Microstructure imaging from a dictionary of Monte Carlo signals: assessment on a rat model of Wallerian degeneration

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Synopsis

We estimate microstructural features of the nervous tissues from diffusion-weighted MRI by using sparse optimization techniques on a dictionary of pre-computed Monte Carlo signals, which more faithfully describe the complex diffusion process in the extra-axonal space of the white matter. The method is validated on synthetic data including single and crossing fibers and on an in vivo rat spinal cord model of Wallerian degeneration. We obtain in vivo microstructural estimates that can be directly related to histological evidence whereas the traditional closed-form formula models DIAMOND and NODDI yield results that are more challenging to interpret physically.

Purpose

Most diffusion-weighted MRI (DW-MRI) microstructure imaging approaches use closed-form formulas of the DW signal attenuation based on simplifying assumptions on the tissue or the diffusion processes and only use Monte Carlo (MC) simulations as synthetic ground-truth for validation.

We instead investigate the estimation of microstructural features by using a dictionary of pre-computed realistic MC diffusion signals that more faithfully describe the complex diffusion process in the extra-axonal space. We evaluate this approach on an in vivo rat spinal cord model of Wallerian degeneration, compare results to those obtained with the DIAMOND[1] and NODDI[2] closed-form formulas and investigate an extension to multi-fascicles *in silico*.

Methods

General signal model: We assume that the normalized DW-MRI signal in a voxel

$$E = \frac{T_{WM}\sum_{k=1}^{K}\nu_k E_k(\mathbf{n}_k) + \nu_{CSF}T_{CSF}E_{CSF}}{(1-\nu_{CSF})T_{WM} + \nu_{CSF}T_{CSF}} = \sum_{k=1}^{K} w_k E_k(\mathbf{n}_k) + w_{CSF}E_{CSF}$$

arises from the contributions of K fascicles of axons of orientations $\mathbf{n}_1,\dots,\mathbf{n}_K$ and an isotropic CSF compartment, neglecting water exchange between compartments. The effective DW-MRI weights w_k are the volume fractions ν_k weighted by the T2-relaxation factors $T=\exp(-TE/T2)$ at echo time TE and the signal E_k of each fascicle arises from MC simulations of water molecules in biologically-relevant substrates, typically featuring geometrical arrangements of cylindrical axons.

Estimation: We consider fascicles represented by a hexagonal packing[3-5] of straight cylinders and precompute single-fascicle signals for $N=832$ combinations of radius index r (from 0.8 µm to 7 µm by steps of 0.2 µm) and density index f (from 0.12 to 0.87 by steps of 0.03) with efficient MC simulations leveraging exact analytical formulas for molecules trapped inside cylinders[6,7]. We then estimate the microstructural parameters in each voxel by rotating the signals along the orientations $\mathbf{n}_k$ estimated a priori using a DIAMOND sub-routine[1] and by solving the problem

$$\mathbf{w}^* = \underset{\substack{\mathbf{w}\geq 0\\ |\mathbf{w}|_1=1}}{\operatorname{argmin}} \left\| y - [\,F_1|\dots|F_K|E_{CSF}\,]\cdot\begin{bmatrix}\mathbf{w}_1\\ \vdots\\ \mathbf{w}_K\\ w_{CSF}\end{bmatrix}\right\|_2^2$$

$$\text{subject to}\quad |\mathbf{w}_k|_0 = 1,\quad k=1,\dots,K,$$

where y contains the DW-MRI acquisitions and the sparsity constraints on the sub-vectors $\mathbf{w}_k$ guarantee that only one fascicle configuration (r,f) per sub-dictionary $F_k=[E(r_1,f_1,\mathbf{n}_k)|\dots|E(r_N,f_N,\mathbf{n}_k)|E_{CSF}]$ contributes to the measured signal. For $K\leq 2$, an exhaustive search of every possible combinations of atoms is performed. For $K=3$, sparsity is enforced via l1-reweighted schemes[8] for computational tractability.

Synthetic experiments: Considering a PGSE protocol containing 6 shells of 36 non-colinear gradient directions at b-values $300, 700, 1500, 2800, 4500$ and $6000\,\mathrm{s/mm^2}$; $TE=23\,\mathrm{ms}$, $\delta=4.5\,\mathrm{ms}$ and $\Delta=12\,\mathrm{ms}$, we simulated DW-MRI signals from our signal model on 3000 synthetic voxels containing up to 3 fascicles and corrupted them with non-central Chi noise (Ncoils=4, SNR=2-50). We assessed the ability of our method, DIAMOND and NODDI to estimate various parameters in terms of mean absolute error (MAE) with the ground-truth values.

In vivo rat data and histology: Three rats underwent unilateral rhizotomy at vertebral levels L2-L3 causing Wallerian degeneration in the ipsilateral gracile fasciculus (GF) of the spinal cord, three other rats serving as controls. Acquisitions were performed *in vivo* 51 days post-surgery at 11.7T (Bruker BioSpec) on all 6 rats using the above-described protocol. The rats were then sacrificed and SMI312 immunostaining revealed a notable axonal loss in the ipsilateral part of the GF primarily affecting small axons, while the contralateral part remained little affected (Figure 2a). For all microstructural properties y from all 3 methods, we evaluated the regression model:

$$y = \beta_0 + \beta_{\text{surgery}} \cdot S + \beta_{\text{ipsi}} \cdot I + \beta_{\text{effect}} \cdot S \cdot I,$$

where S and I are binary variables indicating surgery or ipsilateral side, incorporating healthy controls, and where β_{effect} is the effect of interest which should be large only for parameters *physically impacted by the surgery*.

Results and discussion

Our method shows consistent results in the 1 and 2-fascicle configurations as the MAE on the isotropic volume fraction ν_{iso} (our ν_{CSF}) and axonal density index f converges to 0 with increasing SNR (Figure 1) but does not exhibit satisfactory convergence with 3 fascicles. The NODDI and DIAMOND estimates do not necessarily converge to the ground-truth values even with one fascicle, suggesting potentially complex relationships between their parameters and the underlying tissue features.

In the *in vivo* rat experiment, we set $\nu_{iso} = 0$ in our method as our manual segmentation of the GF did not contain CSF, reducing our estimation to a single-fascicle dictionary lookup[9]. Unsurprisingly, significant differences are observed with all models, reflecting the dramatic alteration of the microstructure caused by Wallerian degeneration. However, the challenge here is to identify the *sources* of those changes. Figures 2 shows that our dictionary-based approach attributes the difference to a decrease in intracellular volume fraction and a slight increase in axonal radius, in keeping with the histology. In contrast, both DIAMOND and NODDI ascribe the difference in diffusion signal to changes in a range of parameters (Figures 2c), making the interpretation of the findings more challenging and possibly misleading.

Conclusion

An approach to microstructure imaging based on a dictionary of MC signals was proposed. When applied to synthetic data, this method demonstrates adequate convergence and accuracy for one and two fascicles. When applied to *in vivo* data of a rat model of Wallerian degeneration, our new method demonstrates its capability to ascribe DW-MRI signal differences to microstructural aberrations that are consistent with histological evidence while DIAMOND and NODDI attribute those differences to a wide range of phenomenological parameters whose interpretation is challenging.

Acknowledgements

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Figures

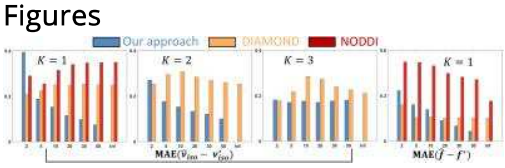

Figure 1: MAE on the estimated CSF isotropic volume fraction (shared by all three methods) in the presence of K=1, 2 and 3 fascicles and on the axonal density f within a fascicle, using nu_icvf for NODDI and (1-nu_iso) as a proxy for DIAMOND. Estimates of NODDI were only considered for single-fascicle configurations given that the model is essentially designed for those configurations.

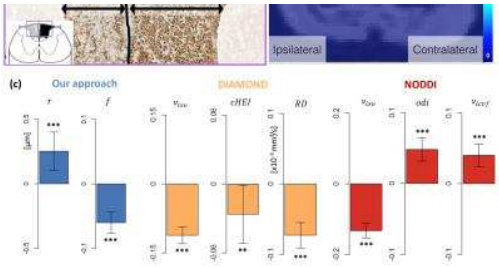

Figure 2: (a) Histology of a slice in the spinal cord with SMI312 immunohistochemistry: darker colors indicate more neurofilaments. (b) Intracellular fraction f of our approach in a random slice of a random rat post-surgery, overlaid on an FA map. (c) Difference in model parameters (cHEI=compartment heterogeneity index, RD=radial diffusivity, odi=orientation dispersion index) measured by the regression parameter associated with the impact of surgery on the ipsilateral side (*** means p<0.001, ** means p<0.01).