

Effect of matrix diffusion on anomalous transport and reactions in cerebral microcirculation

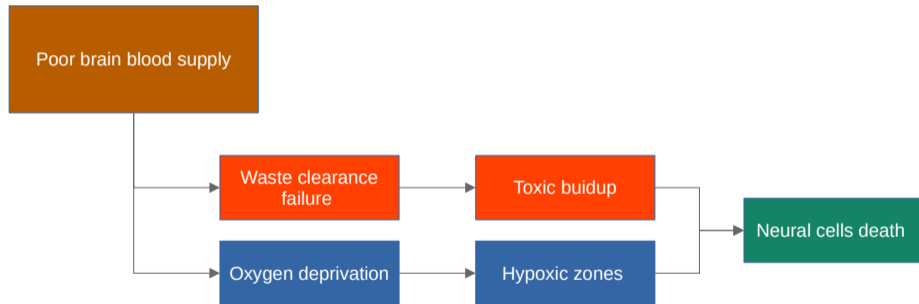
Dimitri Fialkovsky, Sylvie Lorthois, Tanguy Le Borgne

Institut de mécanique des fluides de Toulouse, Géosciences Rennes

May 20, 2026

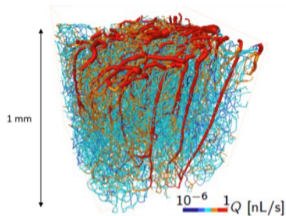
Alzheimer's disease and vascular health

Two pathways from vascular dysregulation supply to cell death :

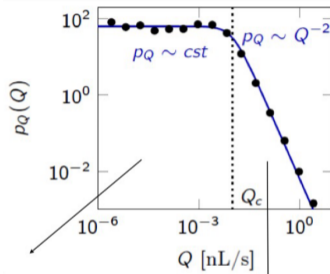


Vascular architecture and hypoxic regions¹

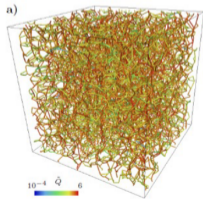
a. Flow in microvascular network



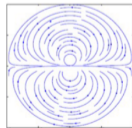
b. Flow rate distribution



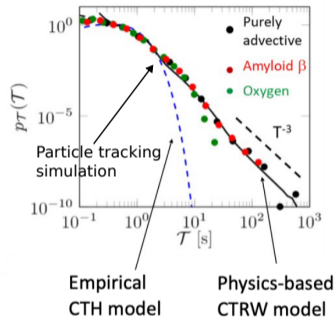
c. Flow in random network



d. dipole flow



e. Travel time distribution



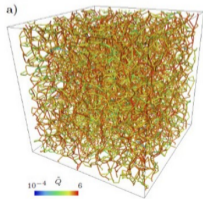
¹Goirand, F. et al., 2021, *Nature communications*.

Vascular architecture and hypoxic regions²

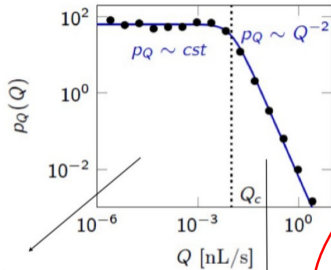
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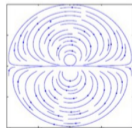
c. Flow in random network



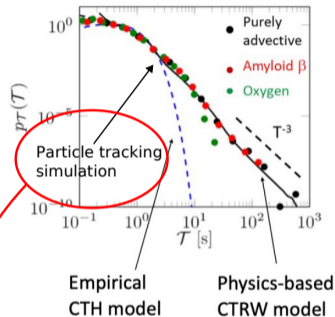
b. Flow rate distribution



d. dipole flow



e. Travel time distribution



- Doesn't account for extravascular diffusion
- Coupled with a first order kinetic model

²Goirand, F. et al., 2021, *Nature communications*.

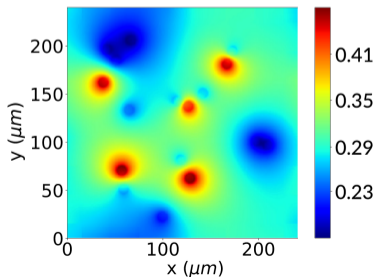
What is the influence of tissue diffusion on travel times ?

Under the hypothesis of a 1st order metabolism, what is the extravascular diffusion's impact on travel time distribution ?

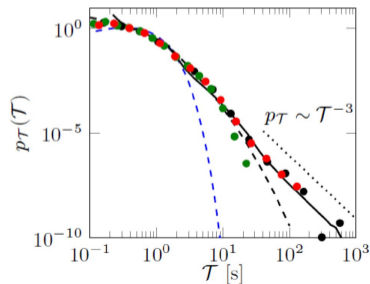
Key ideas :

- $\tau_{D_p} \ll \tau_{adv} \Rightarrow$ 1st order metabolism
- 1st order metabolism \Rightarrow Equivalent travel time distribution through Laplace transform method

Extravascular concentration field of a synthetic capillary bed's cutting plane ϕ/ϕ_{max}



Travel time distribution for simplified transport model

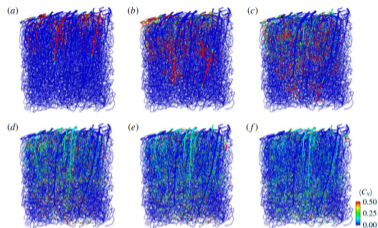


1. Coupled transport model accounting for extravascular diffusion and reaction
2. Asymptotic validation of the coupled diffusive model
3. Extravascular diffusion impact on travel times inside a network

Coupled transport model accounting for extravascular diffusion and reaction

Coupled diffusive model

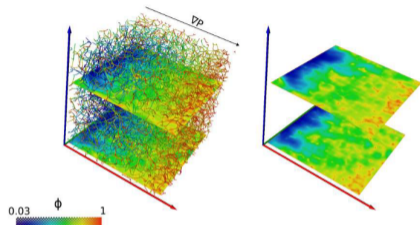
Intravascular transport (in Λ)³:



$$U_{eff} \frac{\partial \langle C_V \rangle}{\partial s} - D_{eff} \frac{\partial^2 \langle C_V \rangle}{\partial s^2} + \frac{q(s)}{\pi R(s)^2} = 0$$

$$\text{with } q(s) = K_{eff} (\langle C_V \rangle - \bar{\phi})$$

Extravascular transport (in Ω)⁴:



$$D_p \nabla^2 \phi = \frac{M}{\phi_0} \phi \quad \text{in } \Omega_\sigma$$
$$- \mathbf{n} (D_p \nabla \phi) = \frac{q(s)}{2\pi R(s)} \quad \text{on } \Omega_\beta$$

³Berg, M. et al., 2020, *Journal of Fluid Mechanics*.

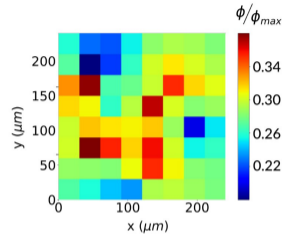
⁴Pastor-Alonso, D. et al., 2024, *PLOS Computational Biology*.

Coupled diffusive model : numerical system ⁵

Green function method : **Semi-analytical** vascular contribution
and **finite volume** boundary contribution

$$\begin{aligned}\phi &= \int_{\partial\Omega_\beta} (\phi \nabla G \cdot \mathbf{n} - G \nabla \phi \cdot \mathbf{n}) dl + \int_{\partial\Omega} (\phi \nabla G \cdot \mathbf{n} - G \nabla \phi \cdot \mathbf{n}) dl \\ &= r + s \quad \text{with} \quad \sum_{m \in \mathcal{N}^k} (\tilde{s}_m - \tilde{s}_k + J(r_m, r_k)) = 0 \quad \text{and} \quad r_k = \sum_{j \in E(\hat{V}_k)} P_j\end{aligned}$$

$$\begin{cases} A \cdot s + B \cdot q = b_{\partial\Omega} & \rightarrow \text{extravascular transport} \\ D \cdot s + E \cdot q + F \cdot C_v = 0 & \rightarrow \text{vessel-tissue exchange} \\ H \cdot q + I \cdot C_v = b_{\partial\Omega_\beta} & \rightarrow \text{intravascular transport} \end{cases}$$

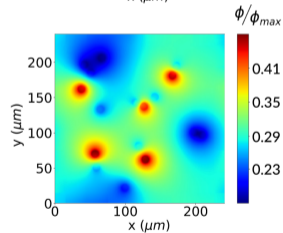
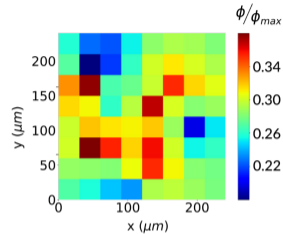


Coupled diffusive model : numerical system ⁶

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$$\begin{aligned}\phi &= \int_{\partial\Omega_\beta} (\phi \nabla G \cdot \mathbf{n} - G \nabla \phi \cdot \mathbf{n}) dl + \int_{\partial\Omega} (\phi \nabla G \cdot \mathbf{n} - G \nabla \phi \cdot \mathbf{n}) dl \\ &= r + s \quad \text{with} \quad \sum_{m \in \mathcal{N}^k} (\tilde{s}_m - \tilde{s}_k + J(r_m, r_k)) = 0 \quad \text{and} \quad r_k = \sum_{j \in E(\hat{V}_k)} P_j\end{aligned}$$

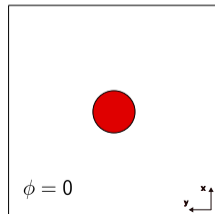
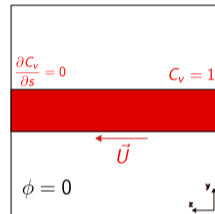
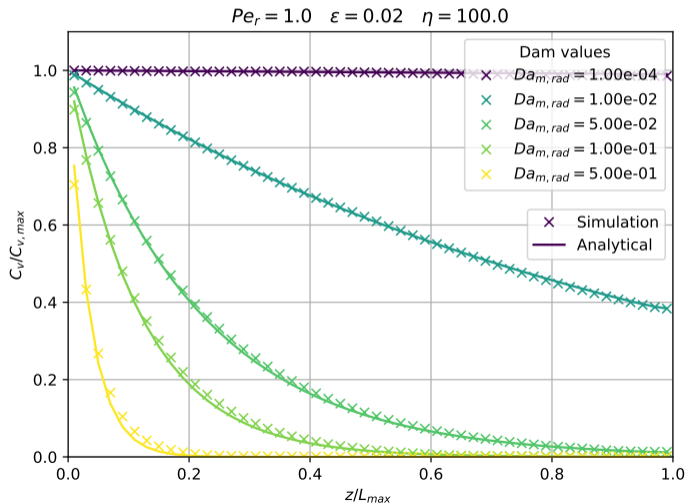
$$\begin{cases} A \cdot s + B \cdot q = b_{\partial\Omega} & \rightarrow \text{extravascular transport} \\ D \cdot s + E \cdot q + F \cdot C_v = 0 & \rightarrow \text{vessel-tissue exchange} \\ H \cdot q + I \cdot C_v = b_{\partial\Omega_\beta} & \rightarrow \text{intravascular transport} \end{cases}$$



Asymptotic validation of the coupled diffusive model

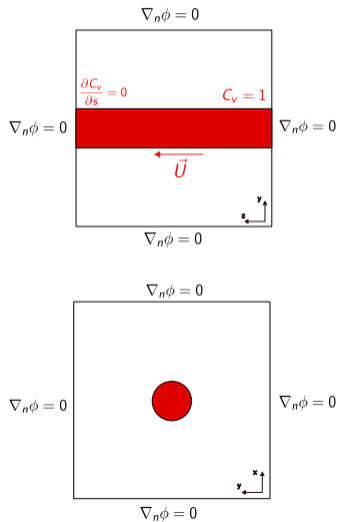
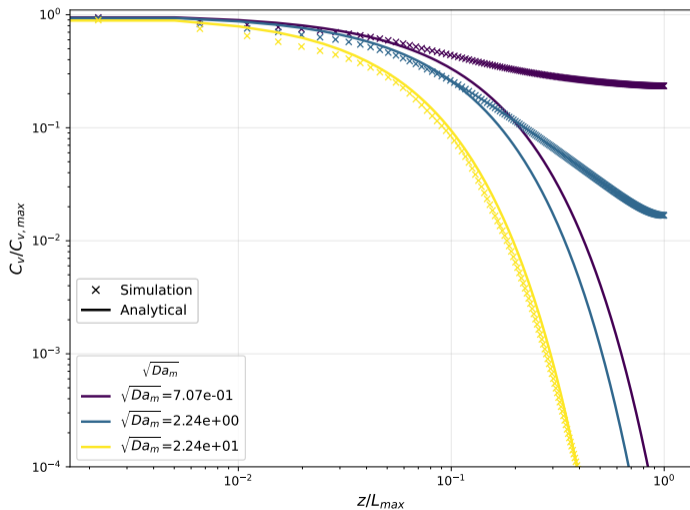
Uncoupled case

Analytical solution for uncoupled case :



Coupled case

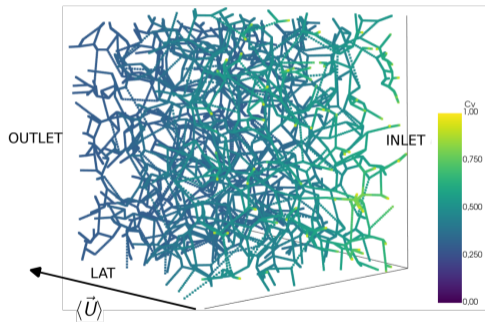
Analytical solution for $\sqrt{Da_m} \gg 1$:



Extravascular diffusion impact on travel times inside a network

Extravascular diffusion impact on travel times inside a network

Tracer transport simulation in a synthetic capillary network



Simplified model (no tissular diffusion)

$$C_{out} = C_{in} e^{-k_{o2} \frac{l_j}{U_j}}$$

Coupled diffusive model

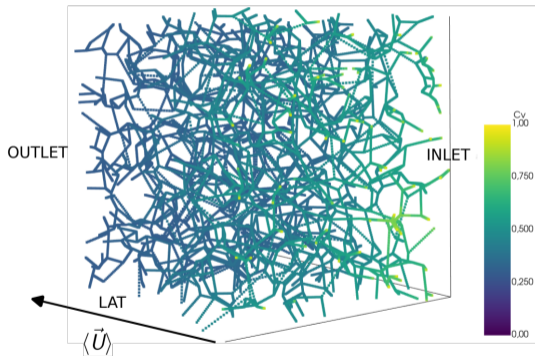
$$U_{eff} \frac{\partial \langle C_v \rangle}{\partial s} - D_{eff} \frac{\partial^2 \langle C_v \rangle}{\partial s^2} + \frac{K_{eff}}{\pi R(s)^2} (\langle C_v \rangle - \bar{\phi}) = 0$$

$$D_p \nabla^2 \phi = \frac{M}{\phi_0} \phi$$

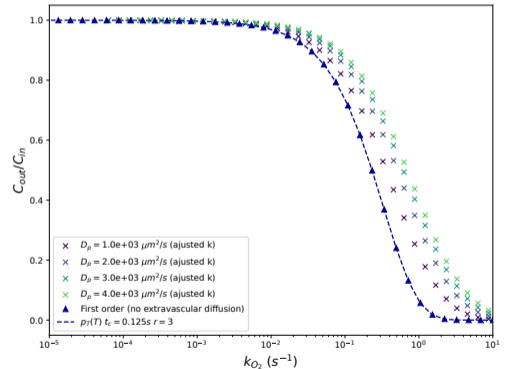
$$-\mathbf{n} (D_p \nabla \phi) = \frac{K_{eff}}{2\pi R(s)} (\langle C_v \rangle - \bar{\phi})$$

Extravascular diffusion impact on travel times inside a network

Tracer transport simulation in a synthetic capillary network



Average outlet concentration vs metabolic speed



Extravascular diffusion impact on travel times inside a network

1st order decay equivalence ($\tau_{D_p} \ll \tau_{adv}$)

$$\frac{C_{out}}{C_{in}} = \int_0^{\infty} p_T(T) e^{-k_{O_2} T} dT$$

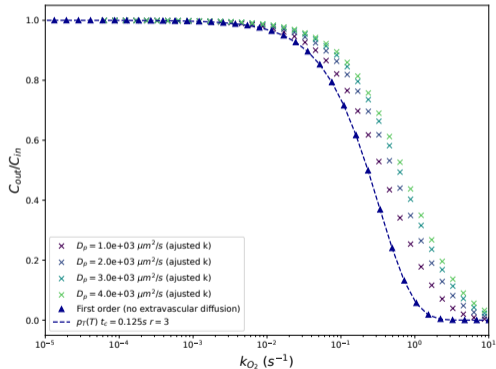
Asymptotic power law determination

$$\mathcal{L}[p_T(T)](k_{O_2}) = 1 - c_{\beta} k_{O_2}^{\beta} + \sum_{i=1}^{\alpha} c_i k_{O_2}^i + o(k_{O_2}^{\beta}),$$

$$\alpha < \beta < \alpha + 1$$

$$p_T(T) \propto T^{-\beta-1}, \quad T \rightarrow +\infty$$

Average outlet concentration vs metabolic speed

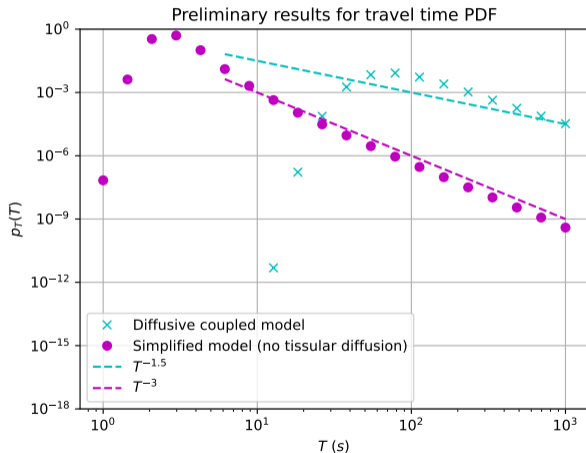


Extravascular diffusion impact on travel times inside a network

1st order decay equivalence

($\tau_{D_p} \ll \tau_{adv}$)

$$\frac{C_{out}}{C_{in}} = \int_0^{\infty} p_T(T) e^{-k_{O_2} T} dT$$



Contributions:

- Validated 3D coupled diffusive model accounting for extravascular diffusion and reaction
- First-order equivalence combined with an asymptotic power law method to quantify the impact of extravascular diffusion on travel times

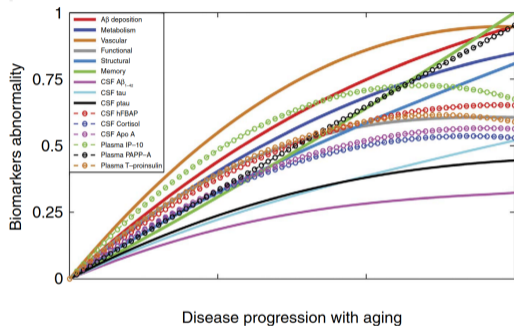
Perspectives:

- Ongoing inverse problem resolution
- Extension to a dipolar flow configuration

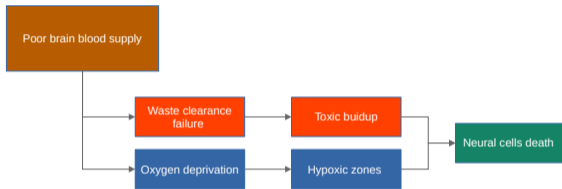
Thank you for your attention



Alzheimer's disease and vascular health

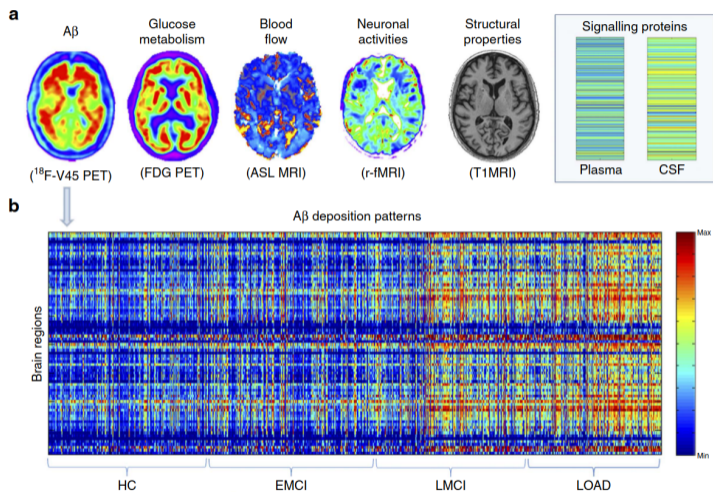


Changes in abnormalities of various biomarkers during Alzheimer's disease progress.⁸

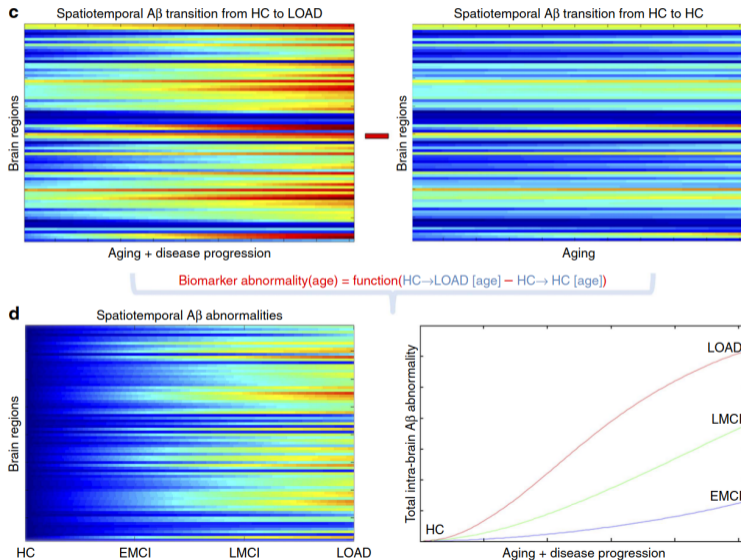


Two pathways from poor brain blood supply to cell death

⁸Iturria-Medina, Y. et al., 2016, *Nature communications*.

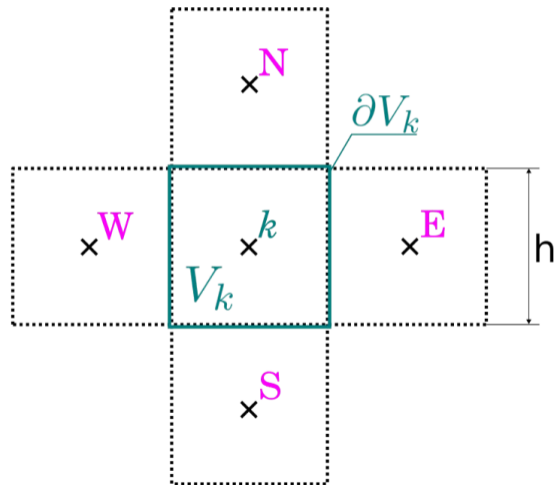


Caption



Problème numérique

Discrétisation du domaine par un maillage cartésien



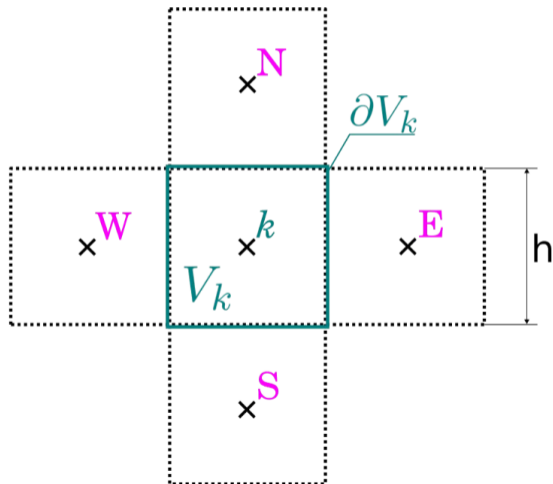
Décomposition des termes

$$r = \sum_{k \in \mathcal{F}} r_k \quad \text{avec } r_k(\mathbf{x}) = 0 \quad \forall \mathbf{x} \notin V_k$$

$$s = \sum_{k \in \mathcal{F}} s_k \quad \text{avec } s_k(\mathbf{x}) = 0 \quad \forall \mathbf{x} \notin V_k$$

Problème numérique

Discrétisation du domaine par un maillage cartésien



- Résolution du terme lent (sans métab.):

$$h_{\Omega} \sum_{m \in \mathcal{N}^k} (\tilde{s}_m - \tilde{s}_k + J_{k,m}) = 0$$

$$J_{k,m} = f(r_k, r_m)$$

avec $\mathcal{N}^k = \{N, S, E, W\}$

- Résolution du terme rapide :

$$r_k = \sum_{j \in E(\hat{V}_k)} P_j$$

avec \hat{V}_k un voisinage de V_k de taille $n \times n$

P_j est une fonction semi-analytique du flux des sources \mathbf{q}_j :

$$\mathbf{q}_j = K_{eff} \left(\langle C_v \rangle_j - \bar{\phi}_j \right)$$

avec

$$\langle C_v \rangle_j = \frac{1}{\pi R_j^2} \iint_{\Omega_{\beta,j}} C_v(r, \theta) dS$$

$$\bar{\phi}_j = \frac{1}{2\pi R_j} \int_{\partial\Omega_{\beta,j}} \phi(R_j, \theta) dl$$

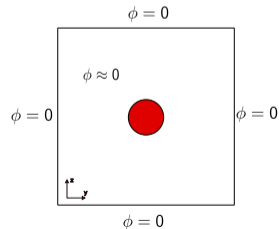
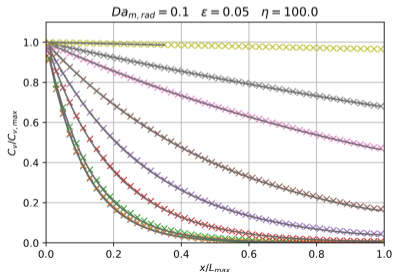
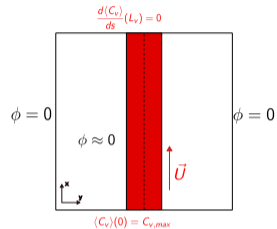
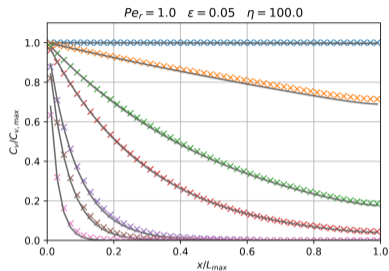
L'estimation de $\bar{\phi}_j$ et de $\langle C_v \rangle_j$ demande une reconstruction du champ de concentration en tout point par interpolation

Metabolic consumption adds a source term to the mass conservation equation.

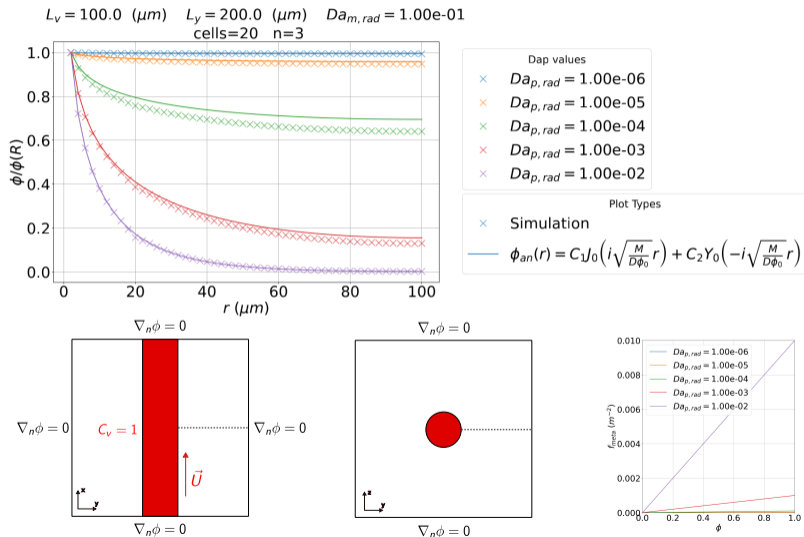
$$h_{\Omega} \sum_{m \in \mathcal{N}^k} (\tilde{s}_m - \tilde{s}_k + J_{k,m}) = \frac{M}{D} (\tilde{s}_k + \tilde{r}_k)$$
$$h_{\Omega} \sum_{m \in \mathcal{N}^k} (\tilde{s}_m - \tilde{s}_k + J_{k,m}) = \frac{M}{D} \int_{V_k} \frac{r + s_k}{r + s_k + \phi_0} dS$$

This may add a step to the numerical solution or simply modify the overall matrix.

Vaisseau simple - concentration intravasculaire - avec échange

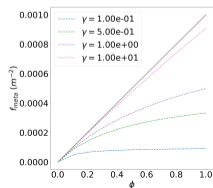
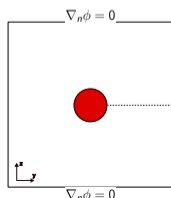
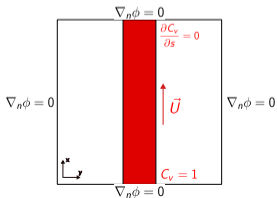
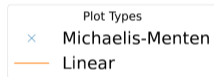
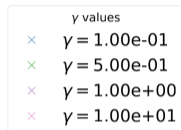
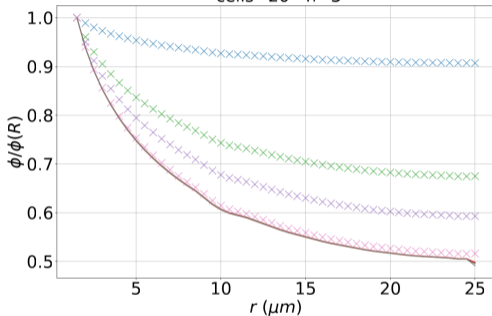


Vaisseau simple - concentration extravasculaire - métabolisme linéaire



Vaisseau simple - concentration extravasculaire - métabolisme non linéaire

$Da_{m,rad} = 1.00e+00$ $Da_{p,rad} = 1.00e-03$ $Pe_{rad} = 5.00e+01$
 cells=20 n=3



Régime *well-mixed*⁹:

$$\epsilon Pe \ll 1$$

$$\epsilon Dam \ll 1$$

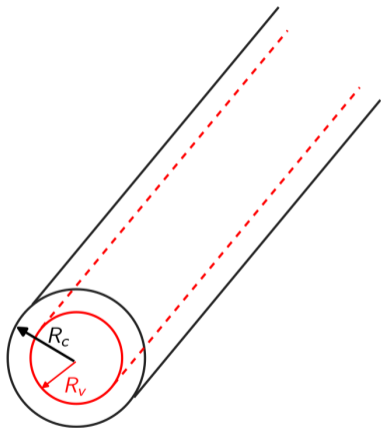
Négligence de la diffusion axiale vis à vis de l'advection :

$$Pe \gg 1$$

⁹Berg, M. et al., 2020, *Journal of Fluid Mechanics*.

Caractérisation du régime du modèle simplifié

Bilan sur un vaisseau :



Flux diffusifs externes et latéraux négligeables vis à vis du métabolisme :

$$\frac{ML_c^2}{D\phi_0} \gg 1$$

$$\frac{M(R_c^2 - R_v^2)}{D\phi_0} \frac{\delta r}{R_c} \gg 1$$

On retrouve la formule de cinétique du 1er ordre avec :

$$k = \frac{8D_v}{R_v^2 + 4\frac{D_v R_v}{K_m}} \quad \& \quad k_{0_2} = \frac{M(R_c^2 - R_v^2)}{\phi_0 R_v^2}$$

Caractérisation du régime du modèle simplifié

Récapitulatif :

$$\text{Well-Mixed} \Rightarrow \begin{cases} \epsilon Pe \ll 1 \\ \epsilon Dam \ll 1 \end{cases}$$

$$\tau_{D_{intra}} \gg \tau_{adv} \Rightarrow Pe \gg 1$$

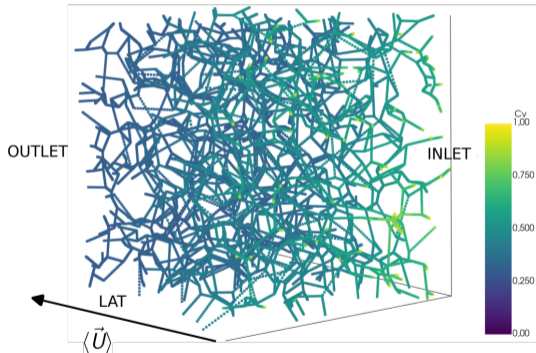
$$\tau_{D_{extra}} \gg \tau_{meta} \Rightarrow \begin{cases} \frac{ML_c^2}{D\phi_0} \gg 1 \\ \frac{M(R_c^2 - R_v^2)}{D\phi_0} \frac{\delta r}{R_c} \gg 1 \end{cases}$$

$$\text{Meta. lin.} \Rightarrow \gamma \gg 1$$

$$\tau_{meta} \gg \tau_{membrane} \Rightarrow 1 \gg \frac{M(R_c^2 - R_v^2)}{4\phi_0 K_m R_v}$$

Extravascular diffusion impact on travel times inside a network

Tracer transport simulation in a synthetic capillary network



Boundary conditions

$$\text{OUTLET} : \frac{dC_v}{ds} = 0 \quad \nabla_n \phi = 0$$

$$\text{INLET} : C_v = 1 \quad \nabla_n \phi = 0$$

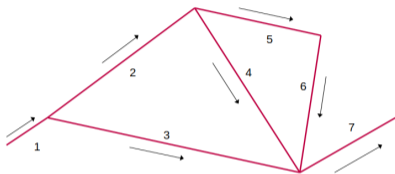
$$\text{LAT} : \frac{dC_v}{ds} = 0 \quad \nabla_n \phi = 0 \quad Q = 0$$

$$\frac{C_{out}}{C_{in}} = f(k_{O_2}) \quad \text{for } k_{reac} \in [10^{-5}, 10^0] \quad (s^{-1})$$

$$k_{O_2} = \frac{M (R_c^2 - R_v^2)}{\phi_0 R_v^2} \rightarrow \text{first order equivalence}$$

Etude comparative

Exemple de réseau :



$$\mathcal{N}_7^{am} = \{3, 4, 6\}$$

Résolution commune de débit :

$$U_{\alpha\beta} = \frac{\pi d_{\alpha\beta}^4}{32\mu l_{\alpha\beta}} (P_\beta - P_\alpha)$$

Modèle de décroissance exponentielle

$$C_i = \frac{1}{\sum Q_j} \sum_{j \in \mathcal{N}_i^{am}} Q_j C_j e^{-k \frac{l_j}{U_j}}$$

Modèle de couplage vaisseaux/tissus

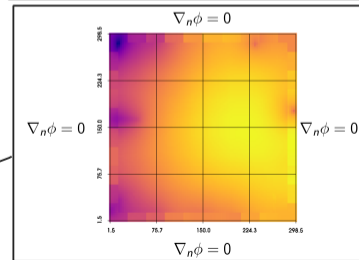
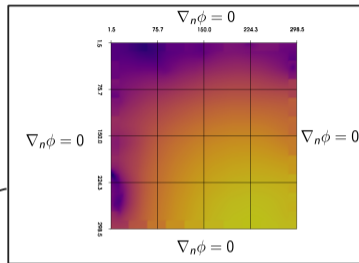
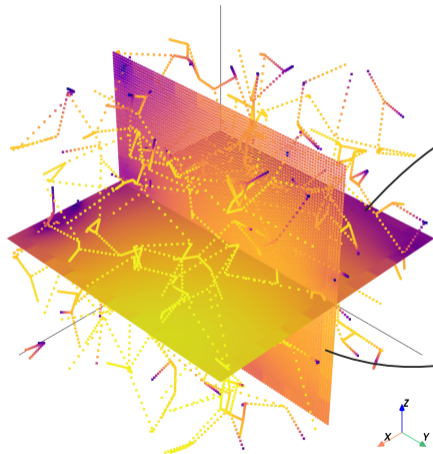
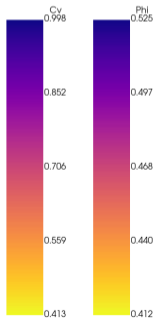
$$U_{eff} \frac{\partial \langle C_v \rangle}{\partial s} - D_{eff} \frac{\partial^2 \langle C_v \rangle}{\partial s^2} + K_{eff} (\langle C_v \rangle - \bar{\phi}) = 0$$

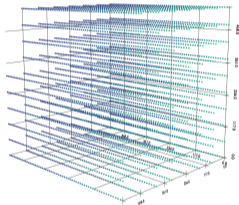
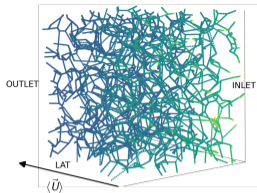
$$D_p \nabla^2 \phi = \frac{M}{\phi_0} \phi$$

$$- \mathbf{n} (D_p \nabla \phi) = \frac{K_{eff} R(s)}{2} (\langle C_v \rangle - \bar{\phi})$$

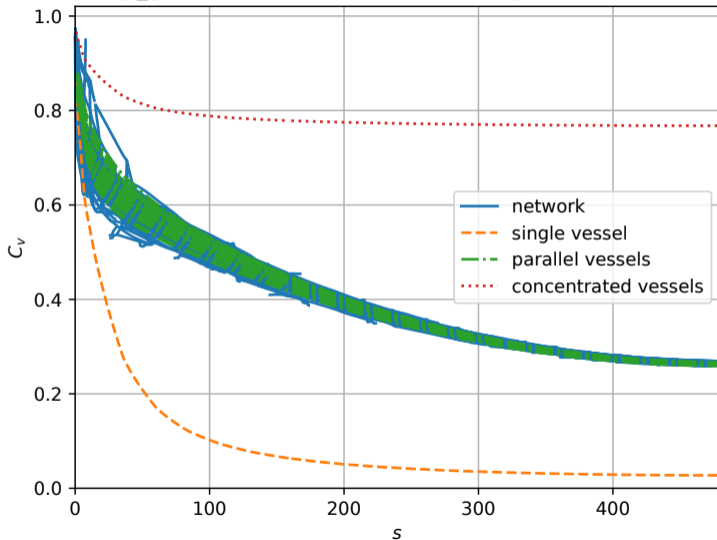
Réseau synthétique Smith





Pe_rad=1.00e+01 Dam_rad=5.00e-02
Dap_rad=8.00e-03 eta=1.00e+00 gamma=1.00e+00





Pe_global=4.00e+01 Dam_global=5.07e+02
Dap_global=3.07e+03 eta=3.75e-01 gamma=1.00e-01



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