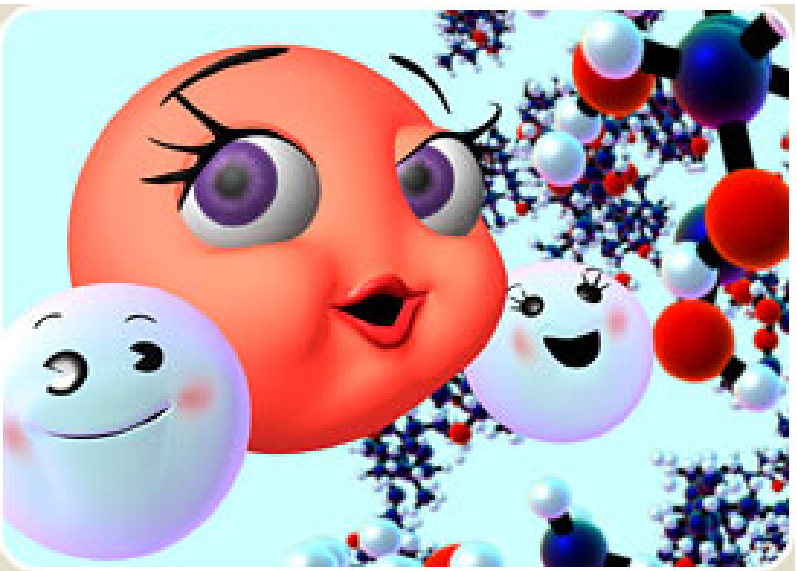


Membranes, water and diffusion: Potential for brain imaging

Denis Le Bihan
NeuroSpin Director, CEA-Saclay, France
Kyoto University, Japan
Institut de France, Academy of Sciences

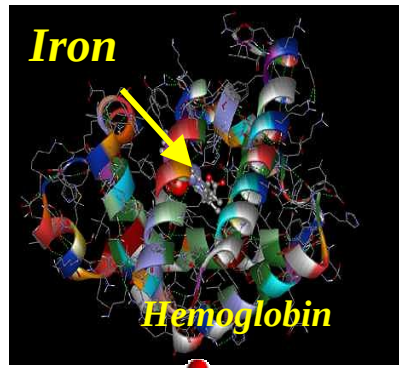
Functional neuroimaging (PET, fMRI): A Water Story

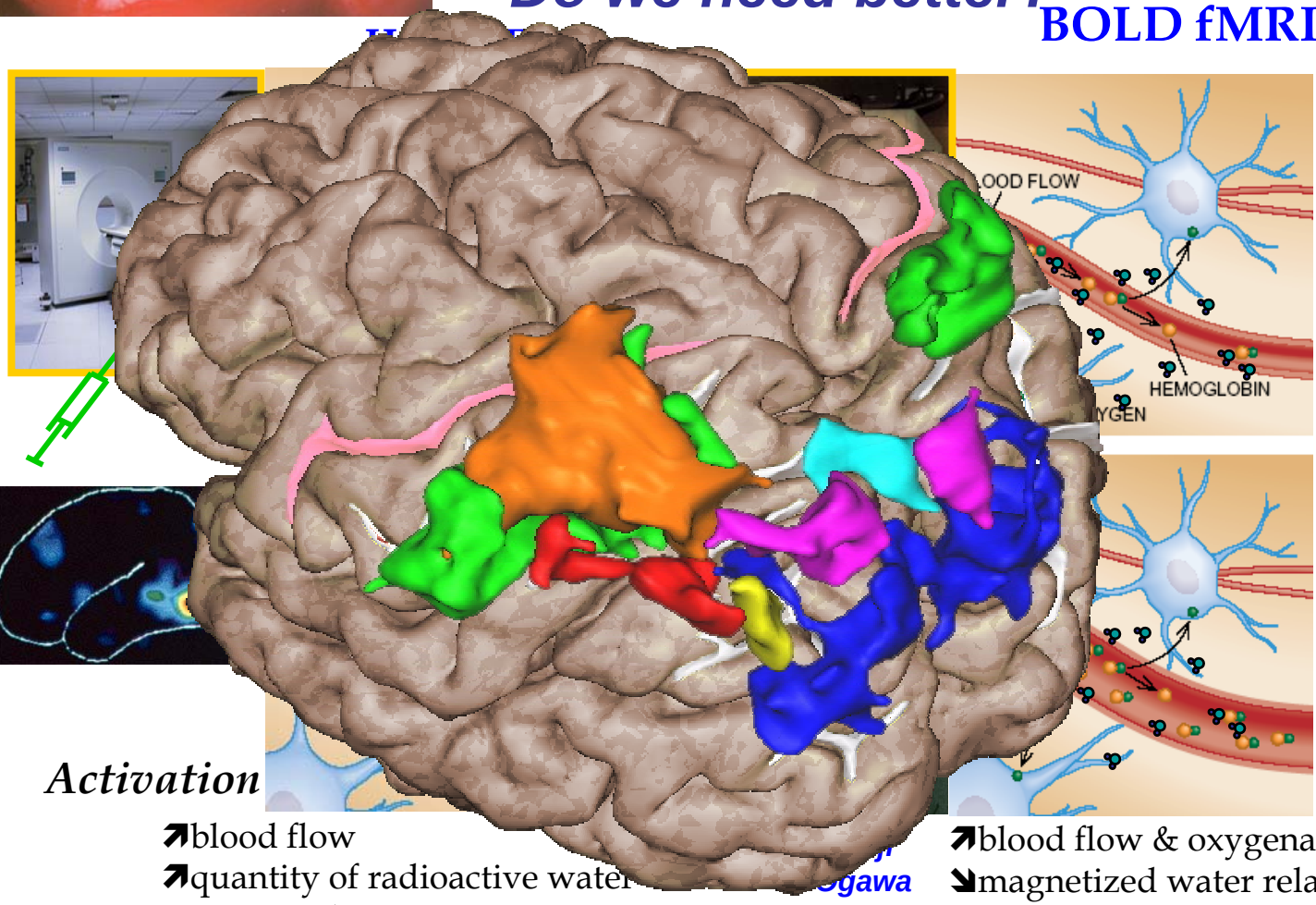
Coupling between blood flow, metabolism and activation

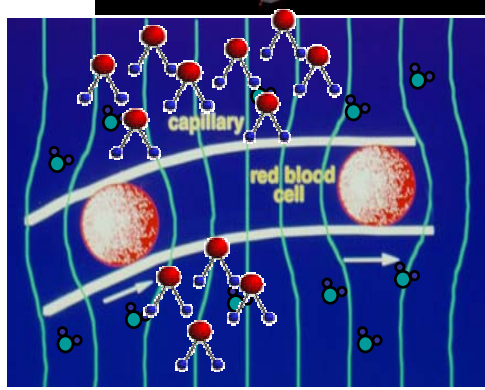
(Roy & Sherrington, 1894)

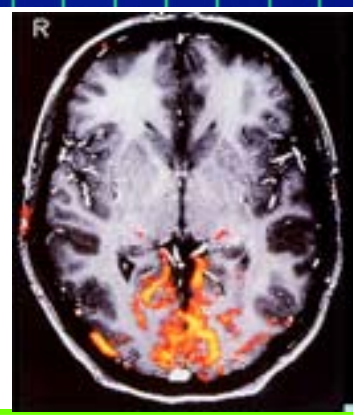
Do we need better?

BOLD fMRI









Activation

↗blood flow
↗quantity of radioactive water in activated tissues

Ogawa

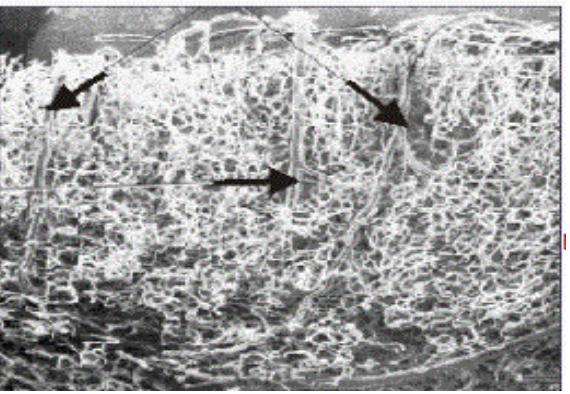
↗blood flow & oxygenation
↘magnetized water relaxation in/near vessels

Radioactive water

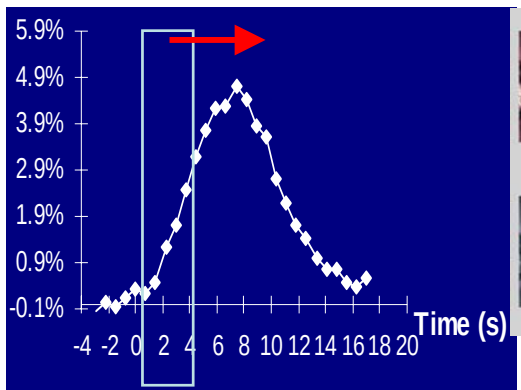
Magnetized water

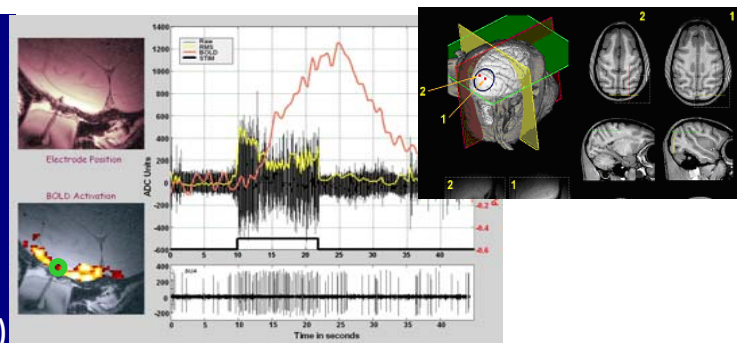
BOLD fMRI: *Hemodynamic events…*

Coupling between CBF, metabolism and activation *(Roy & Sherrington, 1894)*

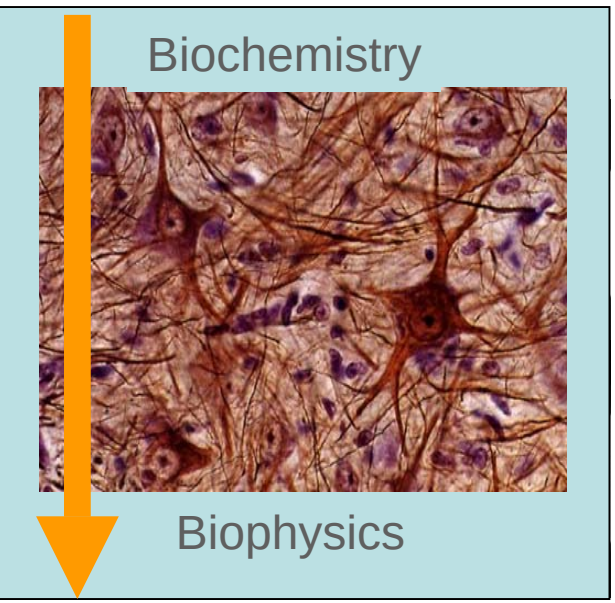


- **Rationale & mechanism? *metabolism*** (glucose) vs ***neurogenic***?
  → *activation of glial cells by glutamate* → *arachidonic acid –> vasodilation/vasoconstriction (Gordon et al. Nature. 456, 745, 2008)*
  → *pO_2? large increase in blood flow but small increase in O_2 consumption*
- **fMRI BOLD not always coupled to neuronal activity or metabolism!** *Anticipatory signals (Sirotin et al. Nature 457, 475, 2009), pathology, drugs: indomethacin, antihistamin,…*





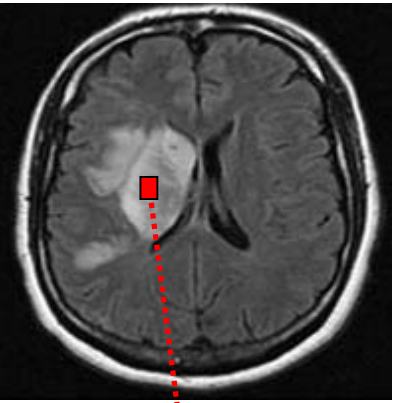
4.7T monkey Logothetis et al. 2001. Nature
→ Functional hyperhemia & local field potentials



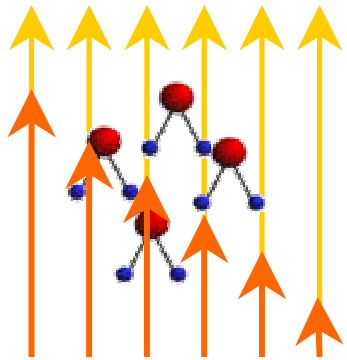
→ *Other more direct mechanisms?*

- ☞ Small induced **electric axonal currents (≈ EEG/MEG)**
- ☞ **Neurotransmission:** Ca^{2+} inflow as seen with MnMRI
- ☞ **Structural events** induced in cortical cells
  → **Water diffusion MRI** *[Darquie et al. PNAS 2001]*

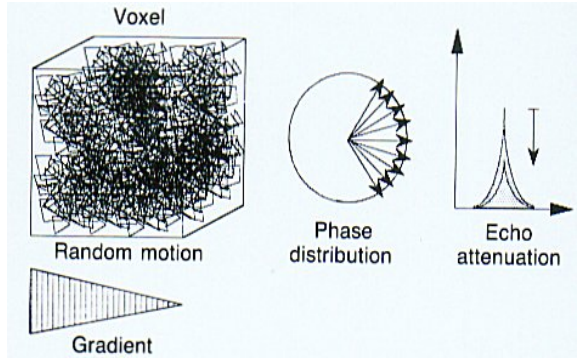
IRM de DIFFUSION



Echelle macroscopique



Eau (noyaux d'hydrogène)

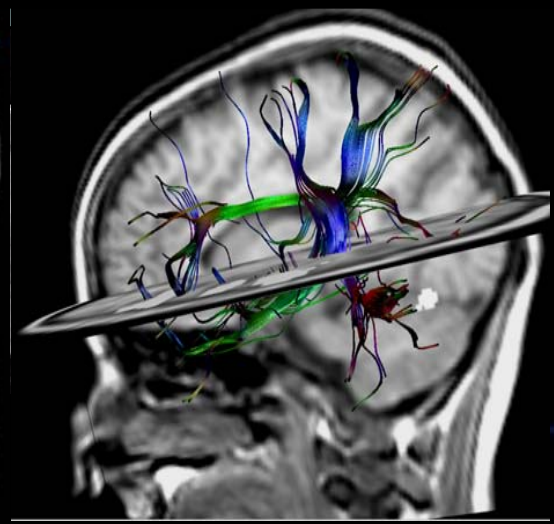


Le Bihan & Breton, CRASS, 1985

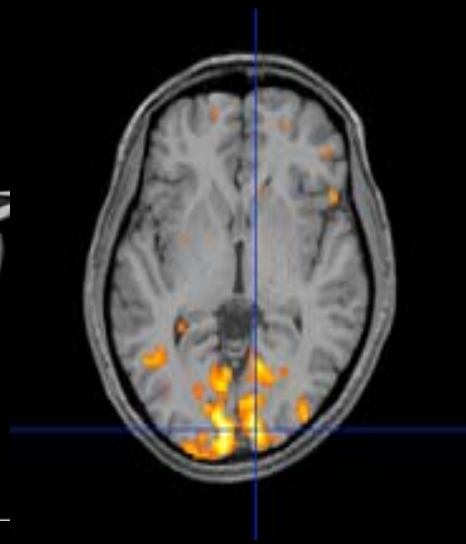
Cancer

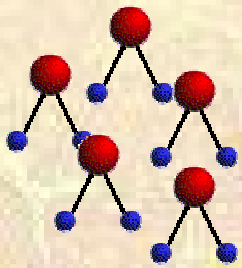
Stroke

Brain connectivity



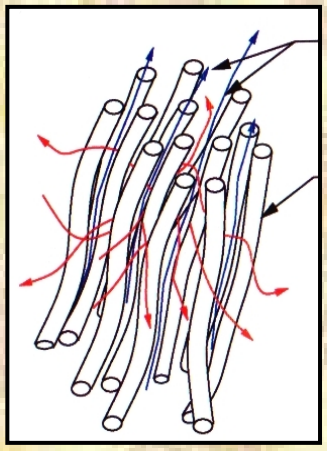
Functional MRI

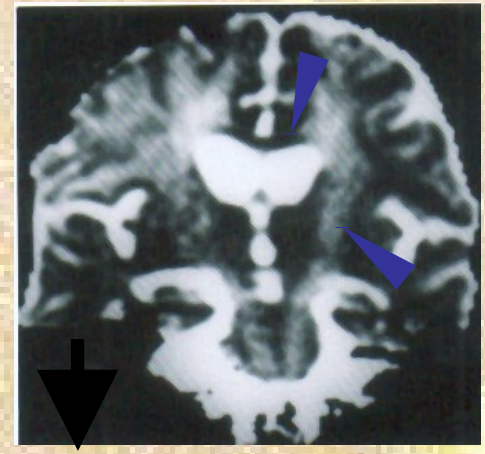


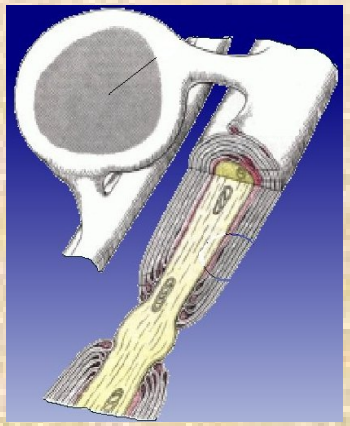


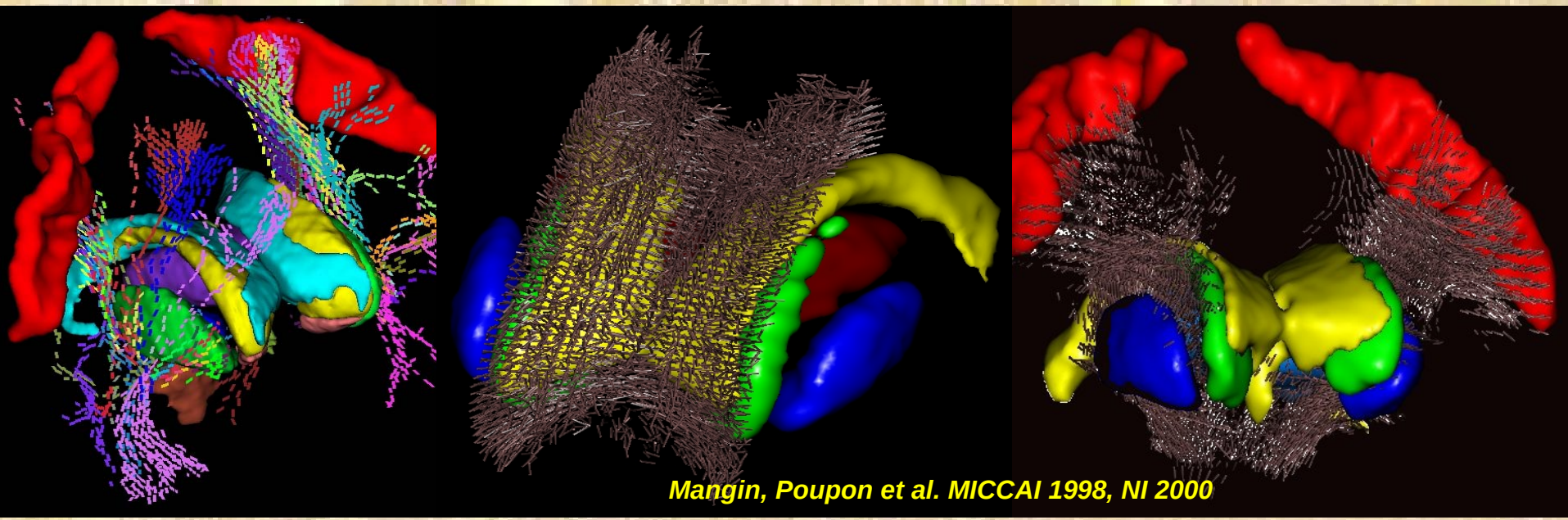
IRM de Diffusion ...

Effet directionnel (anisotropie)…





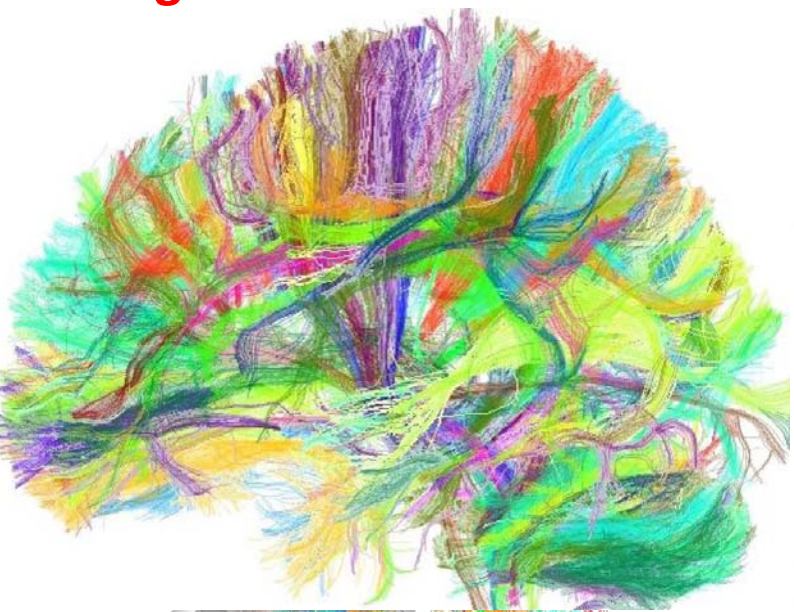


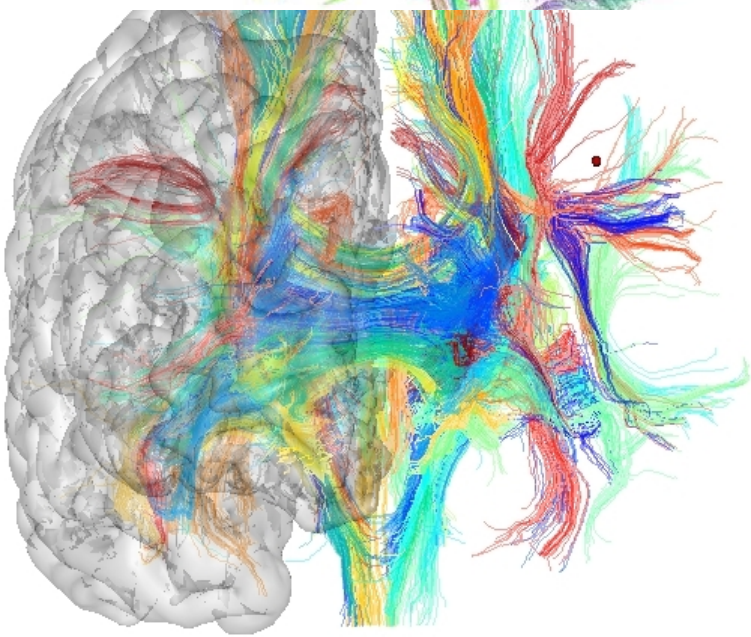


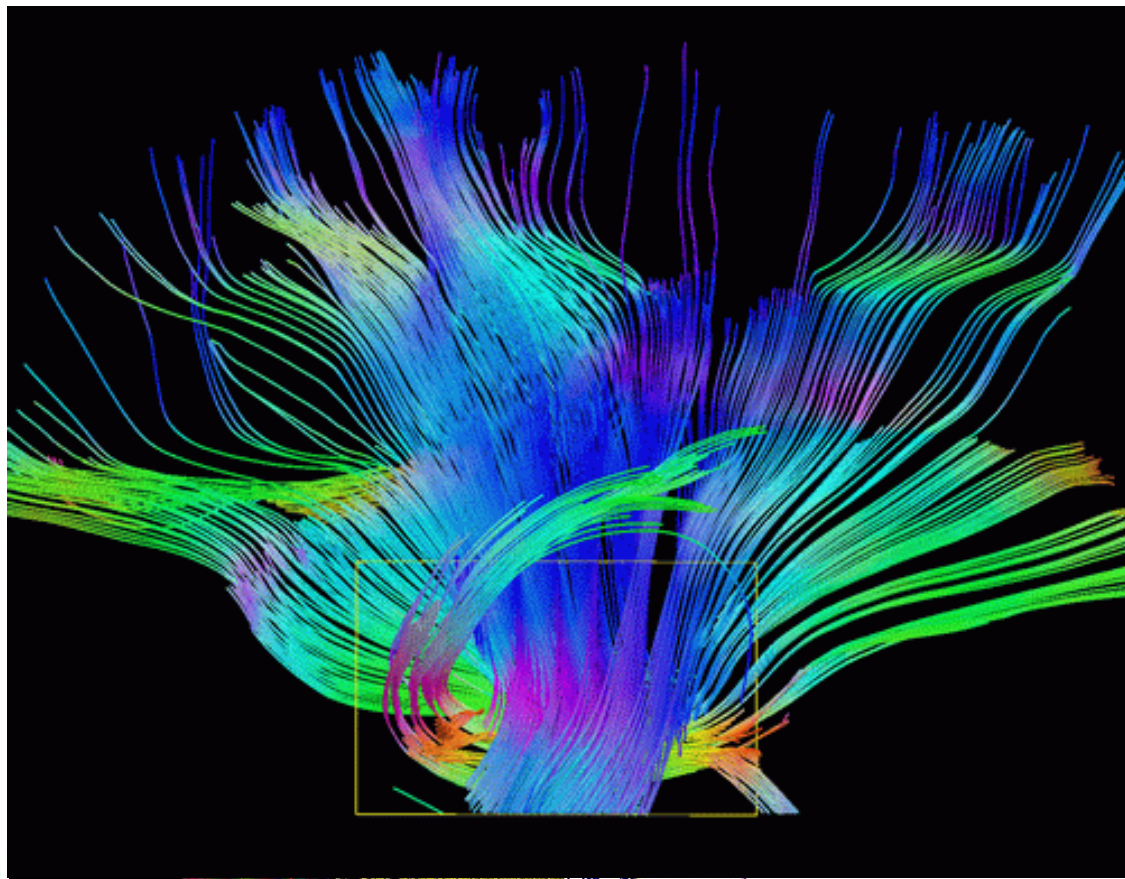
Mangin, Poupon et al. MICCAI 1998, NI 2000

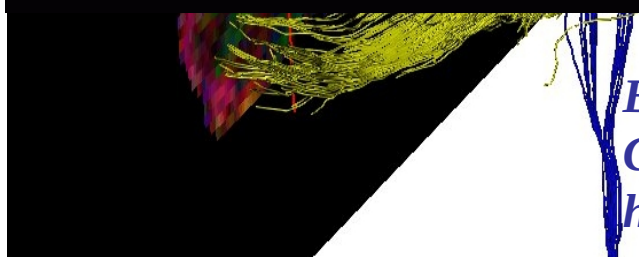
… vers la connectivité cérébrale

Du mouvement brownien à la connectivité cérébrale:
L'imagerie du Tenseur de diffusion (Basser & Le Bihan, 1992-94)



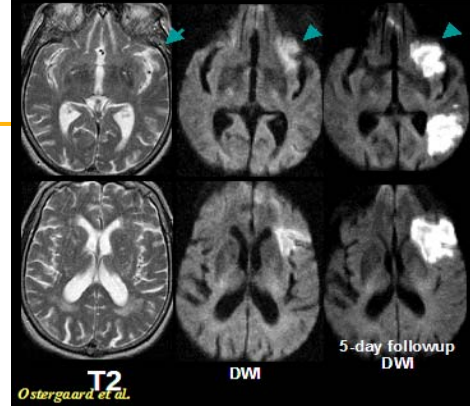






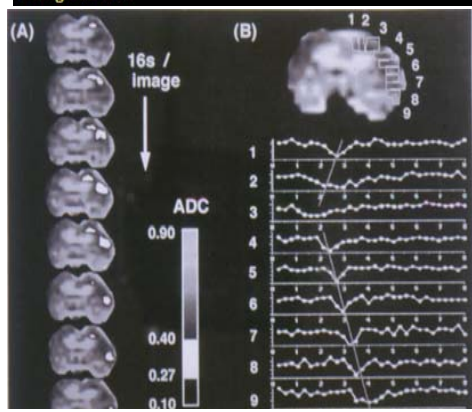
BrainVISA software
Cointepas et al.
http://brainvisa.info

Diffusion-sensitized MRI: tissue events

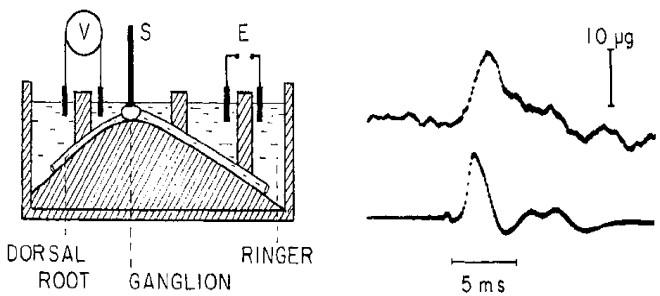


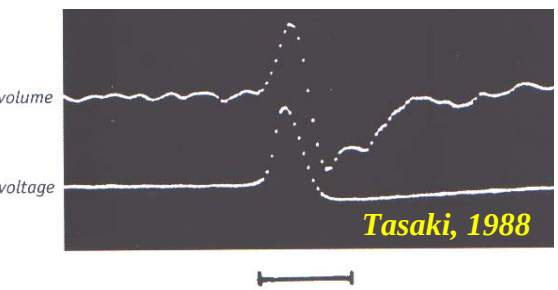
1 - Cell swelling ⇔ Decreased water diffusion

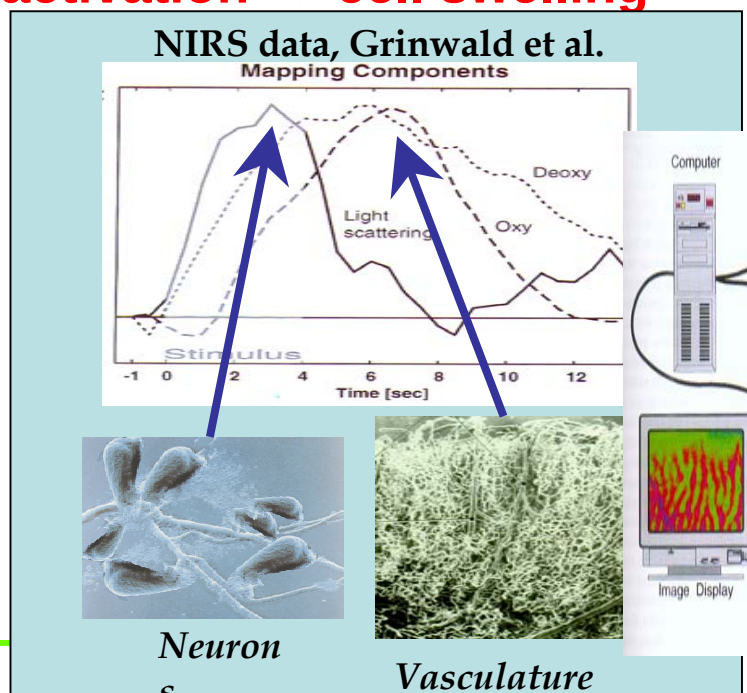
- ✓ **Change in water diffusion coefficient with osmolality**
  - High osmolality → cell *shrinking*, *increased* diffusion
  - Low osmolality → cell *swelling*, *decreased* diffusion
- ✓ **Decreases water diffusion have been reported in**
  - ***Stroke***
  - ***Extra-physiological activation***: status epilepticus induced by bicuculline and cortical electroshocks (Zhong), spreading depression (Sotak, Moseley)

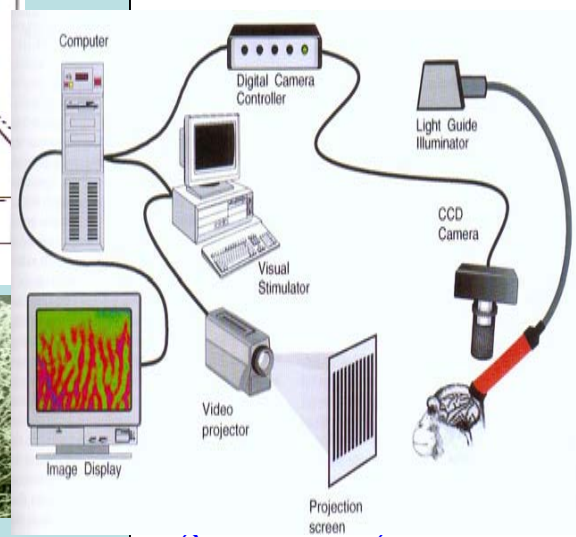


2 - *Physiological* neuronal activation ⇔ cell swelling



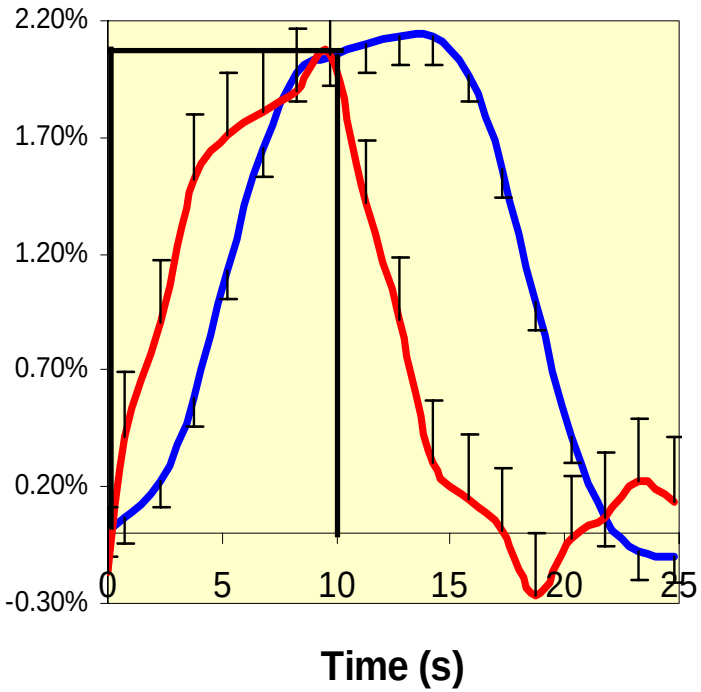


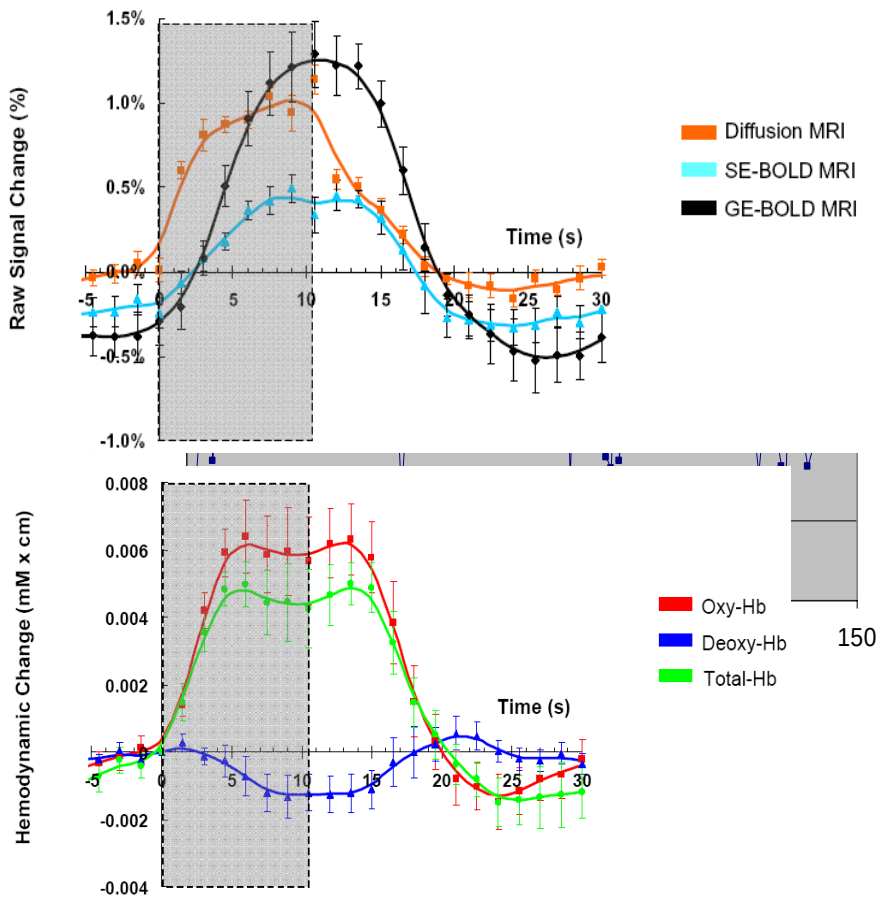




Optical imaging

Diffusion-sensitized fMRI @ 3T





Early response (<vascular events)

deoxyHb≈ Δ rCBF

oxyHb≈ Δ rCBF-CMRO²

Total Hb≈ Δ rCBV

Simultaneous measurement of NIRS, BOLD and DfMRI

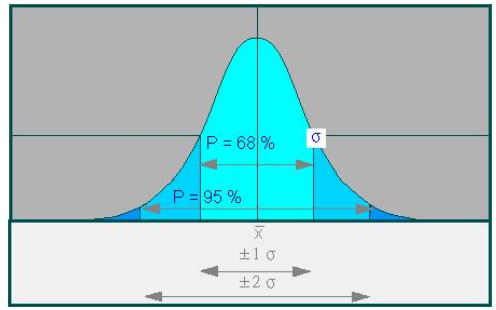
Le Bihan et al. PNAS 103, 8263-8268, 2006

(Satoru Kohno et al. JCBFM in press)

Water diffusion model in the brain:

Back to Einstein…

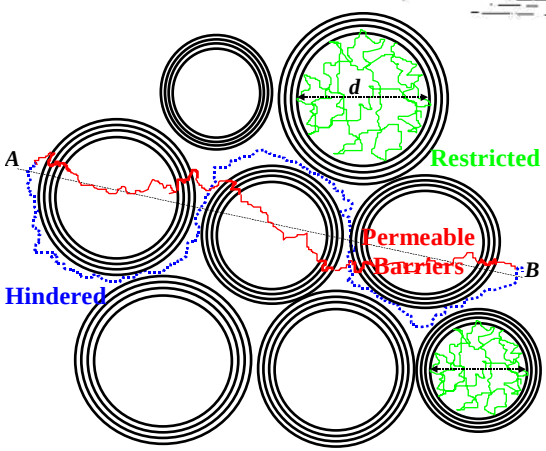
$$\overline{P}(R,t_d) = \frac{1}{\sqrt{4\pi D t_d}} e^{-\frac{R^2}{4Dt_d}}$$

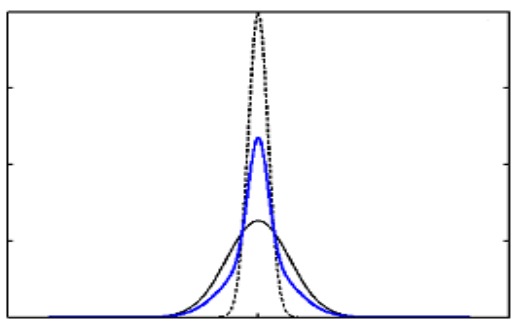


Free diffusion = Gaussian distribution of displacements

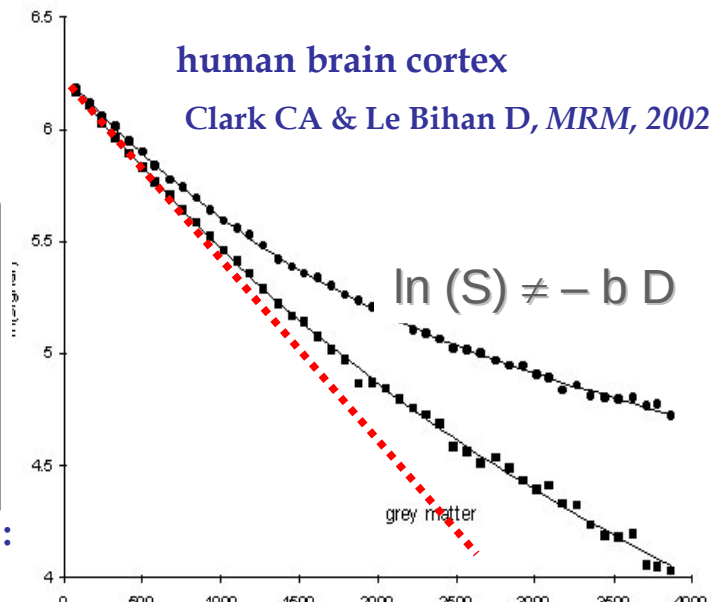
For MRI: S=exp (-b D)

$$\langle x^2 \rangle = 2\,Dt$$



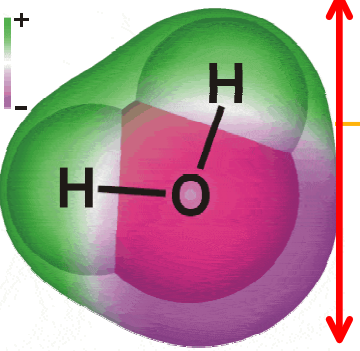


Displacement profil (*q-space*) :
Gaussian 1 + Gaussian 2



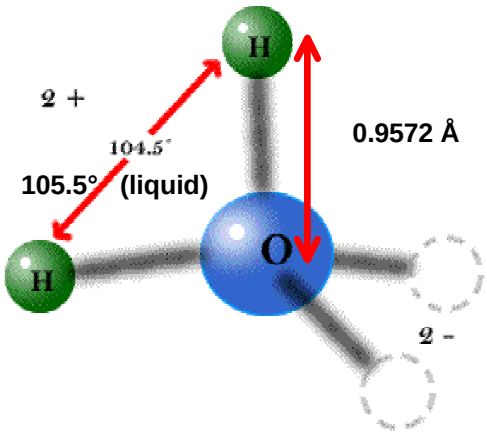
Biexponential behavior: diffusion is not 'free' → 2 water pools?

The *water* molecule



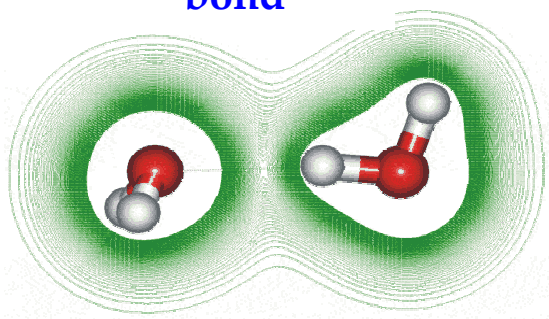
3.2 Å

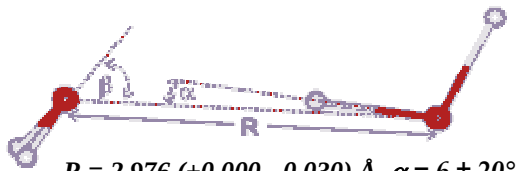
'Water is H_2O, hydrogen two parts, oxygen one, but there is also a third thing, that makes it water and nobody knows what it is.' *D H Lawrence (1885-1930)*



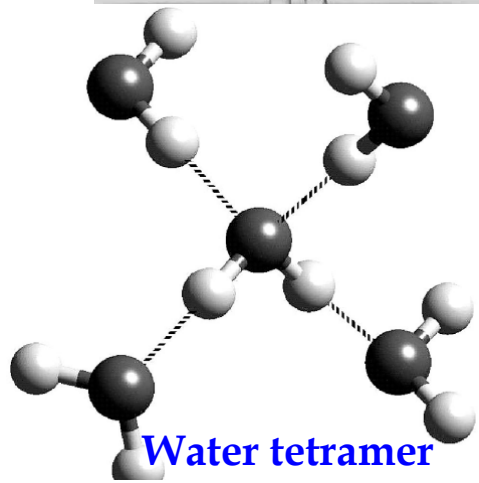
Ball and stick model of water.

Hydrogen bond

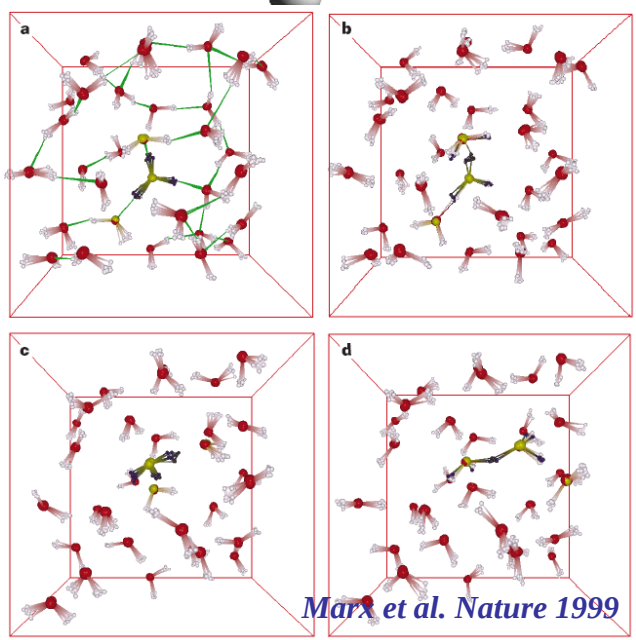




R = 2.976 (+0.000, -0.030) Å, $\alpha = 6 \pm 20°$, $\beta = 57 \pm 10°$



Water tetramer

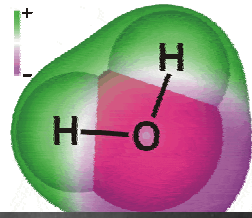


Marx et al. Nature 1999

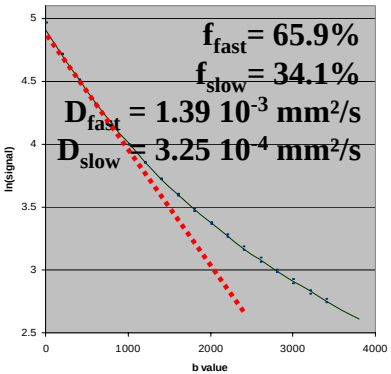
→ Liquid water: tetrahedral H-bond network with local defects

Proton mobility (diffusion) decreases with increase degree of structuring (lower density of local defects)

Brain water diffusion model: structured water



Visual cortex

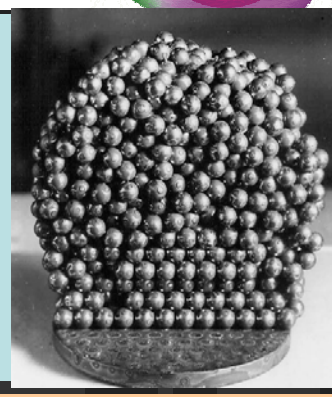


$\ln(S) \neq -b\,D$

2 KINDS OF WATER IN CELLS: SLOW + FAST DIFFUSION POOLS

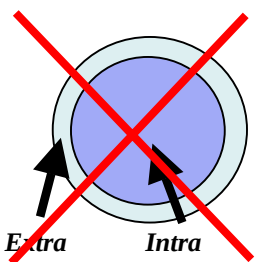
Water-membrane interface:
Long-range electrostatic trapping

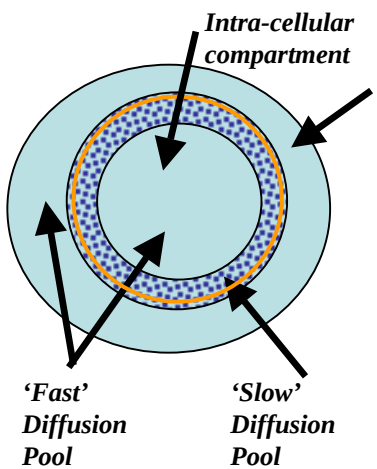
-Protein « ***trapping*** » effects: ***structured*** water
-Extend to adherent water layers out to ***180nm***
(Xu & Yeung, Science 1998, Vogler, 1998)
-≈ 30% of cell water *(Pissis, 1987)*



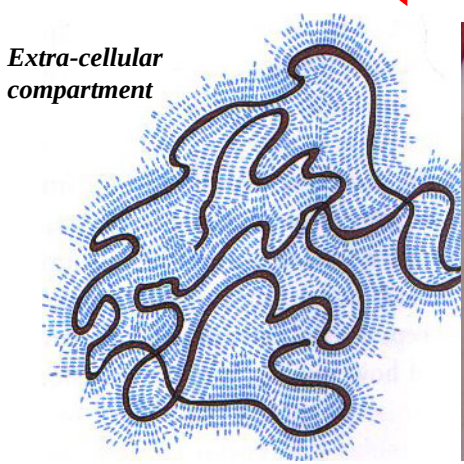
- **"Slow" diffusion pool: structured water "bound" to membranes**

☞ ***ADC changes with membrane surface interaction (cell size, anisotropy, cellularity,…)***





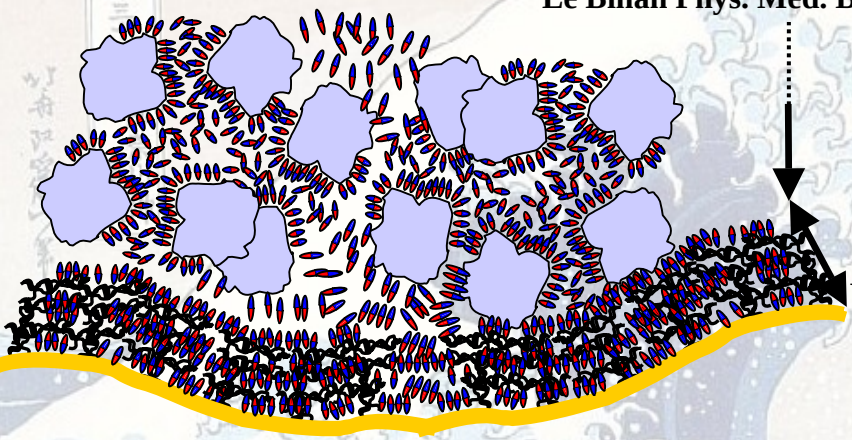
Cell swelling: ↘ ADC, ↗ f_{slow}



2 KINDS OF WATER IN CELLS: SLOW + FAST DIFFUSION POOLS

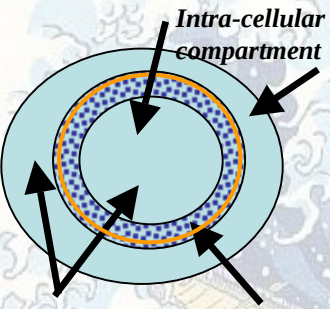
Slow diffusion pool :*membrane interactions*

Le Bihan Phys. Med. Biol. 52 R57-R90, 2007

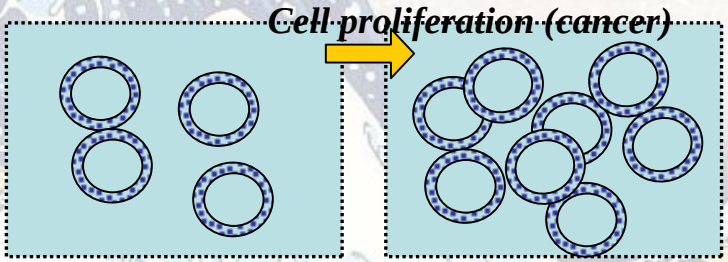


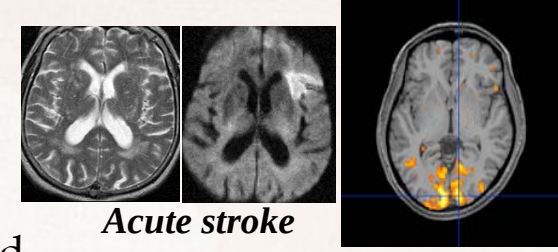
Fast pool: Bulk water and proteins-bound water

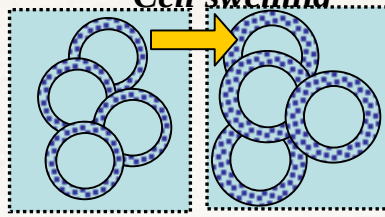
Slow pool: Membrane-bound water (w/c*ytoskeleton* ± **40 nm**)

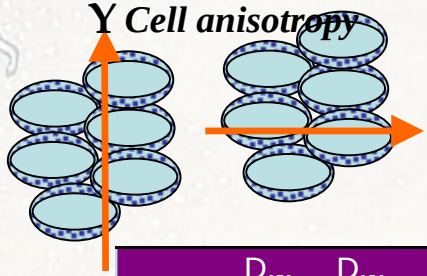


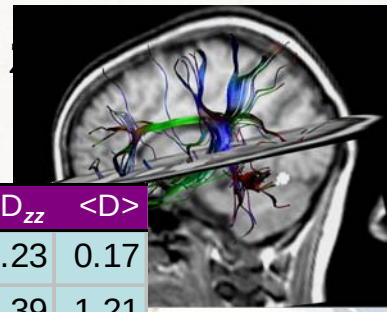
Membranes: ↓ADC, ↑f_{slow}







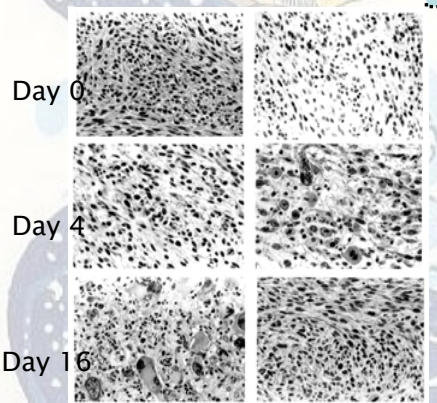


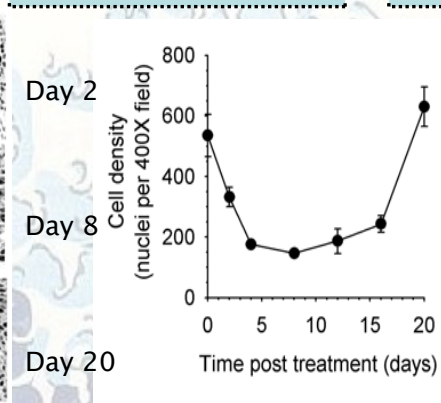


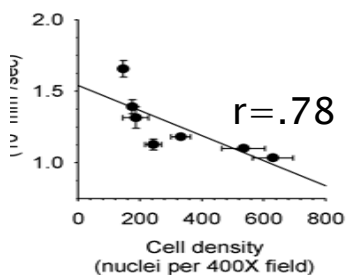
	D_{xx}	D_{yy}	D_{zz}	<D>
D_{slow}	0.14	0.13	0.23	0.17
D_{fast}	1.12	1.13	1.39	1.21
f_{slow}	0.49	0.41	0.11	0.33

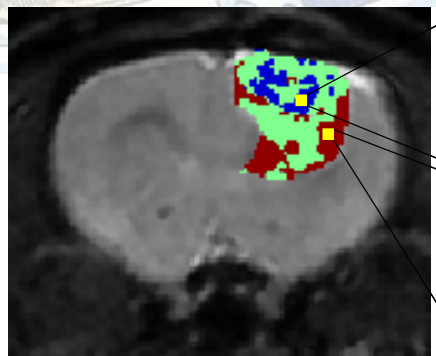
Human brain white matter
Clark & Le Bihan, *MRM, 2002*

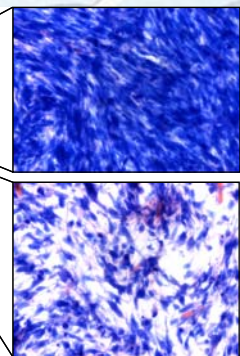
Ross B. J. Natl. Cancer Inst, 92, 2029-2036, 2000





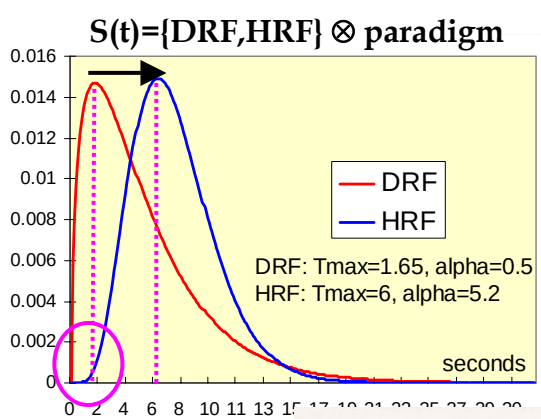


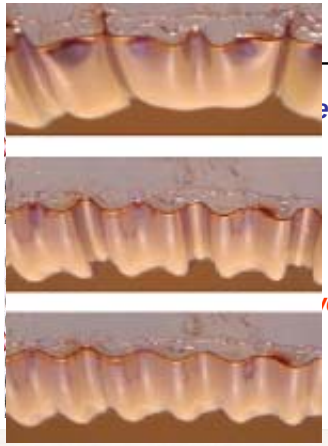




Water diffusion fMRI: *Cell membrane events …*

Fast coupling between ion fluxes, membrane depolarization and water structure

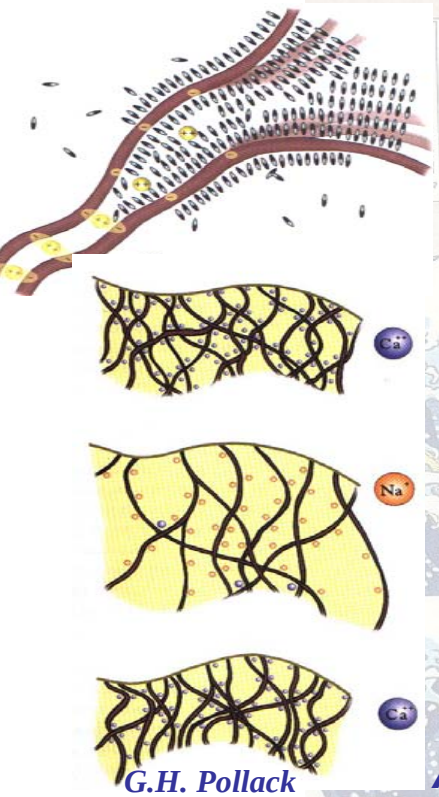




–**Mechanism**: *fluxes of ions AND water*

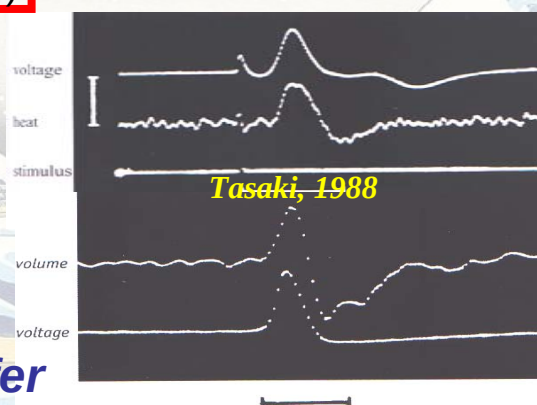
- Swelling of neurons (soma, ***dendrites***) and glial cells
- Membrane surface scales with square of cell size
- **Phase transition** (↗order) of water near polarized membranes AND attached *polymer-gel matrix*

Stress and Fold Localization in Thin Elastic Membranes
Pocivavsek et al. Science 230;912-916, 2008



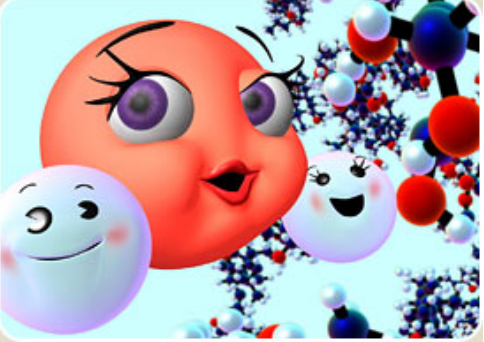
- **Action potentials** → ***Phase transition***
- Require ***cytoskeleton*** integrity (*Matsumoto*)
- Cytoskeleton undergoes physical changes (*Sato*)
- Calcium is critical (*Tasaki, 1988*)
- Transient cellular expansion (***swelling***) and ***water*** influx (*Tasaki*)
- Transient liberation of ***heat*** (23μ°C *Tasaki*)

Induction of hemodvnamic response (=Cold)??



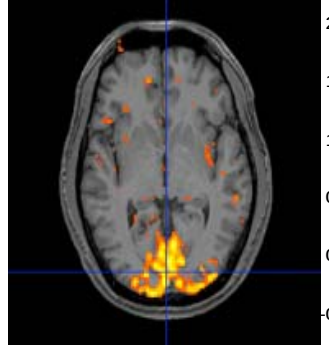
→ Water seems to play a central role in cell activation physiology

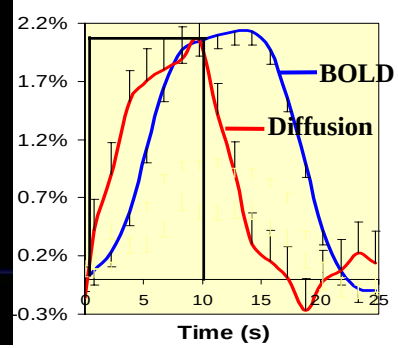
Action potential, cell swelling, heat transfer



Water: the molecule of the *mind* ?

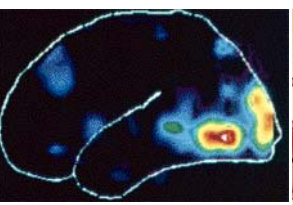
Le Bihan D. The 'wet mind'
Phys. Med. Biol. 52:557-90, 2007

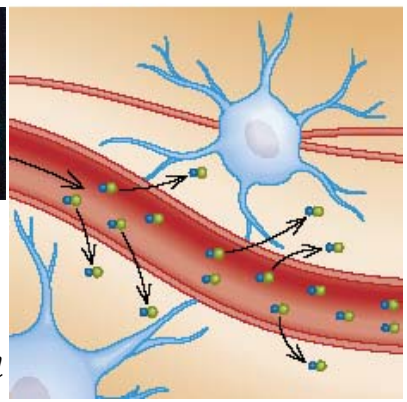


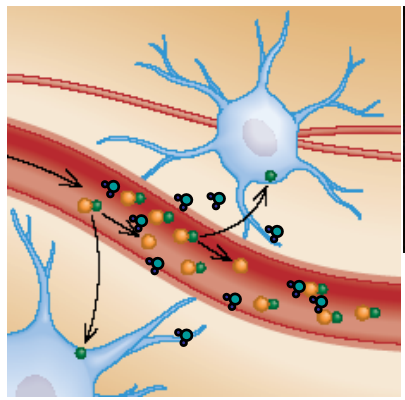


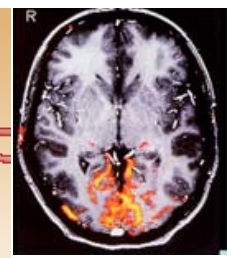
DIFFUSION fMRI

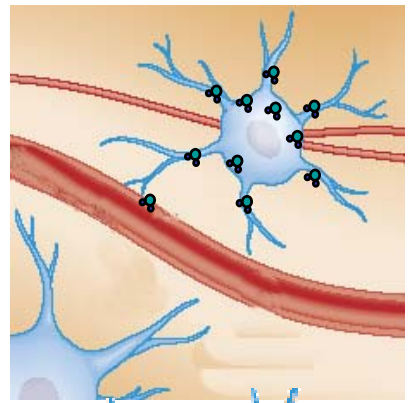
- **Active role of water in cell depolarization, action potential?**
  -more water influx in cells than expected from ion transferts
- **Role of blood water in heat transfert (increase in CBF)?**
  -activation --> heat release
  -increase of CBF and metabolism (energy demand) more to restore baseline conditions after activation, 'housekeeping'
- **Role of cell structure changes (swelling) in information flow**
  -neurons & glial cells as (reversible) piezo-electric transducers
  -faster than neurotransmission for local, intracotical networks

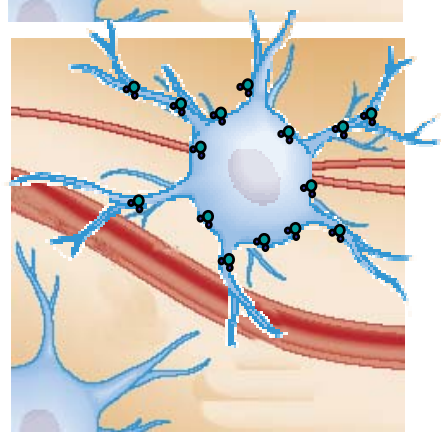












Activation

↗blood flow
↗quantity of radioactive water in activated tissues

↗blood flow & oxygenation
↘magnetized water relaxation in/near vessels

↗cell size and membrane surface
↘diffusion of water near membranes

Radioactive water *Magnetized water* *Plain brain water*