Diffusion and Functional Brain Imaging

Pietro Gori

Enseignant-chercheur
Equipe IMAGES - Télécom Paris (IPParis)
pietro.gori@telecom-paris.fr

Summary

1. Introduction
2. Diffusion Weighted MRI
   - Diffusion tensor imaging
3. Tractography
4. Functional NeuroImaging (EEG and MEG)

Introduction

Tissue molecular diffusion

- Diffusion MRI
  - quantifies molecular diffusion (mainly water) in living tissues non-invasively
  - used in clinics and research to map the architecture of the white matter tracts, pelvic nerves, myocardiac fibers, etc.

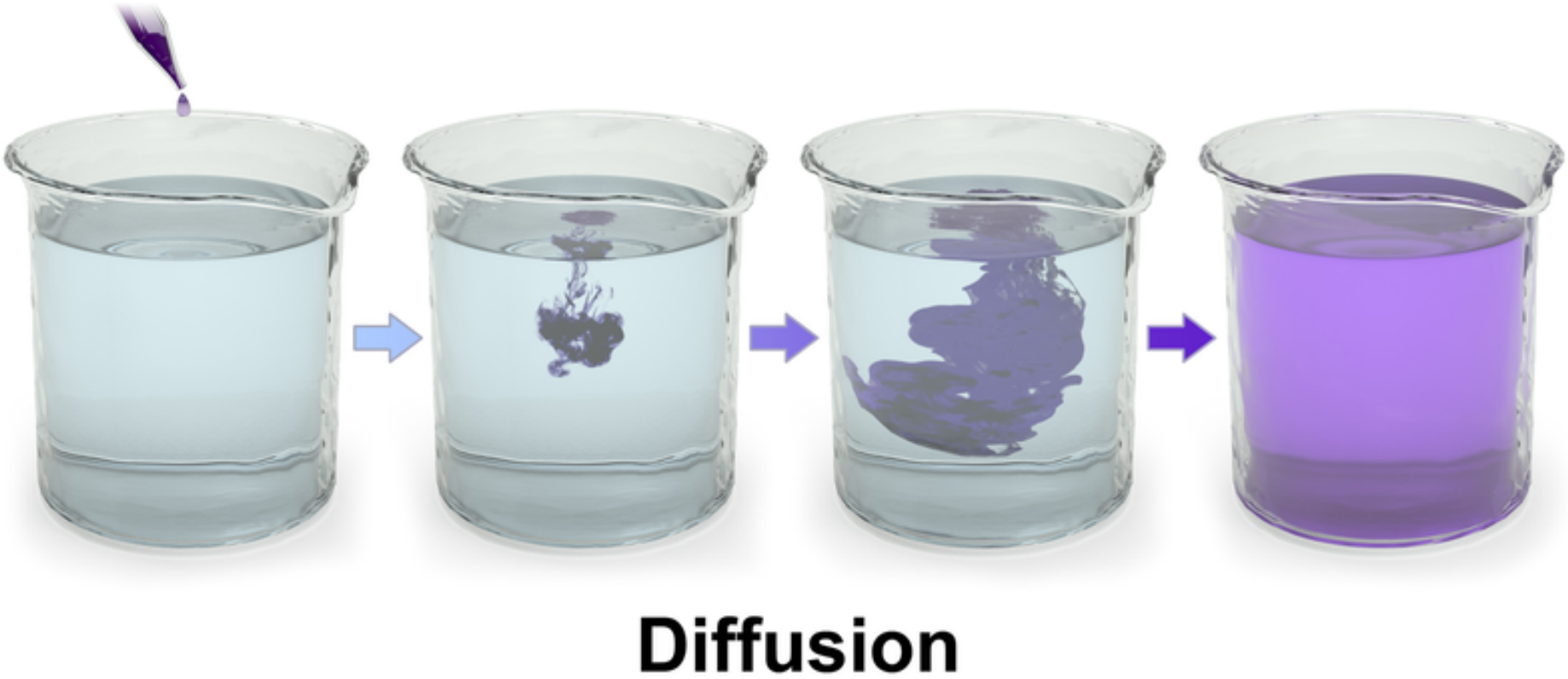
Functional information

- PET
  - low temporal and spatial resolution
- f-MRI
  - good spatial resolution
  - average temporal resolution
- EEG, MEG
  - very good temporal resolution
  - good spatial resolution (especially MEG) but no direct localization

Diffusion

Definition of diffusion

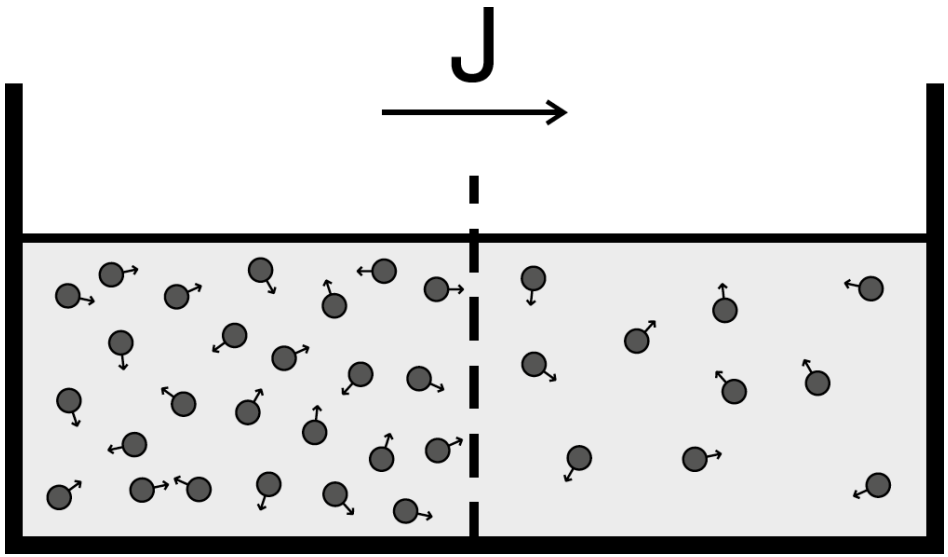
Diffusion is a mass transport process where molecules move without bulk motion. Drop of ink will diffuse without bulk water motion.



Fick's laws of diffusion

$$\boldsymbol{J} = -D\nabla c(\boldsymbol{x}, t) \tag{1}$$

The flux of particles $\boldsymbol{J}$ arises from a gradient ∇ in concentration $c(\boldsymbol{x}, t)$ at a certain spatial position $\boldsymbol{x}$ and time point t. We assume that the medium is isotropic, D is a scalar diffusion coefficient, and thus the diffusion is the same in all directions. Due to the minus sign, the flux $\boldsymbol{J}$ goes from high concentration to low concentration.



Fick's laws of diffusion

From the first Fick's law and the law of conservation of mass, we can write:

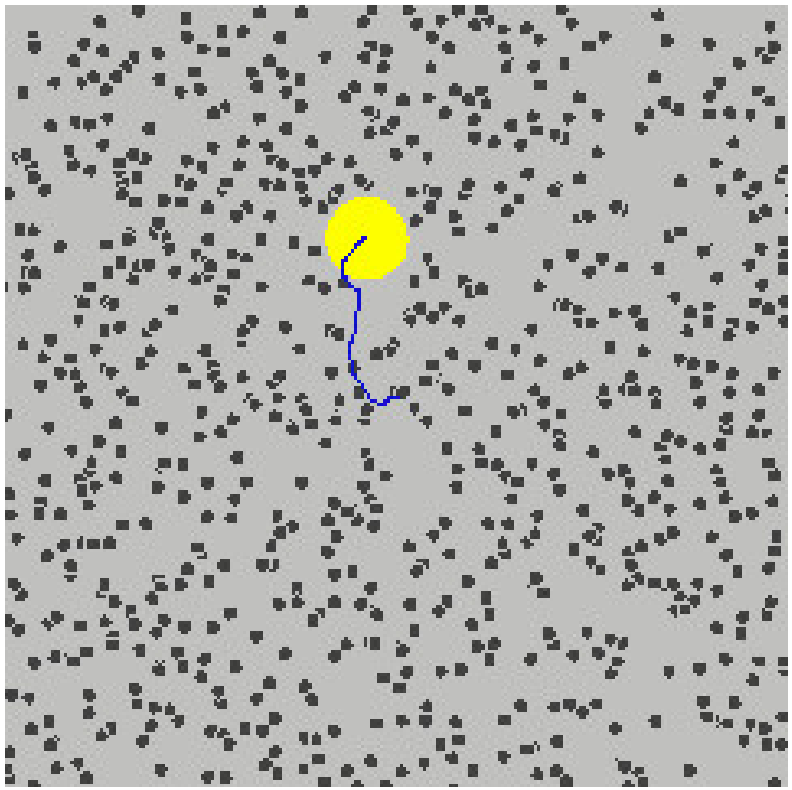
$$\underbrace{\frac{\partial c(\boldsymbol{x},t)}{\partial t} + \text{div}\boldsymbol{J} = 0}_{\text{conservation of mass}} \rightarrow \frac{\partial c(\boldsymbol{x},t)}{\partial t} = \text{div}(D\nabla c(\boldsymbol{x},t)) = D\nabla^2 c(\boldsymbol{x},t)) \tag{2}$$

This is the second law of Fick, known as *diffusion equation* and, if the medium is isotropic, it is similar to the heat equation. The symbol div means divergence and ∇^2 is the Laplace operator.

The Fick's equations are macroscopic. How can we explain the Brownian motion ?

Brownian motion

Random motion due to heat of particles suspended in a fluid. Each particle stays for a certain period τ in a precise location before moving to a random new location. Each particle acts independently ! **Microscopic movement**.



Einstein's contribution

Einstein reconciles the Fickian and the Brownian pictures by introducing the "displacement distribution" $p(\boldsymbol{x}, t|\boldsymbol{x}_0, t_0)$, which quantifies the fraction of particles moving from $\boldsymbol{x}_0$ at time t_0 to $\boldsymbol{x}$ after a time t at a fixed temperature. It obeys to the partial differential equation [2]:

$$\frac{\partial p(\boldsymbol{x}, t|\boldsymbol{x}_0, t_0)}{\partial t} = \mathrm{div}(D\nabla p(\boldsymbol{x}, t|\boldsymbol{x}_0, t_0)) \tag{3}$$

If $t_0 = 0$ the solution is the Gaussian distribution [2]:

$$p(\boldsymbol{x}, t|\boldsymbol{x}_0, 0) = \frac{1}{\sqrt{(2\pi Dt)^3}} \exp\left(-\frac{(\boldsymbol{x} - \boldsymbol{x}_0)^2}{4Dt}\right) \tag{4}$$

Einstein's equation

- If number of particles is large and they are free to diffuse, their ensemble average is:

$$\langle (\boldsymbol{x} - \boldsymbol{x}_0)^2 \rangle = 2Ddt \tag{5}$$

- This is the Einstein's equation where d is the number of dimension. $\langle (\boldsymbol{x} - \boldsymbol{x}_0)^2 \rangle$ refers to the mean squared displacement of the particles. It means that a particle in $\boldsymbol{x}_0$ at time $t_0 = 0$ will move in all directions around $\boldsymbol{x}_0$ with the same probability. The isoprobability surface is a sphere.

Apparent Diffusion Coefficient (ADC)

$$D = \frac{\langle (\boldsymbol{x} - \boldsymbol{x}_0)^2 \rangle}{2dt} \tag{6}$$

- The diffusion constant D relates the average displacement of the molecules over an area $(\boldsymbol{x} - \boldsymbol{x}_0)^2$ to the observation time t. *The higher the value of D, the more mobile the molecules !*
- As for the T_2 and T_2^* in the previous lecture, in the clinical setting we can not measure D but an Apparent Diffusion Coefficient (ADC or D_{eff}). Diffusion in vivo can not be separated from other sources of water mobility, such as the membrane permeability, due to the "low" MRI spatial resolution (i.e. mm).
- Typical values are $t = 10 - 50\ ms$, $\langle (\boldsymbol{x} - \boldsymbol{x}_0)^2 \rangle = 10 - 12\ \mu m^2$

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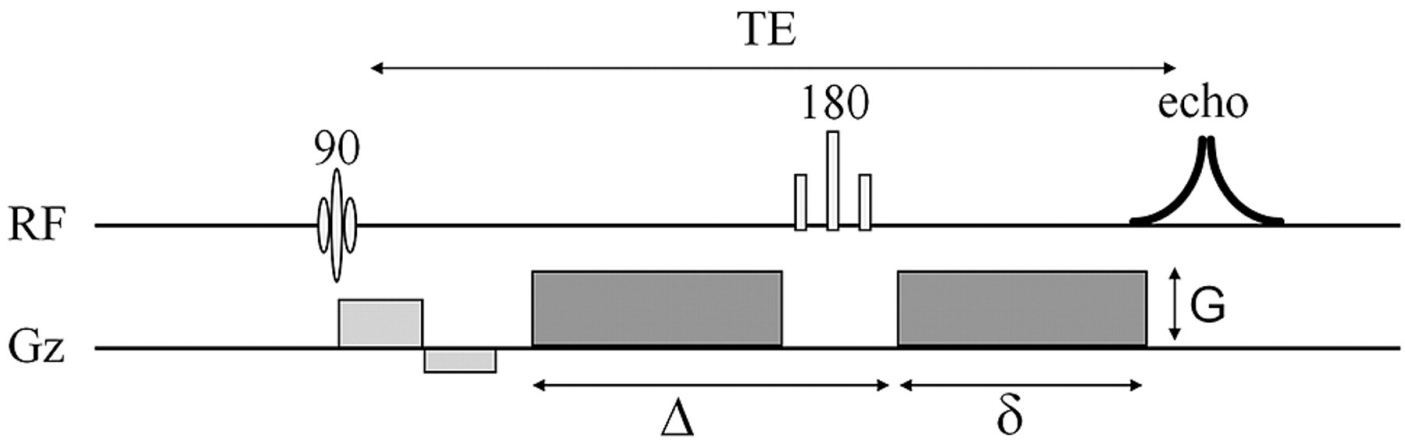
Stejskal-Tanner diffusion encoding



- A diffusion-weighted (DW) pulse is a T2-weighted spin-echo sequence with the addition of two diffusion gradients which are applied along the same axis before and after the 180° pulse. See Fig. from [3].
- The two gradients have the same magnitude G and duration δ but opposite direction (180°) ! Remember that we can choose any axis using combinations of G_x, G_y and G_z
- After the first gradient, protons begin to precess at different rates. Since the protons are moving, the second gradient will not refocus the spins and there will be a loss in the signal intensity

Diffusion weighted MRI

$$\frac{S_b^k}{S_0} = \exp(-b \cdot \text{ADC}) \tag{7}$$

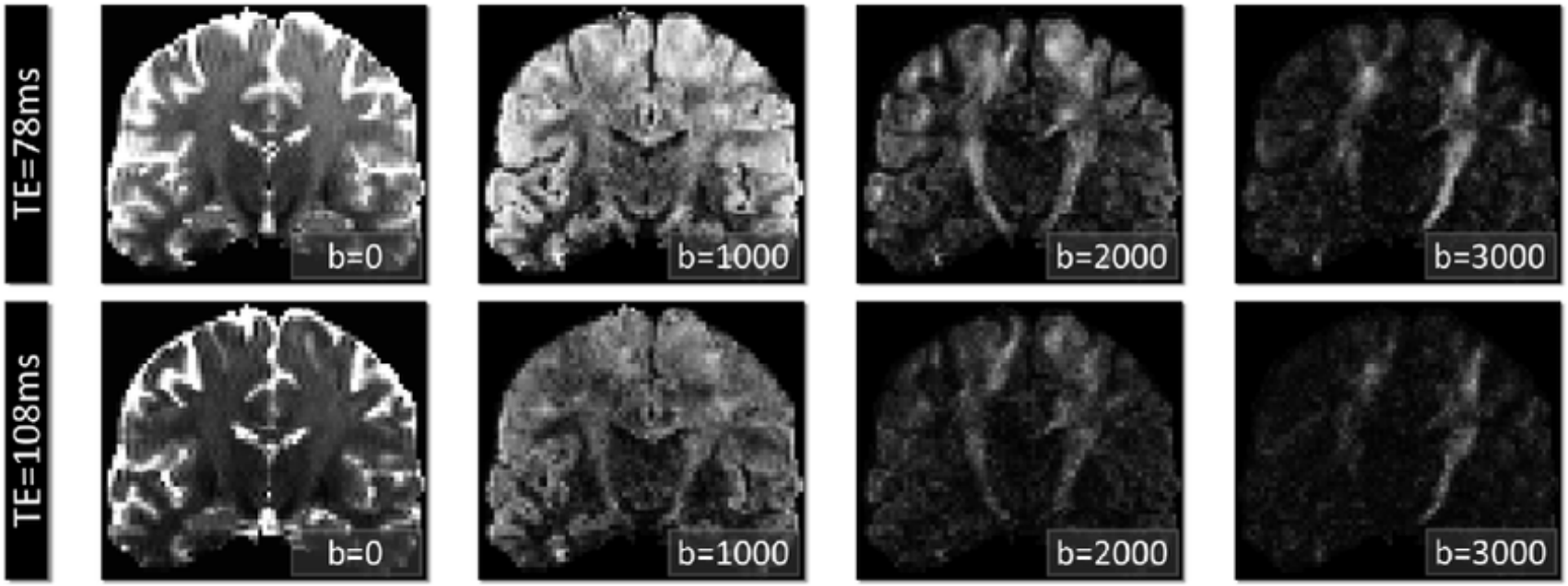
- S_b^k is the diffusion-weighted signal intensity with a gradient applied along a direction k, S_0 is the diffusion-weighted signal intensity without gradient and b is related to the degree of diffusion-weighting. Using rectangular pulses we have:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \tag{8}$$

- where γ is the gyromagnetic ratio and Δ is the span of time between the first gradient and the 180° pulse. Usual values of b are between 1000 and 3000.

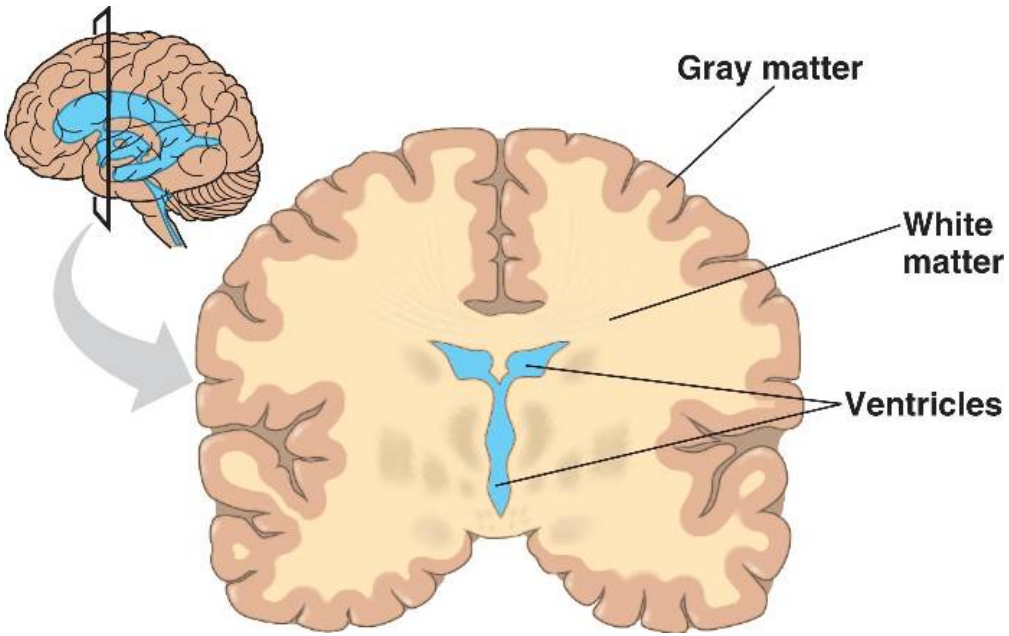
Diffusion weighted MRI

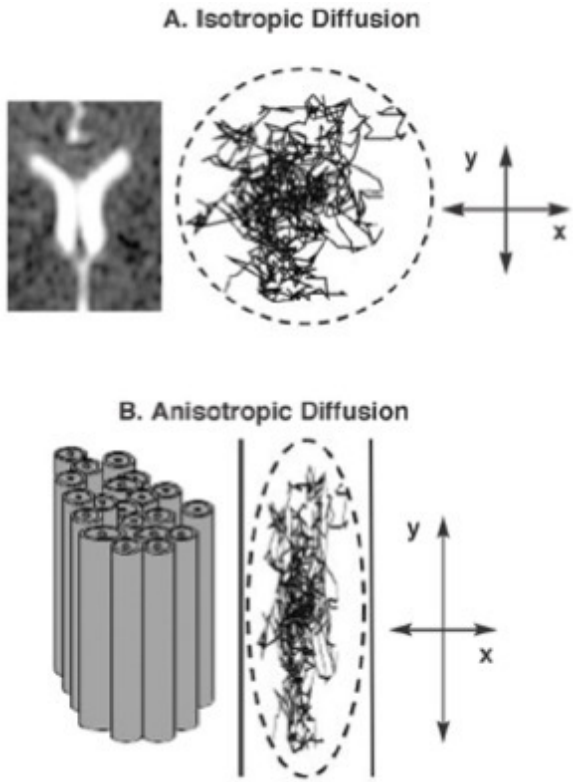
- By raising b we increase the loss of signal intensity. This means increasing either G and/or δ and/or Δ
- b and TE are linked by the relationship $TE \approx \left(\frac{12b}{\gamma^2}\right)^{1/3}$ [4]
- Higher b-values increase *contrast* but they also make DW MRI more sensitive to subject motion, lead to a longer TE and to a lower SNR. Trade-off (see Fig. from [4])



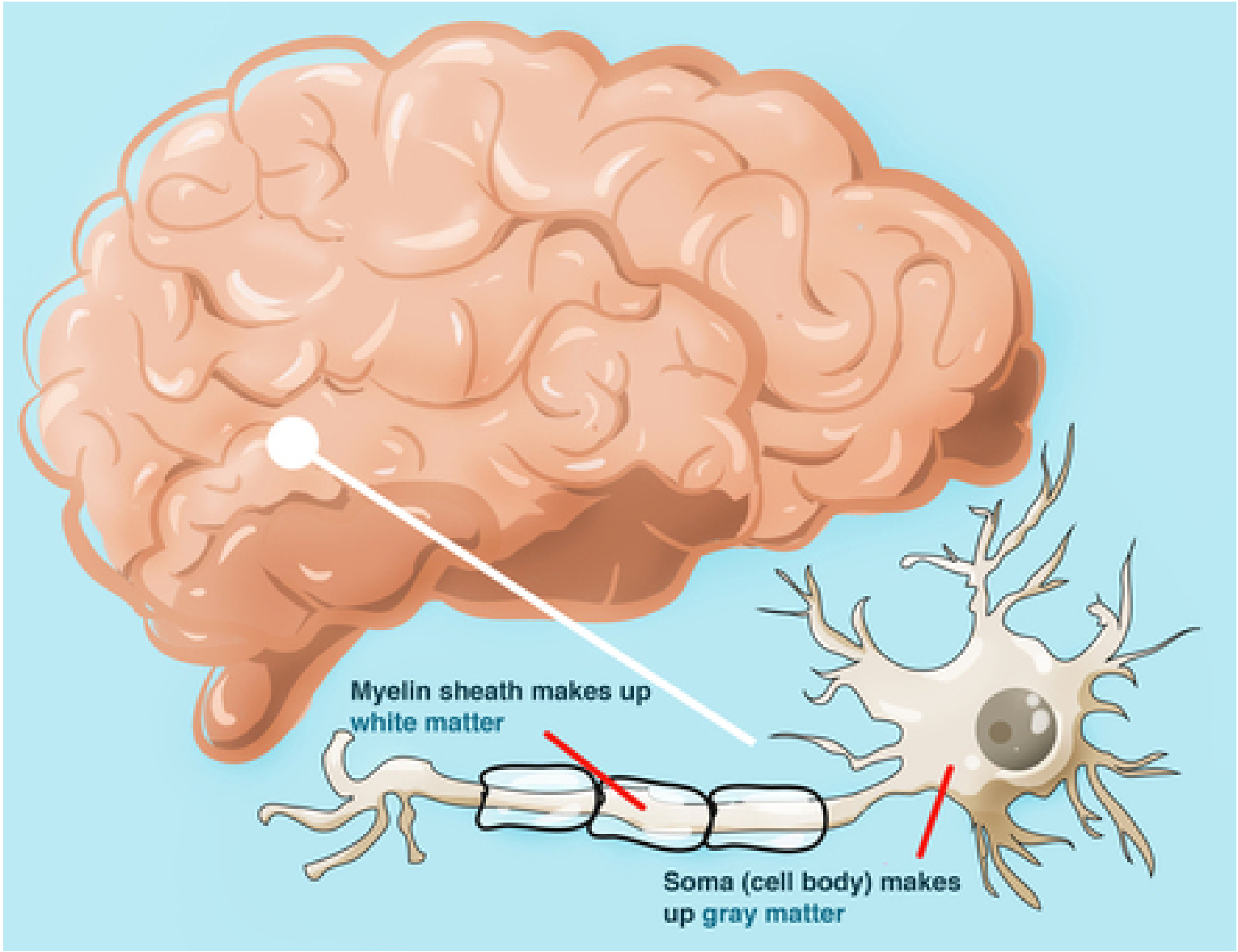
Diffusion weighted MRI

- In **isotropic** diffusion, molecular motion is equal in all directions. Examples in the human brain are the CSF and the gray matter.
- White matter tracts (mainly myelinated axons) make water molecules follow a precise direction (parallel to thh tract). **Anisotropic** diffusion.





Diffusion weighted MRI

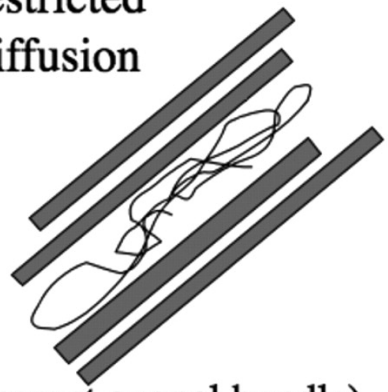
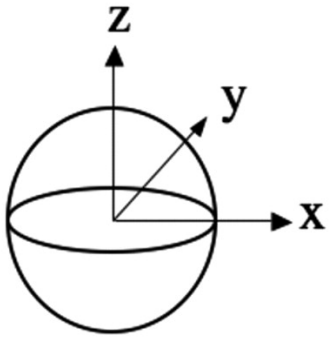
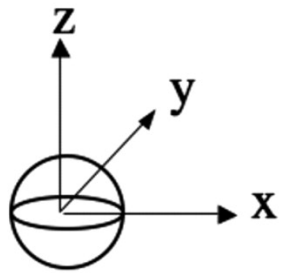
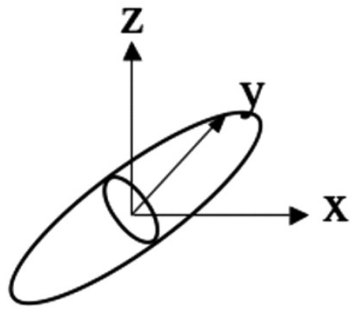


Diffusion tensor imaging

- For isotropic tissues we just need 2 image acquisitions: 1 without gradient $b = 0$ and 1 with a gradient in any direction
- For anisotropic tissues we need at least 7 image acquisitions: 1 without gradient $b = 0$ and 6 with gradients in different noncollinear directions $\rightarrow$ Diffusion tensor $\boldsymbol{D}$ can be calculated
- The diffusion tensor is a 3x3 covariance matrix which describes the ADC in the 3D space. The diagonal elements ($D_{ij} > 0$) are the diffusion variances along the three orthogonal directions x, y and z. The off-diagona elements are the covariance terms between the three directions.

$$\boldsymbol{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \tag{9}$$

Diffusion tensor imaging

	Isotropic, unrestricted diffusion	Isotropic, restricted diffusion	Anisotropic, restricted diffusion
Diffusion Trajectory	 (free water)	 (random barriers present)	 (coherent axonal bundle)
Diffusion Ellipsoid			
Diffusion Tensor	$\begin{bmatrix} D & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & D \end{bmatrix}$	$\begin{bmatrix} D_{eff} & 0 & 0 \\ 0 & D_{eff} & 0 \\ 0 & 0 & D_{eff} \end{bmatrix}$ $D_{eff} < D$	$\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$

Diffusion tensor imaging

- We can rewrite the previous equations using a tensor $\boldsymbol{D}$ instead than a scalar D:

$$\boldsymbol{J} = -\boldsymbol{D}\nabla c(\boldsymbol{x}, t) \tag{10}$$

$$p(\boldsymbol{x}, t|\boldsymbol{x}_0, 0) = \frac{1}{\sqrt{(4\pi t)^3|\boldsymbol{D}|}} \exp\left(-\frac{(\boldsymbol{x}-\boldsymbol{x}_0)^T\boldsymbol{D}^{-1}(\boldsymbol{x}-\boldsymbol{x}_0)}{4t}\right) \tag{11}$$

$$\frac{S_b}{S_0} = \exp - \left(\sum_{i=x,y,z}\sum_{j=x,y,z} b_{i,j}D_{i,j}\right) \tag{12}$$

$$b_{i,j} = \gamma^2 G_i G_j(\delta^2(\Delta - \delta/3)) \tag{13}$$

Diffusion tensor imaging

$$\begin{aligned}\log \frac{S_b}{S_0} = &- b_{x,x}D_{x,x} - b_{y,y}D_{y,y} - b_{z,z}D_{z,z} \\ &- 2b_{x,y}D_{x,y} - 2b_{x,z}D_{x,z} - 2b_{y,z}D_{y,z}\end{aligned} \tag{14}$$

- We have six unknowns to estimate. Thus we need at least 6 diffusion-encoding images (i.e. gradients) from different noncollinear directions, in addition to one acquisition with $b = 0$
- We perform N ($N > 6$) measurements (i.e. gradients) in different non-collinear directions

Diffusion tensor imaging

- Let $\boldsymbol{S}$ be the $[N, 1]$ vector containing $[\log \frac{S_b^1}{S_0}, ..., \log \frac{S_b^k}{S_0}, ..., \log \frac{S_b^N}{S_0}]^T$ for every measurement k
- Let $\boldsymbol{B}$ be the $[N, 6]$ matrix containing the values of b:

$$\boldsymbol{B} = - \begin{bmatrix} b_{xx}^1 & b_{yy}^1 & b_{zz}^1 & 2b_{x,y}^1 & 2b_{x,z}^1 & 2b_{y,z}^1 \\ ... & ... & ... & ... & ... & ... \\ b_{xx}^k & b_{yy}^k & b_{zz}^k & 2b_{x,y}^k & 2b_{x,z}^k & 2b_{y,z}^k \\ ... & ... & ... & ... & ... & ... \\ b_{xx}^N & b_{yy}^N & b_{zz}^N & 2b_{x,y}^N & 2b_{x,z}^N & 2b_{y,z}^N \end{bmatrix} \tag{15}$$

- Let $\boldsymbol{d}$ be the $[6, 1]$ vector containing the values of $\boldsymbol{D}$: $[D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}]$
- It results: $\boldsymbol{S} = \boldsymbol{B}\boldsymbol{d}$

Diffusion tensor imaging

- How to find the diffusion coefficients in $\boldsymbol{d}$ from the Eq. $\boldsymbol{S} = \boldsymbol{B}\boldsymbol{d}$?
- Inverse: $\boldsymbol{d} = \boldsymbol{B}^{-1}\boldsymbol{S} \rightarrow$ it works with square matrix, only 6 measurements, we perfectly fit the data, even the noise !
- More measurements to reduce the effect of the noise. No more square matrix. One could then minimize $||\boldsymbol{S} - \boldsymbol{B}\boldsymbol{d}||_F^2$ which is OLS (Ordinary Least Squares): $\boldsymbol{d} = (\boldsymbol{B}^T\boldsymbol{B})^{-1}\boldsymbol{B}^T\boldsymbol{S}$
- OLS assumes homoskedasticity (variance of elements in $\boldsymbol{S}$ is the same) but this is not true since we take log. We will have higher variance for low signal and viceversa. A possible solution is to use a weighted least square approach: $\boldsymbol{d} = (\boldsymbol{B}^T\Sigma^{-1}\boldsymbol{B})^{-1}\boldsymbol{B}^T\Sigma^{-1}\boldsymbol{S}$ where Σ is a diagonal matrix with the squares of S_{bi}^k
- Due to the $\exp$ term, non-linear regression techniques can also be applied directly on $\frac{S_{bi}}{S_0}$.

Diffusion tensor imaging - Considerations

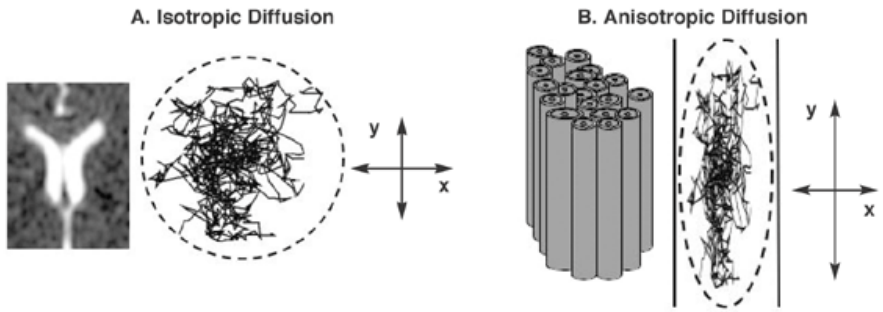
- Accuracy of DTI depends on the number of measurements (i.e. gradient directions) $\rightarrow$ more measurements, less noise, more scan time !
- Image SNR can be improved by using larger voxels $\rightarrow$ increase partial volume effect (i.e. mix/average of different tissues) !

Diffusion tensor parameters

- The three principal diffusion axes are the eigenvectors of $\boldsymbol{D}$:

$$\boldsymbol{W}^T \boldsymbol{D} \boldsymbol{W} = \boldsymbol{\Lambda} = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \tag{16}$$

- where the columns of $\boldsymbol{W}$ are the eigenvectors of $\boldsymbol{D}$ and the λ_i are the relative eigenvalues
- $\boldsymbol{w}_1$ and λ_1 indicate the direction and magnitude of greatest water diffusion (principal direction of axonal bundle)



Diffusion tensor parameters

Different diffusion metrics are used to describe the microstructure in each voxel. The two most important ones are:

- Average diffusivity $D_{av} = \mathrm{Tr}(\boldsymbol{D})/3$. This is also called *magnitude of diffusion* (MD) or ADC
- Fractional Anisotropy (FA):

$$\mathrm{FA} = \sqrt{\frac{3}{2}}\sqrt{\frac{(\lambda_1 - D_{av})^2 + (\lambda_2 - D_{av})^2 + (\lambda_3 - D_{av})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \tag{17}$$

- FA is 0 when the the diffusion in the voxel is perfectly isotropic and 1 when is perfectly anisotropic, namely diffusion occurs only along the first eigenvector.

Diffusion tensor parameters

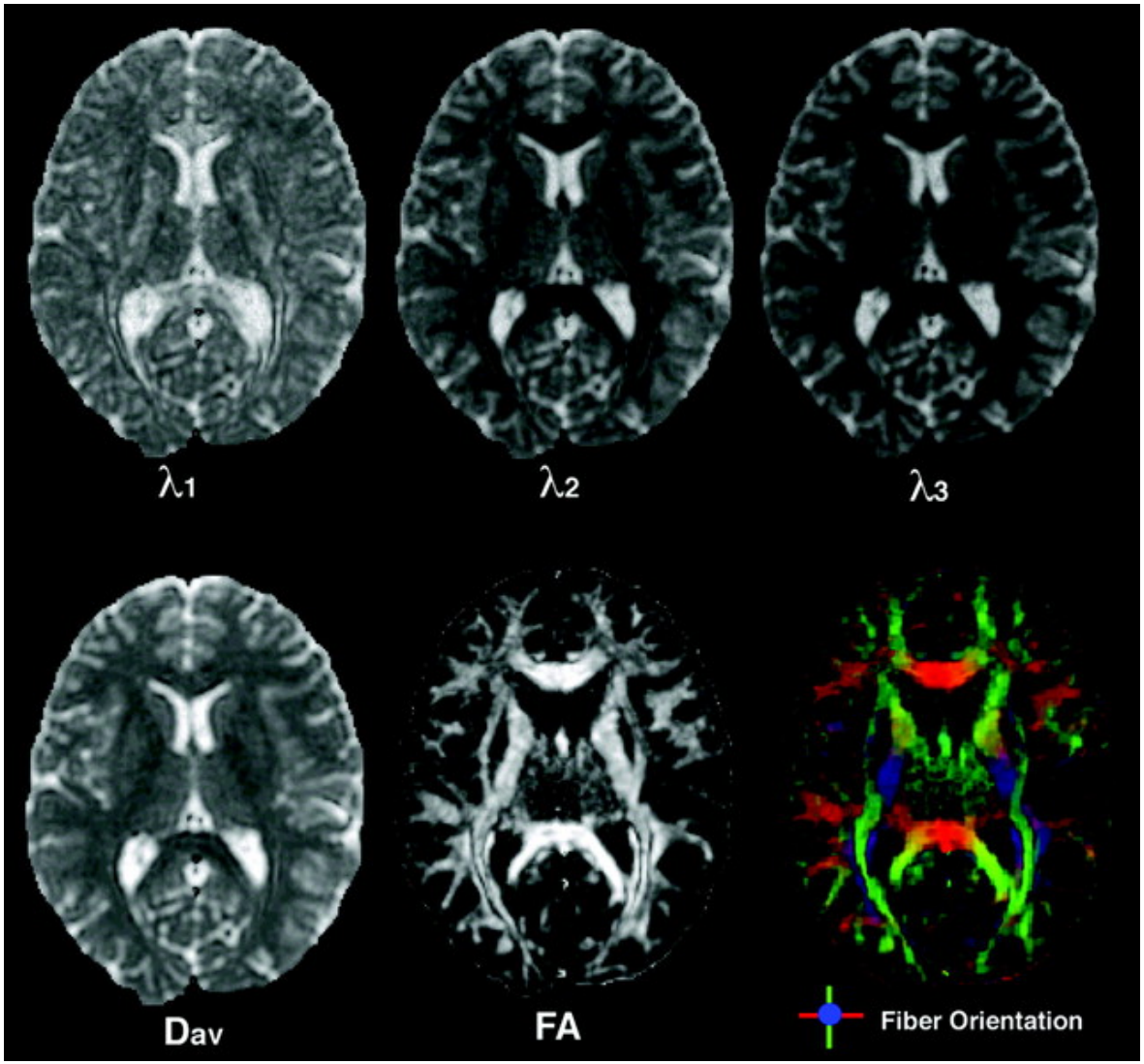


Figure 1: Image taken from [3]

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Fiber tractography

- **Fiber tractography** is the most advanced technique to model and visualize neural pathways
- It uses the directional information from diffusion measurements at each voxel to estimate the trajectories of the neural pathways
- It can be divided into *deterministic* and *probabilistic* methods.
- Deterministic methods use only the main direction at each voxel (e.g. principal eigenvector)
- Probabilistic methods compute a probability density function of possible trajectories

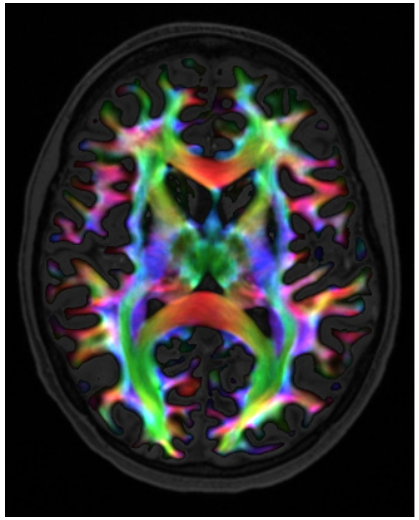
Deterministic streamline tractography

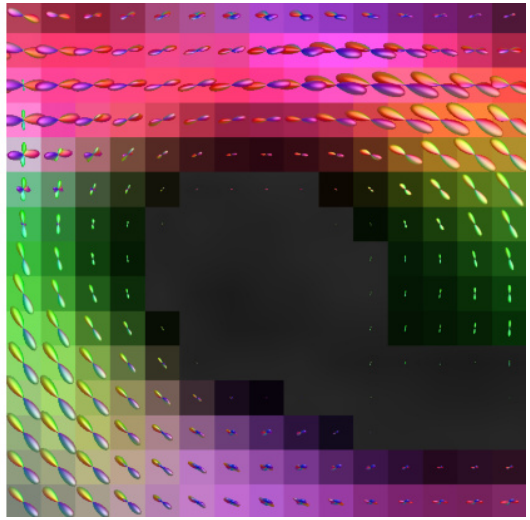
- Streamlines (or fibers) are estimated by integrating the PDE:

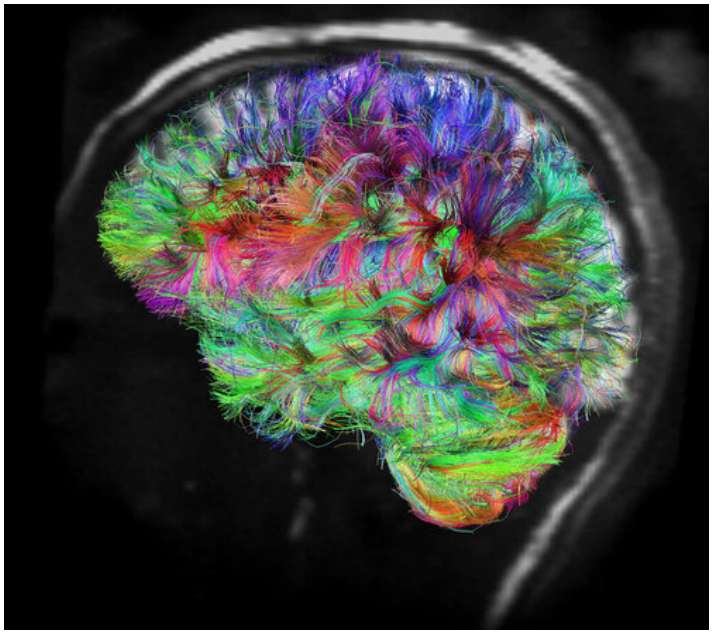
$$\frac{\partial \boldsymbol{r}(t)}{\partial t} = v(\boldsymbol{r}(t)) \tag{18}$$

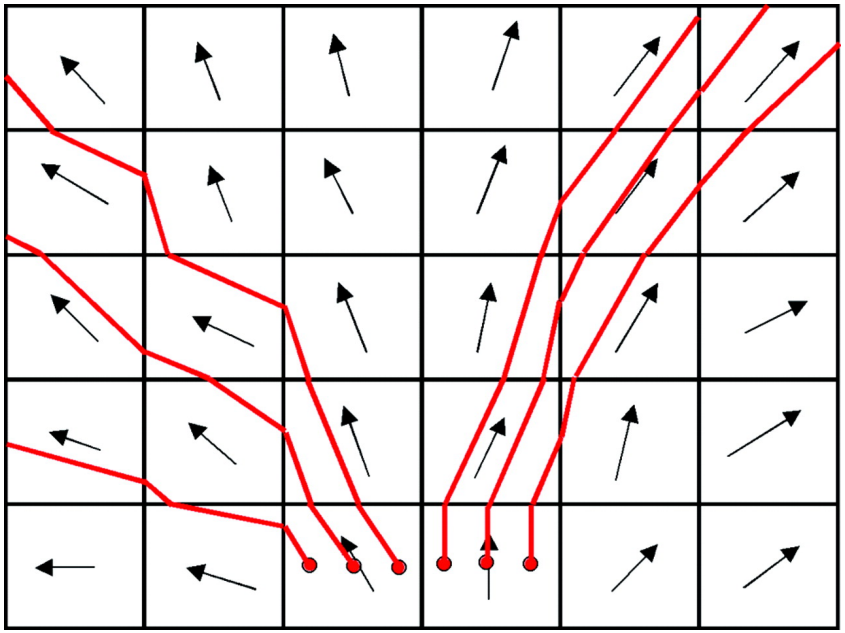
- where $\boldsymbol{r}$ is the path, t is the "time" step and v is the vector field defining the tangent to local path direction [2].
- Most of the algorithms use the principal eigenvector $\boldsymbol{e}_1$ at each voxel as v and they approximate Eq.18 using a Taylor expansion: $\boldsymbol{r}(t_{k+1}) \approx \boldsymbol{r}(t_k) + \tau \boldsymbol{e}_1(\boldsymbol{r}(t_k))$
- Starting from a "seed" location within a voxel $\boldsymbol{r}(t_k)$, we compute the eigenvector $\boldsymbol{e}_1$ of the voxel and we move along that trajectory of a step-size τ

Deterministic streamline tractography









Fiber tractography - Stopping criteria and constraints

- We can put several seeds within a certain ROI or within the entire brain (whole brain tractography) $\rightarrow$ first strategy may lead to incomplete tract reconstruction, second strategy is preferred
- Common stopping criteria are: low FA (e.g. FA$<$0.2), bending angle too high (it depends on the bundle), mask of white matter used as boundary
- Common post-processing in clinics and research: after a whole-brain tractography a specific neuro-anatomical tract is selected by manually drawing one or more ROIs

Fiber tractography - Stopping criteria and constraints

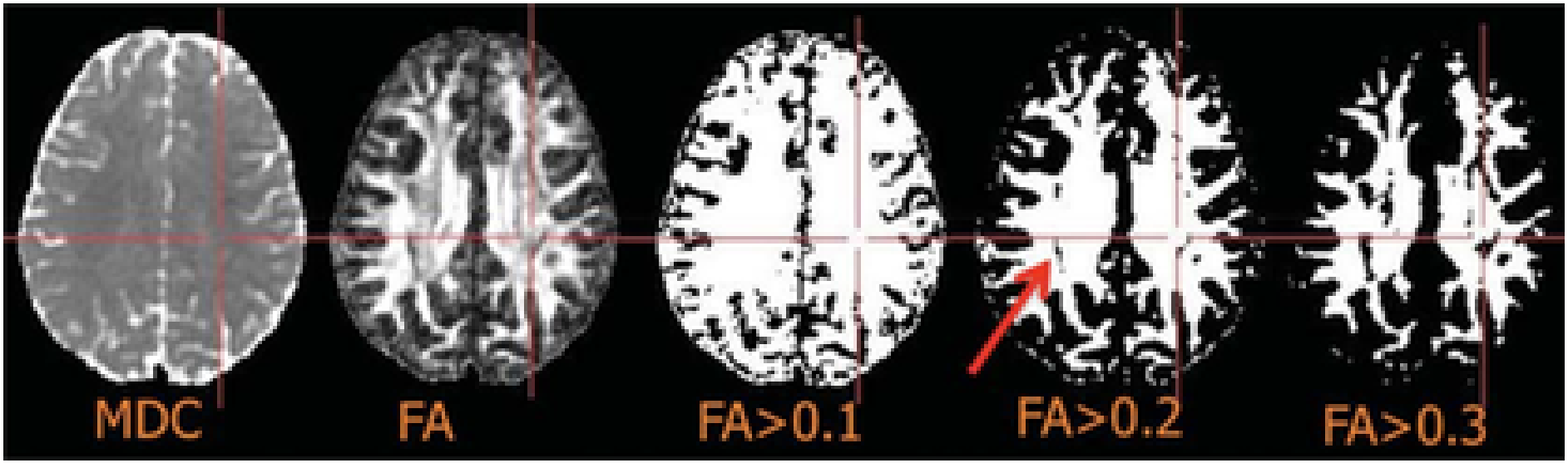


Figure 2: Image taken from [2]

DTI - Applications

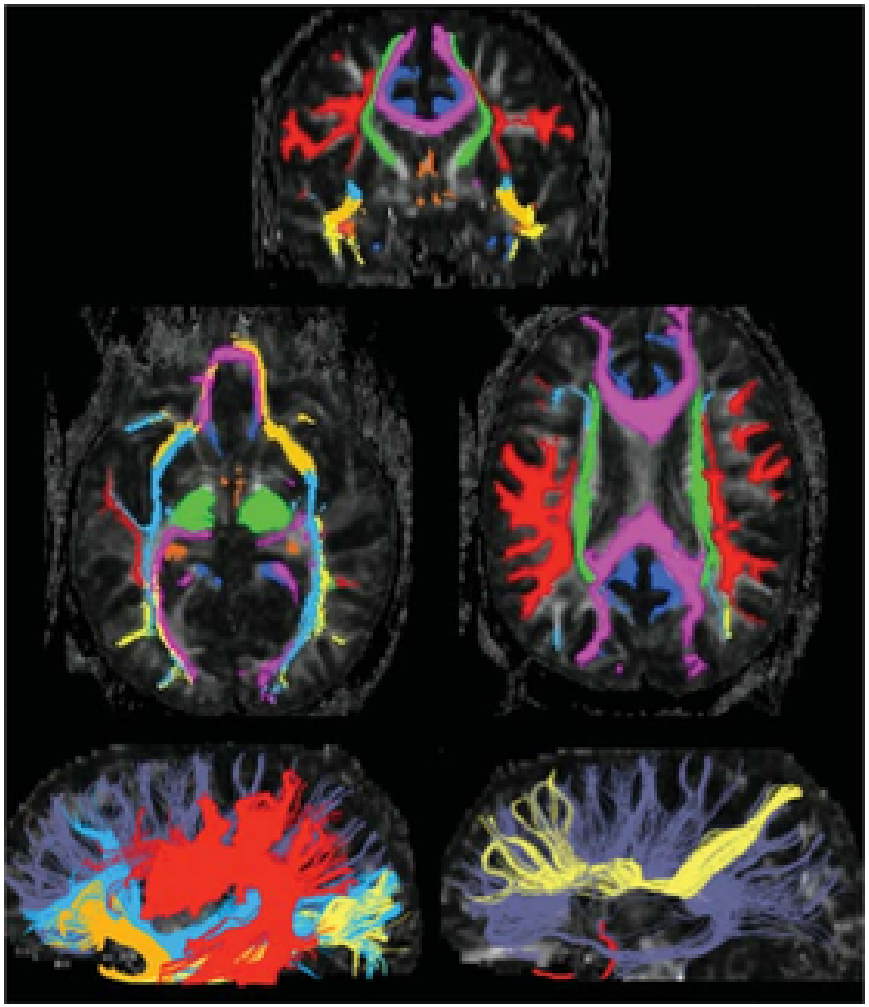


Figure 3: Segmentation of major white matter pathways of the brain. Image taken from [2]

DTI - Applications

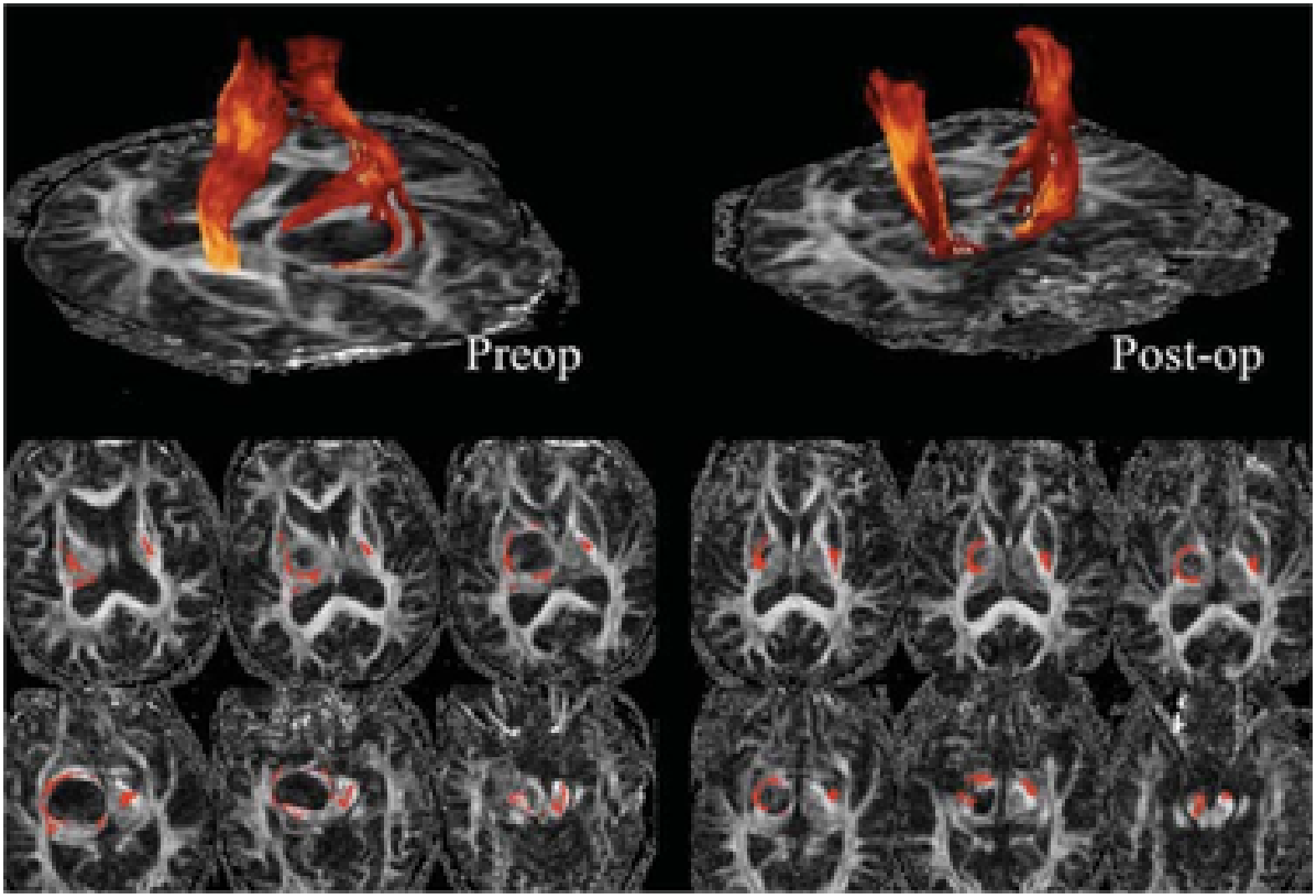


Figure 4: Comparison of corticospinal tract before and after surgical resection of tumor. Image taken from [2]

DTI - Limitations

- **Crossing fibers**: when in a voxel we have a crossing between two neural pathways a single-tensor model is inaccurate $\rightarrow$ principal eigenvector might not be coincident with the direction of the neural pathways
- Possible solutions: multiple tensor or advanced diffusion image acquisition methods such as Q-ball, diffusion spectrum imaging and HARDI [2].

DTI limitations

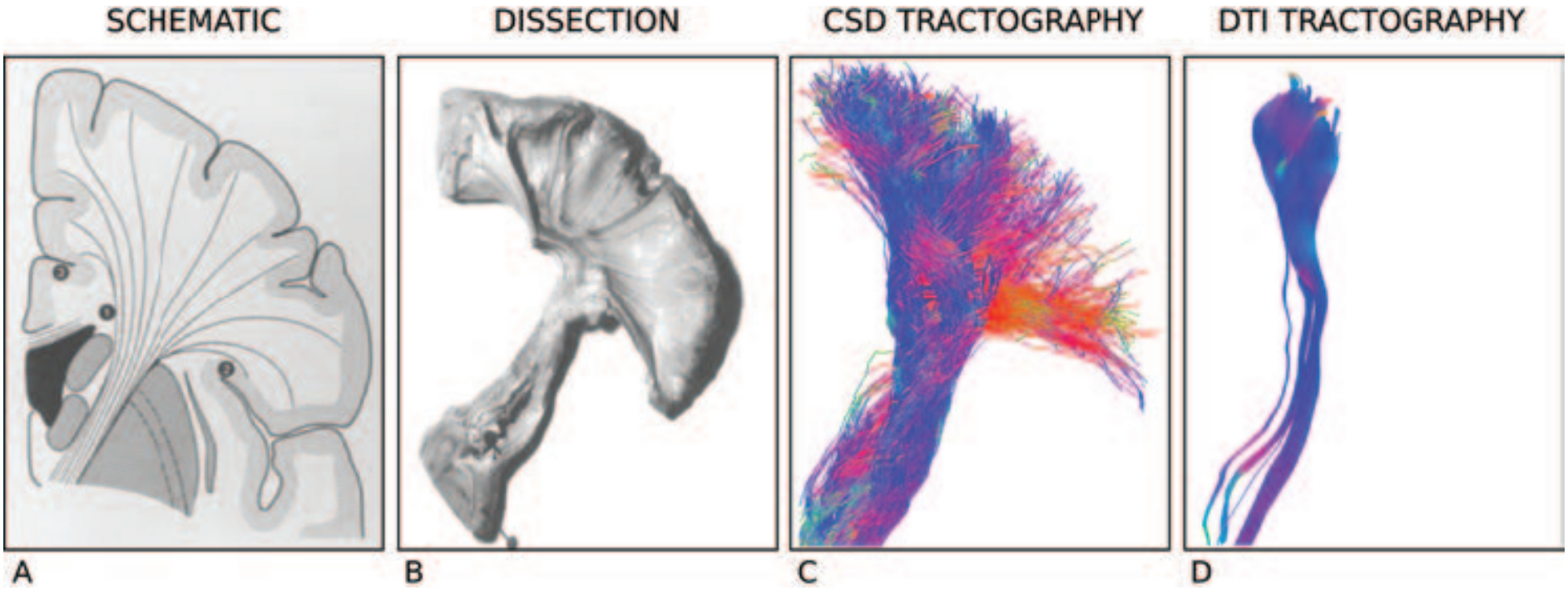
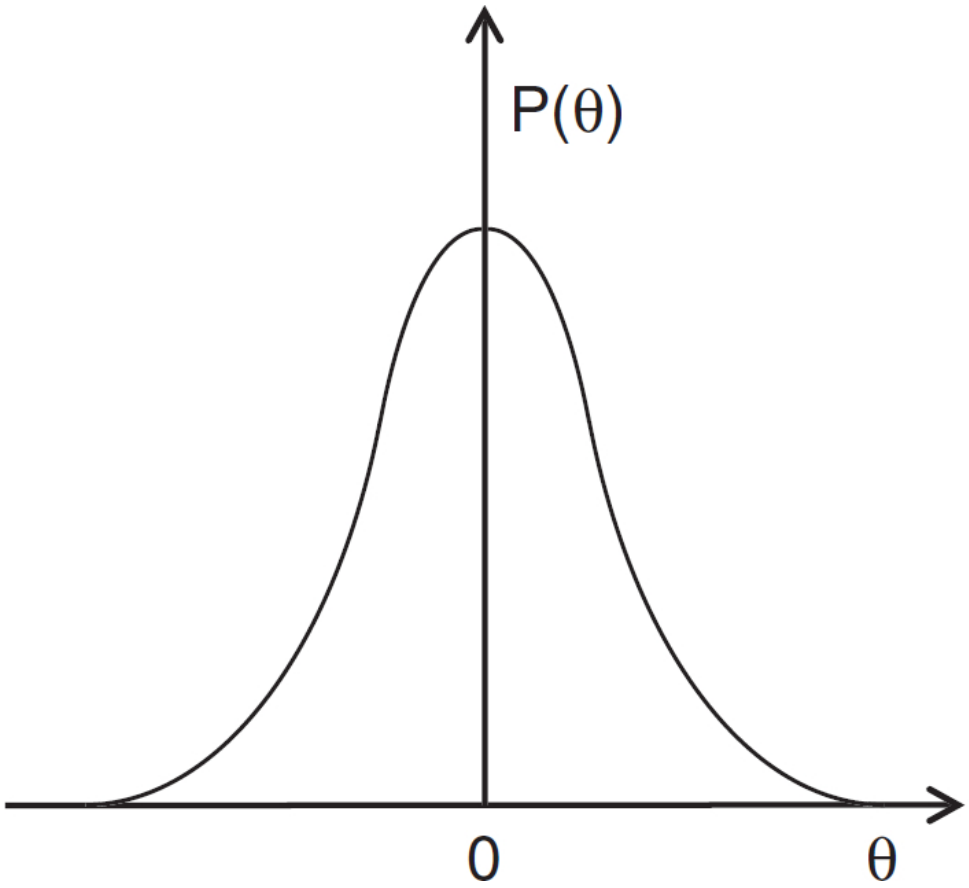


Figure 5: Comparison of two diffusion models: DTI and CSD (constrained spherical deconvolution). Image taken from "*J Neurosurg 118, 2013*"

Probabilistic tractography

- Noise in the data, coarse voxel resolution (partial volume/bundle effect), imperfect model of diffusion $\rightarrow$ limitations for correct estimate of neural pathways from DWI data.
- Instead than using e_1 one can compute the *pdf* of the fiber orientation, using Gaussian distributions, Bayesian methods or bootstrap methods, and sample a direction from this distribution
- From every seed, we create several streamlines (i.e. 1000) where we sample each time a different direction at each voxel $\rightarrow$ this provides a degree of dispersion of the fibers due to uncertainty in the data

Probabilistic tractography



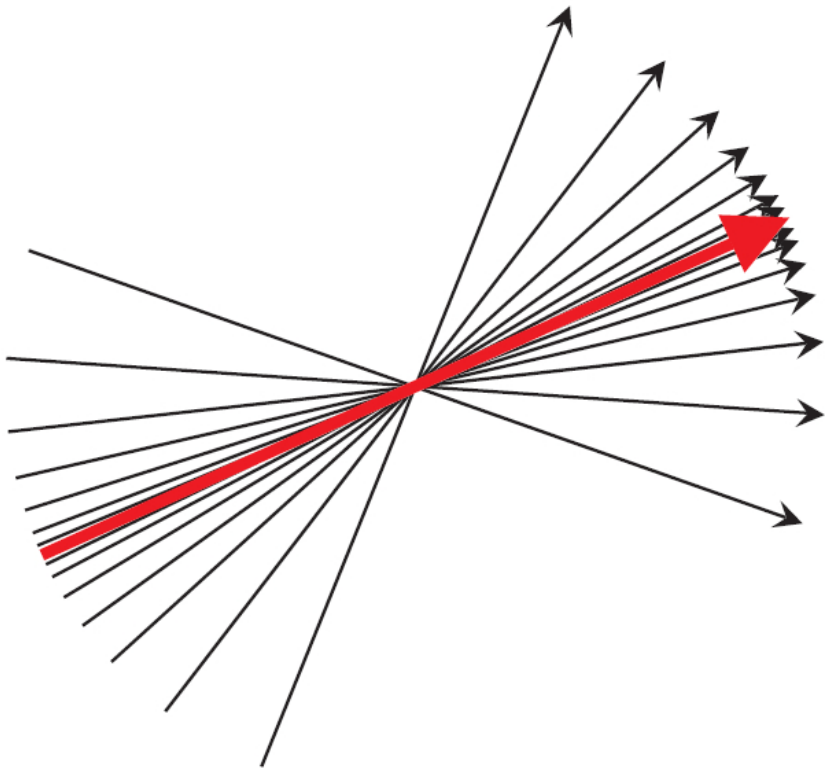


Figure 6: Pdf of fiber orientation with a single neural pathway. Image taken from [2]

Probabilistic tractography

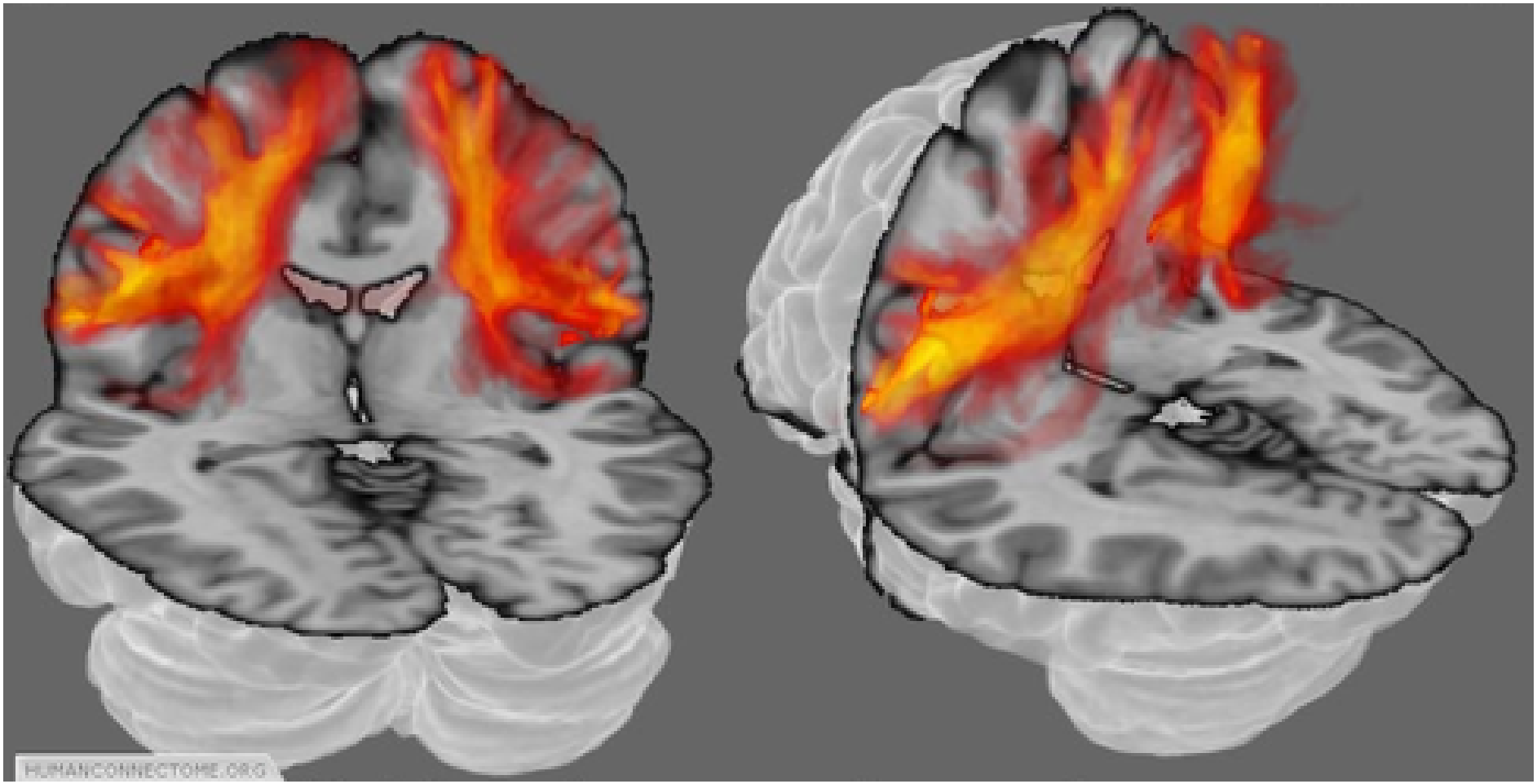


Figure 7: Connectivity distributions estimated with probabilistic tractography. Image taken from HCP.

Probabilistic Vs Deterministic tractography

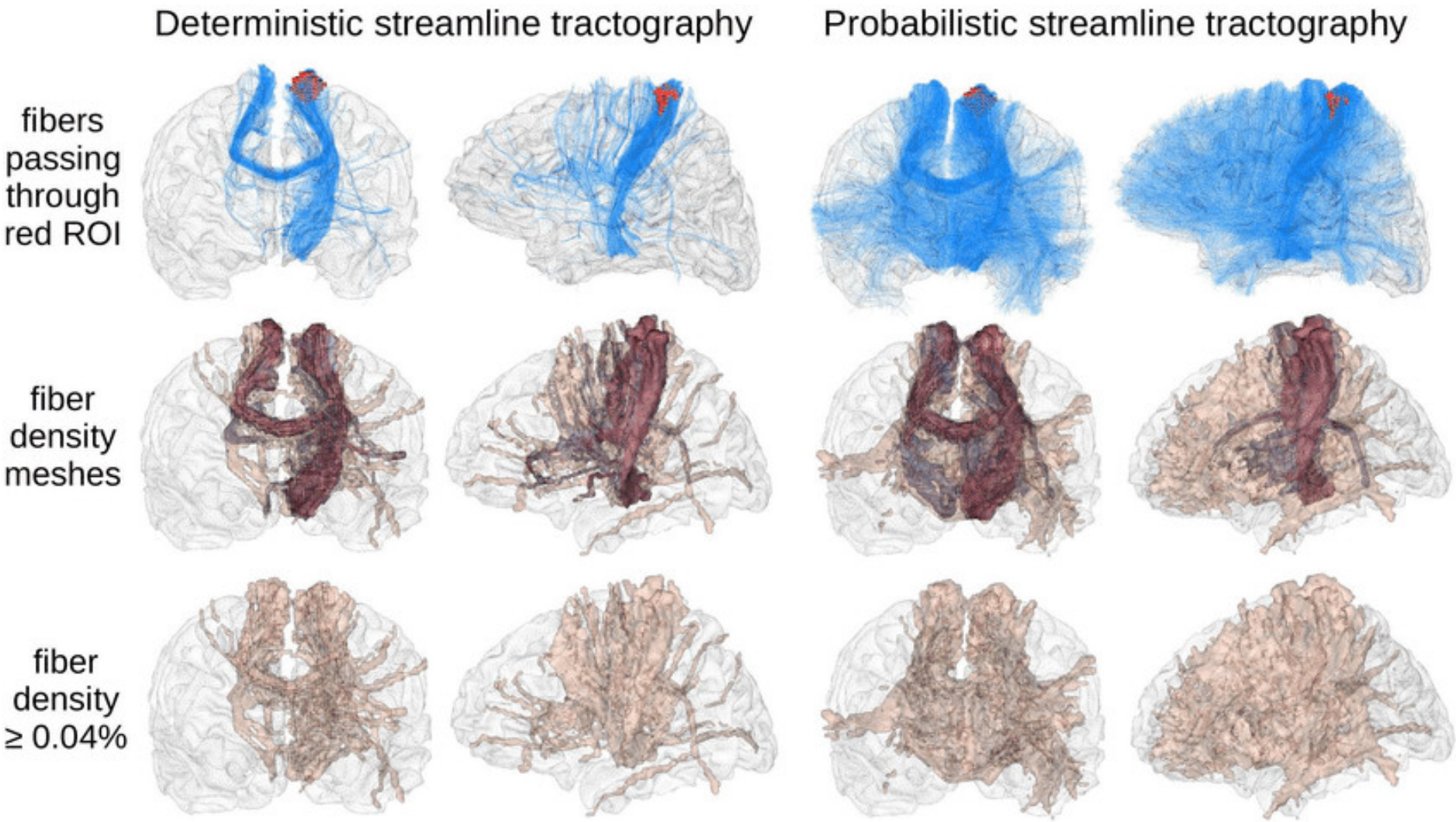


Figure 8: Image taken from the PhD Thesis of P. Guevara

Diffusion MRI - Conclusions

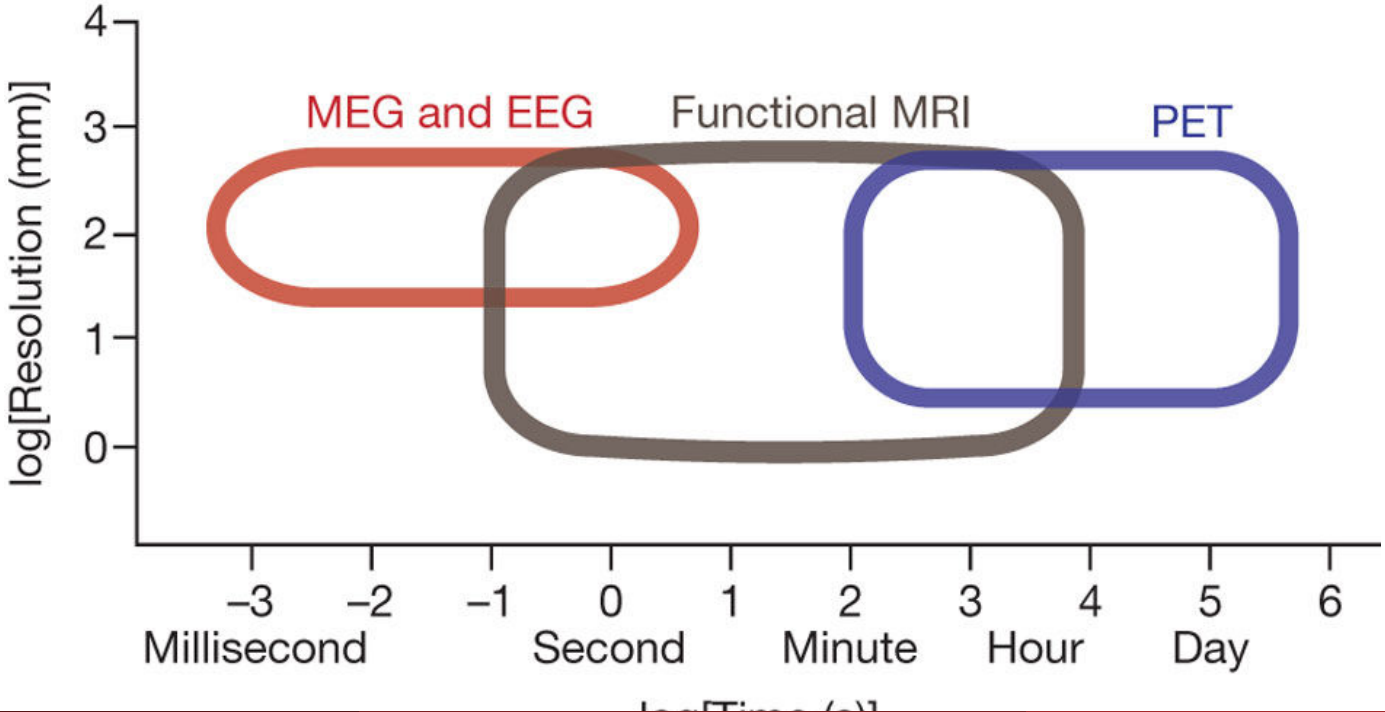
- Anisotropic diffusion in white matter. Isotropic diffusion in gray matter and CSF.
- Diffusion tensor can describe orientation of neural pathways at each voxel $\rightarrow$ problem with crossing fiber
- Tractography estimates the trajectory of many axons (neural pathways) within the white matter of the brain and it models/visualizes them as 3D polylines $\rightarrow$ due to the coarse resolution of DWI (mm^3) we can not model single axons (μm)
- Probabilistic tractography estimates a pdf of fiber orientation at each voxel and not only the most likely direction as in the deterministic tractography

Summary

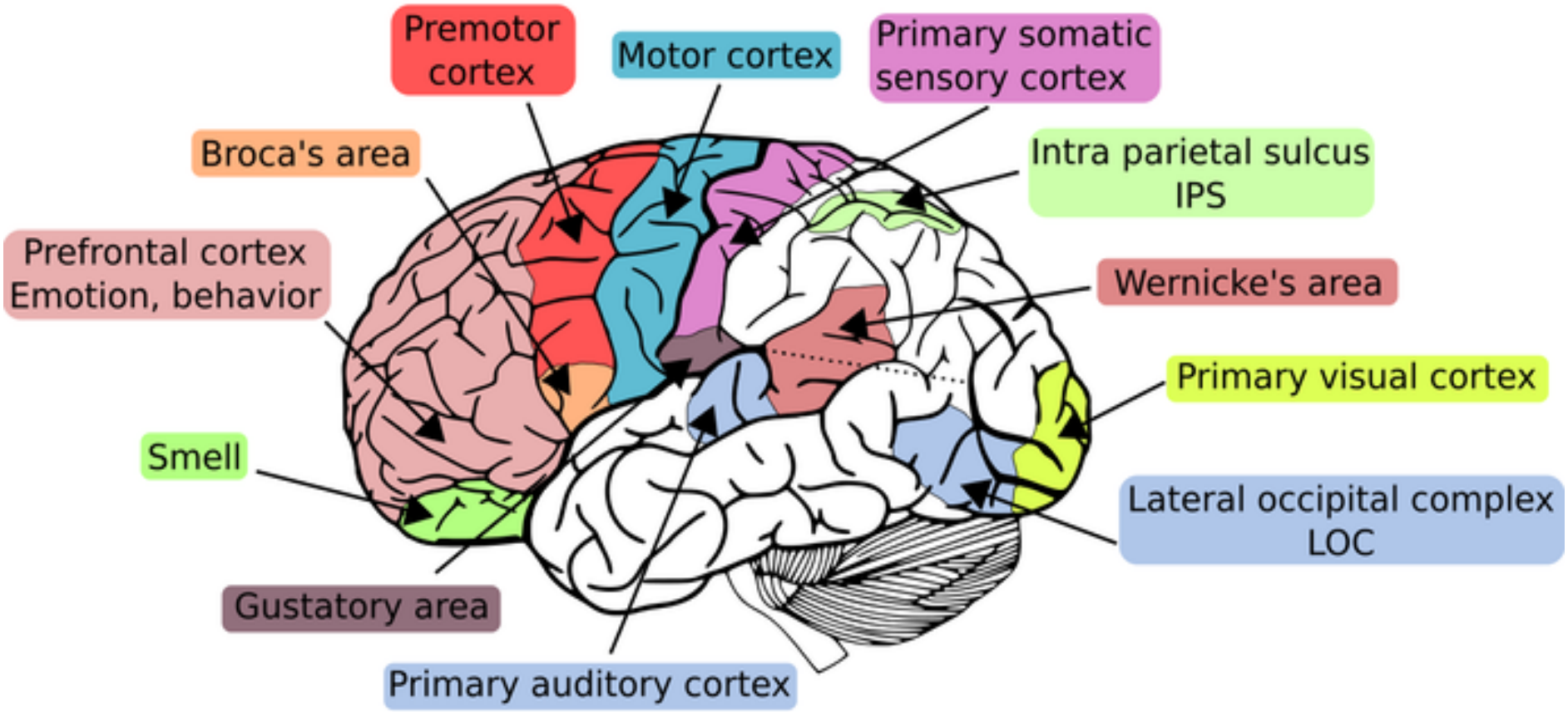
1. Introduction
2. Diffusion Weighted MRI
   - Diffusion tensor imaging
3. Tractography
4. Functional NeuroImaging (EEG and MEG)

Functional NeuroImaging

- PET
  - low temporal and spatial resolution
- f-MRI
  - good spatial resolution
  - average temporal resolution
- EEG, MEG
  - very good temporal resolution
  - good spatial resolution (especially MEG) but no direct localization

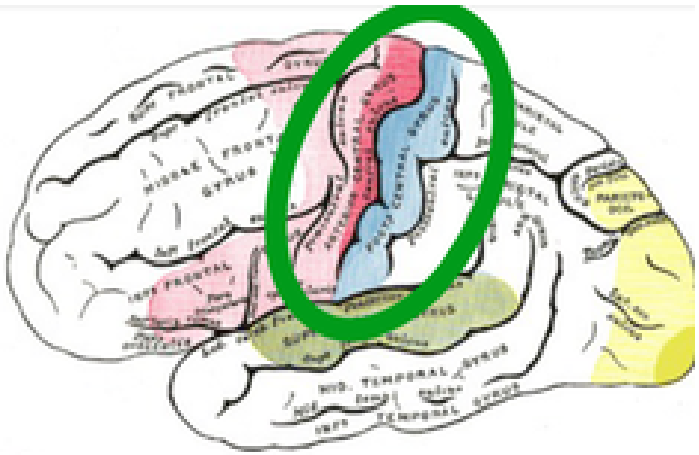


Relation between anatomy and function

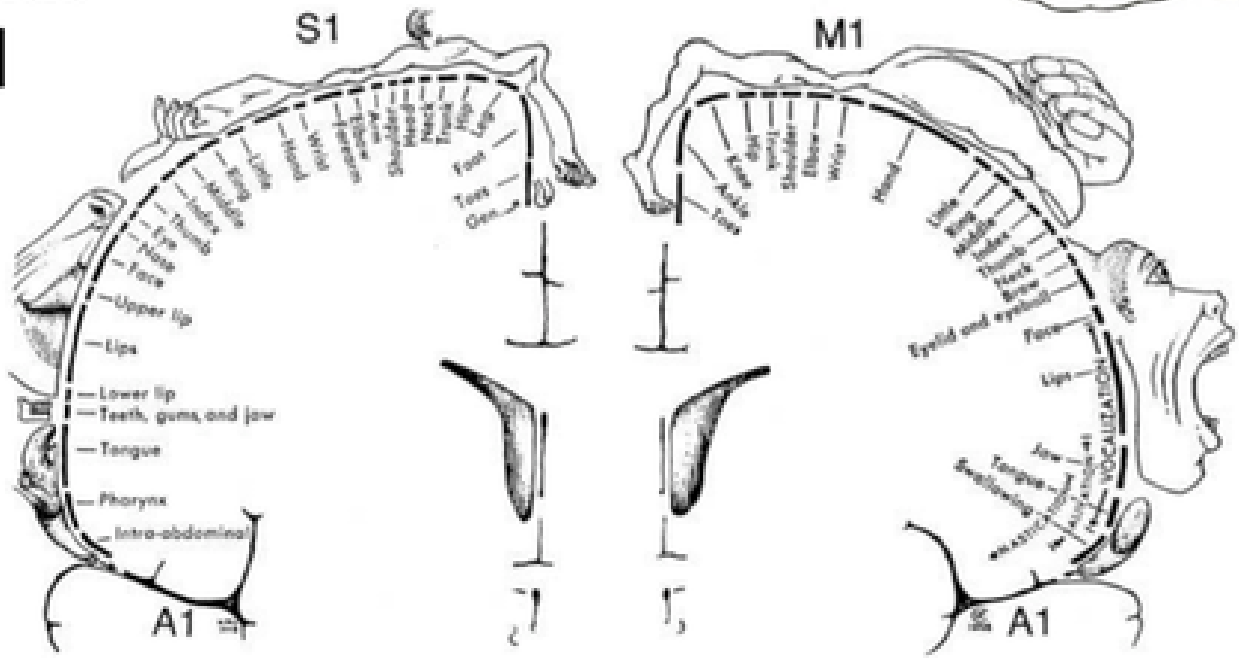


Cortex of the brain can be divided in areas which are dedicated to a certain motor or sensory function

Relation between anatomy and function



Homonculus
[Penfield 50]



Primary Somatosensory Cortex (S1)

Primary Motor Cortex (M1)

Neurons as current generators

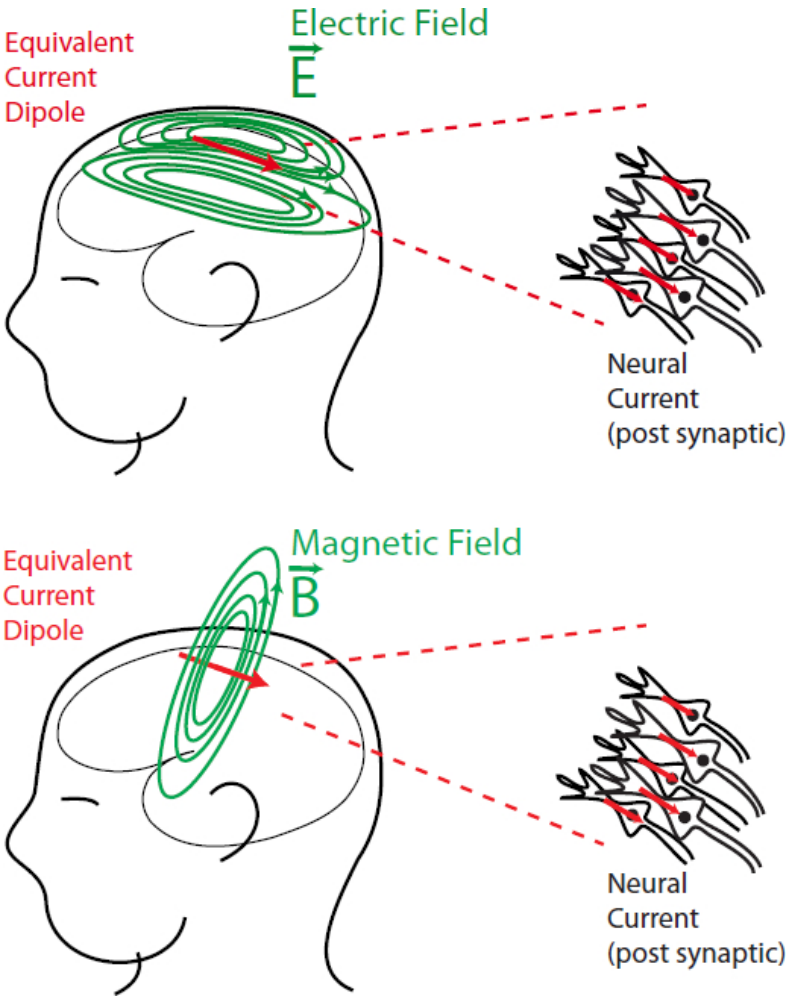


Figure 9: Source: A. Gramfort

- Sensory stimuli activates neurons of the cortex $\rightarrow$ neurons generate time-varying local electrical currents (currents dipoles model [5])
- According to the Maxwell's equations, we can compute electric potential (EEG) and magnetic fields (MEG)

Neurons as current generators

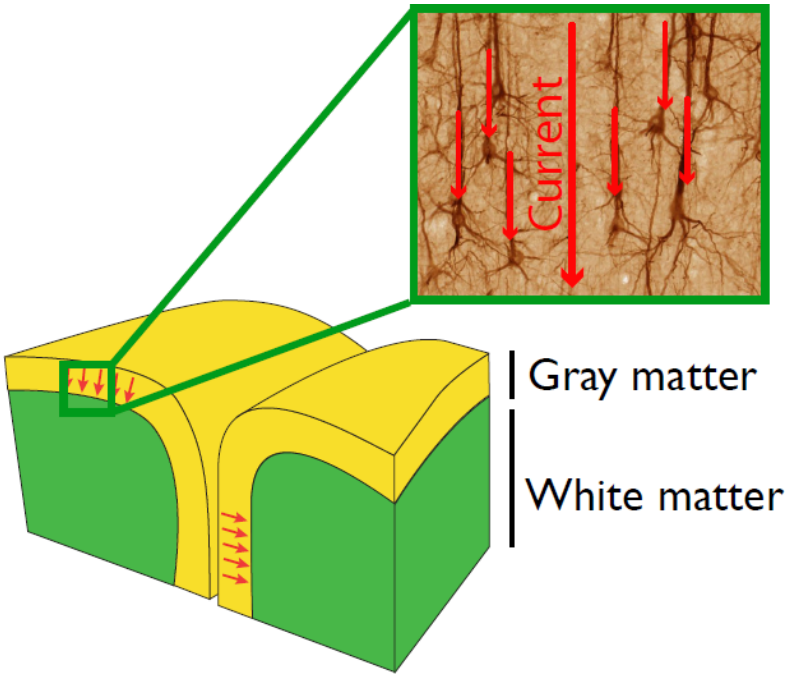


Figure 10: Source: A. Gramfort

- To generate a detectable signal, we need thousands of neurons spatially aligned and synchronously activated $\rightarrow$ Pyramidal cells are the major contributor to EEG/MEG. They are perpendicular to the cortical surface

Electroencephalography (EEG)

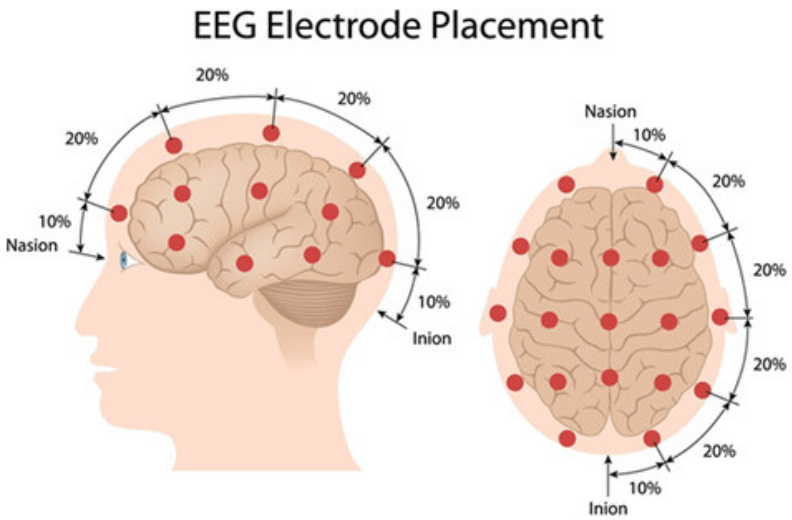


Figure 11: The international 10-20 system for scalp electrodes placement

- Discovered in 1875 by Richard Caton
- Electrodes are placed in precise and reproducible locations along the scalp
- Electrodes can be non-invasive and invasive
- Recording lasts typically between 15-30 minutes
- Up to 256 electrodes using a cap or a net

Magnetoencephalography (MEG)

Figure 12: Example of magnetically shielded room. From Wikipedia.

- Discovered in 1968 by David Cohen
- Signals emitted by the brain (fT) are smaller than Earth's magnetic field and magnetic noise (μT) $\rightarrow$ magnetic shielding is necessary
- Very sensitive magnetometer are needed to measure the subtle magnetic field of the brain. Most used is SQUID (superconducting quantum interference device)

Magnetoencephalography (MEG)

Figure 13: Example of MEG

- Non-invasive
- No magnets, no X-rays
- Almost no noise
- Patient can sit or lay down
- Record signals from up to 300 sensors simultaneously
- MEG device is 10 to 100 times more expensive than an EEG system

M/EEG Measurements

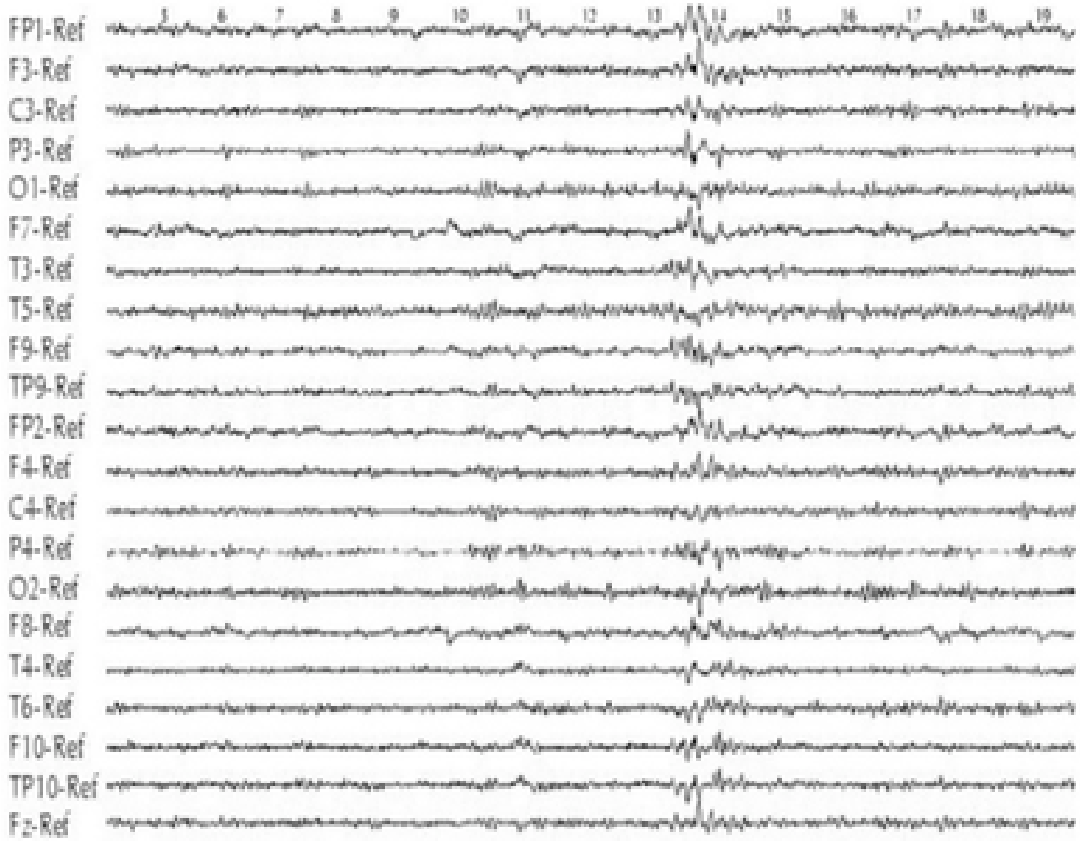


Figure 14: Example of EEG signals. Sampling is usually between 250 and 1000 Hz.

- High temporal resolution. What about spatial resolution ?

M/EEG Measurements

- At each time instant EEG sensors measure an electric potential field

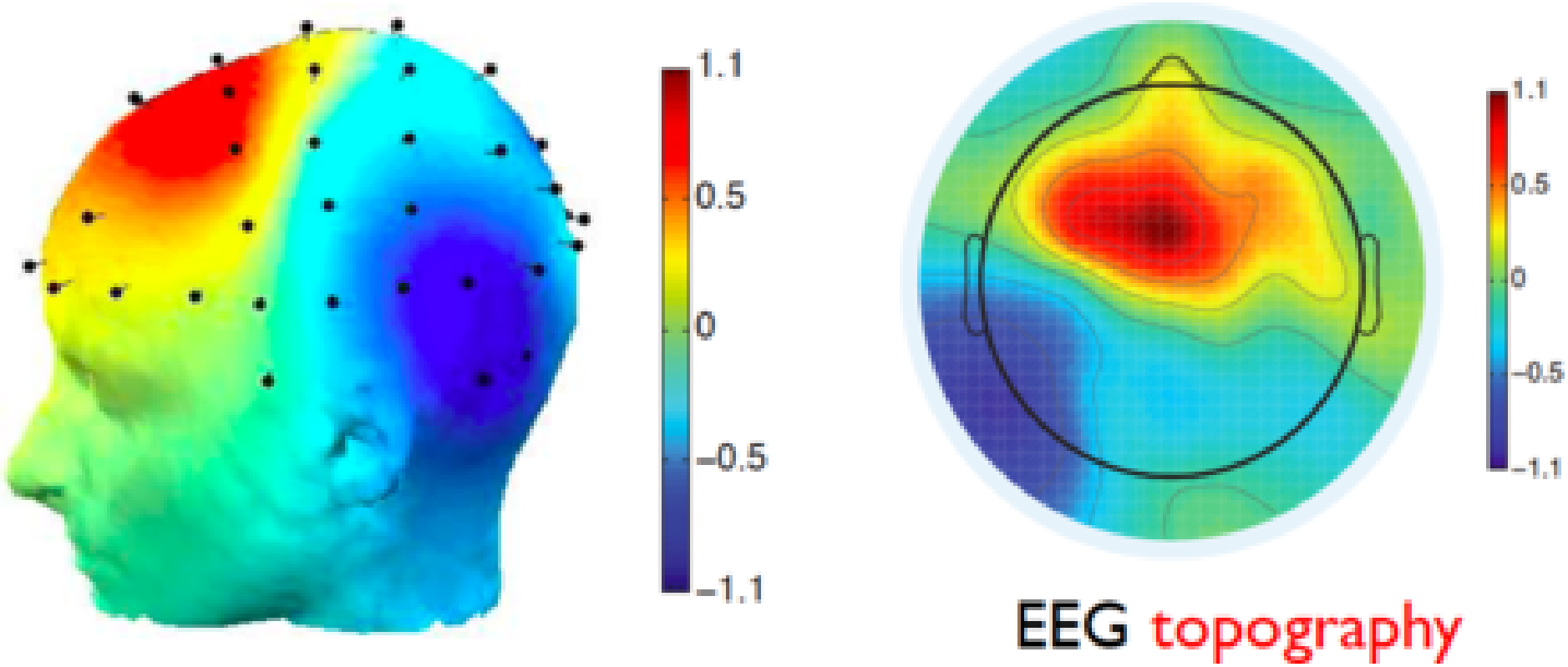


Figure 15: Source: A. Gramfort

M/EEG Measurements

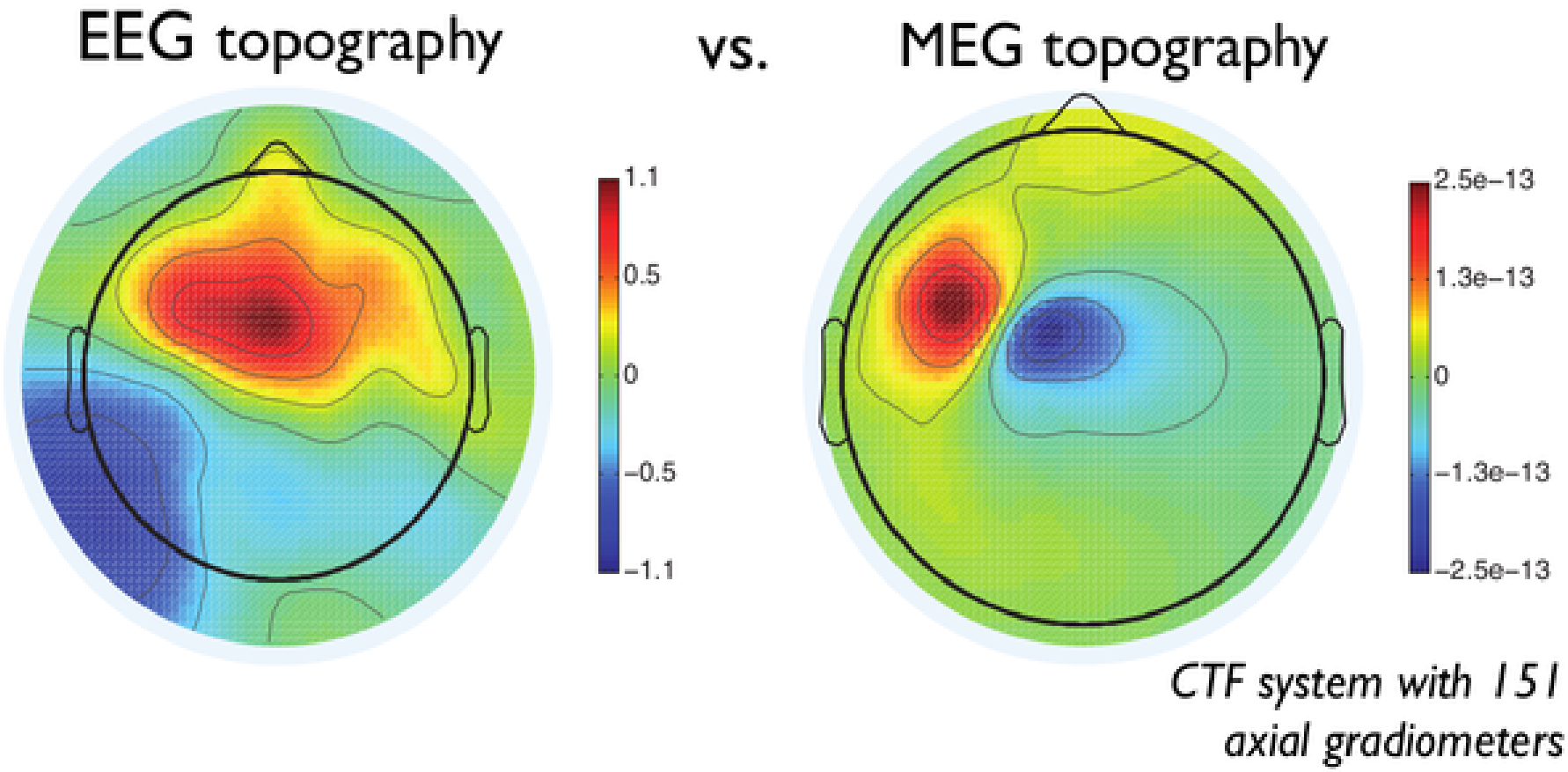
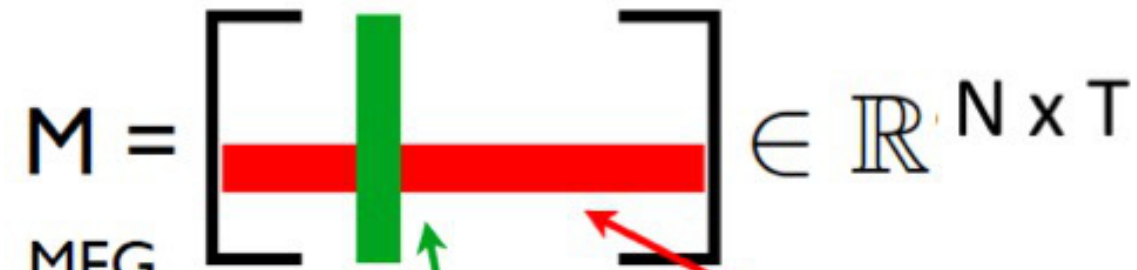


Figure 16: Source: A. Gramfort

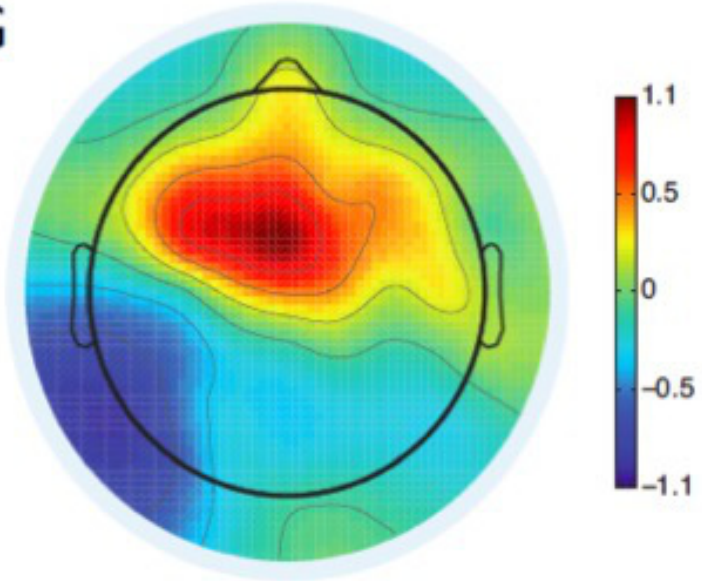
- **MEG has a better spatial resolution**.

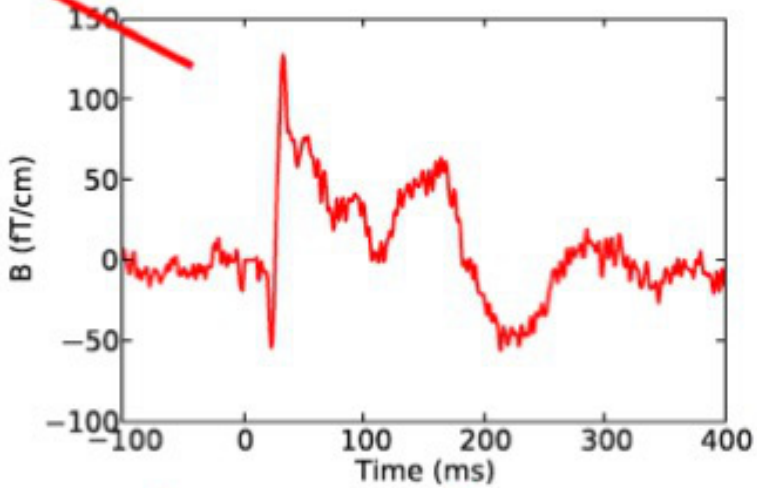
M/EEG Measurements



N : Nb of sensors

T : Nb of time points





Time

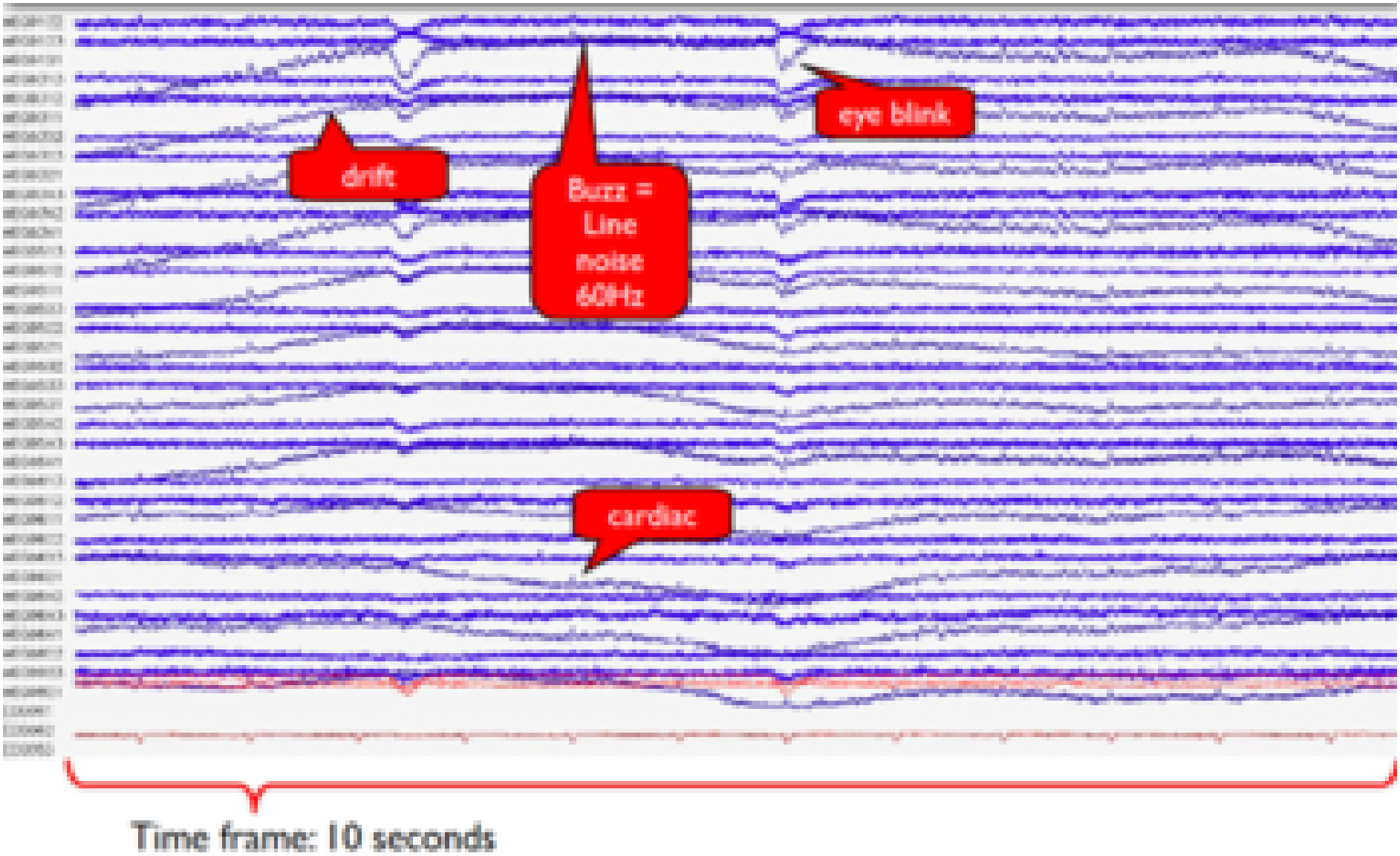
1 column = 1 topography

1 row = 1 time series on 1 sensor

M/EEG Challenges

1. **Signal Extraction**
   - Signal processing, Denoising, Artifact rejection
2. **Forward Problem**
   - Maxwell Equations, Numerical solvers, Finite and Boundary Element Method (BEM and FEM), Image Segmentation and meshing for head modeling
3. **Inverse problem**
   - Deconvolution problem, ill-posed problem

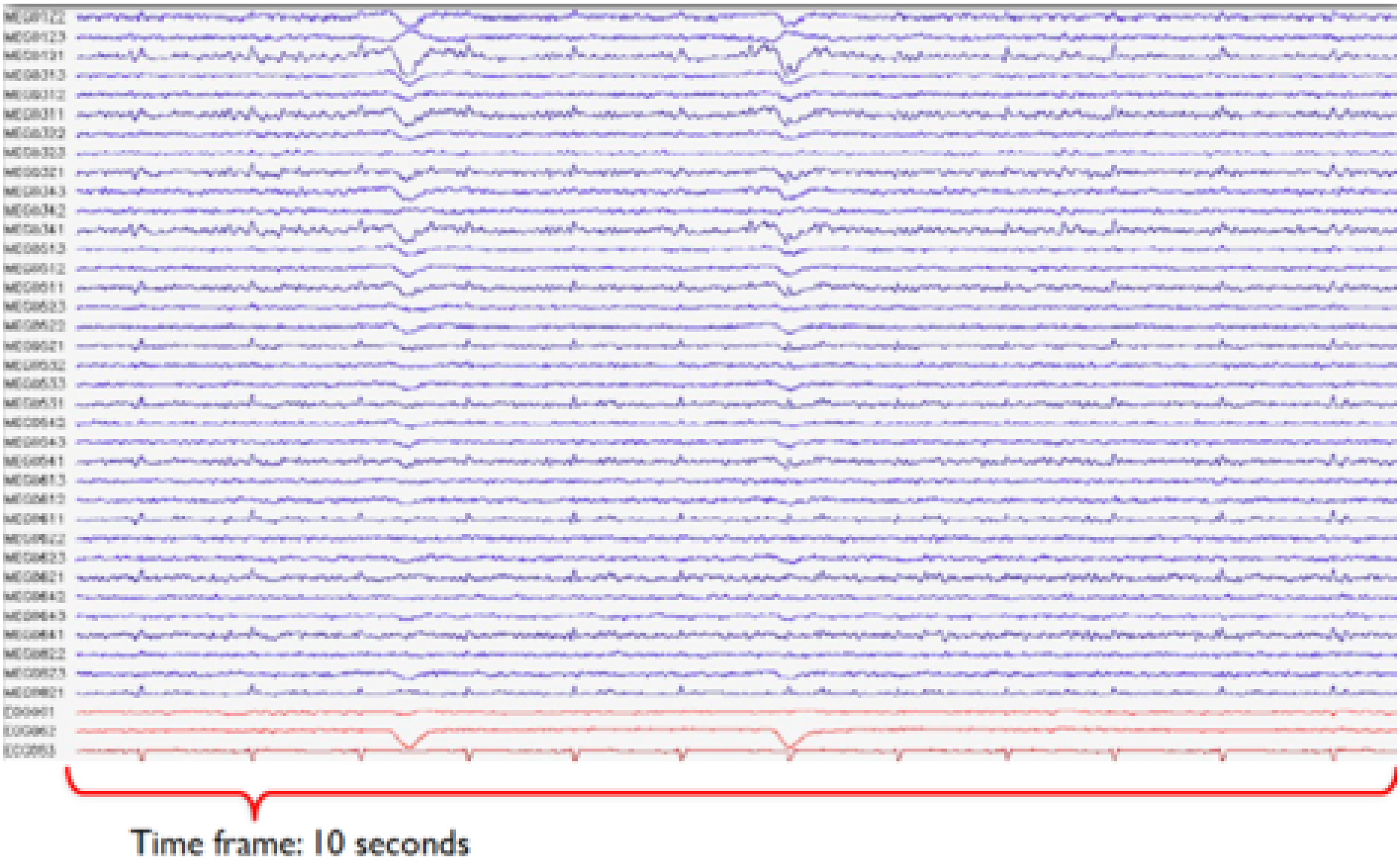
Artifacts


drift
Buzz = Line noise 60Hz
eye blink
cardiac
Time frame: 10 seconds

Artifacts

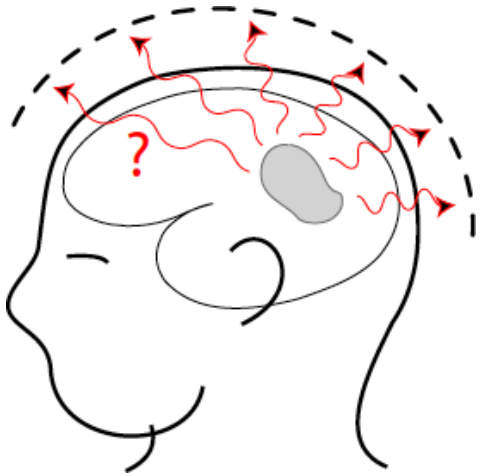
- High-pass filter (0.5–1 Hz) to remove low frequency artifacts such as movement artifacts (e.g. eye blink)
- Low-pass filter (35–70 Hz) to remove high-frequency artifacts such as EMG (electromyogram) artifacts
- Specific filters (e.g. notch filter) can be used to remove artifacts caused by the electrical power lines (50 or 60 Hz)
- Independent component analysis (ICA) can also be used to separate artifacts from EEG signal

Signal filtered (1-40 Hz)



Forward problem

- Predict the scalp electric potential g (and the magnetic field) produced by the activation of the neurons (currents dipole model)

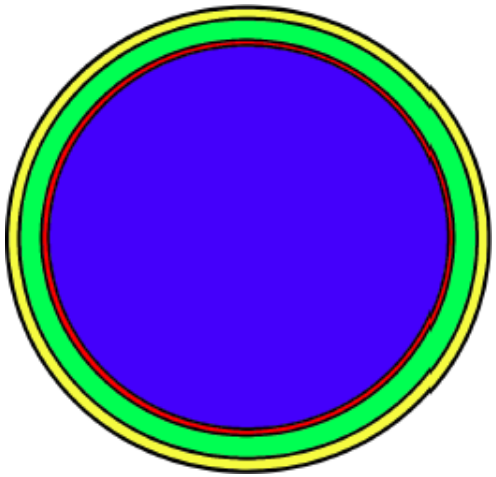


- Solve Poisson's equation, via Maxwell's equations, to find the scalp potential $g(\boldsymbol{r}, \boldsymbol{r}_{dip}, \boldsymbol{d})$ at an electrode position $\boldsymbol{r}$ due to multiple dipoles i (ensemble of neurons activated) with a dipole moment equal to $\boldsymbol{d} = d\boldsymbol{e}_d$, where d is the magnitude, $\boldsymbol{e}_d$ the orientation and it is positioned at $\boldsymbol{r}_{dip}$.
  The electrode potential at $\boldsymbol{r}$ is: $M(\boldsymbol{r}) = \sum_i g(\boldsymbol{r}, \boldsymbol{r}_{dip_i}, \boldsymbol{e}_{d_i}) d_i$

Forward problem

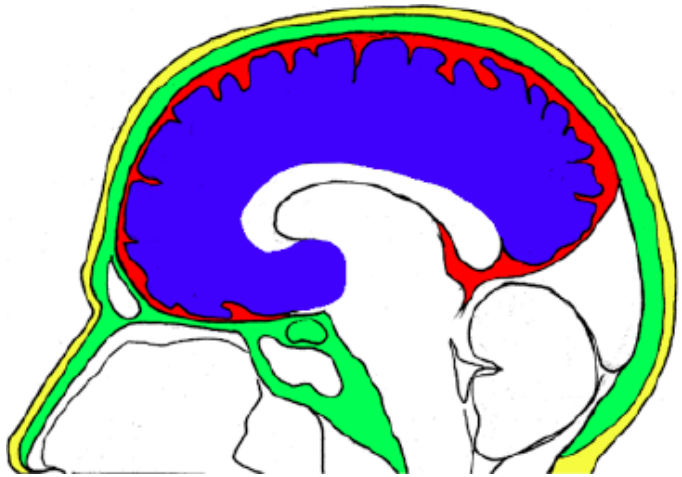
- To solve this equation we need to model the properties of the different tissues of the head (skin, skull, gray matter, white matter, etc.)
- Main hypothesis: conductivity is piecewise-constant between different tissues

Sphere model



Analytical solution, fast to compute, very coarse and imprecise

Realistic model



Approximate solution (numerical solver), more precise

Forward problem

- For N electrodes, p dipoles, T time samples and noise $\boldsymbol{E}$, we have [7]:

$$\boldsymbol{M} = \boldsymbol{G}\boldsymbol{X} + \boldsymbol{E} \tag{19}$$

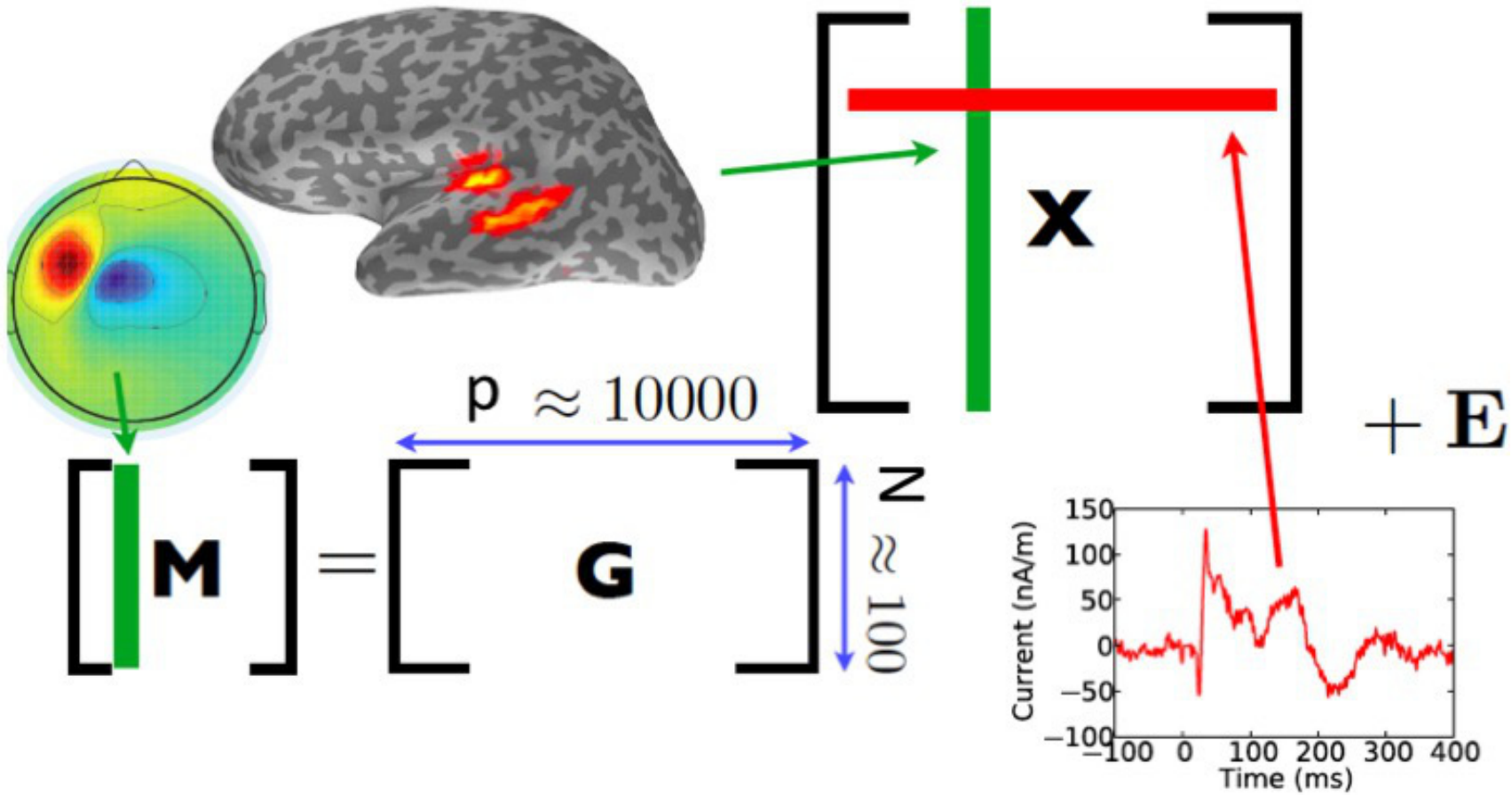
$$\boldsymbol{M} = \begin{bmatrix} M(\boldsymbol{r}_1, t_1) & \dots & M(\boldsymbol{r}_1, t_T) \\ \dots & \dots & \dots \\ M(\boldsymbol{r}_N, t_1) & \dots & M(\boldsymbol{r}_N, t_T) \end{bmatrix} = [N \times T] \tag{20}$$

$$\boldsymbol{G} = \begin{bmatrix} g(\boldsymbol{r}_1, \boldsymbol{r}_{dip_1}, \boldsymbol{e}_{d_1}) & \dots & g(\boldsymbol{r}_1, \boldsymbol{r}_{dip_p}, \boldsymbol{e}_{d_p}) \\ \dots & \dots & \dots \\ g(\boldsymbol{r}_N, \boldsymbol{r}_{dip_1}, \boldsymbol{e}_{d_1}) & \dots & g(\boldsymbol{r}_N, \boldsymbol{r}_{dip_p}, \boldsymbol{e}_{d_p}) \end{bmatrix} = [N \times p] \tag{21}$$

$$\boldsymbol{X} = \begin{bmatrix} d_1(t_1) & \dots & d_1(t_T) \\ \dots & \dots & \dots \\ d_p(t_1) & \dots & d_p(t_T) \end{bmatrix} = [p \times T] \tag{22}$$

Inverse problem

- Recover the current generators $\boldsymbol{X}$ that produce the M/EEG measurements $\boldsymbol{M}$
- Ill-posed problem, more unknowns than number of equations $\rightarrow$ Regularization !



Inverse problem framework

$$\boldsymbol{X}^* = \arg\min_{\boldsymbol{X}} ||\boldsymbol{M} - \boldsymbol{G}\boldsymbol{X}||_F^2 + \gamma\phi(\boldsymbol{X}) \tag{23}$$

- $||\boldsymbol{M} - \boldsymbol{G}\boldsymbol{X}||_F^2$: Data-term. It measures how well the model fits the data.
- $\phi(\boldsymbol{X})$: Regularization term. It controls the complexity of $\boldsymbol{X}$ by imposing a constraint. Examples are the L2 $||\boldsymbol{X}||_2^2$ (ridge) or L1 $||\boldsymbol{X}||_1$ (Lasso) norms.
- γ is the trade-off between data fidelity term and regularization, usually fixed by the user.

Comparison between EEG and MEG

EEG

- Portable and cheap
- Low spatial resolution
- Long time for subject preparation
- Sensitive to both perpendicular and parallel dipoles to the scalp
- It sees more and in more depth, but it is less able to localize the activity

MEG

- Shielded room and expensive
- Better spatial resolution. Magnetic fields are less distorted by head tissue.
- Less time to prepare a subject
- Insensitive to dipoles perpendicular to the scalp
- It sees less but it localizes better the activity

By Combining EEG and MEG , we can remove from the EEG measurements the signals coming from the surface detected with the MEG. This allows the analysis of deeper brain signals.

Applications - EEG

The rhythmic activity of EEG can be divided into bands of frequency:

- **Delta** ($<$4 Hz): found during sleep and in babies
- **Theta** (4-7 Hz): related to drowsiness in adults and teens
- **Alpha** (8-13 Hz): eyes closed and relaxation; coma
- **Beta** ($>$14 Hz): active thinking, focus, anxiety

Applications - Epilepsy

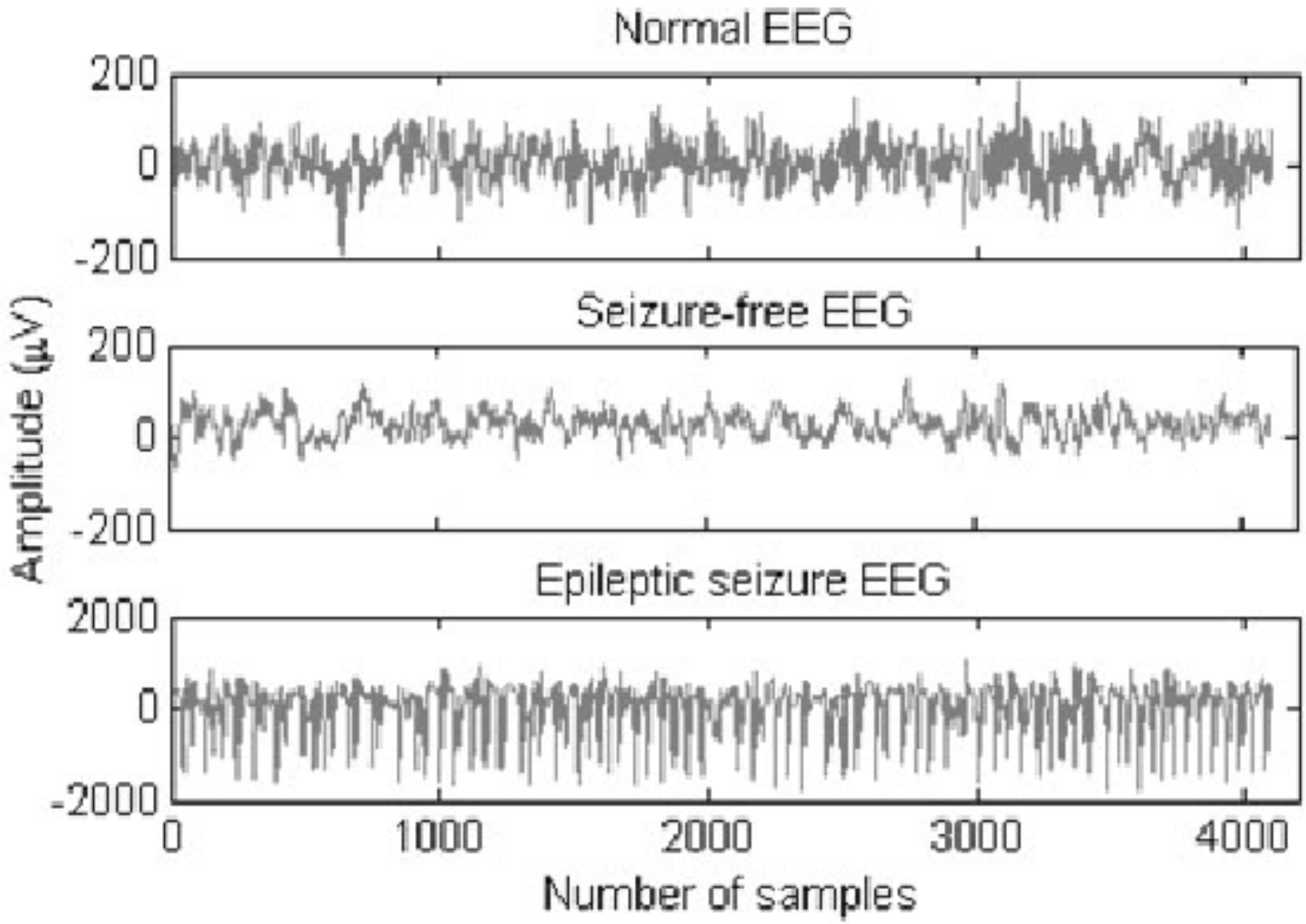
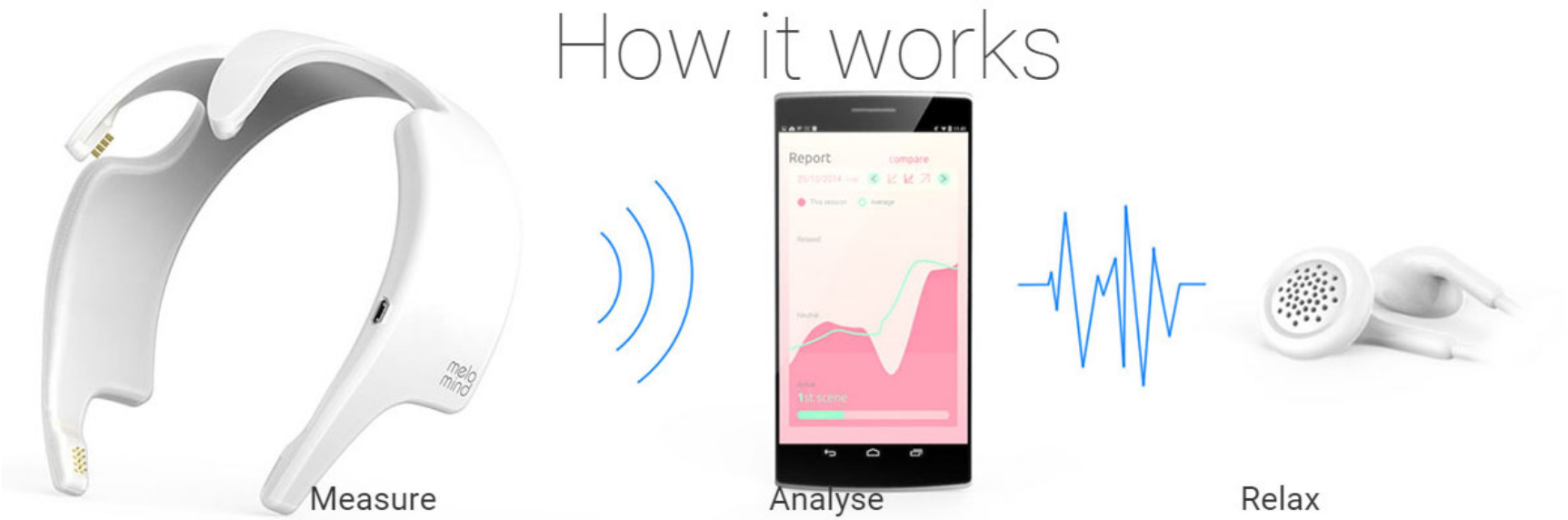


Figure 17: Comparison of normal and epileptic EEG signal. From *NN World 22(3)*

Applications - EEG - Melomind



- StartUp myBrain Technologies built here in Paris - Creators have an academic itinerary similar to yours...
- A new drug-free, easy-to-use, and perfectly safe solution to stress. They identified the cognitive neuro-marker linked to relaxation and created a coaching app and an EEG headset to enhance patient's abilities to relax.

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