Modeling cerebral blood flow : recent advances and perspectives

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2 : Centre de Recherche Cerveau et Cognition, UMR 5549

Toulouse University, France

Context & Bibliography

- Brain intra-cortical vascular network

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  - Pial arteries

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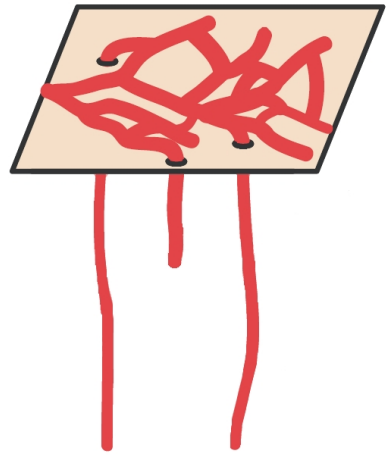
- Brain intra-cortical vascular network
  - Pial arteries
  - Penetrating arterioles



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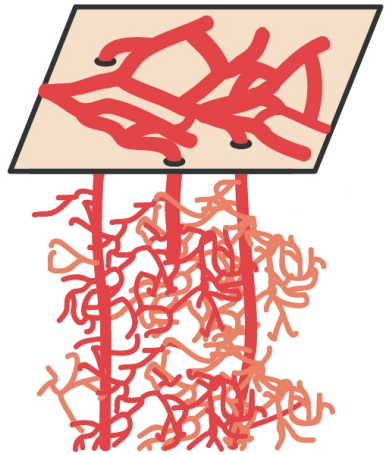
  - Capillary micro-vessels



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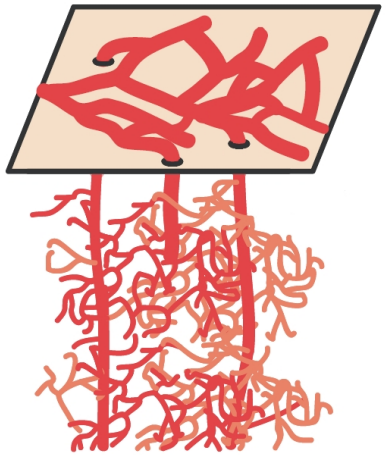

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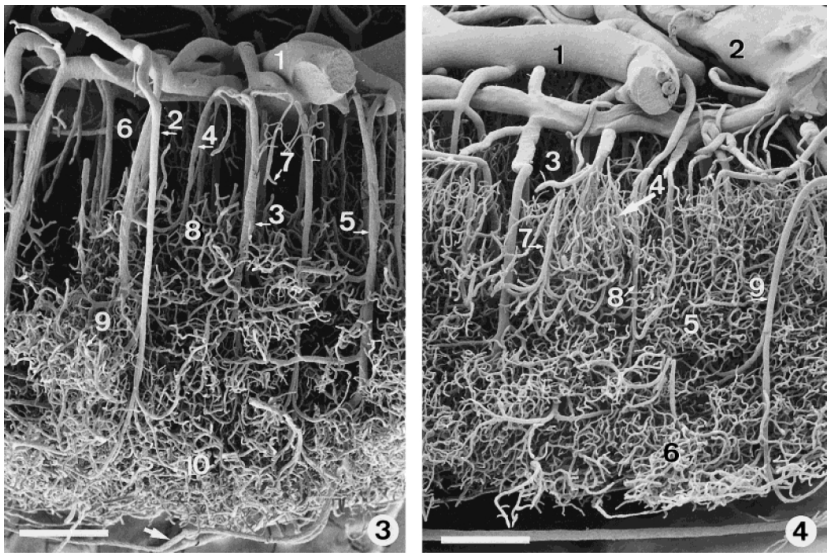
Reina-De La Torre *et al.* (1998) *Anat. Rec.*



375 μm 430 μm

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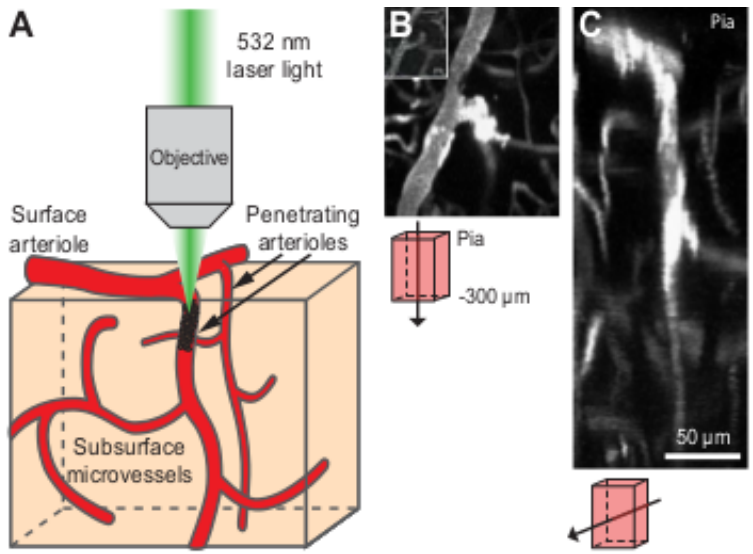

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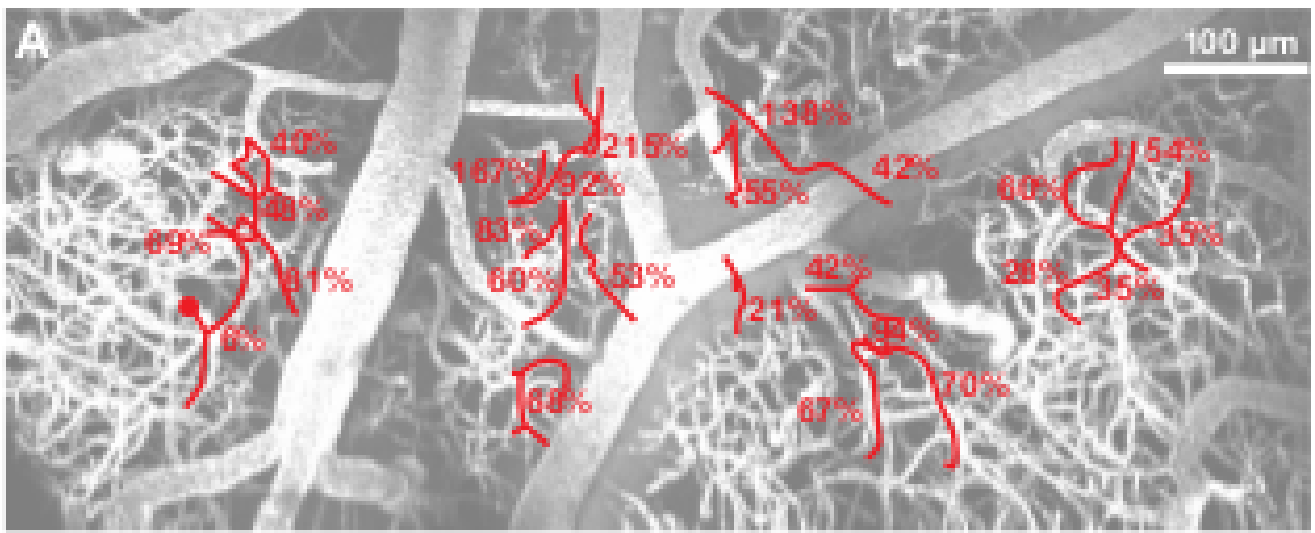

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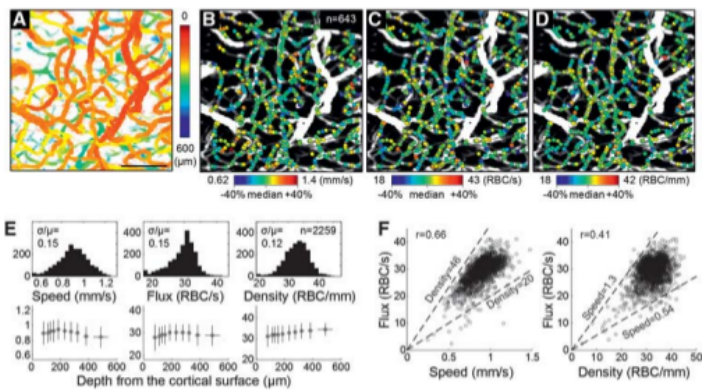

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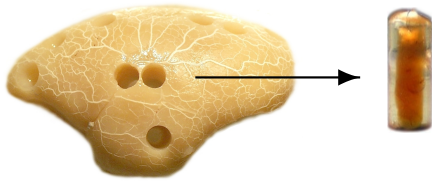
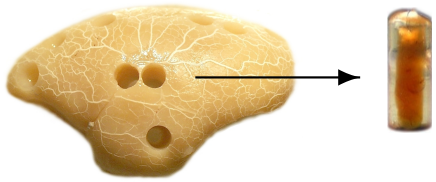
  - Doppler optical coherence tomography (Lee *et al.* (2013), *JCBFM*)
  - Synchrotron imaging, ...
- Micro-vascular blood flow studies
  - Blood modelling (Pries *et al.* (1990) *Circ. Res.*, Pries & Secomb (2005) *Am. J. Physiol.*, ...)
  - Understanding network influence (Pries *et al.* (1995, 1996) *Am. J. Physiol.*, ...)

Samples preparation and images acquisition

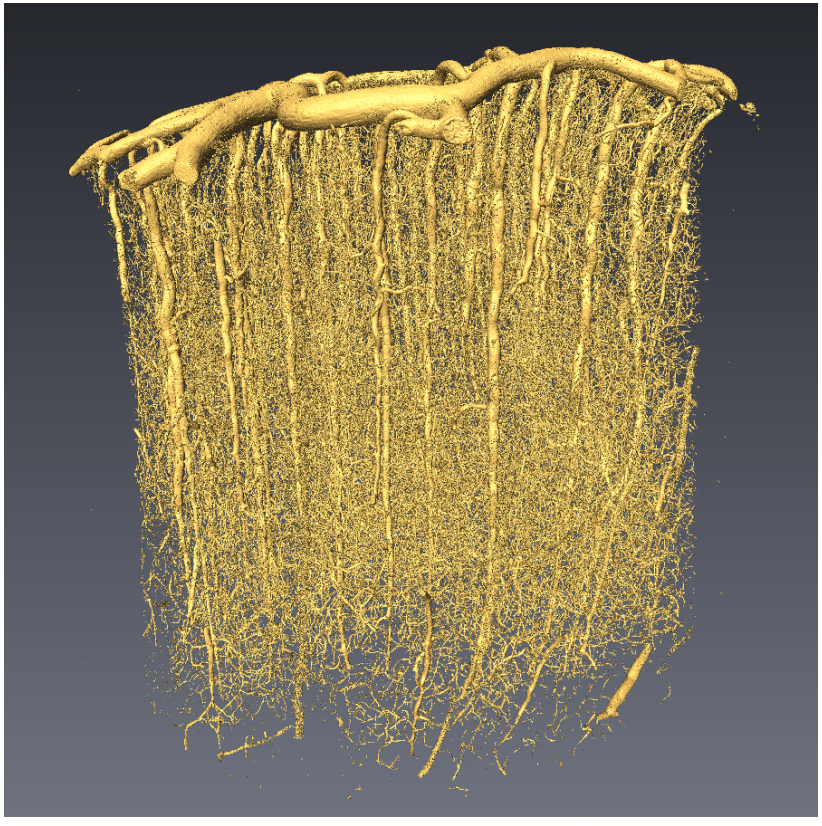
- Injection of barium contrast agent



Samples preparation and images acquisition



- Injection of barium contrast agent
- X-ray micro-tomography at ESRF (Grenoble, France)



Marmoset adult
Motor cortex

3.3 mm of height and diameter

Resolution 1.4 µm

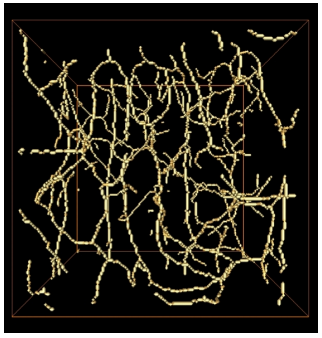
- Detailed in Plouraboué *et al.* (2004) *J. Micros.*

Images post-processing

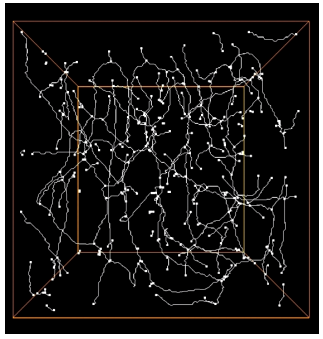
- Skeletonization (Risser *et al.* (2009) *Int. J. Dev. Neurosci.*)



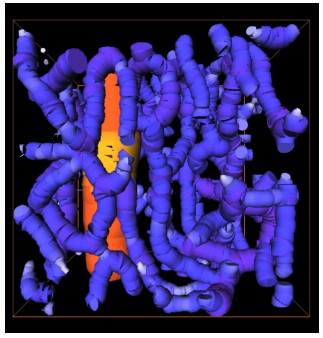
Segmented network



Thinning



Vectorization



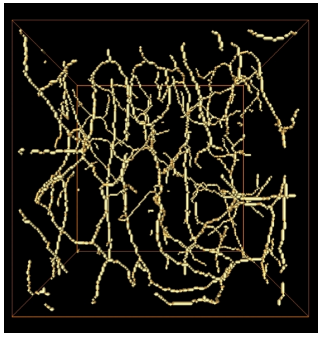
Solid skeleton

Images post-processing

- Skeletonization (Risser *et al.* (2009) *Int. J. Dev. Neurosci.*)



Segmented network



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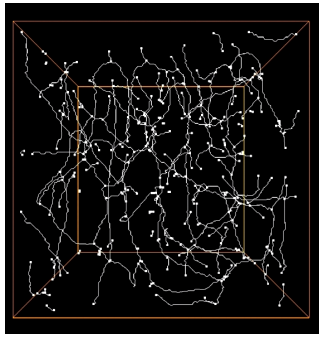

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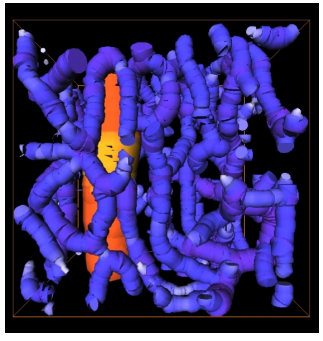
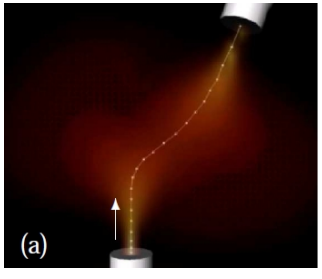
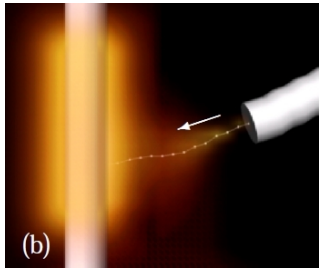


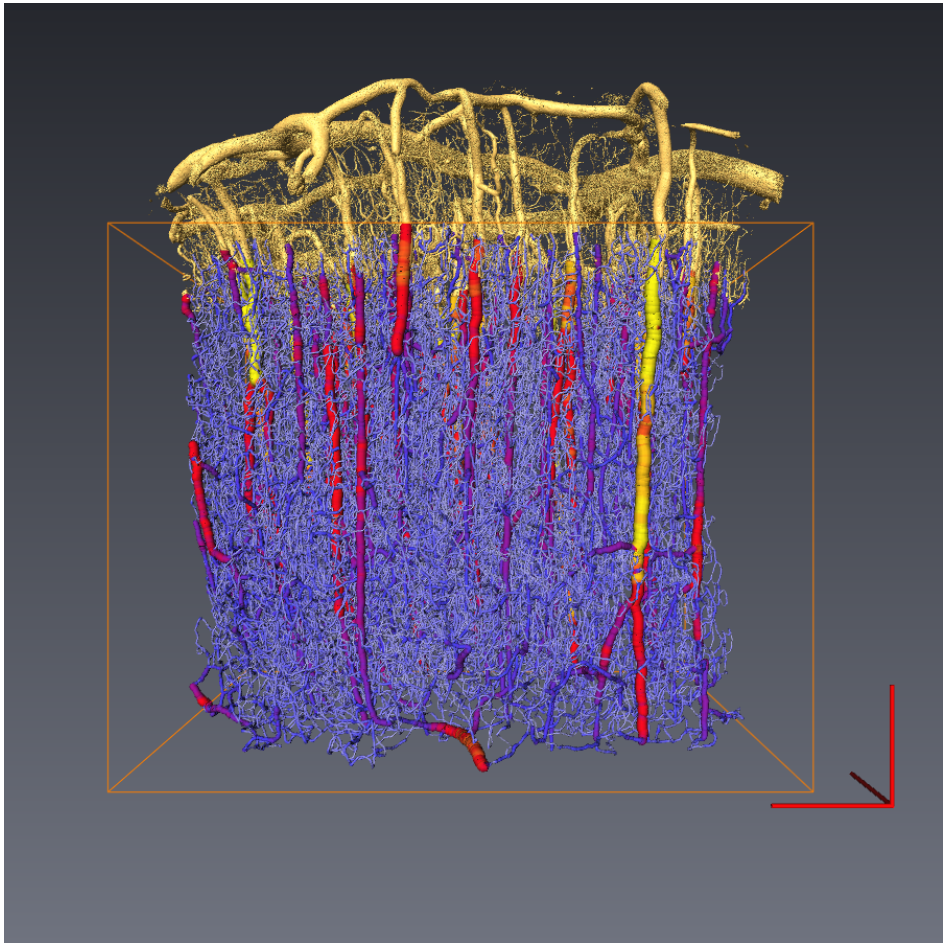
Solid skeleton

- Tensor voting (Risser *et al.* (2008) *IEEE T. Med. Imaging*)





Sample visualisation



Scale bar 500 µm

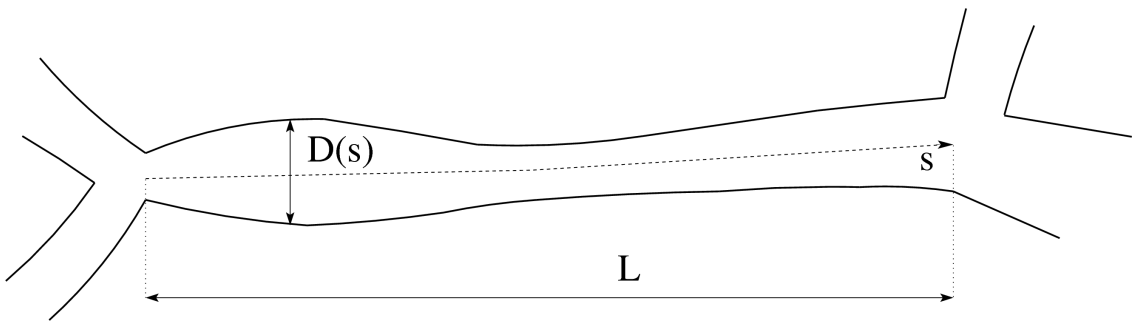
Pial matter

Intra-cortical network
Diameter color-coded representation

Volume 18 mm^3
16 000 vascular segments

Hydrodynamic model

- Vascular flow context
  - Typical vascular segment : $D/L \sim 1/10$ (Risser *et al.* (2009) *Int. J. Dev. Neurosci.*)
  - Womersley number : $\alpha = D\sqrt{\omega/\nu} \ll 1$
  - Reynolds number : $Re = UD/\nu \ll 1$



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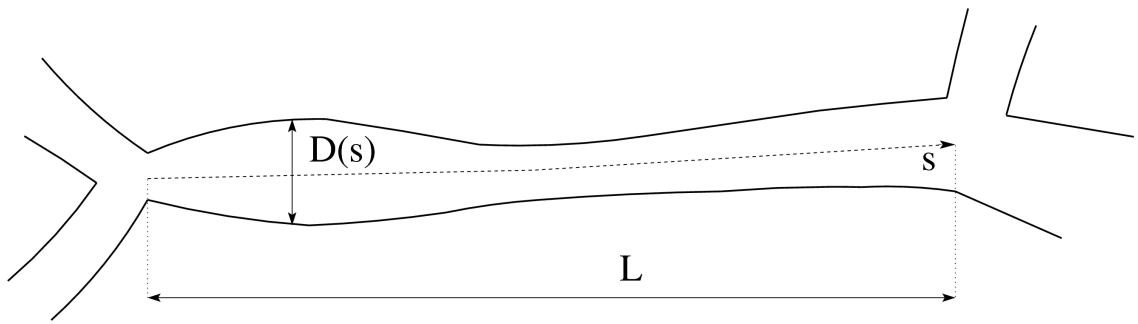

$\Rightarrow$ Lubrication approximation is an adapted framework (and gravity is weak)

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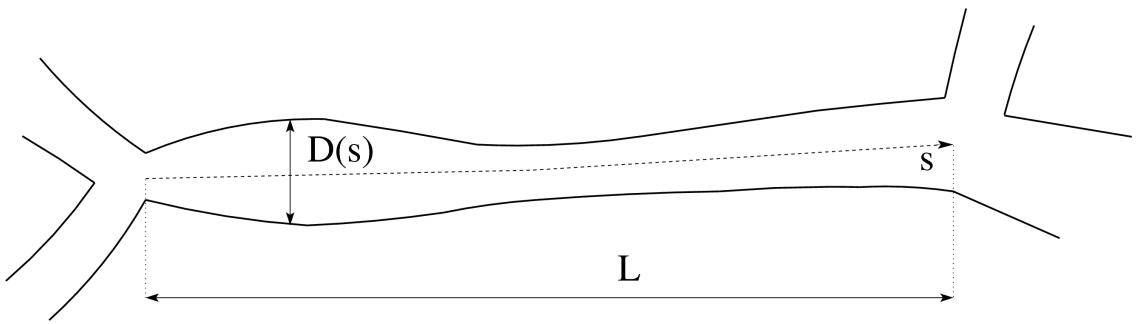

$\Rightarrow$ Lubrication approximation is an adapted framework (and gravity is weak)

- Pressure/flux relation : $$Q = -\frac{\pi}{128}\frac{D^4(s)}{\mu_a(s)}\frac{\partial p}{\partial s}$$

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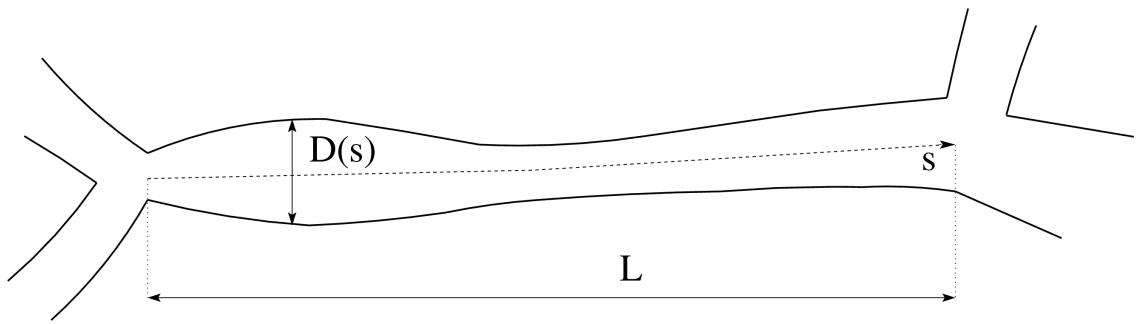

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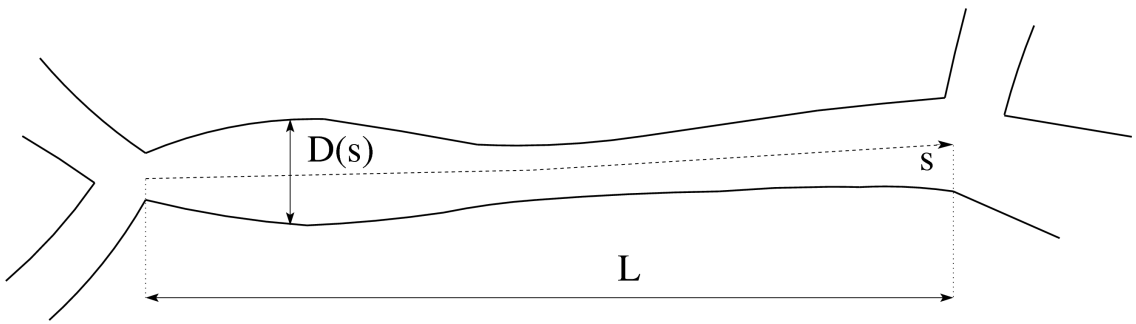

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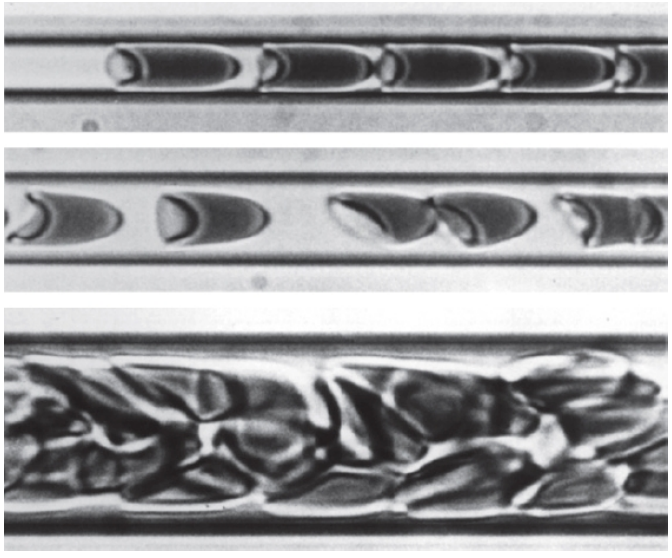
- Neglecting complex effects at bifurcations
- Non-deformable vessels

Viscosity laws

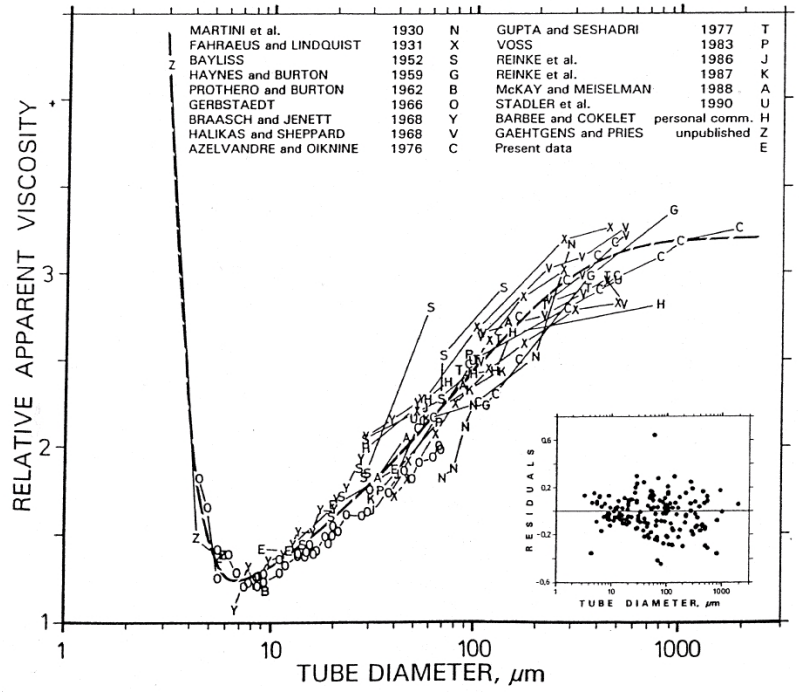
- ▷ Blood composition : erythrocytes (45 %), leukocytes and thrombocytes (1 %), plasma
- ▷ Fåhræus-Lindqvist effect

in vitro



Microcirculation (2002) *Academic Press*

Pries *et al.* (1992) *Am. J. Physiol.*



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- Blood composition : erythrocytes (45 %), leukocytes and thrombocytes (1 %), plasma
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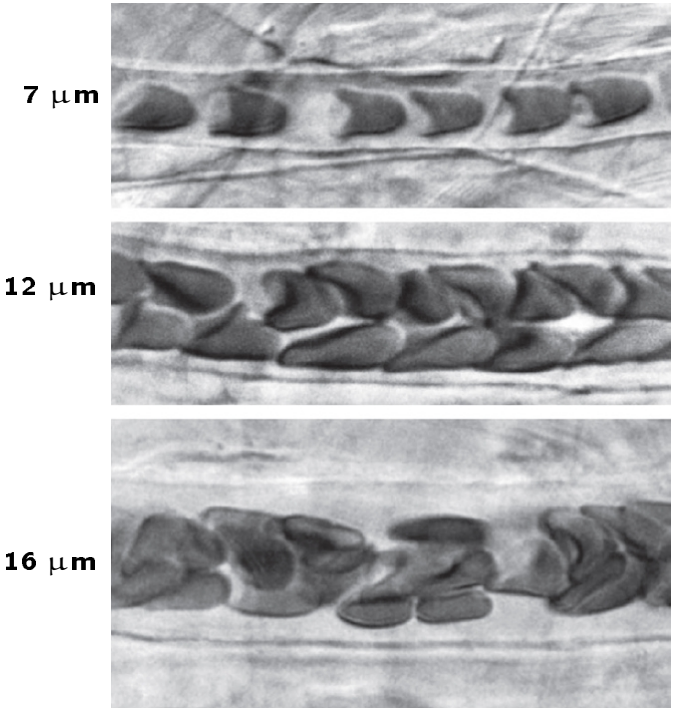
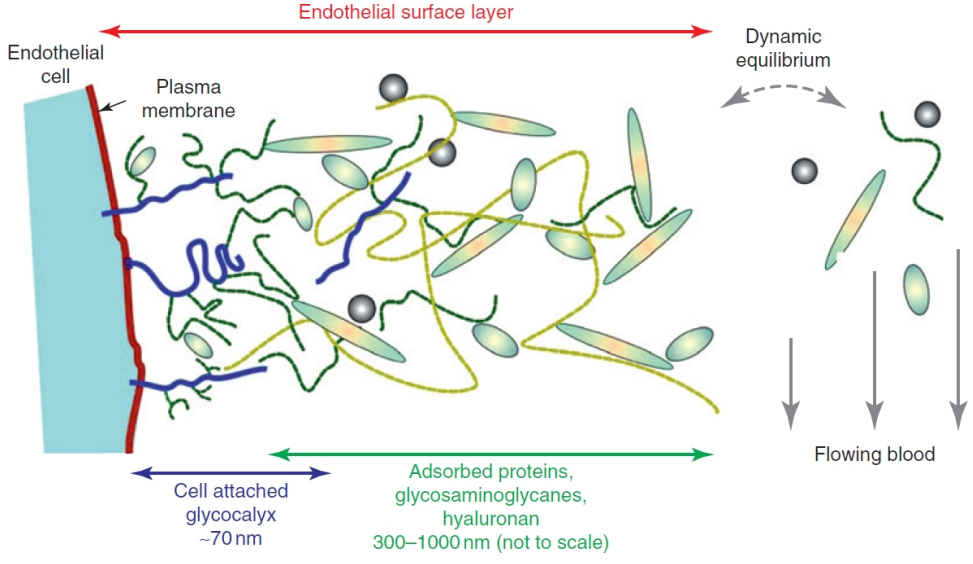
in vivo





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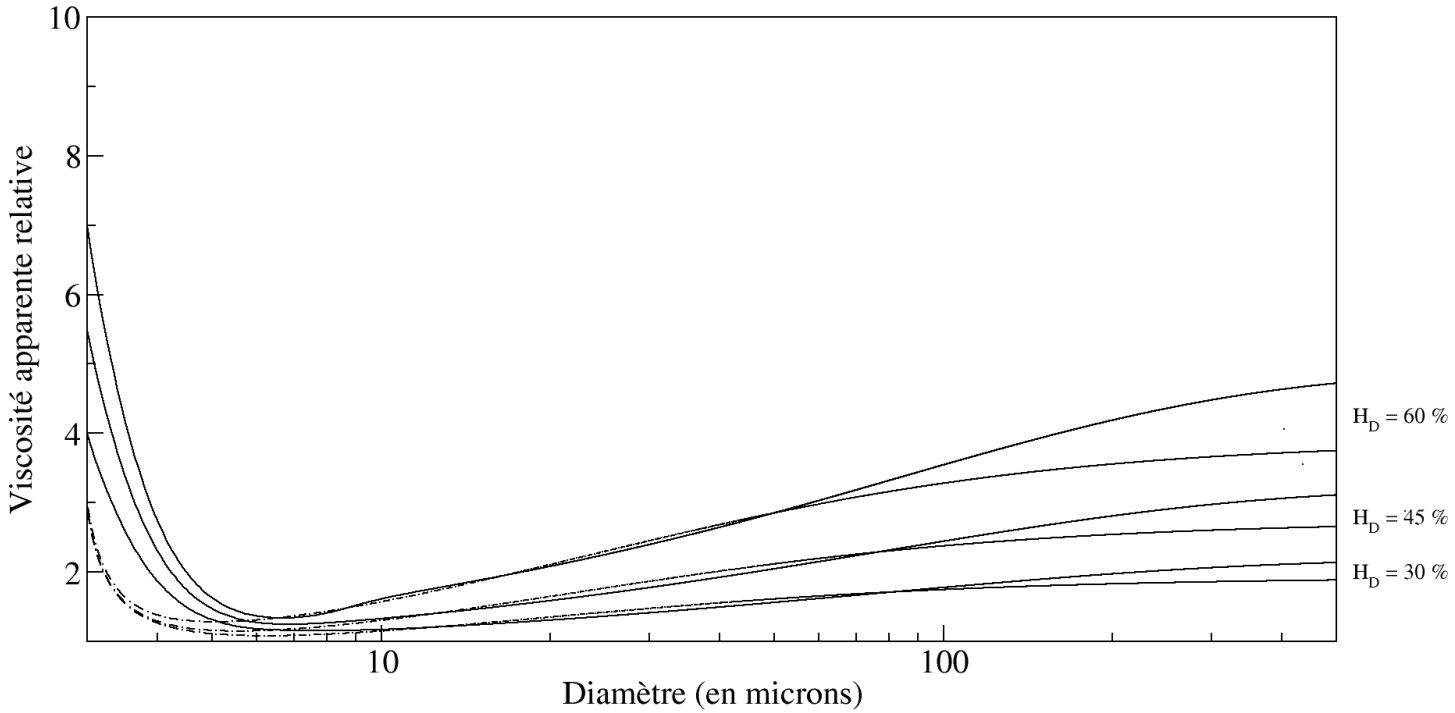

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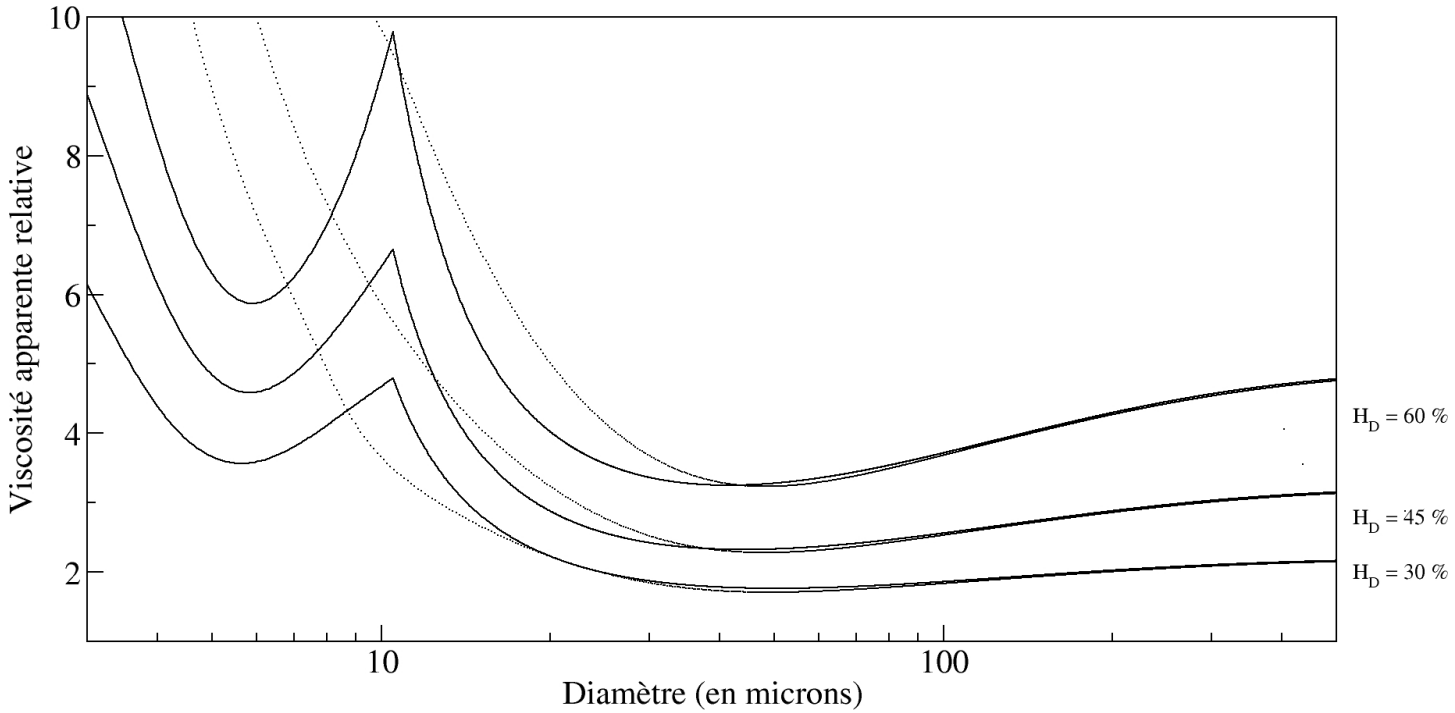
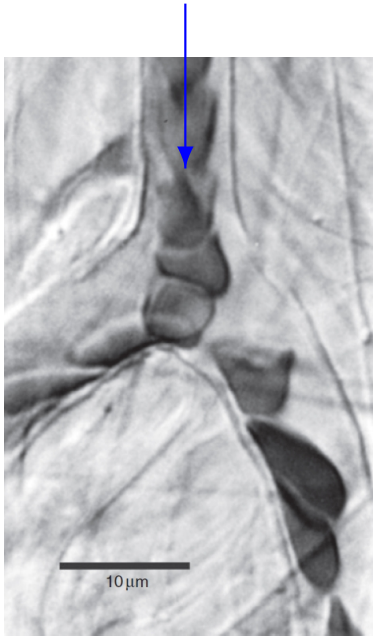


Phase separation

- Non-uniform repartition of RBC at diverging bifurcation



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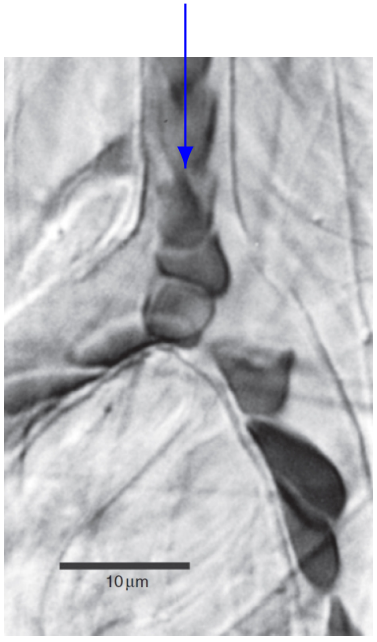

Microcirculation (2002) *Academic Press*

- Non-uniform repartition of RBC at diverging bifurcation

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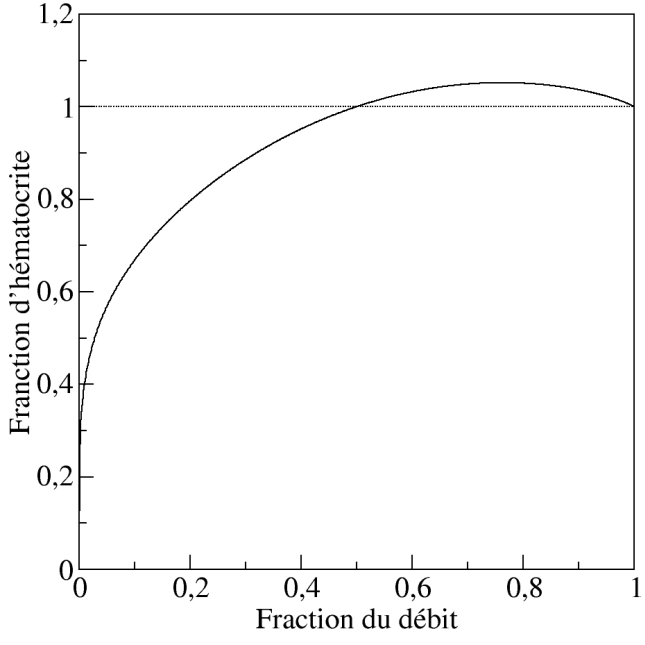
  - Dellimore *et al.* (1983) *Am. J. Physiol.*
    depending on flux and input hematocrit



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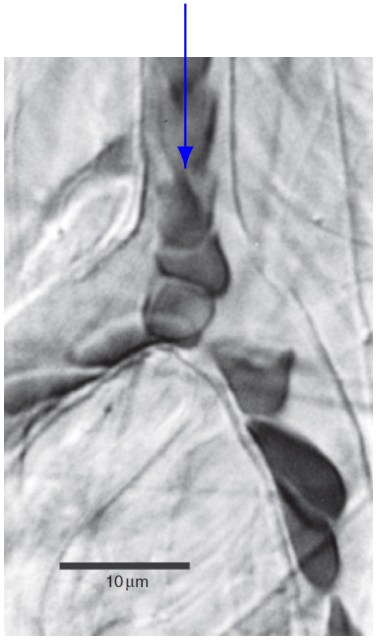

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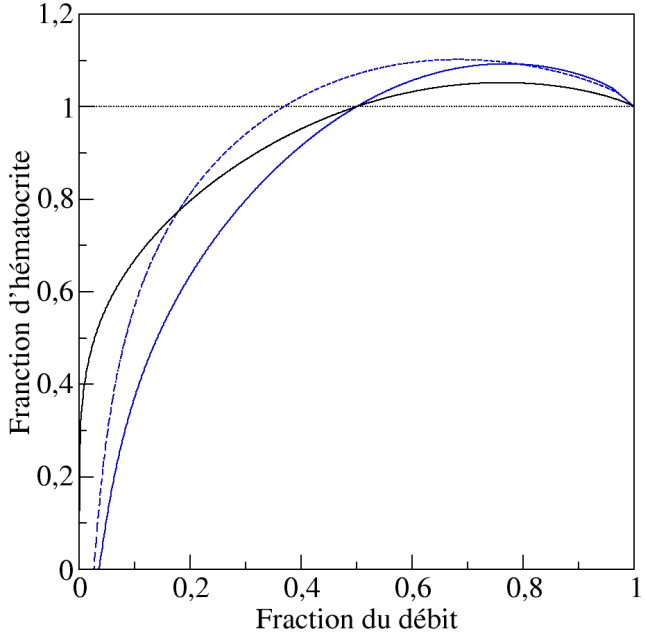
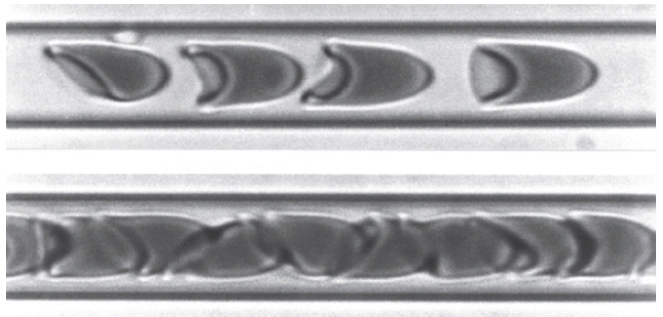
    Pries & Secomb (2005) *Am. J. Physiol.*
    depending on flux, hematocrit and diameters



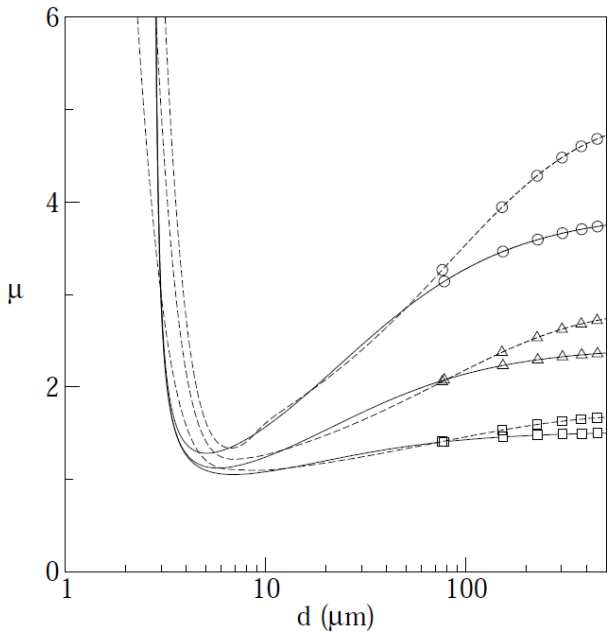
(*in vitro* effective viscosity laws

- Pressure/flux relationship : $Q = -\frac{\pi}{128}\frac{D^4}{\mu_a(H,D)}\frac{\partial p}{\partial z}$
  avec $\mu_a(H,D) = \mu_p\,\mu(H,D)$

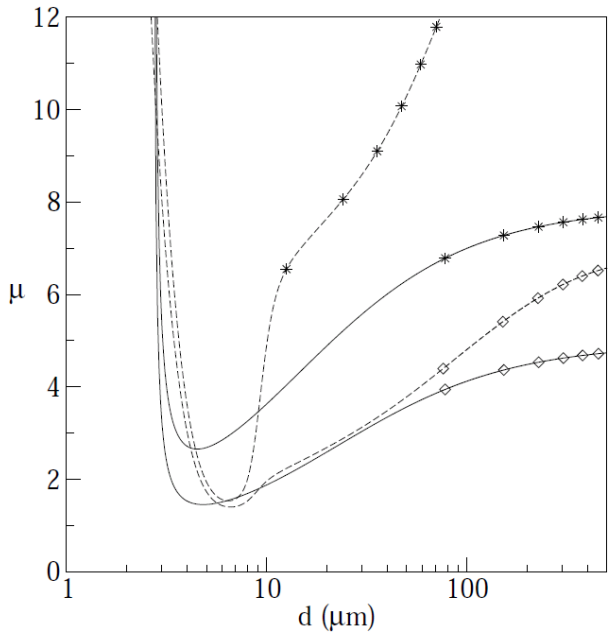
Tube de $7\mu m$: $H = 0.2$ et $H = 0.52$



- Continuous models :
  Pries et al. (1990) Circ. Res. **(dotted lines)**
  Kiani & Hudetz (1991) Biorheology **(continuous lines)** Microcirculation, Academic Press (2002)
  Y. Davit and P. Peyla, Europhys. Lett., 83, 6, 2008.

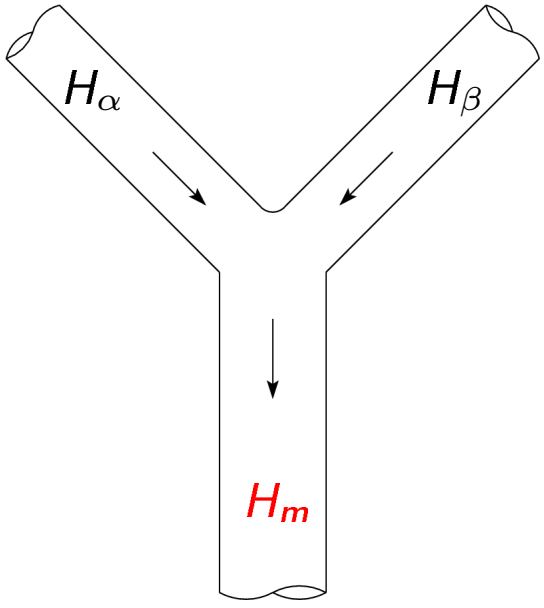


$H = 0.2,\ 0.4$ et 0.6



$H = 0.7$ et 0.9

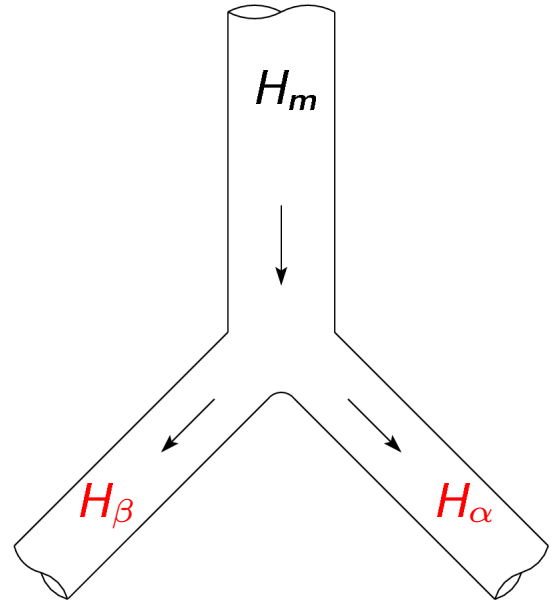
Convergent and divergent bifurcations



Convergent bifurcation

Known : H_α et H_β
Unknown : H_m

One relation is enough :
$H_m Q_m = H_\alpha Q_\alpha + H_\beta Q_\beta$
$H_m = H_\alpha \gamma_\alpha + H_\beta \gamma_\beta$

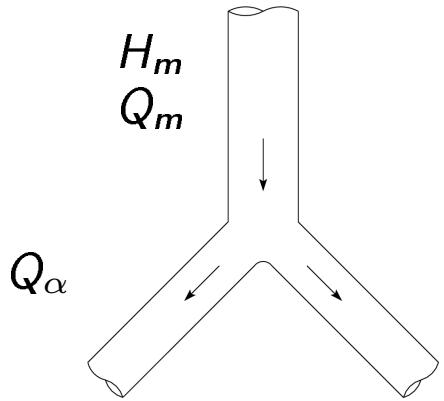


Divergent bifurcation

Known : H_m
Unknown : H_α et H_β

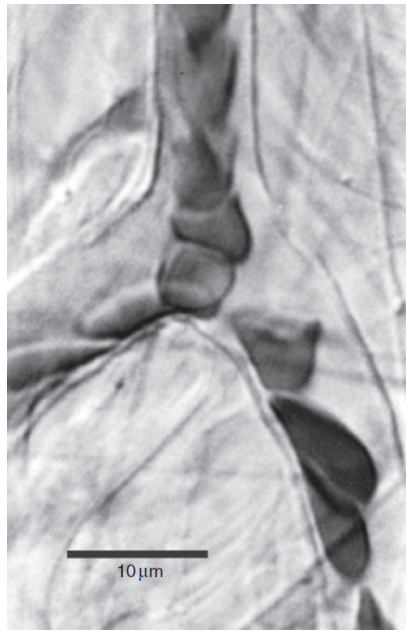
One relation is not enough !

Empirical relationship for phase separation

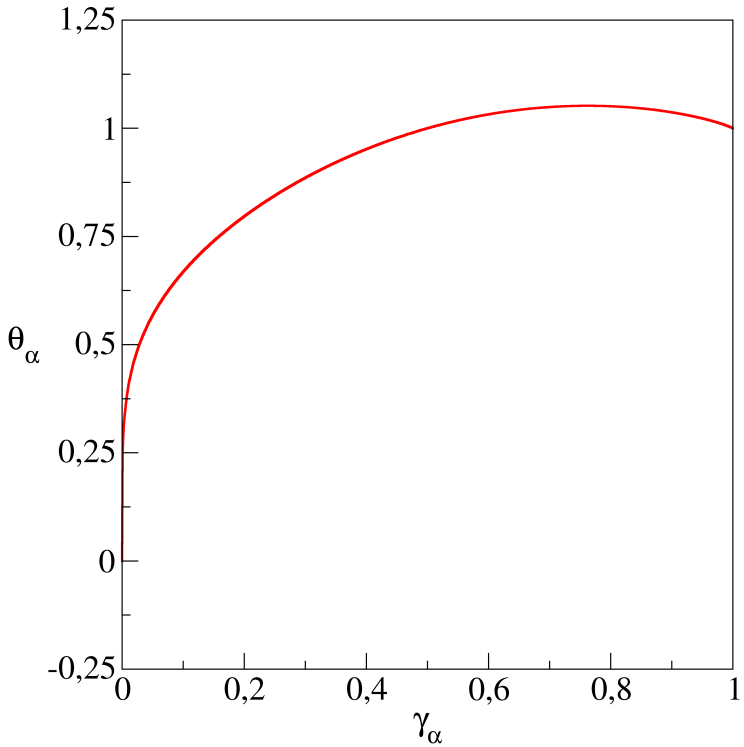


Divergent Bifurcation

$$\theta_\alpha = \frac{H_\alpha}{H_m} = f\left(\frac{Q_\alpha}{Q_m} = \gamma_\alpha\right)$$

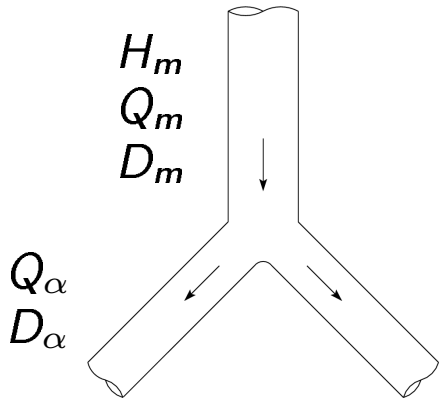


Microcirculation, Academic Press (2002



Dellimore et al., Am. J. Physiol. (1983)

Empirical relationship for phase separation

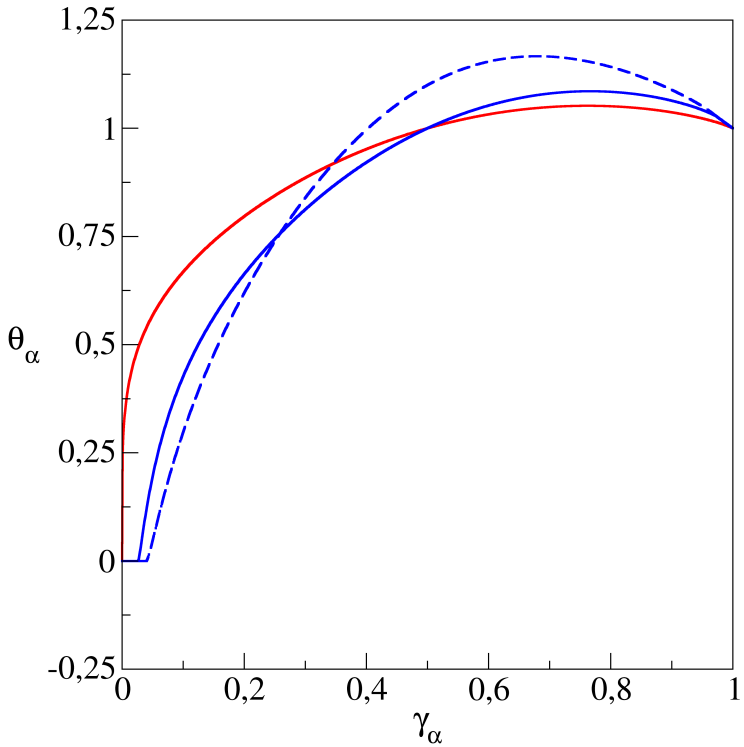


Divergent Bifurcation

$$\theta_\alpha = \frac{H_\alpha}{H_m} = f(\gamma_\alpha, \frac{D_{\alpha,\beta}}{D_m})$$



Microcirculation, Academic Press (2002



Dellimore et al., Am. J. Physiol. (1983)

Pries et al., Microvasc. Res. (1989)

...

Iterative procedure

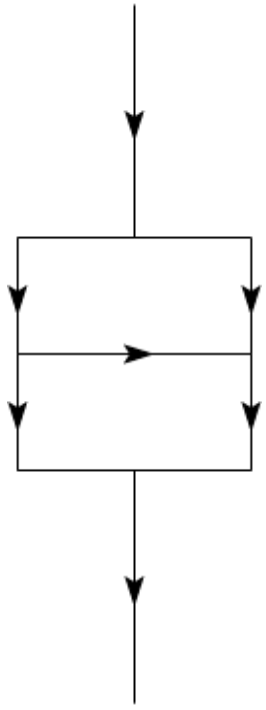
- Pressure (linear system)

$$\sum_{i \in J} Q_i = \sum_{i \in J} -\frac{\pi}{128} \frac{D^4}{\mu_a(H, D)} \frac{\Delta p}{L} = 0$$

- Hematocrit distribution (following the flow)

$$\theta_{\alpha,\beta} = f(\gamma_\alpha, \gamma_\beta, ...)$$

$$\theta_\alpha \gamma_\alpha + \theta_\beta \gamma_\beta = 1$$



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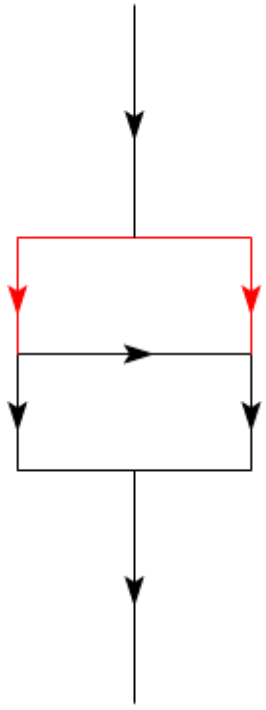

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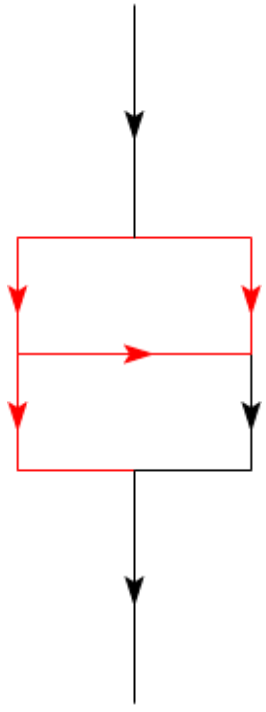

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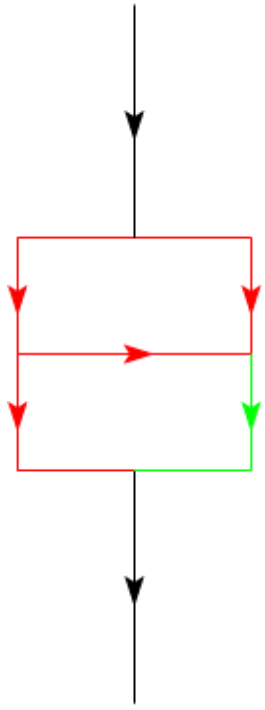

Iterative procedure

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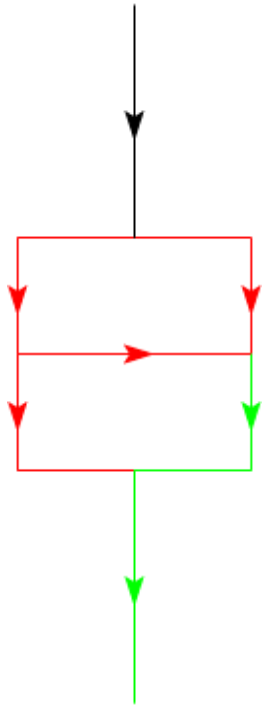


- Hematocrit distribution (following the flow)

$$\theta_{\alpha,\beta} = f(\gamma_\alpha, \gamma_\beta, ...)$$

$$\theta_\alpha \gamma_\alpha + \theta_\beta \gamma_\beta = 1$$

- Iterative procedure (fixed point) (Pries et al. (1990) Circ. Res.)

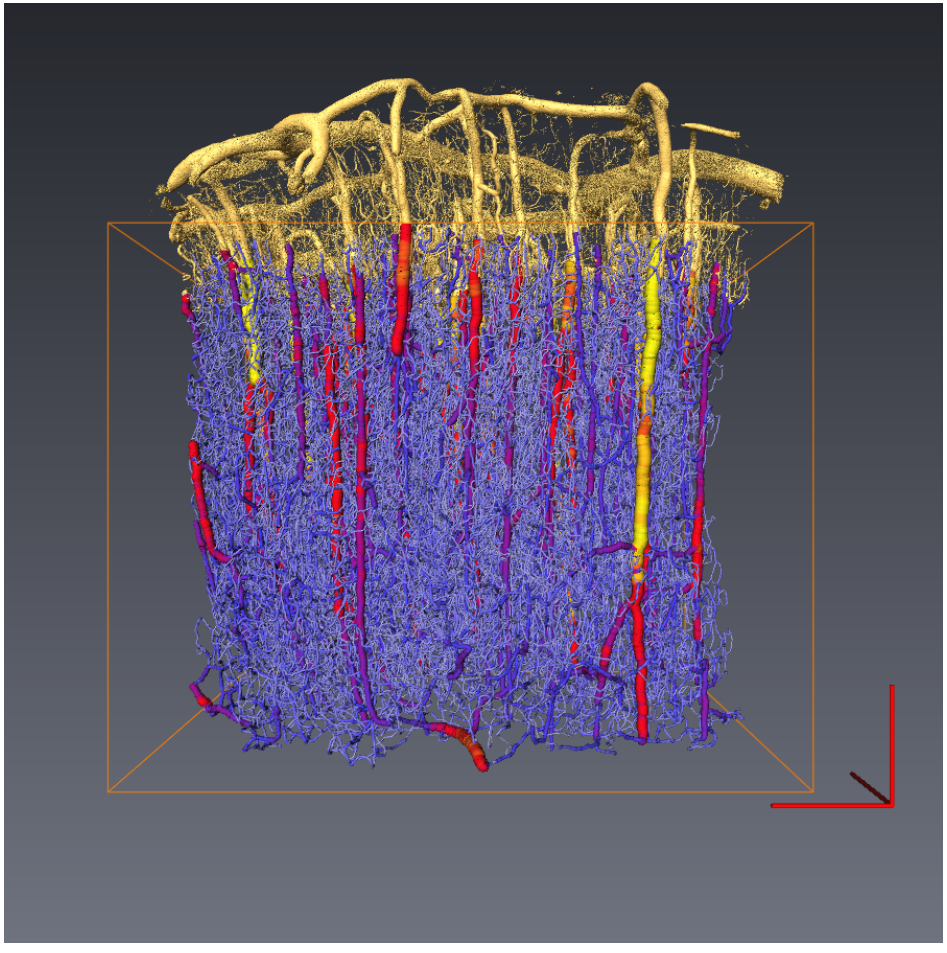
$$p^{(k)} \rightarrow h^{(k)} \rightarrow p^{(k+1)}$$

Various methodological problems

Problems with phase separation models

- Different possible parametrisations
- Model dependant results
- Possible convergence problems

Sample visualisation



Pial matter

Dirichlet boundary conditions imposition (pressure and hematocrit)

Intra-cortical network

Diameter color-coded representation

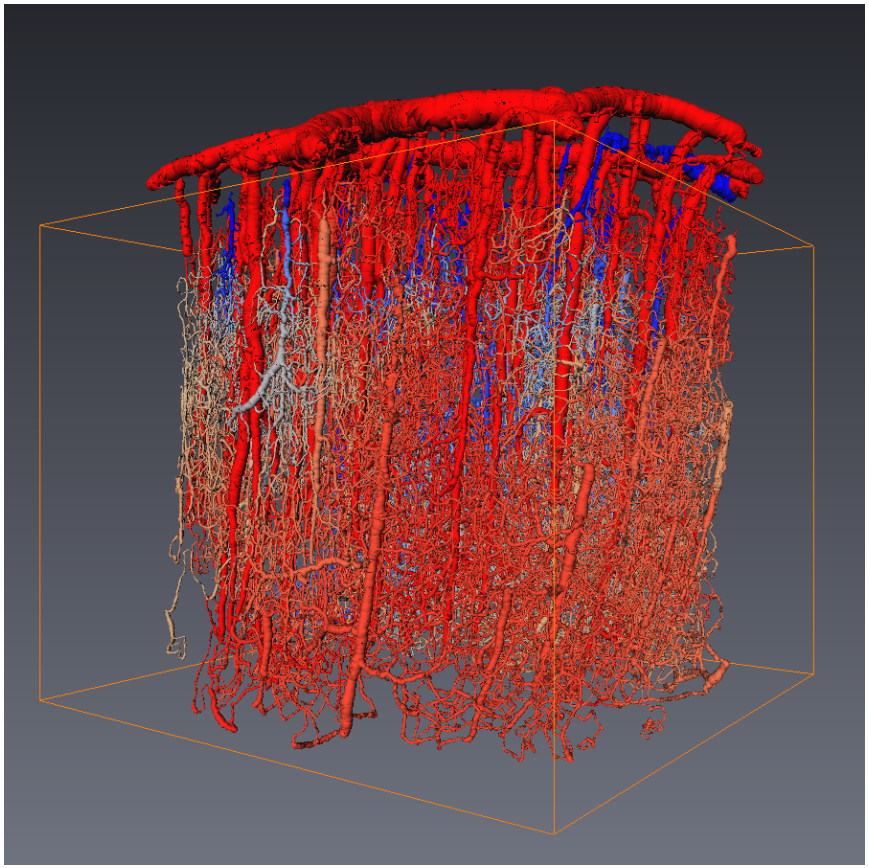
Zero-flux boundary conditions

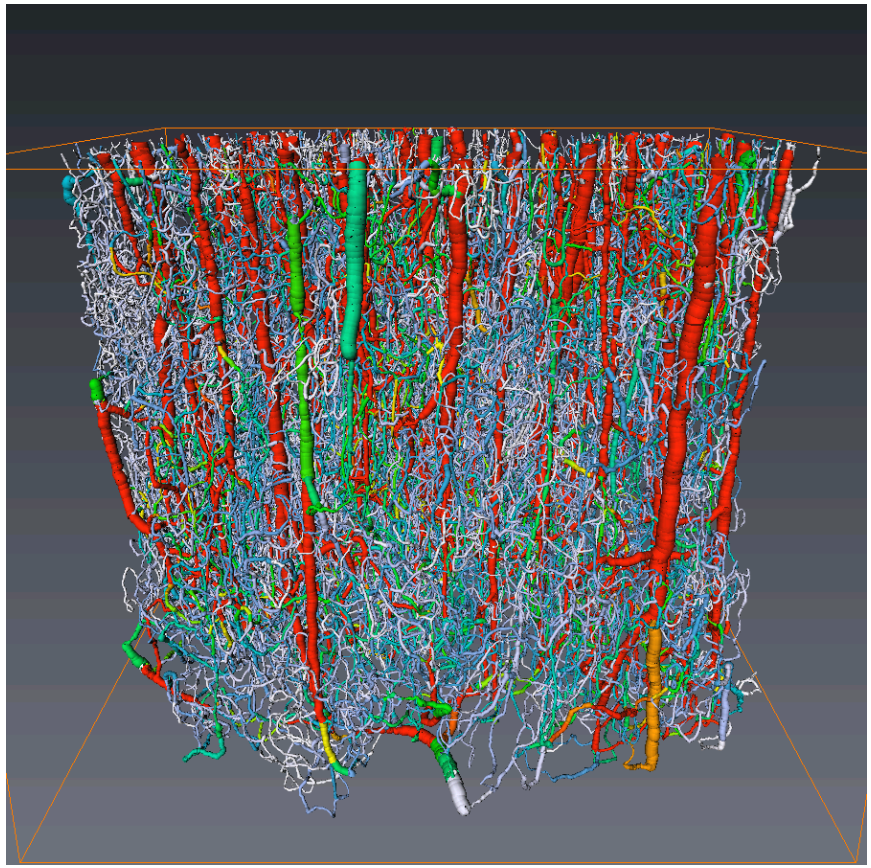
Evaluation of pressure, hematocrit and flux distributions

Volume 18 mm^3

16 000 vascular segments

Quasi-static pressure & flux distributions





Obtained using viscosity and phase separation laws proposed by

Pries & Secomb (2005) *Am. J. Physiol.* and a systemic hematocrit of 45 %

Guibert et al. (2010) *JCBFM*

Sensitivity analysis of Guibert et al. (2010) *JCBFM*

Apparent Viscosity Model : (AVM)
Phase Separation Models : (PSM)

- Pressure field is weakly sensitive to AVM

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Perfusion/Drainage territories

Guibert et al. (2012) *Neuroimage*

Perfusion Territory

Perfusion/Drainage territories

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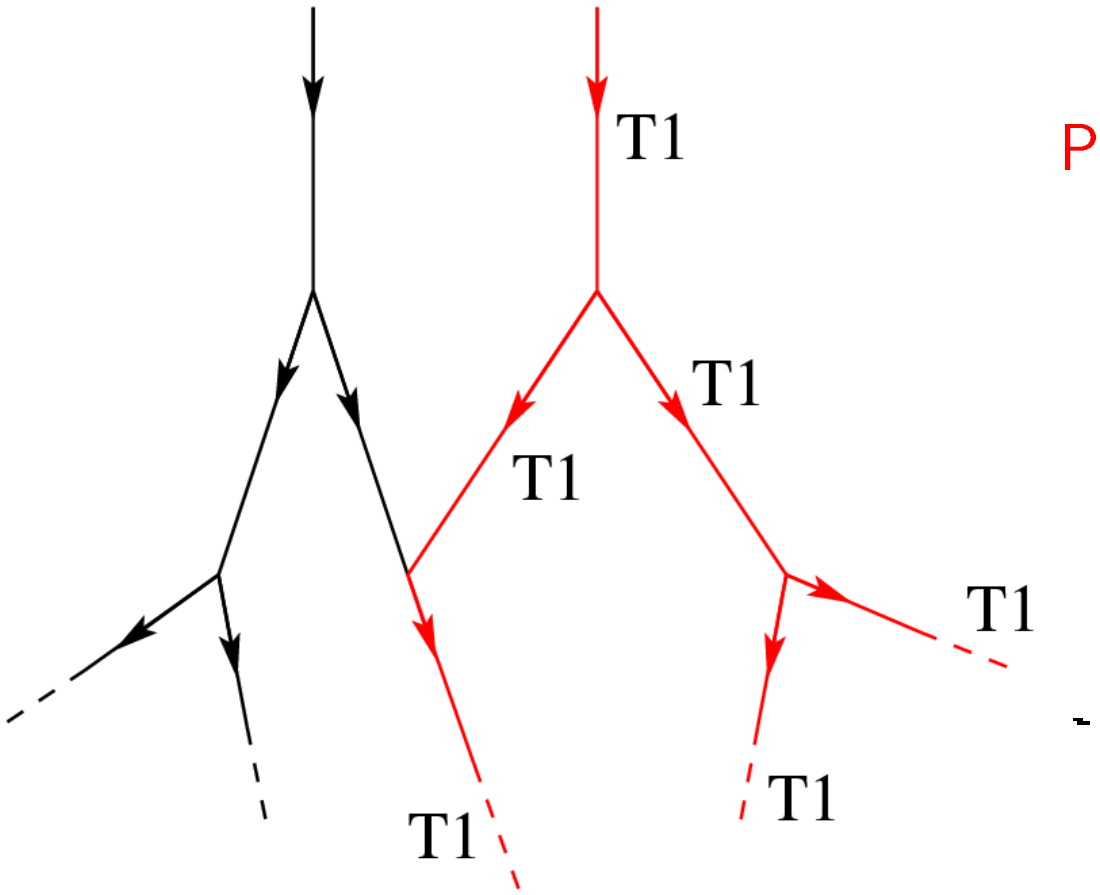
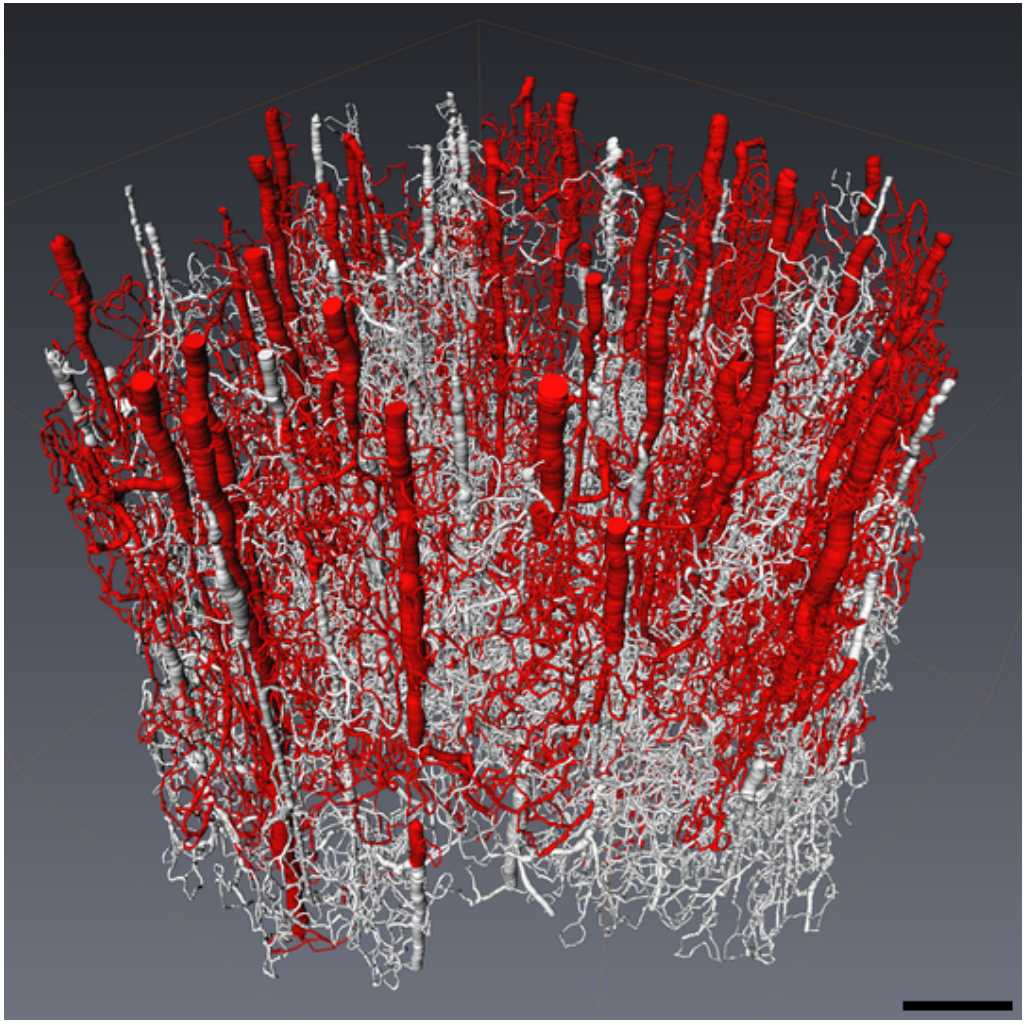


Perfusion Territory

Perfusion/Drainage territories

Guibert et al. (2012) *Neuroimage*



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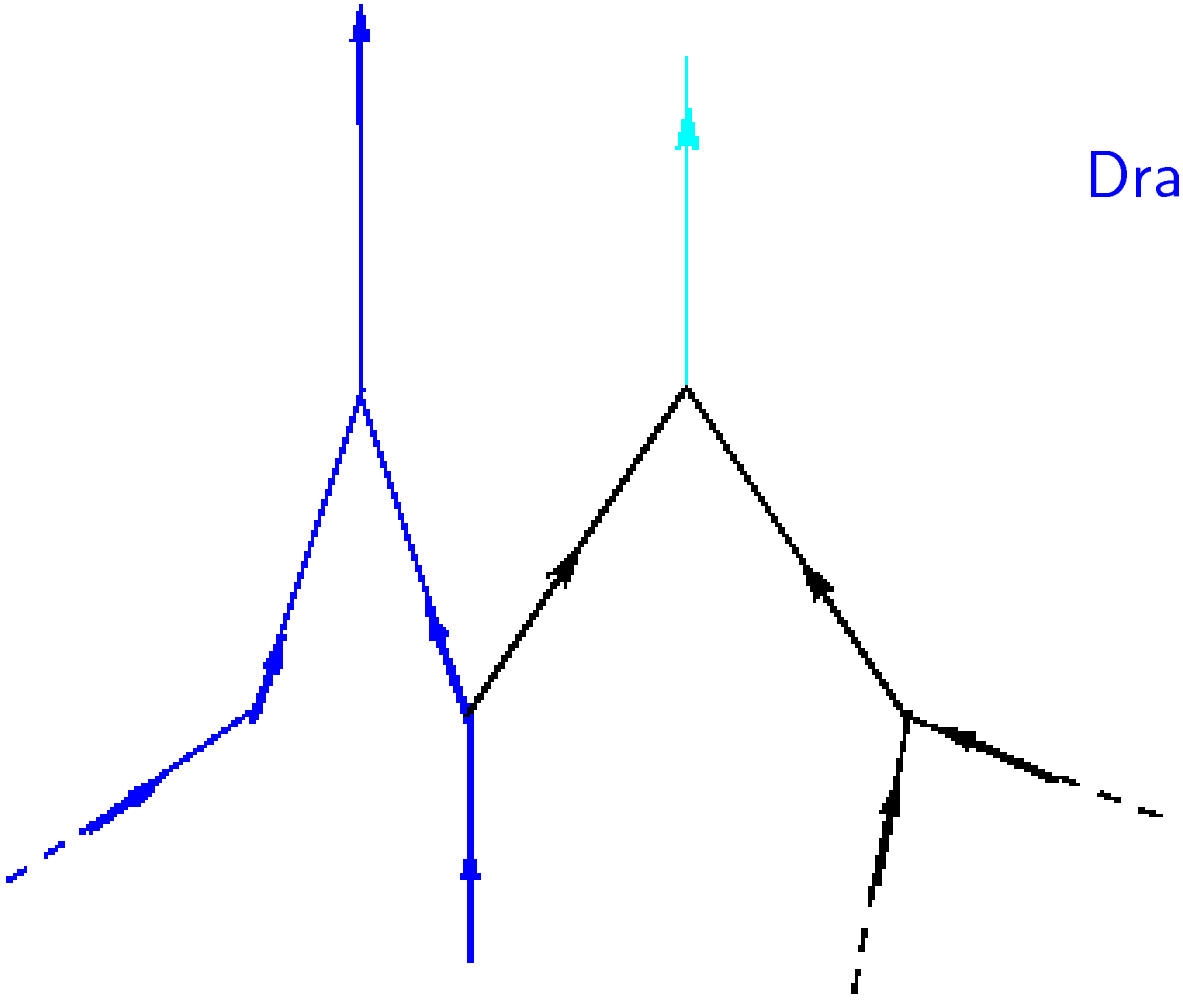
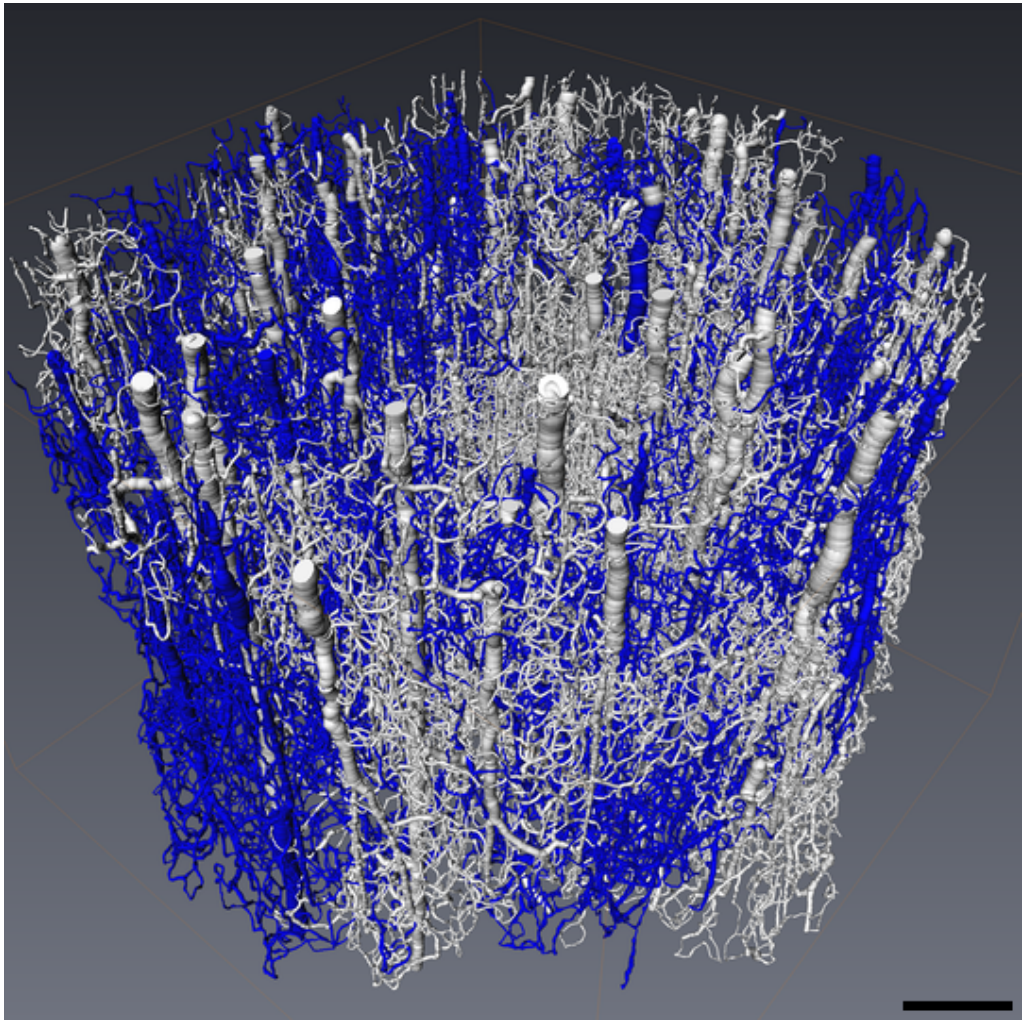


Drainage Territory

Perfusion/Drainage territories

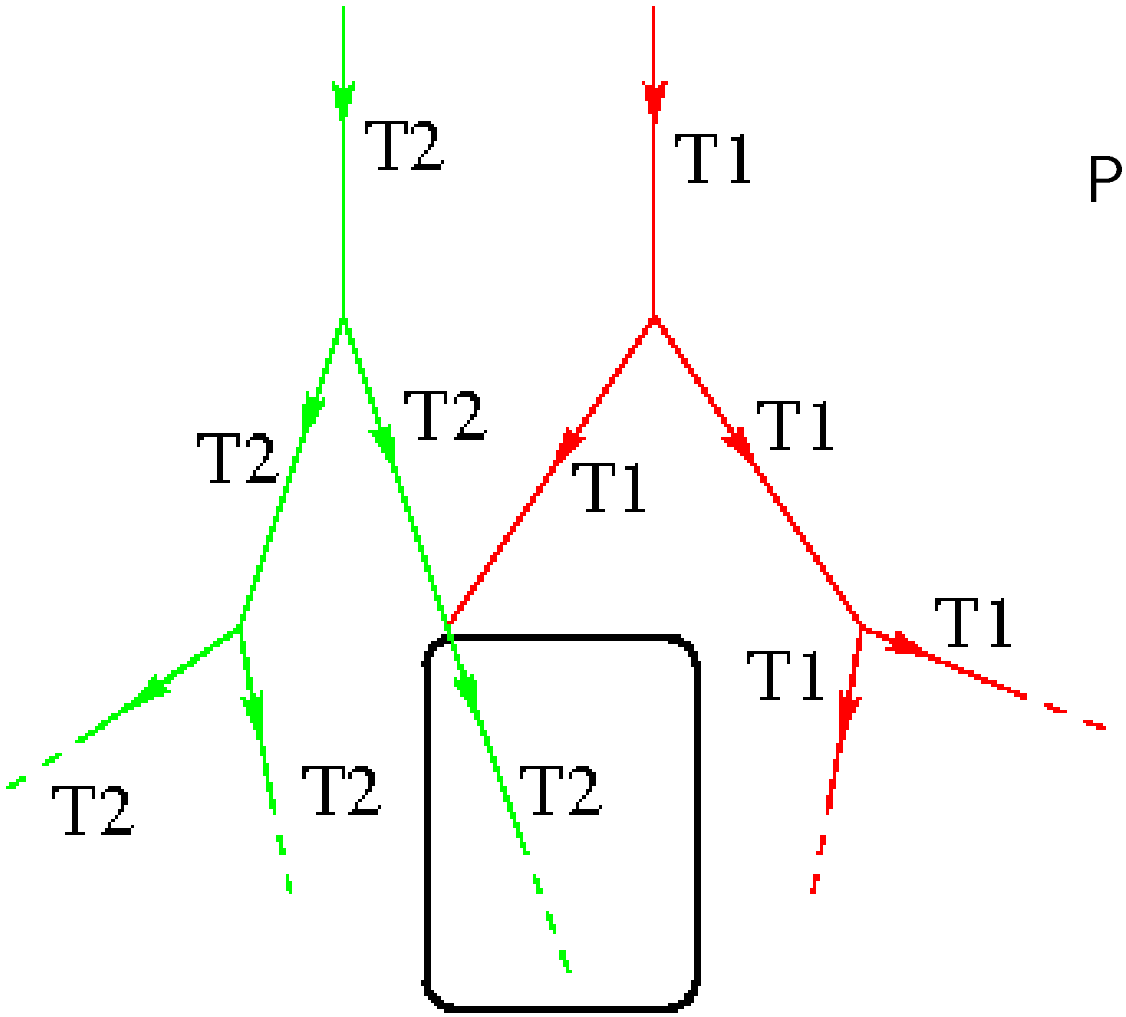
Guibert et al. (2012) *Neuroimage*



Drainage Territory

Preferential Vascular territories

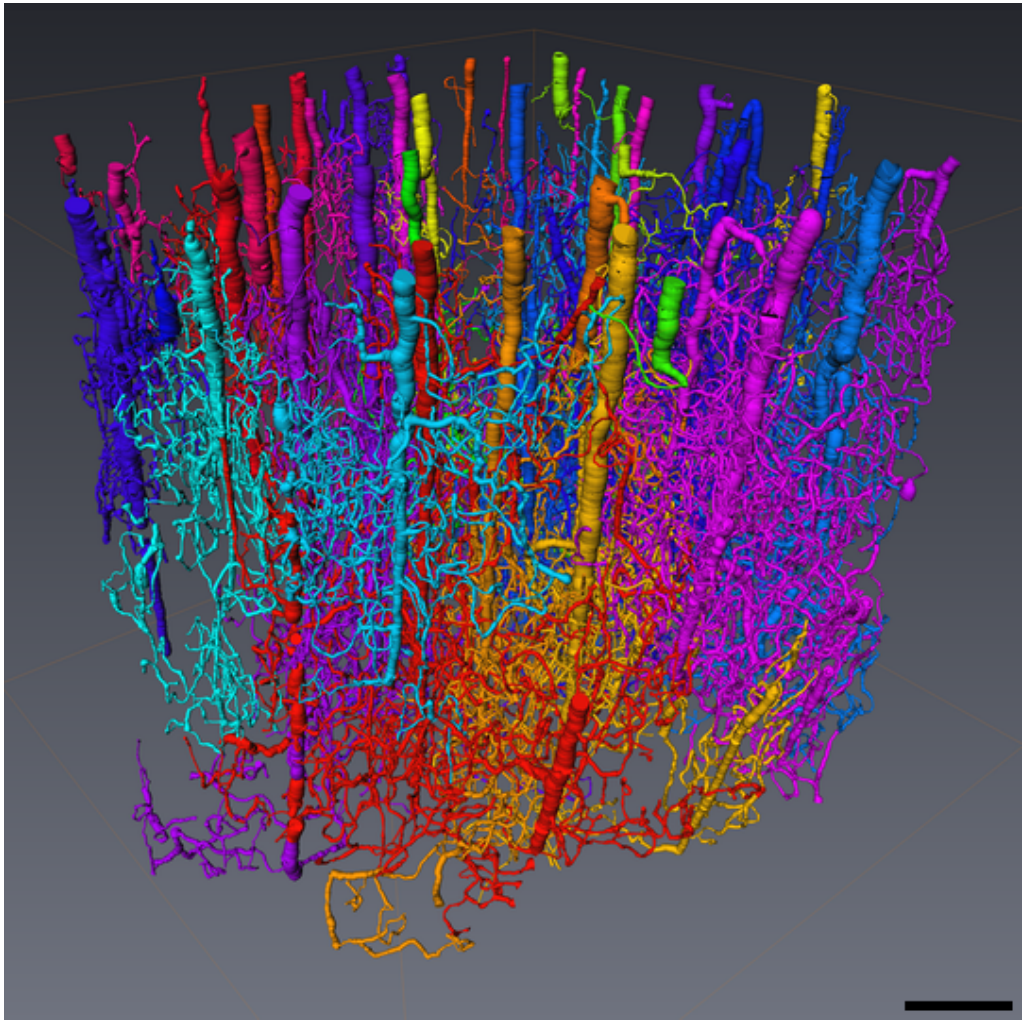
Guibert et al. (2012) *Neuroimage*



Preferential Territory

Preferential Vascular territories

Guibert et al. (2012) *Neuroimage*



Preferential Territory

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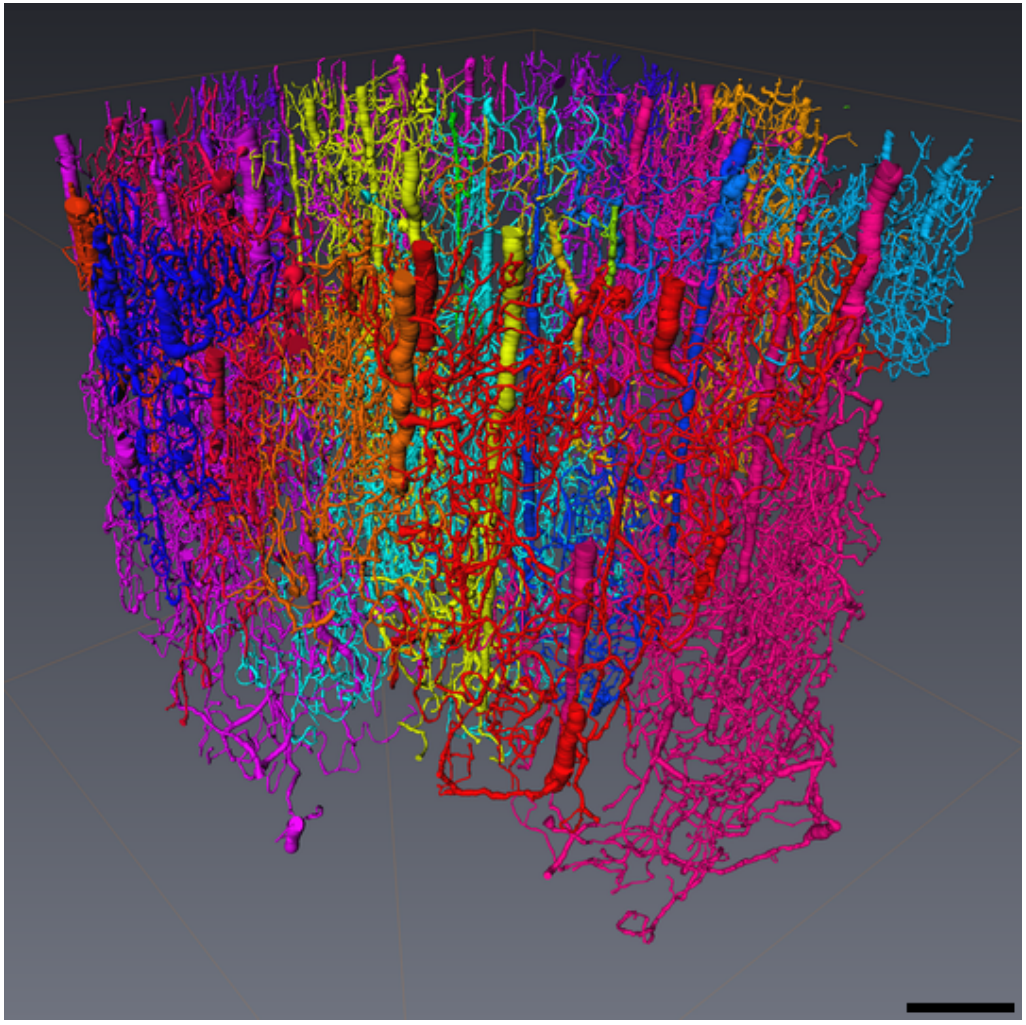
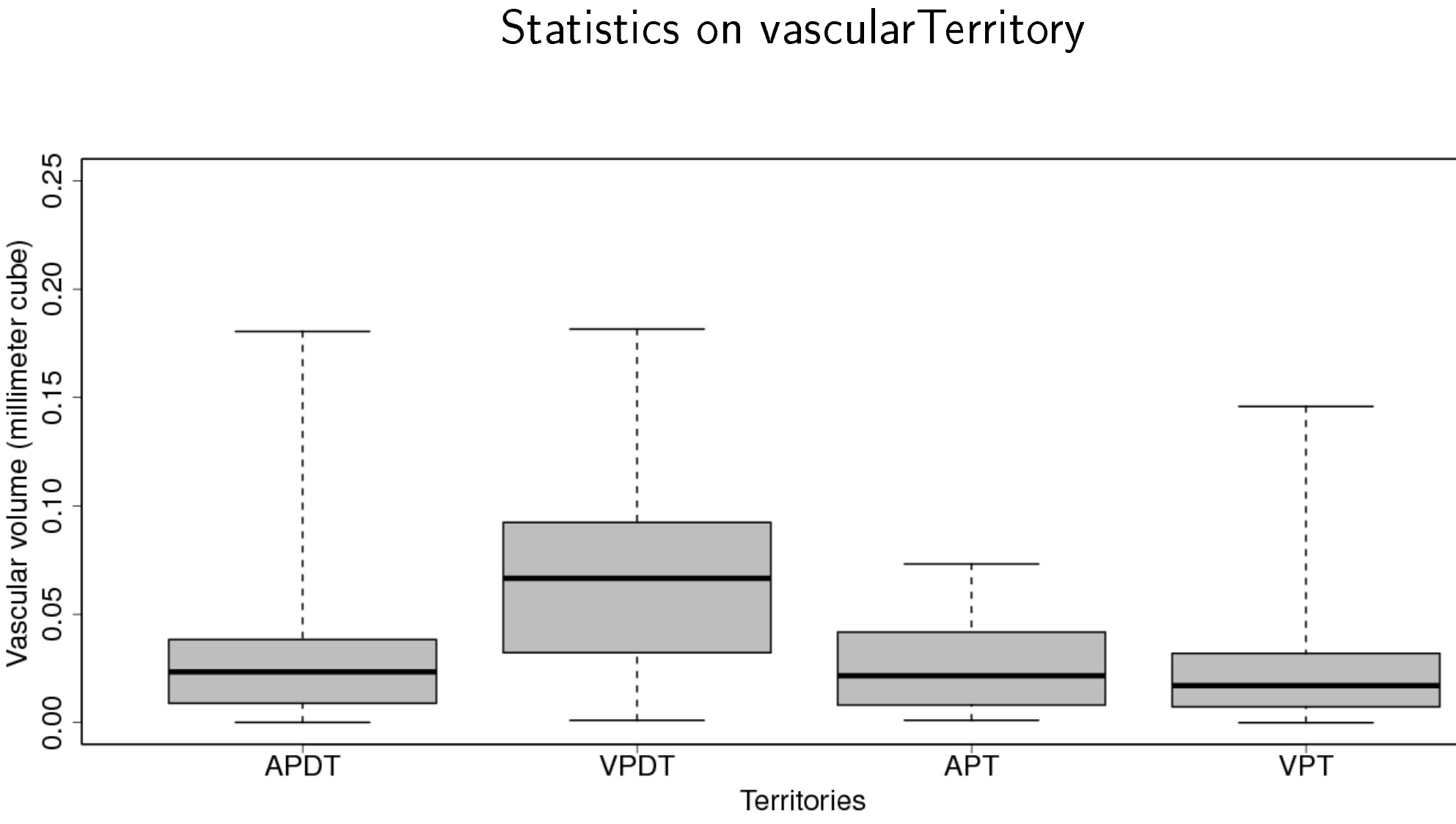
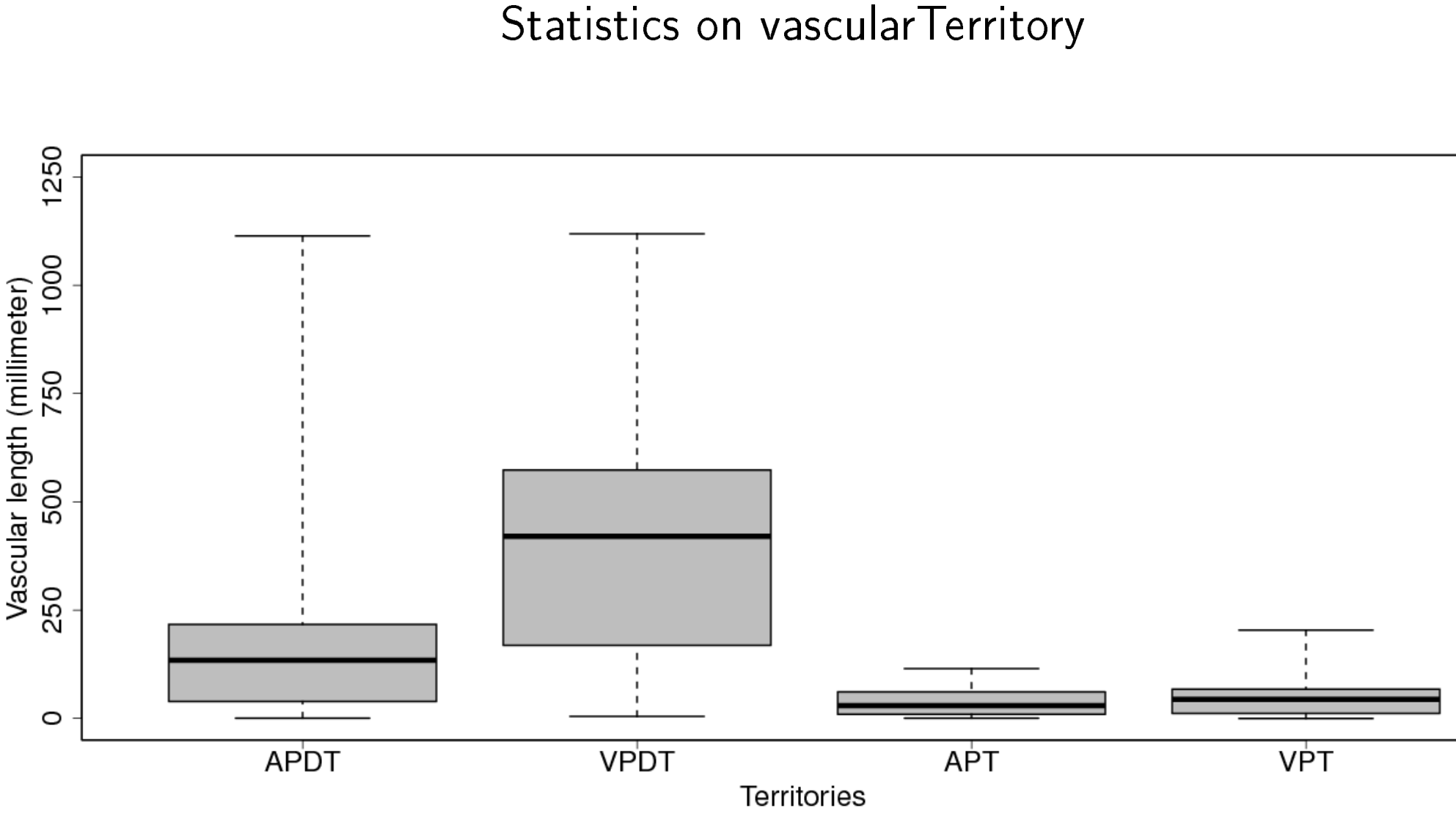


Preferential Territory

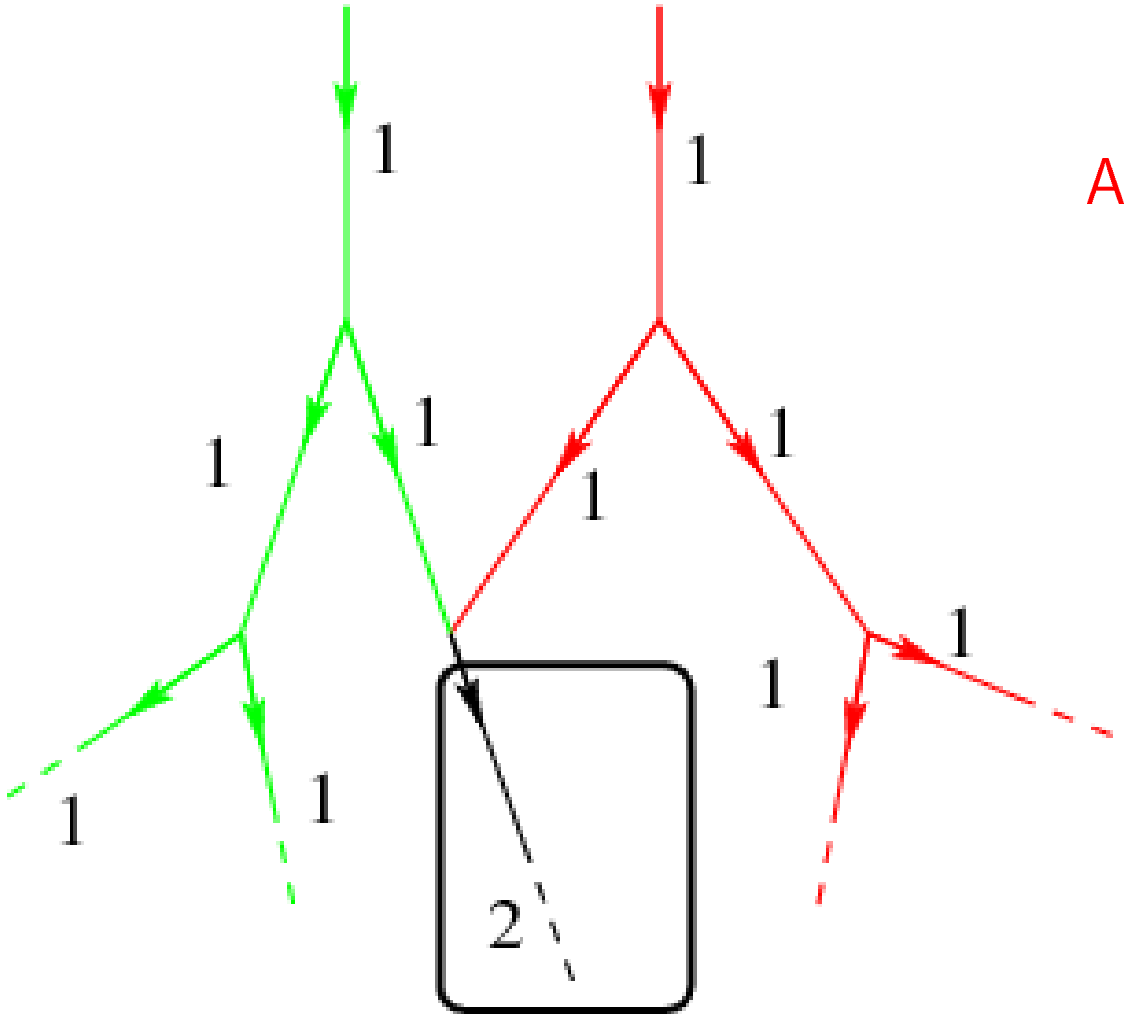
Preferential Vascular territories



Preferential Vascular territories

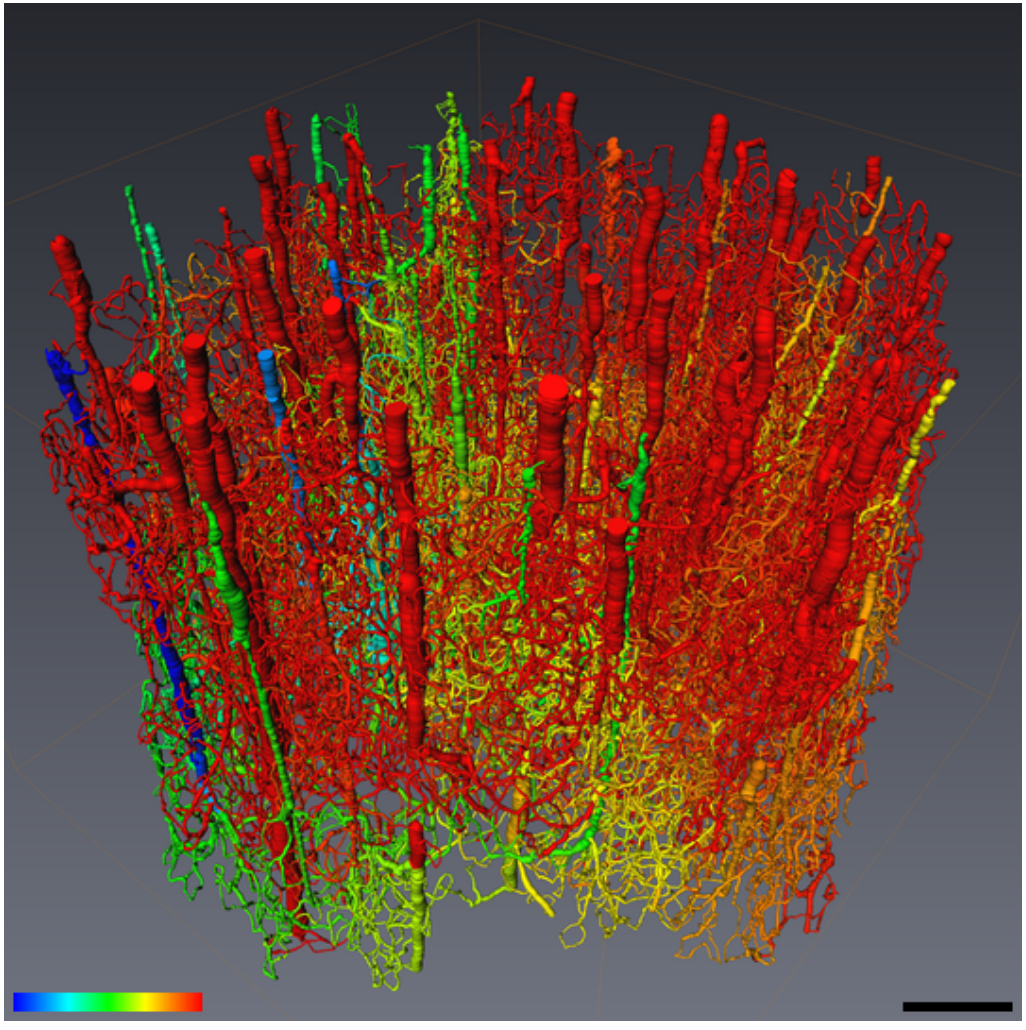


Robustness index



Arterial Robutness map (RM)

Robustness index



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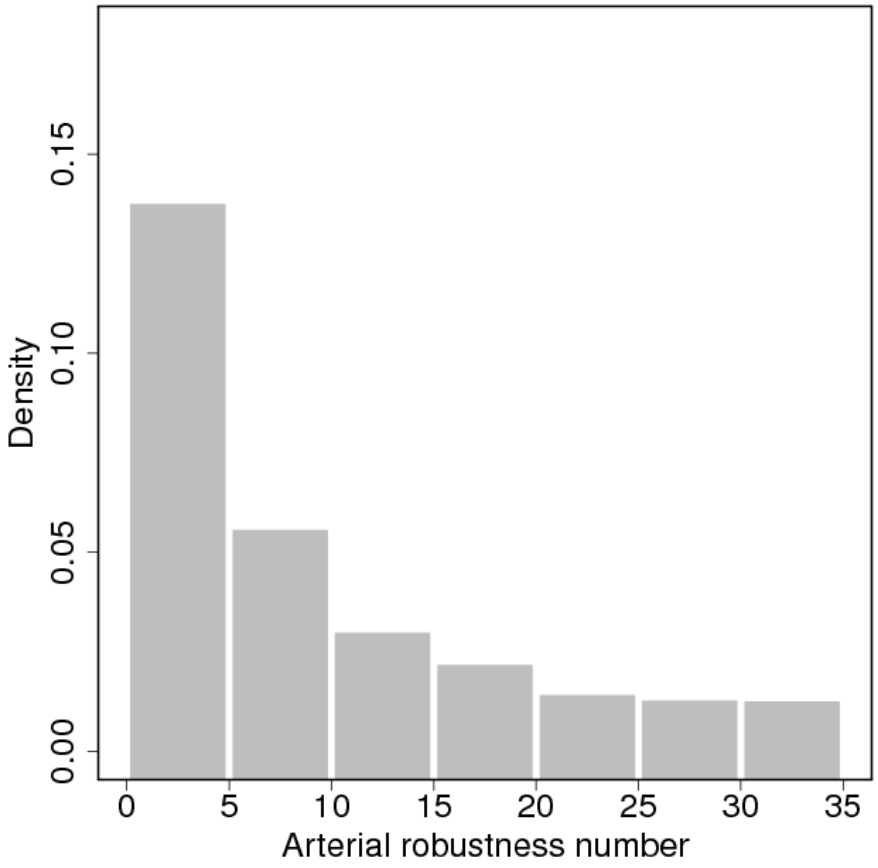
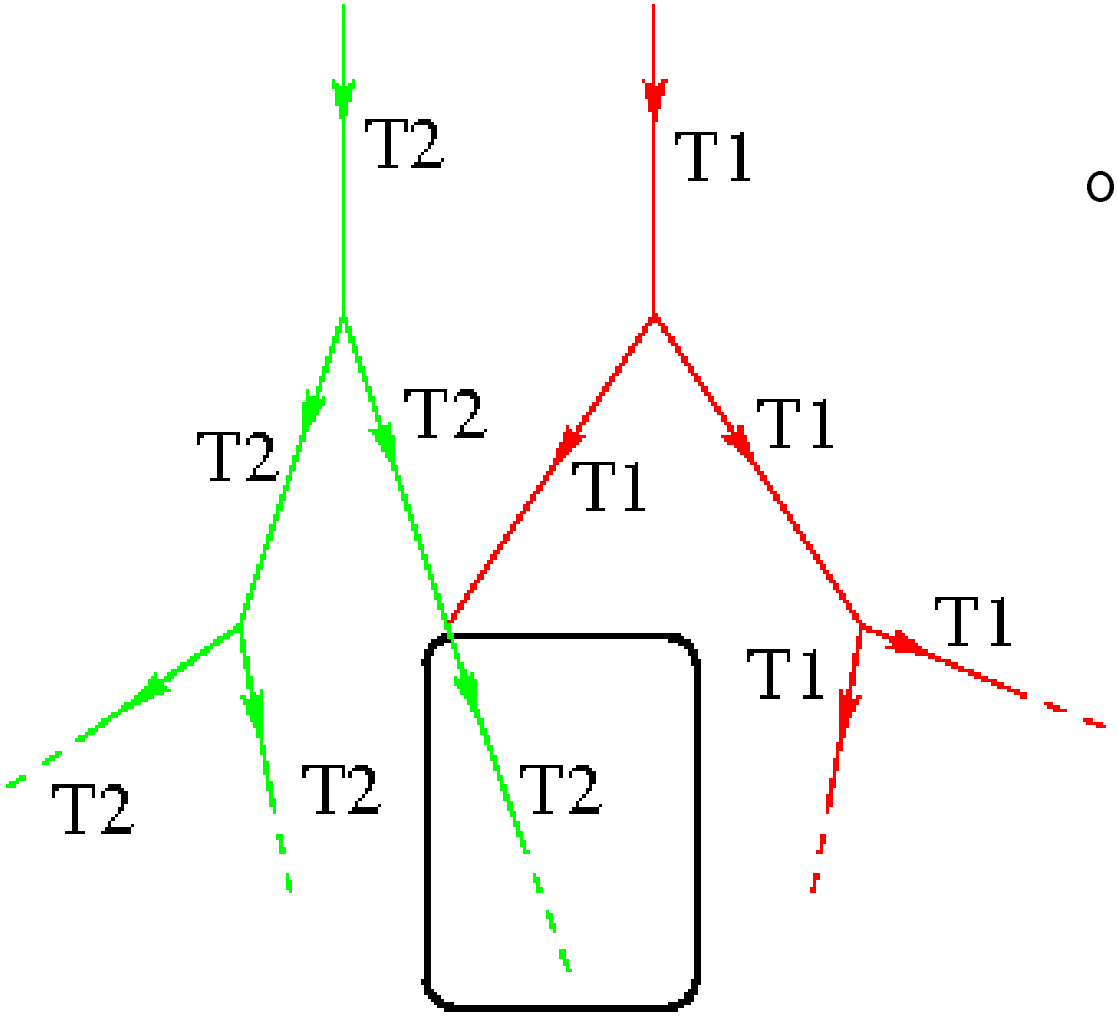


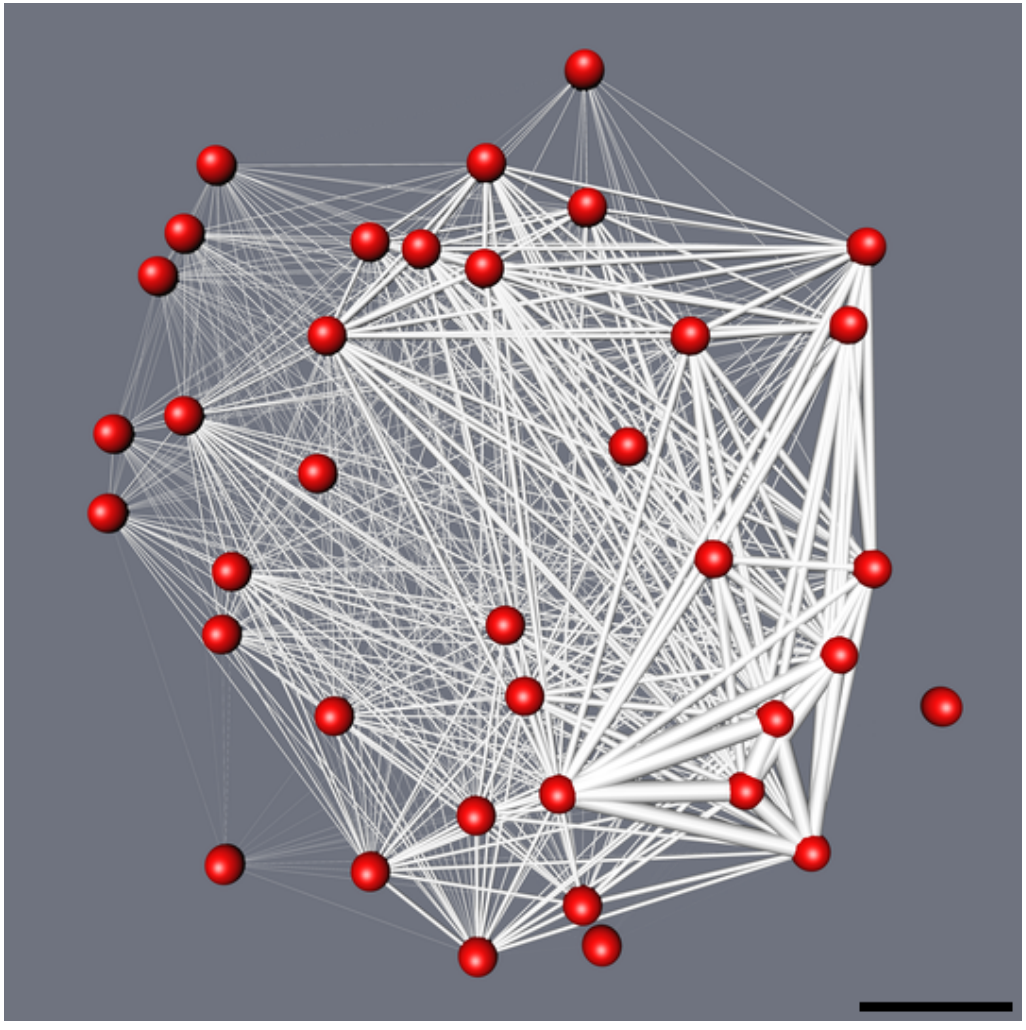
Histogram Arterial (RM)

Perfusion/Drainage territory overlapping



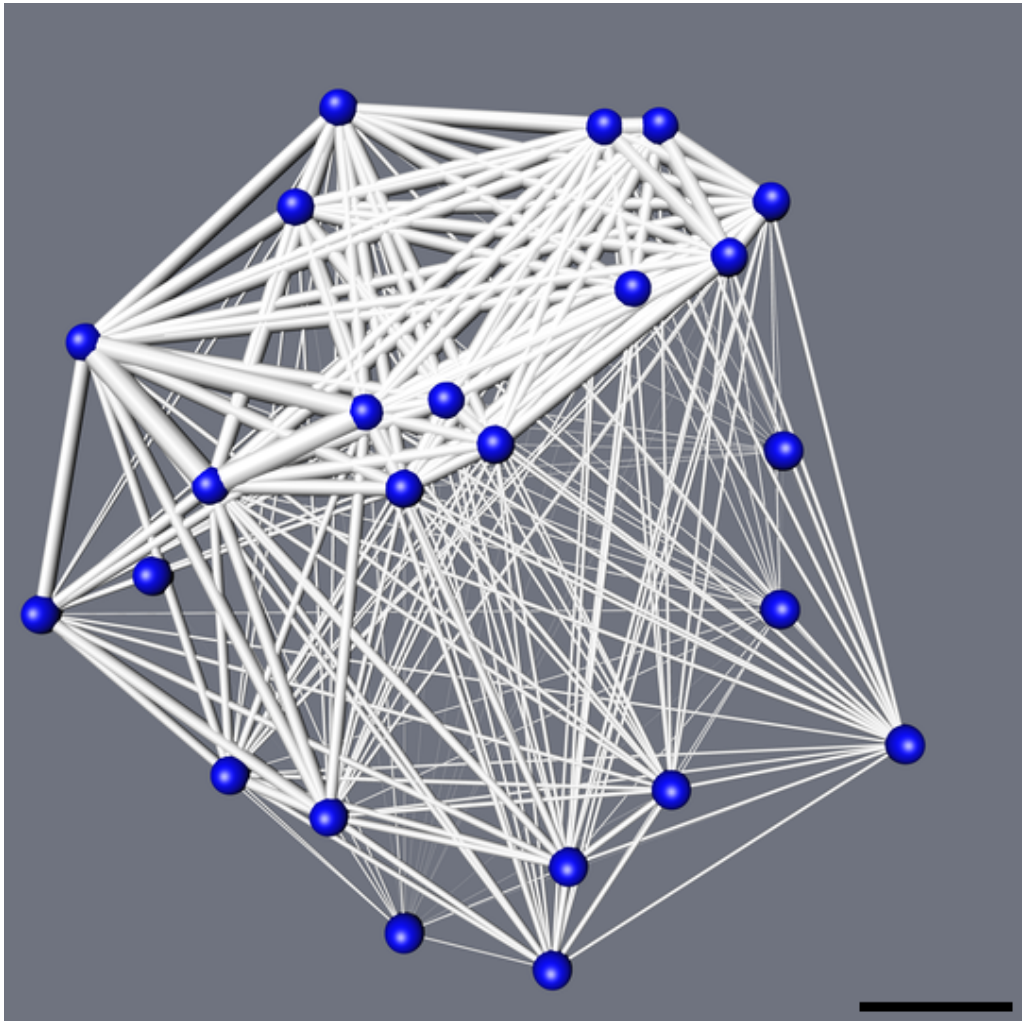
overlapping

Perfusion/Drainage territory overlapping



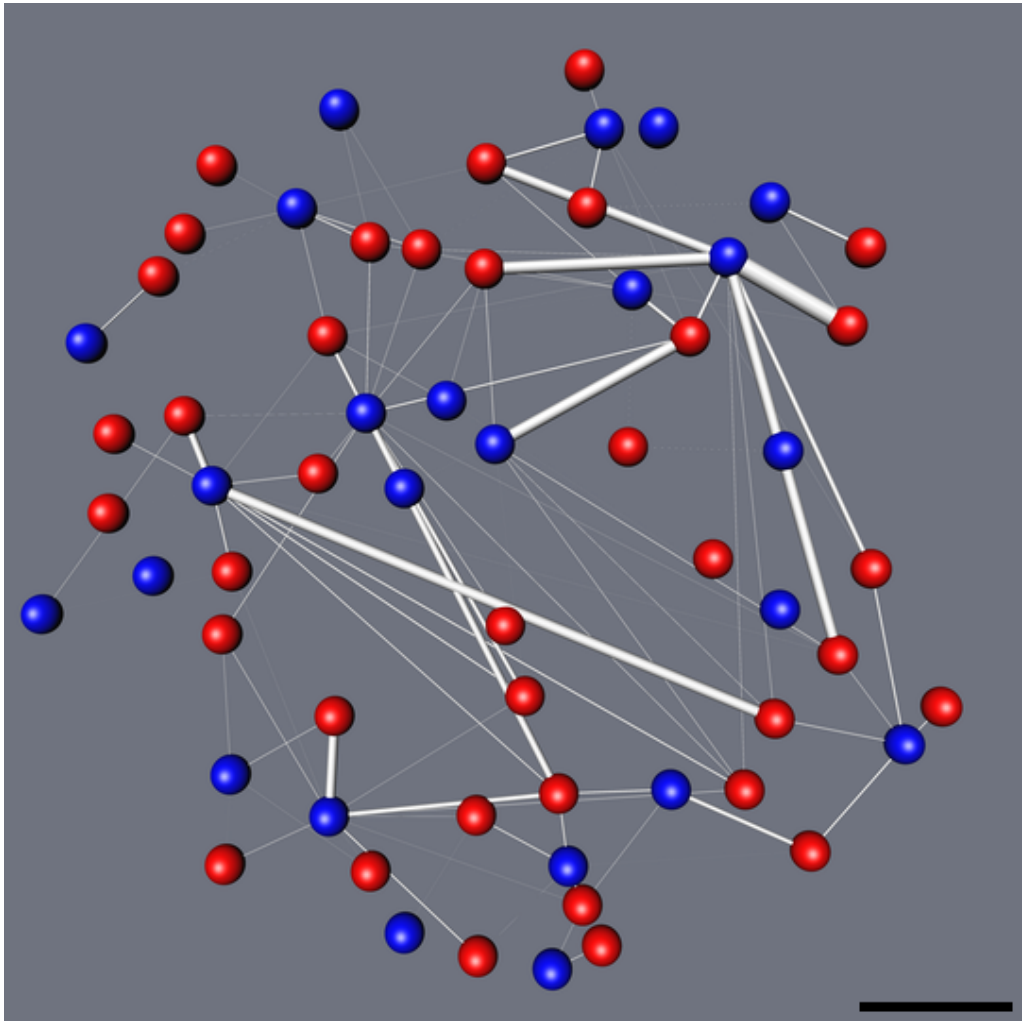
Perfusion Volume

Perfusion/Drainage territory overlapping



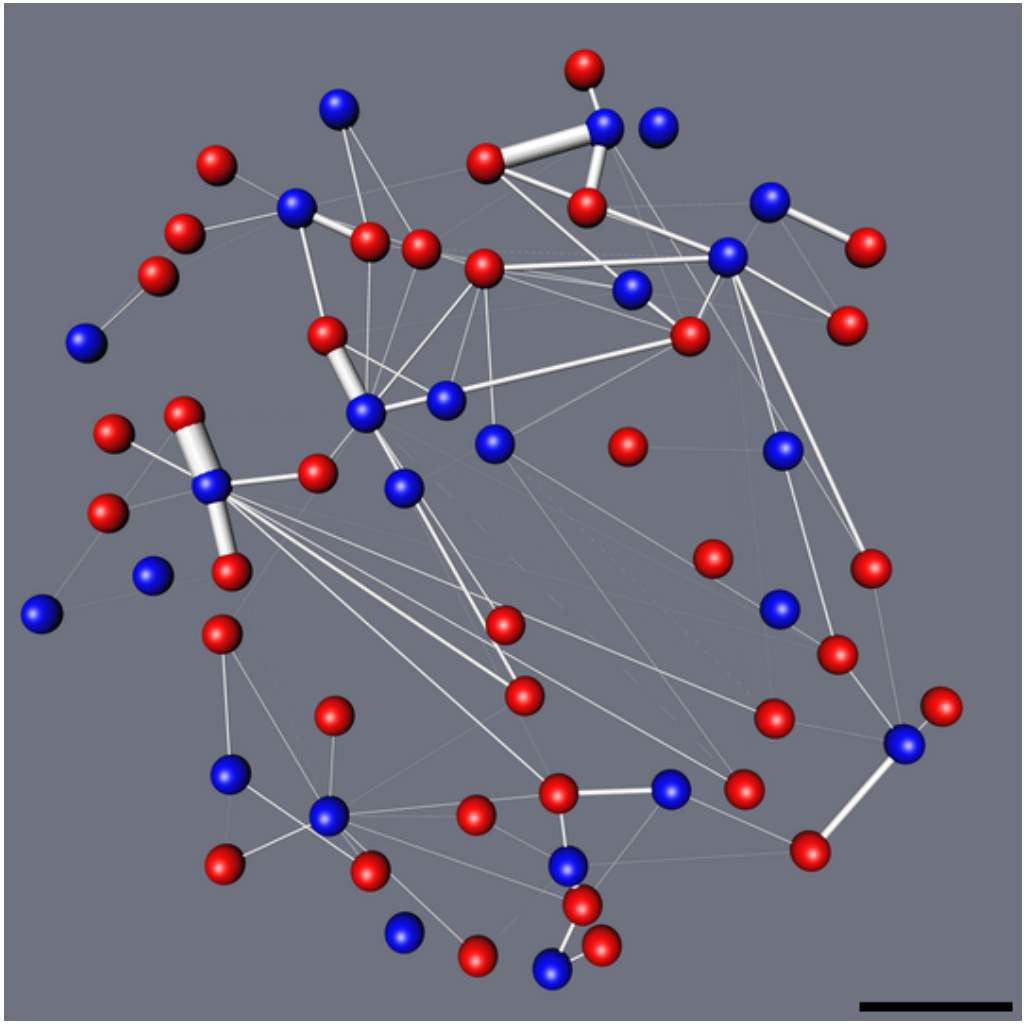
Drainage Volume

Preferentiel couplings between preferentiel territories



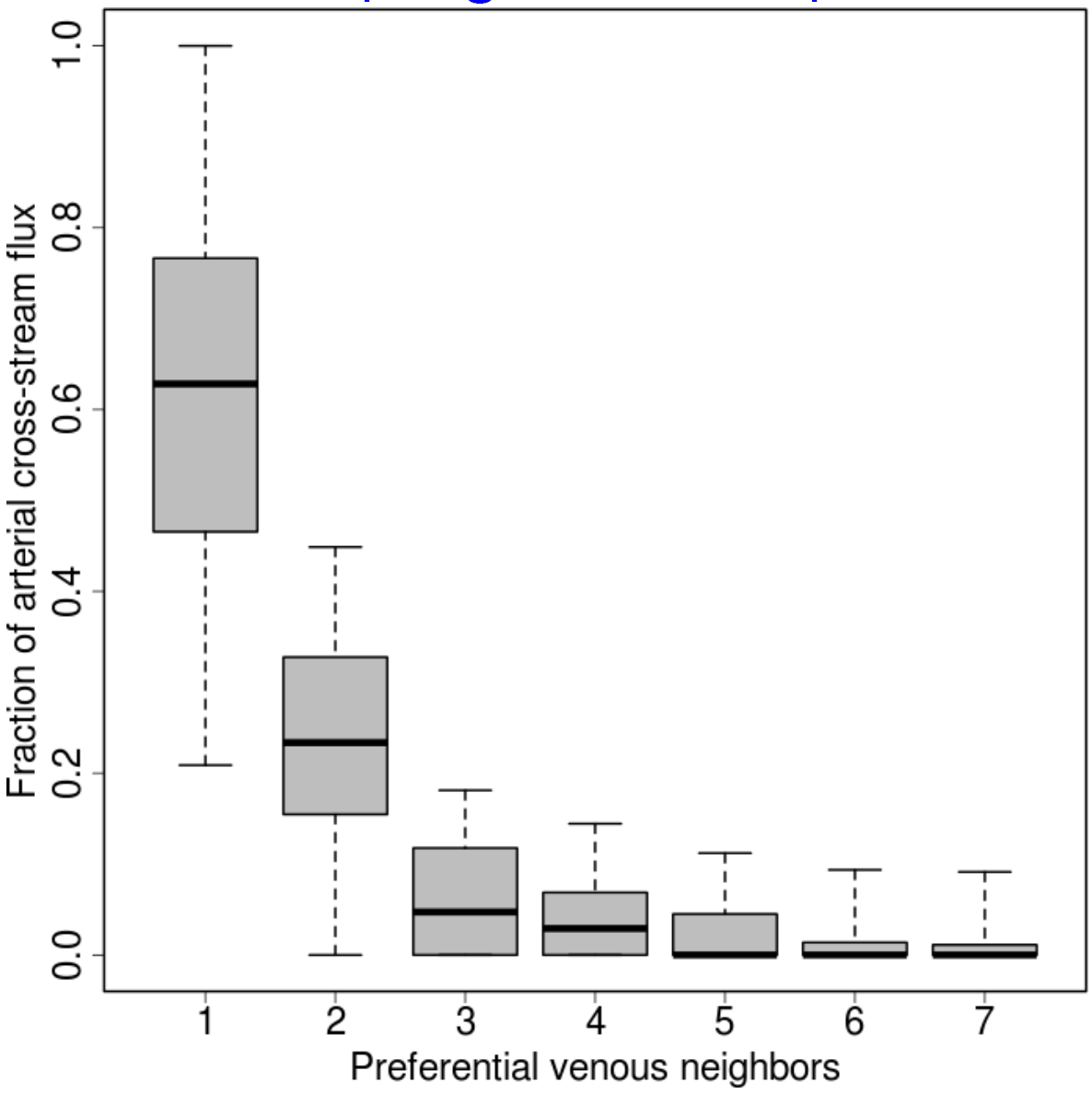
$A \cap V$ Volume

Preferentiel couplings between preferentiel territories



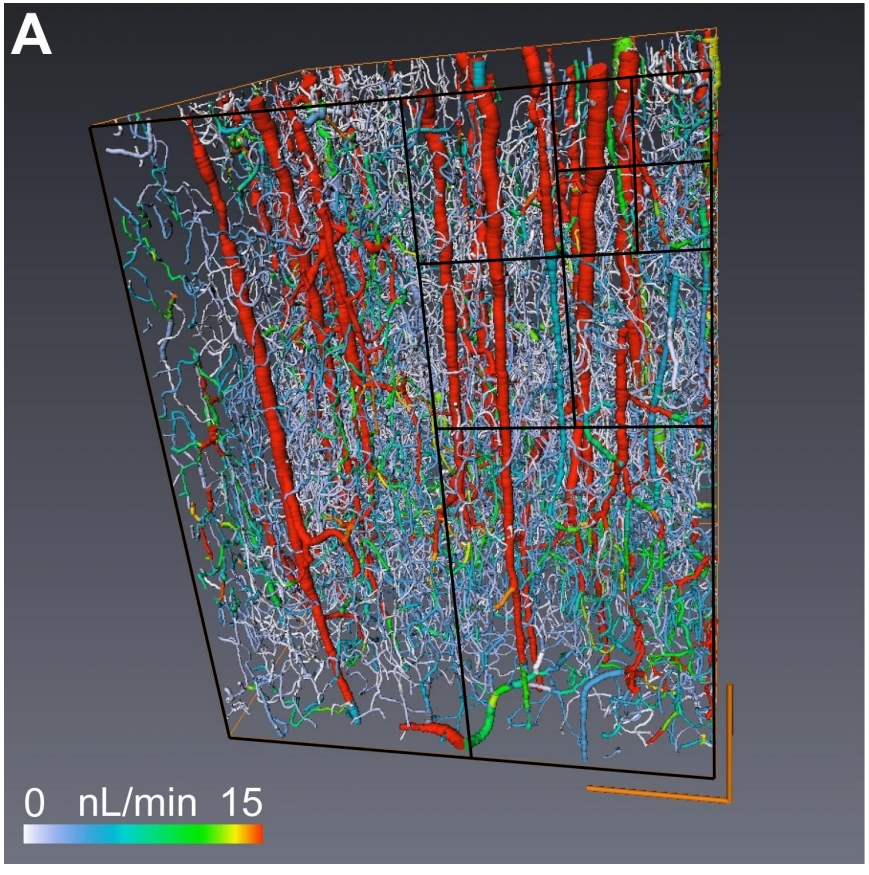
Perfusion⇒Drainage flux

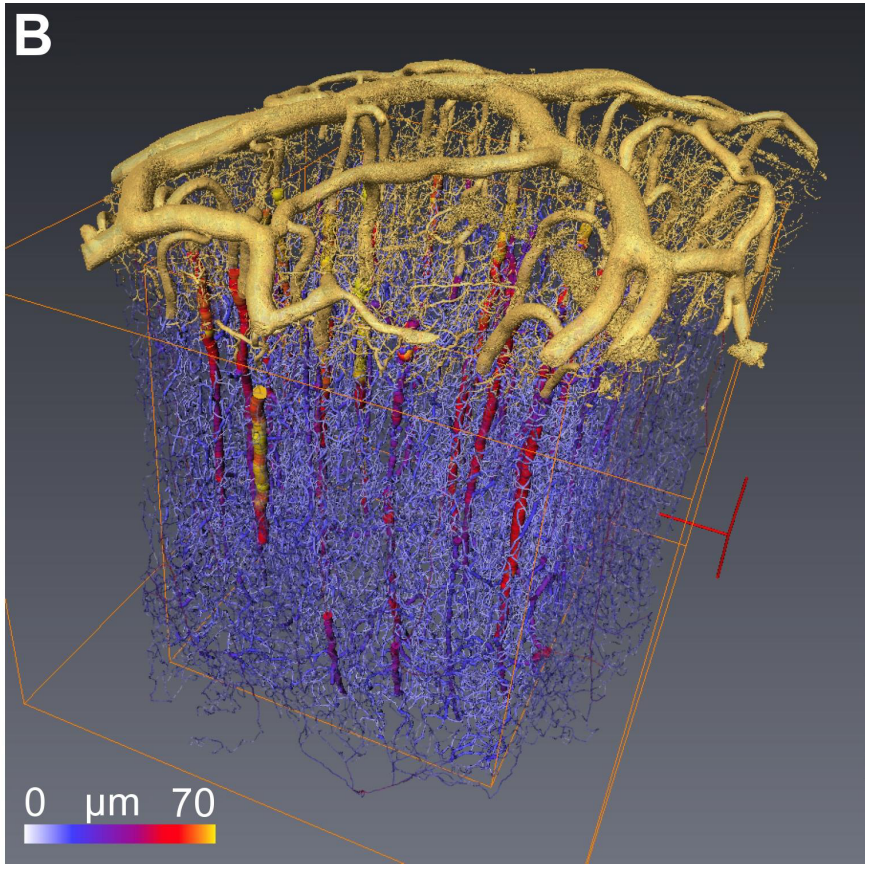
Preferentiel couplings between preferentiel territories



Cerebral blood flow normalization

Guibert et al. (2013) *JCBFM*





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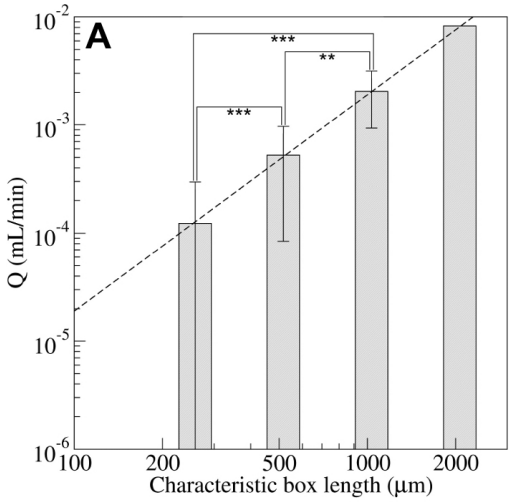
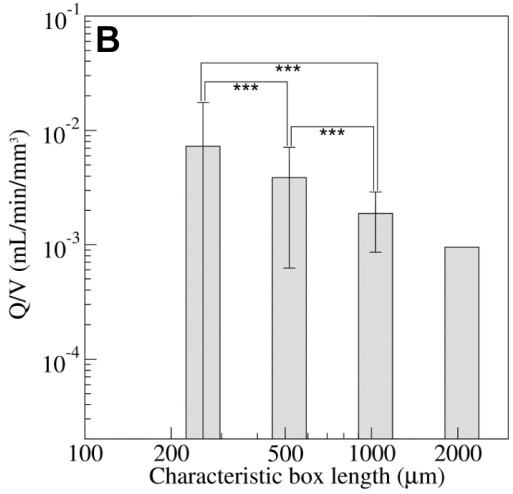
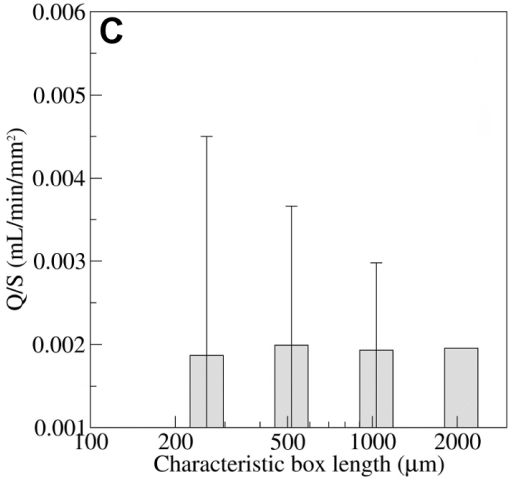
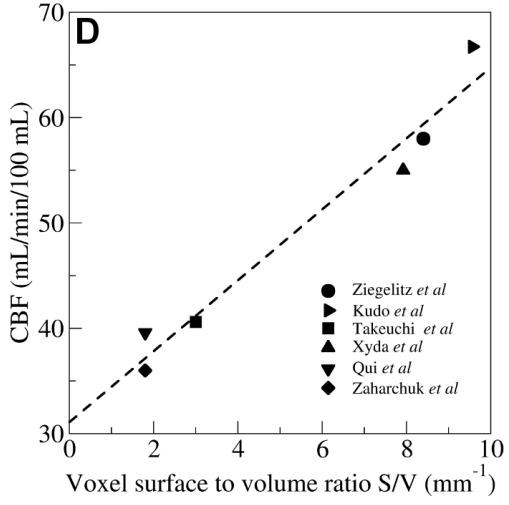
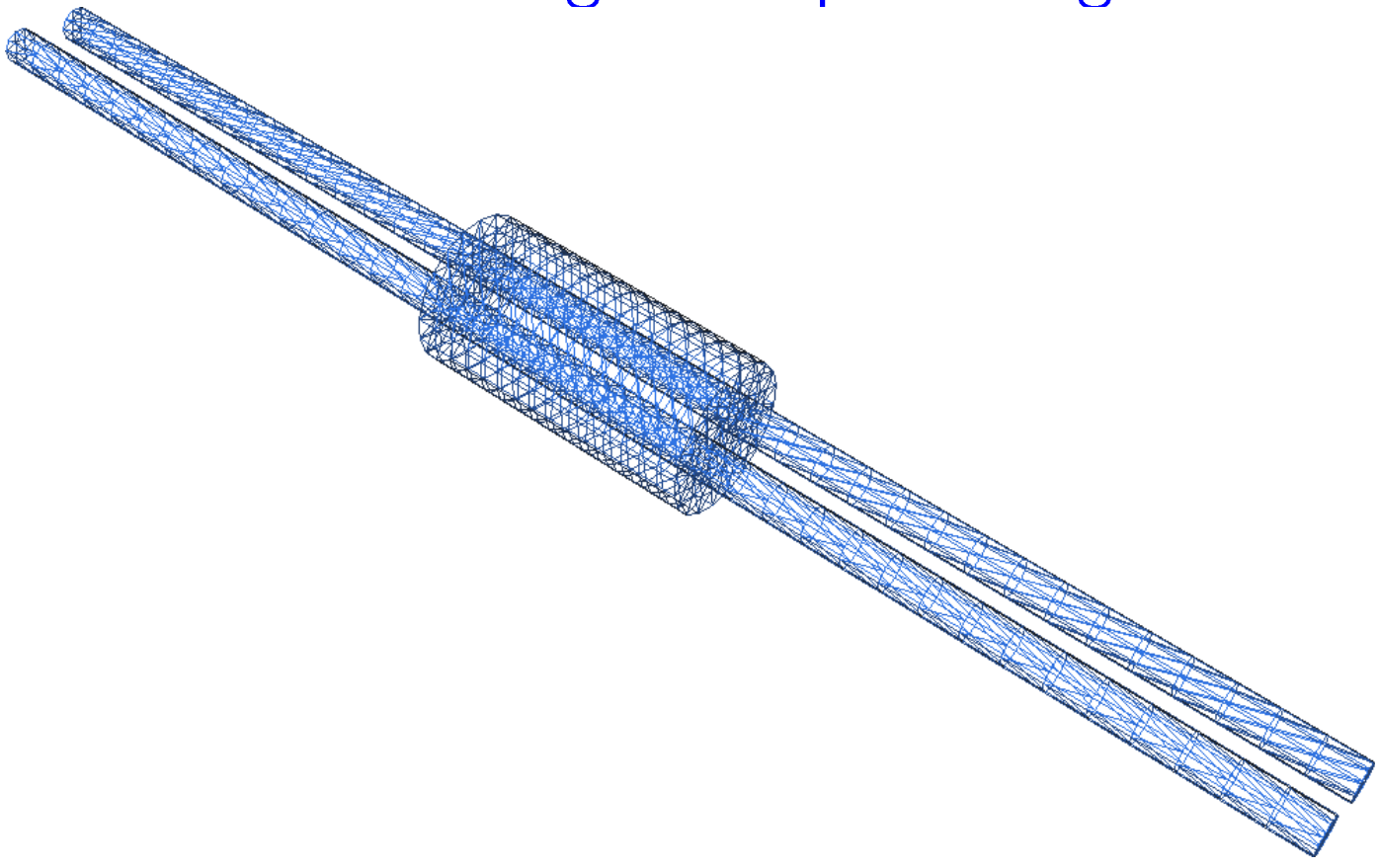




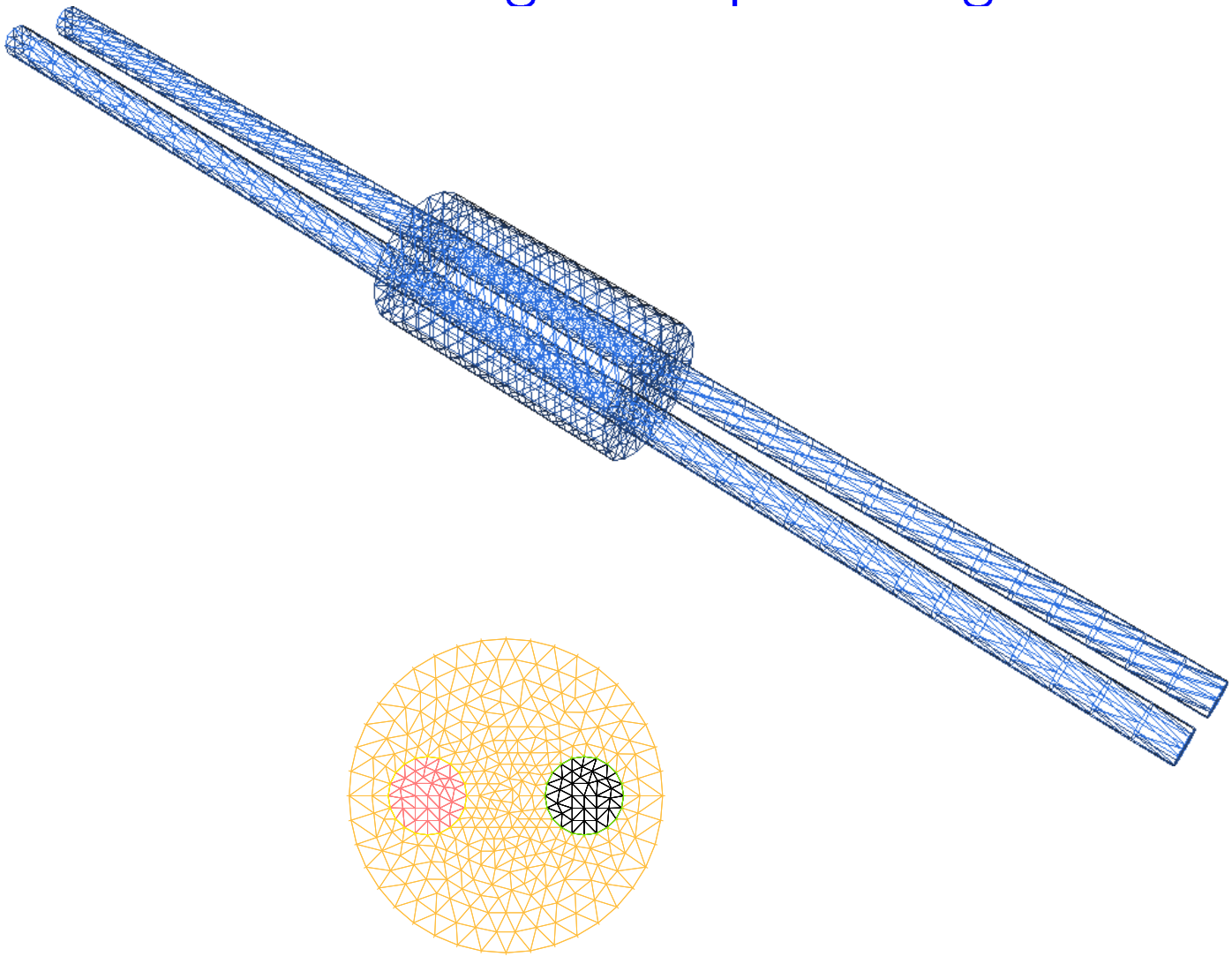




Transfer modelling in simple configurations

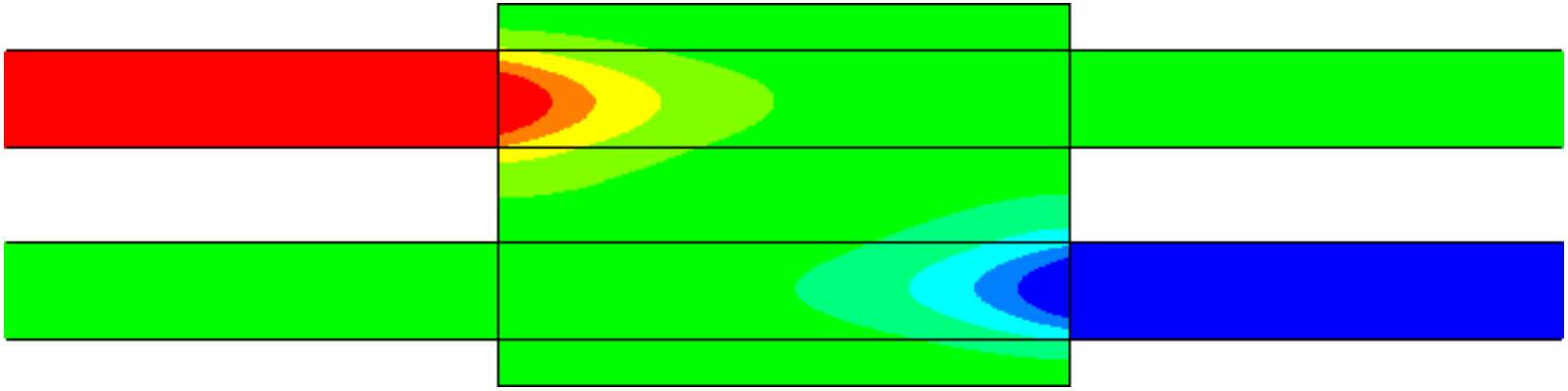


Transfer modelling in simple configurations



Transfer modelling in simple configurations

Pierre et al (2014) *JCP*



Conclusion

▷ New tools for a deep investigation of intra-cerebral flows (imaging + vectorization)

▷ Drastic numerical simplification for a network model formulation

▷ Pressure/Hematocrit/Flux fields computation over large volume of grey matter

▷ Apparent viscosity much more important than phase separation for blood fluxes

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▷ Neirest neihgbourg preferential couplings A $\Rightarrow$ V : 80% from first 2 V

References

▷ L. Risser, F. Plouraboué, A. Steyer, P. Cloetens, G. Le Duc & C. Fonta, From homogeneous to fractal normal and tumorous micro-vascular networks in the brain, **27**, 293-303. *JCBFM*, 2007.

▷ L. Risser, F. Plouraboué & X. Descombes, 3D Vessel Network Extraction from High Resolution X-Ray Images by Tensor Voting, *IEEE transaction in medical imaging.*, **27**, 5, 674-687, 2007.

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▷ C. Pierre, J. Bouyssier, F. de Gournay , F. Plouraboué, Numerical computation of 3D heat transfer in complex parallel heat exchangers using generalized Graetz modes, *JCP*, **268**, 84-105, 2014.

Alternatives ?

Conservation laws

$$\sum_{i \in J} Q_i = 0$$

$$\sum_{i \in J} H_i Q_i = 0$$

are they enough for closing the problem ?

Apparently no because :

(a) They do seem to provide enough relations

(b) There is a trivial solution which fulfills all convervation laws $H_i = cte$

Conservation law formulation

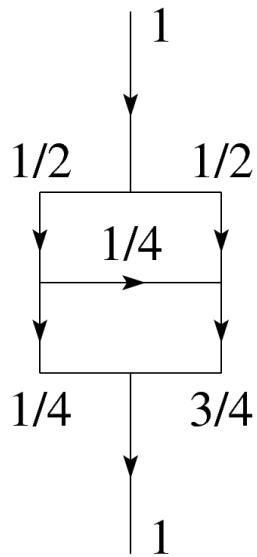
(a) Formulation

Let us consider an *hematocrit potentiel* $\Delta H_N = H$
Unknowns : 7 $H \longrightarrow 6$ H_N

Conservation law are written inside inner nodes : 4 + 2 CL
So that the problem is closed !

Exemple : $A\,\mathbf{H_N} = b$

$$A = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 & 0 \\ 1 & -2 & 1/2 & 1/2 & 0 & 0 \\ 0 & 1/2 & -1 & 1/4 & 1/4 & 0 \\ 0 & 1/2 & 1/4 & -3/2 & 3/4 & 0 \\ 0 & 0 & 1/4 & 3/4 & -2 & 1 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix} \text{ and } b = \begin{pmatrix} 0.45 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0.45 \end{pmatrix}$$



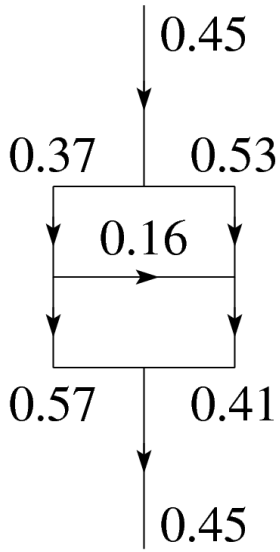
Several solutions

(b) Several solutions are possibles since $Ker\, A = \mathbf{1} = H_N^{(0)}$

Any linear combinaison $\mathbf{H_N} + \lambda H_N^{(0)}$ is solution

This is not a problem since $\Delta \mathbf{H_N} = \mathbf{H}$ is unique !

Exemple : fulfills conservation laws and $\mathbf{H}$ is not spatiallly homogeneous !



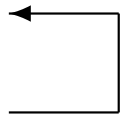
Coupling Pressure and Hematocrit

- Effective viscosity model

$$\sum_{i \in J} Q_i = 0$$

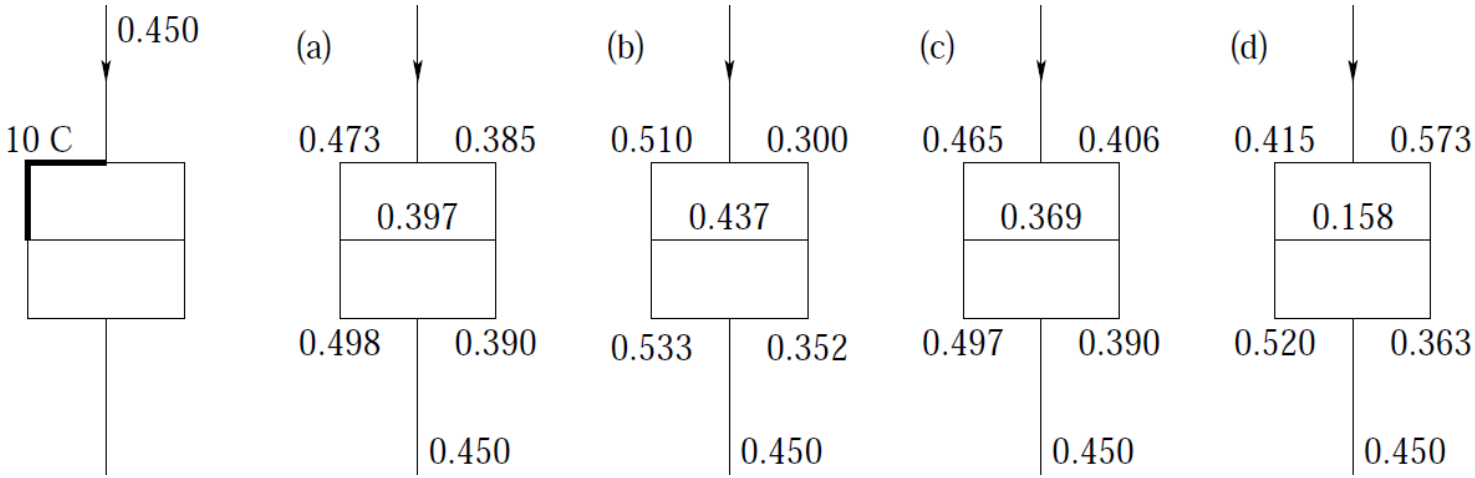
- Coupled linear systems

$$A_1 \, \mathbf{p}_{(k)} = b_1$$
$$A_2 \, \mathbf{h}_{(k)} = b_2$$



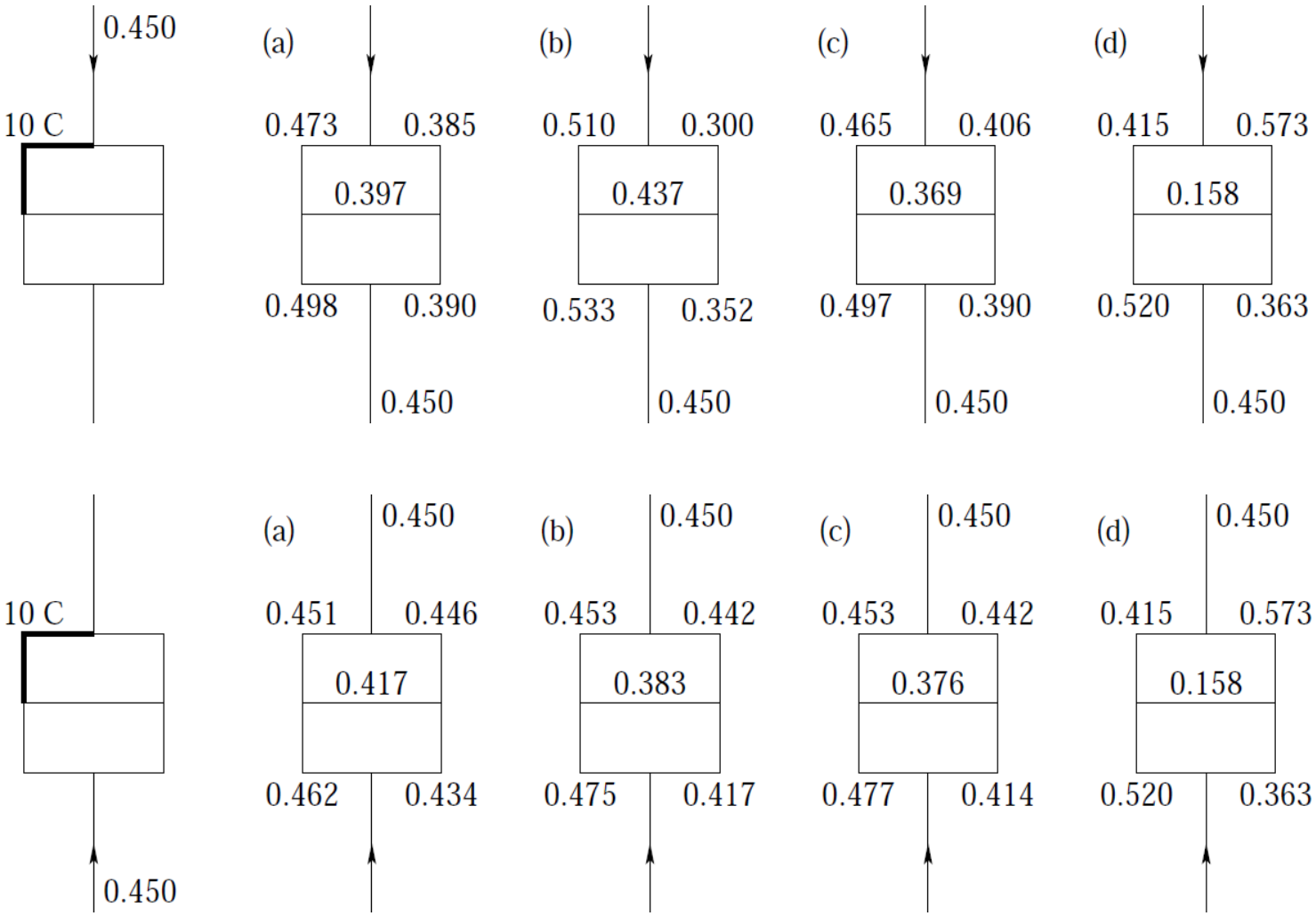
until convergence

- Compararison with prescribed viscosity models (Pries et al. (1990) Circ. Res.)



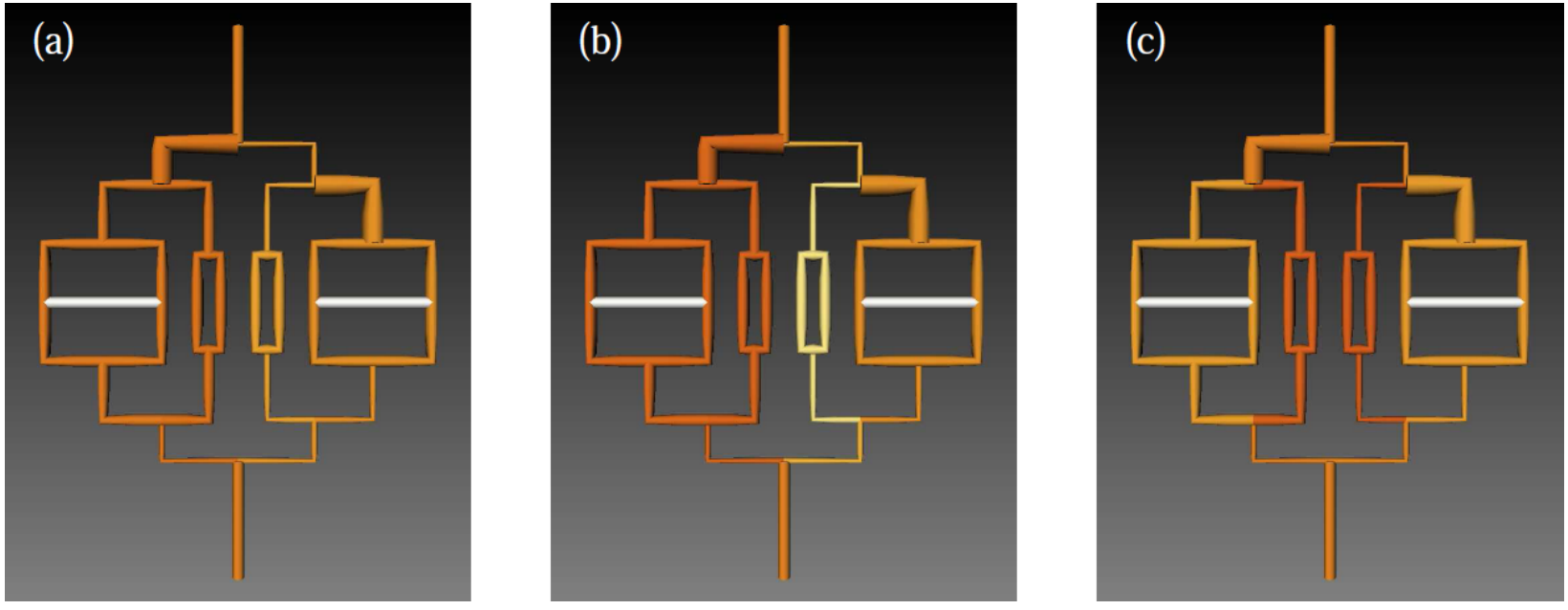
(a) Dellimore et al. (1983), (b) Fenton et al. (1985) et (c) Pries et al. (1989)

Properties of the obtained solutions



(a) Dellimore et al. (1983), (b) Fenton et al. (1985) et (c) Pries et al. (1989)

More complex networks



Viscosity laws of Pries et al. (1990) and various phase separation models :
(a) Dellimore et al. (1983), (b) Pries et al. (1989) and (c) our network approach