Using Porous Media to Bridge Multiple Scales and Guide Clinical Experiments

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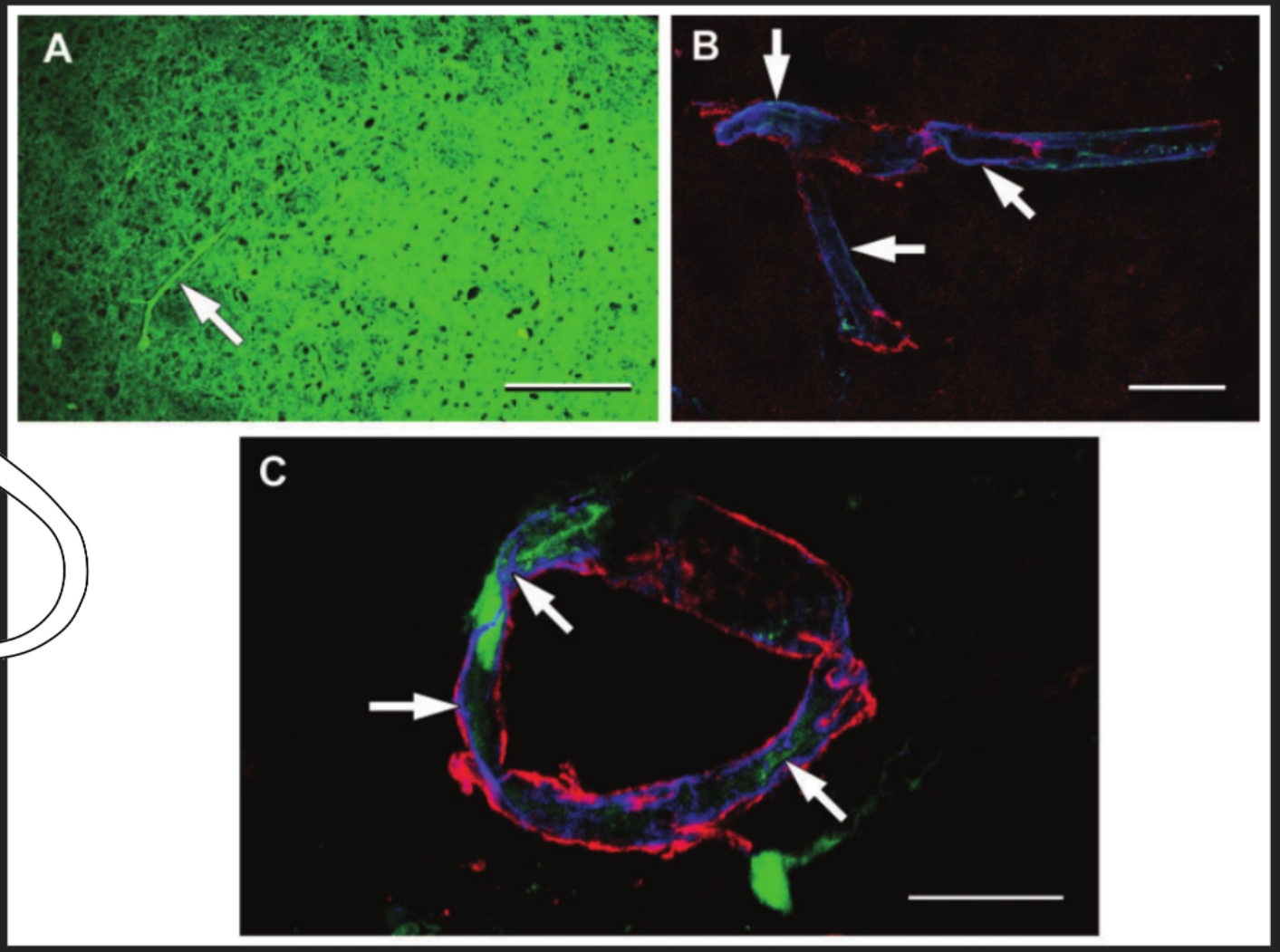
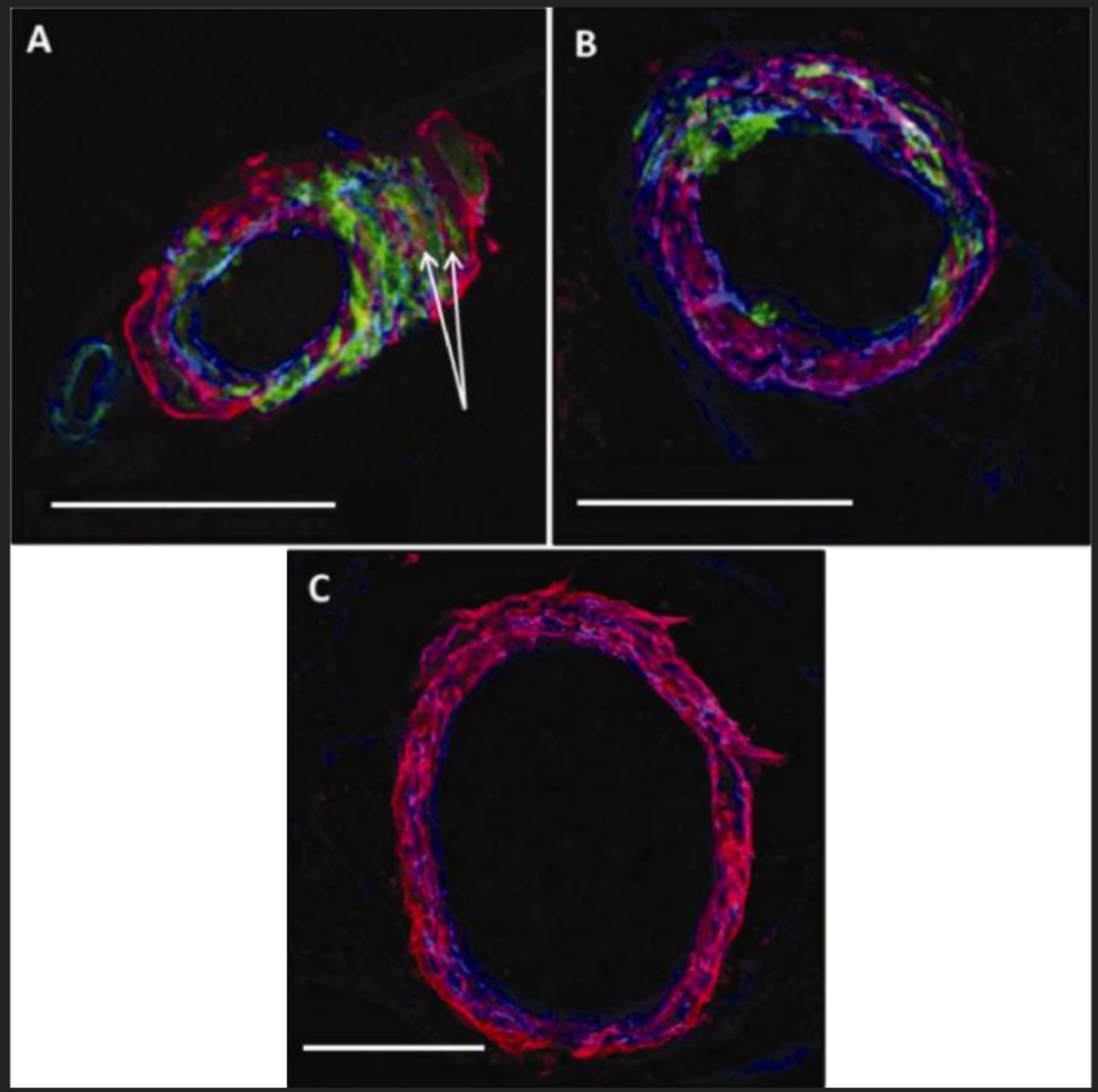
Injection experiments in mice reveal tracer pathways



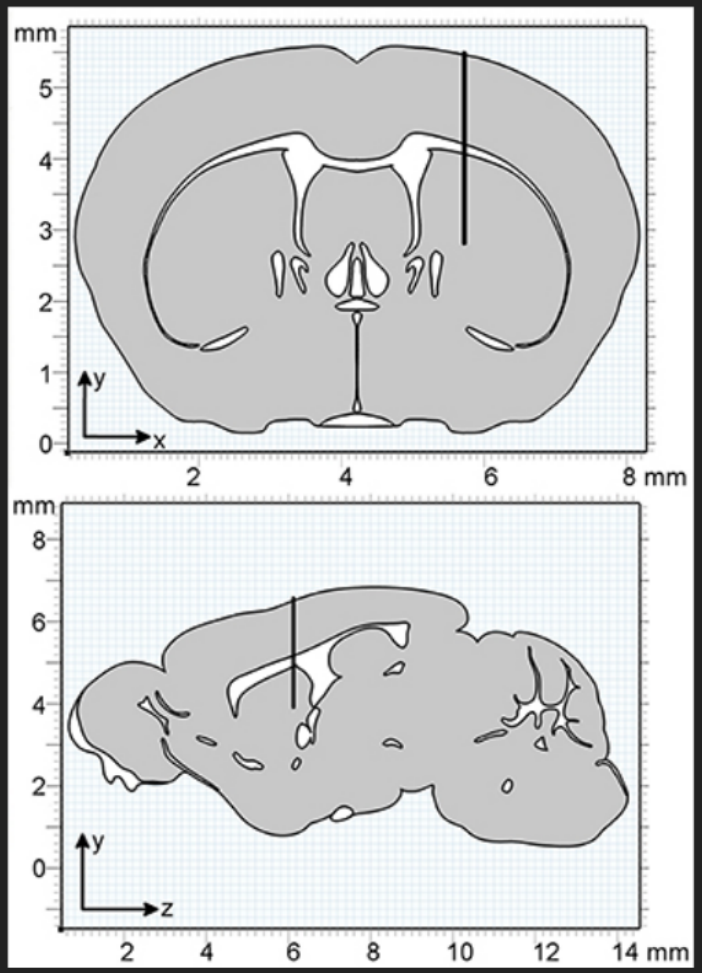
Carare et al. (2008), Neuropathology and Applied Neurobiology 34 (2): 131-144

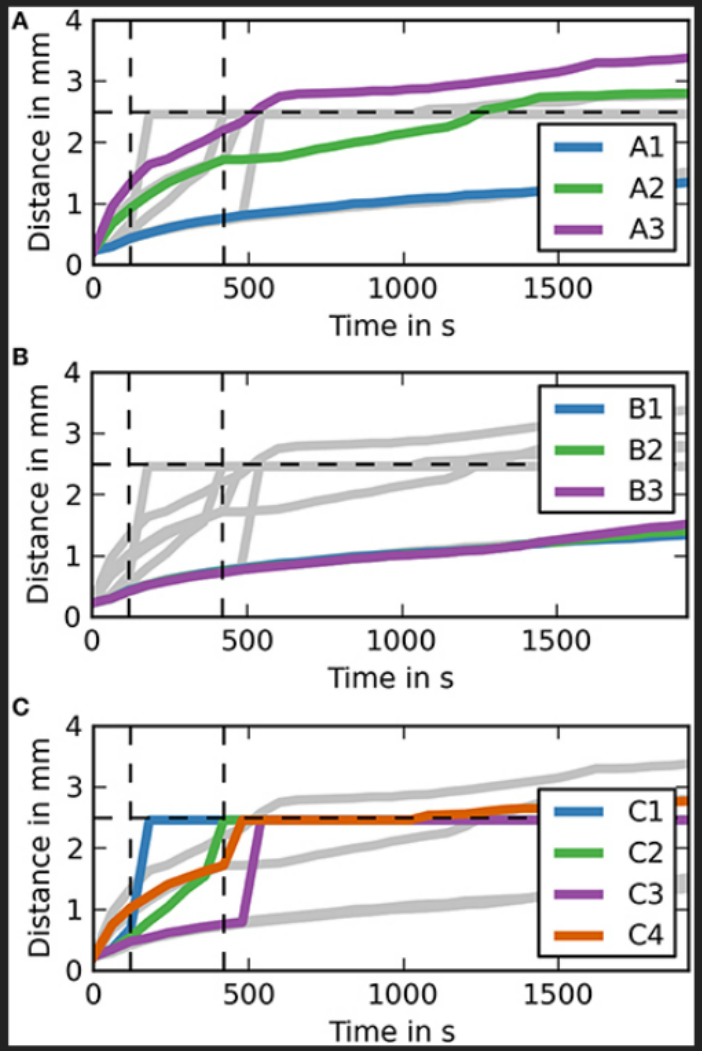
Tracer pathways correlate with Alzheimer's pathology



Keable et al. (2015), Biochimica et Biophysica Acta 1862 (5): 1037-1046

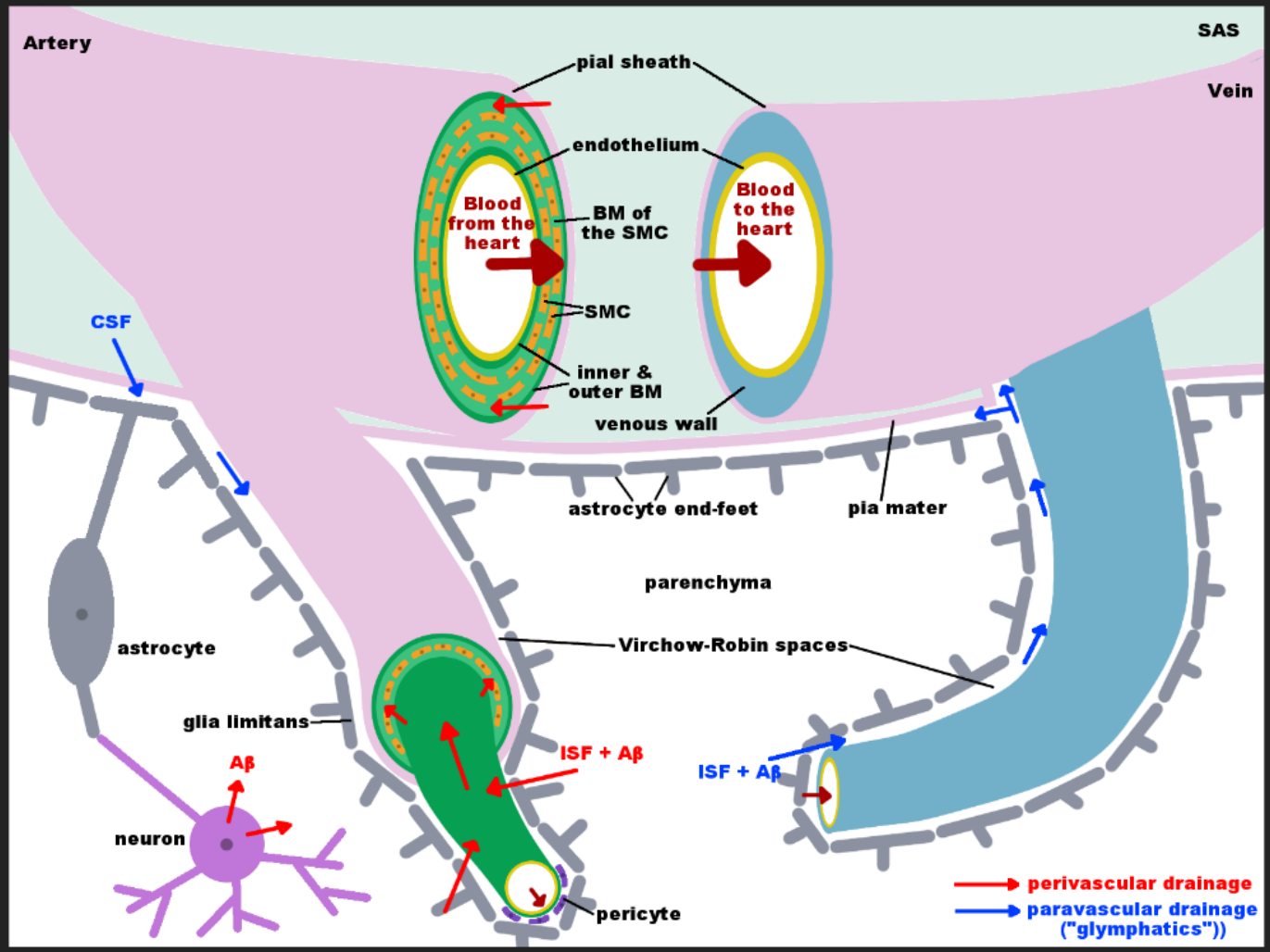
"That's probably just diffusion through the extracellular space!"



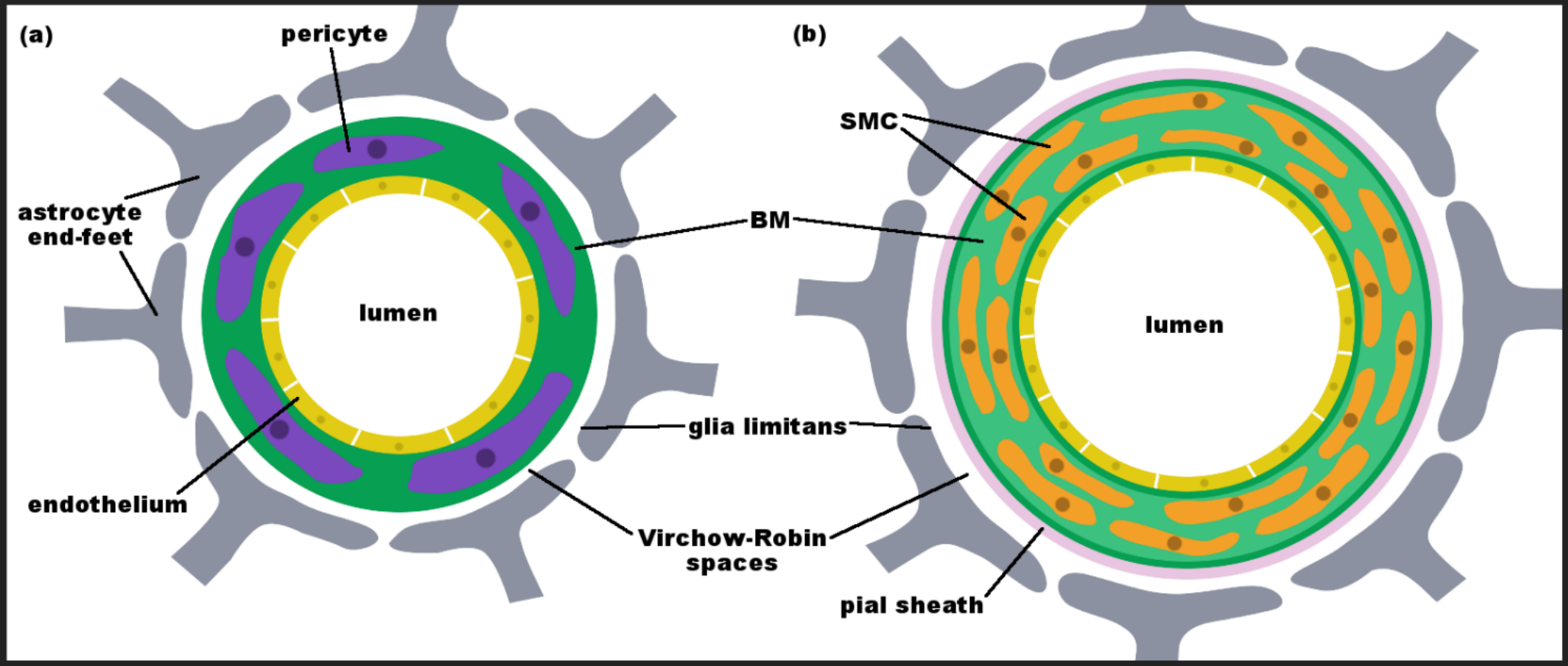


Diem et al. (2016), Frontiers in Ageing Neuroscience 8: 18

The physiology is pretty complex...



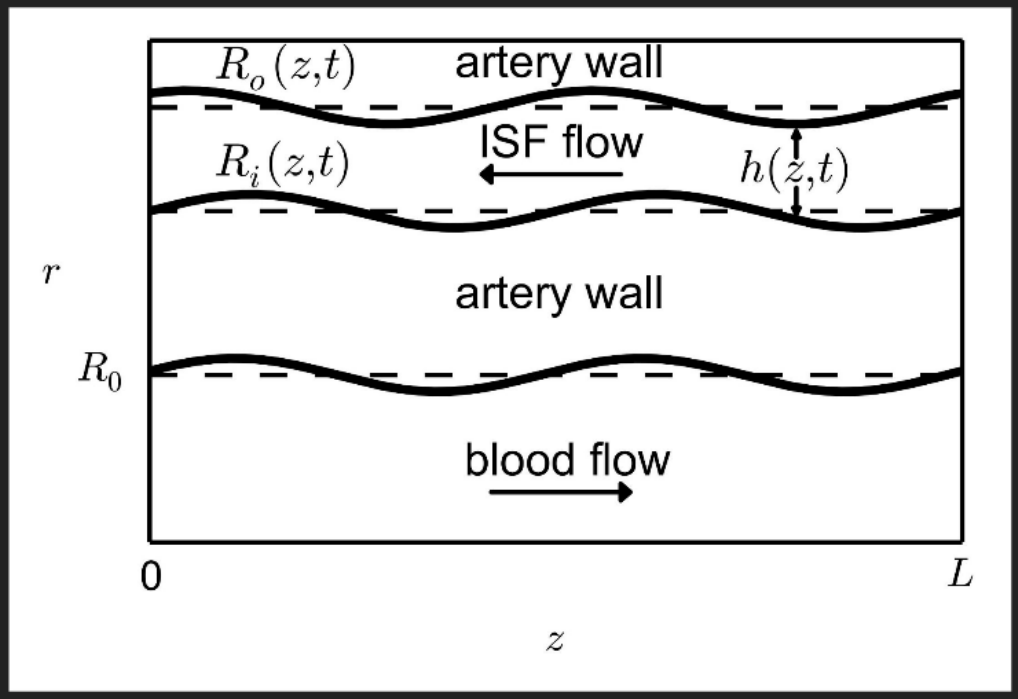
Cerebral artery anatomy 101



BM: Thin film flow inside a porous medium

$$\boldsymbol{q} = -\frac{k}{\mu}\nabla p$$

$$\frac{\partial q_1}{\partial z} + \frac{1}{r}\frac{\partial}{\partial r}\left(r q_2\right) = 0$$



Boundary conditions:

$$\frac{D}{Dt}\left(r - R_i(z,t)\right) = 0$$

$$\frac{\partial}{\partial t}\left(\gamma R_i(z,t) \cdot h_{\mathrm{bm}}(z,t)\right) = \frac{\partial}{\partial z}\left(R_i(z,t) \cdot h_{\mathrm{bm}}(z,t) \cdot K(p_z) \cdot p_z\right)$$

Schley et al. (2006), Journal of Theoretical Biology 238 (4): 962-974.
Diem et al. (2017), Frontiers in Neuroscience 11:475

BM pressure is directly proportional to artery wall stress

$$0 = \frac{1}{r}\frac{\partial}{\partial r}(r\tau_{rr}) + \frac{1}{r}\frac{\partial \tau_{r\theta}}{\partial \theta} - \frac{\tau_{\theta\theta}}{r}$$

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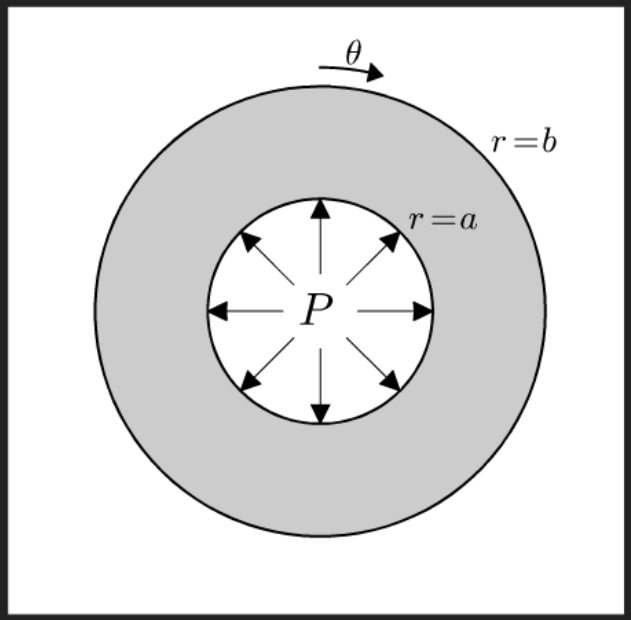


Boundary conditions:

$$\tau_{rr} = -P$$
$$\tau_{r\theta} = 0$$

on r = a

$$\tau_{rr} = 0$$
$$\tau_{r\theta} = 0$$

on r = b

Diem et al. (2017), Frontiers in Neuroscience 11:475

Recovering stresses using an Airy stress function

$$0 = \frac{\tau_{rr}}{r} + \frac{d\tau_{rr}}{dr} - \frac{\tau_{\theta\theta}}{r}$$

$$\tau_{rr} = -P \quad \text{on } r = a$$
$$\tau_{rr} = 0 \quad \text{on } r = b$$

$$\nabla^4 \mathcal{A}(r) = 0$$

$$\tau_{rr} = \frac{1}{r}\frac{d\mathcal{A}(r)}{dr}$$

$$\tau_{\theta\theta} = \frac{d^2\mathcal{A}(r)}{dr^2}$$

$$\mathcal{A}(r) = k_1 r^2 + k_2 + k_3 r^2 \log(r) + k_4 \log(r)$$

$$\mathcal{A}(r) = \frac{Pa^2b^2}{a^2 - b^2} \cdot \log\left(\frac{r}{b}\right) + \frac{Pa^2}{2(a^2 - b^2)}(b^2 - r^2)$$

$$\tau_{rr} = \frac{Pa^2}{b^2 - a^2}\left(1 - \frac{b^2}{r^2}\right) = -P_{BM}$$

Diem et al. (2017), Frontiers in Neuroscience 11:475

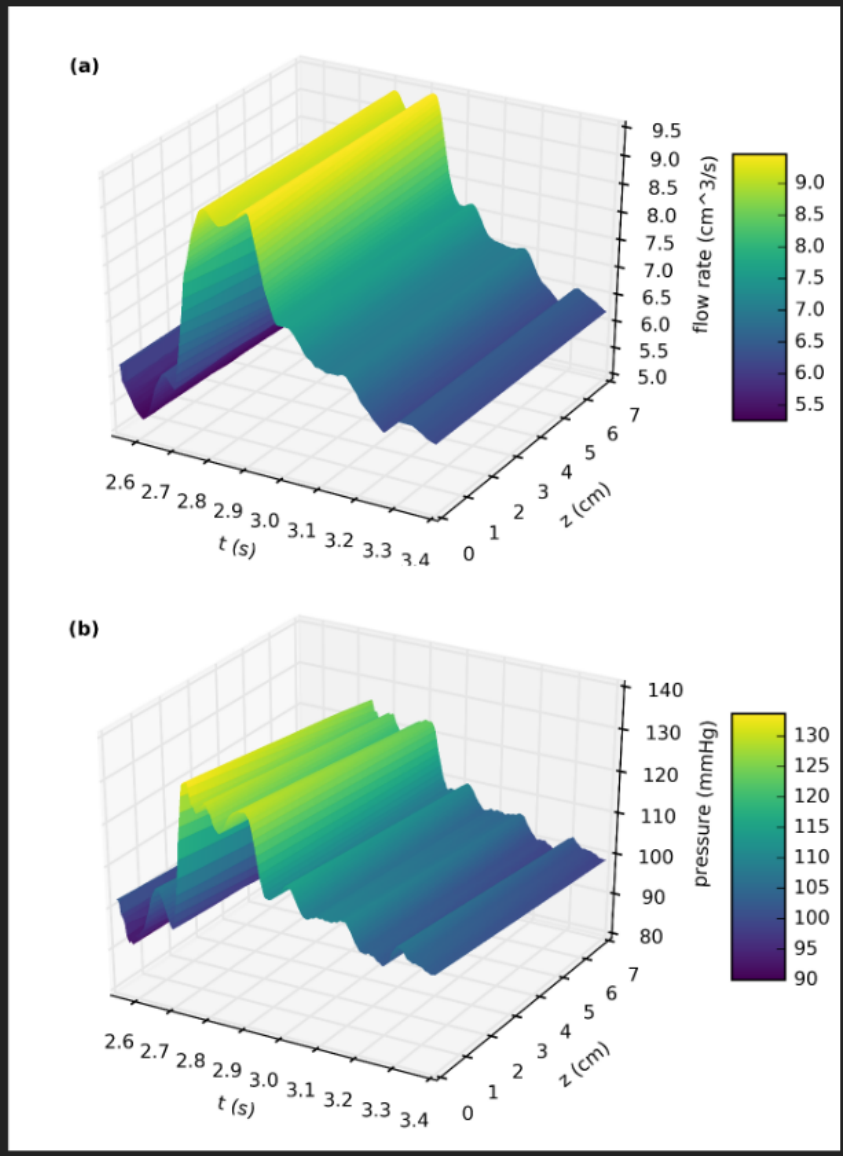
Blood flow through the MCA

$$\frac{\partial \boldsymbol{U}}{\partial t} + \frac{\partial \boldsymbol{F}}{\partial z} = \boldsymbol{S}$$

$$\boldsymbol{U} = \begin{pmatrix} A(z,t) \\ Q(z,t) \end{pmatrix}, \boldsymbol{S} = \begin{pmatrix} 0 \\ S_1 \end{pmatrix}$$

$$\boldsymbol{F} = \begin{pmatrix} Q(z,t) \\ \frac{Q(z,t)^2}{A(z,t)} + f(r_0)\sqrt{A_0(z)A(z,t)} \end{pmatrix}$$

$$S_1 = -\frac{2\pi R(z,t)}{\delta_b \mathrm{Re}} \frac{Q(z,t)}{A(z,t)} + \left(2\sqrt{A(z,t)}\left(\sqrt{\pi} f(r_0) + \sqrt{A_0(z)} \frac{df(r_0)}{dr_0}\right) - A(z,t)\frac{df(r_0)}{dr_0}\right)\frac{dr_0(z)}{dz}.$$



Olufsen et al. (2000), Annals of Biomedical Engineering 28 (11): 1281-1299
https://github.com/akdiem/vampy
Diem and Bressloff (2017), Journal of Open Research Software 5:17

VaMpy

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REPORT

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie[1,*], Hongyi Kang[1,*], Qiwu Xu[1], Michael J. Chen[1], Yonghong Liao[1], Meenakshisundaram Thiyagarajan[1], John O'Do…

+ See all authors and affiliations

Science 18 Oct 2013:
Vol. 342, Issue 6156, pp. 373-377
DOI: 10.1126/science.1241224

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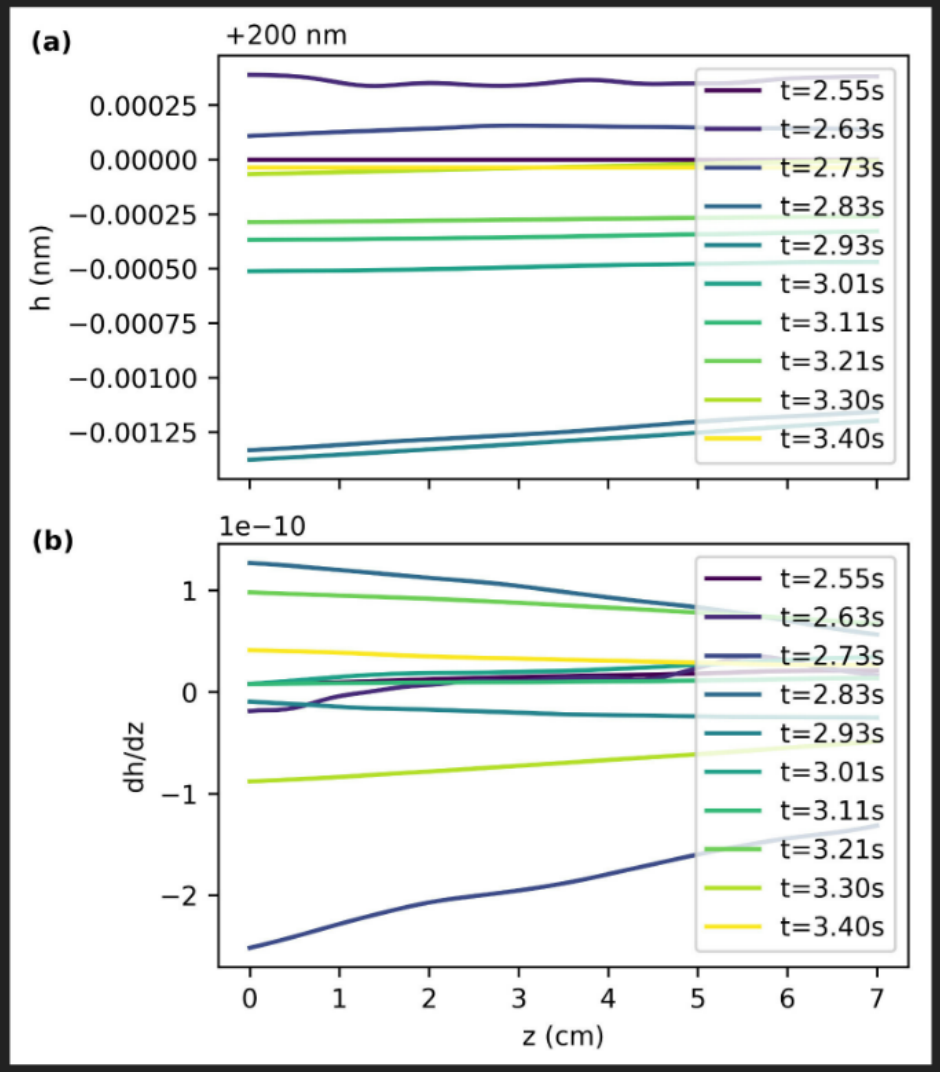
Why do we sleep? To clean our brains, say US scientists

Cerebral spinal fluid found to pump around the brain of sleeping mice, flushing out waste products like a biological dishwasher

IPAD through the MCA

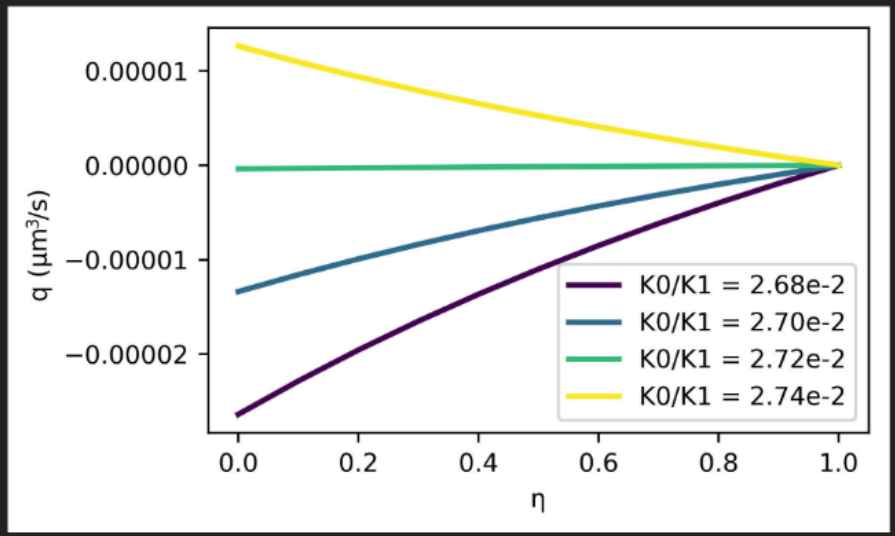


$$k = \mu K(p_z)$$

$$K(p_z) = \begin{cases} K_0 & p_z < 0 \\ K_1 & p_z \geq 0, \end{cases}$$

q = -1.12e-3 um3/s for **K0/K1 = 0.01**

A single turnover of ISF (280 ml) would take 1e11 days (0.3 billion years)



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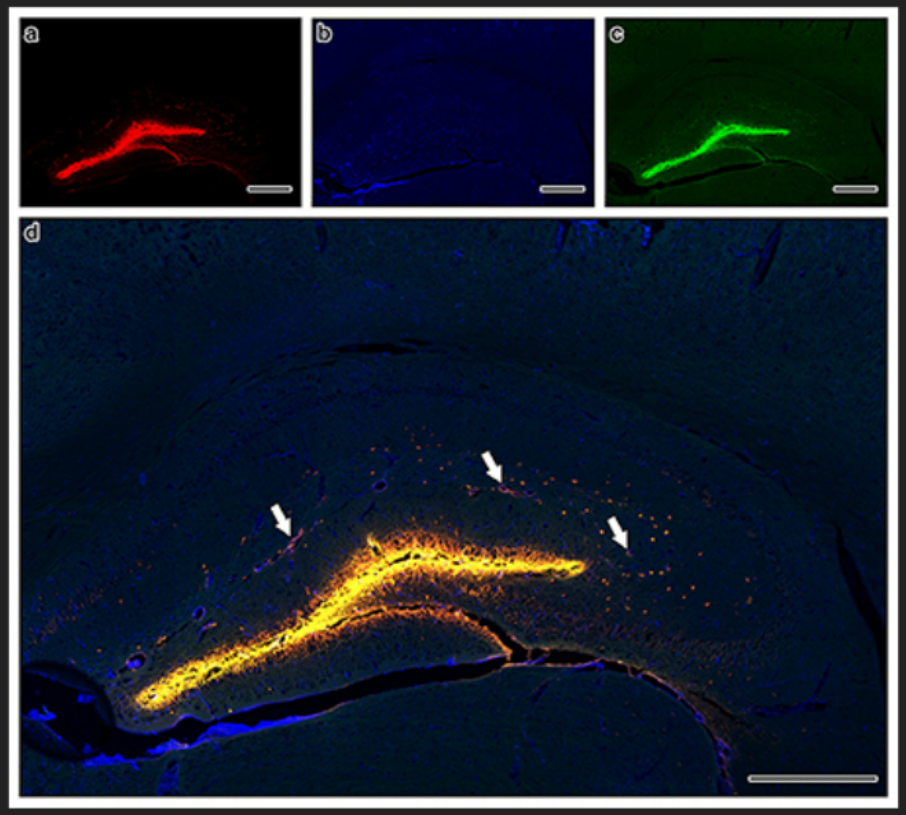
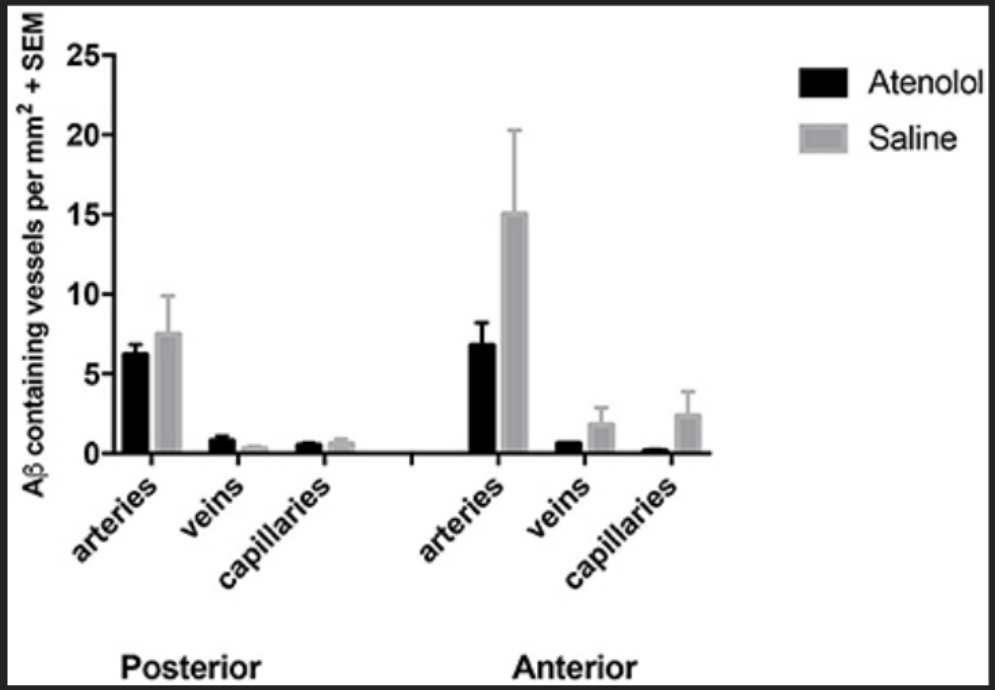
Experimental verification





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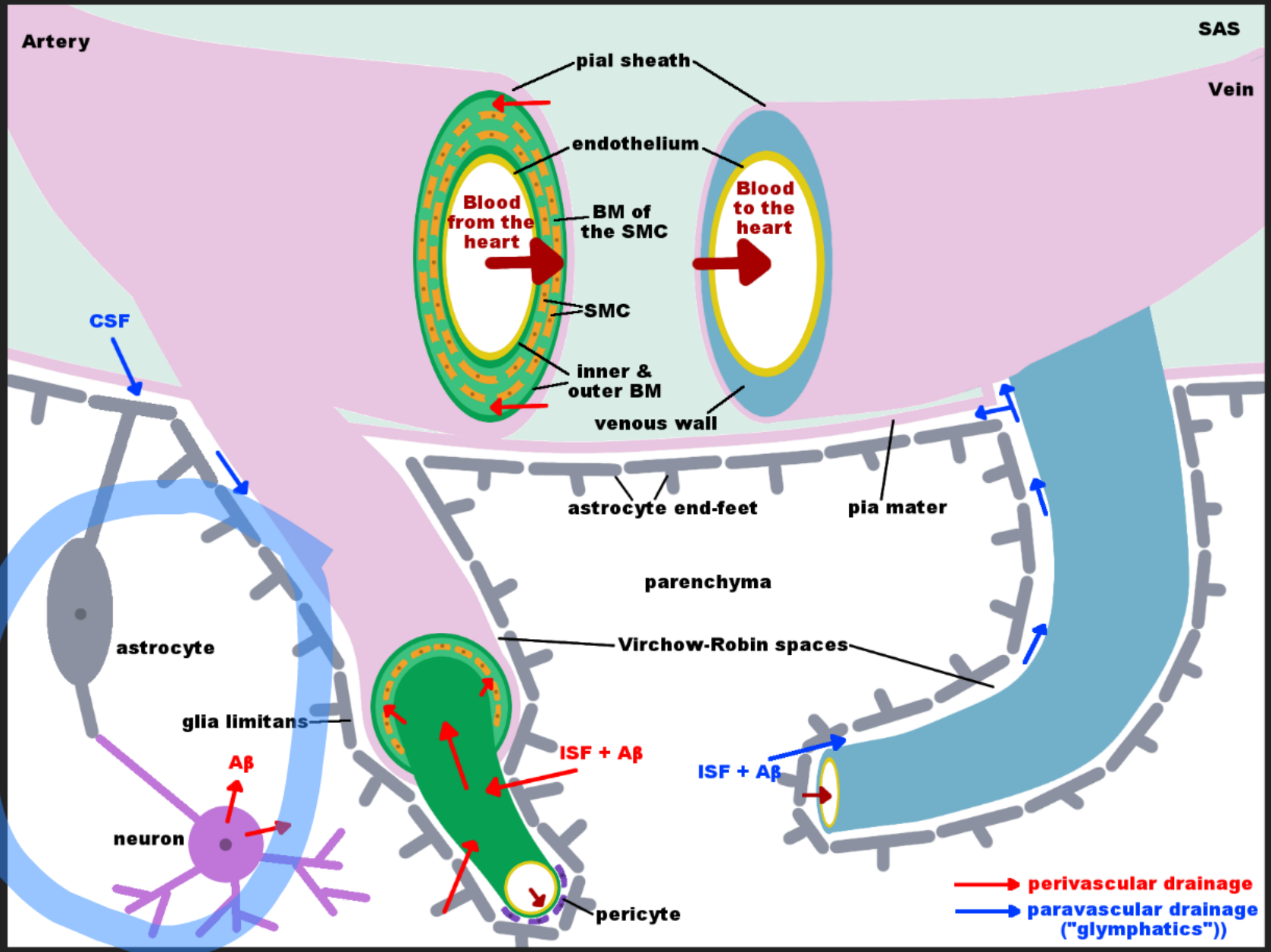
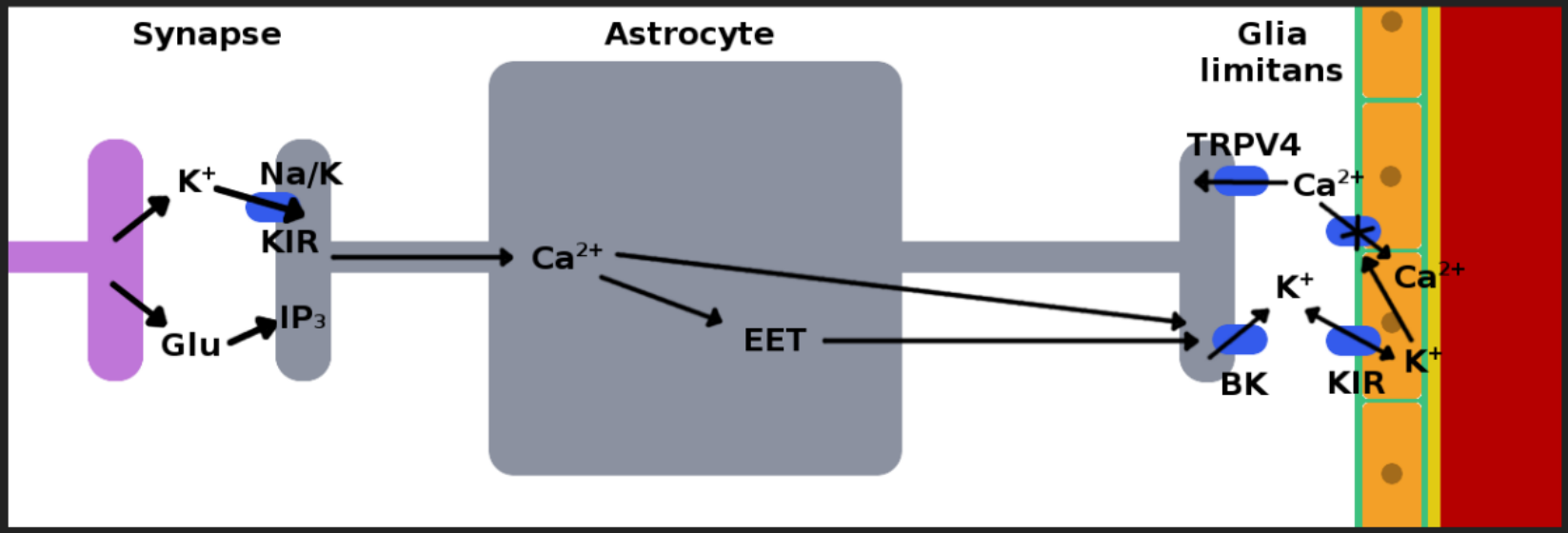
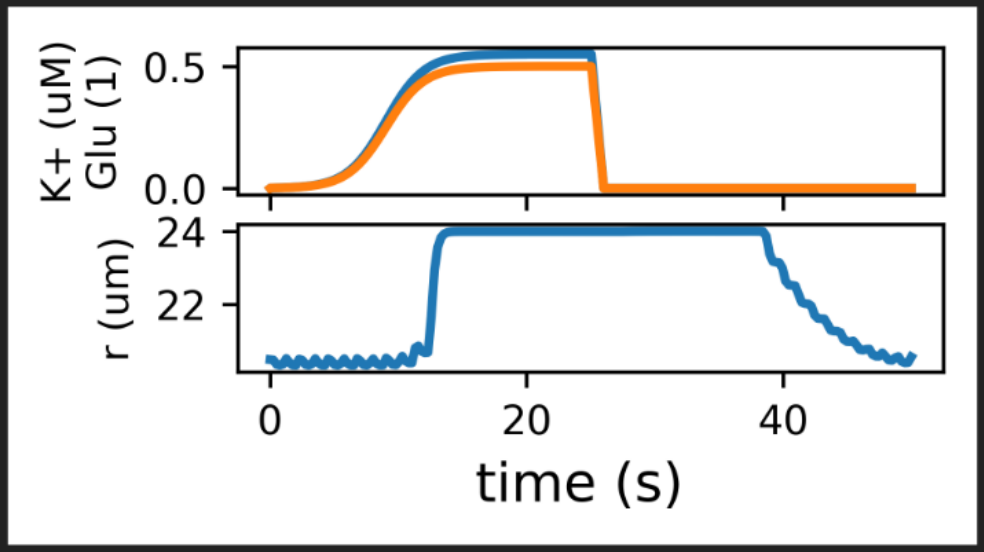
Neurovascular unit to the rescue!



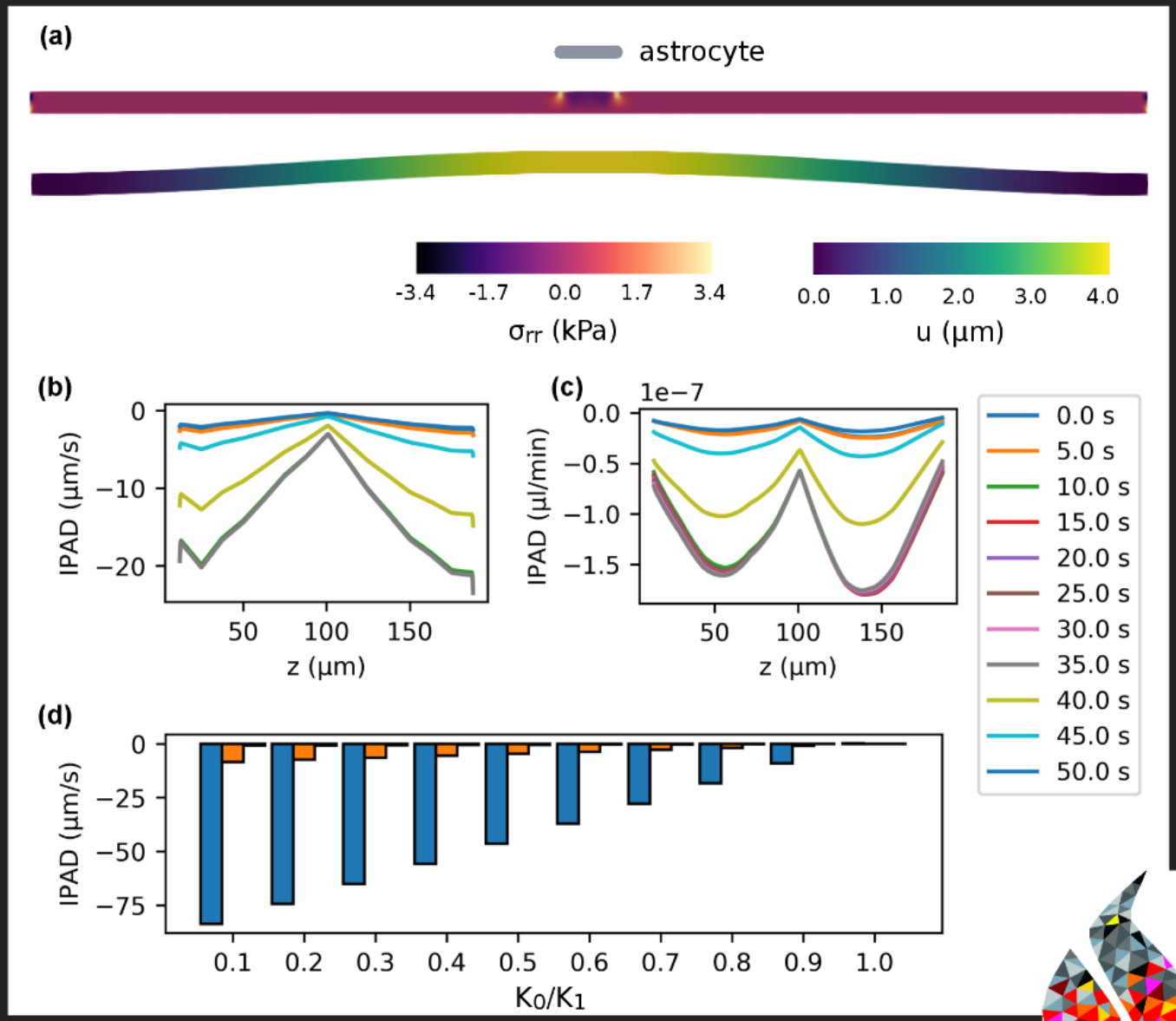
Neurovascular unit to the rescue!





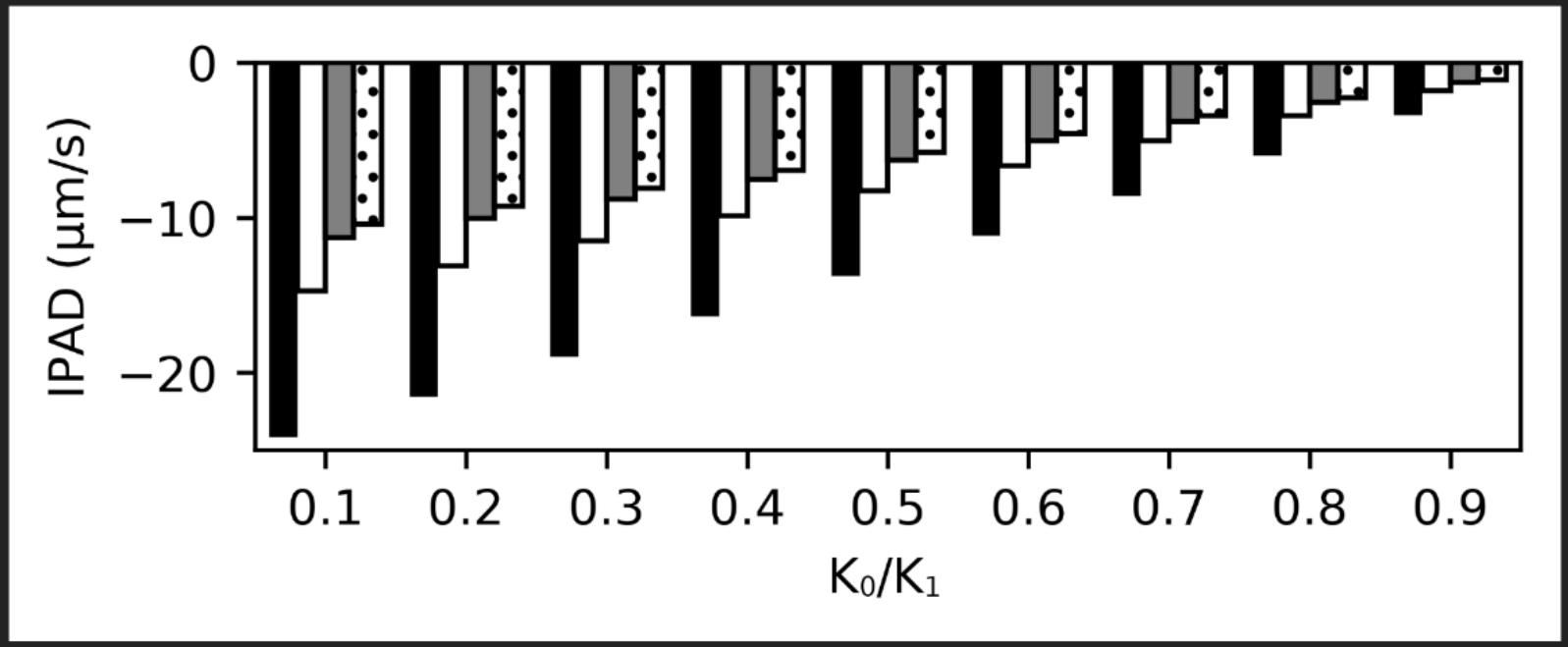
Diem (2017), ReScience 3(1): 9
Witthoft and Karniadakis (2012), Journal of Theoretical Biology 311: 80-93

Neurovascular unit to the rescue!



FENICS PROJECT

NVU model is quite robust



Conclusion: Mental and physical activity could be the key to prevent Alzheimer's!

Meanwhile, in our competitors' lab...

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A Little Alcohol Helps the Brain Flush Waste

If you drink moderately—say, a couple of glasses of wine per day—you may want to toast your glymphatic system. It helps clear your brain of metabolites, including the proteins that are associated with Alzheimer's disease and other forms of dementia. According to new research from the University of Rochester, the glymphatic system may work better if you consume low amounts of alcohol.

Thanks!

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Papers:
Diem et al. (2016) Frontiers in Ageing Neuroscience 8: 18
Diem and Bressloff (2017) Journal of Open Research Software 5: 1
Diem et al. (2017) Frontiers in Neuroscience 11: 475
Diem et al. (2018) PloS One, under review, preprint arXiv:1710.01117