Upscaling mass transfer in brain capillary networks

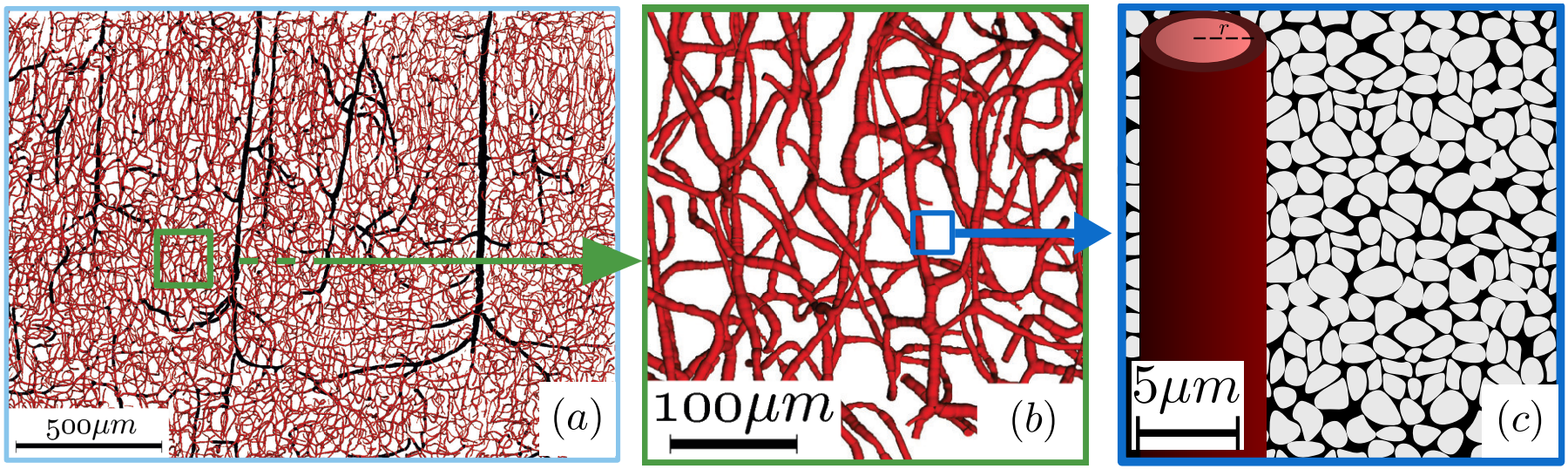
Vincent Doyeux, Yohan Davit, Michel Quintard, Sylvie Lorthois

Fluid Mechanics Institute of Toulouse (IMFT) - France

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**.

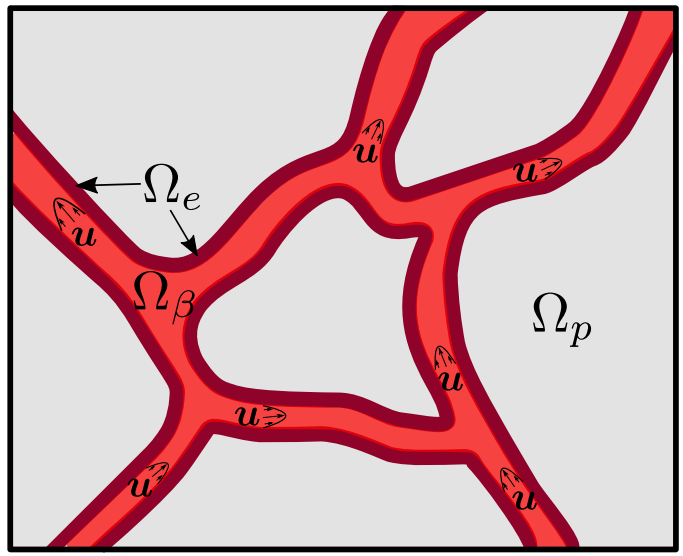


Macroscopic scale Microscopic scale Sub-Microscopic scale

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

$$\begin{aligned} \partial_\tau c_\beta + \boldsymbol{u}\cdot\boldsymbol{\nabla} c_\beta \quad & -D_v \Delta c_\beta = 0 \quad \text{in } \Omega_\beta \\ \partial_\tau c_t \quad & -D_t \Delta c_t = 0 \quad \text{in } \Omega_t \end{aligned}$$

$$\begin{aligned} c_\beta \quad &= \quad c_t \quad && \text{on } \partial\Omega_{\beta t} \\ D_v \boldsymbol{\nabla} c_\beta \cdot \boldsymbol{n} \quad &= \quad D_t \boldsymbol{\nabla} c_t \cdot \boldsymbol{n} \quad && \text{on } \partial\Omega_{\beta t} \end{aligned}$$

Upscaled representation of the capillary domain

Upscaled model for the two concentrations

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

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

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

Volume averaging

Averaging equations

$$\begin{aligned} \langle \partial_\tau c_\beta + \boldsymbol{u}\cdot\boldsymbol{\nabla} c_\beta \quad & -D_v \Delta c_\beta \rangle = 0 \quad \text{in } \Omega_\beta \\ \langle \partial_\tau c_t \quad & -D_t \Delta c_t \rangle = 0 \quad \text{in } \Omega_t \end{aligned}$$

Decomposition in averaged and deviation

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

- 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 $\widetilde{c_\beta}$ and $\widetilde{c_t}$.

Deviation terms as linear combination of averaged values and their gradients

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

Volume averaging

Decomposition of deviation terms

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

Effective coefficients associated

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

Closure problem on s_β and s_t coefficients:

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

Take-home idea

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

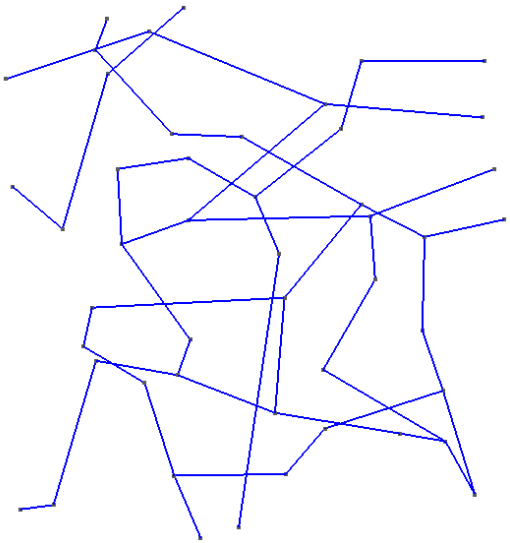
Computational Framework

Solution proposed:

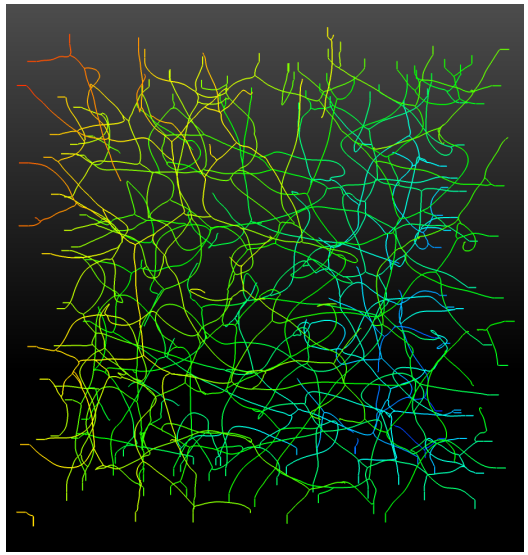
- C++/Parallel Finite element library [1]Feel++
- Use a distance function field to capture the domain geometries
  - Mesh adaptation from distance function
  - Sub-domain localization to solve Stokes problem
  - Fictitious domain to solve advection/diffusion problem

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

Network geometries



$(150\ \mu m)^3$ network.
Secomb (2000)



$(300\ \mu m)^3$ network.
Ross (2005), Tsai (2009), Kleinfeld (2011), Kaufhold 2012, Blinder (2013)

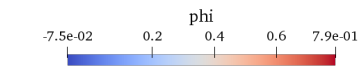
- Segment networks extracted from biological images (center-line detection)
- Need to mesh inner and outer domains (vessels and tissue)
- Difficult to mesh automatically with CAD software (design of bifurcations)
- Geometry representation needs to be robust and automated
- Solution: use a fictitious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

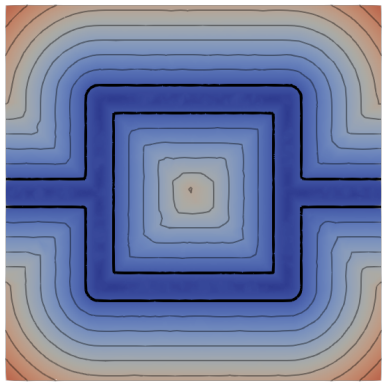
Levelset field

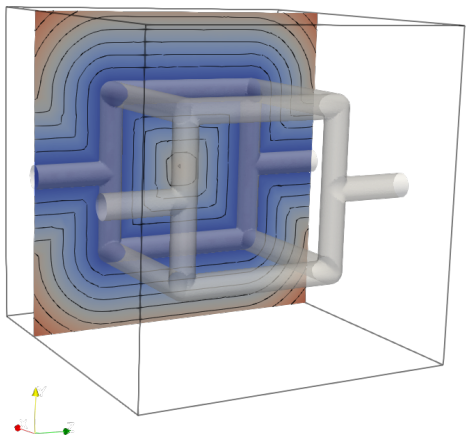
Defining ϕ_i, the distance field to centerline S_i of a vessel of radius r_i

The distance field to the closest vessel boundary of the network is:

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







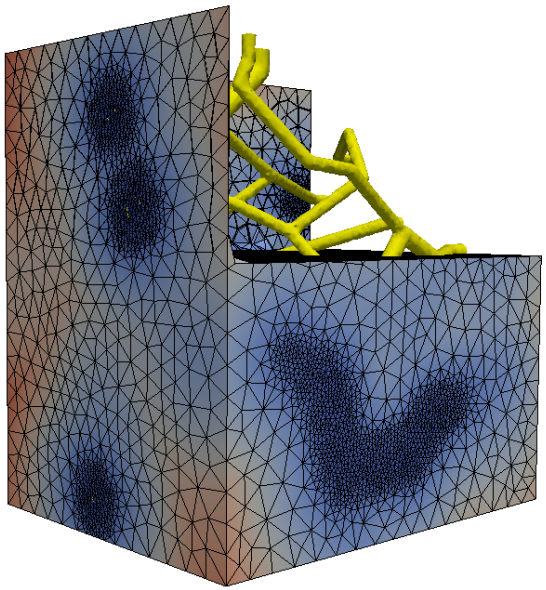
Properties of ϕ:

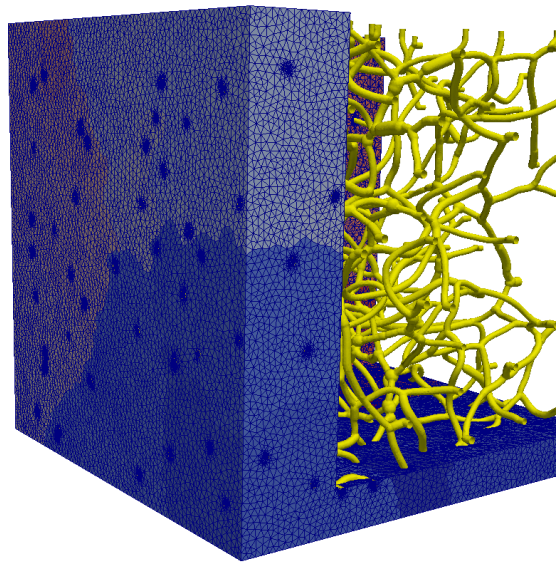
- $\phi(\boldsymbol{x}) < 0$ if $\boldsymbol{x} \in \Omega_\beta$
- $\phi(\boldsymbol{x}) > 0$ if $\boldsymbol{x} \in \Omega_t$
- $\phi(\boldsymbol{x}) = 0$ if $\boldsymbol{x} \in \partial\Omega_{\beta t}$

Mesh adaptation from distance function

Target mesh size field calculated from levelset field

$$h(\boldsymbol{x}) = \begin{cases} h_{\min}, & |\phi(\boldsymbol{x})| \leq R_1, \\ \alpha|\phi(\boldsymbol{x})| + \beta, & R_1 \leq |\phi(\boldsymbol{x})| \leq R_2, \\ h_{\max}, & |\phi(\boldsymbol{x})| \geq R_2 \end{cases}$$





Transport equations

Two domain problem

$$\begin{aligned} \partial_\tau c_\beta + \boldsymbol{u}\cdot\boldsymbol{\nabla} c_\beta \quad & -D_v \Delta c_\beta = 0 \quad \text{in } \Omega_v \\ \partial_\tau c_t \quad & -D_t \Delta c_t = 0 \quad \text{in } \Omega_t \end{aligned}$$

$$\begin{aligned} c_\beta &= c_t && \text{on } \partial\Omega_{\beta t} \\ D_\beta \boldsymbol{\nabla} c_\beta \cdot \boldsymbol{n} &= D_t \boldsymbol{\nabla} c_t \cdot \boldsymbol{n} && \text{on } \partial\Omega_{\beta t} \end{aligned}$$

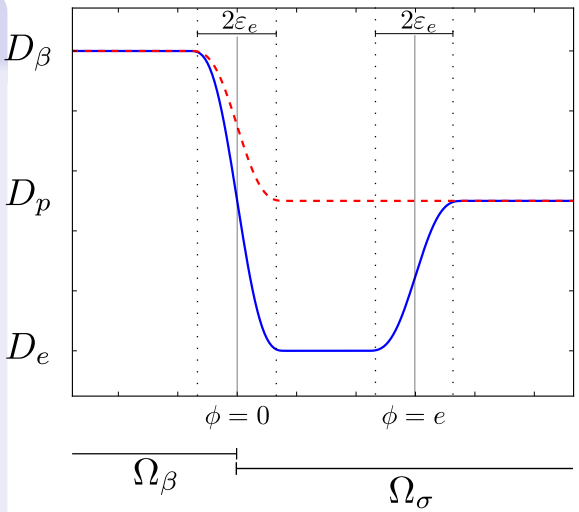
$$\begin{aligned} &\text{Prescribed B.Cs for } c_\beta && \text{on } \partial\Omega_\beta \setminus \partial\Omega_{\beta t} \\ &\text{Prescribed B.Cs for } c_t && \text{on } \partial\Omega_t \setminus \partial\Omega_{\beta t} \end{aligned}$$

One domain problem with spacialized coefficients

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

$$\text{Prescribed B.Cs for } c \quad \text{on } \partial\Omega$$

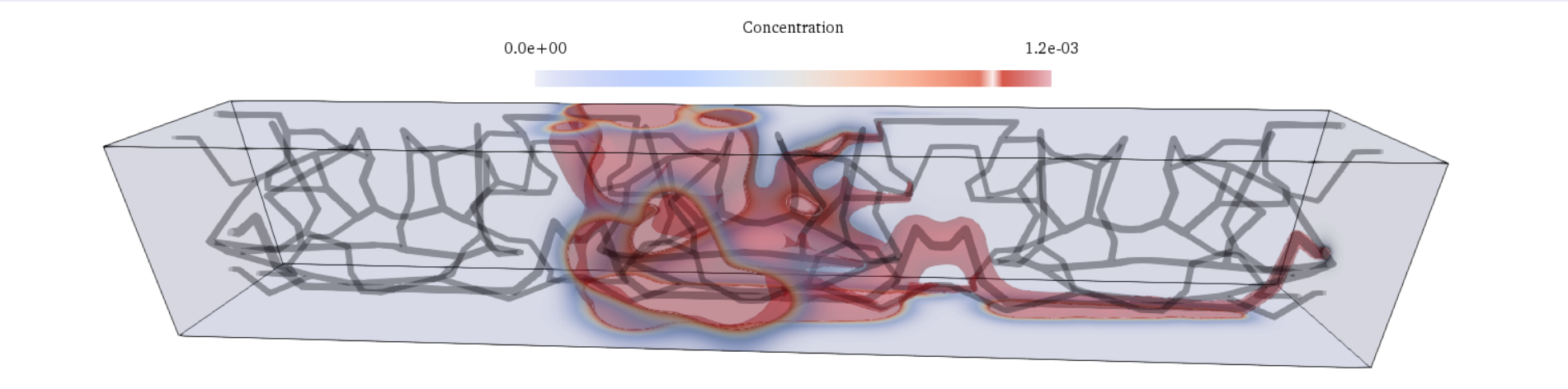
- Velocity $\boldsymbol{u}$ is obtained by solving Stokes equation on the vessel domain only.
- Diffusion coefficient spatialized to take into account the BBB.



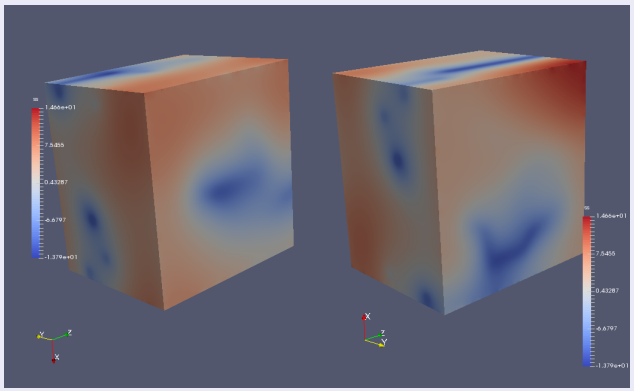
PDEs solved by our framework

The frameworks of fictitious network allows to solve:

The microscopic problem (DNS)



Closure equations to get the effective coefficients

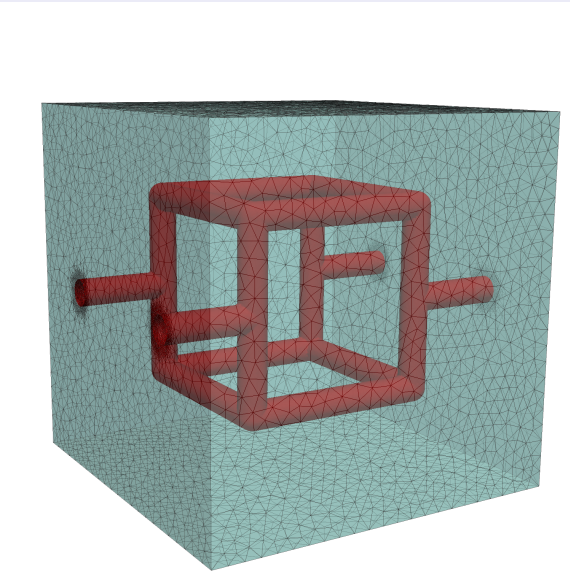


Upscaled model

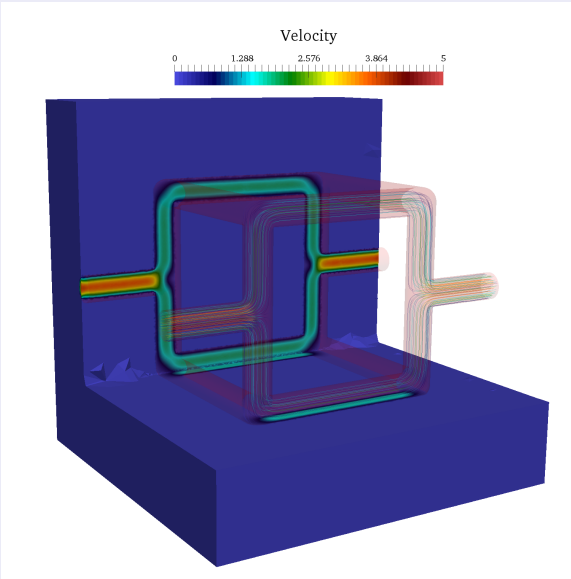
- Monolitic solver used for the upscaled model
- Mesh is a simple box

Test Case, order 3 network.

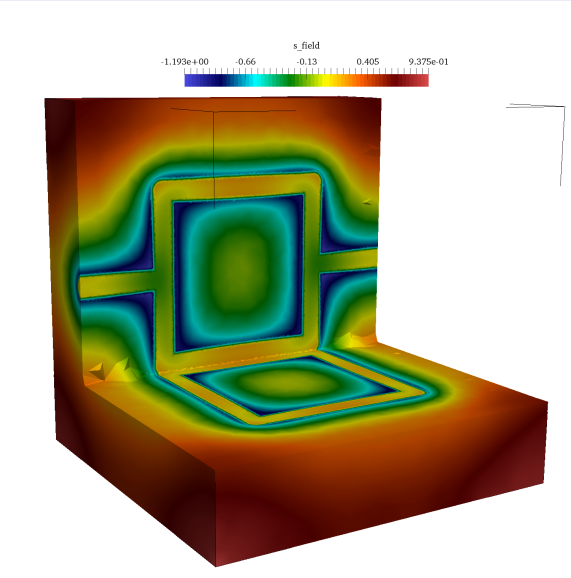
Representative Elementary Volume, size $(2 \times 2 \times 2)$



Geometry and mesh.



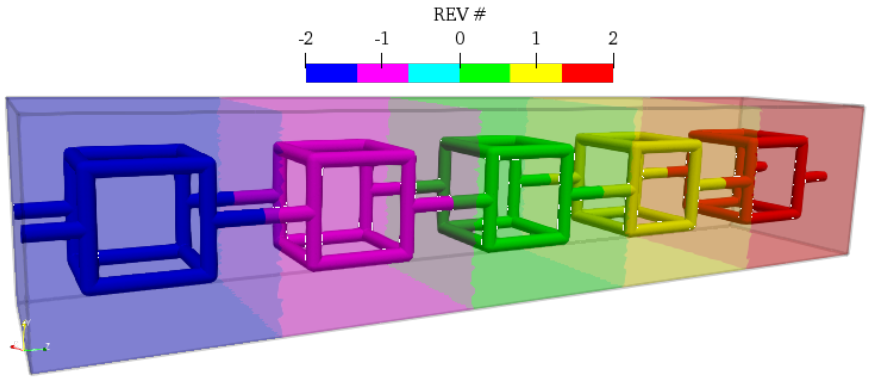
Velocity field.



Closure variable

Comparison DNS - Homogenized model

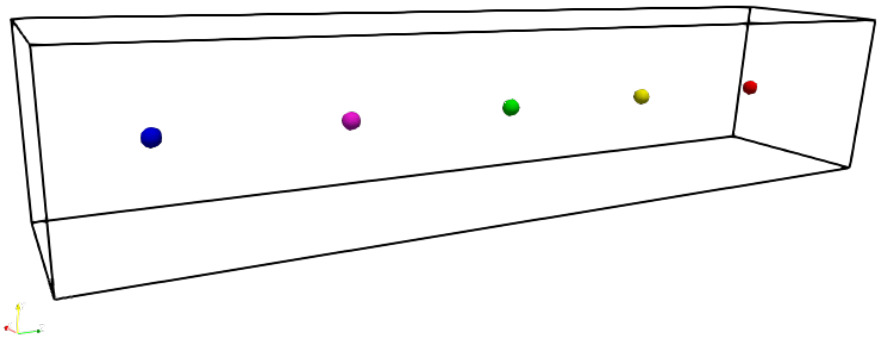
Direct Numerical Simulation (DNS)



DNS

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

Darcy Scale

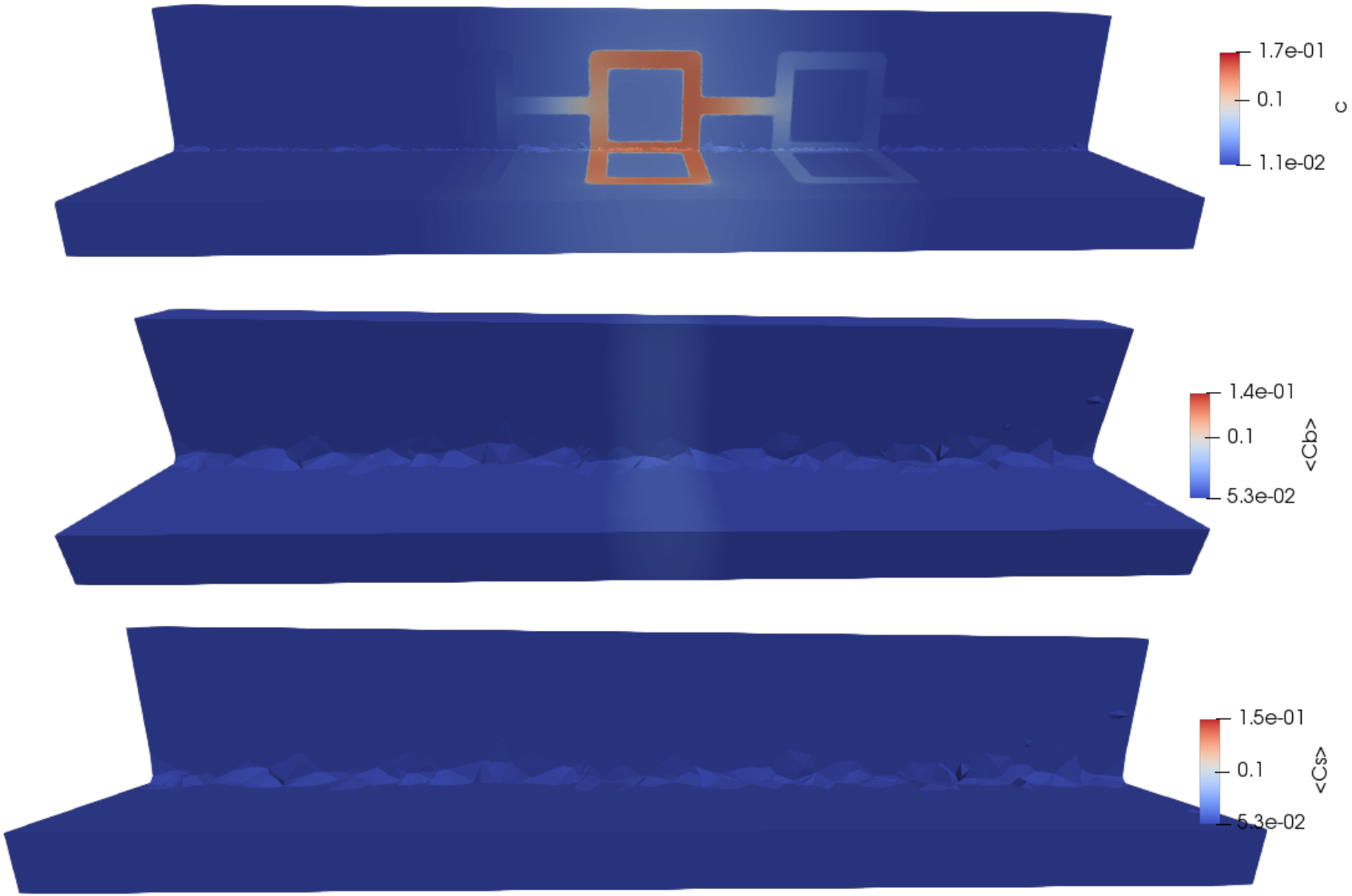


Darcy Scale

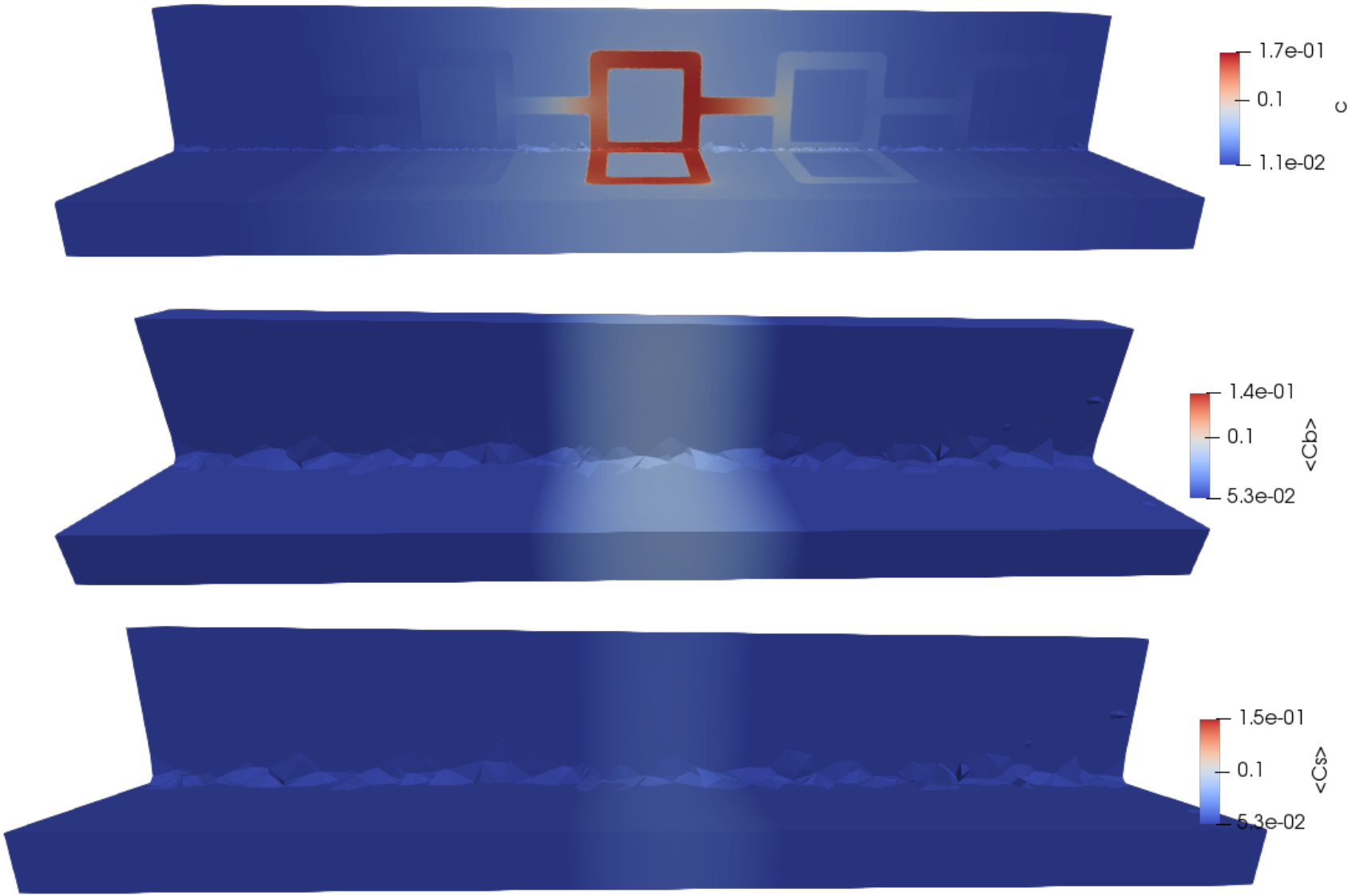
- Number of elements (tetrahedrons): 3×10^4
- Computational Cost: 10 min on 20 cores

Simulation Visualization

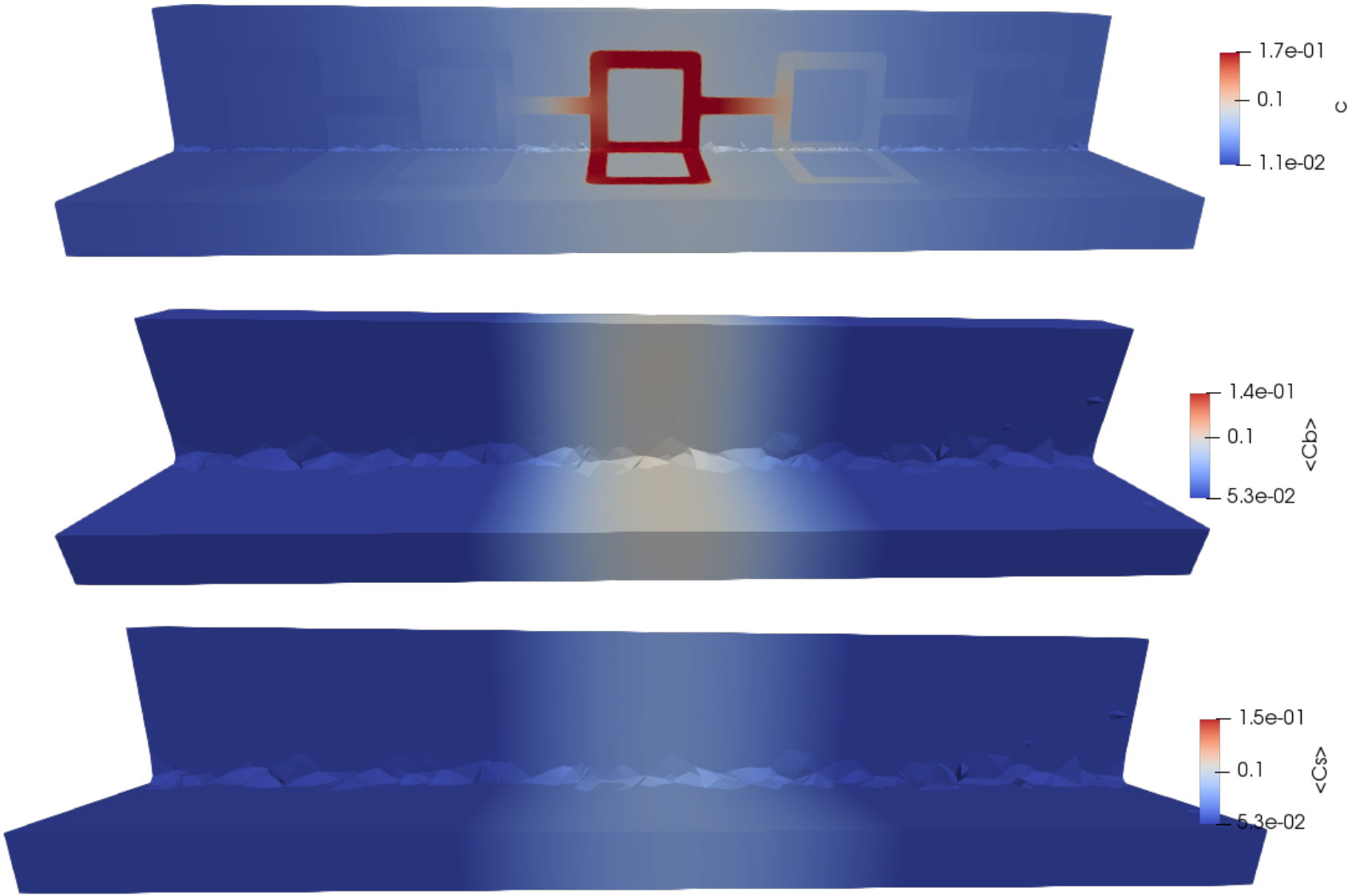
Simulation Visualization



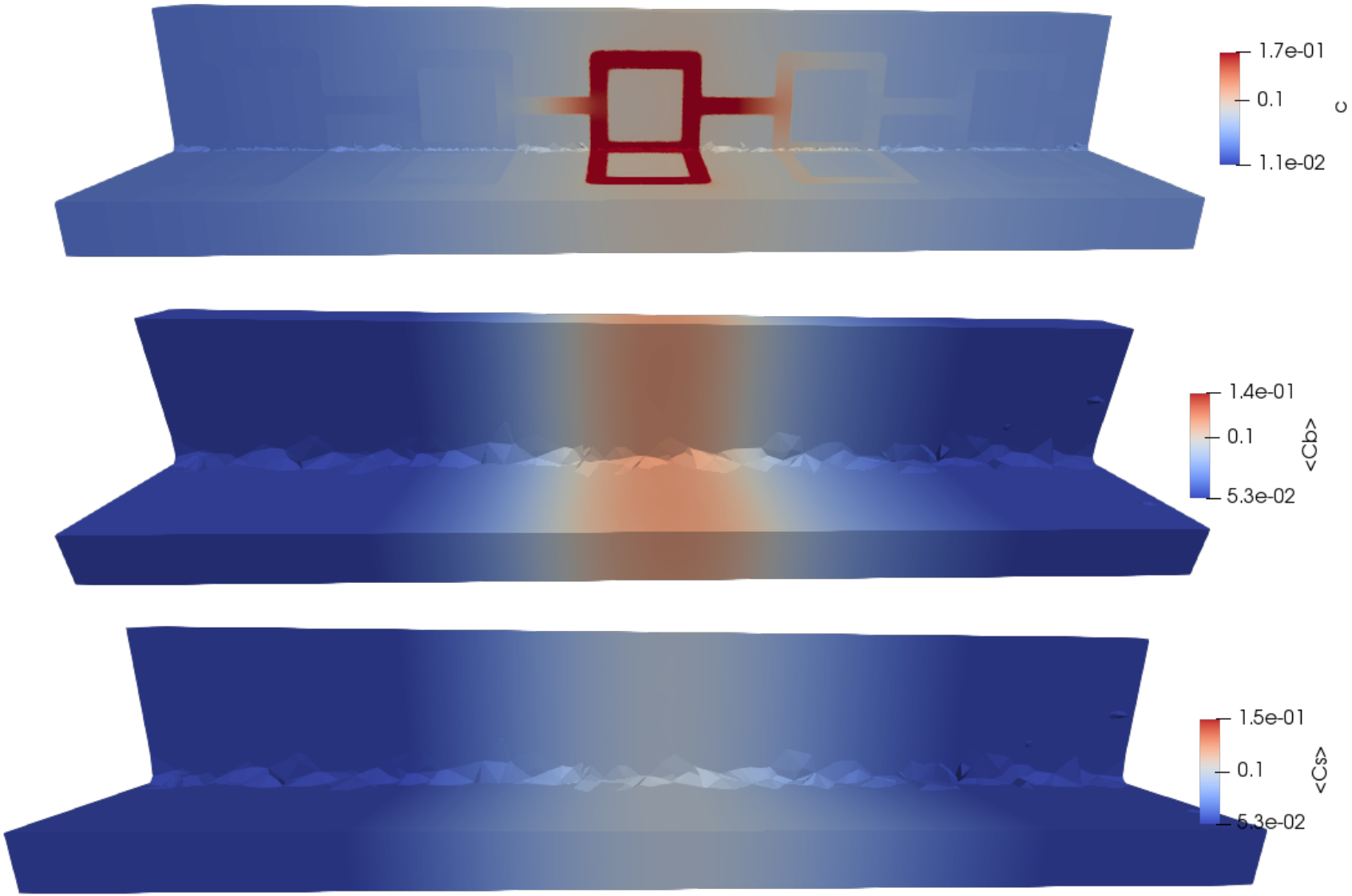
Simulation Visualization



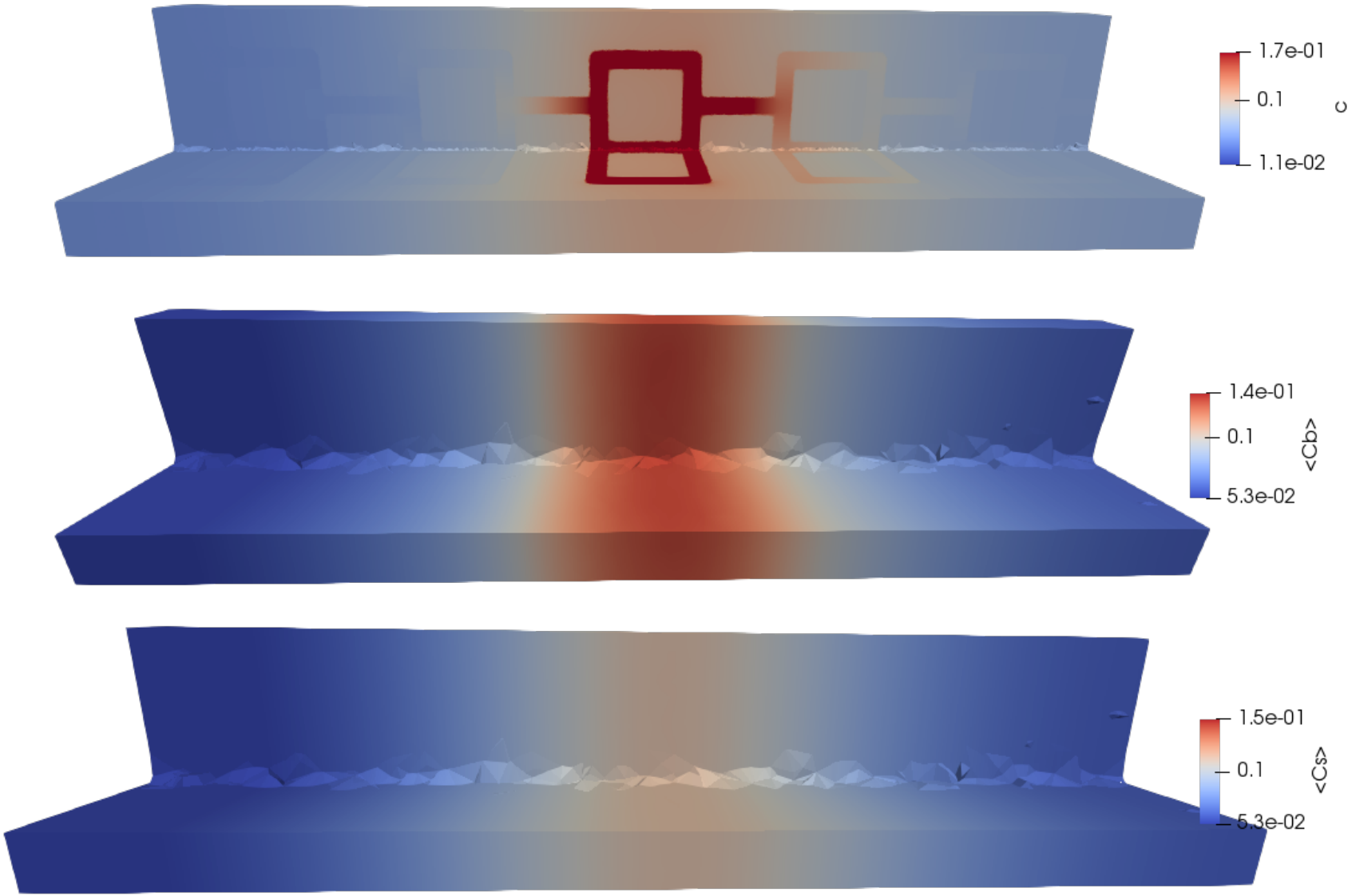
Simulation Visualization



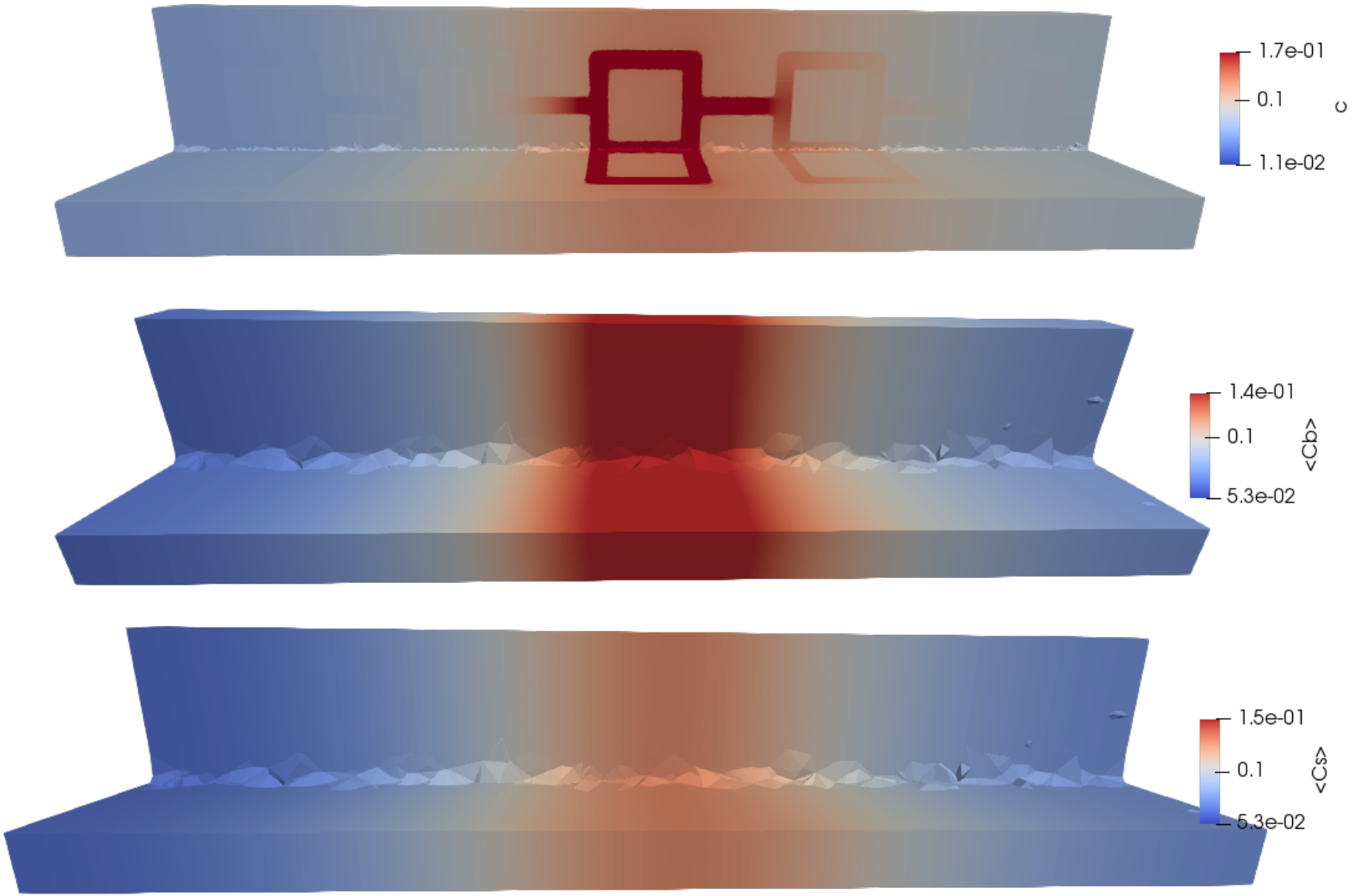
Simulation Visualization



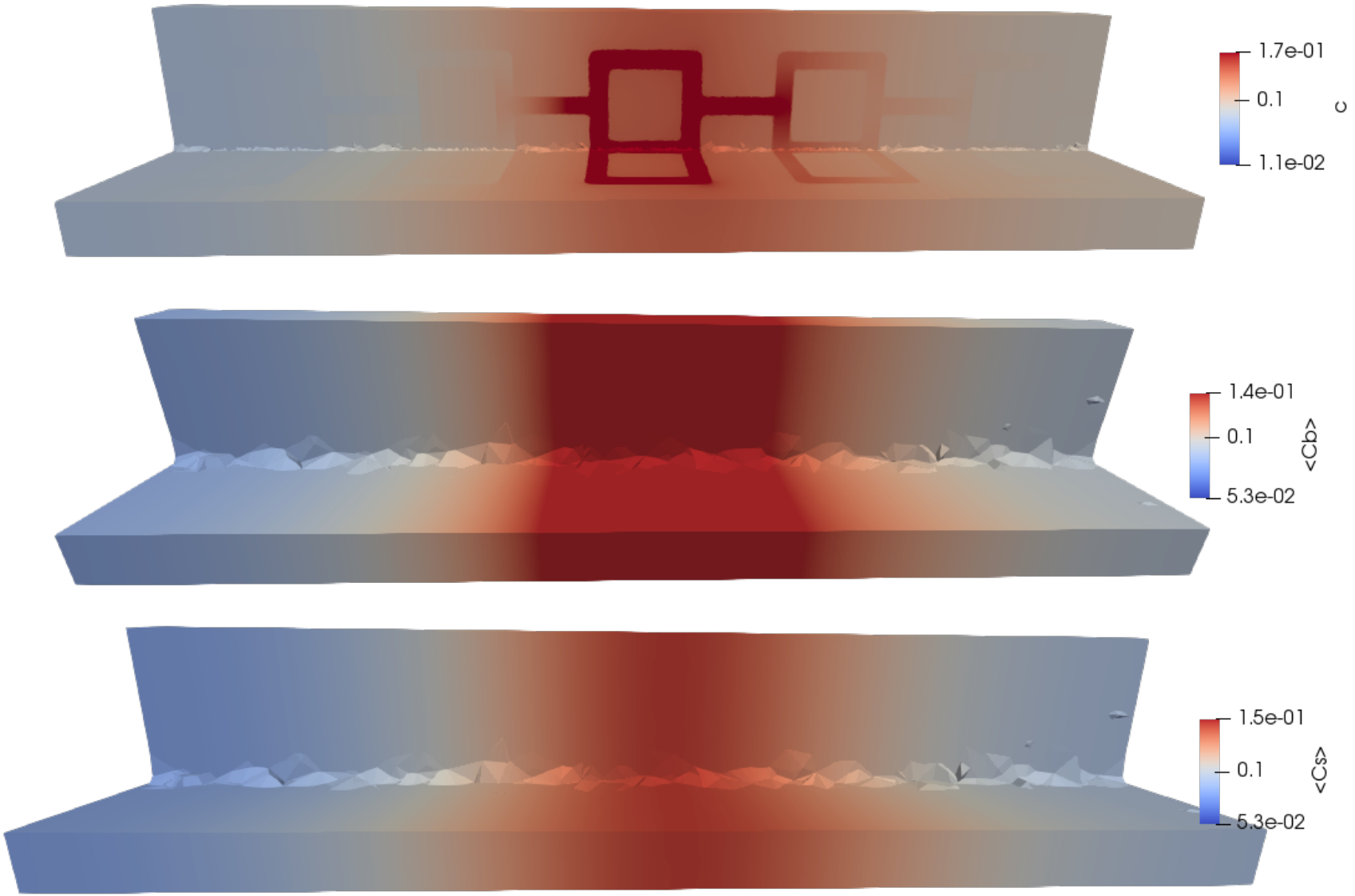
Simulation Visualization



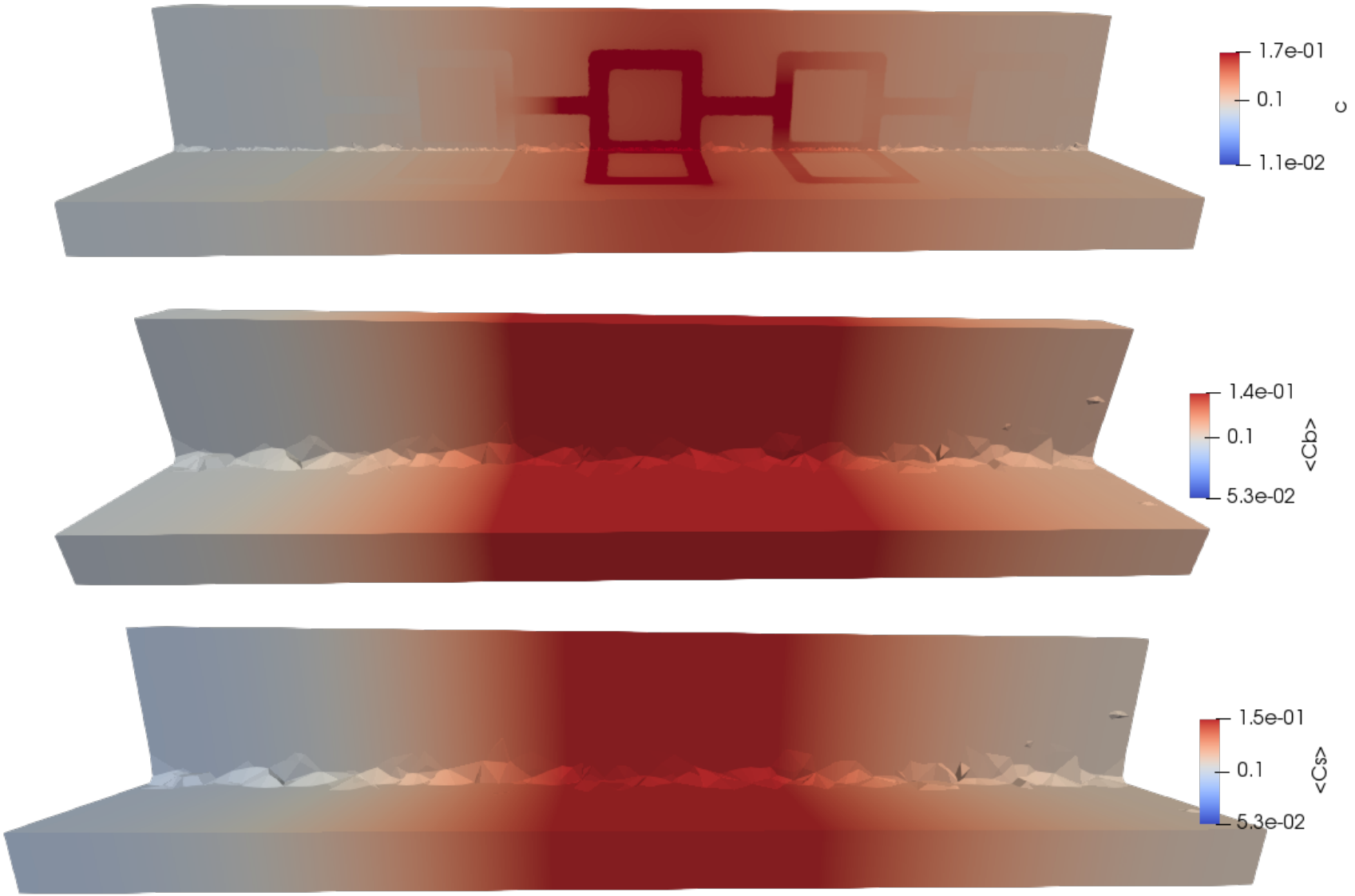
Simulation Visualization



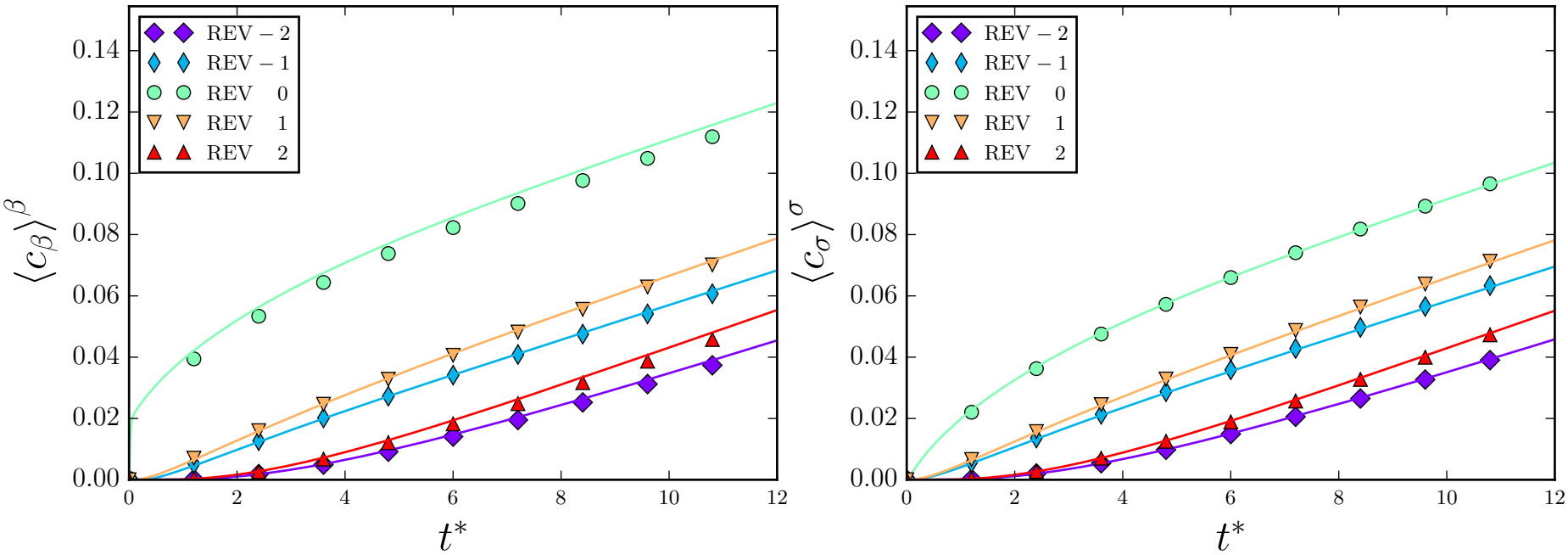
Simulation Visualization



Simulation Visualization



Quantitative comparison

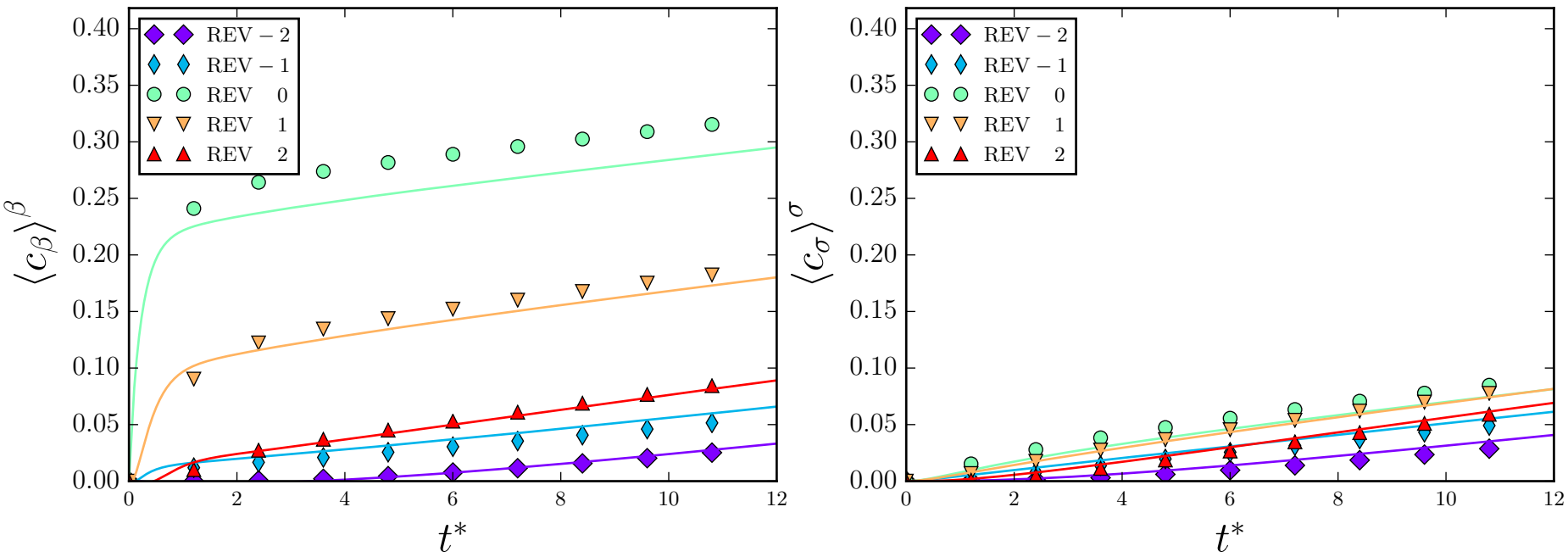


$$P_e^{\mathrm{REV}} = 1,\ K_m = 3 \times 10^{-2}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

Quantitative comparison

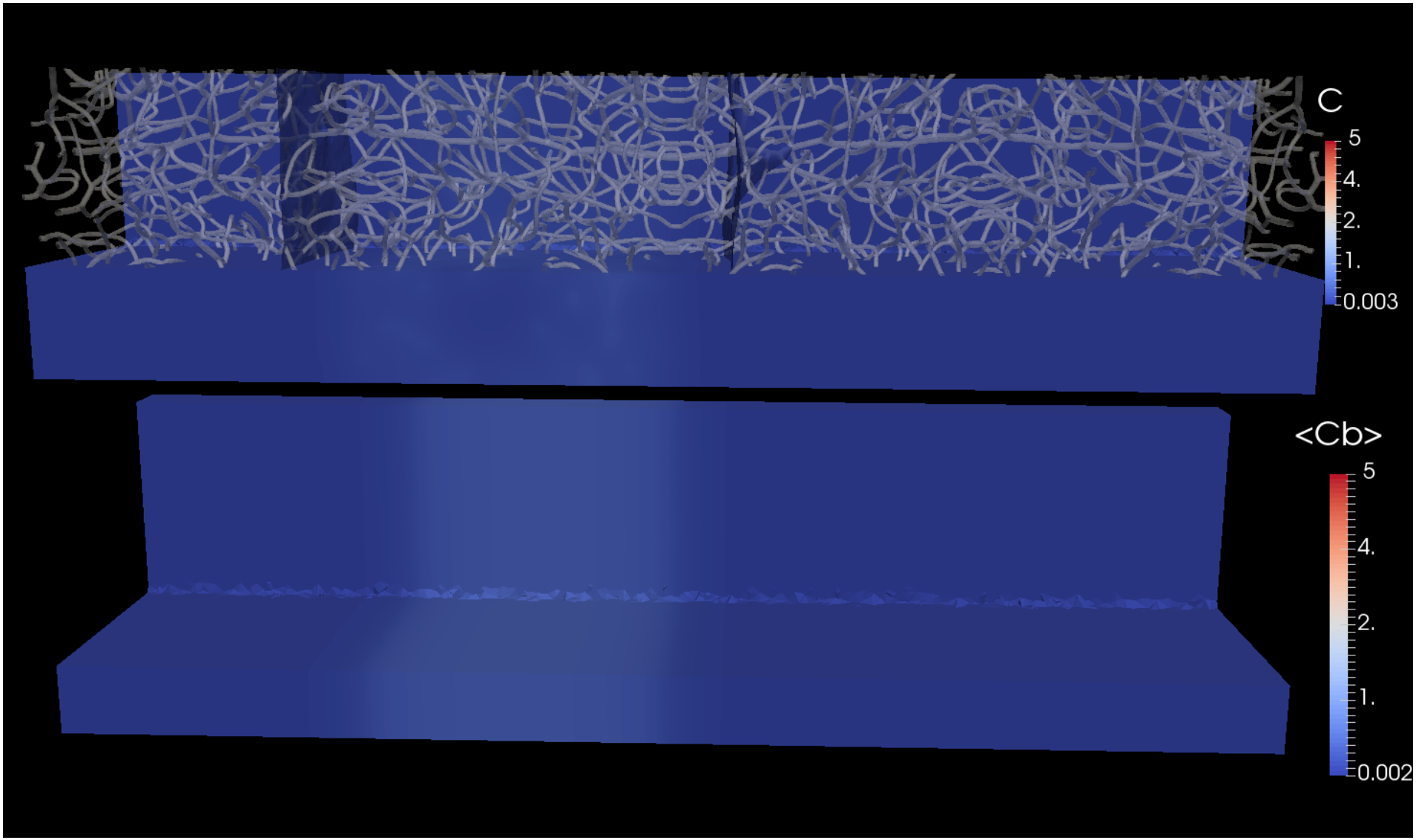


$$P_e^{\mathrm{REV}} = 10,\ K_m = 3 \times 10^{-4}$$

Adimentional coefficients

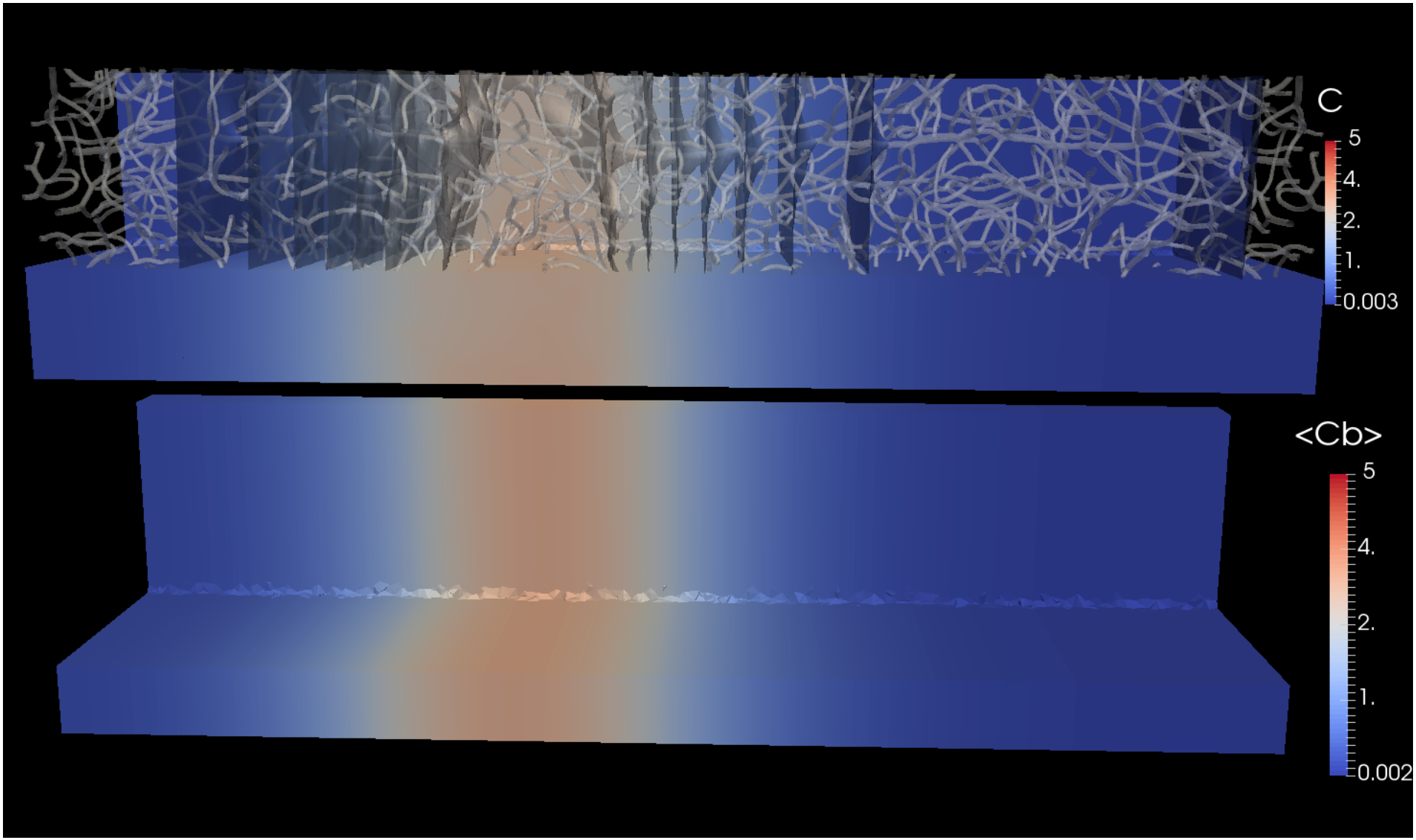
- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

Anatomical Network



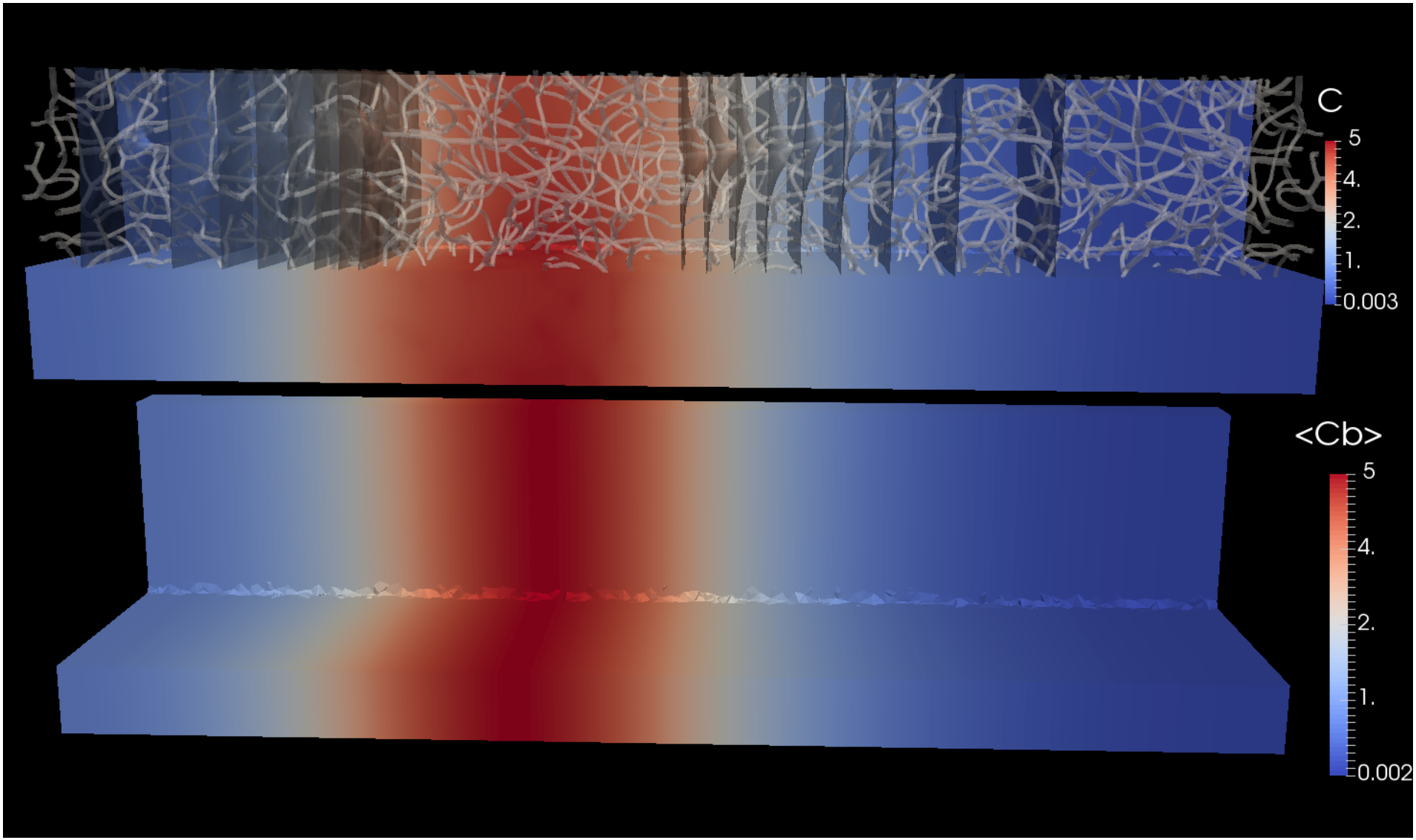
$\frac{1}{4}$

Anatomical Network



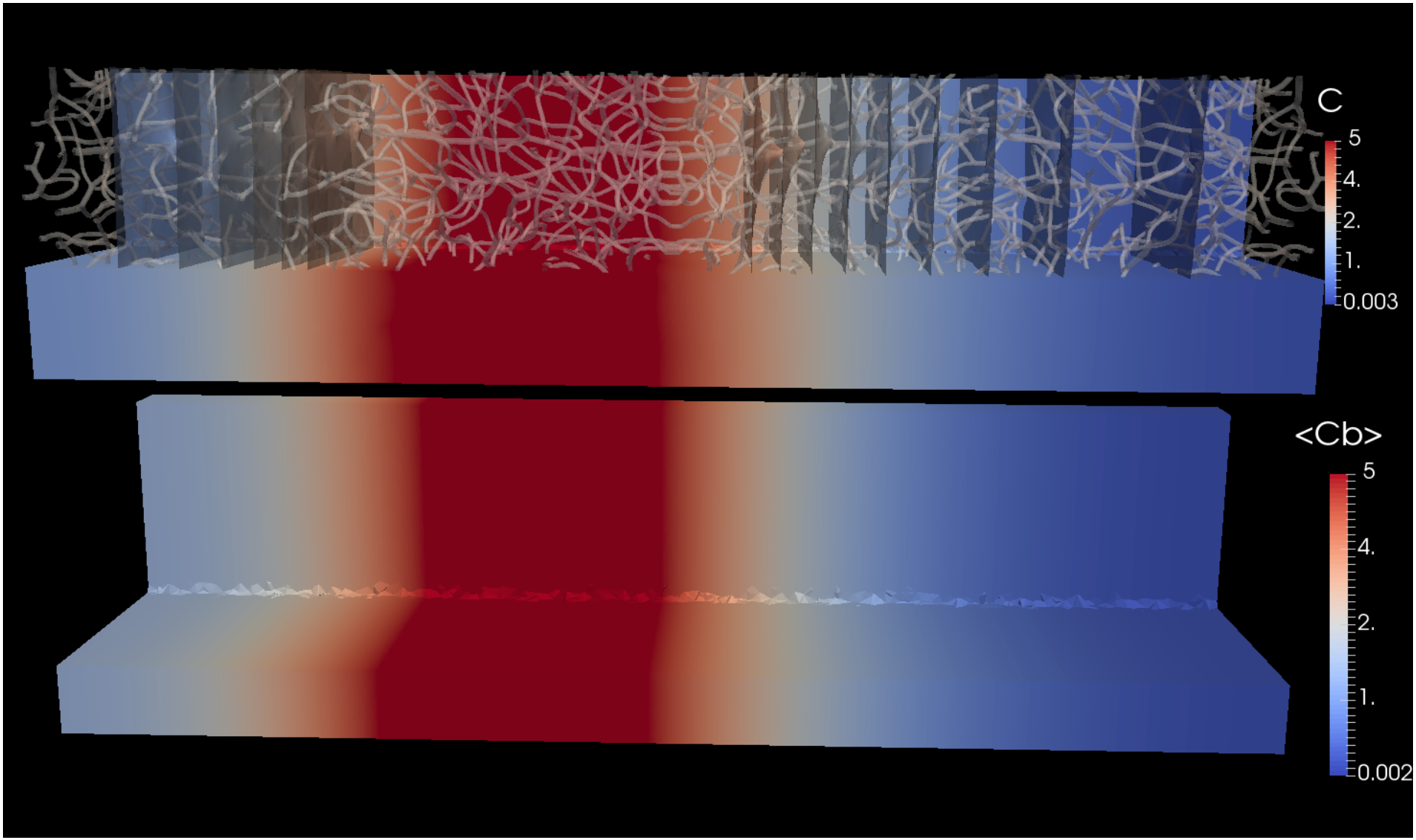
$\frac{2}{4}$

Anatomical Network



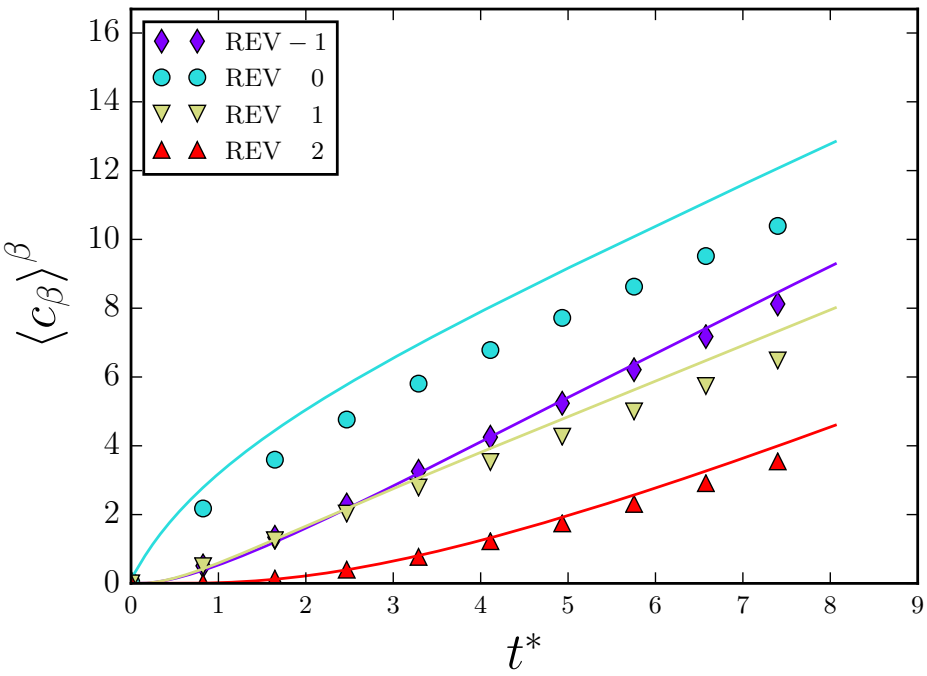
$\frac{3}{4}$

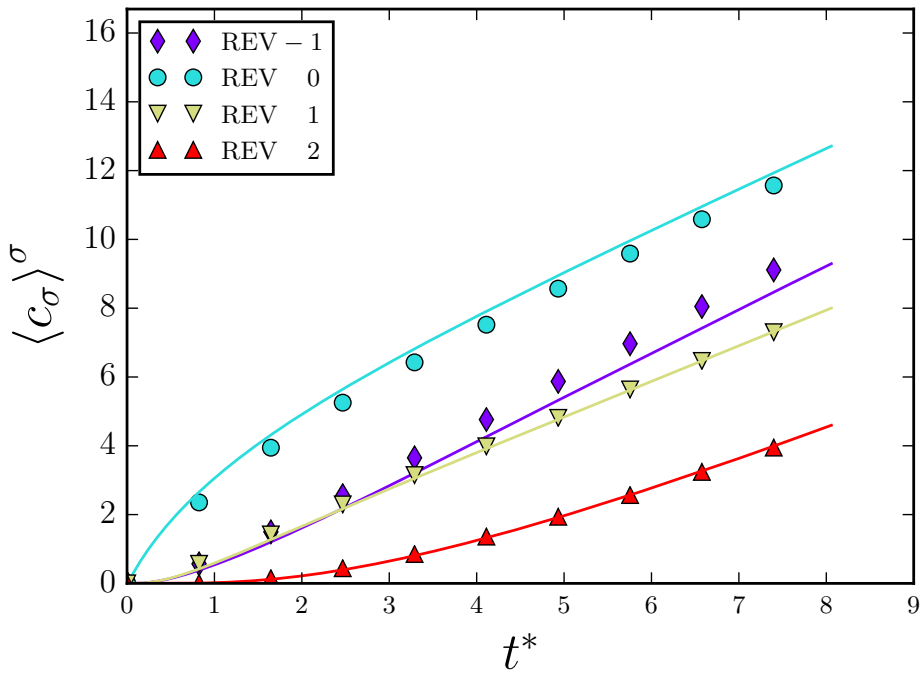
Anatomical Network



$\frac{4}{4}$

Quantitative comparison





$$P_e^{\mathrm{REV}} = 1,\ K_m = 3 \times 10^{-2}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

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:

$$\Omega_{v_h} \subset \Omega_h,\ \Omega_{v_h} = \bigcup_i \left(\Omega_{e_i} \mid \pi^{P^0_{dh}}_{\Omega_{e_i}}(\phi) < 0 \right)$$

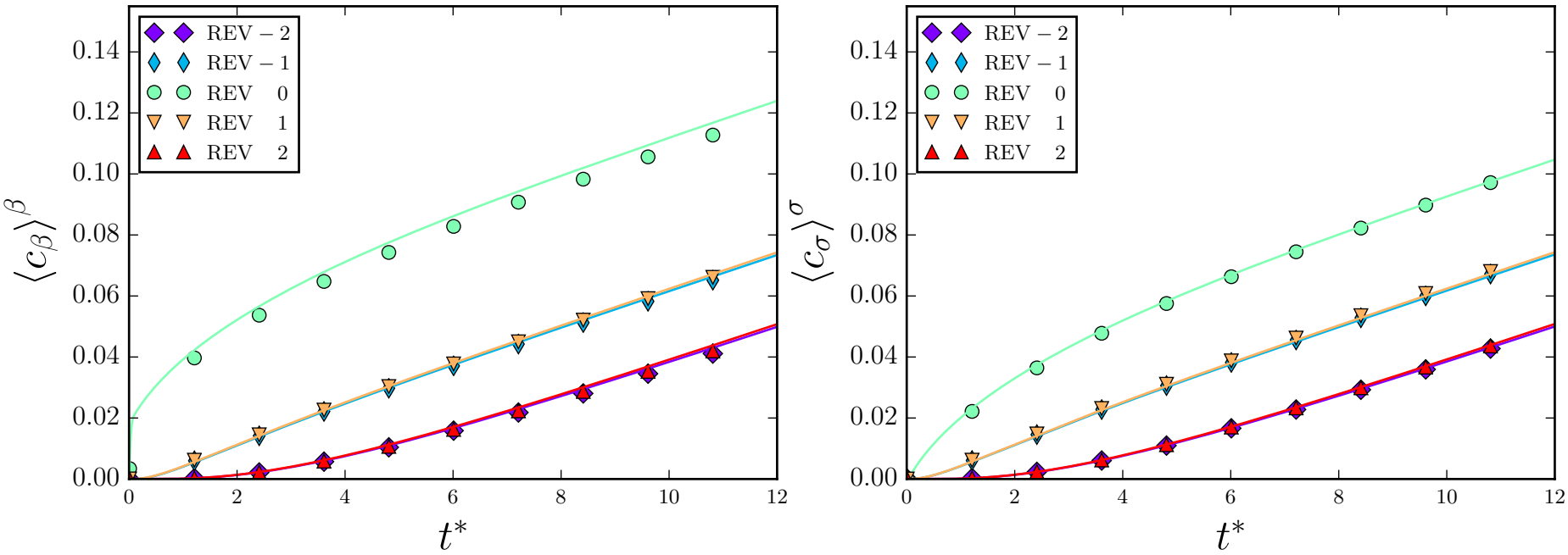
  An example of projection function on a elements is given by:

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

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

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

All results, order 3

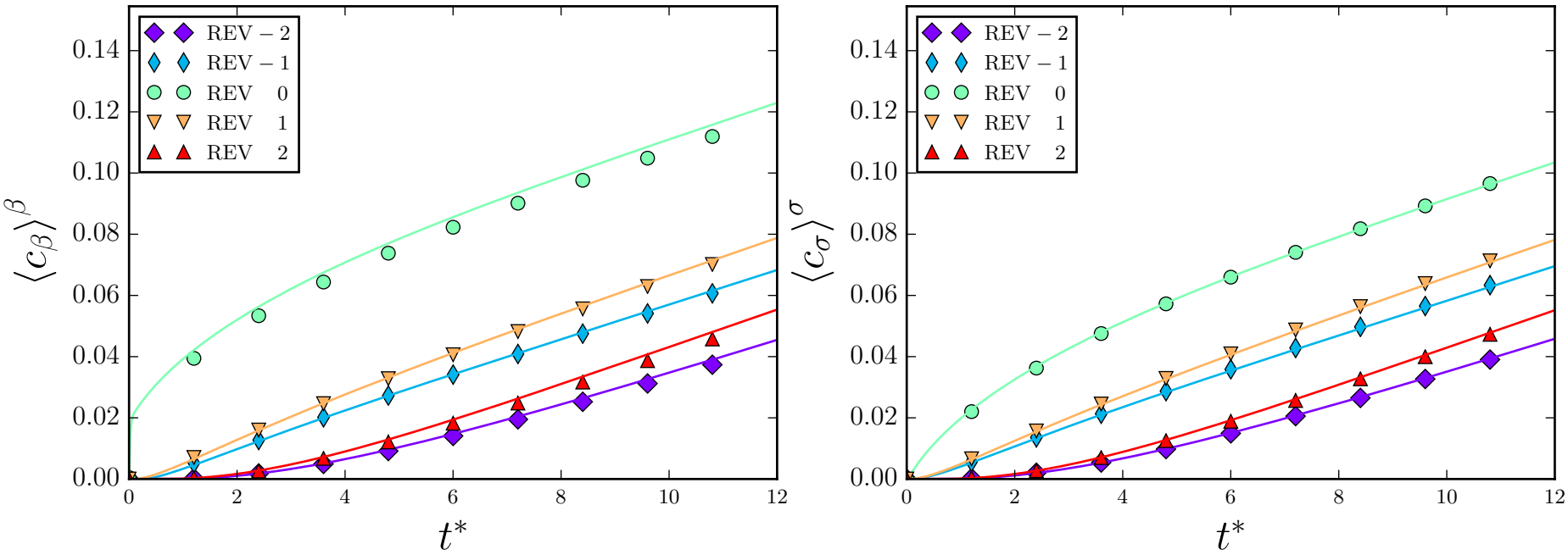


$$P_e^{\mathrm{REV}} = 0.1,\ K_m = 3 \times 10^{-2}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

All results, order 3

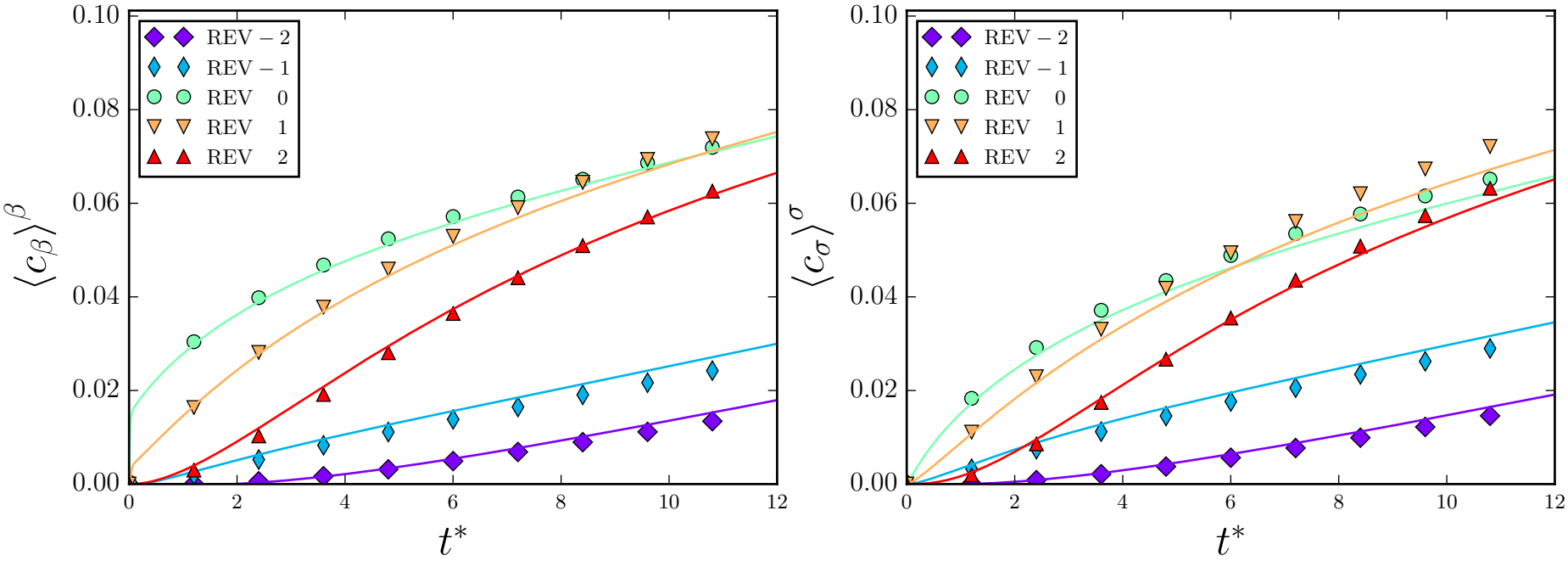


$$P_e^{\mathrm{REV}} = 1,\ K_m = 3 \times 10^{-2}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

All results, order 3

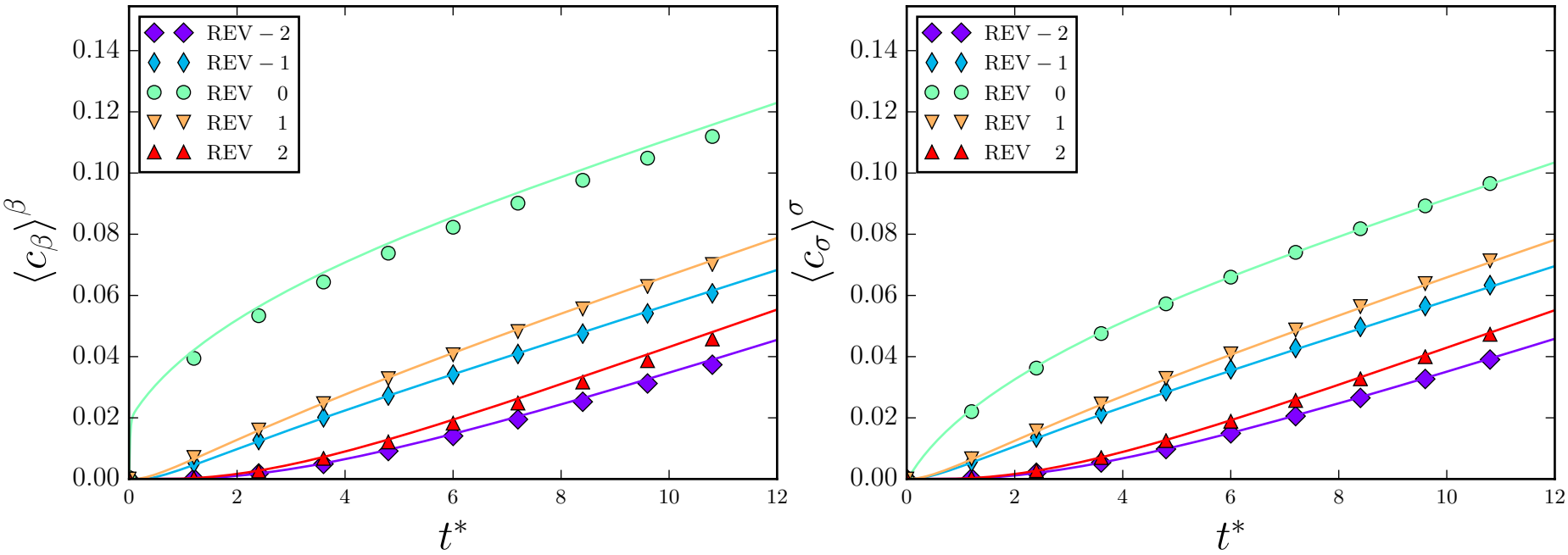


$$P_e^{\mathrm{REV}} = 10,\ K_m = 3 \times 10^{-2}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

All results, order 3

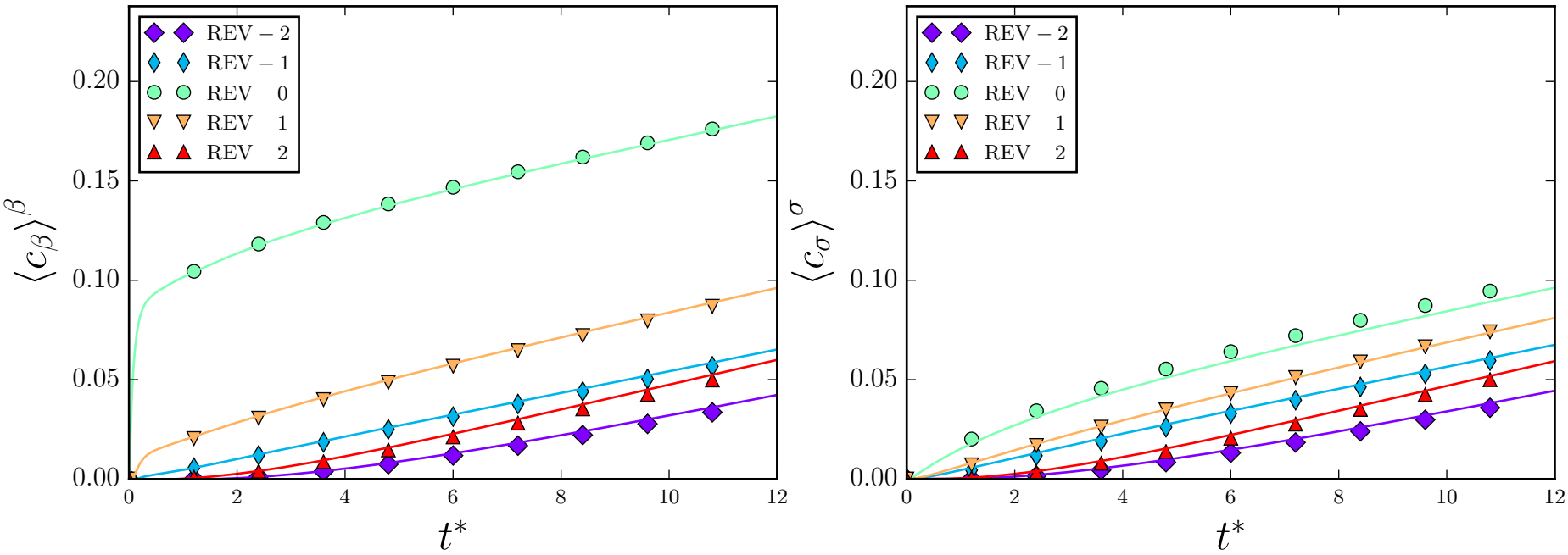


$$P_e^{\mathrm{REV}} = 1,\ K_m = 3 \times 10^{-2}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

All results, order 3

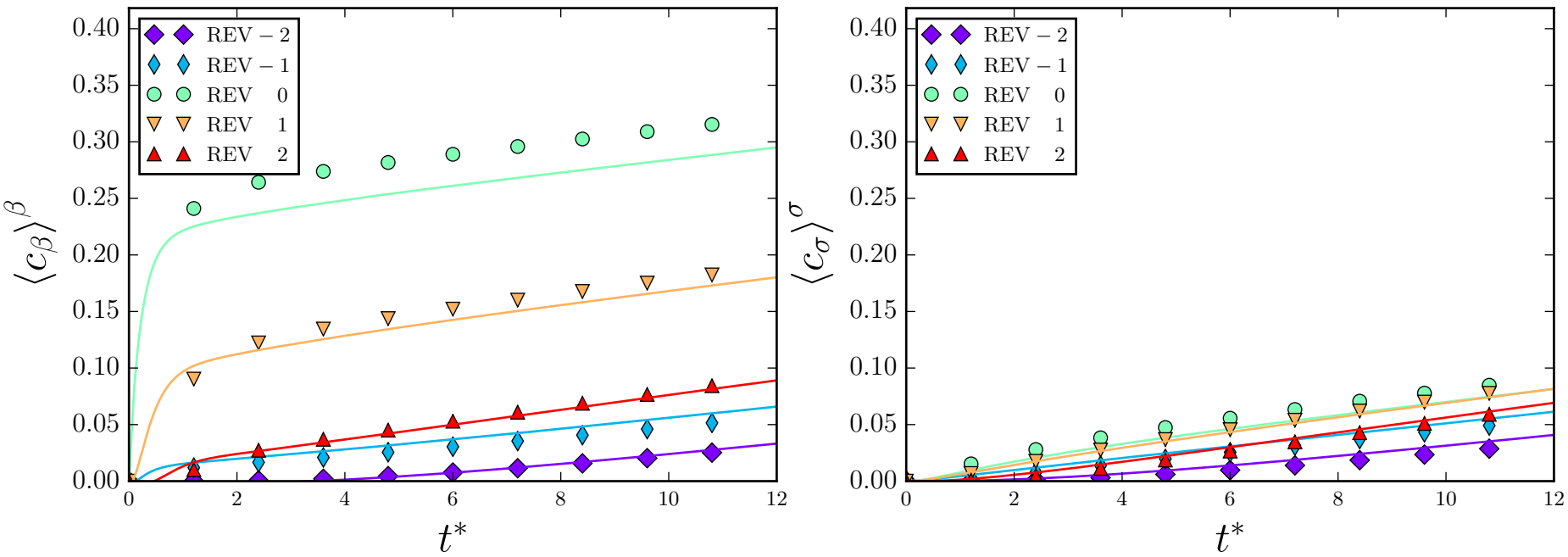


$$P_e^{\mathrm{REV}} = 1,\ K_m = 3 \times 10^{-3}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$

All results, order 3



$$P_e^{\mathrm{REV}} = 10,\ K_m = 3 \times 10^{-4}$$

Adimentional coefficients

- Péclet number $P_e^{\mathrm{REV}} = \dfrac{\langle \boldsymbol{u} \rangle_z^\beta \, L^{\mathrm{REV}}}{D_v}$
- Membrane Permeability $K_m^* = \dfrac{D_e}{D_v} \dfrac{r}{e}$