Perivascular pathways and the dimension-2 gap

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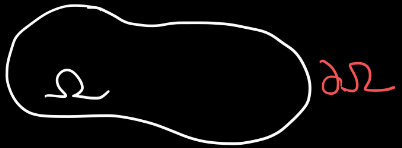
Laplace's equation, boundary conditions, and the trace theorem

Define $u \in H^1_g(\Omega) \equiv W^{1,2}_g(\Omega)$ such that

$$\int_\Omega \operatorname{grad} u \cdot \operatorname{grad} v \, \mathrm{d}x = 0 \quad \forall\, v \in H^1_0(\Omega)$$

where $H^1_g = \{u \in L^2 \mid \operatorname{grad} u \in L^2 \mid \operatorname{tr} u = g\}$



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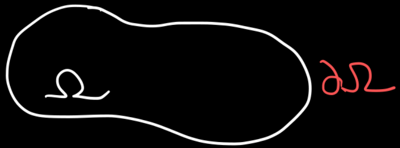

In what sense is u solving

$$\begin{aligned} -\Delta u &= 0 \quad \text{in } \Omega, \\ u &= g \quad \text{on } \partial\Omega, \end{aligned}$$

... in terms of continuity, differentiability ...?

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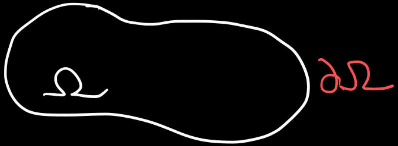

For $\Omega \subset \mathbb{R}^d$ $(d > 1)$, $u \in H^1_g$ need not be continuous; e.g.

$$u(x, y) = \sqrt{-\ln(x^2 + y^2)} \in H^1(\Omega \subset \mathbb{R}^2)$$

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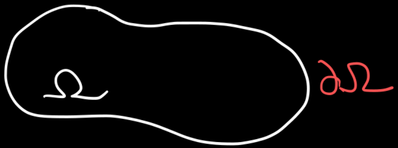

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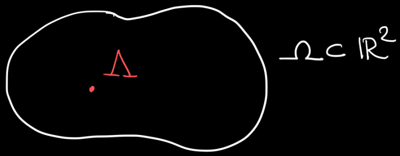
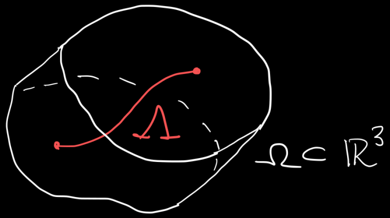
Theorem (Trace theorem)

Assume that Ω is bounded and Lipschitz. There exists a linear operator $\operatorname{tr} : W^{1,p}(\Omega) \to L^p(\partial\Omega)$ such that for $1 \leqslant p < \infty$

$$\begin{aligned} \operatorname{tr} u &= u|_{\partial\Omega}, && \forall\, u \in W^{1,p} \cap C(\bar{\Omega}), \\ \|\operatorname{tr} u\|_{L^p(\partial\Omega)} &\lesssim \|u\|_{W^{1,p}(\Omega)} && \forall\, u \in W^{1,p}(\Omega). \end{aligned}$$

When are traces with higher dimensional gaps well-defined?





Consider a submanifold $\Lambda \subset \Omega$ of dimension $d-2$.

When is $u|_\Lambda$ well-defined and in what sense?

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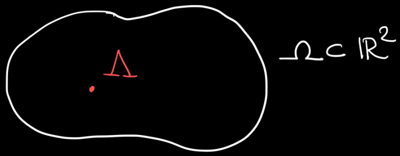

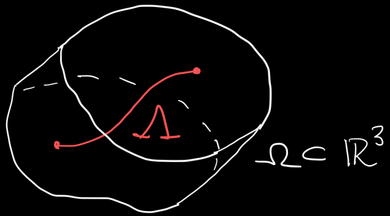

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Theorem (Sobolev embedding theorem–)

If $\Omega \subset \mathbb{R}^d$ *is Lipschitz, then for* $p \geq \frac{d}{2}$,

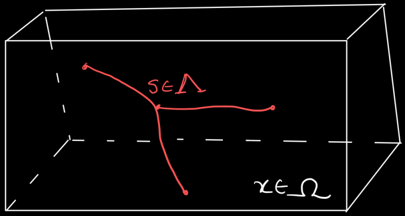
$$W^{2,p}(\Omega) \subseteq C(\bar{\Omega}).$$

Theorem (Morrey's inequality–)

If $\Omega \subset \mathbb{R}^d$ *is Lipschitz, then for* $p > d$,

$$W^{1,p}(\Omega) \subseteq C(\Omega).$$

Systems of elliptic equations coupled between $d \times (d-2)$D domains



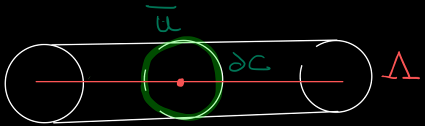
Find $u : \Omega \to \mathbb{R}$ and $\hat{u} : \Lambda \to \mathbb{R}$ such that

$$-\operatorname{div}(k \operatorname{grad} u) - f(u, \hat{u}) = 0 \quad \text{in } \Omega,$$
$$-\partial_s(\hat{k}\partial_s \hat{u}) + \hat{f}(u, \hat{u}) = 0 \quad \text{in } \Lambda.$$

Here, k and $\hat{k}$ are the respective hydraulic conductivities, and f and $\hat{f}$ represent the flux into Ω from Λ and into Λ from Ω, respectively.

$$\hat{f}(u, \hat{u}) = \beta(\hat{u} - \bar{u}), \qquad \bar{u} = \|\partial C\|^{-1} \int_{\partial C} u \, \mathrm{d}\theta,$$
$$f(u, \hat{u}) = \hat{f}(u, \hat{u})\delta_\Lambda.$$

[D'Angelo and Quarteroni (2008)]

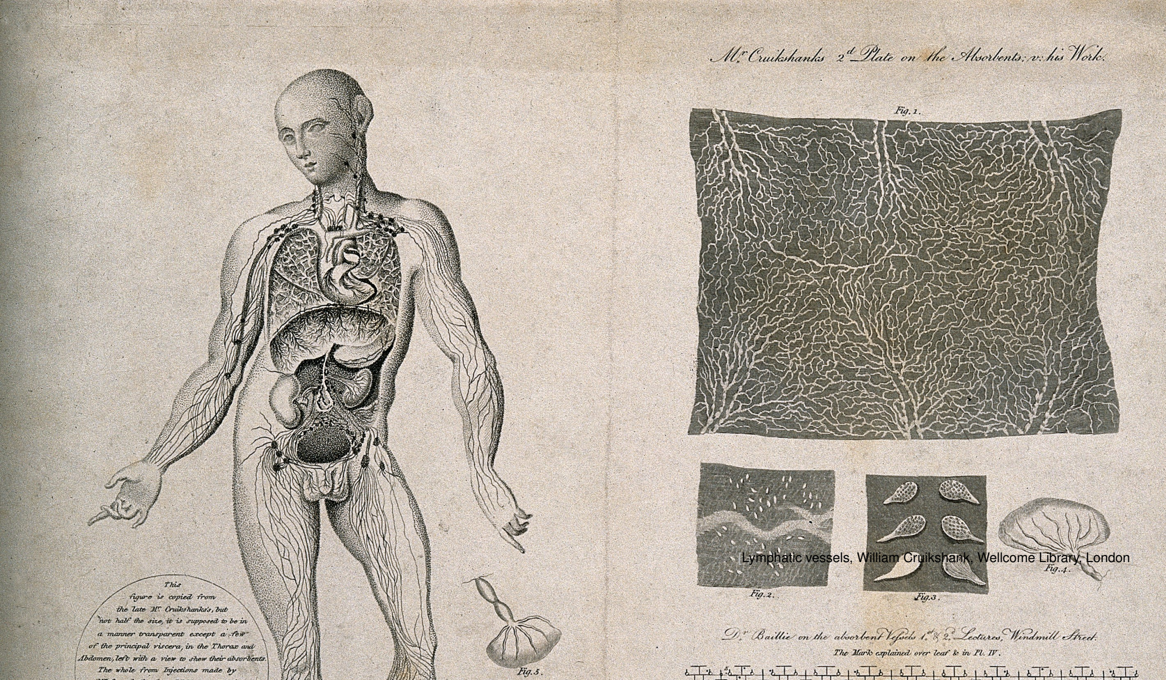


Example: tissue perfusion

Consider steady perfusion in a biological tissue represented by Ω and an embedded network of topologically one-dimensional blood vessels Λ.

Define spatial coordinates: $x \in \Omega \subset \mathbb{R}^d$ and $s \in \Lambda \subset \mathbb{R}$.

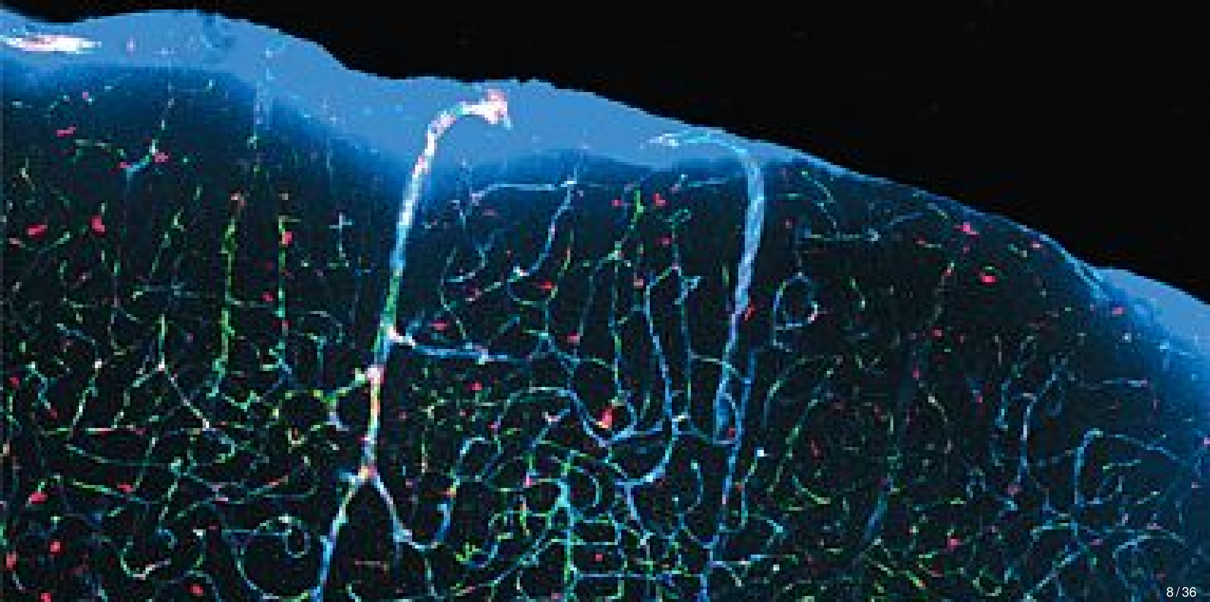
[Zebrafish vasculature, Eunice Kennedy Shriver National Institute of Child Health and Human Development]



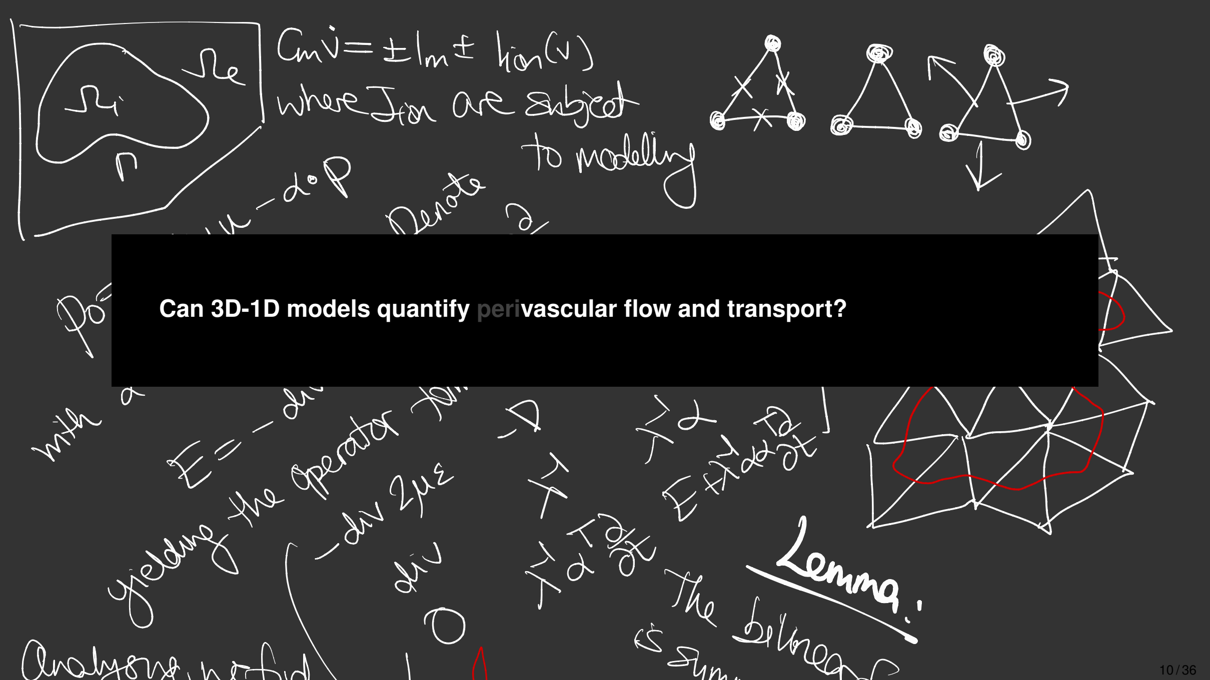
Lymphatic vessels, William Cruikshank, Wellcome Library, London

[Pepper roots, New York Times Illustration, Jonathan Bartlett (Dec 14 2020)]

[Perivascular spaces, NIH Research Matters Graphics, Maiken Nedergaard (Oct 28 2013)]



Can 3D-1D models quantify perivascular flow and transport?



Can 3D-1D models quantify perivascular flow and transport?

The D'A-Q. 3D-1D equations are well-posed in weighted Sobolev spaces (only)

[D'Angelo and Quarteroni (2008)]

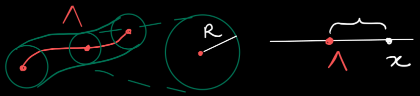
Find $u : \Omega \to \mathbb{R}$ and $\hat{u} : \Lambda \to \mathbb{R}$ such that

$$-\operatorname{div}(k \operatorname{grad} u) - \beta(\hat{u} - \bar{u})\delta_\Lambda = 0 \quad \text{in } \Omega, \qquad \text{(3a)}$$

$$-\partial_s(\hat{k}\partial_s \hat{u}) + \beta(\hat{u} - \bar{u}) = 0 \quad \text{in } \Lambda, \qquad \text{(3b)}$$

where $\bar{u}$ is a circumferential average:

$$\bar{u}(s) = (2\pi R)^{-1} \int_0^{2\pi} u(s, R, \theta)\, \mathrm{d}\theta, \quad s \in \Lambda.$$



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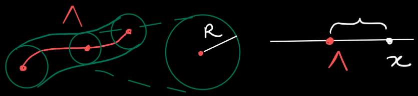

Idea: Analyze the decoupled elliptic problem with (low regularity) line measure terms: given $\hat{u}$, find $u : \Omega \to \mathbb{R}$ solving (3a).

[Stampacchia (1965), Brezis and Strauss (1973), Scott (1973), Casas (1985)]

What are U, V such that $u \in U$ solves

$$(k \operatorname{grad} u, \operatorname{grad} v)_\Omega + (\beta \bar{u}, v)_\Lambda = (\beta \hat{u}, v)_\Lambda, \qquad (4)$$

for all $v \in V$? (Not $H^1(\Omega)$!)

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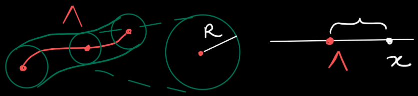

Introduce weighted Sobolev spaces $\alpha \in (-1, 1)$:

$$L^2_\alpha(\Omega) = \{u \,|\, \operatorname{dist}^\alpha u \in L^2(\Omega), \operatorname{dist}(x) = \operatorname{dist}(x, \Lambda)\}$$

$$H^1_\alpha(\Omega) = \{u \in L^2_\alpha(\Omega) \,|\, \operatorname{grad} u \in L^2_\alpha(\Omega)^d\}$$

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Theorem (Well-posedness, D'A & Q (2008))

There exists $0 < \alpha < 1$ such that (4) with $U = \mathring{H}^1_\alpha(\Omega)$, $V = H^1_{-\alpha}(\Omega)$ is well-posed.

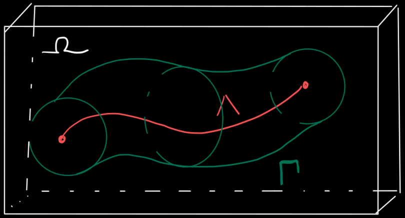
Proof.

Via a generalized Lax-Milgram theorem, continuity and coercivity in the weighted spaces. □

Coupling over the interface surface gives well-posedness in standard Sobolev spaces

[Köppl, Vidotto, Wohlmuth, Zunino (2018) ($d = 2$)]

Consider the curve Λ, the cylinder surface Γ, and the embedding domain $\Omega \subset \mathbb{R}^d$.



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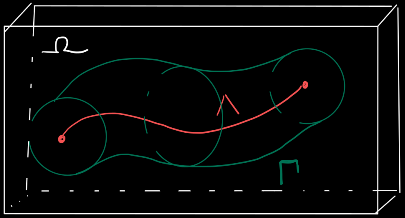

New idea: Analyze the decoupled 3D problem with (not line but) surface measure terms: given $\tilde{u} : \Gamma \to \mathbb{R}$, find $u : \Omega \to \mathbb{R}$ such that

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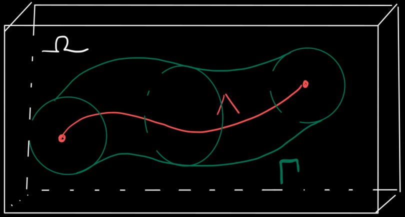

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Theorem (Well-posedness, KVWZ (2018))

For R sufficiently small, (5) *is well-posed for* $U \times V = H^1_0(\Omega) \times H^{-1}(\Omega)$, *and*

$$u \in H^1_0(\Omega) \cap H^{\frac{3}{2}-\epsilon}$$

Proof.

Lax-Milgram with tailored trace inequality. □

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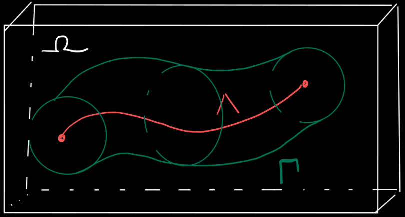

Q1 Existence and uniqueness of solutions?

Q2 How are these equations derived?

Q3 What is the modelling error?

Q4 What is the approximation error?

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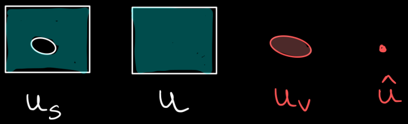
How well do coupled 3D-1D elliptic problems approximate their 3D-3D counter parts?



How large are the modelling errors:

$$\|u_v - \hat{u}\|_{X(\Omega_v)} \leqslant \dots,$$
$$\|u_s - u\|_{Y(\Omega_s)} \leqslant \dots \qquad ?$$

[Köppl, Vidotto, Wohlmuth, Zunino (2018), Laurino and Zunino (2019)]

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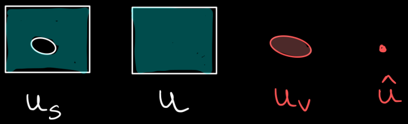

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find $u_s : \Omega_s \to \mathbb{R}$, $u_v : \Omega_v \to \mathbb{R}$:

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The surface-coupled 3D-1D elliptic problem over
$\Omega \times \Lambda$: find $\hat{u} : \Lambda \to \mathbb{R}$, $u : \Omega = \Omega_s \cup \Omega_v \to \mathbb{R}$:

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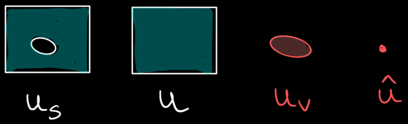

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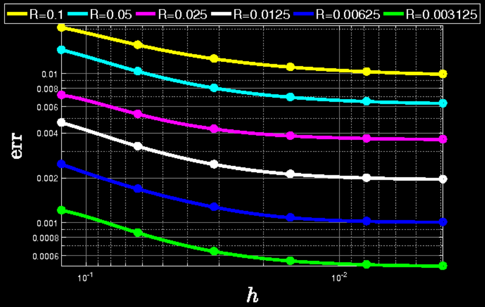
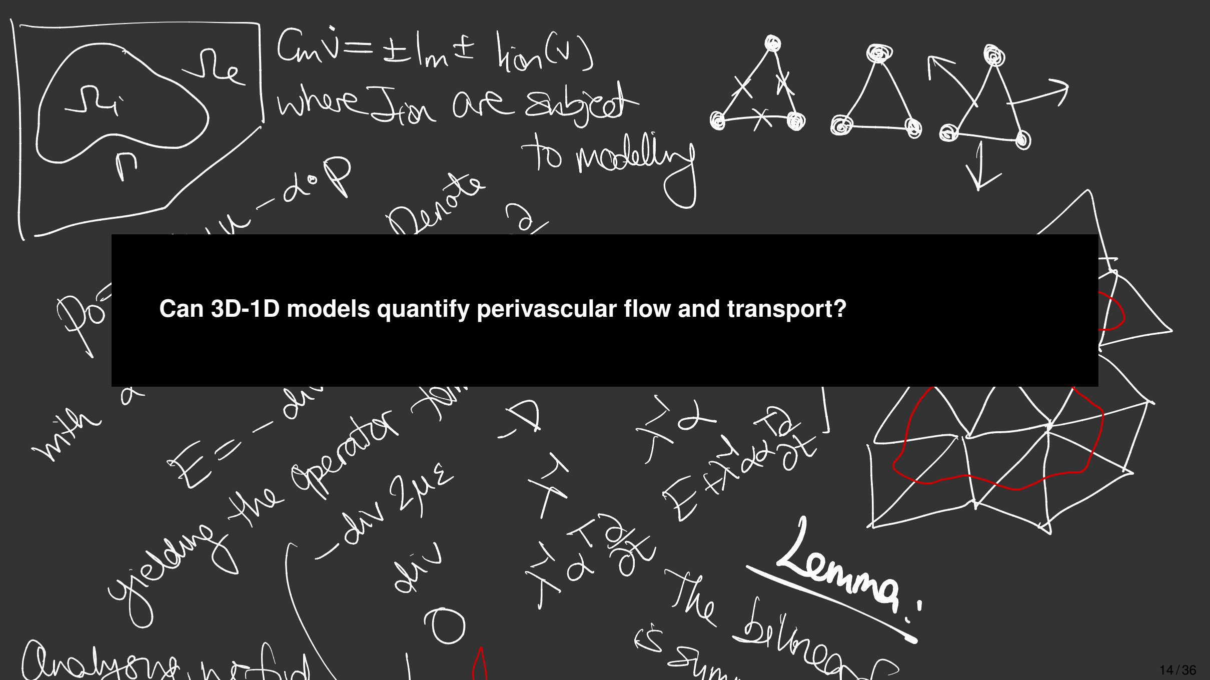
[Köppl, Vidotto, Wohlmuth, Zunino (2018), Laurino and Zunino (2019)]

Example (KVWZ, Fig. 2): Numerical modelling errors

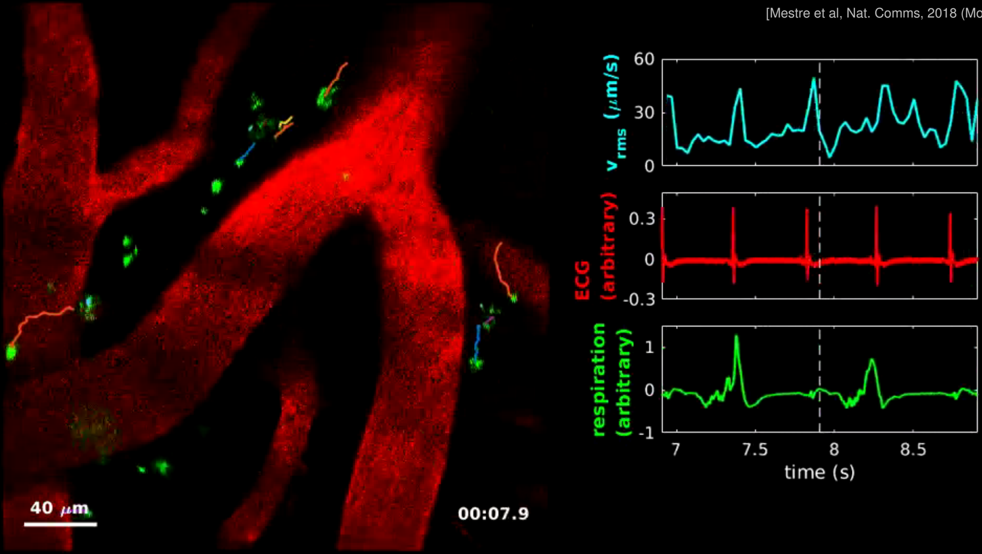


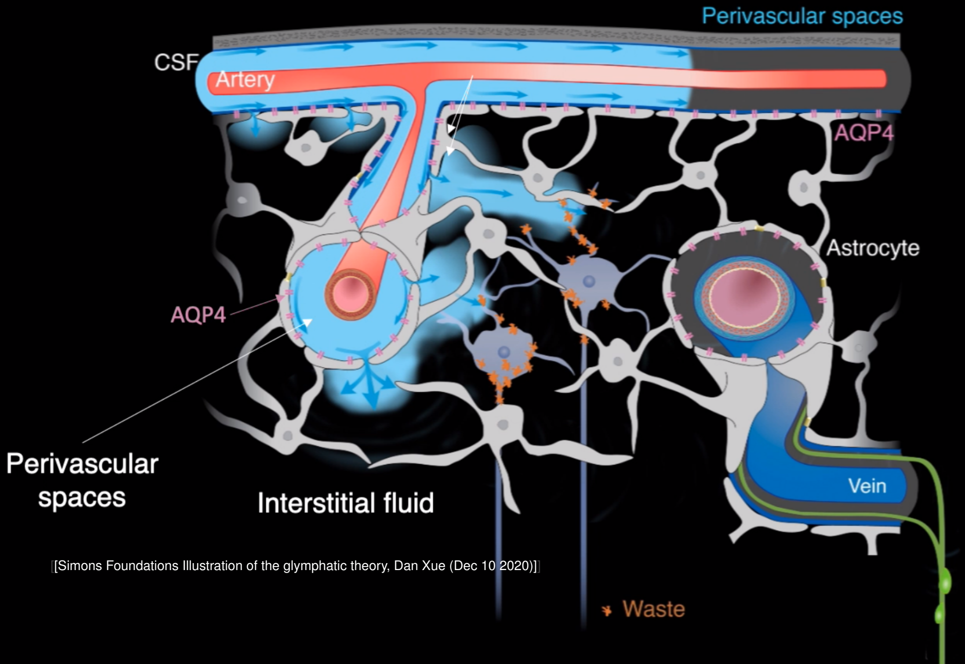


Can 3D-1D models quantify perivascular flow and transport?

Molecular transport via perivascular pathways underpins human brain clearance

[Mestre et al, Nat. Comms, 2018 (Movie S2)]





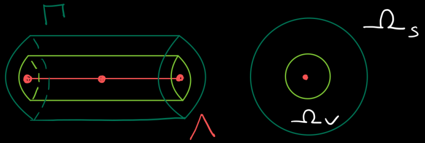
[Simons Foundations Illustration of the glymphatic theory, Dan Xue (Dec 10 2020)]

Iliff et al, 2012
Louveau et al., 2015

Time-dependent transport by convection and diffusion in moving perivascular spaces

[Masri, Zeinhofer, Kuchta, Rognes (2023)]

Consider a generalized annular cylinder $\Omega_v(t)$ with center line Λ representing a perivascular space (PVS) and its outer surroundings $\Omega_s(t)$, and their interface Γ.



Time-dependent transport by convection and diffusion in moving perivascular spaces

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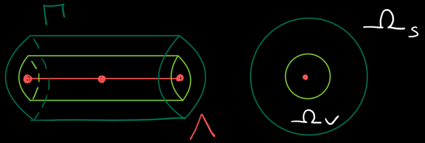

The net velocity $\tilde{u}_i = u_i - w$ is the convective velocity u_i relative to domain velocity w $(i \in \{v, s\})$.

3D-3D PVS-tissue transport

Find the concentrations $c_v(t) : \Omega_v(t) \to \mathbb{R}$ and $c_s(t) : \Omega_s(t) \to \mathbb{R}$ such that

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$$-(D_v \operatorname{grad} c_v - \tilde{u}_v c_v) \cdot n_v - \zeta(c_v - c_s) = 0 \quad \text{on } \Gamma(t),$$

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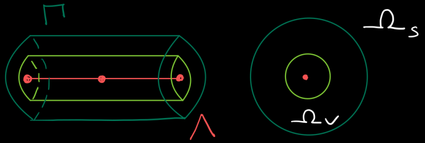

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Theorem

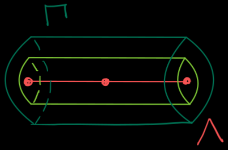
Under natural assumptions on the geometry, there exists a unique solution $(c_v(t), c_s(t)) \in W$ that is uniformly bounded in terms of the data.

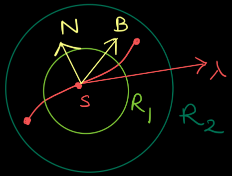
Proof.

Use abstract framework for parabolic PDEs on evolving surfaces (Alphonse et al, 2015). □

3D perivascular transport is described by 1D axial transport for constant cross-sections

[Masri, Zeinhofer, Kuchta, Rognes (2023)]





The perivascular space

$$\Omega_v(t) = \{\lambda(s) + r\cos(\theta)N(s) + r\sin(\theta)B(s),\\ 0 < s < L, 0 \leqslant \theta < 2\pi, R_1 < r < R_2\}$$

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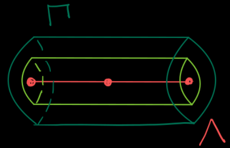

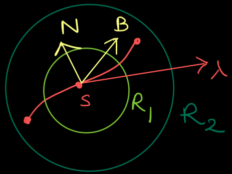

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For each cross-section $\Theta(s)$ with area $A(s)$, outer boundary $\partial\Theta_2$ and perimeter $P(s)$, define

$$\langle f\rangle(s) = \frac{1}{A(s)}\int_{\Theta(s)} f \quad \text{(cross-section average)}$$

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If $c_v(t) : \Omega_v(t) \to \mathbb{R}$ solves

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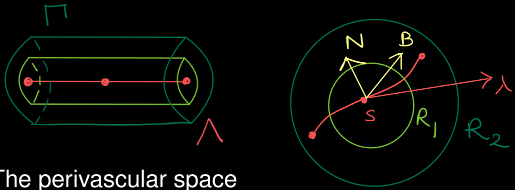

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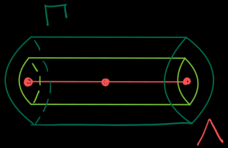

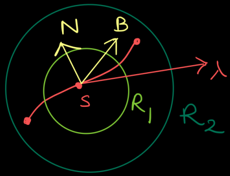

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Proof.

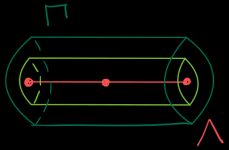
Integrate (7) over segment S of $\Omega_v(t)$, $s \in (s_1, s_2)$ e.g.

$$\int_S \partial_t c_v = \partial_t \int_S c_v - \int_{\partial S} c_v w\cdot n$$
$$= \int_{s_1}^{s_2} \partial_t(A\langle c_v\rangle) - \int_{\partial S} c_v w \cdot n.$$

Coupled 3D-1D perivascular transport equations are well-posed over $H^1(\Omega) \times H^1(\Lambda)$

[Masri, Zeinhofer, Kuchta, Rognes (2023)]

Surface coupling: Observe that (after i.b.p.):



$$\int_{\Gamma} (c_s - c_v) v = \int_{\Lambda} \int_{\partial \Theta_2} (c_s - c_v) v$$

$$\approx \int_{\Lambda} \int_{\partial \Theta_2} (\bar{c}_s - \bar{c}_v) \bar{v} = \int_{\Lambda} P (\bar{c}_s - \hat{c}) \bar{v}$$

$\square$

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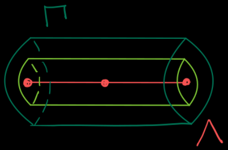

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Introduce bounded extension $\mathcal{E} : X(\Omega_s) \to Y(\Omega)$.

Coupled 3D-1D perivascular transport equations

Find $c : (0,T) \times \Omega \to \mathbb{R}$ and $\hat{c} : (0,T) \times \Lambda \to \mathbb{R}$ s.t.

$$\langle \partial_t c, v\rangle + a_\Omega(c,v) + b_\Lambda(\bar{c} - \hat{c}, \bar{v}) = \langle \mathcal{E} f, v\rangle \quad \forall\, v,$$
$$\langle A\partial_t \hat{c}, \hat{v}\rangle + a_\Lambda(c,v) + b_\Lambda(\hat{c} - \bar{c}, \hat{v}) = \langle \bar{f}, \hat{v}\rangle \quad \forall\, \hat{v}.$$

The bilinear forms:

$$a_\Omega(c,v) = (\mathcal{E} D_s \operatorname{grad} c - \mathcal{E} u_s c, \operatorname{grad} v)_\Omega,$$
$$a_\Lambda(\hat{c},\hat{v}) = (D_v A \partial_s \hat{c} - A\langle u_{v,s}\rangle \hat{c}, \partial_s \hat{v})_\Lambda + (\partial_t A \hat{c}, \hat{v})_\Lambda,$$
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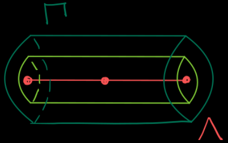


Theorem

Assuming uniformly bounded data (A, $\langle u_{v,s}\rangle$, $\mathcal{E}u_s$, $\mathcal{E}D_s$), the coupled 3D-1D perivascular transport equations is well-posed over

$$\{c \in L^2(0,T,H^1_0(\Omega)), \partial_t c \in L^2(0,T,H^{-1}(\Omega))\}\times$$
$$\{\hat{c} \in L^2(0,T,H^1_A(\Lambda)), \partial_t \hat{c} \in L^2(0,T,H^{-1}_A(\Lambda))\}$$

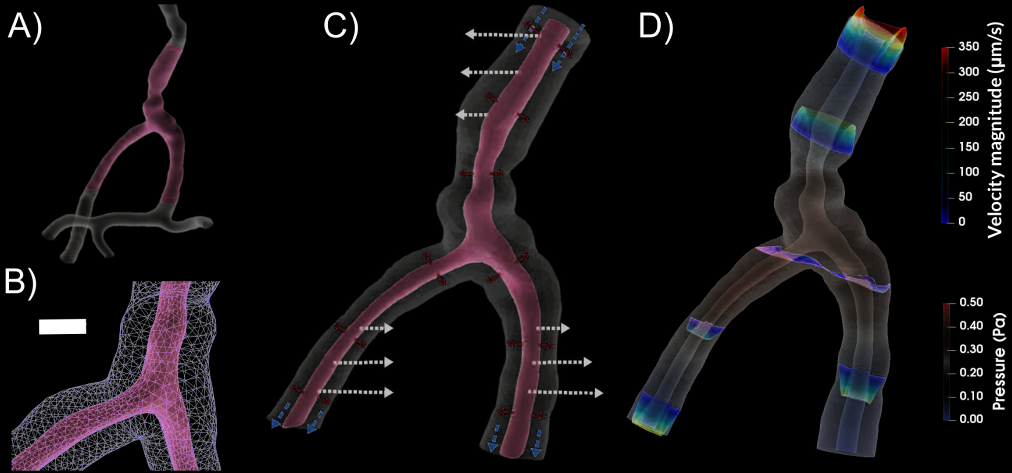
Proof.

Use J.-L. Lions theorem over $H^1_0(\Omega) \times H^1_A(\Lambda)$ and show that the coupled variational form is continuous and satisfies a Gårding-type inequality. □

Perivascular flow underlying perivascular transport

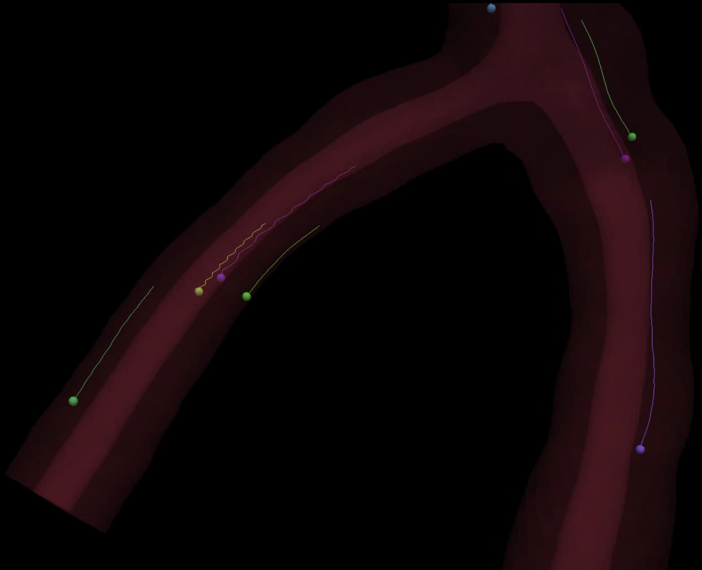
What are the mechanisms underlying perivascular flow

[Daversin-Catty, Vinje, Mardal, Rognes (2020)]



Incompressible Stokes flow (low Reynolds, low Womersley numbers)

Rigid motions, arterial wall pulsations and a static pressure gradient induced PVS transport in agreement with experimental findings



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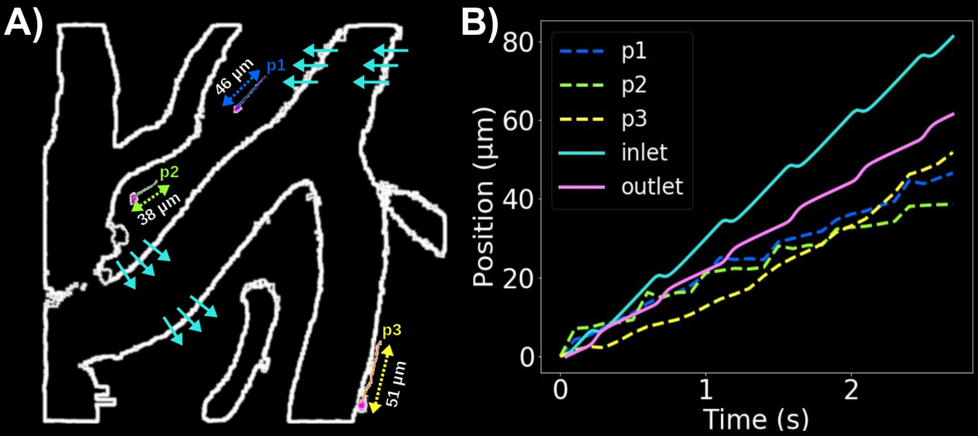
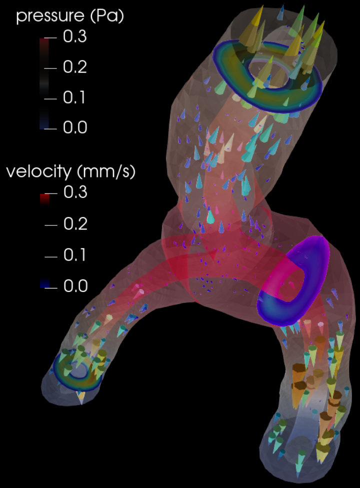
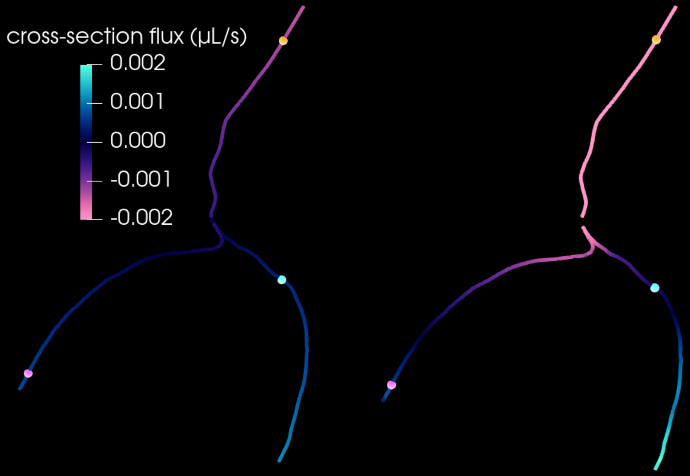


Wall pulsation frequency: 2.2 Hz. Static pressure gradient: 1.46 mmHg.

Motion- and pressure-driven perivascular flow is well-approximated by 1D models

[Daversin-Catty, Gjerde, Rognes (2022)]





Can 3D-1D models quantify perivascular flow and transport?

Will the 3D-3D and 3D-1D perivascular transport models agree for infinitely thin vessels?

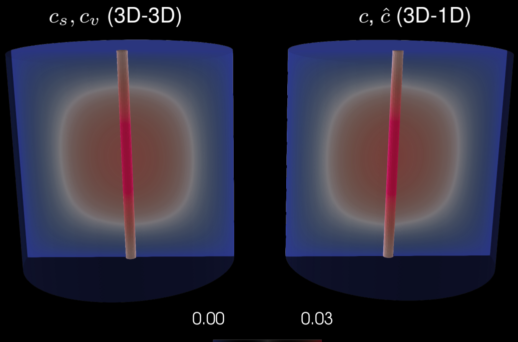
[Masri, Zeinhofer, Kuchta, Rognes (2023)]

Target: To quantify the modelling errors in the PVS:

$$\|c_v - \hat{c}\|_{L^2(0,T,L^2(\Omega_v))},$$

and in the surroundings

$$\|c_s - c\|_{L^2(0,T,L^2(\Omega_s))}.$$



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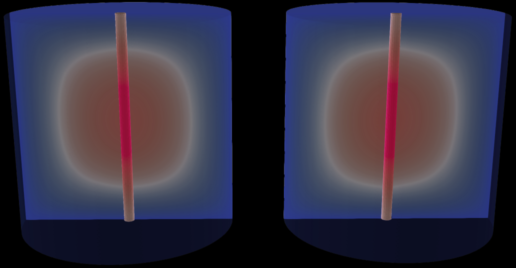
c_s, c_v (3D-3D) $\qquad$ c, $\hat{c}$ (3D-1D)



3D-3D model

$c_s(t) : \Omega_s(t) \to \mathbb{R}$, $c_v(t) : \Omega_v(t) \to \mathbb{R}$ solve:

$$\begin{aligned} \partial_t c_s - \operatorname{div}(D \operatorname{grad} c_s - u c_s) &= f \text{ in } \Omega_s, \\ \partial_t c_v - \operatorname{div}(D \operatorname{grad} c_v - u c_v) &= f \text{ in } \Omega_v, \\ (D \operatorname{grad} c_v - \tilde{u} c_v) \cdot n + \zeta(c_v - c_s) &= 0 \text{ on } \Gamma, \end{aligned}$$

+flux balance at Γ, boundary and initial conditions.

3D-1D model

$c(t) : \Omega \to \mathbb{R}$, $\hat{c}(t) : \Lambda \to \mathbb{R}$ solve:

$$\partial_t c - \operatorname{div}(\mathcal{E} D \operatorname{grad} c - \mathcal{E} u c) + \zeta(\bar{c} - \hat{c})\delta_\Gamma = \mathcal{E} f \text{ in } \Omega$$

$$\partial_t (A\hat{c}) - \partial_s \left(D A \partial_s \hat{c} - A\langle u_s \rangle \hat{c}\right) + P\zeta(\hat{c} - \bar{c}) = A\langle f \rangle$$

Quantifying how the modelling error in perivascular spaces (PVS) depend on their width ϵ

[Masri, Zeinhofer, Kuchta, Rognes (2023)]

Proof ($w = 0$, $D = 1$, $\zeta = 1$, $f = 0$).

Introduce PVS modelling error $e = c_v - \hat{c}$.

(I) Introduce a dual problem,

$$-\langle \partial_t h, \phi \rangle + (\operatorname{grad} h, \operatorname{grad} \phi) + (h, \phi)_\Gamma \\ - (u \operatorname{grad} h, \phi) = (g, \phi) \quad \forall\, \phi \in H^1(\Omega_v),$$

that is stable in $L = L^2(0, T, L^2(\Omega_v))$

$$\|h, \operatorname{grad} h\|_L + \cdots \lesssim \|g\|_L.$$

□

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$$
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$$

(II) Use duality ($g, \phi = e$) to obtain error identity

$$
\begin{aligned}
\|e\|_L^2 = \int_0^T &((u_v - \hat{u}_v)\hat{c}, \operatorname{grad} h) + (c_s, h)_\Gamma - (P\bar{c}, \bar{h})_\Lambda \\
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$$\|e\|_L^2 = \int_0^T ((u_v - \hat{u}_v)\hat{c}, \operatorname{grad} h) + (c_s, h)_\Gamma - (P\bar{c}, \bar{h})_\Lambda + (\langle h \rangle - \bar{h}, \bar{c} - \hat{c})_\Gamma + (e(0), h(0))) + \dots$$

Recall that

$$\langle v \rangle = \frac{1}{A} \int_\Theta v, \qquad \bar{v} = \frac{1}{P} \int_{\partial\Theta_2} v.$$

(III) Bound each term e.g.

$$(\langle h \rangle - \bar{h}, \bar{c} - \hat{c})_\Gamma \leqslant \|\langle h \rangle - \bar{h}\|_\Gamma \|\bar{c} - \hat{c}\|_\Gamma \leqslant \|\langle h \rangle - h\|_\Gamma \|\bar{c} - \hat{c}\|_\Gamma$$

□

Quantifying how the modelling error in perivascular spaces (PVS) depend on their width ϵ

[Masri, Zeinhofer, Kuchta, Rognes (2023)]

Proof ($w = 0$, $D = 1$, $\zeta = 1$, $f = 0$).

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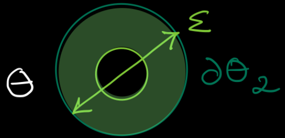
Trace inequality?

□

The trace inequality in non-convex domains and dependence on the domain size

[Masri, Zeinhofer, Kuchta, Rognes (2023)]



Lemma (Trace versus PVS)

For an annulus Θ with diameter $\epsilon = 2R_2$, the following trace inequality holds, with K independent of ϵ, for $v \in H^1(\Theta)$

$$\|v\|^2_{L^2(\partial\Theta)} \leqslant K \left(\epsilon^{-1}\|v\|^2_{L^2(\Theta)} + \epsilon\|\operatorname{grad} v\|^2_{L^2(\Theta)}\right)$$

Proof.

Use similar argument as standard result for convex domains and e.g. circles, argue for smooth functions and use density in $H^1(\Theta)$. □

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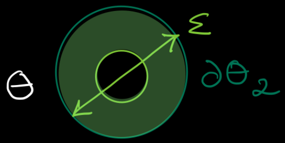

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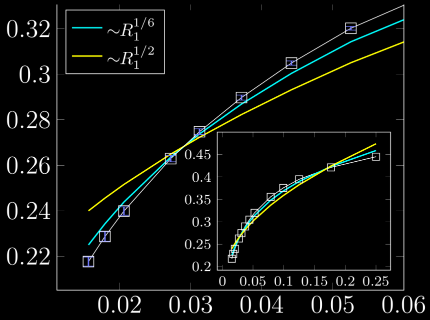
$$\|v\|^2_{L^2(\Gamma)} \leqslant K\epsilon|\ln\epsilon|\|v\|^2_{H^1(\Omega_s)}$$



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Poincaré inequality? □

The Poincaré inequality in non-convex domains and dependence on the domain size

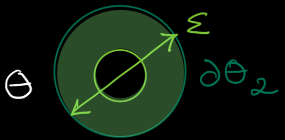
Lemma (Poincaré inequality over an annulus)

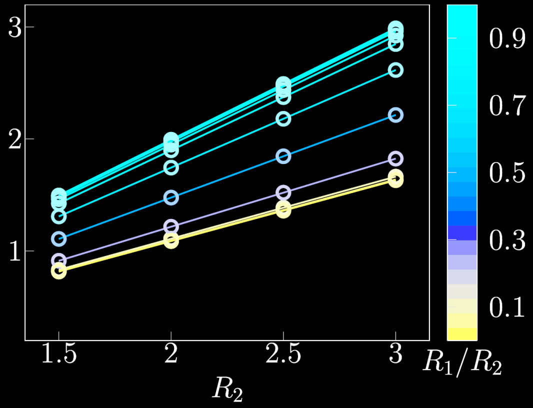
For an annulus Θ of diameter ϵ, there exists a constant K independent of ϵ such that

$$\|v - \langle v \rangle\|_{L^2(\Theta)} \leqslant K\epsilon \|\operatorname{grad} v\|_{L^2(\Theta)}, \quad \forall\, v \in H^1(\Theta)$$

Proof.

Lack of convexity is not a problem here, see e.g. Guermond and Ern (2021). □





$K\epsilon$ depends linearly on $\epsilon = 2R_2$, both as $R_1 \to 0$, and $R_1 \to R_2$.

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For $v \in H^1(\Omega_v)$,

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The modelling error in the perivascular spaces decays as $(\epsilon|\ln\epsilon|)^{1/2}$ modulo non-axial data

[Masri, Zeinhofer, Kuchta, Rognes (2023)]

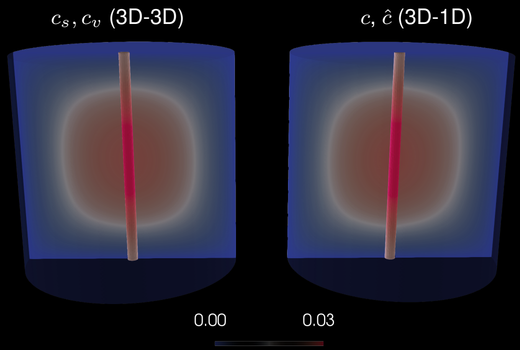
Theorem (Model error in the perivascular space)

Let c_v, c_s be weak solutions to the coupled 3D-3D perivascular transport problem and assume that $c_v(0) \in H^1(\Omega_v)$. Let $c, \hat{c}$ be the weak solutions to the reduced coupled 3D-1D perivascular transport problem.

Then, for $\epsilon = \max \operatorname{diam} \Theta(s,t)$

$$\|c_v - \hat{c}\|_{L^2(0,T;L^2(\Omega_v))} \lesssim \epsilon + \epsilon^{1/2} + (\epsilon|\ln\epsilon|)^{1/2} + \|u_{v,r}, u_{v,\theta}\| + \max \partial_s |R_1, R_2|$$

Here, the inequality constant(s) depend on the data, parameters and the solutions $c, \hat{c}$, and c_s, but are bounded independently of ϵ.



$(h_{\max} \approx 0.02)$

2ϵ	E_v	rate
0.1	4.39×10^{-4}	-
0.05	5.26×10^{-5}	3.06
0.025	1.41×10^{-5}	1.90
0.0125	7.90×10^{-6}	0.84

The modelling error in the surroundings decays as $(\epsilon|\ln\epsilon|)^{1/2}$ for regular solutions

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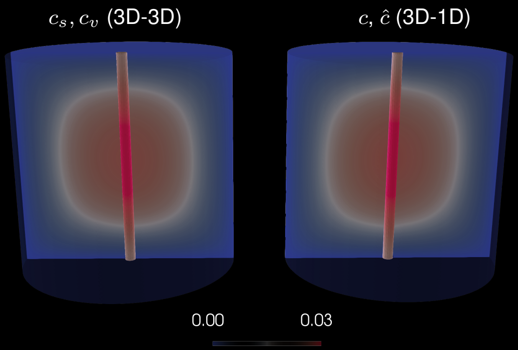
Then, for $\epsilon = \max \operatorname{diam} \Theta(s,t)$

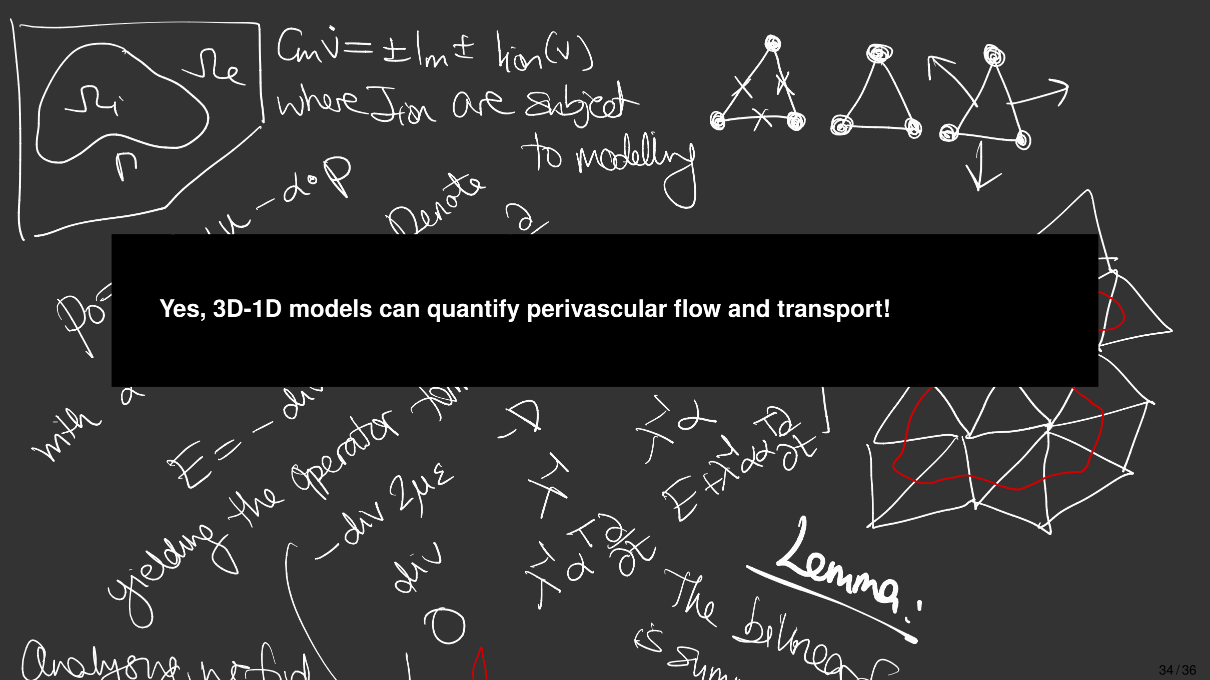
$$\|c_s - c\|_{L^2(0,T;L^2(\Omega_s(t)))} \lesssim \epsilon^{2/3} + \epsilon|\ln\epsilon| + (\epsilon|\ln\epsilon|)^{1/2}.$$

Here, the inequality constant(s) depend on the data, parameters, and solutions c, c_s and c_v, but are bounded independently of ϵ.

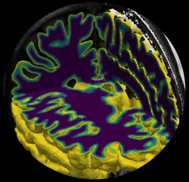


$(h_{\max} \approx 0.02)$

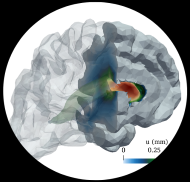
2ϵ	E_s	rate
0.1	4.43×10^{-4}	-
0.05	1.38×10^{-4}	1.69
0.025	3.64×10^{-5}	1.92
0.0125	9.74×10^{-6}	1.90



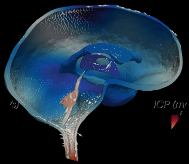
Yes, 3D-1D models can quantify perivascular flow and transport!



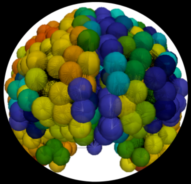
Solute transport



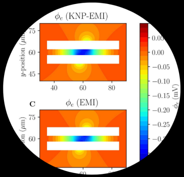
Brain mechanics



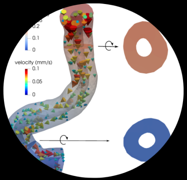
CSF flow



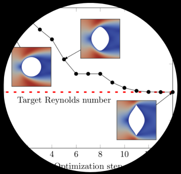
Neurodegeneration



Ions and osmosis



Model reduction



Optimal control

Software

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Miroslav Kuchta (Simula)
Rami Masri (Simula)
Kent-Andre Mardal (Oslo/Simula)
Vegard Vinje (Simula)
Marius Zeinhofer (Simula)
... a special thanks to Johannes Ring (Simula)
... and many others

Core message

Mathematical models can give new insight into medicine, – and the human brain gives an extraordinary rich setting for mathematics and numerics!

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simula waterscales EMIx The Research Council of Norway