Diffusion Imaging I

By:
Osama Abdullah

Lecture 1 outline

- Introduction.
  - What is diffusion?
  - Diffusion and signal attenuation.
  - Diffusion imaging.
- How to capture diffusion?
  - Diffusion sensitizing gradients.
    - Spin Echo.
    - Gradient Echo.
    - Quantitative description.
    - What is the *b*-value?
    - High *b*-value problems.
- Diffusion imaging pulse sequence.
  - Pulsed Gradient Spin Echo.
  - Single shot EPI.
  - RARE.
  - STEAM.
- Diffusion basics.
  - Einstein equation.
  - Factors that affect diffusion.
  - Diffusion tensor.
  - Anisotropic vs. isotropic diffusion.
- Diffusion Imaging techniques:
  - Introduction
  - Family of techniques
    - Diffusion weighted imaging.
      - Concept.
      - Quantitative description.
      - Limitations
    - Quantitative apparent diffusion coefficient.
      - Definition.
      - Linear and nonlinear fitting.
      - Clinical applications.

Ref: Handbook of MRI pulse sequences (P. 274-280 and 830-853)

Lecture 2 outline

- Family of diffusion techniques, cont'd
  - Diffusion tensor imaging
    - Quantitative description.
    - Finding the diffusion tensor.
    - Scalar and vector parameters extracted from the diffusion tensor (RA, FA, MD, PE, and Tractography)
  - q-space imaging
    - Quatitative description.
    - Definition of q.
    - How to conduct a q-space experiment?
- Paper discussion:

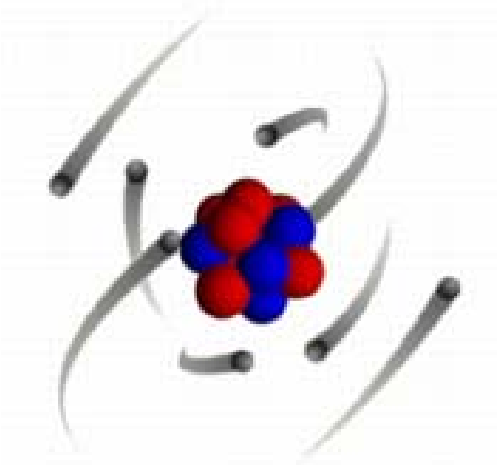
  Assaf et al 2002: "High b-value q-space analyzed diffusion-weighted MRI: Application to multiple sclerosis". Magn Reson Med 47:115-126, 2002 Wiley-Liss, Inc.

What is diffusion?

- The Brownian motion of molecules in a medium.

- Brownian motion

  The random movement of colloidal particles through a liquid or gas.



- In the presence of B_1, water molecules will cause phase dispersion of the transverse magnetization and hence, signal loss.

- The attenuation degree depends on:
  - The structure of the tissue.
  - Physical and physiological state of the tissue.
  - Microenvironment.

Diffusion Imaging

- MRI methods designed to explore tissue diffusion properties.
- The data acquisition methods are called *diffusion imaging pulse sequences.*
- Can be performed on 1D, 2D or 3D.
- 2D is the most commonly used.

How to capture diffusion?

Motion Sensitizing Gradients:

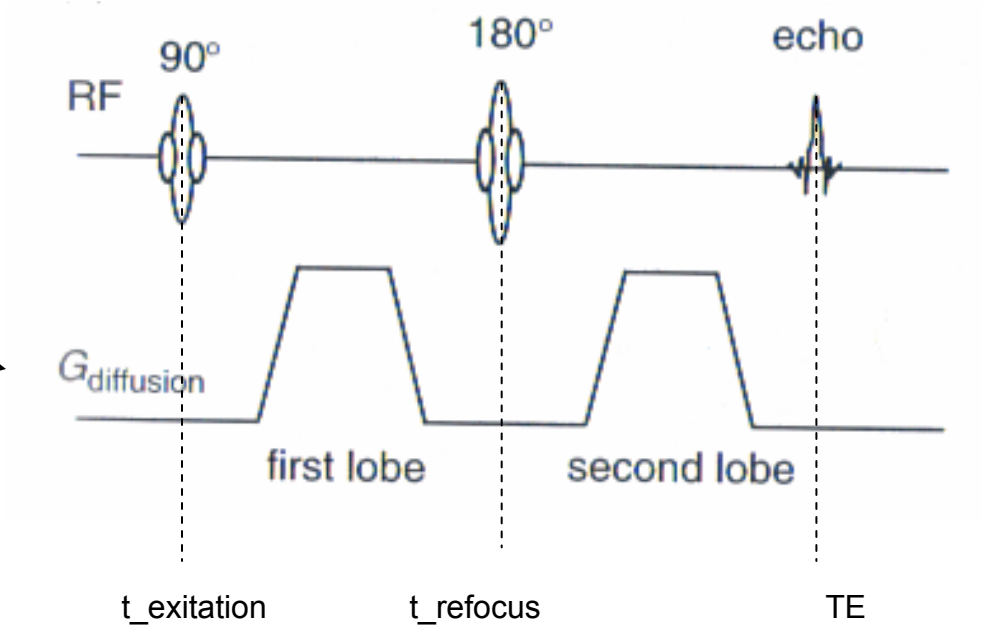
Diffusion Weighting Gradients

Diffusion weighting gradients

- Proposed by Stejskal and Tanner (1965).
- Increase the sensitivity of MRI signal to molecular diffusion.
- Consists of two lobes with ***equal*** areas, maximum amplitude allowed, and a longer pulse width than most of the imaging gradients
- Synonyms: Bipolar gradient, Stejskal-Tanner gradient.

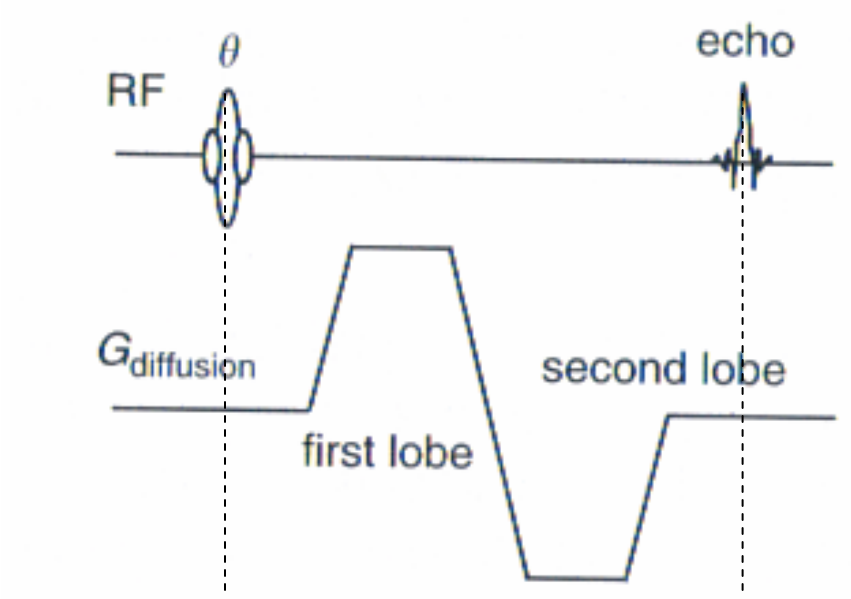
Spin Echo

Can be applied to any axis



$$\int_{t\_exitation}^{t\_refocus} G_d(t)\,dt = \int_{t\_refocus}^{TE} G_d(t)\,dt$$

Gradient Echo



$$\int_{t\_refocus}^{TE} G_d(t)\,dt = 0$$

- Using the diffusion weighting gradient will result in signal attenuation due to water diffusion.

- The degree of attenuation is proportional with:
  - Diffusion Coefficient, ***D*** (mm^2/s)
  - ***b***-value (s/mm^2)

Quantitative description

- The phase accumulated in the presence of a diffusion weighting gradient is:

$$\phi = \int_0^t \Delta\omega \, dt' = \gamma \int_0^t \vec{G}(t') . \vec{r}(t) \, dt'$$

Where:

- *r(t) is the location of a spins isochromat*
- *G(t') is the diff. grad waveform*

- Random moving spins will accumulate different phases, and because of their random motion, phases will cancel out and hence signal loss will occur.

- The resultant MRI signal *S* is related to the variance of a Gaussian phase distribution, $\Phi^{2:}$

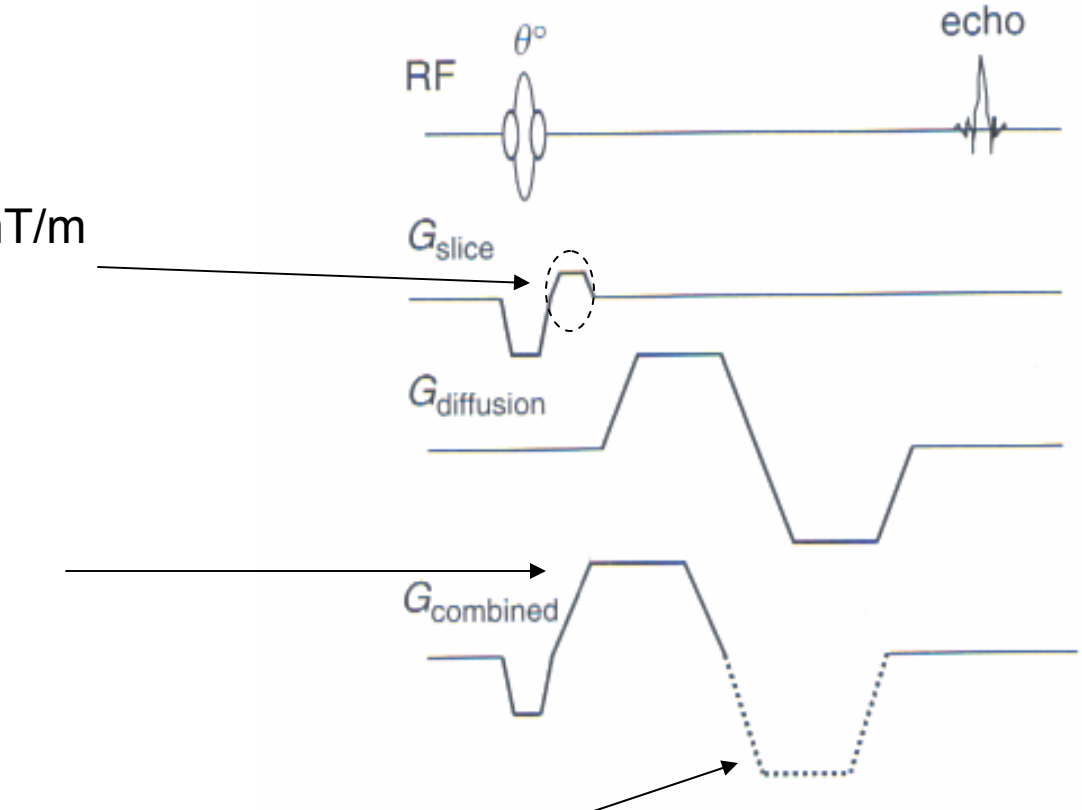
$$S = S_0 \exp(-\langle\Phi^{2}\rangle) = S_0 \exp(-bD)$$

Where:

  - S_0 *is the signal intensity in the absence of diffusion.*
  - *b-values depends on:*
    - » *Gradient shape & amplitude*
    - » *Separation of the lobes*
    - » *Pulse width*

Example

Area = 10 ms . mT/m



Combined gradient lobe:

- T_{ramp}= 2 ms
- $T_{plateau}$= 5 ms
- G = 30 mT/m

System parameters:

- *h = 40 mT/m*
- S_R = *150 T/m/s*

Design the 2nd waveform

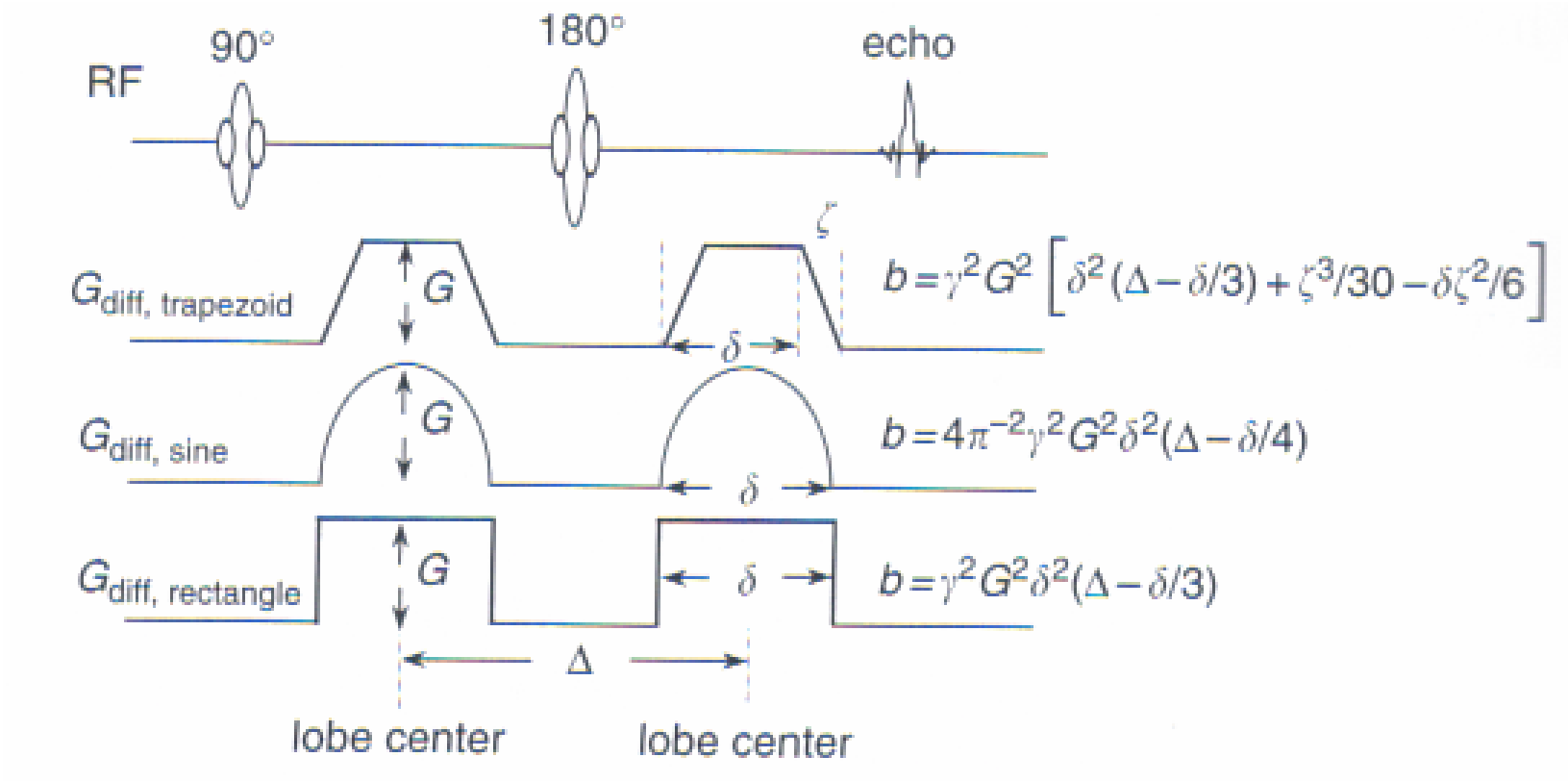
b-value

- b-value is related to an arbitrary waveform G(t) by:

$$b = (2\pi)^2 \int_0^{TE} \vec{k}(t).\vec{k}(t)\,dt$$

$$\vec{k}(t) = \frac{\gamma}{2\pi} \int_o^t \vec{G}(t')\,dt'$$

b-values for commonly used diffusion-gradient waveforms in SE



- Consider a rectangular gradient lobe of amplitude 25 mT/m and with a separation of 50 ms. To obtain a b-value of 1000 s/mm^2 we need the pulse width to be:

$$\delta = 22.99\,\mathrm{ms}$$

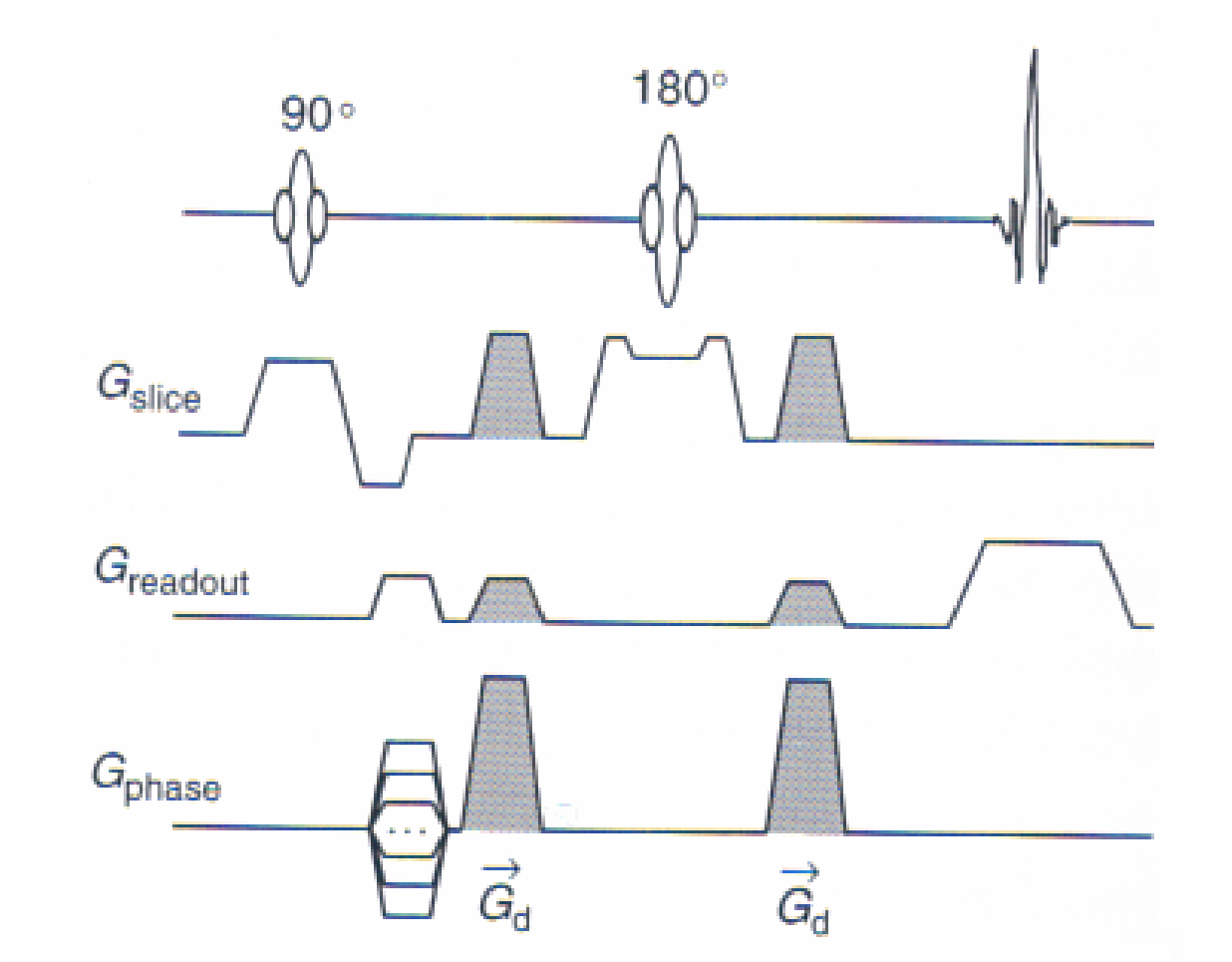
Problems associated with having high *b*-values

- Long TE
  - Reduces the SNR (wait longer time before reading the echo).
  - T_2 *shine through effect:* unwanted T_2 weighting in the diffusion weighted image.
- Concomitant fields (depends on G^2/B_0).
- Eddy currents
  - Geometric distortion (in diffusion weighted EPI pulse sequences).

Diffusion imaging pulse sequences

- Pulsed Gradient Spin Echo (PGSE).
- Single-shot-spin-echo EPI.
- RARE (FSE).
- Stimulated echo pulse sequences.

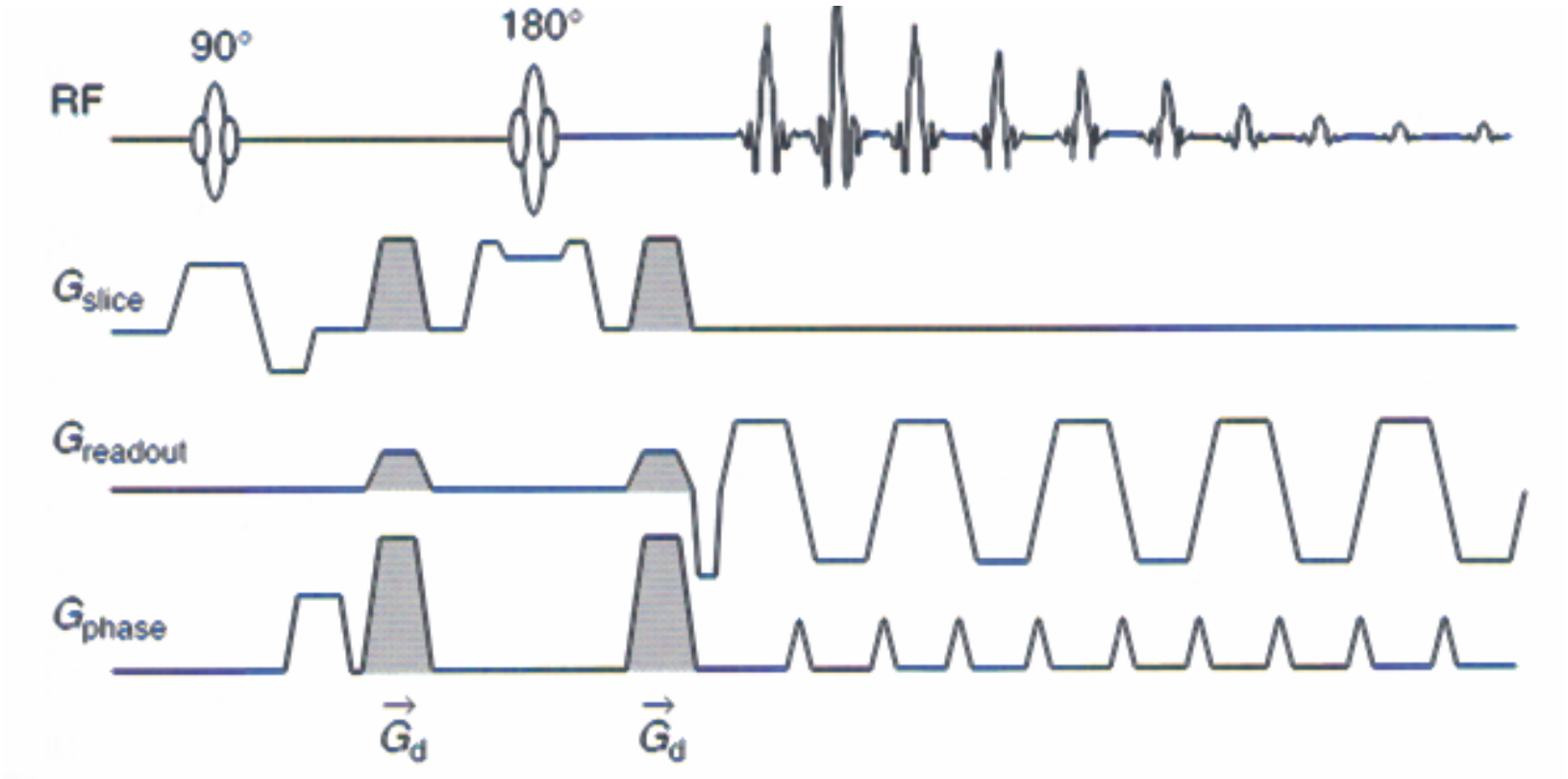
Diffusion weighted spin echo pulse sequences



S.E. pulse sequences cont'd

- Very long data acquisition (10-20 minutes).
- Needs motion correction, using *Navigator echoes.*
- *Excellent quality and high resolution images with minimum artifacts if motion induced phase error are corrected.*

Single-shot-spin-echo EPI

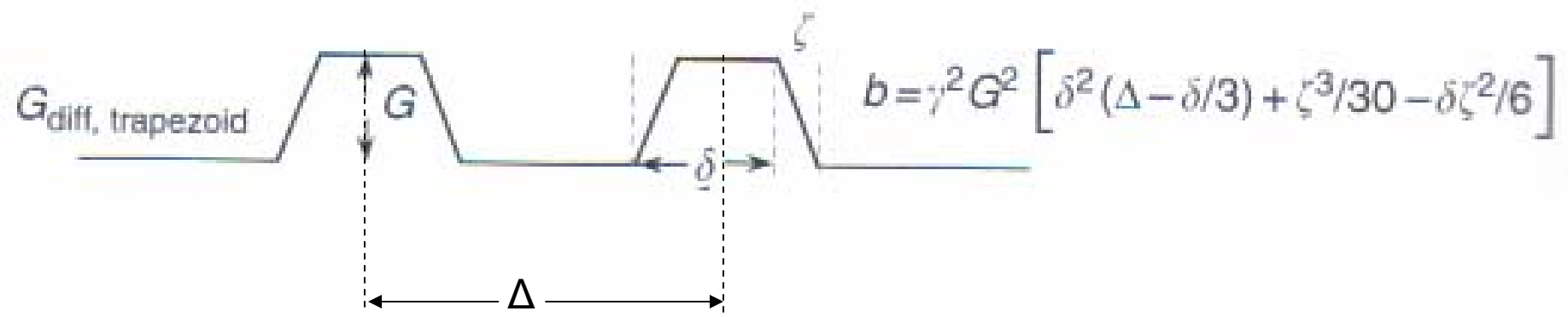


Single-shot-spin-echo EPI cont'd

- Most commonly used due to:
  - High acquisition speed (less than 100 ms/image)
  - High motion insensitivity
- How to increase the acquisition speed?

Reduce TE

How to reduce TE while keeping high *b*-value?



How to reduce TE while keeping high *b*-value?

- Use the maximal gradient amplitude and minimize the pulse width.
- Use “maximal slue rate”

  → problems:
  - Peripheral nerve stimulation.
  - Eddy current consideration, especially with the usage of diffusion-weighting gradients.

  – Beside of that, using higher slew rate will reduce the ramp time which is much smaller than the plateau time.

EPI Disadvantages

- Distortion due to susceptibility variation
  - Difficult to correct even when using high-order shimming
  - Susceptibility artifacts increase linearly with increasing B_0
- Nyquist ghosting due to eddy currents.

Diffusion weighted RARE (FSE) sequences

- Not commonly used as EPI.
- It is ***not*** straightforward to implement; since the diffusion-weighting gradient lobes will violate the CPMG condition.
- This will cause inconsistent phase errors between the spin echoes and the stimulated echoes, leading to signal loss.

Carr-Purcell-Meiboom-Gill (CPMG) conditions

1. Refocusing pulses must be
    1. 90^o out of phase with respect to the excitation pulse
    2. Evenly positioned with equal spacing between any two pulses
    3. The spacing between pulses must equal to twice the interval between the excitation and the first refocusing pulse.
2. Phase accumulated by a spin isochromat between any two consecutive refocusing pulses must be equal

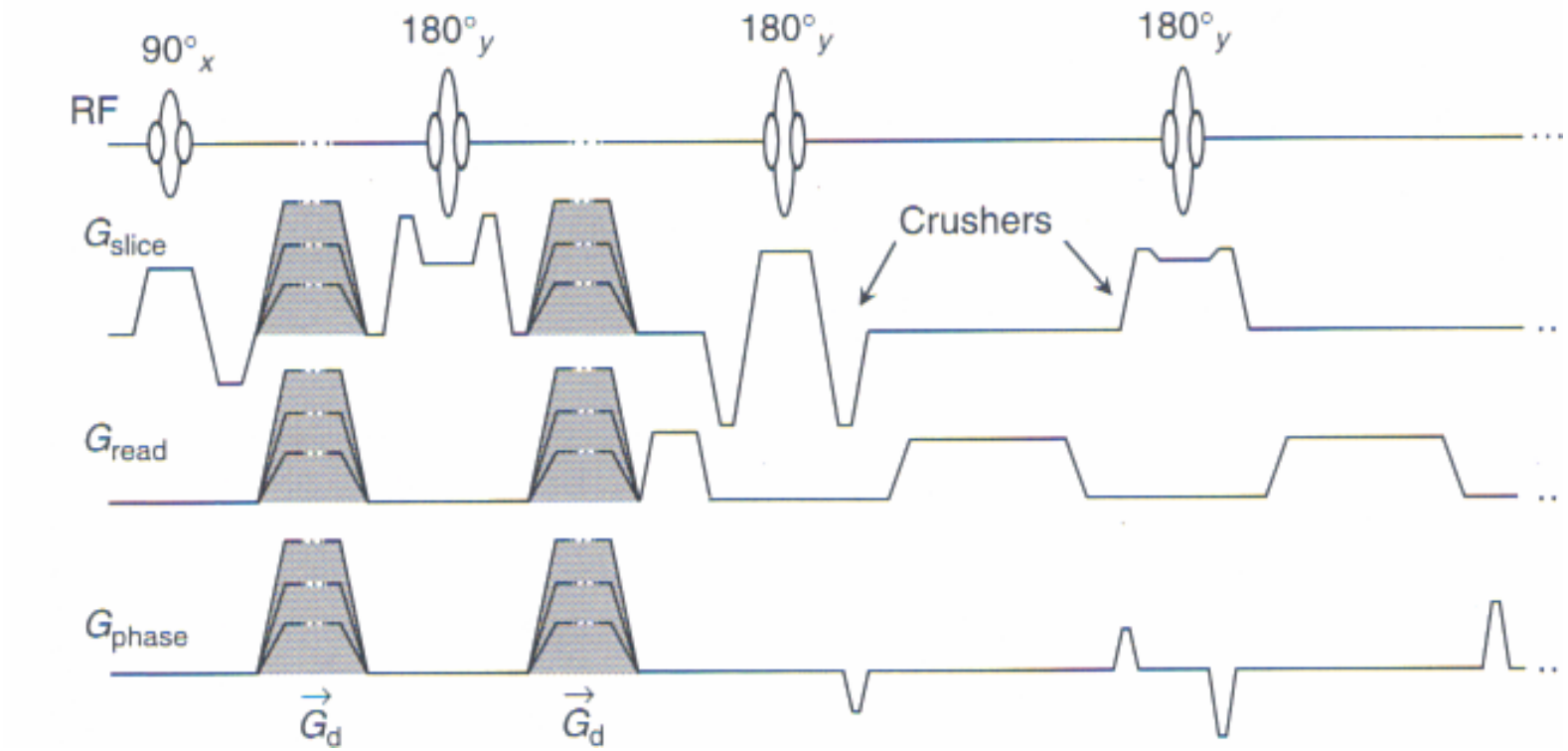
When these conditions are met, primary and stimulated echoes occur only at the mid-point between two consecutive refocusing pulses and carry the same phase

- To overcome the CPMG problem, different methods can be used:

A. Diffusion-weighted RARE pulse sequences with crushers

B. Split acquisition of fast spin echo signals for diffusion imaging (SPLICE)

A. Diffusion-weighted RARE pulse sequences with crushers



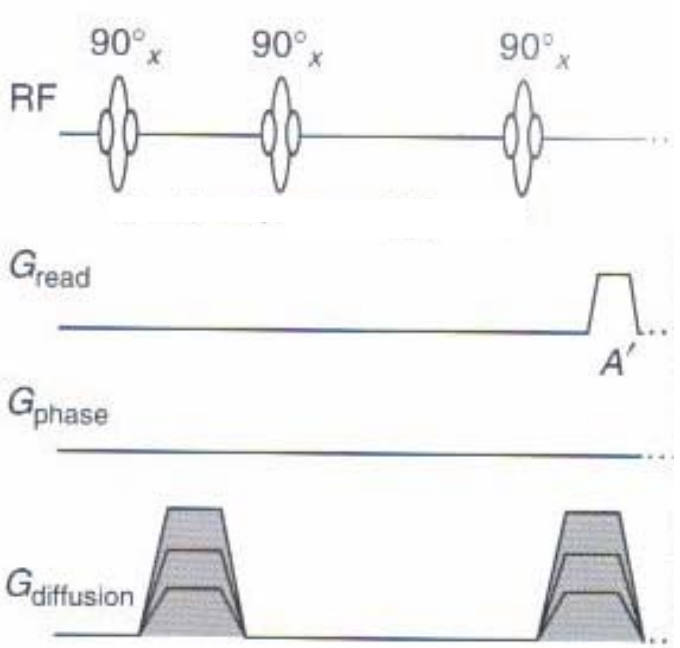
- Crushers will eliminate stimulated echoes while preserving the spin echo signals.

- This method does not satisfy the CPMG conditions, but signal loss could be minimized if
  - B_1 field is homogeneous
  - RF refocusing pulses are close to 180^o

B. Split acquisition of fast spin echo signals for diffusion imaging (SPLICE)

Diffusion Preparation:

- Prepare the transverse magnetization with the proper diffusion weighting.
- Store the diffusion-prepared magnetization in the longitudinal axis.
- Recall this magnetization by employing stimulated echoes.

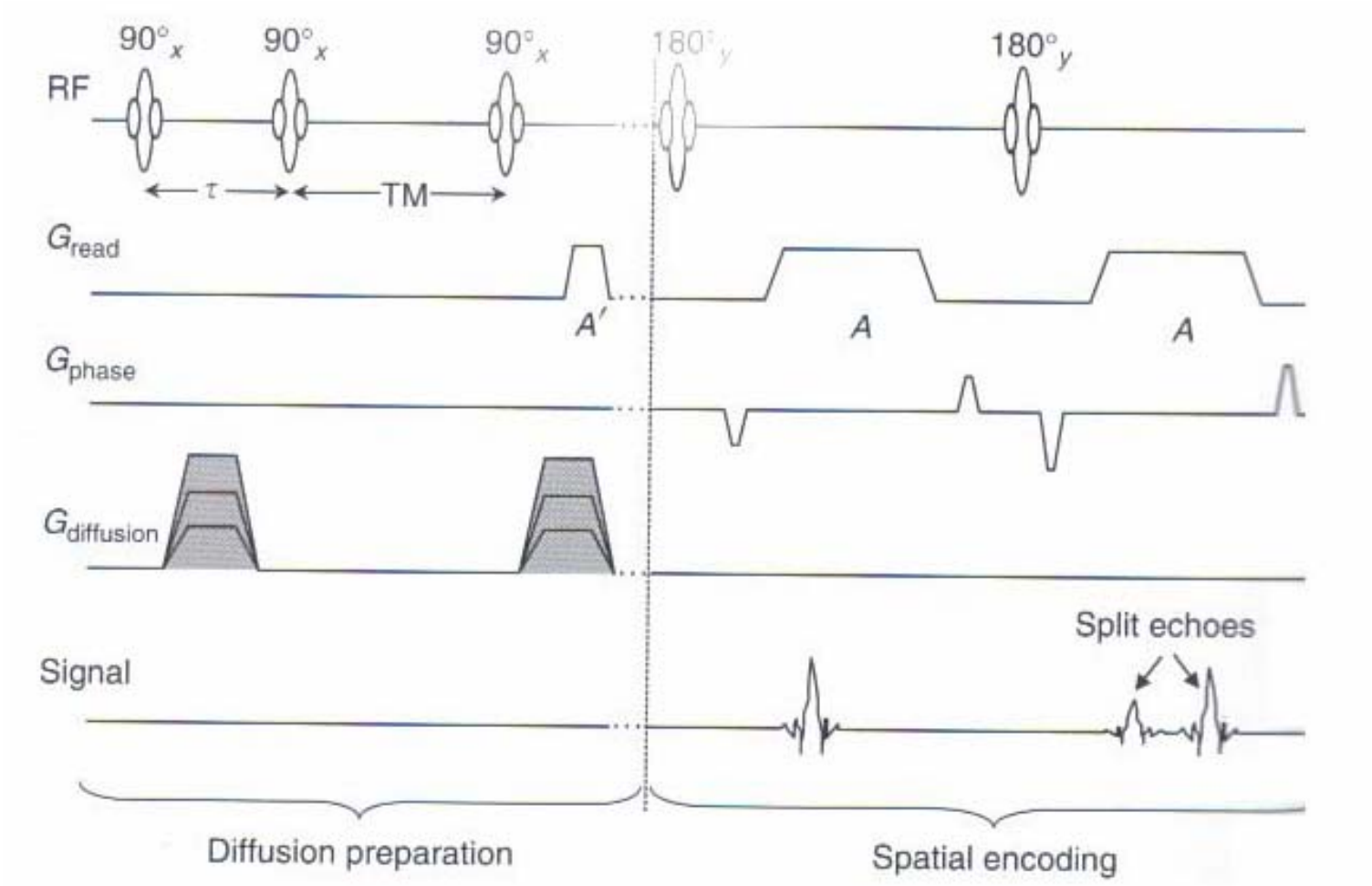


Advantages of diffusion preparation

- Diffusion weighting gradients will contribute to the lobe separation Δ, thus high *b*-values can be obtained.

- In the same time, storing the magnetization in longitudinal axis will ***not*** experience T_2 or T_2^* dephasing during the interval *TM.*

Split echoes of FSE for diffusion imaging Pulse Sequence

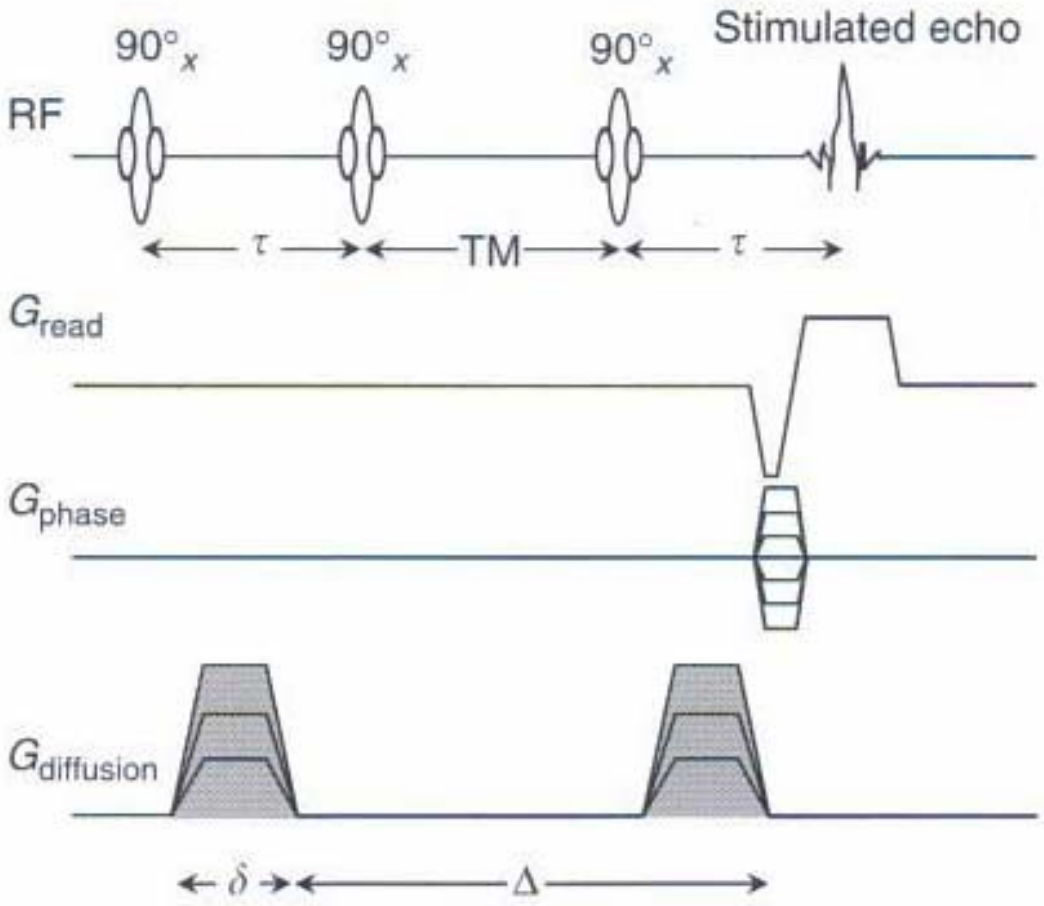


- Imperfect refocusing pulses and imbalanced readout gradient waveform are used. CPMG condition is violated and hence spin echoes and stimulated echoes are ***no*** longer in phase.

- After the first echo, two families of echoes will be formed in the echo train:
  - Spin echoes
  - Stimulated echoes

- Readout window is long so that two separate echoes are acquired. Then two separate DW images are reconstructed and their magnitudes are combined to improve the SNR.
- Problems:
  - Long reading window leads to image blurring and shorter echo train length.

Stimulated echo pulse sequences (STEAM)



STEAM cont'd

- High *b-values without incurring TE-induced signal loss.*
- Lower SNR compared to SE and SE-EPI sequences with the same TE; because the maximal amplitude of the stimulated echo is only one-half of that of the spin echo.

- High-speed DW STEAM can be obtained if the third RF pulse is replaced by a series of low flip angle pulses separated by short TR.

Review

- Introduction.
- Diffusion sensitizing gradients.
- Diffusion imaging pulse sequences.
- Diffusion basics.
- Diffusion Imaging techniques:
    - Diffusion weighted imaging.
    - Quantitative apparent diffusion coefficient.

Basics of diffusion

- Einstein equation describes the behavior of unrestricted diffusion of molecules:

$$r_{rms} = \sqrt{2Dt}$$

Where:

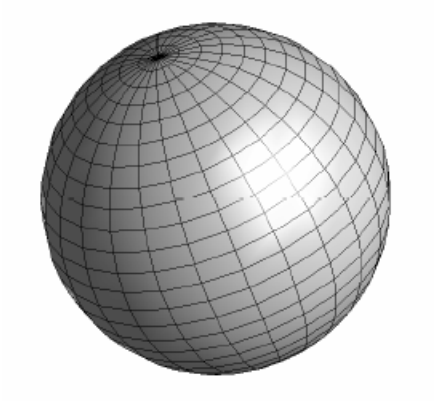
- r_{rms} is the 1D root-mean-squared displacement (distance)
- *D* is the diffusion coefficient (distance^2 / time)
- t is the diffusion time

Factors that affect diffusion

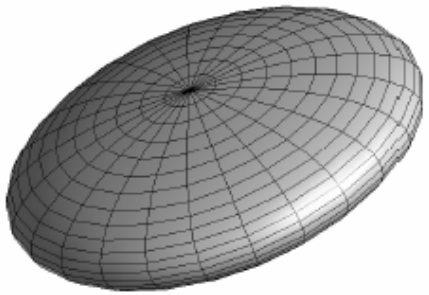
- Presence of macromolecules, organelles, cell membrane and other cellular and sub-cellular structures.
- These structures act as “obstacles” to molecular diffusion and so reduce the diffusion coefficient of water.
- For example, intracellular diffusion coefficient is less than extracellular space due to higher concentration of organelles inside the cells.

Diffusion models

- Isotropic
  - No orientation dependence.



- Anisotropic
  - Diffusion depends on spatial orientation.



Diffusion tensor

- To express the diffusion direction mathematically, diffusion can be expressed as a 2nd rank tensor:

$$\overset{\Rightarrow}{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

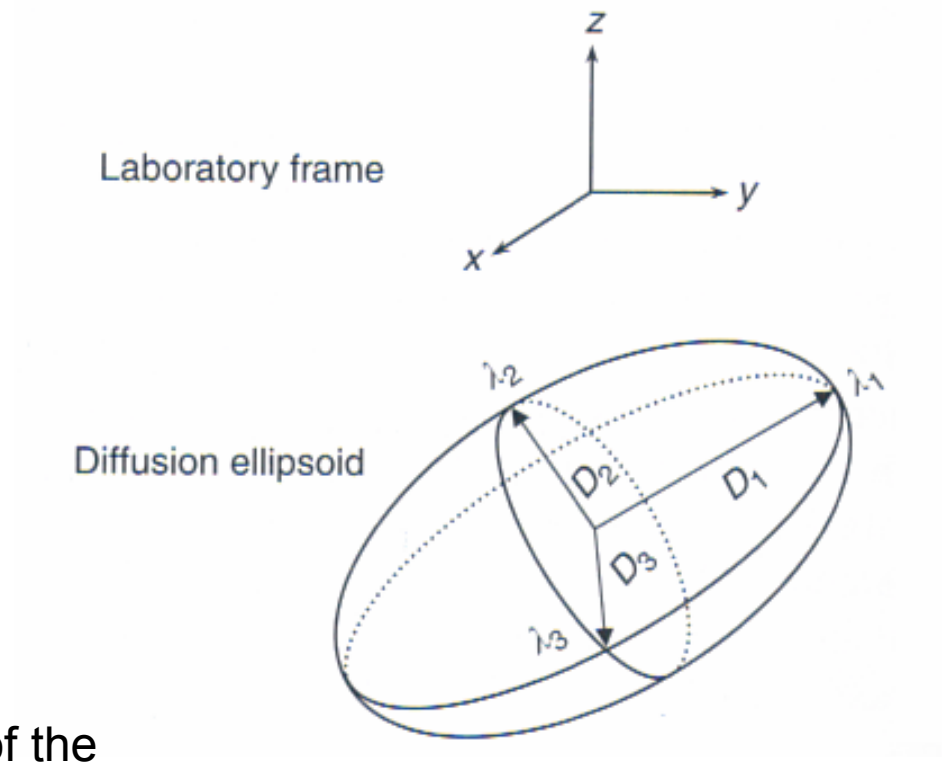
$$\overrightarrow{\overrightarrow{D}} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

Where:

- Diagonal elements represent the diffusion coefficient along that direction (in Laboratory frame of reference).
- The off-diagonal elements represent the degree of correlation between random motion in two directions.
- All the elements are *real* and the matrix is *symmetric.*

Diffusion models cont'd

$$\begin{cases} r_1 = \sqrt{2D_1 t} \\ r_2 = \sqrt{2D_2 t} \\ r_3 = \sqrt{2D_3 t} \end{cases}$$



Diffusion boundary is the surface of the diffusion ellipsoid.

Isotropic vs. Anisotropic

- Cerebrospinal fluid (CSF):
  - Isotropic diffusion (fast diffusion).
  - Off diagonal elements of the diffusion tensor are zeros.
  - Diagonal elements are equal; $D_{xx} = D_{yy} = D_{zz} = D$

- White matter and Skeletal muscle:
  - Anisotropic diffusion.
  - Diffusion coefficient along fiber tract is much larger than of other directions:

    (Principal diffusion direction)
  - Can reveal fiber orientation and connectivity.

Diffusion imaging techniques

- Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC), *Le Bihan 1986.*
- Diffusion Tensor Imaging (DTI), *Basser 1994.*
- Magnetic Resonance Tractography, *Xue 1999*
- q-space imaging*, Callaghan 1991.*
- High Angular Resolution Diffusion (HARD) imaging, *Frank 2002.*

I. Diffusion Weighted Imaging (*DWI)*

- Basic diffusion relation:

$$S = S_0 e^{-bD}$$

Where:

- S: Voxel intensity with diffusion weighting
- S_0: Voxel intensity *without* diffusion weighting
- D: Diffusion coefficient along the gradient direction
- *b: The b-value*

- Contrast of DW image depends on the gradient direction, i.e., contrast is spatially dependent.
- To remove this dependence, apply three gradients along three orthogonal directions and take the mean of the resulting diffusion coefficients .

$$S_x = S_0 e^{-b_{xx} D_{xx}}$$

$$S_y = S_0 e^{-b_{yy} D_{yy}}$$

$$S_z = S_0 e^{-b_{zz} D_{zz}}$$

Note that D_{xx}, D_{yy}, D_{zz} are the diagonal elements of the diffusion tensor

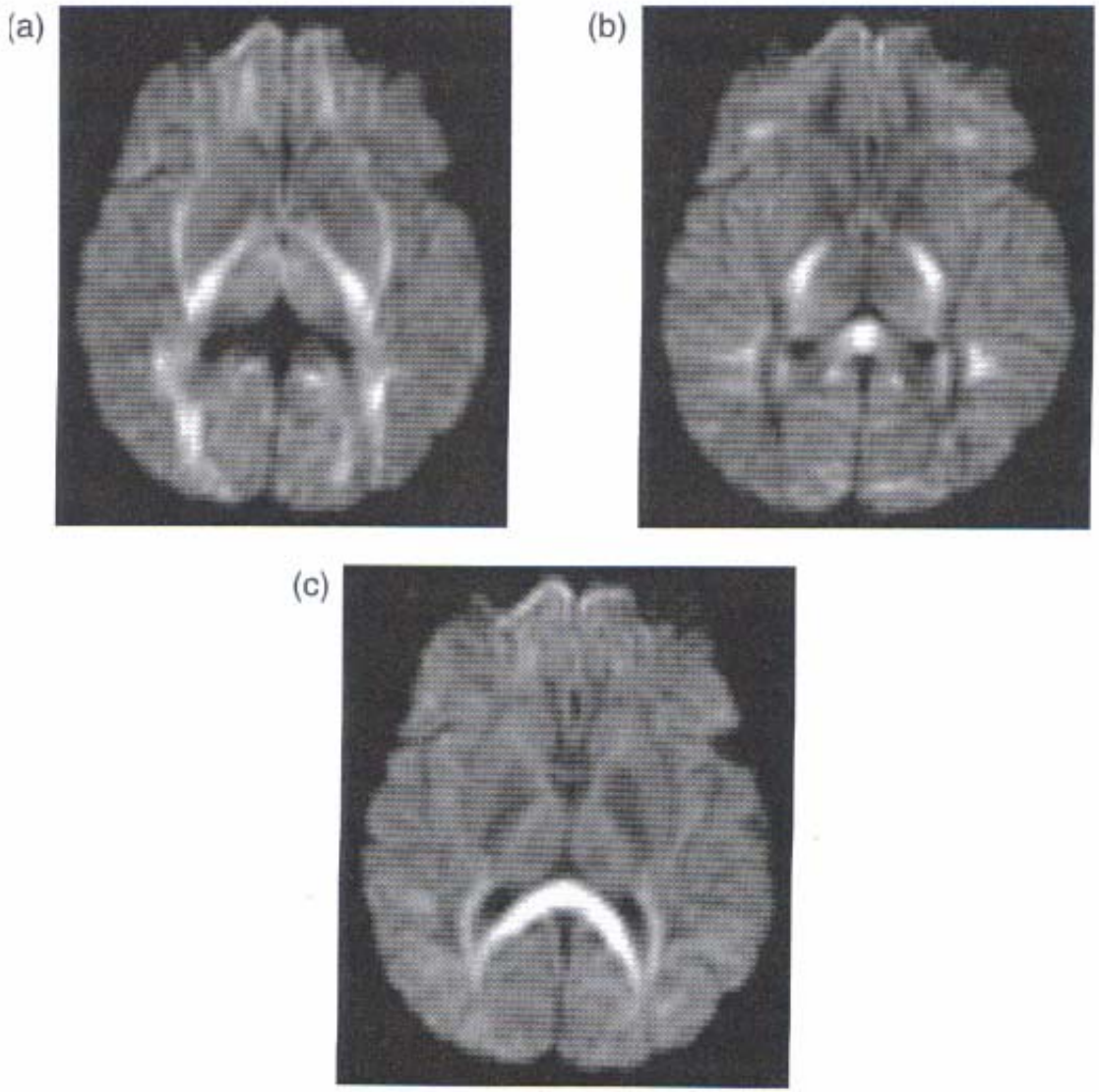


FIGURE 17.18 Three diffusion-weighted images acquired with the same *b*-value, but different gradient directions. Images are acquired with gradients along the (a) right-left, (b) anterior-posterior, and (c) superior-inferior directions.

- If $b_{xx} = b_{yy} = b_{zz} = b$, *then the geometric mean of the three signals is:*

$$S_{xyz} = \sqrt[3]{S_x S_y S_z} = S_0 e^{-b(D_{xx}+D_{yy}+D_{zz})/3} = S_0 e^{-b\ D_{trace}/3}$$

Where:

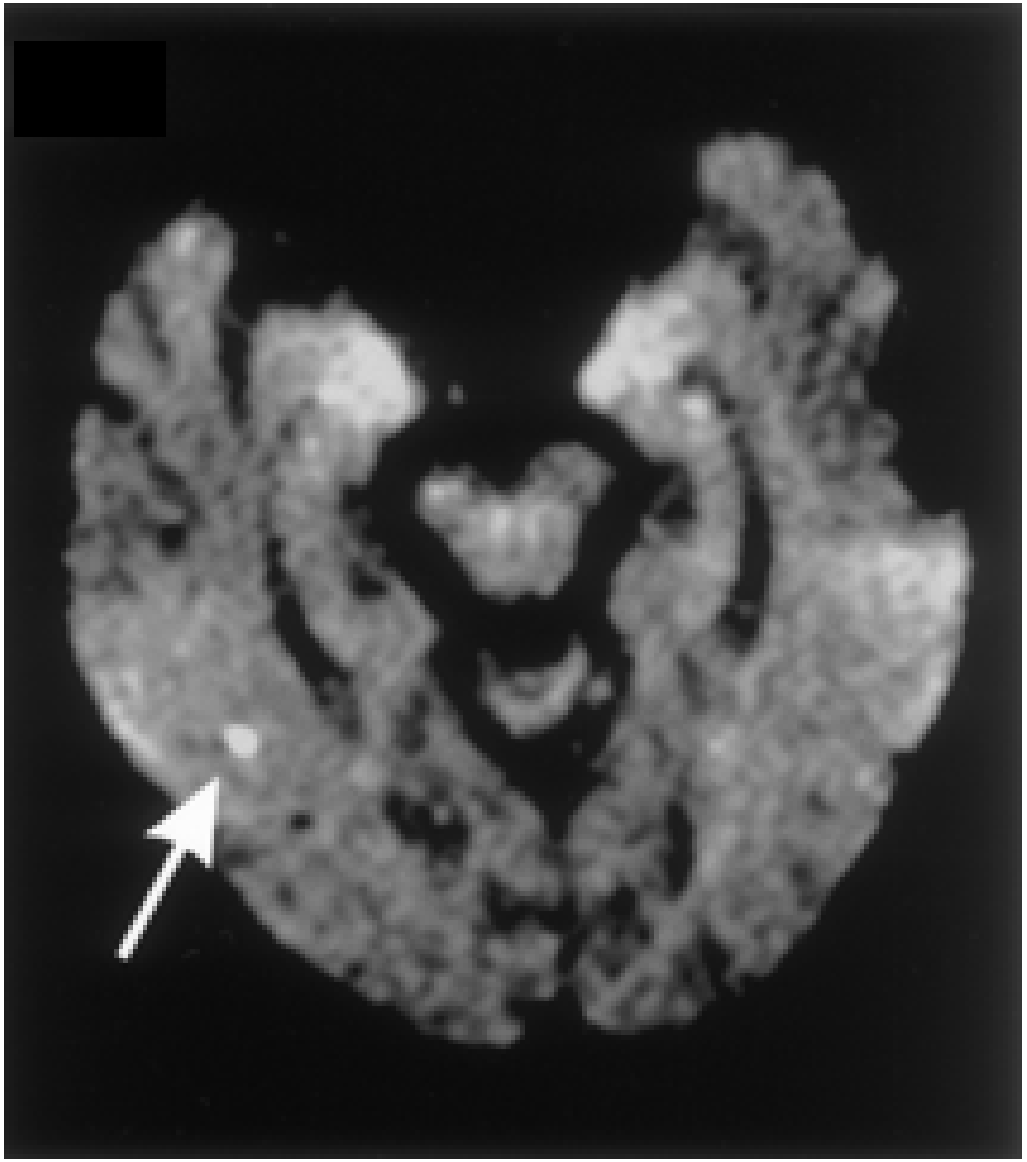
- D_{trace}: is the sum of the diffusion tensor diagonal elements

Diffusion Trace weighted "or Isotropic" DW image

- Clinical application of DWI: Cerebral Ischemia

  – Early detection of cerebral ischemia.

  – Infected regions exhibit hyperintense signal compared to healthy brain tissue, which is not observed by T_1 and T_2.



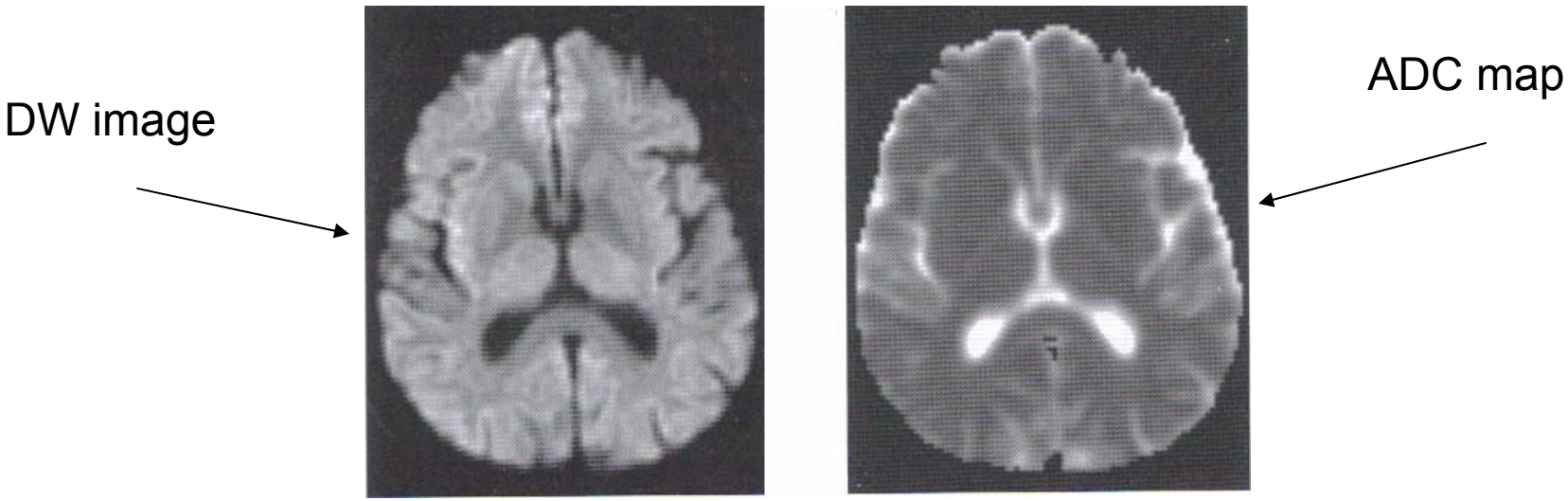
II. Quantitative Apparent Diffusion Coefficient (ADC)

- A series of DW images acquired with multiple *b*-values:

$$S_1 = S_0 e^{-b_1 D}, S_2 = S_0 e^{-b_2 D} \ldots S_n = S_0 e^{-b_n D}$$

- S_0 should be calculated separately without any diffusion weighting, and S_i to be calculated with different *b-values.*
- Each signal may represent the geometric mean to remove the orientation dependence
- Diffusion map is reconstructed on pixel by pixel basis in two ways:
  - Linear regression fitting.
  - Nonlinear fitting.

- Linear fitting:
  - Between $\ln(S_0/S_i)$ and b_i to obtain the diffusion coefficient map D.
  - Image contrast is inverted compared to DW image.



- Nonlinear fitting (exponential diffusion image):
  - Similar to the one of T_2 mapping based on a series of T_2-weighted images with varying TE.
  - Perform the nonlinear fit based on the exponential relation:

$$S = S_0 e^{-bD}$$

Example

- Diffusion weighting gradient, b = 500 s/mm^2
- Imaging gradients contribution, b = 40 s/mm^2
- Measured DW signal: S = 0.4 S_0
- Find *D*
  - Neglecting imaging gradients
  - Considering image gradients
- Solution
  - *D = ln(0.4)/-500 = 1.8 x 10^{-3} mm^2/s*
  - *D = ln(0.4)/(-540) = 1.7 x 10^{-3} mm^2/s*

  So D will be overestimated if the imaging gradients contribution is not considered

Total gradients contribution to the *b*-value

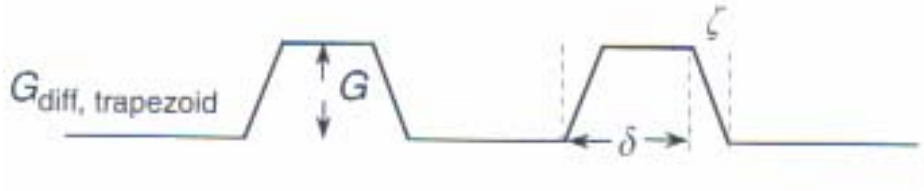
Cross term

$$b = c_1 G_d^2 + c_2 G_d G_{im} + c_3 G_{im}^2$$

Where:

- *G_d is the diffusion gradient*
- *G_{im} is any imaging gradient*
- *c_1, c_2 and c_3 are constants that depends on the gradient used.*

$$c_1 = \gamma^2 [\delta^2 (\Delta - \frac{\delta}{3}) + \frac{\zeta^3}{30} - \frac{\delta \xi^2}{6}]$$



- Cross terms:
  - Cross terms varies with gradient direction since imaging gradients waveforms differ along the three axes.
  - Imaging gradients contribution:
    - False diffusion anisotropy.
    - Overestimation of the *ADC value.*
  - Cross-term correction for readout and slice-selection can be used (but not the phase encoding, why?)

Biexponential Decay

- In some tissues (e.g. brain), diffusion signal follows a biexponential signal decay according to:

$$S = S_0(\zeta e^{-bD_f} + (1-\zeta)e^{-bD_s})$$

Where:

- ξ and (1-ξ) are the compartmental fractions.
- D_f is the fast diffusing component.
- D_s is the slow diffusing component.

Shine through effect

- The effect of T_2 tissue relaxation in diffusion imaging.
- To minimize the Shine through effect:
  - Have a long TR
  - Short TE ($TE<3T_2$)
- Use quantitative ADC mapping to reduce TE. How?
  - Use only two values *b*-values, one without diffusion (S_0) and the other with diffusion weighting (*b=1000 s/mm²).*
  - *Obtain ADC directly by solving* $S = S_0 e^{-bD}$