Physics of Diffusion Weighted Imaging:

Introduction to Diffusion Weighted Imaging

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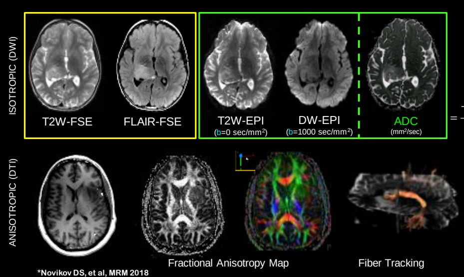
The Physics of Diffusion Imaging

- Learning Objectives:
  - Understand the motivating biophysics underlying current diffusion models
  - Learn modern techniques for optimizing the DWI acquisition
  - Understand key pitfalls and limitations of DWI
- Today's talks
  - Introduction to Diffusion Weighted Imaging (R. Jason Stafford, PhD)
  - Advances in DWI Acquisitions (Ken-Pin Hwang, PhD)
  - Diffusion Imaging in the Brain (Nathan Yanasak, PhD)
- This session followed by Advanced DWI: Applications for Radiation Oncology

Diffusion is a probe of tissue water microenvironment

All models are wrong … but some are useful.
George Box



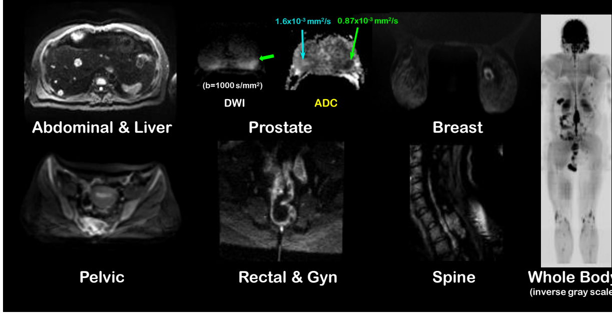
$$= \frac{-\ln\left(\frac{S_{Trace}}{S_0}\right)}{\Delta b}$$

$$ADC_{iso} = \frac{Tr(D)}{3}$$

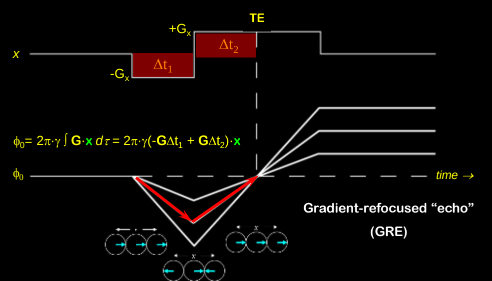
$$FA = \sqrt{\frac{3}{2}}\sqrt{\frac{\sum(\lambda_i - \langle\lambda\rangle)^2}{\sum \lambda_i{}^2}}$$

Nucifora PG, et al., Radiology. 2007 Nov;245(2):367-84.; *Novikov DS, et al, MRM 2018

Expanding role of diffusion outside the brain



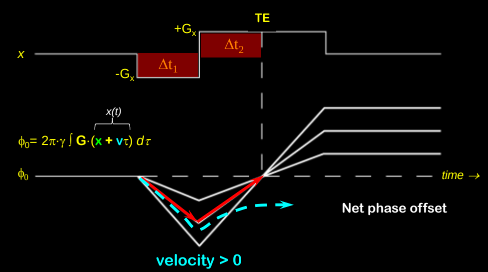
Gradients modulate spin phase based on their location



$\phi_0 = 2\pi\cdot\gamma\int \mathbf{G}\cdot x\, d\tau = 2\pi\cdot\gamma(-\mathbf{G}\Delta t_1 + \mathbf{G}\Delta t_2)\cdot x$

Gradient-refocused "echo" (GRE)

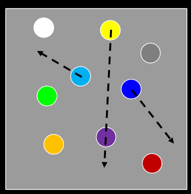
Gradients modulate spin phase based on their location



$\phi_0 = 2\pi\cdot\gamma\int \mathbf{G}\cdot(x + v\tau)\, d\tau$

Net phase offset

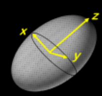
Motion Due to Molecular Self-Diffusion



$\langle \Delta x_i^2 \rangle = \sigma^2 = 2D_i t$

$\Delta r_{avg} = \sqrt{6Dt}$ µm (3D isotropic)

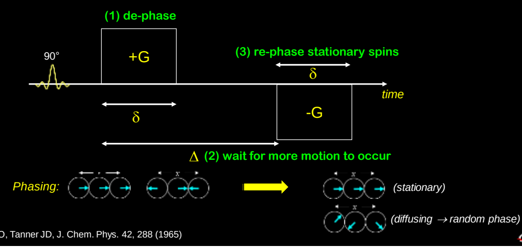
- Random (Brownian) motion vs flow
- Microscopic extension of Fick's Law
  - $J = -D\frac{\partial P}{\partial x} \rightarrow \boxed{\frac{\partial P}{\partial t} = D\frac{\partial^2 P}{\partial x^2}}$
  - $P(\Delta x, t) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\Delta x/2\sigma^2}$ — *Free diffusion propagator: Probability for displacement Δx during t*
- Microstructural boundaries → *anisotropy*
- $D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$ (diffusion tensor)
- $D_{iso} = \frac{Tr(D)}{3}$ & $FA = \sqrt{\frac{3}{2}}\sqrt{\frac{\sum(\lambda_i - \langle\lambda\rangle)^2}{\sum \lambda_i^2}}$



Einstein, A., *Investigations on the Theory of the Brownian Movement*. 1956

Bipolar Gradients for Diffusion Weighting

$$S = S_0\, exp\left\{-(\gamma G \delta)^2 \cdot \left(\Delta - \frac{\delta}{3}\right) \cdot D\right\} = S_0\, exp(-b \cdot D)$$



Stejskal EO, Tanner JD, J. Chem. Phys. 42, 288 (1965)

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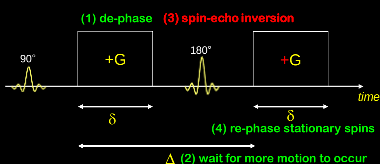
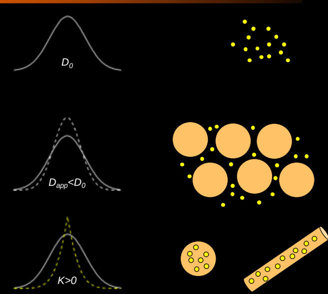


Stejskal EO, Tanner JD, J. Chem. Phys. 42, 288 (1965)

Different modes of molecular diffusion

- **Free**
  - Gaussian distributed
  - D_{H_2O} ~ 3x10^{-3} mm²/s @ 37°C
- **Hindered** (D_{app})
  - Tortuosity: $\lambda = (D_0/D_{app})^{½}$
- **Restricted**
  - Non-Gaussian



Impact of diffusion on signal

Bloch-Torrey* formulation (sans relaxation and bulk flow): $\frac{\partial \vec{M}}{\partial t} = \gamma \vec{M} \times \vec{B} + D\nabla^2 \vec{M}$

Accumulated phase for arbitrary gradient over time: $\varphi(t) = \gamma \int_0^t \vec{G}(\tau) \cdot \vec{r}(\tau) d\tau$

Phase modulates signal over volume: $S(G,t) = \int \rho(r)\, e^{-i\varphi(G,r,t)} dr$

However, the spins experience random motion over time: $S(G,t) = \int \rho(r) \left\{ \int P(\Delta r, t) \cdot e^{-i\varphi(G,\Delta r,t)} d\Delta r \right\} dr$

Loss of coherence leads to irreversible signal loss: $\Longrightarrow S(b) = S_0 e^{-\langle \varphi^2 \rangle} = \boxed{S_0 e^{-bD}}$

Where *b* is defined from the heterogeneous solution: $b = \gamma^2 \int_0^{TE} \left[\int_0^t \vec{G}(\tau)\, d\tau\right]^2 dt = (\gamma G \delta)^2 \cdot \left(\Delta - \frac{\delta}{3}\right)$

Sensitivity to diffusion function G pulse and mixing time: $\boxed{S = S_0\, exp\left\{-(\gamma G \delta)^2 \cdot \left(\Delta - \frac{\delta}{3}\right) \cdot D\right\}}$

*Torrey, H C (1956). "Bloch Equations with Diffusion Terms". Physical Review 104 (3): 563–565.

A Tale of Two Spaces: From k to q

Linear gradient phasing of signal: $\varphi(t) = \gamma \int_0^t \vec{G}(\tau) \cdot \vec{r}(\tau) d\tau$

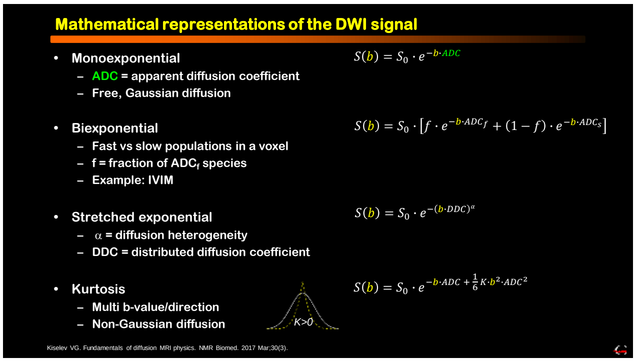
Encoding gradients => k-space formalism: $\vec{k}(t) = \gamma \int_0^t \vec{G}(\tau)\, d\tau$, $S(k,t) = \int \rho(r)\, e^{-ikr} dr$

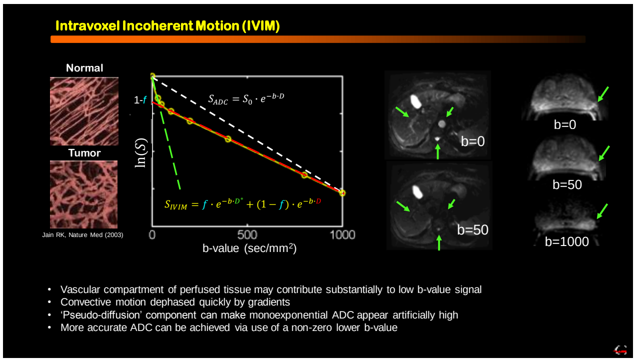
Diffusion gradients => q-space (displacement) formalism: $\vec{q}(t) = \gamma \int_0^t \vec{G}(\tau)\, d\tau$, $S(q,t) = \int \rho(r)\, e^{-iqr} dr$ → $b = q^2 t$

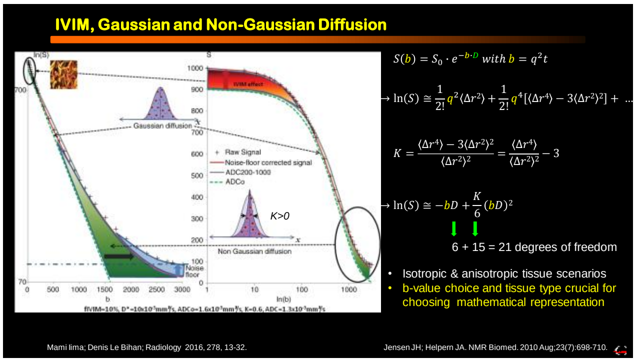
Q-space signal impact is a result of the diffusion propagator: $S(q,\Delta) = \int \rho(r) \left\{ \int P(\Delta r, \Delta) \cdot e^{-iq\Delta r} d\Delta r \right\} dr$

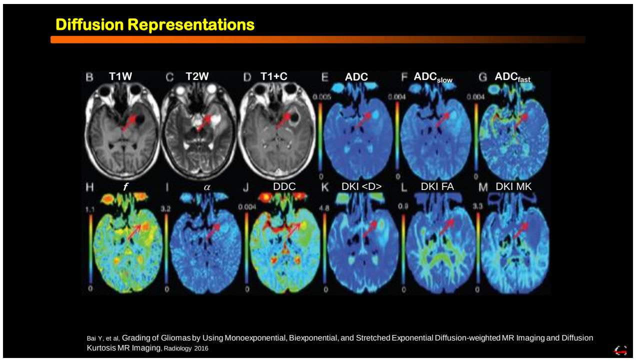
Q-space signal has Fourier relationship to P(Δr,Δ): $E(q,\Delta) = \int P(\Delta r, \Delta) \cdot e^{-iq\Delta r} d\Delta r = FT\{P(\Delta r, \Delta)\}$
(sampling "q-space" is diffusion spectrum imaging)

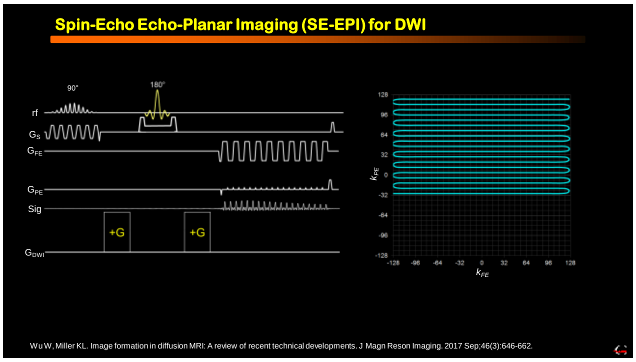
*Torrey, H C (1956). "Bloch Equations with Diffusion Terms". Physical Review 104 (3): 563–565.

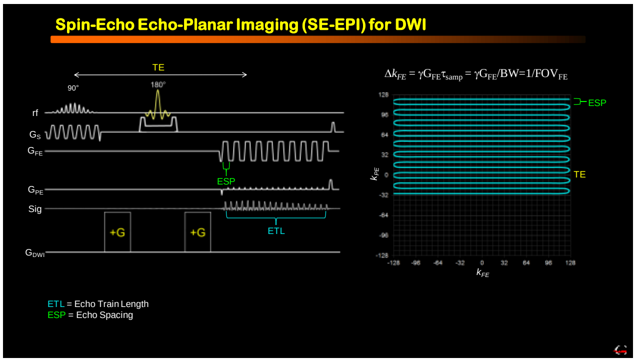

Mathematical representations of the DWI signal
Monoexponential
ADC = apparent diffusion coefficient
Free, Gaussian diffusion
$S(b) = S_0 \cdot e^{-b \cdot ADC}$
Biexponential
Fast vs slow populations in a voxel
f = fraction of ADC_f species
Example: IVIM
$S(b) = S_0 \cdot [f \cdot e^{-b \cdot ADC_f} + (1-f) \cdot e^{-b \cdot ADC_s}]$
Stretched exponential
α = diffusion heterogeneity
DDC = distributed diffusion coefficient
$S(b) = S_0 \cdot e^{-(b \cdot DDC)^{\alpha}}$
Kurtosis
Multi b-value/direction
Non-Gaussian diffusion
K>0
$S(b) = S_0 \cdot e^{-b \cdot ADC + \frac{1}{6} K \cdot b^2 \cdot ADC^2}$
Kiselev VG. Fundamentals of diffusion MRI physics. NMR Biomed. 2017 Mar;30(3).

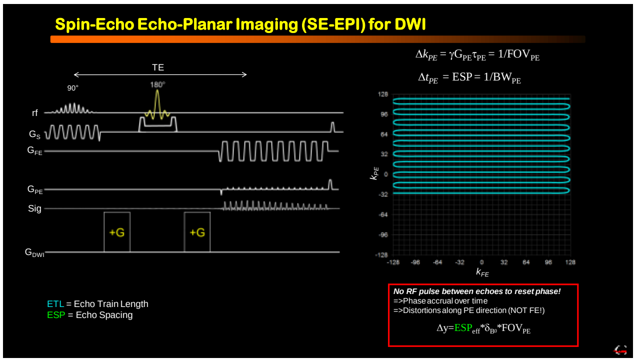

Intravoxel Incoherent Motion (IVIM)
Normal
Tumor
Jain RK, Nature Med (2003)
1-f
$S_{ADC} = S_0 \cdot e^{-b \cdot D}$
$S_{IVIM} = f \cdot e^{-b \cdot D^*} + (1-f) \cdot e^{-b \cdot D}$
ln(S)
0
500
1000
b-value (sec/mm²)
b=0
b=50
b=0
b=50
b=1000
Vascular compartment of perfused tissue may contribute substantially to low b-value signal
Convective motion dephased quickly by gradients
'Pseudo-diffusion' component can make monoexponential ADC appear artificially high
More accurate ADC can be achieved via use of a non-zero lower b-value

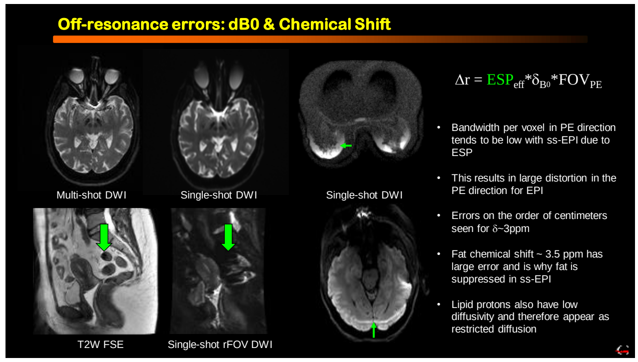

IVIM, Gaussian and Non-Gaussian Diffusion
Gaussian diffusion
Raw Signal
Noise-floor corrected signal
ADC200-1000
ADCo
K>0
Non Gaussian diffusion
Noise floor
$S(b) = S_0 \cdot e^{-b \cdot D}$ with $b = q^2 t$
$\rightarrow \ln(S) \cong \frac{1}{2!} q^2 \langle \Delta r^2 \rangle + \frac{1}{2!} q^4 [\langle \Delta r^4 \rangle - 3 \langle \Delta r^2 \rangle^2] + \ldots$
$K = \frac{\langle \Delta r^4 \rangle - 3 \langle \Delta r^2 \rangle^2}{\langle \Delta r^2 \rangle^2} = \frac{\langle \Delta r^4 \rangle}{\langle \Delta r^2 \rangle^2} - 3$
$\rightarrow \ln(S) \cong -bD + \frac{K}{6} (bD)^2$
6 + 15 = 21 degrees of freedom
Isotropic & anisotropic tissue scenarios
b-value choice and tissue type crucial for choosing mathematical representation
Mami Iima; Denis Le Bihan; Radiology 2016, 278, 13-32.
Jensen JH; Helpem JA. NMR Biomed. 2010 Aug;23(7):698-710.

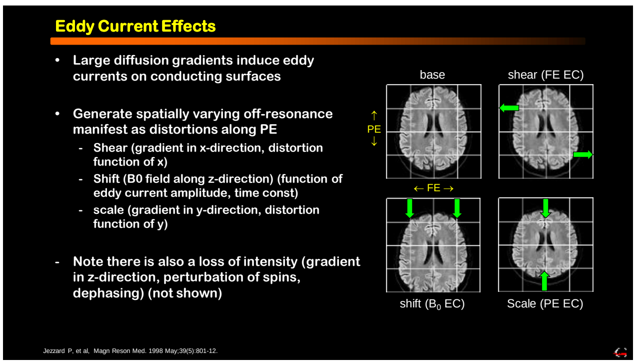

Diffusion Representations
B T1W
C T2W
D T1+C
E ADC
F ADC slow
G ADC fast
H f
I α
J DDC
K DKI <D>
L DKI FA
M DKI MK
Bai Y, et al, Grading of Gliomas by Using Monoexponential, Biexponential, and Stretched Exponential Diffusion-weighted MR Imaging and Diffusion Kurtosis MR Imaging, Radiology 2016

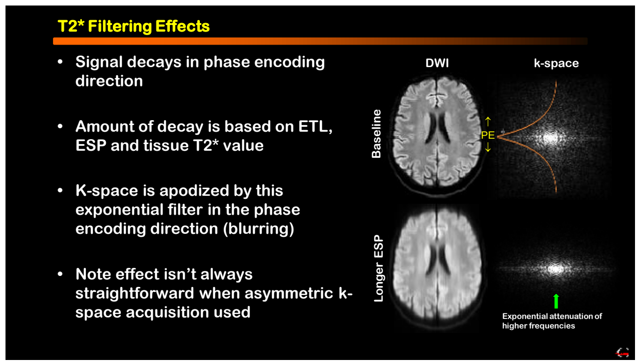

Spin-Echo Echo-Planar Imaging (SE-EPI) for DWI
90°
180°
rf
Gs
GFE
GPE
Sig
GDWI
+G
+G
kPE
kFE
Wu W, Miller KL. Image formation in diffusion MRI: A review of recent technical developments. J Magn Reson Imaging. 2017 Sep;46(3):646-662.

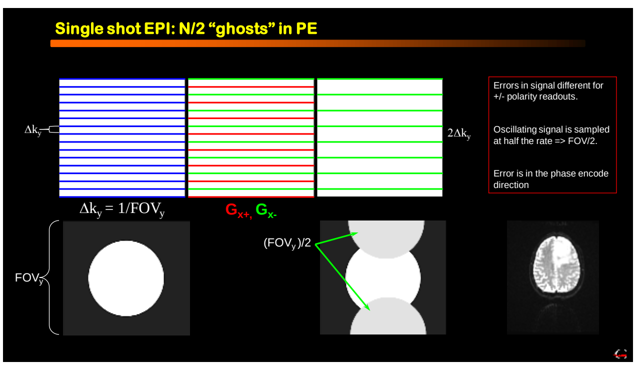

Spin-Echo Echo-Planar Imaging (SE-EPI) for DWI
TE
90°
180°
rf
Gs
GFE
GPE
Sig
GDWI
+G
+G
ESP
ETL
$\Delta k_{FE} = \gamma G_{FE} \tau_{samp} = \gamma G_{FE}/BW = 1/FOV_{FE}$
ESP
TE
kPE
kFE
ETL = Echo Train Length
ESP = Echo Spacing

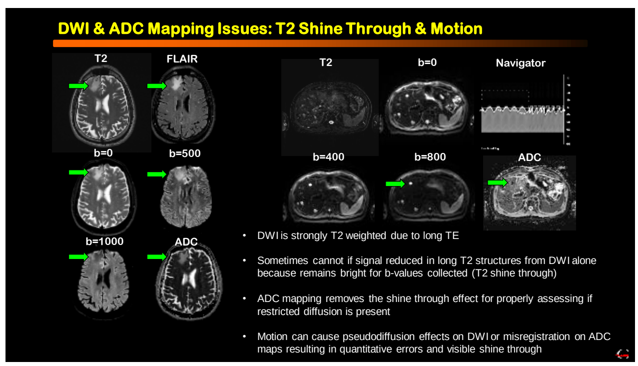

Spin-Echo Echo-Planar Imaging (SE-EPI) for DWI
$\Delta k_{PE} = \gamma G_{PE}\tau_{PE} = 1/FOV_{PE}$
Δt_{PE} = ESP = 1/BW$_{PE}$
TE
90°
180°
rf
G_S
G_{FE}
G_{PE}
Sig
+G
+G
G_{DWI}
k_{PE}
k_{FE}
ETL = Echo Train Length
ESP = Echo Spacing
No RF pulse between echoes to reset phase!
=>Phase accrual over time
=>Distortions along PE direction (NOT FE!)
$\Delta y = ESP_{eff} * \delta_{B0} * FOV_{PE}$


Off-resonance errors: dB0 & Chemical Shift
$\Delta r = ESP_{eff} * \delta_{B0} * FOV_{PE}$
Multi-shot DWI
Single-shot DWI
Single-shot DWI
T2W FSE
Single-shot rFOV DWI
Bandwidth per voxel in PE direction tends to be low with ss-EPI due to ESP
This results in large distortion in the PE direction for EPI
Errors on the order of centimeters seen for δ~3ppm
Fat chemical shift ~ 3.5 ppm has large error and is why fat is suppressed in ss-EPI
Lipid protons also have low diffusivity and therefore appear as restricted diffusion

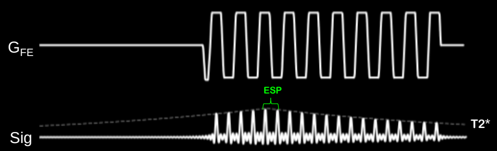

Eddy Current Effects
Large diffusion gradients induce eddy currents on conducting surfaces
Generate spatially varying off-resonance manifest as distortions along PE
Shear (gradient in x-direction, distortion function of x)
Shift (B0 field along z-direction) (function of eddy current amplitude, time const)
scale (gradient in y-direction, distortion function of y)
Note there is also a loss of intensity (gradient in z-direction, perturbation of spins, dephasing) (not shown)
base
shear (FE EC)
PE
← FE →
shift (B_0 EC)
Scale (PE EC)
Jezzard P, et al, Magn Reson Med. 1998 May;39(5):801-12.


T2* Filtering Effects
Signal decays in phase encoding direction
Amount of decay is based on ETL, ESP and tissue T2* value
K-space is apodized by this exponential filter in the phase encoding direction (blurring)
Note effect isn't always straightforward when asymmetric k-space acquisition used
DWI
k-space
Baseline
PE
Longer ESP
Exponential attenuation of higher frequencies


Single shot EPI: N/2 "ghosts" in PE
Δk_y
$2\Delta k_y$
$\Delta k_y = 1/FOV_y$
G_{x+}, G_{x-}
Errors in signal different for +/- polarity readouts.
Oscillating signal is sampled at half the rate => FOV/2.
Error is in the phase encode direction
FOV_y
$(FOV_y)/2$


DWI & ADC Mapping Issues: T2 Shine Through & Motion
T2
FLAIR
b=0
b=500
b=1000
ADC
T2
b=0
Navigator
b=400
b=800
ADC
DWI is strongly T2 weighted due to long TE
Sometimes cannot if signal reduced in long T2 structures from DWI alone because remains bright for b-values collected (T2 shine through)
ADC mapping removes the shine through effect for properly assessing if restricted diffusion is present
Motion can cause pseudodiffusion effects on DWI or misregistration on ADC maps resulting in quantitative errors and visible shine through

Echo Spacing and Echo Train Tradeoffs



Large ESP	=> effective bandwidth per pixel in phase encode direction small
	=> susceptible to large phase errors from ΔB, ΔG, ***chemical shift***
	=> Ramp sampling and “Multi-shot” or intervleaved reduces: $ESP_{eff} = ESP_0/N_{shot}$
Long ETL	=> long readout time
	=> compromise resolution (T2* apodization of signal)
	=> Partial Fourier in PE and parallel imaging reduces ETL and min TE
Large BW	=> Decrease ESP and ETL
	=> SNR penalty from reduced sampling time
	=> SNR benefit from reduced readout period and shorter TE

$\Delta k_{PE} = \gamma G_{PE}\tau_{PE} = 1/FOV_{PE}$

$\Delta t_{PE} = ESP = 1/BW_{PE}$

$\Delta k_{FE} = \gamma G_{FE}\tau_{samp} = \gamma G_{FE}/BW = 1/FOV_{FE}$

No RF pulse between echoes to reset phase!
=>Phase accrual over time
=>Distortions along PE direction (NOT FE!)

$\Delta y = ESP_{eff} * \delta_{B0} * FOV_{PE}$

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Thank you for your time!

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