Probabilistic Quantification of Glymphatic Transport: A Bayesian Inverse Modeling Framework Applied to the Gonzo Dataset

Henrik Finsberg[1], **Matteo Croci** [2], **Thomas M. Surowiec**[3, 4], **Marie E. Rognes**[3]

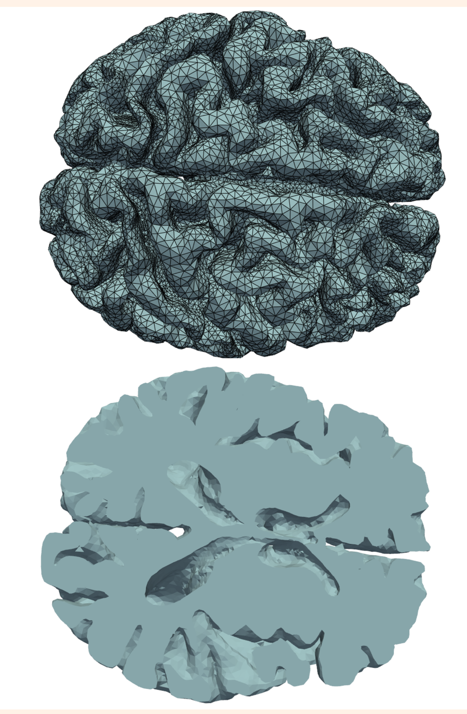
[1]Department of Computational Physiology, Simula Research Laboratory, 0164 Oslo, Norway
[2] Basque Center for Applied Mathematics (BCAM), Bilbao, Spain
[3]Department of Numerical Analysis and Scientific Computing, Simula Research Laboratory, 0164 Oslo, Norway
[4]SURE-AI: The Norwegian Centre for Sustainable, Risk-averse and Ethical AI, Simula Research Laboratory, 0164 Oslo, Norway

Introduction

The clearance of metabolic waste, such as amyloid-β, is central to understanding neurodegenerative pathology. The glymphatic theory [1] challenges traditional diffusion models by proposing advective clearance, yet verifying this via MRI remains a severely ill-posed inverse problem. Deterministic models often fail to distinguish between bulk flow and enhanced diffusion [2]. To resolve this, we adapt a scalable Bayesian inversion methodology [3] applied to the "Gonzo" dataset [4]. By formulating the problem probabilistically, we quantify posterior distributions for diffusion, advection, and reaction parameters. This approach moves beyond a simple "best fit" to explicitly map the landscape of uncertainty, identifying regions where physiology is mathematically distinguishable from epistemic uncertainty.

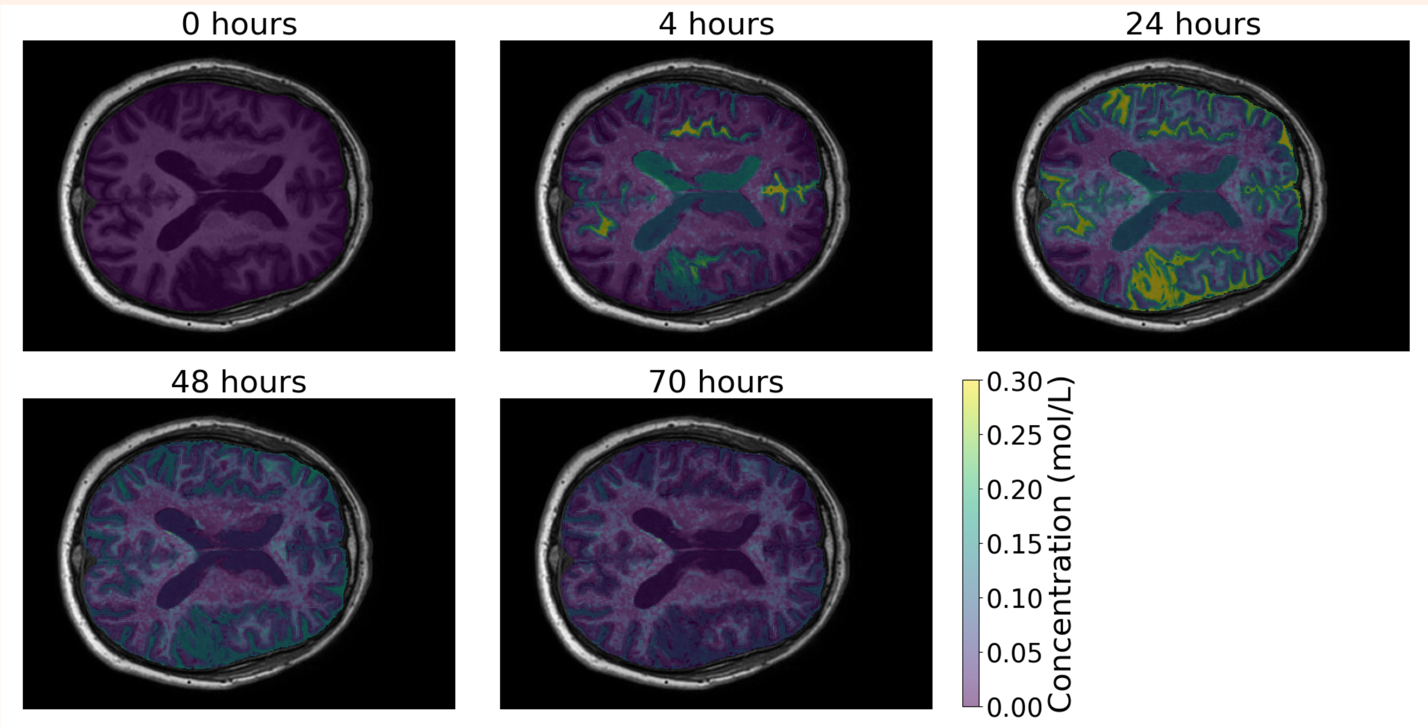
The Gonzo dataset

To showcase the methodology we will use the "Gonzo" dataset, released by Riseth et al. (2025)[4].

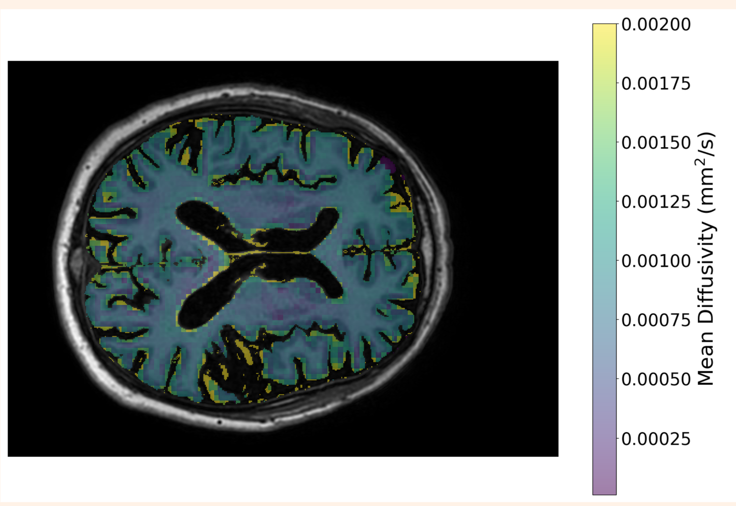


◁ **Figure:** Showing the mesh with a total of 99 755 vertices and 492 359 cells. Right panel shows the complete mesh with the edges of the tetrahedrons highligthed, while the left panel shows a clipped mesh where we see the fluid filled ventricles.

The dataset provides a comprehensive 72-hour record of tracer evolution in a single healthy volunteer, including unstructured triangulated volume meshes derived from T1-weighted imaging, tracer concentration maps derived from T_1 relaxometry at 0, 4, 24, 48, and 70 hours and full tensor maps, derived from DTI enabling the construction of anisotropic diffusion coefficients ($\mathbf{D}^*$).



△ **Figure:** Showing slices of 3D MRI images from that Gonzo dataset after 0, 4, 24, 48 and 70 hours after tracer injection. The colormaps shows the amount of tracer concentration within a given voxel.



◁ **Figure:** Shows the mean diffusivity tensor derived from diffusion tensor imaging (DTI), which is used in the diffusion term to account for known anisotropy ($\mathbf{D}^*(\mathbf{x})$). The mean diffusivity (MD) values for white matter and gray matter are found to be 0.77 ± 0.17 μm^2/s and $1.05\pm0.17\mu$m^2/s respectively

Forward modeling

We model the tracer concentration $c(\mathbf{x}, t)$ using the Advection-Diffusion-Reaction PDE on the domain Ω (brain parenchyma):

$$\frac{\partial c}{\partial t} + \underbrace{\nabla \cdot (c\phi)}_{\text{Advection}} - \underbrace{\nabla \cdot (\alpha \mathbf{D}^* \nabla c)}_{\text{Enhanced Diffusion}} + \underbrace{rc}_{\text{Clearance}} = 0, \quad \mathbf{x} \in \Omega \tag{1}$$

where:

- $\mathbf{D}^*(\mathbf{x})$: Anisotropic diffusion tensor derived from DTI (Gonzo dataset).
- $\alpha(\mathbf{x})$: Scalar diffusion enhancement field (unknown).
- $\phi(\mathbf{x})$: Advective velocity vector field (unknown). Assumed to be divergence free ($\nabla \cdot \phi = 0$)
- $r(\mathbf{x})$: Local clearance rate field (unknown).

Initial Conditions: $c(\mathbf{x}, t) = 0$
Boundary Conditions: Dirichlet conditions

$$c(\mathbf{x}, t) = g(\mathbf{x}, t), \quad \mathbf{x} \in \partial\Omega \tag{2}$$

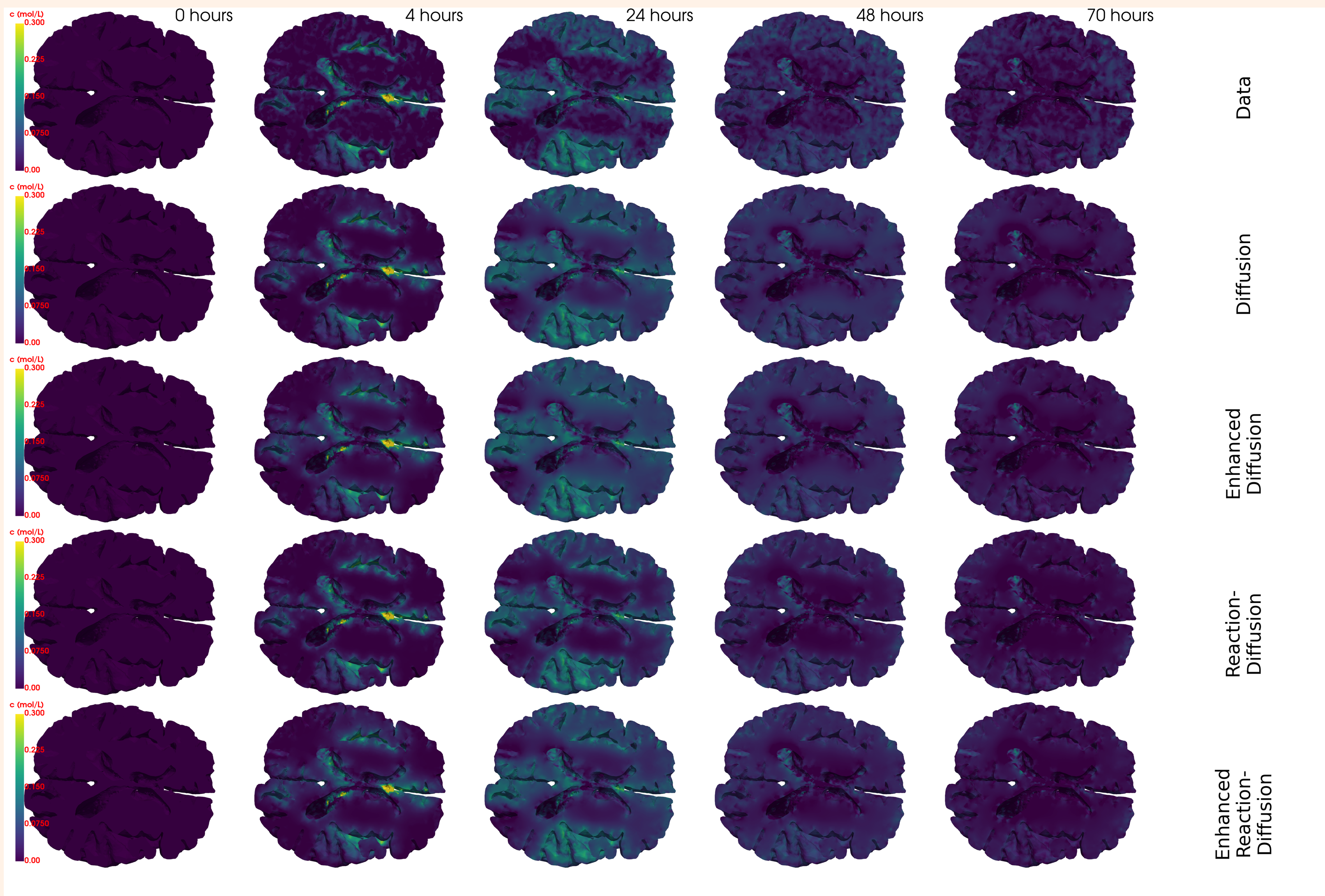
where $g(\mathbf{x}, t)$ is taken from the concentration maps from [1].
The problem is discretized with linear Lagrange elements in space and a Crank-Nicolson scheme in time. The problem reads find $c^{n+1} \in H^1(\Omega)$ (subject to BCs) such that

$$\frac{c^{n+1} - c^n}{\Delta t} + \phi \cdot \nabla c^{n+1/2} - \nabla \cdot (\alpha \mathbf{D}^* \nabla c^{n+1/2}) + rc^{n+1/2} = 0. \tag{3}$$

with $c^0 = 0$

Example forward simulations

We perform some initial simulations with pure diffusion ($\phi = 0$ and $r = 0$) different scalar diffusion enhancement ($\alpha = 1$ and $\alpha = 3.5$), which is based on values from [2]. Similarly we perform some initial simulations with the reaction term turned on also using vales from [2], i.e with $r = 31 \times 10^{-4}$ min^{-1}. All simulations are done using a time step of 15 minutes. The results are shown in the figure below



△ **Figure:** Top row shows the concentration data interpolated onto the mesh. Second, third, forth and fifth row shows respectively the simulations using pure diffusion ($\alpha = 1, r = 0$), enhanced diffusion $\alpha = 3.5, r = 0$, reaction-diffusion ($\alpha = 1, r = 31 \times 10^{-4}$ min^{-1}) and enhanced reaction diffusion ($\alpha = 3.5, r = 31 \times 10^{-4}$ min^{-1}).

Bayesian inverse modelling

We observe tracer concentrations $\mathbf{d} \in \mathbb{R}^{n_d \times n_t}$ across n_d voxels and $n_t = 5$ scans. Following [3], we seek the posterior distribution of the uncertain parameters $m \in \mathcal{M}$ (representing α, ϕ, r) via Bayes' theorem:

$$\frac{d\nu_{\text{post}}}{d\nu_{\text{prior}}} \propto \pi_{\text{like}}(\mathbf{d}|m). \tag{4}$$

Assuming additive Gaussian noise $d = \mathcal{F}(m) + \eta$, where $\mathcal{F}$ maps parameters to observables via the PDE, the likelihood is:

$$\pi_{\text{like}}(\mathbf{d}|m) \propto \exp\left\{-\sum_{i=1}^{n_t} \frac{1}{2} \|\mathcal{F}_i(m) - d_i\|^2_{\Gamma^{-1}_{\text{noise}}}\right\}. \tag{5}$$

We assign Gaussian Random Field (GRF) priors $m \sim \mathcal{N}(m_{pr}, \mathcal{C}_{pr})$, with covariance defined by the differential operator [5]:

$$\mathcal{C}_{pr} \equiv \mathcal{A}^{-2} = (-\gamma\Delta + \delta I)^{-2}. \tag{6}$$

Combining these yields the posterior $\nu_{\text{post}}(m|\mathbf{d})$. We employ a **Low-Rank Laplace Approximation**, $\nu^{LA}_{\text{post}} \propto \mathcal{N}(m_{\text{MAP}}, \mathcal{C}_{\text{post}})$, where the MAP estimate is found via optimization:

$$m_{\text{MAP}} = \arg\min_{m \in \mathcal{M}} -\log \nu_{\text{post}}(m|\mathbf{d}), \tag{7}$$

and the covariance of the Laplace approximation is given by the inverse of the Hessian of the negative log-posterior.

$$\mathcal{C}_{\text{post}} = \mathcal{H}(m_{\text{MAP}})^{-1}. \tag{8}$$

To avoid the prohibitive inversion of the Hessian, we approximate $\mathcal{C}_{\text{post}}$ by solving the generalized eigenvalue problem for the data-misfit Hessian $\mathcal{H}_{\text{misfit}}$ relative to the prior precision:

$$\mathcal{H}_{\text{misfit}} v_i = \lambda_i \mathcal{C}_{pr}^{-1} v_i. \tag{9}$$

Finally, we construct the posterior covariance using the Woodbury identity, retaining only the k dominant eigenmodes:

$$\Gamma_{\text{post}} \approx \mathcal{C}_{pr} - \sum_{i=1}^{k} \frac{\lambda_i}{1 + \lambda_i} (v_i \otimes v_i). \tag{10}$$

References

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