

Upscaling mass transfer in brain capillary networks

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Hybrid continuous/network models for large scale simulation

Simulating Mass Transfer in the brain: a multi-scale problem

- Multi-scale problem (arterio-venous, capillary, parenchyma)
- Continuous representation of Parenchyma (Nicholson 2001, Kojic 2017, Holter 2017)
- Still need to explicitly resolve the vessels
- Upscale the capillary bed, including vessels and parenchyma
- Coupling with explicit arterio-venous tree is different for the capillaries and parenchyma. **Two concentrations necessary**.



Homogenization - Equations

2 Fictitious Domain Framework



Mass transfer model at capillary scale

Hypotheses

- Parenchyma and endothelium are **purely diffusive** domains
- Parenchyma + endothelium = tissue, $\Omega_p \cup \Omega_e = \Omega_t$
- D_t spacially varying (small in Ω_e)
- Red blood cells are neglected



Two-phase capillary bed model

$$\begin{array}{rcl} \partial_{\tau}c_{\beta} + \boldsymbol{u} \cdot \boldsymbol{\nabla} c_{\beta} & -D_{v}\Delta c_{\beta} = 0 & \text{in } \Omega_{\beta} \\ \partial_{\tau}c_{t} & -D_{t}\Delta c_{t} = 0 & \text{in } \Omega_{t} \end{array}$$
$$\begin{array}{rcl} c_{\beta} & = & c_{t} & \text{on } \partial\Omega_{\beta t} \\ D_{v}\boldsymbol{\nabla} c_{\beta} \cdot \boldsymbol{n} & = & D_{t}\boldsymbol{\nabla} c_{t} \cdot \boldsymbol{n} & \text{on } \partial\Omega_{\beta t} \end{array}$$

Upscaled representation of the capillary domain

Upscaled model for the two concentrations

$$\varepsilon_{\beta}\partial_{\tau} \langle c_{\beta} \rangle^{\beta} + (\varepsilon_{\beta} \langle \boldsymbol{u} \rangle^{\beta} - \boldsymbol{u}_{\beta\beta}) \cdot \boldsymbol{\nabla} \langle c_{\beta} \rangle^{\beta} - \boldsymbol{u}_{\beta t} \cdot \boldsymbol{\nabla} \langle c_{t} \rangle^{t} + \tau_{m} (\langle c_{\beta} \rangle^{\beta} - \langle c_{t} \rangle^{t})$$
$$= \nabla \cdot (\boldsymbol{K}_{\beta\beta} \boldsymbol{\nabla} \langle c_{\beta} \rangle^{\beta}) + \nabla \cdot (\boldsymbol{K}_{\beta t} \boldsymbol{\nabla} \langle c_{t} \rangle^{t})$$

$$\varepsilon_t \partial_\tau \langle c_t \rangle^t - \boldsymbol{u}_{tt} \cdot \boldsymbol{\nabla} \langle c_t \rangle^t - \boldsymbol{u}_{t\beta} \cdot \boldsymbol{\nabla} \langle c_\beta \rangle^\beta + \tau_m (\langle c_t \rangle^t - \langle c_\beta \rangle^\beta)$$
$$= \nabla \cdot (\boldsymbol{K}_{tt} \boldsymbol{\nabla} \langle c_t \rangle^t) + \nabla \cdot (\boldsymbol{K}_{t\beta} \boldsymbol{\nabla} \langle c_\beta \rangle^\beta)$$

- Equations solved on a domain without explicit representation of vessels
- Presence of capillary network taken into account through effective coefficients

Volume averaging

Averaging equations

$$\begin{array}{ll} \langle \partial_{\tau} c_{\beta} + \boldsymbol{u} \cdot \boldsymbol{\nabla} c_{\beta} & -D_{v} \Delta c_{\beta} \rangle = 0 & \text{in } \Omega_{\beta} \\ \langle \partial_{\tau} c_{t} & -D_{t} \Delta c_{t} \rangle = 0 & \text{in } \Omega_{t} \end{array}$$

Decomposition in averaged and deviation

$$\begin{array}{ll} c_{\beta} &= \langle c_{\beta} \rangle^{\beta} + \widetilde{c_{\beta}} & & \langle \widetilde{c_{\beta}} \rangle &= 0 \\ c_{t} &= \langle c_{t} \rangle^{t} + \widetilde{c_{t}} & & \langle \widetilde{c_{t}} \rangle &= 0 \end{array}$$

- We obtain equations on $\langle c_{\beta} \rangle^{\beta}$ and $\langle c_{t} \rangle^{t}$
- Equations depend on deviation terms $\widetilde{c_{\beta}}$ and $\widetilde{c_t}$
- Need closure equations on $\widetilde{c_{\beta}}$ and $\widetilde{c_t}$.
- Subtracting equations on the mean to microscopic equations leads to equations on $\tilde{c_{\beta}}$ and $\tilde{c_t}$.

Deviation terms as linear combination of averaged values and their gradients

$$\begin{split} \widetilde{c_{\beta}} &= \boldsymbol{b}_{\beta\beta} \cdot \boldsymbol{\nabla} \left\langle c_{\beta} \right\rangle^{\beta} + \boldsymbol{b}_{\beta t} \cdot \boldsymbol{\nabla} \left\langle c_{t} \right\rangle^{t} - s_{\beta} \left(\left\langle c_{\beta} \right\rangle^{\beta} - \left\langle c_{t} \right\rangle^{t} \right) \\ \widetilde{c_{t}} &= \boldsymbol{b}_{t\beta} \cdot \boldsymbol{\nabla} \left\langle c_{\beta} \right\rangle^{\beta} + \boldsymbol{b}_{tt} \cdot \boldsymbol{\nabla} \left\langle c_{t} \right\rangle^{t} - s_{t} \left(\left\langle c_{\beta} \right\rangle^{\beta} - \left\langle c_{t} \right\rangle^{t} \right) \end{split}$$

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Volume averaging

Decomposition of deviation terms

$$\widetilde{c_{\beta}} = \mathbf{b}_{\beta\beta} \cdot \nabla \langle c_{\beta} \rangle^{\beta} + \mathbf{b}_{\beta t} \cdot \nabla \langle c_{t} \rangle^{t} - \mathbf{s_{\beta}} \left(\langle c_{\beta} \rangle^{\beta} - \langle c_{t} \rangle^{t} \right)^{t}$$

$$\widetilde{c_{t}} = \mathbf{b}_{t\beta} \cdot \nabla \langle c_{\beta} \rangle^{\beta} + \mathbf{b}_{tt} \cdot \nabla \langle c_{t} \rangle^{t} - \mathbf{s_{t}} \left(\langle c_{\beta} \rangle^{\beta} - \langle c_{t} \rangle^{t} \right)^{t}$$

Closure problem on s_{β} and s_t coefficients:

Effective coefficients associated

$$\begin{aligned} \boldsymbol{u}_{\beta\beta} &= \langle \tilde{\boldsymbol{u}} \boldsymbol{s}_{\beta} \rangle - \frac{D_{\beta}}{V} \int_{\partial \Omega_{\beta t}} \boldsymbol{n}_{\beta t} \boldsymbol{s}_{\beta} dA \\ \tau_{m} &= -\frac{1}{V} \int_{\partial \Omega_{\beta t}} \boldsymbol{n}_{\beta t} \cdot D_{\beta} \boldsymbol{\nabla} \boldsymbol{s}_{\beta} dA \end{aligned}$$

$$\nabla \cdot (D_{\beta} \nabla s_{\beta}) - \varepsilon_{\beta} \tau_m + u \cdot \nabla s_{\beta} = 0 \quad \text{on } \Omega_{\beta} \\ -D_t \Delta s_t - \varepsilon_t \tau_m = 0 \quad \text{on } \Omega_t \\ \tau_m - \frac{1}{V} \int_{\partial \Omega_{\beta t}} (\boldsymbol{n} \cdot D_{\beta} \nabla s_{\beta}) \, dV = 0 \\ \boldsymbol{s}_{\beta} - \boldsymbol{s}_t = 1 \quad \text{on } \partial \Omega_{\beta t} \\ \boldsymbol{n} \cdot D_{\beta} \nabla s_{\beta} - \boldsymbol{n} \cdot D_t \nabla s_t = 0 \quad \text{on } \partial \Omega_{\beta t} \\ \langle s_{\beta} \rangle^{\beta} = 0 \\ \langle s_t \rangle^t = 0 \end{cases}$$

Take-home idea

Obtaining the effective coefficients necessitates to solve PDEs on a Representative Elementary Volume of the micro-structure

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Computational Framework

Solution proposed:

- C++/Parallel Finite element library ¹FEEL++
- Use a distance function field to capture the domain geometries
 - ▶ Mesh adaptation from distance function
 - Sub-domain localization to solve Stokes problem
 - ▶ Fictitious domain to solve advection/diffusion problem

¹Prud'homme et. al. (2016), feelpp.org

1 Homogenization - Equations

2 Fictitious Domain Framework

3 Verification

Network geometries





(300 µm)³ network. Ross (2005), Tsai (2009), Kleinfeld (2011), Kaufhold 2012, Blinder (2013)

- Segment networks extracted from biological images (center-line detection)
- Need to mesh inner and outer domains (vessels and tissue)
- Difficult to mesh automatically with CAD software (design of bifurcations)
- Geometry representation needs to be robust and automated
- Solution: use a fictitious domain method

Levelset field

Defining ϕ_i , the distance field to centerline S_i of a vessel of radius r_i The distance field to the closest vessel boundary of the network is:

$$\phi(\boldsymbol{x}) = \min_{i=0}^{\text{Nb Vessels}} \operatorname{dist}(\boldsymbol{x}, S_i) - r_i$$



Properties of ϕ :

•
$$\phi(\boldsymbol{x}) < 0$$
 if $\boldsymbol{x} \in \Omega_{\beta}$

•
$$\phi(\boldsymbol{x}) > 0$$
 if $\boldsymbol{x} \in \Omega_t$

•
$$\phi(\boldsymbol{x}) = 0$$
 if $\boldsymbol{x} \in \partial \Omega_{\beta t}$





Mesh adaptation from distance function

Target mesh size field calculated from levelset field

$$h(oldsymbol{x}) = \left\{egin{array}{cc} h_{\min}, & |\phi(oldsymbol{x})| \leq R_1, \ lpha |\phi(oldsymbol{x})| + eta, & R_1 \leq |\phi(oldsymbol{x})| \leq R_2, \ h_{\max}, & |\phi(oldsymbol{x})| \geq R_2 \end{array}
ight.$$





Transport equations

Two domain problem

$$\partial_{\tau}c_{\beta} + \boldsymbol{u} \cdot \boldsymbol{\nabla}c_{\beta} - D_{v}\Delta c_{\beta} = 0 \quad \text{in } \Omega_{v}$$
$$\partial_{\tau}c_{t} - D_{t}\Delta c_{t} = 0 \quad \text{in } \Omega_{t}$$
$$c_{\beta} = c_{t} \quad \text{on } \partial\Omega_{\beta t}$$
$$D_{\beta}\boldsymbol{\nabla}c_{\beta}\cdot\boldsymbol{n} = D_{t}\boldsymbol{\nabla}c_{t}\cdot\boldsymbol{n} \quad \text{on } \partial\Omega_{\beta t}$$
Prescribed B.Cs for $c_{\beta} \quad \text{on } \partial\Omega_{\lambda} \setminus \partial\Omega_{\beta t}$ Prescribed B.Cs for $c_{t} \quad \text{on } \partial\Omega_{t} \setminus \partial\Omega_{\beta t}$

One domain problem with spacialized coefficients

 $\partial_{\tau} c + \boldsymbol{u} \cdot \boldsymbol{\nabla} c - D(\phi) \Delta c = 0 \quad \text{in } \Omega$

Prescribed B.Cs for c on $\partial \Omega$

- Velocity **u** is obtained by solving Stokes equation on the vessel domain only.
- Diffusion coefficient spatialized to take into account the BBB.



PDEs solved by our framework

The frameworks of fictitious network allows to solve:

The microscopic problem (DNS)



Closure equations to get the effective coefficients



Upscaled model

- Monolitic solver used for the upscaled model
- Mesh is a simple box

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1 Homogenization - Equations

2 Fictitious Domain Framework



Test Case, order 3 network.

Representative Elementary Volume, size $(2 \times 2 \times 2)$



Comparison DNS - Homogenized model

Direct Numerical Simulation (DNS)



Darcy Scale

DNS

- Number of elements (tetrahedrons): 8.5×10^6
- Computational Cost: 1h on 100 cores



Darcy Scale

- Number of elements (tetrahedrons): 3×10^4
- Computational Cost: 10 min on 20 cores



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 $\frac{2}{9}$















Quantitative comparison



Quantitative comparison











Anatomical network case

Quantitative comparison



• Péclet number
$$P_e^{\text{REV}} = \frac{\langle \boldsymbol{u} \rangle_z^r L^{-1/r}}{D_v}$$

• Membrane Permeability
$$K_m^* = \frac{D_e}{D_v} \frac{r}{e}$$

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Conclusion and perspective

Conclusion

- Two-phase representation of the capillaries and tissue
- Sucessful upscaling of the capillary bed
- Framework using fictitious domain for DNS and Closure equations

In the future...

- Coupling with arterio-venous tree (1D-3D) or (3D-3D)
- Include the RBCs
- Include non linear consumption in tissue (Michaelis-Menten like)

Thank you!

Use of the distance function

Distance function used to:

• define a sub-domain:

$$\Omega_{v_h} \subset \Omega_h, \ \Omega_{v_h} = \bigcup_i \left(\Omega_{e_i} \mid \pi_{\Omega_{e_i}}^{P_{d_h}^0}(\phi) < 0 \right)$$

An example of projection function on a elements is given by:

$$\pi^{P^0_{dh}}_{\Omega_{e_i}} = \begin{cases} -1, & \text{if } \phi < 0 \text{ on at least one dof of } \Omega_{e_i} \\ 1 & \text{else} \end{cases}$$

• define continuously quantities having a different value in the domains thanks to a smoothed Heaviside function (level set method):

$$H_{\varepsilon}(\phi) = \begin{cases} 0, & \phi \leq -\varepsilon, \\ \text{smooth variations,} & -\varepsilon \leq \phi \leq \varepsilon, \\ 1, & \phi \geq \varepsilon \end{cases}$$













• Membrane Permeability
$$K_m^* = \frac{D_e}{D_v} \frac{r}{e}$$