UQ of parenchymal tracer distribution using random diffusion and convective velocity fields

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New Results

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Uncertainty quantification of parenchymal tracer distribution using random diffusion and convective velocity fields

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This article is a preprint and has not been peer-reviewed [what does this mean?].

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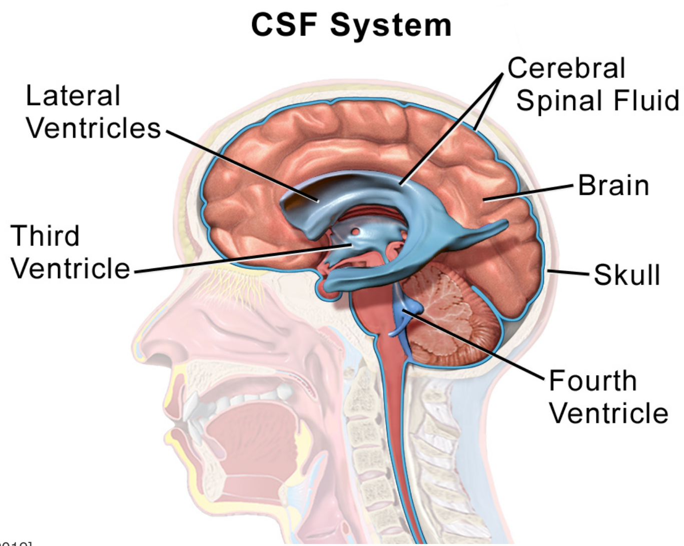
ABSTRACT

Background Influx and clearance of substances in the brain parenchyma occur by a combination of diffusion and convection, but the relative importance of thiese mechanisms is unclear. Accurate modeling of tracer distributions in the brain relies on parameters that are partially unknown and with literature values varying up to 7 orders of magnitude. In this work, we rigorously quantified the variability of tracer enhancement in the brain resulting from uncertainty in diffusion and convection model parameters.

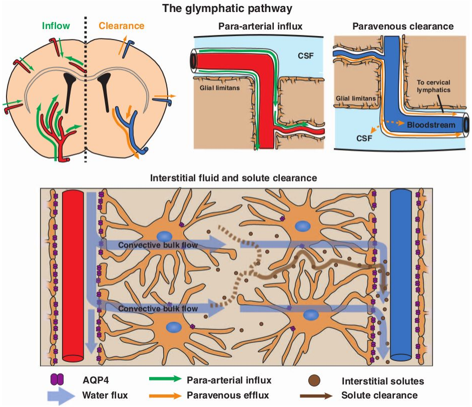
Introduction

The brain is surrounded by cerebrospinal fluid

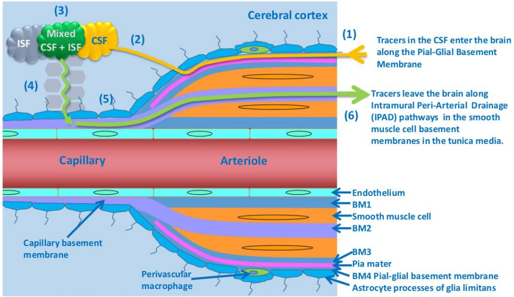


[Wikimedia Commons, 2019]

What are the modes of solute transport in the brain parenchyma?



Diffusion?
Convection?
Directionality?



Pathways for influx of CSF into the brain and drainage of CSF/ISF out of the brain along periarterial basement membranes

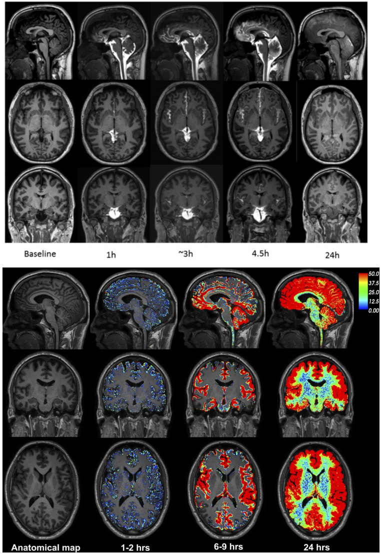
eLIFE elifesciences.org RESEARCH ARTICLE

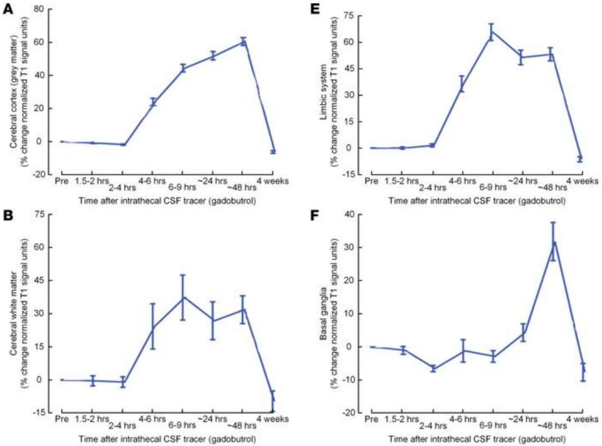
Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma

Alex J Smith[1,2]*, Xiaoming Yao[1,2], James A Dix[1,2], Byung-Ju Jin[1,2], Alan S Verkman[1,2]*

[Iliff et al (2012), Albargothy et al (2018), Smith et al (2018)]

CSF tracer distributes brain-wide and centripetally in humans





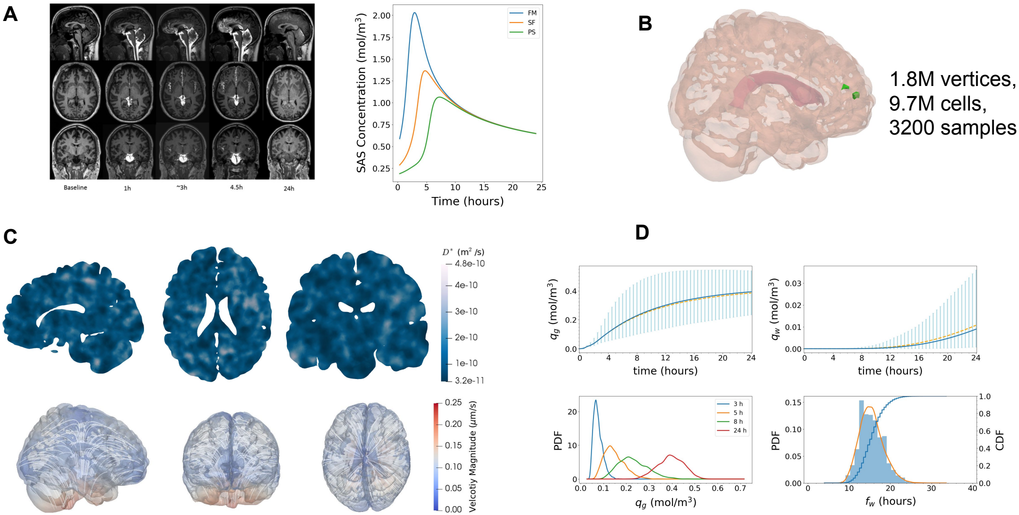
"... unlikely that diffusion alone explains brain-wide distribution."

[Ringstad et al (2017), Ringstad et al (2018)]

"Finally, an overarching need is to reduce uncertainty regarding the anatomy and fluid dynamic parameters characterizing the perivascular and paravascular spaces, which may vary among species and between genders."

[Carare, Sharp, and Martin, FBCNS, 2019]

5 convection-diffusion-reaction models with stochastic coefficients



[Croci et al (2019)]

Methods and Results

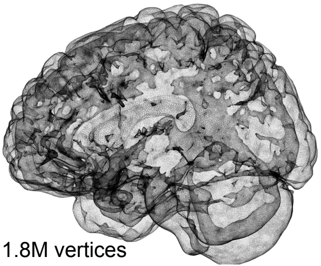
Tracer evolution modelled by a diffusion-convection-reaction equation

In the parenchyma

Find the solute concentration $c = c(t, x, \omega)$ such that

$$\partial_t c + \mathrm{div}(vc) - \mathrm{div}(D^* \nabla c) + rc = 0$$

for $x \in \mathcal{D}$, $\omega \in \Omega$ and $t \in (0, T)$ where $v = v(x, \omega)$ is a stochastic bulk velocity, $D^* = D^*(x, \omega)$ is a stochastic effective diffusion coefficient, and $r \leq 0$ is a drainage parameter.

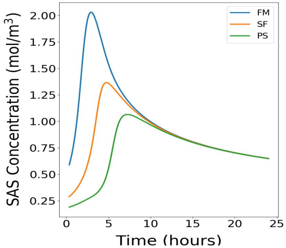


1.8M vertices
9.7M cells

Boundary conditions

Tracer spreads upwards through the SAS:

$$\begin{aligned} c &= c_{\mathrm{CSF}}(c)\, h(t, x_3) && \text{(SAS)} \\ D^* \nabla c \cdot n &= 0 && \text{(Ventricles)} \end{aligned}$$



Defining a stochastic velocity field representing the "glymphatic" pathway: modelling assumptions

ISF follows separate inflow and outflow routes: entering the brain along paraarterial spaces and exiting along paravenous spaces [Jessen et al, 2015].

1. The velocity field correlation length λ is comparable to the (mean) distance between arterioles and venules ($\lambda = 1.02$ mm).
2. Paraarterial or paravenous spaces are equally likely at any point in space. ($\mathbb{E}[v_{x/y/z}] = 0$.)
3. Conservation of mass ($\operatorname{div} v = 0$, $v \in C^1$).

To satisfy these stipulations, we define

$$v(x,\omega) = v_{\text{avg}}\, \eta(\lambda)\, 10^{-\mathcal{E}(\omega)} \left(\nabla \times [X(x,\omega), Y(x,\omega), Z(x,\omega)]^T\right), \tag{1}$$

such that $\mathbb{E}[\|v\|] = v_{\text{avg}} = 0.17\,\mu$m/s, allowing for $3\times$ larger and $10\times$ smaller values [Nicholson (2001)] with low probability, with X, Y, Z i.i.d Matérn fields, $\eta(\lambda)$ a scaling factor and $\mathcal{E}(\omega)$ an exponentially distributed random variable.

[Croci et al (2019)]

Numerical methods and implementation

To solve the convection-diffusion equation we used

1. Piecewise linear finite elements in space.
2. A second-order (implicit midpoint) finite difference discretization in time with $\Delta t = 15$ min. The Dirichlet boundary condition was handeled explicitly.
3. The Collins brain mesh consisting of 1 875 249 vertices and 9 742 384 cells.
4. An outer box of dimensions 0.16 x 0.21 x 0.17 (m^3) with mesh size 0.0023 m for sampling of the Gaussian fields

The solver was implemented in Python using FEniCS. We used the PETSc implementation of the GMRES algorithm preconditioned with the BoomerAMG algebraic multigrid algorithm from Hypre. Matplotlib and Paraview were used for visualization.

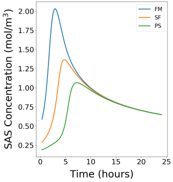
Tracer evolution after injection of 0.5 mmol of gadobutrol assuming constant effective diffusion and no bulk velocity

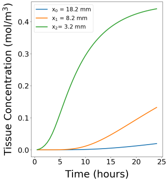
Model 0

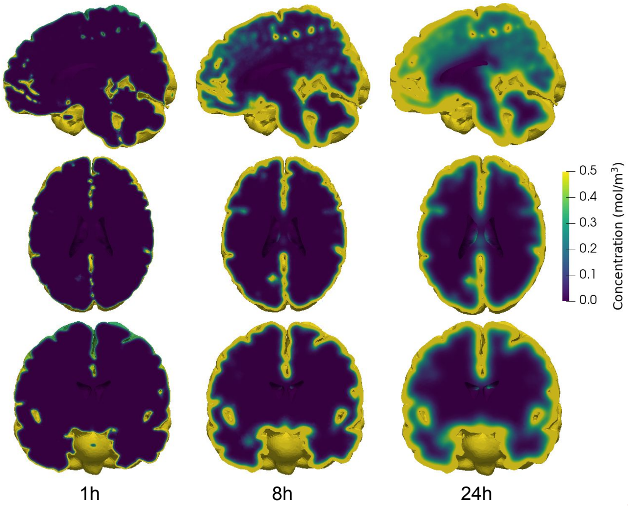
$D^* = D^*_{\mathrm{Gad}} = 1.2 \times 10^{-10}$ m/s^2,
$v = 0$, $r = 0$.

Key observations

In 24h, tracer has penetrated substantially into gray matter, but not into deep central regions.







Effects of input uncertainty can be quantified for measurable outputs

Amount in gray Q_g and white matter Q_w at time τ:

$$Q_{g/w}(\omega) = \int_{D_{g/w}} c(\tau, x, \omega)\,\mathrm{d}x$$

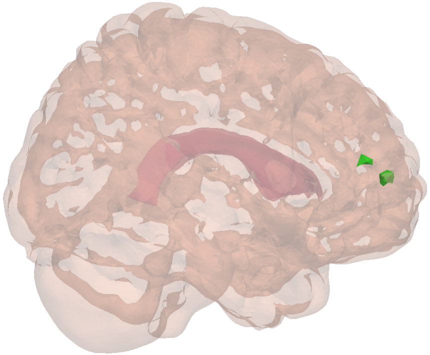
Average conc. in gray q_g and white q_w regions:

$$q_{g/w}(\omega) = \frac{1}{|S_{g/w}|} \int_{S_{g/w}} c(\tau, x, \omega)\,\mathrm{d}x,$$

White matter (F_w) and region (f_w) activation time:

$$F_w(\omega) = \{\min t \mid \int_{\Omega_w} c(t, x, \omega)\,\mathrm{d}x / n_0 > 10\%\},$$

$$f_w(\omega) = \{\min t \mid \frac{1}{|S_w|} \int_{S_w} c(t, x, \omega)\,\mathrm{d}x > 1\,\text{mmol/m}^3\}.$$



Sampling using Monte Carlo
($N = 3200$)

What do we expect from diffusion alone?

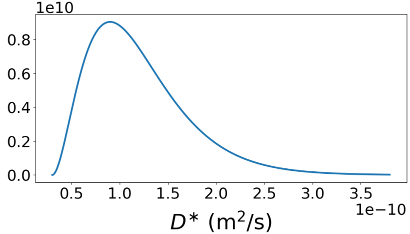
What is the effect of uncertainty in diffusion coefficient magnitude?

Model D1

Stochastic diffusion constant ($\mathbb{E}(D^*) = D^*_{\mathrm{Gad}}$):

$$D^*(\omega) = 0.25\, D^*_{\mathrm{Gad}} + D^*_{\gamma}(\omega).$$

$v = 0$, $r = 0$.



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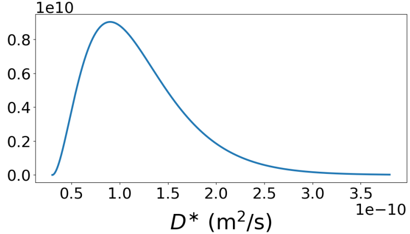
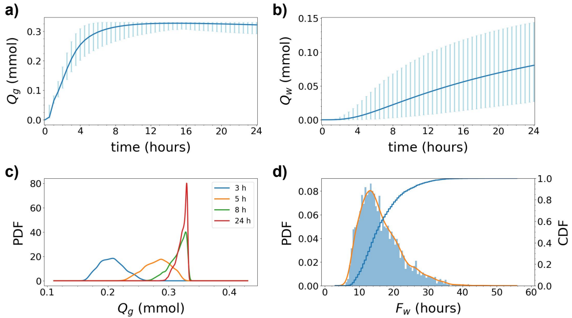




Key observations

- Expected amount in gray matter peaks around 15h
- Expected amount in white matter still increasing at 24h
- Substantial variation in all outputs

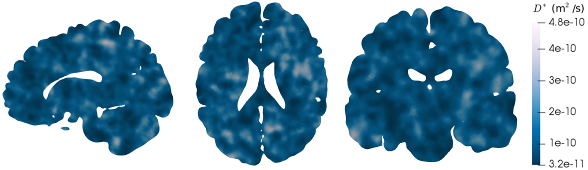
What is the effect of uncertainty in diffusion heterogeneity?

Model D2

Stochastic diffusion field:

$$D^*(x, \omega) = 0.25\, D^*_{\text{Gad}} + D^*_f(x, \omega),$$

$D^*_f(x, \omega)$ is Gamma-distributed with correlation length 1 cm. $v = 0$, $r = 0$.



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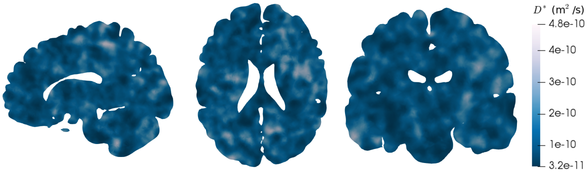
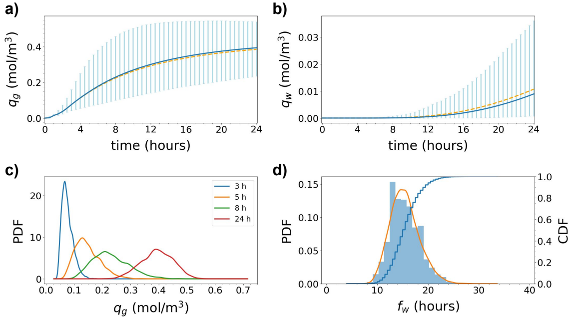




Key observations

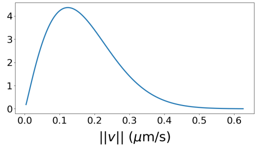
- Heterogeneity does not affect expected values
- Low variability in $Q_{g/w}$ (not shown)
- Variability in $q_{g/w}$: uncertainty in heterogeneity leads to range of likely tracer concentrations in smaller regions

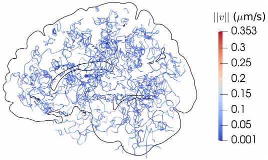
What about convection?

What is the effect of an (uncertain) "glymphatic" circulation?

Model V1

Stochastic velocity field $v(x, \omega)$ with $\mathbb{E}(\|v(x)\|) \approx 0.17\,\mu$m/s and , $D^* = D^*_{\mathrm{Gad}}$, $r = 0$.





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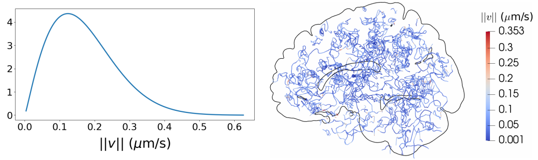
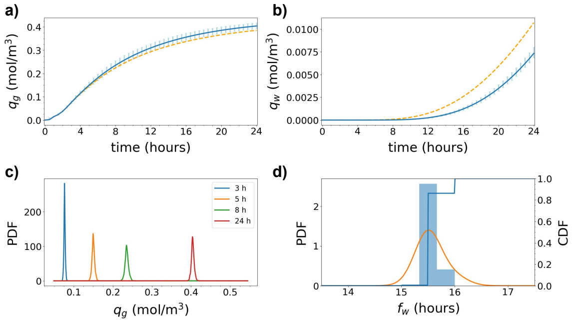
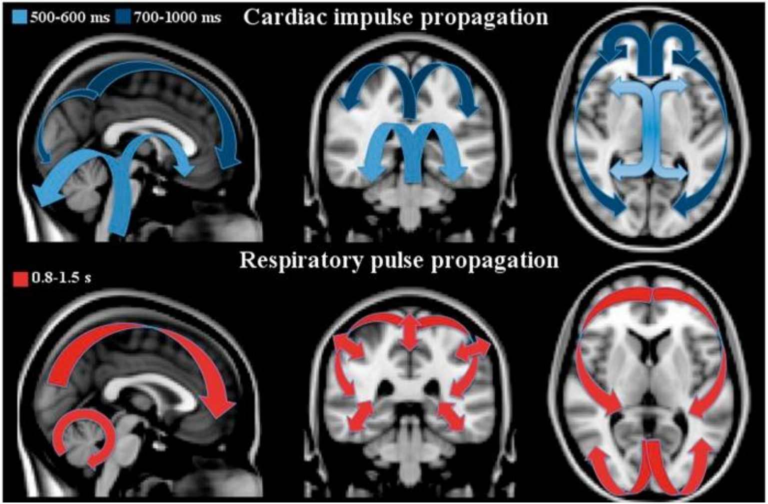




Key observations

- "Glymphatic" circulation does not enhance global tracer influx in gray or white compared to pure diffusion
- Variability very low in all outputs resulting in narrow sample ranges (compared to e.g. diffusion models)

Spatial directionality induced by cardiac impulse propagation?



[Kiviniemi et al (2016)]

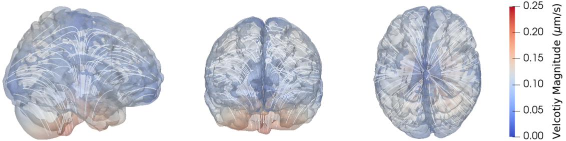
What is the effect of a "glymphatic" circulation with directionality?

Model V2

Additional global velocity field
representing induced pulse propagation

$$v(x, \omega) = v_{\mathrm{V1}}(x, \omega) + v_{\mathrm{dir}}(x)$$

$D^* = D^*_{\mathrm{Gad}}$, $r = 0$.



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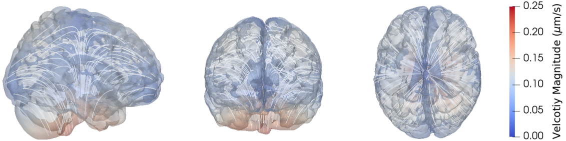
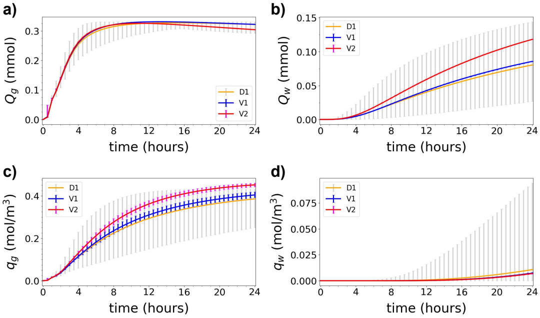




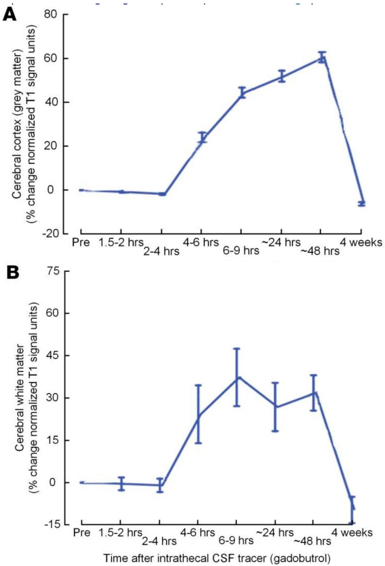
Key observations

- Expected amount of tracer in white matter increase (faster transport).
- Average tracer concentration in gray region larger than for diffusion (with very high confidence)

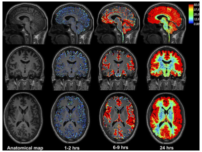
Discussion/Conclusion

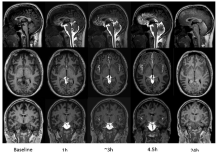
Comparison of time-to-peak enhancement with MRI studies

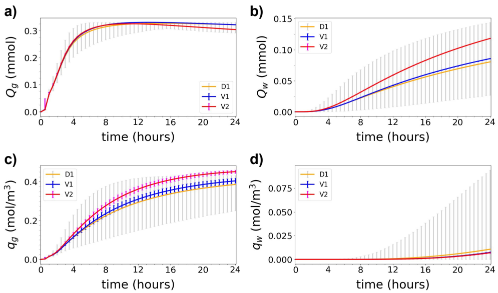
- Most of reported time-to-peak enhancement values in (Ringstad et al (2017, 2018)) are within the 99.73\% confidence interval of diffusion only.
- Clinical observations of shorter time-to-peak enhancement in white (vs gray) matter regions are not consistent with any of our computational models (!)
- Diffusion models do not seem to underestimate amount of tracer in gray matter at given times compared to clinical observations (?!)



Figures from Ringstad et al. (2017, 2018)







Summary of findings

Uncertainty in the diffusion parameters substantially impacted all output quantities.

Diffusion was not sufficient, with high likelihood, to transport tracer deep into the parenchyma

A glymphatic velocity did not increase transport into any region considered – unless augmented by an additional flow field with a prescribed directionality – in which case, transport was increased with overwhelming likelihood.

simula waterscales

The Research Council of Norway

erc European Research Council

Bonus material

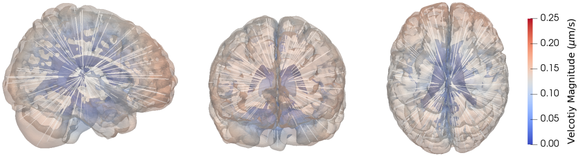
Alternative velocity model with capillary filtration

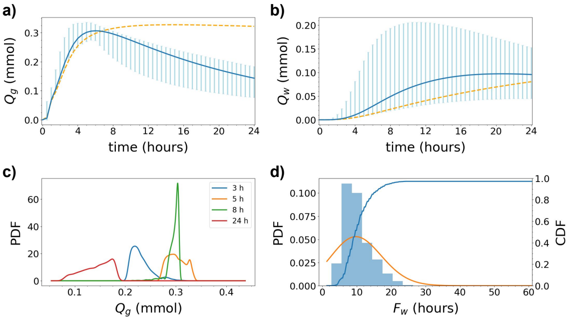
Model V3

Stochastic velocity field

$$v(x, \omega) = \bar{v}(\omega)\tilde{v}(x)$$

$$D^* = D^*_{\text{Gad}},\ r = -1 \times 10^{-5}\ \text{s}^{-1}.$$





Key observations

- Expected amount of tracer in gray and white matter peak within time frame (6-8 hs vs 19-22 hs)
- Substantial variability in amount of tracer in white (and gray) matter.