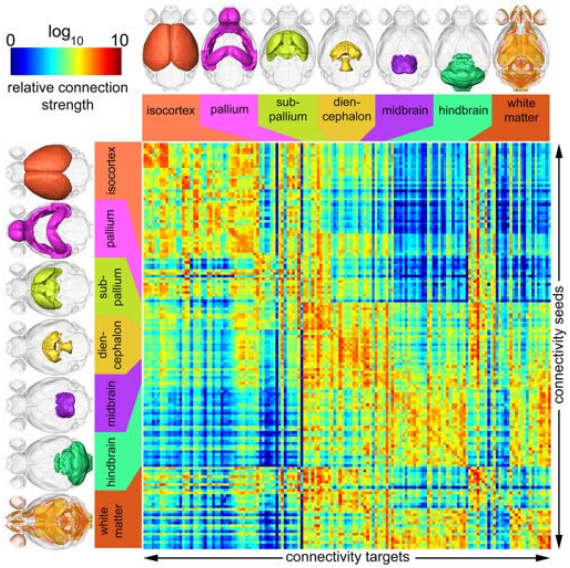
# Diffusion MRI: connectomics

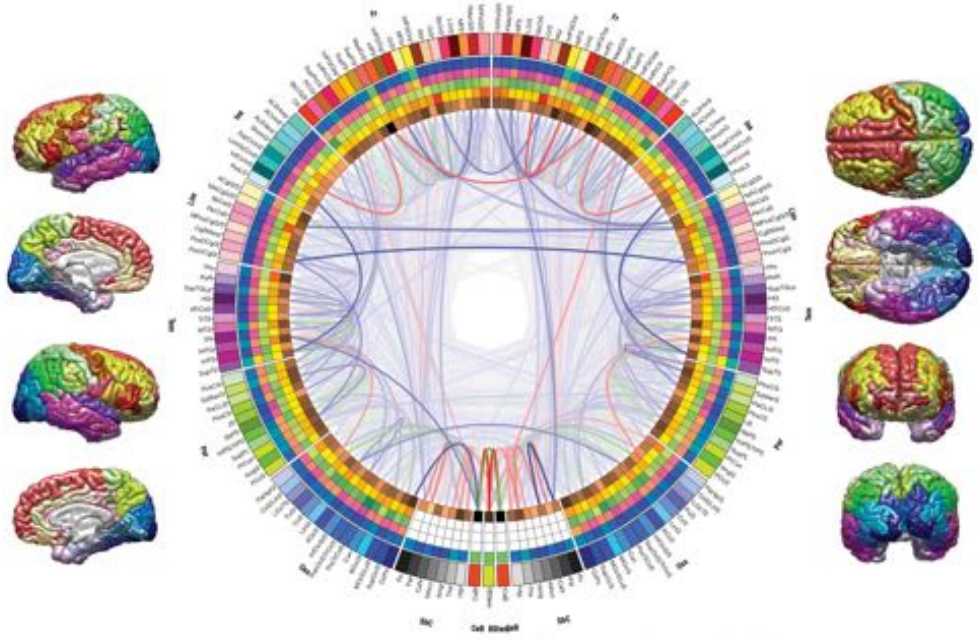
# Outline

- What is "**connectomics**"?
  - Structural vs functional connectome
  - Main components: WM fibers + GM regions
- How to build a **connectome**?
  - Typical pipeline
  - Main issues
- How to **quantify the connection strength**?
  - State of the art
  - Is it really quantitative?
- Problem of **validation**
  - Dissection, tracing and synthetic phantoms
  - Tractometer evaluation system

# What is connectomics? (1/3)

- Production and study of **connectomes**
  - **Connectome**: comprehensive *map of connections* within an organism's nervous system



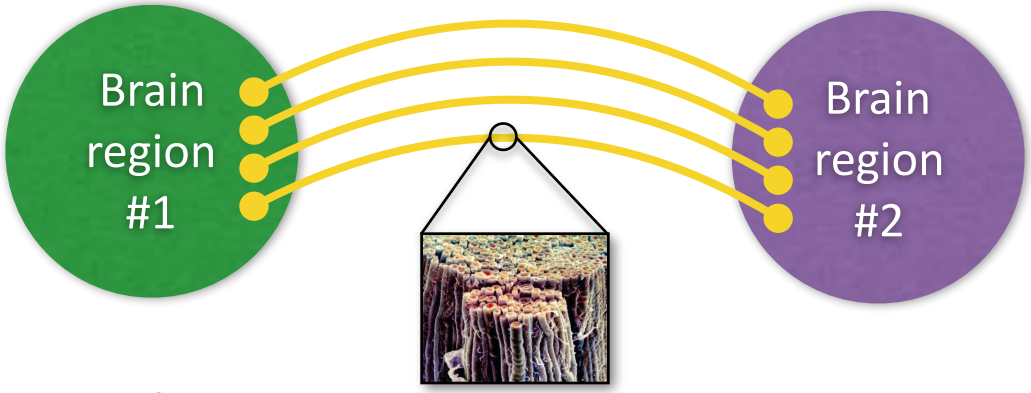



- **Name** simultaneously coined in 2005 by:
  - **Patric Hagmann** in his PhD thesis: "*From Diffusion MRI to Brain Connectomics*"
  - **Olaf Sporns** in his paper: "*The Human Connectome: A Structural Description of the Human Brain*" (PLoS Computational Biology)

# What is connectomics? (2/3)

## **Structural** connectome

- Two brain regions are "connected" **if there is a fiber bundle** between them
- *Diffusion MRI*



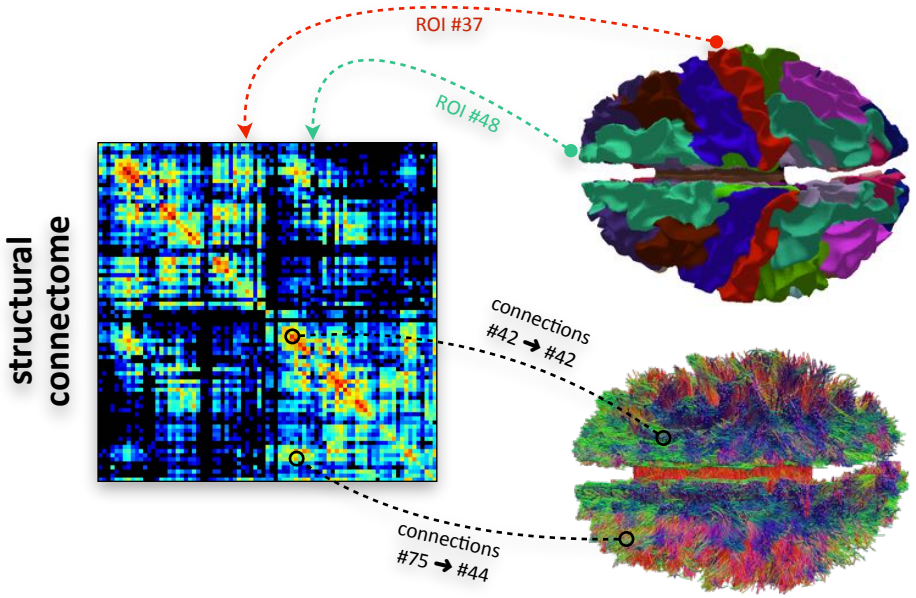

## **Functional** connectome

- Two brain regions are "connected" **if there is temporal correlation** between spatially remote neurophysiological *events*
- *Functional MRI*, *Electroencephalography* (EEG), *Magnetoencephalography* (MEG) …

# What is connectomics? (3/3)

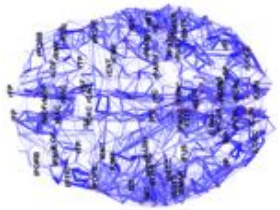
## Main components of a structural connectome

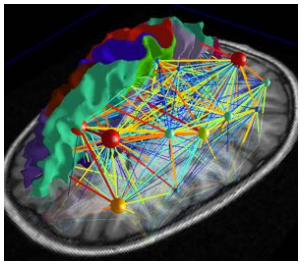
- **Gray matter** (GM) parcellation
  - Defines the spatial location of the *regions-of-interest* (ROIs) chosen for the connectivity analysis
- **White matter** (WM) fiber bundles
  - Define the *strength* (or other features) *of the physical connections* between these ROIs

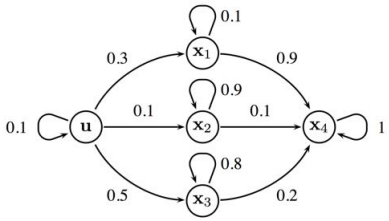



## Can be seen as a **graph/network**

- **Nodes**: gray matter ROIs
- **Edges**: white matter bundles





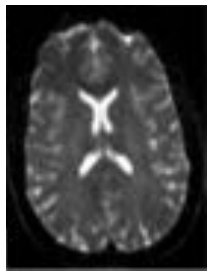



## Use **graph theory** to analyze the connectivity

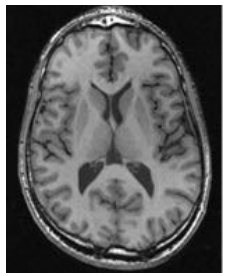
# How to estimate a connectome with dMRI? (1/3)

## Typical pipeline divided in two parts

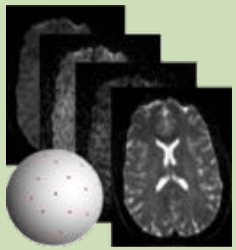
- **Segmentation of the gray matter** into different ROIs
  - This step usually requires an *additional acquisition* containing anatomical details
- Reconstruction of the **white matter fiber bundles**
  - *Diffusion MRI tractography*

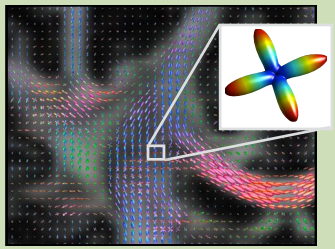


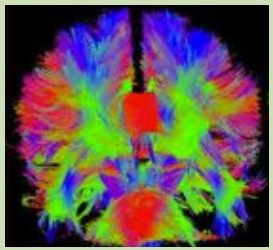
**diffusion** weighted



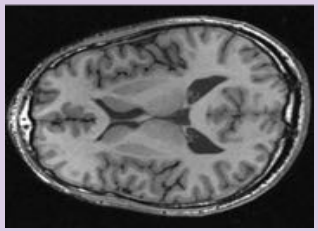
**T1** weighted

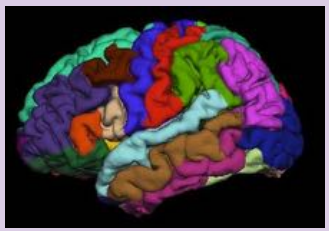




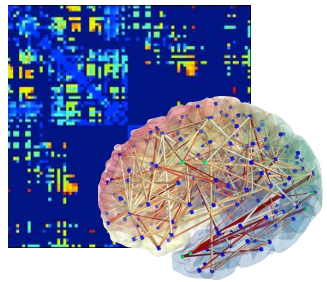


**diffusion MRI** acquisition





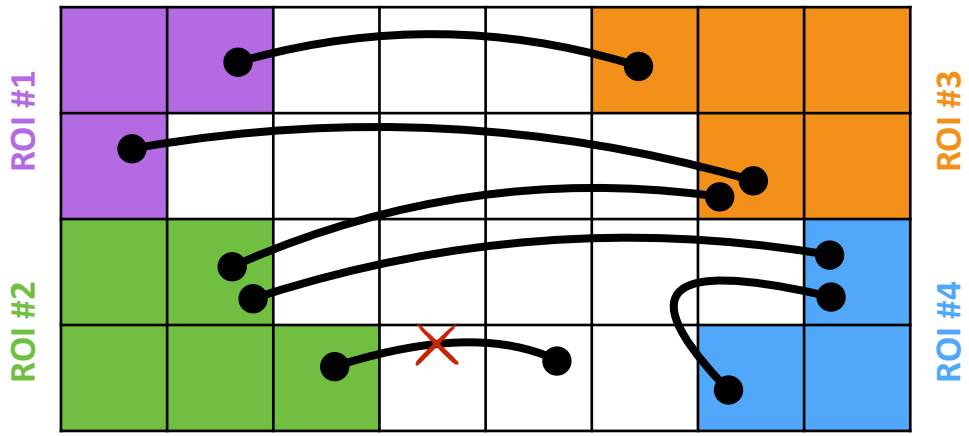
**structural/anatomical** acquisition



# How to estimate a connectome with dMRI? (2/3)

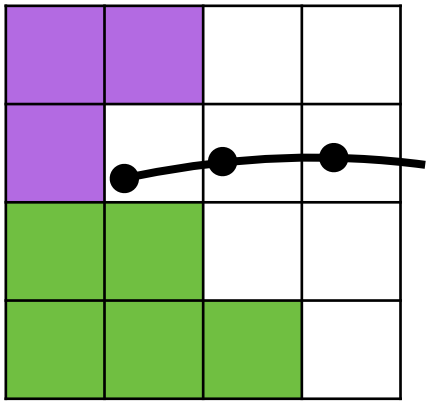
## Combine the two pieces of information

- Simplest approach: **check endpoints** and **count fibers** connecting two ROIs

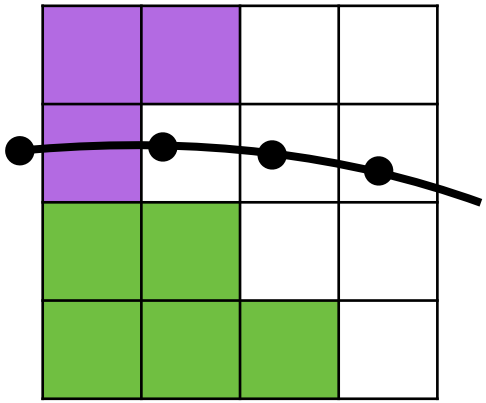



| | #1 | #2 | #3 | #4 |
|---|---|---|---|---|
| #1 | 0 | 0 | 2 | 0 |
| #2 | 0 | 0 | 1 | 1 |
| #3 | 2 | 1 | 0 | 0 |
| #4 | 0 | 1 | 0 | 1 |

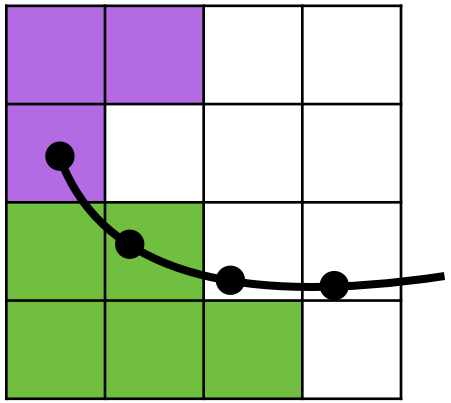
## What to do in these cases?



**Shall we really discard it?**
**Does it connect #1 or #2?**



**Does it connect or not?**



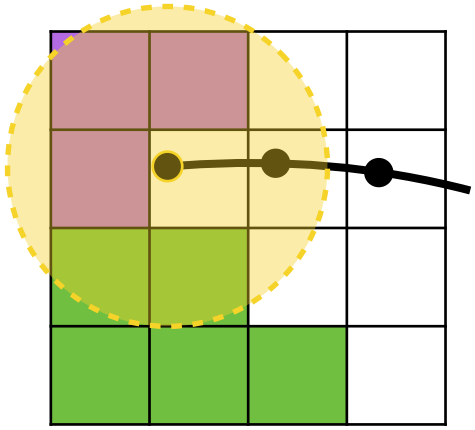
**Does it connect #1 or #2?**

# How to estimate a connectome with dMRI? (3/3)

- **Best solution would be** to *include constraints* for fibers terminating in the gray matter *directly into tractography*
  - *Very few methods* implement this strategy, as usually it's too complex
    - e.g. *geodesic approaches* intrinsically enforce this constraint
  - Usually, *this is left for successive analysis steps*
  - This introduces *variability in the estimation*
    - Many fibers discarded
    - Arbitrarily associated to ROIs

$$\operatorname{argmin} \underbrace{\frac{1}{2}\|\Phi\mathbf{x}-\mathbf{y}\|_2^2}_{\text{data fitness}} + \lambda \underbrace{\Psi(\mathbf{x})}_{\text{regularization}}$$

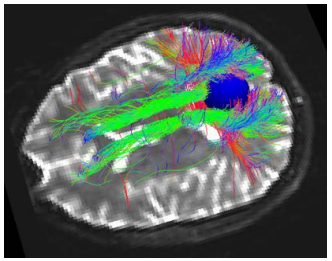
- **Possible workaround**
  - Do not look only at the *endpoints* per se
  - **Consider a neighborhood** and *use statistics or heuristics* to determine the proper assignment
    - e.g. count voxels belonging to each ROI inside this neighborhood
  - *NB*: **be consistent** for all subjects

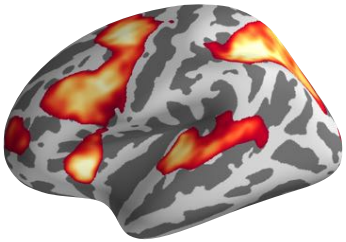


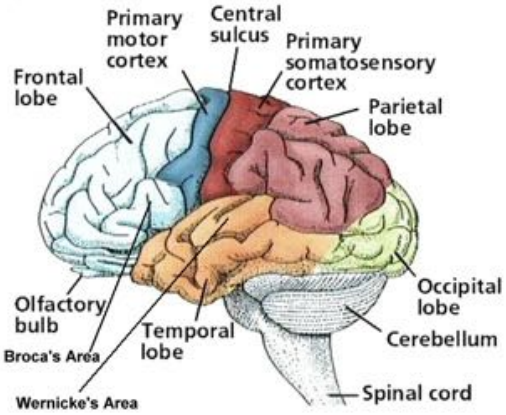
# How to define the nodes?

## Different approaches

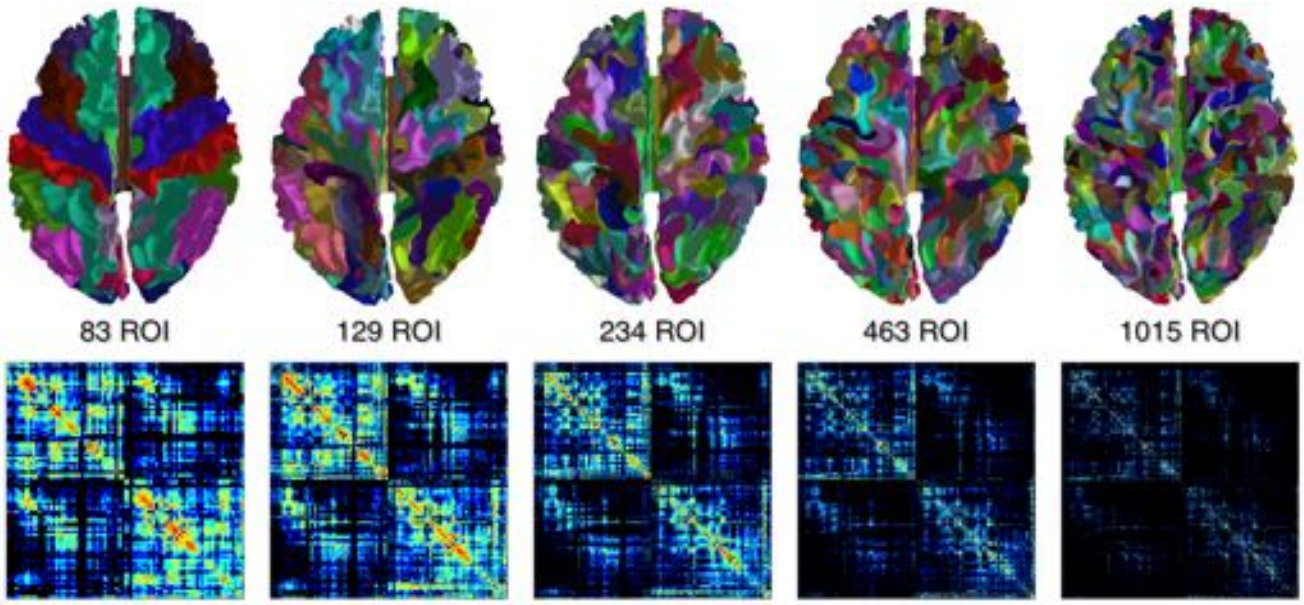
- *Manually* segmented ROIs
- *Anatomically* defined
- Defined with *other modalities*, e.g. fMRI
- *Random*





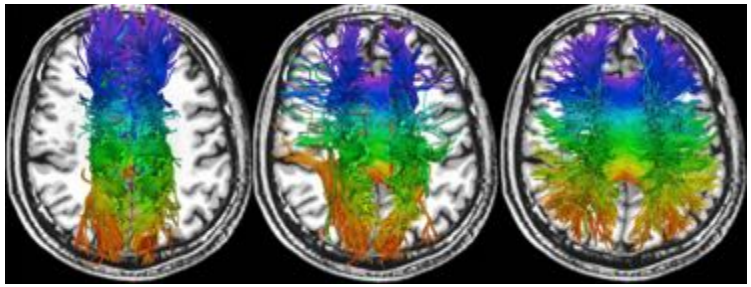



## Multiscale analysis

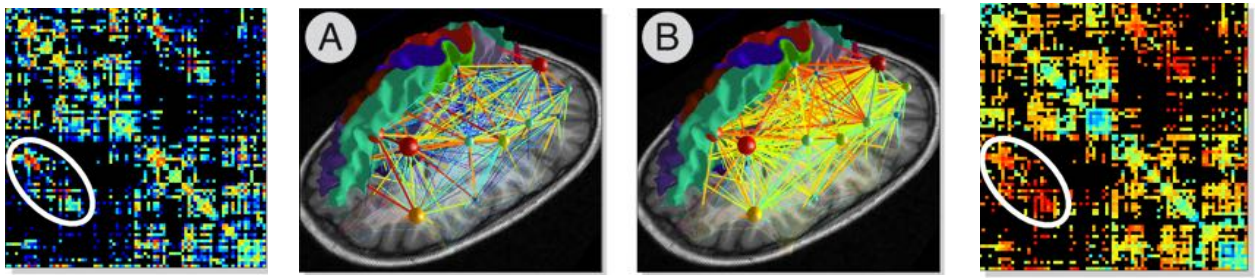


# How to define the edges? (1/3)

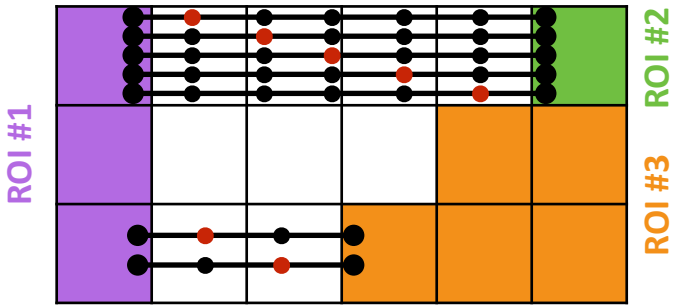
- Clearly, using **tractography**!
  - As many *different algorithms* exist…
  - …**different connectivity estimates** are expected!



- More importantly: **what do we put in the edges**?
  - Different definitions of **connection strength** proposed in the literature
    i.e. connectomes are *multivariate*

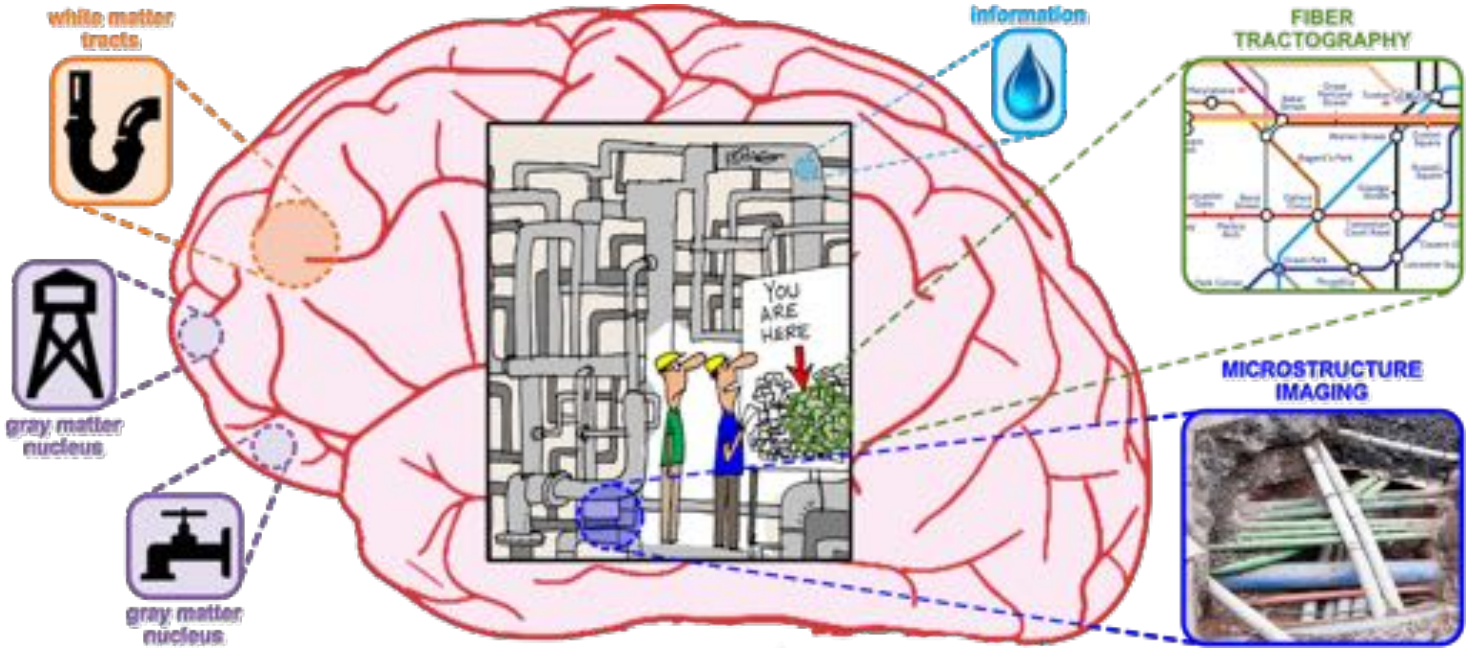



  - Most common choice: **fiber count**
  - *Normalization* by the distance between ROIs
    - To compensate for more seeds in longer fibers
  - *Normalization* by the area of the ROIs
    - To compensate for more seeds in bigger ROIs



# How to define the edges? (2/3)

- What is **connection strength**?
- "**Water supply network**" metaphor:




- Which **questions** would we like **to ask**?
  - Is my house *connected* to any water source?
  - If so, *how many pipes* are there? *How big* are they?
  - *If there is a damage* in district A, will my house be affected?

# How to define the edges? (3/3)

- Can we answer these questions?

  **Is tractography quantitative?**

[Jbabdi et al., 2011]

> One frustrating thing about tractography is that it takes a quantitative acquisition method (diffusion MRI) and makes it less quantitative. That is, less quantitative from the point of view of connectivity. Of course, diffusion MR is a quantitative method: it allows us to calculate the—albeit apparent—diffusion coefficient with great accuracy. Hence we can use

## Local reconstruction

### Diffusion features

- Diffusion Tensor Imaging *(Basser et al, 1994)*
- Diffusion Spectrum Imaging *(Wedeen et al, 2000)*
- PAS-MRI *(Jansons and Alexander, 2003)*
- Spherical Deconvolution *(Tournier et al, 2004)*
- Diffusion Orientation Transform *(Ozarslan et al, 2006)*
- Q-BALL in Constant Solid Angle *(Aganj et al, 2010)*
- …

### Microstructure features

- Ball-and-stick *(Behrens et al, 2003)*
- CHARMED *(Assaf et al, 2005)*
- AxCaliber *(Assaf et al, 2008)*
- MMWMD *(Alexander et al, 2010)*
- NODDI *(Zhang et al, 2012)*
- …

## Tractography

### Line-propagation

- FACT *(Mori et al, 1999)*
- RK4 *(Basser et al, 2000)*
- …

### Probabilistic

- PICo *(Parker et al, 2003)*
- ProbTrackX *(Behrens et al, 2003)*
- …

### Front-evolution

- Fast marching tractography *(Parker et al, 2002)*
- Anisotropic geodesic tractography *(Jbabdi et al, 2008)*
- …

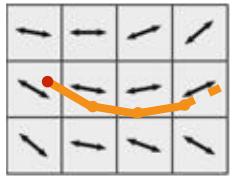
### Global energy-minimization

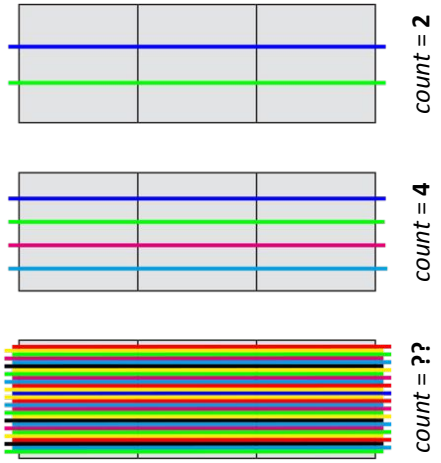
- GIBBS tracking *(Kreher et al, 2008)*
- Spin-glass tractography *(Fillard et al, 2009)*
- …

So far considered as **separate** problems

# Connectivity mapping: state of the art (1/3)

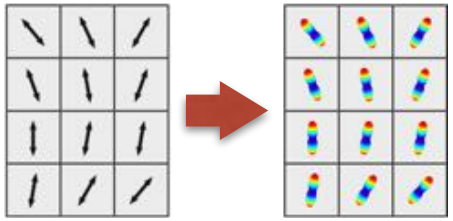
## Line-propagation tractography



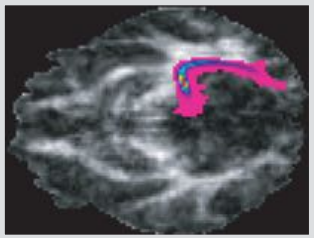



- Fibers are simple “lines”, have “no volume”
- This is true for also for *geodesic* approaches
  - i.e. they’re based on line-propagation
- Quantification only by means of **fiber count**
- Dependent on tracking parameters [Girard et al., 2014]
  - e.g. doubling the number of seeds, more fibers are reconstructed
- **Not quantitative** [Jones, 2010; Jbabdi et al., 2011; Jones et al., 2013]

## Probabilistic variant



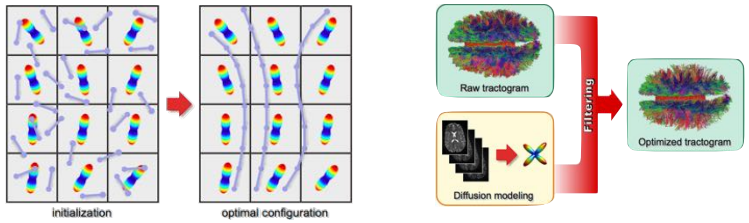
- Estimation of **probability of connection** maps
  - By seeding a large number of fibers
  - More informative, as it adds confidence levels to tracts
- **No significant benefits for connectivity**
- Quantification by these probabilities ≠ “connection strength”
  [Jones, 2010; Jbabdi et al., 2011; Jones et al., 2013]

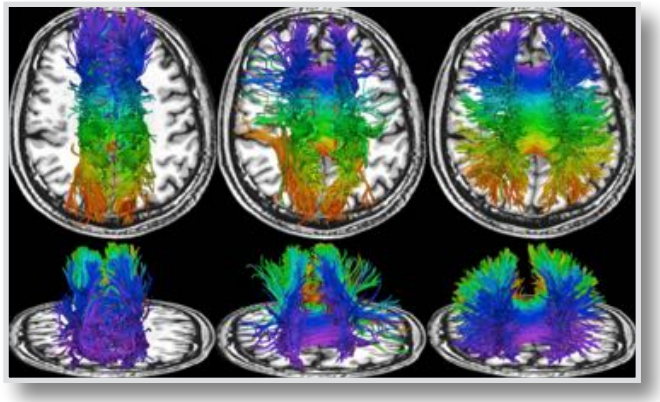


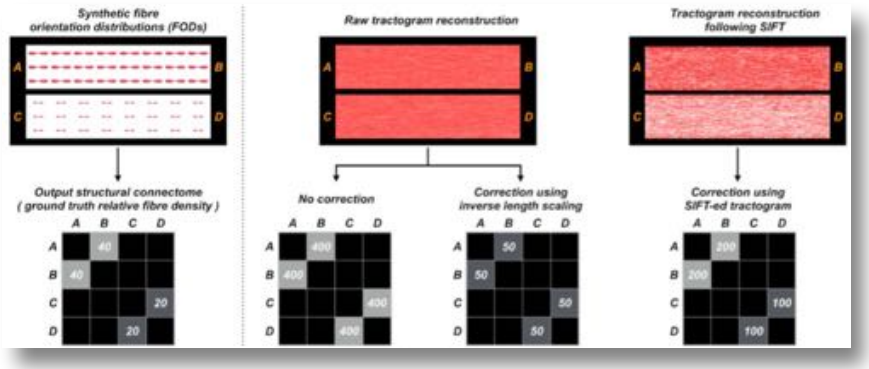
# Connectivity mapping: state of the art (2/3)

## Global inverse problem

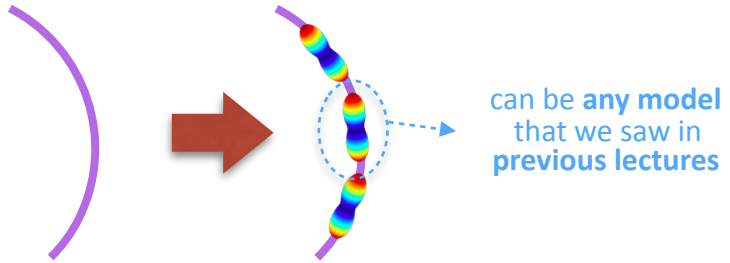
- **Higher quality** of reconstructions
  [Smith et al., 2015; Yeh et al., 2016; Kreher et al., 2008; Fillard et al., 2009]






- **Complexity** leaves many open-questions for connectivity (e.g. partial fibers)
- More quantitative (**slightly**)
  - i.e. fibers have contribution




- Forward-model based on **orientation information only** (e.g. tensor, fODF etc…)
  - *Biophysical models* may provide access to more quantitative features of the fibers
    *e.g. density* and *average axon diameter*

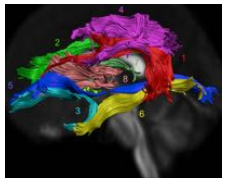
# Connectivity mapping: state of the art (3/3)

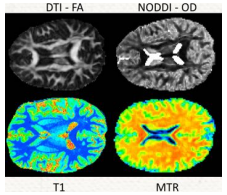
## Tractometry/connectometry [Bells et al., 2011; De Santis et al., 2013; Yeh et al., 2013; …]

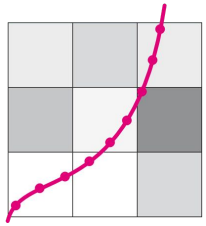
- Tractography as such is not quantitative…
- …then, combine it with **other quantitative maps**!

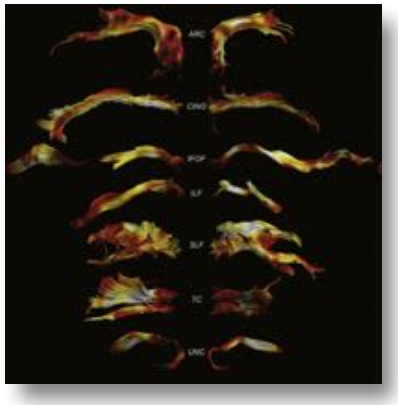
## Procedure

- **Step 1**: estimate fiber bundles with any tractography method
- **Step 2**: extract a scalar map from any modality
- **Step 3**: evaluate the map values along fiber trajectories



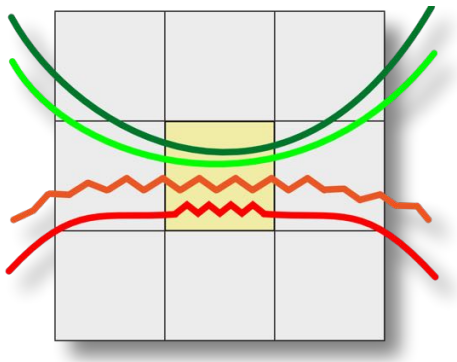


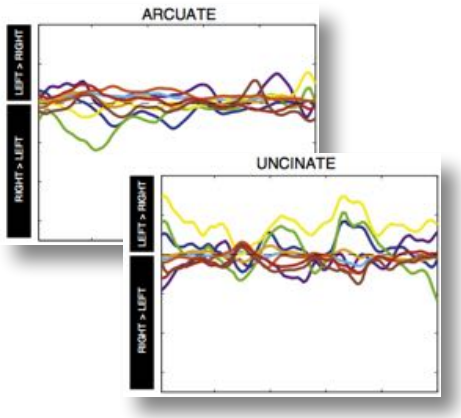





## Notes

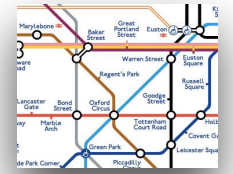
- More quantitative (**slightly**)
- The measures are **indirect**
  - i.e. voxel-specific, not bundle-specific
- **Superposition of effects**





# Can we improve the estimation of connectivity?

- One possibility would be to **combine the information** from:
  - *Local reconstruction*
  - *Tractography*



## Local reconstruction

### Diffusion features

- Diffusion Tensor Imaging *(Basser et al, 1994)*
- Diffusion Spectrum Imaging *(Wedeen et al, 2000)*
- PAS-MRI *(Jansons and Alexander, 2003)*
- Spherical Deconvolution *(Tournier et al, 2004)*
- Diffusion Orientation Transform *(Ozarslan et al, 2006)*
- Q-BALL in Constant Solid Angle *(Aganj et al, 2010)*
- …

### Microstructure features

- Ball-and-stick *(Behrens et al, 2003)*
- CHARMED *(Assaf et al, 2005)*
- AxCaliber *(Assaf et al, 2008)*
- MMWMD *(Alexander et al, 2010)*
- NODDI *(Zhang et al, 2012)*
- …

## Tractography

### Line-propagation

- FACT *(Mori et al, 1999)*
- RK4 *(Basser et al, 2000)*
- …

### Probabilistic

- PICo *(Parker et al, 2003)*
- ProbTrackX *(Behrens et al, 2003)*
- …

### Front-evolution

- Fast marching tractography *(Parker et al, 2002)*
- Anisotropic geodesic tractography *(Jbabdi et al, 2008)*
- …

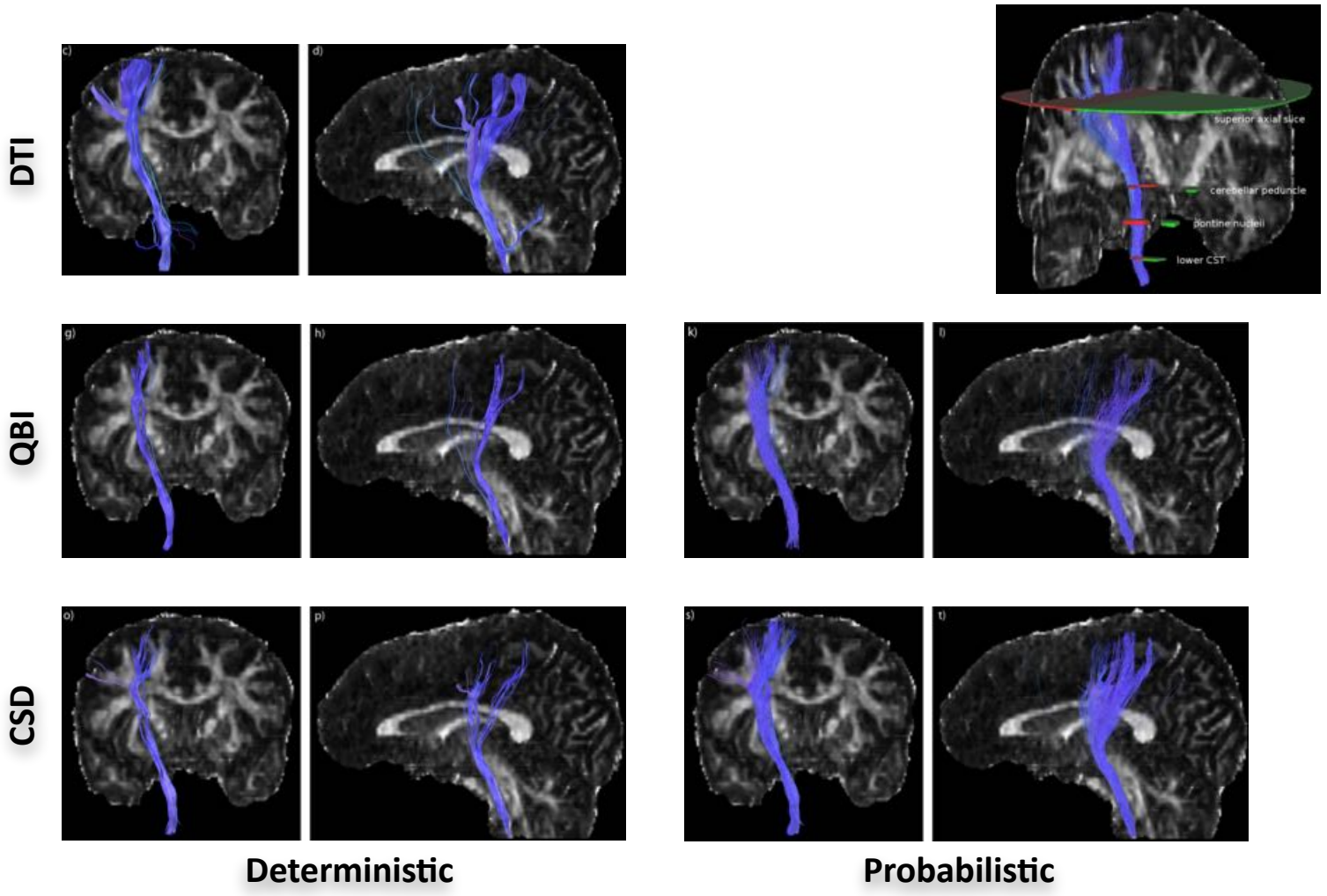
### Global energy-minimization

- GIBBS tracking *(Kreher et al, 2008)*
- Spin-glass tractography *(Fillard et al, 2009)*
- …

- New frontier in dMRI: **microstructure informed tractography**

# The problem of validation (1/5)

- **How can we be sure** that a bundle from tractography is real?




- Validation is an **open issue** in connectivity analysis

# The problem of validation (2/5)

- The **ground truth** would be…
  - *Kill* the subject
  - *Extract* the brain
  - *Check every single axon* for a match


- Not feasible for a number of reasons
  - **It is not "ethic"** to kill everyone after a scan just to check if our algorithm is right…
  - Connectomics works at the **macroscale**, axonal connections are at the **microscale**
  - The **complexity** of this procedure is way off the table

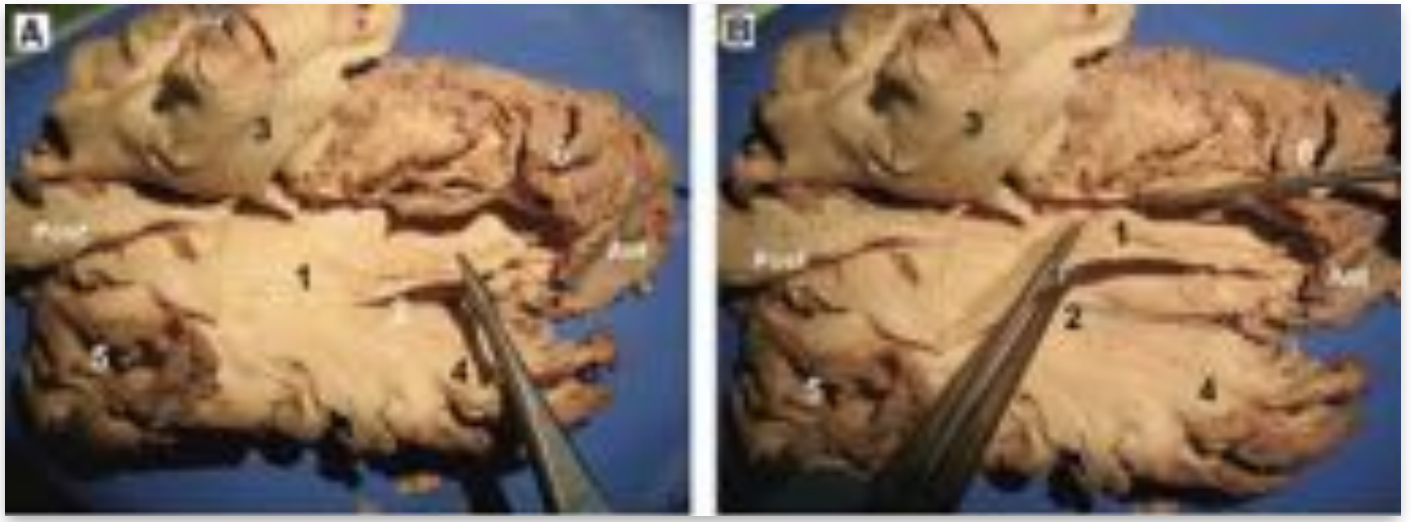
- Alternatives methods
  - **Brain dissection**
  - **Axonal tracing**
  - **Synthetic phantoms**

# The problem of validation (3/5)

## Brain dissection



- Brain is *extracted* and *prepared*
  i.e. frozen, defrosted and fixed in formalin (or similar)
- **Use a scalpel** to *remove unwanted tissue* and *expose nerve bundles*



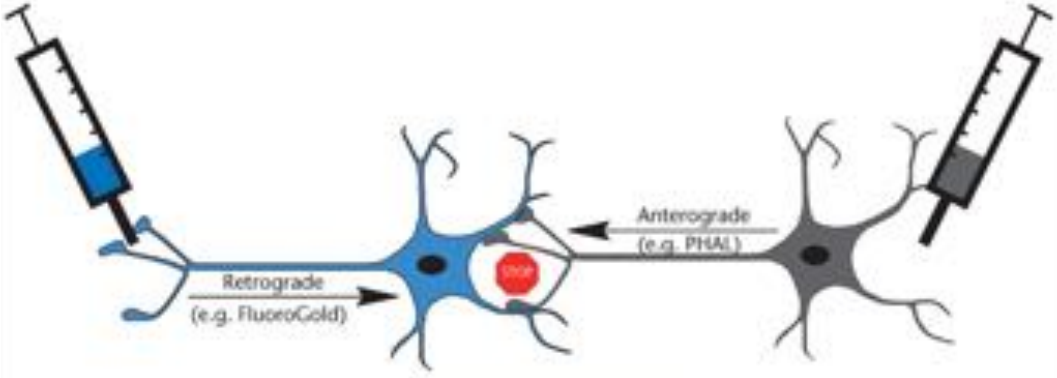

## Main limitations

- Can be only performed **ex-vivo**
- Only **few bundles** can be followed and studied
  - *Destructive procedure*: while "carving with the scalpel", layers of bundles are wiped out
  - *No full brain* comparison with dMRI connectomics

# The problem of validation (4/5)

## Axonal tracing

- Based on the visualization of the biological process of **axonal transport**
- **Injection** of visualizable **tracer molecules** into the brain, e.g. Green Fluorescent Protein (GFP)




- **Molecules are absorbed** locally by the cell body of various neurons
- **Transported** to the axon terminals (or other way round, i.e. *anterograde* vs *retrograde*)

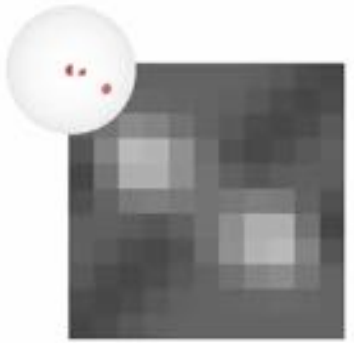
## Main limitations

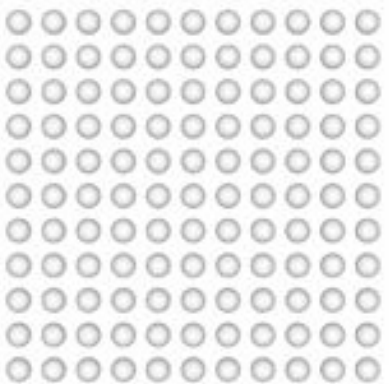
- Can be only performed **ex-vivo**
- Only **few axons** can be traced
  - *Single axons are traced*, not bundles
  - *No full brain* comparison with dMRI connectomics

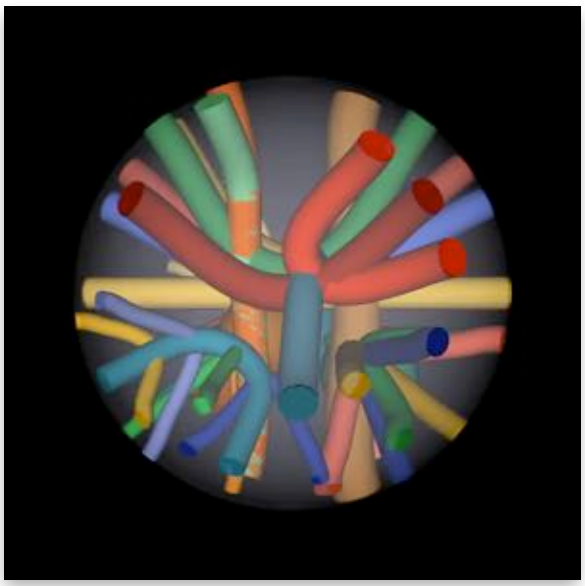
# The problem of validation (5/5)

## Synthetic phantoms

- Geometry created **mimicking a real brain**
  *e.g. crossing fibers, bending, CSF contamination etc*
- **dMRI signal** can be either
  - **Synthetically simulated** according to state-of-the-art models
  - Actually acquired from **physical phantoms**
- **Known ground-truth connections**
  *i.e. we know which ROIs are connected*
- Example: *phantomas* [www.emmanuelcaruyer.com/phantomas.php]

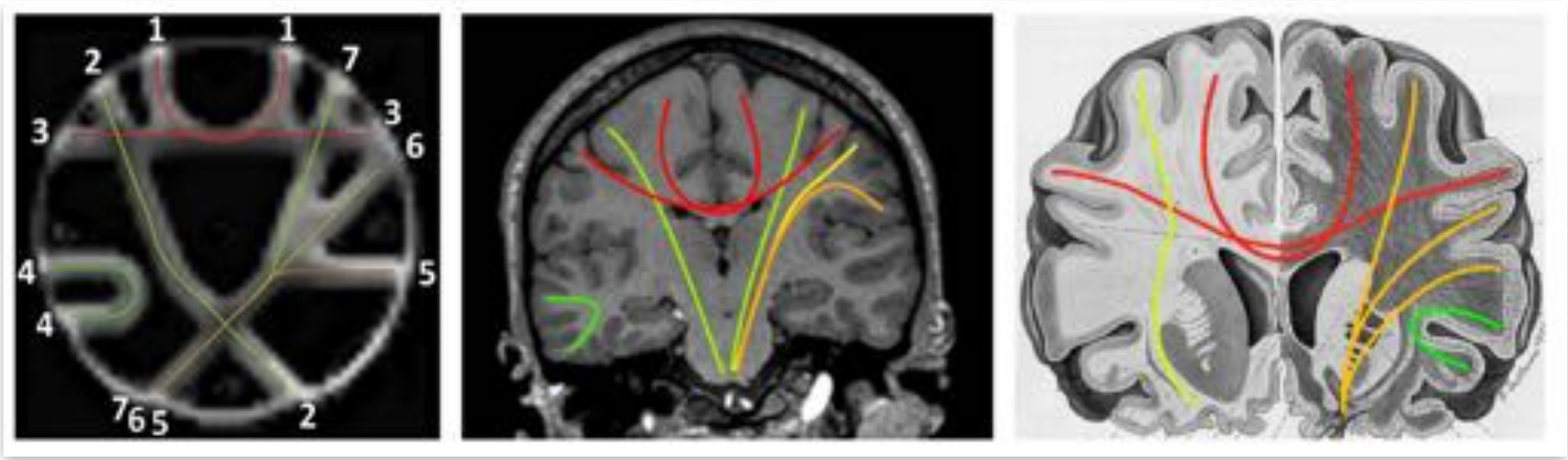




# Tractometer evaluation system (1/4)

- **Physical phantom** mimicking a slice of the brain [Poupon et al. 2010]



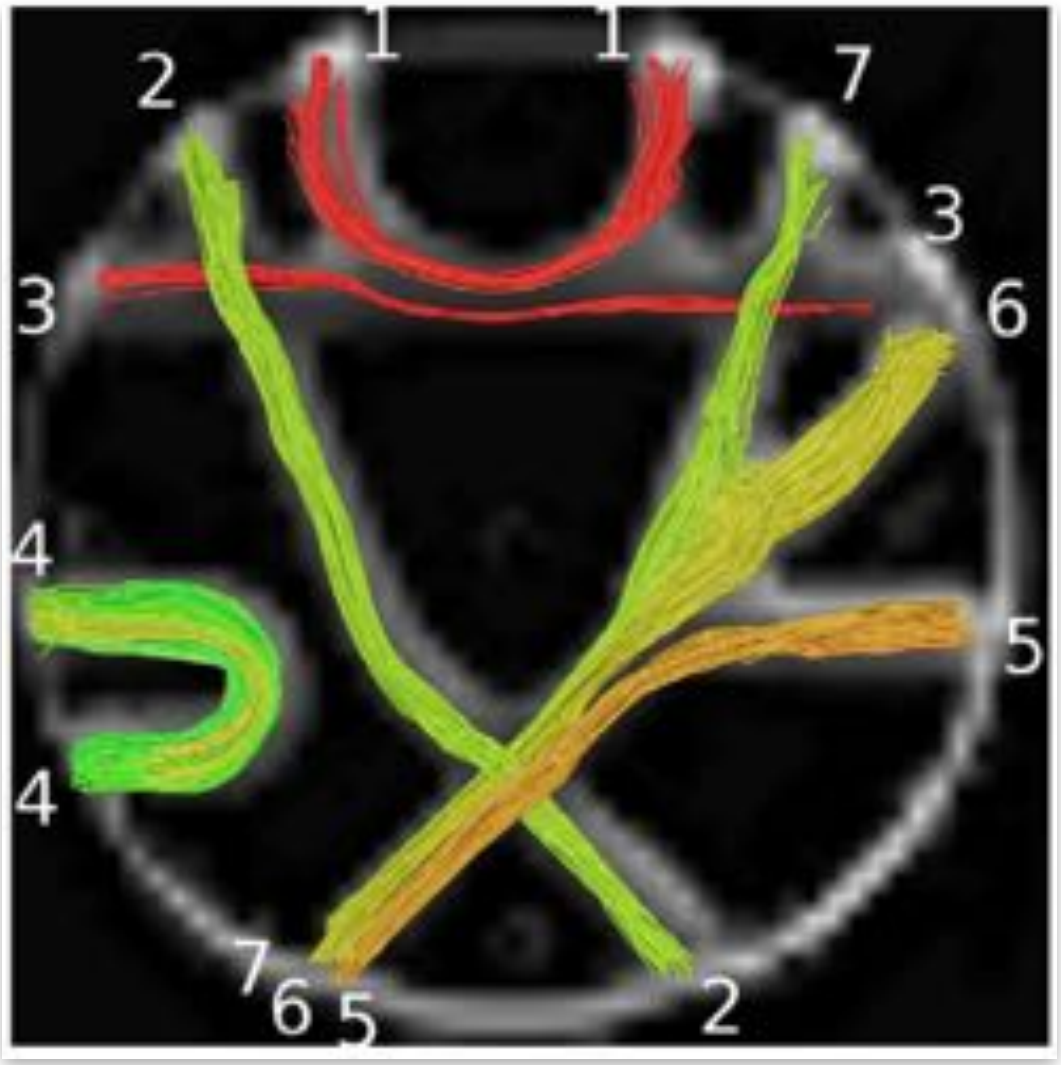

- **Metrics** to evaluate connectivity [Côté et al., 2013]
  - *Valid Connections* (**VC**)
  - *Invalid Connections* (**IC**)
  - *No Connections* (**NC**)

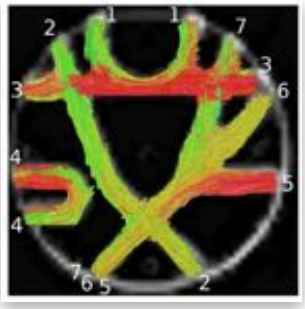
  Reported as **% of streamlines**
  - *Valid Bundles* (**VB**)
  - *Invalid Bundles* (**IB**)

  Reported as **number of bundles**

# Tractometer evaluation system (2/4)

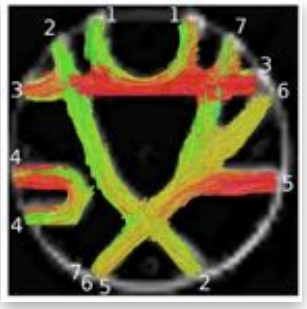
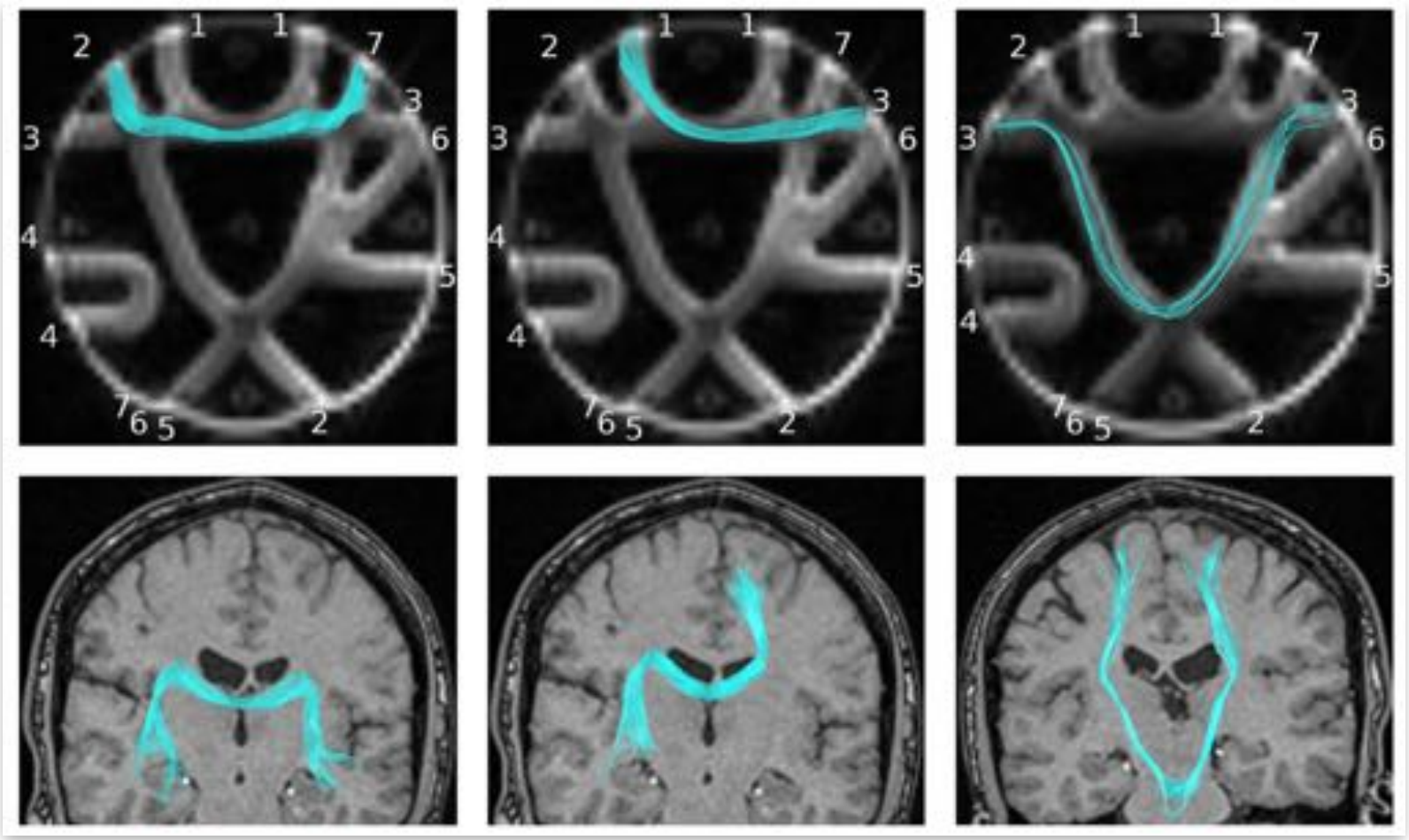
- **Examples**: valid connections



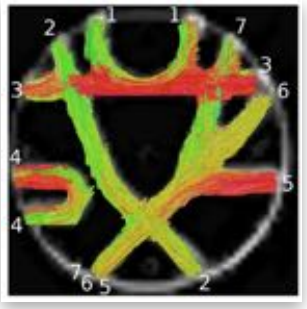
# Tractometer evaluation system (3/4)

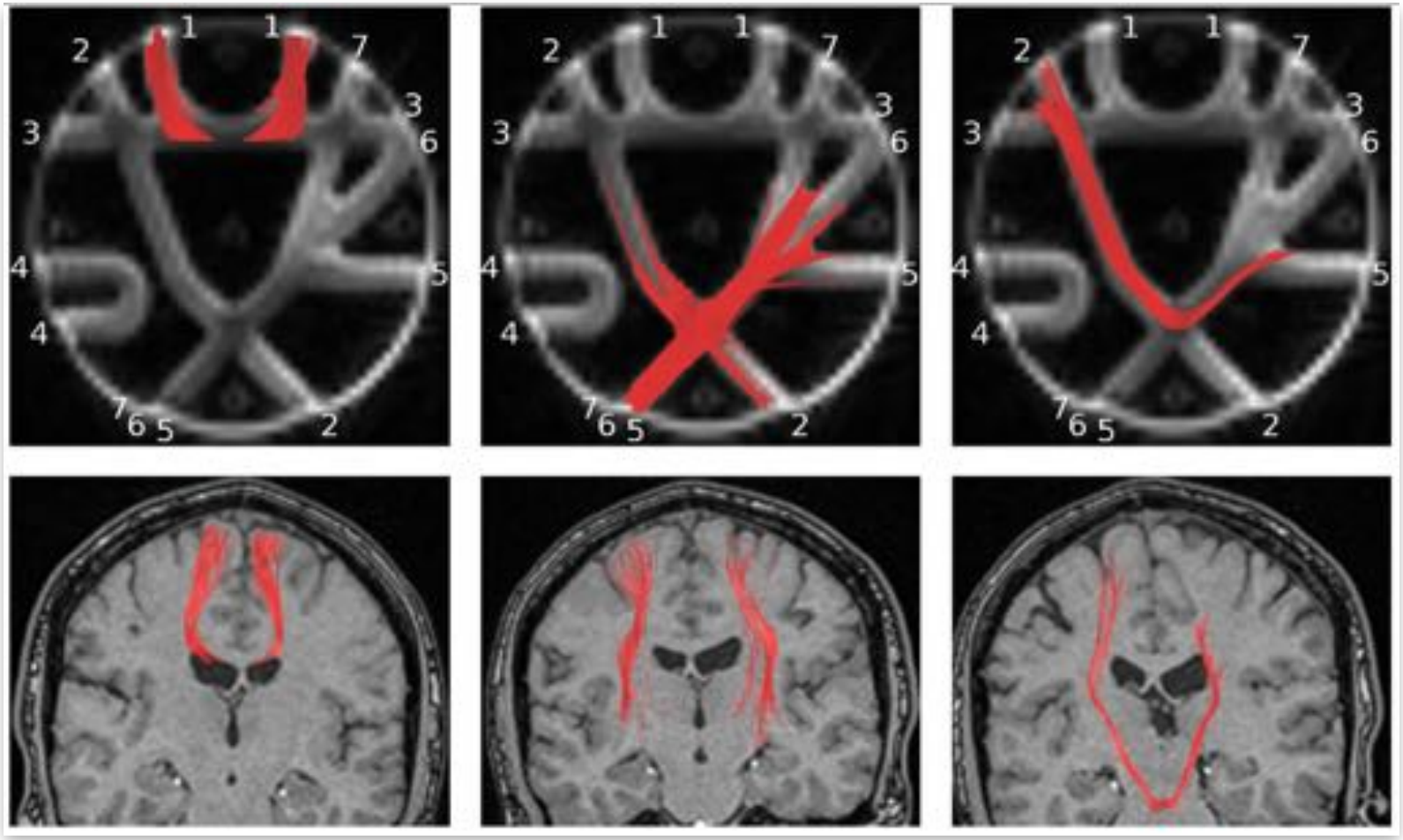
- **Examples**: invalid connections

# Tractometer evaluation system (4/4)

- **Examples**: no connections





# Questions?

# Comments?

# Suggestions?