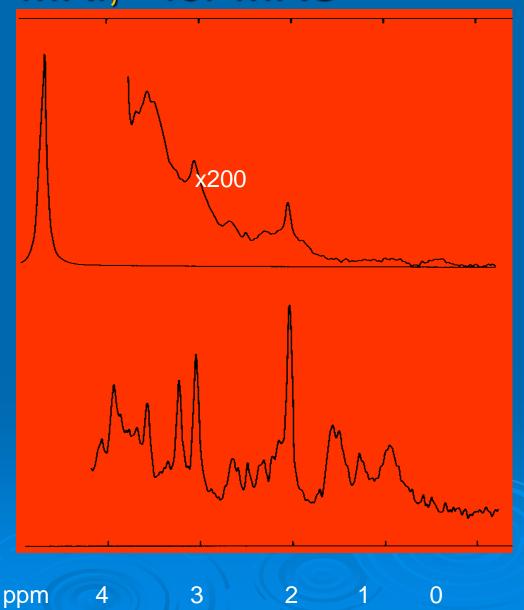




Water: + for MRI, - for MRS

Before suppression

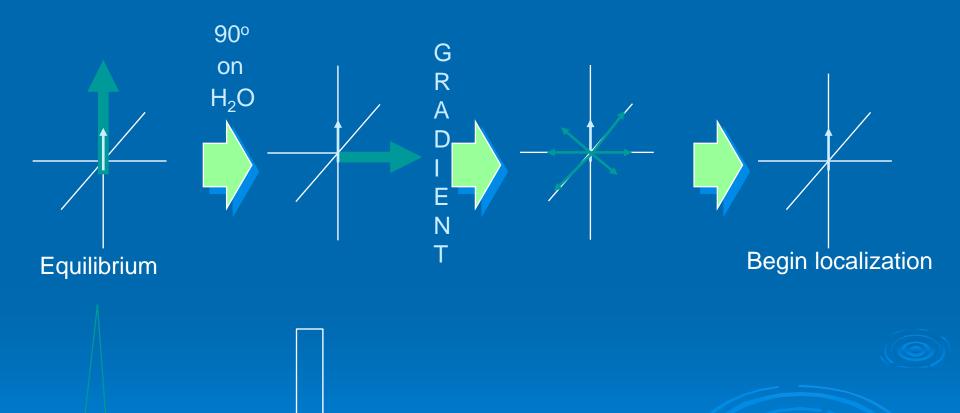
After suppression









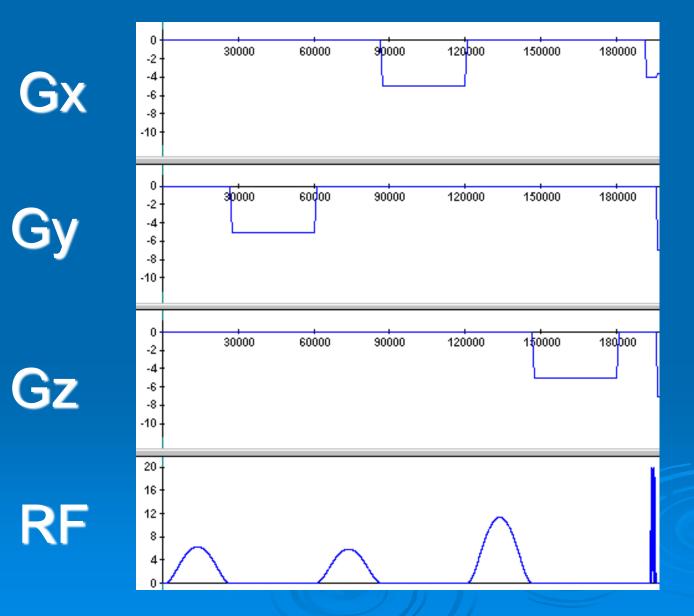


Spectrum

111

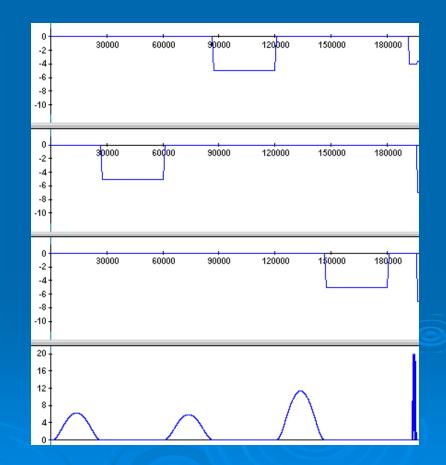
RF frequency response

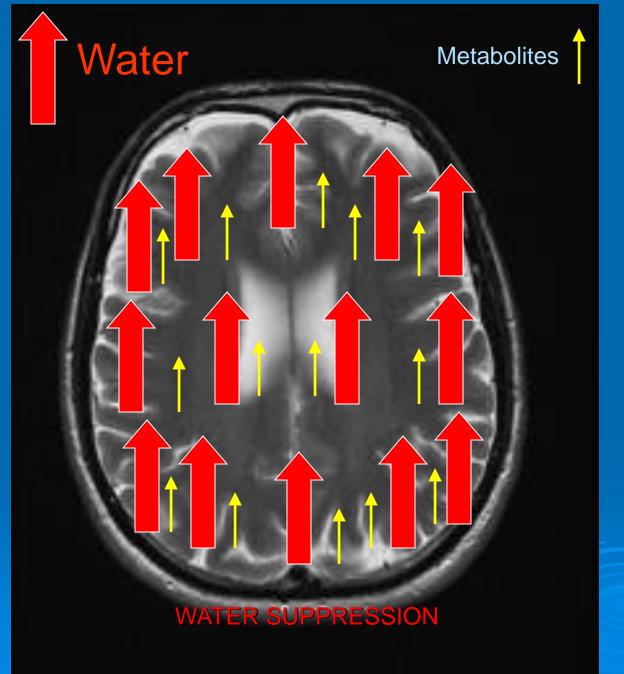
CHESS (global)



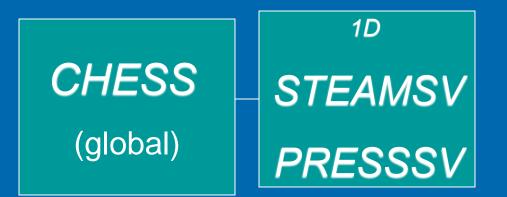
Water Suppression

- Nomal water signal is ~
 5000 times stronger than metabolites
- Need to reduce it at least by 1000 times to get the right dynamic range.
- Common way is by frequency selective pulses followed by dephasing gradient.





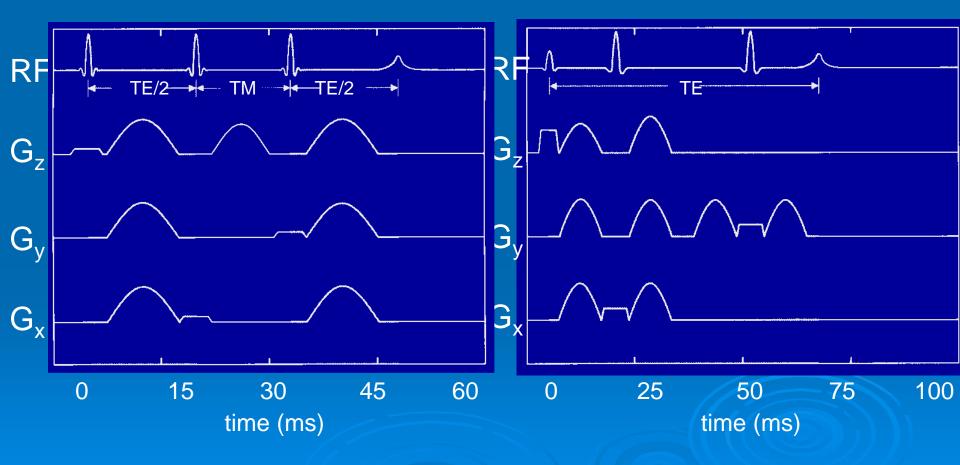




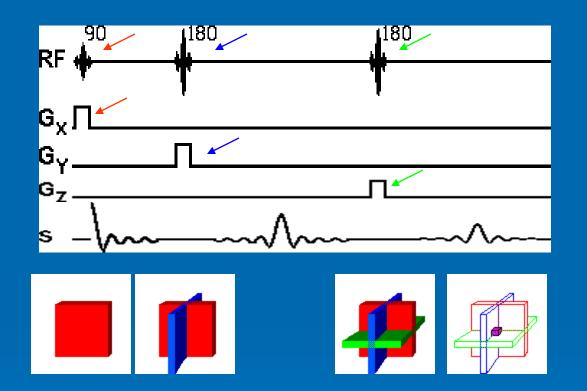


Localization STEAM

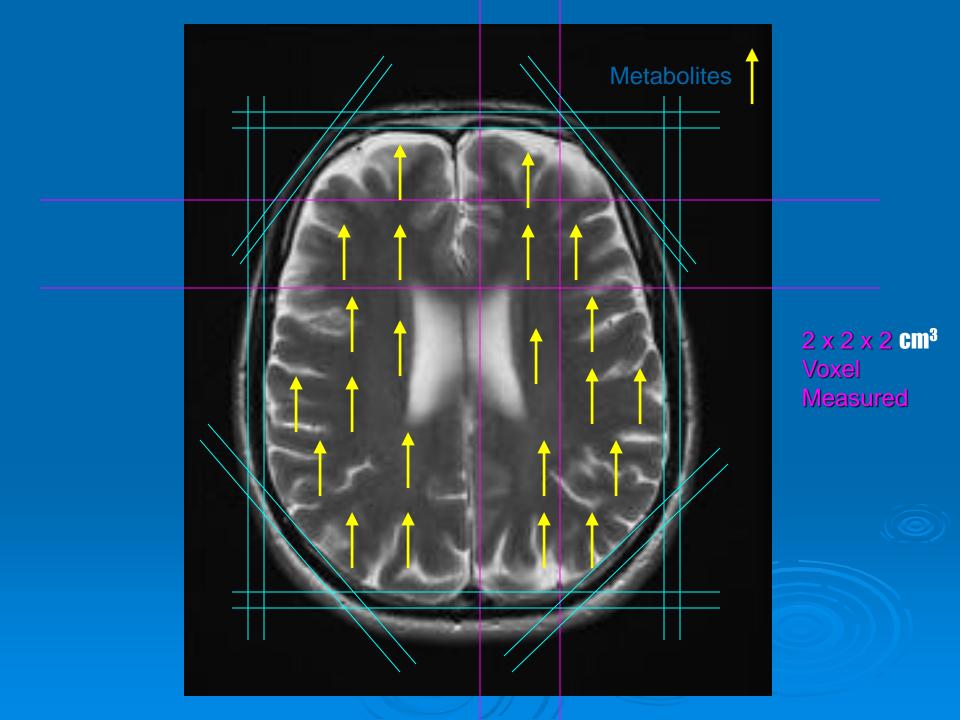




PRESS-SV Sequence



A second echo is recorded as the signal. FT the echo to produces an NMR spectrum.



2x2x2 cm³ Voxel, 5 Slīces

Inferior

Superior

Shown are 5 vertically adjacent brain slides, each 4 mm thick (20 mm or 2cm total)

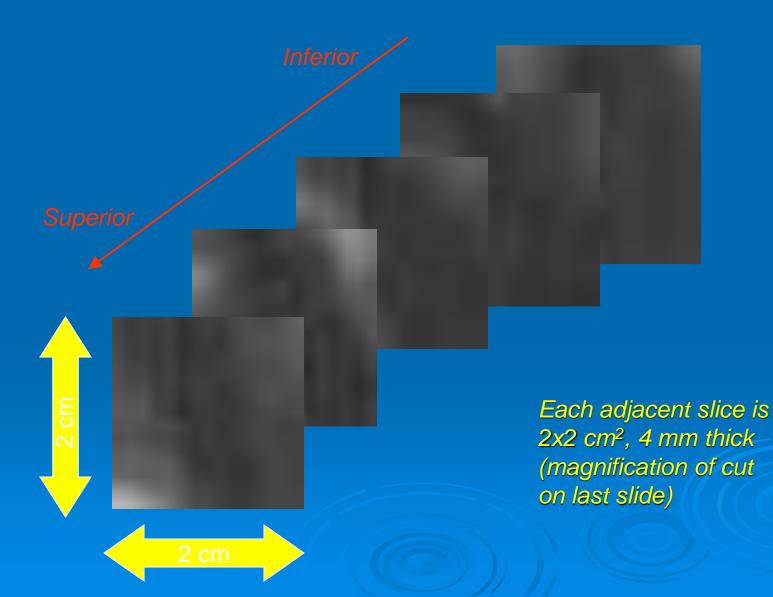
2x2x2 cm³ Voxel, 5 Slices

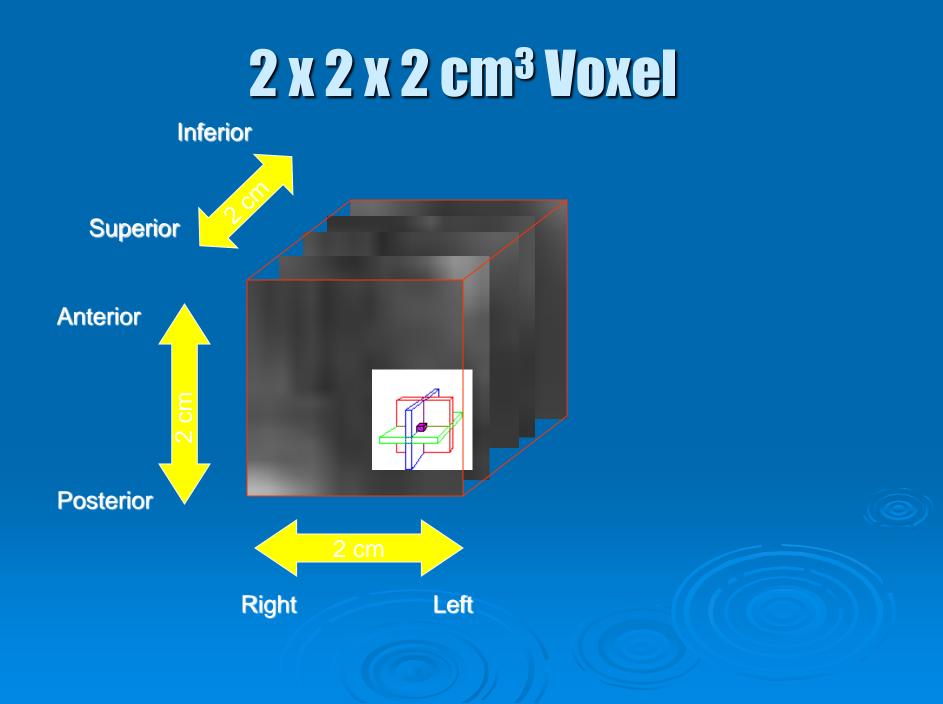
Inferior

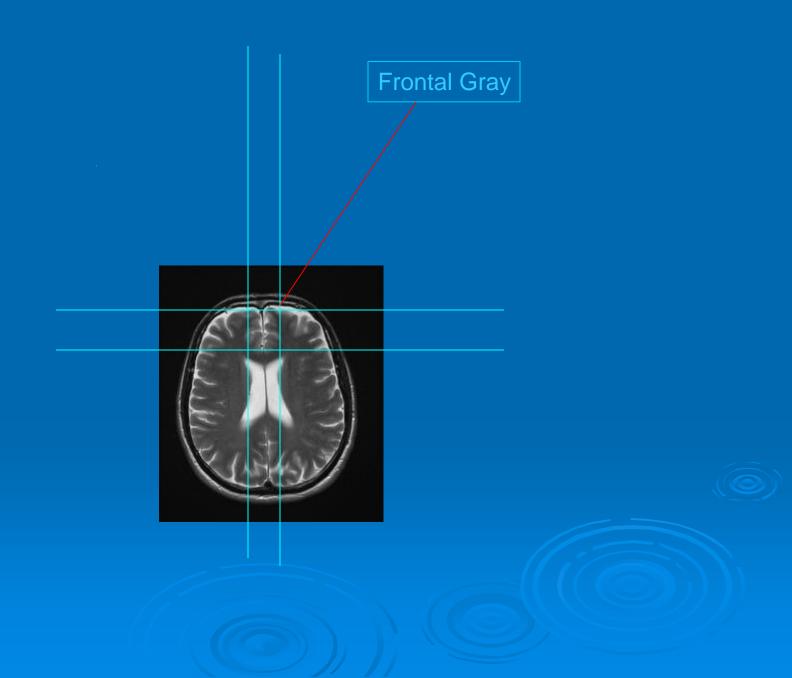
Superior

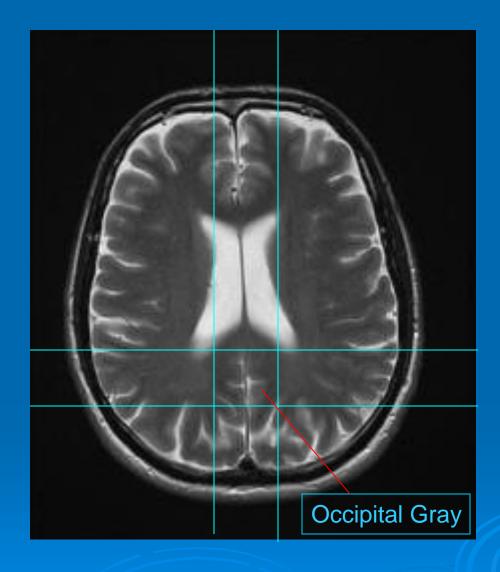
2 cm x 2 cm Voxel cut is made in all five adjacent brain slices

5 Adjacent Voxel Slices

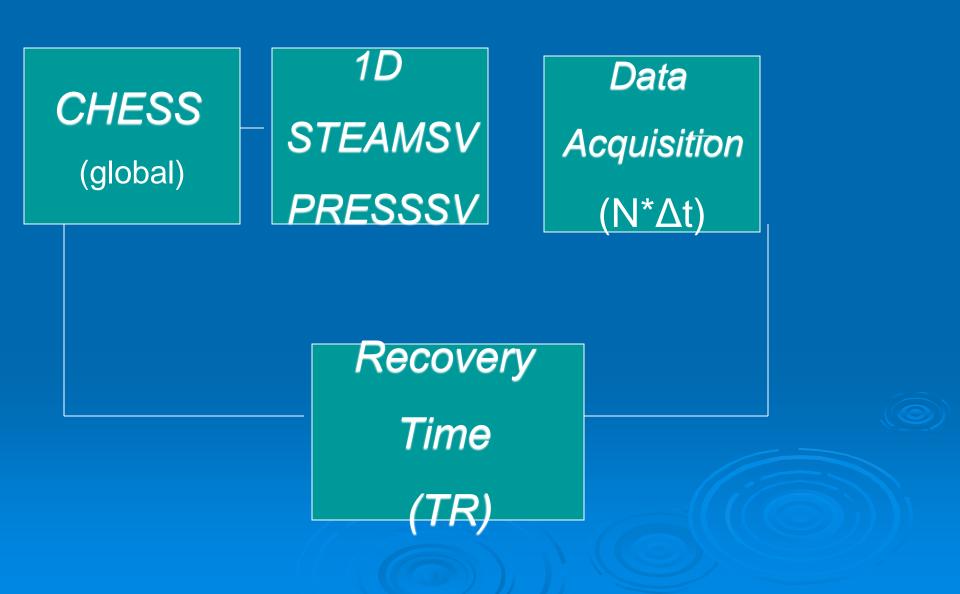


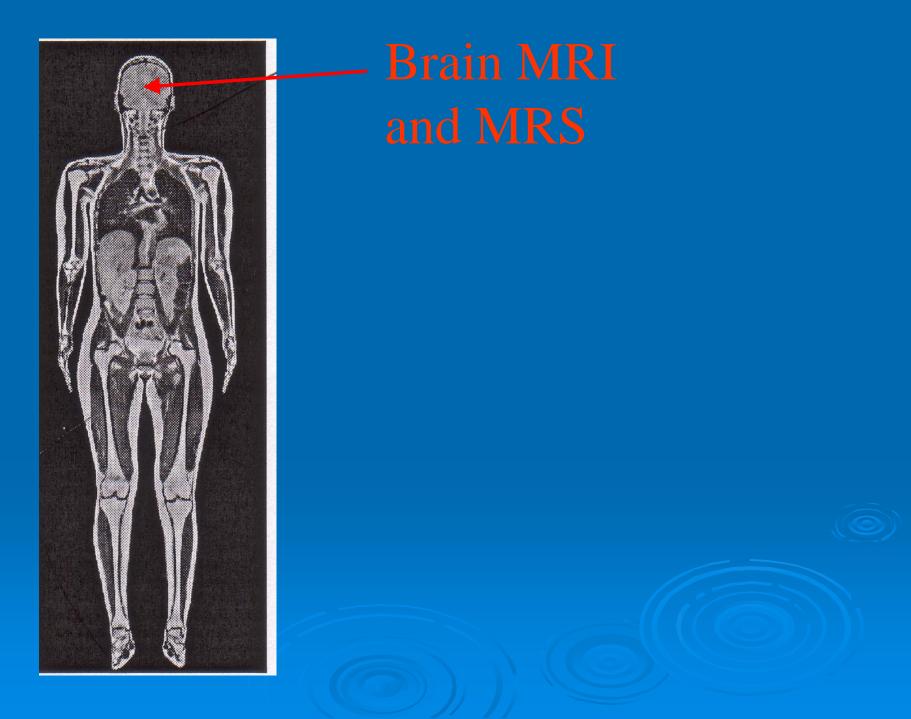






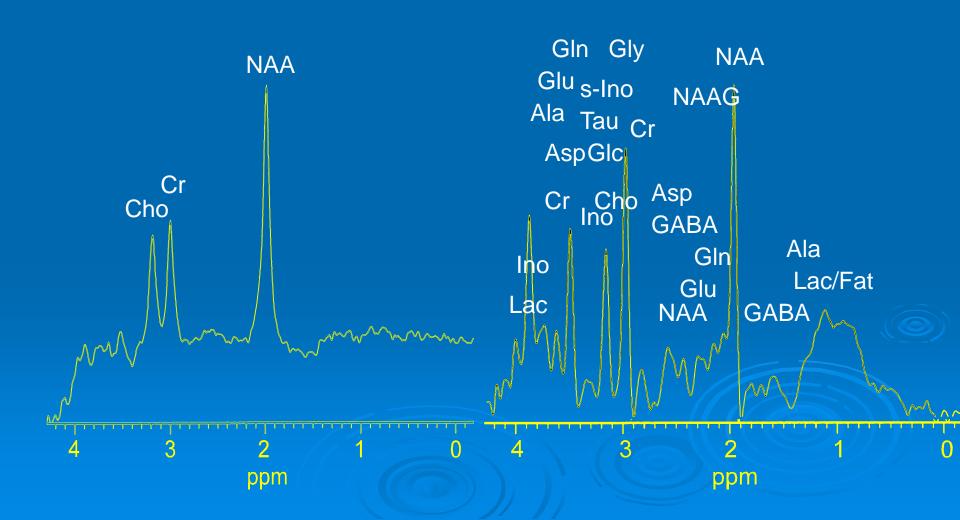




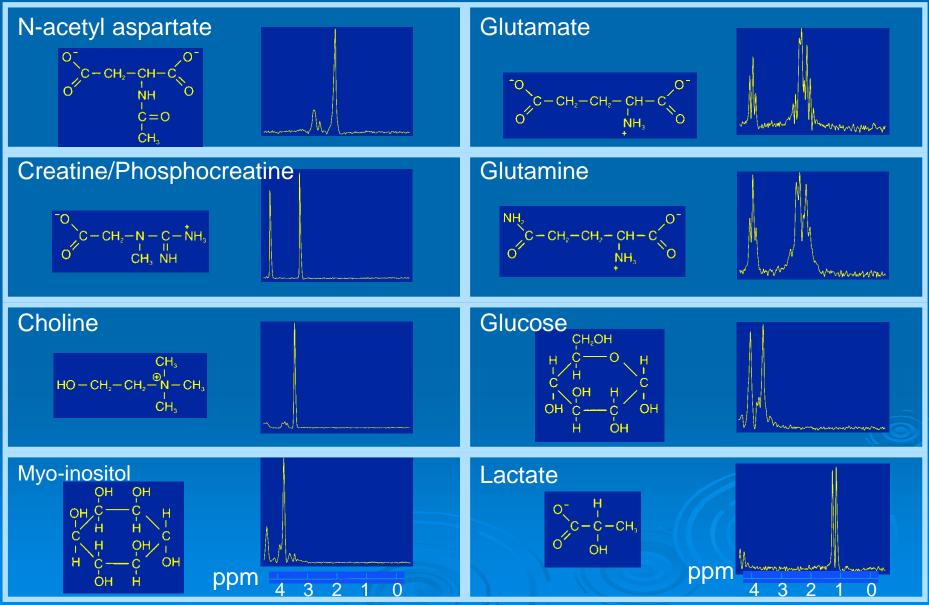


That was then ... STEAM, TE=270ms, TR=1500ms

This is now. STEAM, TE=20ms, TR=1500ms



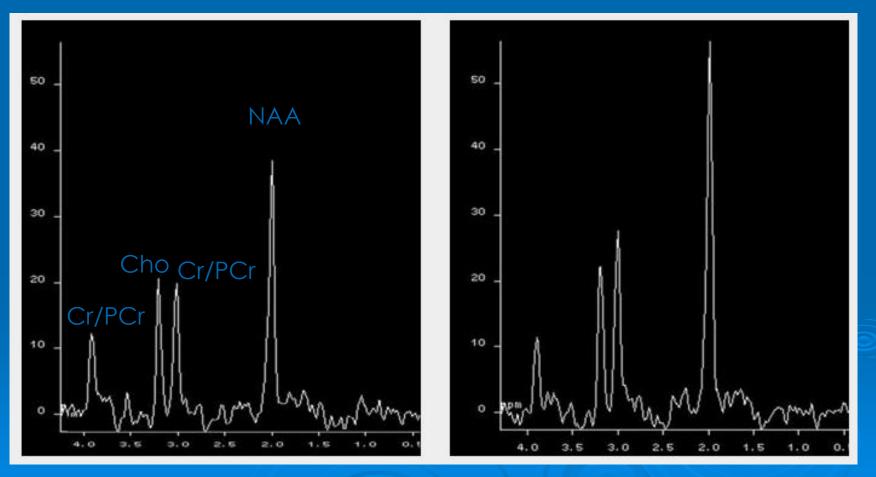
Cerebral metabolites



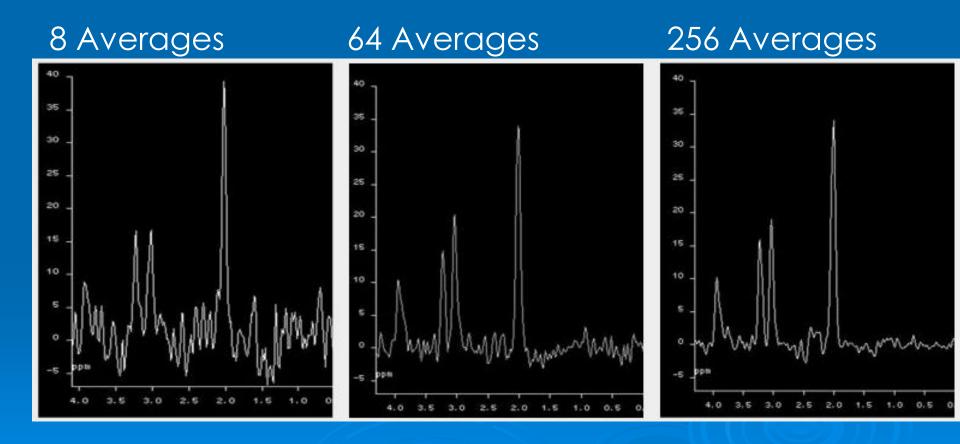
Effect of Repetition Time (TR)

TR = 1500 ms

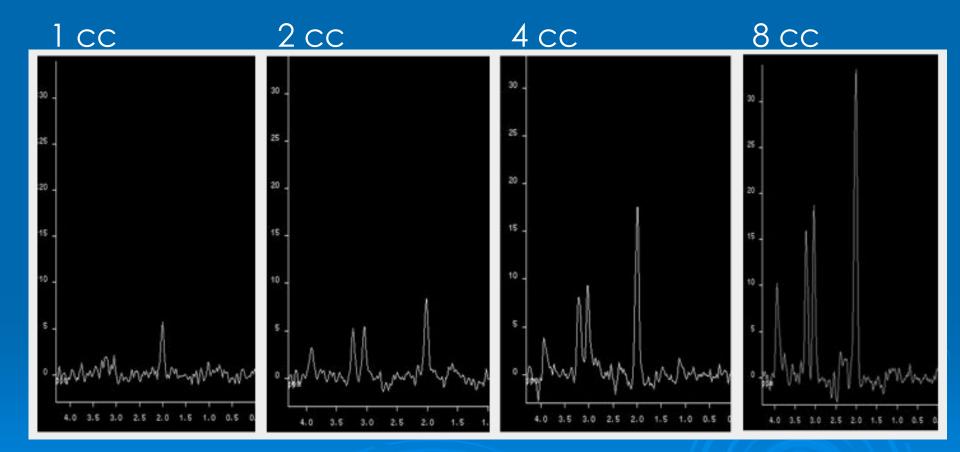
TR = 5000 ms



Effect of Signal Averaging



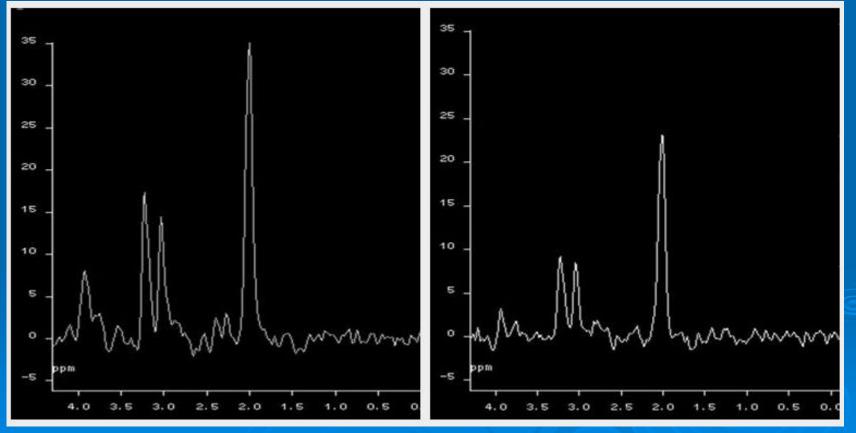
Effect of Voxel Size



Effect of Echo Time, TE

TE = 144 ms

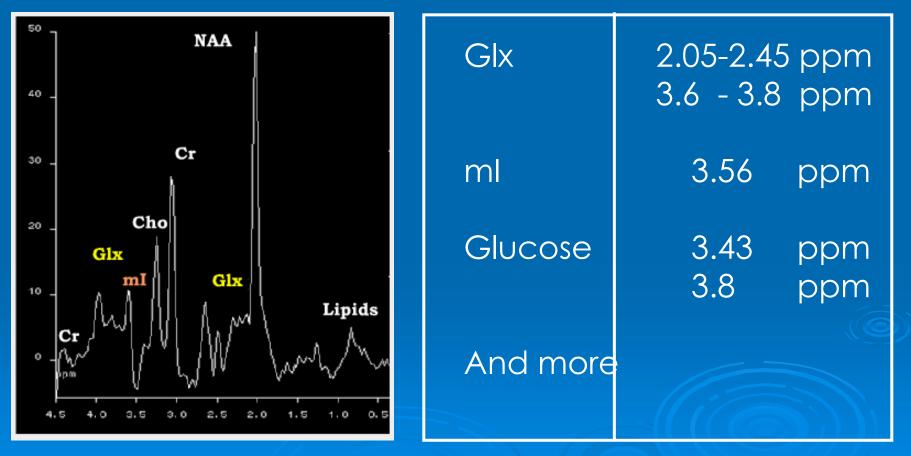
TE = 288 ms



Short TE¹H Brain Spectrum

Healthy volunteer

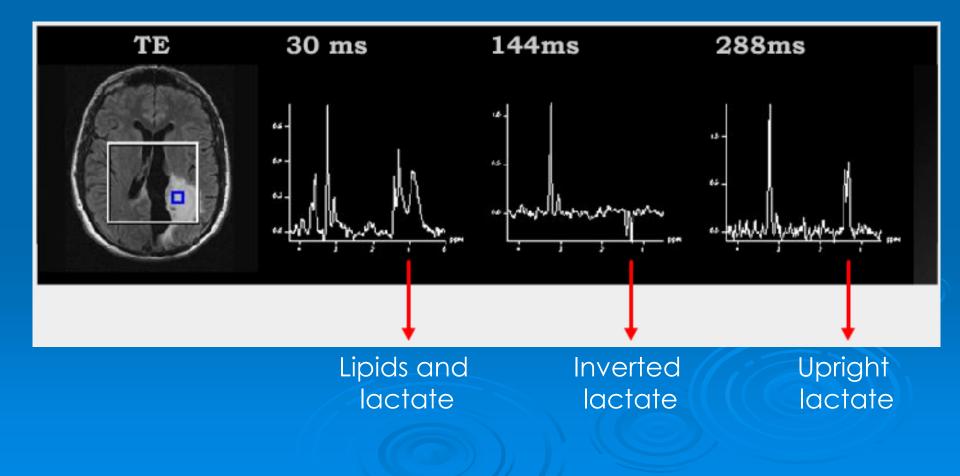
Additional Peaks

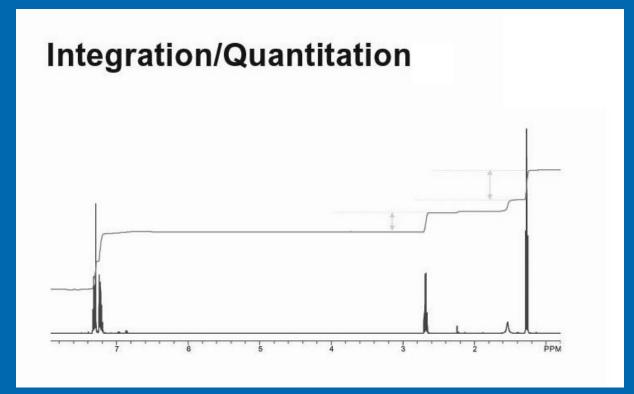


Metabolite (normal cerebral concentration)	Increased concentration	Decreased concentration	
Myoinositol (m1) (5 mM)	normal neonatal brain, Alzheimer disease, diabetes mellitus, recovered hypoxia, hyperosmolar states	chronic hepatic encephalopathy, hepatic encephalopathy, stroke, neoplasms	
Creatine (Cr) and Phosphocreatine (PCr) (8 mM)	head trauma, hyperosmolar states, increases with age	hypoxia, stroke, neoplasms, infant brain	
Glucose (G) (1 mM)	diabetes mellitus, ? parenteral feeding, ?hypoxic encephalopathy	not detectable	
Choline (Cho) (1.5 mM)	head trauma, diabetes, neonatal brain, post liver transplant, neoplasms, chronic hypoxia, hyperosmolar states, ? Alzheimer disease	asymptomatic liver disease, hepatic encephalopathy, stroke, nonspecific dementia	
Aceto-acetate, acetone, ethanol, aromatic amino acids, propane-diol	detectable in specific settings	not detectable	

The Lactate Doublet

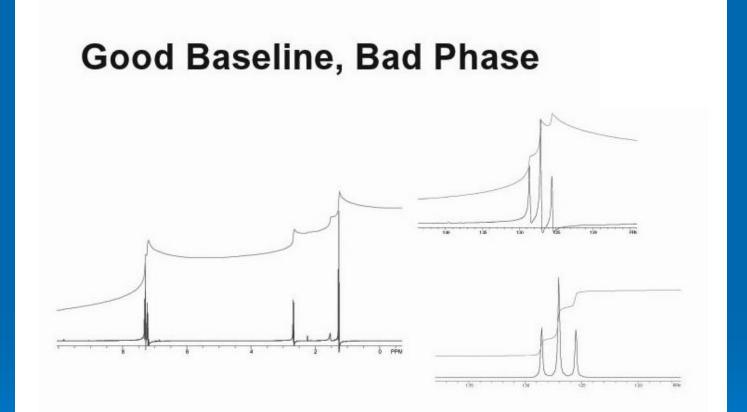
Tumor spectra: showing no NAA, \uparrow Cho, \uparrow mI, \uparrow lactate





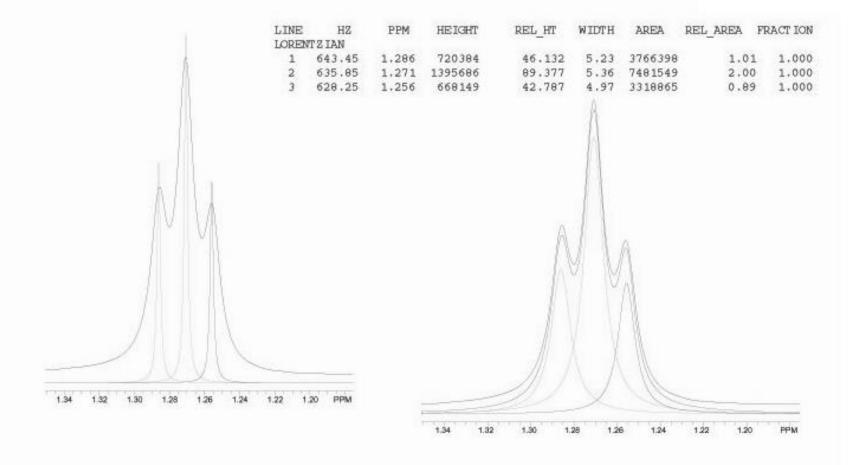
When you have resonances which are not overlapping with each other then the integral (area) of the spectral resonances (peaks) can be used to calculate the number of protons under each peak.

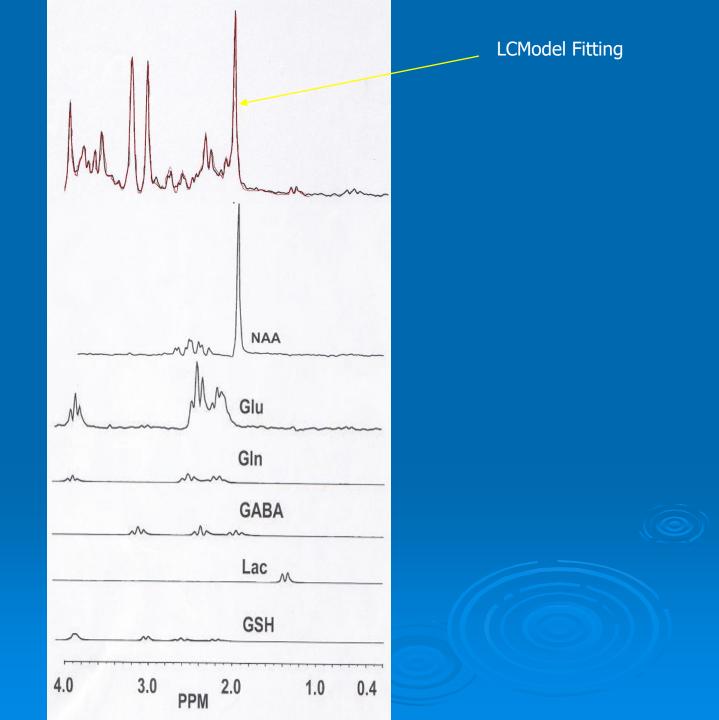
You need good baseline and correct phase



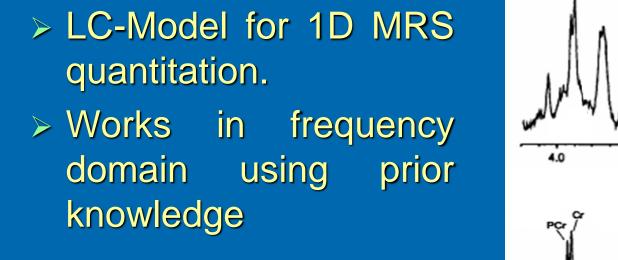
You need sophisticated spectral fitting algorithms for quantification

Deconvolution...line-fitting

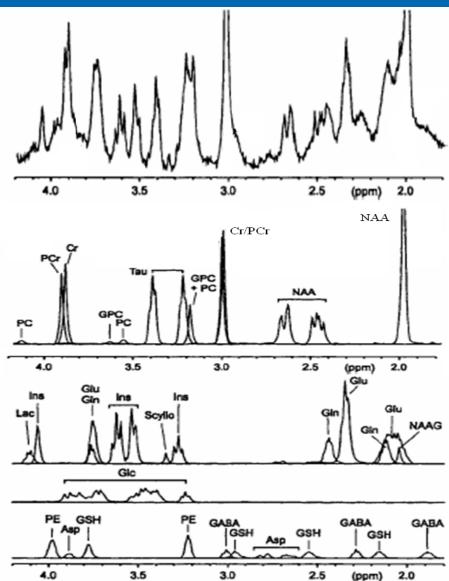




1D MRS Quantitation



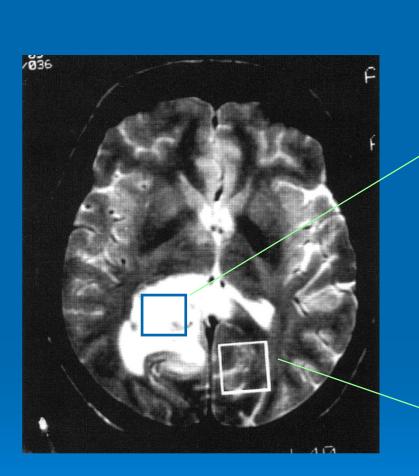


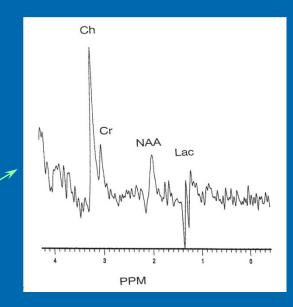


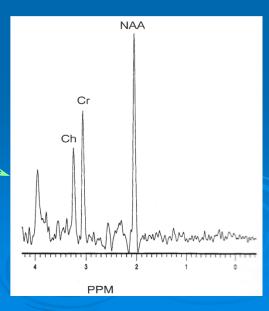


3. Selected Applications of MR Spectroscopy











IDH1 R132H mutation and 2-HG

•Somatic mutations of the isocitrate dehydrogenase 1 and 2 genes (IDH1 and IDH2) have recently been implicated in gliomagenesis and are found in approximately 80% of World Health Organization (WHO) grade II-III gliomas and secondary glioblastomas (WHO grade IV) in humans.

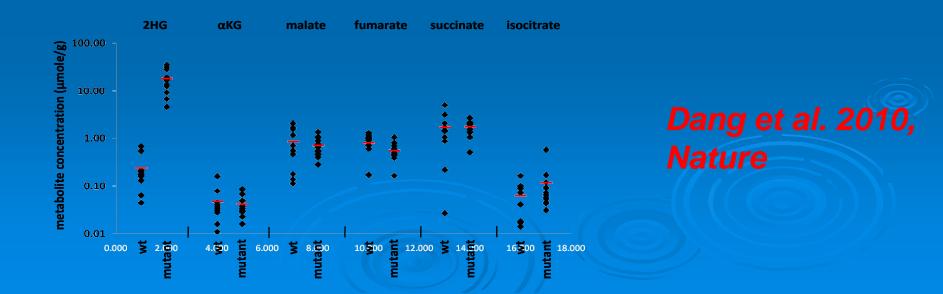
•Vast majority of IDH1 mutant, high-grade gliomas have evolved from lower grade lesions.





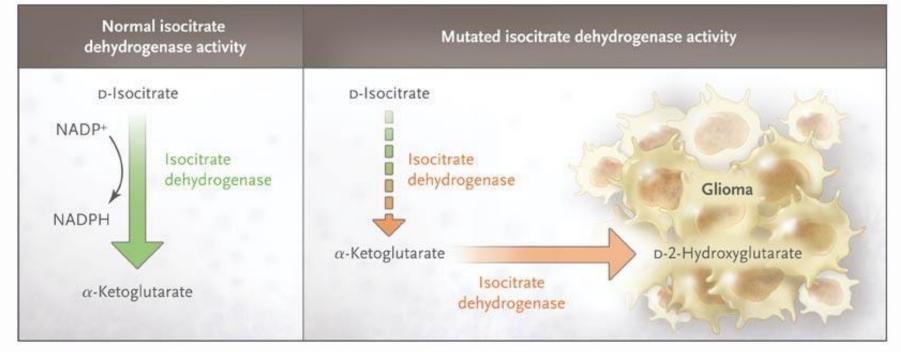
IDH1 R132H mutation and 2-HG

A recent work by Dang and co-workers reported a mutation observed in the isocitrate dehydrogenase1 (IDH1) gene, which occurs in the majority of grade II and grade III gliomas and secondary glioblastomas, resulting in significant elevation of 2HG in these tumors.





IDH1 R132H mutation produces 2-HG

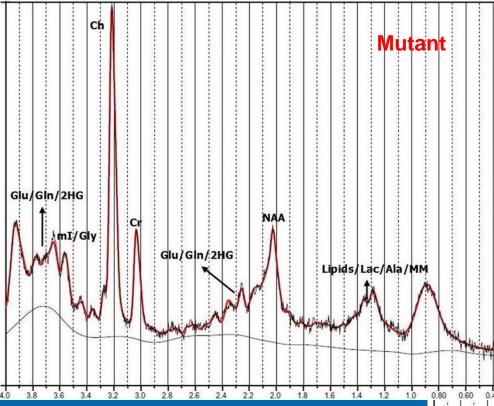


Smeitnik, J. "Metabolism, Gliomas, and IDH1," N Eng J Med 362: 1144-45, 2010

Pope et al. 2012 Andrenosi et al. 2012 Elkhaked et al. 2012 Choi et al. 2012



Scanner	:	Siemens 3T Trio-Tim	
Coil	:	12 Channel receive	
Subjects	:	24 brain tumor	
Mutant Tumor	:	9 (Mean age 43 years)	
Wild Tumor	:	15 (Mean age 59 years)	
Tumor Grade	:	14 primary GBM (grade IV), 6 oligodendroglioma (grade III), and 4 low grade (grade II)	



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9 HEALS

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Published in final edited form as: J Neurooncol. 2012 March ; 107(1): 197–205. doi:10.1007/s11060-011-0737-8.

Non-invasive detection of 2-hydroxyglutarate and other metabolites in IDH1 mutant glioma patients using magnetic resonance spectroscopy

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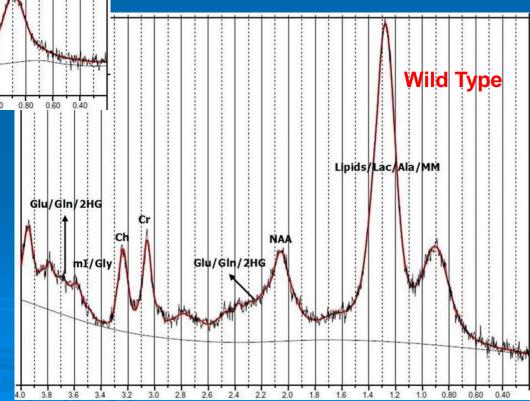
Arthur P. Chou.

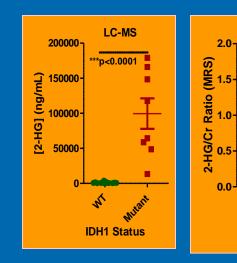
Department of Neurosurgery, David Geffen School of Medicine at UCLA, University of California at Los Angeles, Gonda Building, Room 3357, 695 Charles Young Drive, Los Angeles, CA 90095-1761, USA LLIAU@mednet.ucla.edu

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Neil Wilson, Department of Radiological Sciences, David Geffen School of Medicine at UCLA, University of California at Los Angeles, Los Angeles, CA 90095, USA Edward Driggers, Hyun G. Jang.





MRS

**p=0.0017

W

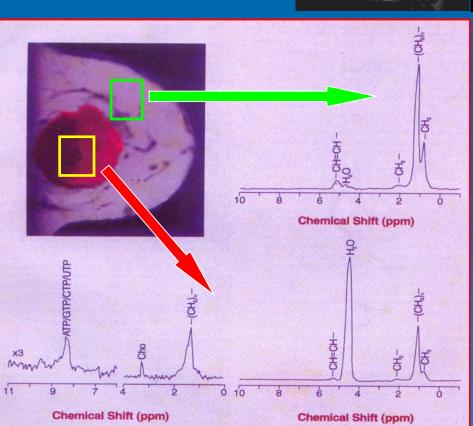
IDH1 Status

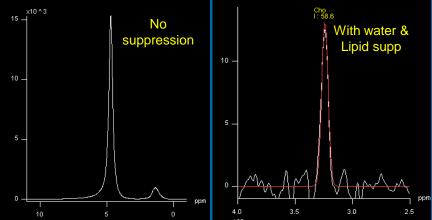
Mutant

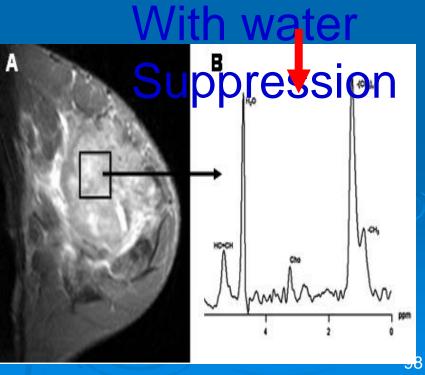
Single voxel MRS – Detection of tCho

With water & fat suppression

Spectra from tumor & Normal portion with only Water suppression

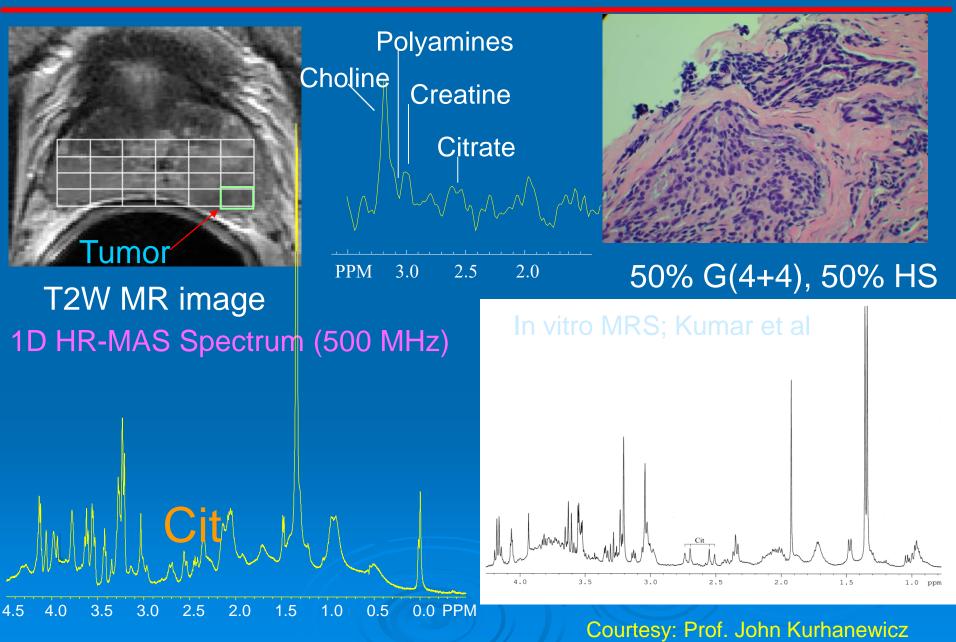


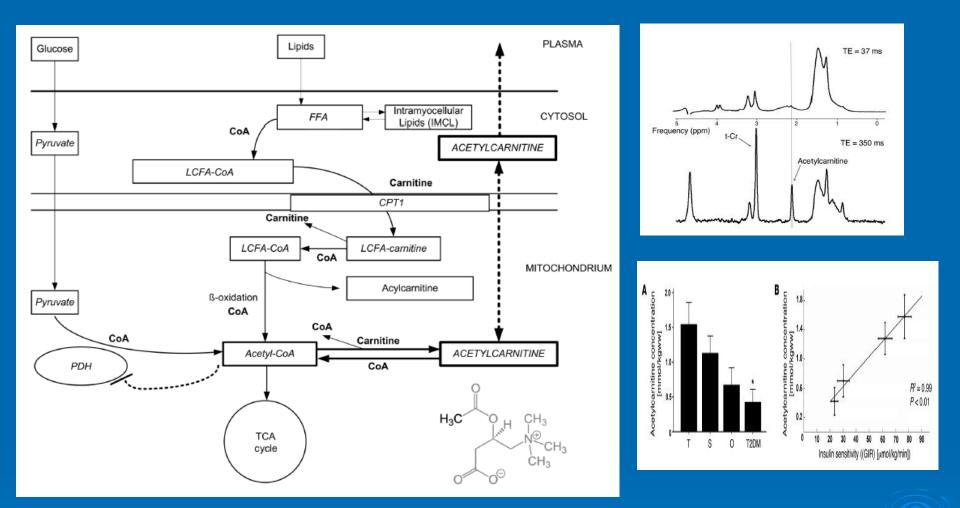




Jagannathan et al Br. J. Cancer 84; 1016-22, 2001

Malignant Prostate Metabolism





Acetylcarnitine is formed in conditions in which acetyl-CoA formation, either as end product of glycolysis or β -oxidation, exceeds its entry into the tricarboxylic (TCA) cycle. Free carnitine can act as a sink for excess acetyl groups in a reversible reaction catalyzed by the enzyme carnitine acetyltransferase (CRAT).

Acetylcarnitine, like other acylcarnitine esters, can readily be exported out of the mitochondria

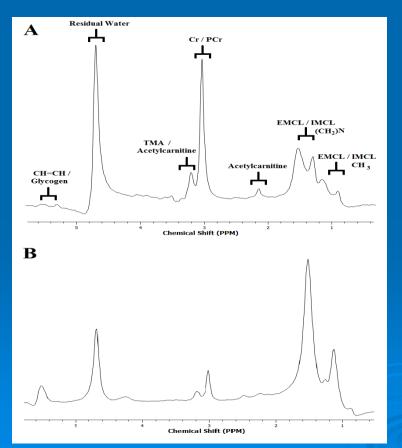
Lindeboom et al. J Clin Inv 2014

1D MR Spectroscopy to detect AcetylCarnitine

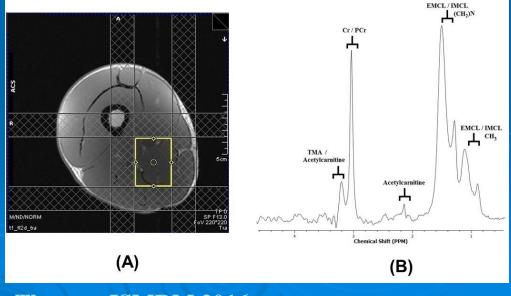


PRESS-localized long TE spectra recorded in the vastus muscles of (A) a 25 year-old healthy subject and (B) a 61 year-old T2D patient

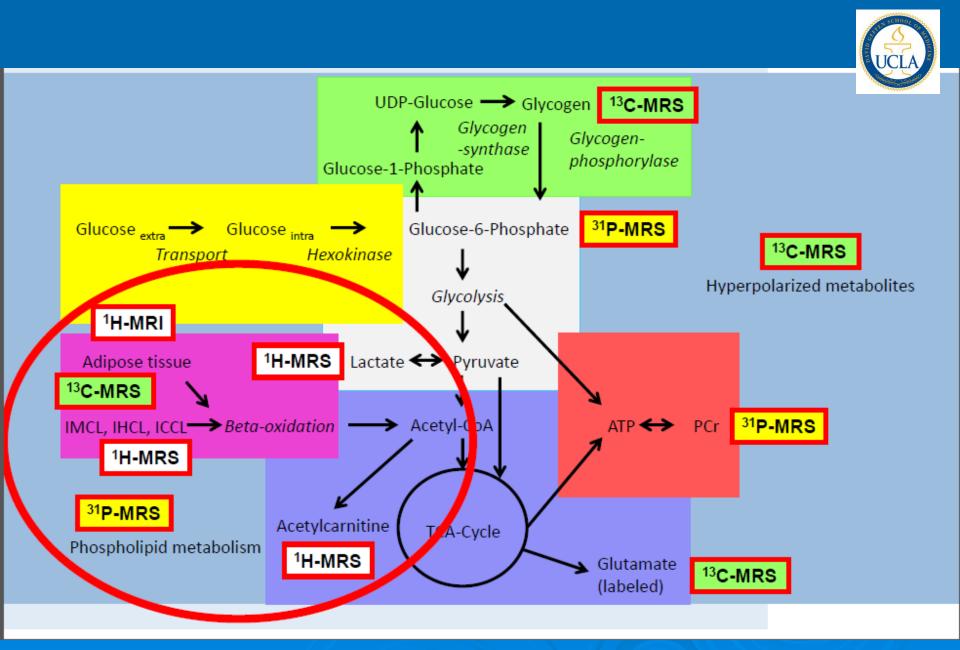




PRESS localization (white box) shown on an axial thigh MRI of a 25 year-old healthy male subject recorded in the mixed medial hip adductor and posterior knee flexor muscle region.



Thomas ISMRM 2016



UCLA



Important Nuclei for Biomedical MR

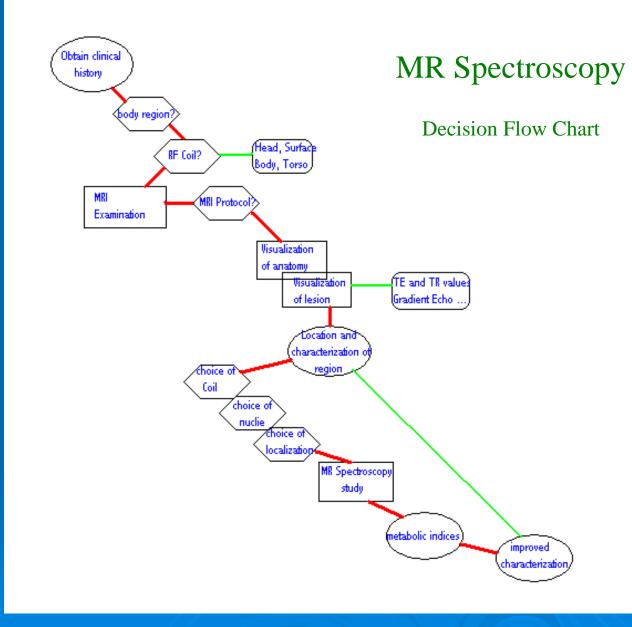
- ¹H Neurotransmitters, amino acids, membrane constituents
- ²H Perfusion, drug metabolism, tissue and cartilage structure.
- ¹³C Glycogen, metabolic rates, substrate preference, drug metabolism, etc.
- ¹⁹F Drug metabolism, pH, Ca²⁺ and other metal ion concentration, pO₂, temperature, etc
- ²³Na Transmembrane Na⁺ gradient, tissue and cartilage structure.
- ³¹P Cellular energetics, membrane constituents, pH_i, [Mg²⁺], kinetics of creatine kinase and ATP hydrolysis.

Important Nuclei for Biomedical MR

Nucleus	Spin	γ, MHz/T	Natural Abundance	Relative Sensitivity
¹ Η	1/2	42.576	99.985	100
² H	1	6.536	0.015	0.96
³ He	1/2	32.433	.00013	44
¹³ C	1/2	10.705	1.108	1.6
¹⁷ O	3/2	5.772	0.037	2.9
¹⁹ F	1/2	40.055	100	83.4
²³ Na	3/2	11.262	100	9.3
³¹ P	1/2	17.236	100	6.6
³⁹ K	3/2	1.987	93.08	.05

How long it takes to perform a single voxel MR Spectroscopy?







2. Fast MR Spectroscopic Imaging

M. Albert Thomas Ph.D. Professor

Department of Radiological Sciences University of California, Los Angeles

M219: Introduction to Magnetic Resonance Imaging/03/06/24



THANK YOU

