Diffusion Imaging in the Brain

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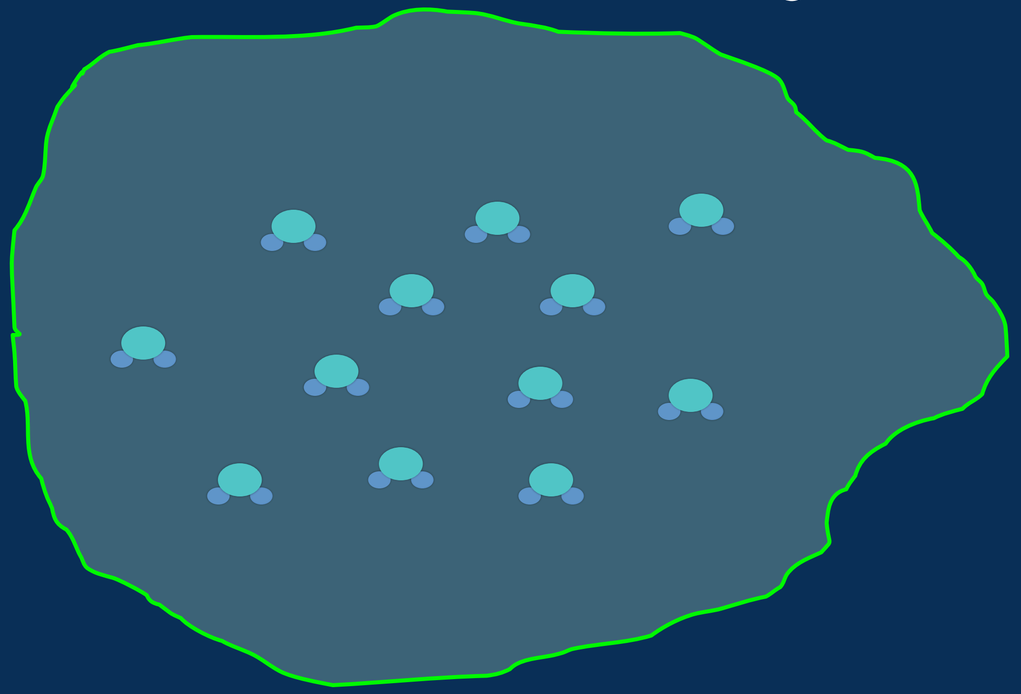
Are we really looking at diffusion, clinically?



Biological ”Diffusion” ≈ self-diffusion of water (1)
+ geometric restrictions (2)
+ “random, slow flow” (3)

$$\frac{\partial n(\vec{r},t)}{\partial t} = \vec{\nabla}\cdot(D(\vec{r})\vec{\nabla}n(\vec{r},t))$$

Inhomogeneous material, or anisotropic diffusion.

Isotropic Diffusion (1)

$$\frac{\partial n(\vec{r},t)}{\partial t} = D\nabla^2 n(\vec{r},t)$$

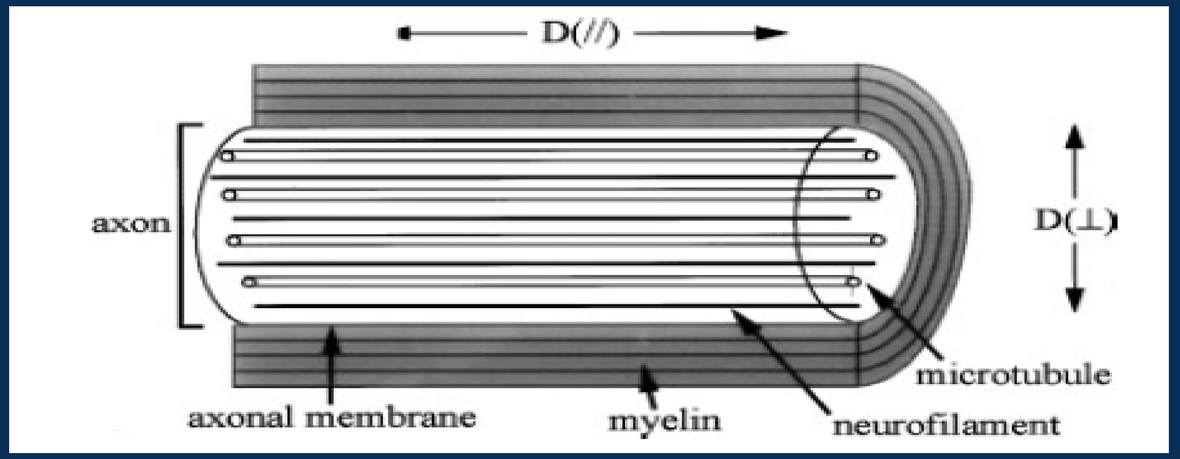
1D solution

$$n(x,t) = \frac{K}{(2Dt)^{1/2}} e^{-x^2/4Dt}$$

Are we really looking at diffusion, clinically?

Biological ”Diffusion” ≈ self-diffusion of water (1)
+ geometric restrictions (2)
+ “random, slow flow” (3)

For the most part, non-gaussian behavior affects both mean diffusivity and diffusive anisotropy.

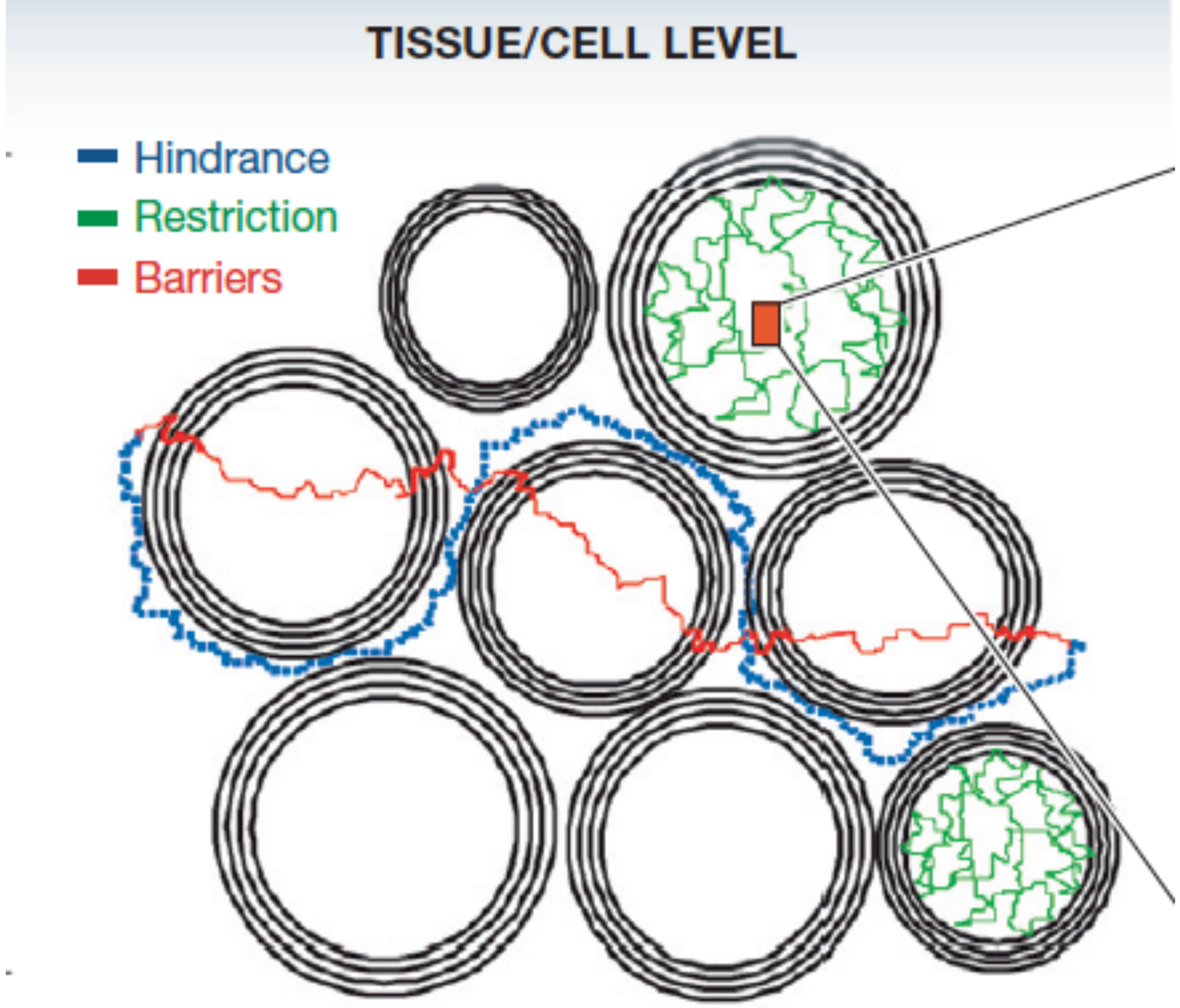


Beaulieu, NMR in Biomed; 2002

Contributing factors:

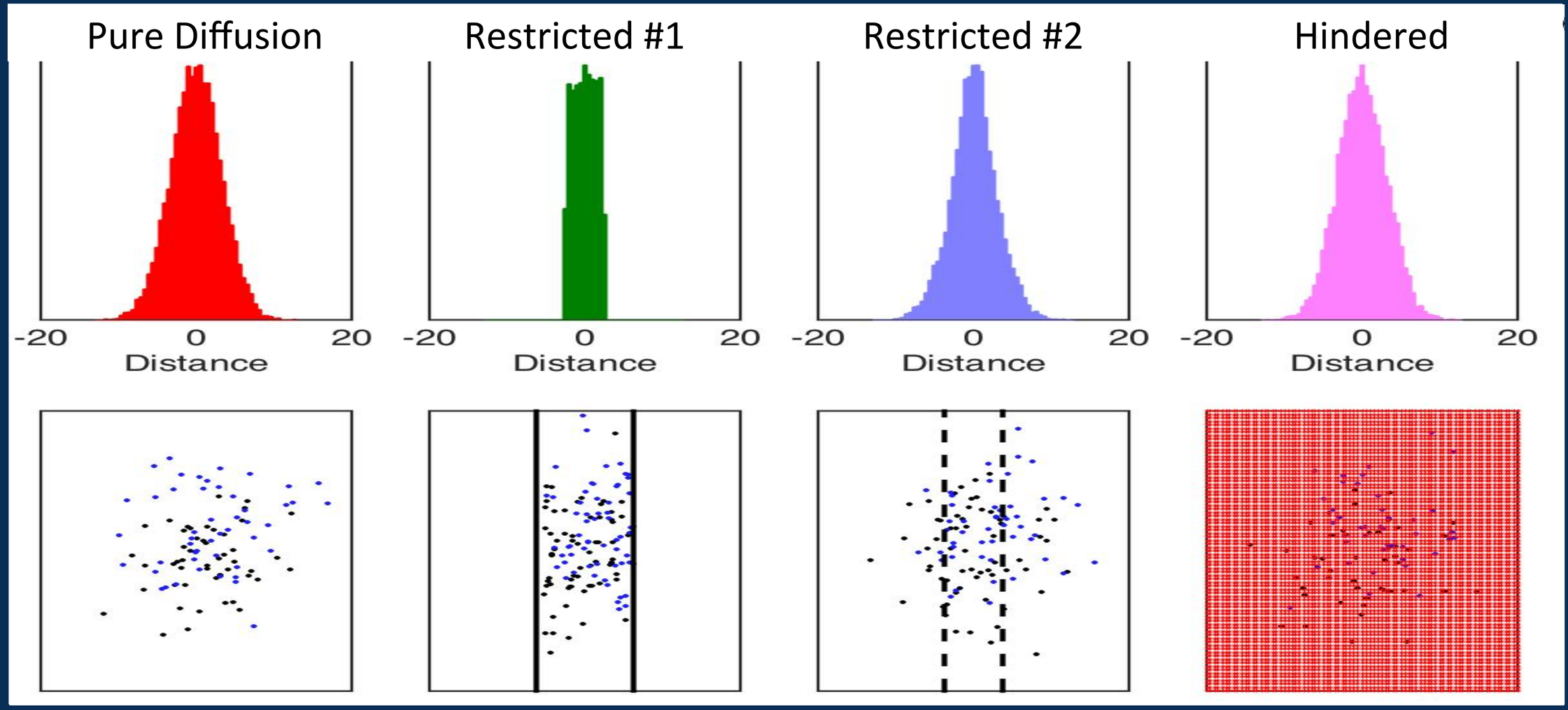
cell membrane
permeability/exchange rate
intra/extra-cellular diffusion
myelin*
inner cell structures
necrosis

Also: relaxation in different compartments → contrast vs. composition



From LiBihan, 2014, EMBO Molecular Medicine

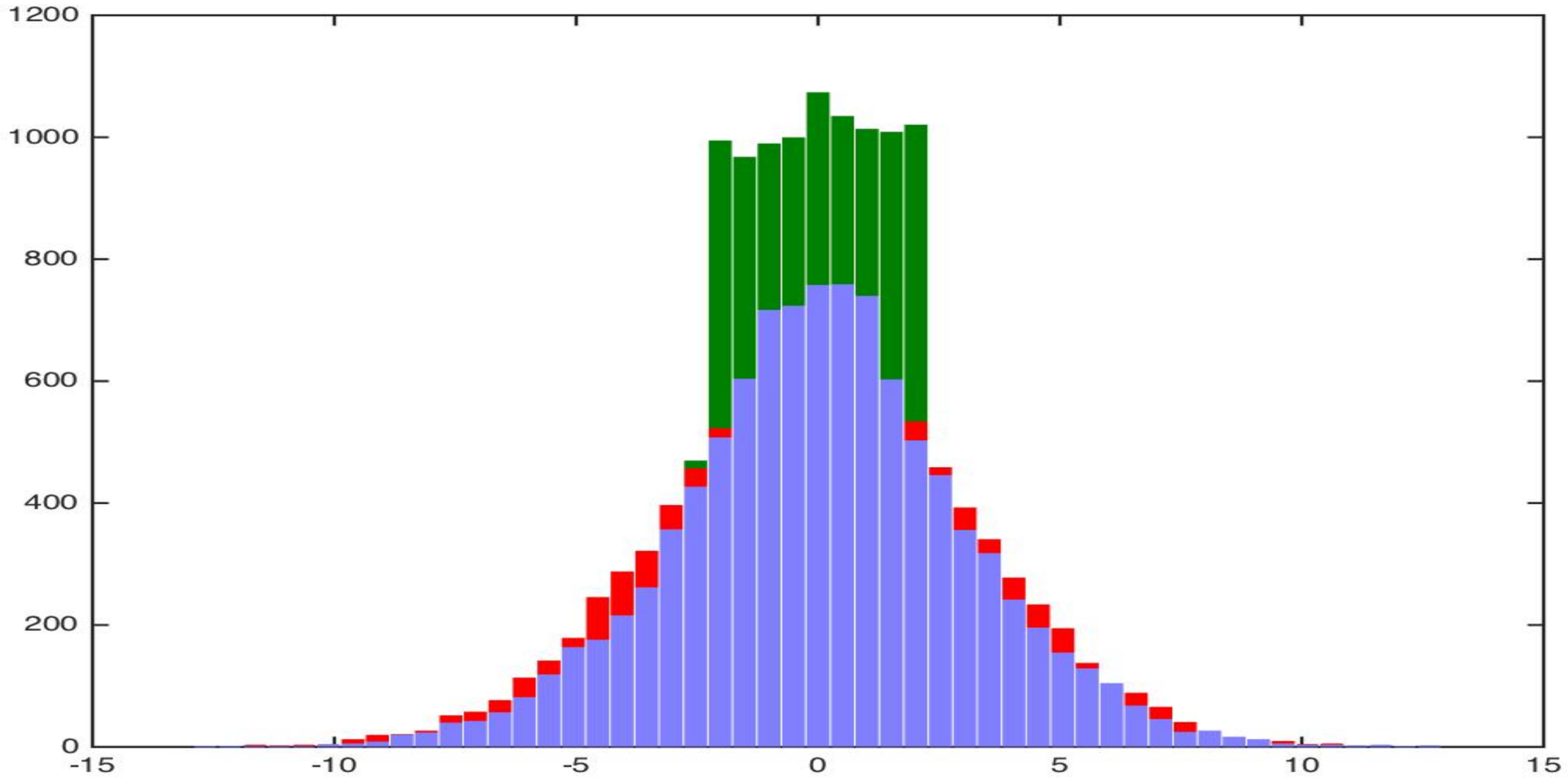
Gaussian vs. Non-Gaussian Demo



1) Non-gaussian qualities depend on diffusion time.

2) Multiple compartments + permeability = reality?

Gaussian vs. Non-Gaussian Demo



1) Non-gaussian qualities depend on diffusion time.

2) Multiple compartments + permeability = reality?

Diffusion Basics

At 25° C,
D = 2.2 x 10^{-3} mm^2 / second
(free water)

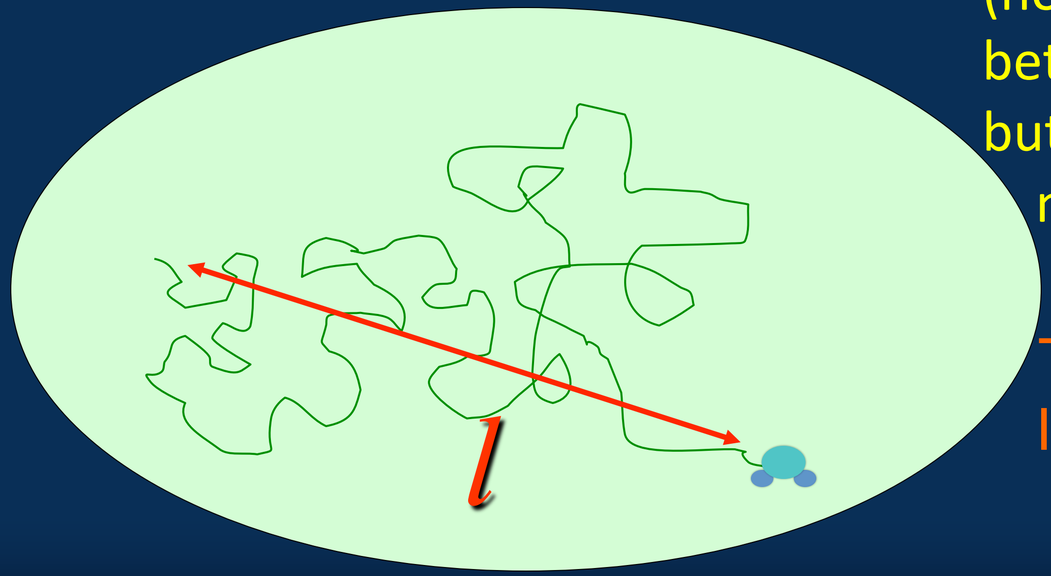
t~ 1 msec: pure diffusivity
t~1 sec: compartmental mixing
t~10-100 msec: geometric constraints

Characteristic Diffusion length (1D):

$$l = \sqrt{2Dt}$$

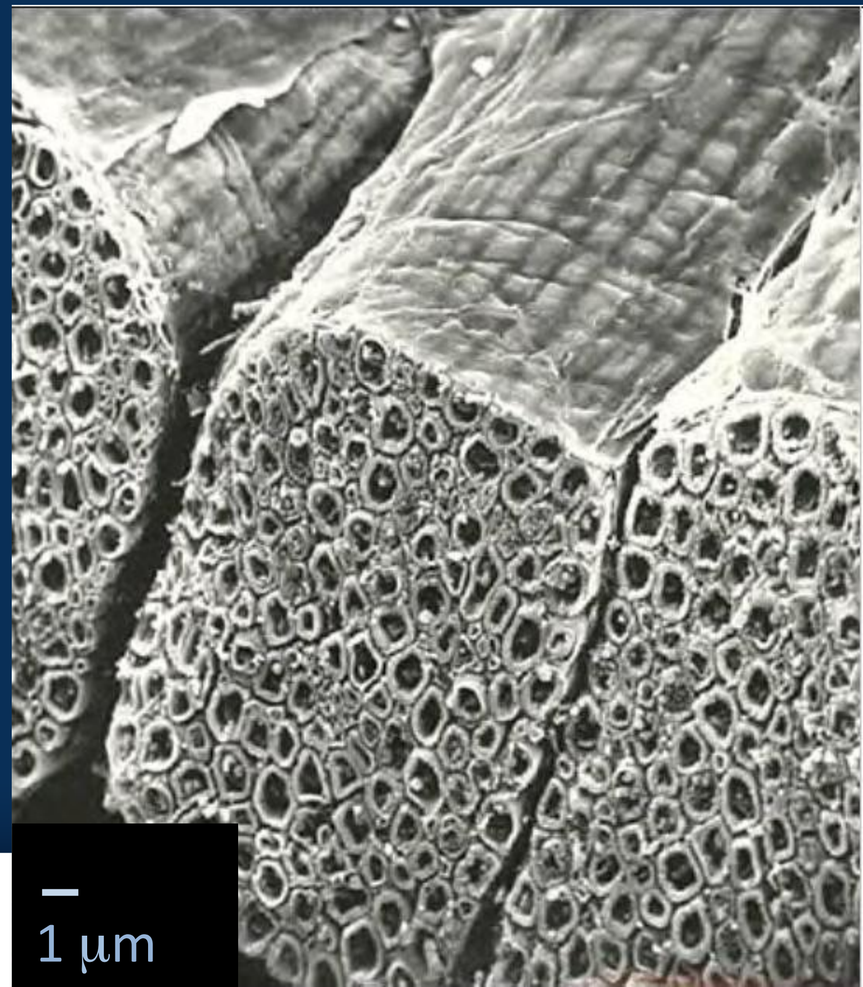
Time between pulses:
t = 10-20 msec (maybe +)

→l ~ 5-15 μm



(not much exchange between compartments, but much contact with membranes).

Typical MRI scale lengths: < 30 μm.



So, what's normal and what's not?

Qualitative: "What does diffusion in healthy tissue look like?"

Fast/slow

Characteristics: anisotropy, non-gaussian, variation with b.

"How does diffusion change with particular pathology?"

Expectations from understanding of tissue and models/theory.

Comparison with contralateral/healthy regions.

"How does that change with disease progression?"

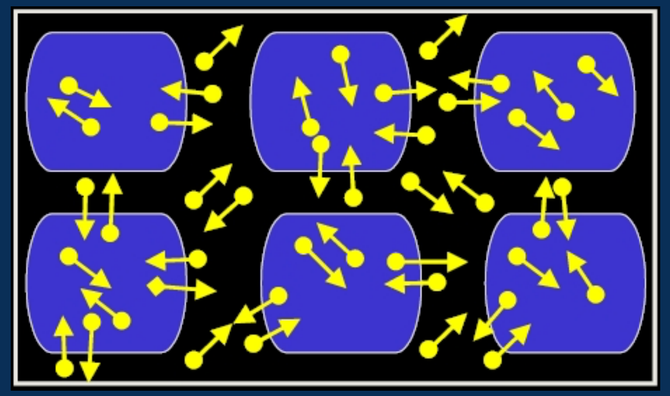
Quantitative: "What values of diffusion metrics are associated with pathology?"

"What values match with viable tissue before intervention?"

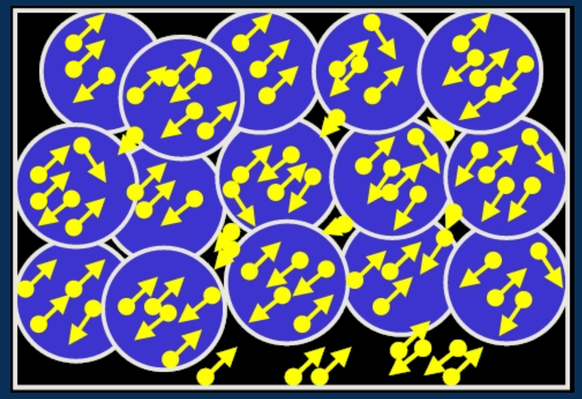
"Grading of pathology with quantifyable values?"

Stroke

Anatomy of an Ischemic Stroke

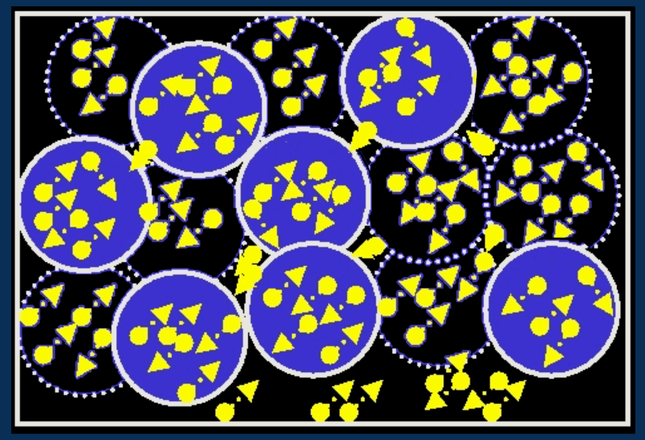


Normal cells



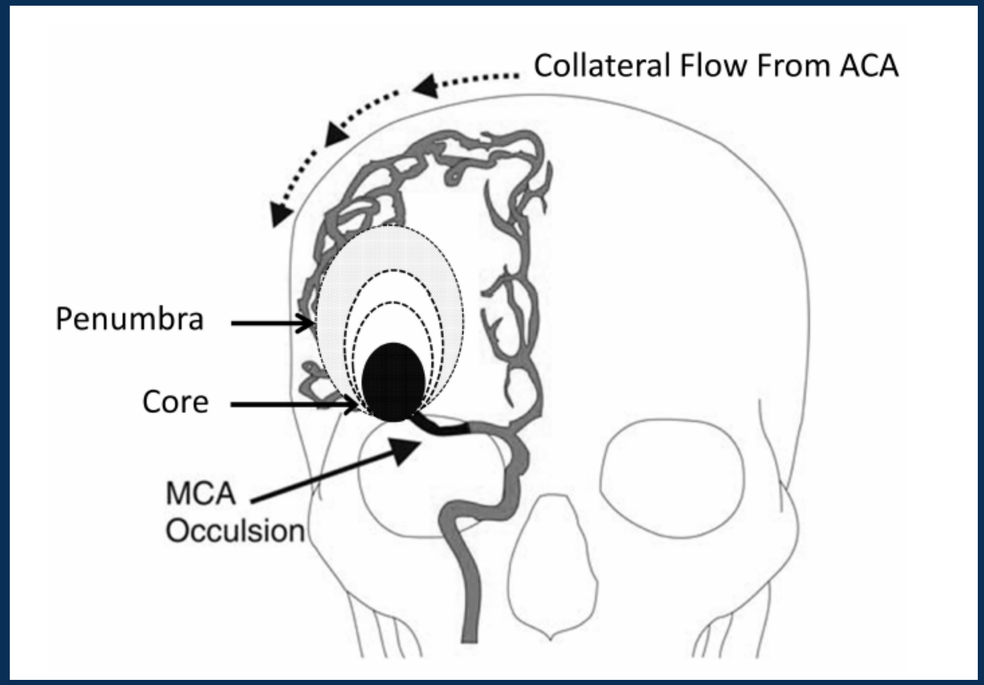
Ischemia disrupts sodium pump—influx of water causes cell swelling **(decreased "diffusion", restricted & hindered diffusion↑)**

From Radaideh, et al. Neurographics, 2002[1, 2002.]



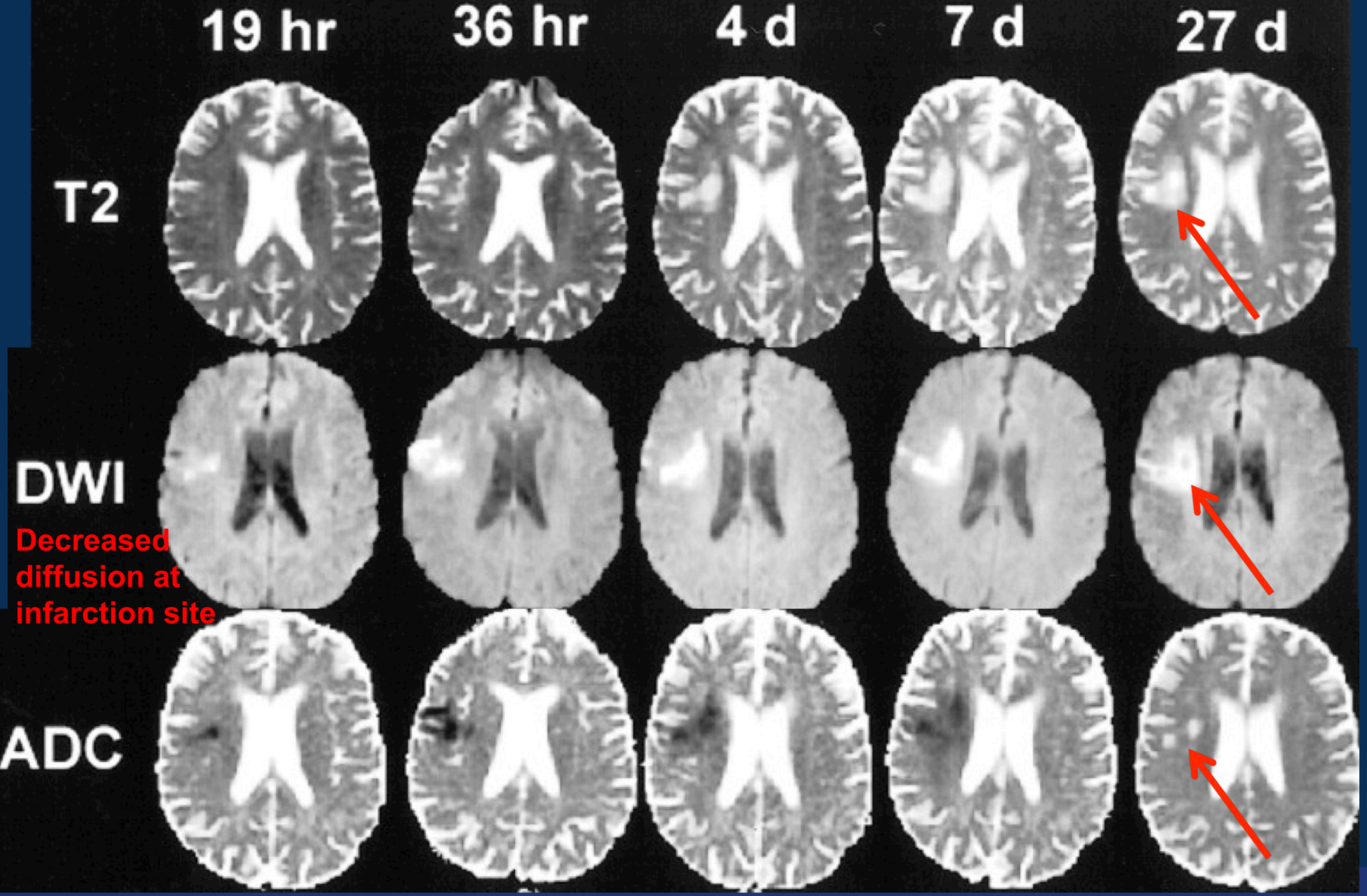
Cytotoxic edema → vasogenic (cell death) **(increased diffusion)**

As stroke progresses, inter- and extra-cellular water diffusion properties (and compartmental fraction) changes → DWI changes



Gonzalez, JMRI, 2012

DWI in a Stroke Protocol



MR images (6000/210/1) in a 67-year-old woman with left hand weakness, left facial droop, and slurred speech.

Clinical standard today: this is where diffusion imaging for stroke stops.

Maarten G. Lansberg et al. AJNR Am J Neuroradiol 2001;22:637-644

<3 x DWI> "/" b0 → ADC

T2 shine through

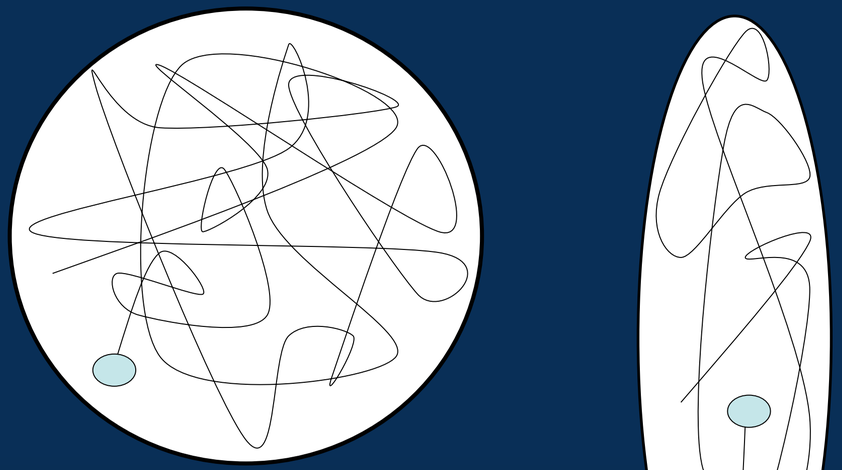
Diffusion Anisotropy Review

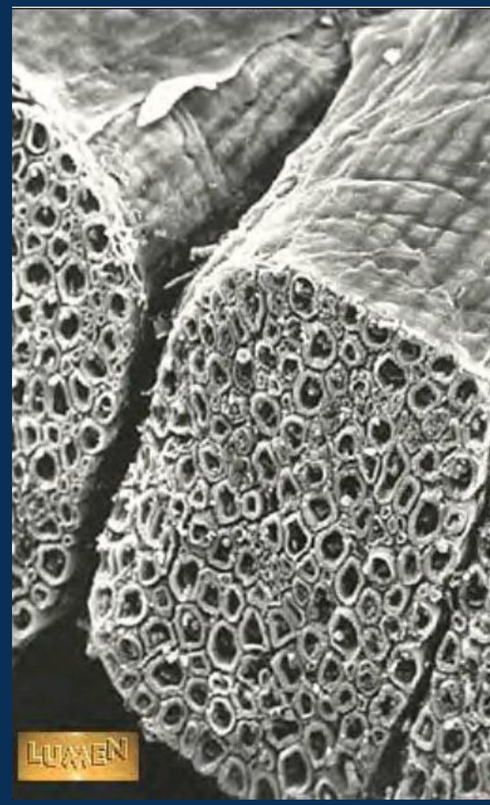
Each application of a diffusion gradient, we measure diffusion in ONE direction. Can apply multiple gradients to examine anisotropy.

In structured tissues, restrictions may depend on direction of diffusion.

E.g., white matter diffusion is highly anisotropy.

Changes in anisotropy → structural breakdown (or plasticity?)





DTI Review

DTI: examine the amount of diffusion along various axes.

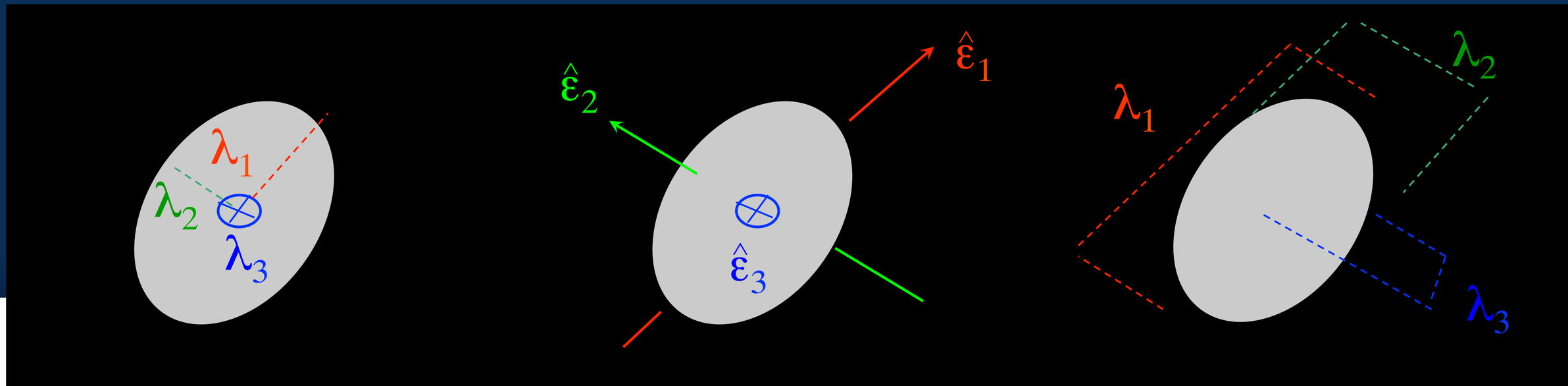
From six or more measurements (+b0), determine tensor in each image voxel:

Nominally distribute gradient directions over sphere.

→ three eigenvalues of diffusion magnitude (e-values: λ_i)
→ three eigenvectors of diffusion direction (e-vectors: ε_ι)

Also, fractional anisotropy (FA).

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



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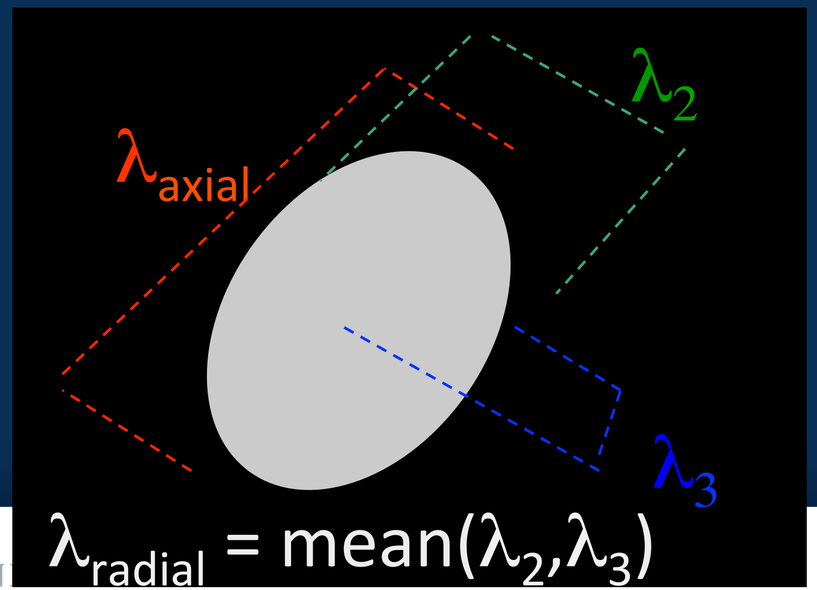
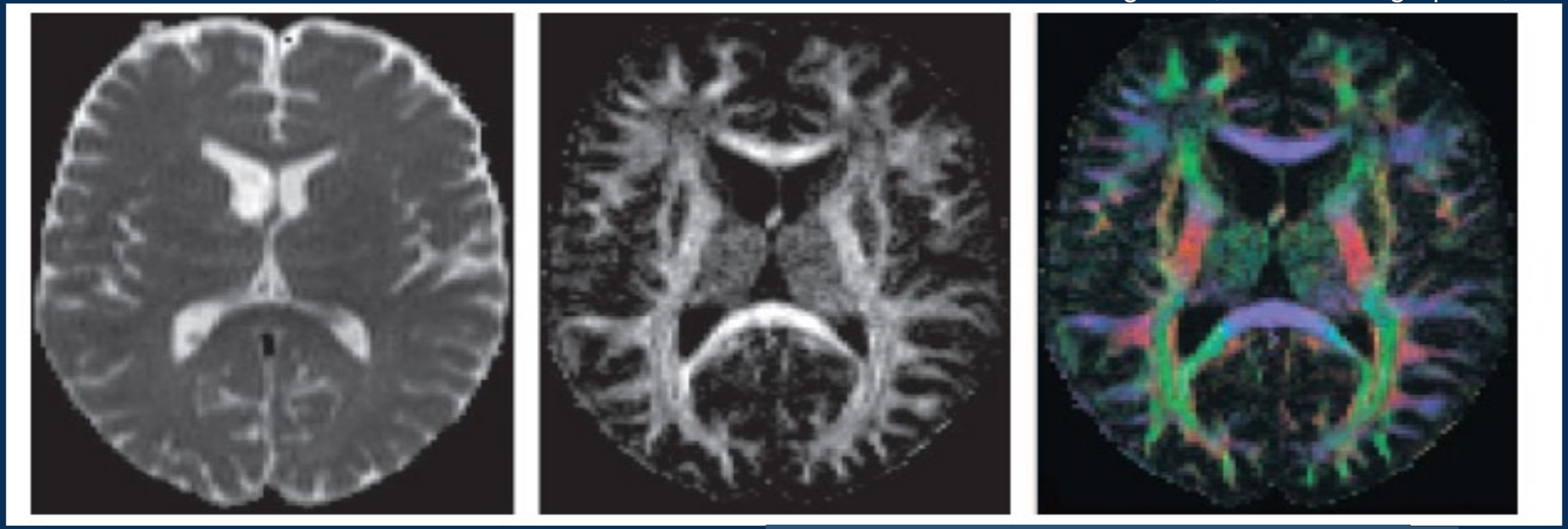
Other WM metrics:
axial,radial diffusivity



Nominally distribute gradient directions over sphere.

DTI Review

From Hagmann, et al. Radiographics, 2006

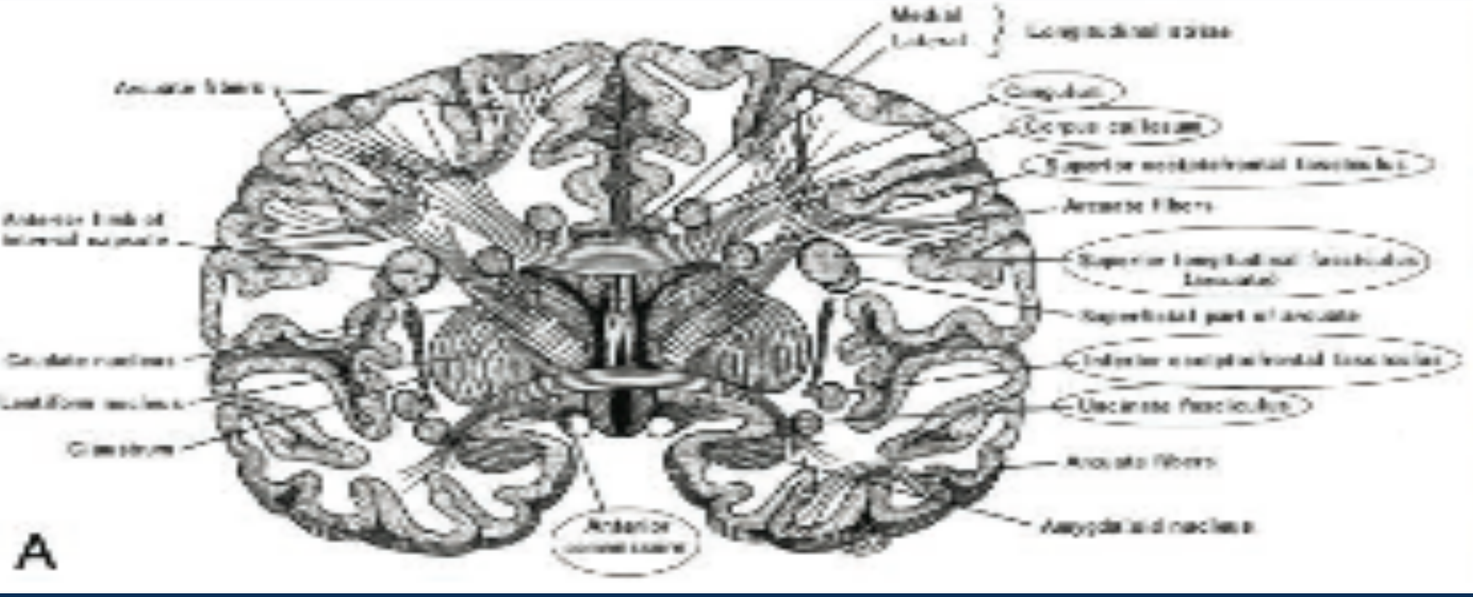


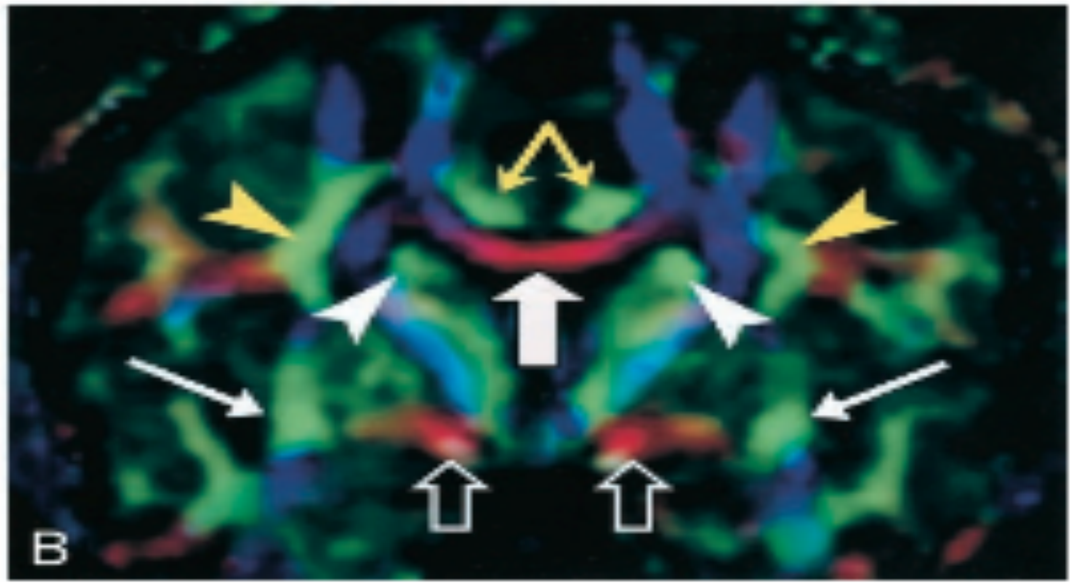
b0 Image (T2-weighted)

FA image (map + color-code)

DTI gives you diffusion magnitude information, anisotropy, and directional information.

DTI Review





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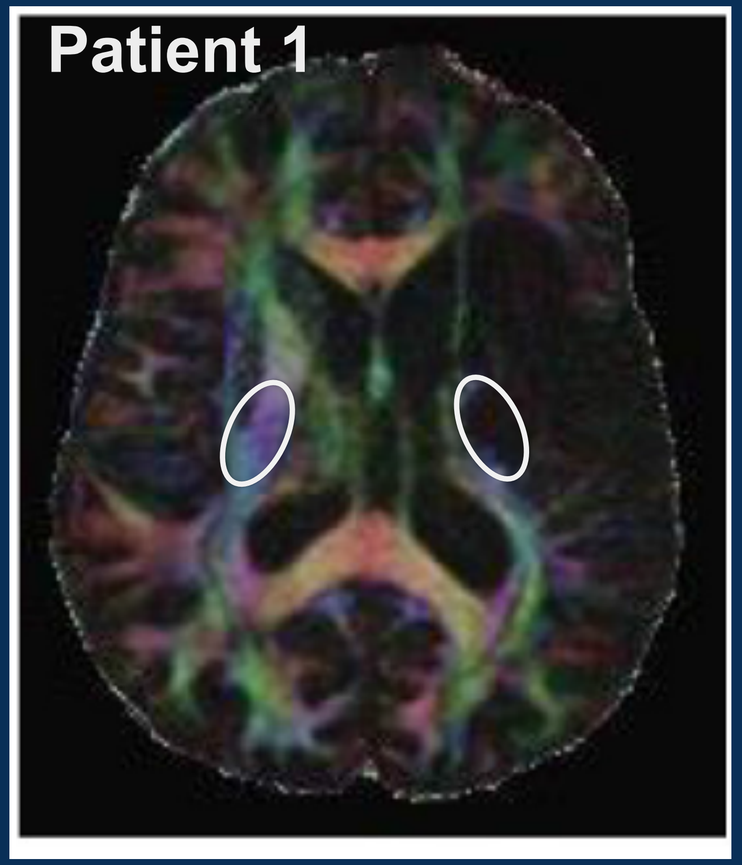
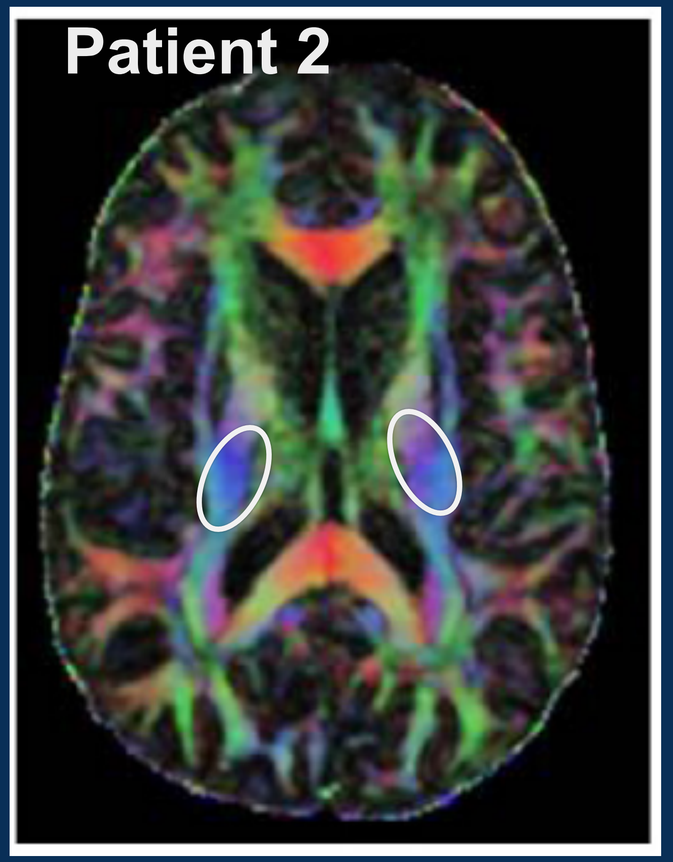
Jellison, et al., AJNR, 2004





DTI in a Stroke Protocol

What is the motor function outcome in stroke rehabilitation?

Monitor DTI metrics longitudinally in the internal capsule (median & 20-month post)

Song et al. Fron. Human Neurosci. 2015

Measure DTI metrics for each hemisphere (posterior limb of IC).

Ratios of metrics (ips. to contr.) at baseline best correlation for *future* motor improvement.

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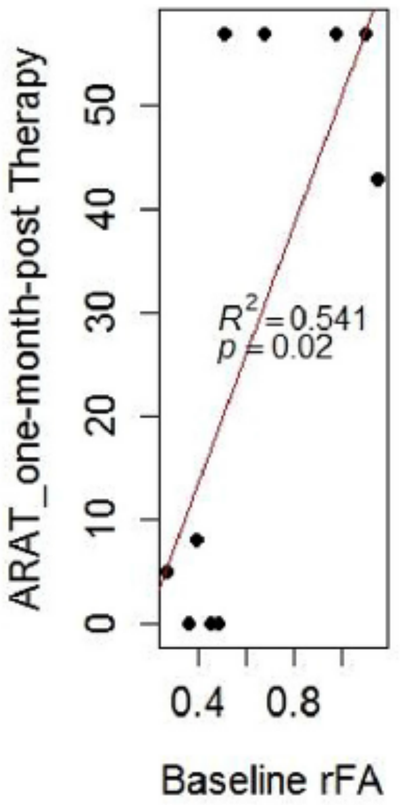

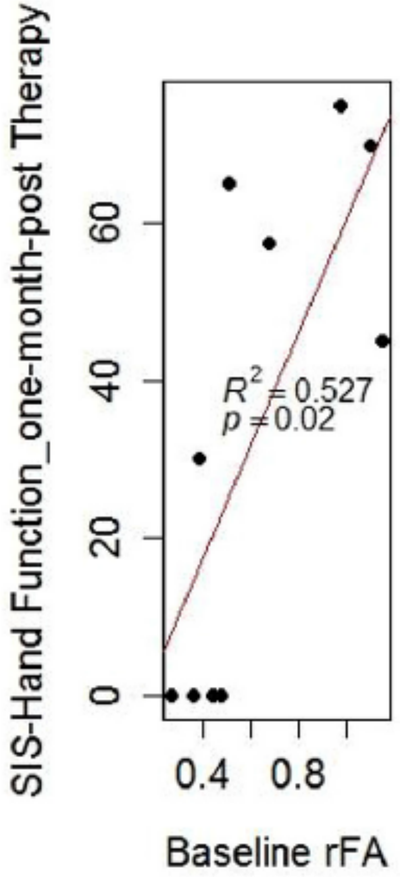

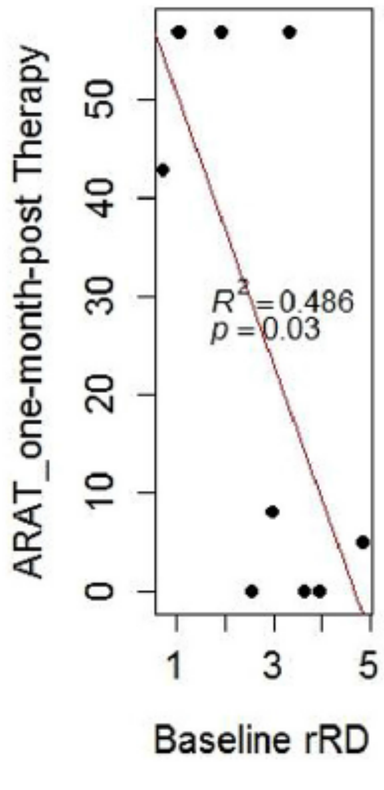

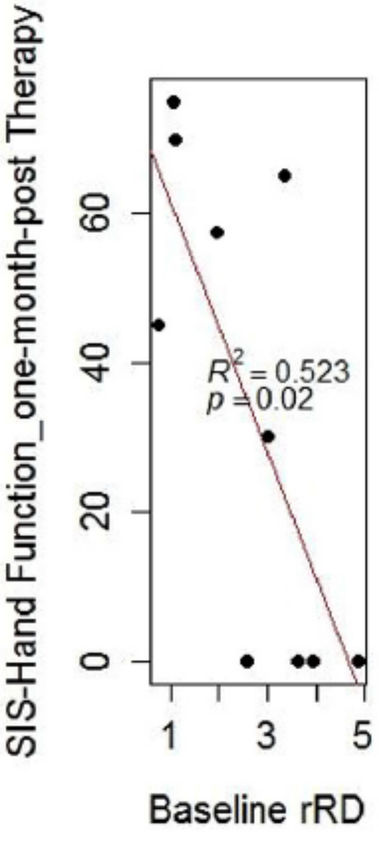

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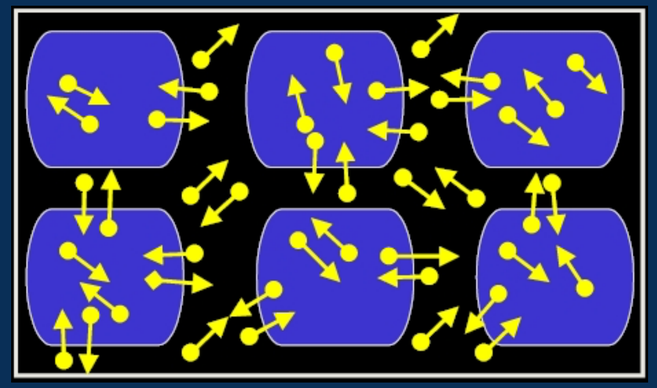
Song et al. Fron. Human Neurosci. 2015

DKI Review

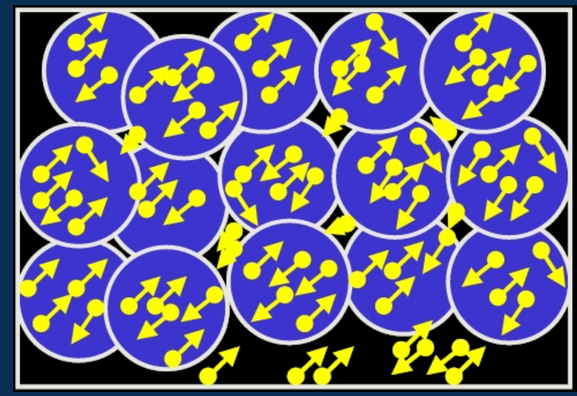
DKI: quantifying the non-gaussian components of diffusion.

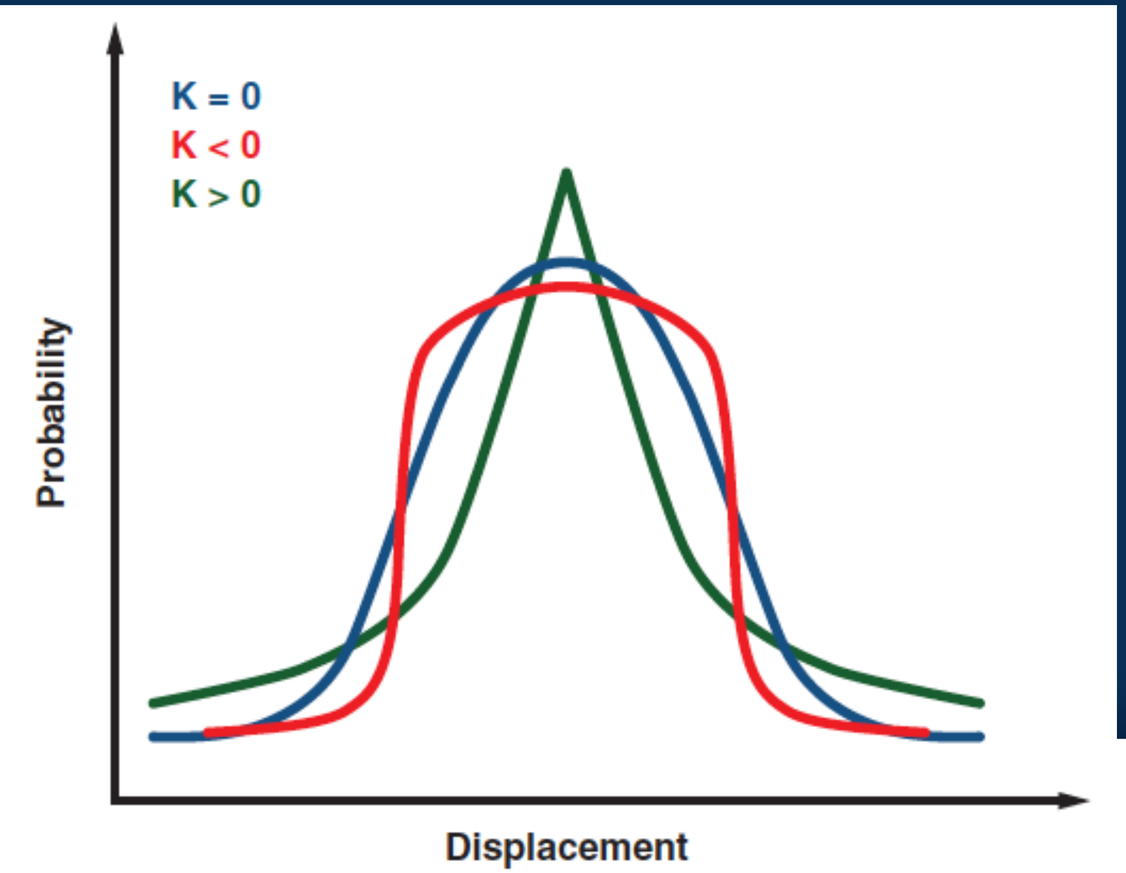
→ How much hindrance is going on?

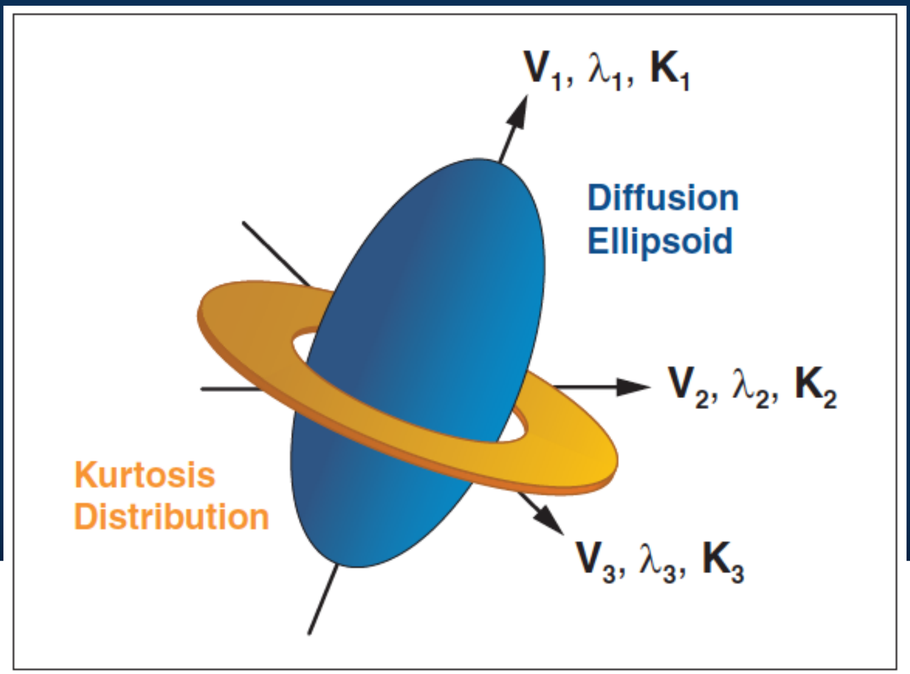
Normal cells



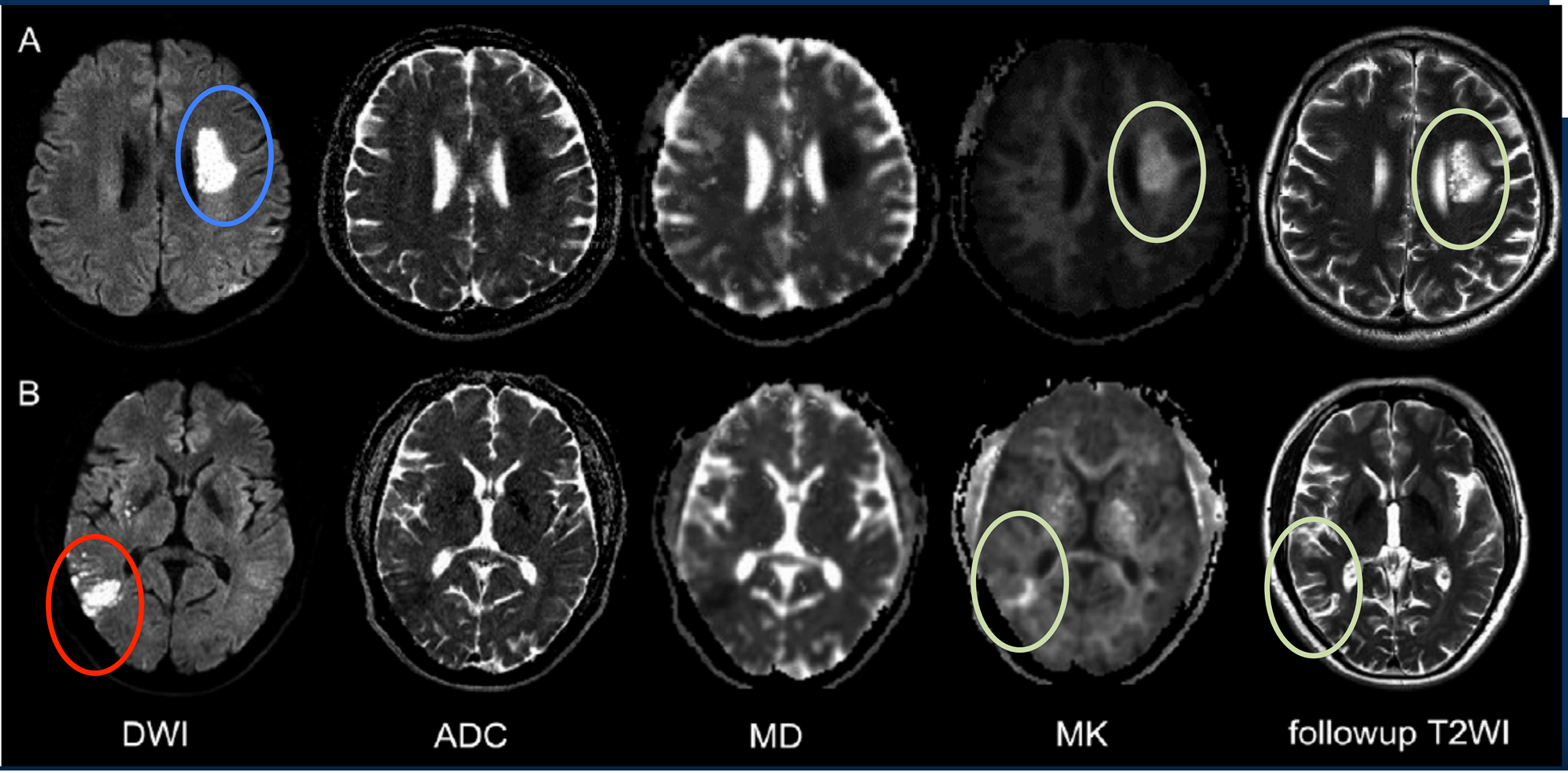
Acute stroke

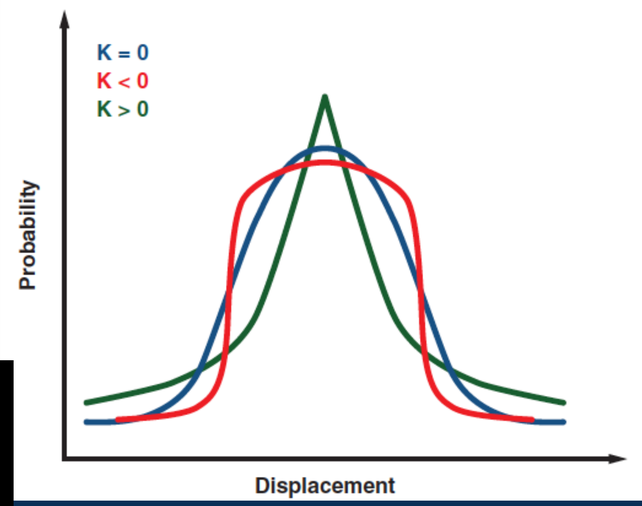






DKI in a Stroke Protocol





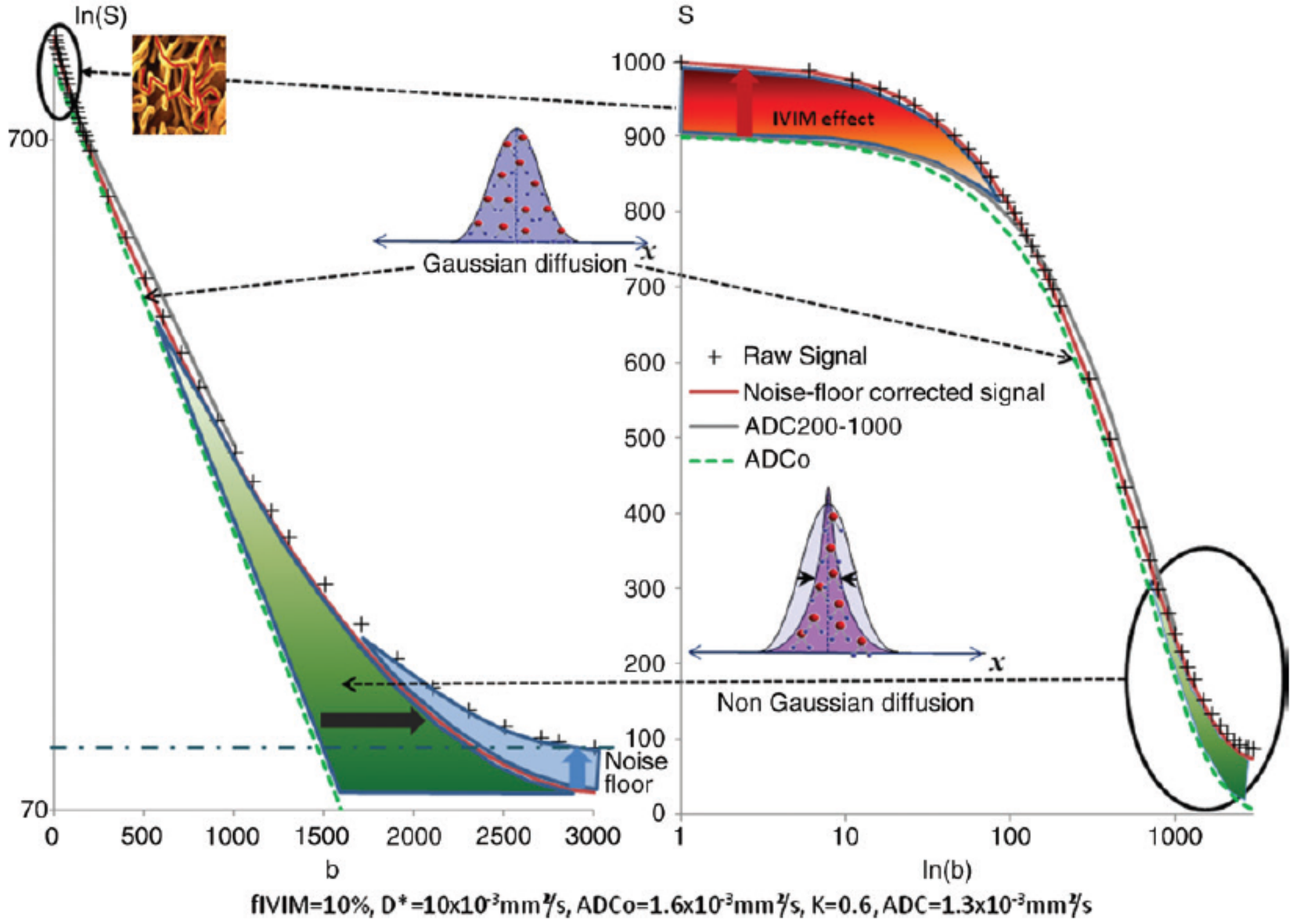
Final lesion size post-intervention

Dark ADC → lower diffusion

Bright mean kurtosis → more hindered diffusion.

Yin et al. Radiology 2018

IVIM Review



Slow perfusion in random directions ~ fast diffusion.

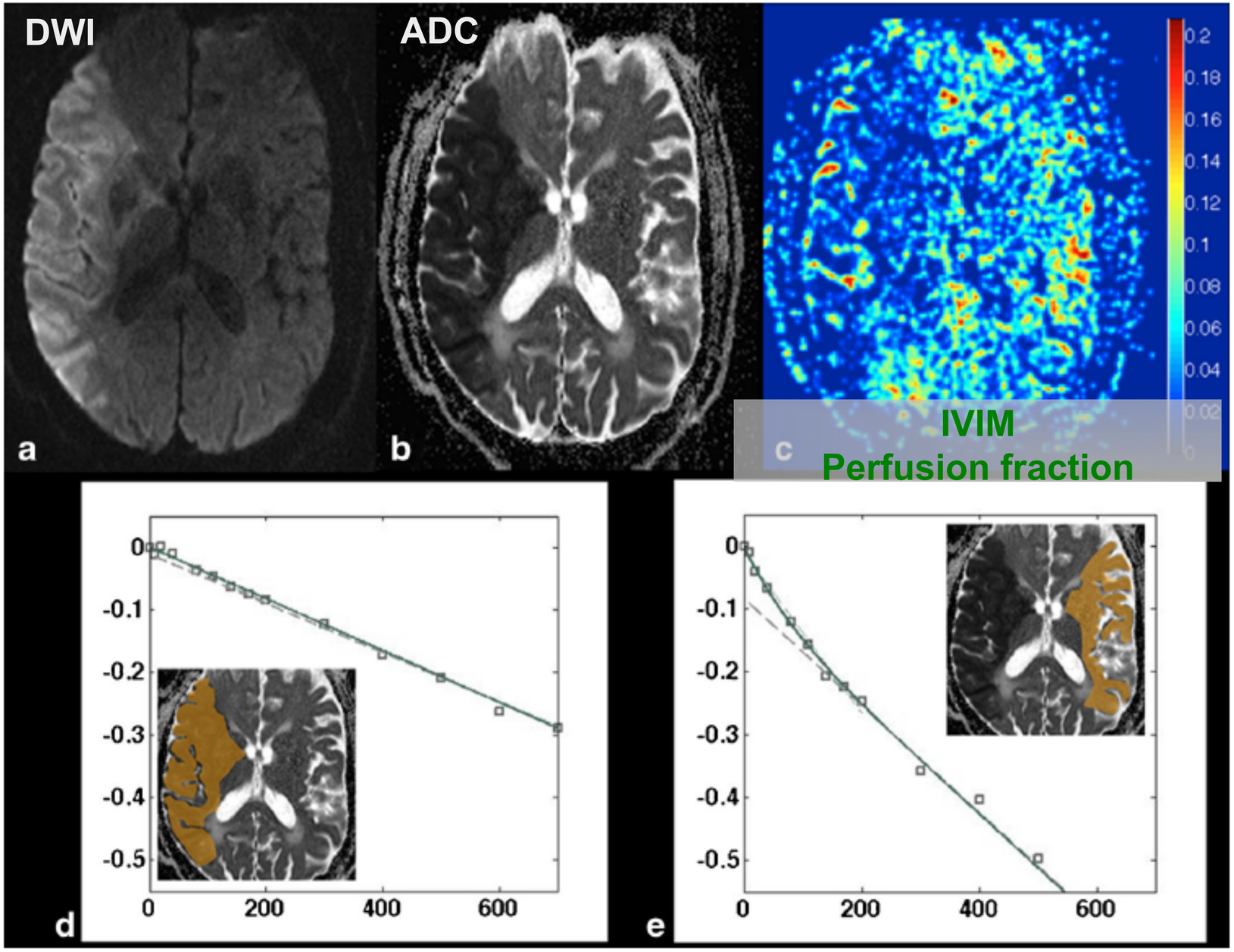
IVIM: quantifying the fraction of microcirculation.

→ How is perfusion affected throughout stroke volume?

Iima & LeBihan. Radiology, 2016

IVIM and Acute Stroke

Microperfusion in stroke core



Federau, et al.
Neuroradiology, 2014

IVIM and Acute Stroke

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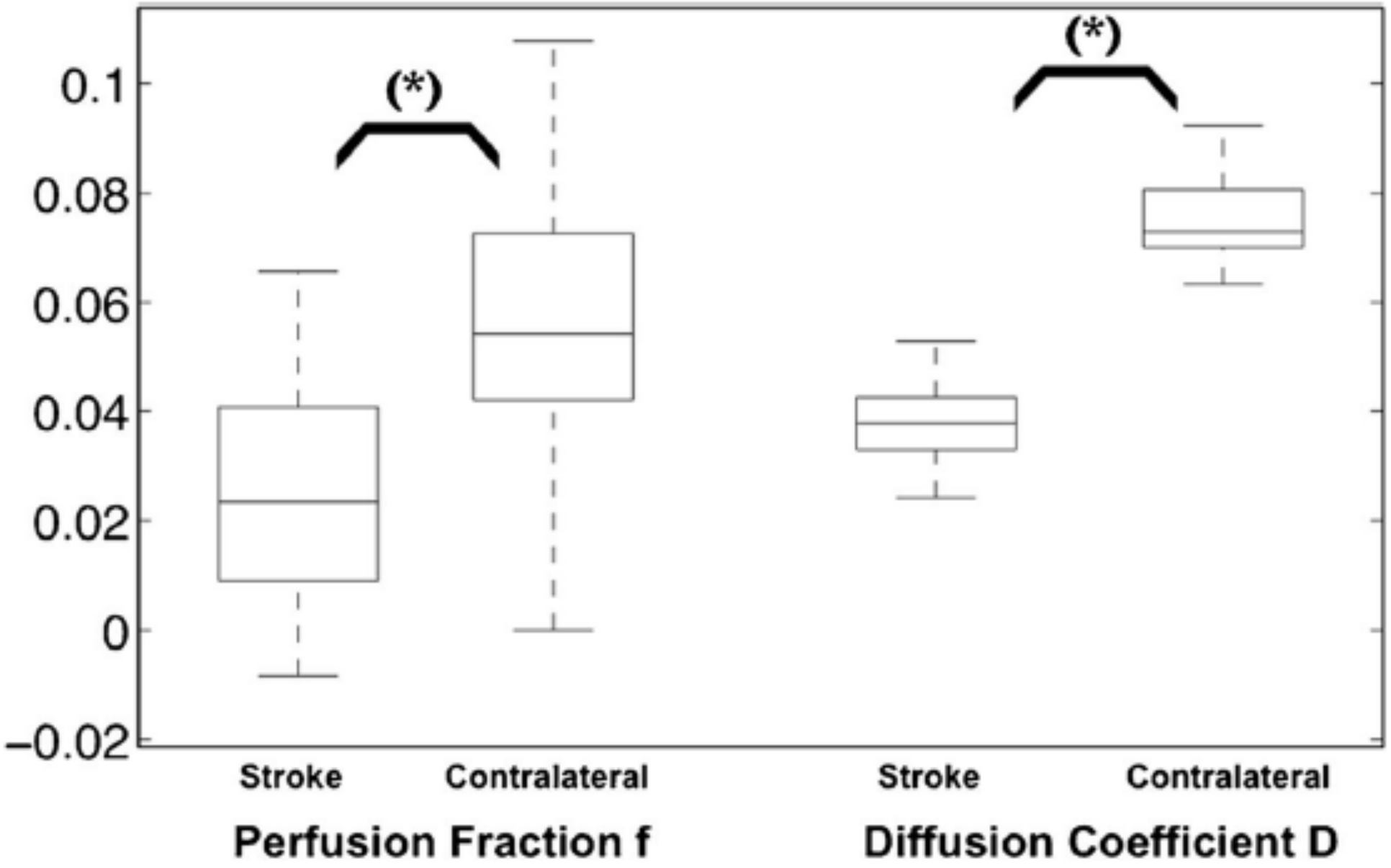


Federau, et al.
Neuroradiology, 2014

Ahem … this is a patient that we're dealing with.

Scanning speed is not irrelevant. pMRI is critical!

E.g., without pMRI:

DWI (3 directions + 1 b0 image (TR~ 16 sec, 30 slices)) scantime: ~ 1 min

DTI (32 directions, 1 b-value + 1 b0) scantime: ~ 8 min *Meh…*

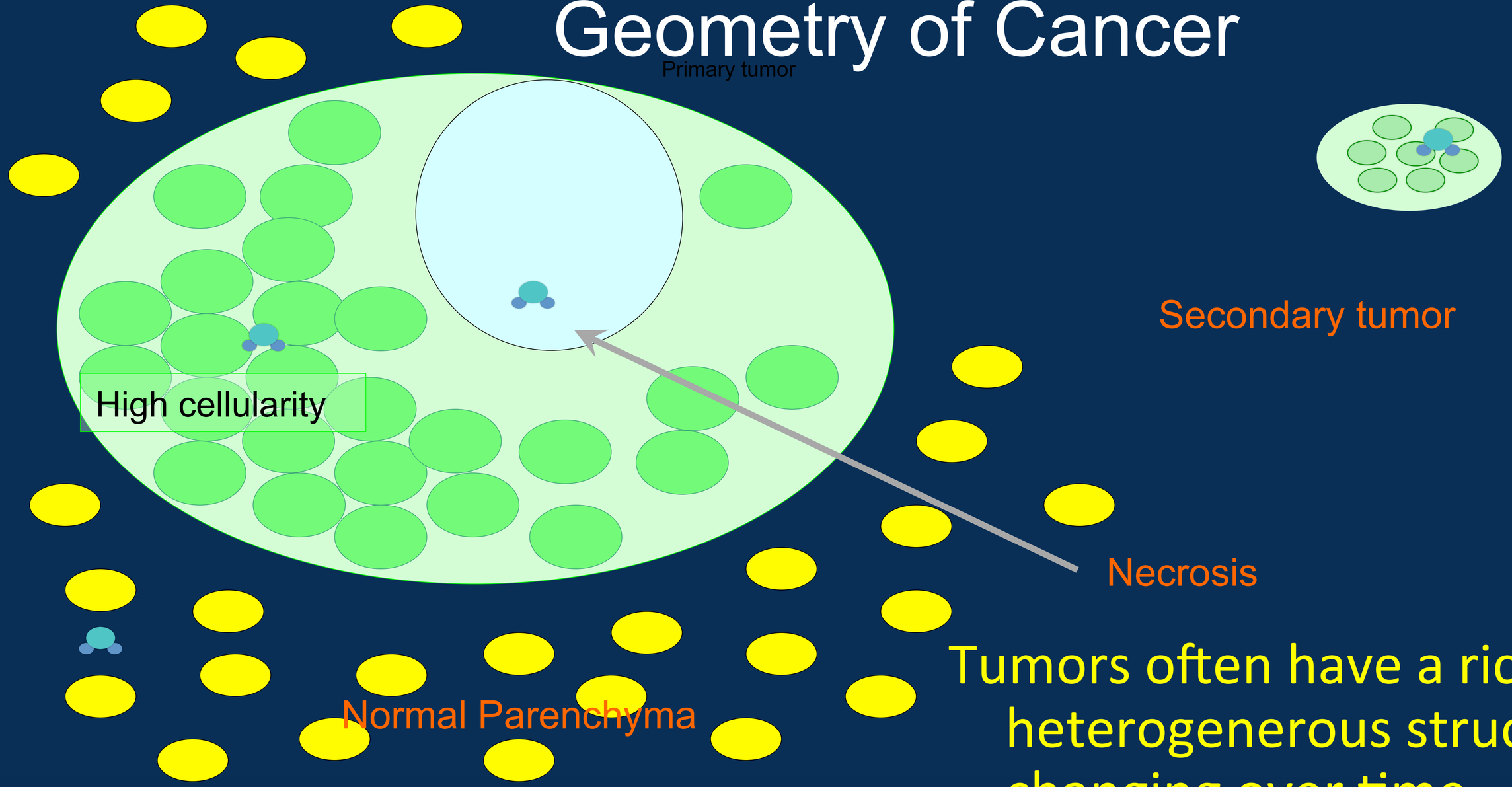
~~DKI (32 directions, 2 b-values + 1 b0) scantime: ~ 16 min~~

~~multi-exponential (DWI scan (3 dir), 16 b-values, NEX increases with b-value to increase SNR → 84 scans) scantime: ~ 21 min~~

~~High Angular Resolution Diffusion Imaging scantime: ~ a long time.~~

Cancer

Geometry of Cancer



Tumors often have a rich, heterogenerous structure, changing over time.

Basics of Visual Diagnosis

Principle #0: Very high ADC = cyst, vasogenic edemic region.

Principle #1: Cellularity correlates inversely with ADC (healthy and pathological).

Principle #2: In structured tissues, infiltration can affect FA, eigenvectors, etc

Basics of Visual Diagnosis

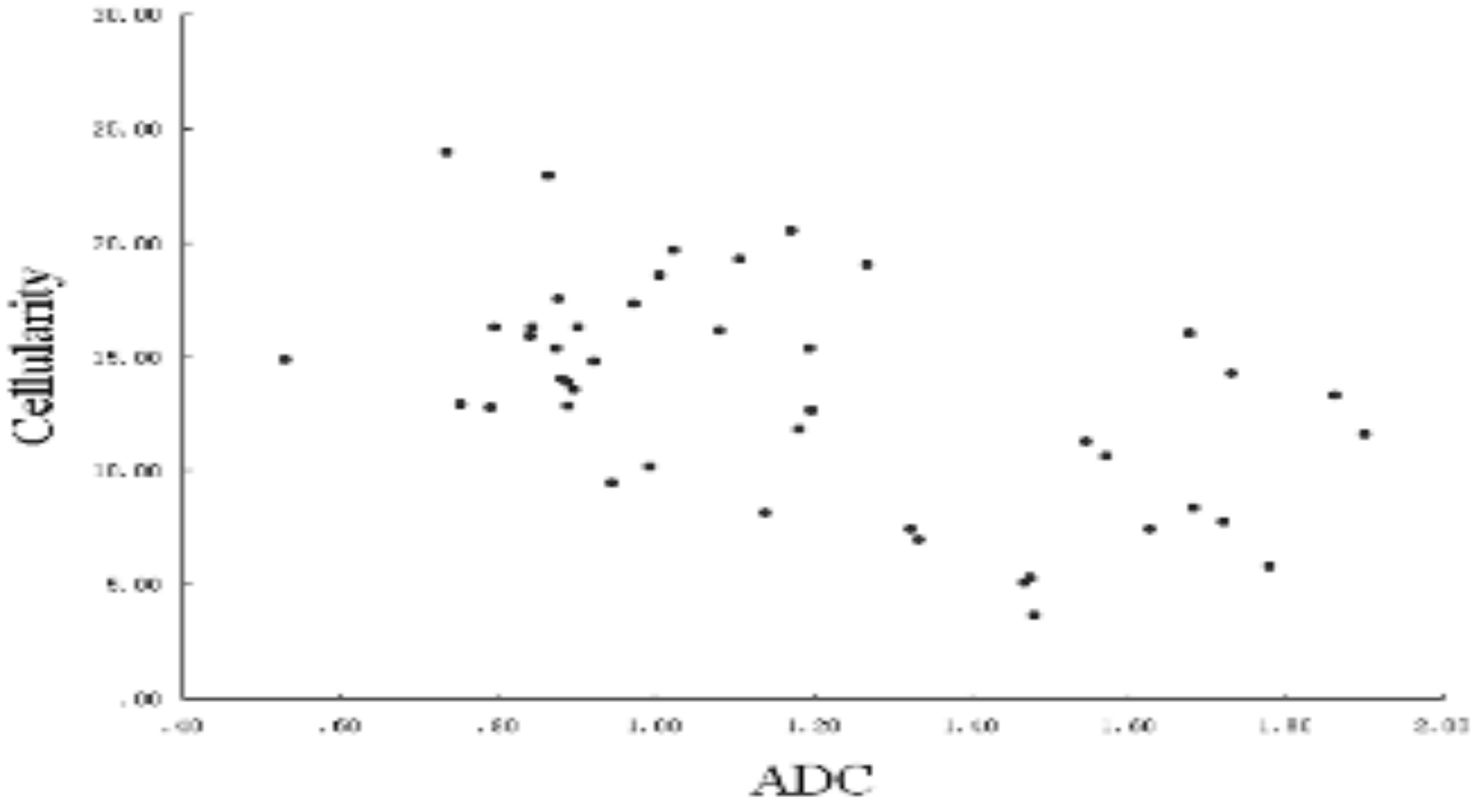


Figure 4. Correlation of tumor cellularity vs. the ADCs ($P < 0.01$, $r = -0.542$).

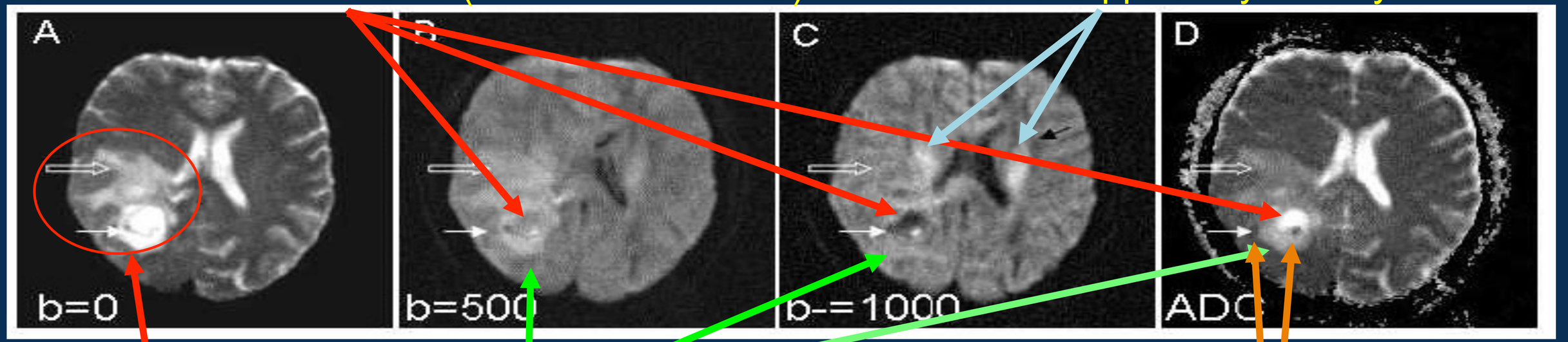
Guo, et al. JMRI, 2002 (cancerous breast lesions)

DWI and Cancer – tumor progression

T2W

Fast diffusion in core (cellular breakdown)

Apparently healthy WM



General Edema

Somewhat fast diffusion in periphery

Hindered diffusion in patches (hypercellularity).

Diffusion behavior can be rich in tumor region.

Applications of Imaging to Cancer

Diagnosis/Classification Tool – heterogeneity vs. homogeneity, ADC value

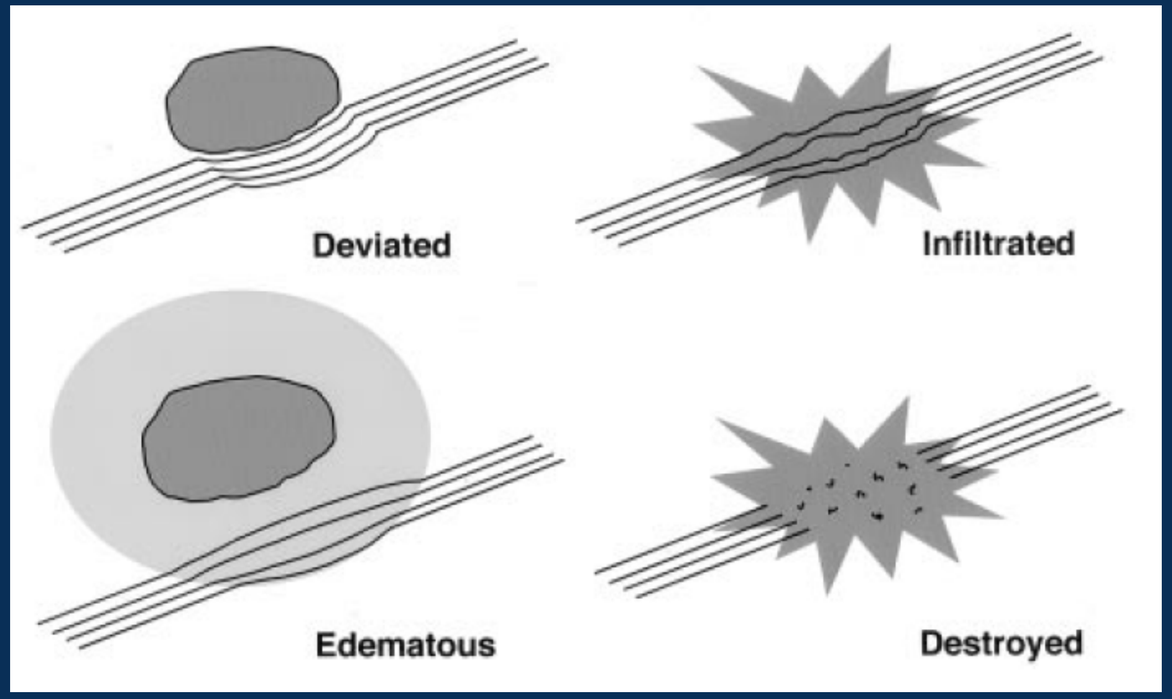
Treatment Planning Tool – ischemia, necrotic core

Treatment Monitoring – changes in ADC value during treatment

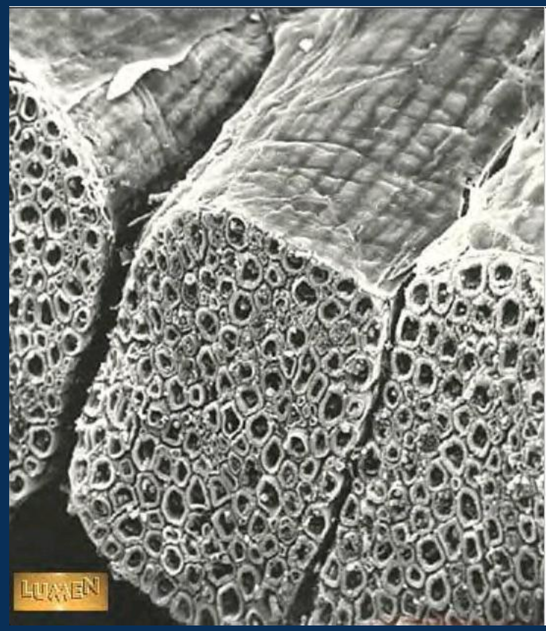
Potential use as a screening tool** – increased cellularity in DWIs (whole body)

Clinically, ADC map offers the most straightforward DW-based tool to interpret (but, less specific about precise tissue changes).

DTI (FA map) to Sort Out Infiltration

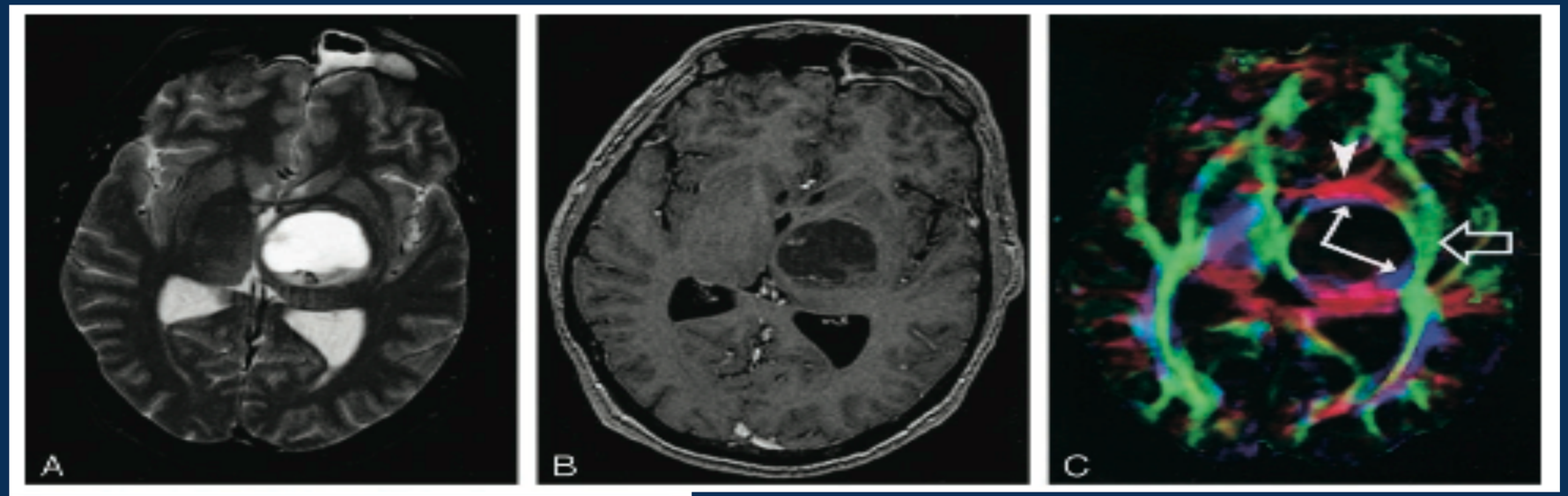


Jellison, et al.,
AJNR, 2004

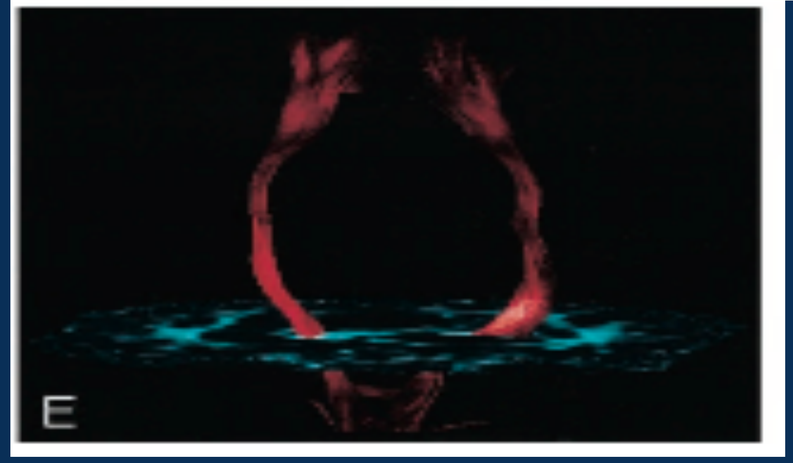


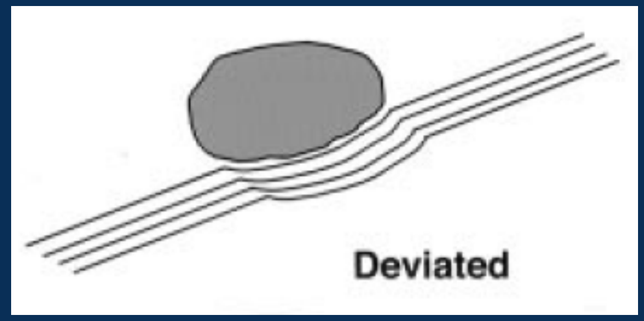
Bilateral inspection of brain tracts can help to reveal the pathology of tumor and/or integrity of WM in case of surgery.

DTI to Sort Out Infiltration



A: T2W
B: post-contrast T1W
C: FA map
D: Tractogram

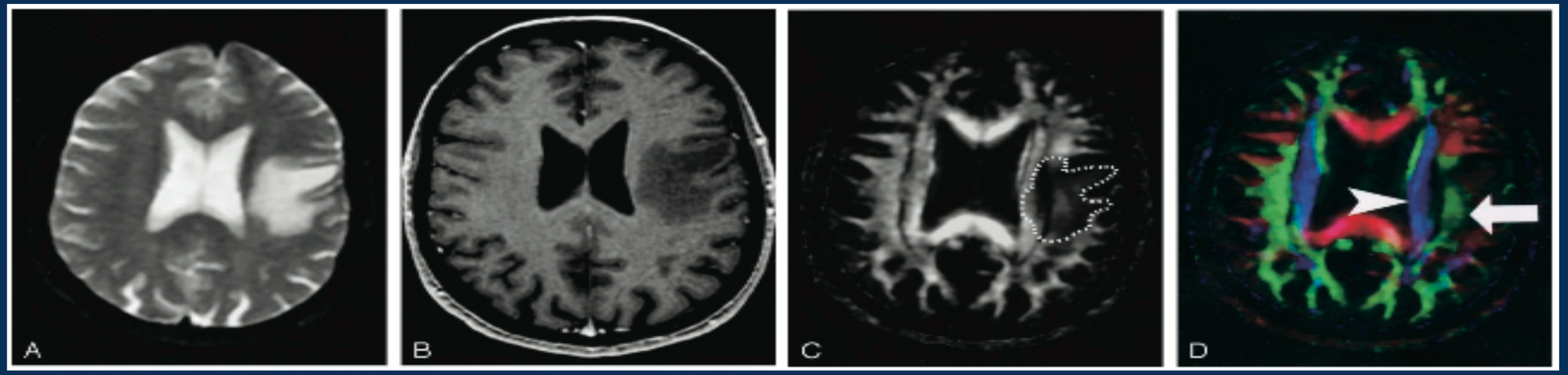


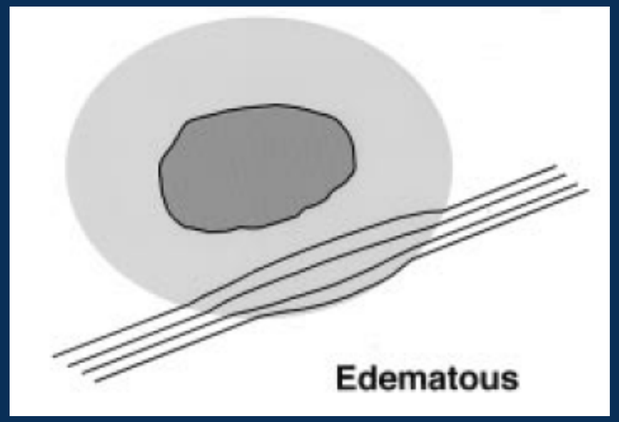


Ganglioglioma, with tracts preserved but shifted in position.

Jellison, et al., AJNR, 2004

DTI to Sort Out Infiltration



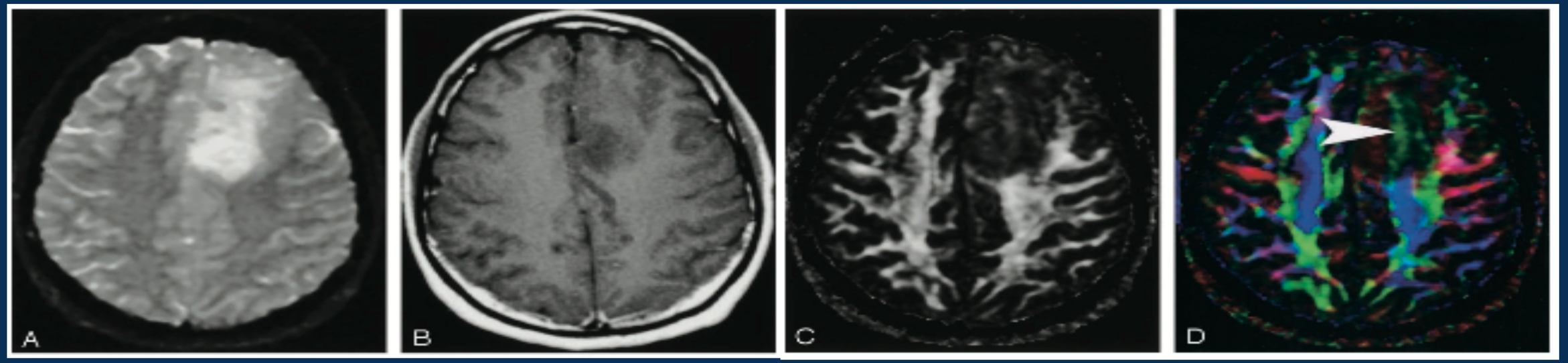


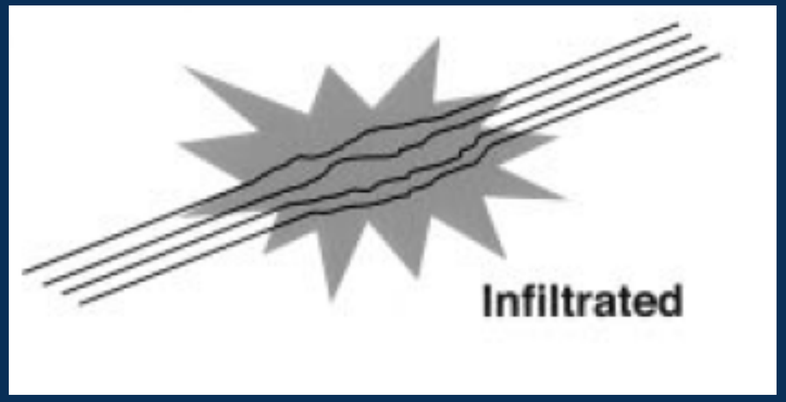
A: T2W
B: post-contrast T1W
C: FA map
D: color-coded FA

Preservation in color (direction) but reduction in FA indicates edema.

Jellison, et al., AJNR, 2004

DTI to Sort Out Infiltration



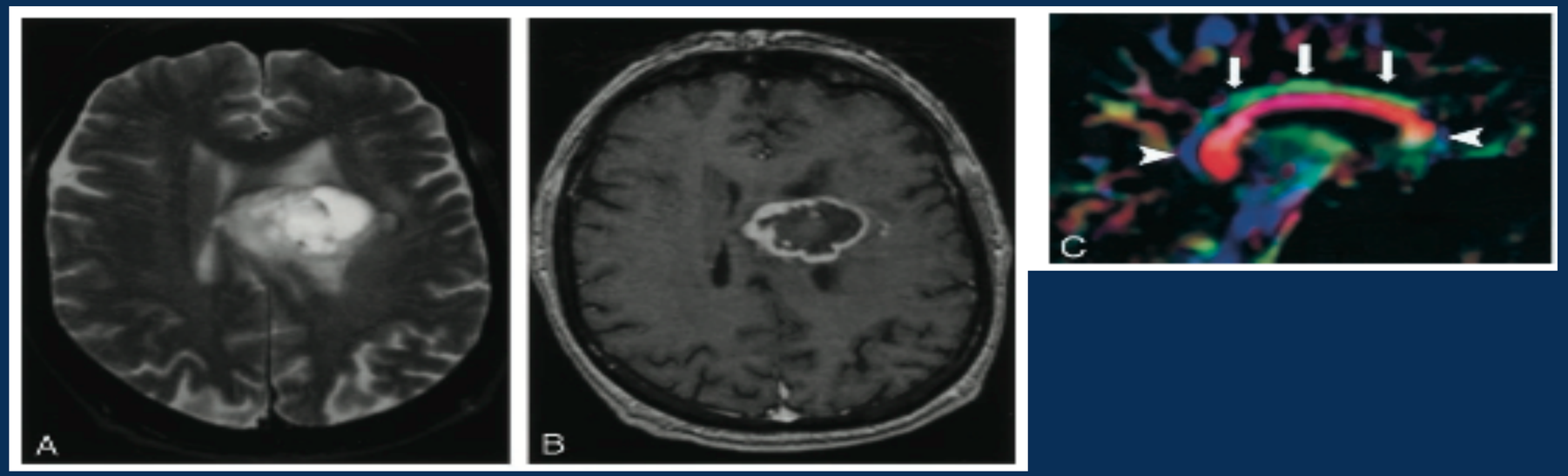


A: T2W
B: post-contrast T1W
C: FA map
D: color-coded FA

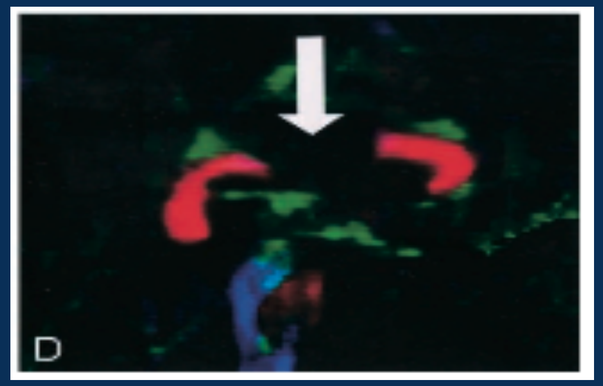
FA reduced and direction distorted, implying disruption (infiltrating astrocytoma).

Jellison, et al., AJNR, 2004

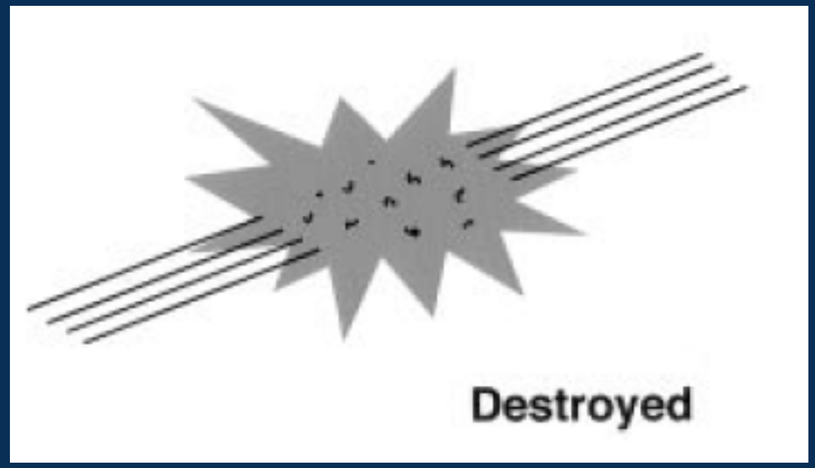
DTI to Sort Out Infiltration



A: T2W
B: post-contrast T1W
C: FA map, normal patient
D: FA map, patient



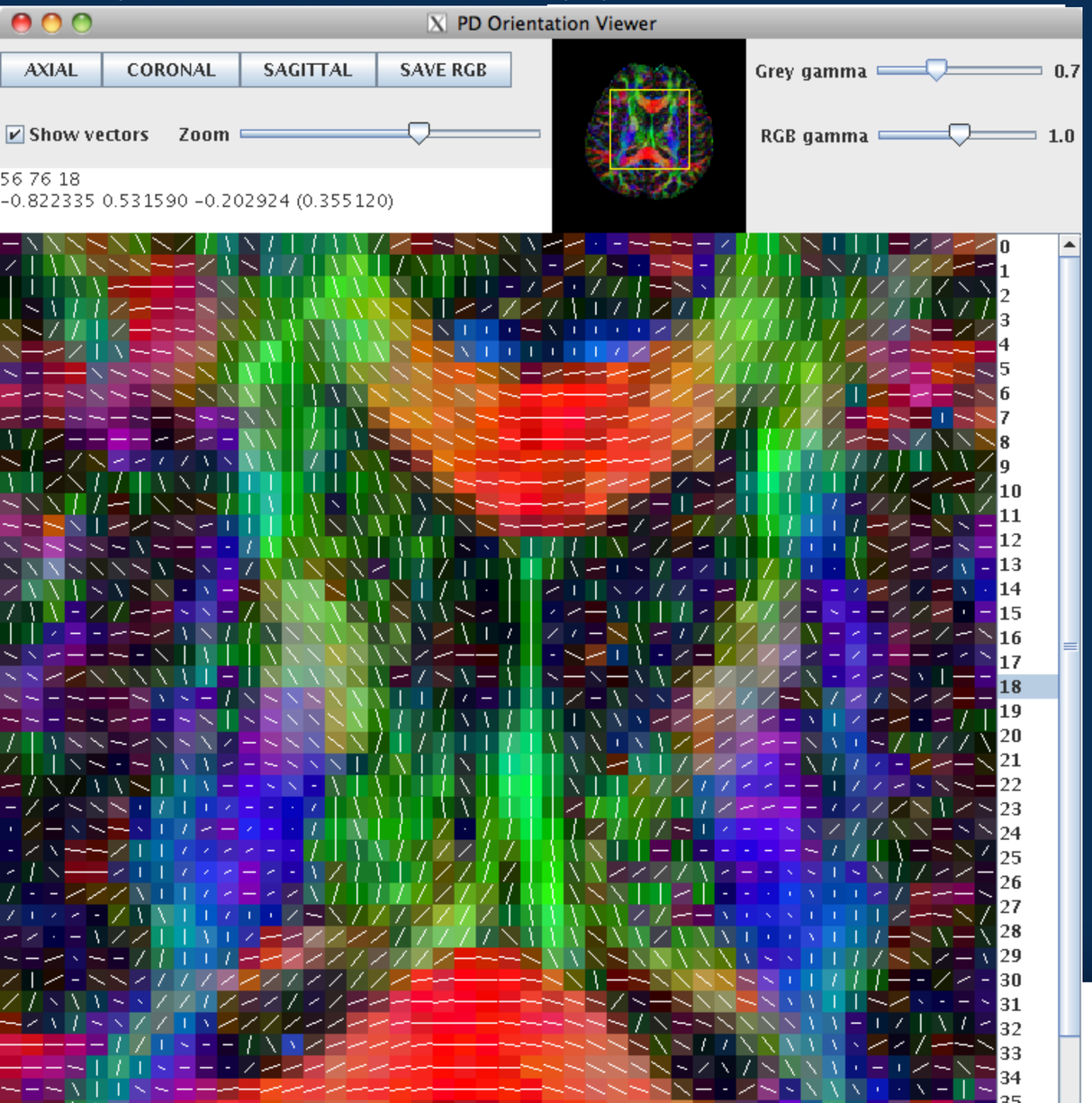
High-grade astrocytoma, with tracts essentially destroyed.



Jellison, et al., AJNR, 2004

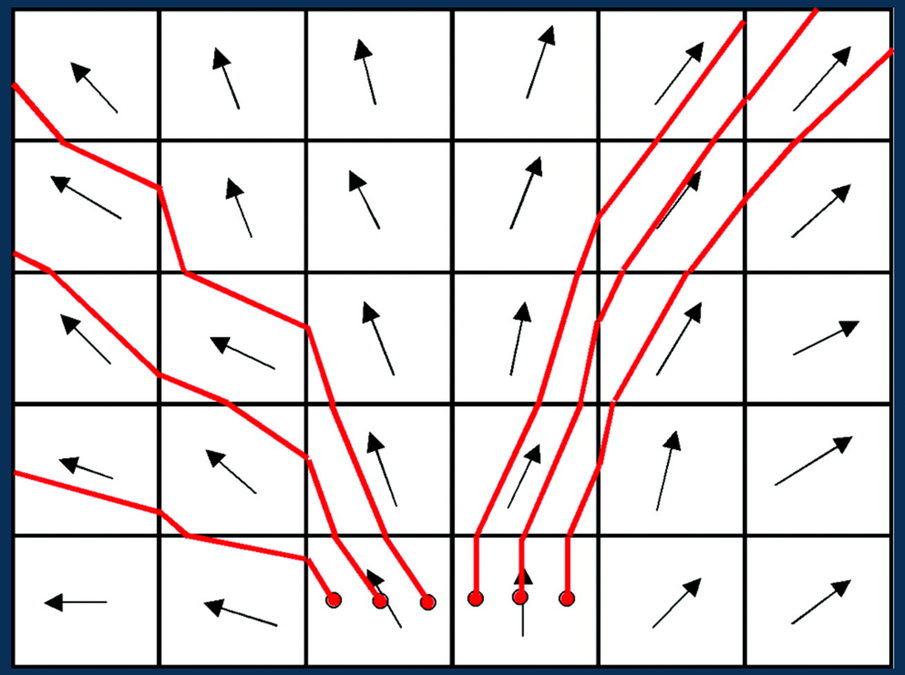
Tractography

From CAMINO image processing manual
http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.DTI



Principle e-vector in DTI (or ODF for HARDI) generally points along neural fiber axial direction.

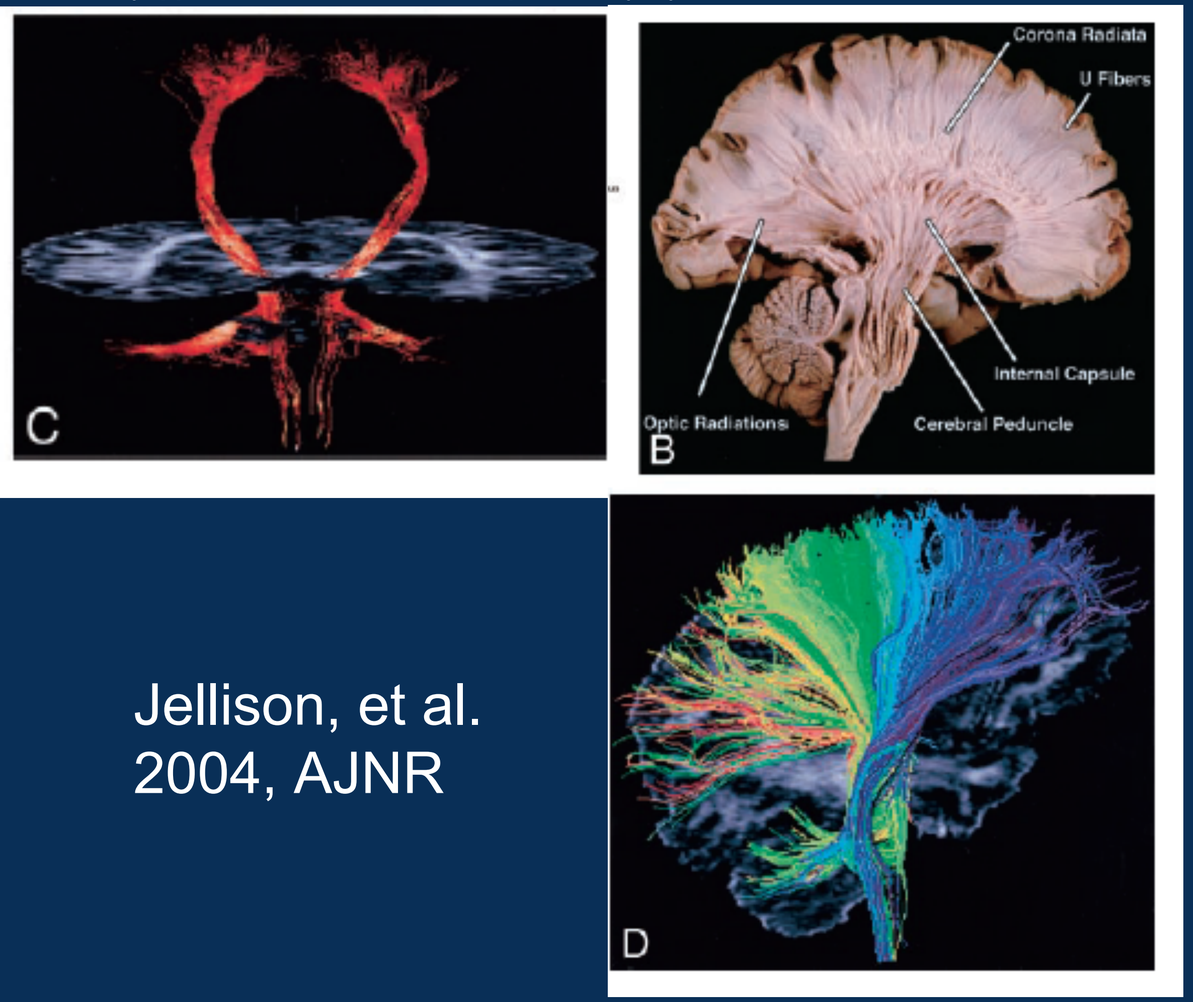
Various software routines to link directions together and generate “tracts”.



Mukherjee, et al., 2008, AJNR

Tractography

From CAMINO image processing manual
http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.DTI



Jellison, et al.
2004, AJNR

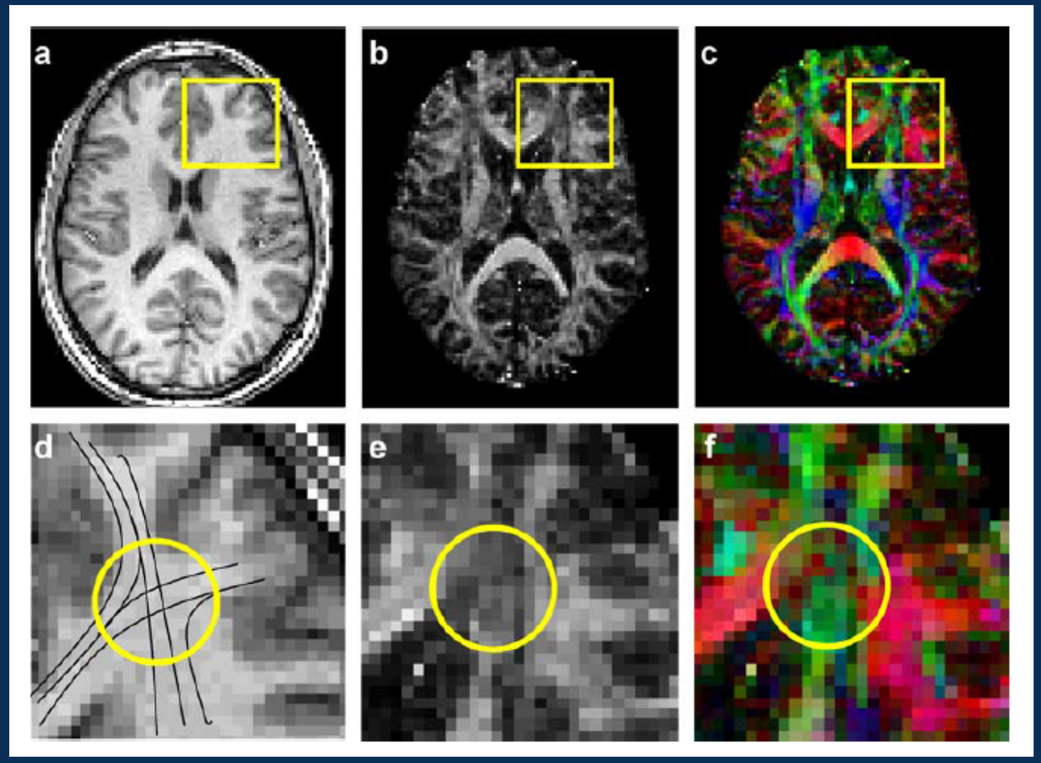
Principle e-vector in DTI (or ODF for HARDI) generally points along neural fiber axial direction.

Various software routines to link directions together and generate “tracts”.

Tracts ≠ neural fibers (but correlation).

Tractography

From CAMINO image processing manual
http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.DTI

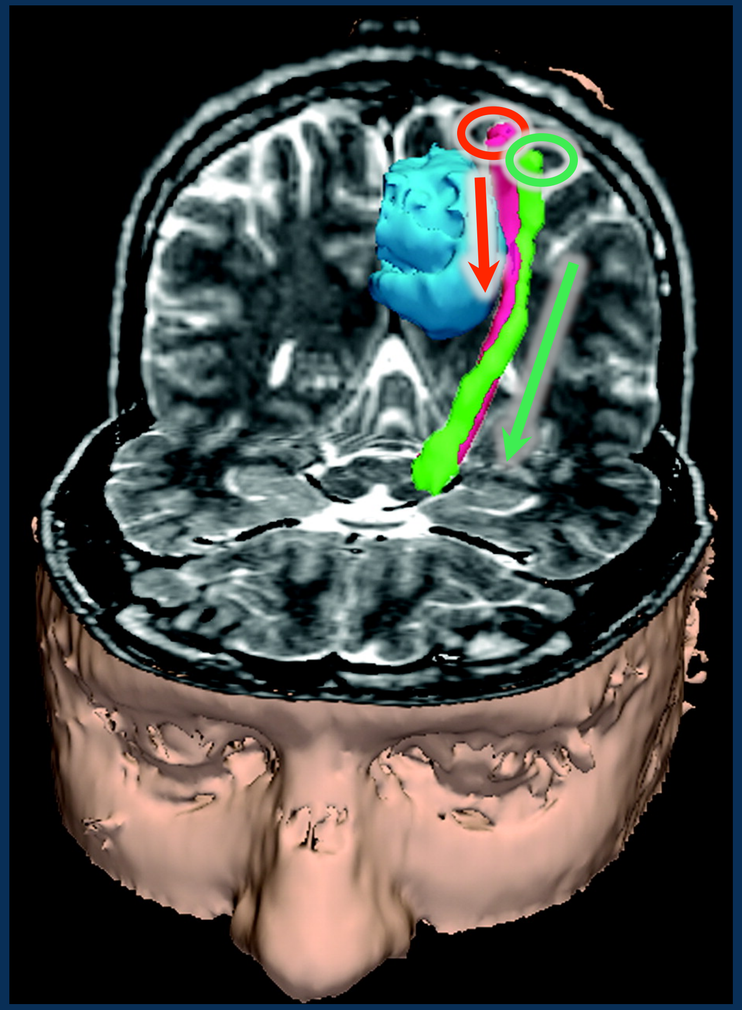


Principle e-vector in DTI (or ODF for HARDI) generally points along neural fiber axial direction.

Various software routines to link directions together and generate “tracts”.

Problems with DTI tractography – crossing fibers in voxel lead to low FA (Assaf & Pasternak, 2008, J Mol Neurosci, 2008)

DTI tractography to examine infiltration



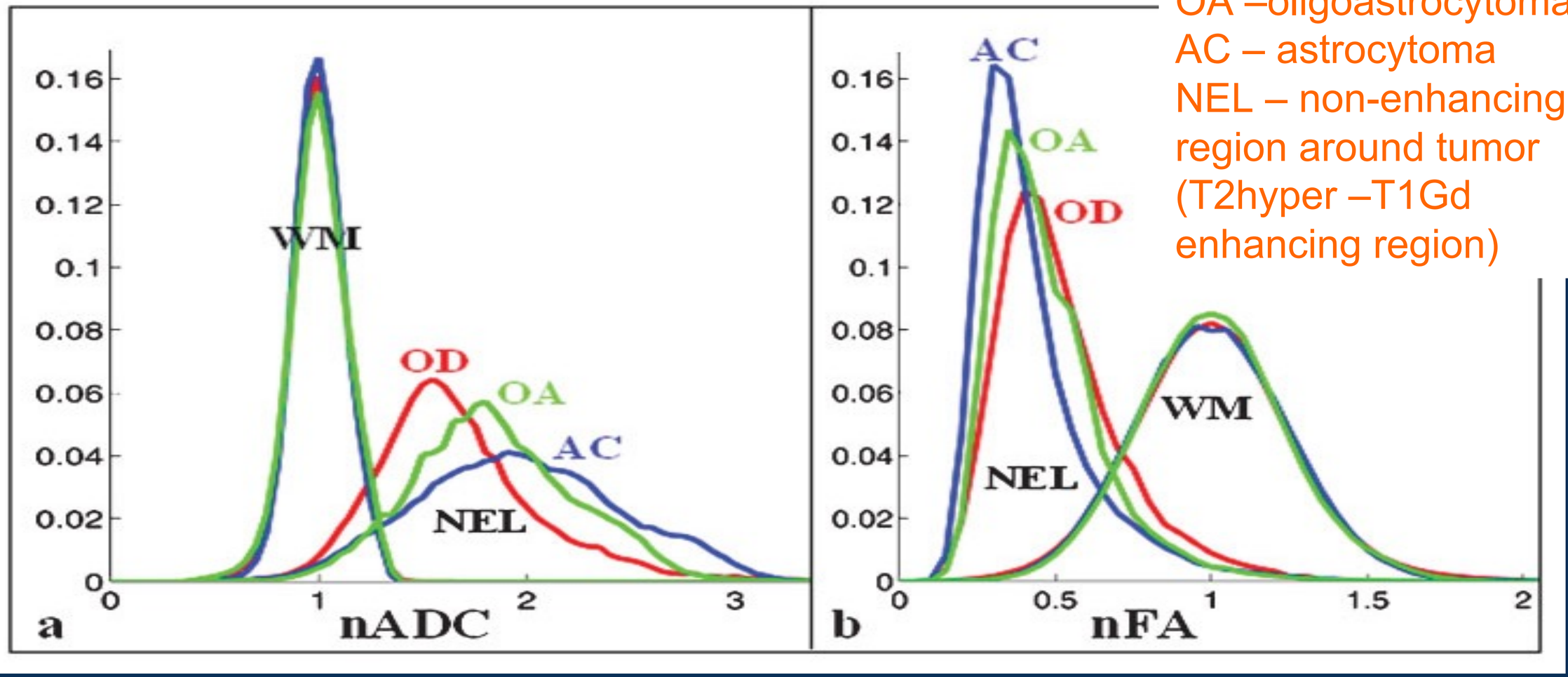
DTI tractography combined with tumor segmentation for pre-surgical planning.

Tracts were seeded using ROIs running through wrist (green) and shoulder (magenta) motor strip regions near cortex.

(Mukherjee, et al., 2008, AJNR)

Brain Imaging – classification (DTI)

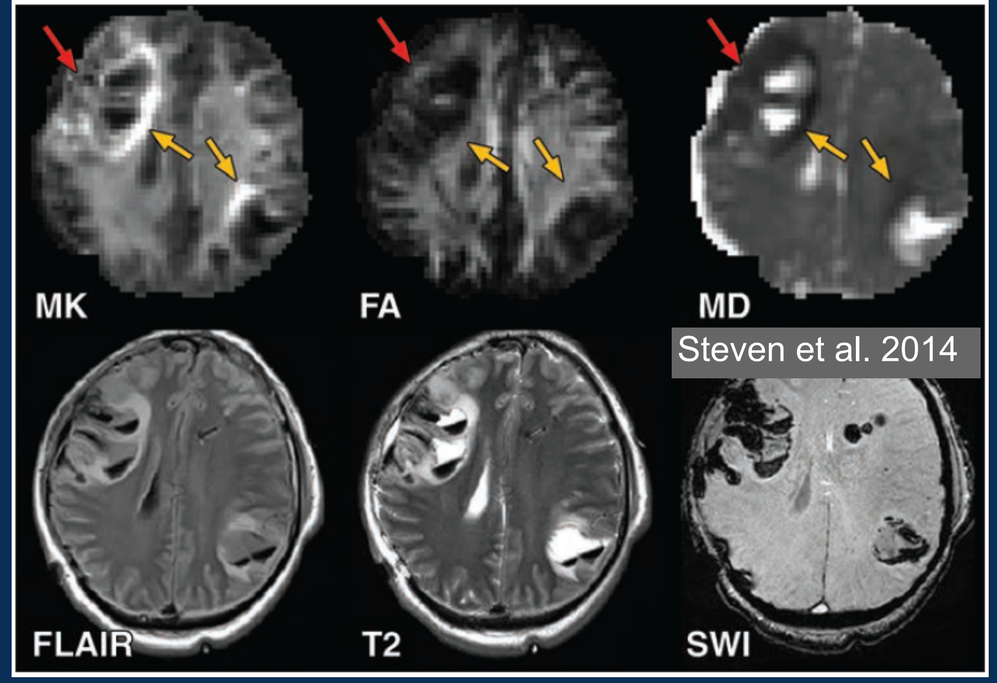
WM – healthy white matter
OD – oligodendroglioma
OA –oligoastrocytoma
AC – astrocytoma
NEL – non-enhancing region around tumor (T2hyper –T1Gd enhancing region)



Normal appearing white matter, and non-enhancing lesion tissues (DTI).
Khayal, et al., NMR Biomed 2009

Many more applications… possibly…

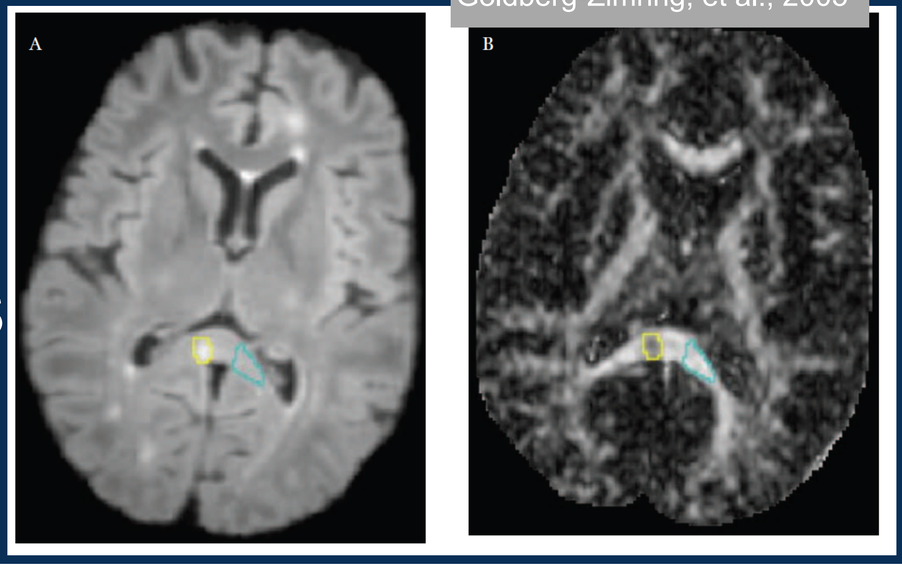
TBI & DKI



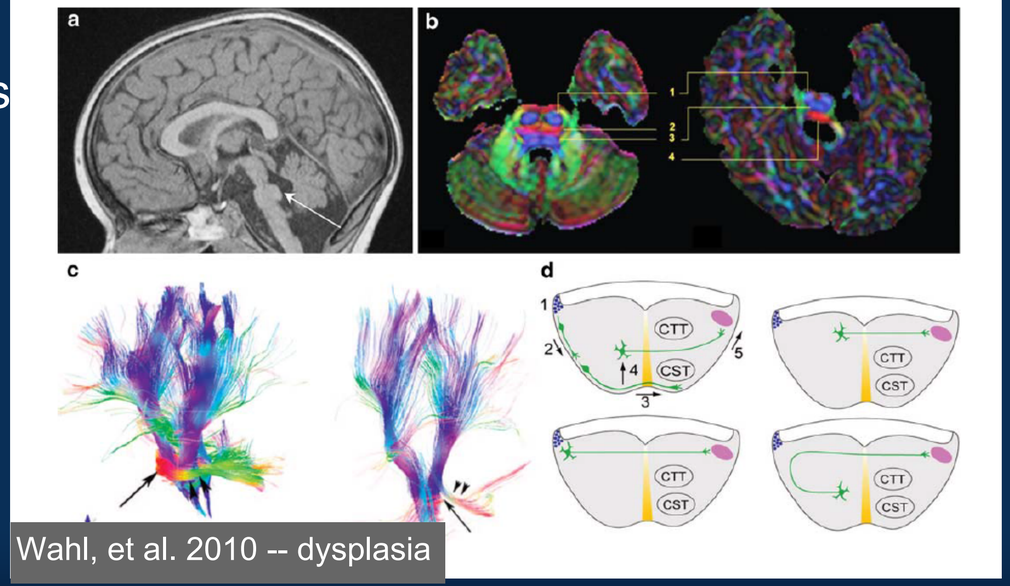
Steven et al. 2014

DWI, DTI, and MS

Goldberg-Zimring, et al., 2005

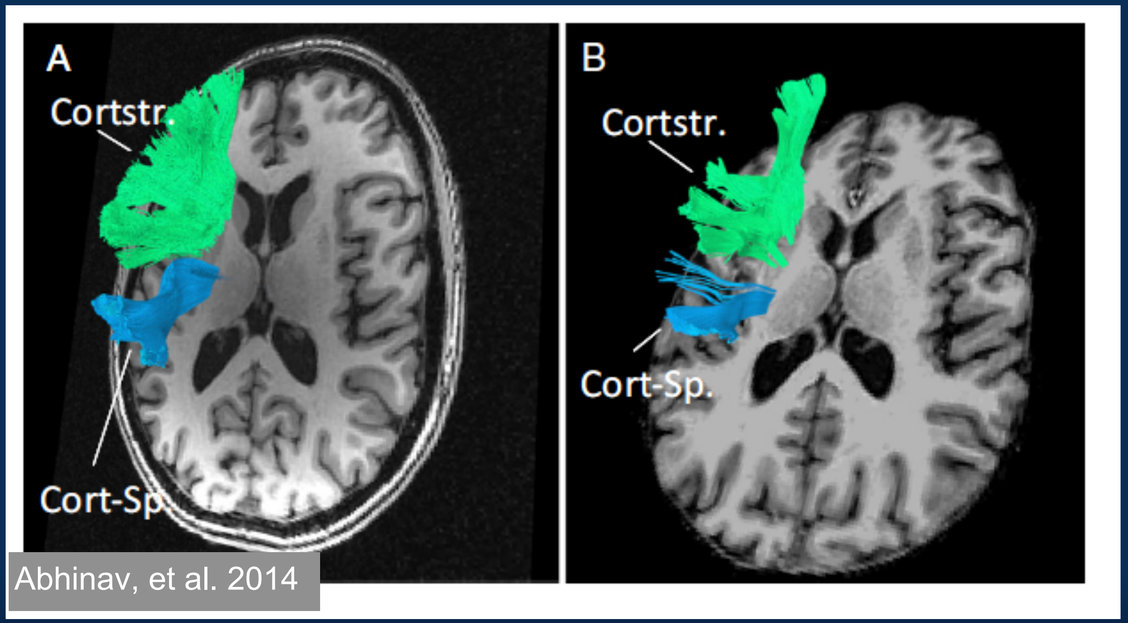


Congenital Malformations



Wahl, et al. 2010 -- dysplasia

Tractography & Huntington's Disease



Abhinav, et al. 2014

Conclusions

- DW-MRI is a powerful tool for looking at changes in tissue microstructure.

- ADC maps provide good qualitative contrast for distinguishing healthy tissue from non-enhancing pathology (cellularity), but less specific about structure.

- More complicated DW-based techniques may provide substantially more information, but more benchmarking/clinical testing required.

Questions?

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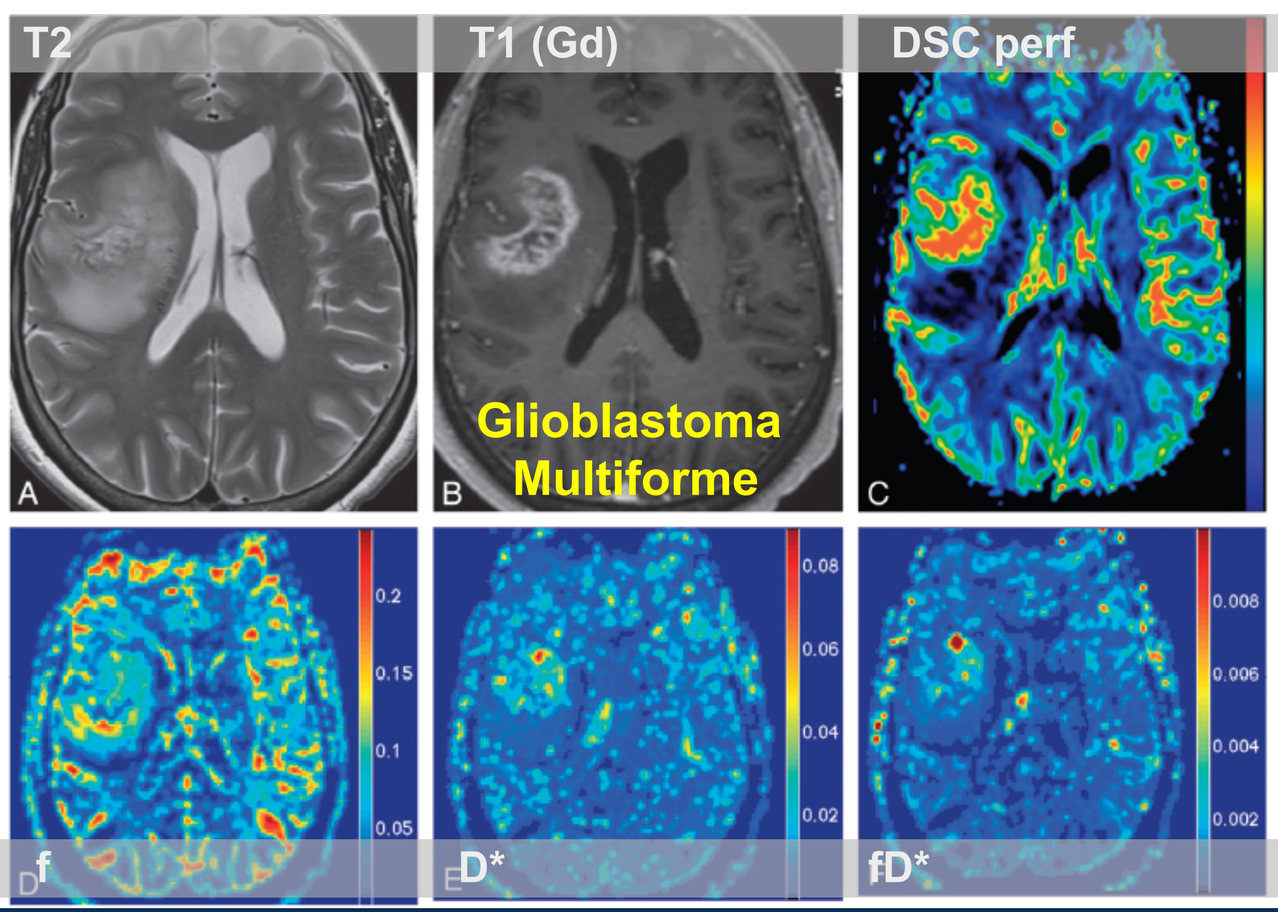
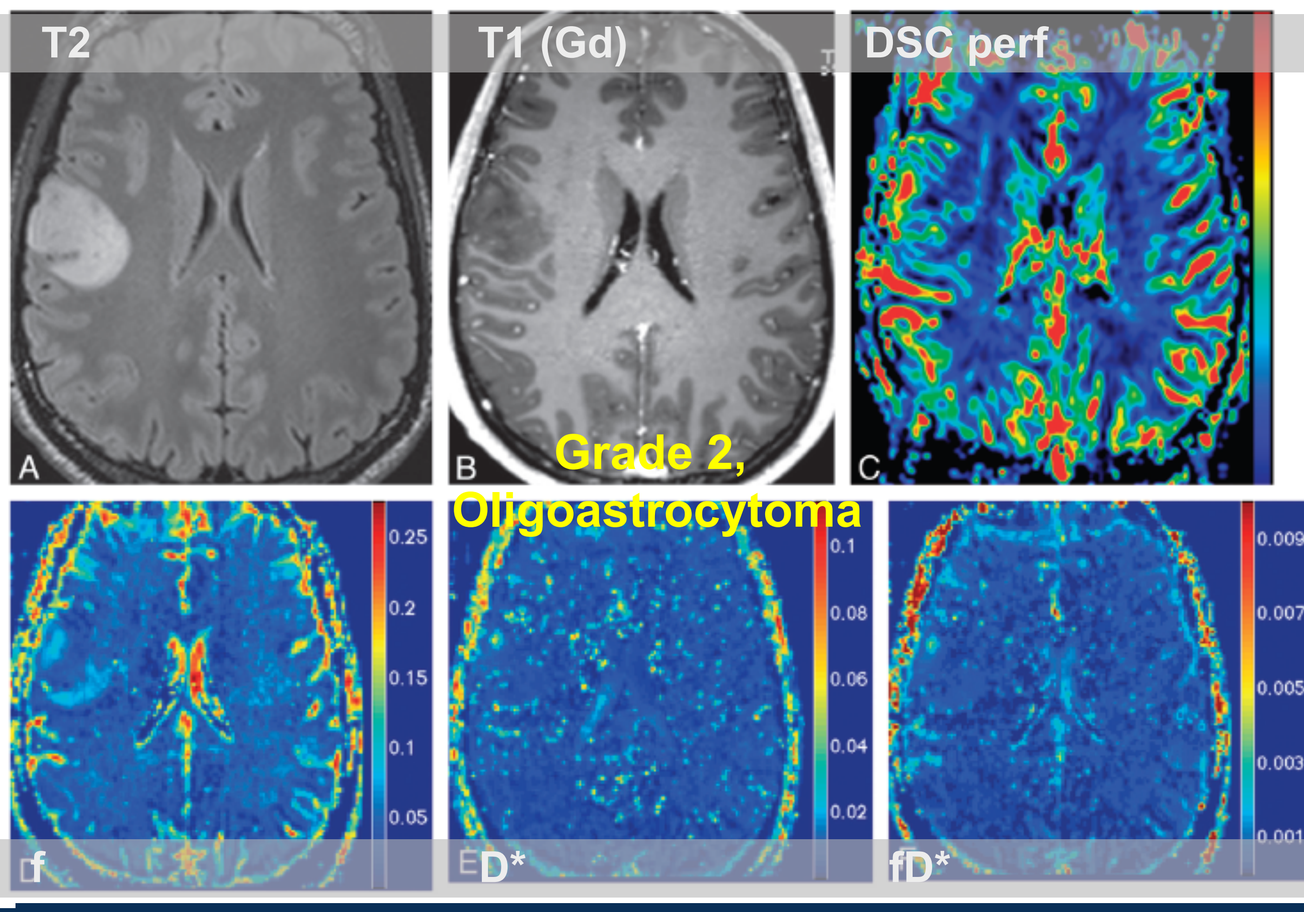
Other Uses (time permitting)



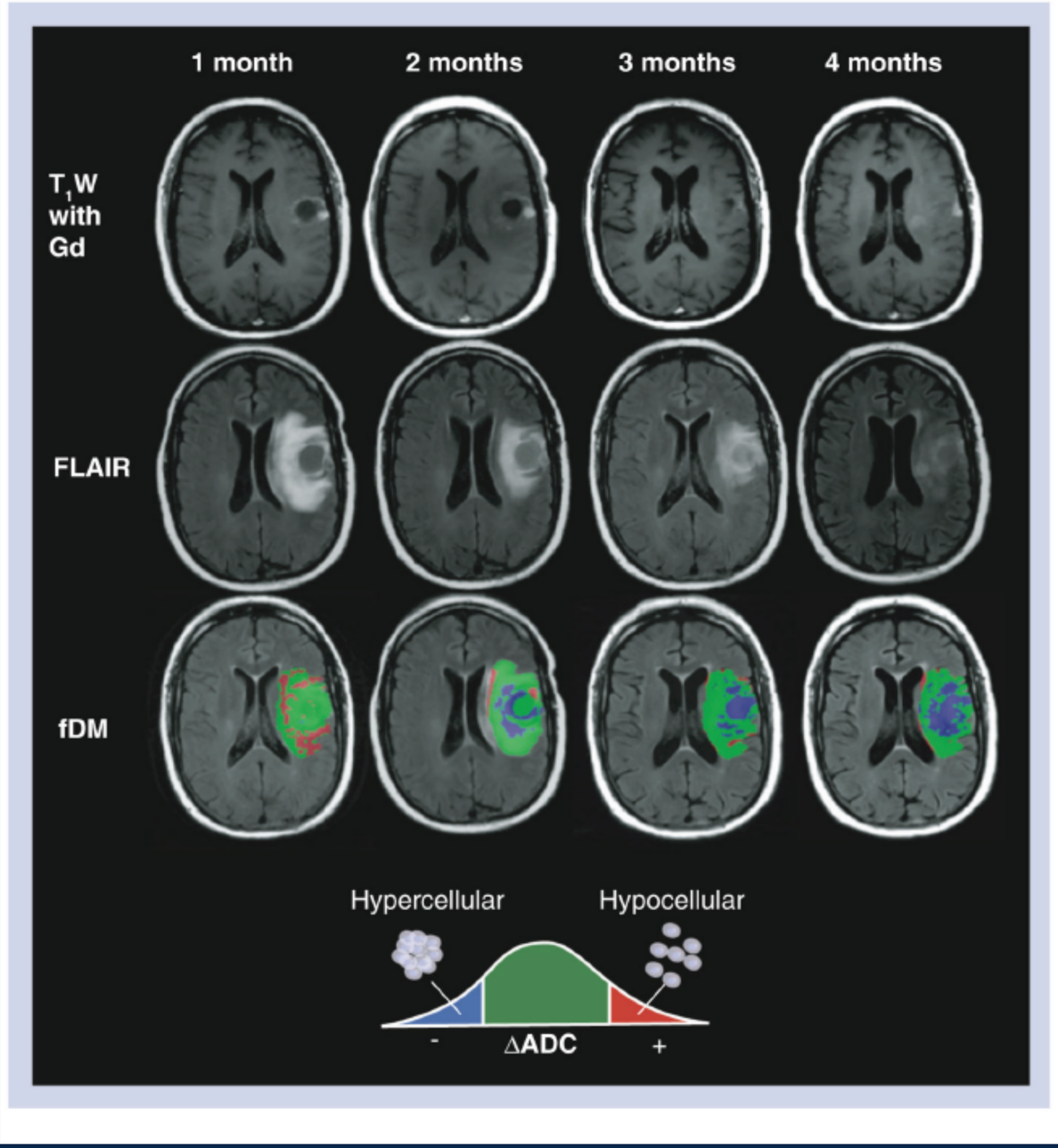


Multi-exponential grading of gliomas

Use of microperfusion to distinguish high and low grade gliomas.

Federau, et al. AJNR 2014

Diffusion and treatment response



Monitoring change in ADC during treatment.

Schmainda, CNS Oncol, 2012

Monitoring Adverse Effects in RT

Nagesh, et al., examined normal-appearing white matter during radiation therapy (J. Rad. Onc., 2008).

Mostly Glioblastoma multiforme patients…