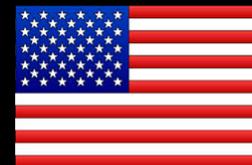


# Macroscopic Magnetic Resonance Imaging of Microscopic Motions: $k + (q, t)$ Space Imaging

Robert W Cox

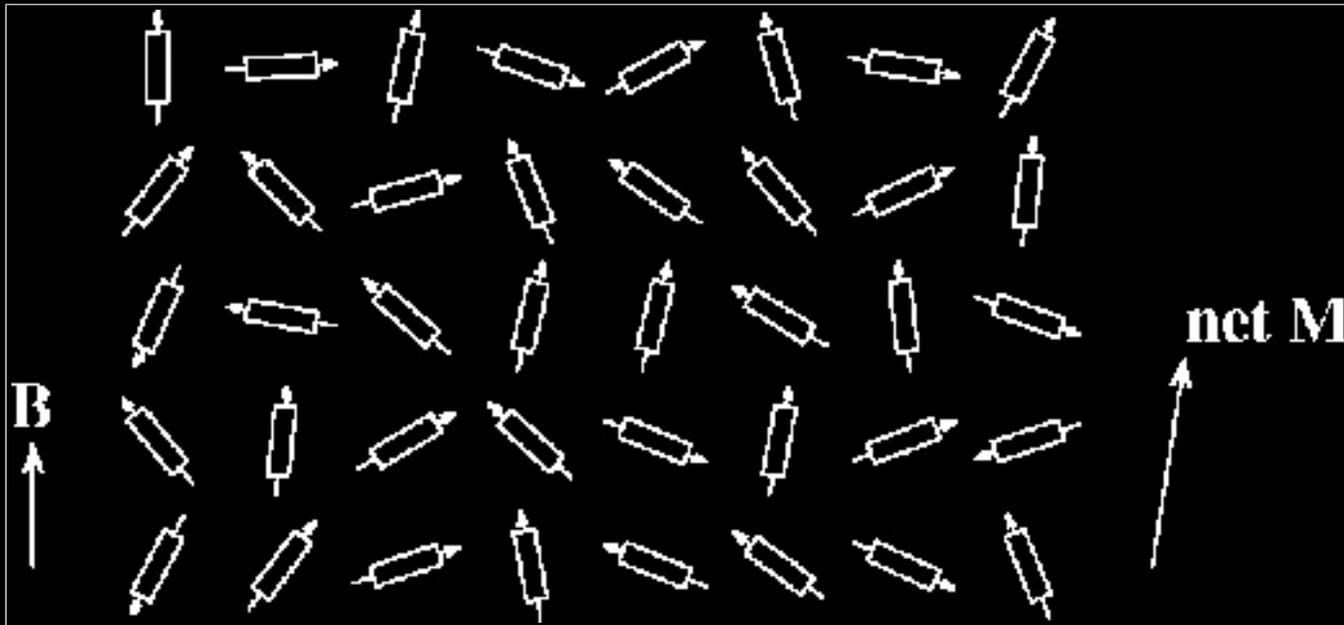
Scientific and Statistical Computing Core  
National Institute of Mental Health  
National Institutes of Health  
Department of Health and Human Services  
Bethesda, Maryland, United States of America



## Summary of NMR Imaging Principles

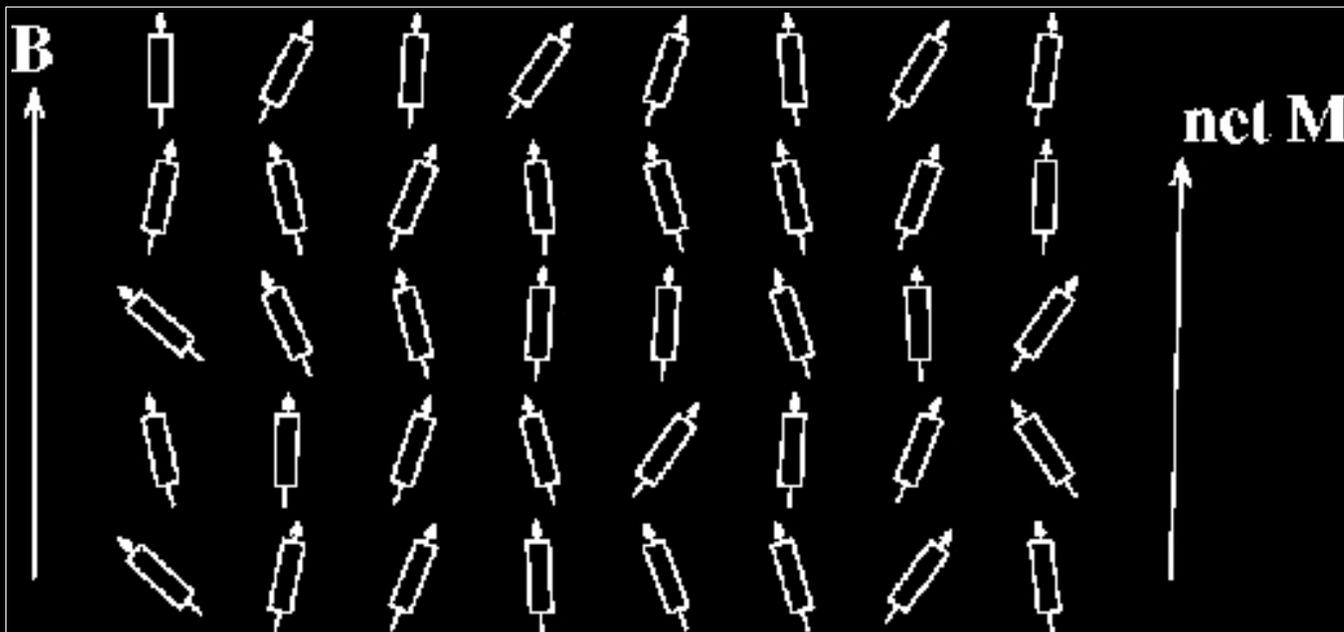
- Immerse  $\text{H}_2\text{O}$ -containing sample in large static magnetic field to magnetize sample (magnetization will be parallel to large  $\vec{B}_0$ )
- Excite magnetization to be transverse to  $\vec{B}_0$  by applying a small resonant magnetic field perpendicular to  $\vec{B}_0$  [ $\approx 3$  ms]
- Turn off transmitter; receive signal re-transmitted by precessing transverse magnetization [ $\approx 20$  ms]
- Manipulate transverse magnetization frequency by making  $\vec{B}$  vary in space and time during signal readout time
  - ◇ Spatial variation of  $\vec{B} \implies$  **frequency encoding**: frequency of signal depends on where it is transmitted from
  - ◇ Can also make signal sensitive to various microscopic features of sample (i.e., below the imaging resolution)
- Reconstruct signal into images using Fourier transform
  - ◇ Since frequency of signal components corresponds to spatial location

# Magnetization of Protons



$\Leftarrow B_0$  small

Alignment Fraction  
 $= 3 \times 10^{-6}$  per  
Tesla



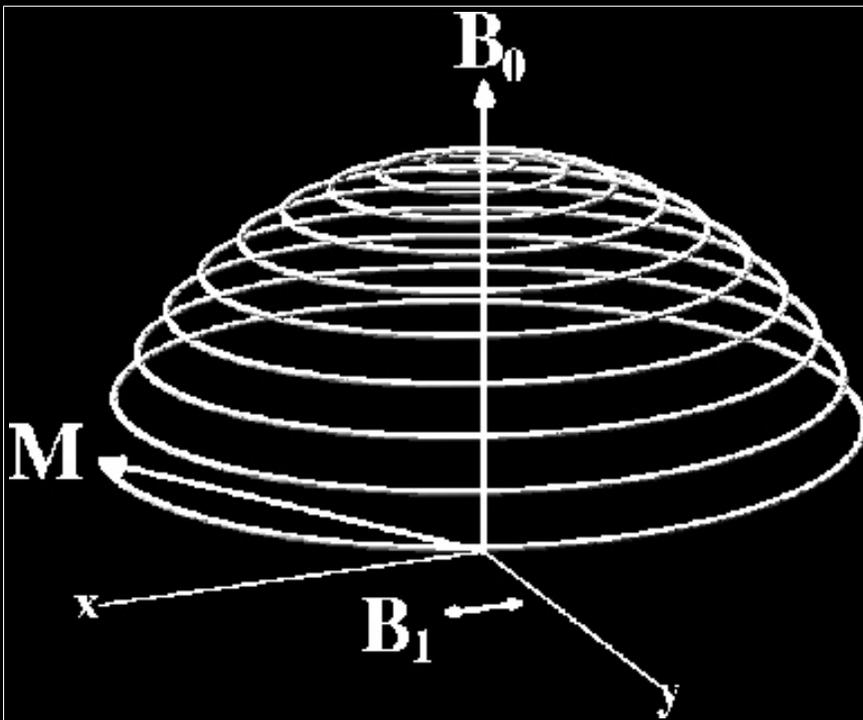
$\Leftarrow B_0$  large

$\vec{M} \propto \vec{B} \implies$   
 $\text{SNR} \propto B_0$

$\implies$   
“More’s Law”:  
More  $B_0$  is better

## Precession of Magnetization Density

- Fundamental law:  $\frac{\partial \vec{M}(\vec{x}, t)}{\partial t} = -\gamma \vec{B}(\vec{x}, t) \times \vec{M}(\vec{x}, t)$ 
  - ◇  $\gamma = 42 \text{ MHz/Tesla} \implies B_0 = 1.5 \text{ T}$  has  $f = 63 \text{ MHz}$
- Equilibrium  $\vec{M}$  is parallel to large applied  $\vec{B} = B_0 \hat{z}$
- To excite away from this state, apply  $\vec{B}_1(t)$  field transverse to  $\hat{z}$  and oscillating at  $\gamma B_0$  frequency:



Typical  $B_1 \approx 10^{-5} \text{ T} \implies$   
time to excite to  $90^\circ$  about 1 ms

## After Excitation: Signal Reception

- Wrap wire coil around object; Faraday's law of induction  $\implies$

$$V(t) \propto \gamma B_0 \iiint H(\vec{x}) M_{\perp}(\vec{x}, t) d^3x$$

- ◇  $V(t)$  = voltage induced in wire coil = signal
- ◇  $M_{\perp}(\vec{x}, t) = M_x(\vec{x}, t) + iM_y(\vec{x}, t)$   
= complex representation of magnetization transverse to  $B_0 \hat{z}$
- ◇ When  $\vec{B}_1 = 0$ ,  $\frac{\partial M_{\perp}}{\partial t} = -i\gamma B_z(\vec{x}, t) M_{\perp}(\vec{x}, t)$
- ◇  $H(\vec{x})$  = reception pattern of coil (Green's function)  
 $\hookrightarrow$  [design goal:  $H(\vec{x}) \approx \text{constant}$ ]
- Goal of imaging: reconstruct  $I(\vec{x}) \approx M_{\perp}(\vec{x}, t = T_E)$ 
  - ◇  $T_E$  = echo time (usually 5–50 ms after excitation)
  - ◇  $M_{\perp}$  decay time constant  $\approx 10$ – $100$  ms
- Tricky part of imaging: wavelength of radiation is huge relative to object: 63 MHz  $\implies \lambda = 4.7$  m

# Macroscopic Imaging Principles

- After excitation, apply **gradient** fields:

$$B_z(x, y, z, t) = B_0 + G_x(t) \cdot x + G_y(t) \cdot y + G_z(t) \cdot z$$

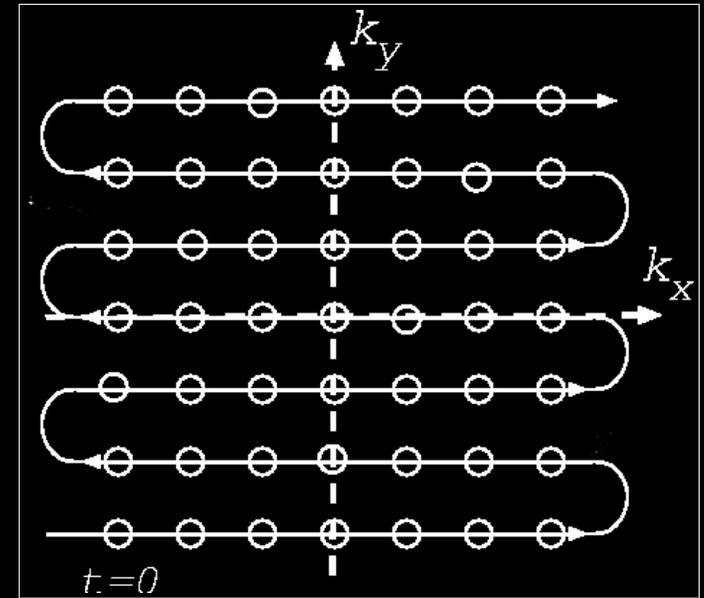
- ◇  $G_{\{x,y,z\}}$  fields are generated by running electric current into coils of wire around object ( $G \approx 10 \text{ mT/m}$ ;  $G \cdot \text{size} \ll B_0$ )
- ◇  $\{x, y, z\}$  **Gradient coil** is designed to produce  $B_z(\vec{x})$  linearly proportional to  $\{x, y, z\}$  spatial coordinate
  - ↪ Combines with static  $B_0$  to change precession frequency of  $M_{\perp}$

- Precession frequency depends on position:

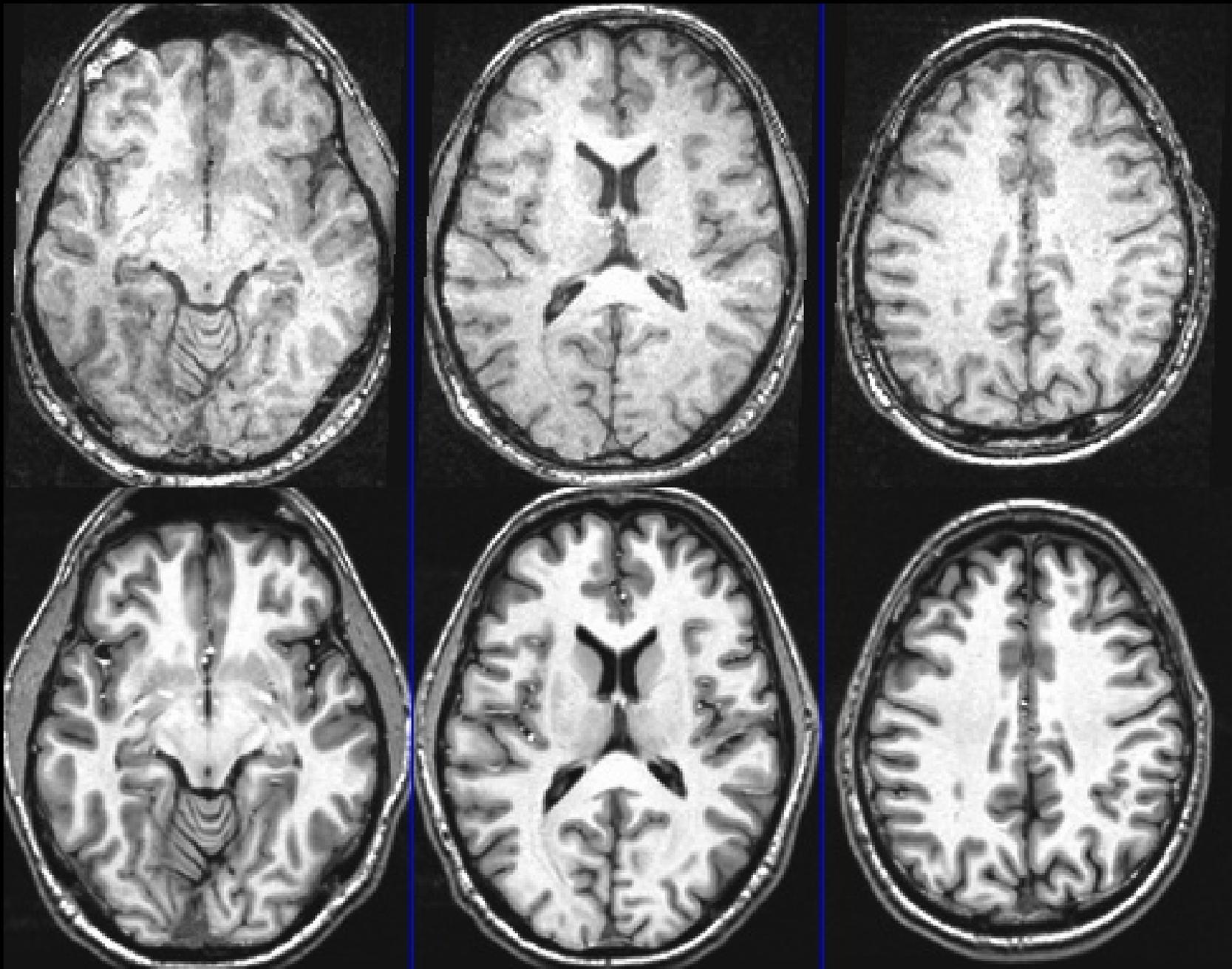
$$M_{\perp}(x, y, z, t) = M_{\perp}(x, y, z, 0)e^{-i\omega_0 t} \\ \times e^{-ik_x(t)x - ik_y(t)y - ik_z(t)z}$$

- ◇  $k_{\{x,y,z\}} = \gamma \int_0^t G_{\{x,y,z\}}(t') dt'$
- ◇ Velocity through **k-space** is proportional to gradient field, which is proportional to voltage applied to gradient coil

- Result: signal  $V(t) \propto \mathcal{F} [H(\vec{x})M_{\perp}(\vec{x}, T_E)] \equiv \hat{M}_{\perp}(\vec{k})$  evaluated at  $\vec{k} = (k_x(t), k_y(t), k_z(t))$
- By manipulating gradient fields:
  - ◇ Can drive through a patch of  $k$ -space
  - ◇ Collect data  $V(t) = \hat{I}(\vec{k}(t))$
  - ◇ Arrange  $V(t)$  into  $\vec{k}(t)$  grid
  - ◇ Inverse FFT gives image  $I(\vec{x})$
- Resolution depends on imaging time
  - ◇ 1 mm resolution in human subjects is typical (minutes)
  - ◇ 10  $\mu\text{m}$  resolution in small samples (plants, tissue) is possible
    - ↪ With special gradient equipment and hours or days of imaging
  - ◇ Signal-to-Noise Ratio (SNR) is low  $\implies$  acquire data many times
  - ◇ Don't have to acquire all of  $k$ -space in each excitation
    - ↪ Multishot imaging: acquire one line of  $k$ -space data per **shot**

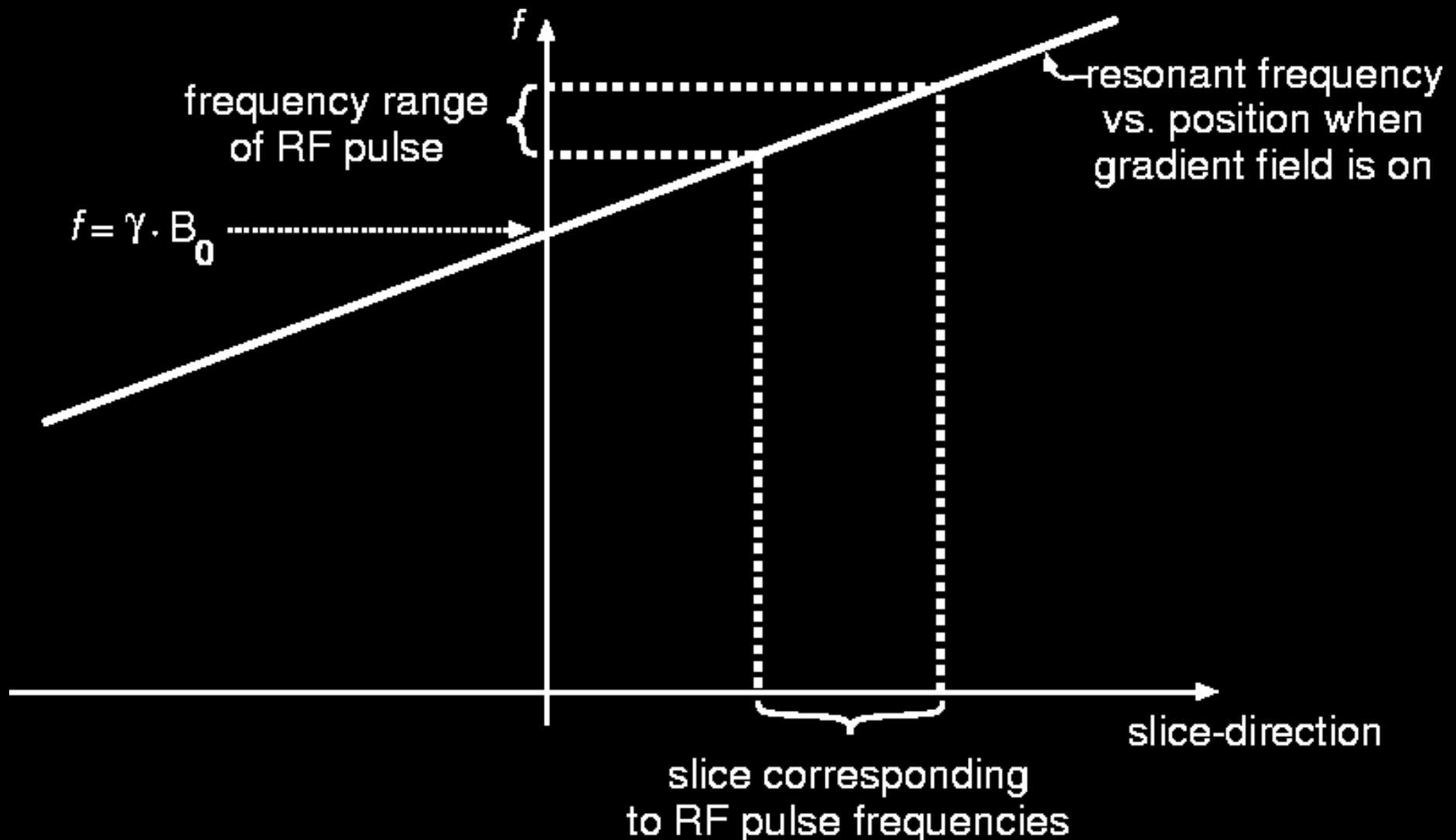


Sample Images: Top=5 minutes; Bottom=40 minutes

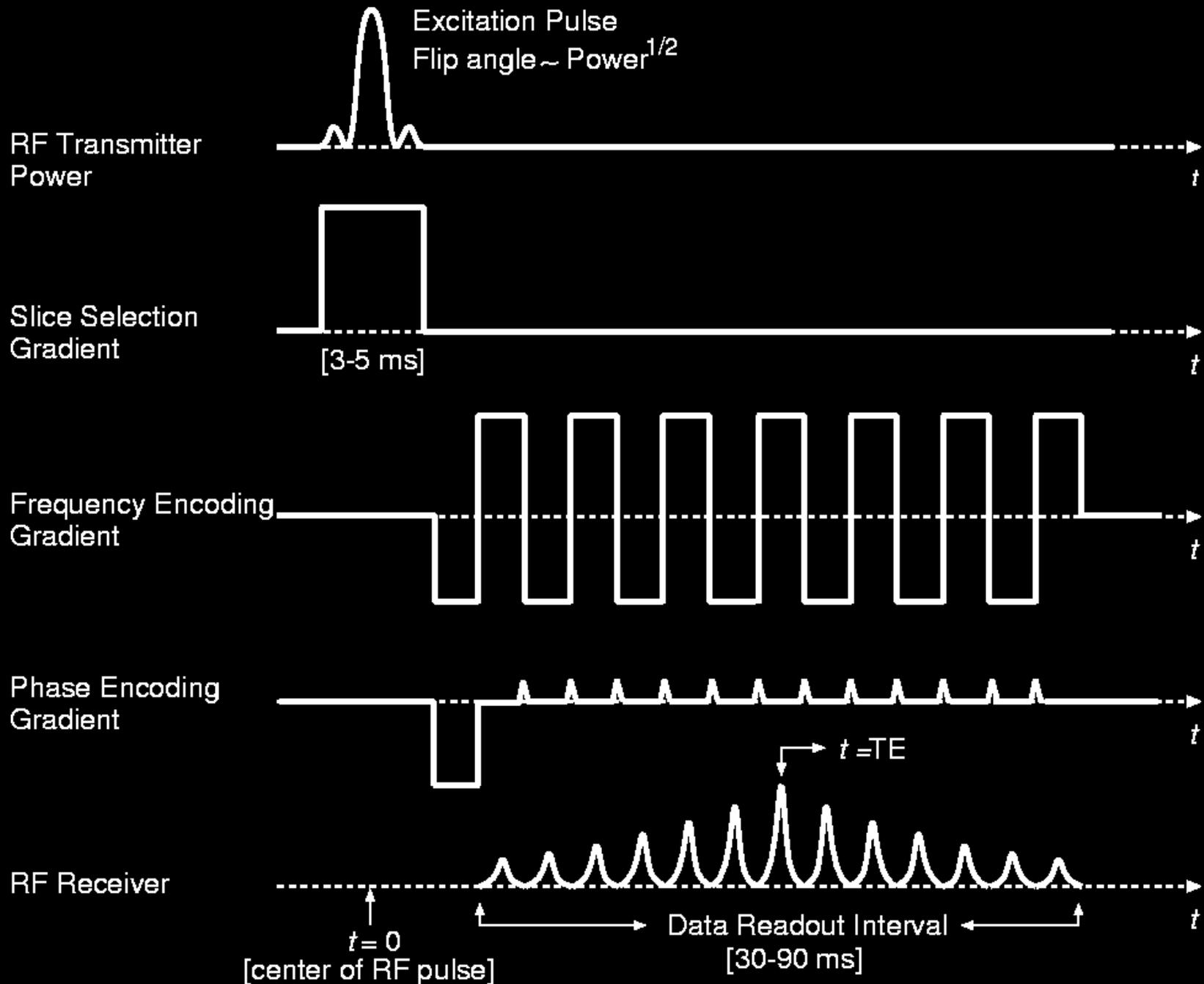


## More Details: Slice Specific Excitation

- By applying a gradient field during  $\vec{B}_1$  excitation, can excite  $M_{\perp}$  in a thin slice only:



# More Details: Sample Imaging Pulse Sequence



## Effects of Moving H<sub>2</sub>O

- When the protons being imaged move during the data readout, the image might be affected
- Modified equation for evolution of transverse magnetization:

$$\frac{\partial M_{\perp}(\vec{x}, t)}{\partial t} = -i\gamma\vec{G}(t) \cdot \vec{x} M_{\perp} - \vec{v} \cdot \nabla_{\vec{x}} M_{\perp} + \nabla_{\vec{x}} \cdot (\mathbf{D} \cdot \nabla_{\vec{x}} M_{\perp})$$

◇  $\vec{v}$  = advection velocity of H<sub>2</sub>O (e.g., blood flow)

◇  $\mathbf{D}$  = diffusion tensor of H<sub>2</sub>O in sample medium

$$V(t) \propto \hat{M}_{\perp}(\vec{k}(t), t = 0)$$

$$\times \exp \left\{ -i \int_0^t \vec{v} \cdot [\vec{k}(t) - \vec{k}(t')] dt' \right\}$$

$$\times \exp \left\{ - \int_0^t [\vec{k}(t) - \vec{k}(t')] \cdot \mathbf{D} \cdot [\vec{k}(t) - \vec{k}(t')] dt' \right\}$$

◇  $\implies$  Velocity changes phase of signal; Diffusion attenuates signal

- Orders of magnitude:

- ◇ Velocity phase change  $\approx |\vec{v}| \cdot |\vec{k}|_{\max} \cdot T_E$

- ◇ Diffusion attenuation exponent  $\approx |\mathbf{D}| \cdot |\vec{k}|_{\max}^2 \cdot T_E$

- ◇  $|\vec{k}|_{\max} = \pi / \Delta x$  [ $\Delta x$  = image resolution]

- ◇  $T_E$  = time in data readout where  $\vec{k}(t)$  is closest to 0

- ↪ This is the point where the signal is largest

- Applications in human imaging ( $\Delta x \approx 1$  mm,  $T_E \approx 10$  ms):

- ◇ Blood flow: 100 mm/s in large arteries; 1 mm/s in capillaries:

- ↪ Larger vessels produce measurable phase changes:

- ↪ About  $1.8^\circ$  phase change per mm/s velocity

- ↪ Blood vessel mixed in with non-moving tissue means can only detect vessels  $\geq 0.5$  mm diameter

- ◇ Movement of heart wall; movement of walls of large arteries

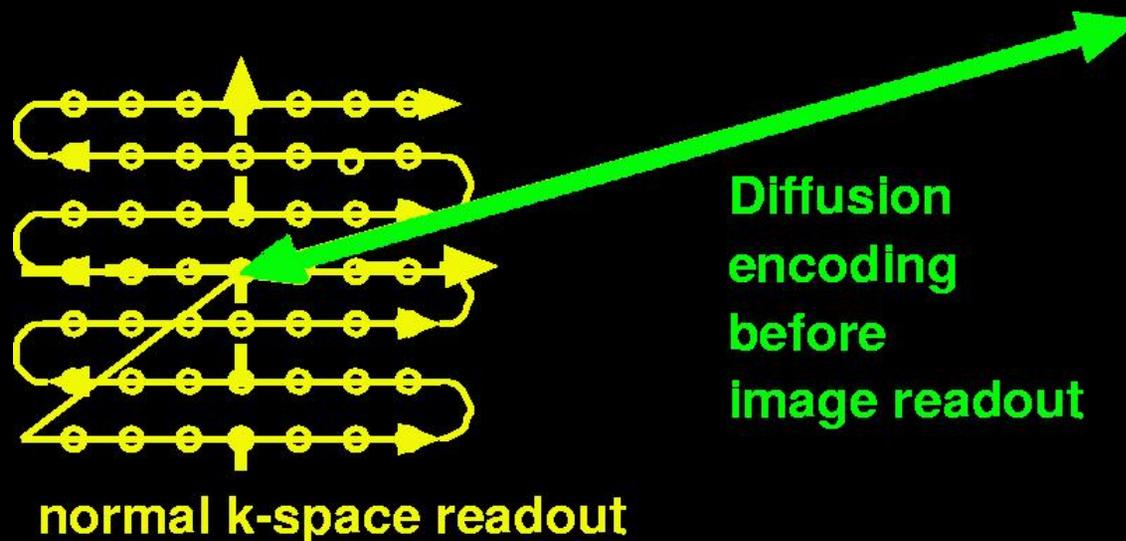
- Diffusion effects are small for normal imaging methods:

- $D \approx 10^{-3} \text{ mm}^2/\text{s} \implies |\mathbf{D}| \cdot \pi^2 / \Delta x^2 \cdot T_E \approx 10^{-4}$

- ◇ N.B.: RMS diffusion distance  $\sqrt{6DT_E} \approx 10 \mu\text{m}$

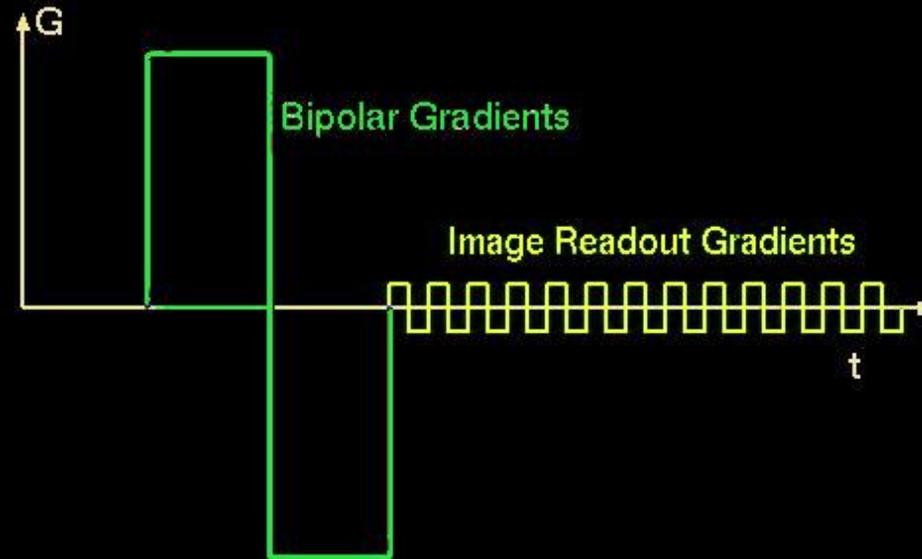
# Diffusion Encoding

- To make diffusion effect measurable, must do something special
  - ◇ Effect is proportional to  $|\vec{k}|^2$
- Must get to much larger values of  $\vec{k}$  than are needed just for imaging
- Then come back to neighborhood of  $\vec{k} = 0$  and do image data acquisition:

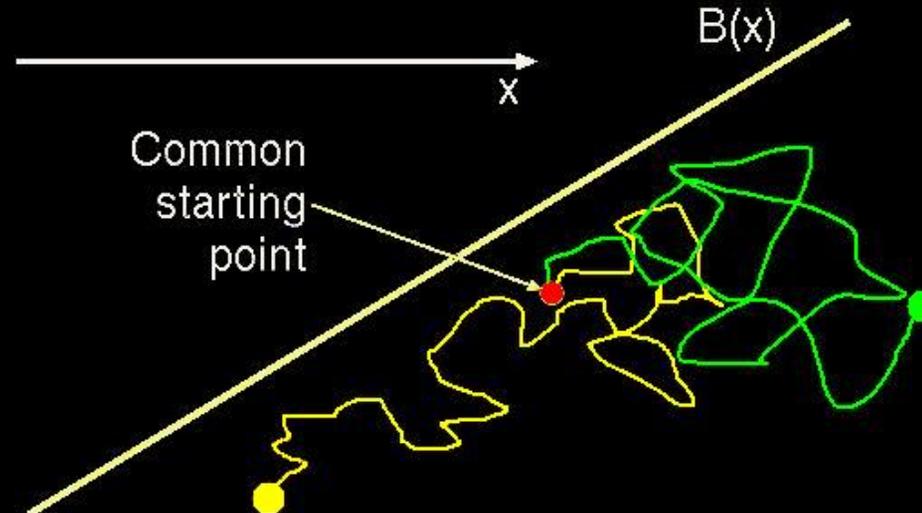


- In practice, to get strong diffusion effect, must go almost 100 times farther out in  $|\vec{k}|$  than is needed for 1 mm spatial resolution

- Idealized gradient sequence used for Diffusion Weighted Imaging:

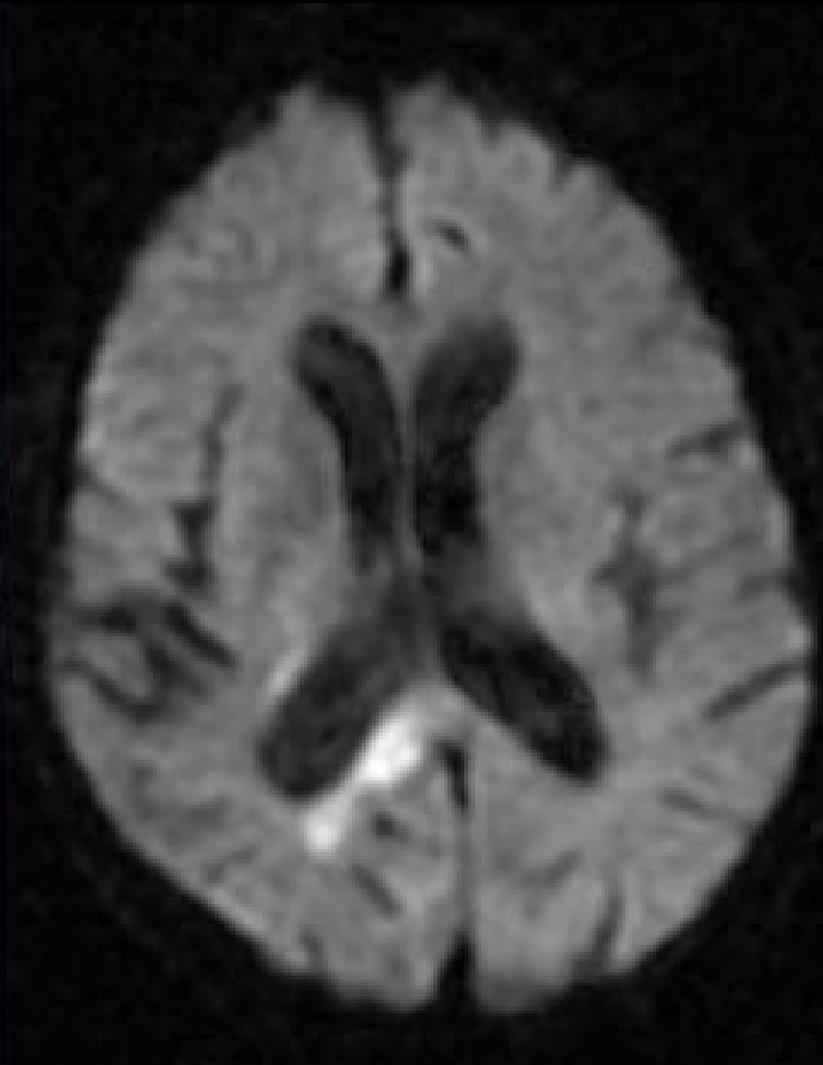
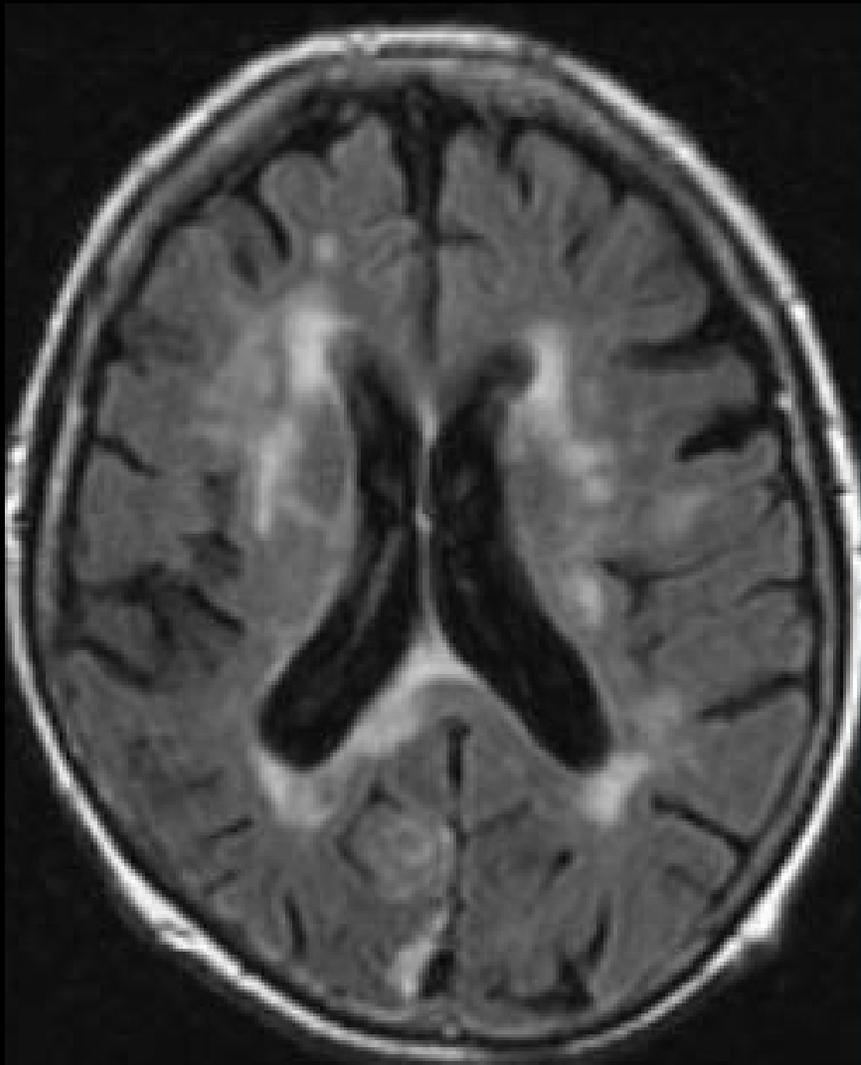


- Random walk through  $B$ -field gradient causes  $^1\text{H}$  spins to experience different frequencies, and so get out of phase, and so the total signal from all spins is attenuated (destructive interference):



Left: Standard Image

Right: Diffusion Weighted Image



Patient after stroke

# Diffusion Tensor Imaging

- For 1 mm resolution imaging, can ignore diffusion effects of standard readout gradients
- Assume diffusion encoding is along a straight line in  $k$ -space:

$$\diamond \vec{k}(t) = \begin{cases} k_{\max}(t/\tau) \hat{k} & 0 < t < \tau \\ k_{\max}(2 - t/\tau) \hat{k} & \tau < t < 2\tau \end{cases}$$

$\hookrightarrow \hat{k}$  is unit vector along encoding direction

$\hookrightarrow k_{\max}$  is maximum value of  $|\vec{k}|$  reached at  $t = \tau$

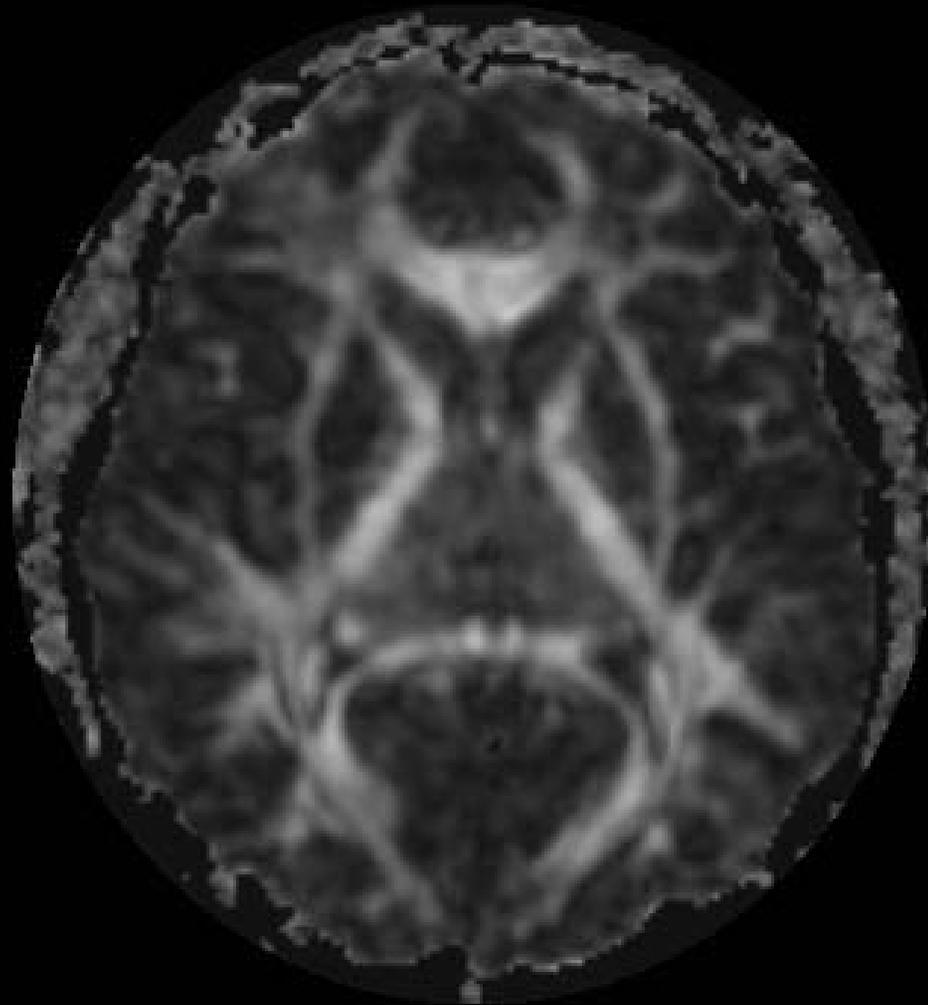
$\diamond$  Image is attenuated by factor  $\exp\{-\frac{2}{3}\tau k_{\max}^2 \hat{k} \cdot \mathbf{D} \cdot \hat{k}\}$

$\diamond$  Example:  $\hat{k} = \hat{x} \implies$  attenuation factor depends on  $D_{xx}$  component of  $\mathbf{D}$  tensor

$\diamond$  Example:  $\hat{k} = [\hat{x} + \hat{y}]/\sqrt{2} \implies$  attenuation factor depends on  $D_{xx} + 2D_{xy} + D_{yy}$

- Result: by taking at least 7 measurements (more is better) can calculate all 6 elements of  $\mathbf{D}$  tensor

- Diffusion of water in brain white matter tracts is not isotropic:  $D_{\parallel}$  is 2–3 times larger than  $D_{\perp}$

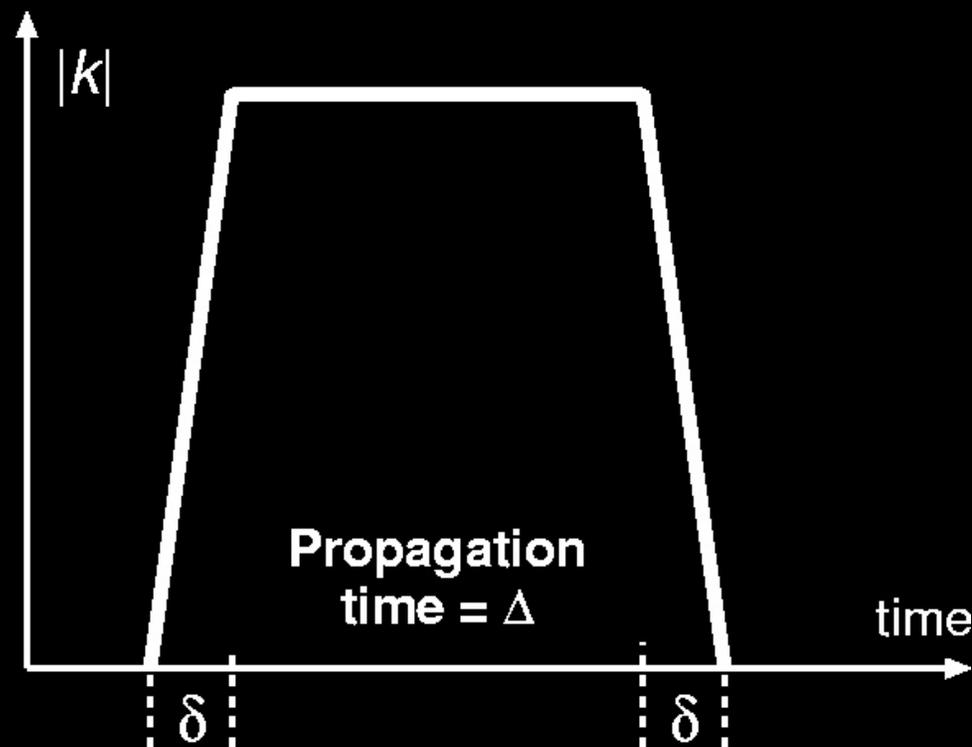


Ratio of largest eigenvalue of  $\mathbf{D}$  to smallest

- Applications: tracing white matter “wires” in brain; detection of demyelinating diseases

## More Complex Microscopic Motions

- Stochastic transport in complex medium (e.g., tissue, rocks) can be complicated
- $q$ -space formalism can be used to image statistics of such motion
- Technique: apply diffusion encoding gradients very rapidly, over time  $\delta$ , waiting time  $\Delta \gg \delta$  before rewinding back to  $\vec{k} = 0$



Followed by normal imaging  $k$ -space readout

- $\vec{q} \equiv \vec{k}_{\max}$  (the peak value during the  $\Delta$  time)

- Assumptions:

- ◇ The medium is homogeneous over the size of an imaging voxel
- ◇ The motion of the  $\text{H}_2\text{O}$  molecules can be described by a propagator function:

$$Prob(\vec{x} = \vec{r}, t = \Delta | \vec{x} = \vec{r}', t = 0) \equiv P(\vec{r} - \vec{r}', \Delta)$$

- ◇  $\delta \ll \Delta$ , so there is little transport while  $|\vec{k}| < |\vec{q}|$
- Then image is attenuated by factor

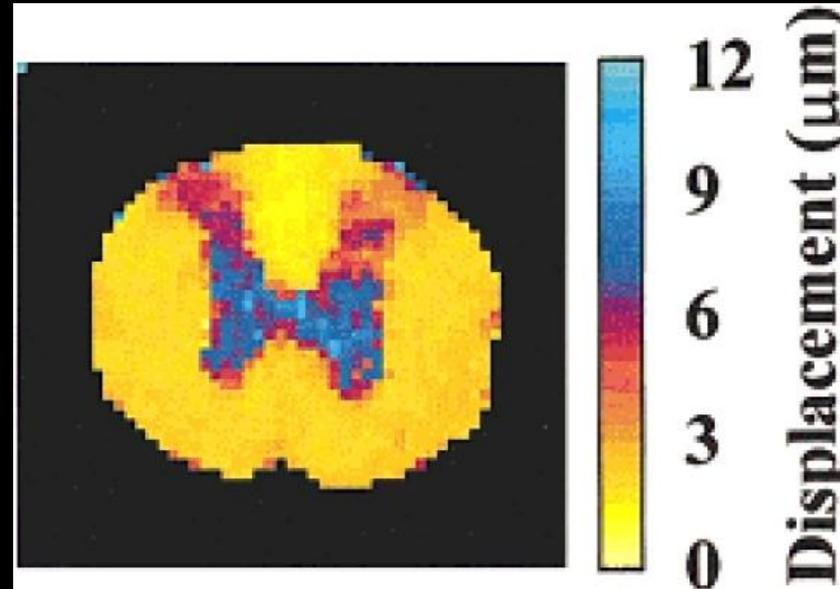
$$E(\vec{q}, \Delta) = \iiint P(\vec{r}, \Delta) e^{-i\vec{q} \cdot \vec{r}} d^3r$$

more than it would be if no diffusion/ $q$ -space encoding had been applied

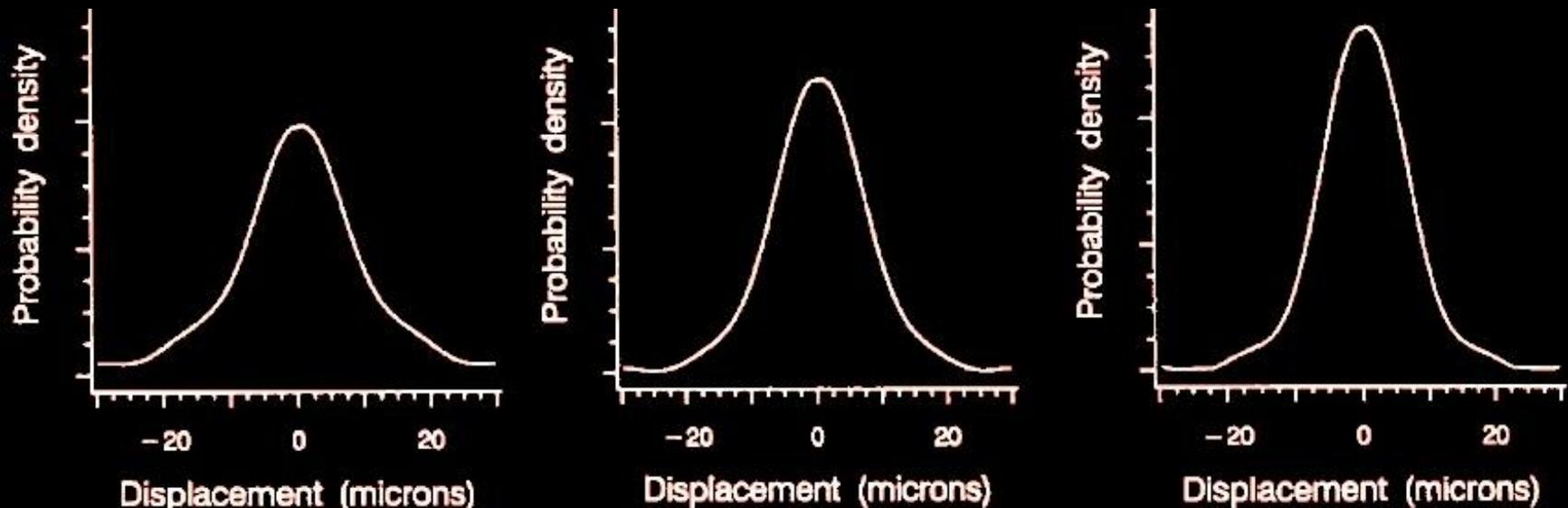
- ◇ Large  $\vec{r}$  limit = small  $\vec{q}$  limit = diffusion

- By acquiring images with enough different values of  $\vec{q}$ , can reconstruct propagator  $P(\vec{r}, \Delta)$

- Application: understanding water diffusion in neural tissue



Mean Displacement images in rat spinal cord



Left=Normal mouse brain

Middle=Ischemic

Right=Post-mortem

- Technical difficulties make  $q$ -space imaging a rarity:
  - ◇ Very time consuming
    - ↪ Signal is weak at large  $|\vec{q}| \implies$  must acquire lots of data for averaging purposes
  - ◇ Need for rapid switching of large gradient fields (small  $\delta$ ) makes reaching large  $\vec{q}$  nearly impossible in humans
    - ↪ Large  $d\mathbf{B}/dt$  induces currents in tissue, can cause nerve stimulation
  - ◇ Most work has been done on rodents (and plants!)
  - ◇ In humans, some work has been done with just a few large  $\vec{q}$  points
    - ↪ Goal is to see if white matter diseases can be tracked this way
    - ↪ It is clear that  $P(\vec{r}, \Delta)$  is not Gaussian in normal white matter
    - ↪ White matter is very complex at the 1–10 micron scale:
      - ▷ Directionality of axon bundles
      - ▷ Intra- and extra-cellular  $\text{H}_2\text{O}$  diffuse differently
      - ▷ Diffusion within myelin sheath is very slow
      - ▷ WM voxel  $\approx 1$  mm contains lots of  $\approx 10 \mu\text{m}$  “stuff”

- Extend  $q$ -space formalism to include  $\text{H}_2\text{O}$  transport during application of gradient fields

◇ Time dependent propagator:  $\delta(\vec{x}) \xrightarrow{t} P(\vec{x}, t)$

$$\text{Diffusion: } P_D(\vec{x}, t) = e^{-\vec{x}^T \mathbf{D}^{-1} \vec{x} / (4t)} / [(4\pi t)^3 \det \mathbf{D}]^{1/2}$$

◇ No gradients during transport of magnetization density  $M_{\perp} \implies$

$$M_{\perp}(\vec{x}, 0) \xrightarrow{t} M_{\perp}(\vec{x}, t) = M_{\perp}(\vec{x}, 0) * P(\vec{x}, t)$$

$$\hat{M}_{\perp}(\vec{q}, 0) \xrightarrow{t} \hat{M}_{\perp}(\vec{q}, t) = \hat{M}_{\perp}(\vec{q}, 0) \hat{P}(\vec{q}, t)$$

$$\frac{\partial \hat{M}_{\perp}(\vec{q}, t)}{\partial t} = \frac{1}{\hat{P}(\vec{q}, t)} \frac{\partial \hat{P}(\vec{q}, t)}{\partial t} \hat{M}_{\perp}(\vec{q}, t)$$

◇ Define  $u(\vec{q}, t) = -\log \hat{P}(\vec{q}, t)$

$$\hat{P}(\vec{q}, t)^{-1} \frac{\partial \hat{P}(\vec{q}, t)}{\partial t} = -\frac{\partial u(\vec{q}, t)}{\partial t} \equiv -u_t(\vec{q}, t)$$

◇ No gradients  $\implies \frac{\partial M_{\perp}(\vec{x}, t)}{\partial t} = \mathcal{F}^{-1} \left\{ -u_t(\vec{q}, t) \hat{M}_{\perp}(\vec{q}, t) \right\}$

- ◇ With magnetic field gradients  $\delta B_z(\vec{x}, t) = \vec{x}^T \vec{G}(t)$ , define  $q$ -space path by  $d\vec{q}(t)/dt = \gamma \vec{G}(t)$ :

$$\begin{aligned} \frac{\partial M_{\perp}(\vec{x}, t)}{\partial t} &= -i\gamma \delta B_z(\vec{x}, t) M_{\perp}(\vec{x}, t) \\ &\quad + \mathcal{F}^{-1} \left\{ -u_t(\vec{q}, t) \hat{M}_{\perp}(\vec{q}, t) \right\} \\ &= -i \frac{d\vec{q}(t)^T}{dt} \vec{x} M_{\perp}(\vec{x}, t) \\ &\quad + \mathcal{F}^{-1} \left\{ -u_t(\vec{q}, t) \hat{M}_{\perp}(\vec{q}, t) \right\} \end{aligned}$$

Generalizes Bloch-Torrey equation for magnetization evolution in the presence of diffusion and field gradients

- ◇ In Fourier coordinates  $\vec{x} \rightarrow \vec{q}$ :

$$\frac{\partial \hat{M}_{\perp}(\vec{q}, t)}{\partial t} - \frac{d\vec{q}(t)^T}{dt} \nabla_{\vec{q}} \hat{M}_{\perp}(\vec{q}, t) = -u_t(\vec{q}, t) \hat{M}_{\perp}(\vec{q}, t)$$

◇ A first order PDE in  $(\vec{q}, t)$  space

⇒ Solve via characteristics, then translate back to imaging  $\vec{k}$ -space (which is small compared to  $\vec{q}$ -space excursions):

$$\hat{M}_{\perp}(\vec{k}, T) = \exp\left[-\int_0^T u_t(\vec{q}(t), t) dt\right] \hat{M}_{\perp}(\vec{k}, 0)$$

$$\text{attenuation} = \mathbf{E} = \exp\left[-\int_0^T u_t(\vec{q}(t), t) dt\right]$$

$$-\log(\mathbf{E}) = \int_0^T u_t(\vec{q}(t), t) dt$$

$$= -\int_0^T \frac{1}{\hat{P}(\vec{q}(t), t)} \frac{\partial \hat{P}(\vec{q}(t), t)}{\partial t} dt$$

◇ General trajectory through  $(q, t)$ -space gives a tomographic result about time evolution of Fourier transform of point spread function

◇ **Unifies and generalizes** the distinct theories of diffusion weighted imaging and q-space imaging

◇ Check with standard  $q$ -space result:

↪ Arbitrary  $P(\vec{x}, T)$ , but with  $\vec{q}(t) = \text{const}$

▷ Since gradients applied only during brief intervals  $\delta \ll \Delta \equiv T$

$$\hookrightarrow \log(\mathbf{E}) = - \int_0^T u_t(\vec{q}, t) dt = -u(\vec{q}, T) = \log \hat{P}(\vec{q}, T)$$

$$\implies \mathbf{E} = \hat{P}(\vec{q}, T)$$

as usual

◇ Check with standard diffusion tensor result:

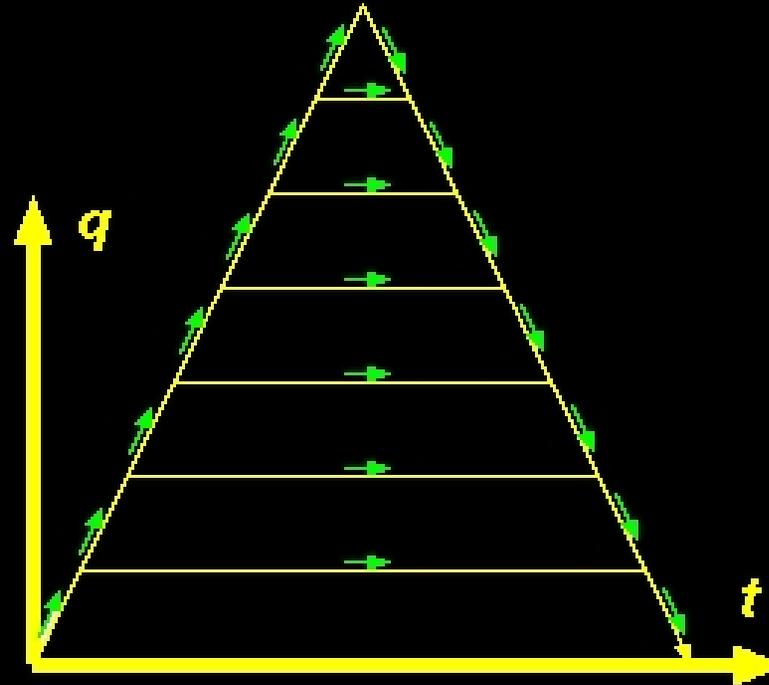
↪ Arbitrary  $\vec{q}(t)$ , but  $\hat{P}(\vec{q}, t) = e^{-t \cdot \vec{q}^T \mathbf{D} \vec{q}}$

$$\implies u_t(\vec{q}, t) = \vec{q}^T \mathbf{D} \vec{q} = \text{const}$$

$$\implies \log(\mathbf{E}) = - \int_0^T \vec{q}(t)^T \mathbf{D} \vec{q}(t) dt$$

as usual

- Possible paths through  $q$ -space, with finite maximum gradient strength:



- ◇ Problem: sampling coverage. Given a maximum gradient strength, simply can't get to large  $|\vec{q}|$  with small  $t$
- ◇ Problem: amount of data. Have to cover a lot of paths through  $(\vec{q}, t)$ -space to get enough projections so can solve for  $u_t(\vec{q}, t)$  and then reconstruct  $\hat{P}(\vec{q}, t)$

- ◇ Only feasible solution I see is to build some reasonable parameterized model for  $\hat{P}(\vec{q}, t)$  and then solve for the parameters
  - ↳ **Example:** ‘higher order’ diffusion ( $\partial^n / \partial x^n$  for  $n > 2$ ) — Liu et al., MRM 2004
    - ▷ Same as assuming  $u_t(\vec{q}, t) = U(\vec{q})$ , and expanding  $U(\vec{q})$  in a power series in  $\vec{q}$
    - ▷ So  $\hat{P}(\vec{q}, t) = e^{-t \cdot U(\vec{q})}$ , and coefficients of  $U(\vec{q})$  expansion are proportional to cumulants of  $P(\vec{x}, t)$
  - ↳ **Example:** ‘hindered + restricted diffusion compartments’ — Assaf et al., MRM 2004
    - ▷ ‘hindered’ diffusion is extra-axonal — fairly free, but has to get around obstacles — described by anisotropic diffusion tensor  $\mathbf{D}$
    - ▷ ‘restricted’ diffusion is intra-axonal — myelin boundaries form impermeable cylinders — described as  $R^2 \mathbf{D}_\perp t \rightarrow \infty$  by
 
$$u(\vec{q}, t) = q_{\parallel}^2 D_{\parallel} t + a R^4 q_{\perp}^2 / (D_{\perp} t) [2 - b R^2 / (D_{\perp} t)]$$
 ( $\parallel$  &  $\perp$  are along & transverse to axon;  $R$  = axon radius)  
 $\perp$  diffusion asymptotes to const attenuation as  $t \rightarrow \infty$ , modeling no  $\text{H}_2\text{O}$  transport across myelin sheath

## Wrapup

- Tomographic result

$$-\log (I[\vec{q}(t)]/I[0]) = \int_0^T \frac{\partial}{\partial t} u(\vec{q}(t), t) dt$$

is a way to unify the mathematical formalization of disparate models that try to blend  $q$ -space and DWI techniques

- Hopefully will allow exploration and generalization of physiologically 'reasonable' models for  $\text{H}_2\text{O}$  transport
  - ◇ Which in turn can give a little insight into the microscopic contents of voxels

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Et alii ...