

Supplementary information for In-silico molecular transport via perivascular networks in the human intracranial space

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ABSTRACT

Supplementary methods and discussion accompanying the main text of *In-silico molecular transport via perivascular networks in the human intracranial space*.

S1 Supplementary methods

These sections provide more detailed descriptions of the mathematical models and numerical approximations considered.

S1.1 Mixed-dimensional transport Notation pertaining to the geometry, variables and flow equations computational domains

S1.1.1 Notation

In terms of geometrical domains, we consider the parenchyma $\Omega_{\text{PAR}} \subset \mathbb{R}^3$ and CSF spaces $\Omega_{\text{CSF}} \subset \mathbb{R}^3$ with $\Omega = \Omega_{\text{PAR}} \cup \Omega_{\text{CSF}}$ (Fig. 1A, Fig. 2A–C). The coordinates in these 3D domains is denoted by x . The interface between the parenchyma and CSF spaces is given by $\partial\Omega_{\text{PAR}} \cap \partial\Omega_{\text{CSF}}$ and we separate it as two parts: the surface of the lateral ventricles Γ_{LV} and the remaining pial interface Γ_{pia} (thus $\partial\Omega_{\text{CSF}} \cap \partial\Omega_{\text{PAR}} = \Gamma_{\text{LV}} \cup \Gamma_{\text{pia}}$). The remaining, outer, boundary of Ω_{CSF} is again separated into two parts: Γ_{SSAS} represents the lower interface towards the spinal subarachnoid space (SSAS), while Γ_{AM} is the outer interface towards the arachnoid and dura membranes. Γ_{AM} is further subdivided into its lower and upper parts: $\Gamma_{\text{AM-L}}$ and $\Gamma_{\text{AM-U}}$. The boundary towards the spinal cord is denoted by Γ_{SC} and given by $\Gamma_{\text{SC}} = \partial\Omega_{\text{PAR}} \setminus \partial\Omega_{\text{CSF}}$.

In addition, we consider two sets of perivascular networks: a periarterial network Λ_a represented by the (connected) centerlines Λ_a^i of the arterial tree, and a perivenous network Λ_v associated with the centerlines Λ_v^i of the veins. Recall that we represent the vascular domains as the union of cylindrical vessels of radius R_1^i surrounding the centerlines Λ^i . Moreover, we consider the surrounding perivascular spaces as the union of annular cylinders Ω^i of inner radius R_1^i and outer radius $R_2^i > R_1^i$ and thus of width $R_2^i - R_1^i$, and remark that we interpret R_2^i and R_1^i as temporal averages (fixed in time), as the pulsations considered in Section S1.5 are beyond the temporal resolution of our model. We denote the outer lateral surface of the periarterial and perivenous spaces by Γ_a and Γ_v , respectively. We omit the subscript a or v when referring to any such network, vessel segment or perivascular outer surface. We assume that Λ is parametrized by the coordinate s , and with a minor abuse of notation, simply write $s \in \Lambda$ to represent the point $\lambda(s)$ on Λ corresponding to s . Finally, we view each perivascular network both as a geometric domain and as a directed graph with the centerlines $\{\Lambda^i\}$ as oriented edges and the connections as nodes \mathcal{V} .

S1.1.1 Solute transport and exchange in intracranial domains (3D) and perivascular networks (1D)

In this section, we describe the mathematical model (eq. (1)), the associated definitions, interface and boundary conditions in further detail. We refer to the main text for explicit parameter values while giving the general, abstract form here, and to the reference ^{1,2} for the derivation and analysis of this 3D–1D model. Recall that we model a concentration field $c = c(x, t)$ for $x \in \Omega$ and $t > 0$ defined in Ω_{PAR} and Ω_{CSF} separately. In each of these domains, c satisfies

$$\partial_t(\phi c) - \nabla \cdot (D \nabla(\phi c)) + \nabla \cdot (uc) + \xi(\bar{c} - \hat{c})\delta_\Gamma = 0 \quad \text{in } \Omega_{\text{CSF}}, \Omega_{\text{PAR}}.$$

In Ω_{PAR} , ϕ is the fluid volume fraction (also known as the porosity) defined in the parenchyma ($\phi \ll 1$ in Ω_{PAR}) and in the CSF spaces ($\phi = 1$ in Ω_{CSF}). In the parenchyma, The notation used for the geometry, model variables and parameters is summarized

in Table S1 and S2.

Symbol	Description
Ω	Full intracranial domain: $\Omega = \Omega_{\text{PAR}} \cup \Omega_{\text{CSF}}$
Ω_{PAR}	Brain parenchyma domain
Ω_{CSF}	Cerebrospinal fluid (CSF) domain
$\partial\Omega_{\text{PAR}} \cap \partial\Omega_{\text{CSF}}$	Parenchyma–CSF interface: $\partial\Omega_{\text{CSF}} \cap \partial\Omega_{\text{PAR}} = \Gamma_{\text{LV}} \cup \Gamma_{\text{pia}}$
Γ_{LV}	Lateral ventricle surface (part of parenchyma–CSF interface)
Γ_{pia}	Pial surface (remainder of parenchyma–CSF interface)
Γ_{SSAS}	Lower CSF boundary toward spinal subarachnoid space
Γ_{AM}	Outer CSF boundary toward arachnoid/dura
$\Gamma_{\text{AM-L}}, \Gamma_{\text{AM-U}}$	Lower/upper parts of Γ_{AM}
Γ_{SC}	Parenchyma–spinal-cord boundary: $\partial\Omega_{\text{PAR}} \setminus \partial\Omega_{\text{CSF}}$
Λ_a, Λ_v	Arterial/venous PVS networks
Λ^i	Individual PVS centerline segment
L_i	Length of a PVS segment Λ^i
R_i^1, R_i^2	Inner/outer radii of the annular PVS
Γ_a, Γ_v	Outer lateral surfaces of periarterial/perivenous PVSs
A^i	Area of the cross-section for PVS segment Λ^i
P^i	Perimeter of the cross-section for PVS segment Λ^i
\mathcal{V}	Graph nodes of the PVS network
$\mathcal{B} \subset \mathcal{V}$	Internal (bifurcation) nodes
$\mathcal{N} \subset \mathcal{V}$	End (leaf) nodes

Table S1. Geometrical notation, refer to (Fig. 1A, Fig. 2A–C)

On the interface between the brain and the CSF spaces $\Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}$, we prescribe the following interface conditions, which represent a semi-permeable interface, writing $c|_{\Omega_{\text{PAR}}} = c_{\text{PAR}}$ and $c|_{\Omega_{\text{CSF}}} = c_{\text{CSF}}$:

$$\begin{aligned} 2(-D\nabla(\phi c) + \mathbf{u}c)|_{\Omega_{\text{PAR}}} \cdot \mathbf{n} &= -(-D\nabla(\phi c) + \mathbf{u}c)|_{\Omega_{\text{CSF}}} \cdot \mathbf{n} && \text{on } \Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}, \\ (-D\nabla(\phi c) + \mathbf{u}c)|_{\Omega_{\text{PAR}}} \cdot \mathbf{n} &= \beta_{\text{pia}}(c_{\text{PAR}} - c_{\text{CSF}}) && \text{on } \Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}, \end{aligned}$$

where $\mathbf{n} = \mathbf{n}_{\text{PAR}}$ is the normal vector field defined over the interface, outward-pointing when viewed from Ω_{PAR} , and $\beta_{\text{pia}} \geq 0$ is a permeability constant.

We supplement and with the following boundary conditions representing a given molecular influx at Γ_{SSAS} , molecular efflux at a constant update rate β_{exit} at $\Gamma_{\text{AM-U}}$, and no influx or efflux elsewhere from the CSF spaces:

$$\begin{aligned} 2(D\nabla(\phi c) - \mathbf{u}c) \cdot \mathbf{n} &= g_{\text{influx}} && \text{on } \Gamma_{\text{SSAS}}, \\ (-D\nabla(\phi c) + \mathbf{u}c) \cdot \mathbf{n} &= \beta_{\text{exit}}c && \text{on } \Gamma_{\text{AM-U}}, \\ (-D\nabla(\phi c) + \mathbf{u}c) \cdot \mathbf{n} &= 0 && \text{on } \Gamma_{\text{AM-L}} \cup \Gamma_{\text{SC}}. \end{aligned}$$

where again \mathbf{n} denotes the outward-pointing boundary normal.

The concentration $\hat{c} = \hat{c}(s, t)$ in the periarterial and perivenous networks ($s \in \Lambda_a, s \in \Lambda_v$), entering in, represents the concentration in the perivascular space averaged over each perivascular cross-section and is governed by

$$\partial_t(A\hat{c}) - \partial_s(\hat{D}A\partial_s\hat{c}) + \partial_s(A\hat{u}\hat{c}) + \xi P(\hat{c} - \bar{c}) = 0 \quad \text{in } \Lambda_a, \Lambda_v,$$

where in Λ_a, Λ_v refers to in each Λ^i in each of these networks. In, $A = A(s)$ is defined as the PVS cross-sectional area; i.e., for each $s \in \Lambda^i$ with associated PVS Ω^i , the area of Ω^i . We consider a mesh $\mathcal{T} = \{E\}$ of $\Omega = \Omega_{\text{PAR}} \cup \Omega_{\text{CSF}}$, consisting of tetrahedral mesh cells E , and conforming to the cross-section $\Theta^i(s)$. Also, \hat{D} is the effective diffusion coefficient, domains Ω_{PAR} and \hat{u} is a convective velocity representing an (average) CSF flow velocity in the axial direction of the perivascular spaces.

To complete, we prescribe bifurcation conditions at internal nodes of the perivascular networks Λ_a, Λ_v and boundary conditions at the end nodes. To this end, define the set of internal nodes $\mathcal{B} \subset \mathcal{V}$ as the set of nodes that are connected to two or

Symbol

ϕ represents the extracellular space volume fraction, and thus c here generally represents the intrinsic (in contrast to the superficial) concentration.
 D is the effective diffusion coefficient of the relevant solute in the respective media which takes different values over the CSF spaces and the ISF spaces.

\mathbf{u} is a convective velocity field representing the flow of CSF in Ω_{CSF} and the flow of ISF in Ω_{PAR} . ξ models a transfer or exchange parameter.

\bar{c}

\bar{c} denotes a lateral average of the concentration over the outer perivascular surfaces, defined for each centerline Λ^i and each point $s \in \Lambda^i$ by

ξ

$\delta\Gamma$

β_{pia}

β_{exit}

g_{influx}

\hat{D}

\hat{u}

p, \hat{p}

\hat{q}

κ

μ

$R_{\text{CSF},0}$

u_{in}

ω, ρ

α_c, α_r

h_{SAS}

R_c, R_r

Table S2. Variable and parameter notation

more edges and the set of end nodes as $\mathcal{N} \subset \mathcal{V}$, write $\hat{c}^i = \hat{c}|_{\Lambda^i}$, and for $y \in \mathcal{B}$ let $\mathcal{E}(y)$ denote the set of (two or three) edges in $\{\Lambda^i\}$ sharing the node y . To impose continuity of the concentrations, we set that the concentrations when viewed from each edge must match at nodes:–

$$\hat{c}^i(y) = \hat{c}^j(y) \quad \forall \Lambda^i, \Lambda^j \in \mathcal{E}(y) \quad \forall y \in \mathcal{B}.$$

Moreover, Ω_{CSF} and to ensure mass conservation, we set that the flux going in and out at nodes should add to zero, or more precisely, that for each $y \in \mathcal{B}$:-

$$\sum_{\Lambda^i \in \mathcal{E}(y)} (\hat{D}^i A^i \partial_s \hat{c}^i(y) - A^i \hat{u}^i(y) \hat{c}^i(y)) n^i(y) = 0.$$

Here the (normal “vector”) function n^i takes the values in $\{-1, 1\}$ and defines an orientation of vertices of edge Λ^i . Specifically, for an edge Λ^i oriented from y_{in} to y_{out} we set-

$$n^i(y_{\text{in}}) = 1, \quad n^i(y_{\text{out}}) = -1.$$

Finally, we impose a homogeneous Neumann condition at all network end nodes to augment :-

$$\hat{D} A \partial_s (\phi \hat{c}) - A \hat{u} \hat{c} = 0 \quad \text{on} \quad \mathcal{N}.$$

45 This no-flux condition states that the network end nodes represent barriers for molecular efflux into or out of the perivascular
 46 network, and thus that all solute exchange between the PVSs and their surroundings takes place via the lateral outer PVS

surface and is regulated by the exchange parameter ξ cf. and . Larger particles have been observed to accumulate within the PVS as the surface arteries penetrate into the brain parenchyma^{4,5}, and is appropriate to represent such behavior. However, to represent a continuously extending PVSs also along penetrating vessels, this condition should be revisited the CSF-brain interface $\Gamma_{pia} \cup \Gamma_{LV}$. We denote the restriction of \mathcal{T} to Ω_{PAR} and Ω_{CSF} by \mathcal{T}_{PAR} and \mathcal{T}_{CSF} , respectively. The collection of all interior facets (i.e. triangular faces of the tetrahedral mesh cells) in \mathcal{T}_{PAR} and \mathcal{T}_{CSF} are denoted by $\mathcal{F}_{L,PAR}$ and $\mathcal{F}_{L,CSF}$, respectively. We define the union of facets interior both to \mathcal{T}_{PAR} and \mathcal{T}_{CSF} as $\mathcal{F}_i = \mathcal{F}_{L,PAR} \cup \mathcal{F}_{L,CSF}$.

S1.1.1 Modelling CSF flow via the incompressible Stokes equations

S1.2 Modelling and simulating steady state CSF flow via the incompressible Stokes equations

The time-independent, incompressible Stokes equations model the flow of an incompressible Newtonian fluid at low Reynolds numbers, and read as follows: over the domain $\Omega_{CSF} \subset \mathbb{R}^3$, find the velocity vector field $\mathbf{u} : \Omega_{CSF} \rightarrow \mathbb{R}^3$ and the pressure field $p : \Omega_{CSF} \rightarrow \mathbb{R}$ such that

$$-\mu \Delta \mathbf{u} + \nabla p = 0 \quad \text{in } \Omega_{CSF}, \quad (1a)$$

$$\nabla \cdot \mathbf{u} = 0 \quad \text{in } \Omega_{CSF}. \quad (1b)$$

In addition, we impose the following boundary conditions to model flow induced by CSF production in the choroid plexus with Γ_{AM-U} as the main efflux site:

$$(\mu \nabla \mathbf{u} \cdot \mathbf{n} - p \mathbf{n}) \cdot \mathbf{n} = -R_{0,CSF,0}(\mathbf{u} \cdot \mathbf{n}), \quad \mathbf{u} \cdot \mathbf{t} = 0 \quad \text{on } \Gamma_{AM-U}, \quad (2a)$$

$$\mathbf{u} = 0 \quad \text{on } \Gamma_{AM-L} \cup \Gamma_{pia} \cup \Gamma_{SSAS}, \quad (2b)$$

$$\mathbf{u} \cdot \mathbf{n} = \frac{1}{|\Gamma_{LV}|} u_{in}, \quad \mathbf{u} \cdot \mathbf{t} = 0 \quad \text{on } \Gamma_{LV}, \quad (2c)$$

where \mathbf{n} and \mathbf{t} denote the unit outward normal and tangent vectors to the boundary respectively, μ is the (dynamic) CSF viscosity, $R_{0,CSF,0} > 0$ is a resistance parameter for CSF efflux, and u_{in} is a given fluid influx, here across the lateral ventricle wall Γ_{LV} . We consider alternative variations of these boundary conditions in connection with estimating dispersion effects induced by CSF pulsatility, see Section S1.4.

S1.2.1 Finite element solution of the incompressible Stokes equations

We consider an $H(\text{div})$ -based finite element approximation of the incompressible Stokes equations (1) defined over Ω_{CSF} with the boundary conditions (2). Following⁶, we approximate the velocity field \mathbf{u} and the pressure field p with the following finite element spaces:

$$\mathbf{V}_{h,g} = \{\mathbf{v} \in H(\text{div}, \Omega_{CSF}) : \mathbf{v}|_E \in \text{BDM}^2(E), E \in \mathcal{T}_{CSF}; \mathbf{v} \cdot \mathbf{n} = 0 \text{ on } \Gamma_{pia} \cup \Gamma_{AM-L} \cup \Gamma_{SSAS}, \mathbf{v} \cdot \mathbf{n} = g \text{ on } \Gamma_{LV}\}$$

$$\mathcal{Q}_h = \{q \in L^2(\Omega_{CSF}) : q|_E \in P^1(E), E \in \mathcal{T}_{CSF}\}.$$

Here, $H(\text{div}, \Omega_{CSF})$ is the space of $L^2(\Omega_{CSF})$ vector fields with $L^2(\Omega_{CSF})$ divergence, BDM^2 is the Brezzi-Douglas-Marini element⁷ of degree 2, g is a given constant, and \mathbf{n} is the unit outward normal vector to each facet. Given any vector \mathbf{v} , the normal and tangential components on each facet are denoted and given by

$$\mathbf{v}_n = (\mathbf{v} \cdot \mathbf{n}) \mathbf{n}, \quad \mathbf{v}_t = \mathbf{v} - \mathbf{v}_n.$$

Since $\mathbf{V}_{h,g} \subset H(\text{div}, \Omega_{CSF})$, then $[\mathbf{v}_n] = 0$ on $\mathcal{F}_{L,CSF}$, the interior facets to Ω_{CSF} . Continuity in the tangential component is enforced weakly via interior penalization. For convenience, we collect all facets exterior to the CSF space Γ_{AM-U} in the set

$$\mathcal{F}_e = \mathcal{F}_{pia} \cup \mathcal{F}_{LV} \cup \mathcal{F}_{AM-L} \cup \mathcal{F}_{AM-U} \cup \mathcal{F}_{SSAS},$$

where facets lying on the pial interface Γ_{pia} are denoted by \mathcal{F}_{pia} , on the lower and upper outer (arachnoid) boundary Γ_{AM-L} and Γ_{AM-U} by \mathcal{F}_{AM-L} and \mathcal{F}_{AM-U} , respectively, on the boundary towards the spinal SAS Γ_{SSAS} by \mathcal{F}_{SSAS} , and on the surface of the lateral ventricles by \mathcal{F}_{LV} . Now, define the form

$$\mathcal{A}_h(\mathbf{u}, \mathbf{v}) = \sum_{E \in \mathcal{T}_{CSF}} \int_E \mu \nabla \mathbf{u} : \nabla \mathbf{v} + \sum_{F \in \mathcal{F}_{L,CSF} \cup \mathcal{F}_e} \left(- \int_F \mu \{ \nabla \mathbf{u} \} \mathbf{n}_F \cdot [\mathbf{v}_t] - \int_F \mu \{ \nabla \mathbf{v} \} \mathbf{n}_F \cdot [\mathbf{u}_t] + \int_F \frac{\sigma \mu}{h_F} [\mathbf{u}_t] \cdot [\mathbf{v}_t] \right), \quad (3)$$

where on exterior facets the average and jump operators take the one-sided values. We set the penalty parameter for the tangential continuity to be $\sigma = 20$. The finite element discretization of the incompressible Stokes equations is then to find $(\mathbf{u}_h, p_h) \in \mathbf{V}_{h,g} \times Q_h$ with $g = \frac{1}{|\Gamma_{\text{LV}}|} u_{\text{in}}$ such that

$$\mathcal{A}_h(\mathbf{u}_h, \mathbf{v}_h) + \sum_{F \in \mathcal{F}_{\text{AM-U}}} \int_F R_{\text{CSF},0}(\mathbf{u}_h \cdot \mathbf{n})(\mathbf{v}_h \cdot \mathbf{n}) - \int_{\Omega_{\text{CSF}}} \nabla \cdot \mathbf{v}_h p_h = 0 \quad \forall \mathbf{v}_h \in \mathbf{V}_{h,0} \quad (4a)$$

$$\int_{\Omega_{\text{CSF}}} \nabla \cdot \mathbf{u}_h q_h = 0 \quad \forall q_h \in Q_h. \quad (4b)$$

60 S1.2.2 Steady flow in perivascular networks induced by pressure differences

61 S1.3 Modeling and simulating steady flow in perivascular networks induced by pressure differences

To model steady flow induced by pressure differences between end nodes in a perivascular network Λ , with edges $\{\Lambda^i\}_i$, internal nodes \mathcal{B} and end nodes \mathcal{N} , we consider the following system of hydraulic network equations^{8–10}. The unknowns are the PVS flux $\hat{q} : \Lambda \rightarrow \mathbb{R}$ and pressure $\hat{p} : \Lambda \rightarrow \mathbb{R}$, which represent the fluid flux and the average pressure across cross-sections of the PVSs, respectively. These are defined for each Λ^i by solving:

$$\hat{q} + \frac{A\kappa}{\mu} \partial_s \hat{p} = 0 \quad \text{in } \Lambda^i, \quad (5a)$$

$$-\partial_s \hat{q} = 0 \quad \text{in } \Lambda^i, \quad (5b)$$

where A is the area of the PVS cross-sections, μ is the CSF viscosity as before, and κ is derived from an assumption of Poiseuille flow in the annular cross-section of the PVS as⁸:

$$\kappa = \frac{1}{8} \left(R_2^2 + R_1^2 - \frac{1}{\ln(R_2/R_1)} (R_2^2 - R_1^2) \right). \quad (6)$$

The PVS flux \hat{q} and the associated average PVS velocity in the axial direction \hat{u} are directly related by the cross-sectional area

$$\hat{q}^i = A^i \hat{u}^i \quad \forall \Lambda^i. \quad (7)$$

In addition, to complete (5), we impose continuity of the fluid pressure and conservation of flux at each internal node. Write $\hat{p}^i = \hat{p}|_{\Lambda^i}$. These conditions then read as: for each $y \in \mathcal{B}$ with connected edges $\mathcal{E}(y)$:

$$\hat{p}^i(y) = \hat{p}^j(y) \quad \forall \Lambda^i, \Lambda^j \in \mathcal{E}(y), \quad (8a)$$

$$\sum_{\Lambda^i \in \mathcal{E}(y)} \hat{q}^i n^i(y) = 0. \quad (8b)$$

where Here the (normal “vector”) function n^i is as defined by — takes the values in $\{-1, 1\}$ and defines an orientation of vertices of edge Λ^i . Specifically, for an edge Λ^i oriented from y_{in} to y_{out} we set

$$n^i(y_{\text{in}}) = 1, \quad n^i(y_{\text{out}}) = -1. \quad (9)$$

Finally, to drive this flow, we impose given fluid pressures p_0 at the network end nodes:

$$\hat{p}(y) = p_0(y) \quad y \in \mathcal{N}. \quad (10)$$

62 In the case where When modelling flow in the perivascular networks Λ_a, Λ_v induced by CSF production, we impose the fluid
63 pressure p_{CSF} computed in the CSF spaces Ω_{CSF} (and its harmonic extensions into Ω_{PAR}) as the given fluid pressures p_0 . Note
64 that we here consider steady PVS flow in a non-moving domain; the effect of domain motion is addressed in Section S1.5.

65 S1.4 Numerical solution of the transport and flow equations

66 We solve the models presented in ?? numerically using finite element methods. The following subsections provide more
67 details, model-by-model.

S1.3.1 Computational mesh entities: definitions and common notation

We consider a mesh $\mathcal{T} = \{E\}$ of $\Omega = \Omega_{\text{PAR}} \cup \Omega_{\text{CSF}}$, consisting of tetrahedral mesh cells E , and conforming to the domains Ω_{PAR} and Ω_{CSF} and to the CSF-brain interface $\Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}$. We denote the restriction of \mathcal{T} to Ω_{PAR} and Ω_{CSF} by \mathcal{T}_{PAR} and \mathcal{T}_{CSF} , respectively. The collection of all interior facets (i.e. triangular faces of the tetrahedral mesh cells) in \mathcal{T}_{PAR} and \mathcal{T}_{CSF} are denoted by $\mathcal{F}_{i,\text{PAR}}$ and $\mathcal{F}_{i,\text{CSF}}$, respectively. We define the union of facets interior both to \mathcal{T}_{PAR} and \mathcal{T}_{CSF} as $\mathcal{F}_i = \mathcal{F}_{i,\text{PAR}} \cup \mathcal{F}_{i,\text{CSF}}$.

S1.3.1 Finite element solution of coupled 3D-1D solute transport equations

We consider the system of coupled 3D-1D solute transport equations given by and with the interface conditions and , the bifurcation conditions and , and the boundary conditions and . We discretize these equations using an implicit finite difference scheme in time, a discontinuous Galerkin (DG) finite element method with upwinding in space for the 3D domain to accurately capture sharp boundary layers, and a continuous Galerkin method for the 1D networks. We remark that the transport in the CSF spaces is highly convection dominated, with an average Péclet number of 402 and maximum of 9542 (assuming a characteristic length of 10 cm, and accounting for the increased diffusivity due to dispersion).

We first consider the discretization of and introduce the discrete space

$$V_h = \{c \in L^2(\Omega) : c|_E \in P^1(E), E \in \mathcal{T}\},$$

where $L^2(\Omega)$ is the space of square-integrable functions defined over Ω and $P^1(E)$ denotes the space of polynomials of total degree ≤ 1 defined over the tetrahedra E . To discretize the diffusion term in , we use a symmetric weighted interior penalty DG formulation, referring to [11] and [12, Section 4.5.2.3] for details on this method. Recall that ϕ is constant in each domain Ω_{PAR} and Ω_{CSF} , and thus in particular that $\nabla(\phi c) = \phi \nabla c$ on each $E \in \mathcal{T}$. Define for $c, v \in V_h^k$:

$$a_h(c, v) = \sum_{E \in \mathcal{T}} \int_E D \phi \nabla c \cdot \nabla v - \sum_{F \in \mathcal{F}_i} \int_F \left(\{D \phi \nabla c\}_w \cdot \mathbf{n}_F [\underline{v}] + \{D \phi \nabla v\}_w \cdot \mathbf{n}_F [\underline{c}] \right) + \sum_{F \in \mathcal{F}_i} \eta \frac{\gamma_{D,F}}{h_F} \int_F [\underline{c}] [\underline{v}].$$

In , for each facet $F \in \mathcal{F}_i$ shared between cells E^1 and E^2 , we associate a facet normal vector \mathbf{n}_F pointing from E^1 to E^2 . The facet diameter is denoted by h_F , the jump $[\cdot]$ is given by $[v] = v|_{E^1} - v|_{E^2}$, and the unweighted average $\{\cdot\}$ and weighed average $\{\cdot\}_w$ are defined as:

$$\{v\} = \frac{1}{2} v|_{E^1} + \frac{1}{2} v|_{E^2}, \quad \{v\}_w = \frac{\kappa_2}{\kappa_1 + \kappa_2} v|_{E^1} + \frac{\kappa_1}{\kappa_1 + \kappa_2} v|_{E^2} \quad \text{where} \quad \kappa_i = (D \phi)|_{E^i}.$$

The parameter $\gamma_{D,F}$ is the harmonic mean of the porosity-weighted diffusion coefficient given by

$$\gamma_{D,F} = \frac{2\kappa_1\kappa_2}{\kappa_1 + \kappa_2},$$

and η is a user-specified penalty parameter (we set $\eta = 1000$). To discretize the convection term in , we use upwinding, see [12, Section 2.3.1] and the references therein. For $c, v \in V_h^k$, define

$$a_h^{\text{up}}(c, v) = - \sum_{E \in \mathcal{T}} \int_E c \mathbf{u} \cdot \nabla v + \sum_{F \in \mathcal{F}_i} \int_F \{u c\} \cdot \mathbf{n}_F [\underline{v}] + \sum_{F \in \mathcal{F}_i} \int_F \frac{|\mathbf{u} \cdot \mathbf{n}_F|}{2} [\underline{c}] [\underline{v}].$$

Our discrete formulation for with the interface conditions and boundary conditions and given initial conditions c_h^0 then reads: for $n = 1, 2, \dots$, with $t^n - t^{n-1} = \tau$, find $c_h^n \in V_h$ such that for all $v \in V_h$:

$$\int_{\Omega} \frac{1}{\tau} (\phi c_h^n - \phi c_h^{n-1}) v + a_h(c_h^n, v) + a_h^{\text{up}}(c_h^n, v) + \int_{\Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}} \beta_{\text{pia}} [c_h^n] [\underline{v}] + \int_{\Gamma_{\text{AM-U}}} \beta_{\text{exit}} c_h^n v + \int_{\Lambda} \xi P \left(\overline{c_h^n} - \hat{c}_h^n \right) \bar{v} = \int_{\Gamma_{\text{SSAS}}} g_{\text{influx}} v.$$

To discretize with the bifurcation conditions and , and the boundary conditions , we use the space of continuous piecewise linear polynomials defined over Λ :

$$\hat{V}_h = \{v \in C^0(\Lambda), v|_{\Lambda^i} \in P^1(\Lambda^i)\},$$

where $P^1(\Lambda^i)$ is the space of linear polynomials on each Λ^i . The discrete formulation then reads: for $n = 1, 2, \dots$, find $\hat{c}_h^n \in \hat{V}_h$ such that for all $\hat{v} \in \hat{V}_h^k$,

$$\int_{\Lambda} \frac{1}{\tau} (A \hat{c}_h^n - A \hat{c}_h^{n-1}) \hat{v} + \int_{\Lambda} \hat{D} A \partial_s \hat{c}_h^n \partial_s \hat{v} - \int_{\Lambda} A \hat{u} \hat{c}_h^n \partial_s \hat{v} + \int_{\Lambda} \xi P(\hat{c}_h^n - \overline{\hat{c}_h^n}) \hat{v} + a_h^{\text{stab}}(\hat{u}; \hat{c}, \hat{v}) = 0.$$

In the above, if \hat{u} is non-zero on Λ^i , then the artificial diffusion a_h^{stab} stabilization term is nonzero and is given below, for more details see for [13, Section 12.6].

$$a_h^{\text{stab}}(\hat{u}; \hat{c}, \hat{v}) = \frac{1}{\|\hat{u}\|_{L^2(\Lambda^i)}} h_{\Lambda^i} \int_{\Lambda^i} A(\hat{u} \partial_s \hat{c}_h)(\hat{u} \partial_s \hat{v}),$$

where h_{Λ^i} is the mesh-size of Λ^i . Note that the condition is enforced weakly in the above formulation.

Summary: The discretization for and complemented with boundary conditions (and), interface and bifurcation conditions (and), and initial conditions $c_h^0 = 0$ and $\hat{c}_h^0 = 0$ is the following:

For $n = 1, 2, \dots$, find $c_h^n \in V_h$ and $\hat{c}_h^n \in \hat{V}_h$ such that the coupled equations and hold for all $v \in V_h$ and for all $\hat{v} \in \hat{V}_h$.

S1.3.1 Finite element solution of the incompressible Stokes equations

We consider an $H(\text{div})$ -based finite element approximation of the incompressible Stokes equations defined over Ω_{CSF} with the boundary conditions . Following⁶, we approximate the velocity field \mathbf{u} and the pressure field p with the following finite element spaces:

$$\begin{aligned} \mathbf{V}_{h,g} &= \{ \mathbf{v} \in H(\text{div}, \Omega_{\text{CSF}}) : \mathbf{v}|_E \in \text{BDM}^2(E), E \in \mathcal{T}_{\text{CSF}}; \mathbf{v} \cdot \mathbf{n} = 0 \text{ on } \Gamma_{\text{pia}} \cup \Gamma_{\text{AM-L}} \cup \Gamma_{\text{SSAS}}, \mathbf{v} \cdot \mathbf{n} = g \text{ on } \Gamma_{\text{LV}} \} \\ Q_h &= \{ q \in L^2(\Omega_{\text{CSF}}) : q|_E \in P^1(E), E \in \mathcal{T}_{\text{CSF}} \}. \end{aligned}$$

Here, $H(\text{div}, \Omega_{\text{CSF}})$ is the space of $L^2(\Omega_{\text{CSF}})$ vector fields with $L^2(\Omega_{\text{CSF}})$ divergence, BDM^2 is the Brezzi-Douglas-Marini element⁷ of degree 2, g is a given constant, and \mathbf{n} is the unit outward normal vector to each facet. Given any vector \mathbf{v} , the normal and tangential components on each facet are denoted and given by

$$\mathbf{v}_n = (\mathbf{v} \cdot \mathbf{n}) \mathbf{n}, \quad \mathbf{v}_t = \mathbf{v} - \mathbf{v}_n.$$

Since $\mathbf{V}_{h,g} \subset H(\text{div}, \Omega_{\text{CSF}})$, then $[\mathbf{v}_n] = 0$ on $\mathcal{F}_{i,\text{CSF}}$, the interior facets to Ω_{CSF} . Continuity in the tangential component is enforced weakly via interior penalization. For convenience, we collect all facets exterior to the CSF space $\Gamma_{\text{AM-U}}$ in the set

$$\mathcal{F}_e = \mathcal{F}_{\text{pia}} \cup \mathcal{F}_{\text{LV}} \cup \mathcal{F}_{\text{AM-L}} \cup \mathcal{F}_{\text{AM-U}} \cup \mathcal{F}_{\text{SSAS}},$$

where facets lying on the pial interface Γ_{pia} are denoted by \mathcal{F}_{pia} , on the lower and upper outer (arachnoid) boundary $\Gamma_{\text{AM-L}}$ and $\Gamma_{\text{AM-U}}$ by $\mathcal{F}_{\text{AM-L}}$ and $\mathcal{F}_{\text{AM-U}}$, respectively, on the boundary towards the spinal SAS Γ_{SSAS} by $\mathcal{F}_{\text{SSAS}}$, and on the surface of the lateral ventricles by \mathcal{F}_{LV} . Now, define the form

$$\mathcal{A}_h(\mathbf{u}, \mathbf{v}) = \sum_{E \in \mathcal{T}_{\text{CSF}}} \int_E \mu \nabla \mathbf{u} : \nabla \mathbf{v} + \sum_{F \in \mathcal{F}_{i,\text{CSF}} \cup \mathcal{F}_e} \left(- \int_F \mu \{ \nabla \mathbf{u} \} \mathbf{n}_F \cdot [\mathbf{v}_t] - \int_F \mu \{ \nabla \mathbf{v} \} \mathbf{n}_F \cdot [\mathbf{u}_t] + \int_F \frac{\sigma \mu}{h_F} [\mathbf{u}_t] \cdot [\mathbf{v}_t] \right),$$

where on exterior facets the average and jump operators take the one-sided values. We set the penalty parameter for the tangential continuity to be $\sigma = 20$. The finite element discretization of the incompressible Stokes equations is then to find $(\mathbf{u}_h, p_h) \in \mathbf{V}_{h,g} \times Q_h$ with $g = \frac{1}{|\Gamma_{\text{LV}}|} u_{\text{in}}$ such that

$$\begin{aligned} \mathcal{A}_h(\mathbf{u}_h, \mathbf{v}_h) + \sum_{F \in \mathcal{F}_{\text{AM-U}}} \int_F R_0(\mathbf{u}_h \cdot \mathbf{n})(\mathbf{v}_h \cdot \mathbf{n}) - \int_{\Omega_{\text{CSF}}} \nabla \cdot \mathbf{v}_h p_h &= 0 \quad \forall \mathbf{v}_h \in \mathbf{V}_{h,0} \\ \int_{\Omega_{\text{CSF}}} \nabla \cdot \mathbf{u}_h q_h &= 0 \quad \forall q_h \in Q_h. \end{aligned}$$

86 S1.3.1 Finite element solution of the perivascular network equations

We consider meshes $\mathcal{I}_a, \mathcal{I}_v$ representing a conforming subdivision of each of the perivascular networks Λ_a, Λ_v . Relative to each mesh \mathcal{I} , we define the space of (discontinuous) piecewise constants $\hat{Z}_h(\mathcal{I})$ and define spaces of continuous piecewise linears $\hat{V}_{h,g}(\mathcal{I})$ with prescribed boundary node values (on \mathcal{N}) given by g :

$$\hat{Z}_h(\mathcal{I}) = \{z \in L^2(\Lambda); z|_{\Lambda^i} \in P^0(\Lambda^i) \forall \Lambda^i \in \mathcal{I}\}, \quad (11)$$

$$\hat{V}_{h,g}(\mathcal{I}) = \{v \in C^0(\Lambda); v|_{\Lambda^i} \in P^1(\Lambda^i), v(x) = g(x) \forall x \in \mathcal{N}\}. \quad (12)$$

To discretize (5) with the bifurcation conditions (8) and boundary conditions (10), we use the space of continuous functions $\hat{Z}_h(\mathcal{I})$ to enforce the continuity of the pressure at bifurcation points, while the conservation of flux is enforced (weakly) through the variational formulation. The discrete variational form of the equations then reads: Find $(\hat{q}, \hat{p}) \in \hat{Z}_h(\mathcal{I}) \times \hat{V}_{h,p_0}(\mathcal{I})$ such that

$$\langle \hat{q}, z \rangle + \langle z, \frac{A\kappa}{\mu} \partial_s \hat{p} \rangle = 0 \quad \forall z \in \hat{Z}_h(\mathcal{I}) \quad (13a)$$

$$\langle \hat{q}, \partial_s w \rangle = 0 \quad \forall w \in \hat{V}_{h,0}(\mathcal{I}). \quad (13b)$$

87 where $\langle \cdot, \cdot \rangle$ denotes the $L^2(\mathcal{I})$ -inner product and ∂_s is defined segment-wise. For a stability and convergence analysis of this
88 discrete model, we refer to [the reference previously presented results](#)¹⁰.

89 S1.4 Estimating dispersion factors from pulsatile CSF flow

90 The cardiac ($\sim 1\text{Hz}$) and respiratory ($\sim 0.25\text{Hz}$) cycles induce pulsatile flow of CSF in the ventricular system and in the cranial
91 and spinal SAS. Pulsatile flow leads to dispersion which in turn may enhance molecular transport^{14–19}. To account for the
92 dispersive effects over a longer time scale (hours to days), and in the absence of measurements or estimates of dispersion
93 coefficients in human CSF spaces, we adapt existing theoretical estimates^{15,17}. More specifically, we compute spatially-varying
94 dispersion enhancement fields R_c and R_r (Fig. 2G, I), associated with the cardiac and respiratory cycles respectively, via the
95 algorithm presented below. These fields then contribute to the diffusion coefficient in Ω_{CSF} in (19) as $D = (1 + R_c + R_r)D^{\text{Gad}}$.

- i) To account for viscous forces, we compute spatially-varying CSF pressure fields p_c^0, p_r^0 in Ω_{CSF} corresponding to the Stokes flow induced by the peak volumetric reduction of the CSF space in the respective cycle (Fig. 2F, H). More precisely, we numerically solve the incompressible Stokes equations (1) equipped with the following boundary conditions mimicking a dilation of the brain parenchyma with the spinal SAS as the only route for CSF efflux:

$$\mathbf{u} = 0 \text{ on } \Gamma_{\text{pia}}; \quad \mu \nabla \mathbf{u} \cdot \mathbf{n} - p \mathbf{n} = 0 \text{ on } \Gamma_{\text{SSAS}}; \quad \mathbf{u} = \frac{u_{\text{LV}}^{\text{in}} \cdot \mathbf{n}}{|\Gamma_{\text{LV}}|} \text{ on } \Gamma_{\text{LV}}; \quad \mathbf{u} = \frac{u_{\text{AM}}^{\text{in}} \cdot \mathbf{n}}{|\Gamma_{\text{skull}}|} \text{ on } \Gamma_{\text{AM}}. \quad (14)$$

96 In the cardiac cycle case, we set $u_{\text{AM}}^{\text{in}} = 6 \text{ ml/s}$ ^{20,21} and $u_{\text{LV}}^{\text{in}} = 0.31 \text{ ml/s}$ ²² to solve for p_c^0 . In the respiratory cycle case, we
97 set $u_{\text{AM}}^{\text{in}} = 1 \text{ ml/s}$ ²³ and $u_{\text{LV}}^{\text{in}} = 0.121 \text{ ml/s}$ ²⁴ to solve for p_r^0 .

- ii) We also estimate the Womersley numbers α_c, α_r associated with the cardiac and respiratory flow patterns, respectively, by the definition

$$\alpha_i^2 = \frac{h_{\text{SAS}}^2 \omega_i \rho}{\mu} \quad i \in \{c, r\}, \quad (15)$$

98 with CSF density $\rho = 10^3 \text{ kg/m}^3$, a mean CSF space width $h_{\text{SAS}} = 1.5 \text{ mm}$, and CSF viscosity μ given in Table. 1. For the
99 cardiac cycle, we consider an angular frequency $\omega_c = 2\pi$, while for the respiratory cycle, we set $\omega_r = 0.5\pi$. The resulting
100 (square) Womersley numbers are $\alpha_c^2 = 20.2$ for the cardiac cycle and $\alpha_r^2 = 5.05$ for the respiratory cycle.

- iii) To account for inertial forces in addition to the viscous forces, we use the Womersley numbers α_c, α_r to calculate upscaled pressure fields p_c^1, p_r^1 from p_c^0, p_r^0 as:

$$p_i^1(x) = \left(1 + \frac{\alpha_i^2}{8}\right) p_i^0(x) \quad \text{for } x \in \Omega_{\text{CSF}}, \quad i \in \{c, r\}. \quad (16)$$

101 Note that this scaling is based on theoretical considerations on the ratio of oscillatory flow to steady flow impedances in a
102 tube [25, Chap. 4.3.].

Parameter	Description	Value(s)	Ref.
Relative PVS size β	$\beta = \beta_i = R_2^i / R_1^i$	2	²⁷
Wave frequency f	Traveling wave frequency of vascular motion	0.1 – 1.0 Hz	²⁶
Wave length λ	Traveling wave length of vascular motion	0.02 – 2 mm	^{26,28}
Wave amplitude	Relative amplitude of inner wall motion	1 – 10%	²⁶
Cardiac frequency f_c	Frequency of human cardiac pulse wave	1.0 Hz	²⁹
Cardiac wave length λ_c	Wave length of human cardiac pulse wave	2.0m	
Cardiac amplitude ε_c	Wall displacement amplitude of cardiac pulse wave	1%	
Vasomotion frequency f_v	Frequency of slow vasomotion wave	0.1 Hz	²⁹
Vasomotion wave length λ_v	Wave length of vasomotion wave	0.02 m	^{26,28}
Vasomotion amplitude ε_v	Wall displacement amplitude of vasomotion wave	10%	^{26,28}

Table S3. Perivascular flow induced by vascular wall motion: overview of parameters.

- iv) Further, assuming unsteady dispersion, we follow Sharp et al.¹⁷ to estimate local enhancement factors S_c, S_r from the non-dimensionalized pressure gradients:

$$S_i(x) = \frac{1}{\alpha_i^3} \frac{1}{\omega_i \mu / h_{\text{SAS}}} |\nabla p_i^1(x)| \quad i \in \{c, r\}. \quad (17)$$

- v) Finally, we define the cardiac and respiratory dispersion enhancement factors R_c and R_r by smoothing S_c and S_r , respectively, to account for the non-local nature of dispersion. Specifically, for $i \in \{c, r\}$, we define $R_i : \Omega_{\text{CSF}} \rightarrow \mathbb{R}^+$ by solving a heuristic weighted Helmholtz problem over Ω_{CSF} with S_i as the right-hand side:

$$-10^{-4} \Delta R_i + R_i = S_i \quad \text{on } \Omega_{\text{CSF}} \quad \text{and} \quad \nabla R_i \cdot \mathbf{n} = 0, \quad \text{on } \partial\Omega_{\text{CSF}}. \quad (18)$$

103 Considering the uncertainty associated with the validity of simplifying assumptions, the resulting estimates of the cardiac and
104 respiratory dispersion factors R_c and R_r should be viewed as heuristic rather than absolute.

105 S1.5 Estimating net perivascular flow induced by peristaltic waves

106 We use the theoretical framework previously introduced by Gjerde et al.²⁶ to compute an analytic estimate of the time-averaged
107 (or *net*) flow rates $\langle Q'_i \rangle$ (mm³/s) induced by peristaltic pumping in a perivascular network $\mathbf{A} = \cup_i \mathbf{A}_i \mathbf{\Lambda} = \cup_i \mathbf{\Lambda}_i^i$. The motion of
108 the (inner) vascular wall is assumed to be described by a periodic traveling (peristaltic) wave of relative amplitude ε , wave
109 length λ (mm) and frequency f , acting normal to the wall and traveling in the antegrade direction (with the blood flow). By
110 definition, the wave number is $k = 2\pi/\lambda$ and the angular frequency is $\omega = 2\pi f$. Each PVS segment $\mathbf{A}_i \mathbf{\Lambda}_i^i$ has length L_i with
111 wave-relative length $\ell_i = kL_i$, baseline inner radius R_1^i , fixed outer radius R_2^i , and outer-to-inner ratio $\beta_i = R_2^i / R_1^i$. These
112 geometric parameters and the assumption of annular cylindrical PVS segments yield hydraulic resistances $\mathcal{R}_{o,i}$ and additional
113 characteristic parameters, see²⁶ for the complete definitions and schematics. Since the analytical estimate is derived under the
114 assumption that $kL_i \approx O(1)$ ²⁶ and has been verified against numerical simulations for kL_i of the order $10^{-1} - 10^2$ [26, Table I],
115 we consider it applicable for the wave lengths and vascular network data considered here in which kL_i range from 0.15 to 30
116 for the strong vasomotion and 0.0015 to 0.30 for the cardiac waves (Table S3).

117 This theoretical formalism²⁶ is defined relative to a network in the form of a directed, bifurcating tree with a single supply
118 node/root i_0 . To extend to a network of cerebral arteries with multiple supply nodes (such as the basilar and two internal carotid
119 arteries in the current data set³⁰), we separate the network Λ into edge-disjoint subnetworks $\Lambda^1, \Lambda^2, \Lambda^3$, one for each of the
120 supply nodes (Fig. 1A–B, Figure S1). Each node is assigned to the subnetwork associated with the nearest supply node, and
121 edges between nodes are preserved (Figure S1B). Next, we compute a minimal, bifurcating and directed tree representation
122 of each subnetwork: $\mathcal{T}^1, \mathcal{T}^2, \mathcal{T}^3$ (Figure S1C). Each tree $\mathcal{T}^j = \cup E_n^j$ consists of the subset of the nodes from Λ^j that have
123 degree 1 (are leaf or root nodes) or degree 3 (are true bifurcation points), and each path between nodes with degree $\neq 2$ in Λ^j is
124 represented in \mathcal{T}^j by an edge E^j with edge length L corresponding to the total length of the original path and edge radius R^j as
125 the average of the path radii.

126 For each subtree $\mathcal{T}^j = \cup_n E_n^j$, we compute the time-averaged downstream flow rate $\langle Q'_n \rangle$ induced by the vascular wall
127 motion for each edge n via [26, eq. (5), (34)] (Figure S1D). We next assign this flow rate $\langle Q'_n \rangle$ to each of the branches $\mathbf{A}_i \mathbf{\Lambda}_i^i$
128 $\mathbf{\Lambda}_i^i$ that form the path E_n^j , thus yielding $\langle Q'_i \rangle$ for each perivascular segment $\mathbf{A}_i \mathbf{\Lambda}_i^i$ while ensuring that mass is conserved
129 (Figure S1E). For the segment(s) ignored in the separation step (Figure S1B), we set a flow rate of zero. Finally, we define the

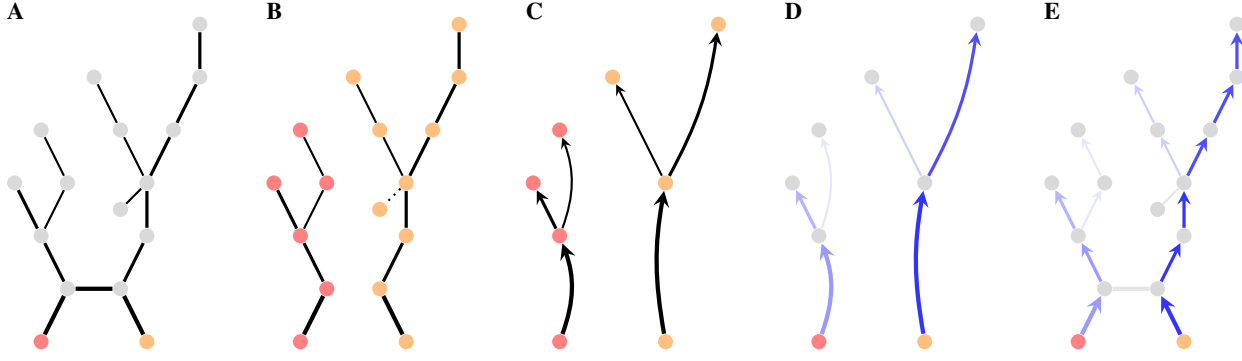


Figure S1. Estimating the perivascular flow induced by vascular wall motion. For a vascular network with vessels represented by edges of varying radii and length connected at nodes (A), and one or more supply nodes (here two, marked in red and orange), we compute one subnetwork for each supply node by proximity (B). Each subnetwork is reduced to a minimal, bifurcating and directed tree while preserving path lengths and averaging radii (C) which is then used to compute the net flow induced by the peristaltic wave in each branch of the minimal subnetworks (D). Finally, we distribute the computed flow onto the original segments (E).

mean longitudinal perivascular velocity induced by the peristaltic wave $\langle \hat{u}_t^x \rangle$ by dividing the flow rate $\langle Q_t' \rangle$ by the cross-section area $A_t = \pi(R_2^2 - R_1^2) = \pi(\beta_t^2 - 1)R_1^2$.

S1.6 Modeling and simulating solute transport and exchange in intracranial domains (3D) and perivascular networks (1D)

In this section, we describe the mathematical model (eq. (1)), the associated definitions, interface and boundary conditions in further detail. We refer to the main text for explicit parameter values while giving the general, abstract form here, and to the reference ^{1,2} for the derivation and analysis of this 3D-1D model. Recall that we model a concentration field $c = c(x, t)$ for $x \in \Omega$ and $t > 0$ defined in Ω_{PAR} and Ω_{CSF} separately. In each of these domains, c satisfies

$$\partial_t(\phi c) - \nabla \cdot (D \nabla(\phi c)) + \nabla \cdot (\mathbf{u} c) + \xi(\bar{c} - \hat{c})\delta_\Gamma = 0 \quad \text{in } \Omega_{\text{CSF}}, \Omega_{\text{PAR}}. \quad (19)$$

In (19), ϕ is the fluid volume fraction (also known as the porosity) defined in the parenchyma ($\phi \ll 1$ in Ω_{PAR}) and in the CSF spaces ($\phi = 1$ in Ω_{CSF}). In the parenchyma, ϕ represents the extracellular space volume fraction, and thus c here generally represents the intrinsic (in contrast to the superficial) concentration ³. Moreover, D is the effective diffusion coefficient of the relevant solute in the respective media which takes different values over the CSF spaces and the parenchyma, depending on tortuosity ³ and dispersive effects; and \mathbf{u} is a convective velocity field representing the flow of CSF in Ω_{CSF} and the flow of ISF in Ω_{PAR} . ξ models a transfer or exchange parameter between the 3D domain (Ω_{PAR} or Ω_{CSF}) and the perivascular networks Λ_a, Λ_v . To summarize,

$$\phi = \begin{cases} 1 & \text{in } \Omega_{\text{CSF}} \\ \phi_{\text{PAR}} & \text{in } \Omega_{\text{PAR}} \end{cases}, \quad D = \begin{cases} D_{\text{CSF}} & \text{in } \Omega_{\text{CSF}} \\ D_{\text{PAR}} & \text{in } \Omega_{\text{PAR}} \end{cases}, \quad \mathbf{u} = \begin{cases} \mathbf{u}_{\text{CSF}} & \text{in } \Omega_{\text{CSF}} \\ \mathbf{u}_{\text{PAR}} & \text{in } \Omega_{\text{PAR}} \end{cases}, \quad \xi = \begin{cases} \xi_{\text{CSF}} & \text{if } |\Omega^i \cap \Omega_{\text{CSF}}| \neq 0 \\ \xi_{\text{EF}} & \text{if } |\Omega^i \cap \Omega_{\text{PAR}}| \neq 0 \end{cases}.$$

In the above, ξ is defined segment-wise: for each centerline Λ^i with surrounding PVS Ω^i , $|\Omega^i \cap \Omega_{\text{PAR}}|$ (resp. $|\Omega^i \cap \Omega_{\text{CSF}}|$) is nonzero whenever Ω^i intersects Ω_{PAR} (resp. Ω_{CSF}). If the surrounding PVS intersects both, then we set $\xi = \xi_{\text{EF}}$ if Ω^i mainly (80 percent) intersects Ω_{PAR} , in which case the interaction with Ω_{CSF} is ignored; otherwise, we set $\xi = \xi_{\text{CSF}}$.

Also in (19), the notation \bar{c} denotes a lateral average of the concentration over the outer perivascular surfaces, defined for each centerline Λ^i and each point $s \in \Lambda^i$ by

$$\bar{c}(s) = \frac{1}{P(s)} \int_{\partial\Theta^i(s)} c$$

where $\partial\Theta^i(s)$ is the outer boundary of the cross-section $\Theta(s)$ of the PVS Ω^i at s and $P(s)$ is the perimeter of $\Theta(s)$. Moreover, for both the periarterial and perivenous networks (Λ_a, Λ_v with outer PVS boundaries Γ_a, Γ_v), the term δ_Γ is concentrated on

the outer lateral surfaces of the PVSs, and defined in terms of its action on any sufficiently smooth function $v : \Omega \rightarrow \mathbb{R}$ such that

$$\langle \xi(\bar{c} - \hat{c})\delta_\Gamma, v \rangle = \int_\Lambda P\xi(\bar{c} - \hat{c})\bar{v},$$

under the assumption that ξ is constant on each $\partial\Theta_2^i$.

On the interface between the brain and the CSF spaces $\Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}$, we prescribe the following interface conditions, which represent a semi-permeable interface, writing $c|_{\Omega_{\text{PAR}}} = c_{\text{PAR}}$ and $c|_{\Omega_{\text{CSF}}} = c_{\text{CSF}}$:

$$(-D\nabla(\phi c) + \mathbf{u}c)|_{\Omega_{\text{PAR}}} \cdot \mathbf{n} = -(-D\nabla(\phi c) + \mathbf{u}c)|_{\Omega_{\text{CSF}}} \cdot \mathbf{n} \quad \text{on } \Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}, \quad (20a)$$

$$(-D\nabla(\phi c) + \mathbf{u}c)|_{\Omega_{\text{PAR}}} \cdot \mathbf{n} = \beta_{\text{pia}}(c_{\text{PAR}} - c_{\text{CSF}}) \quad \text{on } \Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}, \quad (20b)$$

where $\mathbf{n} = \mathbf{n}_{\text{PAR}}$ is the normal vector field defined over the interface, outward-pointing when viewed from Ω_{PAR} , and $\beta_{\text{pia}} \geq 0$ is a permeability constant.

We supplement (19) and (20) with the following boundary conditions representing a given molecular influx at Γ_{SSAS} , molecular efflux at a constant update rate β_{exit} at $\Gamma_{\text{AM-U}}$, and no influx or efflux elsewhere from the CSF spaces:

$$(D\nabla(\phi c) - \mathbf{u}c) \cdot \mathbf{n} = g_{\text{influx}} \quad \text{on } \Gamma_{\text{SSAS}}, \quad (21a)$$

$$(-D\nabla(\phi c) + \mathbf{u}c) \cdot \mathbf{n} = \beta_{\text{exit}}c \quad \text{on } \Gamma_{\text{AM-U}}, \quad (21b)$$

$$(-D\nabla(\phi c) + \mathbf{u}c) \cdot \mathbf{n} = 0 \quad \text{on } \Gamma_{\text{AM-L}} \cup \Gamma_{\text{SC}}. \quad (21c)$$

where again \mathbf{n} denotes the outward-pointing boundary normal.

The concentration $\hat{c} = \hat{c}(s, t)$ in the periarterial and perivenous networks ($s \in \Lambda_a, s \in \Lambda_v$), entering in (19), represents the concentration in the perivascular space averaged over each perivascular cross-section and is governed by

$$\partial_t(A\hat{c}) - \partial_s(\hat{D}A\partial_s\hat{c}) + \partial_s(A\hat{u}\hat{c}) + \xi P(\hat{c} - \bar{c}) = 0 \quad \text{in } \Lambda_a, \Lambda_v, \quad (22)$$

where in Λ_a, Λ_v refers to in each Λ^i in each of these networks. In (22), $A = A(s)$ is defined as the PVS cross-sectional area; i.e., for each $s \in \Lambda^i$ with associated PVS Ω^i , the area of the cross-section $\Theta^i(s)$. Also, \hat{D} is the effective diffusion coefficient, and \hat{u} is a convective velocity representing an (average) CSF flow velocity in the axial direction of the perivascular spaces.

To complete (22), we prescribe bifurcation conditions at internal nodes of the perivascular networks Λ_a, Λ_v and boundary conditions at the end nodes. To this end, define the set of internal nodes $\mathcal{B} \subset \mathcal{V}$ as the set of nodes that are connected to two or more edges and the set of end nodes as $\mathcal{N} \subset \mathcal{V}$, write $\hat{c}^i = \hat{c}|_{\Lambda^i}$, and for $y \in \mathcal{B}$ let $\mathcal{E}(y)$ denote the set of (two or three) edges in $\{\Lambda^i\}$ sharing the node y . To impose continuity of the concentrations, we set that the concentrations when viewed from each edge must match at nodes:

$$\hat{c}^i(y) = \hat{c}^j(y) \quad \forall \Lambda^i, \Lambda^j \in \mathcal{E}(y) \quad \forall y \in \mathcal{B}. \quad (23)$$

Moreover, to ensure mass conservation, we set that the flux going in and out at nodes should add to zero, or more precisely, that for each $y \in \mathcal{B}$:

$$\sum_{\Lambda^i \in \mathcal{E}(y)} (\hat{D}^i A^i \partial_s \hat{c}^i(y) - A^i \hat{u}^i(y) \hat{c}^i(y)) n^i(y) = 0. \quad (24)$$

Here the normal n^i is as defined in (9).

Finally, we impose a homogeneous Neumann condition at all network end nodes to augment (22):

$$\hat{D}A\partial_s(\phi\hat{c}) - A\hat{u}\hat{c} = 0 \quad \text{on } \mathcal{N}. \quad (25)$$

This no-flux condition states that the network end nodes represent barriers for molecular efflux into or out of the perivascular network, and thus that all solute exchange between the PVSs and their surroundings takes place via the lateral outer PVS surface and is regulated by the exchange parameter ξ cf. (19) and (22). Larger particles have been observed to accumulate within the PVS as the surface arteries penetrate into the brain parenchyma^{4,5}, and (25) is appropriate to represent such behavior. However, to represent a continuously extending PVSs also along penetrating vessels, this condition should be revisited.

S1.6.1 Finite element solution of coupled 3D-1D solute transport equations

We consider the system of coupled 3D-1D solute transport equations given by (19) and (22) with the interface conditions (20), the bifurcation conditions (23) and (24), and the boundary conditions (21) and (25). We discretize these equations using an implicit finite difference scheme in time, a discontinuous Galerkin (DG) finite element method with upwinding in space for the 3D domain to accurately capture sharp boundary layers, and a continuous Galerkin method for the 1D networks. We remark that the transport in the CSF spaces is highly convection dominated, with an average Péclet number of 402 and maximum of 9542 (assuming a characteristic length of 10 cm, and accounting for the increased diffusivity due to dispersion).

We first consider the discretization of (19) and introduce the discrete space

$$V_h = \{c \in L^2(\Omega) : c|_E \in P^1(E), E \in \mathcal{T}\}, \quad (26)$$

where $L^2(\Omega)$ is the space of square-integrable functions defined over Ω and $P^1(E)$ denotes the space of polynomials of total degree ≤ 1 defined over the tetrahedra E . To discretize the diffusion term in (19), we use a symmetric weighted interior penalty DG formulation, referring to ¹¹ and [12, Section 4.5.2.3] for details on this method. Recall that ϕ is constant in each domain Ω_{PAR} and Ω_{CSF} , and thus in particular that $\nabla(\phi c) = \phi \nabla c$ on each $E \in \mathcal{T}$. Define for $c, v \in V_h^k$:

$$a_h(c, v) = \sum_{E \in \mathcal{T}} \int_E D \phi \nabla c \cdot \nabla v - \sum_{F \in \mathcal{F}_i} \int_F \left(\{D \phi \nabla c\}_w \cdot \mathbf{n}_F [v] + \{D \phi \nabla v\}_w \cdot \mathbf{n}_F [c] \right) + \sum_{F \in \mathcal{F}_i} \eta \frac{\gamma_{D,F}}{h_F} \int_F [c][v]. \quad (27)$$

Here, for each facet $F \in \mathcal{F}_i$ shared between cells E^1 and E^2 , we associate a facet normal vector \mathbf{n}_F pointing from E^1 to E^2 . The facet diameter is denoted by h_F , the jump $[\cdot]$ is given by $[v] = v|_{E^1} - v|_{E^2}$, and the unweighted average $\{\cdot\}$ and weighed average $\{\cdot\}_w$ are defined as:

$$\{v\} = \frac{1}{2} v|_{E^1} + \frac{1}{2} v|_{E^2}, \quad \{v\}_w = \frac{\kappa_2}{\kappa_1 + \kappa_2} v|_{E^1} + \frac{\kappa_1}{\kappa_1 + \kappa_2} v|_{E^2} \quad \text{where} \quad \kappa_i = (D \phi)|_{E^i}. \quad (28)$$

In (27) the parameter $\gamma_{D,F}$ is the harmonic mean of the porosity-weighted diffusion coefficient given by

$$\gamma_{D,F} = \frac{2\kappa_1\kappa_2}{\kappa_1 + \kappa_2}, \quad (29)$$

and η is a user-specified penalty parameter (we set $\eta = 1000$). To discretize the convection term in (19), we use upwinding, see [12, Section 2.3.1] and the references therein. For $c, v \in V_h^k$, define

$$a_h^{\text{up}}(c, v) = - \sum_{E \in \mathcal{T}} \int_E c \mathbf{u} \cdot \nabla v + \sum_{F \in \mathcal{F}_i} \int_F \{ \mathbf{u} c \} \cdot \mathbf{n}_F [v] + \sum_{F \in \mathcal{F}_i} \int_F \frac{|\mathbf{u} \cdot \mathbf{n}_F|}{2} [c][v]. \quad (30)$$

Our discrete formulation for (19) with the interface conditions (20) and boundary conditions (21) and given initial conditions c_h^0 then reads: for $n = 1, 2, \dots$, with $t^n - t^{n-1} = \tau$, find $c_h^n \in V_h$ such that for all $v \in V_h$:

$$\int_{\Omega} \frac{1}{\tau} (\phi c_h^n - \phi c_h^{n-1}) v + a_h(c_h^n, v) + a_h^{\text{up}}(c_h^n, v) + \int_{\Gamma_{\text{pia}} \cup \Gamma_{\text{LV}}} \beta_{\text{pia}} [c_h^n] [v] + \int_{\Gamma_{\text{AM-U}}} \beta_{\text{exit}} c_h^n v + \int_{\Lambda} \xi P(\bar{c}_h^n - \hat{c}_h^n) \bar{v} = \int_{\Gamma_{\text{SSAS}}} g_{\text{influx}} v. \quad (31)$$

To discretize (22) with the bifurcation conditions (23) and (24), and the boundary conditions (25), we use the space of continuous piecewise linear polynomials defined over Λ :

$$\hat{V}_h = \{v \in C^0(\Lambda), v|_{\Lambda^i} \in P^1(\Lambda^i)\}, \quad (32)$$

where $P^1(\Lambda^i)$ is the space of linear polynomials on each Λ^i . The discrete formulation then reads: for $n = 1, 2, \dots$, find $\hat{c}_h^n \in \hat{V}_h$ such that for all $\hat{v} \in \hat{V}_h^k$:

$$\int_{\Lambda} \frac{1}{\tau} (A \hat{c}_h^n - A \hat{c}_h^{n-1}) \hat{v} + \int_{\Lambda} \hat{D} A \partial_s \hat{c}_h^n \partial_s \hat{v} - \int_{\Lambda} A \hat{u} \hat{c}_h^n \partial_s \hat{v} + \int_{\Lambda} \xi P(\hat{c}_h^n - \bar{c}_h^n) \hat{v} + a_h^{\text{stab}}(\hat{u}; \hat{c}, \hat{v}) = 0. \quad (33)$$

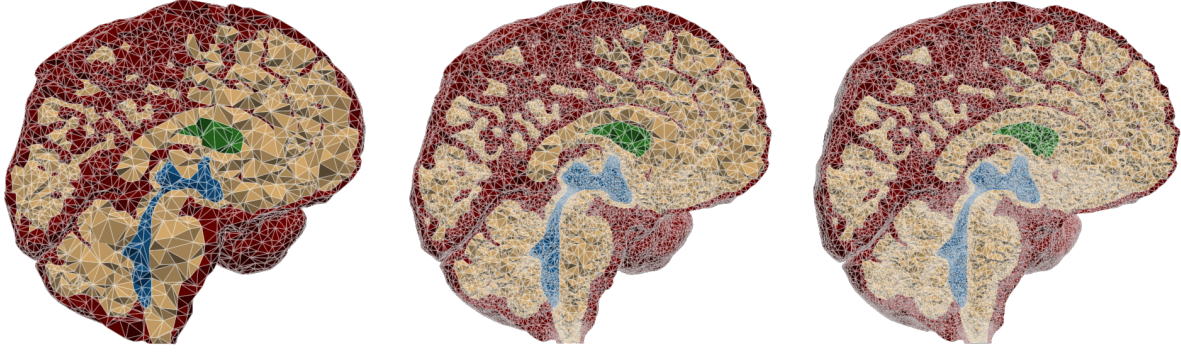


Figure S2. Illustration of the three different meshes; from left to right: low resolution, standard resolution, high resolution.

In the above, if \hat{u} is non-zero on Λ^i , then the artificial diffusion a_h^{stab} stabilization term is nonzero and is given below, for more details see for [13, Section 12.6].

$$a_h^{\text{stab}}(\hat{u}; \hat{c}, \hat{v}) = \frac{1}{\|\hat{u}\|_{L^2(\Lambda^i)}} h_{\Lambda^i} \int_{\Lambda^i} A(\hat{u} \partial_s \hat{c}_h)(\hat{u} \partial_s \hat{v}), \quad (34)$$

where h_{Λ^i} is the mesh-size of Λ^i . Note that the condition (24) is enforced weakly in the above formulation.

Summary. The discretization for (19) and (22) complemented with boundary conditions ((21) and (25)), interface and bifurcation conditions ((20), (8), and (23)), and initial conditions $c_h^0 = 0$ and $\hat{c}_h^0 = 0$ is the following. For $n = 1, 2, \dots$, find $c_h^n \in V_h$ and $\hat{c}_h^n \in \hat{V}_h$ such that the coupled equations (31) and (33) hold for all $v \in V_h$ and for all $\hat{v} \in \hat{V}_h$.

S1.7 Numerical verification

We assess the numerical accuracy and convergence of our simulation results by performing a series of experiments with different spatial and temporal resolutions. Specifically, we generate a sequence of three meshes (Figure S2) with an increasing number of computational mesh vertices and cells, solve all relevant simulation steps (CSF flow and intracranial transport computations) for the baseline model on each mesh, and compare the results across meshes with respect to a set of key quantities of interest. The mesh refinement employed here is localized near expected sharp concentration gradients. This allows us to better capture dynamics and reduce undershoots, see Figure S3. Similarly, we investigate the effect of the time step size by solving the intracranial transport model on the standard resolution mesh with different time steps: 1, 2, and 4 minutes.

Considering the mean tracer concentrations in the CSF, parenchyma and arterial and venous PVS domain over the first 24 h after injection, we observe negligible changes with both mesh and time refinement (Figure S3 and Figure S5). As an additional verification step, we compute the mean and maximum dispersion enhancement factor, the maximum CSF pressure and velocity in both the cardiac-driven and CSF production-induced flow fields, and mean concentrations at 3, 6, 12 and 24 h for all mesh resolutions and time steps (Figure S4). While the maximum dispersion factor increases by about 60 % from the low resolution to the standard mesh, it stabilizes with the next refinement step. All other quantities change with less than 10 % with mesh refinement, and less than 1 % with time refinement. We thus conclude that the standard resolution mesh and a time step of 2 min offer sufficient accuracy for our simulations, and remark that all reported results are obtained with the standard resolution mesh.

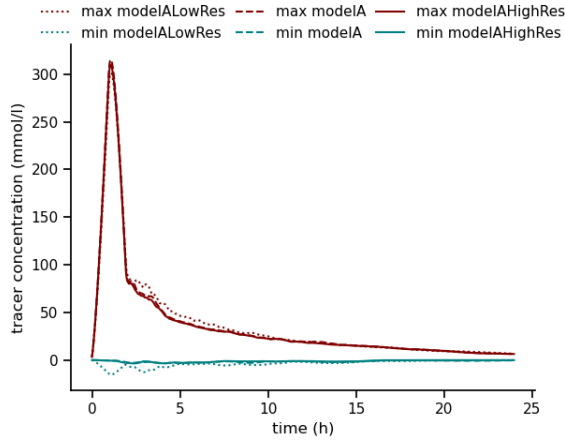
Finally, to check for numerical mass conservation, we perform an additional simulation not allowing for tracer efflux across the outer boundary, and confirm that the total amount of tracer is preserved over time after the initial influx phase (Figure S6).

S2 Supplementary discussion

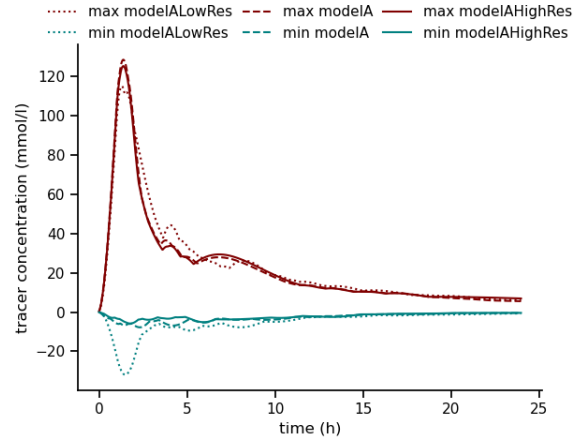
S2.1 Extended model-validation comparison with literature

In addition to the comparison of our in-silico predictions of tracer enrichment and clearance against glymphatic MRI, we here compare auxiliary model quantities against the literature as additional model validation.

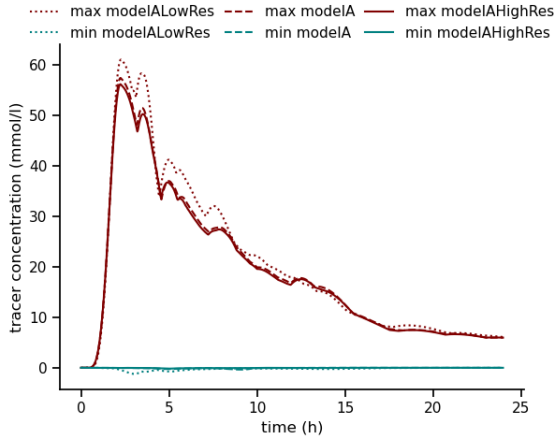
CSF flow and pressures in the SAS and ventricular system The dynamics of human CSF flow and pressure are better quantified, by way of clinical imaging, in-vitro studies, and computational modelling, in other areas of the ventricular system^{20,22,31–35}. Linninger et al³¹ model CSF flow and pressure dynamics induced by CSF production and cardiac pulsatility under normal and hydrocephalic conditions, and report of very good agreement with Cine (phase-contrast) MRI measurements.



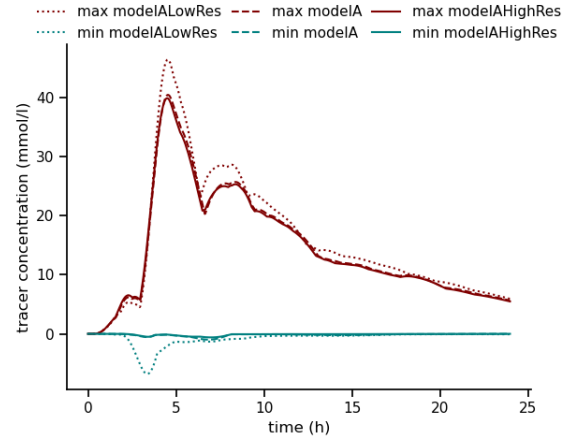
(a) Minimum and maximum tracer concentration in the CSF under mesh refinement



(b) Minimum and maximum tracer concentration in the parenchyma under mesh refinement



(c) Minimum and maximum tracer concentration in PVs around arteries under mesh refinement



(d) Minimum and maximum tracer concentration in PVs around veins under mesh refinement

Figure S3. Minimum and maximum tracer concentrations over the first 24 h after injection on the CSF and parenchyma (a), and the arterial and venous PVS (b) computed on the low resolution (LowRes), standard and high resolution (HighRes) meshes with a timestep of 2 min for the baseline model (Model A).

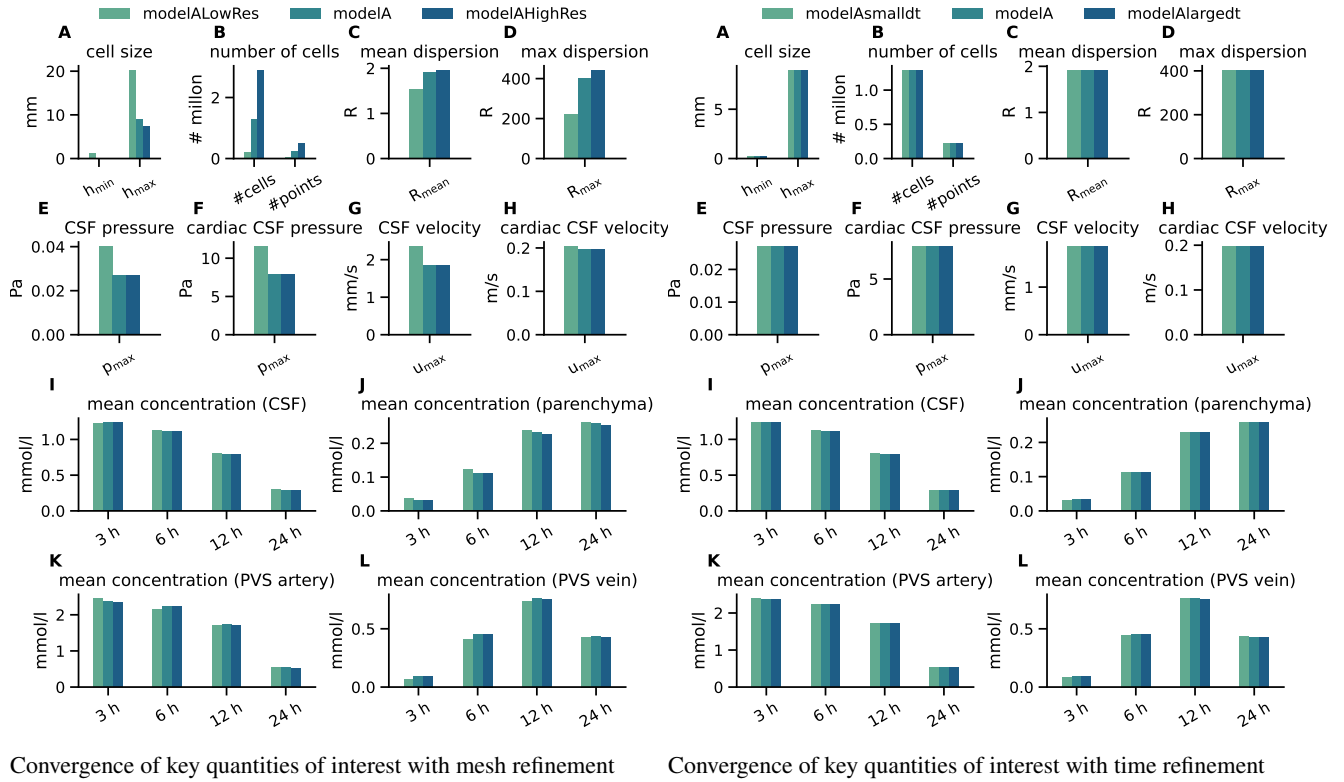


Figure S4. For both left and right panels: A: Minimal (h_{min}) and maximal (h_{max}) mesh cell sizes (computed as cell circumradius $\times 2$); B: number of mesh vertices and tetrahedral cells in each mesh; C: mean cardiac dispersion enhancement factor R ; D: maximum cardiac dispersion enhancement factor R ; E: maximum pressure in steady CSF production flow; F: maximum pressure in cardiac-driven CSF flow; G: maximum CSF velocity in steady CSF production flow; H: maximum CSF velocity in cardiac-driven CSF flow; I–L: mean tracer concentration in the CSF, parenchyma, arterial PVS and venous PVS after 3, 6, 12 and 24 hours.

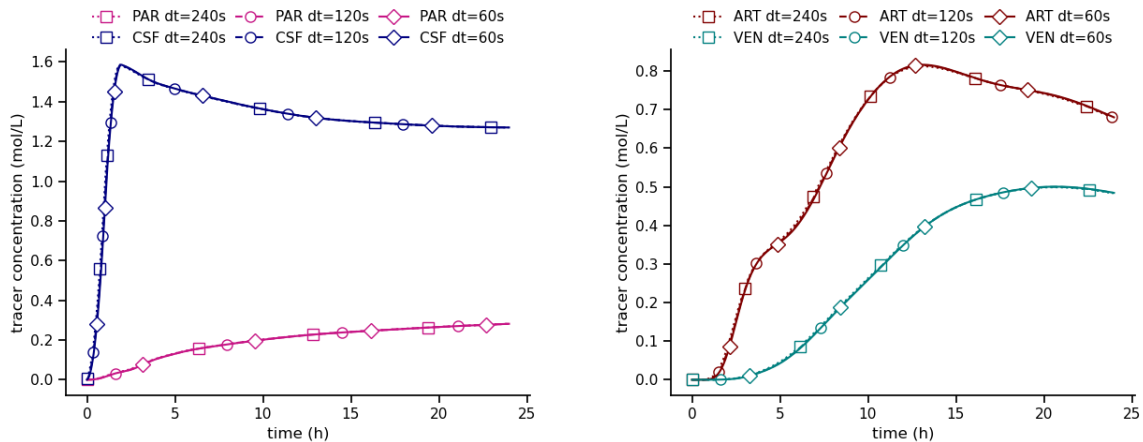


Figure S5. Mean tracer concentrations after up to 24 h in the CSF and parenchyma (a), and the arterial and venous PVS (b) computed on the standard resolution mesh for timesteps of 1, 2, and 4 minutes (dt of 60, 120, or 240 seconds)

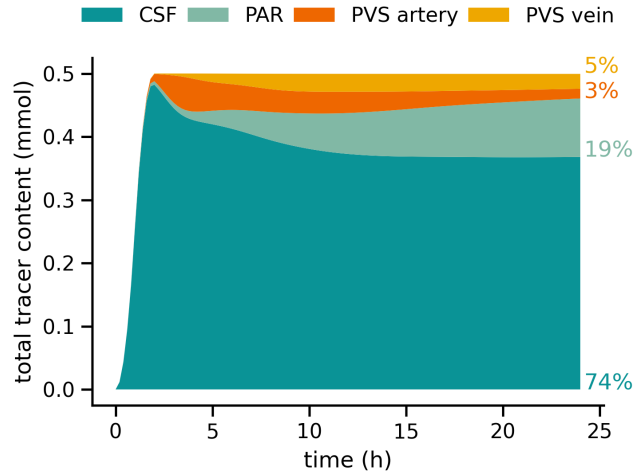


Figure S6. Total tracer content in the CSF, parenchyma, and arterial and venous PVS for a variant of the baseline model without tracer outflow. The total amount of tracer is constant after the initial influx phase demonstrating that the numerical scheme conserves mass globally.

Our estimates of the maximum intracranial pressure difference, 10 Pa from the cardiac contribution and 26 mPa from CSF production, is in perfect agreement with their maximum transmantle pressure difference of ~ 10 Pa, and also in very good agreement with mean pressure differences of 11.5 Pa measured clinically between sensors placed subdurally and in the lateral ventricle²². Liu et al³⁵ report of cardiac and respiratory pressure differences across the aqueduct of 12.1 ± 5.7 Pa and 9.5 ± 7.2 Pa, respectively; thus our baseline estimate of the respiratory contribution 1.4 Pa may be an underestimation. On the other hand, our cardiac- and respiratory-driven CSF flow estimates peak at 19.8 cm/s and 4.8 cm/s in the caudal direction, respectively, which are higher than phase-contrast MRI measurements of cardiac and respiratory CSF flow components^{36,37}. Some variation in CSF flow velocities is expected considering that the values from MRI represent averages³⁷ and that the geometry of the CSF spaces strongly affects peak velocities^{20,22}. Hornkjøl et al³³ model the flow dynamics induced by CSF production in the choroid plexus and report a peak CSF velocity of 8.9 mm/s in the aqueduct, which is $4.8 \times$ higher than our values of 1.85 mm/s. Given that we use the same production rate, this deviation again illustrates the impact of potential differences in the (aqueduct) geometry on local velocities.

Dispersion in the SAS, ventricular system and PVS This pulsatile flow of CSF in the SAS, ventricular system and PVSs leads to an increase in effective solute diffusivity^{16–18,38,39} via a process known as Taylor dispersion^{14,15}. Previous estimates of the magnitude of this effect in the CSF spaces vary significantly: from an enhancement factor of 0.05–1 in periarterial spaces surrounding penetrating arteries^{16,19}, to 5–100 in the spinal subarachnoid space^{17,38,39}, and up to more than 10000 in surface periarterial spaces^{17,18}. Additionally, high-resolution MRI measurements by Hirschler et al.⁴⁰ revealed that CSF mobility in regions with high pulsatility is approximately tenfold greater than the self-diffusion of water. The large variability can (at least partly) be attributed to methodological differences; e.g. different assumptions on the medium, domain width, pressure differences and/or fluid velocities, the diversity of CSF flow characteristics, as well as a high likelihood of spatial variations. Hornkjøl et al³³ consider model variations with constant dispersion factors from 1 up to 1000, and indicate that a value of 10 gives the better agreement with the clinically observed enrichment. Our spatially-varying estimates of the dispersion enhancement factors R_c, R_r (with $D = (1 + R_c + R_r)D^{\text{Gad}}$) range from 0 to 200 for the cardiac contribution R_c and 0 to 320 for the respiratory contribution R_r ; and is thus compatible within the previously reported spectrum.

Investigating the link between cardiac pulsatility and the resulting diffusion enhancement factor, we compute for R different levels of cardiac pulsatility. We reduce the inflow boundary conditions of 6 ml/s (across the SAS outer surface) and 0.31 ml/s (across the lateral ventricle surface) by 25 %, 50 %, 75 % and 100 % to model lower cardiac pulsatility, revealing that R scales quadratically with the reduction of inflow (Figure S7). This behaviour directly reflects the nature of our model - the Stokes flow is linear in its boundary conditions, and the diffusion enhancement factor quadratic in the predicted pressure gradient - and simultaneously underscores the substantial role of pulsatility in shaping intracranial transport.

Shapes, sizes and structures of the PVS The shapes, sizes and structures of the PVSs likely vary between species (e.g. mice vs. humans), between spatial compartments (e.g. surface vs. parenchymal), between vessel types (arteries vs. arterioles vs. veins),

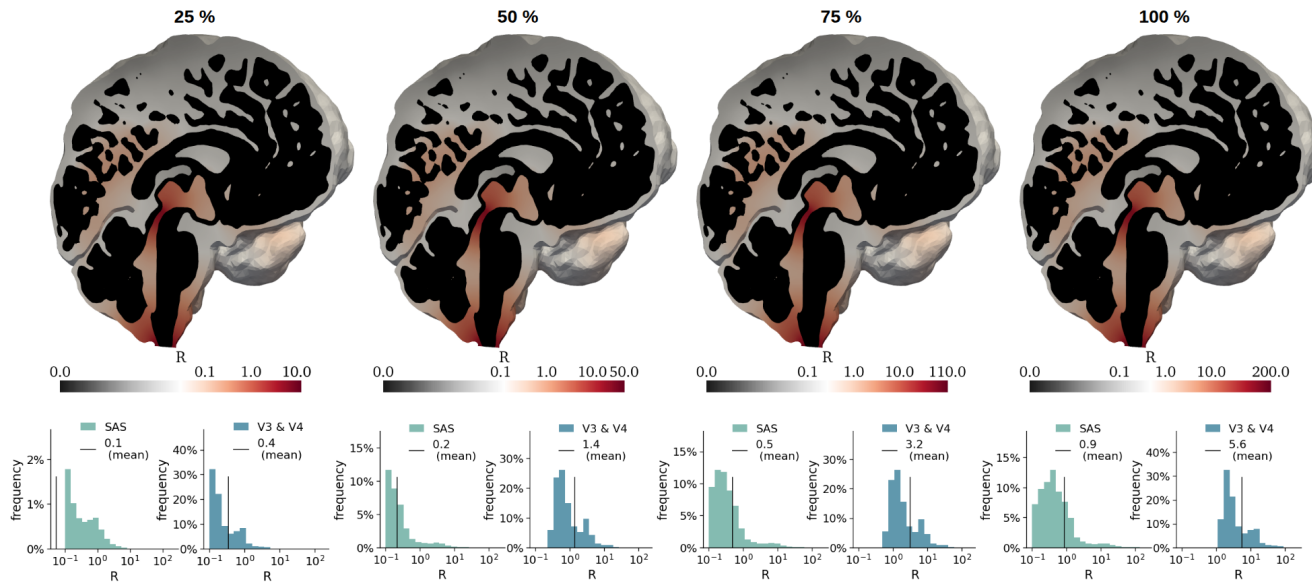


Figure S7. Comparison of cardiac-driven diffusion enhancement factors for different levels of cardiac pulsatility. From left to right: The diffusion enhancement factor R_c for 25%, 50%, 75% and 100% of the inflow boundary conditions of 6 ml/s and 0.31 ml/s across the SAS outer surface and the lateral ventricle surface, respectively.

and in pathologies^{4,5,27,41–47}. In terms of shape, the PVSs are commonly represented as annular (elliptic) cylinders, though it is well recognized that this represents an idealization^{4,45–49}. In terms of sizes, Raicevic et al⁴⁶ note that the variation in PVS area is larger between PVS segments than along a single PVS segment and that the PVS area increases with lumen area. In mice, reports of the ratio between PVS and lumen area range from ≈ 0.35 – 0.43 ⁴⁵ up to ≈ 1.12 – 1.4 ^{4,46}. In humans, the PVS may be as wide as the associated surface artery and up to $4\times$ wider in iNPH subjects²⁷, which would correspond to substantially larger PVS area ratios (3 or higher). To reflect the human scale, we here represent each PVS segment as an annular cylinder with inner radius R_1 and outer radius R_2 of width and area proportional to that of the corresponding blood vessel ($R_2 = 2R_1$ at baseline, $R_2 = 3R_1$ for enlarged PVS). The hydraulic resistance of annular cross-sections is $1 - 6\times$ ⁴⁸ larger than more elongated cross-sections and thus our estimates of the pressure-induced PVS velocities are conservative.

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