

Diffusion MRI Theory Methods and Applications

Topic: Magnetic Resonance Diffusion Imaging: Introduction and Concepts

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Contents

- Basic Schemes for Sensitization of MR Images to the Diffusion Process
- Specific Issues in Implementing Diffusion MRI
- What Do We See in the Water Diffusion Maps?

- **Diffusion coefficients** may be determined by measuring the concentration of molecular species at different times using either physical or chemical methods based on the classical **first Fick law**.
- Spatially resolved methods can also be used, such as infrared spectroscopy or Rayleigh scattering or even magnetic resonance imaging (MRI) to study the diffusion of contrast agents.
- Einstein's equation: $\langle X \rangle^2 = 2DT_d$, where $\langle X \rangle^2$ is the average mean-squared diffusion distance along one direction and T_d is the diffusion time.

Basic Schemes for Sensitization of MR Images to the Diffusion Process

- Constant Field Gradient Spin Echo
- Pulsed Field Gradient Spin Echo (PFGSE)
- Stimulated Echo Sequence
- Gradient Echo Techniques

- Most diffusion MRI studies have been based on the seminal work of Stejskal and Tanner (1965), who introduced the **pulsed field gradient (PFG)** method.
- It is only the component (or projection) of the diffusion displacements parallel to the direction of the magnetic field gradient which has an effect.

Constant Field Gradient Spin Echo

- In the presence of a time invariant, constant gradient G_0 , the attenuation of the signal $A(n, TE) = \exp(-\gamma^2 G_0^2 DTE^3 / 12n)$.
- The presence of a constant gradient during the radiofrequency (RF) pulses of the imaging sequence
 - severely impairs the selected slice profile.
 - results in a broadening of the bandwidth and a signal-to-noise (SNR) reduction.
- Constant background magnetic field gradients results from
 - magnetic susceptibility differences between tissues.
 - the presence of **bulk magnetic susceptibility (BMS)** contrast agents (or deoxyhemoglobin) in the vasculature.

Pulsed Field Gradient Spin Echo (PFGSE)

- The echo attenuation is given by (Stejskal and Tanner, 1965):
$$A(TE) = \exp(-\gamma^2 G^2 D \delta^2 (\Delta - \delta/3)).$$
- Only the component of the molecular diffusion motion along the direction of the gradient pulses is sampled, not the three-dimensional motion.
- However, the realistic shape of the gradient pulses must be considered, since rectangular pulses are not achievable on clinical scanners.
- Diffusion may then become the ultimate parameter to limit the achievable spatial resolution.
- The minimum length of molecular diffusion paths detectable with gradient-pulsed NMR is primarily determined by the intensity of the gradient pulses.

- Lack of gradient power is usually compensated by using somewhat longer gradient pulse widths, so that the classical condition $\delta \ll \Delta$ is never satisfied.
- If the duration of the pulses is ignored, significant underestimation of the diffusion distances may result.
- Another problem arising when increasing Δ is that TE must be increased and substantial signal loss occurs through T_2 relaxation.
- In practice, one gets the highest sensitivity by placing gradient pulses simultaneously on the three axes or by disposing the imaging and diffusion-sensitizing gradient pulses.
- However, blank intervals are usually necessary to minimize the effects of **eddy currents** that may be induced by the switching of such strong gradient pulses.
- An elegant solution to reduce eddy currents is to use a pair of sinusoidal gradient pulses, as the time variations in gradient amplitudes are smoother than with square pulses.

Figure 5.1a Two-dimensional Fourier transform scheme.

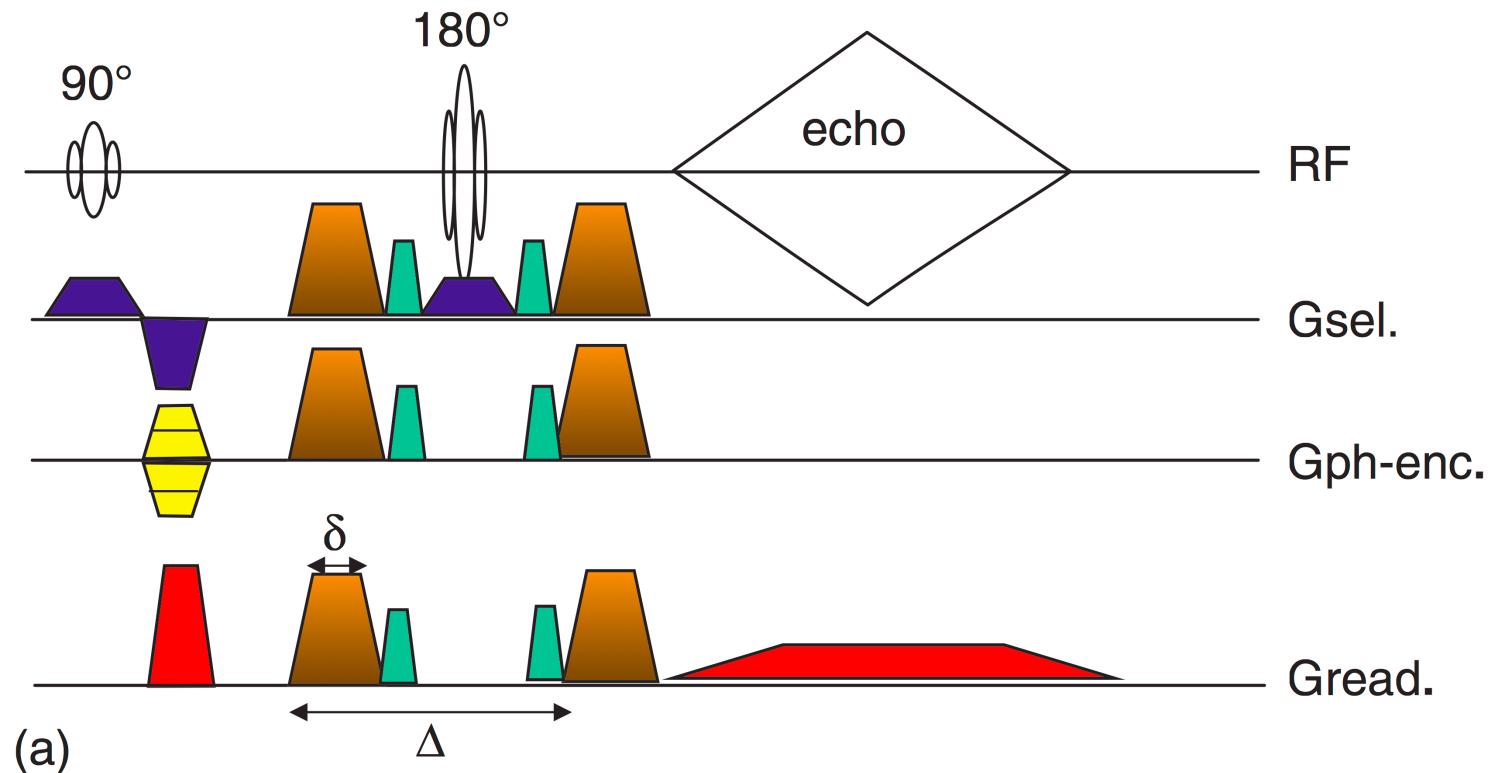
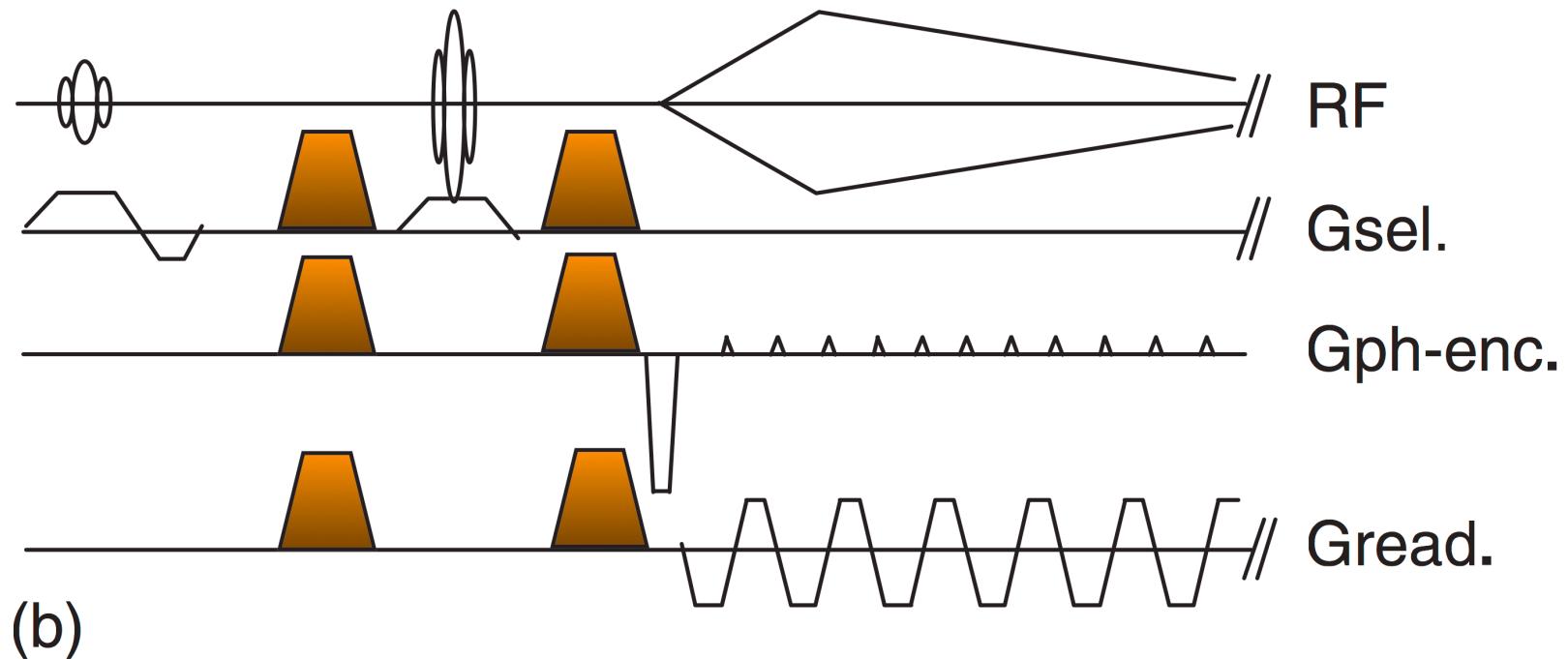
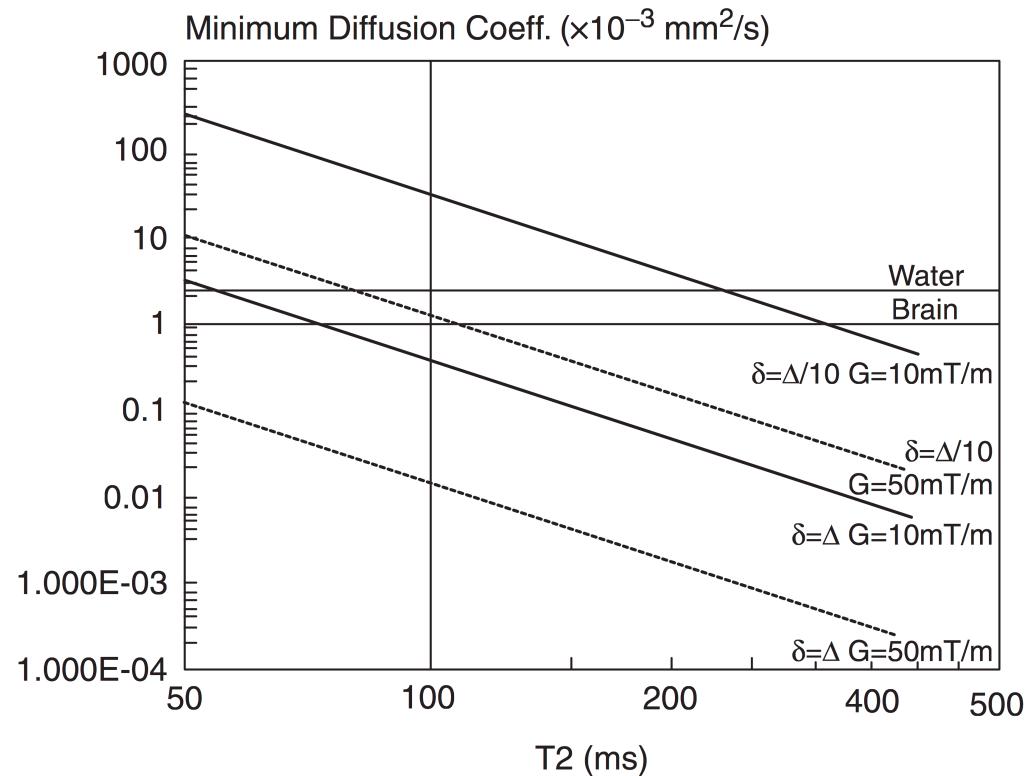


Figure 5.1b Echo-planar imaging scheme.



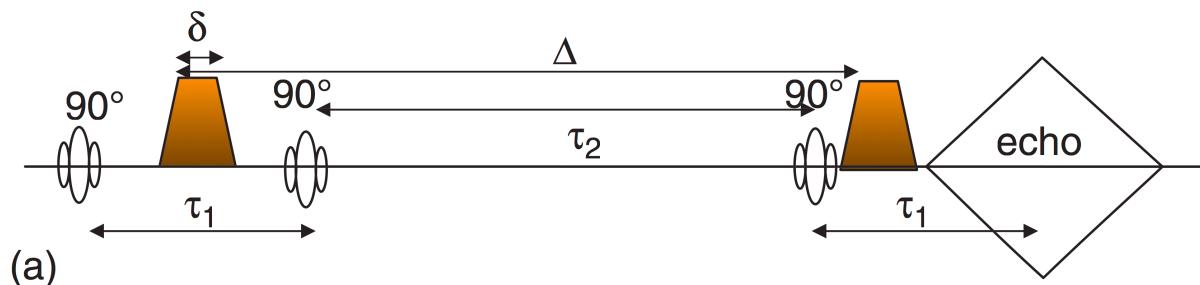
- On the right side of the 180° RF pulse, the diffusion gradient pulse usually fills up as much of the available time interval between the right crusher pulse (green) and the readout (Gread.) gradient (red) as possible in order to maximize gradient duration and b-value.
- The largest b -values are obtained by inserting the left diffusion gradient pulse as early as possible in the sequence.

Figure 5.2 Minimum measurable diffusion coefficient.



Stimulated Echo Sequence

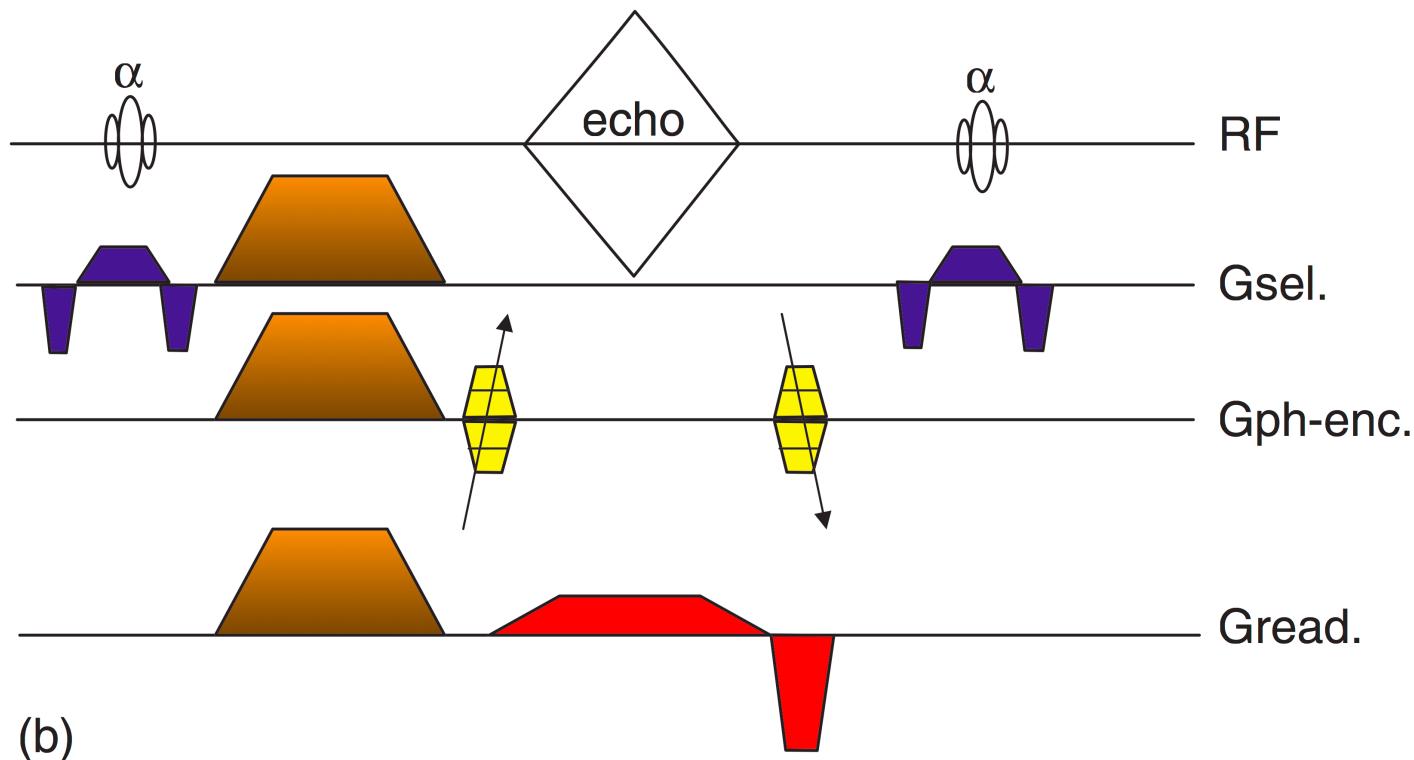
- The **stimulated-echo sequence**, which allows the effective diffusion time to be increased without penalizing the signal by T_2 relaxation effects.
- A stimulated echo is generated from a sequence consisting of three radiofrequency (RF) pulses separated by time intervals τ_1 and τ_2 .
- Gradient pulses must be inserted within the first and the third periods of the stimulated echo sequence.



Gradient Echo Techniques

- Because gradient-echo sequences are sensitive to T_2^* , which is generally shorter than T_2 , echo times must be even shorter than with spin-echo sequences to maintain good SNR, which makes it impractical.
- The effects of diffusion and relaxation are intrinsically mingled.
- Steady-state free precession (SSFP) sequence remain a fast way of performing diffusion MRI with high signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR).

Figure 5.3b Steady-state free precession (SSFP) sequence.



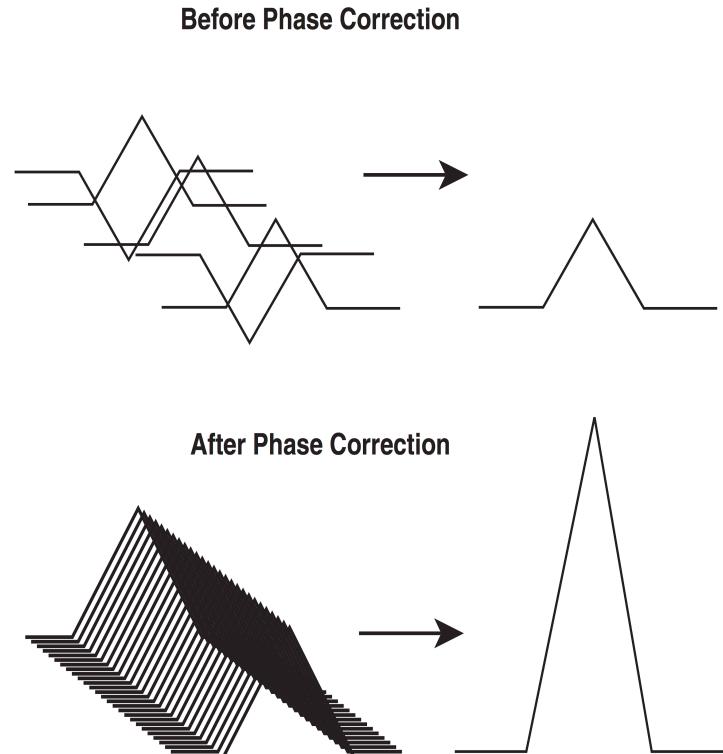
Specific Issues in Implementing Diffusion MRI

- Encoding Schemes
- Gradient Interactions, the b -Factor, and the b -Matrix
 - Imaging gradients
 - Anisotropic diffusion
 - Background gradients
- Other Approaches
 - Multiple PG sequences
 - Non-Multi-Pulse Gradient schemes
 - Diffusion spectroscopic imaging

Encoding Schemes

- Once a diffusion-sensitizing sequence has been chosen for contrast, a spatial encoding scheme must be chosen.
 - Spin echo **two-dimensional Fourier transform (2DFT)** imaging method
- Motion (and flow) is responsible for a net phase shift of the echo without signal loss.
- Artifacts result if discontinuities occur between the cycles (and corresponding k-space lines) of the imaging sequence.

- The successive phase shifts appear as incoherent if motion (or flow) varies from line to line.
- Results of such temporal incoherence are commonly visible as 'ghosts' along the phase-encoding direction.
- These ghosts are particularly intense in the presence of the diffusion gradients and render the diffusion measurements meaningless.



- **Cardiac gating** has been used to mitigate this problem (so that motion pattern remains identical from line to line).
- It is difficult to compensate diffusion imaging sequences for motion, since the use of successive bipolar gradient pulses considerably reduces sensitivity to diffusion.
- Other encoding schemes have been investigated, which are either less prone to motion artifacts or are faster, such as
 - Line-integral projection reconstruction
 - Stimulated-echo sequences associated with low-flip angle fast sequences
 - Single-shot technique, such as echo-planar imaging (EPI)

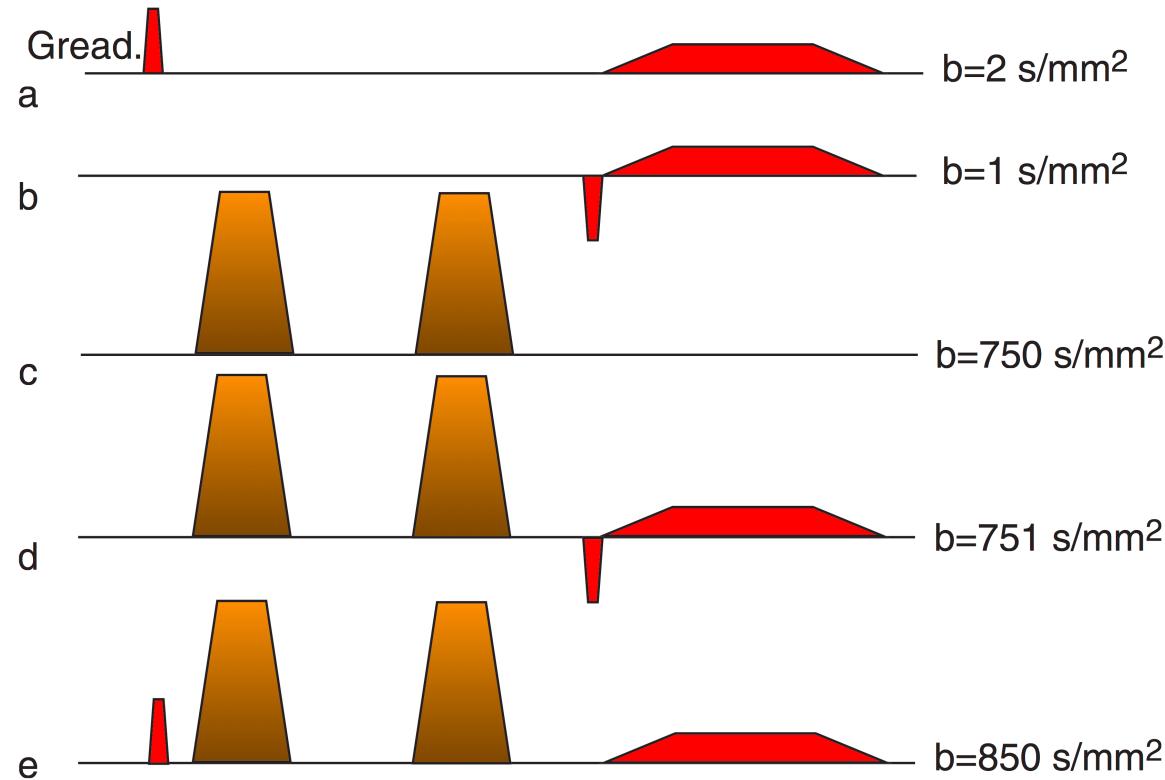
- EPI is obtained by switching the echo signal formation in a train of gradient echoes, by means of a large gradient whose polarity is very rapidly inverted, as many times as are required to achieve the desired image resolution.
- With EPI, motion artifacts are virtually eliminated. The accuracy on diffusion achieved with EPI is generally extremely good, as many images differently sensitized to diffusion can be generated and averaged or combined because of the very short acquisition time per image.
- The EPI technique is the method of reference for in vivo diffusion imaging, although it is very vulnerable to susceptibility artifacts responsible for image distortion or signal dropout, and to chemical shift artifacts that require efficient fat suppression.

- Gradient instability may arise when gradient amplifiers are driven hard for fast switching of large gradient intensities. Variations from shot to shot of the bipolar gradient balance result in widely distributed ghost artifacts and signal dropouts.
- Eddy currents are generated mainly in the cryostat when switching rapidly large gradient pulses. Eddy currents may also be a major cause of image distortion and misregistration
- Eddy currents can be removed at the source by using actively shielded gradient coils, which have no fringe fields and thus do not generate eddy currents.

Imaging gradients

- When inserting gradient pulses for diffusion sensitization, the combination of the imaging and the diffusion gradient pulses produce cross-terms, which lead to significant diffusion-related attenuation effects.
- A more general formalism must then be developed to solve the Bloch-Torrey equation, including all gradient pulses present in the sequence
- It was suggested very early on to summarize all gradient effects (diffusion and imaging pulses) in a term generally known as the ***b*-factor**: $b = \gamma^2 \int_0^{TE} [\int_0^t G(t') dt']^2 dt$.
- The signal attenuation is then reduced to a simple, convenient expression: $A = \exp(-bD)$.

Figure 5.5 Effect of cross-terms between imaging and diffusion gradient pulses (gold trapezoids) on the b -value.



Anisotropic diffusion

- The proper way to address anisotropic diffusion is to consider the **diffusion tensor**.
- Diffusion is no longer characterized by a single scalar coefficient but by a symmetric tensor, D , which fully describes molecular mobility along each axis and correlation between displacements along these axes.

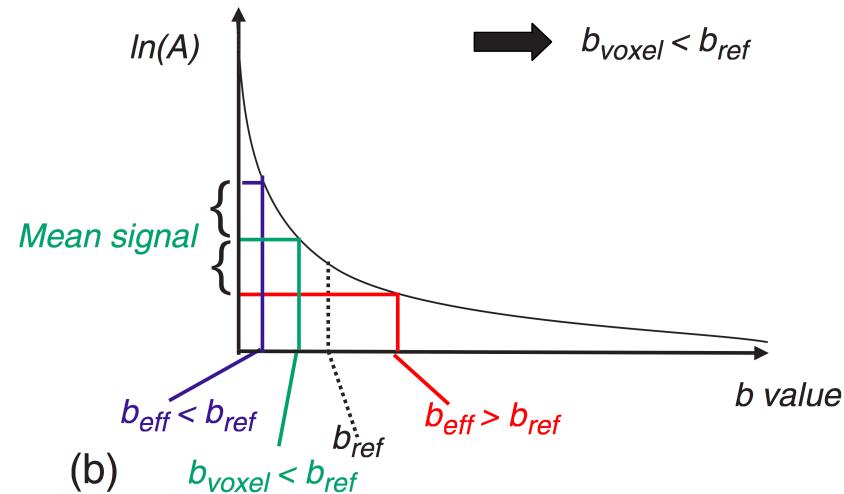
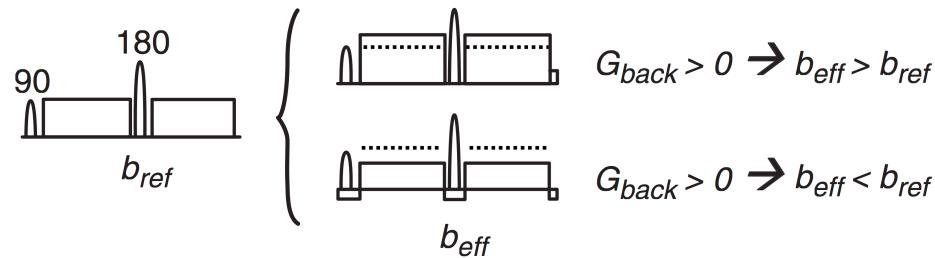
$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

- In practice, measurements are made in the reference frame [x,y,z] of the gradients, and therefore, the echo attenuation then becomes: $A = \exp(-\sum_{i=x,y,z} \sum_{j=x,y,z} b_{ij} D_{ij})$.

Background gradients

- Local gradient inhomogeneity may arise from the imperfect shimming of the magnet and from field inhomogeneities in the sample.
- If cross-terms with the background gradients are not eliminated, the logarithm of the echo attenuation, A , is no longer linear with the b -factor.
- Simulations and experiments have shown that when local gradients are randomly distributed in space for their orientation, the b -factor is physically decreased.
- Gradient inhomogeneity results in a local decrease of the b -factor and leads to an apparent decrease of the diffusion coefficient when using without correction.
- Corrected b -factor: $b_{eff} = b[1 - 0.5\gamma^2 \Delta \sigma^2 D(TE - (\Delta - \delta)/2)^2]$, where σ^2 is the variance of the local gradients assuming a Gaussian distribution.

Figure 5.7 Effects of background gradients.



Multiple PG sequences

- In the context of diffusion anisotropy, multiple pairs of gradient pulses may allow the cancellation of orientation effects.
- Another important domain is the elimination of cross-terms with background gradients and eddy currents.

Non-Multi-Pulse Gradient schemes

- Diffusion measurements can also be achieved by means of the RF (B1) field.
- With RF gradients, extremely short switching times can be achieved, since there are no eddy currents from gradient hardware.

Diffusion spectroscopic imaging

- diffusion measurements of larger molecules that are more tissue- or compartment-specific appear to be more promising for tissue characterization.
- molecular diffusion coefficients usually obey the Stoke-Einstein equation, linking the diffusion coefficient with the molecular size

What Do We See in the Water Diffusion Maps?

- Diffusion-Weighted MRI and Diffusion Maps
- IVM and the Apparent Diffusion Coefficient Concept
 - Intravoxel incoherent motion
- Elementary Diffusion Processes in Biological Tissues
 - Restricted diffusion
 - Permeable barriers
 - Tortuosity
 - Interaction with macromolecules
 - Interaction with polar surfaces
 - Hindered diffusion

- A Global Picture
 - The biexponential model
 - Variations of water diffusion with cell size
 - A conceptual model?

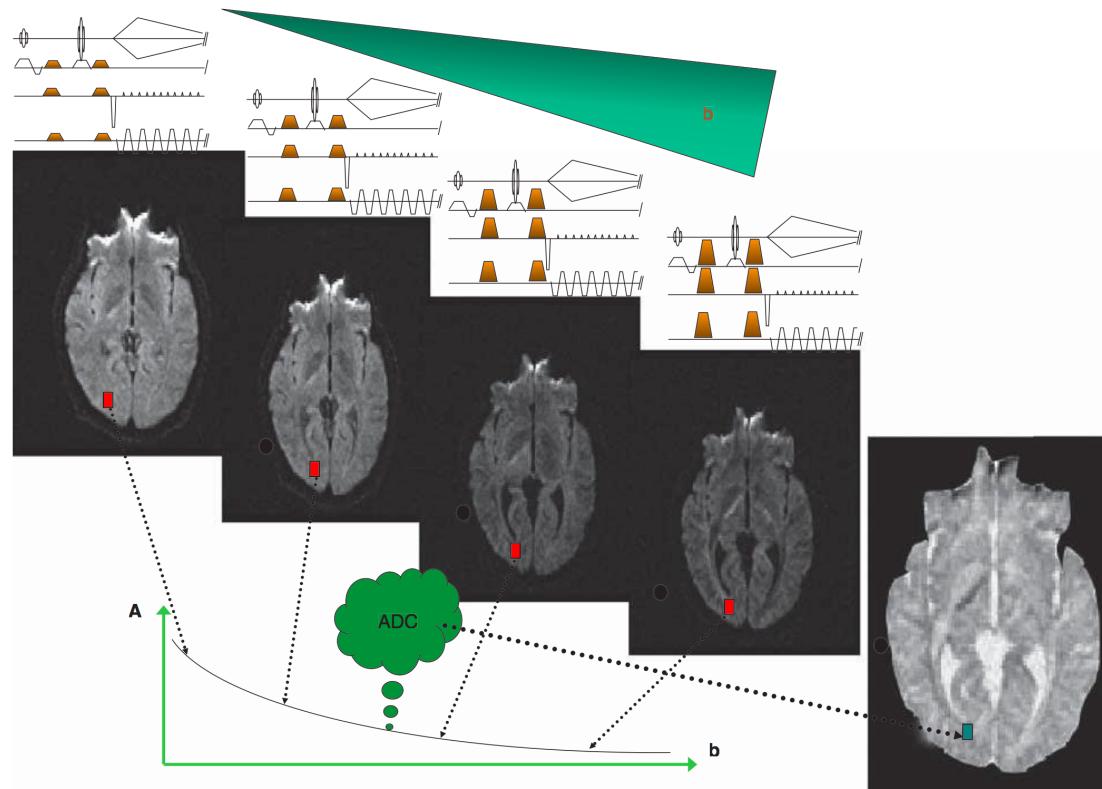
Diffusion-Weighted MRI and Diffusion Maps

- One must be aware that the content of "diffusion weighted" (DW) images is affected by many other parameters than diffusion, as they are also usually strongly T_1 and T_2 weighted.
- For a typical spin-echo sequence, the overall signal attenuation is given by
$$A = [1 - \exp(-TR/T_1)] \exp(-TE/T_2) \exp(-bD).$$
- In theory, it is possible to get rid of T_1 and T_2 contrast and obtain pure maps of the diffusion coefficient by acquiring two images with different b -values, b and b_0 :

$$D_{x,y,z} = -\ln[A_{x,y,z}(b)/A_{x,y,z}(b_0)]/(b - b_0).$$

- **Error propagation theory** (Xing et al., 1997) shows that it is better to accumulate n_1 and n_2 measurements at each of the low and large b -factors, b and b_0 , than to use a range of b -factors.
- The accuracy dD/D is then obtained from the raw image signal-to-noise ratio (SNR):
$$dD/D = [\exp(2Db_0)/n_1 + \exp(2Db)/n_2]^{1/2} / [\text{SNR} \cdot D(b - b_0)].$$
- Diffusion images can be obtained by fitting the signal intensity of each pixel obtained for different b -values using regression analysis ([Fig 5.8](#)).
- The logarithm of the signal attenuation versus b -factor should appear as a straight line, the slope of which is the diffusion coefficient.
- However, deviation from linearity is expected in tissues, where diffusion is not free.
- Multiple b -value acquisitions allow the nature of the diffusion process to be investigated and get further information on tissue microstructure and dynamics.

Figure 5.8 Diffusion-weighted and diffusion-calculated (ADC) images.



Intravoxel incoherent motion

- A potential confounding factor in diffusion MRI results from movement of the blood in the microvasculature.
- Although the difference in spatial scale between the elementary processes of diffusion (nanometers) and **pseudo-diffusion** (tens of micrometers) extends across five orders of magnitude, associated diffusion and pseudo-diffusion coefficients only differ by roughly one order of magnitude.
- This relatively small difference is due to these coefficients combining the effects of elementary particle velocity and distance.

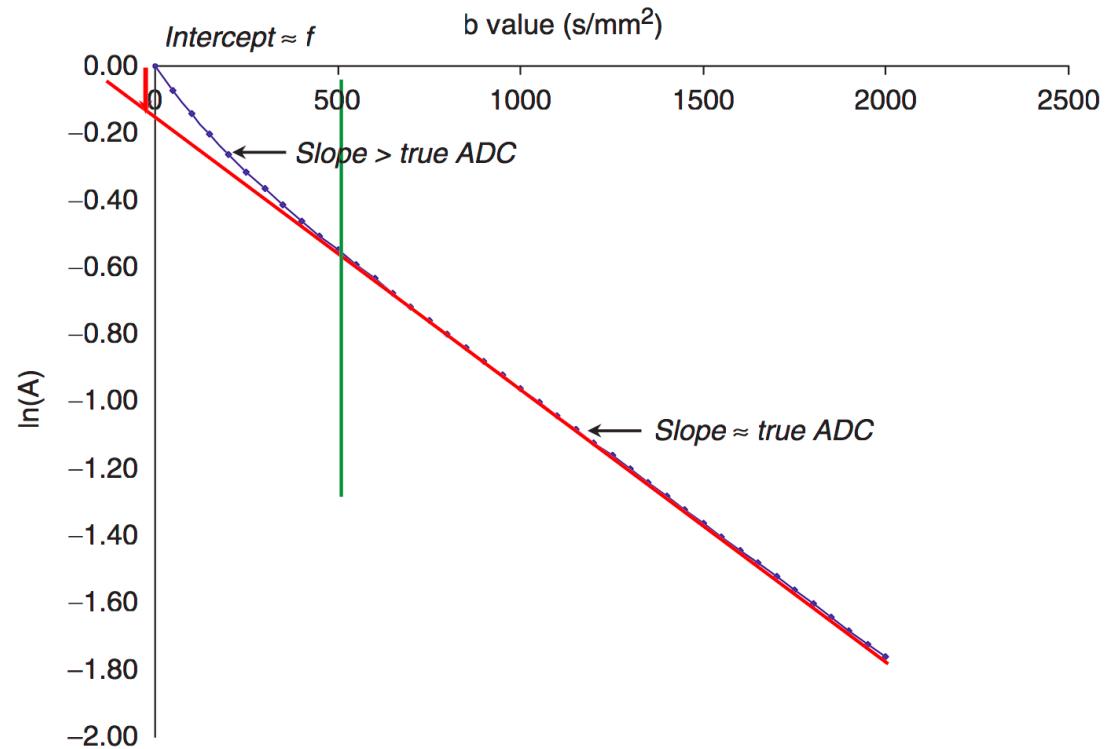
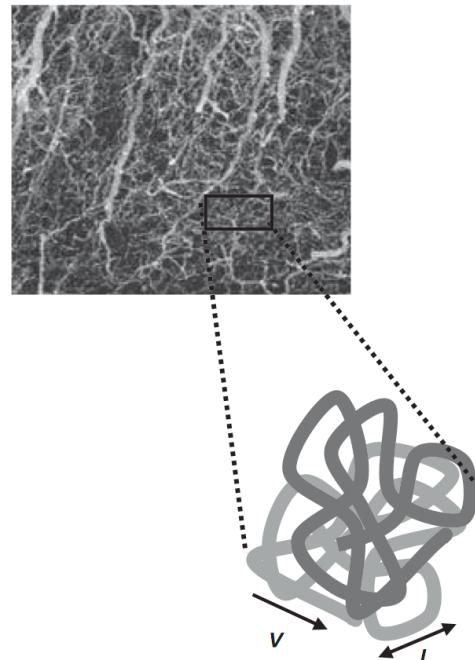
- The **intravoxel incoherent motion (IVIM)** concept has been introduced as a means to cover all molecular displacements to which "diffusion" MRI could be sensitive.
- Flow of blood in the brain pseudo-randomly oriented microvasculature may mimic a random walk (**IVIM effect**).
- Perfusion is expected to be present with very low b -values (< 200 s/mm²) in the form of a curve at the origin of the plot of $\ln(A)$ versus b ([Fig. 5.9](#)), with a biexponential shape.
- Signal from large vessels with rapid flow disappears quickly with very low b -values, whereas smaller vessels with slower flow might still contribute to the IVIM signal acquired with b -values on the order of 600 s/mm².
- Estimation of the diffusion coefficient from only two b -values (e.g., 0 and 1000 s/mm²) could then potentially include perfusion effects and result in an overestimation of the true diffusion coefficient.

- It was suggested that the complex incoherent motion processes occurring in biological tissue be portrayed on a voxel scale using the microscopic, free diffusion physical model, but replacing the physical diffusion coefficient, D , with a global parameter, the **apparent diffusion coefficient (ADC)**, to take into account diffusion and pseudo-diffusion processes:

$$\text{ADC} = -\ln[A(b)/A(b_0)]/(b - b_0)$$

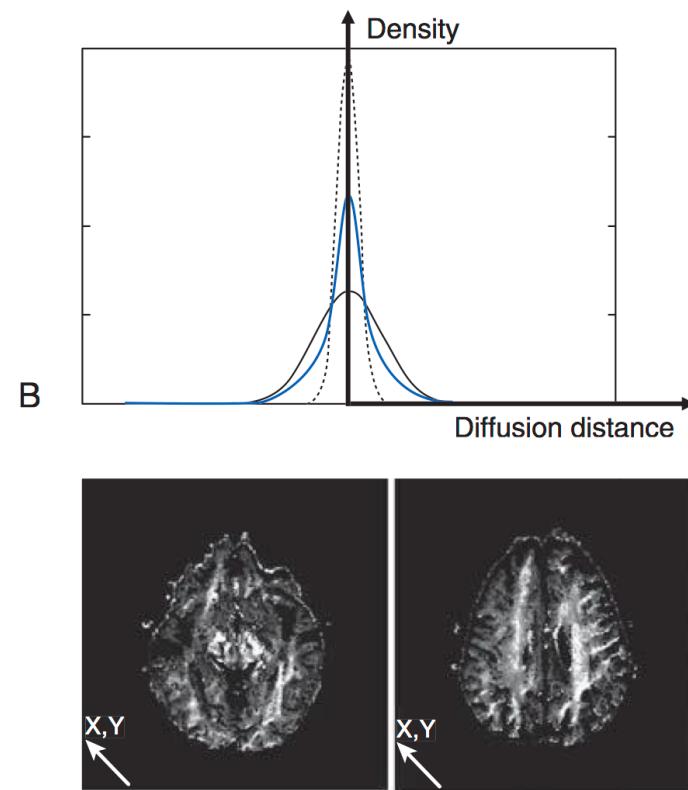
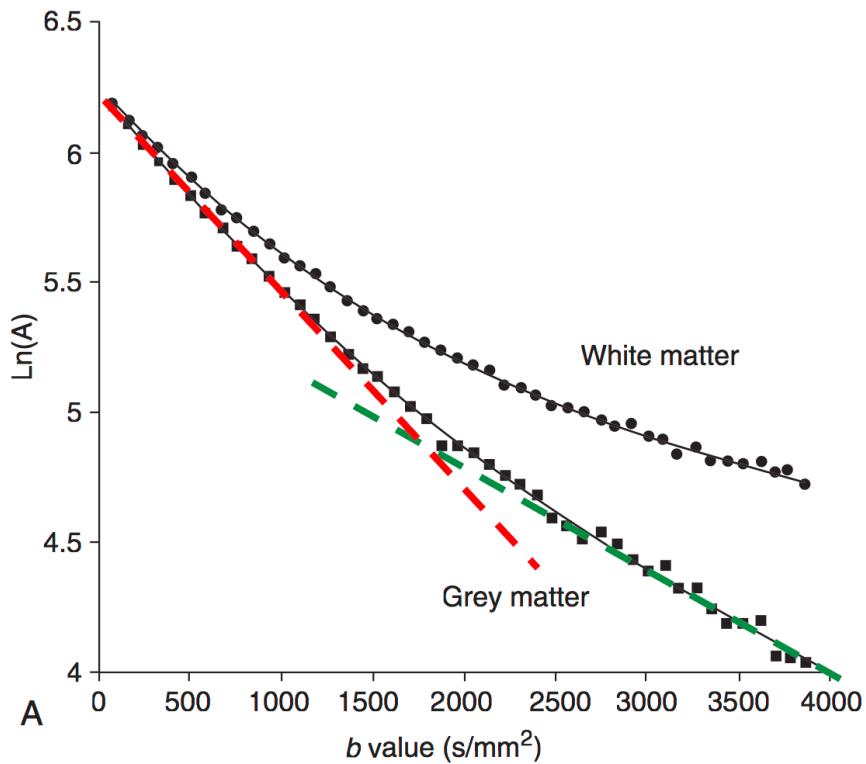
- The ADC can be linked to a "perfusion fraction," f , close to the flowing blood volume.
- For small blood volumes and with $b_0 = 0$, one gets $\text{ADC} \simeq D + f/b$.
- ADC will depend strongly on the choice and range of b -values. ([Fig. 5.9](#))
- It is the diffusion path to which the NMR experiment is actually sensitive, not the diffusion coefficient.

Figure 5.9 Intravoxel incoherent motion (IVIM) concept.



- In fact, many studies have experimentally established that the water diffusion-sensitized MRI signal attenuation in certain parts of brain tissue as a function of the b -value could not be well described by a single exponential decay.
- Diffusion data gathered using the q-space approach clearly demonstrate that the water diffusion process cannot be modeled by a single Gaussian distribution. ([Fig. 5.10](#))
- The averaging, smoothing effect resulting from this scaling presumes some homogeneity in the voxel.
- ADCs derived from images acquired at low b -values will be larger than those obtained from higher b -values.
- The curvature can be well described by a combination of two exponentials corresponding to two compartments in slow or intermediate exchange, a **fast diffusion pool** (FDP, red line) and a **slow diffusion pool** (SDP, green asymptote).

Figure 5.10 Hindered diffusion.



Restricted diffusion

- Restricted diffusion effects depend on
 - the shape of the restricting volumes (spherical, cylindrical, parallel walls)
 - the type of MRI experiment (constant or pulsed gradients)
- Suppose diffusion restricted in a spherical cavity of radius R_0 . In the limit where free diffusion distance largely exceeds R_0 , the attenuation is independent of the diffusion time:
$$A = \exp[-(\gamma\delta G)^2 R_0^2 / 5].$$
- Hence, the ADC decreases when the diffusion time is increased.

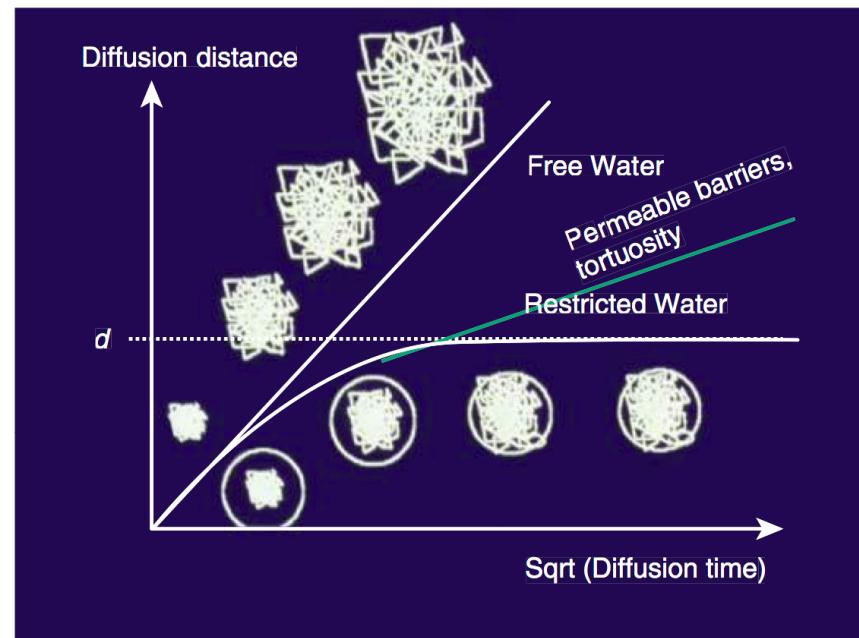
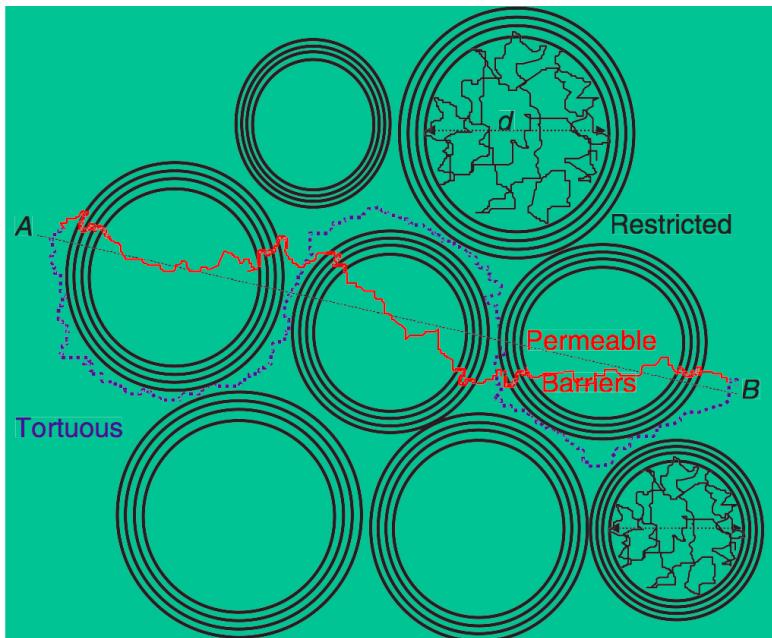
Permeable barriers

- In biological tissues, walls may not be reflecting boundaries but, rather, partially absorbing or permeable borders.
- In the case of equally spaced, plane barriers having a **permeability constant κ** . When the diffusion time increases, the ADC decreases, as expected for restricted diffusion, but saturates at a level, $\text{ADC}_{\text{asymp}}$, which depends on the permeability constant:
$$\text{ADC}_{\text{asymp}} = D_0 / (1 + D_0 / \kappa a)$$
, where a is the barrier spacing.

Tortuosity

- **Tortuosity** is a concept that molecules can no longer diffuse in a "straight" way between two locations, but must diffuse around structures that are impermeable to them.
- **Tortuosity effect** results in
 - a longer diffusion time needed to diffuse between the two locations
 - an apparent decrease in the diffusion distance covered in a given diffusion time and in the measured ADC
- This tortuosity effect is classically expressed quantitatively using a **tortuosity coefficient**, λ , such that $\text{ADC} = D/\lambda^2$.
- Reduced value for water diffusion in the extracellular space results not from geometric factors caused by obstructing cells but from interactions with the extracellular matrix.

Figure 5.11 Elementary mechanisms of hindered diffusion.



Interaction with polar surfaces

- The density and distribution of charges along a plane surface could help propagate the structuring effect on water molecules beyond several layers.
- The water diffusion coefficient varies according to the water content and is further reduced near the membrane surface.

Hindered diffusion

- High viscosity, macromolecular crowding and restriction effects have been proposed as explanations for water diffusion reduction in the intracellular space.
- Tortuosity effects for diffusion of tracers in the extracellular space.
- Diffusion in tissues is certainly multifactorial, with several elementary processes contributing to deviation from Gaussian behavior and the reduced ADC.

The biexponential model

- The overall effect of hindered diffusion in biological tissues is the deviation in the plot of the logarithm of the signal attenuation versus b -factor from a straight line.
- The interest of this biexponential model is that it is the exact counterpart to a biophysical model, namely the presence of two water diffusion pools, the **slow and fast diffusion phases** (SDP and FDP, respectively).
- Biexponential model:

$$A = f_{\text{slow}} \exp(-bD_{\text{slow}}) + f_{\text{fast}} \exp(-bD_{\text{fast}})$$

, where f and D are the volume fraction and the diffusion coefficient, with $f_{\text{slow}} + f_{\text{fast}} = 1$.

Variations of water diffusion with cell size

- The drop in ADC that is observed during acute brain ischemia has been clearly correlated with cell swelling associated with cytotoxic edema.
- The global water ADC decrease probably results from a shift in balance between the fast and the slow diffusion water pools.
- Cell swelling has been shown to result in an increase in SDP fraction, whereas the SDP and FDP diffusion coefficients do not change.

A conceptual model?

- In summary, the FDP and the SDP would correspond to two differently structured water pools, rather than to specific water compartments.

Figure 5.12 A conceptual model explaining the observed biphasic diffusion behavior of water in biological tissues.

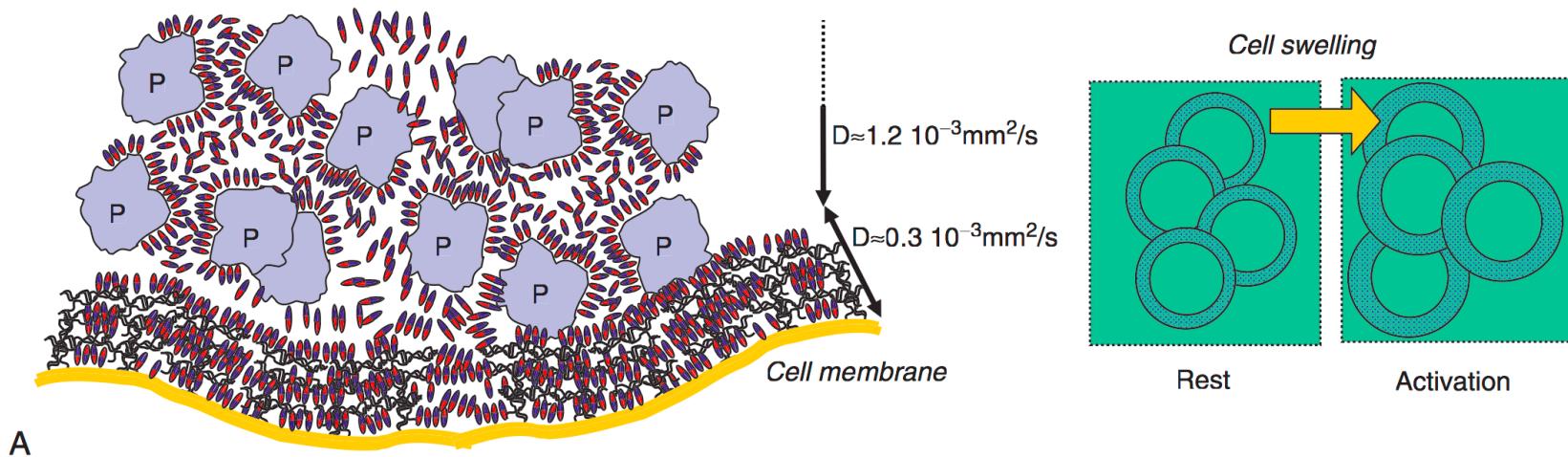


Figure 5.12 A conceptual model explaining the observed biphasic diffusion behavior of water in biological tissues.

