

Multi-compartmental model of glymphatic clearance of solutes in brain tissue

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Abstract

The ~~Glymphatic~~glymphatic system is the subject of numerous pieces of research in ~~Biology. Mathematical modeling~~biology. Mathematical modelling plays a considerable role in this field since it can indicate the possible physical effects ~~in~~of this system and validate the biologists' hypotheses. The available mathematical models that describe the system at the scale of the brain (*i.e.* the macroscopic scale) are often solely based on the diffusion equation and do not consider the fine structures formed by the perivascular spaces. We therefore propose a mathematical model representing the time and space evolution of a mixture flowing through multiple compartments of the brain. We adopt a macroscopic point of view in which the compartments are all present at any point in space. The equations system is composed of two coupled equations for each compartment: One equation for the pressure of a fluid and one for the mass concentration of a ~~molecule~~solute. The fluid and solute can move from one compartment to another according to certain membrane conditions ~~modeled~~modelled by transfer functions. We propose to apply this new ~~modeling~~modelling framework to the clearance of ¹⁴C-inulin from the rat brain.

1 Introduction

The proposed glymphatic system [46] explains ~~the~~ clearance of metabolic waste from the brain and has been the subject of many pieces of research in the past decade [43, 2, 48][46, 43, 2, 48]. The glymphatic theory suggests that clearance of metabolic solutes in the brain is facilitated by specific pathways for exchange between interstitial fluid (ISF) and cerebrospinal fluid (CSF). This exchange occurs via perivascular spaces (PVSs), ~~that are small fluid-filled~~small fluid-filled spaces surrounding blood vessels. According to the glymphatic theory, CSF enters the parenchyma via periarterial spaces and exits it via perivenous spaces. Furthermore, Iliff *et al.* [46] suggested that a bulk flow of fluid occurs in the interstitial space between periarterial and perivenous spaces draining metabolic waste out of the brain. Understanding the glymphatic system is critically important since its impairment may be linked to neurodegenerative diseases such as Alzheimer's ~~disease~~disease [88].

Even after a decade of research to verify this theory, many questions remain to be answered: *i)* Does the circulation of CSF as described by Iliff *et al.* [46] (inflow around arteries and outflow around veins) ~~really~~ occur? *ii)* What are the mechanisms explaining the movement of CSF in the perivascular spaces? *iii)* Does convection in the interstitial space occur, and is this flow sufficient to dominate transport?

In vivo studies using two-photon microscopy have imaged flow along periarterial spaces at the pial surface in the same direction as blood [14, 66], suggesting these spaces act as an entry to

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Figure 1: Illustrative representation of the three test cases. Red arrows indicate the movement of fluids through the compartments and blue arrows the diffusive movement of ^{14}C -inulin. Double arrows indicate that the movement could be directed in both directions and is, a priori, not known. With exception of the blood compartments, the arrows pointing to the outside of any compartment denotes a connection of this compartment with the subarachnoid space. *AEF* denotes the *astrocyte endfeet barrier* and *BBB* the *blood-brain barrier*.

the brain. However, the direction and magnitude of flow in penetrating PVS is still debated [9]. Furthermore, the question of the existence of a bulk flow of fluid within the extracellular space (ECS) as proposed by Iliff *et al.* [46] remains open. Indeed, some pieces of research indicate that solute transport in the ECS is dominated by diffusion [6, 43, 96], while others claim that diffusion alone can not explain the transport of tracer within the brain [104, 87][104, 87, 100]. In a recent study, Ray *et al.* [86] concluded that the transport of large molecules is dominated by convection, given the expected ECS flow rates reported in the literature. Convection-diffusion equations have been widely used to study transport within the brain [86, 104, 43, 73, 98, 87, 21]. These works helped to gain some insights into the relevant mechanisms that may play a role for in the clearance of interstitial solutes. However, in these works, the fluid velocities and concentrations are averaged between ECS and PVS (and all other routes of transport) to capture the overall spread of solutes. For a review of current fluid models available for mathematical and computational representations of the glymphatic system, we refer the reader to [52].

In contrast, multiple-compartment-coupled discrete-continuous models that can distinguish between different compartments represent different structures such as blood vessels and tissue have been used to study for example, for example, drug transport to the lung [33] or clot fragmentation [30], the brain [80] and tissue in general [94] with great detail. However, these models require detailed information on vessel structure and require too many degrees of freedom to study the brain at the macroscale.

To circumvent these limitations, homogenized models have been successfully applied to represent infiltration in porous media [45]. Such framework has been successfully applied to represent the transport of solute and fluid in the ECS and vascular network of vascularized tumors [93, 95, 78]. In full-scale full-scale patient-specific geometries, multiple-network poroelastic theory (MPET) have has been used to study exchange between multiple fluid compartments contained within the (elastic) brain tissue [15, 16, 7, 103, 105, 40, 39]. However, the MPET equations have not yet been investigated in terms of the transport of tracers or solutes in the context of the glymphatic system.

In this paper, we therefore develop a homogenized model to describe the glymphatic system and the blood flow at the scale of the rat brain (Figure Fig 1). To validate the relevancy of our modelling framework, we study the clearance of the molecule ^{14}C -inulin from the rat brain. ^{14}C -inulin is known not to cross the blood-brain-barrier (BBB) and is therefore well suited for investigating the mechanisms behind the clearance of large proteins from the brain tissue. Consequently, it has been used in experimental studies of the glymphatic system (e.g. [109, 38]), which provide reference values for the expected clearance rates of our model. In particular, the presented multi-compartment model represents a movement of CSF through different structures including the subarachnoid space (SAS), including the PVSs, the ECS and the blood vascular tree. This modeling vasculature, while the subarachnoid space (SAS) is included via boundary conditions. This modelling of the fluid movement is coupled to a diffusion-convection equations for each compartment to represent the clearance of ^{14}C -inulin from the brain. Our model suggests that without blood filtration, transport is explained mainly by diffusion within the brain. However, when ISF is allowed to filtrate across the vascular wall, PVS flow was reversed is reversed, and clearance from the ECS is substantially increased.

2 Methods

2.1 Mathematical models

Notations We denote by $\Omega \subset \mathbb{R}^3$ the spatial domain, *i.e.* the rat brain. We assume that the boundary $\partial\Omega$ of this domain is sufficiently smooth. Therefore, we denote by $\mathbf{x} \in \Omega$ any point of this domain such that the coordinates are given by $\mathbf{x} = (x_1, x_2, x_3)$. ~~We emphasize that, in the rest of this article, Bold symbols will be used to denote vectors, we use bold symbols.~~ Since we model the time evolution of the glymphatic system, our time-space domain is denoted by $\Omega_T = \Omega \times [0, T]$, ~~with for some finite $T > 0$ a finite time.~~ We test two ~~different~~ mathematical models: ~~First, a~~ pure diffusion model in a single compartment and ~~then~~ a multi-compartment model, which includes both diffusive and convective ~~transports. We use the following notation convention: when transport. When~~ an unknown or a parameter is indicated with a subscript, it denotes its compartment. The subscripts $a, c,$ and v ~~are used to~~ denote the arterial, capillary and venous blood networks, respectively. Similarly, the subscripts pa, pc, pv ~~are used to~~ denote the periarterial, pericapillary and perivenous fluid networks. The subscript e indicates the ECS.

The diffusion equation Denoting by $c_e = c_e(t, \mathbf{x})$ the solute concentration in ISF, the diffusion equation reads

$$\frac{\partial c_e}{\partial t} = D_e^* \Delta c_e, \quad \forall \mathbf{x} \in \Omega, \quad t \in (0, T]. \quad (1)$$

Here, D_e^* is the effective diffusion coefficient of ~~the molecule~~ ^{14}C -inulin in the ECS ~~—and~~ $\Delta = \nabla \cdot \nabla$ is the Laplace operator *i.e.* $\Delta f = \frac{\partial^2 f}{\partial x_1^2} + \frac{\partial^2 f}{\partial x_2^2} + \frac{\partial^2 f}{\partial x_3^2}$ (for a general scalar function f).

The multi-compartment model To take into account the different structures in which the fluid flows, we consider the multiple compartments as depicted in the schematic illustrations given in Fig 1. We denote by J the set of compartments (J can thus be modified to describe all three test cases shown in Fig 1), and we denote the pressure in the j -th compartment by $p_j = p_j(t, \mathbf{x})$ and for the solute concentration, $c_j = c_j(t, \mathbf{x})$. The fluid flow in our model is computed via static MPET equations [8, 103] [7, 103] without displacements. The velocity fields are defined using Darcy's law [28] for flow in porous media, which stipulates that the velocity is proportional to the opposite of the gradient of the fluid's pressure, *i.e.*

$$\mathbf{v}_j = - \frac{\kappa_j}{\mu_j} \nabla p_j, \quad (2)$$

where κ_j is the permeability coefficient for the fluid in compartment j and μ_j is the dynamic viscosity of the fluid in the compartment. We denote by ϕ_j the porosity of the j -th compartment (*i.e.* the relative volume taken by the pores of this compartment). We emphasize that the compartments are all present at any point $\mathbf{x} \in \Omega$. ~~Thus, under~~ Under the assumption of incompressible flow, then for all $\mathbf{x} \in \Omega, t \in (0, T]$, ~~we have~~ the equations' systems ~~for each $j \in J$ is~~ given by

$$\begin{cases} -\nabla \cdot \left(\frac{\kappa_j}{\phi_j \mu_j} \nabla p_j \right) = r_j, \\ \frac{\partial c_j}{\partial t} - \frac{\kappa_j}{\phi_j \mu_j} \nabla \cdot (c_j \nabla p_j) - D_j^* \Delta c_j = s_j. \end{cases} \quad (3)$$

Here, ~~κ_j is the permeability coefficient of the fluid, μ_j is the dynamic viscosity of the fluid,~~ D_j^* is the effective diffusion coefficient in the j -th compartment, and r_j, s_j are the transfer functions to model the exchanges between the compartments and will be described in the next paragraph.

Remark 1. *For simplicity reasons, we consider the porosity, permeability and diffusion coefficients to be isotropic homogeneous, i.e. no spatial variation are is considered for these parameters.*

Remark 2. *We note that c_j ~~denote~~ denotes the microscopic fluid ~~concentrations~~ concentration, which is related to the macroscopic or total concentration via $c_j^{\text{total}} = c_j * \phi_j$.*

Transfer functions The transfer functions in System (3) model the exchange of fluid, r_j , and solutes, s_j , between the different compartments. These compartments are either separated by a membrane or are in communication with other directly connected to vessels along the same tree (*e.g.* an artery branching to capillaries or the PVS around arteries branching to the PVS around capillaries. We assume the possibility of PVS around capillaries in line with *e.g.* [41].

When the compartments are separated by a membrane, the fluid flows from one compartment to another due to a difference ~~of~~ in pressure which is related to the hydraulic conductivity of the membrane, *i.e.*

$$r_j = \frac{1}{\phi_j} \sum_{i \in J, i \neq j} \gamma_{j,i} [(p_i - p_j) - \sigma_{i,j}(\pi_i - \pi_j)], \quad (4)$$

with

$$\gamma_{j,i} = L_{i,j} \frac{|S_{i,j}|}{|\Omega|}, \quad (5)$$

where $|\Omega| = \int_{\Omega} 1 \, d\mathbf{x} = 2313 \, \text{mm}^3$ is the brain volume (computed from our rat brain mesh), $L_{i,j}$ is the hydraulic conductivity of the membrane separating the i -th and j -th compartments, $\frac{|S_{i,j}|}{|\Omega|}$ is the ratio between the surface of the membrane and the total volume of the tissue, and $\sigma_{i,j}$ is the osmotic reflection coefficient for the membrane. This reflection coefficient corresponds to a specific solute. In this work, we only consider osmotic effects due to plasma cells in the blood where π_j is the osmotic pressure. The solute crosses the membrane due to the combination of two effects: Either via convection of fluid through the pores of the membrane or via diffusion. These two effects are modelled by the transfer functions (see *e.g.* [47])

$$s_j = \frac{1}{\phi_j} \sum_{i \in J, i \neq j} \lambda_{j,i}(c_i - c_j) + \frac{(c_j + c_i)}{2} \tilde{\gamma}_{j,i}(p_i - p_j - \sigma_{i,j}(\pi_i - \pi_j)), \quad (6)$$

where this time

$$\lambda_{j,i} = P_{i,j} \frac{|S_{i,j}|}{|\Omega|}, \quad \tilde{\gamma}_{j,i} = \gamma_{j,i}(1 - \sigma_{\text{reflect}}),$$

in which $P_{i,j}$ is the permeability of the membrane separating the i -th and j -th compartments to the solute and σ_{reflect} reflects the solvent-drag reflection coefficient.

In the case of a continuous transition between compartments (~~e.g., such as~~ between arteries and capillaries), no membrane is present (~~and we thus and we~~ set $P_{i,j} = 0$). ~~We provide in Subsection 2.3 values.~~ Values for the exchange coefficients ~~$\gamma_{j,i}, \tilde{\gamma}_{j,i}, \lambda_{j,i}, \gamma_{j,i}, \tilde{\gamma}_{j,i}$ and $\lambda_{j,i}$ are given in Subsection 2.3.~~

Clearance of ^{14}C -inulin To study the clearance of ^{14}C -inulin from the rat brain, we consider ~~3 variations.~~ model variations.

We first assume that the bulk flow of fluid in the interstitial space is negligible ~~;~~ and transport occurs only due to diffusion in the interstitial space ~~only~~. Hence, we use Equation (1). Clearance of ^{14}C -inulin occurs at the brain surface and is modelled by appropriate boundary conditions ~~that are~~ described below. This scenario is represented by Test case 1 on Fig 1.

Secondly, we consider a clearance of ^{14}C -inulin due to the glymphatic system. Hence, we use System (3) with $|J| = 4$ compartments: ECS, PVS around arteries, PVS around capillaries, and PVS around veins. Test case 2 in Fig 1 depicts this scenario. CSF is assumed to flow from the PVS around arteries to the PVS around capillaries or in the ECS. From the PVS around capillaries, CSF flows to the ECS or ~~to~~ the PVS around veins. From the ECS, CSF may be reabsorbed in the PVS around veins or capillaries. Clearance from the brain may occur at the brain surface from the ECS, the PVS around veins and the PVS around arteries.

Thirdly, we add the effect of ~~the~~ blood vasculature. Indeed, cerebral blood vessels are not impermeable , and some fluid could leak from them to the other structures [74]. This case is depicted by Test case 3 in Fig 1.

For the sake of clarity, in the following, we refer to these 3 applications of our **modeling** **modelling** framework as

- **Pure diffusion model: Test case 1.** Diffusion only in the interstitial space modeled by Equation (1).
- **4-compartment model: Test case 2.** Clearance from the glymphatic system using System (3) with $J = 4$ compartments.
- **7-compartment model: Test case 3.** Clearance from the glymphatic system and considering the blood perfusion that could affect fluid movement using System (3) with $J = 7$ compartments.

2.2 Initial and boundary conditions

Initial condition We consider the application in which the solute is injected directly into the ECS of the rat brain, and assume that the initial ^{14}C -inulin concentration is given as a three-dimensional Gaussian around the **center-centre** of injection \mathbf{s} (see Fig 2b),

$$c_e(0, \mathbf{x}) = C^0 \exp \frac{|\mathbf{x} - \mathbf{s}|^2}{\sigma^2} \exp - \frac{|\mathbf{x} - \mathbf{s}|^2}{\sigma^2} \quad (7)$$

where $C^0 = 1.0 \cdot C^0$ is a reference concentration, and σ determines the initial spread of the solute after injection. The reference concentration is chosen such that the integral of the initial condition over the domain matches the injected tracer amount. Already for $\sigma = 1\text{mm}$, the initial condition quickly decays towards zero. More than 96% of the total mass is located within a ball of radius 2mm surrounding the injection point, and the concentration values outside of this region have minimal impact. However, to ensure that also the initial condition adheres to the prescribed boundary conditions (below), we project the initial condition onto a space of functions which vanish at the boundary. We emphasize that the initial condition is the same for the case of a single compartment and when multiple compartments are considered. In the following, we present numerical results for which the initial point of injection is located in the right hemisphere with coordinates $\mathbf{s} = (4, 2, 3)$.

Boundary conditions To generate a relevant bulk flow within the PVSs, we assume a slight pressure difference between the boundary of the PVSs around arteries and veins. We know that intracranial pressure in a rat is $4 \pm 0.74\text{mmHg}$ (see [90]). ISF pressure has been measured in rat [108] and is $3.43 \pm 0.65\text{mmHg}$.

Therefore, we supplement the pressure equations with

$$\begin{cases} -\frac{\kappa_e}{\mu_{\text{CSF}}} \frac{\partial p_e}{\partial \boldsymbol{\nu}}(t, \mathbf{x}) = L_{e,\text{SAS}}(p_{\text{SAS}} - p_e), & -\frac{\kappa_{pa}}{\mu_{\text{CSF}}} \frac{\partial p_{pa}}{\partial \boldsymbol{\nu}}(t, \mathbf{x}) = L_{\text{PVSpial},pa}(p_{\text{PVSpial}} - p_{pa}), \\ \frac{\partial p_{pc}}{\partial \boldsymbol{\nu}}(t, \mathbf{x}) = 0, & p_{pv} = 3.26 \text{ mmHg}, \end{cases} \quad (8)$$

on $\partial\Omega$, $t > 0$, with $\boldsymbol{\nu}$ being the **outward-outward-pointing** normal vector to the boundary $\partial\Omega$ and $p_{\text{PVSpial}} = 4.74\text{mmHg}$ is $p_{\text{PVSpial}} = 4.74\text{mmHg}$ the CSF pressure inside the PVS of pial arteries and $p_{\text{SAS}} = 3.74\text{mmHg}$ $p_{\text{SAS}} = 3.26\text{mmHg}$ is the CSF pressure inside the SAS. **The coefficients $L_{\text{PVSpial},pa}$ and $L_{\text{SAS},e}$** We emphasize that these pressure values have been chosen to be in the biologically relevant threshold compared to measurements [90]. The coefficients $L_{\text{PVSpial},pa}$ and $L_{\text{SAS},e}$ are related to the permeability of the pial surface of the brain for the CSF (specified in Appendix A).

Considering the If cerebral blood perfusion is included in the model (test case 3), then fluid movement is affected and we need additional parameters, namely

$$\begin{cases} -\frac{\kappa_a}{\mu_a} \frac{\partial p_a}{\partial \boldsymbol{\nu}}(t, \mathbf{x}) = \frac{B_{\text{blood}}}{|\partial\Omega|} \\ \frac{\partial p_c}{\partial \boldsymbol{\nu}}(t, \mathbf{x}) = 0, & p_v(t, \mathbf{x}) = 7.0 \text{ mmHg}, \end{cases} \quad \text{on } \partial\Omega, t \geq 0, \quad (9)$$

with $p_{\text{blood}} = 120 \text{ mmHg}$ (see [42]) $B_{\text{blood}} = 2.32 \text{ mL/min}$ (see Table 7 in Appendix A and assuming a 2g rat brain) and $|\partial\Omega|$ is the area of the surface of the rat brain.

For the concentration equations, different boundary conditions are considered. The first and simplest approach is to use homogeneous Dirichlet boundary conditions to represent clearance from the tissue and zero-flux boundary conditions for the compartments that are not in communication with the SAS. ~~Namely~~ Since the periarterial, perivenous and extracellular spaces represent possible outflow routes, we impose Dirichlet boundary conditions for the concentration equations in ~~the periarterial, perivenous and extracellular spaces since these compartments represent possible outflow routes~~ these compartments. For the other compartments, we assume that there is no flow at the ~~surface of the brain~~ brain's surface. Thus, we have

$$\begin{cases} c_j|_{\partial\Omega} = 0, & \text{for } j = \{pa, pv, e\}, \\ \frac{\partial \left(D_j \nabla c_j + \frac{\kappa_j}{\mu_j} c_j \nabla p_j \right)}{\partial \nu} = 0 & \text{on } \partial\Omega, \text{ and for } j = \{pc\}. \end{cases}$$

This condition assumes that no membrane restricts ^{14}C -inulin movement over the pial surface. Moreover, the clearance of solutes from the SAS is assumed to be sufficiently quick, so that ^{14}C -inulin concentration in the CSF stays zero.

Alternatively, the solute concentration in the CSF within the SAS may be represented by a time-dependent boundary condition. Still assuming instant absorption at the surface, we modify the Dirichlet boundary conditions to

$$c_j|_{\partial\Omega} = g(t), \quad \text{for } j = \{pa, pv, e\}, \quad t > 0, \quad (10)$$

where $g(t)$ is given as the total amount of ~~molecules~~ ^{14}C -inulin that has been cleared from the brain up to that time, averaged over the CSF volume V_{CSF} in the ~~fluid-filled~~ fluid-filled space surrounding the brain, *i.e.* the SAS. The rate of change of ~~molecules~~ ^{14}C -inulin tracer within the brain, per unit of time, is given by

$$\frac{d}{dt} \int_{\Omega} \sum_{j \in J} \phi_j c_j \, d\mathbf{x} = \sum_{j \in J} \int_{\Omega} \phi_j \frac{\partial c_j}{\partial t} \, d\mathbf{x} = - \int_{\partial\Omega} \mathbf{q} \cdot \boldsymbol{\nu} \, ds, \quad (11)$$

in which \mathbf{q} is the ~~mass-total~~ total mass flux from all the compartments at the surface of the brain (we recall that $\boldsymbol{\nu}$ is the outward pointing normal to the surface of the brain). For each compartment, this flux is given by the combination of diffusion and convection

$$\mathbf{q} = \sum_{j \in J} -D_j \nabla c_j + c_j \mathbf{v}_j, \quad \mathbf{v}_j = -\frac{\kappa_j}{\mu_j} \nabla p_j.$$

A decrease of ~~molecules~~ ^{14}C -inulin within the brain, corresponds to an increase of concentration in the SAS, and vice-versa. Therefore, g satisfies the linear ordinary differential equation

$$\begin{cases} \frac{dg}{dt} &= -\alpha g(t) + \frac{1}{V_{\text{CSF}}} \int_{\partial\Omega} \mathbf{q} \cdot \boldsymbol{\nu} \, ds, \\ g(0) &= 0, \end{cases} \quad (12)$$

where $\alpha > 0$ is the rate of CSF absorption from the SAS. This model assumes instantaneous absorption of ~~molecules~~ ^{14}C -inulin in the CSF, and instant mixing of the solute within the whole SAS.

If $\alpha = 0$, the latter Dirichlet boundary condition may be interpreted as a model for conservation of ~~the amount of molecules~~. Thus, assuming that the molecules are intracranial ^{14}C -inulin. Assuming that ^{14}C -inulin is not eliminated from the SAS, an alternate formulation of this condition is given by

$$\sum_{j \in J} \int_{\Omega} \phi_j c_j \, d\mathbf{x} + g(t) V_{\text{CSF}} = N_0, \quad (13)$$

where $N_0 = \sum_{j \in J} \int_{\Omega} \phi_j c_j(0, \mathbf{x}) \, d\mathbf{x}$ is the total amount of ~~molecules~~¹⁴C-inulin initially injected into the brain. Thus, ~~this time for this case,~~ g is ~~simply~~ given by

$$g(t) = \frac{1}{V_{\text{CSF}}} \left(N_0 - \sum_{j \in J} \int_{\Omega} \phi_j c_j \, d\mathbf{x} \right). \quad (14)$$

We test the effect of all three different concentration boundary conditions (Homogeneous, Conservation (10) with Equation (14), and Decay (10) with Equation (12)) on clearance of ¹⁴C-inulin from the brain.

2.3 Parameter values

2.3.1 For the convection-diffusion equation

¹⁴C-inulin diffusion coefficient The free diffusion coefficient for ¹⁴C-inulin is $D_{\text{free}} = 2.98 \times 10^{-4} \text{ mm}^2/\text{s}$ as reported in [56], and the tortuosity of the rat brain is given by $\lambda = 1.7$ (see [107]). Hence, the effective diffusion coefficient of ¹⁴C-inulin in the rat brain is given by

$$D^* = \frac{D_{\text{free}}}{\lambda^2} = 1.03 \times 10^{-4} \text{ mm}^2/\text{s}.$$

2.3.2 For the multi-compartment model

Porosity coefficients From [24], we know that the volume fraction of the extracellular space of rats is

$$\phi_e = 0.14.$$

From [79], the volume fraction of blood is estimated to be

$$V_{\text{Blood}} = 3.29 \times V_{\text{Brain}}/100.$$

Furthermore, using the fractions of arteries, veins, and capillaries stated in [58][84], we obtain

$$\phi_a = 0.0069, \quad \phi_c = 0.011, \quad \phi_v = 0.015.$$

The porosity of the PVS in human white matter is estimated to ~~$V_{\text{PVS}} \approx 0.3 \times V_{\text{Brain}}/100$~~ (see ~~e.g. [10]~~) be around 1% [11]. This value is unknown for the rat, ~~hence.~~ Hence, we assume that the relation holds without relying on measurements. ~~From the estimated~~ Based on percentages of arterial, venous, and capillary blood volume, we ~~estimate~~ assume a similar volume fraction distribution for the corresponding perivascular spaces:

$$\phi_{pa} = \underline{0.00060.0021}, \quad \phi_{pc} = \underline{0.00030.0033}, \quad \phi_{pv} = \underline{0.00210.0046}.$$

Fluid parameters The interstitial fluid and plasma in the blood compartments are assumed to possess different properties. The dynamic viscosity of blood and CSF is given by respectively [39] and [17]. We have

$$\mu_a = \mu_v = \mu_c = 2.67 \times 10^{-3} \text{ Pa.s}, \text{ and } \mu_{pa} = \mu_{pv} = \mu_{pc} = \mu_e = 7.0 \times 10^{-4} \text{ Pa.s}.$$

In [106], the authors used experimentally obtained resistance coefficients for several compartments. From the definition of these resistances, we can compute the ~~following permeability coefficients~~ permeability coefficients in several compartments (see Appendix A for details). The remaining permeabilities are obtained from [31] and [49].

$$\begin{aligned} \kappa_a &= 3.30 \times 10^{-6} \text{ mm}^2, & \kappa_v &= 6.59 \times 10^{-6} \text{ mm}^2, & \kappa_c &= 8.8 \times 10^{-9} \text{ mm}^2, \\ \kappa_{pa} &= 1.0 \times 10^{-11} \text{ mm}^2, & \kappa_{pv} &= 6.51 \times 10^{-9} \text{ mm}^2, & \kappa_{pc} &= 3.54 \times 10^{-13} \text{ mm}^2, \\ \kappa_e &= 2.0 \times 10^{-11} \text{ mm}^2. \end{aligned}$$

The baseline values for the fluid parameters are summarized in Table 1.

Symbol	Unit	Meaning	Value	Reference
D	mm^2/s	Free diffusion coefficient	$D_{\text{free}}^{^{14}\text{C-inulin}} = 2.98 \times 10^{-4}$	[56]
D^*	mm^2/s	Apparent diffusion coefficient	$D^{*,^{14}\text{C-inulin}} = 1.03 \times 10^{-4}$	[56]
κ_j	mm^2	Permeability	$\kappa_a = 3.30 \times 10^{-6}, \kappa_v = 6.59 \times 10^{-6}, \kappa_c = 8.8 \times 10^{-9},$ $\kappa_{pa} = 1.0 \times 10^{-11}, \kappa_{pv} = 6.51 \times 10^{-9}, \kappa_{pc} = 3.54 \times 10^{-13}, \kappa_e = 2.0 \times 10^{-11}$	[43] and computed
ϕ_j	No unit	Porosity	$\phi_e = 0.14, \phi_a = 0.0071, \phi_c = 0.011, \phi_v = 0.016$ $\phi_{pa} = 0.0021, \phi_{pc} = 0.0033, \phi_{pv} = 0.0046$	[24, 79, 58] and computed
μ_j	Pas	Viscosity	$\mu_{pa} = \mu_{pv} = \mu_{pc} = \mu_e = 7.0 \times 10^{-4}$ $\mu_a = \mu_v = \mu_c = 2.67 \times 10^{-3}$	[17] [103]

Table 1: Baseline fluids (Blood and CSF) viscosity, permeability, porosity and diffusion parameters.

Exchange coefficients We ~~first start by start with~~ the exchange coefficients from blood to tissue, *i.e.* $\gamma_{e,a}, \gamma_{e,c}, \gamma_{e,v}$. ~~For these latter, we use the definition~~, defined by

$$\gamma_{j,i} = L_{i,j} \frac{|S_{i,j}|}{|\Omega|}.$$

As in [92], we use the hydraulic conductivities reported in [36, 53, 89]. We ~~thus~~ use the following values

$$L_{a,e} = 9.1 \times 10^{-10} \text{ mm}/(\text{sPa}), \quad L_{c,e} = 1.0 \times 10^{-10} \text{ mm}/(\text{sPa}), \quad L_{v,e} = 2.0 \times 10^{-11} \text{ mm}/(\text{sPa}).$$

Furthermore, from [97], we estimate the ratio between the surface area of capillaries and brain volume to

$$\frac{|S_{c,e}|}{|\Omega|} = 9 \text{ mm}^{-1}.$$

Using the computations performed in [29], we assume that the surface density of capillaries is ~~3~~ three times greater than the surface density of arteries and veins, *i.e.*

$$\frac{|S_{a,e}|}{|\Omega|} = 3 \text{ mm}^{-1}, \quad \frac{|S_{v,e}|}{|\Omega|} = 3 \text{ mm}^{-1}.$$

Altogether, we obtain

$$\gamma_{e,a} = 2.7 \times 10^{-9} (\text{sPa})^{-1}, \quad \gamma_{e,c} = 9.0 \times 10^{-10} (\text{sPa})^{-1}, \quad \gamma_{e,v} = 6.0 \times 10^{-11} (\text{sPa})^{-1}.$$

Then, we turn to the values of the exchange parameters from PVSs to ECS, *i.e.* $\gamma_{e,pa}, \gamma_{e,pc}, \gamma_{e,pv}$. From the 1D resistance parameters in [106], we compute the following coefficients (see Appendix A for details about the computations)

$$\gamma_{e,pa} = 2.2 \times 10^{-7} (\text{sPa})^{-1}, \quad \gamma_{e,pc} = \underline{1.09.2} \times 10^{-9} (\text{sPa})^{-1}, \quad \gamma_{e,pv} = 2.0 \times 10^{-7} (\text{sPa})^{-1}.$$

From the previous values, we determine the following exchange coefficients for the transfer between blood vessels and PVSs (see Appendix A for details)

$$\gamma_{pa,a} = \underline{2.762.8} \times 10^{-9} (\text{sPa})^{-1}, \quad \gamma_{pc,c} = \underline{9.21.0} \times 10^{-9} (\text{sPa})^{-1}, \quad \gamma_{pv,v} = 6.0 \times 10^{-11} (\text{sPa})^{-1}.$$

For the exchanges between compartments corresponding to the branching of blood ~~vessel~~ vessels, we use

$$\gamma_{c,a} = \frac{B_{\text{flow}}}{\Delta p_{c,a} |\Omega|} = 3.3 \times 10^{-6} (\text{sPa})^{-1}, \quad \gamma_{v,c} = \frac{B_{\text{flow}}}{\Delta p_{v,c} |\Omega|} = \underline{1.09.7} \times 10^{\underline{-5-6}} (\text{sPa})^{-1}.$$

where $B_{\text{flow}} = \underline{2.4 \text{ mL/min}} \cdot B_{\text{flow}} = \underline{116 \text{ mL/100g/min}}$ (from [68][57]), and $\Delta p_{v,c}$ ~~corresponds~~ $\Delta p_{c,a}, \Delta p_{v,c}$ correspond to the blood pressure ~~drop~~ drops between vessels. We assume a $\Delta p_{c,a} = \underline{40 \text{ mmHg}}$ $\Delta p_{c,a} = \underline{40 \text{ mmHg}}$ blood pressure drop from arteries to capillaries and a $\Delta p_{v,c} = \underline{13 \text{ mmHg}}$ $\Delta p_{v,c} = \underline{13 \text{ mmHg}}$ blood pressure drop from capillaries to veins.

Similarly, to obtain the transfer coefficients for connected PVS compartments, we assume that the CSF flow in PVS is proportional to CSF production $Q_{\text{CSF}} = 3.38 \mu\text{L}/\text{min}$. This latter value from [20] corresponds to an upper estimate of the CSF production in our case since more recent works using another technique of measurement found $1.40 \mu\text{L}/\text{min}$ for CSF production rate [51]. Using the production rate of CSF as flow in the PVS is, of course, an upper estimate of what the actual flow in the network is. Then, assuming $\Delta p_{pa,pc} = 1 \text{ mmHg}$ and $\Delta p_{pc,pv} = 0.25 \text{ mmHg}$, we arrive to

$$\gamma_{pa,pc} = 1.83 \times 10^{-7} (\text{Pa s})^{-1}, \quad \gamma_{pc,pv} = 7.31 \times 10^{-7} (\text{Pa s})^{-1}.$$

To compute the exchange coefficients between the pial surface artery PVSs and the arterial PVS as well as for the exchange between ECS and SAS, we adapt the fluid resistance coefficient for this space from the one used in [106] to obtain (see Appendix A)

$$L_{\text{PVSpial},pa} = 1.25 \times 10^{-6} (\text{s Pa})^{-1}, \text{ and } L_{e,\text{SAS}_{e,\text{SAS}}} = 3.13 \times 10^{-7} (\text{s Pa})^{-1}.$$

The osmotic pressure in the capillary compartment has been reported to be 20 mmHg [50]. We thus set $\pi_a = \pi_c = \pi_v = 20 \text{ mmHg}$ and $\pi_e = \pi_{pa} = \pi_{pc} = \pi_{pv} = 0.2 \times \pi_c$ (extravascular osmotic pressures have been chosen from the fact that due to the BBB the osmotic pressure in the ECS within the brain is known to be lower than 30% of the capillary one [50]).

We now define the advective mass exchange coefficients using the equation

$$\tilde{\gamma}_{j,i}^{14\text{C-inulin}} = \gamma_{j,i} (1 - \sigma_{ij,\text{reflect}}^{14\text{C-inulin}}),$$

where $\sigma_{ij,\text{reflect}}^{14\text{C-inulin}}$ is the reflection coefficient for the ~~molecule~~^{14C-inulin} and the membrane under consideration. Since Inulin is approximately 5000 Da in size (measured in [102]), we set

$$\sigma_{ij,\text{reflect}}^{14\text{C-inulin}} = 0.2,$$

for all the membranes.

The diffusive permeabilities through the astrocyte endfeet (AEF) membrane for ¹⁴C-inulin test case 2 and 3 ~~are~~ are computed from [60, 67] (see Appendix A for details)

$$P_{pa,e}^{14\text{C-inulin}} = P_{pv,e}^{14\text{C-inulin}} = \underline{1.251.2} \times 10^{\underline{-5-3}} \text{ mm s}^{-1}, \quad P_{pc,e}^{14\text{C-inulin}} = \underline{1.914.1} \times 10^{\underline{-6-4}} \text{ mm s}^{-1}.$$

From the two previous parameters, we defined for the 7 compartments system $\gamma_{pa,a}$, $\gamma_{pc,c}$, $\gamma_{pv,v}$, $\gamma_{e,pa}$, $\gamma_{e,pc}$, $\gamma_{e,pv}$ and $\gamma_{e,v}$ as well as their corresponding transfer coefficients for ~~the two~~^{14C-inulin} molecules.

The transfer of solutes between vessel compartments for which the connection exists without a membrane is assumed to be solely driven by convection, and the fact that ¹⁴C-inulin does not cross the BBB implies

$$P_{a,pa}^{14\text{C-inulin}} = P_{v,pv}^{14\text{C-inulin}} = P_{c,pc}^{14\text{C-inulin}} = P_{a,c}^{14\text{C-inulin}} = P_{c,v}^{14\text{C-inulin}} = P_{pa,pc}^{14\text{C-inulin}} = P_{pc,pv}^{14\text{C-inulin}} = 0,$$

~~and for vessels in communications~~For connected vessel compartments, the solvent-drag reflection coefficient is assumed to be $\sigma_{\text{reflect}} = 1$.

Altogether, we obtain the transfer coefficients reported in Table 2.

The last value we specify is the CSF volume surrounding the brain, *i.e.* in the subarachnoid space. This parameter value is required to define the boundary conditions. The reported values for this volume vary in the literature, ranging from $90 \mu\text{L}$ [77] to $520 \mu\text{L}$ [55], but seem to be consistently in the region 5-20% of the total intracranial volume. For the simulations in this paper, we will assume that the CSF volume is 10.8% of the total intracranial volume, as reported by [69]. Assuming that the intracranial volume ~~consist~~^{consists} of brain tissue and the CSF spaces, ~~then~~ this value corresponds to a CSF volume of $V_{\text{CSF}} = 0.12 \times |\Omega|$, where $|\Omega|$ is the volume of the brain tissue.

Symbol	Unit	Meaning	Value	Reference
$\gamma_{i \rightarrow j}$	1/(Pa s)	Fluid mass transfer coefficient	$\gamma_{a,e} = 2.7 \times 10^{-9}, \gamma_{v,e} = 6 \times 10^{-11}, \gamma_{c,e} = 9 \times 10^{-10}$ $\gamma_{pa,e} = 2.19 \times 10^{-7}, \gamma_{pv,e} = 1.95 \times 10^{-7}, \gamma_{pc,e} = 9.20 \times 10^{-9}$ $\gamma_{a,pa} = 2.76 \times 10^{-9}, \gamma_{v,pv} = 6.00 \times 10^{-11}, \gamma_{c,pc} = 9.98 \times 10^{-10}$ $\gamma_{a,c} = 3.14 \times 10^{-6}, \gamma_{c,v} = 9.65 \times 10^{-6}$ $\gamma_{pa,pc} = 1.83 \times 10^{-7}, \gamma_{pc,pv} = 7.31 \times 10^{-7}$ $\gamma_{pv,spial,pa} = 1.25 \times 10^{-6}, \gamma_{c,SAS} = 3.13 \times 10^{-7}$	Computed
$\gamma_{i \rightarrow j}^{14C\text{-inulin}}$	1/(Pa s)	Advective mass transfer coefficient	Given by Eq. (22)	
$\lambda_{i \rightarrow j}$	s ⁻¹	Solute mass transfer coefficient	$\lambda_{pa,e}^{14C\text{-inulin}} = 3.70 \times 10^{-3}, \lambda_{pv,e}^{14C\text{-inulin}} = 3.72 \times 10^{-3}, \lambda_{pc,e}^{14C\text{-inulin}} = 3.70 \times 10^{-3}$	Computed from [59]

Table 2: Baseline diffusive and convective exchange parameters.

Remark 3. In the previous section, all the parameter values required to model the clearance of $^{14}C\text{-inulin}$ using Equation (1) or System (3) have been ~~precised~~specified. Coefficients for which no value has been specified are assumed to be zero. ~~This is the case for example, e.g.~~ for exchange coefficients between compartments that are not in communication.

Remark 4. Most ~~of the~~ parameter values have been found using measurements from in-vitro or in-vivo biological experiments. However, we have indicated the ones for which the values are adapted from the literature or the works from which we extracted the values and estimated these parameters using numerical simulations. We recall that Appendix A provides details about the estimates and computed coefficients.

2.4 Model variations

Sensitivity analysis Some of the parameters used in this model may be uncertain or, to some degree, unknown. It is not clear a-priori how these uncertainties may affect the output from the model. We therefore set out to investigate the model sensitivity to changes in unknown or critical parameters. Each parameter was varied, taking into account the relative uncertainty found in the literature. In particular, we changed ECS permeability (κ_e) by a factor between 0.1 and 1000, periarterial permeability (κ_{pa}) by a factor 0.01 to 1000, pericapillary permeability (κ_{pc}) by a factor 0.01 to 1000, CSF pressure (p_{SAS}) by a factor 0.5 to 2, diffusive transfer between the periarterial and extracellular network ($P_{pa,e}^{14C\text{-inulin}}$) by a factor 0.01 to 1000. In addition, we tested a change in apparent diffusion D^* by a factor of 0.5 to 2 and a change in periarterial porosity between 0.1 and 50.

Parameter	Factors of variation
κ_e	{0.1, 1, 10, 100, 1000}
κ_{pa}	{0.01, 0.1, 1, 10, 100, 1000}
κ_{pc}	{0.01, 0.1, 1, 10, 100, 1000}
p_{SAS}	{0.5, 0.75, 1, 1.5, 2}
$P_{pa,e}^{14C\text{-inulin}}$	{0.01, 0.1, 1, 10, 100, 1000}
$\gamma_{pa,a}$	{0.1, 0.5, 1, 2, 5}
D^*	{0.5, 0.75, 1, 1.5, 2}
ϕ_{pa}	{0.1, 0.5, 1, 10, 20}

Table 3: Factors of variation for each of the tested parameters.

For the 7-compartment model, we further changed the BBB permeability between the arterial and periarterial compartments ($\gamma_{pa,a}$) by a factor of 0.1 to 5. For a complete overview of all parameter variations for the sensitivity analysis, see Table 3. To save computational cost, the sensitivity analysis was performed on the mesh of resolution 16, which yield a few % faster clearance than the 32 mesh used in the simulations (for details see Appendix C).

The effect of CSF clearance It has been suggested that the flow of CSF in the SAS plays a major role ~~for-in~~ clearance also from the brain parenchyma [83, 44]. In the present study, the

effect of CSF clearance from the SAS is ~~modeled~~ modelled by three different boundary conditions for the concentration: 1) A homogeneous Dirichlet condition as described by Equation (2.2), representing instantaneous clearance from the SAS, 2) CSF/ISF exchange and conservation of ~~tracer molecules~~ ^{14}C -inulin in the intracranial compartment (Equation (13)), and 3) CSF/ISF exchange and exponential decay of particles from the SAS due to CSF production and absorption (Equation (12)).

The effect of sleep Xie *et al.* [109] reported an increase of the ECS porosity when the animal is sleeping, which may increase convective transport in the brain [100]. Indeed, they indicated that the porosity of the ECS in the awake state is $\phi_e^{\text{awake}} = 0.14$ whereas, in the sleeping state, they measured $\phi_e^{\text{sleep}} = 0.23$. Using the Kozeny-Carman equation, this leads to the relation (see [101] for example)

$$\kappa_e^{\text{sleep}} = 5.5 \times \kappa_e^{\text{awake}}.$$

Recent results [18] indicate that when the animal is asleep, dilation and reduction of the perivascular spaces are observed due to vasomotion. Assuming that the vasomotion leads on average to an enhancement of PVS porosities and that the contraction of the blood vessels leads to a constant factor C_ϕ of increase of porosity for these spaces *i.e.*

$$\phi_j^{\text{sleep}} = C_\phi \phi_j^{\text{awake}}.$$

Then, assuming free (Poiseuille) fluid flow in perivascular spaces, a change of porosity creates a modification of the permeability leading to

$$\kappa_j^{\text{sleep}} = C_\phi^2 \kappa_j^{\text{awake}},$$

(see Appendix A for details). We assume that the parameter values corresponding to the awake state are given by the baseline values of Table 1. Based on the measurements from [18], we use an upper estimate of PVS variations during sleep, and assume $C_\phi = 4$.

The effect of communication with blood The blood vessels composing the cerebral vasculature are not completely impermeable, and there is a debate going on to which ~~extend~~ extent CSF/ISF communicates with the microcirculation [74]. We consider both a 4-compartment model (test case 2) that assumes no communication between CSF/ISF and blood, and ~~additionally~~ a 7-compartment model (test case 3) where fluid can exchange between the blood vessels and the perivascular spaces around them.

2.5 Quantities of interest

Figure 2: a): The computational mesh of the rat brain used for most of the simulations within this article. The meshing procedure is described in section 2.6. For the given mesh, the maximum cell size is $\approx 1/32$ times the diameter of the mesh. b): The initial ^{14}C -inulin concentration within the ~~in the~~ ECS, simulating an injection directly into the brain tissue.

~~To study the clearance of, we integrate the concentration for different volumes.~~ To study how sample size variations from experimental data could affect the results, we integrate the concentrations over several cubes ~~ω~~ $\omega \subset \Omega$ of varying sizes embedded in the brain mesh to represent possible measurement samples of the brain. In addition, we assess the mass of ~~molecules~~ ^{14}C -inulin in the entire brain Ω .

For the first test case (ECS only), the relative mass of ~~molecules~~¹⁴C-inulin in the entire brain at time t is denoted by

$$c_{tot}(t) := \frac{\int_{\Omega} \phi_e c_e(t, \mathbf{x}) \, d\mathbf{x}}{\int_{\Omega} \phi_e c_e(0, \mathbf{x}) \, d\mathbf{x}}.$$

The relative mass of ~~molecule~~¹⁴C-inulin in the ECS within a cube $\omega \subset \Omega$ ~~centered~~centred around the injection point is ~~indicated by~~ defined as

$$c_{\omega}(t) := \frac{\int_{\omega} \phi_e c_e(t, \mathbf{x}) \, d\mathbf{x}}{\int_{\omega} \phi_e c_e(0, \mathbf{x}) \, d\mathbf{x}}.$$

For the other test cases (~~44~~, and 7-compartments), the relative mass of ~~molecules~~¹⁴C-inulin in the entire brain and within a cube $\omega \subset \Omega$ at time t is denoted by

$$c_{tot}(t) := \frac{\int_{\Omega} \sum_{j \in J} \phi_j c_j(t, \mathbf{x}) \, d\mathbf{x}}{\int_{\Omega} \phi_e c_e(0, \mathbf{x}) \, d\mathbf{x}}, \quad c_{\omega}(t) := \frac{\int_{\omega} \sum_{j \in J} \phi_j c_j(t, \mathbf{x}) \, d\mathbf{x}}{\int_{\omega} \phi_e c_e(0, \mathbf{x}) \, d\mathbf{x}},$$

respectively.

We further measure the fluid velocity in the different compartments. From the solution of the pressure equations, we compute the vector fields

$$\mathbf{u}_j = -\frac{\kappa_j}{\phi_j \mu_j} \nabla p_j, \quad j \in J, \quad (15)$$

to obtain the velocity inside the j -th compartment. From these computed velocity fields \mathbf{u}_j , we compute the average velocity within a compartment $u_{aver,j}$ and the maximal velocity $u_{max,j}$ given by

$$u_{aver,j} = \frac{\int_{\Omega} |\mathbf{u}_j| \, d\mathbf{x}}{|\Omega|} \frac{\int_{\Omega} \sqrt{\mathbf{u}_j \cdot \mathbf{u}_j} \, d\mathbf{x}}{|\Omega|}, \quad u_{max,j} = \|\sqrt{\mathbf{u}_j \cdot \mathbf{u}_j}\|_{L^\infty}, \quad (16)$$

To compute the volume of fluid transferring between compartment j and compartment i , we use

$$Q_{j,i} = \int_{\Omega} \gamma_{j,i} (p_i - p_j) \, d\mathbf{x}. \quad (17)$$

To compute the volume of CSF exchanged between ~~the~~ compartment j and the SAS, we use

$$Q_{j,SAS} = \int_{\partial\Omega} \left(-\frac{\kappa_j}{\mu_j} \nabla p_j \cdot \boldsymbol{\nu} \right) \, ds. \quad (18)$$

To compute the mass of ~~molecules~~¹⁴C-inulin moving from compartment i to j , we use [47]:

$$M_{ji}(t) = \int_{\Omega} \lambda_{j,i} (c_i - c_j) + \frac{(c_j + c_i)}{2} \tilde{\gamma}_{j,i} (p_i - p_j - \sigma_{i,j} (\pi_i - \pi_j)) \, d\mathbf{x}. \quad (19)$$

2.6 Computational mesh, solution method and verification

The computational mesh used for the simulations in this paper was constructed from the "Waxholm Space Atlas of the Sprague Dawley Rat Brain v4" (RRID: SCR_017124) [76, 54][76, 75, 54], available under the licence CC-BY-SA 4.0 (<https://creativecommons.org/licenses/by-sa/4.0/>) at ~~the following link:~~ <https://www.nitrc.org/projects/whs-sd-atlas>. The atlas provides a detailed segmentation of different regions within the rat brain.

~~For the atlas generation in the previous study~~ In the original study behind the atlas [76], the animal was anaesthetized by intraperitoneal injection of a mixture of Nembutal (Ovation Pharmaceuticals, Inc., Lake Forest, IL) and butorphanol, and transcardially perfused with 0.9% saline and ProHance (10:1 v:v) for 4 minutes followed by a flush of ProHance in 10% ~~phosphate~~

~~buffered-phosphate-buffered~~ formalin (1:10 v:v). All procedures and experiments in their work ~~was-were~~ approved by the Duke University Institutional Animal Care and Use Committee [76].

Since the models in this paper do not separate between tissue from different regions of the brain, ~~we are mainly interested in the segmentation is mainly of interest for removing unwanted sections. Most importantly, we wanted to remove the segments representing the ventricles, which are removed from the final mesh. The ventricle various parts of the ventricles. Moreover, we removed some external artefacts such as the spinal trigeminal tract, the optic nerves, and parts of the auditory system [75].~~

The various segments in the raw data file have a few irregularities. For example, in regions where the lateral ventricles are very thin, small groups of unlabeled voxels create holes in the ~~3D-reconstruction-3D reconstruction~~ of the ventricles. To repair these irregularities, we have made use of **3D Slicer**¹, an open-source software application for visualization and analysis of medical images [35]. 3D Slicer provides a segment editor with tools for manual ~~labeling~~ labelling of voxels, hole filling and surface smoothing. After refining the segmentation of the ventricular system, it may be removed from the original volume ~~;~~ to create a realistic representation of the brain surface. The surface is exported as an `stl`-file to be used in the meshing algorithm.

The creation of the computational mesh is performed by SVMTK², which provides a python API for 3D mesh generation methods from the CGAL library. The mesh generation algorithm consists of a Delaunay refinement process followed by an optimization phase [3]. Following the procedures described in [63], we created the mesh illustrated in Fig 2a.

To solve the equations (1) and (3), we use the finite element method for the discretization in space and an implicit Euler method to integrate the resulting ordinary differential systems in time.

In this paper, we choose a resolution for the spatial mesh of $h = 1/32$. The temporal domain is $[0, T]$ with $T = 360$ min with a time step ~~of~~ $\Delta t = 1$ min. Details of the mesh and time resolutions can be found in Appendix C.2. The numerical scheme has been implemented using the FEniCS Library [4, 62], and the linear system was solved using the generalized minimal residual method (GMRES) and the incomplete LU (ILU) preconditioner. Our code is publicly available on GitHub at the following link: <https://github.com/jorgenriseth/multicompartment-solute-transport>.

3 Results

3.1 CSF flow in the 4-compartment model

Fig 3 depicts the pressure fields inside the different compartments for the 4-compartment model. We observe that for baseline parameter values, the pressure gradients in the different fields give a bulk flow of fluid in line with the ~~glympathic-glymphatic~~ theory. Indeed, using Equation (15), our model represents an inflow of CSF from the surface of the brain in the PVS of arteries and an outflow from the PVS of veins. Smaller pressure gradients leading to lower velocities directed from the surface to the depth of the brain are also seen in the ECS and the PVS of capillaries.

Figure 3: Pressure fields in the 4 compartments (left: coronal cut, right: sagittal cut)

Computing the transfer of CSF between the compartments using Equation (17), we obtain

$$Q_{pa,e} = 0.72 \mu\text{L}/\text{min}, \quad Q_{e,pv} = 0.27 \mu\text{L}/\text{min}, \quad Q_{e,pc} = 4.4 \times 10^{-3} \mu\text{L}/\text{min}.$$

¹<https://www.slicer.org/>

²<https://github.com/SVMTK/SVMTK>

Compartment	u_{aver} (in $\mu\text{m/s}$)	u_{max} (in $\mu\text{m/s}$)
PVS arteries	2.8 9.5×10^{-1}	27 7.9
ECS	4.9×10^{-3} 3.3×10^{-3}	7.3×10^{-2} 6.0×10^{-2}
PVS veins	0.74 4.4×10^{-1}	5.2 3.0
PVS capillaries	3.4×10^{-2} 4.0×10^{-3}	0.18 2.7×10^{-2}

Table 4: Velocities of CSF in the different compartments for baseline parameter values.

The transfer between the compartments and the SAS is computed in the same way using Equation (18), and we obtain

$$Q_{\text{SAS},e} = \underline{0.360.22} \mu\text{L/min}, \quad Q_{\text{SAS},pa} = \underline{0.720.94} \mu\text{L/min}, \quad Q_{pv,\text{SAS}} = \underline{0.370.68} \mu\text{L/min}.$$

In this notation, we choose subscripts such that the flow occurs from the first denoted compartment to the second (e.g. flow occurs from the PVS of arteries to the ECS). -

From these pressure fields, we compute the velocity of the CSF in the compartments using Equation (15). We report the average velocities u_{aver} and the maximal ones u_{max} for each compartment in Table 4.

3.2 Transport within the brain

In the following two subsections, we report the relative amount of ^{14}C -inulin in the entire brain from the diffusion and the 4-compartment simulations using Equation (10) with (12) as ~~boundary conditions~~ standard boundary conditions (aside from Subsection 3.2.4 the boundary condition used for the concentration equations will always be (10) with (12) and will be referred to as "Decay" boundary conditions). We then vary the size of the measurement sample (*i.e.* the domain in which the remaining mass of ^{14}C -inulin is computed) and the boundary conditions.

3.2.1 Diffusion in the ECS only

Pure diffusion steadily decreased the ~~amount of tracers~~ tracer amount found within the brain over the entire simulation time, and $\sim 53\%$ of the tracer remains after 6 hours (Fig 4a, blue dashed line). If we assume an exponential decay between the first- and the last time point, the clearance corresponds to a rate constant of 0.0018/min. Fig 4c shows the distribution of ^{14}C -inulin transported by pure diffusion (*i.e.* Equation (1)) in the ECS at different points in time. The tracer spreads radially out from the point of injection, and peak concentration has decreased drastically after $T = 360$ min. At the first time step, some very small negative values appear near the tail of the Gaussian curve, but are smoothed out over time.

3.2.2 4-compartment convection-diffusion

Fig 5 shows the spatial distribution of ^{14}C -inulin concentration over time in all 4 compartments considered in ^{14}C -inulin test case 2. Initially, the tracer is contained only in the ECS where it ~~first was~~ was first injected. Already after 10 minutes, the concentration spreads equally to all compartments. From all time points on, the tracer spreads radially outwards in all compartments, similar to the test case for pure diffusion. We note here that even with equal concentrations, the total mass of tracer differs between each compartment due to differences in porosity. ^{14}C -inulin is thus mainly still contained to the ECS in the 4-compartment model. The tracer in the 4-compartment convection-diffusion model is cleared from the brain slightly faster compared to diffusion alone and $\sim \underline{4950}$ % of the tracer remains in the brain after 6 hours, corresponding to a rate constant of 0.0023/min.

Figure 4: a) Relative ^{14}C -inulin mass located within regions of varying size surrounding the injection point. Solid lines result from the multi-compartment model simulations, while dashed lines result from diffusion only in the ECS. b) Relative ^{14}C -inulin mass located in the totality of the brain for the different boundary conditions. Solid lines result from the multi-compartment model simulations, while dashed lines result from diffusion only in the ECS. c) Evolution in space and time of ^{14}C -inulin relative concentration in the ECS for test case 1 (single diffusion). The ~~color~~-colour scale is chosen for a visual comparison between all time points.

3.2.3 Effect of the measurement sample

Fig 4a shows the evolution of the relative mass of ^{14}C -inulin inside the rat brain and in samples of the brain of different sizes (cubes of side length 2mm, 4mm, and 5mm). The boundary conditions for the concentration equations correspond to the ~~time-dependent~~-time-dependent Dirichlet boundary conditions (12). For the smallest measurement sample, the relative mass of tracers remaining in the sample after 6 hours were $\sim 15\%$ for diffusion and for the 4-compartment model (compared to 53% and ~~49~~50% for the entire brain). ~~In general, we~~ We observe that as the measurement sample size increases, the mass of ^{14}C -inulin remaining in the sample increases.

3.2.4 Effect of the concentration in the subarachnoid space

Fig 4b shows the evolution of the relative mass of ^{14}C -inulin for the three different boundary conditions for the concentration equations: Homogeneous Dirichlet boundary condition, conservation of the mass in the subarachnoid space (corresponding to Equation (10) with (14)), and clearance of ~~molecules~~- ^{14}C -inulin in the subarachnoid space (corresponding to Equation (10) with (12)). Fig 4b compares the relative mass of tracer for the diffusion model (dashed lines) to the four-compartment model (solid lines). In both models, the homogeneous Dirichlet boundary conditions lead to fast clearance from the tissue with $\sim 33\sim 33\%$ remaining in the brain after 6 hours (For both diffusion only and the 4-compartment simulations). When the concentration of ^{14}C -inulin is computed using the ~~time-dependent~~-time-dependent Dirichlet boundary conditions representing tracer conservation in the SAS, the mass of tracers is close to plateau level at 68% or 72% at 6 hours (corresponding to a clearance rate of $\sim 0.001/\text{min}$). With the ~~time dependent~~-time-dependent boundary conditions modelling absorption of CSF in SAS, the relative tracer mass steadily decreases, and ends up ~~in~~ between the two previously described cases with ~~49-53~~50-53% of the tracer remaining in the brain after 6 hours.

3.3 Variations of the 4-compartment model

Figure 5: Evolution in time and space of the relative ^{14}C -inulin amount in the rat brain (frontal cut at the injection point) within the 4 compartments of test case 2.

3.3.1 Sensitivity analysis

For several parameters, value changes of several orders of magnitude do not drastically alter the results. A full overview of model sensitivity changes in parameters is shown in Table 3. In particular, for the extracellular and pericapillary permeabilities (κ_e , κ_{pc}), subarachnoid space pressure (p_{SAS}) and the periarterial to extracellular diffusive transfer ($P_{pa,e}$), there is less than 1% difference in tracer mass between the tested parameter values.

Figure 6: Comparison of ^{14}C -inulin clearance for different variations of porosity and permeability coefficients. "MC Baseline" denotes the clearance curve given by the multi-compartment model with baseline parameter values and is hidden by the dashed curve "Diffusion", representing the clearance given by the application of the Diffusion model in the ECS compartment only. The enhancement of ECS porosity leads to the curve denoted "MC enhancement ECS" and the increase of the porosities in all the compartments gives the clearance curve denoted "MC enhancement ECS+PVS"

An increase of 1000 in periarterial permeability reduces the tracer mass by 10%, while a decrease gives no difference in output. With a change in the diffusion constant, the final tracer mass increases by 43.2% when the diffusion coefficient is decreased by a factor 2 and decreases by 36.2% when the diffusion coefficient is increased by a factor 2. An increase in periarterial porosity slightly delayed clearance, and with an increase of a factor 20, the tracer mass at the final timestep is increased by 7.4%.

3.3.2 Effect of an increase in ECS porosity

It is postulated that sleep has an effect on the clearance of solutes in the brain [109]. The accepted hypothesis is that the ECS porosity increases during sleep, enhancing the convection in this space and even dominating diffusion [109, 100]. This is better measured by the Péclet number Pe that measures the importance of convection over diffusion ($Pe < 1$ if diffusion dominates while $Pe > 1$ if convection is preponderant).

With an increase of ECS porosity from 0.14 to 0.23, we find no relevant difference for the total amount of CSF transferring in the total CSF transfer between the compartments. Interestingly, we find that the maximum velocity in the ECS increases to $u_{\max} = 9.7 \times 10^{-2} \mu\text{m/s}$ (from $7.3 \times 10^{-2} \mu\text{m/s}$ to $7.9 \times 10^{-2} \mu\text{m/s}$ (from $6.0 \times 10^{-2} \mu\text{m/s}$) and the average velocity of CSF in ECS increases to $6.6 \times 10^{-3} \mu\text{m/s}$ (from $4.9 \times 10^{-3} \mu\text{m/s}$ to $4.0 \times 10^{-3} \mu\text{m/s}$ (from $3.3 \times 10^{-3} \mu\text{m/s}$). See Table 4 for all reference velocities computed with baseline parameter values. The Péclet number in ECS increases from 3.2×10^{-2} for baseline coefficients to 3.9×10^{-2} after ECS porosity increase.

Tracer clearance is slightly slower for the four-compartment model when ECS porosity is increased (blue versus orange line, Fig 6). As Since the velocity field in the ECS is directed from the surface of the brain towards the ventricles, inwards from the brain surface, solutes are transported away from the sinks at the domain boundaries. Hence, additional flow in the ECS slows down clearance in this compartment, and the relative mass of tracers within the brain is, in this case 56, 57% after 6 hours.

3.3.3 Effect of an increase in PVS porosity

Increasing the PVS porosity by a factor of 4, increases clearance decreases the clearance slightly from the brain via PVS. The relative mass of tracers found in the brain after 6 hours decreased from 53 increases from 50 % during baseline to 4253% with increased PVS porosity (Figure Fig 6, blue versus red line). Indeed, since Since the diffusive transfer between the compartments tends to average the concentration between them, increasing the porosity of PVSs increases the mass of ^{14}C -inulin in these compartments. Since the PVS of veins is larger than the other and is a outflow arteries is now larger and is an inflow route (with a convective field directed to the surface depth of the brain), clearance of ^{14}C -inulin appears faster lower.

3.3.4 Combined enhancement of the extracellular volume and perivascular spaces

Combining the increase of both ECS and PVS porosity and permeability, we obtain the following computed amount of CSF transfer between the compartments

$$\begin{aligned} Q_{pa,e} &= 2.2 \mu\text{L}/\text{min}, & Q_{e,pv} &= 1.0 \mu\text{L}/\text{min}, & Q_{e,pc} &= 2.4 \times 10^{-3} \mu\text{L}/\text{min}, \\ Q_{e,SAS} &= 1.0 \mu\text{L}/\text{min}, & Q_{SAS,pa} &= 2.3 \mu\text{L}/\text{min}, & Q_{pv,SAS} &= 1.1 \mu\text{L}/\text{min}. \end{aligned}$$

We also obtain the maximum and averaged velocities reported in Table 5.

Compartment	u_{aver} (in $\mu\text{m}/\text{s}$)	u_{max} (in $\mu\text{m}/\text{s}$)
PVS arteries	4.5 <u>1.8</u>	26 <u>9.2</u>
ECS	1.2×10^{-2} <u>9.1×10^{-3}</u>	0.15 <u>0.12</u>
PVS veins	0.97 <u>0.73</u>	6.4 <u>4.6</u>
PVS capillaries	4.2×10^{-2} <u>7.0×10^{-3}</u>	15×10^{-2} <u>2.0×10^{-2}</u>

Table 5: Velocities of CSF in the different compartments for an increase of porosity and permeability in all the 4 compartments.

With an increase in both ECS and PVS permeability, we observe a very similar clearance compared to ~~baseline values (Figure~~ when the ECS porosity is increased (Fig 6, blue-orange versus green line). The clearance of ^{14}C -inulin ~~is initially slightly faster with the enhanced porosity, however~~ after 6 hours pure diffusion and for the 4-compartment model reach both 53 with increased porosity in ECS and PVS reach $\sim 58\%$ of ^{14}C -inulin mass in this case.

3.4 7-compartment model: Additional effect of cerebral blood perfusion

Using the baseline parameter values for the second and the third test cases, we obtain the ~~velocity pressure~~ pressure fields in the ~~PVS of arteries-ECS~~ PVS of arteries-ECS shown in Fig 7a. Interestingly, the leakage of fluid from arteries and capillaries to the PVSs ~~occurring~~ occurring in the 7-compartment model ~~changes~~ changes the pressure fields compared to the 4-compartment model (shown in Fig 3), in which the PVSs were assumed to be isolated from the blood. In contrast to the 4-compartment model, the fluid flow in the PVS of arteries and the ECS is directed towards the brain surface. In addition, flow velocities are increased compared to the 4-compartment model (see Table 6 for details).

Fig 7b shows the clearance curves of ^{14}C -inulin obtained with all three test cases (pure diffusion, 4-compartment, 7-compartment). We observe that with the additional effect of blood perfusion, the clearance is much faster compared to both pure diffusion and all variations of the 4-compartment model. Only ~~~ 5~~ ~ 23 % of the tracer remains in the brain after 6 hours for the 7-compartment model (compared to 53% and ~~49~~ 50% for pure diffusion and the 4-compartment model). The clearance rate for the 7-compartment model with baseline parameter values is thus 0.0041/min, which is close to twice the clearance rate for the 4-compartment model, see Subsection 3.2.2).

Computing the fluid flow between the different compartments using Equation (17), we find

$$\begin{aligned} Q_{a,pa} &= 2.6 \mu\text{L}/\text{min}, & Q_{v,pv} &= 4.2 \times 10^{-3} \mu\text{L}/\text{min}, & Q_{c,pc} &= 2.3 \times 10^{-1} \mu\text{L}/\text{min}, \\ Q_{pa,e} &= 1.29 \mu\text{L}/\text{min}, & Q_{e,pv} &= 7.5 \times 10^{-1} \mu\text{L}/\text{min}, & Q_{e,pc} &= 1.9 \times 10^{-2} \mu\text{L}/\text{min}, \\ Q_{a,\text{influx}} &= 2.3 \text{ mL}/\text{min}, & Q_{v,\text{outflow}} &= 1.8 \text{ mL}/\text{min}, & Q_{e,SAS} &= 3.5 \mu\text{L}/\text{min}, \\ & & Q_{SAS,pa} &= 6.9 \times 10^{-1} \mu\text{L}/\text{min}, & Q_{pv,SAS} &= 2.0 \mu\text{L}/\text{min}. \end{aligned}$$

3.4.1 Sensitivity analysis

Compartment	u_{aver} (in $\mu\text{m/s}$)	u_{max} (in $\mu\text{m/s}$)
Arterial blood	3.3×10^2 3.88×10^3	6.4×10^3 69×10^3
Venous blood	46 88×10^1	3.1×10^2 5.6×10^3
Capillary blood	4.2 1.2	1.4×10^2 28
PVS arteries	27 0.69	1.5×10^2 5.8
ECS	1.3×10^{-2} 4.3×10^{-3}	6.8×10^{-2} 7.1×10^{-2}
PVS veins	31 2.7	1.8×10^2 18
PVS capillaries	0.21 2.8×10^{-3}	1.0 1.9×10^{-2}

Table 6: Velocities of CSF and blood in the different compartments for baseline values coefficients for test case 3.

Figure 7: ~~aa-b)~~ Comparison of ~~velocity fields pressure~~ in ~~PVS arteries ECS~~ for ~~the test case 2-cases 3 a)~~ and ~~3.-2 b)~~. The velocity field is ~~directed opposite of the gradient of pressure. Thus the velocity is mostly~~ oriented to the outside of the brain, and the magnitude is larger when blood is considered in the model. ~~bc)~~ Comparison of ^{14}C -inulin clearance for test case 2 with baseline parameter values and increase of ECS and PVSs porosities with test case 3. "MC Baseline" denotes the clearance curve given by the multi-compartment model with baseline parameter values. The enhancements of ECS and PVSs porosities lead to the curve denoted "MC enhancement ECS+PVS", and the result of test case 3 is denoted "MC 7-compartments"

~~Similar to the 4-compartment model, we found that results were robust to changes in several model parameters. For all parameter changes except changes in the arterial to periarterial fluid transfer ($\gamma_{pa,a}$), the diffusion coefficient (D) and the periarterial porosity (ϕ_{pa}), the tracer mass in the brain at the final time step changed less than 3.1% compared to baseline parameters. As the total mass is already low at the final time step due to rapid convective transport, a constriction in fluid transport from the blood vessels to the periarterial space had a drastic effect. Changing this transport parameter by a factor of 0.1 increased the mass at the final timestep by 82.3%. An increase in the transport parameter by a factor of 5 had an opposite but still drastic effect, with a 96.8% reduction in tracer mass compared to the baseline case. Increasing the diffusion coefficient by a factor 2 led to a 19.7% decrease in tracer mass after 6 hours, while decreasing the diffusion by a factor 2 led to an increase of 21.1%. Changes in periarterial porosity had a smaller effect with a 2.0% decrease in tracer mass when ϕ_{pa} was reduced by a factor 0.1, and an increase of 29.4% when the porosity was increased by a factor of 20.~~

4 Discussion

The main goal of this article is to propose a multi-compartment model representing ~~the fluid~~ movement and solute transport in the brain. We apply our model to the ~~modelling of the~~ glymphatic system at the scale of the rat brain. We design our model and numerical method to explore different scenarios and hypotheses related to ~~clearance of molecules the clearance of~~ ^{14}C -inulin from the brain. Indeed, changing the parameter values for permeability, porosity, ~~and~~ exchange coefficients allows ~~to represent for example us to represent, for example,~~ the possible effect of sleep, the disruption of a membrane, an enhanced CSF flow in the parenchyma or the effect of blood perfusion on the standard picture depicted by the ~~Glymphatic-glymphatic~~ theory. Furthermore, the numerical results explore different situations and allow ~~to access us to~~ ~~assess~~ the importance of different modelling aspects, such as the boundary conditions ~~but also~~ ~~biological-experimental-aspects, and experimental biological aspects,~~ such as the importance of the measurement sample. To ~~the best of the authors knowledge knowledge,~~ this is the first attempt ~~of at~~ using a multi-compartment model to combine fluid flow and transport of solute at the scale of the entire brain. This work is largely built upon works related to blood perfusion in

tissues [93, 95, 78].

Effect of the measurement sample The effect of the measurement sample is depicted in Fig 4a. Our results show that if the measurement sample is small, clearance appears to be faster compared to larger samples or the entire brain. This information needs to be taken into account when quantitatively comparing biological experiments to simulations (e.g. clearance curves). For instance, comparisons between simulation results and the results obtained by, e.g. Iliff et al. [46] and measurements in a piece of tissue or slice (e.g. tracer influx in Xie et al. [109]) is not straightforward. According to simulations of transport in mice [86], diffusion is quantitatively comparable to experimental data on Aqp4 null mice with relative $A\beta$ -concentration. However, with a convective velocity field, simulations match the wild-type mice experiments. We argue that our results can not be compared to the results from Ray et al. [86] due to the difference in measurement sample. When measuring the entire brain, clearance curves differ from those measured in a cube of arbitrary size, as shown in Fig 4a).

Modelling the clearance of ^{14}C -inulin from the SAS using boundary conditions Usually, mathematical models representing clearance of ~~molecules~~ ^{14}C -inulin from the brain use homogeneous Dirichlet boundary conditions for the concentrations (e.g. see [43, 98]). This modelling assumes that clearance in the SAS is instantaneous ~~which is in reality, which in reality, is~~ not the case. Some studies have taken this into account by adding a mass conservation between the brain and the SAS [21]. However, the numerical results presented ~~on-in~~ Fig 4b show that taking the concentration of solutes in the CSF in the SAS into account leads to much slower clearance rates (there are 39% less relative ^{14}C -inulin mass cleared assuming conservation of ~~molecules~~ ^{14}C -inulin in SAS than for homogeneous Dirichlet boundary conditions after 6 hours). Even when adding an absorption rate of CSF in SAS, we also obtain slower clearance rates compared to homogeneous Dirichlet boundary conditions (There is a difference of 20% of relative ^{14}C -inulin mass after 6 hours between the boundary conditions modelling slower clearance from the CSF in the SAS and the homogeneous boundary condition). Hence, our results indicate that forthcoming mathematical models should be careful with the choice of boundary conditions to obtain biologically relevant results.

Baseline parameter values for the ~~multi-compartment~~ 4-compartment model ~~corresponds to the awake state~~ Even though the model ~~comprises a lot of~~ includes many parameters, most of them can be estimated using measurements reported in the literature. Using baseline parameter values, diffusion in the ECS (test case 1) gives clearance results very similar to the ones given by the 4-compartment model considering the PVSs as being isolated from the effect of blood perfusion (test case 2). The results from these models correspond qualitatively to the clearance results reported in Xie et al. [109] ~~for the awake state. Therefore, but the absolute clearance is slightly slower. Measuring both absolute recovery and rate constant, Xie et al. report an absolute recovery of $\sim 60\%$ and a rate constant of around 0.006. Regarding recovery, we have similar values, but for the rate constant we find a value of only 0.002/min. This difference may be explained by the lack of full recovery (i.e. a steady state plateau level) in the experimental data. Overall,~~ these results indicate that ~~the baseline parameter values correspond to the an animal in the awake state and that~~ diffusion in the ECS is the main mechanism to explain the observed clearance. ~~The latter point is explained by the much larger volume fraction of ECS compared to the PVSs, but also that an additional mechanism is needed.~~ Most of the ^{14}C -inulin mass is ~~thus~~ contained and cleared within the ECS. Therefore, even though the Péclet number is higher in the PVSs than in the ECS ($Pe = 9.4$ in the PVS of arteries compared to $Pe = 1.6 \times 10^{-2}$ in the ECS), most of the transport still occurs in the latter. We also note that the maximal velocity in PVS arteries obtained from baseline coefficient values (see Table 4) is close to the measurements of CSF velocity in the PVS arteries at the pial surface in [66, 14] ($7.9 \mu\text{m/s}$ in our work compared

to $18 \mu\text{m/s}$ in Mestre *et al.* [66]). We also note that the location of the maximal velocity we obtained is close to the surface of the brain where the gradient of the pressure is the largest in the PVS arteries compartment (see Fig 3). ISF velocity has also been reported to be around $0.1 - 0.25 \mu\text{m/s}$ by Cserr *et al.* [22, 23] and numerical results obtained in [82] indicated a peak velocity in the ECS close to the surface of the brain and with magnitude $u_{\text{max}} = 0.5 \mu\text{m/s}$. Similar fluid velocities in the parenchyma have been reported by Nicholson [72] and Abbott [1] while a numerical study [21] have shown that even a velocity of $1 \mu\text{m/s}$ may play a complementary role in transport within the parenchyma. Ray *et al.* [86] obtained using a computational model a bulk flow velocity in the ECS of $0.008 - 0.42 \mu\text{m/s}$. Altogether, our model compares well with the previously cited results with an average velocity in the ECS of $u_{\text{aver}} = 0.0033 \mu\text{m/s}$ and a peak velocity located close to the surface of the brain of $0.06 \mu\text{m/s}$ (see Table 4). We note that our average velocities are slightly lower than experimental results. However, movement in the parenchyma is typically measured by lumping all compartments together while we report each compartment separately. This difference may explain the discrepancy between our simulations and experimental data of flow in the ECS.

Increasing the porosity of the ECS slows the clearance of ^{14}C -inulin Since the work of Xie *et al.* [109], sleep is believed to play an important role in the clearance of ~~molecules~~ ^{14}C -inulin. In [109], an increase ~~of in~~ the porosity of the ECS was measured when the animal was asleep. Our results show that when only the ECS porosity was increased, the clearance of ^{14}C -inulin was slower. This may be explained by the fact that increasing the ECS porosity leads to smaller concentration gradients, hence decreasing diffusive movement. However, in this scenario, we assumed that the diffusion coefficient remained constant. Furthermore, the increased ECS porosity only led to a 74% increase in average velocity, and still, the Péclet number remains small ($\text{Pe} = 2.2 \times 10^{-2}$ after ECS porosity increase) in the ECS.

Compared to the usual representation of the glymphatic system in which vessels are clearly spaced, and convective movement occurs between them, our multi-compartment model represents this effect through the exchange terms. The enhancement of the ECS porosity allows for more fluid transfer from the ECS to PVS veins (as shown in Subsection 3.3.4), hence, capturing well the hypothesized faster convective movement in the ECS from the PVS of arteries to the PVS of veins during sleep. However, the usual schematic representation of the glymphatic system does not allow ~~us~~ to consider the directions of the pressure gradients in the ECS at the scale of the brain. If we assume that the convective movement in the PVS of arteries is generated by a pressure gradient, our results show fluid flow in the ECS directed inwards from the surface of the brain. This latter counters the diffusive movement and, hence, slows down the clearance of solutes. This could indicate an effect that is neglected in the current glymphatic theory and needs further ~~investigations~~ investigation.

The minor effect of increased porosity in our model seems to indicate that to obtain the measured effect of sleep (see Xie *et al.* [109]), another induced change must take place. Recent results from [18] indicate that sleep also induces vasomotion in the brain. If we assume that sleep induces a general vasoconstriction trend, we can model this effect by reducing the radius of blood vessels, and hence, the PVS width increases. Therefore, porosity and permeability coefficients are adapted correspondingly (see Appendix A). This leads to an enhanced CSF movement in all structures (e.g. an increase of ~~350~~305% of fluid volume from the PVS of arteries to the ECS) and affects the clearance of ^{14}C -inulin. The clearance curves shown in Fig 6 clearly reveal that the clearance is ~~faster-slower~~ for the scenario in which PVS ~~porosities are increased~~. ~~Furthermore permeabilities are increased with a magnitude associated with sleep. When the permeability is further increased, our sensitivity analysis revealed a nonlinear effect, and faster clearance is observed. This indicates that the vasomotion of arteries only could contribute positively to clearance, and that a multi-compartment system such as the brain may involve complex, non intuitive interaction between compartments. However, it is worth mentioning to obtain similar results as the ones obtained in that even when varying key parameters such as~~

ECS, periarterial and pericapillary permeability with orders of magnitude we did not obtained rate constants as observed by Xie *et al.* [109] for ^{14}C -inulin clearance for in sleeping animals (45% clearance after 4 hours), we would need to increase only the porosity of the PVSs in an unrealistic way. Therefore, our results for the 4-compartment rate constant of $\sim 0.015/\text{min}$. These results indicate that the improvement of clearance due to sleep does not seem to be explained only by an increase of the porosity coefficients in the ECS and PVSs.

Fluid leakage from the blood vessels improve ^{14}C -inulin clearance and make the peri-arterial-periarterial space an outflow route Using biologically relevant parameter values, our results indicate that if the effect of leakage from the blood vessels is taken into account, the flow of CSF in the ECS and PVS of arteries is reversed compared to the standard picture of the glymphatic theory. With the inclusion of blood vessels, the flow direction is in line with the proposed hypothesis by Cserr *et al.* [25]. Hence, the PVS arteries compartment becomes an outflow route in this case as observed in Fig 7a. Additionally, the flow is also reversed in the ECS compared to the 4-compartment model (as observed in Fig 7a-b). This leads to a faster clearance of ^{14}C -inulin as observed in Fig 7c. For the fluid velocities in all compartments are all increased in this case compared to the 4-compartment model case. We obtain a Péclet number of 4.1×10^{-2} , which still indicates that diffusion in the interstitial space is the dominant effect for transport. However, referring to Croci *et al.* [21], we emphasize that even a small increase in velocities in the ECS could lead to a significant change in transport that could explain our enhanced clearance for that case. The sensitivity analysis also revealed that increasing the diffusion coefficient has less effect on the 7-compartment model, suggesting that convection play more prominent role in this case. Indeed, for this third test case, the relative amount of ^{14}C -inulin decays exponentially with $\sim 52\%$ of relative ^{14}C -inulin mass after 6 hours. The shape for the clearance curve corresponds more to the sleeping animals' results from Xie *et al.* [109], however with standard parameters, the rate constant in our model was around 3-4 times lower than the rate constant observed experimentally. However, the sensitivity analysis revealed that increased blood filtration (by a factor around 100) in the 7-compartment model gave a rate constant of $\sim 0.014/\text{min}$. Therefore, combining our results from the 4- and 7-compartment models seem to indicate that the transfer of fluid between blood vessels and PVSs and ECS provide a great potential to increase clearance during sleep. This could be related again to observed vasomotion of cerebral vessels during sleep [18].

Limitations and further works Our model is based on a homogenization procedure that represents the different structures (ECS, PVS, blood vessels) as a continuum. We know that porous media can be homogenized into a single continuous medium if the pores distance does not exceed a certain value. Usually, the derivation of the macroscopic model is assumed to be correct if the ratio between the length scale of the pores (in our case the distance between vessels) and the length scale of the chamber is less than one. In our model, this holds true for most compartments (see Shipley *et al.* [95] for homogenization related issues). However, we emphasize that this ratio is close to one for cerebral arterioles and venules. Therefore, our macroscopic continuous view of the glymphatic system and cerebral blood perfusion has to be viewed as a coarse approximation of the real phenomenon. This strong modelling assumption could be relaxed by considering a 1D-3D model (see *e.g.* [27]) in which the ECS only is represented as a continuous medium only the ECS and capillaries are represented as continuous media while the other structures are modelled by 1D lines. This one-dimensional curves within the domain.

1D-3D models provide a more detailed description of the pressure-field and solute transport. However, this type of model can describe more accurately the glymphatic system and the cerebral vascular tree but is too requires very high resolution meshes with cell sizes on the scale of the radius of the blood vessels to properly model fluid and solute exchange between tissue and the 1D structures [37]. It is therefore currently too computationally costly to be used at the scale of the total brain. However whole brain. Nevertheless, some of the observations and assumptions

from this present work could be tested and verified more accurately with such a 1D-3D model. The comparison between these two types of models will be the subject of a future work.

In our article, the clearance of solutes from the CSF in the SAS is taken into account using a simplified boundary condition. Indeed, we assumed that once the solute reaches the SAS it diffuses instantaneously within the CSF in this region. We plan to derive more rigorously these boundary conditions in a future work ~~by first modelling to first model~~ fluid movement inside a three dimensional subarachnoid space and then ~~seeking to seek~~ effective boundary conditions while studying the asymptotic limit of zero width for the subarachnoid space.

Furthermore, due to the complexity induced by the modelling of the different compartments and exchange between them, there are 8 coefficients per compartment (some of them might be shared between two compartments, for example for the exchange through a shared membrane). Some measurements of these parameters exist, however sometimes in different species (rats versus humans), and we have to the best of our ability translated parameters to reflect rat physiology. In addition, the measured values may suffer from experimental uncertainties. ~~This can be clearly seen if we take for the example the permeability of~~ The present model could also be used to investigate phenomena with continuous production and clearance of substances that are naturally produced in the brain [64, 12]. However, for this application additional parameters would be needed, and given the already complex parameter space, this addition were therefore not considered in the present study.

To study uncertainties about parameter values, we performed a sensitivity analysis. However, inverse modelling may also be used to find parameter values numerically. Optimization techniques have been previously used to estimate parameters in the context of the glymphatic system [104]. To optimize parameters, PDE constrained optimization techniques (see e.g. [99] about inverse problems and [5] for PDE-constrained optimization) have to be applied to our model to minimize the error between the output of our model and results from experiments. Two main difficulties arise in our case. First, the ECS κ_e . We can find in the literature very different values for this coefficient as previously mentioned by Holter *et al.* [43]. This illustrates the uncertainty concerning the ECS permeability value on which many of the other permeabilities are based (see Appendix A). Furthermore, understanding the effect of small variations of all parameter values on the results is out of scope of the present study. Sensitivity analysis for some of the important parameters will be dimension of the subject of a forthcoming work. inverse problem (the number of parameters to optimize) is very large but based on our sensitivity analysis and on experimental works, some of them can be fixed and, hence, decrease the computational cost of the optimization by reducing the dimension. The second issue comes with experimental data and whether sufficient data is available to perform parameter optimization on our model.

In our study, we made some variations of parameter values to model ~~possible increase of a possible increase in~~ ECS or PVSs volumes. The enhancement of ECS volume is reported in [109]. However, the increase of PVSs volume has been measured recently in [18] and does not appear to be ~~a fixed parameter fixed~~ but rather a ~~time dependent time dependent~~ value. Indeed, oscillations, vasoconstrictions and vasodilatations may occur over a few minutes (see Fig 2d in [18]). If the effect of these oscillations in porosity were accounted for in our model, the equations would change drastically ($\phi(t)$ becomes a ~~time dependent time dependent~~ function and stays in the time derivative of both the concentration and pressure equations). Adding the effect in the system forces us to keep the time derivative in the pressure equation and solve ~~at each time step~~ a coupled system of equations at each time step for each compartment. This will increase ~~tremendously~~ the computational cost of the simulations tremendously.

The use of standard continuous finite elements for the discretization of the diffusion equation leads to the presence of small oscillations of the numerical solution. See e.g. [63] for details about this effect and some remarks about stabilization, which could be included in further works. However, we note that integrated quantities over large domains (e.g. the brain) ~~is are~~ not affected as small oscillations around zero concentration ~~evens even~~ out. In this work, we arranged the scale on the figures so that no negative values for the concentration appear visually.

Conclusion In this paper, we presented a multi-compartment model for fluid and solute transport with application to the glymphatic system of a rat brain. The model allows us to test the effect of different physiological changes (e.g. sleep) and assess different theories concerning fluid flow and transport in the brain. Unless blood filtration was added to the model, diffusion was the main driving force for transport. However, as our simulations show, only a small leakage from blood vessels increased clearance by an order of magnitude.

A Computing biologically relevant parameters

A.1 Permeability coefficients

In the present article ~~we mostly use another definition~~, we use a definition of the permeability coefficients that can be obtained from the resistance values given in [106]. Even though this work deals with a one-dimensional ~~latter work considers a one-dimensional~~ model, a relation between these 1D resistances ~~to and~~ 3D permeabilities can be found. Indeed, assuming that we have any a 1D line ~~is~~ embedded into a 3D cylinder of length L and ~~cross-sectional~~ cross-sectional area A , the volumetric flux in the 1D geometry is given by the Poiseuille equation

$$Q = \frac{1}{R} \Delta p,$$

where R is the resistance in the 1D geometry and Δp is the pressure difference between the two ends of the line. Then, if we assume that the flow in the 3D cylinder is given only by the flow in the line, Darcy's law gives the relation

$$Q = \frac{\kappa}{\mu} \frac{A}{L} \Delta p = \frac{1}{R} \Delta p,$$

where κ is the averaged permeability and μ is the dynamic viscosity. Altogether, we obtain

$$\kappa = \frac{\mu L}{R A}. \quad (20)$$

~~The coefficient~~ For all compartments, $\frac{L}{A}$ is ~~arbitrary because it depends on the choice of cylinder for the homogenization step~~ related to the length scale of the brain. Therefore, knowing the permeability of the ECS ~~for example~~, for example, from [43], ~~is enough to find the value of this coefficient and gives a direct relation and the resistance as computed by [106]~~, we obtain a constant relationship between R_j and κ_j . ~~These resistance coefficients R for all compartments. Resistance coefficients R_j for the different compartments can be found in [106].~~ Choosing a permeability for the ECS of $\kappa_e = 2.0 \times 10^{-11} \text{ mm}^2$, a CSF dynamic viscosity of $\mu_e = 0.7 \times 10^{-3} \text{ Pa s}$, and the resistance coefficient $R_e = 4.56 (\text{Pa s})/\text{mm}^3$ indicated in [106] we have

$$\frac{L}{A} = 1.11.3 \times 10^{-7} \text{ mm}^{-1},$$

and we obtain the values for the permeability coefficients

$$\kappa_{pa} = 1.0 \times 10^{-11} \text{ mm}^2, \kappa_{pv} = 6.51 \times 10^{-9} \text{ mm}^2, \kappa_{pc} = 3.54 \times 10^{-13} \text{ mm}^2.$$

Then, from [31] and [49], as well as choosing a dynamic viscosity of blood $\mu_{\text{blood}} = 2.67 \times 10^{-3} \text{ Pa s}$ [103]

$$\kappa_a = 3.30 \times 10^{-6} \text{ mm}^2, \kappa_v = 6.59 \times 10^{-6} \text{ mm}^2, \kappa_c = 1.148.8 \times 10^{-9 \text{ mm}^2 - 9} \text{ mm}^2.$$

~~However~~, It is worth mentioning that in previous works, related to multi-compartment modelling of the glymphatic system, several authors evaluated these coefficients through numerical ~~testings~~ testing, leading to very different values. Indeed, from [103, 39, 32] in which the

MPET equations are used to represent the movement of CSF through different compartments in the brain, permeabilities are

$$\kappa_a = \kappa_v = \kappa_c = \kappa_{pa} = \kappa_{pv} = \kappa_{pc} = 1.0 \times 10^{-4} \text{ mm}^2, \text{ and } \kappa_e = 1.4 \times 10^{-8} \text{ mm}^2.$$

Therefore, we obtain a difference between these two parameter sets of several order-orders of magnitude, leading to tremendous differences in fluid movement.

A.2 Transfer coefficients

Following the Starling equation, the definition of the coefficients ~~is~~ for transfer between vessels and tissues is

$$\gamma_{i,j} = L_{i,j} \frac{|S_{i,j}|}{|\Omega|}, \quad (21)$$

where ~~L_{ij}~~ $L_{i,j}$ is the hydraulic conductivity of the membrane (in mm/(sPa)), $\frac{|S_{ij}|}{|\Omega|}$ ~~$\frac{|S_{i,j}|}{|\Omega|}$~~ is the ratio between the surface area of the vessel per unit of volume of tissue (in mm⁻¹).

We know the ratio $\frac{|S_{i,j}|}{|\Omega|}$, but we are missing the value of the hydraulic conductivity for some of the considered membranes. For the transfer from blood vessels to ECS, we can find the value of the hydraulic conductivity of the BBB at the different levels (*i.e.* arteries, capillaries and veins). ~~The~~ These values are reported in the main body of this article, in Section 2.

For the transfer coefficients between PVSs and the ECS, we use the following method. We search for a suitable relation between the 1D resistance parameters from [106] and the 3D exchange coefficients $\gamma_{j,i}$. In the following, we assume that the transfer coefficients for the PVSs to ECS are comparable between ~~human-to-rat~~ humans and rats.

Starting from the volumetric flow $Q_{j,i}$ through a 1D structure

$$Q_{j,i} = \frac{1}{R_{j,i}}(p_i - p_j),$$

where $R_{j,i}$ is the resistance through the structure and using the fact that this same volumetric flux in 3D is given by

$$Q_{j,i} = \int_{\Omega} \gamma_{j,i}(p_i - p_j) \, dx,$$

assuming that the pressure difference $(p_i - p_j)(x)$ is constant in space (which is not unreasonable since the transfer coefficient is homogeneous in space as well), we obtain the relation

$$\gamma_{j,i} = \frac{1}{R_{j,i} |\Omega|}.$$

We emphasize that since the resistance coefficients reported here are for human ~~humans~~, the volume $|\Omega|$ is the volume of the human brain, *i.e.* ~~$|\Omega| = 1 \times 10^{-6} \text{ mm}^3$~~ $|\Omega| = 1 \times 10^6 \text{ mm}^3$. Thus, from this equation, we can define the transfer coefficient in a different manner using only the 1D resistances estimated in [106] and the volume of our computational domain.

We apply the previously presented method to compute the exchange coefficients between PVSs and ECS. We obtain

$$\gamma_{pa,e} = 2.19 \times 10^{-7} (\text{Pa s})^{-1}, \gamma_{pv,e} = 1.95 \times 10^{-7} (\text{Pa s})^{-1}, \gamma_{pc,e} = \underline{9.989.19} \times 10^{\underline{-10-9}} (\text{Pa s})^{-1}.$$

For the exchange from blood vessels to ECS, we obtain

$$\gamma_{a,e} = \underline{5.732.73} \times 10^{-9} (\text{Pa s})^{-1}, \quad \gamma_{v,e} = \underline{1.266.00} \times 10^{\underline{-10-11}} (\text{Pa s})^{-1}, \quad \gamma_{c,e} = \underline{1.269.00} \times 10^{\underline{-9-10}} (\text{Pa s})^{-1}.$$

To compute the fluid exchange coefficients between blood vessels and PVSs, we compute the resistance of the ~~blood-brain-barrier~~ blood-brain-barrier at the different levels (*i.e.* arteries,

veins, capillaries) and subtract to it the resistance of the astrocyte end-feet barrier. We obtain the relation

$$R_{a,pa} = \frac{1}{\gamma_{e \leftarrow a} |\Omega|} \frac{1}{\gamma_{a,e} |\Omega|} - R_{pa,e}, \quad R_{a,pvv,pv} = \frac{1}{\gamma_{e \leftarrow v} |\Omega|} \frac{1}{\gamma_{v,e} |\Omega|} - R_{pv,e}.$$

Knowing these resistances and using the previous method, we can compute the coefficients

$$\gamma_{a,pa} = 5.892.76 \times 10^{-9} (\text{Pa s})^{-1}, \quad \gamma_{v,pv} = 1.266.00 \times 10^{-11} (\text{Pa s})^{-1}, \quad \gamma_{c,pc} = 9.98 \times 10^{-10} (\text{Pa s})^{-1}.$$

~~For the capillary level, we use the method from [92] to obtain the resistance of the BBB membrane in which we suppressed the AEF membrane. We obtain~~

$$\gamma_{c,pc} = 2.98 \times 10^{-9} (\text{Pa s})^{-1}.$$

Next, we need to specify the transfer coefficients for connected spaces, *e.g.* from arteries to capillaries. To do so, we use the equation

$$\gamma_{j,i} = \frac{Q}{|\Delta p_{i,j}|},$$

where Q is the flow rate of fluid (CSF or blood) and $\Delta p_{i,j}$ denotes the pressure drop from one compartment to the other. ~~Using a cerebral blood flow of $Q_{\text{blood}} = 700 \text{ mm}^3/\text{s}$, Using values~~

Name	Unit	Value	Reference
Cerebral blood flow (CBF)	mL/g/min	1.16	[57]
CSF production rate	$\mu\text{L}/\text{min}$	3.38	[20]
Mean arterial blood pressure (MAP)	mmHg	95	[26]
Pial venous pressure	mmHg	7	[65]
Pial arteriolar pressure	mmHg	56	[65, 13]

Table 7: Blood and CSF parameters

~~from Table 7 and using a value of 2.0 g for the weight of the brain (see [81]) as well as a pressure drop from arteries to capillaries of $\Delta p_{a,c} = 50 \text{ mmHg}$, and a pressure drop from capillaries to veins of $\Delta p_{a,c} = 10 \text{ mmHg}$, we obtain~~

$$\gamma_{a,c} = 1.053.14 \times 10^{-7-6} (\text{Pa s})^{-1}, \quad \gamma_{c,v} = 5.259.65 \times 10^{-7-6} (\text{Pa s})^{-1}.$$

Then, assuming a total flow rate of CSF through perivascular spaces of $Q_{\text{CSF}} = 3.33 \text{ mm}^3/\text{s}$ ~~(which corresponds to CSF production rate, see [51], and clearly represents an upper estimate of the actual flow in the PVS)~~, and a pressure drop from PVS arteries to PVS capillaries of $\Delta p_{pa,pc} = 1 \text{ mmHg}$, and a pressure drop from PVS capillaries to PVS veins of $\Delta p_{pa,pc} = 0.25 \text{ mmHg}$ ~~(both of these latter values are assumed to be correct but we emphasize that we could not find any measurement in the literature)~~, we obtain

$$\gamma_{pa,pc} = 2.501.83 \times 10^{-8-7} (\text{Pa s})^{-1}, \quad \gamma_{c,vpc,pv} = 1.007.31 \times 10^{-7} (\text{Pa s})^{-1}.$$

The coefficients $\tilde{\gamma}_{j,i}$ are given by the value of the reflection coefficient $\sigma_{\text{reflect},ij}$ and the equation

$$\tilde{\gamma}_{j,i}^{14\text{C-inulin}} = \gamma_{j,i} (1 - \sigma_{\text{reflect},ij}^{14\text{C-inulin}}). \quad (22)$$

We also define the hydraulic permeability of the fluid at the pial surface to define the Robin boundary conditions. Therefore, we search the 3D coefficients $\gamma_{i,j}$ using the previous method.

and we then compute the hydraulic conductivity L_{ij} that we can use in the definition of the boundary conditions. We assume that the boundary permeability for the ECS compartment is given by a resistance coefficient that we assume to be twice larger than the resistance coefficient of the PVS of arteries, *i.e.* $R_{e,SAS} = 2 \times R_{pa}$ (we emphasize again that we could not find a measurement of this hydraulic conductivity at the pial surface of the brain). Then, using the relation

$$L_{i,j} = \frac{1}{R_{i,j} |S_{i,j}|},$$

where $|S_{i,j}|$ corresponds to the surface area of the pial membrane of the human brain ($\approx 1750 \times 10^2 \text{ mm}^2$), we obtain

$$L_{e,SAS} = 3.13 \times 10^{-7} \text{ mm/(Pasmm/(Pa s))}, \quad L_{pa,SAS} = 1.25 \times 10^{-6} \text{ mm/(Pas)mm/(Pa s)}.$$

The next coefficient to define is $\lambda_{i,j}$ for the mass transfer of the solute. Following the definition of diffusive mass transfer, we know that

$$\lambda_{i,j} = P_{i,j} \frac{A_{\text{vessel}}}{V_{\text{tissue}}}, \quad (23)$$

where $P_{i,j}$ is the permeability (in mm/s) between the two compartments.

The diffusive permeabilities are computed using the method from [61], namely for the permeability to the molecule $\alpha = {}^{14}\text{C}$ -inulin, we have

$$P^\alpha = \frac{1}{\pi D_v} \sum_{r \in F} \frac{1}{R_r^\alpha},$$

where D_v corresponds to the diameter of the considered vessel ($10 \times 10^{-3} \text{ mm}$ for capillaries [34], 50×10^{-3} for arterioles and venules [70, 71]), F is the set of index-index set corresponding to the different layers of the membrane for which we compute the permeability, R_r^α is the resistances to solute transport for the different layers. For the AEF barrier, the only layer to cross is the astrocyte endfeet processes. We have the definition of the resistance

$$R_{\text{AEF}} = \frac{L_{\text{AEF}}}{2B_{\text{AEF}}D_{\text{AEF}}^\alpha},$$

where L_{AEF} is the width of the membrane, $2B_{\text{AEF}}$ is the width between two astrocyte endfeet (at the perivenous and periarterial level, we take $B_{\text{AEF}} = 250 \text{ nm}$ and at the pericapillary level, we take $B_{\text{AEF}} = 25 \text{ nm}$), and D_{AEF}^α is the diffusion coefficient in this same cleft. Assuming that the cleft has a cylindrical shape, the latter parameter is assumed to be given from the relation [67]

$$\begin{cases} D_{\text{AEF}}^\alpha = D_{\text{free}}^\alpha (1 - 2.10444\beta + 2.08877\beta^3 - 0.094813\beta^5 - 1.372\beta^6), \\ \beta = \frac{a^\alpha}{B_{\text{AEF}}}, \end{cases}$$

in which a^α is the solute radius. The Stokes radius of inulin is indicated to be $a^{\text{Inulin}} = 15.2 \times 10^{-7} \text{ mm}$ in [91].

The permeabilities are computed from the method in [61]. For, we have Finally, we obtain

$$\lambda_{pa,e}^{14\text{C-inulin}} = 5.983.70 \times 10^{-5-3} \text{ s}^{-1}, \quad \lambda_{pv,e}^{14\text{C-inulin}} = 5.973.72 \times 10^{-5-3} \text{ s}^{-1}, \quad \lambda_{pc,e}^{14\text{C-inulin}} = 3.633.70 \times 10^{-5-3} \text{ s}^{-1}.$$

A.3 Variations of PVS porosities

In our article, we assumed some variations of the PVSs volume. Using the resistance formula provided in [106] which gives

$$R \propto \frac{1}{r_1^4},$$

where r_1 is the inner radius of the PVS. Thus, with our equation for the permeability coefficient (20), we obtain the proportionality relation

$$\kappa_j \propto r_1^4.$$

Furthermore, assuming that the PVSs are just holed cylinders, the change of volume is proportional to the change in r_1^2 . Therefore, from the two previous proportionality relations, we obtain ~~the that~~ multiplying the volume of the PVS by a constant C results in multiplying the permeability by the square of this constant.

B ~~Varying Mesh Resolution and Time Steps~~Sensitivity analysis

Figure 8: ~~Sensitivity analysis of the 4-compartment model. Each curve represents a change in the parameter of a given factor. The largest effects were seen in changes in the periarterial permeability, the diffusion coefficient and the periarterial porosity.~~

Figure 9: ~~Sensitivity analysis of the 7-compartment model. Each curve represents a change in the parameter of a given factor. The undisputed greatest effect was seen in changes in the convective fluid transfer permeability between the periarterial and arterial networks.~~

C Numerical verification

C.1 Method of manufactured solutions

To ensure the correctness of the implemented numerical solver, we use the method of manufactured solutions. Consider the square $\Omega = [-1, 1]^2$, and define the functions

$$p_j(x, y) = a_j \cos(\pi x/2) \cos(\pi y/2) + p_j^0, \quad c_j(x, y, t) = b_j(1 - t/T)(x^2 + y^2) + c_j^0 \quad (24)$$

for $j \in \{e, pa, pc, pv\}$, where a_j, b_j, p_j^0 and c_j^0 are some predetermined constants and T is the end time of the simulations. For these functions to be valid solutions, we need to augment each of the modelling equations by an additional source term, chosen such that the functions defined in (24) solve the problem. Since the model with the additional source terms defines a more general form of our original problem, then a solution algorithm for the multi-compartment model *with* sources should be able to solve the problem *without* the source terms as well (which is equivalent to setting each of the sources to f_j).

Fig 10 plots the errors of the numerically obtained solutions compared to the analytically correct solutions defined in (24) for varying mesh resolution. Denoting by $V = H^1(\Omega)^{|J|}$, where $|J| = 4$ is the number of compartments in the model, the error for the pressure equations is measured in the norm

$$\|u\|_V = \sqrt{\sum_j \|u_j\|_{H^1(\Omega)}^2}, \quad (25)$$

The time-dependent concentration equations error for they are measured in the following approximate Bochner-space norm,

$$\|u\|_{L^2([0, T], V)} = \sqrt{\int_0^T \|u(t)\|_V^2 dt} \approx \sqrt{\sum_{n=0}^{N-1} \frac{\Delta t}{2} (\|u^n\|_V^2 + \|u^{n+1}\|_V^2)}, \quad (26)$$

where u^n , $n = 0, \dots, N$ is the numerical solution at time t_n .

Figure 10: Error of the numerical solution for varying mesh resolution, supplemented by a dashed black line indicating the expected convergence rate. a) Convergence plot for the pressure equation. The error converges quadratically with respect to cell size, measured in the norm defined in (25). b) Convergence plot for the concentration equation. The error converges linearly with respect to cell size, measured in the Bochner-space norm (26).

As shown in Fig 10a, the solver for the pressure equations exhibits quadratic convergence with respect to the largest cell size h_{\max} , as expected from the Bramble-Hilbert lemma applied to piecewise linear elements on a shape-regular triangulation [19, p. 79 Theorem 6.4]. Similarly, figure 10b shows a linear error convergence with respect to the cell size, as expected from e.g. [85, Theorem 5.1 p. 134].

These results verify the correctness of the implemented numerical solver and that the baseline parameters do not introduce any significant numerical challenges. We can not, however, exclude that some numerical issues are introduced when going to the complex three-dimensional geometries of the brain. In Section C.2, we take some further steps to verify that the reported clearance curves behave as expected with regard to the mesh resolution.

C.2 Clearance curves under varying mesh resolution and time steps

~~This appendix illustrates the effect of the~~ This section investigates how the clearance curves for the entire rat brain are impacted by varying mesh resolution and the size of time steps ~~on the results of the simulations presented throughout this paper used in the simulations~~. Following the procedure from Section 2.6, we create different meshes of varying resolution. The smallest and largest cell size corresponding to each of the resolutions are listed in Table 8. For each of

Resolution	h_{\min}	h_{\max}
16	0.265	2.374
32	0.154	1.190
64	0.073	0.622

Table 8: The smallest and largest cell size h of the mesh for different values of the resolution argument provided to SVMTK.

these meshes, we simulate a pure diffusion model to investigate the impact of mesh resolution on different tracer measurements of interest. Results can be found in Fig 11. We observe a slight difference between the clearance curves obtained from the mesh with resolution 16 and the mesh with resolution 32. However, the clearance curves obtained from the 64- and ~~the~~ 32-resolution mesh are virtually indistinguishable. We conclude that our scheme converges for the pure diffusion model and the mesh with resolution 32 produces accurate results.

Figure 11: The evolution of tracer measurements relative to the initial value, plotted for varying mesh resolution. The simulations were run for a pure diffusion model using the tracer decay model and a time step of 1 minute. a) Relative mass within the entire brain. b) Relative mass within a cube with side lengths of 2mm. c) Relative concentration at the injection point.

Similarly, we investigate the impact of varying the time step sizes on the clearance curves. The results are shown in ~~in~~ Fig 12 and illustrate that a time step of $\delta t = 60$ seconds, ~~as used in our simulations,~~ is sufficiently accurate.

Next, we plot the clearance curves for the 7-compartment model for both varying mesh resolutions and time step size in Fig 13. The behaviour for the full model is similar to the pure diffusion model ~~and indicate~~ and indicates that further refining the mesh or reducing the time steps will have minimal impact on the clearance curves, especially if we compare it to the uncertainty in other parameters.

Figure 12: The evolution of tracer measurements relative to the initial value in the pure diffusion model, plotted for varying time step sizes. The simulations were done using the tracer decay model and a mesh with resolution 32. a) Relative mass within the entire brain. b) Relative mass within a cube with side lengths of 2mm. c) Relative concentration at the injection point.

Figure 13: The evolution of total tracer mass relative to the initial value in the 7-compartment model, plotted for a) varying mesh resolution (with a timestep of 60s) and b) varying time step sizes (with mesh resolution 32).

Finally, we study the convergence properties of the numerical method for solving ~~the~~ pressure equations. We use the solution of the 64-resolution mesh as a reference solution and compute the L^2 and H^1 error norm with the solutions for the different mesh refinement levels. We obtain the results stated in Table 9 for second-order Lagrange polynomials.

Resolution	L^2 -error norm	order	H^1 -error norm	order
8	748		2302	
16	404	0.89	1659	0.47
32	82	2.29	851	0.96

Table 9: Computed L^2 and H^1 error norms and convergence orders for our numerical method to solve the pressure equation of the multi-compartment model using ~~second-order~~ second-order Lagrange elements