# Upscaling mass transfer in brain capillary networks 

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## To cite this version:

Vincent Doyeux, Yohan Davit, Michel Quintard, Sylvie Lorthois. Upscaling mass transfer in brain capillary networks. ECCM-ECFD 2018 (6th European Conference on Computational Mechanics (Solids, Structures and Coupled Problems) (ECCM 6) and the 7th European Conference on Computational Fluid Dynamics (ECFD 7), Jun 2018, Glasgow, United Kingdom. pp.0. hal-03656518

HAL Id: hal-03656518

## https://hal.science/hal-03656518

Submitted on 2 May 2022

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## To cite this version:

Doyeux, Vincent and Davit, Yohan and Quintard, Michel and Lorthois, Sylvie. Upscaling mass transfer in brain capillary networks. (2018) In: ECCM-ECFD 2018 (6th European Conference on Computational Mechanics (Solids, Structures and Coupled Problems) (ECCM 6) and the 7th European
Conference on Computational Fluid Dynamics (ECFD 7), 1115 June 2018 (Glasgow, United Kingdom). (Unpublished)

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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 explicitely 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.


Macroscopic scale


Microscopic scale


Sub-Microscopic scale
(1) Homogenization - Equations
(2) Fictitious Domain Framework
(3) Verification

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 $\Omega_{e}$ )
- Red blood cells are neglected



## Two-phase capillary bed model

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

Upscaled representation of the capillary domain

Upscaled model for the two concentrations

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

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

Volume averaging
Averaging equations

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

Decomposition in averaged and deviation

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

- We obtain equations on $\left\langle c_{\beta}\right\rangle^{\beta}$ and $\left\langle c_{t}\right\rangle^{t}$
- 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 $\widetilde{c_{\beta}}$ and $\widetilde{c_{t}}$.

Deviation terms as linear combination of averaged values and their gradients

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

## Volume averaging

Decomposition of deviation terms

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

Effective coefficients associated

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

Closure problem on $s_{\beta}$ and $s_{t}$ coefficients:

$$
\begin{array}{rll}
-\nabla \cdot\left(D_{\beta} \boldsymbol{\nabla} s_{\beta}\right)-\varepsilon_{\beta} \tau_{m}+\boldsymbol{u} \cdot \boldsymbol{\nabla} s_{\beta} & =0 & \text { on } \Omega_{\beta} \\
-D_{t} \Delta s_{t}-\varepsilon_{t} \tau_{m} & =0 & \text { on } \Omega_{t} \\
\tau_{m}-\frac{1}{V} \int_{\partial \Omega_{\beta t}}\left(\boldsymbol{n} \cdot D_{\beta} \boldsymbol{\nabla} s_{\beta}\right) d V & =0 & \\
s_{\beta}-s_{t} & =1 & \text { on } \partial \Omega_{\beta t} \\
\boldsymbol{n} \cdot D_{\beta} \boldsymbol{\nabla} s_{\beta}-\boldsymbol{n} \cdot D_{t} \boldsymbol{\nabla} s_{t} & =0 & \text { on } \partial \Omega_{\beta t} \\
\left\langle s_{\beta}\right\rangle^{\beta} & =0 & \\
\left\langle s_{t}\right\rangle^{t} & =0 &
\end{array}
$$

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

## Computational Framework

Solution proposed:

- C++/Parallel Finite element library ${ }^{1}$ Feel++
- 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
${ }^{1}$ Prud'homme et. al. (2016), feelpp.org


## (1) Homogenization - Equations

(2) Fictitious Domain Framework

## Network geometries



$(300 \mu \mathrm{~m})^{3}$ 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 $\phi_{i}$, 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:

$$
\phi(\boldsymbol{x})=\min _{i=0}^{\text {Nb Vessels }} \operatorname{dist}\left(\boldsymbol{x}, S_{i}\right)-r_{i}
$$

Properties of $\phi$ :

- $\phi(\boldsymbol{x})<0$ 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

$$
h(\boldsymbol{x})=\left\{\begin{array}{cc}
h_{\min }, & |\phi(\boldsymbol{x})| \leq R_{1} \\
\alpha|\phi(\boldsymbol{x})|+\beta, & R_{1} \leq|\phi(\boldsymbol{x})| \leq R_{2} \\
h_{\max }, & |\phi(\boldsymbol{x})| \geq R_{2}
\end{array}\right.
$$



## Transport equations

## Two domain problem

$$
\begin{array}{rll}
\partial_{\tau} c_{\beta}+\boldsymbol{u} \cdot \nabla c_{\beta} & -D_{v} \Delta c_{\beta}=0 & \text { in } \Omega_{v} \\
\partial_{\tau} c_{t} & -D_{t} \Delta c_{t}=0 & \text { in } \Omega_{t} \\
c_{\beta}= & c_{t} & \text { on } \partial \Omega_{\beta t} \\
D_{\beta} \nabla c_{\beta} \cdot \boldsymbol{n}= & D_{t} \nabla c_{t} \cdot \boldsymbol{n} & \text { on } \partial \Omega_{\beta t}
\end{array} \begin{aligned}
\text { Prescribed B.Cs for } c_{\beta} & \text { on } \partial \Omega_{\beta} \backslash \partial \Omega_{\beta t} \\
\text { Prescribed B.Cs for } c_{t} & \text { on } \partial \Omega_{t} \backslash \partial \Omega_{\beta t}
\end{aligned}
$$

One domain problem with spacialized coefficients

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

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

- Velocity $\boldsymbol{u}$ 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


# (1) Homogenization - Equations 

(2) Fictitious Domain Framework
(3) Verification

## Test Case, order 3 network.

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


Geometry and mesh.


Velocity field.


Closure variable

## Comparison DNS - Homogenized model

## Direct Numerical Simulation (DNS)



## DNS

- Number of elements (tetrahedrons): $8.5 \times 10^{6}$
- Computational Cost: 1h on 100 cores

Darcy Scale


## Darcy Scale

- Number of elements (tetrahedrons): $3 \times 10^{4}$
- Computational Cost: 10 min on 20 cores


## Simulation Visualization



## Simulation Visualization



## Simulation Visualization



## Simulation Visualization



## Simulation Visualization



## Simulation Visualization



## Simulation Visualization



## Simulation Visualization


$\frac{8}{9}$

## Simulation Visualization



## Quantitative comparison



## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
- Membrane Permeability $K_{m}^{*}=\frac{D_{e}}{D_{v}} \frac{r}{e}$


## Quantitative comparison



## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
- Membrane Permeability $K_{m}^{*}=\frac{D_{e}}{D_{v}} \frac{r}{e}$


## Anatomical Network



## Anatomical Network



## Anatomical Network



## Anatomical Network



## Quantitative comparison



$$
P_{e}^{\mathrm{REV}}=1, K_{m}=3 \times 10^{-2}
$$

## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
- Membrane Permeability $K_{m}^{*}=\frac{D_{e}}{D_{v}} \frac{r}{e}$


## 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:

$$
\pi_{\Omega_{e_{i}}}^{P_{d h}^{0}}=\left\{\begin{array}{cc}
-1, & \text { if } \phi<0 \text { on at least one dof of } \Omega_{e_{i}} \\
1 & \text { else }
\end{array}\right.
$$

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

$$
H_{\varepsilon}(\phi)=\left\{\begin{array}{cc}
0, & \phi \leq-\varepsilon \\
\text { smooth variations, } & -\varepsilon \leq \phi \leq \varepsilon \\
1, & \phi \geq \varepsilon
\end{array}\right.
$$

## All results, order 3



## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
- Membrane Permeability $K_{m}^{*}=\frac{D_{e}}{D_{v}} \frac{r}{e}$


## All results, order 3



## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
- Membrane Permeability $K_{m}^{*}=\frac{D_{e}}{D_{v}} \frac{r}{e}$


## All results, order 3



## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
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## All results, order 3



## Adimentional coefficients

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## All results, order 3



## Adimentional coefficients

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## All results, order 3



## Adimentional coefficients

- Péclet number $P_{e}^{\mathrm{REV}}=\frac{\langle\boldsymbol{u}\rangle_{z}^{\beta} L^{\mathrm{REV}}}{D_{v}}$
- Membrane Permeability $K_{m}^{*}=\frac{D_{e}}{D_{v}} \frac{r}{e}$

