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# Diffusion MRI-Based Cytoarchitecture Measurements in Brain Gray Matter using Likelihood-Free Inference

Maeliss Jallais<sup>1</sup>, Pedro L. C. Rodrigues<sup>1</sup>, Alexandre Gramfort<sup>1</sup>, and Demian Wassermann<sup>1</sup>  
<sup>1</sup>Université Paris-Saclay, Inria, CEA, Palaiseau, France

## Synopsis

We propose a new method to solve the inverse problem of relating the diffusion MRI signal with cytoarchitectural characteristics in brain gray matter. Specifically, our method has quantitative sensitivity to soma density and volume. Our solution is twofold. First, we propose a new forward model that relates summary statistics of the dMRI signal with tissue parameters, relying on six b-shells only. We then apply a likelihood-free inference based algorithm to invert the proposed model, which not only estimates the tissue parameters that best describe the acquired diffusion signal, but also a full posterior distribution over the parameter space.

## Introduction

Effective characterisation of the brain grey matter cytoarchitecture with quantitative sensitivity to soma density and volume remains an unsolved challenge in diffusion MRI (dMRI). Current methods require demanding acquisitions and stabilise parameter fitting by enforcing constraints. Yet, these still encounter large indetermination areas in the solution space making the results unstable<sup>1</sup>. We propose a new forward model requiring only six relatively sparse b-shells and that avoids indeterminacies.

## Methods

**Modeling Brain Gray Matter with a 3-compartment Model.** We model grey matter tissue as three-compartmental<sup>2</sup>, moving away from the Standard Model designed for white matter. The acquired signal is considered as resulting from a convex mixture of signals arising from somas, neurites, and extra-cellular space (ECS), under a no-exchanges assumption<sup>2</sup>. Our direction-averaged grey matter signal model is then:

$$\frac{\bar{S}(q)}{S(0)} = f_n \bar{S}_{\text{neurites}}(q, D_a) + f_s \bar{S}_{\text{somas}}(q, D_s, r_s) + f_{\text{ECS}} \bar{S}_{\text{ECS}}(q, D_e), \text{ with } q(b) = \frac{1}{2\pi} \sqrt{\frac{b}{\tau}}$$

$f_n$ ,  $f_s$  and  $f_{\text{ECS}}$  represent neurites, somas and ECS signal fractions respectively ( $f_n + f_s + f_{\text{ECS}} = 1$ );  $D_a$  axial diffusivity inside neurites;  $D_s$  and  $D_e$  somas and extra-cellular diffusivities; and  $r_s$  the average soma radius. Neurites are modeled as 0-radius impermeable cylinders<sup>3</sup>:

$$\bar{S}_{\text{neurites}}(q) \simeq \frac{1}{4\sqrt{\pi\tau D_a}} \cdot q^{-1}$$

Somas are modeled as spheres and follow the GPD approximation<sup>4</sup>:

$$-\log \bar{S}_{\text{somas}}(q) = C(r_s, D_s) \cdot q^2 = q^2 \frac{2}{D_s \delta^2} \sum_{m=1}^{\infty} \frac{\alpha_m^{-4}}{\alpha_m^2 r_s^2 - 2} \cdot \left( 2\delta - \frac{2 + e^{-\alpha_m^2 D_s (\Delta - \delta)} - e^{-\alpha_m^2 D_s \delta} - e^{-\alpha_m^2 D_s \Delta} + e^{-\alpha_m^2 D_s (\Delta + \delta)}}{\alpha_m^2 D_s} \right)$$

We exploit this relation to extract a parameter  $C_s = C(r_s, D_s)[m^2]$  which, at fixed diffusivity  $D_s$  is modulated by the soma radius. The ECS is approximated as isotropic Gaussian diffusion:

$$-\log(\bar{S}_{\text{ECS}}(q)) = (2\pi q)^2 \tau D_e$$

**An Invertible 3-compartment Model: dMRI Summary Statistics.** Solving the inverse problem directly from Eq.1 leads to indeterminacies and bad parameter estimations. We therefore introduce rotationally invariant summary statistics to relate the dMRI signal to tissue parameters.

First, we compute a q-bounded RTOP, a direct measure of the restrictions of the diffusing fluid molecule motion<sup>5</sup>:

$$\text{RTOP}(q) = 4\pi \int_0^q \frac{\bar{S}(\eta)}{S(0)} \eta^2 d\eta$$

For q large enough,  $\text{RTOP}(q)$  on our 3-compartment model (Eq.1) becomes:

$$\text{RTOP}(q) = \underbrace{f_s \left( \frac{\pi}{C_s} \right)^{3/2} + \frac{f_{\text{ECS}}}{8(\pi\tau D_e)^{3/2}}}_{a_{\text{fit}}} + \underbrace{\frac{f_n}{2} \cdot \sqrt{\frac{\pi}{\tau D_a}}}_{b_{\text{fit}}} \cdot q^2$$

Three different q-values are needed to estimate  $a_{\text{fit}}$  and  $b_{\text{fit}}$ .

Secondly, we extended LEMONADE<sup>1</sup>, based on a moment decomposition for small q-values, to our 3-compartment model and extract four rotational invariant scalar indices that quantify grey matter microstructure:

$$\begin{cases} M^{(2),0} = f_n D_a + 3f_s \frac{C_s}{(2\pi)^2 \tau} + 3f_{\text{ECS}} D_e \\ M^{(2),2} = f_n D_a p_2 \\ M^{(4),0} = f_n D_a^2 + 5f_s \left( \frac{C_s}{(2\pi)^2 \tau} \right)^2 + 5f_{\text{ECS}} D_e^2 \\ M^{(4),2} = f_n D_a^2 p_2 \end{cases}$$

where  $p_2$  is a scalar measure of neurite orientation dispersion<sup>1</sup>. A minimum of three q-values with  $b(q) \approx 3\text{ms}/\mu\text{m}^2$  are required.

We assume  $D_e$  nearly-constant per subject acquisition and estimate it as the mean diffusivity in the subject's ventricles<sup>6</sup>. Combining equations 6 and 7 and adding the  $f_n + f_s + f_{\text{ECS}} = 1$  constraint, we obtain a system of 7 equations and 6 unknowns.

Solving the inverse problem via likelihood free inference. We invert our model using a Bayesian approach based on likelihood-free inference (LFI)<sup>7</sup>. Our algorithm produces an approximation of the full posterior distribution  $p(\theta | x_0)$  over the parameter space for a given observation  $x_0$ . This can be used to determine which parameter vector  $\theta=(D_a, C_s, p_2, f_s, f_n, f_{\text{ECS}})$  is the most likely to have produced  $x_0$  and the corresponding confidence intervals. Moreover, it describes in which regions of the parameter space the model presents indeterminacies. Our LFI procedure follows the setup from<sup>8</sup> and approximates the posterior distribution using normalizing flows (a special class of deep neural networks) trained over a set of repeated simulations from the forward model.

## Results and Discussion

**Simulations.** We validated the proposed method using LFI on neuron simulations from neuromorpho.org using dmipy<sup>9</sup>. We present on Fig.2 results for  $\theta=(1.7, 905, 0.5, 0.5, 0.3, 0.2)$ , which corresponds to spheres with a  $35\mu\text{m}$  diameter and  $2.3\mu\text{m}^2/\text{ms}$  diffusivity. Two acquisition setups have been considered, both with  $\delta/\Delta = 12.9/21.8\text{ms}$  and 128 b-shells with uniformly distributed directions. Setup  $\mathcal{A}$  corresponds to an "ideal" case with 10 b-values between 0 and  $10\text{ms}/\mu\text{m}^2$ . Setup  $\mathcal{B}$  reproduces the more challenging setup from the HCP MGH dataset<sup>10</sup>, with only 5 b-values: 0, 1, 3, 5, and  $10\text{ms}/\mu\text{m}^2$ . We interpolated an extra point at  $0.1\text{ms}/\mu\text{m}^2$  using MAPL<sup>11</sup> to improve moment estimation on the Spiked LEMONADE step. On Fig.3, we estimate the soma radius and diffusivity separately. LFI is unable to determine among all possible solutions which one is the ground truth, but using the parameter  $C_s$  instead of  $r_s$  and  $D_s$  enables to avoid model indeterminacy. A low standard deviation is also observed for signals generated in grey matter tissue conditions, where a soma predominance is expected (Fig.4).

**Experiments.** We applied the proposed method to the HCP MGH Adult Diffusion dataset<sup>10</sup>, whose acquisition is similar to setup  $\mathcal{B}$ .  $D_e$  was estimated as the mean diffusivity in the ventricles. Fig.5 presents the mean estimations across subjects, where overlay colormaps are masked showing only areas where parameters are stable, i.e. when their value was larger than 2 times the LFI-obtained standard deviation of the fitted posterior. Our figure assesses qualitatively the results on soma size by comparing with nissl-stained histological studies<sup>12,13,14</sup>. This qualitative comparison shows good agreement between different cortical areas and our parameter  $C_s$  which, under nearly-constant intra-soma diffusion  $D_s$ , is modulated by soma size.

## Conclusion

We presented a methodology based on Bayesian inference with modern tools from neural networks to estimate the tissue parameters and their full posterior distribution out of grey matter dMRI signals. This rich description provides many useful tools, such as assessing the quality of the parameter estimation or characterizing regions in the parameter space where it is harder to invert the model. Moreover, our proposal alleviates limitations from current methods by not requiring physiologically unrealistic constraints on the parameters and avoiding indeterminacies when estimating them.

## Acknowledgements

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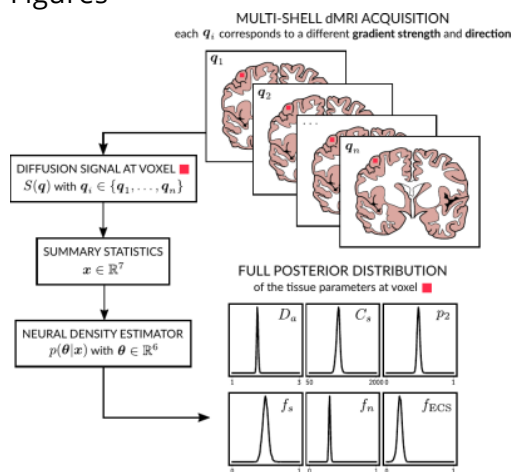
This work was supported by the ERC-StG NeuroLang grant number 757672 and the ANR/NSF NeuroRef grants.

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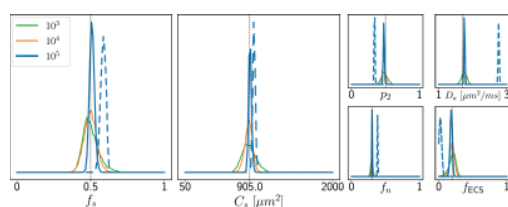
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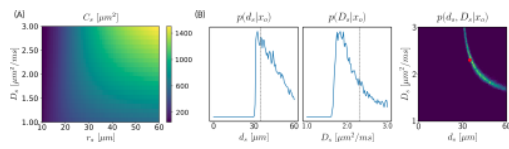
## Figures



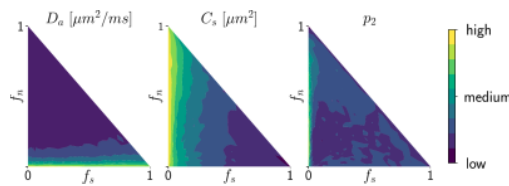
Visual abstract. On the top right we illustrate a multi-shell dMRI acquisition. Based on the proposed 3-compartment model, we then extract summary statistics from it. Applying a neural density estimator we can both estimate the tissue parameters and their full posterior distribution.



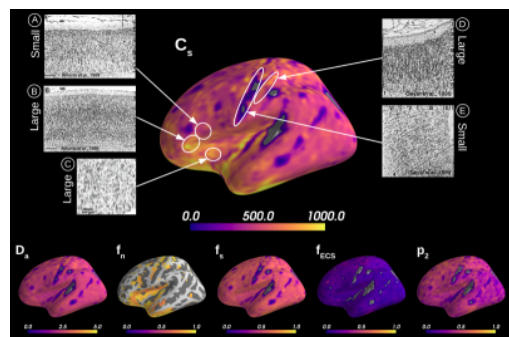
Histograms of  $10^4$  samples of the approximate posterior distribution with observed dMRI signals generated under two acquisition setups,  $\mathcal{A}$  and  $\mathcal{B}$ . Vertical black dashed lines represent ground truth values of  $\theta_0$  which generated the observed signals. Different colors show how the posterior distribution gets sharper as the number  $N$  of simulations in the training dataset increases. Solid curves indicate results for setup  $\mathcal{A}$ , which are very close to the true values, and dashed curves for setup  $\mathcal{B}$ , which present a bias.



(A)  $C_s$  dependence on soma radius  $r_s$  and diffusivity  $D_s$ . We see that there are several values of  $(r_s, D_s)$  that yield the same  $C_s$ . (B) Histograms of  $10^4$  samples from the marginal and joint posterior distributions of  $d_s = 2r_s$  and  $D_s$ . The ridge in the joint distribution indicates that there are several possible values for the pair  $(d_s, D_s)$  with high probability, which are those yielding the same  $C_s$ . Estimating  $C_s$  directly bypasses this indeterminacy.



Logarithm of the standard deviations for the marginal posterior distribution of  $D_a$ ,  $C_s$ , and  $p_2$  with different choices of ground truth parameters (varying  $f_s$  and  $f_n$ ). We see that when the signal fraction of somas decreases ( $f_s \rightarrow 0$ ) the standard deviation of the  $C_s$  estimation increases; and when less neurites are present ( $f_n \rightarrow 0$ ) the standard deviation of  $p_2$  and  $D_a$  increases. A low standard deviation is also observed for signals generated in grey matter tissue conditions, where a soma predominance is expected.



Microstructural measurements averaged over 31 HCP MGH subjects. We deemed stable measurements with a z-score larger than 2, where the standard deviation on the posterior estimates was estimated through our LFI fitting approach. In comparing with Nissl-stained cytoarchitectural studies we can qualitatively evaluate our parameter  $C_s$ : Broadmann area 44 (A) has smaller soma size in average than area 45 (B)<sup>13</sup>; large von Economo neurons predominate the superior anterior insula (C)<sup>12</sup>; precentral gyrus (E) shows very small somas while post-central (D) larger ones<sup>14</sup>.