Diffusion imaging of the brain: technical considerations and practical applications

David G. Norris

FC Donders Centre for Cognitive Neuroimaging
Nijmegen

Sustaining the physiologist in measuring the atomic movements upon which vitality and thought depend

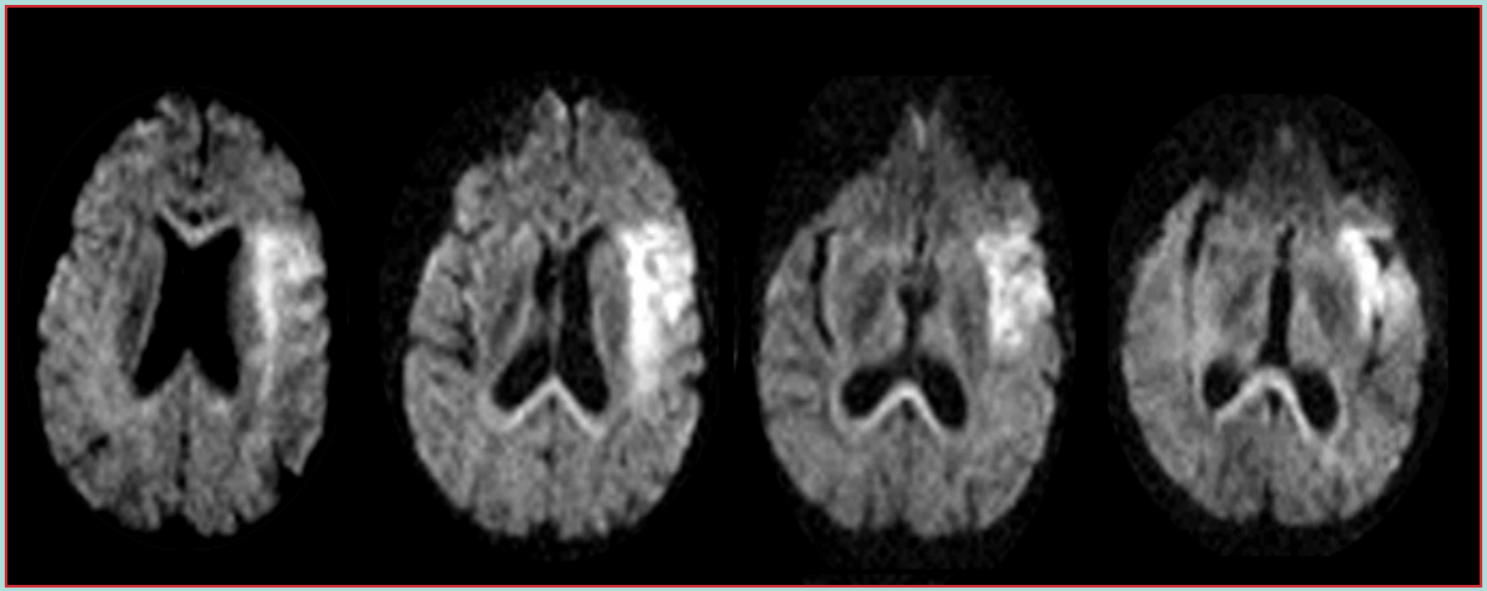
after

W.C. Roberts-Austen

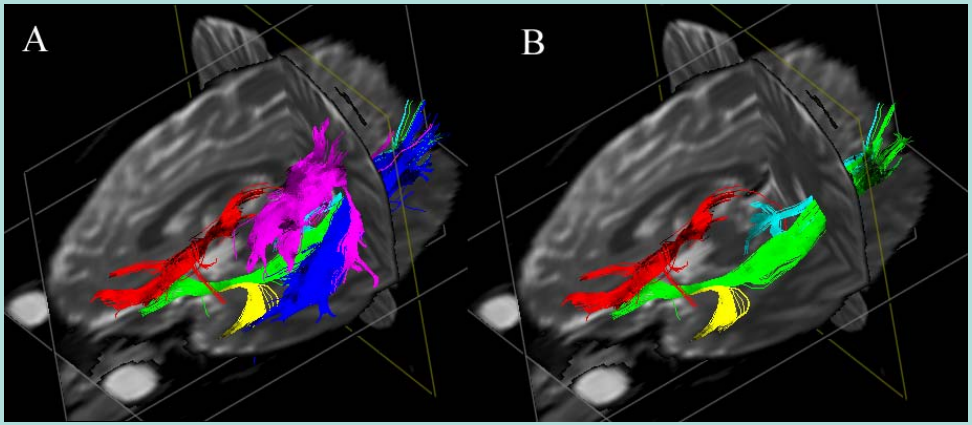
Introduction

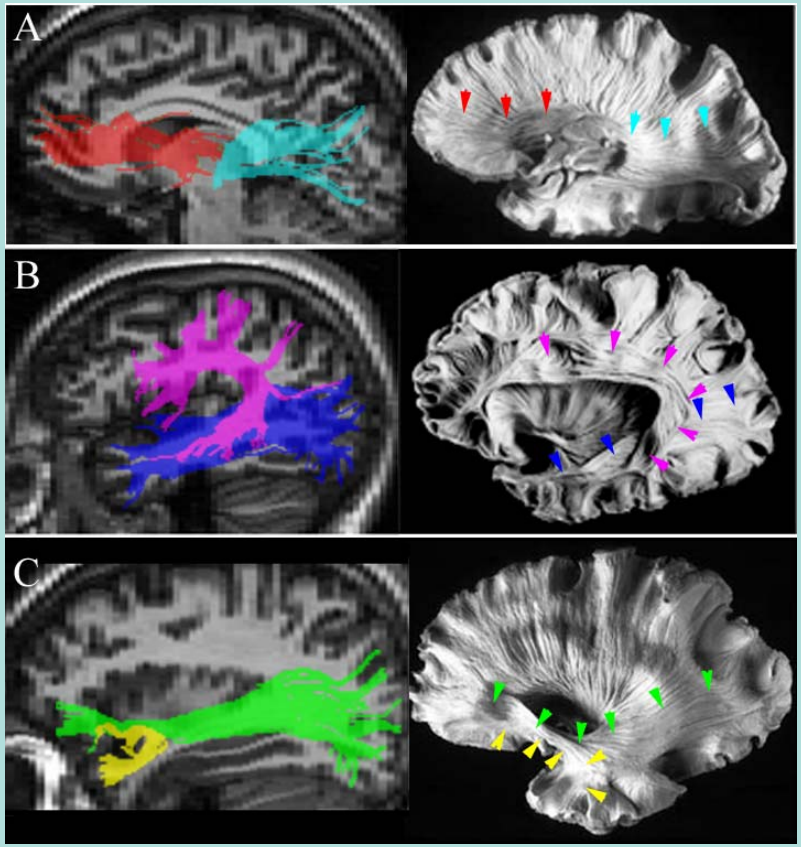
- Diffusion-weighted magnetic resonance imaging has become important in bio-medical applications for two reasons:
  - Diagnosis. Particularly of brain infarcts.
  - Fibre-Tracking. Useful both in planning neurosurgery and for mapping connections in the brain.

During infarction the signal attenuation in diffusion weighted imaging is reduced and infarcted regions appear bright.



3D views and comparison with anatomical preparation





Red: Anterior thalamic radiation
Light Blue: Posterior thalamic radiation
Pink: Superior longitudinal fascicules
Blue: Inferior longitudinal fascicules
Green: Inferior fronto-occipital fasc.
Yellow: Uncinate fiber

Courtesy of Susumo Mori (Johns Hopkins)

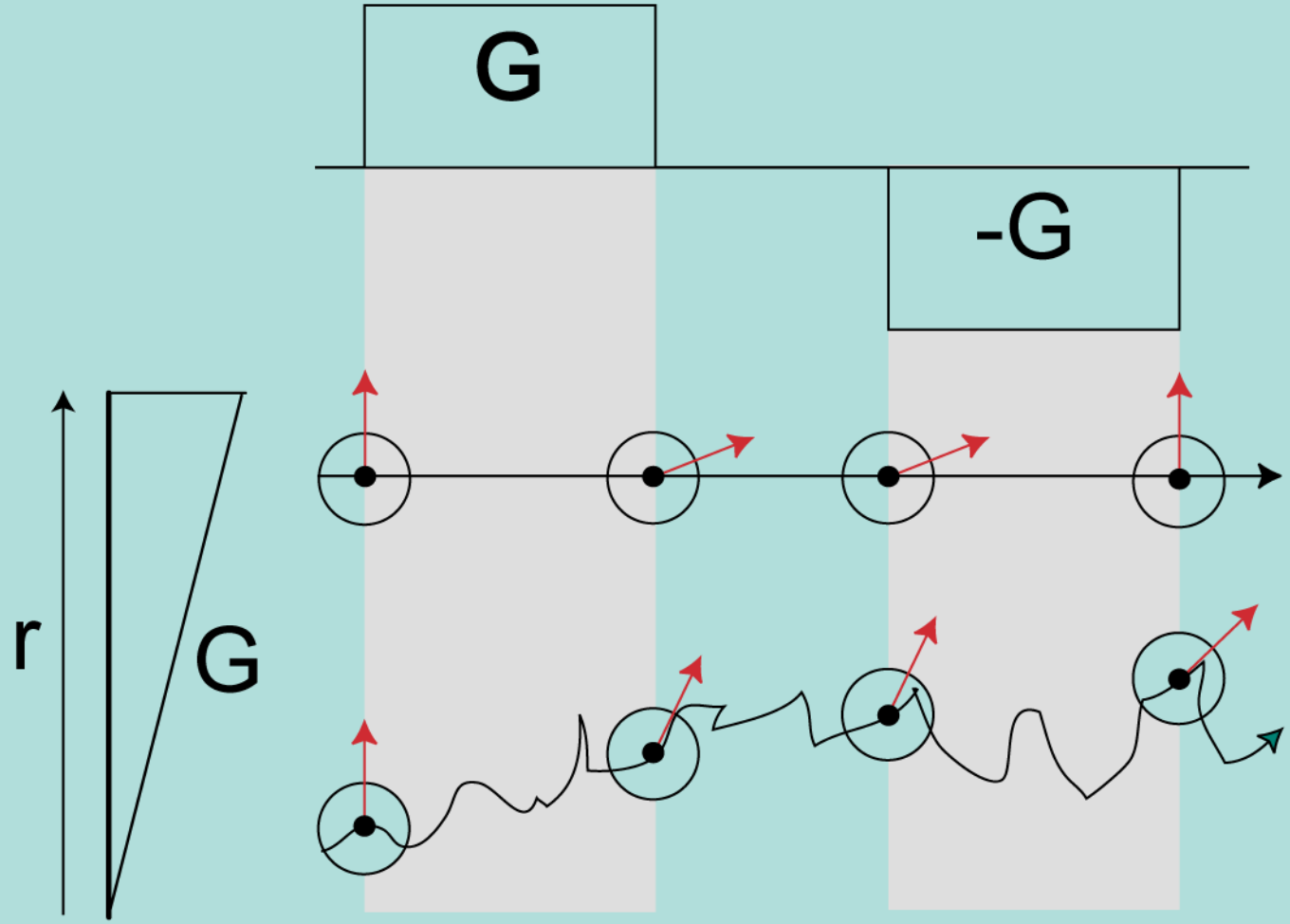
Contents

- Basic NMR diffusion experiment
- Diffusion in tissue
- Anisotropic diffusion
- Confounds: eddy currents and motion
- Fibre tracking

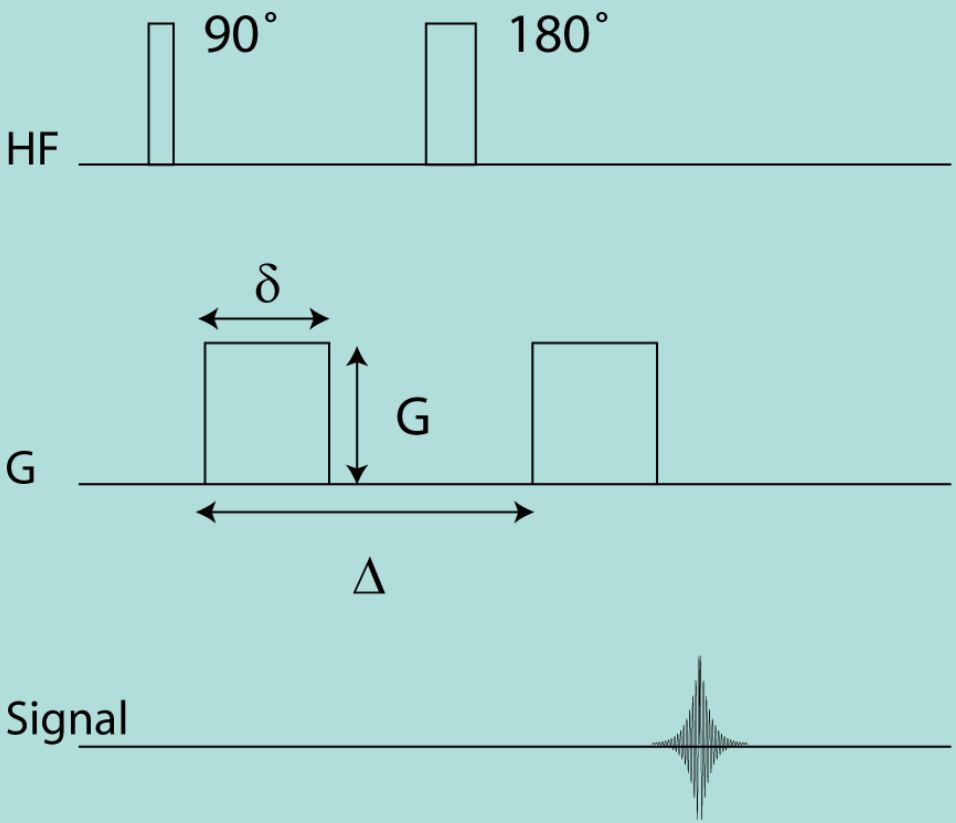
Basic Theory

All MR methods for detecting diffusion are based on the loss of phase coherence resulting from stochastic motion in the presence of a magnetic field gradient.

Diffusing spins acquire a phase difference



Pulsed Gradient Spin-Echo

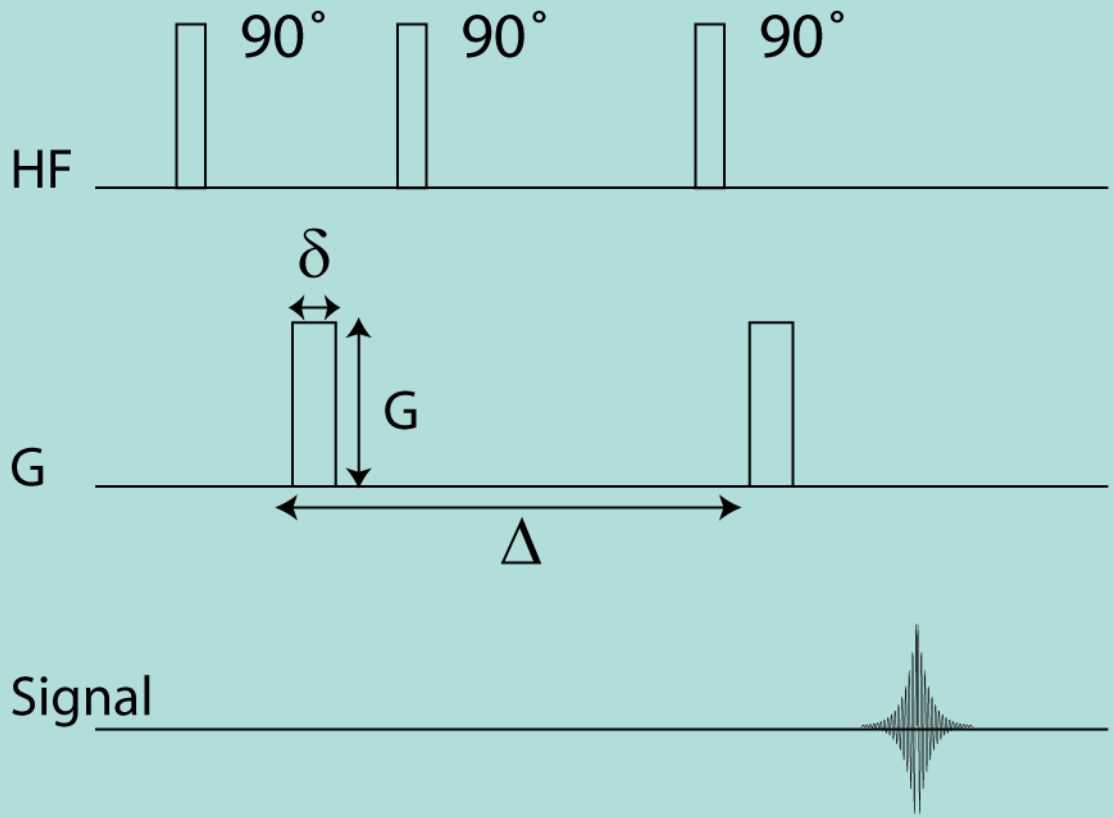


Attenuation for this experiment is given by:

$$\mathbf{M}_{xy}(\mathbf{r},t) = M_0 \exp\left(-(\gamma G\delta)^2(\Delta - \delta/3)D\right)$$

The *b*-value is defined as: $b = (\gamma G\delta)^2(\Delta - \delta/3)$

Pulsed Gradient Stimulated-Echo



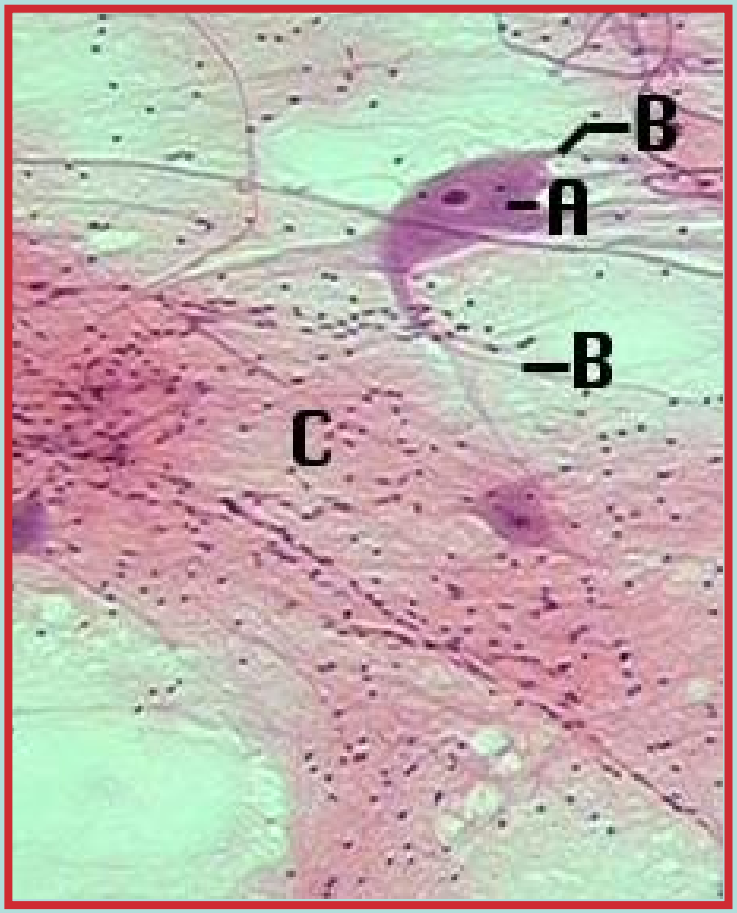
- Stimulated echo only offers half the signal intensity of a spin echo, but…
- Gives access to very high attenuation factors, and…
- To very long diffusion times

Biophysical situation?

Diffusion MR allows us to probe tissue microstructure on the micrometer scale. Key relationship is Einstein equation:

$$\left\langle \mathbf{r}^2 \right\rangle = 6D\tau_D$$

with typical values of D about 10^{-3} mm^2 s^{-1} and diffusion times of about 80 ms (required for a reasonable diffusion attenuation) we obtain mean path length of approx. 20 μm.



Stained microscopic picture of brain tissue

A-cell body

B-axon and dendrite

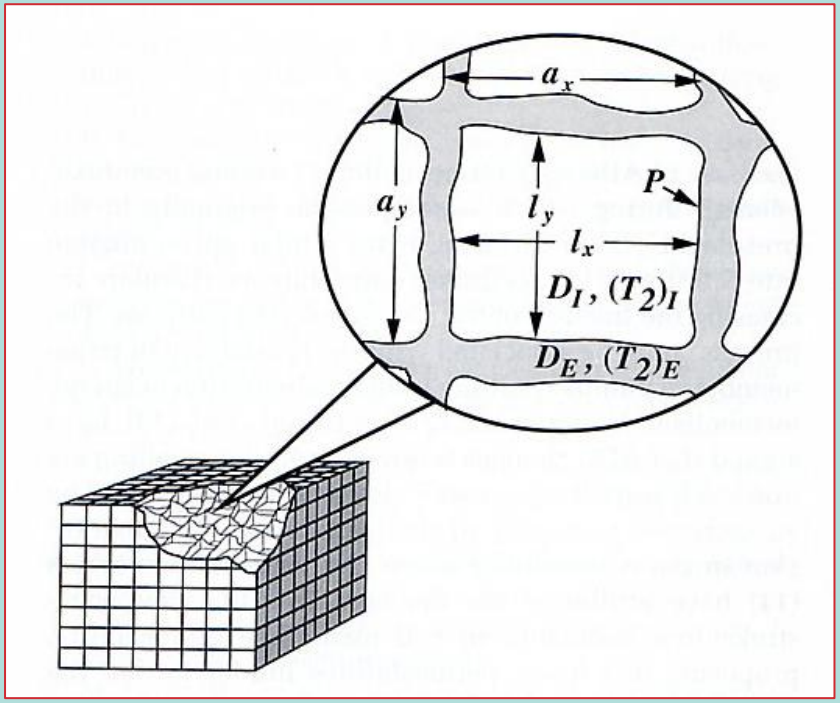
C-neuroglia

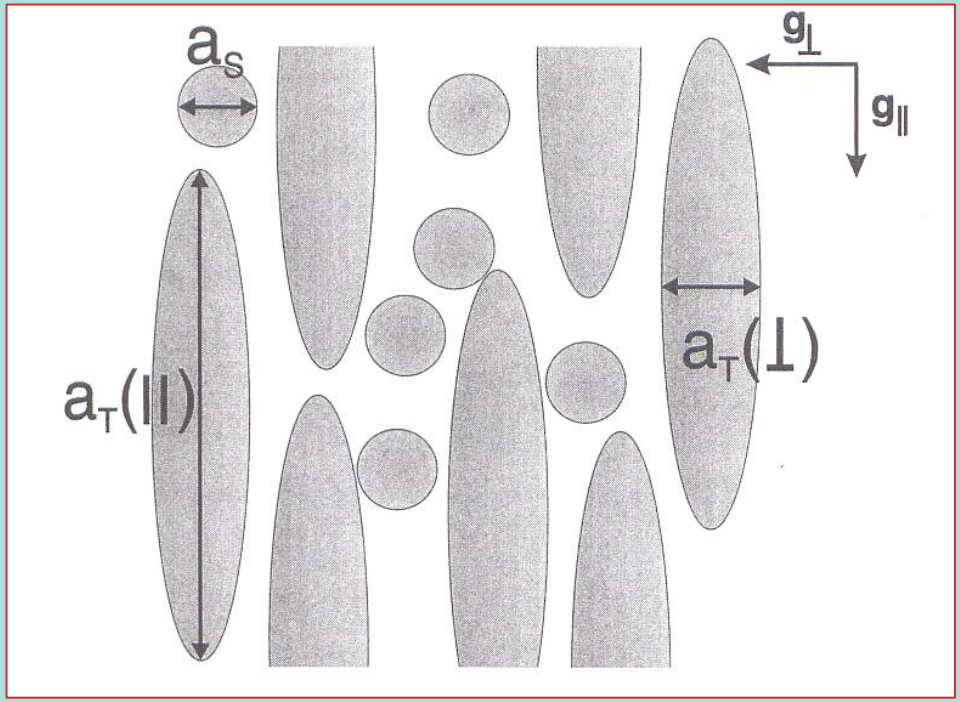
Biophysical Situation

Brain tissue has an intravascular compartment of about 4% by volume. The remainder is divided between extra- and intracellular spaces in the ratio of 1:4. Water exchanges between these three compartments.

Simplest model is two compartments separated by a membrane of limited permeability. Diffusion in the intracellular compartment may be restricted by the cell membrane. In the extracellular space the diffusion length will be reduced by the requirement to diffuse around the cells. Diffusion coefficient often termed ADC: Apparent Diffusion Coefficient

Typical modeling approaches





- Implicit in most models is an assumption that the relative sizes of the intra- and extracellular spaces and the degree of extracellular tortuosity determine ADC.
- The lack of morphological information makes it difficult to model experimental data exactly.

Pathological Models

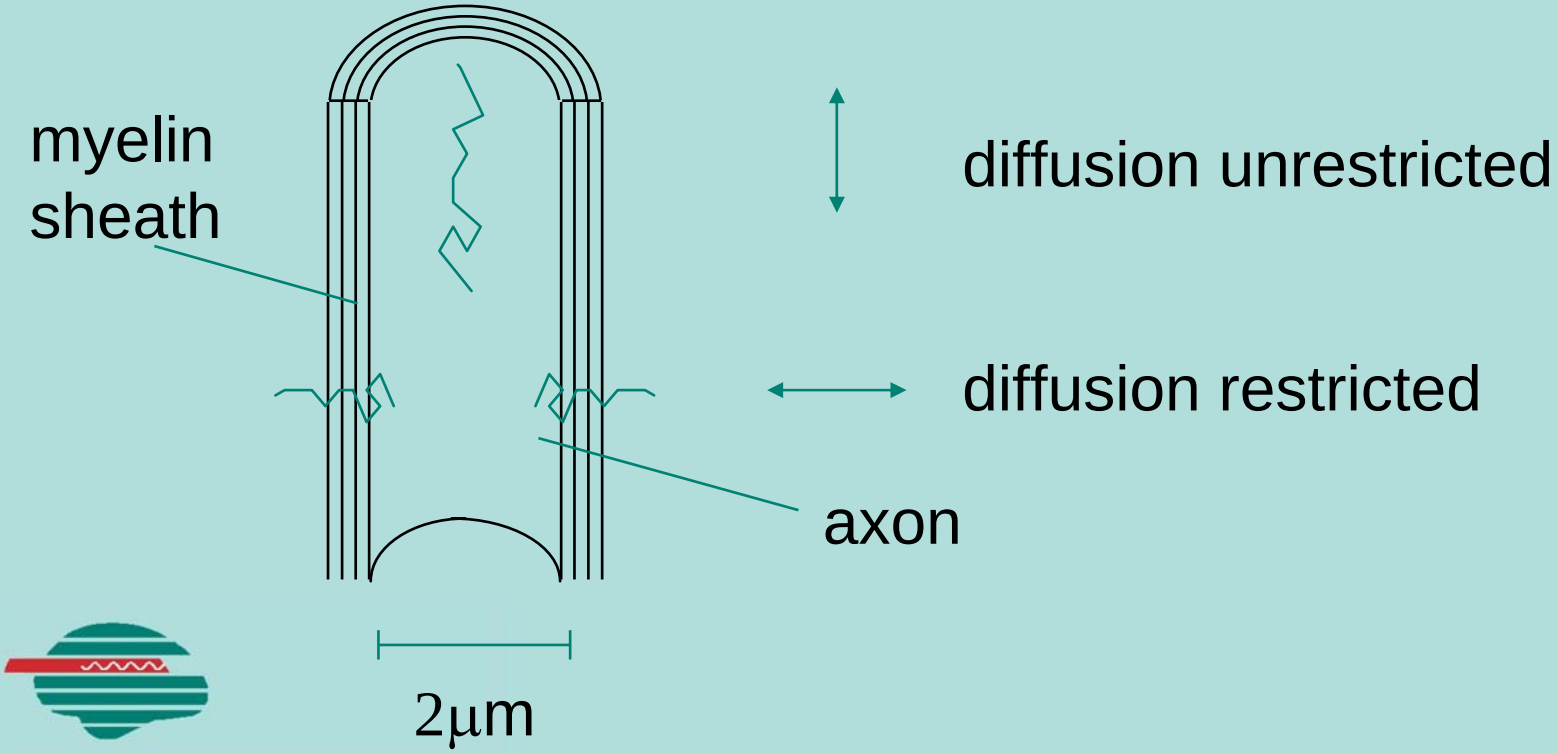
- In cerebral infarction a marked reduction in ADC occurs simultaneously with cell swelling and increased tortuosity.
- A fall in intracellular diffusion is also needed to make models work, but this has not been found experimentally

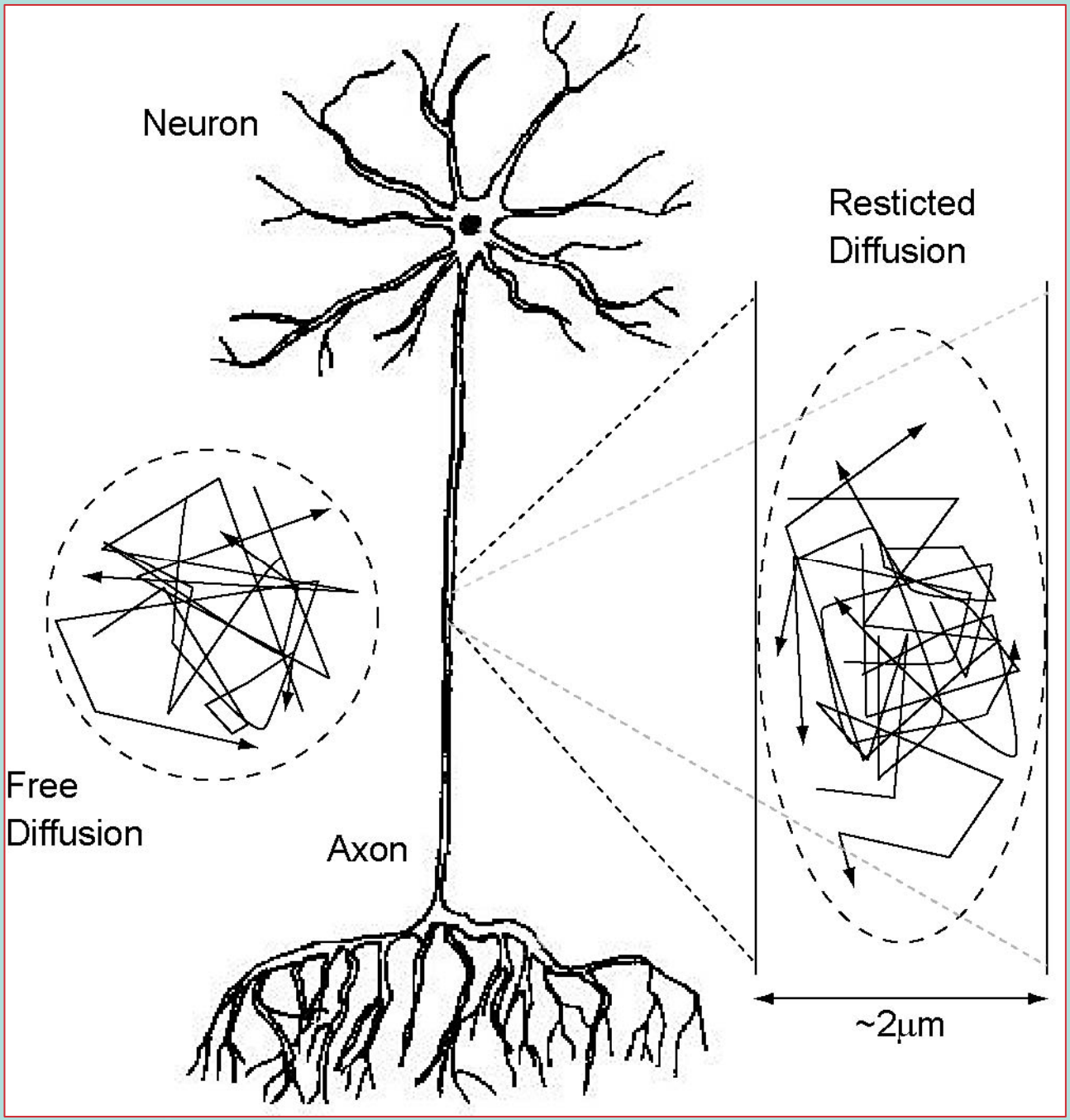
Relevant posters

- #76 Fast optical tracking of diffusion in brain extracellular space. Hrabe and Hrabetova
- #77 Dead spaces hinder diffusion and contribute to tortuosity of brain extracellular space. Hrabetova et al
- #86 Measurement of lcal diffusion properties in brain tissue. Nicholson et al

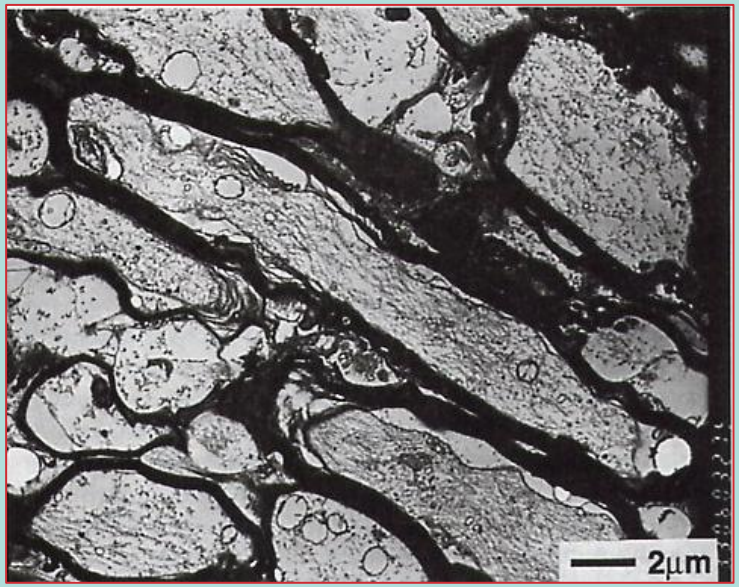
Basis of Anisotropy

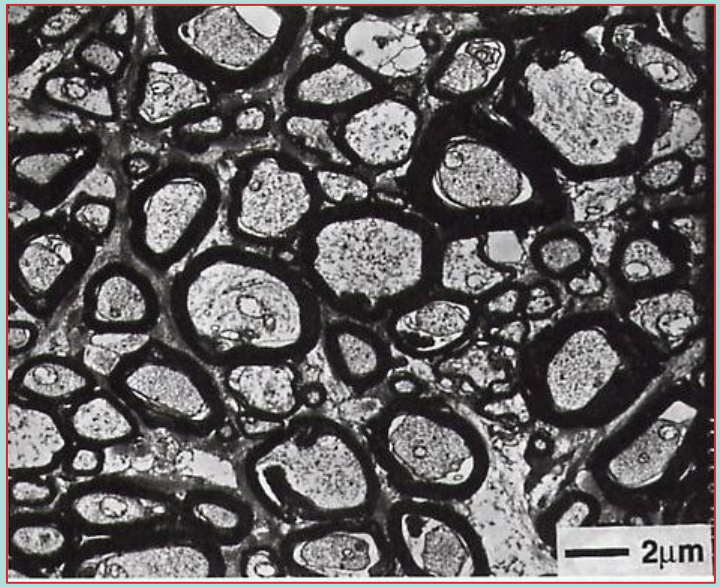
The myelin sheath around axons form an obstacle to water diffusion.



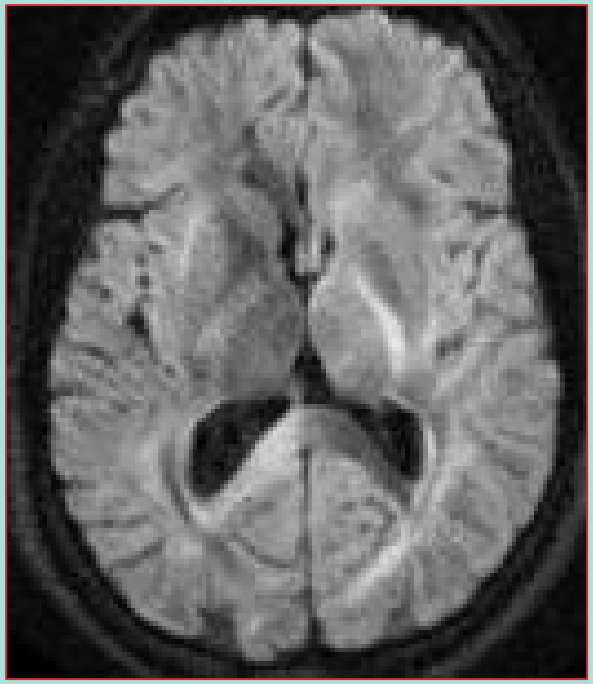

Neuron
Restricted
Diffusion
Free
Diffusion
Axon
~2μm

Electron micrographs of nerve tissue parallel and perpendicular to tract orientation

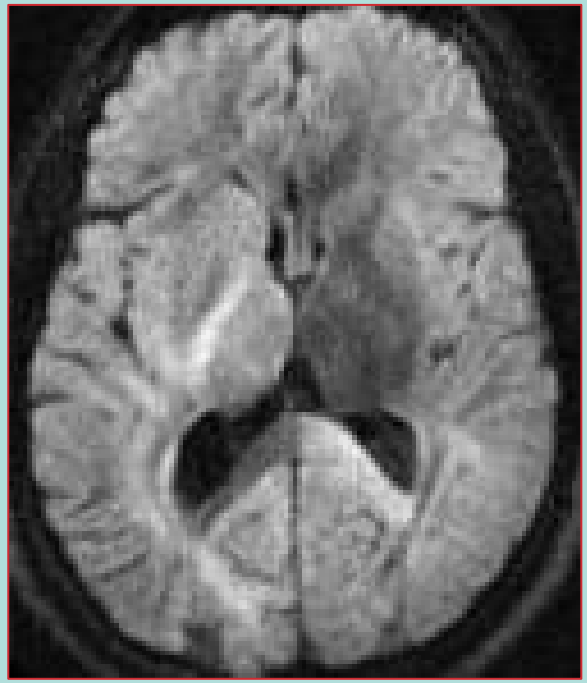




The effect of different orientations of the diffusion weighting gradient on the signal from white matter as a result of anisotropy.



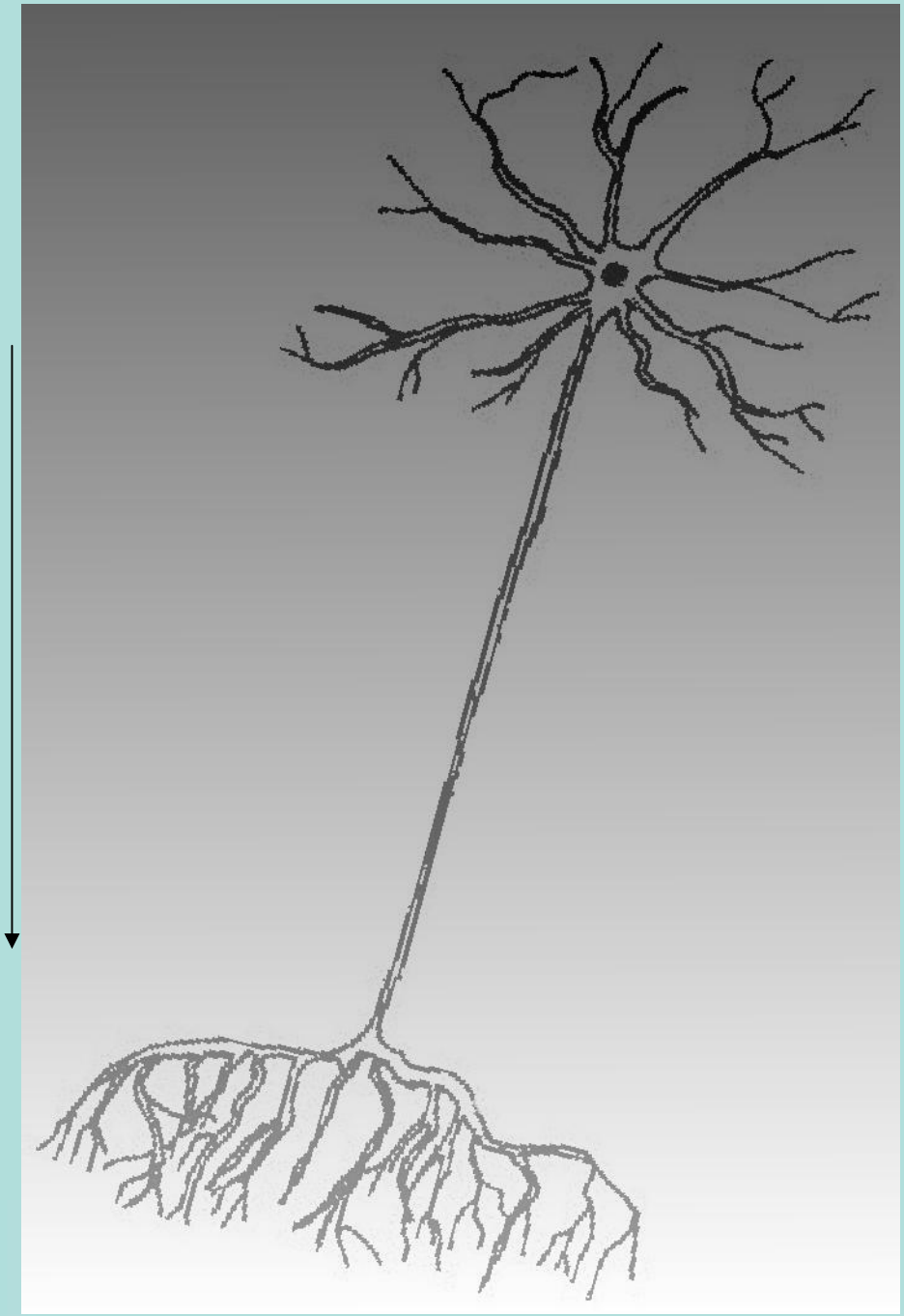
(-x,y)



(x,y)

Slides courtesy: Ted Truard

∇C



J

The diffusion tensor has the form:

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

The on-diagonal elements reflect diffusion parallel to a concentration gradient, the off-diagonal elements the component of diffusion perpendicular to it.

- To measure the diffusion tensor you need to perform at least six independent measurements as there are six elements in this symmetrical tensor.
- Also need to know proton density.
- A regression analysis gives the full tensor information from which a number of scalar values can be obtained.

Eigenvalues and eigenvectors

As the determinant of the diffusion tensor is positive definite there will always be three positive eigenvalues of the tensor. The three eigenvectors define the principal axes for the diffusion ellipsoid.

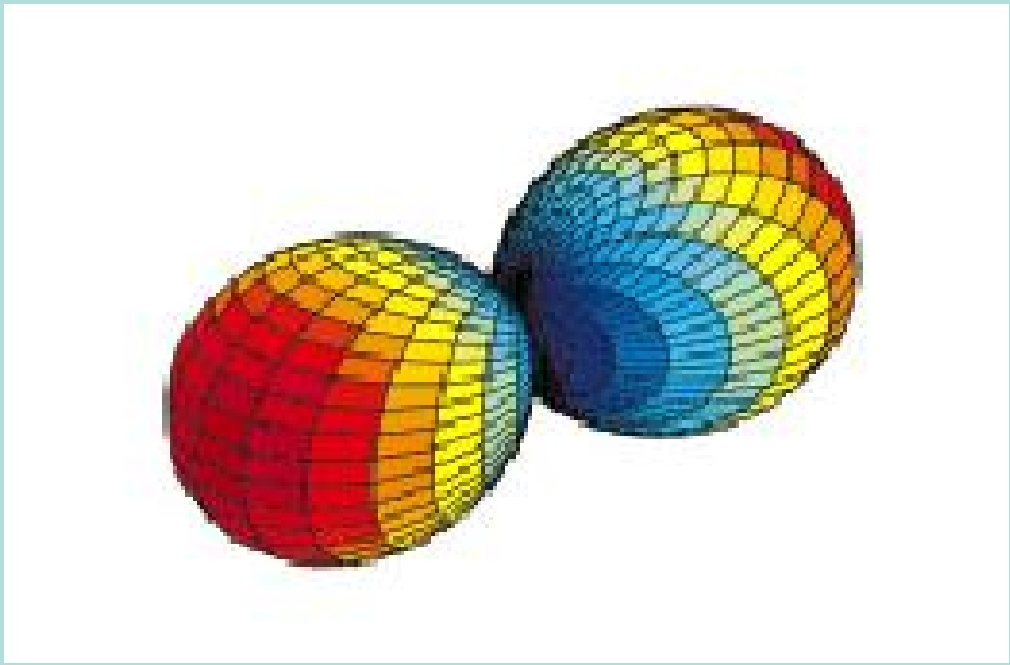
The diffusion ellipsoid

If we consider diffusion along the principal axes and seek the tensor analogue of the Einstein relationship ($\langle r^2 \rangle = 2Dt$) then

$$\mathbf{r}^{\mathrm{T}} \boldsymbol{\Lambda}^{-1} \mathbf{r} = 2t \; or \; \frac{x^2}{\lambda_1} + \frac{y^2}{\lambda_2} + \frac{z^2}{\lambda_3} = 2t$$

So the half axes of the ellipsoid are $a_i = \sqrt{2t\lambda_i}$

The ADC surface of the ellipsoid is a ‘peanut’

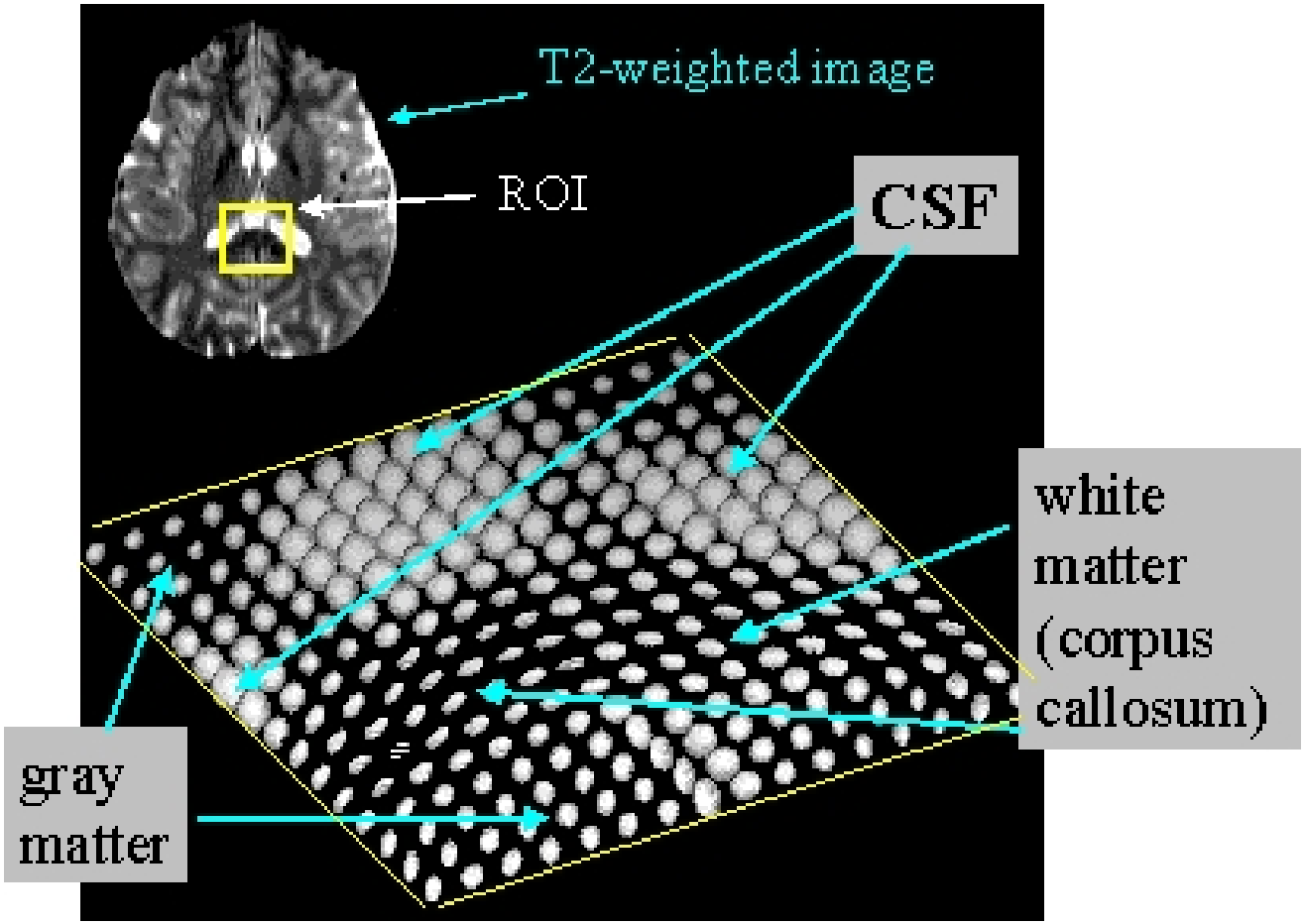


From Frank *Magnetic Resonance in Medicine* **45**, 935-939 (2001)

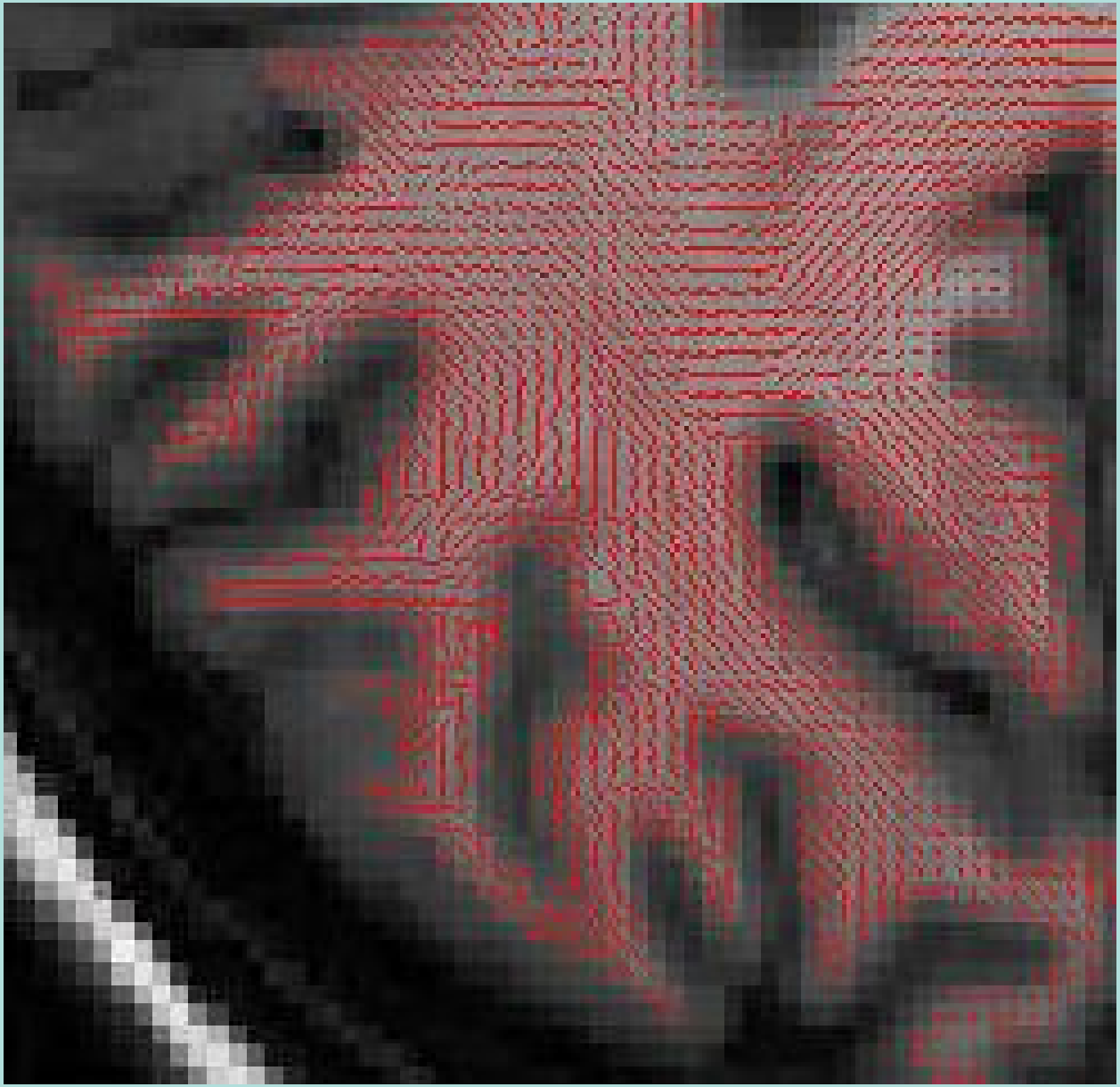
Visualisation

- The full tensor contains a large amount of information. Display of the ellipsoid is difficult but instructive.
- The orientation of the largest eigenvector is a precursor for fibre tracking.
- Color coding the axes: RGB for me needs a good knowledge of color mixing.

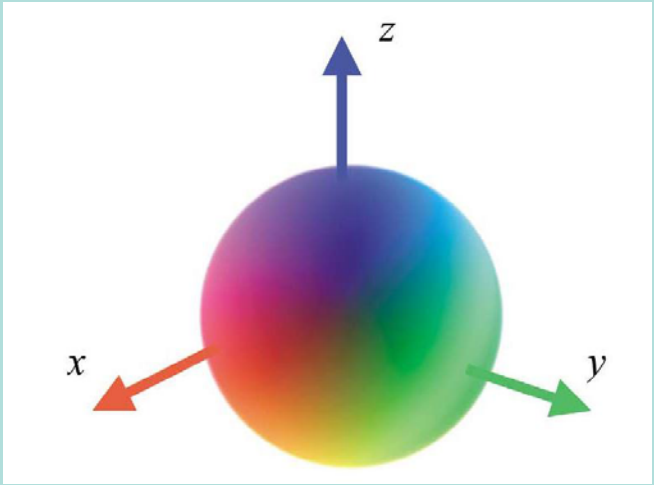
Measured Diffusion Ellipsoids

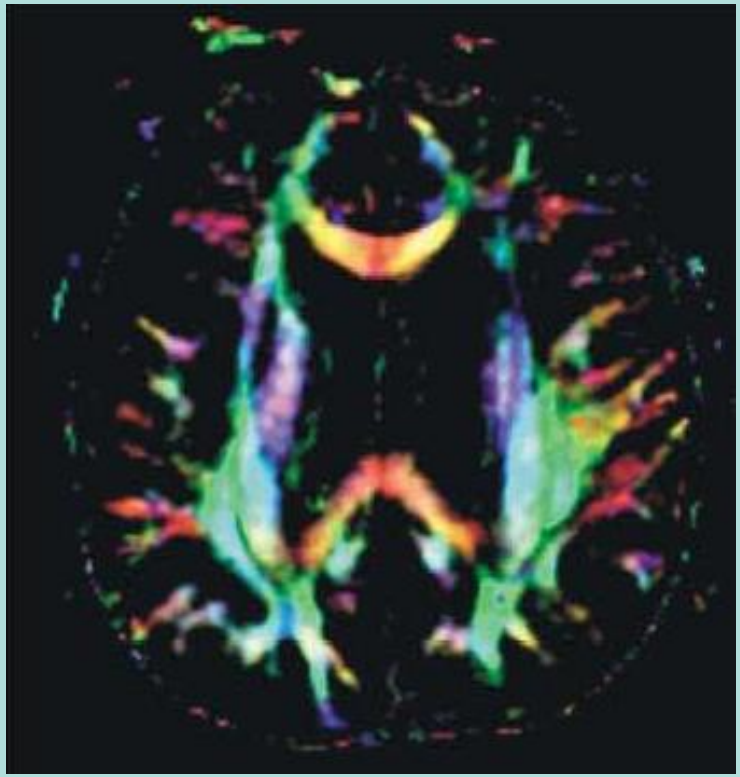


Pierpaoli et al, **Radiology** 1996; 201: 637-648.



Colour coding

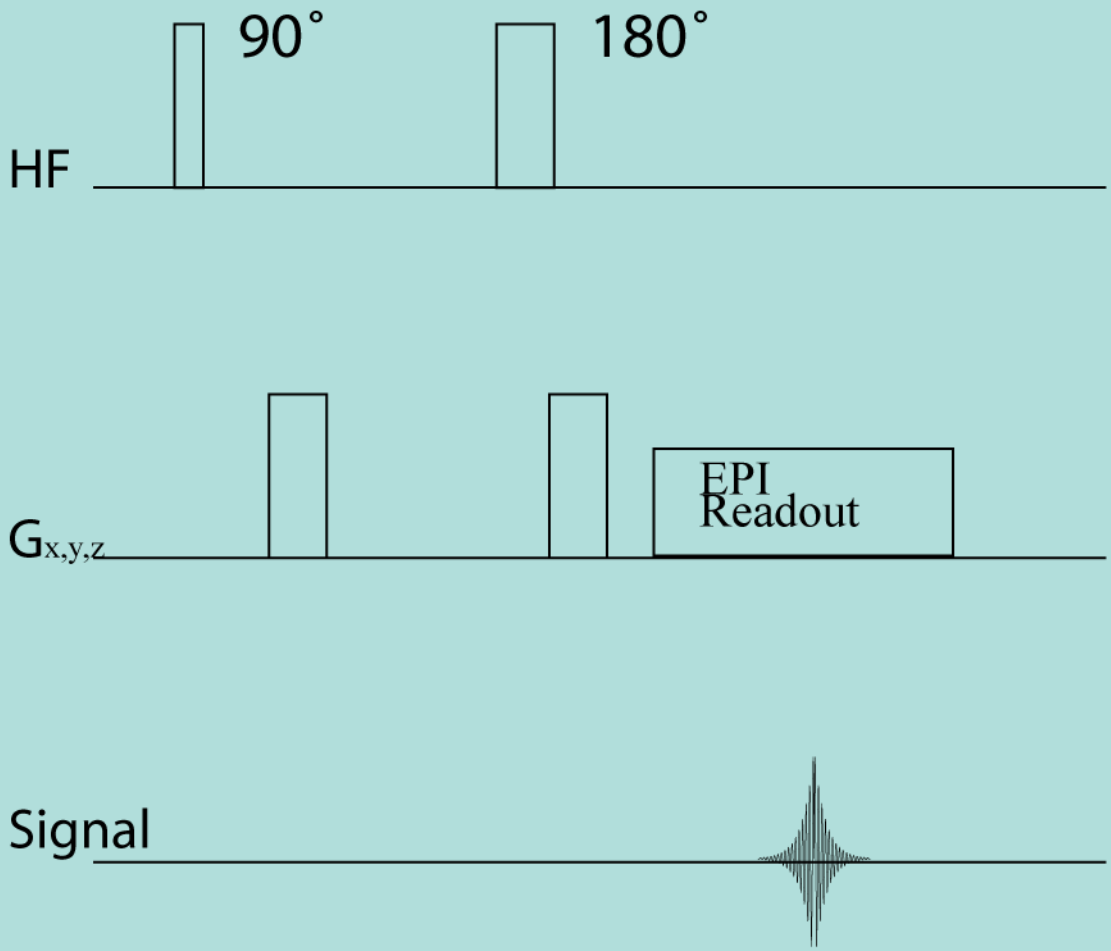




From Masutani, et al. *European Journal of Radiology* **46**, 53-66 (2003)

Combining diffusion weighting and imaging

- Need pulsed magnetic field gradients for both spatial encoding and diffusion weighting.
- In human imaging, though not in MR microscopy, the diffusion weighting effect of the imaging gradients is negligible.
- ‘Cleanest’ method is building block approach which keeps the diffusion and imaging parts separate from each other.


90°
180°
HF
Gx,y,z
EPI
Readout
Signal

EPI. Salient features

- Collects data for complete image after one excitation.
- Places heavy requirements on gradient systems.
- Prone to artifacts: shift, scale, shear, voids.
- Spatial resolution limited to matrices of 64×64 or maximally 128×128.
- Can scan whole brain within seconds

Eddy current effects 1

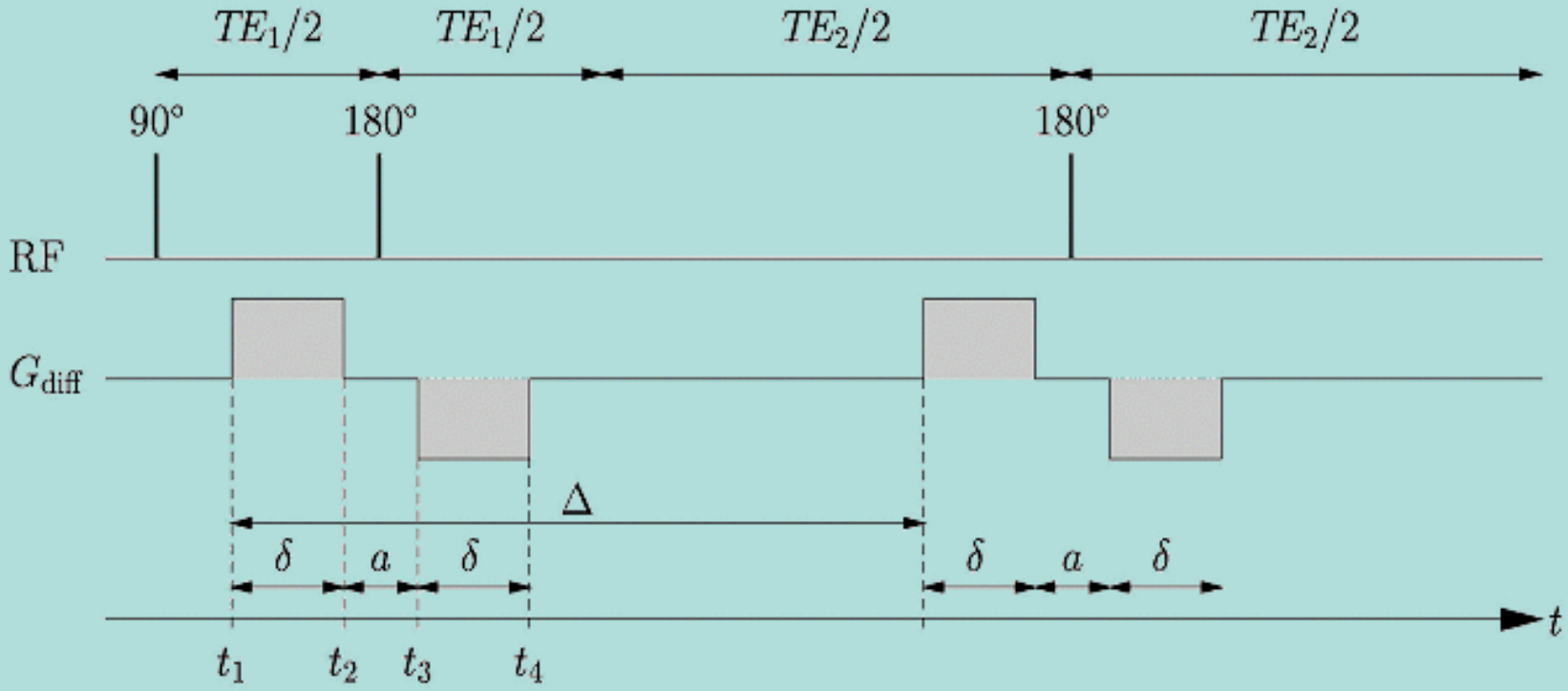
- Eddy currents are generally considered as constant during the imaging sequence.
- In reality they drop-off exponentially, but the approximation is acceptable for EPI.
- This means that eddy currents can be treated in the same way as effects of main field inhomogeneity.

Eddy current effects 2

- The eddy current can be considered as producing a constant extra gradient parallel to the direction of the diffusion weighting gradient, and/or a frequency offset.
- The severity of eddy currents will depend on the strength of the gradients causing them. In tensor imaging multiple orientations of the weighting gradient and multiple strengths are used, and so these effects must be eliminated.

Solutions to eddy current artifacts

- Measure eddy current effects and eliminate in the post-processing.
- Tailor the diffusion-weighting part of the pulse-sequence to give lower eddy currents.



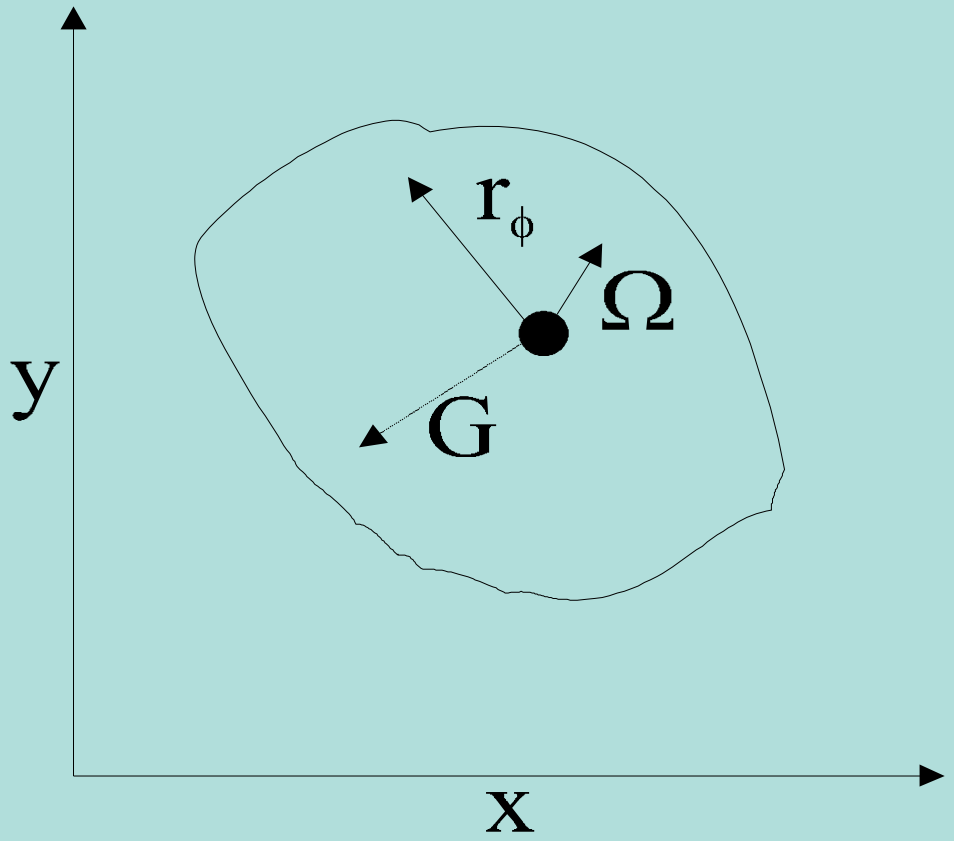
$$b = (2\delta\gamma G)^2\left(\Delta - \frac{a}{2} - \frac{2\delta}{3}\right)$$

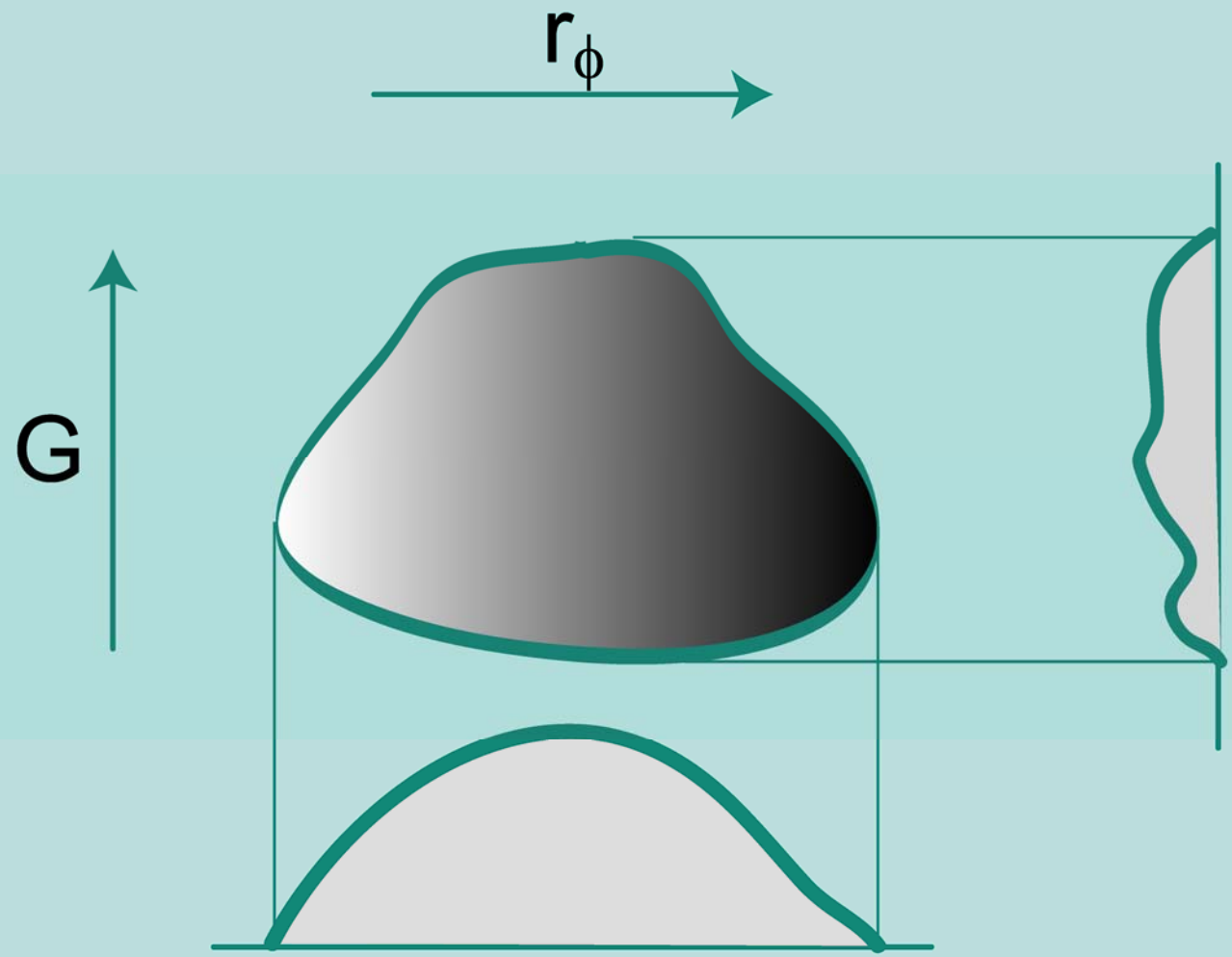
General effects of bulk motion

- Translation causes a global phase shift given by $\phi = \gamma G v \delta \Delta$.
- Rotation causes a phase gradient across the object which, according to the Fourier shift theorem is equivalent to a shift in *k*-space.

Direction of the phase gradient is given by the cross product of the vectors of the diffusion weighting gradient and of the axis of rotation.

$$\mathbf{r}_\phi = \gamma \mathbf{G} \times \Omega$$




r_ϕ
G

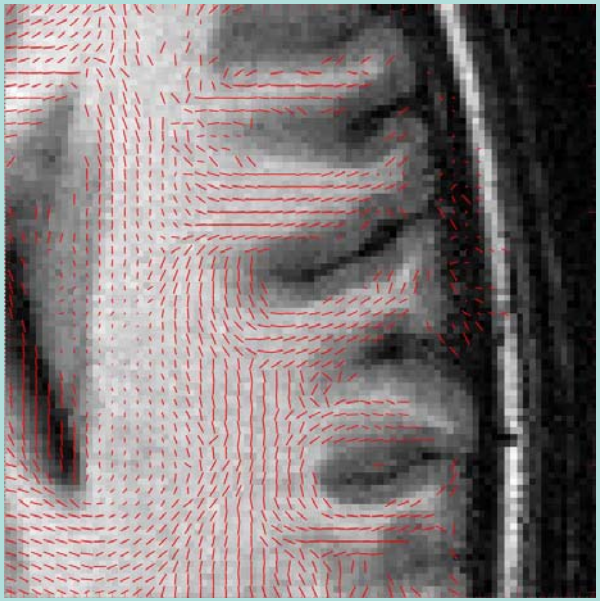
- So you are only safe from the effects of rotation if the diffusion-weighting gradient is parallel to the phase-encoding gradient!
- Multi-excitation experiments require phase-correction between excitations.

Pulsatile motion of the brain

- Common correction methods have implicit assumption that brain moves as a rigid body (no distortion).
- The pulsatile nature of arterial flow causes non-linear motion during up to about 200 ms post R-wave.
- Maximum velocities are 1.5-2 mm sec^{-1}. Highest velocities are along inferior superior axis.
- For these reasons it is currently best to use a sensitive single shot method, like EPI.

Fibre Tracking

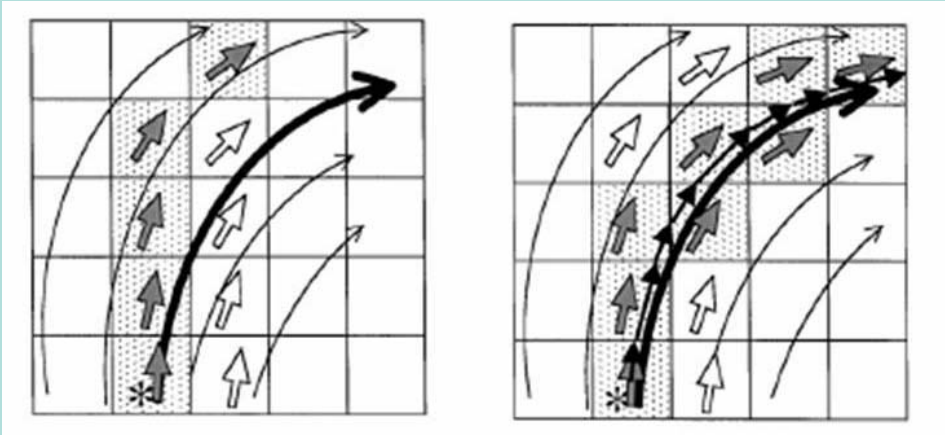
- Surprisingly knowledge of fibre tracts in humans is not perfect.
- Animals easier to study as active transport in cells can be used.
- Fibre tracking in humans offers the possibility of combining neuroanatomical with functional information.



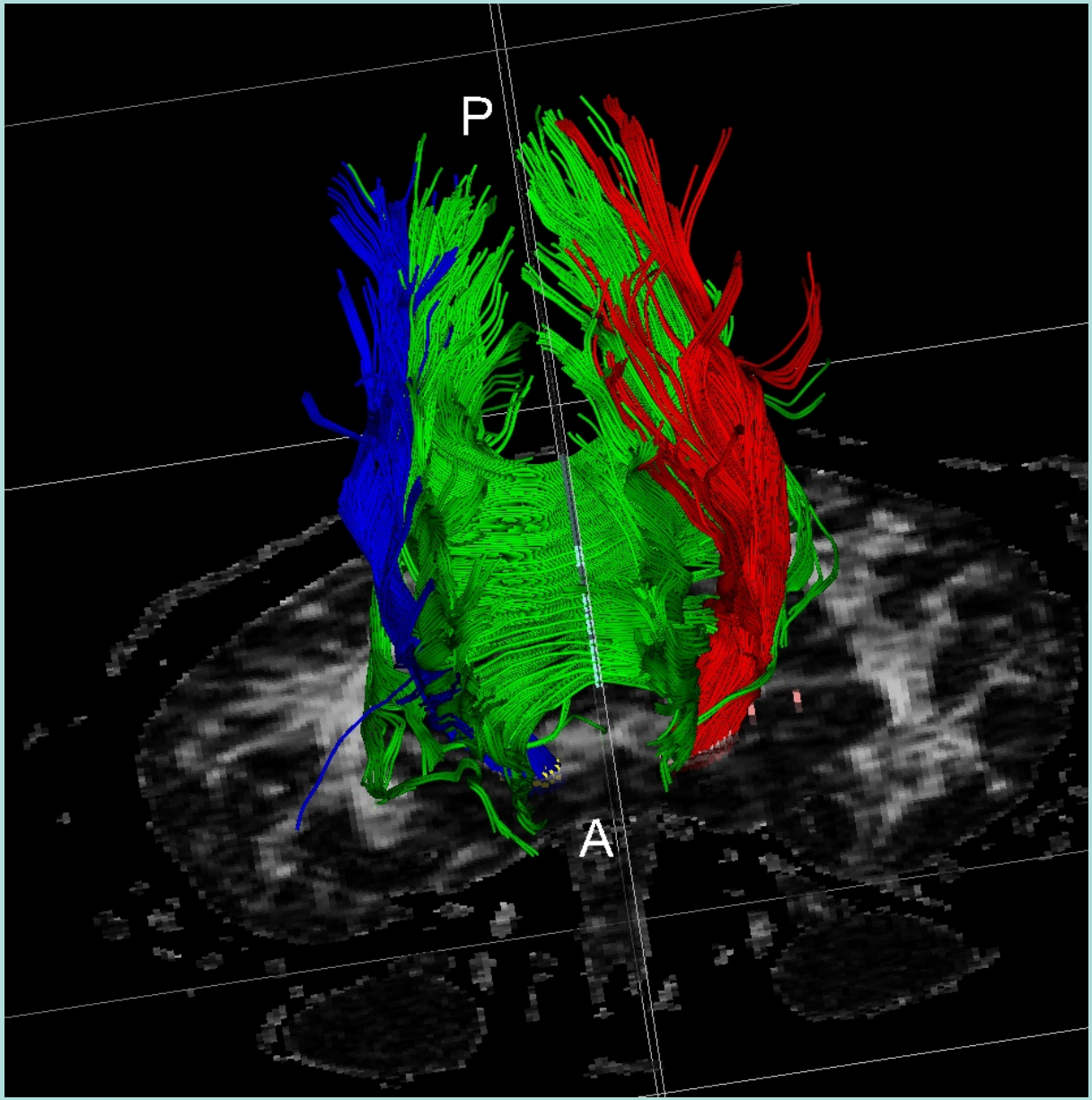
- In all algorithms criteria are developed to connect all the vectors
- How do we deal with discrete voxels and continuous fibers?

Line propagation methods

- Susumu Mori et al. Annals of Neurology 1999
- Fiber Assignment by Continuous Tracking (FACT)
- Tracking through a voxel with constant direction
- End point defined by the occurrence of sudden transitions in the fiber orientation (low-curvature hypothesis)



Mori et al. 1999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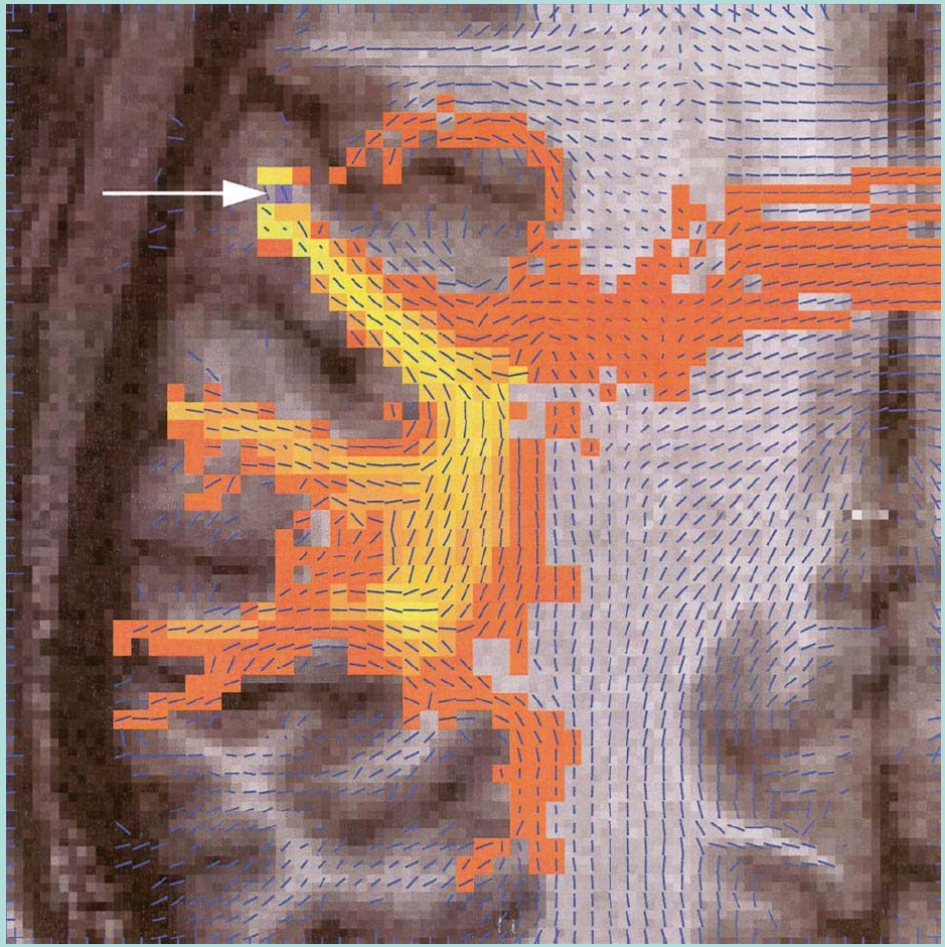
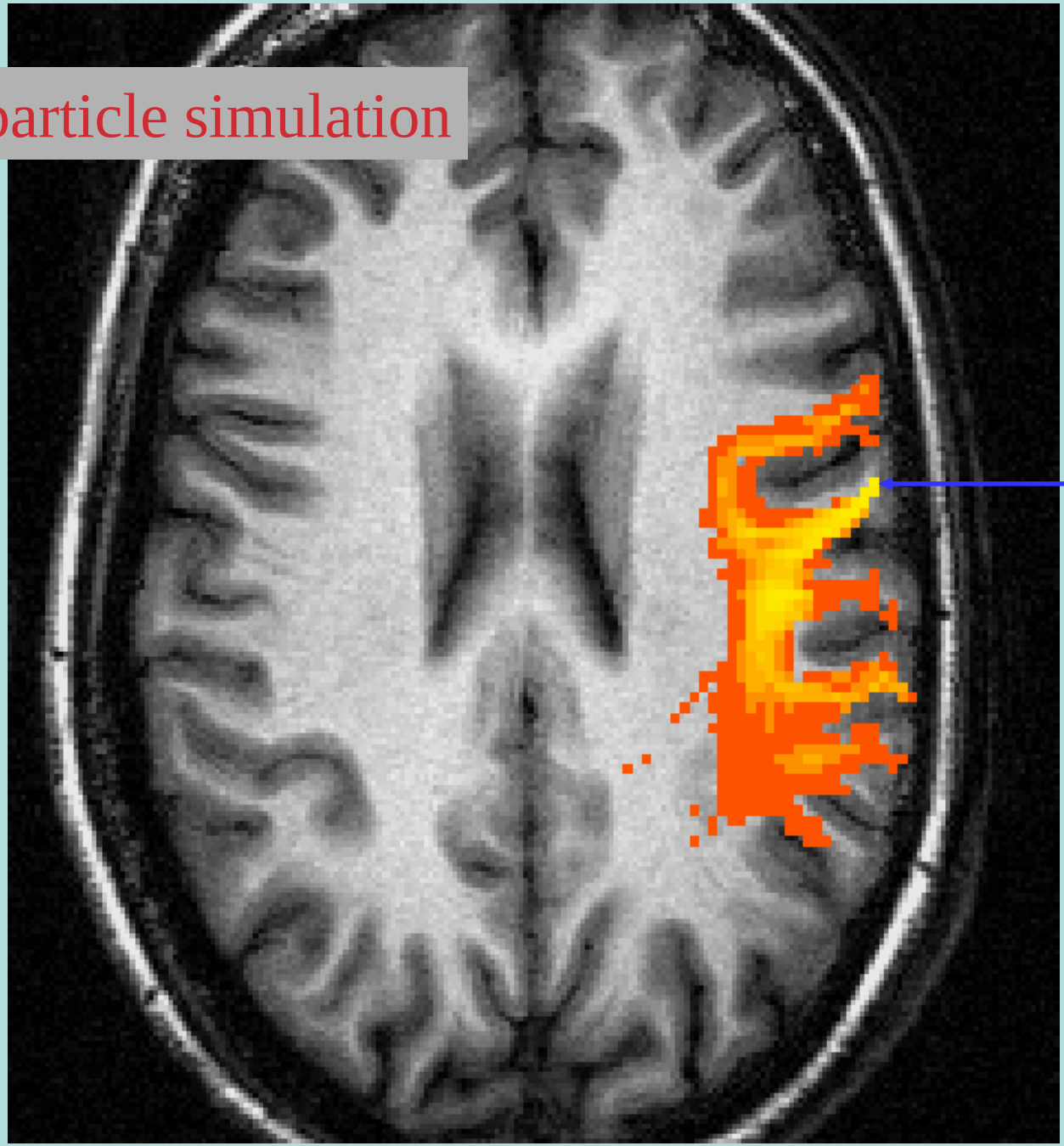
Probability-based methods

- Martin Koch et al. Neuroimage 2002
- From the seed point a (macroscopic) random walk is performed.
- The probability of this random walk going in a certain direction is determined by the diffusion tensor
- This procedure is then repeated in a Monte-Carlo simulation
- The frequency with which a voxel was encountered in the walk serves as an informal measure of connectivity
- This measure decreases with distance to seed voxel.

Probability-based methods



Jumping particle simulation

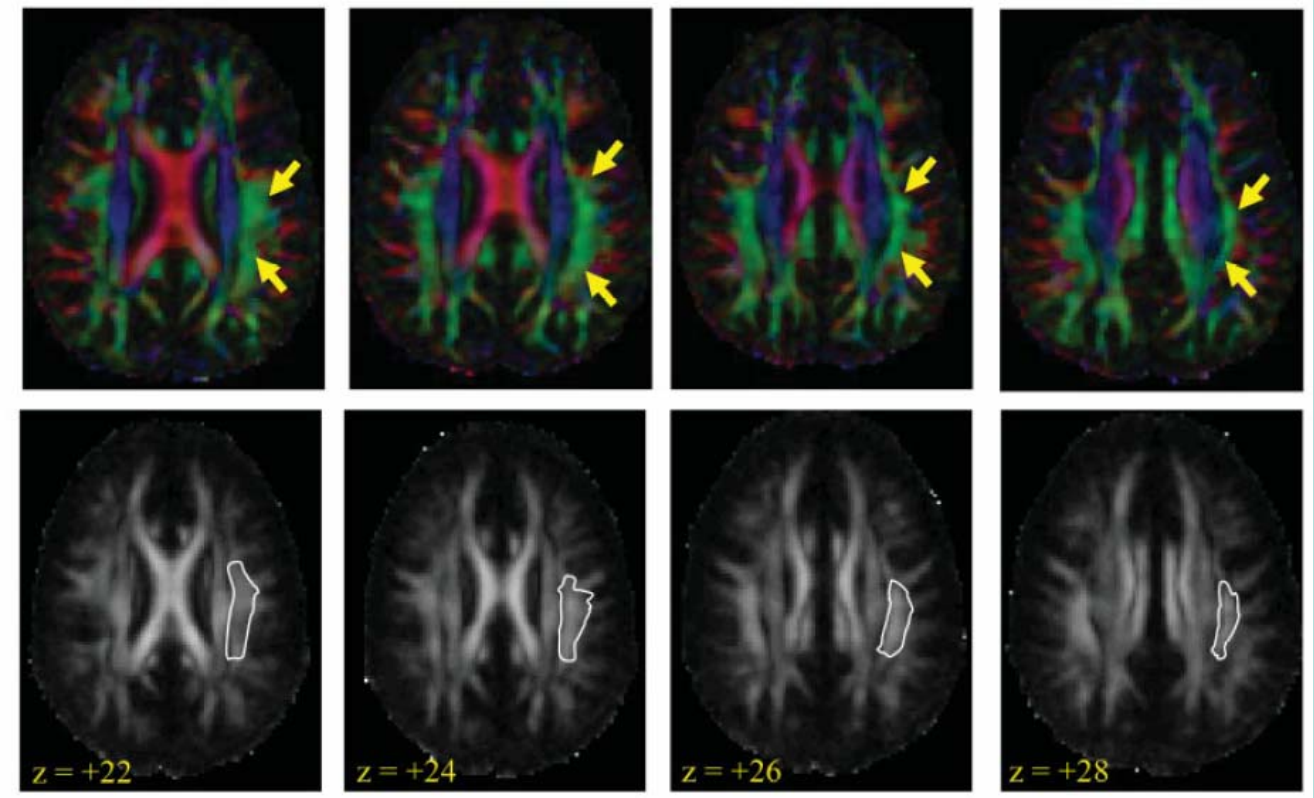


Evaluation

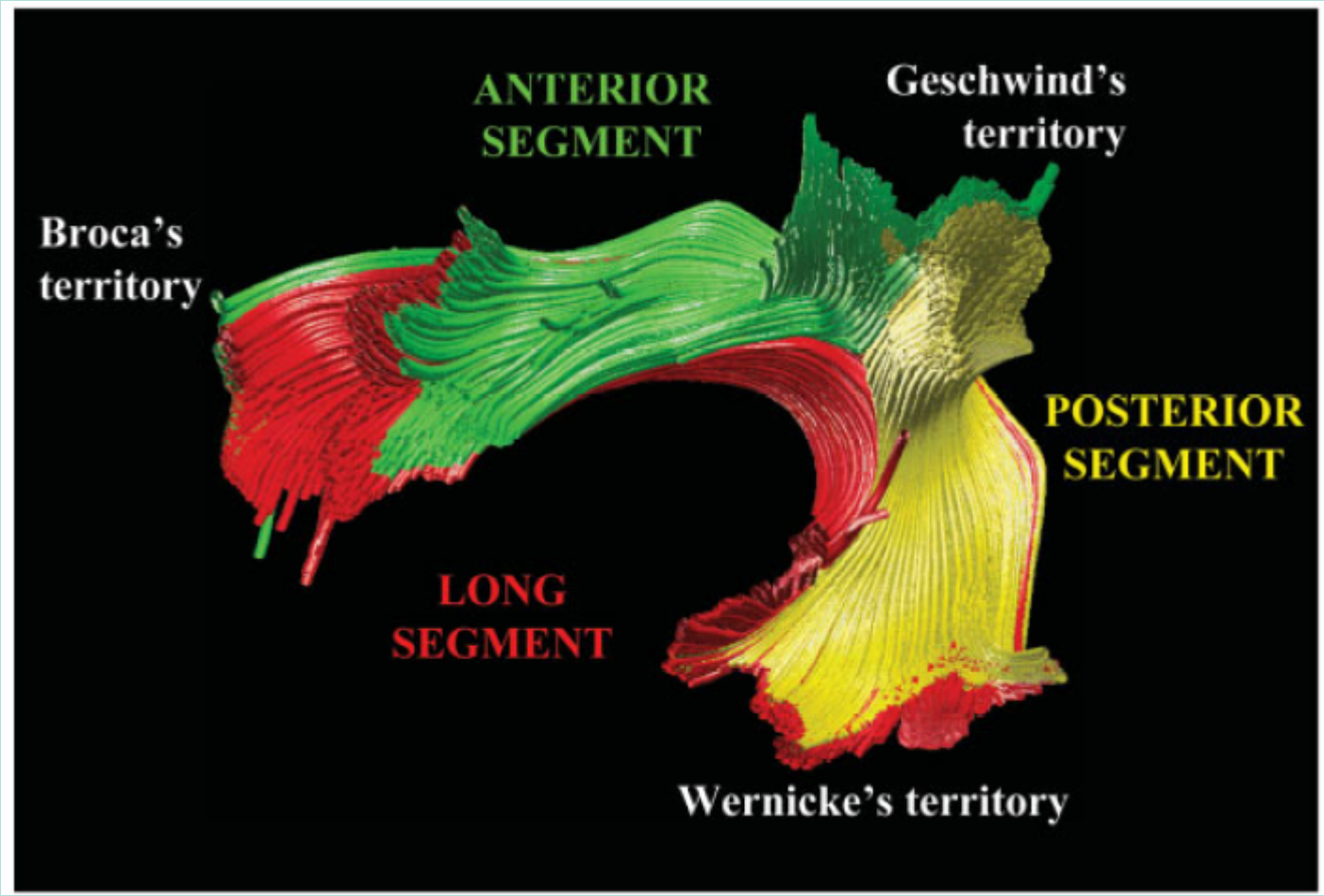
- Streamline-based methods lend themselves to good 3D visualization
- They don’t give information about the certainty with which a tract is calculated
- Probability-based methods are difficult to visualize in 3D
- They give information about the likelihood of the tract
- This likelihood is (mostly) informal
- Their probability decreases over distance

Applications

- Catani et al. Annals of Neurology 2005
- Is there another area connected (other than Broca and Wernicke) via the arcuate fasciculus

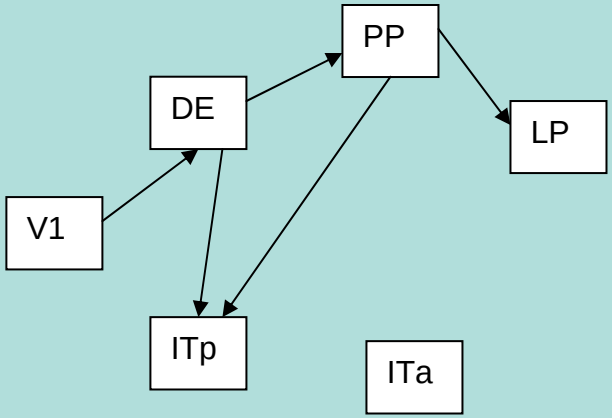


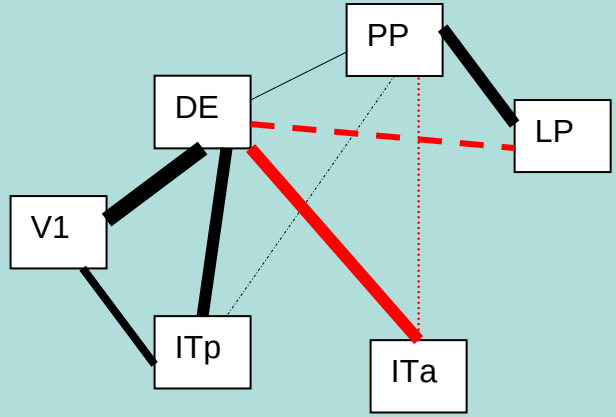
Applications



Connectivity

- Neuroscience moving away from which areas activate in task performance to how networks interact.
- Models based on anatomical hypotheses, many from macaque monkey.
- Can now start to test in humans





V1 = striate cortex
DE = dorsal extrastriate visual cortex
PP = posterior parietal cortex
LP = lateral parietal cortex
ITp = posterior inferotemporal cortex
ITa = parahippocampal gyrus

Legend

Proposed connection
Non-proposed connection
Connection found after reanalysis with low FA

Connection found in six subjects
Connection found in five subjects
Connection found in four subjects
Connection found in three
Connection found in two subjects
Connection found in one subject1

Acknowledgements

- Hubert Fonteijn
- Martin Koch