

Perivascular fibrosis as a mechanical bottleneck.

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Scar-forming cells deposit collagen inside the channels that carry fluid through the brain and clear its waste. Because flow through a narrow channel scales steeply with its open volume, a small deposit should cost a disproportionate share of clearance, and the signals it fails to clear should drive further deposition. The result is a feed-forward loop with a threshold: below it, scarring resolves; above it, clearance decline sustains itself.

“None of the individual links is new. Closing them into a loop with a critical point is.”

Hypothesis and synthesis paper. No new experimental data are reported; every model output is an estimate under illustrative parameters, not a finding.

01

The argument.

Four links, each supported separately in the literature. The claim that they close into a loop is new.

01 Deposition

Injury, inflammation or chronic vascular stress activates perivascular fibroblasts, which deposit collagen I, fibronectin and basement membrane into the perivascular space.

02 Obstruction

The matrix shrinks the open volume of the channel and stiffens the vessel wall, lowering both the channel's conductance and the arterial motion that drives flow.

03 Retention

Slower exchange concentrates what would otherwise be cleared: TGF-beta, damage-associated molecules and protein aggregates.

04 Re-activation

Retained TGF-beta and the stiffer matrix activate the same fibroblasts, and cells pulling on stiff matrix release active TGF-beta already stored in it.

STEP 04 FEEDS STEP 01. THE LOOP CLOSES, AND IT HAS A THRESHOLD.

Live model.

Two parts of the model, running live in your browser from the paper's equations. Drag the controls to change the inputs. The model runs in the browser at <https://arcasdynamics.com/research/perivascular-fibrosis>.

Fig. 1a

Tracer particles flow through the perivascular space beside a pulsing artery. As matrix fills the channel, flow falls faster than the open space does: about three times faster at small fills.

Fig. 1b

Each line is one starting amount of matrix, run forward in time. Below the threshold at $F = 0.276$ the scar resolves; above it, the system locks into a state with 6.3% of baseline clearance.

Status

Model estimates under illustrative parameters, not measurements.

The equations.

01 THIN-GAP LUBRICATION

$$Q \propto \frac{h^3 \Delta P}{\mu L} \Rightarrow \frac{Q}{Q_0} = (1 - f)^3$$

Filling 10, 20 and 30% of the gap costs 27, 49 and 66% of the flow.

02 FIT TO REALISTIC CROSS-SECTIONS

$$\frac{Q}{Q_0} \approx (1 - f)^{2.75}$$

From resistance falling about 1,700-fold as area rises 15-fold (Tithof et al., 2019). The exponent is a fit to their figures, not a value they state.

03 POROUS MEDIUM, KOZENY-CARMAN

$$k = \frac{d^2 \varphi^3}{180 (1 - \varphi)^2}$$

Porosity falling from 0.40 to 0.30, a 25% loss of open volume, cuts permeability by about 69%.

$$\frac{dF}{dt} = a \frac{S}{K_S + S} + b \frac{F^n}{F^n + \theta^n} - d F$$

Solute-driven activation, stiffness-driven self-activation and matrix turnover. Clearance falls as $C = (1 - F)^3$, and the solute sits at the steady state that clearance allows.

04

What it builds on.

Published findings the model rests on, as the paper cites them.

About 40%

fall in amyloid-beta clearance in aged mice, alongside a 27% drop in arteriolar pulsatility

KRESS ET AL., 2014, ANNALS OF NEUROLOGY · [HTTPS://DOI.ORG/10.1002/ANA.24271](https://doi.org/10.1002/ANA.24271)

About 60%

fall in glymphatic exchange after traumatic brain injury, lasting at least a month

ILIFF ET AL., 2014, JOURNAL OF NEUROSCIENCE · [HTTPS://DOI.ORG/10.1523/JNEUROSCI.3020-14.2014](https://doi.org/10.1523/JNEUROSCI.3020-14.2014)

24%

higher adjusted risk of dementia after traumatic brain injury, in a cohort of 2,794,852 people

FANN ET AL., 2018, THE LANCET PSYCHIATRY · [HTTPS://DOI.ORG/10.1016/S2215-0366\(18\)30065-8](https://doi.org/10.1016/S2215-0366(18)30065-8)

1,700×

fall in hydraulic resistance as a perivascular channel's cross-section grows 15-fold

TITHOF ET AL., 2019, FLUIDS AND BARRIERS OF THE CNS · [HTTPS://DOI.ORG/10.1186/S12987-019-0140-Y](https://doi.org/10.1186/S12987-019-0140-Y)

05

Predictions.

Each one names the result that would refute it.

P1 Collagen predicts clearance

Refuted if perivascular collagen adds no independent variance to regional clearance, or AQP4 polarisation dominates it.

STATE: UNTESTED

P2 Losses are amplified

Refuted if fractional clearance loss is at or below the fractional loss of open volume.

STATE: UNTESTED

P3 A threshold, with hysteresis

Refuted if graded injury gives a graded, fully reversible relation, with no range where outcomes split into two groups.

STATE: UNTESTED

P4 Early treatment works, late does not

Refuted if an intervention long after the threshold restores clearance as well as an early one.

STATE: UNTESTED

P5 The sleeve stiffens as tissue softens

Refuted if the perivascular sleeve is no stiffer than the surrounding parenchyma in injured or aged tissue.

STATE: UNTESTED

P6 Dilation feeds narrowing

Refuted if dilated and collagen-rich segments of the same vessel are spatially unrelated.

STATE: UNTESTED

06

How to test it.

First test: Stiffness around the vessel wall

Atomic force or Brillouin microscopy on acute slices, registered to vessel position, measuring stiffness across the first 20 micrometres from the wall alongside YAP and TAZ in perivascular fibroblasts.

TESTS P5

Experiment 2: Collagen against AQP4

Tracer clearance in young, aged and injured mice, with perivascular collagen, vessel density and AQP4 polarisation measured in the same animals, using optical clearing to avoid fixation artefacts. About 10 animals per group (model estimate).

TESTS P1, P6

Experiment 3: Graded injury, timed treatment

Cortical impact at graded depths, with clearance imaged at one week, one month and three months, looking for two separate outcome groups; then partial anti-fibrotic treatment given early or late.

TESTS P3, P4

07

Where it could be wrong.

The stiffness direction may be wrong.

Bulk brain tissue softens with injury, Alzheimer's disease and age. The model needs a locally stiffer sleeve around the vessel, which has not been measured.

Perivascular spaces enlarge in disease.

Enlarged spaces look like the opposite of obstruction. The model places dilation upstream of a restriction on the same vessel, which Prediction 6 tests.

The strongest evidence is meningeal.

Fibrosis is known to obstruct fluid flow in the meninges. Extending that into the brain's own perivascular channels is the new and unproven part.

Both feedback arms are fragile.

If the sleeve does not stiffen and retention is weak for a short-range signal, nothing holds the loop closed, and the model reduces to one-way obstruction with no threshold.

How to cite.

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<https://arcasdynamics.com/research/perivascular-fibrosis>

