Brains in motion

Computational modelling of the brain's waterscape

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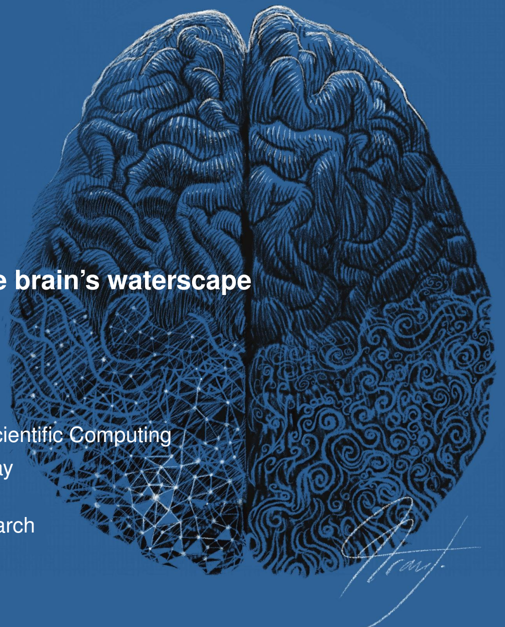
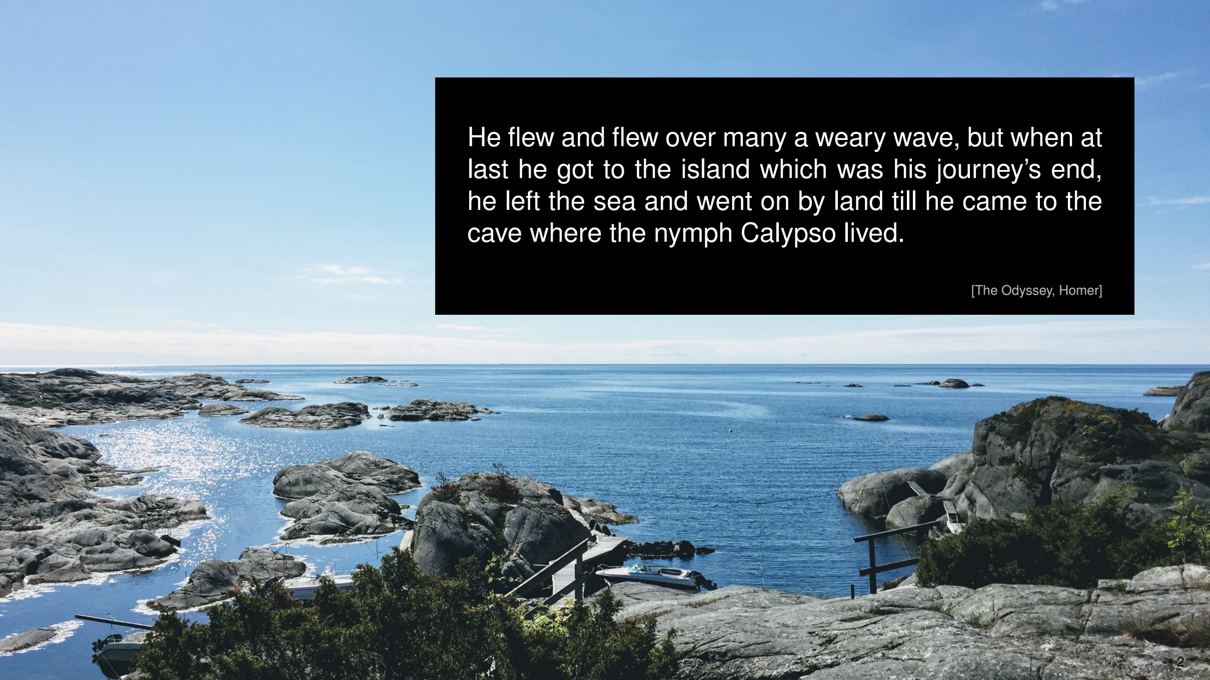
K. G. Jebsen Centre for Brain Fluid Research



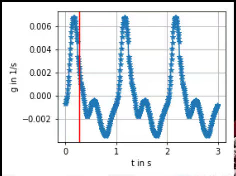


He flew and flew over many a weary wave, but when at last he got to the island which was his journey’s end, he left the sea and went on by land till he came to the cave where the nymph Calypso lived.

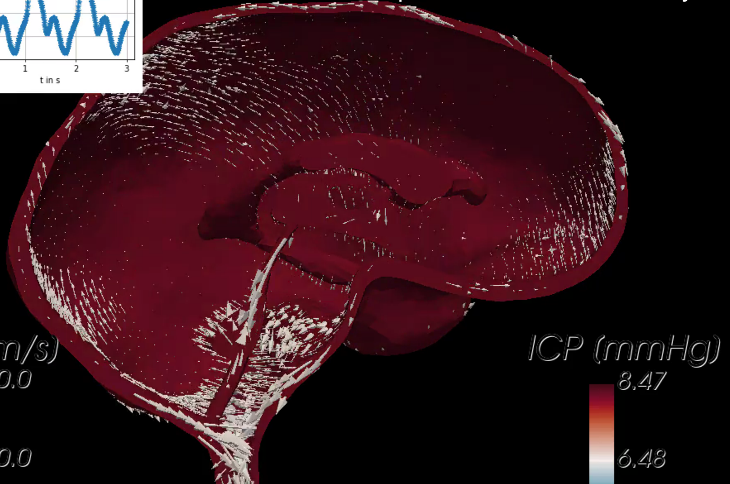
[The Odyssey, Homer]

The brain and its cerebrospinal fluid (CSF) environment pulsates in synchrony with the cardiac and respiratory cycles

Causemann et al. [2022]

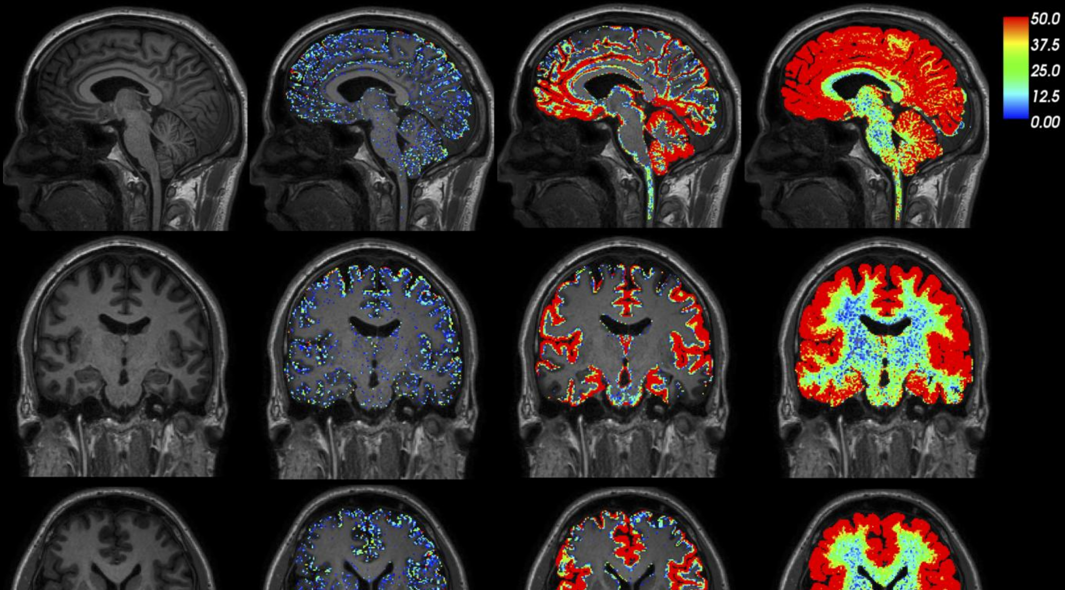


Coupled Biot & Stokes equations (Brain & CSF)
Total pressure formulation, Taylor–Hood elements

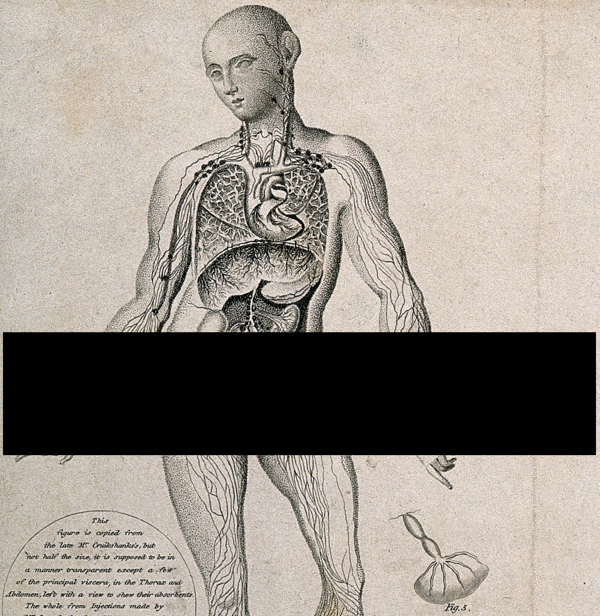


MRI reveals human brain-wide tracer enhancement and clearance

Ringstad et al. [2017, 2018]



Mr. Cruikshanks 2d Plate on the Absorbents; v: his Work.

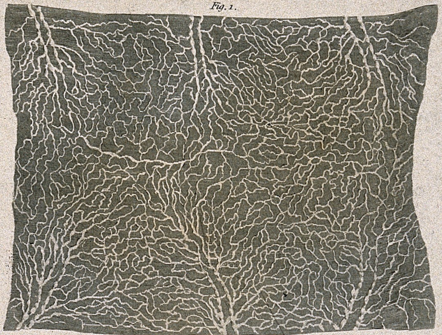


[redacted]

This figure is copied from the late Mr. Cruikshanks's, but not half the size, it is supposed to be in a manner transparent except a few of the principal viscera, in the Thorax and Abdomen, left with a view to shew their absorbents. The whole from Injections made by

Fig. 5.

Fig. 1.



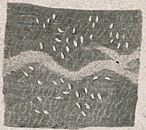


Fig. 2.

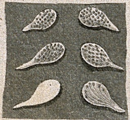


Fig. 3.

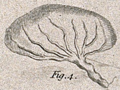
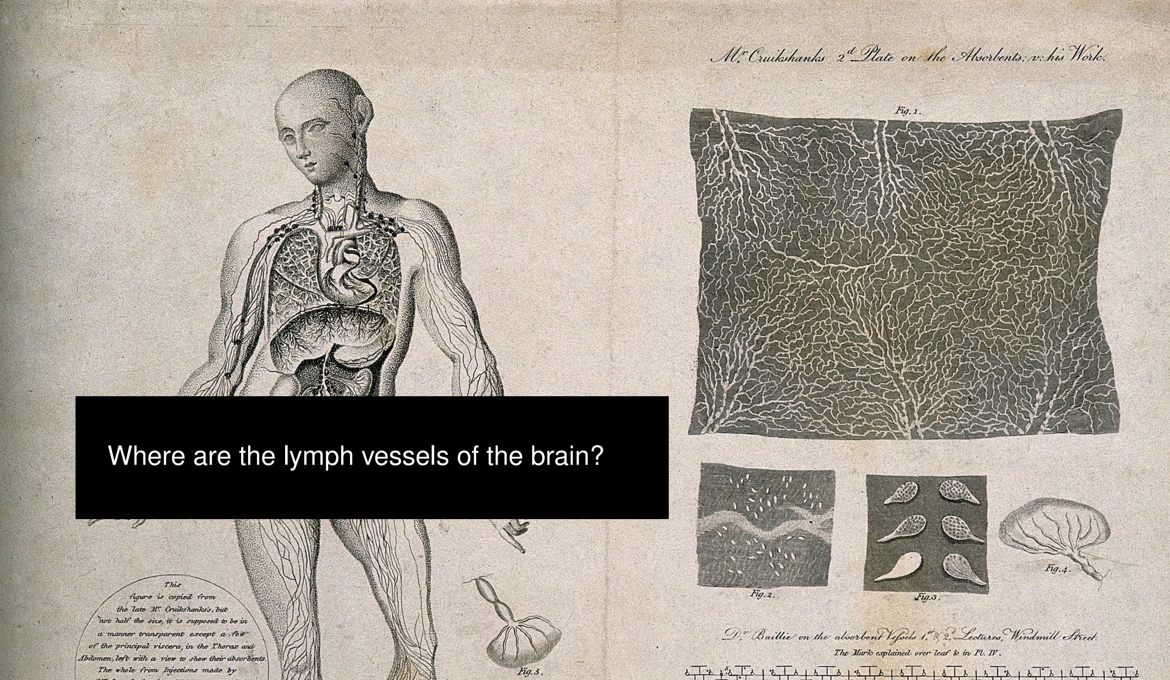


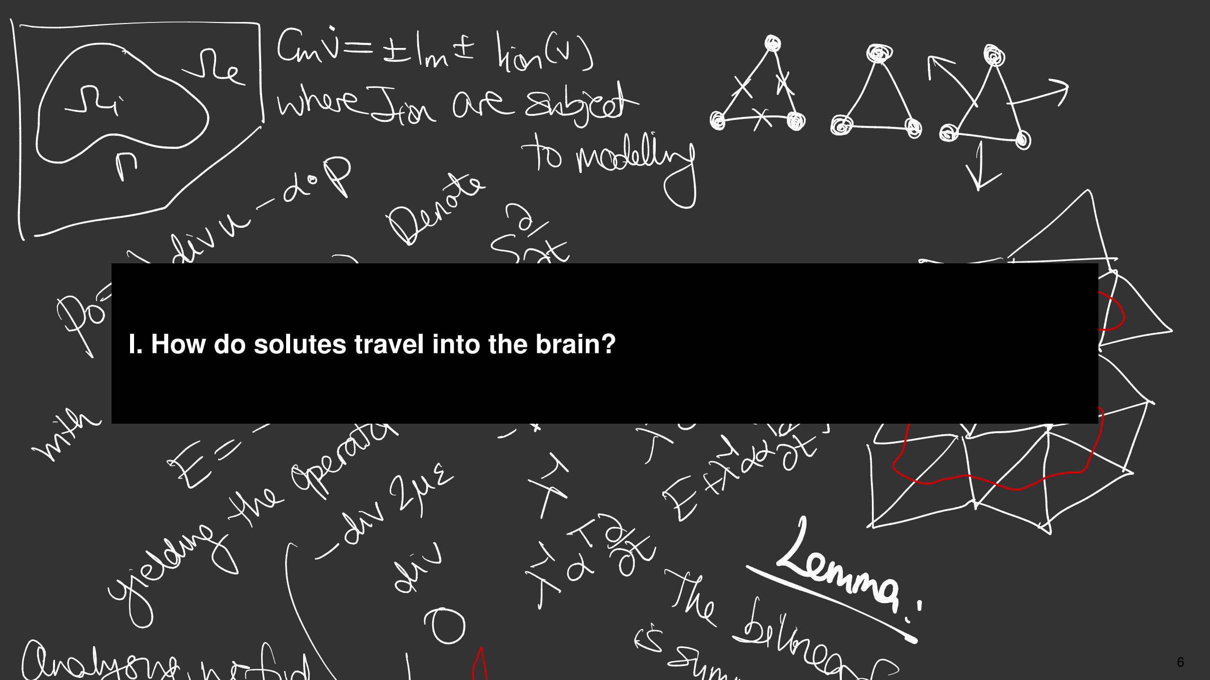
Fig. 4.

Dr. Baillie on the absorbent Vessels 1st & 2. Lectures, Windmill Street.

The Marks explained over leaf & in Pl. IV.

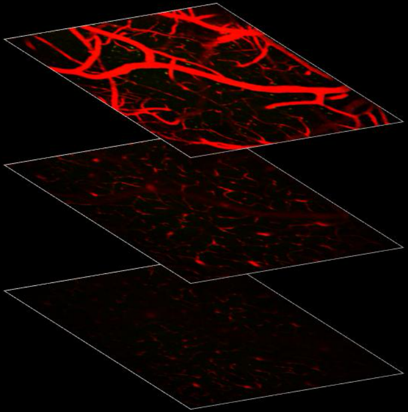


Where are the lymph vessels of the brain?

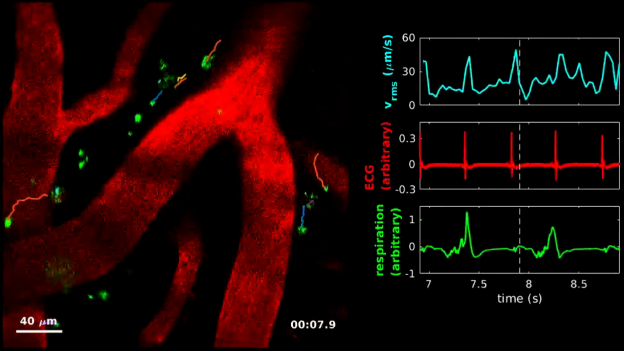


I. How do solutes travel into the brain?

Solutes travel via preferential perivascular pathways – driven by ...?



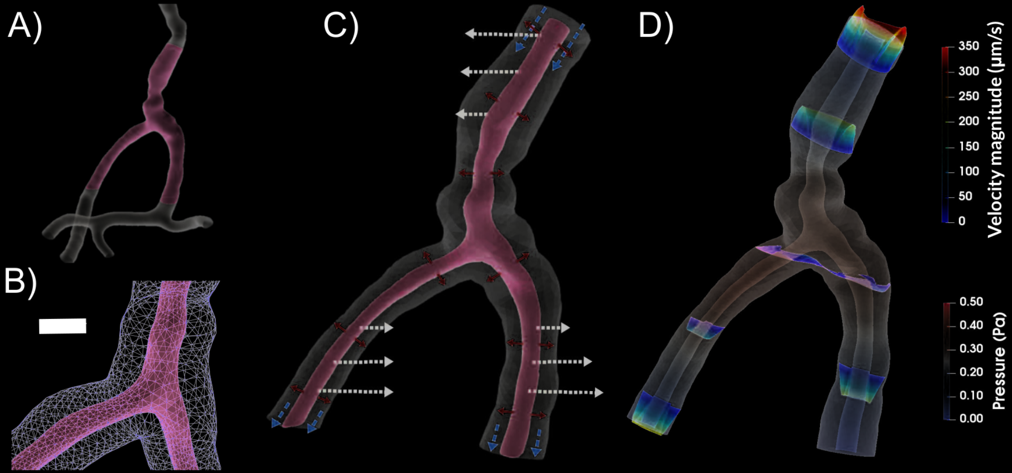
[Iliff et al, Sci. Transl. Med, 2012 (Movie S1)]



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

What mechanisms drive perivascular flow and transport?

Daversin-Catty et al. [2020]



Incompressible Stokes flow (low Reynolds, low Womersley numbers)

Model length and wave speed modulate PVS velocity and net flow

Daversin-Catty et al. [2020]

PVS thought example:

Annular cylinder L (mm) long

Wave speed $c = 1000$ mm/s

Frequency $f = 10$ Hz $= 10$ /s

Wave length λ is speed divided by frequency:

$$\lambda = c/f = 100\,\text{mm}$$

For instance:

L = 1 mm = 0.01 λ

L = 50 mm = 0.5 λ

L = 100 mm = 1 λ

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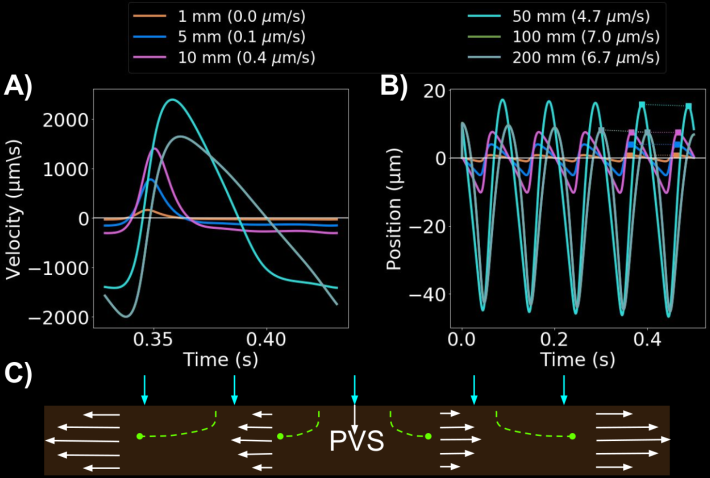

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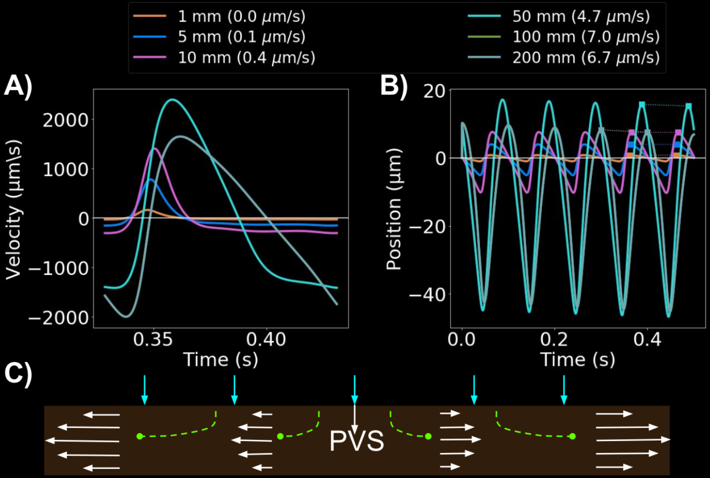
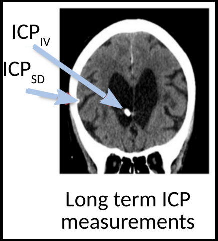


[Wang and Olbricht (2011), Thomas (2019), Carr et al (2021): $L \gg \lambda$]

ICP (gradients) pulsate in sync with cardiac and respiratory cycles

Vinje et al. [2019]



[Eide and Sæhle (2010)]

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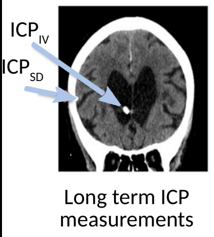
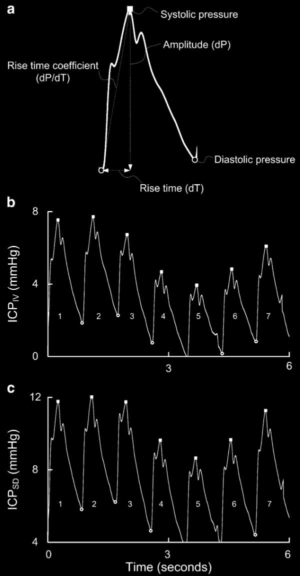


[Eide and Sæhle (2010)]



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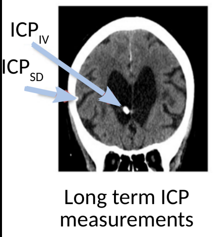

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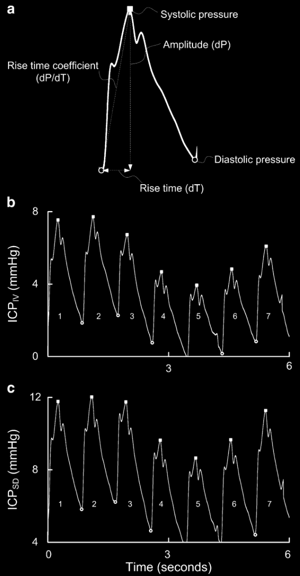

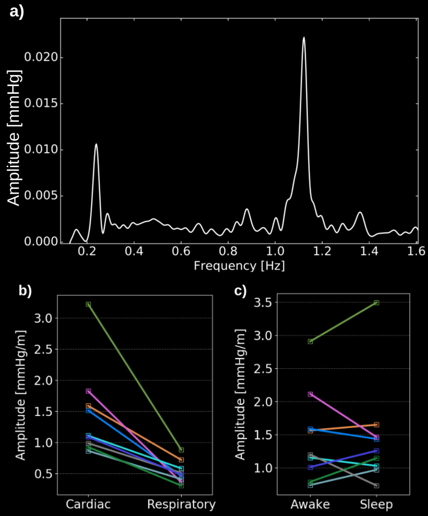

$$\mathrm{dICP}(t) \approx a_c \sin(2\pi f_c t) + a_r \sin(2\pi f_r t)$$

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

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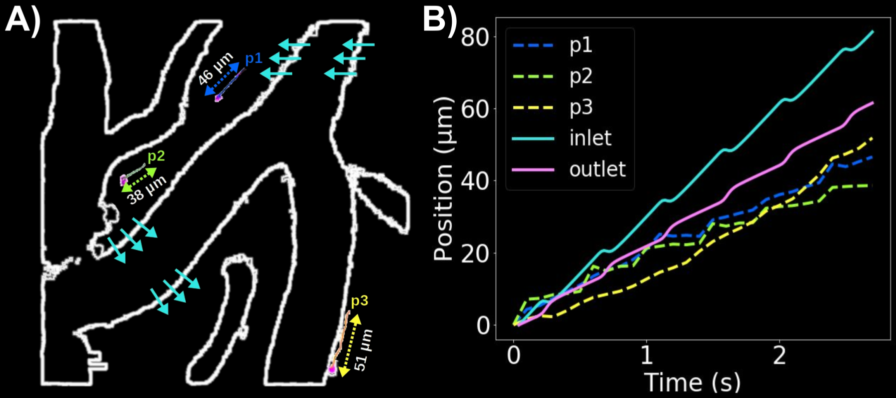
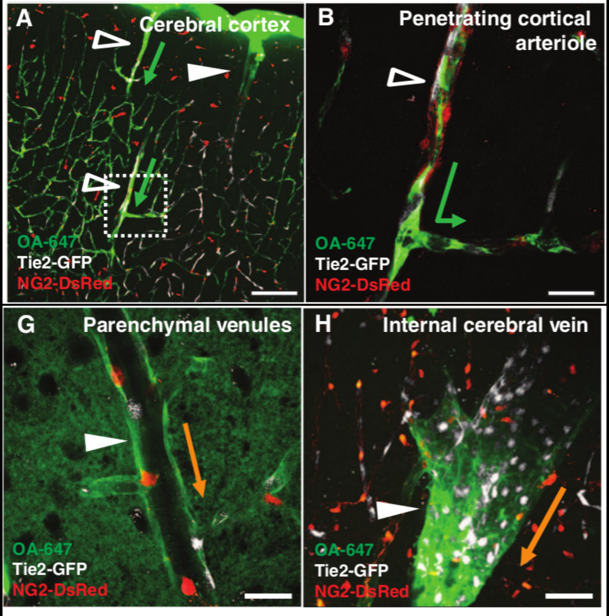


Wall pulsation frequency: 2.2 Hz. Static pressure gradient: 1.46 mmHg.

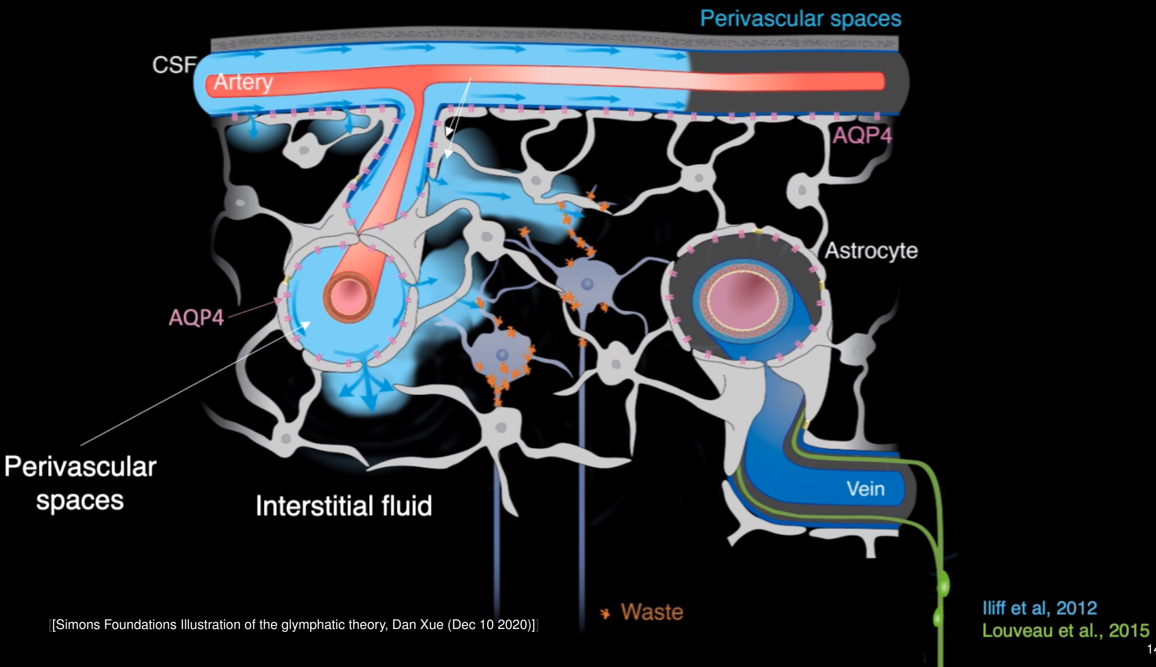
II. Where do solutes travel into and out of the brain?

Periarterial entry? (t = 10 min)

Perivenous exit? (t = 180 min)

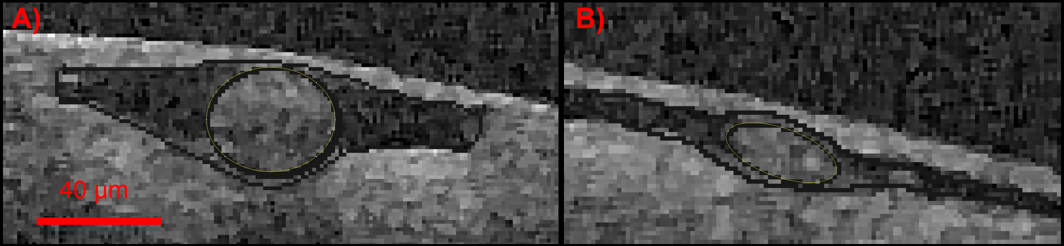


[Iliff et al, Sci. Transl. Med, 2012 (Fig 3)]



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

How do geometrical differences between periarterial and perivenous spaces affect their CSF flow patterns?



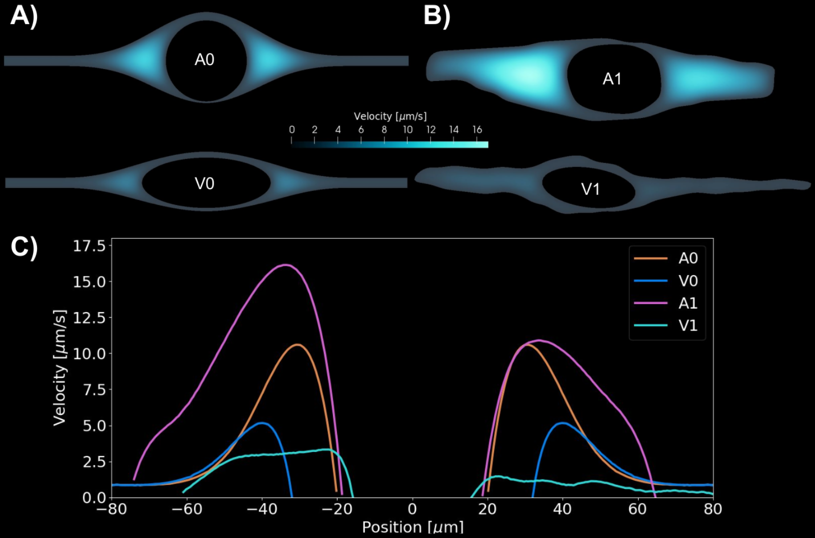
In vivo OCT images of blood vessels taken of the surface of a human brain (courtesy of Erik N. T. P. Bakker and colleagues). Scale after scaling to mouse scale

With these images (and idealized versions) as representative cross-sections, compute the CSF velocity and net flow along the length of the perivascular space given a static pressure gradient (of 1.46 mmHg/m).

Next, compute tracer concentration (2000 kDa) transported by diffusion and convection in the respective PVSs.

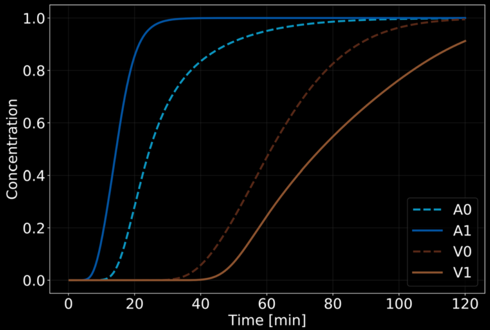
Same pressure gradient induce higher velocities and higher net flow in periarterial than in perivenous spaces

Vinje et al. [2021]

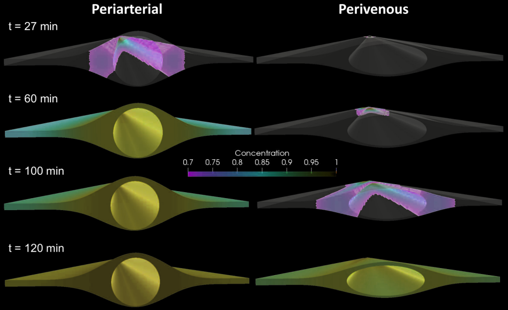


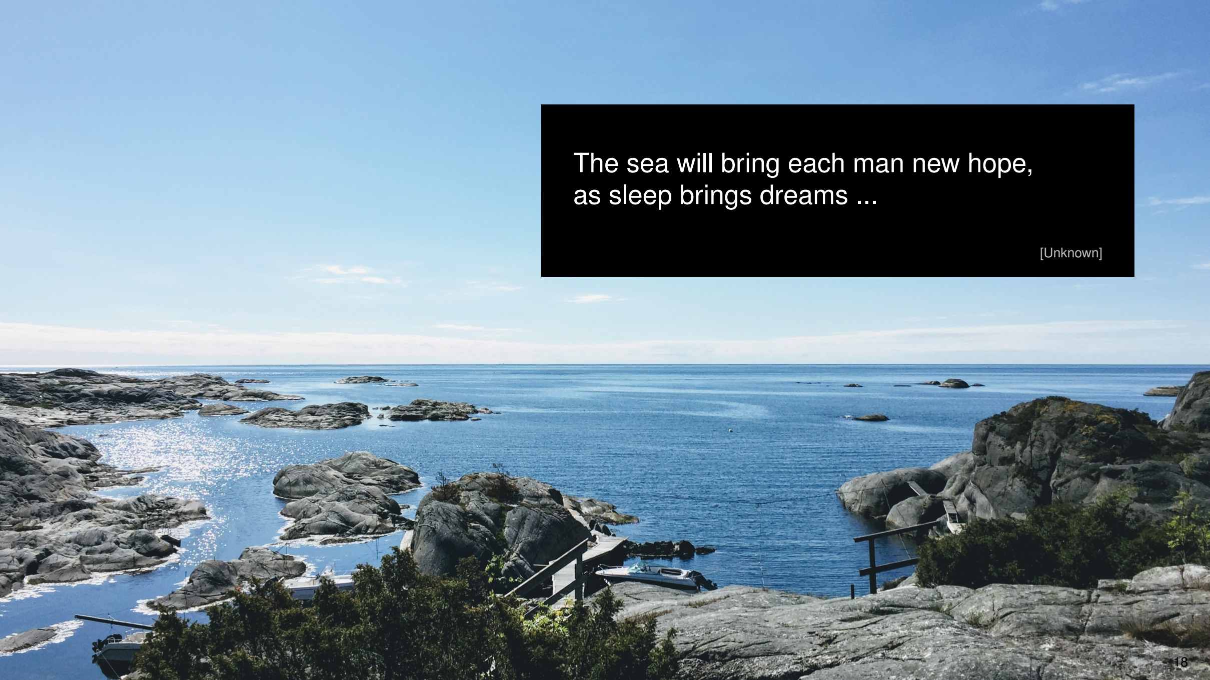
Differences in geometry lead to more rapid tracer transport and earlier arrival times in periarterial compared to perivenous spaces

Vinje et al. [2021]



Concentration at measurement site
(5 mm downstream from injection site)

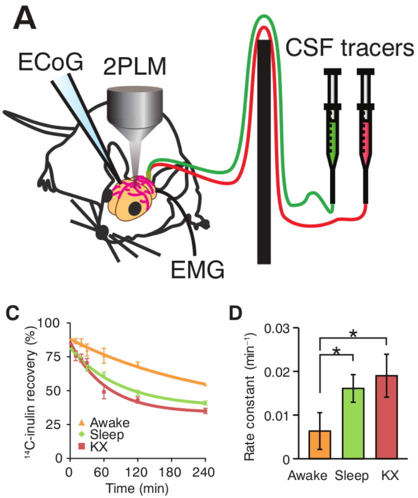


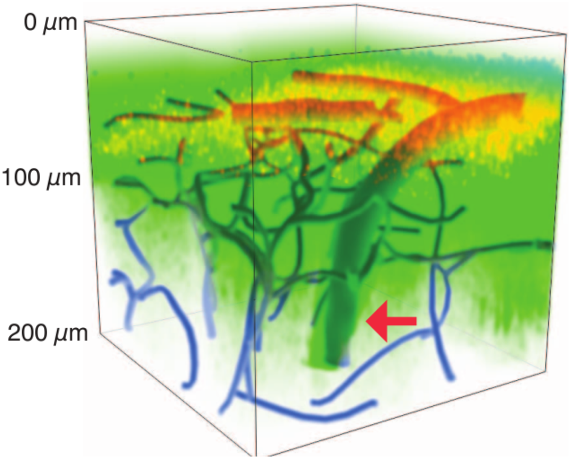


The sea will bring each man new hope,
as sleep brings dreams ...

[Unknown]

Sleep: a fundamental driver of metabolic clearance from the brain?

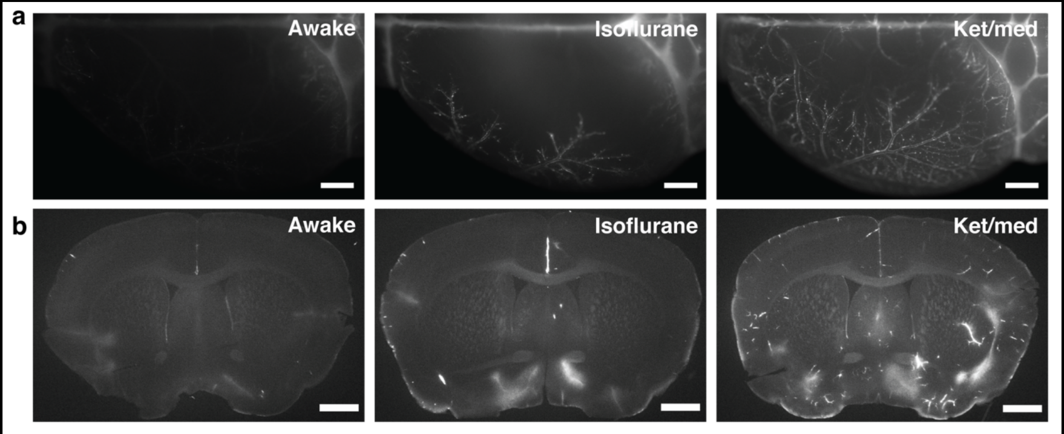




Xie et al. [2013], Fultz et al. [2019], Ma et al. [2019], Bojarskaite et al. [2023], Vinje et al. [2023], Miao et al. [2024]

III. How is solute transport affected by CSF flow during sleep?

"Sleep" affects CSF outflux and tracer availability at brain surface

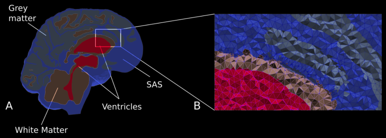


"...the spread of tracer to the PVS of the brain surface was directly related to the amount of tracer remaining at the basal cisterns and indirectly proportional to the amount that had reached the systemic blood."

[Ma et al, Acta Neuropathologica, 2019 (p. 159, Fig 1)]

Increased CSF production (as when awake) limits brain tracer influx

[Hornkjøl et la, CSF circulation and dispersion yield rapid clearance from intracranial compartments, Front. Bioeng. Biotechnol, 2022]



Given CSF production g, find the CSF velocity u and pressure p in Ω_F

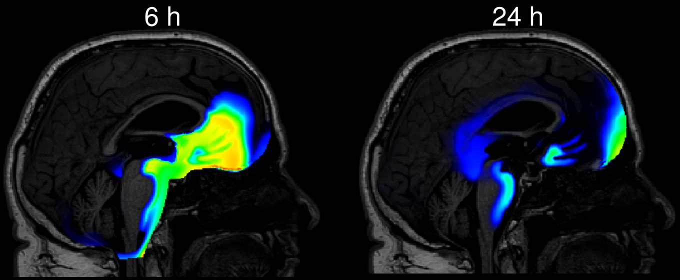
$$\mu \nabla^2 u - \nabla p = 0,$$
$$\nabla \cdot u = g,$$

with restricted outflux at $\partial\Omega_{\text{out}}$

$$\mu \nabla u \cdot n - pn = -R_0 u \cdot n,$$

and the concentration c in $\Omega_F \cup \Omega_B$

$$\phi \frac{\partial c}{\partial t} + \phi u \cdot \nabla c - \nabla \cdot (\phi \alpha D \nabla c) = 0.$$



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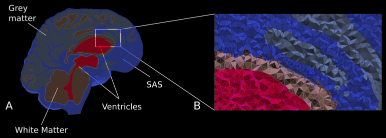

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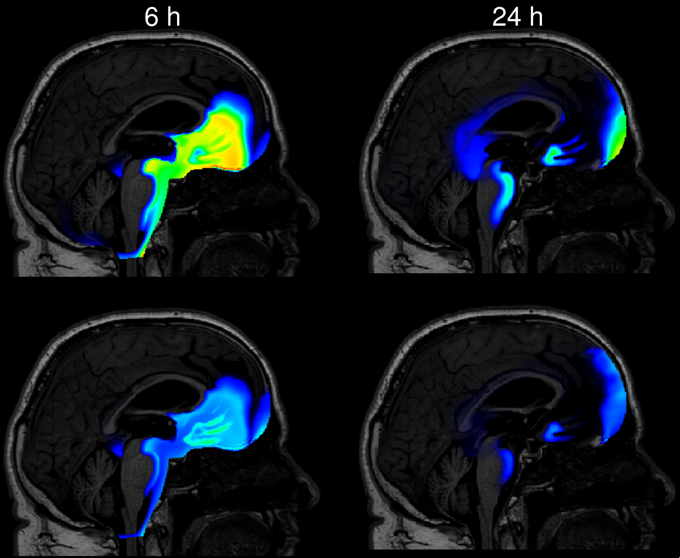
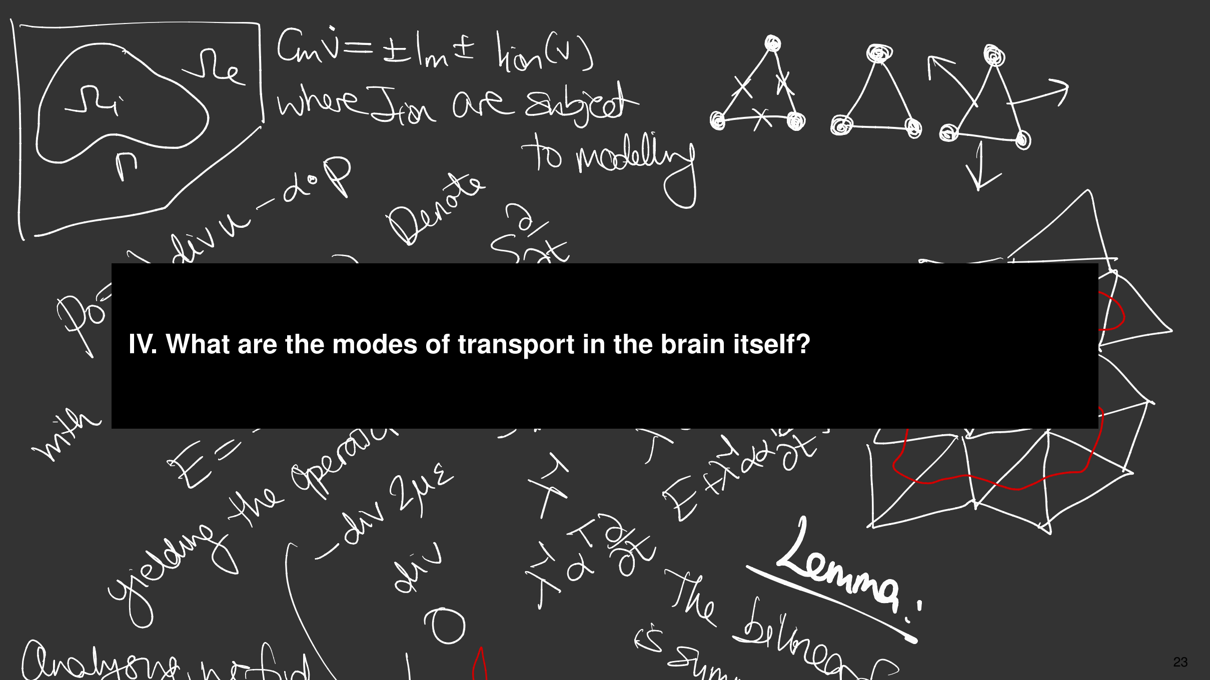
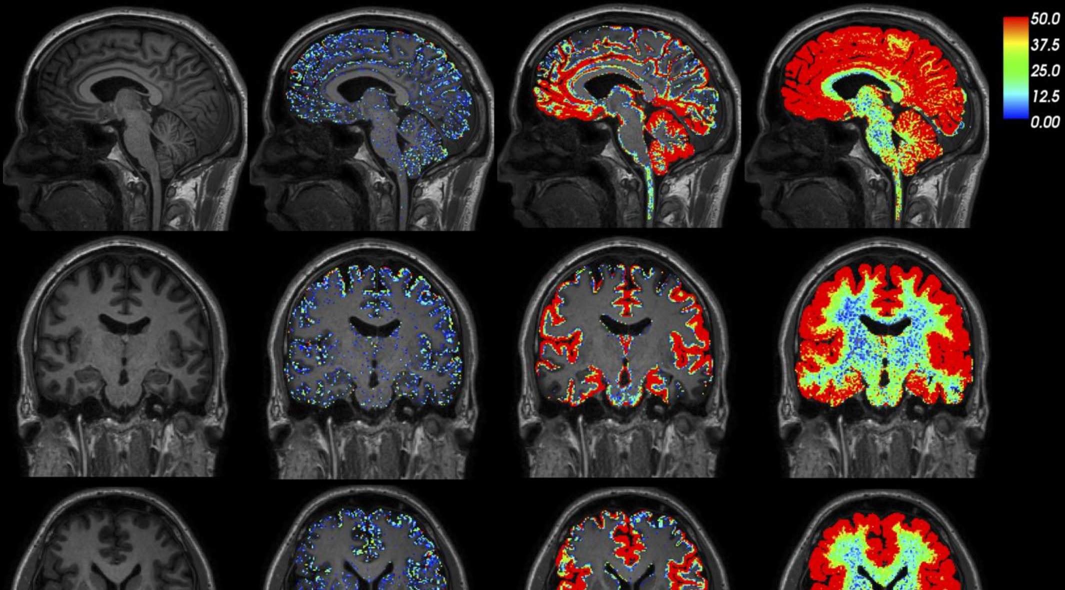




IV. What are the modes of transport in the brain itself?

MRI reveals human brain-wide tracer enhancement and clearance

Ringstad et al. [2017, 2018]



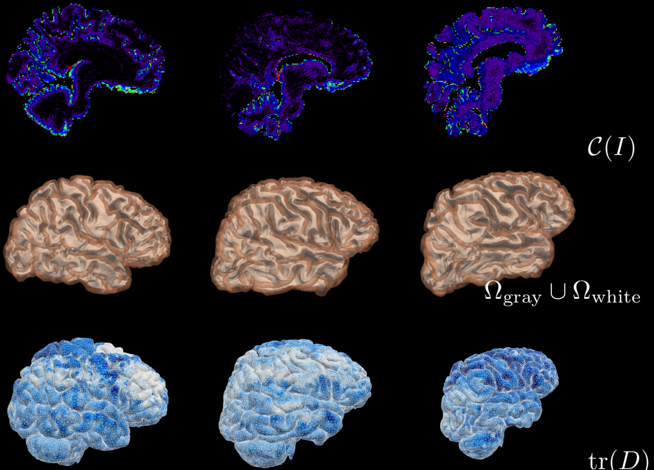
Individualized finite element models of brain molecular transport and clearance

Vinje et al. [2023]


Find $c = c(x, t)$ for $x \in \Omega$, $t > 0$:

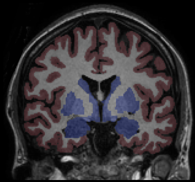
$$c_t - \operatorname{div} D \operatorname{grad} c = 0 \qquad \text{in } \Omega$$
$$c = \mathcal{C}(I) \qquad \text{on } \partial\Omega$$

Continuous linear finite elements
$1 - 5$M cells:
$h \approx 0.2 - 5.6$mm



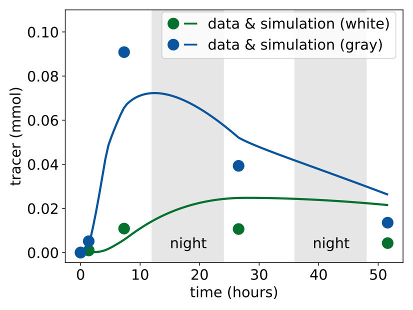
Transport by diffusion and dispersion underestimates molecular brain influx or clearance

Croci et al. [2019], Vinje et al. [2023]



$$\int_{\Omega_{\mathrm{gray}}} c(x,t)\,\mathrm{d}x$$

$$\int_{\Omega_{\mathrm{white}}} c(x,t)\,\mathrm{d}x$$



$$c_t - \operatorname{div} D \operatorname{grad} c = 0$$

Iliff et al. [2012], Smith and Verkman [2019], Ray et al. [2019], Troyetsky et al. [2021], Ray et al. [2021], Hladky and Barrand [2022]

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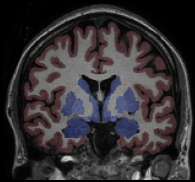

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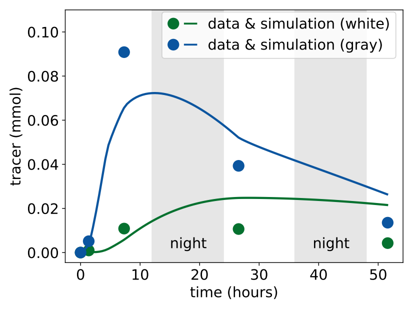
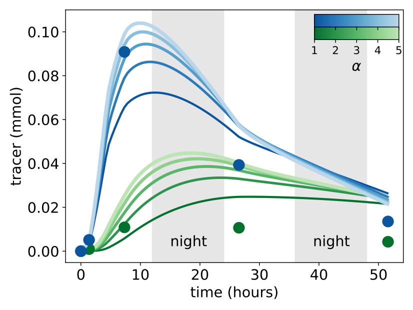


$$c_t - \mathrm{div}\, D\, \mathrm{grad}\, c = 0$$

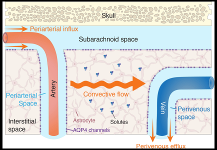


$$c_t - \mathrm{div}\, \alpha D\, \mathrm{grad}\, c = 0$$

Iliff et al. [2012], Smith and Verkman [2019], Ray et al. [2019], Troyetsky et al. [2021], Ray et al. [2021], Hladky and Barrand [2022]

Is there a quantifiable (bulk) flow of interstitial fluid in brain tissue?

[Helen Cserr (credit: R. Cserr)]



[Kwong et al (Fig 1, 2020)]

Convection of cerebral interstitial fluid and its role in brain volume regulation

H F Cserr, M Depasquale, C S Patlak, R G Pullen

[Cserr et al (1986), Hladky and Barrand (2014), Smith et al (2017)]
[Abbott et al (2018), Hablitz and Nedergaard (2021), ...]

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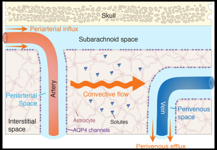

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Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence

Stephen B Hladky [1], Margery A Barrand [1]

Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma

Alex J Smith, Xiaoming Yao, James A Dix, Byung-Ju Jin, Alan S Verkman

The role of brain barriers in fluid movement in the CNS: is there a 'glymphatic' system?

N. Joan Abbott, Michelle E. Pizzo, Jane E. Preston, Damir Janigro & Robert G. Thorne

The Glymphatic System: A Novel Component of Fundamental Neurobiology

Lauren M. Hablitz and Maiken Nedergaard

[Cserr et al (1986), Hladky and Barrand (2014), Smith et al (2017)]
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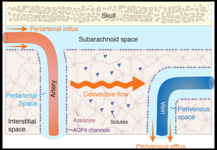


[Kwong et al (Fig 1, 2020)]

Convection of cerebral interstitial fluid and its role in brain volume regulation

H F Cserr, M Depasquale, C S Patlak, R G Pullen

Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence

Stephen B Hladky [1], Margery A Barrand [1]

Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma

Alex J Smith, Xiaoming Yao, James A Dix, Byung-Ju Jin, Alan S Verkman

The role of brain barriers in fluid movement in the CNS: is there a 'glymphatic' system?

N. Joan Abbott, Michelle E. Pizzo, Jane E. Preston, Damir Janigro & Robert G. Thorne

The Glymphatic System: A Novel Component of Fundamental Neurobiology

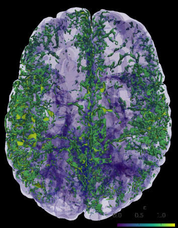
Lauren M. Hablitz and Maiken Nedergaard

[Cserr et al (1986), Hladky and Barrand (2014), Smith et al (2017)]
[Abbott et al (2018), Hablitz and Nedergaard (2021), ...]

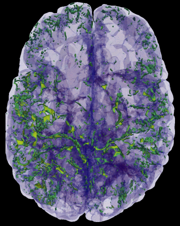
With a velocity field $\phi : \Omega \to \mathbb{R}^d$, find $c : \Omega \times [0, T] \to \mathbb{R}$:

$$c_t + \operatorname{div}(c\phi) - \operatorname{div} D \operatorname{grad} c = 0 \quad \text{in } \Omega,$$
$$c = \mathcal{C}(I) \quad \text{on } \partial\Omega$$

A few observations $\mathcal{C}(I)$ on Ω available

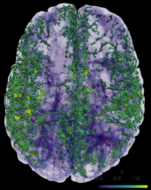


24h

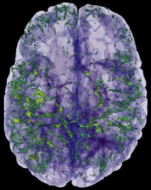


48 h

Determining a fluid flow field from images via optical flow methods

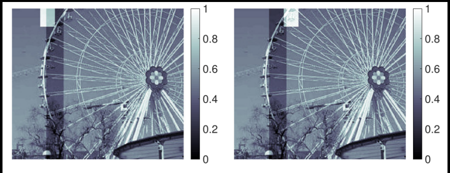


c_1 at t_1

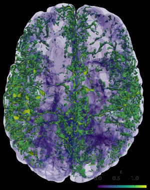


c_2 at t_2

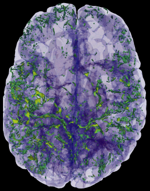
$\tau = t_2 - t_1$



Determining a fluid flow field from images via optical flow methods

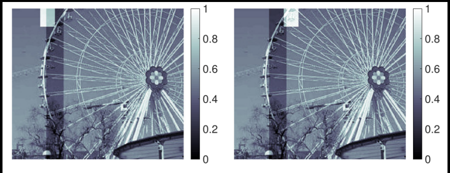


c_1 at t_1



c_2 at t_2

$\tau = t_2 - t_1$



Given $c_1, c_2 : \Omega \to \mathbb{R}$ at t_1, t_2, $\alpha > 0$, and

$$f = c_t + \phi \cdot \operatorname{grad} c,$$
$$R = \| \operatorname{grad} \phi \|_{L^2(\Omega)},$$

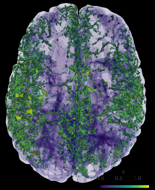
find an optimal $\phi \in H^1(\Omega; \mathbb{R}^d)$:

$$\min_{\phi} \int_{t_1}^{t_2} \int_{\Omega} f^2 \, \mathrm{d}x \, \mathrm{d}t + \alpha^2 R^2,$$

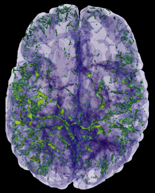
e.g. via the Euler-Lagrange equations.

[Horn and Schunck (1981), Wildes et al (2000)]

Determining a fluid flow field from images via optical flow methods

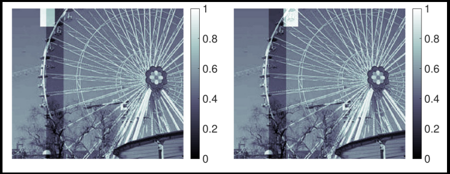


c_1 at t_1



c_2 at t_2

$\tau = t_2 - t_1$



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e.g. via the Euler-Lagrange equations.

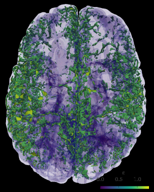
[Horn and Schunck (1981), Wildes et al (2000)]

Monge-Kantorovich mass transfer:

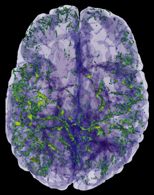
$$R = \|c\phi \cdot \phi\|_{L^1([t_1,t_2]) \times L^1(\Omega)}$$

[..., Benamou and Bernier (2000), Mueller et al (2013), ...]

Determining a fluid flow field from images via optical flow methods

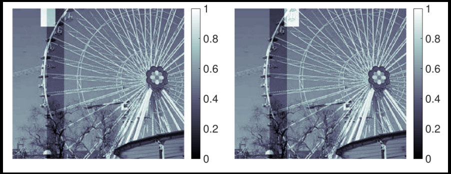


c_1 at t_1



c_2 at t_2

$\tau = t_2 - t_1$



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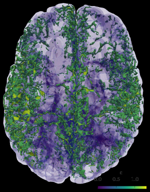
[..., Benamou and Bernier (2000), Mueller et al (2013), ...]

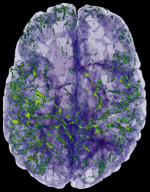
But not a viable approach here!

- Sensitive to regularization α
- Discrete derivatives of non-smooth data ($\nabla_h c_1$, $\Delta_h c_1$)
- Optical flow ignores diffusion

Recovering approximations of fluid flow fields accounting for diffusion



c_1 at t_1



c_2 at t_2

$\tau = t_2 - t_1$

Optimal Convection-Diffusion (OCD)

Given $c_1, c_2 : \Omega \to \mathbb{R}$ at t_1, t_2, $\alpha > 0$,
optimize

$$\min_{c,\phi} \|c(t_2) - c_2\|^2_{L^2(\Omega)} + \alpha^2 R^2,$$

subject to $c(t_1) = c_1$ and for $t \in (t_1, t_2]$:

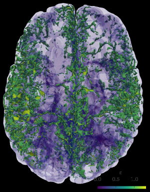
$$c_t + \operatorname{div}(c\phi) - \operatorname{div} D \operatorname{grad} c = 0. \quad (2)$$

[$\sim$ Andreev et al (2015), Glowinski et al (2022)]

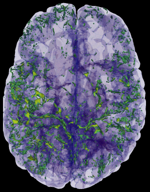
Let $c_t \approx \delta_\tau c \equiv \frac{1}{\tau}(c - c_1)$

[Alnæs et al (2015), Farrell et al (2013), Vinje et al (2023)]

Recovering approximations of fluid flow fields accounting for diffusion



c_1 at t_1



c_2 at t_2

$\tau = t_2 - t_1$

Optimal Convection-Diffusion (OCD)

Given $c_1, c_2 : \Omega \to \mathbb{R}$ at t_1, t_2, $\alpha > 0$, optimize

$$\min_{c,\phi} \|c(t_2) - c_2\|^2_{L^2(\Omega)} + \alpha^2 R^2,$$

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$$c_t + \operatorname{div}(c\phi) - \operatorname{div} D \operatorname{grad} c = 0. \quad (2)$$

[∼ Andreev et al (2015), Glowinski et al (2022)]

Let $c_t \approx \delta_\tau c \equiv \frac{1}{\tau}(c - c_1)$

Iterative optimization approach

Define the reduced functional $J : H(\operatorname{div}, \Omega) \to \mathbb{R}$

$$J(\phi) = \|c(\phi)(t_2) - c_2\|^2_{L^2(\Omega)} + \alpha^2 R^2$$

where $\phi \mapsto c(\phi)$ by c solving (2).

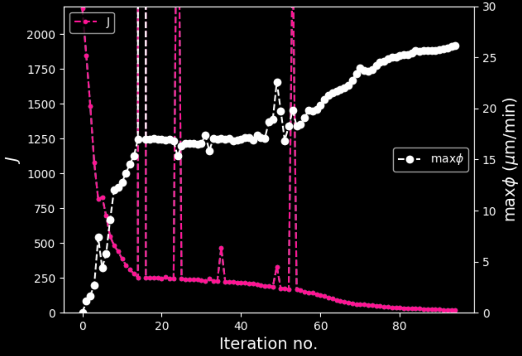
Solve

$$\min_{\phi} J(\phi)$$

via e.g. scipy (L-BFGS), FEniCS, Dolfin-adjoint.

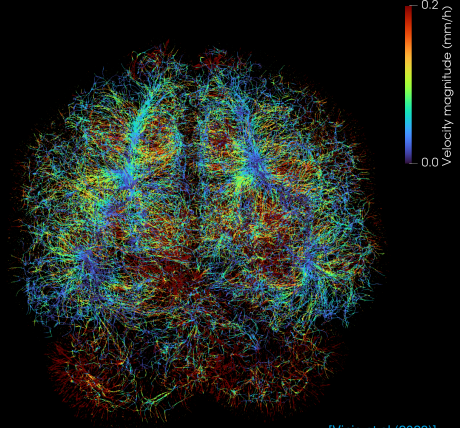
[Alnæs et al (2015), Farrell et al (2013), Vinje et al (2023)]

OCD approach yields robust approximation of average velocities

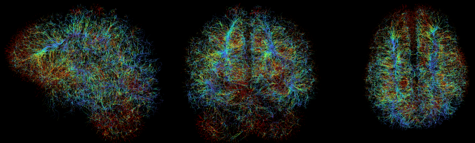


Average speed $\bar{\phi} = \frac{1}{|\Omega|} \int_{\Omega} |\phi| \, \mathrm{d}x$ (μm/min):

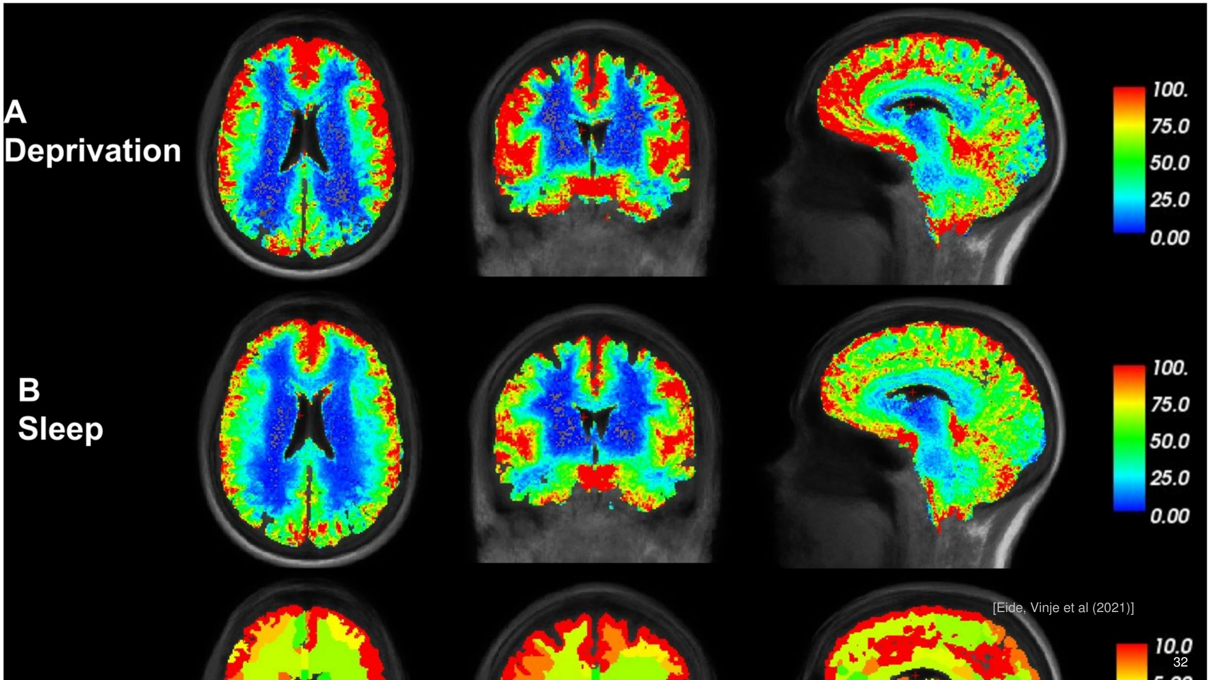
n vs. α^2	10^{-3}	10^{-4}	10^{-5}
16	2.83	3.67	4.00
32	2.33	2.83	2.83



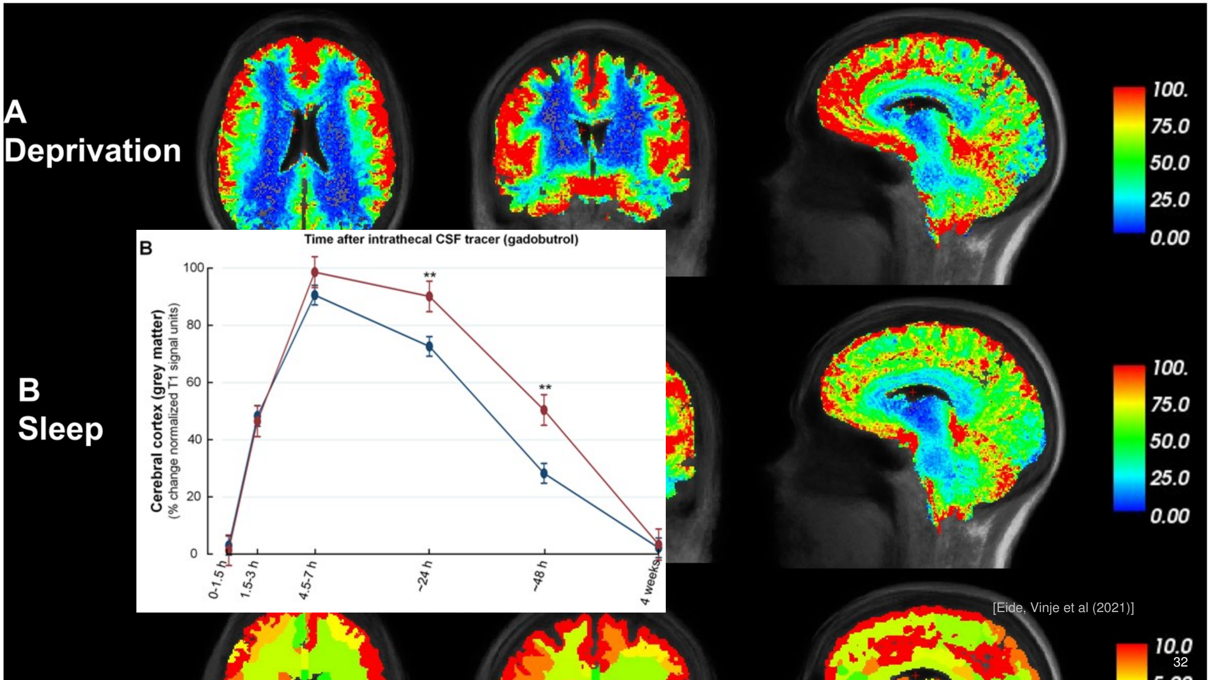
[Vinje et al (2023)]



V. Do we sleep in order to clean the brain?

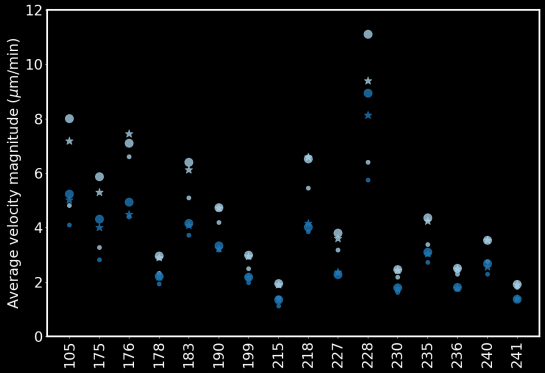


[Eide, Vinje et al (2021)]



[Eide, Vinje et al (2021)]

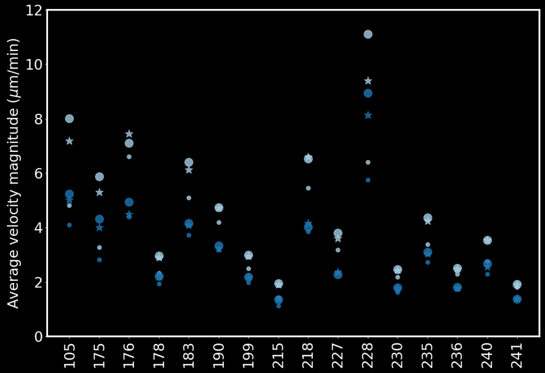
Estimate ϕ between 24h and 48h images for each patient.



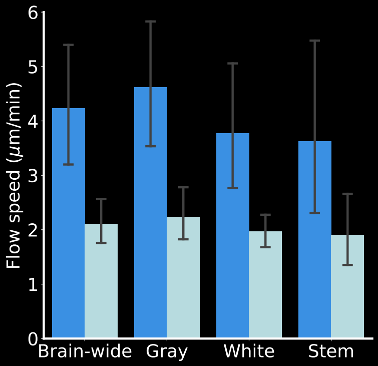
Average flow speed $\bar{\phi}$ for $\alpha^2 = 10^{-3}$ (dots), 10^{-4} (stars), 10^{-5} (circles) for low-res (light blue) and standard meshes (blue).

Convective velocities are reduced (by x2) after sleep-deprivation

Estimate ϕ between 24h and 48h images for each patient.

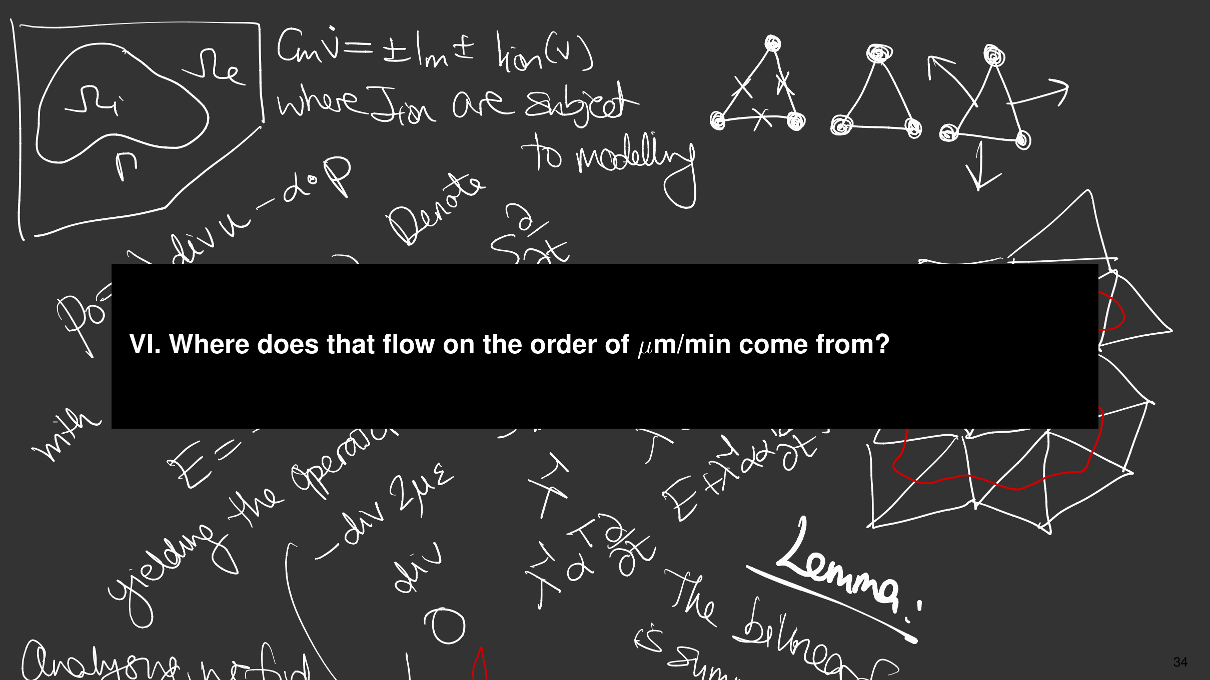


Average flow speed $\bar{\phi}$ for $\alpha^2 = 10^{-3}$ (dots), 10^{-4} (stars), 10^{-5} (circles) for low-res (light blue) and standard meshes (blue).

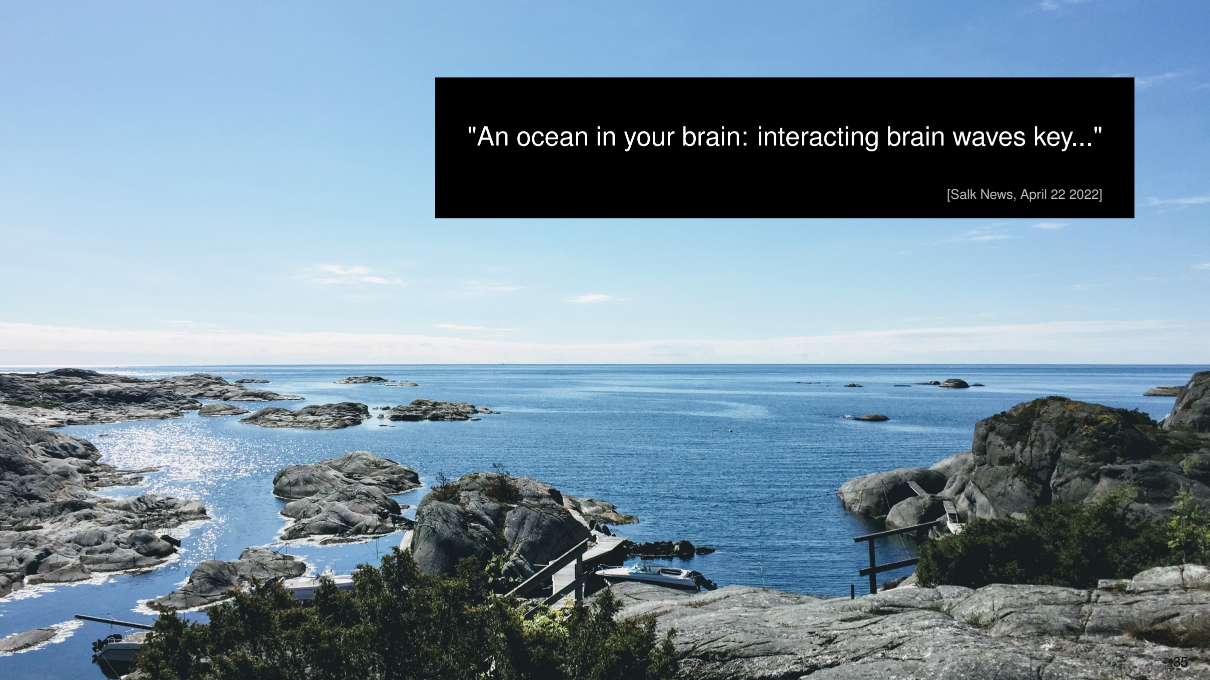


N = 11 + 7

4.23 vs. 2.11 μm/min (p=0.0057)

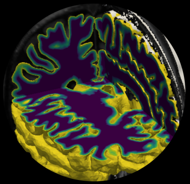


VI. Where does that flow on the order of μm/min come from?

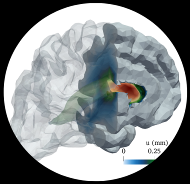


"An ocean in your brain: interacting brain waves key..."

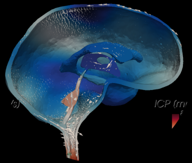
[Salk News, April 22 2022]



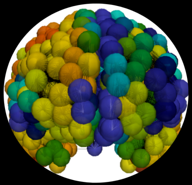
Solute transport and clearance



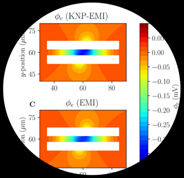
Brain mechanics



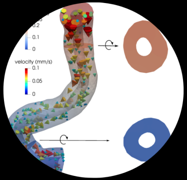
Cerebrospinal fluid flow and pulsatility



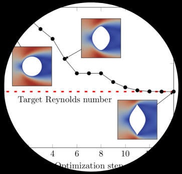
Neurodegeneration



Ions and osmosis



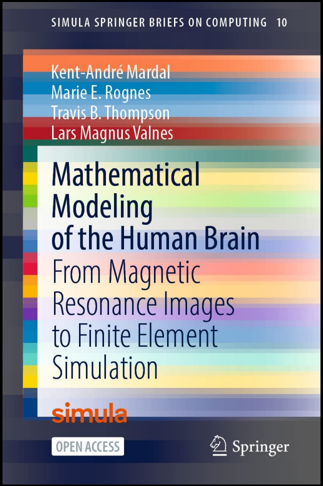
Mixed-dimensional PDEs

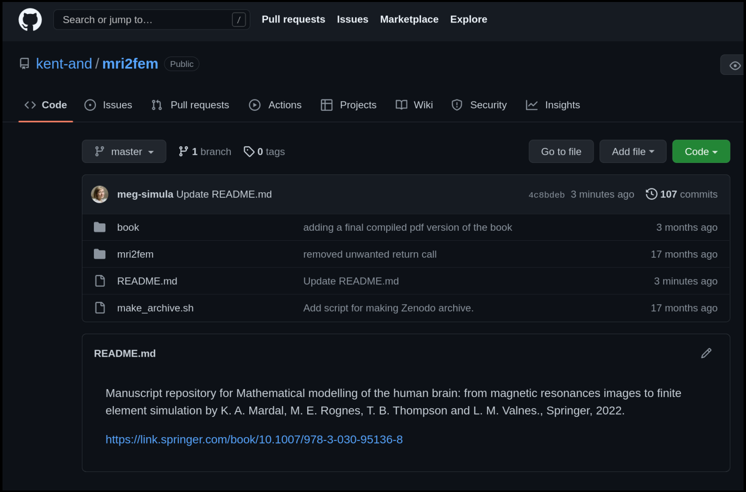


Optimization

Simulation technology

Mathematical modeling of the human brain: from MRI to FEM





[https://github.com/kent-and/mri2fem]

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Kent-Andre Mardal (Oslo/Simula)
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Marte Julie Sætra (Simula)
Travis B. Thompson (Oxford)
Lars Magnus Valnes (Oslo University Hospital)
Vegard Vinje (Simula)
Bastian Zapf (Oslo)
... a special thanks to Johannes Ring (Simula)

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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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