Diffusion Magnetic Resonance Imaging
Part 1: Theory & Methods

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M284: Principles of Neuroimaging

Overview

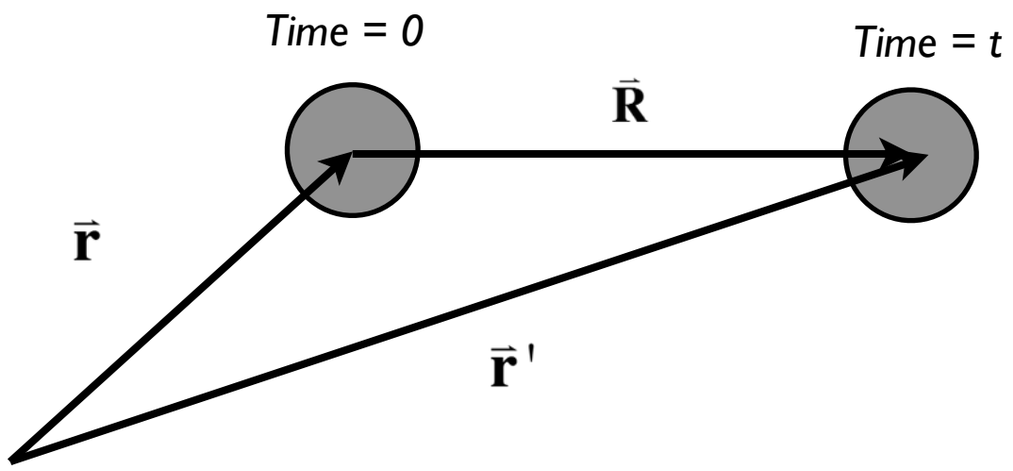
- Today's Lecture
  - Basic Diffusion MRI Physics
  - How do we measure diffusion? What are the assumptions?
  - What factors influence our measures of diffusion?
  - Simulations & Random Walks
  - Anisotropic diffusion & Diffusion Tensor Imaging
  - Mono-, bi-, and stretched-exponential diffusion imaging
  - Diffusion kurtosis imaging (DKI)
  - q-space, q-ball, and diffusion spectral imaging (DSI)

Overview

- **Next Time**
  - Brief Review
  - Tractography (Deterministic & Probabilistic)
  - Applications
    - Neuro-Oncology
    - Neurotrauma
    - Alzheimer's Disease
    - Parkinson's Disease
    - Epilepsy
    - Chronic Pain

Molecular Translational Dynamics

- The NMR signal is not detected for a single spin, but rather via a coherent superposition of *many* spins
- As such, we need to adopt an "ensemble-averaged" view in order to understand the behavior of the entire system
- This means taking into account spin movement, whether that be coherent motion (velocity) or incoherent motion (diffusion)
- The motion of a spin *i* can be characterized by some time-dependent displacement $\mathbf{r}_i(t)$ relative to an arbitrary origin point



Molecular Translational Dynamics

- Since we are talking about ensembles of spins, it is helpful to talk in terms of statistics and *probability of finding a spin at a particular location at a particular time*

- The probability of finding that a spin will have displacement r' at time t, given the starting position r is $P(\mathbf{r}|\mathbf{r}', t)$

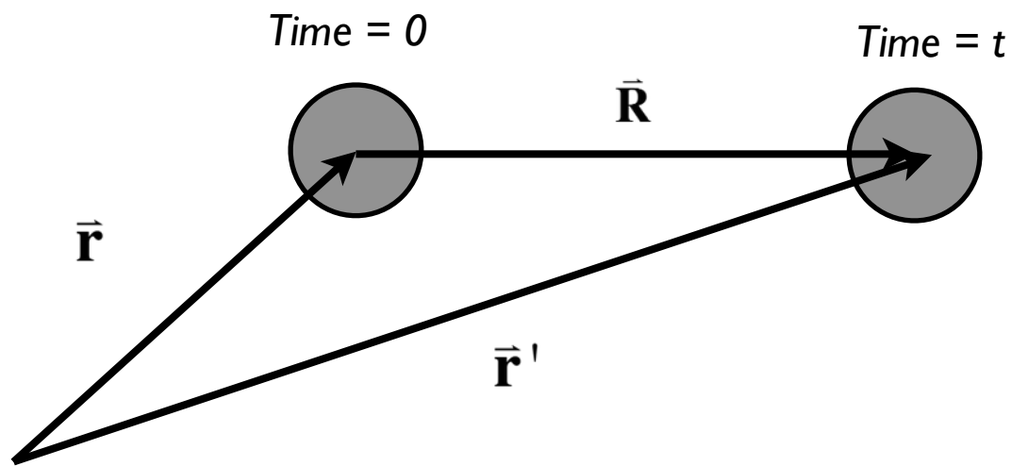
- This is the probability of finding *a particular* scattering spin positioned at ($\mathbf{r}'$, t) if there was a scattering *by the same* spin at ($\mathbf{r}$,t). [Spin Self-Correlation]

- The total probability of finding a spin at position $\mathbf{r}'$ at time t given an initial position of $\mathbf{r}$ is

$$\Psi(\vec{\mathbf{r}},t) = \int \Psi(\mathbf{r},0) P(\mathbf{r}\,|\,\mathbf{r}',t)\, d\mathbf{r}$$

$$\Psi(\vec{\mathbf{r}},0) = \rho(\vec{\mathbf{r}})$$

Particle Density



Fick's Law of Diffusion

- An application of the function $\Psi(\vec{\mathbf{r}},t)$ is using Fick's Law of Self Diffusion
- **Fick's first law of diffusion** says "the particle flux (per unit area per unit time) is proportional to the particle concentration gradient."

$$\vec{\mathbf{J}} = -D\nabla C$$

Spin Particle Flux

Diffusion Coefficient (Diffusivity)

Spin Concentration

- By applying the *conservation of mass*, $\frac{\partial C}{\partial t} = -\nabla \cdot \vec{\mathbf{J}}$ we arrive at **Fick's second law of diffusion:**

$$\frac{\partial C}{\partial t} = -\nabla \cdot \vec{\mathbf{J}} = \nabla \cdot (D\nabla C)$$

Fick's Law of Diffusion

- If we start with the initial condition $C(\vec{\mathbf{r}},0) = \delta(\vec{\mathbf{r}}' - \vec{\mathbf{r}})$

Impulse

- We see that (in our experiment) concentration can be written in terms of the probability of a spin at time 0 (or just spin density)

$$C(\vec{\mathbf{r}},0) = \delta(\vec{\mathbf{r}}' - \vec{\mathbf{r}}) = P(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}',0)$$

- And we can rewrite Fick's second law in terms of spin density/concentration as:

$$\frac{\partial}{\partial t} P(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}',t) = \nabla \cdot \left(D \nabla P(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}',t) \right)$$

- Assuming the diffusion coefficient is a constant (doesn't change over space or constant for a single voxel)

$$\frac{\partial}{\partial t} P(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}',t) = D \nabla^2 P(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}',t)$$

Fick's Law of Diffusion for NMR

- Assuming no restricted diffusion (or the boundary conditions: $P\left(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}', t\right) \rightarrow 0$ as $\vec{\mathbf{r}}' \rightarrow \infty$)

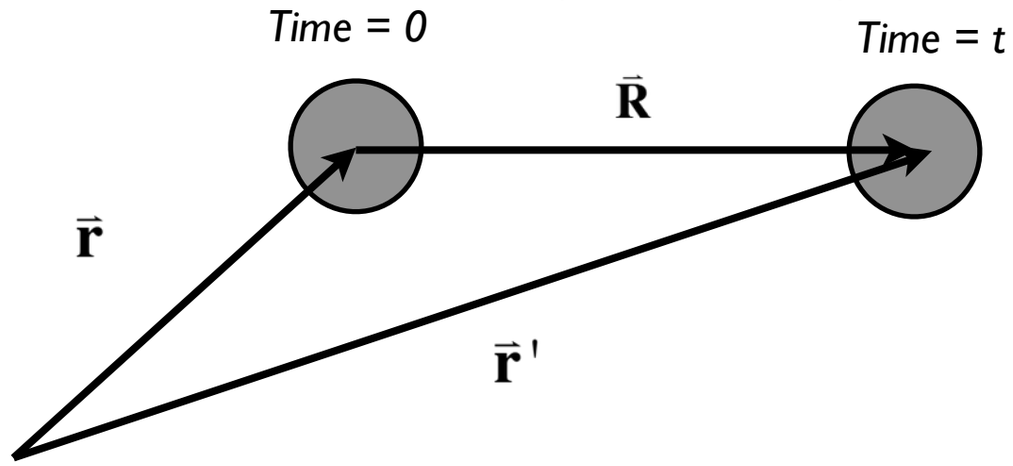
- The solution becomes:

$$P\left(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}', t\right) = \left(\frac{1}{\sqrt{4\pi Dt}}\right)^3 e^{-\frac{\left(\vec{\mathbf{r}}' - \vec{\mathbf{r}}\right)^2}{4Dt}}$$

Gaussian Distribution

- Note that the solution to this probability relies on $\left(\vec{\mathbf{r}}' - \vec{\mathbf{r}}\right)$ and not the initial position. Therefore, defining $\vec{\mathbf{R}} = \left(\vec{\mathbf{r}}' - \vec{\mathbf{r}}\right)$ yields:

$$P\left(\vec{\mathbf{R}}, t\right) = \left(\frac{1}{\sqrt{4\pi Dt}}\right)^3 e^{-\frac{\vec{\mathbf{R}}^2}{4Dt}}$$



Fick's Law of Diffusion for NMR

- We can expand this equation in 3-D as:

$$P\left(\vec{\mathbf{R}},t\right)=\left(\frac{1}{\sqrt{4\pi Dt}}\right)^{3}\cdot e^{-\frac{x^2}{4Dt}}\cdot e^{-\frac{y^2}{4Dt}}\cdot e^{-\frac{z^2}{4Dt}}$$

- If we are only concerned with the diffusion in 1-D (say the z-direction), the integration results in

$$P\left(z,t\right)=\left(\frac{1}{\sqrt{4\pi Dt}}\right)e^{-\frac{z^2}{4Dt}}$$

- Central limit theorem says that the average displacement must be zero (because no net coherent motion, or velocity, is considered)

$$\langle z\rangle=0$$

Fick's Law of Diffusion for NMR

- Therefore, the second moment (variance) of spin displacement can be found as

$$\left\langle z^2 \right\rangle = \int_{-\infty}^{\infty} z^2 P(z,t)\, dz$$

$$\left\langle z^2 \right\rangle = 2Dt$$

- Note that this is also the same as the variance in the *change* of displacements, since we previously assumed *z = 0*.

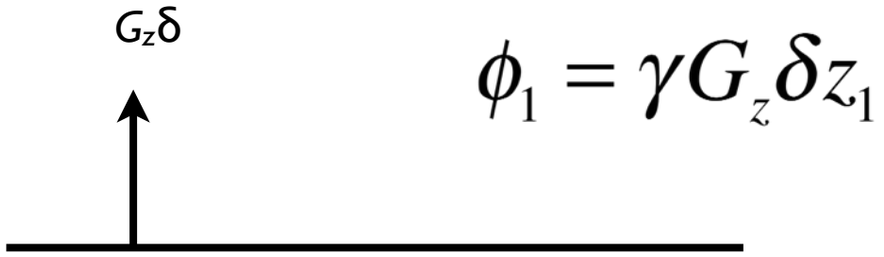
$$\left\langle \left(z_2 - z_1 \right)^2 \right\rangle = 2Dt$$

$$\left\langle dz^2 \right\rangle = 2Dt$$

Measuring Displacement using NMR

- In order to measure the displacement of spins we must employ *motion probing gradients*

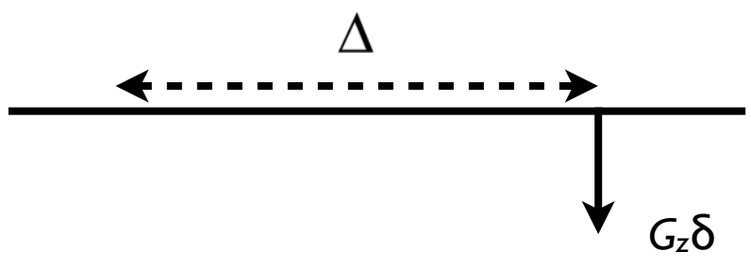
- In an ideal sense, let's employ an impulse gradient in the z-direction with magnitude $\mathbf{G_z\delta}$, which will to phase encoding the spin's initial position:



$$\phi_1 = \gamma G_z \delta z_1$$

- Then, at some time Δ later, we employ a gradient of equal amplitude of opposite polarity:

$$\phi_2 = -\gamma G_z \delta z_2$$

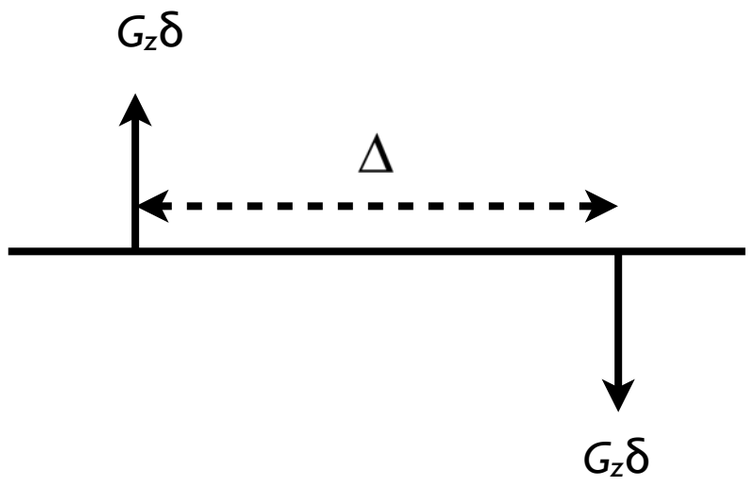


Measuring Displacement using NMR

- The net accumulated phase can be found as:

$$\phi_2 + \phi_1 = \gamma G_z \delta z_1 - \gamma G_z \delta z_2$$

$$d\phi = \gamma G_z \delta \left(z_1 - z_2 \right)$$



- The second moment (variance) in phase is thus:

$$\left\langle d\phi^2 \right\rangle = \left(\gamma G_z \delta \right)^2 \left\langle \left(z_1 - z_2 \right)^2 \right\rangle$$

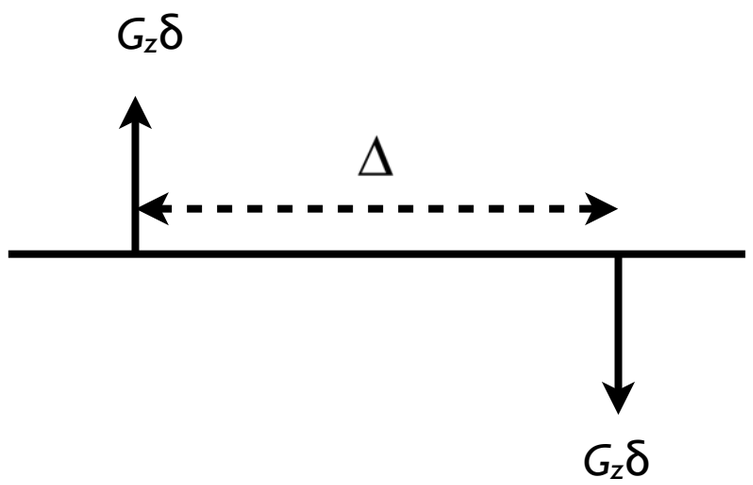
Measuring Displacement using NMR

- Substituting the definition for diffusivity found in **Fick's second law of diffusion for NMR:**

$$\left\langle d\phi^2 \right\rangle = \left(\gamma G_z \delta\right)^2 \left\langle \left(z_1 - z_2\right)^2 \right\rangle$$

$$\left\langle \left(z_2 - z_1\right)^2 \right\rangle = 2Dt \leftarrow \Delta$$

$$\left\langle d\phi^2 \right\rangle = \left(\gamma G_z \delta\right)^2 2D\Delta$$

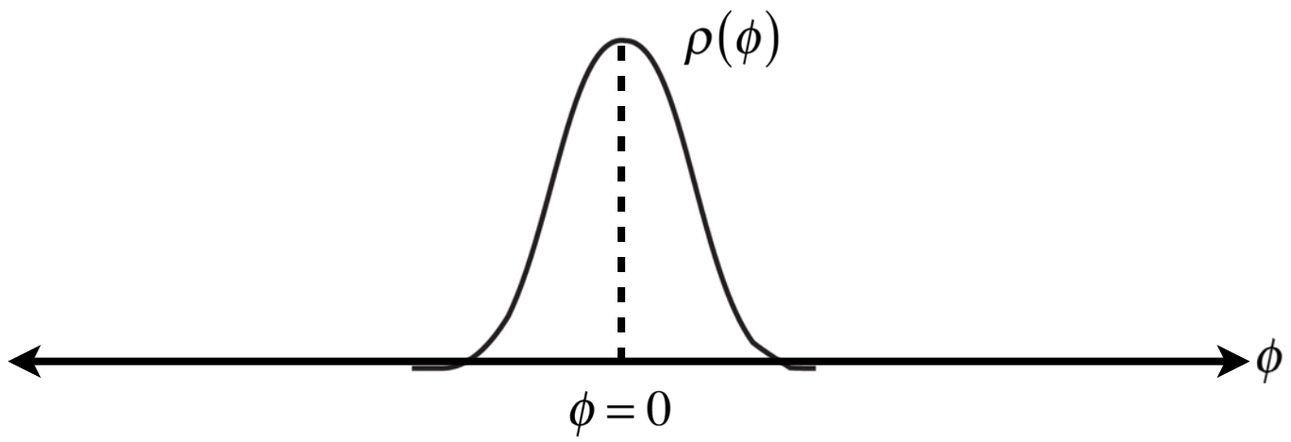


- The diffusivity, *D*, can be found as:

$$D = \frac{\left\langle d\phi^2 \right\rangle}{2\Delta\left(\gamma G_z \delta\right)^2}$$

Measuring Displacement using NMR

- How do we measure $\langle d\phi^2 \rangle$?
- If we could measure all the spins in the system individually, then we could construct the spin PDF and estimate variance
- However, we only obtain a single NMR signal for a voxel representing the ensemble average spin signal
- For intravoxel, incoherent motion only (no flow...i.e. no phase bias), the ensemble average spin density $\rho(\phi)$ will occur at $\phi = 0$



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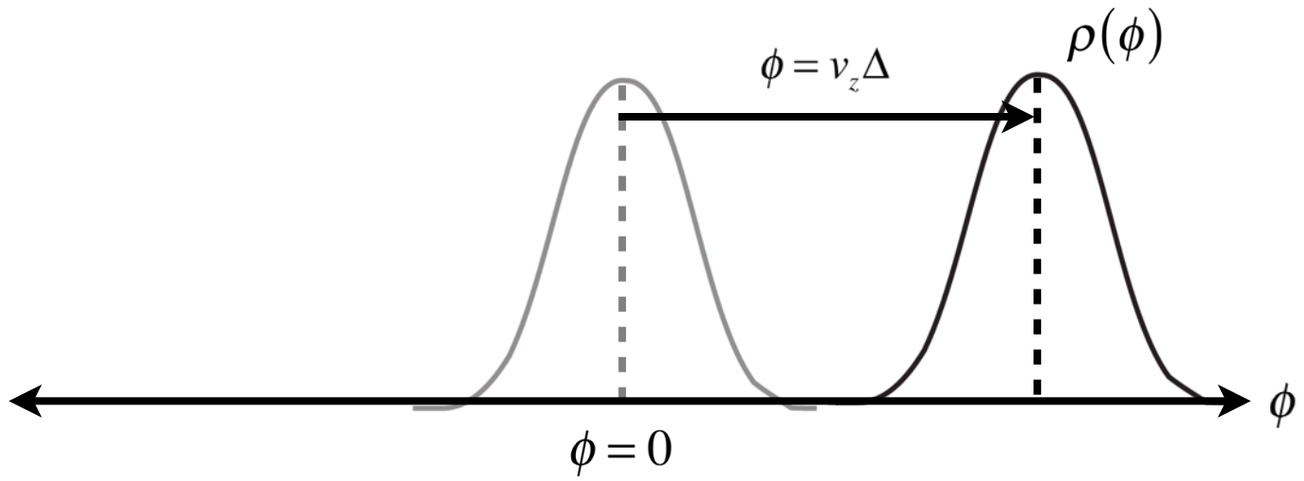
- If there is coherent motion (flow), the phase accumulation will be $\langle \phi \rangle = v_z \Delta$



Measuring Displacement using NMR

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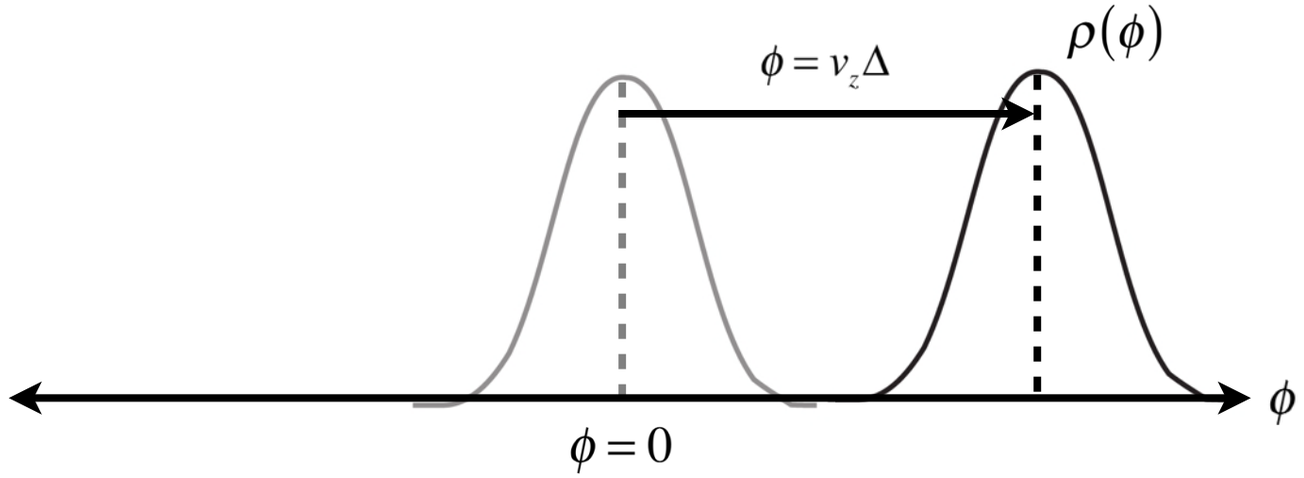
- If there is coherent motion (flow), the phase accumulation will be $\langle \phi \rangle = v_z \Delta$
- Fortunately, we have an equation to describe the shape of the spin density PDF



Measuring Displacement using NMR

- Recall the probability of a spin diffusing a distance *z* at time *t* is:

$$P(z,t) = \left(\frac{1}{\sqrt{4\pi Dt}}\right) e^{-\frac{z^2}{4Dt}}$$

- Substituting our definitions for the current experiment:

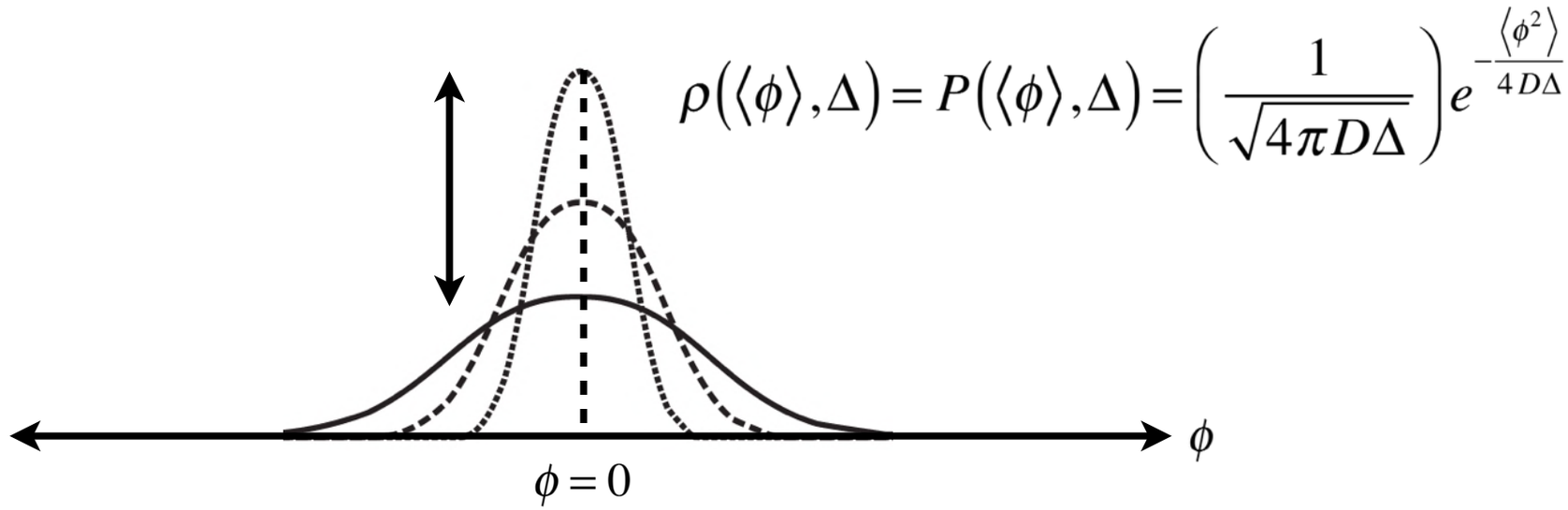
$$P(z_2 \mid z_1, \Delta) = \left(\frac{1}{\sqrt{4\pi D\Delta}}\right) e^{-\frac{(z_1 - z_2)^2}{4D\Delta}}$$

$$P(\langle\phi\rangle, \Delta) = \left(\frac{1}{\sqrt{4\pi D\Delta}}\right) e^{-\frac{\langle\phi^2\rangle}{4D\Delta}}$$

Gaussian Distribution

Measuring Displacement using NMR

- We see from inspection that the variance in Φ results in attenuation of the NMR signal



- If we think about this in terms of individual spins in an ensemble, the total NMR signal can be estimated by:

$$S(TE,TR,\Delta) = A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right) \cdot \sum_{n=1}^{N} e^{-j\cdot\phi_n}$$

Coil Factor/Coupling

Spin Density

Phase from Individual Diffusing Spins with application of "diffusion sensitizing gradients"

Measuring Displacement using NMR

- This sum can be evaluated once the net phase distribution is known
- Assuming free diffusion in a homogeneous medium and conditional probability of finding a spin initially at z_1 at z_2 at time Δ:

$$S(TE,TR,\Delta) = A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right) \cdot \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} P(z_2 \mid z_1, \Delta) e^{j\gamma G_z \delta \cdot (z_1 - z_2)} \, dz_1 \, dz_2$$

- For which the conditional probability follows the Gaussian approximation (for free diffusion):

$$P(z_2 \mid z_1, \Delta) = \left(\frac{1}{\sqrt{4\pi D\Delta}}\right) e^{-\frac{(z_1 - z_2)^2}{4D\Delta}}$$

- If we think about this in terms of individual spins in an ensemble, the total NMR signal can be estimated by:

$$S(TE,TR,\Delta) = A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right) \cdot e^{-(\gamma G_z \delta)^2 D\Delta}$$

The Diffusion Weighted Imaging Experiment

- If we now run our experiment **once with the diffusion sensitizing gradients turned on** and **once without diffusion sensitizing gradients** (but same TE, TR, etc)

$$\frac{S(TE,TR,\Delta)}{S(TE,TR)} = \frac{A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right) \cdot e^{-(\gamma G_z \delta)^2 D\Delta}}{A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right)} = e^{-(\gamma G_z \delta)^2 D\Delta}$$

$$\frac{S}{S_0} = e^{-(\gamma G_z \delta)^2 D\Delta} = e^{-bD}$$

Signal attenuation with increasing D

where

$$b = (\gamma G_z \delta)^2 \Delta$$

b-value
"level of diffusion weighting"
"Gradient Factor"

The Diffusion Weighted Imaging Experiment

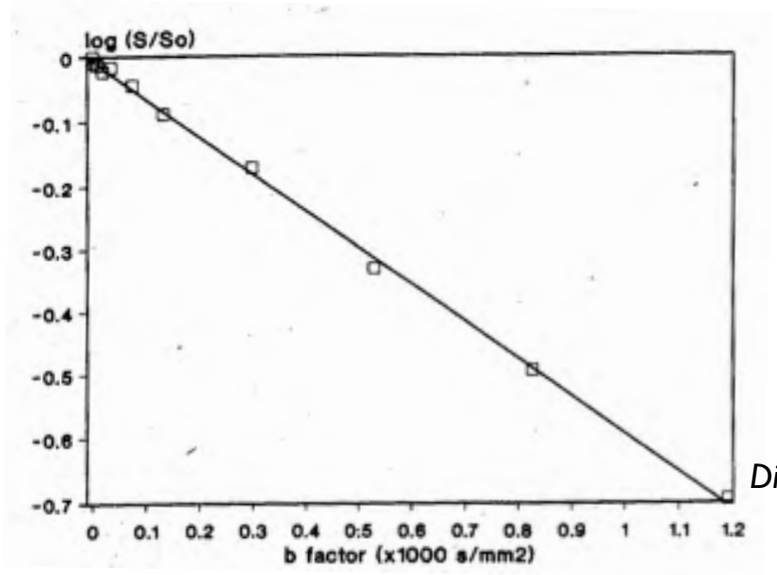
- The diffusion coefficient can be estimated by:

$$D = -\frac{1}{b}\ln\left(\frac{S}{S_0}\right)$$

- If two diffusion weighted images is used (different b-values), then diffusivity can be calculated by:

$$D = -\frac{1}{b_2 - b_1}\ln\left(\frac{S_2}{S_1}\right)$$

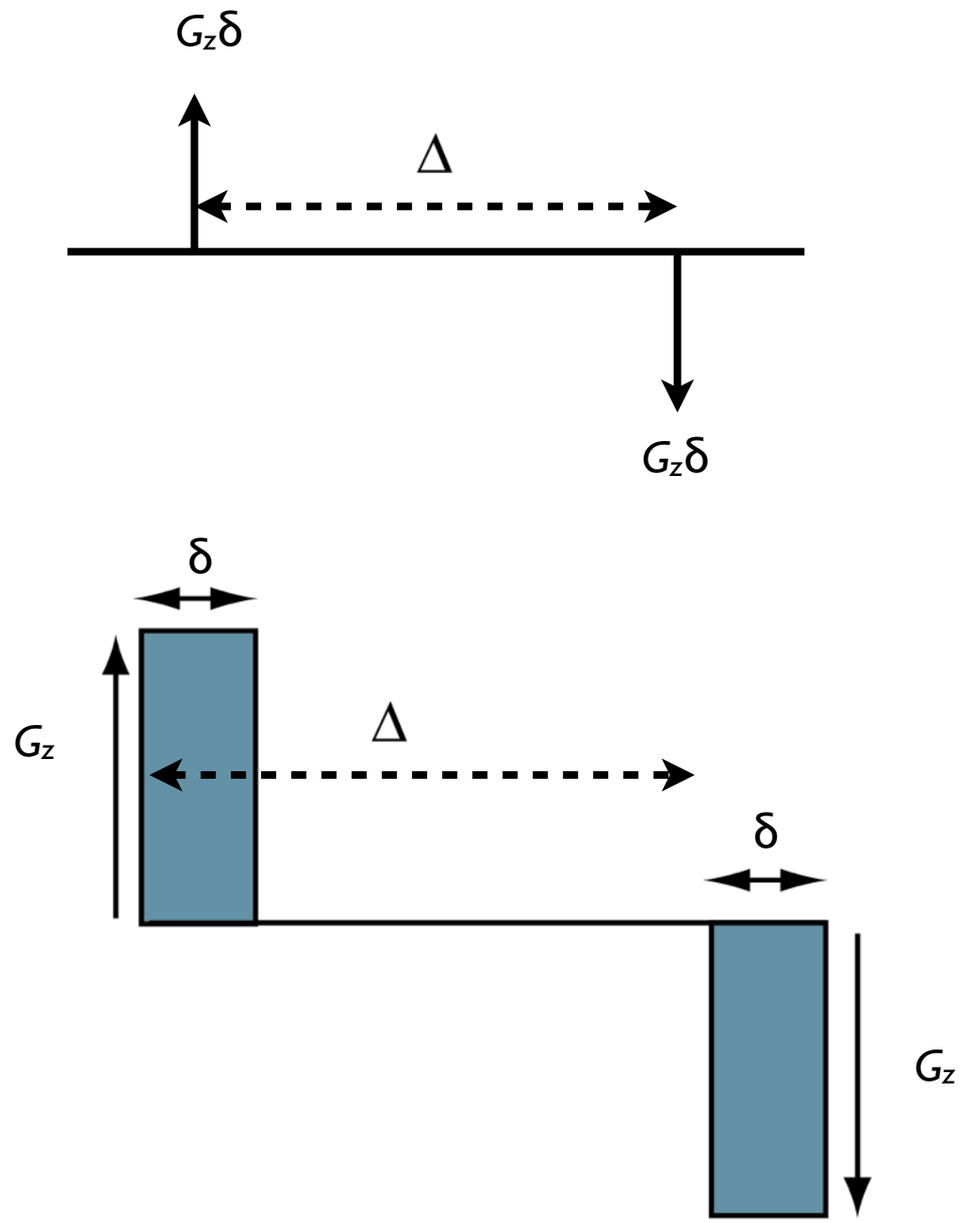
- Or if more than two diffusion weighted images are used, linear regression can be used to fit *ln(S) vs. b*



Le Bihan & Basser, Diffusion and Perfusion MRI, Raven Press, 1995

Pulsed Gradient Diffusion Experiment

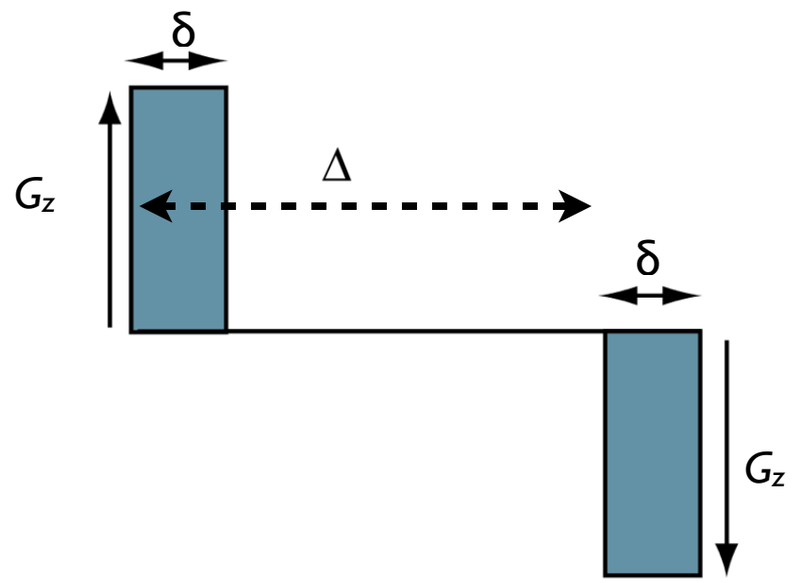
- Recall we previously assumed gradient impulses with amplitude $\mathbf{G_z\delta}$, but what happens when we use a pulsed gradient (fixed duration) instead?



Pulsed Gradient Diffusion Experiment

- The phase accumulation after the first pulse is calculated as:

$$\phi_1 = \gamma \int_0^{\delta} G_z \cdot z_1 \, dt = \gamma G_z \delta z_1$$



- And the phase accumulation after the second pulse is:

$$\phi_2 = \gamma \int_{\Delta}^{\Delta+\delta} G_z \cdot z_2 \, dt = \gamma G_z \delta z_2$$

- Thus, the net phase accumulation is *the same as the impulse case*

$$d\phi = \gamma G_z \delta \left(z_1 - z_2 \right)$$

- This is will work for $\delta \ll \Delta$

The Bloch-Torrey Equations

- Formally, we can express the total magnetization in terms of intravoxel incoherent motion (diffusion) and intravoxel coherent motion (flow) as:

$$\frac{\partial \vec{\mathbf{M}}}{\partial t} = \gamma \vec{\mathbf{M}} \times \vec{\mathbf{B}} - \begin{pmatrix} \frac{1}{T_2} & 0 & 0 \\ 0 & \frac{1}{T_2} & 0 \\ 0 & 0 & \frac{1}{T_1} \end{pmatrix} \vec{\mathbf{M}} + \vec{\mathbf{M}}_0 \begin{pmatrix} 0 \\ 0 \\ \frac{1}{T_1} \end{pmatrix} \underbrace{- \nabla \cdot \vec{\mathbf{v}} \left| \vec{\mathbf{M}} \right|}_{IVCM} + \underbrace{\nabla \cdot \left(D \nabla \vec{\mathbf{M}} \right)}_{IVIM}$$

Velocity

- Ignoring the effects of T1, T2, and Flow, and assuming diffusivity is uniform through the medium (in a voxel), we can simplify to:

$$\frac{\partial \vec{\mathbf{M}}(\vec{\mathbf{r}},t)}{\partial t} = \gamma \vec{\mathbf{M}}(\vec{\mathbf{r}},t) \times \vec{\mathbf{B}} + D \nabla^2 \vec{\mathbf{M}}(\vec{\mathbf{r}},t)$$

Transverse Relaxation

The Bloch-Torrey Equations

- If we apply a uniform gradient $\vec{\mathbf{B}}(\vec{\mathbf{r}},t)=\vec{\mathbf{G}}(t)\cdot\vec{\mathbf{r}}\hat{z}$ into this equation:

$$\frac{\partial\vec{\mathbf{M}}(\vec{\mathbf{r}},t)}{\partial t}=-j\gamma\left(\vec{\mathbf{r}}\cdot\vec{\mathbf{G}}\right)\vec{\mathbf{M}}(\vec{\mathbf{r}},t)+D\nabla^2\vec{\mathbf{M}}(\vec{\mathbf{r}},t)$$

- The solution to this equation is:

$$\vec{\mathbf{M}}(\vec{\mathbf{r}},t)=M_0(\vec{\mathbf{r}})e^{-D\gamma^2\int_0^t\left[\left(\int_0^{t''}\left(\vec{\mathbf{G}}(t')\right)dt'\right)^2\right]dt''}$$

- which can also be expressed as

$$\vec{\mathbf{M}}(\vec{\mathbf{r}},t)=M_0(\vec{\mathbf{r}})e^{-D\int_0^t\mathbf{k}(t')\cdot\mathbf{k}(t')dt'}$$

$$\mathbf{k}(t)=\gamma\int_0^t\vec{\mathbf{G}}(t')dt'$$

The Bloch-Torrey Equations

- Or

$$\vec{\mathbf{M}}(\vec{\mathbf{r}},t) = M_0(\vec{\mathbf{r}})e^{-bD}$$

$$b = \int_0^t \mathbf{k}(t') \cdot \mathbf{k}(t') dt'$$

$$\mathbf{k}(t) = \gamma \int_0^t \vec{\mathbf{G}}(t') dt'$$

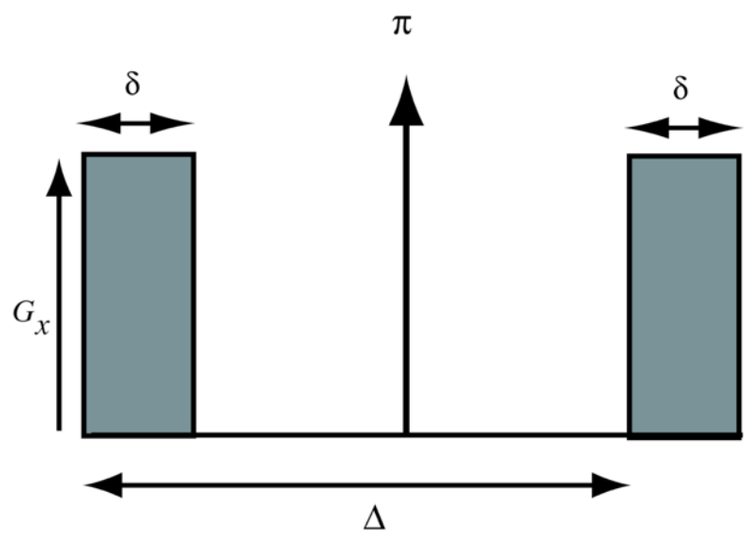
DWI Experiments

- For the **Gradient Echo** NMR experiment at echo time TE:

$$\vec{\mathbf{M}}(TE) = \vec{\mathbf{M}}_0 e^{-D\cdot\gamma^2\cdot\int_0^{TE}\left[\int_0^t \vec{\mathbf{G}}(t')dt'\right]^2 dt}$$

- For the **Pulsed Gradient Spin Echo (PGSE)** NMR experiment at echo time TE:

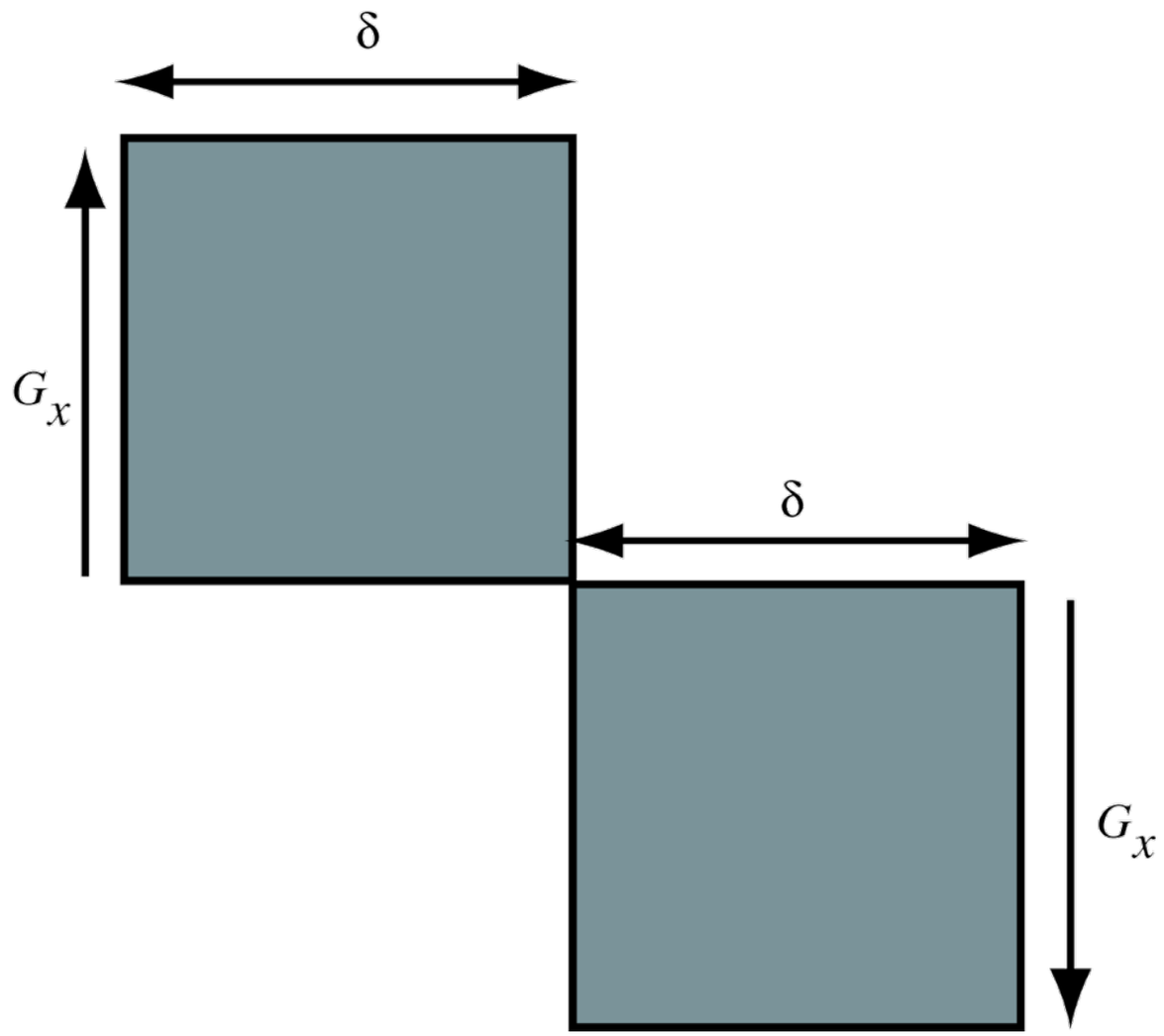
$$\vec{\mathbf{M}}(TE) = \vec{\mathbf{M}}_0 e^{-D\cdot\gamma^2\cdot\left[\int_0^{TE/2}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)^2 dt - 4\cdot\int_0^{TE/2}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)dt\cdot\int_{TE/2}^{TE}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)dt + 4\int_{TE/2}^{TE}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)^2 dt\right]}$$



DWI Experiments

- **Bipolar Gradients with Gradient Echo**

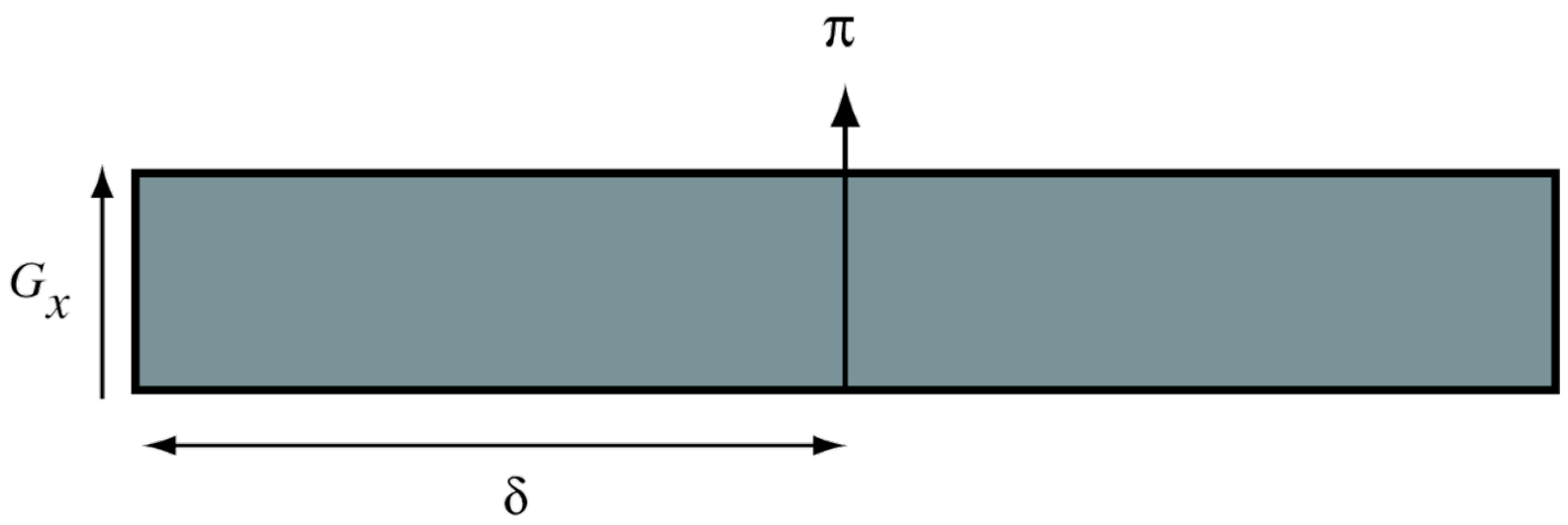
$$b = \frac{2}{3}\gamma^2 G_x^2 \delta^3$$



DWI Experiments

- **Constant Gradient Spin Echo**

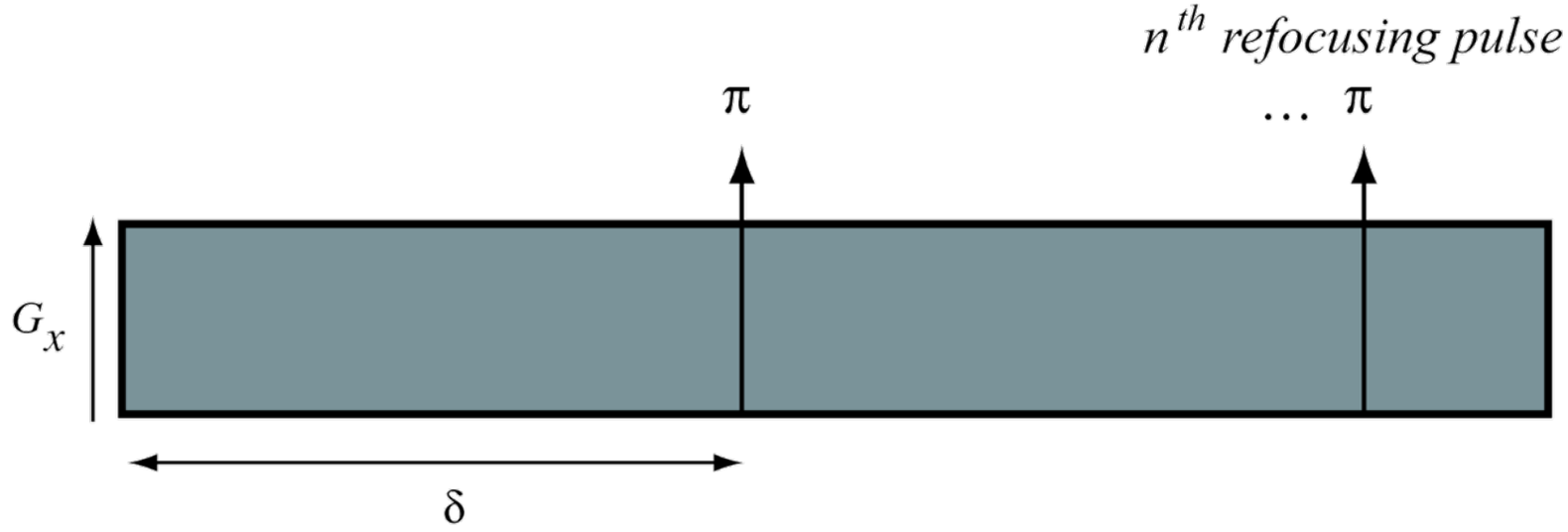
$$b = \frac{2}{3}\gamma^2 G_x^2 \delta^3$$



DWI Experiments

- **Constant Gradient Multiple Spin Echo**

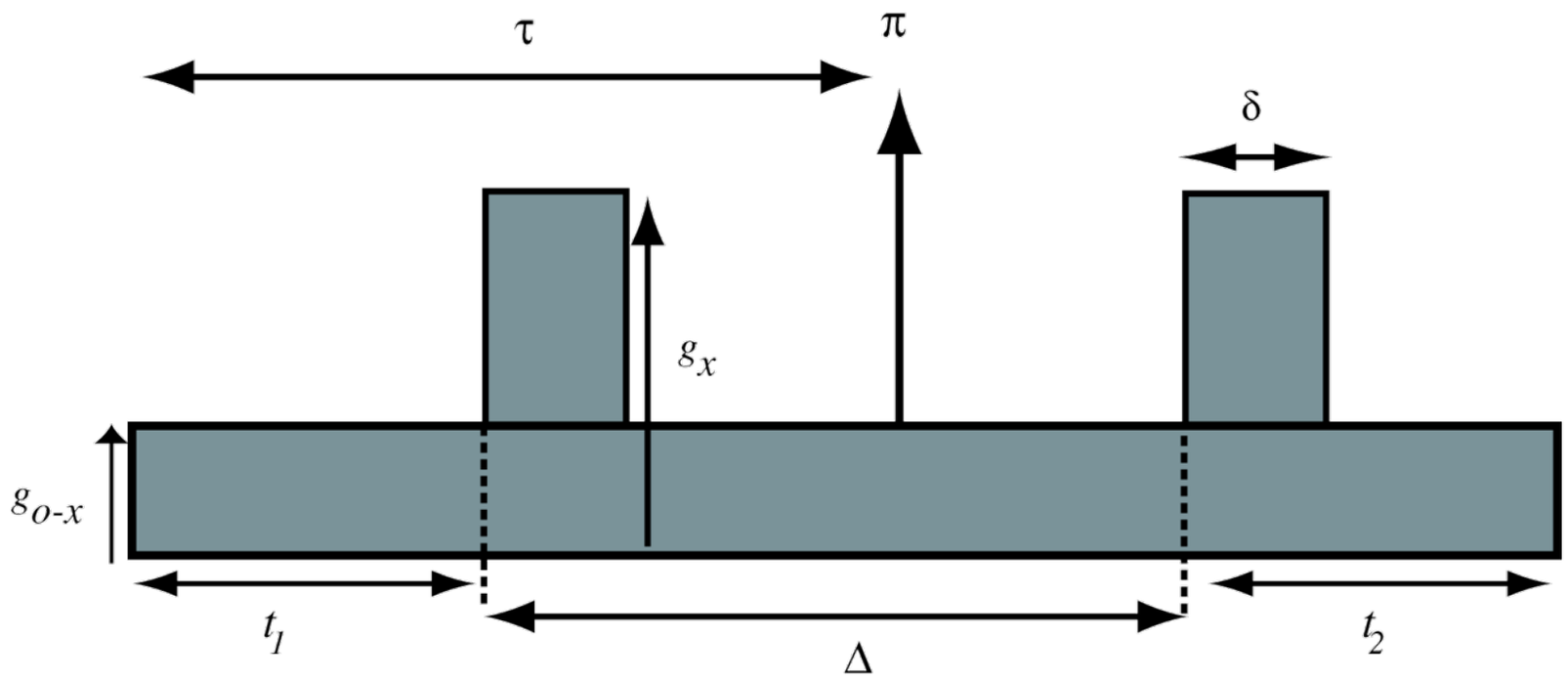
$$b = \frac{\gamma^2 G_x^2 \delta^3}{3n^2}$$



DWI Experiments

- **PGSE + Constant Gradient Spin Echo** (From Stejskal & Tanner, 1965):

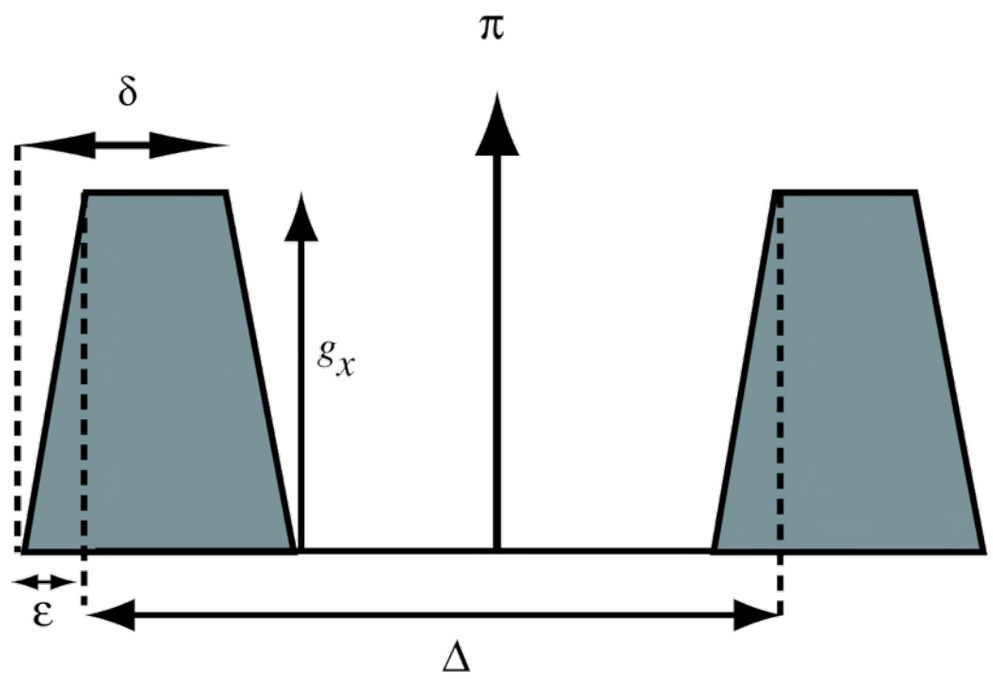
$$b = \gamma^2 \left\{ \frac{2}{3}\tau^3 g_{0-x}^2 + \delta^2 \left(\Delta - \frac{1}{3}\delta \right) g_x^2 + \delta \left[\left(t_1^2 + t_2^2 \right) + \delta \left(t_1 + t_2 \right) + \frac{2}{3}\delta^2 - 2\tau^2 \right] g_x g_{0-x} \right\}$$



DWI Experiments

- **PGSE-Trapezoidal Approximation**

$$b = \gamma^2 G_x^2 \left[\delta^2 \left(\Delta - \frac{\delta}{3} \right) + \frac{\varepsilon^3}{30} - \frac{\delta \cdot \varepsilon^2}{6} \right]$$

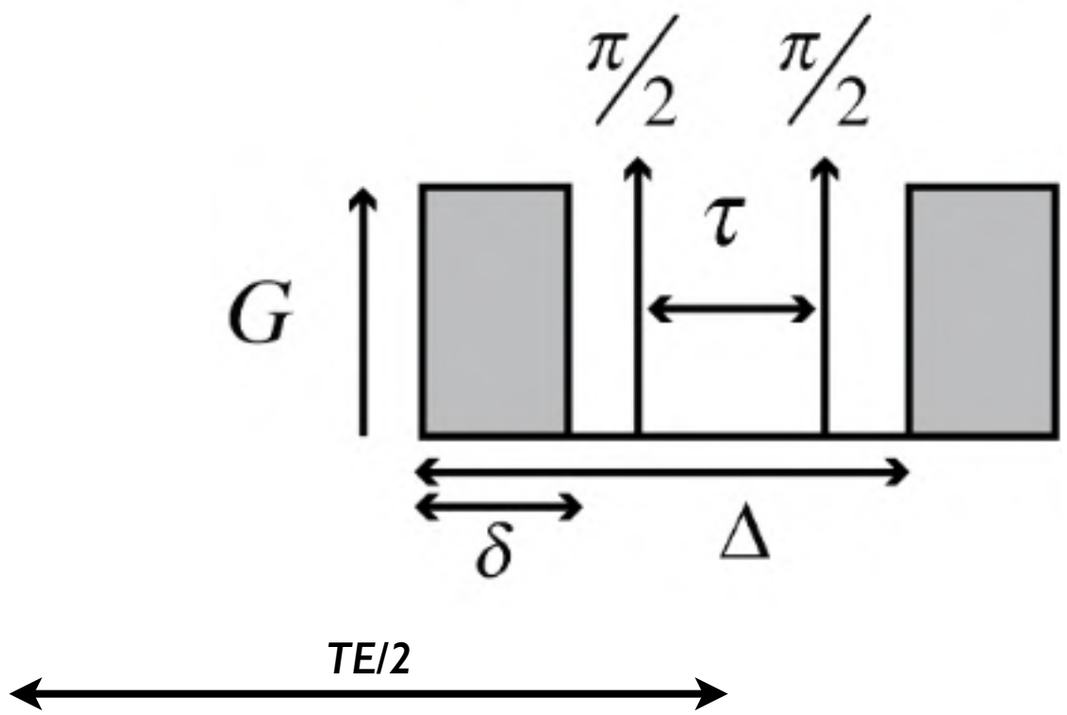


DWI Experiments

- **PGSE using STEAM (stimulated echo acquisition mode)**

  Advantage of long mixing time with little T2 decay because magnetization is stored in the longitudinal orientation

$$b=\gamma^2\cdot\left[\int_0^{TE/2}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)^2 dt-4\cdot\int_0^{TE/2}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)dt\cdot\int_{TE/2}^{TE}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)dt+4\int_{TE/2}^{TE}\left(\int_0^t \vec{\mathbf{G}}(t')dt'\right)^2 dt\right]$$



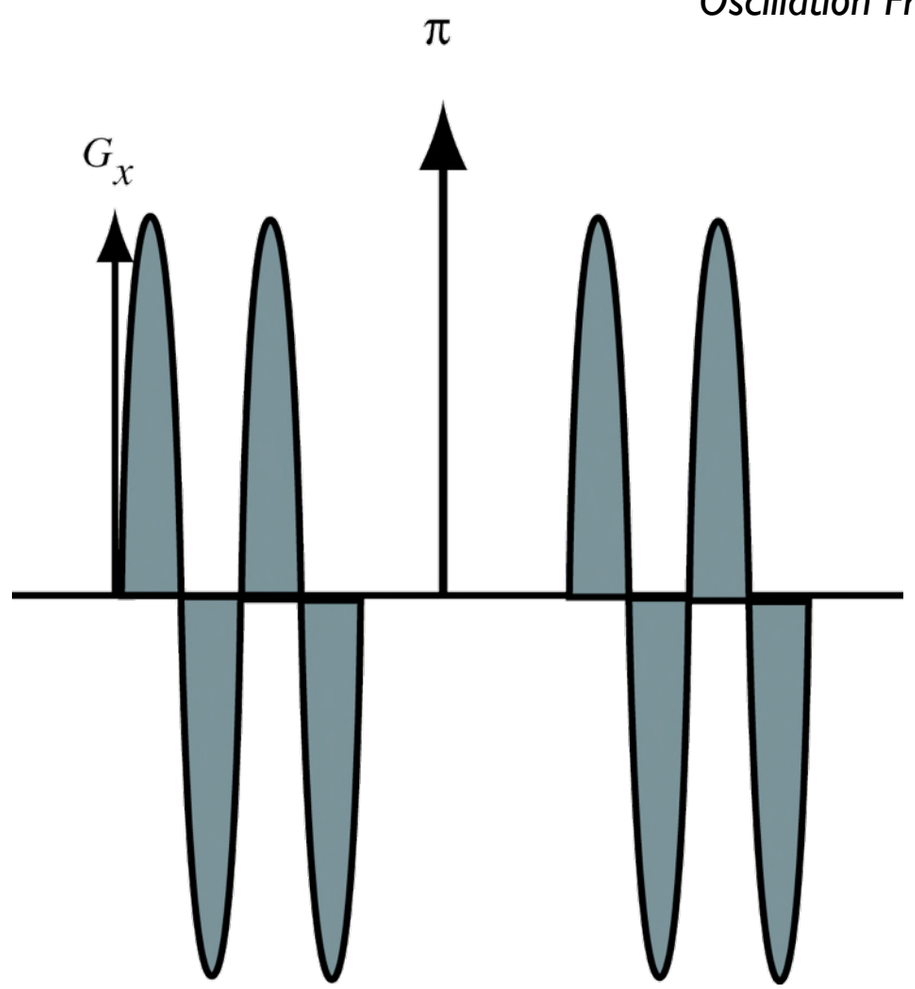
DWI Experiments

- **Oscillating Gradient Spin Echo (OGSE)**

$$b = \gamma^2 G_x^2 \frac{3n}{4\pi^2 f^3}$$

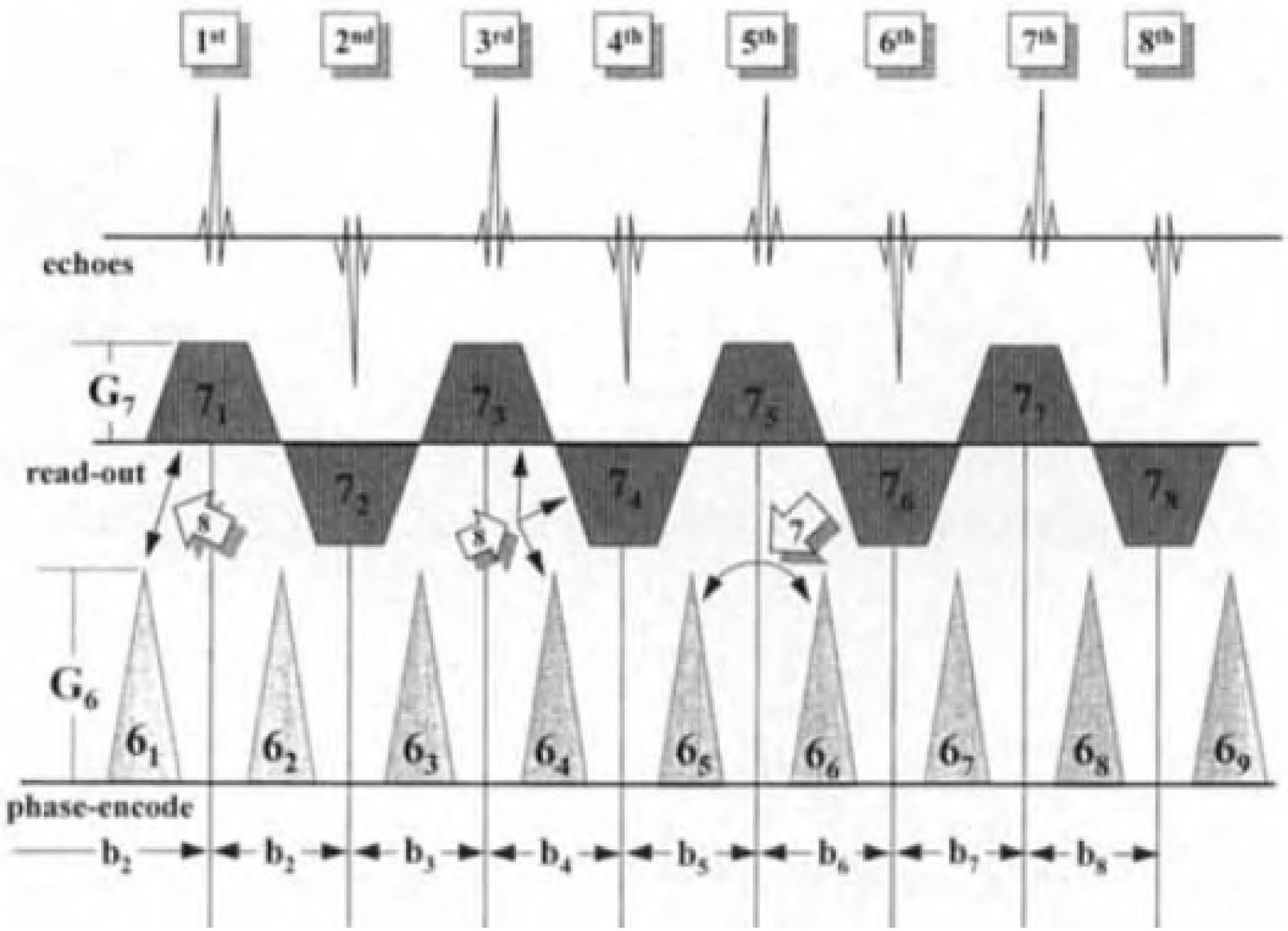
Number of Cycles

Oscillation Frequency



DWI Experiments

- **Effects of Echoplanar Readout** ***(Mattiello J, Basser PJ, Le Bihan D, Magn Reson Med 1997, 37: 292-300)***



Assumption of No Boundaries

- Recall we assumed no boundaries to diffusion so $P\left(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}', t\right) \to 0$ as $\vec{\mathbf{r}}' \to \infty$

- Resulting in

$$P\left(\vec{\mathbf{r}} \mid \vec{\mathbf{r}}', t\right) = \left(\frac{1}{\sqrt{4\pi Dt}}\right)^3 e^{-\frac{\left(\vec{\mathbf{r}}' - \vec{\mathbf{r}}\right)^2}{4Dt}}$$

Gaussian Distribution

- In most conventional NMR experiments, the diffusion time *t* (analogous to ~Δ-δ/3 in PGSE) is around 15-30 *ms*, meaning for a diffusion coefficient of $3 \times 10^{-3} mm^2/s$ (approx free water) results in a mean (1D) displacement of

$$dx = \sqrt{2 \cdot D \cdot \Delta} = 212\mu m - 300\mu m$$

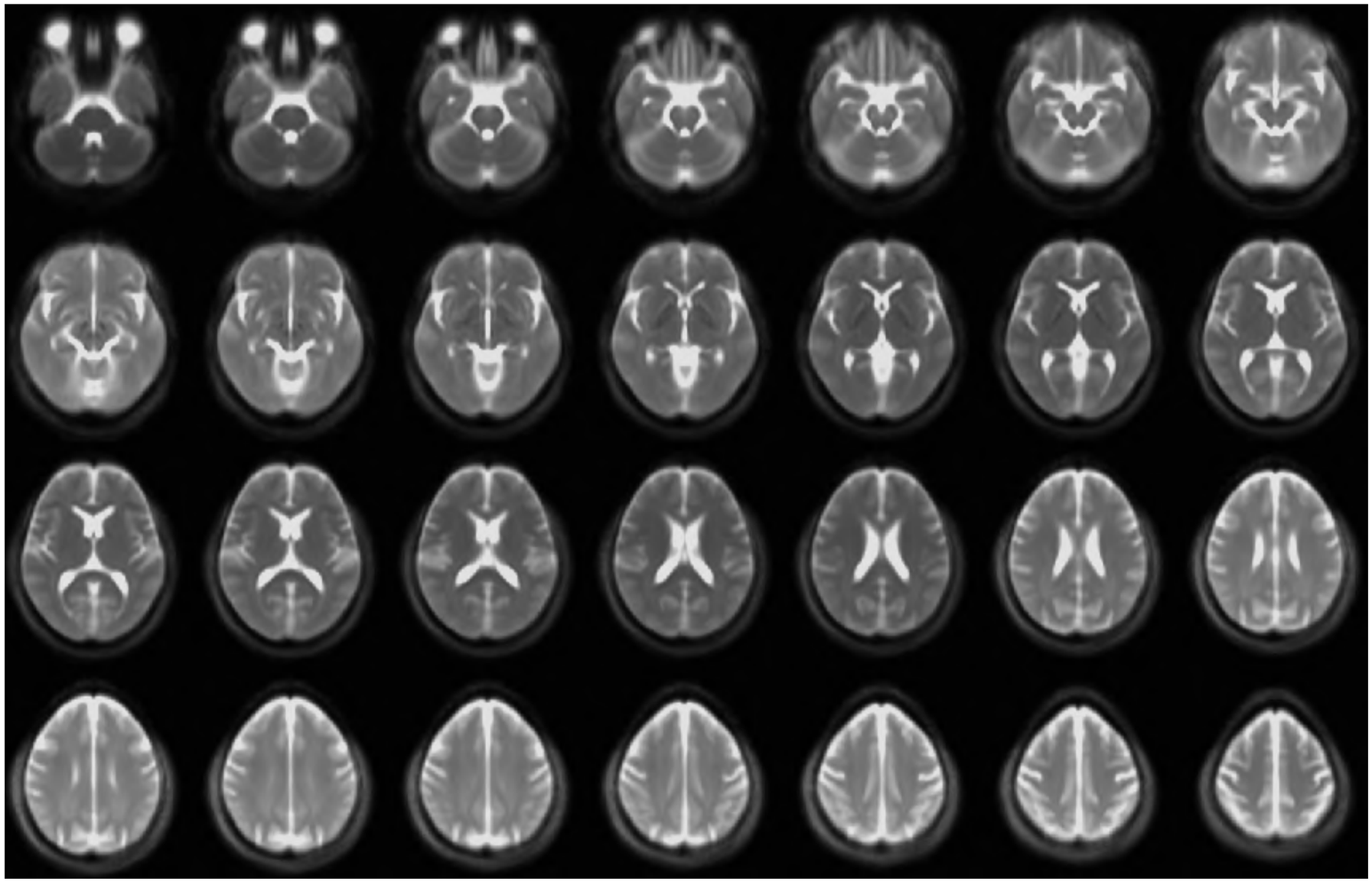
- Cells in the body vary from ~4μm to 100μm in diameter

- This means our assumption of "no boundaries" or "free diffusion" is invalid!

Assumption of No Boundaries

- The measured diffusivity is therefore termed the ***Apparent Diffusion Coefficient (ADC)*** because we cannot accurately measure diffusivity using conventional MRI systems

$$\vec{\mathbf{M}}(\vec{\mathbf{r}},t) = M_0(\vec{\mathbf{r}})e^{-b\cdot ADC}$$



n = 200 Subjects
In collaboration with Dr. Kristen Tillisch & Emeran Meyer
Center for Neurobiology of Stress

Factors that Influence Diffusion Measurements

- Diffusion Time, $\tau \sim \Delta - \delta/3$:
  - The diffusion time (mixing time) determines the sensitivity to compartment size

$$\langle dx \rangle = \sqrt{2D\Delta}$$

- Compartment Size:
  - If compartment size < diffusion compartment sensitivity then we observe an ADC (vs. D)

$$ADC = \frac{\langle dx \rangle^2}{2\Delta}$$

- Tortuosity of the diffusion compartment:

$$ADC = \frac{D}{\theta^2} \qquad \theta = \frac{l_{actual}}{\langle r - r_0 \rangle}$$

- Viscosity and Temperature

$$D = \frac{kT}{6\pi\eta R}$$

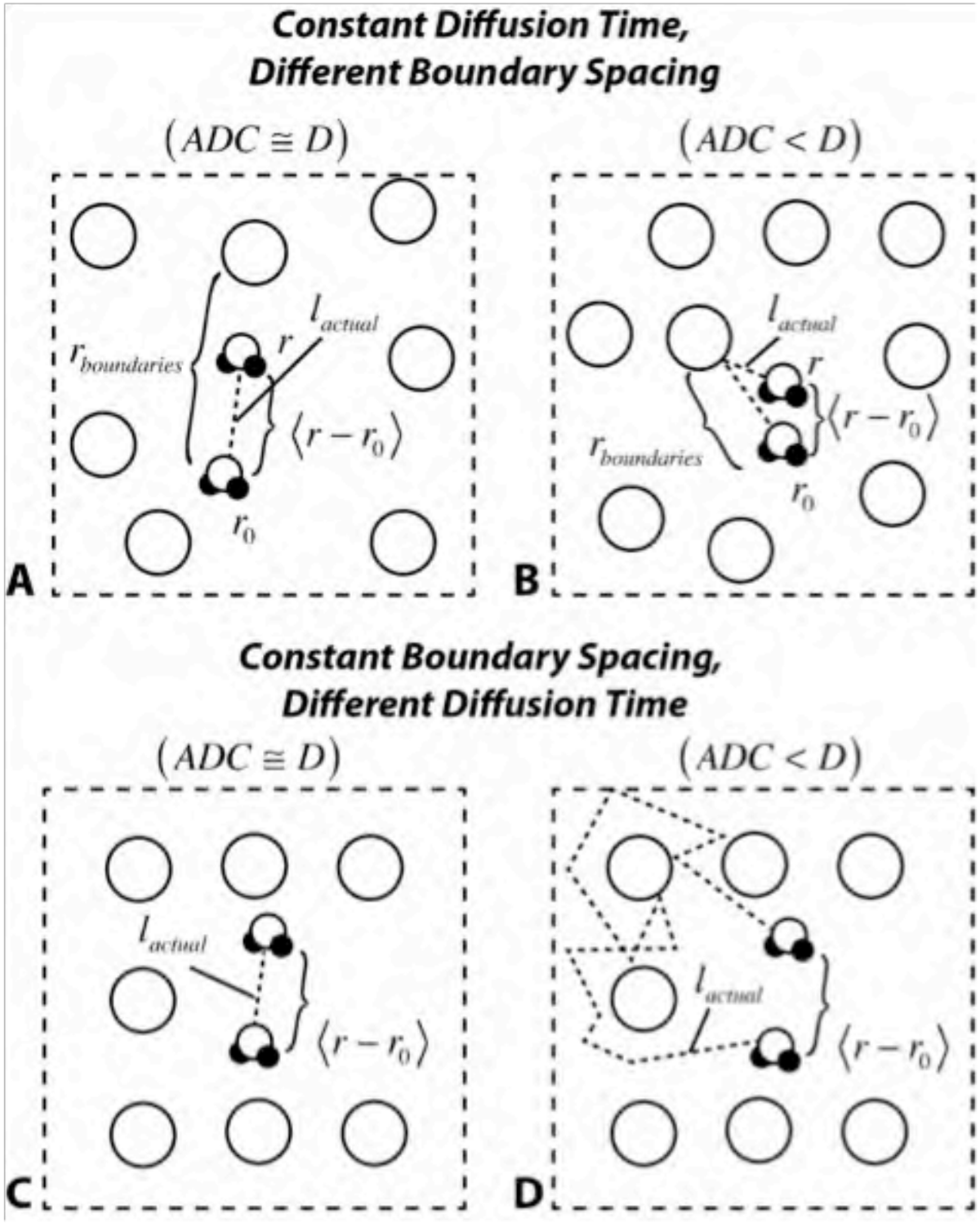
Temperature

Viscosity

Factors that Influence Diffusion Measurements

$$ADC = \frac{D}{\theta^2}$$

$$\theta = \frac{l_{actual}}{\langle r - r_0 \rangle}$$



Simple Diffusion NMR Simulations

- We will revisit the "unrestricted diffusion" assumption again later (q-space, kurtosis imaging, multiexponential diffusion, stretched exponential diffusion, double pulsed gradient, diffusion spectral imaging, and advanced applications)

- However, we can use the signal equation to simulate spins in different environments and estimate the resulting signal (assuming δ<<Δ PGSE)

$$S(TE,TR,\Delta) = A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right) \cdot \sum_{n=1}^{N} e^{-j \cdot \phi_n}$$

Phase accumulated for the n^{th} spin

- First, let's introduce the "Random Walk"

Random Walk

- Let's assume the 1D case first for simplicity
- A spin at a given position x is said to jump to a new spatial position $x + \varepsilon_i\delta$ every τ_d seconds
- Here, δ represents a very small positional change and ε_i is a random number with values ± 1
- During application of a linear gradient $dB/dx = G_x$ in the x-direction, the external magnetic field a spin experiences after the j^{th} time step is

$$B\left(j\cdot\tau_d\right)=B(0)+G\cdot\delta\sum_{i=1}^{j}\varepsilon_i$$

- The *deviation* in the magnetic field at time $t = j \cdot \tau_d$ with respect to the initial position at $t = 0$ is:

$$\Delta B\left(j\cdot\tau_d\right)=B\left(j\cdot\tau_d\right)-B(0)$$

- And thus the phase accumulated at time $t = j \cdot \tau_d$ is:

$$\phi\left(j\cdot\tau_d\right)=-\gamma\cdot\tau_d\sum_{j=1}^{N}\Delta B\left(j\cdot\tau_d\right) \qquad \phi\left(j\cdot\tau_d\right)=-G\cdot\delta\cdot\gamma\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_i$$

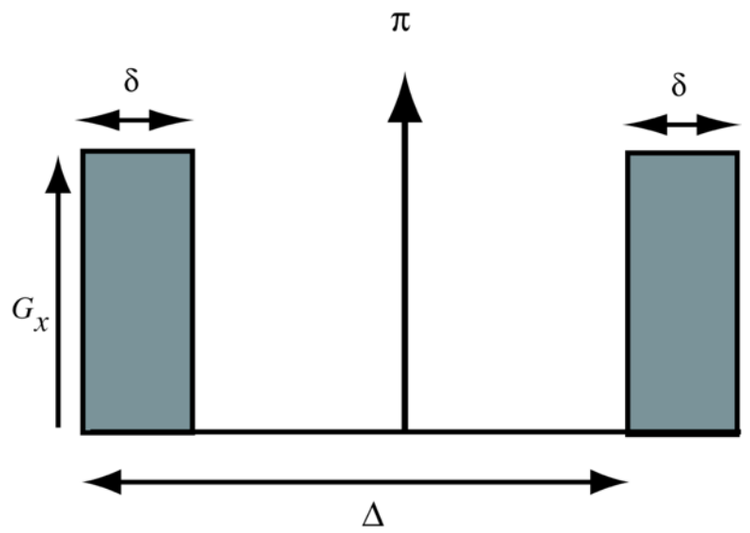
Random Walk

- Using the PGSE approximation (δ<<Δ), the resulting NMR signal is

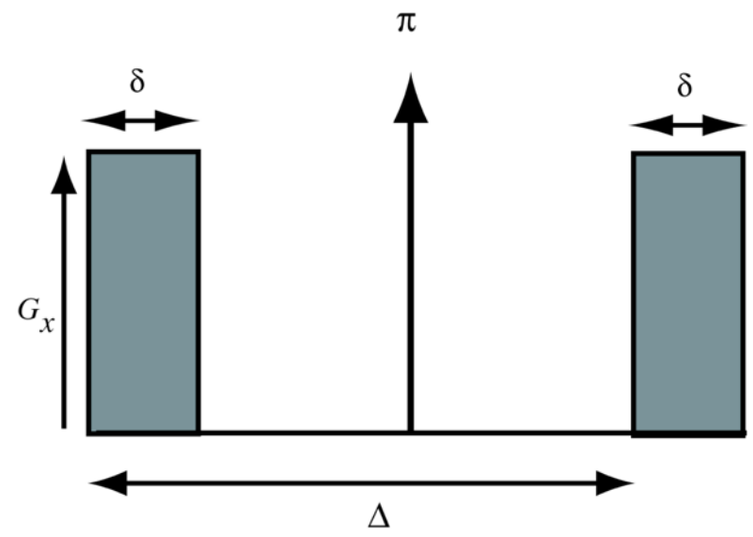
$$S(TE,TR,\Delta) = A \cdot \rho \cdot e^{-TE/T2} \cdot \left(1 - e^{-TR/T1}\right) \cdot \sum_{n=1}^{N} e^{-j \cdot \phi_n}$$

$$\phi_n = \gamma \left(\int_0^{\delta} \vec{\mathbf{G}}(t) \cdot \vec{\mathbf{r}}_1(t)\, dt - \int_{\Delta}^{\Delta+\delta} \vec{\mathbf{G}}(t) \cdot \vec{\mathbf{r}}_2(t)\, dt \right)$$

$$\phi_n = \gamma \left(\int_0^{\delta} G_x(t) \cdot \overbrace{\delta \cdot \tau_d \sum_{j=1}^{N} \sum_{i=1}^{j} \varepsilon_{1i} \Big|_{t=0}^{t=\delta}}^{\text{Distance traveled during first pulse}} dt - \int_{\Delta}^{\Delta+\delta} G_x(t) \cdot \overbrace{\delta \cdot \tau_d \sum_{j=1}^{N} \sum_{i=1}^{j} \varepsilon_{2i} \Big|_{t=\Delta}^{t=\Delta+\delta} + \delta \cdot \tau_d \sum_{j=1}^{N} \sum_{i=1}^{j} \varepsilon_{\Delta i} \Big|_{t=\delta}^{t=\Delta} + \delta \cdot \tau_d \sum_{j=1}^{N} \sum_{i=1}^{j} \varepsilon_{1i} \Big|_{t=0}^{t=\delta}}^{\text{Distance traveled from beginning to end of second pulse}} dt \right)$$



Random Walk



$$\phi_n = \gamma\left(\int_0^{\delta} G_x(t)\cdot\delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{1i}\Big|_{t=0}^{t=\delta}dt - \int_{\Delta}^{\Delta+\delta} G_x(t)\cdot\delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{2i}\Big|_{t=\Delta}^{t=\Delta+\delta} + \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{\Delta i}\Big|_{t=\delta}^{t=\Delta} + \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{1i}\Big|_{t=0}^{t=\delta}dt\right)$$

Distance traveled during first pulse

Distance traveled from beginning to end of second pulse

Position during first pulse

Position during second pulse

Position during "Mixing" Period

Position during first pulse

$$\vec{\mathbf{r}}_1(t) = \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{1i}\Big|_{t=0}^{t=\delta}$$

$$\vec{\mathbf{r}}_2(t) = \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{2i}\Big|_{t=\Delta}^{t=\Delta+\delta} + \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{\Delta i}\Big|_{t=\delta}^{t=\Delta} + \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{1i}\Big|_{t=0}^{t=\delta}$$

Random Walk

- Can use this equation to simulate biophysical environments
  - Boundaries, permeable membranes, etc.
  - Can make these simulations very complicated (different gradient shapes, model T1/T2, flow, etc.)

$$\phi_n = \gamma\left(\int_0^{\delta} G_x(t)\cdot\delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{1i}\Big|_{t=0}^{t=\delta}dt - \int_{\Delta}^{\Delta+\delta} G_x(t)\cdot\delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{2i}\Big|_{t=\Delta}^{t=\Delta+\delta} + \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{\Delta i}\Big|_{t=\delta}^{t=\Delta} + \delta\cdot\tau_d\sum_{j=1}^{N}\sum_{i=1}^{j}\varepsilon_{1i}\Big|_{t=0}^{t=\delta}dt\right)$$

Distance traveled during first pulse

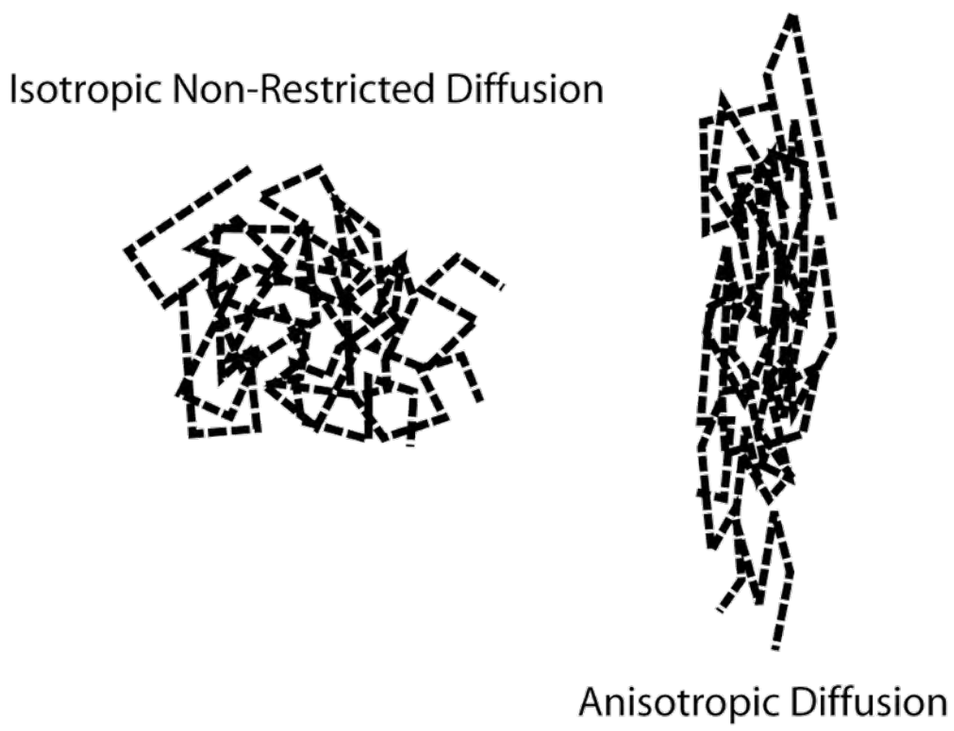
Distance traveled from beginning to end of second pulse

Position during first pulse

Position during first pulse

Assumption of Isotropic Diffusion

- Until now, we have assumed that diffusivity is uniform and have only measured diffusivity in 1 direction
- If diffusion is anisotropic (i.e. unequal in all directions) we may over/under estimate the diffusion coefficient if we measure only a single direction
- In **Diffusion Tensor Imaging (DTI)** we make 1D diffusion measurements in multiple directions, then construct the mathematical 3x3 tensor field that describes the magnitude *and* direction of spin self-diffusion



The Self-Diffusion Tensor

- The traditional diffusion tensor is constructed from 6 independent diffusion sensitizing directions, and a single $b = 0$ image

- The diffusion coefficients for each of these 6 directions are calculated by

$$\vec{Y} = \begin{bmatrix} D_1 \\ D_2 \\ \vdots \\ D_6 \end{bmatrix} = \begin{bmatrix} -\frac{1}{b}\ln\left(\frac{S_1}{S_0}\right) & -\frac{1}{b}\ln\left(\frac{S_2}{S_0}\right) & \cdots & -\frac{1}{b}\ln\left(\frac{S_6}{S_0}\right) \end{bmatrix}^T$$

- where D_i are the diffusion coefficients, S_i are the MR signal after the i^{th} diffusion direction was applied, b is the b-factor, and S_0 is the MR signal with no diffusion weighting.

The Self-Diffusion Tensor

- The measured diffusion coefficients can be written as:

$$D_i = g_{xi}^2 D_{xx} + g_{yi}^2 D_{yy} + g_{zi}^2 D_{zz} + 2g_{xi}g_{yi}D_{xy} + 2g_{xi}g_{zi}D_{xz} + 2g_{yi}g_{zi}D_{yz}$$

- where *gxi* represents the normalized gradient vector direction in the x-direction for the i^{th} diffusion direction, and D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, and D_{yz} are the diffusion tensor components

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

- The matrix solution to the diffusion tensor can be written as:

$$\vec{D} = \vec{H}^{-1}\vec{Y}$$

where

$$\vec{H} = \begin{bmatrix} g_{x1}^2 & g_{y1}^2 & g_{z1}^2 & 2g_{x1}g_{y1} & 2g_{x1}g_{z1} & 2g_{y1}g_{z1} \\ g_{x2}^2 & g_{y2}^2 & g_{z2}^2 & 2g_{x2}g_{y2} & 2g_{x2}g_{z2} & 2g_{y2}g_{z2} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ g_{x6}^2 & g_{y6}^2 & g_{z6}^2 & 2g_{x6}g_{y6} & 2g_{x6}g_{z6} & 2g_{y6}g_{z6} \end{bmatrix}$$

The Self-Diffusion Tensor

- For > 6 directions, least-squares regression (or some other type of fitting algorithm) must be used to find the solution

$$\vec{D} = \vec{H}^{-1}\vec{Y}$$

$$\vec{Y} = \begin{bmatrix} D_1 \\ D_2 \\ \vdots \\ D_n \end{bmatrix} = \begin{bmatrix} -\frac{1}{b}\ln\left(\frac{S_1}{S_0}\right) & -\frac{1}{b}\ln\left(\frac{S_2}{S_0}\right) & \cdots & -\frac{1}{b}\ln\left(\frac{S_n}{S_0}\right) \end{bmatrix}^T$$

$$\vec{H} = \begin{bmatrix} g_{x1}^2 & g_{y1}^2 & g_{z1}^2 & 2g_{x1}g_{y1} & 2g_{x1}g_{z1} & 2g_{y1}g_{z1} \\ g_{x2}^2 & g_{y2}^2 & g_{z2}^2 & 2g_{x2}g_{y2} & 2g_{x2}g_{z2} & 2g_{y2}g_{z2} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ g_{xn}^2 & g_{yn}^2 & g_{zn}^2 & 2g_{xn}g_{yn} & 2g_{xn}g_{zn} & 2g_{yn}g_{zn} \end{bmatrix}$$

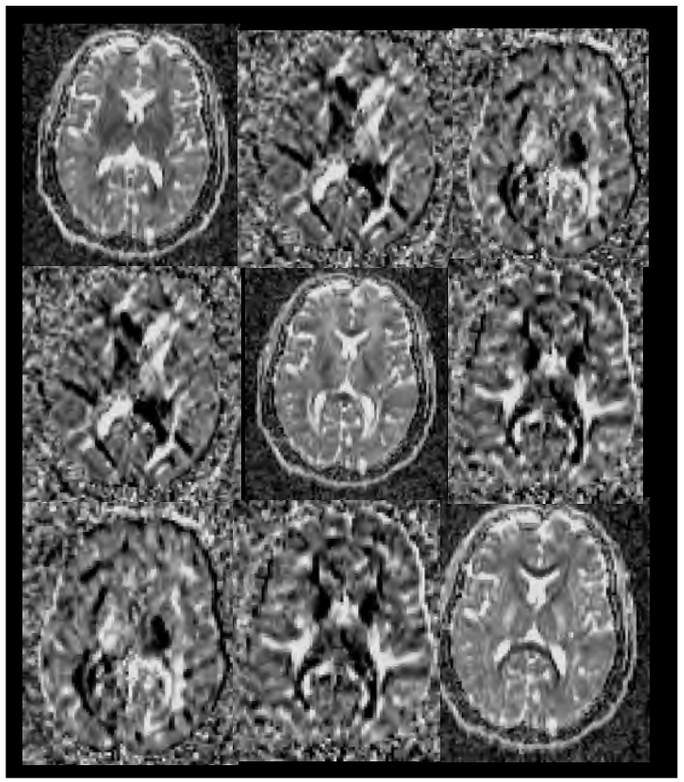
The Self-Diffusion Tensor

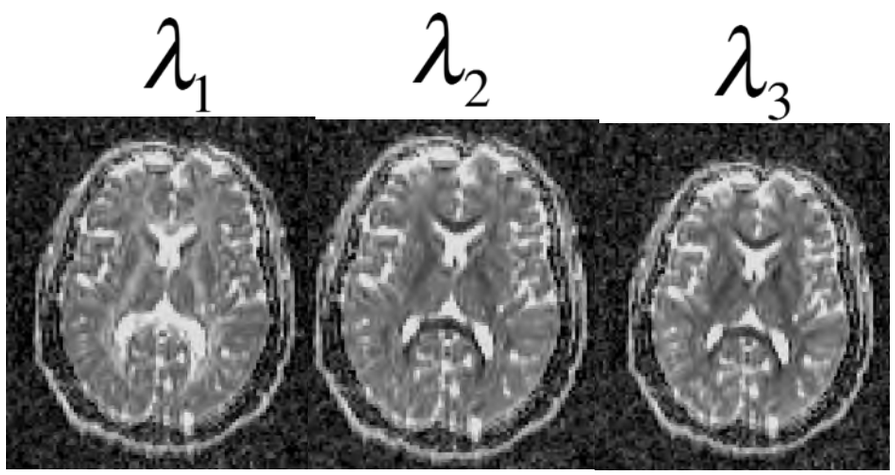
$$\vec{D} = \begin{bmatrix} D_{xx} & D_{yy} & D_{zz} & D_{xy} & D_{xz} & D_{yz} \end{bmatrix}^T$$

Reorganize

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

Symmetry





Solve Eigenvalue Equation

$$\left(\vec{D} - \lambda \vec{I}\right)\vec{v} = 0$$

3 Eigenvalues:
Diffusion magnitude in orthogonal directions

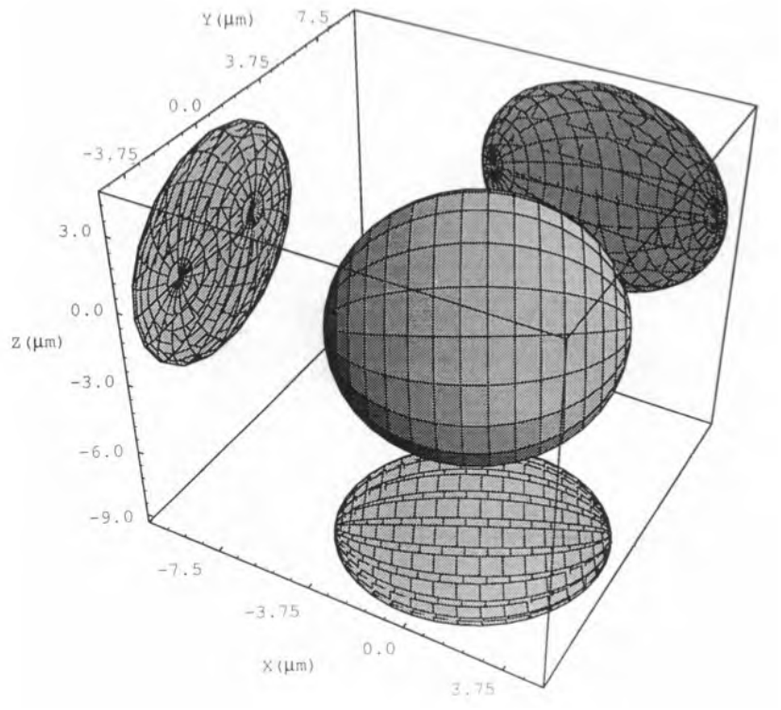
3 Eigenvectors:
Diffusion direction with respect to original coordinate system

The Self-Diffusion Tensor Ellipsoid Model

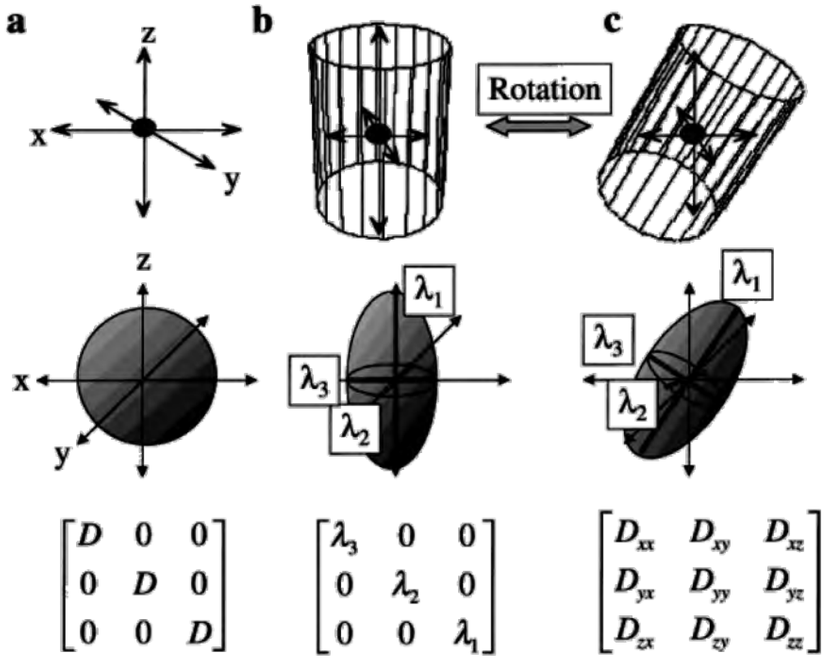
The 3x3 diffusion tensor equation = conic section equation for an ellipsoid:

$$D_i = g_{xi}^2 D_{xx} + g_{yi}^2 D_{yy} + g_{zi}^2 D_{zz} + 2g_{xi}g_{yi}D_{xy} + 2g_{xi}g_{zi}D_{xz} + 2g_{yi}g_{zi}D_{yz}$$

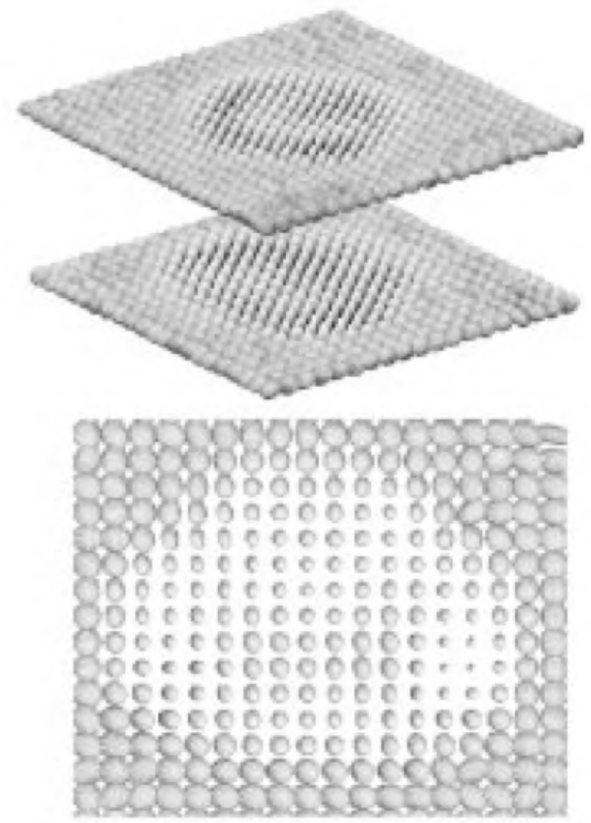
$$\left(\frac{x'}{\sqrt{2\lambda_1\tau}}\right)^2 + \left(\frac{y'}{\sqrt{2\lambda_2\tau}}\right)^2 + \left(\frac{z'}{\sqrt{2\lambda_3\tau}}\right)^2 = 1$$



From: Basser, *Biophys J*, 1994



From: Mori, *Anat Rec*, 1999

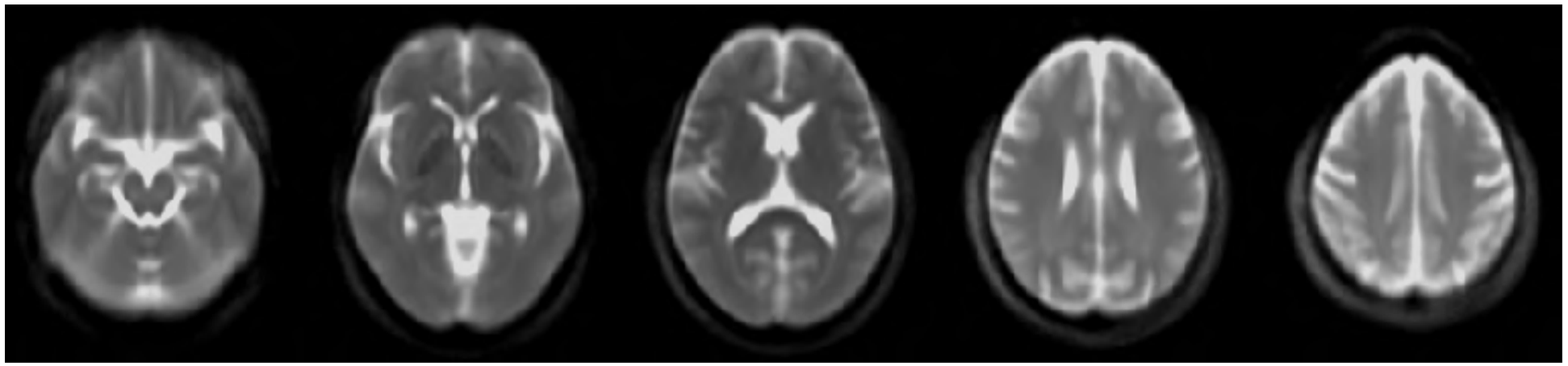


From: Ellingson, *Concepts in MR*, 2008

The Self-Diffusion Tensor

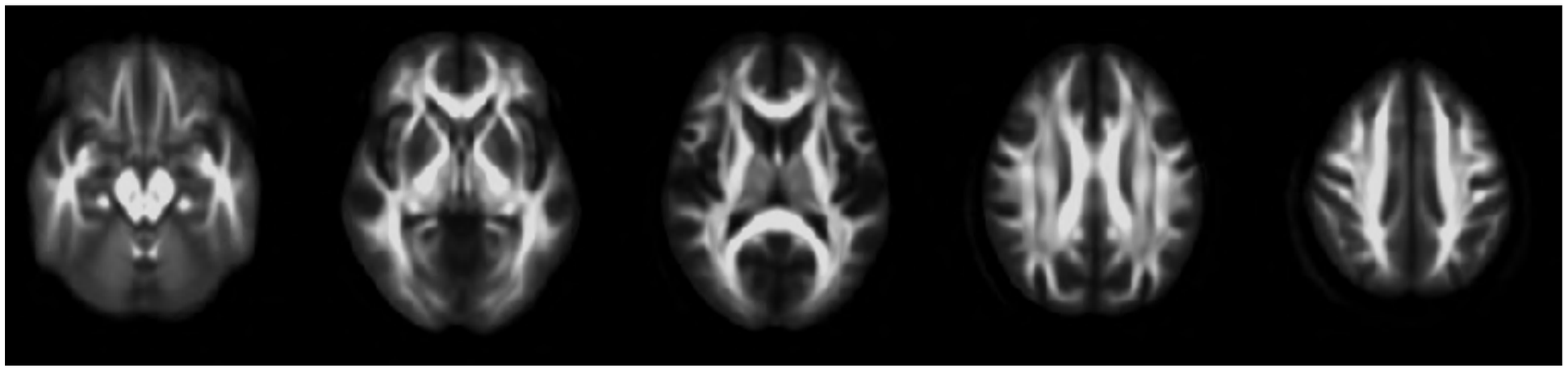
- Diffusion Tensor "Stains"
  - Mean Diffusivity (Trace ADC)

$$MD = \lambda' = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$



  - Fractional Anisotropy (FA)

$$FA = \sqrt{\frac{3\left[\left(\lambda_1 - \lambda'\right)^2 + \left(\lambda_2 - \lambda'\right)^2 + \left(\lambda_3 - \lambda'\right)^2\right]}{2\left(\lambda_1^2 + \lambda_2^2 + \lambda_3^2\right)}}$$



The Self-Diffusion Tensor

- We will revisit DTI later in "Applications" Lecture

Monoexponential Diffusion

- Recall we assumed no boundaries to diffusion so:

$$P\left(\vec{\mathbf{r}}'\,|\,\vec{\mathbf{r}},t\right)\rightarrow 0 \text{ as } \vec{\mathbf{r}}'\rightarrow\infty$$

$$P\left(\vec{\mathbf{r}}'-\vec{\mathbf{r}}=0,t\right)\rightarrow 0 \text{ as } t\rightarrow\infty$$

- Resulting in

$$P\left(\vec{\mathbf{r}}'\,|\,\vec{\mathbf{r}},t\right)=\left(\frac{1}{\sqrt{4\pi Dt}}\right)^3 e^{-\frac{\left(\vec{\mathbf{r}}'-\vec{\mathbf{r}}\right)^2}{4Dt}}$$

Gaussian Distribution

- Since we can only measure diffusion in a single direction at one time,

$$P\left(z,t\right)=\left(\frac{1}{\sqrt{4\pi Dt}}\right) e^{-\frac{z^2}{4Dt}}$$

- This approximation during a bipolar motion probing gradient:

$$\frac{S}{S_0}=e^{-\left(\gamma G_z \delta\right)^2 D\Delta}=e^{-bD}$$

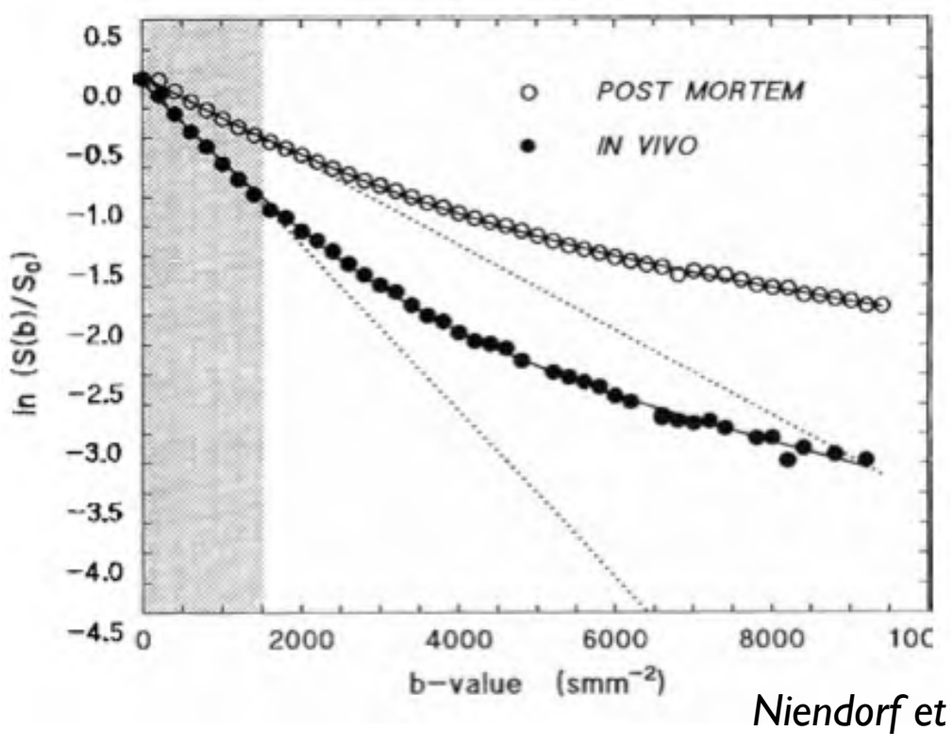
Monoexponential Diffusion

- We see that the assumption of a single, nonrestricted compartment results in a single exponential

$$\frac{S}{S_0} = e^{-(\gamma G_z \delta)^2 D\Delta} = e^{-bD}$$

- Not only does this assume that diffusion is *not restricted*, but it also assumes a **single compartment** (single diffusion coefficient "D")

- Early investigations have shown that water diffusion in the brain is ***not*** monoexponential (at high b-values)

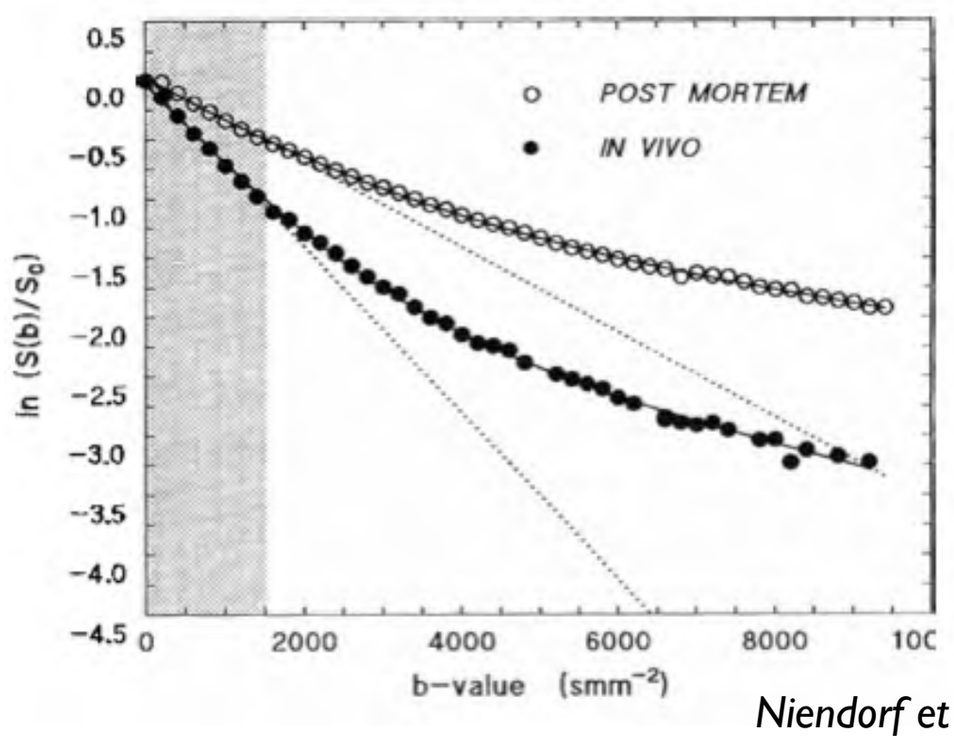


Niendorf et al., MRM, 1996

Biexponential Diffusion

- This lead to development of a biexponential diffusion model (sum of two Gaussians)
- Still doesn't deal with the assumption of non-restricted diffusion
- Hypothesized to be biologically relevant (intracellular, slow vs. extracellular, fast)

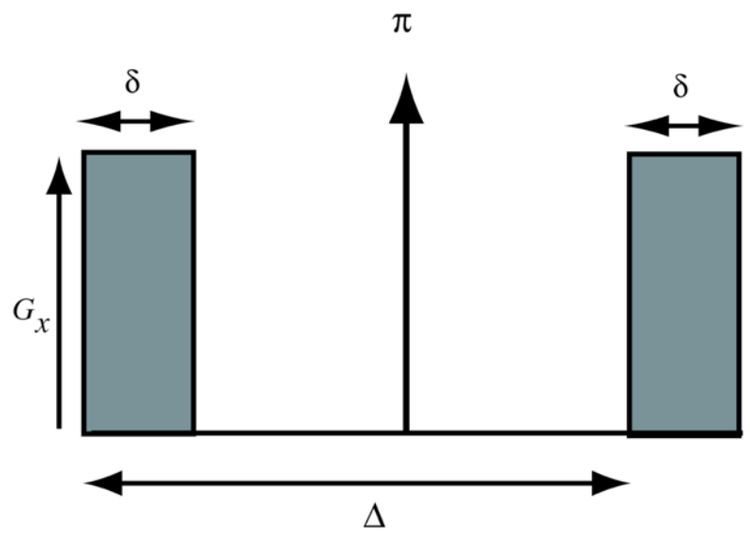
$$\frac{S(b)}{S_0} = A_1 e^{-b \cdot D_{fast}} + A_2 e^{-b \cdot D_{slow}}$$



Niendorf et al., MRM, 1996

Biexponential Diffusion - Two Compartment Model

- Let's examine this model in more detail:
- For the PGSE experiment, diffusion time $\tau = \Delta - \delta/3$
- Brain tissue is composed (primarily) of intracellular and extracellular subregions, partitioned by *semipermeable* cell membranes (vascular space is < 5% total brain volume)
- The exchange between intracellular and extracellular water taking place during the diffusion time τ must be considered with respect to the mean lifetime $\tau_{in(ex)}$ of water molecules in both environments



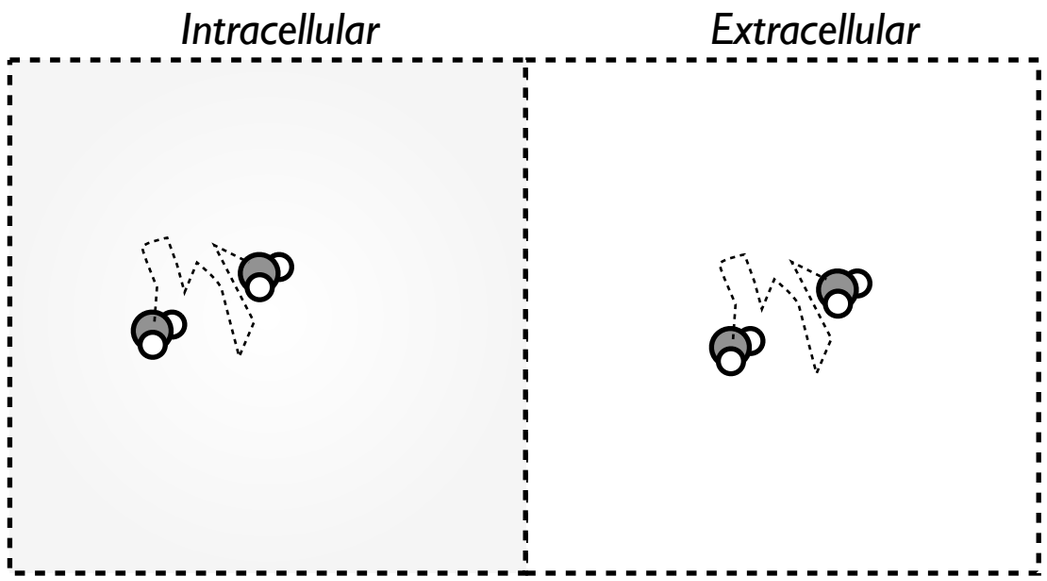
Biexponential Diffusion - Two Compartment Model

- **<u>In the short diffusion time limit</u>:**
  - Diffusion time τ is negligibly short in comparison to the mean life time in either compartment

$$\tau \ll \tau_{in(ex)}$$

  - The system will behave as two *<u>distinct</u>* nonexchanging compartments
  - Echo attenuation is the linear superposition of two monoexponential functions

$$\frac{S(b)}{S_0} = f_{in} e^{-bD_{in}} + f_{ex} e^{-bD_{ex}}$$



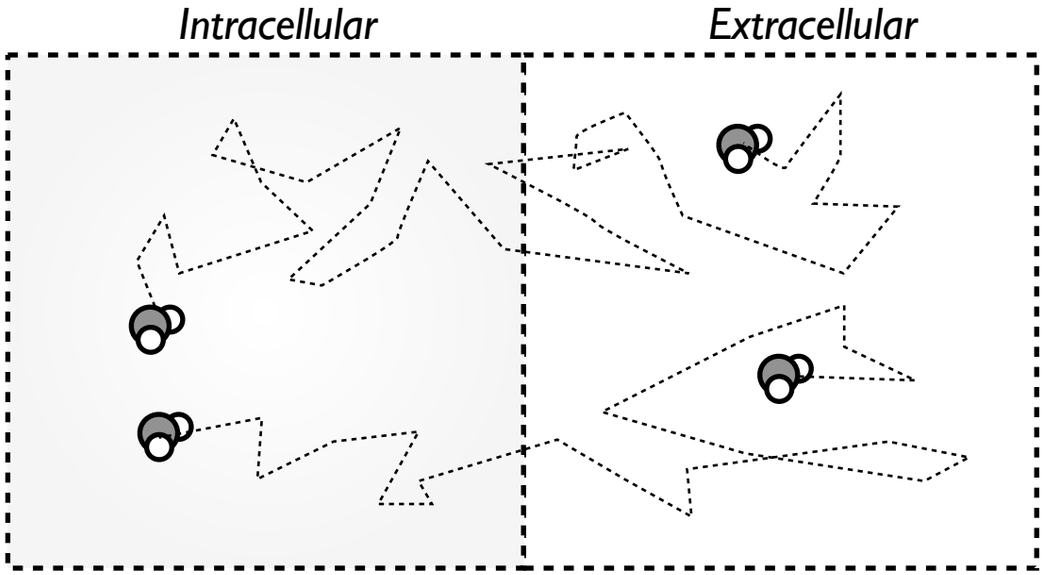
Biexponential Diffusion - Two Compartment Model

- **<u>In the long diffusion time limit</u>:**
  - Diffusion time τ is very long in comparison to the mean life time in either compartment

$$\tau \gg \tau_{in(ex)}$$

  - The system will behave as *<u>one</u>* perfectly mixed (completely exchanged) compartment
  - Echo attenuation is monoexponential

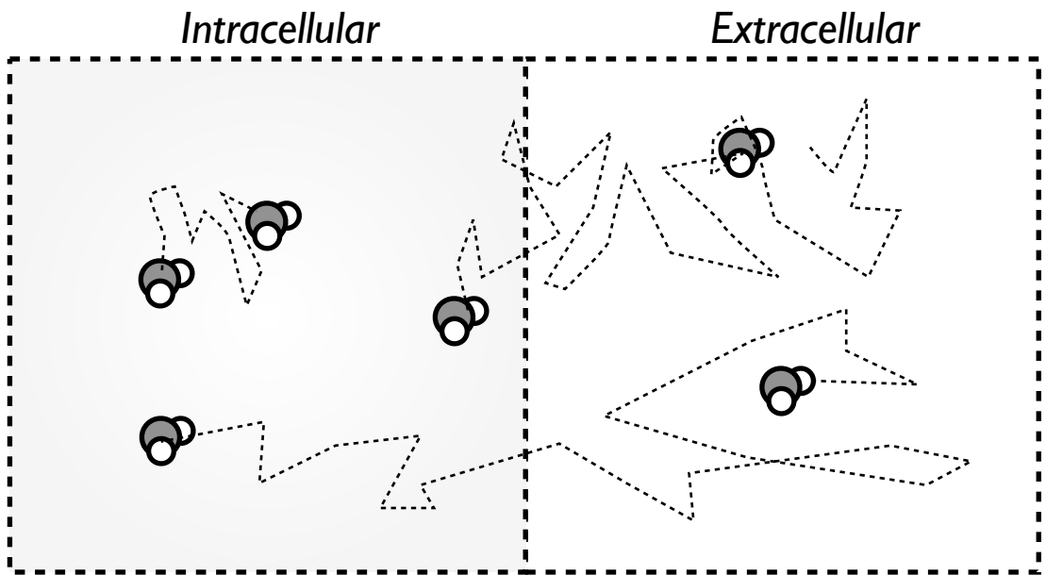
$$\frac{S(b)}{S_0} = e^{-b\left(f_{in}D_{in} + f_{ex}D_{ex}\right)} \qquad ADC = f_{in}D_{in} + f_{ex}D_{ex}$$



Biexponential Diffusion - Two Compartment Model

- **<u>Intermediate diffusion time limit</u>:**
  - Analytic derivation in Kärger et al. (*Adv Magn Reson, 1988)*
  - Fits "apparent" biexponential parameters

$$\frac{S(b)}{S_0} = f'_{in}\, e^{-bD'_{in}} + f'_{ex}\, e^{-bD'_{ex}}$$



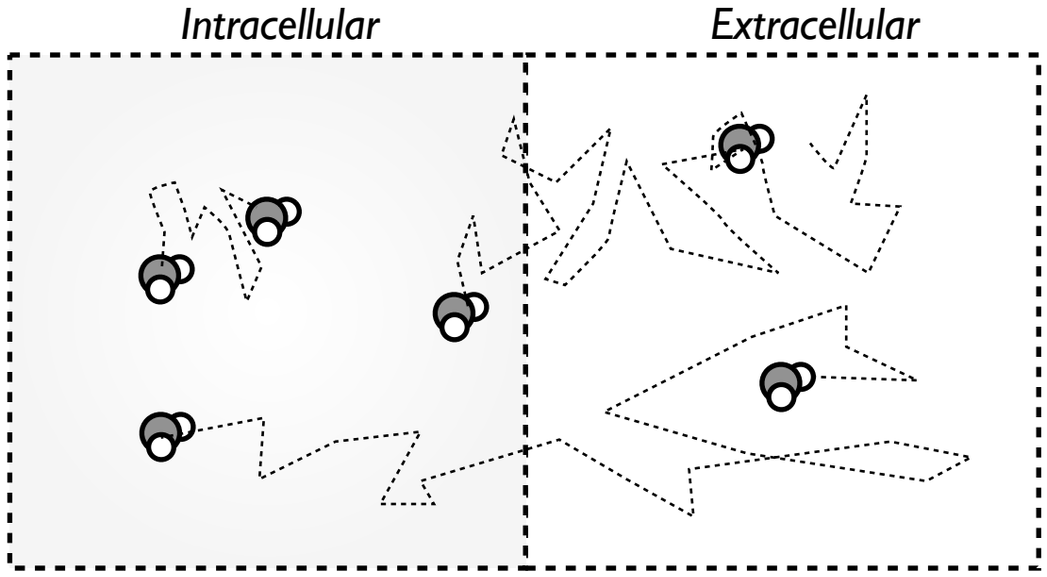
Biexponential Diffusion - Two Compartment Model

- **<u>Intermediate diffusion time limit</u>:**
  - Analytic derivation in Kärger et al. (*Adv Magn Reson, 1988)*
  - Fits "apparent" biexponential parameters

$$D'_{ex(in)} = \frac{1}{2}\left[D_{ex} + D_{in} + \frac{1}{(\gamma\delta G)^2}\left(\frac{1}{\tau_{ex}} + \frac{1}{\tau_{in}}\right) \pm \left(\left(D_{in} - D_{ex} + \frac{1}{(\gamma\delta G)^2}\left(\frac{1}{\tau_{in}} - \frac{1}{\tau_{ex}}\right)\right)^2 + \left(\frac{4}{(\gamma\delta G)^2 \tau_{in}\tau_{ex}}\right)\right)^{1/2}\right]$$

Extracellular

Intracellular



Biexponential Diffusion - Two Compartment Model

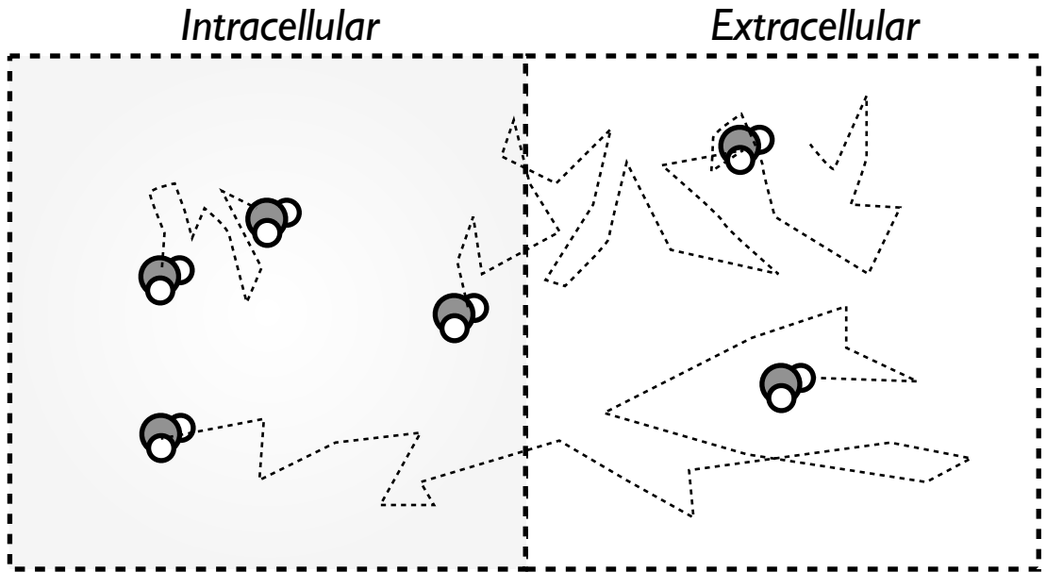
- **<u>Intermediate diffusion time limit</u>:**
  - Analytic derivation in Kärger et al. (*Adv Magn Reson, 1988)*

$$f'_{ex} = 1 - f'_{in}$$

$$f'_{in} = \frac{1}{D'_{in} - D'_{ex}}\left(f_{ex}D_{ex} + f_{in}D_{in} - D'_{ex}\right)$$

  - Biologically (in the brain) $f_{in} \approx 0.8$ and $f_{ex} \approx 0.2$

- $D_{in} < D_{ex}$ due to higher protein concentrations and viscosity in cytosol
- ***<u>Decrease</u>*** in τ will ***<u>increase</u>*** deviation from monoexponential



Biexponential Diffusion - Two Compartment Model

- Although this model is appealing, careful studies have shown the volume fractions calculated are actually flipped from expected (Mulkern *NMR Biomed*, 1999; Clark CA, *Magn Reson Med*, 2000)

- Tissue is more complex than two compartments (*we haven't discussed the potential contributions of permeability of the "semi" permeable membrane*)

- The result of these findings is that these biexponential diffusion coefficeints are no longer referred to as "intra" and "extra" cellular diffusion coefficients

- Instead, they are "fast" and "slow" diffusion coefficients and "fast" and "slow" diffusion compartments

$$\frac{S(b)}{S_0} = f \cdot e^{-b \cdot D_{fast}} + (1-f) e^{-b \cdot D_{slow}}$$

Stretched (continuous) Exponential Model

- The experiments by Mulkern and Clark in 1999-2000 resulted in a new exploration of diffusion models for explaining the non-monoexponential diffusion behavior

- In brain tumors, the environment is highly heterogeneous (cell sizes, shapes, tortuosity of EC space, edema, changes in extracellular matrix)

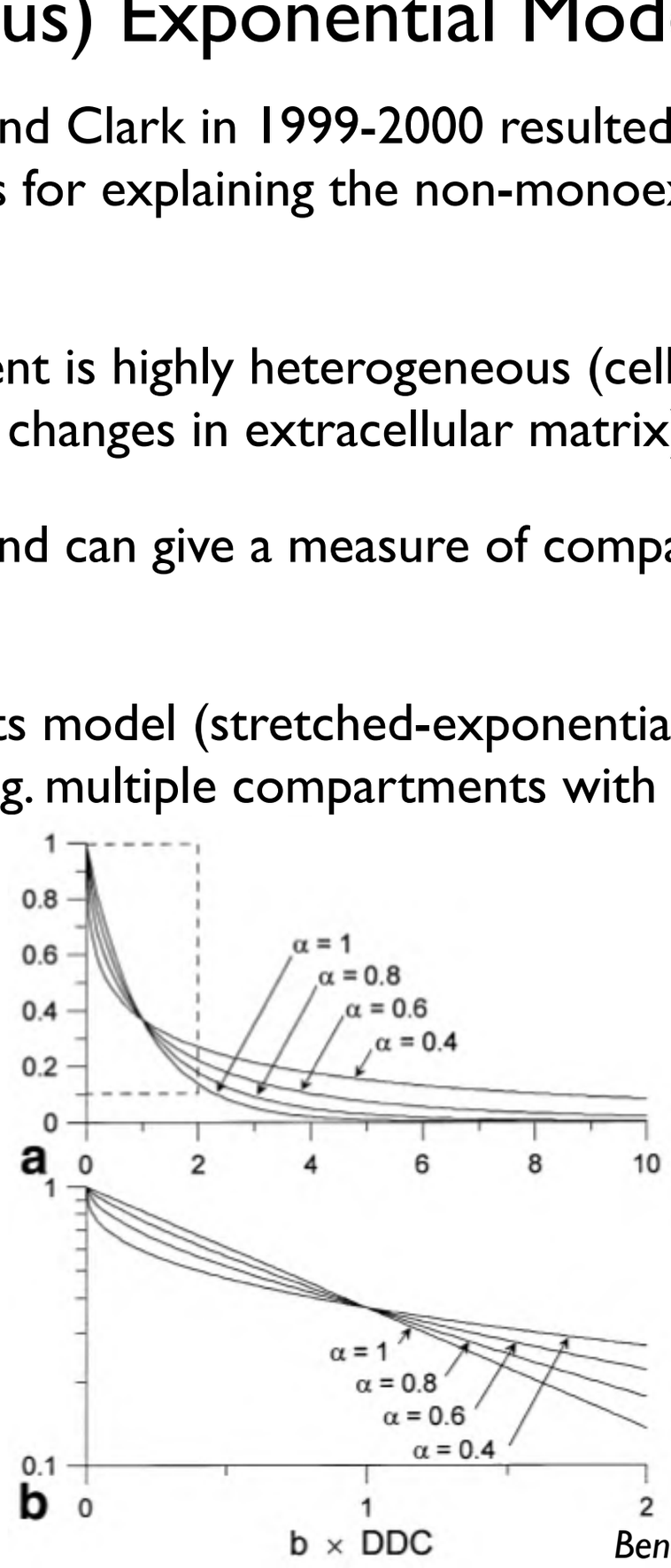
- Need a model that is flexible and can give a measure of compartment *heterogeneity*

- The Kohlrausch-Williams-Watts model (stretched-exponential model) has been used in many areas of NMR (e.g. multiple compartments with different T2)

Heterogeneity Index
0 < α < 1

$$\frac{S(b)}{S_0} = e^{-(b \cdot DDC)^{\alpha}}$$

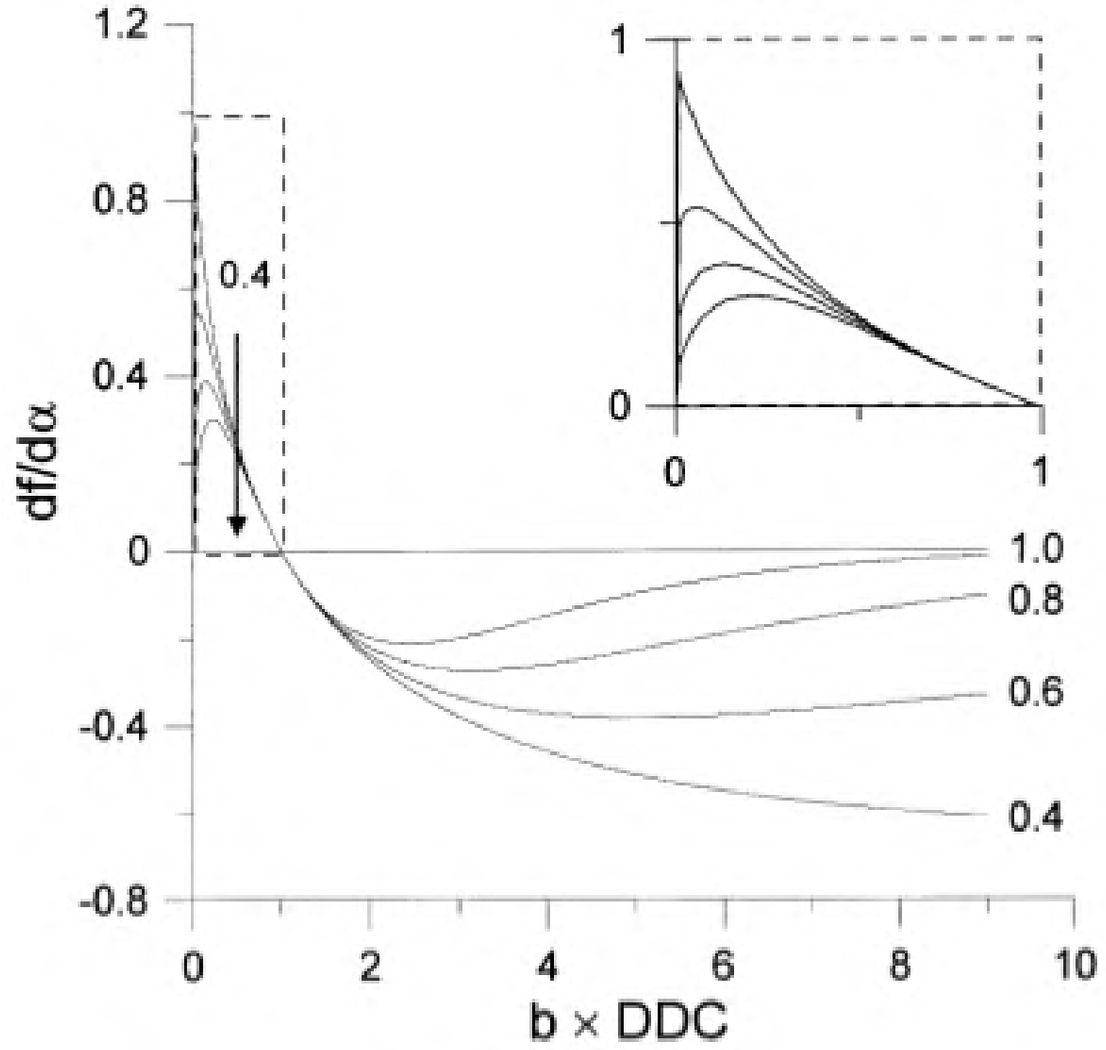
Distributed Diffusion Coefficient



Bennett, MRM, 2003

Stretched (continuous) Exponential Model

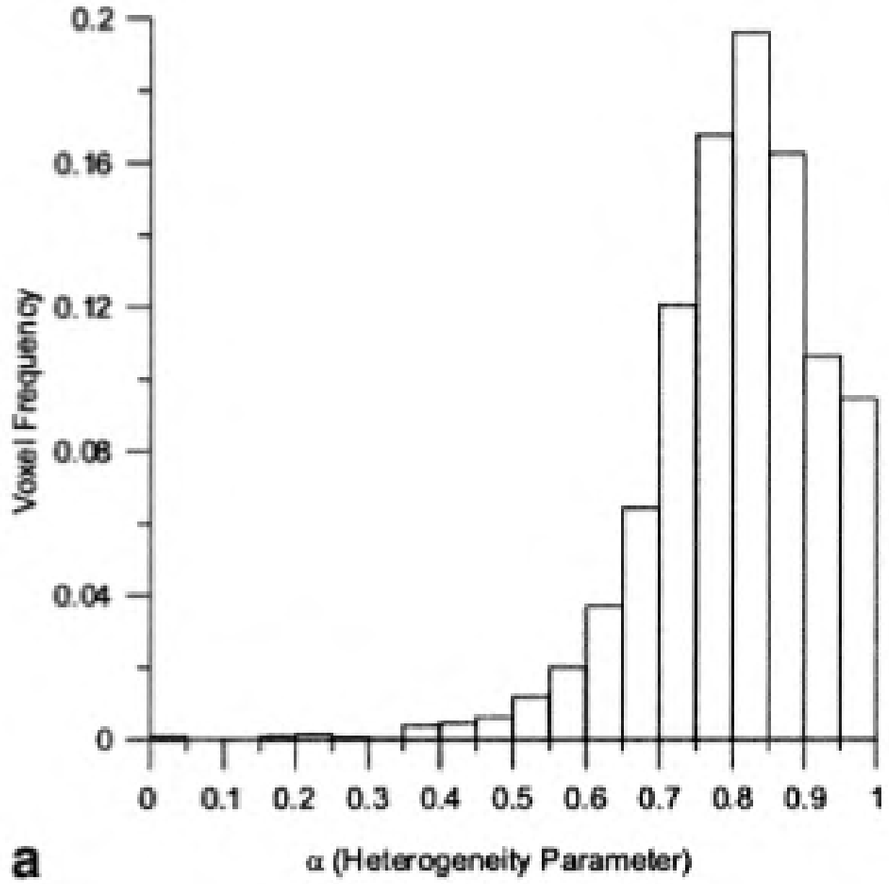
- Sensitivity of the diffusion signal due to changes in α

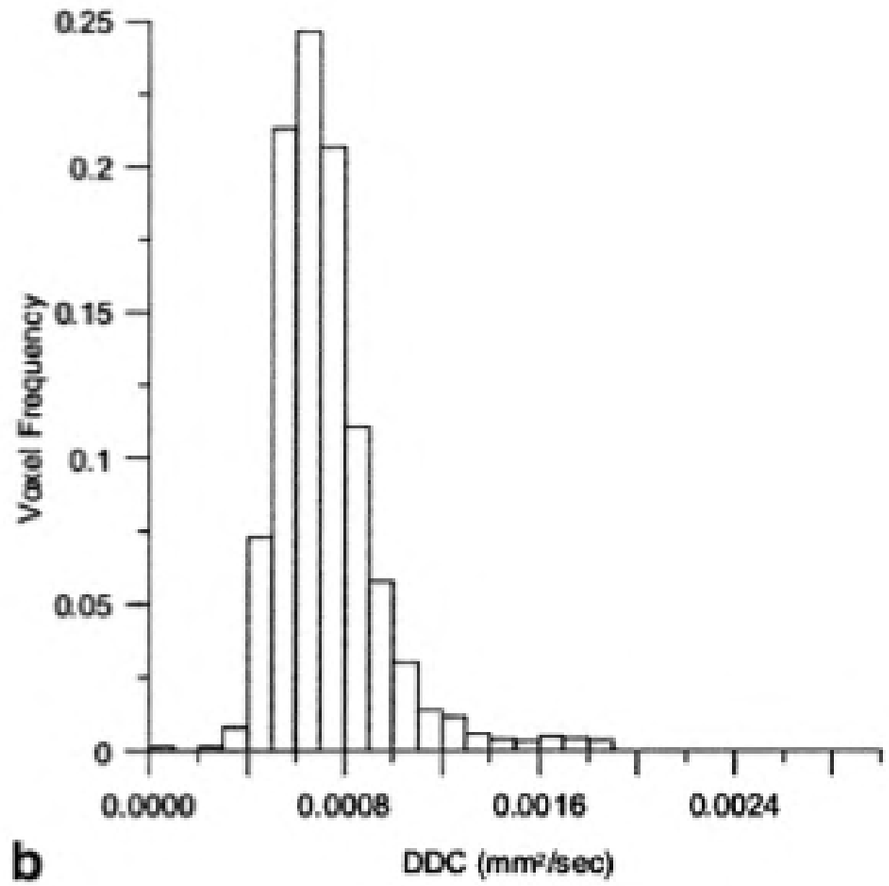


Bennett, MRM, 2003

Stretched (continuous) Exponential Model

- Normal values in (rat) brain

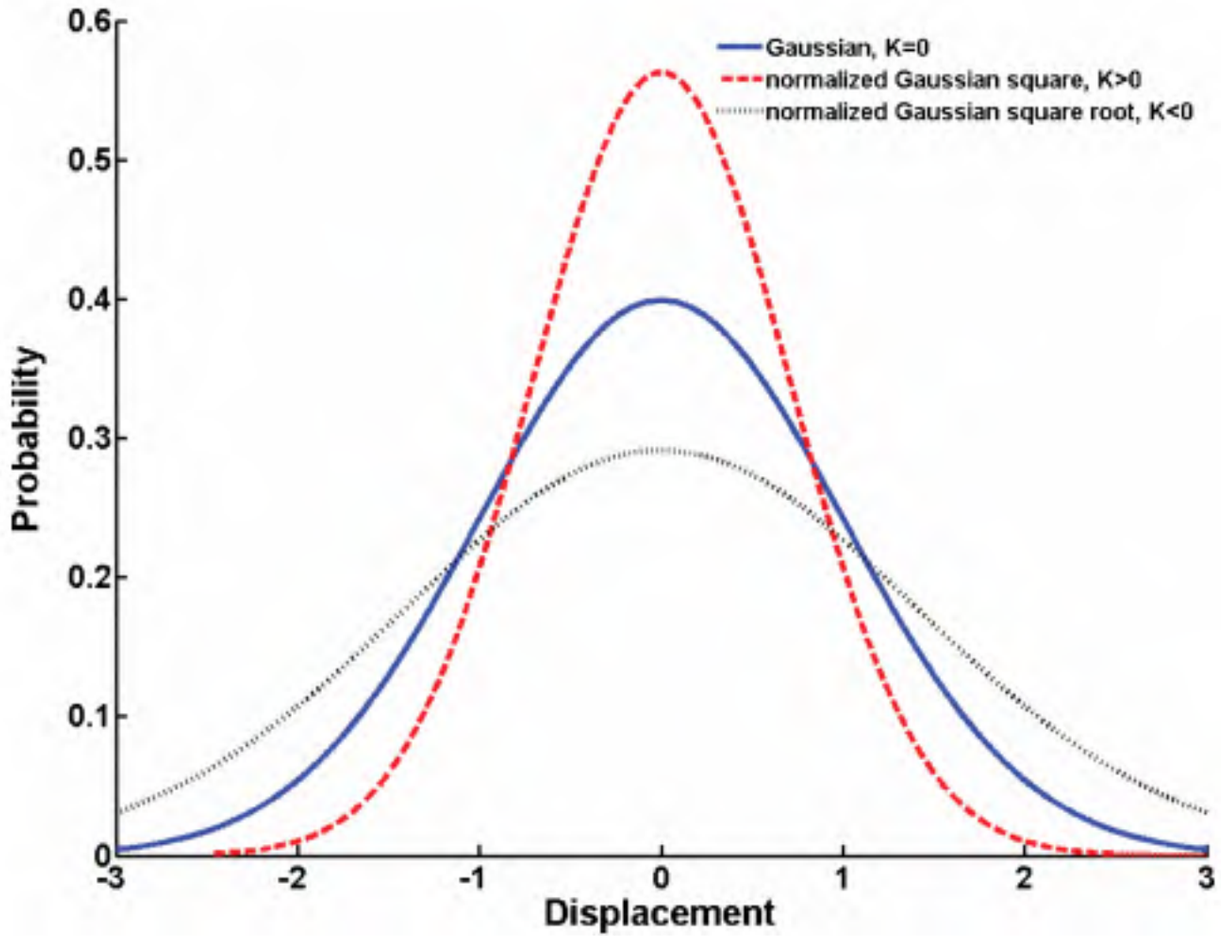




Bennett, MRM, 2003

Diffusion Kurtosis Imaging (DKI)

- Until now, we have assumed diffusion is non-restricted = Gaussian PDF
- If diffusion time is long compared to compartment size, the boundaries/ compartments can cause diffusion water molecules to "reflect" or "scatter"
- This results in deviation from Gaussian PDF and "kurtosis" in the PDF arises



Wu et al., NMR Biomed, 2010

Forth order moment about the mean

$$K = \frac{\mu_4}{\sigma^4}$$

(Standard Deviation) ^{4}

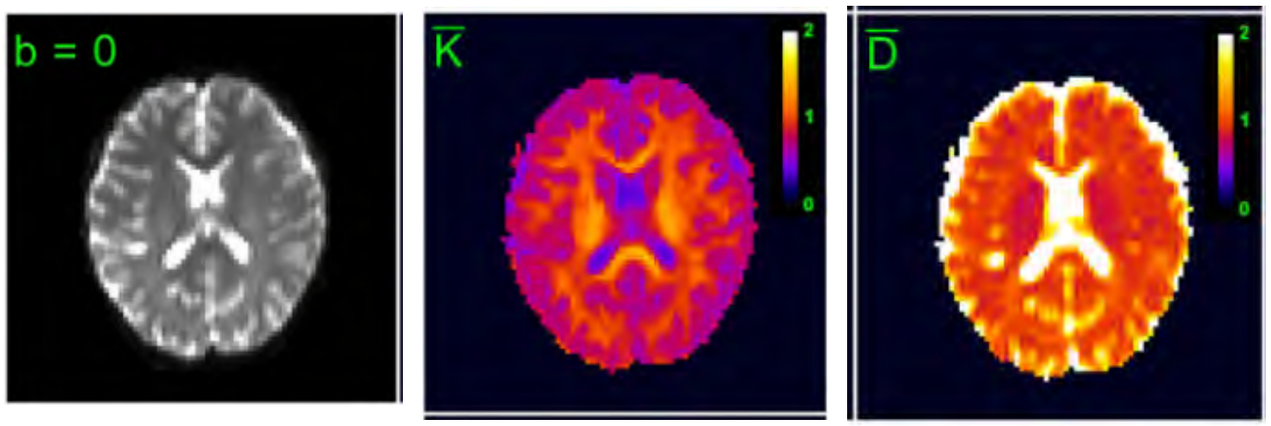
Diffusion Kurtosis Imaging (DKI)

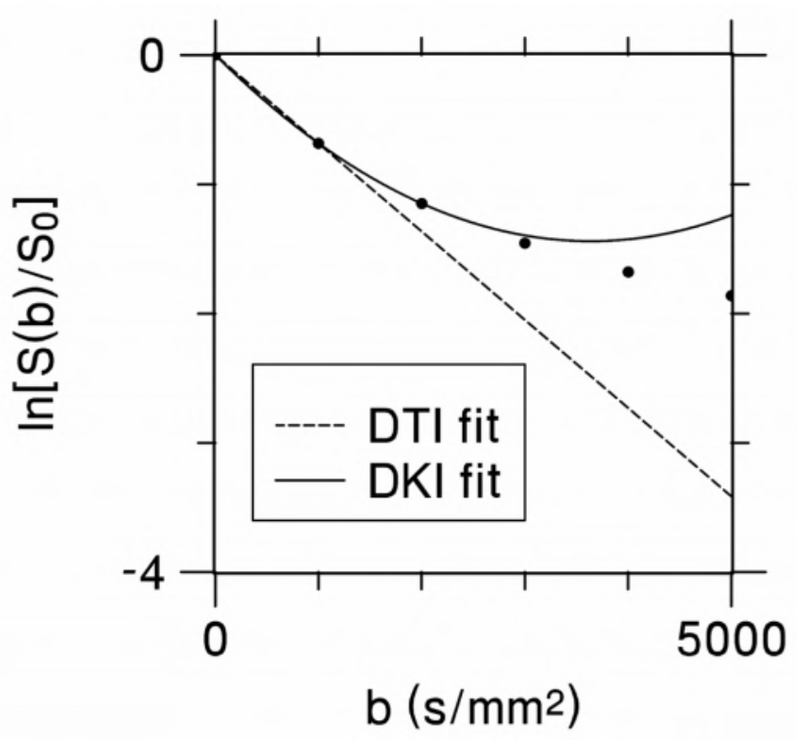
- Until now, we have assumed diffusion is non-restricted = Gaussian PDF
- If diffusion time is long compared to compartment size, the boundaries/ compartments can cause diffusion water molecules to "reflect" or "scatter"
- This results in deviation from Gaussian PDF and "kurtosis" in the PDF arises
- For the 1D DWI experiment, Kurtosis can be found by:

Deviation from Monoexponential

$$\frac{S(b)}{S_0} = e^{-bD+\frac{1}{6}b^2D^2K}$$

Monoexponential





Jensen, NMR Biomed, 2010

The *q*-Space Propagator

- Previously, we have seen that NMR provides a mechanism for molecular labeling via the characteristic Larmor frequencies of the component nuclei
- This label is the phase of the transverse magnetization, a concept that is at the heart of MRI
- Diffusion MRI is performed by first providing a spatial label to nuclei at one instant of time, then checking that labeling at a later time to see if it moved.
- If we could measure the label shift on the individual nuclei, then we can deduce the motion
- The measurement of microscopic (translational) motion, therefore, is performed by measuring phase differences
- For this the spin echo is ideally suited

The *q*-Space Propagator

- In *q*-space imaging, we will be perturbing the diffusion sensitizing gradient amplitude in order to study the *reflection* of spins off boundaries
- Assume a homogeneous medium (voxel, single diffusion coefficient)
- Use the assumption/PGSE sequence w/ $\delta \ll \Delta$
- Recall that the NMR signal will depend on the *probability density function* of spin displacements and the NMR "encoding"

$$\frac{S_\Delta(\vec{\mathbf{G}})}{S_0} = E_\Delta(\vec{\mathbf{G}}) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} P(\vec{\mathbf{r}}' \mid \vec{\mathbf{r}}, \Delta) \cdot e^{j\gamma\delta\cdot\vec{\mathbf{G}}\cdot(\vec{\mathbf{r}}'-\vec{\mathbf{r}})} d\vec{\mathbf{r}}'\, d\vec{\mathbf{r}}$$

- ***Big Picture:*** *1) Keep diffusion time Δ large enough to bounce off boundaries, 2) Use the gradient ↑**G** to ↑ϕ to probe smaller and smaller compartments using phase, 3) average signal represents the "ensemble" behavior of spins restricted in the compartment*

The *q*-Space Propagator

- We see that from this equation that we can use the gradient **G** to probe a range of phase distributions for a fixed diffusion time, Δ

$$\frac{S_\Delta(\vec{\mathbf{G}})}{S_0} = E_\Delta(\vec{\mathbf{G}}) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} P(\vec{\mathbf{r}}'\,|\,\vec{\mathbf{r}},\Delta)\cdot e^{j\gamma\delta\cdot\vec{\mathbf{G}}\cdot(\vec{\mathbf{r}}'-\vec{\mathbf{r}})}d\vec{\mathbf{r}}'\,d\vec{\mathbf{r}}$$

- If we substitute a new "reciprocal space vector" or "diffusion wave vector" ***q*** defined as

$$\vec{\mathbf{q}} = \gamma\delta\vec{\mathbf{G}}$$

$$\vec{\mathbf{R}} = \vec{\mathbf{r}}'-\vec{\mathbf{r}}$$

- And substitute the distance vector

- The signal equation becomes

$$E_\Delta(\vec{\mathbf{q}}) = \int_{-\infty}^{\infty} P(\vec{\mathbf{R}},\Delta)e^{j\vec{\mathbf{q}}\cdot\vec{\mathbf{R}}}d\vec{\mathbf{R}}$$

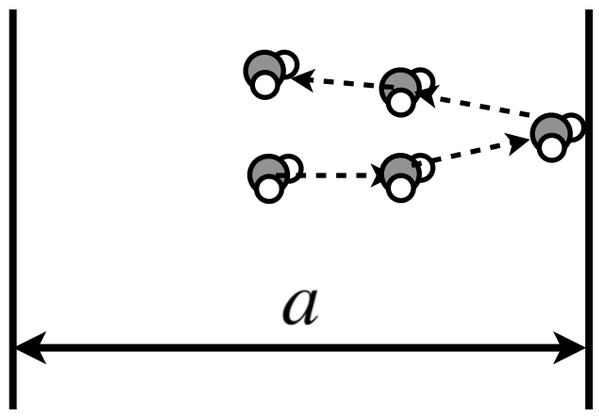
The *q*-Space Propagator

- From inspection, we can see that if we collect the signal amplitude as we increase the gradient amplitude ("sample q-space") we can use the Fourier transform to recover the PDF for a certain diffusion time Δ

$$E_{\Delta}(\vec{\mathbf{q}}) = \int_{-\infty}^{\infty} P(\vec{\mathbf{R}}, \Delta) e^{j\vec{\mathbf{q}}\cdot\vec{\mathbf{R}}} d\vec{\mathbf{R}} \qquad \vec{\mathbf{q}} = \gamma\delta\vec{\mathbf{G}}$$

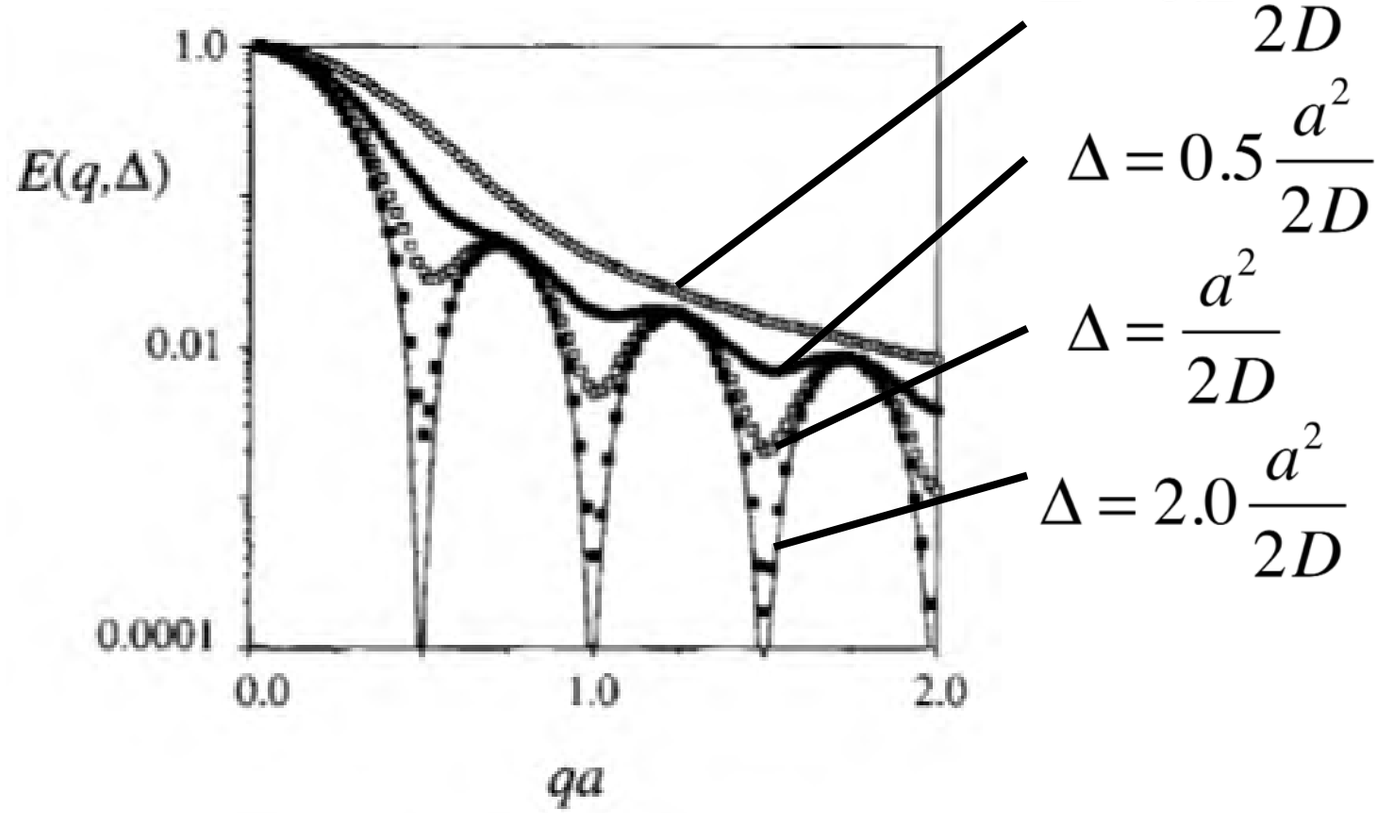
- Until now we have assumed a diffusion coefficient, *D* that is fast enough to cause spins to "reflect" off the boundaries at least as large as ***a*** in diameter in diffusion time Δ

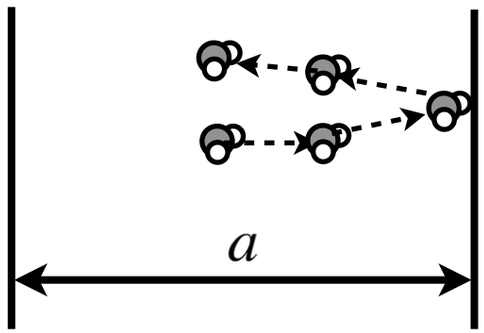
- This results in the necessary condition $\Delta \gg \frac{a^2}{2D}$



The *q*-Space Propagator

$$E_{\Delta}(\vec{\mathbf{q}}) = \int_{-\infty}^{\infty} P(\vec{\mathbf{R}}, \Delta) e^{j\vec{\mathbf{q}}\cdot\vec{\mathbf{R}}} d\vec{\mathbf{R}}$$



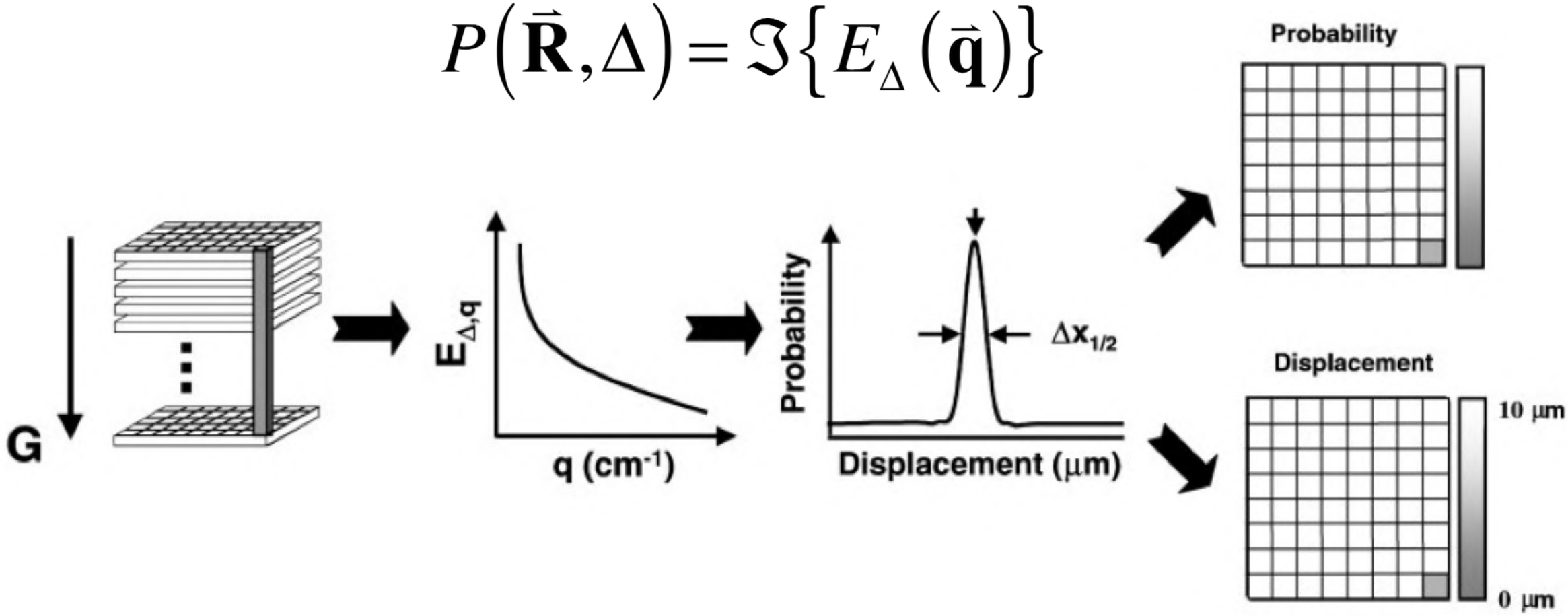


Callaghan, J Magn Reson A, 1995

The *q*-Space Propagator

$$E_{\Delta}(\vec{\mathbf{q}}) = \int_{-\infty}^{\infty} P(\vec{\mathbf{R}},\Delta) e^{j\vec{\mathbf{q}}\cdot\vec{\mathbf{R}}} d\vec{\mathbf{R}}$$

$$P(\vec{\mathbf{R}},\Delta) = \Im\{E_{\Delta}(\vec{\mathbf{q}})\}$$

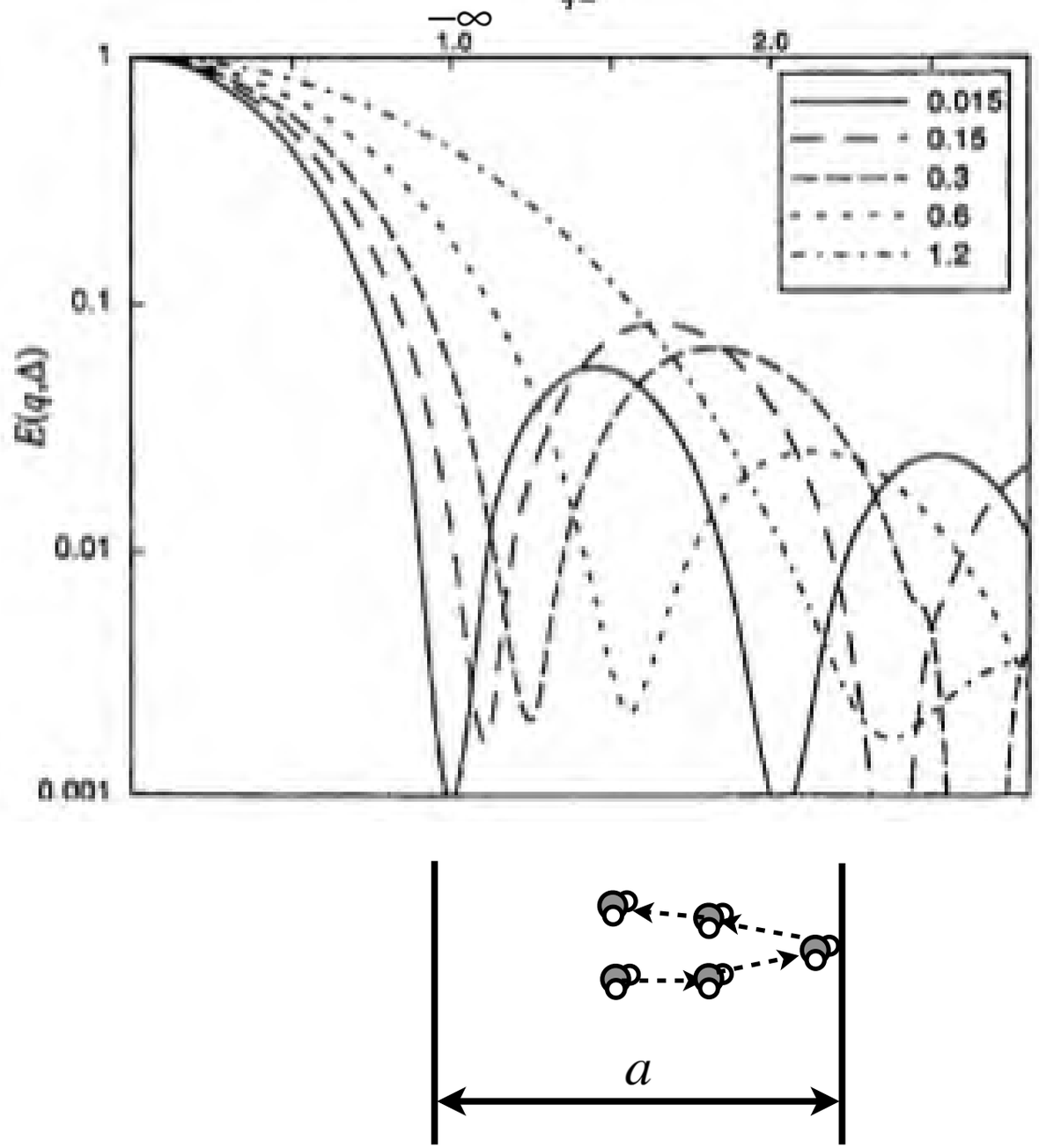


Coy A, Callaghan, J Chem Phys, 1994

The *q*-Space Propagator

$$E_{\Delta}(\vec{\mathbf{q}}) = \int_{-\infty}^{\infty} P(\vec{\mathbf{R}}, \Delta) e^{j\vec{\mathbf{q}}\cdot\vec{\mathbf{R}}} d\vec{\mathbf{R}}$$

$$\delta \text{ in } \frac{a^2}{D}$$



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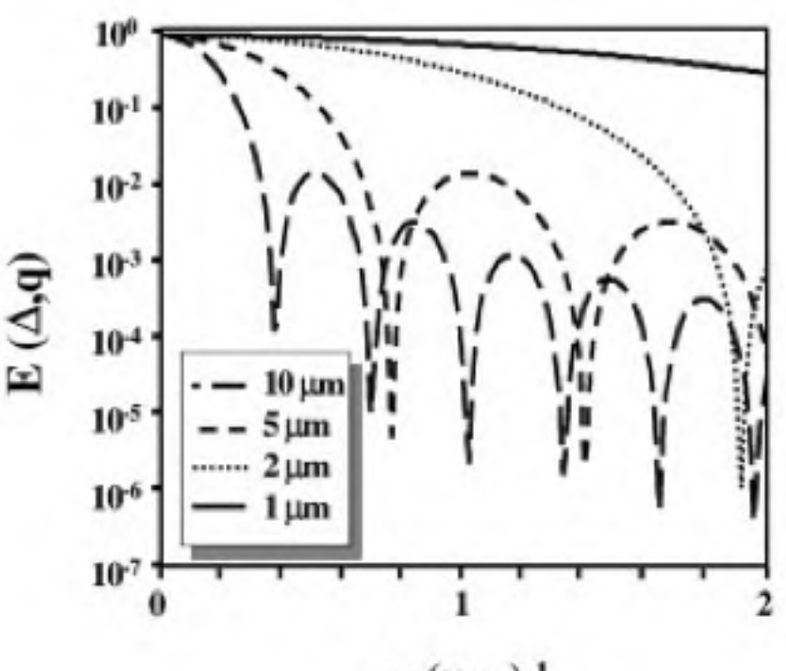
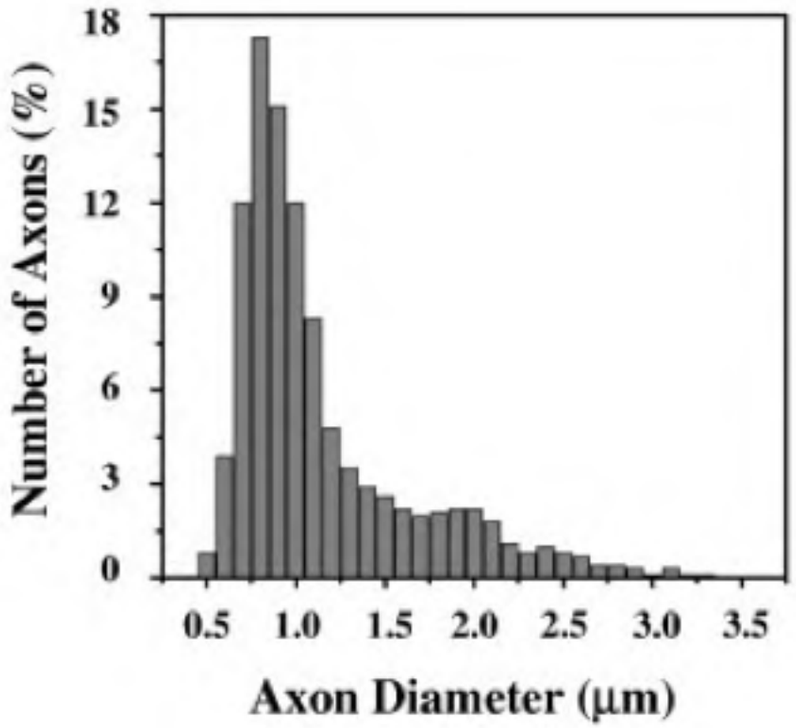
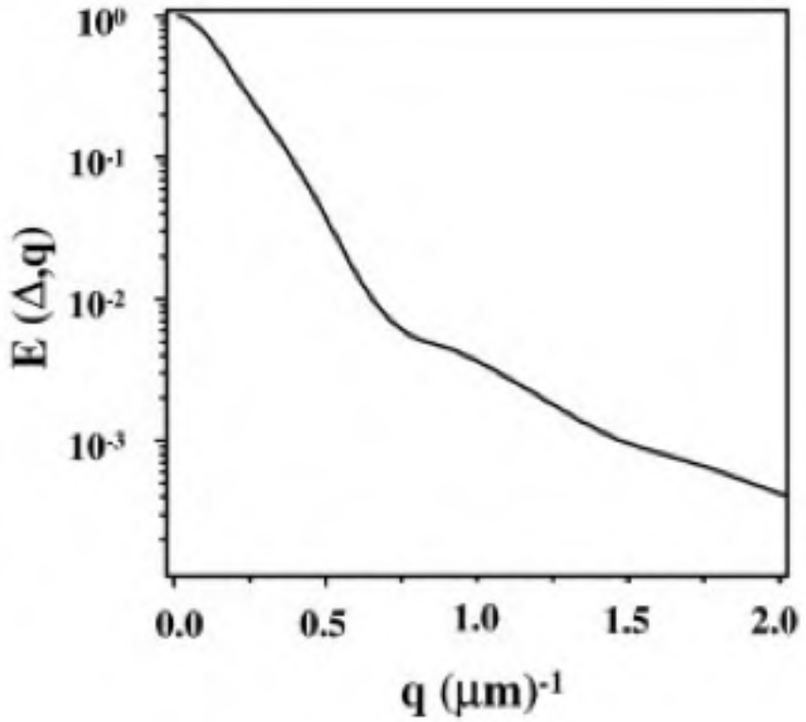
The *q*-Space Propagator

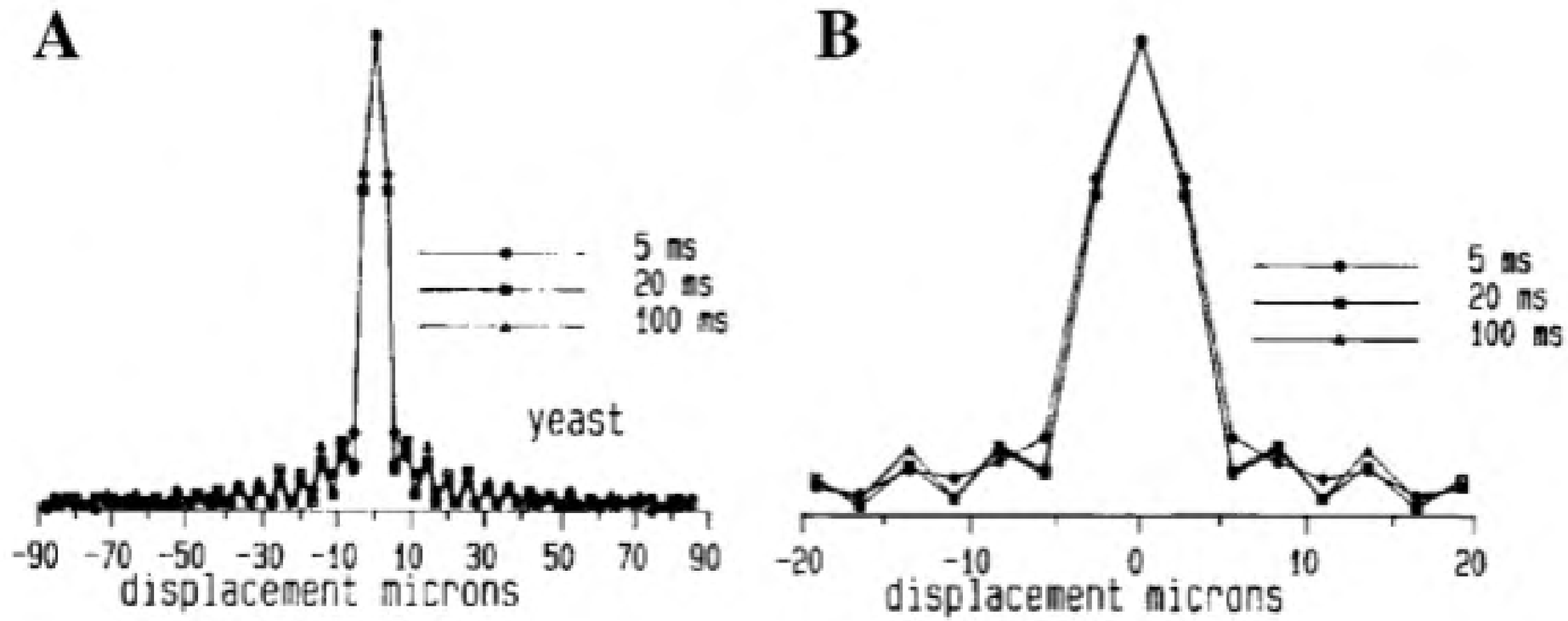






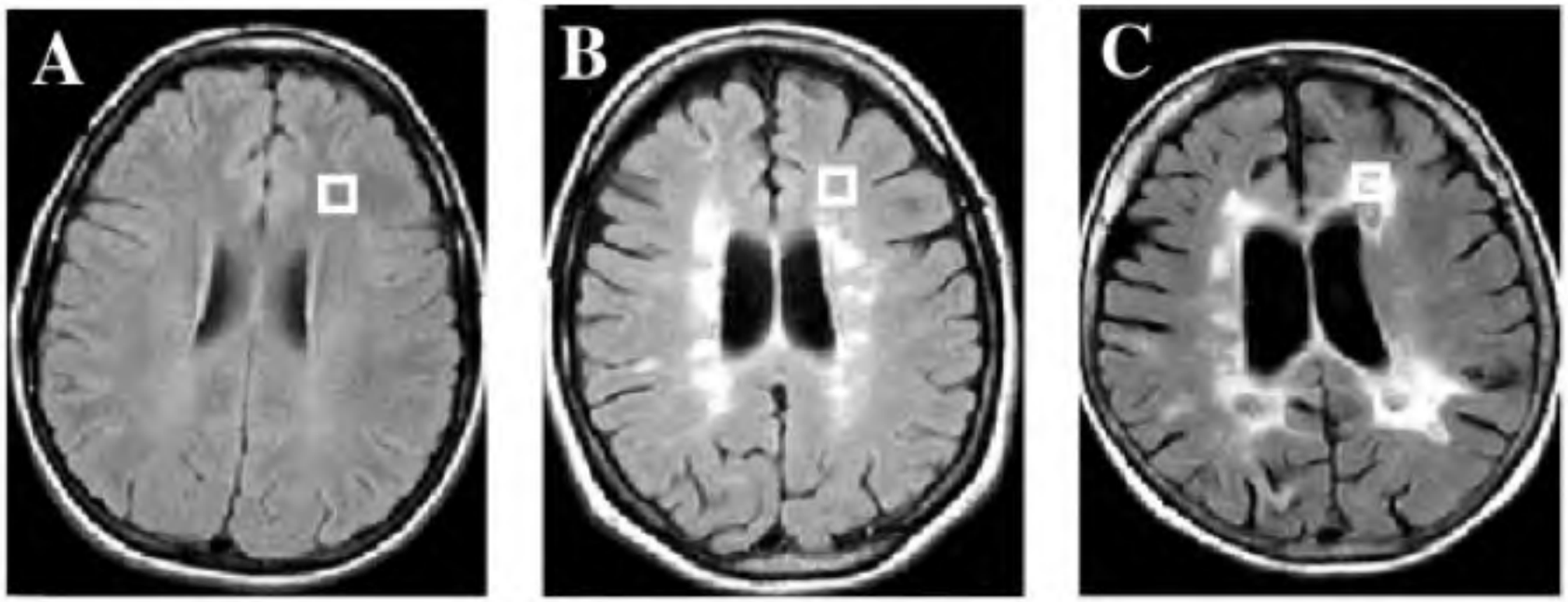
Cohen, NMR Biomed, 2002

The *q*-Space Propagator



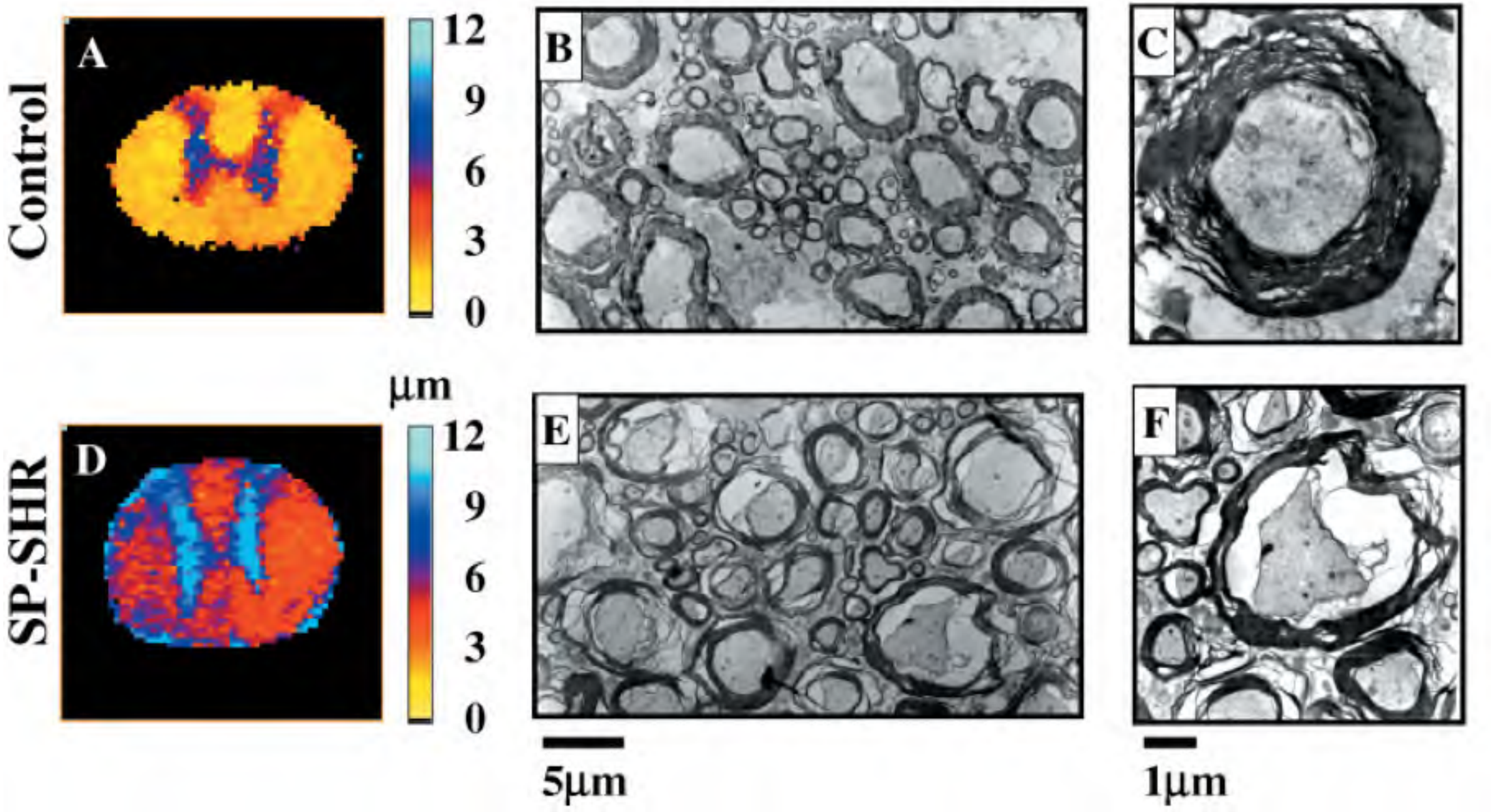
Cory, Magn Reson Med, 1990

The *q*-Space Propagator



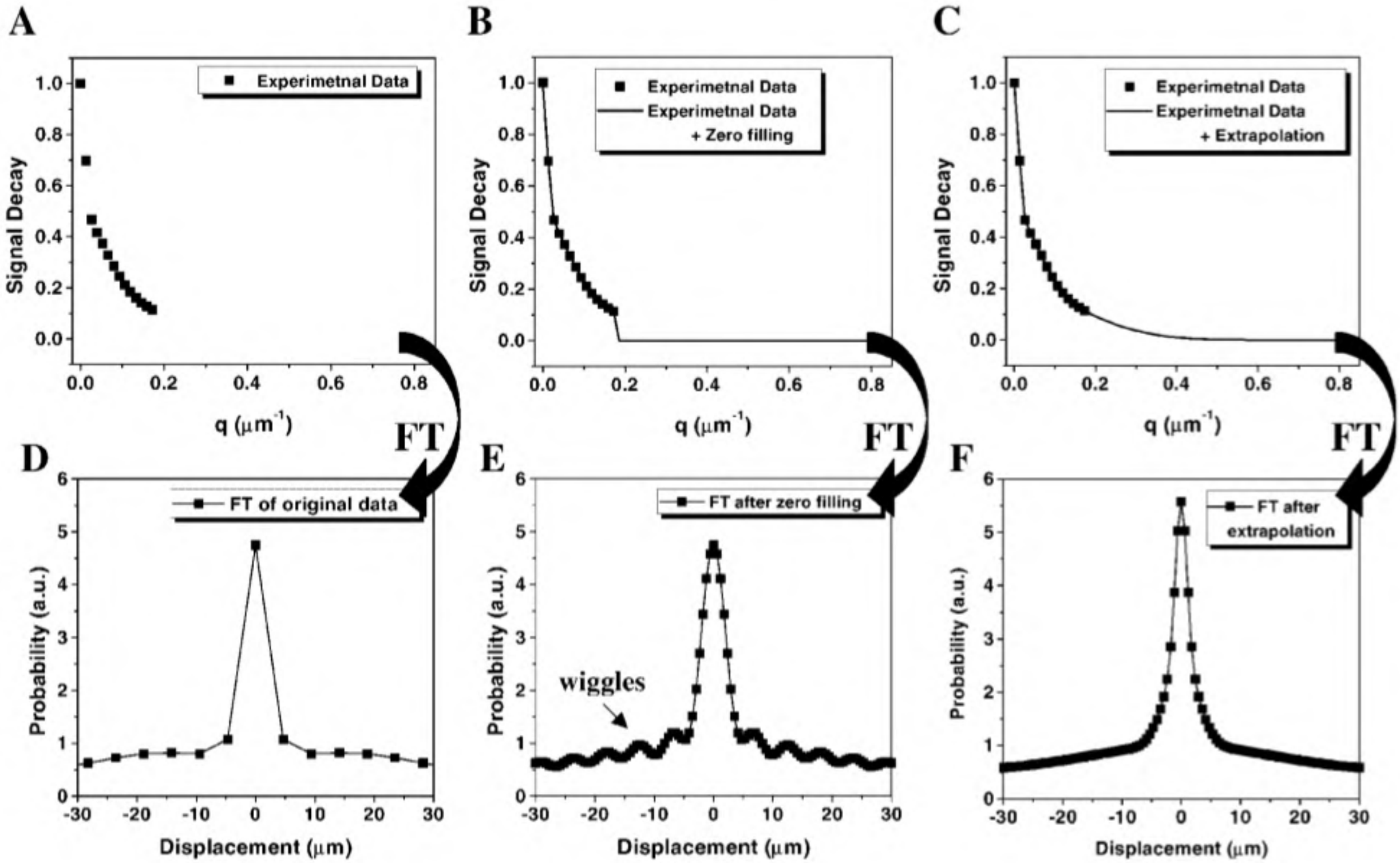
Assaf, Magn Reson Med, 2002

The *q*-Space Propagator



Cohen, NMR Biomed, 2002
Assaf, Magn Reson Med, 2002

The *q*-Space Propagator



Cohen, NMR Biomed, 2002

Q-Ball Imaging

- Until now, we have considered q-space imaging in 1D
- If we expand to 3D, this is known as q-ball imaging

$$P\left(\vec{\mathbf{R}},\Delta\right)=\Im\left\{E_{\Delta}\left(\vec{\mathbf{q}}\right)\right\}$$

- The goal is to determine the ***orientation distribution function ODF*** which tells us information about the orientation of microstructures

- For Q-Ball imaging, we set **|q|** (sensitive to the same compartment size), but vary the gradient orientation (unit vector **u**).
- If we assume a Gaussian PDF, we can deduce the compartment size *P(q**u**)*

$$\psi\left(\vec{\mathbf{u}}\right)=\frac{1}{Z}\int_{0}^{\infty}P\left(q\vec{\mathbf{u}}\right)dq$$

Cohen, NMR Biomed, 2002

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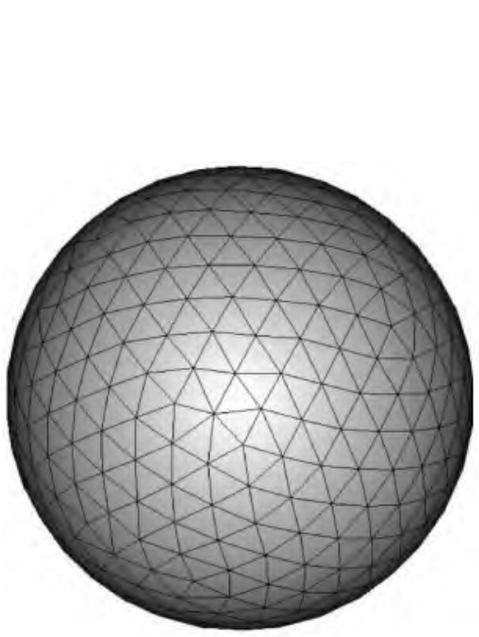
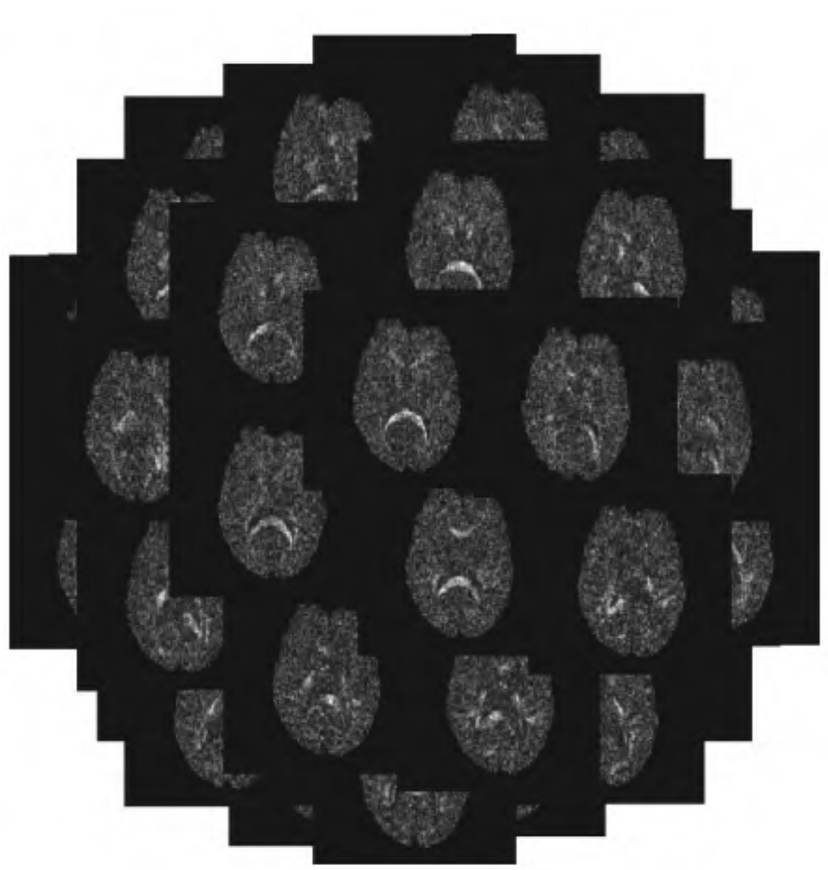
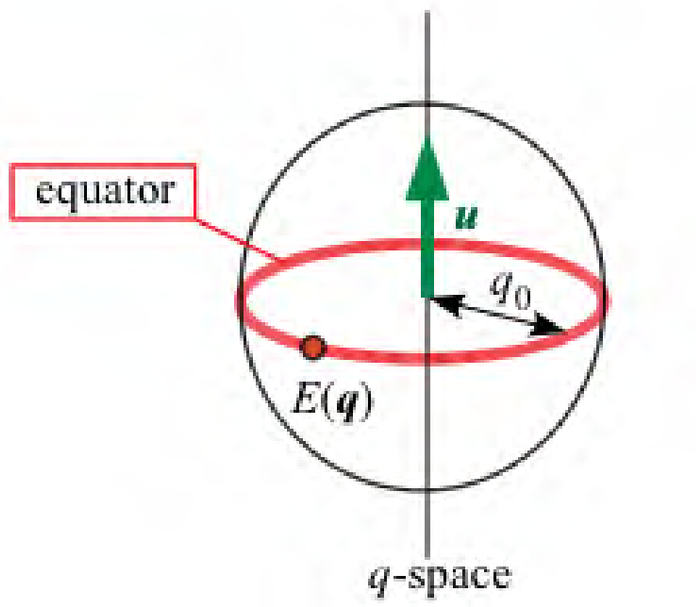




Tuch, Magn Reson Med, 2004

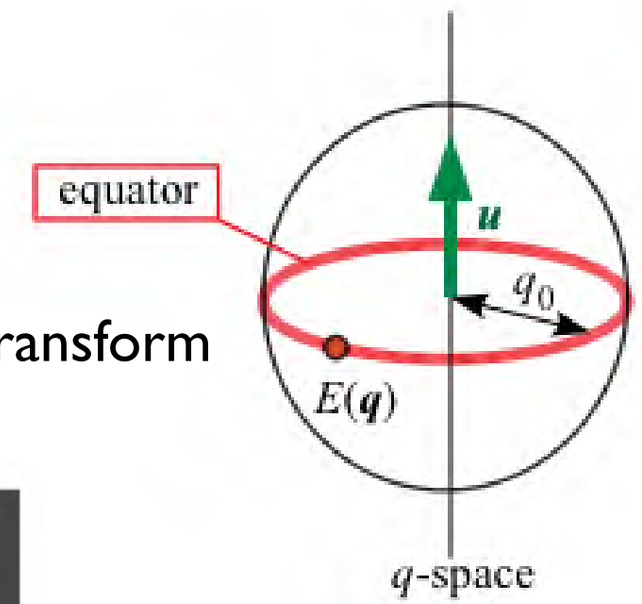


Perrin, 2005

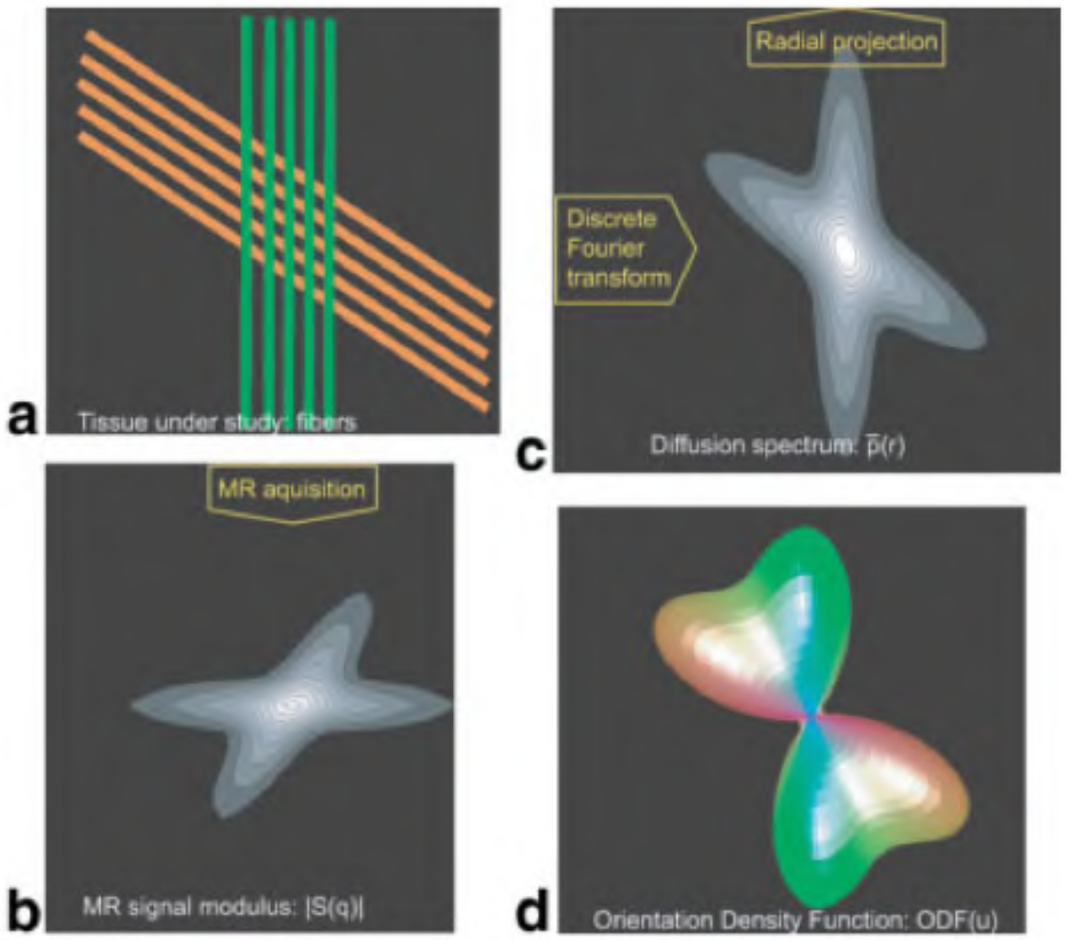
Q-Ball Imaging

- The direction of largest (preferential) diffusivity will be perpendicular to the orientation of highest signal amplitude with fixed *q*

$$\psi(\vec{\mathbf{u}}) = \frac{1}{Z}\int_0^\infty P(R\vec{\mathbf{u}})dR$$



- The ODF can be approximated using the Funk-Radon Transform



Wedeen, Magn Reson Med, 2005

Q-Ball Imaging

$$\psi(\mathbf{u}) \approx \frac{1}{Z}\,\mathcal{G}_{q'}[E(\mathbf{q})],$$

Funk-Radon Transform (Approximation)

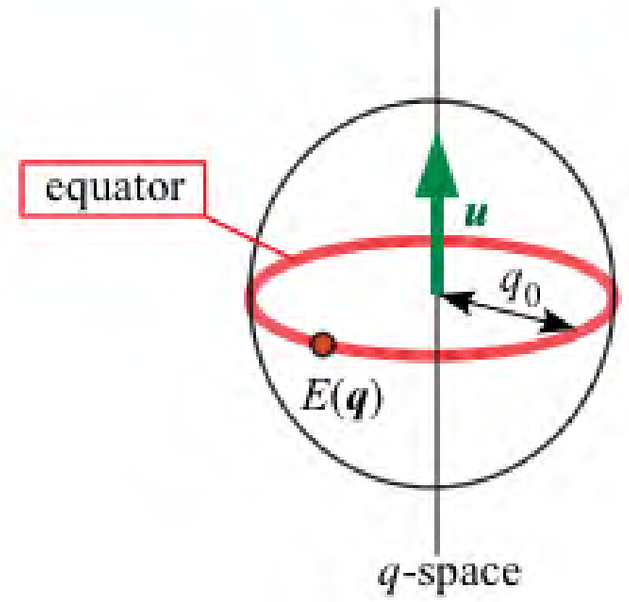
$$\psi(\mathbf{u}) = \mathcal{G}_{q'}[E(\mathbf{q})]$$

Exact Solution

Zeroth order Bessel function

$$= 2\pi q' \int P(r,\theta,z) J_0(2\pi q' r) r\,dr\,d\theta\,dz,$$

q' = set q-value for experiment



$$\psi(\mathbf{u}) = \mathcal{G}_{q'}[E(\mathbf{q})] = 2\pi q' \int \mathcal{H}[X[P]]d\theta.$$

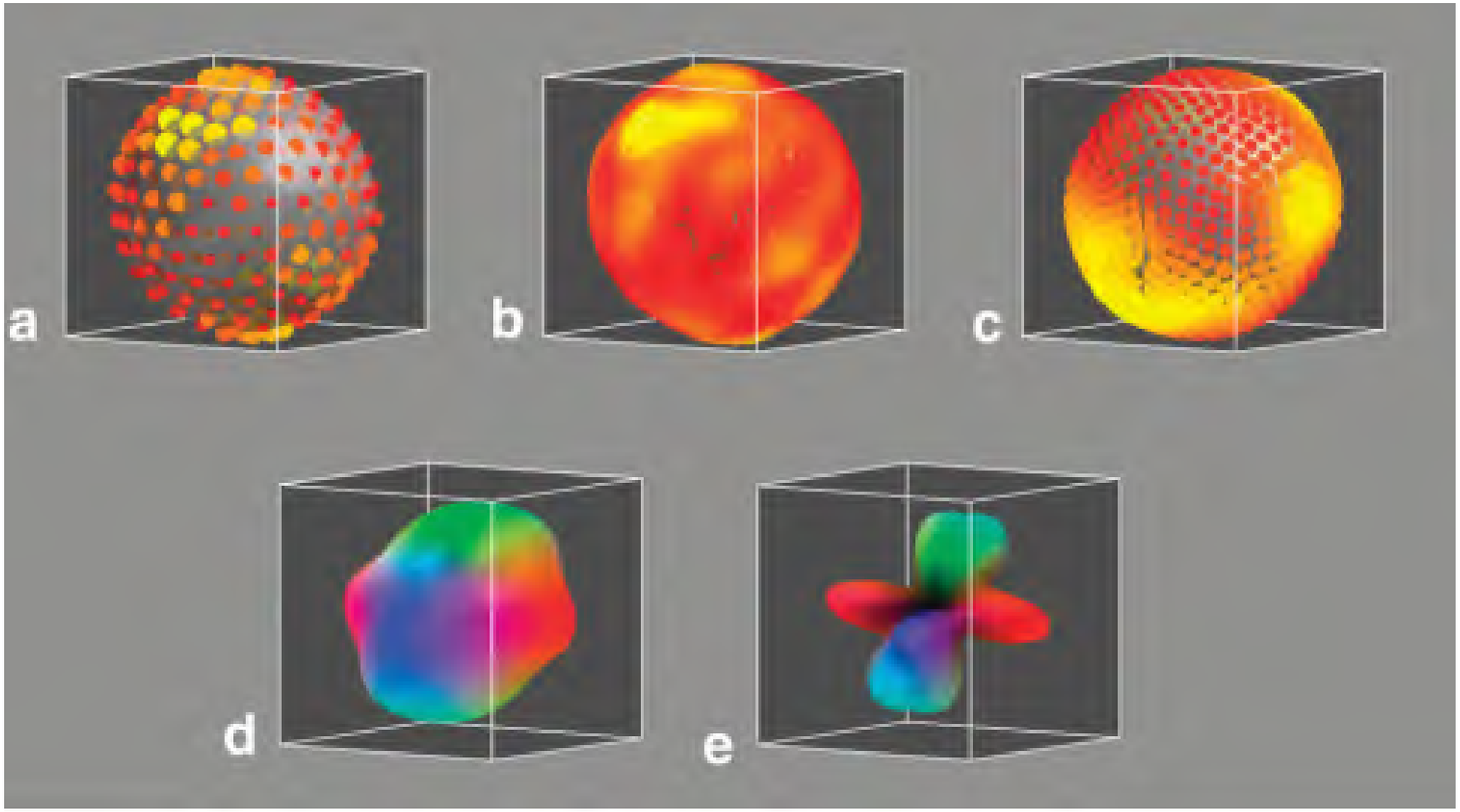
$$\mathcal{H}[f(r,\theta,z)] = \int f(r,\theta,z) J_0(2\pi k r) r\,dr$$

Hankel Transform

$$X[f(r,\theta,z)] = \int f(r,\theta,z)\,dz$$

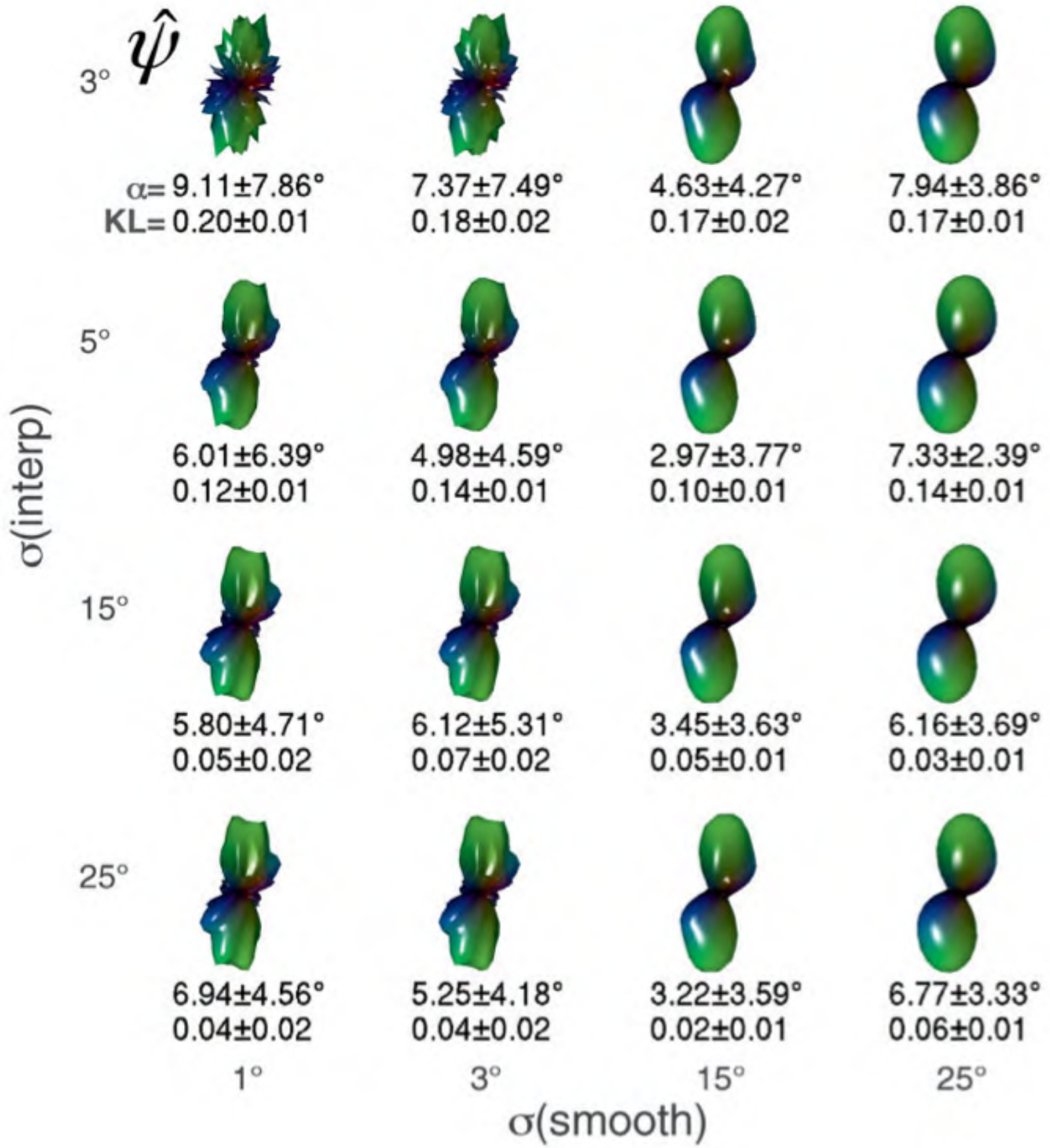
Planar Radon Transform

Q-Ball Imaging



Tuch, Magn Reson Med, 2004

Q-Ball Imaging



Tuch, Magn Reson Med, 2004

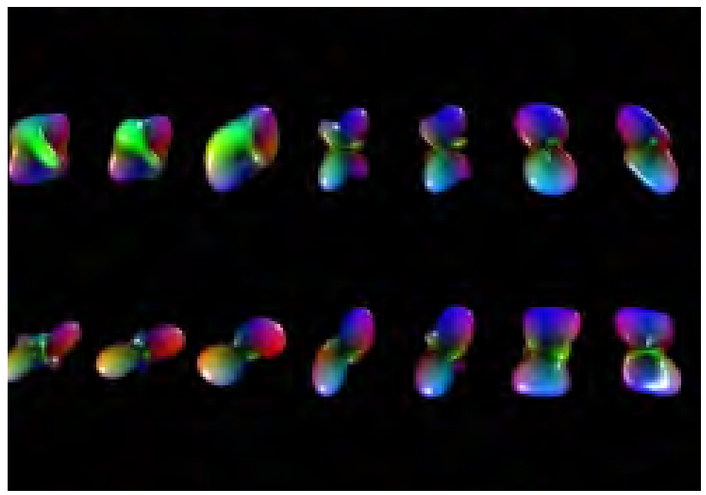
Diffusion Spectral Imaging

- It is possible to construct a large "grid" with *q*-values, sampling q-space in 3D
- The PDF can be reconstructed by Fourier transform as:

$$P\left(\vec{\mathbf{R}},\Delta\right)=\frac{1}{\left(2\pi\right)^3}\int_{\Re^3}\left|E_\Delta\left(\vec{\mathbf{q}}\right)\right|e^{-j\vec{\mathbf{q}}\cdot\vec{\mathbf{R}}}d^3\vec{\mathbf{q}}$$

- We can then resample this PDF in cylindrical coordinates to find ODF

$$\psi\left(\vec{\mathbf{u}}\right)=\int_{\Re^+}P_\Delta\left(r\vec{\mathbf{u}}\right)r^2dr$$



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Diffusion Spectral Imaging

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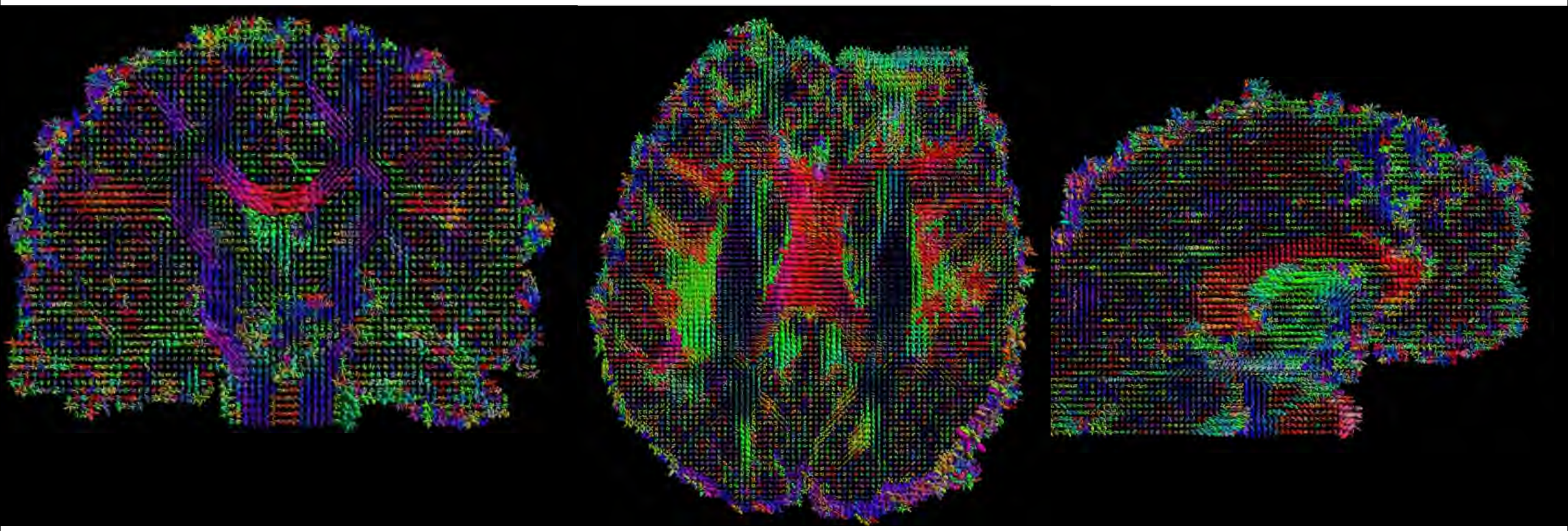
$$\psi\left(\vec{\mathbf{u}}\right)=\int_{\Re^+}P_\Delta\left(r\vec{\mathbf{u}}\right)r^2dr$$

Human Connectome Proiect



Diffusion Spectral Imaging

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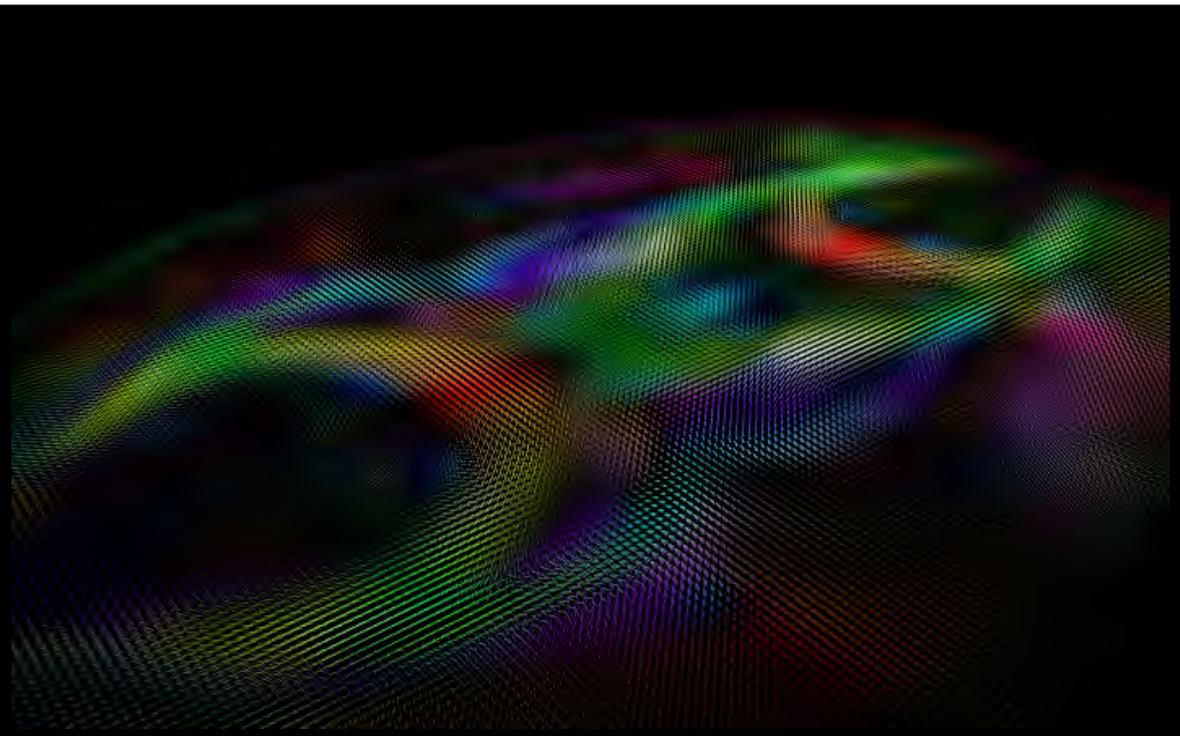
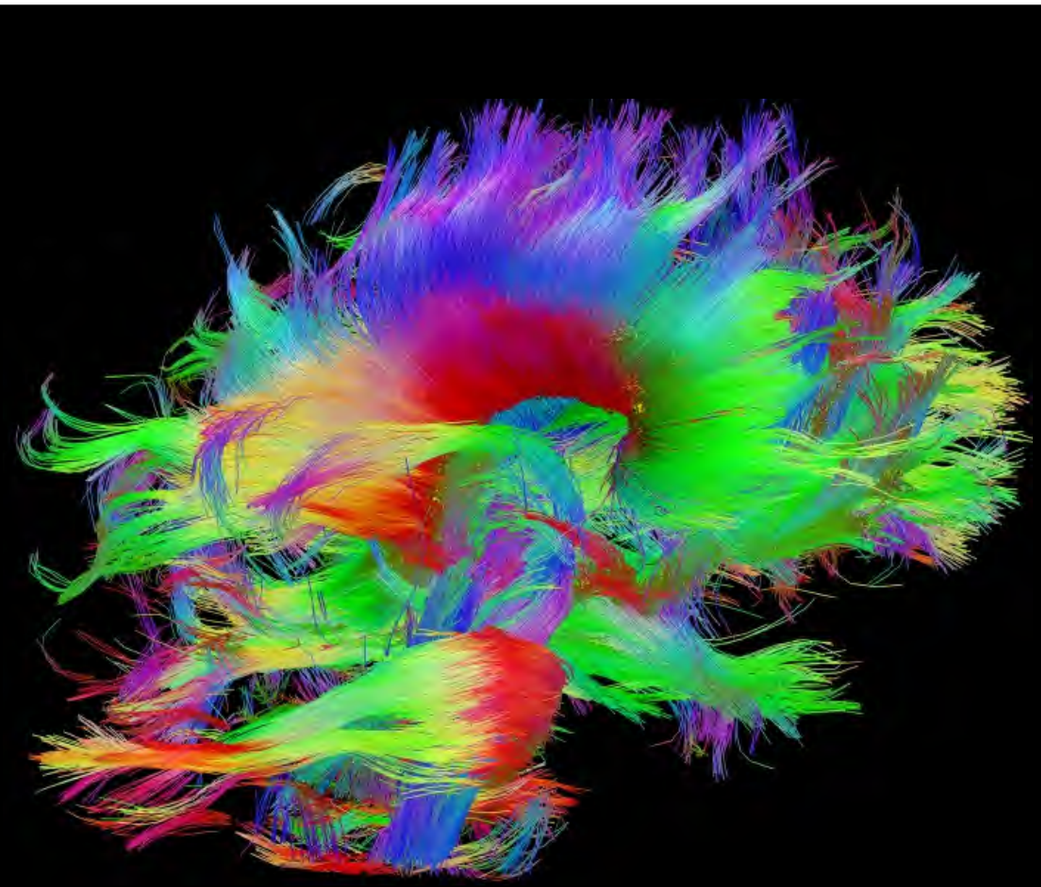
Human Connectome Proiect





Next Lecture…

- Tractography (Deterministic & Probabilistic)
- Applications
  - Neuro-Oncology
  - Neurotrauma
  - Alzheimer's Disease
  - Parkinson's Disease
  - Epilepsy
  - Chronic Pain