BASICS OF MAGNETIC RESONANCE SPECTROSCOPY (MRS)

Principles of Neuroimaging B– 2016
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presented by

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http://www.cis.rit.edu/htbooks/nmr/bnmr.htm

OUTLINE

- Elementary MRS Physics (10 min)
  - chemical shift effect
- Major ^{1}H MRS Metabolites (10 min)
- MRS Methods (30 min)
  - acquisition
  - post-processing
- Questions (5-10 min)

PRELIMINARIES

^{1}H MRS Applications in Neurology

- quantitating metabolic sequelae of hypoxia
  - Lac, Cr (tissue damage, acidosis, pO2, reversibility)
- mapping cell (especially neuronal) damage
  - NAA, Lac (extent and intensity of damage); Cho, Cr (gliosis often masks neuron loss on MRI)
- evaluating myelination and membrane breakdown
  - normal brain maturation: age↑ => Cho↓, NAA ↑; membrane breakdown: Cho↑
- diagnosing inborn errors of metabolism
  - leukodystrophies, mitochondrial disorders, enzyme defects, and others

NMR-Visible Nuclei (Half-Integral Spin)

^{1}H – water, lipids, amino acids, many other metabolites
$\gamma = 267 \times 10^{8}$ rad/sT

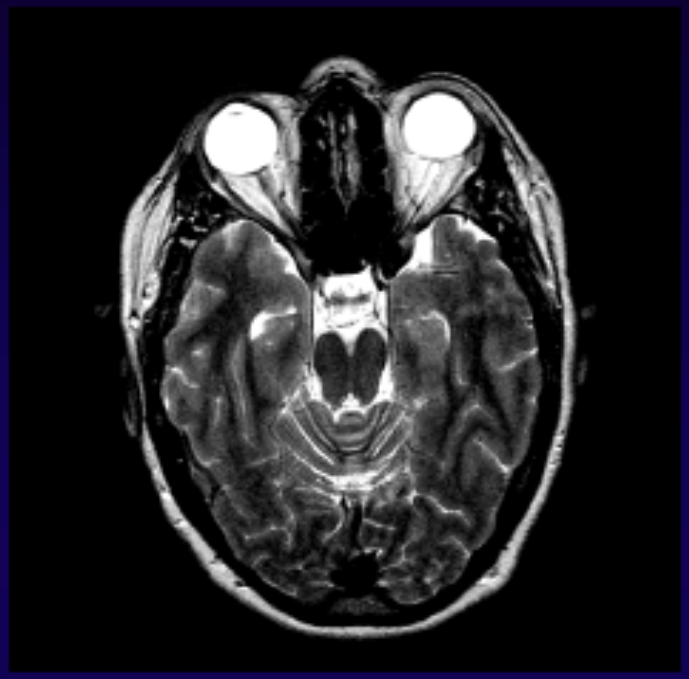
^{31}P – ATP/ADP/AMP nucleosides, energetics, pH determination
$\gamma = 108 \times 10^{8}$ rad/sT

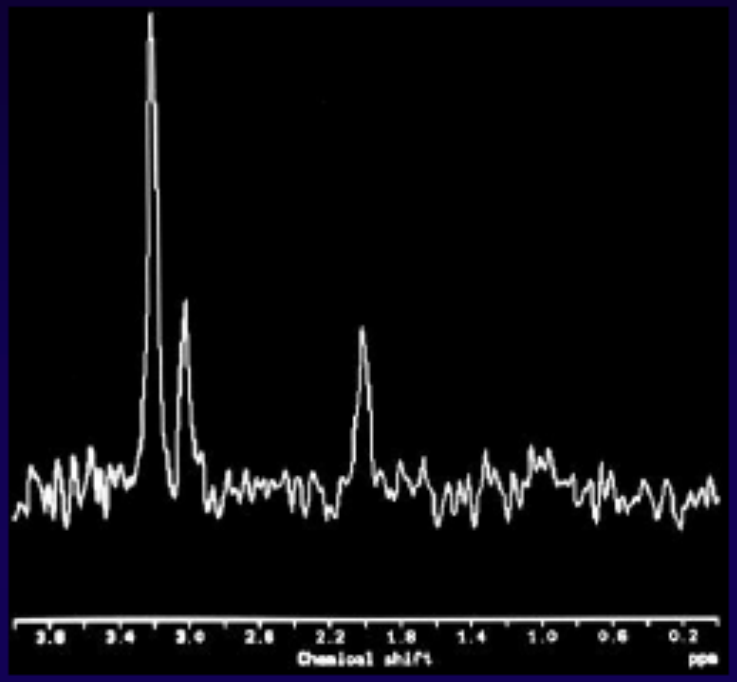
^{13}C - amino acids, neurotransmitters, glucose, lipids, acetate
$\gamma = 67 \times 10^{8}$ rad/sT

^{15}N - metabolism of ammonia, amino acids
^{19}F - pharmacokinetics of fluoxetine and fluvoxamine
^{23}Na - effects of hypoxia, challenges to Na pumps
^{2}H - metabolism of fats
^{7}Li - pharmacokinetics of lithium

ELEMENTARY MRS PHYSICS

Basics of MRS





MR Imaging and Spectroscopy share the same physical principle!

- MRI looks at the geometrical distribution of water molecules
- MRS looks at the chemical composition of the tissue of interest and displays it in a spectrum

MRS ACQUISITION PROCEDURE

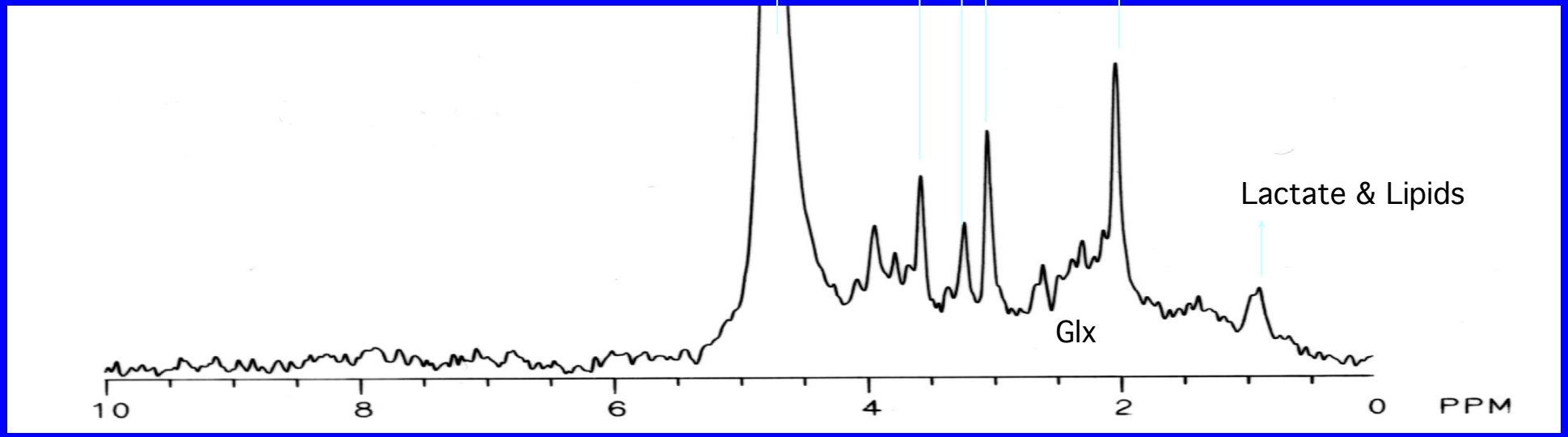
- place patient in strong magnetic field (MRI scanner)
- expose to RF induction signal from transmitter across a continuous frequency range
- record intensity of RF response at each frequency

=> series of peaks (Magnetic Resonance Spectrum)

peak frequency <=> chemical functional group common to a small family of molecules (metabolites)

peak area (intensity) $\propto$ metabolite concentration

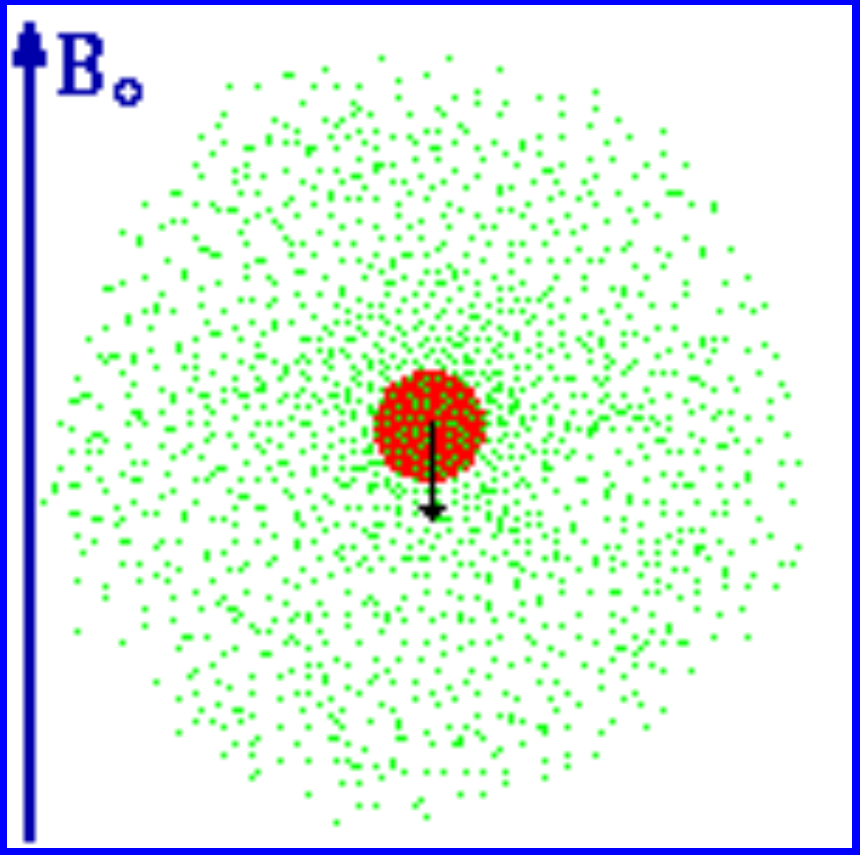
Brain Proton MR Spectrum - Key Signals



Glutamate (Glu) + Glutamine (Gln) = Glx

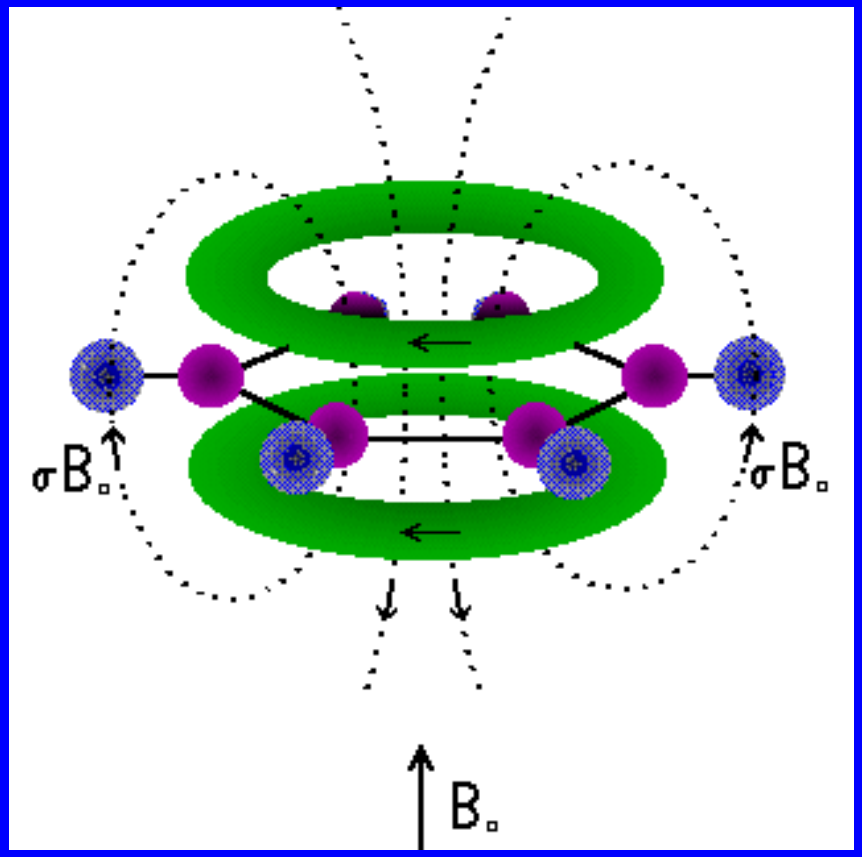
CHEMICAL SHIFT EFFECT

CHEMICAL SHIFT EFFECT (Shielding)



$$B = B_0(1-\sigma)$$

CHEMICAL SHIFT EFFECT (Enhancement-- Deshielding)

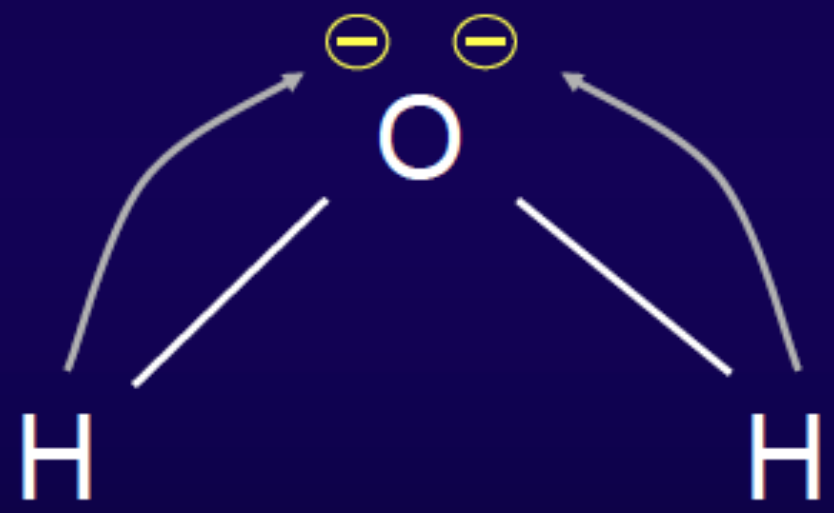


$$B = B_0(1-\sigma)$$

Chemical Shift

Chemical environment ⇒ shielding

water



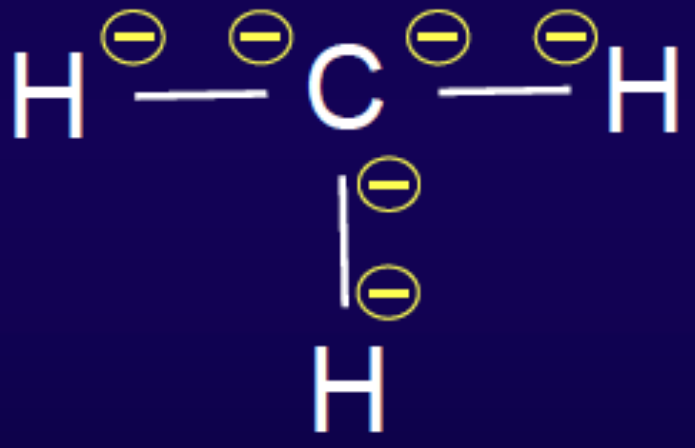
ion bonding

H deprived from electron

weak shielding

=> sense higher B0-field

fat



covalent bonding

shared electrons

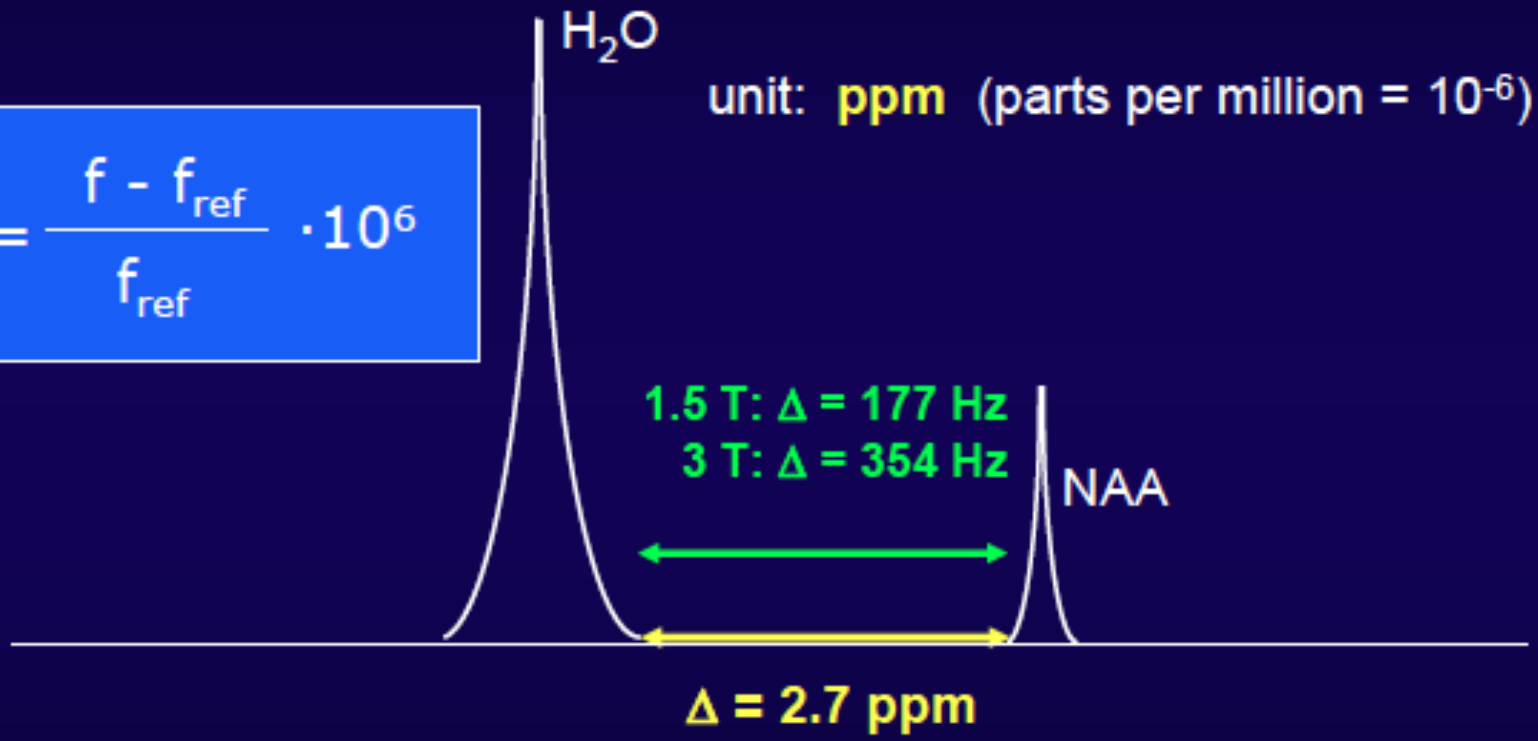
strong shielding

=> sense lower B0-field

Chemical shift

$$\delta\,[\mathrm{Hz}] = f - f_{ref}$$

$$\delta\,[\mathrm{ppm}] = \frac{f - f_{ref}}{f_{ref}} \cdot 10^6$$



^{1}H: $f_{ref} = f_{TMS}$ TMS: tetramethylsilane $Si(CH_3)_4$ => f_{NAA} = 2.02 ppm

^{31}P: $f_{ref} = f_{PCr}$

Chemical shift

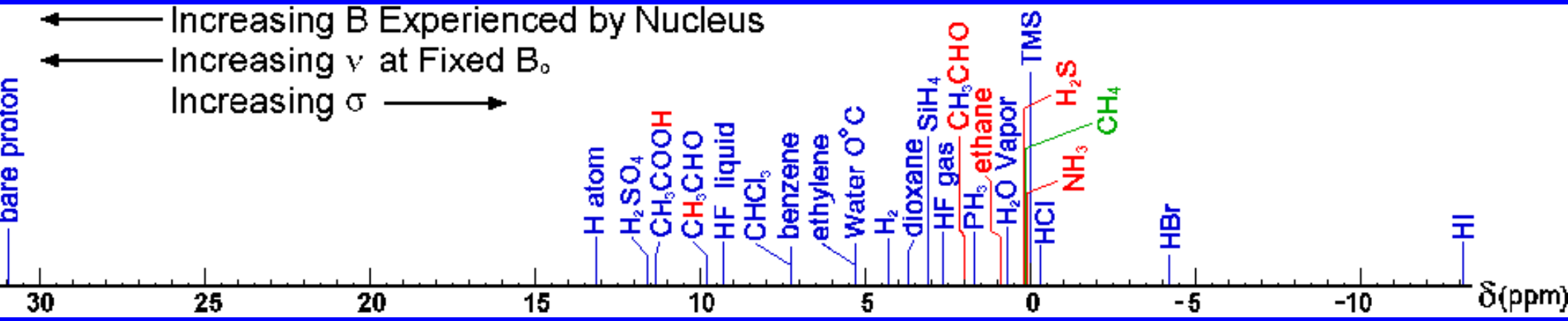
IMPORTANT:

- The chemical shift expressed in ppm is independent of the magnetic field strength !
  - e.g. NAA is always at 2 ppm

- The value of 1ppm in Hz is different at different field strength and for different nuclei:

	1.5 T	3 T
1H :	1ppm = 63.87 Hz	1ppm = 127.74 Hz
31P :	1ppm = 25.86 Hz	1ppm = 51.72 Hz

CHEMICAL SHIFT EFFECT



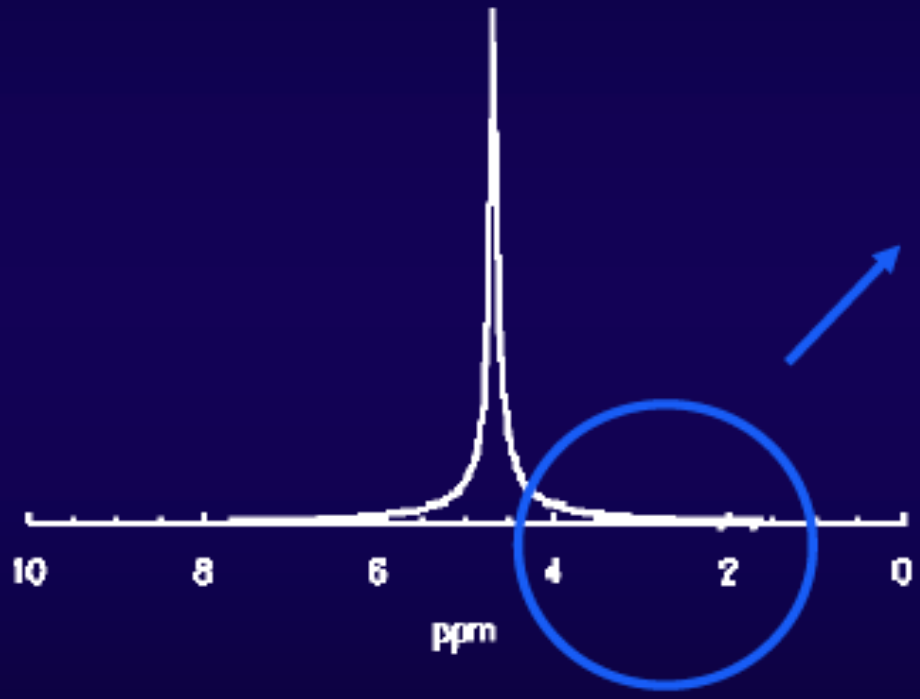
$$B = B_0(1-\sigma)$$

$$\delta(\text{ppm}) = \frac{f - f_0}{f_0} \times 10^6$$

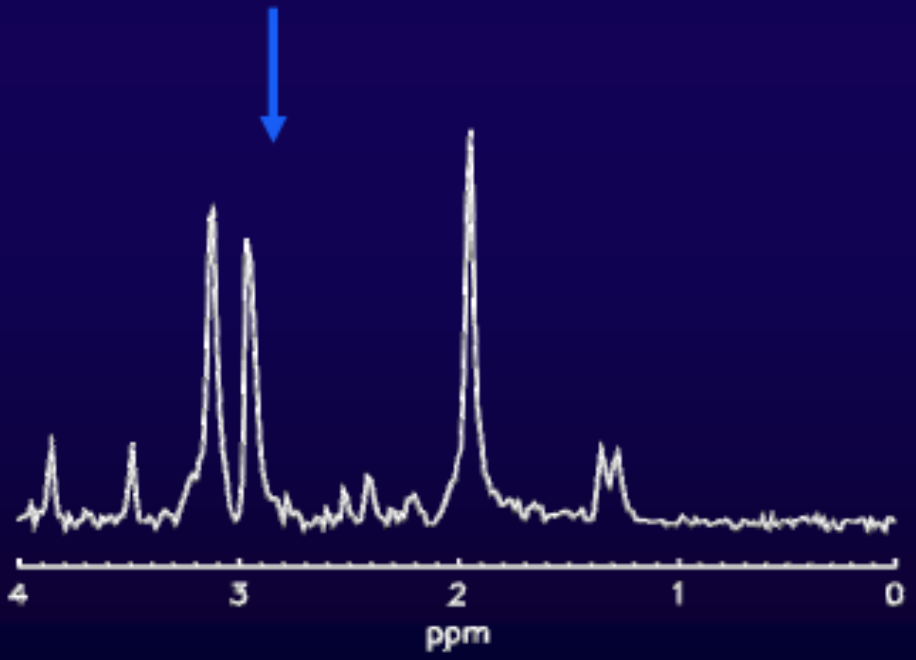
MAJOR ^{1}H MRS METABOLITES

^1H MR Spectroscopy *in vivo*

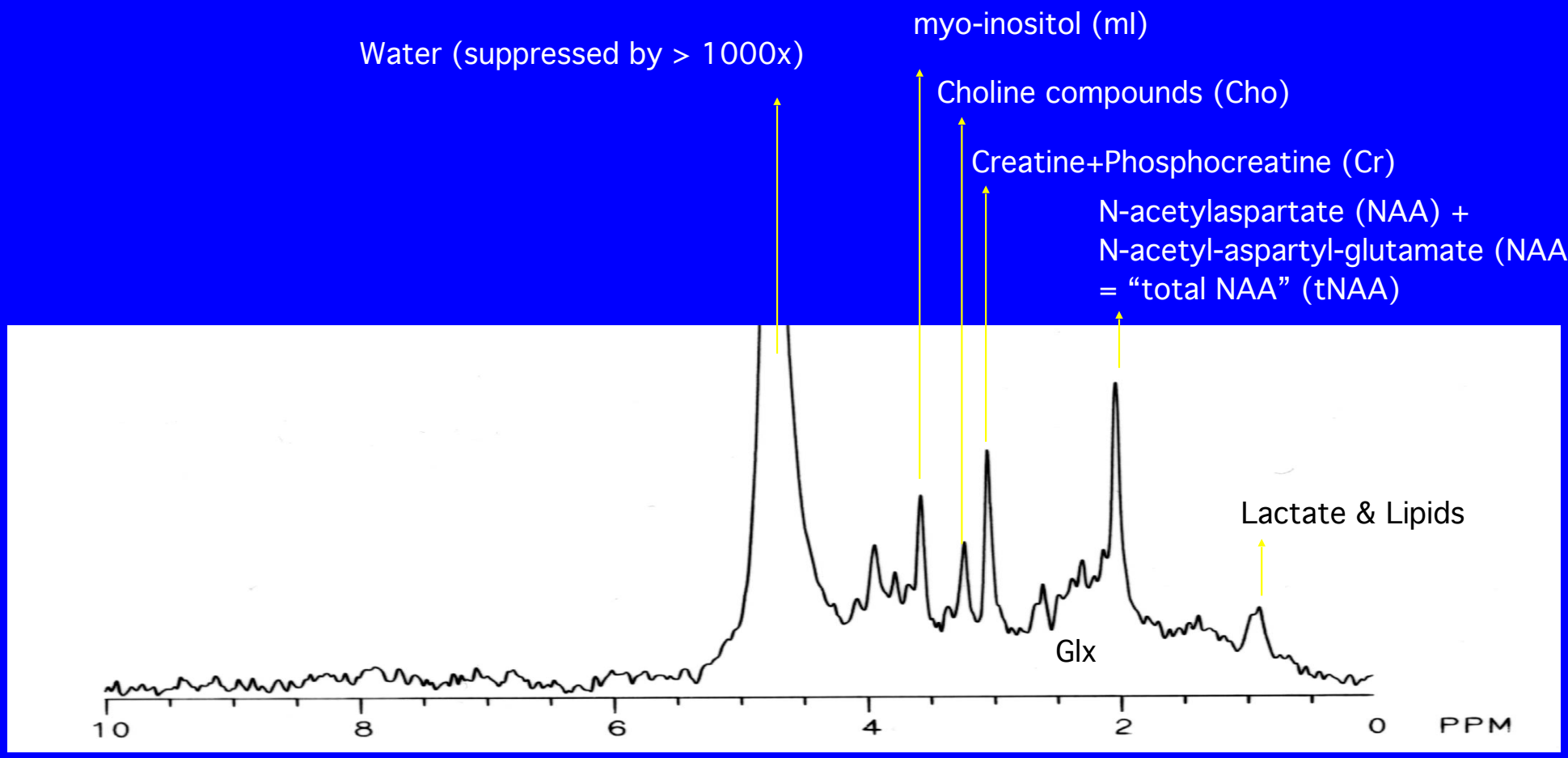
=> We are interested in the *small* peaks



Water suppression



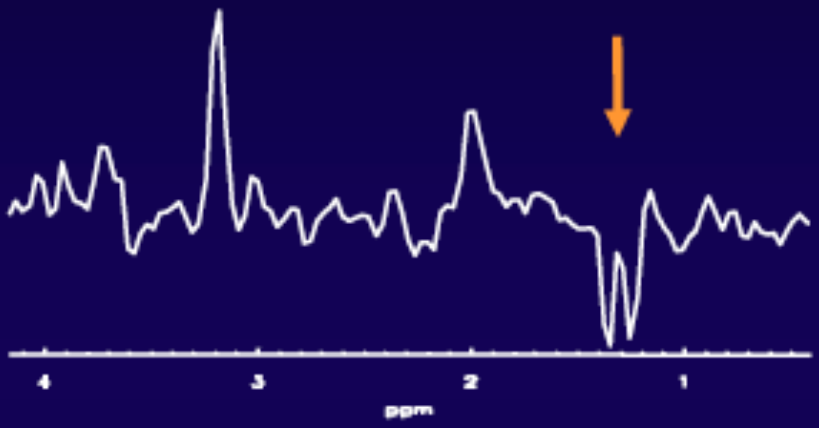
Brain Proton MR Spectrum - Key Signals



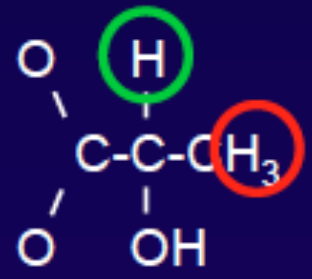
Glutamate (Glu) + Glutamine (Gln) = Glx

Lactate

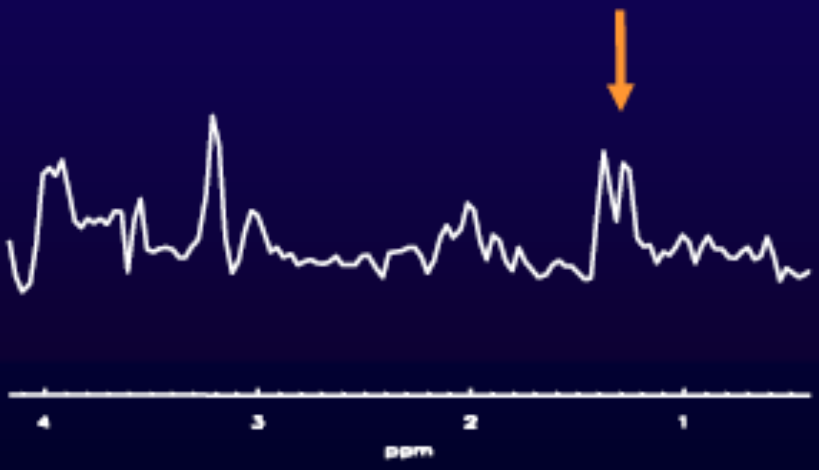
TE = 144 ms = 1/J



~ 1 mM



TE = 288 ms = 2/J



CH_3 doublet 1.33 ppm

CH quartet 4.11 ppm

Lactate = Lac

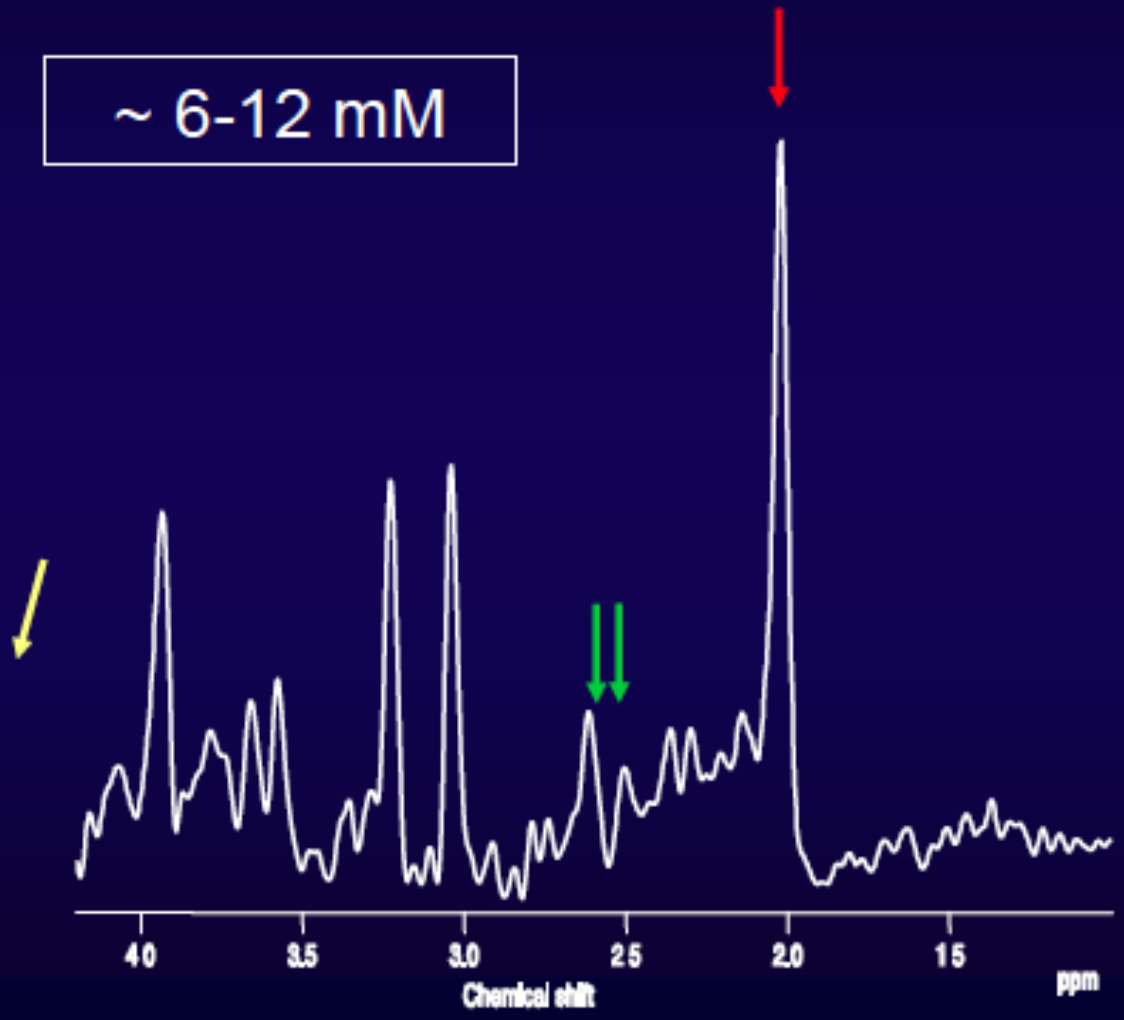
Function: Sign of impaired energy metabolism, impaired oxygen delivery (anaerobic glycolysis).

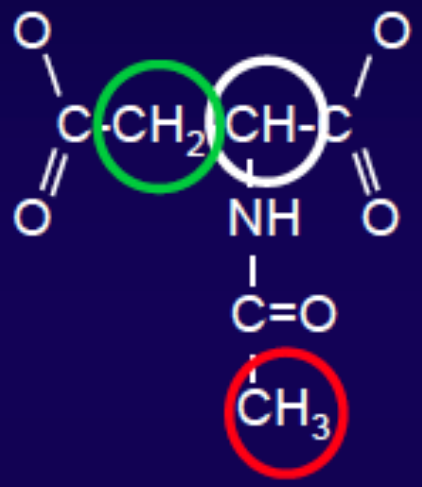
Not or hardly detectable in normal brain tissue (~1 mM)

Lac Increase: Stroke, An-/Hypoxia,
Mitochondrial diseases,
Tumors (Brain and Metastases),
Epileptic discharges,
Abscesses/Infection,
Prolonged neuronal activation (?)

N-Acetyl Aspartate = NAA

~ 6-12 mM





CH_3 2.02 ppm

CH_2 2.69 & 2.49 ppm

CH 4.39 ppm

UD 2008

N-Acetyl Aspartate = NAA

Function:

1. Neuronal marker i.e. concentration correlates with neuronal density
2. Neuronal function, i.e. synthesis is energy-dependent, therefore concentration correlates with neuronal function

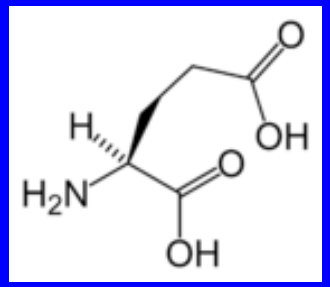
NAA Decrease: Tumor, Stroke, Epilepsy, Hyp-/Anoxia, Inflammation, Dementia, Trauma

NAA Increase: Brain Development and Maturation
Canavan's Disease (aspartoacylase deficiency)

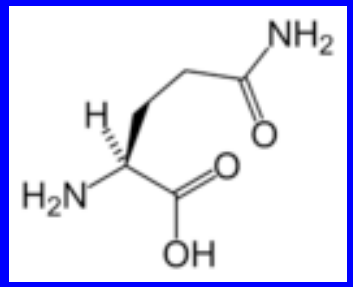
Glutamate (Glu)+Glutamine (Gln)=Glx (2.1-2.5 ppm)

- **Glu excitatory amino acid NT, synthesized in neurons**
- **Gln neutral form of Glu, synthesized in glia**
- **interact with Krebs Cycle (energetics)**
- **Glu excitotoxicity presumed in many diseases**

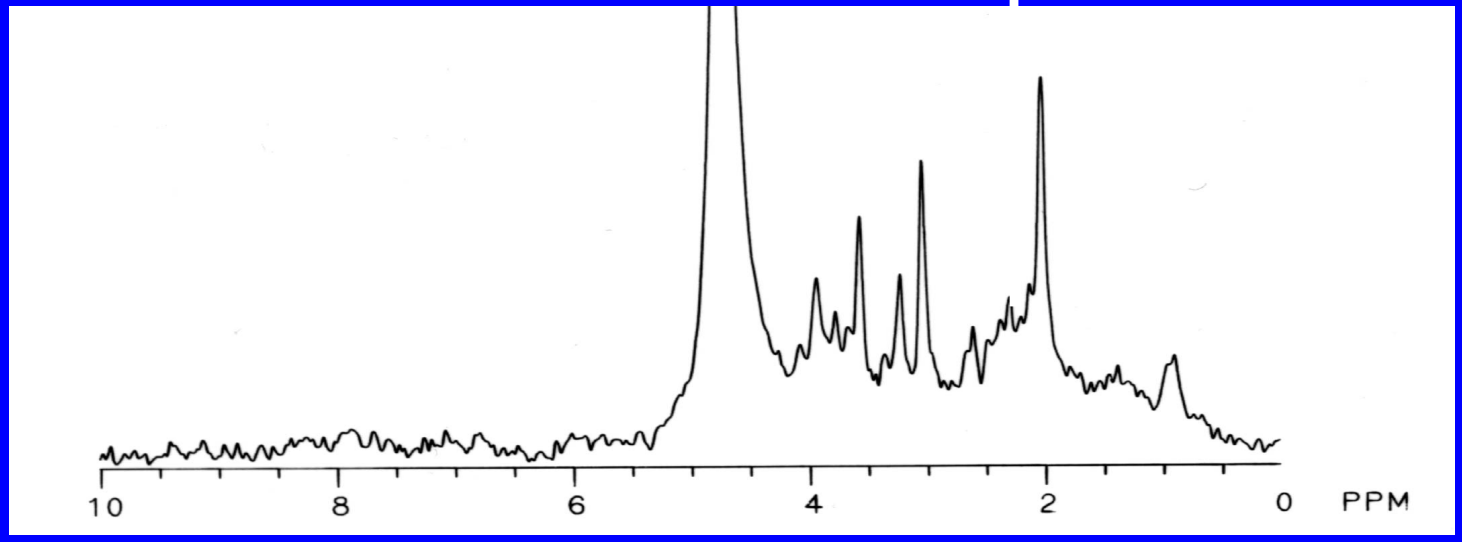
Glu



+

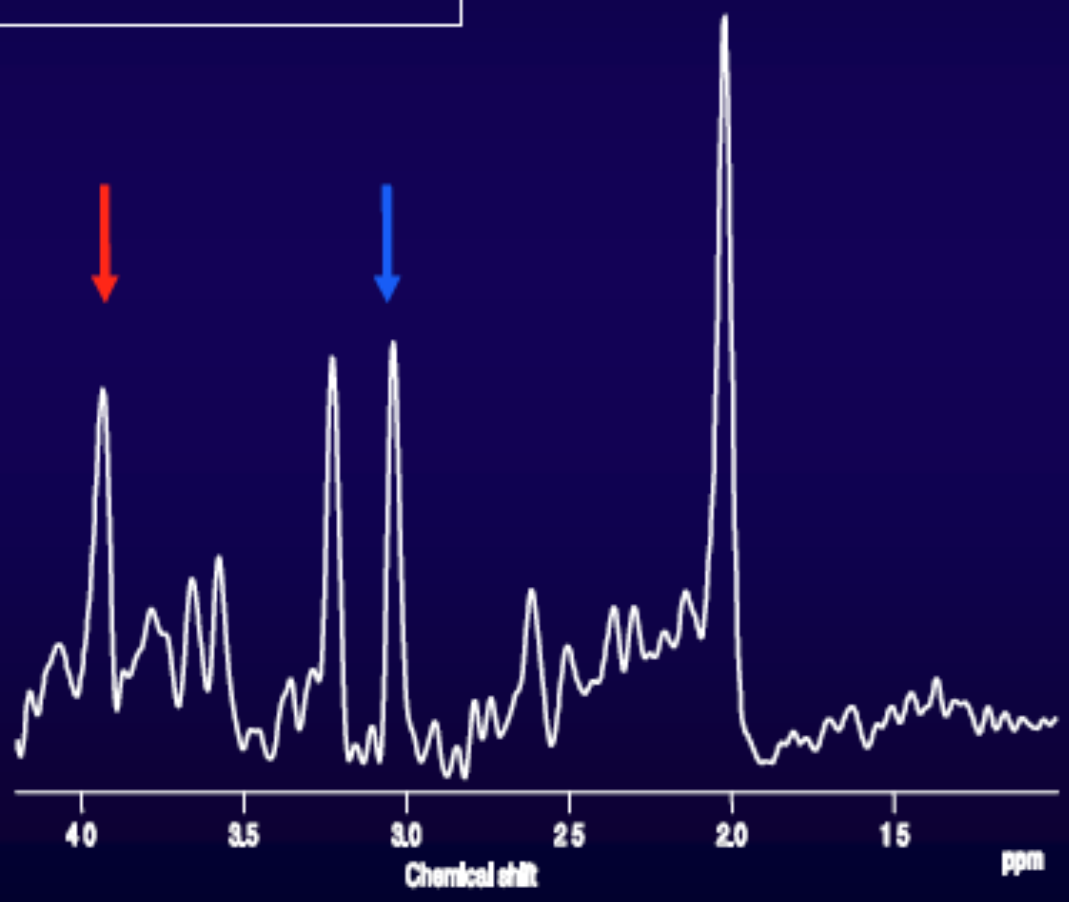


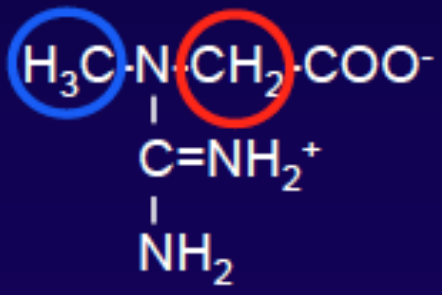
Gln



Creatine / Phosphocreatine = Cre

~ 6-12 mM





CH_3 3.03 ppm

CH_2 3.93 ppm

UD 2008

Creatine / Phosphocreatine = Cre

Function: 1. Energy Buffer:

$$H + PCr + ADP \Leftrightarrow ATP + Cr$$

2. Energy shuttle: "Energy transport" from production (mitochondria) to energy utilizing sites

The CRE peak is often stable and therefore may serve as an internal reference

Exceptions:

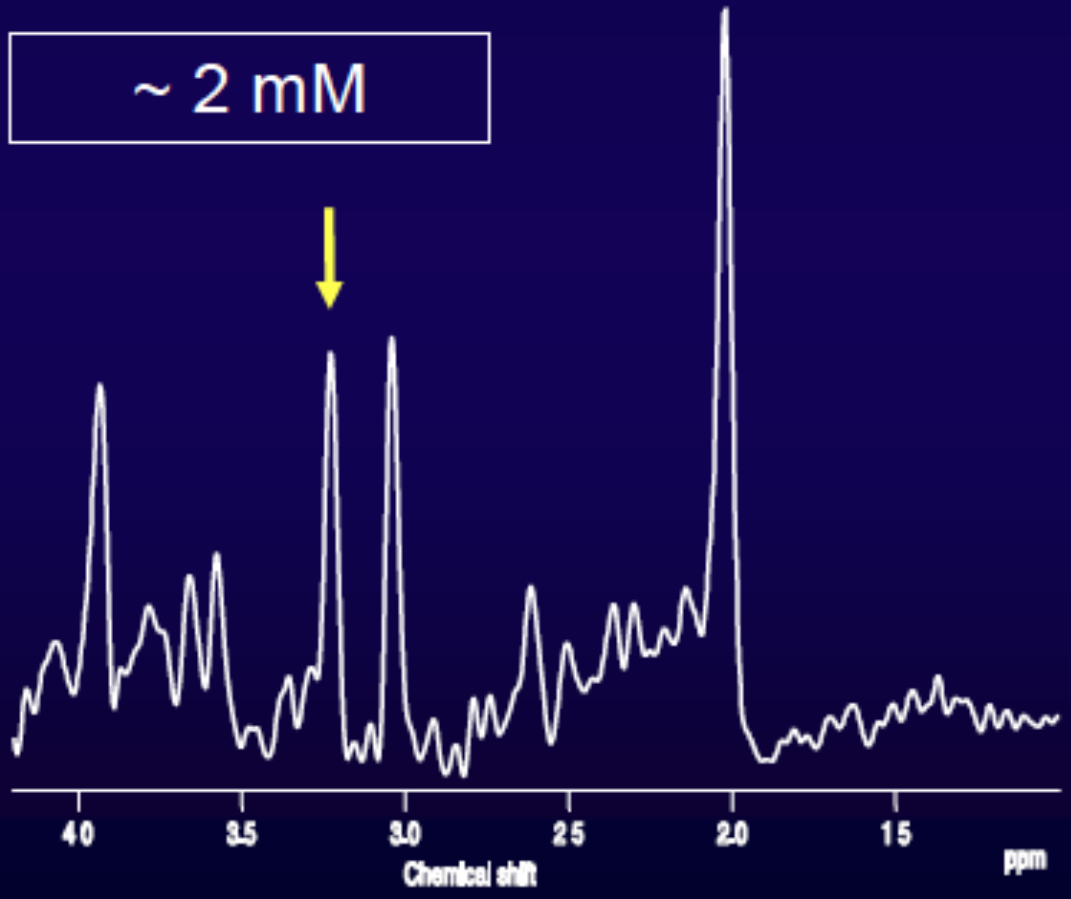
Cr/PCr Decrease: Acute and subacute stroke, Brain tumor, Brain metastasis, Abscesses, Inborn errors of Creatine synthesis

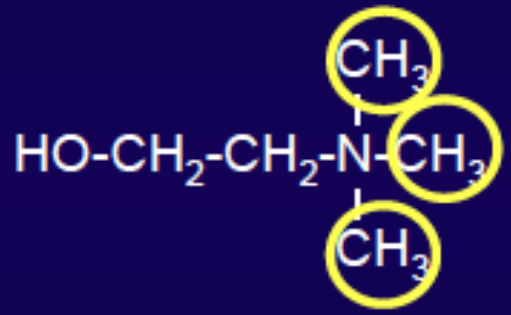
Choline-Containing Compounds = Cho

Cho = phosphorylcholine and glycerophosphorylcholine,

no contribution from acetylcholine

~ 2 mM





CH_3 3.22 ppm

CH_2 3.54 & 4.05 ppm

Choline-Containing Compounds = Cho

Function: Involved in pathways of phospholipid synthesis and degradation.

=> reflecting membrane synthesis and degradation

Cho Increase: Brain Tumors,
MS-Plaques,
Stroke,
Inflammation,
White Matter Diseases

Cho Decrease: Hepatic Encephalopathy,
Necrosis

myo-Inositol (ml; 3.54 ppm)

cyclic monosaccharide

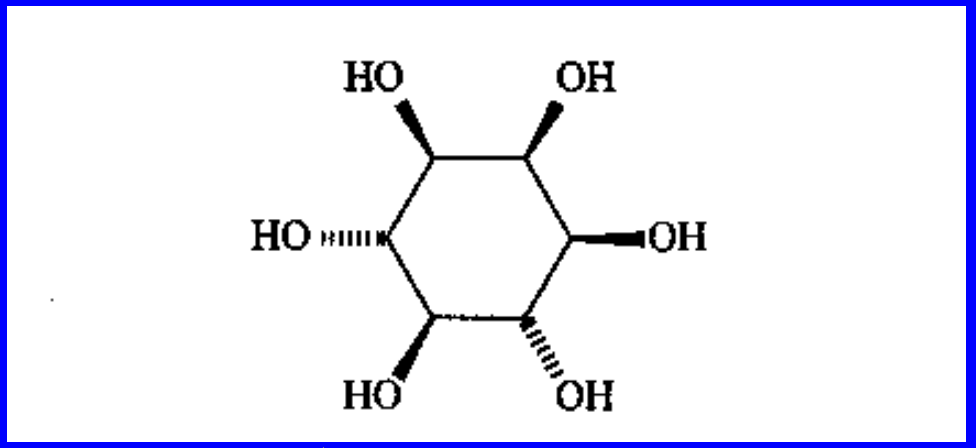
more abundant in glia

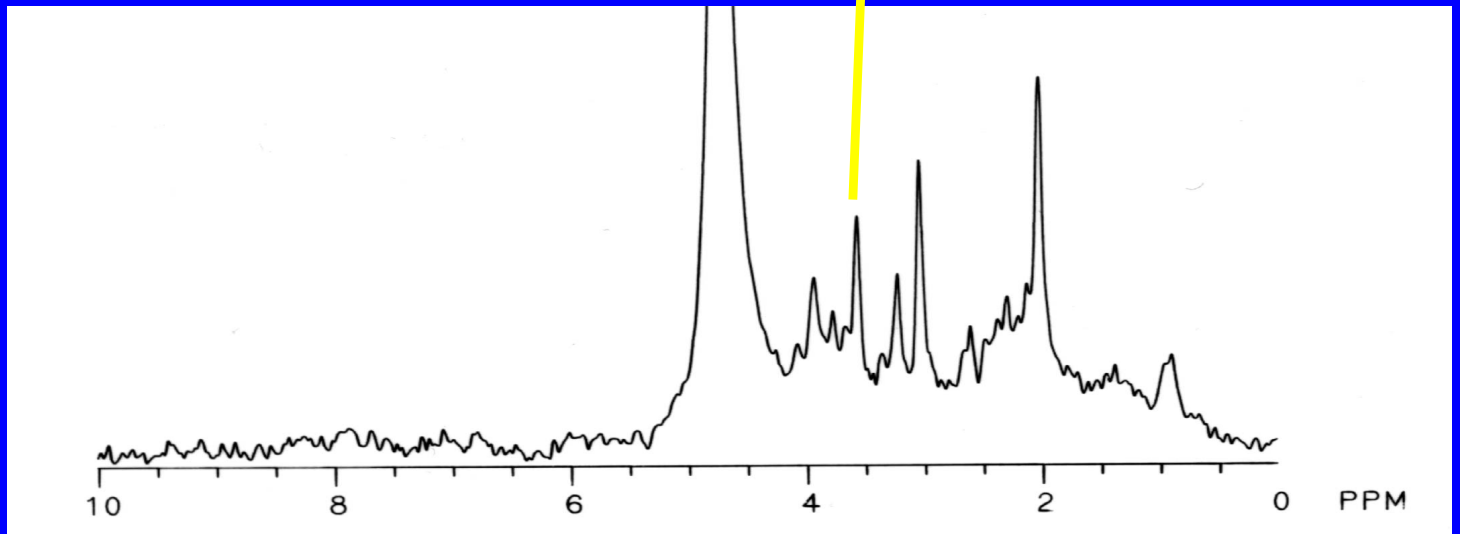
cellular second-messenger

cell-membrane metabolism

elevated in Alzheimer's

disease





MRS METHODS
(acquisition, post-processing)

4 STEPS TO ALL MRS ACQUISITION

- positioning (prescription)
- shimming
- water-suppression (^{1}H MRS only)
- excitation (and reception)

POSITIONING (PRESCRIPTION)

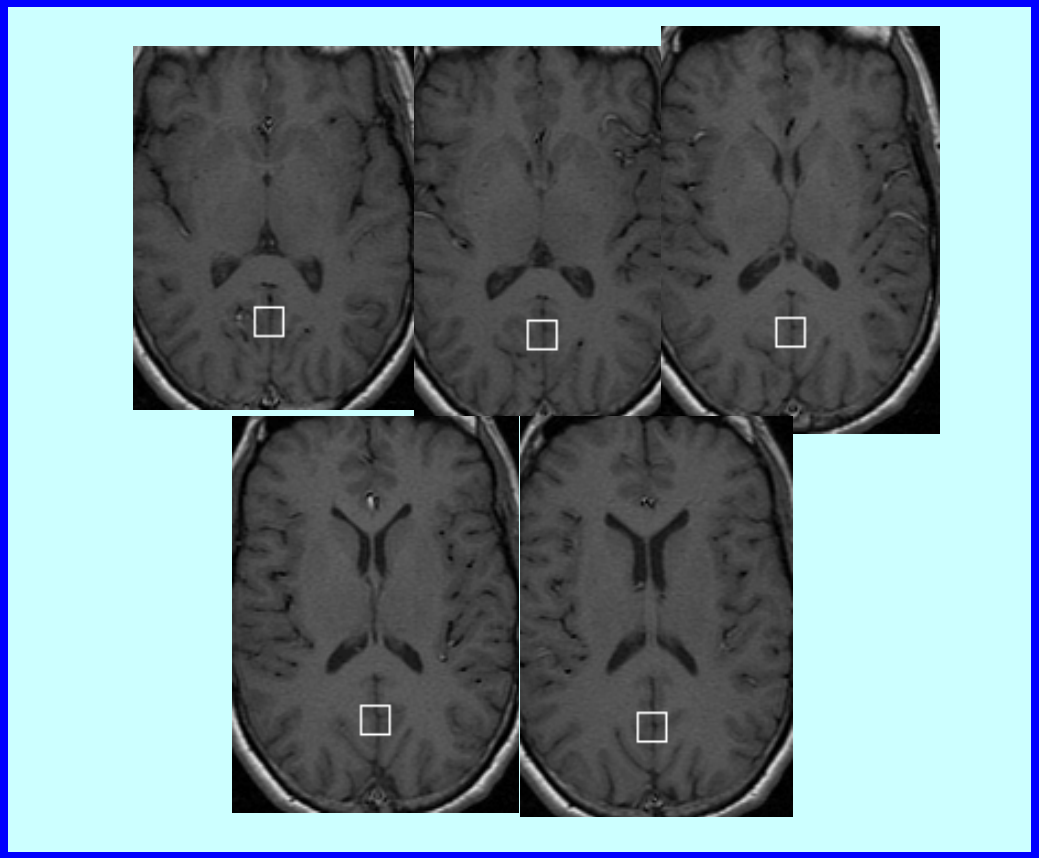
Localization

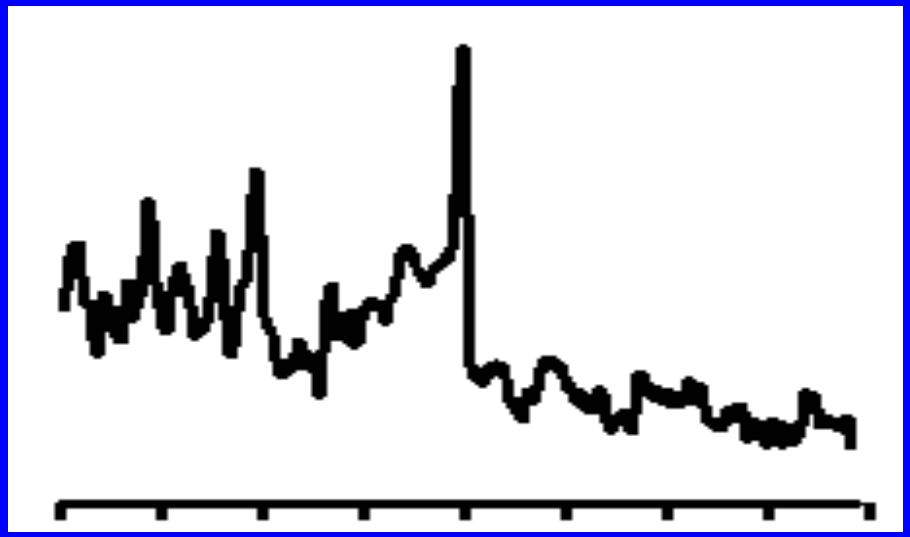
- Single Voxel techniques:
  - PRESS (selective excitation for ^{1}H MRS)
  - STEAM (selective excitation for ^{1}H MRS)
  - ISIS (encoding scheme for ^{31}P MRS)
  - …
- Multivoxel techniques:
  - Spectroscopic Imaging / Chemical Shift Imaging (CSI)
  - Hadamard encoding

Single-Voxel MRS Procedure

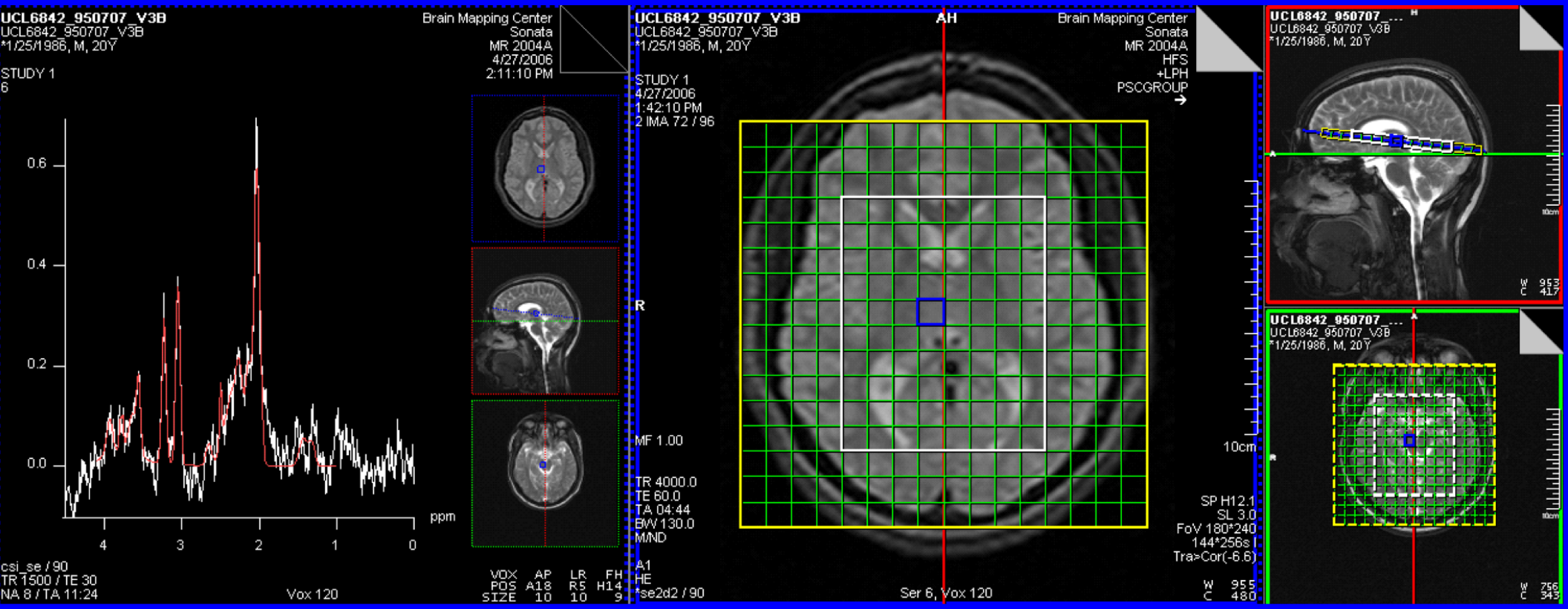
select a volume element (voxel) of interest (> 2 cc)

acquire a spectrum from that voxel (< 1 min)





MAGNETIC RESONANCE SPECTROSCOPIC IMAGING (MRSI)

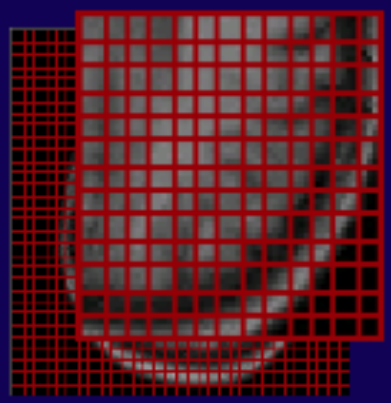


O'Neill, Frew, Alger et al. (2006)

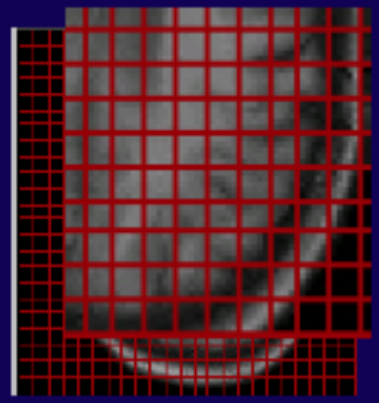
Typical MRSI Scan Times

Assume FOV = 240, 1.5 cm slice thickness, TR = 1.5 s:

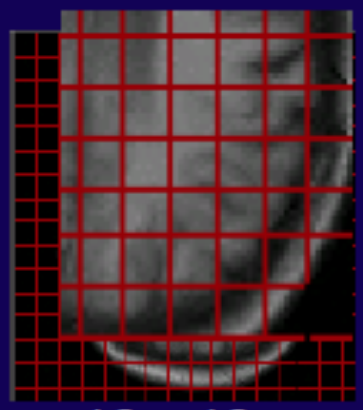
grid size	voxel size (mm^3)	voxel volume (ml)	scan time
32 x 32	7.5*7.5*15	0.84 ml	26 min
24 x 24	10*10*15	1.5 ml	14.5 min
16 x 16	15*15*15	3.4 ml	6.5 min
8 x 8	30*30*15	13.5 ml	2 min



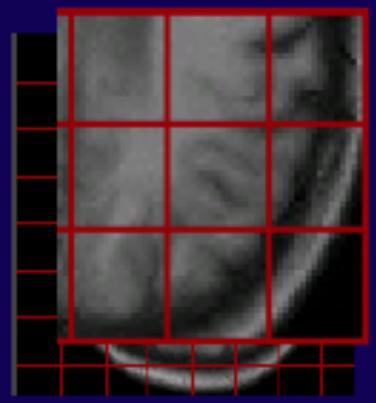
32 x 32



24 x 24



16 x 16

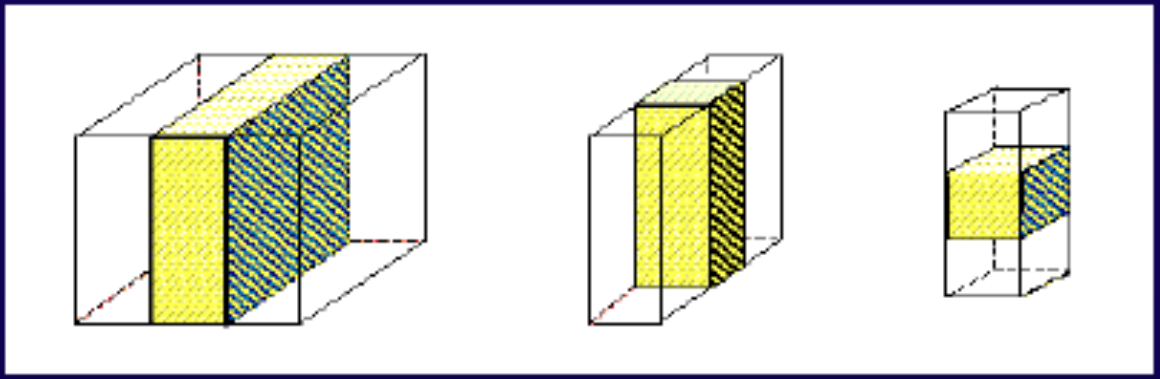


8 x 8

Localization by gradients

in each direction a gradient field defines one slice

=> the intersection of these slices is the selected volume of interest



These methods can also be used in addition to a localization with a surface coil to profit from high SNR.

Spectroscopic Imaging: Localization

2 Sets of Geometries:

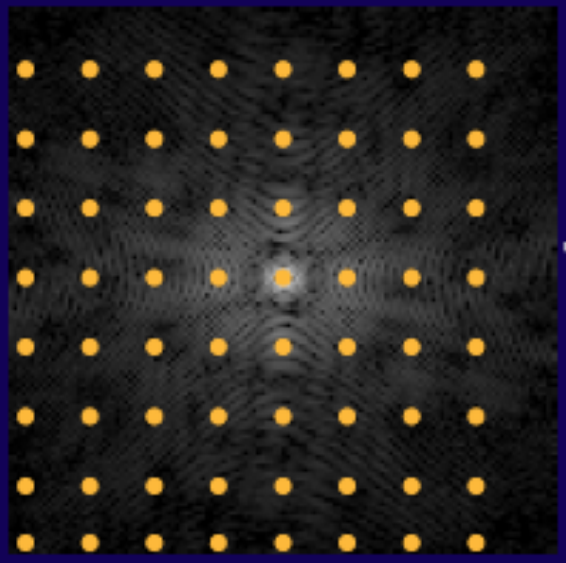
- Volume selection: echo volume selection (PRESS, STEAM)
  - to define 1-3 dimensions
  - to suppress unwanted signals from adjacent structures (e.g. reduce fat signal of skull)

- In plane position encoding: phase encoding
  - in 2 or 3 dimensions
  - Voxel size will determine resolution of metabolite images
  - Voxel size and FOV will determine scan duration

Spectroscopic Imaging

- *each phase encoding step acquires signal from the whole VOI*
- *# voxels in space = # k-space points = # averages*
- *Reconstruction: 2D spatial FT, 1D temporal FT*

k-space



FT

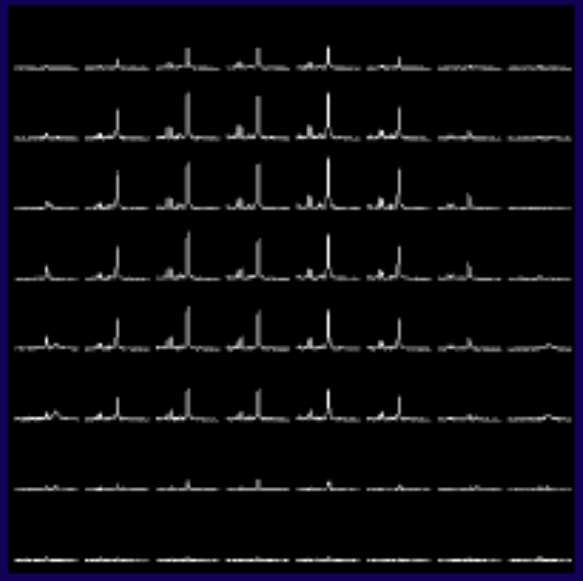
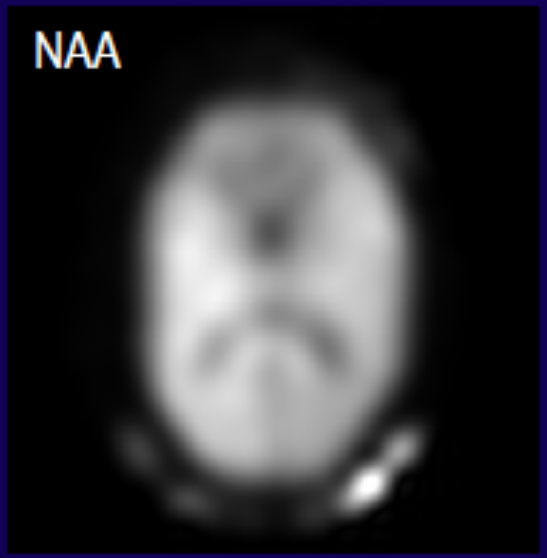
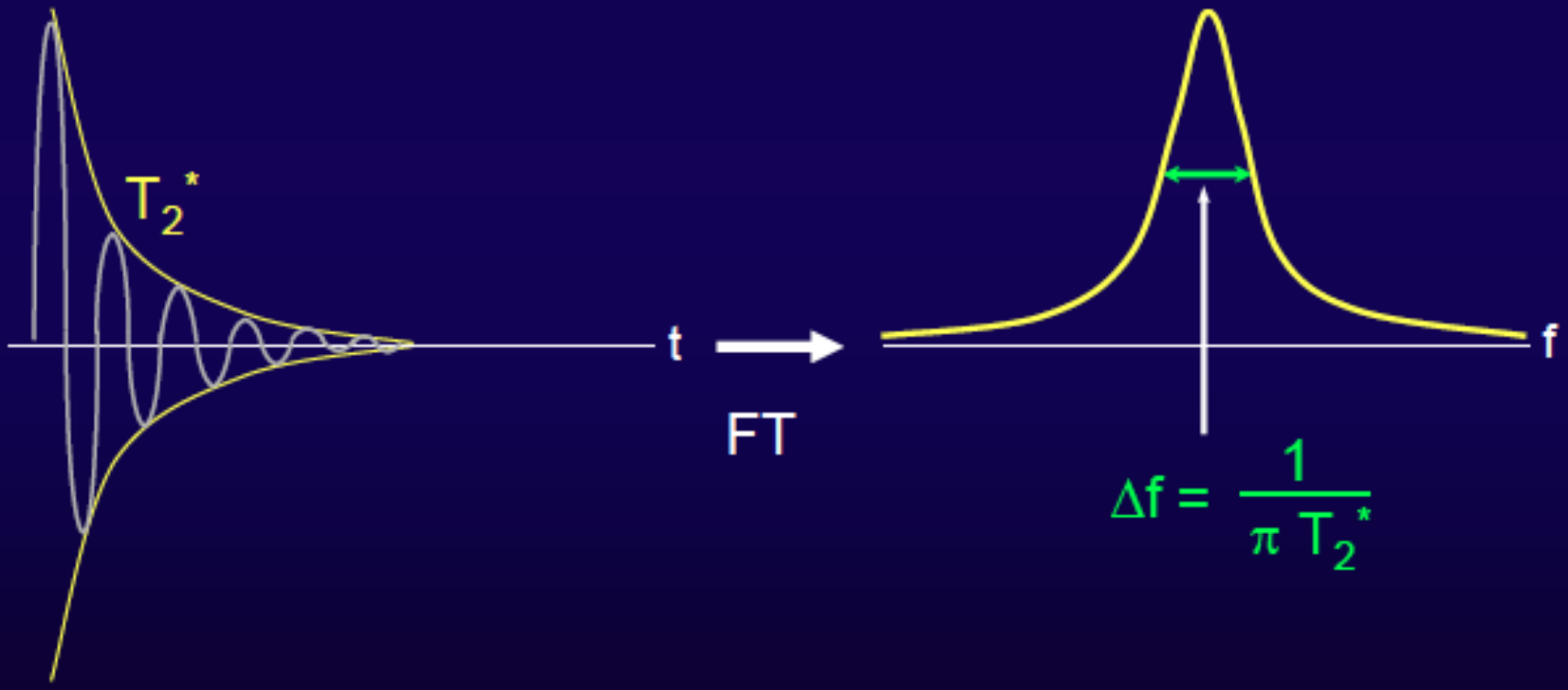


image space

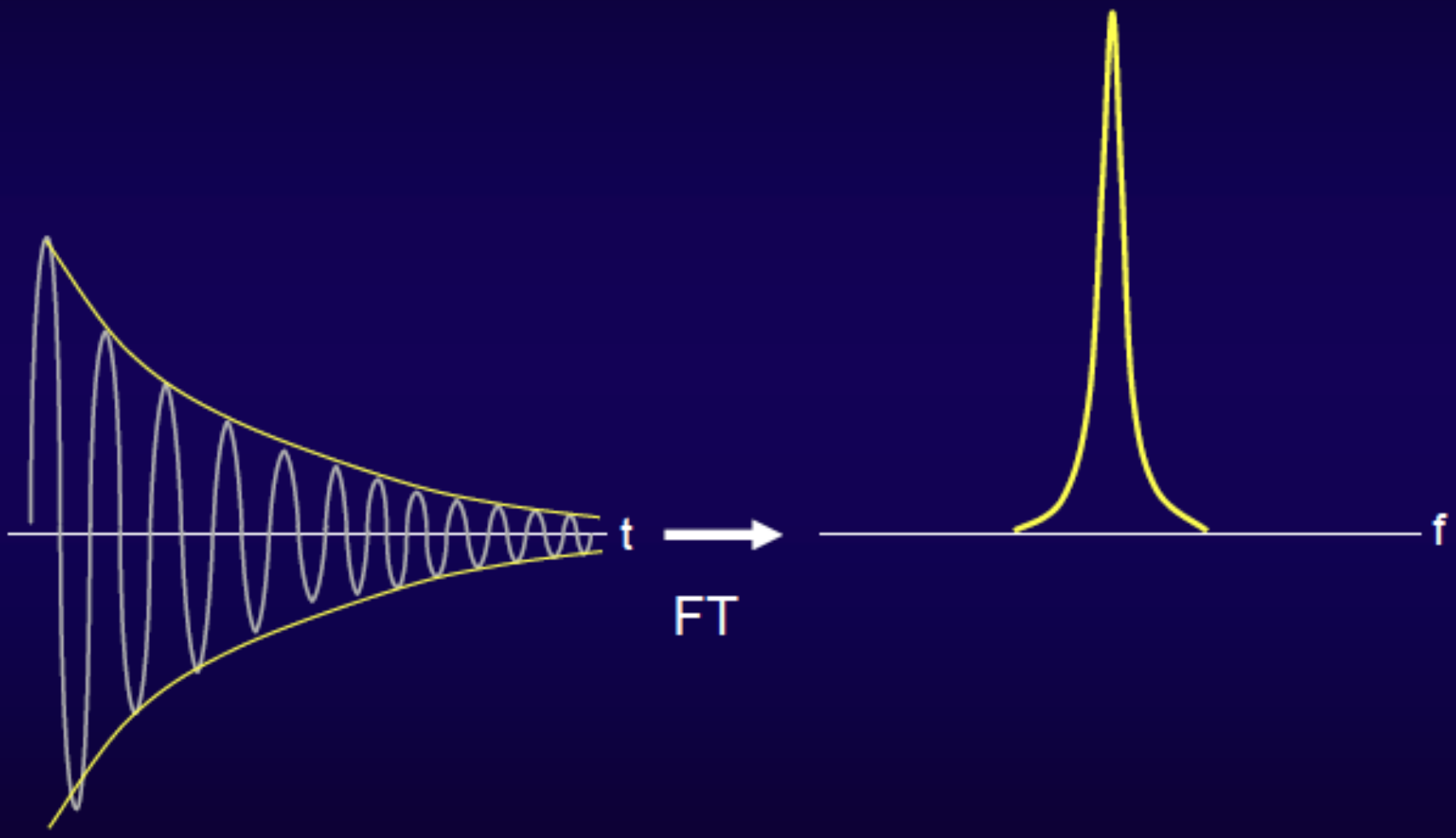


SHIMMING

Shimming



Shimming



WATER-SUPPRESSION

CHEMICAL SHIFT SELECTIVE (CHESS)

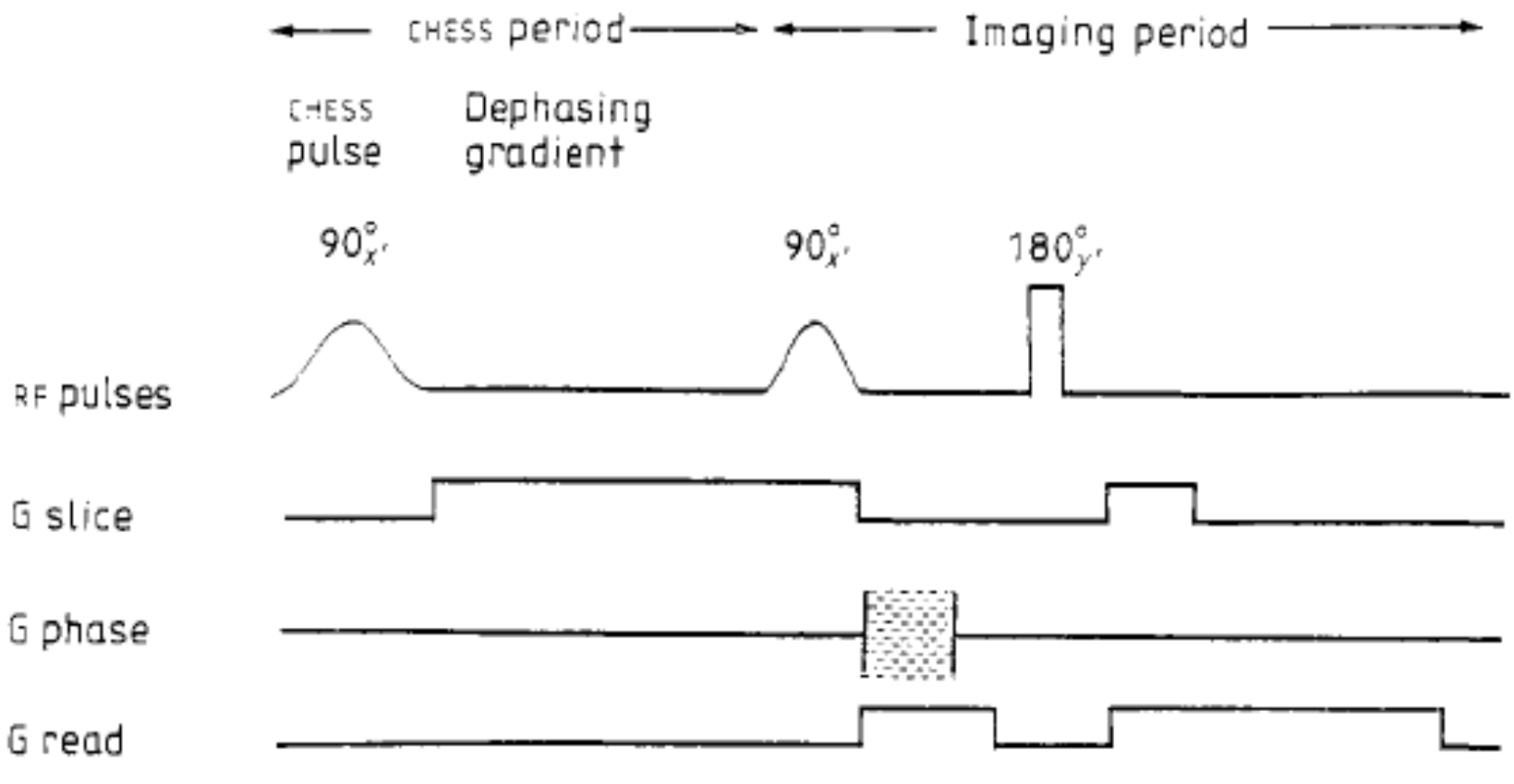
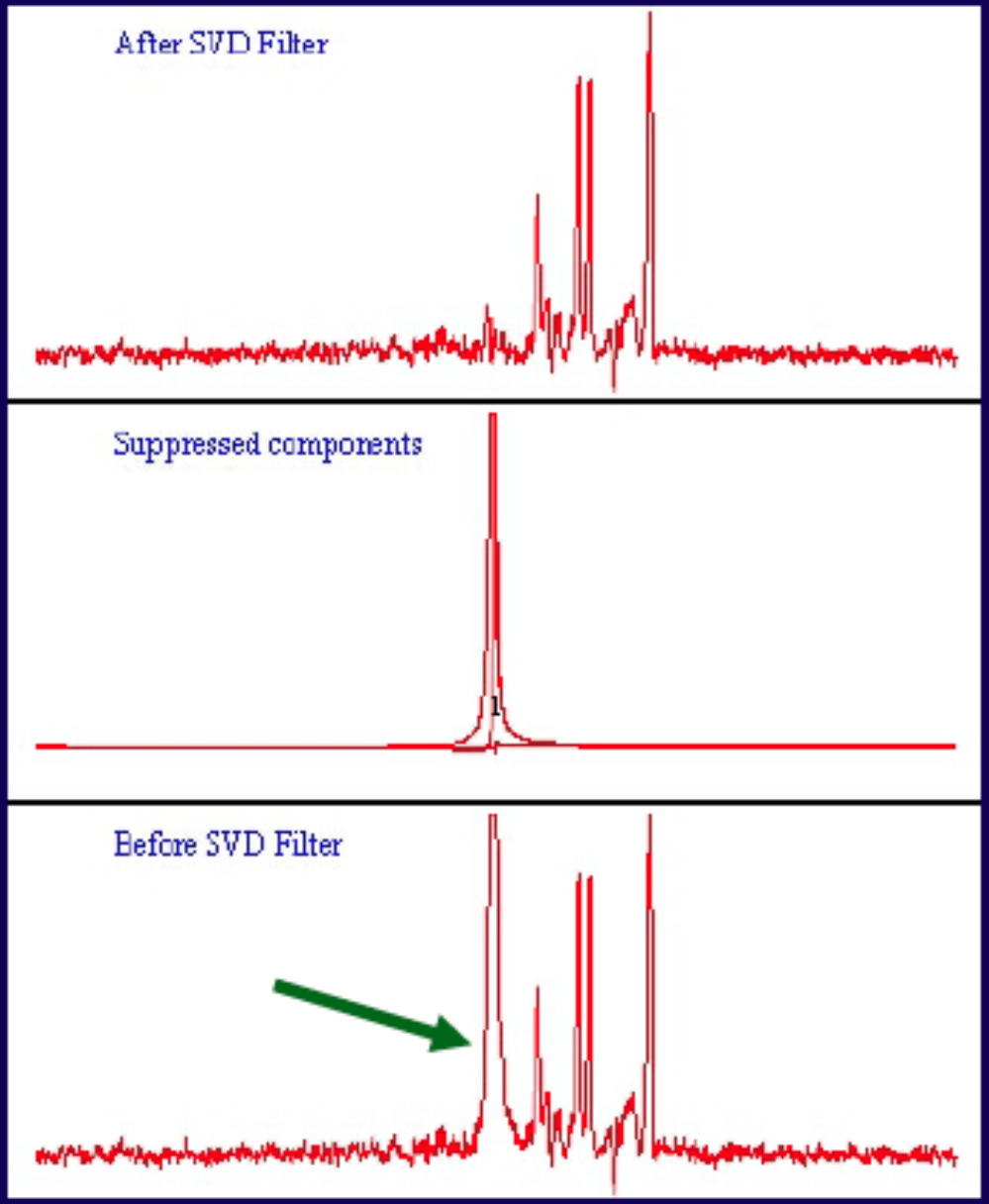


Figure 1. Schematic diagram of the CHESS imaging sequence.

Haase et al. (1985)

Elimination of water residue

- 'hlsvd' = single value decomposition



EXCITATION
(Pulse-Sequences)

Influence of echo time

short TE (30 ms)

long TE (144 ms)

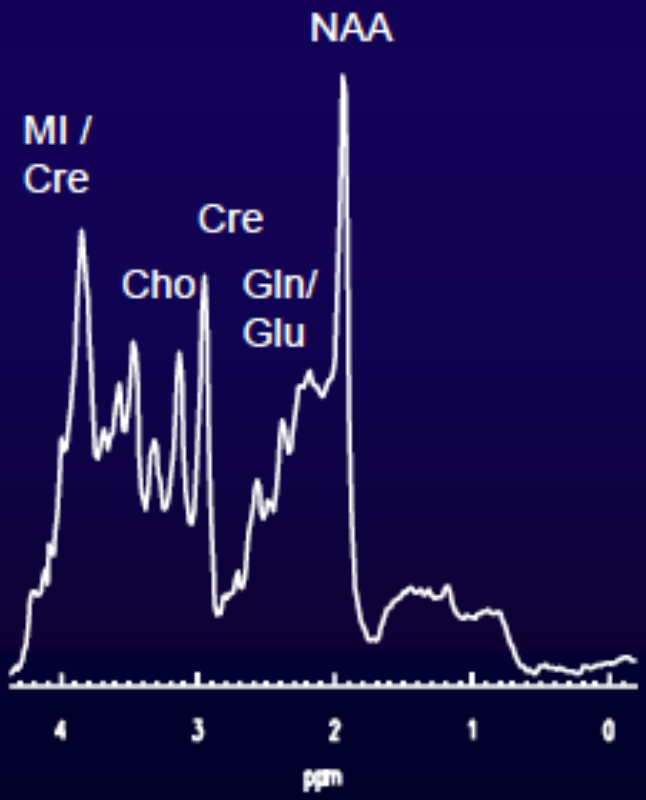
long TE (288 ms)

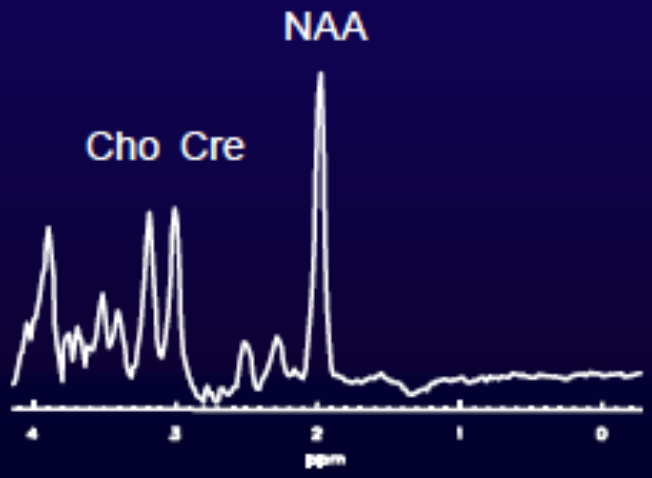
+ clear baseline

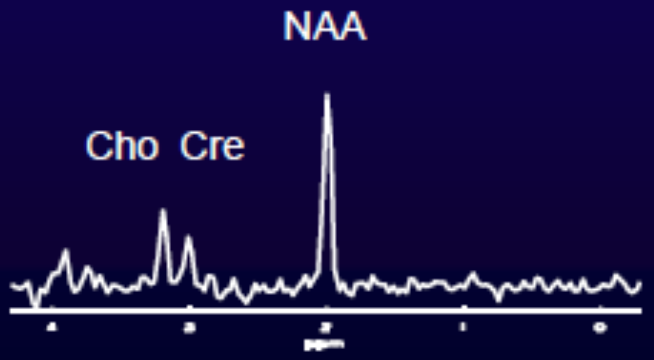
+ easier quantification

- Loss of SNR with T2

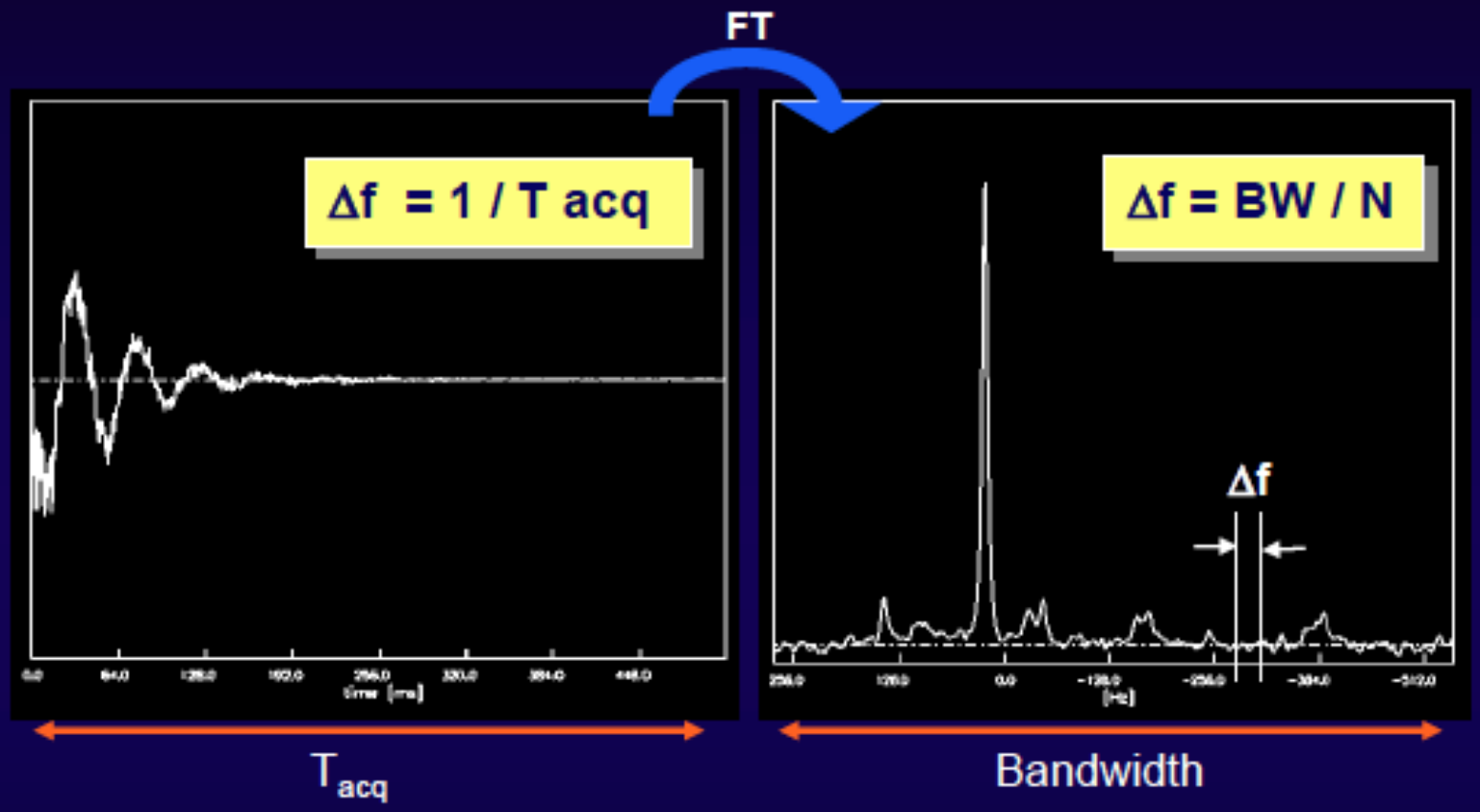
- Some metabolites only visible at short TE!







Acquisition Time and Spectral Resolution



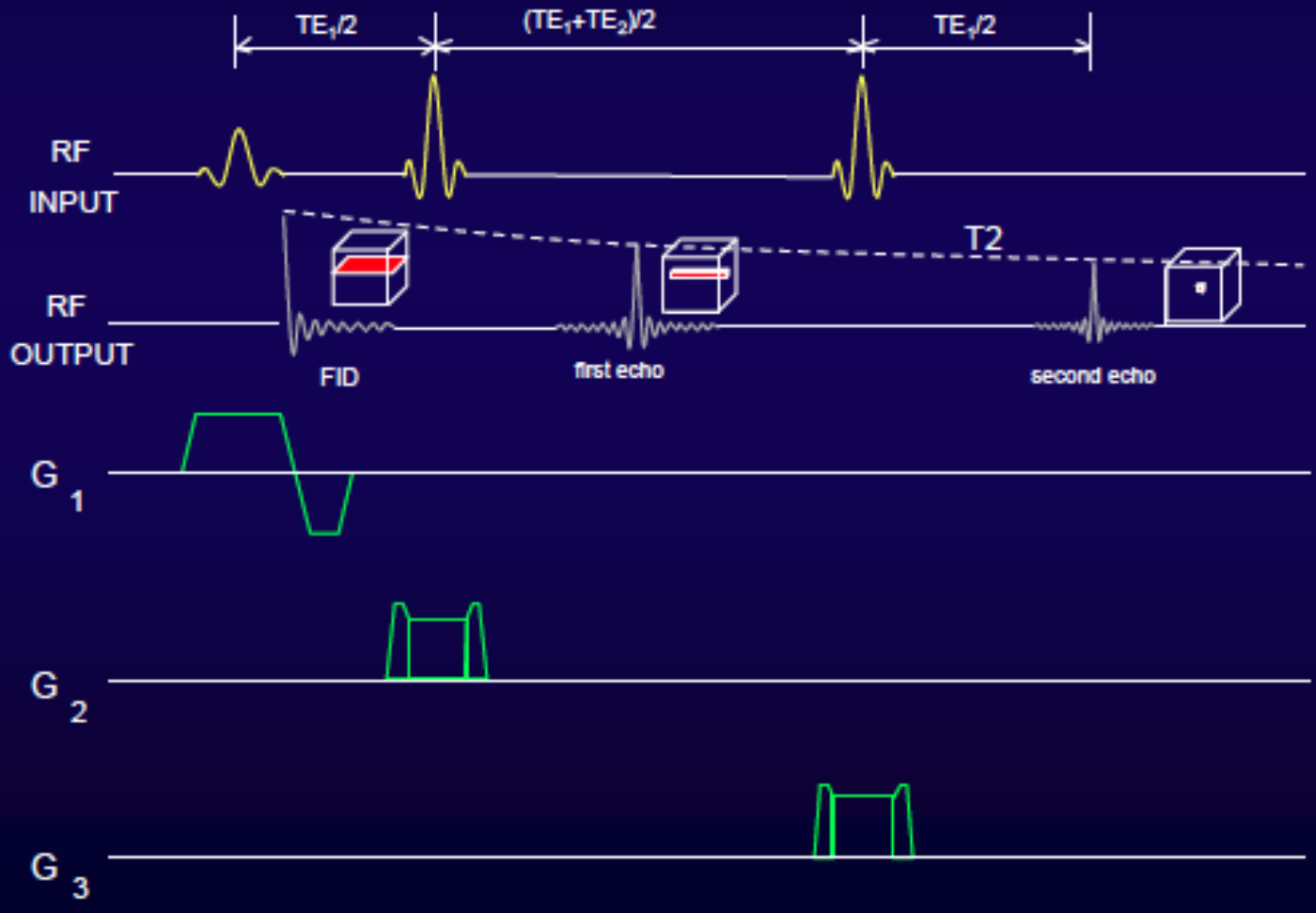
Spectral resolution $\Delta f = 1 / T_{acq}$

Spectral resolution Δf = BW / samples

=> acquisition time depends on spectral resolution!

Localization: PRESS

PRESS = Point RESolved Spectroscopy



Localization: PRESS

Advantages:

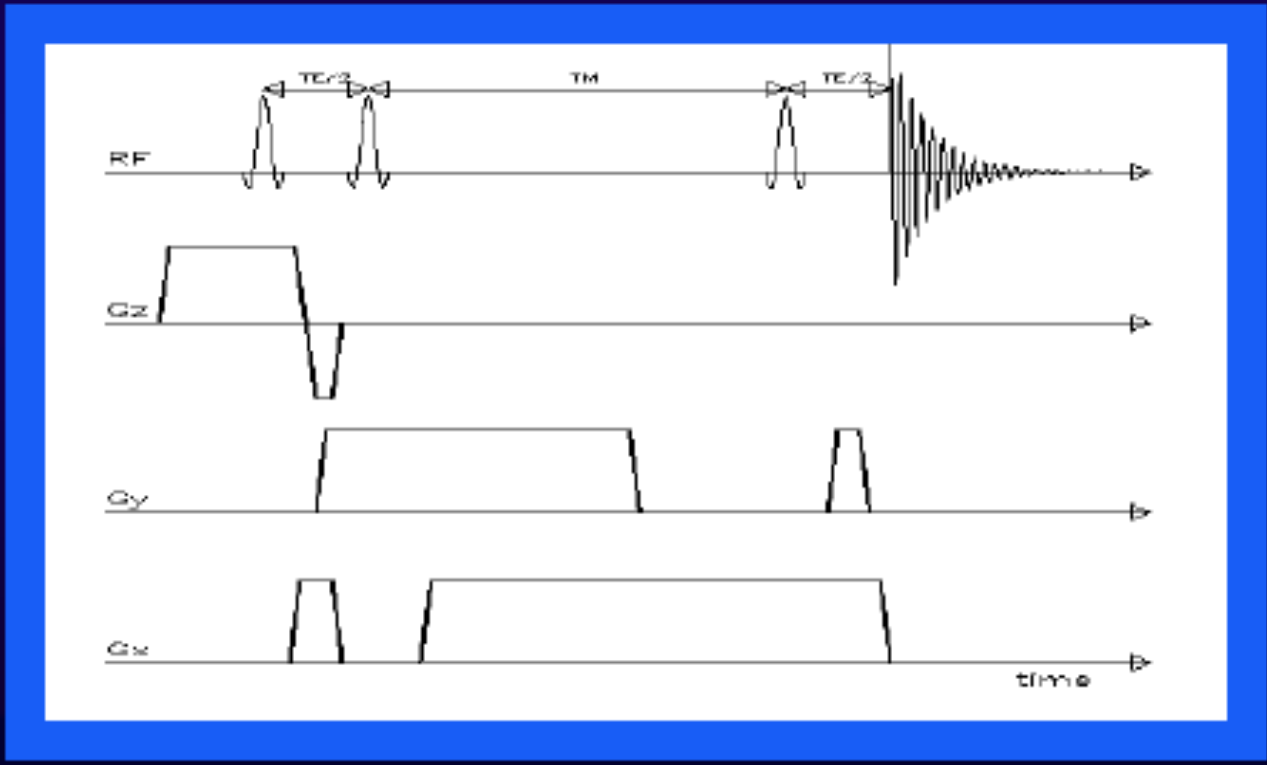
- good localization and strong suppression of signals outside the selected volume in one measurement
  => widely used for ^{1}H spectroscopy
- less motion sensitive than STEAM

Disadvantages:

- minimal TE: ~ 19 ms => unsuitable for ^{31}P spectroscopy

Localization: STEAM

- STEAM = Stimulated Echo Acquisition Mode
- 3 slice selective 90° pulses => stimulated echo after TE + TM



Localization: STEAM

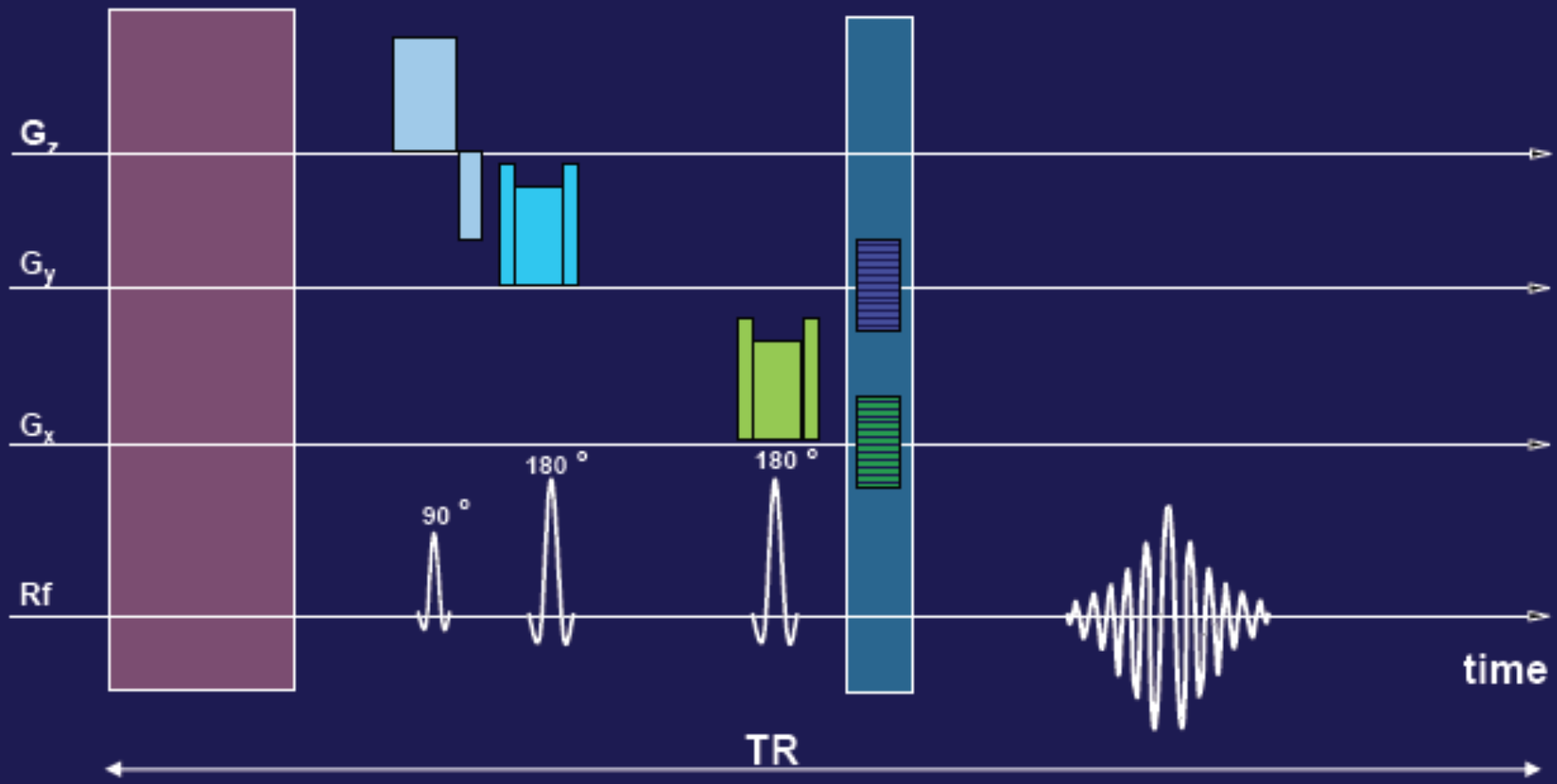
Advantages:

- allows shorter echo times than PRESS (~10 ms)
- better water suppression than PRESS
- less chemical shift artefacts (no 180 refocusing pulses)

Disadvantages:

- signal intensities are only **half** of those obtained with PRESS

Conventional Spectroscopic Imaging



Water and lipid suppression,

OVS

Localization

(PRESS)

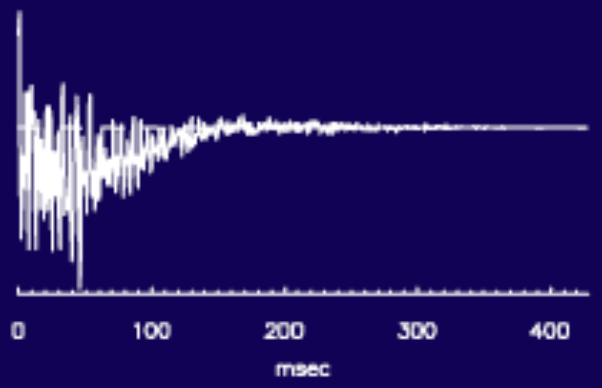
Phase Encoding

Acquisition

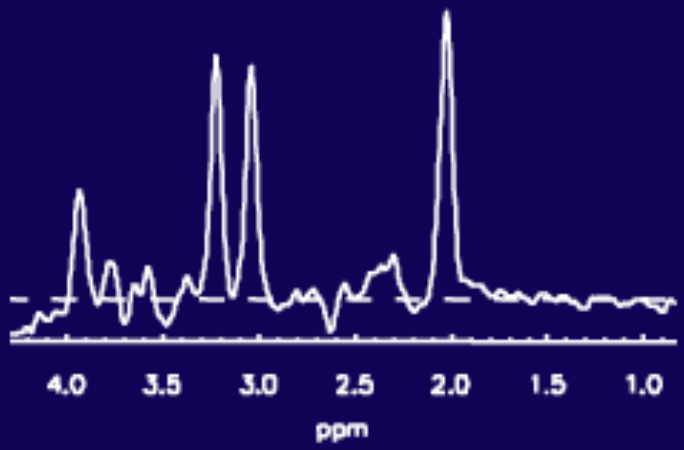
MRS POST-PROCESSING

Outline

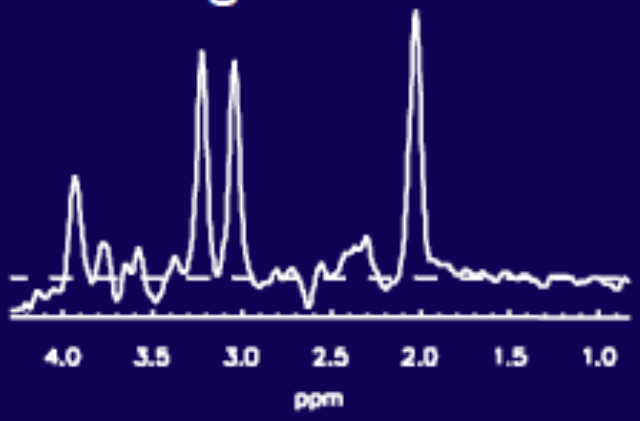
- Postprocessing
  - How to get from



to



- Quantification
  - How to get from



to

Cho: 2.31 mM

Cre: 7.1 mM

NAA: 12.4 mM

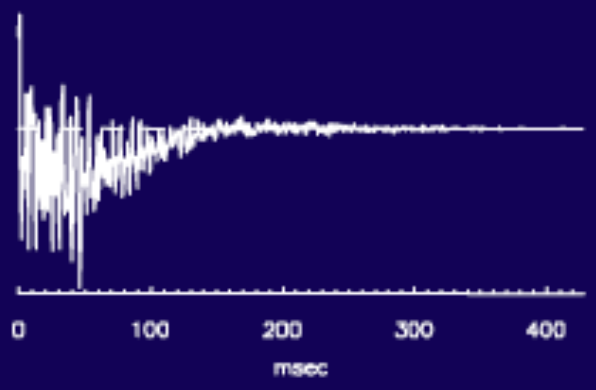
Postprocessing

- *Time domain signal corrections:*
  - Elimination of water residue
  - DC corrections
  - Zerofilling
  - Filtering (exponential, Gaussian, …)
- *Fourier Transform*
- *Frequency domain signal correction:*
  - Phase corrections
  - Baseline correction
  - shifting

Quantification

- *Peak fitting*
  - Integration
  - Gaussian line fitting
- *Linear combination of basis-spectra: LCModel*
- *FID fitting*
  - Example: MRUI
- *Absolute quantification*
  - How to get [mMol]
  - Phantom calibration method

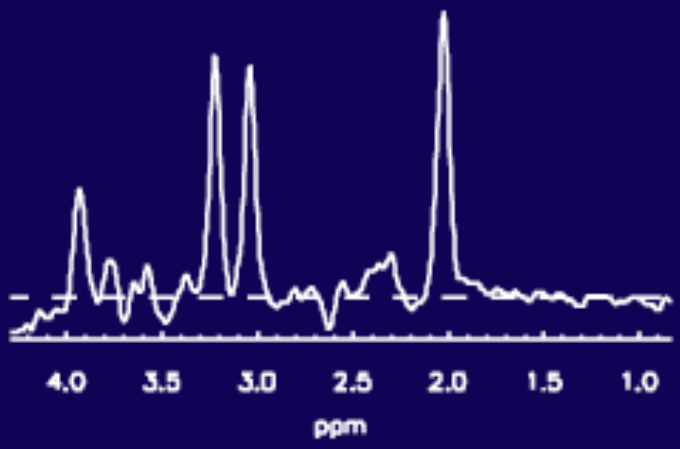
Time domain ⟷ Frequency domain



FID

FT

IFT



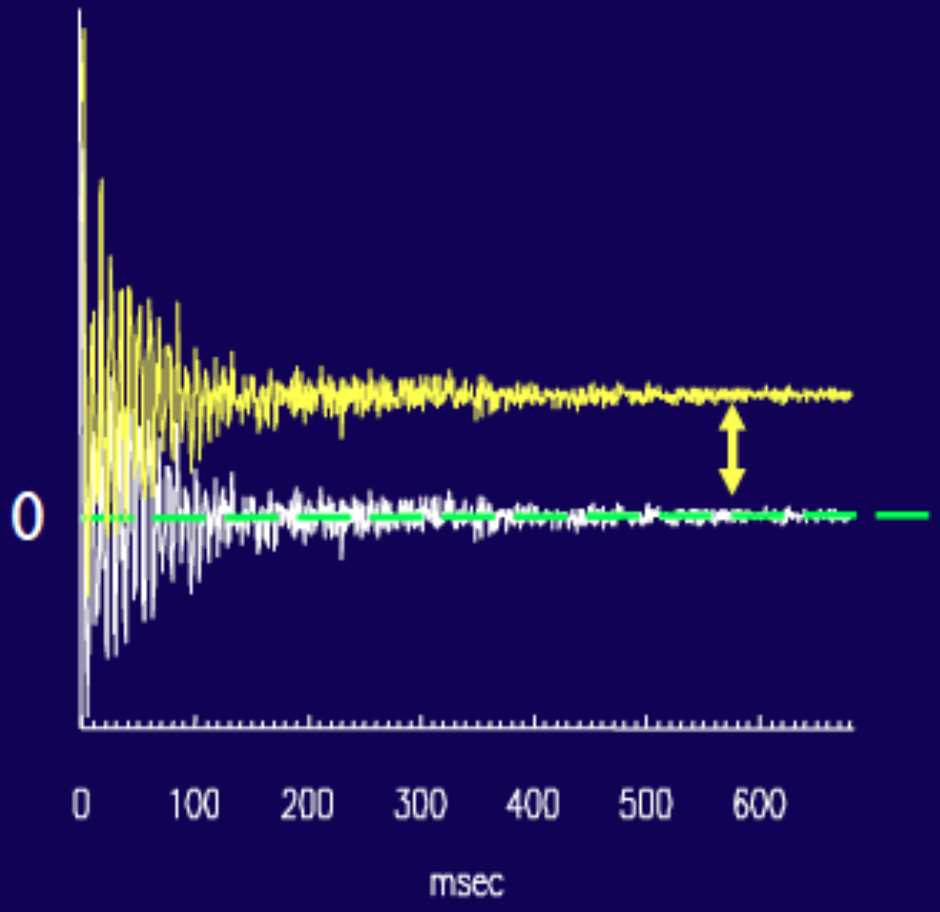
Spectrum

time domain

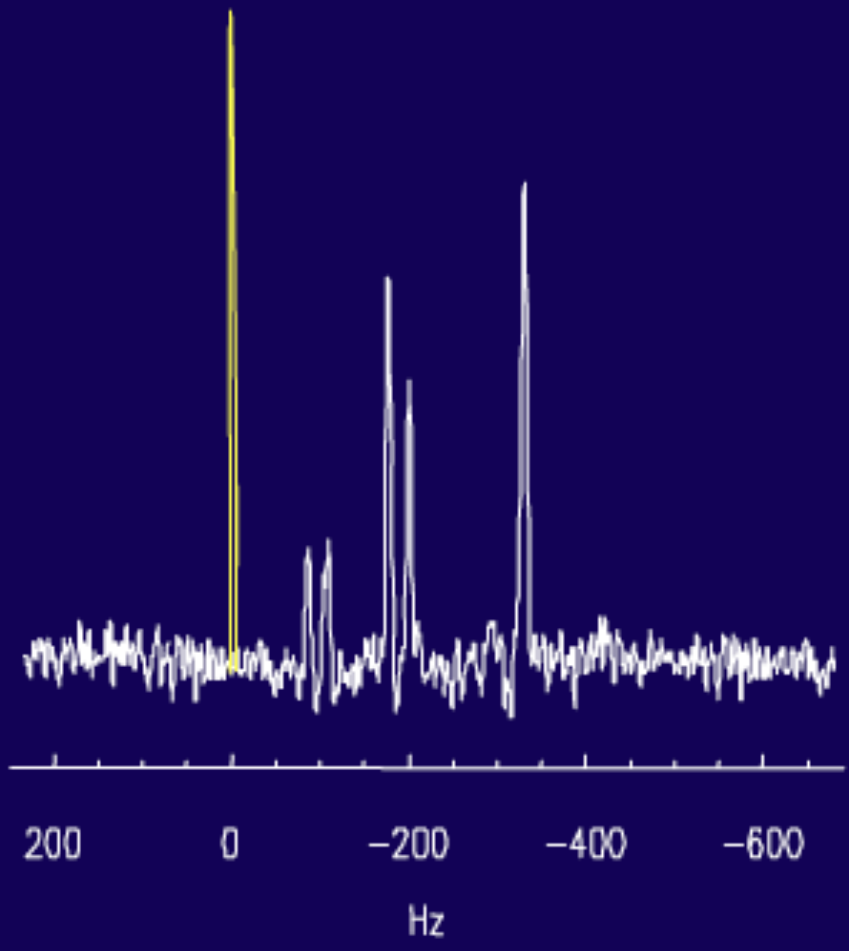
frequency domain

DC correction

- Done in time domain
  = baseline correction of FID

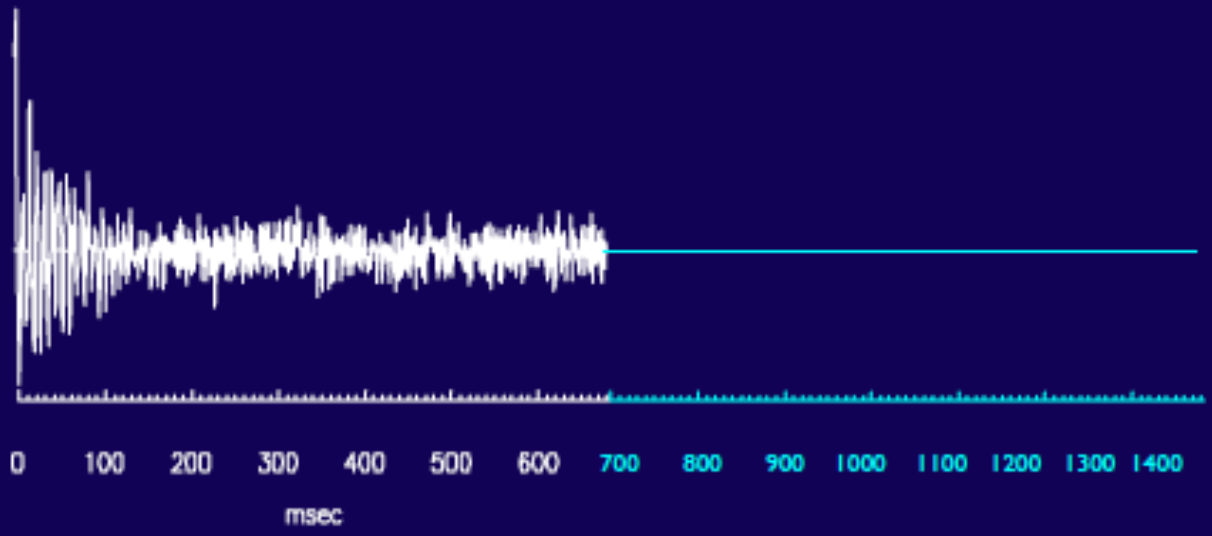


δ-peak at 0 Hz



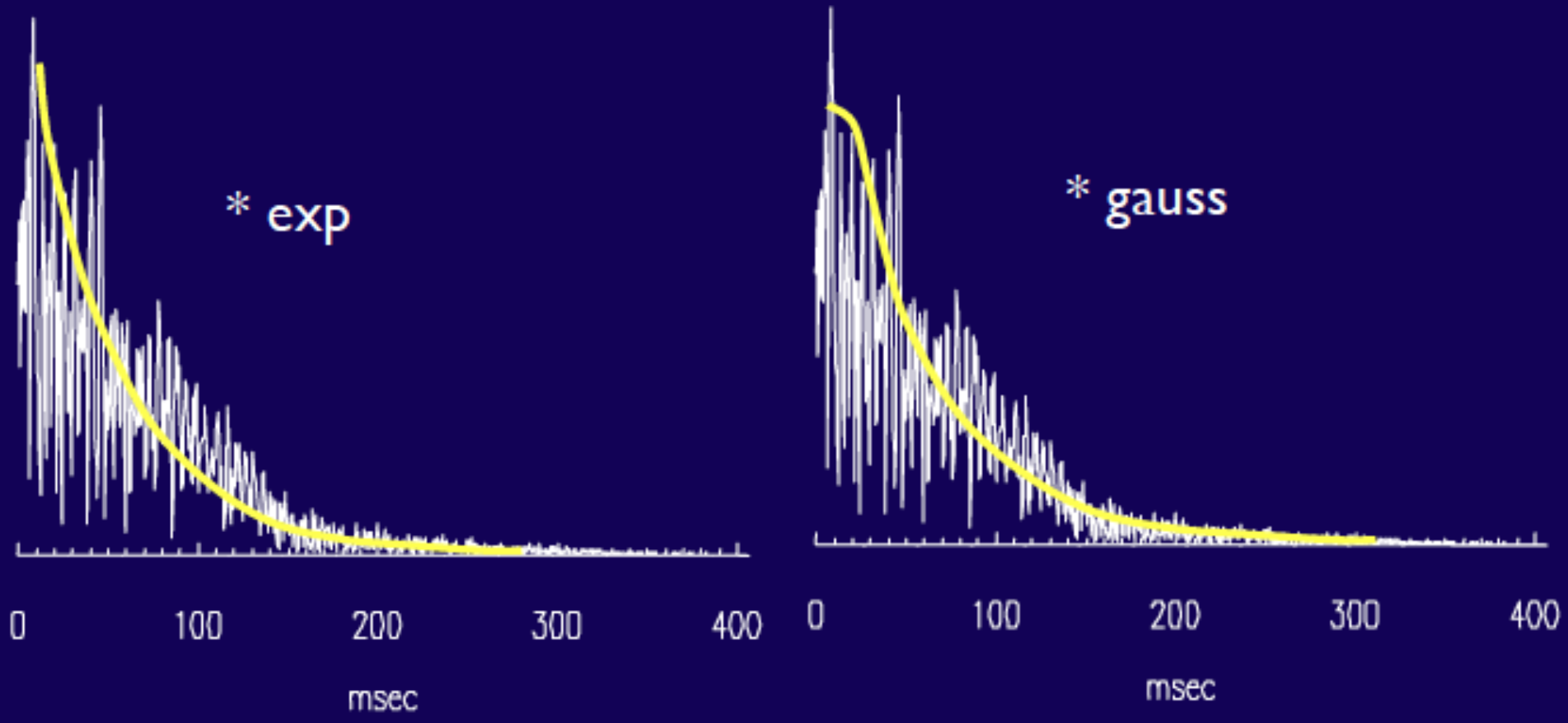
Zero filling

- Done in time domain
  = interpolation to higher spectral resolution



Filtering

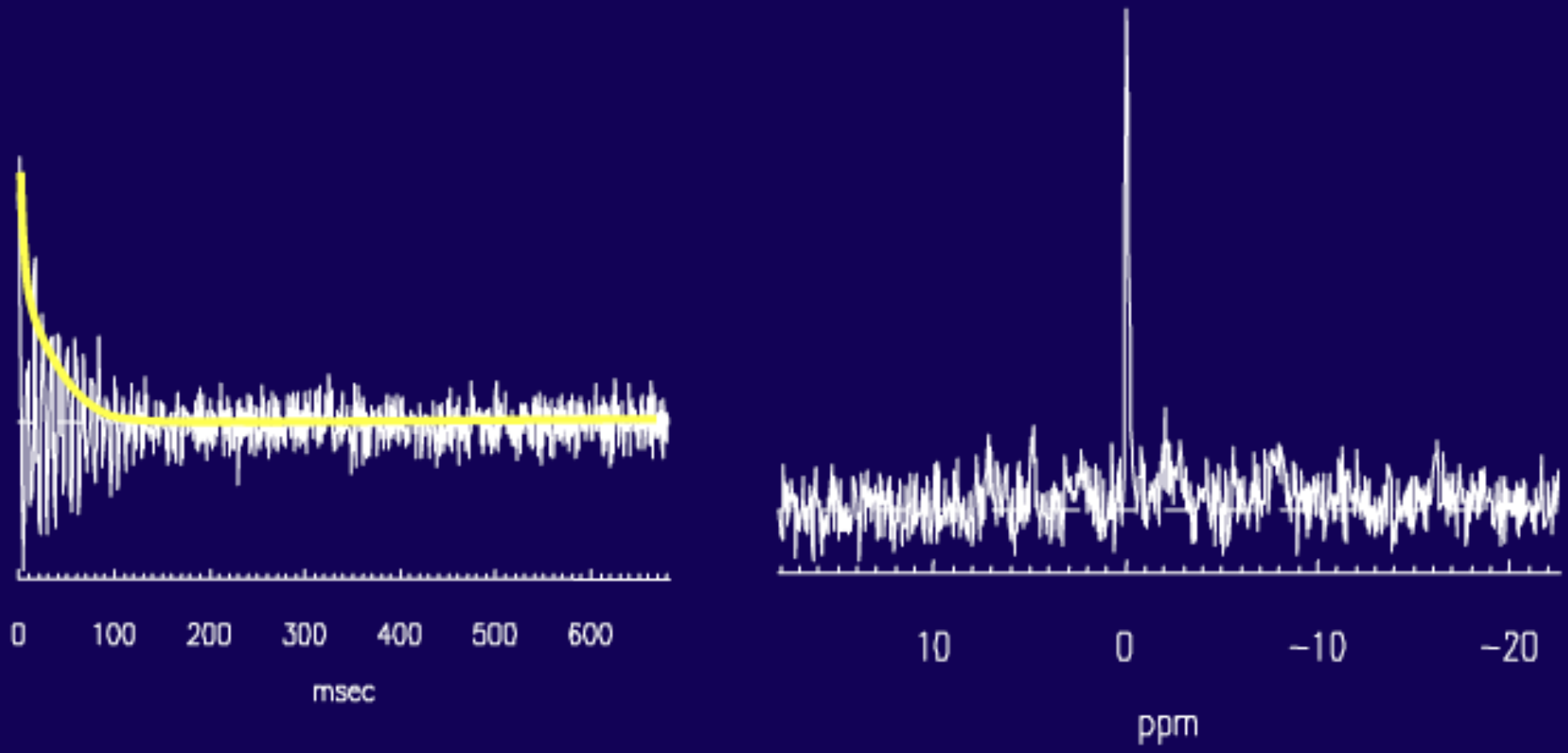
- Done in the time domain:
  - Multiplication with an exponential or Gaussian function



Filtering

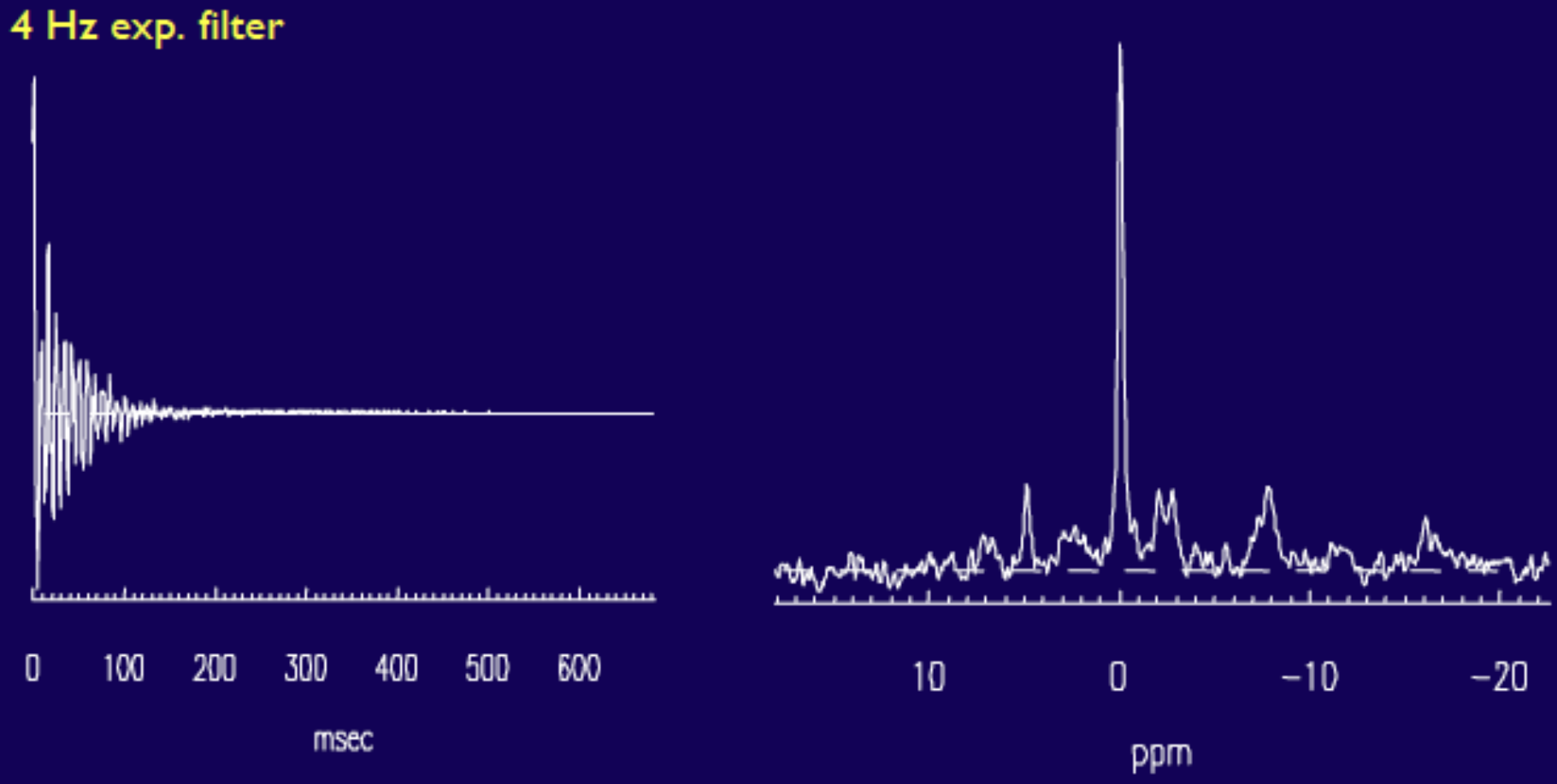
- Done in the time domain:
  - Multiplication with an exponential or Gaussian function

no filter



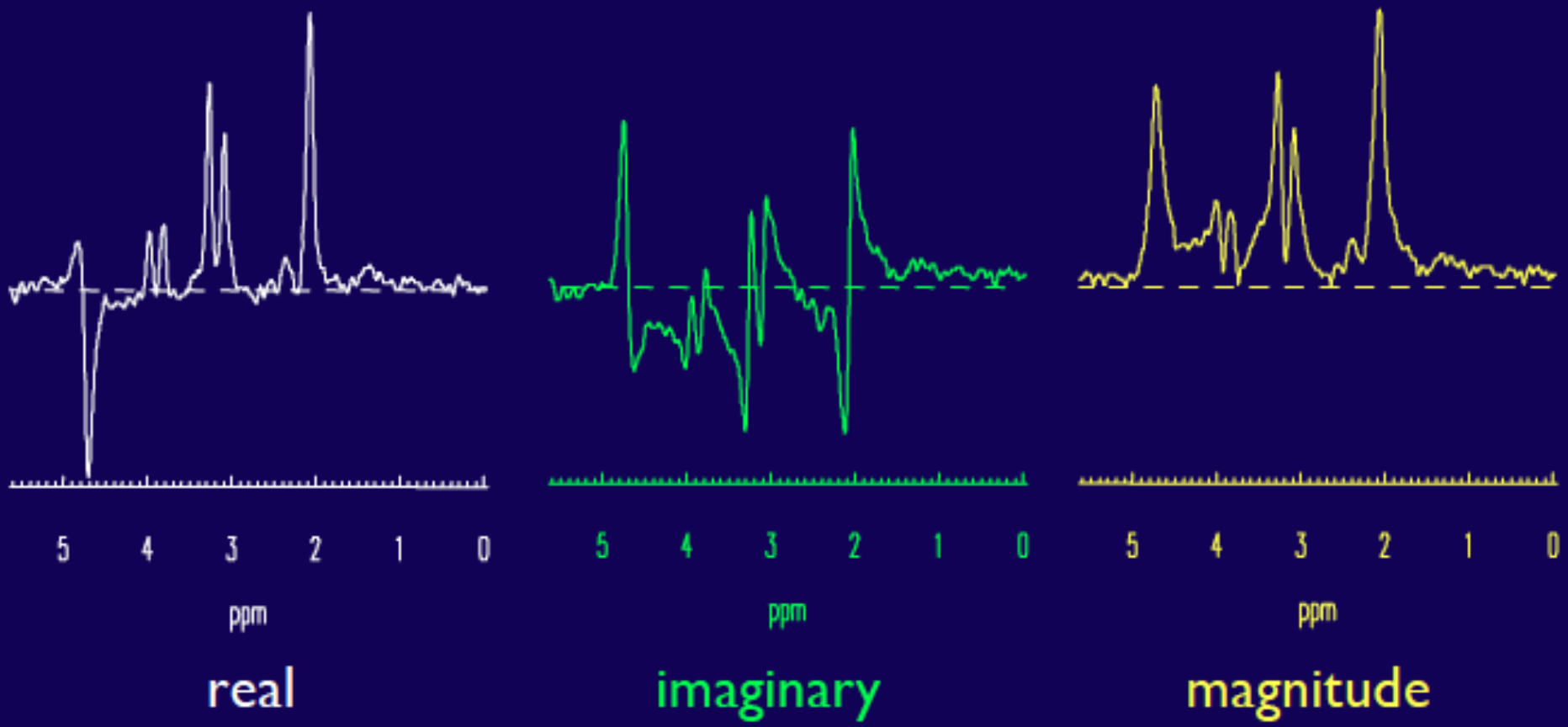
Filtering

- Done in the time domain:
  - Multiplication with an exponential or Gaussian function



Phase correction

- Done in spectral domain
- all spectroscopy data are complex data

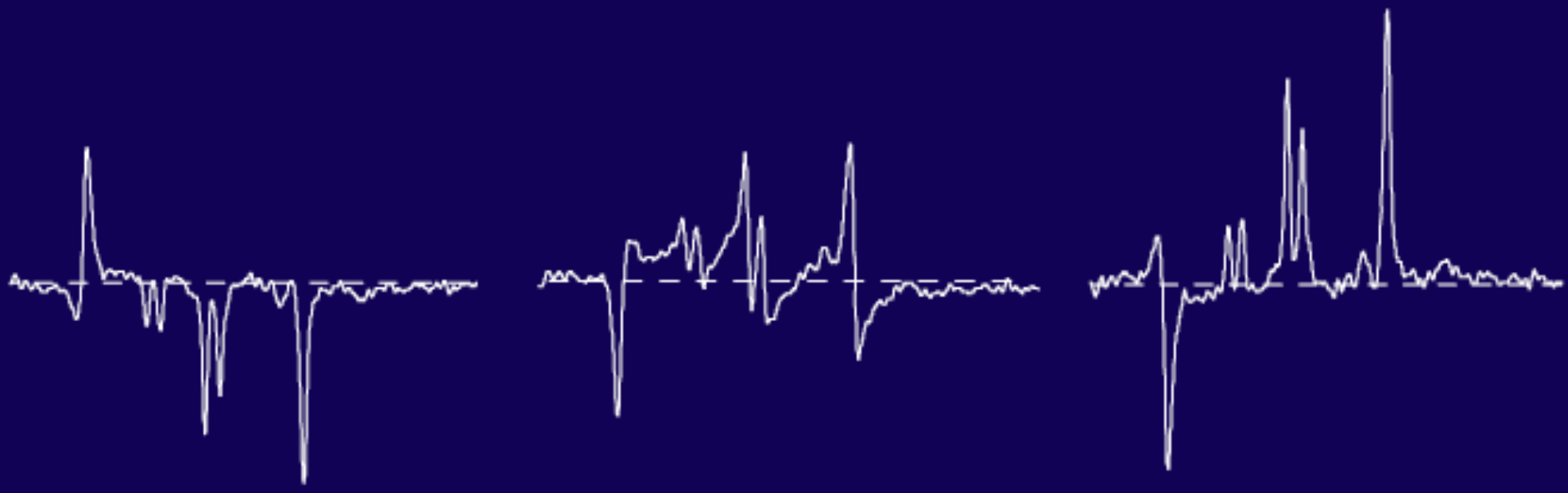


Phase correction

- 'zero order' phase correction:
- => all peaks have same (constant) phase distortion

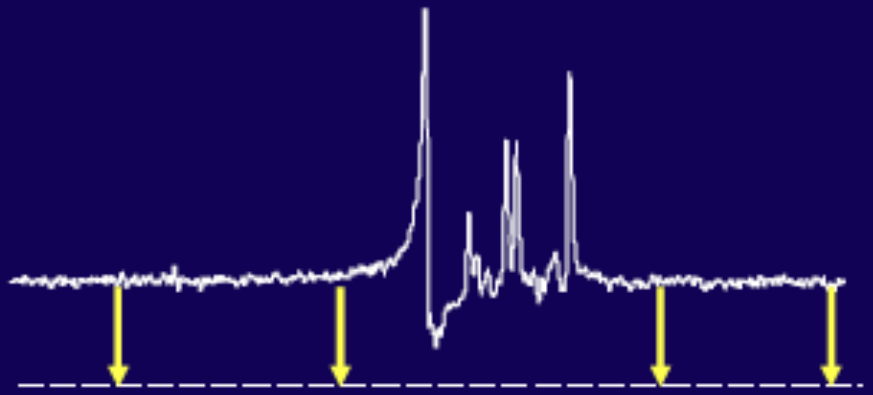
  => maximize the amplitude of singlet peaks

  => have flat baseline at both sides of singlet peaks



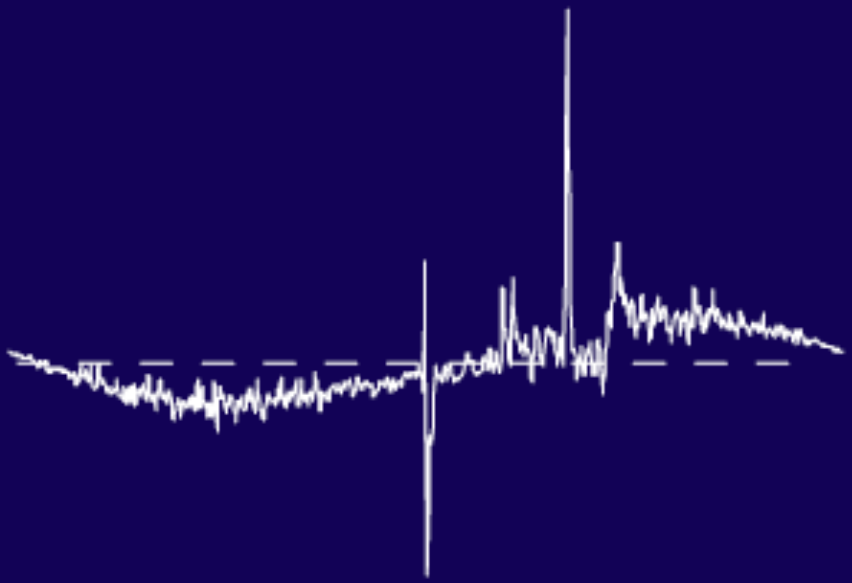
Baseline correction

- Done in spectral domain



⇒ ***constant*** **baseline correction**

(subtract mean of x last points)



⇒ ***polynomial*** **baseline correction**

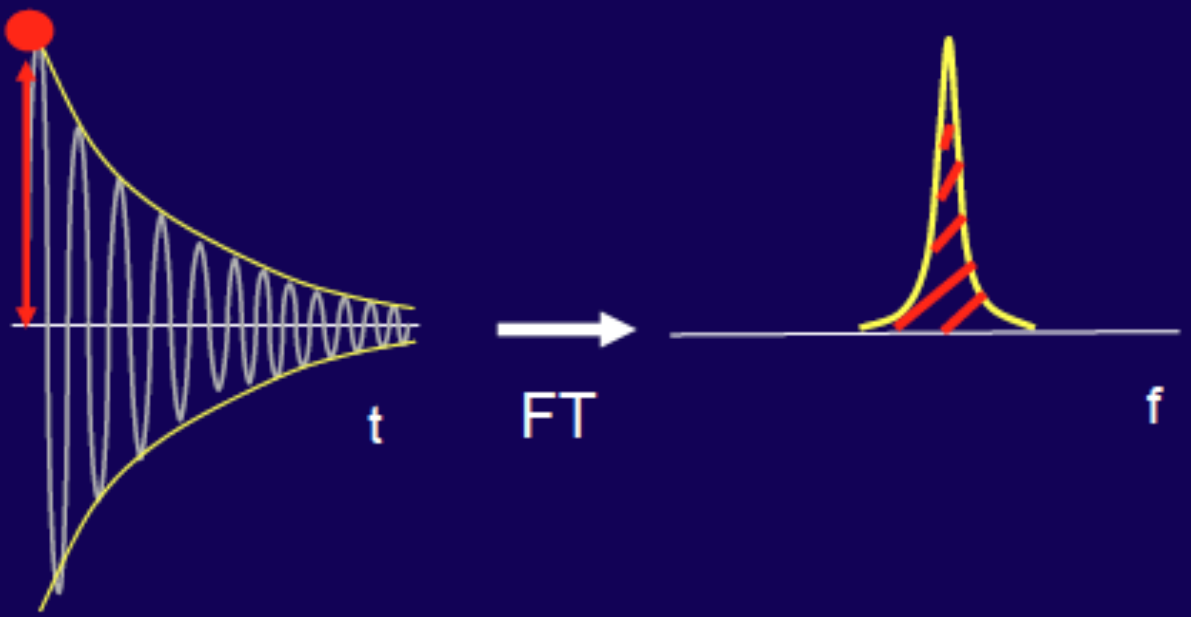
(fit polynomial curve through regions define as baseline)

Quantification

Remember:

area under peak ~ concentration of metabolite

"time domain fitting"



"peak fitting"

=> amplitude (first point of FID) ~ area under peak

Peak fitting

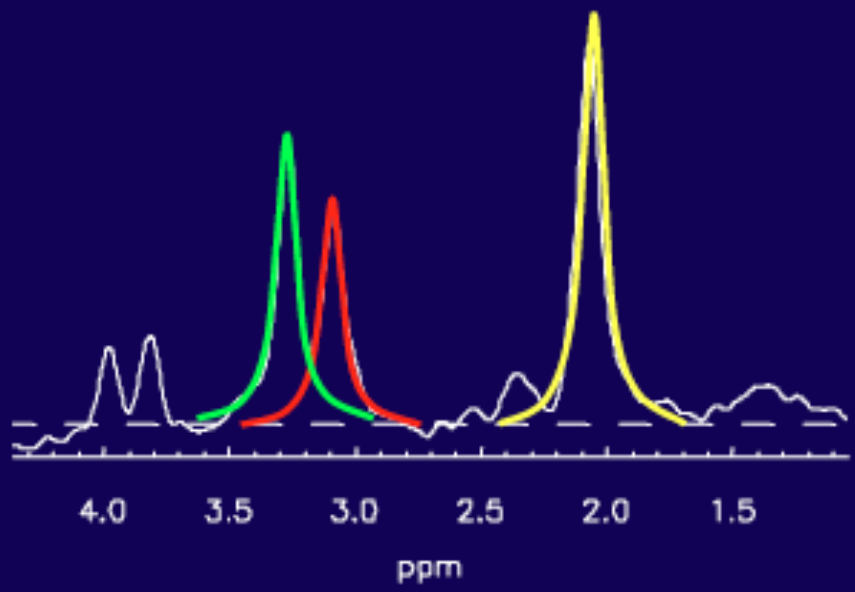
- Fit peaks with Gaussian or Lorentzian line shapes

Problems:

- depends on phasing
=> take magnitude spectra ?

- baseline

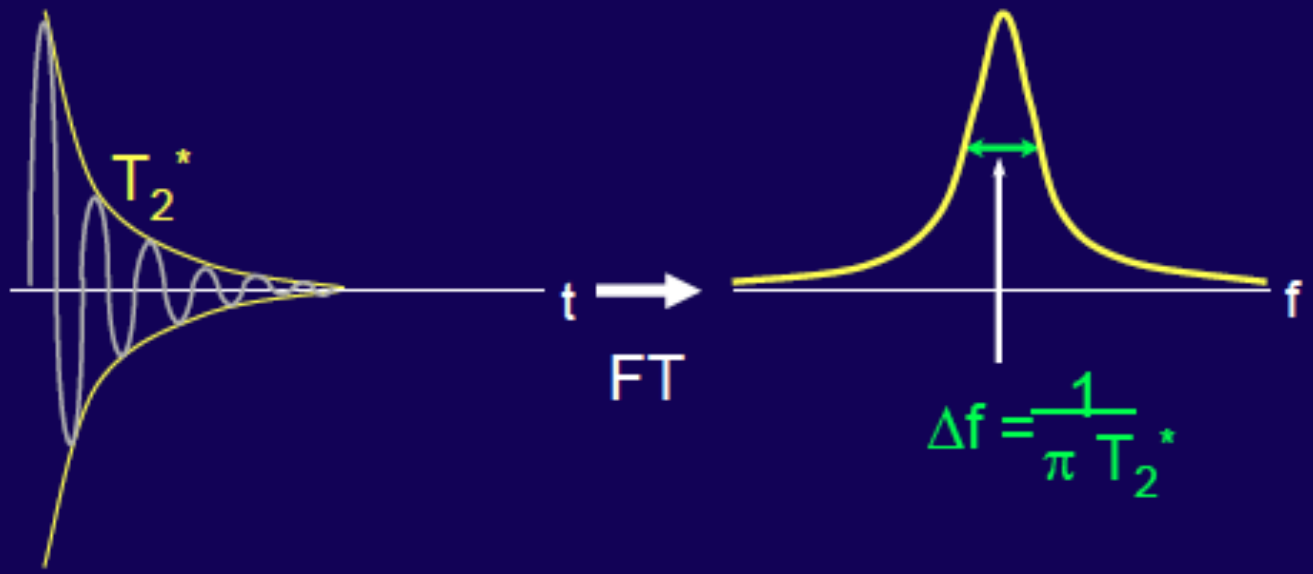
- problem for small peaks or poor shim



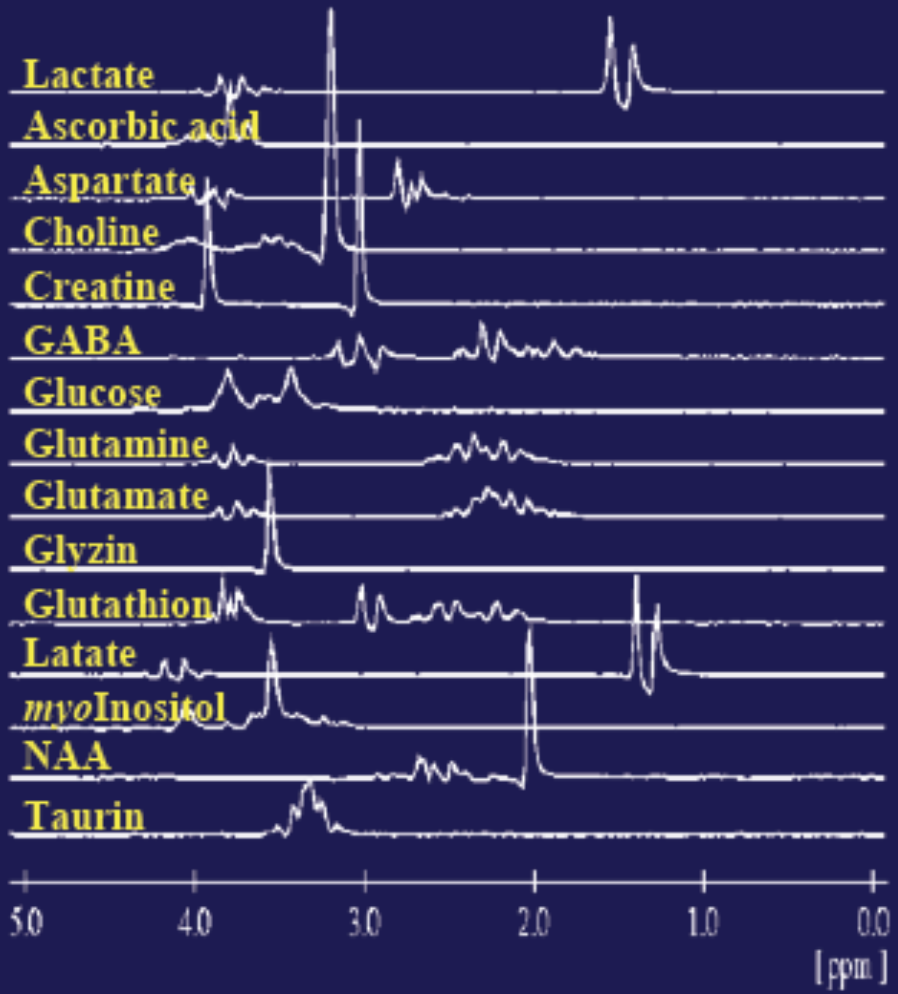
Time domain fitting

- *Fit amplitude of first point of FID for every frequency-component*

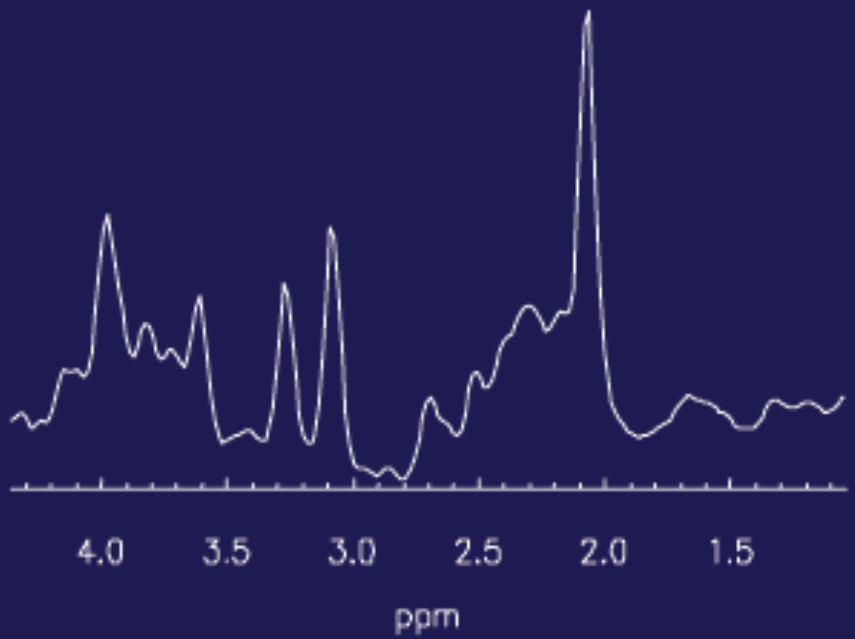
time domain	⇔	*frequency domain*
frequency, $\nu=\omega/2\pi$		**resonance position ν**
relaxation rate, T_2^*		**linewidth (i.e. FWHM)**
amplitude, M_0 (first point)		**area under Lorentzian line**



Linear combination of basis-spectra



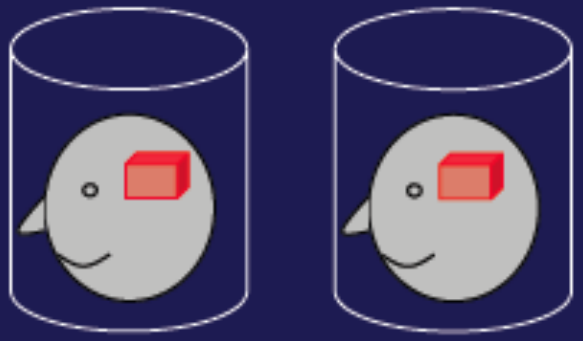
a*Cho + b*Cr + c*NAA +…



Absolute Quantitation

- *Internal water reference*

  ⇒ assumes stable and known water concentration



$$\frac{C_{met}}{C_{water} * \text{rel.water content}} = \frac{S_{met}}{S_{water}}$$

⇒ water content can differ in pathologies

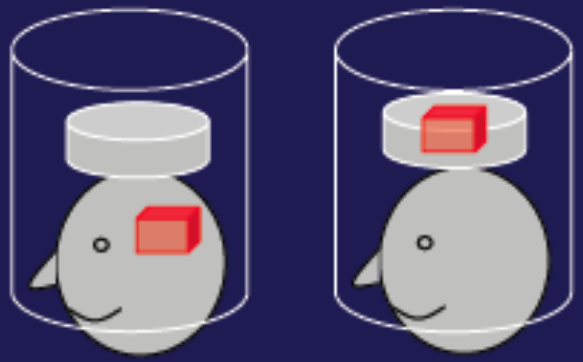
⇒ concentration depends highly on CSF-content in voxel

⇒ unsuppressed water spectrum needs to be measured from same voxel (is done automatically => save raw data!)

Absolute Quantitation

- *External reference calibration*

  => Phantom with known concentration



$$\frac{C_{met}}{C_{phantom}} = \frac{S_{met}}{S_{phantom}}$$

$\Rightarrow$ acquire spectrum both in vivo and in phantom

$\Rightarrow$ careful about coil sensitivities when using surface coils!