Understanding brain micro-structure using diffusion magnetic resonance imaging (dMRI)

Jing-Rebecca Li

Equipe DEFI CMAP, Ecole Polytechnique

Institut national de recherche en informatique et en automatique (INRIA) Saclay, France

DeFI

Houssem Haddar
Simona Schiavi (current PhD)
Gabrielle Fournet (current PhD)
Dang Van Nguyen (former PhD)
Julien Coatleven (former Post-doc)
Fabien Caubet (former Post-doc)

Denis Le Bihan
Cyril Poupon
Luisa Ciobanu
Khieu Van Nguyen (current PhD)
Hang Tuan Nguyen (former PhD)

Timeline of our work on brain diffusion MRI

DMRI for tissue widely used 1990/2000-present, simple models

2008-2010 Formulate the mathematical problem for tissue (neurons and other cells)

2010-present Full-scale simulation and reduced model of dMRI signal due to tissue

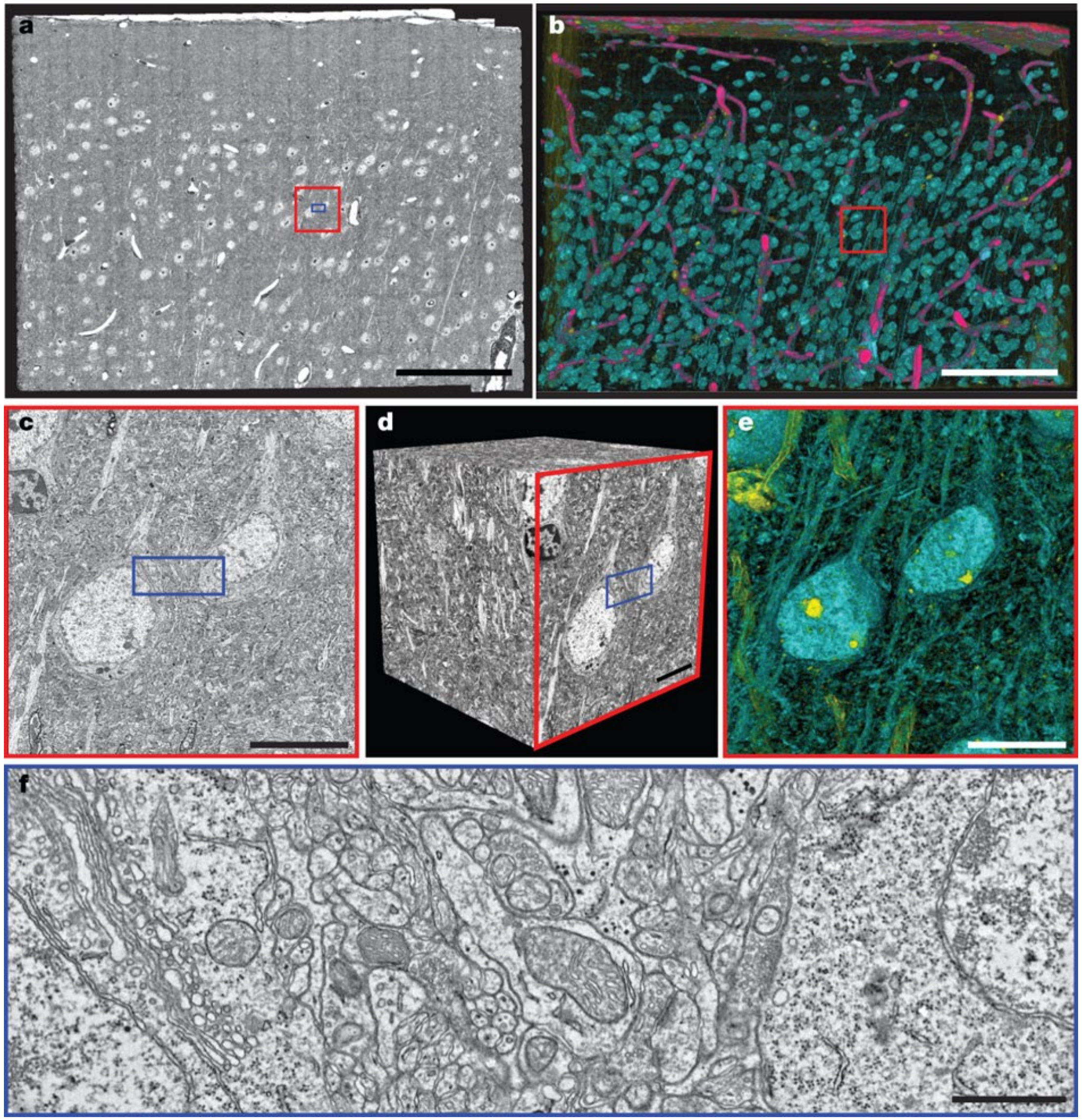
Intra-voxel incoherent motion (IVIM)
DMRI for micro-vessels started to be used 2000/2010

2013-present IVIM experiments to characterize brain micro-vessels

2015 Simulation and modeling of dMRI signal due to micro-vessels

Outline

1. Brain micro-structure is complex
2. MRI using "diffusion encoding" to "see" micro-structure
3. DMRI signal due to tissue (neurons+other cells)
4. DMRI signal due to micro-vessels



Large-scale Electron Micrograph

Pink: blood vessels

Yellow: nucleoli, oligodendrocyte nuclei, and myelin

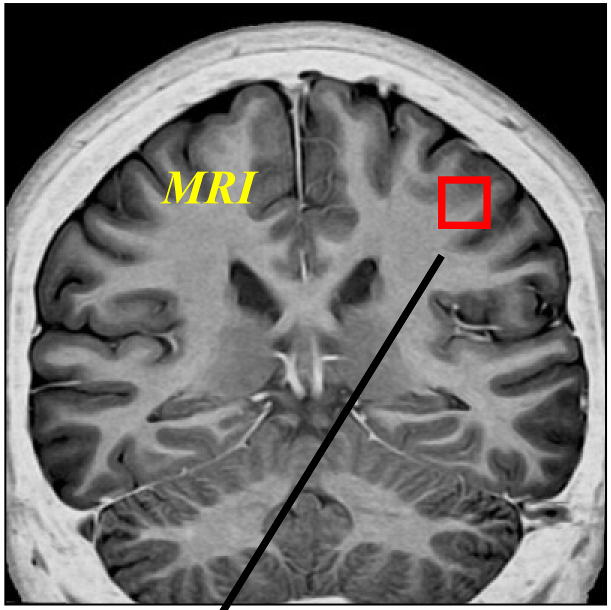
Aqua: cell bodies and dendrites.

Scale bars: a, b, 100 μm; c–e, 10μm; f, 1 μm.

Bock *et al. Nature* **471**, 177-182 (2011)

Magnetic resonance imaging (MRI)

Non-invasive, *in-vivo*



Spatial resolution:
One voxel = O(1 mm)
Much bigger than micro-structure

MRI signal: water proton magnetization over a volume called a voxel.

To give image contrast, magnetization is weighted by some quantity of the local tissue environment.

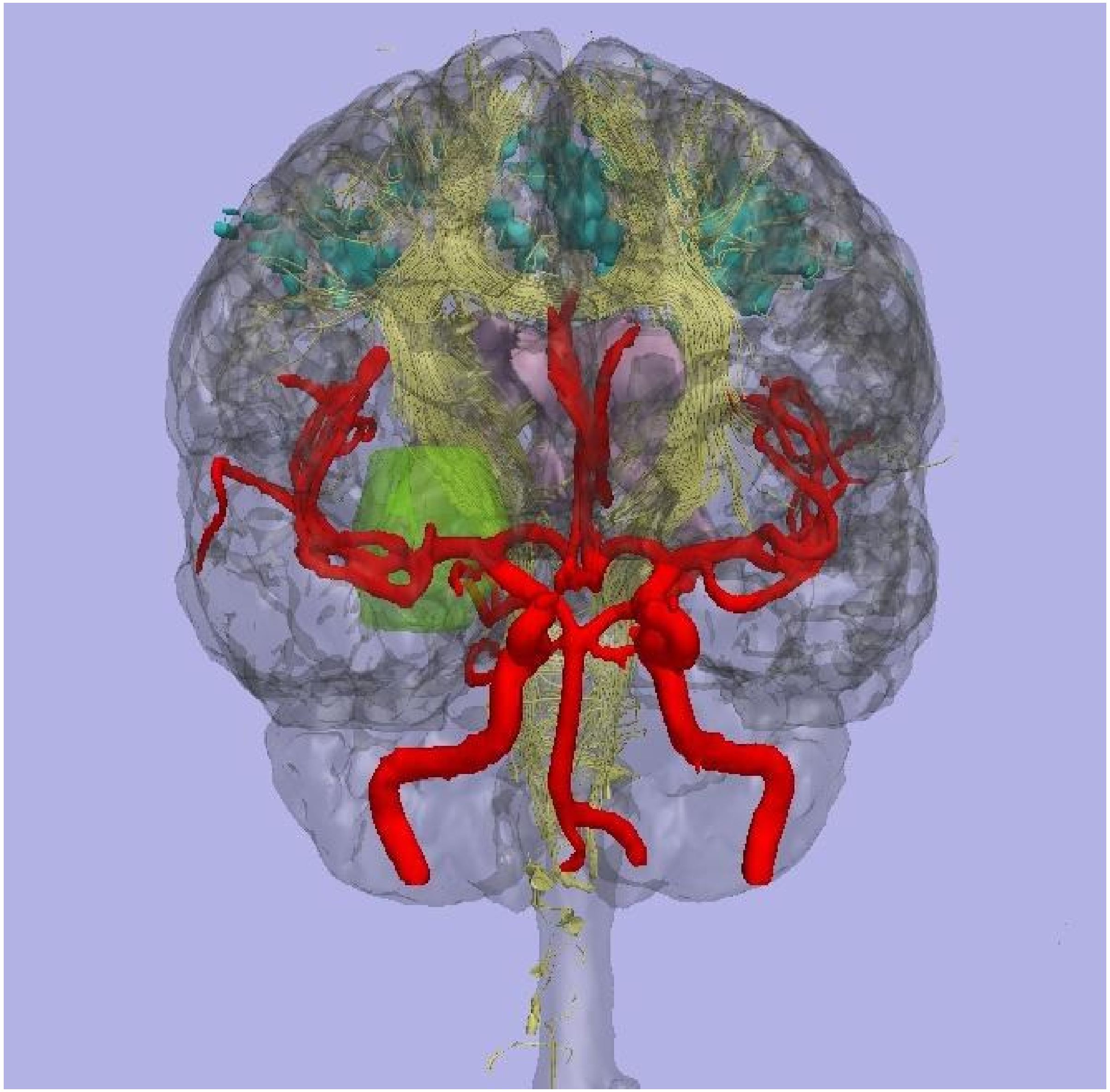
Contrast: (tissue structure)

1. Spin (water) density

2. Relaxation (T1,T2,T2*)

3. Water displacement (diffusion)

in each voxel



MRI contrasts

Gray: cortical surface.

Teal: fMRI activations

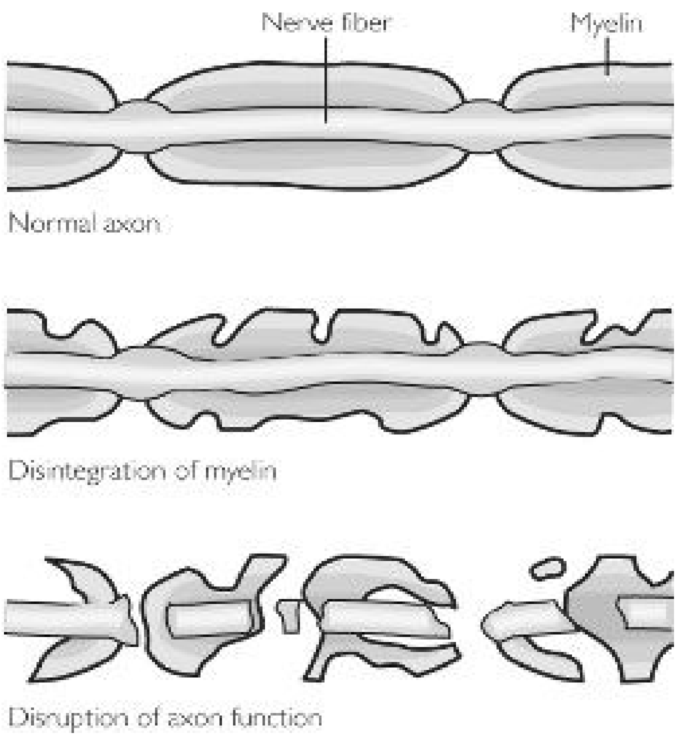
Red: arteries in red

Bright green: tumor

Yellow: white matter fiber

Diffusion Tensor and Functional MRI Fusion with Anatomical MRI for Image-Guided Neurosurgery. Sixth International Conference on Medical Image Computing and Computer-Assisted Intervention - MICCAI'03.

Diffusion MRI



Jonas: Mosby's Dictionary of Complementary and Alternative Medicine. (c) 2005, Elsevier.

Diffusion MRI can measure average incoherent displacement of water in a voxel during 10s of milliseconds

Displacement of water can tell us about cellular structure

Understanding of biomechanics of cells, structure of brain

Potential clinical value

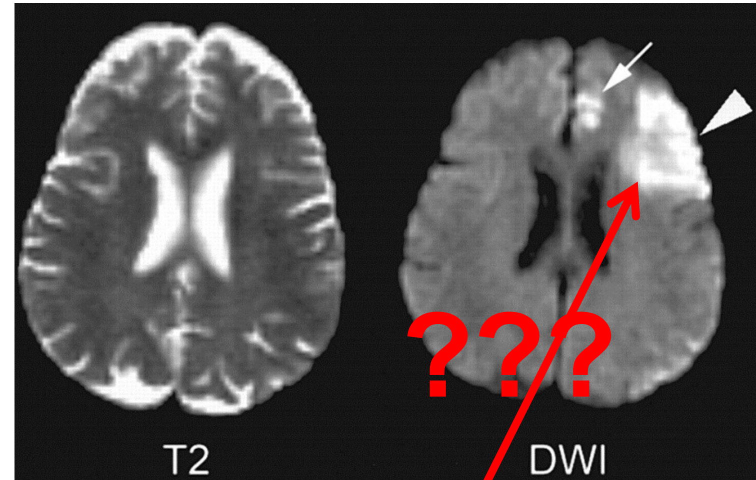
- Structure change in diseases

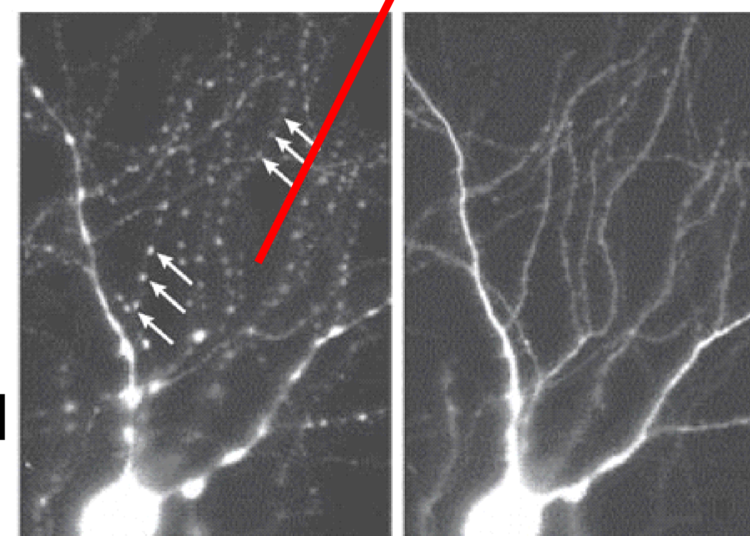
- Standard MRI: T2 relaxation (T2 contrast) at different spatial positions of brain

- In <u>diffusion</u> MRI (recently developed) magnetization is weighted by water displacement due to Brownian motion over 10s of ms (called measured diffusion time).

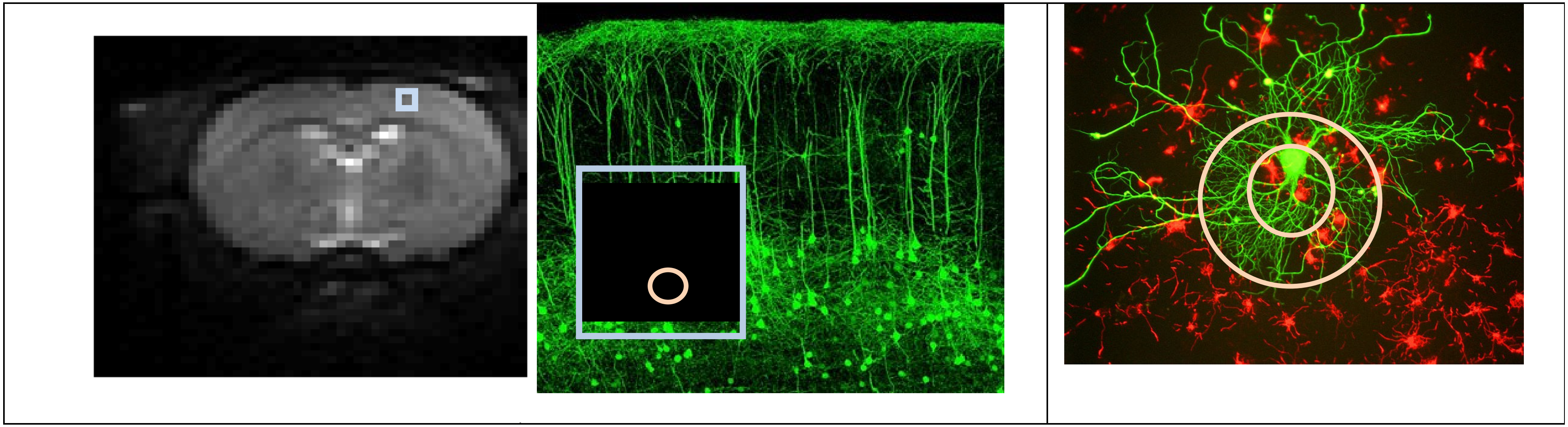
- Water displacement depends on local cell environment, hindered by cell membranes.

- Right: T2 contrast does not show dendrite beading hours after stroke, diffusion weighted image (DWI) does.





Nature Reviews | Neuroscience

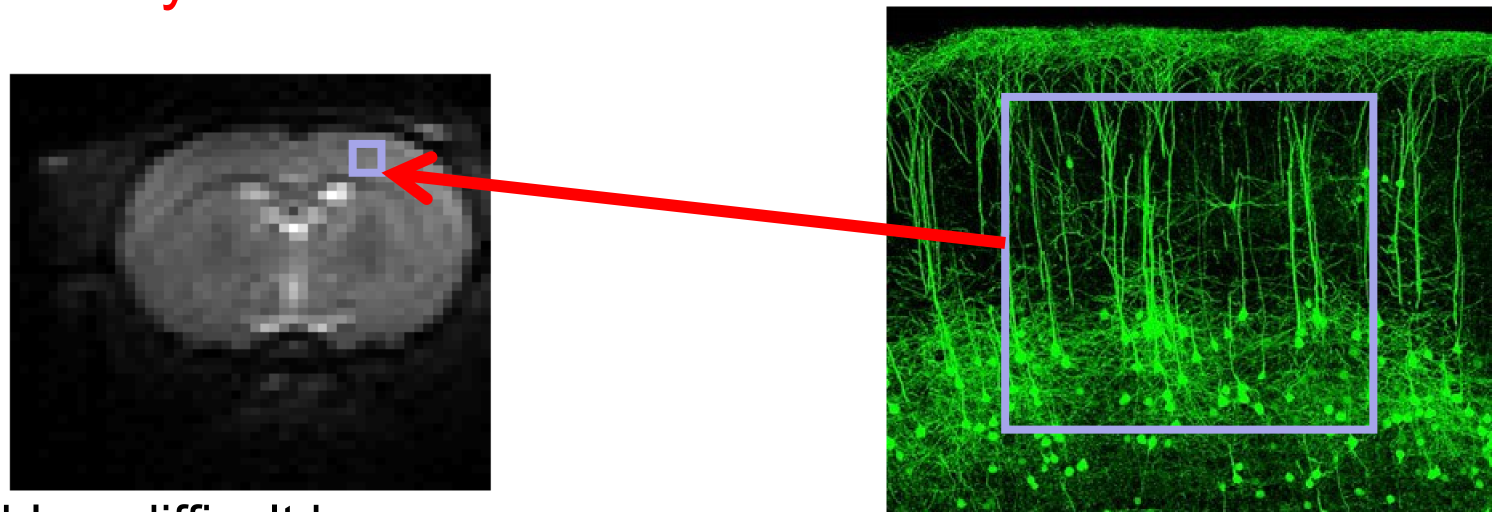


DMRI measures **incoherent water motion** during “diffusion time” between 10-40ms.

Root mean squared displacement: 6-13 μm

Voxel : 2mm x 2mm x 2 mm.

Goal: quantify dMRI contrast in terms of tissue micro-structure



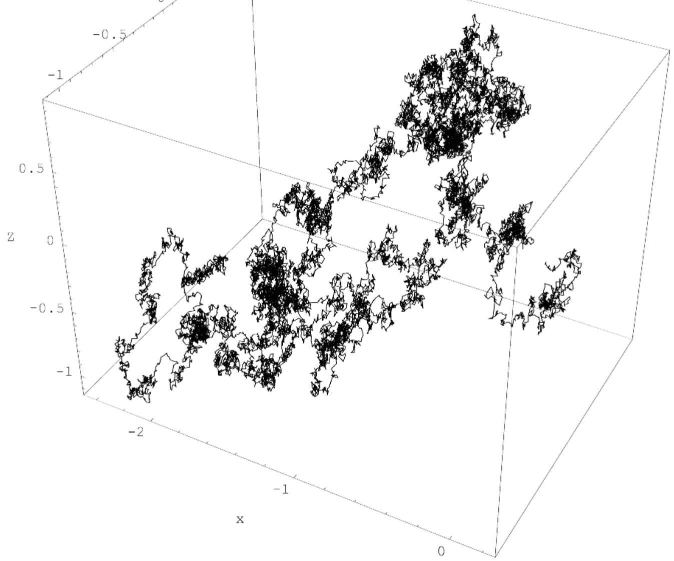
This problem difficult because:

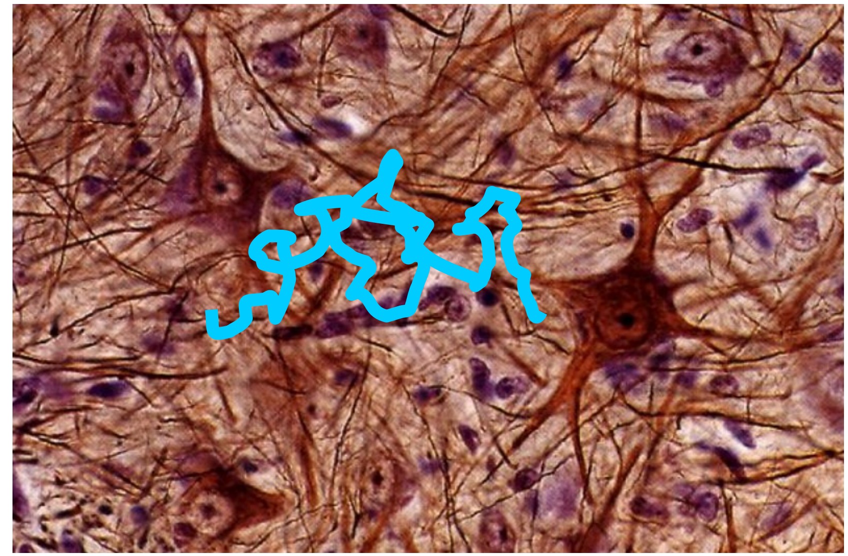
1. Dendrites (trees) and extra-cellular (EC) space (complement of densely packed dendrites) are anisotropic, numerically lower dimensional (dendrites 1 dim, EC 2 dim).
2. Multiple scales (5 orders of magnitude difference).

Extra-cellular space thickness 10-30nm	Dendrite radius 0.5-0.9 μm	Soma diameter 1-10μm	DMRI voxel 2mm

3. Cell membranes are permeable to water. Cells must be coupled together.

Simple (original) model of dMRI
Brain: 70 percent water
Brownian motion of water molecules





Mean-squared displacement
Can be obtained by dMRI

$$u(\vec{x},t,|\,\vec{x}_0) = \frac{e^{-\frac{\left\|\vec{x}-\vec{x}_0\right\|^2}{4\pi Dt}}}{(4\pi Dt)^{\frac{d}{2}}}$$

$$MSD = \int u(\vec{x},t,|\,\vec{x}_0)\left(\vec{x}-\vec{x}_0\right)^2 dx = 2dDt$$

How diffusion MRI assigns contrast to displacement

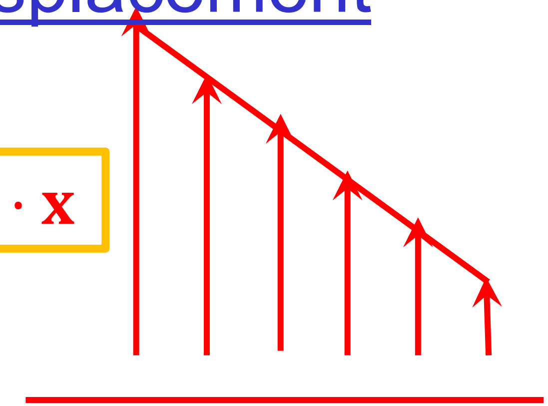
Water ^1H (hydrogen nuclei), spin ½

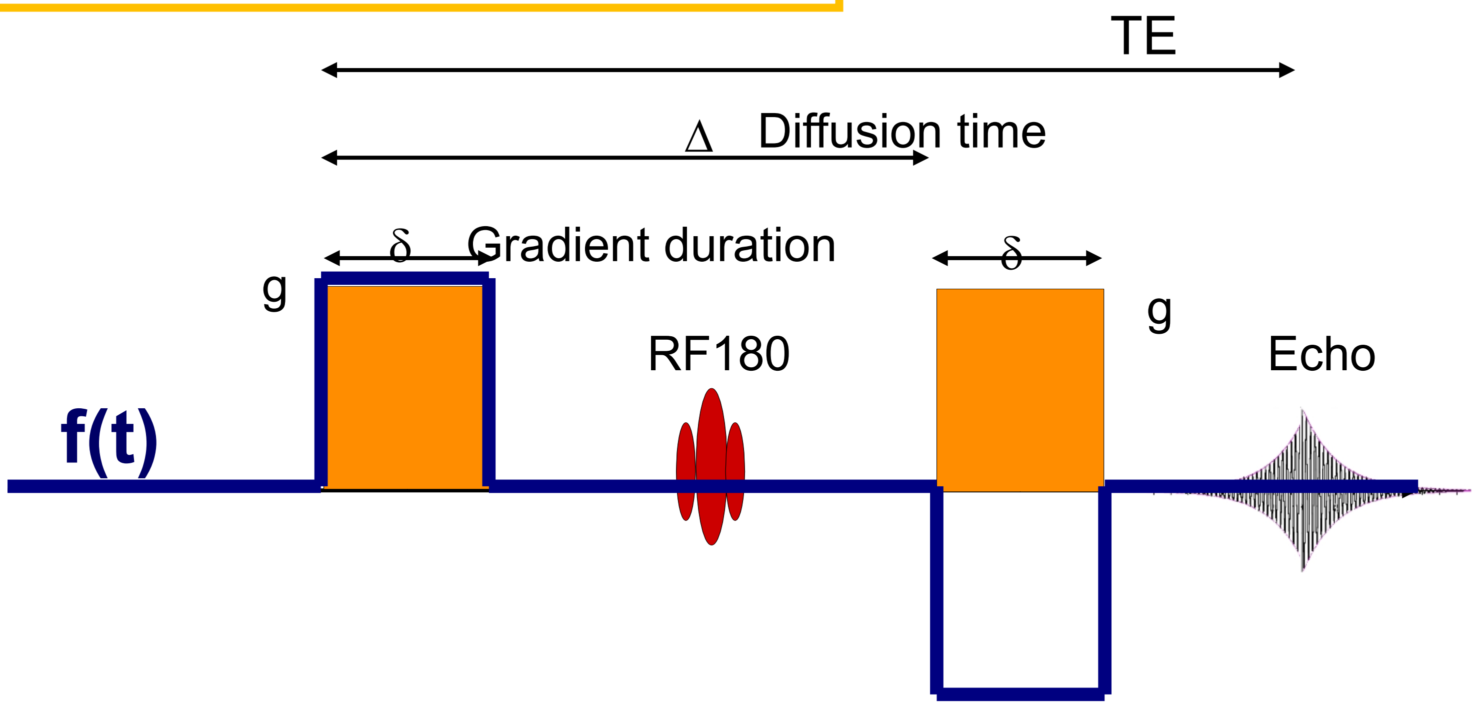
Precession Larmor frequency:

$$\int_t \gamma B(\mathbf{x}, t)\, dt$$

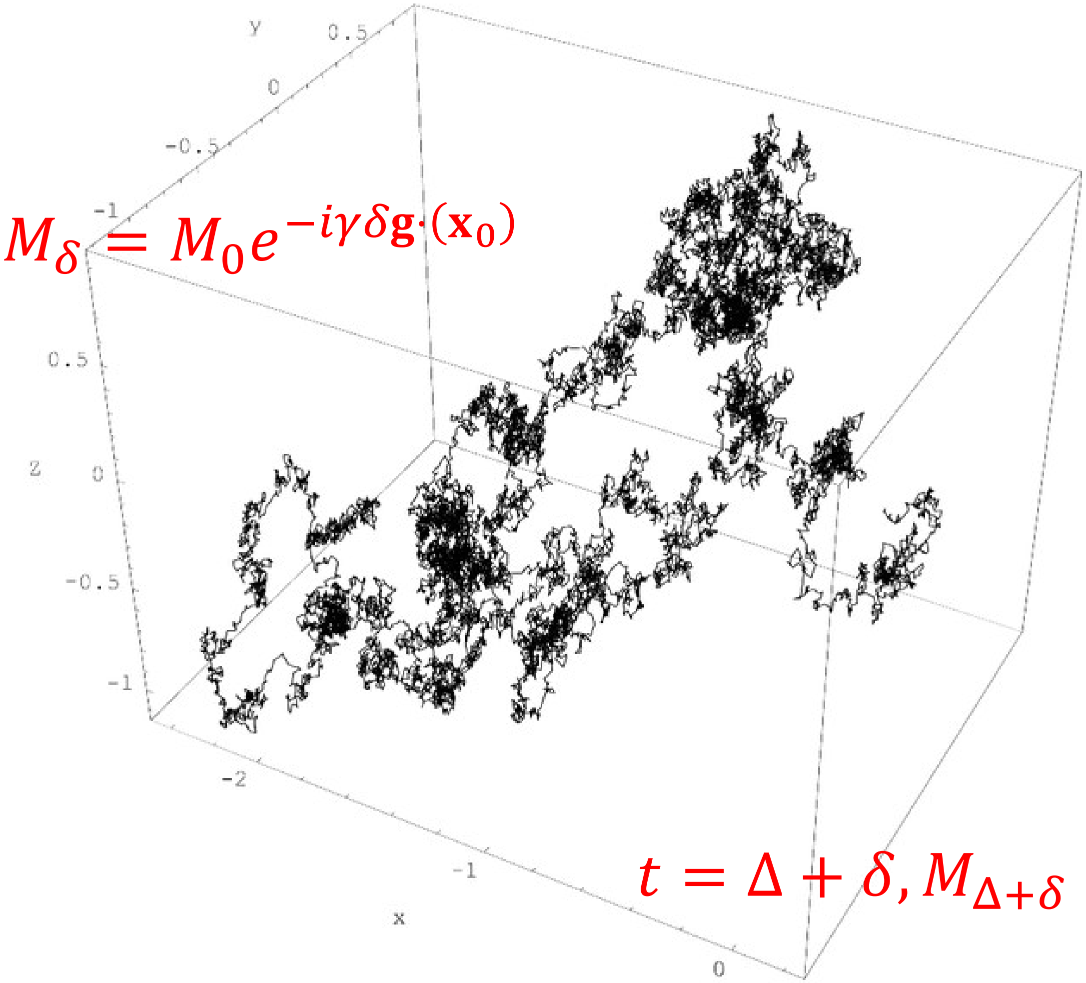
Proton: $\gamma/2\pi$ = 42.57 MHz / Tesla

$$B(\mathbf{x}, t) = f(t)\, \mathbf{g} \cdot \mathbf{x}$$



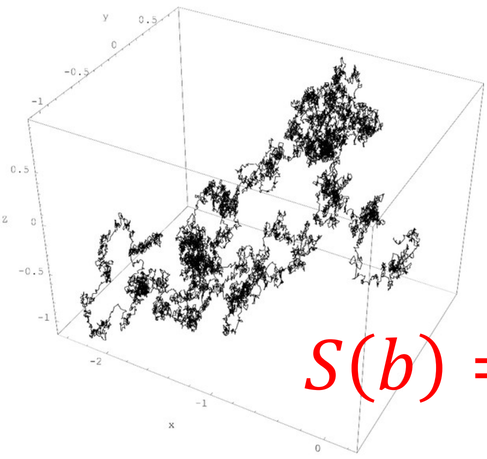


Pulsed gradient spin echo (PGSE) sequence (Stejskal-Tanner-1965)



$t = 0$: $M_\delta = M_0 e^{-i\gamma\delta\mathbf{g}\cdot(\mathbf{x}_0)}$

$t = \Delta + \delta, M_{\Delta+\delta} = M_0 e^{i\gamma\delta\mathbf{g}\cdot(\mathbf{x}_{\Delta+\delta} - \mathbf{x}_0)}$



$$u(\mathbf{x}, t, |\mathbf{x}_0) = \frac{e^{-\frac{\|\mathbf{x}-\mathbf{x}_0\|^2}{4Dt}}}{(4\pi D t)^{\frac{3}{2}}}$$

$$S(b) = \int_{\mathbf{x}\in V}\int_{\mathbf{x}_0\in V} u(\mathbf{x}, \Delta+\delta|\mathbf{x}_0\,)\, e^{i\gamma\delta\mathbf{g}\cdot(\mathbf{x}(\Delta+\delta)-\mathbf{x}(0))}\, d\mathbf{x}\, d\mathbf{x}_0$$

$$= e^{-D\,\gamma^2\delta^2\|\mathbf{g}\|^2\left(\Delta-\frac{\delta}{3}\right)}$$

$$b(\mathbf{g}, \Delta, \delta) \equiv \gamma^2\delta^2\|\mathbf{g}\|^2\left(\Delta-\frac{\delta}{3}\right),$$

Experimental parameters

g **Δ,** δ can be varied

$ADC \equiv -\frac{\mathrm{d}}{\mathrm{db}}\log(S(b))$:

“apparent diffusion coefficient”

Fitted at every voxel

MSD/(2Δ) = ADC

Brain gray matter: ADC around 10^{-3} mm²/s

Root MSD: 6-13 μm

Diffusion is not Gaussian in biological tissues

(In each voxel)

Human visual cortex

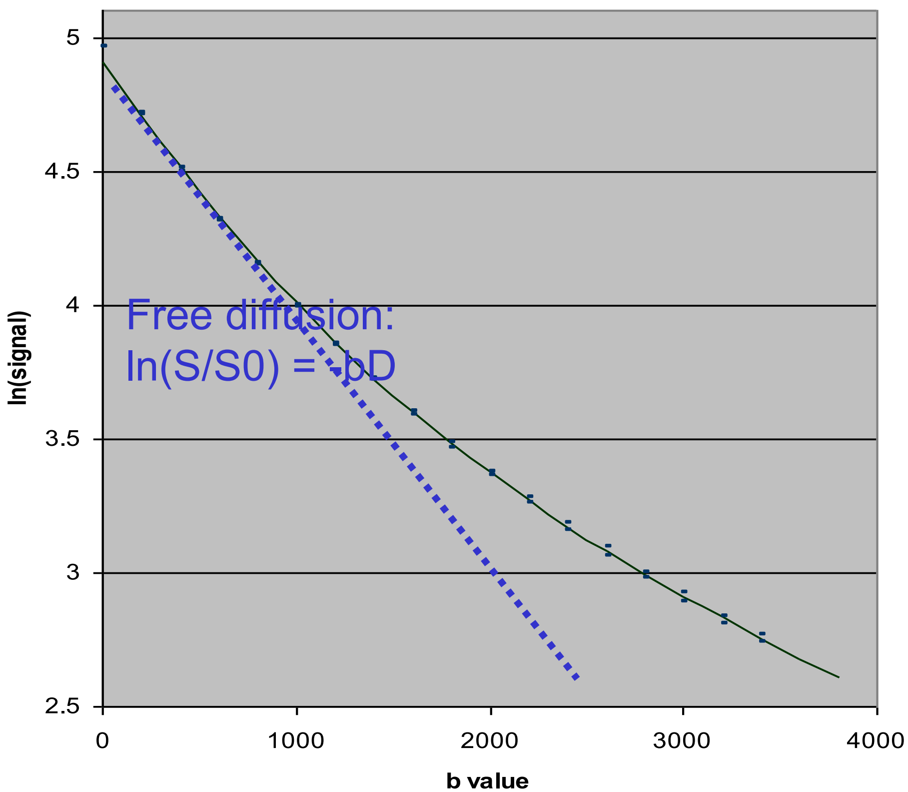
(Le Bihan et al. PNAS 2006).

$$\frac{S}{S_0} \neq e^{-(ADC)b}$$

Log plot not a straight line.

Simple model is "wrong"

Physicists try a different simple model



$$\boxed{\frac{S}{S_0} = f_{fast} e^{-D_{fast} b} + f_{slow} e^{-D_{slow} b}.}$$

f_{fast}= 65.9%, f_{slow}= 34.1%

D_{fast} = 1.39 10^{-3} mm²/s,
D_{slow} = 3.25 10^{-4} mm²/s

Reference model: Bloch-Torrey PDE

$$\frac{\partial M^j(\mathbf{x},t|\mathbf{g})}{\partial t} = i\,\gamma f(t)(\mathbf{g}\cdot\mathbf{x})M^j(\mathbf{x},t|\mathbf{g}) + \nabla\cdot\left(\mathrm{D}^{\mathrm{j}}\nabla M^j(\mathbf{x},t|\mathbf{g})\right), \mathbf{x}\in\Omega^j\ .$$

PDE with interface condition between cells and the extra-cellular space

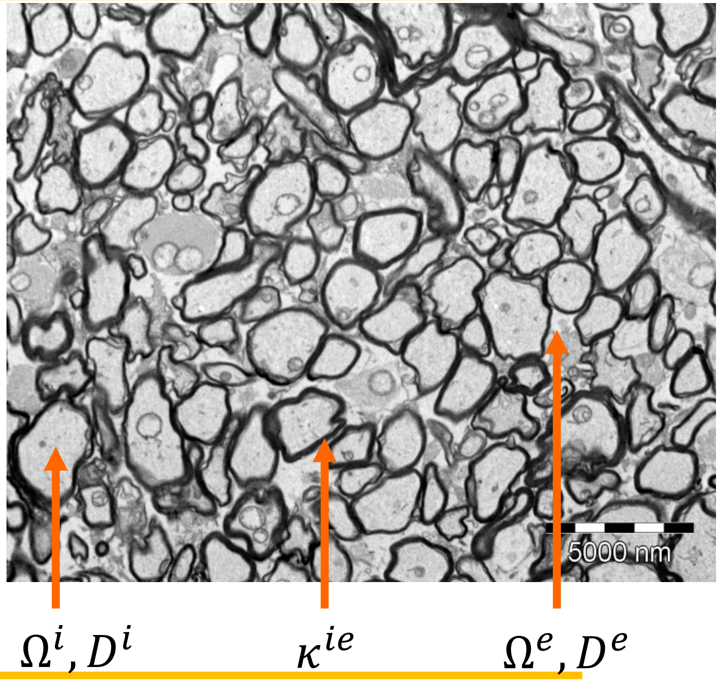
$$D^j\nabla M^j(\mathbf{x},t\,|\mathbf{g})\cdot\mathbf{n}^{\mathrm{j}}(\mathbf{x}) = -D^k\,\nabla M^k\,(\mathbf{x},t|\mathbf{g})\cdot\mathbf{n}^{\mathrm{k}}(\mathbf{x}),\qquad \mathbf{x}\in\Gamma^{jk},$$

$$D^j\nabla M^j(\mathbf{x},t\,|\mathbf{g})\cdot\mathbf{n}^{\mathrm{j}}(\mathbf{x}) = \boldsymbol{\kappa}\left(M^j\,(\mathbf{x},t,|\mathbf{g}) - M^k(\mathbf{x},t|\mathbf{g})\right),\qquad \mathbf{x}\in\Gamma^{jk},$$

$$S(\mathbf{g},T_{end}) = \sum_j\int_{\mathbf{x}\in\Omega^j} M^j(\mathbf{x},t|\mathbf{g})d\mathbf{x}\ \approx \exp(-ADC\ b_{experi}).$$

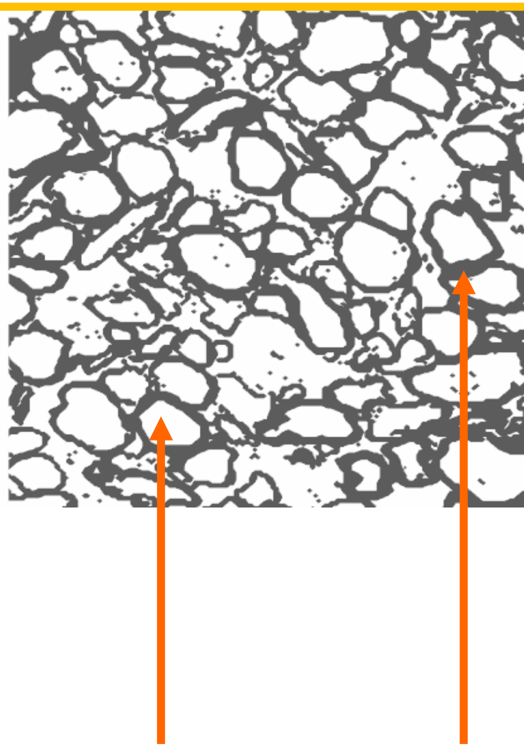
M: magnetization
g: magnetic field gradient
T_{end}: diffusion time

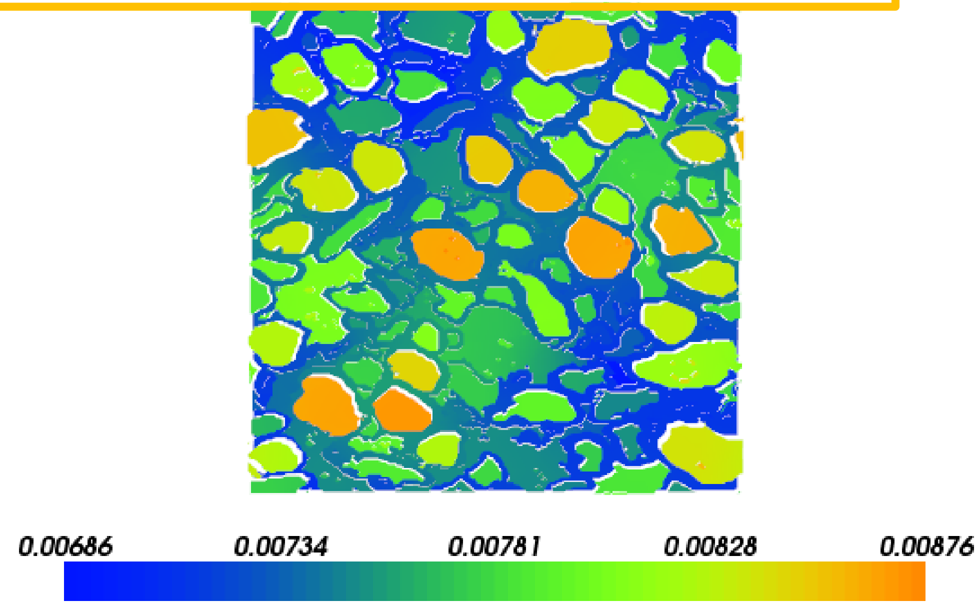
From signal, want to quantify
cell geometry and membrane permeability.



1. *Numerical simulation of diffusion MRI signals using an adaptive time-stepping method, J.-R. Li, D. Calhoun, C. Poupon, D. Le Bihan. Physics in Medicine and Biology, 2013.*

2. *A finite elements method to solve the Bloch-Torrey equation applied to diffusion magnetic resonance imaging, D.V. Nguyen, J.R. Li, D. Grebenkov, D. Le Bihan, Journal of Computational Physics, 2014.*



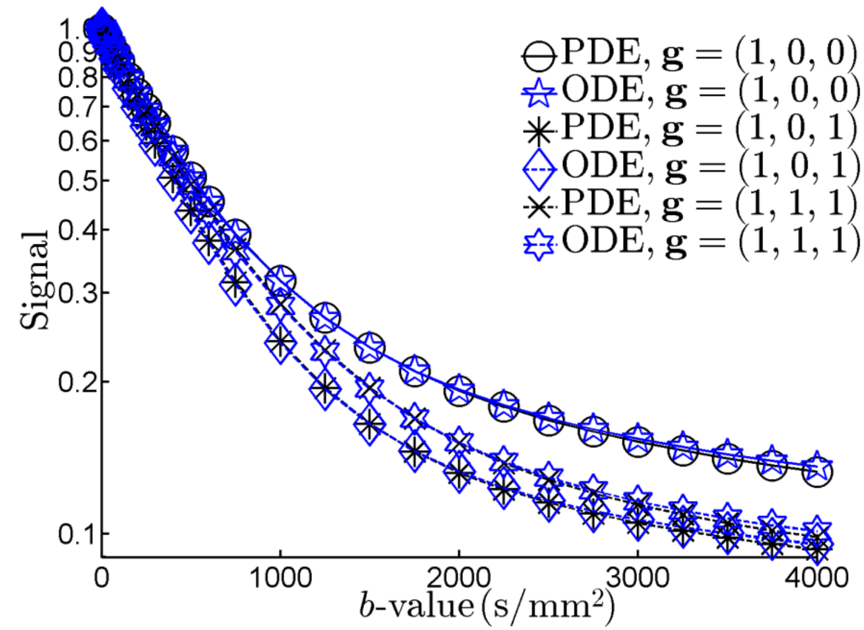


$M(\mathbf{x}, t\,|\mathbf{g})$

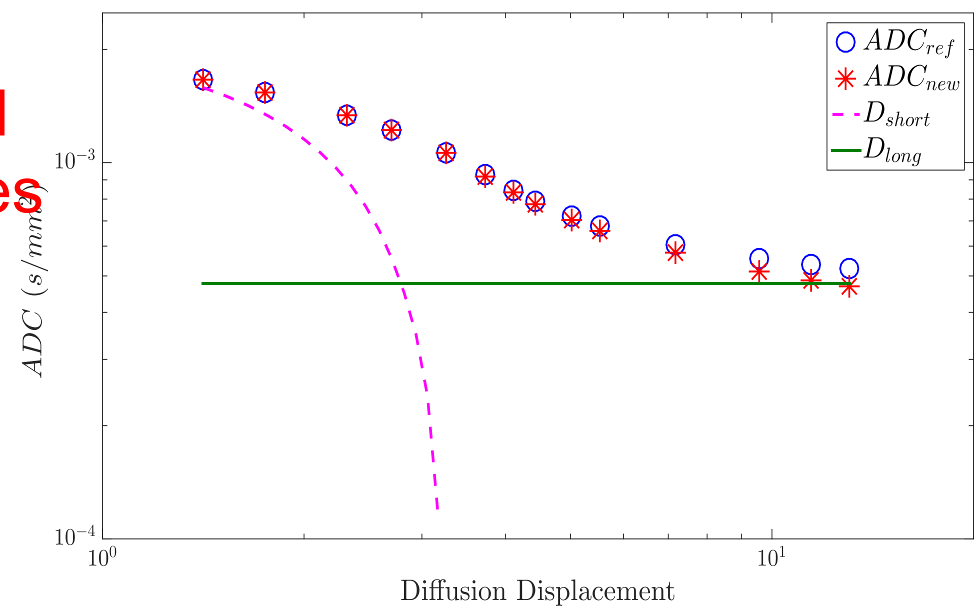
D^i D^e

On-going work (2013 →)
Mathematical analysis

2012: Obtained macroscopic (ODE) model using homogenization
Valid in long diffusion time regime.



More relevant to brain dMRI:
2013: Look for macroscopic model valid at wide range of diffusion times



PhD Simona Schiavi 2013-present (co-directed w. H. Haddar)

Timeline of our work on brain diffusion MRI

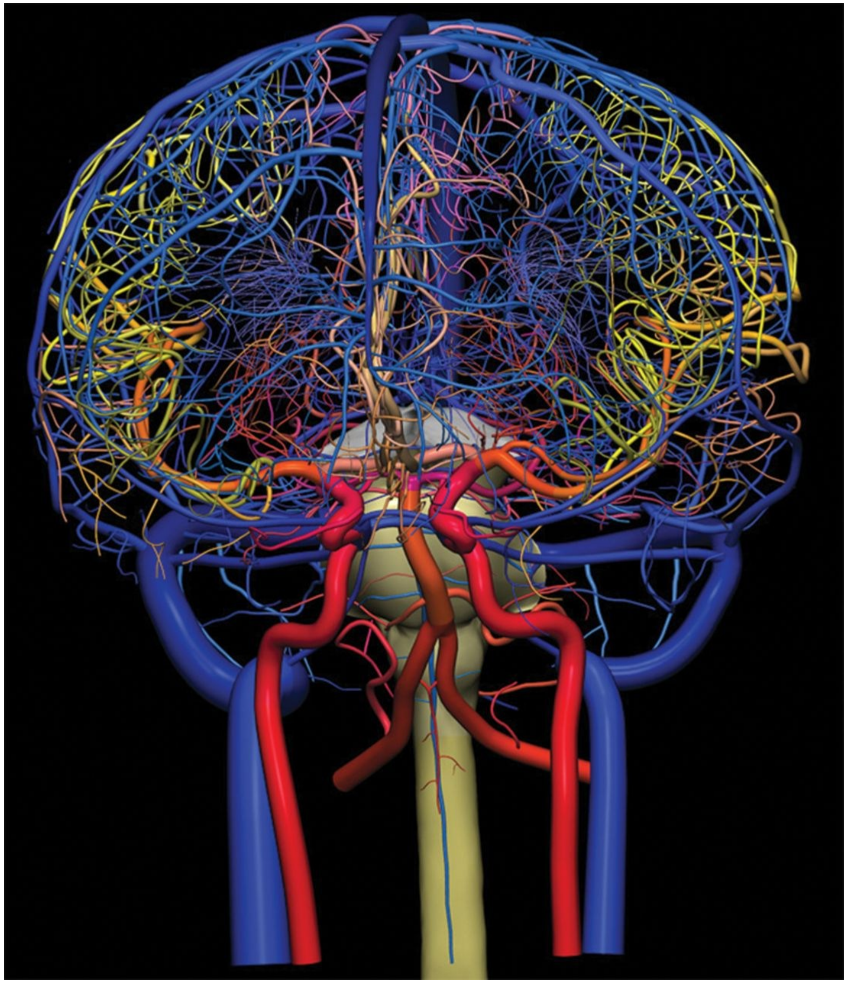
(DMRI for micro-vessels started to be used 2000/2010, simple models)

Intra-voxel incoherent motion (IVIM)

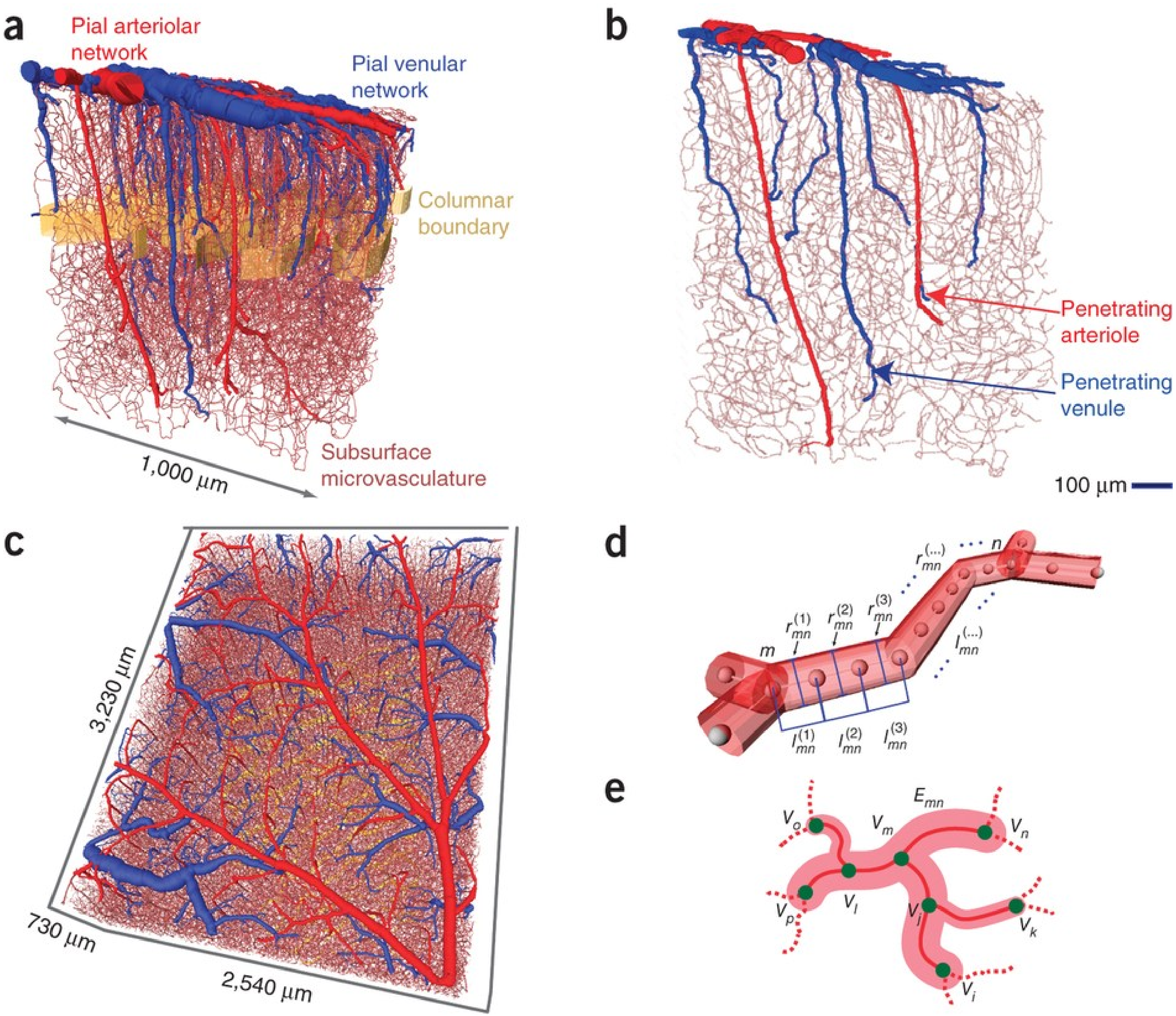
2013-present DMRI experiments to characterize brain micro-vessels

2015 Simulation and modeling of dMRI signal due to micro-vessels

The cerebro-vasculature



Dragos A. Nita Neurology 2012;79:e10

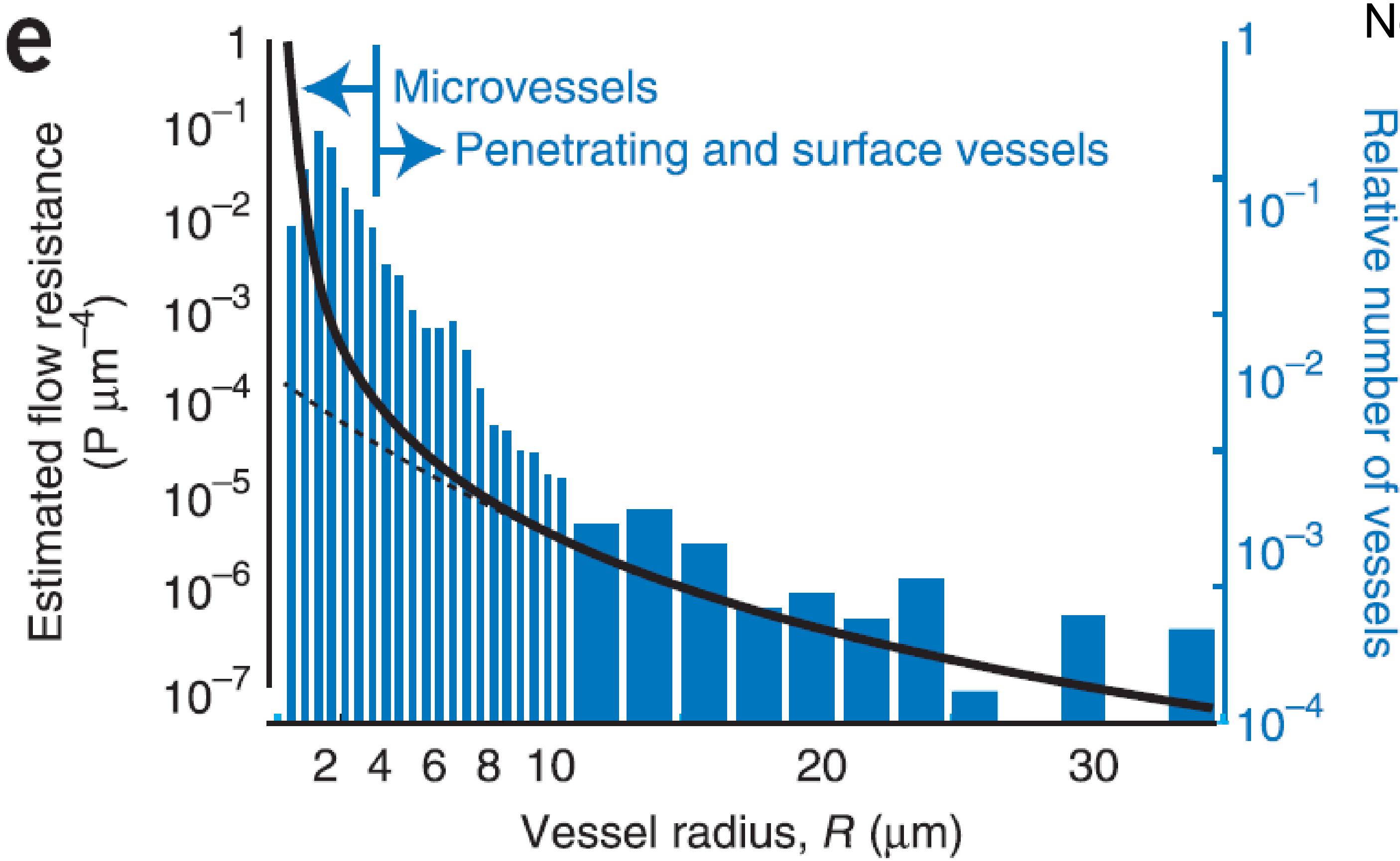


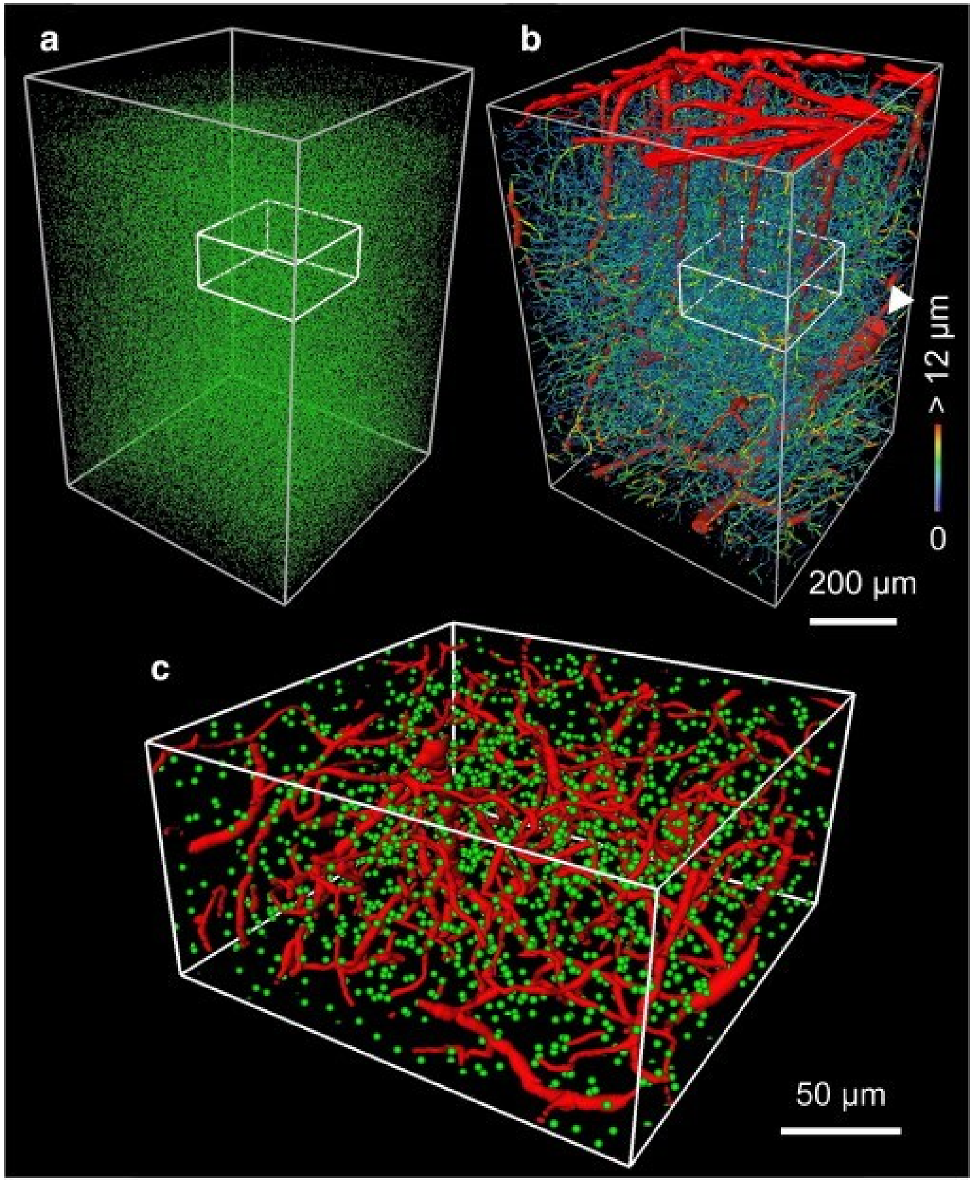
The cortical angiome: an interconnected vascular network with noncolumnar patterns of blood flow

Blinder et al. Nature Neuroscience 2013

The cortical angiome: an interconnected vascular network with noncolumnar patterns of blood flow

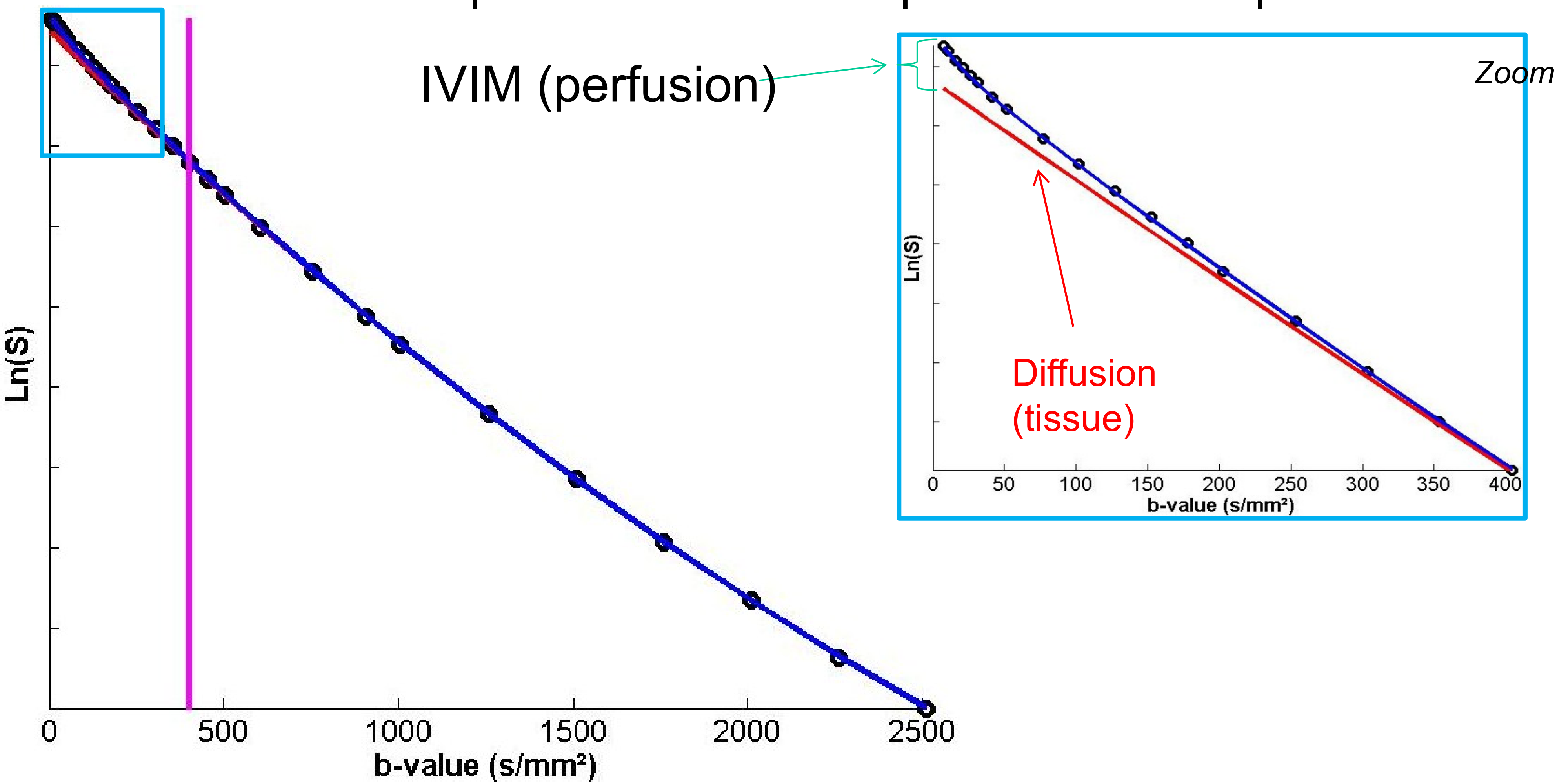
Blinder et al. Nature Neuroscience 2013



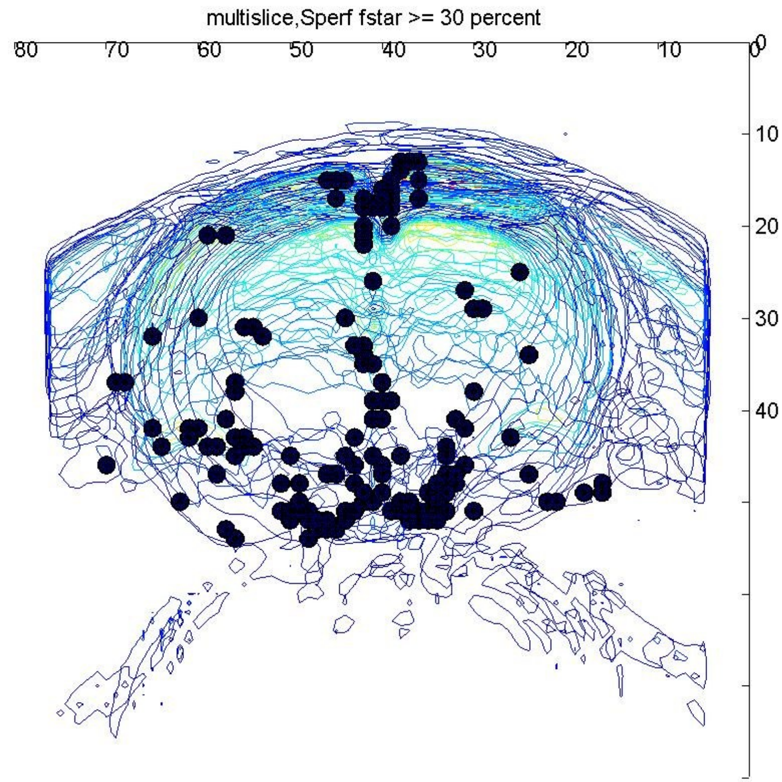


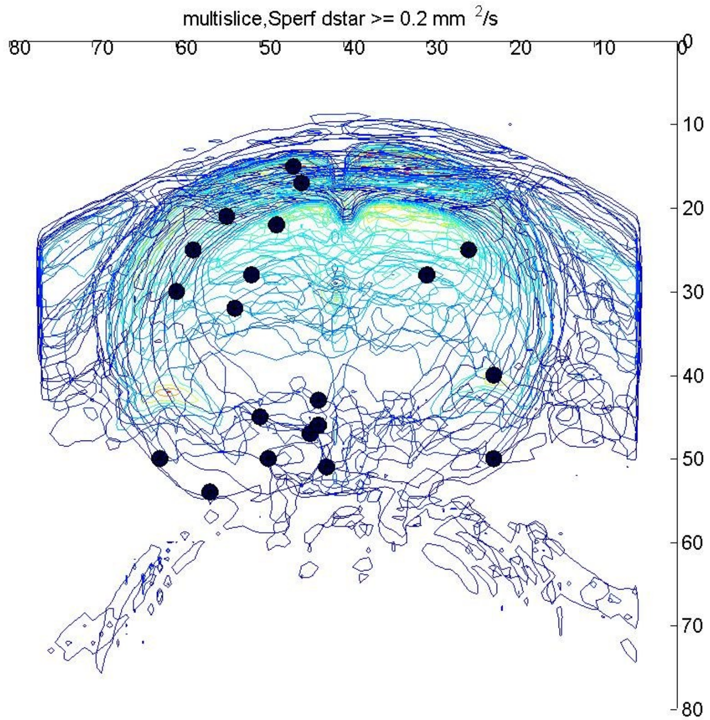
Jingpeng Wu, Yong He, Zhongqin Yang, Congdi Guo, Qingming Luo, Wei Zhou, Shangbin Chen, Anan Li, Benyi Xiong, Tao Jiang, Hui Gong
NeuroImage 2014

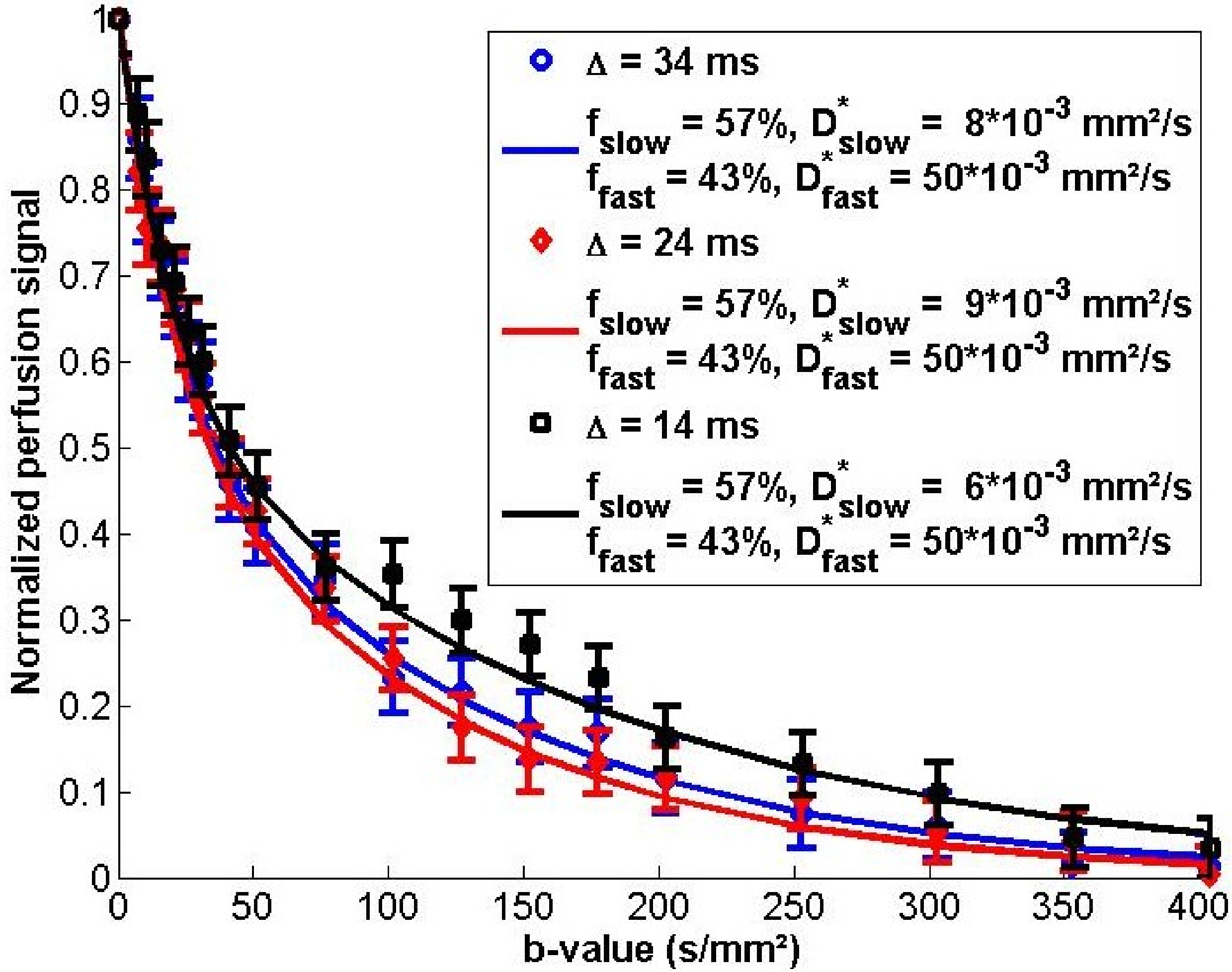
Experimental data acquired at Neurospin



The IVIM (perfusion) signal is what remains after removing the diffusion (tissue) component of the MRI signal.


multislice,Sperf fstar >= 30 percent
80
70
60
50
40
30
20
10
0
10
20
30
40

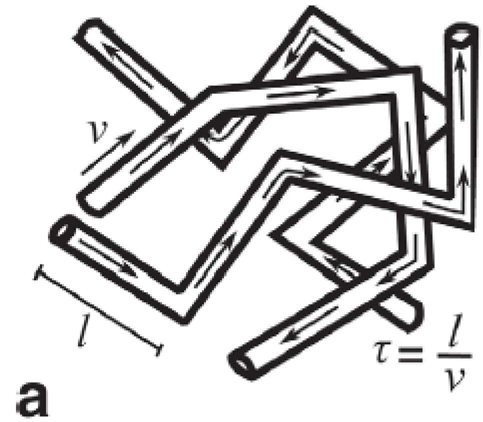

multislice,Sperf dstar >= 0.2 mm ^{2}/s
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80



Simple model: suppose there are two pools of blood:
a « slow » pool (0.2 < v < 4.2 mm/s)
a « fast » pool (4.2 < v < 15 mm/s).

Numerical simulations of microvascular networks

Step 1
Create a microvascular network consisting of capillary segments: (length L, direction $\vec{e}$ and blood flow velocity v)



Example of a simulated microvascular network

Step 2
Calculate the IVIM signal coming from this network using:

$$\frac{S}{S_0} = e^{-i\varphi} \quad \varphi = \gamma \int_0^{TE} \vec{x}(t) \cdot \vec{G}(t)\, dt$$

- φ - phase of the MRI signal
- $\vec{x}(t)$ - spin position vector
- $\vec{G}(t)$ - encoding gradient vector

Step 3
Generate simulated signals for Gaussian distributions of lengths (L = 50 ± 50 μm [1]) and velocities ($v \pm \sigma_v$), with v varying between 0.2 and 15 mm/s and σ_v between 0.05 and 1

Two pools of blood:

Interpretation of data

$$F_{IVIM} = f_{slow} e^{-bD^*_{slow}} + f_{fast} e^{-bD^*_{fast}}$$

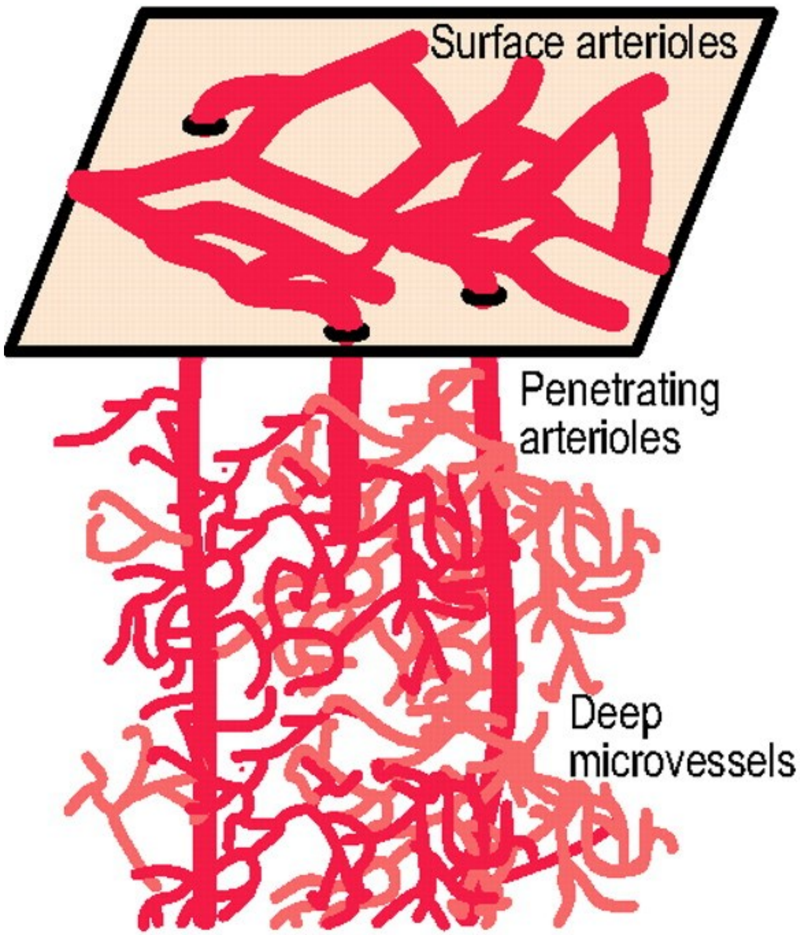
⇒A « fast » pool: flow within vessels with significant sizes relative to the voxel size

⇒$\boldsymbol{v_{fast}}$ = 7.92 ± 3.95 mm/s, coherent with medium size vessels such as penetrating arterioles or venules [1]

⇒A « slow » pool: flow in small vessels and capillaries (classical IVIM model)

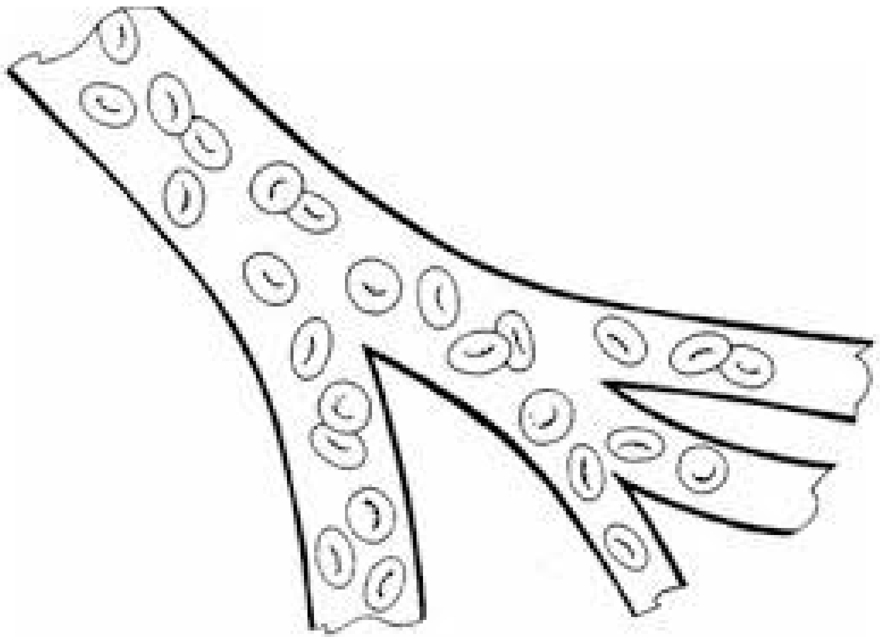
⇒D^*_{slow} 15 times smaller than D^*_{fast}

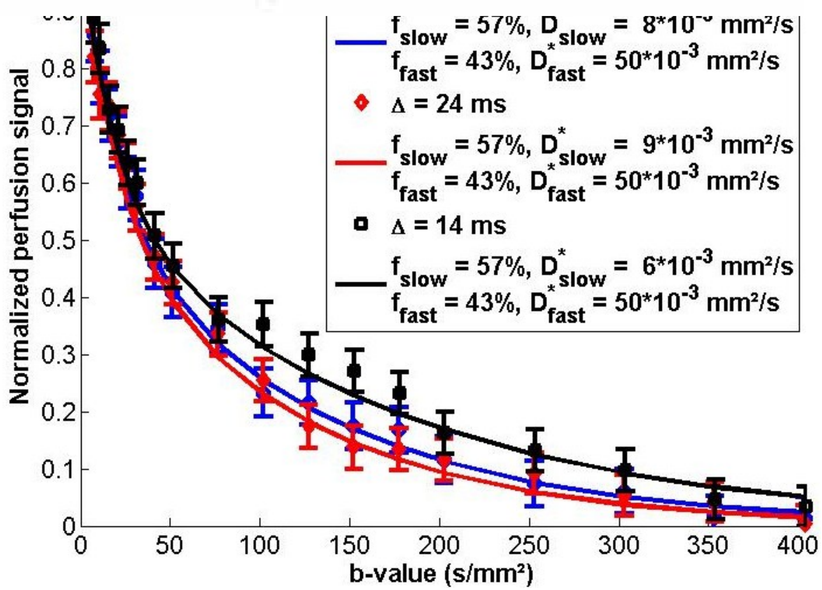
⇒$\boldsymbol{v_{slow}}$ = 1.72 ± 0.30 mm/s, coherent with capillary bed vessels [2]



Credit: Nishimura N., 2007, PNAS

[1] Linninger A. A., 2013, Ann Biomed Eng, [2] Unekawa M., 2010, Brain Res





Need more sophisticated simulations to explain data

In the brain cortex 5 percent blood volume.

Blood contains red blood cells (50 percent volume)
and plasma (50 percent volume)

Red blood cells contain 70 percent water
Plasma is 92 percent water.

Ready for some fluids simulations to get average blood water displacement during 10s of milliseconds!

Thank you!

(Welcome any suggestions and ideas)