Nuclear Magnetic Resonance

Neuroscience Study Program 2002/2003

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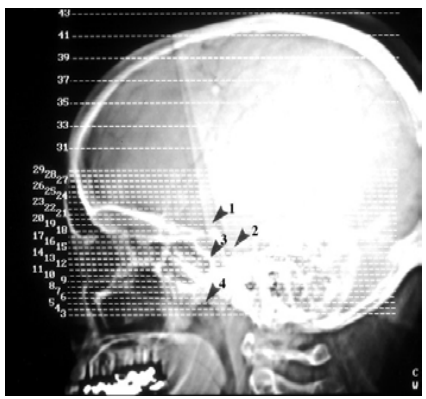
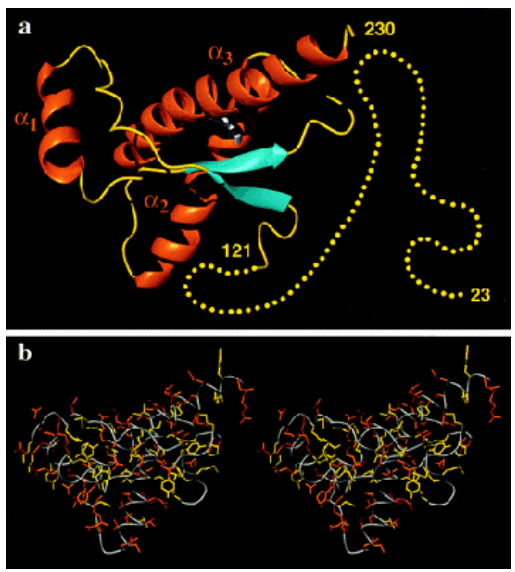
Outline

1) Solution NMR and its application to Structural biology
2) Solid-state NMR
3) Magnetic resonance spectroscopy in vivo (MRS)
4) Magnetic resonance imaging (MRI)
   - functional MRI (fMRI)





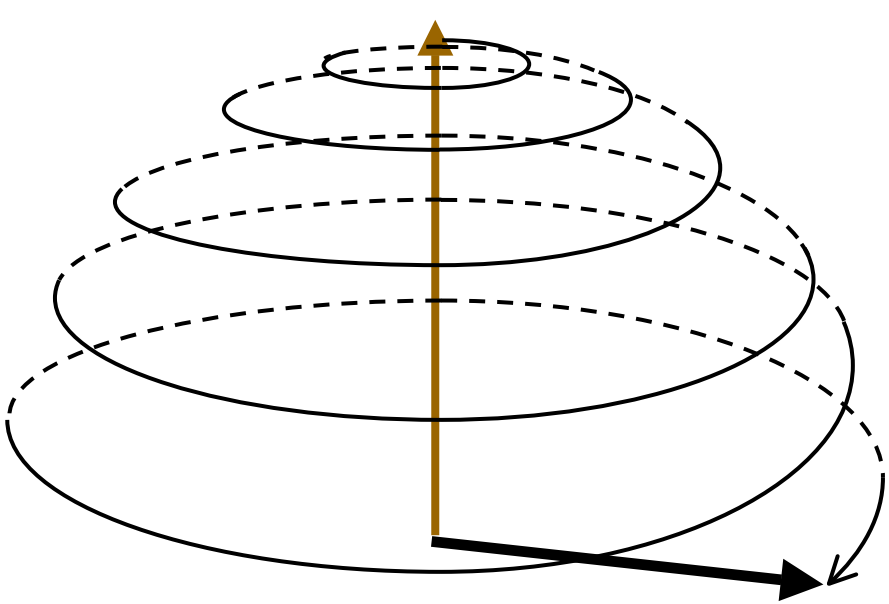
A) Solution NMR

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

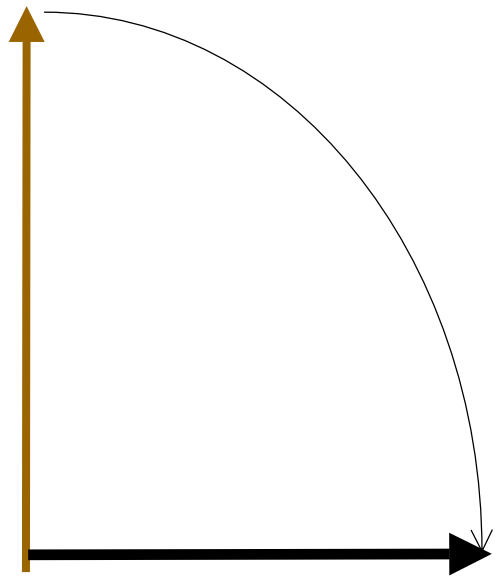
http://www.spectroscopynow.com

Please see the handouts for the Solution NMR part!

RF Excitation



m

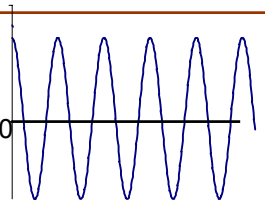


rotating frame

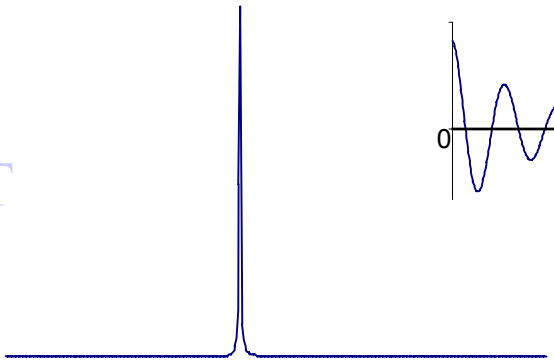
No Relaxation

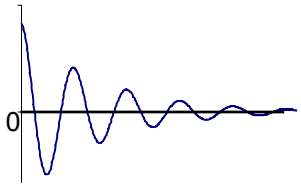
With Relaxation

M_x



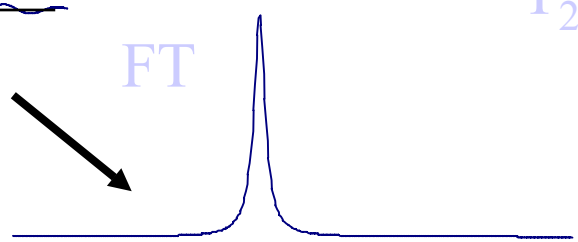
FT



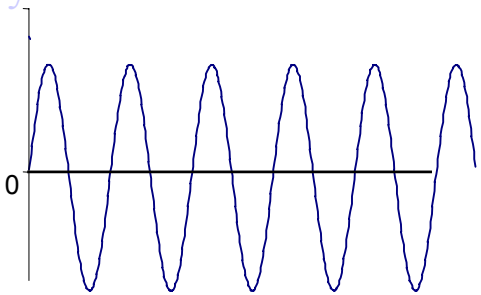


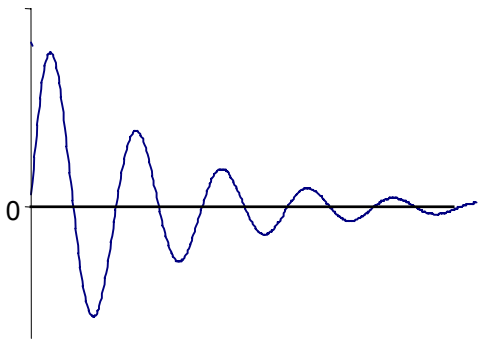
T_2

FT



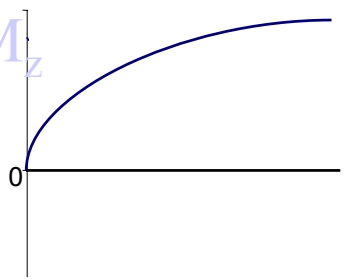
M_y





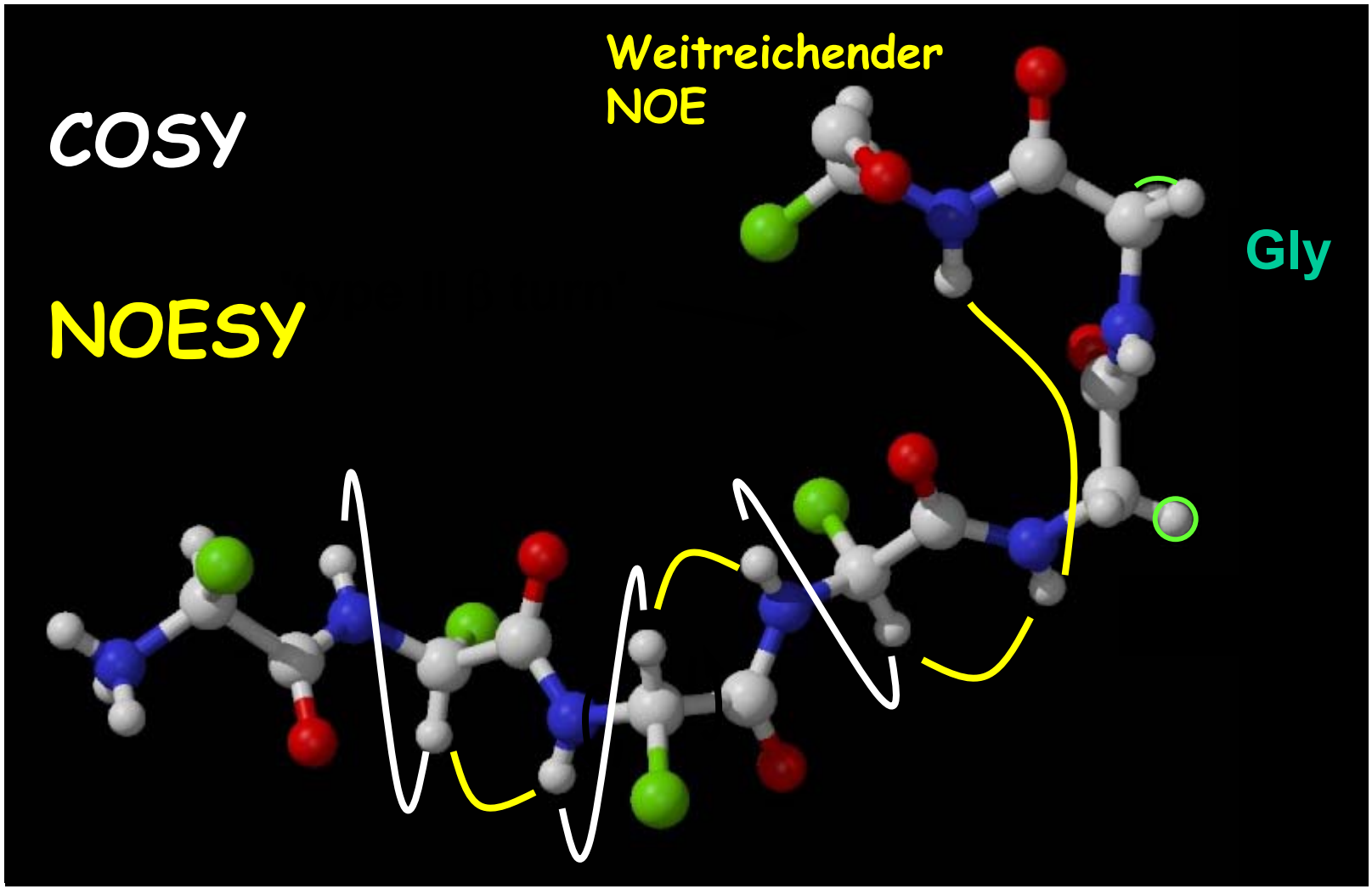
T_2

M_z



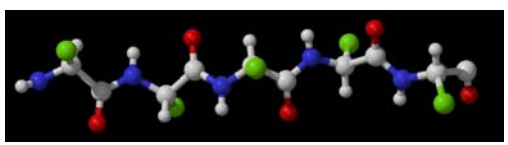
T_1

Sequential assignment of resonances



NMR structure calculation

molecular dynamics



Solution NMR: an example, ...

(page 9-13)

B) Solid-state NMR

Key facts

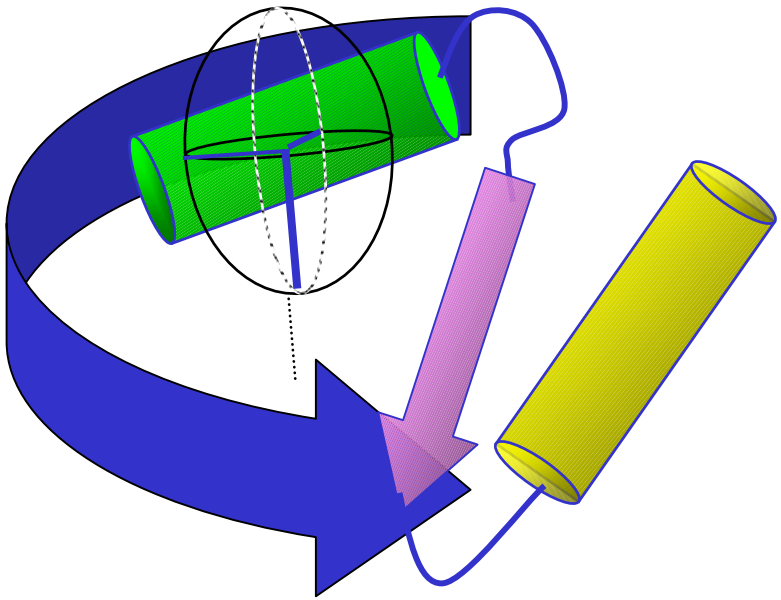
- Solid-state NMR = NMR spectroscopy for static or slowly tumbling molecules
- Same physical principles as solution NMR
- Interactions are orientation-dependent
- Improvement of resolution and sensitivity by either (1) preparation of uniaxially oriented samples or (2) magic angle spinning (MAS)
- Proton detection difficult due to strong dipolar interaction → ^{13}C and ^{15}N detection
- Reintroduction of specific dipolar interactions to obtain structural information
- 2002: First 3D structure of a SH3 domain by solid-state MAS NMR (*Nature* 420, 98-102)

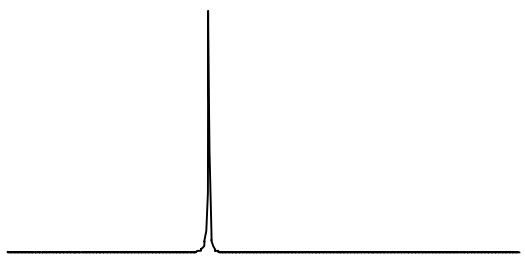
Physical and chemical conditions

- Partially immobilized peptides or proteins
  - gel-like or hydrated samples
- Immobilized proteins
  - powders, frozen lipid or detergent mixtures

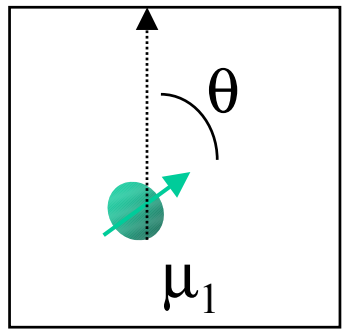
- Potential biological targets
  - aggregated proteins, fibrils, membrane proteins

NMR in solution: Isotropic interactions

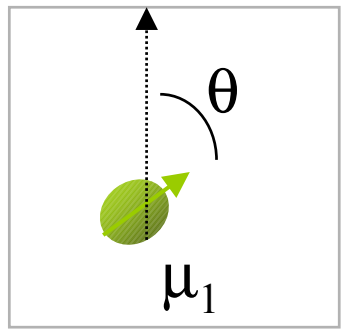




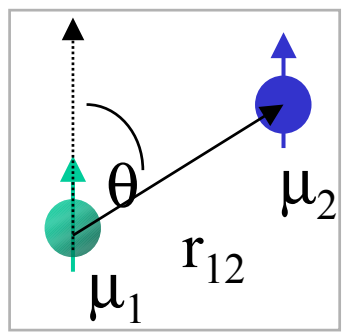
Chemical shift



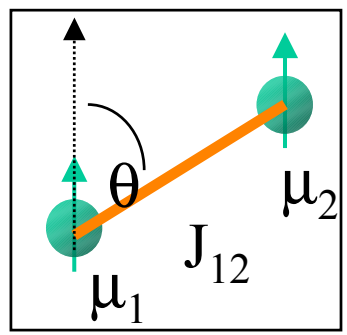
quadrupolar coupling



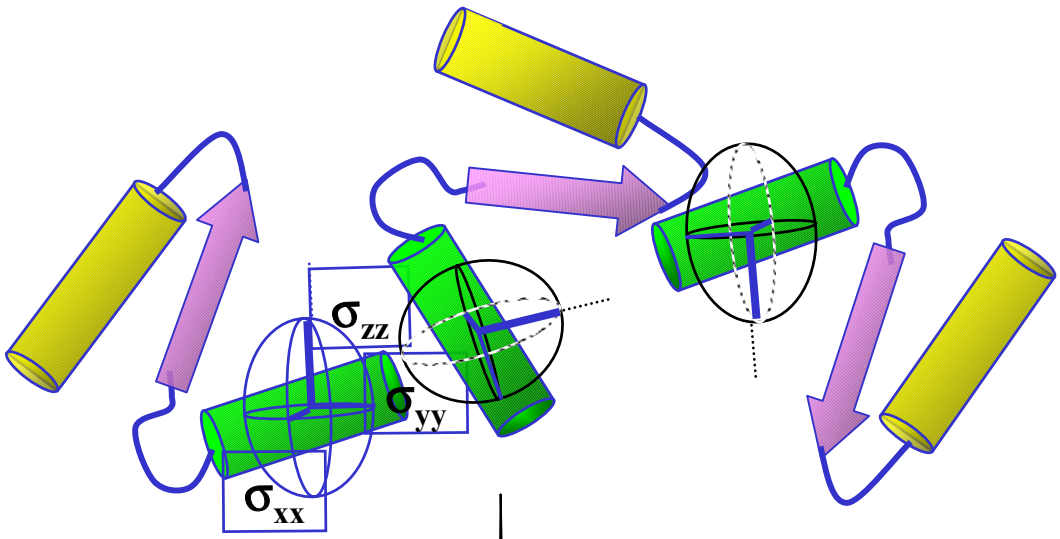
Dipolar coupling

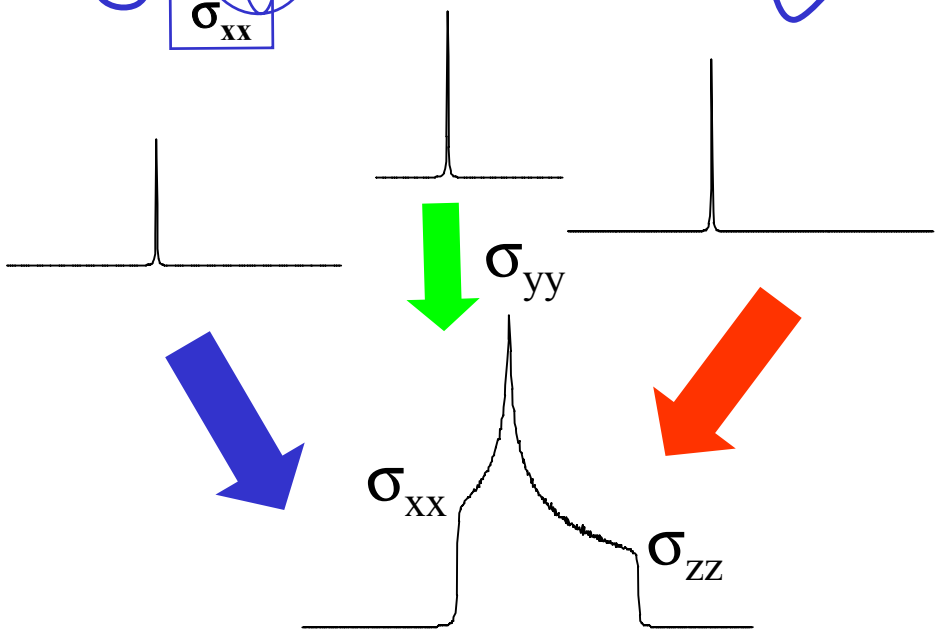


Scalar coupling

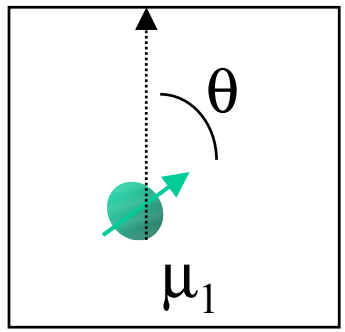


NMR in the Solid-state: Anisotropic interactions

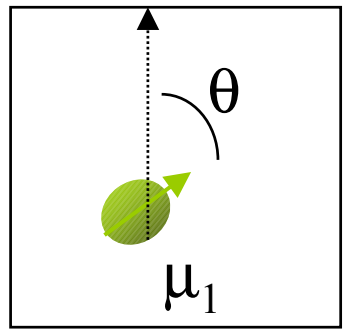




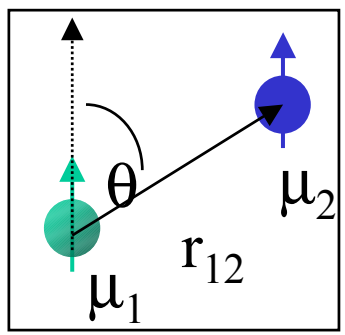
Chemical shift



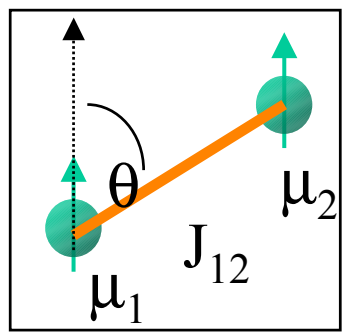
quadrupolar coupling



Dipolar coupling

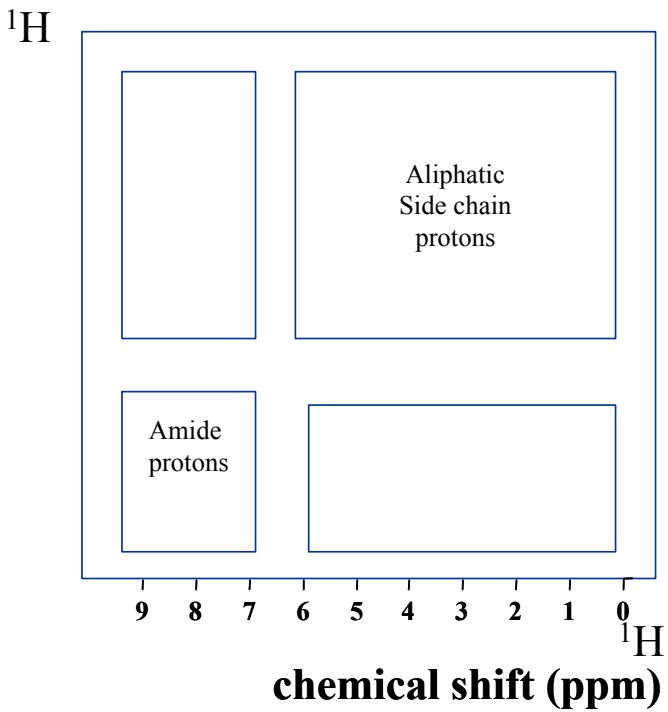


Scalar coupling



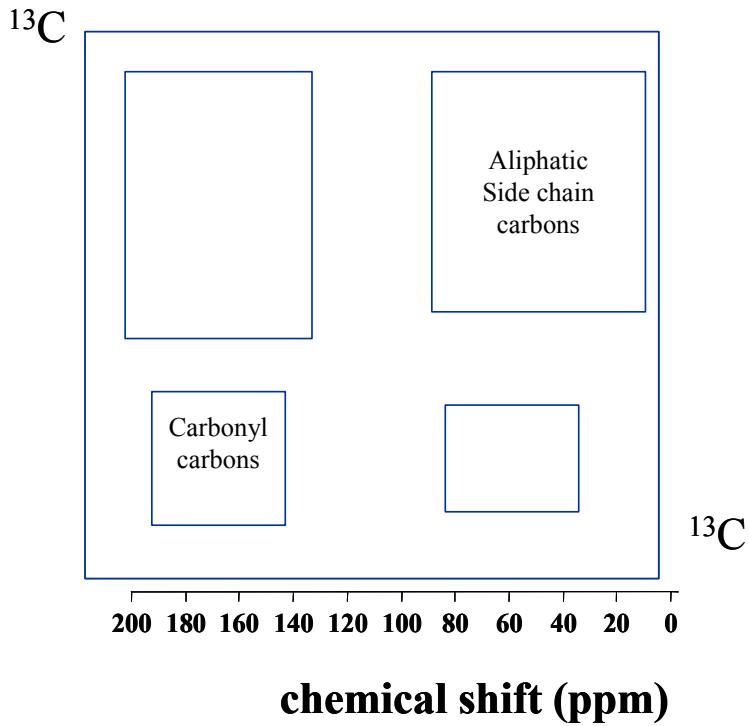
Solution versus solid-state spectra

Solution-state



TOCSY, COSY, NOESY

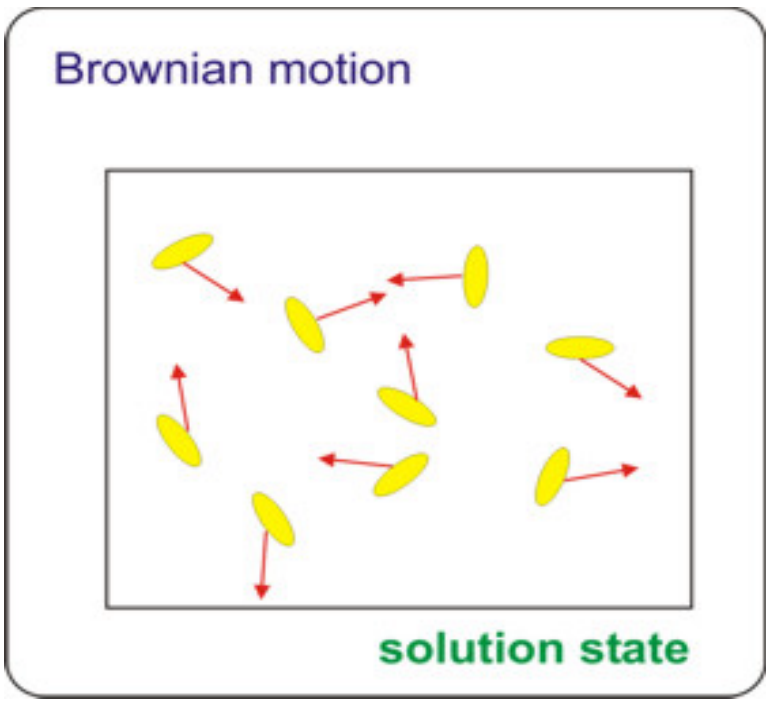
Solid-state

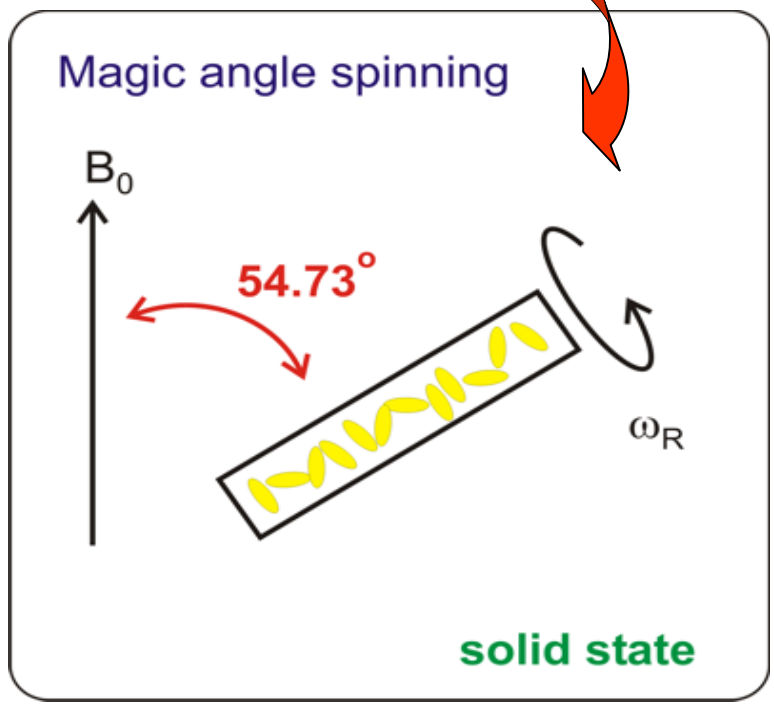


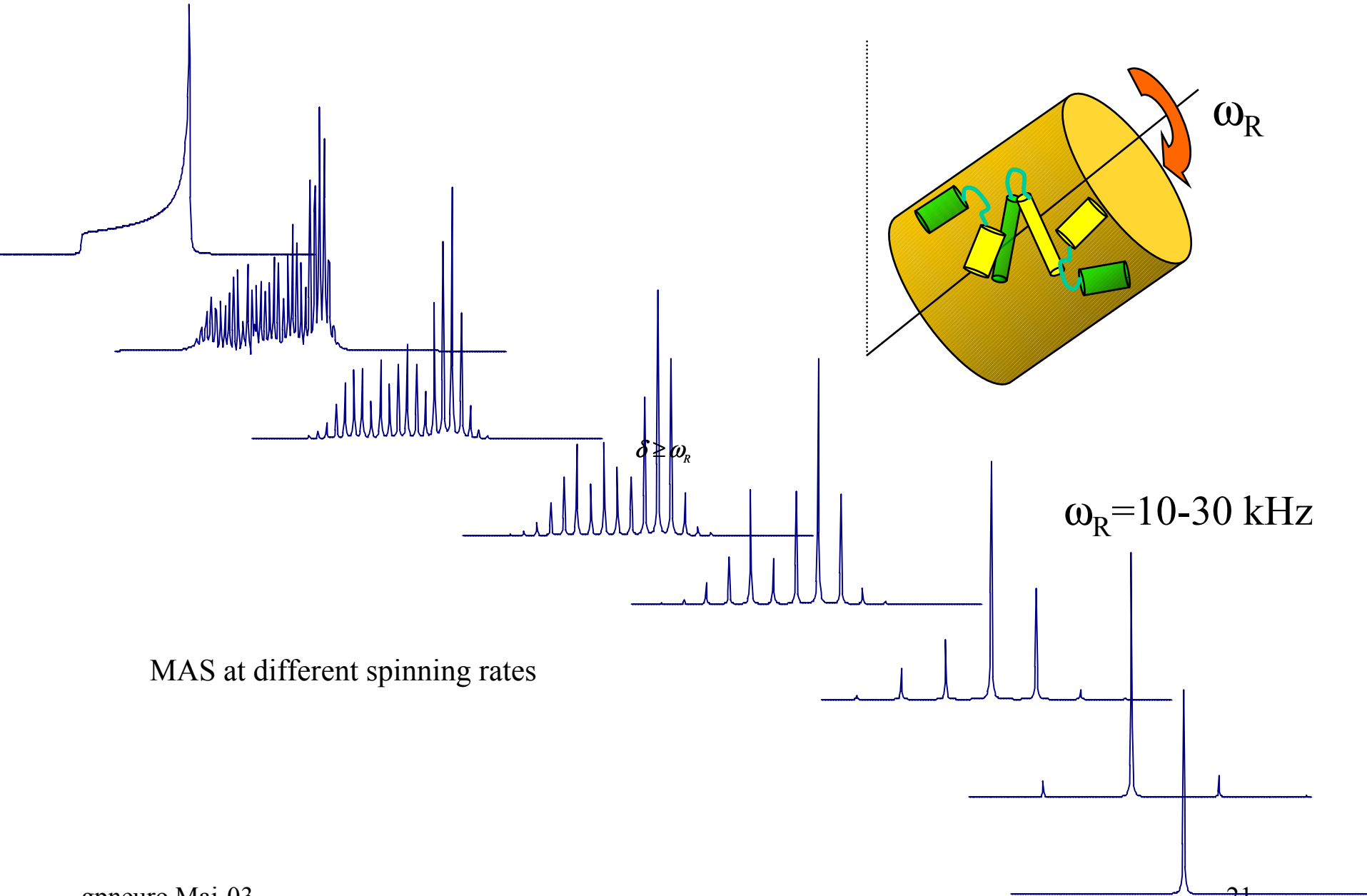
CC and CHHC correlation experiments

High resolution in the Solid-state I: MAS

coherent averaging of unoriented samples



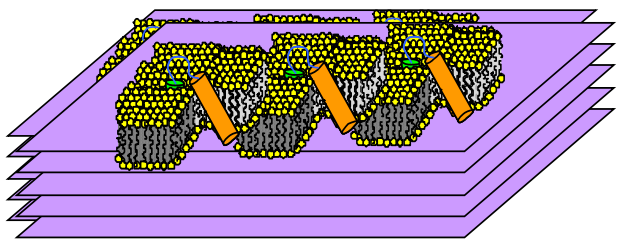




MAS at different spinning rates

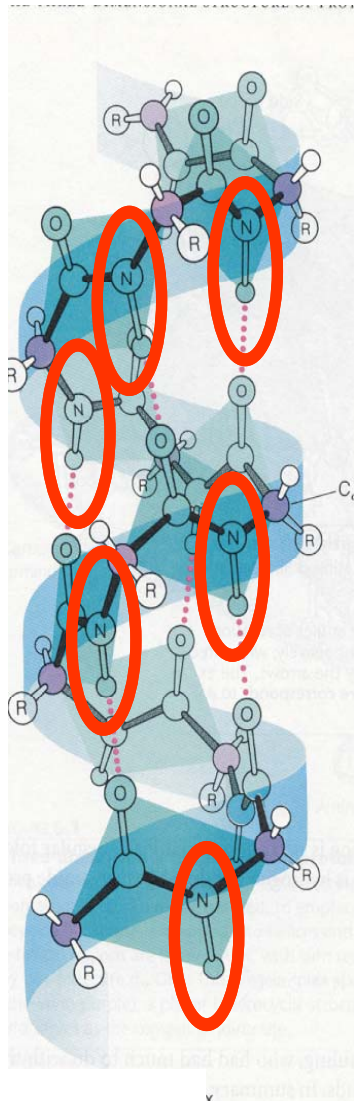
High resolution in the Solid-state II: Uniaxially oriented bilayers

a

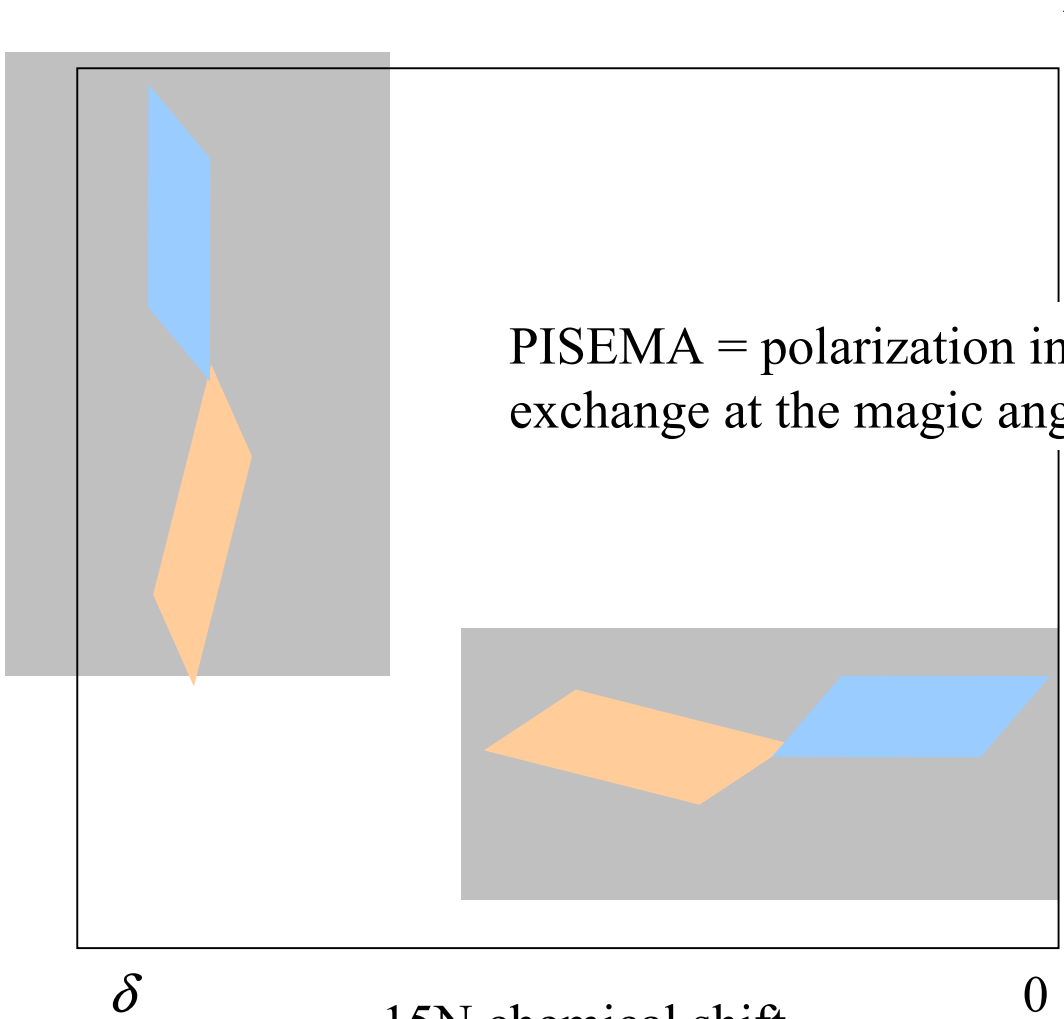


Z

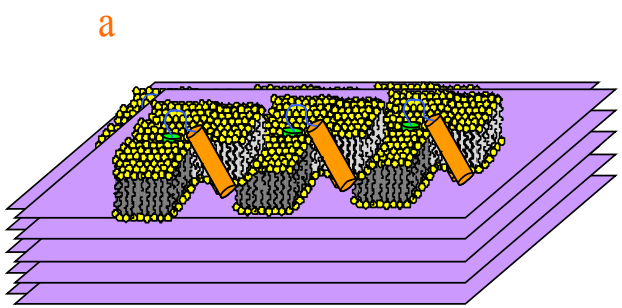
d

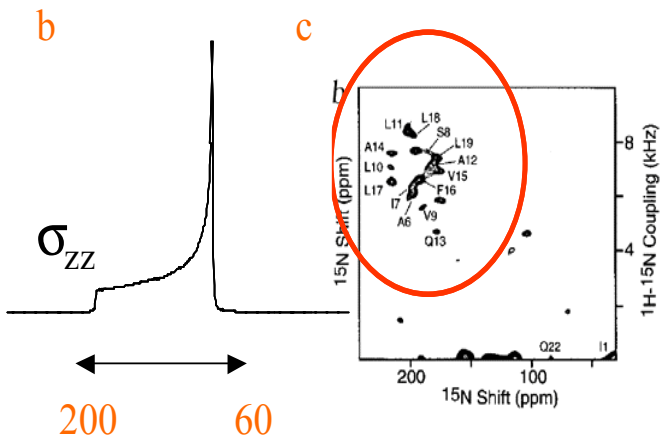


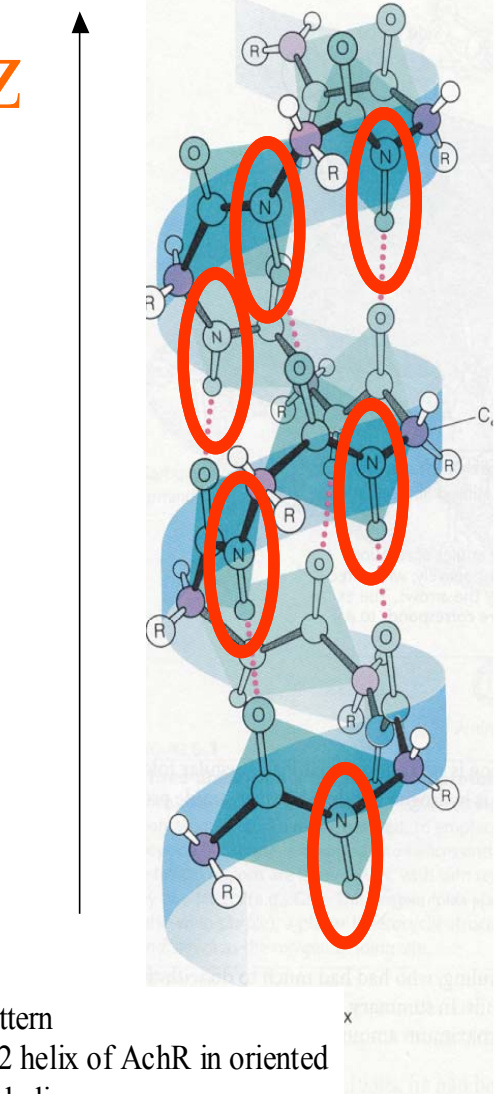
PISEMA spectra of perfect α-helices



Pisa wheels





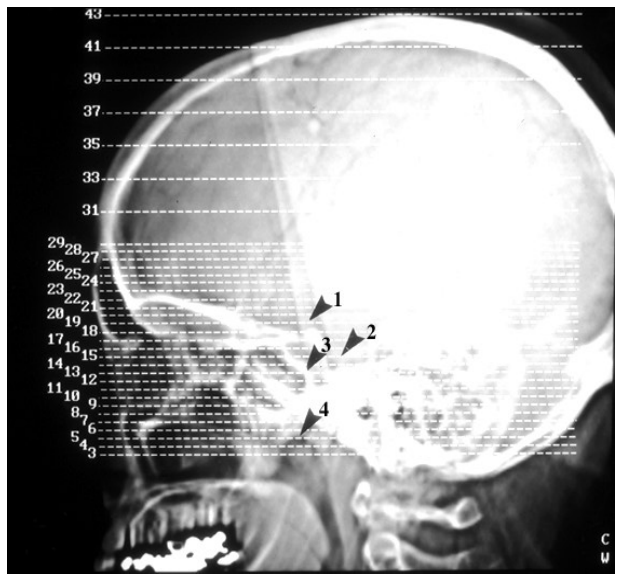


(a) macroscopically oriented membrane protein. (b) powder pattern of an unoriented 15N-1H dipolar tensor. (c) spectrum of the M2 helix of AchR in oriented Bilayers. (d) orientation of the NH vectors in a transmembrane helix.

C) Magnetic resonance imaging -physical principles

http://www.cis.rit.edu/htbooks/mri

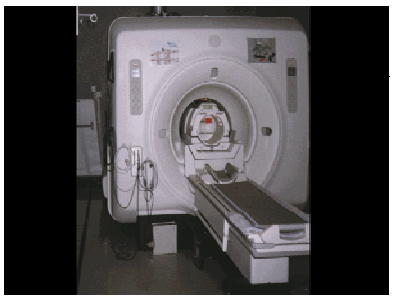
http://www.spectroscopynow.com

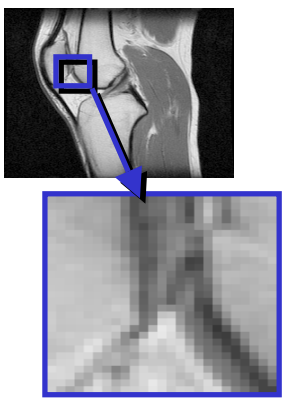


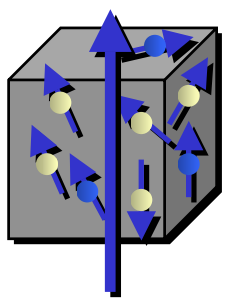
Key facts

- MRI = Imaging technique used to produce high quality images of the inside of the human body
- MRI is based on the principles of NMR
- MRI produces an image of the NMR signal that comes from a thin slice or a small volume of the human body
- Protons in water molecules are the dominant nuclear species in the human body
- In 1973 MRI was first demonstrated by Paul Lauterbur
- In 1993 functional MRI (fMRI) was developed. This technique allows the mapping of the function of the various regions of the human brain.

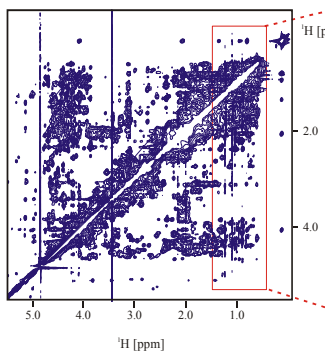
MRI - NMR

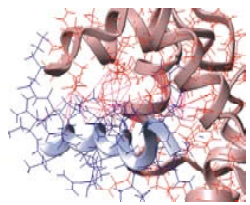


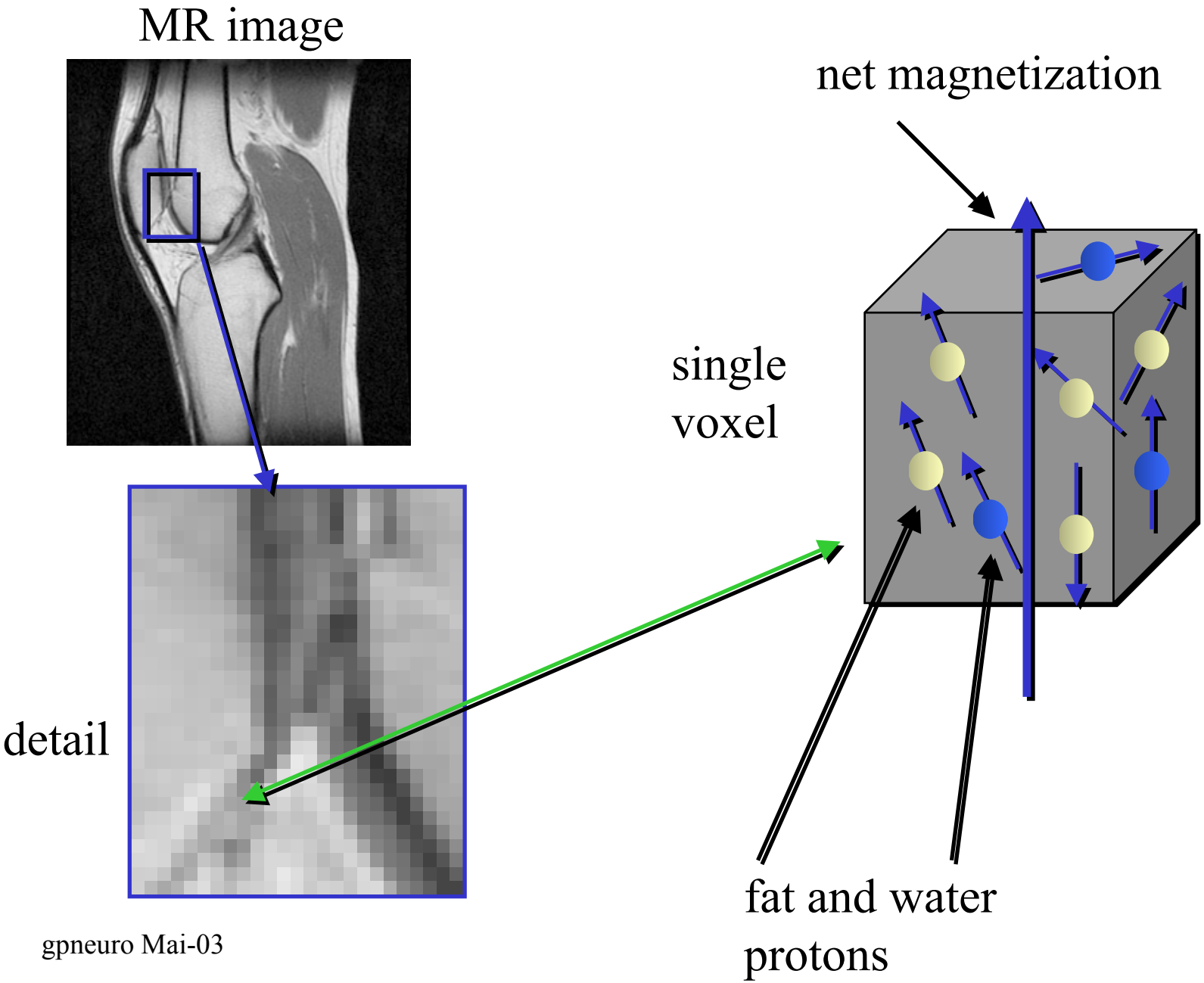




2D NOESY

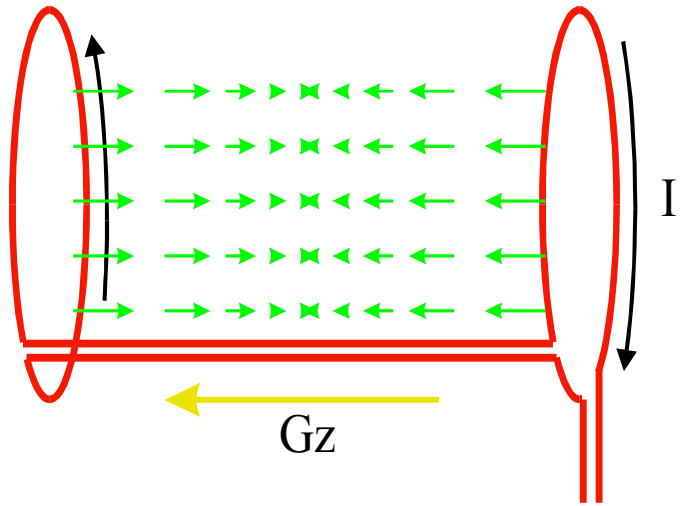




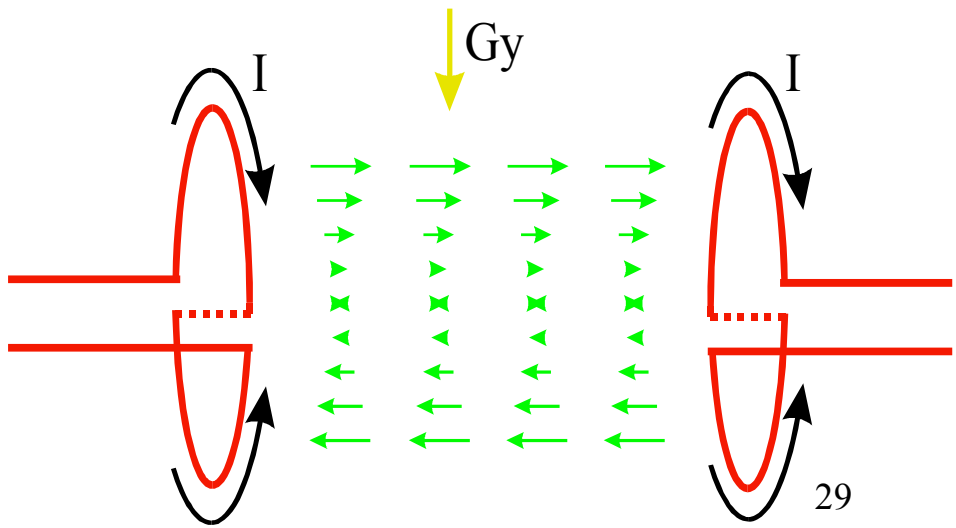

MR image
net magnetization
single
voxel
detail
fat and water
protons

Gradient coils

- Field always along z
- Gradient along x, y, or z
- Usually, only one gradient active at a time, but can combine to give any arbitrary direction



$$\underline{B} = (B_0 + G_x x + G_y y + G_z z)\hat{\underline{z}}$$



Spatial encoding

- Three gradient coils allow the magnetic field to vary in any direction (linear combination)
- Spatial information comes from the variation in Larmor frequency due to the field gradient
- No moving parts to acquire different views/acquisition parameters

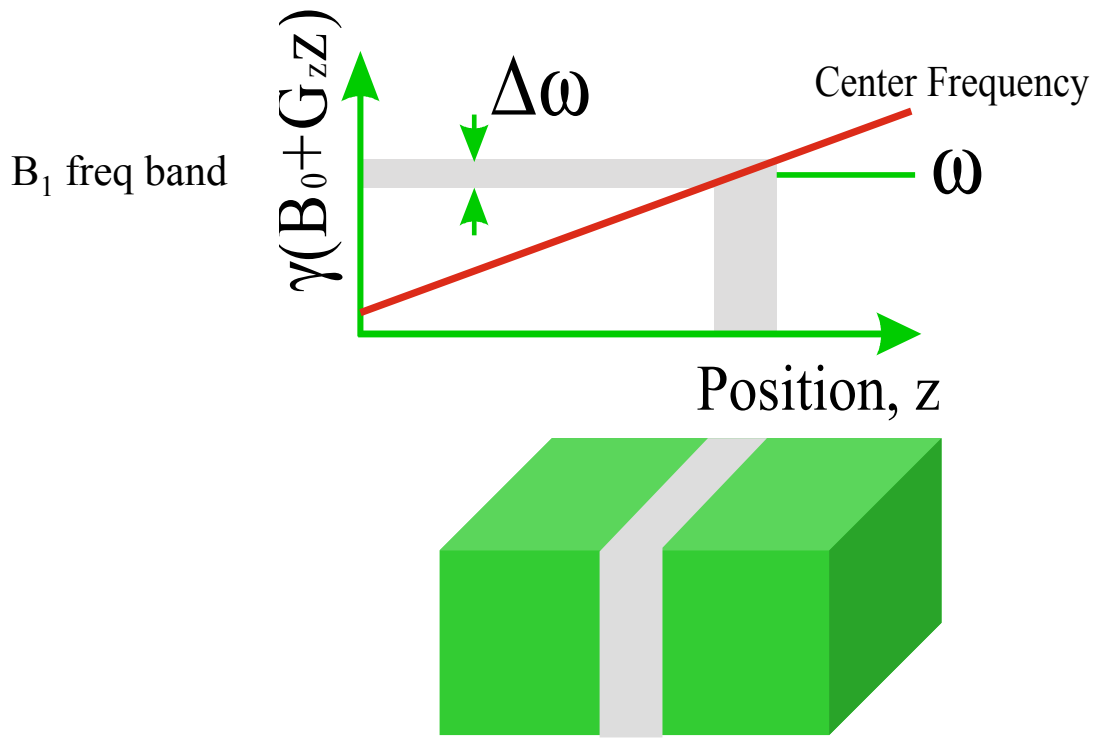
$$\underline{B} = (B_0 + G_x x + G_y y + G_z z)\hat{\underline{z}}$$

Slice selection – dimension 1

Spatial-varying resonance frequency during RF excitation

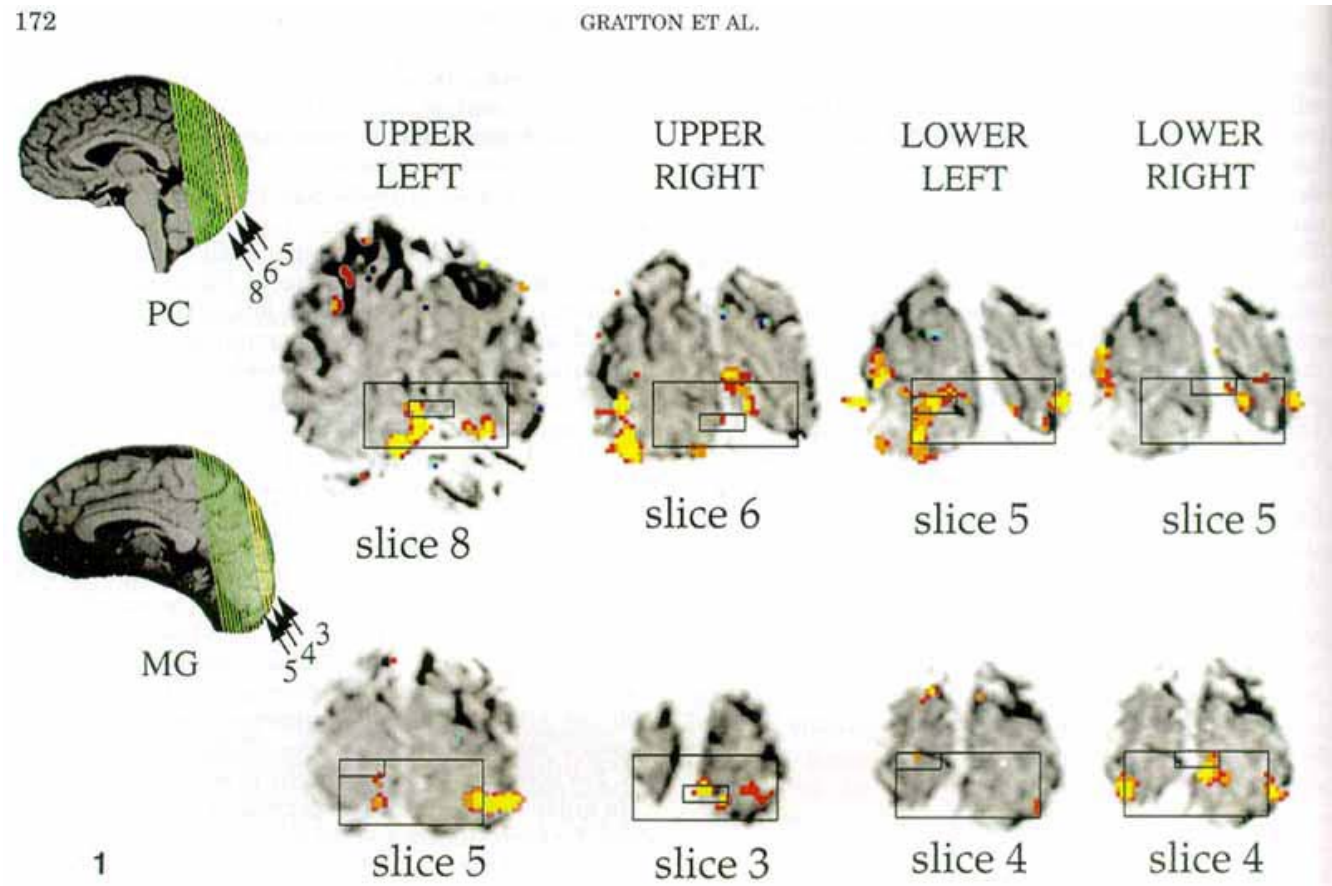
$$\underline{B} = (B_0 + G_z z)\hat{\underline{z}}$$

$$\Rightarrow \omega = \gamma(B_0 + G_z z)$$

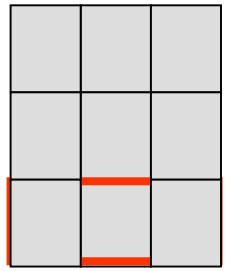


Excited location

Slice profile


UPPER LEFT
UPPER RIGHT
LOWER LEFT
LOWER RIGHT
PC
8 6 5
slice 8
slice 6
slice 5
slice 5
MG
5 4 3
slice 5
slice 3
slice 4
slice 4
1

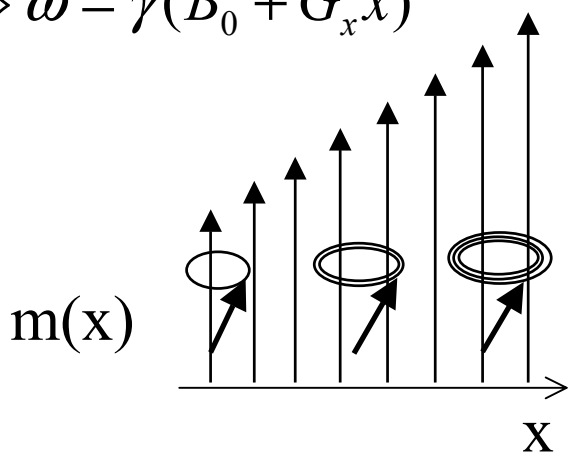
Frequency encoding – dim. 2



Application of magnetic field gradient along x-axis during data read-out ➔ Frequency of signal depends on the x-position of the spins from which it is generated

$$\underline{B} = (B_0 + G_x x)\hat{\underline{z}}$$

$$\Rightarrow \omega = \gamma(B_0 + G_x x)$$

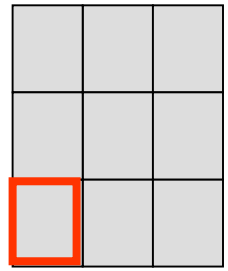


$$S(t) \sim e^{i\gamma Bt}$$

$$S(t) \sim \int m(x) e^{i\gamma G_x x t} dx$$

$$k_x = \gamma G_x t$$

Phase encoding – dimension 3



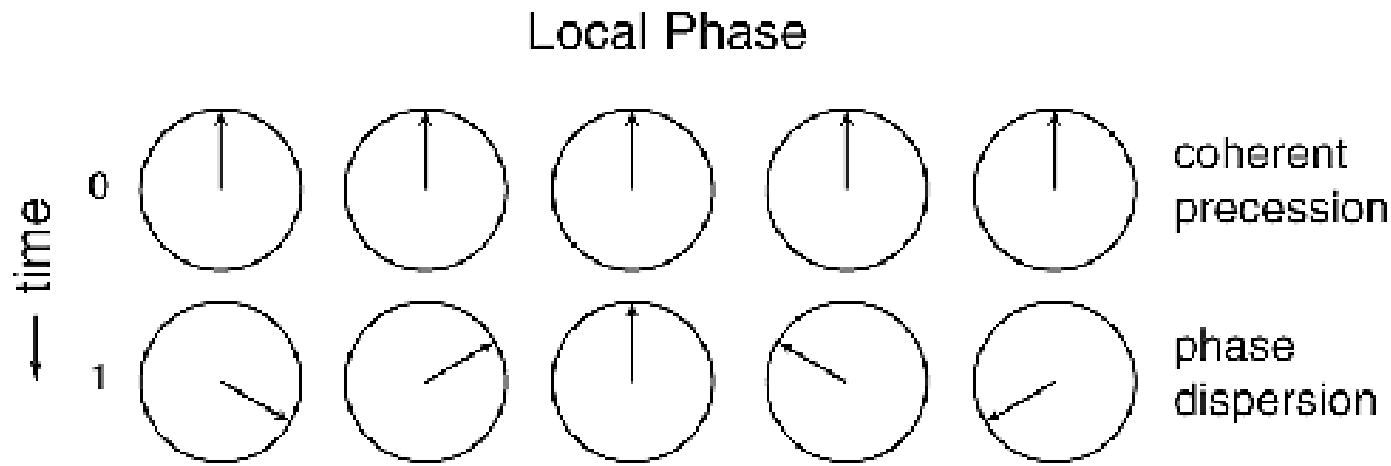
Apply magnetic field gradient along y-axis prior to read-out for a time Δt (before frequency encoding and after slice selection) ➔ Phase of spins depends on y-position

$$\underline{B} = (B_0 + G_y y)\hat{\underline{z}}$$

$$\Rightarrow \omega = \gamma(B_0 + G_y y) = \omega_0 + \Delta\omega$$

$$\Delta\theta = \Delta\omega.\Delta t$$

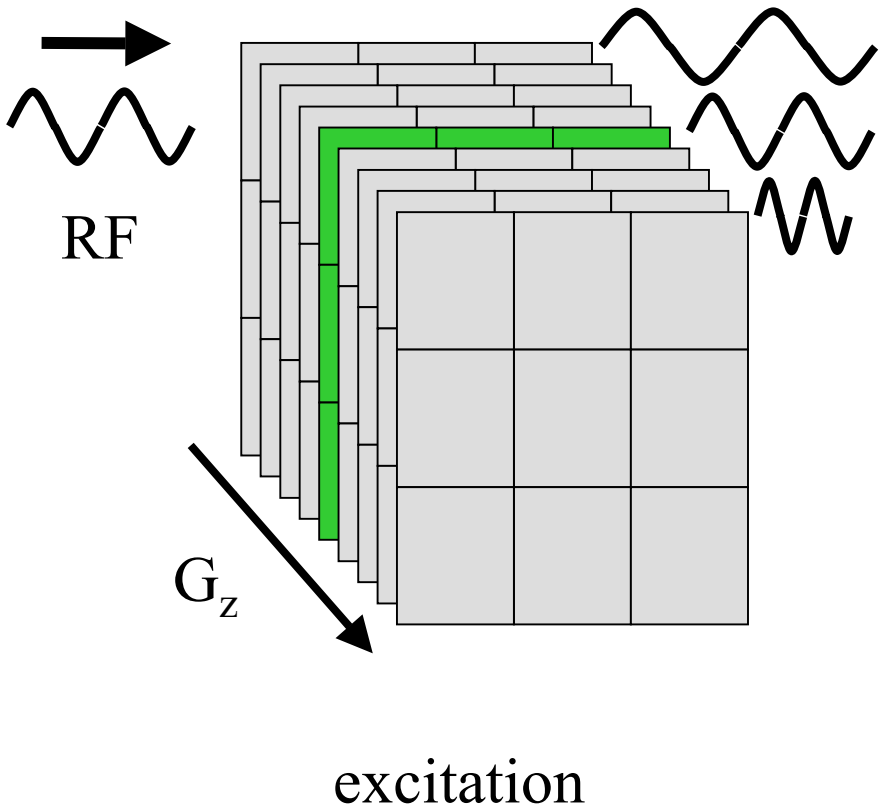
Repeat RF excitation and detection with different gradient area.


Local Phase
time
0
1
coherent
precession
phase
dispersion

Spatial encoding - summary

slice selection

phase & frequency encoding



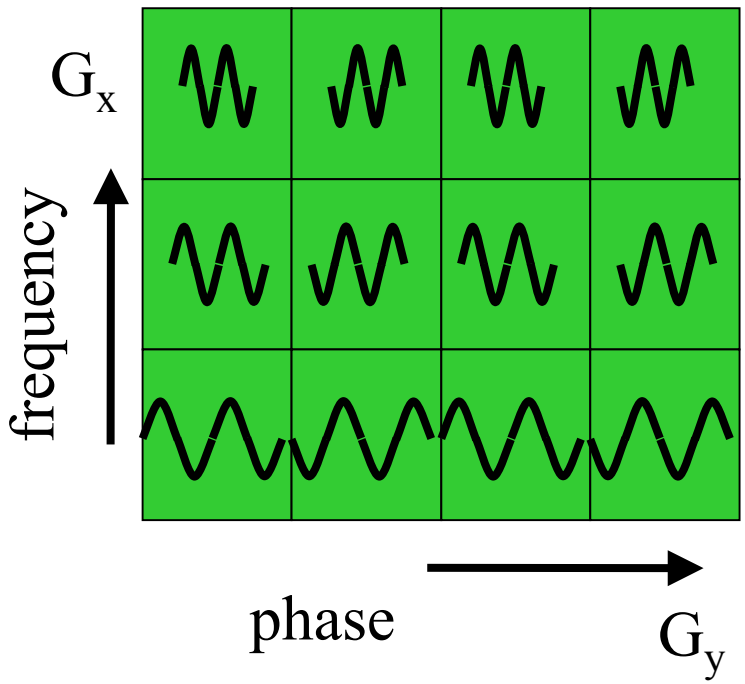


Image Reconstruction

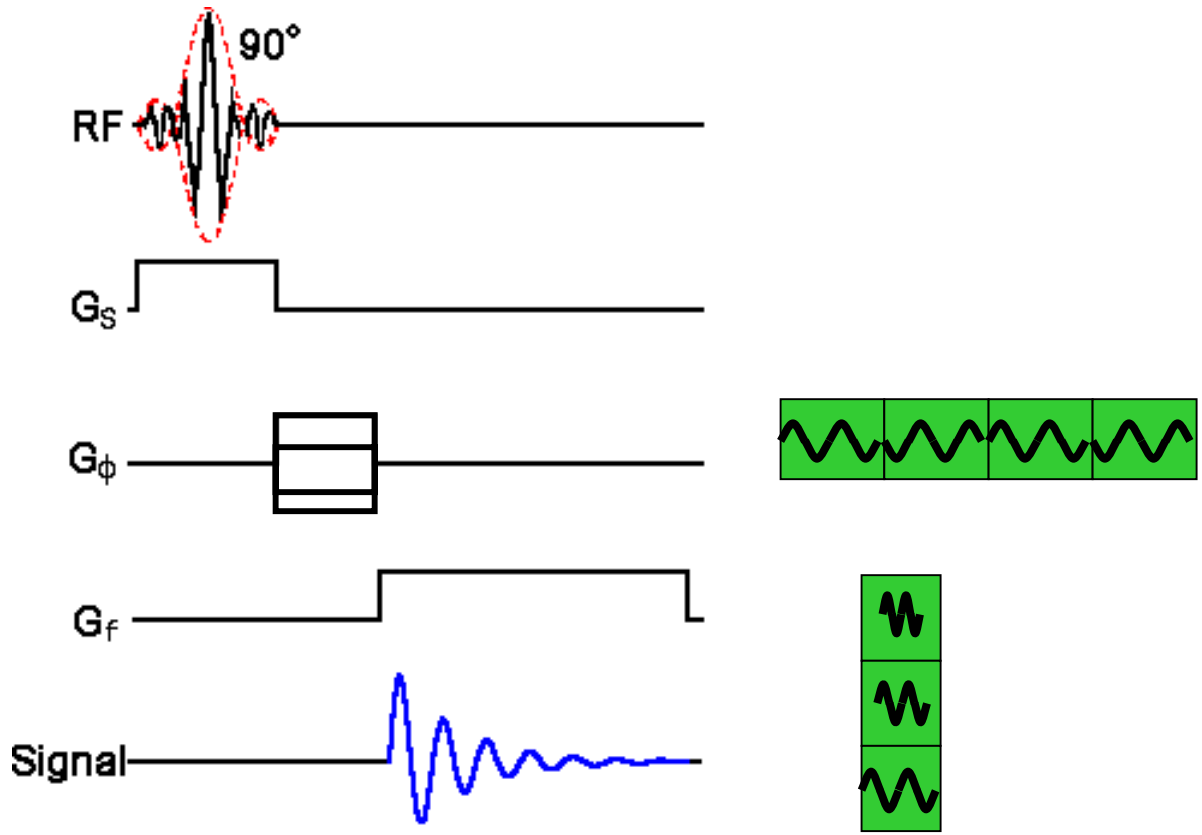
- Spins from all positions (voxels) contribute signals to each measurement
- The frequency and phase of the signal from each voxel is determined by its spatial position
- How do we form an image?

→ Fourier Transformation in 2 directions (← 2D NMR !)

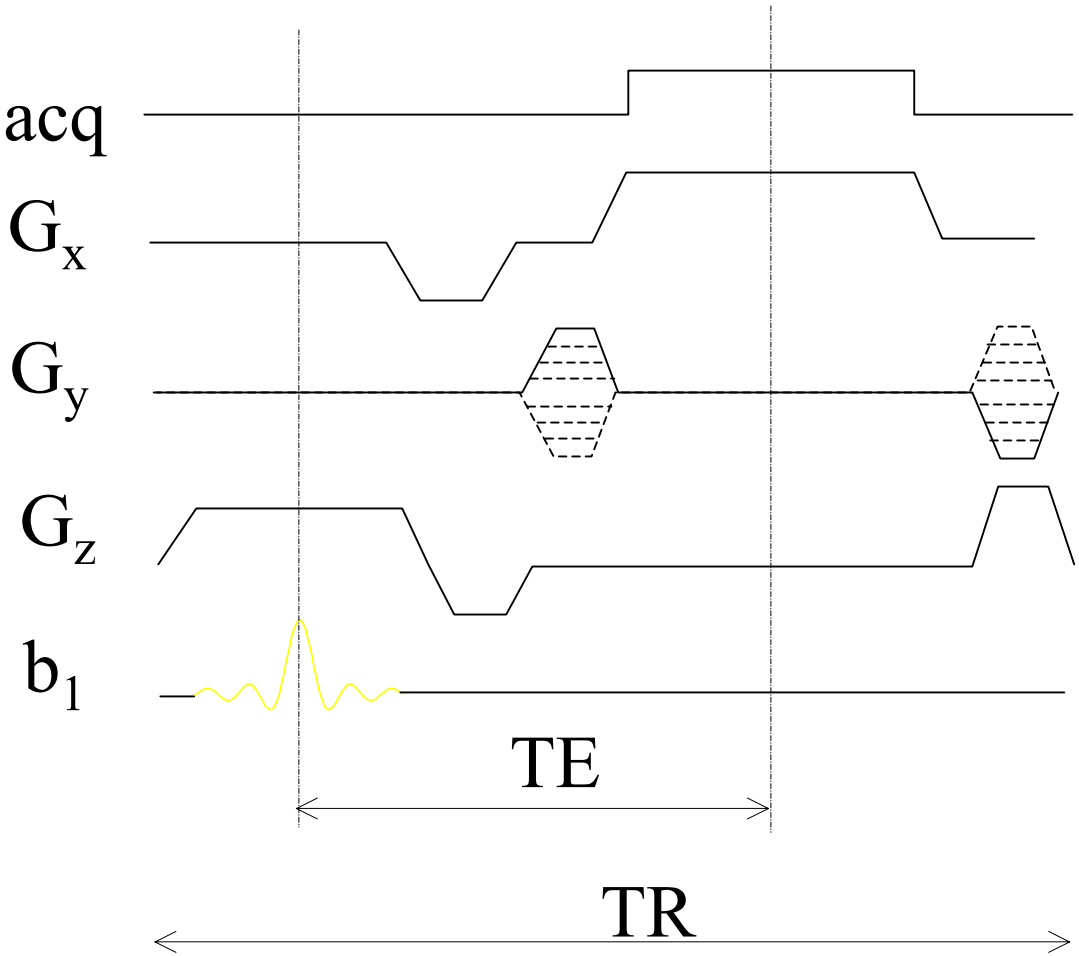
- Frequency encoding direction
- Phase encoding direction

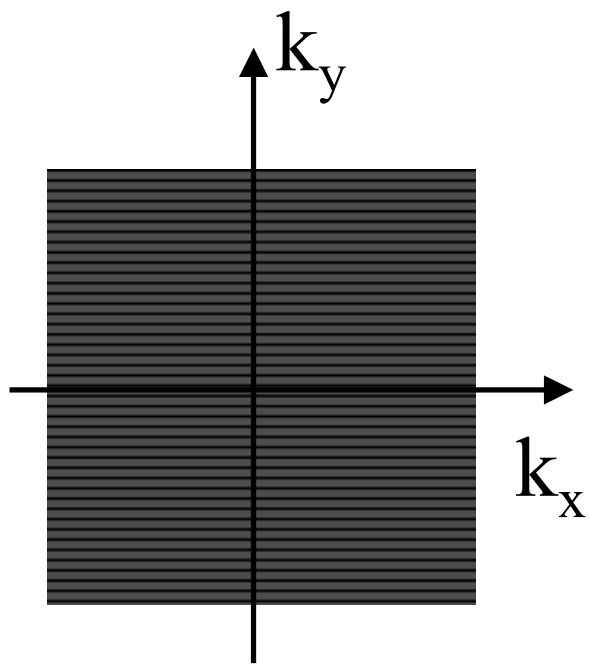
- Intensities of data peaks converted into intensities of pixels

FT imaging sequence



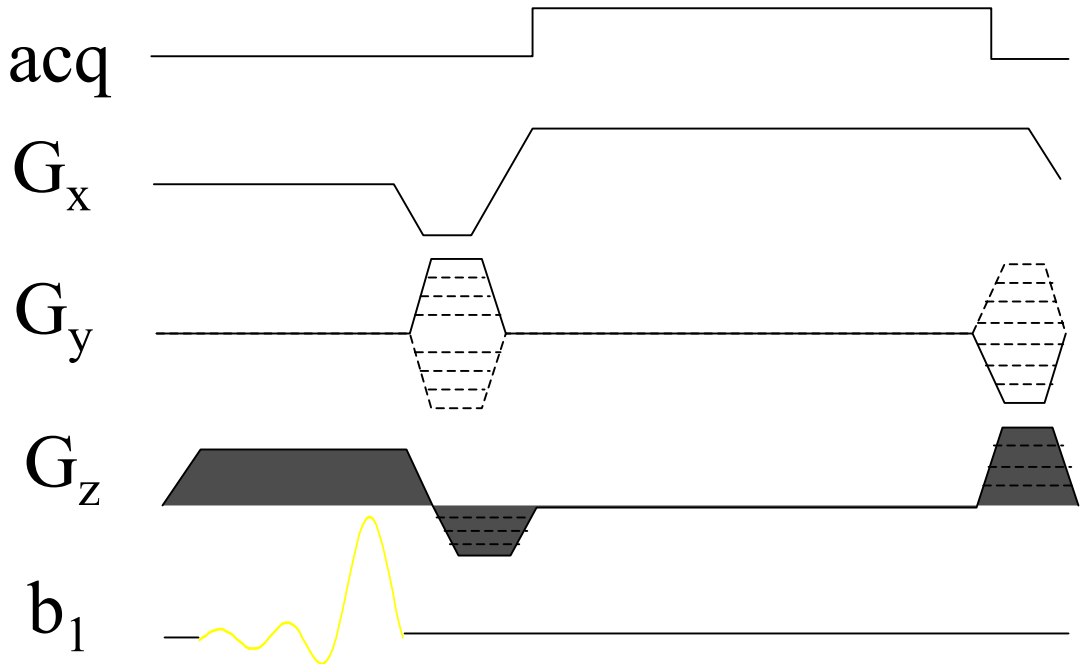
2D Sequence (gradient echo)

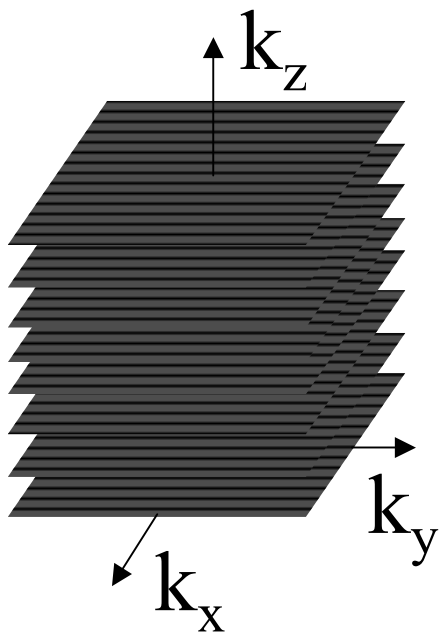




Scan time = $N_y TR$

3D Sequence (gradient echo)





Scan time = $N_y N_z TR$

Tissue Contrast

contrast = the ability to discriminate different tissues based on their relative brightness

- intrinsic factors
  - relative quantity of protons
    - tissue proton density
  - relaxation properties of tissues
    - T_1 & T_2 relaxation
- secondary factors
  - flow
  - contrast agents

Relaxation

relaxation = return to equilibrium

After we have delivered energy to the nuclei in our sample at the Larmor frequency, there are two possible ways for the sample to lose this energy

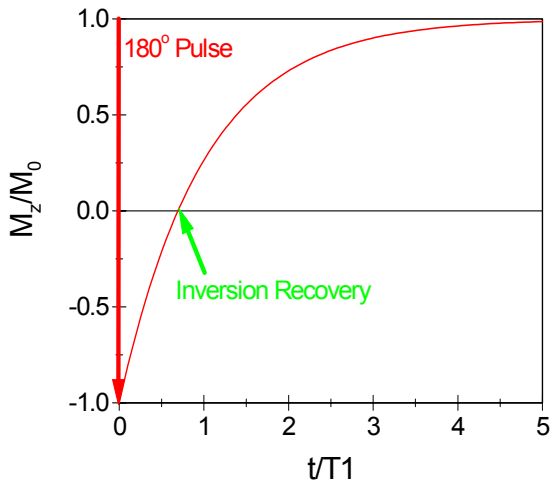
- spontaneous emission (negligible effect at RF frequencies; ~ ω^3)
- induced emission (energy emission requires interaction of the nucleus with its external environment; the nature of energy emission depends strongly on the environment of the excited nucleus)

Bloch equation

$$\frac{d\vec{M}}{dt} = \gamma\vec{M} \times \vec{B} + \frac{1}{T_1}\left(M_0 - M_z\right)\hat{z} + \frac{1}{T_2}\vec{M}_\perp$$

- Longitudinal relaxation

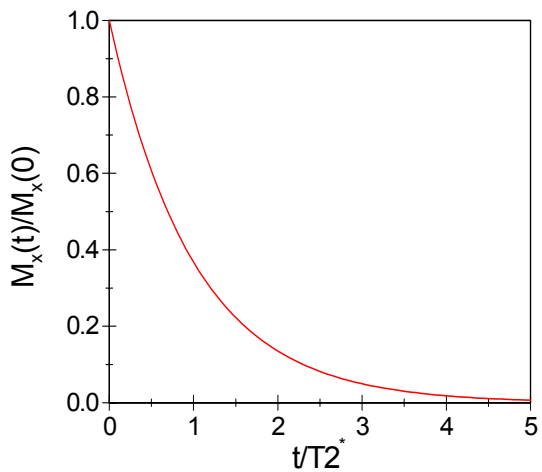
$$M_z(t) = M_0(1 - e^{-t/T_1})$$



- Transverse relaxation

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

$$M_\perp(t) = M_\perp(0)e^{-t/T_2^*}$$



T_1 Relaxation

- Time constant of recovery of longitudinal component of magnetization
- origin:
    - reflection of spin thermal interactions with the environment (i.e. the lattice)
    - induced emission: molecules moving near the Larmor frequency will induce relaxation
        - pure water: molecular motion too fast long T_1
        - solids: molecular motion too slow long T_1
        - tissue: molecular motion near Larmor freq short T_1

T_2 Relaxation

- Time constant of disappearance of transverse magnetization
- origin:
    - Spins in high and low energy state exchange energy but do not loose energy to the surrounding lattice (induced emission)
    - Each nucleus experiences slight, temporary changes in local field due to slow interactions with other nuclei (spin-spin interactions). This causes temporary changes in Larmor frequency leading to permanent phase dispersion.

- T_1 is a part of T_2 (as longitudinal component grows, transverse component decays) → T_1 is always greater or equal to T_2
- Typical relaxation times for brain white mater:

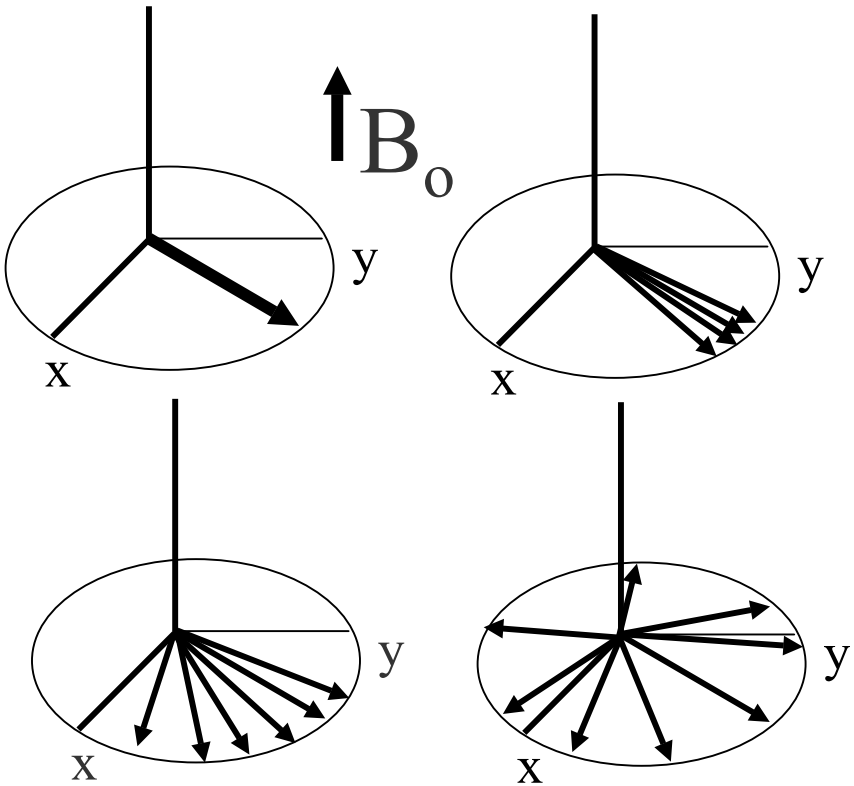
$T_1 \sim 500$ ms $T_2 \sim 70$ ms

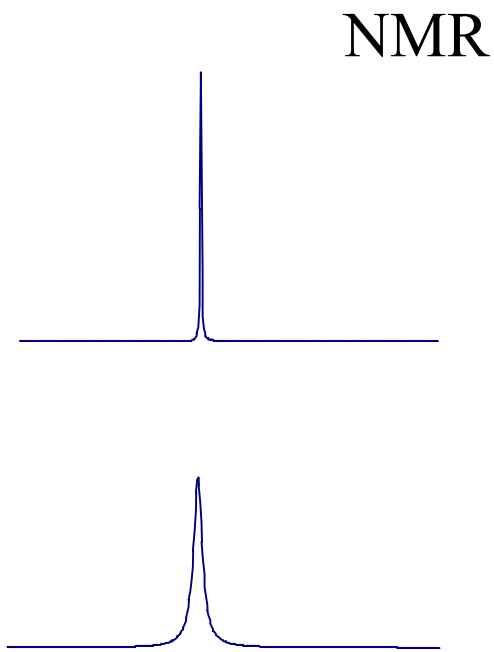
T_2* Relaxation

- T_2^* versus T_2
  - True T_2: decay of transverse magnetization due to "natural" processes at the molecular level
  - T_2^*: the observed or effective decay of transverse magnetization due to magnetic field inhomogeneity and susceptibility effects within a voxel (this can be reversible, unlike T_2 decay)

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

Spin dephasing





Imaging sequences

Goals

- generate an RF signal perpendicular to $\mathbf{B}_0$
- generate tissue contrast
- minimize artifacts

Sequences

- gradient echo
- spin echo
- inversion recovery

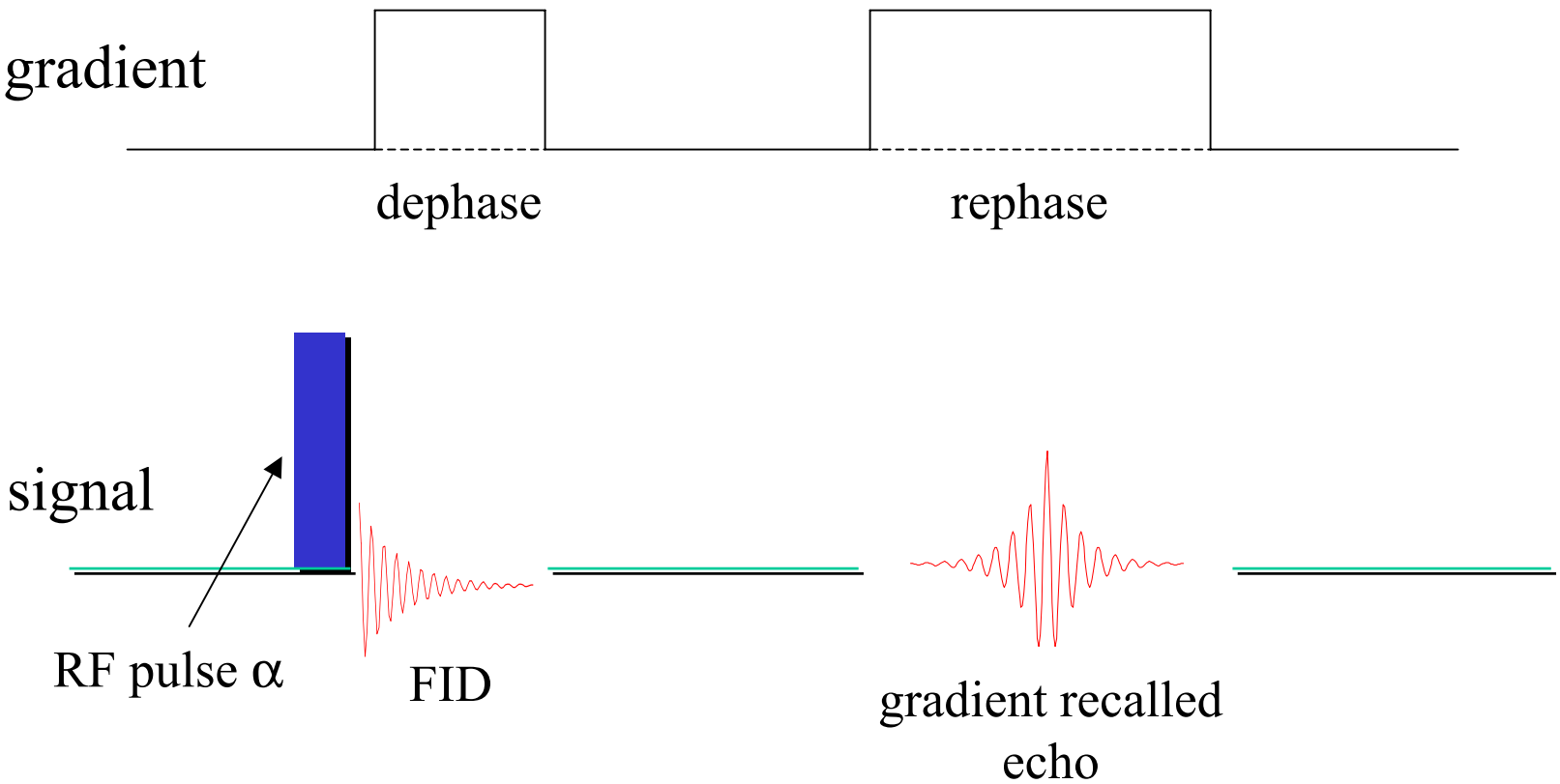
MRI Parameters

- TR = Repetition time; the time between one acquisition and the next.
- TE = Echo time; the time from the RF excitation to the center of the echo being received.
- Flip angle = angle to which H nuclei magnetization is tipped (flip angle increases with the amplitude of the RF pulse and its duration)
- SAR = "Specific Absorption Rate"; dosage (mass normalized rate of RF energy coupling to biologic tissue [watts/kg])
  - 0.4 W/kg averaged over the whole body, or 8.0 W/kg peak SAR in any 1g of tissue, and 3.2 W/kg averaged over the head
- FOV = field of view; distance across the image

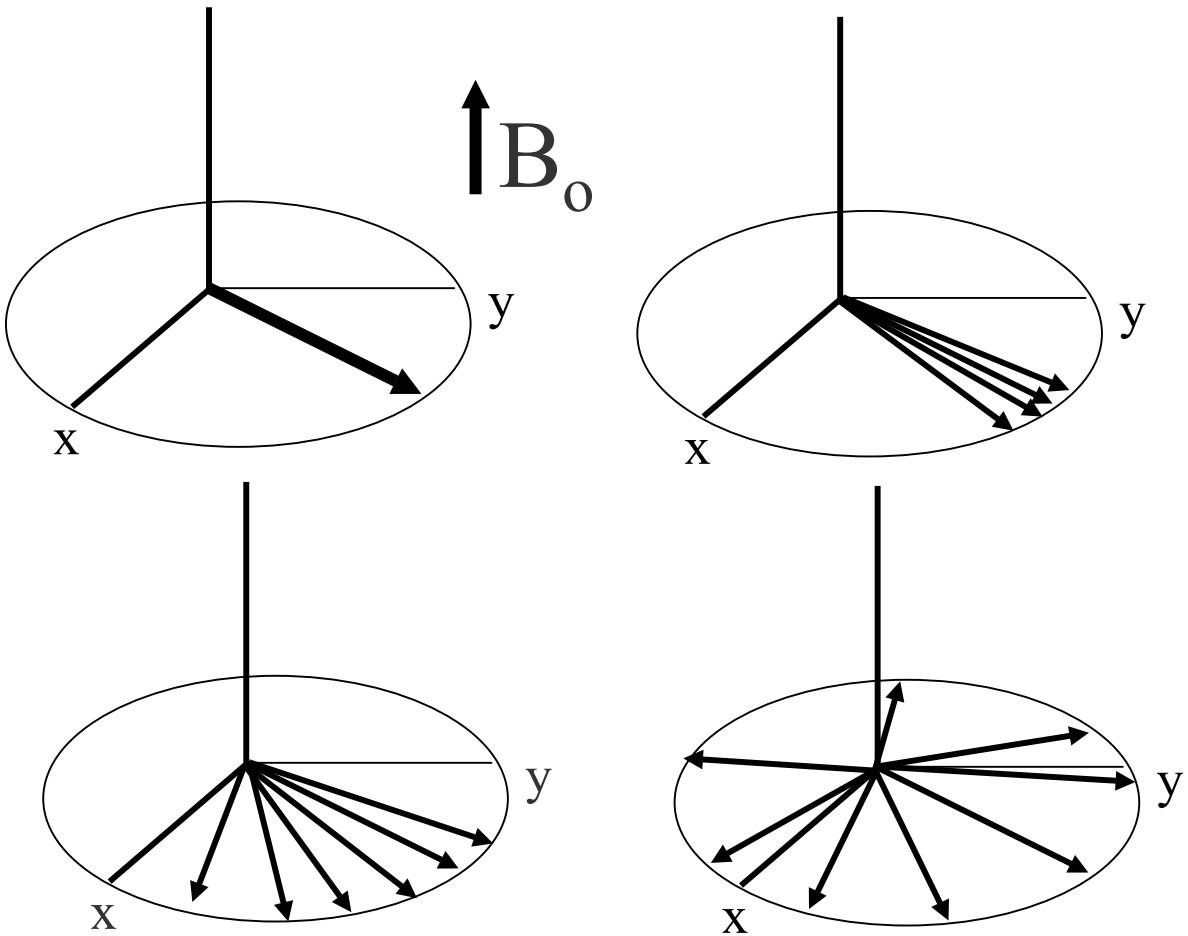
Gradient Echo

- simplest sequence
  - alpha flip-gradient recalled echo
- 3 parameters
  - TR
  - TE
  - flip angle

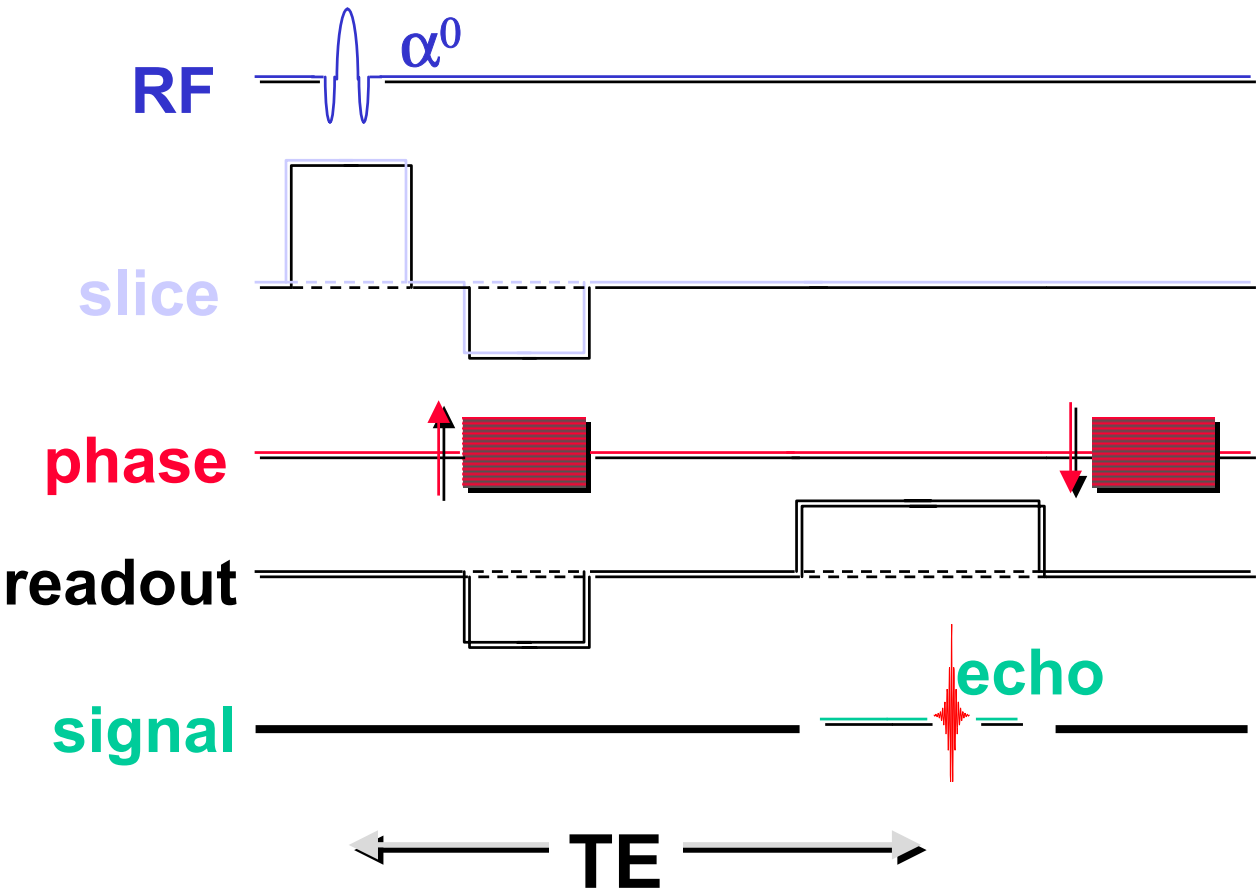
Gradient Echo



Spin dephasing



Gradient Echo



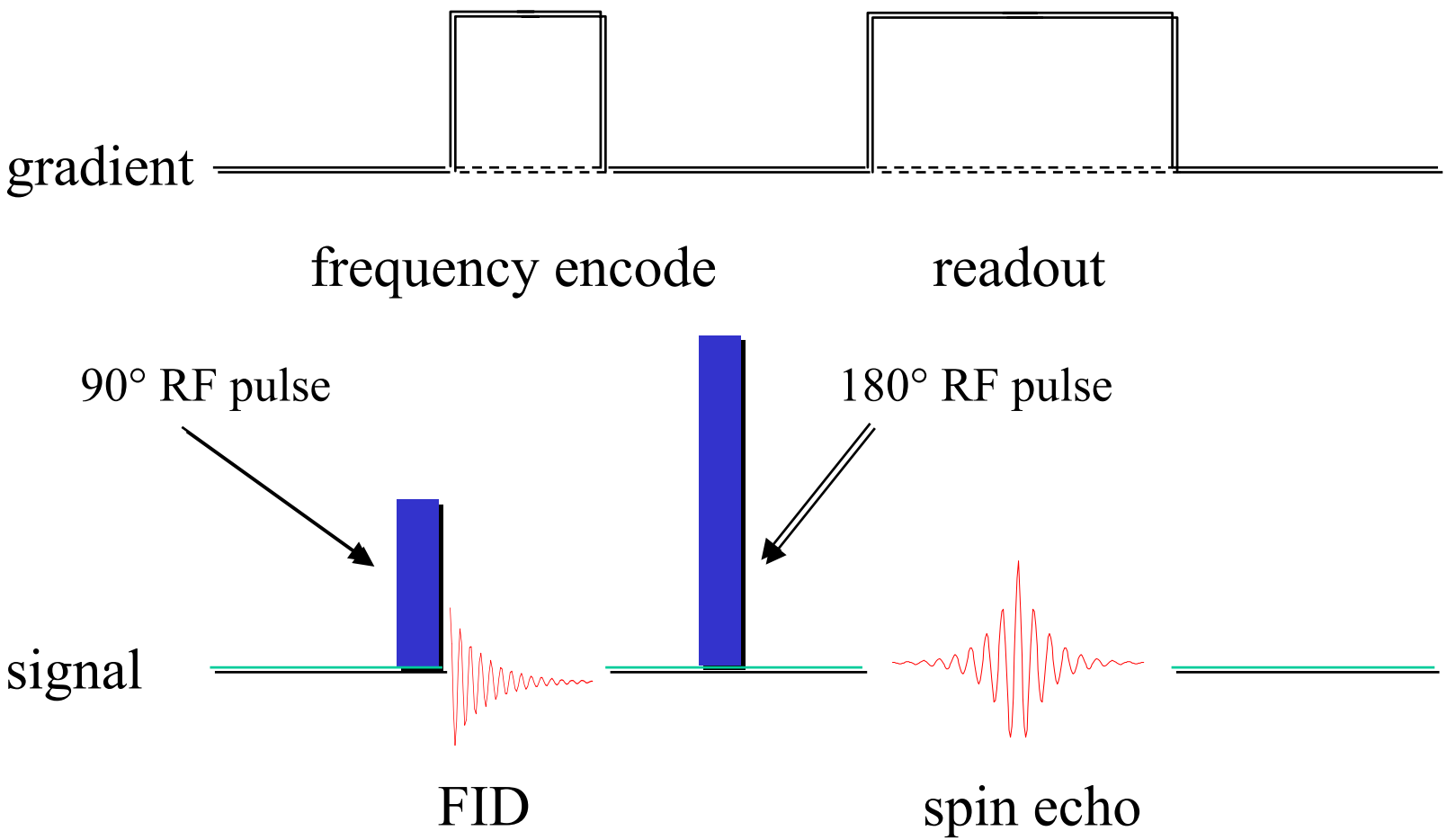
Gradient Echo

- **advantages**
  - faster imaging
    - can use shorter TR and shorter TEs than spin echo (SE)
  - low flip angle deposits less energy
    - more slices per TR than spin echo
    - decreases SAR
  - compatible with 3D acquisitions
- **disadvantages**
  - difficult to generate good T_2* weighting
  - magnetic field inhomogeneities cause signal loss
    - worse with increasing TE times
    - susceptibility effects
    - dephasing of water and fat protons

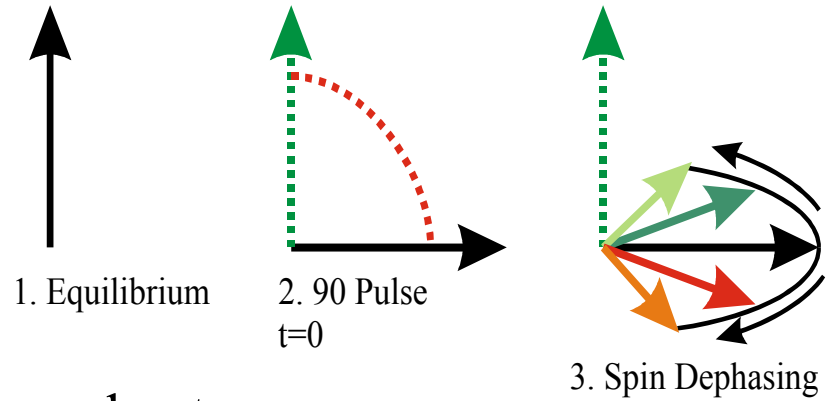
Spin Echo

- widely used sequence
  - 90-180-echo
- 2 parameters
  - TR
  - TE
- generates T_1, PD, and T_2 weighted images
- minimizes artifacts

Spin Echo


gradient
frequency encode
readout
90° RF pulse
180° RF pulse
signal
FID
spin echo

Spin Echo

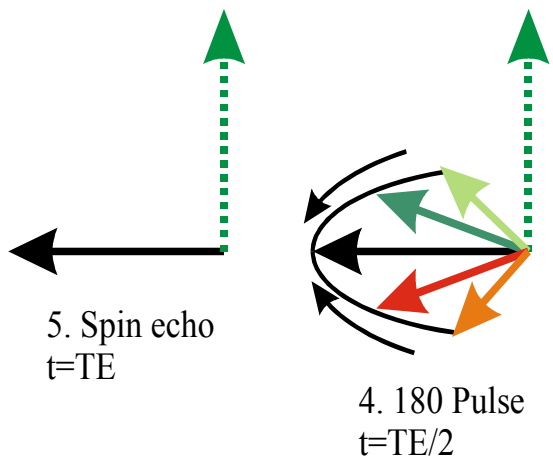


180° pulse eliminates signal loss due to

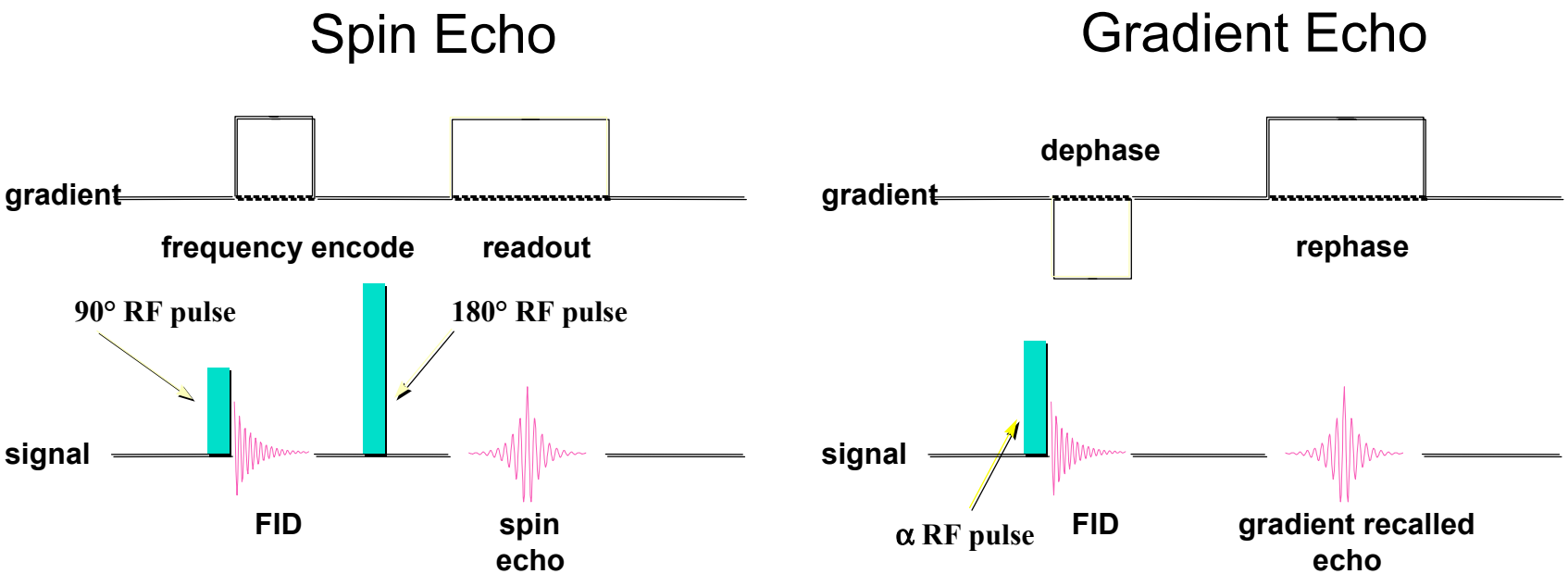
- field inhomogeneities
- susceptibility effects
- water/fat dephasing

→all signal decay is caused by

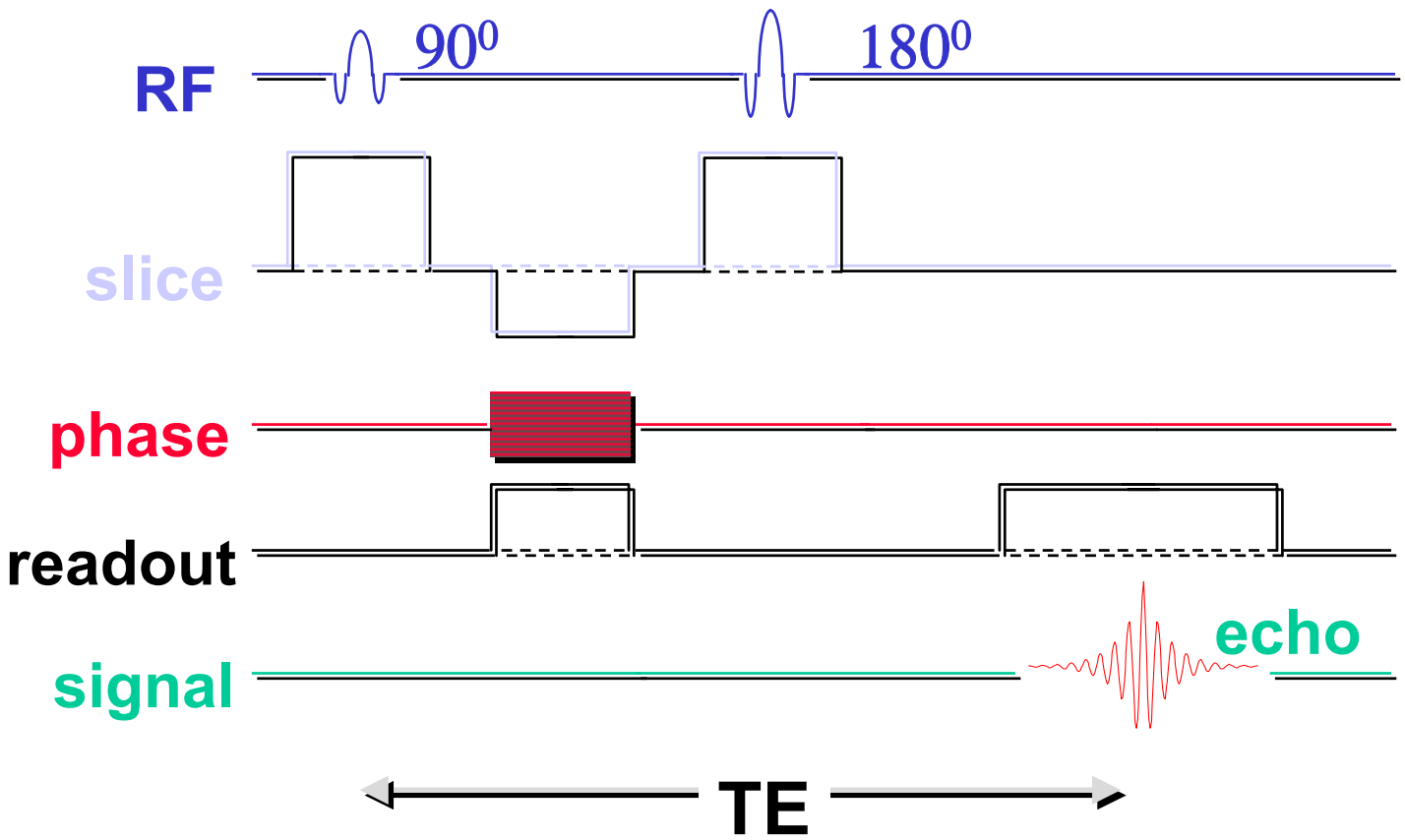
T_2 relaxation only



Gradient versus Spin echo



Spin Echo



Spin Echo

- **advantages**
  - high signal to noise
  - least artifact prone sequence
  - contrast mechanisms easier to understand

- **disadvantages**
  - high SAR than gradient echo because of 90^0 and 180^0 RF pulses
  - long TR times are incompatible with 3D acquisitions

TR and T_1

- If TR is considerably longer than T_1, then MR signal is fully recovered at the time of the next RF pulse → MR signal is not sensitive to T_1 → It would be sensitive to proton density (**density-weighted image**)
- A density-weighted image is also obtained at very short TRs, when longitudinal magnetization had recovered very little and there is little difference between tissues → However, in this case the problem is that there is little MR signal to measure →The trick is to reduce the flip angle
- With small flip angles there is little longitudinal relaxation to do

→ there is enough MR signal to measure even after a short TR

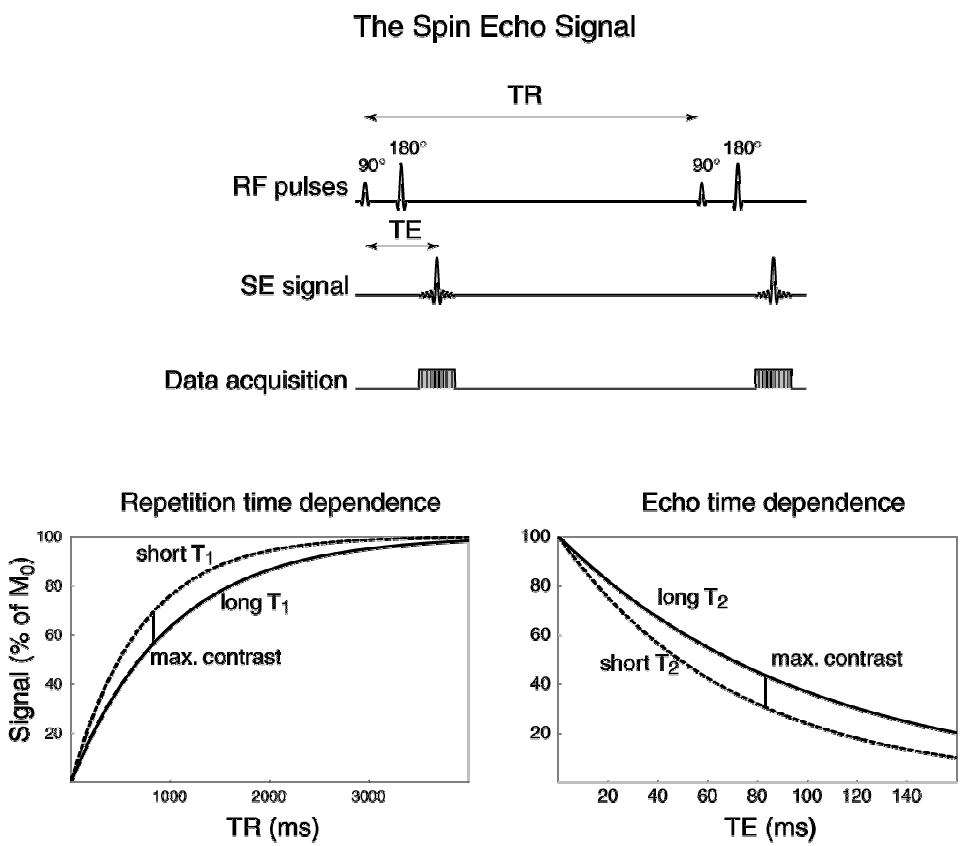
T_1 / T_2 -weighted image

- T_1 – weighted image
  - For the image to be sensitive to T_1, one needs a TR shorter then $T_{1,}$
  - T1 relaxation times increase as field strength increases (for same parameters, there is less T1 contrast at higher magnetic fields)
- T_2 – weighted image
  - For the image to be sensitive to T_2, one needs a TR shorter then T_2 or T_2*

- The signal from different tissues recovers at a different rate, depending of their T_1

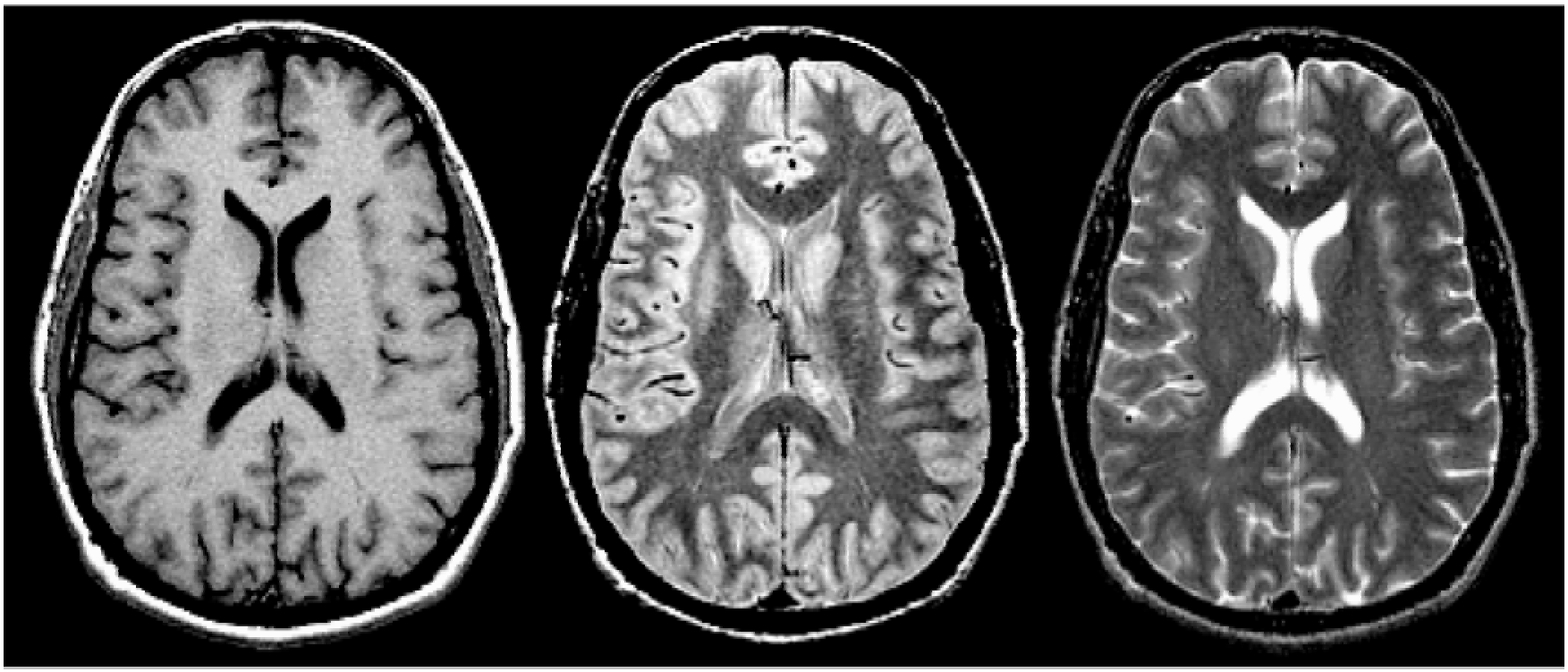
→ It is desirable to measure the MR signal during recovery

Contrast in MR Images



- T_1 weighted
  - short TR (450-850)
  - short TE (10-30)
- T_2 weighted
  - long TR (2000 +)
  - long TE (> 60)
- PD weighted
  - long TR, short TE

Spin Echo Images



T_1-weighted
(TR=600, TE=11)

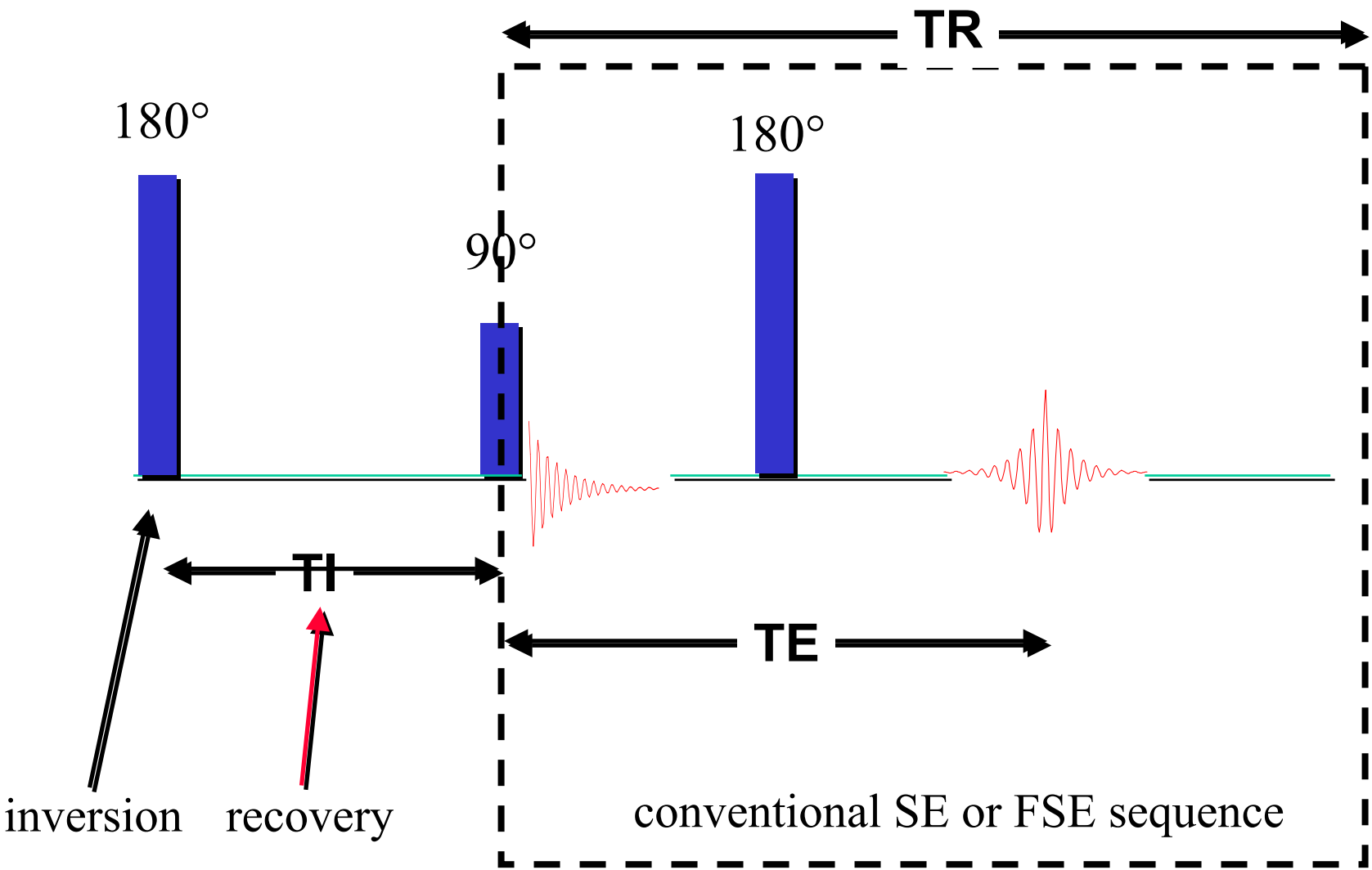
Density-weighted
(TR=3000, TE=17)

T_2-weighted
(TR=3800, TE=102)

Inversion Recovery

- initially used to generate heavily T_1 weighted images
- popular in U.K. for brain imaging
- 180^0 inversion pulse followed by a spin echo or fast spin echo sequence
- three image parameters
  - TI
  - TR
  - TE

Inversion Recovery



STIR

- = Short T_1 inversion recovery imaging
- "fat nulling"
- exploits the zero crossing effect of IR imaging
  - all signal is in XY plane after TI time and subsequent 90^0 pulse produces no signal
  - optimal inversion time for fat nulling dependent on T_1 relaxation time

Field Strength (Tesla)	TI time (msec)
0.3	80
0.5	110
1.0	130
1.5	150

STIR

advantages

- robust technique
  - works better than fat saturation over a large FOV (>30 cms)
  - better at lower field strengths
- high visibility for fluid
  - long T_1 bright on STIR
  - long T_2 bright on STIR, given long enough TE

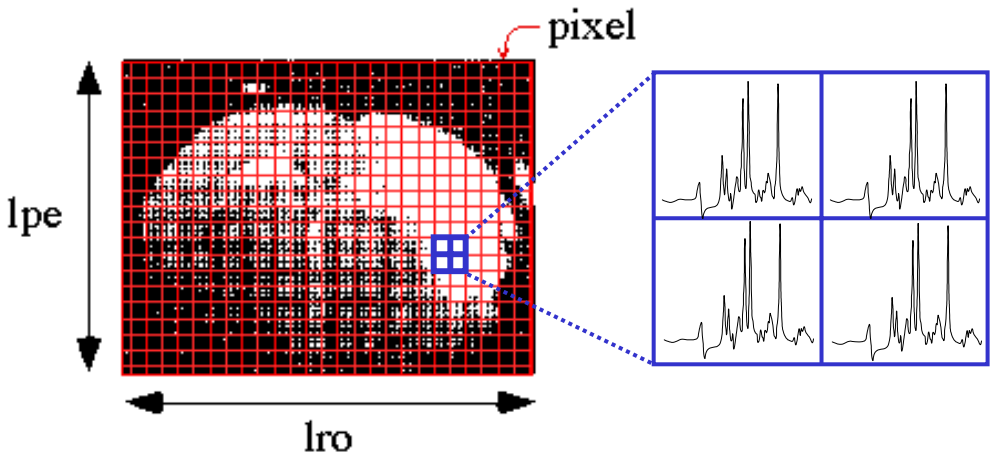
disadvantages

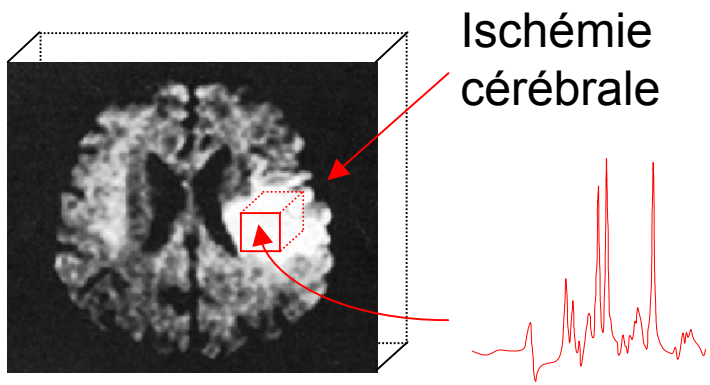
- poor S/N
  - improved with multiple averages (FSE)
  - improved with shorter TE times
- incompatible with gadolinium
  - shorter T_1 relaxation post-contrast

D) Magnetic resonance spectroscopy

Key facts

- MRS = NMR on intact biological tissue
- Identification of different chemical compounds by their frequency
- First reported by Moon and Richards in 1973 on intact red blood cells (using P-31 MRS)
- Useful for looking at disorders of metabolism, tumors and certain inflammatory diseases
- Used for primary brain tumors, infections such as AIDS, ...

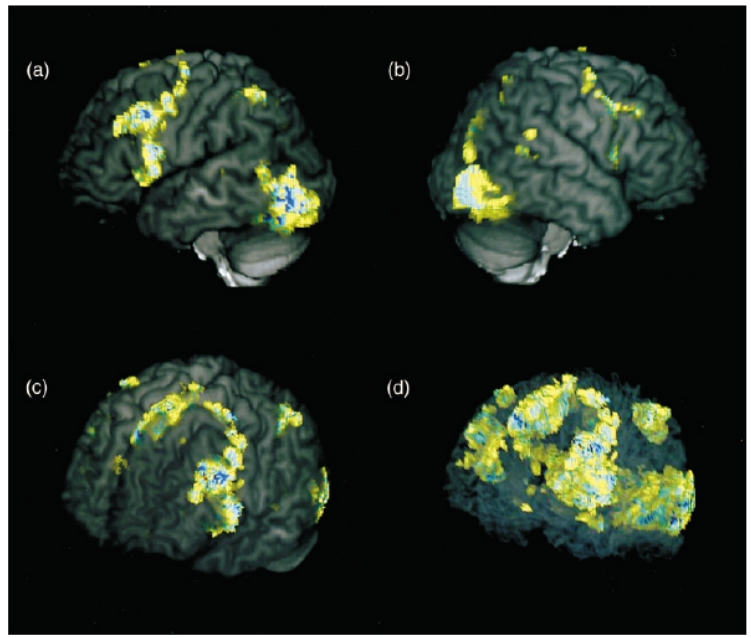

pixel
lpe
lro


Ischémie
cérébrale

E) Functional MRI

Functional MRI (fMRI)

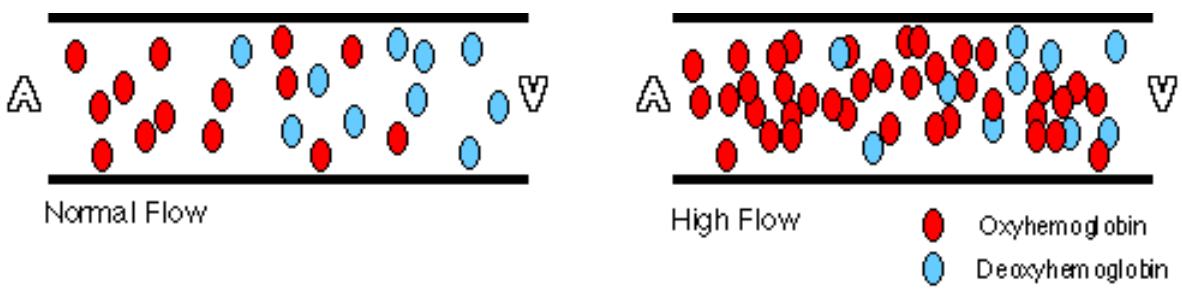
- Developed in 1990/1992
- Technique to obtain functional information from the central nervous system noninvasively
- Detection of increases in blood flow associated with activation of parts of the brain



- Contrast not between different types of tissue but between exactly the same tissue when that tissue is more active or less active

Blood oxygen level dependent contrast (BOLD)

- Activation of an area of the brain causes an increase in blood flow to that area that is greater than that needed to keep up with the oxygen demands of the tissues. This results in a net increase in intravascular oxyhemogobin and a decrease in deoxyhemoglobin. Deoxyhemoglobin is paramagnetic, resulting in shorting of the T_2* of the brain and decrease in signal. Less deoxyhemoglobin as a result of increase in blood flow results in an overall increase in signal



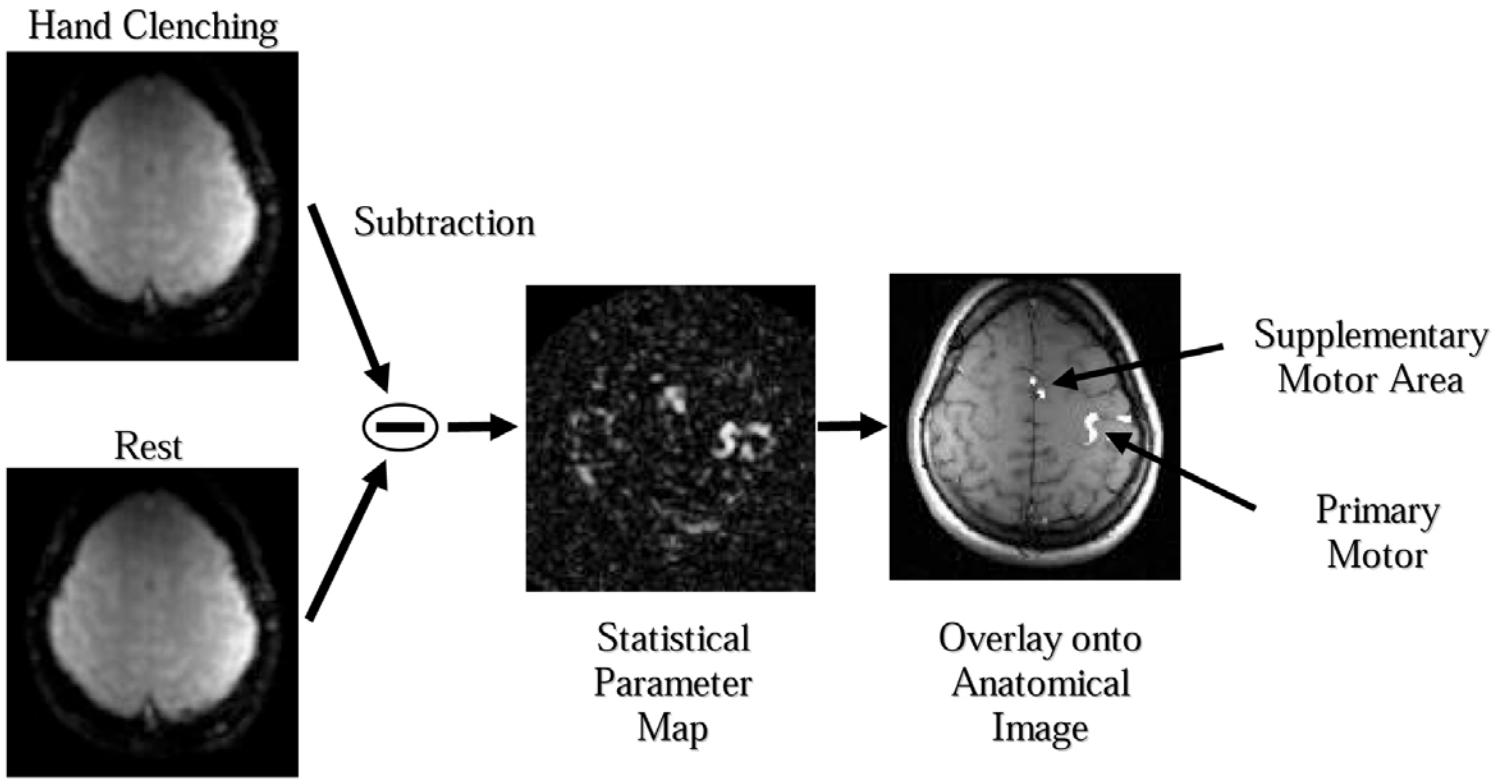


Figure 9. Graphical description of a functional MRI experiment: images from two behavioral conditions are subtracted to yield regions of brain activity. In this case, a hand clenching task was used to define the primary and supplementary motor control areas in the brain.

Problems

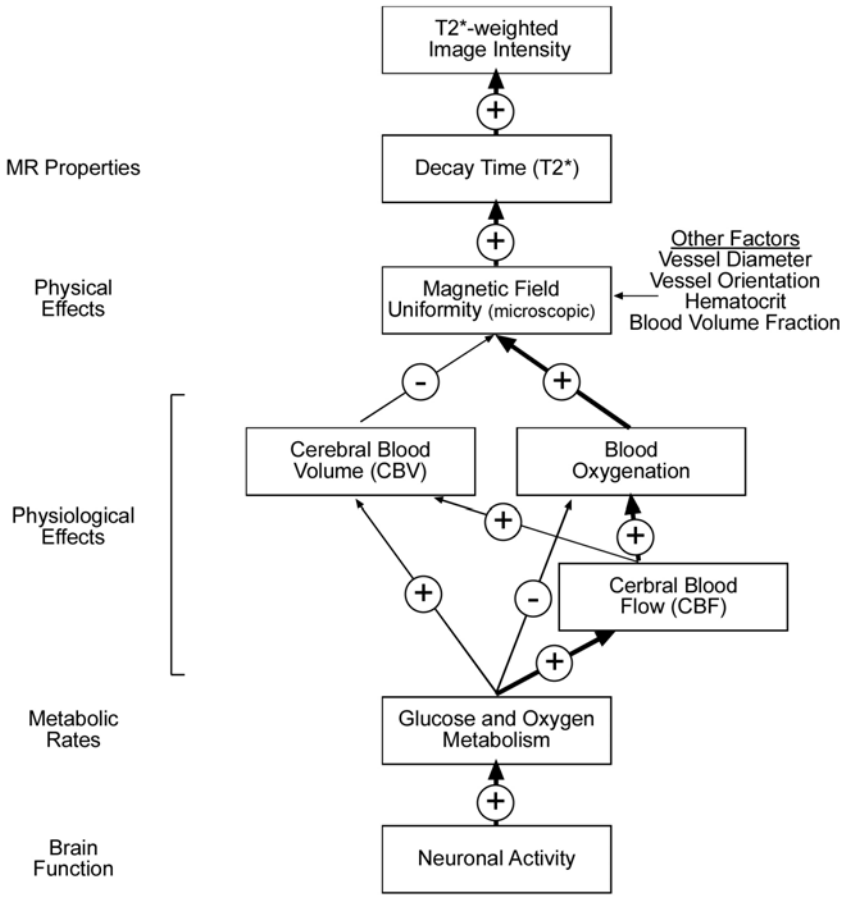


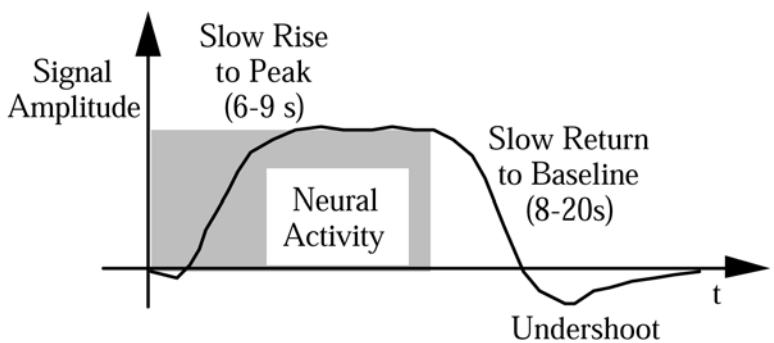
Figure 8. Schematic of interactions in the formation of the BOLD signal. Positive/negative arrows indicate positive/negative correlations between the parameters. The right most pathway (in bold arrows) is the most significant effect in most BOLD fMRI.

There is not a one-to-one correspondence between T_2 and the neural activity that we are trying to measure.

There are pathways that might decrease the decay rate and hence results in a decreased MR signal!

Problems

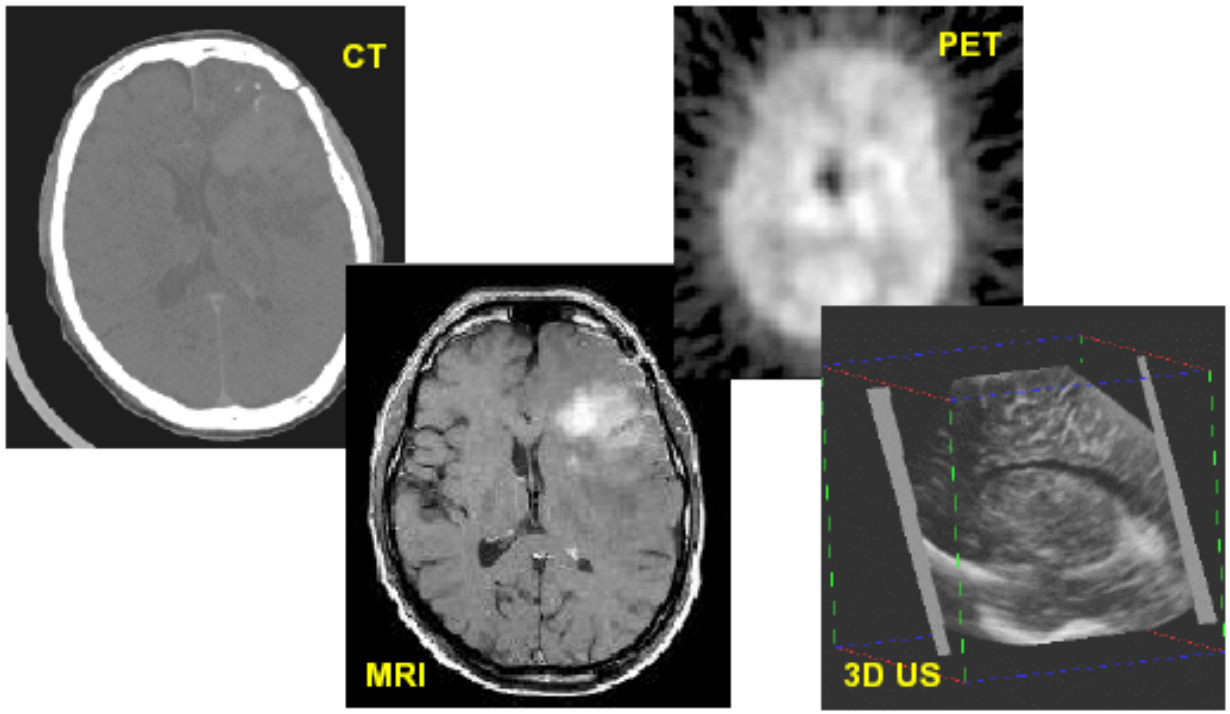
- Small size in of activation related response leaves it susceptible to noise (low SNR) from:
  - thermal and electromagnetic noise from the subject
  - reception coil, preamps and other electronics
  - quantization noise from analog to digital conversion
  - head movement (problem especially for speech tasks)
- uncontrolled neuronal events
  - differences in the manner in which a task is performed
  - neuronal events associated with behavior unrelated to task
  - spontaneous firing of networks
- MRI response is delayed and relatively slow compared to brain activity



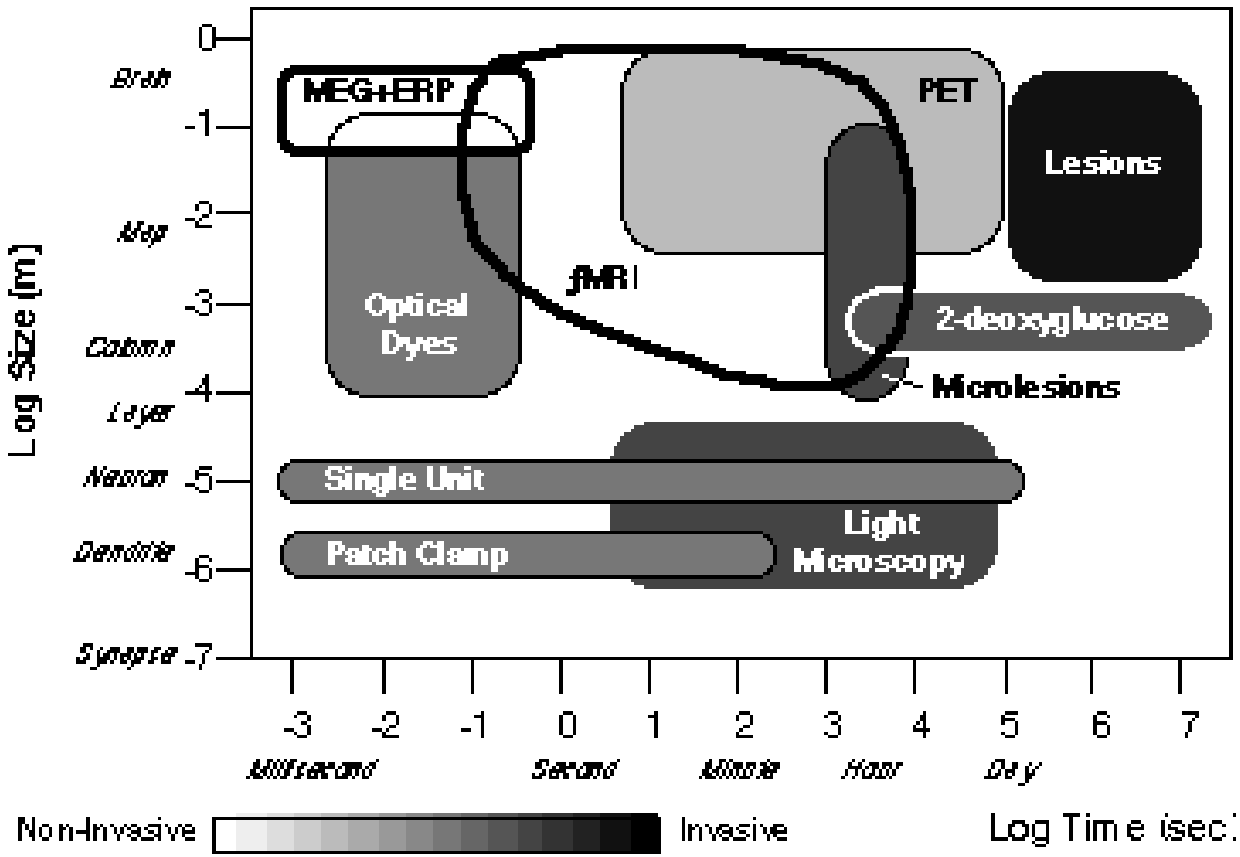
Dealing with the issues!

- rapid data acquisition techniques
  - EPI (echo-planar imaging)
  - FLASH (fast low angle shot)
- special reception coils
- increasing static magnetic field intensity
- SNR depends on temporal resolution - lower temporal resolution
- post-processing techniques, movement correction algorithms
- different gradient systems
- multi-shot techniques
- head restraints and bite bars

Imaging the brain



Comparison of different methods



Imaging brain activity: Advantages of fMRI

- noninvasive
- Signal does not require injections of radioactive isotopes
- Total scan time can be very short (1.5 – 2.0 min per run; temporal resolution of < 1s possible)
- In-plane resolution of the functional image is generally about 1.5 x 1.5 mm (resolutions < 1 mm are possible)
- Offers repeated studies of individual subjects and patients
- MRI units widely available and less costly than positron emission tomography (PET) systems

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