Microfluidics 2019
Sète, Octobre 2019

Blood flow and mass transfers in brain microcirculation

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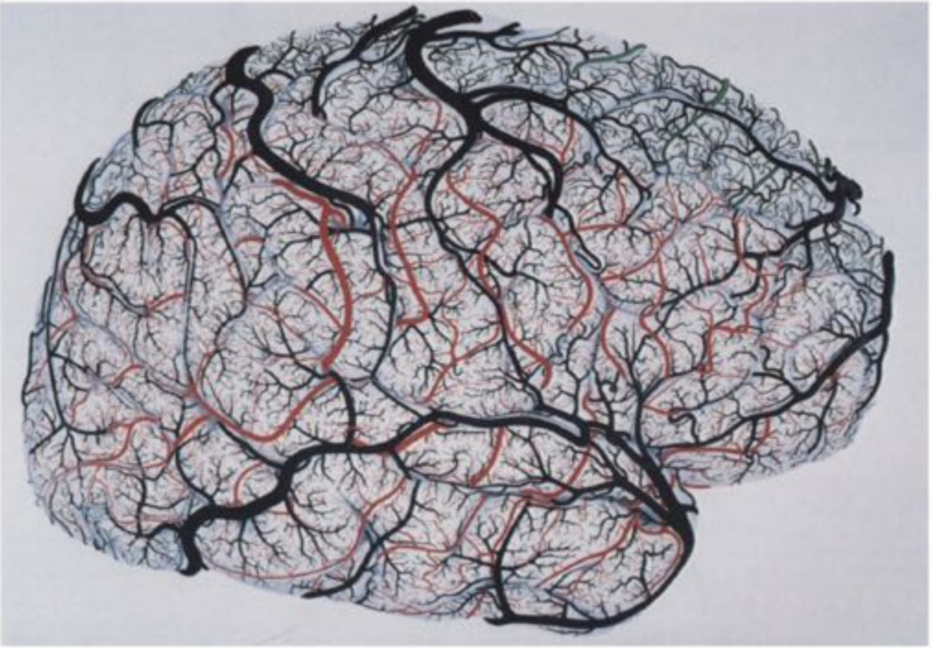
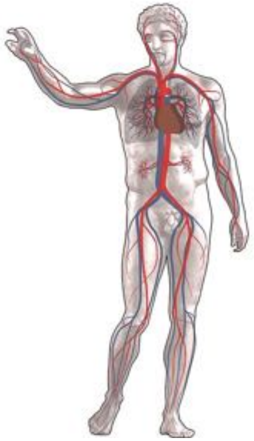
Brain microcirculation

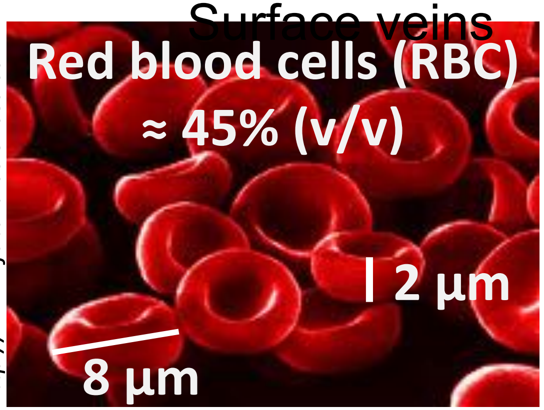
Structure

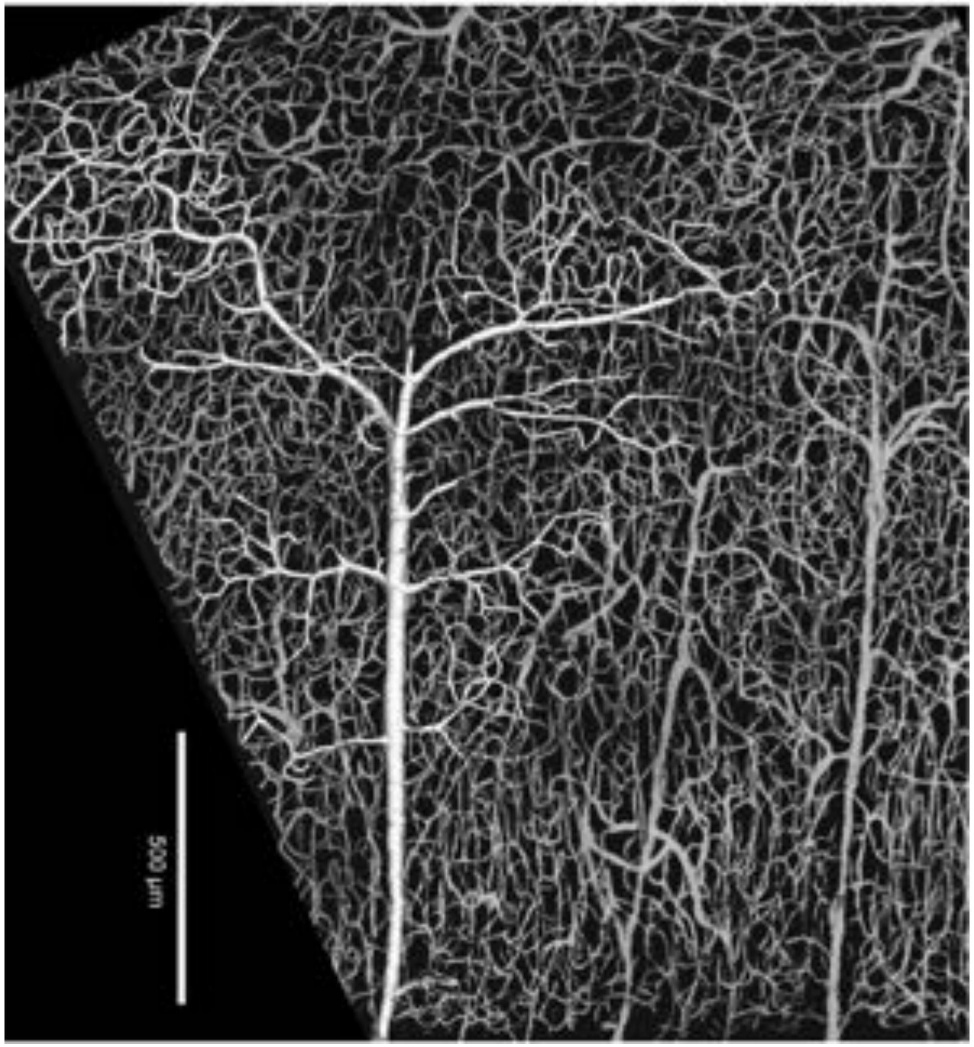


Duvernoy et al. Brain Res Bull 1981 Surface arteries
Surface veins



http://www.futura-sciences.com





Surface veins Surface arteries

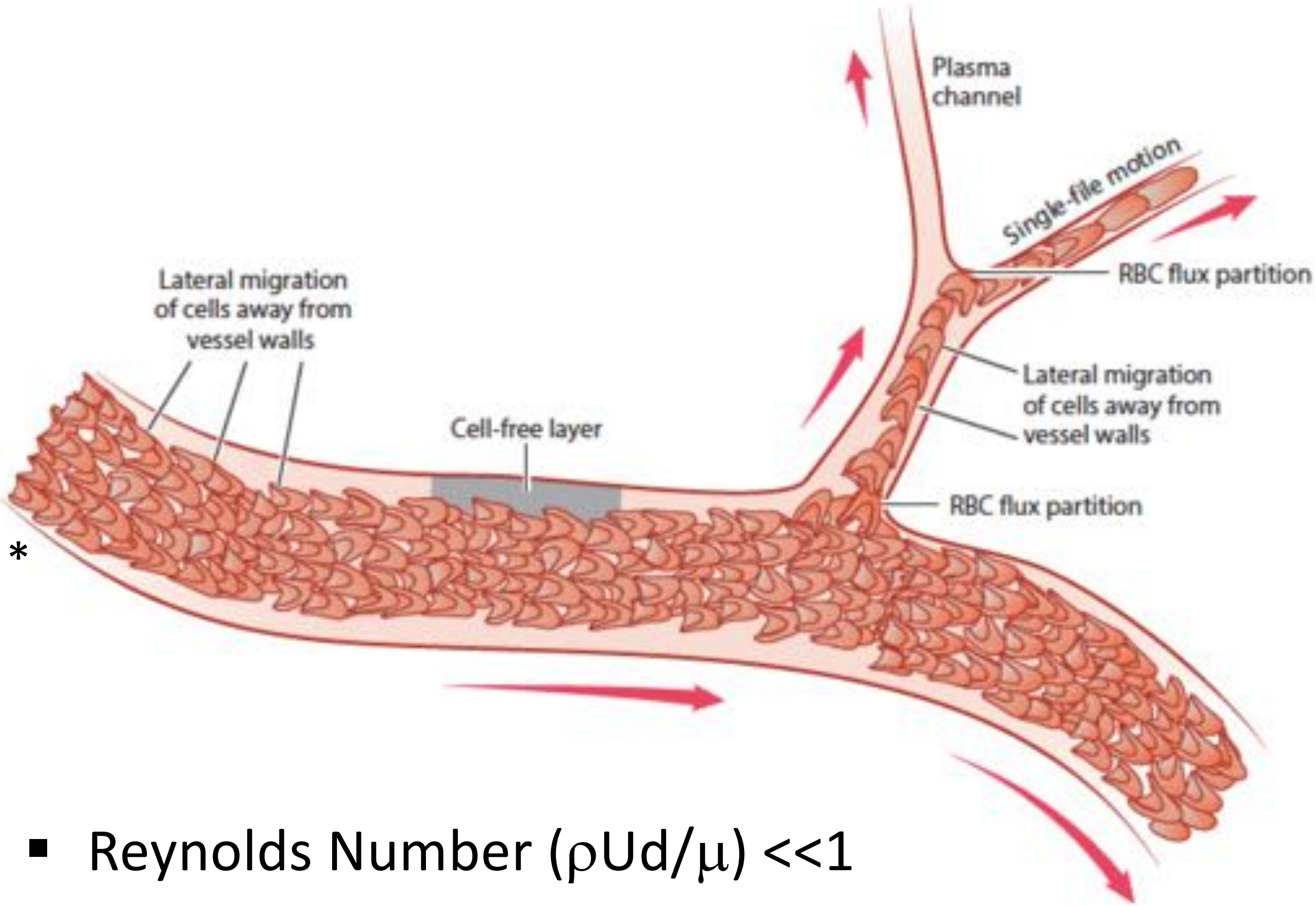
Cassot et al. Microcirculation 2006

Outline

- Brain versus other organs
  - What is generic ?
  - What is specific ?
- Why study brain microcirculation ?
  - In health
  - In disease
- Investigation tools and associated scales
- Blood flow in networks
- Mass transfers in networks
- Blood flow at organ scale

What is generic ?

The physics of red blood cell flows



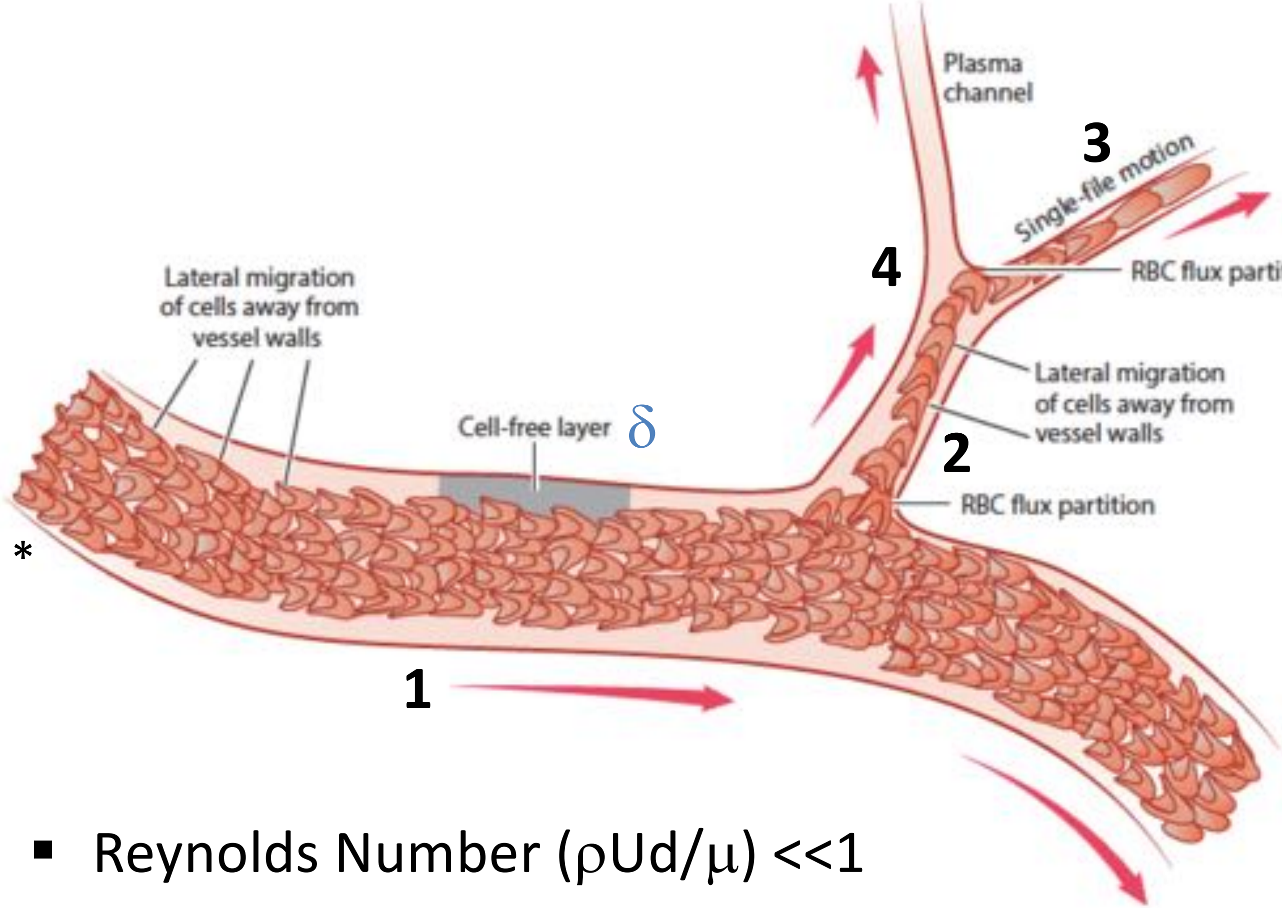
*

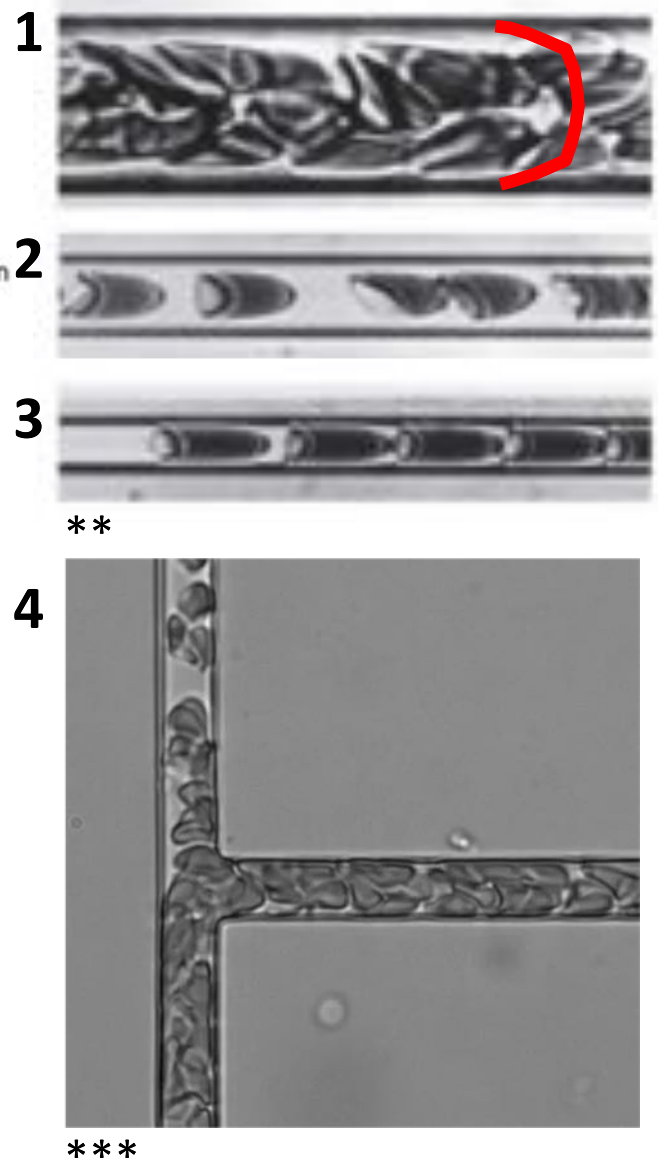
- Reynolds Number ($\rho Ud/\mu$) <<1
- Womersley number ($\rho\omega d^2/\mu$) <<1
- Hematocrit (H) ~ 0.45
- Confinement ratio (L_{RBC}/d) : 0.5 to 2

* Secomb Ann Rev Fluid Mech 2017

What is generic ?

The physics of red blood cell flows





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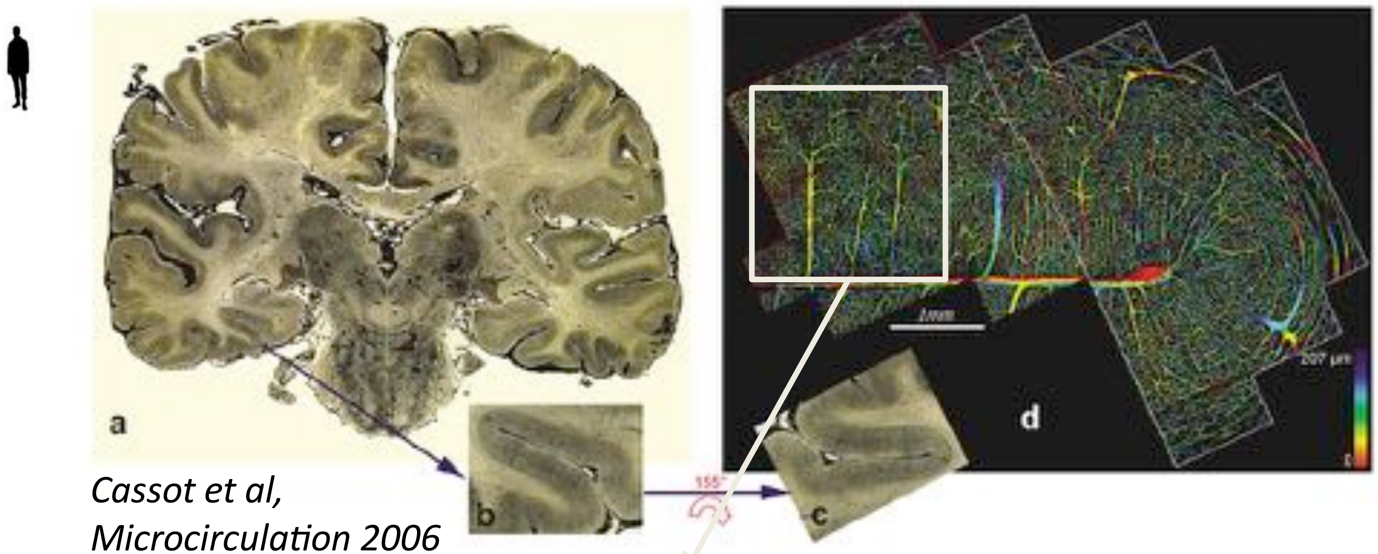
* Secomb Ann Rev Fluid Mech 2017, ** Handbook of Physiology Microcirculation 2002, *** PhD A. Merlo

What is generic ?

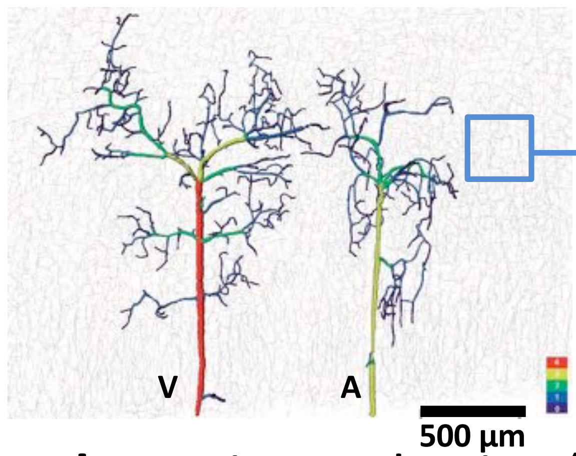
The general organization of the vascular architecture

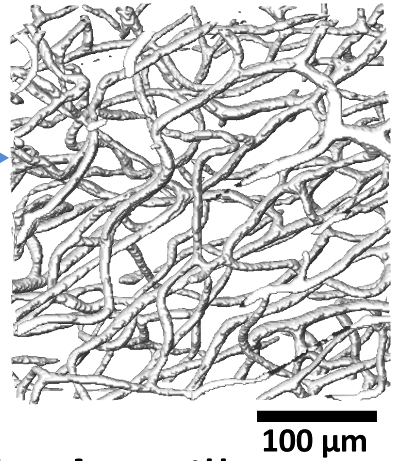
- ❑ **Brain networks are multi-scale, with two components**



Cassot et al, Microcirculation 2006

Cassot et al, Microcirculation 2006





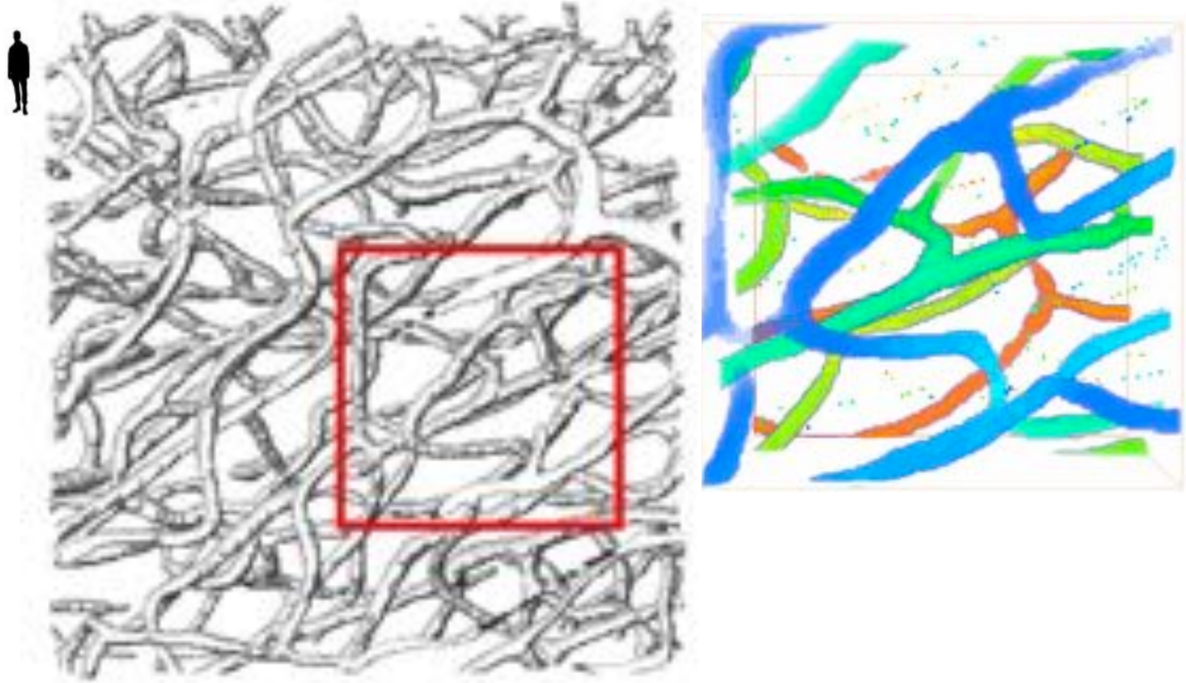
Lorthois et al, JTB 2010

Fractal arteries and veins (1%) **Meshed** capillary networks

What is generic ?

The general organization of the vascular architecture

- ❑ **Capillary networks in the brain are 3-connected, space-filling**



- ▪ Looped and random at small scale
- ▪ Homogeneous & Space-filling above ~50µn
  (Each point in the tissue is close to a capilla

➔ REV / Porous medium

- ❑ Volume density
  ~2 %
- ❑ Exchange surface
  ~5 mm^2/mm^3
- ❑ Cumulative length
  ~500 mm/mm^3

Cassot et al. 2006

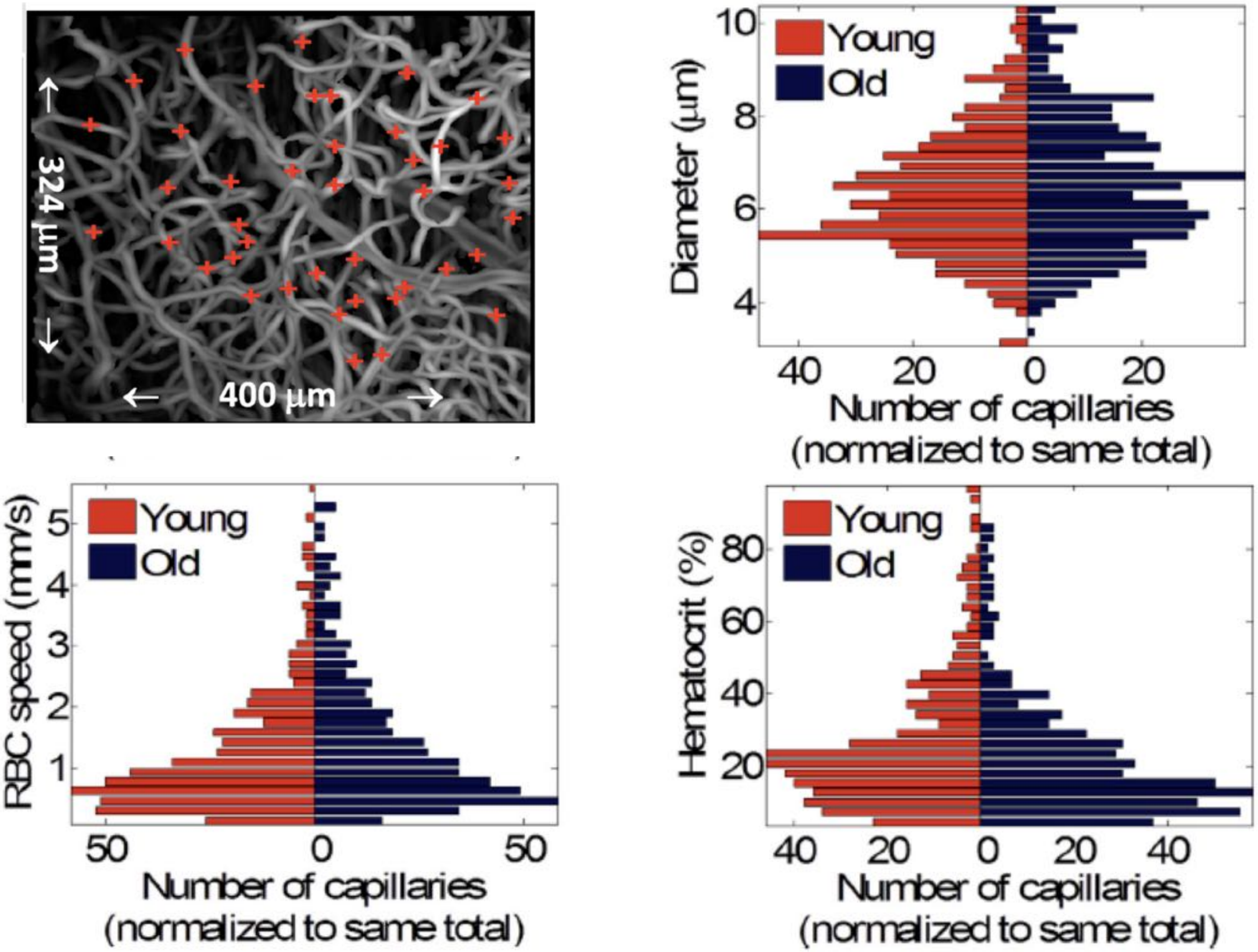
Heinzer et al. 2006

Risser et al. 2007

* *Lorthois and Cassot, J Theor Biol, 2010*

What is generic ?

The tremendous heterogeneity of hemodynamic parameters

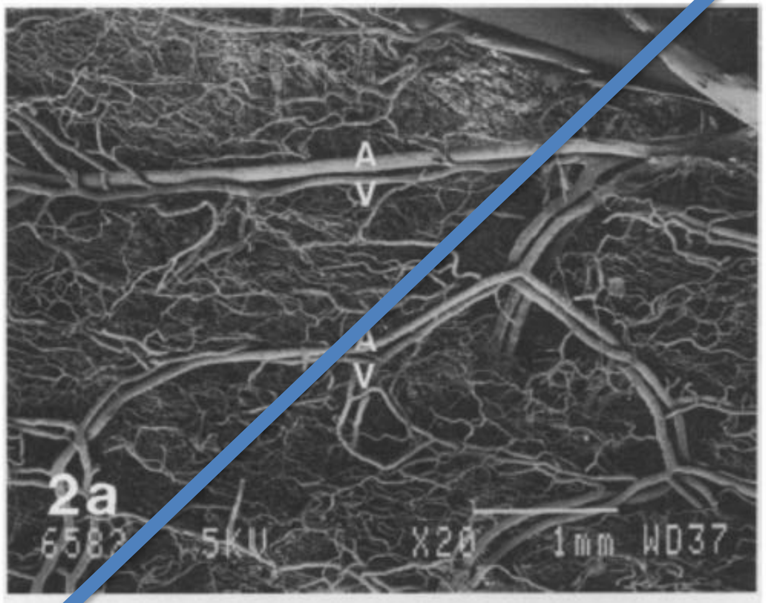


MICE

What is specific ?

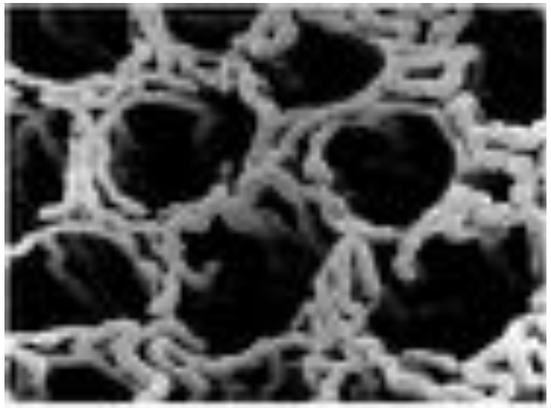
The details of the vascular architecture

Arterioles and venules

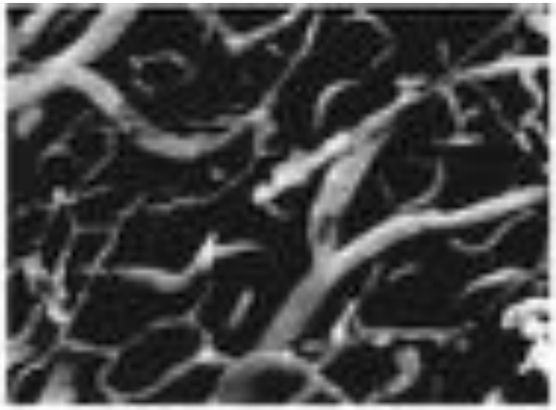


Human temporary muscle
Cheung et al. *J. Anatomy* 1996

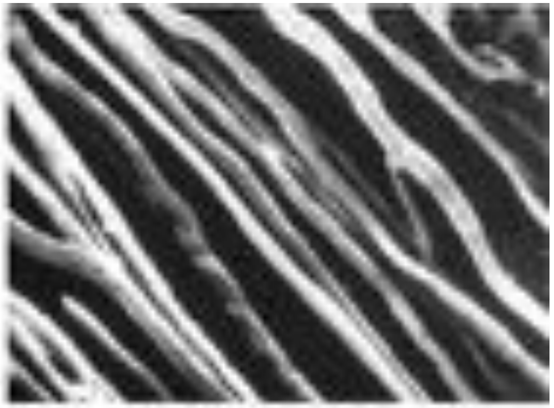
Capillary network



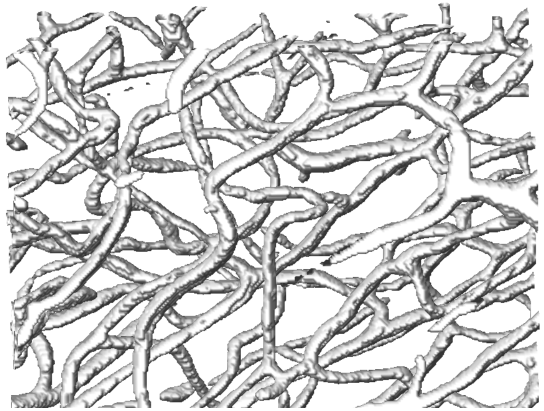
Colon



Subcutis



Skeletal muscle

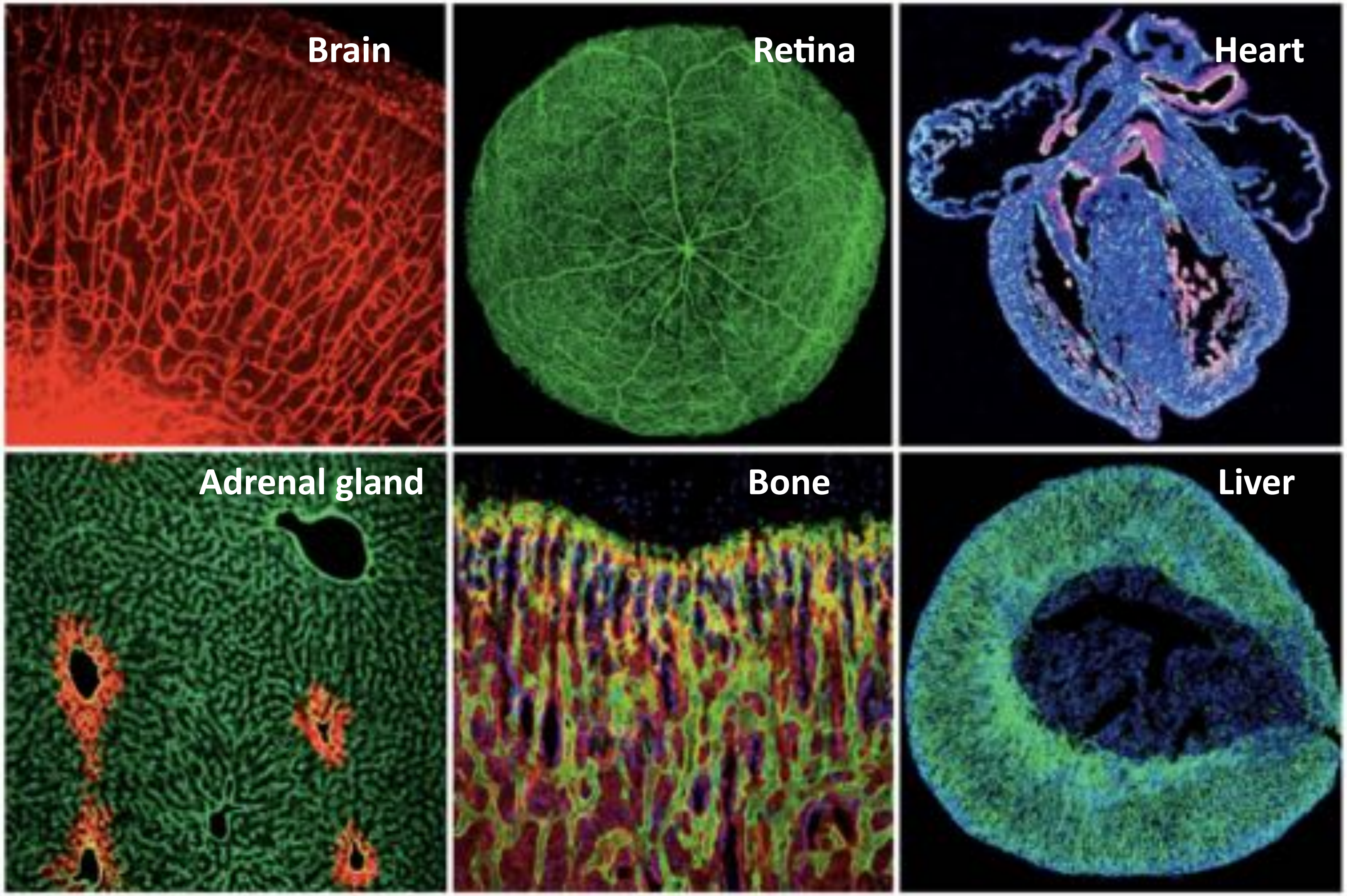


Brain cortex

Vaupel et al. Sem rad onc, 2004 *Cassot et al. Microcirculation 2006*

What is specific ?

The details of the vascular architecture



Augustin et al. Science, 2017

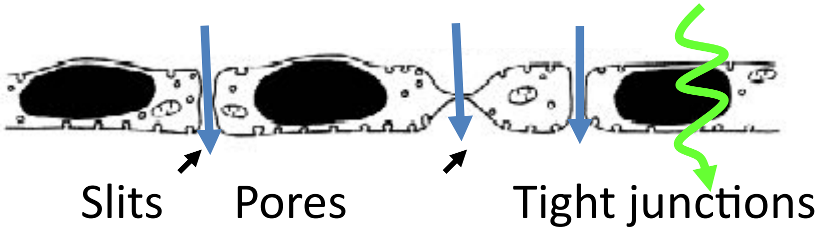
What is specific ?

The need for a constant microenvironment

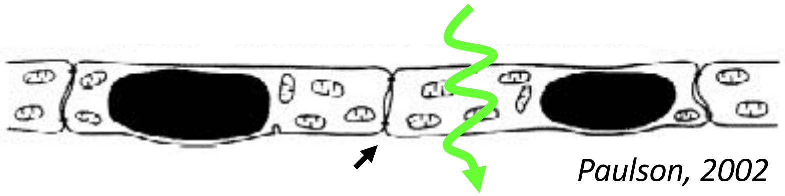
- **Ionic / Osmotic balance**
  - Neurotransmitters / Electrical impulse
  - Constant volume (Skull)
- **Protection against neurotoxicity**

➔ Existence of the Blood-Brain Barrier

Ehrlich 1885, Goldman 1913



Muscle capillary endothelium



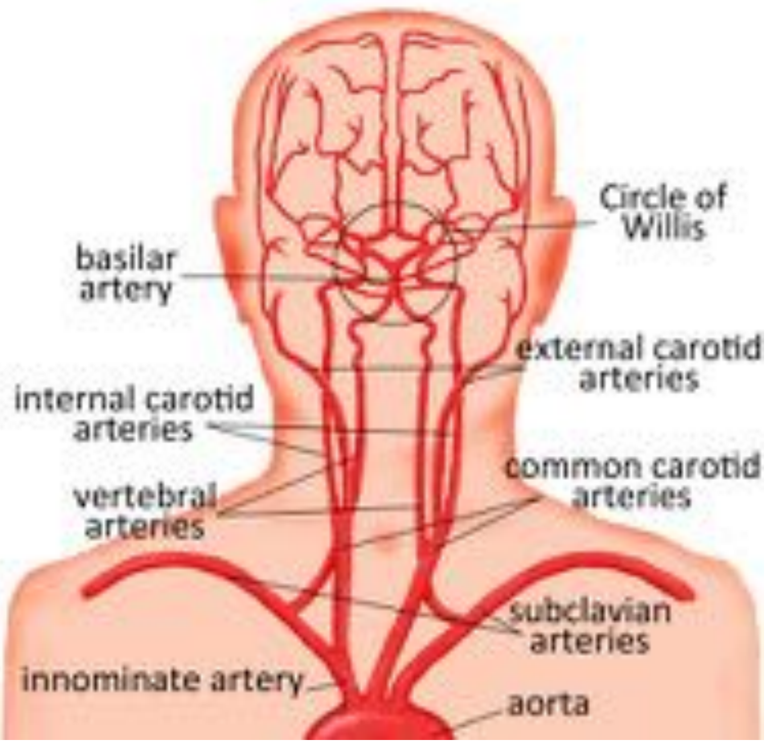
Brain capillary endothelium

What is specific ?

High metabolic activity / No energy storage

- **A high metabolic activity (energy demand)**
  - Brain weight ~2% total weight
  - Brain blood flow ~15 to 20% of total flow
- **No energy storage**

→ **Existence of redundancies**
- Circle of Willis
- Connections between cerebral arteries
- Connections between surface vessels



What is specific ?

High metabolic activity / No energy storage

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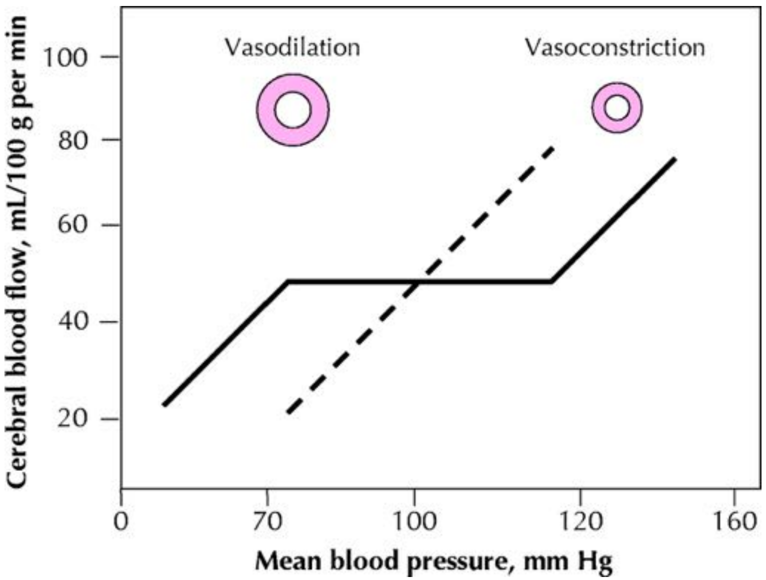
- ❑ **No energy storage**

➔ **Two distinct regulation pathways**

Brain autoregulation : global

Neurovascular coupling : local

Semplicini et Calo, 2005



Hamilton et al. 2012

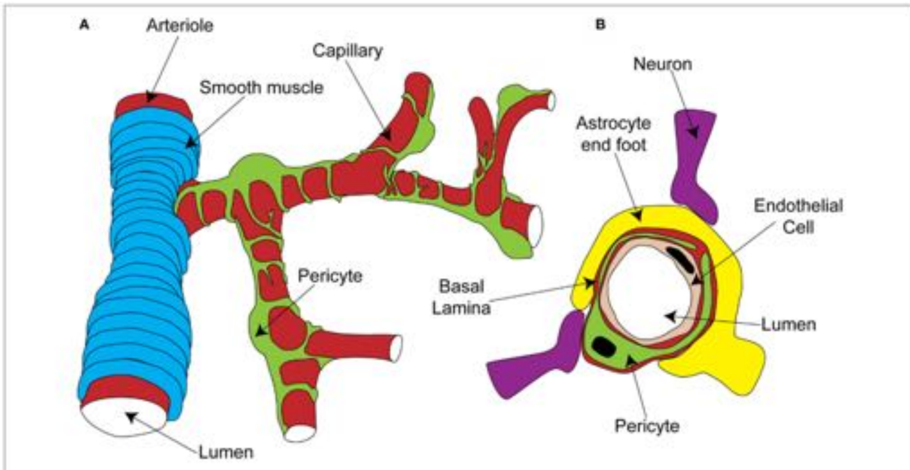


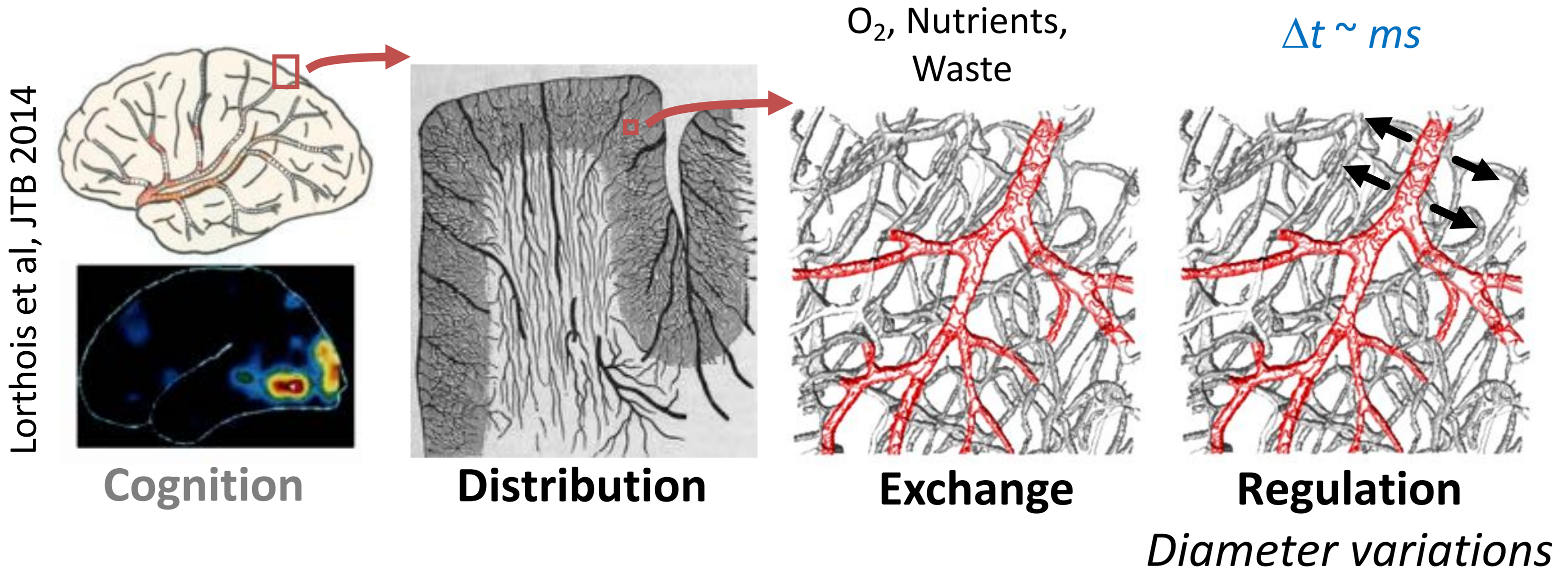
FIGURE 1 | Organisation of the capillary neurovascular unit. (A) Rings of smooth muscle encircle arterioles, while pericytes send processes along and around capillaries, without fully covering the vessel. **(B)** Pericytes are located outside the endothelial cells and are separated from them and the parenchyma by a layer of basal lamina. In the parenchyma, astrocyte end-feet and neuronal terminals are closely associated with the capillary.

Outline

- ❑ Brain versus other organs
  - What is generic ?
  - What is specific ?
- ❑ **Why study brain microcirculation ?**
  - In health
  - In disease
- ❑ **Investigation tools and associated scales**
- ❑ **Blood flow in networks**
- ❑ **Mass transfers in networks**
- ❑ Blood flow at organ scale

Brain Microcirculation

- **… plays a key role in brain physiology**

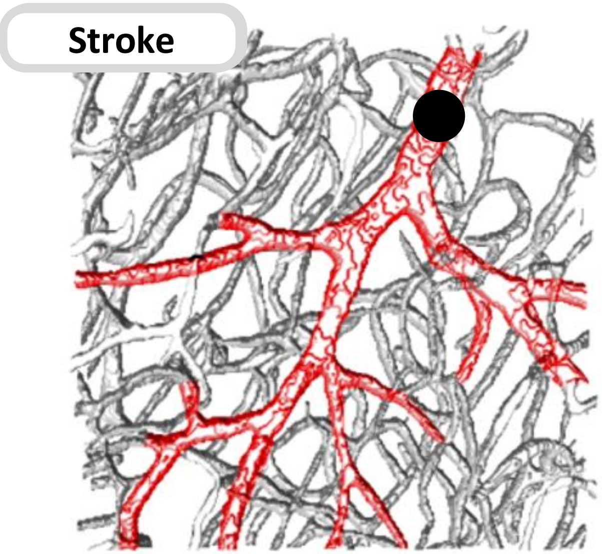


- **… and in our ability to observe the functioning brain**
  - Neuro-vascular coupling
  - Hemodynamically-based functional imaging techniques ($H_2 0^{15}$ PET, fMRI)

Brain Microcirculation

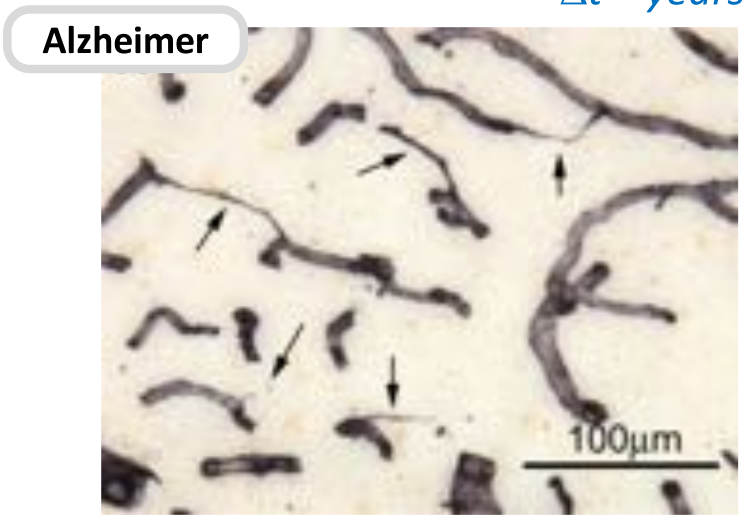
■ … is involved in disease

- ❑ Stroke
- ❑ Neurodegenerative disease (Alzheimer)



Vessel occlusions

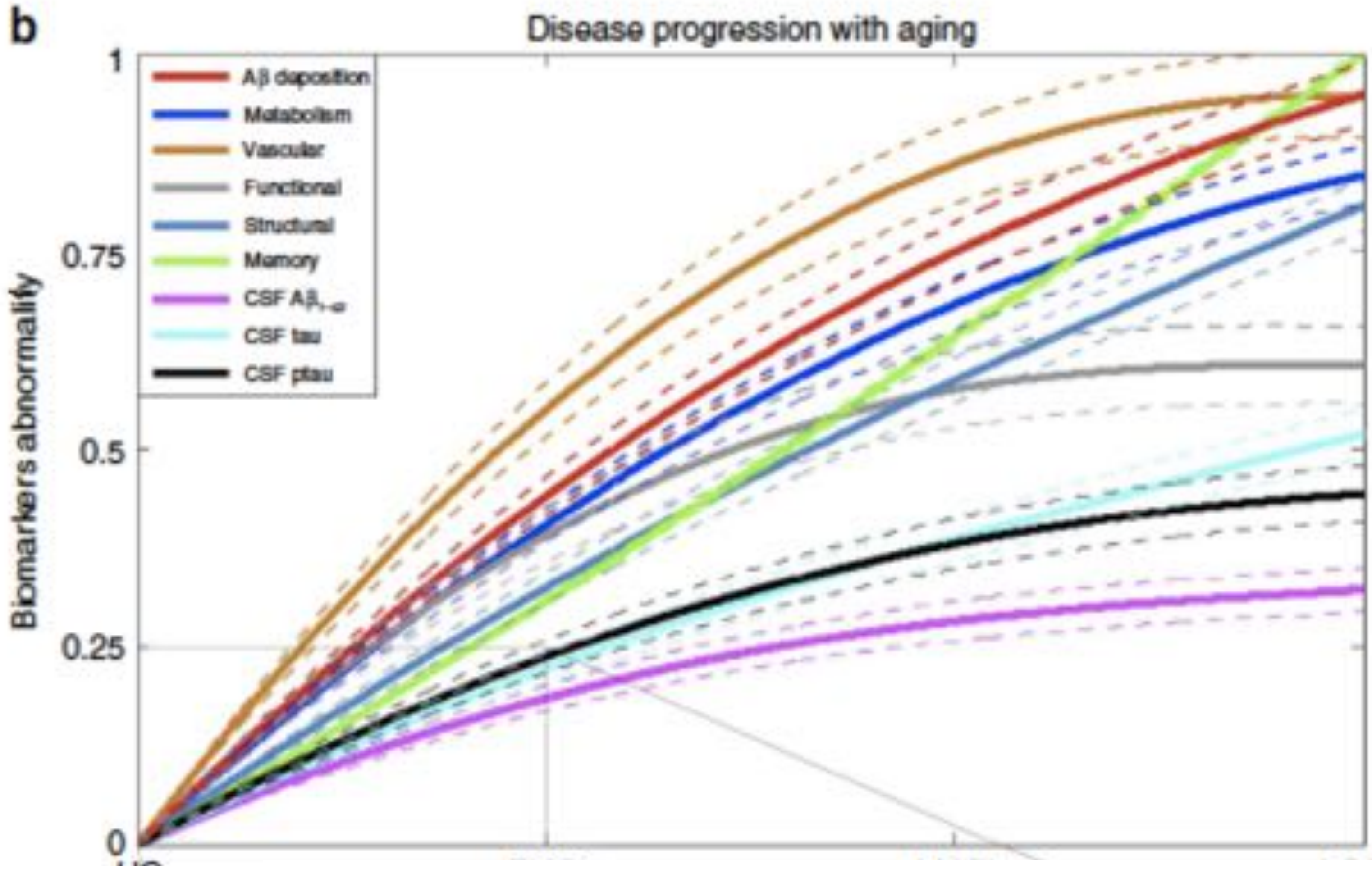
Δt ~ years



Hunter et al. 2012

Progressive disappearance

Brain Microcirculation



Healthy Control | **Early Mild Cognitive Impair** | **Late Mild Cognitive Impairment** | **Probable Alzheimer's Disease Patient**

1. Iturria-Medina et al., Nature Communications, 2016

Brain Microcirculation

- **… is involved in disease**
  - ❑ Stroke
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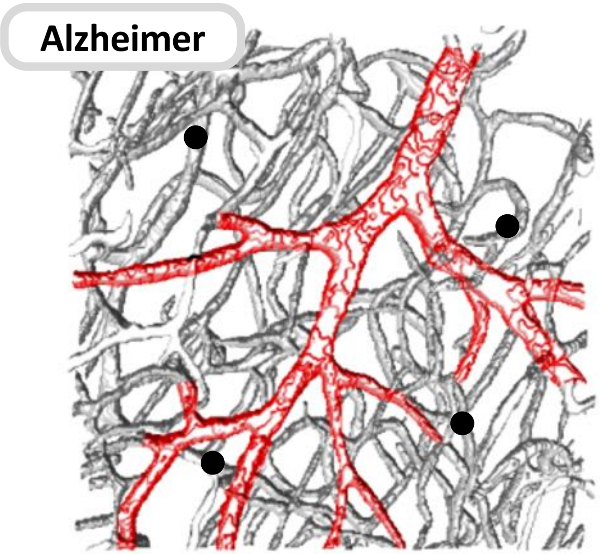

Vessel occlusions

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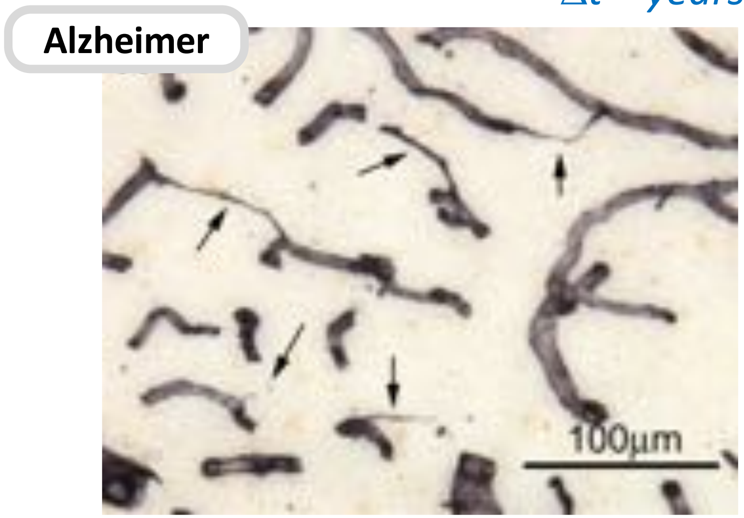

Hunter et al. 2012

Progressive disappearance

Brain Microcirculation in Alzheimer's disease

Vascular damage

Occlusions

Vessel disappearance

Functional impairment

Reduced blood flow

Increased heterogenity

Onset of hypoxia

Aβ accumulation

Impaired regulation

Cognitive decline

Outline

- ❑ **Brain versus other organs**
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  - In disease
- ❑ **Investigation tools and associated scales**
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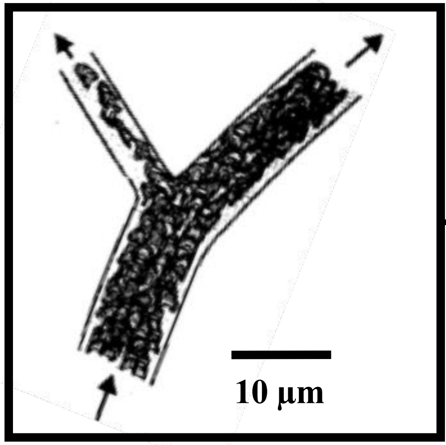
- ❑ **Blood flow at organ scale**

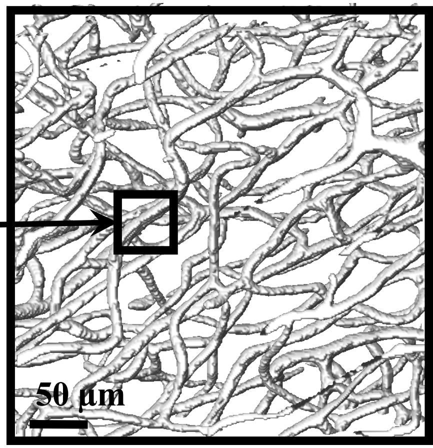
Investigation tools and associated scales

Microscopic scale



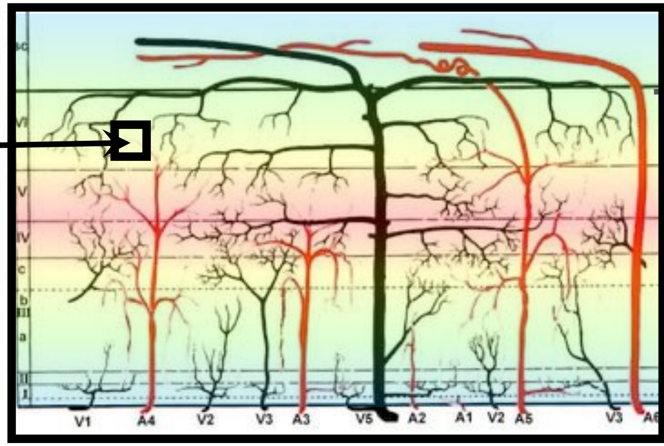
50 µm

Mesoscopic scale



300 µm

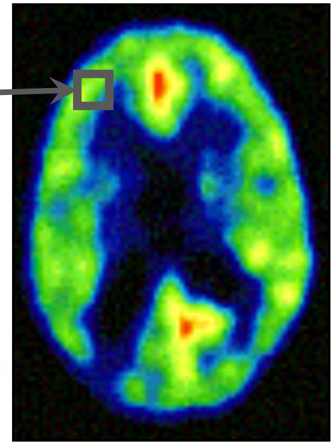
Macroscopic scale



1 mm

10 mm (mice)

Brain scale



10 cm (human)

Size

1 µm RBCs

10 µm Microvessels

1 mm

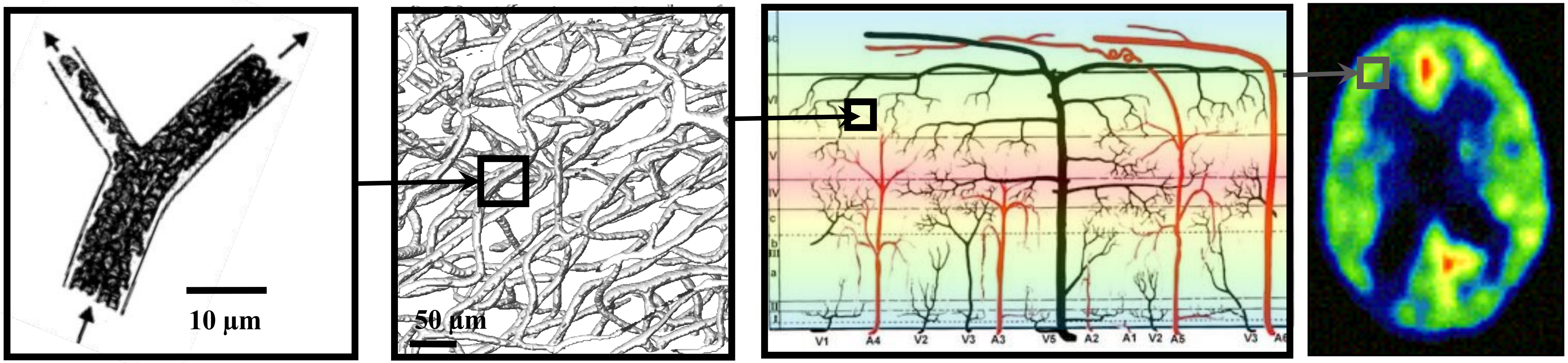
IRM/PET

**Reso-
lution**

Investigation tools and associated scales

In vivo experimental methods

Microscopic scale | **Mesoscopic scale** | **Macroscopic scale** | **Brain scale**



50 µm | 300 µm | 1 mm | 10 mm (mice) | 10 cm (human)

Size →

Resolution ↓: 1 µm, 10 µm, 1 mm

Intravital multiphoton microscopy

IRM/PET

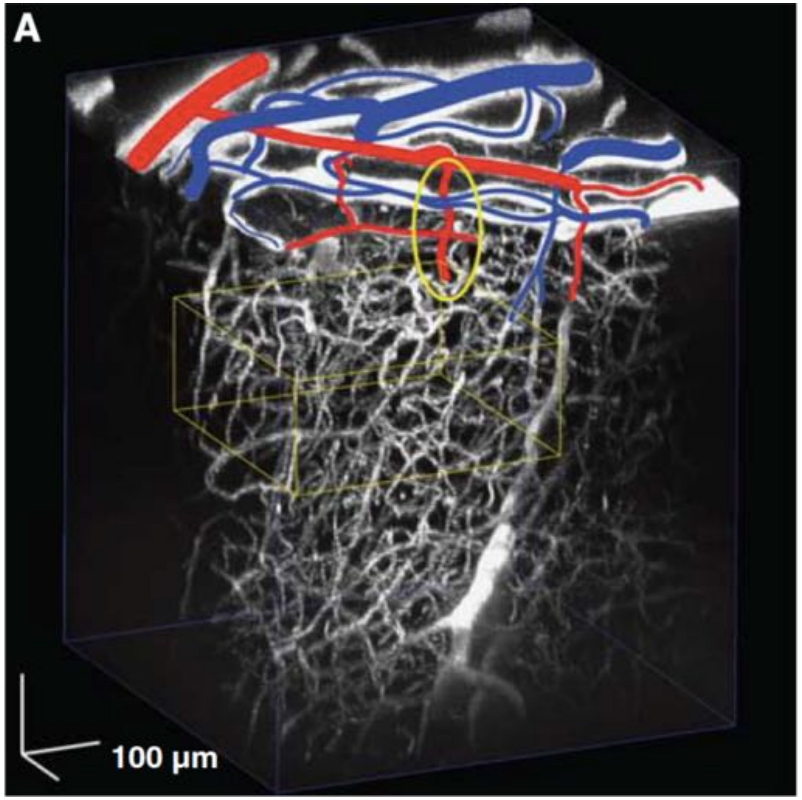
Reso-
lution

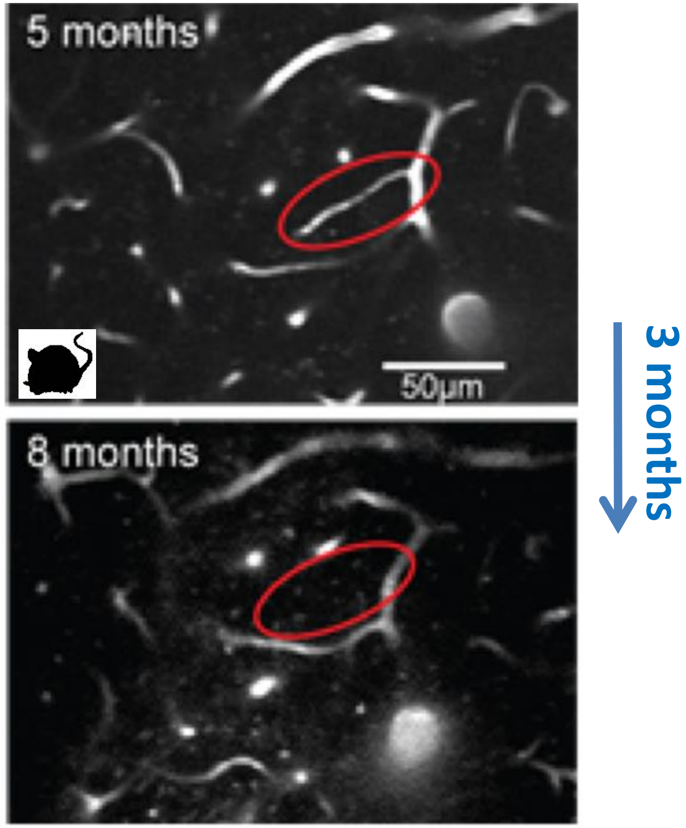
Intravital multiphoton microscopy

Structure

- ❑ **Healthy and diseased (Alzheimer) animal models**

*





Nozomi Nishimura, Personal data

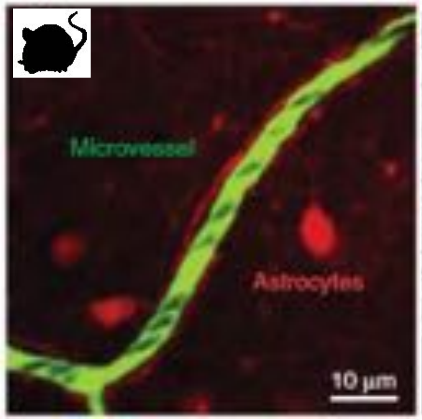
*Nishimura et al. JCBFM 2010

Intravital multiphoton microscopy

Function

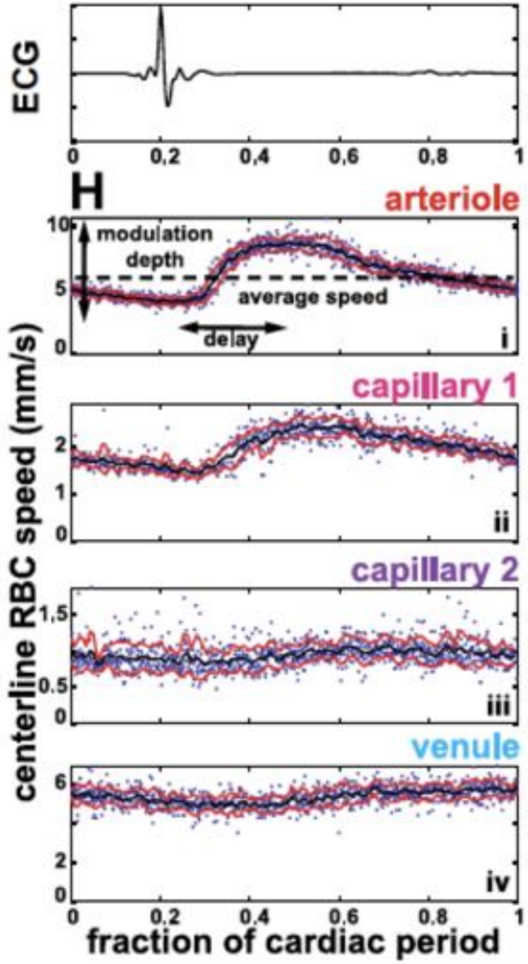
Red Blood Cell velocity

30 s



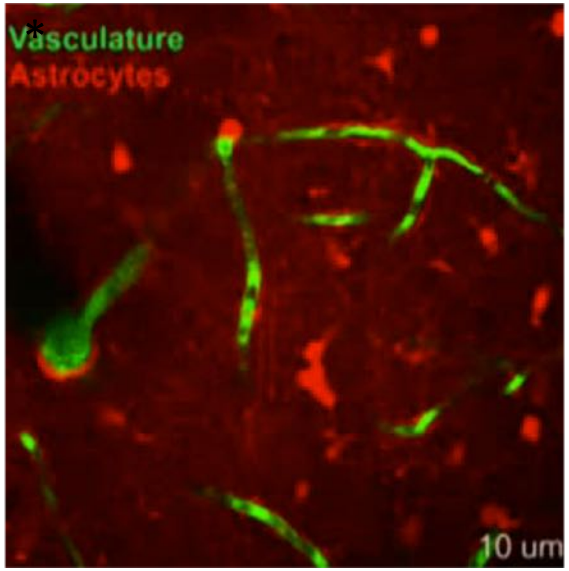
Shih et al. 2012

Nishimura et al. 2007



Santisakultarm et al. *Am J Phys* 2011

*

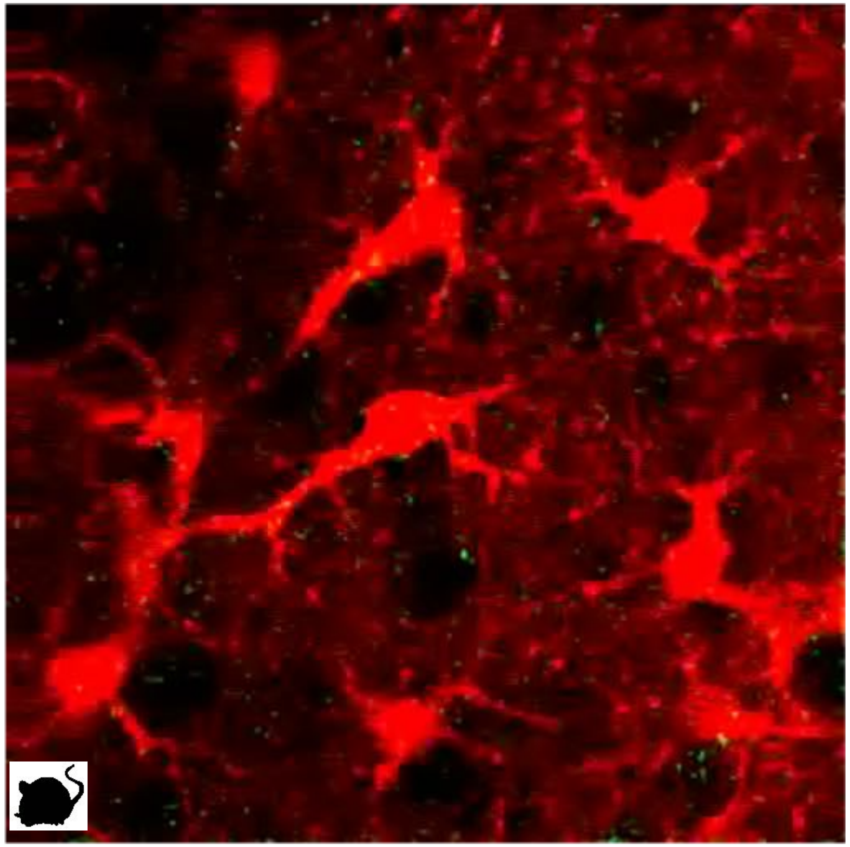


*From Andy Shih, https://www.youtube.com/watch?v=YV1TpkNB0S4

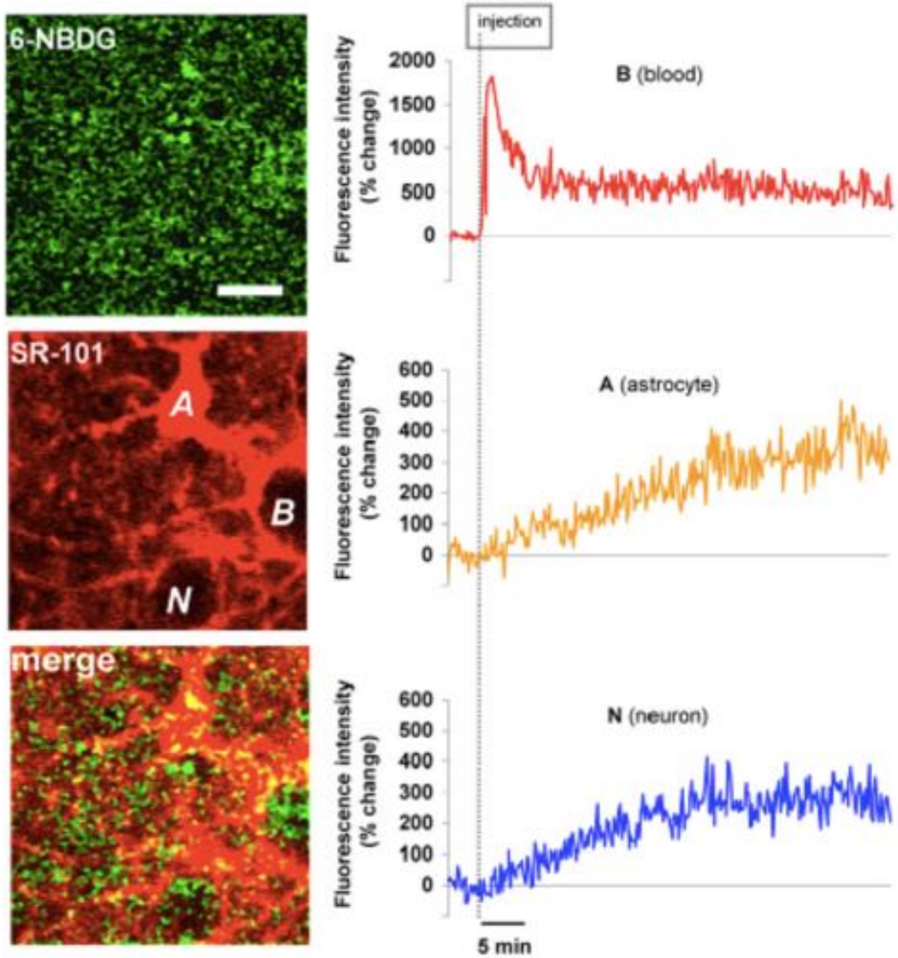
Intravital multiphoton microscopy

Function

Glucose Exchange (6NBDG)



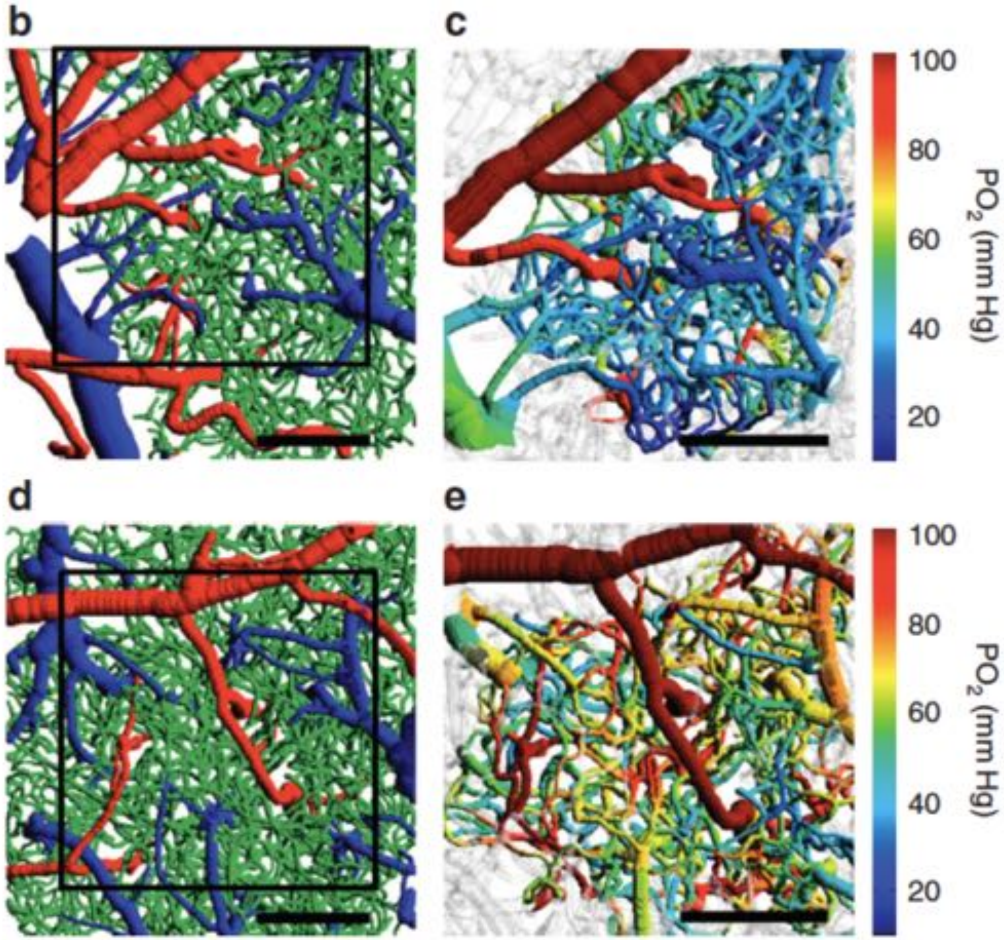
Chuquet et al. 2010



Intravital multiphoton microscopy

Function

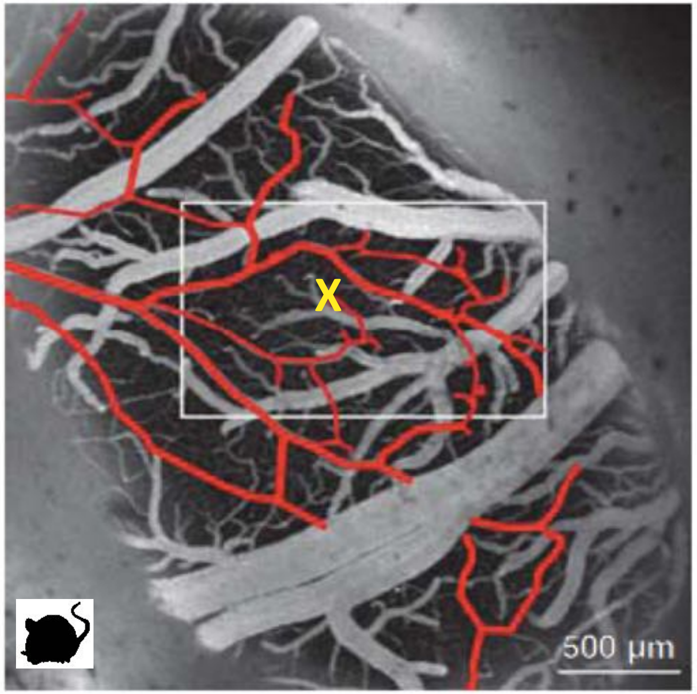
Oxygen partial pressure



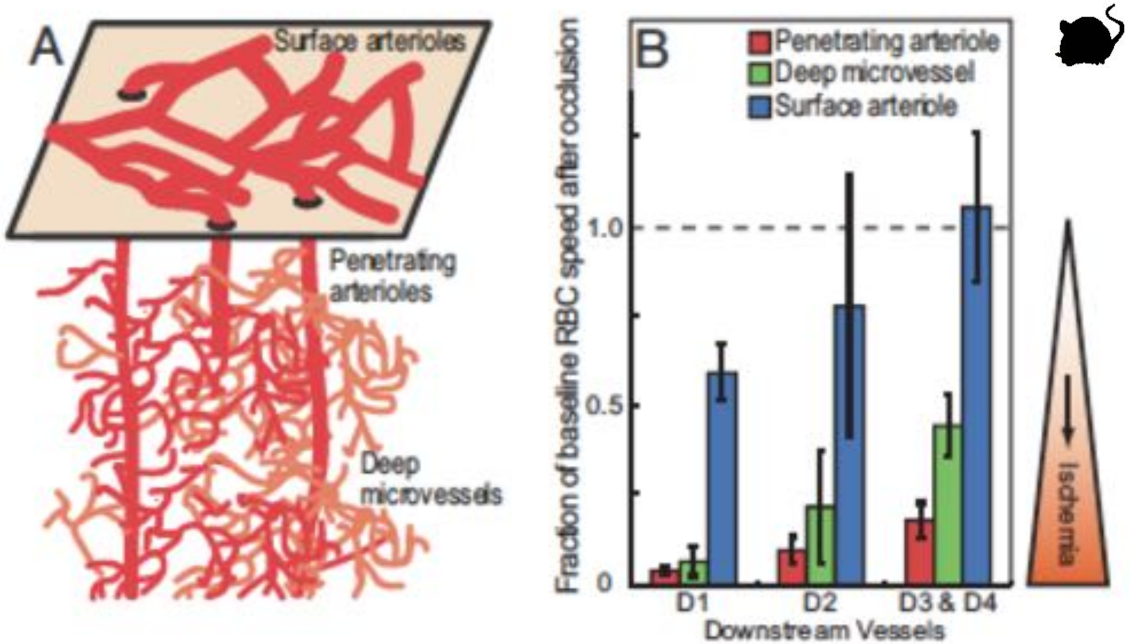
Intravital multiphoton microscopy

Function

Robustness to controlled perturbations: localized obstructions



Nishimura et al. JCBFM 2010



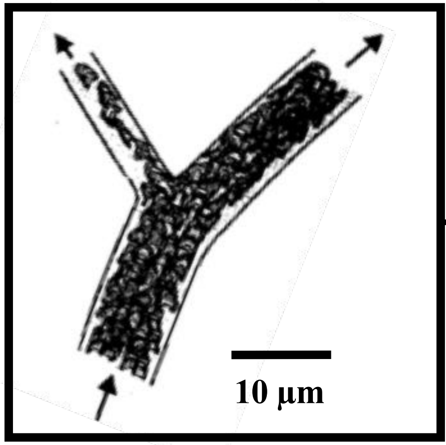
Nishimura et al. PNAS 2007

"Penetrating arterioles are a bottleneck in the perfusion of neocortex"

Investigation tools and associated scales

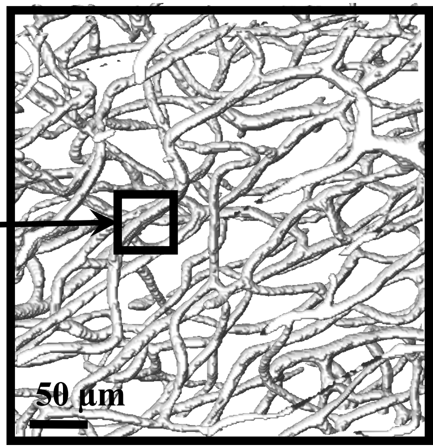
In vitro experimental methods

Microscopic scale



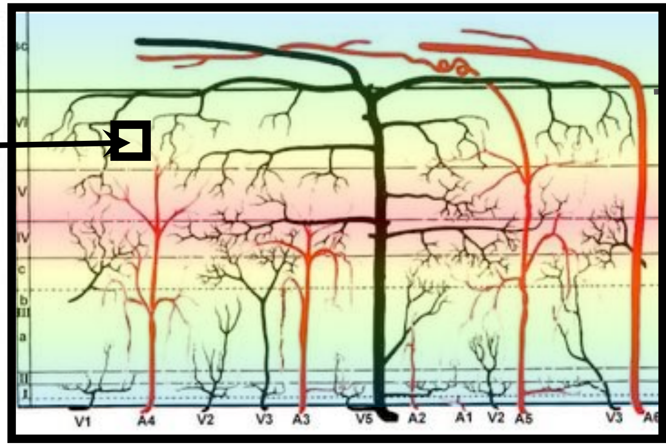
50 µm

Mesoscopic scale



300 µm

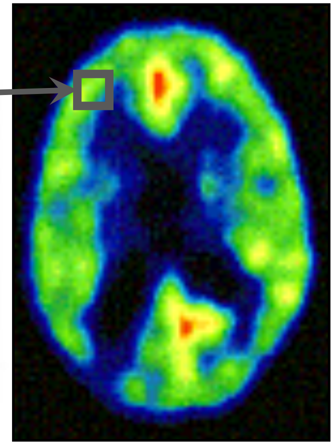
Macroscopic scale



1 mm

10 mm (mice)

Brain scale



10 cm (human)

Microfluidics

Size

1 µm

Intravital multiphoton microscopy

10 µm

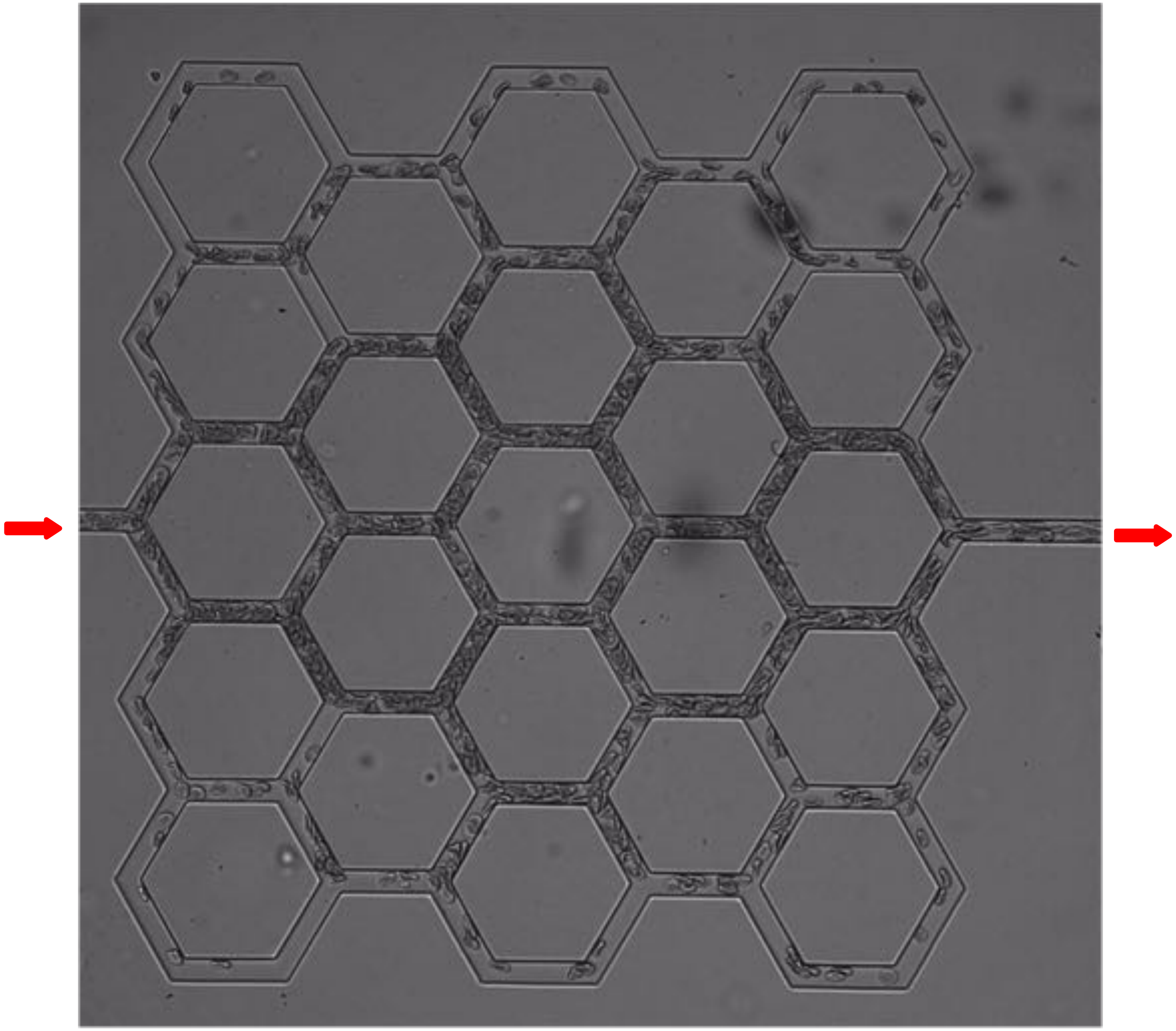
1 mm

IRM/PET

Reso-
lution

Microfluidics

W=10 µm
L=50 µm
H_t=8%

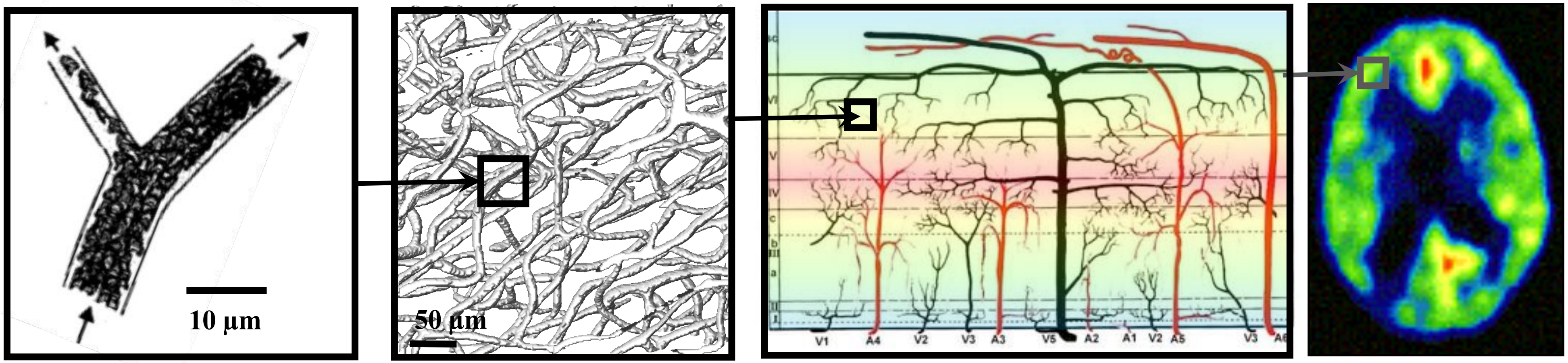


Roman et al. Microvascular research 2012, Roman et al. Biomicrofluidics 2016, PhD A. Merlo

Investigation tools and associated scales

Numerical simulation

Microscopic scale | Mesoscopic scale | Macroscopic scale | Brain scale



50 µm | 300 µm | 1 mm | 10 mm (mice) | 10 cm (human)

Microfluidics

Size

1 µm

Intravital multiphoton microscopy

RBC resolved simulation

10 µm

1 mm

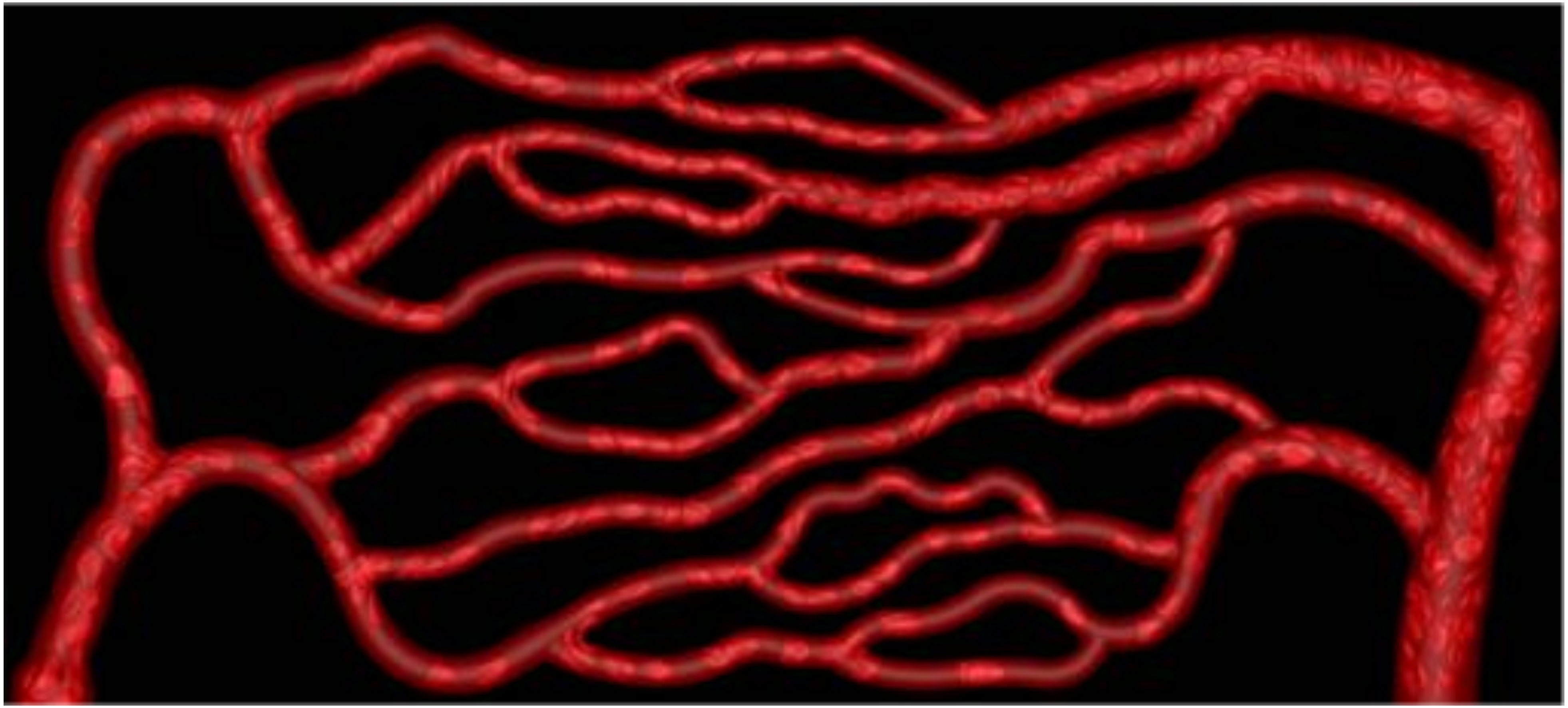
IRM/PET

Reso-
lution

RBC resolved simulations

Some examples

IBM / FV / FE / front-tracking method

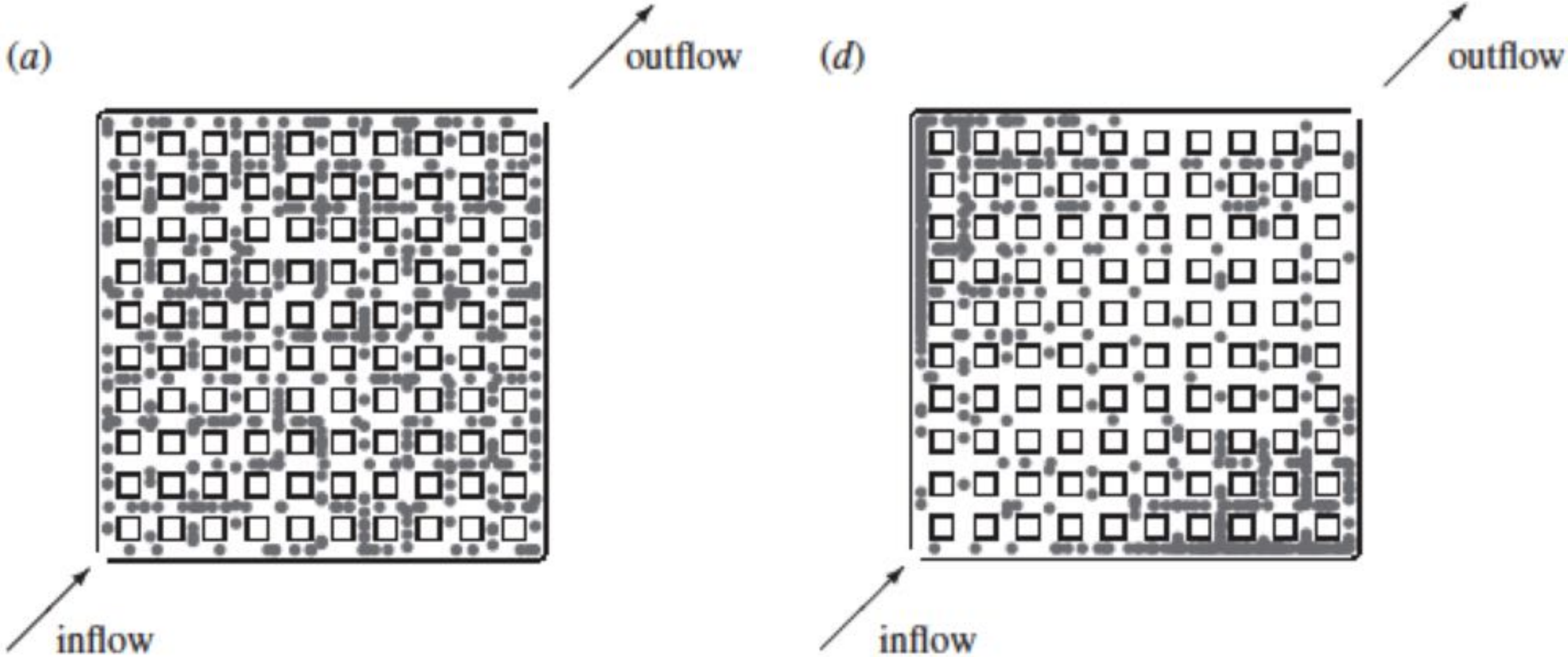


http://bagchi.rutgers.edu

RBC resolved simulations

Some examples

Lagrangian tracking of RBCs in a network

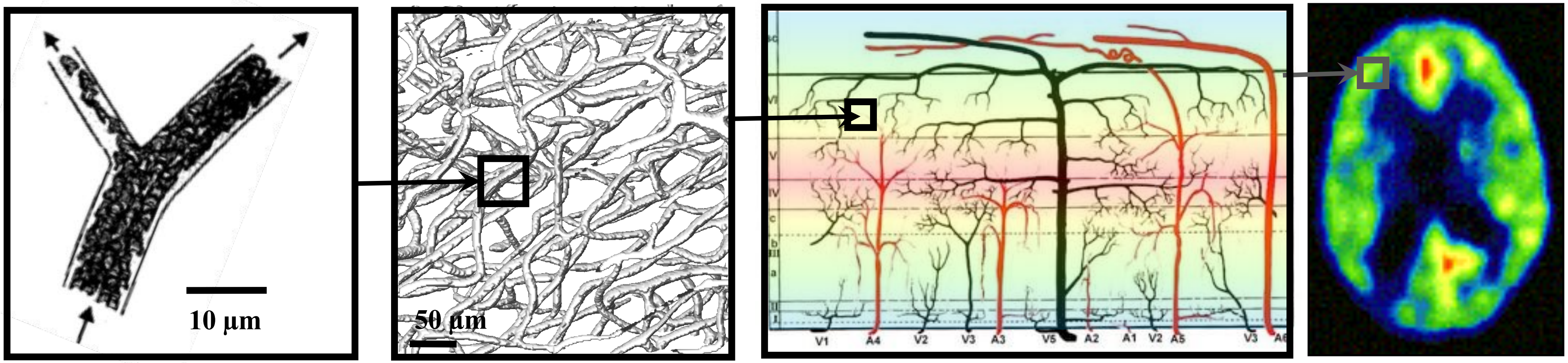


Obrist et al. Philos Trans Royal Soc A: Mathematical, 2010

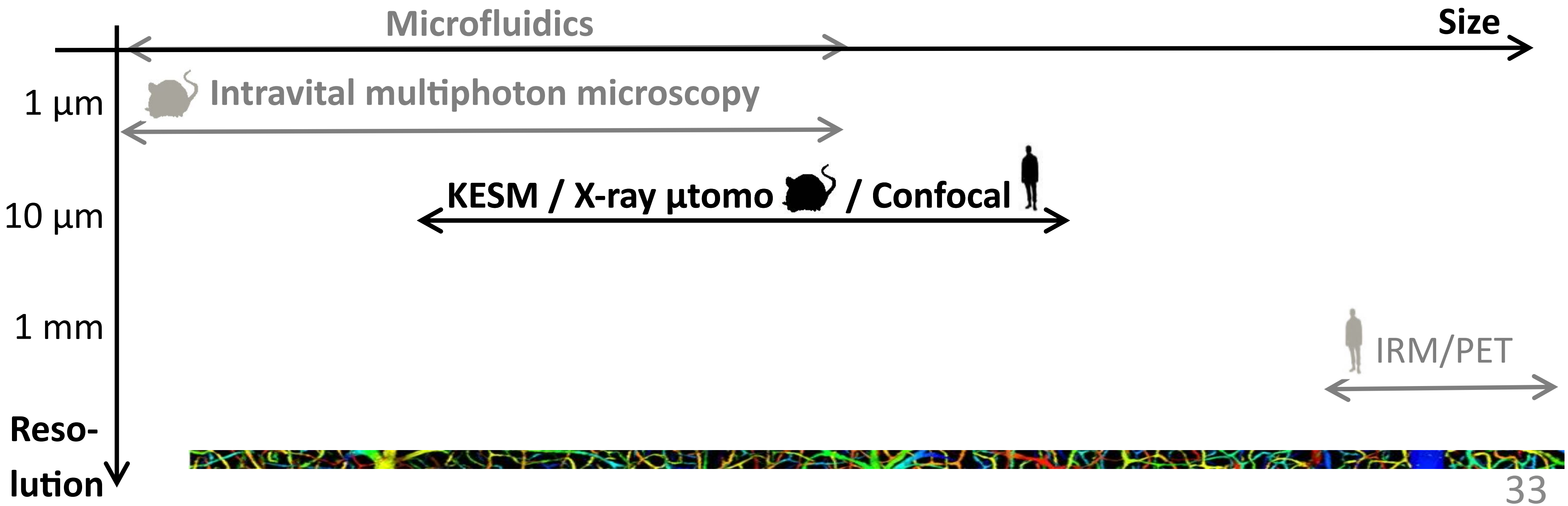
Investigation tools and associated scales

Post-mortem experimental methods

Microscopic scale | **Mesoscopic scale** | **Macroscopic scale** | **Brain scale**

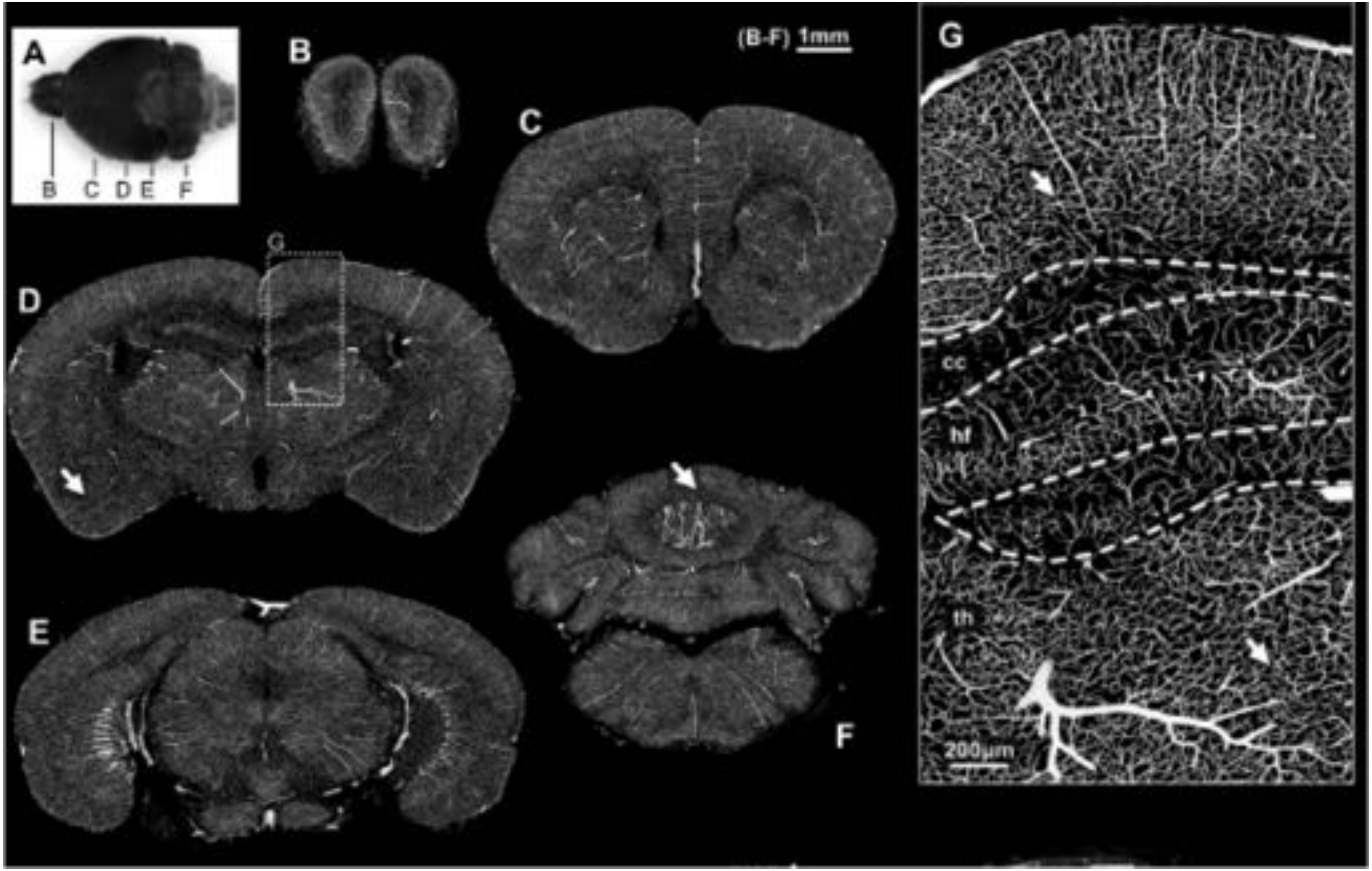


50 µm | 300 µm | 1 mm | 10 mm (mice) | 10 cm (human)



Knife-Edge Scanning Microscopy

(Micro-Optical Sectioning Tomography)

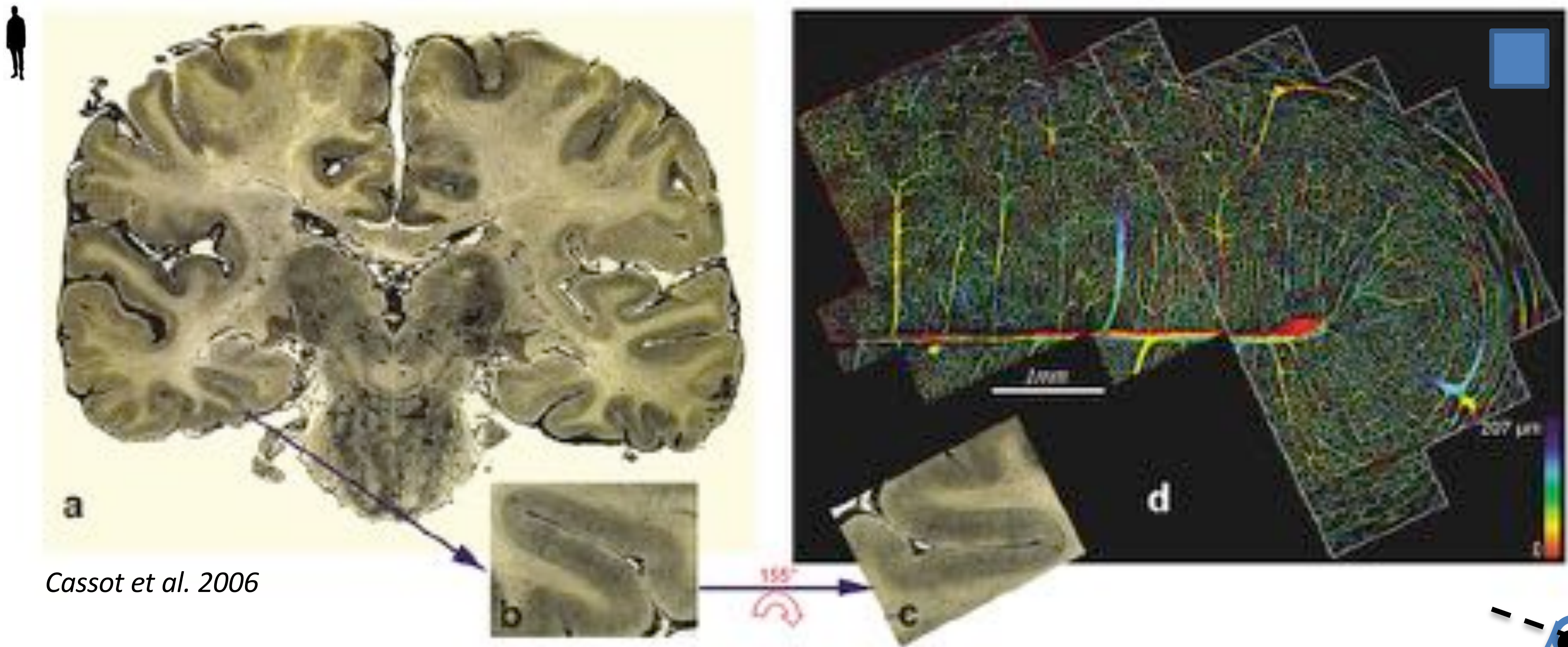


Mayerich et al. *Biomed Optics Express, 2011 Xue et al. PLOS ONE 2014*

Human anatomical database (Inserm Tonic)

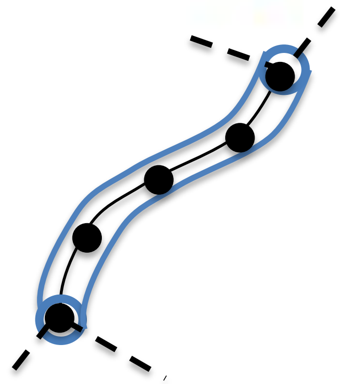
post mortem confocal imaging

- ❑ **60 year old, abdominal lymphoma**



Cassot et al. 2006

- ❑ 1.2 x 1.2 x 3 µm^3 in areas as large as 10 mm^2 x 300 µm
- ❑ Vascular network graph (centerlines, radii, connectivity)
- ❑ Morphometric analysis (segments, bifurcations)*

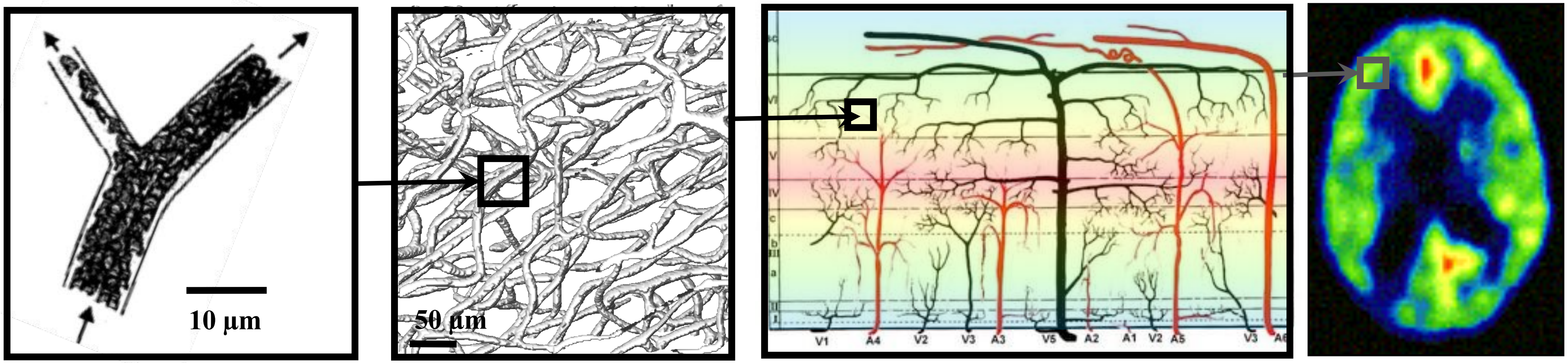


*Cassot et al. 2006, 2010, Lauwers et al. 2008, Lorthois et al. 2014

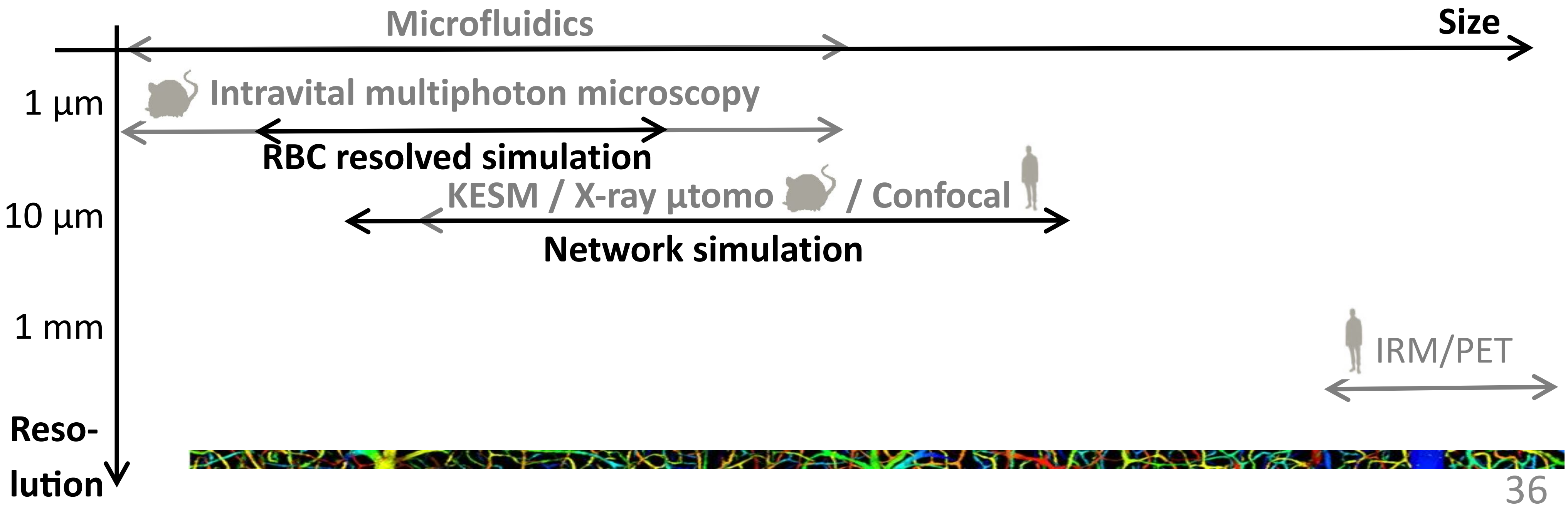
Investigation tools and associated scales

Numerical simulation

Microscopic scale | Mesoscopic scale | Macroscopic scale | Brain scale



50 µm | 300 µm | 1 mm | 10 mm (mice) | 10 cm (human)



Outline

- **Brain versus other organs**
  - What is generic ?
  - What is specific ?
- **Why study brain microcirculation ?**
  - In health
  - In disease
- **Investigation tools and associated scales**
- **Blood flow in networks**
- **Mass transfers in networks**
- **Blood flow at organ scale**

Blood flow in networks

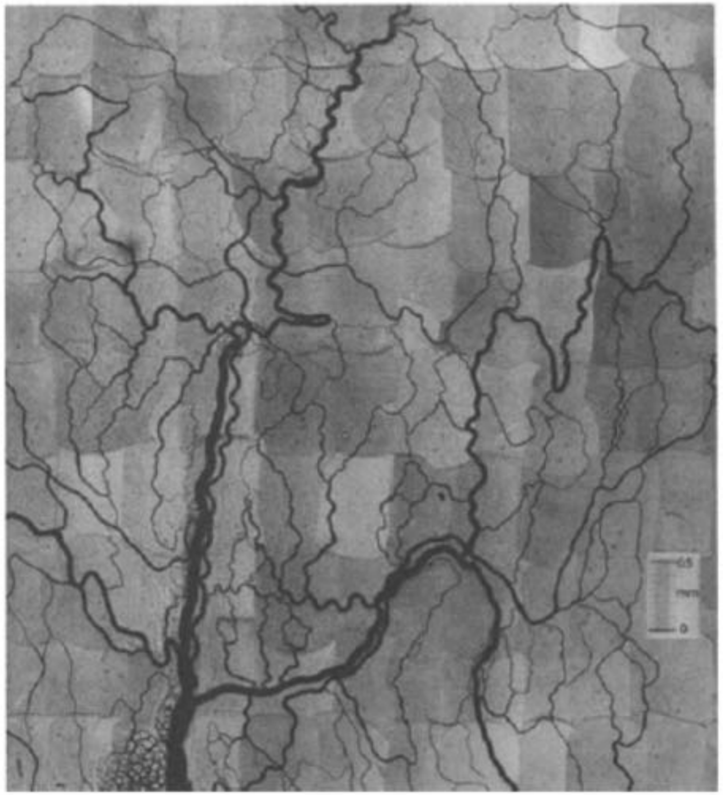
Modeling framework

Blood Flow in Microvascular Networks

Experiments and Simulation

A.R. Pries, T.W. Secomb, P. Gaehtgens, and J.F. Gross

- In vivo experiments
  - Rat mesentery
  - Structure (R, L, Connectivity)
  - Hemodynamic data (Q, H_{tube})



Pries et al. *Circulation Research* 1990

Blood flow in networks

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  - The blood is viewed as an equivalent fluid (i.e. at vessel scale)
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  - A first guess on their coefficient is based on experiments (in vivo or in glass tubes)
- Simulation/Experiments
  - The values of these coefficients are adjusted to best match the *in vivo* measurements
  - This gives insights on biophysical aspects of blood flow in the microvaculature

Pries et al. *Circ Res* 1990, Rasmussen et al. *Microcirculation* 2018, Pries et al. *Cardiovascular Res* 1996

The blood as an equivalent fluid

Apparent viscosity and relative viscosity

If the fluid is Newtonian and the flow is laminar, we have the Hagen-Poiseuille formula [Eq. (8) of Sec. 3.3]:

$$\frac{\Delta p}{\Delta L} = \frac{8\mu}{\pi a^4}\dot{Q}, \tag{1}$$

where Δp is the pressure drop in length ΔL, μ is the coefficient of viscosity of the fluid, a is the radius of the tube, and $\dot{Q}$ is the volume rate of flow. If the fluid is blood, this equation does not apply; but we can still measure $\Delta p/\Delta L$ and $\dot{Q}$, and use Eq. (1) to calculate a coefficient μ_{app}:

$$\mu_{app} = \frac{\pi a^4}{8}\frac{1}{\dot{Q}}\frac{\Delta p}{\Delta L}. \tag{2}$$

The μ so computed is defined as the *apparent coefficient of viscosity for the circular cylindrical tube*,

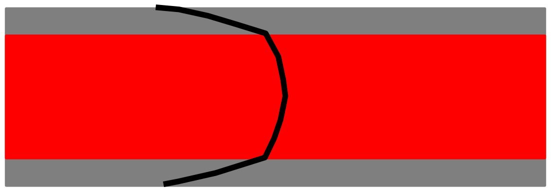
Eq. (2) is formally identical to Poiseuille equation
but this does not imply a parabolic velocity profile
(nor any other assumption on the shape of the velocity profile)

The blood as an equivalent fluid

Apparent viscosity and relative viscosity

Apparent and relative viscosities are not intrinsic properties of the blood; they are properties of the blood and blood vessel interaction, and depend on the data reduction procedure. There are as many definitions for apparent viscosities as there are good formulas for well-defined problems. Examples are: Stokes flow around a falling sphere, channel flow, flow through an orifice, and flow in a cylindrical tube.

The simplest well-defined model for blood : a two-fluid model with fixed δ



$\mu_{in} du/dy]_{-} = \mu_{out} du/dy]_{+}$

$\mu_{app} = \mu_{out}/[(1-\delta/R)^4(\mu_{out}/\mu_{in}-1)+1]$

Fung « Biomechanics: Mechanical Properties of Living Tissues, Section 5.1 » 1981

The blood as an equivalent fluid

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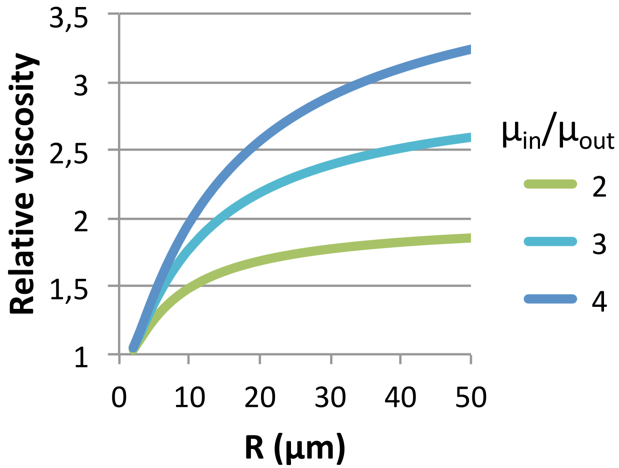


$$\mu_{app}=\mu_{out}/[(1-\delta/R)^4(\mu_{out}/\mu_{in}-1)+1]$$

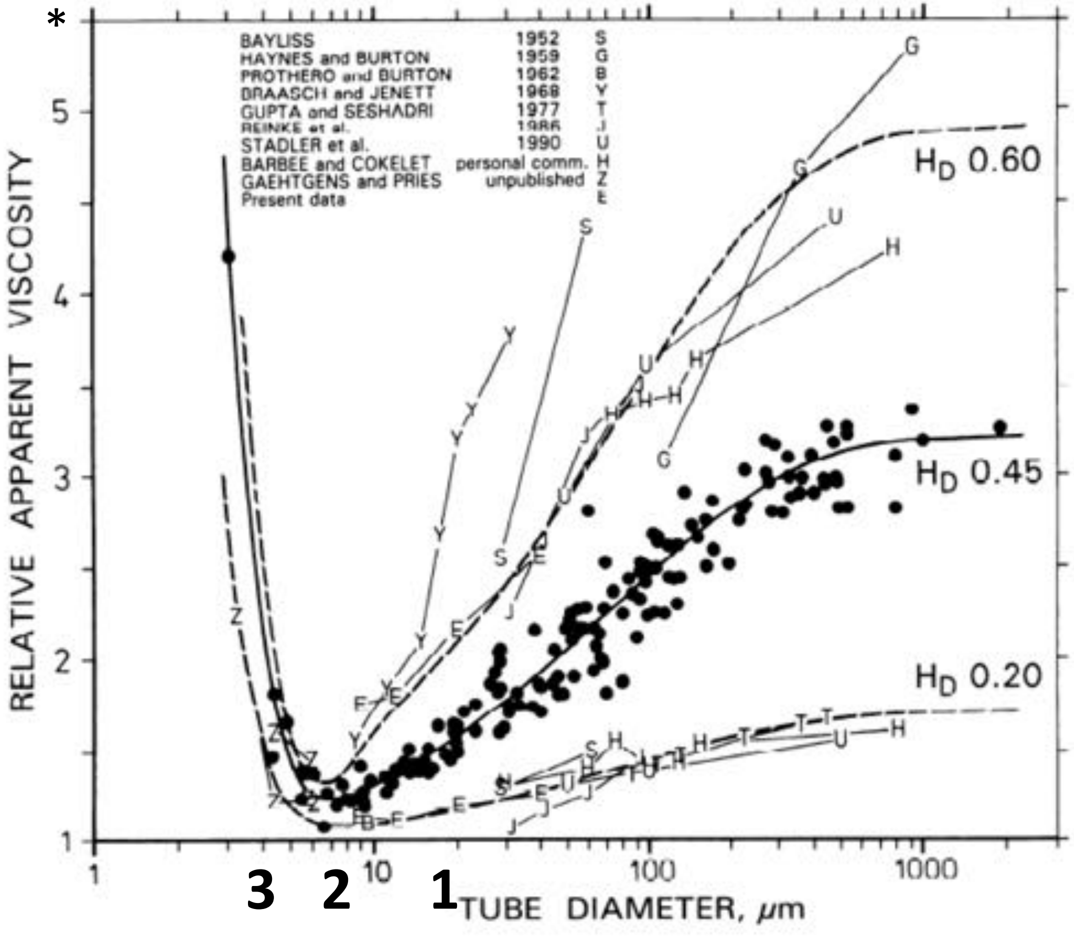
$$\mu_{rel}=\mu_{app}/\mu_{plasma}=[Q_{plasma}/Q_{blood}]_{\text{same } \Delta P}$$

Fung « Biomechanics: Mechanical Properties of Living Tissues, Section 5.1 » 1981

The blood as an equivalent fluid

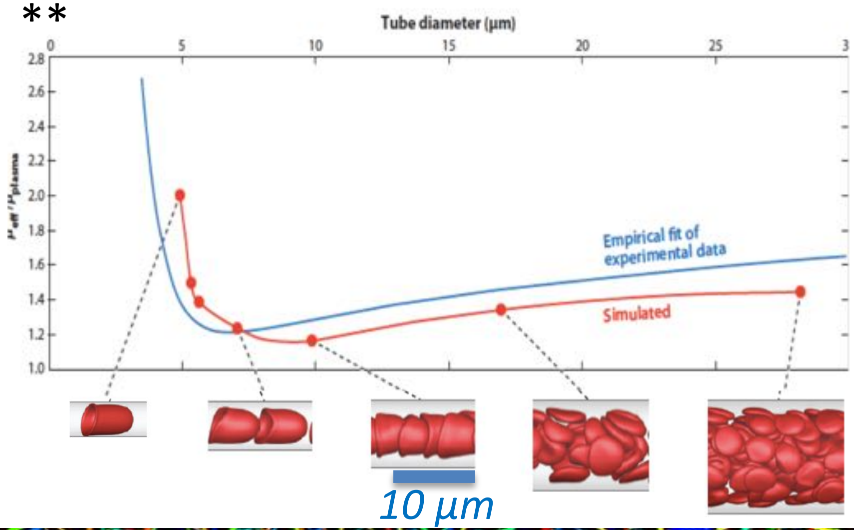
Apparent viscosity and relative viscosity

*



$$\mu_{rel} = f(d,\boldsymbol{H})$$

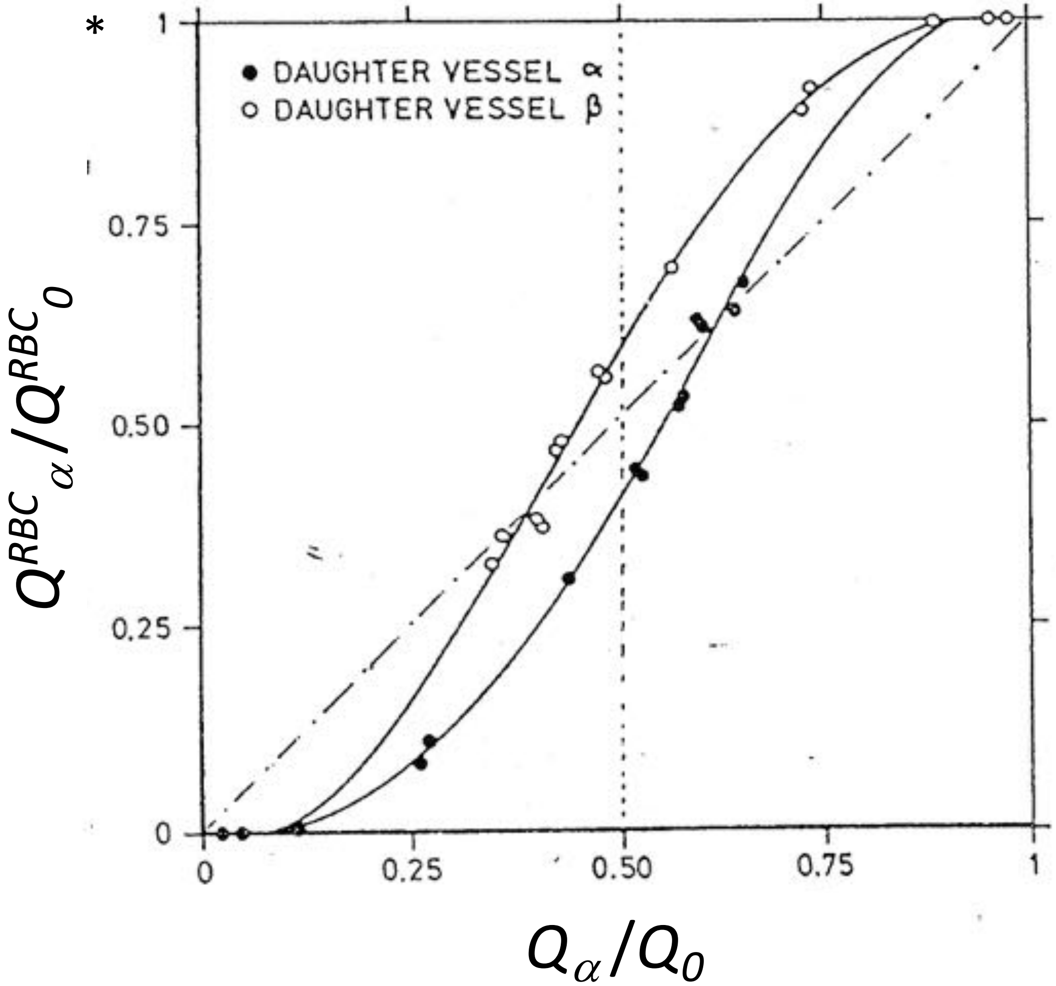
**

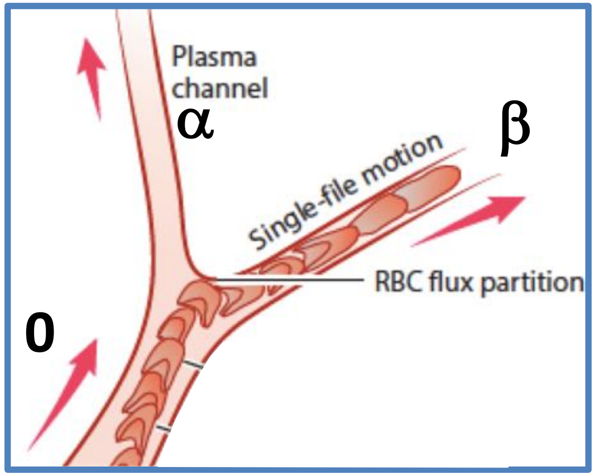


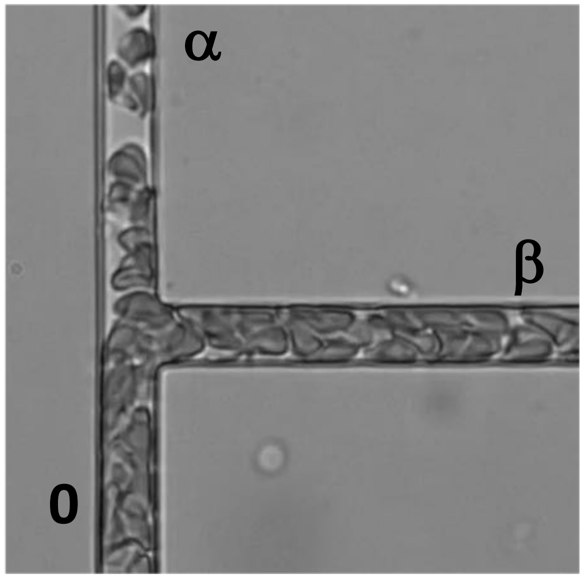
* Pries et al. Am J Physiol 1992 , ** Freund, Ann. Rev. Fluid Mech 2014

The blood as an equivalent fluid

Bifurcation law







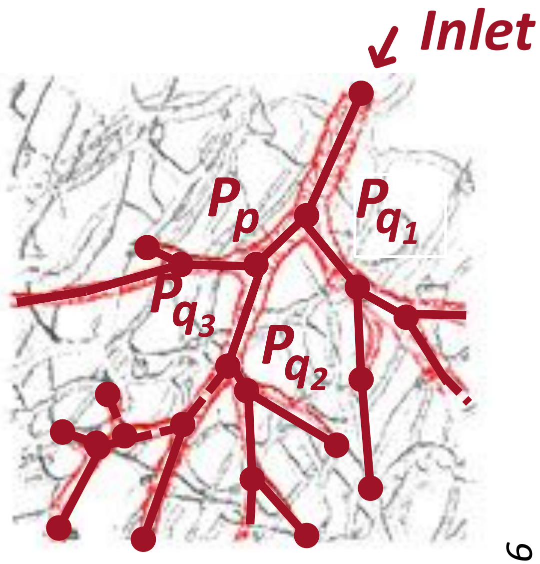
$$Q^{RBC}_{\alpha}/Q^{RBC}_{0}=g(Q_{\alpha}/Q_0, H_0, d_0, d_{\alpha}/d_0, d_{\beta}/d_0)$$

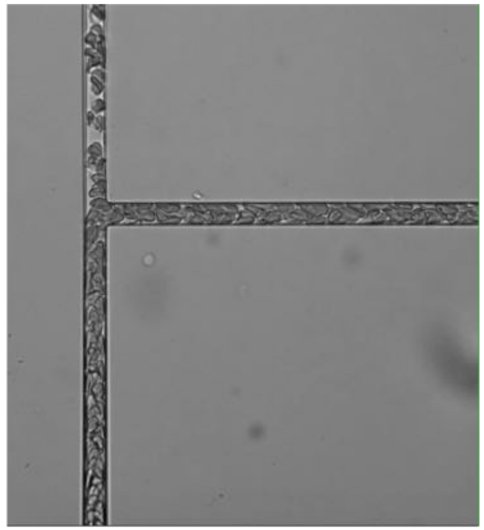
* Pries et al. Microvascular Research 1989, ** Roman et al. Biomicrofluidics 2016.

Blood flow in networks

Modeling framework

- The vascular network is represented as a graph, with prescribed BCs
- A uniform hematocrit distribution (H=0.45) is assumed
- The viscosity μ_{app} in each vessel depends on its diameter *d* and hematocrit *H* (Pries et al. 1996)
- Their resistance *R* is deduced $R = (128\, \mu_{app} L)/(\pi d^4)$
- Mass conservation $\left(\sum_i [R_{pq_i}{}^{-1} (P_{q_i} - P_p)] = 0\right)$ is solved yielding the **pressures** at each node
- **Flow rate** in each vessel is deduced using the linear relationship $Q_{pq_i} = R_{pq_i}{}^{-1} (P_{q_i} - P_p)$
- **Hematocrit** in each vessel is deduced using a bifurcation law for phase separation (Pries et al. 1996)





Roman et al. Biomicrofluidics 2016

Lorthois et al. Neuroimage, 2011a

Blood flow in networks
Modeling framework

Blood Flow in Microvascular Networks

Experiments and Simulation

A.R. Pries, T.W. Secomb, P. Gaehtgens, and J.F. Gross

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Pries et al. *Circ Res* 1990, Rasmussen et al. *Microcirculation* 2018, Pries et al. *Cardiovascular Res* 1996

Blood flow in networks
Modeling framework

- **Flow direction**

913 seg. 546 seg. 436 seg.

TABLE 2. Evaluation of Model Simulation in the Rat Mesentery Under Six Different Sets of Input Conditions

Condition	H_D	Viscosity law	Network A (913 seg.)		Network B (546 seg.)		Network C (436 seg.)	
			N_{INV}	$r^2_{H_D}$	N_{INV}	$r^2_{H_D}$	N_{INV}	$r^2_{H_D}$
1	Predicted	In vitro	44 (4.8%)	0.060	30 (5.5%)	0.133	13 (3.0%)	0.177
2	Predicted	Uniform	25 (2.7%)	0.080	24 (4.4%)	0.163	7 (1.6%)	0.226
3	Predicted	Modified	15 (1.6%)	0.148	25 (4.6%)	0.183	2 (0.5%)	0.333
4	Measured	In vitro	69 (7.6%)	...	47 (8.6%)	...	22 (5.0%)	...
5	Measured	Uniform	25 (2.7%)	...	24 (4.4%)	...	7 (1.6%)	...
6	Measured	Modified	20 (2.2%)	...	29 (5.3%)	...	3 (0.7%)	...

H_D, discharge hematocrit; N_{INV}, segments in which the predicted flow direction was inverted relative to observation; $r^2_{H_D}$, the squared coefficient of correlation between predicted and measured discharge hematocrits in all vessel segments. H_D was either predicted from the phase-separation effect or measured in vivo.

(Pries *et al.* 1990)

- **Minimisation of the number of vessels with wrong flow direction**

  ➔ *In vivo* viscosity law

Blood flow in networks

Modeling framework

- **In vivo viscosity law**

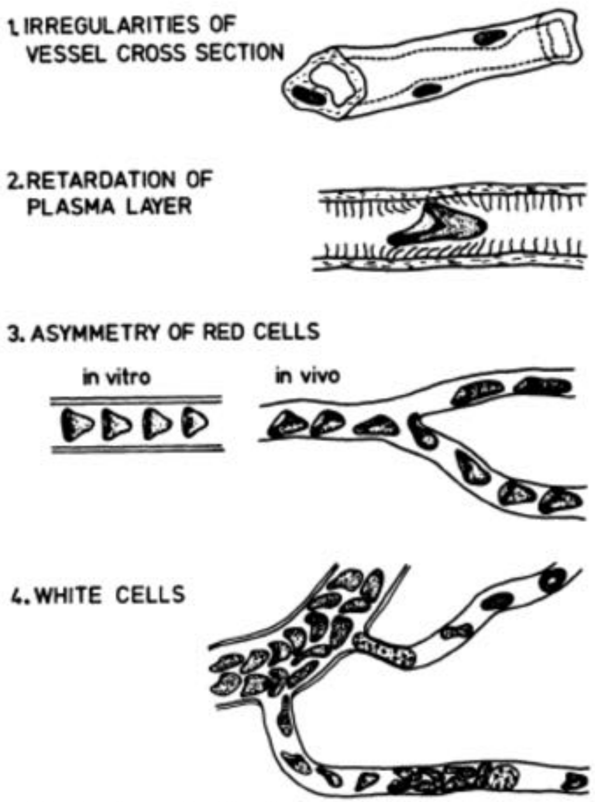
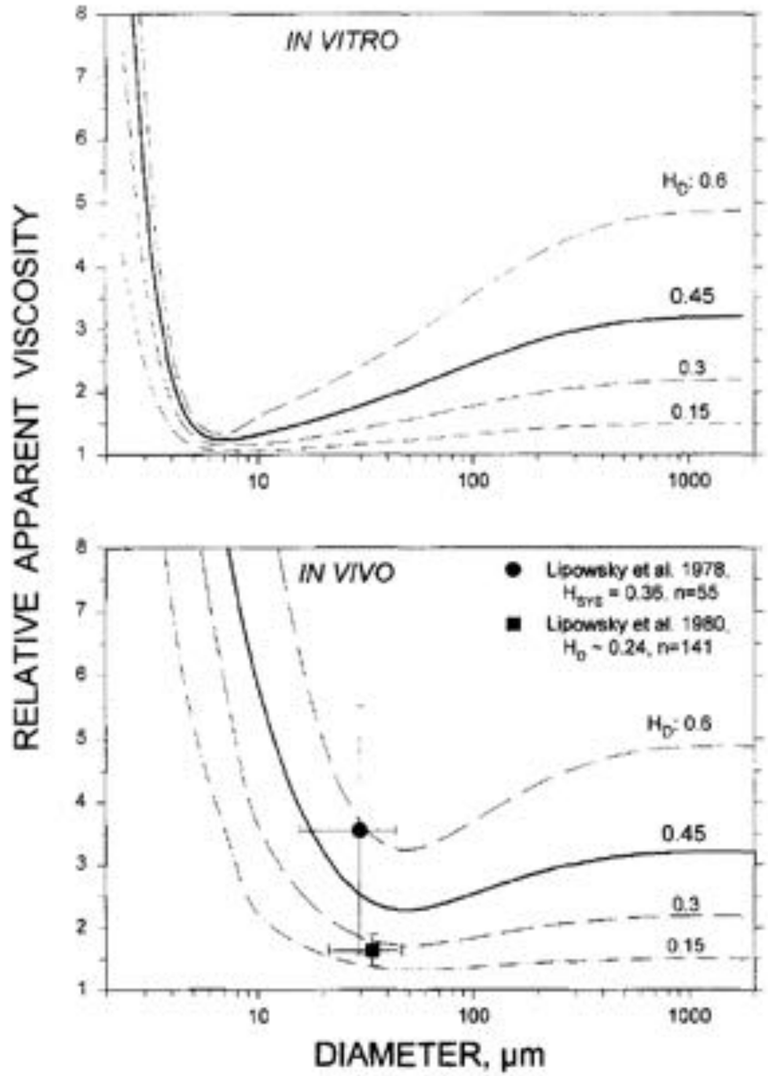


FIGURE 8. *Schematic drawings showing possible reasons for high resistance in small microvessels.*



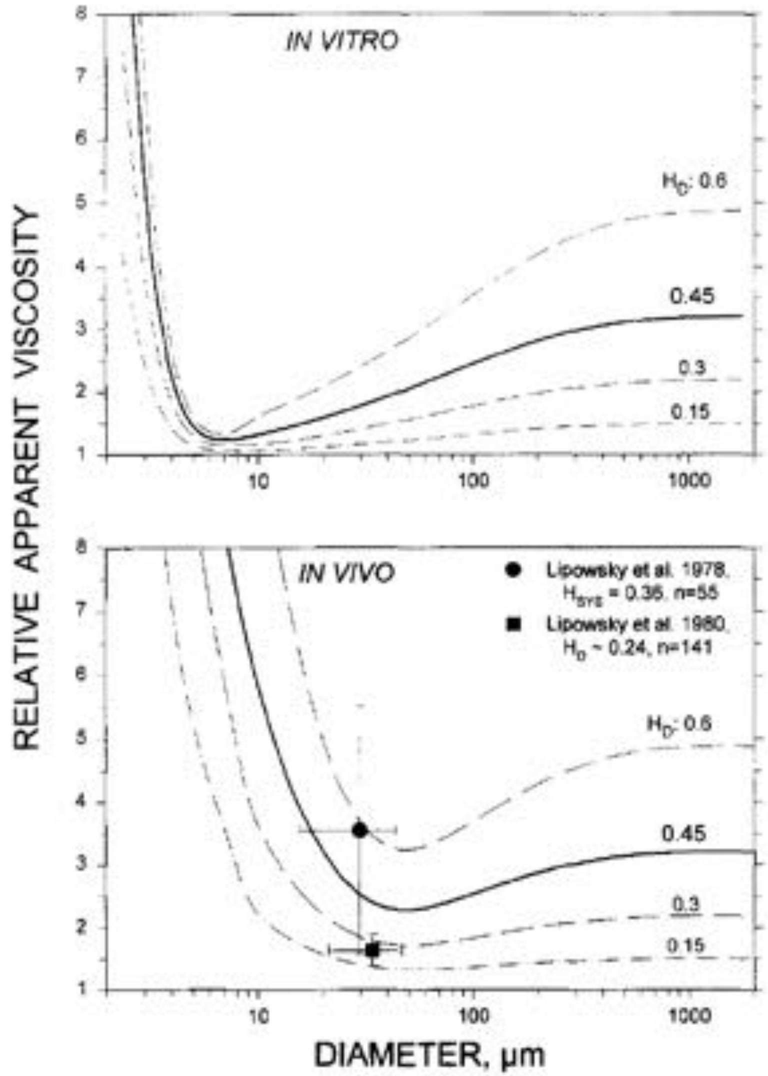
(Pries *et al.* 1990)

Blood flow in networks

Modeling framework

- **In vivo viscosity law**

comparison with the original viscosity law (Figure 1) shows a marked viscosity increase in the low diameter range. It should be cautioned, however, that this viscosity relation cannot be considered as a precise, quantitative representation of effective blood viscosity in vivo. Model results with comparable values of N_{INV} and $r^2_{H_D}$ could be achieved with a number of viscosity relations that exhibit significant quantitative differences to those described by Equation 7. All these relations, however, are qualitatively similar in predicting a viscosity increase with decreasing vessel diameter below about 15 μm. The results presented

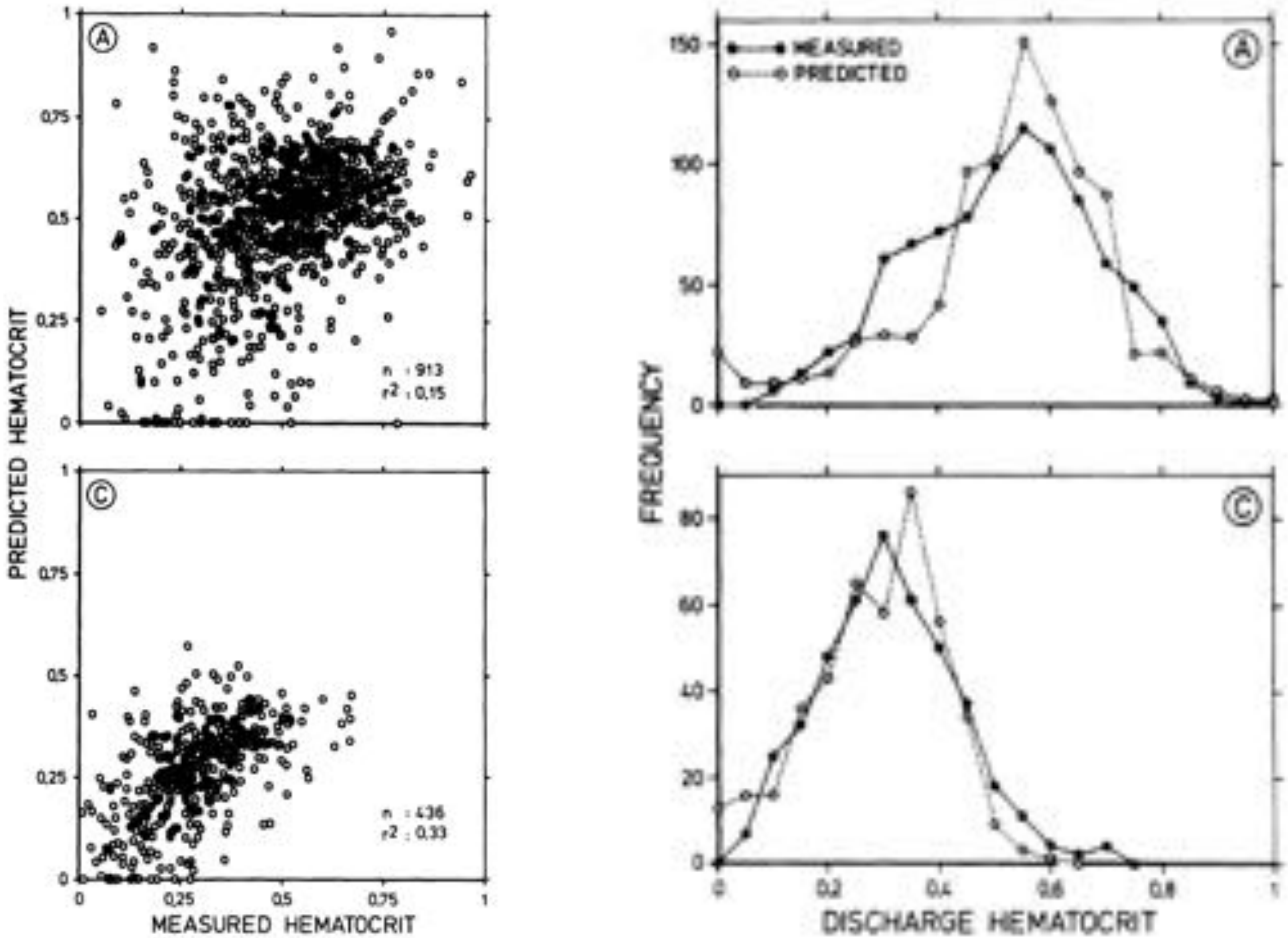


(Pries *et al.* 1990)

Blood flow in networks

Validation against in vivo data

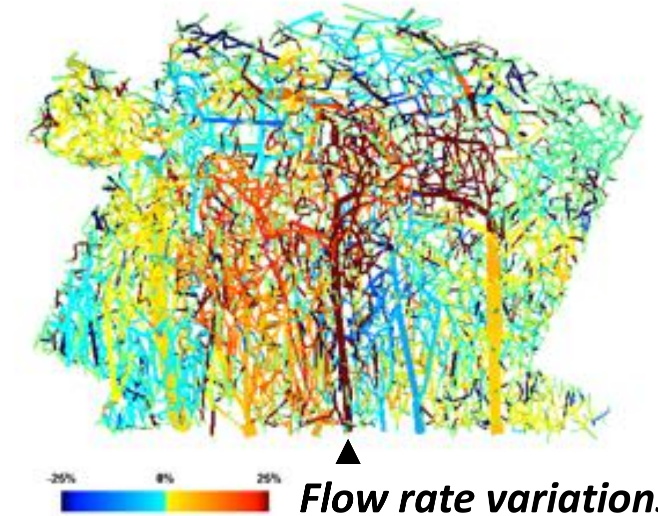
- ❑ **Hematocrit**



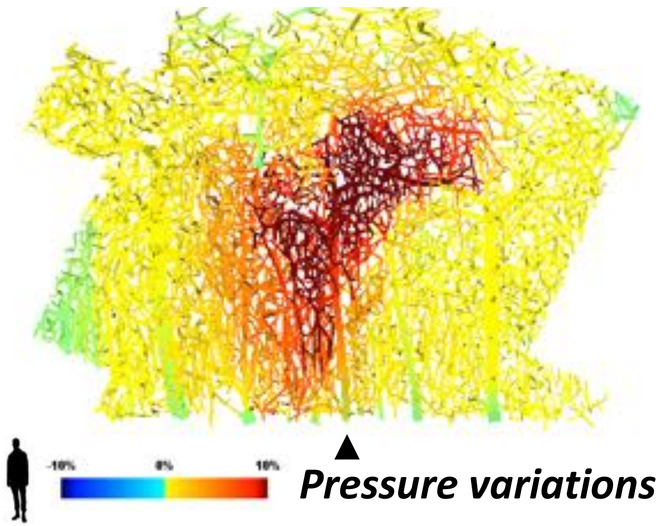
(Pries *et al.* 1990)

Blood flow in networks
Back to the brain…

- ❑ **Strengths***
  - Changes in vascular structure (vessel occlusions, vessel dilations) can be easily imposed
  - Post-processing is versatile
    - Spatial maps : baseline parameters, parameter variations induced by changes in structure
    - Spatial averages
    - Passive tracer injection : vascular territories, transit time distributions, lagrangian analysis
    - Correlations between variables: e.g. flow variation = f(topological distance)



Flow rate variations



Pressure variations

* *Lorthois et al. Neuroimage, 2011a&b*

Blood flow in networks

Back to the brain…

❑ Strengths*

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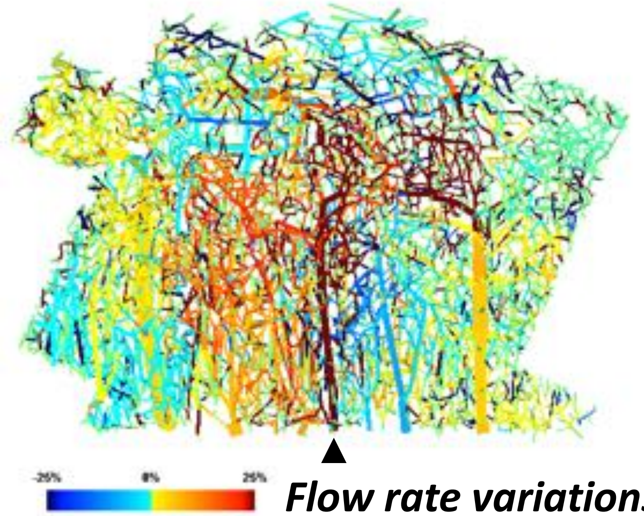
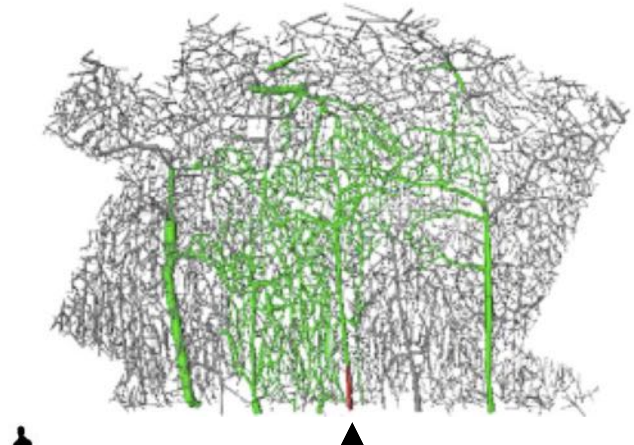


Flow rate variations



Vascular territory

* *Lorthois et al. Neuroimage, 2011a&b*

Blood flow in networks

Back to the brain…

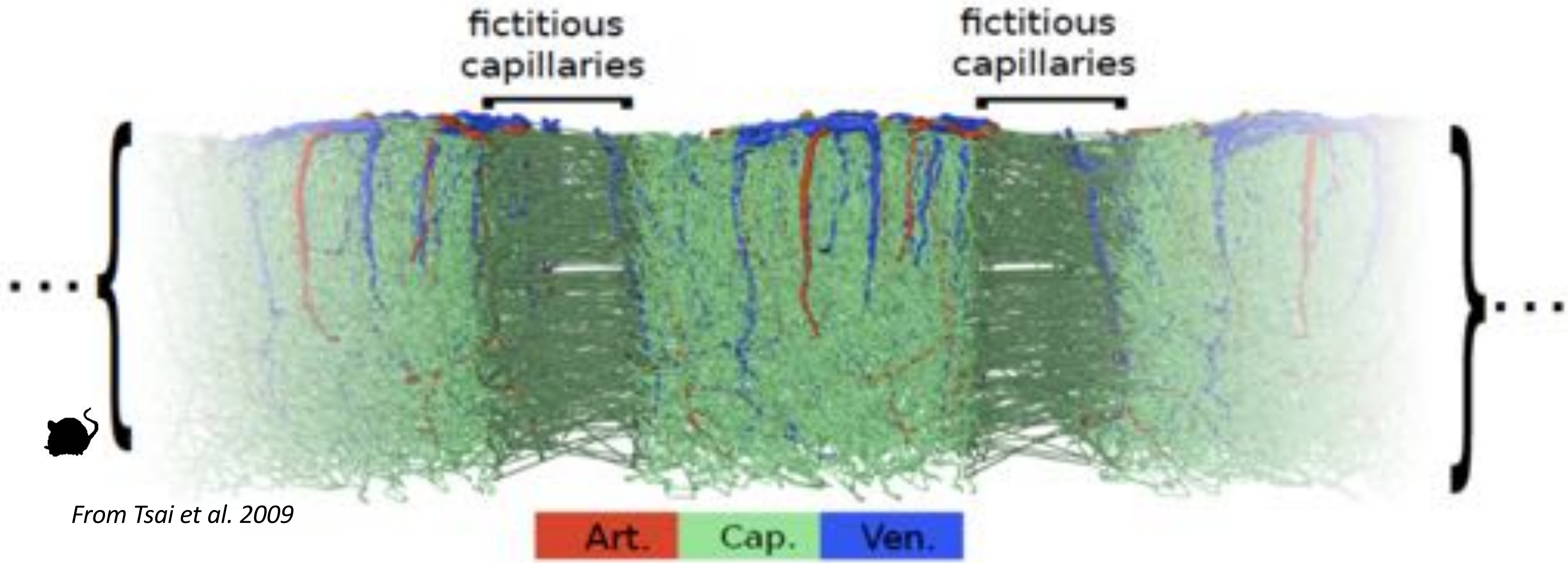
- **Weaknesses**
  - Need of comprehensive high resolution anatomical data
  - Sensitivity to vessel diameters, boundary conditions, domain size ?
    - ➔ Critical for the exploitation of human data (post-mortem, slices)

Blood flow in networks

Back to the brain…

- ❑ **Weaknesses**
  - Need of comprehensive high resolution anatomical data
  - Sensitivity to vessel diameters, boundary conditions, domain size ?
    - ➔ Critical for the exploitation of human data (post-mortem, slices)

- ❑ **Validation vs. mice experimental data in large domains**



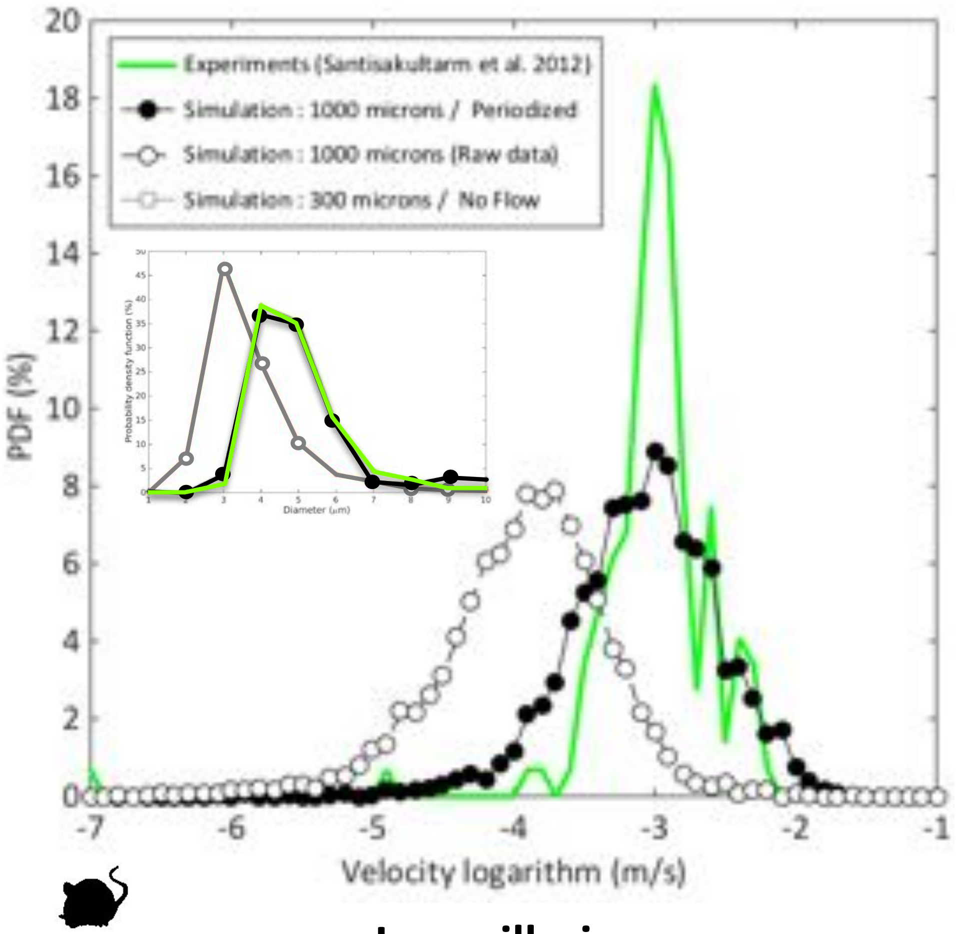
From Tsai et al. 2009

Cruz-Hernandez et al. Nature Neuroscience 2019

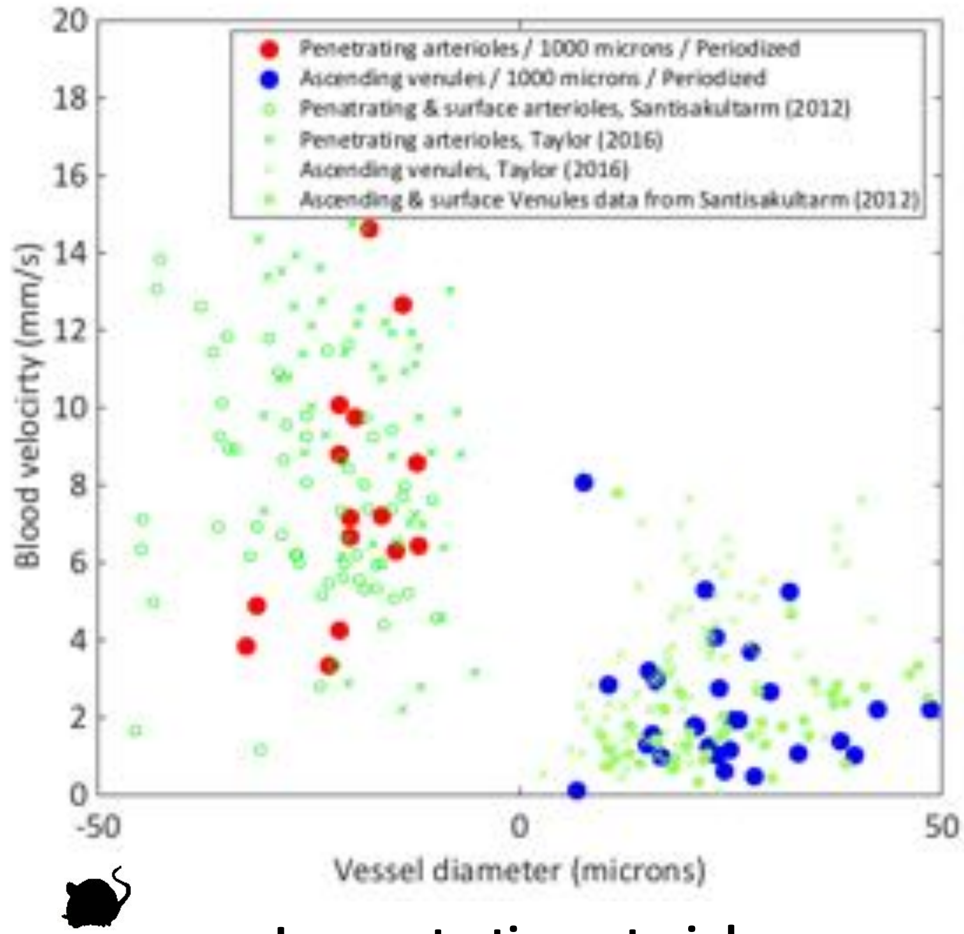
Blood flow in networks

Back to the brain…

❑ **Comparison of velocity distributions with TPSLM experiments**



In capillaries
(less than 300 µm under brain surface)



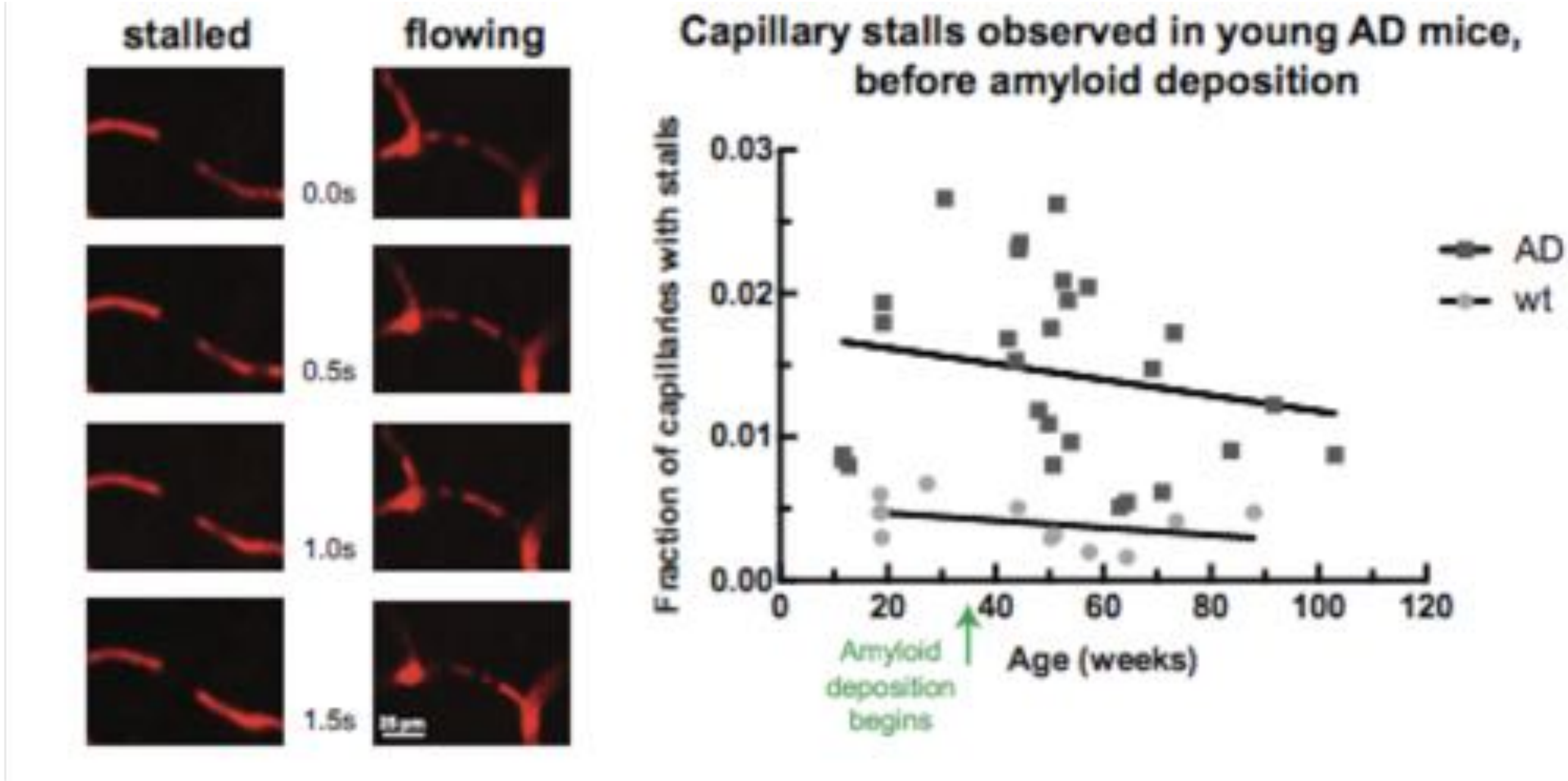
In penetrating arterioles
and ascending venules

Cruz-Hernandez et al. Nature Neuroscience 2019

Blood flow in networks

Vascular component of AD: impact of small initial perturbation

- ❑ In APP/PS1 mice, ~2% capillaries are stalled by leucocytes*



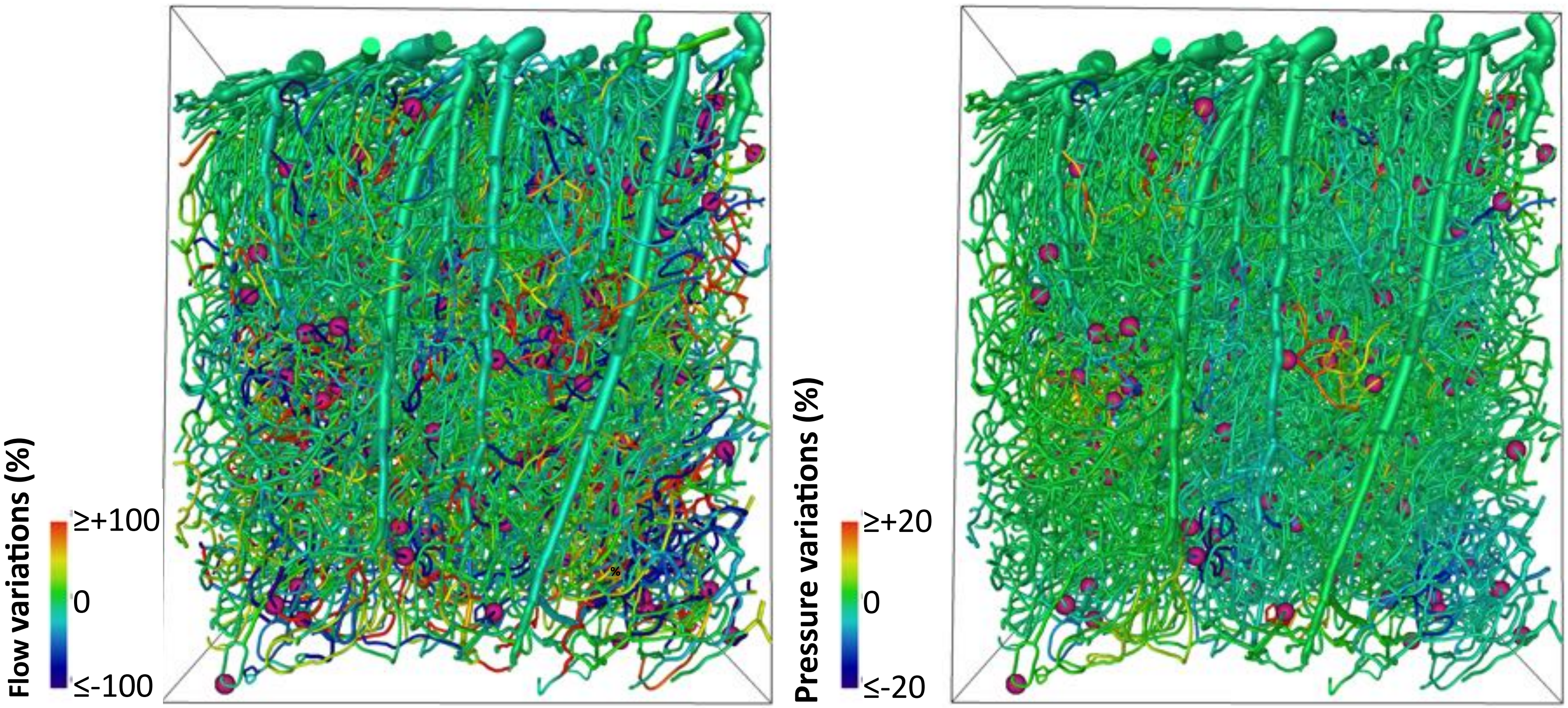
- ❑ Pharmacological removal of stalls increases blood flow and improves memory performance

Cruz-Hernandez et al. Nature Neuroscience 2019

Blood flow in networks

Vascular component of AD: impact of small initial perturbation

- **Effect of random capillary occlusions on blood flow patterns**
  - 2% capillary occlusions
  - Assuming no changes in perfusion pressure, no diameter variations

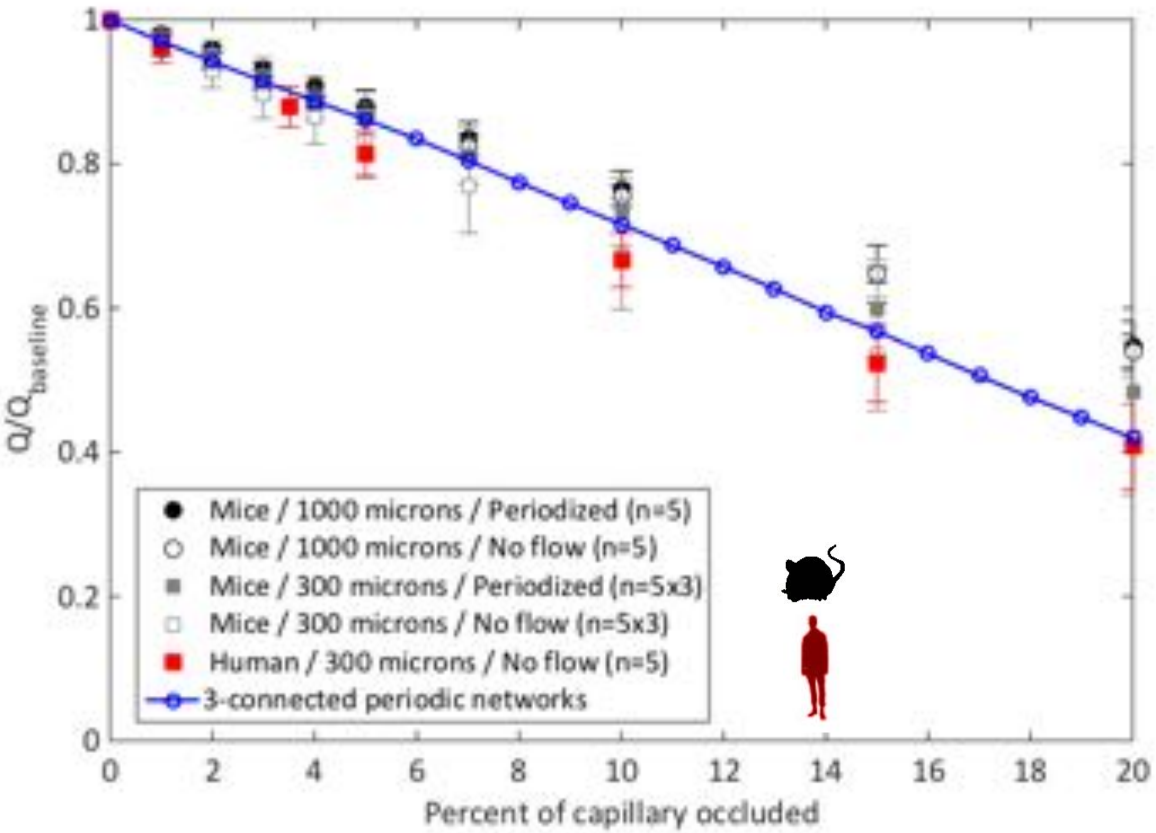


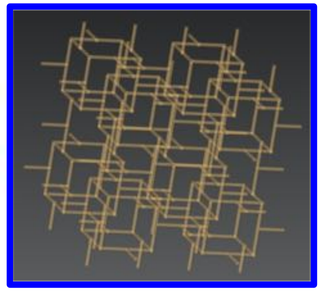
Cruz-Hernandez et al. Nature Neuroscience 2019

Blood flow in networks

Vascular component of AD: impact of small initial perturbation

- ❑ **Effect of random capillary occlusions on global blood flow**





➔ **No threshold** (versus Hudetz, Microvasc. Res. 1993)

➔ **Similar blood flow reduction mice, humans and 3-connected mesh**

Cruz-Hernandez et al. Nature Neuroscience 2019

Outline

- ❑ **Brain versus other organs**
  - What is generic ?
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  - In disease
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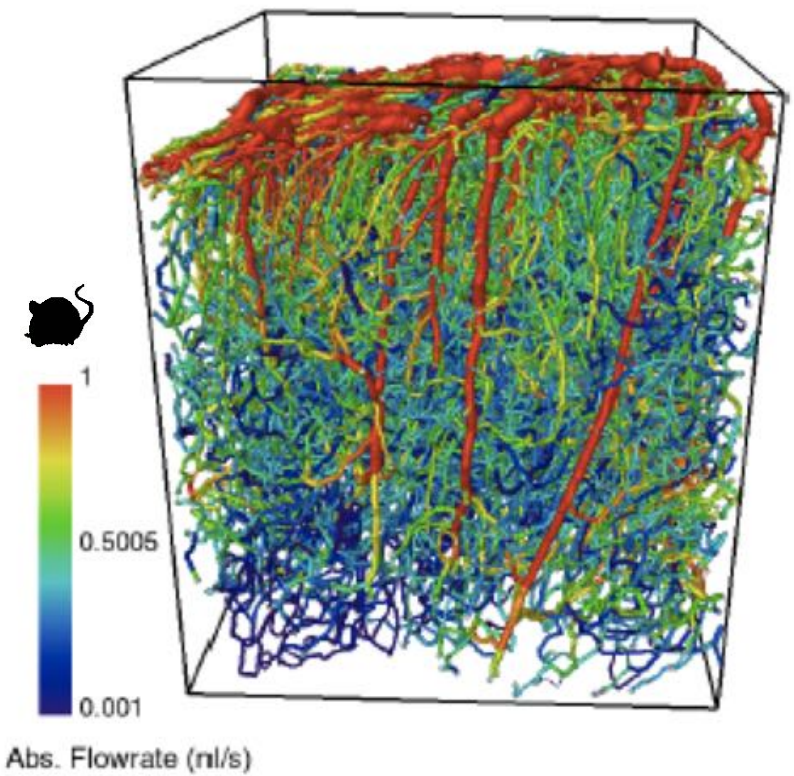
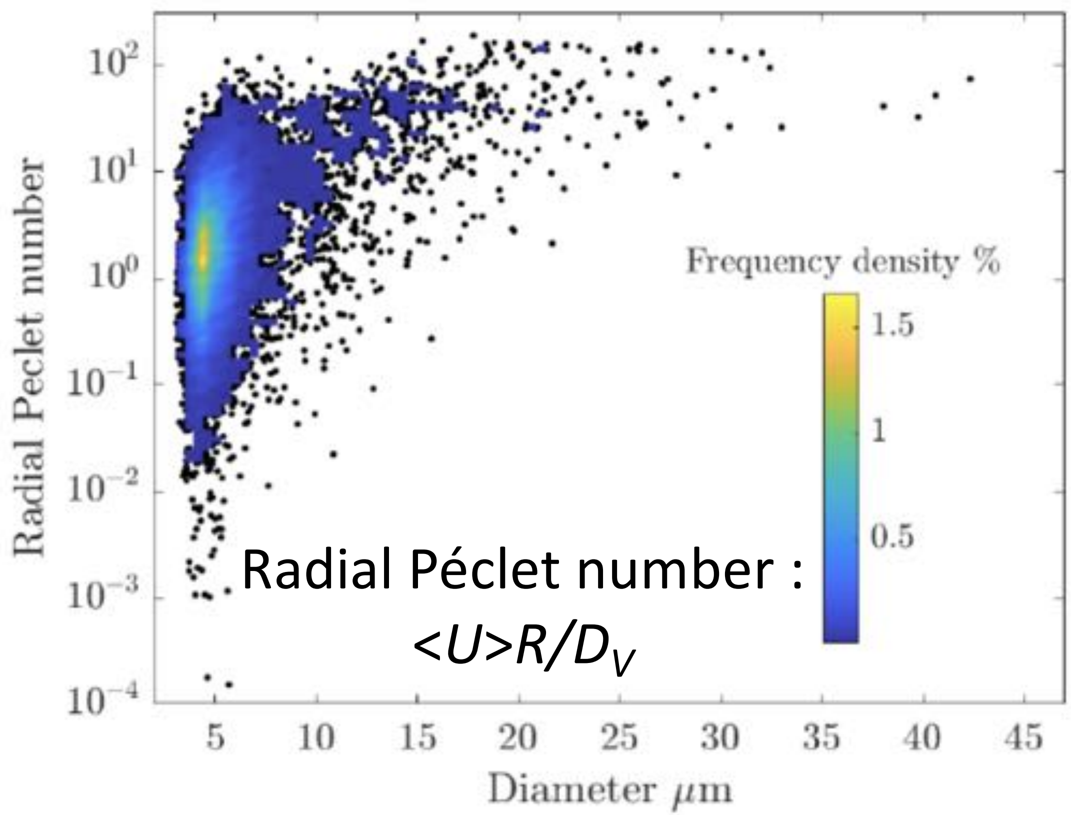
- ❑ **Mass transfers in networks**
- ❑ **Blood flow at organ scale**

Distribution of Péclet numbers





Radial Péclet number : $\langle U \rangle R/D_V$

Extension to mass transfers :

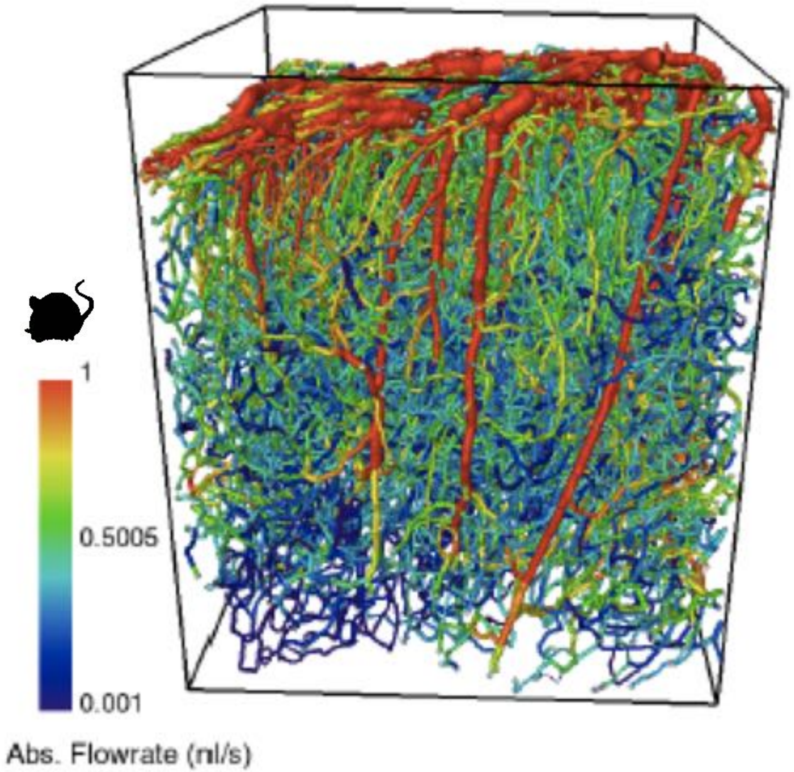
What are the errors of a network approach where radial concentration gradients are neglected in vessels (well-mixed model*) ?

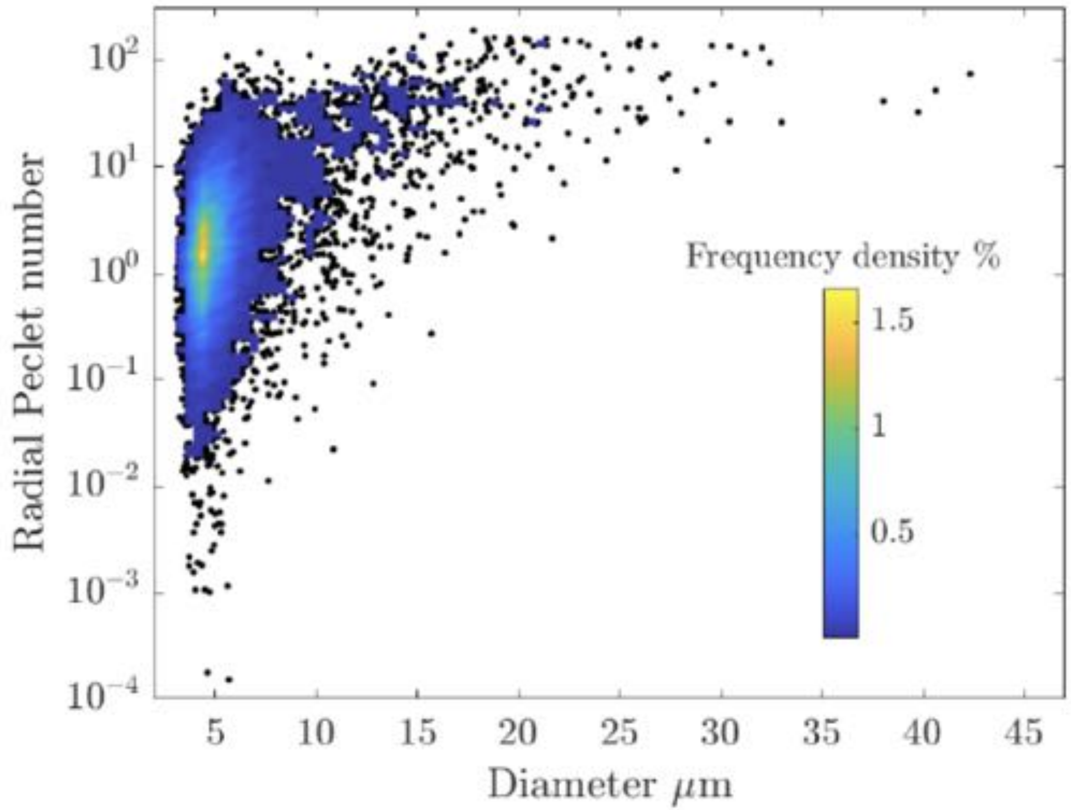
PhD Maxime Berg

*Secomb et al. 2004, Fang et al. 2008, Reichold et al. 2009, Linninger et al. 2013, *Sweeney et al. 2018*

Extension to mass transfers :

Distribution of Péclet numbers





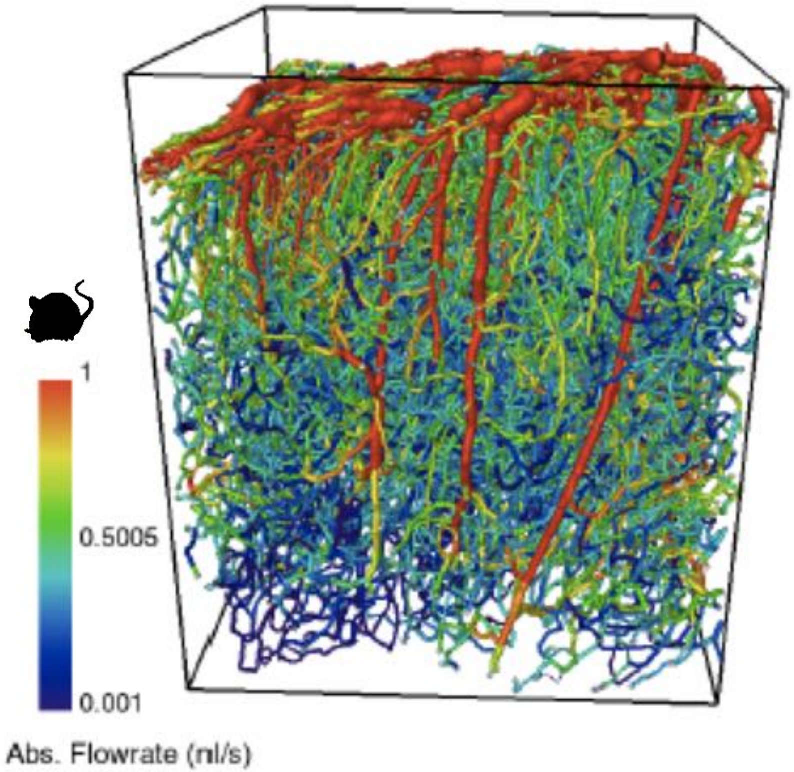
Radial Péclet number : $Pe_R = \langle U \rangle R/D_V$

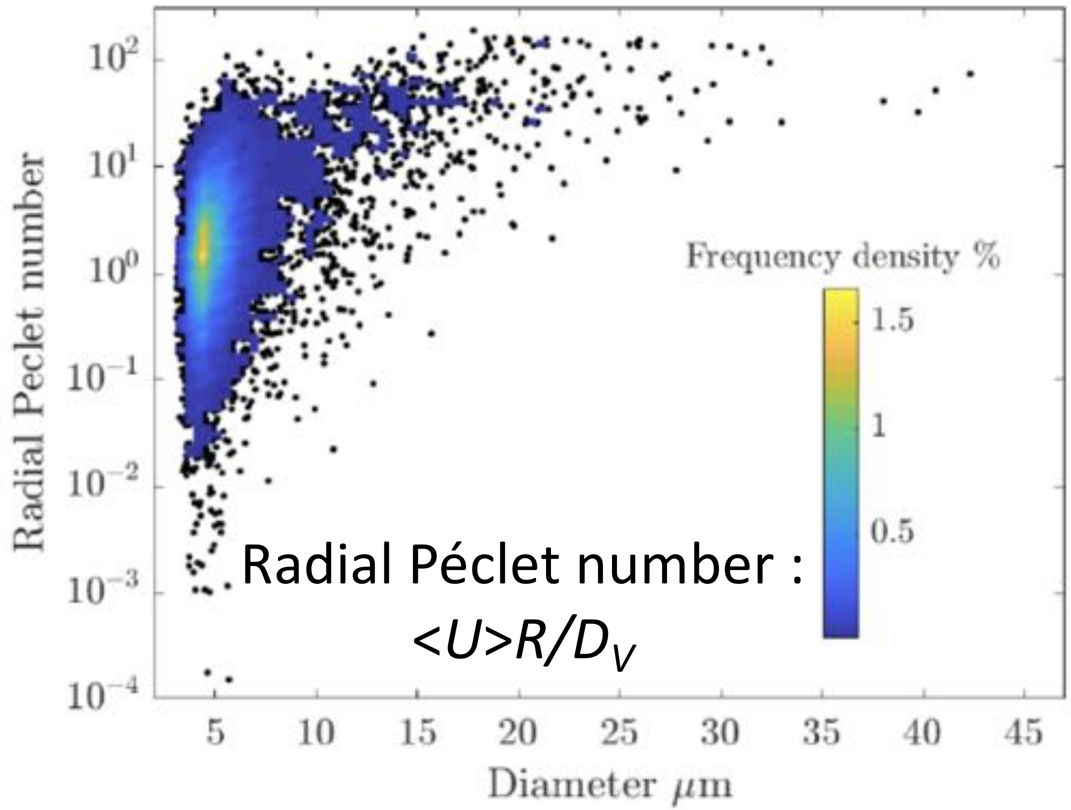
Length for complete mixing : $L \sim Pe_R\ R$

PhD Maxime Berg

Extension to mass transfers :

Distribution of Péclet numbers





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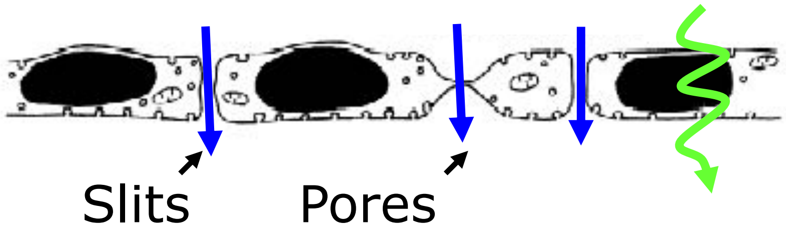
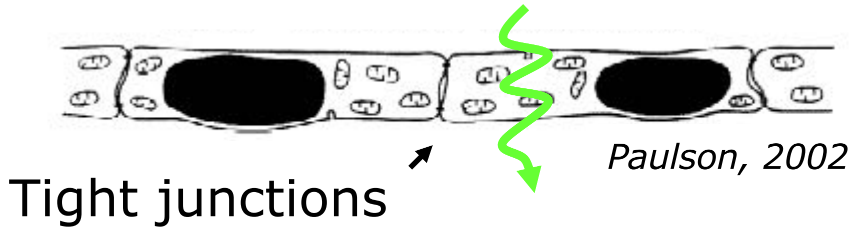
Mass transfers at vessel scale
Phenomenology and simplifications

- **Blood brain barrier**
  - Ionic/Osmotic balance (neuronal communication / constrained volume)
  - Protection against neuro-toxics



Muscle capillary endothelium



Brain capillary endothelium

Damköhler number :

- **Boundary conditions at vessel surface**
  - Flux continuity: $\mathcal{D}_V \nabla C_V.\mathbf{n}=\mathcal{D}^*_{tissue} \nabla C_{tissue}.\mathbf{n}$
  - Membrane condition : $\mathcal{D}_V \nabla C_V.\mathbf{n}=-K_m(C_V-\lambda C_{tissue})$

Mass transfers at vessel scale

A 1D effective equation within vessels (ε<<1)

- **Asymptotic limit of small tissue concentration**
  - Membrane condition : $\mathcal{D}_V \nabla C_V.\mathbf{n} = -K_m(C_V - \lambda C_{tissue})$

    ➔ Robin condition : $\mathcal{D}_V \nabla C_V.\mathbf{n} = -K_m C_V$

- **Volume averaging with closure (coll. Y. Davit, M. Quintard)**

$$\frac{\partial \langle C_V \rangle}{\partial t} + U_{eff} \cdot \nabla \langle C_V \rangle - D_{eff} \nabla^2 \langle C_V \rangle + K_{eff} \langle C_V \rangle = 0$$

where $U_{eff} = Pe\,(1 + U_+)$ $\qquad \epsilon = \frac{R}{L}$

$$D_{eff} = 1 + \frac{(\epsilon Pe)^2}{Pe_c^2} \qquad Pe = \frac{\langle U \rangle L}{D_V}$$

$$K_{eff} = \frac{8\epsilon^{-1} Da_m}{\epsilon Da_m + 4}, \qquad Da_m = \frac{K_m L}{D_V}$$

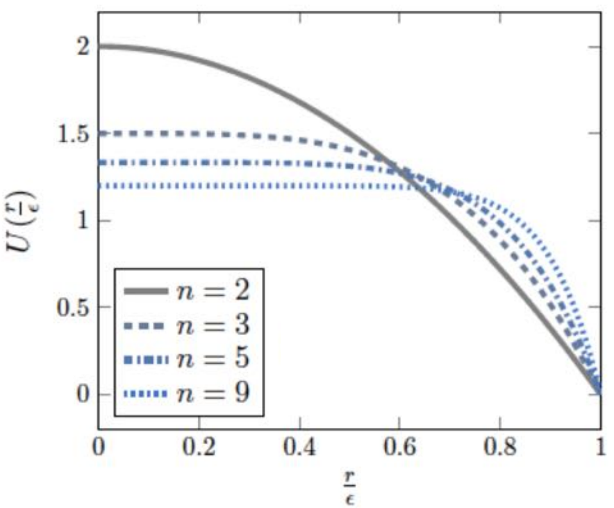
and $U+$ and Pe_c depend on ε, Da_m and the shape of the velocity profile.

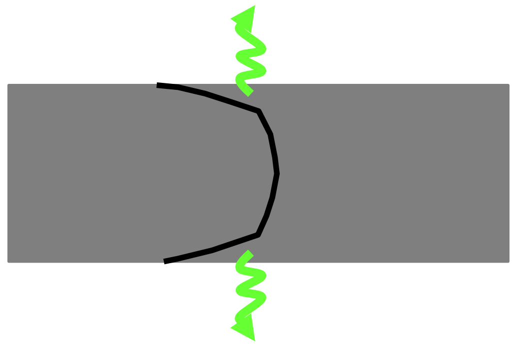
Berg et al. Journal of Fluid Mechnaics, in press

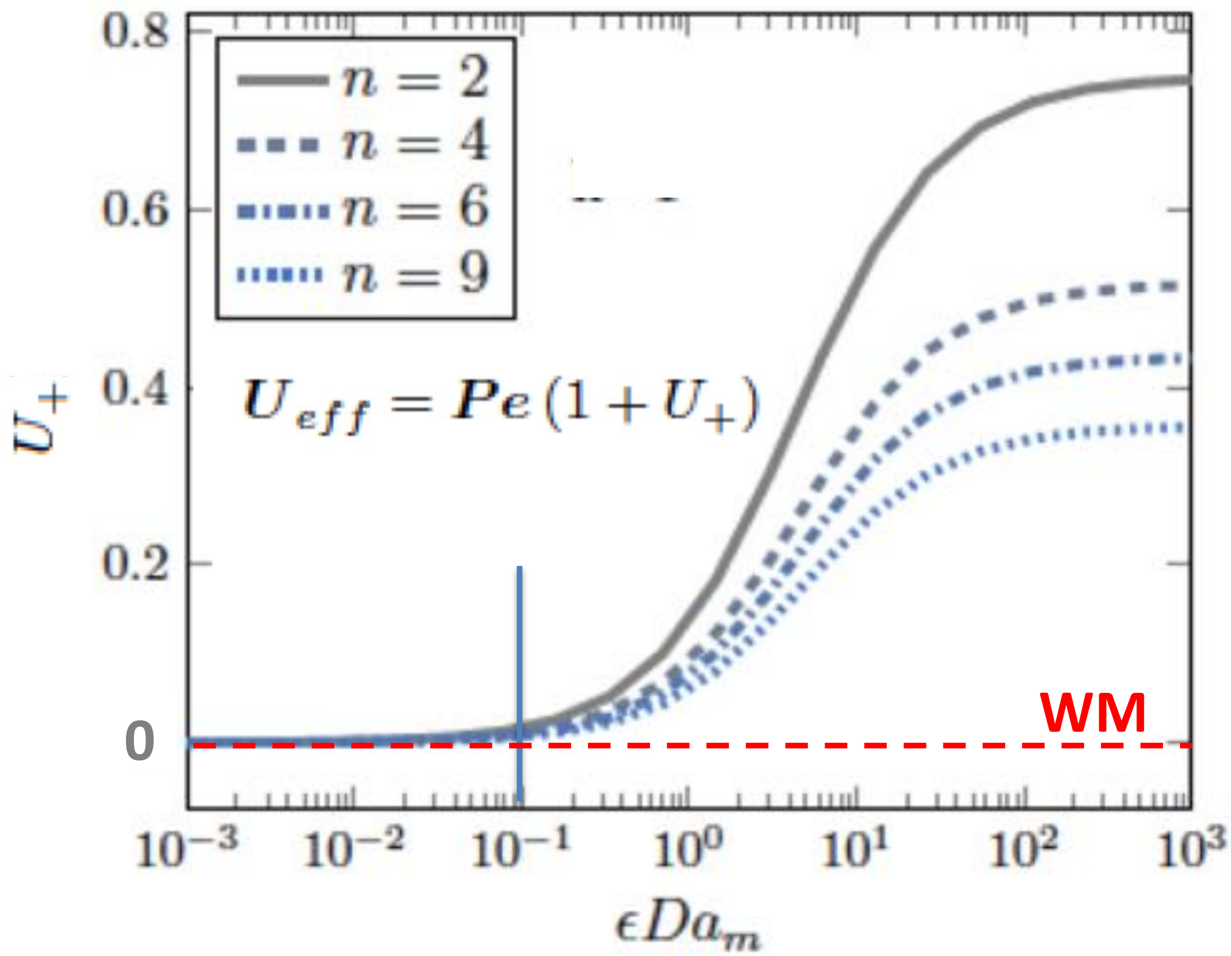
Mass transfers at vessel scale

A 1D effective equation within vessels (ε<<1)

- ❑ **Effective velocity**





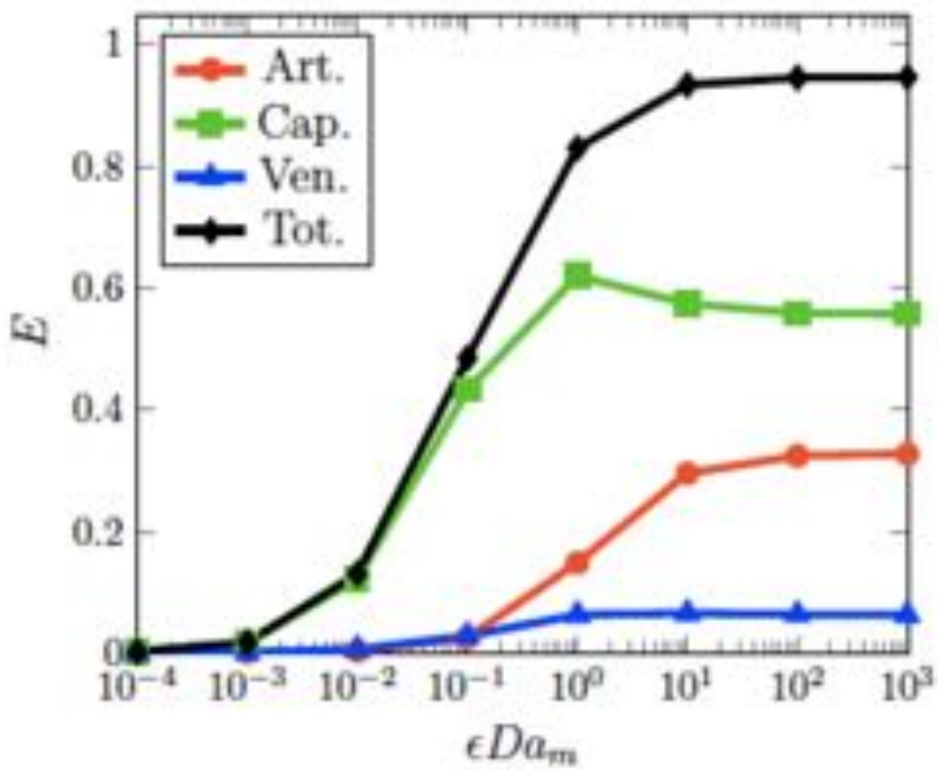


Impact at network scale

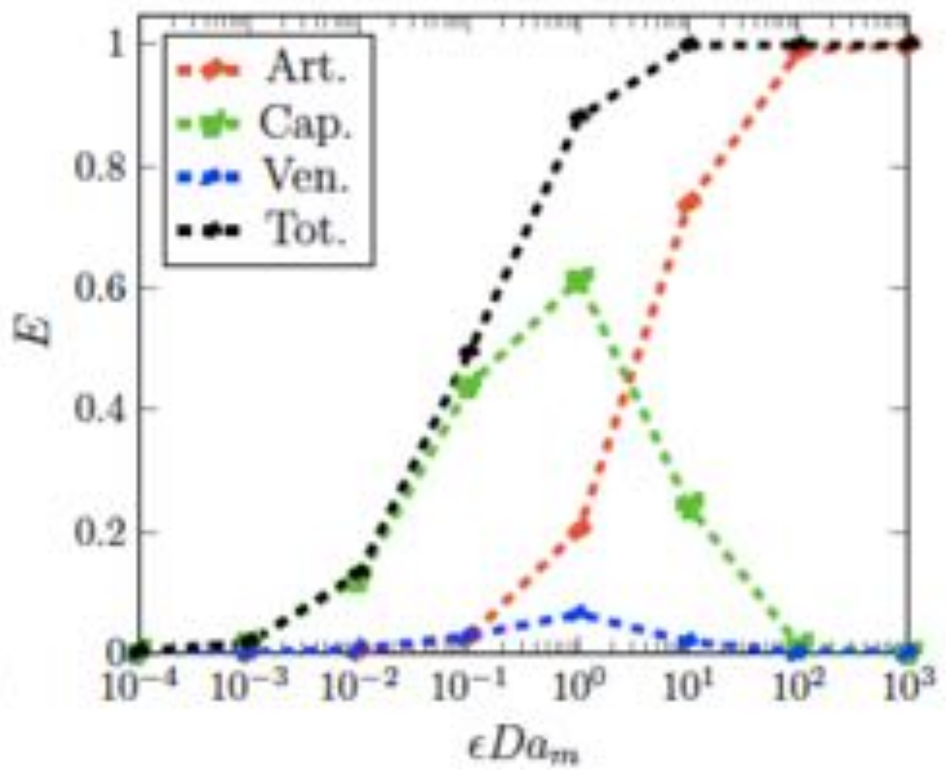
Poiseuille velocity profiles

- **Stationnary extraction (flux through vessel walls / entry flux)**

Effective model



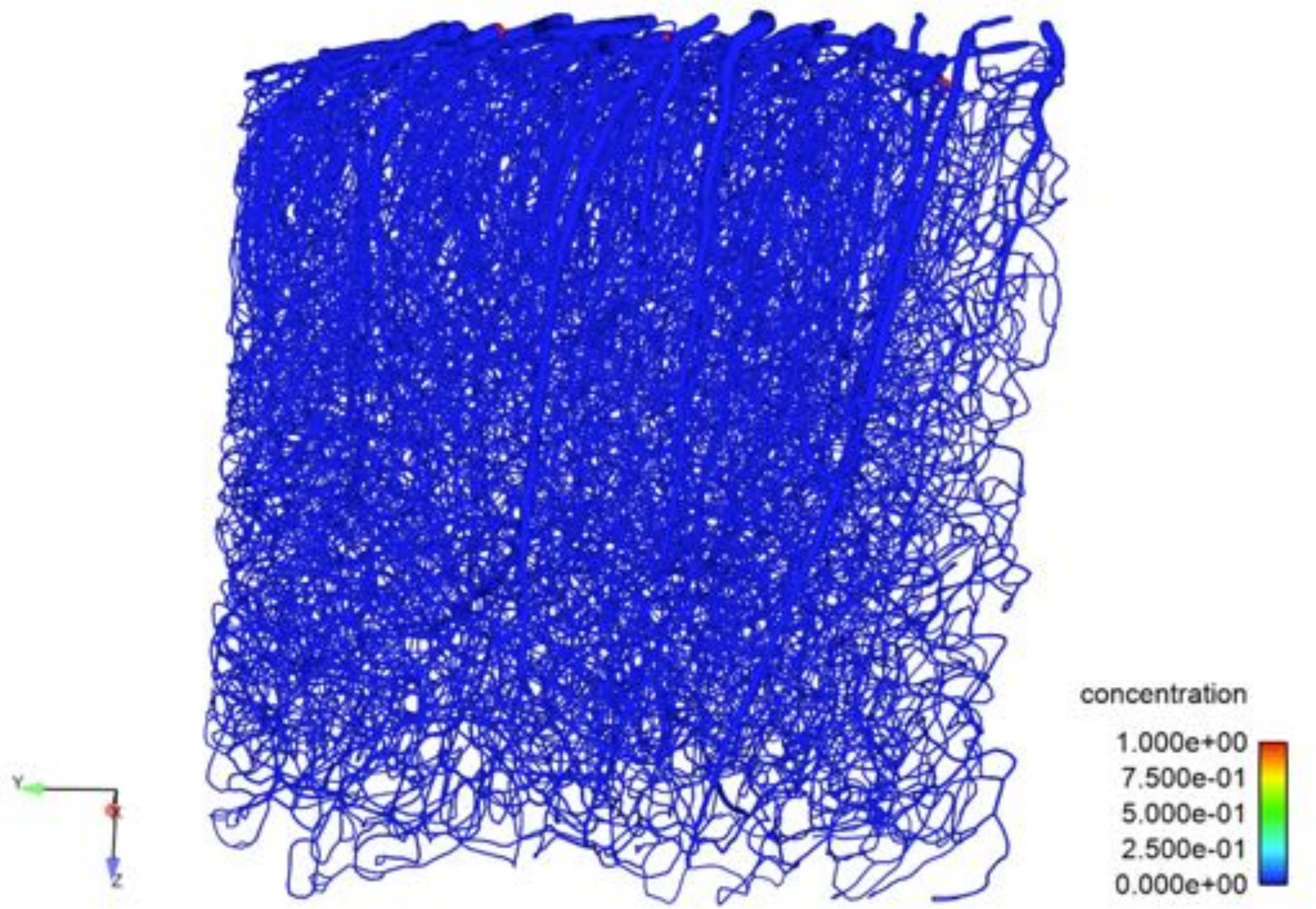
WM model



Berg et al. Journal of Fluid Mechnaics, in press

Mass transfers at network scale
Network model

- ❑ **Intravascular tracer**



- ❑ **Coupling with tissue**

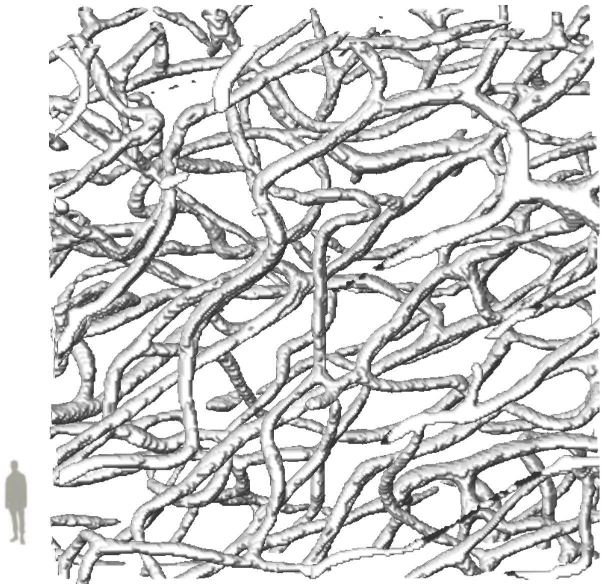
Berg et al. Journal of Fluid Mechnaics, in press

Outline

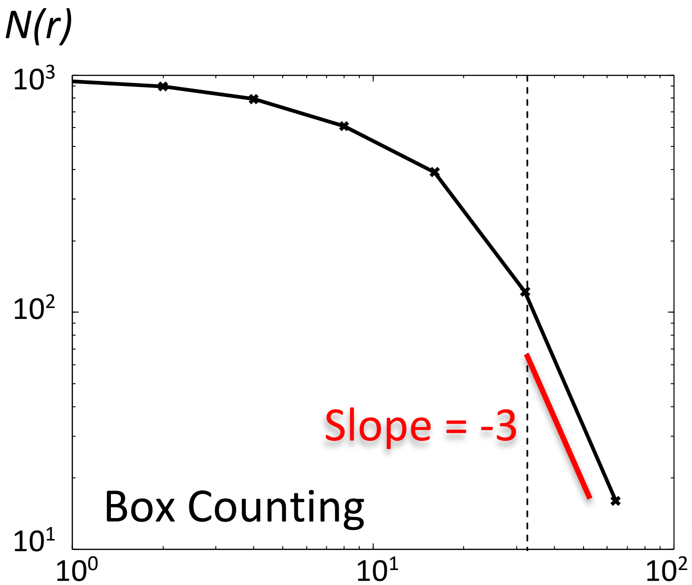
- Why study brain microcirculation ?
  - In health
  - In disease
- Brain versus other organs
  - What is generic ?
  - What is specific ?
- Investigation tools and associated scales
- Blood flow in networks
- **Blood flow at organ scale**

Extension to larger scales

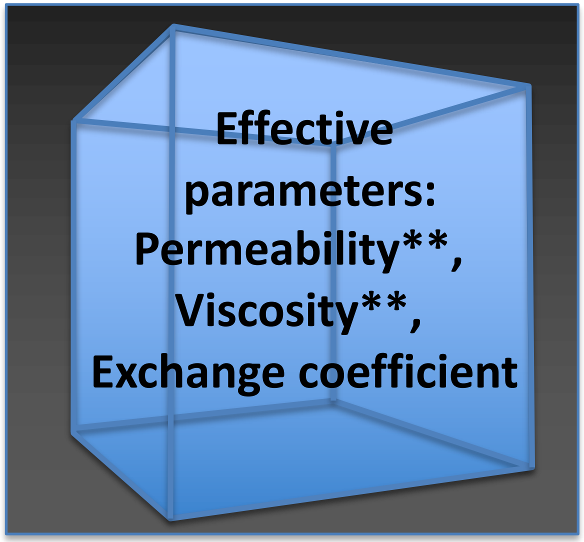
Model reduction at mesoscale



Anatomical data*



Multi-scale analysis*

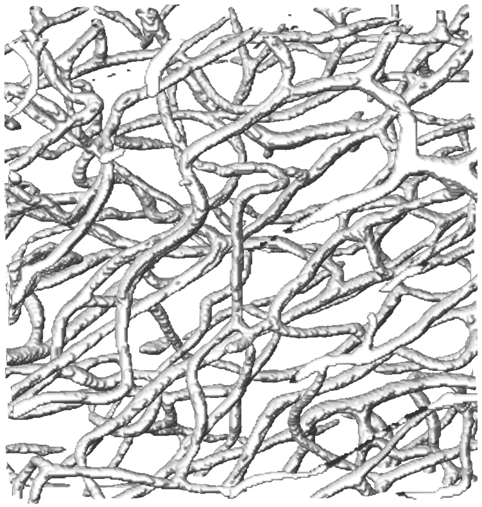


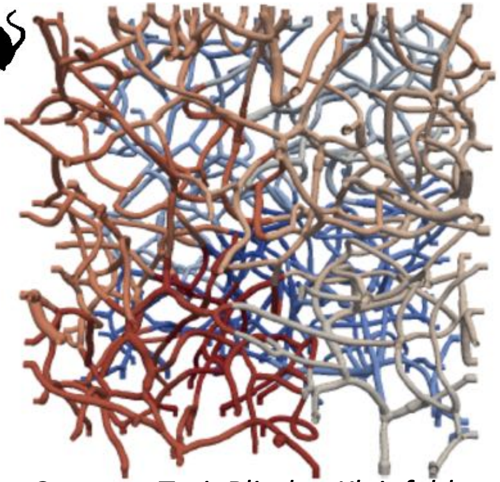
Equivalent continuum

*Lorthois & Cassot, Journal of Theoretical Biology 2011, ** Peyrounette et al. PLOS ONE 2018

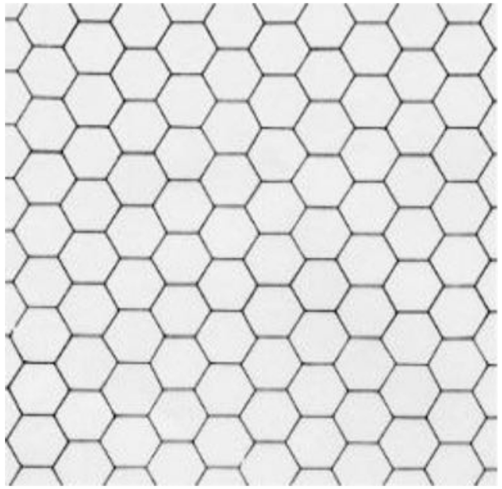
Note : Model capillary networks

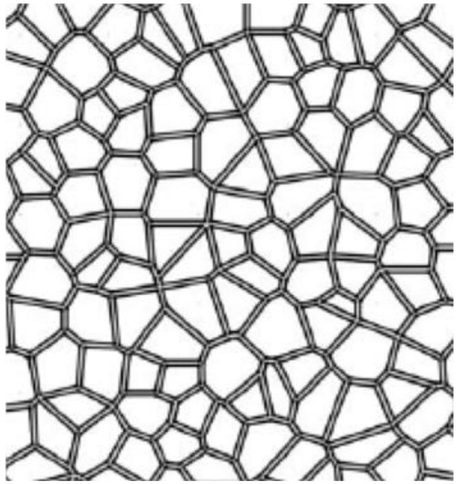
- ❑ **Space-filling, 3-connected, looped networks**



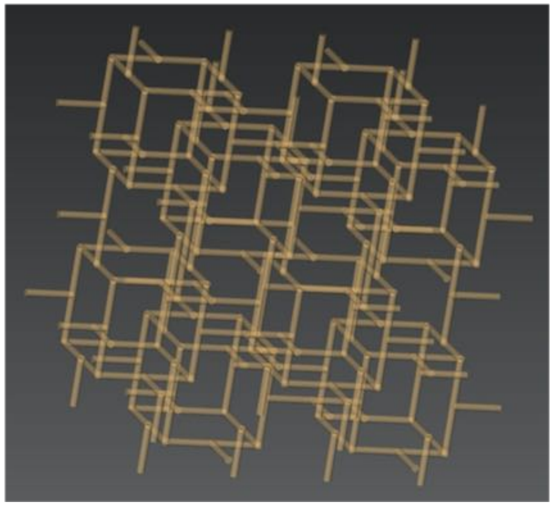


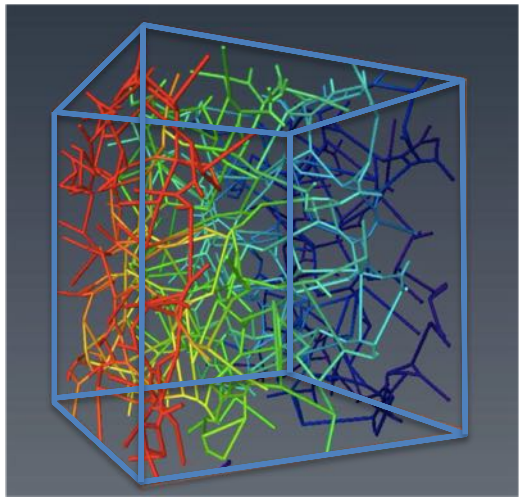
Courtesy Tsai, Blinder, Kleinfeld





Lorthois et al, JTB 2010



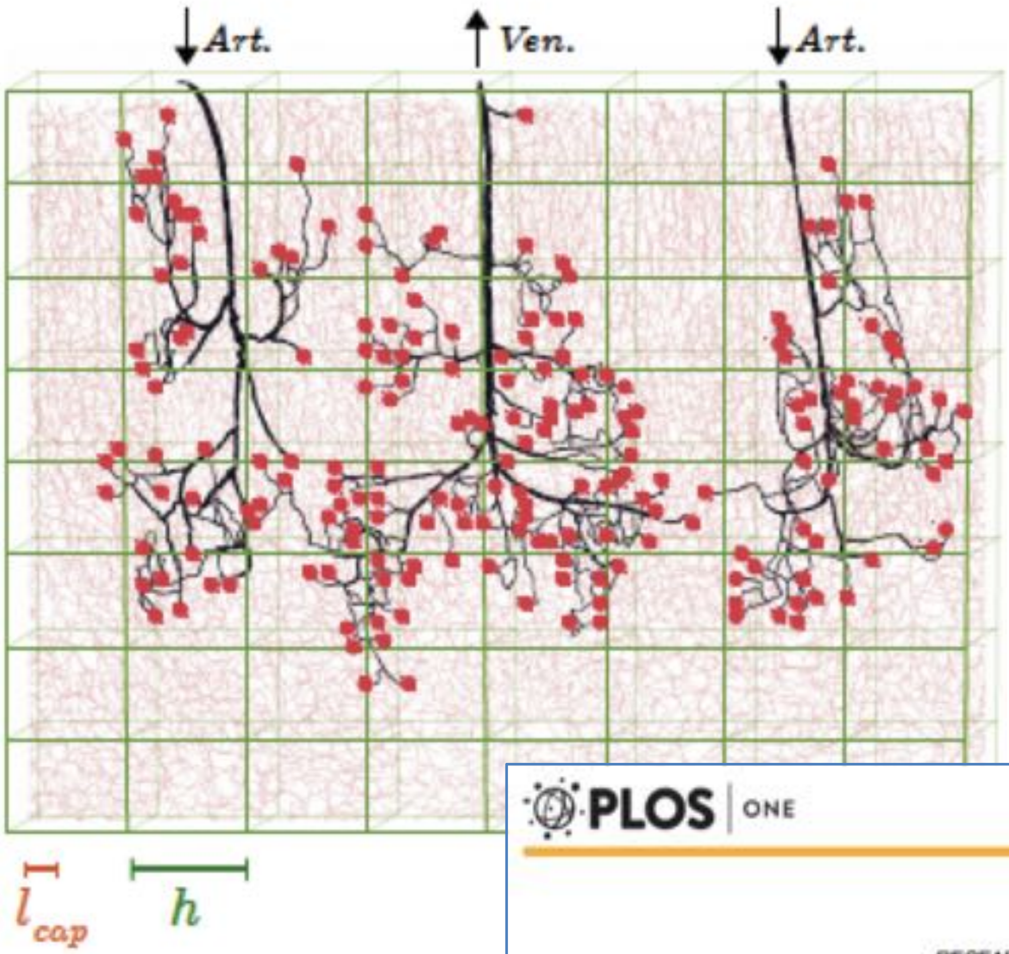


Smith et al. tbs

Smith et al. Frontiers in Physiology, 2019

Extension to larger scales

Hybrid network/continuous approach for blood flow



- ❑ Network approach in the **arteriolar and venular trees**
- ❑ Replacing the capillary bed by a **continuum** discretized using FV method
- ❑ Developing a multiscale coupling model at the coupling points ●

PLOS | ONE

RESEARCH ARTICLE

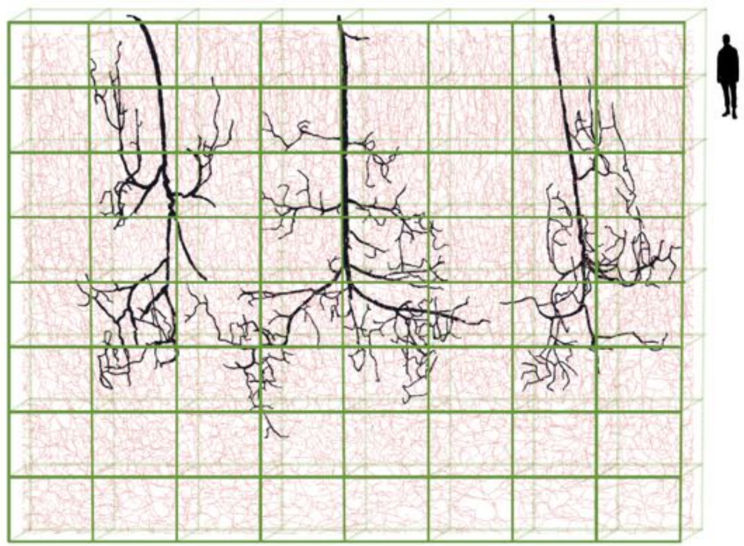
Multiscale modelling of blood flow in cerebral microcirculation: Details at capillary scale control accuracy at the level of the cortex

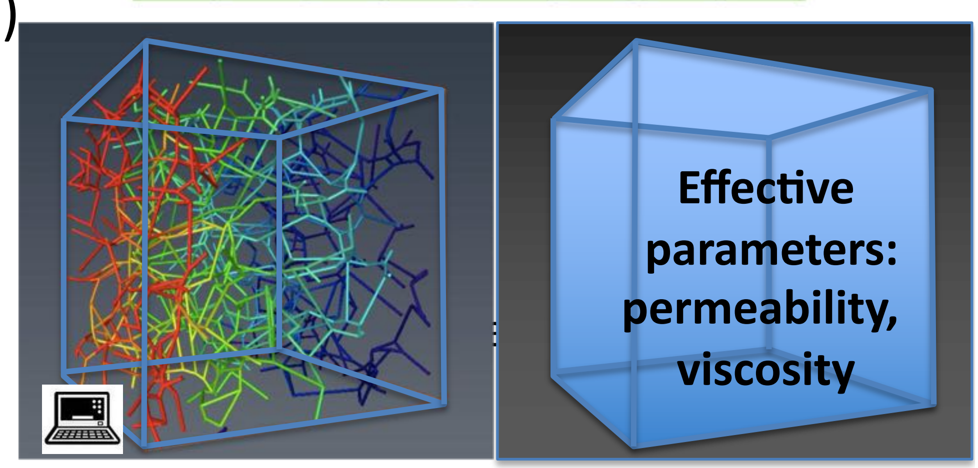
Peyrounette et al. *PLOS ONE* 2018

Blood flow at network scale

Hybrid network/continuous approach

- Uniform hematocrit
- Art / Ven : Human data
  (Cassot et al. 2006)
- Capillaries :
  Synthetic networks
  ➡️ Equivalent continuum
  (Permeability, effective viscosity)
- Multi-scale coupling condition
- 750 000 vessel-equivalent
  - 1200 coarse meshes:
    Darcy equation (Finite Volume)
  - 600 Art / Ven:
    Linear network approach
  - 275 coupling points



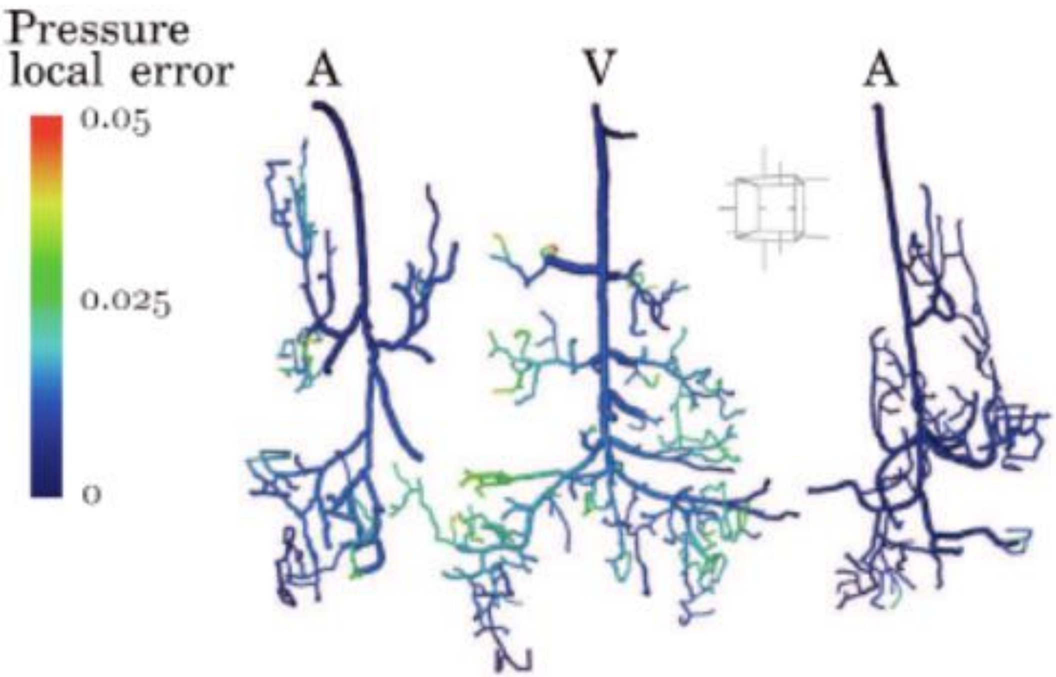


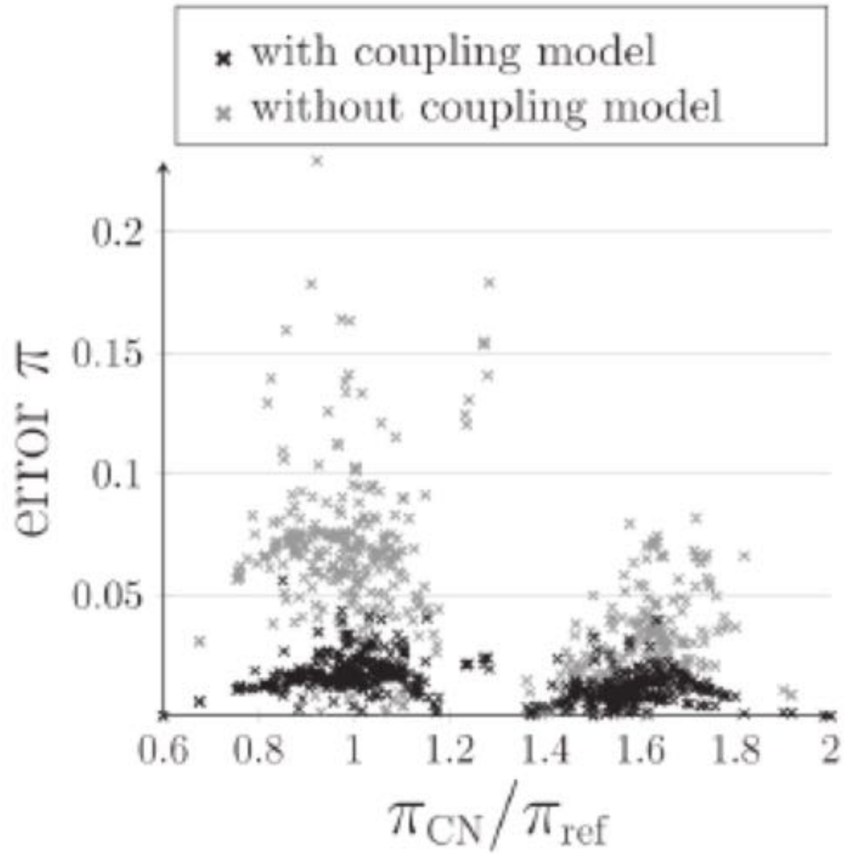
Peyrounette et al. *PLOS ONE* 2018

Blood flow at network scale

Hybrid network/continuous approach

- ❑ **Validation by comparison with network approach**





➡️ 1D / coarse 3D multi-scale coupling condition is are needed*

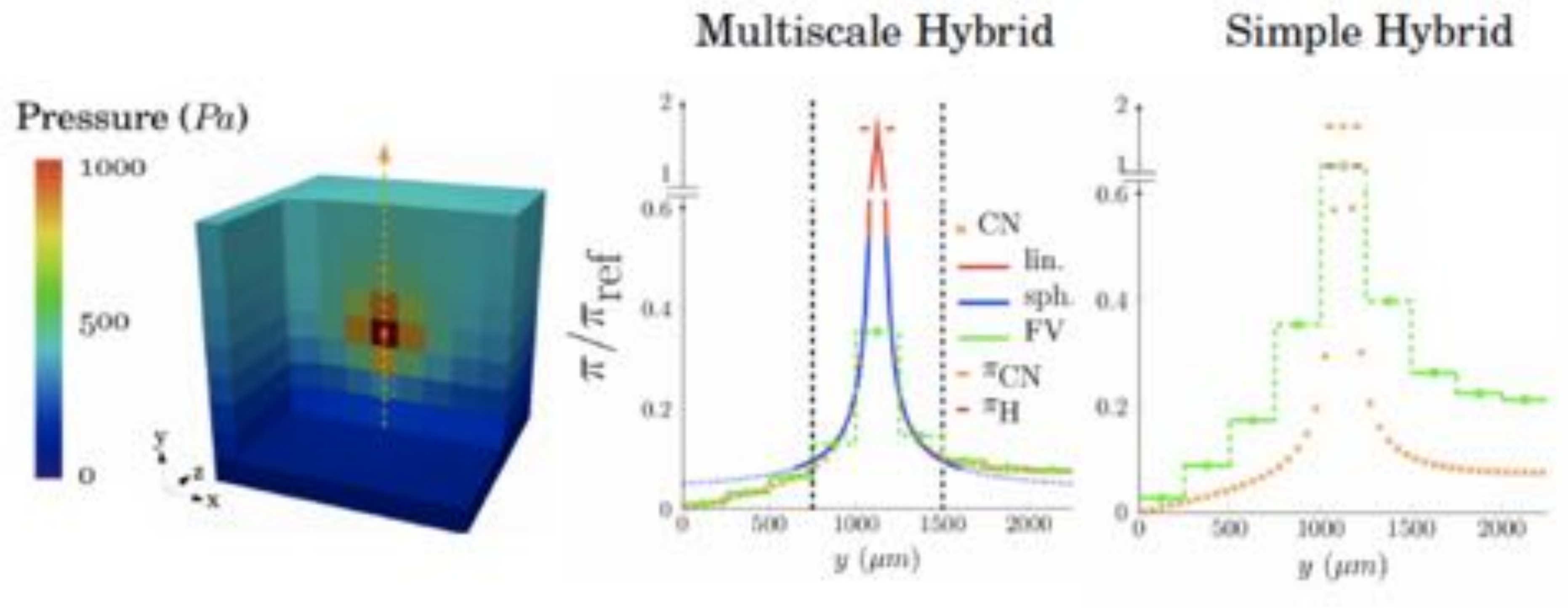
Peyrounette et al. *PLOS ONE* 2018

Blood flow at network scale

Hybrid network/continuous approach

- **Why a non-trivial coupling condition is needed ?**
  - Strong pressure gradients around coupling points
  - Poor scale separation

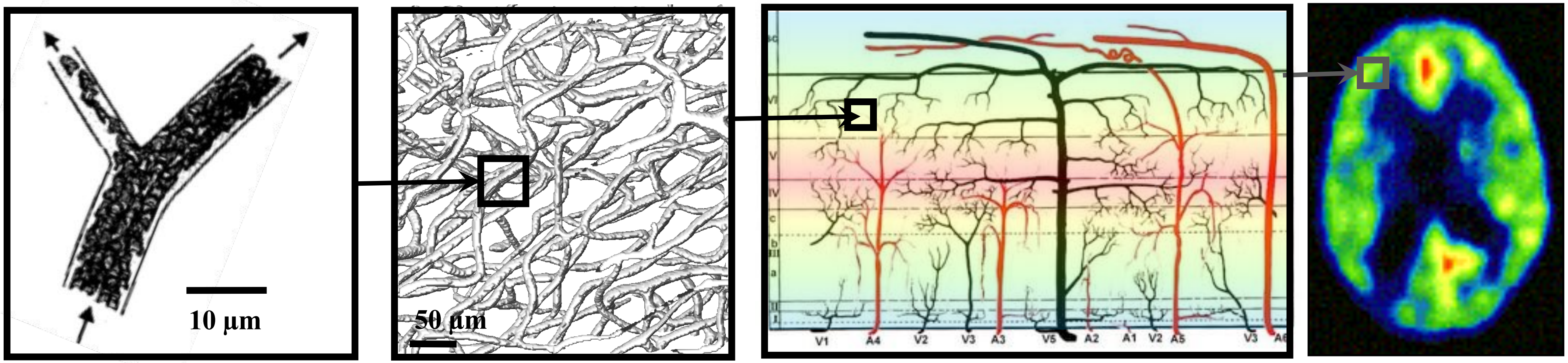
➡️ $\pi_s = f(P_s^i, q_s)$ vs. $\pi_s = P_s$



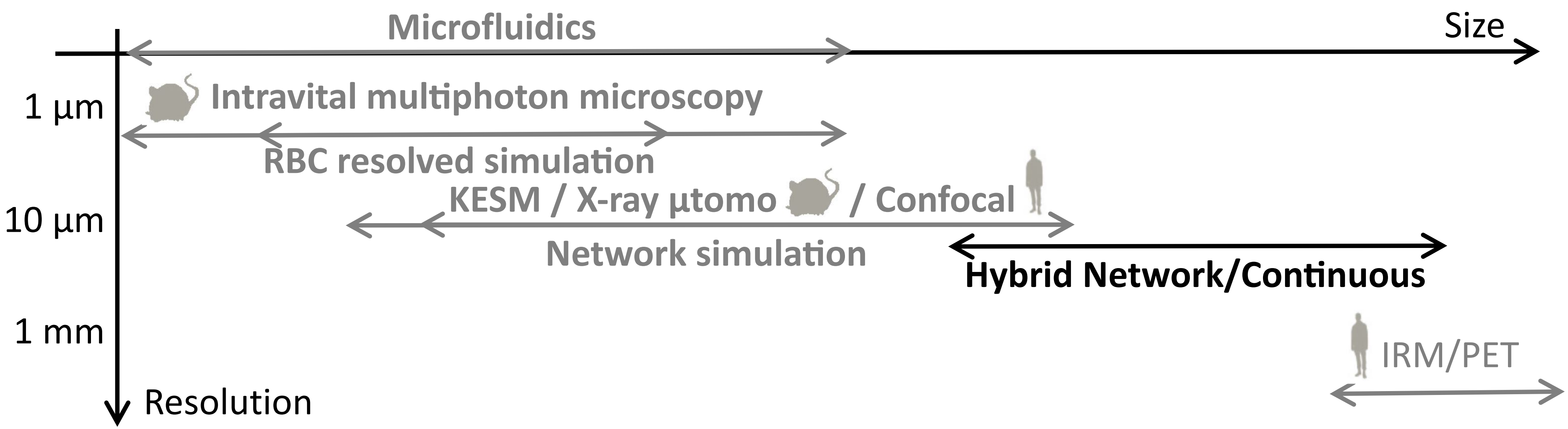
Investigation tools and associated scales

Numerical simulation

Microscopic scale | Mesoscopic scale | Macroscopic scale | Brain scale



50 µm | 300 µm | 1 mm | 10 mm (mice) | 10 cm (human)



Conclusions

Focused on methods and didn't answer much questions

- **Tremendous progress of the experimental investigation tools…**
  - ❑ Structure, RBC velocity, pulsatility, glucose, oxygen, …
- **… has been driven by fundamental questions in neuroscience**
  - ❑ Neuro-vascular coupling
  - ❑ Interpretation of functional imaging
  - ❑ Role of microcirculation in brain disease
- **This generated a huge amount of high resolution data…**
  - ❑ In various species, age and disease conditions at various scales
- **… which need modeling for coherent understanding**
- **There is a huge potential**
  - ❑ For understanding the brain, with perspectives in the clinics
  - ❑ For understanding fundamental questions in hemophysics

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