Diffusion MRI Theory Methods and Applications

Topic: Physics of Diffusion

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Contents

The History of Diffusion

- Brownian Motion and Einstein
    - Fick's law
    - Brownian motion, the Einstein derivation

Brownian Motion and Einstein

- Einstein recognized that Brownian motion was associated with diffusion, the flux of particles arising from a gradient in concentration.

Fick's law

- **Fick's first law**: $J = -D\nabla n(r,t)$
- **Fick's second law**: $\frac{\partial n}{\partial t} = D\nabla^2 n$
- Fick's laws still applied in the case of self-diffusion where no macroscopic gradient existed.

Brownian motion, the Einstein derivation

- Einstein's key step was to consider a small displacement δx of the Brownian particle under the net force, such that the free energy is minimized for a finite volume of particles.
- Einstein proposed that the drift of particles caused by the force K would need to be balanced by a diffusion current in the opposite direction.

Probabilities and Molecular Ensembles

The Propagator Description

- Conditional probability $P(r|r',t)$: a particle (or molecule) starting at r at time zero will move to r' after a time t.
- Therefore, $n(r',t) = \int n(r,0)P(r|r',t)dr$
- $\frac{\partial}{\partial t}P(r|r',t) = D\nabla^2 P(r|r',t)$ is true only for an **isotropic medium** where the diffusion is indeed a simple scalar property.
- $P(r|r',t) = (4\pi Dt)^{3/2}\exp(-\frac{(r'-r)^2}{4Dt})$
- The idea of an ensemble is introduced as $\langle A\rangle = \sum_s P(s)A(s)$, where $\langle A\rangle$ is the ensemble average, s is a possible state of the system in the ensemble and $P(s)$ is the probability of that state.
- **Einstein equation for diffusion**: $\langle (r'-r)^2\rangle = 6Dt$, and $\langle (r'-r)^2\rangle = 2Dt$ in one dimension.

The Diffusion Tensor

- In **anisotropic media**, it is necessary to define a diffusion tensor and rewrite the differential equation as $\frac{\partial}{\partial t} P(r|r',t) = \nabla \cdot [\mathbb{D} \nabla P(r|r',t)]$.
- $\mathbb{D}$ is known as the **diffusion tensor** and describes how the particle flux in any direction is related to the probability gradient in any direction.

Flow and Dispersion

- The molecular motion is not only governed by self-diffusion but also by flow and dispersion.
- **Dispersion** is the process whereby molecules that start together in the same vicinity become separated as a result of translational motions.
- In the **Eulerian** perspective, one describes a space-fixed velocity field, $v_E(r,t)$, specifying the local fluid velocity at each position in the sample at every time.
- In the **Lagrangian** description our perspective is fluid element fixed. For every particle we follow the fluctuating velocity, $v_L(t)$, while the particle migrates.

- In the Lagrangian description, the entire particle set provides the statistical ensemble for the calculation of average parameters, whereas in the Eulerian view, such averaging is by definition over the spatial array.
- This ensemble averaging, in the Lagrangian case, represents a mean involving a sum over particles, while in the Eulerian case it represents an integral over volume.
- A longer characteristic time is defined by the duration of flow over the larger-length scale associated with the **representative elementary volume (REV)**.

Spin Echoes and Diffusion

- Fourier Perspectives for Imaging and Displacement
  - q-Space imaging: the average propagator
  - Frequency domain measurement of diffusion
- Restricted Diffusion
  - Diffusive diffraction
  - The short time limit and surface-to-volume effects
- Inverse Laplace Transform

The Hahn and Carr-Purcell Experiments

- Carr and Purcell (1954) showed that the echoes could be repeated successively in a train consisting of a 90° RF pulse followed by a train of 180° RF pulses.
- Meiboom and Gill (1958) applied the 180° pulses with phases shifted in quadrature with respect to the initial 90° RF pulse. This sequence is thus known as a **Carr-Purcell-Meiboom-Gill (CPMG) train**.

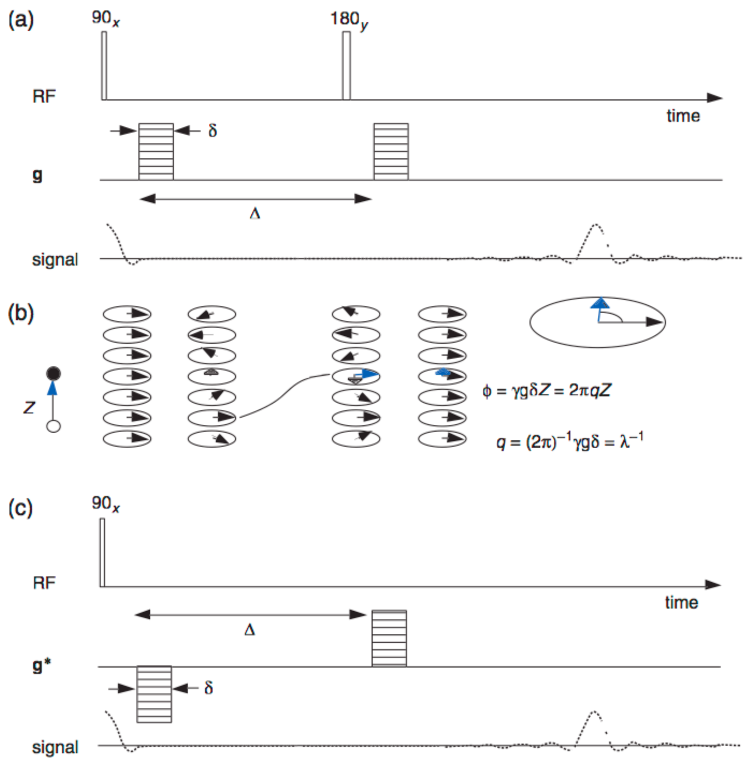
Magnetic Field Gradients and Spin Phase Evolution

- Larmor frequencies of the spins are designed to show a simple spatial dependence to simply quantify the translational motion: $\boldsymbol{\omega}(\boldsymbol{r}) = \gamma B_0 + \gamma \boldsymbol{g} \cdot \boldsymbol{r}$
- The phase shift acquired by spins at position $\boldsymbol{r}$ in the presence of a gradient field depends on the evolution time t as $\exp(i\gamma \boldsymbol{g} \cdot \boldsymbol{r} t)$.

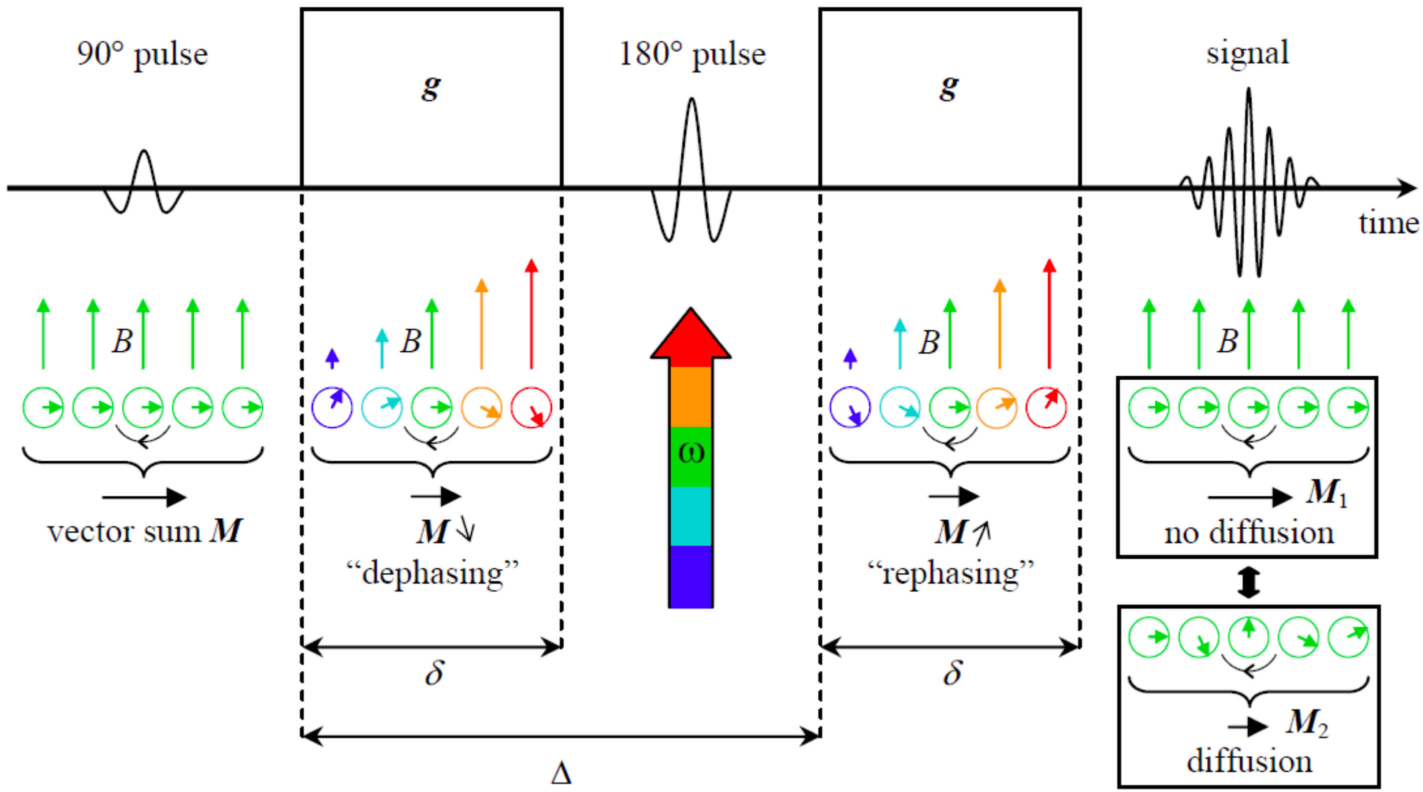
The Bloch-Torrey equation

- The effect of molecular self-diffusion and velocity in NMR can be accounted for in a description by Torrey (1956), in which an additional term is introduced in the Bloch equations as **Bloch-Torrey Equation**: $\frac{dM}{dt} = -i\gamma g \cdot r - \frac{M}{T_2} + D\nabla^2 M - v\nabla M$. Therefore, M is a function of both r and t: $M(r,t) = E(t)\exp(-i\gamma r \cdot \int_0^t g(t')dt')\exp(-t/T_2)$.

The Stejskal-Tanner experiment



- **Pulsed gradient spin echo (PGSE)**: in 1963, McCall, Douglass, and Anderson suggested that the gradient might be most usefully applied in the form of rectangular pulses inserted respectively in the **dephasing** and **rephasing** parts of the echo sequence, but gated off during RF pulse transmission and signal detection.



90° pulse
g
180° pulse
g
signal
time
B
B
B
B
vector sum M
M↓
"dephasing"
ω
M↑
"rephasing"
M1
no diffusion
M2
diffusion
δ
δ
Δ

The propagator method for narrow gradient pulse PGSE NMR

- **Narrow-gradient pulse approximation** assumes the pulses are sufficiently short that $\delta << \Delta$ and that the motion over their duration may be neglected.
- The effect of the first gradient pulse is to impart a phase shift $\gamma\delta \boldsymbol{g} \cdot \boldsymbol{r}$ to a spin located at position $\boldsymbol{r}$. This phase shift is subsequently inverted by the 180° RF pulse.
- Suppose that the molecule containing the spin has moved to $\boldsymbol{r}'$ at the time of the second gradient pulse. The net phase shift following this pulse will be $\gamma\delta \boldsymbol{g} \cdot (\boldsymbol{r}' - \boldsymbol{r})$.
- **Echo signal**: $E(g, \Delta) = \int P(R, \Delta) \exp(-\gamma\delta \boldsymbol{g} \cdot \boldsymbol{R}) d\boldsymbol{R}$, where there is a Fourier relationship between $E(g, \Delta)$ and $P(R, \Delta)$. The phase shifts appearing in the equation depend only on the dynamic displacement $\boldsymbol{R} = \boldsymbol{r}' - \boldsymbol{r}$.

Inhomogeneous local fields

- In the case of the fluctuating local field offset, there is clearly an upper bound, and ΔB_0 oscillates about 0 as the molecules migrate.
- Translational motion causes the nuclear spins to experience a time-dependent field, $\Delta B_0(t)$, and hence a time-dependent frequency offset, $\Delta\omega_0(t) = \gamma\Delta B_0(t)$.
- The effect of fluctuating local fields on the nuclear transverse magnetization can be treated using the **Anderson-Weiss theory**.

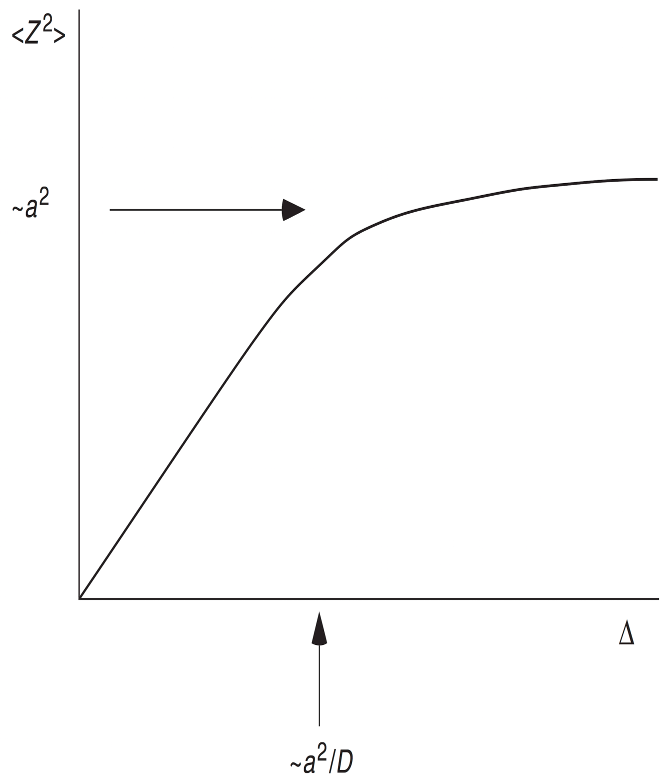
q-Space imaging: the average propagator

- A **q-space** is defined as $q = (2\pi)^{-1}\gamma\delta g$. Therefore, $E(q,\Delta) = \int P(R,\Delta)\exp(i2\pi q \cdot R)dR$, which means acquisition of the signal in q-space permits us to image $P(R,t)$.
- The representation of $E(q)$ by the average phase shift $< \exp(i2\pi q \cdot R) >$ leads to a useful **Taylor expansion**: $E(q) = 1 - (1/2!)(2\pi q)^2 < Z^2 > + (1/4!)(2\pi q)^4 < Z^4 >$, where Z is the component of displacement along the gradient direction defined by q.
- The initial decay of $E(q)$ with respect to q will always yield the ensemble-averaged mean-squared displacement, $< Z^2 >$.
- The effective diffusion coefficient, defined by $D_{eff} =< Z^2 > /2\Delta$, can be derived from the low q limit of the spin echo attenuation.

Frequency domain measurement of diffusion

- An alternative method of encoding for translational motion is to apply the **effective gradient waveform** in an oscillatory manner over an extended period.
    - Multi-echo Carr-Purcell-Meiboom-Gill spin echo train with a constant background gradient
    - Time oscillatory gradient in a multiple-gradient echo train.
- The diffusion spectrum is simply the Fourier transform of the molecular velocity autocorrelation function.

Restricted Diffusion



- When molecular diffusion is restricted by some barrier, the propagator will deviate from its classical Gaussian form.
- For $\Delta >> a^2/D$, the mean-squared displacement will appear to be time-independent and on the order of a^2.
- For restricted diffusion, $E(q)$ may exhibit the increase of echo amplitude as q is increased.

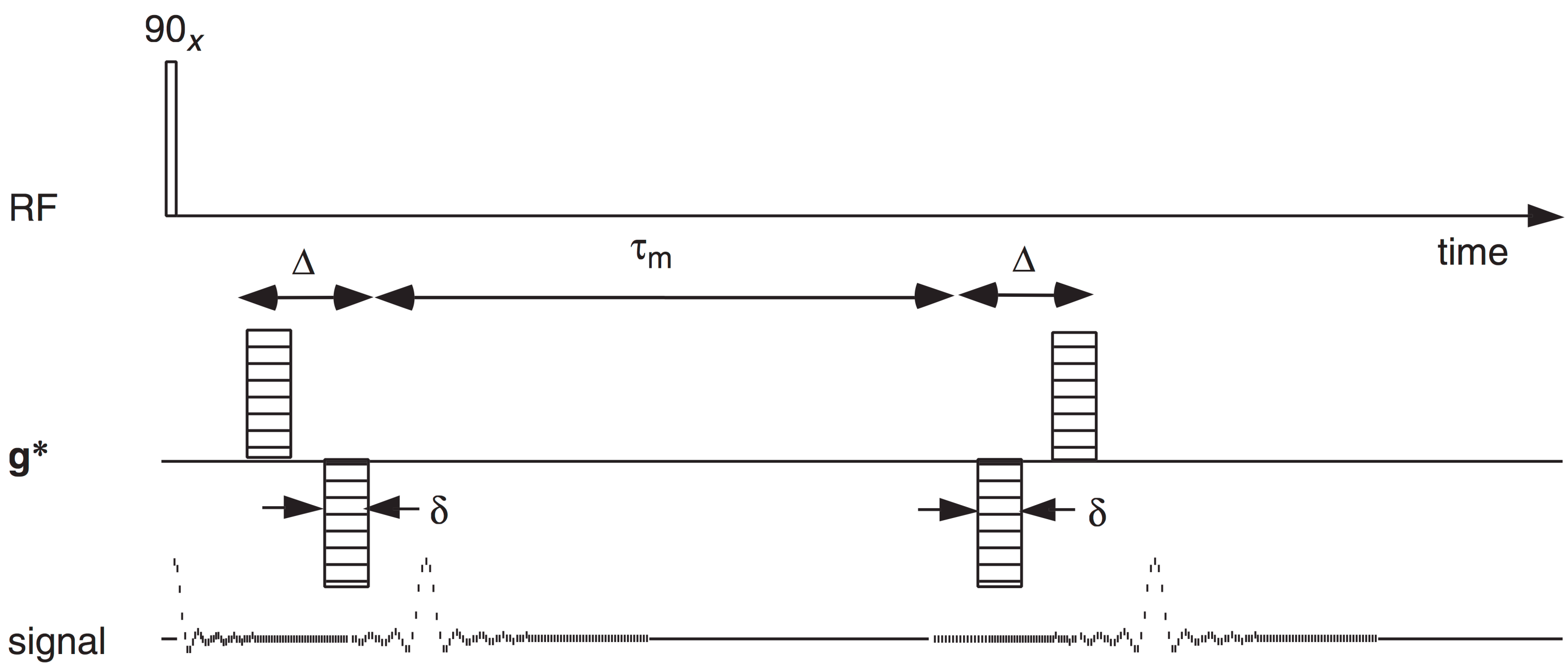
Inverse Laplace Transform

- In many situations where diffusion is being measured, different molecular species or differing molecular environments lead to a multiplicity of diffusion coefficients and hence a multiexponential decay. A natural transformation for such echo attenuation data would be the **inverse Laplace transform**.
- The usual approach to inverse Laplace is to adopt a **non-negative least-squares (NNLS)** fitting procedure.
- It is unstable to small variations in the input data and is numerically ill defined.

Doubled Gradient Pulse Pairs

- Double Pulsed Gradient Spin Echo
  - Flow compensation and the velocity autocorrelation function
  - Pore effects
- Two-Dimensional Encoding
  - Velocity exchange and diffusion exchange spectroscopy
  - Diffusion correlation

Double Pulsed Gradient Spin Echo



Flow compensation and the velocity autocorrelation function

- Two gradient pulse pairs are applied on the same spin magnetization, but over different time intervals, Δ, separated by a "mixing time," τ_m.
- The double PGSE NMR experiment will yield twice the stochastic part of the exponent for single PGSE NMR and $E_D = |E_S|^2$.
- Consider the case where flow is present, in particular, dispersive flow, $v(t)$, comprising a mean flow $< v >$ and fluctuating part, $u(t)$.
- In compensated double PGSE, the mean flow term, $< v >$ is canceled, and the experiment is sensitive only to the stochastic part of the flow.

Pore effects

- Suppose free diffusion applies. Then the pulse sequences all return the same answer, namely that the diffusive attenuation is twice that of a single gradient pulse pair.
- Suppose, however, restricted diffusion applies, such that $\Delta >> a^2/D$. Then each pulse pair of the sequence of Figure 4.5 gives $|S(q)|^2$, leading to $|S(q)|^4$ overall, while the sequence of Figure 4.5c and hence of Figure 4.5b gives a single pore factor $|S(q)|^2$.

Figure 4.5a

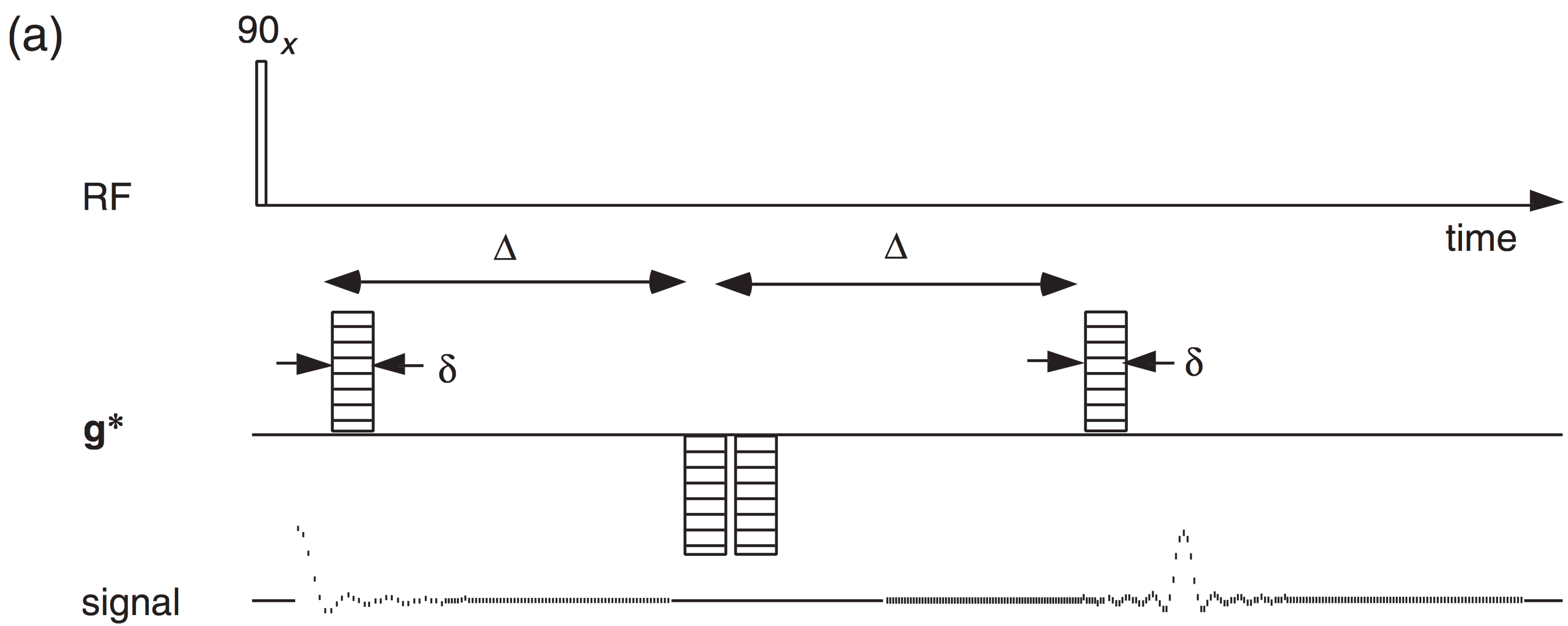


Figure 4.5b

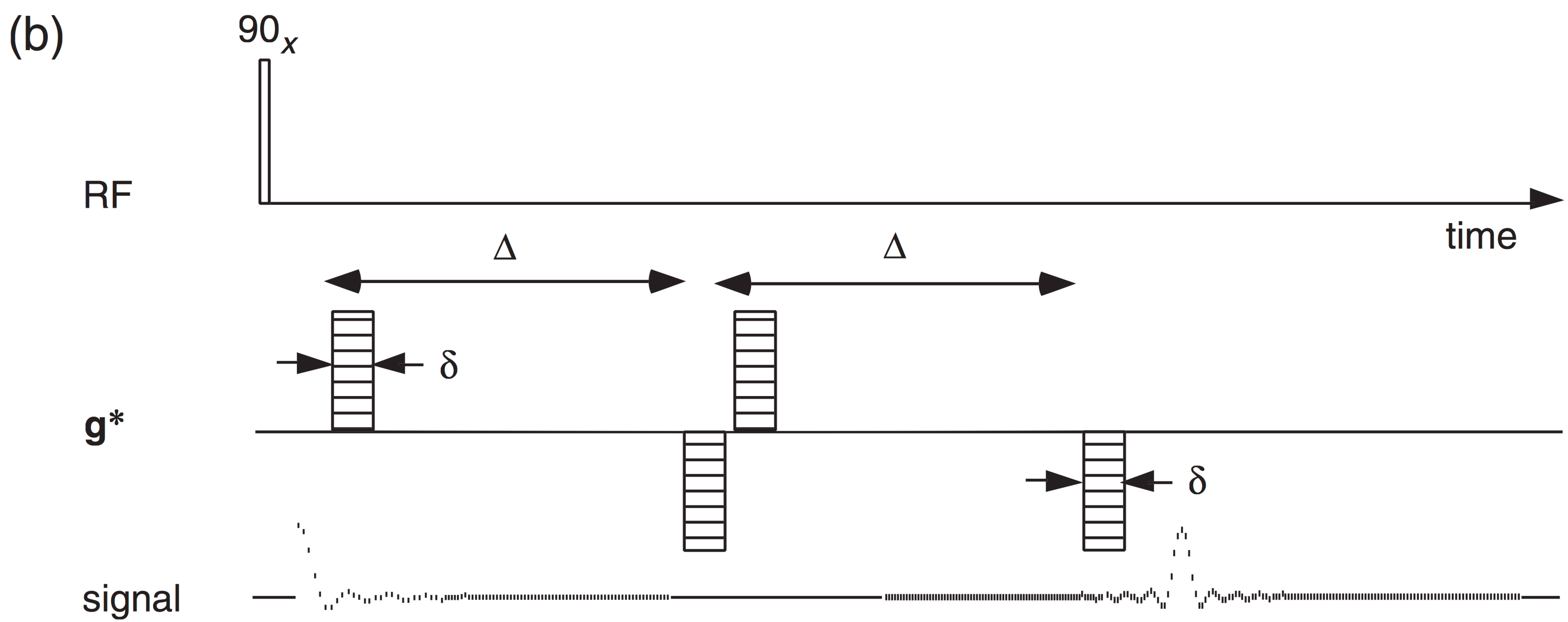
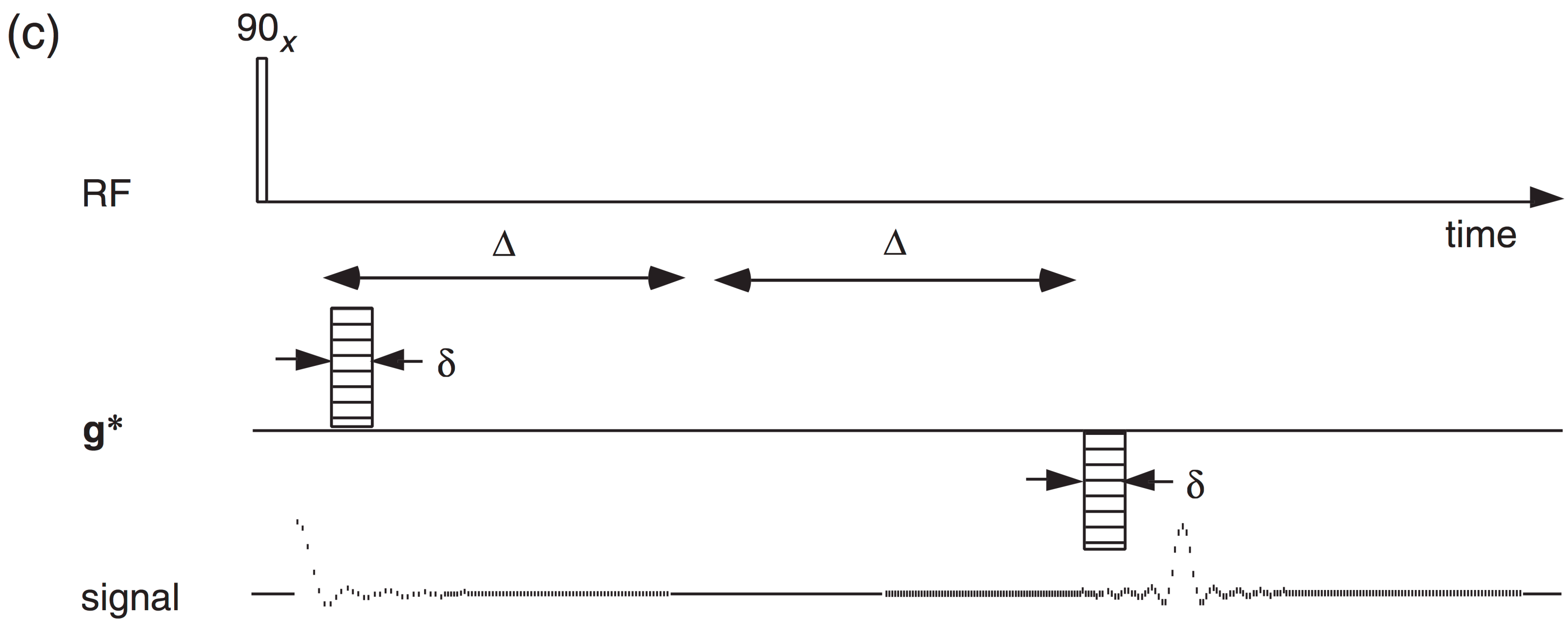


Figure 4.5c



Conclusion

- Whether using a gradient echo or a spin echo, the method can be analyzed in terms of an effective gradient, g^*.
- The effect in the case of diffusion and flow, along with all the influence of imaging gra- dients or local inhomogeneous fields, can be analyzed using the **Bloch-Torrey relations**.
- The simple Fourier relationship between the echo attenuation signal and the displacement propagator only holds in the narrow-gradient pulse approximation.